Package 'signet'

April 15, 2020

Type Package

Title signet: Selection Inference in Gene NETworks

Version 1.6.0

Date 2018-11-22

Description An R package to detect selection in biological pathways.
Using gene selection scores and biological pathways data,
one can search for high-scoring subnetworks of genes within pathways
and test their significance.

Depends R (>= 3.4.0)

Imports graph, igraph, RBGL, graphics, utils, stats, methods

Suggests graphite, BiocStyle, knitr, rmarkdown

biocViews Software, Pathways, DifferentialExpression, GeneExpression,
NetworkEnrichment, GraphAndNetwork, KEGG

License GPL-2

LazyData true

RoxygenNote 6.1.1

VignetteBuilder knitr

git_url https://git.bioconductor.org/packages/signet

git_branch RELEASE_3_10

git_last_commit fd60d46

git_last_commit_date 2019-10-29

Date/Publication 2020-04-14

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`kegg_human` *Pathway examples. See* `browseVignettes("signet")` *to see how to prepare the pathways for running simulated annealing.*

Description

Pathway examples. See `browseVignettes("signet")` to see how to prepare the pathways for running simulated annealing.

Usage

```
kegg_human
```

Format

An object of class `list` of length 3.

`nullDist` *Null distribution*

Description

Generate the high-scores null distribution to compute empirical p-values for each biological pathway.

Usage

```
nullDist(pathways, scores, n = 1000, background)
```

Arguments

`pathways`	A list of graphNEL objects.
`scores`	A data frame in which the first column corresponds to the gene ID and the second column contains the gene scores.
`n`	Number of null high-scores to compute (default = 1000).
`background`	Optional. Background distribution computed using the backgroundDist function.

Value

A vector of subnetworks scores obtained under the null hypothesis. Must be used as input of the testSubnet function.

Examples

```
# Get KEGG pathways from the package graphite:
# library(graphite)
# kegg <- pathways("hsapiens", "kegg")
# kegg_human <- lapply(kegg, pathwayGraph)

data(daub13) # load the gene scores

# generate the null distribution (here, only 5 values, but
# at least 1000 are advised)
null <- nullDist(kegg_human, scores, n = 5)
```

`scores` *Example of gene selection scores.*

Description

A dataset of gene selection scores.

Usage

```
scores
```

Format

A data frame with 17918 rows and 2 variables:

gene Gene identifier (Entrez gene ID)

score Gene selection score ...

Details

These gene scores are the one used in Daub et al. (2013). For a set of SNPs, a z-score has been computed to represent an overall genetic differentiation among several human populations. A gene score corresponds to the maximal value among SNPs located within a given gene.

The table has been generated using the pipeline described here ("Human populations project"): https://github.com/CMPG/polysel

Source

Daub, J. T., Hofer, T., Cutivet, E., Dupanloup, I., Quintana-Murci, L., Robinson-Rechavi, M., & Excoffier, L. (2013). Evidence for polygenic adaptation to pathogens in the human genome. Molecular biology and evolution, 30(7), 1544-1558.

searchSubnet *Search for a high scoring subnetwork*

Description

A simulated annealing algorithm to find the highest scoring subnetwork within a graph.

Usage

```
searchSubnet(pathway, scores, iterations = 1000, background)
```

Arguments

pathway	A gene network, or a list of gene networks, in the graphNEL format.
scores	A data frame with two columns: gene identifiers list (IDs have to be the same as for the pathways, e.g. Entrez) and associated scores.
iterations	Number of iterations.
background	For development purposes.

Value

A signet object or a list of signet objects. Each signet object consists in a table with gene IDs, their state, their score; the subnetwork score and size and the p-value.

Examples

```
# Get KEGG pathways from the package graphite:
# library(graphite)
# kegg <- pathways("hsapiens", "kegg")
# kegg_human <- lapply(kegg, pathwayGraph)

data(daub13) # load the example gene scores

#run the search in all the pathways with 2500 iterations (default)
example <- searchSubnet(kegg_human, scores)
summary(example)
```

signet *Selection Inference in Gene NETworks*

Description

Implements a simulated annealing approach to search for high scoring subnetworks of genes within biological pathways and to test for their significance.

Examples

```
## A complete workflow is described in signet vignette:
browseVignettes("signet")
```

Signet-class *An S4 class to represent a pathway and the results of the associated simulated annealing run.*

Description

An S4 class to represent a pathway and the results of the associated simulated annealing run.

Usage

```
## S4 method for signature 'Signet'
show(object)

## S4 method for signature 'Signet'
summary(object)

## S4 method for signature 'Signet,missing'
plot(x, y, ...)

## S4 method for signature 'Signet'
initialize(.Object, pathway, scores, iterations)
```

Arguments

object	A signet object.
x	A signet object.
y	Omitted when plotting a Signet object.
...	Other graphical parameters.
.Object	Object to initialize.
pathway	Biological pathway (graphNEL object).
scores	Gene scores list.
iterations	Number of simulated annealing iterations.

Value

A plot of the simulated annealing run.

A signet object.

Methods (by generic)

- show: Print the summary a Signet object.
- summary: Print the summary of a Signet object
- plot: Plot a Signet object
- initialize: Initialize a Signet object

Slots

`connected_comp` A graphNEL object (biological pathway)

`network` A data frame (gene IDs and scores)

`SA` A data frame (information on the simulated annealing run)

`subnet_score` A numeric value (subnetwork score)

`aggregate_score` A numeric value (aggregate subnetwork score)

`mean_score` A numeric value (average gene score in the pathway)

`subnet_size` An integer value (subnetwork size)

`subnet_genes` A factor (subnetwork genes)

`p.value` A numeric value (empirical p-value)

`SignetList-class` *An S4 class to represent a list of "Signet" objects.*

Description

An S4 class to represent a list of "Signet" objects.

Usage

```
## S4 method for signature 'SignetList'
initialize(.Object, list)

## S4 method for signature 'SignetList'
x[[i]]

## S4 method for signature 'SignetList,ANY,missing'
x[i, j, ..., drop = TRUE]

## S4 method for signature 'SignetList'
summary(object, ...)
```

Arguments

`.Object`	A SignetList object.
`list`	A list of Signet objects.
`x`	A SignetList object.
`i`	Index specifying elements to extract or replace.
`j`	Unused for SignetList objects.
`...`	Unused for SignetList objects.
`drop`	Unused for SignetList objects.
`object`	A SignetList object.

Value

Results of the simulated annealing run for a lisst of pathways.

A SignetList object.

A data frame containing summary statistics for each element (network and subnetwork sizes, subnetwork score, p-value, significant genes list)

Methods (by generic)

- `initialize`: Initialize a SignetList
- `[[`: Access the ith element (signet object) of the SignetList
- `[`: Access the ith element (signet object) of the SignetList
- `summary`: Summarize the SignetList.

Slots

`results` A list of Signet objects.

---

testSubnet *Test the significance of high-scoring subnetworks found using simulated annealing.*

Description

Test the significance of high-scoring subnetworks found using simulated annealing.

Usage

```
testSubnet(sigObj, null)
```

Arguments

`sigObj`	A list of signet objects obtained using the searchSubnet function.
`null`	Vector of null subnetwork scores generated using the `nullDist` function.

Value

For each signet object, a p-value is computed given the provided emnpirical null distribution.

Examples

```
# Get KEGG pathways from the package graphite:
# library(graphite)
# kegg <- pathways("hsapiens", "kegg")
# kegg_human <- lapply(kegg, pathwayGraph)

data(daub13) # load the gene scores from Daub et al. (2013)

#run the search in all the pathways with 2500 iterations (default)
example <- searchSubnet(kegg_human, scores)
```

```
# generate the null distribution (here, only 5 values, but
# at least 1000 are advised)
null <- nullDist(kegg_human, scores, n = 5)
example <- testSubnet(example, null) #now, 'example' includes p-values
summary(example)
```

---

writeXGMML *Write Cytoscape input file*

Description

This function allows to write an XGMML file to represent the results in Cytoscape.

Usage

```
writeXGMML(sigObj, filename = "signet_output.xgmml", threshold = 0.01)
```

Arguments

sigObj	A signet or signetList object.
filename	The desired file name. Default is "signet_output.xgmml".
threshold	Significance threshold (default: 0.01). If a signetList is provided, all subnetworks with a p-value below this threshold will be merged and represented.

Value

Writes an XGMML file in the working directory. If a single pathway (signet object) is provided, the whole pathway is represented and nodes belonging to the highest-scoring subnetwork (HSS) are highlighted in red. If a list of pathways (signetList) is provided, all subnetworks with a p-value below a given threshold (default: 0.01) are merged and represented. Note that in this case, only the nodes belonging to HSS are kept for representation.

Examples

```
# Get KEGG pathways from the package graphite:
# library(graphite)
# kegg <- pathways("hsapiens", "kegg")
# kegg_human <- lapply(kegg, pathwayGraph)

data(daub13) # load the gene scores from Daub et al. (2013)

#run the search in all the pathways with 2500 iterations (default)
example <- searchSubnet(kegg_human, scores)

#write Cytoscape input file for the first pathway:
writeXGMML(example[[1]], filename=tempfile())
```

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