Package 'RTopper'

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Type Package

Title This package is designed to perform Gene Set Analysis across multiple genomic platforms

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Imports limma, multtest

Suggests org.Hs.eg.db, KEGGREST, GO.db

Description the RTopper package is designed to perform and integrate gene set enrichment results across multiple genomic platforms.

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`RTopper-package` *A package to perform run Gene Set Enrichment across genomic platforms*

Description

Gene sets analysis considers whether genes sharing a biological property also behave in a related way in experimental data. This technique is commonly used in high throughput genomic analyses to assist results interpretation, and has been successfully applied in cancer genome projects for integrating information from multiple genome-wide assays. The `RTopper` package uses gene sets analysis to overcome the diversity of genomic data providing the statistical framework for integration across data types.

Details

Package:	RTopper
Type:	Package
Version:	0.1
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License:	GPL version 3 or newer

RTopper package features

`Rtopper` enables two gene set-based data integration approaches:

1. Integration+GSA: computing integrated gene-to-phenotype association scores, followed by conventional gene sets analysis;
2. GSA+Integration: computing consensus significance score after all data types are analyzed individually;
3. Use of alternative enrichment test: `RTopper` uses the Wilcoxon rank-sum test for enrichment testing, however alternative tests can be defined and used;
4. Multiple testing correction: `RTopper` enables adjustment of p-values obtained from enrichment analysis;

Author(s)

Luigi Marchionni <marchion@jhu.edu>

References

Svitlana Tyekucheva, Luigi Marchionni, Rachel Karchin, and Giovanni Parmigiani. "Integrating diverse genomic data using gene sets." Manuscript submitted.

adjustPvalGSE *Multiple testing correction*

Description

This function is an interface to the mt.rawp2adjp function contained in the multtest package. adjustPvalGSE works on outputs from runBatchGSE and combineGSE returning adjusted p-values

Usage

```
adjustPvalGSE(gseOut, proc = "BH", alpha = 0.05 , na.rm = FALSE)
```

Arguments

gseOut	list of lists, either the output from runBatchGSE, or the output from combineGSE
proc	character, the method to be used for p-values adjusting. This parameter will be passed to the mt.rawp2adjp function from the multtest package. The available options include: "Bonferroni", "Holm", "Hochberg", "SidakSS", code"SidakSD", "BH" (the default), "BY", "ABH", and "TSBH"
alpha	numeric, the nominal type I error rate
na.rm	logical, the option for handling NA values in the list of raw p-values

Details

The adjustPvalGSE function performs p-value adjusting for multiple testing correction on the list of lists resulting from enrichment analysis obtained using the runBatchGSE and combineGSE functions. This functions is based on the mt.rawp2adjp function contained in the multtest package.

Value

For each vector of p-value contained in the gseOut input object a data.frame is returned, containing original p-value and corrected p-values

Author(s)

Luigi Marchionni <marchion@jh.edu>

References

Svitlana Tyekucheva, Luigi Marchionni, Rachel Karchin, and Giovanni Parmigiani. "Integrating diverse genomic data using gene sets." Manuscript submitted.

Examples

```
###load gse analysis results for separate gene-to-phenotype score
data(gseResultsSep)

###adjust for multiple testing using the Benjamini and Hochberg method
gseABS.int.BH <- adjustPvalGSE(gseResultsSep)

###adjust for multiple testing using the Holm method
gseABS.int.holm <- adjustPvalGSE(gseResultsSep, proc = "Holm")
```

combineGSE *Combines GSE results*

Description

Combines GSE results obtained from a sepatate set of gene-to-phenotypes scores

Usage

```
combineGSE(gseOut, method)
```

Arguments

gseOut	a list of lists containing the enrichment results to be combined. This is usually the the output of runBatchGSE obtained from a set of distinct genes-to-phenotype scores (usually one per genomic platform)
method	character, this argument specifies the method used to combine the enrichment results obtained from distinct genes-to-phenotype scores (usually one per genomic platform). Available options are the computation of the geometric or arithmetic means, the use of the median, the selection of the minimun or the maximum enrichment score, and the random selection of a score (respectively "geometricMean", "mean", "median", "min", "max", and "random")

Details

This function summarize enrichment results obtained from distinct gene-to-phenotypes scores (usually one per genomic platform) by one of several alternative methods.

Value

The output is a list of lists containing integrated enrichment results for all FGS collections

Author(s)

Luigi Marchionni <marchion@jhu.edu>

References

Svitlana Tyekucheva, Luigi Marchionni, Rachel Karchin, and Giovanni Parmigiani. "Integrating diverse genomic data using gene sets." Manuscript submitted.

Examples

```
###load gse analysis results for separate gene-to-phenotype score
data(gseResultsSep)

###combine enrichment score results using geometric mean
gseABS.sep.geoMean <- combineGSE(gseResultsSep, method="geometricMean")

###combine enrichment score results using maximum value
gseABS.sep.max <- combineGSE(gseResultsSep, method="max")
```

computeDrStat *Computes gene-to-phenotype associations scores*

Description

computeDrStat Computes gene-to-phenotype associations scores, using as input the output from convertToDr.

Usage

```
computeDrStat(data, columns = c(1:(ncol(data)-1)), method = "dev", integrate = TRUE)
```

Arguments

data	a list of data.frames containing genomic measurements. Each element of dataIntersection must account for the same set of patients(columns) and genes (rows)
columns	a data.frame indicating patients' phenotypic class
method	character, the number of genomic platforms
integrate	logical, wheter to integrate the gene-to-phenotype scores across platform or return separates scores for each platform

Details

This function allows computing gene-to-phenotype association scores, using as input the gene-centered list produced by computeDr. The computeDrStat function works separately on each gene-centered data.frame created by the convertToDr function, assuming that the phenotype information is stored in the last column named "response". It is possible computing both separate association scores for each platform, as well as an integrated score, as specified by the integrate arguments. There are currently three methods available for obtaining the scores (see Tyekucheva et al, manuscript under review), as specified by the methods argument:

"dev": this approach computes the score as the difference of deviances;

"aic": this approach computes the score as the Akaike information criterion for model selection;

"bic": this approach computes the score as the penalized likelihood ratio;

Value

A list of named vectors containing separate or integrared gene-to-phenotype association scores.

Author(s)

Luigi Marchionni <marchion@jhu.edu>

References

Svitlana Tyekucheva, Luigi Marchionni, Rachel Karchin, and Giovanni Parmigiani. "Integrating diverse genomic data using gene sets." Manuscript submitted.

Examples

```
###load data
data(exampleData)

###convert
dataDr <- convertToDr(dat, pheno, 4)

###compute the integrated score
bicStatIntegrated <- computeDrStat(dataDr, columns = c(1:4), method="bic", integrate = TRUE)

###compute separate scores for each genomic platform
bicStatSeparate <- computeDrStat(dataDr, columns = c(1:4), method="bic", integrate = FALSE)
```

`convertToDr` *Converts genomic data to a list suitable for computing gene-to-phenotype scores*

Description

`convertToDr` converts genomic data into a list further used for computing gene-to-phenotype association scores.

Usage

```
convertToDr(dataIntersection, response, nPlatforms = length(data))
```

Arguments

`dataIntersection`	a list of data.frames containing genomic measurements. Each element of `dataIntersection` must account for the same set of patients(columns) and genes (rows)
`response`	a data.frame indicating patients' phenotypic class
`nPlatforms`	numeric, the number of genomic platforms

Details

This function coverts a list of data.frames containing distinct genomic measurtements performed on the same patients into a gene-centered used in further analyses for computing gene-to-phenotype scores. Data.frame in the input list (`dataIntersection`) must have the same dimentions, with columns being patients, and rows being genes. Column names identify the patients, while rownames identify the genes. The argument `response` is used to pass phenotypic information about samples to be analyzed. This is a simple two columns data.frame in which the first column correspond to patients identifiers, and the second column to the phenotypic response encoded as binary class (using the integers 0 and 1). The `nPlatforms` argument specifies the number of platforms that will be analyzed.

Value

A list of data.frames, one for each analyzed gene, summarizing all genomic measurements and phenotipic information across patients and platforms.

Author(s)

Luigi Marchionni <marchion@jhu.edu>

References

Svitlana Tyekucheva, Luigi Marchionni, Rachel Karchin,and Giovanni Parmigiani "Integrating diverse genomic data using gene sets." Manuscript submitted.

Examples

```
###load data
data(exampleData)

###convert
dataDr <- convertToDr(dat, pheno, 4)
```

---

dat *A test dataset for the RTopper package*

Description

A small subset of pre-processed Glioblasoma Multiforme (GBM) genomic data from The Cancer Genome Atlas (TCGA) project, encompassing Differential Gene Expression (DGE), and Copy Number Variation (CNV). Can be used as input to `convertToDr`.

Usage

```
data(exampleData)
```

Format

This object is a `list` of 4 `data.frames` containing genomic measurements obtained across distinct genomic scopes (copy number variation and gene expression), platforms (Affymetrix and Agiles), and laboratories. In particular each `data.frame` consist of 500 gene measurements (by rows), for 95 distinct patients (by columns) from the following 4 distinct platforms:

`"dat.affy"`: DGE obtained using Affymetrix microarrays;

`"dat.agilent"`: DGE obtained using Agilent microarrays;

`"dat.cnvHarvard"`: CNV data obtained at Harvard;

`"dat.cnvMskcc"`: CNV data obtained at Memorial Sloan Ketterng Cancer Center;

Source

The Cancer Genome Atlas (TCGA) project http://cancergenome.nih.gov/

References

The Cancer Genome Atlas (TCGA) Research Network. "Comprehensive genomic characterization defines human glioblastoma genes and core pathways". *Nature*, 2008, October 23; 455(7216): 1061-1068

Examples

```
data(exampleData)
ls()
class(dat)
names(dat)
sapply(dat,class)
sapply(dat,dim)
```

`fgsList` *A list of Functional Gene Set (FGS) to be used to run the examples in the RTopper package*

Description

A `list` containing distinct types of FGS (i.e. Gene Ontology, KEGG pathways). Each FGS is type is a `list` of named `chararacter` vectors, one for each FGS, containing the gene identifiers. Vectors names describe the FGS. Can be used as input to `runBatchGSE`.

Usage

```
data(fgsList)
```

Format

This object is a `list` of length two:

`"go"`: this is a `list` of 5 `character` vectors, corresponding to 5 distinct Gene Ontology (GO) terms. Genes annotated to each GO term are identified by their gene symbol;

`"kegg"`: this is a `list` of 5 `character` vectors, corresponding to 5 distinct KEGG pathways. Genes annotated to each KEGG pathway are identified by their gene symbol;

Source

The FGS were obtained from the `org.Hs.eg.db` pakage, (use the `org.Hs.eg` function to see the content); These FGS were annotated using data from `GO.db` and `KEGGREST` packages (use the `GO` and `keggGet` functions to see the content).

Examples

```
data(fgsList)
class(fgsList)
names(fgsList)
str(fgsList)
```

gseResultsSep *A list of separated gene set enrichment p-values to be used to run the examples in the RTopper package*

Description

A list containing distinct named numeric vectors corresponding to the gene set enrichment p-value separately computed with runBatchGSE for each distinct data set. Note that for each data set there are two set of p-values, one for GO and one for KEGG. These separate p-values can be combined across data sets by the combineGSE function. Can be used as input to adjustPvalGSE.

Usage

```
data(gseResultsSep)
```

Format

This object is a list of length four:

"dat.affy": a list of legnth two: "go" is a numeric vector of length 5, containing the p-values resulting from gene set enrichment analysis of 5 GO terms on Affymetrix gene expression data; "keg" is a numeric vector of length 5, containing the p-values resulting from gene set enrichment analysis of 5 KEGG pathways on Affymetrix gene expression data;

"dat.agilent": a list of legnth two: "go" is a numeric vector of length 5, containing the p-values resulting from gene set enrichment analysis of 5 GO terms on Agilent gene expression data; "keg" is a numeric vector of length 5, containing the p-values resulting from gene set enrichment analysis of 5 KEGG pathways on Agilent gene expression data;

"dat.cnvHarvard": a list of legnth two: "go" is a numeric vector of length 5, containing the p-values resulting from gene set enrichment analysis of 5 GO terms on Harvard CNV data; "keg" is a numeric vector of length 5, containing the p-values resulting from gene set enrichment analysis of 5 KEGG pathways on Harvard CNV data;

"dat.cnvMskcc": a list of legnth two: "go" is a numeric vector of length 5, containing the p-values resulting from gene set enrichment analysis of 5 GO terms on MSKCC CNV data; "keg" is a numeric vector of length 5, containing the p-values resulting from gene set enrichment analysis of 5 KEGG pathways on MSKCC CNV data;

Source

Computed using the runBatchGSE function from the TCGA data contained in sepScores and fgsList.

Examples

```
data(gseResultsSep)
class(gseResultsSep)
names(gseResultsSep)
str(gseResultsSep)
```

intScores *A list of genomic scores integrated across distinct data sets to be used to run the examples in the RTopper package*

Description

A `list` containing a named `numeric` vector corresponding to the genomic score resulting from the integration across distinct data set. These integrated gene-to-phenotype scores are computed by the `computeDrStat` function. Can be used as input to `runBatchGSE`.

Usage

```
data(intScores)
```

Format

This object is a `list` of length one:

`"integrated"`: a `numeric` vector of length 500, corresponding to the integrated phenotype association scores computed for each of the 500 genes used in the examples;

Source

Computed using the `computeDrStat` function from the TCGA data contained in `dat` and `pheno`.

Examples

```
data(intScores)
class(intScores)
names(intScores)
str(intScores)
```

pheno *A test dataset for the RTopper package*

Description

A `data.frame` with 2 columns containing the phenotypic class indicator for the 95 patients analyzed and used in the examples. Can be used as input to `convertToDr`.

Usage

```
data(exampleData)
```

Format

This object is a `data.frame` with two columns:

`"Sample"`: the first column contains the patients identifiers;

`"Class"`: the second columns contain a numeric indicator (0 or 1) corresponding to the phenotypic class of each patient;

Source

The Cancer Genome Atlas (TCGA) project http://cancergenome.nih.gov/

References

The Cancer Genome Atlas (TCGA) Research Network. "Comprehensive genomic characterization defines human glioblastoma genes and core pathways". *Nature*, 2008, October 23; 455(7216): 1061-1068

Examples

```
data(exampleData)
class(pheno)
colnames(pheno)
str(pheno)
```

`runBatchGSE` *To perform GSE analysis over multipple experiments and functional themes*

Description

The `runBatchGSE` function enables performing Gene Set Enrichment analysis over multiple ranking statistics and multiple lists of gene sets. By default this function is an interface to the `geneSetTest` in the `limma` package, and most of the arguments passed to `runBatchGSE` are indeed passed to such lower level function. As an alternative the user can also define and pass to `runBatchGSE` a custom function, defining the ranking statistics and the gene set membership in the same way done for `geneSetTest` (see Details below).

Usage

```
runBatchGSE(dataList, fgsList, ...)
```

Arguments

`dataList`	a list containing the gene-to-phenotype scores to be used as ranking statistics in the GSE analysis. This list is usually produced by running `computeDrStat`
`fgsList`	a list of FGS collection, in which each element is a list of character vectors, one for each gene set
`...`	additional arguments to be passed to lower level functions (see details below)

Details

This function performs enrichment analysis for all the gene-to-phenotype scores (argument `dataList`) passed to it over a list of F unctional Gene Set (FGS) (argument `fgsList`), returning a p-value for each FGS. Additional arguments can be bassed to this function to modify the way the enrichment test is performed, as follows:

`absolute` logical, this specifies whether the absolute values of the ranking statistics should be used in the test (the default being TRUE)

gseFunc a function to perform GSE analysis. If not specified the default is the geneSetTest function from the limma package. If a function is specified by the user, the membership of the analyzed genes to a FGS, and the ranking statistics must be defined in the same way this is done for geneSetTest, and the new function must return an integer (usually a p-value) (see the help for geneSetTest)

The following main arguments are used by geneSetTest:

type character, specifies the type of statistics used to rank the genes by geneSetTest: 'f' for F-like statistics (default), 't' for t-like statistics, or 'auto' for an educated guess

alternative character, defines the alternative with the following possible options: 'mixed' (default), 'either', 'up' or 'down', 'two.sided', 'greater', or 'less'

ranks.only logical, if TRUE (default) only ranks will be used by geneSetTest

nsim numeric, the number of randomly selected sets of genes to be used in simulations to compute the p-value

Value

The output is a list of lists containing the set of enrichment results for all gene-to-phenotype scores and FGS collections used as input.

Author(s)

Luigi Marchionni <marchion@jhu.edu>

References

Svitlana Tyekucheva, Luigi Marchionni, Rachel Karchin, and Giovanni Parmigiani. "Integrating diverse genomic data using gene sets." Manuscript submitted.

Examples

```
###require limma to run the example
require(limma)

###load integrated gene-to-phenotype scores
data(intScores)

###load separate gene-to-phenotype scores
data(sepScores)

###load list of functional gene sets
data(fgsList)

###run GSE analysis in batch with default parameters
gseABS.int <- runBatchGSE(dataList=intScores, fgsList=fgsList)

###run GSE analysis in batch with alternative parameters
gseABS.sep <- runBatchGSE(dataList=sepScores, fgsList=fgsList,
        absolute=FALSE, type="t", alternative="up")

###run GSE analysis in batch passing an enrichment function
gseUP.int.2 <- runBatchGSE(dataList=intScores, fgsList=fgsList,
      absolute=FALSE, gseFunc=wilcoxGST, alternative="up")

###define and use a new enrichment function
```

```
gseFunc <- function (selected, statistics, threshold) {
 diffExpGenes <- statistics > threshold
 tab <- table(diffExpGenes, selected)
 pVal <- fisher.test(tab)[["p.value"]]
 }
gseUP.sep.2 <- runBatchGSE(dataList=sepScores, fgsList=fgsList,
     absolute=FALSE, gseFunc=gseFunc, threshold=7.5)
```

`sepScores` *A list of separate gene-to-phenotype association scores, obtained indipendently for each distinct data set to be used to run the examples in the RTopper package*

Description

A `list` containing distinct named `numeric` vectors corresponding to the gene-to-phenotype association scores resulting from the sepatate analysis of each data set. These separate gene-to-phenotype scores are compurted by `computeDrStat` function. Can be used as input to `runBatchGSE`.

Usage

```
data(sepScores)
```

Format

This object is a `list` of length four, one element for data set:

`"dat.affy"`: a `numeric` vector of length 500, corresponding to the sepatate phenotype association scores computed for Affymetrix gene expression data;

`"dat.agilent"`: a `numeric` vector of length 500, corresponding to the separate phenotype association scores computed for Agilent gene expression data;

`"dat.cnvHarvard"`: a `numeric` vector of length 500, corresponding to the separate phenotype association scores computed for Harvard CNV data;

`"dat.cnvMskcc"`: a `numeric` vector of length 500, corresponding to the separate phenotype association scores computed for the MSKCC CNV data;

Source

Computed using the `computeDrStat` function from the TCGA data contained in `data`.

Examples

```
data(sepScores)
class(sepScores)
names(sepScores)
str(sepScores)
```

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