# Package 'mSigAct'

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```
Title Mutational Signature Activity Analysis ('mSigAct')

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```

Description Analyze the ``activities" of mutational signatures in one or more mutational spectra. 
'mSigAct' stands for mutational Signature Activity. mSigAct uses a maximum likelihood approach to estimate (conservatively) whether there is evidence that a particular set of mutational signatures is present in a spectrum. It can also determine a \*minimal\* subset of signatures needed to plausibly reconstruct an observed spectrum. This sparse assign signatures functionality is \*deliberately biased\* toward using as few signatures as possible. There is also functionality to do a maximum a posteriori estimate of signature activity, which makes use of information on the proportion of tumors in a given type that have a particular signature combined with the likelihood that a particular combination of signatures generated an observed spectrum.

```
License GPL-3
URL https://github.com/steverozen/mSigAct
BugReports https://github.com/steverozen/mSigAct/issues
Encoding UTF-8
Language en-US
Depends R (>= 4.0),
RoxygenNote 7.2.2
biocViews
Imports dplyr,
     ICAMS (>= 2.3.5.9002),
     lsa,
     nloptr,
     PCAWG7 (>= 0.1.0.9003),
     philentropy,
     quadprog,
     stats,
     sets,
     tibble,
     utils
```

**Remotes** github::steverozen/ICAMS@master, github::steverozen/PCAWG7@master

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```
Suggests BSgenome.Hsapiens.1000genomes.hs37d5, devtools, htmlwidgets, ipc, knitr, profvis, rmarkdown, testthat (>= 2.1.0), usethis
```

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Return a character vector of some common cancer types

## Description

CancerTypes

Return a character vector of some common cancer types

## Usage

```
CancerTypes()
```

## **Examples**

```
cancer.types <- CancerTypes()</pre>
```

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cossim

Cosine similarity with useful argument types

## Description

Calls cosine.

#### Usage

```
cossim(v1, v2)
```

## **Arguments**

v1 A vector or single-column matrix v2 A vector or single-column matrix

## **Examples**

DefaultManyOpts

Set default options for many functions, especially nloptr

## Description

Set default options for many functions, especially nloptr

## Usage

```
DefaultManyOpts(likelihood.dist = "multinom")
```

#### **Arguments**

```
likelihood.dist
```

The probability distribution used to calculate the likelihood, can be either "multinom" (multinomial distribution) or "neg.binom" (negative binomial distribution).

**ExposureProportions** 

#### Value

A list with the following elements

**global.opts** A sub-list with several options for nloptr, q.v., for the global optimization phase.

**local.opts** A sub-list with several options for nloptr, q.v., for the local optimization phase.

**nbinom.size** Only appearing if likelihood.dist = "neg.binom". The dispersion parameter for the negative binomial distribution; smaller is more dispersed. See NegBinomial.

**trace** If > 0 print progress messages.

**global\_eval\_f** The objective function for the global optimization phase.

**local\_eval\_f** The objective function for the local optimization phase.

**local\_eval\_g\_ineq** The inequality constraint function for the local optimization phase.

**likelihood.dist** The probability distribution used to calculate the likelihood.

#### **Examples**

```
my.opts <- DefaultManyOpts()
my.opts$trace <- 10</pre>
```

ExposureProportions

Return the proportions of tumors of a given cancer type that have a particular signature

## Description

Return the proportions of tumors of a given cancer type that have a particular signature

#### Usage

```
ExposureProportions(
  mutation.type,
  cancer.type,
  all.sigs = NULL,
  drop.sigs.no.info = TRUE,
  must.include = character(),
  must.include.prop = 0.1
)
```

#### Arguments

```
mutation.type
A character string, one of "SBS96", "SBS192", "ID", "DBS78".

cancer.type A character string. For some common cancer types, see CancerTypes for more details.

all.sigs An optional matrix of known signatures, with column names being signatures ids. Only used to drop signatures not present in all.sigs.

drop.sigs.no.info
    If TRUE, drop signatures not present in the column names of all.sigs.
```

must.include A character vector of signature IDs that must be included, even if they have not previously been observed in that cancer type. The associated proportion is specified by must.include.prop.

```
must.include.prop
```

The value used for the expected proportion of signatures in must.include but not previously observed in the given cancer.type.

#### Value

A numerical vector of the proportion of tumors of type cancer.type with each signature for those signatures observed in cancer. type. The names are the signature ids.

## **Examples**

```
cancer.types <- CancerTypes()</pre>
cancer.types
sigs.prop <- ExposureProportions(mutation.type = "SBS96",</pre>
                                    cancer.type = "Lung-AdenoCA")
```

LLHSpectrumMultinom

Likelihood that 1 observed spectrum was generated from a vector of expected mutation counts using multinomial distribution

## **Description**

Likelihood that 1 observed spectrum was generated from a vector of expected mutation counts using multinomial distribution

#### Usage

```
LLHSpectrumMultinom(spectrum, expected.counts, verbose = FALSE)
```

#### **Arguments**

spectrum An observed spectrum (a numeric vector) expected.counts

> A vector of expected mutation counts, one expected count for each mutation type. We want to know the likelihood that this model generated the observed spectrum, assuming each mutational type generates counts according to a multinomial distribution with the given expected.counts (argument prob to

Multinom).

If TRUE print messages under some circumstances. verbose

#### Value

log(likelihood(spectrum | expected.counts)), or, in more detail, the multinomial likelihood that each element of the spectrum (i.e., the count for each mutation type e.g. ACT > AAT) was generated from the expected count for that mutation type using multinomial distribution. 6 MAPAssignActivity

#### **Description**

This function also can do sparse assignment by specifying use.sparse.assign = TRUE.

#### Usage

```
MAPAssignActivity(
  spectra,
  sigs,
  sigs.presence.prop,
  output.dir,
  max.level = 5,
  p.thresh = 0.05,
  m.opts = DefaultManyOpts(),
  num.parallel.samples = 5,
  mc.cores.per.sample = min(20, 2^max.level),
  progress.monitor = NULL,
  seed = NULL,
  max.subsets = 1000,
  use.sparse.assign = FALSE,
  drop.low.mut.samples = TRUE
)
```

#### **Arguments**

The spectra (multiple spectra) to be reconstructed. spectra A numerical matrix, possibly an ICAMS catalog. sigs sigs.presence.prop The proportions of samples that contain each signature. A numerical vector (values between 0 and 1), with names being a subset of colnames (sigs). See ExposureProportions for more details. output.dir Directory path to save the output file. max.level The maximum number of signatures to try removing. p.thresh If the p value for a better reconstruction with a set of signatures (as opposed to without that set of signatures) is > than this argument, then we can use exposures without this set. See DefaultManyOpts. m.opts num.parallel.samples The (maximum) number of samples to run in parallel. On Microsoft Windows machines it is silently changed to 1. Each sample in turn can require multiple

machines it is silently changed to 1. Each sample in turn can require multiple cores, as governed by mc.cores.per.sample.

```
{\tt mc.cores.per.sample}
```

The maximum number of cores to use for each sample. On Microsoft Windows machines it is silently changed to 1.

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progress.monitor

Function called at the start of each new level (number of signatures to try excluding). Must take named arguments value and detail, and no others. Designed for a AsyncProgress progress bar function.

seed

Random seed; set this to get reproducible results. (The numerical optimization is in two phases; the first, global phase might rarely find different optima depending on the random seed.)

max.subsets

This argument provides a way to heuristically limit the amount of time spent by this function. Larger values of this argument will tend to allow longer running times. The algorithm successively tries to remove all subsets of 1 signature, 2 signatures, 3 signatures, etc., down to max.level. (Not every subset is tested at each level; if a subset was already found to be necessary the algorithm does not test supersets of that subset.) If at any level the algorithm needs to test more than max.subsets this function will not proceed.

use.sparse.assign

Whether to use sparse assignment. If TRUE, arguments designed for Maximum A Posteriori assignment such as sigs.presence.prop will be ignored.

drop.low.mut.samples

Whether to exclude low mutation samples from the analysis. If  $\mathtt{TRUE}$  ( $\mathtt{default}$ ), samples with SBS total mutations less than 100, DBS or ID total mutations less than 25 will be dropped.

#### Value

A list with the elements:

- proposed.assignment: Proposed signature assignment for spectra with the highest MAP found. If use.sparse.assign = TRUE, this will be the most sparse set of signatures that can plausibly explain spectra.
- proposed.reconstruction: Proposed reconstruction of spectra based on MAP. If use.sparse.assign = TRUE, this will be the reconstruction based on sparse assignment.
- reconstruction.distances: Various distances and similarities between spectra and proposed.reconstruction.
- all.tested: All tested possible ways to reconstruct each sample in spectra.
- alt.solutions: A tibble showing all the alternative solutions that are statistically as good as the proposed.assignment that can plausibly reconstruct spectra.
- time.for.assignment: Value from system.time for running MAPAssignActivity1 for each sample in spectra.
- error.messages: Only appearing if there are errors running MAPAssignActivity.

The elements proposed.assignment, proposed.reconstruction, reconstruction.distances, all.tested, time.for.assignment will be NULL if the algorithm could not find the optimal reconstruction or there are errors coming out for all samples.

#### **Examples**

```
## Not run:
# This is a long running example unless parallel computing is supported on your machine
indices <- grep("Lung-AdenoCA", colnames(PCAWG7::spectra$PCAWG$SBS96))
spectra <- PCAWG7::spectra$PCAWG$SBS96[, indices[1:2], drop = FALSE]
sigs <- PCAWG7::signature$genome$SBS96</pre>
```

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PlotExposure

Plot exposures in multiple plots each with a manageable number of samples

#### **Description**

Plot exposures in multiple plots each with a manageable number of samples

## Usage

```
PlotExposure(
   exposure,
   samples.per.line = 30,
   plot.proportion = FALSE,
   xlim = NULL,
   ylim = NULL,
   legend.x = NULL,
   legend.y = NULL,
   cex.legend = 0.9,
   cex.yaxis = 1,
   cex.xaxis = NULL,
   plot.sample.names = TRUE,
   yaxis.labels = NULL,
   ...
)
```

## **Arguments**

exposure

Exposures as a numerical matrix (or data.frame) with signatures in rows and samples in columns. Rownames are taken as the signature names and column names are taken as the sample IDs. If you want exposure sorted from largest to smallest, use SortExposure. Do not use column names that start with multiple underscores. The exposures will often be mutation counts, but could also be e.g. mutations per megabase.

samples.per.line

Number of samples to show in each plot.

plot.proportion

Plot exposure proportions rather than counts.

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xlim, ylim	Limits for the x and y axis. If NULL(default), the function tries to do something reasonable.			
legend.x, leg	The x and y co-ordinates to be used to position the legend.			
cex.legend	A numerical value giving the amount by which legend plotting text and symbols should be magnified relative to the default.			
cex.yaxis	A numerical value giving the amount by which y axis values should be magnified relative to the default.			
cex.xaxis	A numerical value giving the amount by which x axis values should be magnified relative to the default. If NULL(default), the function tries to do something reasonable.			
plot.sample.names				
	Whether to plot sample names below the x axis. Default is TRUE.			
yaxis.labels	User defined y axis labels to be plotted. If $\mathtt{NULL}(default)$ , the function tries to do something reasonable.			
•••	Other arguments passed to barplot. If ylab is not included, it defaults to a value depending on plot.proportion. If col is not supplied the function tries to do something reasonable.			

#### Value

An **invisible** list whose first element is a logic value indicating whether the plot is successful. The second element is a numeric vector giving the coordinates of all the bar midpoints drawn, useful for adding to the graph.

## **Examples**

 $\begin{array}{ll} {\tt PlotExposureToPdf} & {\tt Plot\ exposures\ in\ multiple\ plots\ each\ with\ a\ manageable\ number\ of} \\ {\tt samples\ to\ PDF} \end{array}$ 

#### **Description**

Plot exposures in multiple plots each with a manageable number of samples to PDF

#### Usage

```
PlotExposureToPdf(
  exposure,
  file,
  mfrow = c(2, 1),
```

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```
mar = c(6, 4, 3, 2),
  oma = c(3, 2, 0, 2),
  samples.per.line = 30,
  plot.proportion = FALSE,
  xlim = NULL,
  ylim = NULL
  legend.x = NULL,
  legend.y = NULL,
  cex.legend = 0.9,
  cex.yaxis = 1,
  cex.xaxis = NULL,
  plot.sample.names = TRUE,
  yaxis.labels = NULL,
 width = 8.2677,
 height = 11.6929,
  . . .
)
```

#### **Arguments**

exposure Exposures as a numerical matrix (or data.frame) with signatures in rows and samples in columns. Rownames are taken as the signature names and col-

umn names are taken as the sample IDs. If you want exposure sorted from largest to smallest, use SortExposure. Do not use column names that start with multiple underscores. The exposures will often be mutation counts, but

could also be e.g. mutations per megabase.

file The name of the PDF file to be produced.

mfrow A vector of the form c (nr, nc). Subsequent figures will be drawn in an nr-

by-nc array on the device by rows.

mar A numerical vector of the form c (bottom, left, top, right) which gives

the number of lines of margin to be specified on the four sides of the plot.

oma A vector of the form c (bottom, left, top, right) giving the size of the

outer margins in lines of text.

samples.per.line

Number of samples to show in each plot.

plot.proportion

Plot exposure proportions rather than counts.

xlim, ylim Limits for the x and y axis. If NULL(default), the function tries to do something

reasonable.

legend.x, legend.y

The x and y co-ordinates to be used to position the legend.

cex.legend A numerical value giving the amount by which legend plotting text and symbols

should be magnified relative to the default.

cex.yaxis A numerical value giving the amount by which y axis values should be magnified

relative to the default.

cex.xaxis A numerical value giving the amount by which x axis values should be magni-

fied relative to the default. If NULL(default), the function tries to do something

reasonable.

plot.sample.names

Whether to plot sample names below the x axis. Default is TRUE.

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yaxis.labels User defined y axis labels to be plotted. If  $\mathtt{NULL}(default)$ , the function tries to do something reasonable.

width, height

The width and height of the graphics region in inches.

Other arguments passed to barplot. If ylab is not included, it defaults to a value depending on plot.proportion. If col is not supplied the function tries to do something reasonable.

#### Value

An **invisible** list whose first element is a logic value indicating whether the plot is successful. The second element is a numeric vector giving the coordinates of all the bar midpoints drawn, useful for adding to the graph.

#### **Examples**

PossibleArtifacts Return a character vector of the IDs of possible SBS96 signature artifacts.

## Description

Return a character vector of the IDs of possible SBS96 signature artifacts.

#### Usage

```
PossibleArtifacts()
```

## **Examples**

```
artifact.sigs <- PossibleArtifacts()</pre>
```

RareSignatures

Return a character vector of the IDs of rare SBS96 signatures.

#### **Description**

Return a character vector of the IDs of rare SBS96 signatures.

#### Usage

```
RareSignatures()
```

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ReadExposure	
ICAGEAPOSAIC	

Read an exposure matrix from a file

## Description

Read an exposure matrix from a file

#### Usage

```
ReadExposure(file, check.names = FALSE)
```

#### **Arguments**

file

CSV file containing an exposure matrix.

check.names

Passed to read.csv. **IMPORTANT**: If TRUE this will replace the double colon in identifiers of the form <tumor\_type>::<sample\_id> with two periods (i.e. <tumor\_type>..<sample\_id>. If check.names is true, generate a warning if double colons were present.

Matrix of exposures.

#### **Examples**

Value

ReconstructSpectrum

Given signatures (sigs) and exposures (exp), return a spectrum or spectra

#### **Description**

Given signatures (sigs) and exposures (exp), return a spectrum or spectra

## Usage

```
ReconstructSpectrum(sigs, exp, use.sig.names = FALSE)
```

## Arguments

sigs Signature as a matrix or data frame, with each row one mutation type (e.g. CCT

> CAT or CC > TT) and each column a signature.

exp The exposures for one or more samples as a matrix or data.frame, with each row

a signature and each column a sample.

use.sig.names

If TRUE check that rownames (exp) is a subset of colnames (sigs), and use only the columns in sigs that are present in exp.

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#### **Details**

Does not care or check if colSums (sigs) == 1. Error checking is minimal since this function is called often.

#### Value

The matrix product sigs % \* % exp after some error checking.

#### **Examples**

SignaturePresenceTest

Test whether a given signature is plausibly present in a catalog.

#### **Description**

Test whether a given signature is plausibly present in a catalog.

## Usage

```
SignaturePresenceTest(
   spectra,
   sigs,
   target.sig.index,
   m.opts = DefaultManyOpts(),
   seed = NULL,
   mc.cores = 2
)
```

#### **Arguments**

spectra	The catalog (matrix) to analyze. This could be an ICAMS catalog or a numerical matrix.		
sigs	A catalog of signatures from which to choose. This could be and ICAMS catalog or a numerical matrix.		
target.sig.index			
	The index of the signature the presence of which we want to test. It can also be the signature id (e.g. "SBS22").		
m.opts	See DefaultManyOpts.		
seed	Random seed; set this to get reproducible results. (The numerical optimization is in two phases; the first, global phase might rarely find different optima depending on the random seed.)		
mc.cores	Number of cores to use. Always silently changed to 1 on Microsoft Windows.		

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#### Value

A list of test results for each sample in spectra. Each sublist contains the following elements:

- loglh.with: The maximum log likelihood of the reconstructed spectrum using all the signatures.
- loglh.without: The maximum log likelihood of the reconstructed spectrum without the target signature.
- statistic: Likelihood ratio test statistic.
- chisq.p: P-value of the likelihood ratio test. The null hypothesis is we can plausibly reconstruct the spectrum without the target signature.
- exp.with: The exposure using all the signatures which generates the maximum log likelihood loglh.with.
- exp.without: The exposure not using the target signature which generates the maximum log likelihood loglh.without.

#### **Examples**

SortExposure

Sort columns of an exposure matrix from largest to smallest (or vice versa)

#### **Description**

Sort columns of an exposure matrix from largest to smallest (or vice versa)

## Usage

```
SortExposure(exposure, decreasing = TRUE)
```

## Arguments

Exposure Exposures as a numerical matrix (or data.frame) with signatures in rows and samples in columns. Rownames are taken as the signature names and column names are taken as the sample IDs.

decreasing If TRUE, sort from largest to smallest.

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#### Value

The original exposure with columns sorted.

#### **Examples**

SparseAssignActivity

Find known signatures that can most sparsely reconstruct each spectrum in a catalog.

#### **Description**

Find known signatures that can most sparsely reconstruct each spectrum in a catalog.

#### Usage

```
SparseAssignActivity(
   spectra,
   sigs,
   output.dir,
   max.level = 5,
   p.thresh = 0.05,
   m.opts = DefaultManyOpts(),
   num.parallel.samples = 5,
   mc.cores.per.sample = min(20, 2^max.level),
   progress.monitor = NULL,
   seed = NULL,
   max.subsets = 1000,
   drop.low.mut.samples = TRUE
)
```

## **Arguments**

```
The spectra (multiple spectra) to be reconstructed.

sigs A numerical matrix, possibly an ICAMS catalog.

output.dir Directory path to save the output file.

max.level The maximum number of signatures to try removing.

p.thresh If the p value for a better reconstruction with a set of signatures (as opposed to without that set of signatures) is > than this argument, then we can use exposures without this set.

m.opts See DefaultManyOpts.
```

num.parallel.samples

The (maximum) number of samples to run in parallel. On Microsoft Windows machines it is silently changed to 1. Each sample in turn can require multiple cores, as governed by mc.cores.per.sample.

mc.cores.per.sample

The maximum number of cores to use for each sample. On Microsoft Windows machines it is silently changed to 1.

progress.monitor

Function called at the start of each new level (number of signatures to try excluding). Must take named arguments value and detail, and no others. Designed for a AsyncProgress progress bar function.

seed

Random seed; set this to get reproducible results. (The numerical optimization is in two phases; the first, global phase might rarely find different optima depending on the random seed.)

max.subsets

This argument provides a way to heuristically limit the amount of time spent by this function. Larger values of this argument will tend to allow longer running times. The algorithm successively tries to remove all subsets of 1 signature, 2 signatures, 3 signatures, etc., down to max.level. (Not every subset is tested at each level; if a subset was already found to be necessary the algorithm does not test supersets of that subset.) If at any level the algorithm needs to test more than max.subsets this function will not proceed.

drop.low.mut.samples

Whether to exclude low mutation samples from the analysis. If  $\mathtt{TRUE}$  ( $\mathtt{default}$ ), samples with SBS total mutations less than 100, DBS or ID total mutations less than 25 will be dropped.

#### Value

A list with the elements:

- proposed.assignment: The most sparse set of signatures that can plausibly explain spectra.
- proposed.reconstruction: The reconstruction based on sparse assignment.
- reconstruction.distances: Various distances and similarities between spectra and proposed.reconstruction.
- all.tested: All tested possible ways to reconstruct each sample in spectra.
- alt.solutions: A tibble showing all the alternative solutions that are statistically as good as the proposed.assignment that can plausibly reconstruct spectra.
- time.for.assignment: Value from system.time for running SparseAssignActivity for each sample in spectra.
- $\bullet \ \, \text{error.messages: Only appearing if there are errors running } \, \text{SparseAssignActivity.}$

The elements proposed.assignment, proposed.reconstruction, reconstruction.distances, all.tested, time.for.assignment will be NULL if the algorithm could not find the optimal reconstruction or there are errors coming out for all samples.

## Examples

```
## Not run:
```

# This is a long running example unless parallel computing is supported on your machine indices <- grep("Lung-AdenoCA", colnames(PCAWG7::spectra\$PCAWG\$SBS96))

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WriteExposure

Write an exposure matrix to a file

#### **Description**

Write an exposure matrix to a file

#### Usage

```
WriteExposure(exposure, file, row.names = TRUE)
```

## **Arguments**

exposure	Exposures as a numerical matrix (or data.frame) with signatures in rows and
	samples in columns. Rownames are taken as the signature names and column
	names are taken as the sample IDs.
file	File to which to write the exposure matrix (as a CSV file).
row.names	Either a logical value indicating whether the row names of exposure are to be
	written along with exposure, or a character vector of row names to be written.

## **Examples**

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