

Package ‘gCMAP’

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Type Package

Title Tools for Connectivity Map-like analyses

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Date 2017-01-26

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Imports Biobase, methods, GSEAlm, Category, Matrix (>= 1.0.9), parallel, annotate, genefilter, AnnotationDbi, DESeq, grDevices, graphics, stats, utils, bigmemory, bigmemoryExtras (>= 1.1.2)

Suggests BiocGenerics, KEGG.db, reactome.db, RUnit, GO.db, mgsa

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Description The gCMAP package provides a toolkit for comparing differential gene expression profiles through gene set enrichment analysis. Starting from normalized microarray or RNA-seq gene expression values (stored in lists of ExpressionSet and CountDataSet objects) the package performs differential expression analysis using the limma or DESeq packages. Supplying a simple list of gene identifiers, global differential expression profiles or data from complete experiments as input, users can use a unified set of several well-known gene set enrichment analysis methods to retrieve experiments with similar changes in gene expression. To take into account the directionality of gene expression changes, gCMAPQuery introduces the SignedGeneSet class, directly extending GeneSet from the GSEABase package. To increase performance of large queries, multiple gene sets are stored as sparse incidence matrices within CMAPCollection eSets. gCMAP offers implementations of 1. Fisher's exact test (Fisher, J R Stat Soc, 1922) 2. The "connectivity map" method (Lamb et al, Science, 2006) 3. Parametric and non-parametric t-statistic summaries (Jiang & Gentleman, Bioinformatics, 2007) and 4. Wilcoxon / Mann-Whitney rank sum statistics (Wilcoxon, Biometrics Bulletin, 1945) as well as wrappers for the 5. camera (Wu & Smyth, Nucleic Acid Res, 2012) 6. mroast and romer

(Wu et al, Bioinformatics, 2010) functions from the limma package and 7. wraps the gsea method from the mgsa package (Bauer et al, NAR, 2010). All methods return CMAPResult objects, an S4 class inheriting from AnnotatedDataFrame, containing enrichment statistics as well as annotation data and providing simple high-level summary plots.

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LazyLoad yes

ByteCompile TRUE

Collate 'AllClasses.R' 'AllGenerics.R' 'SignedGeneSet-accessors.R'
 'utility-functions.R' 'camera_score-methods.R'
 'connectivity_score-methods.R' 'featureScore-methods.R'
 'fisher_score-methods.R' 'geneIndex-methods.R'
 'gsealm_jg_score-methods.R' 'gsealm_score-methods.R'
 'incidence-methods.R' 'mgsa_score-methods.R'
 'mapIdentifiers-methods.R' 'minSetSize-methods.R'
 'mroast_score-methods.R' 'romer_score-methods.R'
 'wilcox_score-methods.R' 'CMAPCollection-accessors.R'
 'CMAPResults-accessors.R'

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| | |
|---------------|---|
| gCMAP-package | <i>Tools for Connectivity Map-like analyses</i> |
|---------------|---|

Description

The gCMAP package provides a toolkit for comparing differential gene expression profiles through gene set enrichment analysis. Starting from normalized microarray or RNA-seq gene expression values (stored in lists of ExpressionSet and CountDataSet objects) the package performs differential expression analysis using the limma or DESeq packages. Supplying a simple list of gene identifiers, global differential expression profiles or data from complete experiments as input, users can use a unified set of several well-known gene set enrichment analysis methods to retrieve experiments with similar changes in gene expression. To take into account the directionality of gene expression changes, gCMAPQuery introduces the SignedGeneSet class, directly extending GeneSet from the GSEABase package. To increase performance of large queries, multiple gene sets are stored as sparse incidence matrices within CMAPCollection eSets. gCMAP offers implementations of 1. Fisher's exact test (Fisher, J R Stat Soc, 1922) 2. The "connectivity map" method (Lamb et al, Science, 2006) 3. Parametric and non-parametric t-statistic summaries (Jiang & Gentleman, Bioinformatics, 2007) and 4. Wilcoxon / Mann-Whitney rank sum statistics (Wilcoxon, Biometrics Bulletin, 1945) as well as wrappers for the 5. camera (Wu & Smyth, Nucleic Acid Res, 2012) 6. mroast and romer (Wu et al, Bioinformatics, 2010) functions from the limma package and 7. wraps the gsea method from the mgsa package (Bauer et al, NAR, 2010). All methods return CMAPResult objects, an S4 class inheriting from AnnotatedDataFrame, containing enrichment statistics as well as annotation data and providing simple high-level summary plots.

Details

| | |
|----------|------------------------------|
| Package: | gCMAP |
| Type: | Package |
| Version: | 1.3.5 |
| Date: | 2013-03-11 |
| Depends: | GSEABase, limma (>= 3.15.14) |

```
Imports:      Biobase, BiocGenerics, methods, GSEAlm, Category, bigmemory, bigmemoryExtras (>= 1.1.2), Matrix (
Suggests:    DESeq, KEGG.db, reactome.db, RUnit, GO.db, mgsa
License:      Artistic-2.0
LazyLoad:    yes
OS_type:     unix
ByteCompile: TRUE
biocViews:   Bioinformatics, Microarray, Software, Pathways, Annotation
Collate:     'AllClasses.R' 'AllGenerics.R' 'SignedGeneSet-accessors.R' 'utility-functions.R' 'camera_score-methods
Built:       R 3.0.0; ; 2013-03-11 17:13:45 UTC; unix
```

Index:

```
.DESeq_nbinom      Function to perform a DESeq analysis to detect
                    differential expression between perturbation
                    and control groups.

CMAPCollection-class Class "'CMAPCollection'"
CMAPResults-class   Class "'CMAPResults'"
GeneSet             Methods for 'GeneSet' and 'GeneColorSet'
KEGG2cmap           Functions to generate species-specific
                    CMAPCollections from Bioconductor KEGG.db,
                    reactome.db or GO.db annotation packages or the
                    wikipathways <URL:
                    http://www.wikipathways.org/index.php/Download_Pathways>
                    project.

SignedGeneSet       Construtor for SignedGeneSet
SignedGeneSet-class Class "'SignedGeneSet'"
annotate_eset_list  Function to compile a data frame with
                    per-instance annotation for a list of eSet
                    objects generated by the 'splitPerturbations'
                    function. The output can be used directly as
                    sample.annotation for the 'NChannelSet'
                    function.

camera_score-methods Methods for Function 'camera_score' in Package
                    'gCMAP'

center_eSet         A function to to center columns of eSet
                    channels on either their kernel density peak,
                    their mean or their median.

connectivity_score  Broad CMAP gene set enrichment metrics
eSetOnDisk          A function to store the assayData of an eSet
                    object as BigMatrix files on disk.

eset_instances      A function to subset an eSet with expression
                    data into smaller datasets, each corresponding
                    to a single perturbation experiment.

featureScores-methods Methods to obtain scores for CMAPCollection
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fisher_score-methods Hypergeometric probability of gene set
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                    'gCMAP'
```

| | |
|------------------------------|---|
| generate_gCMAP_NChannelSet | Generate a perturbation profile library from expression sets of control/treatment pairs |
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| gsealm_score-methods | Methods for Function 'gsealm_score' in Package 'gCMAP' |
| induceCMAPCollection-methods | Methods for Function 'induceCMAPCollection' in Package 'gCMAP' |
| mapNmerge | A function to map eSet featureNames and calculate summaries for many-to-one mapping features |
| matrix_or_big.matrix-class | Class '"matrix_or_big.matrix"' |
| memorize | Create a new NChannelSet instance by selecting specific channels and load BigMatrix assayData into memory, if present |
| mergeCMAPs | This function merged two eSets. |
| mgsa_score-methods | Model-based gene set analysis (MGSA) |
| minSetSize | GeneSetCollection length filtering |
| mroast_score-methods | Methods for Function 'mroast_score' in Package 'gCMAP' |
| pairwise_DESeq | Generate statistics associated with pairwise differential expression from RNAseq count data |
| pairwise_compare | Generate statistics associated with pairwise differential expression |
| romer_score-methods | Methods for Function 'romer_score' in Package 'gCMAP' |
| signedRankSumTest | An implementation of the Wilcox rank sum test / Mann-Whitney test that takes into account the direction / sign of gene set members and possibly the correlation between cases |
| splitPerturbations | Function to split an ExpressionSet downloaded from ArrayExpress based on the experimental factors present in the phenoData slot |
| wilcox_score-methods | Methods for Function 'wilcox_score' in Package 'gCMAP' |
| zScores | Function to calculate z-scores from p-values |

Further information is available in the following vignettes:

| | |
|------------------|---------------|
| diffExprAnalysis | main (source) |
| gCMAP | main (source) |

Author(s)

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| | |
|--------------------|--|
| annotate_eset_list | <i>Function to compile a data frame with per-instance annotation for a list of eSet objects generated by the splitPerturbations function. The output can be used directly as sample.annotation for the NChannelSet function.</i> |
|--------------------|--|

Description

For each eSet in the 'eset.list', the pData slot is examined. Perturbation instances are identified as a match to 'perturbation' in the 'cmap.column' of the pData slot. The first matching row is extracted and transferred into the output data.frame, which contains one row for each eSet in the 'eset.list'. Only annotation columns found in the pData slots of all eSets in the 'eset.list' are returned.

Usage

```
annotate_eset_list(eset.list, cmap.column = "cmap", perturbation = "perturbation")
```

Arguments

| | |
|--------------|--|
| eset.list | A list of eSet objects, usually generated by a call to the splitPerturbations functions |
| cmap.column | The name of the pData column for eSets in 'eset.list' identifying treatment and control samples. |
| perturbation | The character string in the 'cmap.column' of the pData column for eSets in 'eset.list' identifying perturbation associated with treated samples. |

Value

A data frame with one row for each eSet in the input 'eset.list' and all columns found in the original eSet pData slot.

Author(s)

Thomas Sandmann

See Also

[splitPerturbations](#)

Examples

```
example( splitPerturbations )
```

camera_score-methods *Methods for Function camera_score in Package gCMAP*

Description

These methods provide a wrapper for the 'Competitive Gene Set Test Accounting for Inter-gene Correlation' function [camera](#). See 'limma' documentation for details.

Usage

```
## S4 method for signature 'eSet,CMAPCollection'
camera_score(experiment,sets,predictor=NULL,
design.matrix=NULL, element="exprs",keep.scores=FALSE,...)

## S4 method for signature 'matrix,CMAPCollection'
camera_score(experiment, sets,...)

## S4 method for signature 'matrix,GeneSet'
camera_score(experiment,sets,...)

## S4 method for signature 'eSet,GeneSet'
camera_score(experiment, sets, element="exprs",...)

## S4 method for signature 'matrix,GeneSetCollection'
camera_score(experiment,sets,...)

## S4 method for signature 'eSet,GeneSetCollection'
camera_score(experiment, sets, element="exprs",...)
```

Arguments

| | |
|---------------|---|
| sets | A CMAPCollection , GeneSetCollection or GeneSet object containing gene sets, with which to query the experiment object. |
| experiment | An eSet or data matrix with numeric data to compare the query object to. |
| predictor | A character vector or factor indicating the phenotypic class of the experiment data columns. Either the 'predictor' or 'design' parameter must be supplied. |
| design.matrix | A design matrix for the experiment. Either the 'predictor' or 'design' parameter must be supplied. If both are supplied, the 'design' is used. |
| element | Character vector specifying which channel of an eSet to extract (defaults to "exprs", alternatives may be e.g. "z", etc.) |
| keep.scores | Logical: keep gene-level scores for all gene sets (Default: FALSE) ? The size of the generated CMAPResults object increases with the number of contained gene sets. For very large collections, setting this parameter to 'TRUE' may require large amounts of memory. |
| ... | Additional arguments passed to downstream methods. |

Value

A [CMAPResults](#) object.

References

Wu, D, and Smyth, GK (2012). Camera: a competitive gene set test accounting for inter-gene correlation. Submitted.

Goeman, JJ, and Buhlmann, P (2007). Analyzing gene expression data in terms of gene sets: methodological issues. *Bioinformatics* 23, 980-987.

Examples

```
data(gCMAPData)
gene.set.collection <- induceCMAPCollection(gCMAPData, "z", higher=2, lower=-2)
sampleNames( gene.set.collection ) <- c("set1", "set2", "set3")

## random score matrix
y <- matrix(rnorm(1000*6),1000,6, dimnames=list(featureNames(gCMAPData), 1:6))

## set1 is differentially regulated
effect <- as.vector(members(gene.set.collection[,1]) * 2)
y[,4:6] <- y[,4:6] + effect

predictor <- c( rep("Control", 3), rep("Case", 3))

res <- camera_score(y, gene.set.collection, predictor = predictor, keep.scores=TRUE)
res

## heatmap of expression scores for set1
set1.expr <- geneScores(res)[["set1"]]
heatmap(set1.expr, scale="none", Colv=NA, labCol=predictor,
        RowSideColors=ifelse( attr(set1.expr, "sign") == "up", "red", "blue"),
        margin=c(7,5))
legend(0.35,0,legend=c("up", "down"),
       fill=c("red", "blue"),
       title="Annotated sign",
       horiz=TRUE, xpd=TRUE)
```

center_eSet

A function to to center columns of eSet channels on either their kernel density peak, their mean or their median.

Description

This function works on the eSet assayDataElement specified as 'channel' and sweeps out either the 'peak', (max of the kernel density), 'mean' or 'median' statistic from each column. A modified eSet containing the centered assayDataElement is returned, with an additional .shift column included in the pData slot recording the shift statistic for each sample.

Usage

```
center_eSet(eset, channel, center = "peak", report.center=FALSE)
```


Arguments

| | |
|---------------|---|
| eset | An eSet object |
| channel | A valid channel / AssayDataElementName of 'eset' |
| center | One of 'peak', 'mean', 'median' or 'none', specifying the statistic to sweep from each column of 'channel' in 'eset'. If 'peak', the max of the kernel density is determined and used a statistic in sweep. If 'none', the original 'eset' is returned. |
| report.center | Logical, include the shift applied to 'channel' in the pData slot of the returned NChannelSet ? |

Value

An eSet of the same class as 'eset' with the centered 'channel' assayData slot. The swept-out statistic is recorded in the 'channel'.shift column of the phenoData slot. In addition, the median absolute deviation around the center is returned.

Author(s)

Thomas Sandmann

See Also

[sweep](#)

Examples

```
data( gCMAPData )

## column means of uncentered z-scores
round( apply( assayDataElement( gCMAPData, "z"), 2, mean, na.rm=TRUE), 2)

## column means of centered z-scores
centered <- center_eSet( gCMAPData, "z", "mean")
round( apply( assayDataElement( centered, "z"), 2, mean, na.rm=TRUE), 2)
```

CMAPCollection-class *Class* "CMAPCollection"

Description

An extension of the eSet class for the efficient storage of (large) gene set collections.

Objects from Class CMAPCollection

Objects can be created by calls of the form `new("CMAPCollection", assayData, phenoData, featureData, experimen`. Alternatively, the user-friendly 'CMAPCollection' method is available.

The `induceCMAPCollection` function can be used to apply thresholds to numerical scores stored in eSet-like objects and returns a CMAPCollection (see examples).

The CMAPCollection class is derived from the virtual `eSet` class. The assayData slot contains information about the membership of genes (rows) in gene sets (columns) in the form of an incidence matrix. The incidence matrix, accessible through the 'members' method, is a 'sparseMatrix' object, in which 1 / -1 entries identify gene set membership of up- and downregulated genes, respectively.

As opposed to the well-established GeneSetCollection class defined in the GSEABase package, the CMAPCollection class stores gene set membership in a matrix format, allowing direct access to individual gene sets as well as the relationships between different sets. The incidence matrix offers memory efficient storage of large gene set collection and can directly be used in matrix-based gene set analyses.

Through direct extension of the virtual eSet class, featureData and phenoData slots are available for storage of gene- and gene-set annotation, respectively. The column 'signed' in the phenoData slot indicates whether the different gene sets (columns) should be considered to be signed to disambiguate cases in which all gene set members are identified by a +1 entry. In this case, 'signed' = TRUE indicates that these genes should be considered upregulated members of the set (and no down-regulated members were identified / stored). If 'signed' = FALSE, no information about directionality is available, e.g. gene set members can be either up- or downregulated.

Slots

assayData: Object of class "AssayData"
 phenoData: Object of class "AnnotatedDataFrame"
 featureData: Object of class "AnnotatedDataFrame"
 experimentData: Object of class "MIxEx"
 annotation: Object of class "character"
 protocolData: Object of class "AnnotatedDataFrame"
 .__classVersion__: Object of class "Versions"

Extends

Class "eSet", directly. Class "VersionedBiobase", by class "eSet", distance 2. Class "Versioned", by class "eSet", distance 3.

Methods

geneIds signature(object = "CMAPCollection"): Returns a list of gene identifiers, with one list entry for each column of the assayDataSlot 'members'.

members signature(object = "CMAPCollection"): Returns the number of gene members in each gene set stored in the collection. For signed sets, also the number of up-/down-regulated members is returned.

members signature(object = "CMAPCollection"): Returns the coincidence matrix as stored in the assayData slot of the CMAPCollection as a sparseMatrix object (rows=genes, columns=gene sets).

signed signature(object = "CMAPCollection"): Returns the 'signed' column of the phenoData slot, indicating whether gene sets should be considered signed (TRUE) or un-signed (FALSE).

signed<- signature(x = "CMAPCollection"): Replacement method for the 'signed' column of phenoData.

minSetSize signature(sets = "CMAPCollection"): Filter CMAPCollection for minimum number of set members.

incidence signature(x = "CMAPCollection"): Returns in the transpose of the coincidence matrix stored in the assayData slot, mirroring the definition of 'incidence' for GeneSetCollections as defined in the GSEABase package.

mergeCollections signature(x = "CMAPCollection", y = "CMAPCollection"): Combines two CMAPCollections into one.

upIds signature(x = "CMAPECollection"): Returns the gene identifiers of all up-regulated gene set members (sign = 1).

downIds signature(x = "CMAPECollection"): Returns the gene identifiers of all down-regulated gene set members (sign = -1).

Note

The CMAPECollections class supports coercion from / to GeneSet and GeneSetCollection objects defined by the GSEABase package, as well as the SignedGeneSet derivative introduced by the gCMAPE package itself.

Author(s)

Thomas Sandmann, sandmann.thomas@gene.com

See Also

[induceCMAPECollection](#), [GeneSetCollection](#), [SignedGeneSet](#)

Examples

```
## empty CMAPECollection
new("CMAPECollection")

## CMAPECollection from matrix
mat <- matrix( sample( c(-1,0,1), 100, replace=TRUE), ncol=10)
cmap <- CMAPECollection( mat )
members( cmap )

## CMAPECollection induced from NChannelSet
data( gCMAPEData )
assayDataElementNames( gCMAPEData )

cmap <- induceCMAPECollection(gCMAPEData, "z", lower=-2, higher=2)
cmap
setSize( cmap )
pData(cmap)
signed(cmap) <- c(TRUE, FALSE, TRUE)
signed(cmap)
head(members(cmap))

out <- fisher_score(cmap[,1], cmap, universe = featureNames( cmap))
out
```

CMAPEResults-class *Class "CMAPEResults"*

Description

This class serves as a container for the output of different gene-set enrichment analysis methods. It directly extends the [AnnotatedDataFrame](#) class by adding two additional slots ('docs' and 'errors' to store information about the analysis run). Data for each queried gene set are stored in the 'data' slot of the [AnnotatedDataFrame](#). Additional information about the data columns, e.g. the definition of 'effect' for the chosen analysis method, is available in the varMetadata slot of the AnnotatedDataFrame and can also be accessed through the 'labels' accessor function.

Details

The AnnotatedDataFrame 'table' is populated by gene set enrichment analysis methods as needed. Explicit accessor and replacement methods exist for the following columns:

- set: Identifiers of the tested gene sets (e.g. obtained from the sampleNames of an analyzed CMAPCollection object).
- trend: The direction of the detected effect, e.g. 'upregulated', 'overrepresented', etc.
- pval: The raw p-value of the observed effect. Default
- effect: The detected effect size, e.g. log odds ratio (returned by 'fisher_score') or summary t-statistic (returned by gsealm_jg_score), etc.
- nSet: The number genes in the query gene sets
- nFound: The number of query set genes detected in the target set, e.g. genes common to both sets. Default:NULL

In addition, gene set annotations can be included in further columns of the 'table' Annotated-DataFrame, e.g. retrieved from the phenoData slot of a CMAPCollection.

Objects from the Class

Objects can be created by calls of the form `new("CMAPIResults", ...)`. CMAPIResults objects are usually created as output by gene set enrichment analysis methods.

Slots

data: A data.frame containing results for different gene sets (rows), with method-specific output stored in the columns.

dimLabels: A character vector of length 2 that provides labels for the rows and columns.

varMetadata: A data.frame with the number of rows equal to the number of columns in 'data' and at least one column, named 'labelDescription', containing additional information about each result column.

.___classVersion__: A 'Versions' object describing the R and Biobase version numbers used to created the instance. Intended for developer use.

docs: Object of class "character" Additional information about the analysis run, usually populated by the gene set enrichment method.

errors: Object of class "list" Intended for warnings or error messages associated with the results.

Methods

cmapTable signature(object = "CMAPIResults"): Returns data and labels stored in the 'table' AnnotatedDataFrame. If no additional parameters are supplied, this method is synonymous with `pData(object@table)`.

Optional parameters: `n` (integer): the number of rows to return. `columns` (character): indicating which columns of the 'table' slot to include in the output.

docs signature(object = "CMAPIResults"): Accessor method for the 'docs' slot.

docs<- signature(x = "CMAPIResults"): Replacement method for the 'docs' slot.

effect signature(object = "CMAPIResults"): Accessor method for the 'effect' column of the 'table' slot.

effect<- signature(x = "CMAPIResults"): Replacement method for the 'effect' column of the 'table' slot.

- errors** signature(object = "CMAResults"): Accessor method for the 'docs' slot.
- errors<-** signature(x = "CMAResults"): Replacement method for the 'docs' slot.
- labels** signature(object = "CMAResults"): Returns information about the data columns of the 'table' slot. Synonymous with varMetadata(object@table).
- labels<-** signature(x = "CMAResults"): Replacement method for the varMetadata slot of the 'table' AnnotatedDataFrame. Replacement value must be a data.frame with as many rows as there are columns in 'table' and contain the column 'labelDescription'. See [AnnotatedDataFrame](#) for details.
- nFound** signature(object = "CMAResults"): Accessor method for the 'nFound' column of the 'table' slot.
- nFound<-** signature(x = "CMAResults"): Replacement method for the 'nFound' column of the 'table' slot.
- nSet** signature(object = "CMAResults"): Accessor method for the 'nSet' column of the 'table' slot.
- nSet<-** signature(x = "CMAResults"): Replacement method for the 'nSet' column of the 'table' slot.
- padj** signature(object = "CMAResults"): Accessor method for the 'padj' column of the 'table' slot.
- padj<-** signature(x = "CMAResults"): Replacement method for the 'padj' column of the 'table' slot.
- plot** signature(x = "CMAResults", y = "ANY"): Returns an overview of the results stored in a CMAResults object: 1. the distribution of scores across all results and 2. a heatmap of rank-ordered effect sizes.
- strip.effect: String specifying the CMAResults column to retrieve scores from. Default:"effect"
 - strip.pval: String specifying the CMAResults column to transform into unsigned z-scores. Only evaluated if 'density.effect' column is not present or is set to 'NULL'.Default:"padj"
 - strip.cutoffs: Numeric vector of length 2. Scores between strip.cutoffs[1] and strip.cutoffs[2] will be displayed in strip.col[2]. Default:c(-3,3)
 - strip.bounds: Numeric vector of length 2 specifying the end points of the color gradient. Scores < strip.cutoffs[1] or > strip.cutoffs[2] will not be distinguishable.Default:c(-6,6)
 - strip.col: Vector of length 3, specifying the colors used in the heatmap strip: strip.col[1] = low scores, strip.col[2] = medium score (excluded from gradient), strip.col[3] = high scores. Default:c("blue","white","red")
 - set.inf: Numerical replacing Inf/-Inf scores in the density plot (default:+/-20)
 - col.upRug plot color for positively correlated instances
 - col.downRug plot color for negatively correlated instances
- pval** signature(object = "CMAResults"): Accessor method for the 'pval' column of the 'table' slot.
- pval<-** signature(x = "CMAResults"): Replacement method for the 'pval' column of the 'table' slot
- set** signature(object = "CMAResults"): Accessor method for the 'set' column of the 'table' slot.
- set<-** signature(x = "CMAResults"): Replacement method for the 'set' column of the 'table' slot.
- show** signature(object = "CMAResults"): Returns a summary of the CMAResult object, including the number rows in the 'table' slot and shows the top five results with the smallest p-values.

trend signature(object = "CMAPResults"): Accessor method for the trend' column of the 'table' slot.

trend<- signature(x = "CMAPResults"): Replacement method for the geneScores' column of the 'table' slot.

geneScores signature(object = "CMAPResults"): Accessor method for the geneScores' column of the 'table' slot. When available, this column stores a list of matrices, one for each row of the CMAPResults object, with raw per-gene scores for all members of the gene set. While the 'show' method displays only a brief summary of the available data, the geneScores method retrieves the full list of score matrices.

zscores signature(x = "CMAPResults"): Transforms adjusted p-values stored in a CMAPResults into z-scores based on the standard normal distribution.

Author(s)

Thomas Sandmann, sandmann.thomas@gene.com

See Also

[AnnotatedDataFrame](#)

Examples

```
## create random score profile
set.seed(123)
z <- rnorm(1000)
names(z) <- paste("g", 1:1000, sep="")

## generate random incidence matrix of gene sets
m <- replicate(1000, {
  s <- rep(0,1000)
  s[ sample(1:1000, 20)] <- 1
  s[ sample(1:1000, 20)] <- -1
  s
})
dimnames(m) <- list(names(z), paste("set", 1:1000, sep=""))

## Set1 is up-regulated
z <- z + m[,1]*2

## create CMAPCollection
cmap <- CMAPCollection(m, signed=rep(TRUE,1000))

## gene-set enrichment test
res <- gsealm_jg_score(z, cmap)
class(res)
res

## overview plot
plot(res)

## rerun, this time store gene-level scores
res <- gsealm_jg_score(z, cmap, keep.scores=TRUE)
res
m <- geneScores(res)
m[["set1"]] ## scores for set1
```

```
## stripplot for set1, colored by annotated sign
gene.signs <- factor( attr(m[["set1"]], "sign"))
boxplot( m[["set1"]] ~ gene.signs,
  ylab="z-score",
  main="Set1",
  col=c("blue", "red"))
```

connectivity_score *Broad CMAP gene set enrichment metrics*

Description

A method for computing Broad CMAP connectivity scores, as described in the reference below. Supporting functions used for computation are also described.

Usage

```
## S4 method for signature 'eSet,CMAPCollection'
connectivity_score(experiment, query, element="z", keep.scores=FALSE)

## S4 method for signature 'matrix,CMAPCollection'
connectivity_score(experiment, query, ...)

## S4 method for signature 'eSet,SignedGeneSet'
connectivity_score(experiment, query, ...)

## S4 method for signature 'matrix,SignedGeneSet'
connectivity_score(experiment, query, ...)

## S4 method for signature 'eSet,GeneSetCollection'
connectivity_score(experiment, query,
  ...)

## S4 method for signature 'matrix,GeneSetCollection'
connectivity_score(experiment, query,...)

## S4 method for signature 'ANY,GeneSet'
connectivity_score(experiment, query, ...)
```

Arguments

| | |
|-------------|---|
| experiment | An eSet or matrix object to query. |
| query | A CMAPCollection , SignedGeneSet , or GeneSetCollection object containing signed gene sets with which to query the experiment object. |
| element | Character string specifying which element of a multi-channel eSet to access for determining tag rank? |
| keep.scores | Logical: keep gene-level scores for all gene sets (Default: TRUE) ? The size of the generated CMAPResults object increases with the number of contained gene sets. For very large collections, consider setting this parameter to 'FALSE' to conserve memory. |
| ... | Additional arguments passed on to downstream functions. |

Value

| | |
|--------------------|--|
| connectivity_score | For the <code>SignedGeneSet</code> method, a vector of s scores, one per instance in experiment. For the <code>GeneSetCollection</code> method, a matrix, with one row per instance in experiment and one column per query set. |
| ks | A signed Kolmogorov-Smirnov type statistic based on the position of the ranks V in the vector 1:n. |
| s | A difference of ks values for V_up vs. V_down, or 0 if both yield the same sign. |
| S | A vector of signed, rescaled scores. After rescaling, 1 corresponds to the maximum positive s score, and -1, to the minimum negative s score. S is typically used to produce the red-grey-green instance heat maps from the reference below. |

Note

Note that as defined by Lamb et al., ks is not symmetric. For $n = 100$, for example, $ks(1, 100)$ is .99 while $ks(100, 100)$ is -1. A further consequence of the Lamb et al. definitions is that the maximum possible score for a perfect positive match depends on query set size. See the example below. Although these properties are not desirable, the intention here is to exactly reproduce the Lamb et al. statistic.

References

Lamb, J. et al. (2006). The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. *Science* 313:1929. Notation for ks, s, and S closely follows the Supporting Online Material there.

Examples

```
data(gCMAPData)

## induce CMAPCollection from z-scores
sets <- induceCMAPCollection(gCMAPData, "z", lower=-3, higher=3)

## Broad CMAP KS scoring: one z-score column
connectivity_score(gCMAPData[,1], sets, element="z")

## multiple z-score columns, results are returned as a list
connectivity_score(gCMAPData, sets)
```

DESeq_nbinom

Function to perform a DESeq analysis to detect differential expression between perturbation and control groups.

Description

This function is a wrapper for a standard DESeq analysis with two classes, perturbation and control, annotated in the 'conditions' column of the cds phenoData slot. First, the size factors are determined using default parameters. Next, a dispersion parameter is estimated using the default (pooled) method. Finally, p-values are estimated for differential expression between treatment and control groups.

Usage

```
.DESeq_nbinom(cds, control = "control", perturb = "perturbation",
  try.hard = FALSE, control_perturb_col = "cmap",...)
```

Arguments

| | |
|---------------------|---|
| cds | A CountDataSet with perturbation and control samples identified in the pData condition slot. |
| control | Character string corresponding to the control factor level of the condition phenoData slot. |
| perturb | Character string corresponding to the perturbation factor level of the condition phenoData slot. |
| try.hard | Logical parameter indicating the function's behavior in case the parametric (default) dispersion estimation fails. If FALSE (default), the function exits with an error. If TRUE, a non-parametric (loess) estimation is attempted instead. |
| control_perturb_col | Column name in phenoData of cds where control/perturbation designations are stored. |
| ... | Any additional parameters passed on to estimateDispersions |

Value

See [nbinomTest](#) for details.

Note

To use this function, please install the suggested Bioconductor package 'DESeq'.

| | |
|------------|--|
| eSetOnDisk | <i>A function to store the assayData of an eSet object as BigMatrix files on disk.</i> |
|------------|--|

Description

If the bigmemoryExtras package is available, this function accepts an eSet object and generates separate file-backed BigMatrix objects for each assayDataElement. Data is only loaded into memory upon subsetting, allowing the retrieval of selected data without loading the (potentially large) object into memory in full.

Usage

```
eSetOnDisk(eset, out.file = NULL)
```

Arguments

| | |
|----------|---|
| eset | An object inheriting from eSet. |
| out.file | The path and basename of the output file. Three files will be generated for each eSet assayDataElement, identified by extending 'out.file' by suffixes. |

Value

An object of the same class as 'eSet', with file-backed big.matrix elements in the assayData slot.

Note

Please see the bigmemoryExtras package for more details on BigMatrix objects.

Author(s)

Thomas Sandmann

See Also

[eSet](#) [memorize](#)

Examples

```
if(suppressWarnings(require("bigmemoryExtras",
  quietly=TRUE, character.only=TRUE))){
  ## load ExpressionSet
  data("sample.ExpressionSet") ## from Biobase
  sample.ExpressionSet ## two assayDataElements: exprs, se

  ## 'exprs' data matrix
  class( assayDataElement( sample.ExpressionSet, "exprs" ) )

  ## convert assayData to BigMatrix objects
  storage.file <- tempfile() ## create path & basemane for BigMatrices
  storage.file

  on.disk <- eSetOnDisk( sample.ExpressionSet, storage.file )
  on.disk ## ExpressionSet
  dir(dirname( storage.file )) ## created 3 files per channel

  class( assayDataElement( on.disk, "exprs" ) ) ## BigMatrix object

  ## BigMatrix objects are loaded only upon subsetting
  assayDataElement( on.disk, "exprs") ## retrieves BigMatrix, NOT matrix
  assayDataElement( on.disk, "exprs")[1:10,1:10] ## loads subset only
  dim( assayDataElement( on.disk, "exprs")[,] ) ## retrieves full matrix

  ## convert back to standard in-memory ExpressionSet
  in.memory <- memorize( on.disk )
  class( assayDataElement( in.memory, "exprs" ) ) ## standard matrix object

  ## remove tempfiles generated for this example
  unlink(paste(storage.file,"*", sep=""))
}
```

| | |
|----------------|---|
| eset_instances | <i>A function to subset an eSet with expression data into smaller datasets, each corresponding to a single perturbation experiment.</i> |
|----------------|---|

Description

This function takes two parameters, an eSet object (e.g. an ExpressionSet or CountDataSet) containing multiple samples, and a numerical matrix defining how these samples should be compared to investigate perturbations of interest. For each perturbation, a separate eSet object is generated, ready for analysis with the [generate_gCMAP_NChannelSet](#) function. Samples can be used in multiple instances, e.g. common controls can be specified in each column of the 'instance.matrix'.

Usage

```
eset_instances(instance.matrix, eset, control_perturb_col = "cmap",
              control = "control", perturb = "perturbation")
```

Arguments

| | |
|---------------------|--|
| instance.matrix | A numeric matrix of -1 and 1's. Each column defines a contrast of interest and indicates whether a sample (row) corresponds to a control sample (-1) or a perturbation sample (1). The row.names of the instance.matrix correspond to sampleNames of 'eset'. Entries other than -1 or 1 will be ignored. |
| eset | An eSet object to be subset into smaller datasets. The row.names of 'eset' must correspond to the row.names of the 'instance.matrix'. |
| control_perturb_col | Character, indicating which phenoData column to use to store 'control' and 'perturb' labels. |
| control | Character, defining the label stored in each new eSet to indicate control samples. |
| perturb | Character, defining the label stored in each new eSet to indicate perturbation samples. |

Value

A list of eSet objects, each corresponding to one instance defined by the columns of 'instance.matrix'.

Note

This function can be used to generate the 'eset.list' required for differential expression analyses with [generate_gCMAP_NChannelSet](#).

Author(s)

Thomas Sandmann, sandmann.thomas@gene.com

See Also

[generate_gCMAP_NChannelSet](#)

Examples

```

library(Biobase)
data(sample.ExpressionSet)

## contains Male/Female and Control/Case annotations
pData( sample.ExpressionSet)

## separate analysis of Male/Female patients
male <- ifelse( pData( sample.ExpressionSet )$type == "Control", -1, 1)
male[which( pData( sample.ExpressionSet )$sex == "Female")] <- 0

female <- ifelse( pData( sample.ExpressionSet )$type == "Control", -1, 1)
female[which( pData( sample.ExpressionSet )$sex == "Male")] <- 0

instance.matrix <- cbind( male, female)
row.names( instance.matrix ) <- sampleNames( sample.ExpressionSet )

eset_instances( instance.matrix, sample.ExpressionSet)

```

featureScores-methods *Methods to obtain scores for CMAPCollection gene sets from a matrix or eSet*

Description

These methods extract the scores for CMAPCollection gene set members from eSet or matrix objects and return them as a list (argument 'query') of lists (argument 'dat') with score vectors. Argument order determines the organization of the list, e.g. if 'query' is a CMAPCollection, one list element is returned for each gene set, containing all score vectors for the respective set. If 'simplify' is set to TRUE, score vectors are combined and a list of matrices is returned instead. Score vectors and matrices carries an additional 'sign' attribute corresponding to the sign annotated in the CMAPCollection.

Usage

```

## S4 method for signature 'CMAPCollection,eSet'
featureScores(query, dat, element="z",simplify=TRUE)

## S4 method for signature 'CMAPCollection,matrix'
featureScores(query,dat, simplify=TRUE)

## S4 method for signature 'CMAPCollection,BigMatrix'
featureScores(query, dat, simplify=TRUE)

## S4 method for signature 'eSet,CMAPCollection'
featureScores(query, dat, element="z")

## S4 method for signature 'matrix,CMAPCollection'
featureScores(query, dat)

## S4 method for signature 'BigMatrix,CMAPCollection'

```

```

featureScores(query, dat)

## S4 method for signature 'CMAPCollection,numeric'
featureScores(query, dat)

## S4 method for signature 'CMAPCollection,CMAPCollection'
featureScores(query, dat)

## S4 method for signature 'numeric,CMAPCollection'
featureScores(query, dat)

## S4 method for signature 'CMAPCollection,matrix_or_big.matrix'
featureScores(query, dat, simplify = TRUE)

## S4 method for signature 'matrix_or_big.matrix,CMAPCollection'
featureScores(query, dat)

```

Arguments

| | |
|----------|--|
| query | A CMAPCollection , eSet or matrix. |
| dat | A CMAPCollection , eSet or matrix. |
| element | Character string specifying which <code>assayDataElement</code> to extract from <code>eSet</code> objects. |
| simplify | Logical: when possible, should score columns for each gene set collected in a matrix ? |

Value

A nested list: one list element for each 'query', containing a list with score vectors for each 'dat'.

Methods

```

signature(query = "CMAPCollection", dat = "eSet") }
signature(query = "CMAPCollection", dat = "matrix") }
signature(query = "CMAPCollection", dat = "BigMatrix") }
signature(query = "eSet", dat = "CMAPCollection") }
signature(query = "matrix", dat = "CMAPCollection") }
signature(query = "BigMatrix", dat = "CMAPCollection") }
signature(query = "CMAPCollection", dat = "numeric") }
signature(query = "CMAPCollection", dat = "CMAPCollection") }
signature(query = "numeric", dat = "CMAPCollection") }
signature(query = "matrix_or_big.matrix", dat = "CMAPCollection") }
signature(query = "CMAPCollection", dat = "matrix_or_big.matrix") }

```

Author(s)

Thomas Sandmann

Examples

```

data(gCMAPData)
## generate CMAPCollection with two sets (drug1, drug2)
sets <- induceCMAPCollection(gCMAPData, "z", higher=-2, lower=2)[,1:2]
sampleNames(sets) <- c("set1", "set2")

## extract per-gene scores as matrices
res <- featureScores(sets, gCMAPData)
class(res) ## list
names(res) ## one element per set
class(res[["set1"]]) ## matrix
dim(res[["set1"]])

## or as lists of score vectors
res2 <- featureScores(sets, gCMAPData, simplify=FALSE)
class(res2[["set1"]]) ## list
length(res2[["set1"]])

## stripplot for set2, colored by annotated sign
m <- res[["set2"]][,"drug2"]
colors <- ifelse( attr(res[["set2"]], "sign") == "up", "red", "blue")
gene.sign <- factor( attr(res[["set2"]], "sign"))
boxplot(
  m ~ gene.sign,
  col=c("blue", "red"),
  ylab="z-score",
  xlab="Query gene sign",
  main="Set 2"
)

```

fisher_score-methods *Hypergeometric probability of gene set enrichment*

Description

A method for computing enrichment probabilities based on the hypergeometric distribution. This method performs an over-representation analysis by generating 2x2 incidence matrices for gene sets provided as 'query' and 'sets' as `GeneSet`, `SignedGeneSet`, `GeneSetCollection` or `CMAPCollection` objects. If 'sets' is an `NChannelSet` object with quantitative data, gene sets are induced on the fly from the channel specified by the 'element' parameter.

Arguments

| | |
|-------------|--|
| query | A <code>CMAPCollection</code> , <code>GeneSet</code> , or <code>GeneSetCollection</code> object containing the 'query' gene sets to compare against the 'sets' |
| sets | A <code>CMAPCollection</code> , <code>GeneSetCollection</code> or <code>GeneSet</code> object |
| universe | A character string of gene ids for all genes that could potentially be of interest, e.g. all genes represented on a microarray, all annotated genes, etc. |
| keep.scores | Logical: store the identifiers for the genes detected in 'query' and 'sets' ? (Default: FALSE) The size of the generated <code>CMAPResults</code> object increases with the number of contained gene sets. For very large collections, setting this parameter to 'TRUE' may require large amounts of memory. |

| | |
|--------------|---|
| element | A character string corresponding to the assayDataElementName of the NChannelSet object to be thresholded on the fly with the induceCMAPCollection . |
| lower | The lower threshold for the induceCMAPCollection . |
| higher | The 'higher' threshold for the induceCMAPCollection . |
| min.set.size | Number of genes a gene set induced by induceCMAPCollection needs to contain to be included in the analysis (Default:5). |
| ... | Additional arguments passed to downstream methods. |

Value

A CMAPResults object

Methods

```
signature(query = "CMAPCollection", sets = "CMAPCollection", universe = "character")
```

```
signature(query = "CMAPCollection", sets = "NChannelSet", universe = "character")
```

```
signature(query = "SignedGeneSet", sets = "CMAPCollection", universe = "character")
```

```
signature(query = "SignedGeneSet", sets = "NChannelSet", universe = "character")
```

```
signature(query = "GeneSet", sets = "CMAPCollection", universe = "character")
```

```
signature(query = "GeneSet", sets = "NChannelSet", universe = "character")
```

```
signature(query = "GeneSetCollection", sets = "CMAPCollection", universe = "character")
```

```
signature(query = "GeneSetCollection", sets = "NChannelSet", universe = "character")
```

```
signature(query = "GeneSet", sets = "GeneSetCollection", universe = "character")
```

```
signature(query = "CMAPCollection", sets = "GeneSetCollection", universe = "character")
```

```
signature(query = "GeneSetCollection", sets = "GeneSetCollection", universe = "character")
```

```
signature(query = "GeneSet", sets = "GeneSet", universe = "character")
```

Note

p-values are corrected for multiple testing separately for each query set, but not across multiple queries.

See Also

[fisher.test](#)

Examples

```
data(gCMAPData)
```

```
gene.set.collection <- induceCMAPCollection(gCMAPData, "z", higher=2, lower=-2)
```

```
## compare all gene sets in the gene.set.collection to each other
```

```
universe = featureNames(gCMAPData)
```

```
fisher_score(gene.set.collection, gene.set.collection, universe = universe)
```

gCMAPData

*Example NChannelSet***Description**

The gCMAPData object is an NChannelSet object with 3 samples x 1000 features x 3 channels (p-value, z-score and log₂fc).

Usage

```
data(gCMAPData)
```

Examples

```
data(gCMAPData)

gene.set.collection <- induceCMAPCollection(gCMAPData, "z", higher=2, lower=-2)

## comparison with a single user-provided profile of z-scores
profile <- assayDataElement(gCMAPData, "z")[,1]
gsealm_jg_score(profile, gene.set.collection)
```

geneIndex-methods

*Methods for Function geneIndex in Package gCMAP***Description**

These methods match a character vector of gene ids to the members of a GeneSet, GeneSetCollection or CMAPCollection and return the match indices.

Usage

```
## S4 method for signature 'CMAPCollection,character'
geneIndex(gene.sets, gene.ids, remove.empty=TRUE)

## S4 method for signature 'GeneSetCollection,character'
geneIndex(gene.sets, gene.ids, remove.empty=TRUE)

## S4 method for signature 'GeneSet,character'
geneIndex(gene.sets, gene.ids, remove.empty=TRUE)
```

Arguments

| | |
|--------------|--|
| gene.sets | A CMAPCollection , GeneSetCollection or GeneSet to match the 'gene.ids' against. |
| gene.ids | A character string of gene identifiers whose position (if any) in the 'gene.sets' is to be determined. |
| remove.empty | Logical parameter specifying whether gene sets without any matching gene.ids should be removed from the output. |

Value

An integer vector or (if a collection was searched) a list of integer vectors with the matching positions of gene.ids in the gene.sets.

Examples

```
## induce CMAPCollection
data(gCMAPData)
gene.set.collection <- induceCMAPCollection(gCMAPData, "z", higher=2, lower=-2)

gene.ids <- geneIds(gene.set.collection[,2]) ## geneIds of the second set
geneIndex(gene.set.collection, gene.ids)
```

```
generate_gCMAP_NChannelSet
```

Generate a perturbation profile library from expression sets of control/treatment pairs

Description

When provided with a list of ExpressionSet or countDataSet objects, comparisons are made between control and perturbation samples on a set basis. To process RNAseq count data, the suggested Bioconductor package 'DESeq' must be available on the system. For countDataSets, a moderated log2 fold change for each set is calculated after variance-stabilizing transformation of the count data is performed globally across all countDataSets in the list.

Usage

```
generate_gCMAP_NChannelSet(
  data.list,
  uids=1:length(data.list),
  sample.annotation=NULL,
  platform.annotation="",
  control_perturb_col="cmap",
  control="control",
  perturb="perturbation",
  limma=TRUE,
  limma.index=2,
  big.matrix=NULL,
  center.z="peak",
  center.log_fc="none",
  report.center=FALSE
)
```

Arguments

| | |
|-----------|--|
| data.list | List of ExpressionSet or CountDataSet objects. Each element includes all array / RNAseq data for a single instance, plus metadata on which samples are perturbation and control. |
| uids | Vector of unique identifiers for the instances in data.list |

| | |
|---------------------|--|
| sample.annotation | An optional data.frame of additional annotation for instances, each row corresponds to one instance, ordered to correspond with the data.list. This is not used for the control/perturbation comparisons, instead it is simply attached to the NChannelSet for future reference. |
| platform.annotation | The name of the platform as used by the annotation package. |
| control_perturb_col | See pairwise_compare. |
| control | See pairwise_compare. |
| perturb | See pairwise_compare. |
| limma | Use limma package to perform moderated t-tests (Default: TRUE) instead of a standard t-test ? |
| limma.index | Integer specifying the index of the parameter estimate for which we to extract t and other statistics. The default corresponds to a two-class comparison with the standard parameterization. The function assumes that there was no missing data, so that test for all genes were performed on the same sample size. |
| big.matrix | Character string providing the path and filename to store the NChannelSets on disk instead of in memory. If 'NULL' (default), an NChannelSet is returned. If not 'NULL', the bigmemoryExtras package will create (or overwrite !) three binary files for each channel of the NChannelSet at the location provided as 'big.matrix', distinguishing files for the different channels by their suffices. To load the NChannelSet into a different R session, the binary files must be accessible. |
| center.z | One of 'none', 'peak', 'mean', 'median', selecting whether / how to center the z-scores for each experiment. Option 'peak' (default) will center on the peak of the z-score kernel density. Options 'mean' and 'median' will center on their respective values instead. |
| center.log_fc | One of 'none', 'peak', 'mean', 'median', selecting whether / how to center the log2 fold-change distribution for each experiment. Option 'peak' will center on the peak of the z-score kernel density. Options 'mean' and 'median' will center on their respective values instead. |
| report.center | Logical, include the z-score / log2 fold change corrections and the median absolute deviation of the respective distribution about zero in the pData slot of the returned NChannelSet ? |

Value

The function returns an [NChannelSet](#) with one channel for each of the columns returned by [pairwise_compare](#). This can be worked with directly (e.g. `assayData(obj)$z`), or specific channels can be converted to regular [ExpressionSet](#) objects (e.g. `es <- channel(obj, "z")`). In the latter case, one would access z by `exprs(es)`. If 'report.center' is TRUE, the `pData` slot of the [NChannelSet](#) contains columns reporting the shift applied to the z-score and / or log2 fold change columns to center the score distributions on zero and the median absolute deviation of the shifted distribution about zero.

Examples

```
## list of ExpressionSets
data("sample.ExpressionSet") ## from Biobase

es.list <- list( sample.ExpressionSet[,1:4],
```

```

        sample.ExpressionSet[,5:8],
        sample.ExpressionSet[,9:12])
names(es.list) <- paste( "Instance", 1:3, sep=".")

de <- generate_gCMAP_NChannelSet(
  es.list,
  1:3,
  platform.annotation = annotation(es.list[[1]]),
  control_perturb_col="type",
  control="Control",
  perturb="Case")

assayDataElementNames(de)
head( assayDataElement(de, "z") )

## Not run:
## processing RNAseq data requires the suggested 'DESeq'
## Bioconductor package.
require( DESeq )
set.seed( 123 )
## list of CountDataSets
cde.list <- lapply( 1:3, function(n) {
  cds <- makeExampleCountDataSet()
  featureNames(cds) <- paste("gene",1:10000, sep="_")
  cds
})

cde <- generate_gCMAP_NChannelSet(cde.list,
  uids=1:3,
  sample.annotation=NULL,
  platform.annotation="Entrez",
  control_perturb_col="condition",
  control="A",
  perturb="B")

assayDataElementNames(cde)

## End(Not run)

```

Description

Additional methods for function GeneSet and GeneColorSet, supporting use of [NChannelSet](#) templates.

Note

The ExpressionSet methods are used verbatim, since only metadata is utilized. Note that collectionType will be ExpressionSet as a result.

gsealm_jg_score-methods

Parametric test for testing normally distributed scores for gene set enrichment

Description

This method implements the 'JG' summary method introduced by Oron et al, 2008, as a stand-alone method to query a set of normally-distributed scores (e.g. t-statistics or z-scores) with gene sets (and vice versa).

Scores for gene-set members are summed, respecting their sign (up- or down-regulated) and the combined score is divided by the square-root of the number of set members.

To fit linear models to an expression profiling experiment instead, please use the `gsealm_jg_score` method instead.

Arguments

| | |
|-------------|---|
| query | An eSet , CMAPCollection , GeneSetCollection , GeneSet , matrix or numeric vector with data and gene ids. If a matrix is provided, gene ids must be provided as row-names. If a vector is provided, gene ids must be provided as names. |
| sets | See 'query' |
| removeShift | Optional parameter indicating that the aggregated test statistic should be centered by subtracting the column means (default=FALSE). Note: this option is not available for analysis of big.matrix backed eSet objects. |
| element | For eSet objects, which assayDataElement should be extracted? (Default="exprs") |
| keep.scores | Logical: keep gene-level scores for all gene sets (Default: FALSE)? The size of the generated CMAPResults object increases with the number of contained gene sets. For very large collections, setting this parameter to 'TRUE' may require large amounts of memory. |
| ... | Additional arguments to be passed on to downstream methods. |

Value

A CMAPResults object or, in case of multi-dimensional queries, a list of CMAPResults objects.

Methods

```
signature(query = "CMAPCollection", sets = "eSet")
signature(query = "CMAPCollection", sets = "matrix")
signature(query = "CMAPCollection", sets = "numeric")
signature(query = "eSet", sets = "CMAPCollection")
signature(query = "eSet", sets = "GeneSet")
signature(query = "eSet", sets = "GeneSetCollection")
signature(query = "GeneSet", sets = "eSet")
signature(query = "GeneSet", sets = "matrix")
signature(query = "GeneSet", sets = "numeric")
```

```
signature(query = "GeneSetCollection", sets = "eSet")
signature(query = "GeneSetCollection", sets = "matrix")
signature(query = "GeneSetCollection", sets = "numeric")
signature(query = "matrix_or_big.matrix", sets = "CMAPCollection")
signature(query = "matrix", sets = "GeneSet")
signature(query = "matrix", sets = "GeneSetCollection")
signature(query = "numeric", sets = "CMAPCollection")
signature(query = "numeric", sets = "GeneSet")
signature(query = "numeric", sets = "GeneSetCollection")
```

References

Gene set enrichment analysis using linear models and diagnostics. Oron AP, Jiang Z, Gentleman R. *Bioinformatics*. 2008 Nov 15;24(22):2586-91. Epub 2008 Sep 11.

Extensions to gene set enrichment. Jiang Z, Gentleman R. *Bioinformatics*. 2007 Feb 1;23(3):306-13. Epub 2006 Nov 24.

Examples

```
data(gCMAPData)
gene.set.collection <- induceCMAPCollection(gCMAPData, "z", higher=2, lower=-2)

## comparison with a single user-provided profile of z-scores
profile <- assayDataElement(gCMAPData, "z")[,1]
gsealm_jg_score(profile, gene.set.collection)

## comparison with of multiple profiles of z-scores to the CMAPCollection
res <- gsealm_jg_score(assayDataElement(gCMAPData, "z"), gene.set.collection)

## first CMAPResult object
res[[1]]

## adjusted p-values from all CMAPResult objects
sapply(res, padj)

## inverted query: CMAPCollection is compared to z-score profiles
gsealm_jg_score(gene.set.collection, assayDataElement(gCMAPData, "z"))[[1]]
```

gsealm_score-methods *Methods for Function gsealm_score in Package gCMAP*

Description

This method extends functions from the GSEAlm package to perform label-permutation based differential expression analysis. In addition to gene set membership, information about the gene sign (up- or down-regulated) is taken into consideration.

Usage

```
## S4 method for signature 'ExpressionSet,CMAPCollection'
gsealm_score(
  query,
  set,
  removeShift=FALSE,
  predictor=NULL,
  formula=NULL,
  nPerm=1000,
  parametric=FALSE,
  respect.sign=TRUE,
  keep.scores=FALSE,
  ...)

## S4 method for signature 'eSet,CMAPCollection'
gsealm_score(query, set, element="exprs", ... )

## S4 method for signature 'matrix,CMAPCollection'
gsealm_score(query, set, predictor=NULL, ...)

## S4 method for signature 'eSet,GeneSetCollection'
gsealm_score(query, set, element="exprs",...)

## S4 method for signature 'matrix,GeneSetCollection'
gsealm_score(query, set, ...)

## S4 method for signature 'ExpressionSet,GeneSet'
gsealm_score(query, set,...)

## S4 method for signature 'ExpressionSet,GeneSetCollection'
gsealm_score(query, set,...)

## S4 method for signature 'eSet,GeneSet'
gsealm_score(query, set, element="exprs", ...)

## S4 method for signature 'matrix,GeneSet'
gsealm_score(query, set, ...)
```

Arguments

| | |
|-------------|--|
| query | An ExpressionSet or matrix with normalized expression data. |
| set | A CMAPCollection , GeneSetCollection or GeneSet object containing gene sets. Gene ids must match those of the 'query' |
| removeShift | logical: should normalization begin with a column-wise removal of the mean shift? Note: this option is not available for analysis of big.matrix backed eSet objects. |
| predictor | A character string identifying one column in the pData slot of a 'query' ExpressionSet from which to construct the formula for the linear model. Ignored if 'formula' is provided. |
| formula | The formula to be used in the linear model. See gsealmPerm for details. |

| | |
|--------------|---|
| nPerm | The number of sample-label permutations to perform. |
| parametric | Logical, if set to 'TRUE', no label permutations are performed. Instead, p-values are calculated based on a parametric approximation. |
| respect.sign | Logical, if set to 'FALSE', gene sign information is ignored, considering up- and down-regulated genes to be equal. |
| element | Character string specifying which element to extract when coercing an ExpressionSet from an eSet subclass. |
| keep.scores | Logical: keep gene-level scores for all gene sets (Default: FALSE) ? The size of the generated CMAPResults object increases with the number of contained gene sets. For very large collections, setting this parameter to 'TRUE' may require large amounts of memory. |
| ... | Additional arguments passed on to downstream functions. |

Value

This method returns a CMAPResults object.

See Also

[gsealmPerm lmPerGene](#)

Examples

```
data(gCMAPData)

## induce gene sets from a collection of z-scores
gene.set.collection <- induceCMAPCollection(
  gCMAPData,
  "z",
  higher=2,
  lower=-2)
sampleNames(gene.set.collection) <- c("set1", "set2", "set3")

## random score matrix
y <- matrix(rnorm(1000*6),1000,6,
            dimnames=list(featureNames(gCMAPData), 1:6))

## set1 is differentially regulated
effect <- as.vector(members(gene.set.collection[,1]) * 2)
y[,4:6] <- y[,4:6] + effect

predictor <- c( rep("Control", 3), rep("Case", 3))

## run analysis and keep gene-level expression scores
res <- gsealm_score(
  y,
  gene.set.collection,
  predictor=predictor,
  nPerm=100,
  keep.scores=TRUE)
res

## heatmap of expression scores for set1
set1.expr <- geneScores(res)[["set1"]]
```

```
heatmap(set1.expr, scale="none", Colv=NA, labCol=predictor,
        RowSideColors=ifelse(
          attr(set1.expr, "sign") == "up", "red", "blue"),
        margin=c(7,5))
legend(0.35,0,legend=c("up", "down"),
       fill=c("red", "blue"),
       title="Annotated sign",
       horiz=TRUE, xpd=TRUE)
```

induceCMAPCollection-methods

Methods for Function induceCMAPCollection in Package gCMAP

Description

This method defines a [CMAPCollection](#) by applying thresholds to an element of an eSet-derived object. For example, applying 'induceCMAPCollection' to a matrix of z-scores stored in an NChannelSet, gene sets can be defined for each of the sample columns stored in the object. (See example section).

Usage

```
## S4 method for signature 'eSet'
induceCMAPCollection(eset,element,lower=NULL,higher=NULL,sign.sets=TRUE)
## S4 method for signature 'matrix'
induceCMAPCollection(eset,element,...)
```

Arguments

| | |
|-----------|--|
| eset | An object derived from class eSet , e.g. an NChannelSet |
| element | A character string corresponding to the assayDataElementName of the 'eset' object to which the thresholds should be applied. |
| lower | The lower threshold. If not 'NULL', genes with a score smaller than 'lower' will be included in the gene set with sign -1. At least one of 'lower' and 'higher' must be specified. |
| higher | The 'higher' threshold. If not 'NULL', genes with a score larger than 'higher' will be included in the gene set with sign +1. At least one of 'lower' and 'higher' must be specified. |
| sign.sets | Logical, indicating whether the 'signed' slot of the generated CMAPCollection should be set to 'TRUE' or 'FALSE'. This parameter should be set to 'FALSE' when the 'element' does not contain information about directionality, e.g. if it is a p-value. |
| ... | Any of the additional arguments detailed above. |

Value

A CMAPCollection object

See Also

[CMAPCollection](#)

Examples

```

data(gCMAPData)
assayDataElementNames(gCMAPData)
cmap <- induceCMAPCollection(gCMAPData, element="z", lower=-2, higher=2)
cmap
notes(cmap)

```

KEGG2cmap

Functions to generate species-specific CMAPCollections from Bioconductor KEGG.db, reactome.db or GO.db annotation packages or the wikipathways http://www.wikipathways.org/index.php/Download_Pathways project.

Description

These functions extract the gene sets defined for a species of interest from the KEGG, Reactome or GO annotation packages or download the latest gene sets from the Wikipathways website and create a CMAPCollections. Wikipathways provides gene identifiers using different annotation sources; the wiki2cmap function only considers Entrez and Ensembl gene identifiers and return a CMAPCollection with Entrez ids. Please note that the GO graph structure will be used to associate every gene with all upstream annotation terms. The relationships between GO categories is not represented in the output CMAPCollection.

Usage

```

KEGG2cmap(species,
           annotation.package,
           min.size=5,
           max.size=200)
reactome2cmap(species,
              annotation.package,
              min.size=5,
              max.size=200)
wiki2cmap(species,
          annotation.package,
          min.size=5,
          max.size=200 )
go2cmap(annotation.package="org.Hs.eg.db",
        ontology="BP",
        evidence=NULL,
        min.size=5,
        max.size=200)

```

Arguments

species Character, the identifier used by the KEGG or Reactome databases to identify the species of interest. For example, human categories are identified by 'Homo sapiens' in the Reactome and 'hsa' in the KEGG database.

annotation.package Character, the name of the Bioconductor annotation package for the species of interest, e.g. 'org.Hs.eg.db' for human gene annotations.

| | |
|----------|--|
| ontology | One of 'BP', 'MF' and 'CC', identifying the 'biological process', 'molecular function' and 'cellular component' gene ontology domain of interest. |
| evidence | Character string identifying the evidence required for a GO annotation to be included in the result. If 'NULL' all annotated terms will be included. |
| min.size | Scalar integer, only gene sets with at least 'min.size' members will be returned. |
| max.size | Scalar integer, only gene sets with no more than 'max.size' members will be returned. |

Value

A [CMAPCollection](#) object.

Author(s)

Thomas Sandmann

See Also

[induceCMAPCollection](#)

Examples

```
## Not run:
KEGG2.hs <- KEGG2cmap( species="hsa",
                      annotation.package="org.Hs.eg.db")
#reactome.hs <- reactome2cmap( species="Homo sapiens",
                              annotation.package="org.Hs.eg.db")
#
wikipathways.hs <- wiki2cmap( species="Homo sapiens",
                             annotation.package="org.Hs.eg.db")

## End(Not run)
```

mapNmerge

A function to map eSet featureNames and calculate summaries for many-to-one mapping features

Description

This function converts the featureNames of an eSet-derived object, either by applying a user-specified translation function (e.g. to remove pre- or suffices) or by referring to the annotation slot of the object to locate the corresponding Bioconductor annotation package.

In cases where multiple features map to the same target identifier, scores are summarized by applying 'summary.fun' (default: mean). For eSet-like object with multiple assayDataElements, each element is summarized separately.

Usage

```
mapNmerge(
  eset,
  translation.fun = NULL,
  get = "ENTREZID",
  verbose = FALSE,
  summary.fun = function(x) mean(x, na.rm = TRUE))
```

Arguments

| | |
|-----------------|---|
| eset | An eSet-like object. |
| translation.fun | A function that will be applied to the results of applying the 'featureNames' method to the eSet. If not 'NULL', this parameter takes precedence and the 'get' parameter will be ignored. |
| get | A character vector specifying the gene identifier universe to be retrieved from the Bioconductor annotation package. |
| verbose | Logical, should basic mapping statistics be returned ? |
| summary.fun | A function that will be applied to the scores after featureName mapping (default: mean). |

Value

An eSet object with the same number of samples as the original and one row for each unique new featureName (after mapping & summary).

Note

For large eSet objects, applying 'summary.fun' can be time-consuming. Other strategies, e.g. based on selecting a single probe for each gene based on cross-sample variability are available in the genefilter package.

Author(s)

Thomas Sandmann, sandmann.thomas@gene.com

Examples

```
## Not run:
## requires hgu95av2.db annotation package

if( require( "hgu95av2.db" ) ) {
  data(sample.ExpressionSet) ## from Biobase
  dim(sample.ExpressionSet)
  head(featureNames(sample.ExpressionSet))
  entrez <- mapNmerge(sample.ExpressionSet)
  dim(entrez)
  head(featureNames(entrez))
}

## End(Not run)
```

matrix_or_big.matrix-class

Class "matrix_or_big.matrix"

Description

Union of base's 'matrix' and bigmemory's 'big.matrix' objects. If the bigmemory package is unavailable, an empty, dummy big.matrix class is created first.

Objects from the Class

A virtual Class: No objects may be created from it.

Note

Helper class used to dispatch methods on either matrix or big.matrix objects.

Author(s)

Thomas Sandmann, sandmann.thomas@gene.com

| | |
|----------|---|
| memorize | <i>Create a new NChannelSet instance by selecting specific channels and load BigMatrix assayData into memory.</i> |
|----------|---|

Description

This function converts BigMatrix objects stored in the assayData slot of NChannelSets into standard matrices, loading them fully into memory. Standard in-memory objects are returned unchanged. Requires bigmemoryExtras package to process BigMatrix objects.

Usage

```
memorize(object, names, ...)
```

Arguments

| | |
|--------|--|
| object | An NChannelSet object. |
| names | Character vector of named channels (default: all channels are returned). |
| ... | Additional arguments. |

Value

Instance of the same class as 'object'.

Note

This function can be applied to any class inheriting from the virtual eSet class. For non NChannelSets, meta data may not be transferred correctly.

Author(s)

Thomas Sandmann

See Also

[eSet](#) [memorize](#) [selectChannels](#)

Examples

```

if( suppressWarnings(require("bigmemoryExtras",
  quietly=TRUE, character.only=TRUE))){
  ## load ExpressionSet
  data("sample.ExpressionSet") ## from Biobase
  sample.ExpressionSet ## two assayDataElements: exprs, se

  ## 'exprs' data matrix
  class( assayDataElement( sample.ExpressionSet, "exprs" ) )

  ## convert assayData to BigMatrix objects
  storage.file <- tempfile() ## create path & basemane for BigMatrices
  storage.file

  on.disk <- eSetOnDisk( sample.ExpressionSet, storage.file )
  on.disk ## ExpressionSet
  dir(dirname( storage.file )) ## created 3 files per channel

  class( assayDataElement( on.disk, "exprs" ) ) ## BigMatrix object

  ## BigMatrix objects are loaded only upon subsetting
  assayDataElement( on.disk, "exprs") ## retrieves BigMatrix, NOT matrix
  head( assayDataElement( on.disk, "exprs")[,] ) ## retrieves matrix

  ## convert back to standard in-memory ExpressionSet
  in.memory <- memorize( on.disk ) ## all channels
  class( assayDataElement( in.memory, "exprs" ) ) ## matrix object
  assayDataElementNames( in.memory )

  in.memory <- memorize( on.disk, names="exprs" ) ## channel "exprs" only
  assayDataElementNames( in.memory )

  ## remove tempfiles generated for this example
  unlink(paste(storage.file,"*", sep=""))
}

```

mergeCMAPs

This function merged two eSets.

Description

This function merges two eSet objects, if all of the following conditions are met:

- Both objects 'x' and 'y' have to be instances of the same class.
- 'x' and 'y' must be annotated with the same character string in their 'annotation' slots.
- 'x' and 'y' must have the same AssayDataElementNames / channels.
- 'x' and 'y' must have distinct sampleNames.
- 'x' and 'y' must have the same varLabels / pData columns.

Usage

```
mergeCMAPs(x, y)
```

Arguments

`x` An eSet.
`y` An eSet of the same class as 'x'

Value

An eSet of the same class as 'x' and 'y'.

Author(s)

Thomas Sandmann, sandmann.thomas@gene.com

Examples

```
library(Biobase)
data( sample.ExpressionSet)

## Not run:
## this doesn't work, because 'x' and 'y' have identical sampleNames
mergeCMAPs( sample.ExpressionSet, sample.ExpressionSet)

## End(Not run)

y <- sample.ExpressionSet
sampleNames( y ) <- paste( sampleNames( y ), "y", sep=".")
mergeCMAPs( sample.ExpressionSet, y )
```

mgsa_score-methods *Model-based gene set analysis (MGSA)*

Description

This method is a wrapper for the mgsa methods from the Bioconductor package mgsa, which must be available on the system for the methods to run. The model-based gene set analysis (MGSA) analyzes all categories at once by embedding them in a Bayesian network, naturally taking overlap between categories into account and avoiding the need for multiple testing correction. Please consult the mgsa help page for more details.

Arguments

`query` A [CMAPCollection](#), [GeneSet](#), or [GeneSetCollection](#) object containing the 'query' gene sets to compare against the 'sets'

`sets` A [CMAPCollection](#), [GeneSetCollection](#) or [GeneSet](#) object

`universe` A character string of gene ids for all genes that could potentially be of interest, e.g. all genes represented on a microarray, all annotated genes, etc.

`keep.scores` Logical: store the identifiers for the genes detected in 'query' and 'sets'? (Default: FALSE) The size of the generated CMAPResults object increases with the number of contained gene sets. For very large collections, setting this parameter to 'TRUE' may require large amounts of memory.

`element` A character string corresponding to the assayDataElementName of the NChannelSet object to be thresholded on the fly with the [induceCMAPCollection](#).

| | |
|--------------|---|
| lower | The lower threshold for the <code>induceCMAPCollection</code> . |
| higher | The 'higher' threshold for the <code>induceCMAPCollection</code> . |
| min.set.size | Number of genes a gene set induced by <code>induceCMAPCollection</code> needs to contain to be included in the analysis (Default:5). |
| ... | Additional arguments passed to mgsa function from the mgsa package, including the following: <ul style="list-style-type: none"> • alpha: Grid of values for the parameter alpha. Values represent probabilities of false-positive events and hence must be in [0,1]. numeric • beta: Grid of values for the parameter beta. Values represent probabilities of false-negative events and hence must be in [0,1]. numeric. • p: Grid of values for the parameter p. Values represent probabilities of term activity and therefore must be in [0,1]. numeric. • steps: The number of steps of each run of the MCMC sampler. integer of length 1. A recommended value is 1e6 or greater. • restarts: The number of different runs of the MCMC sampler. integer of length 1. Must be greater or equal to 1. A recommended value is 5 or greater. • threads: The number of threads that should be used for concurrent restarts. A value of 0 means to use all available cores. Defaults to 'getOption(mc.cores, default=0)', which will instruct mgsa to use all available cores. |

Value

A CMAPResults object. The reported p-values represent '1-marginal posterior probability'. For the 'effect' column, the p-values have been transformed to z-scores using a standard normal distribution.

Methods

```
signature(query = "GeneSet", sets = "CMAPCollection", universe = "character")
signature(query = "GeneSet", sets = "NChannelSet", universe = "character")
signature(query = "SignedGeneSet", sets = "CMAPCollection", universe = "character")

signature(query = "SignedGeneSet", sets = "NChannelSet", universe = "character")
signature(query = "GeneSetCollection", sets = "CMAPCollection", universe = "character")

signature(query = "GeneSetCollection", sets = "NChannelSet", universe = "character")

signature(query = "GeneSetCollection", sets = "GeneSetCollection", universe = "character")

signature(query = "GeneSet", sets = "GeneSetCollection", universe = "character")
signature(query = "GeneSet", sets = "GeneSet", universe = "character")
signature(query = "CMAPCollection", sets = "CMAPCollection", universe = "character")

signature(query = "CMAPCollection", sets = "GeneSetCollection", universe = "character")
```

Note

This Bayesian approach does not require any additional correction of p-values for multiple testing. For consistency, the returned CMAPResults object contains a padj column duplicating the content of the pval column.

See Also

mgsa

Examples

```
if( is.element("mgsa", installed.packages()[,1])){
  require( "mgsa", character.only = TRUE )

  data(gCMAPData)
  gene.set.collection <- induceCMAPCollection(gCMAPData, "z",
  higher=2, lower=-2)

  ## compare all gene sets in the gene.set.collection
  ## to each other
  universe = featureNames(gCMAPData)
  mgsa_score(gene.set.collection, gene.set.collection,
  universe = universe)
}
```

minSetSize-methods *GeneSetCollection length filtering*

Description

This function filters a GeneSetCollection by removing all contained GeneSets that do not include at least the user-specified number of genes also found in the user-specified universe.

Usage

```
## S4 method for signature 'CMAPCollection'
minSetSize(sets, universe=NULL, min.members = 5)
```

Arguments

| | |
|-------------|---|
| sets | A CMAPCollection object. |
| universe | Optional character vector of gene identifiers to be considered as the universe. Only geneIds included in the universe will count toward the gene set membership counts. If 'NULL' (default), all featureNames of the CMAPCollection will be considered. |
| min.members | Number of genes (in the universe) a gene set needs to contain to be retained. |

Value

A CMAPCollection with all gene sets containing more than the specified number of members.

Author(s)

Thomas Sandmann

Examples

```
data(gCMAPData)
gene.set.collection <- induceCMAPCollection(gCMAPData, "z", higher=2, lower=-2)

minSetSize(gene.set.collection, min.members=100)
```

mroast_score-methods *Methods for Function mroast_score in Package gCMAP*

Description

These methods provide a wrapper for the Rotation Gene Set Tests function `mroast` mroast tests whether any of the genes in the set are differentially expressed.

Usage

```
## S4 method for signature 'eSet,CMAPCollection'
mroast_score(
  experiment,
  sets,
  predictor=NULL,
  design.matrix=NULL,
  element="exprs",
  keep.scores=FALSE,
  ...)

## S4 method for signature 'matrix,CMAPCollection'
mroast_score(experiment, sets,...)

## S4 method for signature 'matrix,GeneSet'
mroast_score(experiment,sets,...)

## S4 method for signature 'eSet,GeneSet'
mroast_score(experiment, sets,...)

## S4 method for signature 'matrix,GeneSetCollection'
mroast_score(experiment,sets,...)

## S4 method for signature 'eSet,GeneSetCollection'
mroast_score(experiment,sets,...)
```

Arguments

| | |
|------------|--|
| sets | A <code>CMAPCollection</code> , <code>GeneSetCollection</code> or <code>GeneSet</code> object containing gene sets, with which to query the experiment object. |
| experiment | An <code>eSet</code> or data matrix with numeric data to compare the query object to. |

| | |
|---------------|---|
| predictor | A character vector or factor indicating the phenotypic class of the experiment data columns. Either the 'predictor' or 'design' parameter must be supplied. |
| design.matrix | A design matrix for the experiment. Either the 'predictor' or 'design' parameter must be supplied. If both are supplied, the 'design' is used. |
| element | Character vector specifying which channel of an eSet to extract (defaults to "expr", alternatives may be e.g. "z", etc.) |
| keep.scores | Logical: keep gene-level scores for all gene sets (Default: FALSE) ? The size of the generated CMAPResults object increases with the number of contained gene sets. For very large collections, setting this parameter to 'TRUE' may require large amounts of memory. |
| ... | Additional arguments passed to downstream methods. |

Value

A `CMAPResults` object.

References

Goeman, JJ, and Buhlmann, P (2007). Analyzing gene expression data in terms of gene sets: methodological issues. *Bioinformatics* 23, 980-987.

Langsrud, O (2005). Rotation tests. *Statistics and Computing* 15, 53-60.

Phipson B, and Smyth GK (2010). Permutation P-values should never be zero: calculating exact P-values when permutations are randomly drawn. *Statistical Applications in Genetics and Molecular Biology*, Volume 9, Article 39.

Routledge, RD (1994). Practicing safe statistics with the mid-p. *Canadian Journal of Statistics* 22, 103-110.

Wu, D, Lim, E, Francois Vaillant, F, Asselin-Labat, M-L, Visvader, JE, and Smyth, GK (2010). ROAST: rotation gene set tests for complex microarray experiments. *Bioinformatics* 26, 2176-2182. <http://bioinformatics.oxfordjournals.org/cgi/content/abstract/btq401?>

Examples

```
data(gCMAPData)
gene.set.collection <- induceCMAPCollection(gCMAPData, "z", higher=2, lower=-2)
sampleNames( gene.set.collection ) <- c("set1", "set2", "set3")

## random score matrix
y <- matrix(rnorm(1000*6),1000,6, dimnames=list(featureNames(gCMAPData), 1:6))
## set1 is differentially regulated
effect <- as.vector(members(gene.set.collection[,1]) * 2)
y[,4:6] <- y[,4:6] + effect

predictor <- c( rep("Control", 3), rep("Case", 3))

res<- mroast_score(y, gene.set.collection, predictor = predictor,keep.scores=TRUE)
res

## heatmap of expression scores for set1
set1.expr <- geneScores(res)[["set1"]]
heatmap(set1.expr, scale="none", Colv=NA, labCol=predictor,
        RowSideColors=ifelse( attr(set1.expr, "sign") == "up", "red", "blue"),
        margin=c(7,5))
```

```

legend(0.35,0,legend=c("up", "down"),
      fill=c("red", "blue"),
      title="Annotated sign",
      horiz=TRUE, xpd=TRUE)

```

| | |
|------------------|---|
| pairwise_compare | <i>Generate statistics associated with pairwise differential expression</i> |
|------------------|---|

Description

When provided with an [ExpressionSet](#), comparisons are made between control and perturbation samples.

Usage

```

pairwise_compare(
  eset,
  control_perturb_col = "cmap",
  control="control",
  perturb="perturbation")
pairwise_compare_limma(
  eset,
  control_perturb_col = "cmap",
  control="control",
  perturb="perturbation",
  limma.index=2)

```

Arguments

| | |
|---------------------|--|
| eset | ExpressionSet with all array data for a single instance, plus metadata on which arrays are perturbation and control. |
| control_perturb_col | Column name in phenoData of eset where control/perturbation designations are stored. |
| control | String designating control samples in the control_perturb_col column. |
| perturb | String designating perturbation samples in the control_perturb_col column. |
| limma.index | Integer specifying the index of the parameter estimate for which we to extract t and other statistics. The default corresponds to a two-class comparison with the standard parameterization. The function assumes that there was no missing data, so that test for all genes were performed on the same sample size. |

Value

The function returns a data frame with the following columns:

| | |
|--------|--|
| log_fc | Log fold-change between perturbed and control data. (A positive value denotes higher expression in the perturbed samples.) |
|--------|--|

| | |
|---|---|
| z | When at least one condition has two or more samples, the pairwise_compare_limma functions uses <code>lmFit</code> , <code>eBayes</code> and <code>topTable</code> to compare the two classes and compute an (uncorrected) limma p-value. The pairwise_compare functions performs a standard t-test instead. For ease of comparison across instances with different numbers of samples, either p-value is converted to the standard normal scale. The result is reported here. As for <code>fc</code> , positive values denote higher expression in perturbed samples. |
| p | When at least one condition has two or more samples, the two-tailed standard (pairwise_compare) or limma p-value (pairwise_compare_limma), as computed by <code>eBayes</code> . Note that this p-value can also be computed from z, via <code>pnorm</code> (doubling for two tails). |

Note

The pairwise_compare functions returns p-values from a standard t-test. The pairwise_compare_limma functions uses the **limma** package instead to perform a moderated t-test.

| | |
|----------------|--|
| pairwise_DESeq | <i>Generate statistics associated with pairwise differential expression from RNAseq count data</i> |
|----------------|--|

Description

When provided with an `CountDataSet`, comparisons are made between control and perturbation samples.

Usage

```
pairwise_DESeq(cds, vst, control_perturb_col = "condition",
control="control", perturb="perturbation", try.hard=FALSE)
```

Arguments

| | |
|---------------------|--|
| cds | <code>CountDataSet</code> with all count data for a single instance, plus metadata on which samples are perturbation and control. |
| vst | Matrix of variance-stabilized count data that must include columns with col-names matching the <code>sampleNames</code> of the <code>cds</code> object. The <code>vst</code> matrix may contain additional columns / samples, which will be ignored. |
| control_perturb_col | Column name in <code>phenoData</code> of <code>cds</code> where control/perturbation designations are stored. |
| control | String designating control samples in the <code>control_perturb_col</code> column. |
| perturb | String designating perturbation samples in the <code>control_perturb_col</code> column. |
| try.hard | Logical parameter indicating how to proceed when DESeq's parametric estimation of the dispersion parameter fails. If set to <code>FALSE</code> (default), the function exits with an error. If set to <code>TRUE</code> , the function will try a non-parametric approach instead. |

Value

The function returns a data frame with the following columns:

| | |
|--------|---|
| log_fc | Moderated log2 fold-change between perturbed and control data. (A positive value denotes higher expression in the perturbed samples.) The change was calculated from the (mean) counts after variance stabilizing transformation. Please consult the DESeq vignette for details on the transformation. |
| z | For ease of comparison across instances with different numbers of samples, the (uncorrected) DESeq p-value is converted to the standard normal scale. The result is reported here. As for log_fc, positive values denote higher expression in perturbed samples. |
| p | p-value for differential expression calculated by the nbinomTest function from the DESeq package. In the absence of replicates, the dispersion parameter is estimated across all samples, ignoring the class labels, by using the blind method of the estimateDispersions function. When replicates are available, the pooled method is used instead. Note that this p-value can also be computed from z, via <code>pnorm</code> (doubling for two tails). |

Note

To use this function, please install the suggested Bioconductor package 'DESeq'.

romer_score-methods *Methods for Function romer_score in Package gCMAP*

Description

These methods provide a wrapper for the Rotation Gene Set Enrichment Analysis function `romer`. Romer performs a competitive test in that the different gene sets are pitted against one another. Instead of permutation, it uses rotation, a parametric resampling method suitable for linear models (Langsrud, 2005).

Usage

```
## S4 method for signature 'eSet,CMAPCollection'
romer_score(experiment,sets,predictor=NULL,
design.matrix=NULL, element="exprs", keep.scores=FALSE, ...)

## S4 method for signature 'matrix,CMAPCollection'
romer_score(experiment, sets,...)

## S4 method for signature 'matrix,GeneSet'
romer_score(experiment,sets,...)

## S4 method for signature 'eSet,GeneSet'
romer_score(experiment, sets,...)

## S4 method for signature 'matrix,GeneSetCollection'
romer_score(experiment,sets,...)

## S4 method for signature 'eSet,GeneSetCollection'
romer_score(experiment, sets,...)
```

Arguments

| | |
|---------------|---|
| sets | A CMAPCollection , GeneSetCollection or GeneSet object containing gene sets, with which to query the experiment object. |
| experiment | An eSet or data matrix with numeric data to compare the query object to. |
| predictor | A character vector or factor indicating the phenotypic class of the experiment data columns. Either the 'predictor' or 'design' parameter must be supplied. |
| design.matrix | A design matrix for the experiment. Either the 'predictor' or 'design' parameter must be supplied. If both are supplied, the 'design' is used. |
| element | Character vector specifying which channel of an eSet to extract (defaults to "exprs", alternatives may be e.g. "z", etc.) |
| keep.scores | Logical: keep gene-level scores for all gene sets (Default: FALSE) ? The size of the generated CMAPResults object increases with the number of contained gene sets. For very large collections, setting this parameter to 'TRUE' may require large amounts of memory. |
| ... | Additional arguments passed to downstream methods. |

Value

A [CMAPResults](#) object.

References

- Langsrud, O, 2005. Rotation tests. *Statistics and Computing* 15, 53-60
- Doerum G, Snipen L, Solheim M, Saeboe S (2009). Rotation testing in gene set enrichment analysis for small direct comparison experiments. *Stat Appl Genet Mol Biol*, Article 34.
- Majewski, IJ, Ritchie, ME, Phipson, B, Corbin, J, Pakusch, M, Ebert, A, Busslinger, M, Koseki, H, Hu, Y, Smyth, GK, Alexander, WS, Hilton, DJ, and Blewitt, ME (2010). Opposing roles of polycomb repressive complexes in hematopoietic stem and progenitor cells. *Blood*, published online 5 May 2010. <http://www.ncbi.nlm.nih.gov/pubmed/20445021>
- Subramanian, A, Tamayo, P, Mootha, VK, Mukherjee, S, Ebert, BL, Gillette, MA, Paulovich, A, Pomeroy, SL, Golub, TR, Lander, ES and Mesirov JP, 2005. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A* 102, 15545-15550

Examples

```
data(gCMAPData)
gene.set.collection <- induceCMAPCollection(gCMAPData, "z", higher=2, lower=-2)
sampleNames( gene.set.collection ) <- c("set1", "set2", "set3")

## random score matrix
y <- matrix(rnorm(1000*6),1000,6, dimnames=list(featureNames(gCMAPData), 1:6))

## set1 is differentially regulated
effect <- as.vector(members(gene.set.collection[,1]) * 2)
y[,4:6] <- y[,4:6] + effect

predictor <- c( rep("Control", 3), rep("Case", 3))

res <- romer_score(y, gene.set.collection, predictor = predictor, keep.scores=TRUE)
res
```

```
## heatmap of expression scores for set1
set1.expr <- geneScores(res)[["set1"]]
heatmap(set1.expr, scale="none", Colv=NA, labCol=predictor,
        RowSideColors=ifelse( attr(set1.expr, "sign") == "up", "red", "blue"),
        margin=c(7,5))
legend(0.35,0,legend=c("up", "down"),
       fill=c("red", "blue"),
       title="Annotated sign",
       horiz=TRUE, xpd=TRUE)
```

| | |
|---------------|--------------------------------------|
| SignedGeneSet | <i>Constructor for SignedGeneSet</i> |
|---------------|--------------------------------------|

Description

The constructor is largely identical to [GeneColorSet](#), but also handles an optional `geneSign` argument, which is an alias for `geneColor`.

Methods

`signature(type = "ANY")` Constructor which uses a template object. See all methods for the [GeneColorSet](#) constructor. If a `geneSign` argument is included by name, it will be used to populate the `geneColor` slot of the returned object.

`signature(type = "missing")` Basic method with no template object.

| | |
|---------------------|------------------------------|
| SignedGeneSet-class | <i>Class "SignedGeneSet"</i> |
|---------------------|------------------------------|

Description

A simple extension of [GeneColorSet](#) which forces `geneColor` to be either "down" or "up" and which ignores `phenotype` and `phenotypeColor` slots.

Objects from the Class

Construct a `SignedGeneSet` with the `SignedGeneSet` constructor method, or with a call to [new](#). Although `SignedGeneSet` derives from the more abstract `GeneColorSet`, not `phenotype` argument is required; if `phenotype` is supplied (or is present in a template object), it will be ignored.

Slots

See [GeneColorSet](#). No additional slots are added.

Extends

Class "[GeneColorSet](#)", directly. Class "[GeneSet](#)", by class "`GeneColorSet`", distance 2.

Methods

Methods specific to SignedGeneSet:

downIds signature(object = "SignedGeneSet"): retrieve geneIds entires for which geneSign == "down".

geneSign signature(obj = "SignedGeneSet"): alias for geneColor slot.

geneSign<- signature(object = "SignedGeneSet", value = "character"): alias for geneColor slot, converting to factor automatically.

geneSign<- signature(object = "SignedGeneSet", value = "factor"): alias for geneColor slot.

initialize signature(.Object = "SignedGeneSet"): on construction, checks for appropriate geneSign/geneColor values and sets phenotype and phenotypeColor to empty strings, since these are ignored. If no geneSign/geneColor values are supplied, "up" will be used by default.

show signature(object = "SignedGeneSet"): same as for [GeneColorSet](#) but suppresses display of unused phenotype and phenotypeColor slots.

upIds signature(object = "SignedGeneSet"): retrieve geneIds entires for which geneSign == "up".

mapIdentifiers signature(object = "SignedGeneSet"): Extends the 'mapIdentifiers' method implemented for GeneSets in the GSEABase package, but rejects target gene ids when multiple different (probe) identifiers with different gene signs (up / down) map to the same target.

incidence signature(object = "SignedGeneSet") and

incidence signature(object = "GeneSetCollection"): Mirror the 'incidence' method implemented for GeneSets in the GSEABase package, but returns sparseMatrix objects containing -1 / +1 to indicate up- and down-regulated gene members.

Examples

```
gene.ids <- letters[1:10]
gene.signs <- rep(c("up","down"), each=5)
SignedGeneSet(gene.ids, geneSign=gene.signs, setName="set1")
```

| | |
|-------------------|--|
| signedRankSumTest | <i>An implementation of the Wilcox rank sum test / Mann-Whitney test that takes into account the direction / sign of gene set members and possibly the correlation between cases</i> |
|-------------------|--|

Description

This test evaluates whether the mean rank of statistics of gene set members is greater or less than the mean rank of the remaining statistic values. It extends the rankSumTestWithCorrelation function from the 'limma' package by taking into account the 'sign' of gene set members by reversing the ranks of down-regulated genes.

Usage

```
signedRankSumTest(statistics, index.up, index.down = NULL,
input.is.ranks=FALSE, correlation=0, df = Inf, adjust.ties=TRUE)
```


Arguments

| | |
|-----------------------------|---|
| <code>statistics</code> | numeric vector giving values of the test statistic. |
| <code>index.up</code> | an index vector such that <code>statistics[index.up]</code> contains the values of the statistic for the up-regulated genes. |
| <code>index.down</code> | an index vector such that <code>statistics[index.down]</code> contains the values of the statistic for the down-regulated genes. |
| <code>correlation</code> | numeric scalar, average correlation between cases in the test group. Cases in the second group are assumed independent of each other and the first group. |
| <code>df</code> | degrees of freedom which the correlation has been estimated. |
| <code>adjust.ties</code> | logical: correct for ties ? |
| <code>input.is.ranks</code> | logical: is 'statistics' a vector of ranks ? If FALSE (default), ranks are computed. If FALSE, 'statistics' is assumed to represent ranks and is used directly. |

Details

Please see the `rankSumTestWithCorrelation` function from the `limma` package for details.

Value

Numeric vector containing U-statistic, z-score and p-value.

Author(s)

Thomas Sandmann

References

- Wu, D, and Smyth, GK (2012). Camera: a competitive gene set test accounting for inter-gene correlation. Submitted.
- Barry, W.T., Nobel, A.B., and Wright, F.A. (2008). A statistical framework for testing functional categories in microarray data. *Annals of Applied Statistics* 2, 286-315.
- Zar, JH (1999). *Biostatistical Analysis* 4th Edition. Prentice-Hall International, Upper Saddle River, New Jersey.

See Also

[rankSumTestWithCorrelation](#)

Examples

```
genes.up <- c(1:10)
genes.down <- c(21:30)

set.seed(123)
scores <- matrix(rnorm(200), ncol=2)

## the first gene set receives increased /
## decreased scores in the first experiment
scores[genes.up,1] <- scores[genes.up ,1] + 1
scores[genes.down,1] <- scores[genes.down,1] - 1

## significantly greater
```

```
signedRankSumTest( statistics = scores[,1],
                  index.up   = genes.up,
                  index.down = genes.down)

## not significant
signedRankSumTest( statistics = scores[,2],
                  index.up   = genes.up,
                  index.down = genes.down)
```

| | |
|--------------------|--|
| splitPerturbations | <i>Function to split an ExpressionSet downloaded from ArrayExpress based on the experimental factors present in the phenoData slot</i> |
|--------------------|--|

Description

The ArrayExpress Bioconductor package provides access to microarray and RNAseq datasets from the EBI's ArrayExpress repository. Sample and experiment annotations are contained in the phenoData slot and can be used to automatically construct single-factor comparisons by subsetting the original ExpressionSet object. This function be used to automatically identify perturbation vs. control comparisons and splits the original dataset in to instance-level objects.

Usage

```
splitPerturbations(
  eset,
  control = "none",
  controlled.factors = NULL,
  factor.of.interest = "Compound",
  ignore.factors = NULL,
  cmap.column = "cmap",
  prefix = NULL)
```

Arguments

| | |
|--------------------|---|
| eset | An eSet object with experimental factors annotated in the phenoData slot. Experimental factors are identified by the prefix of the column name, specified in the 'prefix' parameter. In ExpressionSets obtained from the ArrayExpress repository experimental factors can be identified by their "^Factor" prefix. |
| control | A character string identifying control samples in the 'factor.of.interest' column. |
| controlled.factors | A character vector specifying which annotation columns should be matched to assign controls to perturbation samples. If the set to NULL shared controls are used for all perturbations. If set to 'all' all experimental factors must be identical between control and perturbation samples. Alternatively, individual factors and their combinations can be specified as a vector, e.g. as c("Vehicle", "Time"). Column names can be abbreviated as long as they uniquely identify the pData column. |
| factor.of.interest | Character string, the name of the pData column containing the factor of interest. Column name can be abbreviated as long as it uniquely identifies the pData column. |

| | |
|-----------------------------|---|
| <code>ignore.factors</code> | A character vector with valid pData names specifying annotation columns to exclude. Column names can be abbreviated as long as they uniquely identify the pData column. |
| <code>cmap.column</code> | Column name for an additional annotation column that will be added to all generated eSets. Used by the <code>generate_gCMAP_NChannelSet</code> function. |
| <code>prefix</code> | String identifying pData columns with experimental factors. Setting the prefix to NULL will include all pData columns. |

Details

To identify 'perturbation versus control' comparisons, the user needs to inspect the phenoData slot (see examples) and choose the appropriate factor of interest as well as a term in this column that identifies experimental control samples. The 'controlled.factors' character string identifies additional factors (= columns in the phenoData slot), in which control samples must match their corresponding perturbation samples.

For example (see example code section), an ExpressionSet may be annotated with two different annotated factors, Compound and Solvent, corresponding to two columns in the pData slot.

The first column is of interest and therefore 'factor.of.interest' should be set to 'Compound'. For each level of 'factor.of.interest' unique experimental conditions are identified based on the remaining pData columns. (To exclude columns, use the 'ignore.factors' parameter.) Separate ExpressionSet objects will be constructed for each unique experimental condition.

To distinguish control samples from perturbations, the 'control' parameter needs to be provided. For example, if control samples in the 'factor.of.interest' column are annotated as 'vehicle', the 'control' parameter should be set to 'vehicle'.

The second column in this example, 'Solvent', contains additional information about the type of vehicle used for each experiment, e.g. DMSO, ethanol, etc. To ensure that each sample is matched to the correct control condition the 'controlled.factors' parameter is set to 'Vehicle' to include this annotation column when assigning control to perturbation samples.

To consider all available annotation columns to match controls, the 'controlled.factors' parameters can be set to 'all' instead. (In this example, either setting the parameter to 'Vehicle' or 'all' yields identical results, as there is only one column in addition to the 'factor.of.interest'.)

Value

A list of eSet objects, one for each unique experimental perturbation with perturbation and control samples.

Warning

Annotations for experiments in public repositories are provided by the uploader and vary widely in quality and notation. This function is expected to handle experiments with clear perturbation / control annotations. Mileage on other datasets may vary.

Note

Only experimental instances with valid controls will be returned.

Author(s)

Thomas Sandmann, sandmann.thomas@gene.com

See Also

[generate_gCMAP_NChannelSet](#) [annotate_eset_list](#)

Examples

```
require(Biobase)
data( sample.ExpressionSet )
head(pData( sample.ExpressionSet))
eset.list <- splitPerturbations( eset=sample.ExpressionSet,
                                factor.of.interest="type",
                                control="Control",
                                controlled.factors="sex",
                                ignore.factors="score",
                                prefix=""
                              )
length( eset.list )
## the first eset contains male Cases & controls
pData( eset.list[[1]])
## the second eset contains female Cases & controls
pData( eset.list[[2]])

## generate data.frame with sample annotations
annotate_eset_list( eset.list)
```

wilcox_score-methods *Methods for Function wilcox_score in Package gCMAP*

Description

These methods provide a wrapper for the Mean-rank Gene Set Test function [wilcoxGST](#). `wilcox_score` is a synonym for `gst_score` with `ranks.only=TRUE`. This test procedure was developed by Michaud et al (2008), who called it mean-rank gene-set enrichment.

Usage

```
## S4 method for signature 'matrix,CMAPCollection'
wilcox_score(experiment, sets, adjust.ties=FALSE, keep.scores=FALSE, ...)

## S4 method for signature 'numeric,CMAPCollection'
wilcox_score(experiment, sets,...)

## S4 method for signature 'eSet,CMAPCollection'
wilcox_score(experiment, sets, element="z",...)

## S4 method for signature 'matrix,GeneSet'
wilcox_score(experiment, sets,...)

## S4 method for signature 'numeric,GeneSet'
wilcox_score(experiment, sets,...)

## S4 method for signature 'eSet,GeneSet'
```

```

wilcox_score(experiment, sets, element="z",...)

## S4 method for signature 'matrix, GeneSetCollection'
wilcox_score(experiment, sets,...)

## S4 method for signature 'numeric, GeneSetCollection'
wilcox_score(experiment, sets,...)

## S4 method for signature 'eSet, GeneSetCollection'
wilcox_score(experiment, sets, element="z",...)

## S4 method for signature 'CMAPCollection, eSet'
wilcox_score(experiment, sets, element="z", adjust.ties=FALSE, keep.scores=FALSE,...)

## S4 method for signature 'CMAPCollection, numeric'
wilcox_score(experiment, sets,...)

## S4 method for signature 'CMAPCollection, matrix'
wilcox_score(experiment, sets,...)

## S4 method for signature 'GeneSet, numeric'
wilcox_score(experiment, sets,...)

## S4 method for signature 'GeneSet, matrix'
wilcox_score(experiment, sets,...)

## S4 method for signature 'GeneSet, eSet'
wilcox_score(experiment, sets, element="z",...)

## S4 method for signature 'GeneSetCollection, numeric'
wilcox_score(experiment, sets,...)

## S4 method for signature 'GeneSetCollection, matrix'
wilcox_score(experiment, sets,...)

## S4 method for signature 'GeneSetCollection, eSet'
wilcox_score(experiment, sets, element="z",...)

```

Arguments

| | |
|-------------|---|
| sets | A CMAPCollection , GeneSetCollection or GeneSet object containing gene sets, with which to query the experiment object. |
| experiment | An eSet or matrix or vector with numeric data to compare the query object to. |
| element | Character vector specifying which channel of an eSet to extract (defaults to "exprs", alternatives may be e.g. "z", etc.) |
| ... | Additional arguments passed on to downstream methods. |
| adjust.ties | Logical: adjust Wilcox-Mann-Whitney statistic in the presence of ties ? (Default: FALSE) |
| keep.scores | Logical: keep gene-level scores for all gene sets (Default: FALSE) ? The size of the generated CMAPResults object increases with the number of contained gene |

sets. For very large collections, setting this parameter to 'TRUE' may require large amounts of memory.

Value

A CMAPResult object

Examples

```
data(gCMAPData)
gene.set.collection <- induceCMAPCollection(gCMAPData, "z", higher=2, lower=-2)

profile <- assayDataElement(gCMAPData[,1], "z")
## one profile versus three sets
wilcox_score(profile, gene.set.collection)

## three sets versus three profiles
wilcox_score(gene.set.collection, gCMAPData)
```

zScores

Function to calculate z-scores from p-values

Description

Function to calculate z-score from a normal distribution from a two-tailed p-value and sign vector (e.g. log2 fold change). To avoid -Inf/Inf z-scores, p-values < 'limit' are set to 'limit'.

Usage

```
zScores(pval, direction=NULL, tails=2, limit=.Machine$double.xmin)
```

Arguments

| | |
|-----------|---|
| pval | Vector with p-values |
| direction | Vector that will be used to determine the sign of the z-scores. Only the sign of the values is considered, so any suitable vectors (e.g. log2 fold change) can be supplied. |
| limit | Numeric (default: .Machine\$double.xmin). pvalues < 'limit' will be set to 'limit' to avoid Inf/-Inf z-scores. Set to NULL to disable. |
| tails | Numeric, either 1 for p-values from one-tailed or 2 for p-values from two-tailed tests. |

Value

A vector of z-scores

Author(s)

Thomas Sandmann

See Also

[qnorm](#)

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