Package 'crmPack'

July 27, 2026

Title Object-Oriented Implementation of Dose Escalation Designs

Version 2.2.1

Description Implements a wide range of dose escalation designs. The focus is on model-based designs, ranging from classical and modern continual reassessment methods (CRMs) based on dose-limiting toxicity endpoints to dual-endpoint designs taking into account a biomarker/efficacy outcome. Bayesian inference is performed via MCMC sampling in JAGS, and it is easy to setup a new design with custom JAGS code. However, it is also possible to implement 3+3 designs for comparison or models with non-Bayesian estimation. The whole package is written in a modular form in the S4 class system, making it very flexible for adaptation to new models, escalation or stopping rules. Further details are presented in Sabanés Bové et al. (2019) <doi:10.18637/jss.v089.i10>.

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URL https://docs.crmpack.org/

BugReports https://github.com/openpharma/crmPack/issues

Depends ggplot2 (>= 3.0.0), graphics, R (>= 4.1.0)

Imports checkmate (>= 2.2.0), dplyr, futile.logger, GenSA, gridExtra, kableExtra, knitr, lifecycle, magrittr, methods, mvtnorm, parallel, parallelly, Rdpack, rjags, rlang, survival, tibble, tidyselect (>= 1.2.0), tools, utils

Suggests bookdown, broom, covr, data.tree, DiagrammeR, ggmcmc, quarto (>= 1.4), rmarkdown, stringr, testthat (>= 3.0.0), tidyr, vdiffr, withr

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'Backfill-class.R' 'Backfill-methods.R'
'CrmPackClass-methods.R' 'Data-validity.R' 'Data-class.R'
'helpers_data.R' 'Data-methods.R' 'ModelParams-validity.R'
'ModelParams-class.R' 'Model-validity.R' 'helpers_jags.R'
'Model-class.R' 'HierarchicalModel-class.R'
'TwoDrugsCombo-class.R' 'Design-validity.R' 'Design-class.R'
'McmcOptions-validity.R' 'McmcOptions-class.R'
'McmcOptions-methods.R' 'Samples-validity.R' 'Samples-class.R'
'logger.R' 'helpers_covr.R' 'mcmc.R' 'Simulations-validity.R'
'Simulations-class.R' 'helpers_broom.R' 'helpers_rules.R'
'Model-methods.R' 'checkmate.R' 'Rules-methods.R'
'Design-methods.R' 'HierarchicalDesign-validity.R'
'HierarchicalDesign-class.R' 'HierarchicalDesign-methods.R'
'fromQuantiles.R' 'Samples-methods.R' 'Simulations-methods.R'
'crmPack-package.R' 'helpers_backfill.R' 'helpers_design.R'
'helpers_knitr.R' 'helpers_knitr_Backfill.R'
'helpers_knitr_CohortSize.R' 'helpers_knitr_Design.R'
'helpers_knitr_GeneralData.R' 'helpers_knitr_GeneralModel.R'
'helpers_knitr_Increments.R' 'helpers_knitr_NextBest.R'
'helpers_knitr_Opening.R' 'helpers_knitr_Recruitment.R'
'helpers_knitr_SafetyWindow.R' 'helpers_knitr_Stopping.R'
'helpers_model.R' 'helpers_samples.R' 'helpers_simulations.R'
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Contents

.DefaultCohortSize . . . 10
and,ArmCondition,ArmCondition-method . . . 11
and,Opening,Opening-method . . . 11
approximate . . . 12
ArmCondition-class . . . 14
ArmConditionAll-class . . . 15
ArmConditionAny-class . . . 15
ArmConditionList-class . . . 16
ArmFinishedCondition-class . . . 17
ArmMinDoseCondition-class . . . 17
armSamples . . . 18
assertions . . . 19
Backfill-class . . . 19
biomarker . . . 20
check_equal . . . 23
check_format . . . 24
check_length . . . 26
check_probabilities . . . 27
check_probability . . . 29
check_probability_range . . . 30
check_range . . . 32
CohortSizeConst-class . . . 33
CohortSizeDLT-class . . . 34
CohortSizeMax-class . . . 35
CohortSizeMin-class . . . 36
CohortSizeOrdinal-class . . . 37
CohortSizeParts-class . . . 38
CohortSizeRandom-class . . . 39
CohortSizeRange-class . . . 40
ComboSimulations-class . . . 41
ComboSimulationsSummary-class . . . 42
crmPack . . . 43
CrmPackClass-class . . . 44
crmPackExample . . . 44
crmPackHelp . . . 44
DADesign-class . . . 45
DALogisticLogNormal-class . . . 47
dapply . . . 49
DASimulations-class . . . 50
Data-class . . . 51

DataCombo-class . . . 53
DataDA-class . . . 54
DataDual-class . . . 56
DataGrouped-class . . . 57
DataMixture-class . . . 58
DataOrdinal-class . . . 59
DataParts-class . . . 60
Design-class . . . 61
DesignArm-class . . . 64
DesignCombo-class . . . 65
DesignGrouped-class . . . 67
DesignOrdinal-class . . . 70
dose . . . 73
doseFunction . . . 77
dose_grid_range . . . 79
DualDesign-class . . . 80
DualEndpoint-class . . . 82
DualEndpointBeta-class . . . 84
DualEndpointEmax-class . . . 86
DualEndpointRW-class . . . 88
DualResponsesDesign-class . . . 89
DualResponsesSamplesDesign-class . . . 91
DualSimulations-class . . . 93
DualSimulationsSummary-class . . . 95
EffFlexi-class . . . 95
efficacy . . . 98
efficacyFunction . . . 100
Effloglog-class . . . 102
enable_logging . . . 105
examine . . . 106
fit . . . 111
fitGain . . . 117
fitPEM . . . 120
FractionalCRM-class . . . 123
gain . . . 124
GeneralData-class . . . 126
GeneralModel-class . . . 127
GeneralSimulations-class . . . 128
GeneralSimulationsSummary-class . . . 129
get,Samples,character-method . . . 131
getEff . . . 132
get_arm_simulations . . . 133
HierarchicalData-class . . . 134
HierarchicalDesign-class . . . 135
HierarchicalModel-class . . . 136
HierarchicalSamples-class . . . 138
HierarchicalSimulations-class . . . 139
HierarchicalSimulationsSummary-class . . . 140

h_all_equivalent . . . 141
h_blind_plot_data . . . 141
h_calc_report_label_percentage . . . 142
h_check_fun_formals . . . 143
h_convert_ordinal_data . . . 143
h_convert_ordinal_model . . . 144
h_convert_ordinal_samples . . . 145
h_default_if_empty . . . 145
h_dose_combo_below_limit . . . 146
h_eval_combo_truth . . . 146
h_find_interval . . . 147
h_format_number . . . 148
h_info_theory_dist . . . 149
h_in_range . . . 149
h_is_positive_definite . . . 150
h_jags_add_dummy . . . 151
h_jags_extract_samples . . . 152
h_jags_get_data . . . 153
h_jags_get_model_inits . . . 154
h_jags_join_models . . . 155
h_jags_write_model . . . 155
h_model_dual_endpoint_beta . . . 156
h_model_dual_endpoint_rho . . . 157
h_model_dual_endpoint_sigma2betaw . . . 158
h_model_dual_endpoint_sigma2w . . . 159
h_next_best_eligible_doses . . . 160
h_next_best_mgsamples_plot . . . 161
h_next_best_mg_ci . . . 162
h_next_best_mg_doses_at_grid . . . 163
h_next_best_mg_plot . . . 164
h_next_best_ncrm_loss_plot . . . 165
h_next_best_tdsamples_plot . . . 166
h_next_best_td_plot . . . 167
h_null_if_na . . . 168
h_obtain_dose_grid_range . . . 169
h_plot_data_cohort_lines . . . 169
h_plot_data_dataordinal . . . 170
h_plot_data_df . . . 173
h_rapply . . . 174
h_slots . . . 175
h_summarize_add_stats . . . 176
h_test_named_numeric . . . 176
h_unpack_stopit . . . 178
h_validate_combine_results . . . 178
h_validate_common_data_slots . . . 179
Increments-class . . . 179
IncrementsComboCartesian-class . . . 180
IncrementsComboOneDrugOnly-class . . . 181

IncrementsDoseLevels-class . . . 182
IncrementsHSRBeta-class . . . 183
IncrementsMaxToxProb-class . . . 184
IncrementsMin-class . . . 185
IncrementsOrdinal-class . . . 186
IncrementsRelative-class . . . 187
IncrementsRelativeDLT-class . . . 188
IncrementsRelativeDLTCurrent-class . . . 189
IncrementsRelativeParts-class . . . 190
knit_print.Backfill . . . 191
LogisticIndepBeta-class . . . 212
LogisticKadane-class . . . 215
LogisticKadaneBetaGamma-class . . . 216
LogisticLogNormal-class . . . 218
LogisticLogNormalGrouped-class . . . 219
LogisticLogNormalMixture-class . . . 221
LogisticLogNormalOrdinal-class . . . 222
LogisticLogNormalSub-class . . . 223
LogisticNormal-class . . . 225
LogisticNormalFixedMixture-class . . . 226
LogisticNormalMixture-class . . . 228
logit . . . 229
match_within_tolerance . . . 230
maxDose . . . 231
maxRecruits . . . 238
maxSize . . . 240
mcmc . . . 241
McmcOptions-class . . . 248
MinimalInformative . . . 249
minSize . . . 251
ModelEff-class . . . 252
ModelLogNormal-class . . . 253
ModelParamsNormal-class . . . 254
ModelPseudo-class . . . 255
ModelTox-class . . . 255
names,Samples-method . . . 256
nextBest . . . 257
NextBest-class . . . 275
NextBestDualEndpoint-class . . . 276
NextBestEWOC-class . . . 278
NextBestInfTheory-class . . . 279
NextBestMaxGain-class . . . 280
NextBestMaxGainSamples-class . . . 281
NextBestMinDist-class . . . 282
NextBestMTD-class . . . 283
NextBestNCRM-class . . . 284
NextBestNCRMLoss-class . . . 285
NextBestOrdinal-class . . . 287

NextBestProbMTDLTE-class . . . 288
NextBestProbMTDMinDist-class . . . 289
NextBestTD-class . . . 290
NextBestTDsamples-class . . . 291
NextBestThreePlusThree-class . . . 292
ngrid . . . 292
NoArmCondition-class . . . 293
OneParExpPrior-class . . . 294
OneParLogNormalPrior-class . . . 295
openArm . . . 296
openCohort . . . 297
Opening-class . . . 301
OpeningAll-class . . . 302
OpeningAny-class . . . 303
OpeningList-class . . . 304
OpeningMinCohorts-class . . . 305
OpeningMinDose-class . . . 305
OpeningMinResponses-class . . . 306
OpeningNone-class . . . 307
or,ArmCondition,ArmCondition-method . . . 308
or,Opening,Opening-method . . . 309
or-Stopping-Stopping . . . 309
or-Stopping-StoppingAny . . . 310
or-StoppingAny-Stopping . . . 311
plot,ComboSimulations,missing-method . . . 312
plot,ComboSimulationsSummary,missing-method . . . 312
plot,Data,ModelTox-method . . . 313
plot,DataCombo,missing-method . . . 314
plot,DataDA,missing-method . . . 315
plot,DataDual,missing-method . . . 316
plot,DataDual,ModelEff-method . . . 317
plot,DualSimulations,missing-method . . . 318
plot,DualSimulationsSummary,missing-method . . . 323
plot,GeneralSimulations,missing-method . . . 326
plot,GeneralSimulationsSummary,missing-method . . . 329
plot,HierarchicalData,missing-method . . . 330
plot,HierarchicalSamples,HierarchicalModel-method . . . 330
plot,PseudoDualFlexiSimulations,missing-method . . . 331
plot,PseudoDualSimulations,missing-method . . . 334
plot,PseudoDualSimulationsSummary,missing-method . . . 337
plot,PseudoSimulationsSummary,missing-method . . . 341
plot,Samples,DALogisticLogNormal-method . . . 344
plot,Samples,DualEndpoint-method . . . 345
plot,Samples,GeneralModel-method . . . 347
plot,Samples,ModelEff-method . . . 348
plot,Samples,ModelTox-method . . . 349
plot,Samples,TwoDrugsCombo-method . . . 351
plot,SimulationsSummary,missing-method . . . 352

plot.gtable . . . 354
plotDualResponses . . . 355
plotGain . . . 357
positive_number . . . 360
prob . . . 360
probFunction . . . 365
probit . . . 366
ProbitLogNormal-class . . . 367
ProbitLogNormalRel-class . . . 368
PseudoDualFlexiSimulations-class . . . 369
PseudoDualSimulations-class . . . 370
PseudoDualSimulationsSummary-class . . . 371
PseudoSimulations-class . . . 372
PseudoSimulationsSummary-class . . . 374
Quantiles2LogisticNormal . . . 376
Recruitment-class . . . 378
RecruitmentRatio-class . . . 378
RecruitmentUnlimited-class . . . 379
RuleDesign-class . . . 380
RuleDesignOrdinal-class . . . 381
SafetyWindow-class . . . 383
SafetyWindowConst-class . . . 383
SafetyWindowSize-class . . . 384
Samples-class . . . 385
saveSample . . . 387
scenario . . . 388
set_seed . . . 395
show,ComboSimulations-method . . . 396
show,ComboSimulationsSummary-method . . . 396
show,DualSimulationsSummary-method . . . 397
show,GeneralSimulations-method . . . 399
show,GeneralSimulationsSummary-method . . . 400
show,HierarchicalData-method . . . 400
show,HierarchicalDesign-method . . . 401
show,HierarchicalModel-method . . . 401
show,HierarchicalSimulations-method . . . 402
show,HierarchicalSimulationsSummary-method . . . 402
show,PseudoDualSimulationsSummary-method . . . 403
show,PseudoSimulationsSummary-method . . . 406
show,SimulationsSummary-method . . . 408
simulate,DADesign-method . . . 410
simulate,Design-method . . . 414
simulate,DesignCombo-method . . . 417
simulate,DesignGrouped-method . . . 419
simulate,DualDesign-method . . . 422
simulate,DualResponsesDesign-method . . . 426
simulate,DualResponsesSamplesDesign-method . . . 429
simulate,HierarchicalDesign-method . . . 433

simulate,RuleDesign-method . . . 435
simulate,TDDesign-method . . . 436
simulate,TDsamplesDesign-method . . . 439
Simulations-class . . . 442
SimulationsSummary-class . . . 444
singleDrugData . . . 445
size . . . 446
Stopping-class . . . 455
StoppingAll-class . . . 456
StoppingAny-class . . . 457
StoppingCohortsNearDose-class . . . 458
StoppingExternal-class . . . 459
StoppingHighestDose-class . . . 460
StoppingList-class . . . 461
StoppingLowestDoseHSRBeta-class . . . 462
StoppingMaxGainCIRatio-class . . . 463
StoppingMinCohorts-class . . . 464
StoppingMinPatients-class . . . 465
StoppingMissingDose-class . . . 466
StoppingMTDCV-class . . . 467
StoppingMTDdistribution-class . . . 468
StoppingOrdinal-class . . . 469
StoppingPatientsNearDose-class . . . 470
StoppingSpecificDose-class . . . 471
StoppingTargetBiomarker-class . . . 472
StoppingTargetProb-class . . . 473
StoppingTDCIRatio-class . . . 474
stopTrial . . . 475
subset-Data . . . 504
summary,ComboSimulations-method . . . 504
summary,DualSimulations-method . . . 505
summary,GeneralSimulations-method . . . 508
summary,HierarchicalSimulations-method . . . 508
summary,PseudoDualFlexiSimulations-method . . . 509
summary,PseudoDualSimulations-method . . . 512
summary,PseudoSimulations-method . . . 515
summary,Simulations-method . . . 518
TDDesign-class . . . 520
TDsamplesDesign-class . . . 522
tidy . . . 524
TITELogisticLogNormal-class . . . 530
TITELogisticLogNormalSub-class . . . 532
TwoDrugsCombo-class . . . 533
update,Data-method . . . 535
update,DataCombo-method . . . 536
update,DataDA-method . . . 538
update,DataDual-method . . . 539
update,DataOrdinal-method . . . 540

update,DataParts-method . . . 542
update,HierarchicalData-method . . . 543
update,ModelPseudo-method . . . 543
Validate . . . 545
v_arm_condition . . . 546
v_backfill . . . 546
v_cohort_size . . . 547
v_data_objects . . . 548
v_design . . . 550
v_general_simulations . . . 551
v_hierarchical_design . . . 552
v_increments . . . 552
v_mcmcoptions_objects . . . 554
v_model_objects . . . 554
v_model_params . . . 557
v_next_best . . . 557
v_opening . . . 559
v_pseudo_simulations . . . 560
v_recruitment . . . 561
v_safety_window . . . 561
v_samples_objects . . . 562
v_stopping . . . 563
windowLength . . . 564
&,Stopping,Stopping-method . . . 568
&,Stopping,StoppingAll-method . . . 569
&,StoppingAll,Stopping-method . . . 569

Index **571**

`.DefaultCohortSize` `CohortSize`

Description

[Stable]

`CohortSize` is a class for cohort sizes.

Usage

```
.DefaultCohortSize()

.DefaultCohortSize()
```

Note

Typically, end users will not use the `DefaultCohortSize()` function.

Typically, end users will not use the `DefaultCohortSize()` function.

See Also

CohortSizeRange, CohortSizeDLT, CohortSizeConst, CohortSizeParts, CohortSizeMin, CohortSizeMin.

---

and,ArmCondition,ArmCondition-method

Logical AND Operator for ArmCondition Objects

Description

[Experimental]

Combines two ArmCondition objects with AND logic using the & operator. This creates an ArmConditionAll object.

Usage

```
## S4 method for signature 'ArmCondition,ArmCondition'
e1 & e2
```

Arguments

e1	(ArmCondition) the first arm condition object.
e2	(ArmCondition) the second arm condition object.

Value

An ArmConditionAll object combining e1 and e2.

---

and,Opening,Opening-method

Logical AND Operator for Opening Objects

Description

[Experimental]

Combines two Opening objects with AND logic using the & operator. This creates an OpeningAll object.

Usage

```
## S4 method for signature 'Opening,Opening'
e1 & e2
```

Arguments

e1	(Opening) the first opening object.
e2	(Opening) the second opening object.

Value

An OpeningAll object combining e1 and e2.

See Also

OpeningAll for more details.

---

approximate *Approximate posterior with (log) normal distribution*

Description

To reproduce the resultant approximate model in the future exactly, include seed = xxxx in the call to approximate.

Usage

```
approximate(object, model, data, ...)

## S4 method for signature 'Samples'
approximate(
  object,
  model,
  data,
  points = seq(from = min(data@doseGrid), to = max(data@doseGrid), length = 5L),
  refDose = median(points),
  logNormal = FALSE,
  verbose = TRUE,
  create_plot = TRUE,
  ...
)
```

Arguments

object	the Samples object
model	the GeneralModel object
data	the Data object
...	additional arguments (see methods)
points	optional parameter, which gives the dose values at which the approximation should rely on (default: 5 values equally spaced from minimum to maximum of the dose grid)

refDose	the reference dose to be used (default: median of points)
logNormal	use the log-normal prior? (not default) otherwise, the normal prior for the logistic regression coefficients is used
verbose	be verbose (progress statements)? (default)
create_plot	add a ggplot2 object to the return value (default)

Value

a list containing the approximation model and, if requested, a ggplot2 object containing a graphical representation of the fitted model

Functions

- approximate(Samples): Here the ... argument can transport additional arguments for Quantiles2LogisticNormal, e.g. in order to control the approximation quality, etc.

Examples

```
# nolint start

# Create some data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(
    0.1,
    0.5,
    1.5,
    3,
    6,
    seq(from = 10, to = 80, by = 2)
  )
)

# Initialize a model
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Get posterior for all model parameters
options <- McmcOptions(
  burnin = 100,
  step = 2,
  samples = 2000
)
set.seed(94)
samples <- mcmc(data, model, options)
```

```
# Approximate the posterior distribution with a bivariate normal
# max.time and maxit are very small only for the purpose of showing the example. They
# should be increased for a real case.
set.seed(94)
approximation <- approximate(
  object = samples,
  model = model,
  data = data,
  logNormal = TRUE,
  control = list(
    threshold.stop = 0.1,
    max.time = 1,
    maxit = 1
  )
)

posterior <- approximation$model

# nolint end
```

ArmCondition-class ArmCondition

Description

[Experimental]

ArmCondition is a virtual class for criteria controlling when a DesignArm opens for enrollment in a HierarchicalDesign.

Usage

```
.DefaultArmCondition()
```

Note

Typically, end users will not use the .DefaultArmCondition() function.

See Also

NoArmCondition, ArmFinishedCondition, ArmMinDoseCondition, ArmConditionAll, ArmConditionAny.

ArmConditionAll-class ArmConditionAll

Description

[Experimental]

ArmConditionAll combines multiple ArmCondition objects using AND logic. An arm opens only if ALL conditions in the list are satisfied.

Usage

```
ArmConditionAll(...)

.DefaultArmConditionAll()
```

Arguments

...	(ArmCondition) arm condition objects to combine with AND logic.

Slots

condition_list (list)
: a list of ArmCondition objects to be combined with AND logic.

Note

Typically, end users will not use the .DefaultArmConditionAll() function.

See Also

ArmCondition, ArmConditionAny, ArmConditionList.

ArmConditionAny-class ArmConditionAny

Description

[Experimental]

ArmConditionAny combines multiple ArmCondition objects using OR logic. An arm opens if ANY condition in the list is satisfied.

Usage

```
ArmConditionAny(...)

.DefaultArmConditionAny()
```

Arguments

`...`	(`ArmCondition`) arm condition objects to combine with OR logic.

Slots

`condition_list` (`list`)
: a list of `ArmCondition` objects to be combined with OR logic.

Note

Typically, end users will not use the `.DefaultArmConditionAny()` function.

See Also

`ArmCondition`, `ArmConditionAll`, `ArmConditionList`.

`ArmConditionList-class` `ArmConditionList`

Description

[Experimental]

`ArmConditionList` is a virtual class for combining multiple `ArmCondition` objects using logical operators. It is used as a base class for `ArmConditionAll` and `ArmConditionAny`.

Usage

```
ArmConditionList(...)

.DefaultArmConditionList()
```

Arguments

`...`	(`ArmCondition`) arm condition objects to combine.

Slots

`condition_list` (`list`)
: a list of `ArmCondition` objects to be combined.

Note

Typically, end users will not use the `.DefaultArmConditionList()` function.

See Also

ArmCondition, ArmConditionAll, ArmConditionAny.

`ArmFinishedCondition-class`
`ArmFinishedCondition`

Description

[Experimental]

ArmFinishedCondition opens an arm when the named arm has finished dose escalation.

Usage

```
ArmFinishedCondition(arm_name)

.DefaultArmFinishedCondition()
```

Arguments

`arm_name`	(`string`) see slot definition.

Slots

`arm_name` (`string`)
: the name of the arm that must have finished.

Note

Typically, end users will not use the `.DefaultArmFinishedCondition()` function.

`ArmMinDoseCondition-class`
`ArmMinDoseCondition`

Description

[Experimental]

ArmMinDoseCondition opens an arm when the named arm has enrolled at least one patient at the specified minimum dose or higher.

Usage

```
ArmMinDoseCondition(arm_name, min_dose)

.DefaultArmMinDoseCondition()
```

Arguments

arm_name	(string) see slot definition.
min_dose	(numeric) see slot definition.

Slots

`arm_name` (`string`)
: the name of the arm whose data are checked.

`min_dose` (`numeric`)
: the minimum dose that must have been reached. For combination arms, this can be a vector of minimum doses for each agent.

Note

Typically, end users will not use the `.DefaultArmMinDoseCondition()` function.

---

armSamples *Extract One Arm's Posterior Draws from a* `HierarchicalSamples` *Object*

Description

[Experimental]

Returns a plain `Samples` object for a single hierarchical arm, with the original arm-level parameter names restored.

Usage

```
armSamples(object, arm)

## S4 method for signature 'HierarchicalSamples,character'
armSamples(object, arm)
```

Arguments

object	(`HierarchicalSamples`) hierarchical posterior draws.
arm	(`character`) name of the arm to extract.

Value

A Samples object containing only the requested arm's parameters.

---

assertions *Additional Assertions for* checkmate

Description

[Experimental]

We provide additional assertion functions that can be used together with the checkmate functions. These are described in individual help pages linked below.

Value

Depending on the function prefix.

- assert_ functions return the object invisibly if successful, and otherwise throw an error message.
- check_ functions return TRUE if successful, otherwise a string with the error message.
- test_ functions just return TRUE or FALSE.

See Also

assert_probabilities(), assert_probability(), assert_probability_range(), assert_length().

Backfill-class *Backfill class*

Description

[Experimental]

Class representing a backfilling rule in a clinical trial design.

Usage

```
Backfill(
  cohort_size = CohortSizeConst(size = 3),
  opening = OpeningMinDose(),
  recruitment = RecruitmentUnlimited(),
  max_size = 1000000L,
  priority = c("highest", "lowest", "random")
)

.DefaultBackfill()
```

Arguments

`cohort_size`	(`CohortSize`) see the slot definition.
`opening`	(`Opening`) see the slot definition.
`recruitment`	(`Recruitment`) see the slot definition.
`max_size`	(`count`) see the slot definition.
`priority`	(`character`) see the slot definition.

Value

An object of class `Backfill`.

Slots

`cohort_size` (`CohortSize`)
: the size of cohorts to be backfilled.

`opening` (`Opening`)
: the opening criteria for backfilling.

`recruitment` (`Recruitment`)
: recruitment criteria for backfilling.

`max_size` (`count`)
: the maximum number of patients to be backfilled.

`priority` (`character`)
: the priority rule for backfilling, one of "highest", "lowest", or "random".

Note

Typically, end users will not use the `.DefaultBackfill()` function.

`biomarker` *Get the Biomarker Levels for a Given Dual-Endpoint Model, Given Dose Levels and Samples*

Description

[Experimental]

Usage

```
biomarker(xLevel, model, samples, ...)

## S4 method for signature 'integer,DualEndpoint,Samples'
biomarker(xLevel, model, samples, ...)
```

Arguments

xLevel	(integer) the levels for the doses the patients have been given w.r.t dose grid. See Data for more details.
model	(DualEndpoint) the model.
samples	(Samples) the samples of model's parameters that store the value of biomarker levels for all doses on the dose grid.
...	not used.

Details

This function simply returns a specific columns (with the indices equal to xLevel) of the biomarker samples matrix, which is included in the the samples object.

Value

The biomarker levels.

Functions

- biomarker(xLevel = integer, model = DualEndpoint, samples = Samples): Extract biomarker values for a DualEndpoint model.

Examples

```
# Create the data.
my_data <- DataDual(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10, 20, 20, 20, 40, 40, 40, 50, 50, 50),
  y = c(0, 0, 0, 0, 0, 0, 1, 0, 0, 1, 1, 0, 0, 1, 0, 1, 1),
  ID = 1:17,
  cohort = c(
    1L,
    2L,
    3L,
    4L,
    5L,
    6L,
    6L,
    6L,
    7L,
```

```
    7L,
    7L,
    8L,
    8L,
    8L,
    9L,
    9L,
    9L
  ),
  w = c(
    0.31,
    0.42,
    0.59,
    0.45,
    0.6,
    0.7,
    0.55,
    0.6,
    0.52,
    0.54,
    0.56,
    0.43,
    0.41,
    0.39,
    0.34,
    0.38,
    0.21
  ),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the Dual-Endpoint model (in this case RW1).
my_model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2betaW = 0.01,
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  rw1 = TRUE
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(
  burnin = 100,
  step = 2,
  samples = 500
)
my_samples <- mcmc(my_data, my_model, my_options)

# Obtain the biomarker levels (samples) for the second dose from the dose grid,
# which is 0.5.
biomarker(
  xLevel = 2L,
```

```
  model = my_model,
  samples = my_samples
)
```

---

check_equal *Check if All Arguments Are Equal*

Description

[Experimental] Elements of `...` must be numeric vectors or scalars.

This function performs an element-by-element comparison of the first object provided in `...` with every other object in `...` and returns `TRUE` if all comparisons are equal within a given tolerance and `FALSE` otherwise.

[Experimental] Elements of `...` must be numeric vectors or scalars.

This function performs an element-by-element comparison of the first object provided in `...` with every other object in `...` and throws an error if they are not.

Usage

```
check_equal(..., tol = sqrt(.Machine$double.eps))

assert_equal(
  ...,
  tol = sqrt(.Machine$double.eps),
  .var.name = vname(x),
  add = NULL
)
```

Arguments

`...`	(`numeric`) vectors to be compared
`tol`	(`numeric`) the maximum difference to be tolerated when judging equality
`.var.name`	[`character(1)`] Name of the checked object to print in assertions. Defaults to the heuristic implemented in `vname`.
`add`	[`AssertCollection`] Collection to store assertion messages. See `AssertCollection`.

Value

`TRUE` if all element-by-element differences are less than `tolerance` in magnitude, `FALSE` otherwise.

`list(...)`, invisibly.

Note

If there are any missing or infinite values in ..., this function returns FALSE, regardless of the values of other elements in ....

If elements in ... are not all of the same length, FALSE is returned.

If there are any missing or infinite values in ..., this function throws an error, regardless of the values of other elements in ....

If elements in ... are not all of the same length, an error is thrown.

See Also

assertions for more details.

Examples

```
check_equal(1:2, 1:2) # TRUE
check_equal(1:2, 2:3) # "Not all equal"
check_equal(Inf, Inf) # "Not all equal"
check_equal(0.01, 0.02) # "Not all equal"
check_equal(0.01, 0.02, tol = 0.05) # TRUE
check_equal(1, c(1, 1)) # "Not all equal"
assert_equal(1:2, 1:2) # no error
assert_equal(0.01, 0.02, tol = 0.05) # no error
```

---

check_format *Check that an argument is a valid format specification*

Description

[Stable]

Usage

```
check_format(x, len = NULL, min.len = NULL, max.len = NULL)

assert_format(
  x,
  len = NULL,
  min.len = NULL,
  max.len = NULL,
  .var.name = checkmate::vname(x),
  add = NULL
)

test_format(x, len = NULL, min.len = NULL, max.len = NULL)

expect_format(
```

```
  x,
  len = NULL,
  min.len = NULL,
  max.len = NULL,
  info = NULL,
  label = vname(x)
)
```

Arguments

x	[any] Object to check.
len	[integer(1)] Exact expected length of x.
min.len	[integer(1)] Minimal length of x.
max.len	[integer(1)] Maximal length of x.
.var.name	[character(1)] Name of the checked object to print in assertions. Defaults to the heuristic implemented in vname.
add	[AssertCollection] Collection to store assertion messages. See AssertCollection.
info	[character(1)] Extra information to be included in the message for the testthat reporter. See expect_that.
label	[character(1)] Name of the checked object to print in messages. Defaults to the heuristic implemented in vname.

Value

TRUE if successful, otherwise a string with the error message.

See Also

assertions for more details.

Examples

```
check_format("%5.2f")
```

check_length *Check if vectors are of compatible lengths*

Description

[Stable]

Two vectors are of compatible size if and only if:

1. At least one vector has size 1
2. or both vectors are of the same size.

Usage

```
check_length(x, len)

assert_length(x, len, .var.name = checkmate::vname(x), add = NULL)

test_length(x, len)
```

Arguments

x	(any) the first vector, any object for which `length()` function is defined.
len	(count) the length of the second vector.
.var.name	[character(1)] Name of the checked object to print in assertions. Defaults to the heuristic implemented in `vname`.
add	[AssertCollection] Collection to store assertion messages. See `AssertCollection`.

Value

`TRUE` if successful, otherwise a string with the error message.

See Also

`assertions` for more details.

Examples

```
check_length(1:5, 1)
check_length(1:5, 6)
check_length(1:5, 5)
check_length(10, 1)
check_length(10, 9)
```

`check_probabilities` *Check if an argument is a probability vector*

Description

[Stable]

Check if every element in a given numerical vector or matrix represents a probability, that is a number within (0, 1) interval, that can optionally be closed at any side.

Usage

```
check_probabilities(
  x,
  bounds_closed = TRUE,
  len = NULL,
  unique = FALSE,
  sorted = FALSE
)

assert_probabilities(
  x,
  bounds_closed = TRUE,
  len = NULL,
  unique = FALSE,
  sorted = FALSE,
  .var.name = checkmate::vname(x),
  add = NULL
)

test_probabilities(
  x,
  bounds_closed = TRUE,
  len = NULL,
  unique = FALSE,
  sorted = FALSE
)

expect_probabilities(
  x,
  bounds_closed = TRUE,
```

```
  len = NULL,
  unique = FALSE,
  sorted = FALSE,
  info = NULL,
  label = vname(x)
)
```

Arguments

x	(numeric) vector or matrix with numerical values to check.
bounds_closed	(logical) should bounds be closed? This can be a scalar or vector of length two. If it is a scalar, then its value applies equally to lower bound 0 and upper bound 1. If this is a vector with two flags, the first flag corresponds to the lower bound 0 only, and the second to the upper bound 1 only.
len	[integer(1)] Exact expected length of x.
unique	[logical(1)] Must all values be unique? Default is FALSE.
sorted	[logical(1)] Elements must be sorted in ascending order. Missing values are ignored.
.var.name	[character(1)] Name of the checked object to print in assertions. Defaults to the heuristic implemented in vname.
add	[AssertCollection] Collection to store assertion messages. See AssertCollection.
info	[character(1)] Extra information to be included in the message for the testthat reporter. See expect_that.
label	[character(1)] Name of the checked object to print in messages. Defaults to the heuristic implemented in vname.

Value

TRUE if successful, otherwise a string with the error message.

Note

If there are any missing or non-finite values in x, this function returns FALSE, regardless of the values of other elements in x.

See Also

assertions for more details.

Examples

```
x <- c(0, 0.2, 0.1, 0.3, 1)
check_probabilities(x)
check_probabilities(x, bounds_closed = FALSE)
check_probabilities(x, bounds_closed = c(FALSE, TRUE))
```

---

check_probability *Check if an argument is a single probability value*

Description

[Stable]

Check if a given value represents a probability, that is a number within (0, 1) interval, that can optionally be closed at any side.

Usage

```
check_probability(x, bounds_closed = TRUE)

assert_probability(
  x,
  bounds_closed = TRUE,
  .var.name = checkmate::vname(x),
  add = NULL
)

test_probability(x, bounds_closed = TRUE)

expect_probability(x, bounds_closed = TRUE, info = NULL, label = vname(x))
```

Arguments

x	(number) a single value to check.
bounds_closed	(logical) should bounds be closed? This can be a scalar or vector of length two. If it is a scalar, then its value applies equally to lower bound 0 and upper bound 1. If this is a vector with two flags, the first flag corresponds to the lower bound 0 only, and the second to the upper bound 1 only.
.var.name	[character(1)] Name of the checked object to print in assertions. Defaults to the heuristic implemented in vname.
add	[AssertCollection] Collection to store assertion messages. See AssertCollection.

info [character(1)]
Extra information to be included in the message for the testthat reporter. See expect_that.

label [character(1)]
Name of the checked object to print in messages. Defaults to the heuristic implemented in vname.

Value

TRUE if successful, otherwise a string with the error message.

See Also

assertions for more details.

Examples

```
check_probability(0.5)
check_probability(0, bounds_closed = FALSE)
check_probability(0, bounds_closed = c(FALSE, TRUE))
```

---

check_probability_range

Check if an argument is a probability range

Description

[Stable]

Check if a given numerical interval represents a probability range, that is a sub-interval of (0, 1) interval, that can optionally be closed at any side.

Usage

```
check_probability_range(x, bounds_closed = TRUE)

assert_probability_range(
  x,
  bounds_closed = TRUE,
  .var.name = checkmate::vname(x),
  add = NULL
)

test_probability_range(x, bounds_closed = TRUE)

expect_probability_range(
  x,
  bounds_closed = TRUE,
```

```
  info = NULL,
  label = vname(x)
)
```

Arguments

x	(number) an interval to check.
bounds_closed	(logical) should bounds be closed? This can be a scalar or vector of length two. If it is a scalar, then its value applies equally to lower bound 0 and upper bound 1. If this is a vector with two flags, the first flag corresponds to the lower bound 0 only, and the second to the upper bound 1 only.
.var.name	[character(1)] Name of the checked object to print in assertions. Defaults to the heuristic implemented in vname.
add	[AssertCollection] Collection to store assertion messages. See AssertCollection.
info	[character(1)] Extra information to be included in the message for the testthat reporter. See expect_that.
label	[character(1)] Name of the checked object to print in messages. Defaults to the heuristic implemented in vname.

Value

TRUE if successful, otherwise a string with the error message.

See Also

assertions for more details.

Examples

```
x <- c(0, 0.2)
check_probability_range(x)
check_probability_range(rev(x))
check_probability_range(x, bounds_closed = FALSE)
check_probability_range(x, bounds_closed = c(FALSE, TRUE))
```

check_range *Check that an argument is a numerical range*

Description

[Stable]

An argument x is a numerical range if and only if (all conditions must be met):

1. Is an object of type: integer or double.
2. Is a vector or length two such that the value of the first number is not less than the second number. Equalness is allowed if and only if unique flag is set to TRUE.
3. Lower bound of the interval is greater than or equal to lower and upper bound of the interval is less than or equal to upper.
4. It contains only finite (given that finite is TRUE) and non-missing values.

Usage

```
check_range(x, lower = -Inf, upper = Inf, finite = FALSE, unique = TRUE)

assert_range(
  x,
  lower = -Inf,
  upper = Inf,
  finite = FALSE,
  unique = TRUE,
  .var.name = checkmate::vname(x),
  add = NULL
)

test_range(x, lower = -Inf, upper = Inf, finite = FALSE, unique = TRUE)

expect_range(
  x,
  lower = -Inf,
  upper = Inf,
  finite = FALSE,
  unique = TRUE,
  info = NULL,
  label = vname(x)
)
```

Arguments

x	[any] Object to check.

lower	[numeric(1)] Lower value all elements of x must be greater than or equal to.
upper	[numeric(1)] Upper value all elements of x must be lower than or equal to.
finite	[logical(1)] Check for only finite values? Default is FALSE.
unique	[logical(1)] Must all values be unique? Default is FALSE.
.var.name	[character(1)] Name of the checked object to print in assertions. Defaults to the heuristic implemented in vname.
add	[AssertCollection] Collection to store assertion messages. See AssertCollection.
info	[character(1)] Extra information to be included in the message for the testthat reporter. See expect_that.
label	[character(1)] Name of the checked object to print in messages. Defaults to the heuristic implemented in vname.

Value

TRUE if successful, otherwise a string with the error message.

See Also

assertions for more details.

Examples

```
check_range(c(1, 5))
check_range(c(-5, 1))
check_range(c(4, 1))
check_range(c(1, 1))
check_range(c(1, 1), unique = FALSE)
check_range(1:3)
```

CohortSizeConst-class CohortSizeConst

Description

[Stable]

CohortSizeConst is the class for fixed and constant size of cohort.

Usage

```
CohortSizeConst(size)

.DefaultCohortSizeConst()
```

Arguments

size	(number) see slot definition.

Slots

`size` (integer)
: cohort size.

Note

Typically, end users will not use the `.DefaultCohortSizeConst()` function.

Examples

```
# Cohort of size 3, constant along the study.
my_size <- CohortSizeConst(size = 3)
```

CohortSizeDLT-class CohortSizeDLT

Description

[Stable]

`CohortSizeDLT` is the class for cohort size based on number of DLTs.

Usage

```
CohortSizeDLT(intervals, cohort_size)

.DefaultCohortSizeDLT()
```

Arguments

intervals	(numeric) see slot definition.
cohort_size	(numeric) see slot definition.

Slots

`intervals` (integer)
: a vector with the left bounds of the relevant DLT intervals.

`cohort_size` (integer)
: a vector with the cohort sizes corresponding to the elements of `intervals`.

Note

Typically, end users will not use the `.DefaultCohortSizeDLT()` function.

Examples

```
# Rule for having cohort of size 1 until no DLT is observed and having cohort
# of size 3 as soon as 1 DLT is observed.
my_size <- CohortSizeDLT(intervals = c(0, 1), cohort_size = c(1, 3))
```

CohortSizeMax-class CohortSizeMax

Description

[Stable]

`CohortSizeMax` is the class for cohort size that is based on maximum of multiple cohort size rules. The `cohort_sizes` slot stores a set of cohort size rules, which are again the objects of class `CohortSize`. The maximum of these individual cohort sizes is taken to give the final cohort size.

Usage

```
.DefaultCohortSizeMax()

CohortSizeMax(cohort_sizes)
```

Arguments

`cohort_sizes`	(`list`) see slot definition.

Slots

`cohort_sizes` (`list`)
: a list of cohort size rules, i.e. objects of class `CohortSize`.

Note

Typically, end users will not use the `.DefaultCohortSizeMax()` function.

Examples

```
# Rule for cohort of size 1 for doses <30 and cohort of size 3 for doses >=30.
my_size1 <- CohortSizeRange(intervals = c(0, 10), cohort_size = c(1, 3))

# Rule for cohort of size 1 until no DLT were observed and cohort of size 3
# as soon as 1 DLT is observed.
my_size2 <- CohortSizeDLT(intervals = c(0, 1), cohort_size = c(1, 3))

# Cohort size rules of class 'CohortSizeMax' which will then be combined with
# the 'max' operation.
mySize <- CohortSizeMax(cohort_sizes = list(my_size1, my_size2))
```

CohortSizeMin-class CohortSizeMin

Description

[Stable]

CohortSizeMin is the class for cohort size that is based on minimum of multiple cohort size rules. The cohort_sizes slot stores a set of cohort size rules, which are again the objects of class CohortSize. The minimum of these individual cohort sizes is taken to give the final cohort size.

Usage

```
CohortSizeMin(cohort_sizes)

.DefaultCohortSizeMin()
```

Arguments

cohort_sizes	(list) see slot definition.

Slots

cohort_sizes (list)
: a list of cohort size rules, i.e. objects of class CohortSize.

Note

Typically, end users will not use the .DefaultCohortSizeMin() function.

Examples

```
# Rule for cohort of size 1 for doses <30 and cohort of size 3 for doses >=30.
my_size1 <- CohortSizeRange(intervals = c(0, 10), cohort_size = c(1, 3))

# Rule for cohort of size 1 until no DLT were observed and cohort of size 3
# as soon as 1 DLT is observed.
my_size2 <- CohortSizeDLT(intervals = c(0, 1), cohort_size = c(1, 3))

# Cohort size rules of class 'CohortSizeMin' which will then be combined with
# the 'min' operation.
my_size <- CohortSizeMin(cohort_sizes = list(my_size1, my_size2))
```

CohortSizeOrdinal-class
CohortSizeOrdinal

Description

[Experimental]

`CohortSizeOrdinal` is the class for cohort size for an ordinal CRM trial.

Usage

```
CohortSizeOrdinal(grade, rule)

.DefaultCohortSizeOrdinal()
```

Arguments

`grade`	(integer) see slot definition.
`rule`	(CohortSize) see slot definition.

Slots

`grade` (integer)
: the grade at which the rule should be applied

`rule` (CohortSize)
: the `CohortSize` rule to apply.

Note

Typically, end users will not use the `.DefaultCohortSizeOrdinal()` function.

Examples

```
CohortSizeOrdinal(
  grade = 1L,
  rule = CohortSizeRange(intervals = c(0, 30), cohort_size = c(1L, 3L))
)
```

`CohortSizeParts-class` `CohortSizeParts`

Description

[Stable]

`CohortSizeParts` is the class for cohort size that changes for the second part of the dose escalation. It works only in conjunction with `DataParts` objects.

Usage

```
CohortSizeParts(cohort_sizes)

.DefaultCohortSizeParts()
```

Arguments

`cohort_sizes`	`(numeric)` see slot definition.

Slots

`cohort_sizes (integer)`
: a vector of length two with two sizes, one for part 1, and one for part 2 respectively.

Note

Typically, end users will not use the `.DefaultCohortSizeParts()` function.

Examples

```
# Part 1 cohort size = 1, Part 2 cohort size = 3.
my_size <- CohortSizeParts(cohort_sizes = c(1, 3))
```

CohortSizeRandom-class
CohortSizeRandom

Description

[Experimental]

CohortSizeRandom is the class for random cohort sizes drawn from a uniform distribution between min_size and max_size (inclusive).

Usage

```
CohortSizeRandom(min_size, max_size)

.DefaultCohortSizeRandom()
```

Arguments

min_size	(integer) see slot definition.
max_size	(integer) see slot definition.

Slots

min_size (integer)
: minimum cohort size.

max_size (integer)
: maximum cohort size.

Note

Typically, end users will not use the .DefaultCohortSizeRandom() function.

Examples

```
# Random cohort size between 1 and 5.
my_size <- CohortSizeRandom(min_size = 1, max_size = 5)
```

`CohortSizeRange-class` `CohortSizeRange`

Description

[Stable]

`CohortSizeRange` is the class for cohort size based on dose range.

Usage

```
CohortSizeRange(intervals, cohort_size)

.DefaultCohortSizeRange()
```

Arguments

`intervals`	(`numeric`) see slot definition.
`cohort_size`	(`numeric`) see slot definition.

Slots

`intervals` (`numeric`)
: a vector with the left bounds of the relevant dose intervals.

`cohort_size` (`integer`)
: an integer vector with the cohort sizes corresponding to the elements of `intervals`.

Note

Typically, end users will not use the `.DefaultCohortSizeRange()` function.

Examples

```
# Example for the rule having cohort of size 1 for doses <30
# and having cohort of size 3 for doses >=30.

my_size <- CohortSizeRange(intervals = c(0, 30), cohort_size = c(1, 3))
```

ComboSimulations-class
ComboSimulations

Description

[Experimental]

This class captures trial simulations from two-drug combination designs (DesignCombo).

It is intentionally separate from Simulations because DataCombo is not a subclass of Data, and final recommendations are dose combinations.

Usage

```
ComboSimulations(
  data,
  doses,
  fit,
  stop_reasons,
  stop_report,
  additional_stats,
  seed
)

.DefaultComboSimulations()
```

Arguments

data	(list) see slot definition.
doses	(matrix) see slot definition.
fit	(list) see slot definition.
stop_reasons	(list) see slot definition.
stop_report	(matrix) see slot definition.
additional_stats	(list) see slot definition.
seed	(integer) see slot definition.

Slots

data (list) produced DataCombo objects.

doses (matrix) final recommended dose combinations; one row per simulation run and two columns (one per drug).

fit (list) final fitted toxicity surfaces for each simulation run.

stop_reasons (list) stopping reasons for each simulation run.

stop_report (matrix) matrix of stopping rule outcomes.

additional_stats (list) list of additional statistical summary values.

seed (integer) random generator state before starting the simulation.

Note

Typically, end users will not use the `.DefaultComboSimulations()` function.

`ComboSimulationsSummary-class` `ComboSimulationsSummary`

Description

[Experimental]

This class captures summary output from `ComboSimulations` objects.

Usage

```
.DefaultComboSimulationsSummary()
```

Slots

`target` (`numeric`) target toxicity interval. Empty if no truth function was supplied.

`nsim` (`integer`) number of simulations.

`n_obs` (`integer`) number of patients in each simulation.

`prop_dlts` (`numeric`) observed proportion of DLTs in each simulation.

`mean_tox_risk` (`numeric`) average fitted toxicity risk in each simulation.

`dose_selected` (`matrix`) selected dose combinations; one row per simulation.

`tox_at_doses_selected` (`numeric`) true toxicity at selected dose combinations (if truth supplied).

`prop_at_target` (`numeric`) proportion of selected combinations within target interval (if truth supplied).

`dose_most_selected` (`numeric`) most frequently selected dose combination.

`obs_tox_rate_at_dose_most_selected` (`numeric`) observed toxicity rate at the most frequently selected combination.

`dose_grid` (`list`) dose grid for each drug.

`stop_report` (`matrix`) matrix of stopping rule outcomes.

`stop_reasons` (`list`) stopping reasons by simulation.

`additional_stats` (`list`) additional statistics.

Note

Typically, end users will not use the `.DefaultComboSimulationsSummary()` function.

crmPack *Object-oriented implementation of CRM designs*

Description

Object-oriented implementation of CRM designs

Author(s)

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References

Sabanés Bové D, Yeung WY, Palermo G, Jaki T (2019). "Model-Based Dose Escalation Designs in R with crmPack." *Journal of Statistical Software*, **89**(10), 1–22. doi:10.18637/jss.v089.i10.

See Also

Useful links:

- https://docs.crmpack.org/
- Report bugs at https://github.com/openpharma/crmPack/issues

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`CrmPackClass-class` `CrmPackClass`

Description

[Experimental]

`CrmPackClass` is a virtual class, from which all other `crmPack` classes inherit.

`crmPackExample` *Open the Example PDF for crmPack*

Description

[Stable]

Calling this helper function opens the `example.pdf` document, residing in the `doc` subfolder of the package installation directory.

Usage

```
crmPackExample()
```

Value

Called for side effects.

`crmPackHelp` *Open the Browser with Help Pages for crmPack*

Description

[Stable]

This convenience function opens your browser with the help pages for crmPack.

Usage

```
crmPackHelp()
```

Value

Called for side effects.

DADesign-class DADesign

Description

[Stable]

This class has special requirements for the `model` and `data` slots in comparison to the parent class `Design`:

Usage

```
DADesign(model, data, safetyWindow, ...)

.DefaultDADesign()
```

Arguments

`model`	(`GeneralModel`) see slot definition.
`data`	(`DataDA`) see slot definition.
`safetyWindow`	(`SafetyWindow`) see slot definition.
`...`	Arguments passed on to `Design` `stopping` (`Stopping`) see slot definition. `increments` (`Increments`) see slot definition. `pl_cohort_size` (`CohortSize`) see slot definition. `backfill` (`Backfill`) see slot definition.

Details

The `safetyWindow` slot should be an instance of the `SafetyWindow` class. It can be customized to specify the duration of the safety window for your trial. The safety window represents the time period required to observe toxicity data from the ongoing cohort before opening the next cohort. Note that even after opening the next cohort, further toxicity data will be collected and analyzed to make dose escalation decisions.

To specify a constant safety window, use the `SafetyWindowConst` constructor. For example:

```
mysafetywindow <- SafetyWindowConst(c(6, 2), 10, 20)
```

Slots

`model (GeneralModel)`
: the model to use, see in particular DALogisticLogNormal, TITELogisticLogNormal and TITELogisticLogNormalSub which make use of the time-to-DLT data.

`data (DataDA)`
: what is the dose grid, any previous data, etc.

`safetyWindow (SafetyWindow)`
: the safety window to apply between cohorts.

Note

Typically, end users will not use the `.DefaultDADesign()` function.

See Also

`SafetyWindowConst` for creating a constant safety window.

Examples

```
empty_data <- DataDA(
  doseGrid = c(
    0.1,
    0.5,
    1,
    1.5,
    3,
    6,
    seq(from = 10, to = 80, by = 2)
  ),
  Tmax = 60
)

npiece <- 10
t_max <- 60

lambda_prior <- function(k) {
  npiece / (t_max * (npiece - k + 0.5))
}

model <- DALogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56,
  npiece = npiece,
  l = as.numeric(t(apply(as.matrix(c(1:npiece), 1, npiece), 2, lambda_prior))),
  c_par = 2
)

my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
```

```
)

my_next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

my_size1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)

my_size2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)

my_size <- maxSize(my_size1, my_size2)

my_stopping1 <- StoppingTargetProb(
  target = c(0.2, 0.35),
  prob = 0.5
)

my_stopping2 <- StoppingMinPatients(nPatients = 50)

my_stopping <- (my_stopping1 | my_stopping2) | StoppingMissingDose()

my_safety_window <- SafetyWindowConst(c(6, 2), 7, 7)

design <- DADesign(
  model = model,
  increments = my_increments,
  nextBest = my_next_best,
  stopping = my_stopping,
  cohort_size = my_size,
  data = empty_data,
  safetyWindow = my_safety_window,
  startingDose = 3
)
```

DALogisticLogNormal-class *DALogisticLogNormal*

Description

[Stable]

DALogisticLogNormal is the class for the logistic model with bivariate (log) normal prior and data augmentation. This class inherits from the LogisticLogNormal class.

Usage

```
DALogisticLogNormal(npiece = 3, l, c_par = 2, cond_pem = TRUE, ...)

.DefaultDALogisticLogNormal()
```

Arguments

npiece	(number) the number of pieces in the PEM.
l	(numeric) a vector used in the lambda prior.
c_par	(numeric) a parameter used in the lambda prior; according to Liu's paper, c_par = 2 is recommended.
cond_pem	(flag) is a conditional piecewise-exponential model used? (default). Otherwise an unconditional model is used.
...	Arguments passed on to LogisticLogNormal mean (numeric) the prior mean vector. cov (matrix) the prior covariance matrix. The precision matrix prec is internally calculated as an inverse of cov. ref_dose (number) the reference dose $x*$ (strictly positive number).

Slots

npiece (number)
: the number of pieces in the PEM.

l (numeric)
: a vector used in the lambda prior.

c_par (numeric)
: a parameter used in the lambda prior; according to Liu's paper, c_par = 2 is recommended.

cond_pem (flag)
: is a conditional piecewise-exponential model used? (default). Otherwise an unconditional model is used.

Note

We still need to include here formula for the lambda prior.

Typically, end users will not use the .DefaultDALogisticLogNormal() function.

See Also

ModelLogNormal, LogisticNormal, LogisticLogNormal.

Examples

```
npiece <- 10
Tmax <- 60 # nolintr

lambda_prior <- function(k) {
  npiece / (Tmax * (npiece - k + 0.5))
}

model <- DALogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56,
  npiece = npiece,
  l = as.numeric(t(apply(as.matrix(c(1:npiece), 1, npiece), 2, lambda_prior))),
  c_par = 2
)
```

---

dapply *Apply a Function to Subsets of Data Frame.*

Description

[Experimental]

`dapply` splits the data `df` into the subsets defined by `f`, and applies function `FUN` to each of the subset. All the results are row-binded and returned as `data.frame` object.

Usage

```
dapply(df, f, FUN, ...)
```

Arguments

`df`	(`data frame`) data set to be divided into groups.
`f`	(`factor` or `formula` or `list`) a factor in the sense that `as.factor(f)` defines the grouping, or a `list` of such factors in which case their interaction is used for the grouping. `f` can also be a formula of the form `~ g1 + ... + gk` to split by the interaction of the variables `g1, ..., gk`. This parameter is passed directly into `split()` function.
`FUN`	(`function`) the function to be applied to each subset of `df` defined by `f`.
`...`	parameters passed to `lapply()`, which is used when applying a function `FUN` over groups defined by `f`.

Value

The `data.frame` object with results from `FUN`.

Examples

```
df <- data.frame(
  dose = c(0.1, 6, 6, 5, 0.1, 5, 6, 6),
  cohort = c("B", "B", "B", "A", "A", "A", "B", "B")
)

dapply(
  df,
  f = ~cohort,
  FUN = function(coh) {
    data.frame(my_cohort = coh$cohort[1], my_max = max(coh$dose))
  }
)

dapply(
  df,
  f = ~cohort,
  FUN = function(coh) {
    coh$dose <- sort(coh$dose, decreasing = TRUE)
    coh
  }
)
```

`DASimulations-class` `DASimulations`

Description

[Stable]

This class captures the trial simulations from DA based designs. In comparison to the parent class `Simulations`, it contains additional slots to capture the time to DLT fits, additional parameters and the trial duration.

Usage

```
DASimulations(trial_duration, ...)

.DefaultDASimulations()
```

Arguments

`trial_duration`	(numeric) see `DASimulations`
`...`	additional parameters from `Simulations`

Slots

`trial_duration` (numeric)
: the vector of trial duration values for all simulations.

Note

Typically, end users will not use the `.DefaultDASimulations()` function.

`Data-class` `Data`

Description

[Stable]

`Data` is a class for the data input. It inherits from `GeneralData`.

Usage

```
Data(
  x = numeric(),
  y = integer(),
  ID = integer(),
  cohort = integer(),
  doseGrid = numeric(),
  placebo = FALSE,
  backfilled = rep(FALSE, length(x)),
  response = rep(NA_integer_, length(x)),
  ...
)

.DefaultData()
```

Arguments

`x`	(`numeric`) the doses for the patients.
`y`	(`integer`) the vector of toxicity events (0 or 1). You can also supply `numeric` vectors, but these will then be converted to `integer` internally.
`ID`	(`integer`) unique patient IDs. You can also supply `numeric` vectors, but these will then be converted to `integer` internally.
`cohort`	(`integer`) the cohort (non-negative sorted) indices. You can also supply `numeric` vectors, but these will then be converted to `integer` internally.
`doseGrid`	(`numeric`) all possible doses.
`placebo`	(`flag`) if `TRUE` the first dose level in the `doseGrid` is considered as placebo.

backfilled	(logical) whether each patient was in a backfill cohort.
response	(integer) whether each patient had a positive efficacy response (1 = yes, 0 = no). May contain NA.
...	not used.

Details

The cohort can be missing if and only if placebo is equal to FALSE.

Slots

x (numeric)
: the doses for the patients.

y (integer)
: the vector of toxicity events (0 or 1 integers).

doseGrid (numeric)
: the vector of all possible doses (sorted), i.e. the dose grid.

nGrid (integer)
: number of gridpoints.

xLevel (integer)
: the levels for the doses the patients have been given, w.r.t doseGrid.

placebo (logical)
: if TRUE the first dose level in the doseGridis considered as PLACEBO.

backfilled (logical)
: whether this patient was in a backfill cohort.

response (integer)
: whether this patient had a positive efficacy response (0 or 1 integers).

Note

ID and cohort can be missing. Then a message will be issued and the variables will be filled with default IDs and best guesses cohort, i.e. a sorted (in ascending order) sequence of values from {1, 2, ...}.

Typically, end users will not use the .DefaultData() function.

Examples

```
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  ID = as.integer(1:8),
  cohort = as.integer(c(1, 2, 3, 4, 5, 6, 6, 6)),
  doseGrid = c(
    0.1,
    0.5,
```

```
    1.5,
    3,
    6,
    seq(from = 10, to = 80, by = 2)
  )
)
my_data
```

DataCombo-class DataCombo

Description

[Experimental]

DataCombo is a class for two-drug combination toxicity data. It inherits from GeneralData and stores patient-level dose combinations.

Usage

```
DataCombo(
  x = matrix(numeric(), ncol = 2L),
  y = integer(),
  ID = integer(),
  cohort = integer(),
  doseGrid = list(drug1 = numeric(), drug2 = numeric()),
  drugNames = names(doseGrid),
  backfilled = rep(FALSE, nrow(x)),
  response = rep(NA_integer_, nrow(x)),
  ...
)

.DefaultDataCombo()
```

Arguments

x	(matrix) numeric matrix with 2 columns giving the doses of the two drugs.
y	(integer) the vector of toxicity events (0 or 1).
ID	(integer) unique patient IDs.
cohort	(integer) the cohort (non-negative sorted) indices.
doseGrid	(list) named list of length 2 with all possible doses for each drug.
drugNames	(character) names of the two drugs.
backfilled	(logical) whether each patient was in a backfill cohort.
response	(integer) whether each patient had a positive efficacy response (1 = yes, 0 = no). May contain NA.
...	not used.

Slots

x (matrix) numeric matrix with 2 columns giving the doses of the two drugs.

y (integer) the vector of toxicity events (0 or 1 integers).

doseGrid (list) named list of length 2 with the possible doses for each drug.

nGrid (integer) number of grid points for each drug.

xLevel (matrix) integer matrix with 2 columns giving the dose levels of x with respect to doseGrid.

drugNames (character) names of the two drugs.

backfilled (logical) whether this patient was in a backfill cohort.

response (integer) whether this patient had a positive efficacy response (0/1/NA).

Note

ID and cohort can be missing. Then a message will be issued and the variables will be filled with default IDs and best guess cohort indices.

Typically, end users will not use the .DefaultDataCombo() function.

Examples

```
## Example for DataCombo ----

DataCombo(
  x = cbind(
    drug1 = c(10, 10, 10, 20, 20, 20),
    drug2 = c(20, 20, 20, 20, 20, 20)
  ),
  y = c(0L, 0L, 1L, 0L, 0L, 0L),
  ID = 1L:6L,
  cohort = c(1L, 1L, 1L, 2L, 2L, 2L),
  doseGrid = list(
    drug1 = c(10, 20, 30),
    drug2 = c(20, 40)
  )
)
```

DataDA-class DataDA

Description

[Stable]

DataDA is a class for the time-to-DLT augmented data. It inherits from Data and it contains additional DLT free survival times.

Usage

```
DataDA(
  u = numeric(),
  t0 = numeric(length(u)),
  Tmax = 0 + .Machine$double.xmin,
  ...
)

.DefaultDataDA()
```

Arguments

u	(numeric) the continuous vector of DLT free survival times.
t0	(numeric) time of initial dosing for each patient. Non-negative values sorted in ascending order. Default to vector of 0s of length equal to length of u.
Tmax	(number) the DLT observation period.
...	parameters passed to Data().

Slots

u (numeric)
: the continuous vector of DLT free survival times.

t0 (numeric)
: time of initial dosing for each patient. Non-negative values sorted in ascending order.

Tmax (number)
: the DLT observation period.

Note

survival time here refers to the time period for which the subject did not experience any DLT, and is not referring to deaths.

Typically, end users will not use the .DefaultDataDA() function.

Examples

```
my_data <- DataDA(
  u = c(42, 30, 15, 5, 20, 25, 30, 60),
  t0 = c(0, 15, 30, 40, 55, 70, 75, 85),
  Tmax = 60,
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 1, 1, 0, 0, 1, 0),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Set up an empty data set.
```

```
empty_data <- DataDA(
  doseGrid = c(0.1, 0.5, 1, 1.5, 3, 6, seq(from = 10, to = 80, by = 2)),
  Tmax = 60
)
empty_data
```

DataDual-class DataDual

Description

[Stable]

DataDual is a class for the dual endpoint data. It inherits from Data and it contains additional biomarker information.

Usage

```
DataDual(w = numeric(), ...)

.DefaultDataDual()
```

Arguments

w	(numeric) the continuous vector of biomarker values.
...	parameters passed to Data().

Slots

w (numeric)
: the continuous vector of biomarker values.

Note

Typically, end users will not use the .DefaultDataDual() function.

Examples

```
my_data <- DataDual(
  w = rnorm(8),
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  doseGrid = c(
    0.1,
    0.5,
    1.5,
    3,
    6,
    seq(from = 10, to = 80, by = 2)
```

```
  )
)
my_data
```

DataGrouped-class DataGrouped

Description

[Stable]

DataGrouped is a class for a two groups dose escalation data set, comprised of a monotherapy (mono) and a combination therapy (combo) arm. It inherits from Data and it contains the additional group information.

Usage

```
DataGrouped(group = character(), ...)

.DefaultDataGrouped()
```

Arguments

group	(factor or character) whether mono or combo was used. If character then will be coerced to factor with the correct levels internally.
...	parameters passed to Data().

Slots

group (factor)
: whether mono or combo was used.

Note

Typically, end users will not use the .DefaultDataGrouped() function.

Examples

```
my_data <- DataGrouped(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 1, 1, 0, 0, 1, 0),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2)),
  group = c("mono", "mono", "mono", "mono", "mono", "mono", "combo", "combo")
)

# Set up an empty data set.
empty_data <- DataGrouped(
  doseGrid = c(0.1, 0.5, 1, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)
empty_data
```

DataMixture-class DataMixture

Description

[Stable]

DataMixture is a class for the data with mixture sharing. It inherits from Data and it contains additional information on the mixture sharing.

Usage

```
DataMixture(xshare = numeric(), yshare = integer(), ...)

.DefaultDataMixture()
```

Arguments

xshare	(numeric) the doses for the share patients.
yshare	(integer) the vector of toxicity events (0 or 1) for the share patients. You can also supply numeric vectors, but these will then be converted to integer internally.
...	parameters passed to Data().

Slots

xshare (numeric)
: the doses for the share patients.

yshare (integer)
: the vector of toxicity events (0 or 1) for the share patients.

nObsshare (count)
: number of share patients.

Note

Typically, end users will not use the .DefaultDataMixture() function.

Examples

```
my_data <- DataMixture(
  xshare = c(12, 14, 16, 18.0),
  yshare = c(0L, 1L, 1L, 1L),
  nObsshare = 4L,
  x = c(0.1, 0.5, 1.5),
  y = c(0, 0, 0),
  ID = 1:3,
  cohort = 1:3,
```

```
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)
my_data
```

DataOrdinal-class DataOrdinal

Description

[Experimental]

DataOrdinal is a class for ordinal toxicity data. It inherits from GeneralData and it describes toxicity responses on an ordinal rather than binary scale.

Usage

```
DataOrdinal(
  x = numeric(),
  y = integer(),
  ID = integer(),
  cohort = integer(),
  doseGrid = numeric(),
  placebo = FALSE,
  yCategories = c(`No DLT` = 0L, DLT = 1L),
  ...
)

.DefaultDataOrdinal()
```

Arguments

x	(numeric) the doses for the patients.
y	(integer) the vector of toxicity events (0 or 1). You can also supply numeric vectors, but these will then be converted to integer internally.
ID	(integer) unique patient IDs. You can also supply numeric vectors, but these will then be converted to integer internally.
cohort	(integer) the cohort (non-negative sorted) indices. You can also supply numeric vectors, but these will then be converted to integer internally.
doseGrid	(numeric) all possible doses.
placebo	(flag) if TRUE the first dose level in the doseGrid is considered as placebo.

yCategories	(named integer) the names and codes for the toxicity categories used in the data. Category labels are taken from the names of the vector. The names of the vector must be unique and its values must be sorted and take the values 0, 1, 2, ...
...	not used.

Details

The cohort can be missing if and only if placebo is equal to FALSE.

Note

This class has been implemented as a sibling of the existing Data class (rather than as a parent or child) to minimise the risk of unintended side effects on existing classes and methods.

The default setting for the yCategories slot replicates the behaviour of the existing Data class.

Typically, end users will not use the .DefaultDataOrdinal() function.

Examples

```
DataOrdinal(
  x = c(10, 20, 30, 40, 50, 50, 50, 60, 60, 60),
  y = as.integer(c(0, 0, 0, 0, 0, 1, 0, 0, 1, 2)),
  ID = 1L:10L,
  cohort = as.integer(c(1:4, 5, 5, 5, 6, 6, 6)),
  doseGrid = c(seq(from = 10, to = 100, by = 10)),
  yCategories = c("No tox" = 0L, "Sub-tox AE" = 1L, "DLT" = 2L),
  placebo = FALSE
)
```

DataParts-class DataParts

Description

[Stable]

DataParts is a class for the data with two study parts. It inherits from Data and it contains additional information on the two study parts.

Usage

```
DataParts(part = integer(), nextPart = 1L, part1Ladder = numeric(), ...)

.DefaultDataParts()
```

Arguments

part	(integer) which part does each of the patients belong to?
nextPart	(count) what is the part for the next cohort (1 or 2)?
part1Ladder	(numeric) what is the escalation ladder for part 1? This shall be an ordered subset of the doseGrid.
...	parameters passed to Data().

Slots

part (integer)
: which part does each of the patients belong to?

nextPart (count)
: what is the part for the next cohort (1 or 2)?

part1Ladder (numeric)
: what is the escalation ladder for part 1? This shall be an ordered subset of the doseGrid.

Note

Typically, end users will not use the .DefaultDataParts() function.

Examples

```
my_data <- DataParts(
  x = c(0.1, 0.5, 1.5),
  y = c(0, 0, 0),
  ID = 1:3,
  cohort = 1:3,
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2)),
  part = c(1L, 1L, 1L),
  nextPart = 1L,
  part1Ladder = c(0.1, 0.5, 1.5, 3, 6, 10)
)
my_data
```

Design-class Design

Description

[Stable]

Design is the class for rule-based designs. The difference between this class and its parent RuleDesign class is that Design class contains additional model, stopping and increments slots.

Usage

```
Design(
  model,
  stopping,
  increments,
  pl_cohort_size = CohortSizeConst(0L),
  backfill = Backfill(opening = OpeningNone()),
  ...
)

.DefaultDesign()
```

Arguments

`model`	(`GeneralModel`) see slot definition.
`stopping`	(`Stopping`) see slot definition.
`increments`	(`Increments`) see slot definition.
`pl_cohort_size`	(`CohortSize`) see slot definition.
`backfill`	(`Backfill`) see slot definition.
`...`	Arguments passed on to `RuleDesign` `nextBest` (`NextBest`) see slot definition. `cohort_size` (`CohortSize`) see slot definition. `data` (`Data`) see slot definition. `startingDose` (`number`) see slot definition. `doseGrid` (`numeric`) the dose grid to be used (sorted).

Slots

`model` (`GeneralModel`)
: the model to be used.

`stopping` (`Stopping`)
: stopping rule(s) for the trial.

`increments` (`Increments`)
: how to control increments between dose levels.

`pl_cohort_size` (`CohortSize`)
: rules for the cohort sizes for placebo, if any planned (defaults to constant 0 placebo patients).

`backfill` (`Backfill`)
: rules for backfilling patients in the trial (defaults to no backfilling).

Note

Typically, end users will not use the `.DefaultDesign()` function.

Examples

```
empty_data <- Data(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))

# Initialize the CRM model.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Choose the rule for selecting the next dose.
my_next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size.
my_size1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
my_size2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
my_size <- maxSize(my_size1, my_size2)

# Choose the rule for stopping.
my_stopping1 <- StoppingMinCohorts(nCohorts = 3)
my_stopping2 <- StoppingTargetProb(
  target = c(0.2, 0.35),
  prob = 0.5
)
my_stopping3 <- StoppingMinPatients(nPatients = 20)
my_stopping <- (my_stopping1 & my_stopping2) |
  my_stopping3 |
  StoppingMissingDose()

# Choose the rule for dose increments.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
```

```
  increments = c(1, 0.33)
)

# Initialize the design.
design <- Design(
  model = my_model,
  nextBest = my_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  data = empty_data,
  startingDose = 3
)
```

DesignArm-class DesignArm

Description

[Experimental]

DesignArm is a light-weight wrapper around Design object for use in a HierarchicalDesign. Use DesignArm() for active arms and HistoricalArm() for non-enrolling historical arms.

Usage

```
DesignArm(name, design, borrow = TRUE, open_when = NoArmCondition())

HistoricalArm(name, data, model, borrow = TRUE)

.DefaultDesignArm()
```

Arguments

name	(string) see slot definition.
design	(Design) see slot definition.
borrow	(flag) see slot definition.
open_when	(ArmCondition) see slot definition.
data	(Data or DataCombo) arm data for historical arms.
model	(GeneralModel or TwoDrugsCombo) arm model for historical arms.

Slots

`name` (`string`)
: the name of the arm.

`active` (`flag`)
: whether the arm is enrolling or not (historical).

`borrow` (`flag`)
: whether this arm may borrow information from other arms when making dose escalation decisions. Only relevant if `active` = `TRUE`.

`open_when` (`ArmCondition`)
: the condition that must be satisfied before this arm opens for enrollment.

`design` (`Design`)
: the design object for this arm.

Note

Typically, end users will not use the `.DefaultDesignArm()` function.

Examples

```
design <- .DefaultDesign()
design_arm <- DesignArm(
  name = "Arm A",
  design = design
)
```

`DesignCombo-class` `DesignCombo`

Description

[Experimental]

`DesignCombo` is the class for two-drug combination dose-escalation designs.

Usage

```
DesignCombo(
  model,
  nextBest,
  stopping,
  increments,
  cohort_size,
  data,
  startingDose,
  backfill = Backfill(opening = OpeningNone())
)

.DefaultDesignCombo()
```

Arguments

model	(TwoDrugsCombo) see slot definition.
nextBest	(NextBestNCRM) see slot definition.
stopping	(Stopping) see slot definition.
increments	(Increments) see slot definition.
cohort_size	(CohortSize) see slot definition.
data	(DataCombo) see slot definition.
startingDose	(numeric) see slot definition.
backfill	(Backfill) see slot definition.

Details

This class stores the same core design components as Design, but uses DataCombo and TwoDrugsCombo to represent two-drug combinations.

Slots

model (TwoDrugsCombo) the model to be used.

nextBest (NextBestNCRM) the rule to select the next dose combination.

stopping (Stopping) stopping rule(s) for the trial.

increments (Increments) how to control increments between dose combinations.

cohort_size (CohortSize) rules for the cohort sizes.

data (DataCombo) specifies dose grids and any previously observed data.

startingDose (numeric) starting dose combination as a numeric vector of length 2.

backfill (Backfill) rules for backfilling patients in the trial.

Note

Typically, end users will not use the .DefaultDesignCombo() function.

Examples

```
empty_data <- DataCombo(
  doseGrid = list(
    drug1 = c(10, 20, 30),
    drug2 = c(20, 40, 60)
  )
)

my_model <- TwoDrugsCombo(
  single_models = list(
    drug1 = LogisticLogNormal(
      mean = c(-0.85, 1),
      cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
      ref_dose = 10
    ),
```

```
    drug2 = LogisticLogNormal(
      mean = c(-0.7, 0.8),
      cov = matrix(c(1.1, -0.3, -0.3, 0.9), nrow = 2),
      ref_dose = 20
    )
  ),
  gamma = 0,
  tau = 1
)

my_next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

my_increments <- IncrementsMin(
  increments_list = list(
    IncrementsComboOneDrugOnly(),
    IncrementsComboCartesian(
      drug1 = IncrementsRelative(intervals = c(0), increments = c(1)),
      drug2 = IncrementsRelative(intervals = c(0), increments = c(1))
    )
  )
)

my_stopping <- StoppingMinPatients(nPatients = 20)

design_combo <- DesignCombo(
  model = my_model,
  nextBest = my_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = CohortSizeConst(3L),
  data = empty_data,
  startingDose = c(drug1 = 10, drug2 = 20)
)
```

`DesignGrouped-class` `DesignGrouped`

Description

[Experimental]

`DesignGrouped` combines two `Design` objects: one for the mono and one for the combo arm of a joint dose escalation design.

Usage

```
DesignGrouped(
```

```
  model,
  mono,
  combo = mono,
  first_cohort_mono_only = TRUE,
  same_dose_for_all = !same_dose_for_start,
  same_dose_for_start = FALSE,
  stop_mono_with_combo = FALSE,
  ...
)
```

Arguments

model	(LogisticLogNormalGrouped) see slot definition.
mono	(Design) see slot definition.
combo	(Design) see slot definition.
first_cohort_mono_only	(flag) see slot definition.
same_dose_for_all	(flag) see slot definition.
same_dose_for_start	(flag) see slot definition.
stop_mono_with_combo	(flag) whether the mono arm should be stopped when the combo arm is stopped (this makes sense when the only real trial objective is the recommended combo dose).
...	not used.

Details

- Note that the model slots inside the mono and combo parameters are ignored (because we don't fit separate regression models for the mono and combo arms). Instead, the model parameter is used to fit a joint regression model for the mono and combo arms together.
- same_dose_for_start = TRUE is useful as an option when we want to use same_dose_for_all = FALSE combined with first_cohort_mono_only = TRUE. This will allow to randomize patients to the mono and combo arms at the same dose as long as the selected dose for the cohorts stay the same. This can therefore further mitigate bias as long as possible between the mono and combo arms.

Slots

model (LogisticLogNormalGrouped)
: the model to be used, currently only one class is allowed.

`mono` (`Design`)
: defines the dose escalation rules for the mono arm, see details.

`combo` (`Design`)
: defines the dose escalation rules for the combo arm, see details.

`first_cohort_mono_only` (`flag`)
: whether first test one mono agent cohort, and then once its DLT data has been collected, we proceed from the second cohort onwards with concurrent mono and combo cohorts.

`same_dose_for_all` (`flag`)
: whether the lower dose of the separately determined mono and combo doses should be used as the next dose for both mono and combo in all cohorts.

`same_dose_for_start` (`flag`)
: indicates whether, when mono and combo are used in the same cohort for the first time, the same dose should be used for both. Note that this is different from `same_dose_for_all` which will always force them to be the same. If `same_dose_for_all = TRUE`, this is therefore ignored. See Details.

Note

Typically, end-users will not use the `.DefaultDesignGrouped()` function.

Examples

```
empty_data <- Data(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))

# Initialize the joint model.
my_model <- LogisticLogNormalGrouped(
  mean = c(-0.85, 0, 1, 0),
  cov = diag(1, 4),
  ref_dose = 56
)

# Choose the rule for selecting the next dose.
my_next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size.
my_size1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
my_size2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
my_size <- maxSize(my_size1, my_size2)

# Choose the rule for stopping.
```

```
my_stopping1 <- StoppingMinCohorts(nCohorts = 3)
my_stopping2 <- StoppingTargetProb(
  target = c(0.2, 0.35),
  prob = 0.5
)
my_stopping3 <- StoppingMinPatients(nPatients = 20)
my_stopping <- (my_stopping1 & my_stopping2) |
  my_stopping3 |
  StoppingMissingDose()

# Choose the rule for dose increments.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Rules to be used for both arms.
one_arm <- Design(
  model = .DefaultModelLogNormal(), # Ignored.
  nextBest = my_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  data = empty_data,
  startingDose = 3
)

# Initialize the design.
design <- DesignGrouped(
  model = my_model,
  mono = one_arm
)

# Alternative options: Here e.g.
# - use both mono in first cohort and afterwards have mono and combo in parallel,
# - in general allow different dose levels for the cohorts,
# - but for the start (i.e. second cohort) have the same dose for mono and combo.
# - Stop mono arm too, when combo arm is stopped.

design2 <- DesignGrouped(
  model = my_model,
  mono = one_arm,
  first_cohort_mono_only = TRUE,
  same_dose_for_all = FALSE,
  same_dose_for_start = TRUE,
  stop_mono_with_combo = TRUE
)
```

DesignOrdinal-class DesignOrdinal

Description

[Experimental]

DesignOrdinal is the class for rule-based ordinal designs. The difference between this class and its parent RuleDesignOrdinal class is that the DesignOrdinal class contains additional model, stopping, increments and pl_cohort_size slots.

Usage

```
DesignOrdinal(
  model,
  stopping,
  increments,
  pl_cohort_size = CohortSizeOrdinal(1L, CohortSizeConst(0L)),
  ...
)

.DefaultDesignOrdinal()
```

Arguments

model	(LogisticLogNormalOrdinal) see slot definition.
stopping	(Stopping) see slot definition.
increments	(Increments) see slot definition.
pl_cohort_size	(CohortSize) see slot definition.
...	Arguments passed on to RuleDesignOrdinal next_best (NextBestOrdinal) see slot definition. cohort_size (CohortSize) see slot definition. data (DataOrdinal) see slot definition. starting_dose (number) see slot definition.

Details

Please note that stopping, increments or cohort size rules need to be wrapped into the corresponding StoppingOrdinal, IncrementsOrdinal or CohortSizeOrdinal classes, before a successful evaluation of the corresponding methods can take place. Note also that these wrappers cannot be nested, i.e., you cannot have an IncrementsOrdinal inside another IncrementsOrdinal (which also would not make sense) because it would not be clear which event grade to use for the methods calculation. However, multiple rules can be combined using the operators defined for these classes, e.g., StoppingOrdinal(1L, rule1 & rule2) | StoppingOrdinal(2L, rule3).

Slots

`model` (`LogisticLogNormalOrdinal`)
: the model to be used.

`stopping` (`Stopping`)
: stopping rule(s) for the trial.

`increments` (`Increments`)
: how to control increments between dose levels.

`pl_cohort_size` (`CohortSize`)
: rules for the cohort sizes for placebo, if any planned (defaults to constant 0 placebo patients).

Note

Typically, end users will not use the `.DefaultDesignOrdinal()` function.

Examples

```
my_size1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
my_size2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
my_size <- CohortSizeOrdinal(1L, maxSize(my_size1, my_size2))

my_stopping1 <- StoppingMinCohorts(nCohorts = 3)
my_stopping2 <- StoppingTargetProb(
  target = c(0.2, 0.35),
  prob = 0.5
)
my_stopping3 <- StoppingMinPatients(nPatients = 20)
my_stopping <- StoppingOrdinal(
  1L,
  (my_stopping1 & my_stopping2) | my_stopping3 | StoppingMissingDose()
)

# Initialize the design.
design <- DesignOrdinal(
  model = LogisticLogNormalOrdinal(
    mean = c(-3, -4, 1),
    cov = diag(c(3, 4, 1)),
    ref_dose = 50
  ),
  next_best = NextBestOrdinal(
    1L,
    NextBestNCRM(
      target = c(0.2, 0.35),
      overdose = c(0.35, 1),
      max_overdose_prob = 0.25
```

```
    )
  ),
  stopping = my_stopping,
  increments = IncrementsOrdinal(
    1L,
    IncrementsRelative(
      intervals = c(0, 20),
      increments = c(1, 0.33)
    )
  ),
  cohort_size = my_size,
  data = DataOrdinal(
    doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100),
    yCategories = c("No tox" = 0L, "Sub-tox AE" = 1L, "DLT" = 2L)
  ),
  starting_dose = 3
)
```

---

dose *Computing the Doses for a given independent variable, Model and Samples*

Description

[Stable]

A function that computes the dose reaching a specific target value of a given variable that dose depends on. The meaning of this variable depends on the type of the model. For instance, for single agent dose escalation model or pseudo DLE (dose-limiting events)/toxicity model, this variable represents the a probability of the occurrence of a DLE. For efficacy models, it represents expected efficacy. The doses are computed based on the samples of the model parameters (samples).

Usage

```
dose(x, model, samples, ...)

## S4 method for signature 'numeric,LogisticNormal,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,LogisticLogNormal,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,LogisticLogNormalOrdinal,Samples'
dose(x, model, samples, grade)

## S4 method for signature 'numeric,LogisticLogNormalSub,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,ProbitLogNormal,Samples'
```

```
dose(x, model, samples)

## S4 method for signature 'numeric,ProbitLogNormalRel,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,LogisticLogNormalGrouped,Samples'
dose(x, model, samples, group)

## S4 method for signature 'numeric,LogisticKadane,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,LogisticKadaneBetaGamma,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,LogisticNormalMixture,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,LogisticNormalFixedMixture,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,LogisticLogNormalMixture,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,DualEndpoint,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,LogisticIndepBeta,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,LogisticIndepBeta,missing'
dose(x, model)

## S4 method for signature 'numeric,Effloglog,missing'
dose(x, model)

## S4 method for signature 'numeric,EffFlexi,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,OneParLogNormalPrior,Samples'
dose(x, model, samples)

## S4 method for signature 'numeric,OneParExpPrior,Samples'
dose(x, model, samples)
```

Arguments

x	(proportion or numeric) a value of an independent variable on which dose depends. The following recycling rule applies when samples is not missing: vectors of size 1 will be

recycled to the size of the sample (i.e. `size(samples)`). Otherwise, `x` must have the same size as the sample.

`model` (`GeneralModel` or `ModelPseudo`)
the model.

`samples` (`Samples`)
the samples of model's parameters that will be used to compute the resulting doses. Can also be missing for some models.

`...` model specific parameters when `samples` are not used.

`grade` (`integer`)
The toxicity grade for which probabilities are required

`group` (`character` or `factor`)
for `LogisticLogNormalGrouped`, indicating whether to calculate the dose for the `mono` or for the `combo` arm.

Details

The `dose()` function computes the doses corresponding to a value of a given independent variable, using samples of the model parameter(s). If you work with multivariate model parameters, then assume that your model specific `dose()` method receives a samples matrix where the rows correspond to the sampling index, i.e. the layout is then `nSamples x dimParameter`.

Value

A `number` or `numeric` vector with the doses. If non-scalar `samples` were used, then every element in the returned vector corresponds to one element of a sample. Hence, in this case, the output vector is of the same length as the sample vector. If scalar `samples` were used or no `samples` were used, e.g. for pseudo DLE/toxicity `model`, then the output is of the same length as the length of the `prob`.

Functions

- `dose(x = numeric, model = LogisticNormal, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).
- `dose(x = numeric, model = LogisticLogNormal, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).
- `dose(x = numeric, model = LogisticLogNormalOrdinal, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).

  In the case of a `LogisticLogNormalOrdinal` model, `dose` returns only the probability of toxicity at the given grade or higher
- `dose(x = numeric, model = LogisticLogNormalSub, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).
- `dose(x = numeric, model = ProbitLogNormal, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).
- `dose(x = numeric, model = ProbitLogNormalRel, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).
- `dose(x = numeric, model = LogisticLogNormalGrouped, samples = Samples)`: method for `LogisticLogNormalGrouped` which needs `group` argument in addition.

- `dose(x = numeric, model = LogisticKadane, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).
- `dose(x = numeric, model = LogisticKadaneBetaGamma, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).
- `dose(x = numeric, model = LogisticNormalMixture, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).
- `dose(x = numeric, model = LogisticNormalFixedMixture, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).
- `dose(x = numeric, model = LogisticLogNormalMixture, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).
- `dose(x = numeric, model = DualEndpoint, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).
- `dose(x = numeric, model = LogisticIndepBeta, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`).
- `dose(x = numeric, model = LogisticIndepBeta, samples = missing)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`). All model parameters (except `x`) should be present in the `model` object.
- `dose(x = numeric, model = Effloglog, samples = missing)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`). All model parameters (except `x`) should be present in the `model` object.
- `dose(x = numeric, model = EffFlexi, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLE (`x`). For this method `x` must be a scalar.
- `dose(x = numeric, model = OneParLogNormalPrior, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLT (`x`).
- `dose(x = numeric, model = OneParExpPrior, samples = Samples)`: compute the dose level reaching a specific target probability of the occurrence of a DLT (`x`).

Note

The `dose()` and `prob()` methods are the inverse of each other, for all `dose()` methods for which its first argument, i.e. a given independent variable that dose depends on, represents toxicity probability.

See Also

`doseFunction()`, `prob()`, `efficacy()`.

Examples

```
# Create some data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
```

```
)

# Initialize a model, e.g. 'LogisticLogNormal'.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Get samples from posterior.
my_options <- McmcOptions(burnin = 100, step = 2, samples = 20)
my_samples <- mcmc(data = my_data, model = my_model, options = my_options)

# Posterior for the dose achieving Prob(DLT) = 0.45.
dose(x = 0.45, model = my_model, samples = my_samples)

# Create data from the 'Data' (or 'DataDual') class.
dlt_data <- Data(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  doseGrid = seq(from = 25, to = 300, by = 25)
)

# Initialize a toxicity model using 'LogisticIndepBeta' model.
dlt_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = dlt_data
)

# Get samples from posterior.
dlt_sample <- mcmc(data = dlt_data, model = dlt_model, options = my_options)

# Posterior for the dose achieving Prob(DLT) = 0.45.
dose(x = 0.45, model = dlt_model, samples = dlt_sample)
dose(x = c(0.45, 0.6), model = dlt_model)
data_ordinal <- .DefaultDataOrdinal()
model <- .DefaultLogisticLogNormalOrdinal()
options <- .DefaultMcmcOptions()
samples <- mcmc(data_ordinal, model, options)

dose(0.25, model, samples, grade = 2L)
```

`doseFunction` *Getting the Dose Function for a Given Model Type*

Description

[Experimental]

A function that returns a dose() method that computes the dose reaching a specific target value of a given independent variable, based on the model specific parameters.

Usage

```
doseFunction(model, ...)

## S4 method for signature 'GeneralModel'
doseFunction(model, ...)

## S4 method for signature 'ModelPseudo'
doseFunction(model, ...)

## S4 method for signature 'LogisticLogNormalOrdinal'
doseFunction(model, grade, ...)
```

Arguments

model	(GeneralModel or ModelPseudo) the model.
...	model specific parameters.
grade	(integer) the toxicity grade for which the dose function is required

Value

A dose() method that computes doses.

Functions

- doseFunction(GeneralModel): Return a dose function for a GeneralModel.
- doseFunction(ModelPseudo): Return a dose function for a ModelPseudo.
- doseFunction(LogisticLogNormalOrdinal): Return a grade-specific dose function for a LogisticLogNormalOrdinal model.

See Also

dose(), probFunction().

Examples

```
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 50
)

dose_fun <- doseFunction(my_model, alpha0 = 2, alpha1 = 3)
dose_fun(0.6)
```

```
data_ordinal <- .DefaultDataOrdinal()
model <- .DefaultLogisticLogNormalOrdinal()
options <- .DefaultMcmcOptions()
suppressWarnings({
  samples <- mcmc(data_ordinal, model, options)
})

doseFunction(
  model,
  alpha1 = samples@data$alpha2,
  beta = samples@data$beta,
  grade = 1L
)(x = 0.75)
doseFunction(
  model,
  alpha2 = samples@data$alpha2,
  beta = samples@data$beta,
  grade = 2L
)(x = 0.25)
```

`dose_grid_range` *Getting the Dose Grid Range*

Description

[Stable]

A function that returns a vector of length two with the minimum and maximum dose in a grid. It returns `c(-Inf, Inf)` if the range cannot be determined, which happens when the dose grid is empty. User can choose whether the placebo dose (if any) should be counted or not.

[Experimental]

Usage

```
dose_grid_range(object, ...)

## S4 method for signature 'Data'
dose_grid_range(object, ignore_placebo = TRUE)

## S4 method for signature 'DataOrdinal'
dose_grid_range(object, ignore_placebo = TRUE)
```

Arguments

`object`	(`Data`) object with dose grid.
`...`	further arguments passed to class-specific methods.
`ignore_placebo`	(`flag`) should placebo dose (if any) not be counted?

Value

A numeric vector containing the minimum and maximum of all the doses in a grid or c(-Inf, Inf).

Examples

```
my_data <- Data(
  x = c(10, 50, 90, 100, 0.001, 20, 30, 30),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  ID = 1:8,
  cohort = c(1L, 2L, 3L, 4L, 5L, 5L, 6L, 6L),
  doseGrid = c(0.001, seq(from = 10, to = 100, by = 10)),
  placebo = TRUE
)
dose_grid_range(my_data)
dose_grid_range(my_data, ignore_placebo = FALSE)
data <- DataOrdinal(
  x = c(10, 20, 30, 40, 50, 50, 50, 60, 60, 60),
  y = as.integer(c(0, 0, 0, 0, 0, 1, 0, 0, 1, 2)),
  ID = 1L:10L,
  cohort = as.integer(c(1:4, 5, 5, 5, 6, 6, 6)),
  doseGrid = c(seq(from = 10, to = 100, by = 10)),
  yCategories = c("No tox" = 0L, "Sub-tox AE" = 1L, "DLT" = 2L),
  placebo = FALSE
)

dose_grid_range(data)
```

DualDesign-class DualDesign

Description

[Stable]

DualDesign is the class for the dual-endpoint CRM design. This class has special requirements for the model and data slots in comparison to the parent class Design.

Usage

```
DualDesign(model, data, ...)

.DefaultDualDesign()
```

Arguments

model	(DualEndpoint) see slot definition.

data (DataDual)
: see slot definition.

... Arguments passed on to Design

stopping (Stopping)
: see slot definition.

increments (Increments)
: see slot definition.

pl_cohort_size (CohortSize)
: see slot definition.

backfill (Backfill)
: see slot definition.

Slots

model (DualEndpoint)
: the model to be used.

data (DataDual)
: specifies dose grid, any previous data, etc.

Note

the nextBest slot can be of any class, this allows for easy comparison with recommendation methods that don't use the biomarker information.

Typically, end users will not use the .DefaultDualDesign() function.

Examples

```
empty_data <- DataDual(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))

# Initialize the CRM model.
my_model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2betaW = 0.01,
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  rw1 = TRUE
)

# Choose the rule for selecting the next dose.
my_next_best <- NextBestDualEndpoint(
  target = c(0.9, 1),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size.
my_size1 <- CohortSizeRange(
  intervals = c(0, 30),
```

```
  cohort_size = c(1, 3)
)
my_size2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
my_size <- maxSize(my_size1, my_size2)

# Choose the rule for stopping.
my_stopping1 <- StoppingTargetBiomarker(
  target = c(0.9, 1),
  prob = 0.5
)
my_stopping <- my_stopping1 | StoppingMinPatients(40) | StoppingMissingDose()

# Choose the rule for dose increments.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Initialize the design.
design <- DualDesign(
  model = my_model,
  data = empty_data,
  nextBest = my_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  startingDose = 3
)
```

`DualEndpoint-class` `DualEndpoint`

Description

[Experimental]

`DualEndpoint` is the general class for the dual endpoint model.

Usage

```
DualEndpoint(mean, cov, ref_dose = 1, use_log_dose = FALSE, sigma2W, rho)

.DefaultDualEndpoint()
```

Arguments

`mean`	(`numeric`) for the probit toxicity model, the prior mean vector.

`cov` (`matrix`)
for the probit toxicity model, the prior covariance matrix. The precision matrix is internally calculated as an inverse of `cov`.

`ref_dose` (`number`)
for the probit toxicity model, the reference dose $x*$ (strictly positive number).

`use_log_dose` (`flag`)
for the probit toxicity model, whether a log transformation of the (standardized) dose should be used?

`sigma2W` (`numeric`)
the biomarker variance. Either a fixed value or Inverse-Gamma distribution parameters, i.e. vector with two elements named `a` and `b`.

`rho` (`numeric`)
either a fixed value for the correlation (between `-1` and `1`), or a named vector with two elements named `a` and `b` for the Beta prior on the transformation `kappa = (rho + 1) / 2`, which is in `(0, 1)`. For example, `a = 1, b = 1` leads to a uniform prior on `rho`.

Details

The idea of the dual-endpoint models is to model not only the dose-toxicity relationship, but also to model, at the same time, the relationship of a PD biomarker with the dose. The sub-classes of this class define how the dose-biomarker relationship is parametrized. This class here shall contain all the common features to reduce duplicate code. (This class however, must not be virtual as we need to create objects of it during the construction of subclass objects.)

The dose-toxicity relationship is modeled with probit regression model

$$probit[p(x)] = betaZ1 + betaZ2 * x/x*,$$

or

$$probit[p(x)] = betaZ1 + betaZ2 * log(x/x*),$$

in case when the option `use_log_dose` is `TRUE`. Here, $p(x)$ is the probability of observing a DLT for a given dose x and $x*$ is the reference dose. The prior

$$(betaZ1, log(betaZ2))\ Normal(mean, cov).$$

For the biomarker response w at a dose x, we assume

$$w(x)\ Normal(f(x), sigma2W),$$

where $f(x)$ is a function of the dose x, which is further specified in sub-classes. The biomarker variance $sigma2W$ can be fixed or assigned an Inverse-Gamma prior distribution; see the details below under slot `sigma2W`.

Finally, the two endpoints y (the binary DLT variable) and w (the biomarker) can be correlated, by assuming a correlation of level rho between the underlying continuous latent toxicity variable z and the biomarker w. Again, this correlation can be fixed or assigned a prior distribution from the scaled Beta family; see the details below under slot `rho`.

Please see the example vignette by typing `crmPackExample()` for a full example.

Slots

`betaZ_params` (`ModelParamsNormal`)
: for the probit toxicity model, it contains the prior mean, covariance matrix and precision matrix which is internally calculated as an inverse of the covariance matrix.

`ref_dose` (`positive_number`)
: for the probit toxicity model, the reference dose.

`use_log_dose` (`flag`)
: for the probit toxicity model, whether a log transformation of the (standardized) dose should be used?

`sigma2W` (`numeric`)
: the biomarker variance. Either a fixed value or Inverse-Gamma distribution parameters, i.e. vector with two elements named `a` and `b`.

`rho` (`numeric`)
: either a fixed value for the correlation (between `-1` and `1`), or a named vector with two elements named `a` and `b` for the Beta prior on the transformation `kappa = (rho + 1) / 2`, which is in `(0, 1)`. For example, `a = 1, b = 1` leads to a uniform prior on `rho`.

`use_fixed` (`logical`)
: indicates whether a fixed value for `sigma2W` or `rho` (for each parameter separately) is used or not. This slot is needed for internal purposes and must not be touched by the user.

Note

Typically, end users will not use the `.DefaultDualEndpoint()` function.

See Also

`DualEndpointRW`, `DualEndpointBeta`, `DualEndpointEmax`.

DualEndpointBeta-class

`DualEndpointBeta`

Description

[Experimental]

`DualEndpointBeta` is the class for the dual endpoint model with beta function for dose-biomarker relationship.

Usage

```
DualEndpointBeta(E0, Emax, delta1, mode, ref_dose_beta = 1, ...)

.DefaultDualEndpointBeta()
```

Arguments

E0	(numeric) either a fixed number or the two uniform distribution parameters.
Emax	(numeric) either a fixed number or the two uniform distribution parameters.
delta1	(numeric) either a fixed positive number or the two parameters of the uniform distribution, that can take only positive values.
mode	(numeric) either a fixed positive number or the two parameters of the uniform distribution, that can take only positive values.
ref_dose_beta	(number) the reference dose $x*$ (strictly positive number). Note that this is different from the ref_dose in the inherited DualEndpoint model).
...	parameters passed to DualEndpoint().

Details

This class extends the DualEndpoint class so that the dose-biomarker relationship $f(x)$ is modelled by a parametric, rescaled beta density function:

$$f(x) = E0 + (Emax - E0) * Beta(delta1, delta2) * (x/x*)^{delta1} * (1 - x/x*)^{delta2},$$

where $x*$ is the maximum dose (end of the dose range to be considered), $delta1$ and $delta2$ are the two beta function parameters, and $E0$, $Emax$ are the minimum and maximum levels, respectively. For ease of interpretation, we use the parametrization based on $delta1$ and the mode, where

$$mode = delta1/(delta1 + delta2),$$

so that multiplying this by $x*$ gives the mode on the dose grid.

All parameters can currently be assigned uniform distributions or be fixed in advance. Note that E0 and Emax can have negative values or uniform distributions reaching into negative range, while delta1 and mode must be positive or have uniform distributions in the positive range.

Slots

E0 (numeric)
: either a fixed number or the two uniform distribution parameters.

Emax (numeric)
: either a fixed number or the two uniform distribution parameters.

delta1 (numeric)
: either a fixed positive number or the two parameters of the uniform distribution, that can take only positive values.

mode (numeric)
: either a fixed positive number or the two parameters of the uniform distribution, that can take only positive values.

ref_dose_beta (positive_number)
: the reference dose $x*$ (note that this is different from the ref_dose in the inherited DualEndpoint model).

Note

Typically, end users will not use the `.DefaultDualEndpointBeta()` function.

See Also

DualEndpoint, DualEndpointRW, DualEndpointEmax.

Examples

```
my_model <- DualEndpointBeta(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  ref_dose = 10,
  use_log_dose = TRUE,
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  E0 = c(0, 100),
  Emax = c(0, 500),
  delta1 = c(0, 5),
  mode = c(1, 15),
  ref_dose_beta = 1000
)
```

DualEndpointEmax-class

DualEndpointEmax

Description

[Experimental]

DualEndpointEmax is the class for the dual endpoint model with Emax function for dose-biomarker relationship.

Usage

```
DualEndpointEmax(E0, Emax, ED50, ref_dose_emax = 1, ...)

.DefaultDualEndpointEmax()
```

Arguments

E0	(numeric) either a fixed number or the two uniform distribution parameters.
Emax	(numeric) either a fixed number or the two uniform distribution parameters.
ED50	(numeric) either a fixed number or the two uniform distribution parameters.

`ref_dose_emax` (number)
: the reference dose $x*$ (strictly positive number). Note that this is different from the `ref_dose` in the inherited `DualEndpoint` model).

`...`
: parameters passed to `DualEndpoint()`.

Details

This class extends the `DualEndpoint` class so that the dose-biomarker relationship $f(x)$ is modelled by a parametric `Emax` function:

$$f(x) = E0 + [(Emax - E0) * (x/x*)]/[ED50 + (x/x*)],$$

where $x*$ is a reference dose, $E0$ and $Emax$ are the minimum and maximum levels for the biomarker, and $ED50$ is the dose achieving half of the maximum effect $0.5*Emax$. All parameters can currently be assigned uniform distributions or be fixed.

Slots

`E0` (`numeric`)
: either a fixed number or the two uniform distribution parameters.

`Emax` (`numeric`)
: either a fixed number or the two uniform distribution parameters.

`ED50` (`numeric`)
: either a fixed number or the two uniform distribution parameters.

`ref_dose_emax` (`positive_number`)
: the reference dose $x*$ (note that this is different from the `ref_dose` in the inherited `DualEndpoint` model).

Note

Typically, end users will not use the `.DefaultDualEndpointEmax()` function.

See Also

`DualEndpoint`, `DualEndpointRW`, `DualEndpointBeta`.

Examples

```
my_model <- DualEndpointEmax(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  E0 = c(0, 100),
  Emax = c(0, 500),
  ED50 = c(10, 200),
  ref_dose_emax = 1000
)
```

DualEndpointRW-class DualEndpointRW

Description

[Experimental]

DualEndpointRW is the class for the dual endpoint model with random walk prior for biomarker.

Usage

```
DualEndpointRW(sigma2betaW, rw1 = TRUE, ...)

.DefaultDualEndpointRW()
```

Arguments

sigma2betaW	(numeric) the prior variance factor of the random walk prior for the biomarker model. Either a fixed value or Inverse-Gamma distribution parameters, i.e. vector with two elements named a and b.
rw1	(flag) for specifying the random walk prior on the biomarker level. When TRUE, random walk of first order is used. Otherwise, the random walk of second order is used.
...	parameters passed to DualEndpoint().

Details

This class extends the DualEndpoint class so that the dose-biomarker relationship $f(x)$ is modelled by a non-parametric random walk of first or second order. That means, for the first order random walk we assume

$$betaW_i - betaW_i - 1\ Normal(0, (x_i - x_i - 1) * sigma2betaW),$$

where $betaW_i = f(x_i)$ is the biomarker mean at the i-th dose gridpoint x_i. For the second order random walk, the second-order differences instead of the first-order differences of the biomarker means follow the normal distribution with 0 mean and $2 * (x_i - x_i - 2) * sigma2betaW$ variance.

The variance parameter $sigma2betaW$ is important because it steers the smoothness of the function $f(x)$, i.e.: if it is large, then $f(x)$ will be very wiggly; if it is small, then $f(x)$ will be smooth. This parameter can either be a fixed value or assigned an inverse gamma prior distribution.

Slots

sigma2betaW (numeric)
: the prior variance factor of the random walk prior for the biomarker model. Either a fixed value or Inverse-Gamma distribution parameters, i.e. vector with two elements named a and b.

`rw1` (`flag`)
: for specifying the random walk prior on the biomarker level. When `TRUE`, random walk of first order is used. Otherwise, the random walk of second order is used.

Note

Non-equidistant dose grids can be used now, because the difference $x_i - x_i - 1$ is included in the modelling assumption above. Please note that due to impropriety of the random walk prior distributions, it is not possible to produce MCMC samples with empty data objects (i.e., sample from the prior). This is not a bug, but a theoretical feature of this model.

Typically, end users will not use the `.DefaultDualEndpointRW()` function.

See Also

`DualEndpoint`, `DualEndpointBeta`, `DualEndpointEmax`.

Examples

```
my_model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  sigma2betaW = 0.01,
  rw1 = TRUE
)
```

DualResponsesDesign-class

DualResponsesDesign.R

Description

[Stable]

This is a class of design based on DLE responses using the `LogisticIndepBeta` model without DLE and efficacy samples. It contains all slots from the `RuleDesign` and `TDsamplesDesign` classes.

Usage

```
DualResponsesDesign(eff_model, data, ...)

.DefaultDualResponsesDesign()
```

Arguments

`eff_model`	(`ModelEff`) see slot definition.
`data`	(`DataDual`) see slot definition.
`...`	Arguments passed on to `TDDesign` `model` (`ModelTox`) see slot definition. `stopping` (`Stopping`) see slot definition. `increments` (`Increments`) see slot definition. `pl_cohort_size` (`CohortSize`) see slot definition.

Slots

`data` (`DataDual`)
: the data set.

`eff_model` (`ModelEff`)
: the pseudo efficacy model to be used.

Note

Typically, end users will not use the `.DefaultDualResponsesDesign()` function.

Examples

```
empty_data <- DataDual(doseGrid = seq(25, 300, 25))

tox_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = empty_data
)

eff_model <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = empty_data
)

my_next_best <- NextBestMaxGain(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)
```

```
my_increments <- IncrementsRelative(
  intervals = c(25, 300),
  increments = c(2, 2)
)

my_size <- CohortSizeConst(size = 3)
my_stopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()

design <- DualResponsesDesign(
  nextBest = my_next_best,
  cohort_size = my_size,
  startingDose = 25,
  model = tox_model,
  eff_model = eff_model,
  data = empty_data,
  stopping = my_stopping,
  increments = my_increments
)
```

`DualResponsesSamplesDesign-class` `DualResponsesSamplesDesign`

Description

[Stable]

This is a class of design based on DLE responses using the `LogisticIndepBeta` model with DLE and efficacy samples. It contain all slots in `RuleDesign` and `TDsamplesDesign` class objects.

Usage

```
DualResponsesSamplesDesign(eff_model, data, ...)

.DefaultDualResponsesSamplesDesign()
```

Arguments

`eff_model`	(`ModelEff`) see slot definition.
`data`	(`DataDual`) see slot definition.
`...`	Arguments passed on to `TDsamplesDesign` `model` (`ModelTox`) see slot definition. `stopping` (`Stopping`) see slot definition.

increments (Increments)
: see slot definition.

pl_cohort_size (CohortSize)
: see slot definition.

Slots

data (DataDual)
: the data set.

eff_model (ModelEff)
: the pseudo efficacy model to be used.

Note

Typically, end users will not use the `.DefaultDualResponsesSamplesDesign()` function.

Examples

```
empty_data <- DataDual(doseGrid = seq(25, 300, 25))

tox_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = empty_data
)
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
tox_samples <- mcmc(empty_data, tox_model, options)

eff_model <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = empty_data
)
eff_samples <- mcmc(empty_data, eff_model, options)

my_next_best <- NextBestMaxGainSamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, prob = 0.3))
  },
  mg_derive = function(mg_samples) {
    as.numeric(quantile(mg_samples, prob = 0.5))
  }
)

my_increments <- IncrementsRelative(
  intervals = c(25, 300),
  increments = c(2, 2)
)
```

```
my_size <- CohortSizeConst(size = 3)
my_stopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()

design <- DualResponsesSamplesDesign(
  nextBest = my_next_best,
  cohort_size = my_size,
  startingDose = 25,
  model = tox_model,
  eff_model = eff_model,
  data = empty_data,
  stopping = my_stopping,
  increments = my_increments
)
```

DualSimulations-class DualSimulations

Description

[Stable]

This class captures the trial simulations from dual-endpoint model based designs. In comparison to the parent class Simulations, it contains additional slots to capture the dose-biomarker fits, and the sigma2W and rho estimates.

Usage

```
DualSimulations(rho_est, sigma2w_est, fit_biomarker, ...)

.DefaultDualSimulations()
```

Arguments

rho_est	(numeric) see DualSimulations
sigma2w_est	(numeric) DualSimulations
fit_biomarker	(list) see DualSimulations
...	additional parameters from Simulations

Slots

`rho_est` (numeric)
: vector of final posterior median rho estimates

`sigma2w_est` (numeric)
: vector of final posterior median sigma2W estimates

`fit_biomarker` (list)
: with the final dose-biomarker curve fits

Note

Typically, end users will not use the `.DefaultDualSimulations()` function.

Examples

```
data_list <- list(
  Data(
    x = 1:2,
    y = 0:1,
    doseGrid = 1:2,
    ID = 1L:2L,
    cohort = 1L:2L
  ),
  Data(
    x = 3:4,
    y = 0:1,
    doseGrid = 3:4,
    ID = 1L:2L,
    cohort = 1L:2L
  )
)

doses <- c(1, 2)
seed <- as.integer(123)

fit <- list(
  c(0.1, 0.2),
  c(0.3, 0.4)
)

stop_report <- matrix(c(TRUE, FALSE), nrow = 2)

stop_reasons <- list("A", "B")

additional_stats <- list(a = 1, b = 1)

dual_simulations_obj <- DualSimulations(
  rho_est = c(0.25, 0.35),
  sigma2w_est = c(0.15, 0.25),
  fit_biomarker = list(c(0.3, 0.4), c(0.4, 0.5)),
  fit = fit,
  stop_report = stop_report,
  stop_reasons = stop_reasons,
  additional_stats = additional_stats,
  data = data_list,
  doses = doses,
  seed = seed
)
```

DualSimulationsSummary-class DualSimulationsSummary

Description

[Stable] This class captures the summary of dual-endpoint simulations output. In comparison to its parent class `SimulationsSummary`, it has additional slots.

Usage

```
.DefaultDualSimulationsSummary()
```

Slots

`biomarker_fit_at_dose_most_selected` (`numeric`)
: fitted biomarker level at most often selected dose.

`mean_biomarker_fit` (`list`)
: list with average, lower (2.5%) and upper (97.5%) quantiles of mean fitted biomarker level at each dose

Note

Typically, end users will not use the `.DefaultDualSimulationsSummary()` function.

EffFlexi-class EffFlexi

Description

[Stable]

`EffFlexi` is the class for the efficacy model in flexible form of prior expressed in form of pseudo data. In this class, a flexible form is used to describe the relationship between the efficacy responses and the dose levels and it is specified as

$$(W|betaW, sigma2W)\ Normal(X * betaW, sigma2W * I),$$

where W is a vector of the efficacy responses, $betaW$ is a column vector of the mean efficacy responses for all dose levels, and X is the design matrix with entries I_i, j that are equal to 1 if subject i is allocated to dose j, and 0 otherwise. The $sigma2W$ is the variance of the efficacy responses which can be either a fixed number or a number from an inverse gamma distribution. This flexible form aims to capture different shapes of the dose-efficacy curve. In addition, the first (RW1) or second order (RW2) random walk model can be used for smoothing data. That is the random walk model is used to model the first or the second order differences of the mean efficacy responses to its neighboring dose levels of their mean efficacy responses.

The RW1 model is given as

$$betaW_j - betaW_j - 1)\ Normal(0, sigma2betaW),$$

and for RW2 as

$$betaW_j - 2 - 2 * betaW_j - 1 + beta_j\ Normal(0, sigma2betaW),$$

where $betaW_j$ is the vector of mean efficacy responses at dose j, and the $sigma2betaW$ is the prior variance which can be either a fixed number or a number from an inverse gamma distribution.

The `eff` and `eff_dose` are the pseudo efficacy responses and dose levels at which these pseudo efficacy responses are observed. Both, `eff` and `eff_dose` must be vectors of length at least 2. The positions of the elements specified in `eff` and `eff_dose` must correspond to each other between these vectors.

Usage

```
EffFlexi(eff, eff_dose, sigma2W, sigma2betaW, rw1 = TRUE, data)

.DefaultEffFlexi()
```

Arguments

`eff`	(`numeric`) the pseudo efficacy responses. Elements of `eff` must correspond to the elements of `eff_dose`.
`eff_dose`	(`numeric`) dose levels that correspond to pseudo efficacy responses in `eff`.
`sigma2W`	(`numeric`) the prior variance of the efficacy responses. This is either a fixed value or a named vector with two positive numbers, the shape (`a`), and the rate (`b`) parameters for the inverse gamma distribution.
`sigma2betaW`	(`numeric`) the prior variance of the random walk model used for smoothing. This is either a fixed value or a named vector with two positive numbers, the shape (`a`), and the rate (`b`) parameters for the inverse gamma distribution.
`rw1`	(`flag`) used for smoothing data for this efficacy model. If it is `TRUE`, the first-order random walk model is used for the mean efficacy responses. Otherwise, the random walk of second order is used.
`data`	(`DataDual`) observed data to update estimates of the model parameters.

Details

This model will output the updated value or the updated values of the parameters of the inverse gamma distributions for $sigma2W$ and $sigma2betaW$. The `EffFlexi` inherits all slots from `ModelEff` class.

Slots

`eff` (`numeric`)
: the pseudo efficacy responses. Each element here must represent responses treated based on one subject. It must be a vector of length at least 2 and the order of its elements must correspond to values specified in `eff_dose`.

`eff_dose` (`numeric`)
: the pseudo efficacy dose levels at which the pseudo efficacy responses are observed. It must be a vector of length at least 2 and the order of its elements must correspond to values specified in `eff`.

`sigma2W` (`numeric`)
: the prior variance of the flexible efficacy form. This is either a fixed value or a named vector with two positive numbers, the shape (`a`), and the rate (`b`) parameters for the gamma distribution.

`sigma2betaW` (`numeric`)
: the prior variance of the random walk model for the mean efficacy responses. This is either a fixed value or a named vector with two positive numbers, the shape (`a`), and the rate (`b`) parameters for the gamma distribution.

`use_fixed` (`logical`)
: indicates whether a fixed value for `sigma2W` and `sigma2betaW` (for each parameter separately) is used or not. This slot is needed for internal purposes and must not be touched by the user.

`rw1` (`flag`)
: used for smoothing data for this efficacy model. If it is `TRUE`, the first-order random walk model is used for the mean efficacy responses. Otherwise, the random walk of second order is used.

`X` (`matrix`)
: the design matrix for the efficacy responses. It is based on both the pseudo and the observed efficacy responses.

`RW` (`matrix`)
: the difference matrix for the random walk model. This slot is needed for internal purposes and must not be used by the user.

`RW_rank` (`integer`)
: is the rank of the difference matrix. This slot is needed for internal purposes and must not be used by the user.

Note

Typically, end users will not use the `.DefaultEffFlexi()` function.

Examples

```
# Obtain prior estimates for the efficacy model in flexible form, given the pseudo data.
# First define an empty data set by defining the dose levels used in the study.
# There are 12 dose levels used in the study, ranging from 25 to 300 mg with
# increments of 25.
emptydata <- DataDual(doseGrid = seq(25, 300, 25))

# Define the pseudo data, i.e.: fixed 2 dose levels 25 and 300 mg (`eff_dose`)
```

```
# and the efficacy responses 1.223 and 2.513 observed at these two dose levels (`eff`).
# The prior variance of the pseudo efficacy responses can be either a fixed value
# or two parameters for the inverse gamma distribution, the shape (a) and the
# rate (b) (`sigma2W`).
# The prior variance of the random walk model can be either a fixed value or two
# parameters for the inverse gamma distribution, the shape (a) and the rate (b)
# (`sigma2betaW`).
my_model <- EffFlexi(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  sigma2W = c(a = 0.1, b = 0.1),
  sigma2betaW = c(a = 20, b = 50),
  rw1 = FALSE,
  data = emptydata
)

# Obtain estimates from the model given some observed data is available.
data <- DataDual(
  x = c(25, 50, 50, 75, 100, 100, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = emptydata@doseGrid
)

my_model1 <- EffFlexi(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  sigma2W = c(a = 0.1, b = 0.1),
  sigma2betaW = c(a = 20, b = 50),
  rw1 = FALSE,
  data = data
)
```

`efficacy` *Computing Expected Efficacy for a Given Dose, Model and Samples*

Description

[Stable]

A function that computes the value of expected efficacy at a specified dose level, based on the model specific parameters. The model parameters (samples) are obtained based on prior specified in form of pseudo data combined with observed responses (if any).

Usage

```
efficacy(dose, model, samples, ...)

## S4 method for signature 'numeric,Effloglog,Samples'
efficacy(dose, model, samples)
```

```
## S4 method for signature 'numeric,Effloglog,missing'
efficacy(dose, model)

## S4 method for signature 'numeric,EffFlexi,Samples'
efficacy(dose, model, samples)
```

Arguments

dose	(numeric) the dose which is targeted. The following recycling rule applies when samples is not missing: vectors of size 1 will be recycled to the size of the sample (i.e. size(samples)). Otherwise, dose must have the same size as the sample.
model	(ModelEff) the efficacy model with pseudo data prior.
samples	(Samples) samples of model's parameters that will be used to compute expected efficacy values. Can also be missing for some models.
...	model specific parameters when samples are not used.

Details

The efficacy() function computes the expected efficacy for given doses, using samples of the model parameter(s). If you work with multivariate model parameters, then assume that your model specific efficacy() method receives a samples matrix where the rows correspond to the sampling index, i.e. the layout is then nSamples x dimParameter.

Value

A numeric vector with the values of expected efficacy. If non-scalar samples were used, then every element in the returned vector corresponds to one element of a sample. Hence, in this case, the output vector is of the same length as the sample vector. If scalar samples were used or no samples were used, e.g. for pseudo DLE/toxicity model, then the output is of the same length as the length of the dose.

Functions

- efficacy(dose = numeric, model = Effloglog, samples = Samples): compute the expected efficacy at a specified dose level, based on the samples of Effloglog model parameters.
- efficacy(dose = numeric, model = Effloglog, samples = missing): compute the expected efficacy at a specified dose level, based on the Effloglog model parameters. All model parameters (except dose) should be present in the model object.
- efficacy(dose = numeric, model = EffFlexi, samples = Samples): compute the expected efficacy at a specified dose level, based on the samples of EffFlexi model parameters. If a given dose in the dose vector is from outside of the dose grid range, the NA_real is returned for this dose and the warning is thrown.

See Also

dose(), prob().

Examples

```
# Obtain the expected efficacy value for a given dose, a given pseudo efficacy
# model (in flexible form for prior) and efficacy samples.

# Empty data (i.e. no observed data), dose grid only.
my_data <- DataDual(doseGrid = seq(25, 300, 25))

my_model <- EffFlexi(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  sigma2W = c(a = 0.1, b = 0.1),
  sigma2betaW = c(a = 20, b = 50),
  rw1 = FALSE,
  data = my_data
)

my_options <- McmcOptions(
  burnin = 100,
  step = 2,
  samples = 200,
  rng_kind = "Mersenne-Twister",
  rng_seed = 94
)

my_samples <- mcmc(data = my_data, model = my_model, options = my_options)

# Efficacy for dose 75.
efficacy(dose = 75, model = my_model, samples = my_samples)

# Obtain the expected efficacy value for a given dose, a given pseudo efficacy
# model (linear log-log efficacy) and no samples.
my_model_ll <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = my_data,
  const = 0
)

efficacy(dose = 75, model = my_model_ll)
```

---

efficacyFunction *Getting the Efficacy Function for a Given Model Type*

Description

[Experimental]

A function that returns an `efficacy()` function that computes expected efficacy for a given dose level, based on the model specific parameters.

Usage

```
efficacyFunction(model, ...)

## S4 method for signature 'ModelEff'
efficacyFunction(model, ...)
```

Arguments

`model`	(`ModelEff`) the model.
`...`	model specific parameters.

Value

A `efficacy()` function that computes expected efficacy.

Functions

- `efficacyFunction(ModelEff)`: Return an efficacy function for a `ModelEff`.

See Also

`efficacy()`.

Examples

```
my_data <- DataDual(
  doseGrid = c(0.001, seq(25, 300, 25)),
  placebo = TRUE
)

my_model <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = my_data,
  const = 2
)

eff_fun <- efficacyFunction(my_model, theta1 = -4.8, theta2 = 3.7)
eff_fun(30)
```

`Effloglog-class` `Effloglog`

Description

[Stable]

`Effloglog` is the class for the linear log-log efficacy model using pseudo data prior. It describes the relationship between continuous efficacy responses and corresponding dose levels in log-log scale. This efficacy log-log model is given as

$$y_i = theta1 + theta2 * log(log(x_i)) + epsilon_i,$$

where y_i is the efficacy response for subject i, x_i is the dose level treated for subject i and $epsilon_i$ is the random error term of efficacy model at subject i. The error term $epsilon_i$ is a random variable that follows normal distribution with mean 0 and variance nu^{-1}, which is assumed to be the same for all subjects. There are three parameters in this model, the intercept $theta1$, the slope $theta2$ and the precision nu of the efficacy responses, also known as the inverse of the variance of the pseudo efficacy responses. It can be a fixed constant or having a gamma distribution. Therefore, a single scalar value or a vector with two positive numbers values must be specified for `nu` slot. If there are some observed efficacy responses available, in the output, `nu` will display the updated value of the precision or the updated values for the parameters of the gamma distribution. The `Effloglog` inherits all slots from `ModelEff` class.

Usage

```
Effloglog(eff, eff_dose, nu, data, const = 0)

.DefaultEffloglog()
```

Arguments

`eff`	(`numeric`) the pseudo efficacy responses. Elements of `eff` must correspond to the elements of `eff_dose`.
`eff_dose`	(`numeric`) dose levels that correspond to pseudo efficacy responses in `eff`.
`nu`	(`numeric`) the precision (inverse of the variance) of the efficacy responses. This is either a fixed value or a named vector with two positive numbers, the shape (`a`), and the rate (`b`) parameters for the gamma distribution.
`data`	(`DataDual`) observed data to update estimates of the model parameters.
`const`	(`number`) the constant value added to the dose level when the dose level value is less than or equal to 1 and a special form of the linear log-log has to be applied (Yeung et al. 2015).

Details

The prior of this model is specified in form of pseudo data. First, at least two dose levels are fixed. Then, using e.g. experts' opinion, the efficacy values that correspond to these dose levels can be obtained, The `eff` and `eff_dose` arguments represent the prior in form of the pseudo data. The `eff` represents the pseudo efficacy values. The `eff_dose` represents the dose levels at which these pseudo efficacy values are observed. Hence, the positions of the elements specified in `eff` and `eff_dose` must correspond to each other between these vectors. Since at least 2 pseudo efficacy values are needed to obtain modal estimates of the intercept and slope parameters, both `eff` and `eff_dose` must be vectors of length at least 2.

The joint prior distribution of the intercept $theta1$ and the slope $theta2$ of this model follows bivariate normal distribution with mean mu and covariance matrix $(nu * Q)^{-1}$. The mean mu is a $2x1$ column vector that contains the prior modal estimates of the intercept and the slope. Scalar nu is the precision of the pseudo efficacy responses and Q is the prior or posterior (given that observed, no DLT data is available) precision matrix. It is specified as $Q = X0^T * X0 + X^T * X$, where $X0$ is a design matrix that is based on pseudo dose levels only, and X is a design matrix that is based on dose levels corresponding to the no DLT efficacy responses observed only (if any). Hence, the $X0$ (or X) will be of size $rx2$, if there are $r >= 2$ pseudo efficacy responses specified (or if there are r no DLT efficacy responses observed in the `data`).

Slots

`eff` (`numeric`)
: the pseudo efficacy responses. Each element here must represent responses treated based on one subject. It must be a vector of length at least 2 and the order of its elements must correspond to values specified in `eff_dose`.

`eff_dose` (`numeric`)
: the pseudo efficacy dose levels at which the pseudo efficacy responses are observed. It must be a vector of length at least 2 and the order of its elements must correspond to values specified in `eff`.

`nu` (`numeric`)
: parameter of the prior precision of pseudo efficacy responses. This is either a fixed value or a named vector with two positive numbers, the shape (`a`), and the rate (`b`) parameters for the gamma distribution.

`use_fixed` (`flag`)
: indicates whether `nu` specified is a fixed value or a vector with two parameters for gamma distribution. This slot is for internal purposes only and must not be used by the user.

`theta1` (`number`)
: the intercept in this efficacy log-log model. This slot is used in output to display the resulting prior or posterior modal estimates obtained based on the pseudo and observed (if any) data.

`theta2` (`number`)
: the slope in this efficacy log-log model. This slot is used in output to display the resulting prior or posterior modal estimates obtained based on the pseudo and observed (if any) data.

`Pcov` (`matrix`)
: refers to the $2x2$ covariance matrix of the estimators of the intercept $theta1$ and the slope $theta2$ parameters in this model. This is used in output to display the resulting prior and posterior covariance matrix of $theta1$ and $theta2$ obtained, based on the pseudo and observed (if any) data. This slot is needed for internal purposes.

`X (matrix)`
: is the design matrix that is based on either the pseudo dose levels or observed dose levels (without DLT). This is used in the output to display the design matrix for the pseudo or the observed efficacy responses.

`Y (numeric)`
: is a vector that either contains the pseudo efficacy responses or observed efficacy responses (without DLT).

`mu (numeric)`
: a vector of the prior or the posterior modal estimates of the intercept ($theta1$) and the slope ($theta2$). This slot is used in output to display as the mean of the prior or posterior bivariate normal distribution for $theta1$ and $theta2$.

`Q (matrix)`
: is the prior or posterior (given that observed, no DLT data is available) precision matrix. It is specified as $Q = X0^T * X0 + X^T * X$, where $X0$ is a design matrix that is based on pseudo dose levels only, and X is a design matrix that is based on dose levels corresponding to the observed, no DLT efficacy values only (if any).

`const (number)`
: a non-negative number (default to 0), leading to the model form described above. In general, the model has the form $y_i = theta1 + theta2 * log(log(x_i + const)) + epsilon_i$, such that dose levels greater than $1 - const$ can be considered as described in Yeung et al. (2015).

Note

Typically, end users will not use the `.DefaultEffloglog()` function.

References

Yeung WY, Whitehead J, Reigner B, Beyer U, Diack C, Jaki T (2015). "Bayesian adaptive dose-escalation procedure for binary and continuous responses utilizing a gain function." *Pharmaceutical Statistics*. doi:10.1002/pst.1706. Published online ahead of print.

Examples

```
# Obtain prior modal estimates given the pseudo data.
# First we use an empty data set such that only the dose levels under
# investigations are given. In total, 12 dose levels are under investigation
# ranging from 25 to 300 mg with increments of 25 (i.e 25, 50, 75, ..., 300).
emptydata <- DataDual(doseGrid = seq(25, 300, 25), placebo = FALSE)

# Define the pseudo data as first by fixing two dose levels 25 and 300 mg (`eff_dose`).
# Then, the efficacy responses observed at these two dose levels are 1.223 and 2.513 (`eff`).
# We specify the prior precision of the pseudo efficacy responses (`nu`) as a vector
# with the shape (a) and the rate (b) parameters for the gamma distribution.
# Obtain modal estimates and other estimates from the model (no observations,
# only pseudo data).
my_model1 <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
```

```
  data = emptydata
)

# Observed data.
my_data <- DataDual(
  x = c(25, 50, 50, 75, 100, 100, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = emptydata@doseGrid
)

# Obtain posterior modal estimates and other estimates from the model given some
# observed data.
my_model2 <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = my_data
)
```

---

enable_logging *Verbose Logging*

Description

[Experimental]

A family of wrappers of selected futile.logger functions that control the logging mechanism in crmPack. The crmPack uses futile.logger package for the logging purposes. All the messages logged in crmPack are logged into crmPack logger at the futile.logger::TRACE level. Hence, enabling verbose logging means that the logging threshold will be set to futile.logger::TRACE for the crmPack logger, and disabling verbose logging means that it will be set to futile.logger::FATAL.

Usage

```
enable_logging()

disable_logging()

is_logging_enabled()

log_trace(msg, ..., capture = FALSE)
```

Arguments

msg	The message to log
...	Optional arguments to populate the format string
capture	Capture print output of variables instead of interpolate

Functions

- enable_logging(): A simple wrapper of futile.logger::flog.threshold() that enables crmPack verbose logging by setting logging threshold to futile.logger::TRACE for crmPack logger.
- disable_logging(): A simple wrapper of futile.logger::flog.threshold() that disables crmPack verbose logging by setting logging threshold to futile.logger::FATAL for crmPack logger.
- is_logging_enabled(): A simple wrapper of futile.logger::flog.logger() that checks whether current threshold level for crmPack logger is verbose, which is futile.logger::TRACE. It returns TRUE if the current logging level is verbose, FALSE otherwise.
- log_trace(): A simple wrapper of futile.logger::flog.trace() that prints a log message in the crmPack logger.

---

examine *Obtain Hypothetical Trial Course Table for a Design*

Description

This generic function takes a design and generates a data.frame showing the beginning of several hypothetical trial courses under the design. This means, from the generated data.frame one can read off:

Usage

```
examine(object, ..., maxNoIncrement = 100L)

## S4 method for signature 'Design'
examine(object, mcmcOptions = McmcOptions(), ..., maxNoIncrement)

## S4 method for signature 'RuleDesign'
examine(object, ..., maxNoIncrement = 100L)

## S4 method for signature 'DADesign'
examine(object, mcmcOptions = McmcOptions(), ..., maxNoIncrement)
```

Arguments

object	(Design or RuleDesign) the design we want to examine
...	additional arguments (see methods)
maxNoIncrement	maximum number of contiguous next doses at 0 DLTs that are the same as before, i.e. no increment (default to 100)
mcmcOptions	(McmcOptions) giving the MCMC options for each evaluation in the trial. By default, the standard options are used

Details

- how many cohorts are required in the optimal case (no DLTs observed) in order to reach the highest dose of the specified dose grid (or until the stopping rule is fulfilled)
- assuming no DLTs are observed until a certain dose level, what the next recommended dose is for all possible number of DLTs observed
- the actual relative increments that will be used in these cases
- whether the trial would stop at a certain cohort

Examining the "single trial" behavior of a dose escalation design is the first important step in evaluating a design, and cannot be replaced by studying solely the operating characteristics in "many trials". The cohort sizes are also taken from the design, assuming no DLTs occur until the dose listed.

Value

The data frame

Functions

- `examine(Design)`: Examine a model-based CRM.
- `examine(RuleDesign)`: Examine a rule-based design.
- `examine(DADesign)`: Examine a model-based CRM.

Examples

```
# Define the dose-grid.
emptydata <- Data(doseGrid = c(1, 3, 5, 10, 15, 20, 25))


# Initialize the CRM model.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Choose the rule for selecting the next dose.
my_next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)


my_size1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
my_size2 <- CohortSizeDLT(
  intervals = c(0, 1),
```

```
  cohort_size = c(1, 3)
)
my_size <- maxSize(my_size1, my_size2)

# Choose the rule for stopping.
my_stopping1 <- StoppingMinCohorts(nCohorts = 3)
my_stopping2 <- StoppingTargetProb(
  target = c(0.2, 0.35),
  prob = 0.5
)
my_stopping3 <- StoppingMinPatients(nPatients = 20)
my_stopping <- (my_stopping1 & my_stopping2) | my_stopping3 | StoppingMissingDose()

# Choose the rule for dose increments.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Initialize the design.
my_design <- Design(
  model = my_model,
  nextBest = my_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  data = emptydata,
  startingDose = 3
)

my_options <- McmcOptions(
  burnin = 10,
  step = 1,
  samples = 20,
  rng_kind = "Super-Duper",
  rng_seed = 94
)


examine(my_design, my_options)


# Example where examine stops because stopping rule already fulfilled.
my_stopping4 <- StoppingMinPatients(nPatients = 3)
my_stopping <- (my_stopping1 & my_stopping2) | my_stopping4

my_design <- Design(
  model = my_model,
  nextBest = my_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  data = emptydata,
```

```
  startingDose = 3
)


examine(my_design, mcmcOptions = my_options)


# Example where examine stops because infinite looping
# (note that here a very low threshold is used for the parameter
# "maxNoIncrement" in "examine" to keep the execution time short).
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.00001)
)

my_stopping <- (my_stopping1 & my_stopping2) | StoppingMissingDose()

design <- Design(
  model = my_model,
  nextBest = my_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  data = emptydata,
  startingDose = 3
)


examine(my_design, mcmcOptions = my_options, maxNoIncrement = 2)

# Define the dose-grid
emptydata <- Data(doseGrid = c(5, 10, 15, 25, 35, 50, 80))

# inizialing a 3+3 design with constant cohort size of 3 and
# starting dose equal 5
myDesign <- RuleDesign(
  nextBest = NextBestThreePlusThree(),
  cohort_size = CohortSizeConst(size = 3L),
  data = emptydata,
  startingDose = 5
)

# Examine the design
set.seed(4235)

examine(myDesign)

# nolint start

# Define the dose-grid and PEM parameters
emptydata <- DataDA(doseGrid = c(
  0.1, 0.5, 1, 1.5, 3, 6,
  seq(from = 10, to = 80, by = 2)
```

```
), Tmax = 60)
# Initialize the mDA-CRM model
npiece_ <- 10
Tmax_ <- 60

lambda_prior <- function(k) {
  npiece_ / (Tmax_ * (npiece_ - k + 0.5))
}

model <- DALogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56,
  npiece = npiece_,
  l = as.numeric(t(apply(as.matrix(c(1:npiece_), 1, npiece_), 2, lambda_prior))),
  c_par = 2
)
# Choose the rule for dose increments
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size
mySize1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
mySize2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
mySize <- maxSize(mySize1, mySize2)

# Choose the rule for stopping
myStopping1 <- StoppingTargetProb(
  target = c(0.2, 0.35),
  prob = 0.5
)
myStopping2 <- StoppingMinPatients(nPatients = 50)

myStopping <- (myStopping1 | myStopping2) | StoppingMissingDose()

# Choose the safety window
mysafetywindow <- SafetyWindowConst(c(6, 2), 7, 7)

# Initialize the design
```

```
design <- DADesign(
  model = model,
  increments = myIncrements,
  nextBest = myNextBest,
  stopping = myStopping,
  cohort_size = mySize,
  data = emptydata,
  safetyWindow = mysafetywindow,
  startingDose = 3
)

set.seed(4235)
# MCMC parameters are set to small values only to show this example. They should be
# increased for a real case.
# This procedure will take a while.
options <- McmcOptions(
  burnin = 10,
  step = 1,
  samples = 100,
  rng_kind = "Mersenne-Twister",
  rng_seed = 12
)

testthat::expect_warning(
  result <- examine(design, mcmcOptions = options, maxNoIncrement = 2),
  "Stopping because 2 times no increment"
)


# nolint end
```

`fit` *Fit method for the Samples class*

Description

Note this new generic function is necessary because the `fitted` function only allows the first argument `object` to appear in the signature. But we need also other arguments in the signature.

Usage

```
fit(object, model, data, ...)

## S4 method for signature 'Samples,GeneralModel,Data'
fit(
  object,
  model,
  data,
  points = data@doseGrid,
```

```
  quantiles = c(0.025, 0.975),
  middle = mean,
  ...
)

## S4 method for signature 'Samples,TwoDrugsCombo,DataCombo'
fit(
  object,
  model,
  data,
  points = as.matrix(do.call(expand.grid, data@doseGrid)),
  quantiles = c(0.025, 0.975),
  middle = mean,
  ...
)

## S4 method for signature
## 'HierarchicalSamples,HierarchicalModel,HierarchicalData'
fit(object, model, data, ...)

## S4 method for signature 'Samples,DualEndpoint,DataDual'
fit(object, model, data, quantiles = c(0.025, 0.975), middle = mean, ...)

## S4 method for signature 'Samples,LogisticIndepBeta,Data'
fit(
  object,
  model,
  data,
  points = data@doseGrid,
  quantiles = c(0.025, 0.975),
  middle = mean,
  ...
)

## S4 method for signature 'Samples,Effloglog,DataDual'
fit(
  object,
  model,
  data,
  points = data@doseGrid,
  quantiles = c(0.025, 0.975),
  middle = mean,
  ...
)

## S4 method for signature 'Samples,EffFlexi,DataDual'
fit(
  object,
```

```
  model,
  data,
  points = data@doseGrid,
  quantiles = c(0.025, 0.975),
  middle = mean,
  ...
)

## S4 method for signature 'Samples,LogisticLogNormalOrdinal,DataOrdinal'
fit(
  object,
  model,
  data,
  points = data@doseGrid,
  quantiles = c(0.025, 0.975),
  middle = mean,
  ...
)
```

Arguments

object	the Samples object
model	the GeneralModel object
data	the Data object
...	passed down to the prob() method.
points	at which dose levels is the fit requested? default is the dose grid
quantiles	the quantiles to be calculated (default: 0.025 and 0.975)
middle	the function for computing the middle point. Default: mean

Value

the data frame with required information (see method details)

Functions

- fit(object = Samples, model = GeneralModel, data = Data): This method returns a data frame with dose, middle, lower and upper quantiles for the dose-toxicity curve
- fit(object = Samples, model = TwoDrugsCombo, data = DataCombo): This method returns a data frame with one row per dose combination and posterior summaries of the DLT probability surface.
- fit(object = HierarchicalSamples, model = HierarchicalModel, data = HierarchicalData): This method delegates to the arm-specific fit methods and returns one combined data frame with an arm column.
- fit(object = Samples, model = DualEndpoint, data = DataDual): This method returns a data frame with dose, and middle, lower and upper quantiles, for both the dose-tox and dose-biomarker (suffix "Biomarker") curves, for all grid points (Note that currently only the grid points can be used, because the DualEndpointRW models only allow that)

- `fit(object = Samples, model = LogisticIndepBeta, data = Data)`: This method return a data frame with dose, middle lower and upper quantiles for the dose-DLE curve using DLE samples for "LogisticIndepBeta" model class
- `fit(object = Samples, model = Effloglog, data = DataDual)`: This method returns a data frame with dose, middle, lower, upper quantiles for the dose-efficacy curve using efficacy samples for "Effloglog" model class
- `fit(object = Samples, model = EffFlexi, data = DataDual)`: This method returns a data frame with dose, middle, lower and upper quantiles for the dose-efficacy curve using efficacy samples for "EffFlexi" model class
- `fit(object = Samples, model = LogisticLogNormalOrdinal, data = DataOrdinal)`: This method returns a data frame with dose, middle, lower and upper quantiles for the dose-efficacy curve using efficacy samples for the "LogisticLogNormalOrdinal" model class

Examples

```
# nolint start

# Create some data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize a model
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Get posterior for all model parameters
options <- McmcOptions(burnin = 100, step = 2, samples = 2000)
set.seed(94)
samples <- mcmc(data, model, options)

# Extract the posterior mean  (and empirical 2.5 and 97.5 percentile)
# for the prob(DLT) by doses
fitted <- fit(
  object = samples,
  model = model,
  data = data,
  quantiles = c(0.025, 0.975),
  middle = mean
)


# ------------------------------------------------
# A different example using a different model
## we need a data object with doses >= 1:
```

```
data <- Data(
  x = c(25, 50, 50, 75, 150, 200, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  doseGrid = seq(from = 25, to = 300, by = 25)
)


model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
## samples must be from 'Samples' class (object slot in fit)
samples <- mcmc(data, model, options)

fitted <- fit(object = samples, model = model, data = data)

# nolint end
# nolint start

# Create some data
data <- DataDual(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10, 20, 20, 20, 40, 40, 40, 50, 50, 50),
  y = c(0, 0, 0, 0, 0, 0, 1, 0, 0, 1, 1, 0, 0, 1, 0, 1, 1),
  w = c(
    0.31,
    0.42,
    0.59,
    0.45,
    0.6,
    0.7,
    0.55,
    0.6,
    0.52,
    0.54,
    0.56,
    0.43,
    0.41,
    0.39,
    0.34,
    0.38,
    0.21
  ),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the Dual-Endpoint model (in this case RW1)
model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2betaW = 0.01,
```

```
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  rw1 = TRUE
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 100, step = 2, samples = 500)
set.seed(94)
samples <- mcmc(data, model, options)

# Extract the posterior mean  (and empirical 2.5 and 97.5 percentile)
# for the prob(DLT) by doses and the Biomarker by doses
fitted <- fit(
  object = samples,
  model = model,
  data = data,
  quantiles = c(0.025, 0.975),
  middle = mean
)

# nolint end
##Obtain the 'fit' the middle, uppper and lower quantiles for the dose-DLE curve
## at all dose levels using a DLE sample, a DLE model and the data
## samples must be from 'Samples' class (object slot)
## we need a data object with doses >= 1:
data <- Data(
  x = c(25, 50, 50, 75, 150, 200, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  doseGrid = seq(from = 25, to = 300, by = 25)
)
## model must be from 'Model' or 'ModelTox' class e.g using 'LogisticIbdepBeta' model class
model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
##options for MCMC
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
## samples must be from 'Samples' class (object slot in fit)
samples <- mcmc(data, model, options)

fit(object = samples, model = model, data = data)
##Obtain the 'fit' the middle, uppper and lower quantiles for the dose-efficacy curve
## at all dose levels using an efficacy sample, a pseudo efficacy model and the data
## data must be from 'DataDual' class
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)
```

```
## model must be from 'ModelEff' e.g using 'Effloglog' class
Effmodel <- Effloglog(
  c(1.223, 2.513),
  c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data,
  c = 0
)
## samples must be from 'Samples' class (object slot in fit)
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
Effsamples <- mcmc(data = data, model = Effmodel, options = options)
fit(object = Effsamples, model = Effmodel, data = data)
# nolint start

##Obtain the 'fit' the middle, uppper and lower quantiles for the dose-efficacy curve
## at all dose levels using an efficacy sample, the 'EffFlexi' efficacy model and the data
## data must be from 'DataDual' class
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)
## model must be from 'ModelEff' e.g using 'Effloglog' class
Effmodel <- EffFlexi(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  sigma2W = c(a = 0.1, b = 0.1),
  sigma2betaW = c(a = 20, b = 50),
  rw1 = FALSE,
  data = data
)

## samples must be from 'Samples' class (object slot in fit)
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
Effsamples <- mcmc(data = data, model = Effmodel, options = options)
fit(object = Effsamples, model = Effmodel, data = data)

# nolint end
model <- .DefaultLogisticLogNormalOrdinal()
ordinal_data <- .DefaultDataOrdinal()
options <- .DefaultMcmcOptions()
samples <- mcmc(ordinal_data, model, options)

grade1_fit <- fit(samples, model, ordinal_data, grade = 1L)
grade2_fit <- fit(samples, model, ordinal_data, grade = 2L)
```

`fitGain` *Get the fitted values for the gain values at all dose levels based on a given pseudo DLE model, DLE sample, a pseudo efficacy model, a Efficacy sample and data. This method returns a data frame with dose, middle, lower and upper quantiles of the gain value samples*

Description

Get the fitted values for the gain values at all dose levels based on a given pseudo DLE model, DLE sample, a pseudo efficacy model, a Efficacy sample and data. This method returns a data frame with dose, middle, lower and upper quantiles of the gain value samples

Usage

```
fitGain(DLEmodel, DLEsamples, Effmodel, Effsamples, data, ...)

## S4 method for signature 'ModelTox,Samples,ModelEff,Samples,DataDual'
fitGain(
  DLEmodel,
  DLEsamples,
  Effmodel,
  Effsamples,
  data,
  points = data@doseGrid,
  quantiles = c(0.025, 0.975),
  middle = mean,
  ...
)
```

Arguments

`DLEmodel`	the DLE pseudo model of ModelTox class object
`DLEsamples`	the DLE samples of Samples class object
`Effmodel`	the efficacy pseudo model of ModelEff class object
`Effsamples`	the efficacy samples of Samples class object
`data`	the data input of DataDual class object
`...`	additional arguments for methods
`points`	at which dose levels is the fit requested? default is the dose grid
`quantiles`	the quantiles to be calculated (default: 0.025 and 0.975)
`middle`	the function for computing the middle point. Default: `mean`

Functions

- `fitGain( DLEmodel = ModelTox, DLEsamples = Samples, Effmodel = ModelEff, Effsamples = Samples, data = DataDual )`: This method returns a data frame with dose, middle, lower, upper quantiles for the gain values obtained given the DLE and the efficacy samples

Examples

```
##Obtain the 'fitGain' the middle, uppper and lower quantiles for the samples of gain values
## at all dose levels using a pseudo DLE model, a DLE sample, a pseudo Efficacy model and
## a efficacy sample
## data must be from 'DataDual' class
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)
## DLE model must be from 'ModelTox' class e.g using 'LogisticIndepBeta' model
DLEmodel <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)

## Efficacy model must be from 'ModelEff' class e.g using 'Effloglog' model
Effmodel <- Effloglog(
  c(1.223, 2.513),
  c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data,
  c = 0
)
## samples must be from 'Samples' class (object slot in fit)
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
##set up the same data set in class 'Data' for MCMC sampling for DLE
data1 <- Data(x = data@x, y = data@y, doseGrid = data@doseGrid)

DLEsamples <- mcmc(data = data1, model = DLEmodel, options = options)
Effsamples <- mcmc(data = data, model = Effmodel, options = options)

fitGain(
  DLEmodel = DLEmodel,
  DLEsamples = DLEsamples,
  Effmodel = Effmodel,
  Effsamples = Effsamples,
  data = data
)
##Obtain the 'fitGain' the middle, uppper and lower quantiles for the samples of gain values
## at all dose levels using a pseudo DLE model, a DLE sample, a pseudo Efficacy model and
## a efficacy sample
## data must be from 'DataDual' class
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
```

```
  placebo = FALSE
)
## DLE model must be from 'ModelTox' class e.g using 'LogisticIndepBeta' model
DLEmodel <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)

## Efficacy model must be from 'ModelEff' class e.g using 'Effloglog' model
Effmodel <- Effloglog(
  c(1.223, 2.513),
  c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data,
  c = 0
)
## samples must be from 'Samples' class (object slot in fit)
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
##set up the same data set in class 'Data' for MCMC sampling for DLE
data1 <- Data(x = data@x, y = data@y, doseGrid = data@doseGrid)

DLEsamples <- mcmc(data = data1, model = DLEmodel, options = options)
Effsamples <- mcmc(data = data, model = Effmodel, options = options)

fitGain(
  DLEmodel = DLEmodel,
  DLEsamples = DLEsamples,
  Effmodel = Effmodel,
  Effsamples = Effsamples,
  data = data
)
```

`fitPEM` *Get the fitted DLT free survival (piecewise exponential model). This function returns a data frame with dose, middle, lower and upper quantiles for the* `PEM` *curve. If hazard=TRUE,*

Description

Get the fitted DLT free survival (piecewise exponential model). This function returns a data frame with dose, middle, lower and upper quantiles for the `PEM` curve. If hazard=TRUE,

Usage

```
fitPEM(
  object,
  model,
  data,
```

```
  quantiles = c(0.025, 0.975),
  middle = mean,
  hazard = FALSE,
  ...
)

## S4 method for signature 'Samples,DALogisticLogNormal,DataDA'
fitPEM(
  object,
  model,
  data,
  quantiles = c(0.025, 0.975),
  middle = mean,
  hazard = FALSE,
  ...
)
```

Arguments

`object`	mcmc samples
`model`	the mDA-CRM model
`data`	the data input, a DataDA class object
`quantiles`	the quantiles to be calculated (default: 0.025 and 0.975)
`middle`	the function for computing the middle point. Default: `mean`
`hazard`	should the the hazard over time be plotted based on the `PEM`? (not default) Otherwise ...
`...`	additional arguments for methods

Functions

- `fitPEM(object = Samples, model = DALogisticLogNormal, data = DataDA)`: This method works for the DALogisticLogNormal model class.

Examples

```
# nolint start

# Create the data
data <- DataDA(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 1, 1, 0, 0, 1, 0),
  ID = 1L:8L,
  cohort = as.integer(c(1:5, 6, 6, 6)),
  doseGrid = c(
    0.1,
    0.5,
    1.5,
    3,
```

```
    6,
    seq(from = 10, to = 80, by = 2)
  ),
  u = c(42, 30, 15, 5, 20, 25, 30, 60),
  t0 = c(0, 15, 30, 40, 55, 70, 75, 85),
  Tmax = 60
)

# Initialize the CRM model used to model the data
npiece_ <- 10
lambda_prior <- function(k) {
  npiece_ / (data@Tmax * (npiece_ - k + 0.5))
}

model <- DALogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56,
  npiece = npiece_,
  l = as.numeric(t(apply(
    as.matrix(c(1:npiece_), 1, npiece_),
    2,
    lambda_prior
  ))),
  c_par = 2
)

# Obtain the posterior

options <- McmcOptions(
  burnin = 10,
  step = 2,
  samples = 1e2
)

set.seed(94)
samples <- mcmc(data, model, options)


# Extract the posterior mean hazard (and empirical 2.5 and 97.5 percentile)
# for the piecewise exponential model
# If hazard=FALSE, the posterior PEM will be plot
fitted <- fitPEM(
  object = samples,
  model = model,
  data = data,
  middle = mean,
  hazard = TRUE,
  quantiles = c(0.25, 0.75)
)

# nolint end
```

`FractionalCRM-class` `FractionalCRM`

Description

[Stable]

`FractionalCRM` is the class for a fractional CRM model based on a one parameter CRM (with normal prior on the log-power parameter) as well as Kaplan-Meier based estimation of the conditional probability to experience a DLT for non-complete observations.

This fractional CRM model follows the paper and code by Yin et al. (2013).

Usage

```
FractionalCRM(...)

.DefaultFractionalCRM()
```

Arguments

`...`	Arguments passed on to `OneParLogNormalPrior`
	`skel_probs (numeric)`
	skeleton prior probabilities. This is a vector of unique and sorted probability values between 0 and 1.
	`dose_grid (numeric)`
	dose grid. It must be must be a sorted vector of the same length as `skel_probs`.
	`sigma2 (number)`
	prior variance of log power parameter alpha.

Note

Typically, end users will not use the `.DefaultTITELogisticLogNormal()` function.

References

Yin G, Zheng S, Xu J (2013). "Fractional dose-finding methods with late-onset toxicity in phase I clinical trials." *Journal of Biopharmaceutical Statistics*, **23**(4), 856–870. doi:10.1080/10543406.2013.789892.

See Also

`TITELogisticLogNormal`.

Examples

```
my_model <- FractionalCRM(
  skel_probs = c(0.1, 0.2, 0.3, 0.4),
  dose_grid = c(10, 30, 50, 100),
  sigma2 = 2
)
```

gain *Compute Gain Values based on Pseudo DLE and a Pseudo Efficacy Models and Using Optional Samples.*

Description

[Stable]

Usage

```
gain(dose, model_dle, samples_dle, model_eff, samples_eff, ...)

## S4 method for signature 'numeric,ModelTox,Samples,ModelEff,Samples'
gain(dose, model_dle, samples_dle, model_eff, samples_eff, ...)

## S4 method for signature 'numeric,ModelTox,missing,Effloglog,missing'
gain(dose, model_dle, samples_dle, model_eff, samples_eff, ...)
```

Arguments

dose	(number or numeric) the dose which is targeted. The following recycling rule applies when samples are not missing: vectors of size 1 will be recycled to the size of the sample. Otherwise, dose must have the same size as the sample.
model_dle	(ModelTox) pseudo DLE (dose-limiting events)/toxicity model.
samples_dle	(Samples) the samples of model's parameters that will be used to compute toxicity probabilities. Can also be missing for some models.
model_eff	(ModelEff) the efficacy model with pseudo data prior.
samples_eff	(Samples) samples of model's parameters that will be used to compute expected efficacy values. Can also be missing for some models.
...	not used.

Details

This function computes the gain values for a given dose level, pseudo DLE and Efficacy models as well as a given DLE and Efficacy samples.

Value

The gain values.

Functions

- `gain( dose = numeric, model_dle = ModelTox, samples_dle = Samples, model_eff = ModelEff, samples_eff = Samples )`: Compute gain values from toxicity and efficacy model samples.
- `gain( dose = numeric, model_dle = ModelTox, samples_dle = missing, model_eff = Effloglog, samples_eff = missing )`: Compute the gain value for a given dose level, pseudo DLE and Efficacy models without DLE and the Efficacy samples.

Examples

```
# Obtain the gain value for a given dose, a pseudo DLE and efficacy models
# as well as DLE and efficacy samples.
emptydata <- DataDual(doseGrid = seq(25, 300, 25), placebo = FALSE)
mcmc_opts <- McmcOptions(burnin = 100, step = 2, samples = 200)

# DLE model and samples.
model_dle <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = emptydata
)

samples_dle <- mcmc(emptydata, model_dle, mcmc_opts)

# Efficacy model (Effloglog) and samples.
model_effloglog <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = emptydata
)

samples_effloglog <- mcmc(emptydata, model_effloglog, mcmc_opts)

# Gain values for dose level 75 and Effloglog efficacy model.
gain(
  dose = 75,
  model_dle = model_dle,
  samples_dle = samples_dle,
  model_eff = model_effloglog,
  samples_eff = samples_effloglog
)

# Efficacy model (EffFlexi) and samples.
model_effflexi <- EffFlexi(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  sigma2W = c(a = 0.1, b = 0.1),
  sigma2betaW = c(a = 20, b = 50),
  rw1 = FALSE,
  data = emptydata
```

```
)

samples_effflexi <- mcmc(emptydata, model_effflexi, mcmc_opts)

# Gain values for dose level 75 and EffFlexi efficacy model.
gain(
  dose = 75,
  model_dle = model_dle,
  samples_dle = samples_dle,
  model_eff = model_effflexi,
  samples_eff = samples_effflexi
)
# Obtain the gain value for a given dose, a pseudo DLE and efficacy models
# without DLE and efficacy samples.
emptydata <- DataDual(doseGrid = seq(25, 300, 25), placebo = FALSE)
data <- Data(doseGrid = seq(25, 300, 25), placebo = FALSE)
mcmc_opts <- McmcOptions(burnin = 100, step = 2, samples = 200)

# DLE model and samples.
model_dle <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)

# Efficacy model and samples.
model_eff <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = emptydata
)

# Gain value for dose level 75.
gain(
  dose = 75,
  model_dle = model_dle,
  model_eff = model_eff
)
```

GeneralData-class GeneralData

Description

[Stable]

GeneralData is a class for general data input.

Usage

```
.DefaultDataGeneral()
```

Slots

`ID (integer)`
: unique patient IDs.

`cohort (integer)`
: the cohort (non-negative sorted) indices.

`nObs (integer)`
: number of observations, a single value.

Note

Typically, end users will not use the `.DefaultDataGeneral()` function.

GeneralModel-class GeneralModel

Description

[Stable]

`GeneralModel` is a general model class, from which all other specific model-like classes inherit.

Usage

```
.DefaultGeneralModel()
```

Slots

`datamodel (function)`
: a function representing the `JAGS` data model specification.

`priormodel (function)`
: a function representing the `JAGS` prior specification.

`modelspecs (function)`
: a function computing the list of the data model and prior model specifications that are required to be specified completely (e.g. prior parameters, reference dose, etc.), based on the data slots that are required as arguments of this function. Apart of data arguments, this function can be specified with one additional (optional) argument `from_prior` of type `logical` and length one. This `from_prior` flag can be used to differentiate the output of the `modelspecs`, as its value is taken directly from the `from_prior` argument of the `mcmc` method that invokes `modelspecs` function. That is, when `from_prior` is `TRUE`, then only `priormodel` JAGS model is used (`datamodel` is not used) by the `mcmc`, and hence `modelspecs` function should return all the parameters that are required by the `priormodel` only. If the value of `from_prior` is `FALSE`, then both JAGS models `datamodel` and `priormodel` are used in the MCMC sampler, and hence `modelspecs` function should return all the parameters required by both `datamodel` and `priormodel`.

`init` (function)
: a function computing the list of starting values for parameters required to be initialized in the MCMC sampler, based on the data slots that are required as arguments of this function.

`datanames` (character)
: the names of all data slots that are used by `datamodel` JAGS function. No other names should be specified here.

`datanames_prior` (character)
: the names of all data slots that are used by `priormodel` JAGS function. No other names should be specified here.

`sample` (character)
: names of all parameters from which you would like to save the MCMC samples.

Note

The `datamodel` must obey the convention that the data input is called exactly in the same way as in the corresponding data class. All prior distributions for parameters should be contained in the model function `priormodel`. The background is that this can be used to simulate from the prior distribution, before obtaining any data.

Typically, end users will not use the `.DefaultGeneralModel()` function.

See Also

`ModelPseudo`.

GeneralSimulations-class GeneralSimulations

Description

[Stable]

This class captures trial simulations. Here also the random generator state before starting the simulation is saved, in order to be able to reproduce the outcome. For this just use `set.seed` with the seed as argument before running `simulate,Design-method`.

Usage

```
GeneralSimulations(data, doses, seed)

.DefaultGeneralSimulations()
```

Arguments

data	(list) see slot definition.
doses	(numeric) see slot definition.
seed	(integer) see slot definition.

Slots

`data` (`list`)
: produced `Data` objects.

`doses` (`numeric`)
: final dose recommendations.

`seed` (`integer`)
: random generator state before starting the simulation.

Note

Typically, end users will not use the `.DefaultGeneralSimulations()` function.

Examples

```
data <- list(
  Data(x = 1:3, y = c(0, 1, 0), doseGrid = 1:3, ID = 1L:3L, cohort = 1L:3L),
  Data(x = 4:6, y = c(0, 1, 0), doseGrid = 4:6, ID = 1L:3L, cohort = 1L:3L)
)

doses <- c(1, 2)

seed <- 123L

simulations <- GeneralSimulations(data, doses, seed)
```

GeneralSimulationsSummary-class
GeneralSimulationsSummary

Description

[Stable]

This class captures the summary of general simulations output. Note that objects should not be created by users, therefore no initialization function is provided for this class.

Usage

```
.DefaultGeneralSimulationsSummary()
```

Slots

`target` (`numeric`)
: target toxicity interval

`target_dose_interval` (`numeric`)
: corresponding target dose interval

`nsim` (`integer`)
: number of simulations

`prop_dlts` (`ANY`)
: A numeric array (multi-dimensional) or list representing proportions of DLTs in the trials

`mean_tox_risk` (`numeric`)
: mean toxicity risks for the patients

`dose_selected` (`numeric`)
: doses selected as MTD

`tox_at_doses_selected` (`numeric`)
: true toxicity at doses selected

`prop_at_target` (`numeric`)
: Proportion of trials selecting target MTD

`dose_most_selected` (`numeric`)
: dose most often selected as MTD

`obs_tox_rate_at_dose_most_selected` (`numeric`)
: observed toxicity rate at dose most often selected

`n_obs` (`ANY`)
: A numeric array (multi-dimensional) or list representing number of patients overall.

`n_above_target` (`integer`)
: number of patients treated above target tox interval

`dose_grid` (`numeric`)
: the dose grid that has been used

`placebo` (`logical`)
: set to TRUE (default is FALSE) for a design with placebo

`any_backfilled` (`flag`)
: indicates if any backfill cohorts were used

`n_backfill` (`ANY`)
: number of patients in backfill cohorts (only if `any_backfilled=TRUE`)

`backfill_doses` (`ANY`)
: list with doses used in backfill cohorts (only if `any_backfilled=TRUE`)

Note

Typically, end users will not use the `.DefaultGeneralSimulationsSummary()` function.

`get,Samples,character-method`
Get specific parameter samples and produce a data.frame

Description

Here you have to specify with `pos` which parameter you would like to extract from the Samples object

Usage

```
## S4 method for signature 'Samples,character'
get(x, pos = -1L, envir = NULL, mode = NULL, inherits = NULL)
```

Arguments

`x`	the Samples object
`pos`	the name of the parameter
`envir`	for vectorial parameters, you can give the indices of the elements you would like to extract. If `NULL`, the whole vector samples will be returned
`mode`	not used
`inherits`	not used

Value

the data frame suitable for use with `ggmcmc`

Examples

```
# nolint start

# Create some data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize a model
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Get posterior for all model parameters
options <- McmcOptions(burnin = 100, step = 2, samples = 2000)
```

```
set.seed(94)
samples <- mcmc(data, model, options)

# now extract the alpha0 samples (intercept of the regression model)
alpha0samples <- get(samples, "alpha0")

# nolint end
```

---

getEff *Extracting Efficacy Responses for Subjects Categorized by the DLT*

Description

[Stable]

A method that extracts efficacy responses for subjects and categorizes it with respect to DLT, i.e. DLT or no DLT. The efficacy responses are reported together with their corresponding dose levels.

Usage

```
getEff(object, ...)

## S4 method for signature 'DataDual'
getEff(object, no_dlt = FALSE)
```

Arguments

object	(DataDual) object from which the responses and dose levels are extracted.
...	further arguments passed to class-specific methods.
no_dlt	(flag) should only no DLT responses be returned? Otherwise, all responses are returned.

Value

list with efficacy responses categorized by the DLT value.

Examples

```
# Example data.
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25)
)

# Get the efficacy response and their corresponding dose levels
```

```
# categorized by the DLT.
getEff(data)
```

`get_arm_simulations` *Extract Arm-Level Simulations from Hierarchical Simulations*

Description

[Experimental]

Rebuilds the simulation object for one hierarchical arm, so that summary calculations can delegate to the existing `Simulations` or `ComboSimulations` methods.

Usage

```
get_arm_simulations(object, arm_name)
```

Arguments

`object`	(`HierarchicalSimulations`) hierarchical simulation results.
`arm_name`	(`string`) hierarchical arm name to extract.

Value

A `Simulations` object for a single-agent arm or a `ComboSimulations` object for a combination arm.

Examples

```
arm_data <- Data(
  x = c(10, 20),
  y = c(0L, 1L),
  doseGrid = c(10, 20),
  ID = 1L:2L,
  cohort = 1L:2L
)
hierarchical_sims <- HierarchicalSimulations(
  data = list(HierarchicalData(arm_a = arm_data)),
  doses = list(list(arm_a = 20)),
  samples = list(HierarchicalSamples(
    data = list(alpha0_arm_a = c(-3, -2)),
    options = McmcOptions(burnin = 1, step = 1, samples = 2),
    arm_samples = list(arm_a = c(alpha0 = "alpha0_arm_a"))
  )),
  fit = list(list(arm_a = data.frame(
    middle = c(0.1, 0.3),
    lower = c(0.05, 0.2),
    upper = c(0.2, 0.4)
```

```
  ))),
  stop_reasons = list(list(arm_a = "Minimum patients")),
  stop_report = list(list(arm_a = c(`Minimum patients` = TRUE))),
  additional_stats = list(list(arm_a = list())),
  seed = 123L
)

get_arm_simulations(hierarchical_sims, "arm_a")
```

`HierarchicalData-class` `HierarchicalData`

Description

[Experimental]

`HierarchicalData` is a class for hierarchical designs, storing the data for all arms together.

Usage

```
HierarchicalData(...)

.DefaultHierarchicalData()
```

Arguments

`...`	named `Data` objects, one for each arm in the trial. The argument names are used as the arm names.

Slots

`arms` (`list`)
: a named list of `Data` objects, one for each arm in the trial. The names of the list are the arm names.

Note

Typically, end users will not use the `.DefaultHierarchicalData()` function directly.

Examples

```
dat_hierarchical <- HierarchicalData(
  mono = .DefaultData(),
  combo = .DefaultDataCombo()
)
```

HierarchicalDesign-class
HierarchicalDesign

Description

[Experimental]

HierarchicalDesign stores a collection of named DesignArm objects and derives the corresponding HierarchicalData and HierarchicalModel objects from them.

Usage

```
HierarchicalDesign(
  ...,
  exchangeable_parameters = list(),
  pool_correlations = list(),
  pool_priors = list()
)

.DefaultHierarchicalDesign()
```

Arguments

...	DesignArm objects describing the trial arms. These can be created with DesignArm() or HistoricalArm().
exchangeable_parameters	(list) see HierarchicalModel().
pool_correlations	(list) see HierarchicalModel().
pool_priors	(list) see HierarchicalModel().

Slots

`arms` (list)
: a named list of DesignArm objects.

`data` (HierarchicalData)
: the hierarchical data object assembled from the arm-specific design data.

`model` (HierarchicalModel)
: the hierarchical model object assembled from the arm-specific design models.

Note

Typically, end users will not use the `.DefaultHierarchicalDesign()` function directly.

HierarchicalModel-class

HierarchicalModel

Description

[Experimental]

HierarchicalModel is a class for the prototype hierarchical model that links compatible single-agent binary outcome arms and/or TwoDrugsCombo arms.

Usage

```
HierarchicalModel(
  ...,
  exchangeable_parameters = list(),
  pool_correlations = list(),
  pool_priors = list()
)

.DefaultHierarchicalModel()
```

Arguments

...	named model objects describing the trial arms.
exchangeable_parameters	a named list describing which parameters are exchangeable across arms. This will be used to define the hierarchical structure of the model. Each list entry contains the arms as names and the parameters to be shared as a string.
pool_correlations	optional named list pairing exactly two scalar entries from exchangeable_parameters into a correlated bivariate hierarchy. Each pair must refer to indices 1 and 2 of the same latent parameter vector in every shared arm. Correlating three or more parameters in one multivariate hierarchy is not supported.
pool_priors	optional named list of hyperprior overrides for entries in exchangeable_parameters. Each entry may contain mu = c(mean, sd) and/or tau = c(meanlog, sdlog).

Details

The class currently stores the structural pieces from the design prototype as a named list of arm-specific models and a named list of exchangeable parameter pools used to dynamically compile a joint JAGS model.

Slots

models_to_arms (list)
: named list of arm-specific models. Each entry must be either a compatible single-agent binary outcome GeneralModel object using nObs, y, and x inputs, or a TwoDrugsCombo object.

`parameter_pools` (`list`)
: named list describing which parameters are exchangeable across arms. Each list entry contains arm names as names and parameter references as values.

`pool_correlations` (`list`)
: named list pairing exactly two scalar exchangeable parameter pools that should use a correlated bivariate normal hierarchy.

`pool_priors` (`list`)
: named list of pool-specific hyperprior overrides.

Note

Typically, end users will not use the `.DefaultHierarchicalModel()` function directly.

See Also

`HierarchicalData`, `TwoDrugsCombo`.

Examples

```
mono_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 10
)

combo_model <- TwoDrugsCombo(
  single_models = list(
    drug1 = LogisticLogNormal(
      mean = c(-0.85, 1),
      cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
      ref_dose = 10
    ),
    drug2 = LogisticLogNormal(
      mean = c(-0.7, 0.8),
      cov = matrix(c(1.1, -0.3, -0.3, 0.9), nrow = 2),
      ref_dose = 20
    )
  ),
  gamma = 0,
  tau = 1
)

my_model <- HierarchicalModel(
  my_mono = mono_model,
  my_combo = combo_model,
  exchangeable_parameters = list(
    mono_intercept = list(
      my_mono = "alpha0",
      my_combo = "alpha0[1]"
    ),
    mono_slope = list(
```

```
      my_mono = "alpha1",
      my_combo = "alpha1[1]"
    )
  )
)

my_model
```

`HierarchicalSamples-class` `HierarchicalSamples`

Description

[Experimental]

`HierarchicalSamples` stores posterior draws from a `HierarchicalModel` together with metadata that maps each hierarchical arm back to its arm-level sample names.

Usage

```
HierarchicalSamples(data, options, arm_samples)

.DefaultHierarchicalSamples()
```

Arguments

`data`	see slot definition.
`options`	see slot definition.
`arm_samples`	see slot definition.

Slots

`arm_samples` (`list`)
: named list with one entry per hierarchical arm. Each entry is a named character vector mapping arm-level parameter names such as `"alpha0"` to the corresponding sample names stored in `data`.

Note

Typically, end users will not use the `.DefaultHierarchicalSamples()` function directly.

HierarchicalSimulations-class
HierarchicalSimulations

Description

[Experimental]

This class captures trial simulations from hierarchical designs (HierarchicalDesign).

Usage

```
HierarchicalSimulations(
  data,
  doses,
  samples,
  fit,
  stop_reasons,
  stop_report,
  additional_stats,
  seed
)

.DefaultHierarchicalSimulations()
```

Arguments

data	(list) see slot definition.
doses	(list) see slot definition.
samples	(list) see slot definition.
fit	(list) see slot definition.
stop_reasons	(list) see slot definition.
stop_report	(list) see slot definition.
additional_stats	(list) see slot definition.
seed	(integer) see slot definition.

Slots

`data (list)`
: produced `HierarchicalData` objects.

`doses (list)`
: final dose recommendations, one named list per simulation run with entries for each hierarchical arm.

`samples (list)`
: final `HierarchicalSamples` objects.

`fit (list)`
: final arm-specific fits for each simulation run.

`stop_reasons (list)`
: arm-specific stopping reasons for each simulation run.

`stop_report (list)`
: arm-specific stopping rule outcomes for each simulation run.

`additional_stats (list)`
: additional arm-specific statistics.

`seed (integer)`
: random generator state before starting the simulation.

Note

Typically, end users will not use the `.DefaultHierarchicalSimulations()` function directly.

HierarchicalSimulationsSummary-class HierarchicalSimulationsSummary

---

Description

[Experimental]

This class captures arm-specific summaries from `HierarchicalSimulations` objects.

Usage

```
.DefaultHierarchicalSimulationsSummary()
```

Slots

`arms (list)`
: named list of arm-level simulation summary objects.

`nsim (integer)`
: number of simulations.

Note

Typically, end users will not use the `.DefaultHierarchicalSimulationsSummary()` function.

h_all_equivalent *Comparison with Numerical Tolerance and Without Name Comparison*

Description

[Experimental]

This helper function ensures a default tolerance level equal to `1e-10`, and ignores names and other attributes. In contrast to `all.equal()`, it always returns a logical type object.

Usage

```
h_all_equivalent(target, current, tolerance = 1e-10)
```

Arguments

`target`	(`numeric`) target values.
`current`	(`numeric`) current values.
`tolerance`	(`number`) relative differences smaller than this are not reported.

Value

`TRUE` when `target` and `current` do not differ up to desired tolerance and without looking at names or other attributes, `FALSE` otherwise.

h_blind_plot_data *Helper Function to Blind Plot Data*

Description

Helper Function to Blind Plot Data

Usage

```
h_blind_plot_data(df, blind, has_placebo, pbo_dose)
```

Arguments

df	(GeneralData) The data to be blinded
blind	(flag) Should the data be blinded?
has_placebo	(flag) Does the data contain a placebo dose?
pbo_dose	(positive_number) The dose to be taken as placebo. Ignored if has_placebo is FALSE

Value

The blinded data

---

h_calc_report_label_percentage

Helper function to calculate percentage of true stopping rules for report label output calculates true column means and converts output into percentages before combining the output with the report label; output is passed to show() *and output with cat to console*

Description

Helper function to calculate percentage of true stopping rules for report label output calculates true column means and converts output into percentages before combining the output with the report label; output is passed to show() and output with cat to console

Usage

```
h_calc_report_label_percentage(stop_report)
```

Arguments

stop_report	object from summary method

Value

named list with label and percentage of rule activation

h_check_fun_formals *Checking Formals of a Function*

Description

[Experimental]

This helper function checks whether a given function `fun` has required or allowed arguments. The argument check is based only on the names of the arguments. No any further logic is verified here.

Usage

```
h_check_fun_formals(fun, mandatory = NULL, allowed = NULL)
```

Arguments

`fun`	(`function`) a function name whose argument names will be checked.
`mandatory`	(`character` or `NULL`) the names of the arguments which must be present in `fun`. If `mandatory` is specified as `NULL` (default) this requirement is ignored.
`allowed`	(`character` or `NULL`) the names of the arguments which are allowed in `fun`. Names that do not belong to `allowed` are simply not allowed. The `allowed` parameter is independent from the `mandatory`, in a sense that if `mandatory` is specified as a `character` vector, it does not have to be repeated in `allowed`. If `allowed` is specified as `NULL` (default), then it means that there must be no any arguments in `fun` (except these ones which are specified in `mandatory`).

h_convert_ordinal_data *Convert a Ordinal Data to the Equivalent Binary Data for a Specific Grade*

Description

[Experimental]

A simple helper function that takes a `DataOrdinal` object and an integer grade and converts them to the equivalent `Data` object.

Usage

```
h_convert_ordinal_data(data_ord, grade)
```

Arguments

data_ord	(DataOrdinal) the DataOrdinal object to covert
grade	(integer) the toxicity grade for which the equivalent data is required.

Value

A Data object.

---

h_convert_ordinal_model

Convert an ordinal CRM model to the Equivalent Binary CRM Model for a Specific Grade

---

Description

[Experimental]

A simple helper function that takes a LogisticLogNormalOrdinal and an integer grade and converts them to the equivalent LogisticLogNormal model.

Usage

```
h_convert_ordinal_model(x, grade)
```

Arguments

x	(LogisticLogNormalOrdinal) the LogisticLogNormalOrdinal model to covert
grade	(integer) the toxicity grade for which the equivalent model is required.

Value

A LogisticLogNormal model.

h_convert_ordinal_samples

Convert a Samples Object from an ordinal Model to the Equivalent Samples Object from a Binary Model

Description

[Experimental]

A simple helper function that converts a `Samples` object from the fit of an ordinal CRM model to that which would have been obtained from fitting a binary CRM model for toxicities of a specified grade to the same observed data.

Usage

```
h_convert_ordinal_samples(obj, grade)
```

Arguments

`obj`	(`Samples`) the `Samples` object to covert
`grade`	(`integer`) the toxicity grade for which the equivalent data is required.

Value

A `Samples` object.

h_default_if_empty

Getting the default value for an empty object

Description

[Stable]

A simple helper function that sets a default value for an empty or missing object, that is an object for which `length()` function returns `0L` or it has length 1 and `is.na()` returns `TRUE`.

Usage

```
h_default_if_empty(x, default)
```

Arguments

`x`	(`any`) an object to handle. It can be any object for which `length()` function is defined.
`default`	(`any`) a default value for `x` object.

Examples

```
h_default_if_empty(character(0), default = "default label")
h_default_if_empty("custom label", default = "default label")
h_default_if_empty(NA, default = "default label")
```

`h_dose_combo_below_limit` *Check if the Doses in a Dose Matrix are Below the Dose Limit.*

Description

[Experimental]

Helper function that checks if the doses in a dose matrix are below the dose limit.

Usage

```
h_dose_combo_below_limit(dose_matrix, dose_limit)
```

Arguments

`dose_matrix`	(`matrix`) a matrix with the doses of the two compounds (columns).
`dose_limit`	(`matrix`) a matrix with two columns: the first column contains the doses for compound 1 and the second column contains the corresponding dose limits for compound 2.

Value

A logical vector indicating whether the doses in each row of the dose matrix are below the corresponding dose limits.

`h_eval_combo_truth` *Helper for Evaluating the True Toxicity Probability at a Dose Combination*

Description

[Experimental]

Evaluates the true toxicity probability at a given dose combination using the provided `truth` function. The `truth` function can be flexible in how it accepts the dose combination as input, and this helper tries different ways to call it in order to extract the toxicity probability.

Usage

```
h_eval_combo_truth(truth, dose_pair, ...)
```

Arguments

`truth`	(`function`) optional function mapping a dose combination to a toxicity probability. It can accept one argument (length-2 numeric vector or one-row matrix) or two numeric arguments (`drug1`, `drug2`).
`dose_pair`	(`numeric`) a length-2 numeric vector representing the dose combination for drug1 and drug2.
`...`	additional arguments passed to `truth`.

Value

A numeric value representing the true toxicity probability at the given dose combination, or `NA_real_` if it cannot be evaluated.

`h_find_interval` *Find Interval Numbers or Indices and Return Custom Number For 0.*

Description

[Stable]

A simple wrapper of `base::findInterval()` function that invokes `base::findInterval()`, takes its output and replaces all the elements with 0 value to a custom number as specified in `replacement` argument.

Usage

```
h_find_interval(..., replacement = -Inf)
```

Arguments

`...`	further arguments passed to `base::findInterval()` function.
`replacement`	(`number`) a custom number to be used as a replacement for 0. Default to `-Inf`.

Examples

```
h_find_interval(1, c(2, 4, 6))
h_find_interval(3, c(2, 4, 6))
h_find_interval(1, c(2, 4, 6), replacement = -1)
```

h_format_number *Conditional Formatting Using C-style Formats*

Description

[Experimental]

This helper function conditionally formats a number with `formatC()` function using `"E"` format and specific number of digits as given by the user. A number is formatted if and only if its absolute value is less than `0.001` or greater than `10000`. Otherwise, the number is not formatted. Additionally, custom prefix or suffix can be appended to character string with formatted number, so that the changes are marked.

Usage

```
h_format_number(x, digits = 5, prefix = "", suffix = "")
```

Arguments

`x`	(`number`) a number to be formatted.
`digits`	(`function`) the desired number of significant digits.
`prefix`	(`string`) a prefix to be added in front of the formatted number.
`suffix`	(`string`) a suffix to be appended after the formatted number.

Value

Either formatted `x` as `string` or unchanged `x` if the formatting condition is not met.

Note

This function was primarily designed as a helper for `h_jags_write_model()` function.

Examples

```
h_format_number(50000)
h_format_number(50000, prefix = "P", suffix = "S")
```

h_info_theory_dist *Calculating the Information Theoretic Distance*

Description

[Experimental]

Helper function which provides the value of the divergence as given by equation in (7) in the reference at https://doi.org/10.1002/sim.8450.

Usage

```
h_info_theory_dist(prob, target, asymmetry)
```

Arguments

prob	(numeric) vector or matrix with probabilities of a DLT occurring.
target	(number) single target probability of a DLT.
asymmetry	(number) describes the rate of penalization for overly toxic does, range 0 to 2.

Examples

```
h_info_theory_dist(c(0.5, 0.2), 0.4, 1.2)
```

h_in_range *Check which elements are in a given range*

Description

[Stable]

A simple helper function that tests whether elements of a given vector or matrix are within specified interval.

Usage

```
h_in_range(x, range = c(0, 1), bounds_closed = TRUE)
```

Arguments

x	(numeric) vector or matrix with elements to test.
range	(numeric) an interval, i.e. sorted two-elements vector.
bounds_closed	(logical) should bounds in the range be treated as closed? This can be a scalar or vector of length two. If it is a scalar, then its value applies to lower bound range[1] and upper bound range[2]. If this is a vector with two flags, the first flag corresponds to the lower bound only, and the second to the upper bound only.

Value

A logical vector or matrix of length equal to the length of x, that for every element of x, indicates whether a given element of x is in the range.

Examples

```
x <- 1:4
h_in_range(x, range = c(1, 3))
h_in_range(x, range = c(1, 3), bounds_closed = FALSE)
h_in_range(x, range = c(1, 3), bounds_closed = c(FALSE, TRUE))
mat <- matrix(c(2, 5, 3, 10, 4, 9, 1, 8, 7), nrow = 3)
h_in_range(mat, range = c(1, 5))
```

---

h_is_positive_definite

Testing Matrix for Positive Definiteness

Description

[Experimental]

This helper function checks whether a given numerical matrix x is a positive-definite square matrix of a given size, without any missing values. This function is used to test if a given matrix is a covariance matrix, since every symmetric positive semi-definite matrix is a covariance matrix.

Usage

```
h_is_positive_definite(x, size = 2, tol = 1e-06)
```

Arguments

x	(matrix) a matrix to be checked.
size	(integer) a size of the square matrix x to be checked against for.

tol (number)
a given tolerance number used to check whether an eigenvalue is positive or not. An eigenvalue is considered as positive if and only if it is greater than the tol.

Details

The positive definiteness test implemented in this function is based on the following characterization valid for real matrices: A symmetric matrix is positive-definite if and only if all of its eigenvalues are posi
In this function an eigenvalue is considered as positive if and only if it is greater than the tol.

Value

TRUE if a given matrix is a positive-definite, FALSE otherwise.

---

h_jags_add_dummy *Appending a Dummy Number for Selected Slots in Data*

Description

[Experimental]

A helper function that appends a dummy value to a given slots in GeneralData class object, if and only if the total number of observations (as indicated by object@nObs) equals to 1. Otherwise, the object is not changed.

Usage

```
h_jags_add_dummy(object, where, dummy = 0)
```

Arguments

object	(GeneralData) object into which dummy values will be added.
where	(character) names of slots in object to which a dummy number will be appended.
dummy	(number) a dummy number that will be appended to selected slots in object. Default to 0.

Value

A GeneralData object with slots updated with dummy number.

Note

The main motivation behind this function is related to the JAGS. If there is only one observation, the data is not passed correctly to JAGS, i.e. e.g. x and y are treated like scalars in the data file. Therefore it is necessary to add dummy values to the vectors in this case As we don't change the number of observations (nObs), this addition of zeros doesn't affect the results of JAGS computations.

Examples

```
# Create some data of class 'Data'
my_data <- Data(
  x = 0.1,
  y = 0,
  doseGrid = c(0.1, 0.5)
)

my_data_2 <- Data(
  x = c(0.1, 0.5),
  y = c(0, 1),
  doseGrid = c(0.1, 0.5)
)

# Append dummy to `x` and `y`.
h_jags_add_dummy(my_data, where = c("x", "y"))

# Append dummy to `x` and `y`. No effect as `my_data_2@nObs != 1`.
h_jags_add_dummy(my_data_2, where = c("x", "y"))
```

---

h_jags_extract_samples

Extracting Samples from JAGS mcarray *Object*

Description

[Stable]

A simple helper function that extracts a sample from `rjags::mcarray.object` S3 class object. The `rjags::mcarray.object` object is used by the `rjags::jags.samples()` function to represent MCMC output from a JAGS model.

Usage

```
h_jags_extract_samples(x)
```

Arguments

x	an `rjags::mcarray.object` object.

h_jags_get_data *Getting Data for* JAGS

Description

[Experimental]

A simple helper function that prepares an object for data argument of `rjags::jags.model()`, which is invoked by `mcmc()` method.

Usage

```
h_jags_get_data(model, data, from_prior)
```

Arguments

model	(GeneralModel) an input model.
data	(GeneralData) an input data.
from_prior	(flag) sample from the prior only? In this case data will not be appended to the output, i.e. only the variables required by the model@priormodel model will be returned in data.

Examples

```
# Create some data from the class `Data`.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

jags_data <- h_jags_get_data(my_model, my_data, from_prior = FALSE)
jags_data
```

h_jags_get_model_inits *Setting Initial Values for* JAGS *Model Parameters*

Description

[Experimental]

A simple helper function that prepares an object for `inits` argument of `rjags::jags.model()`, which is invoked by `mcmc()` method. The `inits` argument specifies initial values for model parameters.

Usage

```
h_jags_get_model_inits(model, data)
```

Arguments

`model`	(`GeneralModel`) an input model.
`data`	(`GeneralData`) an input data.

Value

A `list` of starting values for parameters required to be initialized in the MCMC JAGS sampler.

Examples

```
# Create some data from the class `Data`.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

h_jags_get_model_inits(model = my_model, data = my_data)
```

h_jags_join_models *Joining* JAGS *Models*

Description

[Stable]

This helper function joins two JAGS models in the way that the body of the second model is appended to the body of the first model (in this order). After that, the first, body-extended model is returned. The arguments of `model1`, `model2` model functions (if any) are not combined in any way.

Usage

```
h_jags_join_models(model1, model2)
```

Arguments

`model1`	(`function`) the first model to join.
`model2`	(`function`) the second model to join.

Value

joined models.

Note

`model1` and `model2` functions must have a multi-expression body, i.e. braced expression(s). Environments or any attributes of the function bodies are not preserved in any way after joining.

h_jags_write_model *Writing JAGS Model to a File*

Description

[Stable]

This function converts a R function with JAGS model into a text and then writes it into a given file. During the "model into text" conversion, the format of numbers of which absolute value is less than `0.001` or greater than `10000` is changed. These numbers will be converted into scientific format with specified number of significant digits using `formatC()` function.

Usage

```
h_jags_write_model(model, file = NULL, digits = 5)
```

Arguments

model	(function) function containing the JAGS model.
file	(string or NULL) the name of the file (including the optional path) where the model will be saved. If NULL, the file will be created in a R_crmPack folder placed under temporary directory indicated by tempdir() function.
digits	(count) a desired number of significant digits for for numbers used in JAGS input, see formatC().

Value

The name of the file where the model was saved.

Note

JAGS syntax allows truncation specification like dnorm(...) I(...), which is illegal in R. To overcome this incompatibility, use dummy operator \%_\% before I(...), i.e. dnorm(...) \%_\% I(...) in the model's code. This dummy operator \%_\% will be removed just before saving the JAGS code into a file. Due to technical issues related to conversion of numbers to scientific format, it is required that the body of a model function does not contain TEMP_NUM_PREF_ or _TEMP_NUM_SUF character constants in its body.

Examples

```
# Some model function
my_model <- function() {
  alpha0 <- mean(1:10)
  alpha1 <- 600000
}

h_jags_write_model(my_model, digits = 5)
```

---

h_model_dual_endpoint_beta

Update certain components of DualEndpoint *model with regard to parameters of the function that models dose-biomarker relationship defined in the* DualEndpointBeta *class.*

Description

[Stable]

A simple helper function that takes DualEndpoint object and updates use_fixed, priormodel, modelspecs, init, sample slots with regard to a given parameter of the dose-biomarker relationship $f(x)$ defined in the DualEndpointBeta class. This update solely depends on whether a given

parameter's value `param` is a fixed-valued scalar or two-elements numeric vector. In the later case, it is assumed that `param` represents two parameters of a probability distribution that will be used in `priormodel` function to generate values for the `param_name` parameter of $f(x)$. See the help page for `DualEndpointBeta` class for more details.

Usage

```
h_model_dual_endpoint_beta(
  param,
  param_name,
  param_suffix = c("_low", "_high"),
  priormodel = NULL,
  de
)
```

Arguments

`param`	(`numeric`) the value of a given `param_name` parameter of the dose-biomarker relationship function $f(x)$. Either a fixed-valued scalar or vector with two elements that are the parameters of a probability distribution that will be used in `priormodel` function to generate values for the `param_name` parameter of $f(x)$.
`param_name`	(`string`) the name of the parameter of $f(x)$, whose value depends on `param`.
`param_suffix`	(`character`) the two suffixes to be appended to the elements of `param_name` and then used when updating `modelspecs`. The value of this argument is ignored when `param` is a scalar.
`priormodel`	(`function` or `NULL`) a function representing the `JAGS` prior specification that will be appended to existing `de@priormodel` specification if `param` is not a scalar. Otherwise, `de@priormodel` remains unchanged.
`de`	(`DualEnpoint`) dual endpoint model whose slots will be updated.

Value

A `DualEndpoint` model with updated `use_fixed`, `priormodel`, `modelspecs`, `init`, `sample` slots.

`h_model_dual_endpoint_rho`

Update `DualEndpoint` class model components with regard to DLT and biomarker correlation.

Description

[Stable]

A simple helper function that takes `DualEndpoint` model existing components (`priormodel`, `modelspecs`, `init`, `sample`), and updates them with regard to DLT and biomarker correlation `rho`.

Usage

```
h_model_dual_endpoint_rho(use_fixed, rho, comp)
```

Arguments

`use_fixed`	(`flag`) indicates whether a fixed value for DLT and biomarker correlation `rho` should be used or not. If `rho` is not supposed to be a fixed value, a prior distribution from the scaled Beta family will be used. See the details below, under `rho` argument.
`rho`	(`numeric`) DLT and biomarker correlation. It must be either a fixed value (between `-1` and `1`), or a named vector with two elements, named `a` and `b` for the Beta prior on the transformation `kappa = (rho + 1) / 2`, which is in `(0, 1)`. For example, `a = 1, b = 1` leads to a uniform prior on `rho`.
`comp`	(`list`) a named list with model components that will be updated. The names should be: `priormodel`, `modelspecs`, `init`, `sample`. For definitions of the components, see `GeneralModel` class. The `modelspecs` and `init` components on `comp` list are specified up to the body of corresponding `GeneralModel@modelspecs` and `GeneralModel@init` functions. These bodies are simply a lists itself.

Value

A `list` with updated model components.

---

h_model_dual_endpoint_sigma2betaw

Update certain components of `DualEndpoint` model with regard to prior variance factor of the random walk.

Description

[Stable]

A simple helper function that takes `DualEndpoint` object and updates `priormodel`, `modelspecs`, `init`, `sample` slots according to the random walk variance.

Usage

```
h_model_dual_endpoint_sigma2betaw(use_fixed, sigma2betaW, de)
```

Arguments

use_fixed	(flag) indicates whether a fixed value for sigma2betaW should be used or not. If sigma2betaW is not supposed to be a fixed value, a prior distribution from the Inverse-Gamma distribution will be used. See the details below, under sigma2betaW argument.
sigma2betaW	(numeric) the prior variance factor of the random walk prior for the biomarker model. Either a fixed value or Inverse-Gamma distribution parameters, i.e. vector with two elements named a and b.
de	(DualEnpoint) dual endpoint model whose slots will be updated.

Value

A DualEndpoint model with updated priormodel, modelspecs, init, sample slots.

See Also

DualEndpointRW.

---

h_model_dual_endpoint_sigma2w

Update DualEndpoint class model components with regard to biomarker regression variance.

Description

[Stable]

A simple helper function that takes DualEndpoint model existing components (priormodel, modelspecs, init, sample), and updates them with regard to to biomarker regression variance sigma2W.

Usage

```
h_model_dual_endpoint_sigma2w(use_fixed, sigma2W, comp)
```

Arguments

use_fixed	(flag) indicates whether a fixed value for the biomarker regression variance sigma2W should be used or not. If sigma2W is not supposed to be a fixed value, a prior distribution from the Inverse-Gamma distribution will be used. See the details below, under sigma2W argument.
sigma2W	(numeric) the biomarker variance. Either a fixed value or Inverse-Gamma distribution parameters, i.e. vector with two elements named a and b.

comp (list)
a named list with model components that will be updated. The names should be: priormodel, modelspecs, init, sample. For definitions of the components, see GeneralModel class. The modelspecs and init components on comp list are specified up to the body of corresponding GeneralModel@modelspecs and GeneralModel@init functions. These bodies are simply a lists itself.

Value

list with updated model components.

---

h_next_best_eligible_doses

Get Eligible Doses from the Dose Grid.

Description

[Experimental]

Helper function that gets the eligible doses from the dose grid. The eligible doses are the doses which do not exceed a given doselimit. For placebo design, if safety allows (i.e. if there is at least one non-placebo dose which does not exceed the dose limit), the placebo dose is then excluded from the eligible doses.

Usage

```
h_next_best_eligible_doses(dose_grid, doselimit, placebo, levels = FALSE)
```

Arguments

dose_grid (numeric)
all possible doses.

doselimit (number)
the maximum allowed next dose.

placebo (flag)
if TRUE the first dose level in the dose_grid is considered as placebo.

levels (flag)
if TRUE the levels of eligible doses are returned, otherwise, the doses (default).

Value

A numeric vector with eligible doses or eligible dose levels if levels flag is TRUE.

Examples

```
dose_grid <- c(0.001, seq(25, 200, 25))
h_next_best_eligible_doses(dose_grid, 79, TRUE)
h_next_best_eligible_doses(dose_grid, 24, TRUE)
```

`h_next_best_mgsamples_plot` *Building the Plot for* `nextBest-NextBestMaxGainSamples` *Method.*

Description

[Experimental]

Helper function which creates the plot for `nextBest-NextBestMaxGainSamples()` method.

Usage

```
h_next_best_mgsamples_plot(
  prob_target_drt,
  dose_target_drt,
  prob_target_eot,
  dose_target_eot,
  dose_mg,
  dose_mg_samples,
  next_dose,
  doselimit,
  dose_grid_range
)
```

Arguments

`prob_target_drt`
(`proportion`)
target DLT probability during the trial.

`dose_target_drt`
(`number`)
target dose estimate during the trial.

`prob_target_eot`
(`proportion`)
target DLT probability at the end of the trial.

`dose_target_eot`
(`number`)
target dose estimate at the end of the trial.

`dose_mg` (`number`)
the dose corresponding to the maximum gain.

`dose_mg_samples`
(`numeric`)
for every sample, the dose (from the dose grid) that gives the maximum gain value.

`next_dose` (`number`)
next best dose.

doselimit (number)
the maximum allowed next dose.

dose_grid_range
(numeric)
dose grid range.

---

h_next_best_mg_ci *Credibility Intervals for Max Gain and Target Doses at* nextBest-NextBestMaxGain *Method.*

Description

[Experimental]

Helper function for nextBest-NextBestMaxGain() method. It computes a 95% credibility intervals for given target dose and max gain dose. It also returns a ratio of upper and lower bounds of the interval.

Usage

```
h_next_best_mg_ci(dose_target, dose_mg, prob_target, placebo, model, model_eff)
```

Arguments

dose_target (number)
target dose estimate.

dose_mg (number)
the dose corresponding to the maximum gain.

prob_target (proportion)
target DLT probability.

placebo (flag)
if TRUE the first dose level in the dose grid used is considered as placebo. This is needed to adjust the max gain dose using efficacy constant value. If the placebo was used, then the model_eff@const is added to dose_mg.

model (ModelTox)
the DLT model.

model_eff (Effloglog)
the efficacy model.

References

Yeung WY, Whitehead J, Reigner B, Beyer U, Diack C, Jaki T (2015). "Bayesian adaptive dose-escalation procedure for binary and continuous responses utilizing a gain function." *Pharmaceutical Statistics*. doi:10.1002/pst.1706. Published online ahead of print.

h_next_best_mg_doses_at_grid *Get Closest Grid Doses for a Given Target Doses for* nextBest-NextBestMaxGain *Method.*

Description

[Experimental]

Helper function that for a given target doses finds the dose in grid that is closest and below the target. There are four different targets in the context of nextBest-NextBestMaxGain() method: $min(`dose_mg`, `dose_target_drt`)$, dose_mg, dose_target_drt or dose_target_eot.

Usage

```
h_next_best_mg_doses_at_grid(
  dose_target_drt,
  dose_target_eot,
  dose_mg,
  dose_grid,
  doselimit,
  placebo
)
```

Arguments

dose_target_drt	(number) target dose estimate during the trial.
dose_target_eot	(number) target dose estimate at the end of the trial.
dose_mg	(number) the dose corresponding to the maximum gain.
dose_grid	(numeric) all possible doses.
doselimit	(number) the maximum allowed next dose.
placebo	(flag) if TRUE the first dose level in the dose_grid is considered as placebo.

`h_next_best_mg_plot` *Building the Plot for* `nextBest-NextBestMaxGain` *Method.*

Description

[Experimental]

Helper function which creates the plot for `nextBest-NextBestMaxGain()` method.

Usage

```
h_next_best_mg_plot(
  prob_target_drt,
  dose_target_drt,
  prob_target_eot,
  dose_target_eot,
  dose_mg,
  max_gain,
  next_dose,
  doselimit,
  data,
  model,
  model_eff
)
```

Arguments

`prob_target_drt` (`proportion`)
target DLT probability during the trial.

`dose_target_drt` (`number`)
target dose estimate during the trial.

`prob_target_eot` (`proportion`)
target DLT probability at the end of the trial.

`dose_target_eot` (`number`)
target dose estimate at the end of the trial.

`dose_mg` (`number`)
the dose corresponding to the maximum gain.

`max_gain` (`number`)
the maximum gain estimate.

`next_dose` (`number`)
next best dose.

doselimit (number)
the maximum allowed next dose.

data (DataDual)
the data object from which the dose grid will be fetched.

model (ModelTox)
the DLT model.

model_eff (Effloglog)
the efficacy model.

---

h_next_best_ncrm_loss_plot *Building the Plot for* nextBest-NextBestNCRMLoss *Method.*

Description

[Experimental]

Helper function which creates the plot for nextBest-NextBestNCRMLoss() method.

Usage

```
h_next_best_ncrm_loss_plot(
  prob_mat,
  posterior_loss,
  max_overdose_prob,
  dose_grid,
  max_eligible_dose_level,
  doselimit,
  next_dose,
  is_unacceptable_specified
)
```

Arguments

prob_mat (numeric)
matrix with probabilities of a grid doses to be in a given interval. If is_unacceptable_specified is TRUE, there must be 4 intervals (columns) in prob_mat: underdosing, target, excessive, unacceptable. Otherwise, there must be 3 intervals (columns): underdosing, target, overdose. Number of rows must be equal to number of doses in a grid.

posterior_loss (numeric)
posterior losses.

max_overdose_prob (number)
maximum overdose posterior probability that is allowed.

`dose_grid` (`numeric`)
dose grid.

`max_eligible_dose_level` (`number`)
maximum eligible dose level in the `dose_grid`.

`doselimit` (`number`)
the maximum allowed next dose.

`next_dose` (`number`)
next best dose.

`is_unacceptable_specified` (`flag`)
is unacceptable interval specified?

`h_next_best_tdsamples_plot` *Building the Plot for* `nextBest-NextBestTDsamples` *Method.*

Description

[Experimental]

Helper function which creates the plot for `nextBest-NextBestTDsamples()` method.

Usage

```
h_next_best_tdsamples_plot(
  dose_target_drt_samples,
  dose_target_eot_samples,
  dose_target_drt,
  dose_target_eot,
  dose_grid_range,
  nextBest,
  doselimit,
  next_dose
)
```

Arguments

`dose_target_drt_samples` (`numeric`)
vector of in-trial samples.

`dose_target_eot_samples` (`numeric`)
vector of end-of-trial samples.

`dose_target_drt` (`number`)
target in-trial estimate.

dose_target_eot
: (number)
target end-of-trial estimate.

dose_grid_range
: (numeric)
range of dose grid.

nextBest
: (NextBestTDsamples)
the rule for the next best dose.

doselimit
: (number)
the maximum allowed next dose.

next_dose
: (number)
next best dose.

`h_next_best_td_plot` *Building the Plot for* `nextBest-NextBestTD` *Method.*

Description

[Experimental]

Helper function which creates the plot for `nextBest-NextBestTD()` method.

Usage

```
h_next_best_td_plot(
  prob_target_drt,
  dose_target_drt,
  prob_target_eot,
  dose_target_eot,
  data,
  prob_dlt,
  doselimit,
  next_dose
)
```

Arguments

prob_target_drt
: (proportion)
target DLT probability during the trial.

dose_target_drt
: (number)
target dose estimate during the trial.

prob_target_eot
: (proportion)
target DLT probability at the end of the trial.

dose_target_eot
: (number)
target dose estimate at the end of the trial.

data
: (Data)
the data object from which the dose grid will be fetched.

prob_dlt
: (numeric)
DLT probabilities for doses in grid.

doselimit
: (number)
the maximum allowed next dose.

next_dose
: (number)
next best dose.

`h_null_if_na` *Getting* `NULL` *for* `NA`

Description

[Stable]

A simple helper function that replaces `NA` object by `NULL` object.

Usage

```
h_null_if_na(x)
```

Arguments

x
: (any)
atomic object of length `1`. For the definition of "atomic", see `is.atomic()`.

Value

`NULL` if `x` is `NA`, otherwise, `x`.

Examples

```
h_null_if_na(NA)
```

h_obtain_dose_grid_range

Helper Function Containing Common Functionality

Description

Used by dose_grid_range-Data and dose_grid_range-DataOrdinal

Usage

```
h_obtain_dose_grid_range(object, ignore_placebo)
```

Arguments

object	(Data or DataOrdinal) the object for which the dose grid range is required
ignore_placebo	(flag) should placebo dose (if any) not be counted?

h_plot_data_cohort_lines

Preparing Cohort Lines for Data Plot

Description

[Experimental]

This helper function prepares a ggplot geom with reference lines separating different cohorts on the plot of Data class object. Lines are either vertical or horizontal of green color and longdash type.

Usage

```
h_plot_data_cohort_lines(cohort, placebo, vertical = TRUE)
```

Arguments

cohort	(integer) the cohort indices.
placebo	(flag) is placebo included in the doses? If it so, this function returns NULL object as in this case all doses in a given cohort are equal and there is no need to separate them.
vertical	(flag) should the line be vertical? Otherwise it is horizontal.

Details

The geom object is returned if and only if `placebo` is equal to `TRUE` and there are more than one unique values in `cohort`. Otherwise, this function returns `NULL` object.

`h_plot_data_dataordinal` *Helper Function for the Plot Method of the Data and DataOrdinal Classes*

Description

[Stable]

A method that creates a plot for `Data` and `DataOrdinal` objects.

[Stable]

A method that creates a plot for `Data` object.

[Experimental]

A method that creates a plot for `DataOrdinal` object.

Usage

```
h_plot_data_dataordinal(
  x,
  blind = FALSE,
  legend = TRUE,
  tox_labels = c(Yes = "red", No = "black"),
  tox_shapes = c(Yes = 17L, No = 16L),
  mark_backfill = FALSE,
  ...
)

## S4 method for signature 'Data,missing'
plot(
  x,
  y,
  blind = FALSE,
  legend = TRUE,
  include_backfill = TRUE,
  mark_backfill = FALSE,
  mark_response = FALSE,
  ...,
  text_size_markings = 9,
  point_cex_markings = 1.1
)

## S4 method for signature 'DataOrdinal,missing'
```

```
plot(
  x,
  y,
  blind = FALSE,
  legend = TRUE,
  tox_labels = NULL,
  tox_shapes = NULL,
  ...
)
```

Arguments

x	(DataOrdinal) object we want to plot.
blind	(flag) indicates whether to blind the data. If TRUE, then placebo subjects are reported at the same level as the active dose level in the corresponding cohort, and DLTs are always assigned to the first subjects in a cohort.
legend	(flag) whether the legend should be added.
tox_labels	(named list of character) the labels of the toxicity categories.
tox_shapes	(names list of integers) the symbols used to identify the toxicity categories.
mark_backfill	(flag) whether to mark backfilled patients with empty shape.
...	not used.
y	(missing) missing object, for compatibility with the generic function.
include_backfill	(flag) whether to include backfilled patients.
mark_response	(flag) whether to mark patients with response with rectangle.
text_size_markings	(number) text size for the markings legend.
point_cex_markings	(number) point size multiplier for the markings legend.

Value

The ggplot2 object.

The ggplot2 object.

The ggplot2 object.

Note

The default values of `tox_shapes` and `tox_labels` result in DLTs being displayed as red triangles and other responses as black circles.

With more than 9 toxicity categories, toxicity symbols must be specified manually.
With more than 5 toxicity categories, toxicity labels must be specified manually.

Examples

```
# Create some data of class 'Data'.
my_data <- Data(
  x = c(0.001, 0.1, 0.1, 0.5, 0.001, 3, 3, 0.001, 10, 10, 10),
  y = c(0, 0, 1, 0, 0, 0, 1, 0, 0, 1, 0),
  cohort = c(1, 1, 1, 2, 3, 3, 3, 4, 4, 4, 4),
  doseGrid = c(0.001, 0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2)),
  placeb = TRUE
)

# Plot the data.
plot(my_data)

# We can also mark backfill patients and response outcomes.
my_data@backfilled <- c(
  FALSE,
  FALSE,
  FALSE,
  FALSE,
  TRUE,
  TRUE,
  TRUE,
  FALSE,
  FALSE,
  FALSE,
  FALSE
)
my_data@response <- as.integer(c(
  NA,
  NA,
  1,
  NA,
  NA,
  0,
  1,
  NA,
  1,
  0,
  0
))
plot(
  my_data,
  mark_backfill = TRUE,
  mark_response = TRUE
```

```
)
data <- DataOrdinal(
  x = c(10, 20, 30, 40, 50, 50, 50, 60, 60, 60),
  y = as.integer(c(0, 0, 0, 0, 0, 1, 0, 0, 1, 2)),
  ID = 1L:10L,
  cohort = as.integer(c(1:4, 5, 5, 5, 6, 6, 6)),
  doseGrid = c(seq(from = 10, to = 100, by = 10)),
  yCategories = c("No tox" = 0L, "Sub-tox AE" = 1L, "DLT" = 2L),
  placebo = FALSE
)

plot(data)
```

`h_plot_data_df` *Preparing Data for Plotting*

Description

[Experimental]

This helper function prepares a `data.frame` object based on `Data` class object. The resulting data frame is used by the plot function for `Data` class objects.

[Experimental]

A method that transforms `GeneralData` objects into a `tibble` suitable for plotting with `ggplot2` methods

Usage

```
h_plot_data_df(data, ...)

h_plot_data_df(data, ...)

## S4 method for signature 'Data'
h_plot_data_df(data, blind = FALSE, legend = TRUE, ...)

## S4 method for signature 'DataOrdinal'
h_plot_data_df(data, blind = FALSE, legend = TRUE, ...)
```

Arguments

`data`	(`Data`) object from which data is extracted and converted into a data frame.
`...`	further arguments passed to `data.frame` constructor. It can be e.g. an extra `column_name = value` pair based on a slot from `x` (which in this case might be a subclass of `Data`) which does not appear in `Data`.
`blind`	(`flag`) should data be blinded? If `TRUE`, then for each cohort, all DLTs are assigned to the first subjects in the cohort. In addition, the placebo (if any) is set to the active dose level for that cohort.

legend (flag)
Display the legend for the toxicity categories

Value

A data.frame object with values to plot.

data.frame containing columns for patient, cohort, dose and toxicity grade

A data.frame object with columns patient, ID, cohort, dose and toxicity.

Methods (by class)

- h_plot_data_df(Data): method for Data.
- h_plot_data_df(DataOrdinal): Class specific method for DataOrdinal

---

h_rapply *Recursively Apply a Function to a List*

Description

[Experimental]

This helper function recursively iterates through a "list-like" object and it checks whether an element is of a given class. If it so, then it replaces that element by the result of an execution of a given function. Otherwise, and if the element is of length greater than 1 (i.e. not a scalar), it replaces that element by the result of h_rapply(), recursively called for that element. In the remaining case, that is, the element is not of a given class and is a scalar, then that element remains unchanged.

Usage

```
h_rapply(x, fun, classes, ...)
```

Arguments

x	(any) "list-like" object for which subsetting operator [[is defined.
fun	(function) a function of one "principal" argument, passing further arguments via ....
classes	(character) class names.
...	further arguments passed to function fun.

Value

"list-like" object of similar structure as x.

Note

This helper function is conceptually similar the same as rapply() function. However, it differs from rapply() in two major ways. First, the h_rapply() is not limited to objects of type list or expression only. It can be any "list-like" object of any type for which subsetting operator [[is defined. This can be, for example, an object of type language, often obtained from the body() function. The second difference is that the flexibility of rapply() on how the result is structured is not available with h_rapply() for the user. That is, with h_rapply() each element of x, which has a class included in classes, is replaced by the result of applying fun to the element. This behavior corresponds to rapply() when invoked with fixed how = replace. This function was primarily designed as a helper for h_jags_write_model() function.

Examples

```
# Some model function.
my_model <- function() {
  alpha0 <- mean(1:10)
  alpha1 <- 600000
}

# Replace format of numbers using `formatC` function.
h_rapply(
  x = body(my_model),
  fun = formatC,
  classes = c("integer", "numeric"),
  digits = 3,
  format = "E"
)
```

---

h_slots *Getting the Slots from a S4 Object*

Description

[Experimental]

This helper function extracts requested slots from the S4 class object. It is a simple wrapper of methods::slot() function.

Usage

```
h_slots(object, names, simplify = FALSE)
```

Arguments

object	(S4) an object from a formally defined S4 class.
names	(character) a vector with names of slots to be fetched. This function assumes that for every element in names, there exists a slot of the same name in the object.

simplify (flag)
should an output be simplified? This has an effect if and only if a single slot is about to be extracted, i.e. names is just a single string.

Value

list with the slots extracted from object according to names, or single slot if simplification is required and possible.

---

h_summarize_add_stats *Helper function to calculate average across iterations for each additional reporting parameter extracts parameter names as specified by user and averaged the values for each specified parameter to show() and output with cat to console*

Description

Helper function to calculate average across iterations for each additional reporting parameter extracts parameter names as specified by user and averaged the values for each specified parameter to show() and output with cat to console

Usage

```
h_summarize_add_stats(stats_list)
```

Arguments

stats_list object from simulation with nested parameter values (sublist for each parameter)

Value

list of parameter names and averaged values for console output

---

h_test_named_numeric *Check that an argument is a named vector of type numeric*

Description

[Stable]

A simple helper function that tests whether an object is a named numerical vector.

Usage

```
h_test_named_numeric(
  x,
  subset.of = NULL,
  must.include = NULL,
  permutation.of = NULL,
  identical.to = NULL,
  disjunct.from = NULL,
  lower = 0 + .Machine$double.xmin,
  finite = TRUE,
  any.missing = FALSE,
  len = 2,
  ...
)
```

Arguments

x	(any) object to check.
subset.of	[character] Names provided in x must be subset of the set subset.of.
must.include	[character] Names provided in x must be a superset of the set must.include.
permutation.of	[character] Names provided in x must be a permutation of the set permutation.of. Duplicated names in permutation.of are stripped out and duplicated names in x thus lead to a failed check. Use this argument instead of identical.to if the order of the names is not relevant.
identical.to	[character] Names provided in x must be identical to the vector identical.to. Use this argument instead of permutation.of if the order of the names is relevant.
disjunct.from	[character] Names provided in x must may not be present in the vector disjunct.from.
lower	[numeric(1)] Lower value all elements of x must be greater than or equal to.
finite	[logical(1)] Check for only finite values? Default is FALSE.
any.missing	[logical(1)] Are vectors with missing values allowed? Default is TRUE.
len	[integer(1)] Exact expected length of x.
...	further parameters passed to checkmate::test_numeric().

Value

TRUE if x is a named vector of type numeric, otherwise FALSE.

Note

This function is based on checkmate::test_numeric() and checkmate::test_names() functions.

Examples

```
h_test_named_numeric(1:2, permutation.of = c("a", "b"))
h_test_named_numeric(c(a = 1, b = 2), permutation.of = c("a", "b"))
h_test_named_numeric(c(a = 1, b = 2), permutation.of = c("b", "a"))
```

---

h_unpack_stopit *Helper function to recursively unpack stopping rules and return lists with logical value and label given*

Description

Helper function to recursively unpack stopping rules and return lists with logical value and label given

Usage

```
h_unpack_stopit(stopit_tree)
```

Arguments

stopit_tree	object from simulate method

Value

named list

---

h_validate_combine_results *Combining S4 Class Validation Results*

Description

[Experimental]

A simple helper function that combines two outputs from calls to result() function which is placed in a slot of Validate() reference class.

Usage

```
h_validate_combine_results(v1, v2)
```

Arguments

v1	(logical or character) an output from result() function from Validate() reference class, to be combined with v2.
v2	(logical or character) an output from result() function from Validate() reference class, to be combined with v1.

Examples

```
h_validate_combine_results(TRUE, "some_message")
```

---

h_validate_common_data_slots

Helper Function performing validation Common to Data and DataOrdinal

---

Description

Helper Function performing validation Common to Data and DataOrdinal

Usage

```
h_validate_common_data_slots(object)
```

Arguments

object	(Data or DataOrdinal) the object to be validated

Value

a Validate object containing the result of the validation

Increments-class Increments

Description

[Stable]

Increments is a virtual class for controlling increments, from which all other specific increments classes inherit.

Usage

```
.DefaultIncrements()
```

Note

Typically, end users will not use the `.DefaultIncrements()` function.

See Also

`IncrementsRelative`, `IncrementsRelativeDLT`, `IncrementsDoseLevels`, `IncrementsHSRBeta`, `IncrementsMin`.

IncrementsComboCartesian-class IncrementsComboCartesian

Description

[Experimental]

`IncrementsComboCartesian` is the class for increments control in combination trials where separate increment rules are defined for each drug and applied independently.

Usage

```
IncrementsComboCartesian(drug1, drug2)

.DefaultIncrementsComboCartesian()
```

Arguments

`drug1`	(`Increments`) see slot definition.
`drug2`	(`Increments`) see slot definition.

Details

Under this rule, the maximum admissible dose for each drug is first computed from the corresponding one-dimensional increment rule. The resulting two-dimensional admissible region is then represented in a matrix form compatible with combination `maxDose` methods.

Slots

`drug1` (`Increments`) increment rule for the first drug.

`drug2` (`Increments`) increment rule for the second drug.

Note

Typically, end users will not use the `.DefaultIncrementsComboCartesian()` function.

Examples

```
# Create independent increment rules for each drug in a two-drug combination
# trial.
drug1_rule <- IncrementsRelative(intervals = c(0, 20), increments = c(1, 0.33))
drug2_rule <- IncrementsRelative(intervals = c(0, 20), increments = c(1, 0.33))

# Combine the one-dimensional rules into a Cartesian combination rule.
my_increments <- IncrementsComboCartesian(
  drug1 = drug1_rule,
  drug2 = drug2_rule
)
```

IncrementsComboOneDrugOnly-class
IncrementsComboOneDrugOnly

Description

[Stable]

IncrementsComboOneDrugOnly is the class for increments control in combination trials when only one drug is allowed to be escalated.

Usage

```
IncrementsComboOneDrugOnly()

.DefaultIncrementsComboOneDrugOnly()
```

Details

Under this rule, when escalating drug 1 to a dose above the last administered drug 1 dose, drug 2 must remain at or below its last administered dose, and vice versa. In other words, at most one drug may be escalated in any given cohort. No parameters are required; the rule is fully defined by the "one drug only" principle.

Note

Typically, end users will not use the `.DefaultIncrementsComboOneDrugOnly()` function.

Examples

```
# Create a rule that allows escalation of only one drug at a time in a
# two-drug combination trial.
my_increments <- IncrementsComboOneDrugOnly()
```

IncrementsDoseLevels-class
IncrementsDoseLevels

Description

[Stable]

IncrementsDoseLevels is the class for increments control based on the number of dose levels.

Usage

```
IncrementsDoseLevels(levels = 1L, basis_level = "last")

.DefaultIncrementsDoseLevels()
```

Arguments

levels	(count) see slot definition.
basis_level	(string) see slot definition.

Slots

`levels` (count)
: maximum number of dose levels to increment for the next dose. It defaults to 1, which means that no dose skipping is allowed, i.e. the next dose can be maximum one level higher than the current base dose. The current base dose level is the dose level used to increment from (see `basis_level` parameter).

`basis_level` (string)
: defines the current base dose level. It can take one out of two possible values: `last` or `max`. If `last` is specified (default), the current base dose level is set to the last dose given. If `max` is specified, then the current base dose level is set to the maximum dose level given.

Note

Typically, end users will not use the `.DefaultIncrementsDoseLevels()` function.

Examples

```
# The rule for dose increments which allows for maximum skip one dose level,
# that is 2 dose levels higher than the last dose given.
my_increments <- IncrementsDoseLevels(levels = 2, basis_level = "last")
```

IncrementsHSRBeta-class

IncrementsHSRBeta

Description

[Experimental]

IncrementsHSRBeta is a class for limiting further increments using a Hard Safety Rule based on the Bin-Beta model. Increment control is based on the number of observed DLTs and number of subjects at each dose level. The probability of toxicity is calculated using a Bin-Beta model with prior (a,b). If the probability exceeds the threshold for a given dose, that dose and all doses above are excluded from further escalation. This is a hard safety rule that limits further escalation based on the observed data per dose level, independent from the underlying model.

Usage

```
IncrementsHSRBeta(target = 0.3, prob = 0.95, a = 1, b = 1)

.DefaultIncrementsHSRBeta()
```

Arguments

target	(proportion) see slot definition.
prob	(proportion) see slot definition.
a	(number) see slot definition.
b	(number) see slot definition.

Slots

target (proportion)
: the target toxicity, except 0 or 1.

prob (proportion)
: the threshold probability (except 0 or 1) for a dose being toxic.

a (number)
: shape parameter $a > 0$ of probability distribution Beta (a,b).

b (number)
: shape parameter $b > 0$ of probability distribution Beta (a,b).

Note

Typically, end users will not use the .DefaultIncrementsHSRBeta() function.

Examples

```
# Limit the escalation with a hard safety criteria to the doses that are below
# the first dose that is toxic with a probability of 0.95.
my_increments <- IncrementsHSRBeta(target = 0.3, prob = 0.95)
```

IncrementsMaxToxProb-class
IncrementsMaxToxProb

Description

[Experimental]

IncrementsMaxToxProb is the class for increments control based on probability of toxicity

Usage

```
IncrementsMaxToxProb(prob)

.DefaultIncrementsMaxToxProb()
```

Arguments

prob	(numeric) see slot definition.

Slots

prob (numeric)
: See Usage Notes below.

Usage Notes

For binary models, prob should be a scalar probability.

For ordinal models, prob should be a named vector containing the maximum permissible probability of toxicity by grade. The names should match the names of the yCategories slot of the associated DataOrdinal object.

Note

Typically, end users will not use the .DefaultIncrementsMaxToxProb() function.

Examples

```
# For use with binary models and data
IncrementsMaxToxProb(prob = 0.35)

# For use with ordinal models and data
IncrementsMaxToxProb(prob = c("DLAE" = 0.2, "DLT" = 0.05))
```

IncrementsMin-class IncrementsMin

Description

[Stable]

IncrementsMin is the class that combines multiple increment rules with the minimum operation. Slot increments_list contains all increment rules, which are itself the objects of class Increments. The minimum of these individual increments is taken to give the final maximum increment.

Usage

```
IncrementsMin(increments_list)

.DefaultIncrementsMin()
```

Arguments

increments_list	(list) see slot definition.

Slots

increments_list (list)
: list with increment rules.

Note

Typically, end users will not use the .DefaultIncrementsMin() function.

Examples

```
# As example, here we are combining 2 different increment rules.

# The first rule is the following:
# maximum doubling the dose if no DLTs were observed at the current dose
# or maximum increasing the dose by 1.33 if 1 or 2 DLTs were observed at the current dose
# or maximum increasing the dose by 1.22 if 3 or more DLTs were observed.
my_increments_1 <- IncrementsRelativeDLT(
  intervals = c(0, 1, 3),
  increments = c(1, 0.33, 0.2)
)

# The second rule is the following:
# maximum doubling the dose if the current dose is <20
# or only maximum increasing the dose by 1.33 if the current dose is >=20.
my_increments_2 <- IncrementsRelative(
  intervals = c(0, 20),
```

```
  increments = c(1, 0.33)
)

# Now we combine the 2 rules.
comb_increments <- IncrementsMin(
  increments_list = list(my_increments_1, my_increments_2)
)
```

`IncrementsOrdinal-class` `IncrementsOrdinal`

Description

[Experimental]

`IncrementsOrdinal` is the class for applying a standard `Increments` rule to the results of an ordinal CRM trial.

Usage

```
IncrementsOrdinal(grade, rule)

.DefaultIncrementsOrdinal()
```

Arguments

`grade`	(`numeric`) see slot definition.
`rule`	(`Increments`) see slot definition.

Slots

`grade` (`integer`)
: the toxicity grade to which the `rule` should be applied.

`rule` (`Increments`)
: the standard `Increments` rule to be applied

Note

Typically, end users will not use the `.DefaultIncrementsOrdinal()` function.

Examples

```
IncrementsOrdinal(
  grade = 1L,
  rule = IncrementsRelative(
    intervals = c(0, 20),
    increments = c(1, 0.33)
  )
)
```

IncrementsRelative-class

IncrementsRelative

Description

[Stable]

IncrementsRelative is the class for increments control based on relative differences in intervals.

Usage

```
IncrementsRelative(intervals, increments)

.DefaultIncrementsRelative()
```

Arguments

intervals	(numeric) see slot definition.
increments	(numeric) see slot definition.

Slots

`intervals` (numeric)
: a vector with the left bounds of the relevant intervals. For example, `intervals = c(0, 50, 100)` specifies three intervals: $(0, 50)$, $[50, 100)$ and $[100, +Inf)$. That means, the right bound of the intervals are exclusive to the interval and the last interval goes from the last value to infinity.

`increments` (numeric)
: a vector of the same length with the maximum allowable relative increments in the `intervals`.

Note

Typically, end users will not use the `.DefaultIncrementsRelative()` function.

Examples

```
# This is the example of a rule for:
# maximum doubling the dose if the current dose is <20
# or only maximum increasing the dose by 1.33 if the current dose is >=20.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
```

IncrementsRelativeDLT-class
IncrementsRelativeDLT

Description

[Stable]

IncrementsRelativeDLT is the class for increments control based on relative differences in terms of DLTs.

Usage

```
IncrementsRelativeDLT(intervals, increments)

.DefaultIncrementsRelativeDLT()
```

Arguments

intervals	(numeric) see slot definition.
increments	(numeric) see slot definition.

Slots

`intervals` (integer)
: a vector with the left bounds of the relevant DLT intervals. For example, `intervals = c(0, 1, 3)` specifies three intervals (sets of DLTs: first, 0 DLT; second 1 or 2 DLTs; and the third one, at least 3 DLTs. That means, the right bound of the intervals are exclusive to the interval and the last interval goes from the last value to infinity.

`increments` (numeric)
: a vector of maximum allowable relative increments corresponding to `intervals`. IT must be of the same length as the length of `intervals`.

Note

This considers all DLTs across all cohorts observed so far.

Typically, end users will not use the `.DefaultIncrementsRelativeDLT()` function.

See Also

IncrementsRelativeDLTCurrent which only considers the DLTs in the current cohort.

Examples

```
# This is the example of a rule for:
# maximum doubling the dose if no DLTs were observed in the whole study so far
# or maximum increasing the dose by 1.33 if 1 or 2 DLTs were observed so far
# or maximum increasing the dose by 1.22 if 3 or more DLTs were observed so far.
my_increments <- IncrementsRelativeDLT(
  intervals = c(0, 1, 3),
  increments = c(1, 0.33, 0.2)
)
```

IncrementsRelativeDLTCurrent-class
IncrementsRelativeDLTCurrent

Description

[Experimental]

IncrementsRelativeDLTCurrent is the class for increments control based on relative differences and current DLTs. The class is based on the number of DLTs observed in the current cohort, but not cumulatively over all cohorts so far.

Usage

```
IncrementsRelativeDLTCurrent(intervals = c(0L, 1L), increments = c(2L, 1L))

.DefaultIncrementsRelativeDLTCurrent()
```

Arguments

intervals	(numeric) see slot definition.
increments	(numeric) see slot definition.

Note

Typically, end users will not use the .DefaultIncrementsRelativeDLTCurrent() function.

See Also

IncrementsRelativeDLT.

Examples

```
# As example, here is the rule for:
# maximum doubling the dose if no DLTs were observed at the current dose
# or maximum increasing the dose by 1.33 if 1 or 2 DLTs were observed at the current dose
# or maximum increasing the dose by 1.22 if 3 or more DLTs were observed.

my_increments <- IncrementsRelativeDLTCurrent(
  intervals = c(0, 1, 3),
  increments = c(1, 0.33, 0.2)
)
```

IncrementsRelativeParts-class

IncrementsRelativeParts

Description

[Stable]

IncrementsRelativeParts is the class for increments control based on relative differences in intervals, with special rules for part 1 and beginning of part 2.

Usage

```
IncrementsRelativeParts(dlt_start, clean_start, ...)

.DefaultIncrementsRelativeParts()
```

Arguments

dlt_start	(count) see slot definition.
clean_start	(count) see slot definition.
...	Arguments passed on to IncrementsRelative intervals (numeric) see slot definition. increments (numeric) see slot definition.

Details

This class works only in conjunction with DataParts objects. If part 2 will just be started in the next cohort, then the next maximum dose will be either dlt_start (e.g. -1) shift of the last part 1 dose in case of a DLT in part 1, or clean_start shift (e.g. -1) in case of no DLTs in part 1, given that clean_start <= 0 (see description of clean_start slot for more details). If part 1 will still be on in the next cohort, then the next dose level will be the next higher dose level in the part1Ladder slot of the data object. If part 2 has been started before, the usual relative increment rules apply, see IncrementsRelative.

Slots

`dlt_start (integer)`
: a scalar, the dose level increment for starting part 2 in case of at least one DLT event in part 1.

`clean_start (integer)`
: a scalar, the dose level increment for starting part 2 in case of no DLTs in part 1. If `clean_start <= 0`, then the part 1 ladder will be used to find the maximum next dose. Otherwise, the relative increment rules will be applied to find the next maximum dose level.

Note

We require that `clean_start >= dlt_start`. However, this precondition is not a prerequisite for any function (except of the class' validation function) that works with objects of this class. It is rather motivated by the semantics. That is, if we observe a DLT in part 1, we cannot be more aggressive than in case of a clean part 1 without DLT.

Typically, end users will not use the `.DefaultIncrementsRelativeParts()` function.

Examples

```
my_increments <- IncrementsRelativeParts(dlt_start = 0, clean_start = 1)
```

---

knit_print.Backfill *Render a* CohortSizeConst *Object*

Description

[Experimental]

[Experimental]

We provide additional utility functions to allow human-friendly rendition of crmPack objects in Markdown and Quarto files

[Experimental]

[Experimental]

[Experimental]

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[Experimental]

[Experimental]

We provide additional utility functions to allow human-friendly rendition of crmPack objects in Markdown and Quarto files. This file contains methods for all design classes, not just those that are direct descendants of `Design`.

[Experimental]

[Experimental]

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We provide additional utility functions to allow human-friendly rendition of crmPack objects in Markdown and Quarto files

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Usage

```
## S3 method for class 'Backfill'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'CohortSizeConst'
knit_print(x, ..., asis = TRUE, label = c("participant", "participants"))

## S3 method for class 'CohortSizeRange'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'CohortSizeDLT'
knit_print(x, ..., tox_label = "toxicity", asis = TRUE)

## S3 method for class 'CohortSizeParts'
knit_print(x, ..., asis = TRUE, label = c("participant", "participants"))

## S3 method for class 'CohortSizeMax'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'CohortSizeMin'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'CohortSizeOrdinal'
knit_print(x, ..., tox_label = "toxicity", asis = TRUE)

## S3 method for class 'CohortSizeRandom'
knit_print(x, ..., asis = TRUE, label = c("participant", "participants"))

## S3 method for class 'StartingDose'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'RuleDesign'
knit_print(x, ..., level = 2L, title = "Design", sections = NA, asis = TRUE)

## S3 method for class 'Design'
knit_print(x, ..., level = 2L, title = "Design", sections = NA, asis = TRUE)
```

```
## S3 method for class 'DesignCombo'
knit_print(x, ..., level = 2L, title = "Design", sections = NA, asis = TRUE)

## S3 method for class 'DualDesign'
knit_print(x, ..., level = 2L, title = "Design", sections = NA, asis = TRUE)

## S3 method for class 'DADesign'
knit_print(x, ..., level = 2L, title = "Design", sections = NA, asis = TRUE)

## S3 method for class 'TDDesign'
knit_print(x, ..., level = 2L, title = "Design", sections = NA, asis = TRUE)

## S3 method for class 'DualResponsesDesign'
knit_print(x, ..., level = 2L, title = "Design", sections = NA, asis = TRUE)

## S3 method for class 'DesignOrdinal'
knit_print(x, ..., level = 2L, title = "Design", sections = NA, asis = TRUE)

## S3 method for class 'DesignGrouped'
knit_print(
  x,
  ...,
  level = 2L,
  title = "Design",
  sections = c(model = "Dose toxicity model", mono = "Monotherapy rules", combo =
    "Combination therapy rules", other = "Other details"),
  asis = TRUE
)

## S3 method for class 'TDsamplesDesign'
knit_print(x, ..., level = 2L, title = "Design", sections = NA, asis = TRUE)

## S3 method for class 'DualResponsesDesign'
knit_print(x, ..., level = 2L, title = "Design", sections = NA, asis = TRUE)

## S3 method for class 'DualResponsesSamplesDesign'
knit_print(x, ..., level = 2L, title = "Design", sections = NA, asis = TRUE)

## S3 method for class 'RuleDesignOrdinal'
knit_print(x, ..., level = 2L, title = "Design", sections = NA, asis = TRUE)

## S3 method for class 'GeneralData'
knit_print(
  x,
  ...,
  asis = TRUE,
  label = c("participant", "participants"),
  full_grid = FALSE,
```

```
  summarise = c("none", "dose", "cohort"),
  summarize = summarise,
  units = NA,
  format_func = h_knit_format_func
)

## S3 method for class 'DataParts'
knit_print(
  x,
  ...,
  asis = TRUE,
  label = c("participant", "participants"),
  full_grid = FALSE,
  summarise = c("none", "dose", "cohort"),
  summarize = summarise,
  units = NA,
  format_func = h_knit_format_func
)

## S3 method for class 'DataCombo'
knit_print(
  x,
  ...,
  asis = TRUE,
  label = c("participant", "participants"),
  units = NA,
  fmt = NA
)

## S3 method for class 'DualEndpoint'
knit_print(
  x,
  ...,
  asis = TRUE,
  use_values = TRUE,
  fmt = "%5.2f",
  units = NA,
  tox_label = "toxicity",
  biomarker_label = "PD biomarker"
)

## S3 method for class 'ModelParamsNormal'
knit_print(
  x,
  use_values = TRUE,
  fmt = "%5.2f",
  params = c("alpha", "beta"),
  preamble = "The prior for &theta; is given by\\n",
```

```
  asis = TRUE,
  theta = "\\theta",
  ...
)

## S3 method for class 'GeneralModel'
knit_print(
  x,
  ...,
  params = c("alpha", "beta"),
  asis = TRUE,
  use_values = TRUE,
  fmt = "%5.2f",
  units = NA
)

## S3 method for class 'HierarchicalModel'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'LogisticKadane'
knit_print(
  x,
  ...,
  asis = TRUE,
  use_values = TRUE,
  fmt = "%5.2f",
  units = NA,
  tox_label = "toxicity"
)

## S3 method for class 'LogisticKadaneBetaGamma'
knit_print(
  x,
  ...,
  asis = TRUE,
  use_values = TRUE,
  fmt = "%5.2f",
  tox_label = "toxicity",
  units = NA
)

## S3 method for class 'LogisticLogNormal'
knit_print(
  x,
  ...,
  use_values = TRUE,
  fmt = "%5.2f",
  params = c(`\\alpha` = "alpha", `log(\\beta)` = "beta"),
```

```
  preamble = "The prior for &theta; is given by\\n",
  asis = TRUE
)

## S3 method for class 'LogisticLogNormalMixture'
knit_print(x, ..., asis = TRUE, use_values = TRUE, fmt = "%5.2f", units = NA)

## S3 method for class 'LogisticLogNormalSub'
knit_print(
  x,
  ...,
  use_values = TRUE,
  fmt = "%5.2f",
  params = c(`\\alpha` = "alpha", `log(\\beta)` = "beta"),
  preamble = "The prior for &theta; is given by\\n",
  asis = TRUE
)

## S3 method for class 'LogisticNormalMixture'
knit_print(x, ..., asis = TRUE, use_values = TRUE, fmt = "%5.2f", units = NA)

## S3 method for class 'LogisticNormalFixedMixture'
knit_print(x, ..., asis = TRUE, use_values = TRUE, fmt = "%5.2f", units = NA)

## S3 method for class 'OneParLogNormalPrior'
knit_print(
  x,
  ...,
  tox_label = "toxicity",
  asis = TRUE,
  use_values = TRUE,
  fmt = "%5.2f"
)

## S3 method for class 'OneParExpPrior'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'LogisticLogNormalGrouped'
knit_print(
  x,
  ...,
  use_values = TRUE,
  fmt = "%5.2f",
 params = c(`\\alpha` = "alpha", `\\beta` = "beta", `log(\\delta_0)` = "delta_0",
    `log(\\delta_1)` = "delta_1"),
  preamble = "The prior for &theta; is given by\\n",
  asis = TRUE
)
```

```
## S3 method for class 'TwoDrugsCombo'
knit_print(x, ..., use_values = TRUE, fmt = "%5.2f", asis = TRUE)

## S3 method for class 'LogisticLogNormalOrdinal'
knit_print(
  x,
  ...,
  use_values = TRUE,
  fmt = "%5.2f",
  params = NA,
  preamble = "The prior for &theta; is given by\\n",
  asis = TRUE
)

## S3 method for class 'LogisticIndepBeta'
knit_print(
  x,
  ...,
  use_values = TRUE,
  fmt = "%5.2f",
  params = NA,
  tox_label = "DLAE",
  preamble = "The prior for &theta; is given by\\n",
  asis = TRUE
)

## S3 method for class 'Effloglog'
knit_print(
  x,
  ...,
  use_values = TRUE,
  fmt = "%5.2f",
  params = NA,
  tox_label = "DLAE",
  eff_label = "efficacy",
  label = "participant",
  preamble = "The prior for &theta; is given by\\n",
  asis = TRUE
)

## S3 method for class 'IncrementsRelative'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'IncrementsRelativeDLT'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'IncrementsDoseLevels'
```

```
knit_print(x, ..., asis = TRUE)

## S3 method for class 'IncrementsHSRBeta'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'IncrementsMin'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'IncrementsComboOneDrugOnly'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'IncrementsComboCartesian'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'IncrementsOrdinal'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'IncrementsRelativeParts'
knit_print(x, ..., asis = TRUE, tox_label = c("toxicity", "toxicities"))

## S3 method for class 'IncrementsRelativeDLTCurrent'
knit_print(x, ..., asis = TRUE, tox_label = c("DLT", "DLTs"))

## S3 method for class 'NextBestMTD'
knit_print(
  x,
  ...,
  target_label = "the 25th centile",
  tox_label = "toxicity",
  asis = TRUE
)

## S3 method for class 'NextBestNCRM'
knit_print(x, ..., tox_label = "toxicity", asis = TRUE)

## S3 method for class 'NextBestThreePlusThree'
knit_print(
  x,
  ...,
  tox_label = c("toxicity", "toxicities"),
  label = "participant",
  asis = TRUE
)

## S3 method for class 'NextBestDualEndpoint'
knit_print(
  x,
  ...,
```

```
  tox_label = "toxicity",
  biomarker_label = "the biomarker",
  biomarker_units = ifelse(x@target_relative, "%", ""),
  asis = TRUE
)

## S3 method for class 'NextBestMinDist'
knit_print(x, ..., tox_label = "toxicity", asis = TRUE)

## S3 method for class 'NextBestInfTheory'
knit_print(
  x,
  ...,
  tox_label = "toxicity",
  citation_text = "Mozgunov & Jaki (2019)",
  citation_link = "https://doi.org/10.1002/sim.8450",
  asis = TRUE
)

## S3 method for class 'NextBestTD'
knit_print(x, ..., tox_label = "toxicity", asis = TRUE)

## S3 method for class 'NextBestMaxGain'
knit_print(x, ..., tox_label = "toxicity", asis = TRUE)

## S3 method for class 'NextBestProbMTDLTE'
knit_print(x, ..., tox_label = "toxicity", asis = TRUE)

## S3 method for class 'NextBestProbMTDMinDist'
knit_print(x, ..., tox_label = "toxicity", asis = TRUE)

## S3 method for class 'NextBestNCRMLoss'
knit_print(
  x,
  ...,
  tox_label = "toxicity",
  asis = TRUE,
  format_func = h_knit_format_func
)

## S3 method for class 'NextBestTDsamples'
knit_print(x, ..., tox_label = "toxicity", asis = TRUE)

## S3 method for class 'NextBestMaxGainSamples'
knit_print(x, ..., tox_label = "toxicity", asis = TRUE)

## S3 method for class 'NextBestOrdinal'
knit_print(x, ..., tox_label = "toxicity", asis = TRUE)
```

```
## S3 method for class 'OpeningMinDose'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'OpeningMinCohorts'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'OpeningNone'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'OpeningMinResponses'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'OpeningList'
knit_print(x, ..., preamble, indent = 0L, asis = TRUE)

## S3 method for class 'OpeningAll'
knit_print(x, ..., preamble, asis = TRUE)

## S3 method for class 'OpeningAny'
knit_print(x, ..., preamble, asis = TRUE)

## S3 method for class 'RecruitmentUnlimited'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'RecruitmentRatio'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'SafetyWindow'
knit_print(x, ..., asis = TRUE, time_unit = "day", label = "participant")

## S3 method for class 'SafetyWindowConst'
knit_print(
  x,
  ...,
  asis = TRUE,
  label = "participant",
  ordinals = c("first", "second", "third", "fourth", "fifth", "sixth", "seventh",
    "eighth", "ninth", "tenth"),
  time_unit = "day"
)

## S3 method for class 'SafetyWindowSize'
knit_print(
  x,
  ...,
  asis = TRUE,
  ordinals = c("first", "second", "third", "fourth", "fifth", "sixth", "seventh",
```

```
    "eighth", "ninth", "tenth"),
  label = "participant",
  time_unit = "day",
  level = 2L
)

## S3 method for class 'StoppingOrdinal'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'StoppingMaxGainCIRatio'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'StoppingList'
knit_print(x, ..., preamble, indent = 0L, asis = TRUE)

## S3 method for class 'StoppingAny'
knit_print(x, ..., preamble, asis = TRUE)

## S3 method for class 'StoppingAll'
knit_print(x, ..., preamble, asis = TRUE)

## S3 method for class 'StoppingTDCIRatio'
knit_print(
  x,
  ...,
  dose_label = "the next best dose",
  tox_label = "toxicity",
  fmt_string =
   paste0("%sIf, at %s, the ratio of the upper to the lower limit of the posterior ",
   "95%% credible interval for %s (targetting %2.0f%%) is less than or equal to "),
  asis = TRUE
)

## S3 method for class 'StoppingTargetBiomarker'
knit_print(
  x,
  ...,
  dose_label = "the next best dose",
  biomarker_label = "the target biomarker",
  fmt_string =
    paste0("%sIf, at %s, the posterior probability that %s is in the range ",
    "(%.2f, %.2f)%s is %.0f%% or more.\n\n"),
  asis = TRUE
)

## S3 method for class 'StoppingLowestDoseHSRBeta'
knit_print(
  x,
```

```
  ...,
  tox_label = "toxicity",
  fmt_string =
   paste0("%sIf, using a Hard Stopping Rule with a prior of Beta(%.0f, %.0f), the ",
     "lowest dose in the dose grid has a posterior probability of %s of ",
     "%.0f%% or more.\n\n"),
  asis = TRUE
)

## S3 method for class 'StoppingMTDCV'
knit_print(
  x,
  ...,
  fmt_string =
   paste0("%sIf the posterior estimate of the robust coefficient of variation of ",
     "the MTD (targetting %2.0f%%), is than or equal to %.0f%%.\n\n"),
  asis = TRUE
)

## S3 method for class 'StoppingMTDdistribution'
knit_print(
  x,
  ...,
  fmt_string =
   "%sIf the mean posterior probability of %s at %.0f%% of %s is at least %4.2f.\n\n",
  dose_label = "the next best dose",
  tox_label = "toxicity",
  asis = TRUE
)

## S3 method for class 'StoppingHighestDose'
knit_print(
  x,
  ...,
  dose_label = "the highest dose in the dose grid",
  asis = TRUE
)

## S3 method for class 'StoppingSpecificDose'
knit_print(x, ..., dose_label = as.character(x@dose), asis = TRUE)

## S3 method for class 'StoppingTargetProb'
knit_print(
  x,
  ...,
  fmt_string =
    paste0("%sIf the probability of %s at %s is in the range [%4.2f, %4.2f] ",
    "is at least %4.2f.\n\n"),
```

```
  dose_label = "the next best dose",
  tox_label = "toxicity",
  asis = TRUE
)

## S3 method for class 'StoppingMinCohorts'
knit_print(x, ..., asis = TRUE)

## S3 method for class 'StoppingMinPatients'
knit_print(x, ..., label = "participant", asis = TRUE)

## S3 method for class 'StoppingPatientsNearDose'
knit_print(
  x,
  ...,
  dose_label = "the next best dose",
  label = "participants",
  asis = TRUE
)

## S3 method for class 'StoppingCohortsNearDose'
knit_print(x, ..., dose_label = "the next best dose", asis = TRUE)

## S3 method for class 'StoppingMissingDose'
knit_print(x, ..., asis = TRUE)
```

Arguments

x	(ModelParamsNormal) the object to be rendered
...	passed to knitr::kable()
asis	(flag) Not used at present
label	(character) the term used to label participants
tox_label	(character) the term used to describe toxicity
level	(count) the markdown level at which the headings for cohort size will be printed. An integer between 1 and 6
title	(character) The text of the heading of the section describing the design
sections	(character) a named vector of length at least 4 defining the headings used to define the sections corresponding to the design's slots. The element names must match the Design's slot names.
full_grid	(flag) Should the full dose grid appear in the output table or simply those doses for

whom at least one evaluable participant is available? Ignored unless summarise == "dose".

summarise (character)
How to summarise the observed data. The default, "none", lists observed data at the participant level. "dose" presents participant counts by dose and "cohort" by cohort.

summarize (character)
Synonym for summarise

units (character)
The units in which the values in doseGrid are

format_func (function)
The function used to format the range table.

fmt (character)
the sprintf format string used to render numerical values. Ignored if use_values is FALSE.

use_values (flag)
print the values associated with hyperparameters, or the symbols used to define the hyper-parameters. That is, for example, mu or 1.

biomarker_label
(character)
the term used to describe the biomarker

params (character)
The names of the model parameters. See Usage Notes below.

preamble (character)
the text that introduces the list of rules

theta (character)
the LaTeX representation of the theta vector

eff_label (character)
the term used to describe efficacy

target_label (character)
the term used to describe the target toxicity rate

biomarker_units
(character)
the units in which the biomarker is measured

citation_text (character)
the text used to cite Mozgunov & Jaki

citation_link (character)
the link to Mozgunov & Jaki

indent (integer)
the indent level of the current stopping rule list. Spaces with length indent * 4 will be prepended to the beginning of the rendered stopping rule list.

time_unit (character)
the word used to describe units of time. See Usage Notes below.

ordinals (character)
a character vector whose nth defines the word used as the written representation of the nth ordinal number.

dose_label (character)
the term used to describe the target dose

fmt_string (character)
the character string that defines the format of the output

Value

a character string that represents the object in markdown.

The markdown representation of the object, as a character string

a character string that represents the object in markdown.

A character string containing a LaTeX rendition of the object.

a character string that represents the object in markdown.

Usage Notes

label describes the trial's participants.

It should be a character vector of length 1 or 2. If of length 2, the first element describes a cohort_size of 1 and the second describes all other cohort_sizes. If of length 1, the character s is appended to the value when cohort_size is not 1.

The default value of col.names is c("Lower", "Upper", "Cohort size") and that of caption is "Defined by the dose to be used in the next cohort". These values can be overridden by passing col.names and caption in the function call.

The by default, the columns are labelled Lower, Upper and Cohort size. The table's caption is Defined by the number of <tox_label[2]> so far observed. These values can be overridden by passing col.names and caption in the function call.

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It should be a character vector of length 1 or 2. If of length 2, the first element describes a single participant and the second describes all other situations. If of length 1, the character s is appended to the value when the number of participants is not 1. The default values of col.names and caption vary depending on the summary requested. The default values can be overridden by passing col.names and caption in the function call.

params must be a character vector of length equal to that of x@mean (and x@cov). Its values represent the parameters of the model as entries in the vector theta, on the left-hand side of "~" in the definition of the prior. If named, names should be valid LaTeX, escaped as usual for R character variables. For example, "\\alpha" or "\\beta_0". If unnamed, names are constructed by prepending an escaped backslash to each value provided.

The default value of col.names is c("Min", "Max", "Increment") and that of caption is "Defined by highest dose administered so far". These values can be overridden by passing col.names and caption in the function call.

The default value of col.names is c("Min", "Max", "Increment") and that of caption is "Defined by number of DLTs reported so far". These values can be overridden by passing col.names and caption in the function call.

label defines how toxicities are described.

It should be a character vector of length 1 or 2. If of length 2, the first element describes a single toxicity and the second describes all other toxicity counts. If of length 1, the character s is appended to the value describing a single toxicity.

The default value of col.names is c("Min", "Max", "Increment") and that of caption is "Defined by number of DLTs in the current cohort". These values can be overridden by passing col.names and caption in the function call.

tox_label defines how toxicities are described.

It should be a character vector of length 1 or 2. If of length 2, the first element describes a single toxicity and the second describes all other toxicity counts. If of length 1, the character s is appended to the value describing a single toxicity.

This section describes the use of label and tox_label, collectively referred to as labels. A label should be a scalar or a vector of length 2. If a scalar, it is converted by adding a second element that is equal to the first, suffixed by s. For example, tox_label = "DLT" becomes tox_label = c("DLT", "DLTs"). The first element of the vector is used to describe a count of 1. The second is used in all other cases.

To use a BibTeX-style citation, specify (for example) citation_text = "@MOZGUNOV", citation_link = "".

label should be a character vector of length 1 or 2. If of length 2, the first element describes a count of 1 and the second describes all other counts. If of length 1, the character s is appended to the value when the count is not 1.

label and time_unit are, collectively, labels.

A label should be a character vector of length 1 or 2. If of length 2, the first element describes a count of 1 and the second describes all other counts. If of length 1, the character s is appended to the value when the count is not 1.

label describes the trial's participants.

It should be a character vector of length 1 or 2. If of length 2, the first element describes a cohort_size of 1 and the second describes all other cohort_sizes. If of length 1, the character s is appended to the value when cohort_size is not 1.

The default value of col.names is c("Lower", "Upper", "Cohort size") and that of caption is "Defined by the dose to be used in the next cohort". These values can be overridden by passing col.names and caption in the function call.

The by default, the columns are labelled Lower, Upper and Cohort size. The table's caption is Defined by the number of <tox_label[2]> so far observed. These values can be overridden by passing col.names and caption in the function call.

label describes the trial's participants.

It should be a character vector of length 1 or 2. If of length 2, the first element describes a single participant and the second describes all other situations. If of length 1, the character s is appended to the value when the number of participants is not 1. The default values of col.names and caption vary depending on the summary requested. The default values can be overridden by passing col.names and caption in the function call.

params must be a character vector of length equal to that of x@mean (and x@cov). Its values represent the parameters of the model as entries in the vector theta, on the left-hand side of "~" in the definition of the prior. If named, names should be valid LaTeX, escaped as usual for R character

variables. For example, "\\alpha" or "\\beta_0". If unnamed, names are constructed by prepending an escaped backslash to each value provided.

The default value of col.names is c("Min", "Max", "Increment") and that of caption is "Defined by highest dose administered so far". These values can be overridden by passing col.names and caption in the function call.

The default value of col.names is c("Min", "Max", "Increment") and that of caption is "Defined by number of DLTs reported so far". These values can be overridden by passing col.names and caption in the function call.

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It should be a character vector of length 1 or 2. If of length 2, the first element describes a single toxicity and the second describes all other toxicity counts. If of length 1, the character s is appended to the value describing a single toxicity.

The default value of col.names is c("Min", "Max", "Increment") and that of caption is "Defined by number of DLTs in the current cohort". These values can be overridden by passing col.names and caption in the function call.

tox_label defines how toxicities are described.

It should be a character vector of length 1 or 2. If of length 2, the first element describes a single toxicity and the second describes all other toxicity counts. If of length 1, the character s is appended to the value describing a single toxicity.

This section describes the use of label and tox_label, collectively referred to as labels. A label should be a scalar or a vector of length 2. If a scalar, it is converted by adding a second element that is equal to the first, suffixed by s. For example, tox_label = "DLT" becomes tox_label = c("DLT", "DLTs"). The first element of the vector is used to describe a count of 1. The second is used in all other cases.

To use a BibTeX-style citation, specify (for example) citation_text = "@MOZGUNOV", citation_link = "".

label should be a character vector of length 1 or 2. If of length 2, the first element describes a count of 1 and the second describes all other counts. If of length 1, the character s is appended to the value when the count is not 1.

label and time_unit are, collectively, labels.

A label should be a character vector of length 1 or 2. If of length 2, the first element describes a count of 1 and the second describes all other counts. If of length 1, the character s is appended to the value when the count is not 1.

label describes the trial's participants.

It should be a character vector of length 1 or 2. If of length 2, the first element describes a cohort_size of 1 and the second describes all other cohort_sizes. If of length 1, the character s is appended to the value when cohort_size is not 1.

The default value of col.names is c("Lower", "Upper", "Cohort size") and that of caption is "Defined by the dose to be used in the next cohort". These values can be overridden by passing col.names and caption in the function call.

The by default, the columns are labelled Lower, Upper and Cohort size. The table's caption is Defined by the number of <tox_label[2]> so far observed. These values can be overridden by passing col.names and caption in the function call.

label describes the trial's participants.

It should be a character vector of length 1 or 2. If of length 2, the first element describes a single participant and the second describes all other situations. If of length 1, the character s is appended to the value when the number of participants is not 1. The default values of col.names and caption vary depending on the summary requested. The default values can be overridden by passing col.names and caption in the function call.

params must be a character vector of length equal to that of x@mean (and x@cov). Its values represent the parameters of the model as entries in the vector theta, on the left-hand side of "~" in the definition of the prior. If named, names should be valid LaTeX, escaped as usual for R character variables. For example, "\\alpha" or "\\beta_0". If unnamed, names are constructed by prepending an escaped backslash to each value provided.

The default value of col.names is c("Min", "Max", "Increment") and that of caption is "Defined by highest dose administered so far". These values can be overridden by passing col.names and caption in the function call.

The default value of col.names is c("Min", "Max", "Increment") and that of caption is "Defined by number of DLTs reported so far". These values can be overridden by passing col.names and caption in the function call.

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It should be a character vector of length 1 or 2. If of length 2, the first element describes a single toxicity and the second describes all other toxicity counts. If of length 1, the character s is appended to the value describing a single toxicity.

The default value of col.names is c("Min", "Max", "Increment") and that of caption is "Defined by number of DLTs in the current cohort". These values can be overridden by passing col.names and caption in the function call.

tox_label defines how toxicities are described.

It should be a character vector of length 1 or 2. If of length 2, the first element describes a single toxicity and the second describes all other toxicity counts. If of length 1, the character s is appended to the value describing a single toxicity.

This section describes the use of label and tox_label, collectively referred to as labels. A label should be a scalar or a vector of length 2. If a scalar, it is converted by adding a second element that is equal to the first, suffixed by s. For example, tox_label = "DLT" becomes tox_label = c("DLT", "DLTs"). The first element of the vector is used to describe a count of 1. The second is used in all other cases.

To use a BibTeX-style citation, specify (for example) citation_text = "@MOZGUNOV", citation_link = "".

label should be a character vector of length 1 or 2. If of length 2, the first element describes a count of 1 and the second describes all other counts. If of length 1, the character s is appended to the value when the count is not 1.

label and time_unit are, collectively, labels.

A label should be a character vector of length 1 or 2. If of length 2, the first element describes a count of 1 and the second describes all other counts. If of length 1, the character s is appended to the value when the count is not 1.

label describes the trial's participants.

It should be a character vector of length 1 or 2. If of length 2, the first element describes a cohort_size of 1 and the second describes all other cohort_sizes. If of length 1, the character s is appended to the value when cohort_size is not 1.

The default value of col.names is c("Lower", "Upper", "Cohort size") and that of caption is "Defined by the dose to be used in the next cohort". These values can be overridden by passing col.names and caption in the function call.

The by default, the columns are labelled Lower, Upper and Cohort size. The table's caption is Defined by the number of <tox_label[2]> so far observed. These values can be overridden by passing col.names and caption in the function call.

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It should be a character vector of length 1 or 2. If of length 2, the first element describes a single participant and the second describes all other situations. If of length 1, the character s is appended to the value when the number of participants is not 1. The default values of col.names and caption vary depending on the summary requested. The default values can be overridden by passing col.names and caption in the function call.

params must be a character vector of length equal to that of x@mean (and x@cov). Its values represent the parameters of the model as entries in the vector theta, on the left-hand side of "~" in the definition of the prior. If named, names should be valid LaTeX, escaped as usual for R character variables. For example, "\\alpha" or "\\beta_0". If unnamed, names are constructed by prepending an escaped backslash to each value provided.

The default value of col.names is c("Min", "Max", "Increment") and that of caption is "Defined by highest dose administered so far". These values can be overridden by passing col.names and caption in the function call.

The default value of col.names is c("Min", "Max", "Increment") and that of caption is "Defined by number of DLTs reported so far". These values can be overridden by passing col.names and caption in the function call.

label defines how toxicities are described.

It should be a character vector of length 1 or 2. If of length 2, the first element describes a single toxicity and the second describes all other toxicity counts. If of length 1, the character s is appended to the value describing a single toxicity.

The default value of col.names is c("Min", "Max", "Increment") and that of caption is "Defined by number of DLTs in the current cohort". These values can be overridden by passing col.names and caption in the function call.

tox_label defines how toxicities are described.

It should be a character vector of length 1 or 2. If of length 2, the first element describes a single toxicity and the second describes all other toxicity counts. If of length 1, the character s is appended to the value describing a single toxicity.

This section describes the use of label and tox_label, collectively referred to as labels. A label should be a scalar or a vector of length 2. If a scalar, it is converted by adding a second element that is equal to the first, suffixed by s. For example, tox_label = "DLT" becomes tox_label = c("DLT", "DLTs"). The first element of the vector is used to describe a count of 1. The second is used in all other cases.

To use a BibTeX-style citation, specify (for example) citation_text = "@MOZGUNOV", citation_link = "".

label should be a character vector of length 1 or 2. If of length 2, the first element describes a count of 1 and the second describes all other counts. If of length 1, the character s is appended to the value when the count is not 1.

label and time_unit are, collectively, labels.

A label should be a character vector of length 1 or 2. If of length 2, the first element describes a count of 1 and the second describes all other counts. If of length 1, the character `s` is appended to the value when the count is not 1.

See Also

`knit_print` for more details.

`LogisticIndepBeta-class`

`LogisticIndepBeta`

Description

[Stable]

`LogisticIndepBeta` is the class for the two-parameters logistic regression dose-limiting events (DLE) model with prior expressed in form of pseudo data. This model describes the relationship between the binary DLE responses and the dose levels. More specifically, it represents the relationship of the probabilities of the occurrence of a DLE for corresponding dose levels in log scale. This model is specified as

$$p(x) = exp(phi1 + phi2 * log(x))/(1 + exp(phi1 + phi2 * log(x)))$$

where $p(x)$ is the probability of the occurrence of a DLE at dose x. The two parameters of this model are the intercept $phi1$ and the slope $phi2$. The `LogisticIndepBeta` inherits all slots from `ModelTox` class.

In the context of pseudo data, the following three arguments are used, `binDLE`, `DLEdose` and `DLEweights`. The `DLEdose` represents fixed dose levels at which the pseudo DLE responses `binDLE` are observed. `DLEweights` represents total number of subjects treated per each dose level in `DLEdose`. The `binDLE` represents the number of subjects observed with DLE per each dose level in `DLEdose`. Hence, all these three vectors must be of the same length and the order of the elements in any of the vectors `binDLE`, `DLEdose` and `DLEweights` must be kept, so that an element of a given vector corresponds to the elements of the remaining two vectors (see the example for more insight). Finally, since at least two DLE pseudo responses are needed to obtain prior modal estimates (same as the maximum likelihood estimates) for the model parameters, the `binDLE`, `DLEdose` and `DLEweights` must all be vectors of at least length 2.

Usage

```
LogisticIndepBeta(binDLE, DLEdose, DLEweights, data)

.DefaultLogisticIndepBeta()
```

Arguments

binDLE	(numeric) the number of subjects observed with a DLE, the pseudo DLE responses, depending on dose levels DLEdose. Elements of binDLE must correspond to the elements of DLEdose and DLEweights.
DLEdose	(numeric) dose levels for the pseudo DLE responses. Elements of DLEdose must correspond to the elements of binDLE and DLEweights.
DLEweights	(numeric) the total number of subjects treated at each of the dose levels DLEdose, pseudo weights. Elements of DLEweights must correspond to the elements of binDLE and DLEdose.
data	(Data) the input data to update estimates of the model parameters.

Details

The pseudo data can be interpreted as if we obtain some observations before the trial starts. It can be used to express our prior, i.e. the initial beliefs for the model parameters. The pseudo data is expressed in the following way. First, fix at least two dose levels, then ask for experts' opinion on how many subjects are to be treated at each of these dose levels and on the number of subjects observed with a DLE. At each dose level, the number of subjects observed with a DLE, divided by the total number of subjects treated, is the probability of the occurrence of a DLE at that particular dose level. The probabilities of the occurrence of a DLE based on this pseudo data are independent and they follow Beta distributions. Therefore, the joint prior probability density function of all these probabilities can be obtained. Hence, by a change of variable, the joint prior probability density function of the two parameters in this model can also be obtained. In addition, a conjugate joint prior density function of the two parameters in the model is used. For details about the form of all these joint prior and posterior probability density functions, please refer to Whitehead and Williamson (1998).

Slots

binDLE (numeric)
: a vector of total numbers of DLE responses. It must be at least of length 2 and the order of its elements must correspond to values specified in DLEdose and DLEweights.

DLEdose (numeric)
: a vector of the dose levels corresponding to It must be at least of length 2 and the order of its elements must correspond to values specified in binDLE and DLEweights.

DLEweights (integer)
: total number of subjects treated at each of the pseudo dose level DLEdose. It must be at least of length 2 and the order of its elements must correspond to values specified in binDLE and DLEdose.

phi1 (number)
: the intercept of the model. This slot is used in output to display the resulting prior or posterior modal estimate of the intercept obtained based on the pseudo data and (if any) observed data/responses.

`phi2` (number)
: the slope of the model. This slot is used in output to display the resulting prior or posterior modal estimate of the slope obtained based on the pseudo data and (if any) the observed data/responses.

`Pcov` (matrix)
: refers to the 2x2 covariance matrix of the intercept ($phi1$) and the slope parameters ($phi2$) of the model. This is used in output to display the resulting prior and posterior covariance matrix of $phi1$ and $phi2$ obtained, based on the pseudo data and (if any) the observed data and responses. This slot is needed for internal purposes.

Note

Typically, end users will not use the `.DefaultLogisticIndepBeta()` function.

References

Whitehead J, Williamson D (1998). "Bayesian decision procedures based on logistic regression models for dose-finding studies." *Journal of Biopharmaceutical Statistics*, **8**(3), 445–467.

Examples

```
# Obtain prior modal estimates given the pseudo data.
# First we used an empty data set such that only the dose levels under
# investigations are given. In total, 12 dose levels are under investigation
# ranging from 25 to 300 mg with increments of 25 (i.e 25, 50, 75, ..., 300).
emptydata <- Data(doseGrid = seq(25, 300, 25))

# Fix two dose levels 25 and 300 mg (DLEdose).
# Total number of subjects treated in each of these levels is 3, (DLEweights).
# The number of subjects observed with a DLE is 1.05 at dose 25 mg and 1.8 at dose 300 mg (binDLE).
my_model1 <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEdose = c(25, 300),
  DLEweights = c(3, 3),
  data = emptydata
)

# Use observed DLE responses to obtain posterior modal estimates.
my_data <- Data(
  x = c(25, 50, 50, 75, 100, 100, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  doseGrid = emptydata@doseGrid
)

my_model2 <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEdose = c(25, 300),
  DLEweights = c(3, 3),
  data = my_data
)
```

`LogisticKadane-class` `LogisticKadane`

Description

[Stable]

`LogisticKadane` is the class for the logistic model in the parametrization of Kadane et al. (1980).

Usage

```
LogisticKadane(theta, xmin, xmax)

.DefaultLogisticKadane()
```

Arguments

`theta`	(`proportion`) the target toxicity probability.
`xmin`	(`number`) the minimum of the dose range.
`xmax`	(`number`) the maximum of the dose range.

Details

Let `rho0` = `p(xmin)` be the probability of a DLT at the minimum dose `xmin`, and let `gamma` be the dose with target toxicity probability `theta`, i.e. $p(gamma) = theta$. Then it can easily be shown that the logistic regression model has intercept

$$[gamma * logit(rho0) - xmin * logit(theta)]/[gamma - xmin]$$

and slope

$$[logit(theta) - logit(rho0)]/[gamma - xmin].$$

The priors are

$$gamma\ Unif(xmin, xmax).$$

and

$$rho0\ Unif(0, theta).$$

Slots

`theta` (`proportion`)
: the target toxicity probability.

`xmin` (`number`)
: the minimum of the dose range.

`xmax` (`number`)
: the maximum of the dose range.

Note

The slots of this class, required for creating the model, are the target toxicity, as well as the minimum and maximum of the dose range. Note that these can be different from the minimum and maximum of the dose grid in the data later on.

Typically, end-users will not use the `.DefaultLogisticKadane()` function.

References

Kadane JB, Dickey JM, Winkler RL, Smith WS, Peters SC (1980). "Interactive Elicitation of Opinion for a Normal Linear Model." *Journal of the American Statistical Association*, **75**(372), 845–854. ISSN 01621459, 1537274X. doi:10.2307/2287171. http://www.jstor.org/stable/2287171.

See Also

`ModelLogNormal`

Examples

```
my_model <- LogisticKadane(theta = 0.33, xmin = 1, xmax = 200)
```

`LogisticKadaneBetaGamma-class`
`LogisticKadaneBetaGamma`

Description

[Experimental]

`LogisticKadaneBetaGamma` is the class for the logistic model in the parametrization of Kadane et al. (1980), using a beta and a gamma distribution as the model priors.

Usage

```
LogisticKadaneBetaGamma(theta, xmin, xmax, alpha, beta, shape, rate)

.DefaultLogisticKadaneBetaGamma()
```

Arguments

`theta`	(`proportion`) the target toxicity probability.
`xmin`	(`number`) the minimum of the dose range.
`xmax`	(`number`) the maximum of the dose range.

alpha (number)
: the first shape parameter of the Beta prior distribution rho0 = p(xmin) the probability of a DLT at the minimum dose xmin.

beta (number)
: the second shape parameter of the Beta prior distribution rho0 = p(xmin) the probability of a DLT at the minimum dose xmin.

shape (number)
: the shape parameter of the Gamma prior distribution gamma the dose with target toxicity probability theta.

rate (number)
: the rate parameter of the Gamma prior distribution gamma the dose with target toxicity probability theta.

Details

Let rho0 = p(xmin) be the probability of a DLT at the minimum dose xmin, and let gamma be the dose with target toxicity probability theta, i.e. $p(gamma) = theta$. Then it can easily be shown that the logistic regression model has intercept

$$[gamma * logit(rho0) - xmin * logit(theta)]/[gamma - xmin]$$

and slope

$$[logit(theta) - logit(rho0)]/[gamma - xmin].$$

The prior for gamma, is

$$gamma\ Gamma(shape, rate).$$

. The prior for rho0 = p(xmin), is

$$rho0\ Beta(alpha, beta).$$

Slots

theta (proportion)
: the target toxicity probability.

xmin (number)
: the minimum of the dose range.

xmax (number)
: the maximum of the dose range.

alpha (number)
: the first shape parameter of the Beta prior distribution of rho0 = p(xmin) the probability of a DLT at the minimum dose xmin.

beta (number)
: the second shape parameter of the Beta prior distribution of rho0 = p(xmin) the probability of a DLT at the minimum dose xmin.

shape (number)
: the shape parameter of the Gamma prior distribution of gamma the dose with target toxicity probability theta.

`rate` (number)
: the rate parameter of the Gamma prior distribution of `gamma` the dose with target toxicity probability `theta`.

Note

The slots of this class, required for creating the model, are the same as in the `LogisticKadane` class. In addition, the shape parameters of the Beta prior distribution of `rho0` and the shape and rate parameters of the Gamma prior distribution of `gamma`, are required for creating the prior model.

Typically, end users will not use the `.Default()` function.

References

Kadane JB, Dickey JM, Winkler RL, Smith WS, Peters SC (1980). "Interactive Elicitation of Opinion for a Normal Linear Model." *Journal of the American Statistical Association*, **75**(372), 845–854. ISSN 01621459, 1537274X. doi:10.2307/2287171. http://www.jstor.org/stable/2287171.

See Also

`ModelLogNormal`, `LogisticKadane`.

Examples

```
my_model <- LogisticKadaneBetaGamma(
  theta = 0.3,
  xmin = 0,
  xmax = 7,
  alpha = 1,
  beta = 19,
  shape = 0.5625,
  rate = 0.125
)
```

LogisticLogNormal-class

`LogisticLogNormal`

Description

[Stable]

`LogisticLogNormal` is the class for the usual logistic regression model with a bivariate normal prior on the intercept and log slope.

Usage

```
LogisticLogNormal(mean, cov, ref_dose = 1)

.DefaultLogisticLogNormal()
```

Arguments

mean	(numeric) the prior mean vector.
cov	(matrix) the prior covariance matrix. The precision matrix prec is internally calculated as an inverse of cov.
ref_dose	(number) the reference dose $x*$ (strictly positive number).

Details

The covariate is the natural logarithm of the dose x divided by the reference dose $x*$, i.e.:

$$logit[p(x)] = alpha0 + alpha1 * log(x/x*),$$

where $p(x)$ is the probability of observing a DLT for a given dose x. The prior

$$(alpha0, log(alpha1))\ Normal(mean, cov).$$

Note

Typically, end users will not use the `.DefaultLogisticLogNormal()` function.

See Also

ModelLogNormal, LogisticNormal, LogisticLogNormalSub, ProbitLogNormal, ProbitLogNormalRel, LogisticLogNormalMixture, DALogisticLogNormal.

Examples

```
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 50
)
my_model
```

LogisticLogNormalGrouped-class
LogisticLogNormalGrouped

Description

[Experimental]

LogisticLogNormalGrouped is the class for a logistic regression model for both the mono and the combo arms of the simultaneous dose escalation design.

Usage

```
LogisticLogNormalGrouped(mean, cov, ref_dose = 1)

.DefaultLogisticLogNormalGrouped()
```

Arguments

`mean`	(`numeric`) the prior mean vector.
`cov`	(`matrix`) the prior covariance matrix. The precision matrix `prec` is internally calculated as an inverse of `cov`.
`ref_dose`	(`number`) the reference dose $x*$ (strictly positive number).

Details

The continuous covariate is the natural logarithm of the dose x divided by the reference dose $x*$ as in `LogisticLogNormal`. In addition, I_c is a binary indicator covariate which is 1 for the combo arm and 0 for the mono arm. The model is then defined as:

$$logit[p(x)] = (alpha0 + I_c * delta0) + (alpha1 + I_c * delta1) * log(x/x*),$$

where $p(x)$ is the probability of observing a DLT for a given dose x, and `delta0` and `delta1` are the differences in the combo arm compared to the mono intercept and slope parameters `alpha0` and `alpha1`. The prior is defined as

$$(alpha0, log(delta0), log(alpha1), log(delta1))\ Normal(mean, cov).$$

Note

Typically, end users will not use the `.DefaultLogisticLogNormalGrouped()` function.

See Also

`ModelLogNormal`, `LogisticLogNormal`.

Examples

```
my_model <- LogisticLogNormalGrouped(
  mean = c(-0.85, 0, 1, 0),
  cov = diag(1, 4),
  ref_dose = 50
)
my_model
```

`LogisticLogNormalMixture-class` `LogisticLogNormalMixture`

Description

[Stable]

`LogisticLogNormalMixture` is the class for standard logistic model with online mixture of two bivariate log normal priors.

Usage

```
LogisticLogNormalMixture(mean, cov, ref_dose, share_weight)

.DefaultLogisticLogNormalMixture()
```

Arguments

`mean`	(`numeric`) the prior mean vector.
`cov`	(`matrix`) the prior covariance matrix. The precision matrix `prec` is internally calculated as an inverse of `cov`.
`ref_dose`	(`number`) the reference dose $x*$ (strictly positive number).
`share_weight`	(`proportion`) the prior weight for the share component.

Details

This model can be used when data is arising online from the informative component of the prior, at the same time with the data of the trial of main interest. Formally, this is achieved by assuming that the probability of a DLT at dose x is given by

$$p(x) = \pi * p1(x) + (1 - \pi) * p2(x)$$

where π is the probability for the model $p(x)$ being the same as the model $p1(x)$, which is the informative component of the prior. From this model data arises in parallel: at doses `xshare`, DLT information `yshare` is observed, in total `nObsshare` data points (see `DataMixture`). On the other hand, $1 - \pi$, is the probability of a separate model $p2(x)$. Both components have the same log normal prior distribution, which can be specified by the user, and which is inherited from the `LogisticLogNormal` class.

Slots

`share_weight` (`proportion`)
: the prior weight for the share component $p_1(x)$.

Note

Typically, end users will not use the `.DefaultLogNormalMixture()` function.

See Also

ModelLogNormal, LogisticNormalMixture, LogisticNormalFixedMixture.

Examples

```
# Decide on the dose grid and MCMC options.
dose_grid <- 1:80
my_options <- McmcOptions()

# Classic model.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 50
)

empty_data <- Data(doseGrid = dose_grid)
prior_samples <- mcmc(empty_data, my_model, my_options)
plot(prior_samples, my_model, empty_data)

# Set up the mixture model and data share object.
model_share <- LogisticLogNormalMixture(
  share_weight = 0.1,
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 50
)

empty_data_share <- DataMixture(
  doseGrid = dose_grid,
  xshare = rep(c(10, 20, 40), each = 4),
  yshare = rep(0L, 12),
)

# Compare with the resulting prior model.
prior_samples_share <- mcmc(empty_data_share, model_share, my_options)
plot(prior_samples_share, model_share, empty_data_share)
```

LogisticLogNormalOrdinal-class

LogisticLogNormalOrdinal

Description

[Experimental]

LogisticLogNormalOrdinal is the class for a logistic lognormal CRM model using an ordinal toxicity scale.

Usage

```
LogisticLogNormalOrdinal(mean, cov, ref_dose)

.DefaultLogisticLogNormalOrdinal()
```

Arguments

mean	(numeric) the prior mean vector.
cov	(matrix) the prior covariance matrix. The precision matrix prec is internally calculated as an inverse of cov.
ref_dose	(number) the reference dose $x*$ (strictly positive number).

Note

Typically, end users will not use the .DefaultLogisticLogNormalOrdinal() function.

Examples

```
LogisticLogNormalOrdinal(
  mean = c(3, 4, 0),
  cov = diag(c(4, 3, 1)),
  ref_dose = 1
)
```

LogisticLogNormalSub-class
LogisticLogNormalSub

Description

[Stable]

LogisticLogNormalSub is the class for a standard logistic model with bivariate (log) normal prior with subtractive dose standardization.

Usage

```
LogisticLogNormalSub(mean, cov, ref_dose = 0)

.DefaultLogisticLogNormalSub()
```

Arguments

`mean`	(`numeric`) the prior mean vector.
`cov`	(`matrix`) the prior covariance matrix. The precision matrix `prec` is internally calculated as an inverse of `cov`.
`ref_dose`	(`number`) the reference dose $x*$.

Details

The covariate is the dose x minus the reference dose $x*$, i.e.:

$$logit[p(x)] = alpha0 + alpha1 * (x - x*),$$

where $p(x)$ is the probability of observing a DLT for a given dose x. The prior

$$(alpha0, log(alpha1))\ Normal(mean, cov).$$

Slots

`params` (`ModelParamsNormal`)
: bivariate normal prior parameters.

`ref_dose` (`number`)
: the reference dose $x*$.

Note

Typically, end-users will not use the `.DefaultLogisticLogNormalSub()` function.

See Also

`LogisticNormal`, `LogisticLogNormal`, `ProbitLogNormal`, `ProbitLogNormalRel`.

Examples

```
my_model <- LogisticLogNormalSub(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 50
)
```

LogisticNormal-class LogisticNormal

Description

[Stable]

LogisticNormal is the class for the usual logistic regression model with a bivariate normal prior on the intercept and slope.

Usage

```
LogisticNormal(mean, cov, ref_dose = 1)

.DefaultLogisticNormal()
```

Arguments

mean	(numeric) the prior mean vector.
cov	(matrix) the prior covariance matrix. The precision matrix prec is internally calculated as an inverse of cov.
ref_dose	(number) the reference dose $x*$ (strictly positive number).

Details

The covariate is the natural logarithm of the dose x divided by the reference dose $x*$, i.e.:

$$logit[p(x)] = alpha0 + alpha1 * log(x/x*),$$

where $p(x)$ is the probability of observing a DLT for a given dose x. The prior

$$(alpha0, alpha1)\ Normal(mean, cov).$$

Note

Typically, end users will not use the .DefaultLogisticNormal() function.

See Also

ModelLogNormal, LogisticLogNormal, LogisticLogNormalSub, ProbitLogNormal, ProbitLogNormalRel, LogisticNormalMixture.

Examples

```
# Define the dose-grid.
empty_data <- Data(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))

my_model <- LogisticNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2)
)

my_options <- McmcOptions(burnin = 10, step = 2, samples = 100)

samples <- mcmc(empty_data, my_model, my_options)
samples
```

LogisticNormalFixedMixture-class
LogisticNormalFixedMixture

Description

[Stable]

LogisticNormalFixedMixture is the class for standard logistic regression model with fixed mixture of multiple bivariate (log) normal priors on the intercept and slope parameters. The weights of the normal priors are fixed, hence no additional model parameters are introduced. This type of prior is often used to better approximate a given posterior distribution, or when the information is given in terms of a mixture.

Usage

```
LogisticNormalFixedMixture(components, weights, ref_dose, log_normal = FALSE)

.DefaultLogisticNormalFixedMixture()
```

Arguments

components	(list) the specifications of the mixture components, a list with ModelParamsNormal objects for each bivariate (log) normal prior.
weights	(numeric) the weights of the components; these must be positive and will be normalized to sum to 1.
ref_dose	(number) the reference dose $x*$ (strictly positive number).
log_normal	(flag) should a log normal prior be specified, such that the mean vectors and covariance matrices are valid for the intercept and log slope?

Details

The covariate is the natural logarithm of the dose x divided by the reference dose $x*$, i.e.:

$$logit[p(x)] = alpha0 + alpha1 * log(x/x*),$$

where $p(x)$ is the probability of observing a DLT for a given dose x. The prior

$$(alpha0, alpha1)\ w1 * Normal(mean1, cov1) + ... + wK * Normal(meanK, covK),$$

if a normal prior is used and

$$(alpha0, log(alpha1))\ w1 * Normal(mean1, cov1) + ... + wK * Normal(meanK, covK),$$

if a log normal prior is used. The weights $w1, ..., wK$ of the components are fixed and sum to 1.

The slots of this class comprise a list with components parameters. Every single component contains the mean vector and the covariance matrix of bivariate normal distributions. Remaining slots are the weights of the components as well as the reference dose. Moreover, a special indicator slot specifies whether a log normal prior is used.

Slots

`components` (`list`)
: the specifications of the mixture components, a list with `ModelParamsNormal` objects for each bivariate (log) normal prior.

`weights` (`numeric`)
: the weights of the components; these must be positive and must sum to 1.

`ref_dose` (`positive_number`)
: the reference dose.

`log_normal` (`flag`)
: should a log normal prior be used, such that the mean vectors and covariance matrices are valid for the intercept and log slope?

Note

Typically, end-users will not use the `.DefaultLogisticNormalFixedMixture()` function.

See Also

`ModelParamsNormal`, `ModelLogNormal`, `LogisticNormalMixture`, `LogisticLogNormalMixture`.

Examples

```
my_model <- LogisticNormalFixedMixture(
  components = list(
    comp1 = ModelParamsNormal(
      mean = c(-0.85, 1),
      cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2)
    ),
    comp2 = ModelParamsNormal(
      mean = c(1, 1.5),
```

```
      cov = matrix(c(1.2, -0.45, -0.45, 0.6), nrow = 2)
    )
  ),
  weights = c(0.3, 0.7),
  ref_dose = 50
)
```

`LogisticNormalMixture-class`
`LogisticNormalMixture`

Description

[Stable]

`LogisticNormalMixture` is the class for standard logistic regression model with a mixture of two bivariate normal priors on the intercept and slope parameters.

Usage

```
LogisticNormalMixture(comp1, comp2, weightpar, ref_dose)

.DefaultLogisticNormalMixture()
```

Arguments

`comp1`	(`ModelParamsNormal`) bivariate normal prior specification of the first component. See `ModelParamsNormal` for more details.
`comp2`	(`ModelParamsNormal`) bivariate normal prior specification of the second component. See `ModelParamsNormal` for more details.
`weightpar`	(`numeric`) the beta parameters for the weight of the first component. It must a be a named vector of length 2 with names `a` and `b` and with strictly positive values.
`ref_dose`	(`number`) the reference dose $x*$ (strictly positive number).

Details

The covariate is the natural logarithm of the dose x divided by the reference dose $x*$, i.e.:

$$logit[p(x)] = alpha0 + alpha1 * log(x/x*),$$

where $p(x)$ is the probability of observing a DLT for a given dose x. The prior

$$(alpha0, alpha1)\ w * Normal(mean1, cov1) + (1 - w) * Normal(mean2, cov2).$$

The weight w for the first component is assigned a beta prior `B(a, b)`.

Slots

`comp1` (`ModelParamsNormal`)
: bivariate normal prior specification of the first component.

`comp2` (`ModelParamsNormal`)
: bivariate normal prior specification of the second component.

`weightpar` (`numeric`)
: the beta parameters for the weight of the first component. It must a be a named vector of length 2 with names `a` and `b` and with strictly positive values.

`ref_dose` (`positive_number`)
: the reference dose.

Note

The weight of the two normal priors is a model parameter, hence it is a flexible mixture. This type of prior is often used with a mixture of a minimal informative and an informative component, in order to make the CRM more robust to data deviations from the informative component.

Typically, end-users will not use the `.DefaultLogisticNormalMixture()` function.

See Also

`ModelParamsNormal`, `ModelLogNormal`, `LogisticNormalFixedMixture`, `LogisticLogNormalMixture`.

Examples

```
my_model <- LogisticNormalMixture(
  comp1 = ModelParamsNormal(
    mean = c(-0.85, 1),
    cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2)
  ),
  comp2 = ModelParamsNormal(
    mean = c(1, 1.5),
    cov = matrix(c(1.2, -0.45, -0.45, 0.6), nrow = 2)
  ),
  weightpar = c(a = 1, b = 1),
  ref_dose = 50
)
```

---

logit *Shorthand for Logit Function*

Description

[Stable]

Computes the logit transformation.

Usage

```
logit(x)
```

Arguments

x	(numeric) the function argument.

Value

The logit of x, computed as `log(x / (1 - x))`.

Examples

```
logit(0.5)
logit(c(0.1, 0.5, 0.9))
```

`match_within_tolerance` *Helper Function for Value Matching with Tolerance*

Description

[Stable]

This is a modified version of `match()` that supports tolerance.

Usage

```
match_within_tolerance(x, table, tolerance = 1e-10)
```

Arguments

x	(numeric) the values to be matched.
table	(numeric) the values to be matched against.
tolerance	(number) the numerical tolerance for comparison.

Value

An integer vector of the same length as x giving the position in table of the first match, or an empty integer vector if table is empty. NA is returned for values in x that have no match.

Examples

```
match_within_tolerance(c(0.1, 0.2, 0.3), c(0.10000001, 0.5, 0.3))
match_within_tolerance(1.5, numeric(0))
```

maxDose *Determine the Maximum Possible Next Dose*

Description

[Stable]

This function determines the upper limit of the next dose based on the `increments`and the `data`.

Usage

```
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsComboOneDrugOnly,DataCombo'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsComboCartesian,DataCombo'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsRelative,Data'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsRelativeDLT,Data'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsRelativeDLTCurrent,Data'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsRelativeParts,DataParts'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsDoseLevels,Data'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsHSRBeta,Data'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsMin,Data'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsMin,DataCombo'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsMin,DataOrdinal'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsOrdinal,DataOrdinal'
maxDose(increments, data, ...)
```

```
## S4 method for signature 'IncrementsMaxToxProb,DataOrdinal'
maxDose(increments, data, model, samples, ...)

## S4 method for signature 'IncrementsMaxToxProb,Data'
maxDose(increments, data, model, samples, ...)
```

Arguments

increments	(Increments) the rule for the next best dose.
data	(Data) input data.
...	additional arguments without method dispatch.
model	(GeneralModel) The model on which probabilities will be based
samples	(Samples) The MCMC samples to which model will be applied

Value

A number, the maximum possible next dose.

Functions

- maxDose(increments = IncrementsComboOneDrugOnly, data = DataCombo): determine the maximum possible next dose levels for a two drug combination, based on the rule that only one drug can be escalated at a time.
- maxDose(increments = IncrementsComboCartesian, data = DataCombo): determine the maximum possible next dose levels for a two drug combination, based on the drug specific increment rules which are applied independently.
- maxDose(increments = IncrementsRelative, data = Data): determine the maximum possible next dose based on relative increments.
- maxDose(increments = IncrementsRelativeDLT, data = Data): determine the maximum possible next dose based on relative increments determined by DLTs so far.
- maxDose(increments = IncrementsRelativeDLTCurrent, data = Data): determine the maximum possible next dose based on relative increments determined by DLTs in the current cohort.
- maxDose(increments = IncrementsRelativeParts, data = DataParts): determine the maximum possible next dose based on relative increments as well as part 1 and beginning of part 2.
- maxDose(increments = IncrementsDoseLevels, data = Data): determine the maximum possible next dose based on the number of dose grid levels. That is, the max dose is determined as the one which level is equal to: base dose level + level increment. The base dose level is the level of the last dose in grid or the level of the maximum dose applied, which is defined in increments object. Find out more in IncrementsDoseLevels.

- maxDose(increments = IncrementsHSRBeta, data = Data): determine the maximum possible next dose for escalation.
- maxDose(increments = IncrementsMin, data = Data): determine the maximum possible next dose based on multiple increment rules, taking the minimum across individual increments.
- maxDose(increments = IncrementsMin, data = DataCombo): determine the maximum possible next dose based on multiple increment rules, taking the minimum across individual increments.
- maxDose(increments = IncrementsMin, data = DataOrdinal): determine the maximum possible next dose based on multiple increment rules, taking the minimum across individual increments.
- maxDose(increments = IncrementsOrdinal, data = DataOrdinal): determine the maximum possible next dose in an ordinal CRM trial
- maxDose(increments = IncrementsMaxToxProb, data = DataOrdinal): determine the maximum possible next dose based on the probability of toxicity
- maxDose(increments = IncrementsMaxToxProb, data = Data): determine the maximum possible next dose based on the probability of toxicity

Examples

```
# Example of usage for `IncrementsComboOneDrugOnly` maxDose method.

# Create two-drug combination data where the last cohort received
# drug1 = 10, drug2 = 20.
my_data <- DataCombo(
  x = cbind(
    drug1 = c(10, 10, 10),
    drug2 = c(20, 20, 20)
  ),
  y = c(0L, 0L, 0L),
  ID = 1L:3L,
  cohort = c(1L, 1L, 1L),
  doseGrid = list(
    drug1 = c(10, 20, 30),
    drug2 = c(20, 40, 60)
  )
)

# Define the one-drug-only escalation rule.
my_increments <- IncrementsComboOneDrugOnly()

# Determine the maximum allowed dose combination.
# For drug1 = 10 (not escalated): drug2 may go up to Inf (unrestricted here).
# For drug1 = 20 or 30 (escalated): drug2 is capped at the last drug2 dose (20).
maxDose(my_increments, my_data)
# Example of usage for `IncrementsComboCartesian` maxDose method.

# Create two-drug combination data where the last cohort received
# drug1 = 10, drug2 = 20.
```

```
my_data <- DataCombo(
  x = cbind(
    drug1 = c(10, 10, 10),
    drug2 = c(20, 20, 20)
  ),
  y = c(0L, 0L, 0L),
  ID = 1L:3L,
  cohort = c(1L, 1L, 1L),
  doseGrid = list(
    drug1 = c(10, 20, 30),
    drug2 = c(20, 40, 60)
  )
)

# Define independent increment rules for each drug.
my_increments <- IncrementsComboCartesian(
  drug1 = IncrementsRelative(intervals = c(0), increments = c(1)),
  drug2 = IncrementsRelative(intervals = c(0), increments = c(1))
)

# Determine the maximum allowed next dose levels.
# Here, the drug1 rule allows escalation up to 20 and the drug2 rule allows
# escalation up to 40. For drug1 values above 20, the combination is not
# admissible and is represented with NA for drug2.
maxDose(my_increments, my_data)
# Example of usage for `IncrementsRelative` maxDose class.

# Create the data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 8, 8, 8),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  ID = 1:8,
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, 8, 10:40)
)

# Define a rule for dose increments which allows for:
#  - doubling the dose if the last dose was below 20,
#  - increasing the dose by 33% of the last dose, only if the last dose was
#    above or equal to 20.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Based on the rule above, the maximum dose allowed is:
max_dose <- maxDose(my_increments, data = my_data)
# Example of usage for `IncrementsRelativeDLT` maxDose class.

# Create the data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 8, 8, 8),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
```

```
  ID = 1:8,
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, 8, seq(from = 10, to = 80, by = 2))
)

# Define a rule for dose increments which allows for:
#  - doubling the dose if no DLTs were yet observed,
#  - increasing the dose by 33% if 1 or 2 DLTs were already observed,
#  - increasing the dose by 20% if at least 3 DLTs were already observed.
my_increments <- IncrementsRelativeDLT(
  intervals = c(0, 1, 3),
  increments = c(1, 0.33, 0.2)
)

# Based on the rule above, the maximum dose allowed is:
max_dose <- maxDose(my_increments, data = my_data)
# Example of usage for `IncrementsRelativeDLTCurrent` maxDose class.

# Create the data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  ID = 1:8,
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Define a rule for dose increments which allows for:
#  - doubling the dose if no DLTs were observed in current (i.e. last) cohort,
#  - only increasing the dose by 33% if 1 or 2 DLTs were observed in current cohort,
#  - only increasing the dose by 20% if at least 3 DLTs were observed in current cohort.
my_increments <- IncrementsRelativeDLTCurrent(
  intervals = c(0, 1, 3),
  increments = c(1, 0.33, 0.2)
)

# Based on the rule above, the maximum dose allowed is:
max_dose <- maxDose(my_increments, data = my_data)
# Example of usage for `IncrementsRelativeParts` maxDose class.

# Create an object of class `DataParts`.
my_data <- DataParts(
  x = c(0.1, 0.5, 1.5),
  y = c(0, 0, 0),
  ID = 1:3,
  cohort = 1:3,
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, 10),
  part = c(1L, 1L, 1L),
  nextPart = 1L,
  part1Ladder = c(0.1, 0.5, 1.5, 3, 6, 10)
)

my_increments <- IncrementsRelativeParts(
```

```
  dlt_start = 0,
  clean_start = 1
)

max_dose <- maxDose(my_increments, data = my_data)
# Example of usage for `IncrementsDoseLevels` maxDose class.

# Create the data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 8, 8, 12, 12, 12, 16, 16, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0, 1, 0, 0, 1, 0, 1),
  ID = 1:14,
  cohort = c(1, 2, 3, 4, 5, 6, 6, 7, 7, 7, 8, 8, 9, 9),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, 8, 10:30)
)

# In this first example we define a rule for dose increments which allows for
# maximum skip one dose level, that is 2 dose levels higher than the last dose
# given.
my_increments_1 <- IncrementsDoseLevels(levels = 2, basis_level = "last")

# Based on the rule above, the maximum dose allowed is:
max_dose_1 <- maxDose(my_increments_1, data = my_data)

# In this second example we define a rule for dose increments which allows for
# maximum skip one dose level, that is 2 dose levels higher than the max dose
# given.
my_increments_2 <- IncrementsDoseLevels(levels = 2, basis_level = "max")

# Based on the rule above, the maximum dose allowed is:
max_dose_2 <- maxDose(my_increments_2, data = my_data)
# Create the data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 8, 8, 8, 6, 6, 6),
  y = c(0, 0, 0, 0, 0, 0, 1, 0, 1, 1, 1),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5, 6, 6, 6),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, 8, seq(from = 10, to = 80, by = 2))
)

# In this example we define a rule for dose increments that limits the further
# dose escalation to doses below 6, because dose 6 is above the probability
# toxicity threshold.
my_increments <- IncrementsHSRBeta(target = 0.3, prob = 0.95)

# Based on the rule above, we then calculate the maximum dose allowed.
my_next_max_dose <- maxDose(my_increments, data = my_data)
# Example of usage for `IncrementsRelativeDLTCurrent` maxDose class.

# Create the data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 8, 8, 8),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  ID = 1:8,
```

```
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, 8, 10:80)
)

# Here, we combine two different increment rules.

# The first rule allows for:
#  - doubling the dose if no DLTs were observed at the current dose,
#  - increasing the dose by 33% if 1 or 2 DLTs were observed at the current dose,
#  - increasing the dose by 22% if 3 or more DLTs were observed.
my_increments_1 <- IncrementsRelativeDLT(
  intervals = c(0, 1, 3),
  increments = c(1, 0.33, 0.2)
)

# The second rule allows for:
#  - doubling the dose if the current dose is <20,
#  - increasing the dose by 33% if the current dose is >=20.
my_increments_2 <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Finally, the maximum dose allowed is computed by taking the minimum dose from
# the maximum doses computed by the two rules.
my_increments <- IncrementsMin(
  increments_list = list(my_increments_1, my_increments_2)
)
max_dose <- maxDose(my_increments, my_data)
# Example of usage for `IncrementsMin` maxDose with DataCombo.

# Create two-drug combination data where the last cohort received
# drug1 = 10, drug2 = 20.
my_data <- DataCombo(
  x = cbind(
    drug1 = c(10, 10, 10),
    drug2 = c(20, 20, 20)
  ),
  y = c(0L, 0L, 0L),
  ID = 1L:3L,
  cohort = c(1L, 1L, 1L),
  doseGrid = list(
    drug1 = c(10, 20, 30),
    drug2 = c(20, 40, 60)
  )
)

# Rule 1: only one drug can be escalated at a time.
rule_one <- IncrementsComboOneDrugOnly()

# Rule 2: independent Cartesian increments for each drug.
rule_two <- IncrementsComboCartesian(
  drug1 = IncrementsRelative(intervals = c(0), increments = c(2)),
```

```
  drug2 = IncrementsRelative(intervals = c(0), increments = c(1))
)

# Combine both rules and take the most conservative allowed dose per row.
my_increments <- IncrementsMin(increments_list = list(rule_one, rule_two))
maxDose(my_increments, my_data)
maxDose(
  increments = IncrementsOrdinal(2L, .DefaultIncrementsRelative()),
  data = .DefaultDataOrdinal()
)
model <- LogisticLogNormalOrdinal(
  mean = c(0.25, 0.15, 0.5),
  cov = matrix(c(1.5, 0, 0, 0, 2, 0, 0, 0, 1), nrow = 3),
  ref_dose = 30
)

emptyData <- DataOrdinal(
  doseGrid = c(1, 3, 9, 25, 50, 75, 100),
  yCategories = c("No tox" = 0L, "DLAE" = 1L, "CRS" = 2L)
)

# For warning regarding tox, see issue #748 https://github.com/openpharma/crmPack/issues/748
suppressWarnings({
  samples <- mcmc(emptyData, model, .DefaultMcmcOptions())
})
toxIncrements <- IncrementsMaxToxProb(prob = c("DLAE" = 0.2, "CRS" = 0.05))
maxDose(toxIncrements, emptyData, model, samples)
model <- LogisticLogNormalOrdinal(
  mean = c(0.25, 0.15, 0.5),
  cov = matrix(c(1.5, 0, 0, 0, 2, 0, 0, 0, 1), nrow = 3),
  ref_dose = 30
)

emptyData <- DataOrdinal(
  doseGrid = c(1, 3, 9, 25, 50, 75, 100),
  yCategories = c("No tox" = 0L, "DLAE" = 1L, "CRS" = 2L)
)

# For warning regarding tox, see issue #748 https://github.com/openpharma/crmPack/issues/748
suppressWarnings({
  samples <- mcmc(emptyData, model, .DefaultMcmcOptions())
})
toxIncrements <- IncrementsMaxToxProb(prob = c("DLAE" = 0.2, "CRS" = 0.05))
maxDose(toxIncrements, emptyData, model, samples)
```

`maxRecruits` *Calculate Maximum Number of Backfill Patients*

Description

[Experimental]

Calculates the maximum number of backfill patients that can be recruited based on the recruitment rule and the active cohort size.

Usage

```
maxRecruits(object, active_cohort_size, ...)

## S4 method for signature 'RecruitmentUnlimited'
maxRecruits(object, active_cohort_size, ...)

## S4 method for signature 'RecruitmentRatio'
maxRecruits(object, active_cohort_size, ...)
```

Arguments

`object`	(`Recruitment`) the recruitment rule.
`active_cohort_size`	(`integer`) the current size of the active dose escalation cohort.
`...`	further arguments (not used).

Value

The maximum number of backfill patients as an `integer`.

Functions

- `maxRecruits(RecruitmentUnlimited)`: method for `RecruitmentUnlimited` class. Returns a very large number (practically unlimited).
- `maxRecruits(RecruitmentRatio)`: method for `RecruitmentRatio` class. Returns `ceiling(ratio * active_cohort_size)`.

See Also

`Recruitment`, `RecruitmentUnlimited`, `RecruitmentRatio`.

Examples

```
# Create a RecruitmentUnlimited object
recruitment <- RecruitmentUnlimited()

# Calculate maximum recruits for various active cohort sizes
max_recruits_10 <- maxRecruits(recruitment, active_cohort_size = 10)
print(max_recruits_10) # Returns 1e6

max_recruits_100 <- maxRecruits(recruitment, active_cohort_size = 100)
print(max_recruits_100) # Still returns 1e6 (unlimited)

# With RecruitmentUnlimited, the active_cohort_size is ignored
```

```
# Create a RecruitmentRatio object with ratio 0.5
recruitment <- RecruitmentRatio(ratio = 0.5)

# Calculate maximum recruits based on active cohort size
# For active cohort of 10: ceiling(0.5 * 10) = 5
max_recruits_10 <- maxRecruits(recruitment, active_cohort_size = 10)
print(max_recruits_10) # 5

# For active cohort of 7: ceiling(0.5 * 7) = ceiling(3.5) = 4
max_recruits_7 <- maxRecruits(recruitment, active_cohort_size = 7)
print(max_recruits_7) # 4

# For active cohort of 15: ceiling(0.5 * 15) = ceiling(7.5) = 8
max_recruits_15 <- maxRecruits(recruitment, active_cohort_size = 15)
print(max_recruits_15) # 8
```

`maxSize` *"MAX" Combination of Cohort Size Rules*

Description

[Stable]

This function combines cohort size rules by taking the maximum of all sizes.

Usage

```
maxSize(...)

## S4 method for signature 'CohortSize'
maxSize(...)
```

Arguments

`...`	Objects of class `CohortSize`.

Value

The combination as an object of class `CohortSizeMax`.

Functions

- `maxSize(CohortSize)`: The method combining cohort size rules by taking maximum.

See Also

`minSize()`

Examples

```
# Here is the rule for:
#   having cohort of size 1 for doses <30
#   and having cohort of size 3 for doses >=30
mySize1 <- CohortSizeRange(intervals = c(0, 30), cohort_size = c(1, 3))

# Here is the rule for:
#   having cohort of size 1 until no DLT were observed
#   and having cohort of size 3 as soon as 1 DLT is observed
mySize2 <- CohortSizeDLT(intervals = c(0, 1), cohort_size = c(1, 3))

# This is combining the two rules above by taking the maximum of the sample sizes of
# the single rules
mySize <- maxSize(mySize1, mySize2)
```

---

mcmc *Obtaining Posterior Samples for all Model Parameters*

Description

[Stable]

This is the function that actually runs the JAGS MCMC machinery to produce posterior samples from all model parameters and required derived values. It is a generic function, so that customized versions may be conveniently defined for specific subclasses of GeneralData, GeneralModel, and McmcOptions input.

Usage

```
mcmc(data, model, options, ...)

## S4 method for signature 'GeneralData,GeneralModel,McmcOptions'
mcmc(data, model, options, from_prior = data@nObs == 0L, ...)

## S4 method for signature 'DataCombo,TwoDrugsCombo,McmcOptions'
mcmc(data, model, options, from_prior = data@nObs == 0L, ...)

## S4 method for signature 'HierarchicalData,HierarchicalModel,McmcOptions'
mcmc(
  data,
  model,
  options,
  from_prior = all(vapply(data@arms, function(arm) arm@nObs == 0L, logical(1L))),
  ...
)

## S4 method for signature 'GeneralData,DualEndpointRW,McmcOptions'
mcmc(data, model, options, from_prior = data@nObs == 0L, ...)
```

```
## S4 method for signature 'GeneralData,DualEndpointBeta,McmcOptions'
mcmc(data, model, options, from_prior = data@nObs == 0L, ...)

## S4 method for signature 'GeneralData,DualEndpointEmax,McmcOptions'
mcmc(data, model, options, from_prior = data@nObs == 0L, ...)

## S4 method for signature 'GeneralData,OneParLogNormalPrior,McmcOptions'
mcmc(data, model, options, from_prior = data@nObs == 0L, ...)

## S4 method for signature 'GeneralData,OneParExpPrior,McmcOptions'
mcmc(data, model, options, from_prior = data@nObs == 0L, ...)

## S4 method for signature 'DataMixture,GeneralModel,McmcOptions'
mcmc(
  data,
  model,
  options,
  from_prior = data@nObs == 0L & data@nObsshare == 0L,
  ...
)

## S4 method for signature 'Data,LogisticIndepBeta,McmcOptions'
mcmc(data, model, options, ...)

## S4 method for signature 'DataDual,Effloglog,McmcOptions'
mcmc(data, model, options, ...)

## S4 method for signature 'DataDual,EffFlexi,McmcOptions'
mcmc(data, model, options, ...)

## S4 method for signature 'DataOrdinal,LogisticLogNormalOrdinal,McmcOptions'
mcmc(data, model, options, ...)
```

Arguments

`data`	(`GeneralData`) an input data.
`model`	(`GeneralModel`) an input model.
`options`	(`McmcOptions`) MCMC options.
`...`	not used.
`from_prior`	(`flag`) sample from the prior only? Default to `TRUE` when number of observations in `data` is `0`. For some models it might be necessary to specify it manually here though.

Value

The posterior samples, an object of class Samples.

Functions

- mcmc(data = GeneralData, model = GeneralModel, options = McmcOptions): Standard method which uses JAGS.
- mcmc(data = DataCombo, model = TwoDrugsCombo, options = McmcOptions): Standard method which uses JAGS. For the TwoDrugsCombo model, the drug names in the model and data must agree.
- mcmc(data = HierarchicalData, model = HierarchicalModel, options = McmcOptions): Standard method which uses JAGS for the dynamically compiled hierarchical model. Arm names in data and model must agree, and combination-arm drug names must match as well.
- mcmc(data = GeneralData, model = DualEndpointRW, options = McmcOptions): Standard method which uses JAGS. For the DualEndpointRW model, it is required that there are at least two (in case of random walk prior of the first order on the biomarker level) or three doses in the grid.
- mcmc(data = GeneralData, model = DualEndpointBeta, options = McmcOptions): Standard method which uses JAGS. For the DualEndpointBeta model, it is required that the value of ref_dose_beta slot is greater than the maximum dose in a grid. This requirement comes from definition of the beta function that is used to model dose-biomarker relationship in DualEndpointBeta model. The other requirement is that there must be at least one dose in the grid.
- mcmc(data = GeneralData, model = DualEndpointEmax, options = McmcOptions): Standard method which uses JAGS. For the DualEndpointEmax model, it is required that there is at least one dose in the grid.
- mcmc(data = GeneralData, model = OneParLogNormalPrior, options = McmcOptions): Standard method which uses JAGS. For the OneParLogNormalPrior model, it is required that the length of skeleton prior probabilities vector should be equal to the length of the number of doses.
- mcmc(data = GeneralData, model = OneParExpPrior, options = McmcOptions): Standard method which uses JAGS. For the OneParExpPrior model, it is required that the length of skeleton prior probabilities vector should be equal to the length of the number of doses.
- mcmc(data = DataMixture, model = GeneralModel, options = McmcOptions): Method for DataMixture with different from_prior default. Samples from the prior only when both the number of observations and the number of shared observations are zero.
- mcmc(data = Data, model = LogisticIndepBeta, options = McmcOptions): Obtain posterior samples for the model parameters based on the pseudo LogisticIndepBeta DLE model. The joint prior and posterior probability density function of the intercept ϕ_1 (phi1) and the slope ϕ_2 (phi2) are given in Whitehead and Williamson (1998). However, since asymptotically, the joint posterior probability density will be bivariate normal, we use the bivariate normal distribution to generate posterior samples of the intercept and the slope parameters. For the prior samples of the intercept and the slope, a bivariate normal distribution with mean and the covariance matrix given in Whitehead and Williamson (1998) is used.

- `mcmc(data = DataDual, model = Effloglog, options = McmcOptions)`: Obtain the posterior samples for the model parameters in the `Effloglog` model. Given the value of ν, the precision of the efficacy responses, the joint prior or the posterior probability of the intercept θ_1 (`theta1`) and the slope θ_2 (`theta2`) is a bivariate normal distribution. The ν (`nu`), the precision of the efficacy responses is either a fixed value or has a gamma distribution. If a gamma distribution is used, the samples of `nu` will be first generated. Then the mean of the `nu` samples will be used to generate samples of the intercept and slope parameters of the model.
- `mcmc(data = DataDual, model = EffFlexi, options = McmcOptions)`: Obtain the posterior samples for the estimates in the `EffFlexi` model. This is the MCMC procedure based on what is described in Lang and Brezger (2004) such that samples of the mean efficacy responses at all dose levels, samples of `sigma2` σ^2, the variance of the efficacy response and samples of `sigma2betaW` $\sigma^2_{\beta_W}$, the variance of the random walk model will be generated. Please refer to Lang and Brezger (2004) for the procedures and the form of the joint prior and posterior probability density for the mean efficacy responses. In addition, both `sigma2` and `sigma2betaW` can be fixed or have an inverse-gamma prior and posterior distribution. Therefore, if the inverse gamma distribution(s) are used, the parameters in the distribution will be first updated and then samples of `sigma2` and `sigma2betaW` will be generated using the updated parameters.
- `mcmc( data = DataOrdinal, model = LogisticLogNormalOrdinal, options = McmcOptions )`: Obtain the posterior samples for the model parameters in the `LogisticLogNormalOrdinal` model.

  The generic `mcmc` method returns a `Samples` object with elements of the `data` slot named `alpha[1]`, `alpha[2]`, ..., `alpha[k]` and `beta` when passed a `LogisticLogNormalOrdinal` object. This makes the "alpha elements" awkward to access and is inconsistent with other model objects. So rename the alpha elements to `alpha1`, `alpha2`, ..., `alpha<k>` for ease and consistency.

Note

The type of Random Number Generator (RNG) and its initial seed used by `JAGS` are taken from the `options` argument. If no initial values are supplied (i.e RNG kind or seed slot in `options` has `NA`), then they will be generated automatically by `JAGS`.

References

Lang S, Brezger A (2004). "Bayesian P-Splines." *Journal of Computational and Graphical Statistics*, **13**(1), 183–212. ISSN 10618600. doi:10.1198/1061860043010. http://www.jstor.org/stable/1391151.

Whitehead J, Williamson D (1998). "Bayesian decision procedures based on logistic regression models for dose-finding studies." *Journal of Biopharmaceutical Statistics*, **8**(3), 445–467.

Examples

```
# Create some data from the class `Data`.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)
```

```
# Initialize the CRM model.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Sample from the posterior distribution.
my_options <- McmcOptions(
  burnin = 100,
  step = 2,
  samples = 1000
)

samples <- mcmc(data = my_data, model = my_model, options = my_options)
samples
# Create some data from the class `DataDual`.
plcb <- 0.001
my_data <- DataDual(
  w = c(13, 77, 86, 26, 27, 36, 37, 97, 21, 49, 87, 48),
  x = c(plcb, 25, 25, 25, plcb, 50, 50, 50, plcb, 100, 100, 100),
  y = c(0L, 0L, 0L, 0L, 0L, 0L, 0L, 0L, 0L, 0L, 1L, 0L),
  doseGrid = c(plcb, seq(25, 300, 25)),
  placebo = TRUE,
  ID = 1:12,
  cohort = c(1L, 1L, 1L, 1L, 2L, 2L, 2L, 2L, 3L, 3L, 3L, 3L)
)

# Initialize the CRM model.
my_model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  sigma2betaW = 0.01,
  rw1 = TRUE
)

# Sample from the posterior distribution.
my_options <- McmcOptions(
  burnin = 50,
  step = 2,
  samples = 4,
  rng_kind = "Mersenne-Twister",
  rng_seed = 1
)

samples <- mcmc(data = my_data, model = my_model, options = my_options)
samples
# Create some data from the class `DataDual`.
plcb <- 0.001
my_data <- DataDual(
```

```
  w = c(13, 77, 86, 26, 27, 36, 37, 97, 21, 49, 87, 48),
  x = c(plcb, 25, 25, 25, plcb, 50, 50, 50, plcb, 100, 100, 100),
  y = c(0L, 0L, 0L, 0L, 0L, 0L, 0L, 0L, 0L, 0L, 1L, 0L),
  doseGrid = c(plcb, seq(25, 300, 25)),
  placebo = TRUE,
  ID = 1:12,
  cohort = c(1L, 1L, 1L, 1L, 2L, 2L, 2L, 2L, 3L, 3L, 3L, 3L)
)

# Initialize the CRM model.
my_model <- DualEndpointBeta(
  mean = c(0, 1),
  cov = diag(2),
  ref_dose = 2,
  use_log_dose = FALSE,
  sigma2W = c(a = 1, b = 2),
  rho = c(a = 1.5, b = 2.5),
  E0 = 2,
  Emax = 50,
  delta1 = 6,
  mode = 9,
  ref_dose_beta = my_data@doseGrid[my_data@nGrid] + 10
)

# Sample from the posterior distribution.
my_options <- McmcOptions(
  burnin = 50,
  step = 2,
  samples = 4,
  rng_kind = "Mersenne-Twister",
  rng_seed = 1
)

samples <- mcmc(data = my_data, model = my_model, options = my_options)
samples
##obtain mcmc DLE samples given the data, LogisticIndepBeta (DLE model) and mcmc simulations options
## data must be of 'Data' class
data <- Data(
  x = c(25, 50, 50, 75, 100, 100, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  doseGrid = seq(25, 300, 25)
)
## model must be of 'LogisticIndepBeta' class
model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
## options must be ''McmcOptions' class
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
set.seed(94)
samples <- mcmc(data = data, model = model, options = options)
```

```
# nolint start
##obtain mcmc efficacy samples given the data, 'Effloglog' model (efficacy model) and
## mcmc simulations options data must be of 'DataDual' class
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)
## model must be of 'Effloglog' class
Effmodel <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data
)

## options must be ''McmcOptions' class
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
set.seed(94)
samples <- mcmc(data = data, model = Effmodel, options = options)
# nolint end
## obtain mcmc efficacy samples given the data, 'EffFlexi' model (efficacy model) and
## mcmc simulations options
## data must be of 'DataDual' class
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25)
)
## model must be of 'EffFlexi' class

effmodel <- EffFlexi(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  sigma2W = c(a = 0.1, b = 0.1),
  sigma2betaW = c(a = 20, b = 50),
  rw1 = FALSE,
  data = data
)

## options must be ''McmcOptions' class
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
set.seed(94)
samples <- mcmc(data = data, model = effmodel, options = options)
ordinal_data <- .DefaultDataOrdinal()
ordinal_model <- .DefaultLogisticLogNormalOrdinal()
mcmc_options <- .DefaultMcmcOptions()

samples <- mcmc(ordinal_data, ordinal_model, mcmc_options)
```

McmcOptions-class McmcOptions

Description

[Stable]

McmcOptions is a class for the three canonical MCMC options as well as Random Number Generator settings.

Usage

```
McmcOptions(
  burnin = 10000L,
  step = 2L,
  samples = 10000L,
  rng_kind = NA_character_,
  rng_seed = NA_integer_
)

.DefaultMcmcOptions()
```

Arguments

burnin	(count) number of burn-in iterations which are not saved.
step	(count) only every step-th iteration is saved after the burn-in.
samples	(count) number of resulting samples.
rng_kind	(string) the name of the RNG type. Possible types are: Wichmann-Hill, Marsaglia-Multicarry, Super-Duper, Mersenne-Twister. If it is NA (default), then the RNG kind will be chosen by [rjags].
rng_seed	(number) RNG seed corresponding to chosen rng_kind. It must be an integer value or NA (default), which means that the seed will be chosen by [rjags].

Slots

iterations (count)
: number of MCMC iterations.

burnin (count)
: number of burn-in iterations which are not saved.

step (count)
: only every step-th iteration is saved after the burnin. In other words, a sample from iteration i = 1,...,iterations, is saved if and only if (i - burnin) mod step = 0.
For example, for iterations = 6, burnin = 0 and step = 2, only samples from iterations 2,4,6 will be saved.

rng_kind (string)
: a Random Number Generator (RNG) type used by rjags. It must be one out of the following four values: base::Wichmann-Hill, base::Marsaglia-Multicarry, base::Super-Duper, base::Mersenne-Twister, or NA_character_. If it is NA_character_ (default), then the RNG kind will be chosen by rjags.

rng_seed (number)
: a Random Number Generator (RNG) seed used by rjags for a chosen rng_kind. It must be an integer scalar or NA_integer_, which means that the seed will be chosen by rjags.

Note

Typically, end users will not use the .DefaultMcmcOptions() function.

Examples

```
# Set up MCMC option in order to have a burn-in of 10000 iterations and
# then take every other iteration up to a collection of 10000 samples.
McmcOptions(burnin = 10000, step = 2, samples = 10000)
```

MinimalInformative *Construct a Minimally Informative Prior*

Description

[Stable]

This function constructs a minimally informative prior, which is captured in a LogisticNormal (or LogisticLogNormal) object.

Based on the proposal by Neuenschwander et al. (2008), a minimally informative prior distribution is constructed. The required key input is the minimum (d_1 in the notation of the Appendix A.1 of that paper) and the maximum value (d_J) of the dose grid supplied to this function. Then threshmin is the probability threshold q_1, such that any probability of DLT larger than q_1 has only 5% probability. Therefore q_1 is the 95% quantile of the beta distribution and hence $p_1 = 0.95$. Likewise, threshmax is the probability threshold q_J, such that any probability of DLT smaller than q_J has only 5% probability ($p_J = 0.05$). The probabilities $1 - p_1$ and p_J can be controlled with the arguments probmin and probmax, respectively. Subsequently, for all doses supplied in the dosegrid argument, beta distributions are set up from the assumption that the prior medians are linear in log-dose (or dose if useLogDose = FALSE) on the logit scale, and Quantiles2LogisticNormal() is used to transform the resulting quantiles into an approximating LogisticNormal (or LogisticLogNormal or LogisticLogNormalSub) model. Note that the reference dose is not required for these computations.

Usage

```
MinimalInformative(
  dosegrid,
  refDose,
  threshmin = 0.2,
  threshmax = 0.3,
  probmin = 0.05,
  probmax = 0.05,
  ...,
  useLogDose = TRUE
)
```

Arguments

dosegrid	(numeric) the dose grid, only positive sorted values are allowed.
refDose	(number) the reference dose. Must be positive if useLogDose = TRUE.
threshmin	(number) any toxicity probability above this threshold would be very unlikely (see probmin) at the minimum dose.
threshmax	(number) any toxicity probability below this threshold would be very unlikely (see probmax) at the maximum dose.
probmin	(number) the prior probability of exceeding threshmin at the minimum dose.
probmax	(number) the prior probability of being below threshmax at the maximum dose.
...	additional arguments for computations, see Quantiles2LogisticNormal(), e.g. refDose and logNormal=TRUE to obtain a minimal informative log normal prior.
useLogDose	(flag) use log(dosegrid / refDose) as dose covariate? If FALSE, pass logNormal = TRUE via ... to obtain a LogisticLogNormalSub model.

Value

See Quantiles2LogisticNormal().

References

Neuenschwander B, Branson M, Gsponer T (2008). "Critical aspects of the Bayesian approach to phase I cancer trials." *Statistics in Medicine*, **27**(13), 2420–2439. https://onlinelibrary.wiley.com/doi/10.1002/sim.3230.

Examples

```
# Setting up a minimal informative prior
# max.time is quite small only for the purpose of showing the example. They
# should be increased for a real case.
set.seed(132)
coarseGrid <- c(0.1, 10, 30, 60, 100)
minInfModel <- MinimalInformative(dosegrid = coarseGrid,
                                  refDose=50,
                                  threshmin=0.2,
                                  threshmax=0.3,
                                  control=## for real case: leave out control
                                    list(max.time=0.1))

# Plotting the result
matplot(x=coarseGrid,
        y=minInfModel$required,
        type="b", pch=19, col="blue", lty=1,
        xlab="dose",
        ylab="prior probability of DLT")
matlines(x=coarseGrid,
         y=minInfModel$quantiles,
         type="b", pch=19, col="red", lty=1)
legend("right",
       legend=c("quantiles", "approximation"),
       col=c("blue", "red"),
       lty=1,
       bty="n")
```

---

minSize *"MIN" Combination of Cohort Size Rules*

Description

[Stable]

This function combines cohort size rules by taking the minimum of all sizes.

Usage

```
minSize(...)

## S4 method for signature 'CohortSize'
minSize(...)
```

Arguments

`...`	Objects of class `CohortSize`.

Value

The combination as an object of class CohortSizeMin.

Functions

- minSize(CohortSize): The method combining cohort size rules by taking minimum.

See Also

maxSize()

Examples

```
# Here is the rule for:
#   having cohort of size 1 for doses <30
#   and having cohort of size 3 for doses >=30
mySize1 <- CohortSizeRange(intervals = c(0, 30), cohort_size = c(1, 3))

# Here is the rule for:
#   having cohort of size 1 until no DLT were observed
#   and having cohort of size 3 as soon as 1 DLT is observed
mySize2 <- CohortSizeDLT(intervals = c(0, 1), cohort_size = c(1, 3))

# This is combining the two rules above by taking the minimum of the sample sizes of
# the single rules
mySize <- minSize(mySize1, mySize2)
```

ModelEff-class ModelEff

Description

[Stable]

ModelEff is the parent class for efficacy models using pseudo data prior. It is dedicated all efficacy models that have their prior specified in the form of pseudo data (as if there is some data before the trial starts).

The data must obey the convention of the DataDual class. This refers to any observed efficacy/biomarker responses (w in DataDual), the dose levels at which these responses are observed (x in DataDual), all dose levels considered in the study (doseGrid in DataDual), and finally other specifications in DataDual class that can be used to generate prior or posterior modal estimates or samples estimates for model parameter(s). If no responses are observed, at least doseGrid has to be specified in data for which prior modal estimates or samples can be obtained for model parameters based on the specified pseudo data.

Usage

```
.DefaultModelEff()
```

Slots

`data (DataDual)`
: observed data that is used to obtain model parameters estimates or samples (see details above).

Note

Typically, end users will not use the `.DefaultModelEff()` function.

See Also

`ModelTox`.

`ModelLogNormal-class  ModelLogNormal`

Description

[Stable]

`ModelLogNormal` is the class for a model with a reference dose and bivariate normal prior on the model parameters `alpha0` and natural logarithm of `alpha1`, i.e.:

$$(alpha0, log(alpha1))\ Normal(mean, cov),$$

. Transformations other than `log`, e.g. identity, can be specified too in `priormodel` slot. The parameter `alpha1` has a log-normal distribution by default to ensure positivity of `alpha1` which further guarantees `exp(alpha1) > 1`. The slots of this class contain the mean vector, the covariance and precision matrices of the bivariate normal distribution, as well as the reference dose. Note that the precision matrix is an inverse of the covariance matrix in the `JAGS`. All ("normal") model specific classes inherit from this class.

Usage

```
ModelLogNormal(mean, cov, ref_dose = 1)

.DefaultModelLogNormal()
```

Arguments

`mean`	(`numeric`) the prior mean vector.
`cov`	(`matrix`) the prior covariance matrix. The precision matrix `prec` is internally calculated as an inverse of `cov`.
`ref_dose`	(`number`) the reference dose $x*$ (strictly positive number).

Slots

`params` (`ModelParamsNormal`)
: bivariate normal prior parameters.

`ref_dose` (`positive_number`)
: the reference dose.

Note

Typically, end users will not use the `.DefaultModelLogNormal()` function.

See Also

`ModelParamsNormal`, `LogisticNormal`, `LogisticLogNormal`, `LogisticLogNormalSub`, `ProbitLogNormal`, `ProbitLogNormalRel`.

`ModelParamsNormal-class` `ModelParamsNormal`

Description

[Experimental]

`ModelParamsNormal` is the class for a bivariate normal model parameters, i.e. the mean vector, covariance matrix and precision matrix. The precision matrix is an inverse of the covariance matrix in the `JAGS` and it is computed internally by the object constructor function.

Usage

```
ModelParamsNormal(mean, cov)

.DefaultModelParamsNormal()
```

Arguments

`mean`	(`numeric`) the prior mean vector.
`cov`	(`matrix`) the prior covariance matrix. The precision matrix `prec` is internally calculated as an inverse of `cov`.

Slots

`mean` (`numeric`)
: the mean vector.

`cov` (`matrix`)
: the covariance matrix.

`prec` (`matrix`)
: the precision matrix, which is an inverse matrix of the `cov`.

Note

Typically, end users will not use the `.ModelPAramsNormal()` function.

See Also

ModelLogNormal, LogisticNormalMixture.

Examples

```
ModelParamsNormal(mean = c(1, 6), cov = diag(2))
```

ModelPseudo-class ModelPseudo

Description

[Stable]

ModelPseudo is the parent class for models that express their prior in the form of pseudo data (as if there is some data before the trial starts).

Usage

```
.DefaultModelPseudo()
```

Note

Typically, end users will not use the `.DefaultModelPseudo()` function.

See Also

GeneralModel.

ModelTox-class ModelTox

Description

[Stable]

ModelTox is the parent class for DLE (dose-limiting events) models using pseudo data prior. It is dedicated for DLE models or toxicity models that have their prior specified in the form of pseudo data (as if there is some data before the trial starts).

The `data` must obey the convention of the Data class. This refers to any observed DLE responses (`y` in Data), the dose levels (`x` in Data) at which these responses are observed, all dose levels considered in the study (`doseGrid` in Data), and finally other specifications in Data class that can be used to generate prior or posterior modal estimates or samples estimates for model parameter(s). If no responses are observed, at least `doseGrid` has to be specified in `data` for which prior modal estimates or samples can be obtained for model parameters based on the specified pseudo data.

Usage

```
.DefaultModelTox()
```

Slots

`data` (`Data`)
: observed data that is used to obtain model parameters estimates or samples (see details above).

Note

Typically, end users will not use the `.DefaultModelTox()` function.

See Also

`ModelEff`.

`names,Samples-method` *The Names of the Sampled Parameters*

Description

[Stable]

A method that returns names of the parameters that are sampled.

Usage

```
## S4 method for signature 'Samples'
names(x)
```

Arguments

`x`	(`Samples`) object with samples.

Examples

```
my_samples <- Samples(
  data = list(alpha = 1:5, beta = 15:19),
  options = McmcOptions(burnin = 2, step = 2, samples = 5)
)

names(my_samples)
```

nextBest *Finding the Next Best Dose*

Description

[Stable]

A function that computes the recommended next best dose based on the corresponding rule `nextBest`, the posterior `samples` from the `model` and the underlying `data`.

Usage

```
nextBest(nextBest, doselimit, samples, model, data, ...)

## S4 method for signature 'NextBestEWOC,numeric,Samples,GeneralModel,Data'
nextBest(nextBest, doselimit = Inf, samples, model, data, ...)

## S4 method for signature 'NextBestMTD,numeric,Samples,GeneralModel,Data'
nextBest(nextBest, doselimit = Inf, samples, model, data, ...)

## S4 method for signature 'NextBestNCRM,numeric,Samples,GeneralModel,Data'
nextBest(nextBest, doselimit = Inf, samples, model, data, ...)

## S4 method for signature
## 'NextBestNCRM,matrix,Samples,TwoDrugsCombo,DataCombo'
nextBest(nextBest, doselimit, samples, model, data, ...)

## S4 method for signature
## 'NextBestNCRM,numeric,Samples,GeneralModel,DataParts'
nextBest(nextBest, doselimit = Inf, samples, model, data, ...)

## S4 method for signature 'NextBestNCRMLoss,numeric,Samples,GeneralModel,Data'
nextBest(nextBest, doselimit = Inf, samples, model, data, ...)

## S4 method for signature
## 'NextBestThreePlusThree,missing,missing,missing,Data'
nextBest(nextBest, doselimit, samples, model, data, ...)

## S4 method for signature
## 'NextBestDualEndpoint,numeric,Samples,DualEndpoint,Data'
nextBest(nextBest, doselimit = Inf, samples, model, data, ...)

## S4 method for signature 'NextBestMinDist,numeric,Samples,GeneralModel,Data'
nextBest(nextBest, doselimit = Inf, samples, model, data, ...)

## S4 method for signature
## 'NextBestInfTheory,numeric,Samples,GeneralModel,Data'
```

```
nextBest(nextBest, doselimit = Inf, samples, model, data, ...)

## S4 method for signature 'NextBestTD,numeric,missing,LogisticIndepBeta,Data'
nextBest(nextBest, doselimit = Inf, model, data, in_sim = FALSE, ...)

## S4 method for signature
## 'NextBestTDsamples,numeric,Samples,LogisticIndepBeta,Data'
nextBest(nextBest, doselimit = Inf, samples, model, data, in_sim, ...)

## S4 method for signature 'NextBestMaxGain,numeric,missing,ModelTox,DataDual'
nextBest(
  nextBest,
  doselimit = Inf,
  model,
  data,
  model_eff,
  in_sim = FALSE,
  ...
)

## S4 method for signature
## 'NextBestMaxGainSamples,numeric,Samples,ModelTox,DataDual'
nextBest(
  nextBest,
  doselimit = Inf,
  samples,
  model,
  data,
  model_eff,
  samples_eff,
  in_sim = FALSE,
  ...
)

## S4 method for signature
## 'NextBestProbMTDLTE,numeric,Samples,GeneralModel,Data'
nextBest(nextBest, doselimit, samples, model, data, ...)

## S4 method for signature
## 'NextBestProbMTDMinDist,numeric,Samples,GeneralModel,Data'
nextBest(nextBest, doselimit, samples, model, data, ...)

## S4 method for signature 'NextBestOrdinal,numeric,Samples,GeneralModel,Data'
nextBest(nextBest, doselimit = Inf, samples, model, data, ...)

## S4 method for signature
## 'NextBestOrdinal,numeric,Samples,LogisticLogNormalOrdinal,DataOrdinal'
nextBest(nextBest, doselimit = Inf, samples, model, data, ...)
```

Arguments

nextBest	(NextBest) the rule for the next best dose.
doselimit	(number or matrix) the maximum allowed next dose. If it is infinity (default), then essentially no dose limit will be applied in the course of dose recommendation calculation. A matrix must be used for two drug combinations.
samples	(Samples) posterior samples from model parameters given data.
model	(ModelTox) the DLT model.
data	(Data or DataCombo) data that was used to generate the samples.
...	additional arguments without method dispatch.
in_sim	(flag) is this method used in simulations? Default as FALSE. If this flag is TRUE and target dose estimates (during trial and end-of-trial) are outside of the dose grid range, the information message is printed by this method.
model_eff	(Effloglog or EffFlexi) the efficacy model.
samples_eff	(Samples) posterior samples from model_eff parameters given data.

Value

A list with the next best dose recommendation (element named value) from the grid defined in data, and a plot depicting this recommendation (element named plot). In case of multiple plots also an element named singlePlots is included. The singlePlots is itself a list with single plots. An additional list with elements describing the outcome of the rule can be contained too.

Functions

- nextBest(nextBest = NextBestEWOC, doselimit = numeric, samples = Samples, model = GeneralModel, data = Data): find the next best dose based on the EWOC rule.
- nextBest(nextBest = NextBestMTD, doselimit = numeric, samples = Samples, model = GeneralModel, data = Data): find the next best dose based on the MTD rule.
- nextBest(nextBest = NextBestNCRM, doselimit = numeric, samples = Samples, model = GeneralModel, data = Data): find the next best dose based on the NCRM method. The additional element probs in the output's list contains the target and overdosing probabilities (across all doses in the dose grid) used in the derivation of the next best dose.
- nextBest(nextBest = NextBestNCRM, doselimit = matrix, samples = Samples, model = TwoDrugsCombo, data = DataCombo): find the next best dose combination based on the NCRM method.
- nextBest(nextBest = NextBestNCRM, doselimit = numeric, samples = Samples, model = GeneralModel, data = DataParts): find the next best dose based on the NCRM method when two parts trial is used.

- `nextBest( nextBest = NextBestNCRMLoss, doselimit = numeric, samples = Samples, model = GeneralModel, data = Data )`: find the next best dose based on the NCRM method and loss function.
- `nextBest( nextBest = NextBestThreePlusThree, doselimit = missing, samples = missing, model = missing, data = Data )`: find the next best dose based on the 3+3 method.
- `nextBest( nextBest = NextBestDualEndpoint, doselimit = numeric, samples = Samples, model = DualEndpoint, data = Data )`: find the next best dose based on the dual endpoint model. The additional list element `probs` contains the target and overdosing probabilities (across all doses in the dose grid) used in the derivation of the next best dose.
- `nextBest( nextBest = NextBestMinDist, doselimit = numeric, samples = Samples, model = GeneralModel, data = Data )`: gives the dose which is below the dose limit and has an estimated DLT probability which is closest to the target dose.
- `nextBest( nextBest = NextBestInfTheory, doselimit = numeric, samples = Samples, model = GeneralModel, data = Data )`: gives the appropriate dose within an information theoretic framework.
- `nextBest( nextBest = NextBestTD, doselimit = numeric, samples = missing, model = LogisticIndepBeta, data = Data )`: find the next best dose based only on the DLT responses and for `LogisticIndepBeta` model class object without DLT samples.
- `nextBest( nextBest = NextBestTDsamples, doselimit = numeric, samples = Samples, model = LogisticIndepBeta, data = Data )`: find the next best dose based only on the DLT responses and for `LogisticIndepBeta` model class object involving DLT samples.
- `nextBest( nextBest = NextBestMaxGain, doselimit = numeric, samples = missing, model = ModelTox, data = DataDual )`: find the next best dose based only on pseudo DLT model `ModelTox` and `Effloglog` efficacy model without samples.
- `nextBest( nextBest = NextBestMaxGainSamples, doselimit = numeric, samples = Samples, model = ModelTox, data = DataDual )`: find the next best dose based on DLT and efficacy responses with DLT and efficacy samples.
- `nextBest( nextBest = NextBestProbMTDLTE, doselimit = numeric, samples = Samples, model = GeneralModel, data = Data )`: find the next best dose based with the highest probability of having a toxicity rate less or equal to the target toxicity level.
- `nextBest( nextBest = NextBestProbMTDMinDist, doselimit = numeric, samples = Samples, model = GeneralModel, data = Data )`: find the next best dose based with the highest probability of having a toxicity rate with minimum distance to the target toxicity level.
- `nextBest( nextBest = NextBestOrdinal, doselimit = numeric, samples = Samples, model = GeneralModel, data = Data )`: find the next best dose for ordinal CRM models.
- `nextBest( nextBest = NextBestOrdinal, doselimit = numeric, samples = Samples, model = LogisticLogNormalOrdinal, data = DataOrdinal )`: find the next best dose for ordinal CRM models.

Examples

```
# Example of usage for `NextBestEWOC` NextBest class.

# Create the data.
my_data <- Data(
```

```
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  ID = 1:8,
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)
my_samples <- mcmc(my_data, my_model, my_options)

# Define the rule for dose increments and calculate the maximum dose allowed.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
next_max_dose <- maxDose(my_increments, data = my_data)

# Define the rule which will be used to select the next best dose
# based on the 'NextBestEWOC' class.
ewoc_next_best <- NextBestEWOC(
  target = 0.30,
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose.
dose_recommendation <- nextBest(
  nextBest = ewoc_next_best,
  doselimit = next_max_dose,
  samples = my_samples,
  model = my_model,
  data = my_data
)

# See the probabilities.
dose_recommendation$probs
# Example of usage for `NextBestMTD` NextBest class.

# Create the data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  ID = 1:8,
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
```

```
)

# Initialize the CRM model used to model the data.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)
my_samples <- mcmc(my_data, my_model, my_options)

# Define the rule for dose increments and calculate the maximum dose allowed.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
next_max_dose <- maxDose(my_increments, data = my_data)

# Define the rule which will be used to select the next best dose
# based on the 'NextBestMTD' class.
mtd_next_best <- NextBestMTD(
  target = 0.33,
  derive = function(mtd_samples) {
    quantile(mtd_samples, probs = 0.25)
  }
)

# Calculate the next best dose.
dose_recommendation <- nextBest(
  nextBest = mtd_next_best,
  doselimit = next_max_dose,
  samples = my_samples,
  model = my_model,
  data = my_data
)
# Example of usage for `NextBestNCRM` NextBest class.

# Create the data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  ID = 1:8,
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
```

```
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)
my_samples <- mcmc(my_data, my_model, my_options)

# Define the rule for dose increments and calculate the maximum dose allowed.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
next_max_dose <- maxDose(my_increments, data = my_data)

# Define the rule which will be used to select the next best dose
# based on the 'NextBestNCRM' class.
nrcm_next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose.
dose_recommendation <- nextBest(
  nextBest = nrcm_next_best,
  doselimit = next_max_dose,
  samples = my_samples,
  model = my_model,
  data = my_data
)

# See the probabilities.
dose_recommendation$probs
# Example of usage for `NextBestNCRM` nextBest method with two-drug `DataCombo`.

# Create two-drug combination data.
my_data <- DataCombo(
  x = cbind(
    drug1 = c(10, 10, 10, 20, 20, 20),
    drug2 = c(20, 20, 20, 20, 20, 20)
  ),
  y = c(0L, 0L, 0L, 0L, 1L, 0L),
  ID = 1L:6L,
  cohort = c(1L, 1L, 1L, 2L, 2L, 2L),
  doseGrid = list(
    drug1 = c(10, 20, 30),
    drug2 = c(20, 40, 60)
  )
)

# Initialize the two-drug combination model.
my_model <- TwoDrugsCombo(
  single_models = list(
    drug1 = LogisticLogNormal(
```

```
      mean = c(-0.85, 1),
      cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
      ref_dose = 10
    ),
    drug2 = LogisticLogNormal(
      mean = c(-0.7, 0.8),
      cov = matrix(c(1.1, -0.3, -0.3, 0.9), nrow = 2),
      ref_dose = 20
    )
  ),
  gamma = 0,
  tau = 1
)

# Set-up MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)
my_samples <- mcmc(my_data, my_model, my_options)

# Define the dose increment rules for two-drug combination.
rule_one <- IncrementsComboOneDrugOnly()
rule_two <- IncrementsComboCartesian(
  drug1 = IncrementsRelative(intervals = c(0), increments = c(2)),
  drug2 = IncrementsRelative(intervals = c(0), increments = c(1))
)
my_increments <- IncrementsMin(increments_list = list(rule_one, rule_two))
next_max_dose <- maxDose(my_increments, data = my_data)

# Define the next best rule based on the NextBestNCRM class.
my_next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose combination.
dose_recommendation <- nextBest(
  nextBest = my_next_best,
  doselimit = next_max_dose,
  samples = my_samples,
  model = my_model,
  data = my_data
)

# See the next best dose combination.
dose_recommendation$value

# See the target and overdose probabilities.
dose_recommendation$probs

# Look at the plot.
dose_recommendation$plot
# Example of usage for `NextBestNCRM-DataParts` NextBest class.
```

```
# Create the data.
my_data <- DataParts(
  x = c(0.1, 0.5, 1.5),
  y = c(0, 0, 0),
  ID = 1:3,
  cohort = 1:3,
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2)),
  part = c(1L, 1L, 1L),
  nextPart = 1L,
  part1Ladder = c(0.1, 0.5, 1.5, 3, 6, 10)
)

# Initialize the CRM model used to model the data.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)
my_samples <- mcmc(my_data, my_model, my_options)

# Define the rule for dose increments and calculate the maximum dose allowed.
my_increments <- IncrementsRelativeParts(
  dlt_start = 0,
  clean_start = 1
)
next_max_dose <- maxDose(my_increments, data = my_data)

# Define the rule which will be used to select the next best dose
# based on the 'NextBestNCRM' class.
nrcm_next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose.
dose_recommendation <- nextBest(
  nextBest = nrcm_next_best,
  doselimit = next_max_dose,
  samples = my_samples,
  model = my_model,
  data = my_data
)

dose_recommendation
# Example of usage for `NextBestNCRMLoss` NextBest class.

# Create the data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
```

```
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  ID = 1:8,
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)
my_samples <- mcmc(my_data, my_model, my_options)

# Define the rule for dose increments and calculate the maximum dose allowed.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
next_max_dose <- maxDose(my_increments, data = my_data)

# Define the rule which will be used to select the next best dose
# based on the class `NextBestNCRMLoss`.
nrcm_loss_next_best <- NextBestNCRMLoss(
  target = c(0.2, 0.35),
  overdose = c(0.35, 0.6),
  unacceptable = c(0.6, 1),
  max_overdose_prob = 0.999,
  losses = c(1, 0, 1, 2)
)

# Calculate the next best dose.
dose_recommendation <- nextBest(
  nextBest = nrcm_loss_next_best,
  doselimit = next_max_dose,
  samples = my_samples,
  model = my_model,
  data = my_data
)

# Next best dose.
dose_recommendation$value

# Look at the probabilities.
dose_recommendation$probs

# Define another rule (loss function of 3 elements).
nrcm_loss_next_best_losses_3 <- NextBestNCRMLoss(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
```

```
  max_overdose_prob = 0.30,
  losses = c(1, 0, 2)
)

# Calculate the next best dose.
dose_recommendation_losses_3 <- nextBest(
  nextBest = nrcm_loss_next_best_losses_3,
  doselimit = next_max_dose,
  samples = my_samples,
  model = my_model,
  data = my_data
)

# Next best dose.
dose_recommendation_losses_3$value

# Look at the probabilities.
dose_recommendation_losses_3$probs
# Example of usage for `NextBestThreePlusThree` NextBest class.

# Create the data.
my_data <- Data(
  x = c(5, 5, 5, 10, 10, 10),
  y = c(0, 0, 0, 0, 1, 0),
  ID = 1:6,
  cohort = c(0, 0, 0, 1, 1, 1),
  doseGrid = c(0.1, 0.5, 1.5, 3, 5, seq(from = 10, to = 80, by = 2))
)

# The rule to select the next best dose will be based on the 3+3 method.
my_next_best <- NextBestThreePlusThree()

# Calculate the next best dose.
dose_recommendation <- nextBest(my_next_best, data = my_data)
# Example of usage for `NextBestDualEndpoint` NextBest class.

# Create the data.
my_data <- DataDual(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10, 20, 20, 20, 40, 40, 40, 50, 50, 50),
  y = c(0, 0, 0, 0, 0, 0, 1, 0, 0, 1, 1, 0, 0, 1, 0, 1, 1),
  ID = 1:17,
  cohort = c(
    1L,
    2L,
    3L,
    4L,
    5L,
    6L,
    6L,
    6L,
    7L,
    7L,
    7L,
```

```
    8L,
    8L,
    8L,
    9L,
    9L,
    9L
  ),
  w = c(
    0.31,
    0.42,
    0.59,
    0.45,
    0.6,
    0.7,
    0.55,
    0.6,
    0.52,
    0.54,
    0.56,
    0.43,
    0.41,
    0.39,
    0.34,
    0.38,
    0.21
  ),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the Dual-Endpoint model (in this case RW1).
my_model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2betaW = 0.01,
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  rw1 = TRUE
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)


my_samples <- mcmc(my_data, my_model, my_options)

# Define the rule for dose increments and calculate the maximum dose allowed.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
next_max_dose <- maxDose(my_increments, data = my_data)

# Define the rule which will be used to select the next best dose. In this case,
```

```
# target a dose achieving at least 0.9 of maximum biomarker level (efficacy)
# and with a probability below 0.25 that prob(DLT)>0.35 (safety).
de_next_best <- NextBestDualEndpoint(
  target = c(0.9, 1),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose.
dose_recommendation <- nextBest(
  nextBest = de_next_best,
  doselimit = next_max_dose,
  samples = my_samples,
  model = my_model,
  data = my_data
)

# See the probabilities.
dose_recommendation$probs

# Joint plot.
print(dose_recommendation$plot)

# Show customization of single plot.
variant1 <- dose_recommendation$singlePlots$plot1 + xlim(0, 20)
print(variant1)

# Example of usage for `NextBestTD` NextBest class.
my_data <- Data(
  x = c(25, 50, 50, 75, 150, 200, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  ID = 1:8,
  cohort = c(1L, 2L, 2L, 3L, 4L, 5L, 6L, 7L),
  doseGrid = seq(from = 25, to = 300, by = 25)
)

my_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = my_data
)

# Target probabilities of the occurrence of a DLT during trial and
# at the end of the trial are defined as 0.35 and 0.3, respectively.
td_next_best <- NextBestTD(prob_target_drt = 0.35, prob_target_eot = 0.3)

# doselimit is the maximum allowable dose level to be given to subjects.
dose_recommendation <- nextBest(
  nextBest = td_next_best,
  doselimit = max(my_data@doseGrid),
  model = my_model,
  data = my_data
```

```
)

dose_recommendation$next_dose_drt
dose_recommendation$plot
# Example of usage for `NextBestTDsamples` NextBest class.
my_data <- Data(
  x = c(25, 50, 50, 75, 150, 200, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  ID = 1:8,
  cohort = c(1L, 2L, 2L, 3L, 4L, 5L, 6L, 7L),
  doseGrid = seq(from = 25, to = 300, by = 25)
)

my_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = my_data
)

# Set-up some MCMC parameters and generate samples.
my_options <- McmcOptions(burnin = 100, step = 2, samples = 800)
my_samples <- mcmc(my_data, my_model, my_options)

# Target probabilities of the occurrence of a DLT during trial and
# at the end of the trial are defined as 0.35 and 0.3, respectively.
# 'derive' is specified such that the 30% posterior quantile of the TD35 and
# TD30 samples will be used as TD35 and TD30 estimates.
tds_next_best <- NextBestTDsamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, probs = 0.3))
  }
)

# doselimit is the maximum allowable dose level to be given to subjects.
dose_recommendation <- nextBest(
  nextBest = tds_next_best,
  doselimit = max(my_data@doseGrid),
  samples = my_samples,
  model = my_model,
  data = my_data
)

dose_recommendation$next_dose_drt
dose_recommendation$plot
# Example of usage for `NextBestMaxGain` NextBest class.

# Create the data.
my_data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
```

```
  ID = 1:8,
  cohort = 1:8,
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)

# 'ModelTox' DLT model, e.g 'LogisticIndepBeta'.
my_model_dlt <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = my_data
)

# 'ModelEff' efficacy model, e.g. 'Effloglog'.
my_model_eff <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = my_data
)

# Target probabilities of the occurrence of a DLT during trial and at the
# end of trial are defined as 0.35 and 0.3, respectively.
mg_next_best <- NextBestMaxGain(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)

# doselimit is the maximum allowable dose level to be given to subjects.
dose_recommendation <- nextBest(
  nextBest = mg_next_best,
  doselimit = 300,
  model = my_model_dlt,
  model_eff = my_model_eff,
  data = my_data
)

dose_recommendation$next_dose
dose_recommendation$plot
# Example of usage for `NextBestMaxGainSamples` NextBest class.

# Create the data.
my_data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  ID = 1:8,
  cohort = 1:8,
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)
```

```
# 'ModelTox' DLT model, e.g 'LogisticIndepBeta'.
my_model_dlt <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = my_data
)

# 'ModelEff' efficacy model, e.g 'Effloglog'.
my_model_effll <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = my_data
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)
my_samples_dlt <- mcmc(my_data, my_model_dlt, my_options)
my_samples_effll <- mcmc(my_data, my_model_effll, my_options)

# Target probabilities of the occurrence of a DLT during trial and at the end of
# trial are defined as 0.35 and 0.3, respectively.
# Use 30% posterior quantile of the TD35 and TD30 samples as estimates of TD35
# and TD30.
# Use 50% posterior quantile of the Gstar (the dose which gives the maxim gain value)
# samples as Gstar estimate.
mgs_next_best <- NextBestMaxGainSamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, prob = 0.3))
  },
  mg_derive = function(mg_samples) {
    as.numeric(quantile(mg_samples, prob = 0.5))
  }
)

dose_recommendation <- nextBest(
  nextBest = mgs_next_best,
  doselimit = max(my_data@doseGrid),
  samples = my_samples_dlt,
  model = my_model_dlt,
  data = my_data,
  model_eff = my_model_effll,
  samples_eff = my_samples_effll
)

dose_recommendation$next_dose
dose_recommendation$plot

# Now using the 'EffFlexi' class efficacy model:
```

```
my_model_effflexi <- EffFlexi(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  sigma2W = c(a = 0.1, b = 0.1),
  sigma2betaW = c(a = 20, b = 50),
  rw1 = FALSE,
  data = my_data
)


my_samples_effflexi <- mcmc(my_data, my_model_effflexi, my_options)

dose_recommendation <- nextBest(
  nextBest = mgs_next_best,
  doselimit = max(my_data@doseGrid),
  samples = my_samples_dlt,
  model = my_model_dlt,
  data = my_data,
  model_eff = my_model_effflexi,
  samples_eff = my_samples_effflexi
)

dose_recommendation$next_dose
dose_recommendation$plot

# Example of usage for `NextBestProbMTDLTE` NextBest class.

# Create the data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  ID = 1:8,
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)
my_samples <- mcmc(my_data, my_model, my_options)

# Define the rule for dose increments and calculate the maximum dose allowed.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
```

```
next_max_dose <- maxDose(my_increments, data = my_data)

# Define the rule which will be used to select the next best dose
# based on the 'NextBestProbMTDLTE' class.
nb_mtd_lte <- NextBestProbMTDLTE(target = 0.33)

# Calculate the next best dose.
dose_recommendation <- nextBest(
  nextBest = nb_mtd_lte,
  doselimit = next_max_dose,
  samples = my_samples,
  model = my_model,
  data = my_data
)
# Example of usage for `NextBestProbMTDMinDist` NextBest class.

# Create the data.
my_data <- Data(
  x = c(1.5, 1.5, 1.5, 2.5, 2.5, 2.5, 3.5, 3.5, 3.5),
  y = c(0, 0, 0, 0, 0, 0, 1, 1, 0),
  ID = 1:9,
  cohort = c(1, 1, 1, 2, 2, 2, 3, 3, 3),
  doseGrid = c(1.5, 2.5, 3.5, 4.5, 6, 7)
)

# Initialize the CRM model used to model the data.
my_model <- my_model <- LogisticKadaneBetaGamma(
  theta = 0.3,
  xmin = 1.5,
  xmax = 7,
  alpha = 1,
  beta = 19,
  shape = 0.5625,
  rate = 0.125
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)
my_samples <- mcmc(my_data, my_model, my_options)

# Define the rule for dose increments and calculate the maximum dose allowed.
my_increments <- IncrementsDoseLevels(levels = 1)

next_max_dose <- maxDose(my_increments, data = my_data)

# Define the rule which will be used to select the next best dose
# based on the 'NextBestProbMTDMinDist' class.
nb_mtd_min_dist <- NextBestProbMTDMinDist(target = 0.3)

# Calculate the next best dose.
dose_recommendation <- nextBest(
  nextBest = nb_mtd_min_dist,
  doselimit = next_max_dose,
```

```
  samples = my_samples,
  model = my_model,
  data = my_data
)
ordinal_data <- .DefaultDataOrdinal()
ordinal_model <- .DefaultLogisticLogNormalOrdinal()
options <- .DefaultMcmcOptions()


ordinal_samples <- mcmc(ordinal_data, ordinal_model, options)

nextBest(
  nextBest = NextBestOrdinal(2L, .DefaultNextBestNCRM()),
  samples = ordinal_samples,
  doselimit = Inf,
  model = ordinal_model,
  data = ordinal_data
)

ordinal_data <- .DefaultDataOrdinal()
ordinal_model <- .DefaultLogisticLogNormalOrdinal()
options <- .DefaultMcmcOptions()


ordinal_samples <- mcmc(ordinal_data, ordinal_model, options)

nextBest(
  nextBest = NextBestOrdinal(2L, .DefaultNextBestNCRM()),
  samples = ordinal_samples,
  doselimit = Inf,
  model = ordinal_model,
  data = ordinal_data
)
```

`NextBest-class` `NextBest`

Description

[Stable]

`NextBest` is a virtual class for finding next best dose, from which all other specific next best dose classes inherit.

Usage

```
.DefaultNextBest()
```

Note

Typically, end users will not use the `DefaultNextBest()` function.

See Also

NextBestEWOC, NextBestMTD, NextBestNCRM, NextBestNCRMLoss, NextBestThreePlusThree, NextBestDualEndpoint, NextBestMinDist, NextBestInfTheory, NextBestTD, NextBestTDsamples, NextBestMaxGain, NextBestMaxGainSamples, NextBestProbMTDLTE, NextBestProbMTDMinDist, NextBestOrdinal.

NextBestDualEndpoint-class

NextBestDualEndpoint

Description

[Experimental]

NextBestDualEndpoint is the class for next best dose that is based on the dual endpoint model.

Usage

```
NextBestDualEndpoint(
  target,
  overdose,
  max_overdose_prob,
  target_relative = TRUE,
  target_thresh = 0.01
)

.DefaultNextBestDualEndpoint()
```

Arguments

target	(numeric) see slot definition.
overdose	(numeric) see slot definition.
max_overdose_prob	(proportion) see slot definition.
target_relative	(flag) see slot definition.
target_thresh	(proportion) see slot definition.

Details

Under this rule, at first admissible doses are found, which are those with toxicity probability to fall in `overdose` category and being below `max_overdose_prob`. Next, it picks (from the remaining admissible doses) the one that maximizes the probability to be in the `target` biomarker range. By default (`target_relative = TRUE`) the target is specified as relative to the maximum biomarker level across the dose grid or relative to the `Emax` parameter in case a parametric model was selected (i.e. `DualEndpointBeta`, `DualEndpointEmax`). However, if `target_relative = FALSE`, then the absolute biomarker range can be used as a target.

Slots

`target (numeric)`
: the biomarker target range that needs to be reached. For example, the target range $(0.8, 1.0)$ and `target_relative = TRUE` means that we target a dose with at least 80% of maximum biomarker level. As an other example, $(0.5, 0.8)$ would mean that we target a dose between 50% and 80% of the maximum biomarker level.

`overdose (numeric)`
: the overdose toxicity interval (lower limit excluded, upper limit included).

`max_overdose_prob (proportion)`
: maximum overdose probability that is allowed.

`target_relative (flag)`
: is `target` specified as relative? If `TRUE`, then the `target` is interpreted relative to the maximum, so it must be a probability range. Otherwise, the `target` is interpreted as absolute biomarker range.

`target_thresh (proportion)`
: a target probability threshold that needs to be fulfilled before the target probability will be used for deriving the next best dose (default to 0.01).

Note

Typically, end users will not use the `.DefaultNextBestDualEndpoint()` function.

Examples

```
# Target a dose achieving at least 0.9 of maximum biomarker level (efficacy)
# and with a probability below 0.25 that prob(DLT) > 0.35 (safety).
my_next_best <- NextBestDualEndpoint(
  target = c(0.9, 1),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Now, using absolute target on the natural biomarker scale.
my_next_best_absolute <- NextBestDualEndpoint(
  target = c(200, 300),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25,
  target_relative = FALSE
)
```

NextBestEWOC-class NextBestEWOC

Description

[Stable]

NextBestEWOC is the class implementing Escalation With Overdose Control (EWOC). It recommends the highest possible dose subject to a probabilistic constraint that the posterior probability of overdosing does not exceed max_overdose_prob. Overdosing is defined as the model-based toxicity probability lying inside the interval given by overdose.

Usage

```
NextBestEWOC(target, overdose, max_overdose_prob)

.DefaultNextBestEWOC()
```

Arguments

target	(proportion) see slot definition.
overdose	(numeric) see slot definition.
max_overdose_prob	(proportion) see slot definition.

Slots

target (proportion)
: target toxicity probability to be achieved, below overdose[1]; only used for simulation reporting purposes.

overdose (numeric)
: the (exclusive) lower and (inclusive) upper boundaries of the toxicity probability interval considered an overdose region. The prototype uses c(0.35, 1) meaning probabilities > 0.35 are treated as overly toxic.

max_overdose_prob (proportion)
: maximum acceptable posterior probability that the next recommended dose is in the overdose interval.

Note

Typically, end users will not use the .DefaultNextBestEWOC() function.

See Also

NextBest, other next-best classes listed in its documentation.

Examples

```
# Example: Define EWOC next best dose rule.
# Target toxicity probability is 0.30. Overdose region is any probability > 0.35.
# We restrict posterior probability of recommending an overdosing dose to <= 0.25.
next_best_ewoc <- NextBestEWOC(
  target = 0.30,
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)
```

NextBestInfTheory-class

NextBestInfTheory

Description

[Stable]

NextBestInfTheory is the class for next best dose that is based on information theory as proposed in https://doi.org/10.1002/sim.8450.

Usage

```
NextBestInfTheory(target, asymmetry)

.DefaultNextBestInfTheory()
```

Arguments

target	(proportion) see slot definition.
asymmetry	(number) see slot definition.

Slots

`target` (proportion)
: target toxicity probability, except 0 or 1.

`asymmetry` (number)
: value of the asymmetry exponent in the divergence function that describes the rate of penalization for overly toxic does. It must be a value from $(0, 2)$ interval.

Note

Typically, end users will not use the `.DefaultNextBestInfTheory()` function.

NextBestMaxGain-class NextBestMaxGain

Description

[Stable]

NextBestMaxGain is the class to find a next best dose with maximum gain value based on a pseudo DLT and efficacy models without samples. It is based solely on the probabilities of the occurrence of a DLT and the values of the mean efficacy responses obtained by using the modal estimates of the DLT and efficacy model parameters. There are two target probabilities of the occurrence of a DLT that must be specified: target probability to be used during the trial and target probability to be used at the end of the trial. It is suitable to use it only with the ModelTox model and ModelEff classes (except EffFlexi).

Usage

```
NextBestMaxGain(prob_target_drt, prob_target_eot)

.DefaultNextBestMaxGain()
```

Arguments

prob_target_drt	(proportion) see slot definition.
prob_target_eot	(proportion) see slot definition.

Slots

`prob_target_drt` (proportion)
: the target probability of the occurrence of a DLT to be used during the trial.

`prob_target_eot` (proportion)
: the target probability of the occurrence of a DLT to be used at the end of the trial.

Note

Typically, end users will not use the `.DefaultNextBestMaxGain()` function.

Examples

```
my_next_best <- NextBestMaxGain(0.35, 0.3)
```

NextBestMaxGainSamples-class
NextBestMaxGainSamples

Description

[Stable]

NextBestMaxGainSamples is the class to find a next best dose with maximum gain value based on a pseudo DLT and efficacy models and DLT and efficacy samples. There are two target probabilities of the occurrence of a DLT that must be specified: target probability to be used during the trial and target probability to be used at the end of the trial. It is suitable to use it only with the ModelTox model and ModelEff classes.

Usage

```
NextBestMaxGainSamples(prob_target_drt, prob_target_eot, derive, mg_derive)

.DefaultNextBestMaxGainSamples()
```

Arguments

prob_target_drt	(proportion) see slot definition in NextBestMaxGain.
prob_target_eot	(proportion) see slot definition in NextBestMaxGain.
derive	(function) see slot definition.
mg_derive	(function) see slot definition.

Slots

`derive` (function)
: derives, based on a vector of posterior dose samples, the target dose that has the probability of the occurrence of DLT equals to either the `prob_target_drt` or `prob_target_eot`. It must therefore accept one and only one argument, which is a numeric vector, and return a number.

`mg_derive` (function)
: derives, based on a vector of posterior dose samples that give the maximum gain value, the final next best estimate of the dose that gives the maximum gain value. It must therefore accept one and only one argument, which is a numeric vector, and return a number.

Note

Typically, end users will not use the `.DefaultNextBestMaxGainSamples()` function.

Examples

```
# Target probability of the occurrence of a DLT during the trial is set to 0.35.
# Target probability of the occurrence of a DLT at the end of the trial is set to 0.3.
# We want the use the 30% posterior quantile (the 30th percentile) of the TD35
# (the dose level with probability of the DLT equals 0.35) and TD30 samples.
# For `mg_derive` function (which takes the sample of doses which give the maximum
# gain), we will use the 50% posterior quantile (the median or th 50th percentile)
# of the sample.
my_next_best <- NextBestMaxGainSamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, prob = 0.3))
  },
  mg_derive = function(mg_samples) {
    as.numeric(quantile(mg_samples, prob = 0.5))
  }
)
```

NextBestMinDist-class NextBestMinDist

Description

[Stable]

NextBestMinDist is the class for next best dose that is based on minimum distance to target probability.

Usage

```
NextBestMinDist(target)

.DefaultNextBestMinDist()
```

Arguments

target	(proportion) see slot definition.

Slots

target (proportion)
: single target toxicity probability, except 0 or 1.

Note

Typically, end users will not use the .DefaultNextBestMinDist() function.

Examples

```
# In the example below, the MTD is defined as the dose with the toxicity rate
# with minimal distance to the target of 30%.
next_best_min_dist <- NextBestMinDist(target = 0.3)
```

NextBestMTD-class NextBestMTD

Description

[Stable]

NextBestMTD is the class for next best dose based on MTD estimate.

Usage

```
NextBestMTD(target, derive)

.DefaultNextBestMTD()
```

Arguments

target	(proportion) see slot definition.
derive	(function) see slot definition.

Slots

target (proportion)
: target toxicity probability, except 0 or 1.

derive (function)
: a function which derives the final next best MTD estimate, based on vector of posterior MTD samples. It must therefore accept one and only one argument, which is a numeric vector, and return a number.

Note

Typically, end users will not use the .DefaultNextBestMTD() function.

Examples

```
# In the example below, the MTD is defined as the dose for which prob(DLE) = 0.33
# and we will use the 25th quantile of the posterior of MTD as our next best dose.
next_best_mtd <- NextBestMTD(
  target = 0.33,
  derive = function(mtd_samples) {
    quantile(mtd_samples, probs = 0.25)
  }
)
```

NextBestNCRM-class NextBestNCRM

Description

[Stable]

NextBestNCRM is the class for next best dose that finds the next dose with high posterior probability to be in the target toxicity interval.

Usage

```
NextBestNCRM(target, overdose, max_overdose_prob)

.DefaultNextBestNCRM()
```

Arguments

target	(numeric) see slot definition.
overdose	(numeric) see slot definition.
max_overdose_prob	(proportion) see slot definition.

Details

To avoid numerical problems, the dose selection algorithm has been implemented as follows: First admissible doses are found, which are those with probability to fall in overdose category being below max_overdose_prob. Next, within the admissible doses, the maximum probability to fall in the target category is calculated. If that is above 5% (i.e. it is not just numerical error), then the corresponding dose is the next recommended dose. Otherwise, the highest admissible dose is the next recommended dose.

Slots

target (numeric)
: the target toxicity interval (limits included).

overdose (numeric)
: the overdose toxicity interval (lower limit excluded, upper limit included). It is used to filter probability samples.

max_overdose_prob (proportion)
: maximum overdose posterior probability that is allowed, except 0 or 1.

Note

Typically, end users will not use the .DefaultNextBestNCRM() function.

Examples

```
# In the example below, the target toxicity interval [0.2, 0.35] while the
# overdose interval is (0.35,1]. Finally we would like to constrain the
# probability of overdosing below 25%.
my_next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)
```

NextBestNCRMLoss-class

NextBestNCRMLoss

Description

[Stable]

NextBestNCRMLoss is the class based on NCRM rule and loss function. This class is similar to NextBestNCRM class, but differences are the addition of loss function and re-defined toxicity intervals, see each toxicity interval documentation and the note for details. As in NCRM rule, first admissible doses are found, which are those with probability to fall in overdose category being below `max_overdose_prob`. Next, within the admissible doses, the loss function is calculated, i.e. `losses %*% target`. Finally, the corresponding dose with lowest loss function (Bayes risk) is recommended for the next dose.

Usage

```
NextBestNCRMLoss(
  target,
  overdose,
  unacceptable = c(1, 1),
  max_overdose_prob,
  losses
)

.DefaultNextBestNCRMLoss()
```

Arguments

`target`	(`numeric`) see slot definition.
`overdose`	(`numeric`) see slot definition.
`unacceptable`	(`numeric`) see slot definition.

`max_overdose_prob`
: (`proportion`)
see slot definition in `NextBestNCRM`.

`losses`
: (`numeric`)
see slot definition.

Slots

`target` (`numeric`)
: the target toxicity interval (limits included). It has to be a probability range excluding 0 and 1.

`overdose` (`numeric`)
: the overdose toxicity interval (lower limit excluded, upper limit included) or the excessive toxicity interval (lower limit excluded, upper limit included) if unacceptable is not provided. It has to be a probability range. It is used to filter probability samples.

`unacceptable` (`numeric`)
: an unacceptable toxicity interval (lower limit excluded, upper limit included). This must be specified if the `overdose` does not include 1. Otherwise, it is `c(1, 1)` (default), which is essentially a scalar equals 1. It has to be a probability range.

`losses` (`numeric`)
: a vector specifying the loss function. If the `unacceptable` is provided, the vector length must be 4, otherwise 3.

Note

The loss function should be a vector of either 3 or 4 values. This is because the loss function values must be specified for each interval, that is under-dosing, target toxicity, and overdosing toxicity or under-dosing, target toxicity, overdosing (excessive) toxicity, and unacceptable toxicity intervals.

Typically, end users will not use the `.DefaultNextBestnCRMLoss()` function.

Examples

```
# In the example below, the target toxicity interval [0.2, 0.35] while the
# overdose interval is (0.35, 1]. We would like to constrain the probability
# of overdosing below 25%. The loss function is c(1, 0, 1, 2).
my_next_best <- NextBestNCRMLoss(
  target = c(0.2, 0.35),
  overdose = c(0.35, 0.6),
  unacceptable = c(0.6, 1),
  max_overdose_prob = 0.25,
  losses = c(1, 0, 1, 2)
)
```

`NextBestOrdinal-class NextBestOrdinal`

Description

[Experimental]

`NextBestOrdinal` is the class for applying a standard `NextBest` rule to the results of an ordinal CRM trial.

Usage

```
NextBestOrdinal(grade, rule)

.DefaultNextBestOrdinal()
```

Arguments

`grade`	(`numeric`) see slot definition.
`rule`	(`NextBest`) see slot definition.

Slots

`grade` (`integer`)
: the toxicity grade to which the `rule` should be applied.

`rule` (`NextBest`)
: the standard `NextBest` rule to be applied

Note

Typically, end users will not use the `.DefaultNextBestOrdinal()` function.

Examples

```
NextBestOrdinal(
  grade = 1L,
  rule = NextBestMTD(
    0.25,
    function(mtd_samples) {
      quantile(mtd_samples, probs = 0.25)
    }
  )
)
```

NextBestProbMTDLTE-class
NextBestProbMTDLTE

Description

[Experimental]

NextBestProbMTDLTE is the class of finding a next best dose that selects the dose with the highest probability of having a toxicity rate less or equal to the toxicity target. The dose is determined by calculating the posterior toxicity probability for each dose per iteration and select the maximum dose that has a toxicity probability below or equal to the target. The dose with the highest frequency of being selected as MTD across iterations is the next best dose. Placebo is not considered in the calculation and removed from the dose grid for any calculations.

Usage

```
NextBestProbMTDLTE(target)

.DefaultNextBestProbMTDLTE()
```

Arguments

target	(numeric) see slot definition.

Slots

target (numeric)
: the target toxicity probability.

Note

Typically, end users will not use the .DefaultNextBestProbMTDLTE() function.

Examples

```
# In the example below, the MTD is defined as the dose with the highest
# probability of having a toxicity rate below 30%.
next_best_prob_mtd_lte <- NextBestProbMTDLTE(target = 0.3)
```

NextBestProbMTDMinDist-class
NextBestProbMTDMinDist

Description

[Experimental]

NextBestProbMTDMinDist is the class of finding a next best dose that selects the dose with the highest probability of having a toxicity rate with the smallest distance to the toxicity target. The dose is determined by calculating the posterior toxicity probability for each dose per iteration and select the dose that has the smallest toxicity probability distance to the target. The dose with the highest frequency of being selected as MTD across iterations is the next best dose. Placebo is not considered as the next dose and for that reason not used in calculations. I.e. for placebo the toxicity probability distance to target is not calculated and taken into account for determination of the next dose.

Usage

```
NextBestProbMTDMinDist(target)

.DefaultNextBestProbMTDMinDist()
```

Arguments

target	(numeric) see slot definition.

Slots

target (numeric)
: the target toxicity probability.

Note

Typically, end users will not use the .DefaultNextBestProbMTDMinDist() function.

Examples

```
# In the example below, the MTD is defined as the dose with the highest
# probability of having a toxicity rate with minimal distance
# to the target of 30%.
next_best_prob_mtd_min_dist <- NextBestProbMTDMinDist(target = 0.3)
```

NextBestTD-class NextBestTD

Description

[Stable]

NextBestTD is the class to find a next best dose based on pseudo DLT model without samples. Namely, it is to find two next best doses, one for allocation during the trial and the second for final recommendation at the end of a trial without involving any samples, i.e. only DLT responses will be incorporated for the dose-allocation. This is based solely on the probabilities of the occurrence of a DLT obtained by using the modal estimates of the model parameters. There are two target probabilities of the occurrence of a DLT that must be specified: target probability to be used during the trial and target probability to be used at the end of the trial. It is suitable to use it only with the ModelTox model class.

Usage

```
.DefaultNextBestTD()

NextBestTD(prob_target_drt, prob_target_eot)
```

Arguments

prob_target_drt	(proportion) see slot definition.
prob_target_eot	(proportion) see slot definition.

Slots

`prob_target_drt` (proportion)
: the target probability (except 0 or 1) of the occurrence of a DLT to be used during the trial.

`prob_target_eot` (proportion)
: the target probability (except 0 or 1) of the occurrence of a DLT to be used at the end of the trial.

Note

Typically, end users will not use the `.DefaultNextBestTD()` function.

Examples

```
my_next_best <- NextBestTD(0.35, 0.3)
```

NextBestTDsamples-class
NextBestTDsamples

Description

[Stable]

NextBestTDsamples is the class to find a next best dose based on Pseudo DLT model with samples. Namely, it is to find two next best doses, one for allocation during the trial and the second for final recommendation at the end of a trial. Hence, there are two target probabilities of the occurrence of a DLT that must be specified: target probability to be used during the trial and target probability to be used at the end of the trial.

Usage

```
NextBestTDsamples(prob_target_drt, prob_target_eot, derive)

.DefaultNextBestTDsamples()
```

Arguments

prob_target_drt	(proportion) see slot definition in NextBestTD.
prob_target_eot	(proportion) see slot definition in NextBestTD.
derive	(function) see slot definition.

Slots

`derive` (function)
: derives, based on a vector of posterior dose samples, the target dose that has the probability of the occurrence of DLT equals to either the `prob_target_drt` or `prob_target_eot`. It must therefore accept one and only one argument, which is a numeric vector, and return a number.

Note

Typically, end users will not use the `.DefaultNextBestTDsamples()` function.

Examples

```
# Target probability of the occurrence of a DLT during the trial is set to 0.35.
# Target probability of the occurrence of a DLT at the end of the trial is set to 0.3.
# We want the use the 30% posterior quantile (the 30th percentile) of the TD35
# (the dose level with probability of the DLT equals 0.35) and TD30 samples.
```

```
my_next_best <- NextBestTDsamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, probs = 0.3))
  }
)
```

`NextBestThreePlusThree-class` `NextBestThreePlusThree`

Description

[Stable]

`NextBestThreePlusThree` is the class for next best dose that implements the classical 3+3 dose recommendation. No input is required, hence this class has no slots.

Usage

```
NextBestThreePlusThree()

.DefaultNextBestThreePlusThree()
```

Note

Typically, end users will not use the `.DefaultNextBestThreePlusThree()` function.

Examples

```
# Next best dose class object using the classical 3+3 design.
my_next_best <- NextBestThreePlusThree()
```

`ngrid` *Number of Doses in Grid*

Description

[Stable]

A function that gets the number of doses in grid. User can choose whether the placebo dose (if any) should be counted or not.

Usage

```
ngrid(object, ignore_placebo = TRUE, ...)

## S4 method for signature 'Data'
ngrid(object, ignore_placebo = TRUE, ...)
```

Arguments

object	(Data) object with dose grid.
ignore_placebo	(flag) should placebo dose (if any) not be counted?
...	further arguments passed to class-specific methods.

Value

integer the number of doses in grid.

Examples

```
my_data <- Data(
  x = c(10, 50, 90, 100, 0.001, 20, 30, 30),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  ID = 1:8,
  cohort = c(1L, 2L, 3L, 4L, 5L, 5L, 6L, 6L),
  doseGrid = c(0.001, seq(from = 10, to = 100, by = 10)),
  placebo = TRUE
)
ngrid(my_data)
ngrid(my_data, ignore_placebo = FALSE)
```

NoArmCondition-class NoArmCondition

Description

[Experimental]

NoArmCondition always opens an active arm immediately. It is the default opening condition for DesignArm objects.

Usage

```
NoArmCondition()

.DefaultNoArmCondition()
```

Note

Typically, end users will not use the .DefaultNoArmCondition() function.

`OneParExpPrior-class` `OneParExpPrior`

Description

[Experimental]

`OneParExpPrior` is the class for a standard CRM with an exponential prior on the power parameter for the skeleton prior probabilities. It is an implementation of a version of the one-parameter CRM (O'Quigley et al. 1990).

Usage

```
OneParExpPrior(skel_probs, dose_grid, lambda)

.DefaultOneParExpPrior()
```

Arguments

`skel_probs`	see slot definition.
`dose_grid`	(`numeric`) dose grid. It must be must be a sorted vector of the same length as `skel_probs`.
`lambda`	see slot definition.

Slots

`skel_fun` (`function`)
: function to calculate the prior DLT probabilities.

`skel_fun_inv` (`function`)
: inverse function of `skel_fun`.

`skel_probs` (`numeric`)
: skeleton prior probabilities. This is a vector of unique and sorted probability values between 0 and 1.

`lambda` (`number`)
: rate parameter of prior exponential distribution for theta.

Note

Typically, end users will not use the `.DefaultOneparExpPrior()` function.

Typically, end users will not use the `.DefaultOneParLogNormalPrior()` function.

References

O'Quigley J, Pepe M, Fisher L (1990). "Continual reassessment method: a practical design for phase 1 clinical trials in cancer." *Biometrics*, **46**(1). doi:10.2307/2531628.

Examples

```
my_model <- OneParExpPrior(
  skel_probs = c(0.1, 0.3, 0.5, 0.7, 0.9),
  dose_grid = 1:5,
  lambda = 2
)
```

`OneParLogNormalPrior-class`
`OneParLogNormalPrior`

Description

[Stable]

`OneParLogNormalPrior` is the class for a standard CRM with a normal prior on the log power parameter for the skeleton prior probabilities.

Usage

```
OneParLogNormalPrior(skel_probs, dose_grid, sigma2)

.DefaultOneParLogNormalPrior()
```

Arguments

`skel_probs`	(`numeric`) skeleton prior probabilities. This is a vector of unique and sorted probability values between 0 and 1.
`dose_grid`	(`numeric`) dose grid. It must be must be a sorted vector of the same length as `skel_probs`.
`sigma2`	(`number`) prior variance of log power parameter alpha.

Value

an instance of the `OneParLogNormalPrior` class

Slots

`skel_fun` (`function`)
: function to calculate the prior DLT probabilities.

`skel_fun_inv` (`function`)
: inverse function of `skel_fun`.

`skel_probs` (`numeric`)
: skeleton prior probabilities. This is a vector of unique and sorted probability values between 0 and 1.

`sigma2` (`number`)
: prior variance of log power parameter alpha.

See Also

ModelLogNormal.

Examples

```
my_model <- OneParLogNormalPrior(
  skel_probs = seq(from = 0.1, to = 0.9, length = 5),
  dose_grid = 1:5,
  sigma2 = 2
)
```

---

openArm *Open a hierarchical design arm?*

Description

[Experimental]

Usage

```
openArm(condition, data, ...)

## S4 method for signature 'NoArmCondition'
openArm(condition, data, ...)

## S4 method for signature 'ArmFinishedCondition'
openArm(condition, data, finished_arms, ...)

## S4 method for signature 'ArmMinDoseCondition'
openArm(condition, data, ...)

## S4 method for signature 'ArmConditionList'
openArm(condition, data, summary_fun, ...)

## S4 method for signature 'ArmConditionAll'
openArm(condition, data, ...)

## S4 method for signature 'ArmConditionAny'
openArm(condition, data, ...)
```

Arguments

condition	(ArmCondition) opening condition to be applied.
data	(HierarchicalData) current hierarchical trial data.
...	further arguments passed to condition-specific methods.

finished_arms (logical)
named vector indicating which arms have finished dose escalation.

summary_fun (function)
to apply to the list of results (e.g. all or any). Only used for ArmConditionList and its subclasses.

Value

TRUE if this arm can be opened, FALSE otherwise.

Functions

- openArm(NoArmCondition): method for NoArmCondition class, which always opens the arm.
- openArm(ArmFinishedCondition): method for ArmFinishedCondition class.
- openArm(ArmMinDoseCondition): method for ArmMinDoseCondition class.
- openArm(ArmConditionList): method for ArmConditionList class.
- openArm(ArmConditionAll): method for ArmConditionAll class. Returns TRUE if ALL arm opening criteria are satisfied.
- openArm(ArmConditionAny): method for ArmConditionAny class. Returns TRUE if ANY arm opening criterion is satisfied.

---

openCohort *Open / recruit backfill patients into a cohort?*

Description

[Experimental]

Usage

```
openCohort(opening, cohort, data, dose, ...)

## S4 method for signature 'OpeningMinDose'
openCohort(opening, cohort, data, dose, ...)

## S4 method for signature 'OpeningMinCohorts'
openCohort(opening, cohort, data, dose, ...)

## S4 method for signature 'OpeningNone'
openCohort(opening, cohort, data, dose, ...)

## S4 method for signature 'OpeningMinResponses'
openCohort(opening, cohort, data, dose, ...)
```

```
## S4 method for signature 'OpeningList'
openCohort(opening, cohort, data, dose, summary_fun, ...)

## S4 method for signature 'OpeningAll'
openCohort(opening, cohort, data, dose, ...)

## S4 method for signature 'OpeningAny'
openCohort(opening, cohort, data, dose, ...)
```

Arguments

opening	(Opening) opening rule to be applied.
cohort	(int) backfill cohort index.
data	(Data) current trial data.
dose	(numeric) the recommended next best dose.
...	further arguments (not used).
summary_fun	(function) to apply to the list of results (e.g., all or any). Only used for OpeningList and its subclasses.

Value

TRUE if this backfill cohort can be opened / recruited into, FALSE otherwise.

Functions

- openCohort(OpeningMinDose): method for OpeningMinDose class.
- openCohort(OpeningMinCohorts): method for OpeningMinCohorts class.
- openCohort(OpeningNone): method for OpeningNone class, which never opens a cohort, i.e. the trial design will not use backfilling.
- openCohort(OpeningMinResponses): method for OpeningMinResponses class.
- openCohort(OpeningList): method for OpeningList class.
- openCohort(OpeningAll): method for OpeningAll class. Returns TRUE if ALL opening criteria are satisfied.
- openCohort(OpeningAny): method for OpeningAny class. Returns TRUE if ANY opening criteria are satisfied.

Examples

```
# Create a simple data object with some dose information
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
```

```
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(1, 2, 3, 4, 5, 6, 6, 6),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Define the opening rule: open backfill cohorts when dose is at least 5
my_opening <- OpeningMinDose(min_dose = 5)

# Check if the first backfill cohort can be opened when the
# cohort has a dose 6, i.e. larger than 5.
# Note that `dose` is not used in this rule.
can_open <- openCohort(my_opening, cohort = 5, data = data, dose = 7)
can_open

# Check if the first backfill cohort can be opened when the
# cohort has a dose 3, i.e. smaller than 5.
# (should return FALSE because dose < min_dose)
can_open_low <- openCohort(my_opening, cohort = 4, data = data, dose = 15)
can_open_low
# Create a data object with multiple cohorts
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Define the opening rule: open backfill cohorts after at least 3 cohorts
my_opening <- OpeningMinCohorts(min_cohorts = 3)

# Check if a backfill cohort can be opened
# Current number of cohorts is 6, so it should open (6 >= 3)
can_open <- openCohort(my_opening, cohort = 1, data = data, dose = 25)
can_open
# Create an OpeningNone object which never opens backfill cohorts
opening <- OpeningNone()

# Create sample trial data
data <- Data(
  x = c(20, 30, 40, 50),
  y = c(0, 0, 1, 0),
  cohort = c(1, 2, 3, 4),
  doseGrid = seq(10, 100, by = 10)
)

# Create dose recommendation
dose <- 60

# Check if backfill cohort should be opened for cohort 5
# OpeningNone always returns FALSE
should_open <- openCohort(opening, cohort = 5, data = data, dose = dose)
print(should_open) # FALSE
# Create an OpeningMinResponses object requiring 2 responses at the cohort dose
```

```
opening <- OpeningMinResponses(min_responses = 2, include_lower_doses = FALSE)

# Create sample trial data with responses at different dose levels
data <- Data(
  x = c(10, 10, 20, 20, 20, 30, 30, 30),
  y = c(0, 1, 0, 1, 0, 1, 1, 0),
  response = c(1, 1, NA, 0, 1, NA, 1, 0),
  cohort = c(1, 1, 2, 2, 2, 3, 3, 3),
  doseGrid = seq(10, 100, by = 10)
)

# Check if backfill cohort can be opened at dose 20
# At dose 20, there is 1 response
should_open <- openCohort(opening, cohort = 2, data = data, dose = 30)
print(should_open) # FALSE

# Check at dose 10 where there are 2 responses
should_open_2 <- openCohort(opening, cohort = 1, data = data, dose = 30)
print(should_open_2) # TRUE
# Create sample trial data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(1, 2, 3, 4, 5, 6, 6, 6),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Create opening criteria:
# - opening1: open if dose >= 10
# - opening2: open if at least 5 cohorts have been treated
opening1 <- OpeningMinDose(min_dose = 10)
opening2 <- OpeningMinCohorts(min_cohorts = 5)

# Combine with AND logic: both must be true
opening_all <- opening1 & opening2

# Test if backfill cohort 7 can be opened
# Cohort 6 dose is 10 (>= 10: TRUE), max cohort is 6 (>= 5: TRUE), so AND is TRUE
should_open <- openCohort(opening_all, cohort = 6, data = data, dose = 20)
print(should_open) # TRUE

# Test if backfill cohort at dose 6 can be opened
# Cohort 4 dose is 3 (>= 10: FALSE), so AND is FALSE
should_open_2 <- openCohort(opening_all, cohort = 4, data = data, dose = 20)
print(should_open_2) # FALSE
# Create sample trial data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(1, 2, 3, 4, 5, 6, 6, 6),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)
```

```
# Create opening criteria:
# - opening1: open if dose >= 20
# - opening2: open if at least 5 cohorts have been treated
opening1 <- OpeningMinDose(min_dose = 20)
opening2 <- OpeningMinCohorts(min_cohorts = 5)

# Combine with OR logic: at least one must be true
opening_any <- opening1 | opening2

# Test if backfill cohort 7 can be opened at dose 10
# Cohort 6 dose is 10 (>= 20: FALSE), max cohort is 6 (>= 5: TRUE), so OR is TRUE
should_open <- openCohort(opening_any, cohort = 6, data = data, dose = 20)
print(should_open) # TRUE

# Test with a different scenario:
# It does not matter which cohort index we give, because
# the number of cohorts is already above 5.
should_open_2 <- openCohort(opening_any, cohort = 1, data = data, dose = 25)
print(should_open_2) # TRUE
```

`Opening-class` `Opening`

Description

[Experimental]

`Opening` is a virtual class for opening criteria, from which all other specific opening criteria classes inherit. The subclasses are used for backfill cohort designs.

Usage

```
.DefaultOpening()
```

Note

Typically, end users will not use the `.DefaultOpening()` function.

See Also

`OpeningMinDose`, `OpeningMinCohorts`, `OpeningNone`, `OpeningMinResponses`, `OpeningAll`, `OpeningAny`.

OpeningAll-class OpeningAll

Description

[Experimental]

OpeningAll combines multiple Opening objects using AND logic. A backfill cohort is opened only if ALL opening criteria in the list are satisfied. This can also be created using the & operator.

Usage

```
OpeningAll(...)

.DefaultOpeningAll()
```

Arguments

...	(Opening) opening objects to combine with AND logic.

Slots

open_list (list) a list of Opening objects to be combined with AND logic.

Note

Typically, end users will not use the .DefaultOpeningAll() function.

See Also

Opening, OpeningAny, OpeningList.

Examples

```
# Create two opening criteria
opening1 <- OpeningMinDose(min_dose = 10)
opening2 <- OpeningMinCohorts(min_cohorts = 3)

# Combine them with AND logic: both must be satisfied
opening_all <- OpeningAll(opening1, opening2)
print(opening_all)

# Alternative: use the & operator
opening_all_alt <- opening1 & opening2
print(opening_all_alt)
```

`OpeningAny-class` `OpeningAny`

Description

[Experimental]

`OpeningAny` combines multiple `Opening` objects using OR logic. A backfill cohort is opened if ANY opening criteria in the list are satisfied. This can also be created using the `|` operator.

Usage

```
OpeningAny(...)

.DefaultOpeningAny()
```

Arguments

`...`	(`Opening`) opening objects to combine with OR logic.

Slots

`open_list` (`list`)
: a list of `Opening` objects to be combined with OR logic.

Note

Typically, end users will not use the `.DefaultOpeningAny()` function.

See Also

`Opening`, `OpeningAll`, `OpeningList`.

Examples

```
# Create two opening criteria
opening1 <- OpeningMinDose(min_dose = 10)
opening2 <- OpeningMinCohorts(min_cohorts = 3)

# Combine them with OR logic: at least one must be satisfied
opening_any <- OpeningAny(opening1, opening2)
print(opening_any)

# Alternative: use the | operator
opening_any_alt <- opening1 | opening2
print(opening_any_alt)
```

`OpeningList-class` `OpeningList`

Description

[Experimental]

`OpeningList` is a virtual class for combining multiple `Opening` objects using logical operators. It is used as a base class for `OpeningAll` and `OpeningAny`.

Usage

```
OpeningList(...)

.DefaultOpeningList()
```

Arguments

`...`	(`Opening`) opening objects to combine.

Slots

`open_list` (`list`) a list of `Opening` objects to be combined.

Note

Typically, end users will not use the `.DefaultOpeningList()` function.

See Also

`Opening`, `OpeningAll`, `OpeningAny`.

Examples

```
# Create two simple opening criteria
opening1 <- OpeningMinDose(min_dose = 10)
opening2 <- OpeningMinCohorts(min_cohorts = 3)

# Create an OpeningList that combines them
opening_list <- OpeningList(opening1, opening2)
print(opening_list)

# You can also create with more than two criteria
opening3 <- OpeningNone()
opening_list_multi <- OpeningList(opening1, opening2, opening3)
print(opening_list_multi)
```

OpeningMinCohorts-class OpeningMinCohorts

Description

[Experimental]

`OpeningMinCohorts` opens backfill cohorts when the overall number of cohorts treated so far in the trial reaches or exceeds a minimum threshold. This can be used to implement a "delayed backfill cohort opening" rule.

Usage

```
OpeningMinCohorts(min_cohorts = 2L)

.DefaultOpeningMinCohorts()
```

Arguments

`min_cohorts`	`(integer)` see slot definition.

Slots

`min_cohorts (integer)`
: the minimum number of cohorts that must have been treated before backfilling can be opened.

Note

Typically, end users will not use the `.DefaultOpeningMinCohorts()` function.

See Also

`Opening` and the other subclasses listed in there.

OpeningMinDose-class OpeningMinDose

Description

[Experimental]

`OpeningMinDose` opens a backfill cohort when the cohort's dose is above or equal to the minimum dose specified. Note that the next recommended dose is not taken into account.

Usage

```
OpeningMinDose(min_dose = 0)

.DefaultOpeningMinDose()
```

Arguments

min_dose	(number) see slot definition.

Slots

`min_dose` (`numeric`)
: the minimum dose at which backfill cohorts can be opened. For combination trials, this can be a vector of minimum doses for each agent.

Note

Typically, end users will not use the `.DefaultOpeningMinDose()` function.

See Also

`Opening` and the other subclasses listed in there.

Examples

```
# Opening backfill cohort when dose is at least 50
my_opening <- OpeningMinDose(min_dose = 50)
```

OpeningMinResponses-class

OpeningMinResponses

Description

[Experimental]

`OpeningMinResponses` opens backfill cohorts when a minimum number of responses has been observed in the trial. The responses can be counted at the cohort's dose level only, or also at lower dose levels if `include_lower_doses` is set to `TRUE`.

Usage

```
OpeningMinResponses(min_responses = 1L, include_lower_doses = FALSE)

.DefaultOpeningMinResponses()
```

Arguments

`min_responses` (count)
see slot definition.

`include_lower_doses` (logical)
see slot definition.

Slots

`min_responses` (count)
the minimum number of responses required before backfill cohorts can be opened (at least 1).

`include_lower_doses` (logical)
if `TRUE`, responses at all doses less than or equal to the cohort's dose are counted. If `FALSE`, only responses at the cohort's dose are counted.

Note

Typically, end users will not use the `.DefaultOpeningMinResponses()` function.

See Also

`Opening` and the other subclasses listed in there.

Examples

```
# Create an OpeningMinResponses object that requires 2 responses
opening <- OpeningMinResponses(min_responses = 2, include_lower_doses = FALSE)

# Display the object
print(opening)

# Create a variant that includes lower doses
opening_inclusive <- OpeningMinResponses(
  min_responses = 2,
  include_lower_doses = TRUE
)
print(opening_inclusive)
```

OpeningNone-class OpeningNone

Description

[Experimental]

`OpeningNone` never opens any backfill cohorts. This can be used when no backfill cohorts should be available in a trial design.

Usage

```
OpeningNone()

.DefaultOpeningNone()
```

Note

Typically, end users will not use the `.DefaultOpeningNone()` function.

`or,ArmCondition,ArmCondition-method`
Logical OR Operator for ArmCondition Objects

Description

[Experimental]

Combines two `ArmCondition` objects with OR logic using the `|` operator. This creates an `ArmConditionAny` object.

Usage

```
## S4 method for signature 'ArmCondition,ArmCondition'
e1 | e2
```

Arguments

`e1`	(`ArmCondition`) the first arm condition object.
`e2`	(`ArmCondition`) the second arm condition object.

Value

An `ArmConditionAny` object combining `e1` and `e2`.

or,Opening,Opening-method *Logical OR Operator for Opening Objects*

Description

[Experimental]

Combines two Opening objects with OR logic using the | operator. This creates an OpeningAny object.

Usage

```
## S4 method for signature 'Opening,Opening'
e1 | e2
```

Arguments

e1	(Opening) the first opening object.
e2	(Opening) the second opening object.

Value

An OpeningAny object combining e1 and e2.

See Also

OpeningAny for more details.

or-Stopping-Stopping *Combine Two Stopping Rules with OR*

Description

[Stable]

The method combining two atomic stopping rules.

Usage

```
## S4 method for signature 'Stopping,Stopping'
e1 | e2
```

Arguments

e1	(Stopping) first stopping rule object.
e2	(Stopping) second stopping rule object.

Value

The StoppingAny object.

Examples

```
## Example of combining two atomic stopping rules with an OR ('|') operator

myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)

myStopping <- myStopping1 | myStopping2
```

---

or-Stopping-StoppingAny

Combine an Atomic Stopping Rule and a Stopping List with OR

Description

[Stable]

The method combining an atomic stopping rule and a stopping list.

Usage

```
## S4 method for signature 'Stopping,StoppingAny'
e1 | e2
```

Arguments

e1	(Stopping) stopping rule object.
e2	(StoppingAny) stopping list object.

Value

The modified StoppingAny object.

Examples

```
## Example of combining an atomic stopping rule with a list of stopping rules
## with an OR ('|') operator

myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)

myStopping3 <- StoppingMinPatients(nPatients = 20)

myStopping <- myStopping3 | (myStopping1 & myStopping2)
```

---

or-StoppingAny-Stopping

Combine a Stopping List and an Atomic Stopping Rule with OR

Description

[Stable]

The method combining a stopping list and an atomic stopping rule.

Usage

```
## S4 method for signature 'StoppingAny,Stopping'
e1 | e2
```

Arguments

e1	(StoppingAny) stopping list object.
e2	(Stopping) stopping rule object.

Value

The modified StoppingAny object.

Examples

```
## Example of combining a list of stopping rules with an atomic stopping rule
## with an OR ('|') operator

myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)

myStopping3 <- StoppingMinPatients(nPatients = 20)

myStopping <- (myStopping1 & myStopping2) | myStopping3
```

`plot,ComboSimulations,missing-method`
Plot `ComboSimulations`

Description

[Experimental]

Summarize two-drug combination simulations with plots.

This plot method can be applied to `ComboSimulations` objects. Possible `types` of plots are:

trajectory Summary of simulated dose trajectories for each drug

dosesTried Average proportions of tested doses for each drug

trajectory2D 2D dose-plane evolution with arrows for dose transitions, and labels showing DLTs/patients plus a step index hint

Usage

```
## S4 method for signature 'ComboSimulations,missing'
plot(x, y, type = c("trajectory", "dosesTried", "trajectory2D"), ...)
```

Arguments

`x`	(`ComboSimulations`) the object we want to plot from.
`y`	(`missing`) not used.
`type`	(`character`) the type of plots you want to obtain.
`...`	not used.

Value

A single `ggplot` object if a single panel is produced, otherwise a `gtable` object.

`plot,ComboSimulationsSummary,missing-method`
Plot `ComboSimulationsSummary`

Description

[Experimental]

Graphical display of combination simulation summaries.

Usage

```
## S4 method for signature 'ComboSimulationsSummary,missing'
plot(
  x,
  y,
  type = c("nObs", "doseSelectedDrug1", "doseSelectedDrug2", "propDLTs"),
  ...
)
```

Arguments

x	(ComboSimulationsSummary) the object we want to plot from.
y	(missing) not used.
type	(character) the types of plots you want to obtain.
...	not used.

Value

A single ggplot object if a single plot is asked for, otherwise a gtable object.

---

plot,Data,ModelTox-method

Plot of the fitted dose-tox based with a given pseudo DLE model and data without samples

---

Description

Plot of the fitted dose-tox based with a given pseudo DLE model and data without samples

Usage

```
## S4 method for signature 'Data,ModelTox'
plot(
  x,
  y,
  xlab = "Dose level",
  ylab = "Probability of DLE",
  showLegend = TRUE,
  ...
)
```

Arguments

x	the data of Data class object
y	the model of the ModelTox class object
xlab	the x axis label
ylab	the y axis label
showLegend	should the legend be shown? (default)
...	not used

Value

This returns the ggplot object for the dose-DLE model plot

Examples

```
## plot the dose-DLE curve given a pseudo DLE model using data without samples
## data must be of 'Data' class
## define the data
data <- Data(
  x = c(25, 50, 50, 75, 100, 100, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  ID = 1L:8L,
  cohort = as.integer(c(1, 2, 2, 3, 4, 4, 5, 6)),
  doseGrid = seq(25, 300, 25)
)
## model must be from 'ModelTox' class e.g 'LogisticIndepBeta' class model
## define the model (see LogisticIndepBeta example)
model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
## plot the dose-DLE curve
## 'x' is the data and 'y' is the model in plot
plot(x = data, y = model)
```

---

plot,DataCombo,missing-method

Plot Method for the DataCombo Class

Description

[Experimental]

A method that creates a plot for DataCombo object.

Usage

```
## S4 method for signature 'DataCombo,missing'
plot(x, y, legend = TRUE, ...)
```

Arguments

x	(DataCombo)
y	(missing)
legend	(flag) whether legends should be displayed.
...	not used.

Value

A gtable object combining two ggplot2 plots.

Examples

```
data <- .DefaultDataCombo()

plot(data)
```

---

plot,DataDA,missing-method

Plot Method for the DataDA Class

Description

[Stable]

A method that creates a plot for DataDA object.

Usage

```
## S4 method for signature 'DataDA,missing'
plot(x, y, blind = FALSE, ...)
```

Arguments

x	(DataDA) object we want to plot.
y	(missing) missing object, for compatibility with the generic function.
blind	(flag) indicates whether to blind the data. If TRUE, then placebo subjects are reported at the same level as the active dose level in the corresponding cohort, and DLTs are always assigned to the first subjects in a cohort.
...	passed to the first inherited method plot after this current method.

Value

The ggplot2 object.

Examples

```
# Create some data of class 'DataDA'.
my_data <- DataDA(
  u = c(42, 30, 15, 5, 20, 25, 30, 60),
  t0 = c(0, 15, 30, 40, 55, 70, 75, 85),
  Tmax = 60,
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 1, 1, 0, 0, 1, 0),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Plot the data.
plot(my_data)
```

---

plot,DataDual,missing-method

Plot Method for the DataDual Class

Description

[Stable]

A method that creates a plot for DataDual object.

Usage

```
## S4 method for signature 'DataDual,missing'
plot(x, y, blind = FALSE, ...)
```

Arguments

x	(DataDual) object we want to plot.
y	(missing) missing object, for compatibility with the generic function.
blind	(flag) indicates whether to blind the data. If TRUE, then placebo subjects are reported at the same level as the active dose level in the corresponding cohort, and DLTs are always assigned to the first subjects in a cohort.
...	passed to the first inherited method plot after this current method.

Value

The ggplot2 object.

Examples

```
# Create some data of class 'DataDual'.
my_data <- DataDual(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  w = rnorm(8),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Plot the data.
plot(my_data)
```

---

plot,DataDual,ModelEff-method

Plot of the fitted dose-efficacy based with a given pseudo efficacy model and data without samples

---

Description

Plot of the fitted dose-efficacy based with a given pseudo efficacy model and data without samples

Usage

```
## S4 method for signature 'DataDual,ModelEff'
plot(
  x,
  y,
  ...,
  xlab = "Dose level",
  ylab = "Expected Efficacy",
  showLegend = TRUE
)
```

Arguments

x	the data of DataDual class object
y	the model of the ModelEff class object
...	not used
xlab	the x axis label
ylab	the y axis label
showLegend	should the legend be shown? (default)

Value

This returns the ggplot object for the dose-efficacy model plot

Examples

```
# nolint start

##plot the dose-efficacy curve given a pseudo efficacy model using data without samples
##data must be of 'DataDual' class
##define the data
data <- DataDual(
  x = c(25, 50, 50, 75, 100, 100, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)
##model must be from 'ModelEff' class e.g 'Effloglog' class model
##define the model (see Effloglog example)
Effmodel <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data
)
## plot the dose-efficacy curve
## 'x' is the data and 'y' is the model in plot
plot(x = data, y = Effmodel)

# nolint end
```

---

plot,DualSimulations,missing-method

Plot DualSimulations

Description

[Stable]

This plot method can be applied to DualSimulations objects in order to summarize them graphically. In addition to the standard plot types, there is:

sigma2W Plot a boxplot of the final biomarker variance estimates in the simulated trials

rho Plot a boxplot of the final correlation estimates in the simulated trials

Usage

```
## S4 method for signature 'DualSimulations,missing'
plot(x, y, type = c("trajectory", "dosesTried", "sigma2W", "rho"), ...)
```

Arguments

x	(DualSimulations) the object we want to plot from.
y	(missing) not used.
type	(character) the type of plots you want to obtain.
...	not used.

Value

A single ggplot object if a single plot is asked for, otherwise a gtable object.

Examples

```
# Define the dose-grid.
emptydata <- DataDual(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))

# Create some data.
my_data <- DataDual(
  x = c(
    0.1,
    0.5,
    1.5,
    3,
    6,
    10,
    10,
    10,
    20,
    20,
    20,
    40,
    40,
    40,
    50,
    50,
    50
  ),
  y = c(
    0,
    0,
    0,
    0,
    0,
    0,
    1,
    0,
    0,
    1,
```

```
  1,
  0,
  0,
  1,
  0,
  1,
  1
),
ID = 1:17,
cohort = c(
  1L,
  2L,
  3L,
  4L,
  5L,
  6L,
  6L,
  6L,
  7L,
  7L,
  7L,
  8L,
  8L,
  8L,
  9L,
  9L,
  9L
),
w = c(
  0.31,
  0.42,
  0.59,
  0.45,
  0.6,
  0.7,
  0.55,
  0.6,
  0.52,
  0.54,
  0.56,
  0.43,
  0.41,
  0.39,
  0.34,
  0.38,
  0.21
),
doseGrid = c(
  0.1,
  0.5,
  1.5,
  3,
  6,
```

```
    seq(from = 10, to = 80, by = 2)
  )
)

# Initialize the CRM model.
my_model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2betaW = 0.01,
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  rw1 = TRUE
)

# Choose the rule for selecting the next dose.
my_next_best <- NextBestDualEndpoint(
  target = c(0.9, 1),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size
mySize1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
mySize2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
mySize <- maxSize(mySize1, mySize2)

# Choose the rule for stopping
myStopping4 <- StoppingTargetBiomarker(
  target = c(0.9, 1),
  prob = 0.5
)
myStopping <- myStopping4 | StoppingMinPatients(40) | StoppingMissingDose()

my_size1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
my_size2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
my_size <- maxSize(my_size1, my_size2)

# Choose the rule for stopping
my_stopping4 <- StoppingTargetBiomarker(
  target = c(0.9, 1),
  prob = 0.5
```

```
)
my_stopping <- my_stopping4 | StoppingMinPatients(40) | StoppingMissingDose()

# Choose the rule for dose increments
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Initialize the design

my_design <- DualDesign(
  model = my_model,
  data = emptydata,
  nextBest = my_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = CohortSizeConst(3),
  startingDose = 3
)

# Define scenarios for the TRUE toxicity and efficacy profiles.
beta_mod <- function(dose, e0, eMax, delta1, delta2, scal) {
  maxDens <- (delta1^delta1) *
    (delta2^delta2) /
    ((delta1 + delta2)^(delta1 + delta2))
  dose <- dose / scal
  e0 + eMax / maxDens * (dose^delta1) * (1 - dose)^delta2
}

true_biomarker <- function(dose) {
  beta_mod(
    dose,
    e0 = 0.2,
    eMax = 0.6,
    delta1 = 5,
    delta2 = 5 * 0.5 / 0.5,
    scal = 100
  )
}

true_tox <- function(dose) {
  pnorm((dose - 60) / 10)
}

# Draw the TRUE profiles
par(mfrow = c(1, 2))
curve(true_tox(x), from = 0, to = 80)
curve(true_biomarker(x), from = 0, to = 80)

# Run the simulation on the desired design.
# We only generate 1 trial outcome here for illustration, for the actual study.
# Also for illustration purpose, we will use 5 burn-ins to generate 20 samples,
```

```
# this should be increased of course.
my_sims <- simulate(
  object = my_design,
  trueTox = true_tox,
  trueBiomarker = true_biomarker,
  sigma2W = 0.01,
  rho = 0,
  nsim = 1,
  parallel = FALSE,
  seed = 9,
  startingDose = 6,
  mcmcOptions = McmcOptions(
    burnin = 1,
    step = 1,
    samples = 2
  )
)

# Plot the results of the simulation.
print(plot(my_sims))
```

---

plot,DualSimulationsSummary,missing-method

Plot Dual-Endpoint Design Simulation Summary

Description

[Stable]

Graphical display of dual-endpoint simulation summary.

This plot method can be applied to DualSimulationsSummary objects in order to summarize them graphically. Possible type of plots at the moment are those listed in plot,SimulationsSummary,missing-method plus:

meanBiomarkerFit Plot showing the average fitted dose-biomarker curve across the trials, together with 95% credible intervals, and comparison with the assumed truth (as specified by the trueBiomarker argument to summary,DualSimulations-method)

You can specify any subset of these in the type argument.

Usage

```
## S4 method for signature 'DualSimulationsSummary,missing'
plot(
  x,
  y,
  type = c("nObs", "doseSelected", "propDLTs", "nAboveTarget", "meanFit",
    "meanBiomarkerFit"),
  ...
)
```

Arguments

x	(DualSimulationsSummary) the object we want to plot from.
y	(missing) not used.
type	(character) the types of plots you want to obtain.
...	not used.

Value

A single ggplot object if a single plot is asked for, otherwise a gtable object.

Examples

```
# Define the dose-grid.
emptydata <- DataDual(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))


# Initialize the CRM model.
my_model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2betaW = 0.01,
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  rw1 = TRUE
)


# Choose the rule for selecting the next dose.
my_next_best <- NextBestDualEndpoint(
  target = c(0.9, 1),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size.
my_size1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
my_size2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
my_size <- maxSize(my_size1, my_size2)

# Choose the rule for stopping.
my_stopping4 <- StoppingTargetBiomarker(
```

```
  target = c(0.9, 1),
  prob = 0.5
)
# Only 10 patients here for illustration!
my_stopping <- my_stopping4 | StoppingMinPatients(10) | StoppingMissingDose()

# Choose the rule for dose increments.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Initialize the design.
my_design <- DualDesign(
  model = my_model,
  data = emptydata,
  nextBest = my_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = CohortSizeConst(3),
  startingDose = 3
)

# Define scenarios for the TRUE toxicity and efficacy profiles.
beta_mod <- function(dose, e0, eMax, delta1, delta2, scal) {
  maxDens <- (delta1^delta1) *
    (delta2^delta2) /
    ((delta1 + delta2)^(delta1 + delta2))
  dose <- dose / scal
  e0 + eMax / maxDens * (dose^delta1) * (1 - dose)^delta2
}


true_biomarker <- function(dose) {
  beta_mod(
    dose,
    e0 = 0.2,
    eMax = 0.6,
    delta1 = 5,
    delta2 = 5 * 0.5 / 0.5,
    scal = 100
  )
}

true_tox <- function(dose) {
  pnorm((dose - 60) / 10)
}

# Draw the TRUE profiles.
par(mfrow = c(1, 2))
curve(true_tox(x), from = 0, to = 80)
curve(true_biomarker(x), from = 0, to = 80)
```

```
# Run the simulation on the desired design.
# We only generate 1 trial outcome here for illustration, for the actual study.
# For illustration purpose we will use 5 burn-ins to generate 20 samples,
# this should be increased of course.
my_sims <- simulate(
  object = my_design,
  trueTox = true_tox,
  trueBiomarker = true_biomarker,
  sigma2W = 0.01,
  rho = 0,
  nsim = 1,
  parallel = FALSE,
  seed = 3,
  startingDose = 6,
  mcmcOptions = McmcOptions(
    burnin = 5,
    step = 1,
    samples = 20
  )
)

# Plot the summary of the Simulations.
plot(summary(my_sims, trueTox = true_tox, trueBiomarker = true_biomarker))
```

`plot,GeneralSimulations,missing-method`
Plot `GeneralSimulations`

Description

[Stable]

Summarize the simulations with plots.

This plot method can be applied to `GeneralSimulations` objects in order to summarize them graphically. Possible types of plots at the moment are:

trajectory Summary of the trajectory of the simulated trials

dosesTried Average proportions of the doses tested in patients

You can specify one or both of these in the `type` argument.

Usage

```
## S4 method for signature 'GeneralSimulations,missing'
plot(x, y, type = c("trajectory", "dosesTried"), ...)
```

Arguments

x	(GeneralSimulations) the object we want to plot from.
y	(missing) not used.
type	(character) the type of plots you want to obtain.
...	not used.

Value

A single ggplot object if a single plot is asked for, otherwise a gtable object.

Examples

```
# nolint start

## obtain the plot for the simulation results
## If only DLE responses are considered in the simulations

## Specified your simulations when no DLE samples are used
## Define your data set first using an empty data set
## with dose levels from 25 to 300 with increments 25
data <- Data(doseGrid = seq(25, 300, 25))

## Specified the model of 'ModelTox' class eg 'LogisticIndepBeta' class model
model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
## Then the escalation rule
tdNextBest <- NextBestTD(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)

## The cohort size, size of 3 subjects
mySize <- CohortSizeConst(size = 3)
## Deifne the increments for the dose-escalation process
## The maximum increase of 200% for doses up to the maximum of the dose specified in the doseGrid
## The maximum increase of 200% for dose above the maximum of the dose specified in the doseGrid
## This is to specified a maximum of 3-fold restriction in dose-esclation
myIncrements <- IncrementsRelative(
  intervals = c(min(data@doseGrid), max(data@doseGrid)),
  increments = c(2, 2)
)
## Specified the stopping rule e.g stop when the maximum sample size of 12 patients has been reached
myStopping <- StoppingMinPatients(nPatients = 12) | StoppingMissingDose()
```

```
## Now specified the design with all the above information and starting with a dose of 25
design <- TDDesign(
  model = model,
  nextBest = tdNextBest,
  stopping = myStopping,
  increments = myIncrements,
  cohort_size = mySize,
  data = data,
  startingDose = 25
)

## Specify the truth of the DLE responses
myTruth <- probFunction(model, phi1 = -53.66584, phi2 = 10.50499)

## Then specified the simulations and generate the trial
## For illustration purpose only 1 simulation is produced (nsim=1).
## The simulations
mySim <- simulate(
  design,
  args = NULL,
  truth = myTruth,
  nsim = 1,
  seed = 819,
  parallel = FALSE
)


## plot the simulations
print(plot(mySim))


## If DLE samples are involved
## The escalation rule
tdNextBest <- NextBestTDsamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, probs = 0.3))
  }
)
## specify the design
design <- TDsamplesDesign(
  model = model,
  nextBest = tdNextBest,
  stopping = myStopping,
  increments = myIncrements,
  cohort_size = mySize,
  data = data,
  startingDose = 25
)
## options for MCMC
## The simulations
## For illustration purpose only 1 simulation is produced (nsim=1).
```

```
# mySim <- simulate(design,
#                   args=NULL,
#                   truth=myTruth,
#                   nsim=1,
#                   seed=819,
#                   mcmcOptions=options,
#                   parallel=FALSE)
#
# ##plot the simulations
# print(plot(mySim))
#

# nolint end
```

`plot,GeneralSimulationsSummary,missing-method`
Plot `GeneralSimulationsSummary`

Description

[Stable]

Graphical display of the general simulation summary.

This plot method can be applied to `GeneralSimulationsSummary` objects in order to summarize them graphically. Possible `types` of plots at the moment are:

nObs Distribution of the number of patients in the simulated trials

doseSelected Distribution of the final selected doses in the trials. Note that this can include zero entries, meaning that the trial was stopped because all doses in the dose grid appeared too toxic.

propDLTs Distribution of the proportion of patients with DLTs in the trials

nAboveTarget Distribution of the number of patients treated at doses which are above the target toxicity interval (as specified by the `truth` and `target` arguments to `summary,GeneralSimulations-method`)

You can specify any subset of these in the `type` argument.

Usage

```
## S4 method for signature 'GeneralSimulationsSummary,missing'
plot(x, y, type = c("nObs", "doseSelected", "propDLTs", "nAboveTarget"), ...)
```

Arguments

`x`	(`GeneralSimulationsSummary`) the object we want to plot from.
`y`	(`missing`) not used.
`type`	(`character`) the types of plots you want to obtain.
`...`	not used.

Value

A single ggplot object if a single plot is asked for, otherwise a gtable object.

---

plot,HierarchicalData,missing-method

Plot Method for the HierarchicalData Class

Description

[Experimental]

A method that creates a combined plot for a HierarchicalData object by arranging the arm-specific Data and DataCombo plots.

Usage

```
## S4 method for signature 'HierarchicalData,missing'
plot(x, y, ncol = NULL, ...)
```

Arguments

x	(HierarchicalData) object we want to plot.
y	(missing) missing object, for compatibility with the generic function.
ncol	(count or NULL) number of columns in the combined plot. If NULL, a compact layout is chosen automatically.
...	passed to the arm-specific plot methods.

Value

A gtable object combining the arm-specific plots, or NULL if no arm plot is available.

---

plot,HierarchicalSamples,HierarchicalModel-method

Plotting hierarchical dose-toxicity model fits

Description

Plotting hierarchical dose-toxicity model fits

Usage

```
## S4 method for signature 'HierarchicalSamples,HierarchicalModel'
plot(x, y, data, ncol = NULL, ...)
```

Arguments

x	the HierarchicalSamples object.
y	the HierarchicalModel object.
data	the HierarchicalData object.
ncol	(count or NULL) number of columns in the combined plot. If NULL, a compact layout is chosen automatically.
...	passed to the arm-specific plot methods.

Value

This returns a gtable object combining the arm-specific fitted plots, or NULL if no arm plot is available.

---

plot,PseudoDualFlexiSimulations,missing-method
Plot PseudoDualFlexiSimulations

Description

[Stable]

Summarize the simulations with plots.

This plot method can be applied to PseudoDualFlexiSimulations objects in order to summarize them graphically. Possible types of plots at the moment are:

trajectory Summary of the trajectory of the simulated trials

dosesTried Average proportions of the doses tested in patients

sigma2 The variance of the efficacy responses

sigma2betaW The variance of the random walk model

You can specify one or both of these in the type argument.

Usage

```
## S4 method for signature 'PseudoDualFlexiSimulations,missing'
plot(x, y, type = c("trajectory", "dosesTried", "sigma2", "sigma2betaW"), ...)
```

Arguments

x	(PseudoDualFlexiSimulations) the object we want to plot from.
y	(missing) missing object, not used.
type	(character) the type of plots you want to obtain.
...	not used.

Value

A single ggplot2 object if a single plot is asked for, otherwise a gtable object.

Examples

```
# Obtain the plot for the simulation results if DLE and efficacy responses
# are considered in the simulations.
emptydata <- DataDual(doseGrid = seq(25, 300, 25))

# The DLE model must be of 'ModelTox' (e.g 'LogisticIndepBeta') class.
dle_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = emptydata
)

# The efficacy model must be of 'EffFlexi' class.
eff_model <- EffFlexi(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  sigma2W = c(a = 0.1, b = 0.1),
  sigma2betaW = c(a = 20, b = 50),
  rw1 = FALSE,
  data = emptydata
)

# The escalation rule using the 'NextBestMaxGainSamples' class.
my_next_best <- NextBestMaxGainSamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, prob = 0.3))
  },
  mg_derive = function(mg_samples) {
    as.numeric(quantile(mg_samples, prob = 0.5))
  }
)

# The cohort size, size of 3 subjects.
my_size <- CohortSizeConst(size = 3)

# Allow increase of 200%.
my_increments <- IncrementsRelative(intervals = 0, increments = 2)

# Define the stopping rule. Stop when the maximum sample size of 36 patients has
# been reached or when the next dose is NA.
my_stopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()

# Specify the design.
design <- DualResponsesSamplesDesign(
  nextBest = my_next_best,
```

```
  cohort_size = my_size,
  startingDose = 25,
  model = dle_model,
  eff_model = eff_model,
  data = emptydata,
  stopping = my_stopping,
  increments = my_increments
)
# Specify the true DLE curve and the true expected efficacy values
# at all dose levels.
my_truth_dle <- probFunction(dle_model, phi1 = -53.66584, phi2 = 10.50499)

my_truth_eff <- c(
  -0.5478867,
  0.1645417,
  0.5248031,
  0.7604467,
  0.9333009,
  1.0687031,
  1.1793942,
  1.2726408,
  1.3529598,
  1.4233411,
  1.4858613,
  1.5420182
)

# The true gain curve.
my_truth_gain <- function(dose) {
  return((myTruthEff(dose)) / (1 + (myTruthDLE(dose) / (1 - myTruthDLE(dose)))))
}

# MCMC options.
my_options <- McmcOptions(burnin = 10, step = 1, samples = 20)

# For illustration purpose only 1 simulation is produced.
my_sim <- simulate(
  object = design,
  args = NULL,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff,
  trueSigma2 = 0.025,
  trueSigma2betaW = 1,
  mcmcOptions = my_options,
  nsim = 1,
  seed = 819,
  parallel = FALSE
)

# Plot the simulated results.
print(plot(my_sim))
```

plot,PseudoDualSimulations,missing-method
Plot PseudoDualSimulations

Description

[Stable]

Summarize the simulations with plots.

This plot method can be applied to PseudoDualSimulations objects in order to summarize them graphically. Possible types of plots at the moment are:

trajectory Summary of the trajectory of the simulated trials

dosesTried Average proportions of the doses tested in patients

sigma2 The variance of the efficacy responses

You can specify one or both of these in the type argument.

Usage

```
## S4 method for signature 'PseudoDualSimulations,missing'
plot(x, y, type = c("trajectory", "dosesTried", "sigma2"), ...)
```

Arguments

x	(PseudoDualSimulations) the object we want to plot from.
y	(missing) missing object, not used.
type	(character) the type of plots you want to obtain.
...	not used.

Value

A single ggplot2 object if a single plot is asked for, otherwise a gtable object.

Examples

```
# Obtain the plot for the simulation results if DLE and efficacy responses
# are considered in the simulations.

# Example to run simulations when no samples are used. The data object
# must be defined with doses >= 1:
emptydata <- DataDual(doseGrid = seq(25, 300, 25), placebo = FALSE)

# The DLE model must be of 'ModelTox' (e.g 'LogisticIndepBeta') class.
dle_model <- LogisticIndepBeta(
```

```
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = emptydata
)

# The efficacy model must be of 'ModelEff' (e.g 'Effloglog') class.
eff_model <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = emptydata
)

# The escalation rule using the 'NextBestMaxGain' class.
my_next_best <- NextBestMaxGain(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)

# Allow increase of 200%.
my_increments <- IncrementsRelative(intervals = 0, increments = 2)

# Cohort size of 3.
my_size <- CohortSizeConst(size = 3)

# Stop only when 36 subjects are treated or next dose is NA.
my_stopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()

# Now specify the design with all the above information and starting with a
# dose of 25 (for details please refer to the 'DualResponsesDesign' example).
my_design <- DualResponsesDesign(
  nextBest = my_next_best,
  model = dle_model,
  eff_model = eff_model,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  data = emptydata,
  startingDose = 25
)

# Specify the true DLE and efficacy curves.
my_truth_dle <- probFunction(dle_model, phi1 = -53.66584, phi2 = 10.50499)
my_truth_eff <- efficacyFunction(
  eff_model,
  theta1 = -4.818429,
  theta2 = 3.653058
)

# Run simulations (for illustration purpose only 1 simulation is produced).

my_sim <- simulate(
```

```
  object = my_design,
  args = NULL,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff,
  trueNu = 1 / 0.025,
  nsim = 1,
  seed = 819,
  parallel = FALSE
)

# Plot the simulation results.
print(plot(my_sim))

# Example if DLE and efficacy samples are involved.
# The escalation rule using the 'NextBestMaxGainSamples' class.
my_next_best <- NextBestMaxGainSamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, prob = 0.3))
  },
  mg_derive = function(mg_samples) {
    as.numeric(quantile(mg_samples, prob = 0.5))
  }
)

# The design of 'DualResponsesSamplesDesign' class.
my_design <- DualResponsesSamplesDesign(
  nextBest = my_next_best,
  cohort_size = my_size,
  startingDose = 25,
  model = dle_model,
  eff_model = eff_model,
  data = emptydata,
  stopping = my_stopping,
  increments = my_increments
)

# Options for MCMC.
my_options <- McmcOptions(burnin = 10, step = 1, samples = 20)

# For illustration purpose only 1 simulation is produced (nsim = 1).
my_sim <- simulate(
  object = my_design,
  args = NULL,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff,
  trueNu = 1 / 0.025,
  nsim = 1,
  mcmcOptions = my_options,
  seed = 819,
  parallel = FALSE
)
```

```
# Plot the simulation results.
print(plot(my_sim))
```

---

plot,PseudoDualSimulationsSummary,missing-method
Plot PseudoDualSimulationsSummary

Description

[Stable]

Plot the summary of PseudoDualSimulations.

This plot method can be applied to PseudoDualSimulationsSummary objects in order to summarize them graphically. Possible type of plots at the moment are those listed in plot,PseudoSimulationsSummary,missing- plus:

meanEffFit Plot showing the fitted dose-efficacy curve. If no samples are involved, only the average fitted dose-efficacy curve across the trials will be plotted. If samples (DLE and efficacy) are involved, the average fitted dose-efficacy curve across the trials, together with the 95% credibility interval; and comparison with the assumed truth (as specified by the trueEff argument to summary,PseudoDualSimulations-method)

You can specify any subset of these in the type argument.

Usage

```
## S4 method for signature 'PseudoDualSimulationsSummary,missing'
plot(
  x,
  y,
  type = c("nObs", "doseSelected", "propDLE", "nAboveTargetEndOfTrial", "meanFit",
    "meanEffFit"),
  ...
)
```

Arguments

x	(PseudoDualSimulationsSummary) the object we want to plot from.
y	(missing) not used.
type	(character) the types of plots you want to obtain.
...	not used.

Value

A single ggplot2 object if a single plot is asked for, otherwise a gtable object.

Examples

```
# Obtain the summary plot for the simulation results if DLE and efficacy
# responses are considered in the simulations.

# In the example when no samples are used a data object with doses >= 1
# needs to be defined.
emptydata <- DataDual(doseGrid = seq(25, 300, 25), placebo = FALSE)

# The DLE model must be of 'ModelTox' (e.g 'LogisticIndepBeta') class.
dle_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = emptydata
)

# The efficacy model of 'ModelEff' (e.g 'Effloglog') class.
eff_model <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = emptydata
)

# The escalation rule using the 'NextBestMaxGain' class.
my_next_best <- NextBestMaxGain(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)

# Allow increase of 200%.
my_increments <- IncrementsRelative(intervals = 0, increments = 2)

# Cohort size of 3.
my_size <- CohortSizeConst(size = 3)

# Stop when 10 subjects are treated (for illustration only).
my_stopping <- StoppingMinPatients(nPatients = 10) | StoppingMissingDose()

## Now specified the design with all the above information and starting with a dose of 25

# Specify the design. (For details please refer to the 'DualResponsesDesign' example.)
my_design <- DualResponsesDesign(
  nextBest = my_next_best,
  model = dle_model,
  eff_model = eff_model,
  stopping = my_stopping,
  increments = my_increments,
```

```
  cohort_size = my_size,
  data = emptydata,
  startingDose = 25
)

# Specify the true DLE and efficacy curves.
my_truth_dle <- probFunction(dle_model, phi1 = -53.66584, phi2 = 10.50499)
my_truth_eff <- efficacyFunction(eff_model, theta1 = -4.818429, theta2 = 3.653058)


# For illustration purpose only 1 simulation is produced.
my_sim <- simulate(
  object = my_design,
  args = NULL,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff,
  trueNu = 1 / 0.025,
  nsim = 1,
  mcmcOptions = McmcOptions(burnin = 10, step = 1, samples = 50),
  seed = 819,
  parallel = FALSE
)

# Summary of the simulations.
my_sum <- summary(
  my_sim,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff
)

# Plot the summary of the simulations.
print(plot(my_sum))


# Example where DLE and efficacy samples are involved.
# Please refer to design-method 'simulate DualResponsesSamplesDesign' examples
# for details.
# Specify the next best method.
my_next_best <- NextBestMaxGainSamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, prob = 0.3))
  },
  mg_derive = function(mg_samples) {
    as.numeric(quantile(mg_samples, prob = 0.5))
  }
)

# Specify the design.
my_design <- DualResponsesSamplesDesign(
  nextBest = my_next_best,
  cohort_size = my_size,
```

```
  startingDose = 25,
  model = dle_model,
  eff_model = eff_model,
  data = emptydata,
  stopping = my_stopping,
  increments = my_increments
)

# MCMC options.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)


# For illustration purpose only 1 simulation is produced.
my_sim <- simulate(
  object = my_design,
  args = NULL,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff,
  trueNu = 1 / 0.025,
  nsim = 1,
  mcmcOptions = my_options,
  seed = 819,
  parallel = FALSE
)


# Generate a summary of the simulations.
my_sum <- summary(
  my_sim,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff
)

# Plot the summary of the simulations.
print(plot(my_sum))


# Example where the 'EffFlexi' class is used for the efficacy model.
eff_model <- EffFlexi(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  sigma2W = c(a = 0.1, b = 0.1),
  sigma2betaW = c(a = 20, b = 50),
  rw1 = FALSE,
  data = emptydata
)

# Specify the design.
my_design <- DualResponsesSamplesDesign(
  nextBest = my_next_best,
  cohort_size = my_size,
  startingDose = 25,
  model = dle_model,
```

```
  eff_model = eff_model,
  data = emptydata,
  stopping = my_stopping,
  increments = my_increments
)

# Specify the true DLE curve and the true expected efficacy values at all dose levels.
my_truth_dle <- probFunction(dle_model, phi1 = -53.66584, phi2 = 10.50499)

my_truth_eff <- c(
  -0.5478867, 0.1645417, 0.5248031, 0.7604467,
  0.9333009, 1.0687031, 1.1793942, 1.2726408,
  1.3529598, 1.4233411, 1.4858613, 1.5420182
)

# Define the true gain curve.
my_truth_gain <- function(dose) {
  return((my_truth_eff(dose)) / (1 + (my_truth_dle(dose) / (1 - my_truth_dle(dose)))))
}


## The simulations
## For illustration purpose only 1 simulation is produced (nsim=1).
mySim <- simulate(
  object = my_design,
  args = NULL,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff,
  trueSigma2 = 0.025,
  trueSigma2betaW = 1,
  nsim = 1,
  mcmcOptions = my_options,
  seed = 819,
  parallel = FALSE
)

# Produce a summary of the simulations.
my_sum <- summary(
  my_sim,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff
)

# Plot the summary of the simulations.
print(plot(my_sim))
```

---

plot,PseudoSimulationsSummary,missing-method

Plot PseudoSimulationsSummary

Description

[Stable]

Graphical display of the simulation summary.

This plot method can be applied to `PseudoSimulationsSummary` objects in order to summarize them graphically. This can be used when only DLE responses are involved in the simulations. This also applied to results with or without samples generated during the simulations.

Usage

```
## S4 method for signature 'PseudoSimulationsSummary,missing'
plot(
  x,
  y,
 type = c("nObs", "doseSelected", "propDLE", "nAboveTargetEndOfTrial", "meanFit"),
  ...
)
```

Arguments

`x`	(`PseudoSimulationsSummary`) the object we want to plot from.
`y`	(`missing`) missing object, not used.
`type`	(`character`) the types of plots you want to obtain.
`...`	not used.

Value

A single `ggplot2` object if a single plot is asked for, otherwise a `gtable` object.

Examples

```
# nolint start

## obtain the plot for the simulation results
## If only DLE responses are considered in the simulations
## Specified your simulations when no DLE samples are used
## Define your data set first using an empty data set
## with dose levels from 25 to 300 with increments 25
data <- Data(doseGrid = seq(25, 300, 25))

## Specified the model of 'ModelTox' class eg 'LogisticIndepBeta' class model
model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
```

```
## Then the escalation rule
tdNextBest <- NextBestTD(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)

## The cohort size, size of 3 subjects
mySize <- CohortSizeConst(size = 3)
## Deifne the increments for the dose-escalation process
## The maximum increase of 200% for doses up to the maximum of the dose specified in the doseGrid
## The maximum increase of 200% for dose above the maximum of the dose specified in the doseGrid
## This is to specified a maximum of 3-fold restriction in dose-esclation
myIncrements <- IncrementsRelative(
  intervals = c(min(data@doseGrid), max(data@doseGrid)),
  increments = c(2, 2)
)
## Specified the stopping rule e.g stop when the maximum sample size of 12 patients has been reached
myStopping <- StoppingMinPatients(nPatients = 12) | StoppingMissingDose()
## Now specified the design with all the above information and starting with a dose of 25
design <- TDDesign(
  model = model,
  nextBest = tdNextBest,
  stopping = myStopping,
  increments = myIncrements,
  cohort_size = mySize,
  data = data,
  startingDose = 25
)

## Specify the truth of the DLE responses
myTruth <- probFunction(model, phi1 = -53.66584, phi2 = 10.50499)

## Then specified the simulations and generate the trial
## For illustration purpose only 1 simulation is produced (nsim=1).
## The simulations
mySim <- simulate(
  design,
  args = NULL,
  truth = myTruth,
  nsim = 1,
  seed = 819,
  parallel = FALSE
)

## Then produce a summary of your simulations
MYSUM <- summary(mySim, truth = myTruth)
## plot the summary of the simulations
print(plot(MYSUM))

## If DLE samples are involved
## The escalation rule
tdNextBest <- NextBestTDsamples(
  prob_target_drt = 0.35,
```

```
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, probs = 0.3))
  }
)
## specify the design
design <- TDsamplesDesign(
  model = model,
  nextBest = tdNextBest,
  stopping = myStopping,
  increments = myIncrements,
  cohort_size = mySize,
  data = data,
  startingDose = 25
)
## options for MCMC
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
## The simulations
## For illustration purpose only 1 simulation is produced (nsim=1).
# mySim <- simulate(design,
#                   args=NULL,
#                   truth=myTruth,
#                   nsim=1,
#                   seed=819,
#                   mcmcOptions=options,
#                   parallel=FALSE)
# ##Then produce a summary of your simulations
# MYSUM <- summary(mySim,
#                  truth=myTruth)
# ##plot the summary of the simulations
# print(plot(MYSUM))

# nolint end
```

`plot,Samples,DALogisticLogNormal-method`
Plotting dose-toxicity model fits

Description

Plotting dose-toxicity model fits

Usage

```
## S4 method for signature 'Samples,DALogisticLogNormal'
plot(x, y, data, hazard = FALSE, ..., showLegend = TRUE)
```

Arguments

x	the Samples object
y	the DALogisticLogNormal object
data	the DataDA object
hazard	see fitPEM for the explanation
...	not used
showLegend	should the legend be shown? (default)

Value

This returns the ggplot object for the dose-toxicity model fit

---

plot,Samples,DualEndpoint-method

Plotting dose-toxicity and dose-biomarker model fits

Description

When we have the dual endpoint model, also the dose-biomarker fit is shown in the plot

Usage

```
## S4 method for signature 'Samples,DualEndpoint'
plot(x, y, data, extrapolate = TRUE, showLegend = FALSE, ...)
```

Arguments

x	the Samples object
y	the DualEndpoint object
data	the DataDual object
extrapolate	should the biomarker fit be extrapolated to the whole dose grid? (default)
showLegend	should the legend be shown? (not default)
...	additional arguments for the parent method plot,Samples,GeneralModel-method

Value

This returns the ggplot object with the dose-toxicity and dose-biomarker model fits

Examples

```
# nolint start

# Create some data
data <- DataDual(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10, 20, 20, 20, 40, 40, 40, 50, 50, 50),
  y = c(0, 0, 0, 0, 0, 0, 1, 0, 0, 1, 1, 0, 0, 1, 0, 1, 1),
  w = c(
    0.31,
    0.42,
    0.59,
    0.45,
    0.6,
    0.7,
    0.55,
    0.6,
    0.52,
    0.54,
    0.56,
    0.43,
    0.41,
    0.39,
    0.34,
    0.38,
    0.21
  ),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the Dual-Endpoint model (in this case RW1)
model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2betaW = 0.01,
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  rw1 = TRUE
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 100, step = 2, samples = 500)
set.seed(94)
samples <- mcmc(data, model, options)

# Plot the posterior mean  (and empirical 2.5 and 97.5 percentile)
# for the prob(DLT) by doses and the Biomarker by doses
#grid.arrange(plot(x = samples, y = model, data = data))

plot(x = samples, y = model, data = data)

# nolint end
```

`plot,Samples,GeneralModel-method`
Plotting dose-toxicity model fits

Description

Plotting dose-toxicity model fits

Usage

```
## S4 method for signature 'Samples,GeneralModel'
plot(
  x,
  y,
  data,
  ...,
  xlab = "Dose level",
  ylab = "Probability of DLT [%]",
  showLegend = TRUE
)
```

Arguments

x	the Samples object
y	the GeneralModel object
data	the Data object
...	not used
xlab	the x axis label
ylab	the y axis label
showLegend	should the legend be shown? (default)

Value

This returns the `ggplot` object for the dose-toxicity model fit

Examples

```
# nolint start

# Create some data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)
```

```
# Initialize a model
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Get posterior for all model parameters
options <- McmcOptions(burnin = 100, step = 2, samples = 2000)
set.seed(94)
samples <- mcmc(data, model, options)

# Plot the posterior mean  (and empirical 2.5 and 97.5 percentile)
# for the prob(DLT) by doses
plot(x = samples, y = model, data = data)

# nolint end
```

`plot,Samples,ModelEff-method`

Plot the fitted dose-efficacy curve using a model from ModelEff class with samples

---

Description

Plot the fitted dose-efficacy curve using a model from ModelEff class with samples

Usage

```
## S4 method for signature 'Samples,ModelEff'
plot(
  x,
  y,
  data,
  ...,
  xlab = "Dose level",
  ylab = "Expected Efficacy",
  showLegend = TRUE
)
```

Arguments

x	the Samples object
y	the ModelEff model class object
data	the Data object
...	not used

xlab	the x axis label
ylab	the y axis label
showLegend	should the legend be shown? (default)

Value

This returns the ggplot object for the dose-efficacy model fit

Examples

```
# nolint start

## we need a data object with doses >= 1:
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)
##plot the dose-efficacy curve with samples using the model from 'ModelEff'
##class e.g. 'Effloglog' class model
##define the model (see Effloglog example)
Effmodel <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data
)
## define the samples obtained using the 'Effloglog' model (see details in 'Samples' example)
##options for MCMC
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
## samples must be of 'Samples' class
samples <- mcmc(data = data, model = Effmodel, options = options)
## plot the fitted dose-efficacy curve including the 95% credibility interval of the samples
## 'x' should be of 'Samples' class and 'y' of 'ModelEff' class
plot(x = samples, y = Effmodel, data = data)
# nolint end
```

---

plot,Samples,ModelTox-method

Plot the fitted dose-DLE curve using a ModelTox class model with samples

---

Description

Plot the fitted dose-DLE curve using a ModelTox class model with samples

Usage

```
## S4 method for signature 'Samples,ModelTox'
plot(
  x,
  y,
  data,
  ...,
  xlab = "Dose level",
  ylab = "Probability of DLT [%]",
  showLegend = TRUE
)
```

Arguments

x	the Samples object
y	the ModelTox model class object
data	the Data object
...	not used
xlab	the x axis label
ylab	the y axis label
showLegend	should the legend be shown? (default)

Value

This returns the ggplot object for the dose-DLE model fit

Examples

```
## we need a data object with doses >= 1:
data <- Data(
  x = c(25, 50, 50, 75, 150, 200, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  doseGrid = seq(from = 25, to = 300, by = 25)
)
## plot the dose-DLE curve with samples using the model from 'ModelTox'
## class e.g. 'LogisticIndepBeta' class model
## define the model (see LogisticIndepBeta example)
model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
## define the samples obtained using the 'LogisticIndepGBeta' model

## Define options for MCMC
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
## (see details in 'Samples' example) samples must be of 'Samples' class
```

```
samples <- mcmc(data = data, model = model, options = options)
## plot the fitted dose-DLE curve including the 95% credibility interval of the samples
## 'x' should be of 'Samples' class and 'y' of 'ModelTox' class
plot(x = samples, y = model, data = data)
```

`plot,Samples,TwoDrugsCombo-method`
Plotting two-drug combination dose-toxicity model fits

Description

Plotting two-drug combination dose-toxicity model fits

Usage

```
## S4 method for signature 'Samples,TwoDrugsCombo'
plot(
  x,
  y,
  data,
  ...,
  xlab = NULL,
  ylab = NULL,
  fillLab = "Probability of DLT [%]",
  showLegend = TRUE
)
```

Arguments

x	the Samples object.
y	the TwoDrugsCombo object.
data	the DataCombo object.
...	passed to fit.
xlab	the x axis label. If NULL, the first drug name is used.
ylab	the y axis label. If NULL, the second drug name is used.
fillLab	the fill legend label.
showLegend	should the legend be shown? (default)

Value

This returns the ggplot object for the two-drug combination dose-toxicity model fit.

plot,SimulationsSummary,missing-method
Plot Model-Based Design Simulation Summary

Description

[Stable]

Graphical display of the simulation summary.

This plot method can be applied to SimulationsSummary objects in order to summarize them graphically. Possible type of plots at the moment are those listed in plot,GeneralSimulationsSummary,missing-method plus:

meanFit Plot showing the average fitted dose-toxicity curve across the trials, together with 95% credible intervals, and comparison with the assumed truth (as specified by the truth argument to summary,Simulations-method)

You can specify any subset of these in the type argument.

Usage

```
## S4 method for signature 'SimulationsSummary,missing'
plot(
  x,
  y,
  type = c("nObs", "doseSelected", "propDLTs", "nAboveTarget", "meanFit"),
  ...
)
```

Arguments

x	(SimulationsSummary) the object we want to plot from.
y	(missing) not used.
type	(character) the types of plots you want to obtain.
...	not used.

Value

A single ggplot object if a single plot is asked for, otherwise a gtable object.

Examples

```
# nolint start

# Define the dose-grid
emptydata <- Data(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))

# Initialize the CRM model
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Choose the rule for selecting the next dose
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size
mySize1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
mySize2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
mySize <- maxSize(mySize1, mySize2)

# Choose the rule for stopping
myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(
  target = c(0.2, 0.35),
  prob = 0.5
)
myStopping3 <- StoppingMinPatients(nPatients = 20)
myStopping <- (myStopping1 & myStopping2) | myStopping3 | StoppingMissingDose()

# Choose the rule for dose increments
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Initialize the design
design <- Design(
  model = model,
  nextBest = myNextBest,
  stopping = myStopping,
  increments = myIncrements,
```

```
  cohort_size = mySize,
  data = emptydata,
  startingDose = 3
)

## define the true function
myTruth <- probFunction(model, alpha0 = 7, alpha1 = 8)

# Run the simulation on the desired design
# We only generate 1 trial outcomes here for illustration, for the actual study
# this should be increased of course
options <- McmcOptions(
  burnin = 5,
  step = 1,
  samples = 10
)
time <- system.time(
  mySims <- simulate(
    design,
    args = NULL,
    truth = myTruth,
    nsim = 1,
    seed = 819,
    mcmcOptions = options,
    parallel = FALSE
  )
)[3]

# Plot the Summary of the Simulations
plot(summary(mySims, truth = myTruth))

# nolint end
```

`plot.gtable` *Plot* `gtable` *Objects*

Description

[Stable]

This is needed because `crmPack` uses `gridExtra::arrangeGrob()` to combine `ggplot2` plots, and the resulting `gtable` object is not plotted otherwise when implicitly printing it in the console.

Usage

```
## S3 method for class 'gtable'
plot(x, ...)

## S3 method for class 'gtable'
print(x, ...)
```

Arguments

x	(gtable) object to print.
...	additional parameters passed to plot.gtable().

Value

Called for side effects.

`plotDualResponses` *Plot of the DLE and efficacy curve side by side given a DLE pseudo model, a DLE sample, an efficacy pseudo model and a given efficacy sample*

Description

Plot of the DLE and efficacy curve side by side given a DLE pseudo model, a DLE sample, an efficacy pseudo model and a given efficacy sample

Plot of the dose-DLE and dose-efficacy curve side by side given a DLE pseudo model and a given pseudo efficacy model without DLE and efficacy samples

Usage

```
plotDualResponses(DLEmodel, DLEsamples, Effmodel, Effsamples, data, ...)

## S4 method for signature 'ModelTox,Samples,ModelEff,Samples'
plotDualResponses(
  DLEmodel,
  DLEsamples,
  Effmodel,
  Effsamples,
  data,
  extrapolate = TRUE,
  showLegend = FALSE,
  ...
)

## S4 method for signature 'ModelTox,missing,ModelEff,missing'
plotDualResponses(DLEmodel, DLEsamples, Effmodel, Effsamples, data, ...)
```

Arguments

DLEmodel	the pseudo DLE model of ModelTox class object
DLEsamples	the DLE samples of Samples class object
Effmodel	the pseudo efficacy model of ModelEff class object

Effsamples	the Efficacy samples of Samples class object
data	the data input of DataDual class object
...	additional arguments for the parent method plot,Samples,GeneralModel-method
extrapolate	should the biomarker fit be extrapolated to the whole dose grid? (default)
showLegend	should the legend be shown? (not default)

Value

This returns the ggplot object with the dose-toxicity and dose-efficacy model fits

Functions

- plotDualResponses(DLEmodel = ModelTox, DLEsamples = Samples, Effmodel = ModelEff, Effsamples = Samples): function still to be documented
- plotDualResponses(DLEmodel = ModelTox, DLEsamples = missing, Effmodel = ModelEff, Effsamples = missing): Plot the DLE and efficacy curve side by side given a DLE model and an efficacy model without any samples

Examples

```
# nolint start

## we need a data object with doses >= 1:
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)
##plot the dose-DLE and dose-efficacy curves in two plots with DLE and efficacy samples
##define the DLE model which must be of 'ModelTox' class
##(e.g 'LogisticIndepBeta' class model)
DLEmodel <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
## define the efficacy model which must be of 'ModelEff' class
## (e.g 'Effloglog' class)
Effmodel <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data
)
##define the DLE sample of 'Samples' class
##set up the same data set in class 'Data' for MCMC sampling for DLE
data1 <- Data(x = data@x, y = data@y, doseGrid = data@doseGrid)
```

```
##Specify the options for MCMC
options <- McmcOptions(burnin = 100, step = 2, samples = 1000)


DLEsamples <- mcmc(data = data1, model = DLEmodel, options = options)
##define the efficacy sample of 'Samples' class
Effsamples <- mcmc(data = data, model = Effmodel, options = options)
##plot the dose-DLE and dose-efficacy curves with two plot side by side.
##For each curve the 95% credibility interval of the two samples are alos given
plotDualResponses(
  DLEmodel = DLEmodel,
  DLEsamples = DLEsamples,
  Effmodel = Effmodel,
  Effsamples = Effsamples,
  data = data
)

# nolint end
# nolint start

## we need a data object with doses >= 1:
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)
##plot the dose-DLE and dose-efficacy curves in two plots without DLE and efficacy samples
##define the DLE model which must be of 'ModelTox' class
##(e.g 'LogisticIndepBeta' class model)
DLEmodel <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
## define the efficacy model which must be of 'ModelEff' class
## (e.g 'Effloglog' class)
Effmodel <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data
)
##plot the dose-DLE and dose-efficacy curves with two plot side by side.
plotDualResponses(DLEmodel = DLEmodel, Effmodel = Effmodel, data = data)

# nolint end
```

`plotGain` *Plot the gain curve in addition with the dose-DLE and dose-efficacy curve using a given DLE pseudo model, a DLE sample, a given efficacy pseudo model and an efficacy sample*

Description

Plot the gain curve in addition with the dose-DLE and dose-efficacy curve using a given DLE pseudo model, a DLE sample, a given efficacy pseudo model and an efficacy sample

Plot the gain curve in addition with the dose-DLE and dose-efficacy curve using a given DLE pseudo model, and a given efficacy pseudo model

Usage

```
plotGain(DLEmodel, DLEsamples, Effmodel, Effsamples, data, ...)

## S4 method for signature 'ModelTox,Samples,ModelEff,Samples'
plotGain(DLEmodel, DLEsamples, Effmodel, Effsamples, data, ...)

## S4 method for signature 'ModelTox,missing,ModelEff,missing'
plotGain(DLEmodel, Effmodel, data, size = c(8L, 8L), shape = c(16L, 17L), ...)
```

Arguments

`DLEmodel`	the dose-DLE model of ModelTox class object
`DLEsamples`	the DLE sample of Samples class object
`Effmodel`	the dose-efficacy model of ModelEff class object
`Effsamples`	the efficacy sample of of Samples class object
`data`	the data input of DataDual class object
`...`	not used
`size`	(`integer`) a vector of length two defining the sizes of the shapes used to identify the doses with, respectively, p(DLE = 0.3) and the maximum gain
`shape`	(`integer`) a vector of length two defining the shapes used to identify the doses with, respectively, p(DLE = 0.3) and the maximum gain

Value

This returns the `ggplot` object for the plot

Functions

- `plotGain( DLEmodel = ModelTox, DLEsamples = Samples, Effmodel = ModelEff, Effsamples = Samples )`: Standard method
- `plotGain( DLEmodel = ModelTox, DLEsamples = missing, Effmodel = ModelEff, Effsamples = missing )`: Standard method

Examples

```
# nolint start

## we need a data object with doses >= 1:
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)
##plot the dose-DLE , dose-efficacy and gain curve in the same plot with DLE and efficacy samples
##define the DLE model which must be of 'ModelTox' class
##(e.g 'LogisticIndepBeta' class model)
DLEmodel <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
## define the efficacy model which must be of 'ModelEff' class
## (e.g 'Effloglog' class)
Effmodel <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data,
  const = 0
)
##define the DLE sample of 'Samples' class
##set up the same data set in class 'Data' for MCMC sampling for DLE
data1 <- Data(x = data@x, y = data@y, doseGrid = data@doseGrid)

##Define the options for MCMC
options <- McmcOptions(burnin = 100, step = 2, samples = 1000)


DLEsamples <- mcmc(data = data1, model = DLEmodel, options = options)
##define the efficacy sample of 'Samples' class
Effsamples <- mcmc(data = data, model = Effmodel, options = options)
##plot the three curves of mean values of the DLEsamples, Effsamples and
##gain value samples (obtained within this plotGain function) at all dose levels
plotGain(
  DLEmodel = DLEmodel,
  DLEsamples = DLEsamples,
  Effmodel = Effmodel,
  Effsamples = Effsamples,
  data = data
)
# nolint end
# nolint start
## we need a data object with doses >= 1:
```

```
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)
##plot the dose-DLE , dose-efficacy and gain curve in the same plot with DLE and efficacy samples
##define the DLE model which must be of 'ModelTox' class
##(e.g 'LogisticIndepBeta' class model)
DLEmodel <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
## define the efficacy model which must be of 'ModelEff' class
## (e.g 'Effloglog' class)
Effmodel <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data
)
##plot the three curves of using modal estimates of model parameters at all dose levels
plotGain(DLEmodel = DLEmodel, Effmodel = Effmodel, data = data)
# nolint end
```

`positive_number` `positive_number`

Description

[Experimental]

The `positive_number` class is a class to store not `NULL`, non `NA`, finite and strictly positive numerical value. It is mainly used to store reference dose value in model classes.

`prob` *Computing Toxicity Probabilities for a Given Dose, Model and Samples*

Description

[Stable]

A function that computes the probability of the occurrence of a DLE at a specified dose level, based on the model parameters (samples).

Usage

```
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,LogisticNormal,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,LogisticLogNormal,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,LogisticLogNormalSub,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,ProbitLogNormal,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,ProbitLogNormalRel,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,LogisticLogNormalGrouped,Samples'
prob(dose, model, samples, group, ...)

## S4 method for signature 'numeric,TwoDrugsCombo,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'matrix,TwoDrugsCombo,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,LogisticKadane,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,LogisticKadaneBetaGamma,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,LogisticNormalMixture,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,LogisticNormalFixedMixture,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,LogisticLogNormalMixture,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,DualEndpoint,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,LogisticIndepBeta,Samples'
prob(dose, model, samples, ...)
```

```
## S4 method for signature 'numeric,LogisticIndepBeta,missing'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,OneParLogNormalPrior,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,OneParExpPrior,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,LogisticLogNormalOrdinal,Samples'
prob(dose, model, samples, grade, cumulative = TRUE, ...)
```

Arguments

dose	(number or numeric) the dose which is targeted. The following recycling rule applies when samples is not missing: vectors of size 1 will be recycled to the size of the sample (i.e. size(samples)). Otherwise, dose must have the same size as the sample.
model	(GeneralModel or ModelTox) the model for single agent dose escalation or pseudo DLE (dose-limiting events)/toxicity model.
samples	(Samples) the samples of model's parameters that will be used to compute toxicity probabilities. Can also be missing for some models.
...	model specific parameters when samples are not used.
group	(character or factor) for LogisticLogNormalGrouped, indicating whether to calculate the probability for the mono or for the combo arm.
grade	(integer or integer_vector) The toxicity grade for which probabilities are required
cumulative	(flag) Should the returned probability be cumulative (the default) or grade-specific?

Details

The prob() function computes the probability of toxicity for given doses, using samples of the model parameter(s). If you work with multivariate model parameters, then assume that your model specific prob() method receives a samples matrix where the rows correspond to the sampling index, i.e. the layout is then nSamples x dimParameter.

Value

A proportion or numeric vector with the toxicity probabilities, or a numeric matrix for methods that evaluate multiple dose combinations at once. If non-scalar samples were used, then every element in the returned vector corresponds to one element of a sample. Hence, in this case, the output vector is of the same length as the sample vector. If scalar samples were used or no samples were used, e.g. for pseudo DLE/toxicity model, then the output is of the same length as the length

of the dose. For matrix-valued dose inputs, the returned matrix contains one column per dose combination. In the case of LogisticLogNormalOrdinal, the probabilities relate to toxicities of grade given by grade.

Functions

- prob(dose = numeric, model = LogisticNormal, samples = Samples): Calculate toxicity probabilities for a LogisticNormal model.
- prob(dose = numeric, model = LogisticLogNormal, samples = Samples): Calculate toxicity probabilities for a LogisticLogNormal model.
- prob(dose = numeric, model = LogisticLogNormalSub, samples = Samples): Calculate toxicity probabilities for a LogisticLogNormalSub model.
- prob(dose = numeric, model = ProbitLogNormal, samples = Samples): Calculate toxicity probabilities for a ProbitLogNormal model.
- prob(dose = numeric, model = ProbitLogNormalRel, samples = Samples): Calculate toxicity probabilities for a ProbitLogNormalRel model.
- prob(dose = numeric, model = LogisticLogNormalGrouped, samples = Samples): method for LogisticLogNormalGrouped which needs group argument in addition.
- prob(dose = numeric, model = TwoDrugsCombo, samples = Samples): method for TwoDrugsCombo for a single dose combination provided as a named numeric vector.
- prob(dose = matrix, model = TwoDrugsCombo, samples = Samples): method for TwoDrugsCombo for one or more dose combinations provided in the rows of a numeric matrix.
- prob(dose = numeric, model = LogisticKadane, samples = Samples): Calculate toxicity probabilities for a LogisticKadane model.
- prob(dose = numeric, model = LogisticKadaneBetaGamma, samples = Samples): Calculate toxicity probabilities for a LogisticKadaneBetaGamma model.
- prob(dose = numeric, model = LogisticNormalMixture, samples = Samples): Calculate toxicity probabilities for a LogisticNormalMixture model.
- prob(dose = numeric, model = LogisticNormalFixedMixture, samples = Samples): Calculate toxicity probabilities for a LogisticNormalFixedMixture model.
- prob(dose = numeric, model = LogisticLogNormalMixture, samples = Samples): Calculate toxicity probabilities for a LogisticLogNormalMixture model.
- prob(dose = numeric, model = DualEndpoint, samples = Samples): Calculate toxicity probabilities for a DualEndpoint model.
- prob(dose = numeric, model = LogisticIndepBeta, samples = Samples): compute toxicity probabilities of the occurrence of a DLE at a specified dose level, based on the samples of LogisticIndepBeta model parameters.
- prob(dose = numeric, model = LogisticIndepBeta, samples = missing): compute toxicity probabilities of the occurrence of a DLE at a specified dose level, based on the LogisticIndepBeta model parameters. All model parameters (except dose) should be present in the model object.
- prob(dose = numeric, model = OneParLogNormalPrior, samples = Samples): Calculate toxicity probabilities for a OneParLogNormalPrior model.
- prob(dose = numeric, model = OneParExpPrior, samples = Samples): Calculate toxicity probabilities for a OneParExpPrior model.
- prob(dose = numeric, model = LogisticLogNormalOrdinal, samples = Samples): Calculate grade-specific toxicity probabilities for a LogisticLogNormalOrdinal model.

Note

The prob() and dose() functions are the inverse of each other, for all dose() methods for which its first argument, i.e. a given independent variable that dose depends on, represents toxicity probability.

See Also

probFunction(), dose(), efficacy().

Examples

```
# Create some data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize a model, e.g. 'LogisticLogNormal'.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Get samples from posterior.
my_options <- McmcOptions(burnin = 100, step = 2, samples = 20)
my_samples <- mcmc(data = my_data, model = my_model, options = my_options)

# Posterior for Prob(DLT | dose = 50).
prob(dose = 50, model = my_model, samples = my_samples)

# Create data from the 'DataDual' class.
data_dual <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(from = 25, to = 300, by = 25)
)

# Initialize a toxicity model using 'LogisticIndepBeta' model.
dlt_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data_dual
)

# Get samples from posterior.
dlt_sample <- mcmc(data = data_dual, model = dlt_model, options = my_options)
```

```
# Posterior for Prob(DLT | dose = 100).
prob(dose = 100, model = dlt_model, samples = dlt_sample)
prob(dose = c(50, 150), model = dlt_model)
```

---

probFunction *Getting the Prob Function for a Given Model Type*

Description

[Experimental]

A function that returns a prob() function that computes the toxicity probabilities for a given dose level, based on the model specific parameters.

Usage

```
probFunction(model, ...)

## S4 method for signature 'GeneralModel'
probFunction(model, ...)

## S4 method for signature 'ModelTox'
probFunction(model, ...)

## S4 method for signature 'LogisticLogNormalOrdinal'
probFunction(model, grade, ...)
```

Arguments

model	(GeneralModel or ModelTox) the model.
...	model specific parameters.
grade	(integer) the toxicity grade for which the dose function is required

Value

A prob() function that computes toxicity probabilities.

Functions

- probFunction(GeneralModel): Return a probability function for a GeneralModel.
- probFunction(ModelTox): Return a probability function for a ModelTox.
- probFunction(LogisticLogNormalOrdinal): Return a grade-specific probability function for a LogisticLogNormalOrdinal model.

See Also

prob(), doseFunction().

Examples

```
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 50
)

prob_fun <- probFunction(my_model, alpha0 = 2, alpha1 = 3)
prob_fun(30)
ordinal_data <- .DefaultDataOrdinal()
ordinal_model <- .DefaultLogisticLogNormalOrdinal()
opts <- .DefaultMcmcOptions()
samples <- mcmc(ordinal_data, ordinal_model, opts)

probFunction(
  ordinal_model,
  grade = 2L,
  alpha2 = samples@data$alpha1,
  beta = samples@data$beta
)(50)
```

---

probit *Shorthand for Probit Function*

Description

[Stable]

Computes the probit (inverse cumulative distribution function of standard normal) transformation.

Usage

```
probit(x)
```

Arguments

x	(numeric) the function argument.

Value

The probit of x, the quantile function of the standard normal distribution.

Examples

```
probit(0.5)
probit(c(0.025, 0.5, 0.975))
```

ProbitLogNormal-class ProbitLogNormal

Description

[Stable]

ProbitLogNormal is the class for probit regression model with a bivariate normal prior on the intercept and log slope.

Usage

```
ProbitLogNormal(mean, cov, ref_dose = 1)

.DefaultProbitLogNormal()
```

Arguments

mean	(numeric) the prior mean vector.
cov	(matrix) the prior covariance matrix. The precision matrix prec is internally calculated as an inverse of cov.
ref_dose	(number) the reference dose $x*$ (strictly positive number).

Details

The covariate is the natural logarithm of dose x divided by a reference dose $x*$, i.e.:

$$probit[p(x)] = alpha0 + alpha1 * log(x/x*),$$

where $p(x)$ is the probability of observing a DLT for a given dose x. The prior

$$(alpha0, log(alpha1))\ Normal(mean, cov).$$

Note

The model used in the DualEndpoint classes is an extension of this model: DualEndpoint supports both ProbitNormal (which is not implemented yet) and ProbitLogNormal models through its use_log_dose slot. ProbitLogNormal has no such flag, so always uses log(x/x*)as a covariate in its model. Therefore this class can be used to check the prior assumptions on the dose-toxicity model, even when sampling from the prior distribution of the dual endpoint model is not possible, when use_log_dose = TRUE is used.

Typically, end users will not use the .DefaultProbitLogNormal() function.

See Also

ModelLogNormal, LogisticNormal, LogisticLogNormal, LogisticLogNormalSub, ProbitLogNormalRel.

Examples

```
my_model <- ProbitLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 7.2
)
```

`ProbitLogNormalRel-class` `ProbitLogNormalRel`

Description

[Stable]

`ProbitLogNormalRel` is the class for probit regression model with a bivariate normal prior on the intercept and log slope.

Usage

```
ProbitLogNormalRel(mean, cov, ref_dose = 1)

.DefaultProbitLogNormalRel()
```

Arguments

`mean`	(`numeric`) the prior mean vector.
`cov`	(`matrix`) the prior covariance matrix. The precision matrix `prec` is internally calculated as an inverse of `cov`.
`ref_dose`	(`number`) the reference dose $x*$ (strictly positive number).

Details

The covariate is the dose x divided by a reference dose $x*$, i.e.:

$$probit[p(x)] = alpha0 + alpha1 * x/x*,$$

where $p(x)$ is the probability of observing a DLT for a given dose x. The prior

$$(alpha0, log(alpha1))\ Normal(mean, cov).$$

Note

This model is also used in the `DualEndpoint` classes, so this class can be used to check the prior assumptions on the dose-toxicity model, even when sampling from the prior distribution of the dual endpoint model is not possible.

Typically, end users will not use the `.DefaultProbitLogNormalRel()` function.

See Also

ModelLogNormal, LogisticNormal, LogisticLogNormal, LogisticLogNormalSub, ProbitLogNormal.

Examples

```
my_model <- ProbitLogNormalRel(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2)
)
```

PseudoDualFlexiSimulations-class
PseudoDualFlexiSimulations

Description

[Stable] This class captures the trial simulations design using both the DLE and efficacy responses using EffFlexi efficacy model. It extends PseudoDualSimulations by adding the capability to capture the sigma2betaW estimates.

Usage

```
PseudoDualFlexiSimulations(sigma2_beta_w_est, ...)

.DefaultPseudoDualFlexiSimulations()
```

Arguments

sigma2_beta_w_est	(numeric) the vector of the final posterior mean sigma2betaW estimates
...	additional parameters from PseudoDualSimulations

Slots

sigma2_beta_w_est (numeric)
: the vector of the final posterior mean sigma2betaW estimates

Note

Typically, end users will not use the .DefaultPseudoFlexiSimulations() function.

PseudoDualSimulations-class
PseudoDualSimulations

Description

[Stable] This class conducts trial simulations for designs using both the DLE and efficacy responses. It defines final values for efficacy fit and DLE, estimates of Gstar, optimal dose and sigma2.

Usage

```
PseudoDualSimulations(
  fit_eff,
  final_gstar_estimates,
  final_gstar_at_dose_grid,
  final_gstar_cis,
  final_gstar_ratios,
  final_optimal_dose,
  final_optimal_dose_at_dose_grid,
  sigma2_est,
  ...
)

.DefaultPseudoDualSimulations()
```

Arguments

fit_eff	(list) see slot definition.
final_gstar_estimates	(numeric) see slot definition.
final_gstar_at_dose_grid	(numeric) see slot definition.
final_gstar_cis	(list) see slot definition.
final_gstar_ratios	(numeric) see slot definition.
final_optimal_dose	(numeric) see slot definition.
final_optimal_dose_at_dose_grid	(numeric) see slot definition.

`sigma2_est` (numeric)
see slot definition.

`...` additional parameters from `PseudoSimulations`

Slots

`fit_eff` (list)
final values of efficacy fit.

`final_gstar_estimates` (numeric)
final Gstar estimates.

`final_gstar_at_dose_grid` (numeric)
final Gstar estimates at dose grid.

`final_gstar_cis` (list)
list of 95% confidence interval for Gstar estimates.

`final_gstar_ratios` (numeric)
ratios of confidence intervals for Gstar estimates.

`final_optimal_dose` (numeric)
final optimal dose.

`final_optimal_dose_at_dose_grid` (numeric)
final optimal dose at dose grid.

`sigma2_est` (numeric)
final sigma2 estimates.

Note

Do not use the `.DefaultPseudoDualSimulations()` function.

PseudoDualSimulationsSummary-class
`PseudoDualSimulationsSummary`

Description

[Stable]

This class captures the summary of the dual responses simulations using pseudo models. It contains all slots from `PseudoSimulationsSummary` object. In addition to the slots in the parent class `PseudoSimulationsSummary`, it contains additional slots for the efficacy model fit information.

Note that objects should not be created by users, therefore no initialization function is provided for this class.

Usage

```
.DefaultPseudoDualSimulationsSummary()
```

Slots

`target_gstar` (`numeric`)
: the target dose level such that its gain value is at maximum

`target_gstar_at_dose_grid` (`numeric`)
: the dose level at dose Grid closest and below Gstar

`gstar_summary` (`table`)
: the six-number table summary (lowest, 25th, 50th (median), 75th percentile, mean and highest value) of the final Gstar values obtained across all simulations

`ratio_gstar_summary` (`table`)
: the six-number summary table of the ratios of the upper to the lower 95% credibility intervals of the final Gstar across all simulations

`eff_fit_at_dose_most_selected` (`numeric`)
: fitted expected mean efficacy value at dose most often selected

`mean_eff_fit` (`list`)
: list with mean, lower (2.5%) and upper (97.5%) quantiles of the fitted expected efficacy value at each dose level.

Note

Typically, end users will not use the `.DefaultPseudoDualSimulationsSummary()` function.

`PseudoSimulations-class`
`PseudoSimulations`

Description

[Stable] This class captures trial simulations from designs using pseudo model. It has additional slots `fit` and `stop_reasons` compared to the general class `GeneralSimulations`.

Usage

```
PseudoSimulations(
  fit,
  final_td_target_during_trial_estimates,
  final_td_target_end_of_trial_estimates,
  final_td_target_during_trial_at_dose_grid,
  final_td_target_end_of_trial_at_dose_grid,
  final_tdeot_cis,
  final_tdeot_ratios,
  final_cis,
  final_ratios,
  stop_report,
  stop_reasons,
  ...
```

```
)

.DefaultPseudoSimulations()
```

Arguments

`fit`	(`list`) see slot definition.
`final_td_target_during_trial_estimates`	(`numeric`) see slot definition.
`final_td_target_end_of_trial_estimates`	(`numeric`) see slot definition.
`final_td_target_during_trial_at_dose_grid`	(`numeric`) see slot definition.
`final_td_target_end_of_trial_at_dose_grid`	(`numeric`) see slot definition.
`final_tdeot_cis`	(`list`) see slot definition.
`final_tdeot_ratios`	(`numeric`) see slot definition.
`final_cis`	(`list`) see slot definition.
`final_ratios`	(`numeric`) see slot definition.
`stop_report`	see `PseudoSimulations`
`stop_reasons`	(`list`) see slot definition.
`...`	additional parameters from `GeneralSimulations`

Slots

`fit` (`list`)
: final fit values.

`final_td_target_during_trial_estimates` (`numeric`)
: final estimates of the `td_target_during_trial`.

`final_td_target_end_of_trial_estimates` (`numeric`)
: final estimates of the `td_target_end_of_trial`.

`final_td_target_during_trial_at_dose_grid` (`numeric`)
: dose levels at dose grid closest below the final `td_target_during_trial` estimates.

`final_td_target_end_of_trial_at_dose_grid (numeric)`
: dose levels at dose grid closest below the final `td_target_end_of_trial` estimates.

`final_tdeot_cis (list)`
: 95% credibility intervals of the final estimates for `td_target_end_of_trial`.

`final_tdeot_ratios (numeric)`
: ratio of the upper to the lower 95% credibility intervals for `td_target_end_of_trial`.

`final_cis (list)`
: final 95% credibility intervals for `td_target_end_of_trial` estimates.

`final_ratios (numeric)`
: final ratios of the upper to the lower 95% credibility interval for `td_target_end_of_trial`.

`stop_report (matrix)`
: outcomes of stopping rules.

`stop_reasons (list)`
: reasons for stopping each simulation run.

Note

Typically, end users will not use the `.DefaultPseudoSimulations()` function.

PseudoSimulationsSummary-class PseudoSimulationsSummary

Description

[Stable]

This class captures the summary of pseudo-models simulations output. Note that objects should not be created by users, therefore no initialization function is provided for this class.

Usage

```
.DefaultPseudoSimulationsSummary()
```

Slots

`target_end_of_trial (numeric)`
: the target probability of DLE wanted at the end of a trial

`target_dose_end_of_trial (numeric)`
: the dose level corresponds to the target probability of DLE wanted at the end of a trial, TDEOT

`target_dose_end_of_trial_at_dose_grid (numeric)`
: the dose level at dose grid corresponds to the target probability of DLE wanted at the end of a trial

`target_during_trial (numeric)`
: the target probability of DLE wanted during a trial

`target_dose_during_trial` (`numeric`)
: the dose level corresponds to the target probability of DLE wanted during the trial. TDDT

`target_dose_during_trial_at_dose_grid` (`numeric`)
: the dose level at dose grid corresponds to the target probability of DLE wanted during a trial

`tdeot_summary` (`table`)
: the six-number table summary, include the lowest, the 25th percentile (lower quartile), the 50th percentile (median), the mean, the 75th percentile and the highest values of the final dose levels obtained corresponds to the target probability of DLE want at the end of a trial across all simulations

`tddt_summary` (`table`)
: the six-number table summary, include the lowest, the 25th percentile (lower quartile), the 50th percentile (median), the mean, the 75th percentile and the highest values of the final dose levels obtained corresponds to the target probability of DLE want during a trial across all simulations

`final_dose_rec_summary` (`table`)
: the six-number table summary, include the lowest, the 25th percentile (lower quartile), the 50th percentile (median), the mean, the 75th percentile and the highest values of the final optimal doses, which is either the TDEOT when only DLE response are incorporated into the escalation procedure or the minimum of the TDEOT and Gstar when DLE and efficacy responses are incorporated, across all simulations

`ratio_tdeot_summary` (`table`)
: the six-number summary table of the final ratios of the upper to the lower 95% credibility intervals of the final TDEOTs across all simulations

`final_ratio_summary` (`table`)
: the six-number summary table of the final ratios of the upper to the lower 95% credibility intervals of the final optimal doses across all simulations

`nsim` (`integer`)
: number of simulations

`prop_dle` (`numeric`)
: proportions of DLE in the trials

`mean_tox_risk` (`numeric`)
: mean toxicity risks for the patients

`dose_selected` (`numeric`)
: doses selected as MTD (target_dose_end_of_trial)

`tox_at_doses_selected` (`numeric`)
: true toxicity at doses selected

`prop_at_target_end_of_trial` (`numeric`)
: Proportion of trials selecting at the dose_grid closest below the MTD, the target_dose_end_of_trial

`prop_at_target_during_trial` (`numeric`)
: Proportion of trials selecting at the dose_grid closest below the target_dose_during_trial

`dose_most_selected` (`numeric`)
: dose most often selected as MTD

`obs_tox_rate_at_dose_most_selected` (`numeric`)
: observed toxicity rate at dose most often selected

`n_obs` (integer)
: number of patients overall

`n_above_target_end_of_trial` (integer)
: number of patients treated above target_dose_end_of_trial

`n_above_target_during_trial` (integer)
: number of patients treated above target_dose_during_trial

`dose_grid` (numeric)
: the dose grid that has been used

`fit_at_dose_most_selected` (numeric)
: fitted toxicity rate at dose most often selected

`mean_fit` (list)
: list with the average, lower (2.5%) and upper (97.5%) quantiles of the mean fitted toxicity at each dose level

`stop_report` (matrix)
: matrix of stopping rule outcomes

Note

Typically, end users will not use the `.DefaultPseudoSimulationsSummary()` function.

Quantiles2LogisticNormal

Convert Prior Quantiles to Logistic (Log) Normal Model

Description

[Stable]

This function uses generalized simulated annealing to optimize a `LogisticNormal` model to be as close as possible to the given prior quantiles.

Usage

```
Quantiles2LogisticNormal(
  dosegrid,
  refDose,
  lower,
  median,
  upper,
  level = 0.95,
  logNormal = FALSE,
  parstart = NULL,
  parlower = c(-10, -10, 0, 0, -0.95),
  parupper = c(10, 10, 10, 10, 0.95),
  seed = 12345,
  verbose = TRUE,
```

```
  control = list(threshold.stop = 0.01, maxit = 50000, temperature = 50000, max.time =
    600),
  useLogDose = TRUE
)
```

Arguments

dosegrid	(numeric) the dose grid.
refDose	(number) the reference dose.
lower	(numeric) the lower quantiles.
median	(numeric) the medians.
upper	(numeric) the upper quantiles.
level	(number) the credible level of the (lower, upper) intervals. Default is 0.95.
logNormal	(flag) use the log-normal prior? If FALSE (default), the normal prior for the logistic regression coefficients is used.
parstart	(numeric or NULL) starting values for the parameters. By default, these are determined from the medians supplied.
parlower	(numeric) lower bounds on the parameters (intercept alpha and the slope beta, the corresponding standard deviations and the correlation).
parupper	(numeric) upper bounds on the parameters.
seed	(count) seed for random number generation.
verbose	(flag) should the function be verbose?
control	(list) additional options for the optimisation routine, see GenSA::GenSA() for more details.
useLogDose	(flag) use log(dosegrid / refDose) as dose covariate? If FALSE, logNormal must be TRUE and a LogisticLogNormalSub model is returned.

Value

A list with the best approximating model (LogisticNormal, LogisticLogNormal, or LogisticLogNormalSub), the resulting quantiles, the required quantiles and the distance to the required quantiles, as well as the final parameters (which could be used for running the algorithm a second time).

Recruitment-class Recruitment

Description

[Experimental]

`Recruitment` is a virtual class for recruitment criteria, from which all other specific recruitment criteria classes inherit. The subclasses are used to specify the maximum number of backfill patients that can be recruited relative to the main trial cohort size.

Usage

```
.DefaultRecruitment()
```

Note

Typically, end users will not use the `.DefaultRecruitment()` function.

See Also

`RecruitmentUnlimited`, `RecruitmentRatio`.

RecruitmentRatio-class RecruitmentRatio

Description

[Experimental]

`RecruitmentRatio` constrains the recruitment of backfill patients based on a ratio to the main trial cohort size. The maximum number of backfill patients is calculated as `ceiling(ratio * active_cohort_size)`.

Usage

```
RecruitmentRatio(ratio = 1)

.DefaultRecruitmentRatio()
```

Arguments

`ratio`	(`number`) see slot definition.

Slots

`ratio` (`number`) the recruitment ratio, specifying the maximum number of backfill patients per patient in the main trial cohort (non-negative).

Note

Typically, end users will not use the `.DefaultRecruitmentRatio()` function.

See Also

`Recruitment` and the other subclasses listed in there.

Examples

```
# Create a RecruitmentRatio object with ratio 0.5
# This means 1 backfill patient for every 2 patients in the active cohort
recruitment <- RecruitmentRatio(ratio = 0.5)
print(recruitment)

# Create a variant with ratio 1 (1:1)
recruitment_one_to_one <- RecruitmentRatio(ratio = 1)
print(recruitment_one_to_one)
```

RecruitmentUnlimited-class
RecruitmentUnlimited

Description

[Experimental]

`RecruitmentUnlimited` allows unlimited recruitment of backfill patients. There is no constraint on the number of backfill patients relative to the main trial cohort size.

Usage

```
RecruitmentUnlimited()

.DefaultRecruitmentUnlimited()
```

Note

Typically, end users will not use the `.DefaultRecruitmentUnlimited()` function.

See Also

`Recruitment` and the other subclasses listed in there.

Examples

```
# Create a RecruitmentUnlimited object
recruitment <- RecruitmentUnlimited()
print(recruitment)

# Calculate maximum recruits for an active cohort of size 10
max_recruits <- maxRecruits(recruitment, active_cohort_size = 10)
print(max_recruits) # Practically unlimited (1e6)
```

`RuleDesign-class` `RuleDesign`

Description

[Stable]

`RuleDesign` is the class for rule-based designs. The difference between this class and the `Design` class is that `RuleDesign` does not contain `model`, `stopping` and `increments` slots.

Usage

```
RuleDesign(nextBest, cohort_size, data, startingDose)

.DefaultRuleDesign()

ThreePlusThreeDesign(doseGrid)
```

Arguments

`nextBest`	(`NextBest`) see slot definition.
`cohort_size`	(`CohortSize`) see slot definition.
`data`	(`Data`) see slot definition.
`startingDose`	(`number`) see slot definition.
`doseGrid`	(`numeric`) the dose grid to be used (sorted).

Functions

- `ThreePlusThreeDesign()`: creates a new 3+3 design object from a dose grid.

Slots

`nextBest` (`NextBest`)
: how to find the next best dose.

`cohort_size` (`CohortSize`)
: rules for the cohort sizes.

`data` (`Data`)
: specifies dose grid, any previous data, etc.

`startingDose` (`number`)
: the starting dose, it must lie on the dose grid in `data`.

Note

Typically, end users will not use the `.DefaultRuleDesign()` function.

Examples

```
# Specify the design to run simulations. The design comprises a model,
# the escalation rule, starting data, a cohort size and a starting dose.

# Initialing a 3+3 design with constant cohort size of 3 and starting dose equal 5.
my_design <- RuleDesign(
  nextBest = NextBestThreePlusThree(),
  cohort_size = CohortSizeConst(size = 3L),
  data = Data(doseGrid = c(5, 10, 15, 25, 35, 50, 80)),
  startingDose = 5
)
# Initialing a 3+3 design with constant cohort size of 3 and starting dose equal 8.
my_design <- ThreePlusThreeDesign(doseGrid = c(8, 10, 15, 25, 35, 50, 80))
```

RuleDesignOrdinal-class
RuleDesignOrdinal

Description

[Experimental]

`RuleDesignOrdinal` is the class for rule-based designs. The difference between this class and the `DesignOrdinal` class is that `RuleDesignOrdinal` does not contain `model`, `stopping` and `increments` slots.

Usage

```
RuleDesignOrdinal(next_best, cohort_size, data, starting_dose)

.DefaultRuleDesignOrdinal()
```

Arguments

next_best	(NextBestOrdinal) see slot definition.
cohort_size	(CohortSize) see slot definition.
data	(DataOrdinal) see slot definition.
starting_dose	(number) see slot definition.

Details

Please note that the cohort size rules need to be wrapped into the corresponding CohortSizeOrdinal class, before a successful evaluation of the corresponding methods can take place. Note also that these wrappers cannot be nested, i.e., you cannot have a CohortSizeOrdinal inside another CohortSizeOrdinal (which also would not make sense) because it would not be clear which event grade to use for the methods calculation. However, multiple rules can be combined using the operators defined, e.g., `CohortSizeMin(list(CohortSizeOrdinal(1L, rule1), CohortSizeOrdinal(2L, rule2)))`.

Slots

`next_best` (NextBestOrdinal)
: how to find the next best dose.

`cohort_size` (CohortSize)
: rules for the cohort sizes.

`data` (DataOrdinal)
: specifies dose grid, any previous data, etc.

`starting_dose` (number)
: the starting dose, it must lie on the dose grid in `data`.

Note

Typically, end users will not use the `.DefaultRuleDesignOrdinal()` function.

Examples

```
RuleDesignOrdinal(
  next_best = NextBestOrdinal(
    1L,
    NextBestMTD(
      target = 0.25,
      derive = function(x) median(x, na.rm = TRUE)
    )
  ),
  cohort_size = CohortSizeOrdinal(1L, CohortSizeConst(size = 3L)),
  data = DataOrdinal(doseGrid = c(5, 10, 15, 25, 35, 50, 80)),
  starting_dose = 5
)
```

SafetyWindow-class SafetyWindow

Description

[Stable]

SafetyWindow is a class for safety window.

Usage

```
.DefaultSafetyWindow()
```

Note

Typically, end users will not use the .DefaultSafetyWindow() function.

See Also

SafetyWindowSize, SafetyWindowConst.

SafetyWindowConst-class SafetyWindowConst

Description

[Stable]

SafetyWindowConst is the class for safety window length and it is used when the gap should be kept constant across cohorts (though it may vary within a cohort).

Usage

```
SafetyWindowConst(gap, follow, follow_min)

.DefaultSafetyWindowConst()
```

Arguments

gap	see slot definition.
follow	see slot definition.
follow_min	see slot definition.

Slots

`gap (integer)`
: a vector, the constant gap between patients.

`follow (count)`
: how long to follow each patient. The period of time that each patient in the cohort needs to be followed before the next cohort opens.

`follow_min (count)`
: minimum follow up. At least one patient in the cohort needs to be followed at the minimal follow up time.

Note

Typically, end users will not use the `.DefaultSafetyWindowConst()` function.

Examples

```
# This is to have along the study constant parameters settings of safety window
# length, regardless of the cohort size.
my_win_len <- SafetyWindowConst(
  gap = c(7, 5, 3),
  follow = 7,
  follow_min = 14
)
```

SafetyWindowSize-class

`SafetyWindowSize`

Description

[Stable]

`SafetyWindowSize` is the class for safety window length based on cohort size. This class is used to decide the rolling rule from the clinical perspective.

Usage

```
SafetyWindowSize(gap, size, follow, follow_min)

.DefaultSafetyWindowSize()
```

Arguments

`gap`	see slot definition.
`size`	see slot definition.
`follow`	see slot definition.
`follow_min`	see slot definition.

Slots

`gap (list)`
: observed period of the previous patient before the next patient can be dosed. This is used as follows. If for instance, the cohort size is 4 and we want to specify three time intervals between these four consecutive patients, i.e. 7 units of time between the 1st and the 2nd patient, 5 units between the 2nd and the 3rd one, and finally 3 units between the 3rd and the 4th one, then, `gap = list(c(7L, 5L, 3L))`. Sometimes, we want that the interval only between the 1st and 2nd patient should be increased for the safety consideration and the rest time intervals should remain constant, regardless of what the cohort size is. Then, `gap = list(c(7L, 3L))` and the the package will automatically repeat the last element of the vector for the remaining time intervals.

`size (integer)`
: a vector with the left bounds of the relevant cohort size intervals. This is used as follows. For instance, when we want to change the `gap` based on the cohort size, i.e. the time interval between the 1st and 2nd patient = 9 units of time and the rest time intervals are of 5 units of time when the cohort size is equal to or larger than 4. And the time interval between the 1st and 2nd patient = 7 units of time and the rest time intervals are 3 units of time when the cohort size is smaller than 4, then we specify both `gap = list(c(7, 3), c(9, 5))` and `size = c(0L, 4L)`. This means, the right bounds of the intervals are excluded from the interval, and the last interval goes from the last value to infinity.

`follow (count)`
: the period of time that each patient in the cohort needs to be followed before the next cohort opens.

`follow_min (count)`
: at least one patient in the cohort needs to be followed at the minimal follow up time.

Note

Typically, end users will not use the `.DefaultSafetyWindowSize()` function.

Examples

```
# Rule for having patient gap (7,3,3,3,...) for cohort size < 4, and
# patient gap (9,5,5,5...) for cohort size >= 4.
my_window_len <- SafetyWindowSize(
  gap = list(c(7, 3), c(9, 5)),
  size = c(1, 4),
  follow = 7,
  follow_min = 14
)
```

`Samples-class` `Samples`

Description

[Stable]

`Samples` is the class to store the MCMC samples.

Usage

```
Samples(data, options)

.DefaultSamples()
```

Arguments

`data`	see slot definition.
`options`	see slot definition.

Slots

`data` (`list`)
: MCMC samples of the parameter. Each entry in this list must be a vector (in case of a scalar parameter) or matrix (in case of a vector-valued parameter) with samples. In case of matrix, every row is a separate sample, while columns correspond to the dimension of the parameter.

`options` (`McmcOptions`)
: MCMC options that were used to generate the samples.

Note

Typically, end users will not use the `.DefaultSamples()` function.

Examples

```
# The MCMC options that were used to generate the samples.
my_options <- McmcOptions(
  burnin = 1000,
  step = 2,
  samples = 1000
)

# Create an object of class 'Samples'
# Here the parameters 'alpha' and 'beta' are randomly generated. Of course, in
# a real example these would be a samples coming from MCMC procedures.
my_samples <- Samples(
  data = list(alpha = rnorm(1000), beta = rnorm(1000)),
  options = my_options
)
```

saveSample *Determining if this Sample Should be Saved*

Description

[Stable]

A method that determines if a sample from a given `iteration` should be saved. The sample should be saved if and only if: it is not in burn-in period and it matches the `step`.

Usage

```
saveSample(object, iteration, ...)

## S4 method for signature 'McmcOptions'
saveSample(object, iteration, ...)
```

Arguments

`object`	(`McmcOptions`) object based on which the answer is determined.
`iteration`	(`count`) the current iteration index.
`...`	not used.

Value

`TRUE` if this sample should be saved.

Functions

- `saveSample(McmcOptions)`: determine if a sample should be saved.

Examples

```
# Set up the MCMC option in order to have a burn-in of 10000 iterations and
# then take every other iteration up to a collection of 10000 samples.
my_options <- McmcOptions(burnin = 10000, step = 2, samples = 10000)

size(my_options)
saveSample(my_options, iteration = 5)
```

scenario *Evaluate a Hypothetical Data Scenario for a Design*

Description

[Experimental]

`scenario()` is a convenience wrapper for evaluating a CRM design at a user-supplied hypothetical data scenario. It runs the model, summarizes the posterior fit, calculates the next dose recommendation, and evaluates the stopping rule for the supplied `data`.

Usage

```
scenario(object, data, mcmcOptions, ...)

## S4 method for signature 'Design,Data,McmcOptions'
scenario(object, data, mcmcOptions = McmcOptions(), ...)

## S4 method for signature 'DesignCombo,DataCombo,McmcOptions'
scenario(object, data, mcmcOptions = McmcOptions(), ...)

## S4 method for signature 'DADesign,DataDA,McmcOptions'
scenario(object, data, mcmcOptions = McmcOptions(), ...)

## S4 method for signature 'HierarchicalDesign,HierarchicalData,McmcOptions'
scenario(object, data, mcmcOptions = McmcOptions(), ...)
```

Arguments

`object`	(`Design`, `DesignCombo`, `DADesign`, or `HierarchicalDesign`) the design to evaluate.
`data`	(`Data`, `DataCombo`, `DataDA`, or `HierarchicalData`) hypothetical data scenario to evaluate.
`mcmcOptions`	(`McmcOptions`) MCMC options for the model fit.
`...`	additional arguments without method dispatch.

Value

A named list containing:

- `data`: the evaluated data scenario.
- `samples`: posterior samples from `mcmc()`.
- `fit`: posterior model fit summary from `fit()`.
- `dose_limit`: maximum allowed next dose from the design's increment rule.
- `next_best`: full next best dose recommendation from `nextBest()`.

- next_dose: recommended dose value for the next cohort.
- cohort_size: active treatment cohort size at next_dose.
- placebo_cohort_size: placebo cohort size at next_dose, if applicable.
- stop: logical stop decision from stopTrial().
- stop_report: named logical vector with stopping rule results.
- stop_reason: stopping-rule message.

Functions

- scenario(object = Design, data = Data, mcmcOptions = McmcOptions): Evaluate a hypothetical scenario for a CRM design.
- scenario(object = DesignCombo, data = DataCombo, mcmcOptions = McmcOptions): Evaluate a hypothetical scenario for a two-drug combination CRM design.
- scenario(object = DADesign, data = DataDA, mcmcOptions = McmcOptions): Evaluate a hypothetical scenario for a time-to-DLT augmented CRM design.
- scenario(object = HierarchicalDesign, data = HierarchicalData, mcmcOptions = McmcOptions): Evaluate a hypothetical scenario for a hierarchical CRM design.

Examples

```
# nolint start

# Define the dose-grid and a hypothetical observed data scenario.
data <- Data(
  x = c(1, 3, 3, 5, 5, 5),
  y = c(0, 0, 0, 0, 1, 0),
  cohort = c(1, 2, 2, 3, 3, 3),
  doseGrid = c(1, 3, 5, 10, 15, 20, 25)
)

# Initialize the CRM model.
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Choose the rule for selecting the next dose.
next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for stopping.
stopping <- StoppingMinPatients(nPatients = 20) | StoppingMissingDose()

# Choose the rule for dose increments.
increments <- IncrementsRelative(
```

```
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Initialize the design.
design <- Design(
  model = model,
  nextBest = next_best,
  stopping = stopping,
  increments = increments,
  cohort_size = CohortSizeConst(3),
  data = Data(doseGrid = data@doseGrid), # empty data here.
  startingDose = 1
)

options <- McmcOptions(
  burnin = 10,
  step = 1,
  samples = 20,
  rng_kind = "Super-Duper",
  rng_seed = 94
)


result <- scenario(design, data, options)
result$fit
result$next_dose
result$cohort_size
result$stop


# nolint end
# nolint start

# Define a hypothetical two-drug scenario.
data <- DataCombo(
  x = cbind(
    drug1 = c(10, 10, 10, 20, 20, 20),
    drug2 = c(20, 20, 20, 20, 20, 20)
  ),
  y = c(0, 0, 1, 0, 0, 0),
  doseGrid = list(drug1 = c(10, 20, 30), drug2 = c(20, 40, 60))
)

model <- TwoDrugsCombo(
  single_models = list(
    drug1 = LogisticLogNormal(
      mean = c(-0.85, 1),
      cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
      ref_dose = 10
    ),
    drug2 = LogisticLogNormal(
      mean = c(-0.7, 0.8),
```

```
      cov = matrix(c(1.1, -0.3, -0.3, 0.9), nrow = 2),
      ref_dose = 20
    )
  ),
  gamma = 0,
  tau = 1
)

increments <- IncrementsMin(
  increments_list = list(
    IncrementsComboOneDrugOnly(),
    IncrementsComboCartesian(
      drug1 = IncrementsRelative(intervals = c(0), increments = c(1)),
      drug2 = IncrementsRelative(intervals = c(0), increments = c(1))
    )
  )
)

design <- DesignCombo(
  model = model,
  nextBest = NextBestNCRM(
    target = c(0.2, 0.35),
    overdose = c(0.35, 1),
    max_overdose_prob = 0.25
  ),
  stopping = StoppingMinPatients(nPatients = 20),
  increments = increments,
  cohort_size = CohortSizeConst(3),
  data = DataCombo(doseGrid = data@doseGrid),
  startingDose = c(drug1 = 10, drug2 = 20)
)

options <- McmcOptions(
  burnin = 10,
  step = 1,
  samples = 20,
  rng_kind = "Super-Duper",
  rng_seed = 94
)


result <- scenario(design, data, options)
result$fit
result$next_dose
result$cohort_size
result$stop


# nolint end
# nolint start

# Define a hypothetical time-to-DLT scenario.
data <- DataDA(
```

```
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 1, 1, 0, 0, 1, 0),
  u = c(42, 30, 15, 5, 20, 25, 30, 60),
  t0 = c(0, 15, 30, 40, 55, 70, 75, 85),
  Tmax = 60,
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2)),
  ID = 1L:8L,
  cohort = as.integer(c(1, 2, 3, 4, 5, 6, 6, 6))
)

npiece <- 10
t_max <- 60
lambda_prior <- function(k) {
  npiece / (t_max * (npiece - k + 0.5))
}

model <- DALogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56,
  npiece = npiece,
  l = as.numeric(t(apply(as.matrix(c(1:npiece), 1, npiece), 2, lambda_prior))),
  c_par = 2
)

size1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
size2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)

design <- DADesign(
  model = model,
  increments = IncrementsRelative(
    intervals = c(0, 20),
    increments = c(1, 0.33)
  ),
  nextBest = NextBestNCRM(
    target = c(0.2, 0.35),
    overdose = c(0.35, 1),
    max_overdose_prob = 0.25
  ),
  stopping = StoppingTargetProb(
    target = c(0.2, 0.35),
    prob = 0.5
  ) | StoppingMinPatients(nPatients = 50) | StoppingMissingDose(),
  cohort_size = maxSize(size1, size2),
  data = DataDA(doseGrid = data@doseGrid, Tmax = data@Tmax),
  safetyWindow = SafetyWindowConst(c(6, 2), 7, 7),
  startingDose = 3
```

```
)

options <- McmcOptions(
  burnin = 10,
  step = 1,
  samples = 20,
  rng_kind = "Super-Duper",
  rng_seed = 94
)


result <- scenario(design, data, options)
result$fit
result$next_dose
result$cohort_size
result$stop


# nolint end
# nolint start

dose_grid <- c(1, 3, 5, 10, 15, 20, 25)

# Define hypothetical observed data for two related arms.
data <- HierarchicalData(
  arm_a = Data(
    x = c(1, 3, 3, 5),
    y = c(0, 0, 0, 1),
    cohort = c(1, 2, 2, 3),
    doseGrid = dose_grid
  ),
  arm_b = Data(
    x = c(1, 1, 3, 3),
    y = c(0, 0, 0, 0),
    cohort = c(1, 1, 2, 2),
    doseGrid = dose_grid
  )
)

model_a <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 10
)
model_b <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 10
)

next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
```

```
  max_overdose_prob = 0.25
)
stopping <- StoppingMinPatients(nPatients = 20) | StoppingMissingDose()
increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

design_a <- Design(
  model = model_a,
  nextBest = next_best,
  stopping = stopping,
  increments = increments,
  cohort_size = CohortSizeConst(3),
  data = Data(doseGrid = dose_grid),
  startingDose = 1
)
design_b <- Design(
  model = model_b,
  nextBest = next_best,
  stopping = stopping,
  increments = increments,
  cohort_size = CohortSizeConst(3),
  data = Data(doseGrid = dose_grid),
  startingDose = 1
)

design <- HierarchicalDesign(
  DesignArm(
    name = "arm_a",
    design = design_a
  ),
  DesignArm(
    name = "arm_b",
    design = design_b
  ),
  exchangeable_parameters = list(
    intercept = list(
      arm_a = "alpha0",
      arm_b = "alpha0"
    ),
    slope = list(
      arm_a = "alpha1",
      arm_b = "alpha1"
    )
  )
)

options <- McmcOptions(
  burnin = 10,
  step = 1,
  samples = 20,
  rng_kind = "Super-Duper",
```

```
  rng_seed = 94
)


result <- scenario(design, data, options)
result$fit
result$next_dose
result$cohort_size
result$stop


# nolint end
```

`set_seed` *Helper Function to Set and Save the RNG Seed*

Description

[Stable]

This code is basically copied from `stats:::simulate.lm`.

Usage

```
set_seed(seed = NULL)
```

Arguments

`seed`	an object specifying if and how the random number generator should be initialized ("seeded"). Either `NULL` (default) or an integer that will be used in a call to `set.seed()` before simulating the response vectors. If set, the value is saved as the `seed` slot of the returned object. The default, `NULL` will not change the random generator state.

Value

The integer vector containing the random number generate state will be returned, in order to call this function with this input to reproduce the obtained simulation results.

`show,ComboSimulations-method`
Show `ComboSimulations` *Objects*

Description

[Experimental]

Display a brief representation of the `ComboSimulations` object.

Usage

```
## S4 method for signature 'ComboSimulations'
show(object)
```

Arguments

`object`	(`ComboSimulations`) the object we want to print.

Value

Invisibly returns the object itself.

`show,ComboSimulationsSummary-method`
Show the Summary of Combination Simulations

Description

[Experimental]

Display a summary of combination simulation results.

Usage

```
## S4 method for signature 'ComboSimulationsSummary'
show(object)
```

Arguments

`object`	(`ComboSimulationsSummary`) the object we want to print.

Value

Invisibly returns a data frame of the results with one row and appropriate column names.

show,DualSimulationsSummary-method
Show the Summary of Dual-Endpoint Simulations

Description

[Stable]

Display a summary of dual-endpoint simulation results.

Usage

```
## S4 method for signature 'DualSimulationsSummary'
show(object)
```

Arguments

object	(DualSimulationsSummary) the object we want to print.

Value

Invisibly returns a data frame of the results with one row and appropriate column names.

Examples

```
# Define the dose-grid.
emptydata <- DataDual(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 30))

# Initialize the CRM model.
my_model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2betaW = 0.01,
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  rw1 = TRUE
)

# Choose the rule for selecting the next dose.
my_next_best <- NextBestDualEndpoint(
  target = c(0.9, 1),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size.
my_size1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
```

```
)
my_size2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
my_size <- maxSize(my_size1, my_size2)

# Choose the rule for stopping.
my_stopping1 <- StoppingTargetBiomarker(
  target = c(0.9, 1),
  prob = 0.5
)

# Stop with a small number of patients for illustration.
my_stopping <- my_stopping1 | StoppingMinPatients(10) | StoppingMissingDose()

# Choose the rule for dose increments.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Initialize the design.
my_design <- DualDesign(
  model = my_model,
  data = emptydata,
  nextBest = my_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = CohortSizeConst(3),
  startingDose = 3
)

# Define scenarios for the TRUE toxicity and efficacy profiles.
beta_mod <- function(dose, e0, eMax, delta1, delta2, scal) {
  maxDens <- (delta1^delta1) *
    (delta2^delta2) /
    ((delta1 + delta2)^(delta1 + delta2))
  dose <- dose / scal
  e0 + eMax / maxDens * (dose^delta1) * (1 - dose)^delta2
}

true_biomarker <- function(dose) {
  beta_mod(
    dose,
    e0 = 0.2,
    eMax = 0.6,
    delta1 = 5,
    delta2 = 5 * 0.5 / 0.5,
    scal = 100
  )
}
```

```
true_tox <- function(dose) {
  pnorm((dose - 60) / 10)
}

# Draw the TRUE profiles.
par(mfrow = c(1, 2))
curve(true_tox(x), from = 0, to = 80)
curve(true_biomarker(x), from = 0, to = 80)

# Run the simulation on the desired design.
# For illustration purposes only 1 trial outcome is generated and 5 burn-ins
# to generate 20 samples are used here.
my_sims <- simulate(
  object = my_design,
  trueTox = true_tox,
  trueBiomarker = true_biomarker,
  sigma2W = 0.01,
  rho = 0,
  nsim = 1,
  parallel = FALSE,
  seed = 3,
  startingDose = 6,
  mcmcOptions = McmcOptions(
    burnin = 5,
    step = 1,
    samples = 20
  )
)

# Show the summary of the simulations.
show(summary(
  my_sims,
  trueTox = true_tox,
  trueBiomarker = true_biomarker
))
```

`show,GeneralSimulations-method`

Show `Simulations` *Objects*

Description

[Stable]

Display a brief representation of the GeneralSimulations object.

Usage

```
## S4 method for signature 'GeneralSimulations'
show(object)
```

Arguments

object	(GeneralSimulations) the object we want to print.

Value

Invisibly returns the object itself.

---

show,GeneralSimulationsSummary-method

Show the Summary of the Simulations

Description

[Stable]

Display a summary of general simulation results.

Usage

```
## S4 method for signature 'GeneralSimulationsSummary'
show(object)
```

Arguments

object	(GeneralSimulationsSummary) the object we want to print.

Value

Invisibly returns a data frame of the results with one row and appropriate column names.

---

show,HierarchicalData-method

Show HierarchicalData *Objects*

Description

[Experimental]

Display a brief representation of the HierarchicalData object.

Usage

```
## S4 method for signature 'HierarchicalData'
show(object)
```

Arguments

object	(HierarchicalData) the object we want to print.

Value

Invisibly returns the object itself.

---

show,HierarchicalDesign-method

Show HierarchicalDesign *Objects*

Description

[Experimental]

Display a brief representation of the HierarchicalDesign object.

Usage

```
## S4 method for signature 'HierarchicalDesign'
show(object)
```

Arguments

object	(HierarchicalDesign) the object we want to print.

Value

Invisibly returns the object itself.

---

show,HierarchicalModel-method

Show HierarchicalModel *Objects*

Description

[Experimental]

Display a brief representation of the HierarchicalModel object.

Usage

```
## S4 method for signature 'HierarchicalModel'
show(object)
```

Arguments

`object`	(`HierarchicalModel`) the object we want to print.

Value

Invisibly returns the object itself.

`show,HierarchicalSimulations-method` *Show* `HierarchicalSimulations` *Objects*

Description

[Experimental]

Display a brief representation of the `HierarchicalSimulations` object.

Usage

```
## S4 method for signature 'HierarchicalSimulations'
show(object)
```

Arguments

`object`	(`HierarchicalSimulations`) the object we want to print.

Value

Invisibly returns the object itself.

`show,HierarchicalSimulationsSummary-method` *Show the Summary of Hierarchical Simulations*

Description

[Experimental]

Display arm-specific hierarchical simulation summaries.

Usage

```
## S4 method for signature 'HierarchicalSimulationsSummary'
show(object)
```

Arguments

object	(HierarchicalSimulationsSummary) the object we want to print.

Value

Invisibly returns a named list of arm-level summary data frames.

---

show,PseudoDualSimulationsSummary-method

Show the Summary of PseudoDualSimulations

Description

[Stable]

Display a summary of pseudo dual simulation results.

Usage

```
## S4 method for signature 'PseudoDualSimulationsSummary'
show(object)
```

Arguments

object	(PseudoDualSimulationsSummary) the object we want to print.

Value

Invisibly returns a data frame of the results with one row and appropriate column names.

Examples

```
# Example where DLE and efficacy responses are considered in the simulations.
# In simulations where no samples are used a data object with doses >= 1 needs
# to be generated.
emptydata <- DataDual(doseGrid = seq(25, 300, 25), placebo = FALSE)

# The DLE model must be of 'ModelTox' (e.g 'LogisticIndepBeta') class.
dle_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = emptydata
)

# The efficacy model of 'ModelEff' (e.g 'Effloglog') class.
eff_model <- Effloglog(
```

```
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = emptydata
)

# The escalation rule using the 'NextBestMaxGain' class.
my_next_best <- NextBestMaxGain(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)

# Allow increase of 200%.
my_increments <- IncrementsRelative(intervals = 0, increments = 2)

# Cohort size of 3.
my_size <- CohortSizeConst(size = 3)

# Stop when 36 subjects are treated or next dose is NA.
my_stopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()

# Specify the design. (For details please refer to the 'DualResponsesDesign' example.)
my_design <- DualResponsesDesign(
  nextBest = my_next_best,
  model = dle_model,
  eff_model = eff_model,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  data = emptydata,
  startingDose = 25
)

# Specify the true DLE and efficacy curves.
my_truth_dle <- probFunction(dle_model, phi1 = -53.66584, phi2 = 10.50499)
my_truth_eff <- efficacyFunction(eff_model, theta1 = -4.818429, theta2 = 3.653058)


# For illustration purpose only 2 simulations are produced.
my_sim <- simulate(
  object = my_design,
  args = NULL,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff,
  trueNu = 1 / 0.025,
  nsim = 2,
  seed = 819,
  parallel = FALSE
)

# Summary of the simulations.
my_sum <- summary(
  my_sim,
```

```
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff
)

# Show the summary of the simulations in a data frame.
show(my_sum)


# Example when DLE and efficacy samples are involved.

# The escalation rule using the 'NextBestMaxGainSamples' class.
my_next_best <- NextBestMaxGainSamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, prob = 0.3))
  },
  mg_derive = function(mg_samples) {
    as.numeric(quantile(mg_samples, prob = 0.5))
  }
)

# The design of 'DualResponsesSamplesDesign' class.
my_design <- DualResponsesSamplesDesign(
  nextBest = my_next_best,
  cohort_size = my_size,
  startingDose = 25,
  model = dle_model,
  eff_model = eff_model,
  data = emptydata,
  stopping = my_stopping,
  increments = my_increments
)

# MCMC options.
# For illustration purpose 50 burn-ins to generate 200 samples are used.
my_options <- McmcOptions(burnin = 50, step = 2, samples = 200)


# For illustration purpose 2 trials are simulated.
my_sim <- simulate(
  object = my_design,
  args = NULL,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff,
  trueNu = 1 / 0.025,
  nsim = 2,
  mcmcOptions = my_options,
  seed = 819,
  parallel = FALSE
)

# Produce a summary of the simulations.
```

```
my_sum <- summary(
  my_sim,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff
)

# Show the summary in data frame for the simulations.
show(my_sum)
```

---

show,PseudoSimulationsSummary-method
Show the Summary of PseudoSimulations

Description

[Stable]

Display a summary of pseudo simulation results.

Usage

```
## S4 method for signature 'PseudoSimulationsSummary'
show(object)
```

Arguments

object	(PseudoSimulationsSummary) the object we want to print.

Value

Invisibly returns a data frame of the results with one row and appropriate column names.

Examples

```
# Obtain the plot for the simulation results if only DLE responses are
# considered in the simulations.

# Specified simulations when no DLE samples are used.
emptydata <- Data(doseGrid = seq(25, 300, 25))

# The design only incorporate DLE responses and DLE samples are involved.
# Specify the model of 'ModelTox' class eg 'LogisticIndepBeta' class model.
my_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = emptydata
)
```

```
# The escalation rule.
td_next_best <- NextBestTD(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)

# The cohort size is 3 subjects.
my_size <- CohortSizeConst(size = 3)

# Allow increase of 200%.
my_increments <- IncrementsRelative(intervals = 0, increments = 2)

# Specify the stopping rule with maximum sample size of 36 patients or when the
# next dose is NA.
my_stopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()

# Specify the design. (For details please refer to the 'TDDesign' example.)
my_design <- TDDesign(
  model = my_model,
  nextBest = td_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  data = emptydata,
  startingDose = 25
)

# Specify the truth of the DLE responses.
my_truth <- probFunction(my_model, phi1 = -53.66584, phi2 = 10.50499)

# For illustration purpose only 1 simulation is produced.
my_sim <- simulate(
  object = my_design,
  args = NULL,
  truth = my_truth,
  nsim = 1,
  seed = 819,
  parallel = FALSE
)

# Summary of the simulations.
my_sum <- summary(
  my_sim,
  truth = my_truth
)

# Show the summary of the simulated results in a data frame.
show(my_sum)

# Example where DLE samples are involved.

# The escalation rule.
```

```
td_next_best <- NextBestTDsamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, probs = 0.3))
  }
)

# The design.
my_design <- TDsamplesDesign(
  model = my_model,
  nextBest = td_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  data = emptydata,
  startingDose = 25
)

# For illustration purposes 2 trails are simulated with 50 burn-ins to generate
# 200 samples.
my_options <- McmcOptions(burnin = 50, step = 2, samples = 200)

my_sim <- simulate(
  object = my_design,
  args = NULL,
  truth = my_truth,
  nsim = 2,
  seed = 819,
  mcmcOptions = my_options,
  parallel = FALSE
)

# Produce a summary of the simulations.
my_sum <- summary(
  my_sim,
  truth = my_truth
)

# Show the summary of the simulated results in a data frame.
show(my_sum)
```

---

show,SimulationsSummary-method

Show the Summary of Model-Based Design Simulations

Description

[Stable]

Display a summary of model-based design simulation results.

Usage

```
## S4 method for signature 'SimulationsSummary'
show(object)
```

Arguments

object	(SimulationsSummary) the object we want to print.

Value

Invisibly returns a data frame of the results with one row and appropriate column names.

Examples

```
# nolint start

# Define the dose-grid
emptydata <- Data(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))

# Initialize the CRM model
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Choose the rule for selecting the next dose
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size
mySize1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
mySize2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
mySize <- maxSize(mySize1, mySize2)

# Choose the rule for stopping
myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(
  target = c(0.2, 0.35),
  prob = 0.5
)
myStopping3 <- StoppingMinPatients(nPatients = 20)
```

```
myStopping <- (myStopping1 & myStopping2) | myStopping3 | StoppingMissingDose()

# Choose the rule for dose increments
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Initialize the design
design <- Design(
  model = model,
  nextBest = myNextBest,
  stopping = myStopping,
  increments = myIncrements,
  cohort_size = mySize,
  data = emptydata,
  startingDose = 3
)

## define the true function
myTruth <- probFunction(model, alpha0 = 7, alpha1 = 8)

# Run the simulation on the desired design
# We only generate 1 trial outcome here for illustration, for the actual study
# this should be increased of course
options <- McmcOptions(
  burnin = 100,
  step = 2,
  samples = 1000
)
time <- system.time(
  mySims <- simulate(
    design,
    args = NULL,
    truth = myTruth,
    nsim = 1,
    seed = 819,
    mcmcOptions = options,
    parallel = FALSE
  )
)[3]

# Show the Summary of the Simulations
show(summary(mySims, truth = myTruth))

# nolint end
```

---

simulate,DADesign-method

Simulate outcomes from a time-to-DLT augmented CRM design

Description

[Stable]

This method simulates dose escalation trials using time-to-DLT data, where the timing of dose-limiting toxicities is explicitly modeled.

Usage

```
## S4 method for signature 'DADesign'
simulate(
  object,
  nsim = 1L,
  seed = NULL,
  truthTox,
  truthSurv,
  trueTmax = NULL,
  args = NULL,
  firstSeparate = FALSE,
  deescalate = TRUE,
  mcmcOptions = McmcOptions(),
  DA = TRUE,
  parallel = FALSE,
  nCores = min(parallel::detectCores(), 5),
  derive = list(),
  ...
)
```

Arguments

`object`	the `DADesign` object we want to simulate data from
`nsim`	(`count`) the number of simulations (default: 1)
`seed`	see `set_seed()`
`truthTox`	(`function`) a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity and the time DLT occurs. Additional arguments can be supplied in `args`.
`truthSurv`	(`function`) a CDF which takes as input a time (vector) and returns the true cumulative probability (vector) that the DLT would occur conditioning on the patient has DLTs.
`trueTmax`	(`number` or `NULL`) the true maximum time at which DLTs can occur. Note that this must be larger than `Tmax` from the `object`'s base data, which is the length of the DLT window, i.e. until which time DLTs are officially declared as such and used in the trial.
`args`	(`data.frame`) data frame with arguments for the `truthTox` function. The column names correspond to the argument names, the rows to the values of the arguments. The

rows are appropriately recycled in the `nsim` simulations. In order to produce outcomes from the posterior predictive distribution, e.g, pass an `object` that contains the data observed so far, `truthTox` contains the `prob` function from the model in `object`, and `args` contains posterior samples from the model.

`firstSeparate` (`flag`)
enroll the first patient separately from the rest of the cohort? (not default) If yes, the cohort will be closed if a DLT occurs in this patient.

`deescalate` (`flag`)
allow deescalation when a DLT occurs in cohorts with lower dose level? (default: TRUE)

`mcmcOptions` (McmcOptions)
object of class `McmcOptions`, giving the MCMC options for each evaluation in the trial. By default, the standard options are used.

`DA` (`flag`)
use dose-adaptation rules? (default: TRUE)

`parallel` (`flag`)
should the simulation runs be parallelized across the clusters of the computer? (not default)

`nCores` (`count`)
how many cores should be used for parallel computing? Defaults to the number of cores on the machine, maximum 5.

`derive` (`list`)
a named list of functions which derives statistics, based on the vector of posterior MTD samples. Each list element must therefore accept one and only one argument, which is a numeric vector, and return a number.

`...` not used

Value

an object of class `Simulations`

Note

Backfill cohorts are not yet implemented and therefore will lead to an error if used in the `DADesign` object.

Examples

```
# nolint start

# Define the dose-grid and PEM parameters
emptydata <- DataDA(
  doseGrid = c(0.1, 0.5, 1, 1.5, 3, 6, seq(from = 10, to = 80, by = 2)),
  Tmax = 60
)

# Initialize the mDA-CRM model
npiece_ <- 10
```

```
Tmax_ <- 60

lambda_prior <- function(k) {
  npiece_ / (Tmax_ * (npiece_ - k + 0.5))
}

model <- DALogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56,
  npiece = npiece_,
  l = as.numeric(t(apply(as.matrix(c(1:npiece_), 1, npiece_), 2, lambda_prior))),
  c_par = 2
)

# Choose the rule for dose increments
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size
mySize1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
mySize2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
mySize <- maxSize(mySize1, mySize2)

# Choose the rule for stopping
myStopping1 <- StoppingTargetProb(
  target = c(0.2, 0.35),
  prob = 0.5
)
myStopping2 <- StoppingMinPatients(nPatients = 50)

myStopping <- (myStopping1 | myStopping2) | StoppingMissingDose()

# Choose the safety window
mysafetywindow <- SafetyWindowConst(c(6, 2), 7, 7)

# Initialize the design
design <- DADesign(
  model = model,
```

```
  increments = myIncrements,
  nextBest = myNextBest,
  stopping = myStopping,
  cohort_size = mySize,
  data = emptydata,
  safetyWindow = mysafetywindow,
  startingDose = 3
)

## set up truth curves
myTruth <- probFunction(model, alpha0 = 2, alpha1 = 3)
curve(myTruth(x), from = 0, to = 100, ylim = c(0, 1))

exp_cond.cdf <- function(x, onset = 15) {
  a <- pexp(28, 1 / onset, lower.tail = FALSE)
  1 - (pexp(x, 1 / onset, lower.tail = FALSE) - a) / (1 - a)
}

# set up simulation settings
options <- McmcOptions(
  burnin = 10,
  step = 1,
  samples = 200
)


mySims <- simulate(design,
  args = NULL,
  truthTox = myTruth,
  truthSurv = exp_cond.cdf,
  trueTmax = 80,
  nsim = 2,
  seed = 819,
  mcmcOptions = options,
  firstSeparate = TRUE,
  deescalate = FALSE,
  parallel = FALSE
)


# nolint end
```

`simulate,Design-method`

Simulate outcomes from a CRM design

Description

[Stable]

Usage

```
## S4 method for signature 'Design'
simulate(
  object,
  nsim = 1L,
  seed = NULL,
  truth,
  truthResponse = plogis,
  args = NULL,
  firstSeparate = FALSE,
  mcmcOptions = McmcOptions(),
  parallel = FALSE,
  nCores = min(parallel::detectCores(), 5),
  derive = list(),
  ...
)
```

Arguments

object	the Design object we want to simulate data from
nsim	(count) the number of simulations (default: 1)
seed	see set_seed()
truth	(function) a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity. Additional arguments can be supplied in args.
truthResponse	(function) a function which takes as input a dose (vector) and returns the probability (vector) for a positive efficacy response.
args	(data.frame) data frame with arguments for the truth function. The column names correspond to the argument names, the rows to the values of the arguments. The rows are appropriately recycled in the nsim simulations. In order to produce outcomes from the posterior predictive distribution, e.g, pass an object that contains the data observed so far, truth contains the prob function from the model in object, and args contains posterior samples from the model.
firstSeparate	(flag) enroll the first patient separately from the rest of the cohort? (not default) If yes, the cohort will be closed if a DLT occurs in this patient.
mcmcOptions	(McmcOptions) object of class McmcOptions, giving the MCMC options for each evaluation in the trial. By default, the standard options are used
parallel	(flag) should the simulation runs be parallelized across the clusters of the computer? (not default)

nCores (count)
how many cores should be used for parallel computing? Defaults to the number of cores on the machine, maximum 5.

derive (list)
a named list of functions which derives statistics, based on the vector of posterior MTD samples. Each list element must therefore accept one and only one argument, which is a numeric vector, and return a number.

... not used

Value

an object of class Simulations

Examples

```
# nolint start

# Define the dose-grid
emptydata <- Data(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))

# Initialize the CRM model
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Choose the rule for selecting the next dose
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size
mySize1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
mySize2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
mySize <- maxSize(mySize1, mySize2)

# Choose the rule for stopping
myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(
  target = c(0.2, 0.35),
  prob = 0.5
)
```

```
myStopping3 <- StoppingMinPatients(nPatients = 20)
myStopping <- (myStopping1 & myStopping2) | myStopping3 | StoppingMissingDose()

# Choose the rule for dose increments
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Initialize the design
design <- Design(
  model = model,
  nextBest = myNextBest,
  stopping = myStopping,
  increments = myIncrements,
  cohort_size = mySize,
  data = emptydata,
  startingDose = 3
)

## define the true function
myTruth <- probFunction(model, alpha0 = 7, alpha1 = 8)

# Run the simulation on the desired design
# We only generate 1 trial outcomes here for illustration, for the actual study
# this should be increased of course
options <- McmcOptions(
  burnin = 5,
  step = 1,
  samples = 10
)

time <- system.time(
  mySims <- simulate(
    design,
    args = NULL,
    truth = myTruth,
    nsim = 1,
    seed = 819,
    mcmcOptions = options,
    parallel = FALSE
  )
)[3]

# nolint end
```

---

simulate,DesignCombo-method

Simulate outcomes from a two-drug combination CRM design

Description

[Experimental]

Usage

```
## S4 method for signature 'DesignCombo'
simulate(
  object,
  nsim = 1L,
  seed = NULL,
  truth,
  args = NULL,
  firstSeparate = FALSE,
  mcmcOptions = McmcOptions(),
  parallel = FALSE,
  nCores = min(parallel::detectCores(), 5),
  derive = list(),
  ...
)
```

Arguments

object	the DesignCombo object we want to simulate data from
nsim	(count) the number of simulations (default: 1).
seed	see set_seed()
truth	(function) a function that takes as input a dose combination (named numeric vector of length 2) and returns the true DLT probability. Additional arguments can be supplied in args.
args	(data.frame) data frame with arguments for the truth function. The column names correspond to the argument names and rows are recycled across simulations.
firstSeparate	(flag) enroll the first patient separately from the rest of the cohort? If yes, the cohort is closed when a DLT occurs in this first patient.
mcmcOptions	(McmcOptions) MCMC options used for each trial evaluation.
parallel	(flag) should simulation runs be parallelized?
nCores	(count) number of cores used when parallel = TRUE.
derive	(list) named list of functions deriving extra statistics from posterior toxicity samples at the final recommended combination.
...	not used.

Value

an object of class ComboSimulations

Note

Backfill cohorts are not yet implemented for DesignCombo simulations and therefore lead to an error if used.

Examples

```
# nolint start

design_combo <- .DefaultDesignCombo()

true_tox_combo <- function(dose) {
  plogis(-6 + 0.08 * dose[1] + 0.06 * dose[2] + 0.001 * dose[1] * dose[2])
}

options <- McmcOptions(
  burnin = 50,
  step = 1,
  samples = 50,
  rng_kind = "Mersenne-Twister",
  rng_seed = 1
)

my_sims_combo <- simulate(
  design_combo,
  truth = true_tox_combo,
  nsim = 1,
  seed = 819,
  mcmcOptions = options,
  parallel = FALSE
)

# nolint end
```

---

simulate,DesignGrouped-method

Simulate Method for the DesignGrouped Class

Description

[Experimental]

A simulate method for DesignGrouped designs.

Usage

```
## S4 method for signature 'DesignGrouped'
simulate(
  object,
  nsim = 1L,
```

```
  seed = NULL,
  truth,
  combo_truth,
  args = data.frame(),
  firstSeparate = FALSE,
  mcmcOptions = McmcOptions(),
  parallel = FALSE,
  nCores = min(parallelly::availableCores(), 5),
  ...
)
```

Arguments

object	(DesignGrouped) the design we want to simulate trials from.
nsim	(number) how many trials should be simulated.
seed	(RNGstate) generated with set_seed().
truth	(function) a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity for the mono arm. Additional arguments can be supplied in args.
combo_truth	(function) same as truth but for the combo arm.
args	(data.frame) optional data.frame with arguments that work for both the truth and combo_truth functions. The column names correspond to the argument names, the rows to the values of the arguments. The rows are appropriately recycled in the nsim simulations.
firstSeparate	(flag) whether to enroll the first patient separately from the rest of the cohort and close the cohort in case a DLT occurs in this first patient.
mcmcOptions	(McmcOptions) MCMC options for each evaluation in the trial.
parallel	(flag) whether the simulation runs are parallelized across the cores of the computer.
nCores	(number) how many cores should be used for parallel computing.
...	not used.

Value

A list of mono and combo simulation results as Simulations objects.

Examples

```
# Assemble ingredients for our group design.
my_stopping <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5) |
  StoppingMinPatients(10) |
  StoppingMissingDose()
my_increments <- IncrementsDoseLevels(levels = 3L)
my_next_best <- NextBestNCRM(
  target = c(0.2, 0.3),
  overdose = c(0.3, 1),
  max_overdose_prob = 0.3
)
my_cohort_size <- CohortSizeConst(3)
empty_data <- Data(
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)
my_model <- LogisticLogNormalGrouped(
  mean = c(-4, -4, -4, -4),
  cov = diag(rep(6, 4)),
  ref_dose = 0.1
)

# Put together the design. Note that if we only specify the mono arm,
# then the combo arm is having the same settings.
my_design <- DesignGrouped(
  model = my_model,
  mono = Design(
    model = my_model,
    stopping = my_stopping,
    increments = my_increments,
    nextBest = my_next_best,
    cohort_size = my_cohort_size,
    data = empty_data,
    startingDose = 0.1
  ),
  first_cohort_mono_only = TRUE,
  same_dose_for_all = TRUE
)

# Set up a realistic simulation scenario.
my_truth <- function(x) plogis(-4 + 0.2 * log(x / 0.1))
my_combo_truth <- function(x) plogis(-4 + 0.5 * log(x / 0.1))
matplot(
  x = empty_data@doseGrid,
  y = cbind(
    mono = my_truth(empty_data@doseGrid),
    combo = my_combo_truth(empty_data@doseGrid)
  ),
  type = "l",
  ylab = "true DLT prob",
  xlab = "dose"
)
legend("topright", c("mono", "combo"), lty = c(1, 2), col = c(1, 2))
```

```
# Start the simulations.
set.seed(123)

my_sims <- simulate(
  my_design,
  nsim = 1, # This should be at least 100 in actual applications.
  seed = 123,
  truth = my_truth,
  combo_truth = my_combo_truth
)

# Looking at the summary of the simulations:
mono_sims_sum <- summary(my_sims$mono, truth = my_truth)
combo_sims_sum <- summary(my_sims$combo, truth = my_combo_truth)

mono_sims_sum
combo_sims_sum

plot(mono_sims_sum)
plot(combo_sims_sum)

# Looking at specific simulated trials:
trial_index <- 1
plot(my_sims$mono@data[[trial_index]])
plot(my_sims$combo@data[[trial_index]])
```

`simulate,DualDesign-method` *Simulate outcomes from a dual-endpoint design*

Description

[Stable]

Usage

```
## S4 method for signature 'DualDesign'
simulate(
  object,
  nsim = 1L,
  seed = NULL,
  trueTox,
  trueBiomarker,
  args = NULL,
  sigma2W,
  rho = 0,
  firstSeparate = FALSE,
```

```
  mcmcOptions = McmcOptions(),
  parallel = FALSE,
  nCores = min(parallel::detectCores(), 5),
  derive = list(),
  ...
)
```

Arguments

object	the DualDesign object we want to simulate data from
nsim	(count) the number of simulations (default: 1)
seed	see set_seed()
trueTox	(function) a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity. Additional arguments can be supplied in args.
trueBiomarker	(function) a function which takes as input a dose (vector) and returns the true biomarker level (vector). Additional arguments can be supplied in args.
args	(data.frame) data frame with arguments for the trueTox and trueBiomarker function. The column names correspond to the argument names, the rows to the values of the arguments. The rows are appropriately recycled in the nsim simulations.
sigma2W	(number) variance for the biomarker measurements
rho	(number) correlation between toxicity and biomarker measurements (default: 0)
firstSeparate	(flag) enroll the first patient separately from the rest of the cohort? (not default) If yes, the cohort will be closed if a DLT occurs in this patient.
mcmcOptions	(McmcOptions) object of class McmcOptions, giving the MCMC options for each evaluation in the trial. By default, the standard options are used
parallel	(flag) should the simulation runs be parallelized across the clusters of the computer? (not default)
nCores	(count) how many cores should be used for parallel computing? Defaults to the number of cores on the machine, maximum 5.
derive	(list) a named list of functions which derives statistics, based on the vector of posterior MTD samples. Each list element must therefore accept one and only one argument, which is a numeric vector, and return a number.
...	not used

Value

an object of class DualSimulations

Note

Backfill cohorts are not yet implemented and therefore will lead to an error if used in the DualDesign object.

Examples

```
# nolint start

# Define the dose-grid
emptydata <- DataDual(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))

# Initialize the CRM model
model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2betaW = 0.01,
  sigma2W = c(a = 0.1, b = 0.1),
  use_log_dose = TRUE,
  ref_dose = 2,
  rho = c(a = 1, b = 1),
  rw1 = TRUE
)

# Choose the rule for selecting the next dose
myNextBest <- NextBestDualEndpoint(
  target = c(0.9, 1),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size
mySize1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
mySize2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
mySize <- maxSize(mySize1, mySize2)

# Choose the rule for stopping
myStopping4 <- StoppingTargetBiomarker(
  target = c(0.9, 1),
  prob = 0.5
)
myStopping <- myStopping4 | StoppingMinPatients(10) | StoppingMissingDose()
```

```
# Choose the rule for dose increments
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Initialize the design
design <- DualDesign(
  model = model,
  data = emptydata,
  nextBest = myNextBest,
  stopping = myStopping,
  increments = myIncrements,
  cohort_size = mySize,
  startingDose = 3
)

# define scenarios for the TRUE toxicity and efficacy profiles
betaMod <- function(dose, e0, eMax, delta1, delta2, scal) {
  maxDens <- (delta1^delta1) *
    (delta2^delta2) /
    ((delta1 + delta2)^(delta1 + delta2))
  dose <- dose / scal
  e0 + eMax / maxDens * (dose^delta1) * (1 - dose)^delta2
}

trueBiomarker <- function(dose) {
  betaMod(
    dose,
    e0 = 0.2,
    eMax = 0.6,
    delta1 = 5,
    delta2 = 5 * 0.5 / 0.5,
    scal = 100
  )
}

trueTox <- function(dose) {
  pnorm((dose - 60) / 10)
}

# Draw the TRUE profiles
par(mfrow = c(1, 2))
curve(trueTox(x), from = 0, to = 80)
curve(trueBiomarker(x), from = 0, to = 80)

# Run the simulation on the desired design
# We only generate 1 trial outcome here for illustration, for the actual study
# this should be increased of course, similarly for the McmcOptions -
# they also need to be increased.

mySims <- simulate(
  design,
```

```
  trueTox = trueTox,
  trueBiomarker = trueBiomarker,
  sigma2W = 0.01,
  rho = 0,
  nsim = 1,
  parallel = FALSE,
  seed = 3,
  startingDose = 6,
  mcmcOptions = McmcOptions(
    burnin = 10,
    step = 1,
    samples = 100
  )
)


# nolint end
```

---

simulate,DualResponsesDesign-method *Simulate dose escalation procedure using both DLE and efficacy responses without samples*

Description

[Stable]

This is a method to simulate dose escalation procedure using both DLE and efficacy responses. This is a method based on the DualResponsesDesign where DLE model used are of ModelTox class object and efficacy model used are of ModelEff class object. In addition, no DLE and efficacy samples are involved or generated in the simulation process.

Usage

```
## S4 method for signature 'DualResponsesDesign'
simulate(
  object,
  nsim = 1L,
  seed = NULL,
  trueDLE,
  trueEff,
  trueNu,
  args = NULL,
  firstSeparate = FALSE,
  parallel = FALSE,
  nCores = min(parallel::detectCores(), 5L),
  ...
)
```

Arguments

object	the DualResponsesDesign object we want to simulate the data from
nsim	(count) the number of simulations (default: 1)
seed	see set_seed()
trueDLE	(function) a function which takes as input a dose (vector) and returns the true probability (vector) of the occurrence of a DLE. Additional arguments can be supplied in args.
trueEff	(function) a function which takes as input a dose (vector) and returns the expected efficacy responses (vector). Additional arguments can be supplied in args.
trueNu	(number) the precision, the inverse of the variance of the efficacy responses
args	(data.frame) data frame with arguments for the trueDLE and trueEff function. The column names correspond to the argument names, the rows to the values of the arguments. The rows are appropriately recycled in the nsim simulations.
firstSeparate	(flag) enroll the first patient separately from the rest of the cohort? (not default) If yes, the cohort will be closed if a DLT occurs in this patient.
parallel	(flag) should the simulation runs be parallelized across the clusters of the computer? (not default)
nCores	(count) how many cores should be used for parallel computing? Defaults to the number of cores on the machine, maximum 5.
...	not used

Value

an object of class PseudoDualSimulations

Examples

```
# nolint start

## Simulate dose-escalation procedure based on DLE and efficacy responses where no DLE
## and efficacy samples are used
## we need a data object with doses >= 1:
data <- DataDual(doseGrid = seq(25, 300, 25), placebo = FALSE)
## First for the DLE model
## The DLE model must be of 'ModelTox' (e.g 'LogisticIndepBeta') class
DLEmodel <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
```

```
  DLEdose = c(25, 300),
  data = data
)

## The efficacy model of 'ModelEff' (e.g 'Effloglog') class
Effmodel <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data
)

## The escalation rule using the 'NextBestMaxGain' class
mynextbest <- NextBestMaxGain(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)


## The increments (see Increments class examples)
## 200% allowable increase for dose below 300 and 200% increase for dose above 300
myIncrements <- IncrementsRelative(
  intervals = c(25, 300),
  increments = c(2, 2)
)
## cohort size of 3
mySize <- CohortSizeConst(size = 3)
## Stop only when 36 subjects are treated
myStopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()
## Now specified the design with all the above information and starting with a dose of 25

## Specified the design(for details please refer to the 'DualResponsesDesign' example)
design <- DualResponsesDesign(
  nextBest = mynextbest,
  model = DLEmodel,
  eff_model = Effmodel,
  stopping = myStopping,
  increments = myIncrements,
  cohort_size = mySize,
  data = data,
  startingDose = 25
)
## Specify the true DLE and efficacy curves
myTruthDLE <- probFunction(DLEmodel, phi1 = -53.66584, phi2 = 10.50499)
myTruthEff <- efficacyFunction(Effmodel, theta1 = -4.818429, theta2 = 3.653058)

## The true gain curve can also be seen
myTruthGain <- function(dose) {
  return((myTruthEff(dose)) / (1 + (myTruthDLE(dose) / (1 - myTruthDLE(dose)))))
}


## Then specified the simulations and generate the trial
```

```
## For illustration purpose only 1 simulation is produced (nsim=1).
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
mySim <- simulate(
  object = design,
  args = NULL,
  trueDLE = myTruthDLE,
  trueEff = myTruthEff,
  trueNu = 1 / 0.025,
  nsim = 1,
  seed = 819,
  parallel = FALSE
)

# nolint end
```

`simulate,DualResponsesSamplesDesign-method`

Simulate dose escalation procedure using DLE and efficacy responses with samples

---

Description

[Stable]

This is a method to simulate dose escalation procedure using both DLE and efficacy responses. This is a method based on the `DualResponsesSamplesDesign` where DLE model used are of `ModelTox` class object and efficacy model used are of `ModelEff` class object (special case is `EffFlexi` class model object). In addition, DLE and efficacy samples are involved or generated in the simulation process.

Usage

```
## S4 method for signature 'DualResponsesSamplesDesign'
simulate(
  object,
  nsim = 1L,
  seed = NULL,
  trueDLE,
  trueEff,
  trueNu = NULL,
  trueSigma2 = NULL,
  trueSigma2betaW = NULL,
  args = NULL,
  firstSeparate = FALSE,
  mcmcOptions = McmcOptions(),
  parallel = FALSE,
  nCores = min(parallel::detectCores(), 5L),
  ...
)
```

Arguments

object	the DualResponsesSamplesDesign object we want to simulate the data from
nsim	(count) the number of simulations (default: 1)
seed	see set_seed()
trueDLE	(function) a function which takes as input a dose (vector) and returns the true probability (vector) of the occurrence of a DLE. Additional arguments can be supplied in args.
trueEff	(function) a function which takes as input a dose (vector) and returns the expected efficacy responses (vector). Additional arguments can be supplied in args.
trueNu	(number) (not with EffFlexi) the precision, the inverse of the variance of the efficacy responses
trueSigma2	(number) (only with EffFlexi) the true variance of the efficacy responses which must be a single positive scalar.
trueSigma2betaW	(number) (only with EffFlexi) the true variance for the random walk model used for smoothing. This must be a single positive scalar.
args	(data.frame) data frame with arguments for the trueDLE and trueEff function. The column names correspond to the argument names, the rows to the values of the arguments. The rows are appropriately recycled in the nsim simulations.
firstSeparate	(flag) enroll the first patient separately from the rest of the cohort? (not default) If yes, the cohort will be closed if a DLT occurs in this patient.
mcmcOptions	(McmcOptions) object of class McmcOptions, giving the MCMC options for each evaluation in the trial. By default, the standard options are used
parallel	(flag) should the simulation runs be parallelized across the clusters of the computer? (not default)
nCores	(count) how many cores should be used for parallel computing? Defaults to the number of cores on the machine, maximum 5.
...	not used

Value

an object of class PseudoDualSimulations or PseudoDualFlexiSimulations

Examples

```
# nolint start

## Simulate dose-escalation procedure based on DLE and efficacy responses where DLE
## and efficacy samples are used
data <- DataDual(doseGrid = seq(25, 300, 25), placebo = FALSE)
## First for the DLE model
## The DLE model must be of 'ModelTox' (e.g 'LogisticIndepBeta') class
DLEmodel <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)

## The efficacy model of 'ModelEff' (e.g 'Effloglog') class
Effmodel <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data
)


## The escalation rule using the 'NextBestMaxGainSamples' class
mynextbest <- NextBestMaxGainSamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, prob = 0.3))
  },
  mg_derive = function(mg_samples) {
    as.numeric(quantile(mg_samples, prob = 0.5))
  }
)

## The increments (see Increments class examples)
## 200% allowable increase for dose below 300 and 200% increase for dose above 300
myIncrements <- IncrementsRelative(
  intervals = c(25, 300),
  increments = c(2, 2)
)
## cohort size of 3
mySize <- CohortSizeConst(size = 3)
## Stop only when 10 subjects are treated (only for illustration such a low
## sample size)
myStopping <- StoppingMinPatients(nPatients = 10) | StoppingMissingDose()
## Now specified the design with all the above information and starting with
## a dose of 25

## Specified the design
design <- DualResponsesSamplesDesign(
```

```
  nextBest = mynextbest,
  cohort_size = mySize,
  startingDose = 25,
  model = DLEmodel,
  eff_model = Effmodel,
  data = data,
  stopping = myStopping,
  increments = myIncrements
)
## specified the true DLE and efficacy curve
myTruthDLE <- probFunction(DLEmodel, phi1 = -53.66584, phi2 = 10.50499)
myTruthEff <- efficacyFunction(Effmodel, theta1 = -4.818429, theta2 = 3.653058)

## The true gain curve can also be seen
myTruthGain <- function(dose) {
  return((myTruthEff(dose)) / (1 + (myTruthDLE(dose) / (1 - myTruthDLE(dose)))))
}

## simulate the trial for 10 times involving samples
## for illustration purposes, in reality larger number of burnin and samples shoud be used
options <- McmcOptions(burnin = 10, step = 1, samples = 50)
## For illustration purpose only 1 simulations are produced (nsim=1).
mySim <- simulate(
  design,
  args = NULL,
  trueDLE = myTruthDLE,
  trueEff = myTruthEff,
  trueNu = 1 / 0.025,
  nsim = 1,
  mcmcOptions = options,
  seed = 819,
  parallel = FALSE
)


## Simulate dose-escalation procedure based on DLE and efficacy responses where DLE
## and efficacy samples are used
## when the efficacy model is of 'EffFlexi' class
Effmodel <- EffFlexi(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  sigma2W = c(a = 0.1, b = 0.1),
  sigma2betaW = c(a = 20, b = 50),
  rw1 = FALSE,
  data = data
)


## Specified the design
design <- DualResponsesSamplesDesign(
  nextBest = mynextbest,
  cohort_size = mySize,
  startingDose = 25,
```

```
  model = DLEmodel,
  eff_model = Effmodel,
  data = data,
  stopping = myStopping,
  increments = myIncrements
)
## specified the true DLE curve and the true expected efficacy values at all dose levels
myTruthDLE <- probFunction(DLEmodel, phi1 = -53.66584, phi2 = 10.50499)

myTruthEff <- c(
  -0.5478867,
  0.1645417,
  0.5248031,
  0.7604467,
  0.9333009,
  1.0687031,
  1.1793942,
  1.2726408,
  1.3529598,
  1.4233411,
  1.4858613,
  1.5420182
)
## The true gain curve can also be seen
d1 <- data@doseGrid
myTruthGain <- (myTruthEff) / (1 + (myTruthDLE(d1) / (1 - myTruthDLE(d1))))


mySim <- simulate(
  object = design,
  args = NULL,
  trueDLE = myTruthDLE,
  trueEff = myTruthEff,
  trueSigma2 = 0.025,
  trueSigma2betaW = 1,
  mcmcOptions = options,
  nsim = 1,
  seed = 819,
  parallel = FALSE
)

# nolint end
```

`simulate,HierarchicalDesign-method`

Simulate outcomes from a hierarchical CRM design

Description

[Experimental]

Usage

```
## S4 method for signature 'HierarchicalDesign'
simulate(
  object,
  nsim = 1L,
  seed = NULL,
  truth,
  truthResponse = plogis,
  args = NULL,
  firstSeparate = FALSE,
  mcmcOptions = McmcOptions(),
  parallel = FALSE,
  nCores = min(parallel::detectCores(), 5),
  derive = list(),
  ...
)
```

Arguments

object	the HierarchicalDesign object we want to simulate data from.
nsim	(count) the number of simulations.
seed	see set_seed().
truth	(function or named list of function) true DLT probability function(s). If a list is supplied, names must match the hierarchical arms.
truthResponse	(function or named list of function) true response probability function(s).
args	(data.frame) arguments for the truth functions.
firstSeparate	(flag) enroll the first patient separately from the rest of the cohort? (not default) If yes, the cohort will be closed if a DLT occurs in this patient.
mcmcOptions	(McmcOptions) object of class McmcOptions, giving the MCMC options for each evaluation in the trial. By default, the standard options are used
parallel	(flag) should the simulation runs be parallelized across the clusters of the computer? (not default)
nCores	(count) how many cores should be used for parallel computing? Defaults to the number of cores on the machine, maximum 5.
derive	(list) a named list of functions which derives statistics, based on the vector of posterior MTD samples. Each list element must therefore accept one and only one argument, which is a numeric vector, and return a number.

...	not used

Value

an object of class HierarchicalSimulations.

`simulate,RuleDesign-method`

Simulate outcomes from a rule-based design

Description

[Stable]

Usage

```
## S4 method for signature 'RuleDesign'
simulate(
  object,
  nsim = 1L,
  seed = NULL,
  truth,
  args = NULL,
  parallel = FALSE,
  nCores = min(parallel::detectCores(), 5L),
  ...
)
```

Arguments

object	the RuleDesign object we want to simulate data from
nsim	(count) the number of simulations (default: 1)
seed	see set_seed()
truth	(function) a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity. Additional arguments can be supplied in args.
args	(data.frame) data frame with arguments for the truth function. The column names correspond to the argument names, the rows to the values of the arguments. The rows are appropriately recycled in the nsim simulations.
parallel	(flag) should the simulation runs be parallelized across the clusters of the computer? (not default)
nCores	(count) how many cores should be used for parallel computing? Defaults to the number of cores on the machine, maximum 5.
...	not used

Value

an object of class GeneralSimulations

Examples

```
# nolint start

# Define the dose-grid
emptydata <- Data(doseGrid = c(5, 10, 15, 25, 35, 50, 80))

# inizialing a 3+3 design with constant cohort size of 3 and
# starting dose equal 5
myDesign <- RuleDesign(
  nextBest = NextBestThreePlusThree(),
  cohort_size = CohortSizeConst(size = 3L),
  data = emptydata,
  startingDose = 5
)

model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 50
)

## define the true function
myTruth <- probFunction(model, alpha0 = 7, alpha1 = 8)

# Perform the simulation
## For illustration purpose only 10 simulation is produced (nsim=10).
threeSims <- simulate(
  myDesign,
  nsim = 10,
  seed = 35,
  truth = myTruth,
  parallel = FALSE
)

# nolint end
```

---

simulate,TDDesign-method

Simulate dose escalation procedure using DLE responses only without samples

---

Description

[Stable]

This is a method to simulate dose escalation procedure only using the DLE responses. This is a method based on the TDDesign where model used are of ModelTox class object and no samples are involved.

Usage

```
## S4 method for signature 'TDDesign'
simulate(
  object,
  nsim = 1L,
  seed = NULL,
  truth,
  args = NULL,
  firstSeparate = FALSE,
  parallel = FALSE,
  nCores = min(parallel::detectCores(), 5L),
  ...
)
```

Arguments

object	the TDDesign object we want to simulate the data from
nsim	(count) the number of simulations (default: 1)
seed	see set_seed()
truth	(function) a function which takes as input a dose (vector) and returns the true probability (vector) of the occurrence of a DLE. Additional arguments can be supplied in args.
args	(data.frame) data frame with arguments for the truth function. The column names correspond to the argument names, the rows to the values of the arguments. The rows are appropriately recycled in the nsim simulations. In order to produce outcomes from the posterior predictive distribution, e.g, pass an object that contains the data observed so far, truth contains the prob function from the model in object, and args contains posterior samples from the model.
firstSeparate	(flag) enroll the first patient separately from the rest of the cohort? (not default) If yes, the cohort will be closed if a DLT occurs in this patient.
parallel	(flag) should the simulation runs be parallelized across the clusters of the computer? (not default)
nCores	(count) how many cores should be used for parallel computing? Defaults to the number of cores on the machine, maximum 5.
...	not used

Value

an object of class PseudoSimulations

Examples

```
# nolint start

## Simulate dose-escalation procedure based only on DLE responses and no DLE samples are used

## The design comprises a model, the escalation rule, starting data,
## a cohort size and a starting dose
## Define your data set first using an empty data set
## with dose levels from 25 to 300 with increments 25
data <- Data(doseGrid = seq(25, 300, 25))

## The design only incorporate DLE responses and DLE samples are involved
## Specified the model of 'ModelTox' class eg 'LogisticIndepBeta' class model
model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
## Then the escalation rule
tdNextBest <- NextBestTD(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)
doseRecommendation <- nextBest(
  tdNextBest,
  doselimit = max(data@doseGrid),
  model = model,
  data = data
)
## Then the starting data, an empty data set
emptydata <- Data(doseGrid = seq(25, 300, 25))
## The cohort size, size of 3 subjects
mySize <- CohortSizeConst(size = 3)
## Deifne the increments for the dose-escalation process
## The maximum increase of 200% for doses up to the maximum of the dose specified in the doseGrid
## The maximum increase of 200% for dose above the maximum of the dose specified in the doseGrid
## This is to specified a maximum of 3-fold restriction in dose-esclation
myIncrements <- IncrementsRelative(
  intervals = c(min(data@doseGrid), max(data@doseGrid)),
  increments = c(2, 2)
)
## Specified the stopping rule e.g stop when the maximum sample size of 36 patients has been reached
myStopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()


## Specified the design(for details please refer to the 'TDDesign' example)
design <- TDDesign(
```

```
  model = model,
  nextBest = tdNextBest,
  stopping = myStopping,
  increments = myIncrements,
  cohort_size = mySize,
  data = data,
  startingDose = 25
)

## Specify the truth of the DLE responses
myTruth <- probFunction(model, phi1 = -53.66584, phi2 = 10.50499)

## then plot the truth to see how the truth dose-DLE curve look like
curve(myTruth(x), from = 0, to = 300, ylim = c(0, 1))


## For illustration purpose only 1 simulation is produced (nsim=1).
mySim <- simulate(
  object = design,
  args = NULL,
  truth = myTruth,
  nsim = 1,
  seed = 819,
  parallel = FALSE
)

# nolint end
```

`simulate,TDsamplesDesign-method`

Simulate dose escalation procedure using DLE responses only with DLE samples

---

Description

[Stable]

This is a method to simulate dose escalation procedure only using the DLE responses. This is a method based on the `TDsamplesDesign` where model used are of `ModelTox` class object DLE samples are also used.

Usage

```
## S4 method for signature 'TDsamplesDesign'
simulate(
  object,
  nsim = 1L,
  seed = NULL,
  truth,
  args = NULL,
```

```
  firstSeparate = FALSE,
  mcmcOptions = McmcOptions(),
  parallel = FALSE,
  nCores = min(parallel::detectCores(), 5L),
  ...
)
```

Arguments

object	the TDsamplesDesign object we want to simulate the data from
nsim	(count) the number of simulations (default: 1)
seed	see set_seed()
truth	(function) a function which takes as input a dose (vector) and returns the true probability (vector) of the occurrence of a DLE. Additional arguments can be supplied in args.
args	(data.frame) data frame with arguments for the truth function. The column names correspond to the argument names, the rows to the values of the arguments. The rows are appropriately recycled in the nsim simulations. In order to produce outcomes from the posterior predictive distribution, e.g, pass an object that contains the data observed so far, truth contains the prob function from the model in object, and args contains posterior samples from the model.
firstSeparate	(flag) enroll the first patient separately from the rest of the cohort? (not default) If yes, the cohort will be closed if a DLT occurs in this patient.
mcmcOptions	(McmcOptions) object of class McmcOptions, giving the MCMC options for each evaluation in the trial. By default, the standard options are used
parallel	(flag) should the simulation runs be parallelized across the clusters of the computer? (not default)
nCores	(count) how many cores should be used for parallel computing? Defaults to the number of cores on the machine, maximum 5.
...	not used

Value

an object of class PseudoSimulations

Examples

```
# nolint start

## Simulate dose-escalation procedure based only on DLE responses with DLE samples involved
```

```
## The design comprises a model, the escalation rule, starting data,
## a cohort size and a starting dose
## Define your data set first using an empty data set
## with dose levels from 25 to 300 with increments 25
data <- Data(doseGrid = seq(25, 300, 25))

## The design only incorporate DLE responses and DLE samples are involved
## Specified the model of 'ModelTox' class eg 'LogisticIndepBeta' class model
model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
## Then the escalation rule
tdNextBest <- NextBestTDsamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, probs = 0.3))
  }
)

## The cohort size, size of 3 subjects
mySize <- CohortSizeConst(size = 3)
## Deifne the increments for the dose-escalation process
## The maximum increase of 200% for doses up to the maximum of the dose specified in the doseGrid
## The maximum increase of 200% for dose above the maximum of the dose specified in the doseGrid
## This is to specified a maximum of 3-fold restriction in dose-esclation
myIncrements <- IncrementsRelative(
  intervals = c(min(data@doseGrid), max(data@doseGrid)),
  increments = c(2, 2)
)
## Specified the stopping rule e.g stop when the maximum sample size of 36 patients has been reached
myStopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()

## Specified the design(for details please refer to the 'TDsamplesDesign' example)
design <- TDsamplesDesign(
  model = model,
  nextBest = tdNextBest,
  stopping = myStopping,
  increments = myIncrements,
  cohort_size = mySize,
  data = data,
  startingDose = 25
)

## Specify the truth of the DLE responses
myTruth <- probFunction(model, phi1 = -53.66584, phi2 = 10.50499)

## then plot the truth to see how the truth dose-DLE curve look like
curve(myTruth(x), from = 0, to = 300, ylim = c(0, 1))
```

```
## Then specified the simulations and generate the trial
## options for MCMC
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
## The simulations
## For illustration purpose only 1 simulation is produced (nsim=1).
mySim <- simulate(
  object = design,
  args = NULL,
  truth = myTruth,
  nsim = 1,
  seed = 819,
  mcmcOptions = options,
  parallel = FALSE
)

# nolint end
```

`Simulations-class` `Simulations`

Description

[Stable]

This class captures the trial simulations from model based designs. Additional slots `fit`, `stop_reasons`, `stop_report`,`additional_stats` compared to the general class `GeneralSimulations`.

Usage

```
Simulations(fit, stop_reasons, stop_report, additional_stats, ...)

.DefaultSimulations()
```

Arguments

`fit`	(`list`) see slot definition.
`stop_reasons`	(`list`) see slot definition.
`stop_report`	see `Simulations`
`additional_stats`	(`list`) see slot definition.
`...`	additional parameters from `GeneralSimulations`

Slots

`fit` (`list`)
: final fits

`stop_reasons` (`list`)
: stopping reasons for each simulation run

`stop_report` matrix of stopping rule outcomes

`additional_stats` list of additional statistical summary

Note

Typically, end users will not use the `.DefaultSimulations()` function.

Examples

```
data <- list(
  Data(
    x = 1:2,
    y = 0:1,
    doseGrid = 1:2,
    ID = 1L:2L,
    cohort = 1L:2L
  ),
  Data(
    x = 3:4,
    y = 0:1,
    doseGrid = 3:4,
    ID = 1L:2L,
    cohort = 1L:2L
  )
)

doses <- c(1, 2)

seed <- as.integer(123)

fit <- list(
  c(0.1, 0.2),
  c(0.3, 0.4)
)

stop_report <- matrix(c(TRUE, FALSE), nrow = 2)

stop_reasons <- list("A", "B")

additional_stats <- list(a = 1, b = 1)

simulations <- Simulations(
  fit = fit,
  stop_report = stop_report,
  stop_reasons = stop_reasons,
  additional_stats = additional_stats,
```

```
  data,
  doses,
  seed
)
```

`SimulationsSummary-class` `SimulationsSummary`

Description

[Stable]

In addition to the slots in the parent class `GeneralSimulationsSummary`, it contains two slots with model fit information.

Usage

```
.DefaultSimulationsSummary()
```

Slots

`stop_report` (`matrix`)
: matrix of stopping rule outcomes

`fit_at_dose_most_selected` (`numeric`)
: fitted toxicity rate at dose most often selected

`additional_stats` (`list`)
: list of additional statistical summary

`mean_fit` (`list`)
: list with the average, lower (2.5%) and upper (97.5%) quantiles of the mean fitted toxicity at each dose level

Note

Typically, end users will not use the `.DefaultSimulationsSummary()` function.

singleDrugData *Extracting Single-Drug Data from Combination Data*

Description

[Experimental]

A method that extracts one drug-specific Data object from a two-drug DataCombo object.

Usage

```
singleDrugData(object, drug, ...)

## S4 method for signature 'DataCombo'
singleDrugData(object, drug)
```

Arguments

object	(DataCombo) object from which single-drug data are extracted.
drug	(string) name of the drug to extract. Must be one of object@drugNames.
...	not used.

Value

A Data object containing dose, dose grid and patient-level outcomes corresponding to the selected drug.

Examples

```
# Example of extracting single-drug data from two-drug combination data.

my_combo_data <- DataCombo(
  x = cbind(
    drug1 = c(10, 10, 20, 20),
    drug2 = c(20, 20, 20, 40)
  ),
  y = c(0L, 1L, 0L, 0L),
  ID = 1L:4L,
  cohort = c(1L, 2L, 3L, 4L),
  doseGrid = list(
    drug1 = c(10, 20, 30),
    drug2 = c(20, 40)
  )
)

# Extract the data for one specific drug.
singleDrugData(my_combo_data, "drug1")
```

size *Size of an Object*

Description

[Stable]

A method that computes the size of a given object. This can be for instance a size of a MCMC sample, or the size of a cohort. See the help of a specific method for more details.

Usage

```
size(object, ...)

## S4 method for signature 'McmcOptions'
size(object, ...)

## S4 method for signature 'CohortSizeRange'
size(object, dose, data)

## S4 method for signature 'CohortSizeDLT'
size(object, dose, data)

## S4 method for signature 'CohortSizeMax'
size(object, dose, data)

## S4 method for signature 'CohortSizeMin'
size(object, dose, data)

## S4 method for signature 'CohortSizeConst'
size(object, dose, ...)

## S4 method for signature 'CohortSizeRandom'
size(object, dose, ...)

## S4 method for signature 'CohortSizeParts'
size(object, dose, data)

## S4 method for signature 'CohortSizeOrdinal'
size(object, dose, data, ...)

## S4 method for signature 'Samples'
size(object, ...)
```

Arguments

object	(McmcOptions or Samples or CohortSize) an object for which the size is computed.

...	not used.
dose	(numeric) the next dose.
data	the data input, an object of class DataOrdinal.

Value

A size of a given object.

Functions

- size(McmcOptions): compute the number of MCMC samples based on McmcOptions object.
- size(CohortSizeRange): Determines the size of the next cohort based on the range into which the next dose falls into.
- size(CohortSizeDLT): Determines the size of the next cohort based on the number of DLTs so far.
- size(CohortSizeMax): Determines the size of the next cohort based on maximum of multiple cohort size rules.
- size(CohortSizeMin): Determines the size of the next cohort based on minimum of multiple cohort size rules.
- size(CohortSizeConst): Constant cohort size.
- size(CohortSizeRandom): Random cohort size drawn uniformly between min and max size.
- size(CohortSizeParts): Determines the size of the next cohort based on the parts.
- size(CohortSizeOrdinal): Determines the size of the next cohort in a ordinal CRM trial.
- size(Samples): get the number of MCMC samples from Samples object.

Examples

```
# Set up the MCMC option in order to have a burn-in of 10000 iterations and
# then take every other iteration up to a collection of 10000 samples.
my_options <- McmcOptions(burnin = 10000, step = 2, samples = 10000)

size(my_options)
# nolint start

# Create the data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
```

```
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 100, step = 2, samples = 2000)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Rule for the cohort size:
#   - having cohort of size 1 for doses <10
#   - and having cohort of size 3 for doses >=10
mySize <- CohortSizeRange(intervals = c(0, 10), cohort_size = c(1, 3))

# Determine the cohort size for the next cohort
size(mySize, dose = doseRecommendation$value, data = data)

# nolint end
# nolint start

# Create the data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(
    0.1,
    0.5,
    1.5,
    3,
    6,
```

```
    seq(from = 10, to = 80, by = 2)
  )
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(
  burnin = 100,
  step = 2,
  samples = 2000
)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Rule for the cohort size:
#   - having cohort of size 1 if no DLTs were yet observed
#   - and having cohort of size 3 if at least 1 DLT was already observed
mySize <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)

# Determine the cohort size for the next cohort
```

```
size(mySize, dose = doseRecommendation$value, data = data)

# nolint end
# nolint start

# Create the data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(
    0.1,
    0.5,
    1.5,
    3,
    6,
    seq(from = 10, to = 80, by = 2)
  )
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(
  burnin = 100,
  step = 2,
  samples = 2000
)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
```

```
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Rule for having cohort of size 1 for doses <30
#      and having cohort of size 3 for doses >=30
mySize1 <- CohortSizeRange(
  intervals = c(0, 10),
  cohort_size = c(1, 3)
)

# Rule for having cohort of size 1 until no DLT were observed
#      and having cohort of size 3 as soon as 1 DLT is observed
mySize2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)

# Combining the two rules for cohort size by taking the maximum of the sample sizes
# of the single rules
mySize <- maxSize(mySize1, mySize2)

# Determine the cohort size for the next cohort
size(mySize, dose = doseRecommendation$value, data = data)

# nolint end
# nolint start

# Create the data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(
    0.1,
    0.5,
    1.5,
    3,
    6,
    seq(from = 10, to = 80, by = 2)
  )
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)
```

```
# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(
  burnin = 100,
  step = 2,
  samples = 2000
)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Rule for having cohort of size 1 for doses <30
#      and having cohort of size 3 for doses >=30
mySize1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)

# Rule for having cohort of size 1 until no DLT were observed
#      and having cohort of size 3 as soon as 1 DLT is observed
mySize2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)

# Combining the two rules for cohort size by taking the minimum of the sample sizes
# of the single rules
mySize <- minSize(mySize1, mySize2)

# Determine the cohort size for the next cohort
size(mySize, dose = doseRecommendation$value, data = data)
```

```
# nolint end
# nolint start

# Create the data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 100, step = 2, samples = 2000)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Rule for having cohorts with constant cohort size of 3
mySize <- CohortSizeConst(size = 3)

# Determine the cohort size for the next cohort
size(mySize, dose = doseRecommendation$value)
```

```
# nolint end
# Rule for having cohorts with random cohort size between 2 and 4
mySize <- CohortSizeRandom(min_size = 2, max_size = 4)

# Determine the cohort size for the next cohort
# This will return a random integer between 2 and 4 (inclusive)
set.seed(123)
size(mySize, dose = 5)
# nolint start

# create an object of class 'DataParts'
data <- DataParts(
  x = c(0.1, 0.5, 1.5),
  y = c(0, 0, 0),
  doseGrid = c(
    0.1,
    0.5,
    1.5,
    3,
    6,
    seq(from = 10, to = 80, by = 2)
  ),
  part = c(1L, 1L, 1L),
  nextPart = 1L,
  part1Ladder = c(0.1, 0.5, 1.5, 3, 6, 10)
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(
  burnin = 100,
  step = 2,
  samples = 2000
)
set.seed(94)
samples <- mcmc(data, model, options)

myIncrements <- IncrementsRelativeParts(
  dlt_start = 0,
  clean_start = 1
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
```

```
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Rule for the cohort size:
mySize <- CohortSizeParts(cohort_sizes = c(1, 3))

# Determine the cohort size for the next cohort
size(mySize, dose = doseRecommendation$value, data = data)

# nolint end
CohortSizeOrdinal(
  grade = 1L,
  rule = CohortSizeRange(intervals = c(0L, 30L), cohort_size = c(1L, 3L))
)
# Set up the MCMC option in order to have a burn-in of 100 iterations and
# then take every other iteration up to a collection of 200 samples.
my_options <- McmcOptions(burnin = 100, step = 2, samples = 200)

my_samples <- Samples(
  data = list(alpha = rnorm(200), beta = rnorm(200)),
  options = my_options
)

size(my_samples)
```

`Stopping-class` `Stopping`

Description

[Stable]

`Stopping` is a class for stopping rules.

Slots

`report_label` (`string`)
: a label for the stopping report. The meaning of this parameter is twofold. If it is equal to `NA_character_` (default), the `report_label` will not be used in the report at all. Otherwise, if it is specified as an empty character (i.e. `character(0)`) in a user constructor, then a default,

class-specific label will be created for this slot. Finally, for the remaining cases, a user can provide a custom label.

See Also

StoppingList, StoppingCohortsNearDose, StoppingPatientsNearDose, StoppingMinCohorts, StoppingMinPatients, StoppingTargetProb, StoppingMTDdistribution, StoppingTargetBiomarker, StoppingHighestDose StoppingMTDCV, StoppingLowestDoseHSRBeta, StoppingSpecificDose.

StoppingAll-class StoppingAll

Description

[Stable]

StoppingAll is the class for testing a stopping rule that consists of many single stopping rules that are in turn the objects of class Stopping. All single stopping rules must be satisfied in order the result of this rule to be TRUE.

Usage

```
StoppingAll(stop_list, report_label = NA_character_)

.DefaultStoppingAll()
```

Arguments

stop_list	(list) see slot definition.
report_label	(string) see slot definition.

Slots

stop_list (list)
: list of stopping rules.

report_label label for reporting

Note

Typically, end users will not use the .DefaultStoppingAll() function.

Examples

```
# Define some stopping rules.
my_stopping1 <- StoppingMinCohorts(nCohorts = 3)
my_stopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)
my_stopping3 <- StoppingMinPatients(nPatients = 20)

# Create a list of stopping rules (of class `StoppingAll`) which would then be
# summarized by the `all` function, meaning that the study would be stopped only
# if all of the single stopping rules are `TRUE`.
my_stopping <- StoppingAll(
  stop_list = c(my_stopping1, my_stopping2, my_stopping3)
)
```

StoppingAny-class StoppingAny

Description

[Stable]

StoppingAny is the class for testing a stopping rule that consists of many single stopping rules that are in turn the objects of class Stopping. At least one single stopping rule must be satisfied in order the result of this rule to be TRUE.

Usage

```
StoppingAny(stop_list, report_label = NA_character_)

.DefaultStoppingAny()
```

Arguments

stop_list	(list) see slot definition.
report_label	(string) see slot definition.

Slots

stop_list (list)
: list of stopping rules.

report_label label for reporting

Note

Typically, end users will not use the .DefaultStoppingAny() function.

Examples

```
# Define some stopping rules.
my_stopping1 <- StoppingMinCohorts(nCohorts = 3)
my_stopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)
my_stopping3 <- StoppingMinPatients(nPatients = 20)

# Create a list of stopping rules (of class `StoppingAny`) which would then be
# summarized by the `any` function, meaning that the study would be stopped if
# any of the single stopping rules is `TRUE`.
my_stopping <- StoppingAny(
  stop_list = c(my_stopping1, my_stopping2, my_stopping3)
)
```

StoppingCohortsNearDose-class
StoppingCohortsNearDose

Description

[Stable]

StoppingCohortsNearDose is the class for stopping based on number of cohorts near to next best dose.

Usage

```
StoppingCohortsNearDose(
  nCohorts = 2L,
  percentage = 50,
  report_label = NA_character_
)

.DefaultStoppingCohortsNearDose()
```

Arguments

nCohorts	(number) see slot definition.
percentage	(number) see slot definition.
report_label	(string or NA) see slot definition.

Slots

nCohorts (number)
: number of required cohorts.

percentage (number)
: percentage (between and including 0 and 100) within the next best dose the cohorts must lie. This is applied for each of the two doses for DataCombo objects.

Note

Typically, end users will not use the .DefaultStoppingCohortsNearDose() function.

Examples

```
# Here, is the rule for stopping the study if at least 3 cohorts were dosed
# at a dose within (1 +/- 0.2) of the next best dose.
my_stopping <- StoppingCohortsNearDose(
  nCohorts = 3,
  percentage = 0.2
)
```

StoppingExternal-class
StoppingExternal

Description

[Experimental]

StoppingExternal is the class for stopping based on an external flag.

Usage

```
StoppingExternal(report_label = NA_character_)

.DefaultStoppingExternal(report_label = NA_character_)
```

Arguments

report_label	(string or NA) see slot definition.

Note

Typically, end users will not use the .DefaultStoppingExternal() function.

Examples

```
my_stopping <- StoppingExternal()
```

StoppingHighestDose-class
StoppingHighestDose

Description

[Experimental]

StoppingHighestDose is the class for stopping based on the highest dose. That is, the stopping occurs when the highest dose is reached.

Usage

```
StoppingHighestDose(report_label = NA_character_)

.DefaultStoppingHighestDose()
```

Arguments

report_label	(string or NA) see slot definition.

Note

Typically, end users will not use the .DefaultStoppingHighestDose() function.

Examples

```
# The following stopping rule is met when:
# - next proposed dose is highest dose, and
# - there are already at least 3 patients on that dose, and
# - we are sure that this dose is safe, e.g. the probability to be in (0%, 20%)
# interval of the DLT rate is above 50%.
my_stopping <- StoppingHighestDose() &
  StoppingPatientsNearDose(nPatients = 3, percentage = 0) &
  StoppingTargetProb(target = c(0, 0.2), prob = 0.5)

# We note that this rule would then need to be combined with the other standard
# stopping rules, when the MTD is found based on being near e.g. a 30% DLT
# probability or having reached maximal sample size, in the manner of:
# stop_rule <- stop_high | stop_low | stop_sample_size # nolintr.
```

StoppingList-class StoppingList

Description

[Stable]

StoppingList is the class for testing a stopping rule that consists of many single stopping rules that are in turn the objects of class Stopping. The summary slot stores a function that takes a logical vector of the size of stop_list and returns a single logical value. For example, if the function all is specified as a summary function, then that all stopping rules defined in stop_list must be satisfied in order the result of this rule to be TRUE.

Usage

```
StoppingList(stop_list, summary)

.DefaultStoppingList()
```

Arguments

stop_list	(list) see slot definition.
summary	(function) see slot definition.

Slots

stop_list (list)
: list of stopping rules.

summary (function)
: a summary function to combine the results of the stopping rules into a single result.

Note

Typically, end users will not use the .DefaultStoppingList() function.

Examples

```
# Define some stopping rules.
my_stopping1 <- StoppingMinCohorts(nCohorts = 3)
my_stopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)
my_stopping3 <- StoppingMinPatients(nPatients = 20)

# Create a list of stopping rules (of class `StoppingList`) which will then be
# summarized (in this specific example) with the `any` function, meaning that
# the study would be stopped if any of the single stopping rules is `TRUE`.
my_stopping <- StoppingList(
```

```
  stop_list = c(my_stopping1, my_stopping2, my_stopping3),
  summary = any
)
```

`StoppingLowestDoseHSRBeta-class` `StoppingLowestDoseHSRBeta`

Description

[Experimental]

`StoppingLowestDoseHSRBeta` is a class for stopping based on a Hard Safety Rule using the Beta posterior distribution with Beta(a,b) prior and a Bin-Beta model based on the observed data at the lowest dose level. The rule is triggered when the first dose is considered to be toxic (i.e. above threshold probability) based on the observed data at the lowest dose level and a Beta(a,b) prior distribution. The default prior is Beta(1,1). In case that placebo is used, the rule is evaluated at the second dose of the dose grid, i.e. at the lowest non-placebo dose.

Usage

```
StoppingLowestDoseHSRBeta(
  target = 0.3,
  prob = 0.95,
  a = 1,
  b = 1,
  report_label = NA_character_
)

.DefaultStoppingLowestDoseHSRBeta()
```

Arguments

`target`	(`proportion`) see slot definition.
`prob`	(`proportion`) see slot definition.
`a`	(`number`) see slot definition.
`b`	(`number`) see slot definition.
`report_label`	(`string` or `NA`) see slot definition.

Slots

`target` (`proportion`)
: the target toxicity.

`prob` (`proportion`)
: the threshold probability for the lowest dose being toxic.

`a` (`number`)
: shape parameter $a > 0$ of probability distribution Beta (a,b).

`b` (`number`)
: shape parameter $b > 0$ of probability distribution Beta (a,b).

Note

This stopping rule is independent from the underlying model.

Typically, end users will not use the `.DefaultStoppingLowestDoseHSRBeta()` function.

Examples

```
# Stopping the study if the first dose is toxic with more than 90%
# probability based on a Beta posterior distribution with Beta(1,1) prior.
my_stopping <- StoppingLowestDoseHSRBeta(
  target = 0.3,
  prob = 0.9
)

# Stopping the study if the first dose is toxic with more than 90%
# probability based on a Beta posterior distribution with Beta(0.5,0.5) prior.
my_stopping <- StoppingLowestDoseHSRBeta(
  target = 0.3,
  prob = 0.9,
  a = 0.5,
  b = 0.5
)
```

StoppingMaxGainCIRatio-class
StoppingMaxGainCIRatio

Description

[Stable]

`StoppingMaxGainCIRatio` is the class for testing a stopping rule that is based on a target ratio of the 95% credibility interval. Specifically, this is the ratio of the upper to the lower bound of the 95% credibility interval's estimate of the: (1) target dose (i.e. a dose that corresponds to a given target probability of the occurrence of a DLT `prob_target`), or (2) max gain dose (i.e. a dose which gives the maximum gain), depending on which one out of these two is smaller.

Usage

```
StoppingMaxGainCIRatio(
  target_ratio = 5,
  prob_target = 0.3,
  report_label = NA_character_
)

.DefaultStoppingMaxGainCIRatio()
```

Arguments

target_ratio	(numeric) see slot definition.
prob_target	(proportion) see slot definition.
report_label	(string or NA) see slot definition.

Slots

`target_ratio` (numeric)
: target for the ratio of the 95% credibility interval's estimate, that is required to stop a trial.

`prob_target` (proportion)
: the target probability of the occurrence of a DLT.

Examples

```
# Define the target stopping ratio (5) and the target probability of a DLT to
# be used (0.3).
my_stopping <- StoppingMaxGainCIRatio(target_ratio = 5, prob_target = 0.3)
.DefaultStoppingMaxGainCIRatio()
```

StoppingMinCohorts-class

StoppingMinCohorts

Description

[Stable]

StoppingMinCohorts is the class for stopping based on minimum number of cohorts.

Usage

```
StoppingMinCohorts(nCohorts = 2L, report_label = NA_character_)

.DefaultStoppingMinCohorts()
```

Arguments

nCohorts	(number) see slot definition.
report_label	(string or NA) see slot definition.

Slots

nCohorts (number)
: minimum required number of cohorts.

Note

Typically, end users will not use the .DefaultStoppingMinCohorts() function.

Examples

```
# As example, here is the rule for stopping the study if at least 6 cohorts
# were already dosed.
my_stopping <- StoppingMinCohorts(nCohorts = 6)
```

StoppingMinPatients-class
StoppingMinPatients

Description

[Stable]

StoppingMinPatients is the class for stopping based on minimum number of patients

Usage

```
StoppingMinPatients(nPatients = 20L, report_label = NA_character_)

.DefaultStoppingMinPatients()
```

Arguments

nPatients	(number) see slot definition.
report_label	(string or NA) see slot definition.

Slots

nPatients (number)
: minimum allowed number of patients.

Note

Typically, end users will not use the `.DefaultStoppingMinPatients()` function.

Examples

```
# As example, here is the rule for stopping the study if at least 20 patients
# were already dosed
my_stopping <- StoppingMinPatients(nPatients = 20)
```

`StoppingMissingDose-class` `StoppingMissingDose`

Description

[Experimental]

`StoppingMissingDose` is the class for stopping based on NA returned by next best dose.

Usage

```
StoppingMissingDose(report_label = NA_character_)

.DefaultStoppingMissingDose()
```

Arguments

`report_label`	(`string` or `NA`) see slot definition.

Note

Typically, end users will not use the `.DefaultStoppingMissingDose()` function.

Examples

```
# The rule for stopping the study if NA or Placebo is returned as
# next best dose.
my_stopping <- StoppingMissingDose()
```

`StoppingMTDCV-class` `StoppingMTDCV`

Description

[Experimental]

`StoppingMTDCV` is a class for stopping rule based on precision of MTD which is calculated as the coefficient of variation (CV) of the MTD. Here, the MTD is defined as the dose that reaches a specific `target` probability of the occurrence of a DLT.

Usage

```
StoppingMTDCV(target = 0.3, thresh_cv = 40, report_label = NA_character_)

.DefaultStoppingMTDCV()
```

Arguments

`target`	(`proportion`) see slot definition.
`thresh_cv`	(`number`) see slot definition.
`report_label`	(`string` or `NA`) see slot definition.

Slots

`target` (`proportion`)
: toxicity target of MTD (except 0 or 1).

`thresh_cv` (`number`)
: threshold (percentage > 0) for CV to be considered accurate enough to stop the trial. The stopping occurs when the CV is less than or equal to `tresh_cv`.

Note

Typically, end users will not use the `.DefaultStoppingMTDCV()` function.

Examples

```
# Stopping the study if the MTD estimation is precise enough, i.e. if robust
# coefficient of variation of the MTD is below 40%.
my_stopping <- StoppingMTDCV(target = 0.3, thresh_cv = 40)
```

StoppingMTDdistribution-class
StoppingMTDdistribution

Description

[Stable]

StoppingMTDdistribution is the class for stopping based on the posterior distribution of the MTD. It is used for the cases where the stopping occurs when the probability of MTD > thresh * next_dose is greater than or equal to prob, where the next_dose is the recommended next best dose. Here, the MTD is defined as the dose that reaches a specific target probability of the occurrence of a DLT.

Usage

```
StoppingMTDdistribution(
  target = 0.33,
  thresh = 0.5,
  prob = 0.9,
  report_label = NA_character_
)

.DefaultStoppingMTDdistribution()
```

Arguments

target	(proportion) see slot definition.
thresh	(proportion) see slot definition.
prob	(proportion) see slot definition.
report_label	(string or NA) see slot definition.

Slots

target (proportion)
: the target toxicity probability (except 0 or 1) defining the MTD.

thresh (proportion)
: the threshold (except 0 or 1) relative to the recommended next best dose.

prob (proportion)
: required minimum probability, except 0 or 1.

Note

Typically, end users will not use the `.DefaultStoppingMTDDistribution()` function.

Examples

```
# As example, here is the rule for stopping the study if there is at least 0.9
# probability that MTD > 0.5 * next_dose. Here MTD is defined as the dose for
# which prob(DLT) = 0.33
my_stopping <- StoppingMTDdistribution(
  target = 0.33,
  thresh = 0.5,
  prob = 0.9
)
```

`StoppingOrdinal-class  StoppingOrdinal`

Description

[Experimental]

`StoppingOrdinal` is the class for stopping based on a Stopping rule applied to a specific toxicity grade in an ordinal CRM trial

Usage

```
StoppingOrdinal(grade, rule)

.DefaultStoppingOrdinal()
```

Arguments

`grade`	(`integer`) see slot definition.
`rule`	(`Stopping`) see slot definition.

Slots

`grade` (`integer`)
: the grade to which the rule should be applied

`rule` (`Stopping`)
: the rule to apply

Note

Typically, end users will not use the `.DefaultStoppingOrdinal()` function.

Examples

```
StoppingOrdinal(
  1L,
  StoppingTargetProb(target = c(0.2, 0.35), prob = 0.6)
)
```

StoppingPatientsNearDose-class
StoppingPatientsNearDose

Description

[Stable]

StoppingPatientsNearDose is the class for stopping based on number of patients near to next best dose.

Usage

```
StoppingPatientsNearDose(
  nPatients = 10L,
  percentage = 50,
  include_backfill = TRUE,
  report_label = NA_character_
)

.DefaultStoppingPatientsNearDose()
```

Arguments

nPatients	(number) see slot definition.
percentage	(number) see slot definition.
include_backfill	(flag) see slot definition.
report_label	(string or NA) see slot definition.

Slots

`nPatients` (number)
: number of required patients.

`percentage` (number)
: percentage (between and including 0 and 100) within the next best dose the patients must lie.

`include_backfill` (flag)
: whether to include backfill patients.

Note

Typically, end users will not use the `.DefaultStoppingPatientsNearDose()` function.

Examples

```
# As example, here is the rule for stopping the study if at least 9 patients
# were dosed at a dose within (1 +/- 0.2) of the next best dose.

my_stopping <- StoppingPatientsNearDose(
  nPatients = 9,
  percentage = 20
)

# Variant which excludes backfill cohorts.

my_stopping <- StoppingPatientsNearDose(
  nPatients = 9,
  percentage = 20,
  include_backfill = FALSE
)
```

StoppingSpecificDose-class

StoppingSpecificDose

Description

[Experimental]

`StoppingSpecificDose` is the class for testing a stopping rule at specific dose of the dose grid and not at the next best dose.

Usage

```
StoppingSpecificDose(
  rule = StoppingTargetProb(target = c(0, 0.3), prob = 0.8),
  dose = 80,
  report_label = NA_character_
)

.DefaultStoppingSpecificDose()
```

Arguments

`rule`	(`Stopping`) see slot definition.
`dose`	(`numeric`) see slot definition.
`report_label`	(`string` or `NA`) see slot definition.

Slots

`rule` (`Stopping`)
: a stopping rule available in this package.

`dose` (`positive_number`)
: a dose that is defined as part of the dose grid of the data.

Note

Typically, end users will not use the `.DefaultStoppingSpecificDose()` function.

Examples

```
# Stop if highest dose 80 is safe.
highest_dose_safe <- StoppingSpecificDose(
  rule = StoppingTargetProb(target = c(0, 0.3), prob = 0.8),
  dose = 80
)

# Stop if lowest dose 10 is toxic.
lowest_dose_toxic <- StoppingSpecificDose(
  rule = StoppingTargetProb(target = c(0.3, 1), prob = 0.8),
  dose = 10
)
```

StoppingTargetBiomarker-class
StoppingTargetBiomarker

Description

[Stable]

StoppingTargetBiomarker is a class for stopping based on probability of target biomarker.

Usage

```
StoppingTargetBiomarker(
  target = c(0.9, 1),
  prob = 0.3,
  is_relative = TRUE,
  report_label = NA_character_
)

.DefaultStoppingTargetBiomarker()
```

Arguments

target	(numeric) see slot definition.
prob	(proportion) see slot definition.
is_relative	(flag) see slot definition.
report_label	(string or NA) see slot definition.

Slots

target (numeric)
: the biomarker target range that needs to be reached. For example, target = c(0.8, 1.0) with is_relative = TRUE means that we target a dose with at least 80% of maximum biomarker level.

is_relative (flag)
: is target relative? If it so (default), then the target is interpreted relative to the maximum, so it must be a probability range. Otherwise, the target is interpreted as absolute biomarker range.

prob (proportion)
: required target probability (except 0 or 1) for reaching sufficient precision.

Note

Typically, end users will not use the .DefaultStoppingTargetBiomarker() function.

Examples

```
# Stopping the study if there is at least 0.5 probability that the biomarker
# (efficacy) is within the biomarker target range of [0.9, 1.0] (relative to the
# maximum for the biomarker).

my_stopping <- StoppingTargetBiomarker(target = c(0.9, 1), prob = 0.5)
```

StoppingTargetProb-class
StoppingTargetProb

Description

[Stable]

StoppingTargetProb is the class for stopping based on the probability of the DLT rate being in the target toxicity interval.

Usage

```
StoppingTargetProb(
  target = c(0.2, 0.35),
  prob = 0.4,
  report_label = NA_character_
)

.DefaultStoppingTargetProb()
```

Arguments

target	(number) see slot definition.
prob	(proportion) see slot definition.
report_label	(string or NA) see slot definition.

Slots

`target` (number)
: the target toxicity interval, e.g. `c(0.2, 0.35)`.

`prob` (proportion)
: required target toxicity probability (except 0 or 1) for reaching sufficient precision.

Note

Typically, end users will not use the `.DefaultStoppingTargetProb()` function.

Examples

```
# As example, here is the rule for stopping the study if the posterior
# probability that [0.2 =< Prob(DLT | dose) <= 0.35] for the next best dose
# is above 0.5.
my_stopping <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)
```

StoppingTDCIRatio-class

StoppingTDCIRatio

Description

[Stable]

`StoppingTDCIRatio` is the class for testing a stopping rule that is based on a target ratio of the 95% credibility interval. Specifically, this is the ratio of the upper to the lower bound of the 95% credibility interval's estimate of the target dose (i.e. a dose that corresponds to a given target probability of the occurrence of a DLT `prob_target`).

Usage

```
StoppingTDCIRatio(
  target_ratio = 5,
  prob_target = 0.3,
  report_label = NA_character_
)

.DefaultStoppingTDCIRatio()
```

Arguments

target_ratio	(numeric) see slot definition.
prob_target	(proportion) see slot definition.
report_label	(string or NA) see slot definition.

Slots

`target_ratio` (numeric)
: target for the ratio of the 95% credibility interval's estimate, that is required to stop a trial.

`prob_target` (proportion)
: the target probability of the occurrence of a DLT.

Note

Typically, end users will not use the `.DefaultStoppingTDCIRatio()` function.

Examples

```
# Define the target stopping ratio (5) and the target probability of a DLT to
# be used (0.3).
my_stopping <- StoppingTDCIRatio(
  target_ratio = 5,
  prob_target = 0.3
)
```

`stopTrial` *Stop the trial?*

Description

[Stable]

This function returns whether to stop the trial.

[Experimental]

[Stable]

[Stable]

[Stable]

[Stable]

[Stable]

[Stable]

[Stable]

[Stable]

Stopping rule based precision of the MTD estimation. The trial is stopped, when the MTD can be estimated with sufficient precision. The criteria is based on the robust coefficient of variation (CV) calculated from the posterior distribution. The robust CV is defined `mad(MTD) / median(MTD)`, where `mad` is the median absolute deviation.

Stopping based based on the lowest non placebo dose. The trial is stopped when the lowest non placebo dose meets the Hard Safety Rule, i.e. it is deemed to be overly toxic. Stopping is based on the observed data at the lowest dose level using a Bin-Beta model based on DLT probability.

[Stable]

[Experimental]

[Experimental]

[Experimental]

[Stable]

[Stable]

[Stable]

[Stable]

Usage

```
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature 'StoppingMissingDose,numeric,ANY,ANY,GeneralData'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature 'StoppingList,ANY,ANY,ANY,ANY'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature 'StoppingAll,ANY,ANY,ANY,ANY'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature 'StoppingAny,ANY,ANY,ANY,ANY'
```

```
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature
## 'StoppingCohortsNearDose,numeric,ANY,ANY,GeneralData'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature
## 'StoppingPatientsNearDose,numeric,ANY,ANY,GeneralData'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature 'StoppingMinCohorts,ANY,ANY,ANY,GeneralData'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature 'StoppingMinPatients,ANY,ANY,ANY,GeneralData'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature
## 'StoppingTargetProb,numeric,Samples,GeneralModel,ANY'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature
## 'StoppingMTDdistribution,numeric,Samples,GeneralModel,Data'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature 'StoppingMTDCV,numeric,Samples,GeneralModel,ANY'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature
## 'StoppingLowestDoseHSRBeta,numeric,Samples,GeneralModel,GeneralData'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature
## 'StoppingTargetBiomarker,numeric,Samples,DualEndpoint,ANY'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature 'StoppingSpecificDose,numeric,ANY,ANY,GeneralData'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature 'StoppingHighestDose,numeric,ANY,ANY,GeneralData'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature
## 'StoppingOrdinal,numeric,ANY,LogisticLogNormalOrdinal,DataOrdinal'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature 'StoppingOrdinal,numeric,ANY,ANY,ANY'
stopTrial(stopping, dose, samples, model, data, ...)
```

```
## S4 method for signature 'StoppingExternal,numeric,ANY,ANY,ANY'
stopTrial(stopping, dose, samples, model, data, external, ...)

## S4 method for signature 'StoppingTDCIRatio,ANY,Samples,ModelTox,ANY'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature 'StoppingTDCIRatio,ANY,missing,ModelTox,ANY'
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature
## 'StoppingMaxGainCIRatio,ANY,Samples,ModelTox,DataDual'
stopTrial(
  stopping,
  dose,
  samples,
  model,
  data,
  TDderive,
  Effmodel,
  Effsamples,
  Gstarderive,
  ...
)

## S4 method for signature
## 'StoppingMaxGainCIRatio,ANY,missing,ModelTox,DataDual'
stopTrial(stopping, dose, model, data, Effmodel, ...)
```

Arguments

stopping	(Stopping) the rule for stopping the trial.
dose	the recommended next best dose.
samples	(Samples) the mcmc samples.
model	(GeneralModel) the model.
data	(Data) input data.
...	additional arguments without method dispatch.
external	(flag) whether to stop based on the external result or not.
TDderive	(function) the function which derives from the input, a vector of the posterior samples called TDsamples of the dose which has the probability of the occurrence of DLE equals to either the targetDuringTrial or targetEndOfTrial, the final next

best TDtargetDuringTrial (the dose with probability of the occurrence of DLE equals to the targetDuringTrial) and TDtargetEndOfTrial estimate.

`Effmodel` (`ModelEff`)
the efficacy model.

`Effsamples` (`Samples`)
the efficacy samples.

`Gstarderive` (`function`)
the function which derives from the input, a vector of the posterior Gstar (the dose which gives the maximum gain value) samples called `Gstarsamples`, the final next best Gstar estimate.

Value

logical value: `TRUE` if the trial can be stopped, `FALSE` otherwise. It should have an attribute `message` which gives the reason for the decision.

Functions

- `stopTrial( stopping = StoppingMissingDose, dose = numeric, samples = ANY, model = ANY, data = GeneralData )`: Stop based on value returned by next best dose.
- `stopTrial( stopping = StoppingList, dose = ANY, samples = ANY, model = ANY, data = ANY )`: Stop based on multiple stopping rules.
- `stopTrial( stopping = StoppingAll, dose = ANY, samples = ANY, model = ANY, data = ANY )`: Stop based on fulfillment of all multiple stopping rules.
- `stopTrial( stopping = StoppingAny, dose = ANY, samples = ANY, model = ANY, data = ANY )`: Stop based on fulfillment of any stopping rule.
- `stopTrial( stopping = StoppingCohortsNearDose, dose = numeric, samples = ANY, model = ANY, data = GeneralData )`: Stop based on number of cohorts near to next best dose.
- `stopTrial( stopping = StoppingPatientsNearDose, dose = numeric, samples = ANY, model = ANY, data = GeneralData )`: Stop based on number of patients near to next best dose.
- `stopTrial( stopping = StoppingMinCohorts, dose = ANY, samples = ANY, model = ANY, data = GeneralData )`: Stop based on minimum number of cohorts.
- `stopTrial( stopping = StoppingMinPatients, dose = ANY, samples = ANY, model = ANY, data = GeneralData )`: Stop based on minimum number of patients.
- `stopTrial( stopping = StoppingTargetProb, dose = numeric, samples = Samples, model = GeneralModel, data = ANY )`: Stop based on probability of target tox interval
- `stopTrial( stopping = StoppingMTDdistribution, dose = numeric, samples = Samples, model = GeneralModel, data = Data )`: Stop based on MTD distribution.
- `stopTrial( stopping = StoppingTargetBiomarker, dose = numeric, samples = Samples, model = DualEndpoint, data = ANY )`: Stop based on probability of targeting biomarker
- `stopTrial( stopping = StoppingSpecificDose, dose = numeric, samples = ANY, model = ANY, data = GeneralData )`: if Stopping rule is met for specific dose of the planned dose grid and not just for the default next best dose.
- `stopTrial( stopping = StoppingHighestDose, dose = numeric, samples = ANY, model = ANY, data = GeneralData )`: Stop when the highest dose is reached.

- stopTrial(stopping = StoppingOrdinal, dose = numeric, samples = ANY, model = LogisticLogNormalOrdina
data = DataOrdinal): Stop based on value returned by next best dose.
- stopTrial(stopping = StoppingOrdinal, dose = numeric, samples = ANY, model = ANY, data = ANY): Stop based on value returned by next best dose.
- stopTrial(stopping = StoppingExternal, dose = numeric, samples = ANY, model = ANY, data = ANY): Stop based on an external flag.
- stopTrial(stopping = StoppingTDCIRatio, dose = ANY, samples = Samples, model = ModelTox, data = ANY): Stop based on StoppingTDCIRatio class when reaching the target ratio of the upper to the lower 95% credibility interval of the estimate (TDtargetEndOfTrial). This is a stopping rule which incorporates only DLE responses and DLE samples are given.
- stopTrial(stopping = StoppingTDCIRatio, dose = ANY, samples = missing, model = ModelTox, data = ANY): Stop based on StoppingTDCIRatio class when reaching the target ratio of the upper to the lower 95% credibility interval of the estimate (TDtargetEndOfTrial). This is a stopping rule which incorporates only DLE responses and no DLE samples are involved.
- stopTrial(stopping = StoppingMaxGainCIRatio, dose = ANY, samples = Samples, model = ModelTox, data = DataDual): Stop based on reaching the target ratio of the upper to the lower 95% credibility interval of the estimate (the minimum of Gstar and TDtargetEndOf-Trial). This is a stopping rule which incorporates DLE and efficacy responses and DLE and efficacy samples are also used.
- stopTrial(stopping = StoppingMaxGainCIRatio, dose = ANY, samples = missing, model = ModelTox, data = DataDual): Stop based on reaching the target ratio of the upper to the lower 95% credibility interval of the estimate (the minimum of Gstar and TDtargetEndOf-Trial). This is a stopping rule which incorporates DLE and efficacy responses without DLE and efficacy samples involved.

Examples

```
## Example of combining stopping rules with '&' and/or '|' operators

myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)
myStopping3 <- StoppingMinPatients(nPatients = 20)

myStopping <- (myStopping1 & myStopping2) | myStopping3
# Example of usage for `StoppingMissingDose` StopTrial class.

# Create the data.
my_data <- Data(
  x = c(0.01, 0.1, 0.5, 3, 6, 10, 10, 10),
  y = c(0, 1, 1, 0, 0, 0, 0, 1),
  cohort = c(1, 1, 2, 3, 4, 5, 5, 5),
  ID = 1:8,
  doseGrid = c(
    0.01,
    0.1,
    0.5,
    1.5,
    3,
    6,
```

```
    seq(from = 10, to = 80, by = 2)
  ),
  placebo = TRUE
)

# Initialize the CRM model used to model the data.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)
my_samples <- mcmc(my_data, my_model, my_options)

# Define the rule for dose increments and calculate the maximum dose allowed.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

next_max_dose <- maxDose(my_increments, data = my_data)

# Define the rule which will be used to select the next best dose based
# on the class 'NextBestNCRM'.
my_next_best <- NextBestNCRM(
  target = c(0.1, 0.25),
  overdose = c(0.2, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose.
dose_recommendation <- nextBest(
  my_next_best,
  doselimit = next_max_dose,
  samples = my_samples,
  model = my_model,
  data = my_data
)

# Define the stopping rule such that the study would be stopped if there is
# no safe active dose returned from dose_recommendation.
my_stopping <- StoppingMissingDose()
my_stopping <- StoppingAny(
  stop_list = c(
    StoppingMinPatients(nPatients = 16),
    StoppingMissingDose()
  )
)

# Evaluate if to stop the trial.
stopTrial(
```

```
  stopping = my_stopping,
  dose = dose_recommendation$value,
  data = my_data,
  model = my_model
)
# nolint start

# Create some data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the stopping rules
myStopping1 <- StoppingMinCohorts(nCohorts = 3)
```

```
myStopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)
myStopping3 <- StoppingMinPatients(nPatients = 20)

# Create a list of stopping rules (of class 'StoppingList') which will then be
# summarized (in this specific example) with the 'any' function, meaning that the study
# would be stopped if 'any' of the single stopping rules is TRUE.
mystopping <- StoppingList(
  stop_list = c(myStopping1, myStopping2, myStopping3),
  summary = any
)

# Evaluate if to stop the Trial
stopTrial(
  stopping = myStopping,
  dose = doseRecommendation$value,
  samples = samples,
  model = model,
  data = data
)

# nolint end
# nolint start

# Create some data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
```

```
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the stopping rules
myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)
myStopping3 <- StoppingMinPatients(nPatients = 20)

# Combine the stopping rules, obtaining (in this specific example) a list of stopping
# rules of class 'StoppingAll'
myStopping <- (myStopping1 | myStopping2) & myStopping3

# Evaluate if to stop the Trial
stopTrial(
  stopping = myStopping,
  dose = doseRecommendation$value,
  samples = samples,
  model = model,
  data = data
)

# nolint end
# nolint start

# Create some data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
set.seed(94)
```

```
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the stopping rules
myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)
myStopping3 <- StoppingMinPatients(nPatients = 20)

# Combine the stopping rules, obtaining (in this specific example) a list of stopping
# rules of class 'StoppingAny'
myStopping <- (myStopping1 | myStopping2) | myStopping3

# Evaluate if to stop the Trial
stopTrial(
  stopping = myStopping,
  dose = doseRecommendation$value,
  samples = samples,
  model = model,
  data = data
)

# nolint end
# nolint start

# Create the data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
```

```
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the stopping rule such that the study would be stopped if at least 3
# cohorts were already dosed within 1 +/- 0.2 of the next best dose
myStopping <- StoppingCohortsNearDose(nCohorts = 3, percentage = 0.2)

# Evaluate if to stop the trial
stopTrial(stopping = myStopping, dose = doseRecommendation$value, data = data)

# nolint end
# nolint start

# Create the data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
```

```
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the stopping rule such that the study would be stopped if at least 9
# patients were already dosed within 1 +/- 0.2 of the next best dose
myStopping <- StoppingPatientsNearDose(nPatients = 9, percentage = 0.2)

# Evaluate if to stop the trial
stopTrial(stopping = myStopping, dose = doseRecommendation$value, data = data)

# nolint end
# nolint start

# Create the data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
```

```
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the stopping rule such that the study would be stopped if at least 6
# cohorts were already dosed
myStopping <- StoppingMinCohorts(nCohorts = 6)

# Evaluate if to stop the trial
stopTrial(stopping = myStopping, dose = doseRecommendation$value, data = data)

# nolint end
# nolint start

# Create the data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
```

```
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the stopping rule such that the study would be stopped if at least 20
# patients were already dosed
myStopping <- StoppingMinPatients(nPatients = 20)

# Evaluate if to stop the trial
stopTrial(stopping = myStopping, dose = doseRecommendation$value, data = data)

# nolint end
# nolint start

# Create the data
data <- Data(
```

```
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the stopping rule such that the study would be stopped if there is at least
# 0.5 posterior probability that [0.2 =< Prob(DLT | next-best-dose) <= 0.35]
myStopping <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)

# Evaluate if to stop the trial
stopTrial(
  stopping = myStopping,
  dose = doseRecommendation$value,
  samples = samples,
  model = model,
  data = data
```

```
)

# nolint end
# nolint start

# Create the data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the stopping rule such that the study would be stopped if there is at least
# 0.9 probability that MTD > 0.5*next_best_dose. Here MTD is defined as the dose for
# which prob(DLE)=0.33
myStopping <- StoppingMTDdistribution(target = 0.33, thresh = 0.5, prob = 0.9)
```

```
# Evaluate if to stop the trial
stopTrial(
  stopping = myStopping,
  dose = doseRecommendation$value,
  samples = samples,
  model = model,
  data = data
)

# nolint end
# Create the data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)
my_samples <- mcmc(my_data, my_model, my_options)

# Define the rule for dose increments and calculate the maximum dose allowed.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
next_max_dose <- maxDose(my_increments, data = my_data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'.
my_next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose.
dose_recommendation <- nextBest(
  my_next_best,
  doselimit = next_max_dose,
  samples = my_samples,
  model = my_model,
  data = my_data
)
```

```
# Define the stopping rule such that the study would be stopped if the
# the MTD can be estimated with sufficient precision, i.e. if robust coefficient
# of variation is below 40%.
my_stopping <- StoppingMTDCV(target = 0.3, thresh_cv = 40)

# Evaluate if to stop the trial.
stopTrial(
  stopping = my_stopping,
  dose = dose_recommendation$value,
  samples = my_samples,
  model = my_model,
  data = my_data
)
# Create the data.
data <- Data(
  x = c(0.1, 0.1, 0.1),
  y = c(0, 0, 1),
  cohort = c(1, 1, 1),
  doseGrid = c(
    0.1,
    0.5,
    1.5,
    3,
    6,
    seq(from = 10, to = 80, by = 2)
  ),
  ID = 1:3
)

# Initialize the CRM model used to model the data.
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior.
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
set.seed(94)

samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

next_max_dose <- maxDose(my_increments, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'.
```

```
my_next_best <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose.
dose_recommendation <- nextBest(
  my_next_best,
  doselimit = next_max_dose,
  samples = samples,
  model = model,
  data = data
)

# Define the stopping rule such that the study would be stopped if first dose
# is toxic based on a Beta posterior distribution with Beta(1,1) prior.
my_stopping <- StoppingLowestDoseHSRBeta(
  target = 0.3,
  prob = 0.9
)

# Evaluate if the trial will be stopped.
stopTrial(
  stopping = my_stopping,
  dose = dose_recommendation$value,
  samples = samples,
  model = model,
  data = data
)

# nolint start

# Create the data
data <- DataDual(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10, 20, 20, 20, 40, 40, 40, 50, 50, 50),
  y = c(0, 0, 0, 0, 0, 0, 1, 0, 0, 1, 1, 0, 0, 1, 0, 1, 1),
  w = c(
    0.31,
    0.42,
    0.59,
    0.45,
    0.6,
    0.7,
    0.55,
    0.6,
    0.52,
    0.54,
    0.56,
    0.43,
    0.41,
    0.39,
    0.34,
```

```
    0.38,
    0.21
  ),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the Dual-Endpoint model (in this case RW1)
model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2betaW = 0.01,
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  rw1 = TRUE
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
set.seed(94)

samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# In this case target a dose achieving at least 0.9 of maximum biomarker level (efficacy)
# and with a probability below 0.25 that prob(DLT)>0.35 (safety)
myNextBest <- NextBestDualEndpoint(
  target = c(0.9, 1),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the stopping rule such that the study would be stopped if if there is at
# least 0.5 posterior probability that the biomarker (efficacy) is within the
# biomarker target range of [0.9, 1.0] (relative to the maximum for the biomarker).
myStopping <- StoppingTargetBiomarker(target = c(0.9, 1), prob = 0.5)

# Evaluate if to stop the trial
```

```
stopTrial(
  stopping = myStopping,
  dose = doseRecommendation$value,
  samples = samples,
  model = model,
  data = data
)

# nolint end
# Create some data.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  ID = 1:8,
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data.
my_model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 50
)

# Set-up some MCMC parameters and generate samples from the posterior.
my_options <- McmcOptions(burnin = 5, step = 1, samples = 10)
my_samples <- mcmc(my_data, my_model, my_options)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'.
my_nb_ncrm <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose.
my_dose_recommendation <- nextBest(
  nextBest = my_nb_ncrm,
  doselimit = 100,
  samples = my_samples,
  model = my_model,
  data = my_data
)

# Define the stopping rules.
highest_dose_safe <- StoppingSpecificDose(
  rule = StoppingTargetProb(target = c(0, 0.3), prob = 0.8),
  dose = 80
)
max_patients <- StoppingMinPatients(nPatients = 20)
patients_near_dose <- StoppingPatientsNearDose(nPatients = 3, percentage = 0)
```

```
# Create a list of stopping rules (of class 'StoppingList') which will then be
# summarized (in this specific example) with the 'any' function, meaning that
# the study would be stopped if 'any' of the single stopping rules is TRUE.
my_stopping <- highest_dose_safe | max_patients | patients_near_dose

# Evaluate if to stop the Trial
stopTrial(
  stopping = my_stopping,
  dose = my_dose_recommendation$value,
  samples = my_samples,
  model = my_model,
  data = my_data
)
# nolint start

# Create the data
data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10, 20, 20, 20, 40, 40, 40, 80, 80, 80),
  y = c(0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0),
  cohort = c(0, 1, 2, 3, 4, 5, 5, 5, 6, 6, 6, 7, 7, 7, 8, 8, 8),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Initialize the CRM model used to model the data
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
```

```
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the stopping rule such that the study would be stopped if there is at least
# 0.5 posterior probability that [0.2 =< Prob(DLT | next-best-dose) <= 0.35]
stopTarget <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)

## now use the StoppingHighestDose rule:
stopHigh <-
  StoppingHighestDose() &
  StoppingPatientsNearDose(nPatients = 3, percentage = 0) &
  StoppingTargetProb(target = c(0, 0.2), prob = 0.5)

## and combine everything:
myStopping <- stopTarget | stopHigh

# Then evaluate if to stop the trial
stopTrial(
  stopping = myStopping,
  dose = doseRecommendation$value,
  samples = samples,
  model = model,
  data = data
)

# nolint end
data <- .DefaultDataOrdinal()
model <- .DefaultLogisticLogNormalOrdinal()
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
samples <- mcmc(data, model, options)

myIncrements <- .DefaultIncrementsOrdinal()
nextMaxDose <- maxDose(myIncrements, data = data)

myNextBest <- .DefaultNextBestOrdinal()

doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

myStopping <- .DefaultStoppingOrdinal()

stopTrial(
  stopping = myStopping,
  dose = doseRecommendation$value,
```

```
  samples = samples,
  model = model,
  data = data
)
data <- .DefaultDataOrdinal()
model <- .DefaultLogisticLogNormalOrdinal()
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
samples <- mcmc(data, model, options)

myIncrements <- .DefaultIncrementsOrdinal()
nextMaxDose <- maxDose(myIncrements, data = data)

myNextBest <- .DefaultNextBestOrdinal()

doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

myStopping <- .DefaultStoppingOrdinal()

stopTrial(
  stopping = myStopping,
  dose = doseRecommendation$value,
  samples = samples,
  model = model,
  data = data
)
my_rule <- StoppingExternal(report_label = "Based on combo stop")

stopTrial(
  my_rule,
  5,
  .DefaultSamples(),
  .DefaultModelLogNormal(),
  .DefaultData(),
  external = TRUE
)
# nolint start

##define the stopping rules based on the 'StoppingTDCIRatio' class
##Using only DLE responses with samples
## we need a data object with doses >= 1:
data <- Data(
  x = c(25, 50, 50, 75, 150, 200, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  doseGrid = seq(from = 25, to = 300, by = 25)
)

##model can be specified of 'Model' or 'ModelTox' class
```

```
##For example, the 'logisticIndepBeta' class model
model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
##define MCMC options
## for illustration purposes, in reality larger number of burnin and samples shoud be used
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
##samples of 'Samples' class
samples <- mcmc(data, model, options)
##define the 'StoppingTDCIRatio' class
myStopping <- StoppingTDCIRatio(target_ratio = 5, prob_target = 0.3)
##Find the next Recommend dose using the nextBest method (plesae refer to nextbest examples)
tdNextBest <- NextBestTDsamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, probs = 0.3))
  }
)

RecommendDose <- nextBest(
  tdNextBest,
  doselimit = max(data@doseGrid),
  samples = samples,
  model = model,
  data = data
)
##use 'stopTrial' to determine if the rule has been fulfilled
##use 0.3 as the target proability of DLE at the end of the trial

stopTrial(
  stopping = myStopping,
  dose = RecommendDose$next_dose_drt,
  samples = samples,
  model = model,
  data = data
)

# nolint end
# nolint start

##define the stopping rules based on the 'StoppingTDCIRatio' class
##Using only DLE responses
## we need a data object with doses >= 1:
data <- Data(
  x = c(25, 50, 50, 75, 150, 200, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  doseGrid = seq(from = 25, to = 300, by = 25)
)
```

```
##model must be of 'ModelTox' class
##For example, the 'logisticIndepBeta' class model
model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)
##define the 'StoppingTDCIRatio' class
myStopping <- StoppingTDCIRatio(target_ratio = 5, prob_target = 0.3)
##Find the next Recommend dose using the nextBest method (plesae refer to nextbest examples)
tdNextBest <- NextBestTD(prob_target_drt = 0.35, prob_target_eot = 0.3)


RecommendDose <- nextBest(
  tdNextBest,
  doselimit = max(data@doseGrid),
  model = model,
  data = data
)
##use 'stopTrial' to determine if the rule has been fulfilled
##use 0.3 as the target proability of DLE at the end of the trial

stopTrial(
  stopping = myStopping,
  dose = RecommendDose$next_dose_drt,
  model = model,
  data = data
)

# nolint end
# nolint start
##define the stopping rules based on the 'StoppingMaxGainCIRatio' class
##Using both DLE and efficacy responses
## we need a data object with doses >= 1:
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)

##DLEmodel must be of 'ModelTox' class
##For example, the 'logisticIndepBeta' class model
DLEmodel <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)

##Effmodel must be  of 'ModelEff' class
```

```
##For example, the 'Effloglog' class model
Effmodel <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data
)
##for illustration purposes, in reality larger number of burnin and samples shoud be used
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
##DLE and efficacy samples must be of 'Samples' class

DLEsamples <- mcmc(data, DLEmodel, options)
Effsamples <- mcmc(data, Effmodel, options)

##define the 'StoppingMaxGainCIRatio' class
myStopping <- StoppingMaxGainCIRatio(target_ratio = 5, prob_target = 0.3)
##Find the next Recommend dose using the nextBest method (plesae refer to nextbest examples)
mynextbest <- NextBestMaxGainSamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, prob = 0.3))
  },
  mg_derive = function(mg_samples) {
    as.numeric(quantile(mg_samples, prob = 0.5))
  }
)

RecommendDose <- nextBest(
  mynextbest,
  doselimit = max(data@doseGrid),
  samples = DLEsamples,
  model = DLEmodel,
  data = data,
  model_eff = Effmodel,
  samples_eff = Effsamples
)
##use 'stopTrial' to determine if the rule has been fulfilled
##use 0.3 as the target proability of DLE at the end of the trial

stopTrial(
  stopping = myStopping,
  dose = RecommendDose$next_dose,
  samples = DLEsamples,
  model = DLEmodel,
  data = data,
  TDderive = function(TDsamples) {
    quantile(TDsamples, prob = 0.3)
  },
  Effmodel = Effmodel,
  Effsamples = Effsamples,
  Gstarderive = function(Gstarsamples) {
    quantile(Gstarsamples, prob = 0.5)
```

```
  }
)

# nolint end
# nolint start

##define the stopping rules based on the 'StoppingMaxGainCIRatio' class
##Using both DLE and efficacy responses
## we need a data object with doses >= 1:
data <- DataDual(
  x = c(25, 50, 25, 50, 75, 300, 250, 150),
  y = c(0, 0, 0, 0, 0, 1, 1, 0),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  doseGrid = seq(25, 300, 25),
  placebo = FALSE
)

##DLEmodel must be of 'ModelTox' class
##For example, the 'logisticIndepBeta' class model
DLEmodel <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)

##Effmodel must be  of 'ModelEff' class
##For example, the 'Effloglog' class model
Effmodel <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = data
)


##define the 'StoppingMaxGainCIRatio' class
myStopping <- StoppingMaxGainCIRatio(target_ratio = 5, prob_target = 0.3)
##Find the next Recommend dose using the nextBest method (plesae refer to nextbest examples)
mynextbest <- NextBestMaxGain(prob_target_drt = 0.35, prob_target_eot = 0.3)

RecommendDose <- nextBest(
  mynextbest,
  doselimit = max(data@doseGrid),
  model = DLEmodel,
  model_eff = Effmodel,
  data = data
)

##use 'stopTrial' to determine if the rule has been fulfilled
##use 0.3 as the target proability of DLE at the end of the trial

stopTrial(
```

```
  stopping = myStopping,
  dose = RecommendDose$next_dose,
  model = DLEmodel,
  data = data,
  Effmodel = Effmodel
)

# nolint end
```

`subset-Data` *Subsetting Operator for the Data Class*

Description

[Stable]

Subset observations (patients) from a `Data` object using numeric or logical indexing.

Usage

```
## S4 method for signature 'Data,numeric,missing,missing'
x[i]

## S4 method for signature 'Data,logical,missing,missing'
x[i]
```

Arguments

`x`	(`Data`) what to subset.
`i`	(`integer` or `logical`) indices or logical vector for subsetting observations.

Value

A `Data` object with the selected observations.

`summary,ComboSimulations-method`
Summarize `ComboSimulations`

Description

[Experimental]

Summarize two-drug combination simulations.

Usage

```
## S4 method for signature 'ComboSimulations'
summary(object, truth, target = c(0.2, 0.35), ...)
```

Arguments

object	(ComboSimulations) the object we want to summarize.
truth	(function) optional function mapping a dose combination to a toxicity probability. It can accept one argument (length-2 numeric vector or one-row matrix) or two numeric arguments (drug1, drug2).
target	(numeric) optional target toxicity interval used only when truth is supplied.
...	additional arguments can be supplied here for truth.

Value

An object of class ComboSimulationsSummary.

---

summary,DualSimulations-method

Summarize Dual-Endpoint Design Simulations

Description

[Stable]

Summarize the dual-endpoint design simulations, relative to given true dose-toxicity and dose-biomarker curves.

Usage

```
## S4 method for signature 'DualSimulations'
summary(object, trueTox, trueBiomarker, target = c(0.2, 0.35), ...)
```

Arguments

object	(DualSimulations) the object we want to summarize.
trueTox	(function) a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity.
trueBiomarker	(function) a function which takes as input a dose (vector) and returns the true biomarker level (vector).
target	(numeric) the target toxicity interval (default: 20-35%) used for the computations.
...	additional arguments can be supplied here for trueTox and trueBiomarker.

Value

An object of class DualSimulationsSummary.

Examples

```
# Define the dose-grid.
emptydata <- DataDual(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))


# Initialize the CRM model.
my_model <- DualEndpointRW(
  mean = c(0, 1),
  cov = matrix(c(1, 0, 0, 1), nrow = 2),
  sigma2betaW = 0.01,
  sigma2W = c(a = 0.1, b = 0.1),
  rho = c(a = 1, b = 1),
  rw1 = TRUE
)

# Choose the rule for selecting the next dose.
my_next_best <- NextBestDualEndpoint(
  target = c(0.9, 1),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for stopping.
my_stopping1 <- StoppingTargetBiomarker(
  target = c(0.9, 1),
  prob = 0.5
)

# For illustration stop with 6 subjects.
my_stopping <- my_stopping1 | StoppingMinPatients(6) | StoppingMissingDose()

# Choose the rule for dose increments.
my_increments <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Initialize the design.
design <- DualDesign(
  model = my_model,
  data = emptydata,
  nextBest = my_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = CohortSizeConst(3),
  startingDose = 3
)
```

```
# Define scenarios for the TRUE toxicity and efficacy profiles.
beta_mod <- function(dose, e0, eMax, delta1, delta2, scal) {
  maxDens <- (delta1^delta1) *
    (delta2^delta2) /
    ((delta1 + delta2)^(delta1 + delta2))
  dose <- dose / scal
  e0 + eMax / maxDens * (dose^delta1) * (1 - dose)^delta2
}

true_biomarker <- function(dose) {
  beta_mod(
    dose,
    e0 = 0.2,
    eMax = 0.6,
    delta1 = 5,
    delta2 = 5 * 0.5 / 0.5,
    scal = 100
  )
}

true_tox <- function(dose) {
  pnorm((dose - 60) / 10)
}

# Draw the TRUE profiles.
par(mfrow = c(1, 2))
curve(true_tox(x), from = 0, to = 80)
curve(true_biomarker(x), from = 0, to = 80)

# Run the simulation on the desired design.
# For illustration purposes 1 trial is simulated with 5 burn-ins to generate 20 samples.
my_sims <- simulate(
  object = design,
  trueTox = true_tox,
  trueBiomarker = true_biomarker,
  sigma2W = 0.01,
  rho = 0,
  nsim = 1,
  parallel = FALSE,
  seed = 3,
  startingDose = 6,
  mcmcOptions = McmcOptions(
    burnin = 5,
    step = 1,
    samples = 20
  )
)

# Summarize the results of the simulations.
summary(
  my_sims,
  trueTox = true_tox,
  trueBiomarker = true_biomarker
```

```
)
```

`summary,GeneralSimulations-method`

Summarize the `GeneralSimulations`*, Relative to a Given Truth*

Description

[Stable]

Summarize simulations relative to a given true dose-toxicity curve.

Usage

```
## S4 method for signature 'GeneralSimulations'
summary(object, truth, target = c(0.2, 0.35), ...)
```

Arguments

`object`	(`GeneralSimulations`) the object we want to summarize.
`truth`	(`function`) a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity.
`target`	(`numeric`) the target toxicity interval (default: 20-35%) used for the computations.
`...`	additional arguments can be supplied here for `truth`.

Value

An object of class `GeneralSimulationsSummary`.

`summary,HierarchicalSimulations-method`

Summarize Hierarchical Design Simulations

Description

[Experimental]

Summarize hierarchical simulations by delegating to the corresponding arm-level simulation summary methods.

Usage

```
## S4 method for signature 'HierarchicalSimulations'
summary(object, truth, target = c(0.2, 0.35), ...)
```

Arguments

object	(HierarchicalSimulations) the object we want to summarize.
truth	(function or named list of function) true DLT probability function(s). If a list is supplied, names must match the hierarchical arms.
target	(numeric or named list of numeric) target toxicity interval(s). If a list is supplied, names must match the hierarchical arms.
...	additional arguments can be supplied here for truth.

Value

An object of class HierarchicalSimulationsSummary.

---

summary,PseudoDualFlexiSimulations-method

Summarize PseudoDualFlexiSimulations

Description

[Stable]

Summary for PseudoDualFlexiSimulations given a pseudo DLE model and the flexible efficacy model.

Usage

```
## S4 method for signature 'PseudoDualFlexiSimulations'
summary(
  object,
  trueDLE,
  trueEff,
  targetEndOfTrial = 0.3,
  targetDuringTrial = 0.35,
  ...
)
```

Arguments

object	(PseudoDualFlexiSimulations) the object we want to summarize.
trueDLE	(function) a function which takes as input a dose (vector) and returns the true probability of DLE (vector).

`trueEff` (numeric)
a vector which takes as input the true mean efficacy values at all dose levels (in order).

`targetEndOfTrial` (number)
the target probability of DLE that are used at the end of a trial. Default at 0.3.

`targetDuringTrial` (number)
the target probability of DLE that are used during the trial. Default at 0.35.

`...` additional arguments can be supplied here for `trueDLE` and `trueEff`.

Value

An object of class `PseudoDualSimulationsSummary`.

Examples

```
# nolint start

## If DLE and efficacy responses are considered in the simulations and the 'EffFlexi' class is used
## we need a data object with doses >= 1:
data <- DataDual(doseGrid = seq(25, 300, 25))
## First for the DLE model
## The DLE model must be of 'ModelTox' (e.g 'LogisticIndepBeta') class
DLEmodel <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = data
)

## for the efficacy model
Effmodel <- EffFlexi(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  sigma2W = c(a = 0.1, b = 0.1),
  sigma2betaW = c(a = 20, b = 50),
  rw1 = FALSE,
  data = data
)


## specified the next best
mynextbest <- NextBestMaxGainSamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, prob = 0.3))
  },
  mg_derive = function(mg_samples) {
    as.numeric(quantile(mg_samples, prob = 0.5))
```

```
  }
)

## The increments (see Increments class examples)
## 200% allowable increase for dose below 300 and 200% increase for dose above 300
myIncrements <- IncrementsRelative(
  intervals = c(25, 300),
  increments = c(2, 2)
)
## cohort size of 3
mySize <- CohortSizeConst(size = 3)
## Stop only when 10 subjects are treated:
## very low sample size is just for illustration here
myStopping <- StoppingMinPatients(nPatients = 10) | StoppingMissingDose()

## Specified the design
design <- DualResponsesSamplesDesign(
  nextBest = mynextbest,
  cohort_size = mySize,
  startingDose = 25,
  model = DLEmodel,
  eff_model = Effmodel,
  data = data,
  stopping = myStopping,
  increments = myIncrements
)
## specified the true DLE curve and the true expected efficacy values at all dose levels
myTruthDLE <- probFunction(DLEmodel, phi1 = -53.66584, phi2 = 10.50499)

myTruthEff <- c(
  -0.5478867,
  0.1645417,
  0.5248031,
  0.7604467,
  0.9333009,
  1.0687031,
  1.1793942,
  1.2726408,
  1.3529598,
  1.4233411,
  1.4858613,
  1.5420182
)


## specify the options for MCMC
# for illustration purposes, in reality larger number of burnin and samples shoud be used
options <- McmcOptions(burnin = 5, step = 1, samples = 10)
## The simulation
## For illustration purpose only 1 simulation is produced (nsim=1).
mySim <- simulate(
  object = design,
  args = NULL,
```

```
  trueDLE = myTruthDLE,
  trueEff = myTruthEff,
  trueSigma2 = 0.025,
  trueSigma2betaW = 1,
  nsim = 1,
  seed = 819,
  parallel = FALSE,
  mcmcOptions = options
)
## summarize the simulation results
summary(mySim, trueDLE = myTruthDLE, trueEff = myTruthEff)

# nolint end
```

`summary,PseudoDualSimulations-method`
Summarize `PseudoDualSimulations`

Description

[Stable]

Summary for Pseudo Dual responses simulations, relative to a given pseudo DLE and efficacy model (except the EffFlexi class model).

Usage

```
## S4 method for signature 'PseudoDualSimulations'
summary(
  object,
  trueDLE,
  trueEff,
  targetEndOfTrial = 0.3,
  targetDuringTrial = 0.35,
  ...
)
```

Arguments

`object`	(`PseudoDualSimulations`) the object we want to summarize.
`trueDLE`	(`function`) a function which takes as input a dose (vector) and returns the true probability (vector) of DLE.
`trueEff`	(`function`) a function which takes as input a dose (vector) and returns the mean efficacy value(s) (vector).

`targetEndOfTrial`
: (number)
the target probability of DLE that are used at the end of a trial. Default at 0.3.

`targetDuringTrial`
: (number)
the target probability of DLE that are used during the trial. Default at 0.35.

`...`
: additional arguments can be supplied here for `trueDLE` and `trueEff`.

Value

An object of class `PseudoDualSimulationsSummary`.

Examples

```
# Obtain the plot for the simulation results if DLE and efficacy responses
# are considered in the simulations.

# Specified simulations when no samples are used.
emptydata <- DataDual(doseGrid = seq(25, 300, 25))

# The DLE model must be of 'ModelTox' (e.g 'LogisticIndepBeta') class.
dle_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = emptydata
)

# The efficacy model of 'ModelEff' (e.g 'Effloglog') class.
eff_model <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = emptydata
)

# The escalation rule using the 'NextBestMaxGain' class.
my_next_best <- NextBestMaxGain(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)

# Allow increase of 200%.
my_increments <- IncrementsRelative(intervals = 0, increments = 2)

# Cohort size of 3.
my_size <- CohortSizeConst(size = 3)

# Stop when 36 subjects are treated or next dose is NA.
my_stopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()

# Specify the design. (For details please refer to the 'DualResponsesDesign' example.)
```

```
my_design <- DualResponsesDesign(
  nextBest = my_next_best,
  model = dle_model,
  eff_model = eff_model,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  data = emptydata,
  startingDose = 25
)

# Specify the true DLE and efficacy curves.
my_truth_dle <- probFunction(dle_model, phi1 = -53.66584, phi2 = 10.50499)
my_truth_eff <- efficacyFunction(eff_model, theta1 = -4.818429, theta2 = 3.653058)


# Specify the simulations and generate the 2 trials.
my_sim <- simulate(
  object = my_design,
  args = NULL,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff,
  trueNu = 1 / 0.025,
  nsim = 2,
  seed = 819,
  parallel = FALSE
)

# Produce a summary of the simulations.
summary(
  my_sim,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff
)


# Example where DLE and efficacy samples are involved.
# Please refer to design-method 'simulate DualResponsesSamplesDesign' examples for details.

# Specify the next best rule.
my_next_best <- NextBestMaxGainSamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, prob = 0.3))
  },
  mg_derive = function(mg_samples) {
    as.numeric(quantile(mg_samples, prob = 0.5))
  }
)

# Specify the design.
my_design <- DualResponsesSamplesDesign(
```

```
  nextBest = my_next_best,
  cohort_size = my_size,
  startingDose = 25,
  model = dle_model,
  eff_model = eff_model,
  data = emptydata,
  stopping = my_stopping,
  increments = my_increments
)

# For illustration purpose 50 burn-ins to generate 200 samples are used.
my_options <- McmcOptions(burnin = 50, step = 2, samples = 200)

# fmt: skip

# For illustration purpose 2 simulation are created.
my_sim <- simulate(
  object = my_design,
  args = NULL,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff,
  trueNu = 1 / 0.025,
  nsim = 2,
  mcmcOptions = my_options,
  seed = 819,
  parallel = FALSE
)

# Produce a summary of the simulations.
summary(
  my_sim,
  trueDLE = my_truth_dle,
  trueEff = my_truth_eff
)
```

---

summary,PseudoSimulations-method

Summarize PseudoSimulations

Description

[Stable]

Summarize the simulations, relative to a given truth.

Usage

```
## S4 method for signature 'PseudoSimulations'
summary(object, truth, targetEndOfTrial = 0.3, targetDuringTrial = 0.35, ...)
```

Arguments

object	(PseudoSimulations) the object we want to summarize.
truth	(function) a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity.
targetEndOfTrial	(number) the target probability of DLE wanted to achieve at the end of a trial.
targetDuringTrial	(number) the target probability of DLE wanted to achieve during a trial.
...	additional arguments can be supplied here for truth.

Value

An object of class PseudoSimulationsSummary.

Examples

```
emptydata <- Data(doseGrid = seq(25, 300, 25))

# The design incorporate DLE responses and DLE samples.
# Specify the model of 'ModelTox' class eg 'LogisticIndepBeta' class model.
my_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = emptydata
)

# The escalation rule.
td_next_best <- NextBestTD(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)

# Cohort size is 3 subjects.
my_size <- CohortSizeConst(size = 3)

# Allow increase of 200%.
my_increments <- IncrementsRelative(intervals = 0, increments = 2)

# Stopp when the maximum sample size of 36 patients has been reached or the next
# dose is NA.
my_stopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()

# Specify the design. (For details please refer to the 'TDDesign' example.)
my_design <- TDDesign(
  model = my_model,
```

```
  nextBest = td_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  data = emptydata,
  startingDose = 25
)

# Specify the truth of the DLE responses.
my_truth <- probFunction(my_model, phi1 = -53.66584, phi2 = 10.50499)

# For illustration purpose 50 burn-ins to generate 200 samples are used.
my_options <- McmcOptions(burnin = 50, step = 2, samples = 200)

# Refer to design-method 'simulate TDDesign' examples for details.
# For illustration purpose only 1 simulation is produced.
my_sim <- simulate(
  object = my_design,
  args = NULL,
  truth = my_truth,
  nsim = 1,
  seed = 819,
  parallel = FALSE,
  mcmcOptions = my_options
)

# Produce a summary of the simulations.
summary(
  my_sim,
  truth = my_truth
)

# Example where DLE samples are involved.

# Specify the next best rule.
td_next_best <- NextBestTDsamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, probs = 0.3))
  }
)

# The design.
my_design <- TDsamplesDesign(
  model = my_model,
  nextBest = td_next_best,
  stopping = my_stopping,
  increments = my_increments,
  cohort_size = my_size,
  data = emptydata,
  startingDose = 25
)
```

```
# For illustration purpose 50 burn-ins to generate 200 samples are used.
my_options <- McmcOptions(burnin = 50, step = 2, samples = 200)

# For illustration purpose 2 trials are simulated.
my_sim <- simulate(
  object = my_design,
  args = NULL,
  truth = my_truth,
  nsim = 2,
  seed = 819,
  mcmcOptions = my_options,
  parallel = FALSE
)

# Produce a summary of the simulations.
summary(
  my_sim,
  truth = my_truth
)
```

`summary,Simulations-method`

Summarize Model-Based Design Simulations

Description

[Stable]

Summarize the model-based design simulations, relative to a given truth.

Usage

```
## S4 method for signature 'Simulations'
summary(object, truth, target = c(0.2, 0.35), ...)
```

Arguments

`object`	(`Simulations`) the object we want to summarize.
`truth`	(`function`) a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity.
`target`	(`numeric`) the target toxicity interval (default: 20-35%) used for the computations.
`...`	additional arguments can be supplied here for `truth`.

Value

An object of class `SimulationsSummary`.

Examples

```
# nolint start

# Define the dose-grid
emptydata <- Data(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))

# Initialize the CRM model
model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

# Choose the rule for selecting the next dose
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size
mySize1 <- CohortSizeRange(
  intervals = c(0, 30),
  cohort_size = c(1, 3)
)
mySize2 <- CohortSizeDLT(
  intervals = c(0, 1),
  cohort_size = c(1, 3)
)
mySize <- maxSize(mySize1, mySize2)

# Choose the rule for stopping
myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(
  target = c(0.2, 0.35),
  prob = 0.5
)
myStopping3 <- StoppingMinPatients(nPatients = 20)
myStopping <- (myStopping1 & myStopping2) | myStopping3 | StoppingMissingDose()

# Choose the rule for dose increments
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)

# Initialize the design
design <- Design(
  model = model,
  nextBest = myNextBest,
  stopping = myStopping,
  increments = myIncrements,
```

```
  cohort_size = mySize,
  data = emptydata,
  startingDose = 3
)

## define the true function
myTruth <- probFunction(model, alpha0 = 7, alpha1 = 8)

# Run the simulation on the desired design
# We only generate 1 trial outcomes here for illustration, for the actual study
# this should be increased of course
options <- McmcOptions(
  burnin = 100,
  step = 2,
  samples = 1000
)
time <- system.time(
  mySims <- simulate(
    design,
    args = NULL,
    truth = myTruth,
    nsim = 1,
    seed = 819,
    mcmcOptions = options,
    parallel = FALSE,
    derive = list(
      max_mtd = max,
      mean_mtd = mean,
      median_mtd = median
    ),
  )
)[3]

# Summarize the Results of the Simulations
summary(mySims, truth = myTruth)

# nolint end
```

TDDesign-class TDDesign

Description

[Stable]

TDDesign is the class of design based only on DLT responses using ModelTox class model (i.e. LogisticIndepBeta) without MCMC samples.

Usage

```
TDDesign(
```

```
  model,
  stopping,
  increments,
  pl_cohort_size = CohortSizeConst(0L),
  ...
)

.DefaultTDDesign()
```

Arguments

`model`	(`ModelTox`) see slot definition.
`stopping`	(`Stopping`) see slot definition.
`increments`	(`Increments`) see slot definition.
`pl_cohort_size`	(`CohortSize`) see slot definition.
`...`	Arguments passed on to `RuleDesign` `nextBest` (`NextBest`) see slot definition. `cohort_size` (`CohortSize`) see slot definition. `data` (`Data`) see slot definition. `startingDose` (`number`) see slot definition. `doseGrid` (`numeric`) the dose grid to be used (sorted).

Slots

`model` (`ModelTox`)
: the pseudo DLT model to be used.

`stopping` (`Stopping`)
: stopping rule(s) for the trial.

`increments` (`Increments`)
: how to control increments between dose levels.

`pl_cohort_size` (`CohortSize`)
: rules for the cohort sizes for placebo, if any planned (defaults to constant 0 placebo patients).

Note

Typically, end users will not use the `.DefaultTDDesign()` function.

Examples

```
empty_data <- Data(doseGrid = seq(25, 300, 25))

my_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = empty_data
)

# The escalation rule.
my_next_best <- NextBestTD(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3
)

my_size <- CohortSizeConst(size = 3)

# The increments for the dose-escalation process:
#  the maximum increase of 200% for doses up to the maximum dose in grid,
#  the maximum increase of 200% for dose above the maximum dose in grid.
my_increments <- IncrementsRelative(
  intervals = range(empty_data@doseGrid),
  increments = c(2, 2)
)

# Stop when the maximum sample size of 36 patients is reached.
my_stopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()

# The design with all the above information and starting with a dose of 25.
# This design incorporates only DLT responses and no DLT samples are involved
# during the simulation.
design <- TDDesign(
  model = my_model,
  stopping = my_stopping,
  increments = my_increments,
  nextBest = my_next_best,
  cohort_size = my_size,
  data = empty_data,
  startingDose = 25
)
```

TDsamplesDesign-class TDsamplesDesign

Description

[Stable]

TDsamplesDesign is the class of design based only on DLT responses using ModelTox class model (i.e. LogisticIndepBeta) as well as MCMC samples obtained for this model.

Usage

```
TDsamplesDesign(
  model,
  stopping,
  increments,
  pl_cohort_size = CohortSizeConst(0L),
  ...
)

.DefaultTDsamplesDesign()
```

Arguments

`model`	(`ModelTox`) see slot definition.
`stopping`	(`Stopping`) see slot definition.
`increments`	(`Increments`) see slot definition.
`pl_cohort_size`	(`CohortSize`) see slot definition.
`...`	Arguments passed on to `RuleDesign` `nextBest` (`NextBest`) see slot definition. `cohort_size` (`CohortSize`) see slot definition. `data` (`Data`) see slot definition. `startingDose` (`number`) see slot definition. `doseGrid` (`numeric`) the dose grid to be used (sorted).

Slots

`model` (`ModelTox`)
: the pseudo DLT model to be used.

`stopping` (`Stopping`)
: stopping rule(s) for the trial.

`increments` (`Increments`)
: how to control increments between dose levels.

`pl_cohort_size` (`CohortSize`)
: rules for the cohort sizes for placebo, if any planned (defaults to constant 0 placebo patients).

Note

Typically, end users will not use the `.DefaultTDsamplesDesign()` function.

Examples

```
empty_data <- Data(doseGrid = seq(25, 300, 25))

my_model <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = empty_data
)

# The escalation rule.
my_next_best <- NextBestTDsamples(
  prob_target_drt = 0.35,
  prob_target_eot = 0.3,
  derive = function(samples) {
    as.numeric(quantile(samples, probs = 0.3))
  }
)

my_size <- CohortSizeConst(size = 3)

# The increments for the dose-escalation process:
#  the maximum increase of 200% for doses up to the maximum dose in grid,
#  the maximum increase of 200% for dose above the maximum dose in grid.
my_increments <- IncrementsRelative(
  intervals = range(empty_data@doseGrid),
  increments = c(2, 2)
)

# Stop when the maximum sample size of 36 patients is reached.
my_stopping <- StoppingMinPatients(nPatients = 36) | StoppingMissingDose()

# The design with all the above information and starting with a dose of 25.
design <- TDsamplesDesign(
  model = my_model,
  stopping = my_stopping,
  increments = my_increments,
  nextBest = my_next_best,
  cohort_size = my_size,
  data = empty_data,
  startingDose = 25
)
```

---

tidy *Tidying* CrmPackClass *objects*

Description

[Experimental]

In the spirit of the broom package, provide a method to convert a CrmPackClass object to a (list of) tibbles.

Following the principles of the broom package, convert a CrmPackClass object to a (list of) tibbles. This is a basic, default representation.

[Experimental]

A method that tidies a GeneralData object.

[Experimental]

A method that tidies a Data object.

[Experimental]

A method that tidies a DataGrouped object.

[Experimental]

A method that tidies a DataDA object.

[Experimental]

A method that tidies a DataDual object.

[Experimental]

A method that tidies a DataParts object.

[Experimental]

A method that tidies a DataMixture object.

[Experimental]

A method that tidies a DataOrdinal object.

[Experimental]

A method that tidies a DataCombo object.

[Experimental]

A method that tidies a HierarchicalData object.

[Experimental]

A method that tidies a HierarchicalModel object.

[Experimental]

A method that tidies a LogisticIndepBeta object.

[Experimental]

A method that tidies a Effloglog object.

Usage

```
tidy(x, ...)

## S4 method for signature 'CrmPackClass'
tidy(x, ...)

## S4 method for signature 'GeneralData'
tidy(x, ...)
```

```
## S4 method for signature 'Data'
tidy(x, ...)

## S4 method for signature 'DataGrouped'
tidy(x, ...)

## S4 method for signature 'DataDA'
tidy(x, ...)

## S4 method for signature 'DataDual'
tidy(x, ...)

## S4 method for signature 'DataParts'
tidy(x, ...)

## S4 method for signature 'DataMixture'
tidy(x, ...)

## S4 method for signature 'DataOrdinal'
tidy(x, ...)

## S4 method for signature 'DataCombo'
tidy(x, ...)

## S4 method for signature 'HierarchicalData'
tidy(x, ...)

## S4 method for signature 'Simulations'
tidy(x, ...)

## S4 method for signature 'ComboSimulations'
tidy(x, ...)

## S4 method for signature 'HierarchicalSimulations'
tidy(x, ...)

## S4 method for signature 'HierarchicalModel'
tidy(x, ...)

## S4 method for signature 'LogisticIndepBeta'
tidy(x, ...)

## S4 method for signature 'Effloglog'
tidy(x, ...)

## S4 method for signature 'IncrementsMaxToxProb'
tidy(x, ...)
```

```
## S4 method for signature 'IncrementsRelative'
tidy(x, ...)

## S4 method for signature 'CohortSizeDLT'
tidy(x, ...)

## S4 method for signature 'CohortSizeMin'
tidy(x, ...)

## S4 method for signature 'CohortSizeMax'
tidy(x, ...)

## S4 method for signature 'CohortSizeRange'
tidy(x, ...)

## S4 method for signature 'CohortSizeParts'
tidy(x, ...)

## S4 method for signature 'IncrementsMin'
tidy(x, ...)

## S4 method for signature 'IncrementsRelative'
tidy(x, ...)

## S4 method for signature 'IncrementsRelativeDLT'
tidy(x, ...)

## S4 method for signature 'IncrementsRelativeParts'
tidy(x, ...)

## S4 method for signature 'NextBestNCRM'
tidy(x, ...)

## S4 method for signature 'NextBestNCRMLoss'
tidy(x, ...)

## S4 method for signature 'DualDesign'
tidy(x, ...)

## S4 method for signature 'DesignCombo'
tidy(x, ...)

## S4 method for signature 'HierarchicalDesign'
tidy(x, ...)

## S4 method for signature 'ArmConditionList'
tidy(x, ...)
```

```
## S4 method for signature 'DesignArm'
tidy(x, ...)

## S4 method for signature 'Samples'
tidy(x, ...)

## S4 method for signature 'HierarchicalSamples'
tidy(x, ...)
```

Arguments

x	(CrmPackClass) the object to be tidied.
...	potentially used by class-specific methods.

Value

A (list of) tibble(s) representing the object in tidy form.

The tibble object.

The tibble object.

The tibble object.

The tibble object.

The tibble object.

The tibble object.

The tibble object.

The tibble object.

The tibble object.

The tibble object.

The list of tibble objects.

The list of tibble objects.

The list of tibble objects.

Usage Notes

The prior observations are indicated by a Cohort value of 0 in the returned tibble.

Examples

```
CohortSizeConst(3) %>% tidy()
.DefaultData() %>% tidy()
.DefaultDataOrdinal() %>% tidy()
.DefaultDataGrouped() %>% tidy()
.DefaultDataDA() %>% tidy()
# Create a sample Data object
```

```
sample_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  cohort = c(1, 2, 3, 4, 5, 6, 6, 6),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2)),
  response = c(0, 0, 0, 0, 0, 1, NA, NA),
  backfilled = c(FALSE, FALSE, FALSE, FALSE, FALSE, FALSE, TRUE, TRUE)
)

# Tidy the Data object
tidied_data <- tidy(sample_data)

# Print the tidied data
print(tidied_data)
.DefaultData() %>% tidy()
.DefaultDataOrdinal() %>% tidy()
.DefaultDataGrouped() %>% tidy()
.DefaultDataDA() %>% tidy()
.DefaultData() %>% tidy()
.DefaultDataOrdinal() %>% tidy()
.DefaultDataGrouped() %>% tidy()
.DefaultDataDA() %>% tidy()
.DefaultData() %>% tidy()
.DefaultDataOrdinal() %>% tidy()
.DefaultDataGrouped() %>% tidy()
.DefaultDataDA() %>% tidy()
.DefaultData() %>% tidy()
.DefaultDataOrdinal() %>% tidy()
.DefaultDataGrouped() %>% tidy()
.DefaultDataDA() %>% tidy()
.DefaultData() %>% tidy()
.DefaultDataOrdinal() %>% tidy()
.DefaultDataGrouped() %>% tidy()
.DefaultDataDA() %>% tidy()
.DefaultData() %>% tidy()
.DefaultDataOrdinal() %>% tidy()
.DefaultDataGrouped() %>% tidy()
.DefaultDataDA() %>% tidy()
.DefaultSimulations() %>% tidy()
.DefaultLogisticIndepBeta() %>% tidy()
.DefaultEffloglog() %>% tidy()
IncrementsMaxToxProb(prob = c("DLAE" = 0.2, "CRS" = 0.05)) %>% tidy()
CohortSizeRange(intervals = c(0, 20), cohort_size = c(1, 3)) %>% tidy()
.DefaultCohortSizeDLT() %>% tidy()
.DefaultCohortSizeMin() %>% tidy()
.DefaultCohortSizeMax() %>% tidy()
.DefaultCohortSizeRange() %>% tidy()
CohortSizeParts(cohort_sizes = c(1, 3)) %>% tidy()
.DefaultIncrementsMin() %>% tidy()
CohortSizeRange(intervals = c(0, 20), cohort_size = c(1, 3)) %>% tidy()
x <- .DefaultIncrementsRelativeDLT()
x %>% tidy()
.DefaultIncrementsRelativeParts() %>% tidy()
```

```
NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
) %>%
  tidy()
.DefaultNextBestNCRMLoss() %>% tidy()
.DefaultDualDesign() %>% tidy()
options <- McmcOptions(
  burnin = 100,
  step = 1,
  samples = 2000
)

emptydata <- Data(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))

model <- LogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56
)

samples <- mcmc(emptydata, model, options)
samples %>% tidy()
```

`TITELogisticLogNormal-class` `TITELogisticLogNormal`

Description

[Stable]

`TITELogisticLogNormal` is the class for TITE-CRM based on a logistic regression model using a bivariate normal prior on the intercept and log slope parameters.

This class inherits from the `LogisticLogNormal`.

Usage

```
TITELogisticLogNormal(weight_method = "linear", ...)

.DefaultTITELogisticLogNormal()
```

Arguments

`weight_method`	(`string`) see the slot description.
`...`	Arguments passed on to `LogisticLogNormal`

`mean` (`numeric`)
: the prior mean vector.

`cov` (`matrix`)
: the prior covariance matrix. The precision matrix `prec` is internally calculated as an inverse of `cov`.

`ref_dose` (`number`)
: the reference dose $x*$ (strictly positive number).

Details

Basically, the adaptive function allocates more weight to each record than the linear function when DLTs are observed early and less weight when DLTs are observed late. When DLT times are evenly distributed both weights are similar. In addition, with more DLTs, the adaptive weights become more extreme and different from the linear weights.

Slots

`weight_method` (`string`)
: the weight function method: either linear or adaptive; see Liu et al. (2013).

Note

Typically, end users will not use the `.DefaultTITELogisticLogNormal()` function.

References

Liu S, Yin G, Yuan Y (2013). "Bayesian data augmentation dose finding with continual reassessment method and delayed toxicity." *The Annals of Applied Statistics*, **7**(4), 2138–2156. doi:10.1214/13AOAS661.

See Also

DALogisticLogNormal, TITELogisticLogNormalSub.

Examples

```
my_model <- TITELogisticLogNormal(
  mean = c(0, 1),
  cov = diag(2),
  ref_dose = 1,
  weight_method = "linear"
)

my_model1 <- TITELogisticLogNormal(
  mean = c(0, 1),
  cov = diag(2),
  ref_dose = 1,
  weight_method = "adaptive"
)
```

TITELogisticLogNormalSub-class
TITELogisticLogNormalSub

Description

[Stable]

TITELogisticLogNormalSub is the class for TITE-CRM based on a logistic regression model with subtractive dose standardization and a bivariate normal prior on the intercept and log slope parameters.

This class inherits from LogisticLogNormalSub.

Usage

```
TITELogisticLogNormalSub(weight_method = "linear", ...)

.DefaultTITELogisticLogNormalSub()
```

Arguments

weight_method	(string) see the slot description.
...	Arguments passed on to LogisticLogNormalSub
	mean (numeric) the prior mean vector.
	cov (matrix) the prior covariance matrix. The precision matrix prec is internally calculated as an inverse of cov.
	ref_dose (number) the reference dose $x*$.

Details

Basically, the adaptive function allocates more weight to each record than the linear function when DLTs are observed early and less weight when DLTs are observed late. When DLT times are evenly distributed both weights are similar. In addition, with more DLTs, the adaptive weights become more extreme and different from the linear weights.

Slots

weight_method (string)
the weight function method: either linear or adaptive; see Liu et al. (2013).

Note

Typically, end users will not use the .DefaultTITELogisticLogNormalSub() function.

References

Liu S, Yin G, Yuan Y (2013). "Bayesian data augmentation dose finding with continual reassessment method and delayed toxicity." *The Annals of Applied Statistics*, **7**(4), 2138–2156. doi:10.1214/13AOAS661.

See Also

TITELogisticLogNormal, DALogisticLogNormal.

Examples

```
my_model <- TITELogisticLogNormalSub(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 50,
  weight_method = "linear"
)

my_model1 <- TITELogisticLogNormalSub(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 50,
  weight_method = "adaptive"
)
```

TwoDrugsCombo-class TwoDrugsCombo

Description

[Experimental]

TwoDrugsCombo is the class for a two-drug combination regression model with fixed priors for the two single-agent dose-toxicity models and an additional interaction parameter.

Usage

```
TwoDrugsCombo(single_models, gamma = 0, tau = 1, log_normal_eta = FALSE)

.DefaultTwoDrugsCombo()
```

Arguments

single_models	(list) named list of length 2 with compatible single-agent GeneralModel objects, one per drug.
gamma	(number) prior mean parameter for the interaction term.
tau	(number) prior precision parameter for the interaction term.
log_normal_eta	(flag) should the interaction term use a log-normal prior?

Details

Let $p(x_1, x_2)$ be the probability of DLT at the dose combination (x_1, x_2). The model combines two single-agent models with an interaction term:

$$\text{odds}(p(x_1, x_2)) = \text{odds}(p_0(x_1, x_2)) * \exp\left(\eta * I(x_1, x_2)\right),$$

where $p_0(x_1, x_2) = 1-(1-p_1(x_1))(1-p_2(x_2))$ and each single-agent probability follows a model $p_j(x_j)$. The normalized dose $\tilde{x}_j$ is extracted from the single-agent model's dose covariate, e.g. x_j/x_j^*, $x_j - x_j^*$, or x_j. The interaction parameter η has either a normal prior or, if `log_normal_eta = TRUE`, a log-normal prior.

Slots

`single_models` (`list`) named list of length 2 containing single-agent `GeneralModel` objects, one per drug. Each model must use `nObs`, `y`, and `x` as data inputs and contain a Bernoulli likelihood for `y` in its `datamodel`.

`ref_dose` (`numeric`) optional reference doses extracted from `single_models`, if provided.

`drug_names` (`character`) the names of the two drugs.

`gamma` (`numeric`) prior mean parameter for the interaction term.

`tau` (`numeric`) prior precision parameter for the interaction term.

`log_normal_eta` (`flag`) should the interaction term use a log-normal prior?

Note

Typically, end users will not use the `.DefaultTwoDrugsCombo()` function.

See Also

`LogisticLogNormal`, `DataCombo`.

Examples

```
my_model <- TwoDrugsCombo(
  single_models = list(
    drug1 = LogisticLogNormal(
      mean = c(-0.85, 1),
      cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
      ref_dose = 10
    ),
    drug2 = LogisticLogNormal(
      mean = c(-0.7, 0.8),
      cov = matrix(c(1.1, -0.3, -0.3, 0.9), nrow = 2),
      ref_dose = 20
    )
  ),
  gamma = 0,
  tau = 1
)

my_model
```

update,Data-method *Updating* Data *Objects*

Description

[Stable]

A method that updates existing Data object with new data.

Usage

```
## S4 method for signature 'Data'
update(
  object,
  x,
  y,
  response = rep(NA_integer_, length(y)),
  ID = length(object@ID) + seq_along(y),
  new_cohort = TRUE,
  check = TRUE,
  backfill = FALSE,
  cohort = NULL,
  ...
)
```

Arguments

object	(Data) object you want to update.
x	(number) the dose level (one level only!).
y	(integer) the DLT vector (0/1 vector) for all patients in this cohort. You can also supply numeric vectors, but these will then be converted to integer internally.
response	(integer) the efficacy response vector (0/1 vector). May contain NA.
ID	(integer) the patient IDs. You can also supply numeric vectors, but these will then be converted to integer internally.
new_cohort	(flag) if TRUE (default) the new data are assigned to a new cohort.
check	(flag) whether the validation of the updated object should be conducted. See details below.
backfill	(flag) whether the new patients being added are from a backfill cohort.

cohort	(int) if provided, the new patients will be assigned to this cohort index. If NULL (default), the cohort index will be determined based on the new_cohort parameter.
...	not used.

Details

The current implementation of this update method allows for updating the Data class object by adding a single dose level x only. However, there might be some use cases where the new cohort to be added contains a placebo and active dose. Hence, such update would need to be performed iteratively by calling the update method twice. For example, in the first call a user can add a placebo, and then in the second call, an active dose. Since having a cohort with placebo only is not allowed, the update method would normally throw the error when attempting to add a placebo in the first call. To allow for such updates, the check parameter should be then set to FALSE for that first call.

Value

The new, updated Data object.

Examples

```
# Create some data of class 'Data'.
my_data <- Data(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Update the data with a new cohort.
my_data1 <- update(my_data, x = 20, y = c(0L, 1L, 1L))
my_data1
```

---

update,DataCombo-method

Updating DataCombo *Objects*

Description

[Experimental]

A method that updates existing DataCombo object with new data.

Usage

```
## S4 method for signature 'DataCombo'
update(
  object,
  x,
```

```
  y,
  response = rep(NA_integer_, length(y)),
  ID = length(object@ID) + seq_along(y),
  new_cohort = TRUE,
  check = TRUE,
  backfill = FALSE,
  cohort = NULL,
  ...
)
```

Arguments

object	(DataCombo)
x	(numeric) named dose combination with one entry for each drug. Names must match object@drugNames.
y	(integer) the DLT vector (0/1 vector) for all patients in this cohort.
response	(integer) the efficacy response vector (0/1 vector). May contain NA.
ID	(integer) the patient IDs.
new_cohort	(flag) if TRUE (default) the new data are assigned to a new cohort.
check	(flag) whether the validation of the updated object should be conducted.
backfill	(flag) whether the new patients being added are from a backfill cohort.
cohort	(int) if provided, the new patients will be assigned to this cohort index. If NULL (default), the cohort index will be determined based on the new_cohort parameter.
...	not used.

Value

The new, updated DataCombo object.

Examples

```
# Create some data of class 'DataCombo'.
my_data <- DataCombo(
  x = cbind(
    drug1 = c(10, 10, 10, 20, 20, 20),
    drug2 = c(20, 20, 20, 20, 20, 20)
  ),
  y = c(0, 0, 1, 0, 0, 0),
  doseGrid = list(drug1 = c(10, 20, 30), drug2 = c(20, 40))
)

# Update the data with a new cohort.
my_data1 <- update(
  my_data,
  x = c(drug1 = 30, drug2 = 40),
  y = c(0L, 1L, 0L)
)
my_data1
```

update,DataDA-method *Updating* DataDA *Objects*

Description

[Stable]

A method that updates existing DataDA object with new data.

Usage

```
## S4 method for signature 'DataDA'
update(object, u, t0, trialtime, y, ..., check = TRUE)
```

Arguments

object	(DataDA) object you want to update.
u	(numeric) the new DLT free survival times for all patients, i.e. for existing patients in the object as well as for new patients.
t0	(numeric) the time that each patient starts DLT observation window. This parameter covers all patients, i.e. existing patients in the object as well as for new patients.
trialtime	(number) current time in the trial, i.e. a followup time.
y	(numeric) the new DLTs for all patients, i.e. for existing patients in the object as well as for new patients.
...	further arguments passed to Data update method update-Data. These are used when there are new patients to be added to the cohort.
check	(flag) whether the validation of the updated object should be conducted. See help for update-Data for more details on the use case of this parameter.

Value

The new, updated DataDA object.

Note

This function is capable of not only adding new patients but also updates existing ones with respect to y, t0, u slots.

Examples

```
# Create an object of class 'DataDA'.
my_data <- DataDA(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 1, 1, 0, 0, 1, 0),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2)),
  u = c(42, 30, 15, 5, 20, 25, 30, 60),
  t0 = c(0, 15, 30, 40, 55, 70, 75, 85),
  Tmax = 60
)

# Update the data.
my_data1 <- update(
  object = my_data,
  y = c(my_data@y, 0), # The 'y' will be updated according to 'u'.
  u = c(my_data@u, 20),
  t0 = c(my_data@t0, 95),
  x = 20,
  trialtime = 120 # This is the global timeline for a trial.
)
my_data1
```

---

update,DataDual-method

Updating DataDual *Objects*

Description

[Stable]

A method that updates existing DataDual object with new data.

Usage

```
## S4 method for signature 'DataDual'
update(object, w, ..., check = TRUE)
```

Arguments

object	(DataDual) object you want to update.
w	(numeric) the continuous vector of biomarker values for all the patients in this update.
...	further arguments passed to Data update method update-Data.
check	(flag) whether the validation of the updated object should be conducted. See help for update-Data for more details on the use case of this parameter.

Value

The new, updated DataDual object.

Examples

```
# Create some data of class 'DataDual'.
my_data <- DataDual(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 0, 0, 0, 0, 1, 0),
  w = rnorm(8),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2))
)

# Update the data with a new cohort.
my_data1 <- update(my_data, x = 20, y = c(0, 1, 1), w = c(0.4, 1.2, 2.2))
my_data1
```

---

update,DataOrdinal-method

Updating DataOrdinal *Objects*

Description

[Experimental]

A method that updates existing DataOrdinal object with new data.

Usage

```
## S4 method for signature 'DataOrdinal'
update(
  object,
  x,
  y,
  ID = length(object@ID) + seq_along(y),
  new_cohort = TRUE,
  check = TRUE,
  ...
)
```

Arguments

object	(DataOrdinal) object you want to update.
x	(number) the dose level (one level only!).

y (integer)
the vector of toxicity grades (0, 1, 2, ...) for all patients in this cohort. You can also supply numeric vectors, but these will then be converted to integer internally.

ID (integer)
the patient IDs. You can also supply numeric vectors, but these will then be converted to integer internally.

new_cohort (flag)
if TRUE (default) the new data are assigned to a new cohort.

check (flag)
whether the validation of the updated object should be conducted. See Details below.

... not used.

Details

The current implementation of this update method allows for updating the DataOrdinal class object by adding a single dose level x only. However, there might be some use cases where the new cohort to be added contains a placebo and active dose. Hence, such update would need to be performed iteratively by calling the update method twice. For example, in the first call a user can add a placebo, and then in the second call, an active dose. Since having a cohort with placebo only is not allowed, the update method would normally throw the error when attempting to add a placebo in the first call. To allow for such updates, the check parameter should be then set to FALSE for that first call.

Value

The new, updated DataOrdinal object.

Examples

```
data <- DataOrdinal(
  x = c(10, 20, 30, 40, 50, 50, 50, 60, 60, 60),
  y = as.integer(c(0, 0, 0, 0, 0, 1, 0, 0, 1, 2)),
  ID = 1L:10L,
  cohort = as.integer(c(1:4, 5, 5, 5, 6, 6, 6)),
  doseGrid = c(seq(from = 10, to = 100, by = 10)),
  yCategories = c("No tox" = 0L, "Sub-tox AE" = 1L, "DLT" = 2L),
  placebo = FALSE
)

update(data, x = 70, y = c(1L, 2L, 1L))
```

update,DataParts-method

Updating DataParts *Objects*

Description

[Stable]

A method that updates existing DataParts object with new data.

Usage

```
## S4 method for signature 'DataParts'
update(object, x, y, ..., check = TRUE)
```

Arguments

object	(DataParts) object you want to update.
x	(number) the dose level (one level only!).
y	(integer) the DLT vector (0/1 vector) for all patients in this cohort. You can also supply numeric vectors, but these will then be converted to integer internally.
...	further arguments passed to Data update method update-Data.
check	(flag) whether the validation of the updated object should be conducted. See help for update-Data for more details on the use case of this parameter.

Value

The new, updated DataParts object.

Examples

```
# Create an object of class 'DataParts'.
my_data <- DataParts(
  x = c(0.1, 0.5, 1.5),
  y = c(0, 0, 0),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2)),
  part = c(1L, 1L, 1L),
  nextPart = 1L,
  part1Ladder = c(0.1, 0.5, 1.5, 3, 6, 10)
)

# Update the data with a new cohort.
# Note that since we reached the last level from 'part1Ladder'
# then the 'nextPart' is switched from '1' to '2'.
```

```
my_data1 <- update(my_data, x = 10, y = 0L)
my_data1
```

---

update,HierarchicalData-method
Updating HierarchicalData *Objects*

Description

[Experimental]

A method that updates one arm in a HierarchicalData object with new data.

Usage

```
## S4 method for signature 'HierarchicalData'
update(object, arm, ..., check = TRUE)
```

Arguments

object	(HierarchicalData) object you want to update.
arm	(string) name of the arm to update.
...	arguments passed to the selected arm's update method.
check	(flag) whether the validation of the updated object should be conducted.

Value

The new, updated HierarchicalData object.

---

update,ModelPseudo-method
Update method for the ModelPseudo *model class. This is a method to update the model class slots (estimates, parameters, variables and etc.), when the new data (e.g. new observations of responses) are available. This method is mostly used to obtain new modal estimates for pseudo model parameters.*

Description

Update method for the ModelPseudo model class. This is a method to update the model class slots (estimates, parameters, variables and etc.), when the new data (e.g. new observations of responses) are available. This method is mostly used to obtain new modal estimates for pseudo model parameters.

Usage

```
## S4 method for signature 'ModelPseudo'
update(object, data, ...)
```

Arguments

object	(ModelPseudo) the model to update.
data	(Data) all currently available of data.
...	not used.

Value

the new ModelPseudo class object.

Examples

```
# Update the 'LogisticIndepBeta' model with new data.
empty_data <- Data(doseGrid = seq(25, 300, 25))

my_model_lib <- LogisticIndepBeta(
  binDLE = c(1.05, 1.8),
  DLEweights = c(3, 3),
  DLEdose = c(25, 300),
  data = empty_data
)

# Then, we have some new observations data.
data <- Data(
  x = c(25, 50, 50, 75, 100, 100, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  ID = 1:8,
  cohort = c(1L, 2L, 2L, 3L, 4L, 4L, 5L, 6L),
  doseGrid = empty_data@doseGrid
)

# Update the model to get new estimates.
new_model_lib <- update(object = my_model_lib, data = data)

# Update the 'Effloglog' model with new data.
empty_data_dual <- DataDual(doseGrid = seq(25, 300, 25), placebo = FALSE)

my_model_eff <- Effloglog(
  eff = c(1.223, 2.513),
  eff_dose = c(25, 300),
  nu = c(a = 1, b = 0.025),
  data = empty_data_dual,
  const = 0
)
```

```
# Data with new observations data.
my_data_dual <- DataDual(
  x = c(25, 50, 50, 75, 100, 100, 225, 300),
  y = c(0, 0, 0, 0, 1, 1, 1, 1),
  w = c(0.31, 0.42, 0.59, 0.45, 0.6, 0.7, 0.6, 0.52),
  ID = 1:8,
  cohort = c(1L, 2L, 2L, 3L, 4L, 4L, 5L, 6L),
  doseGrid = empty_data_dual@doseGrid
)

# Update the model to get new estimates.
new_model_eff <- update(object = my_model_eff, data = my_data_dual)
```

`Validate` `Validate`

Description

[Stable]

The `Validate` class is a Reference Class to help programming validation for new S4 classes.

Details

Starting from an empty `msg` vector, with each check that is returning `FALSE` the vector gets a new element - the string explaining the failure of the validation.

Fields

`msg` (`character`)
the cumulative messages.

Methods

`check(test, string = "")` Check whether the `test` is `TRUE`; if so, return `NULL`. Otherwise, add the `string` message into the cumulative messages vector `msg`.

`result()` Return either cumulative messages vector `msg` (which contains the error messages from all the checks), or `NULL`, if `msg` is empty (i.e. all the checks were successful).

v_arm_condition *Internal Helper Functions for Validation of* ArmCondition *Objects*

Description

[Experimental]

These functions are only used internally to validate the format of an input ArmCondition or inherited classes and therefore not exported.

Usage

```
v_arm_finished_condition(object)

v_arm_min_dose_condition(object)
```

Arguments

object	(ArmCondition) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_arm_finished_condition(): validates that the ArmFinishedCondition object contains a valid arm_name slot.
- v_arm_min_dose_condition(): validates that the ArmMinDoseCondition object contains valid arm_name and min_dose slots.

v_backfill *Internal Helper Functions for Validation of* Backfill *Objects*

Description

[Experimental]

These functions are only used internally to validate the format of an input Backfill object and therefore not exported.

Usage

```
v_backfill(object)
```

Arguments

object	(Backfill) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_backfill(): validates that the Backfill object contains valid slots.

---

v_cohort_size *Internal Helper Functions for Validation of CohortSize Objects*

Description

[Stable]

These functions are only used internally to validate the format of an input CohortSize or inherited classes and therefore not exported.

Usage

```
v_cohort_size_range(object)

v_cohort_size_dlt(object)

v_cohort_size_const(object)

v_cohort_size_random(object)

v_cohort_size_parts(object)

v_cohort_size_max(object)
```

Arguments

object	(CohortSize) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_cohort_size_range(): validates that the CohortSizeRange object contains valid intervals and cohort_size slots.
- v_cohort_size_dlt(): validates that the CohortSizeDLT object contains valid intervals and cohort_size slots.
- v_cohort_size_const(): validates that the CohortSizeConst object contains valid size slot.
- v_cohort_size_random(): validates that the CohortSizeRandom object contains valid min_size and max_size slots.
- v_cohort_size_parts(): validates that the CohortSizeParts object contains valid sizes slot.
- v_cohort_size_max(): validates that the CohortSizeMax object contains valid cohort_sizes slot.

---

v_data_objects *Internal Helper Functions for Validation of* GeneralData *Objects*

Description

[Stable]

These functions are only used internally to validate the format of an input GeneralData or inherited classes and therefore not exported.

Usage

```
v_general_data(object)

h_doses_unique_per_cohort(dose, cohort)

h_combo_doses_unique_per_cohort(x, cohort)

v_data(object)

v_data_dual(object)

v_data_parts(object)

v_data_mixture(object)

v_data_da(object)

v_data_ordinal(object)

v_data_grouped(object)
```

```
v_data_combo(object)

v_hierarchical_data(object)
```

Arguments

object	(GeneralData) object to validate.
dose	(numeric) dose values.
cohort	(integer)
x	(matrix)

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

TRUE if dose is unique per cohort, otherwise FALSE.

TRUE if x is unique per cohort, otherwise FALSE.

Functions

- v_general_data(): validates that the GeneralData object contains unique ID, non-negative cohort indices and ID and cohort vectors are of the same length nObs.
- h_doses_unique_per_cohort(): helper function which verifies whether the dose values are unique in each and every different cohort.
- h_combo_doses_unique_per_cohort(): helper function which verifies whether the two-drug dose combination is unique in each cohort.
- v_data(): validates that the Data object contains valid elements with respect to their types, dependency and length.
- v_data_dual(): validates that the DataDual object contains valid biomarker vector with respect to its type and the length.
- v_data_parts(): validates that the DataParts object contains valid elements with respect to their types, dependency and length.
- v_data_mixture(): validates that the DataMixture object contains valid elements with respect to their types, dependency and length.
- v_data_da(): validates that the DataDA object contains valid elements with respect to their types, dependency and length.
- v_data_ordinal(): validates that the DataOrdinal object contains valid elements with respect to their types, dependency and length.
- v_data_grouped(): validates that the DataGrouped object contains valid group information.
- v_data_combo(): validates that the DataCombo object contains valid two-drug combination data.
- v_hierarchical_data(): validates that the HierarchicalData object contains valid arms.

v_design *Internal Helper Functions for Validation of* RuleDesign *Objects*

Description

[Stable]

These functions are only used internally to validate the format of an input RuleDesign or inherited classes and therefore not exported.

[Experimental]

These functions are only used internally to validate the format of an input RuleDesignOrdinal or inherited classes and therefore not exported.

Usage

```
v_rule_design(object)

v_rule_design_ordinal(object)

v_design_combo(object)

v_design_grouped(object)
```

Arguments

object	(RuleDesignOrdinal) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_rule_design(): validates that the RuleDesign object contains valid startingDose.
- v_rule_design_ordinal(): validates that the RuleDesignOrdinal object contains valid starting_dose.
- v_design_combo(): validates that the DesignCombo object contains valid startingDose.
- v_design_grouped(): validates that the DesignGrouped object contains valid flags.

v_general_simulations *Internal Helper Functions for Validation of* GeneralSimulations *Objects*

Description

[Stable]

These functions are only used internally to validate the format of an input GeneralSimulations or inherited classes and therefore not exported.

Usage

```
v_general_simulations(object)

v_simulations(object)

v_hierarchical_simulations(object)

v_combo_simulations(object)

v_dual_simulations(object)

v_da_simulations(object)
```

Arguments

object	(GeneralSimulations) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_general_simulations(): validates that the GeneralSimulations object contains valid data object and valid dose simulations.
- v_simulations(): validates that the Simulations object contains valid object fit, stop_reasons, stop_report, and additional_stats compared to the general class GeneralSimulations.
- v_hierarchical_simulations(): validates that the HierarchicalSimulations object contains valid hierarchical data, posterior samples, fits, and stopping outputs.
- v_combo_simulations(): validates that the ComboSimulations object contains valid combo data, recommended dose combinations, model fit, and stopping outputs.
- v_dual_simulations(): validates that the DualSimulations object and capture the dose-biomarker fits, and the sigma2W and rho estimates.
- v_da_simulations(): validates that the DASimulations object contains valid trial_duration the vector of trial duration values for all simulations.

v_hierarchical_design *Internal Helper Functions for Validation of* HierarchicalDesign *Objects*

Description

[Experimental]

These functions are only used internally to validate the format of an input HierarchicalDesign or related classes and therefore not exported.

Usage

```
v_design_arm(object)

v_hierarchical_design(object)
```

Arguments

object	(HierarchicalDesign) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_design_arm(): validates that the DesignArm object contains valid slots.
- v_hierarchical_design(): validates that the HierarchicalDesign object contains valid hierarchical arm metadata.

v_increments *Internal Helper Functions for Validation of* Increments *Objects*

Description

[Stable]

These functions are only used internally to validate the format of an input Increments or inherited classes and therefore not exported.

Usage

```
v_increments_relative(object)

v_increments_relative_parts(object)

v_increments_relative_dlt(object)

v_increments_dose_levels(object)

v_increments_hsr_beta(object)

v_increments_min(object)

v_increments_maxtoxprob(object)

v_increments_ordinal(object)

v_cohort_size_ordinal(object)
```

Arguments

object	(Increments) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_increments_relative(): validates that the IncrementsRelative object contains valid intervals and increments parameters.
- v_increments_relative_parts(): validates that the IncrementsRelativeParts object contains valid dlt_start and clean_start parameters.
- v_increments_relative_dlt(): validates that the IncrementsRelativeDLT object contains valid intervals and increments parameters.
- v_increments_dose_levels(): validates that the IncrementsDoseLevels object contains valid levels and basis_level option.
- v_increments_hsr_beta(): validates that the IncrementsHSRBeta object contains valid probability target, threshold and shape parameters.
- v_increments_min(): validates that the IncrementsMin object contains a list with Increments objects.
- v_increments_maxtoxprob(): validates the IncrementsMaxToxProb
- v_increments_ordinal(): validates that the IncrementsOrdinal object contains valid grade and standard Increments rule.
- v_cohort_size_ordinal(): validates that the CohortSizeOrdinal object contains valid grade and standard CohortSize rule.

v_mcmcoptions_objects *Internal Helper Functions for Validation of* McmcOptions *Objects*

Description

[Stable]

These functions are only used internally to validate the format of an input McmcOptions or inherited classes and therefore not exported.

Usage

```
v_mcmc_options(object)
```

Arguments

object	(McmcOptions) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_mcmc_options(): validates that the McmcOptions object contains valid integer scalars iterations, burnin and step as well as proper parameters for Random Number Generator.

v_model_objects *Internal Helper Functions for Validation of* GeneralModel *and* ModelPseudo *Objects*

Description

[Stable]

These functions are only used internally to validate the format of an input GeneralModel and ModelPseudo or inherited classes and therefore are not exported.

Usage

```
v_general_model(object)

v_model_logistic_kadane(object)

v_model_logistic_kadane_beta_gamma(object)

v_model_logistic_normal_mix(object)

v_model_logistic_normal_fixed_mix(object)

v_model_logistic_log_normal_mix(object)

v_model_two_drugs_combo(object)

v_hierarchical_model(object)

v_model_dual_endpoint(object)

v_model_dual_endpoint_rw(object)

v_model_dual_endpoint_beta(object)

v_model_dual_endpoint_emax(object)

v_model_logistic_indep_beta(object)

v_model_eff_log_log(object)

v_model_eff_flexi(object)

v_model_da_logistic_log_normal(object)

v_model_tite_logistic_log_normal(object)

v_model_one_par_exp_normal_prior(object)

v_model_one_par_exp_prior(object)

v_logisticlognormalordinal(object)
```

Arguments

object	(GeneralModel) or (ModelPseudo) object to validate.

Value

A `character` vector with the validation failure messages, or `TRUE` in case validation passes.

Functions

- `v_general_model()`: validates that the names of the arguments in `init` function are included in `datanames` or `datanames_prior` slots.
- `v_model_logistic_kadane()`: validates that the logistic Kadane model parameters are valid.
- `v_model_logistic_kadane_beta_gamma()`: validates that the logistic Kadane model parameters with a beta and gamma prior are valid.
- `v_model_logistic_normal_mix()`: validates that `weightpar` is valid.
- `v_model_logistic_normal_fixed_mix()`: validates that `component` is a list with valid `ModelParamsNormal` objects as well as `weights` are correct.
- `v_model_logistic_log_normal_mix()`: validates that `share_weight` represents probability.
- `v_model_two_drugs_combo()`: validates that `TwoDrugsCombo` slots are valid.
- `v_hierarchical_model()`: validates that `HierarchicalModel` slots are valid.
- `v_model_dual_endpoint()`: validates that `DualEndpoint` class slots are valid.
- `v_model_dual_endpoint_rw()`: validates that `DualEndpointRW` class slots are valid.
- `v_model_dual_endpoint_beta()`: validates that `DualEndpointBeta` class slots are valid.
- `v_model_dual_endpoint_emax()`: validates that `DualEndpointEmax` class slots are valid.
- `v_model_logistic_indep_beta()`: validates that `LogisticIndepBeta` class slots are valid.
- `v_model_eff_log_log()`: validates that `Effloglog` class slots are valid.
- `v_model_eff_flexi()`: validates that `EffFlexi` class slots are valid.
- `v_model_da_logistic_log_normal()`: validates that `DALogisticLogNormal` class slots are valid.
- `v_model_tite_logistic_log_normal()`: validates that `TITELogisticLogNormal` class slots are valid.
- `v_model_one_par_exp_normal_prior()`: validates that `OneParLogNormalPrior` class slots are valid.
- `v_model_one_par_exp_prior()`: validates that `OneParExpPrior` class slots are valid.
- `v_logisticlognormalordinal()`: confirms that cov is diagonal

v_model_params *Internal Helper Functions for Validation of Model Parameters Objects*

Description

[Experimental]

These functions are only used internally to validate the format of an object with model parameters or inherited classes and therefore not exported.

Usage

```
v_model_params_normal(object)
```

Arguments

object	(ModelParamsNormal) multivariate normal parameters object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_model_params_normal(): a helper function that validates multivariate normal parameters.

v_next_best *Internal Helper Functions for Validation of* NextBest *Objects*

Description

[Stable]

These functions are only used internally to validate the format of an input NextBest or inherited classes and therefore not exported.

Usage

```
v_next_best_mtd(object)

v_next_best_ncrm(object)

v_next_best_ncrm_loss(object)

v_next_best_dual_endpoint(object)
```

```
v_next_best_min_dist(object)

v_next_best_ewoc(object)

v_next_best_inf_theory(object)

v_next_best_td(object)

v_next_best_td_samples(object)

v_next_best_max_gain_samples(object)

v_next_best_prob_mtd_lte(object)

v_next_best_prob_mtd_min_dist(object)

v_next_best_ordinal(object)
```

Arguments

object	(NextBest) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_next_best_mtd(): validates that the NextBestMTD object contains valid target probability and derive function.
- v_next_best_ncrm(): validates that the NextBestNCRM object contains valid target probability, overdose and max_overdose_prob probability ranges.
- v_next_best_ncrm_loss(): validates that the NextBestNCRMLoss object contains valid objects.
- v_next_best_dual_endpoint(): validates that the NextBestDualEndpoint object contains valid probability objects.
- v_next_best_min_dist(): validates that the NextBestMinDist object contains valid target object.
- v_next_best_ewoc(): validates that the NextBestEWOC object contains valid target, overdose and max_overdose_prob parameters.
- v_next_best_inf_theory(): validates that the NextBestInfTheory object contains valid target and asymmetry objects.
- v_next_best_td(): validates that the NextBestTD object contains valid prob_target_drt and prob_target_eot probabilities.
- v_next_best_td_samples(): validates that the NextBestTDsamples object contains valid derive function.

- `v_next_best_max_gain_samples()`: validates that the `NextBestMaxGainSamples` object contains valid `derive` and `mg_derive` functions.
- `v_next_best_prob_mtd_lte()`: validates that the `NextBestProbMTDLTE` object contains valid `target` probability and `method` string value.
- `v_next_best_prob_mtd_min_dist()`: validates that the `NextBestProbMTDMinDist` object contains valid `target` probability and `method` string value.
- `v_next_best_ordinal()`: validates that the `NextBestOrdinal` object contains valid `grade` and standard `NextBest` rule.

`v_opening` *Internal Helper Functions for Validation of* `Opening` *Objects*

Description

[Experimental]

These functions are only used internally to validate the format of an input `Opening` or inherited classes and therefore not exported.

Usage

```
v_opening_min_dose(object)

v_opening_min_cohorts(object)

v_opening_min_responses(object)
```

Arguments

`object`	(`Opening`) object to validate.

Value

A `character` vector with the validation failure messages, or `TRUE` in case validation passes.

Functions

- `v_opening_min_dose()`: validates that the `OpeningMinDose` object contains valid `min_dose` slot.
- `v_opening_min_cohorts()`: validates that the `OpeningMinCohorts` object contains valid `min_cohorts` slot.
- `v_opening_min_responses()`: validates that the `OpeningMinResponses` object contains valid `min_responses` and `include_lower_doses` slots.

v_pseudo_simulations *Internal Helper Functions for Validation of* PseudoSimulations *Objects*

Description

[Stable]

These functions are only used internally to validate the format of an input PseudoSimulations or inherited classes and therefore not exported.

Usage

```
v_pseudo_simulations(object)

v_pseudo_dual_simulations(object)

v_pseudo_dual_flex_simulations(object)
```

Arguments

object	(PseudoSimulations) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_pseudo_simulations(): validates that the PseudoSimulations object contains valid fit, FinalTDtargetEndOfTrialEstimates , FinalTDtargetDuringTrialAtDoseGrid,FinalTDtargetEndOfTrialAtDo , FinalTDEOTCIs, FinalTDEOTRatios, FinalCIs, FinalRatios, object and valid stopReasons simulations.
- v_pseudo_dual_simulations(): validates that the PseudoDualSimulations object contains valid fit_eff, final_gstar_estimates , final_gstar_at_dose_grid, final_gstar_cis , final_gstar_ratios, final_optimal_dose, final_optimal_dose_at_dose_grid object and valid sigma2_est simulations.
- v_pseudo_dual_flex_simulations(): validates that the PseudoDualFlexiSimulations object contains valid sigma2_beta_w_est vector of the final posterior mean sigma2betaW estimates.FinalGstarEstimates , FinalGstarAtDoseGrid,

v_recruitment *Internal Helper Functions for Validation of* Recruitment *Objects*

Description

[Experimental]

These functions are only used internally to validate the format of an input Recruitment or inherited classes and therefore not exported.

Usage

```
v_recruitment_ratio(object)
```

Arguments

object	(Recruitment) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_recruitment_ratio(): validates that the RecruitmentRatio object contains valid ratio slot.

v_safety_window *Internal Helper Functions for Validation of* SafetyWindow *Objects*

Description

[Stable]

These functions are only used internally to validate the format of an input SafetyWindow or inherited classes and therefore not exported.

Usage

```
v_safety_window_size(object)

v_safety_window_const(object)
```

Arguments

object	(SafetyWindow) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_safety_window_size(): validates that the SafetyWindowSize object contains valid slots.
- v_safety_window_const(): validates that the SafetyWindowConst object contains valid slots.

---

v_samples_objects *Internal Helper Functions for Validation of* Samples *Objects*

Description

These functions are only used internally to validate the format of an input Samples or inherited classes and therefore not exported.

Usage

```
v_samples(object)

v_hierarchical_samples(object)
```

Arguments

object	(Samples) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_samples(): validates that the Samples object contains valid data slot.
- v_hierarchical_samples(): validates that the HierarchicalSamples object contains valid per-arm sample mappings.

v_stopping *Internal Helper Functions for Validation of* Stopping *Objects*

Description

[Stable]

These functions are only used internally to validate the format of an input Stopping or inherited classes and therefore not exported.

Usage

```
v_stopping_cohorts_near_dose(object)

v_stopping_patients_near_dose(object)

v_stopping_min_cohorts(object)

v_stopping_min_patients(object)

v_stopping_target_prob(object)

v_stopping_mtd_distribution(object)

v_stopping_mtd_cv(object)

v_stopping_target_biomarker(object)

v_stopping_list(object)

v_stopping_all(object)

v_stopping_tdci_ratio(object)
```

Arguments

object	(Stopping) object to validate.

Value

A character vector with the validation failure messages, or TRUE in case validation passes.

Functions

- v_stopping_cohorts_near_dose(): validates that the StoppingCohortsNearDose object contains valid nCohorts and percentage parameters.

- v_stopping_patients_near_dose(): validates that the StoppingPatientsNearDose object contains valid nPatients and percentage parameters.
- v_stopping_min_cohorts(): validates that the StoppingMinCohorts object contains valid nCohorts parameter.
- v_stopping_min_patients(): validates that the StoppingMinPatients object contains valid nPatients parameter.
- v_stopping_target_prob(): validates that the StoppingTargetProb object contains valid target and prob parameters.
- v_stopping_mtd_distribution(): validates that the StoppingMTDdistribution object contains valid target, thresh and prob parameters.
- v_stopping_mtd_cv(): validates that the StoppingMTDCV object contains valid probability target and percentage threshold.
- v_stopping_target_biomarker(): validates that the StoppingTargetBiomarker object contains valid target, is_relative and probslots.
- v_stopping_list(): validates that the StoppingList object contains valid stop_list, summary slots.
- v_stopping_all(): validates that the StoppingAll object contains valid stop_list slot.
- v_stopping_tdci_ratio(): validates that the StoppingTDCIRatio object contains valid target_ratio and prob_target slots.

---

windowLength *Determine the Safety Window Length of the Next Cohort*

Description

[Stable]

This function determines the safety window length of the next cohort.

Usage

```
windowLength(safetyWindow, size, ...)

## S4 method for signature 'SafetyWindowSize'
windowLength(safetyWindow, size, data, ...)

## S4 method for signature 'SafetyWindowConst'
windowLength(safetyWindow, size, ...)
```

Arguments

safetyWindow	(SafetyWindow) the rule, an object of class SafetyWindow.
size	(integer) the next cohort size.

...	additional arguments without method dispatch.
data	(DataDA) the data input, an object of class DataDA.

Value

The windowLength as a list of safety window parameters (gap, follow, follow_min).

Functions

- windowLength(SafetyWindowSize): Determine safety window length based on the cohort size.
- windowLength(SafetyWindowConst): Constant safety window length.

Examples

```
# nolint start

# Create the data
data <- DataDA(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 1, 1, 0, 0, 1, 0),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2)),
  u = c(42, 30, 15, 5, 20, 25, 30, 60),
  t0 = c(0, 15, 30, 40, 55, 70, 75, 85),
  Tmax = 60
)

# Initialize the CRM model used to model the data
npiece_ <- 10
lambda_prior <- function(k) {
  npiece_ / (data@Tmax * (npiece_ - k + 0.5))
}

model <- DALogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56,
  npiece = npiece_,
  l = as.numeric(t(apply(
    as.matrix(c(1:npiece_), 1, npiece_),
    2,
    lambda_prior
  ))),
  c_par = 2
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
set.seed(94)
samples <- mcmc(data, model, options)
```

```
# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the rule which will be used to select the next cohort size
# based on the class 'CohortSizeConst'
mySize <- CohortSizeConst(size = 3)

# Determine the cohort size for the next cohort
sizeRecommendation <- size(mySize, dose = doseRecommendation$value, data = data)

# Rule for the safety window length:
#   -having patientGap as (0,7,3,3,...) for cohort size <4
#   -and having patientGap as (0,9,5,5,...) for cohort size >=4
myWindowLength <- SafetyWindowSize(
  gap = list(c(7, 3), c(9, 5)),
  size = c(1, 4),
  follow = 7,
  follow_min = 14
)

# Determine the safety window parameters for the next cohort
windowLength(myWindowLength, size = sizeRecommendation)

# nolint end
# nolint start

# Create the data
data <- DataDA(
  x = c(0.1, 0.5, 1.5, 3, 6, 10, 10, 10),
  y = c(0, 0, 1, 1, 0, 0, 1, 0),
  doseGrid = c(0.1, 0.5, 1.5, 3, 6, seq(from = 10, to = 80, by = 2)),
  u = c(42, 30, 15, 5, 20, 25, 30, 60),
```

```
  t0 = c(0, 15, 30, 40, 55, 70, 75, 85),
  Tmax = 60
)

# Initialize the CRM model used to model the data
npiece_ <- 10
lambda_prior <- function(k) {
  npiece_ / (data@Tmax * (npiece_ - k + 0.5))
}

model <- DALogisticLogNormal(
  mean = c(-0.85, 1),
  cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
  ref_dose = 56,
  npiece = npiece_,
  l = as.numeric(t(apply(
    as.matrix(c(1:npiece_), 1, npiece_),
    2,
    lambda_prior
  ))),
  c_par = 2
)

# Set-up some MCMC parameters and generate samples from the posterior
options <- McmcOptions(burnin = 100, step = 2, samples = 200)
set.seed(94)
samples <- mcmc(data, model, options)

# Define the rule for dose increments and calculate the maximum dose allowed
myIncrements <- IncrementsRelative(
  intervals = c(0, 20),
  increments = c(1, 0.33)
)
nextMaxDose <- maxDose(myIncrements, data = data)

# Define the rule which will be used to select the next best dose
# based on the class 'NextBestNCRM'
myNextBest <- NextBestNCRM(
  target = c(0.2, 0.35),
  overdose = c(0.35, 1),
  max_overdose_prob = 0.25
)

# Calculate the next best dose
doseRecommendation <- nextBest(
  myNextBest,
  doselimit = nextMaxDose,
  samples = samples,
  model = model,
  data = data
)

# Define the rule which will be used to select the next cohort size
```

```
# based on the class 'CohortSizeConst'
mySize <- CohortSizeConst(size = 3)

# Determine the cohort size for the next cohort
sizeRecommendation <- size(mySize, dose = doseRecommendation$value, data = data)

# Rule for having safety window length with constant safety window parameters
myWindowLength <- SafetyWindowConst(gap = c(7, 3), follow = 7, follow_min = 14)

# Determine the safety window parameters for the next cohort
windowLength(myWindowLength, size = sizeRecommendation)

# nolint end
```

`&,Stopping,Stopping-method`

Combine Two Stopping Rules with AND

Description

[Stable]

The method combining two atomic stopping rules.

Usage

```
## S4 method for signature 'Stopping,Stopping'
e1 & e2
```

Arguments

`e1`	(`Stopping`) first stopping rule object.
`e2`	(`Stopping`) second stopping rule object.

Value

The `StoppingAll` object.

Examples

```
## Example of combining two atomic stopping rules with an AND ('&') operator

myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)

myStopping <- myStopping1 & myStopping2
```

&,Stopping,StoppingAll-method

Combine an Atomic Stopping Rule and a Stopping List with AND

Description

[Stable]

The method combining an atomic stopping rule and a stopping list.

Usage

```
## S4 method for signature 'Stopping,StoppingAll'
e1 & e2
```

Arguments

e1	(Stopping) stopping rule object.
e2	(StoppingAll) stopping list object.

Value

The modified StoppingAll object.

Examples

```
## Example of combining an atomic stopping rule with a list of stopping rules
## with an AND ('&') operator

myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)

myStopping3 <- StoppingMinPatients(nPatients = 20)

myStopping <- myStopping3 & (myStopping1 | myStopping2)
```

&,StoppingAll,Stopping-method

Combine a Stopping List and an Atomic Stopping Rule with AND

Description

[Stable]

The method combining a stopping list and an atomic stopping rule.

Usage

```
## S4 method for signature 'StoppingAll,Stopping'
e1 & e2
```

Arguments

e1	(StoppingAll) stopping list object.
e2	(Stopping) stopping rule object.

Value

The modified StoppingAll object.

Examples

```
## Example of combining a list of stopping rules with an atomic stopping rule
## with an AND ('&') operator

myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(target = c(0.2, 0.35), prob = 0.5)

myStopping3 <- StoppingMinPatients(nPatients = 20)

myStopping <- (myStopping1 | myStopping2) & myStopping3
```

Index

∗ **methods**
approximate, 12
examine, 106
fit, 111
fitGain, 118
fitPEM, 120
get,Samples,character-method, 131
plot,Data,ModelTox-method, 313
plot,DataDual,ModelEff-method, 317
plot,Samples,ModelEff-method, 348
plot,Samples,ModelTox-method, 349
plotDualResponses, 355
plotGain, 358
tidy, 524
∗ **package**
crmPack, 43
∗ **regression**
examine, 106
.ArmCondition *(*ArmCondition-class*)*, 14
.ArmConditionAll *(*ArmConditionAll-class*)*, 15
.ArmConditionAny *(*ArmConditionAny-class*)*, 15
.ArmConditionList *(*ArmConditionList-class*)*, 16
.ArmFinishedCondition *(*ArmFinishedCondition-class*)*, 17
.ArmMinDoseCondition *(*ArmMinDoseCondition-class*)*, 17
.Backfill *(*Backfill-class*)*, 19
.CohortSizeConst *(*CohortSizeConst-class*)*, 33
.CohortSizeDLT *(*CohortSizeDLT-class*)*, 34
.CohortSizeMax *(*CohortSizeMax-class*)*, 35
.CohortSizeMin *(*CohortSizeMin-class*)*, 36
.CohortSizeOrdinal *(*CohortSizeOrdinal-class*)*, 37
.CohortSizeParts *(*CohortSizeParts-class*)*, 38
.CohortSizeRandom *(*CohortSizeRandom-class*)*, 39
.CohortSizeRange *(*CohortSizeRange-class*)*, 40
.ComboSimulations *(*ComboSimulations-class*)*, 41
.ComboSimulationsSummary *(*ComboSimulationsSummary-class*)*, 42
.CrmPackClass *(*CrmPackClass-class*)*, 44
.DADesign *(*DADesign-class*)*, 45
.DALogisticLogNormal *(*DALogisticLogNormal-class*)*, 47
.DASimulations *(*DASimulations-class*)*, 50
.Data *(*Data-class*)*, 51
.DataCombo *(*DataCombo-class*)*, 53
.DataDA *(*DataDA-class*)*, 54
.DataDual *(*DataDual-class*)*, 56
.DataGrouped *(*DataGrouped-class*)*, 57
.DataMixture *(*DataMixture-class*)*, 58
.DataOrdinal *(*DataOrdinal-class*)*, 59
.DataParts *(*DataParts-class*)*, 60
.DefaultArmCondition *(*ArmCondition-class*)*, 14
.DefaultArmConditionAll *(*ArmConditionAll-class*)*, 15
.DefaultArmConditionAny *(*ArmConditionAny-class*)*, 15
.DefaultArmConditionList *(*ArmConditionList-class*)*, 16
.DefaultArmFinishedCondition *(*ArmFinishedCondition-class*)*, 17
.DefaultArmMinDoseCondition *(*ArmMinDoseCondition-class*)*, 17
.DefaultBackfill *(*Backfill-class*)*, 19
.DefaultCohortSize, 10
.DefaultCohortSizeConst

(CohortSizeConst-class), 33
.DefaultCohortSizeDLT (CohortSizeDLT-class), 34
.DefaultCohortSizeMax (CohortSizeMax-class), 35
.DefaultCohortSizeMin (CohortSizeMin-class), 36
.DefaultCohortSizeOrdinal (CohortSizeOrdinal-class), 37
.DefaultCohortSizeParts (CohortSizeParts-class), 38
.DefaultCohortSizeRandom (CohortSizeRandom-class), 39
.DefaultCohortSizeRange (CohortSizeRange-class), 40
.DefaultComboSimulations (ComboSimulations-class), 41
.DefaultComboSimulationsSummary (ComboSimulationsSummary-class), 42
.DefaultDADesign (DADesign-class), 45
.DefaultDALogisticLogNormal (DALogisticLogNormal-class), 47
.DefaultDASimulations (DASimulations-class), 50
.DefaultData (Data-class), 51
.DefaultDataCombo (DataCombo-class), 53
.DefaultDataDA (DataDA-class), 54
.DefaultDataDual (DataDual-class), 56
.DefaultDataGeneral (GeneralData-class), 126
.DefaultDataGrouped (DataGrouped-class), 57
.DefaultDataMixture (DataMixture-class), 58
.DefaultDataOrdinal (DataOrdinal-class), 59
.DefaultDataParts (DataParts-class), 60
.DefaultDesign (Design-class), 61
.DefaultDesignArm (DesignArm-class), 64
.DefaultDesignCombo (DesignCombo-class), 65
.DefaultDesignGrouped (DesignGrouped-class), 67
.DefaultDesignOrdinal (DesignOrdinal-class), 70
.DefaultDualDesign (DualDesign-class), 80
.DefaultDualEndpoint (DualEndpoint-class), 82
.DefaultDualEndpointBeta (DualEndpointBeta-class), 84
.DefaultDualEndpointEmax (DualEndpointEmax-class), 86
.DefaultDualEndpointRW (DualEndpointRW-class), 88
.DefaultDualResponsesDesign (DualResponsesDesign-class), 89
.DefaultDualResponsesSamplesDesign (DualResponsesSamplesDesign-class), 91
.DefaultDualSimulations (DualSimulations-class), 93
.DefaultDualSimulationsSummary (DualSimulationsSummary-class), 95
.DefaultEffFlexi (EffFlexi-class), 95
.DefaultEffloglog (Effloglog-class), 102
.DefaultFractionalCRM (FractionalCRM-class), 123
.DefaultGeneralModel (GeneralModel-class), 127
.DefaultGeneralSimulations (GeneralSimulations-class), 128
.DefaultGeneralSimulationsSummary (GeneralSimulationsSummary-class), 129
.DefaultHierarchicalData (HierarchicalData-class), 134
.DefaultHierarchicalDesign (HierarchicalDesign-class), 135
.DefaultHierarchicalModel (HierarchicalModel-class), 136
.DefaultHierarchicalSamples (HierarchicalSamples-class), 138
.DefaultHierarchicalSimulations (HierarchicalSimulations-class), 139
.DefaultHierarchicalSimulationsSummary (HierarchicalSimulationsSummary-class), 140
.DefaultIncrements (Increments-class), 179
.DefaultIncrementsComboCartesian (IncrementsComboCartesian-class),

180
.DefaultIncrementsComboOneDrugOnly (IncrementsComboOneDrugOnly-class), 181
.DefaultIncrementsDoseLevels (IncrementsDoseLevels-class), 182
.DefaultIncrementsHSRBeta (IncrementsHSRBeta-class), 183
.DefaultIncrementsMaxToxProb (IncrementsMaxToxProb-class), 184
.DefaultIncrementsMin (IncrementsMin-class), 185
.DefaultIncrementsOrdinal (IncrementsOrdinal-class), 186
.DefaultIncrementsRelative (IncrementsRelative-class), 187
.DefaultIncrementsRelativeDLT (IncrementsRelativeDLT-class), 188
.DefaultIncrementsRelativeDLTCurrent (IncrementsRelativeDLTCurrent-class), 189
.DefaultIncrementsRelativeParts (IncrementsRelativeParts-class), 190
.DefaultLogisticIndepBeta (LogisticIndepBeta-class), 212
.DefaultLogisticKadane (LogisticKadane-class), 215
.DefaultLogisticKadaneBetaGamma (LogisticKadaneBetaGamma-class), 216
.DefaultLogisticLogNormal (LogisticLogNormal-class), 218
.DefaultLogisticLogNormalGrouped (LogisticLogNormalGrouped-class), 219
.DefaultLogisticLogNormalMixture (LogisticLogNormalMixture-class), 221
.DefaultLogisticLogNormalOrdinal (LogisticLogNormalOrdinal-class), 222
.DefaultLogisticLogNormalSub (LogisticLogNormalSub-class), 223
.DefaultLogisticNormal (LogisticNormal-class), 225
.DefaultLogisticNormalFixedMixture (LogisticNormalFixedMixture-class), 226
.DefaultLogisticNormalMixture (LogisticNormalMixture-class), 228
.DefaultMcmcOptions (McmcOptions-class), 248
.DefaultModelEff (ModelEff-class), 252
.DefaultModelLogNormal (ModelLogNormal-class), 253
.DefaultModelParamsNormal (ModelParamsNormal-class), 254
.DefaultModelPseudo (ModelPseudo-class), 255
.DefaultModelTox (ModelTox-class), 255
.DefaultNextBest (NextBest-class), 275
.DefaultNextBestDualEndpoint (NextBestDualEndpoint-class), 276
.DefaultNextBestEWOC (NextBestEWOC-class), 278
.DefaultNextBestInfTheory (NextBestInfTheory-class), 279
.DefaultNextBestMTD (NextBestMTD-class), 283
.DefaultNextBestMaxGain (NextBestMaxGain-class), 280
.DefaultNextBestMaxGainSamples (NextBestMaxGainSamples-class), 281
.DefaultNextBestMinDist (NextBestMinDist-class), 282
.DefaultNextBestNCRM (NextBestNCRM-class), 284
.DefaultNextBestNCRMLoss (NextBestNCRMLoss-class), 285
.DefaultNextBestOrdinal (NextBestOrdinal-class), 287
.DefaultNextBestProbMTDLTE (NextBestProbMTDLTE-class), 288
.DefaultNextBestProbMTDMinDist (NextBestProbMTDMinDist-class), 289
.DefaultNextBestTD (NextBestTD-class), 290

.DefaultNextBestTDsamples (NextBestTDsamples-class), 291
.DefaultNextBestThreePlusThree (NextBestThreePlusThree-class), 292
.DefaultNoArmCondition (NoArmCondition-class), 293
.DefaultOneParExpPrior (OneParExpPrior-class), 294
.DefaultOneParLogNormalPrior (OneParLogNormalPrior-class), 295
.DefaultOpening (Opening-class), 301
.DefaultOpeningAll (OpeningAll-class), 302
.DefaultOpeningAny (OpeningAny-class), 303
.DefaultOpeningList (OpeningList-class), 304
.DefaultOpeningMinCohorts (OpeningMinCohorts-class), 305
.DefaultOpeningMinDose (OpeningMinDose-class), 305
.DefaultOpeningMinResponses (OpeningMinResponses-class), 306
.DefaultOpeningNone (OpeningNone-class), 307
.DefaultProbitLogNormal (ProbitLogNormal-class), 367
.DefaultProbitLogNormalRel (ProbitLogNormalRel-class), 368
.DefaultPseudoDualFlexiSimulations (PseudoDualFlexiSimulations-class), 369
.DefaultPseudoDualSimulations (PseudoDualSimulations-class), 370
.DefaultPseudoDualSimulationsSummary (PseudoDualSimulationsSummary-class), 371
.DefaultPseudoSimulations (PseudoSimulations-class), 372
.DefaultPseudoSimulationsSummary (PseudoSimulationsSummary-class), 374
.DefaultRecruitment (Recruitment-class), 378
.DefaultRecruitmentRatio (RecruitmentRatio-class), 378
.DefaultRecruitmentUnlimited (RecruitmentUnlimited-class), 379
.DefaultRuleDesign (RuleDesign-class), 380
.DefaultRuleDesignOrdinal (RuleDesignOrdinal-class), 381
.DefaultSafetyWindow (SafetyWindow-class), 383
.DefaultSafetyWindowConst (SafetyWindowConst-class), 383
.DefaultSafetyWindowSize (SafetyWindowSize-class), 384
.DefaultSamples (Samples-class), 385
.DefaultSimulations (Simulations-class), 442
.DefaultSimulationsSummary (SimulationsSummary-class), 444
.DefaultStoppingAll (StoppingAll-class), 456
.DefaultStoppingAny (StoppingAny-class), 457
.DefaultStoppingCohortsNearDose (StoppingCohortsNearDose-class), 458
.DefaultStoppingExternal (StoppingExternal-class), 459
.DefaultStoppingHighestDose (StoppingHighestDose-class), 460
.DefaultStoppingList (StoppingList-class), 461
.DefaultStoppingLowestDoseHSRBeta (StoppingLowestDoseHSRBeta-class), 462
.DefaultStoppingMTDCV (StoppingMTDCV-class), 467
.DefaultStoppingMTDdistribution (StoppingMTDdistribution-class), 468
.DefaultStoppingMaxGainCIRatio (StoppingMaxGainCIRatio-class), 463
.DefaultStoppingMinCohorts (StoppingMinCohorts-class), 464
.DefaultStoppingMinPatients

(StoppingMinPatients-class), 465
.DefaultStoppingMissingDose (StoppingMissingDose-class), 466
.DefaultStoppingOrdinal (StoppingOrdinal-class), 469
.DefaultStoppingPatientsNearDose (StoppingPatientsNearDose-class), 470
.DefaultStoppingSpecificDose (StoppingSpecificDose-class), 471
.DefaultStoppingTDCIRatio (StoppingTDCIRatio-class), 474
.DefaultStoppingTargetBiomarker (StoppingTargetBiomarker-class), 472
.DefaultStoppingTargetProb (StoppingTargetProb-class), 473
.DefaultTDDesign (TDDesign-class), 520
.DefaultTDsamplesDesign (TDsamplesDesign-class), 522
.DefaultTITELogisticLogNormal (TITELogisticLogNormal-class), 530
.DefaultTITELogisticLogNormalSub (TITELogisticLogNormalSub-class), 532
.DefaultTwoDrugsCombo (TwoDrugsCombo-class), 533
.Design (Design-class), 61
.DesignArm (DesignArm-class), 64
.DesignCombo (DesignCombo-class), 65
.DesignGrouped (DesignGrouped-class), 67
.DesignOrdinal (DesignOrdinal-class), 70
.DualDesign (DualDesign-class), 80
.DualEndpoint (DualEndpoint-class), 82
.DualEndpointBeta (DualEndpointBeta-class), 84
.DualEndpointEmax (DualEndpointEmax-class), 86
.DualEndpointRW (DualEndpointRW-class), 88
.DualResponsesDesign (DualResponsesDesign-class), 89
.DualResponsesSamplesDesign (DualResponsesSamplesDesign-class), 91
.DualSimulations (DualSimulations-class), 93
.DualSimulationsSummary (DualSimulationsSummary-class), 95
.EffFlexi (EffFlexi-class), 95
.Effloglog (Effloglog-class), 102
.FractionalCRM (FractionalCRM-class), 123
.GeneralData (GeneralData-class), 126
.GeneralModel (GeneralModel-class), 127
.GeneralSimulations (GeneralSimulations-class), 128
.GeneralSimulationsSummary (GeneralSimulationsSummary-class), 129
.HierarchicalData (HierarchicalData-class), 134
.HierarchicalDesign (HierarchicalDesign-class), 135
.HierarchicalModel (HierarchicalModel-class), 136
.HierarchicalSamples (HierarchicalSamples-class), 138
.HierarchicalSimulations (HierarchicalSimulations-class), 139
.HierarchicalSimulationsSummary (HierarchicalSimulationsSummary-class), 140
.IncrementsComboCartesian (IncrementsComboCartesian-class), 180
.IncrementsComboOneDrugOnly (IncrementsComboOneDrugOnly-class), 181
.IncrementsDoseLevels (IncrementsDoseLevels-class), 182
.IncrementsHSRBeta (IncrementsHSRBeta-class), 183
.IncrementsMaxToxProb (IncrementsMaxToxProb-class), 184
.IncrementsMin (IncrementsMin-class), 185

.IncrementsOrdinal (IncrementsOrdinal-class), 186
.IncrementsRelative (IncrementsRelative-class), 187
.IncrementsRelativeDLT (IncrementsRelativeDLT-class), 188
.IncrementsRelativeDLTCurrent (IncrementsRelativeDLTCurrent-class), 189
.IncrementsRelativeParts (IncrementsRelativeParts-class), 190
.LogisticIndepBeta (LogisticIndepBeta-class), 212
.LogisticKadane (LogisticKadane-class), 215
.LogisticKadaneBetaGamma (LogisticKadaneBetaGamma-class), 216
.LogisticLogNormal (LogisticLogNormal-class), 218
.LogisticLogNormalGrouped (LogisticLogNormalGrouped-class), 219
.LogisticLogNormalMixture (LogisticLogNormalMixture-class), 221
.LogisticLogNormalOrdinal (LogisticLogNormalOrdinal-class), 222
.LogisticLogNormalSub (LogisticLogNormalSub-class), 223
.LogisticNormal (LogisticNormal-class), 225
.LogisticNormalFixedMixture (LogisticNormalFixedMixture-class), 226
.LogisticNormalMixture (LogisticNormalMixture-class), 228
.McmcOptions (McmcOptions-class), 248
.ModelEff (ModelEff-class), 252
.ModelLogNormal (ModelLogNormal-class), 253
.ModelParamsNormal (ModelParamsNormal-class), 254
.ModelPseudo (ModelPseudo-class), 255
.ModelTox (ModelTox-class), 255
.NextBestDualEndpoint (NextBestDualEndpoint-class), 276
.NextBestEWOC (NextBestEWOC-class), 278
.NextBestInfTheory (NextBestInfTheory-class), 279
.NextBestMTD (NextBestMTD-class), 283
.NextBestMaxGain (NextBestMaxGain-class), 280
.NextBestMaxGainSamples (NextBestMaxGainSamples-class), 281
.NextBestMinDist (NextBestMinDist-class), 282
.NextBestNCRM (NextBestNCRM-class), 284
.NextBestNCRMLoss (NextBestNCRMLoss-class), 285
.NextBestOrdinal (NextBestOrdinal-class), 287
.NextBestProbMTDLTE (NextBestProbMTDLTE-class), 288
.NextBestProbMTDMinDist (NextBestProbMTDMinDist-class), 289
.NextBestTD (NextBestTD-class), 290
.NextBestTDsamples (NextBestTDsamples-class), 291
.NextBestThreePlusThree (NextBestThreePlusThree-class), 292
.NoArmCondition (NoArmCondition-class), 293
.OneParExpPrior (OneParExpPrior-class), 294
.OneParLogNormalPrior (OneParLogNormalPrior-class), 295
.Opening (Opening-class), 301
.OpeningAll (OpeningAll-class), 302
.OpeningAny (OpeningAny-class), 303
.OpeningList (OpeningList-class), 304
.OpeningMinCohorts (OpeningMinCohorts-class), 305
.OpeningMinDose (OpeningMinDose-class), 305
.OpeningMinResponses

(OpeningMinResponses-class), 306
.OpeningNone (OpeningNone-class), 307
.ProbitLogNormal (ProbitLogNormal-class), 367
.ProbitLogNormalRel (ProbitLogNormalRel-class), 368
.PseudoDualFlexiSimulations (PseudoDualFlexiSimulations-class), 369
.PseudoDualSimulations (PseudoDualSimulations-class), 370
.PseudoDualSimulationsSummary (PseudoDualSimulationsSummary-class), 371
.PseudoSimulations (PseudoSimulations-class), 372
.PseudoSimulationsSummary (PseudoSimulationsSummary-class), 374
.Recruitment (Recruitment-class), 378
.RecruitmentRatio (RecruitmentRatio-class), 378
.RecruitmentUnlimited (RecruitmentUnlimited-class), 379
.RuleDesign (RuleDesign-class), 380
.RuleDesignOrdinal (RuleDesignOrdinal-class), 381
.SafetyWindowConst (SafetyWindowConst-class), 383
.SafetyWindowSize (SafetyWindowSize-class), 384
.Samples (Samples-class), 385
.Simulations (Simulations-class), 442
.SimulationsSummary (SimulationsSummary-class), 444
.StoppingAll (StoppingAll-class), 456
.StoppingAny (StoppingAny-class), 457
.StoppingCohortsNearDose (StoppingCohortsNearDose-class), 458
.StoppingExternal (StoppingExternal-class), 459
.StoppingHighestDose (StoppingHighestDose-class), 460
.StoppingList (StoppingList-class), 461
.StoppingLowestDoseHSRBeta (StoppingLowestDoseHSRBeta-class), 462
.StoppingMTDCV (StoppingMTDCV-class), 467
.StoppingMTDdistribution (StoppingMTDdistribution-class), 468
.StoppingMaxGainCIRatio (StoppingMaxGainCIRatio-class), 463
.StoppingMinCohorts (StoppingMinCohorts-class), 464
.StoppingMinPatients (StoppingMinPatients-class), 465
.StoppingMissingDose (StoppingMissingDose-class), 466
.StoppingOrdinal (StoppingOrdinal-class), 469
.StoppingPatientsNearDose (StoppingPatientsNearDose-class), 470
.StoppingSpecificDose (StoppingSpecificDose-class), 471
.StoppingTDCIRatio (StoppingTDCIRatio-class), 474
.StoppingTargetBiomarker (StoppingTargetBiomarker-class), 472
.StoppingTargetProb (StoppingTargetProb-class), 473
.TDDesign (TDDesign-class), 520
.TDsamplesDesign (TDsamplesDesign-class), 522
.TITELogisticLogNormal (TITELogisticLogNormal-class), 530
.TITELogisticLogNormalSub (TITELogisticLogNormalSub-class), 532
.TwoDrugsCombo (TwoDrugsCombo-class), 533
[,Data,logical,missing,missing-method (subset-Data), 504

[,Data,numeric,missing,missing-method
(subset-Data), 504
[[, *174*, *175*
&,ArmCondition,ArmCondition-method
(and,ArmCondition,ArmCondition-method),
11
&,Opening,Opening-method
(and,Opening,Opening-method),
11
&,Stopping,Stopping-method, 568
&,Stopping,StoppingAll-method, 569
&,StoppingAll,Stopping-method, 569

all.equal(), *141*
and,ArmCondition,ArmCondition-method,
11
and,Opening,Opening-method, 11
and-Stopping-Stopping
(&,Stopping,Stopping-method),
568
and-Stopping-StoppingAll
(&,Stopping,StoppingAll-method),
569
and-StoppingAll-Stopping
(&,StoppingAll,Stopping-method),
569
approximate, 12
approximate,Samples-method
(approximate), 12
ArmCondition, *11*, *14–17*, *308*, *546*
ArmCondition (ArmCondition-class), 14
ArmCondition-class, 14
ArmConditionAll, *11*, *14–17*
ArmConditionAll
(ArmConditionAll-class), 15
ArmConditionAll-class, 15
ArmConditionAny, *14–17*, *308*
ArmConditionAny
(ArmConditionAny-class), 15
ArmConditionAny-class, 15
ArmConditionList, *15*, *16*
ArmConditionList
(ArmConditionList-class), 16
ArmConditionList-class, 16
ArmFinishedCondition, *14*, *17*, *546*
ArmFinishedCondition
(ArmFinishedCondition-class),
17
ArmFinishedCondition-class, 17
ArmMinDoseCondition, *14*, *17*, *546*
ArmMinDoseCondition
(ArmMinDoseCondition-class), 17
ArmMinDoseCondition-class, 17
armSamples, 18
armSamples,HierarchicalSamples,character-method
(armSamples), 18
assert_equal (check_equal), 23
assert_format (check_format), 24
assert_length (check_length), 26
assert_length(), *19*
assert_probabilities
(check_probabilities), 27
assert_probabilities(), *19*
assert_probability (check_probability),
29
assert_probability(), *19*
assert_probability_range
(check_probability_range), 30
assert_probability_range(), *19*
assert_range (check_range), 32
AssertCollection, *23*, *25, 26*, *28, 29*, *31*, *33*
assertions, 19, *24–26*, *28*, *30, 31*, *33*

Backfill, *546, 547*
Backfill (Backfill-class), 19
Backfill-class, 19
base::findInterval(), *147*
biomarker, 20
biomarker,integer,DualEndpoint,Samples-method
(biomarker), 20
biomarker-DualEndpoint (biomarker), 20
body(), *175*

check_equal, 23
check_format, 24
check_length, 26
check_probabilities, 27
check_probability, 29
check_probability_range, 30
check_range, 32
checkmate::test_names(), *178*
checkmate::test_numeric(), *177, 178*
CohortSize, *10*, *35, 36*, *240*, *251*, *547*
CohortSize (.DefaultCohortSize), 10
CohortSize-class (.DefaultCohortSize),
10
CohortSizeConst, *11*, *33*, *548*

CohortSizeConst (CohortSizeConst-class), 33
CohortSizeConst-class, 33
CohortSizeDLT, *11*, *34*, *548*
CohortSizeDLT (CohortSizeDLT-class), 34
CohortSizeDLT-class, 34
CohortSizeMax, *35*, *240*, *548*
CohortSizeMax (CohortSizeMax-class), 35
CohortSizeMax-class, 35
CohortSizeMin, *11*, *36*, *252*
CohortSizeMin (CohortSizeMin-class), 36
CohortSizeMin-class, 36
CohortSizeOrdinal, *37*, *71*, *382*, *553*
CohortSizeOrdinal (CohortSizeOrdinal-class), 37
CohortSizeOrdinal-class, 37
CohortSizeParts, *11*, *38*, *548*
CohortSizeParts (CohortSizeParts-class), 38
CohortSizeParts-class, 38
CohortSizeRandom, *39*, *548*
CohortSizeRandom (CohortSizeRandom-class), 39
CohortSizeRandom-class, 39
CohortSizeRange, *11*, *40*, *548*
CohortSizeRange (CohortSizeRange-class), 40
CohortSizeRange-class, 40
ComboSimulations, *42*, *133*, *312*, *396*, *418*, *551*
ComboSimulations (ComboSimulations-class), 41
ComboSimulations-class, 41
ComboSimulationsSummary, *505*
ComboSimulationsSummary (ComboSimulationsSummary-class), 42
ComboSimulationsSummary-class, 42
crmPack, 43
crmPack-package (crmPack), 43
CrmPackClass, *44*
CrmPackClass (CrmPackClass-class), 44
CrmPackClass-class, 44
crmPackExample, 44
crmPackHelp, 44

DADesign, *411*
DADesign (DADesign-class), 45
DADesign-class, 45
DALogisticLogNormal, *46*, *47*, *121*, *219*, *345*, *531*, *533*, *556*
DALogisticLogNormal (DALogisticLogNormal-class), 47
DALogisticLogNormal-class, 47
dapply, 49
DASimulations, *50*, *551*
DASimulations (DASimulations-class), 50
DASimulations-class, 50
Data, *12*, *21*, *41*, *51*, *54*, *56–58*, *60*, *113*, *129*, *144*, *170*, *174*, *255*, *314*, *330*, *347*, *348*, *350*, *445*, *504*, *525*, *535*, *536*, *549*
Data (Data-class), 51
Data(), *55–58*, *61*
Data-class, 51
data.frame, *49*, *174*
DataCombo, *41*, *53*, *66*, *314*, *330*, *351*, *445*, *525*, *534*, *536*, *537*, *549*
DataCombo (DataCombo-class), 53
DataCombo-class, 53
DataDA, *54*, *121*, *315*, *345*, *525*, *538*, *549*, *565*
DataDA (DataDA-class), 54
DataDA-class, 54
DataDual, *56*, *118*, *252*, *316*, *317*, *345*, *356*, *358*, *525*, *539*, *540*, *549*
DataDual (DataDual-class), 56
DataDual-class, 56
DataGrouped, *57*, *525*, *549*
DataGrouped (DataGrouped-class), 57
DataGrouped-class, 57
DataMixture, *58*, *221*, *243*, *525*, *549*
DataMixture (DataMixture-class), 58
DataMixture-class, 58
DataOrdinal, *59*, *143*, *170*, *174*, *447*, *525*, *540*, *541*, *549*
DataOrdinal (DataOrdinal-class), 59
DataOrdinal-class, 59
DataParts, *38*, *60*, *190*, *525*, *542*, *549*
DataParts (DataParts-class), 60
DataParts-class, 60
Design, *45*, *61*, *66*, *67*, *80*, *81*, *106*, *380*, *415*
Design (Design-class), 61
Design-class, 61
DesignArm, *14*, *64*, *135*, *293*, *552*
DesignArm (DesignArm-class), 64
DesignArm(), *64*, *135*
DesignArm-class, 64

DesignCombo, *41*, *65*, *418*, *419*, *550*
DesignCombo *(DesignCombo-class)*, 65
DesignCombo-class, 65
DesignGrouped, *67*, *419*, *550*
DesignGrouped *(DesignGrouped-class)*, 67
DesignGrouped-class, 67
DesignOrdinal, *71*, *381*
DesignOrdinal *(DesignOrdinal-class)*, 70
DesignOrdinal-class, 70
disable_logging *(enable_logging)*, 105
dose, 73
dose(), *76*, *78*, *100*, *364*
dose,numeric,DualEndpoint,Samples-method *(dose)*, 73
dose,numeric,EffFlexi,Samples-method *(dose)*, 73
dose,numeric,Effloglog,missing-method *(dose)*, 73
dose,numeric,LogisticIndepBeta,missing-method *(dose)*, 73
dose,numeric,LogisticIndepBeta,Samples-method *(dose)*, 73
dose,numeric,LogisticKadane,Samples-method *(dose)*, 73
dose,numeric,LogisticKadaneBetaGamma,Samples-method *(dose)*, 73
dose,numeric,LogisticLogNormal,Samples-method *(dose)*, 73
dose,numeric,LogisticLogNormalGrouped,Samples-method *(dose)*, 73
dose,numeric,LogisticLogNormalMixture,Samples-method *(dose)*, 73
dose,numeric,LogisticLogNormalOrdinal,Samples-method *(dose)*, 73
dose,numeric,LogisticLogNormalSub,Samples-method *(dose)*, 73
dose,numeric,LogisticNormal,Samples-method *(dose)*, 73
dose,numeric,LogisticNormalFixedMixture,Samples-method *(dose)*, 73
dose,numeric,LogisticNormalMixture,Samples-method *(dose)*, 73
dose,numeric,OneParExpPrior,Samples-method *(dose)*, 73
dose,numeric,OneParLogNormalPrior,Samples-method *(dose)*, 73
dose,numeric,ProbitLogNormal,Samples-method *(dose)*, 73
dose,numeric,ProbitLogNormalRel,Samples-method *(dose)*, 73
dose-DualEndpoint *(dose)*, 73
dose-EffFlexi *(dose)*, 73
dose-Effloglog-noSamples *(dose)*, 73
dose-LogisticIndepBeta *(dose)*, 73
dose-LogisticIndepBeta-noSamples *(dose)*, 73
dose-LogisticKadane *(dose)*, 73
dose-LogisticKadaneBetaGamma *(dose)*, 73
dose-LogisticLogNormal *(dose)*, 73
dose-LogisticLogNormalGrouped *(dose)*, 73
dose-LogisticLogNormalMixture *(dose)*, 73
dose-LogisticLogNormalOrdinal *(dose)*, 73
dose-LogisticLogNormalSub *(dose)*, 73
dose-LogisticNormal *(dose)*, 73
dose-LogisticNormalFixedMixture *(dose)*, 73
dose-LogisticNormalMixture *(dose)*, 73
dose-OneParExpPrior *(dose)*, 73
dose-OneParLogNormalPrior *(dose)*, 73
dose-ProbitLogNormal *(dose)*, 73
dose-ProbitLogNormalRel *(dose)*, 73
dose_grid_range, 79
dose_grid_range,Data-method *(dose_grid_range)*, 79
dose_grid_range,DataOrdinal-method *(dose_grid_range)*, 79
dose_grid_range-Data *(dose_grid_range)*, 79
doseFunction, 77
doseFunction(), *76*, *366*
doseFunction,GeneralModel-method *(doseFunction)*, 77
doseFunction,LogisticLogNormalOrdinal-method *(doseFunction)*, 77
doseFunction,ModelPseudo-method *(doseFunction)*, 77
doseFunction-GeneralModel *(doseFunction)*, 77
doseFunction-LogisticLogNormalOrdinal *(doseFunction)*, 77
doseFunction-ModelPseudo *(doseFunction)*, 77
DualDesign, *80*, *423*
DualDesign *(DualDesign-class)*, 80
DualDesign-class, 80
DualEndpoint, *82*, *85–89*, *156–159*, *345*, *367*,

368, *556*
DualEndpoint *(*DualEndpoint-class*)*, 82
DualEndpoint(), *85*, *87*, *88*
DualEndpoint-class, 82
DualEndpointBeta, *84*, *87*, *89*, *156*, *157*, *243*, *277*, *556*
DualEndpointBeta *(*DualEndpointBeta-class*)*, 84
DualEndpointBeta-class, 84
DualEndpointEmax, *84*, *86*, *89*, *243*, *277*, *556*
DualEndpointEmax *(*DualEndpointEmax-class*)*, 86
DualEndpointEmax-class, 86
DualEndpointRW, *84*, *86–88*, *159*, *243*, *556*
DualEndpointRW *(*DualEndpointRW-class*)*, 88
DualEndpointRW-class, 88
DualResponsesDesign, *426*, *427*
DualResponsesDesign *(*DualResponsesDesign-class*)*, 89
DualResponsesDesign-class, 89
DualResponsesSamplesDesign, *429*, *430*
DualResponsesSamplesDesign *(*DualResponsesSamplesDesign-class*)*, 91
DualResponsesSamplesDesign-class, 91
DualSimulations, *93*, *318*, *424*, *551*
DualSimulations *(*DualSimulations-class*)*, 93
DualSimulations-class, 93
DualSimulationsSummary, *323*, *506*
DualSimulationsSummary *(*DualSimulationsSummary-class*)*, 95
DualSimulationsSummary-class, 95

EffFlexi, *95*, *99*, *244*, *280*, *369*, *429*, *430*, *556*
EffFlexi *(*EffFlexi-class*)*, 95
EffFlexi-class, 95
efficacy, 98
efficacy(), *76*, *101*, *364*
efficacy,numeric,EffFlexi,Samples-method *(*efficacy*)*, 98
efficacy,numeric,Effloglog,missing-method *(*efficacy*)*, 98
efficacy,numeric,Effloglog,Samples-method *(*efficacy*)*, 98
efficacy-EffFlexi *(*efficacy*)*, 98
efficacy-Effloglog *(*efficacy*)*, 98
efficacy-Effloglog-noSamples *(*efficacy*)*, 98
efficacyFunction, 100
efficacyFunction,ModelEff-method *(*efficacyFunction*)*, 100
efficacyFunction-ModelEff *(*efficacyFunction*)*, 100
Effloglog, *99*, *102*, *244*, *260*, *525*, *556*
Effloglog *(*Effloglog-class*)*, 102
Effloglog-class, 102
enable_logging, 105
examine, 106
examine,DADesign-method *(*examine*)*, 106
examine,Design-method *(*examine*)*, 106
examine,RuleDesign-method *(*examine*)*, 106
expect_format *(*check_format*)*, 24
expect_probabilities *(*check_probabilities*)*, 27
expect_probability *(*check_probability*)*, 29
expect_probability_range *(*check_probability_range*)*, 30
expect_range *(*check_range*)*, 32
expect_that, *25*, *28*, *30*, *31*, *33*

fit, 111, *351*
fit,HierarchicalSamples,HierarchicalModel,HierarchicalData *(*fit*)*, 111
fit,Samples,DualEndpoint,DataDual-method *(*fit*)*, 111
fit,Samples,EffFlexi,DataDual-method *(*fit*)*, 111
fit,Samples,Effloglog,DataDual-method *(*fit*)*, 111
fit,Samples,GeneralModel,Data-method *(*fit*)*, 111
fit,Samples,LogisticIndepBeta,Data-method *(*fit*)*, 111
fit,Samples,LogisticLogNormalOrdinal,DataOrdinal-method *(*fit*)*, 111
fit,Samples,TwoDrugsCombo,DataCombo-method *(*fit*)*, 111
fitGain, 117
fitGain,ModelTox,Samples,ModelEff,Samples,DataDual-method *(*fitGain*)*, 118
fitPEM, 120, *345*
fitPEM,Samples,DALogisticLogNormal,DataDA-method *(*fitPEM*)*, 120
fitted, *111*

formatC(), *148*, *155*, *156*
FractionalCRM, *123*
FractionalCRM *(*FractionalCRM-class*)*, 123
FractionalCRM-class, 123
futile.logger, *105*
futile.logger::FATAL, *105*, *106*
futile.logger::flog.logger(), *106*
futile.logger::flog.threshold(), *106*
futile.logger::flog.trace(), *106*
futile.logger::TRACE, *105*, *106*

gain, 124
gain,numeric,ModelTox,missing,Effloglog,missing-method *(*gain*)*, 124
gain,numeric,ModelTox,Samples,ModelEff,Samples-method *(*gain*)*, 124
gain-ModelTox-Effloglog-noSamples *(*gain*)*, 124
gain-ModelTox-ModelEff *(*gain*)*, 124
GeneralData, *51*, *53*, *59*, *126*, *151*, *173*, *241*, *525*, *548*, *549*
GeneralData *(*GeneralData-class*)*, 126
GeneralData-class, 126
GeneralModel, *12*, *113*, *127*, *136*, *158*, *160*, *241*, *255*, *347*, *533*, *534*, *554*
GeneralModel *(*GeneralModel-class*)*, 127
GeneralModel-class, 127
GeneralSimulations, *326*, *372*, *373*, *399*, *436*, *442*, *551*
GeneralSimulations *(*GeneralSimulations-class*)*, 128
GeneralSimulations-class, 128
GeneralSimulationsSummary, *329*, *444*, *508*
GeneralSimulationsSummary *(*GeneralSimulationsSummary-class*)*, 129
GeneralSimulationsSummary-class, 129
GenSA::GenSA(), *377*
get,Samples,character-method, 131
get_arm_simulations, 133
getEff, 132
getEff,DataDual-method *(*getEff*)*, 132
getEff-DataDual *(*getEff*)*, 132
ggmcmc, *131*
ggplot, *314*, *317*, *345*, *347*, *349–351*, *356*, *358*
ggplot2, *171*, *315*, *316*
gridExtra::arrangeGrob(), *354*

h_all_equivalent, 141
h_blind_plot_data, 141
h_calc_report_label_percentage, 142
h_check_fun_formals, 143
h_combo_doses_unique_per_cohort *(*v_data_objects*)*, 548
h_convert_ordinal_data, 143
h_convert_ordinal_model, 144
h_convert_ordinal_samples, 145
h_default_if_empty, 145
h_dose_combo_below_limit, 146
h_doses_unique_per_cohort *(*v_data_objects*)*, 548
h_eval_combo_truth, 146
h_find_interval, 147
h_format_number, 148
h_in_range, 149
h_info_theory_dist, 149
h_is_positive_definite, 150
h_jags_add_dummy, 151
h_jags_extract_samples, 152
h_jags_get_data, 153
h_jags_get_model_inits, 154
h_jags_join_models, 155
h_jags_write_model, 155
h_jags_write_model(), *148*, *175*
h_model_dual_endpoint_beta, 156
h_model_dual_endpoint_rho, 157
h_model_dual_endpoint_sigma2betaw, 158
h_model_dual_endpoint_sigma2w, 159
h_next_best_eligible_doses, 160
h_next_best_mg_ci, 162
h_next_best_mg_doses_at_grid, 163
h_next_best_mg_plot, 164
h_next_best_mgsamples_plot, 161
h_next_best_ncrm_loss_plot, 165
h_next_best_td_plot, 167
h_next_best_tdsamples_plot, 166
h_null_if_na, 168
h_obtain_dose_grid_range, 169
h_plot_data_cohort_lines, 169
h_plot_data_dataordinal, 170
h_plot_data_df, 173
h_plot_data_df,Data-method *(*h_plot_data_df*)*, 173
h_plot_data_df,DataOrdinal-method *(*h_plot_data_df*)*, 173
h_rapply, 174
h_slots, 175

h_summarize_add_stats, 176
h_test_named_numeric, 176
h_unpack_stopit, 178
h_validate_combine_results, 178
h_validate_common_data_slots, 179
HierarchicalData, *134, 135*, *137*, *140*, *330, 331*, *400*, *525*, *543*, *549*
HierarchicalData (HierarchicalData-class), 134
HierarchicalData-class, 134
HierarchicalDesign, *14*, *64*, *135*, *139*, *401*, *434*, *552*
HierarchicalDesign (HierarchicalDesign-class), 135
HierarchicalDesign-class, 135
HierarchicalModel, *135, 136*, *138*, *331*, *401*, *525*, *556*
HierarchicalModel (HierarchicalModel-class), 136
HierarchicalModel(), *135*
HierarchicalModel-class, 136
HierarchicalSamples, *138*, *140*, *331*, *562*
HierarchicalSamples (HierarchicalSamples-class), 138
HierarchicalSamples-class, 138
HierarchicalSimulations, *140*, *402*, *435*, *551*
HierarchicalSimulations (HierarchicalSimulations-class), 139
HierarchicalSimulations-class, 139
HierarchicalSimulationsSummary, *509*
HierarchicalSimulationsSummary (HierarchicalSimulationsSummary-class), 140
HierarchicalSimulationsSummary-class, 140
HistoricalArm (DesignArm-class), 64
HistoricalArm(), *64*, *135*

Increments, *179*, *185*, *552*
Increments (Increments-class), 179
Increments-class, 179
IncrementsComboCartesian, *180*
IncrementsComboCartesian (IncrementsComboCartesian-class), 180
IncrementsComboCartesian-class, 180
IncrementsComboOneDrugOnly, *181*
IncrementsComboOneDrugOnly (IncrementsComboOneDrugOnly-class), 181
IncrementsComboOneDrugOnly-class, 181
IncrementsDoseLevels, *180*, *182*, *232*, *553*
IncrementsDoseLevels (IncrementsDoseLevels-class), 182
IncrementsDoseLevels-class, 182
IncrementsHSRBeta, *180*, *183*, *553*
IncrementsHSRBeta (IncrementsHSRBeta-class), 183
IncrementsHSRBeta-class, 183
IncrementsMaxToxProb, *184*, *553*
IncrementsMaxToxProb (IncrementsMaxToxProb-class), 184
IncrementsMaxToxProb-class, 184
IncrementsMin, *180*, *185*, *553*
IncrementsMin (IncrementsMin-class), 185
IncrementsMin-class, 185
IncrementsOrdinal, *71*, *186*, *553*
IncrementsOrdinal (IncrementsOrdinal-class), 186
IncrementsOrdinal-class, 186
IncrementsRelative, *180*, *187*, *190*, *553*
IncrementsRelative (IncrementsRelative-class), 187
IncrementsRelative-class, 187
IncrementsRelativeDLT, *180*, *188, 189*, *553*
IncrementsRelativeDLT (IncrementsRelativeDLT-class), 188
IncrementsRelativeDLT-class, 188
IncrementsRelativeDLTCurrent, *189*
IncrementsRelativeDLTCurrent (IncrementsRelativeDLTCurrent-class), 189
IncrementsRelativeDLTCurrent-class, 189
IncrementsRelativeParts, *190*, *553*
IncrementsRelativeParts (IncrementsRelativeParts-class), 190
IncrementsRelativeParts-class, 190
is.atomic(), *168*
is.na(), *145*

is_logging_enabled *(*enable_logging*)*, 105

knit_print, *212*
knit_print *(*knit_print.Backfill*)*, 191
knit_print.Backfill, 191
knitr::kable(), *205*

lapply(), *49*
length(), *26*, *145*
list, *528*
log_trace *(*enable_logging*)*, 105
LogisticIndepBeta, *89*, *91*, *212*, *243*, *260*, *363*, *520*, *522*, *525*, *556*
LogisticIndepBeta *(*LogisticIndepBeta-class*)*, 212
LogisticIndepBeta-class, 212
LogisticKadane, *215*, *218*
LogisticKadane *(*LogisticKadane-class*)*, 215
LogisticKadane-class, 215
LogisticKadaneBetaGamma, *216*
LogisticKadaneBetaGamma *(*LogisticKadaneBetaGamma-class*)*, 216
LogisticKadaneBetaGamma-class, 216
LogisticLogNormal, *47*, *48*, *144*, *218*, *220*, *221*, *224*, *225*, *249*, *254*, *367*, *369*, *377*, *530*, *534*
LogisticLogNormal *(*LogisticLogNormal-class*)*, 218
LogisticLogNormal-class, 218
LogisticLogNormalGrouped, *75*, *219*, *362*, *363*
LogisticLogNormalGrouped *(*LogisticLogNormalGrouped-class*)*, 219
LogisticLogNormalGrouped-class, 219
LogisticLogNormalMixture, *219*, *221*, *227*, *229*
LogisticLogNormalMixture *(*LogisticLogNormalMixture-class*)*, 221
LogisticLogNormalMixture-class, 221
LogisticLogNormalOrdinal, *144*, *223*, *244*
LogisticLogNormalOrdinal *(*LogisticLogNormalOrdinal-class*)*, 222
LogisticLogNormalOrdinal-class, 222
LogisticLogNormalSub, *219*, *223*, *225*, *249*, *250*, *254*, *367*, *369*, *377*, *532*
LogisticLogNormalSub *(*LogisticLogNormalSub-class*)*, 223
LogisticLogNormalSub-class, 223
LogisticNormal, *48*, *219*, *224*, *225*, *249*, *254*, *367*, *369*, *376*, *377*
LogisticNormal *(*LogisticNormal-class*)*, 225
LogisticNormal-class, 225
LogisticNormalFixedMixture, *222*, *226*, *229*
LogisticNormalFixedMixture *(*LogisticNormalFixedMixture-class*)*, 226
LogisticNormalFixedMixture-class, 226
LogisticNormalMixture, *222*, *225*, *227*, *228*, *255*
LogisticNormalMixture *(*LogisticNormalMixture-class*)*, 228
LogisticNormalMixture-class, 228
logit, 229

match(), *230*
match_within_tolerance, 230
maxDose, 231
maxDose,IncrementsComboCartesian,DataCombo-method *(*maxDose*)*, 231
maxDose,IncrementsComboOneDrugOnly,DataCombo-method *(*maxDose*)*, 231
maxDose,IncrementsDoseLevels,Data-method *(*maxDose*)*, 231
maxDose,IncrementsHSRBeta,Data-method *(*maxDose*)*, 231
maxDose,IncrementsMaxToxProb,Data-method *(*maxDose*)*, 231
maxDose,IncrementsMaxToxProb,DataOrdinal-method *(*maxDose*)*, 231
maxDose,IncrementsMin,Data-method *(*maxDose*)*, 231
maxDose,IncrementsMin,DataCombo-method *(*maxDose*)*, 231
maxDose,IncrementsMin,DataOrdinal-method *(*maxDose*)*, 231
maxDose,IncrementsOrdinal,DataOrdinal-method *(*maxDose*)*, 231

maxDose,IncrementsRelative,Data-method (maxDose), 231
maxDose,IncrementsRelativeDLT,Data-method (maxDose), 231
maxDose,IncrementsRelativeDLTCurrent,Data-method (maxDose), 231
maxDose,IncrementsRelativeParts,DataParts-method (maxDose), 231
maxDose-IncrementsComboCartesian (maxDose), 231
maxDose-IncrementsComboOneDrugOnly (maxDose), 231
maxDose-IncrementsDoseLevels (maxDose), 231
maxDose-IncrementsHSRBeta (maxDose), 231
maxDose-IncrementsMaxToxProb (maxDose), 231
maxDose-IncrementsMin (maxDose), 231
maxDose-IncrementsOrdinal (maxDose), 231
maxDose-IncrementsRelative (maxDose), 231
maxDose-IncrementsRelativeDLT (maxDose), 231
maxDose-IncrementsRelativeDLTCurrent (maxDose), 231
maxDose-IncrementsRelativeParts (maxDose), 231
maxRecruits, 238
maxRecruits,RecruitmentRatio-method (maxRecruits), 238
maxRecruits,RecruitmentUnlimited-method (maxRecruits), 238
maxRecruits-RecruitmentRatio (maxRecruits), 238
maxRecruits-RecruitmentUnlimited (maxRecruits), 238
maxSize, 240
maxSize(), *252*
maxSize,CohortSize-method (maxSize), 240
maxSize-CohortSize (maxSize), 240
mcmc, 241
mcmc(), *153*, *154*
mcmc,Data,LogisticIndepBeta,McmcOptions-method (mcmc), 241
mcmc,DataCombo,TwoDrugsCombo,McmcOptions-method (mcmc), 241
mcmc,DataDual,EffFlexi,McmcOptions-method (mcmc), 241
mcmc,DataDual,Effloglog,McmcOptions-method (mcmc), 241
mcmc,DataMixture,GeneralModel,McmcOptions-method (mcmc), 241
mcmc,DataOrdinal,LogisticLogNormalOrdinal,McmcOptions-method (mcmc), 241
mcmc,GeneralData,DualEndpointBeta,McmcOptions-method (mcmc), 241
mcmc,GeneralData,DualEndpointEmax,McmcOptions-method (mcmc), 241
mcmc,GeneralData,DualEndpointRW,McmcOptions-method (mcmc), 241
mcmc,GeneralData,GeneralModel,McmcOptions-method (mcmc), 241
mcmc,GeneralData,OneParExpPrior,McmcOptions-method (mcmc), 241
mcmc,GeneralData,OneParLogNormalPrior,McmcOptions-method (mcmc), 241
mcmc,HierarchicalData,HierarchicalModel,McmcOptions-method (mcmc), 241
mcmc-Data-LogisticIndepBeta (mcmc), 241
mcmc-DataDual-EffFlexi (mcmc), 241
mcmc-DataDual-Effloglog (mcmc), 241
mcmc-DataMixture (mcmc), 241
mcmc-DataOrdinal-LogisticLogNormalOrdinal (mcmc), 241
mcmc-GeneralData (mcmc), 241
mcmc-GeneralData-DualEndpointBeta (mcmc), 241
mcmc-GeneralData-DualEndpointEmax (mcmc), 241
mcmc-GeneralData-DualEndpointRW (mcmc), 241
mcmc-GeneralData-OneParExpPrior (mcmc), 241
mcmc-GeneralData-OneParLogNormalPrior (mcmc), 241
McmcOptions, *106*, *241*, *248*, *412*, *415*, *418*, *423*, *430*, *434*, *440*, *554*
McmcOptions (McmcOptions-class), 248
McmcOptions-class, 248
mean, *113*, *118*, *121*
methods::slot(), *175*
MinimalInformative, 249
minSize, 251
minSize(), *240*
minSize,CohortSize-method (minSize), 251
minSize-CohortSize (minSize), 251

ModelEff, *96*, *102*, *118*, *252*, *256*, *280*, *281*, *317*, *348*, *355*, *358*, *426*, *429*
ModelEff *(*ModelEff-class*)*, 252
ModelEff-class, 252
ModelLogNormal, *48*, *216*, *218–220*, *222*, *225*, *227*, *229*, *253*, *255*, *296*, *367*, *369*
ModelLogNormal *(*ModelLogNormal-class*)*, 253
ModelLogNormal-class, 253
ModelParamsNormal, *226–229*, *254*
ModelParamsNormal *(*ModelParamsNormal-class*)*, 254
ModelParamsNormal-class, 254
ModelPseudo, *128*, *255*, *543*, *544*, *554*
ModelPseudo *(*ModelPseudo-class*)*, 255
ModelPseudo-class, 255
ModelTox, *118*, *212*, *253*, *255*, *260*, *280*, *281*, *290*, *314*, *349*, *350*, *355*, *358*, *426*, *429*, *437*, *439*, *520*, *522*
ModelTox *(*ModelTox-class*)*, 255
ModelTox-class, 255

names,Samples-method, 256
names-Samples *(*names,Samples-method*)*, 256
NextBest, *275*, *278*, *557*
NextBest *(*NextBest-class*)*, 275
nextBest, 257
nextBest,NextBestDualEndpoint,numeric,Samples,DualEndpoint,Data-method *(*nextBest*)*, 257
nextBest,NextBestEWOC,numeric,Samples,GeneralModel,Data-method *(*nextBest*)*, 257
nextBest,NextBestInfTheory,numeric,Samples,GeneralModel,Data-method *(*nextBest*)*, 257
nextBest,NextBestMaxGain,numeric,missing,ModelTox,Data,Dual-method *(*nextBest*)*, 257
nextBest,NextBestMaxGainSamples,numeric,Samples,ModelTox,Data,Dual-method *(*nextBest*)*, 257
nextBest,NextBestMinDist,numeric,Samples,GeneralModel,Data-method *(*nextBest*)*, 257
nextBest,NextBestMTD,numeric,Samples,GeneralModel,Data-method *(*nextBest*)*, 257
nextBest,NextBestNCRM,matrix,Samples,TwoDrugsComboData,Combo-method *(*nextBest*)*, 257
nextBest,NextBestNCRM,numeric,Samples,GeneralModel,Data-method *(*nextBest*)*, 257
nextBest,NextBestNCRM,numeric,Samples,GeneralModel,DataParts-method *(*nextBest*)*, 257
nextBest,NextBestNCRMLoss,numeric,Samples,GeneralModel,Dat *(*nextBest*)*, 257
nextBest,NextBestOrdinal,numeric,Samples,GeneralModel,Data *(*nextBest*)*, 257
nextBest,NextBestOrdinal,numeric,Samples,LogisticLogNormal *(*nextBest*)*, 257
nextBest,NextBestProbMTDLTE,numeric,Samples,GeneralModel,D *(*nextBest*)*, 257
nextBest,NextBestProbMTDMinDist,numeric,Samples,GeneralMod *(*nextBest*)*, 257
nextBest,NextBestTD,numeric,missing,LogisticIndepBeta,Data *(*nextBest*)*, 257
nextBest,NextBestTDsamples,numeric,Samples,LogisticIndepBe *(*nextBest*)*, 257
nextBest,NextBestThreePlusThree,missing,missing,missing,Da *(*nextBest*)*, 257
NextBest-class, 275
nextBest-NextBestDualEndpoint *(*nextBest*)*, 257
nextBest-NextBestEWOC *(*nextBest*)*, 257
nextBest-NextBestInfTheory *(*nextBest*)*, 257
nextBest-NextBestMaxGain *(*nextBest*)*, 257
nextBest-NextBestMaxGainSamples *(*nextBest*)*, 257
nextBest-NextBestMinDist *(*nextBest*)*, 257
nextBest-NextBestMTD *(*nextBest*)*, 257
nextBest-NextBestNCRM *(*nextBest*)*, 257
nextBest-NextBestNCRM-DataParts *(*nextBest*)*, 257
nextBest-NextBestNCRMLoss *(*nextBest*)*, 257
nextBest-NextBestOrdinal *(*nextBest*)*, 257
nextBest-NextBestProbMTDLTE *(*nextBest*)*, 257
nextBest-NextBestProbMTDMinDist *(*nextBest*)*, 257
nextBest-NextBestTD *(*nextBest*)*, 257
nextBest-NextBestTDsamples *(*nextBest*)*, 257
nextBest-NextBestThreePlusThree *(*nextBest*)*, 257
NextBestDualEndpoint, *276*, *558*
NextBestDualEndpoint *(*NextBestDualEndpoint-class*)*, 276
NextBestDualEndpoint-class, 276
NextBestEWOC, *276*, *278*, *558*

NextBestEWOC *(NextBestEWOC-class)*, 278
NextBestEWOC-class, 278
NextBestInfTheory, *276*, *279*, *558*
NextBestInfTheory *(NextBestInfTheory-class)*, 279
NextBestInfTheory-class, 279
NextBestMaxGain, *276*, *280*, *281*
NextBestMaxGain *(NextBestMaxGain-class)*, 280
NextBestMaxGain-class, 280
NextBestMaxGainSamples, *276*, *281*, *559*
NextBestMaxGainSamples *(NextBestMaxGainSamples-class)*, 281
NextBestMaxGainSamples-class, 281
NextBestMinDist, *276*, *282*, *558*
NextBestMinDist *(NextBestMinDist-class)*, 282
NextBestMinDist-class, 282
NextBestMTD, *276*, *283*, *558*
NextBestMTD *(NextBestMTD-class)*, 283
NextBestMTD-class, 283
NextBestNCRM, *276*, *284–286*, *558*
NextBestNCRM *(NextBestNCRM-class)*, 284
NextBestNCRM-class, 284
NextBestNCRMLoss, *276*, *285*, *558*
NextBestNCRMLoss *(NextBestNCRMLoss-class)*, 285
NextBestNCRMLoss-class, 285
NextBestOrdinal, *276*, *287*, *559*
NextBestOrdinal *(NextBestOrdinal-class)*, 287
NextBestOrdinal-class, 287
NextBestProbMTDLTE, *276*, *288*, *559*
NextBestProbMTDLTE *(NextBestProbMTDLTE-class)*, 288
NextBestProbMTDLTE-class, 288
NextBestProbMTDMinDist, *276*, *289*, *559*
NextBestProbMTDMinDist *(NextBestProbMTDMinDist-class)*, 289
NextBestProbMTDMinDist-class, 289
NextBestTD, *276*, *290*, *291*, *558*
NextBestTD *(NextBestTD-class)*, 290
NextBestTD-class, 290
NextBestTDsamples, *276*, *291*, *558*
NextBestTDsamples *(NextBestTDsamples-class)*, 291
NextBestTDsamples-class, 291
NextBestThreePlusThree, *276*, *292*
NextBestThreePlusThree *(NextBestThreePlusThree-class)*, 292
NextBestThreePlusThree-class, 292
ngrid, 292
ngrid,Data-method *(ngrid)*, 292
ngrid-Data *(ngrid)*, 292
NoArmCondition, *14*, *293*
NoArmCondition *(NoArmCondition-class)*, 293
NoArmCondition-class, 293

OneParExpPrior, *243*, *294*, *556*
OneParExpPrior *(OneParExpPrior-class)*, 294
OneParExpPrior-class, 294
OneParLogNormalPrior, *123*, *243*, *295*, *556*
OneParLogNormalPrior *(OneParLogNormalPrior-class)*, 295
OneParLogNormalPrior-class, 295
openArm, 296
openArm,ArmConditionAll-method *(openArm)*, 296
openArm,ArmConditionAny-method *(openArm)*, 296
openArm,ArmConditionList-method *(openArm)*, 296
openArm,ArmFinishedCondition-method *(openArm)*, 296
openArm,ArmMinDoseCondition-method *(openArm)*, 296
openArm,NoArmCondition-method *(openArm)*, 296
openArm-ArmConditionAll *(openArm)*, 296
openArm-ArmConditionAny *(openArm)*, 296
openArm-ArmConditionList *(openArm)*, 296
openArm-ArmFinishedCondition *(openArm)*, 296
openArm-ArmMinDoseCondition *(openArm)*, 296
openArm-NoArmCondition *(openArm)*, 296
openCohort, 297
openCohort,OpeningAll-method *(openCohort)*, 297
openCohort,OpeningAny-method *(openCohort)*, 297

openCohort,OpeningList-method (openCohort), 297
openCohort,OpeningMinCohorts-method (openCohort), 297
openCohort,OpeningMinDose-method (openCohort), 297
openCohort,OpeningMinResponses-method (openCohort), 297
openCohort,OpeningNone-method (openCohort), 297
openCohort-OpeningAll (openCohort), 297
openCohort-OpeningAny (openCohort), 297
openCohort-OpeningList (openCohort), 297
openCohort-OpeningMinCohorts (openCohort), 297
openCohort-OpeningMinDose (openCohort), 297
openCohort-OpeningMinResponses (openCohort), 297
openCohort-OpeningNone (openCohort), 297
Opening, *11*, *301–307*, *309*, *559*
Opening (Opening-class), 301
Opening-class, 301
OpeningAll, *11*, *12*, *301–304*
OpeningAll (OpeningAll-class), 302
OpeningAll-class, 302
OpeningAny, *301–304*, *309*
OpeningAny (OpeningAny-class), 303
OpeningAny-class, 303
OpeningList, *302–304*
OpeningList (OpeningList-class), 304
OpeningList-class, 304
OpeningMinCohorts, *301*, *305*, *559*
OpeningMinCohorts (OpeningMinCohorts-class), 305
OpeningMinCohorts-class, 305
OpeningMinDose, *301*, *305*, *559*
OpeningMinDose (OpeningMinDose-class), 305
OpeningMinDose-class, 305
OpeningMinResponses, *301*, *306*, *559*
OpeningMinResponses (OpeningMinResponses-class), 306
OpeningMinResponses-class, 306
OpeningNone, *301*, *307*
OpeningNone (OpeningNone-class), 307
OpeningNone-class, 307
or,ArmCondition,ArmCondition-method, 308
or,Opening,Opening-method, 309
or-Stopping-Stopping, 309
or-Stopping-StoppingAny, 310
or-StoppingAny-Stopping, 311

plot,ComboSimulations,missing-method, 312
plot,ComboSimulationsSummary,missing-method, 312
plot,Data,missing-method (h_plot_data_dataordinal), 170
plot,Data,ModelTox-method, 313
plot,DataCombo,missing-method, 314
plot,DataDA,missing-method, 315
plot,DataDual,missing-method, 316
plot,DataDual,ModelEff-method, 317
plot,DataOrdinal,missing-method (h_plot_data_dataordinal), 170
plot,DualSimulations,missing-method, 318
plot,DualSimulationsSummary,missing-method, 323
plot,GeneralSimulations,missing-method, 326
plot,GeneralSimulationsSummary,missing-method, 329
plot,HierarchicalData,missing-method, 330
plot,HierarchicalSamples,HierarchicalModel-method, 330
plot,PseudoDualFlexiSimulations,missing-method, 331
plot,PseudoDualSimulations,missing-method, 334
plot,PseudoDualSimulationsSummary,missing-method, 337
plot,PseudoSimulationsSummary,missing-method, 341
plot,Samples,DALogisticLogNormal-method, 344
plot,Samples,DualEndpoint-method, 345
plot,Samples,GeneralModel-method, 347
plot,Samples,ModelEff-method, 348
plot,Samples,ModelTox-method, 349
plot,Samples,TwoDrugsCombo-method, 351
plot,SimulationsSummary,missing-method, 352

plot-ComboSimulations-missing (plot,ComboSimulations,missing-method), 312
plot-ComboSimulationsSummary-missing (plot,ComboSimulationsSummary,missing-method), 312
plot-Data (h_plot_data_dataordinal), 170
plot-DataCombo (plot,DataCombo,missing-method), 314
plot-DataDA (plot,DataDA,missing-method), 315
plot-DataDual (plot,DataDual,missing-method), 316
plot-DualSimulations-missing (plot,DualSimulations,missing-method), 318
plot-DualSimulationsSummary-missing (plot,DualSimulationsSummary,missing-method), 323
plot-GeneralSimulations-missing (plot,GeneralSimulations,missing-method), 326
plot-GeneralSimulationsSummary-missing (plot,GeneralSimulationsSummary,missing-method), 329
plot-HierarchicalData (plot,HierarchicalData,missing-method), 330
plot-PseudoDualFlexiSimulations-missing (plot,PseudoDualFlexiSimulations,missing-method), 331
plot-PseudoDualSimulations-missing (plot,PseudoDualSimulations,missing-method), 334
plot-PseudoDualSimulationsSummary-missing (plot,PseudoDualSimulationsSummary,missing-method), 337
plot-PseudoSimulationsSummary-missing (plot,PseudoSimulationsSummary,missing-method), 341
plot-SimulationsSummary-missing (plot,SimulationsSummary,missing-method), 352
plot.gtable, 354
plot.gtable(), *355*
plotDualResponses, 355
plotDualResponses,ModelTox,missing,ModelEff,missing-method (plotDualResponses), 355
plotDualResponses,ModelTox,Samples,ModelEff,Samples-method (plotDualResponses), 355
plotGain, 357
plotGain,ModelTox,missing,ModelEff,missing-method (plotGain), 358
plotGain,ModelTox,Samples,ModelEff,Samples-method (plotGain), 358
positive_number, *360*, 360
print.gtable (plot.gtable), 354
prob, 360
prob(), *76*, *100*, *113*, *364–366*
prob,matrix,TwoDrugsCombo,Samples-method (prob), 360
prob,numeric,DualEndpoint,Samples-method (prob), 360
prob,numeric,LogisticIndepBeta,missing-method (prob), 360
prob,numeric,LogisticIndepBeta,Samples-method (prob), 360
prob,numeric,LogisticKadane,Samples-method (prob), 360
prob,numeric,LogisticKadaneBetaGamma,Samples-method (prob), 360
prob,numeric,LogisticLogNormal,Samples-method (prob), 360
prob,numeric,LogisticLogNormalGrouped,Samples-method (prob), 360
prob,numeric,LogisticLogNormalMixture,Samples-method (prob), 360
prob,numeric,LogisticLogNormalOrdinal,Samples-method (prob), 360
prob,numeric,LogisticLogNormalSub,Samples-method (prob), 360
prob,numeric,LogisticNormal,Samples-method (prob), 360
prob,numeric,LogisticNormalFixedMixture,Samples-method (prob), 360
prob,numeric,LogisticNormalMixture,Samples-method (prob), 360
prob,numeric,OneParExpPrior,Samples-method (prob), 360
prob,numeric,OneParLogNormalPrior,Samples-method (prob), 360
prob,numeric,ProbitLogNormal,Samples-method (prob), 360

prob,numeric,ProbitLogNormalRel,Samples-method (prob), 360
prob,numeric,TwoDrugsCombo,Samples-method (prob), 360
prob-DualEndpoint (prob), 360
prob-LogisticIndepBeta (prob), 360
prob-LogisticIndepBeta-noSamples (prob), 360
prob-LogisticKadane (prob), 360
prob-LogisticKadaneBetaGamma (prob), 360
prob-LogisticLogNormal (prob), 360
prob-LogisticLogNormalGrouped (prob), 360
prob-LogisticLogNormalMixture (prob), 360
prob-LogisticLogNormalOrdinal (prob), 360
prob-LogisticLogNormalSub (prob), 360
prob-LogisticNormal (prob), 360
prob-LogisticNormalFixedMixture (prob), 360
prob-LogisticNormalMixture (prob), 360
prob-OneParExpPrior (prob), 360
prob-OneParLogNormalPrior (prob), 360
prob-ProbitLogNormal (prob), 360
prob-ProbitLogNormalRel (prob), 360
prob-TwoDrugsCombo (prob), 360
prob-TwoDrugsCombo-matrix (prob), 360
probFunction, 365
probFunction(), *78*, *364*
probFunction,GeneralModel-method (probFunction), 365
probFunction,LogisticLogNormalOrdinal-method (probFunction), 365
probFunction,ModelTox-method (probFunction), 365
probFunction-GeneralModel (probFunction), 365
probFunction-LogisticLogNormalOrdinal (probFunction), 365
probFunction-ModelTox (probFunction), 365
probit, 366
ProbitLogNormal, *219*, *224*, *225*, *254*, *367*, *369*
ProbitLogNormal (ProbitLogNormal-class), 367
ProbitLogNormal-class, 367
ProbitLogNormalLogDose (ProbitLogNormal-class), 367
ProbitLogNormalRel, *219*, *224*, *225*, *254*, *367*, *368*
ProbitLogNormalRel (ProbitLogNormalRel-class), 368
ProbitLogNormalRel-class, 368
PseudoDualFlexiSimulations, *331*, *430*, *560*
PseudoDualFlexiSimulations (PseudoDualFlexiSimulations-class), 369
PseudoDualFlexiSimulations-class, 369
PseudoDualSimulations, *334*, *369*, *427*, *430*, *560*
PseudoDualSimulations (PseudoDualSimulations-class), 370
PseudoDualSimulations-class, 370
PseudoDualSimulationsSummary, *337*, *510*, *513*
PseudoDualSimulationsSummary (PseudoDualSimulationsSummary-class), 371
PseudoDualSimulationsSummary-class, 371
PseudoSimulations, *371*, *373*, *438*, *440*, *560*
PseudoSimulations (PseudoSimulations-class), 372
PseudoSimulations-class, 372
PseudoSimulationsSummary, *342*, *371*, *516*
PseudoSimulationsSummary (PseudoSimulationsSummary-class), 374
PseudoSimulationsSummary-class, 374

Quantiles2LogisticNormal, *13*, 376
Quantiles2LogisticNormal(), *249*, *250*

rapply(), *175*
Recruitment, *239*, *378*, *379*, *561*
Recruitment (Recruitment-class), 378
Recruitment-class, 378
RecruitmentRatio, *239*, *378*, *561*
RecruitmentRatio (RecruitmentRatio-class), 378
RecruitmentRatio-class, 378
RecruitmentUnlimited, *239*, *378*, *379*

RecruitmentUnlimited (RecruitmentUnlimited-class), 379
RecruitmentUnlimited-class, 379
rjags, 249
rjags::jags.model(), 153, 154
rjags::jags.samples(), 152
rjags::mcarray.object, 152
RuleDesign, 61, 62, 89, 91, 106, 380, 435, 521, 523, 550
RuleDesign (RuleDesign-class), 380
RuleDesign-class, 380
RuleDesignOrdinal, 71, 381, 550
RuleDesignOrdinal (RuleDesignOrdinal-class), 381
RuleDesignOrdinal-class, 381

SafetyWindow, 383, 561, 564
SafetyWindow (SafetyWindow-class), 383
SafetyWindow-class, 383
SafetyWindowConst, 46, 383, 562
SafetyWindowConst (SafetyWindowConst-class), 383
SafetyWindowConst-class, 383
SafetyWindowSize, 383, 384, 562
SafetyWindowSize (SafetyWindowSize-class), 384
SafetyWindowSize-class, 384
Samples, 12, 18, 19, 113, 118, 131, 145, 243, 244, 345, 347, 348, 350, 351, 355, 356, 358, 386, 562
Samples (Samples-class), 385
Samples-class, 385
saveSample, 387
saveSample,McmcOptions-method (saveSample), 387
saveSample-McmcOptions (saveSample), 387
scenario, 388
scenario,DADesign,DataDA,McmcOptions-method (scenario), 388
scenario,Design,Data,McmcOptions-method (scenario), 388
scenario,DesignCombo,DataCombo,McmcOptions-method (scenario), 388
scenario,HierarchicalDesign,HierarchicalData,McmcOptions-method (scenario), 388
scenario-DADesign (scenario), 388
scenario-Design (scenario), 388
scenario-DesignCombo (scenario), 388
scenario-HierarchicalDesign (scenario), 388
set.seed, 128
set.seed(), 395
set_seed, 395
set_seed(), 411, 415, 418, 420, 423, 427, 430, 434, 435, 437, 440
show(), 142, 176
show,ComboSimulations-method, 396
show,ComboSimulationsSummary-method, 396
show,DualSimulationsSummary-method, 397
show,GeneralSimulations-method, 399
show,GeneralSimulationsSummary-method, 400
show,HierarchicalData-method, 400
show,HierarchicalDesign-method, 401
show,HierarchicalModel-method, 401
show,HierarchicalSimulations-method, 402
show,HierarchicalSimulationsSummary-method, 402
show,PseudoDualSimulationsSummary-method, 403
show,PseudoSimulationsSummary-method, 406
show,SimulationsSummary-method, 408
show-ComboSimulations (show,ComboSimulations-method), 396
show-ComboSimulationsSummary (show,ComboSimulationsSummary-method), 396
show-DualSimulationsSummary (show,DualSimulationsSummary-method), 397
show-GeneralSimulations (show,GeneralSimulations-method), 399
show-GeneralSimulationsSummary (show,GeneralSimulationsSummary-method), 400
show-HierarchicalData (show,HierarchicalData-method), 400
show-HierarchicalDesign (show,HierarchicalDesign-method),

401
show-HierarchicalModel (show,HierarchicalModel-method), 401
show-HierarchicalSimulations (show,HierarchicalSimulations-method), 402
show-HierarchicalSimulationsSummary (show,HierarchicalSimulationsSummary-method), 402
show-PseudoDualSimulationsSummary (show,PseudoDualSimulationsSummary-method), 403
show-PseudoSimulationsSummary (show,PseudoSimulationsSummary-method), 406
show-SimulationsSummary (show,SimulationsSummary-method), 408
simulate,DADesign-method, 410
simulate,Design-method, 414
simulate,DesignCombo-method, 417
simulate,DesignGrouped-method, 419
simulate,DualDesign-method, 422
simulate,DualResponsesDesign-method, 426
simulate,DualResponsesSamplesDesign-method, 429
simulate,HierarchicalDesign-method, 433
simulate,RuleDesign-method, 435
simulate,TDDesign-method, 436
simulate,TDsamplesDesign-method, 439
simulate-DesignGrouped (simulate,DesignGrouped-method), 419
Simulations, *41*, *50*, *93*, *133*, *412*, *416*, *420*, *442*, *551*
Simulations (Simulations-class), 442
Simulations-class, 442
SimulationsSummary, *95*, *352*, *518*
SimulationsSummary (SimulationsSummary-class), 444
SimulationsSummary-class, 444
singleDrugData, 445
singleDrugData,DataCombo-method (singleDrugData), 445
singleDrugData-DataCombo (singleDrugData), 445
size, 446
size,CohortSizeConst-method (size), 446
size,CohortSizeDLT-method (size), 446
size,CohortSizeMax-method (size), 446
size,CohortSizeMin-method (size), 446
size,CohortSizeOrdinal-method (size), 446
size,CohortSizeParts-method (size), 446
size,CohortSizeRandom-method (size), 446
size,CohortSizeRange-method (size), 446
size,McmcOptions-method (size), 446
size,Samples-method (size), 446
size-CohortSizeConst (size), 446
size-CohortSizeDLT (size), 446
size-CohortSizeMax (size), 446
size-CohortSizeMin (size), 446
size-CohortSizeOrdinal (size), 446
size-CohortSizeParts (size), 446
size-CohortSizeRandom (size), 446
size-CohortSizeRange (size), 446
size-McmcOptions (size), 446
size-Samples (size), 446
split(), *49*
Stopping, *455*, *563*
Stopping (Stopping-class), 455
Stopping-class, 455
StoppingAll, *456*, *564*, *568–570*
StoppingAll (StoppingAll-class), 456
StoppingAll-class, 456
StoppingAny, *310*, *311*, *457*
StoppingAny (StoppingAny-class), 457
StoppingAny-class, 457
StoppingCohortsNearDose, *456*, *458*, *563*
StoppingCohortsNearDose (StoppingCohortsNearDose-class), 458
StoppingCohortsNearDose-class, 458
StoppingExternal, *459*
StoppingExternal (StoppingExternal-class), 459
StoppingExternal-class, 459
StoppingHighestDose, *456*, *460*
StoppingHighestDose (StoppingHighestDose-class), 460
StoppingHighestDose-class, 460
StoppingList, *456*, *461*, *564*

StoppingList *(StoppingList-class)*, 461
StoppingList-class, 461
StoppingLowestDoseHSRBeta, *456*, *462*
StoppingLowestDoseHSRBeta *(StoppingLowestDoseHSRBeta-class)*, 462
StoppingLowestDoseHSRBeta-class, 462
StoppingMaxGainCIRatio, *463*
StoppingMaxGainCIRatio *(StoppingMaxGainCIRatio-class)*, 463
StoppingMaxGainCIRatio-class, 463
StoppingMinCohorts, *456*, *464*, *564*
StoppingMinCohorts *(StoppingMinCohorts-class)*, 464
StoppingMinCohorts-class, 464
StoppingMinPatients, *456*, *465*, *564*
StoppingMinPatients *(StoppingMinPatients-class)*, 465
StoppingMinPatients-class, 465
StoppingMissingDose, *466*
StoppingMissingDose *(StoppingMissingDose-class)*, 466
StoppingMissingDose-class, 466
StoppingMTDCV, *456*, *467*, *564*
StoppingMTDCV *(StoppingMTDCV-class)*, 467
StoppingMTDCV-class, 467
StoppingMTDdistribution, *456*, *468*, *564*
StoppingMTDdistribution *(StoppingMTDdistribution-class)*, 468
StoppingMTDdistribution-class, 468
StoppingOrdinal, *71*, *469*
StoppingOrdinal *(StoppingOrdinal-class)*, 469
StoppingOrdinal-class, 469
StoppingPatientsNearDose, *456*, *470*, *564*
StoppingPatientsNearDose *(StoppingPatientsNearDose-class)*, 470
StoppingPatientsNearDose-class, 470
StoppingSpecificDose, *456*, *471*
StoppingSpecificDose *(StoppingSpecificDose-class)*, 471
StoppingSpecificDose-class, 471
StoppingTargetBiomarker, *456*, *472*, *564*
StoppingTargetBiomarker *(StoppingTargetBiomarker-class)*, 472
StoppingTargetBiomarker-class, 472
StoppingTargetProb, *456*, *473*, *564*
StoppingTargetProb *(StoppingTargetProb-class)*, 473
StoppingTargetProb-class, 473
StoppingTDCIRatio, *474*, *480*, *564*
StoppingTDCIRatio *(StoppingTDCIRatio-class)*, 474
StoppingTDCIRatio-class, 474
stopTrial, 475
stopTrial,StoppingAll,ANY,ANY,ANY,ANY-method *(stopTrial)*, 475
stopTrial,StoppingAny,ANY,ANY,ANY,ANY-method *(stopTrial)*, 475
stopTrial,StoppingCohortsNearDose,numeric,ANY,ANY,GeneralD *(stopTrial)*, 475
stopTrial,StoppingExternal,numeric,ANY,ANY,ANY-method *(stopTrial)*, 475
stopTrial,StoppingHighestDose,numeric,ANY,ANY,GeneralData- *(stopTrial)*, 475
stopTrial,StoppingList,ANY,ANY,ANY,ANY-method *(stopTrial)*, 475
stopTrial,StoppingLowestDoseHSRBeta,numeric,Samples,Genera *(stopTrial)*, 475
stopTrial,StoppingMaxGainCIRatio,ANY,missing,ModelTox,Data *(stopTrial)*, 475
stopTrial,StoppingMaxGainCIRatio,ANY,Samples,ModelTox,Data *(stopTrial)*, 475
stopTrial,StoppingMinCohorts,ANY,ANY,ANY,GeneralData-metho *(stopTrial)*, 475
stopTrial,StoppingMinPatients,ANY,ANY,ANY,GeneralData-meth *(stopTrial)*, 475
stopTrial,StoppingMissingDose,numeric,ANY,ANY,GeneralData- *(stopTrial)*, 475
stopTrial,StoppingMTDCV,numeric,Samples,GeneralModel,ANY-m *(stopTrial)*, 475
stopTrial,StoppingMTDdistribution,numeric,Samples,GeneralM *(stopTrial)*, 475
stopTrial,StoppingOrdinal,numeric,ANY,ANY,ANY-method *(stopTrial)*, 475
stopTrial,StoppingOrdinal,numeric,ANY,LogisticLogNormalOrd *(stopTrial)*, 475
stopTrial,StoppingPatientsNearDose,numeric,ANY,ANY,General *(stopTrial)*, 475

stopTrial,StoppingSpecificDose,numeric,ANY,ANY,GeneralData-method (stopTrial), 475
stopTrial,StoppingTargetBiomarker,numeric,Samples,DualEndpoint,ANY-method (stopTrial), 475
stopTrial,StoppingTargetProb,numeric,Samples,GeneralModel,ANY-method (stopTrial), 475
stopTrial,StoppingTDCIRatio,ANY,missing,ModelTox,ANY-method (stopTrial), 475
stopTrial,StoppingTDCIRatio,ANY,Samples,ModelTox,ANY-method (stopTrial), 475
stopTrial-StoppingAll (stopTrial), 475
stopTrial-StoppingAny (stopTrial), 475
stopTrial-StoppingCohortsNearDose (stopTrial), 475
stopTrial-StoppingExternal (stopTrial), 475
stopTrial-StoppingHighestDose (stopTrial), 475
stopTrial-StoppingList (stopTrial), 475
stopTrial-StoppingLowestDoseHSRBeta (stopTrial), 475
stopTrial-StoppingMaxGainCIRatio (stopTrial), 475
stopTrial-StoppingMinCohorts (stopTrial), 475
stopTrial-StoppingMinPatients (stopTrial), 475
stopTrial-StoppingMissingDose (stopTrial), 475
stopTrial-StoppingMTDCV (stopTrial), 475
stopTrial-StoppingMTDdistribution (stopTrial), 475
stopTrial-StoppingOrdinal (stopTrial), 475
stopTrial-StoppingPatientsNearDose (stopTrial), 475
stopTrial-StoppingSpecificDose (stopTrial), 475
stopTrial-StoppingTargetBiomarker (stopTrial), 475
stopTrial-StoppingTargetProb (stopTrial), 475
stopTrial-StoppingTDCIRatio (stopTrial), 475
subset-Data, 504
summary,ComboSimulations-method, 504
summary,DualSimulations-method, 505
summary,GeneralSimulations-method, 508
summary,HierarchicalSimulations-method, 508
summary,PseudoDualFlexiSimulations-method, 509
summary,PseudoDualSimulations-method, 512
summary,PseudoSimulations-method, 515
summary,Simulations-method, 518
summary-ComboSimulations (summary,ComboSimulations-method), 504
summary-DualSimulations (summary,DualSimulations-method), 505
summary-GeneralSimulations (summary,GeneralSimulations-method), 508
summary-HierarchicalSimulations (summary,HierarchicalSimulations-method), 508
summary-PseudoDualFlexiSimulations (summary,PseudoDualFlexiSimulations-method), 509
summary-PseudoDualSimulations (summary,PseudoDualSimulations-method), 512
summary-PseudoSimulations (summary,PseudoSimulations-method), 515
summary-Simulations (summary,Simulations-method), 518

TDDesign, *90*, *437*, *520*
TDDesign (TDDesign-class), 520
TDDesign-class, 520
TDsamplesDesign, *89*, *91*, *439*, *440*, *522*
TDsamplesDesign (TDsamplesDesign-class), 522
TDsamplesDesign-class, 522
tempdir(), *156*
test_format (check_format), 24
test_length (check_length), 26
test_probabilities (check_probabilities), 27
test_probability (check_probability), 29
test_probability_range (check_probability_range), 30
test_range (check_range), 32

ThreePlusThreeDesign (RuleDesign-class), 380
tibble, *528*
tidy, 524
tidy,ArmConditionList-method (tidy), 524
tidy,CohortSizeDLT-method (tidy), 524
tidy,CohortSizeMax-method (tidy), 524
tidy,CohortSizeMin-method (tidy), 524
tidy,CohortSizeParts-method (tidy), 524
tidy,CohortSizeRange-method (tidy), 524
tidy,ComboSimulations-method (tidy), 524
tidy,CrmPackClass-method (tidy), 524
tidy,Data-method (tidy), 524
tidy,DataCombo-method (tidy), 524
tidy,DataDA-method (tidy), 524
tidy,DataDual-method (tidy), 524
tidy,DataGrouped-method (tidy), 524
tidy,DataMixture-method (tidy), 524
tidy,DataOrdinal-method (tidy), 524
tidy,DataParts-method (tidy), 524
tidy,DesignArm-method (tidy), 524
tidy,DesignCombo-method (tidy), 524
tidy,DualDesign-method (tidy), 524
tidy,Effloglog-method (tidy), 524
tidy,GeneralData-method (tidy), 524
tidy,HierarchicalData-method (tidy), 524
tidy,HierarchicalDesign-method (tidy), 524
tidy,HierarchicalModel-method (tidy), 524
tidy,HierarchicalSamples-method (tidy), 524
tidy,HierarchicalSimulations-method (tidy), 524
tidy,IncrementsMaxToxProb-method (tidy), 524
tidy,IncrementsMin-method (tidy), 524
tidy,IncrementsRelative-method (tidy), 524
tidy,IncrementsRelativeDLT-method (tidy), 524
tidy,IncrementsRelativeParts-method (tidy), 524
tidy,LogisticIndepBeta-method (tidy), 524
tidy,NextBestNCRM-method (tidy), 524
tidy,NextBestNCRMLoss-method (tidy), 524
tidy,Samples-method (tidy), 524
tidy,Simulations-method (tidy), 524
tidy-ArmConditionList (tidy), 524
tidy-CohortSizeDLT (tidy), 524
tidy-CohortSizeMax (tidy), 524
tidy-CohortSizeMin (tidy), 524
tidy-CohortSizeParts (tidy), 524
tidy-CohortSizeRange (tidy), 524
tidy-ComboSimulations (tidy), 524
tidy-CrmPackClass (tidy), 524
tidy-Data (tidy), 524
tidy-DataCombo (tidy), 524
tidy-DataDA (tidy), 524
tidy-DataDual (tidy), 524
tidy-DataGrouped (tidy), 524
tidy-DataMixture (tidy), 524
tidy-DataOrdinal (tidy), 524
tidy-DataParts (tidy), 524
tidy-DesignArm (tidy), 524
tidy-DesignCombo (tidy), 524
tidy-DualDesign (tidy), 524
tidy-Effloglog (tidy), 524
tidy-GeneralData (tidy), 524
tidy-HierarchicalData (tidy), 524
tidy-HierarchicalDesign (tidy), 524
tidy-HierarchicalModel (tidy), 524
tidy-HierarchicalSamples (tidy), 524
tidy-HierarchicalSimulations (tidy), 524
tidy-IncrementsMaxToxProb (tidy), 524
tidy-IncrementsMin (tidy), 524
tidy-IncrementsRelative (tidy), 524
tidy-IncrementsRelativeDLT (tidy), 524
tidy-IncrementsRelativeParts (tidy), 524
tidy-LogisticIndepBeta (tidy), 524
tidy-NextBestNCRM (tidy), 524
tidy-NextBestNCRMLoss (tidy), 524
tidy-Samples (tidy), 524
tidy-Simulations (tidy), 524
TITELogisticLogNormal, *46*, *123*, *530*, *533*, *556*
TITELogisticLogNormal (TITELogisticLogNormal-class), 530
TITELogisticLogNormal-class, 530
TITELogisticLogNormalSub, *46*, *531*, *532*
TITELogisticLogNormalSub (TITELogisticLogNormalSub-class), 532
TITELogisticLogNormalSub-class, 532

TwoDrugsCombo, *66*, *136*, *137*, *243*, *351*, *363*, *533*, *556*
TwoDrugsCombo *(*TwoDrugsCombo-class*)*, 533
TwoDrugsCombo-class, 533

update,Data-method, 535
update,DataCombo-method, 536
update,DataDA-method, 538
update,DataDual-method, 539
update,DataOrdinal-method, 540
update,DataParts-method, 542
update,HierarchicalData-method, 543
update,ModelPseudo-method, 543
update-Data *(*update,Data-method*)*, 535
update-DataCombo *(*update,DataCombo-method*)*, 536
update-DataDA *(*update,DataDA-method*)*, 538
update-DataDual *(*update,DataDual-method*)*, 539
update-DataOrdinal *(*update,DataOrdinal-method*)*, 540
update-DataParts *(*update,DataParts-method*)*, 542
update-HierarchicalData *(*update,HierarchicalData-method*)*, 543
update-ModelPseudo *(*update,ModelPseudo-method*)*, 543

v_arm_condition, 546
v_arm_finished_condition *(*v_arm_condition*)*, 546
v_arm_min_dose_condition *(*v_arm_condition*)*, 546
v_backfill, 546
v_cohort_size, 547
v_cohort_size_const *(*v_cohort_size*)*, 547
v_cohort_size_dlt *(*v_cohort_size*)*, 547
v_cohort_size_max *(*v_cohort_size*)*, 547
v_cohort_size_ordinal *(*v_increments*)*, 552
v_cohort_size_parts *(*v_cohort_size*)*, 547
v_cohort_size_random *(*v_cohort_size*)*, 547
v_cohort_size_range *(*v_cohort_size*)*, 547
v_combo_simulations *(*v_general_simulations*)*, 551
v_da_simulations *(*v_general_simulations*)*, 551
v_data *(*v_data_objects*)*, 548
v_data_combo *(*v_data_objects*)*, 548
v_data_da *(*v_data_objects*)*, 548
v_data_dual *(*v_data_objects*)*, 548
v_data_grouped *(*v_data_objects*)*, 548
v_data_mixture *(*v_data_objects*)*, 548
v_data_objects, 548
v_data_ordinal *(*v_data_objects*)*, 548
v_data_parts *(*v_data_objects*)*, 548
v_design, 550
v_design_arm *(*v_hierarchical_design*)*, 552
v_design_combo *(*v_design*)*, 550
v_design_grouped *(*v_design*)*, 550
v_dual_simulations *(*v_general_simulations*)*, 551
v_general_data *(*v_data_objects*)*, 548
v_general_model *(*v_model_objects*)*, 554
v_general_simulations, 551
v_hierarchical_data *(*v_data_objects*)*, 548
v_hierarchical_design, 552
v_hierarchical_model *(*v_model_objects*)*, 554
v_hierarchical_samples *(*v_samples_objects*)*, 562
v_hierarchical_simulations *(*v_general_simulations*)*, 551
v_increments, 552
v_increments_dose_levels *(*v_increments*)*, 552
v_increments_hsr_beta *(*v_increments*)*, 552
v_increments_maxtoxprob *(*v_increments*)*, 552
v_increments_min *(*v_increments*)*, 552
v_increments_ordinal *(*v_increments*)*, 552
v_increments_relative *(*v_increments*)*, 552
v_increments_relative_dlt *(*v_increments*)*, 552
v_increments_relative_parts *(*v_increments*)*, 552
v_logisticlognormalordinal

(v_model_objects), 554
v_mcmc_options (v_mcmcoptions_objects), 554
v_mcmcoptions_objects, 554
v_model_da_logistic_log_normal (v_model_objects), 554
v_model_dual_endpoint (v_model_objects), 554
v_model_dual_endpoint_beta (v_model_objects), 554
v_model_dual_endpoint_emax (v_model_objects), 554
v_model_dual_endpoint_rw (v_model_objects), 554
v_model_eff_flexi (v_model_objects), 554
v_model_eff_log_log (v_model_objects), 554
v_model_logistic_indep_beta (v_model_objects), 554
v_model_logistic_kadane (v_model_objects), 554
v_model_logistic_kadane_beta_gamma (v_model_objects), 554
v_model_logistic_log_normal_mix (v_model_objects), 554
v_model_logistic_normal_fixed_mix (v_model_objects), 554
v_model_logistic_normal_mix (v_model_objects), 554
v_model_objects, 554
v_model_one_par_exp_normal_prior (v_model_objects), 554
v_model_one_par_exp_prior (v_model_objects), 554
v_model_params, 557
v_model_params_normal (v_model_params), 557
v_model_tite_logistic_log_normal (v_model_objects), 554
v_model_two_drugs_combo (v_model_objects), 554
v_next_best, 557
v_next_best_dual_endpoint (v_next_best), 557
v_next_best_ewoc (v_next_best), 557
v_next_best_inf_theory (v_next_best), 557
v_next_best_max_gain_samples (v_next_best), 557
v_next_best_min_dist (v_next_best), 557
v_next_best_mtd (v_next_best), 557
v_next_best_ncrm (v_next_best), 557
v_next_best_ncrm_loss (v_next_best), 557
v_next_best_ordinal (v_next_best), 557
v_next_best_prob_mtd_lte (v_next_best), 557
v_next_best_prob_mtd_min_dist (v_next_best), 557
v_next_best_td (v_next_best), 557
v_next_best_td_samples (v_next_best), 557
v_opening, 559
v_opening_min_cohorts (v_opening), 559
v_opening_min_dose (v_opening), 559
v_opening_min_responses (v_opening), 559
v_pseudo_dual_flex_simulations (v_pseudo_simulations), 560
v_pseudo_dual_simulations (v_pseudo_simulations), 560
v_pseudo_simulations, 560
v_recruitment, 561
v_recruitment_ratio (v_recruitment), 561
v_rule_design (v_design), 550
v_rule_design_ordinal (v_design), 550
v_safety_window, 561
v_safety_window_const (v_safety_window), 561
v_safety_window_size (v_safety_window), 561
v_samples (v_samples_objects), 562
v_samples_objects, 562
v_simulations (v_general_simulations), 551
v_stopping, 563
v_stopping_all (v_stopping), 563
v_stopping_cohorts_near_dose (v_stopping), 563
v_stopping_list (v_stopping), 563
v_stopping_min_cohorts (v_stopping), 563
v_stopping_min_patients (v_stopping), 563
v_stopping_mtd_cv (v_stopping), 563
v_stopping_mtd_distribution (v_stopping), 563
v_stopping_patients_near_dose (v_stopping), 563

v_stopping_target_biomarker
(v_stopping), 563
v_stopping_target_prob (v_stopping), 563
v_stopping_tdci_ratio (v_stopping), 563
Validate, *545*, 545
Validate(), *178, 179*
vname, *23*, *25, 26*, *28–31*, *33*

windowLength, 564
windowLength,SafetyWindowConst-method
(windowLength), 564
windowLength,SafetyWindowSize-method
(windowLength), 564
windowLength-SafetyWindowConst
(windowLength), 564
windowLength-SafetyWindowSize
(windowLength), 564