

Package ‘bnem’

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Type Package

Title Training of logical models from indirect measurements of perturbation experiments

Version 1.2.0

Description bnem combines the use of indirect measurements of Nested Effects Models (package mnem) with the Boolean networks of CellNOptR. Perturbation experiments of signalling nodes in cells are analysed for their effect on the global gene expression profile. Those profiles give evidence for the Boolean regulation of down-stream nodes in the network, e.g., whether two parents activate their child independently (OR-gate) or jointly (AND-gate).

Depends R (>= 4.1)

License GPL-3

Encoding UTF-8

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Imports CellNOptR, matrixStats, snowfall, Rgraphviz, cluster, flexclust, stats, RColorBrewer, epiNEM, mnem, Biobase, methods, utils, graphics, graph, affy, binom, limma, sva, vsn, rmarkdown

VignetteBuilder knitr

Suggests knitr, BiocGenerics

BugReports <https://github.com/MartinFXP/bnem/issues>

URL <https://github.com/MartinFXP/bnem/>

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| | |
|------------|-------------------|
| absorption | <i>Absorption</i> |
|------------|-------------------|

Description

applies absorption law to a disjunctive normal form

Usage

```
absorption(bString, model = NULL)
```

Arguments

| | |
|---------|--|
| bString | a disjunctive normal form or binary vector according to model |
| model | Model object including the search space, if available. See CellNOptR::preprocessing. |

Value

bString after absorption law

Author(s)

Martin PirkI

Examples

```
graph <- c("A+B=C", "A=C")
absorption(graph)
```

absorptionII

Inverse absorption

Description

applies "inverse" absorption law to a disjunctive normal form

Usage

```
absorptionII(bString, model = NULL)
```

Arguments

bString a disjunctive normal form or binary vector according to model
model Model object including the search space, if available. See CellNOptR::preprocessing.

Value

bString after "inverse" absorption law

Author(s)

Martin PirkI

Examples

```
graph <- c("A+B=C", "A=C")
absorptionII(graph)
```

| | |
|----------|------------------|
| addNoise | <i>Add noise</i> |
|----------|------------------|

Description

Adds noise to simulated data

Usage

```
addNoise(sim, sd = 1)
```

Arguments

| | |
|-----|---|
| sim | bnemsim object from simBoolGtn |
| sd | standard deviation for the rnorm function |

Value

noisy fold-change matrix

Author(s)

Martin Pirkl

Examples

```
sim <- simBoolGtn(Sgenes = 10, maxEdges = 10, negation=0.1,layer=1)
fc <- addNoise(sim,sd=1)
```

| | |
|-----|---|
| bcr | <i>B-Cell receptor signalling perturbations</i> |
|-----|---|

Description

Processed data from experiments with a stimulated B-Cell receptor (bcr) and perturbed signalling genes. The raw data is available at <https://www.ncbi.nlm.nih.gov/geo/> with accession id GSE68761. For the process steps we refer to the publication Martin Pirkl, Elisabeth Hand, Dieter Kube, Rainer Spang, Analyzing synergistic and non-synergistic interactions in signalling pathways using Boolean Nested Effect Models, Bioinformatics, Volume 32, Issue 6, 15 March 2016, Pages 893–900, <https://doi.org/10.1093/bioinform> Alternatively see also the function processDataBCR for details and for reproduction.

Usage

```
bcr
```

References

Martin Pirkl, Elisabeth Hand, Dieter Kube, Rainer Spang, Analyzing synergistic and non-synergistic interactions in signalling pathways using Boolean Nested Effect Models, *Bioinformatics*, Volume 32, Issue 6, 15 March 2016, Pages 893–900, <https://doi.org/10.1093/bioinformatics/btv680>

Examples

```
data(bcr)
```

bnem

Boolean Nested Effects Model main function

Description

This function takes a prior network and normalized perturbation data as input and trains logical functions on that prior network

Usage

```
bnem(  
  search = "greedy",  
  fc = NULL,  
  expression = NULL,  
  egenes = NULL,  
  pkn = NULL,  
  design = NULL,  
  stimuli = NULL,  
  inhibitors = NULL,  
  signals = NULL,  
  CNolist = NULL,  
  model = NULL,  
  sizeFac = 10^-10,  
  NAFac = 1,  
  parameters = list(cutOffs = c(0, 1, 0), scoring = c(0.1, 0.2, 0.9)),  
  parallel = NULL,  
  method = "cosine",  
  relFit = FALSE,  
  verbose = TRUE,  
  reduce = TRUE,  
  parallel2 = 1,  
  initBstring = NULL,  
  popSize = 100,  
  pMutation = 0.5,  
  maxTime = Inf,  
  maxGens = Inf,  
  stallGenMax = 10,  
  relTol = 0.01,
```

```

priorBitString = NULL,
selPress = c(1.2, 1e-04),
fit = "linear",
targetBstring = "none",
elitism = NULL,
inversion = NULL,
selection = c("t"),
type = "SOCK",
exhaustive = FALSE,
delcyc = FALSE,
seeds = 1,
maxSteps = Inf,
node = NULL,
absorpII = TRUE,
draw = TRUE,
prior = NULL,
maxInputsPerGate = 2
)

```

Arguments

| | |
|------------|--|
| search | Type of search heuristic. Either "greedy", "genetic" or "exhaustive". "greedy" uses a greedy algorithm to move through the local neighbourhood of a initial hyper-graph. "genetic" uses a genetic algorithm. "exhaustive" searches through the complete search space and is not recommended. |
| fc | m x l matrix of foldchanges of gene expression values or equivalent input (normalized pvalues, logodds, ...) for m E-genes and l contrasts. If left NULL, the gene expression data is used to calculate naive foldchanges. |
| expression | Optional normalized m x l matrix of gene expression data for m E-genes and l experiments. |
| egenes | list object; each list entry is named after an S-gene and contains the names of egenes which are potential children |
| pkn | Prior knowledge network as output by CellNOptR::readSIF. |
| design | Optional n x l design matrix with n S-genes and l experiments. If available. If kept NULL, bnem needs either stimuli, inhibitors or a CNolist object. |
| stimuli | Character vector of stimuli names. |
| inhibitors | Character vector of inhibitors. |
| signals | Optional character vector of signals. Signals are S-genes, which can directly regulate E-genes. If left NULL, all stimuli and inhibitors are defined as signals. |
| CNolist | CNolist object (see package CellNOptR), if available. |
| model | Model object including the search space, if available. See CellNOptR::preprocessing. |
| sizeFac | Size factor penelizing the hyper-graph size. |
| NAFac | factor penelizing NAs in the data. |

| | |
|----------------|--|
| parameters | parameters for discrete case (not recommended); has to be a list with entries cutOffs and scoring: cutOffs = c(a,b,c) with a (cutoff for real zeros), b (cutoff for real effects), c = -1 for normal scoring, c between 0 and 1 for keeping only relevant between -1 and 0 for keeping only a specific quantile of E-genes, and c > 1 for keeping the top c E-genes; scoring = c(a,b,c) with a (weight for real effects), c (weight for real zeros), b (multiplier for effects/zeros between a and c); |
| parallel | Parallelize the search. An integer value specifies the number of threads on the local machine or a list object as in list(c(1,2,3), c("machine1", "machine2", "machine3")) specifies the threads distributed on different machines (local or others). |
| method | Scoring method can be "cosine", a correlation, or a distance measure. See ?cor and ?dist for details. |
| relFit | if TRUE a relative fit for each E-gene is computed (not recommended) |
| verbose | TRUE for verbose output |
| reduce | if TRUE reduces the search space for exhaustive search |
| parallel2 | if TRUE parallelises the starts and not the search itself |
| initBstring | Binary vector for the initial hyper-graph. |
| popSize | Population size (only "genetic"). |
| pMutation | Probability between 0 and 1 for mutation (only "genetic"). |
| maxTime | Define a maximal time (seconds) for the search. |
| maxGens | Maximal number of generations (only "genetic"). |
| stallGenMax | Maximum number of stall generations (only "genetic"). |
| relTol | Score tolerance for networks defined as optimal but with a lower score as the real optimum (only "genetic"). |
| priorBitString | Binary vector defining hyper-edges which are added to every hyper-graph. E.g. if you know hyper-edge 55 is definitely there and to fix that, set priorBitString[55] <- 1 (only "genetic"). |
| selPress | Selection pressure between 1 and 2 (if fit="linear") and greater 2 (for fit "non-linear") for the stochastic universal sampling (only "genetic"). |
| fit | "linear" or "nonlinear fit for stochastic universal sampling |
| targetBstring | define a binary vector representing a network; if this network is found, the computation stops |
| elitism | Number of best hyper-graphs transferred to the next generation (only "genetic"). |
| inversion | Number of worst hyper-graphs for which their binary strings are inversed (only "genetic"). |
| selection | "t" for tournament selection and "s" for stochastic universal sampling (only "genetic"). |
| type | type of the parallelisation on multiple machines (default: "SOCK") |
| exhaustive | If TRUE an exhaustive search is conducted if the genetic algorithm would take longer (only "genetic"). |
| delcyc | If TRUE deletes cycles in all hyper-graphs (not recommended). |

| | |
|------------------|--|
| seeds | how many starts for the greedy search? (default: 1); uses the n-dimensional cube (n = number of S-genes) to maximize search space coverage |
| maxSteps | Maximal number of steps (only "greedy"). |
| node | vector of S-gene names, which are used in the greedy search; if node = NULL all nodes are considered |
| absorpII | Use inverse absorption (default: TRUE). |
| draw | If TRUE draws the network evolution. |
| prior | Binary vector. A 1 specifies hyper-edges which should not be optimized (only "greedy"). |
| maxInputsPerGate | If no model is supplied, one is created with maxInputsPerGate as maximum number of parents for each hyper-edge. |

Value

List object including the optimized hyper-graph, its corresponding binary vector for full hyper-graph and optimized scores.

Author(s)

Martin Pirkl

See Also

nem

Examples

```
sifMatrix <- rbind(c("A", 1, "B"), c("A", 1, "C"), c("B", 1, "D"),
c("C", 1, "D"))
temp.file <- tempfile(pattern="interaction",fileext=".sif")
write.table(sifMatrix, file = temp.file, sep = "\t",
row.names = FALSE, col.names = FALSE,
quote = FALSE)
PKN <- CellNOptR::readSIF(temp.file)
CNOList <- dummyCNOList("A", c("B","C","D"), maxStim = 1,
maxInhibit = 2, signals = c("A", "B","C","D"))
model <- CellNOptR::preprocessing(CNOList, PKN, maxInputsPerGate = 100)
expression <- matrix(rnorm(nrow(slot(CNOList, "cues"))*10), 10,
nrow(slot(CNOList, "cues")))
fc <- computeFc(CNOList, expression)
initBstring <- rep(0, length(model$reacID))
res <- bnem(search = "greedy", model = model, CNOList = CNOList,
fc = fc, pkn = PKN, stimuli = "A", inhibitors = c("B","C","D"),
parallel = NULL, initBstring = initBstring, draw = FALSE, verbose = FALSE,
maxSteps = Inf)
```

| | |
|--------|----------------------------|
| bnemBs | <i>Bootstraped Network</i> |
|--------|----------------------------|

Description

Runs Bootstraps on the data

Usage

```
bnemBs(fc, x = 10, f = 0.5, replace = TRUE, startString = NULL, ...)
```

Arguments

| | |
|-------------|--|
| fc | m x l matrix of foldchanges of gene expression values or equivalent input (normalized pvalues, logodds, ...) for m E-genes and l contrasts. If left NULL, the gene expression data is used to calculate naive foldchanges. |
| x | number of bootstraps |
| f | percentage to sample, e.g. f = 0.5 samples only 50 the amount of E-genes as the original data |
| replace | if TRUE classical bootstrap, if FALSE sub-sampling without replacement |
| startString | matrix with each row being a string denoting a network to start inference several times with a specific network |
| ... | additional parameters for the bnem function |

Value

list with the accumulation of edges in x and the number of bootstraps in n

Author(s)

Martin Pirkl

Examples

```
sifMatrix <- rbind(c("A", 1, "B"), c("A", 1, "C"), c("B", 1, "D"),
c("C", 1, "D"))
temp.file <- tempfile(pattern="interaction",fileext=".sif")
write.table(sifMatrix, file = temp.file, sep = "\t",
row.names = FALSE, col.names = FALSE,
quote = FALSE)
PKN <- CellNOptR::readSIF(temp.file)
CNolist <- dummyCNolist("A", c("B","C","D"), maxStim = 1,
maxInhibit = 2, signals = c("A", "B","C","D"))
model <- CellNOptR::preprocessing(CNolist, PKN, maxInputsPerGate = 100)
expression <- matrix(rnorm(nrow(slot(CNolist, "cues"))*10), 10,
nrow(slot(CNolist, "cues")))
fc <- computeFc(CNolist, expression)
```

```

initBstring <- rep(0, length(model$reacID))
res <- bmemBs(search = "greedy", model = model, CNolist = CNolist,
fc = fc, pkn = PKN, stimuli = "A", inhibitors = c("B","C","D"),
parallel = NULL, initBstring = initBstring, draw = FALSE, verbose = FALSE,
maxSteps = Inf)

```

computeFc

Compute differential effects

Description

computes differential effects given an activation pattern (absolute gene expression or truth table)

Usage

```
computeFc(CNolist, y)
```

Arguments

| | |
|---------|---|
| CNolist | CNolist object (see package CellNOptR), if available. |
| y | activation pattern according to the annotation in CNolist |

Value

numeric matrix with annotated response scheme

Author(s)

Martin Pirkl

Examples

```

sifMatrix <- rbind(c("A", 1, "B"), c("A", 1, "C"), c("B", 1, "D"),
c("C", 1, "D"))
temp.file <- tempfile(pattern="interaction",fileext=".sif")
write.table(sifMatrix, file = temp.file, sep = "\t",
row.names = FALSE, col.names = FALSE,
quote = FALSE)
PKN <- CellNOptR::readSIF(temp.file)
CNolist <- dummyCNolist("A", c("B","C","D"), maxStim = 1, maxInhibit = 2,
signals = c("A", "B","C","D"))
model <- CellNOptR::preprocessing(CNolist, PKN, maxInputsPerGate = 100)
expression <- matrix(rnorm(nrow(slot(CNolist, "cues"))*10), 10,
nrow(slot(CNolist, "cues")))
fc <- computeFc(CNolist, expression)

```

| | |
|--------------|----------------------------|
| convertGraph | <i>Convert normal form</i> |
|--------------|----------------------------|

Description

converts a disjunctive normal form into a conjunctive normal form and vice versa; input graph as disjunctive normal form like that: `c("A+B=D", "C=D", "G+F=U", ...)`; output is the dual element also in disjunctive normal form;

Usage

```
convertGraph(g)
```

Arguments

`g` graph in normal form

Value

converted graph normal form

Author(s)

Martin Pirkl

Examples

```
g <- "A+B=C"
g2 <- convertGraph(g)
```

| | |
|--------------|-----------------------------|
| dummyCNolist | <i>Create dummy CNolist</i> |
|--------------|-----------------------------|

Description

creates a general CNolist object from meta information

Usage

```
dummyCNolist(  
  stimuli = NULL,  
  inhibitors = NULL,  
  maxStim = 0,  
  maxInhibit = 0,  
  signals = NULL  
)
```

Arguments

| | |
|------------|--|
| stimuli | Character vector of stimuli names. |
| inhibitors | Character vector of inhibitors. |
| maxStim | maximal number of stimulated genes for a single experiment |
| maxInhibit | maximal number of inhibited genes for a single experiment |
| signals | Optional character vector of signals. Signals are S-genes, which can directly regulate E-genes. If left NULL, all stimuli and inhibitors are defined as signals. |

Value

CNolist object

Author(s)

Martin Pirkl

Examples

```
sifMatrix <- rbind(c("A", 1, "B"), c("A", 1, "C"), c("B", 1, "D"),
  c("C", 1, "D"))
temp.file <- tempfile(pattern="interaction",fileext=".sif")
write.table(sifMatrix, file = temp.file, sep = "\t",
  row.names = FALSE, col.names = FALSE,
  quote = FALSE)
PKN <- CellNOptR::readSIF(temp.file)
CNolist <- dummyCNolist("A", c("B","C","D"), maxStim = 1, maxInhibit = 2,
  signals = c("A", "B","C","D"))
```

epiNEM2Bg

Switch between epiNEM and B-NEM

Description

Convert epiNEM model into general Boolean graph. Only needed for comparing accuracy of inferred network for bnem and epiNEM.

Usage

```
epiNEM2Bg(t)
```

Arguments

t full epiNEM model

Value

differential effects pattern

Author(s)

Martin Pirkl

See Also

CreateTopology

Examples

```
topology <- epiNEM::CreateTopology(3, 1, force = TRUE)
topology <- unlist(unique(topology), recursive = FALSE)
extTopology <- epiNEM::ExtendTopology(topology$model, 100)
b <- epiNEM2Bg(extTopology)
```

 findResiduals

Compute residuals

Description

calculates residuals (data and optimized network do not match) and visualizes them

Usage

```
findResiduals(
  bString,
  CN0list,
  model,
  fc = NULL,
  expression = NULL,
  egenes = NULL,
  parameters = list(cutOffs = c(0, 1, 0), scoring = c(0.1, 0.2, 0.9)),
  method = "s",
  sizeFac = 10^-10,
  main = "residuals for decoupled vertices",
  sub = paste0("green residuals are added effects (left positive,",
    " right negative) and red residuals are deleted ", "effects"),
  cut = TRUE,
  parallel = NULL,
  verbose = TRUE,
  ...
)
```

Arguments

| | |
|---------|--|
| bString | Binary vector denoting the network given a model |
| CN0list | CN0list object (see package CellNOptR), if available. |
| model | Model object including the search space, if available. See CellNOptR::preprocessing. |

| | |
|------------|--|
| fc | m x l matrix of foldchanges of gene expression values or equivalent input (normalized pvalues, logodds, ...) for m E-genes and l contrasts. If left NULL, the gene expression data is used to calculate naive foldchanges. |
| expression | Optional normalized m x l matrix of gene expression data for m E-genes and l experiments. |
| egenes | list object; each list entry is named after an S-gene and contains the names of egenes which are potential children |
| parameters | parameters for discrete case (not recommended); has to be a list with entries cutOffs and scoring: cutOffs = c(a,b,c) with a (cutoff for real zeros), b (cutoff for real effects), c = -1 for normal scoring, c between 0 and 1 for keeping only relevant between -1 and 0 for keeping only a specific quantile of E-genes, and c > 1 for keeping the top c E-genes; scoring = c(a,b,c) with a (weight for real effects), c (weight for real zeros), b (multiplier for effects/zeros between a and c); |
| method | Scoring method can be "cosine", a correlation, or a distance measure. See ?cor and ?dist for details. |
| sizeFac | Size factor penelizing the hyper-graph size. |
| main | Main title of the figure. |
| sub | Subtitle of the figure. |
| cut | If TRUE does not visualize experiments/S-genes which do not have any residuals. |
| parallel | Parallelize the search. An integer value specifies the number of threads on the local machine or a list object as in list(c(1,2,3), c("machine1", "machine2", "machine3")) specifies the threads distributed on different machines (local or others). |
| verbose | TRUE for verbose output |
| ... | additional parameters for epiNEM::HeatmapOP |

Value

numeric matrices indicating experiments and/or genes, where the network and the data disagree

Author(s)

Martin Pirkl

Examples

```
sifMatrix <- rbind(c("A", 1, "B"), c("A", 1, "C"), c("B", 1, "D"),
c("C", 1, "D"))
temp.file <- tempfile(pattern="interaction",fileext=".sif")
write.table(sifMatrix, file = temp.file, sep = "\t",
row.names = FALSE, col.names = FALSE,
quote = FALSE)
PKN <- CellNOptR::readSIF(temp.file)
CNolist <- dummyCNolist("A", c("B","C","D"), maxStim = 1, maxInhibit = 2,
signal = c("A", "B","C","D"))
model <- CellNOptR::preprocessing(CNolist, PKN, maxInputsPerGate = 100)
```

```

expression <- matrix(rnorm(nrow(slot(CNolist, "cues"))*10), 10,
nrow(slot(CNolist, "cues")))
fc <- computeFc(CNolist, expression)
initBstring <- rep(0, length(model$reacID))
res <- bnem(search = "greedy", CNolist = CNolist, fc = fc, model = model,
parallel = NULL, initBstring = initBstring, draw = FALSE, verbose = FALSE,
maxSteps = Inf)
rownames(fc) <- seq_len(nrow(fc))
## val <- validateGraph(CNolist = CNolist, fc = fc, model = model,
## bString = res$bString, Egenes = 10, Sgene = 4)
residuals <- findResiduals(res$bString, CNolist, model, fc = fc)

```

plot.bnem

plot bnem object

Description

plots the boolean network as disjunctive normal form

Usage

```

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

```

Arguments

| | |
|-----|---|
| x | bnemsim object |
| ... | further arguments; see function mnem::plotDnf |

Value

plot of boolean network

Author(s)

Martin Pirkl

Examples

```

sifMatrix <- rbind(c("A", 1, "B"), c("A", 1, "C"), c("B", 1, "D"),
c("C", 1, "D"))
temp.file <- tempfile(pattern="interaction",fileext=".sif")
write.table(sifMatrix, file = temp.file, sep = "\t",
row.names = FALSE, col.names = FALSE,
quote = FALSE)
PKN <- CellNOptR::readSIF(temp.file)
CNolist <- dummyCNolist("A", c("B","C","D"), maxStim = 1,
maxInhibit = 2, signals = c("A", "B","C","D"))
model <- CellNOptR::preprocessing(CNolist, PKN, maxInputsPerGate = 100)

```

```

expression <- matrix(rnorm(nrow(slot(CNolist, "cues"))*10), 10,
nrow(slot(CNolist, "cues")))
fc <- computeFc(CNolist, expression)
initBstring <- rep(0, length(model$reacID))
res <- bnem(search = "greedy", model = model, CNolist = CNolist,
fc = fc, pkn = PKN, stimuli = "A", inhibitors = c("B","C","D"),
parallel = NULL, initBstring = initBstring, draw = FALSE, verbose = FALSE,
maxSteps = Inf, seeds = 10)
plot(res)

```

plot.bnemBs

Plot Bootstrap result

Description

Shows the result of a Bootstrap with either edge frequencies or confidence intervals

Usage

```

## S3 method for class 'bnemBs'
plot(
  x,
  scale = 3,
  shift = 0.1,
  cut = 0.5,
  dec = 2,
  ci = 0,
  cip = 0.95,
  method = "exact",
  ...
)

```

Arguments

| | |
|--------|---|
| x | bnemBs object |
| scale | numeric value for scaling the edgewidth |
| shift | numeric value for shifting the edgewidth |
| cut | shows only edges with a fraction larger than cut |
| dec | integer for function round |
| ci | if TRUE shows confidence intervals |
| cip | range for the confidence interval, e.g. 0.95 |
| method | method to use for confidence interval computation (see function binom.confint from package binom) |
| ... | additional parameters for the function mnem::plotDnf |

Value

plot of the network from the bootstrap

Author(s)

Martin Pirkl

Examples

```
sifMatrix <- rbind(c("A", 1, "B"), c("A", 1, "C"), c("B", 1, "D"),
  c("C", 1, "D"))
temp.file <- tempfile(pattern="interaction",fileext=".sif")
write.table(sifMatrix, file = temp.file, sep = "\t",
  row.names = FALSE, col.names = FALSE,
  quote = FALSE)
PKN <- CellNOptR::readSIF(temp.file)
CNolist <- dummyCNolist("A", c("B","C","D"), maxStim = 1,
  maxInhibit = 2, signals = c("A", "B", "C", "D"))
model <- CellNOptR::preprocessing(CNolist, PKN, maxInputsPerGate = 100)
expression <- matrix(rnorm(nrow(slot(CNolist, "cues"))*10), 10,
  nrow(slot(CNolist, "cues")))
fc <- computeFc(CNolist, expression)
initBstring <- rep(0, length(model$reacID))
res <- bnemBs(search = "greedy", model = model, CNolist = CNolist,
  fc = fc, pkn = PKN, stimuli = "A", inhibitors = c("B","C","D"),
  parallel = NULL, initBstring = initBstring, draw = FALSE, verbose = FALSE,
  maxSteps = Inf)
```

plot.bnemsim

plot simulation object

Description

plots the boolean network from a simulation as disjunctive normal form

Usage

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

Arguments

x bnemsim object
 ... further arguments; see function `mnem::plotDnf`

Value

plot of boolean network

Author(s)

Martin Pirkl

Examples

```
sim <- simBoolGtn()
plot(sim)
```

processDataBCR

BCR perturbation reproduction

Description

Produce the application data from the BCR paper of Pirkl, et al., 2016, Bioinformatics. Raw data is available at <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE68761>

Usage

```
processDataBCR(path = "", combsign = FALSE)
```

Arguments

| | |
|----------|---|
| path | path to the CEL.gz/Cel files |
| combsign | if TRUE includes all covariates in ComBat analysis to estimate batch effects. |

Value

list with the full foldchanges and expression matrix, a reduced foldchange matrix and the design matrix for the computations

Author(s)

Martin Pirkl

Examples

```
## Not run:
processDataBCR()

## End(Not run)
data(bcr)
```

| | |
|-----------|---------------------------|
| randomDnf | <i>sample normal form</i> |
|-----------|---------------------------|

Description

creates a random normal form or hyper-graph

Usage

```
randomDnf(  
  vertices = 10,  
  negation = TRUE,  
  max.edge.size = NULL,  
  max.edges = NULL,  
  dag = FALSE  
)
```

Arguments

| | |
|---------------|--|
| vertices | number of vertices |
| negation | if TRUE, negations (NOT gates) are allowed |
| max.edge.size | maximal number of inputs per edge |
| max.edges | maximal number of hyper-edges |
| dag | if TRUE, graph will be acyclic |

Value

random hyper-graph in normal form

Author(s)

Martin Pirkl

Examples

```
g <- randomDnf(10)
```

| | |
|-------------|---------------------|
| reduceGraph | <i>Reduce graph</i> |
|-------------|---------------------|

Description

reduces the size of a graph, if possible, to an equivalent sub-graph

Usage

```
reduceGraph(bString, model, CNOList)
```

Arguments

| | |
|---------|--|
| bString | binary vector indicating the sub-graph given a model |
| model | Model object including the search space, if available. See CellNOptR::preprocessing. |
| CNOList | CNOList object (see package CellNOptR), if available. |

Value

equivalent sub-graph denoted by a bString

Author(s)

Martin Pirkl

Examples

```
sifMatrix <- rbind(c("A", 1, "B"), c("A", 1, "C"), c("B", 1, "D"),
c("C", 1, "D"))
temp.file <- tempfile(pattern="interaction",fileext=".sif")
write.table(sifMatrix, file = temp.file, sep = "\t",
row.names = FALSE, col.names = FALSE,
quote = FALSE)
PKN <- CellNOptR::readSIF(temp.file)
CNOList <- dummyCNOList("A", c("B","C","D"), maxStim = 1, maxInhibit = 2,
signal = c("A", "B","C","D"))
model <- CellNOptR::preprocessing(CNOList, PKN, maxInputsPerGate = 100)
bString <- reduceGraph(rep(1, length(model$reacID)), model, CNOList)
```

| | |
|----------|--------------------------------|
| scoreDnf | <i>score a boolean network</i> |
|----------|--------------------------------|

Description

computes the score of a boolean network given the model and data

Usage

```
scoreDnf(
  bString,
  CNolist,
  fc,
  expression = NULL,
  model,
  method = "cosine",
  sizeFac = 10^-10,
  NAFac = 1,
  parameters = list(cutOffs = c(0, 1, 0), scoring = c(0.25, 0.5, 2)),
  NEMlist = NULL,
  relFit = FALSE,
  verbose = FALSE
)
```

Arguments

| | |
|------------|--|
| bString | binary string denoting the boolean network |
| CNolist | CNolist object (see package CellNOptR), if available. |
| fc | m x l matrix of foldchanges of gene expression values or equivalent input (normalized pvalues, logodds, ...) for m E-genes and l contrasts. If left NULL, the gene expression data is used to calculate naive foldchanges. |
| expression | Optional normalized m x l matrix of gene expression data for m E-genes and l experiments. |
| model | Model object including the search space, if available. See CellNOptR::preprocessing. |
| method | Scoring method can be "cosine", a correlation, or a distance measure. See ?cor and ?dist for details. |
| sizeFac | Size factor penelizing the hyper-graph size. |
| NAFac | factor penelizing NAs in the data. |
| parameters | parameters for discrete case (not recommended); has to be a list with entries cutOffs and scoring: cutOffs = c(a,b,c) with a (cutoff for real zeros), b (cutoff for real effects), c = -1 for normal scoring, c between 0 and 1 for keeping only relevant between -1 and 0 for keeping only a specific quantile of E-genes, and c > 1 for keeping the top c E-genes; scoring = c(a,b,c) with a (weight for real effects), c (weight for real zeros), b (multiplier for effects/zeros between a and c); |

| | |
|---------|--|
| NEMlist | NEMlist object (optional) |
| relFit | if TRUE a relative fit for each E-gene is computed (not recommended) |
| verbose | TRUE for verbose output |

Value

numeric value (score)

Author(s)

Martin Pirkl

Examples

```
sim <- simBoolGtn()
scoreDnf(sim$bString, sim$CNOList, sim$fc, model=sim$model)
```

simBoolGtn

Sample random network and simulate data

Description

Draws a random prior network, samples a ground truth from the full boolean extension and generates data

Usage

```
simBoolGtn(
  Sgenes = 10,
  maxEdges = 25,
  stimGenes = 2,
  layer = 1,
  frac = 0.1,
  maxInDeg = 2,
  dag = TRUE,
  maxSize = 2,
  maxStim = 2,
  maxInhibit = 1,
  Egenes = 10,
  flip = 0.33,
  reps = 1,
  keepsif = FALSE,
  negation = 0.25,
  allstim = FALSE,
  and = 0.25,
  positive = TRUE,
  verbose = FALSE
)
```

Arguments

| | |
|------------|--|
| Sgenes | number of S-genes |
| maxEdges | number of maximum edges (upper limit) in the DAG |
| stimGenes | number of stimulated S-genes |
| layer | scaling factor for the sampling of next Sgene layer of the prior. high (5-10) mean more depth and low (0-2) means more breadth |
| frac | fraction of hyper-edges in the ground truth (GTN) |
| maxInDeg | maximum number of incoming hyper-edges |
| dag | if TRUE, graph will be acyclic |
| maxSize | maximum number of S-genes in a hyper-edge |
| maxStim | maximum of stimulated S-genes in an experiment (=data samples) |
| maxInhibit | maximum number of inhibited S-genes in an experiment (=data samples) |
| Egenes | number of E-genes per S-gene, e.g. 10 S-genes and 10 E-genes will return 100 E-genes overall |
| flip | fraction of inhibited E-genes |
| reps | number of replicates |
| keepsif | if TRUE does not delete sif file, which encodes the prior network |
| negation | sample probability for negative or NOT edges |
| allstim | full network in which all S-genes are also stimulated |
| and | probability for AND-gates in the GTN |
| positive | if TRUE, sets all stimulation edges to activation, else samples inhibitory edges by 'negation' probability |
| verbose | TRUE for verbose output |

Value

list with the corresponding prior graph, ground truth network and data

Author(s)

Martin Pirkl

Examples

```
sim <- simBoolGtn()
plot(sim)
```

`simulateStatesRecursive`*Simulate states*

Description

simulates the activation pattern (truth table) of a hyper-graph and annotated perturbation experiments

Usage

```
simulateStatesRecursive(CNOList, model, bString, NEMlist = NULL)
```

Arguments

| | |
|----------------------|--|
| <code>CNOList</code> | CNOList object (see package CellNOptR), if available. |
| <code>model</code> | Model object including the search space, if available. See CellNOptR::preprocessing. |
| <code>bString</code> | binary vector denoting the sub-graph given model |
| <code>NEMlist</code> | NEMlist object only for devel |

Value

return the truth tables for certain perturbation experiments as a numeric matrix

Author(s)

Martin Pirkel

Examples

```
sifMatrix <- rbind(c("A", 1, "B"), c("A", 1, "C"), c("B", 1, "D"),
c("C", 1, "D"))
temp.file <- tempfile(pattern="interaction",fileext=".sif")
write.table(sifMatrix, file = temp.file, sep = "\t",
row.names = FALSE, col.names = FALSE,
quote = FALSE)
PKN <- CellNOptR::readSIF(temp.file)
CNOList <- dummyCNOList("A", c("B","C","D"), maxStim = 1, maxInhibit = 2,
signal = c("A", "B","C","D"))
model <- CellNOptR::preprocessing(CNOList, PKN, maxInputsPerGate = 100)
states <- simulateStatesRecursive(CNOList, model,
rep(1, length(model$reacID)))
```

| | |
|------------|---------------------------|
| transClose | <i>transitive closure</i> |
|------------|---------------------------|

Description

calculates transitive closure of a hyper-graph

Usage

```
transClose(g, max.iter = NULL, verbose = FALSE)
```

Arguments

| | |
|----------|------------------------------------|
| g | hyper-graph in normal form |
| max.iter | maximal iteration till convergence |
| verbose | TRUE for verbose output |

Value

transitive closure in normal form

Author(s)

Martin Pirkl

Examples

```
g <- c("A=B", "B=C")
gclose <- transClose(g)
```

| | |
|----------|-----------------------------|
| transRed | <i>transitive reduction</i> |
|----------|-----------------------------|

Description

calculates transitive reduction of a hyper-graph in normal form

Usage

```
transRed(g, max.iter = NULL, verbose = FALSE)
```

Arguments

| | |
|----------|---|
| g | hyper-graph in normal form |
| max.iter | maximal number of iterations till convergence |
| verbose | TRUE for verbose output |

Value

transitive reduction of the hyper-graph in normal form

Author(s)

Martin Pirkl

Examples

```
g <- c("A=B", "A=C", "B=C", "B=D", "!A=D")
gred <- transRed(g)
```

validateGraph

validate graph

Description

plotting the observed differential effects of an effect reporter and the expected differential effects of the regulating signalling gene

Usage

```
validateGraph(  
  CN0list,  
  fc = NULL,  
  expression = NULL,  
  model,  
  bString,  
  Egenes = 25,  
  Sgene = 1,  
  parameters = list(cutOffs = c(0, 1, 0), scoring = c(0.1, 0.2, 0.9)),  
  plot = TRUE,  
  disc = 0,  
  affyIds = TRUE,  
  relFit = FALSE,  
  xrot = 25,  
  Rowv = FALSE,  
  Colv = FALSE,  
  dendrogram = "none",  
  soft = TRUE,  
  colSideColors = NULL,  
  affychip = "hgu133plus2",  
  method = "s",  
  ranks = FALSE,  
  breaks = NULL,  
  col = "RdYlGn",  
  sizeFac = 10^-10,
```

```

    order = "rank",
    verbose = TRUE,
    ...
)

```

Arguments

| | |
|---------------|--|
| CNOlist | CNOlist object (see package CellNOptR), if available. |
| fc | m x l matrix of foldchanges of gene expression values or equivalent input (normalized pvalues, logodds, ...) for m E-genes and l contrasts. If left NULL, the gene expression data is used to calculate naive foldchanges. |
| expression | Optional normalized m x l matrix of gene expression data for m E-genes and l experiments. |
| model | Model object including the search space, if available. See CellNOptR::preprocessing. |
| bString | Binary string denoting the hyper-graph. |
| Egenes | Maximal number of visualized E-genes. |
| Sgene | Integer denoting the S-gene. See colnames(getSignals(CNOlist)[[1]]) to match integer with S-gene name. |
| parameters | parameters for discrete case (not recommended); has to be a list with entries cutOffs and scoring: cutOffs = c(a,b,c) with a (cutoff for real zeros), b (cutoff for real effects), c = -1 for normal scoring, c between 0 and 1 for keeping only relevant between -1 and 0 for keeping only a specific quantile of E-genes, and c > 1 for keeping the top c E-genes; scoring = c(a,b,c) with a (weight for real effects), c (weight for real zeros), b (multiplier for effects/zeros between a and c); |
| plot | Plot the heatmap. If FALSE, only corresponding information is printed. |
| disc | Discretize the data. |
| affyIds | Experimental. Turn Affymetrix Ids into HGNC gene symbols. |
| relFit | if TRUE a relative fit for each E-gene is computed (not recommended) |
| xrot | See function epiNEM::HeatmapOP |
| Rowv | See function epiNEM::HeatmapOP |
| Colv | See function epiNEM::HeatmapOP |
| dendrogram | See function epiNEM::HeatmapOP |
| soft | if TRUE, assigns weights to the expected pattern |
| colSideColors | See function epiNEM::HeatmapOP |
| affychip | Define Affymetrix chip used to generate the data (optional and experimental). |
| method | Scoring method can be "cosine", a correlation, or a distance measure. See ?cor and ?dist for details. |
| ranks | if TRUE, turns data into ranks |
| breaks | See function epiNEM::HeatmapOP |
| col | See function epiNEM::HeatmapOP |
| sizeFac | Size factor penelizing the hyper-graph size. |

| | |
|---------|--|
| order | Order by "rank", "name" or "none" |
| verbose | TRUE for verbose output |
| ... | additional arguments for epiNEM::HeatmapOP |

Value

lattice object with matrix information

Author(s)

Martin Pirkl

Examples

```
sifMatrix <- rbind(c("A", 1, "B"), c("A", 1, "C"), c("B", 1, "D"),
c("C", 1, "D"))
temp.file <- tempfile(pattern="interaction",fileext=".sif")
write.table(sifMatrix, file = temp.file, sep = "\t",
row.names = FALSE, col.names = FALSE,
quote = FALSE)
PKN <- CellNOptR::readSIF(temp.file)
CNOList <- dummyCNOList("A", c("B","C","D"), maxStim = 1, maxInhibit = 2,
signal = c("A", "B","C","D"))
model <- CellNOptR::preprocessing(CNOList, PKN, maxInputsPerGate = 100)
expression <- matrix(rnorm(nrow(slot(CNOList, "cues"))*10), 10,
nrow(slot(CNOList, "cues")))
fc <- computeFc(CNOList, expression)
initBstring <- rep(0, length(model$reacID))
res <- bnem(search = "greedy", CNOList = CNOList, fc = fc,
model = model, parallel = NULL, initBstring = initBstring, draw = FALSE,
verbose = FALSE, maxSteps = Inf)
rownames(fc) <- seq_len(nrow(fc))
val <- validateGraph(CNOList = CNOList, fc = fc, model = model,
bString = res$bString, Egenes = 10, Sgene = 4)
```

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