

Package ‘difconet’

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Title Differential Coexpressed Networks

Depends R (>= 3.1.0), gplots

Imports stats, utils, stringr, data.table, mvtnorm, graphics,
grDevices

Description Estimation of DIFFerential COexpressed NETworks using diverse and user metrics.

This package is basically used for three functions related to the estimation of differential coexpression.

First, to estimate differential coexpression where the coexpression is estimated, by default, by Spearman correlation. For this, a metric to compare two correlation distributions is needed. The package includes 6 metrics. Some of them needs a threshold. A new metric can also be specified as a user function with specific parameters (see difconet.run). The significance is be estimated by permutations.

Second, to generate datasets with controlled differential correlation data. This is done by either adding noise, or adding specific correlation structure.

Third, to show the results of differential correlation analyses. Please see <<http://bioinformatica.mty.itesm.mx/difconet>> for further information.

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URL <http://bioinformatica.mty.itesm.mx/difconet>

NeedsCompilation no

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difconet.build.controlled.dataset

*GENERATES A DATASET CONTROLLING FOR NOISE AND
GENES CONNECTED IN NETWORKS*

Description

This function takes a normal dataset and generate simulated tumor stages by adding progressive levels of noise. It may add artificial networks of genes connected at given correlations that can progressively increase or decrease their level of correlation.

Usage

```
difconet.build.controlled.dataset(data,
  noise.genes = round(nrow(data)*0.1),
  noise.sigma = c(0.0, 0.1, 0.2),
  nonoise.sigma = c(0.0, 0.01, 0.01),
  netcov = matrix(c(
    0.90, 0.90, 0.75, 0.75, 0.60, 0.60, 0.45, 0.45, 0.30, 0.30,
    0.15, 0.15, 0.30, 0.30, 0.45, 0.45, 0.60, 0.60, 0.75, 0.75,
    0.95, 0.95, 0.80, 0.80, 0.65, 0.65, 0.50, 0.50, 0.35, 0.35,
    0.10, 0.10, 0.25, 0.25, 0.40, 0.40, 0.55, 0.55, 0.70, 0.70,
    1.00, 1.00, 0.85, 0.85, 0.70, 0.70, 0.55, 0.55, 0.40, 0.40,
    0.05, 0.05, 0.20, 0.20, 0.35, 0.35, 0.50, 0.50, 0.65, 0.65
  ), ncol=3),
  genes.nets = 10,
  corfunc=function(a,b) cor(a,b,method="spearman"),
  verbose = TRUE)
```

Arguments

data	data.frame or matrix representing the normal dataset. Rows are genes and columns are samples.
noise.genes	the number of genes from data that will be noised.
noise.sigma	Levels of gaussian noise to be added (at zero mean) expressed in a cumulative manner.
nonoise.sigma	Levels of gaussian noise to be added (at zero mean) for the rest of the genes.
netcov	numeric matrix of correlation levels for networks, rows represent networks and columns represent stages.
genes.nets	The number of genes in each generated network.

corfunc	Correlation method used.
verbose	Print progress.

Details

This function generates a simulated tumor progression dataset based on normal data. The progression is done by stages. The number of stages is given by the length of noise.sigma. Each stage will have the same dimensions than data (plus the networks). The stages will be N, T1, T2, and so on. The N is meant to be the data itself with no noise but for generality, the first element of noise.sigma specifies the level of noise for N (default to 0). The next values of noise.sigma will be used to generate T1, T2, and so on. Thus the returned data will be estimated by $N = \text{data} + \text{noise.sigma}[1]$, $T1 = N + \text{noise.sigma}[2]$, $T2 = T1 + \text{noise.sigma}[3]$, and so on. Note that noise.sigma will be added only to a specific number of rows given by noise.genes. The value returned is a list of the generated matrices. In top of that, the nonoise.sigma specify the level of noise added to those genes not selected to be noised. This is meant to be lower levels of noise than noise.sigma to avoid that data in stages is just a copy of previous data. This function also adds full connected networks of genes connected at netcov levels. The data added has mean=0 and sd=1. The number of rows represent the networks added. The columns represent the stages.

Value

List of stages.

Author(s)

Elpidio Gonzalez and Victor Trevino <vtrevino@itesm.mx>

References

Gonzalez-Valbuena and Trevino 2017 Metrics to Estimate Differential Co-Expression Networks
Journal Pending **volume** 00–10

See Also

[difconet.noise.inspection](#). [difconet.run](#).

Examples

```
## Not run: difconet.noise.inspection(normaldata, tumordata, sigma=0:15/10)
```

difconet.noise.inspection

*PLOT ESTIMATED CORRELATION DISTRIBUTION AFTER
ADDING NOISE*

Description

Plots the estimated correlation distribution of a normal dataset after adding different levels of gaussian noise. It is used to estimate the level of noise needed to be added to a normal dataset to match the correlation distribution of a tumor dataset. This assumes that the correlation distribution of the tumor dataset is sharper around zero.

Usage

```
difconet.noise.inspection(ndata, tdata, sigma=c(0.5, 0.75, 1.25), maxgenes=5000,  
  corfunc=function(a,b) cor(a,b,method="spearman"))
```

Arguments

ndata	The normal dataset. Rows are genes and columns are samples.
tdata	The tumor dataset. Rows are genes and columns are samples. Rows of tumor and normal datasets should be the same.
sigma	Levels of gaussian noise to be added (at zero mean).
maxgenes	Number of genes used to estimate the correlation distribution. If the number of rows in normal/tumor datasets are larger than maxgenes, maxgenes random genes are used for the estimation.
corfunc	Correlation method used.

Details

Plots the estimated density of correlation distributions of normal, tumor, and normal after adding sigma levels of noise.

Value

Nothing.

Author(s)

Elpidio Gonzalez and Victor Trevino <vtrevino@itesm.mx>

References

Gonzalez-Valbuena and Trevino 2017 Metrics to Estimate Differential Co-Expression Networks
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See Also

[difconet.build.controlled.dataset.difconet.run](#).

Examples

```
## Not run: difconet.noise.inspection(normaldata, tumordata, sigma=0:15/10)
```

```
difconet.plot.gene.correlations
      PLOTS THE CORRELATIONS OF A SPECIFIC GENE
```

Description

Draw scatter plots of the correlations of a specific gene.

Usage

```
difconet.plot.gene.correlations(dObj, gene,
  stages=1:length(dObj$stages.data), type=c("density","scatter")[1],
  main=rownames(dObj$stages.data[[1]])[gene],
  legends=TRUE, plot=TRUE, ... )
```

Arguments

dObj	The difconet object.
gene	Numeric or character. The gene index/rowname whose correlations will be drawn.
stages	Numeric or character. The stages to be included. If type="scatter" and more than two stages, a call to pairs is used instead of plot.
type	Character. The type of plot density or scatter .
main	Character. The main title passed to plot.
legends	Logical. Specifies whether the legends are drawn when type="density" .
plot	Logical. Specifies whether the plots are actually drawn (to get the correlations).
...	Further parameters passed to plot/pairs.

Details

Run the whole process of estimation differences in correlations for a given dataset. The estimations are done for all **metric** values, all **cutoff** values across all **comparisons**.

Value

The correlations of the gene across stages (invisible).

Author(s)

Elpidio Gonzalez and Victor Trevino <vtrevino@itesm.mx>

References

Gonzalez-Valbuena and Trevino 2017 Metrics to Estimate Differential Co-Expression Networks
Journal Pending **volume** 00–10

See Also

[difconet.run](#).

Examples

```
xdata <- matrix(rnorm(1000), ncol=100)
xpredictor <- sample(c("A","B","C","D"),100,replace=TRUE)
dObj <- difconet.run(xdata, xpredictor, metric = 4, num_perms = 10,
  comparisons = list(c("A","D"), c("A","B"), c("B","D")),
  perm_mode = "columns")

#Top highest metric in first comparison but showing correlations in only 3 stages
difconet.plot.gene.correlations(dObj, order(dObj$combstats[[1]][,"M4.dist"],
  decreasing=TRUE)[1], type="s", stages=1:3)
#Bottom lowest metric in second comparison showing all stages
difconet.plot.gene.correlations(dObj, order(dObj$combstats[[2]][,"M4.dist"],
  decreasing=TRUE)[1], type="d")
#Another specific gene (3), showing densities of correlations
difconet.plot.gene.correlations(dObj, 3, type="d")
```

```
difconet.plot.histograms.heatmap2
```

*PLOT A HEATMAP REPRESENTATION OF THE DISTRIBUTION
OF CORRELATIONS OF MANY GENES*

Description

Draw a heatmap whose rows are genes and columns are segments of the histogram of the distribution of correlations per gene. The height/density of the histogram is shown in colors.

Usage

```
difconet.plot.histograms.heatmap2(dObj,
  genes=1:10,
  stages=1:length(dObj$stages.data),
  qprobs=c(0,.50,.975,.995), ...)
```

Arguments

dObj	The difconet object.
genes	Numeric or character. The gene indexes/rownames included.
stages	Numeric or character. The stages to be included.
qprobs	The quantiles used to draw the heatmap. Should be 4 points. Each has specific color codes.
...	Further parameters passed to plot/pairs.

Details

A heatmap is draw representing the distribution of correlations of several genes across stages.

Value

Nothing.

Author(s)

Elpidio Gonzalez and Victor Trevino <vtrevino@itesm.mx>

References

Gonzalez-Valbuena and Trevino 2017 Metrics to Estimate Differential Co-Expression Networks
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See Also

[difconet.run](#).

Examples

```
xdata <- matrix(rnorm(1000), ncol=100)
xpredictor <- sample(c("A","B","C","D"),100,replace=TRUE)
dObj <- difconet.run(xdata, xpredictor, metric = 4, num_perms = 10,
  comparisons = list(c("A","D"), c("A","B"), c("B","D")),
  perm_mode = "columns")

#Top highest metric in first comparison but showing correlations in only 3 stages
difconet.plot.gene.correlations(dObj, order(dObj$combstats[[1]][, "M4.dist"],
  decreasing=TRUE)[1], type="s", stages=1:3)
#Bottom lowest metric in second comparison showing all stages
difconet.plot.gene.correlations(dObj, order(dObj$combstats[[2]][, "M4.dist"],
  decreasing=TRUE)[1], type="d")
#Another specific gene (1), showing densities of correlations
difconet.plot.gene.correlations(dObj, 1, type="d")
```

 difconet.run

 RUNS A DIFCONET ANALYSIS

Description

Estimates the DIFFerential CORrelation NETworks analysis from a given dataset.

Usage

```
difconet.run(data, predictor, metric=c(1,2,3,4,5,6), cutoff=0.3, blocs=5000,
  num_perms=10, comparisons="all", perm_mode="columns", use_all_perm = TRUE,
  save_perm=FALSE, speedup=0, verbose=TRUE, metricfunc=NULL,
  corfunc=function(a,b) cor(a,b,method="spearman") )
```

Arguments

data	data.frame or matrix represent the dataset. Genes in rows, samples in columns.
predictor	Factor or numeric vector representing the classes of each column in data. The correlations will be estimated for each class separately.
metric	The metrics needed to be calculated. Valid values are 1 to 6 and 8. 1 to 6 are already implemented and shown in details. 8 specifies a user-defined metric specified in metricfunc.
cutoff	Cut off values used for metric 1 and/or 3.
blocs	Number of rows per block. Because of memory issues, the correlations are estimated by blocks of genes. This value represent the size of the block. Larger values requires more memory if needed. Lower values require more cycles and therefore it is slower but makes it computable depending on database size and memory.
num_perms	Number of permutations.
comparisons	Character or list. If character, it could be "all" to specify all possible combinations of classes. If set to "seq", classes are taken in order and comparisons are done by first versus second, second versus third, and so on. If this is a list containing vectors of two elements, the estimations are done for the specific comparisons included (numeric or character).
perm_mode	Character. It determines the how the permuted data is generated. It can be permuted by "columns", permuted by "rows" (all classes/stages), or permuted by rows within each class separately using "rows.class", or "all" in which all data is shuffled.
use_all_perm	Logical. If TRUE, it uses all permuted data to estimate the p-value, otherwise it uses only the same row permutations to estimate the p-value (it requires a lot more permutations).
save_perm	Logical. If TRUE, it save all permuted data. It may require more memory.

speedup	Numeric. Determines whether the calculation will be sped up. This is experimental. The value specify which metric will be used to speed up. This is done by modeling the dependency of the metric and p-value using 1 percent of the rows.
verbose	Logical. Determines if printing progress information.
metricfunc	Function. Specify the function to be used if a metric==8 is included. The function should receive dObj, a, and b which correspond to the difconet object and the a and b vectors of correlations needed to estimate the value of the metric. It is assumed a distance-like measure (non-negative) and values close to 0 means no difference whereas larger values represent more dissimilar correlations.
corfunc	Function. Specify the function that estimates the correlations, similar to the cor function. The default uses cor and spearman coefficients.

Details

Run the whole process of estimation differences in correlations for a given dataset. The estimations are done for all **metric** values, all **cutoff** values across all **comparisons**.

Value

A difconet object represented as a list. The items are the followings:

stage	Vector. A copy of predictor (classes).
labels	Vector. The levels or values of the different classes.
comparisons	The specified comparisons parameter.
num_perms	The specified number of permutations num_perms parameter.
perm_mode	The specified number of permutations perm_mode parameter.
use_all_perm	The specified number of permutations use_all_perm parameter.
speedup	The specified speedup parameter.
verbose	The specified verbose parameter.
metricfunc	The specified metricfunc parameter.
combinations	A data.frame of the combinations that were compared.
stages.data	A list of datasets. This is only the original data split by classes.
combstats	A list of all comparisons made. Each element contains a matrix whose rows represent the genes and columns represent the results of all metrics (metric.dist : metric value, metric.p : p-value, metric.q : q-value, metric.expr.p : p-value of differential expression for comparison purposes, metric.expr.q : q-value of differential expression.)
combdens	A list of the densities of the metric for observed data and permutations. This can be used to compare the estimated metric statistics.
permutations	List. If save_perm==TRUE , it saves all permuted data.

Author(s)

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References

Gonzalez-Valbuena and Trevino 2017 Metrics to Estimate Differential Co-Expression Networks
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See Also

[difconet.build.controlled.dataset.](#)

Examples

```
xdata <- matrix(rnorm(1000), ncol=100)
xpredictor <- sample(c("A","B","C","D"),100,replace=TRUE)
dObj <- difconet.run(xdata, xpredictor, metric = 4, num_perms = 10,
  comparisons = list(c("A","D"), c("A","B"), c("B","D")),
  perm_mode = "columns")
```

```
## Not run:
#xpredictor contains A, B, C, and D.
#xdata contains the data matrix
dObj <- difconet.run(xdata, xpredictor,
  metric = c(1,2,4),
  cutoff = 0.6,
  blocs = 7000,
  num_perms = 10,
  comparisons = list(c("A","D"), c("A","B"), c("B","D")),
  perm_mode = "columns")
```

```
## End(Not run)
```

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