Package 'NMAoutlier'

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Title Detecting Outliers in Network Meta-Analysis

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Author Maria Petropoulou [aut, cre] (<https://orcid.org/0000-0002-7147-3644>), Guido Schwarzer [aut] (<https://orcid.org/0000-0001-6214-9087>), Agapios Panos [aut], Dimitris Mavridis [aut] (<https://orcid.org/0000-0003-1041-4592>)

Maintainer Maria Petropoulou <petropoulou@imbi.uni-freiburg.de>

URL https://github.com/petropouloumaria/NMAoutlier

Description A set of functions providing several outlier (i.e., studies with extreme findings) and influential detection measures and methodologies in network meta-analysis :
- simple outlier and influential detection measures
- outlier and influential detection measures by considering study deletion (shift the mean)
- plots for outlier and influential detection measures
- Q-Q plot for network meta-analysis
- Forward Search algorithm in network meta-analysis.
- forward plots to monitor statistics in each step of the forward search algorithm
- forward plots for summary estimates and their confidence intervals in each step of forward search algorithm.

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Contents

`NMAoutlier-package` *NMAoutlier: Brief overview of measures and methodologies for detection of outlying and influential studies in network meta-analysis.*

Description

R package **NMAoutlier** provides methods and tools to detect outlier and influential studies in network meta-analysis.

Details

R package **NMAoutlier** is a tool to detect outliers (studies with extreme results) and influential studies in network meta-analysis (Petropoulou, 2020). The package can calculate: simple outlier and influential measures; outlier and influential measures considered study deletion (shift the mean); the outlier detection methodology with Forward Search (FS) algorithm (Petropoulou et al., 2021). All proposed outlier and influential detection methods were fitted the frequentist NMA model by graph theory introduced by Rücker (2012) and implemented inR package **netmeta**.

The **NMAoutlier** package implements the following methods described in Petropoulou (2020).

- **Simple outlier and influential detection measures** (function `NMAoutlier.measures`):
  1. raw residuals,
  2. standardized residuals,
  3. studentized residuals,
  4. Mahalanobis distance,
  5. leverage;
- **Outlier and influential detection measures considered study deletion (shift the mean)** (function `NMAoutlier.measures`):
  1. raw deleted residuals,
  2. standardized deleted residuals,
  3. studentized deleted residuals,
  4. Cook's distance,
  5. COVRATIO,

6. weight leave one out,
7. leverage leave one out,
8. heterogeneity leave one out,
9. R heterogeneity,
10. R Qtotal,
11. R Qheterogeneity,
12. R Qinconsistency,
13. DFBETAS;

- Plots of the several outlier and influential detection (simple and deletion) measures (function (`measplot`));
- Q-Q plot for network meta-analysis (function `Qnetplot`);
- **Forward Search algorithm in network meta-analysis** (function (`NMAoutlier`)) based on Petropoulou et al. (2021);
- forward plots (`fwdplot`) with monitoring statistics in each step of the FS algorithm:
  1. P-scores (Rücker & Schwarzer, 2015),
  2. z-values for difference of direct and indirect evidence with back-calculation method (König et al., 2013; Dias et al., 2010),
  3. standardized residuals,
  4. heterogeneity variance estimator,
  5. Cook's distance,
  6. ratio of variances,
  7. Q statistics (Krahn et al., 2013);
- forward plots (`fwdplotest`) for summary treatment estimates in each iteration of the FS algorithm (Petropoulou et al., 2021).

Type `help(package = "NMAoutlier")` for a listing of R functions available in **NMAoutlier**.

Type `citation("NMAoutlier")` on how to cite **NMAoutlier** in publications.

To report problems and bugs, please send an email to Dr. Maria Petropoulou <petropoulou@imbi.uni-freiburg.de>.

The development version of **NMAoutlier** is available on GitHub https://github.com/petropouloumaria/NMAoutlier.

Author(s)

Petropoulou Maria <petropoulou@imbi.uni-freiburg.de>.

References

Dias S, Welton NJ, Caldwell DM, Ades AE (2010): Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine*, **29**, 932–44

König J, Krahn U, Binder H (2013): Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. *Statistics in Medicine*, **32**, 5414–29

Krahn U, Binder H, König J (2013): A graphical tool for locating inconsistency in network meta-analyses. *BMC Medical Research Methodology*, **13**, 35

Petropoulou M (2020): Exploring methodological challenges in network meta-analysis models and developing methodology for outlier detection. *PhD dissertation*

Petropoulou M, Salanti G, Rücker G, Schwarzer G, Moustaki I, Mavridis D (2021): A forward search algorithm for detecting extreme study effects in network meta-analysis. *Statistics in Medicine*

Rücker G (2012): Network meta-analysis, electrical networks and graph theory. *Research Synthesis Methods*, **3**, 312–24

Rücker G, Schwarzer G (2015): Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Medical Research Methodology*, **15**, 58

`fwdplot` *Forward plot(s) to monitor selected statistic(s)/method(s)*

Description

This function generates forward plot(s) to monitor selected statistic(s) and/or method(s). The function creates a plot of the selected monitoring measure throughout the iterations of the Forward Search algorithm. Candidate statistics to be monitored can be: P-score; z-values by back-calculation method to derive indirect estimates from direct pairwise comparisons and network estimates; standardized residuals; heterogeneity variance estimator; Cook's distance; ratio of variances; Q statistics (Overall heterogeneity / inconsistency Q statistic (`Q`), overall heterogeneity Q statistic (`Q`), between-designs Q statistic (`Q`), based on a random effects design-by-treatment interaction model).

Usage

```
fwdplot(x, stat, select.st = NULL)
```

Arguments

`x`	an object of class NMAoutlier (mandatory).
`stat`	statistical measure to be monitored in forward plot(s) (mandatory), available choices are: "pscore", "nsplit", "estand", "heterog", "cook", "ratio", or "Q" (can be abbreviated).
`select.st`	selected statistic (pscore/nsplit/estand) for selected treatment(s)/comparison(s)/study

Details

Plot of statistical measures for each iteration of search. Vertical axis provides the FS iterations. Horizontal axis provides the values of the monitoring statistical measure.

Author(s)

Maria Petropoulou <petropoulou@imbi.uni-freiburg.de>

Examples

```
## Not run:
data(smokingcessation, package = "netmeta")
smokingcessation$id <- 1:nrow(smokingcessation)

study912 <- subset(smokingcessation, id %in% 9:12)
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data = study912,
                        sm = "OR")

# Forward search algorithm
#
FSresult <- NMAoutlier(p1, P = 1, small.values = "bad", n_cores = 2)

# forward plot for Cook's distance
fwdplot(FSresult, "cook")

data(smokingcessation, package = "netmeta")

# Transform data from arm-based to contrast-based format
# Use 'sm' argument for odds ratios.
# Use function pairwise from netmeta package

p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data=smokingcessation,
                        sm="OR")

# Forward Search algorithm
FSresult <- NMAoutlier(p1, small.values = "bad")
FSresult

# forward plot for Cook's distance
fwdplot(FSresult, "cook")

# forward plot for ratio of variances
fwdplot(FSresult, "ratio")

# forward plot for heterogeneity estimator
fwdplot(FSresult, "heterog")

# forward plot for Q statistics
fwdplot(FSresult, "Q")

# forward plot for P-scores
fwdplot(FSresult, "pscore")

# forward plot monitoring P-scores for treatment A
fwdplot(FSresult,"pscore", "A")
```

```
# forward plot for z-values of disagreement of direct and indirect evidence
fwdplot(FSresult, "nsplit")

# forward plot for z-values of disagreement of direct and indirect evidence
# monitoring treatment comparison A versus B
fwdplot(FSresult, "nsplit", "A:B")

# forward plot for standardized residual for study 4
fwdplot(FSresult, "estand", 4)

## End(Not run)
```

`fwdplotest` *Forward plots of summary treatment estimates*

Description

Forward plots of summary treatment estimates with their 95 percent confidence intervals.

Usage

```
fwdplotest(x)
```

Arguments

x	object of class NMAoutlier (mandatory).

Details

Plot of summary treatment estimates and their confidence intervals for each FS iteration. Vertical axis provides the FS iterations. Horizontal axis provides summary treatment estimates.

Author(s)

Maria Petropoulou <petropoulou@imbi.uni-freiburg.de>

Examples

```
## Not run:
data(smokingcessation, package = "netmeta")
smokingcessation$id <- 1:nrow(smokingcessation)

study912 <- subset(smokingcessation, id %in% 9:12)
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data = study912,
                        sm = "OR")
```

```
# Forward search algorithm
#
FSresult <- NMAoutlier(p1, P = 1, small.values = "bad", n_cores = 2)

# Forward plot for summary treatment estimates and their confidence
# intervals
#
fwdplotest(FSresult)

data(smokingcessation, package = "netmeta")

# Transform data from arm-based format to contrast-based format
# We use 'sm' argument for odds ratios.
# We use function pairwise from netmeta package
#
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data=smokingcessation,
                        sm="OR")

# forward search algorithm
FSresult <- NMAoutlier(p1, small.values = "bad")

# Forward plot for summary treatment estimates
# and their confidence intervals
fwdplotest(FSresult)

## End(Not run)
```

`Gupta2013` *Network meta-analysis comparing interventions for actinic keratosis*

Description

Network meta-analysis dataset for comparing interventions for actinic keratosis.

Format

A data frame in contrast format with the following columns:

logOR	log odds ratio
selogOR	standard error of log odds ratio
id	study ID
t1	first treatment
t2	second treatment

Details

The dataset compares the relative effects of nine interventions:

- placebo / vehicle (including placebo-PDT) (treatment 1),
- diclofenac 3 percent in 2.5 percent hyaluronic acid (DCF/HA) (treatment 2),
- 5-fluorouracil (5-FU) 0.5 percent (treatment 3),
- imiquimod (IMI) 5 percent (treatment 4),
- methyl aminolaevulinate (MAL)-PDT (treatment 5),
- 5-aminolaevulinic acid (ALA)-photodynamic therapy (PDT) (treatment 6),
- 5-fluorouracil (5-FU) 5.0 percent (treatment 7),
- cryotherapy (treatment 8),
- ingenol mebutate (IMB) 0.015-0.05 percent (treatment 9).

The outcome is the number of individuals with participant complete clearance or equivalent efficacy. These data are in contrast format with effect size the odds ratio (OR). The arm-level data were used in Gupta and Paquet (2013).

Source

Gupta AK, Paquet M (2013): Network meta-analysis of the outcome participant complete clearance in nonimmunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review. *British Journal of Dermatology*, **169**, 250–9

Examples

```
data(Gupta2013)
# Conduct forward search algorithm for the network of actinic keratosis
#
FSresult <- NMAoutlier(logOR, selogOR, t1, t2, id, data = Gupta2013, n_cores = 2)

# Plovide the forward plot for z-values from difference of direct and
# indirect evidence
#
fwdplot(FSresult, "nsplit")

# Provide forward plot for Q statistic
#
fwdplot(FSresult, "Q")
```

`measplot` *Plot(s) to monitor selected outlier and influential measure(s).*

Description

This function generates plot(s) of the selected outlier detection measure(s) for each study included in the network. Candidate statistics to be monitored are: Standardized residual; Studentized residual; Mahalanobis distance and leverage.

The function also generates plot(s) of the selected outlier detection measure(s) considering a deletion of each study included in the network (Shift the mean measures). Candidate statistics to be monitored are: Standardized deleted residual; Studentized deleted residual; Cook distance between the treatment estimates for study j and treatment estimates when study j is removed; Ratio of determinants of variance-covariance matrix of treatment estimates for study j to treatment estimates when study j is removed; weight leave one out;leverage leave one out; heterogeneity estimator leave one out; R statistic for heterogeneity; R statistic for Q (`Qtotal`), R statistic for heterogeneity Q (`Qhet`), R statistic for Qinconsistency (`Qinc`), DFbetas.

Usage

```
measplot(object, stat, measure = "simple")
```

Arguments

`object`	an object of class NMAoutlier.measures (mandatory).
`stat`	selected statistical outlier and influential detection measure (mandatory), For simply outlier and influential measures available choices are: ("estand"/ "estud"/ "mah"/ "leverage"). For outlier and influential deletion measures available choices are: ("estand.deleted", "estud.deleted", "leverage.leaveoneout", "weight.leaveoneout", "heterog.leaveoneout", "covratio", "cook", "rheterogeneity", "restimates", "rqhet", "rqinc", "rqtotal", "dfbetas")
`measure`	Outlier and influential detection measures. Simple measures (default: "simple") and measures considered study deletion (measure = "deletion").

Details

Plot of outlier and influential (simple or/and deletion) detection measures for each study included in the network. Vertical axis provides each study included in the network (or the study deleted for outlier deletion measures). Horizontal axis provides a monitoring outlier and influential detection measure.

Author(s)

Maria Petropoulou <petropoulou@imbi.uni-freiburg.de>

Examples

```
data(smokingcessation, package = "netmeta")
smokingcessation$id <- 1:nrow(smokingcessation)

study912 <- subset(smokingcessation, id %in% 9:12)
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data = study912,
                        sm = "OR")

# Outlier and influential detection measures for each study in the
# network
measures <- NMAoutlier.measures(p1)

# plot of standardized residuals for each study
measplot(measures, "estand")

# plot of Mahalanobis distance values for each study
measplot(measures, "mah")

# plot of leverage values for each study
measplot(measures, "leverage")

## Not run:
# Outlier detection measures considered deletion each time of an
# included study
deletion <- NMAoutlier.measures(p1, measure = "deletion")

# plot for R statistic for heterogeneity estimator
measplot(deletion, "rheterogeneity", measure = "deletion")

# plot for R statistic for Qinconsistency
measplot(deletion, "rqinc", measure = "deletion")

# plot of COVRATIO values when considering deletion for each study
measplot(deletion, "covratio", measure = "deletion")

## End(Not run)
```

`NMAoutlier` *Forward Search algorithm in network meta-analysis*

Description

This function employs the Forward Search algorithm to detect outliers and influential studies fitted in network meta-analysis model from graph-theory. This is an outlying diagnostic tool to detect outliers and studies that are potential sources for heterogeneity and inconsistency in network meta-analysis.

Monitoring measures during the search are:

- outlier detection measures (standardized residuals, Cook's distance, ratio of variance);
- ranking measures (P-scores);
- heterogeneity and inconsistency measures (Q statistics for overall heterogeneity / inconsistency, inconsistency by design-by-treatment interaction model, z-values for comparison between direct and indirect evidence by back-calculation method).

A description of the outlier detection methodology can be found in Petropoulou et al. (2021).

Usage

```
NMAoutlier(
  TE,
  seTE,
  treat1,
  treat2,
  studlab,
  data = NULL,
  crit1 = "R",
  crit2 = "R",
  studies = NULL,
  P = 100,
  sm,
  Isub = NULL,
  reference = "",
  small.values = "good",
  n_cores = NULL,
  ...
)
```

Arguments

TE	Estimate of treatment effect, i.e. difference between first and second treatment (e.g. log odds ratio, mean difference, or log hazard ratio). This can also be a pairwise object (i.e. the result of pairwise function of netmeta package). In this case, the pairwise object should include the following: TE, seTE, treat1, treat2, studlab
seTE	Standard error of treatment estimate.
treat1	Label/Number for first treatment.
treat2	Label/Number for second treatment.
studlab	Study labels (important when multi arm studies are included).
data	A data frame containing the study information.
crit1	A character string indicating the criterion to be used for selecting the initial subset, this criterion may be the minimum of median absolute residuals ("R") or the maximum of median absolute likelihood contributions ("L"). Default value is "R".

crit2	A character string indicating the criterion to be used for selecting the study entered from non-basic set to basic set, this criterion may be the minimum of absolute residuals ("R") or the maximum of absolute likelihood contributions ("L"). Default value is "R".
studies	An optional vector specifying the number of the initial subset of studies. The default value is the maximum of the number of treatments and the 20 percent of the total number of studies.
P	An optional vector specifying the number of candidate sample of studies (with length equal to studies) for the choice of the initial subset. Default value is 100.
sm	A character string indicating underlying summary measure, e.g., "RD", "RR", "OR", "ASD", "HR", "MD", "SMD", or "ROM".
Isub	A vector for the studies to be included in the initial subset (default: NULL, the initial subset not specified by the user).
reference	Reference treatment group.
small.values	A character string indicating if small values are considered beneficial (option:"good") or harmfull (option:"bad") on outcome. This is requirement for p-scores computation. The default value is considered benefial outcome ("good").
n_cores	The number of cores that the process is running using the parallel (default: NULL, the process is running using all the available cores)
...	Additional arguments passed on to netmeta.

Details

FS algorithm for network meta-analysis model from graph theory is described in Petropoulou et al. (2021).

Let n be the number of treatments and let m be the number of pairwise treatment comparisons. If there are only two-arm studies, m is equal to the number of studies. Let TE and seTE be the vectors of observed effects and their standard errors. Comparisons belonging to multi-arm studies are identified by identical study labels (argument studlab).

The FS algorithm is an outlier diagnostic iterative procedure. FS algorithm apart from three steps. It starts with a subset of studies and it gradually adds studies until all studies entered. After the search, statistical measures are monitored for sharp changes.

In more detail, the FS algorithm starts with an initial subset of the dataset with size l. Let (argument P) (eg. $P = 100$) a large number of candidate subset of studies with size l. The candidate subset that optimize the criterion (argument crit1) is taken as the initial subset (considered ideally to be outlying-free). Criterion (crit1) to be used for selecting the initial subset, can be the minimum of median absolute residuals "R" or the maximum of median absolute likelihood contributions "L". It is conventionally refer this subset as basic set, whereas the remaining studies constitute the non-basic set.

The FS algorithm gradually adds studies from the non-basic to the basic subset based on how close the former studies are to the hypothesized model fit in the basic set. A study from non-basic set entered into the basic set if optimize the criterion (argument crit2). Criterion (crit2) for selecting the study from non-basic to basic set may be the minimum of median absolute residuals "R" or the maximum of median absolute likelihood contributions "L". The algorithm order the studies

according to their closeness to the basic set by adding the study that optimize the criterion from non-basic set to basic set.

The process is repeated until all studies are entered into the basic set. The number of iterations of algorithm *index* is equal to the total number of studies minus the number of studies entered into the initial subset. Through the FS procedure, parameter estimates (summary estmates, heterogeneity estimator) and other statistics of interest (outlying measures, heterogeneity and inconsistency measures, ranking measures) are monitored. In each iteration, network meta-analysis model from graph theory (Rücker, 2012) is fitted (`netmeta` function) with R package **netmeta**.

Monitoring statistical measures for each FS iteration can be:

Outlying detection measures: Standardized residuals (arithmetic mean in case of multi-arm studies); Cook's statistic; Ratio of determinants of variance-covariance matrix

Ranking measures: P-scores for ranking of treatments (Rücker G & Schwarzer G, 2015) for each basic set with implementation of (`netrank` function) from R package **netmeta**.

Heterogeneity and inconsistency measures: Overall heterogeneity / inconsistency Q statistic (`Q`) This is the design-based decomposition of Cochran Q as provided by Krahn et al. (2013); Overall heterogeneity Q statistic (`Q`); Between-designs Q statistic (`Q`), based on a random effects model with square-root of between-study variance estimated embedded in a full design-by-treatment interaction model. Implementation with (`decomp.design` function) from R package **netmeta**; Z-values (Dias et al., 2010; König et al., 2013) for comparison between direct and indirect evidence in each iteration of forward search algorithm. By monitoring difference of direct and indirect evidence, potential sources of consistency can be detected with the implementation of (`netsplit` function) from R package **netmeta** for each iteration of the search.

Value

An object of class `NMAoutlier`; a list containing the following components:

`dat`	Matrix containing the data `"TE"`, `"seTE"`, `"studlab"`, `"treat1"`, `"treat2"` as defined above.
`length.initial`	The number of studies that constitute the initial (outlying-clean) subset of studies.
`index`	The number of iterations of forward search algorithm.
`basic`	Studies entered into the basic set in each iteration of the search. At the first iteration, basic set constitute the studies that are included in the basic-initial subset. The number of studies in the first iteration is equal to length.initial.
`taub`	Heterogeneity estimator variance for basic set in each iteration of forward search algorithm.
`Qb`	Overall heterogeneity - inconsistency Q statistic (`Q`) for the basic set in each iteration of forward search algorithm.
`Qhb`	Overall heterogeneity Q statistic (`Q`) for the basic set in each iteration of forward search algorithm.
`Qib`	Overall inconsistency Q statistic (`Q`) from design-by-treatment interaction model for the basic set in each iteration of forward search algorithm.
`estb`	Summary estimates for each treatment for the basic set in each iteration of forward search algorithm.

lb	Lower 95% confidence interval of summary estimates for the basic set in each iteration of forward search algorithm.
ub	Upper 95% confidence interval of summary estimates for the basic set in each iteration of forward search algorithm.
Ratio	Ratio of determinants (COVRATIOj) of variance-covariance matrix of treatment estimates at iteration j to that iteration at (j-1).
cook_d	Cook's statistic (Cj) at iteration j of forward search algorithm.
p.score	P-score for ranking each treatment for the basic set in each iteration of forward search algorithm.
dif	Z-values for comparison between direct and indirect evidence for each iteration of forward search algorithm. Based on back-calculation method to derive indirect estimates from direct pairwise comparisons and network estimates.
estand	Standardized residuals for each study for the basic set in each iteration of forward search algorithm.
call	Function call

Author(s)

Maria Petropoulou <petropoulou@imbi.uni-freiburg.de>

References

Dias S, Welton NJ, Caldwell DM, Ades AE (2010): Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine*, **29**, 932–44

König J, Krahn U, Binder H (2013): Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. *Statistics in Medicine*, **32**, 5414–29

Krahn U, Binder H, König J (2013): A graphical tool for locating inconsistency in network meta-analyses. *BMC Medical Research Methodology*, **13**, 35

Petropoulou M, Salanti G, Rücker G, Schwarzer G, Moustaki I, Mavridis D (2021): A forward search algorithm for detecting extreme study effects in network meta-analysis. *Statistics in Medicine*

Rücker G (2012): Network meta-analysis, electrical networks and graph theory. *Research Synthesis Methods*, **3**, 312–24

Rücker G, Schwarzer G (2015): Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Medical Research Methodology*, **15**, 58

Examples

```
## Not run:
data(smokingcessation, package = "netmeta")
smokingcessation$id <- 1:nrow(smokingcessation)

study912 <- subset(smokingcessation, id %in% 9:12)
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data = study912,
```

```
                        sm = "OR")

# Forward search algorithm
#
FSresult <- NMAoutlier(p1, P = 1, small.values = "bad", n_cores = 2)
FSresult

data(smokingcessation, package = "netmeta")

# Transform data from arm-based to contrast-based format
# We use 'sm' argument for odds ratios.
# We use function pairwise from netmeta package
#
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data = smokingcessation,
                        sm = "OR")

# Forward search algorithm
#
FSresult1 <- NMAoutlier(p1, small.values = "bad")

# Basic set for each iteration of forward search algorithm
#
FSresult1$basic

# Forward search algorithm using the criteria (crit1, crit2)
# with the maximum of absolute likelihood contributions ("L")
#
FSresult2 <- NMAoutlier(p1, crit1 = "L", crit2 = "L",
                        small.values = "bad")
FSresult2

## End(Not run)
```

`NMAoutlier.measures` *Outlier and influential detection measures in network meta-analysis.*

Description

This function calculates several (simple or/and deletion) measures for detection of outliers and influential studies in network meta-analysis.

Outlier and influential detection measures are:

- Simple outlier and influential measures for each study (Raw residuals, Standardized residuals, Studentized residuals, Mahalanobis distance, leverage).

- Outlier and influential deletion measures for each study (Shift the mean) (Raw deleted residuals, Standardized deleted residuals, Studentized deleted residuals, Cook distance between the treatment estimates for study j and treatment estimates when study j is removed; Ratio of determinants of variance-covariance matrix of treatment estimates for study j to treatment estimates when study j is removed; weight leave one out;leverage leave one out; heterogeneity estimator leave one out; R statistic for heterogeneity; R statistic for Q (`Qtotal`), R statistic for heterogeneity Q (`Qhet`), R statistic for Qinconsistency (`Qinc`), DFbetas.)

Usage

```
NMAoutlier.measures(
  TE,
  seTE,
  treat1,
  treat2,
  studlab,
  data = NULL,
  sm,
  reference = "",
  measure = "simple",
  ...
)
```

Arguments

`TE`	Estimate of treatment effect, i.e. difference between first and second treatment (e.g. log odds ratio, mean difference, or log hazard ratio).
`seTE`	Standard error of treatment estimate.
`treat1`	Label/Number for first treatment.
`treat2`	Label/Number for second treatment.
`studlab`	Study labels (important when multi arm studies are included).
`data`	A data frame containing the study information.
`sm`	A character string indicating underlying summary measure, e.g., `"RD"`, `"RR"`, `"OR"`, `"ASD"`, `"HR"`, `"MD"`, `"SMD"`, or `"ROM"`.
`reference`	Reference treatment group.
`measure`	Outlier and influential detection measures, simple measures (default: "simple") or outlier and influential detection measures considered study deletion (measure = "deletion").
`...`	Additional arguments passed on to `netmeta`.

Details

Outlier and influential detection measures (simple or deletion) for network meta-analysis. Network meta-analysis from graph-theory [Rücker, 2012] is fitted with (`netmeta` function) of R package **netmeta** [Rücker et al., 2015].

A description of the outlier and influential detection measures in the context of network meta-analysis can be found in Petropoulou (2020).

Let n be the number of treatments in a network and let m be the number of pairwise treatment comparisons. If there are only two-arm studies, m is the number of studies. Let TE and seTE be the vectors of observed effects and their standard errors. Comparisons belonging to multi-arm studies are identified by identical study labels (argument studlab).

This function calculates outlier and influential detection measures for each study. Simple outlier and influential measures (measure = "simple") are: Raw residuals, Standardized residuals, Studentized residuals, Mahalanobis distance and leverage for each study. For deletion outlier and influential measures (measure = "deletion"): Standardized deleted residual; Studentized deleted residual; Cook distance between the treatment estimates for study j and treatment estimates when study j is removed; Ratio of determinants of variance-covariance matrix of treatment estimates for study j to treatment estimates when study j is removed; Weight leave one out;leverage leave one out; heterogeneity estimator leave one out; R statistic for heterogeneity; R statistis for estimates; R statistic for Q (Qtotal), R statistic for heterogeneity Q (Qhet), R statistic for Qinconsistency (Qinc), DFbetas.

Value

An object of class NMAoutlier.measures; with a list containing the following components when choosing simple measures:

dat	Matrix containing the data "TE", "seTE", "studlab", "treat1", "treat2" as defined above.
eraw	Raw residual for each study included in the network.
estand	Standardized residual for each study included in the network.
estud	Studentized residual for each study included in the network.
Mah	Mahalanobis distance for each pairwise comparison.
Mah.distance	Mahalanobis distance for each study included in the network.
leverage	Leverage for each study included in the network.
measure	type of measure used.
call	Function call

a list containing the following components,when choosing deletion measures:

dat	Matrix containing the data "TE", "seTE", "studlab", "treat1", "treat2" as defined above.
eraw.deleted	Raw deleted residual for each study included in the network.
estand.deleted	Standardized deleted residual for each study included in the network.
estud.deleted	Studentized deleted residual for each study included in the network.
Cooks.distance	Cook distance between the treatment estimates for study j and treatment estimates when study j is removed
Covratio	Ratio of determinants of variance-covariance matrix of treatment estimates for study j to treatment estimates when study j is removed.
w.leaveoneout	Weight leave one out.

`H.leaveoneout`	Leverage leave one out.
`heterog.leaveoneout`	Heterogeneity estimator leave one out.
`Rheterogeneity`	R statistic for heterogeneity.
`Restimates`	R statistis for estimates.
`RQtotal`	R statistic for Q (`Qtotal`).
`RQhet`	R statistic for heterogeneity Q (`Qhet`).
`RQinc`	R statistic for Qinconsistency (`Qinc`).
`DFbetas`	DFbetas.
`measure`	type of measure used.
`call`	Function call

Author(s)

Maria Petropoulou <petropoulou@imbi.uni-freiburg.de>

References

Rücker G (2012): Network meta-analysis, electrical networks and graph theory. *Research Synthesis Methods*, **3**, 312–24

Rücker G, Schwarzer G (2015): Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Medical Research Methodology*, **15**, 58

Petropoulou M (2020): Exploring methodological challenges in network meta-analysis models and developing methodology for outlier detection. *PhD dissertation*

Examples

```
data(smokingcessation, package = "netmeta")
smokingcessation$id <- 1:nrow(smokingcessation)

study912 <- subset(smokingcessation, id %in% 9:12)
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data = study912,
                        sm = "OR")


# Outlier and influential detection measures for studies 9, 10, 11, 12
meas <- NMAoutlier.measures(p1)

# Standardized residual for each study included in the network
meas$estand

## Not run:
# Outlier and influential deletion measures for studies 9, 10, 11, 12.
delete <- NMAoutlier.measures(p1, measure = "deletion")
```

```
# Standardized deleted residual for studies 9, 10, 11, 12.
delete$estand.deleted

data(smokingcessation, package = "netmeta")

# Transform data from arm-based to contrast-based format
# We use 'sm' argument for odds ratios.
# We use function pairwise from netmeta package
#
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data = smokingcessation,
                        sm = "OR")

# Outlier and influential detection measures for each study in the network
meas <- NMAoutlier.measures(p1, measure = "simple")

# Mahalanobis distance for each study included in the network
meas$Mah

## End(Not run)
```

`Qnetplot` *Q-Q plot for network meta-analysis (Q-Q netplot).*

Description

This function generates the Q-Q plot for network meta-analyisis model.

Usage

```
Qnetplot(data)
```

Arguments

`data`	object of class NMAoutlier.measures (mandatory).

Details

Plot of Q-squared Mahalanobis distance for each study included in the network meta-analysis. Vertical axis provides the Q-squared Mahalanobis distance for each i study included in the network meta-analysis. Horizontal axis provides Q estimated quantiles (theoretical quantiles from the normal distribution). A reference line is fitted from the cartesian points of the two measures. The Q-Q plot can visualize studies that are away from the reference line (potiential outliers).

Q-Q plot for network meta-analysis has been introduced by Petropoulou (2020).

Author(s)

Maria Petropoulou <petropoulou@imbi.uni-freiburg.de>

References

Petropoulou M (2020): Exploring methodological challenges in network meta-analysis models and developing methodology for outlier detection. *PhD dissertation*

Examples

```
data(smokingcessation, package = "netmeta")

p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data = smokingcessation,
                        sm = "OR")

# Outlier and influential detection measures
measures <- NMAoutlier.measures(p1)

# Mahalanobis distance values for each study in the network
measures$Mah

# Q-Q netplot for the network of smoking cessation dataset
Qnetplot(measures)
```

Schoenberg2013 *Network meta-analysis comparing the effects after Laparoscopic Heller myotomy.*

Description

Network meta-analysis dataset comparing the effects after Laparoscopic Heller myotomy.

Format

A data frame in contrast format with the following columns:

logOR	log odds ratio
selogOR	standard error of log odds ratio
id	study ID
t1	first treatment
t2	second treatment

Details

The dataset compares the effects after Laparoscopic Heller myotomy. The outcome is the number of individuals with successful rates at 12 months. These data are in contrast format with effect size odds ratio (OR) and its standard error. Arm-level data can be found in Schoenberg et al. (2013).

Source

Schoenberg MB, Marx S, Kersten JF, Rösch T, Belle S, Kähler G, Vassiliou MC, Lüth S, von Renteln D (2013): Laparoscopic Heller myotomy versus endoscopic balloon dilatation for the treatment of achalasia: a network meta-analysis. *Annals of Surgery*, **258**, 943–52

Examples

```
data(Schoenberg2013)
# Conduct forward search algorithm for the network of Laparoscopic
# Heller myotomy
#
FSresult <- NMAoutlier(logOR, selogOR, t1, t2, id, data = Schoenberg2013, n_cores = 2)

# Draw forward plot for z-values from difference of direct and
# indirect evidence
#
fwdplot(FSresult, "nsplit")
```

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