

Package ‘PPInfer’

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Type Package

Title Inferring functionally related proteins using protein interaction networks

Description Interactions between proteins occur in many, if not most, biological processes. Most proteins perform their functions in networks associated with other proteins and other biomolecules. This fact has motivated the development of a variety of experimental methods for the identification of protein interactions. This variety has in turn ushered in the development of numerous different computational approaches for modeling and predicting protein interactions. Sometimes an experiment is aimed at identifying proteins closely related to some interesting proteins. A network based statistical learning method is used to infer the putative functions of proteins from the known functions of its neighboring proteins on a PPI network. This package identifies such proteins often involved in the same or similar biological functions.

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PPInfer-package	<i>Inferring functionally related proteins using protein interaction networks</i>
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Description

Interactions between proteins occur in many, if not most, biological processes. Most proteins perform their functions in networks associated with other proteins and other biomolecules. This fact has motivated the development of a variety of experimental methods for the identification of protein interactions. This variety has in turn ushered in the development of numerous different computational approaches for modeling and predicting protein interactions. Sometimes an experiment is aimed at identifying proteins closely related to some interesting proteins. A network based statistical learning method is used to infer the putative functions of proteins from the known functions of its neighboring proteins on a PPI network. This package identifies such proteins often involved in the same or similar biological functions.

Details

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Author(s)

Dongmin Jung, Xijin Ge

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Description

The connection between nodes depends on the proportion of overlapping genes between two categories.

Usage

```
enrich.net(x, gene.set, node.id, node.name = node.id, pvalue,
           n = 50, numChar = NULL, pvalue.cutoff = 0.05,
           edge.cutoff = 0.05, degree.cutoff = 0,
           edge.width = function(x) {10*x^2},
           node.size = function(x) {2.5*log10(x)},
           group = FALSE, group.color = c('red', 'green'),
           group.shape = c('circle', 'square'),
           legend.parameter = list('topright'),
           show.legend = TRUE, ...)
```

Arguments

x	a result with category and p-value of gene sets
gene.set	gene sets which is already used for functional enrichment
node.id	name of gene sets
node.name	label of nodes in the network (default: node.id)
pvalue	pvalues for categories
n	number of top categories (default: 50)
numChar	the maximal number of characters of the label of gene sets
pvalue.cutoff	nodes with p-values which are greater than pvalue.cutoff are removed (default: 0.05)
edge.cutoff	edges with the proportion which is less than edge.cutoff are removed (default: 0.05)
degree.cutoff	nodes with the degrees which are less than degree.cutoff are removed (default: 0)
edge.width	width of edges
node.size	size of nodes
group	variable for group
group.color	color for group (default: red and green for 2 groups)
group.shape	shape for group (default: circle and square for 2 groups)
legend.parameter	list of parameters for the legend
show.legend	show the legend (default: TRUE)
...	additional parameters for the igraph

Value

plot for the network. The size of nodes is proportional to the size of gene sets. The more significant categories are, the less transparent their nodes are.

Author(s)

Dongmin Jung, Xijin Ge

References

Yu G, Wang L, Yan G and He Q (2015). "DOSE: an R/Bioconductor package for Disease Ontology Semantic and Enrichment analysis." *Bioinformatics*, 31(4), pp. 608-609.

See Also

igraph

Examples

```
data(examplePathways)
data(exampleRanks)
set.seed(1)
result.GSEA <- fgsea(examplePathways, exampleRanks, nperm = 1000)
enrich.net(result.GSEA, examplePathways, node.id = 'pathway',
           pvalue = 'pval', edge.cutoff = 0.6, degree.cutoff = 1,
           n = 50, vertex.label.cex = 0.75, show.legend = FALSE,
           edge.width = function(x) {5*sqrt(x)},
           layout = igraph::layout.kamada.kawai)
```

GSEA.barplot

Visualize the gene set enrichment analysis

Description

For the functional enrichment analysis, we can visualize the result from the gene set enrichment analysis.

Usage

```
GSEA.barplot(object, category, score, pvalue, top = 10,
             sort = NULL, decreasing = FALSE, numChar = NULL,
             title = NULL, transparency = 0.5, plot = TRUE)
```

Arguments

object	a table with category, enrichment score and p-value of gene sets
category	name of gene sets
score	enrichment score
pvalue	p-value of gene sets
top	the number of top categories (default: 10)
sort	a variable used for sorting data

decreasing	logical indicating whether ascending or descending order (default: FALSE)
numChar	the maximal number of characters of the name of gene sets
title	title for the plot
transparency	transparency (default: 0.5)
plot	return plot when plot is true, otherwise return table (default: TRUE)

Value

GSEA barplot

Author(s)

Dongmin Jung, Xijin Ge

References

Yu G, Wang L, Yan G and He Q (2015). "DOSE: an R/Bioconductor package for Disease Ontology Semantic and Enrichment analysis." *Bioinformatics*, 31(4), pp. 608-609.

See Also

ggplot2

Examples

```
data(examplePathways)
data(exampleRanks)
set.seed(1)
result.GSEA <- fgsea(examplePathways, exampleRanks, nperm = 1000)
GSEA.barplot(result.GSEA, category = 'pathway', score = 'NES',
              pvalue = 'pval', sort = 'NES', decreasing = TRUE)
```

net.infer

Inferring functionally related proteins using networks

Description

Proteins can be classified by using networks to identify functionally closely related proteins.

Usage

```
net.infer(target, kernel, top = NULL, cross = 0,
          C = 1, nu = 0.2, epsilon = 0.1, cache1 = 40,
          tol1 = 0.001, shrinking1 = TRUE, cache2 = 40,
          tol2 = 0.001, shrinking2 = TRUE)
```

Arguments

target	set of interesting proteins or target class
kernel	the regularized Laplacian matrix for a graph
top	number of top proteins most closely related to target class (default: all proteins except for target and pseudo-absence class)
cross	if a integer value $k > 0$ is specified, a k -fold cross validation on the training data is performed to assess the quality of the model
C	cost of constraints violation for SVM (default: 1)
nu	The nu parameter for OCSVM (default: 0.2)
epsilon	epsilon in the insensitive-loss function for OCSVM (default: 0.1)
cache1	cache memory in MB for OCSVM (default: 40)
tol1	tolerance of termination criterion for OCSVM (default: 0.001)
shrinking1	option whether to use the shrinking-heuristics for OCSVM (default: TRUE)
cache2	cache memory in MB for SVM (default: 40)
tol2	tolerance of termination criterion for SVM (default: 0.001)
shrinking2	option whether to use the shrinking-heuristics for SVM (default: TRUE)

Value

list	list of a target class used in the model
error	training error
CVerror	cross validation error, (when cross > 0)
top	top proteins
score	decision values for top proteins

Author(s)

Dongmin Jung, Xijin Ge

References

Senay, S. D. et al. (2013). Novel three-step pseudo-absence selection technique for improved species distribution modelling. PLOS ONE. 8(8), e71218.

See Also

ksvm

Examples

```
# example 1
## Not run:
string.db.9606 <- STRINGdb$new(version = '11', species = 9606,
                              score_threshold = 999)
string.db.9606.graph <- string.db.9606$get_graph()
K.9606 <- net.kernel(string.db.9606.graph)
rownames(K.9606) <- substring(rownames(K.9606), 6)
colnames(K.9606) <- substring(colnames(K.9606), 6)
target <- colnames(K.9606)[1:100]
```

```
infer <- net.infer(target, K.9606, 10)

## End(Not run)

# example 2
data(litG)
litG <- igraph.from.graphNEL(litG)
sg <- decompose(litG, min.vertices = 50)
sg <- sg[[1]]
K <- net.kernel(sg)
litG.infer <- net.infer(names(V(sg))[1:10], K, top=20)
```

net.infer.ST

*Inferring functionally related proteins with self training***Description**

This function is the self-training version of net.infer. The function net.infer is the special case of net.infer.ST where a single iteration is conducted.

Usage

```
net.infer.ST(target, kernel, top = NULL, C = 1, nu = 0.2,
             epsilon = 0.1, cache1 = 40, tol1 = 0.001, shrinking1 = TRUE,
             cache2 = 40, tol2 = 0.001, shrinking2 = TRUE, thrConf = 0.9,
             maxIts = 10, percFull = 1, verbose = FALSE)
```

Arguments

target	set of interesting proteins or target class
kernel	the regularized Laplacian matrix for a graph
top	number of top proteins most closely related to target class (default: all proteins except for target and pseudo-absence class)
C	cost of constraints violation for SVM (default: 1)
nu	The nu parameter for OCSVM (default: 0.2)
epsilon	epsilon in the insensitive-loss function for OCSVM (default: 0.1)
cache1	cache memory in MB for OCSVM (default: 40)
tol1	tolerance of termination criterion for OCSVM (default: 0.001)
shrinking1	option whether to use the shrinking-heuristics for OCSVM (default: TRUE)
cache2	cache memory in MB for SVM (default: 40)
tol2	tolerance of termination criterion for SVM (default: 0.001)
shrinking2	option whether to use the shrinking-heuristics for SVM (default: TRUE)
thrConf	A number between 0 and 1, indicating the required classification confidence for an unlabelled case to be added to the labelled data set with the label predicted by the classification algorithm (default: 0.9)
maxIts	The maximum number of iterations of the self-training process (default: 10)
percFull	A number between 0 and 1. If the percentage of labelled cases reaches this value the self-training process is stopped (default: 1)
verbose	A boolean indicating the verbosity level of the function. (default: FALSE)

Value

list	list of a target class used in the model
error	training error
top	top proteins
score	decision values for top proteins

Author(s)

Dongmin Jung, Xijin Ge

See Also

self.train

Examples

```
data(litG)
litG <- igraph.from.graphNEL(litG)
sg <- decompose(litG, min.vertices = 50)
sg <- sg[[1]]
K <- net.kernel(sg)
litG.infer.ST <- net.infer.ST(names(V(sg))[1:10], K, top=20)
```

net.kernel	<i>Kernel matrix for a graph</i>
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Description

This function gives the regularized Laplacian matrix for a graph.

Usage

```
net.kernel(g, decay = 0.5)
```

Arguments

g	graph
decay	decaying constant (default: 0.5)

Value

the regularized Laplacian matrix

Author(s)

Dongmin Jung, Xijin Ge

See Also

laplacian_matrix

Examples

```
# example 1
## Not run:
string.db.9606 <- STRINGdb$new(version = '11', species = 9606,
                              score_threshold = 999)
string.db.9606.graph <- string.db.9606$get_graph()
K.9606 <- net.kernel(string.db.9606.graph)

## End(Not run)

# example 2
data(litG)
litG <- igraph.from.graphNEL(litG)
sg <- decompose(litG, min.vertices=50)
sg <- sg[[1]]
K <- net.kernel(sg)
```

ORA

*Over-representation Analysis***Description**

the result from the over-representation analysis

Usage

```
ORA(pathways, gene.id, minSize = 1, maxSize = Inf,
    p.adjust.methods = NULL)
```

Arguments

pathways	list of gene sets
gene.id	set of genes
minSize	Minimal size of a gene set
maxSize	Maximal size of a gene set
p.adjust.methods	a correction method

Value

ORA result

Author(s)

Dongmin Jung, Xijin Ge

See Also

fisher.test

Examples

```
data(examplePathways)
data(exampleRanks)
geneNames <- names(exampleRanks)
set.seed(1)
gene.id <- sample(geneNames, 100)
ORA(examplePathways, gene.id)
```

ORA.barplot

*Visualize the over-representation analysis***Description**

For the functional enrichment analysis, we can visualize the result from the over-representation analysis.

Usage

```
ORA.barplot(object, category, size, count, pvalue, top = 10,
            sort = NULL, decreasing = FALSE, p.adjust.methods = NULL,
            numChar = NULL, title = NULL, transparency = 0.5,
            plot = TRUE)
```

Arguments

object	a table with category, size, count and p-value of gene sets
category	name of gene sets
size	size of gene sets
count	count of gene sets
pvalue	p-value of gene sets
top	the number of top categories (default: 10)
sort	a variable used for sorting data
decreasing	logical indicating whether ascending or descending order (default: FALSE)
p.adjust.methods	a correction method
numChar	the maximal number of characters of the name of gene sets
title	title for the plot
transparency	transparency (default: 0.5)
plot	return plot when plot is true, otherwise return table (default: TRUE)

Value

ORA barplot

Author(s)

Dongmin Jung, Xijin Ge

References

Yu G, Wang L, Yan G and He Q (2015). "DOSE: an R/Bioconductor package for Disease Ontology Semantic and Enrichment analysis." *Bioinformatics*, 31(4), pp. 608-609.

See Also

p.adjust, ggplot2

Examples

```
data(examplePathways)
data(exampleRanks)
geneNames <- names(exampleRanks)
set.seed(1)
gene.id <- sample(geneNames, 100)
result.ORA <- ORA(examplePathways, gene.id)
ORA.barplot(result.ORA, category = "Category", size = "Size",
             count = "Count", pvalue = "pvalue", sort = "pvalue")
```

ppi.infer.human	<i>Inferring functionally related proteins using protein networks for human</i>
-----------------	---

Description

This function is designed for human protein-protein interaction from STRING database. Default format is 'hgnc'. The number of proteins is 10 in default. Note that the number of proteins used as a target may be different from the number of proteins in the input since mapping between formats is not always one-to-one in getBM.

Usage

```
ppi.infer.human(target, kernel, top = 10, classifier = net.infer,
                input = "hgnc_symbol", output = "hgnc_symbol", ...)
```

Arguments

target	set of interesting proteins or target class
kernel	the regularized Laplacian matrix for a graph
top	number of top proteins most closely related to target class (default: 10)
classifier	net.infer or net.infer.ST (default: net.infer)
input	input format
output	output format
...	additional parameters for the chosen classifier

Value

list	list of a target class used in the model
error	training error
CVerror	cross validation error, (when cross > 0 in net.infer)
top	top proteins
score	decision values for top proteins

Author(s)

Dongmin Jung, Xijin Ge

See Also

net.infer, net.infer.ST, getBM

Examples

```
# example 1
string.db.9606 <- STRINGdb$new(version = '11', species = 9606,
                              score_threshold = 999)
string.db.9606.graph <- string.db.9606$get_graph()
K.9606 <- net.kernel(string.db.9606.graph)
rownames(K.9606) <- substring(rownames(K.9606), 6)
colnames(K.9606) <- substring(colnames(K.9606), 6)
target <- colnames(K.9606)[1:100]
infer.human <- ppi.infer.human(target, K.9606, input = "ensembl_peptide_id")

## Not run:
# example 2
library(graph)
data(apopGraph)
target <- nodes(apopGraph)
apoptosis.infer <- ppi.infer.human(target, K.9606, 100)

# example 3
library(KEGGgraph)
library(KEGG.db)
pName <- "p53 signaling pathway"
pId <- mget(pName, KEGGPATHNAME2ID)[[1]]
getKGMLurl(pId, organism = "hsa")
p53 <- system.file("extdata/hsa04115.xml", package="KEGGgraph")
p53graph <- parseKGML2Graph(p53, expandGenes=TRUE)

entrez <- translateKEGGID2GeneID(nodes(p53graph))
httr::set_config(httr::config(ssl_verifypeer = FALSE))
human.ensembl <- useEnsembl(biomart = "ensembl", dataset = "hsapiens_gene_ensembl")
target <- getBM(attributes=c('entrezgene', 'hgnc_symbol'),
               filter = 'entrezgene', values = entrez,
               mart = human.ensembl)[,2]
p53.infer <- ppi.infer.human(target, K.9606, 100)

## End(Not run)
```

ppi.infer.mouse

Inferring functionally related proteins using protein networks for mouse

Description

This function is designed for mouse protein-protein interaction from STRING database. Default format is 'mgi'. The number of proteins is 10 in default. Note that the number of proteins used as a target may be different from the number of proteins in the input since mapping between formats is not always one-to-one in getBM.

Usage

```
ppi.infer.mouse(target, kernel, top = 10, classifier = net.infer,
               input = "mgi_symbol", output = "mgi_symbol", ...)
```

Arguments

target	set of interesting proteins or target class
kernel	the regularized Laplacian matrix for a graph
top	number of top proteins most closely related to target class (default: 10)
classifier	net.infer or net.infer.ST (default: net.infer)
input	input format
output	output format
...	additional parameters for the chosen classifier

Value

list	list of a target class used in the model
error	training error
CVerror	cross validation error, (when cross > 0 in net.infer)
top	top proteins
score	decision values for top proteins

Author(s)

Dongmin Jung, Xijin Ge

See Also

net.infer, net.infer.ST, getBM

Examples

```
string.db.10090 <- STRINGdb$new(version = '11', species = 10090,
                                score_threshold = 999)
string.db.10090.graph <- string.db.10090$get_graph()
K.10090 <- net.kernel(string.db.10090.graph)
rownames(K.10090) <- substring(rownames(K.10090), 7)
colnames(K.10090) <- substring(colnames(K.10090), 7)
target <- colnames(K.10090)[1:100]
infer.mouse <- ppi.infer.mouse(target, K.10090, input="ensembl_peptide_id")
```

self.train.kernel	<i>Self training for a kernel matrix</i>
-------------------	--

Description

This function can be used for classification of semi-supervised data by using the kernel support vector machine.

Usage

```
self.train.kernel(K, y, type = 'response', C = 1, cache = 40,
                  tol = 0.001, shrinking = TRUE, thrConf = 0.9,
                  maxIts = 10, percFull = 1, verbose = FALSE)
```

Arguments

K	kernel matrix
y	lable vector
type	one of response, probabilities ,votes, decision indicating the type of output (default: response)
C	cost of constraints violation for SVM (default: 1)
cache	cache memory in MB for SVM (default: 40)
tol	tolerance of termination criterion for SVM (default: 0.001)
shrinking	option whether to use the shrinking-heuristics for OCSVM (default: TRUE)
thrConf	A number between 0 and 1, indicating the required classification confidence for an unlabelled case to be added to the labelled data set with the label predicted by the classification algorithm (default: 0.9)
maxIts	The maximum number of iterations of the self-training process (default: 10)
percFull	A number between 0 and 1. If the percentage of labelled cases reaches this value the self-training process is stoped (default: 1)
verbose	A boolean indicating the verbosity level of the function (default: FALSE)

Value

prediction from the SVM

Author(s)

Dongmin Jung, Xijin Ge

References

Torgo, L. (2016) Data Mining using R: learning with case studies, second edition, Chapman & Hall/CRC.

Examples

```
data(litG)
litG <- igraph.from.graphNEL(litG)
sg <- decompose(litG, min.vertices = 50)
sg <- sg[[1]]
K <- net.kernel(sg)
y <- rep(NA, length(V(sg)))
y[1:10] <- 1
y[11:20] <- 0
y <- factor(y)
self.train.kernel(K, y)
```

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