Package ‘viper’

March 29, 2017

Version 1.8.0
Date 2013-04-09
Title Virtual Inference of Protein-activity by Enriched Regulon analysis
Author Mariano J Alvarez <reef103@gmail.com>
Maintainer Mariano J Alvarez <reef103@gmail.com>
Depends R (>= 2.14.0), Biobase, methods
Imports mixtools, stats, parallel, e1071, KernSmooth
Suggests bcellViper
Description Inference of protein activity from gene expression data, including the VIPER and msVIPER algorithms
License file LICENSE
biocViews SystemsBiology, NetworkEnrichment, GeneExpression, FunctionalPrediction, GeneRegulation
RoxygenNote 5.0.1
NeedsCompilation no

R topics documented:

  aecdf ................................................................. 2
  approx2d .......................................................... 3
  aracne2regulon .................................................... 3
  aracne2regulon4cnv ............................................. 4
  aREA ................................................................. 5
  as.dist.signatureDistance ....................................... 6
  bootstrapmsviper ............................................... 6
  bootstrapTtest .................................................... 7
  bootstrapViper ..................................................... 8
  comNames .......................................................... 9
  distMode ........................................................... 9
  fcvarna ............................................................. 10
  filterColMatrix ................................................. 11
  filterCV ........................................................... 11
  filterRowMatrix .................................................. 12
  frcv ............................................................... 12
  frvarna ............................................................. 13
Description

This function generates an empirical null model that computes a normalized statistics and p-value.

Usage

```r
aecdf(dnull, symmetric = FALSE, n = 100)
```

Arguments

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>dnull</td>
<td>Numerical vector representing the null model</td>
</tr>
<tr>
<td>symmetric</td>
<td>Logical, whether the distribution should be treated as symmetric around zero and only one tail should be approximated</td>
</tr>
<tr>
<td>n</td>
<td>Integer indicating the number of points to evaluate the empirical cumulative probability function</td>
</tr>
</tbody>
</table>
**approxk2d**

**Value**

function with two parameters, x and alternative

**Description**

This function uses a gaussian kernel to estimate the joint density distribution at the specified points

**Usage**

approxk2d(x, gridsize = 128, pos = x)

**Arguments**

- **x**: Matrix of x and y points
- **gridsize**: number or vector indicating the size of the greed where to estimate the density
- **pos**: Matrix of coordinates to evaluate the density

**Value**

Vector of density estimates

**Examples**

```r
x <- rnorm(500)
y <- x+rnorm(500)
kde2 <- approxk2d(cbind(x, y))
plot(x, y, pch=20, col=hsv(0, kde2/max(kde2), 1))
```

**aracne2regulon**

*Regulon object generation from ARACNe results*

**Description**

This function generates a regulon object from ARACNe results and the corresponding expression dataset

**Usage**

aracne2regulon(afile, eset, gene = FALSE, format = c("adj", "3col"), verbose = TRUE)
Arguments

- **afile**: Character string indicating the name of the ARACNe network file
- **eset**: Either a character string indicating the name of the expression-dataset file, an ExpressionSet object or a gene expression matrix with genes (probes) in rows and samples in columns
- **gene**: Logical, whether the probes should be collapsed at the gene level
- **format**: Character string, indicating the format of the aracne file, either adj for adjacency matrixes generated by aracne, or 3col when the interactome is represented by a 3 columns text file, with regulator in the first column, target in the second and mutual information in the third column
- **verbose**: Logical, whether progression messages should be printed in the terminal.

Value

Regulon object

See Also

msviper, viper

Examples

data(bcellViper, package="bcellViper")
adjfile <- file.path(find.package("bcellViper"), "aracne", "bcellaracne.adj")
regul <- aracne2regulon(adjfile, dset)
print(regul)

Description

This function generates a regulon object from ARACNe results and the corresponding expression dataset when correction for CNV have been applied

Usage

```
aracne2regulon4cnv(afile, eset, regeset, gene = FALSE, format = c("adj", "3col"), verbose = TRUE)
```

Arguments

- **afile**: Character string indicating the name of the ARACNe network file
- **eset**: Either a character string indicating the name of the expression-dataset file, an ExpressionSet object or a gene expression matrix with genes (probes) in rows and samples in columns, where the expression was corrected by CNV
- **regeset**: Either a character string indicating the name of the expression-dataset file, an ExpressionSet object or a gene expression matrix with genes (probes) in rows and samples in columns
gene Logical, whether the probes should be collapsed at the gene level
format Character string, indicating the format of the aracne file, either adj for adjacency matrices generated by aracne, or 3col when the interactome is represented by a 3 columns text file, with regulator in the first column, target in the second and mutual information in the third column
verbose Logical, whether progression messages should be printed in the terminal.

Value Regulon object

See Also msviper, viper

Examples
data(bcellViper, package="bcellViper")
adjfile <- file.path(find.package("bcellViper"), "aracne", "bcellaracne.adj")
regul <- aracne2regulon(adjfile, dset)
print(regul)

Description
This function performs wREA enrichment analysis on a set of signatures

Usage
aREA(eset, regulon, method = c("auto", "matrix", "loop"), minsize = 20,
cores = 1, wm = NULL, verbose = FALSE)

Arguments
eset Matrix containing a set of signatures, with samples in columns and traits in rows
regulon Regulon object
method Character string indicating the implementation, either auto, matrix or loop
minsize Integer indicating the minimum allowed size for the regulons
cores Integer indicating the number of cores to use (only 1 in Windows-based systems)
wm Optional numeric matrix of weights (0; 1) with same dimension as eset
verbose Logical, whether a progress bar should be shown

Value List of two elements, enrichment score and normalized enrichment score
as.dist.signatureDistance

Distance matrix from signatureDistance objects

Description
This function transforms a signatureDistance object into a dist object

Usage
```r
## S3 method for class 'signatureDistance'
as.dist(m, diag = FALSE, upper = FALSE)
```

Arguments
- `m`: signatureDistance object
- `diag`: parameter included for compatibility
- `upper`: parameter included for compatibility

Value
Object of class dist

Debootstrapmsviper

bootstrap msviper bootstraps integration

Description
This function integrates the bootstrap msviper results

Usage
```r
bootstrapmsviper(mobj, method = c("mean", "median", "mode"))
```

Arguments
- `mobj`: msviper object
- `method`: Character string indicating the method to use, either mean, median or mode

Value
msviper object

See Also
- msviper
### Examples

```r
data(bcellViper, package="bcellViper")
sig <- bootstrapTtest(dset, "description", c("CB", "CC"), "N")
mra <- msviper(sig, regulon)
plot(mra, cex=.7)
```

### Description

This function generates a bootstrapped signature matrix by t-test

### Usage

```r
bootstrapTtest(x, ...)
```

#### ## S4 method for signature 'matrix'
```r
bootstrapTtest(x, y, per = 100, seed = 1, cores = 1,
verbose = TRUE)
```

#### ## S4 method for signature 'ExpressionSet'
```r
bootstrapTtest(x, pheno, group1, group2, per = 100,
seed = 1, verbose = TRUE)
```

### Arguments

- **x**
  Matrix containing the test dataset
- **...**
  Additional parameters added to keep compatibility
- **y**
  Matrix containing the reference dataset
- **per**
  Integer indicating the number of permutations
- **seed**
  Integer indicating the seed for the permutations, 0 for disable it
- **cores**
  Integer indicating the number of cores to use (set to 1 in Windows-based systems)
- **verbose**
  Logical whether progress should be reported
- **pheno**
  Character string indicating the phenotype data to use
- **group1**
  Vector of character strings indicating the category from phenotype pheno to use as test group
- **group2**
  Vector of character strings indicating the category from phenotype pheno to use as control group

### Value

Matrix of z-scores with genes in rows and permutations in columns

### See Also

`ms viper`
Examples

data(bcellViper, package="bcellViper")
d1 <- exprs(dset)
sig <- bootstrapTtest(d1[, 1:10], d1[, 11:20], per=100)
dim(sig)
plot(density(sig[1907, ]))
data(bcellViper, package="bcellViper")
sig <- bootstrapTtest(dset, "description", "CB", "N", per=100)
dim(sig)
plot(density(sig[1907, ]))

Description

This function performs a viper analysis with bootstraps

Usage

bootstrapViper(eset, regulon, nes = TRUE, bootstraps = 10, cores = 1,
verbose = TRUE)

Arguments

eset ExpressionSet object or Numeric matrix containing the expression data, with
samples in columns and genes in rows
regulon Object of class regulon
nes Logical, whether the enrichment score reported should be normalized
bootstraps Integer indicating the number of bootstraps iterations to perform. Only the scale
method is implemented with bootstraps.
cores Integer indicating the number of cores to use (only 1 in Windows-based systems)
verbose Logical, whether progression messages should be printed in the terminal

Value

A list containing a matrix of inferred activity for each regulator gene in the network across all
samples and the corresponding standard deviation computed from the bootstrap iterations.

See Also

viper
Examples

data(bcellViper, package="bcellViper")
d1 <- exprs(dset)
res <- viper(d1[, 1:50], regulon, bootstraps=10) # Run only on 50 samples to reduce computation time
dim(d1)
d1[1:5, 1:5]
regulon
dim(res$nes)
res$nes[1:5, 1:5]
res$sd[1:5, 1:5]

comNames

Combinatorial annotation

Description

This function converts combinatorial annotations

Usage

comNames(x, annot)

Arguments

x Character vector of gene name combinations, where the combinations are separated by –
annot Vector of gene names with geneID as names attribute

Value

Converted annotations

See Also

msviper

distMode

Mode of continuous distributions

Description

This function computes the mode for continuous distributions

Usage

distMode(x, adj = 1)

Arguments

x Numeric data vector
adj Number indicating the adjustment for the kernel bandwidth
fcvarna

Value

Number

Examples

data(bcellViper, package="bcellViper")
d1 <- exprs(dset)
mean(d1[, 1])
median(d1[, 1])
distMode(d1[, 1])
plot(density(d1[, 1]))
abline(v=c(mean(d1[, 1]), median(d1[, 1]), distMode(d1[, 1])), col=c("green", "red", "blue"))
legend("topleft", c("Mean", "Median", "Mode"), col=c("green", "red", "blue"), lwd=4)

---

fcvarna  Variance of columns for arrays with NA values

Description

This function computes the variance by columns ignoring NA values

Usage

fcvarna(x)

Arguments

x  Numeric matrix

Value

1-column matrix with the variance by column results

Examples

data(bcellViper, package="bcellViper")
tmp <- exprs(dset)[, 1:10]
tmp[round(runif(100, 1, length(tmp)))] <- NA
fcvarna(tmp)
filterColMatrix  
*Filter for columns of a matrix with no loss of col and row names*

**Description**
This function filters the columns of a matrix returning always a two dimensional matrix

**Usage**
```
filterColMatrix(x, filter)
```

**Arguments**
- `x` Matrix
- `filter` Logical or numerical index of columns

**Value**
Matrix

filterCV  
*Coefficient of variation filter*

**Description**
This function filter redundant probes based on the highest coefficient of variation

**Usage**
```
filterCV(expset, ...)
```

**Arguments**
- `expset` Expression set or Matrix containing the gene expression data, with samples in columns and probes in rows. The colnames attribute should contain the sample names and the rownames attribute should contain the unique geneIDs
- `...` Additional parameters added to keep compatibility

**Value**
CV filtered dataset
Examples

data(bcellViper, package="bcellViper")
d1 <- exprs(dset)
tmp <- rownames(d1)
tmp[round(runif(10, 1, length(tmp)))] <- tmp[1]
rownames(d1) <- tmp
dim(d1)
d1 <- filterCV(d1)
dim(d1)

filterRowMatrix
Filter for rows of a matrix with no loss of col and row names

Description
This function filters the rows of a matrix returning always a two dimensional matrix

Usage

filterRowMatrix(x, filter)

Arguments

x Matrix

filter Logical or numerical index of rows

Value
Matrix

frcv
Coefficient of variations for rows

Description
This function computes the coefficient of variation (CV) by rows

Usage

frcv(x)

Arguments

x Numeric matrix

Value
1-column matrix with the coefficient of variation by row results
**Examples**

```r
data(bcellViper, package="bcellViper")
tmp <- exprs(dset)[1:10, ]
tmp[round(runif(100, 1, length(tmp)))] <- NA
frcv(tmp)
```

**frvarna**  
*Variance of rows for arrays with NA values*

**Description**

This function computes the variance by rows ignoring NA values.

**Usage**

```r
frvarna(x)
```

**Arguments**

- `x` Numeric matrix

**Value**

1-column matrix with the variance by row results

**Examples**

```r
data(bcellViper, package="bcellViper")
tmp <- exprs(dset)[1:10, ]
tmp[round(runif(100, 1, length(tmp)))] <- NA
frvarna(tmp)
```

**groupPwea3**  
*Proportionally Weighted Enrichment Analysis for gene-set groups*

**Description**

This function performs a Proportionally Weighted Enrichment Analysis on groups of gene-sets.

**Usage**

```r
groupPwea3(rlist, groups, nullpw = NULL, alternative = c("two.sided", "less", "greater"), per = 0, minsize = 5, cores = 1, verbose = TRUE)
```
integrateSignatures

Arguments

- **rlist**: Named vector containing the scores to rank the expression profile or matrix where columns contain bootstrapped signatures
- **groups**: List of gene-sets (regulons), each component is a list of two vectors: *TFmode* containing the TFMoA index (-1; 1) and *likelihood* containing the interaction relative likelihood
- **nullpw**: Numerical matrix representing the null model, with genes as rows (geneID as rownames) and permutations as columns
- **alternative**: Character string indicating the alternative hypothesis, either two.sided, greater or less
- **per**: Integer indicating the number of permutations for the genes in case "nullpw" is omitted
- **minsize**: Integer indicating the minimum size for the regulons
- **cores**: Integer indicating the number of cores to use (only 1 in Windows-based systems)
- **verbose**: Logical, whether progression messages should be printed in the terminal

Value

A list containing four matrices:

- **es**: Enrichment score
- **nes**: Normalized Enrichment Score
- **size**: Regulon size
- **p.value**: Enrichment p.value

Description

This function integrates signatures represented as columns in the input matrix using self-weighting average

Usage

integrateSignatures(signature, score = 1)

Arguments

- **signature**: Numeric matrix containing the signatures as z-scores or NES, genes in rows and signatures in columns
- **score**: Number indicating the exponent score for the weight

Value

Vector containing the integrated signatures
**Examples**

```r
data(bcellViper, package="bcellViper")
sig <- bootstrapTtest(dset, "description", "CB", "N", per=100)
isig <- integrateSignatures(sig)
plot(density(sig))
lines(density(isig, adj=1.5), col="red")
```

---

**ledge**  
*Leading-edge analysis*

**Description**

This function performs a Leading-Edge analysis on an object of class msviper.

**Usage**

```r
ledge(mobj)
```

**Arguments**

- `mobj`  
  msviper class object

**Value**

msviper object updated with a ledge slot

**See Also**

- `msvrier`

**Examples**

```r
data(bcellViper, package="bcellViper")
sig <- rowTtest(dset, "description", "CB", "N")$statistic
mra <- msviper(sig, regulon)
mra <- ledge(mra)
summary(mra)
```

---

**loadExpset**  
*Loading expression sets*

**Description**

This function load an expression file into a matrix.

**Usage**

```r
loadExpset(filename)
```
msviper

Arguments
filename Character string indicating the name of the expression file

Value
List containing a numeric matrix of expression data with samples in columns and probes in rows; and a vector of gene mapping annotations

msviper msVIPER

Description
This function performs MAster Regulator INference Analysis

Usage
msviper(ges, regulon, nullmodel = NULL, pleiotropy = FALSE, minsize = 25, adaptive.size = FALSE, ges.filter = TRUE, synergy = 0, level = 10, pleiotropyArgs = list(regulators = 0.05, shadow = 0.05, targets = 10, penalty = 20, method = "adaptive"), cores = 1, verbose = TRUE)

Arguments
ges Vector containing the gene expression signature to analyze, or matrix with columns containing bootstrapped signatures
regulon Object of class regulon
nullmodel Matrix of genes by permutations containing the NULL model signatures. A parametric approach equivalent to shuffle genes will be used if nullmodel is omitted.
pleiotropy Logical, whether correction for pleiotropic regulation should be performed
minsize Number indicating the minimum allowed size for the regulons
adaptive.size Logical, whether the weight (likelihood) should be used for computing the regulon size
ges.filter Logical, whether the gene expression signature should be limited to the genes represented in the interactome
synergy Number indicating the synergy computation mode: (0) for no synergy computation; (0-1) for establishing the p-value cutoff for individual TFs to be included in the synergy analysis; (>1) number of top TFs to be included in the synergy analysis
level Integer, maximum level of combinatorial regulation
pleiotropyArgs list of 5 numbers for the pleotropy correction indicating: regulators p-value threshold, pleiotropic interaction p-value threshold, minimum number of targets in the overlap between pleiotropic regulators, penalty for the pleiotropic interactions and the pleiotropy analysis method, either absolute or adaptive
cores Integer indicating the number of cores to use (only 1 in Windows-based systems)
verbose Logical, whether progression messages should be printed in the terminal
msviper-class

Value

A msviper object containing the following components:

- **signature**: The gene expression signature
- **regulon**: The final regulon object used
- **es**: Enrichment analysis results including regulon size, normalized enrichment score and p-value
- **param**: msviper parameters, including minsize, adaptive.size

See Also

viper

Examples

```r
data(bcellViper, package="bcellViper")
sig <- rowTtest(dset, "description", c("CB", "CC"), "N")$statistic
dnull <- ttestNull(dset, "description", c("CB", "CC"), "N", per=100) # Only 100 permutations to reduce computation
mra <- msviper(sig, regulon, dnull)
plot(mra, cex=.7)
```

Description

This class contains the results generated by the msviper function

Slots

- **signature**: Matrix containing the gene expression signature
- **regulon**: Object of class regulon
- **es**: List containing 6 objects:
  - **es$es**: Named vector of class numeric containing the enrichment scores
  - **es$nes**: Named vector of class numeric containing the normalized enrichment scores
  - **es$nes.se**: Named vector of class numeric containing the standard error for the normalized enrichment score
  - **es$size**: Named vector of class numeric containing the size -number of target genes- for each regulator
  - **es$p.value**: Named vector of class numeric containing the enrichment p-values
  - **es$nes.bt**: Matrix containing the normalized enrichment score if the msviper test is performed with bootstraps
- **param**: List containing 3 elements:
  - **param$minsize**: Integer indicating the minimum allowed size for the regulons
  - **param$adaptive.size**: Logical indicating whether the weight (likelihood) should be used for computing the regulon size
  - **param$iterative**: Logical indicating whether a two step analysis with adaptive redundancy estimation should be performed
nullmodel: Matrix of genes by permutations containing the NULL model signatures

tledge: List containing the leading edge genes for each regulator. This slot is added by the tledge function

shadow: Two columns matrix containing the gene names for the shadow pairs. The first column contain the most probable regulator and the second column the one that was identified because a shadow effect

---

**msviperAnnot**  
*msVIPER annotation change*

**Description**

This function changes the annotation of genes in msviper objects

**Usage**

```r
msviperAnnot(mobj, annot, complete = TRUE)
```

**Arguments**

- `mobj`: msviper object generated by `msviper` function
- `annot`: Vector of character strings containing the gene names and gene identifiers as vector names attribute
- `complete`: Logical, whether the signature and target names should be also transformed

**Value**

msviper object with updated annotations

**See Also**

`msviper`

**Examples**

```r
data(bcellViper, package="bcellViper")
sig <- rowTtest(dset, "description", "CB", "N")$statistic
mra <- msviper(sig, regulon)
tmp <- unique(c(names(mra$regulon), rownames(mra$signature)))
annot <- 1:length(tmp)
names(annot) <- tmp
plot(mra, cex=.7)
mra <- msviperAnnot(mra, annot)
plot(mra, cex=.7)
```
**msviperClass**  

**msviperClass**  

**msVIPER class**  

**Description**  

This function generates an instance of the msviper class from a signature, NES signature and regulon object  

**Usage**  

```r  
msviperClass(nes, signature, regulon, nullmodel = NULL)  
```

**Arguments**  

- **nes**  
  Numeric vector of NES values  
- **signature**  
  Numeric vector of gene expression signature  
- **regulon**  
  Instance of class regulon  
- **nullmodel**  
  Optional matrix containing the signatures for the null model  

**Value**  

msviper class object  

**Examples**  

```r  
data(bcellViper, package="bcellViper")  
sig <- rowTtest(dset, "description", c("CB", "CC"), "N")$statistic  
mra <- msviper(sig, regulon)  
mra1 <- msviperClass(mra$es$nes, sig, regulon)  
summary(mra1)  
plot(mra1)  
```

---

**msviperCombinatorial**  

**msviper combinatorial analysis**  

**Description**  

This function performs combinatorial analysis for msviper objects  

**Usage**  

```r  
msviperCombinatorial(mobj, regulators = 100, nullmodel = NULL,  
minsize = NULL, adaptive.size = NULL, level = 10, cores = 1,  
processAll = FALSE, verbose = TRUE)  
```
msviperSynergy

**Arguments**

- **mobj**: ms viper object generated by ms viper function
- **regulators**: Either a number between 0 and 1 indicating the p-value cutoff for individual TFs to be included in the combinations analysis; (>1) indicating the number of top TFs to be included in the combinations analysis; or a vector of character strings indicating the TF IDs to be included in the analysis
- **nullmodel**: Matrix of genes by permutations containing the NULL model signatures. Taken from mobj by default
- **minsize**: Number indicating the minimum allowed size for the regulons, taken from mobj by default
- **adaptive.size**: Logical, whether the weight (likelihood) should be used for computing the size, taken from mobj by default
- **level**: Integer, maximum level of combinatorial regulation
- **cores**: Integer indicating the number of cores to use (only 1 in Windows-based systems)
- **processAll**: Logical, whether all pairs, even if not significant, should be processed for synergy
- **verbose**: Logical, whether progression messages should be printed in the terminal

**Value**

A ms viper object

**See Also**

- ms viper

**Examples**

```r
data(bcellViper, package="bcellViper")
sig <- rowTtest(dset, "description", c("CB", "CC"), "N")$statistic
dnull <- tttestNull(dset, "description", c("CB", "CC"), "N", per=100) # Only 100 permutations to reduce computation time
mra <- msviper(sig, regulon, dnull)
mra <- msviperCombinatorial(mra, 20)
plot(mra, cex=.7)
```

---

This function performs a synergy analysis for combinatorial regulation

**Usage**

msviperSynergy(mobj, per = 1000, seed = 1, cores = 1, verbose = TRUE)
Arguments

- **mobj**: msviper object containing combinatorial regulation results generated by `msviperCombinatorial`
- **per**: Integer indicating the number of permutations
- **seed**: Integer indicating the seed for the permutations, 0 for disable it
- **cores**: Integer indicating the number of cores to use (only 1 in Windows-based systems)
- **verbose**: Logical, whether progression messages should be printed in the terminal

Value

Updated msviper object containing the synergy p-value

See Also

- `msviper`

Examples

```r
data(bcellViper, package="bcellViper")
sig <- rowTtest(dset, "description", c("CB", "CC"), "N")$statistic
dnull <- ttestNull(dset, "description", c("CB", "CC"), "N", per=100) # Only 100 permutations to reduce computation time
mra <- msviper(sig, regulon, dnull)
mra <- msviperCombinatorial(mra, 20)
mra <- msviperSynergy(mra)
summary(mra)
```

### Description

This function generate a plot for msviper results showing the enrichment of the target genes for each significant master regulator on the gene expression signature

Usage

```r
## S3 method for class 'msviper'
plot(x, mrs = 10, color = c("cornflowerblue", "salmon"),
     pval = NULL, bins = 500, cex = 0, density = 0, smooth = 0,
     sep = 0.2, hybrid = TRUE, include = c("expression", "activity"),
     gama = 2, ...)```

Arguments

- **x**: msviper object produced by `msviper` function
- **mrs**: Either an integer indicating the number of master regulators to include in the plot, or a character vector containing the names of the master regulators to include in the plot
- **color**: Vector of two components indicating the colors for the negative and positive parts of the regulon
- **pval**: Optional matrix of p-values to include in the plot
**pruneRegulon**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><code>bins</code></td>
<td>Number of bins to split the vector of scores in order to compute the density color of the bars</td>
</tr>
<tr>
<td><code>cex</code></td>
<td>Number indicating the text size scaling, 0 indicates automatic scaling</td>
</tr>
<tr>
<td><code>density</code></td>
<td>Integer indicating the number of steps for the kernel density. Zero for not plotting it</td>
</tr>
<tr>
<td><code>smooth</code></td>
<td>Number indicating the proportion of point for smoothing the density distribution. Zero for not using the smoother</td>
</tr>
<tr>
<td><code>sep</code></td>
<td>Number indicating the separation from figure and text</td>
</tr>
<tr>
<td><code>hybrid</code></td>
<td>Logical, whether the 3-tail approach used for computing the enrichment should be reflected in the plot</td>
</tr>
<tr>
<td><code>include</code></td>
<td>Vector indicating the information to include as heatmap to the right of the msviper plot: expression and activity</td>
</tr>
<tr>
<td><code>gama</code></td>
<td>Positive number indicating the exponential transformation for the activity and expression color scale</td>
</tr>
</tbody>
</table>

**Value**

Nothing, a plot is generated in the default output device

**See Also**

`msviper`

**Examples**

```r
data(bcellViper, package="bcellViper")
sig <- rowTtest(dset, "description", c("CB", "CC"), "N")$statistic
dnull <- ttestNull(dset, "description", c("CB", "CC"), "N", per=100) # Only 100 permutations to reduce computation time
mra <- msviper(sig, regulon, dnull)
plot(mra, cex=.7)
```

---

**pruneRegulon**  
**Prune Regulons**

**Description**

This function limits the maximum size of the regulons

**Usage**

`pruneRegulon(regulon, cutoff = 50, eliminate = FALSE)`

**Arguments**

- `regulon` Object of class regulon
- `cutoff` Number indicating the maximum size for the regulons (maximum number of target genes)
- `eliminate` Logical whether regulons smaller than `cutoff` should be eliminated
**Value**

Prunned regulon

**See Also**

*viper*, *msviper*

**Examples**

```r
data(bcellViper, package="bcellViper")
hist(sapply(regulon, function(x) sum(x$likelihood)/max(x$likelihood)), nclass=20)
preg <- pruneRegulon(regulon, 400)
hist(sapply(preg, function(x) sum(x$likelihood)/max(x$likelihood)), nclass=20)
```

---

**pwea3NULLf**  
**Null model function**

**Description**

This function generates the NULL model function, which computes the normalized enrichment score and associated p-value.

**Usage**

```r
pwea3NULLf(pwnull, cores = 1, verbose = TRUE)
```

**Arguments**

- **pwnull**: Object generated by `pwea3NULLgroups` function
- **cores**: Integer indicating the number of cores to use (only 1 in Windows-based systems)
- **verbose**: Logical, whether progression messages should be printed in the terminal

**Value**

List of function to compute NES and p-value

---

**pwea3NULLgroups**  
**Regulon-specific NULL model**

**Description**

This function generates the regulon-specific NULL models.

**Usage**

```r
pwea3NULLgroups(pwnull, groups, cores = 1, verbose = TRUE)
```
rowTtest

Arguments

pwnull  Numerical matrix representing the null model, with genes as rows (geneID as rownames) and permutations as columns

groups List containing the regulons

cores Integer indicating the number of cores to use (only 1 in Windows-based systems)

verbose Logical, whether progression messages should be printed in the terminal

Value

A list containing two elements:

groups  Regulon-specific NULL model containing the enrichment scores

ss  Direction of the regulon-specific NULL model

regulon-class  The regulon class

Description

This class contains interactome data

Slots

List of regulators with the following slots:

tfmode: Named vector of class numeric containing the regulator mode of action scores, with target genes as name attribute

likelihood: Vector of class numeric containing the relative likelihood for each target gene

rowTtest  Student’s t-test for rows

Description

This function performs a Student’s t-test on each row of a matrix

Usage

rowTtest(x, ...)

## S4 method for signature 'matrix'
rowTtest(x, y = NULL, mu = 0,
     alternative = "two.sided")

## S4 method for signature 'ExpressionSet'
rowTtest(x, pheno, group1, group2 = NULL, mu = 0,
     alternative = "two.sided")
scale.signatureDistance

Arguments

- **x**: ExpressionSet object or Numerical matrix containing the test samples
- **...**: Additional parameters added to keep compatibility
- **y**: Optional numerical matrix containing the reference samples. If omitted x will be tested against mean = mu
- **mu**: Number indicating the alternative hypothesis when y is omitted
- **alternative**: Character string indicating the tail for the test, either two.sided, greater or lower
- **pheno**: Character string indicating the phenotype data to use
- **group1**: Vector of character strings indicating the category from phenotype pheno to use as test group
- **group2**: Vector of character strings indicating the category from phenotype pheno to use as control group

Value

List of Student-t-statistic (statistic) and p-values (p.value)

Examples

```r
data(bcellViper, package="bcellViper")
d1 <- exprs(dset)
res <- rowTtest(d1[, 1:10], d1[, 11:20])
res$statistic[1:5, ]
res$p.value[1:5, ]
data(bcellViper, package="bcellViper")
res <- rowTtest(dset, "description", "CB", "N")
res$statistic[1:5, ]
res$p.value[1:5, ]
```

scale.signatureDistance

*Scaling of signatureDistance objects*

Description

This function scales the signatureDistance so its range is (-1, 1)

Usage

```r
## S3 method for class 'signatureDistance'
scale(x, center = TRUE, scale = TRUE)
```

Arguments

- **x**: signatureDistance object
- **center**: Not used, given for compatibility with the generic function scale
- **scale**: Not used, given for compatibility with the generic function scale

Value

Scaled signatureDistance object
scaleGroups | Signatures with grouping variable

Description

scaleGroups compares each group vs. the remaining groups using a Student’s t-test

Usage

scaleGroups(x, groups)

Arguments

x | Numerical matrix with genes in rows and samples in columns

groups | Vector of same length as columns has the dset containing the labels for grouping the samples

Details

This function compute signatures using groups information

Value

Numeric matrix of signatures (z-scores) with genes in rows and groups in columns

Examples

data(bcellViper, package="bcellViper")
res <- scaleGroups(exprs(dset)[, 1:20], rep(1:4, rep(5, 4)))
res[1:5, ]

shadow | Shadow analysis for msviper objects

Description

This function performs shadow analysis on msviper objects

Usage

shadow(mobj, regulators = 0.01, targets = 10, shadow = 0.01, per = 1000, nullmodel = NULL, minsize = NULL, adaptive.size = NULL, iterative = NULL, seed = 1, cores = 1, verbose = TRUE)
shadowRegulon

Arguments

* mobj: msviper object generated by msviper
* regulators: This parameter represents different ways to select a subset of regulators for performing the shadow analysis. It can be either a p-value cutoff, the total number of regulons to be used for computing the shadow effect, or a vector of regulator ids to be considered
* targets: Integer indicating the minimum number of common targets to compute shadow analysis
* shadow: Number indicating the p-value threshold for the shadow effect
* per: Integer indicating the number of permutations
* nullmodel: Null model in matrix format
* minsize: Integer indicating the minimum size allowed for the regulons
* adaptive.size: Logical, whether the target weight should be considered when computing the regulon size
* iterative: Logical, whether a two-step analysis with adaptive redundancy estimation should be performed
* seed: Integer indicating the seed for the permutations, 0 for disable it
* cores: Integer indicating the number of cores to use (only 1 in Windows-based systems)
* verbose: Logical, whether progression messages should be printed in the terminal

Value

An updated msviper object with an additional slot (shadow) containing the shadow pairs

See Also

`msviper`

Examples

```r
data(bcellViper, package="bcellViper")
sig <- rowTtest(dset, "description", c("CB", "CC"), "N")$statistic
dnull <- ttestNull(dset, "description", c("CB", "CC"), "N", per=100) # Only 100 permutations to reduce computation time
mra <- msviper(sig, regulon, dnull)
mra <- shadow(mra, regulators=10)
summary(mra)
```

## shadowRegulon

**Correction for pleiotropy**

Description

This function penalizes the regulatory interactions based on pleiotropy analysis

Usage

```
shadowRegulon(ss, nes, regul, regulators = 0.05, shadow = 0.05,
    targets = 10, penalty = 2, method = c("absolute", "adaptive"))
```
signatureDistance

Arguments

- `ss`: Named vector containing the gene expression signature
- `nes`: Named vector containing the normalized enrichment scores
- `regul`: Regulon object
- `regulators`: Number indicating the number of top regulators to consider for the analysis or the p-value threshold for considering significant regulators
- `shadow`: Number indicating the p-value threshold for considering a significant shadow effect
- `targets`: Integer indicating the minimal number of overlapping targets to consider a pair of regulators for pleiotropy analysis
- `penalty`: Number higher than 1 indicating the penalty for the pleiotropic interactions. 1 = no penalty
- `method`: Character string indicating the method to use for computing the pleiotropy, either absolute or adaptive

Value

Corrected regulon object

signatureDistance  Signature Distance

Description

This function computes the similarity between columns of a data matrix

Usage

```R
signatureDistance(dset1, dset2 = NULL, nn = NULL, groups = NULL, scale. = TRUE, two.tails = TRUE, ws = 2)
```

Arguments

- `dset1`: Dataset of any type in matrix format, with features in rows and samples in columns
- `dset2`: Optional Dataset. If provided, distance between columns of dset and dset2 are computed and reported as rows and columns, respectively; if not, distance between all possible pairs of columns from dset are computed
- `nn`: Optional size for the signature, default is either the full signature or 10 percent of it, depending or whether ws=0 or not
- `groups`: Optional vector indicating the group ID of the samples
- `scale.`: Logical, whether the data should be scaled
- `two.tails`: Logical, whether a two tails, instead of 1 tail test should be performed
- `ws`: Number indicating the exponent for the weighting the signatures, the default of 0 is uniform weighting, 1 is weighting by SD
signatureDistance-class

Value

Object of class signatureDistance as a matrix of normalized enrichment scores

Examples

data(bcellViper, package="bcellViper")
dd <- signatureDistance(exprs(dset))
dd[1:5, 1:5]
scale(dd)[1:5, 1:5]
as.matrix(as.dist(dd))[1:5, 1:5]

signatureDistance-class

signatureDistance

Description

This class contains the results generated by signatureDistance function.

Slots

Matrix of class numeric containing the similarity scores

summary.msviper

List msviper results

Description

This function generates a table of msviper results

Usage

## S3 method for class 'msviper'
summary(object, mrs = 10, ...)

Arguments

object msviper object
mrs Either number of top MRs to report or vector containing the genes to display
... Given for compatibility with the summary generic function

Value

Data.frame with results
ttestNull

Null model by sample permutation testing

Description

This function performs sample permutation and t-test to generate a null model.

Usage

```r
# S4 method for signature 'matrix'
ttestNull(x, y, per = 1000,repos = TRUE, seed = 1,cores = 1, verbose = TRUE)

# S4 method for signature 'ExpressionSet'
ttestNull(x, pheno, group1, group2, per = 1000,repos = TRUE, seed = 1, verbose = TRUE)
```

Arguments

- `x` ExpressionSet object or Matrix containing the test dataset
- `...` Additional parameters added to keep compatibility
- `y` Matrix containing the reference dataset
- `per` Integer indicating the number of permutations
- `repos` Logical, whether the permutations should be performed with reposition
- `seed` Integer indicating the seed for the permutations, 0 for disable it
- `cores` Integer indicating the number of cores to use (set to 1 in windows systems)
- `verbose` Logical, whether progression messages should be printed in the terminal
- `pheno` Character string indicating the phenotype data to use
- `group1` Vector of character strings indicating the category from phenotype pheno to use as test group
- `group2` Vector of character strings indicating the category from phenotype pheno to use as control group

Value

Matrix of z-scores with genes in rows and permutations in columns

See Also

`msviper`, `viper`
Examples

```r
data(bcellViper, package="bcellViper")
d1 <- exprs(dset)
dnull <- ttestNull(d1[, 1:10], d1[, 11:20], per=100)
dim(dnull)
plot(density(dnull))
data(bcellViper, package="bcellViper")
dnull <- ttestNull(dset, "description", "CB", "CC", per=100)
dim(dnull)
plot(density(dnull))
```

Description

This function performs Virtual Inference of Protein-activity by Enriched Regulon analysis

Usage

```r
viper(eset, regulon, dnull = NULL, pleiotropy = FALSE, nes = TRUE,
method = c("scale", "rank", "mad", "ttest", "none"), bootstraps = 0,
minsize = 25, adaptive.size = FALSE, eset.filter = TRUE,
pleiotropyArgs = list(regulators = 0.05, shadow = 0.05, targets = 10,
penalty = 20, method = "adaptive"), cores = 1, verbose = TRUE)
```

Arguments

- **eset**: ExpressionSet object or Numeric matrix containing the expression data or gene expression signatures, with samples in columns and genes in rows
- **regulon**: Object of class regulon
- **dnull**: Numeric matrix for the null model, usually generated by `nullTtest`
- **pleiotropy**: Logical, whether correction for pleiotropic regulation should be performed
- **nes**: Logical, whether the enrichment score reported should be normalized
- **method**: Character string indicating the method for computing the single samples signature, either scale, rank, mad, ttest or none
- **bootstraps**: Integer indicating the number of bootstraps iterations to perform. Only the scale method is implemented with bootstraps.
- **minsize**: Integer indicating the minimum number of targets allowed per regulon
- **adaptive.size**: Logical, whether the weighting scores should be taken into account for computing the regulon size
- **eset.filter**: Logical, whether the dataset should be limited only to the genes represented in the interactome
- **pleiotropyArgs**: List of 5 numbers for the pleotropy correction indicating: regulators p-value threshold, pleiotropic interaction p-value threshold, minimum number of targets in the overlap between pleiotropic regulators, penalty for the pleiotropic interactions and the method for computing the pleiotropy, either absolute or adaptive
- **cores**: Integer indicating the number of cores to use (only 1 in Windows-based systems)
- **verbose**: Logical, whether progression messages should be printed in the terminal
Value

A matrix of inferred activity for each regulator gene in the network across all samples

See Also

`msviper`

Examples

data(bcellViper, package="bcellViper")
d1 <- exprs(dset)
res <- viper(d1, regulon)
dim(d1)
d1[1:5, 1:5]
regulon
dim(res)
res[1:5, 1:5]

viperRPT

Description

This function computes residual post-translational activity

Usage

viperRPT(vipermat, expmat, weights = matrix(1, nrow(vipermat), ncol(vipermat),
dimnames = list(rownames(vipermat), colnames(vipermat))),
method = c("spline", "lineal", "rank"), robust = FALSE, cores = 1)

Arguments

- `vipermat`: Numeric matrix containing the viper protein activity inferences
- `expmat`: Numeric matrix or expressionSet containing the expression data
- `weights`: List of numeric matrix of sample weights
- `method`: Character string indicating the method to use, either rank, lineal or spline
- `robust`: Logical, whether the contribution of outliers is down-weighted by using a gaussian kernel estimate for the join probability density
- `cores`: Integer indicating the number of cores to use

Value

Matrix of RPT-activity values

See Also

`viper`
Examples

```r
data(bcellViper, package="bcellViper")
vipermat <- viper(dset, regulon)
rpt <- viperRPT(vipermat, dset)
rpt[1:5, 1:5]
```

**viperSignature**  
*Generic S4 method for signature and sample-permutation null model for VIPER*

**Description**

This function generates a viperSignature object from a test dataset based on a set of samples to use as reference.

**Usage**

```r
viperSignature(eset, ...)
```

### S4 method for signature 'ExpressionSet'

```r
viperSignature(eset, pheno, refgroup,  
method = c("ttest", "zscore", "mean"), per = 1000, seed = 1,  
cores = 1, verbose = TRUE)
```

### S4 method for signature 'matrix'

```r
viperSignature(eset, ref, method = c("ttest", "zscore",  
"mean"), per = 1000, seed = 1, cores = 1, verbose = TRUE)
```

**Arguments**

- `eset`: ExpressionSet object or numeric matrix containing the test dataset, with genes in rows and samples in columns.
- `...`: Additional parameters added to keep compatibility.
- `pheno`: Character string indicating the phenotype data to use.
- `refgroup`: Vector of character string indicating the category of `pheno` to use as reference group.
- `method`: Character string indicating how to compute the signature and null model, either `ttest`, `zscore` or `mean`.
- `per`: Integer indicating the number of sample permutations.
- `seed`: Integer indicating the seed for the random sample generation. The system default is used when set to zero.
- `cores`: Integer indicating the number of cores to use (only 1 in Windows-based systems).
- `verbose`: Logical, whether progression messages should be printed in the terminal.
- `ref`: Numeric matrix containing the reference samples (columns) and genes in rows.

**Value**

- `viperSignature` S3 object containing the signature and null model.
Examples

```r
data(bcellViper, package="bcellViper")
ss <- viperSignature(dset, "description", c("N", "CB", "CC"), per=100) # Only 100 permutations to reduce computation time
res <- viper(ss, regulon)
dim(exprs(dset))
exprs(dset)[1:5, 1:5]
regulon
dim(res)
exprs(res)[1:5, 1:5]
data(bcellViper, package="bcellViper")
d1 <- exprs(dset)
pos <- pData(dset)[["description"]] %in% c("N", "CB", "CC")
ss <- viperSignature(d1[, !pos], d1[, pos], per=100) # Only 100 permutations to reduce computation time, but it is recommended to perform at least 1000 permutations
res <- viper(ss, regulon)
dim(d1)
d1[1:5, 1:5]
regulon
dim(res)
res[1:5, 1:5]
```

viperSignature-class  
`viperSignature`

Description

This class contains the results produced by the `viperSignature` function

Slots

- `signature`: Matrix of class numeric with genes in rows and samples in columns containing the gene expression signatures
- `nullmodel`: Matrix of class numeric with genes in rows and permutations in columns containing the sample-permutation based signatures to be used as NULL model

viperSimilarity  
`VIPER similarity`

Description

If `ws` is a single number, weighting is performed using an exponential function. If `ws` is a 2 numbers vector, weighting is performed with a symmetric sigmoid function using the first element as inflection point and the second as trend.

Usage

```r
viperSimilarity(x, nn = NULL, w = c(4, 2), method = c("two.sided", "greater", "less"))
```
viperSimilarity

Arguments

- **x**: Numeric matrix containing the VIPER results with samples in columns and regulators in rows
- **nn**: Optional number of top regulators to consider for computing the similarity
- **ws**: Number indicating the weighting exponent for the signature, or vector of 2 numbers indicating the inflection point and the value corresponding to a weighting score of .1 for a sigmoid transformation, only used if `nn` is omitted
- **method**: Character string indicating whether the most active (greater), less active (less) or both tails (two.sided) of the signature should be used for computing the similarity

Details

This function computes the similarity between VIPER signatures

Value

- `signatureDistance` object

Examples

```r
data(bcellViper, package="bcellViper")
dd <- viperSimilarity(exprs(dset))
dd[1:5, 1:5]
scale(dd)[1:5, 1:5]
as.matrix(as.dist(dd))[1:5, 1:5]
```
Index

aecdf, 2
approxk2d, 3
aracne2regulon, 3
aracne2regulon4cnv, 4
aREA, 5
as.dist.signatureDistance, 6
bootstrapmsviper, 6
bootstrapTtest, 7
bootstrapTtest,ExpressionSet-method (bootstrapTtest), 7
bootstrapTtest,matrix-method (bootstrapTtest), 7
bootstrapViper, 8
comNames, 9
distMode, 9
fcvarna, 10
filterColMatrix, 11
filterCV, 11
filterCV,ExpressionSet-method (filterCV), 11
filterCV,matrix-method (filterCV), 11
filterRowMatrix, 12
frcv, 12
frvarna, 13
groupPwea3, 13
integrateSignatures, 14
ledge, 15
loadExpset, 15
msviper, 4–7, 9, 15, 16, 18, 20–23, 27, 30, 32
msviper-class, 17
msviperAnnot, 18
msviperClass, 19
msviperCombinatorial, 19
msviperSynergy, 20
plot.msviper, 21
pruneRegulon, 22
pwea3NULLf, 23
pwea3NULLgroups, 23
regulon-class, 24
rowTtest, 24
rowTtest,ExpressionSet-method (rowTtest), 24
rowTtest,matrix-method (rowTtest), 24
scale.signatureDistance, 25
scaleGroups, 26
shadow, 26
shadowRegulon, 27
signatureDistance, 28
signatureDistance-class, 29
summary.msviper, 29
ttestNull, 30
ttestNull,ExpressionSet-method (ttestNull), 30
ttestNull,matrix-method (ttestNull), 30
viper, 4, 5, 8, 17, 23, 30, 31, 32
viperRPT, 32
viperSignature, 33
viperSignature,ExpressionSet-method (viperSignature), 33
viperSignature,matrix-method (viperSignature), 33
viperSignature-class, 34
viperSimilarity-class, 34
viperSimilarity, 34