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.

Depends R (>= 4.1)

License GPL-3

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Suggests knitr, RUnit, BiocGenerics, STRINGdb, devtools, rmarkdown, GOSemSim, AnnotationHub, org.Sc.sgd.db, BiocStyle

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R topics documented:

`AddLogicGates` *Add logic.*

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", "RelA"))
model2 <- AddLogicGates("RelA", "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 yu 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 logial 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 kock-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 creeates acorresponding 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 kock-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,
  ...
)
```

Arguments

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

Value

lattice object/matrix

Author(s)

Martin Pirkl & Oscar Perpinan at http://oscarperpinan.github.io/rastervis/

Examples

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

Mll *Evaluation of graphs*

Description

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

Usage

```
Mll(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 <- Mll(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 *Plot screen.*

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 *Plot simulations.*

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 *Rank enrichment*

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` *graph-based GO similarity scores, string GO annotations for Sameith et al., 2015 data*

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` *sig. of string interaction scores for Sameith et al., 2015 data*

Description

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

Examples

```
data(sameith_string)
```

`samscreen` *Example data: epiNEM results for the Sameith et al., 2015 knock-out screen*

Description

The result of the epiNEM analysis of the data from "http://www.holstegelab.nl/publications/ sv/signaling_redundancy/downlo
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 *Example data: simulation results*

Description

Contains simulation results. How they were aquired is explained in the vignette. The data conists of a list of data matrices holding sensitivity and specificity (spec, sens) of network edges for the variious 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 *Compare algorithms.*

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 poitive 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 *graph-based GO similarity scores, string GO annotations for van Wageningen et al., 2015 data*

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 *sig. of string interaction scores for van Wageningen et al., 2010 data*

Description

The data consists of a list including a vectors of pairs (for interactions) and a corresponding list of interaction scores derived form 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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