

# Package ‘mnda’

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**Type** Package

**Title** Multiplex Network Differential Analysis (MNDA)

**Version** 1.0.9

## Description

Interactions between different biological entities are crucial for the function of biological systems. In such networks, nodes represent biological elements, such as genes, proteins and microbes, and their interactions can be defined by edges, which can be either binary or weighted. The dysregulation of these networks can be associated with different clinical conditions such as diseases and response to treatments.

However, such variations often occur locally and do not concern the whole network.

To capture local variations of such networks, we propose multiplex network differential analysis (MNDA).

MNDA allows to quantify the variations in the local neighborhood of each node (e.g. gene) between the two given clinical states, and to test for statistical significance of such variation.

Yousefi et al. (2023) <[doi:10.1101/2023.01.22.525058](https://doi.org/10.1101/2023.01.22.525058)>.

**License** GPL (>= 3)

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as.igraph	<i>Convert mnda graph data to igraph</i>
-----------	--

---

## Description

Convert mnda graph data to igraph

## Usage

```
as.igraph(mnda.graph, edge.threshold = 0)
```

## Arguments

mnda.graph      mnda graph data  
edge.threshold   numeric

## Value

igraph object

## Examples

```
data = example_data()
graph = as.igraph(mnda.graph = data[["mnda_graph_example"]])
```

---

as.mnda.graph	<i>Convert adjacency matrix to mnda graph data</i>
---------------	--

---

**Description**

Convert adjacency matrix to mnda graph data

**Usage**

```
as.mnda.graph(adj.list, outcome = NULL)
```

**Arguments**

adj.list	list of adjacency matrices with matching nodes
outcome	graph outcomes or graph labels. If NULL, outcome = 1:N_graphs.

**Value**

mnda.graph data

**Examples**

```
data = example_data()
adj.list = list(data[["adj_mat_example"]], data[["adj_mat_example"]])
graph.data = as.mnda.graph(adj.list)
```

---

Distance	<i>Function to calculate distance between two vectors</i>
----------	---

---

**Description**

Function to calculate distance between two vectors

**Usage**

```
Distance(x, y, method = "cosine")
```

**Arguments**

x	numeric vector
y	numeric vector
method	distance calculation method: cosine (default), dot.prod, euclidian, manhattan, chebyshev, coassociation

**Value**

the distance value

**Examples**

```
x = c(1,2,3)
y = c(6,4,6)
Distance(x,y)
```

---

EDNN

*Encoder decoder neural network (EDNN) function*


---

**Description**

Encoder decoder neural network (EDNN) function

**Usage**

```
EDNN(
  X,
  Y,
  Xtest,
  embedding_size = 2,
  epochs = 10,
  batch_size = 5,
  l2reg = 0,
  demo = TRUE,
  verbose = TRUE
)
```

**Arguments**

X	concatenated adjacency matrices for different layers containing the nodes in training phase
Y	concatenated random walk probability matrices for different layers containing the nodes in training phase
Xtest	concatenated adjacency matrices for different layers containing the nodes in test phase. Can be = X for transductive inference.
embedding_size	the dimension of embedding space, equal to the number of the bottleneck hidden nodes.
epochs	maximum number of pocks. An early stopping callback with a patience of 5 has been set inside the function (default = 10).
batch_size	batch size for learning (default = 5).
l2reg	the coefficient of L2 regularization for the input layer (default = 0).
demo	a boolean vector to indicate this is a demo example or not
verbose	if <i>TRUE</i> a progress bar is shown.

**Value**

The embedding space for Xtest.

**Examples**

```
myNet = network_gen(N_nodes = 50)
graphData = myNet[["data_graph"]]
edge.list = graphData[,1:2]
edge.weight = graphData[,3:4]
XY = ednn_IOPrepare(edge.list, edge.weight)
X = XY[["X"]]
Y = XY[["Y"]]
embeddingSpace = EDNN(X = X, Y = Y, Xtest = X)
```

---

ednn\_IOPrepare

*Preparing the input and output of the EDNN for a multiplex graph*


---

**Description**

Preparing the input and output of the EDNN for a multiplex graph

**Usage**

```
ednn_IOPrepare(
  edge.list,
  edge.weight,
  outcome = NULL,
  indiv.index = NULL,
  edge.threshold = 0,
  walk.rep = 10,
  n.steps = 5,
  random.walk = TRUE,
  verbose = TRUE
)
```

**Arguments**

edge.list	edge list as a dataframe with two columns.
edge.weight	edge weights as a dataframe. Each column corresponds to a graph. By default, the colnames are considered as outcomes unless indicated in outcome argument.
outcome	clinical outcomes for each graph. If not mentioned, the colnames(edge.weight) are considered by default.
indiv.index	the index of individual networks.
edge.threshold	numeric value to set edge weights below the threshold to zero (default: 0). the greater edge weights do not change.

`walk.rep`            number of repeats for the random walk (default: 100).  
`n.steps`             number of the random walk steps (default: 5).  
`random.walk`        boolean value to enable the random walk algorithm (default: TRUE).  
`verbose`             if *TRUE* a progress bar is shown.

**Value**

the input and output required to train the EDNN

**Examples**

```

myNet = network_gen(N_nodes = 50)
graphData = myNet[["data_graph"]]
edge.list = graphData[,1:2]
edge.weight = graphData[,3:4]
XY = ednn_I0prepare(edge.list, edge.weight)
X = XY[["X"]]
Y = XY[["Y"]]
  
```

---

example\_data

*Example Data*

---

**Description**

Example Data

**Usage**

```
example_data()
```

**Value**

example data as a list: "adj\_mat\_example", "igraph\_example", "mnda\_graph\_example"

**Examples**

```
data = example_data()
```

---

 mnda\_distance\_test\_isn

*Test the embedding distances of local neighbors change between the two conditions for ISNs.*

---

## Description

Test the embedding distances of local neighbors change between the two conditions for ISNs.

## Usage

```
mnda_distance_test_isn(
  Distance,
  y,
  stat.test = "wilcox.test",
  p.adjust.method = "none"
)
```

## Arguments

Distance	a distance list obtained by the <code>mnda_node_distance()</code> function.
y	vector with the length equal to the number of individuals.
stat.test	statistical test used to detect the nodes <code>c("t.test", "wilcox.test")</code> (default: <code>wilcox.test</code> )
p.adjust.method	method for adjusting p-value (including methods on <code>p.adjust.methods</code> ). If set to "none" (default), no adjustment will be performed.

## Details

The adjusted p-values for each node is calculated based on their distance variation between the two conditions.

## Value

The adjusted pvalues for each node.

## Examples

```
ISN1 = network_gen(N_nodes = 50, N_var_nodes = 5, N_var_nei = 40, noise_sd = .01)
ISN2 = network_gen(N_nodes = 50, N_var_nodes = 5, N_var_nei = 40, noise_sd = .01)
graph_data = cbind(ISN1[["data_graph"]], ISN1[["data_graph"]][,3:4])
embeddingSpaceList = mnda_embedding(graph.data=graph_data, outcome=c(1,2,1,2),
  indv.index=c(1,1,2,2), train.rep=2, random.walk=FALSE)
Dist = mnda_node_distance(embeddingSpaceList)
Result = mnda_distance_test_isn(Dist, y = c(1,2))
```

---

mnda\_embedding

*Calculate the embedding space for a multiplex network*


---

### Description

Calculate the embedding space for a multiplex network

### Usage

```
mnda_embedding(
  graph.data,
  outcome,
  indiv.index = NULL,
  edge.threshold = 0,
  train.rep = 50,
  embedding.size = 2,
  epochs = 10,
  batch.size = 5,
  l2reg = 0,
  walk.rep = 100,
  n.steps = 5,
  random.walk = TRUE,
  demo = TRUE,
  verbose = TRUE
)
```

### Arguments

graph.data	dataframe of the graph data containing edge list and edge weights. column 1 and 2 consisting of the edge list (undirected). column 3 and 4 consisting the edge weights corresponding to each graph, respectively.
outcome	a vector of outcomes for each network.
indv.index	the index of individual networks.
edge.threshold	numeric value to set edge weights below the threshold to zero (default: 0). the greater edge weights do not change.
train.rep	numeric value to set the number of EDNN training repeats (default: 50).
embedding.size	the dimension of embedding space, equal to the number of the bottleneck hidden nodes (default: 5).
epochs	maximum number of pocks. An early stopping callback with a patience of 5 has been set inside the function (default = 10).
batch.size	batch size for learning (default = 5).
l2reg	the coefficient of L2 regularization for the input layer (default = 0).
walk.rep	number of repeats for the random walk (default: 100).
n.steps	number of the random walk steps (default: 5).

random.walk      boolean value to enable the random walk algorithm (default: TRUE).  
 demo              a boolean vector to indicate this is a demo example or not  
 verbose          if *TRUE* a progress bar is shown.

**Value**

a list of embedding spaces for each node.

**Examples**

```

myNet = network_gen(N_nodes = 50, N_var_nodes = 5, N_var_nei = 40, noise_sd = .01)
graph_data = myNet[["data_graph"]]
embeddingSpaceList = mnda_embedding(graph.data=graph_data, outcome=c(1,2),
train.rep=2, random.walk=FALSE)

```

---

mnda\_embedding\_2layer *Calculate the embedding space for a two layer multiplex network*

---

**Description**

Calculate the embedding space for a two layer multiplex network

**Usage**

```

mnda_embedding_2layer(
  graph.data,
  edge.threshold = 0,
  train.rep = 50,
  embedding.size = 2,
  epochs = 10,
  batch.size = 5,
  l2reg = 0,
  walk.rep = 100,
  n.steps = 5,
  random.walk = TRUE,
  null.perm = TRUE,
  demo = TRUE,
  verbose = TRUE
)

```

**Arguments**

graph.data      dataframe of the graph data containing edge list and edge weights. column 1 and 2 consisting of the edge list (undirected). column 3 and 4 consisting the edge weights corresponding to each graph, respectively.

edge.threshold	numeric value to set edge weights below the threshold to zero (default: 0). the greater edge weights do not change.
train.rep	numeric value to set the number of EDNN training repeats (default: 50).
embedding.size	the dimension of embedding space, equal to the number of the bottleneck hidden nodes (default: 5).
epochs	maximum number of pocks. An early stopping callback with a patience of 5 has been set inside the function (default = 10).
batch.size	batch size for learning (default = 5).
l2reg	the coefficient of L2 regularization for the input layer (default = 0).
walk.rep	number of repeats for the random walk (default: 100).
n.steps	number of the random walk steps (default: 5).
random.walk	boolean value to enable the random walk algorithm (default: TRUE).
null.perm	boolean to enable permuting two random graphs and embed them, along with the main two graphs, for the null distribution (default: TRUE).
demo	a boolean vector to indicate this is a demo example or not
verbose	if <i>TRUE</i> a progress bar is shown.

**Value**

a list of embedding spaces for each node.

**Examples**

```
myNet = network_gen(N_nodes = 50, N_var_nodes = 5, N_var_nei = 40, noise_sd = .01)
graph_data = myNet[["data_graph"]]
embeddingSpaceList = mnda_embedding_2layer(graph.data=graph_data, train.rep=5, walk.rep=5)
```

---

mnda\_node\_detection\_2layer

*Detecting the nodes whose local neighbors change bweteen the two conditions.*

---

**Description**

Detecting the nodes whose local neighbors change bweteen the two conditions.

**Usage**

```
mnda_node_detection_2layer(
  embeddingSpaceList,
  p.adjust.method = "none",
  alpha = 0.05,
  rank.prc = 0.1,
  volcano.plot = TRUE,
  ranksum.sort.plot = FALSE
)
```

**Arguments**

embeddingSpaceList	a list obtained by the mnda_embedding_2layer() function.
p.adjust.method	method for adjusting p-value (including methods on p.adjust.methods). If set to "none" (default), no adjustment will be performed.
alpha	numeric value of significance level (default: 0.05)
rank.prc	numeric value of the rank percentage threshold (default: 0.1)
volcano.plot	boolean value for generating the Volcano plot (default: TRUE)
ranksum.sort.plot	boolean value for generating the sorted rank sum plot (default: FALSE)

**Details**

Calculating the distance of node pairs in the embedding space and check their significance. To find the significantly varying nodes in the 2-layer-network, the distance between the corresponding nodes are calculated along with the null distribution. The null distribution is obtained based on the pairwise distances on null graphs. if in mnda\_embedding\_2layer function null.perm=FALSE, the multiplex network does not have the two randomly permuted graphs, thus the distances between all the nodes will be used for the null distribution.

**Value**

the highly variable nodes

**Examples**

```
myNet = network_gen(N_nodes = 50, N_var_nodes = 5, N_var_nei = 40, noise_sd = .01)
graph_data = myNet[["data_graph"]]
embeddingSpaceList = mnda_embedding_2layer(graph.data=graph_data, train.rep=5, walk.rep=5)
Nodes = mnda_node_detection_2layer(embeddingSpaceList)
```

---

mnda_node_distance	<i>Detecting the nodes whose local neighbors change between the two conditions for ISNs.</i>
--------------------	--

---

**Description**

Detecting the nodes whose local neighbors change between the two conditions for ISNs.

**Usage**

```
mnda_node_distance(embeddingSpaceList)
```

**Arguments**

embeddingSpaceList  
a list obtained by the mnda\_embedding\_2layer() function.

**Details**

Calculating the distance of node pairs in the embedding space and check their significance. To find the significantly varying nodes in the 2-layer-network, the distance between the corresponding nodes are calculated along with the null distribution. The null distribution is obtained based on the pairwise distances on null graphs. if in mnda\_embedding\_2layer function null.perm=FALSE, the multiplex network does not have the two randomly permuted graphs, thus the distances between all the nodes will be used for the null distribution.

**Value**

the distances for each repeat

**Examples**

```
myNet = network_gen(N_nodes = 50, N_var_nodes = 5, N_var_nei = 40, noise_sd = .01)
graph_data = myNet[["data_graph"]]
embeddingSpaceList = mnda_embedding(graph.data=graph_data, outcome=c(1,2),
indv.index=c(1,1), train.rep=2, random.walk=FALSE)
Dist = mnda_node_distance(embeddingSpaceList)
```

---

network\_gen

*Multiplex Network Generation*

---

**Description**

Multiplex Network Generation

**Usage**

```
network_gen(N_nodes = 100, N_var_nodes = 5, N_var_nei = 90, noise_sd = 0.1)
```

**Arguments**

N_nodes	number of nodes in the graph
N_var_nodes	number of nodes whose neighborhood should change from layer 1 to 2
N_var_nei	number of neighbors that should be changing from layer 1 to 2
noise_sd	the standard deviation of the noise added to the edge weights

**Details**

In this script we generate random pairs of gene co-expression networks, which are different only in a few (pre-set) number of nodes.

**Value**

No return value, called to plot subgraphs

**Examples**

```
myNet = network_gen(N_nodes = 100)
graphData = myNet[["data_graph"]]
varNodes = myNet[["var_node_set"]]
```

---

*p\_val\_norm*

*Calculate p.value for x given a Gaussian null pdf*

---

**Description**

Calculate p.value for x given a Gaussian null pdf

**Usage**

```
p_val_norm(x, null.pdf, alternative = "two.sided")
```

**Arguments**

- x                    numeric value
- null.pdf            a numeric vector of null distribution samples
- alternative        alterative test including: "two.sided" [default], "greater", and "less"

**Value**

p.value

**Examples**

```
p.val = p_val_norm(1, rnorm(1000,0,1))
```

---

`p_val_rank`                      *Calculate p.value for x given a null pdf using ranks*

---

**Description**

Calculate p.value for x given a null pdf using ranks

**Usage**

```
p_val_rank(x, null.pdf, alternative = "two.sided")
```

**Arguments**

<code>x</code>	numeric value
<code>null.pdf</code>	a numeric vector of null distribution samples
<code>alternative</code>	alterative test including: "two.sided" [default], "greater", and "less"

**Value**

p.value

**Examples**

```
p.val = p_val_rank(1, 1:100)
```

---

`Rank`                                      *Ranking a vector*

---

**Description**

Ranking a vector

**Usage**

```
Rank(x, decreasing = FALSE)
```

**Arguments**

<code>x</code>	a numeric vector
<code>decreasing</code>	logical. Should the sort order be increasing or decreasing? (default: FALSE)

**Details**

hint: What is the difference between Order and Rank

Order: [the index of the greatest number, ..., the index of the smallest number]

Rank: [the rank of the 1st number, ..., the rank of the last number]

In Rank, the order of the numbers remains constant so can be used for ranksum.

ex)

```
> a = c(10, 20, 50, 30, 40)
```

```
> order(a)
```

```
[1] 1 2 4 5 3]]
```

```
> Rank(a)
```

```
[1] 1 2 5 3 4
```

**Value**

the rank of the vector elements

**Examples**

```
a = c(10, 20, 50, 30, 40)
```

```
Rank(a)
```

---

RepRandomWalk

*Repetitive Fixed-length (weighted) random walk algorithm*

---

**Description**

Repetitive Fixed-length (weighted) random walk algorithm

**Usage**

```
RepRandomWalk(  
  graph,  
  Nrep = 100,  
  Nstep = 5,  
  weighted_walk = TRUE,  
  verbose = TRUE  
)
```

**Arguments**

graph	an igraph object
Nrep	number of repeats (default:100)
Nstep	maximum number steps (default:5)
weighted_walk	choose the <i>weighted walk</i> algorithm if <i>TRUE</i> and <i>simple random walk</i> if <i>FALSE</i> . (default: <i>TRUE</i> )
verbose	if <i>TRUE</i> a progress bar is shown.

**Value**

Steps (S): The total number of times a node is visited starting from the corresponding node in the row. Probabilities (P): The node visit probabilities starting from the corresponding node in the row.

**Examples**

```
data = example_data()
RW = RepRandomWalk(graph = data[["igraph_example"]])
Steps = RW[["Steps"]]
Probabilities = RW[["Probabilities"]]
```

---

subgraph\_difference\_plot

*Visualization of a difference subgroup using a circular graph*

---

**Description**

Visualization of a difference subgroup using a circular graph

**Usage**

```
subgraph_difference_plot(
  mnda.graph,
  node.importance,
  n.var.nodes = 5,
  n.neigh = 10,
  diff.threshold = 0,
  edge.width = c(0.5, 4)
)
```

**Arguments**

mnda.graph	mnda.graph data
node.importance	named numeric vector of the node importance to sort the nodes clockwise.
n.var.nodes	number of variable nodes to show
n.neigh	number of neighboring nodes to show
diff.threshold	edge threshold
edge.width	numeric value to adjust the thickness of the edges in plot. Two modes are defined: [i] two numbers indicating the min and max (default: c(0.5,4)); or [ii] a single number that weights the min/max of original edge weights.

**Value**

nothing to return

**Examples**

```
myNet = network_gen(N_nodes = 100, N_var_nodes = 5, N_var_nei = 90, noise_sd = .01)
graph_data = myNet[["data_graph"]]
node_importance_dummy = 1:100
names(node_importance_dummy) = 1:100
subgraph_difference_plot(graph_data, node.importance = node_importance_dummy)
```

subgraph\_plot

*Visualization of a subgroup using a circular graph***Description**

Visualization of a subgroup using a circular graph

**Usage**

```
subgraph_plot(
  graph,
  node_set,
  labels = NULL,
  node.importance = NULL,
  n.nodes = NULL,
  node_size = 5,
  font_size = 4,
  edge_width = c(0.5, 4),
  margin = 2.5
)
```

**Arguments**

graph	an igraph object
node_set	the names or indices of the nodes around which the subgroup is plotted.
labels	the labels of the nodes to be indicated. Labels should be a named vector if the node_set consists of the node names.
node.importance	named numeric vector of the node importance to sort the nodes clockwise.
n.nodes	number of nodes to be displayed. If NULL, all the node_set and their neighbors are considered.
node_size	size of the nodes in plot (default: 5)
font_size	font size of labels if available (default: 4)
edge_width	numeric value to adjust the thickness of the edges in plot. Two modes are defined: [i] two numbers indicating the min and max (default: c(0.5,4)); or [ii] a single number that weights the min/max of original edge weights.
margin	the figure margin (default: 2.5)

**Details**

This function plots a sub-graph given by a set of nodes as circular plot. the main inputs to the function are: a graph (as an igraph object) and a set of nodes (e.g. highly variable nodes) around which the subgroup is calculated.

**Value**

nothing to return

**Examples**

```
data = example_data()
subgraph_plot(graph = data[["igraph_example"]], node_set = "a")
```

---

 WeightdRandomWalk

*Weighted Random Walk algorithm*


---

**Description**

Weighted Random Walk algorithm

**Usage**

```
WeightdRandomWalk(graph, startNode, maxStep = 5, node_names = FALSE)
```

**Arguments**

graph	an igraph object
startNode	the starting node (i.e. a node name or a node index)
maxStep	maximum number steps (default:5)
node_names	a list of names for nodes

**Value**

The set of nodes passed by the random walker.

**Examples**

```
data = example_data()
nodePath = WeightdRandomWalk(graph = data[["igraph_example"]], startNode = 1)
```

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