

# Package ‘viper’

December 5, 2023

**Version** 1.37.0

**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** devel

**git\_last\_commit** 4dfd568

**git\_last\_commit\_date** 2023-10-24

**Repository** Bioconductor 3.19

**Date/Publication** 2023-12-04

## Table of 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**

rlist	Named vector containing the scores to rank the expression profile or matrix where columns contains bootstrapped signatures
groups	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
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

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 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
<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**

<code>x</code>	signatureDistance object
<code>center</code>	Not used, given for compatibility with the generic function <code>scale</code>
<code>scale</code>	Not used, given for compatibility with the generic function <code>scale</code>

**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 msviper results</i>
-----------------	-----------------------------

---

**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**

```
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**

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**

```

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