

# Package ‘signeR’

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**Type** Package

**Title** Empirical Bayesian approach to mutational signature discovery

**Version** 2.10.0

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**Description** The signeR package provides an empirical Bayesian approach to mutational signature discovery. It is designed to analyze single nucleotide variation (SNV) counts in cancer genomes, but can also be applied to other features as well. Functionalities to characterize signatures or genome samples according to exposure patterns are also provided.

**License** GPL-3

**Imports** BiocGenerics, Biostrings, class, grDevices, GenomeInfoDb, GenomicRanges, IRanges, nloptr, methods, stats, utils, PMCMRplus, parallel, pvclust, ppclust, clue, survival, maxstat, survivalAnalysis, future, VGAM, MASS, kkn, glmnet, e1071, randomForest, ada, future.apply, ggplot2, pROC, pheatmap, RColorBrewer, listenv, reshape2, scales, survminer, dplyr, ggpubr, cowplot, tibble, readr, shiny, shinydashboard, shinycssloaders, shinyWidgets, bsplus, DT, magrittr, tidyr, BiocFileCache, proxy, rtracklayer, BSgenome

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**LinkingTo** Rcpp, RcppArmadillo (>= 0.7.100)

**SystemRequirements** C++11

**URL** <https://github.com/TojalLab/signeR>

**LazyData** true

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**ByteCompile** TRUE

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|                |  |
|----------------|--|
| signeR-package | <i>Empirical Bayesian approach to mutational signature discovery</i> |
|----------------|--|

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Description

The signeR package provides an empirical Bayesian approach to mutational signature discovery. It is designed to analyze single nucleotide variation (SNV) counts in cancer genomes, but can also be applied to other features as well. Functionalities to characterize signatures or genome samples according to exposure patterns are also provided.

## Details

signeR package focuses on the characterization and analysis of mutational processes. Its functionalities can be divided into three steps. Firstly, it provides tools to process VCF files and generate matrices of SNV mutation counts and mutational opportunities, both divided according to a 3bp context (mutation site and its neighboring bases). Secondly, the main part of the package takes those matrices as input and applies a Bayesian approach to estimate the number of underlying signatures and their mutational profiles. Thirdly, the package provides tools to correlate the activities of those signatures with other relevant information, e.g. clinical data, to infer conclusions about the analyzed genome samples, which can be useful for clinical applications.

## Author(s)

Rodrigo Drummond, Rafael Rosales, Renan Valieris, Israel Tojal da Silva

Maintainer: Renan Valieris <renan.valieris@accamargo.org.br>

## References

This work has been submitted to Bioinformatics under the title "signeR: An empirical Bayesian approach to mutational signature discovery".

L. B. Alexandrov, S. Nik-Zainal, D. C. Wedge, P. J. Campbell, and M. R. Stratton. Deciphering Signatures of Mutational Processes Operative in Human Cancer. *Cell Reports*, 3(1):246-259, Jan. 2013. doi:10.1016/j.celrep.2012.12.008.

A. Fischer, C. J. Illingworth, P. J. Campbell, and V. Mustonen. EMu: probabilistic inference of mutational processes and their localization in the cancer genome. *Genome biology*, 14(4):R39, Apr. 2013. doi:10.1186/gb-2013-14-4-r39.

## Examples

```
vignette(package="signeR")
```

---

cosmic\_data

*COSMIC Mutational Signatures*

---

## Description

COSMIC Mutational Signatures Data Files (SBS) v3.2.

## Usage

```
data("cosmic_data")
```

**Format**

A data frame with 96 observations on the following 75 variables.

Substitution.Type a character vector

Trinucleotide a character vector

Somatic.Mutation.Type a character vector

SBS1 a numeric vector

SBS2 a numeric vector

SBS3 a numeric vector

SBS4 a numeric vector

SBS5 a numeric vector

SBS6 a numeric vector

SBS7a a numeric vector

SBS7b a numeric vector

SBS7c a numeric vector

SBS7d a numeric vector

SBS8 a numeric vector

SBS9 a numeric vector

SBS10a a numeric vector

SBS10b a numeric vector

SBS11 a numeric vector

SBS12 a numeric vector

SBS13 a numeric vector

SBS14 a numeric vector

SBS15 a numeric vector

SBS16 a numeric vector

SBS17a a numeric vector

SBS17b a numeric vector

SBS18 a numeric vector

SBS19 a numeric vector

SBS20 a numeric vector

SBS21 a numeric vector

SBS22 a numeric vector

SBS23 a numeric vector

SBS24 a numeric vector

SBS25 a numeric vector

SBS26 a numeric vector

SBS27 a numeric vector

SBS28 a numeric vector  
SBS29 a numeric vector  
SBS30 a numeric vector  
SBS31 a numeric vector  
SBS32 a numeric vector  
SBS33 a numeric vector  
SBS34 a numeric vector  
SBS35 a numeric vector  
SBS36 a numeric vector  
SBS37 a numeric vector  
SBS38 a numeric vector  
SBS39 a numeric vector  
SBS40 a numeric vector  
SBS41 a numeric vector  
SBS42 a numeric vector  
SBS43 a numeric vector  
SBS44 a numeric vector  
SBS45 a numeric vector  
SBS46 a numeric vector  
SBS47 a numeric vector  
SBS48 a numeric vector  
SBS49 a numeric vector  
SBS50 a numeric vector  
SBS51 a numeric vector  
SBS52 a numeric vector  
SBS53 a numeric vector  
SBS54 a numeric vector  
SBS55 a numeric vector  
SBS56 a numeric vector  
SBS57 a numeric vector  
SBS58 a numeric vector  
SBS59 a numeric vector  
SBS60 a numeric vector  
SBS84 a numeric vector  
SBS85 a numeric vector  
SBS86 a numeric vector  
SBS87 a numeric vector  
SBS88 a numeric vector  
SBS89 a numeric vector  
SBS90 a numeric vector

**Source**

[https://cancer.sanger.ac.uk/signatures/documents/453/COSMIC\\_v3.2\\_SBS\\_GRCh38.txt](https://cancer.sanger.ac.uk/signatures/documents/453/COSMIC_v3.2_SBS_GRCh38.txt)

---

DiffExp

Differential Exposure Analysis

---

**Description**

DiffExp : Identify signatures with significantly different activities among sample groups.

**Usage**

```
## S4 method for signature 'SignExp,character'
DiffExp(signexp_obj, labels, max_instances=200,
        method=kruskal.test, contrast="all", quant=0.5, cutoff=0.05,
        p.adj= "BH", plot_to_file=FALSE, file="Diffexp_boxplot.pdf",
        colored=TRUE, relative = FALSE, ...)
```

**Arguments**

|               |  |
|---------------|--|
| signexp_obj   | a SignExp object returned by signeR function.  |
| labels        | sample labels used to define sample groups.  |
| max_instances | Maximum number of the exposure matrix instances to be analyzed. If the number of available E instances is bigger than this parameter, a subset of those will be randomly selected for analysis.  |
| method        | algorithm used to compare each signature exposure among sample groups. Default is kruskal.test, which leads to the use of Kruskal-Wallis Rank Sum Test.  |
| contrast      | defines which sample groups will be considered in the analysis. Default is "all", which leads the algorithm to evaluate the null hypothesis of exposure levels being constant in all groups. Instead, if this parameter contains a list of group labels, the algorithm will evaluate the null hypothesis of exposure levels being constant among those groups. |
| quant         | the p-values quantile which, after log-transform, will be used as DES (Differential Exposure Score). Default is 0.5, which means the median log-transformed p-value will be considered as DES.   |
| p.adj         | correction method for p-values adjust at the post-hoc tests performed when there are more than two group labels. See p.adjust for options.   |
| cutoff        | threshold for p-values quantile for signatures to be considered as showing differential exposure.  |
| plot_to_file  | Whether to save the plot to the file parameter. Default is FALSE.  |
| file          | Output file to export p-values boxplot.  |
| colored       | Boolean variable, if TRUE boxplots of differentially exposed signatures will be colored in green, cutoff line will be colored in red and line segments showing the transformed p-value quantile used for DE evaluation will be colored in blue. Otherwise the plot will be black & white.  |

|          |  |
|----------|--|
| relative | Whether tests should be performed on absolute or relative signature contributions to each sample mutation. Default is FALSE (absolute contributions will be tested). |
| ...      | additional parameters for test algorithm defined by the method parameter.  |

**Value**

A list with the following items:

|             |  |
|-------------|--|
| Pvquant     | boolean array with one entry for each signature, indicating whether it shows differential exposure.  |
| Pvalues     | matrix containing all computed p-values, with one row for each signature.  |
| MostExposed | for each differentially exposed signature, this array contains the label of the group where it showed higher levels of exposure. Contains NA for signatures not showing differential exposure.   |
| Differences | List of matrices, exported only when there are more than two groups in the analysis and any signature is found to be differentially active. Each matrix corresponds to one of the highlighted signatures and show the results of comparisons among groups, with the significant ones marked as TRUE. |

**Examples**

```
# assuming signatures is the return value of signeR()

# labels vector, one for each sample
my_labels <- c("a","a","b","b")

diff_exposure <- DiffExp(signatures$SignExposures,labels=my_labels)

# see also
vignette(package="signeR")
```

---

ExposureClassify

---

*Classify samples by exposure levels*


---

**Description**

Assign unlabeled samples to previously defined groups.

**Usage**

```
## S4 method for signature 'SignExp,character'
ExposureClassify(signexp_obj, labels,
  method="knn", max_instances=200, k=3, weights=NA, plot_to_file=FALSE,
  file="Classification_barplot.pdf", colors=NA_character_, min_agree=0.75,...)
```

**Arguments**

|                            |   |
|----------------------------|---|
| <code>signexp_obj</code>   | A SignExp object returned by <code>signeR</code> function.  |
| <code>labels</code>        | Sample labels. Every sample labeled as NA will be classified according to its mutational profile and the profiles of labeled samples.   |
| <code>method</code>        | Classification algorithm used. Default is k-Nearest Neighbors (kNN). Any other algorithm may be used, as long as it is customized to satisfy the following conditions:<br>Input: a matrix of labeled samples, with one sample per line and one feature per column; a matrix of unlabeled samples to classify, with the same structure; an array of labels, with one entry for each labeled sample.<br>Output: an array of assigned labels, one for each unlabeled sample. |
| <code>max_instances</code> | Maximum number of the exposure matrix instances to be analyzed. If the number of available E instances is bigger than this parameter, a subset of those will be randomly selected for analysis.   |
| <code>k</code>             | Number of nearest neighbors considered for classification, used only if <code>method="kNN"</code> . Default is 3.   |
| <code>weights</code>       | Vector of weights applied to the signatures when performing classification. Default is NA, which leads all the signatures to have <code>weight=1</code> .   |
| <code>plot_to_file</code>  | Whether to save the plot to the file parameter. Default is FALSE.   |
| <code>file</code>          | File that will be generated with classification graphic output.   |
| <code>colors</code>        | Array of color names, one for each sample class. Colors will be recycled if the length of this array is less than the number of classes.  |
| <code>min_agree</code>     | Minimum frequency of agreement among individual classifications. Samples showing a frequency of agreement below this value are considered as "undefined". Default is 0.75.  |
| <code>...</code>           | additional parameters for classification algorithm (defined by "method" above).   |

**Value**

A list with the following items:

|                       |   |
|-----------------------|---|
| <code>class</code>    | The assigned classes for each unlabeled sample.   |
| <code>freq</code>     | Classification agreement for each unlabeled sample: the relative frequency of assignment of each sample to the group specified in "class".  |
| <code>,</code>        |   |
| <code>allfreqs</code> | Matrix with one column for each unlabeled sample and one row for each class label. Contains the assignment frequencies of each sample to each class.  |
| <code>probs</code>    | As above, a matrix with unlabeled samples in columns and class labels in rows. Contains the average probability, among repeated exposure classifications, of each sample belonging to each class. |



## Examples

```
# assuming signatures is the return value of signeR()

my_labels <- c("a","a","a","a",NA,"b","b","b","b",NA)
Class <- ExposureClassify(signatures$SignExposures, labels=my_labels)

# see also
vignette(package="signeR")
```

---

|                    |  |
|--------------------|--|
| ExposureClassifyCV | <i>k-fold cross-validation of sample classification by exposure levels</i> |
|--------------------|--|

---

## Description

Splits labeled samples in k groups (default k=8), keeping the proportion of classes stable among groups. Classify samples in each group according to the k-1 remaining ones. Gather results and evaluate global classification performance.

## Usage

```
## S4 method for signature 'SignExp,character'
ExposureClassifyCV(signexp_obj, labels, method="knn",
  max_instances=200, k=3, weights=NA, plot_to_file=FALSE,
  file="Classification_CV_barplot.pdf", colors=NA_character_,
  min_agree=0.75, fold=8, ...)
```

## Arguments

|               |  |
|---------------|--|
| signexp_obj   | A SignExp object returned by signeR function.  |
| labels        | Sample labels. Unlabeled samples (NA labels) will be ignored.  |
| method        | <p>Classification algorithm used. Default is k-Nearest Neighbors (kNN). Any other algorithm may be used, as long as it is customized to satisfy the following conditions:</p> <p>Input: a matrix of labeled samples, with one sample per line and one feature per column; a matrix of unlabeled samples to classify, with the same structure; an array of labels, with one entry for each labeled sample.</p> <p>Output: an array of assigned labels, one for each unlabeled sample.</p> |
| max_instances | Maximum number of the exposure matrix instances to be analyzed. If the number of available E instances is bigger than this parameter, a subset of those will be randomly selected for analysis.  |
| k             | Number of nearest neighbors considered for classification, used only if method="kNN". Default is 3.  |
| weights       | Vector of weights applied to the signatures when performing classification. Default is NA, which leads all the signatures to have weight=1.  |

|              |  |
|--------------|--|
| plot_to_file | Whether to save the plot to the file parameter. Default is FALSE.  |
| file         | File that will be generated with cross validation graphic output.  |
| colors       | Array of color names, one for each sample class. Colors will be recycled if the length of this array is less than the number of classes.                                   |
| min_agree    | Minimum frequency of agreement among individual classifications. Samples showing a frequency of agreement below this value are considered as "undefined". Default is 0.75. |
| fold         | Number of subsets in which labeled samples will be split   |
| ...          | additional parameters for classification algorithm (defined by "method" above).  |

### Value

A list with the following items:

|                  |   |
|------------------|---|
| confusion_matrix | Contingency table of attributed sample classes against original labels.   |
| class            | The assigned classes for each sample.   |
| freq             | Classification agreement for each sample: the relative frequency of assignment of each sample to the group specified in "class".  |
| allfreqs         | Matrix with one column for each sample and one row for each class label. Contains the assignment frequencies of each sample to each class.  |
| probs            | As above, a matrix with samples in columns and class labels in rows. Contains the average probability, among repeated exposure classifications, of each sample belonging to each class. |

### Examples

```
# assuming signatures is the return value of signeR()

my_labels <- c("a","a","a","a","a","b","b","b","b","b")
ClassCV <- ExposureClassifyCV(signatures$SignExposures, labels=my_labels,fold=5)

# see also
vignette(package="signeR")
```

---

|                     |   |
|---------------------|---|
| ExposureCorrelation | <i>Exposure correlation analysis (given a known sample feature)</i> |
|---------------------|---|

---

### Description

ExposureCorrelation : Identify signatures which are significantly correlated with a provided (numeric) sample feature.

**Usage**

```
## S4 method for signature 'SignExp,numeric'
ExposureCorrelation(Exposures, feature,
  method="spearman", max_instances=200, cutoff_pvalue=0.05, quant=0.5,
  plot_to_file=FALSE, file="ExposureCorrelation_plot.pdf",
  colors=TRUE,...)
```

**Arguments**

|               |  |
|---------------|--|
| Exposures     | a SignExp object returned by signeR function or a matrix of exposures (with signatures in rows and a column for each sample).  |
| feature       | numeric feature associated with each sample, such as age, weight or the expression of a gene.  |
| method        | a character string indicating which correlation coefficient should be used for the test. Options are "pearson", "kendall", or "spearman" (default).  |
| max_instances | Maximum number of the exposure matrix instances to be analyzed. If the number of available E instances is bigger than this parameter, a subset of those will be randomly selected for analysis.  |
| cutoff_pvalue | threshold for p-values quantile for signatures to be considered as showing significant correlation.  |
| quant         | the p-values quantile which, after log-transform, will be used for selecting significantly correlated signatures. Default is 0.5, which means the median p-value will be considered.   |
| plot_to_file  | Whether to save the plot to the file parameter. Default is FALSE.  |
| file          | Output file to export p-values boxplot and scatterplots showing the correlations of exposures and the provided feature.  |
| colors        | Boolean variable, if TRUE p-values boxplots of significantly correlated signatures will be colored in green, cutoff line will be colored in red and line segments showing the transformed p-value quantile used for significance evaluation will be colored in blue. Otherwise the plot will be black & white. |
| ...           | additional parameters for test algorithm defined by the method parameter.  |

**Value**

A list with the following items:

|                       |   |
|-----------------------|---|
| Significance          | boolean array with one entry for each signature, indicating whether it shows significant correlation with the provided feature. |
| Correlation_quantiles | vector of correlation quantiles, with one entry for each signature.   |
| Pvalues_quantiles     | vector of p-values quantiles used for significance evaluation.  |
| Correlations          | matrix containing all computed correlations, with one row for each signature.   |
| Pvalues               | matrix containing all computed p-values, with one row for each signature.   |

## Examples

```
# assuming signatures is the return value of signeR()

# feature vector, with one value for each sample
my_feature <- rnorm(30,100,20)+signatures$SignExposures@Exp[1,,1]

Exp_corr <- ExposureCorrelation(signatures$SignExposures,feature=my_feature)

# see also
vignette(package="signeR")
```

---

ExposureGLM

*Exposure Generalized Linear Model*


---

## Description

Fits a GLM to exposure data, with a given sample feature as the target of the model.

## Usage

```
## S4 method for signature 'SignExp,numeric'
ExposureGLM(Exposures, feature, max_instances=200,
  cutoff_pvalue=0.05,quant=0.5, plot_to_file=FALSE,
  file="ExposureGLM_plot.pdf",colors=TRUE,...)
```

## Arguments

|               |  |
|---------------|--|
| Exposures     | A SignExp object returned by signeR function or a matrix of exposures (with signatures in rows and a column for each sample).  |
| feature       | numeric feature associated with each sample, such as age, weight or the expression of a gene.  |
| max_instances | Maximum number of the exposure matrix instances to be analyzed. If the number of available E instances is bigger than this parameter, a subset of those will be randomly selected for analysis.  |
| cutoff_pvalue | threshold for p-values quantile for signatures to be considered as significant on the model.   |
| quant         | p-values quantile used to evaluate if signatures are significant. Default is 0.5, meaning that median p-values are adopted.  |
| plot_to_file  | Whether to save plots to the file parameter. Default is FALSE.   |
| file          | Output file to export p-values boxplot and scatterplots showing the correlations of exposures and the provided feature.  |
| colors        | Boolean variable, if TRUE p-values boxplots of significantly correlated signatures will be colored in green, cutoff line will be colored in red and line segments showing the transformed p-value quantile used for significance evaluation will be colored in blue. Otherwise the plot will be black & white. |
| ...           | additional parameters for test algorithm defined by the method parameter.  |

**Value**

A list with the following items:

|              |   |
|--------------|---|
| Significance | boolean array with one entry for each signature, indicating whether it shows a significant contribution to the model. |
| Stats        | matrix of model statistics, with one line for each signature.   |
| Pvalues      | vector of p-values used for significance evaluation.  |

**Examples**

```
# assuming signatures is the return value of signeR()

my_feature <- rnorm(30,100,20)+signatures$SignExposures@Exp[1,,1]
EGlm <- ExposureGLM(signatures$SignExposures, feature=my_feature)

# see also
vignette(package="signeR")
```

---

|                  |                                   |
|------------------|-----------------------------------|
| ExposureSurvival | <i>Exposure survival analysis</i> |
|------------------|-----------------------------------|

---

**Description**

ExposureSurvival: Given survival data, identify signatures that are significantly related to differences in hazards.

**Usage**

```
## S4 method for signature 'SignExp,Surv'
ExposureSurvival(signexp_obj, surv, max_instances=200,
  method=logrank, quant=0.5, cutoff_pvalue=0.05, cutoff_hr=NA,
  plot_to_file=FALSE, file="ExposureSurvival_plot.pdf",
  colors=TRUE, ...)
```

**Arguments**

|               |   |
|---------------|---|
| signexp_obj   | a SignExp object returned by signeR function.   |
| surv          | a Surv object from package survival or a matrix with columns "time" and "status" (the last indicates whether 1:an event occurred or 0:there was a loss of follow up).                           |
| max_instances | Maximum number of the exposure matrix instances to be analyzed. If the number of available E instances is bigger than this parameter, a subset of those will be randomly selected for analysis. |
| method        | a character string indicating which approach should be used for the test. Options are "logrank" (default) or "cox" (fit a Cox proportional hazards model to data).                              |

|               |   |
|---------------|---|
| quant         | the quantile of p-values and hazard ratios which will be used for selecting survival significant signatures. Default is 0.5, which means the median p-value and hazard ratio will be considered.  |
| cutoff_pvalue | threshold for p-values quantile for signatures to be considered as significant.   |
| cutoff_hr     | threshold for hazard ratio quantile for signatures to be considered as significant.   |
| plot_to_file  | Whether to save the plot to the file parameter. Default is FALSE.   |
| file          | Output file to export p-values boxplots and Kaplan-Meier curves.  |
| colors        | Boolean variable, if TRUE p-values boxplots of significant signatures will be colored in green, cutoff line will be colored in red and line segments showing the transformed p-value quantile used for significance evaluation will be colored in blue. Otherwise the plot will be black & white. |
| ...           | additional parameters for test algorithm defined by the method parameter.   |

## Value

A list with the following items:

|                       |  |
|-----------------------|--|
| Significance          | boolean array with one entry for each signature, indicating whether its levels of exposure are significant to survival.  |
| Correlation_quantiles | vector of correlation quantiles, with one entry for each signature.  |
| pvalues               | vector of p-values used for significance evaluation.   |
| limits                | vector containing one cut value for the exposures of each signature, such that splitting the samples according to this value leads to maximal differences in survival among generated groups.  |
| Groups                | matrix containing one line for each signature, defining a division of the samples into two groups according to their exposures, such that survival differences between the groups are maximal. |

## Examples

```
# assuming signatures is the return value of signeR()

# feature vector, with one value for each sample
library(survival)
my_surv <- Surv(rnorm(30,730,100),sample(c(0:1),30,replace=TRUE))

Exp_corr <- ExposureSurvival(signatures$SignExposures, surv = my_surv)

# see also
vignette(package="signeR")
```

---

|                   |                           |
|-------------------|---------------------------|
| ExposureSurvModel | <i>Exposure Cox model</i> |
|-------------------|---------------------------|

---

## Description

ExposureSurvModel: Given survival data, fits a multivariate Cox proportional hazards model to exposure data.

## Usage

```
## S4 method for signature 'SignExp, Surv'
ExposureSurvModel(Exposures, surv, adddata,
  max_instances=200, quant=0.5, cutoff_pvalue=0.05, cutoff_hr=NA,
  plot_to_file=FALSE, file="ExposureSurvival_plot.pdf", colors=TRUE, ...)
```

## Arguments

|               |   |
|---------------|---|
| Exposures     | A SignExp object returned by signeR function or a matrix of exposures (with signatures in rows and a column for each sample).   |
| surv          | a Surv object from package survival or a matrix with columns "time" and "status" (the last indicates whether 1:an event occurred or 0:there was a loss of follow up).   |
| adddata       | a data frame with additional data (one sample per row) that will be used in the Cox model along with exposure data.   |
| max_instances | Maximum number of the exposure matrix instances to be analyzed. If the number of available E instances is bigger than this parameter, a subset of those will be randomly selected for analysis.   |
| quant         | the quantile of p-values and hazard ratios which will be used for selecting survival significant signatures. Default is 0.5, which means the median p-value and hazard ratio will be considered.  |
| cutoff_pvalue | threshold for p-values quantile for signatures to be considered as significant.   |
| cutoff_hr     | threshold for hazard ratio quantile for signatures to be considered as significant.   |
| plot_to_file  | Whether to save the plot to the file parameter. Default is FALSE.   |
| file          | Output file to export p-values boxplots and Kaplan-Meier curves.  |
| colors        | Boolean variable, if TRUE p-values boxplots of significant signatures will be colored in green, cutoff line will be colored in red and line segments showing the transformed p-value quantile used for significance evaluation will be colored in blue. Otherwise the plot will be black & white. |
| ...           | additional parameters for test algorithm defined by the method parameter.   |

**Value**

A list with the following items:

|              |   |
|--------------|---|
| Significance | boolean array with one entry for each signature, indicating whether its levels of exposure are significant to survival. |
| Stats        | data frame containing hazard ratios and pvalues for signatures (one per line) on fitted Cox models.                     |

**Examples**

```
# assuming signatures is the return value of signeR()

# feature vector, with one value for each sample
library(survival)
my_surv <- Surv(rnorm(30,730,100),sample(c(0:1), 30, replace = TRUE))

Exp_corr <- ExposureSurvModel(signatures$SignExposures, surv = my_surv)

# see also
vignette(package="signeR")
```

---

FuzzyClustExp

*Fuzzy Clustering of exposure data*


---

**Description**

FuzzyClustExp : Performs fuzzy C-means clustering of samples, based on exposures. The number of clusters is defined by optimizing the PBMF index of obtained clustering.

**Usage**

```
## S4 method for signature 'SignExp,numeric'
FuzzyClustExp(signexp_obj, max_instances=200, Clim,
               method.dist="euclidean", method.clust="fcm", relative=FALSE,
               m=2, plot_to_file=FALSE, file="FuzzyClustExp.pdf",colored=TRUE)
```

**Arguments**

|               |   |
|---------------|---|
| signexp_obj   | a SignExp object returned by signeR function.   |
| max_instances | Maximum number of the exposure matrix instances to be analyzed. If the number of available E instances is bigger than this parameter, a subset of those will be randomly selected for analysis. |
| Clim          | number of groups range, a vector with minimum and maximum accepted number of groups. The algorithm will maximize the PBMF-index within this range.  |
| method.dist   | used distance metric  |
| method.clust  | clustering method. Either "fcm", default, for fuzzy C-means or "km" for k-means.  |



|              |  |
|--------------|--|
| relative     | Whether to normalize exposures of each sample so that they sum up to one. Default is FALSE, thus clustering samples by the absolute contributions of signatures to mutation counts. Otherwise, clustering will be based on relative contributions. |
| m            | Exponent used in PBMF-index  |
| plot_to_file | Whether to save a heatmap of results to the file parameter. Default is FALSE.  |
| file         | Output file to export a heatmap with the levels of pertinence of samples to found groups.  |
| colored      | Whether plots will be in color or B&W. Default is TRUE.  |

### Value

A list with the following items: Meanfuzzy=Meanfuzzy, AllFuzzy=Fuzzy[[1]], Centroids=Fuzzy[[2]]

|           |   |
|-----------|---|
| Meanfuzzy | Final clustering: mean levels of pertinence of samples to found groups.                           |
| AllFuzzy  | All levels of pertinence of samples to found groups in repeated runs of the clustering algorithm. |
| Centroids | All centroids of found groups in repeated runs of the clustering algorithm.                       |

### Examples

```
# assuming signatures is the return value of signeR()

# Limits to number of groups:
cl <- c(2,4)

FuzClust <- FuzzyClustExp(signatures$SignExposures, Clim = cl)

# see also
vignette(package="signeR")
```

---

|                |   |
|----------------|---|
| generateMatrix | <i>count matrix and opportunity matrix generators</i> |
|----------------|---|

---

### Description

genCountMatrixFromVcf : generate a count matrix from a VCF file.  
 genCountMatrixFromMAF : generate a count matrix from an MAF file.  
 genOpportunityFromGenome : generate an opportunity matrix from a target regions set.

### Usage

```
genCountMatrixFromVcf(bsgenome, vcfobj)
genCountMatrixFromMAF(bsgenome, maf_file)
genOpportunityFromGenome(bsgenome, target_regions, nsamples=1)
```

**Arguments**

|                             |  |
|-----------------------------|--|
| <code>bsgenome</code>       | A BSgenome object, equivalent to the genome used for the variant call.                           |
| <code>vcfobj</code>         | A VCF object. See VCF-class from the VariantAnnotation package.                                  |
| <code>maf_file</code>       | Path to a MAF file.  |
| <code>target_regions</code> | A GRanges object, describing the target region analyzed by the variant caller.                   |
| <code>nsamples</code>       | Number of samples to generate the matrix, should be the same number as rows of the count matrix. |

**Value**

A matrix of samples x (96 features).  
Each feature is an SNV change with a 3bp context.

**Examples**

```
library(rtracklayer)
library(VariantAnnotation)

# input files, variant call and target
vcf_file <- system.file("extdata", "example.vcf", package="signeR")
bed_file <- system.file("extdata", "example.bed", package="signeR")
maf_file <- system.file("extdata", "example.maf", package="signeR")

# BSgenome, will depend on your variant call
library(BSgenome.Hsapiens.UCSC.hg19)

vcfobj <- readVcf(vcf_file, "hg19")
mut <- genCountMatrixFromVcf(BSgenome.Hsapiens.UCSC.hg19, vcfobj)

target_regions <- import(con=bed_file, format="bed")
opp <- genOpportunityFromGenome(BSgenome.Hsapiens.UCSC.hg19,
  target_regions, nsamples=nrow(mut))

mut <- genCountMatrixFromMAF(BSgenome.Hsapiens.UCSC.hg19, maf_file)

# see also
vignette(package="signeR")
```

**Description**

HClustExp: Performs hierarchical clustering of samples, based on exposures.

**Usage**

```
## S4 method for signature 'SignExp,numeric'
HClustExp(signexp_obj, Med_exp=NA,
          max_instances=200, method.dist="euclidean", method.hclust="average",
          use.cor=FALSE, relative=FALSE, plot_to_file=FALSE,
          file="HClustExp_dendrogram.pdf", colored=TRUE)
```

**Arguments**

|                            |  |
|----------------------------|--|
| <code>signexp_obj</code>   | a SignExp object returned by <code>signeR</code> function.   |
| <code>Med_exp</code>       | optional matrix with (median) exposures.   |
| <code>max_instances</code> | Maximum number of the exposure matrix instances to be analyzed. If the number of available E instances is bigger than this parameter, a subset of those will be randomly selected for analysis.  |
| <code>method.dist</code>   | used distance metric   |
| <code>method.hclust</code> | clustering method.   |
| <code>use.cor</code>       | used in <code>pv.distance</code>   |
| <code>relative</code>      | Whether to normalize exposures of each sample so that they sum up to one. Default is FALSE, thus clustering samples by the absolute contributions of signatures to mutation counts. Otherwise, clustering will be based on relative contributions. |
| <code>plot_to_file</code>  | Whether to save a heatmap of results to the file parameter. Default is FALSE.  |
| <code>file</code>          | Output file to export a heatmap with the levels of pertinence of samples to found groups.  |
| <code>colored</code>       | Whether plots will be in color or B&W. Default is TRUE.  |

**Value**

A `pvclust` object, as described in package `pvclust`.

**Examples**

```
# assuming signatures is the return value of signeR()

HClust <- HClustExp(signatures$SignExposures)

# see also
vignette(package="signeR")
```

---

 methods

*SignExp* class methods
 

---

**Description**

setSamples: Define sample names for a SignExp object, according to the "names" argument.

setMutations: Define mutation names for a SignExp object, according to the "mutations" argument.

Normalize: Normalize a SignExp object so that the entries of each signature sum up to one.

Reorder\_signatures: Change the order of the signatures in a SignExp object. The new signature order will be defined by the "ord" argument.

Reorder\_samples: Change samples order, according to ord parameter.

Reorder\_mutations: Change mutations order, according to ord parameter.

Average\_sign: Exports an approximation of the signatures obtained by the averages of the samples for the signature matrix P.

Median\_sign: Exports an approximation of the signatures obtained by the medians of the samples for signature matrix P.

Average\_exp: Exports an approximation of the exposures obtained by the averages of the samples for exposure matrix E.

Median\_exp: Exports an approximation of the exposures obtained by the medians of the samples for exposure matrix E.

**Usage**

```
## S4 method for signature 'SignExp'
setSamples(signexp_obj, names)
## S4 method for signature 'SignExp'
setMutations(signexp_obj, mutations)
## S4 method for signature 'SignExp'
Normalize(signexp_obj)
## S4 method for signature 'SignExp,numeric'
Reorder_signatures(signexp_obj, ord)
## S4 method for signature 'SignExp,numeric'
Reorder_samples(signexp_obj, ord)
## S4 method for signature 'SignExp,numeric'
Reorder_mutations(signexp_obj, ord)
```

```
## S4 method for signature 'SignExp'
Average_sign(signexp_obj, normalize=TRUE)
## S4 method for signature 'SignExp'
Median_sign(signexp_obj, normalize=TRUE)
## S4 method for signature 'SignExp'
Average_exp(signexp_obj, normalize=TRUE)
## S4 method for signature 'SignExp'
Median_exp(signexp_obj, normalize=TRUE)
```

### Arguments

|                          |  |
|--------------------------|--|
| <code>signexp_obj</code> | a SignExp object returned by <code>signeR</code> function. e.g.: <code>sig\$SignExposures</code> |
| <code>names</code>       | Vector of sample names.  |
| <code>mutations</code>   | Vector of mutations, e.g. "C>A:TCG".   |
| <code>normalize</code>   | Whether the signatures should be normalized before extracting approximations. Default is TRUE.   |
| <code>ord</code>         | Vector with the new signature order.   |

### Value

`setSamples`, `setMutations`, `Normalize` and `Reorder_*` returns a modified SignExp object.  
`Average_sign`, `Median_sign`, `Average_exp` and `Median_exp` return a matrix with the corresponding approximation.

### Examples

```
# each function needs the SignExposures object
# which is part of the result of the signeR() call
signexp <- Normalize(signatures$SignExposures)
signexp <- Reorder_signatures(signatures$SignExposures,ord=c(2,1))
matrix_p <- Median_sign(signatures$SignExposures)
# etc ...

# see also
vignette(package="signeR")
```

---

plots

*signeR plot functions*


---

### Description

**BICboxplot:** Plot the measured values of the Bayesian Information Criterion (BICs) for tested model dimensions.

**Paths:** Plot the convergence of the Gibbs sampler for signatures and exposures on separate charts.

**SignPlot:** Plot the mutational signatures in a bar chart, with error bars according to the variation of individual entries along the generated Gibbs samples.

**SignHeat:** Plot the mutation signatures in a heatmap.

**ExposureBarplot:** Barplot of estimated exposure values, showing the contribution of the signatures to the mutation counts of each genome sample.

**ExposureBoxplot:** Boxplot of exposure values, showing their variation along the generated Gibbs samples.

**ExposureHeat:** Plot a heatmap of the exposures, along with a dendrogram of the samples grouped by exposure levels.

### Usage

```
BICboxplot(signerOut, plot_to_file=FALSE, file="Model_selection_BICs.pdf")
## S4 method for signature 'SignExp'
Paths(signexp_obj, plot_to_file=FALSE,
      file_suffix="plot.pdf", plots_per_page=4, ...)
## S4 method for signature 'SignExp'
SignPlot(signexp_obj, plot_to_file=FALSE,
      file="Signature_plot.pdf", pal="bcr1", threshold=0, plots_per_page=4,
      gap=1, reord=NA, ...)
## S4 method for signature 'SignExp'
SignHeat(signexp_obj, plot_to_file=FALSE,
      file="Signature_heatmap.pdf", nbins=50, pal="roh", ...)
## S4 method for signature 'SignExp'
ExposureBarplot(signexp_obj, plot_to_file=FALSE,
      file="Exposure_barplot.pdf", col='tan2', threshold=0, relative=FALSE,
      title="", show_samples=NA, ...)
## S4 method for signature 'SignExp'
ExposureBoxplot(signexp_obj, plot_to_file=FALSE,
      file="Exposure_boxplot.pdf", col='tan2', threshold=0, show_samples=NA,
      plots_per_page=4, reord=NA, ...)
## S4 method for signature 'SignExp'
ExposureHeat(signexp_obj, plot_to_file=FALSE,
      file="Exposure_heatmap.pdf", nbins=50, pal="roh", distmethod="euclidean",
      clustermethod="complete", show_samples=NA, ...)
```

### Arguments

|                           |   |
|---------------------------|---|
| <code>signexp_obj</code>  | A <code>SignExp</code> object returned by <code>signer</code> function. e.g.: <code>sig\$SignExposures</code> |
| <code>signerOut</code>    | The list returned by the <code>signer</code> function.  |
| <code>plot_to_file</code> | Whether to save the plot to the file parameter. Default is <code>FALSE</code> .                               |
| <code>file</code>         | Output pdf file of the plots.   |

|                |   |
|----------------|---|
| pal            | Color palette used. Options are: "brew", "lba", "bcr1", "bcr2", "bw", "rdh", "roh", "blh" or "bph".   |
| threshold      | Entries below this value will be rounded to 0. Default is 0 (all entries are kept).   |
| plots_per_page | How many plots in a single page, default is 4.  |
| gap            | Distance between consecutive bars on the plot.  |
| reord          | Order of signatures for plotting. Should be a permutation of 1:nsig, where nsig is the number of signatures. By default, signatures are ordered by the total exposure, in decreasing order.   |
| nbins          | The range of signature entries is divided into this number of bins for plotting, each bin corresponding to a different color.   |
| file_suffix    | The suffix of the output file.  |
| col            | Single color name for boxplots.   |
| distmethod     | Distance measure used for grouping samples. Default is "euclidean", see the documentation of the dist function for other options.   |
| clustermethod  | Agglomeration method used for grouping samples. Default is "complete", see the documentation of the hclust function for other options.  |
| relative       | Whether to normalize exposures of each sample so that they sum up to one. Default is FALSE, thus generating a plot of absolute contributions of signatures to mutation counts. Otherwise, relative contributions will be displayed.   |
| title          | Main title added to the plot. Default is no title.  |
| show_samples   | Whether sample names will be shown in the plot. Default is NA, which leads to sample names being displayed only when there are less than 30 samples. However, even if show_samples=TRUE, due to display limitations sample names are not shown if there are more than 50 samples. |
| ...            | .   |

### Value

The plot result is exported to the current graphic device. If plot\_to\_file=TRUE, the plot is saved in the file defined by the file argument.

### Examples

```
# each plot function needs the SignExposures object
# which is part of the result of the signeR() call
SignPlot(signatures$SignExposures)
Paths(signatures$SignExposures)
# etc ...

# BICboxplot needs the returned list itself
BICboxplot(signatures)

# see also
vignette(package="signeR")
```

signeR

*signeR***Description**

Generates the signatures.

**Usage**

```
signeR(M, Mheader = TRUE, samples = "rows", Opport = NA,
       Oppheader = FALSE, P = NA, fixedP = FALSE,
       nsig = NA, nlim = c(NA, NA),
       try_all = FALSE, BICsignificance = FALSE, critical_p = 0.05,
       ap = NA, bp = NA, ae = NA, be = NA,
       lp = NA, le = NA, var.ap = 10, var.ae = 10,
       start = "lee", testing_burn = 1000, testing_eval = 1000,
       main_burn = 10000, main_eval = 2000,
       estimate_hyper = FALSE, EMit_lim=100, EM_eval = 100,
       parallelization = "multisession")
```

**Arguments**

|                 |  |
|-----------------|--|
| M               | mutation counts matrix of samples x features.  |
| Mheader         | if M has colnames defined use TRUE, if FALSE a default order will be assumed.  |
| samples         | if the samples are row-wise or column-wise in M, default is "row".   |
| Opport          | context count matrix of samples x features in the target genome or region.   |
| Oppheader       | if Opport has header defined.  |
| P               | Previously known matrix of signatures. If provided, can be fixed along algorithm iterations or just used as an initial value (see next parameter)  |
| fixedP          | If TRUE, provided P matrix will be fixed along iterations.   |
| nsig            | number of signatures, which can be provided or estimated by the algorithm.   |
| nlim            | define an interval to search for the optimal number of signatures.   |
| try_all         | if TRUE, all possible values for nsig will be tested   |
| BICsignificance | if TRUE, BICs will be considered different only if their distribution is significantly different. In case of ties in BICs comparison, signer will adopt the model with fewer signatures. |
| critical_p      | level of significance for BICs distribution to be considered different   |
| ap              | shape parameter of the gamma distribution used to generate the entries of a matrix of rate parameters of the gamma distributions which generate signatures.                              |
| bp              | rate parameter of the gamma distribution used to generate the entries of a matrix of rate parameters of the gamma distributions which generate signatures.                               |



|                 |  |
|-----------------|--|
| ae              | shape parameter of the gamma distribution used to generate the entries of a matrix of rate parameters of the gamma distributions which generate exposures.                                     |
| be              | rate parameter of the gamma distribution used to generate the entries of a matrix of rate parameters of the gamma distributions which generate exposures.                                      |
| lp              | parameter of the exponential distribution used to generate the entries of a matrix of shape parameters of the gamma distributions which generate signatures.                                   |
| le              | parameter of the exponential distribution used to generate the entries of a matrix of shape parameters of the gamma distributions which generate exposures.                                    |
| var.ap          | variance of the gamma distribution used to generate proposals for shape parameters of signatures   |
| var.ae          | variance of the gamma distribution used to generate proposals for shape parameters of exposures  |
| start           | NMF algorithm used to generate initial values for signatures and exposures, options: "brunet", "KL", "lee", "Frobenius", "offset", "nsNMF", "ls-nmf", "pe-nmf", "siNMF", "snmf/r" or "snmf/l". |
| testing_burn    | number of burning iterations of the Gibbs sampler used to estimate the number of signatures in data. Corresponds to R0 at Algorithm 1 on signeR paper.   |
| testing_eval    | number of iterations of the Gibbs sampler used to estimate the number of signatures in data. Corresponds to R2 at Algorithm 1 on signeR paper.   |
| EM_eval         | number of samples generated at each iteration of the EM algorithm. Corresponds to R1 at Algorithm 1 on signeR paper.   |
| main_burn       | number of burning iterations of the final Gibbs sampler.   |
| main_eval       | number of iterations of the final Gibbs sampler.   |
| estimate_hyper  | if TRUE, algorithm estimates optimal values of ap,bp,ae,be,lp,le. Start values can still be provided.  |
| EMit_lim        | limit of EM iterations for the estimation of hyper-hyperparameters ap,bp,ae,be,lp,le. Default is 100. Corresponds to U at Algorithm 1 on signeR paper.   |
| parallelization | strategy of computation parallelization, see future::plan help   |

## Value

signeR output is a list with the following items:

|               |  |
|---------------|--|
| Nsign         | selected number of signatures.   |
| tested_n      | array containing the numbers of signatures tested by the algorithm.                  |
| Test_BICs     | list of measured BIC values when testing different numbers of signatures.            |
| Phat          | Estimated signatures, median of P samples.   |
| Ehat          | Estimated exposures, median of E samples.  |
| SignExposures | SignExp object which contains the set of samples for the model parameters.           |
| Bics          | measured BIC values on the final run of the sampler.                                 |
| HyperParam    | evolution of estimated hyperparameters when testing different numbers of signatures. |

Examples

```
vignette(package="signer")
```

---

|            |  |
|------------|--|
| signerFlow | <i>Launch signerFlow R Shiny web app</i> |
|------------|--|

---

Description

Launch signerFlow R Shiny web app locally

Usage

```
signerFlow()
```

---

|         |                      |
|---------|----------------------|
| SignExp | <i>SignExp class</i> |
|---------|----------------------|

---

Description

Keep samples for signature and exposure matrices.

Value

Object fields:

- @Sign            array of signature matrix samples.
- @Exp            array of exposure matrix samples.
- @sigSums        Signature sums for each sample, organized by row. Normalizing factors.
- @samples        Genome sample IDs.
- @mutations     mutation names.
- @normalized    boolean variable, indicating whether Sign array has been normalized.

---

|                   |                                 |
|-------------------|---------------------------------|
| tcga_similarities | <i>TCGA Cosmic similarities</i> |
|-------------------|---------------------------------|

---

**Description**

TCGA Cosmic similarities calculated by signeR.

**Usage**

```
data("tcga_similarities")
```

**Format**

A data frame with 112 observations on the following 80 variables.

sigs a character vector  
project a character vector  
SBS1 a numeric vector  
SBS10a a numeric vector  
SBS10b a numeric vector  
SBS10c a numeric vector  
SBS10d a numeric vector  
SBS11 a numeric vector  
SBS12 a numeric vector  
SBS13 a numeric vector  
SBS14 a numeric vector  
SBS15 a numeric vector  
SBS16 a numeric vector  
SBS17a a numeric vector  
SBS17b a numeric vector  
SBS18 a numeric vector  
SBS19 a numeric vector  
SBS2 a numeric vector  
SBS20 a numeric vector  
SBS21 a numeric vector  
SBS22 a numeric vector  
SBS23 a numeric vector  
SBS24 a numeric vector  
SBS25 a numeric vector  
SBS26 a numeric vector

SBS27 a numeric vector  
SBS28 a numeric vector  
SBS29 a numeric vector  
SBS3 a numeric vector  
SBS30 a numeric vector  
SBS31 a numeric vector  
SBS32 a numeric vector  
SBS33 a numeric vector  
SBS34 a numeric vector  
SBS35 a numeric vector  
SBS36 a numeric vector  
SBS37 a numeric vector  
SBS38 a numeric vector  
SBS39 a numeric vector  
SBS4 a numeric vector  
SBS40 a numeric vector  
SBS41 a numeric vector  
SBS42 a numeric vector  
SBS43 a numeric vector  
SBS44 a numeric vector  
SBS45 a numeric vector  
SBS46 a numeric vector  
SBS47 a numeric vector  
SBS48 a numeric vector  
SBS49 a numeric vector  
SBS5 a numeric vector  
SBS50 a numeric vector  
SBS51 a numeric vector  
SBS52 a numeric vector  
SBS53 a numeric vector  
SBS54 a numeric vector  
SBS55 a numeric vector  
SBS56 a numeric vector  
SBS57 a numeric vector  
SBS58 a numeric vector  
SBS59 a numeric vector  
SBS6 a numeric vector

SBS60 a numeric vector  
SBS7a a numeric vector  
SBS7b a numeric vector  
SBS7c a numeric vector  
SBS7d a numeric vector  
SBS8 a numeric vector  
SBS84 a numeric vector  
SBS85 a numeric vector  
SBS86 a numeric vector  
SBS87 a numeric vector  
SBS88 a numeric vector  
SBS89 a numeric vector  
SBS9 a numeric vector  
SBS90 a numeric vector  
SBS91 a numeric vector  
SBS92 a numeric vector  
SBS93 a numeric vector  
SBS94 a numeric vector

---

|             |  |
|-------------|--|
| tcga_tumors | <i>TCGA tumors used on TCGA Explorer</i> |
|-------------|--|

---

**Description**

List of TCGA tumors used on TCGA Explorer

**Usage**

```
data("tcga_tumors")
```

**Format**

A data frame with 37 observations on the following 2 variables.

projectID a character vector  
projectName a character vector

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