Package ‘ToPASeq’

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Title   Package for Topology-based Pathway Analysis of RNASeq data
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Description Implementation of seven methods for topology-based pathway analysis of both RNASeq and microarray data: SPIA, DEGraph, TopologyGSA, TAPPA, PRS, PWEA and a visualization tool for a single pathway.
Depends graphite (>= 1.16), gRbase, graph, locfit, Rgraphviz
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ToPASeq-package ................................................................. 2
AdjacencyMatrix2Pathway ................................................... 3
CePa ................................................................. 4
clipper ................................................................. 6
collectWeightsPRS .......................................................... 8
convertIdentifiersByVector ............................................. 9
DEGraph ................................................................. 10
estimateCF .............................................................. 11
graphNEL2Pathway ......................................................... 12
ToPASeq-package

Package for topology-based pathway analysis of microarray and RNASeq data

Description

The package implements several methods for topology-based pathway analysis of microarray data. The methods present in here are: SPIA, TopologyGSA, DEGraph, Clipper, PWEA, TAPPA, TBS. SPIA, PWEA and TBS were also adapted for RNASeq data.

Details

<table>
<thead>
<tr>
<th>Package:</th>
<th>ToPASeq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type:</td>
<td>Package</td>
</tr>
<tr>
<td>Version:</td>
<td>1.0</td>
</tr>
<tr>
<td>Date:</td>
<td>2014-03-04</td>
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<tr>
<td>License:</td>
<td>AGPL-3</td>
</tr>
</tbody>
</table>

Author(s)

Ivana Ihnatova

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Examples

```r
## Not run:
if (require(DEGraph)) {
  data("Loi2008_DEGraphVignette")
  pathways<-biocarta[1:10]
  SPIA(exprLoi2008, classLoi2008,pathways , type="MA", logFC.th=-1, IDs="entrez")
```
DEGraph(exprLoi2008, classLoi2008, pathways, type="MA")
TAPPA(exprLoi2008, classLoi2008, pathways, type="MA")
TopologyGSA(exprLoi2008, classLoi2008, pathways, type="MA", nperm=200)
Clipper( exprLoi2008, classLoi2008+1, pathways.type="MA", test="mean")
PWEA(exprLoi2008, classLoi2008, pathways, type="MA", nperm=100)
TBS( exprLoi2008, classLoi2008, pathways, type="MA", logFC.th=-1, nperm=100)

if (require(gageData)) {
  data(hnrnp.cnts)
group<-c(rep("sample",4), rep("control",4))
SPIA( hnrnp.cnts, group, biocarta[1:10], type="RNASeq", logFC.th=-1, IDs="entrez", test="limma")
DEGraph(hnrnp.cnts, group, biocarta[1:10], type="RNASeq", norm.method="TMM")
TAPPA( hnrnp.cnts, group, biocarta[1:10], type="RNASeq", norm.method="TMM")
TopologyGSA(hnrnp.cnts, group, biocarta[1:10], type="RNASeq", nperm=200, norm.method="TMM")
Clipper(hnrnp.cnts, group, biocarta[1:10], type="RNASeq", norm.method="TMM")
PWEA(hnrnp.cnts, group, biocarta[1:10], type="RNASeq", test="limma", nperm=100)
TBS(hnrnp.cnts, group, biocarta[1:10], type="RNASeq", logFC.th=-1, nperm=100, test="limma")
}

### End(Not run)

---

AdjacencyMatrix2Pathway

*Function to coerce an adjacency matrix to a Pathway*

### Description

The function coerces an adjacency matrix to a Pathway. Two types of matrices are allowed. The first one, where 1 denotes an edge between two nodes and 0 otherwise. This matrix is coerced into a simply pathway were type of all edges is set to "process". The second type of adjacency matrix contains: 1 for an activation, -1 for an inhibition and 0 otherwise (=no edge between two nodes). In this case, activations are set to "process(activation)" and inhibition to "process(inhibition)". The symetricity of the matrix is used to decide between directed and undirected graph. Symmetric matrix is expected for undirected graph and only the lower triangle of the matrix is used to extract the edges of the graph.

### Usage

AdjacencyMatrix2Pathway(adjmat, name = "pathway", ident = "unknown", database = "unknown", species = "unknown", date = NULL)

### Arguments

- **adjmat**: An adjacency matrix describing the pathway topology
- **name**: A character, name of the pathway. Defaults to "pathway"
- **ident**: A character, type of the identificators, e.g "gene symbol"
- **database**: A character, the name of the database the topology comes from
- **species**: A character, the species to which the topology belong
- **date**: A date, the date the topology was created
CePa

Value
An object of class Pathway, id is the same as title - name of the pathway

Author(s)
Ivana Ihnatova

Examples
```r
genes<-paste("gene",1:10,sep="")
adjmat<-matrix(sample(c(0,0,0,1),100,TRUE),10,10,dimnames=list(genes,genes))
p<-AdjacencyMatrix2Pathway(adjmat)
head(edges(p))

adjmat<-matrix(sample(c(0,0,0,1,-1),100,TRUE),10,10,dimnames=list(genes,genes))
p<-AdjacencyMatrix2Pathway(adjmat)
head(edges(p))
```

Description
The function runs CePa method on microarray or RNA-Seq data. The implementation includes the identification of differentially expressed genes and transformation of pathways' topologies to an appropriate form. The ORA version of the CePa method is implemented and covers centralities: equal-weight, in-degree, out-degree, in-reach, out-reach and betweenness.

Usage
```
CePa(x, group, pathways, type, preparePaths=TRUE, norm.method=NULL, test.method=NULL, p.th=0.05, logFC.th=2, nperm=1000,
both.directions=TRUE, maxNodes=150, minEdges=0, commonTh=2, filterSPIA=FALSE, convertTo="none", convertBy=NULL)
```

Arguments
- **x**: An ExpressionSet object or a gene expression data matrix or count matrix, rows refer to genes, columns to samples
- **group**: Name or number of the phenoData column or a character vector or factor that contains required class assignments
- **pathways**: A list of pathways in a form from graphite package or created by preparePathways()
- **type**: Type of the data, "MA" for microarray, "RNASeq" for RNA-Seq, DEtable data.frame from differential expression analysis, or DEGlist a list of: log fold-changes of differentially expressed genes and names of the all genes analyses
- **preparePaths**: Logical, by default the pathways are transformed with preparePathways(). Use FALSE, if you have done this transformation separately
- **norm.method**: Character, the method to normalize RNAseq data. If NULL then TMM-normalization is performed. Possible values are: "TMM", "DESeq2", "rLog", "none". Ignored for type: "MA", "DEtable", "DElist"
test.method  Character, the method for differential expression analysis of RNAseq data. If NULL then "voomlimma" is used. Possible values are: "DESeq2", "voomlimma", "vstlimma", "edgeR". Ignored for type: "MA", "DEtable", "DElist"

p.th  Numeric, threshold for p-values of tests for differential expression of genes. Use 1 if you don’t want any threshold to be applied

logFC.th  Numeric, threshold for log fold-change of a gene to identify the gene as differentially expressed. Use negative if you don’t want any threshold to be applied

nperm  Numeric, number of permutations

both.directions, maxNodes, minEdges, commonTh, filterSPIA, convertTo, convertBy

Arguments for the preparePathways()

Value

A list:

res  A matrix, each row refers to one pathway, each column to one centrality and the value is a p-value.

topo.sig  A list of weights for genes (nodes) in individual pathways

degtest  A numeric vector of gene-level differential expression statistics of all genes in the dataset

Author(s)

Ivana Ihnatova

References


See Also

preparePathways

Examples

```r
if (require(DEGraph)) {
  data("Loi2008_DEGraphVignette")
  pathways<-pathways("hsapiens","biocarta")[1:10]
  CePa(exprLoi2008, classLoi2008, pathways, type="MA", logFC.th=-1)
}
## Not run:
if (require(gageData)) {
  data(hnrnp.cnts)
  hnrnp.cnts<hnrnp.cnts[rowSums(hnrnp.cnts)>0,]
  group<-c(rep("sample",4), rep("control",4))

  pathways<-pathways("hsapiens","biocarta")[1:10]
  SPIA( hnrnp.cnts, group, pathways, type="RNASeq", logFC.th=-1, IDs="entrez", test="vstlimma")
}
## End(Not run)
```
clipper is a method for topological gene set analysis. It implements a two-step empirical approach based on the exploitation of graph decomposition into a junction tree to reconstruct the most relevant signal path. In the first step clipper selects significant pathways according to statistical tests on the means and the concentration matrices of the graphs derived from pathway topologies. Then, it "clips" the whole pathway identifying the signal paths having the greatest association with a specific phenotype.

Usage

```r
clipper(x, group, pathways, type, preparePaths=TRUE, norm.method=NULL, test.method=NULL, method="mean", testCliques=FALSE, nperm=1000, alphaV=0.05, b=1000, permute=TRUE, portions=FALSE, both.directions=TRUE, maxNodes=150, minEdges=0, commonTh=2, filterSPIA=FALSE, convertTo="none")
```

Arguments

- `x`: An `ExpressionSet` object or a gene expression data matrix or count matrix, rows refer to genes, columns to samples.
- `group`: Name or number of the phenoData column or a character vector or factor that contains required class assigments.
- `pathways`: A list of pathways in a form from `graphite` package or created by `preparePathways()`.
- `type`: Type of the input data, "MA" for microarray and "RNASeq" for RNA-Seq.
- `preparePaths`: Logical, by default the pathways are transformed with `preparePathways()`.
- `norm.method`: Character, the method to normalize RNAseq data. If `NULL` then TMM-normalization is performed. Possible values are: "TMM", "DESeq2", "rLog", "none".
- `test.method`: Character, the method for differential expression analysis of RNAseq data. If `NULL` then "voomlimma" is used. Possible values are: "DESeq2", "voomlimma", "vstlimma", "edgeR". This analysis is needed only for the visualization.
- `method`: Character, "mean" or "var", the kind of test to perform on the cliques.
- `testCliques`: Logical, if `TRUE` then the test is applied also on the cliques of the each pathway. It is a very time consuming calculation, especially for many or big pathways.
- `nperm`: Number of permutations.
- `alphaV`: Numeric, the threshold for variance test. The calculation of mean test depends on the result of variance test.
- `b`: number of permutations for mean analysis.
- `permute`: always performs permutations in the concentration matrix test. If `FALSE`, the test is made using the asymptotic distribution of the log-likelihood ratio. This option should be use only if samples size is >=40 per class.
- `portions`: Logical, if `TRUE` then the most transcriptionally altered portions of the graph is also detected, if `FALSE` (default) only whole pathway is tested.
- `both.directions`, `maxNodes`, `minEdges`, `commonTh`, `filterSPIA`, `convertTo`, `convertBy`: Arguments for the `preparePathways()` function.
Value

A list. First slot is a data frame containing p-values and q-values of mean and variance tests on pathways. The second slot is a list containing data.frames of the most affected paths in each pathway. The columns of the data frames contain: 1 - Index of the starting clique 2 - Index of the ending clique 3 - Index of the clique where the maximum value is reached 4 - length of the path 5 - maximum score of the path 6 - average score along the path 7 - percentage of path activation 8 - impact of the path on the entire pathway 9 - clique involved and significant 10 - clique forming the path 11 - genes forming the significant cliques 12 - genes forming the path

topo.sig

if test Cliques=TRUE, a list where each slot contains the p-values and a list of cliques in one pathway. NULL otherwise

degtest

A data.frame of gene-level differential expression statistics

Note

If there are NA's only in columns 3 to 7, then a junction tree could not be formed.

Author(s)

Ivana Ihnatova

References


See Also

preparePathways

Examples

if (require(DEGraph)) {
  data("Loi2008_DEGraphVignette")
  pathways<-pathways("hsapiens","kegg")[[1]]
  clipper( exprLoi2008, classLoi2008, pathways,type="MA", convertTo="none")
}
## Not run:
if (require(gageData)) {
  data(hnrnp.cnts)
  hnrnp.cnts<-hnrnp.cnts[rowSums(hnrnp.cnts)>0,]
  group<-c(rep("sample",4), rep("control",4))
  pathways<-pathways("hsapiens","kegg")[[1:3]]
  clipper(hnrnp.cnts, group,pathways, type="RNASeq", norm.method="TMM", convertTo="none")
}
collectWeightsPRS

*Function to calculate gene-level weights for topology-based pathway analysis*

**Description**

The functions calculate gene-level weights defined in various topology-based pathway analysis methods (PRS, SPIA, PWEA). In PRS, it is the number of downstream differentially expressed genes. TIF, the statistic defined in PWEA, is related to the ratio of correlation and distance of genes. SPIA defines the so called net perturbation factors.

**Usage**

```r
collectWeightsPRS(de, all, pathways)
collectWeightsSPIA(de, all, pathways)
prepareTIF(pathways, exprs, alpha)
```

**Arguments**

- `de`: Named numeric vector, the log fold-changes of the differentially expressed genes
- `all`: Character vector of all genes measured in the experiment
- `pathways`: A list of pathways, each pathway is an object of class `Pathway` transformed via `preparePathways()` for the particular method
- `exprs`: A numeric matrix, gene expression data matrix, rows refer to genes, columns to samples
- `alpha`: Numeric, a threshold to control the magnitude. In TIF calculation, the effect of a gene on a few nearby and tightly correlated genes can be washed out if the gene influences many other genes weakly. The threshold suppresses this washing-out

**Value**

A list, each slot is a vector of gene-level weights for one pathway

**Author(s)**

Ivana Ihnatova

**Examples**

```r
pathways<-pathways("hsapiens","kegg")[1:3]
de<-setNames(rnorm(30),sample(nodes(pathways[[1]]),30))
all<-nodes(pathways[[1]])

path<preparePathways(pathways[1:3], method="SPIA", genes=all, both.direction=TRUE, convertTo="none")
collectWeightsSPIA(de, all, path)
```
convertIdentifiersByVector

Function to convert identifiers in pathways by user specified vector

Description

The function converts identifiers of nodes in a pathway. It uses the user specified named vector for the conversion.

Usage

convertIdentifiersByVector(pathway, conv.table, id.type="unknown")

Arguments

pathway An object of class Pathway
conv.table A named vector in which names correspond to the identifiers present in the pathway and values are the new identifiers to which conversion happens
id.type A character, the type of the identifiers provided e.g "TAIR" for TAIR numbers. This is for informative purposes only.

Value

A Pathway in which identifiers have been converted

Author(s)

Ivana Ihnatova

See Also

convertIdentifiers

Examples

g<-kegg["Asthma"]
conv<-setNames(paste("gene", 1:length(nodes(g)), sep=""), nodes(g))
gc<-convertIdentifiersByVector(g, conv, "dummy")
nodes(gc)
edges(gc)
DEGraph

Function to use DEGraph method on microarray or RNA-Seq data

Description

DEGraph implements recent hypothesis testing methods which directly assess whether a particular gene network is differentially expressed between two conditions. It employs Graph Laplacian, Fourier transformation and multivariate T2-statistic.

Usage

DEGraph(x, group, pathways, type, preparePaths=TRUE, norm.method=NULL, test.method=NULL, overall="biggest", useInteractionSigns=TRUE, EdgeAttrs=NULL, both.directions=TRUE, maxNodes=150, minEdges=0, commonTh=2, filterSPIA=FALSE, convertTo="none")

Arguments

x
An ExpressionSet object or a gene expression data matrix or count matrix, rows refer to genes, columns to samples.
group
Name or number of the phenoData column or a character vector or factor that contains required class assignments.
pathways
A list of pathways in a form from graphite package or created by preparePathways().
type
Type of the data, "MA" for microarray and "RNASeq" for RNA-Seq.
preparePaths
Logical, by default the pathways are transformed with preparePathways(). Use FALSE, if you have done this transformation separately.
norm.method
Character, the method to normalize RNAseq data. If NULL then TMM-normalization is performed. Possible values are: "TMM", "DESeq2", "rLog", "none".
test.method
Character, the method for differential expression analysis of RNAseq data. If NULL then "voomlimma" is used. Possible values are: "DESeq2", "voomlimma", "vstlimma", "edgeR". This analysis is needed only for the visualization.
overall
Character, how should the overall p-value for a pathway be calculated. The possible values are: "mean", "min", "biggest". "biggest" returns the p-value of the biggest connected component.
useInteractionSigns
Logical, should types of interaction be included in the analysis?
EdgeAttrs
A list containing two data.frames. See makeDefaultEdgeData() for the details. The interactions are assigned signs according to the beta column of the second data.frame. The procedure is similar to the SPIA method.
both.directions, maxNodes, minEdges, commonTh, filterSPIA, convertTo, convertBy
Arguments for the preparePathways()

Value

A list:
res
Results from analysis of individual pathways. The first column refers to the overall p-value for a pathway. Then groups of four columns follows. One group refers to one connected component and contains a pair of p-values (without and with Fourier transformation), graph and number of Fourier components used in the test. The number of groups is equal to the highest number of components.
Function to estimate multi-subunit protein complexes and gene families in a pathway

Description

Function estimates the multi-subunit protein complexes and gene families in a pathway. A protein complex consists of proteins connected by undirected binding interaction. A gene family is a set of nodes with same outgoing and/or incoming edges.

Usage

```r
estimateCF(graph)
```
graphNEL2Pathway

Arguments

graph  An object of class Pathway

Value

complexes  A list of estimated protein complexes’
families  A list of estimated gene families

The function attempts to assign a representative name to each gene family. The representative name is a common part of the names of individual genes. This approach, however, may lead to ambiguities or missings. Then a general name in a form of family1, family2, etc. All the complexes are named analogously as complex1, complex2.

Author(s)

Ivana Ihnatova

See Also

reduceGraph

Examples

path<-pathways("hsapiens","kegg")[[1]]
estimateCF(path)

graphNEL2Pathway  Function to coerce a graphNEL to a Pathway

Description

The function coerces a graphNEL to a Pathway. It attempts to recover the edge types from "edgeType" attribute of edgeData. The result contains only the edge types present in the graph. If the edgeData do not contain this attribute, then "process(indirect effect)" is used in order to preserve directionality.

Usage

graphNEL2Pathway(graph, name = "pathway", ident = "unknown", database = "unknown", species = "unknown", date = NULL)

Arguments

graph  A graphNEL object to be coerced.
name  A character, name of the pathway. Defaults to "pathway"
ident  A character, type of the identifiers, e.g "gene symbol"
database  A character, the name of the database the topology comes from
species  A character, the species to which the topology belong
date  A date, the date the topology was created
**Value**

A coerced Pathway

**Note**

When this function is applied on `x` as reversed operation to `pathwayGraph` then the order of the edges may differ as well as the directionality of "process(indirect)" edges as they are set as undirected by `graphNEL2Pathway`.

**Author(s)**

Ivana Ihnatova

**Examples**

```r
pathway<-pathways("hsapiens","kegg")[[1]]
pathway<-pathwayGraph(pathway)
pathway

set.seed(123)
rg <- randomEGraph(LETTERS[1:20], edges = 30)
p<-graphNEL2Pathway(rg)
p
head(edges(p))
```

---

**KEGG2Pathway**  
*Function to parse KEGG KGML file into a Pathway*

**Description**

The function parses a KGML file from KEGG into a Pathway.

**Usage**

```r
KEGG2Pathway(file, expandGenes = TRUE, expandCom = TRUE, nongene = c("keep", "propagate", "discard"), ident = "KEGGnative", database = "KEGG", species = NULL)
```

**Arguments**

- `file`  
  Character, the name of the file to be parsed. Download manually or in bulk from KEGG

- `expandGenes`  
  Logical, should multi-gene nodes be expanded into separate nodes?

- `expandCom`  
  Logical, should undirected binding interactions be added between nodes from one group (usually multi-subunit protein complex, which is turned into a clique)

- `nongene`  
  Character, how should be the non-gene nodes parsed? If "discard" they are removed from the pathway. If "propagate", they are removed but the interactions are preserved (e.g. if gene A interacts with compound c and compound c interacts with gene B, then the interaction between A and B is preserved. Otherwise, they are kept in the pathway topology)

- `ident`  
  Character, the type of the node identifiers.

- `database`  
  Character, the name of the database

- `species`  
  Character, the three-letter code for the species-specific pathways. If NULL then, the first 3 letters from the file are used.
Value

A Pathway

Author(s)

Ivana Ihnatova

---

**Description**

This function creates a list containing auxiliary data needed in SPIA method for conversion between edge types and dividing interaction into three categories: positive, negative and neutral.

**Usage**

`makeDefaultEdgeData`

**Details**

The first slot called `graphite2SPIA` contains a mapping table between edge types in topologies from graphite and edge types which are used in the implementation of SPIA in SPIA package. All of the edge types present in the topologies must be also covered by this table otherwise the method could not be applied.

The second slot called `beta` divides the 25 interaction types into three categories: positive (`beta=1`), negative (`beta=-1`) and neutral (`beta=0`) in the sense of gene regulation. Only user familiar with all the details of SPIA should change this.

**Value**

A list of two data frames explained in the Details. The format is:

```
$ graphite2SPIA: chr [1:26, 1:2] "binding" "control(In(ACTIVATION))" "control(In(INHIBITION))" ...
..- attr(*, "dimnames")=List of 2
...$ beta: num [1:25] 1 0 0 1 -1 1 0 -1 -1 0 ...
```

**Source**

The data are manually curated from the unexported objects from graphite package version 1.10.1.

**Examples**

```
str(makeDefaultEdgeData())
```
parseKEGG

Function to covert KEGG pathways for topology-based pathway analysis

Description

The function processes KGML files from KEGG located on local drive to the format suitable for topology-based pathway analysis. The processing is method-specific and the processed object can be used only with the matching method.

Usage

parseKEGG(pathfolder, method)

Arguments

pathfolder A character, path to the folder with KGML files. For working directory use "./"
method A character, name of the method. Currently implemented are: SPIA, PRS, CePa, DEGraph, clipper

Details

Nodes, relations and reactions found in KGML files are processed as in the original implementation of the methods, or as stated in the original publication. For clipper, the graphite’s approach described in Sales, 2012 was used.

preparePaths=FALSE must be used in functions that apply the method e.g. SPIA()

Value

List of parsed pathways. The exact form is method-specific.

Author(s)

Ivana Ihnatova

Examples

## Not run:
# to parse all xml files in the working directory
parseKEGG("./", "PRS")

## End(Not run)
Description

This class represents a biological pathway. changeInteraction and changeDirection are a new generic function designed for Pathway class.

Methods

edges signature(object = "Pathway"): retrieves the data.frame describing the pathway edges.

nodes signature(object = "Pathway"): retrieves the vector enumerating the identifiers of the pathway nodes.

The methods below perform basic topological analysis of a pathway. They were defined as generic in graph for graph class. They were implemented for Pathway in this package.

degree signature(object = "Pathway", Nodes = "character") Returns the number of incoming or outgoing edges for nodes in Nodes.

degree signature(object = "Pathway", Nodes = "missing") Returns the number of incoming or outgoing edges for all nodes in object.

numNoEdges signature(objGraph = "Pathway") Returns the number of nodes without any edge.

mostEdges signature(objGraph = "Pathway") Returns the nodes with most edges.

acc signature(object = "Pathway", index = "character") Returns the set of nodes accessible from nodes in index. The undirected edges are considered as bidirected (directed in both directions).

connComp signature(object = "Pathway") Returns the connected components present in a pathway. They are returned as list where each slot refers to one component and contains the relevant nodes. The undirected edges are considered as bidirected (directed in both directions).

edges signature(object = "Pathway", which = "character") Returns the edges relevant to node(s) in which.

isAdjacent signature(object = "Pathway", from = "character", to = "character") Returns whether nodes in from and to are adjacent (there is an edge starting in from and ending in to).

isConnected signature(object = "Pathway") Returns TRUE if a pathway contains only one connected component.

isDirected signature(object = "Pathway") Returns TRUE if all edges in a pathway are directed.

edgemode signature(object = "Pathway") Returns the type of edges in a pathway: directed, undirected or both.

numEdges signature(object = "Pathway") Returns the number of edges in a pathway.

numNodes signature(object = "Pathway") Returns the number of nodes in a pathway.

edgeNames signature(object = "Pathway") Returns the names of the edges in a following format: starting node ~ ending node.

All of the methods below return an object of class Pathway with modified topology.

intersection signature(x = "Pathway", y = "Pathway") compute the intersection of the two supplied graphs. They must have identical nodes.
join signature(x = "Pathway", y = "Pathway") returns the joining of the two graphs. It is similar to intersection but does not require the identical nodes

union signature(x = "Pathway", y = "Pathway") compute the union of the two supplied graphs. They must have identical nodes.

subGraph signature(snodes = "character", graph = "Pathway") Given a set of nodes and a pathway this function creates and returns subgraph with only the supplied nodes and any edges between them

clearNode signature(node = "character", object = "Pathway") Clears all edges incoming and outgoing edges from node

removeEdge signature(from = "character", to = "character", graph = "Pathway") removes all directed edges starting in from and ending in to and undirected edges between from and to

removeNode signature(node = "character", object = "Pathway") removes node(s) node from a pathway object

nodes<- signature(x = "Pathway", value = "character") sets node labels of pathway object to value

convertIdentifiers signature(x = "Pathway", to = "character") converts the node identifiers/labels in a pathway. to is the name of one of the columns provided by an Annotation package (e.g. "SYMBOL"

---

**preparePathways**

Function to prepare pathways for topology-based pathway analysis

**Description**

Functions transforms pathways from graphite package (stored as Pathway-class) into formats required in the particular topology-based method implemented in this package. It also converts identifiers in the pathways and filters pathways according to several criteria.

**Usage**

```r
preparePathways(pathways, method, both.directions, genes, maxNodes = 150, minEdges = 0, commonTh = FALSE, convertTo = "entrez", convertBy = NULL, EdgeAttrs = NULL)
```

**Arguments**

- **pathways** A list of pathways, individual pathways are objects of class Pathway stored in PathwayList
- **method** A character, the pathways will be transformed according to the needs of the particular method. Possible values are: "TAPPA", "PRS", "PWEA", "TopologyGSA", "clipper", "DEGraph"
- **both.directions** Logical, indicates how should be the undirected edges directed. If TRUE, an undirected edge is substituted with two directed edges with opposite directions (e.g. A-B becomes A->B and B->A). If FALSE, then an undirected edge is substituted with one directed edge which preserves the order of nodes (e.g. A-B becomes A->B).
- **genes** Character vector, vector of gene identifiers in the expression data
- **maxNodes** Numeric, maximal number of nodes. Pathways with more nodes are filtered out.
- **minEdges** Numeric, minimal number of edges. Pathways with less edges are filtered out.
commonTh Numeric, threshold for number of nodes present in the data. Pathways with less node-identifiers matching to genes are filtered out.

filterSPIA Logical, if TRUE applies filter defined in the SPIA method (relates to the calculation of inversion matrix).

convertTo Character. If "none" no conversion is performed. Otherwise, the function converts node-identifiers in pathways as in graphite. It uses annotation package for the mapping.

convertBy Named character vector, names of the element must match the node-identifiers and the values are the new identifiers to be replaced. This is a more general option designed for pathways outside graphite.

EdgeAttrs A list of two tables required for the filter from SPIA method. See makeDefaultEdgeData for the details.

Value
A list of the transformed pathways

Author(s)
Ivana Ihnatova

See Also
makeDefaultEdgeData

Examples

#Creating dummy set of genes
set.seed(123)
pathways<-pathways("hsapiens","kegg")[1:3]
genesc<-unname(unlist(lapply(pathways[1:3], nodes)))
genesc<-sample(genesc, length(genesc)*0.9)

#Applying the function
paths<-preparePathways(pathways[1:3], "TAPPA", TRUE, genesc, maxNodes=65, convertTo="none")
paths

PRS Function to use PRS method on microarray or RNA-Seq data

Description
A function runs PRS method on a gene expression data matrix or count matrix and vector dividing samples into two groups and a set of pathways from graphite package. The PRS method (please see Reference for the details) was adapted to graphite’s graphs where each node is represented only by one gene.
Usage

```r
PRS(x, group, pathways, type, preparePaths=TRUE, norm.method=NULL, test.method=NULL, p.th=0.05, logFC.th=2, nperm=1000, both.directions=TRUE, maxNodes=150, minEdges=0, commonTh=2, filterSPIA=FALSE, convertTo="none", convertBy=NULL)
```n
Arguments

- **x**: An ExpressionSet object or a gene expression data matrix or count matrix, rows refer to genes, columns to samples
- **group**: Name or number of the phenoData column or a character vector or factor that contains required class assignments
- **pathways**: A list of pathways in a form from `graphite` package or created by `preparePathways()`
- **type**: Type of the data, "MA" for microarray, "RNASeq" for RNA-Seq, `DEtable` data.frame from differential expression analysis, or `DEGlist` a list of: log fold-changes of differentially expressed genes and names of the all genes analyses
- **preparePaths**: Logical, by default the pathways are transformed with `preparePathways()`. Use FALSE, if you have done this transformation separately
- **norm.method**: Character, the method to normalize RNAseq data. If NULL then TMM-normalization is performed. Possible values are: "TMM", "DESeq2", "rLog", "none". Ignored for type: "MA","DEtable","DEGlist"
- **test.method**: Character, the method for differential expression analysis of RNAseq data. If NULL then "voomlimma" is used. Possible values are: "DESeq2", "voomlimma", "vstlimma", "edgeR". Ignored for type: "MA","DEtable","DEGlist"
- **p.th**: Numeric, threshold for p-values of tests for differential expression of genes. Use 1 if you don’t want any threshold to be applied
- **logFC.th**: Numeric, threshold for log fold-change of a gene to identify the gene as differentially expressed. Use negative if you don’t want any threshold to be applied
- **nperm**: Numeric, number of permutations
- **both.directions**, **minEdges**, **commonTh**, **filterSPIA**, **convertTo**, **convertBy**: Arguments for the `preparePathways()`

Value

- A list,
  - **res**: A data frame with normalized score, p-value and FDR-adjusted p-value for each pathway
  - **topo.sig**: A list with log fold-changes and number of downstream differentially expressed nodes for nodes of individual pathways
  - **degtest**: A named vector of statistics from testing the differential expression of genes

Author(s)

- Ivana Ihnatova

References

PWEA

Function to use PWEA method on microarray or RNA-Seq data

Description

The function runs PWEA method (please see References for the details) on gene expression data matrix, vector specifying to which group a sample belongs and a list of pathway graphs. Briefly, it is a weighted GSEA-like method. The weights are based on the distance and Pearson’s correlation between genes in a pathway.

Usage

PWEA(x, group, pathways, type, preparePaths=TRUE, norm.method=NULL, test.method=NULL, tif=NULL, alpha=0.05, nperm=1000, ncores=NULL, both.directions=TRUE, maxNodes=150, minEdges=0, commonTh=2, filterSPIA=FALSE, convertTo="none", convertBy=NULL)

Arguments

x An ExpressionSet object or a gene expression data matrix or count matrix, rows refer to genes, columns to samples. Or a list of two data.frames: observed and random (after group permutations) of statistics of differential expression of genes

group Name or number of the phenoData column or a character vector or factor that contains required class assignments

pathways A list of pathways in a form from graphite package or created by preparePathways()

type Type of the data, "MA" for microarray, "RNASeq" for RNA-Seq or "DEtable" for a list of observed and random gene-level statistics

preparePaths Logical, by default the pathways are transformed with preparePathways(). Use FALSE, if you have done this transformation separately

Examples

if (require(DEGraph)) {
  data("Loi2008_DEGraphVignette")
  pathways<-pathways("hsapiens","biocarta")[1:10]
  PRS( exprLoi2008, classLoi2008, pathways, type="MA", logFC.th=-1, nperm=100)
}
## Not run:
if (require(gageData)) {
  data(hnrnp.cnts)
  hnrnp.cnts<-hnrnp.cnts[rowSums(hnrnp.cnts)>0,]
  group<-c(rep("sample",4), rep("control",4))
  pathways<-pathways("hsapiens","biocarta")[1:10]
  PRS(hnrnp.cnts, group, pathways, type="RNASeq", logFC.th=-1, nperm=100, test="vstlimma")
}
## End(Not run)
norm.method Character, the method to normalize RNAseq data. If NULL then TMM-normalization is performed. Possible values are: "TMM", "DESeq2", "rLog", "none"

test.method Character, the method for differential expression analysis of RNAseq data. If NULL then "voomlimma" is used. Possible values are: "DESeq2", "voomlimma", "vstlimma", "edgeR"

tif A list of Topology Influence Factor's. One slot refers to one pathway. Use prepareTIF() to create it. It is required only if type="DEtable"

alpha Numeric, a threshold value used during TIF calculation

nperm Numeric, number of permutations. Used only if x %in% c("MA", "RNASeq")
ncores Numeric, number of cores. Used only if x %in% c("MA", "RNASeq"). The permutations are calculated in parallel way both.directions, maxNodes, minEdges, commonTh, filterSPIA, convertTo, convertBy

Arguments for the preparePathways()

Value

A list

res A data frame, rows refer to pathways. It contains: Enrichment score for a pathway, p-value and p-value adjusted for multiple hypothesis testing by Benjamini-Hochberg’s FDR method. NA's if less than 2 nodes are present in the data

topo.sig A list, topology influence factors for the genes in individual pathways. NULL if less than 2 nodes are present in the data

degtest A named vector of statistics from testing the differential expression

Author(s)

Ivana Ihnatova

References


See Also

preparePathways, prepareTIF

Examples

## Not run:
if (require(DEGraph)) {
  data("Loi2008_DEGraphVignette")
  pathways<-pathways("hsapiens", "biocarta")[1:10]
  PWEA(exprLoi2008, classLoi2008, pathways, type="MA", nperm=100)
}

if (require(gageData)) {
  data(hnrnp.cnts)
  hnrnp.cnts<-hnrnp.cnts[rowSums(hnrnp.cnts)>0,]
  group<-c(rep("sample",4), rep("control",4))
  pathways<-pathways("hsapiens", "biocarta")[1:10]
PWEA(hnrnp.cnts, group, pathways, type="RNASeq", test="vstlimma", nperm=100)
}
## End(Not run)

reduceGraph

Function to reduce the pathway graph

Description

Function simplifies a pathway graph topology. It merges a user specified nodes into a one. The specified set of nodes must be either a gene family or a protein complex. By a gene family we mean a set of genes with same outgoing or incoming edges. On the other hand, a protein complex is a set of nodes with only undirected binding edges between them and the number of edges is equal to the complex size.

Usage

reduceGraph(graph, reduction)

Arguments

graph An object of class Pathway, a pathway to be reduced
reduction A named list of reductions to be made.

Value

A Pathway

Author(s)

Ivana Ihnatova

Examples

pathways<-pathways("hsapiens","kegg")["Prolactin signaling pathway"]
pathways<-convertIdentifiers(pathways[[1]], "SYMBOL")

#gr<-as(pathways,"pathway")
red<-list(RAS=c("NRAS","KRAS","HRAS"), SHC=c("SHC1","SHC4","SHC2","SHC3"))
reduced<-reduceGraph(pathways, red)
reduced

par(mfrow=c(1,2))
nA<-list(fillcolor=c(NRAS="red", KRAS="red", HRAS="red", SHC1="green", SHC4="green", SHC2="green", SHC3="green"))
plot(as(pathways,"graphNEL"), nodeAttrs=nA, attrs=list(node=list(fontsize=30, height=40)), main="Before")
plot(as(reduced,"graphNEL"),
 nodeAttrs=list(fillcolor=c(RAS="red", SHC="green")), attrs=list(node=list(fontsize=30, height=40)), main="After")

#this throws an error, "RELA","FOS","NFKB1" is not correct set of genes
## Not run:
res functions to extract parts of object

**Description**
Function extracts part of an object named "res", "topo.sig", "degtable"

**Usage**
res(object)
topo.sig(object)
degtable(object)

**Arguments**
object Object of defined class. Methods for topResult are available in this package

**Value**
Extracted parts of an object. Data type varies between parts and the origin of the object

**Author(s)**
Ivana Ihnatova

---

SPIA function to use SPIA method on microarray or RNA-Seq data

**Description**
The function runs SPIA method on microarray or RNA-Seq data. The implementatio includes the identification of differentially expressed genes and transformation of pathways’ topologies to an appropriate form. The SPIA method combines two independent p-values. One p-value comes from overrepresentation analysis and the other is so called pertubation factor.

**Usage**
SPIA(x, group, pathways, type, preparePaths=TRUE, norm.method=NULL, test.method=NULL, p.th=0.05, logFC.th=2, nperm=1000, combine="fisher", both.directions=TRUE, maxNodes=150, minEdges=0, commonTh=2, filterSPIA=FALSE, convertTo="none", ...)
Arguments

x  An ExpressionSet object or a gene expression data matrix or count matrix, rows refer to genes, columns to samples

group  Name or number of the phenoData column or a character vector or factor that contains required class assignments

pathways  A list of pathways in a form from graphite package or created by preparePathways()

type  Type of the data, "MA" for microarray, "RNASeq" for RNA-Seq, DEtable data.frame from differential expression analysis, or DEGlist a list of: log fold-changes of differentially expressed genes and names of the all genes analyses

preparePaths  Logical, by default the pathways are transformed with preparePathways(). Use FALSE, if you have done this transformation separately

norm.method  Character, the method to normalize RNAseq data. If NULL then TMM-normalization is performed. Possible values are: "TMM", "DESeq2", "rLog", "none". Ignored for type: "MA", "DEtable", "DElist"

test.method  Character, the method for differential expression analysis of RNAseq data. If NULL then "voomlimma" is used. Possible values are: "DESeq2", "voomlimma", "vstlimma", "edgeR". Ignored for type: "MA", "DEtable", "DElist"

p.th  Numeric, threshold for p-values of tests for differential expression of genes. Use 1 if you don’t want any threshold to be applied

logFC.th  Numeric, threshold for log fold-change of a gene to identify the gene as differentially expressed. Use negative if you don’t want any threshold to be applied

nperm  Numeric, number of permutations

combine  Character, the method to combine p-values. Defaults to "fisher" for Fisher’s method. The other possible value is "norminv" for the normal inversion method.

both.directions, maxNodes, minEdges, commonTh, filterSPIA, convertTo, convertBy  Arguments for the preparePathways()

Value

A list:

res  A matrix with columns as described below: pSize - Pathway size, number of genes, NDE - Number of differentially expressed genes, pNDE - P-value of the overrepresentation part of the method, tA - The observed total preturbation accumulation in the pathway, pPERT - P-value of the perturbation part of the method, p - Combined p-value (overrepresentation and perturbation), pFdr - False discovery rate adjusted p, pFWER - FWER adjusted p, Status - If a pathway was identified as Activated or Inhibited

topo.sig  A list of accumulated perturbation factors and log fold-changes for genes in individual pathways

degtest  A numeric vector of gene-level differential expression statistics of all genes in the dataset

Author(s)

Ivana Ihnatova
References


See Also

preparePathways

Examples

if (require(DEGraph)) {
  data("Loi2008_DEGraphVignette"
  pathways<-pathways("hsapiens","biocarta")[1:10]
  SPIA(exprLoi2008, classLoi2008,pathways, type="MA", logFC.th=-1)
}
## Not run:
if (require(gageData)) {
  data(hnrnp.cnts)
  hnrnp.cnts<-hnrnp.cnts[rowSums(hnrnp.cnts)>0,]
  group<-c(rep("sample",4), rep("control",4))

  pathways<-pathways("hsapiens","biocarta")[1:10]
  SPIA( hnrnp.cnts, group, pathways, type="RNASeq", logFC.th=-1, IDs="entrez", test="vstlimma")
}
## End(Not run)

SPIA4analysis

Function to further process pathways for SPIA

Description

The functions further process pathways prepared by parseKEGG() by "SPIA" method. SPIA4analysis prepares pathways for SPIA() function. SPIA2graph creates graphs, that can be used to visualize the pathway structure. Note, that the information about the edge type is lost during creation.

Usage

SPIA4analysis(pathways, EdgeAttrss = NULL)
SPIA2graph(pathways)

Arguments

pathways A list of pathways as obtained from parseKEGG
EdgeAttrss A list of edge attributes. If NULL, it is created by makeDefaultEdgeData().
Value

List of pathways

Author(s)

Ivana Ihnatova

See Also

parseKEGG

Examples

```r
## Not run:
spiapt<-parseKEGG("./", "SPIA")
spiapt<-SPIA4analysis(spiapt)
SPIA(GEDM, group, spiapt, type="MA", preparePaths=FALSE)
## End(Not run)
```

TAPPA

Function to use TAPPA method on microarray or RNA-Seq data

Description

The function analyses the differential expression of pathways via TAPPA method. Expression is compared between two groups of samples by Mann-Whitney test. P-values are later adjusted for multiple hypothesis testing by Benjamini-Hochberg’s FDR method.

Usage

```r
TAPPA(x, group, pathways, type, preparePaths=TRUE, norm.method=NULL, test.method=NULL, test=t.test, normalize=TRUE, verbose=FALSE, both.directions=TRUE,
maxNodes=150, minEdges=0, commonTh=2, filterSPIA=FALSE, convertTo="none", convertBy=NULL)
```

Arguments

- `x`: An ExpressionSet object or a gene expression data matrix or count matrix, rows refer to genes, columns to samples
- `group`: Name or number of the phenoData column or a character vector or factor that contains required class assignments
- `pathways`: A list of pathways in a form from graphite package or created by preparePathways()
- `type`: Type of the input data, "MA" for microarray and "RNASeq" for RNA-Seq
- `preparePaths`: Logical, by default the pathways are transformed with preparePathways(). Use FALSE, if you have done this transformation separately
- `norm.method`: Character, the method to normalize RNAseq data. If NULL then TMM-normalization is performed. Possible values are: "TMM", "DESeq2", "rLog", "none"
- `test.method`: Character, the method for differential expression analysis of RNAseq data. If NULL then "voomlimma" is used. Possible values are: "DESeq2", "voomlimma", "vstlimma", "edgeR"
- `maxNodes`: Maximum number of nodes in a pathway graph
- `minEdges`: Minimum number of edges in a pathway graph
- `commonTh`: Common threshold for adjustment of p-values
- `filterSPIA`: Logical, if TRUE pathways are filtered to contain only genes from input data
- `convertTo`: Character, the method to convert the pathways to a format that can be used by TAPPA
- `convertBy`: Character, the method to convert the pathways to a format that can be used by TAPPA

This analysis is needed only for the visualization.
Function implementing a statistical test comparing PCI scores between groups. It is employed as `test(PCI~group)`$p.value$, where PCI is a numeric vector of the same length as group.

**normalize** Logical, should data be normalized?

**verbose** Logical, if TRUE names of the pathways are printed as they are analysed.

**both.directions, maxNodes, minEdges, commonTh, filterSPIA, convertTo, convertBy** Arguments for the `preparePathways()`

**Value**

A list,

**res** A data frame, rows refer to pathways. Columns contain: number of valid PCI-scores, median, min and max of the PCI scores for each group of samples, p-value of the test (p.val) and adjusted p-value (p.adj). If less than two nodes are present in the data, the function puts NA’s in all columns.

**topo.sig** NULL, it is preserved for the compatibility with other methods implemented in this package.

**degtest** A numeric vector of gene-level differential expression statistics

**Author(s)**

Ivana Ihnatova

**References**


**See Also**

`preparePathways`

**Examples**

```r
if (require(DEGraph)) {
  data("Loi2008_DEGraphVignette")
  pathways<-pathways("hsapiens","biocarta")[1:10]
  TAPPA(exprLoi2008, classLoi2008, pathways, type="MA")
}

## Not run:
if (require(gageData)) {
  data(hnrnp.cnts)
  group<-c(rep("sample",4), rep("control",4))
  hnrnp.cnts<-hnrnp.cnts[rowSums(hnrnp.cnts)>0,]
  pathways<-pathways("hsapiens","biocarta")[1:10]
  TAPPA( hnrnp.cnts, group, pathways, type="RNASeq", norm.method="TMM")
}

## End(Not run)
```
Description

These functions are provided for compatibility with older versions of ‘ToPASeq’ only, and will be defunct at the next release.

Details

The following functions are deprecated and will be made defunct; use the replacement indicated below:

- AdjacencyMatrix2pathway: `AdjacencyMatrix2Pathway`
- graphNEL2pathway: `graphNEL2Pathway`
- KEGG2pathway: `KEGG2Pathway`

Usage

`TopologyGSA(x, group, pathways, type, preparePaths=TRUE, norm.method=NULL, test.method=NULL, method="mean", alpha=0.05, testCliques=FALSE, ...,
both.directions=TRUE, maxNodes=150, minEdges=0, commonTh=2, filterSPIA=FALSE, convertTo="none")`

Arguments

- `x`: An ExpressionSet object or a gene expression data matrix or count matrix, rows refer to genes, columns to samples
- `group`: Name or number of the phenoData column or a character vector or factor that contains required class assignments
- `pathways`: A list of pathways in a form from `graphite` package or created by `preparePathways()`
- `type`: Type of the input data, "MA" for microarray and "RNASeq" for RNA-Seq
- `preparePaths`: Logical, by default the pathways are transformed with `preparePathways()`. Use `FALSE`, if you have done this transformation separately
- `norm.method`: Character, the method to normalize RNAseq data. If `NULL` then TMM-normalization is performed. Possible values are: "TMM", "DESeq2", "rLog", "none"
- `test.method`: Character, the method for differential expression analysis of RNAseq data. If `NULL` then "voomlimma" is used. Possible values are: "DESeq2", "voomlimma", "vstlimma", "edgeR". This analysis is needed only for the visualization.
- `method`: Either "var" and "mean". Determine the type of test used by `TopologyGSA`. 

Function to use TopologyGSA method on microarray or RNA-Seq data

Description

TopologyGSA method uses graphical models to test the differential expression of a pathway. It also highlights pathway components involved in the deregulation.

Usage

`TopologyGSA(x, group, pathways, type, preparePaths=TRUE, norm.method=NULL, test.method=NULL, method="mean", alpha=0.05, testCliques=FALSE, ...,
both.directions=TRUE, maxNodes=150, minEdges=0, commonTh=2, filterSPIA=FALSE, convertTo="none")`

Arguments

- `x`: An ExpressionSet object or a gene expression data matrix or count matrix, rows refer to genes, columns to samples
- `group`: Name or number of the phenoData column or a character vector or factor that contains required class assignments
- `pathways`: A list of pathways in a form from `graphite` package or created by `preparePathways()`
- `type`: Type of the input data, "MA" for microarray and "RNASeq" for RNA-Seq
- `preparePaths`: Logical, by default the pathways are transformed with `preparePathways()`. Use `FALSE`, if you have done this transformation separately
- `norm.method`: Character, the method to normalize RNAseq data. If `NULL` then TMM-normalization is performed. Possible values are: "TMM", "DESeq2", "rLog", "none"
- `test.method`: Character, the method for differential expression analysis of RNAseq data. If `NULL` then "voomlimma" is used. Possible values are: "DESeq2", "voomlimma", "vstlimma", "edgeR". This analysis is needed only for the visualization.
- `method`: Either "var" and "mean". Determine the type of test used by `TopologyGSA`. 

alpha Numeric, threshold for statistical significance of variance test. It influences the method for the mean test
testCliques Logical, if TRUE, then the test is also performed on individual cliques. It can be very computationally complex.
... Other arguments to be passed to the method. See details for better explanation
both.directions, maxNodes, minEdges, commonTh, filterSPIA, convertTo, convertBy
Arguments for the preparePathways()

Details

The method requires a Directed Acyclic Graph (DAG). Therefore if a pathway contain also undirected or bidirected edges and error is thrown.

The user can further specify for the mean test:
1. **perms** number of permutations of the test,
2. **paired** logical flag. If TRUE Hotelling test for paired samples is calculated and the test on the variances is not performed

Or for the variance test:
1. **variance** logical flag. If TRUE the estimates of the covariance matrices are included in the result.
2. **s1** First group covariance matrix estimation.
3. **s2** Second group covariance matrix estimation.

Value

A list

res a list with one entry for each successfully analyzed pathway
topo.sig if testCliques=TRUE, a list where each slot contains the pvalues and a list of cliques in one pathway. NULL otherwise
degtest A numeric vector of gene-level differential expression statistics

Author(s)

Ivana Ihnatova

References

Massa MS, Chiogna M, Romualdi C. Gene set analysis exploiting the topology of a pathway. BMC System Biol. 2010 Sep 1;4:121.

Examples

```r
## Not run:
if (require(DEGraph)) {
  data("Loi2008_DEGraphVignette")
  pathways<-pathways("hsapiens","biocarta")[1:10]
  TopologyGSA(exprLoi2008, classLoi2008, pathways, type="MA", method="mean", alpha=0.05, perms=200)
  TopologyGSA(exprLoi2008, classLoi2008, pathways, type="MA", method="mean", alpha=0.05, perms=200, testCliques=TRUE)
```
if (require(gageData)) {
  data(hnrnp.cnts)
  group<-c(rep("sample",4), rep("control",4))
  hnrnp.cnts<-hnrnp.cnts[rowSums(hnrnp.cnts)>0,]
  pathways<-pathways("hsapiens","biocarta")[1:10]
  TopologyGSA(hnrnp.cnts, group, pathways, type="RNASeq", method="mean", alpha=0.05, perms=200, norm.method="TMM")
}
## End(Not run)
Index

*Topic classes
Pathway-method, 16

*Topic htest
CePa, 4
clipper, 6
DEGraph, 10
PRS, 18
PWEA, 20
SPIA, 23
TAPPA, 26
TopologyGSA, 28

*Topic manip
AdjacencyMatrix2Pathway, 3
convertIdentifiersByVector, 9
estimateCF, 11
graphNEL2Pathway, 12
KEGG2Pathway, 13
makeDefaultEdgeData, 14
parseKEGG, 15
preparePathways, 17
reduceGraph, 22
res, 23
SPIA4analysis, 25

*Topic package
ToPASeq-package, 2

*Topic univar
collectWeightsPRS, 8

acc,Pathway,character-method (Pathway-method), 16
addEdge,character,character,Pathway,numeric-method (Pathway-method), 16
addNode,character,Pathway,list-method (Pathway-method), 16
AdjacencyMatrix2Pathway, 3, 28
AdjacencyMatrix2pathway (ToPASeq-deprecated), 28

CePa, 4
changeDirection (Pathway-method), 16
changeInteraction,character,character,Pathway,character-method (Pathway-method), 16
clearNode,character,Pathway-method (Pathway-method), 16
clipper, 6
collectWeightsPRS, 8
collectWeightsSPIA (collectWeightsPRS), 8
connComp,Pathway-method (Pathway-method), 16
convertIdentifiers, 9
convertIdentifiers,Pathway,character-method (Pathway-method), 16
convertIdentifiersByVector, 9
DEGraph, 10
degree,Pathway,character-method (Pathway-method), 16
degree,Pathway,missing-method (Pathway-method), 16
degtable (res), 23
degtable,Pathway-method (Pathway-method), 16
degtable,Pathway,character-method (Pathway-method), 16
degtable,Pathway,missing-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16

degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16
degtable,Pathway,numeric-method (Pathway-method), 16

intersection,Pathway,Pathway-method (Pathway-method), 16
isAdjacent,Pathway,character,character-method (Pathway-method), 16
isConnected,Pathway-method (Pathway-method), 16
isDirected,Pathway-method (Pathway-method), 16

31
join, Pathway, Pathway-method (Pathway-method), 16
KEGG2Pathway, 13, 28
KEGG2pathway (ToPASeq-deprecated), 28
makeDefaultEdgeData, 18
makeDefaultEdgeData (makeDefaultEdgeData), 14
makeDefaultEdgeData, 14
mostEdges, Pathway-method (Pathway-method), 16
nodes, Pathway-method (Pathway-method), 16
nodes<-, Pathway, character-method (Pathway-method), 16
numEdges, Pathway-method (Pathway-method), 16
numNodes, Pathway-method (Pathway-method), 16
numNoEdges, Pathway-method (Pathway-method), 16
parseKEGG, 15, 26
Pathway-method, 16
preparePathways, 5, 7, 11, 17, 20, 21, 25, 27
prepareTIF, 21
prepareTIF (collectWeightsPRS), 8
PRS, 18
PWEA, 20
reduceGraph, 12, 22
removeEdge, character, character, Pathway-method (Pathway-method), 16
removeNode, character, Pathway-method (Pathway-method), 16
res, 23
show, Pathway-method (Pathway-method), 16
SPIA, 23
SPIA2graph (SPIA4analysis), 25
SPIA4analysis, 25
subGraph, character, Pathway-method (Pathway-method), 16
TAPPA, 26
ToPASeq (ToPASeq-package), 2
ToPASeq-deprecated, 28
ToPASeq-package, 2
topo.sig (res), 23
TopologyGSA, 28
union, Pathway, Pathway-method (Pathway-method), 16