

Package ‘viper’

May 18, 2024

Version 1.38.0

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

Encoding UTF-8

RoxygenNote 6.1.1

git_url <https://git.bioconductor.org/packages/viper>

git_branch RELEASE_3_19

git_last_commit 0c90a96

git_last_commit_date 2024-04-30

Repository Bioconductor 3.19

Date/Publication 2024-05-17

Contents

aecdf	3
approxk2d	3
aracne2regulon	4
aracne2regulon4cnv	5
aREA	6

as.dist.signatureDistance	6
bootstrapmsviper	7
bootstrapTtest	8
bootstrapViper	9
comNames	10
distMode	11
fcvarna	11
filterColMatrix	12
filterCV	12
filterRowMatrix	13
frcv	14
frvarna	14
groupPwea3	15
integrateSignatures	16
ledge	16
loadExpset	17
msviper	18
msviper-class	19
msviperAnnot	20
msviperClass	21
msviperCombinatorial	21
msviperSynergy	22
plot.msviper	23
pruneRegulon	25
pwea3NULLf	26
pwea3NULLgroups	26
regulon-class	27
rowTtest	27
scale.signatureDistance	28
scaleGroups	29
shadow	29
shadowRegulon	31
signatureDistance	31
signatureDistance-class	32
sigT	33
summary.msviper	33
ttestNull	34
viper	35
viperRPT	36
viperSignature	37
viperSignature-class	38
viperSimilarity	39

aecdf *Approximate empirical commulative distribution function*

Description

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

Usage

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

Arguments

dnull	Numerical vector representing the null model
symmetric	Logical, whether the distribution should be treated as symmetric around zero and only one tail should be approximated
n	Integer indicating the number of points to evaluate the empirical cumulative probability function

Value

function with two parameters, x and alternative

approxk2d *approxk2d*

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 grid where to estimate the density
pos	Matrix of coordinates to evaluate the density

Value

Vector of density estimates

Examples

```
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	<i>Regulon object generation from ARACNe results</i>
----------------	--

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, a 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)
```

aracne2regulon4cnv *Regulon object generation from ARACNe results corrected by cnv*

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, a 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, a 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)
```

aREA *analytic Rank-based Enrichment Analysis*

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

```
## 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

bootstrapmsviper *msviper bootstraps integration*

Description

This function integrates the bootstrap msviper results

Usage

```
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

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

bootstrapTtest	<i>Bootstrapped signature by t-test</i>
----------------	---

Description

This function generates a bootstrapped signature matrix by t-test

Usage

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

[msviper](#)

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, ]))

```

bootstrapViper

*bootstrapsViper***Description**

This function performs a viper analysis with bootstraps

Usage

```

bootstrapViper(eset, regulon, nes = TRUE, bootstraps = 10,
  eset.filter = FALSE, adaptive.size = TRUE, minsize = 20,
  mvws = 1, 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.
eset.filter	Logical, whether the dataset should be limited only to the genes represented in the interactome
adaptive.size	Logical, whether the weighting scores should be taken into account for computing the regulon size
minsize	Integer indicating the minimum number of targets allowed per regulon
mvws	Number or vector indicating either the exponent score for the metaViper weights, or the inflection point and trend for the sigmoid function describing the weights in metaViper
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	<i>Mode of continuous distributions</i>
----------	---

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

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	<i>Variance of columns for arrays with NA values</i>
---------	--

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	<i>Filter for columns of a matrix with no loss of col and row names</i>
-----------------	---

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	<i>Coefficient of variation filter</i>
----------	--

Description

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

Usage

```
filterCV(expset, ...)

## S4 method for signature 'matrix'
filterCV(expset)

## S4 method for signature 'ExpressionSet'
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

```
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

```
frvarna(x)
```

Arguments

x Numeric matrix

Value

1-column matrix with the variance by row results

Examples

```
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

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

Arguments

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

integrateSignatures *Integrate signatures*

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

```
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

```
ledge(mobj)
```

Arguments

mobj	msviper class object
------	----------------------

Value

msviper object updated with a ledge slot

See Also

[msviper](#)

Examples

```
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

```
loadExpset(filename)
```

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

<code>ges</code>	Vector containing the gene expression signature to analyze, or matrix with columns containing bootstraped signatures
<code>regulon</code>	Object of class <code>regulon</code>
<code>nullmodel</code>	Matrix of genes by permutations containing the NULL model signatures. A parametric approach equivalent to shuffle genes will be used if <code>nullmodel</code> is ommitted.
<code>pleiotropy</code>	Logical, whether correction for pleiotropic regulation should be performed
<code>minsize</code>	Number indicating the minimum allowed size for the regulons
<code>adaptive.size</code>	Logical, whether the weight (likelihood) should be used for computing the regulon size
<code>ges.filter</code>	Logical, whether the gene expression signature should be limited to the genes represented in the interactome
<code>synergy</code>	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
<code>level</code>	Integer, maximum level of combinatorial regulation
<code>pleiotropyArgs</code>	list of 5 numbers for the pleiotropy 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
<code>cores</code>	Integer indicating the number of cores to use (only 1 in Windows-based systems)
<code>verbose</code>	Logical, whether progression messages should be printed in the terminal

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

```
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)
```

msviper-class

The msviper class

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

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

```
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

```
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	<i>msVIPER class</i>
--------------	----------------------

Description

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

Usage

```
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

```
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	<i>msviper combinatorial analysis</i>
----------------------	---------------------------------------

Description

This function performs combinatorial analysis for msviper objects

Usage

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

Arguments

mobj	msviper object generated by msviper 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 msviper object

See Also

[msviper](#)

Examples

```
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)
mra <- msviperCombinatorial(mra, 20)
plot(mra, cex=.7)
```

msviperSynergy

msviper synergy analysis

Description

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

```
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)
mra <- msviperCombinatorial(mra, 20)
mra <- msviperSynergy(mra)
summary(mra)
```

plot.msviper

Plot msviper results

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

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

Value

Nothing, a plot is generated in the default output device

See Also

[msviper](#)

Examples

```
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)
```

pruneRegulon	<i>Prune Regulons</i>
--------------	-----------------------

Description

This function limits the maximum size of the regulons

Usage

```
pruneRegulon(regulon, cutoff = 50, adaptive = TRUE,  
             eliminate = FALSE, wm = NULL)
```

Arguments

regulon	Object of class regulon
cutoff	Number indicating the maximum size for the regulons (maximum number of target genes)
adaptive	Logical, whether adaptive size should be used (i.e. $\text{sum}(\text{likelihood}^2)$)
eliminate	Logical whether regulons smaller than cutoff should be eliminated
wm	Optional numeric vector of weights (0; 1) for the genes

Value

Pruned regulon

See Also

[viper](#), [msviper](#)

Examples

```
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

```
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

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

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	<i>The regulon class</i>
---------------	--------------------------

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	<i>Student's t-test for rows</i>
----------	----------------------------------

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")
```

Arguments

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

Value

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

Examples

```
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

```
## 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	<i>Signatures with grouping variable</i>
-------------	--

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	<i>Shadow analysis for msviper objects</i>
--------	--

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)
```

Arguments

<code>mobj</code>	msviper object generated by <code>msviper</code>
<code>regulators</code>	This parameter represent 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
<code>targets</code>	Integer indicating the minimum number of common targets to compute shadow analysis
<code>shadow</code>	Number indicating the p-value threshold for the shadow effect
<code>per</code>	Integer indicating the number of permutations
<code>nullmodel</code>	Null model in marix format
<code>minsize</code>	Integer indicating the minimum size allowed for the regulons
<code>adaptive.size</code>	Logical, whether the target weight should be considered when computing the regulon size
<code>iterative</code>	Logical, whether a two step analysis with adaptive redundancy estimation should be performed
<code>seed</code>	Integer indicating the seed for the permutations, 0 for disable it
<code>cores</code>	Integer indicating the number of cores to use (only 1 in Windows-based systems)
<code>verbose</code>	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

```
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)
mra <- shadow(mra, regulators=10)
summary(mra)
```

shadowRegulon	<i>Correction for pleiotropy</i>
---------------	----------------------------------

Description

This function penalize 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"))
```

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	<i>Signature Distance</i>
-------------------	---------------------------

Description

This function computes the similarity between columns of a data matrix

Usage

```
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 on 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

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

sigT	<i>Sigmoid transformation</i>
------	-------------------------------

Description

This function transforms a numeric vector using a sigmoid function

Usage

```
sigT(x, slope = 20, inflection = 0.5)
```

Arguments

x	Numeric vector
slope	Number indicating the slope at the inflection point
inflection	Number indicating the inflection point

Value

Numeric vector

summary.msviper	<i>List msvipr results</i>
-----------------	----------------------------

Description

This function generates a table of msvipr results

Usage

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

Arguments

object	msvipr 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

```
ttestNull(x, ...)  
  
## 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

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

```

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))

```

viper

*VIPER***Description**

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

Usage

```

viper(eset, regulon, dnull = NULL, pleiotropy = FALSE, nes = TRUE,
      method = c("none", "scale", "rank", "mad", "ttest"), bootstraps = 0,
      minsize = 25, adaptive.size = FALSE, eset.filter = TRUE,
      mvws = 1, 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 or list of objects of class regulon for metaVIPER analysis
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 #' @param mvws Number or vector indicating either the exponent score for the metaViper weights, or the inflection point and trend for the sigmoid function describing the weights in metaViper

pleiotropyArgs list of 5 numbers for the pleiotropy 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

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 joint probability density

cores Integer indicating the number of cores to use

Value

Matrix of RPT-activity values

See Also

[viper](#)

Examples

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

viperSignature	<i>Generic S4 method for signature and sample-permutation null model for VIPER</i>
----------------	--

Description

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

Usage

```
viperSignature(eset, ...)

## S4 method for signature 'ExpressionSet'
viperSignature(eset, pheno, refgroup,
  method = c("zscore", "ttest", "mean"), per = 100, bootstrap = TRUE,
  seed = 1, cores = 1, verbose = TRUE)

## S4 method for signature 'matrix'
viperSignature(eset, ref, method = c("zscore",
  "ttest", "mean"), per = 100, bootstrap = TRUE, 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 indicatig 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
bootstrap	Logical, whether null model should be estimated with bootstrap. In this case, only reference samples are used.
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

```

data(bcellViper, package="bcellViper")
ss <- viperSignature(dset, "description", c("N", "CB", "CC"), per=100) # Only 100 permutations to reduce computation time, but it is not accurate
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 not accurate
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	<i>VIPER similarity</i>
-----------------	-------------------------

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

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

Arguments

<code>x</code>	Numeric matrix containing the VIPER results with samples in columns and regulators in rows
<code>nn</code>	Optional number of top regulators to consider for computing the similarity
<code>ws</code>	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 <code>nn</code> is omitted
<code>method</code>	Character string indicating whether the most active (<code>greater</code>), less active (<code>less</code>) or both tails (<code>two.sided</code>) of the signature should be used for computing the similarity

Details

This function computes the similarity between VIPER signatures

Value

signatureDistance object

Examples

```
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, 3
approxk2d, 3
aracne2regulon, 4
aracne2regulon4cnv, 5
aREA, 6
as.dist.signatureDistance, 6

bootstrapmsviper, 7
bootstrapTtest, 8
bootstrapTtest, ExpressionSet-method
 (bootstrapTtest), 8
bootstrapTtest, matrix-method
 (bootstrapTtest), 8
bootstrapViper, 9

comNames, 10

distMode, 11

fcvarna, 11
filterColMatrix, 12
filterCV, 12
filterCV, ExpressionSet-method
 (filterCV), 12
filterCV, matrix-method (filterCV), 12
filterRowMatrix, 13
frcv, 14
frvarna, 14

groupPwea3, 15

integrateSignatures, 16

ledge, 16
loadExpset, 17

msviper, 4, 5, 7, 8, 10, 17, 18, 20, 22–25, 30,
 34, 36
msviper-class, 19
msviperAnnot, 20
msviperClass, 21
msviperCombinatorial, 21
msviperSynergy, 22

plot.msviper, 23
pruneRegulon, 25
pwea3NULLf, 26
pwea3NULLgroups, 26

regulon-class, 27
rowTtest, 27
rowTtest, ExpressionSet-method
 (rowTtest), 27
rowTtest, matrix-method (rowTtest), 27

scale.signatureDistance, 28
scaleGroups, 29
shadow, 29
shadowRegulon, 31
signatureDistance, 31
signatureDistance-class, 32
sigT, 33
summary.msviper, 33

ttestNull, 34
ttestNull, ExpressionSet-method
 (ttestNull), 34
ttestNull, matrix-method (ttestNull), 34

viper, 4, 5, 10, 19, 25, 34, 35, 37
viperRPT, 36
viperSignature, 37
viperSignature, ExpressionSet-method
 (viperSignature), 37
viperSignature, matrix-method
 (viperSignature), 37
viperSignature-class, 38
viperSimilarity, 39