Package ‘NetPathMiner’

April 26, 2017

Version 1.12.0
Date 2014 onwards
Title NetPathMiner for Biological Network Construction, Path Mining and Visualization
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Description NetPathMiner is a general framework for network path mining using genome-scale networks. It constructs networks from KGML, SBML and BioPAX files, providing three network representations, metabolic, reaction and gene representations. NetPathMiner finds active paths and applies machine learning methods to summarize found paths for easy interpretation. It also provides static and interactive visualizations of networks and paths to aid manual investigation.
Depends R (>= 3.0.2), igraph (>= 1.0)
Suggests rBiopaxParser (>= 2.1), RCurl, graph
License GPL (>= 2)
URL https://github.com/ahmohamed/NetPathMiner
NeedsCompilation yes
SystemRequirements libxml2, libSBML (>= 5.5)
Biarch TRUE
biocViews GraphAndNetwork, Pathways, Network, Clustering, Classification
RoxygenNote 5.0.1

R topics documented:

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NetPathMiner-package

General framework for network extraction, path mining.

Description

NetPathMiner implements a flexible module-based process flow for network path mining and visualization, which can be fully integrated with user-customized functions. NetPathMiner supports construction of various types of genome scale networks from KGML, SBML and BioPAX formats, enabling its utility to most common pathway databases. NetPathMiner also provides different visualization techniques to facilitate the analysis of even thousands of output paths.
assignEdgeWeights

Author(s)
Ahmed Mohamed <mohamed@kuicr.kyoto-u.ac.jp>

assignEdgeWeights Assigning weights to network edges

Description
This function computes edge weights based on a gene expression profile.

Usage
assignEdgeWeights(microarray, graph, use.attr, y, weight.method = "cor",
complex.method = "max", missing.method = "median",
same.gene.penalty = "median", bootstrap = 100, verbose = TRUE)

Arguments
microarray Microarray should be a Dataframe or a matrix, with genes as rownames, and samples as columns.
graph An annotated igraph object.
use.attr An attribute name to map microarray rows (genes) to graph vertices. The attribute must be annotated in graph, and the values correspond to rownames of microarray. You can check the coverage and if there are complex vertices using getAttrStatus. You can eliminate complexes using expandComplexes.
y Sample labels, given as a factor or a character vector. This must be the same size as the columns of microarray
weight.method A function, or a string indicating the name of the function to be used to compute the edge weights. The function is provided with 2 numerical vectors (2 rows from microarray), and it should return a single numerical value (or NA). The default computes Pearson’s correlation.
complex.method A function, or a string indicating the name of the function to be used in weighting edges connecting complexes. If a vertex has >1 attribute value, all possible pairwise weights are first computed, and given to complex.method. The default function is max.
missing.method A function, or a string indicating the name of the function to be used in weighting edges when one of the vertices lack expression data. The function is passed all edge weights on the graph. Default is median.
same.gene.penalty A numerical value to be assigned when 2 adjacent vertices have the same attribute value, since correlation and similarity measure will give perfect scores. Alternatively, same.gene.penalty can be a function, computing the penalty from all edge weights on the graph (excluding same-gene and missing values). The default is to take the median
bootstrap An integer n, where the weight.method is performed on n permutations of the gene profiles, and taking the median value. Set it to NA to disable bootstrapping.
verbose Print the progress of the function.
Value

The input graph with edge.weight as an edge attribute. The attribute can be a list of weights if y labels were provided.

Author(s)

Ahmed Mohamed

Examples

```r
## Convert a metabolic network to a reaction network.
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson's correlation.
data(ex_microarray) # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph,
weight.method = "cor", use.attr="miriam.uniprot",
y=factor(colnames(ex_microarray)), bootstrap = FALSE)

# Using Spearman correlation, assigning missing edges to -1
## Not run:
assignEdgeWeights(microarray, graph, use.attr="miriam.affy.probeset",
y=factor(colnames(microarray)),
weight.method = function(x1,x2) cor(x1,x2, method="spearman"),
missing.method = -1)
## End(Not run)
```

biopax2igraph

Processes BioPAX objects into igraph objects

Description

This function takes BioPAX objects (level 2 or 3) as input, and returns either a metabolic or a signaling network as output.

Usage

```r
biopax2igraph(biopax, parse.as = c("metabolic", "signaling"),
expand.complexes = FALSE, inc.sm.molecules = FALSE, verbose = TRUE)
```

Arguments

- **biopax**: BioPAX object generated by `readBiopax`.
- **parse.as**: Whether to process file into a metabolic or a signaling network.
- **expand.complexes**: Split protein complexes into individual gene nodes. Ignored if `parse.as`="metabolic".
- **inc.sm.molecules**: Include small molecules that are participating in signaling events. Ignored if `parse.as`="metabolic".
- **verbose**: Whether to display the progress of the function.
Details
This function requires rBiopaxParser installed.

Users can specify whether files are processes as metabolic or signaling networks.

Metabolic networks are given as bipartite graphs, where metabolites and reactions represent vertex types. Reactions are constructed from Conversion classes, connecting them to their corresponding Lefts and Rights. Each reaction vertex has genes attribute, listing all Catalysis relationships of this reaction. As a general rule, reactions inherit all annotation attributes of its catalyzig genes.

Signaling network have genes as vertices and edges represent interactions, such as activation / inhibition. Genes participating in successive reactions are also connected. Signaling interactions are constructed from Control classes, where edges are drawn from controller to controlled.

All annotation attributes are extracted from XRefs associated with the vertices, and are stored according to MIRIAM guidelines (miraim.db, where db is the database name).

Value
An igraph object, representing a metabolic or a signaling network.

Author(s)
Ahmed Mohamed

See Also
Other Database extraction methods: KGML2igraph, SBML2igraph

Examples
if(require(rBiopaxParser)){
  data(ex_biopax)
  # Process biopax as a metabolic network
  g <- biopax2igraph(ex_biopax)
  plotNetwork(g)

  # Process SBML file as a signaling network
  g <- biopax2igraph(ex_biopax, parse.as="signaling", expand.complexes=TRUE)
}

---

colorVertexByAttr Computes colors for vertices according to their attributes.

Description
This function returns a list of colors for vertices, assigned similar colors if they share a common attribute (ex: in the same pathway, etc).

Usage
colorVertexByAttr(graph, attr.name, col.palette = palette())
expandComplexes

Arguments

graph An annotated igraph object.
attr.name The attribute name (ex: "pathway") by which vertices will be colored. Complex attributes, where a vertex belongs to more than one group, are supported.
col.palette A color palette, or a palette generating function (ex: col.palette=rainbow ).

Value
A list of colors (in HEX format) for vertices.

Author(s)
Ahmed Mohamed

See Also
Other Plotting methods: layoutVertexByAttr, plotAllNetworks, plotClassifierROC, plotClusterMatrix, plotCytoscapeGML, plotNetwork, plotPathClassifier, plotPaths

Examples
data("ex_kgml_sig")
v.colors <- colorVertexByAttr(ex_kgml_sig, "pathway")
plotNetwork(ex_kgml_sig, vertex.color=v.colors)

expandComplexes Expand reactions / complexes into their gene constituents.

Description
These are general functions to expand vertices by their attributes, i.e. create a separate vertex for each attribute value.

Usage
expandComplexes(graph, v.attr, keep.parent.attr = "^pathway", expansion.method = c("normal", "duplicate"), missing.method = c("keep", "remove", "reconnect"))
makeGeneNetwork(graph, v.attr = "genes", keep.parent.attr = "^pathway", expansion.method = "duplicate", missing.method = "remove")
**expandComplexes**

**Arguments**

- **graph**
  An annotated igraph object.

- **v.attr**
  Name of the attribute which vertices are expanded to.

- **keep.parent.attr**
  A (List of) regex expressions representing attributes to be inherited by daughter vertices. If "all" is passed, all parent attributes are inherited.

- **expansion.method**
  If "duplicate", attribute values sharing more than one parent vertex are duplicated for each vertex they participate in. For example, if one gene G1 catalyzes reactions R1, R2; then G1##R1, and G1##R2 vertices are created. If "normal" only one vertex (G1) is created, and inherit all R1 and R2 connections and attributes.

- **missing.method**
  How to deal with vertices with no attribute values. "keep" retains the parent node, "remove" simply deletes the vertex, and "reconnect" removes the vertex and connect its neighbours to each other (to prevent graph cuts).

**Details**

These functions can be very useful when merging networks constructed from different databases. For example, to match a network created from Reactome to a KEGG network, you can expand metabolite vertices by "miriam.kegg.compound" attribute.

**Value**

A new graph with vertices expanded.

makeGeneNetwork returns a graph, where nodes are genes, and edges represent participation in succesive reactions.

**Author(s)**

Ahmed Mohamed

**See Also**

Other Network processing methods: makeReactionNetwork, rmSmallCompounds, simplifyReactionNetwork, vertexDeleteReconnect

**Examples**

```r
## Make a gene network from a reaction network.
data(ex_sbml) # A bipartite metabolic network.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)
ggraph <- makeGeneNetwork(rgraph)

## Expand vertices into their constituent genes.
data(ex_kgml_sig) # Ras and chemokine signaling pathways in human
ggraph <- expandComplexes(ex_kgml_sig, v.attr = "miriam.ncbigene",
keep.parent.attr = c("pathway", "compartment"))

## Create a separate vertex for each compartment. This is useful in duplicating metabolite vertices in a network.
## Not run:
graph <- expandComplexes(graph, v.attr = "compartment",
```
extractPathNetwork

keep.parent.attr = "all",
expansion.method = "duplicate",
missing.method = "keep")

## End(Not run)

extractPathNetwork Creates a subnetwork from a ranked path list

Description

Creates a subnetwork from a ranked path list generated by pathRanker.

Usage

extractPathNetwork(paths, graph)

Arguments

paths The paths extracted by pathRanker.
graph A annotated igraph object.

Value

A subnetwork from all paths provided. If paths are computed for several labels (sample categories), a subnetwork is returned for each label.

Author(s)

Ahmed Mohamed

See Also

Other Path ranking methods: getPathsAsEIDs, pathRanker, samplePaths

Examples

## Prepare a weighted reaction network.
## Conver a metabolic network to a reaction network.
data(ex_sbml)  # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson's correlation.
data(ex_microarray)  # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph,
weight.method = "cor", use.attr="miriam.uniprot",
y=factor(colnames(ex_microarray)), bootstrap = FALSE)

## Get ranked paths using probabilistic shortest paths.
ranked.p <- pathRanker(rgraph, method="prob.shortest.path",
K=20, minPathSize=6)
### Biopax example data

**Description**

A dataset containing Porphyrin metabolism pathway in Biopax Level 3 and parsed with `readBiopax`.

**Examples**

```r
data(ex_biopax)
ex_biopax
```

### Singaling network from KGML example

**Description**

An example igraph object representing Ras and chemokine signaling pathways in human extracted from KGML files.

**Examples**

```r
data(ex_kgml_sig)
plotNetwork(ex_kgml_sig, vertex.color="pathway")
```

### An microarray data example.

**Description**

An microarray data example. This is part of the ALL dataset, for demonstration purposes.

**Examples**

```r
data(ex_microarray)
```
### ex_sbml

*Metabolic network from SBML example*

**Description**

An example igraph object representing bipartite metabolic network of Carbohydrate metabolism extracted from SBML file from Reactome database.

**Examples**

```r
  data(ex_sbml)
  plotNetwork(ex_sbml, vertex.color="compartment.name")
```

### getAttrStatus

*Get / Set vertex attribute names and coverage*

**Description**

These functions report the annotation status of the vertices of a given network, modify or remove certain annotations.

**Usage**

```r
  getAttrStatus(graph, pattern = "^miriam.")
  getAttrNames(graph, pattern = "")
  getAttribute(graph, attr.name)
  setAttribute(graph, attr.name, attr.value)
  rmAttribute(graph, attr.name)
```

**Arguments**

- `graph`: An annotated igraph object.
- `pattern`: A regex expression representing attribute name pattern.
- `attr.name`: The attribute name.
- `attr.value`: A list of attribute values. This must be the same size as the number of vertices.

**Details**

NetPathMiner stores all its vertex annotation attributes in a list, and stores them collectively as a single `attr`. This is not to interfere with `attributes` from igraph package. All functions here target NetPathMiner annotations only.
getGeneSetNetworks

Generate geneset networks from an annotated network.

Description

This function generates geneset networks based on a given network, by grouping vertices sharing common attributes (in the same pathway or compartment).

Usage

getGeneSetNetworks(graph, use.attr = "pathway", format = c("list", "pathway-class"))
getGeneSets

Generate genesets from an annotated network.

Description

This function generates genesets based on a given network, by grouping vertices sharing common attributes (in the same pathway or compartment). Genes associated with each vertex can be specified through `gene.attr` argument.

Arguments

- **graph**: An annotated igraph object.
- **use.attr**: The attribute by which vertices are grouped (typically pathway, or GO).
- **format**: The output format. If "list" is specified, a list of subgraphs are returned (default). If "pathway-class" is specified, a list of pathway-class objects are returned. Pathway-class is used by graphite package to run several methods of topology-based enrichment analyses.

Value

A list of geneset networks as igraph or Pathway-class objects.

Author(s)

Ahmed Mohamed

See Also

- getGeneSets

Examples

```r
# Ras and chemokine signaling pathways in human
getsetnets <- getGeneSetNetworks(ex_kgml_sig, use.attr="pathway")

# Integration with graphite package
if(require(graphite) & require(clipper) & require(ALL)){
  getsetnets <- getGeneSetNetworks(ex_kgml_sig, use.attr="pathway", format="pathway-class")
  path <- convertIdentifiers(getsetnets$Chemokine signaling pathway, "entrez")
  genes <- nodes(path)
  data(ALL)
  all <- as.matrix(exprs(ALL[1:length(genes),1:20]))
  classes <- c(rep(1,10), rep(2,10))
  rownames(all) <- genes
  runClipper(path, all, classes, "mean", pathThr=0.1)
}
```

---

**Arguments**

- **graph**: An annotated igraph object.
- **use.attr**: The attribute by which vertices are grouped (typically pathway, or GO).
- **format**: The output format. If "list" is specified, a list of subgraphs are returned (default). If "pathway-class" is specified, a list of pathway-class objects are returned. Pathway-class is used by graphite package to run several methods of topology-based enrichment analyses.

**Value**

A list of geneset networks as igraph or Pathway-class objects.

**Author(s)**

Ahmed Mohamed

**See Also**

- getGeneSets

**Examples**

```r
data(ex_kgml_sig) # Ras and chemokine signaling pathways in human
genesetnets <- getGeneSetNetworks(ex_kgml_sig, use.attr="pathway")

# Integration with graphite package
if(require(graphite) & require(clipper) & require(ALL)){
  genesetnets <- getGeneSetNetworks(ex_kgml_sig, use.attr="pathway", format="pathway-class")
  path <- convertIdentifiers(genesetnets$Chemokine signaling pathway, "entrez")
  genes <- nodes(path)
  data(ALL)
  all <- as.matrix(exprs(ALL[1:length(genes),1:20]))
  classes <- c(rep(1,10), rep(2,10))
  rownames(all) <- genes
  runClipper(path, all, classes, "mean", pathThr=0.1)
}
```
getPathsAsEIDs

Convert a ranked path list to edge ids of a graph

Description

Convert a ranked path list to Edge ids of a graph, where paths can come from a different representation (for example matching path from a reaction network to edges on a metabolic network).
Usage
getPathsAsEIDs(paths, graph)

Arguments
paths The paths extracted by pathRanker.
graph A annotated igraph object.

Value
A list of edge ids on the provided graph.

Author(s)
Ahmed Mohamed

See Also
Other Path ranking methods: extractPathNetwork, pathRanker, samplePaths

Examples
## Prepare a weighted reaction network.
## Convert a metabolic network to a reaction network.
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson's correlation.
#data(ex_microarray) # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph,
weight.method = "cor", use.attr="miriam.uniprot",
y=factor(colnames(ex_microarray)), bootstrap = FALSE)

## Get ranked paths using probabilistic shortest paths.
ranked.p <- pathRanker(rgraph, method="prob.shortest.path",
K=20, minPathSize=6)

## Get the edge ids along paths in the reaction graph.
path.eids <- getPathsAsEIDs(ranked.p, rgraph)

## Get the edge ids along paths in the original metabolic graph.
path.eids <- getPathsAsEIDs(ranked.p, ex_sbml)
Usage

```
KGML2igraph(filename, parse.as = c("metabolic", "signaling"),
            expand.complexes = FALSE, verbose = TRUE)
```

Arguments

- `filename`: A character vector containing the KGML files to be processed. If a directory path is provided, all *.xml files in it and its subdirectories are included.
- `parse.as`: Whether to process file into a metabolic or a signaling network.
- `expand.complexes`: Split protein complexes into individual gene nodes. This argument is ignored if `parse.as = "metabolic"`
- `verbose`: Whether to display the progress of the function.

Details

Users can specify whether files are processed as metabolic or signaling networks.

Metabolic networks are given as bipartite graphs, where metabolites and reactions represent vertex types. This is constructed from `<reaction>` xml node in KGML file, connecting them to their corresponding substrates and products. Each reaction vertex has a `genes` attribute, listing all genes associated with the reaction. As a general rule, reactions inherit all annotation attributes of its catalyzing genes.

Signaling network have genes as vertices and edges represent interactions, such as activation/inhibition. Genes participating in successive reactions are also connected. Signaling parsing method processes `<ECrel>`, `<PPrel>` and `<PCrel>` interactions from KGML files.

To generate a genome scale network, simply provide a list of files to be parsed, or put all file in a directory, as pass the directory path as `filename`

Value

An igraph object, representing a metabolic or a signaling network.

Author(s)

Ahmed Mohamed

See Also

Other Database extraction methods: `SBML2igraph`, `biopax2igraph`

Examples

```
if(is.loaded("readkgmlfile")){ # This is false if libxml2 wasn't available at installation.
  filename <- system.file("extdata", "hsa00860.xml", package="NetPathMiner")

  # Process KGML file as a metabolic network
  g <- KGML2igraph(filename)
  plotNetwork(g)

  # Process KGML file as a signaling network
  g <- KGML2igraph(filename, parse.as="signaling", expand.complexes=TRUE)
  plotNetwork(g)
```
layoutVertexByAttr

A graph layout function, which groups vertices by attribute.

Description

This function generates a layout for igraph objects, keeping vertices with the same attribute (ex: in the same pathway, etc) close to each other.

Usage

layoutVertexByAttr(graph, attr.name, cluster.strength = 1, layout = layout.auto)

Arguments

graph An annotated igraph object.
attr.name The attribute name by which vertices are laid out.
cluster.strength A number indicating tie strengths between vertices with the same attribute. The larger it is, the closer the vertices will be.
layout A layout function, ideally a force-directed layout function, such as layout.fruchterman.reingold and layout.kamada.kawai.

Value

A two-column matrix indicating the x and y positions of vertices.

Author(s)

Ahmed Mohamed

See Also

Other Plotting methods: colorVertexByAttr, plotAllNetworks, plotClassifierROC, plotClusterMatrix, plotCytoscapeGML, plotNetwork, plotPathClassifier, plotPaths

Examples

data("ex_kgml_sig")
v.layout <- layoutVertexByAttr(ex_kgml_sig, "pathway")
plotNetwork(ex_kgml_sig, vertex.color="pathway", layout=v.layout)

v.layout <- layoutVertexByAttr(ex_kgml_sig, "pathway", cluster.strength=5)
plotNetwork(ex_kgml_sig, vertex.color="pathway", layout=v.layout)
**makeReactionNetwork**

Convert metabolic network to reaction network.

**Description**

This function removes metabolite nodes keeping them as edge attributes. The resulting network contains reaction nodes only, where edges indicate that a metabolite produced by one reaction is consumed by the other.

**Usage**

```r
makeReactionNetwork(graph, simplify = FALSE)
```

**Arguments**

- `graph` A metabolic network.
- `simplify` An option to remove translocation and spontaneous reactions that require no catalyzing genes. Translocation reactions are detected from reaction name (SBML, BioPAX), or by having identical substrates and products.

**Value**

A reaction network.

**Author(s)**

Ahmed Mohamed

**See Also**

Other Network processing methods: `expandComplexes`, `rmSmallCompounds`, `simplifyReactionNetwork`, `vertexDeleteReconnect`

**Examples**

```r
## Convert a metabolic network to a reaction network.
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)
```

---

**NPMdefaults**

Default values for NetPathMiner

**Description**

This function gets a NetPathMiner default value for a variable.

**Usage**

```r
NPMdefaults(value)
```
pathClassifier

Arguments

value a character string indicating the variable name.

Details

NetPathMiner defines the following defaults:

• small.comp.ls Dataframe of ubiquitous metabolites. Used by rmSmallCompounds.
• bridge Dataframe of attributes supported by Brigde Database. Used by fetchAttribute.
• bridge.organisms A list of bridge supported organisms. Used by fetchAttribute.
• bridge.web The base URL for Brigde Database webservice. Used by fetchAttribute.

Value

The default value for the given variable.

Author(s)

Ahmed Mohamed

Examples

# Get the default list of small compounds (uniquitous metabolites).
PnPdefaults("small.comp.ls")

pathClassifier

HME3M Markov pathway classifier.

Description

HME3M Markov pathway classifier.

Usage

pathClassifier(paths, target.class, M, alpha = 1, lambda = 2,
               hme3miter = 100, plriter = 1, init = "random")

Arguments

paths The training paths computed by pathsToBinary
target.class The label of the target class to be classified. This label must be present as a label
              within the paths$y object
M Number of components within the paths to be extracted.
alpha The PLR learning rate. (between 0 and 1).
lambda The PLR regularization parameter. (between 0 and 2)
plriter Maximum number of PLR iterations. It will stop when likelihood change is < 0.001.
ininit Specify whether to initialize the HME3M responsibilities with the 3M model -
         random is recommended.
Details
Take care with selection of lambda and alpha - make sure you check that the likelihood is always increasing.

Value
A list with the following elements. A list with the following values

- **h**: A dataframe with the EM responsibilities.
- **theta**: A dataframe with the Markov parameters for each component.
- **beta**: A dataframe with the PLR coefficients for each component.
- **proportions**: The probability of each HME3M component.
- **posterior.probs**: The HME3M posterior probability.
- **likelihood**: The likelihood convergence history.
- **plrplr**: The posterior predictions from each components PLR model.
- **path.probabilities**: The 3M probabilities for each path belonging to each component.
- **params**: The parameters used to build the model.
- **y**: The binary response variable used by HME3M. A 1 indicates the location of the target.class labels in paths$y
- **perf**: The training set ROC curve AUC.
- **label**: The HME3M predicted label for each path.
- **component**: The HME3M component assignment for each path.

Author(s)
Timothy Hancock and Ichigaku Takigawa

References
Hancock, Timothy, and Mamitsuka, Hiroshi: A Markov Classification Model for Metabolic Pathways, Workshop on Algorithms in Bioinformatics (WABI), 2009
Hancock, Timothy, and Mamitsuka, Hiroshi: A Markov Classification Model for Metabolic Pathways, Algorithms for Molecular Biology 2010

See Also
Other Path clustering & classification methods: pathCluster, pathsToBinary, plotClassifierROC, plotClusterMatrix, plotPathClassifier, plotPathCluster, predictPathClassifier, predictPathCluster

Examples
```r
## Prepare a weighted reaction network.
## Conver a metabolic network to a reaction network.
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson's correlation.
```
data(ex_microarray) # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph, 
weight.method = "cor", use.attr="miriam.uniprot", 
y=factor(colnames(ex_microarray)), bootstrap = FALSE)

## Get ranked paths using probabilistic shortest paths.
ranked.p <- pathRanker(rgraph, method="prob.shortest.path", 
K=20, minPathSize=6)

## Convert paths to binary matrix.
ybinpaths <- pathsToBinary(ranked.p)
p.class <- pathClassifier(ybinpaths, target.class = "BCR/ABL", M = 3)

## Contingency table of classification performance
table(ybinpaths$y,p.class$label)

## Plotting the classifier results.
plotClassifierROC(p.class)
plotClusters(ybinpaths, p.class)

---

### pathCluster

**3M Markov mixture model for clustering pathways**

**Description**

3M Markov mixture model for clustering pathways

**Usage**

pathCluster(ybinpaths, M, iter = 1000)

**Arguments**

- `ybinpaths` The training paths computed by `pathsToBinary`.
- `M` The number of clusters.
- `iter` The maximum number of EM iterations.

**Value**

A list with the following items:

- `h` The posterior probabilities that each path belongs to each cluster.
- `labels` The cluster membership labels.
- `theta` The probabilities of each gene for each cluster.
- `proportions` The mixing proportions of each path.
- `likelihood` The likelihood convergence history.
- `params` The specific parameters used.
pathRanker

Author(s)
Ichigaku Takigawa
Timothy Hancock

References

See Also
Other Path clustering & classification methods: pathClassifier, pathsToBinary, plotClassifierROC, plotClusterMatrix, plotPathClassifier, plotPathCluster, predictPathClassifier, predictPathCluster

Examples
## Prepare a weighted reaction network.
## Convert a metabolic network to a reaction network.
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson's correlation.
data(ex_microarray) # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph,
weight.method = "cor", use.attr="miriam.uniprot", bootstrap = FALSE)

## Get ranked paths using probabilistic shortest paths.
ranked.p <- pathRanker(rgraph, method="prob.shortest.path",
K=20, minPathSize=8)

## Convert paths to binary matrix.
ybinpaths <- pathsToBinary(ranked.p)
p.cluster <- pathCluster(ybinpaths, M=2)
plotClusters(ybinpaths, p.cluster)

---

pathRanker Extracting and ranking paths from a network

Description
Given a weighted igraph object, path ranking finds a set of node/edge sequences (paths) to maximize the sum of edge weights. pathRanker(method="prob.shortest.path") extracts the K most probable paths within a weighted network. pathRanker(method="pvalue") extracts a list of paths whose sum of edge weights are significantly higher than random paths of the same length.

Usage
pathRanker(graph, method = c("prob.shortest.path", "pvalue"), start, end,
verbose = TRUE, ...)
pathRanker

Arguments

- **graph**: A weighted igraph object. Weights must be in `edge.weights` or `weight` attributes.
- **method**: Which path ranking method to use.
- **start**: A list of start vertices, given by their vertex id.
- **end**: A list of terminal vertices, given by their vertex id.
- **verbose**: Whether to display the progress of the function.
- **...**: Method-specific parameters. See Details section.

Details

The input here is `graph`. A weight must be assigned to each edge. Bootstrapped Pearson correlation edge weights can be assigned to each edge by `assignEdgeWeights`. However, the specification of the edge weight is flexible with the condition that increasing values indicate stronger relationships between vertices.

**Probabilistic Shortest Paths**: `pathRanker(method="prob.shortest.path")` finds the K most probable loopless paths given a weighted network. Before the paths are ranked, the edge weights are converted into probabilistic edge weights using the Empirical Cumulative Distribution (ECDF) over all edge weights. This is called ECDF edge weight. The ECDF edge weight serves as a probabilistic rank of the most important gene-gene interactions. The probabilistic nature of the ECDF edge weights allows for a significance test to determine if a path contains any functional structure or is simply a random walk. The probability of a path is simply the product of all ECDF weights along the path. This is computed as a sum of the logs of the ECDF edge weights.

The following arguments can be passed to `pathRanker(method="prob.shortest.path")`:
- **K**: Maximum number of paths to extract. Defaults to 10.
- **minPathSize**: The minimum number of edges for each extracted path. Defaults to 1.
- **normalize**: Specify if you want to normalize the probabilistic edge weights (across different labels) before extracting the paths. Defaults to TRUE.

**P-value method**: `pathRanker(method="pvalue")` searches all paths between the specified start and end vertices, and if a significant path is found it returns it. However, it doesn’t search for the best path between the start and terminal vertices, as there could be many paths which lead to the same terminal vertex, and searching through all of them is time-consuming. We just stop when the first significant path is found.

All provided edge weights are recaled from 0-1. Path significance is calculated based on the empirical distribution of random paths of the same length. This can be estimated using `samplePaths` and passed as an argument.

The following arguments can be passed to `pathRanker(method="pvalue")`:
- **sampledpaths**: The empirical results from `samplePaths`.
- **alpha**: The P-value cut-off. Defaults to 0.01.

Value

A list of paths where each path has the following items:

- **gene**: The ordered sequence of genes visited along the path.
- **compounds**: The ordered sequence of compounds visited along the path.
- **weights**: The ordered sequence of the log(ECDF edge weights) along the path.
- **distance**: The sum of the log(ECDF edge weights) along each path. (A sum of logs is a product)
### pathsToBinary

**Converts the result from pathRanker into something suitable for pathClassifier or pathCluster.**

#### Description
Converts the result from pathRanker into something suitable for pathClassifier or pathCluster.

#### Usage

```r
pathsToBinary(ypaths)
```

#### Arguments

- `ypaths` The result of `pathRanker`.
Details

Converts a set of pathways from `pathRanker` into a list of binary pathway matrices. If the pathways are grouped by a response label then the `pathsToBinary` returns a list labeled by response class where each element is the binary pathway matrix for each class. If the pathways are from `pathRanker` then a list with a single element containing the binary pathway matrix is returned. To look up the structure of a specific binary path in the corresponding `ypaths` object simply use matrix index by calling `ypaths[[ybinpaths$pidx[i,]]]`, where `i` is the row in the binary paths object you wish to reference.

Value

A list with the following elements.

- **paths**: All paths within `ypaths` converted to a binary string and concatenated into the one matrix.
- **y**: The response variable.
- **pidx**: An matrix where each row specifies the location of that path within the `ypaths` object.

Author(s)

Timothy Hancock and Ichigaku Takigawa

See Also

Other Path clustering & classification methods: `pathClassifier`, `pathCluster`, `plotClassifierROC`, `plotClusterMatrix`, `plotPathClassifier`, `plotPathCluster`, `predictPathClassifier`, `predictPathCluster`

Examples

```r
## Prepare a weighted reaction network.
## Conver a metabolic network to a reaction network.
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson's correlation.
data(ex_microarray) # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph,
weight.method = "cor", use.attr="miriam.uniprot",
y=factor(colnames(ex_microarray)), bootstrap = FALSE)

## Get ranked paths using probabilistic shortest paths.
ranked.p <- pathRanker(rgraph, method="prob.shortest.path",
K=20, minPathSize=6)

## Convert paths to binary matrix.
ybinpaths <- pathsToBinary(ranked.p)
p.cluster <- pathCluster(ybinpaths, M=3)
plotClusters(ybinpaths, p.cluster, col=c("red", "green", "blue") )
```
plotAllNetworks

Highlighting ranked paths over multiple network representations.

Description

This function highlighting ranked paths over different network representations, metabolic, reaction and gene networks. The functions finds equivalent paths across different networks and marks them.

Usage

plotAllNetworks(paths, metabolic.net = NULL, reaction.net = NULL, gene.net = NULL, path.clusters = NULL, plot.clusters = TRUE, col.palette = palette(), layout = layout.auto, ...)

Arguments

paths The result of pathRanker.
metabolic.net A bipartite metabolic network.
reaction.net A reaction network, resulting from makeReactionNetwork.
gene.net A gene network, resulting from makeGeneNetwork.
path.clusters The result from pathCluster or pathClassifier.
plot.clusters Whether to plot clustering information, as generated by plotClusters
col.palette A color palette, or a palette generating function (ex: col.palette=rainbow).
layout Either a graph layout function, or a two-column matrix specifying vertex coordinates.
... Additional arguments passed to plotNetwork.

Value

Highlights the path list over all provided networks.

Author(s)

Ahmed Mohamed

See Also

Other Plotting methods: colorVertexByAttr, layoutVertexByAttr, plotClassifierROC, plotClusterMatrix, plotCytoscapeGML, plotNetwork, plotPathClassifier, plotPaths
Examples

```r
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

# Calculate Pearson's correlation.
data(ex_microarray) # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph, weight.method = "cor", use.attr="miriam.uniprot", y=factor(colnames(ex_microarray)), bootstrap = FALSE)

# Get ranked paths using probabilistic shortest paths.
ranked.p <- pathRanker(rgraph, method="prob.shortest.path", K=20, minPathSize=6)

plotAllNetworks(ranked.p, metabolic.net = ex_sbml, reaction.net = rgraph, vertex.label = "", vertex.size = 4)
```

### plotClassifierROC

Diagnostic plots for `pathClassifier`.

#### Description

Diagnostic plots for `pathClassifier`.

#### Usage

```r
plotClassifierROC(mix)
```

#### Arguments

- `mix` The result from `pathClassifier`.

#### Value

Diagnostic plots of the result from `pathClassifier`. `itemTopROC` curves for the posterior probabilities (`mix$posterior.probs`) and for each HME3M component (`mix$h`). This gives information about what response label each relates to. A ROC curve with an AUC $< 0.5$ relates to $y = 0$. Conversely ROC curves with AUC $> 0.5$ relate to $y = 1$. `itemBottom`The likelihood convergence history for the HME3M model. If the parameters `alpha` or `lambda` are set too large then the likelihood may decrease.

#### Author(s)

Timothy Hancock and Ichigaku Takigawa
plotClusterMatrix

See Also

Other Path clustering & classification methods: pathClassifier, pathCluster, pathsToBinary, plotClusterMatrix, plotPathClassifier, plotPathCluster, predictPathClassifier, predictPathCluster
Other Plotting methods: colorVertexByAttr, layoutVertexByAttr, plotAllNetworks, plotClusterMatrix, plotCytoscapeGML, plotNetwork, plotPathClassifier, plotPaths

plotClusterMatrix  
Plots the structure of all path clusters

Description

Plots the structure of all path clusters

Usage

plotClusterMatrix(ybinpaths, clusters, col = rainbow(clusters$params$M),
                   grid = TRUE)

plotClusterProbs(clusters, col = rainbow(clusters$params$M))

plotClusters(ybinpaths, clusters, col, ...)

Arguments

ybinpaths  The training paths computed by pathsToBinary.
clusters   The pathway cluster model trained by pathCluster or pathClassifier.
col        Colors for each path cluster.
grid       A logical, whether to add a grid to the plot
...         Extra parameters passed to plotClusterMatrix

Value

plotClusterMatrix plots an image of all paths the training dataset. Rows are the paths and columns are the genes (features) included within each path. Paths are colored according to cluster membership.

plotClusterProbs The training set posterior probabilities for each path belonging to a 3M component.

plotClusters: combines the two plots produced by plotClusterProbs and plotClusterMatrix.

Author(s)

Ahmed Mohamed

See Also

Other Path clustering & classification methods: pathClassifier, pathCluster, pathsToBinary, plotClassifierROC, plotPathClassifier, plotPathCluster, predictPathClassifier, predictPathCluster
Other Plotting methods: colorVertexByAttr, layoutVertexByAttr, plotAllNetworks, plotClassifierROC, plotCytoscapeGML, plotNetwork, plotPathClassifier, plotPaths
Examples

```r
## Prepare a weighted reaction network.
## Conver a metabolic network to a reaction network.
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson's correlation.
data(ex_microarray) # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph,
weight.method = "cor", use.attr="miriam.uniprot",
y=factor(colnames(ex_microarray)), bootstrap = FALSE)

## Get ranked paths using probabilistic shortest paths.
ranked.p <- pathRanker(rgraph, method="prob.shortest.path",
K=20, minPathSize=8)

## Convert paths to binary matrix.
ybinpaths <- pathsToBinary(ranked.p)
p.cluster <- pathCluster(ybinpaths, M=2)
plotClusters(ybinpaths, p.cluster, col=c("red", "blue") )
```

plotCytoscapeGML

Plots an annotated igraph object in Cytoscape.

Description

plotCytoscape function has been removed because RCytoscape is no longer present in Bioconductor. Future plans will use RCy3 for Cytoscape plotting, once RCy3 is supported on MacOS and Windows. plotCytoscapeGML exports the network plot in GML format, that can be later imported into Cytoscape (using "import network from file" option). This function is compatible with all Cytoscape versions.

Usage

```r
plotCytoscapeGML(graph, file, layout = layout.auto, vertex.size, vertex.label,
vertex.shape, vertex.color, edge.color)
```

Arguments

- `graph`: An annotated igraph object.
- `file`: Output GML file name to which the network plot is exported.
- `layout`: Either a graph layout function, or a two-column matrix specifying vertex coordinates.
- `vertex.size`: Vertex size. If missing, the vertex attribute "size" (`V(g)$size`) will be used.
- `vertex.label`: Vertex labels. If missing, the vertex attribute "label" (`V(g)$label`)
plotCytoscapeGML

) will be used. If missing, vertices are labeled by their name.

vertex.shape

Vertex shape in one of igraph shapes. If missing, the vertex attribute “shape” (V(g)$shape) will be used. Shapes are converted from igraph convention to Cytoscape convention. ”square”,”rectangle” and ”rectangle” are converted to ”RECT”, ”csquare” and ”crectangle” are converted to ”ROUND_RECT”, all other shapes are considered ”ELLIPSE”

vertex.color

A color or a list of colors for vertices. Vertices with multiple colors are not supported. If missing, the vertex attribute ”color” (V(g)$color) will be used.

edge.color

A color or a list of colors for edges. If missing, the edge attribute ”color” (E(g)$color) will be used.

Value

For plotCytoscapeGML, results are written to file.

Author(s)

Ahmed Mohamed

See Also

Other Plotting methods: colorVertexByAttr, layoutVertexByAttr, plotAllNetworks, plotClassifierROC, plotClusterMatrix, plotNetwork, plotPathClassifier, plotPaths

Examples

data(“ex_sbml”)
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)
v.layout <- layoutVertexByAttr(rgraph, ”compartment”)
v.color <- colorVertexByAttr(rgraph, ”compartment”)

# Export network plot to GML file
plotCytoscapeGML(rgraph, file=“example.gml”, layout=v.layout,
vertex.color=v.color, vertex.size=10)
**plotNetwork**  
*Plots an annotated igraph object.*

**Description**

This function is a wrapper function for `plot.igraph`, with 2 main additions. 1. Add the ability to color vertices by their attributes (see examples), accompanied by an informative legend. 2. Resize `vertex.size`, `edge.arrow.size`, `label.cex` according to the plot size and the size of the network.

**Usage**

```r
plotNetwork(graph, vertex.color, col.palette = palette(),
layout = layout.auto, legend = TRUE, ...)
```

**Arguments**

- `graph`  
  An annotated igraph object.
- `vertex.color`  
  A list of colors for vertices, or an attribute names (ex: "pathway") by which vertices will be colored. Complex attributes, where a vertex belongs to more than one group, are supported. This can also be the output of `colorVertexByAttr`.
- `col.palette`  
  A color palette, or a palette generating function (ex: `col.palette=rainbow`).
- `layout`  
  Either a graph layout function, or a two-column matrix specifying vertex coordinates.
- `legend`  
  Whether to plot a legend. The legend is only plotted if vertices are colored by attribute values.
- `...`  
  Additional arguments passed to `plot.igraph`.

**Value**

Produces a plot of the network.

**Author(s)**

Ahmed Mohamed

**See Also**

Other Plotting methods: `colorVertexByAttr`, `layoutVertexByAttr`, `plotAllNetworks`, `plotClassifierROC`, `plotClusterMatrix`, `plotCytoscapeGML`, `plotPathClassifier`, `plotPaths`

**Examples**

```r
data("ex_kgml_sig")
plotNetwork(ex_kgml_sig, vertex.color="pathway")
plotNetwork(ex_kgml_sig, vertex.color="pathway", col.palette=heat.colors)
plotNetwork(ex_kgml_sig, vertex.color="pathway",
            col.palette=c("red", "green","blue","grey"))
```
plotPathClassifier

Plots the structure of specified path found by pathClassifier.

Description

Plots the structure of specified path found by pathClassifier.

Usage

plotPathClassifier(ybinpaths, obj, m, tol = NULL)

Arguments

ybinpaths The training paths computed by pathsToBinary
obj The pathClassifier pathClassifier
m The path component to view.
tol A tolerance for 3M parameter theta which is the probability for each edge within each cluster. If the tolerance is set all edges with a theta below that tolerance will be removed from the plot.

Value

Produces a plot of the paths with the path probabilities and prediction probabilities and ROC curve overlayed.

Center Plot An image of all paths the training dataset. Rows are the paths and columns are the genes (vertices) included within each pathway. A colour within image indicates if a particular gene (vertex) is included within a specific path. Colours flag whether a path belongs to the current HME3M component (P > 0.5).
Center Right The training set posterior probabilities for each path belonging to the current 3M component.
Center Top The ROC curve for this HME3M component.
Top Bar Plots Theta: The 3M component probabilities - indicates the importance of each edge is to a path. Beta: The PLR coefficient - the magnitude indicates the importance of the edge to the classify the response.

Author(s)

Timothy Hancock and Ichigaku Takigawa

See Also

Other Path clustering & classification methods: pathClassifier, pathCluster, pathsToBinary, plotClassifierROC, plotClusterMatrix, plotPathCluster, predictPathClassifier, predictPathCluster
Other Plotting methods: colorVertexByAttr, layoutVertexByAttr, plotAllNetworks, plotClassifierROC, plotClusterMatrix, plotCytoscapeGML, plotNetwork, plotPaths
Examples

```r
## Prepare a weighted reaction network.
## Convert a metabolic network to a reaction network.
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson's correlation.
data(ex_microarray) # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph, 
weight.method = "cor", use.attr="miriam.uniprot", 
y=factor(colnames(ex_microarray)), bootstrap = FALSE)

## Get ranked paths using probabilistic shortest paths.
ranked.p <- pathRanker(rgraph, method="prob.shortest.path", 
K=20, minPathSize=6)

## Convert paths to binary matrix.
ybinpaths <- pathsToBinary(ranked.p)
p.class <- pathClassifier(ybinpaths, target.class = "BCR/ABL", M = 3)

## Plotting the classifier results.
plotClassifierROC(p.class)
plotClusters(ybinpaths, p.class)
```

plotPathCluster

Plots the structure of specified path cluster

Description

Plots the structure of specified path found by pathCluster.

Usage

```r
plotPathCluster(ybinpaths, clusters, m, tol = NULL)
```

Arguments

- `ybinpaths`: The training paths computed by `pathsToBinary`.
- `clusters`: The pathway cluster model trained by `pathCluster` or `pathClassifier`.
- `m`: The path cluster to view.
- `tol`: A tolerance for 3M parameter theta which is the probability for each edge within each cluster. If the tolerance is set all edges with a theta below that tolerance will be removed from the plot.

Value

Produces a plot of the paths with the path probabilities and cluster membership probabilities.

Center Plot 
An image of all paths the training dataset. Rows are the paths and columns are the genes (features) included within each path.
plotPaths

Right
The training set posterior probabilities for each path belonging to the current 3M component.

Top Bar Plots
The 3M component probabilities - indicates the importance of each edge to a pathway.

Author(s)
Timothy Hancock and Ichigaku Takigawa

See Also
Other Path clustering & classification methods: pathClassifier, pathCluster, pathsToBinary, plotClassifierROC, plotClusterMatrix, plotPathClassifier, predictPathClassifier, predictPathCluster

Examples

```r
## Prepare a weighted reaction network.
## Conver a metabolic network to a reaction network.
data(ex_sbml)  # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson's correlation.
data(ex_microarray)  # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph,
                           weight.method = "cor", use.attr="miriam.uniprot", bootstrap = FALSE)

## Get ranked paths using probabilistic shortest paths.
ranked.p <- pathRanker(rgraph, method="prob.shortest.path",
                       K=20, minPathSize=8)

## Convert paths to binary matrix.
ybinpaths <- pathsToBinary(ranked.p)
p.cluster <- pathCluster(ybinpaths, M=2)
plotPathCluster(ybinpaths, p.cluster, m=2, tol=0.05)
```

---

**plotPaths**

Plots an annotated igraph object highlighting ranked paths.

---

**Description**

This function plots a network highlighting ranked paths. If path.clusters are provided, paths in the same cluster are assigned similar colors.

**Usage**

```r
plotPaths(paths, graph, path.clusters = NULL, col.palette = palette(),
          layout = layout.auto, ...)
```
Arguments

paths   The result of pathRanker.
gaith   An annotated igraph object.
path.clusters The result from pathCluster or pathClassifier.
col.palette A color palette, or a palette generating function (ex: col.palette=rainbow).
layout   Either a graph layout function, or a two-column matrix specifying vertex coordinates.
...      Additional arguments passed to plotNetwork.

Value

Produces a plot of the network with paths highlighted. If paths are computed for several labels (sample categories), a plot is created for each label.

Author(s)

Ahmed Mohamed

See Also

Other Plotting methods: colorVertexByAttr, layoutVertexByAttr, plotAllNetworks, plotClassifierROC, plotClusterMatrix, plotCytoscapeGML, plotNetwork, plotPathClassifier

Examples

```r
## Prepare a weighted reaction network.
## Conver a metabolic network to a reaction network.
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson's correlation.
data(ex_microarray) # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph,
weight.method = "cor", use.attr="miriam.uniprot",
y=factor(colnames(ex_microarray)), bootstrap = FALSE)

## Get ranked paths using probabilistic shortest paths.
ranked.p <- pathRanker(rgraph, method="prob.shortest.path",
K=20, minPathSize=6)

## Plot paths.
plotPaths(ranked.p, rgraph)

## Convert paths to binary matrix, build a classifier.
ybinpaths <- pathsToBinary(ranked.p)
p.class <- pathClassifier(ybinpaths, target.class = "BCR/ABL", M = 3)

## Plotting with clusters, on a metabolic graph.
plotPaths(ranked.p, ex_sbml, path.clusters=p.class)
```
predictPathClassifier

**Description**

Predicts new paths given a pathClassifier model.

**Usage**

```r
predictPathClassifier(mix, newdata)
```

**Arguments**

- `mix` The result from `pathClassifier`.
- `newdata` A data.frame containing the new paths to be classified.

**Value**

A list with the following elements.

- `h` The posterior probabilities for each HME3M component.
- `posterior.probs` The posterior probabilities for HME3M model to classify the response.
- `label` A vector indicating the HME3M cluster membership.
- `component` The HME3M component membership for each pathway.
- `path.probabilities` The 3M path probabilities.
- `plr.probabilities` The PLR predictions for each component.

**Author(s)**

Timothy Hancock and Ichigaku Takigawa

**See Also**

Other Path clustering & classification methods: `pathClassifier`, `pathCluster`, `pathsToBinary`, `plotClassifierROC`, `plotClusterMatrix`, `plotPathClassifier`, `plotPathCluster`, `predictPathCluster`

**Examples**

```r
## Prepare a weighted reaction network.
## Conver a metabolic network to a reaction network.
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson’s correlation.
data(ex_microarray) # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph,
weight.method = "cor", use.attr="miriam.uniprot",
```
predictPathCluster

Predicts new paths given a pathCluster model

Description
Predicts new paths given a pathCluster model.

Usage
predictPathCluster(pfit, newdata)

Arguments

- **pfit**: The pathway cluster model trained by `pathCluster` or `pathClassifier`.
- **newdata**: The binary pathway dataset to be assigned a cluster label.

Value
A list with the following elements:

- **labels**: a vector indicating the 3M cluster membership.
- **posterior.probs**: a matrix of posterior probabilities for each path belonging to each cluster.

Author(s)
Ichigaku Takigawa
Timothy Hancock

See Also
Other Path clustering & classification methods: `pathClassifier`, `pathCluster`, `pathsToBinary`, `plotClassifierROC`, `plotClusterMatrix`, `plotPathClassifier`, `plotPathCluster`, `predictPathClassifier`

Examples

```
## Prepare a weighted reaction network.
## Conver a metabolic network to a reaction network.
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
```
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson's correlation.
data(ex_microarray) # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph,
weight.method = "cor", use.attr="miriam.uniprot", bootstrap = FALSE)

## Get ranked paths using probabilistic shortest paths.
ranked.p <- pathRanker(rgraph, method="prob.shortest.path",
K=20, minPathSize=8)

## Convert paths to binary matrix.
ybinpaths <- pathsToBinary(ranked.p)
p.cluster <- pathCluster(ybinpaths, M=2)

## just an example of how to predict cluster membership.
pclust.pred <- predictPathCluster(p.cluster, ybinpaths$paths)

registerMemoryErr

Internal method to register memory errors.

Description

Internal method to register memory errors, caused by compiled code. This method is used only by
the package, and should not be invoked by users.

Usage

registerMemoryErr(method)

Arguments

method

The method which generated the error.

Author(s)

Ahmed Mohamed

rmSmallCompounds

Remove uniquitous compounds from a metabolic network

Description

This function removes uniquitous compounds (metabolites connected to numerous reactions) from
a metabolic network. These compounds are reaction cofactors and currency compounds, such as
ATP, CO2, etc. A path through these metabolites may not be biologically meaningful. The default
small compound list is derived from Reactome, containing keeg.compound, pubchem.compound,
ChEBI and CAS identifiers.
Usage

```r
rmSmallCompounds(graph, method = c("remove", "duplicate"),
    small.comp.ls = NPMdefaults("small.comp.ls"))
```

Arguments

- **graph**: A metabolic network.
- **method**: How to handle small compounds. Either simply delete these vertices "remove" (default), or make a separate vertex for each reaction they participate in "duplicate".
- **small.comp.ls**: A list of small compounds to be used.

Value

A modified graph, with the small compounds removed or duplicated.

Author(s)

Ahmed Mohamed

See Also

Other Network processing methods: `expandComplexes`, `makeReactionNetwork`, `simplifyReactionNetwork`, `vertexDeleteReconnect`

Examples

```r
data(ex_sbml)

sbml.removed <- rmSmallCompounds(ex_sbml, method="remove")
```

---

**samplePaths**

*Creates a set of sample path p-values for each length given a weighted network*

Description

Randomly traverses paths of increasing lengths within a set network to create an empirical pathway distribution for more accurate determination of path significance.

Usage

```r
samplePaths(graph, max.path.length, num.samples = 1000, num.warmup = 10,
    verbose = TRUE)
```
samplePaths

Arguments

- **graph**: A weighted igraph object. Weights must be in `edge.weights` or `weight` attributes.
- **max.path.length**: The maximum path length.
- **num.samples**: The number of paths to sample.
- **num.warmup**: The number of warm up paths to sample.
- **verbose**: Whether to display the progress of the function.

Details

Can take a bit of time.

Value

A matrix where each row is a path length and each column is the number of paths sampled.

Author(s)

- Timothy Hancock
- Ahmed Mohamed

See Also

Other Path ranking methods: `extractPathNetwork`, `getPathsAsEIDs`, `pathRanker`

Examples

```r
## Prepare a weighted reaction network.
## Conver a metabolic network to a reaction network.
data(ex_sbml) # bipartite metabolic network of Carbohydrate metabolism.
rgraph <- makeReactionNetwork(ex_sbml, simplify=TRUE)

## Assign edge weights based on Affymetrix attributes and microarray dataset.
# Calculate Pearson's correlation.
data(ex_microarray) # Part of ALL dataset.
rgraph <- assignEdgeWeights(microarray = ex_microarray, graph = rgraph,
                           weight.method = "cor", use.attr="miriam.uniprot",
y=factor(colnames(ex_microarray)), bootstrap = FALSE)

## Get significantly correlated paths using "p-value" method.
## First, establish path score distribution by calling "samplePaths"
pathsample <- samplePaths(rgraph, max.path.length=10,
                           num.samples=100, num.warmup=10)

## Get all significant paths with p<0.1
significant.p <- pathRanker(rgraph, method = "pvalue",
                            sampledpaths = pathsample ,alpha=0.1)
```
SBML2igraph \(\text{Processes SBML files into igraph objects}\)

**Description**
This function takes SBML files as input, and returns either a metabolic or a signaling network as output.

**Usage**
```
SBML2igraph(filename, parse.as = c("metabolic", "signaling"),
            miriam.attr = "all", gene.attr, expand.complexes, verbose = TRUE)
```

**Arguments**
- **filename** A character vector containing the SBML files to be processed. If a directory path is provided, all *.xml and *.sbml files in it and its subdirectories are included.
- **parse.as** Whether to process file into a metabolic or a signaling network.
- **miriam.attr** A list of annotation attributes to be extracted. If "all", then all attributes written in MIRIAM guidelines (see Details) are extracted (Default). If "none", then no attributes are extracted. Otherwise, only attributes matching those specified are extracted.
- **gene.attr** An attribute to distinguish species representing genes from those representing small molecules (see Details). Ignored if parse.as="metabolic".
- **expand.complexes** Split protein complexes into individual gene nodes. Ignored if parse.as="metabolic", or when gene.attr is not provided.
- **verbose** Whether to display the progress of the function.

**Details**
Users can specify whether files are processes as metabolic or signaling networks.

Metabolic networks are given as bipartite graphs, where metabolites and reactions represent vertex types. This is constructed from **ListOfReactions** in SBML file, connecting them to their corresponding substrates and products (**ListOfSpecies**). Each reaction vertex has genes attribute, listing all modifiers of this reaction. As a general rule, reactions inherit all annotation attributes of its catalyzing genes.

Signaling network have genes as vertices and edges represent interactions. Since SBML format may represent singling events as reaction, all species are assumed to be genes (rather than small molecules). For a simple path \(S0 \rightarrow R1 \rightarrow S1\), in signaling network, the path will be \(S0 \rightarrow M(R1) \rightarrow S1\) where \(M(R1)\) is \(R1\) modifier(s). To distinguish gene species from small molecules, user can provide gene.attr (for example: miriam.uniprot or miriam.ncbigene) where only annotated species are considered genes.

All annotation attributes written according to MIRIAM guidelines (either urn:miriam:xxx:xxx or http://identifiers.org/xxx/xxx) are extracted by default. Non-conforming attributes can be extracted by specifying miriam.attr.

To generate a genome scale network, simply provide a list of files to be parsed, or put all file in a directory, as pass the directory path as filename.
simplifyReactionNetwork

Note: This function requires libSBML installed (Please see the installation instructions in the vignette). Some SBML level-3 files may require additional libraries also (An informative error will be displayed when parsing such files). Please visit http://sbml.org/Documents/Specifications/SBML_Level_3/Packages for more information.

Value
An igraph object, representing a metabolic or a signaling network.

Author(s)
Ahmed Mohamed

See Also
Other Database extraction methods: KGML2igraph, biopax2igraph

Examples
if(is.loaded("readsbmlfile")){ # This is false if libSBML wasn’t available at installation.
  filename <- system.file("extdata", "porphyrin.sbml", package="NetPathMiner")

  # Process SBML file as a metabolic network
  g <- SBML2igraph(filename)
  plotNetwork(g)

  # Process SBML file as a signaling network
  g <- SBML2igraph(filename, parse.as="signaling",
                   gene.attr="miriam.uniprot",expand.complexes=TRUE)
  dev.new()
  plotNetwork(g)
}

simplifyReactionNetwork

   Removes reactions with no gene annotations

Description
This function removes reaction vertices with no gene annotations as indicated by the parameter gene.attr, and connect their neighbour vertices to preserve graph connectivity. This is particularly meaningful when reactions are translation or spontaneous reactions, which are not catalysed by genes.

Usage
simplifyReactionNetwork(reaction.graph, gene.attr = "genes",
  remove.missing.genes = TRUE, reconnect.threshold = vcount(reaction.graph))
**stdAttrNames**

**Arguments**

- *reaction.graph*  A reaction network.
- *gene.attr*  The attribute to be considered as "genes". Reactions missing this annotation, will be removed.
- *remove.missing.genes*  If FALSE, only tranlocation and spontaneous reactions are removed, otherwise all reactions with no gene annotations are removed.
- *reconnect.threshold*  An argument passed to `vertexDeleteReconnect`

**Value**

A simplified reaction network.

**Author(s)**

Ahmed Mohamed

**See Also**

Other Network processing methods: `expandComplexes`, `makeReactionNetwork`, `rmSmallCompounds`, `vertexDeleteReconnect`

**Examples**

```r
data(ex_sbml)
rgraph <- makeReactionNetwork(ex_sbml, simplify=FALSE)

## Removes all reaction nodes with no annotated genes.
rgraph <- simplifyReactionNetwork(rgraph, remove.missing.genes=TRUE)
```

---

### stdAttrNames

**MIRIAM annotation attributes**

**Description**

These functions deal with conforming with MIRIAM annotation guidelines, conversion and mapping between MIRIAM identifiers.

**Usage**

```r
stdAttrNames(graph, return.value = c("matches", "graph"))
fetchAttribute(graph, organism = "Homo sapiens", target.attr, source.attr, bridge.web = NPMdefaults("bridge.web"))
```
toGraphNEL

Converts an annotated igraph object to graphNEL

Description

Converts an annotated igraph object to graphNEL

Usage

toGraphNEL(graph, export.attr = "")
Arguments

- **graph**: An annotated igraph object.
- **export.attr**: A regex expression representing vertex attributes to be exported to the new graphNEL object. Supplying an empty string "" (default) will export all attributes.

Value

A graphNEL object.

Author(s)

Ahmed Mohamed

Examples

data(ex_kgml_sig) # Ras and chemokine signaling pathways in human
graphNEL <- toGraphNEL(ex_kgml_sig, export.attr="^miriam.")

Description

This function removes vertices given as *vids* and connects their neighbours as long as the shortest path between the neighbours are below the *reconnect.threshold*.

Usage

```
vertexDeleteReconnect(graph, vids, reconnect.threshold = vcount(graph),
                      copy.attr = NULL)
```

Arguments

- **graph**: A reaction network.
- **vids**: Vertex ids to be removed.
- **reconnect.threshold**: If the shortest path between vertices is larger than this threshold, they are not reconnected.
- **copy.attr**: A function, or a list of functions, combine edge attributes. Edge attributes of new edges (between reconnected neighbours) are obtained by combining original edges attributes along the shortest path between reconnected neighbors.

Value

A modified graph.

Author(s)

Ahmed Mohamed
vertexDeleteReconnect

See Also

Other Network processing methods: expandComplexes, makeReactionNetwork, rmSmallCompounds, simplifyReactionNetwork

Examples

## Remove all reaction vertices from a bipartite metabolic network
## keeping only metabolite vertices.

data(ex_sbml)

graph <- vertexDeleteReconnect(ex_sbml, vids=which(V(ex_sbml)$reactions))
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