

Package ‘epiNEM’

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Type Package

Title epiNEM

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Description epiNEM is an extension of the original Nested Effects Models (NEM). EpiNEM is able to take into account double knockouts and infer more complex network signalling pathways. It is tailored towards large scale double knock-out screens.

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License GPL-3

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| | |
|---------------|-------------------|
| AddLogicGates | <i>Add logic.</i> |
|---------------|-------------------|

Description

extend model with node representing logic gate

Usage

```
AddLogicGates(child, logic, model)
```

Arguments

| | |
|-------|-------------------------|
| child | define the child |
| logic | define the logical gate |
| model | normal model |

Value

model list with additional logic gate

Examples

```
model <- CreateRandomGraph(c("Ikk1", "Ikk2", "Re1A"))
model2 <- AddLogicGates("Re1A", "OR", model)
```

CreateExtendedAdjacency

Create an extended adjacency matrix

Description

extend adjacency matrices taking cycles and logics into account. For every given start state, the final state is computed using BoolNet.

Usage

```
CreateExtendedAdjacency(network, mutants, experiments)
```

Arguments

| | |
|-------------|--------------------------------------|
| network | network created by BoolNet from file |
| mutants | vector of single knockouts |
| experiments | vector of all knockouts |

Value

extended adjacency matrix

Examples

```
library(BoolNet)
data(cellcycle)
extModel <- CreateExtendedAdjacency(cellcycle,
c(cellcycle$genes, "CycD.Rb"), cellcycle$genes)
```

CreateRandomGraph *Create a random graph*

Description

Returns a model graph with randomly sampled edges. Every possible edge has a probability to exist in the graph.

Usage

```
CreateRandomGraph(pathwayGenes, edgeProb = 0.5)
```

Arguments

pathwayGenes vector of genes in the pathway
edgeProb probability of random edge

Value

adjacency matrix

Examples

```
graph <- CreateRandomGraph(c("Ikk1", "Ikk2", "RelA"))
```

CreateTopology *Create Topology.*

Description

Create topology for a randomly generated pathway topology

Usage

```
CreateTopology(single, double, force = TRUE)
```

Arguments

single number of single knockouts
double number of double knockouts
force if true the random model will have a sophisticated logical gate

Value

adjacency matrix

Examples

```
model <- CreateTopology(3, 1)
```

epiAnno *Gate visualisation.*

Description

Plots logical gate data annotation. The 8 heatmaps visualize what perfect data would look like in respective to each logical gate. Perfect data is equivalent to Boolean truth tables.

Usage

```
epiAnno()
```

Value

plot of heatmaps showing the silencing scheme (=expected data, truth tables)

Author(s)

Martin Pirkl

References

https://en.wikipedia.org/wiki/Boolean_algebra

Examples

```
epiAnno()
```

epiNEM *Epistatic NEMs - main function.*

Description

This function contains the inference algorithm to learn logical networks from knock-down data including double knock-downs.

Usage

```
epiNEM(
  filename = "random",
  method = "greedy",
  nIterations = 10,
  nModels = 0,
  random = list(single = 4, double = 1, reporters = 100, FPrate = 0.1, FNrate = 0.1,
    replicates = 1),
  ltype = "marginal",
  para = c(0.13, 0.05),
  init = NULL
)
```

Arguments

| | |
|-------------|--|
| filename | A binary, tab-delimited matrix. Columns: single and double knockdowns. Rows: genes showing effect or not? Default: random; artificial data is generated to 'random' specifications |
| method | greedy or exhaustive search. Default: greedy |
| nIterations | number of iterations. Default: 10 |
| nModels | number of Models. Default: 0 |
| random | list specifying how the data should be generated: no. of single mutants, no. of double mutants, no. of reporterGenes, FP-rate, FN-rate, no. of replicates |
| ltype | likelihood either "marginal" or "maximum" |
| para | false positive and false negative rates |
| init | adjacency matrix to initialise the greedy search |

Value

List object with an adjacency matrix denoting the network, the model of the silencing scheme (rows are knock-downs, columns are signalling genes), a string with the inferred logical gates, a column indices denoting position of logical gates, the log transformed likelihood and the effect reporter distribution (rows are the signalling genes including the null node).

Author(s)

Madeline Diekmann

See Also

nem

Examples

```
data <- matrix(sample(c(0,1), 100*4, replace = TRUE), 100, 4)
colnames(data) <- c("A", "A.B", "B", "C")
rownames(data) <- paste("E", 1:100, sep = "_")
```

```
res <- epiNEM(data, method = "exhaustive")  
plot(res)
```

epiScreen

Analyse large double knock-out screen.

Description

This function is used to analyse knock-out screens with multiple double and single knock-outs combined in one data set.

Usage

```
epiScreen(data, ...)
```

Arguments

| | |
|------|---|
| data | data matrix containing multiple single and double knock-downs in columns and effect reporters in the rows |
| ... | additional parameters, e.g. for the main epiNEM function |

Value

list object with vectors of double knock-downs, single knock-downs and two matrices with doubles in the columns and singles in the rows. The first matrix denotes the respective logical gate for the triple and the second matrix the log-likelihood

Author(s)

Martin Pirkl

Examples

```
data <- matrix(sample(c(0,1), 100*9, replace = TRUE), 100, 9)  
colnames(data) <- c("A.B", "A.C", "B.C", "A", "B", "C", "D", "E", "G")  
rownames(data) <- paste("E", 1:100, sep = "_")  
res <- epiScreen(data)
```

ExtendTopology *Extending topology of normal "nem"*

Description

Extending topology of normal "nem"

Usage

```
ExtendTopology(topology, nReporters)
```

Arguments

topology model of a topology from CreateTopology
nReporters number of effects reporters

Value

extended topology in which reporters are linked to pathway genes

Author(s)

Madeline Diekmann

See Also

CreateTopology

Examples

```
topology <- CreateTopology(3, 1, force = TRUE)
topology <- unlist(unique(topology), recursive = FALSE)
extTopology <- ExtendTopology(topology$model, 100)
```

GenerateData *Generate data from extended model.*

Description

Given a model created from CreateTopology and ExtendTopology, this function creates a corresponding artificial data matrix, which is used as a ground truth for simulation studies.

Usage

```
GenerateData(model, extTopology, FPrate, FNrate, replicates)
```

Arguments

| | |
|-------------|---|
| model | model of a topology from CreateTopology |
| extTopology | extended topology |
| FPrate | false positive rate |
| FNrate | false negative rate |
| replicates | number of replicates |

Value

data matrix with effect reporters as rows and knock-downs (including double knock-downs) as columns.

Author(s)

Madeline Diekmann

See Also

CreateTopology

Examples

```
topology <-  
CreateTopology(3, 1, force = TRUE)  
topology <-  
unlist(unique(topology), recursive = FALSE)  
extTopology <-  
ExtendTopology(topology$model, 100)  
sortedData <-  
GenerateData(topology$model, extTopology, 0.05, 0.13, 3)
```

HeatmapOP

Heatmap.

Description

Heatmap function based on the lattice package more information: ?xyplot

Usage

```
HeatmapOP(  
  x,  
  col = "RdYlGn",  
  colNA = "grey",  
  coln = 11,  
  bordercol = "grey",  
  borderwidth = 0.1,
```

```

breaks = "sym",
main = "",
sub = "",
dendrogram = "none",
colorkey = "right",
Colv = TRUE,
Rowv = TRUE,
xrot = 90,
yrot = 0,
shrink = c(1, 1),
cexCol = 1,
cexRow = 1,
cexMain = 1,
cexSub = 1,
colSideColors = NULL,
aspect = "fill",
contour = FALSE,
useRaster = FALSE,
xlab = NULL,
ylab = NULL,
colSideColorsPos = "top",
clust = NULL,
clusterx = NULL,
axis.padding = 0.5,
legend = NULL,
...
)

```

Arguments

| | |
|--------------------------|--|
| <code>x</code> | Matrix. |
| <code>col</code> | Color. See <code>brewer.pal.info</code> for all available color schemes. Alternatively, any number of colors, which are then used to create a color gradient. E.g., <code>c('blue','red')</code> produces a color scheme with a gradient from blue to red. |
| <code>colNA</code> | color for NAs; default is grey |
| <code>coln</code> | Number of colors. |
| <code>bordercol</code> | Border color. |
| <code>borderwidth</code> | Border width. |
| <code>breaks</code> | Defines the breaks in the color range. "sym" makes the breaks symmetric around 0. |
| <code>main</code> | Main title. |
| <code>sub</code> | Subtitle. |
| <code>dendrogram</code> | Draw dendrogram with "both", "col" or "row", or do not draw with "none". |
| <code>colorkey</code> | Draw colorkey "left", "right" (default), "top", "bottom" or NULL for no colorkey. See <code>?lattice::levelplot</code> for more complex colorkey options. |
| <code>Colv</code> | Cluster columns (TRUE) or not (FALSE). |

| | |
|------------------|--|
| Rowv | Cluster rows (TRUE) or not (FALSE). |
| xrot | Rotate the column names by degree. |
| yrot | Rotate the row names by degree. |
| shrink | c(x,y) defines a range of size for the data boxes from low to high. |
| cexCol | Font size of column names. |
| cexRow | Font size of row names. |
| cexMain | Font size of main title. |
| cexSub | Font size of subtitle. |
| colSideColors | Defines a numeric vector to annotate columns with different colors. |
| aspect | "iso" for quadratic boxes or "fill" for stretched boxes. |
| contour | TRUE adds a contour plot. |
| useRaster | TRUE to add raster visuals |
| xlab | Label for the x-axis. |
| ylab | Label for the y-axis. |
| colSideColorsPos | Place colSideColors at the "top" or "bottom". |
| clust | p, s, or k for correlation clustering |
| clusterx | Optional data matrix y with the same dimensions as x. x's columns or rows are sorted by the cluster information of y. Col- and rownames of y must be in the same order as in x. |
| axis.padding | padding around the heatmap (0.5 is no padding, default) |
| legend | list object. For parameters see base function ?legend for details. x and y parameters are relative to the inside of the heatmap and are between 0 and 1. E.g., to place the legend outside of the heatmap x and y need to be either less than 0 or greater than 1. |
| ... | Optional arguments. |

Value

lattice object/matrix

Author(s)

Martin Pirkel & Oscar Perpinan at <http://oscarperpinan.github.io/rastervis/>

Examples

```
x <- matrix(rnorm(50), 10, 5)
HeatmapOP(x, dendrogram = "both", aspect = "iso", xrot = 45)
```

M11 *Evaluation of graphs*

Description

Computes marginal log-likelihood for model Phi given observed data matrix D1

Usage

```
M11(Phi, D1, D0, ltype = "marginal", para = c(0.13, 0.05))
```

Arguments

| | |
|-------|--|
| Phi | model to be evaluated |
| D1 | observed data matrix |
| D0 | complementary D1 |
| ltype | likelihood type either "marginal" or "maximum" |
| para | false positive and false negative rates |

Value

list with likelihood poster probability, egene positions

Examples

```
Phi <- matrix(sample(c(0,1), 9, replace = TRUE), 3, 3)
data <- matrix(sample(c(0,1), 3*10, replace = TRUE), 10, 3)
rownames(Phi) <- colnames(Phi) <- colnames(data) <- c("Ikk1", "Ikk2", "RelA")
score <- M11(Phi, D1 <- data, D0 <- 1 - data)
```

perm.rank.test *AUC permutation test*

Description

computes the area under the rank enrichment score curve and does a permutation test to compute the p-value

Usage

```
perm.rank.test(
  x,
  y = NULL,
  alternative = c("two.sided", "less", "greater"),
  iter = 1000
)
```

Arguments

| | |
|-------------|---|
| x | numeric vector of ranks |
| y | numeric vector of the superset of x |
| alternative | character for test type: 'less', 'greater', 'two.sided' |
| iter | integer number of iterations |

Value

p-value

Author(s)

Martin Pirkl

Examples

```
x <- 1:10
y <- 1:100
perm.rank.test(x,y,alternative='less')
perm.rank.test(x,y,alternative='greater')
```

plot.epiNEM

Plot pathway.

Description

Plots the winning pathway structure

Usage

```
## S3 method for class 'epiNEM'
plot(x, ...)
```

Arguments

| | |
|-----|------------------------|
| x | object of class epiNEM |
| ... | other arguments |

Value

plot of the logical network

Examples

```
data <- matrix(sample(c(0,1), 100*4, replace = TRUE), 100, 4)
colnames(data) <- c("A", "A.B", "B", "C")
rownames(data) <- paste("E", 1:100, sep = "_")
res <- epiNEM(data, method = "exhaustive")
plot(res)
```

| | |
|----------------|---------------------|
| plot.epiScreen | <i>Plot screen.</i> |
|----------------|---------------------|

Description

Plots the sresults of a systematic knock-out screen

Usage

```
## S3 method for class 'epiScreen'
plot(
  x,
  global = TRUE,
  ind = NULL,
  colorkey = TRUE,
  cexGene = 1,
  off = 0.05,
  cexLegend = 1,
  ...
)
```

Arguments

| | |
|-----------|---|
| x | object of class epiScreen |
| global | plot global distribution or for each pair (FALSE) |
| ind | index of pairs to plot |
| colorkey | if TRUE prints colorkey |
| cexGene | size of modulator annotation |
| off | relative distance from the gene names to the respective likelihoods |
| cexLegend | font size of the legend |
| ... | other arguments |

Value

plot(s) of an epiNEM screen analysis

Examples

```
data <- matrix(sample(c(0,1), 100*9, replace = TRUE), 100, 9)
colnames(data) <- c("A.B", "A.C", "B.C", "A", "B", "C", "D", "E", "G")
rownames(data) <- paste("E", 1:100, sep = "_")
res <- epiScreen(data)
plot(res)
plot(res, global = FALSE, ind = 1:3)
```

| | |
|-------------|--------------------------|
| plot.epiSim | <i>Plot simulations.</i> |
|-------------|--------------------------|

Description

Plots the simulation results

Usage

```
## S3 method for class 'epiSim'  
plot(x, ...)
```

Arguments

| | |
|-----|------------------------|
| x | object of class epiSim |
| ... | other arguments |

Value

plot(s) of an epiNEM simulation analysis

Examples

```
res <- SimEpiNEM(runs = 1)  
plot(res)
```

| | |
|-----------------|------------------------|
| rank.enrichment | <i>Rank enrichment</i> |
|-----------------|------------------------|

Description

Infers a signalling pathway from peerturbation experiments.

Usage

```
rank.enrichment(  
  data,  
  list,  
  list2 = NULL,  
  n = 1000,  
  main = NULL,  
  col1 = "RdBu",  
  col2 = rgb(1, 0, 0, 0.75),  
  col3 = rgb(0, 0, 1, 0.75),  
  blim = NULL,  
  p = NULL,
```

```

    lwd = 3,
    test = wilcox.test,
    vis = "matrix",
    verbose = FALSE,
    ...
)

```

Arguments

| | |
|---------|--|
| data | m times l matrix with m observed genes and l variables with numeric values to rank the genes |
| list | list of of vectors of genes |
| list2 | optional list with same length as list |
| n | length of the gradient (maximum: m) |
| main | character string for main header; if NULL uses the column names of data by default |
| col1 | color of the gradient |
| col2 | color of the first list |
| col3 | color of the second list2 |
| blim | numeric vector of length two with the lower and upper bounds for the gradient |
| p | numeric adjustment (length four) of the left side of the gradient (low means more to the left, high more to the right) the right side of the enrichment lines and the top positions of the additional matrices in case of vis='matrices' |
| lwd | line width of the enrichment lines |
| test | test function for the enrichment p-value; must have input argument and output values same as perm.rank.test; e.g., wilcox.test or ks.test (here 'less' and 'greater' are switched!) |
| vis | method for visualisation: 'matrix' uses one matrix heatmap for; 'matrices' uses several matrices (experimental), 'colside' uses the colSideColors argument for the ticks of genes in list/list2 (can use a lot of memory; experimental) |
| verbose | if TRUE gives prints additional output |
| ... | additional arguments for epiNEM::HeatmapOP |

Value

transitively closed matrix or graphNEL

Author(s)

Martin Pirkl

Examples

```
data <- matrix(rnorm(100*2),100,2)
rownames(data) <- 1:100
colnames(data) <- LETTERS[1:2]
list <- list(first = as.character(sample(1:100, 10)), second = as.character(sample(1:100, 20)))
rank.enrichment(data,list)
```

| | |
|------------|--|
| sameith_GO | <i>graph-based GO similarity scores, string GO annotations for Sameith et al., 2015 data</i> |
|------------|--|

Description

The data consists of lists including epiNEM identified and general similarity scores and GO annotations for each triple. For details see the vignette.

Examples

```
data(sameith_GO)
```

| | |
|----------------|--|
| sameith_string | <i>sig. of string interaction scores for Sameith et al., 2015 data</i> |
|----------------|--|

Description

The data consists of a list including a vectors of pairs (for interactions) and a corresponding list of interaction scores derived from the string database. For details see the vignette.

Examples

```
data(sameith_string)
```

| | |
|-----------|---|
| samscreen | <i>Example data: epiNEM results for the Sameith et al., 2015 knock-out screen</i> |
|-----------|---|

Description

The result of the epiNEM analysis of the data from "http://www.holstegelab.nl/publications/sv/signaling_redundancy/download". The data consists of a list of matrices with the likelihoods (ll) for each analysed triple of signalling genes and the inferred logic (logic) for each triple. The signalling genes or modulators C are the rows and the signalling genes from the double knock-downs are in the columns. For details see the vignette.

Examples

```
data(samscreen)
```

| | |
|-----|---|
| sim | <i>Example data: simulation results</i> |
|-----|---|

Description

Contains simulation results. How they were acquired is explained in the vignette. The data consists of a list of data matrices holding sensitivity and specificity (spec, sens) of network edges for the various methods compared to the ground truth, sensitivity and specificity (sens2, spec2) of the expected data for epiNEM and Boolean NEMs and accuracy of the inferred logics for both. The different methods are in the rows and the columns denote the different independent simulation runs.

Examples

```
data(sim)
```

| | |
|-----------|----------------------------|
| SimEpiNEM | <i>Compare algorithms.</i> |
|-----------|----------------------------|

Description

Compares different network reconstruction algorithm on simulated data.

Usage

```
SimEpiNEM(
  runs = 10,
  do = c("n", "e"),
  random = list(FPrate = 0.1, FNrate = c(0.1, 0.5), single = 3, double = 1, reporters =
    10, replicates = 2),
  maxTime = FALSE,
  forceLogic = TRUE,
  epiNEMsearch = "greedy",
  bNEMsearch = "genetic",
  ...
)
```

Arguments

| | |
|--------|---|
| runs | number simulation runs |
| do | string vector of algorithms to compare: e (epiNEM), n (Nested Effects Models), b (B-NEM), p (PC algorithm), a (Aracne), e.g. c("e", "n", "p") |
| random | list of false positive rate FPrate, false negative rates FNrate, number of single knock-downs single, number of double knock-downs double, number of effect reporters reporters and number of replicates replicates |

| | |
|--------------|---|
| maxTime | TRUE if the algorithms are bound to a maximum running time in respect to epiNEM |
| forcelogic | if TRUE the randomly sampled ground truth network includes a complex logic with probability 1 |
| epinemsearch | greedy or exhaustive search for epiNEM |
| bnemsearch | genetic or greedy search for B-NEM |
| ... | additional parameters |

Value

returns list of specificity and sensitivity of inferred edges (spec, sens) and inferred expected data (spec2, sens2) and accuracy of logics (logics) and running time (time)

Author(s)

Martin Pirkl

Examples

```
res <- SimEpiNEM(runs = 1)
```

| | |
|---------------|---|
| wageningen_GO | <i>graph-based GO similarity scores, string GO annotations for van Wageningen et al., 2015 data</i> |
|---------------|---|

Description

The data consists of lists including epiNEM identified and general similarity scores and GO annotations for each triple. For details see the vignette.

Examples

```
data(wageningen_GO)
```

| | |
|-------------------|---|
| wageningen_string | <i>sig. of string interaction scores for van Wageningen et al., 2010 data</i> |
|-------------------|---|

Description

The data consists of a list including a vectors of pairs (for interactions) and a corresponding list of interaction scores derived from the string database. For details see the vignette.

Examples

```
data(wageningen_string)
```

wagscreen

Example data: epiNEM results for the Wageningen et al., 2010 knock-out screen
"http://www.holstegelab.nl/publications/GSTF_geneticinteractions/downloads/del_mutants_limma.txt"

Description

The data consists of a list of matrices with the likelihoods (ll) for each analysed triple of signalling genes and the inferred logic (logic) for each triple. The signalling genes or modulators C are the rows and the signalling genes from the double knock-downs are in the columns. For details see the vignette.

Examples

```
data(wagscreen)
```

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