

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.

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URL <https://github.com/steverozen/mSigAct>

BugReports <https://github.com/steverozen/mSigAct/issues>

Encoding UTF-8

LazyData true

Language en-US

Depends R (>= 4.0),

RoxygenNote 7.1.2

VignetteBuilder knitr

biocViews

Imports dplyr,
ICAMS (>= 2.3.5.9002),
ICAMSextra (>= 0.0.3.9999),
lsa,
nloptr,
PCAWG7 (>= 0.1.0.9003),
philentropy,
quadprog,
stats,
sets,
tibble,
utils

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

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

R topics documented:

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CancerTypes	<i>Return a character vector of some common cancer types</i>
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Description

Return a character vector of some common cancer types

Usage

CancerTypes()

Examples

cancer.types <- CancerTypes()

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

```
spectrum <- PCAWG7::spectra$PCAWG$SBS96[, 1, drop = FALSE]
SBS96.sigs <- PCAWG7::signature$genome$SBS96
exposure <- PCAWG7::exposure$PCAWG$SBS96[, 1, drop = FALSE]
reconstructed.spectrum <- ReconstructSpectrum(sigs = SBS96.sigs,
                                              exp = exposure,
                                              use.sig.names = TRUE)
cosine <- cossim(spectrum, reconstructed.spectrum)
```

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).

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
```

ExposureProportions	<i>Return the proportions of tumors of a given cancer type that have a particular signature</i>
---------------------	---

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

<code>mutation.type</code>	A character string, one of "SBS96", "SBS192", "ID", "DBS78".
<code>cancer.type</code>	A character string. For some common cancer types, see CancerTypes for more details.
<code>all.sigs</code>	An optional matrix of known signatures, with column names being signature ids. Only used to drop signatures not present in <code>all.sigs</code> .
<code>drop.sigs.no.info</code>	If TRUE, drop signatures not present in the column names of <code>all.sigs</code> .
<code>must.include</code>	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 <code>must.include.prop</code> .

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

LLHSpectrumMultinom	<i>Likelihood that 1 observed spectrum was generated from a vector of expected mutation counts using multinomial distribution</i>
---------------------	---

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

<code>spectrum</code>	An observed spectrum (a numeric vector)
<code>expected.counts</code>	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 <code>expected.counts</code> (argument <code>prob</code> to Multinom).
<code>verbose</code>	If TRUE print messages under some circumstances.

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.

MAPAssignActivity	<i>Find Maximum A Posteriori (MAP) assignment of signature exposures that explain multiple spectra</i>
-------------------	--

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

<code>spectra</code>	The spectra (multiple spectra) to be reconstructed.
<code>sigs</code>	A numerical matrix, possibly an ICAMS catalog.
<code>sigs.presence.prop</code>	The proportions of samples that contain each signature. A numerical vector (values between 0 and 1), with names being a subset of <code>colnames(sigs)</code> . See ExposureProportions for more details.
<code>output.dir</code>	Directory path to save the output file.
<code>max.level</code>	The maximum number of signatures to try removing.
<code>p.thresh</code>	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.
<code>m.opts</code>	See DefaultManyOpts .
<code>num.parallel.samples</code>	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 <code>mc.cores.per.sample</code> .
<code>mc.cores.per.sample</code>	The maximum number of cores to use for each sample. On Microsoft Windows machines it is silently changed to 1.

<code>progress.monitor</code>	Function called at the start of each new level (number of signatures to try excluding). Must take named arguments <code>value</code> and <code>detail</code> , and no others. Designed for a AsyncProgress progress bar function.
<code>seed</code>	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.)
<code>max.subsets</code>	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 <code>max.level</code> . (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 <code>max.subsets</code> this function will not proceed.
<code>use.sparse.assign</code>	Whether to use sparse assignment. If TRUE, arguments designed for Maximum A Posteriori assignment such as <code>sigs.presence.prop</code> will be ignored.
<code>drop.low.mut.samples</code>	Whether to exclude low mutation samples from the analysis. If TRUE (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
sigs.prop <- ExposureProportions(mutation.type = "SBS96",
```

```

                                cancer.type = "Lung-AdenoCA")
MAP.out <- MAPAssignActivity(spectra = spectra,
                            sigs = sigs,
                            sigs.presence.prop = sigs.prop,
                            output.dir = file.path(tempdir(), "Lung-AdenoCA"),
                            max.level = length(sigs.prop) - 1,
                            p.thresh = 0.05 / ncol(spectra),
                            num.parallel.samples = 2,
                            mc.cores.per.sample = 10)

## End(Not run)

```

PossibleArtifacts	<i>Return a character vector of the IDs of possible SBS96 signature artifacts.</i>
-------------------	--

Description

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

Usage

```
PossibleArtifacts()
```

Examples

```
artifact.sigs <- PossibleArtifacts()
```

RareSignatures	<i>Return a character vector of the IDs of rare SBS96 signatures.</i>
----------------	---

Description

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

Usage

```
RareSignatures()
```

ReconstructSpectrum	<i>Given signatures (sigs) and exposures (exp), return a spectrum or spectra</i>
---------------------	--

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.

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

```
spectra <- PCAWG7::spectra$PCAWG$SBS96[, 1:2, drop = FALSE]
SBS96.sigs <- PCAWG7::signature$genome$SBS96
exposure <- PCAWG7::exposure$PCAWG$SBS96[, 1:2, drop = FALSE]
reconstructed.spectra <- ReconstructSpectrum(sigs = SBS96.sigs,
                                             exp = exposure,
                                             use.sig.names = TRUE)
```

SignaturePresenceTest	<i>Test whether a given signature is plausibly present in a catalog.</i>
-----------------------	--

Description

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

Usage

```
SignaturePresenceTest(
  spectra,
  sigs,
  target.sig.index,
  m.opts = NULL,
  seed = NULL,
  mc.cores = 10
)
```

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 an ICAMS catalog or a numerical matrix.
target.sig.index	The index of the signature the presence of which we want to test.
m.opts	If NULL use the return from calling DefaultManyOpts . For documentation 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.

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

```
indices <- grep("Lung-AdenoCA", colnames(PCAWG7::spectra$PCAWG$SBS96))
spectra <- PCAWG7::spectra$PCAWG$SBS96[, indices[1:2], drop = FALSE]
sigs <- PCAWG7::signature$genome$SBS96
sigs.prop <- ExposureProportions(mutation.type = "SBS96",
                                cancer.type = "Lung-AdenoCA")
sigs.to.use <- sigs[, names(sigs.prop), drop = FALSE]
# Test whether SBS17a is plausibly present in the spectra
sig.index <- which(colnames(sigs.to.use) == "SBS17a")
```

```
sig.presence.test.out <- SignaturePresenceTest(spectra = spectra,
                                              sigs = sigs.to.use,
                                              target.sig.index = sig.index,
                                              seed = 2581,
                                              mc.cores = 2)
```

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

<code>spectra</code>	The spectra (multiple spectra) to be reconstructed.
<code>sigs</code>	A numerical matrix, possibly an ICAMS catalog.
<code>output.dir</code>	Directory path to save the output file.
<code>max.level</code>	The maximum number of signatures to try removing.
<code>p.thresh</code>	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.
<code>m.opts</code>	See DefaultManyOpts .
<code>num.parallel.samples</code>	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 <code>mc.cores.per.sample</code> .
<code>mc.cores.per.sample</code>	The maximum number of cores to use for each sample. On Microsoft Windows machines it is silently changed to 1.


```
num.parallel.samples = 2,  
mc.cores.per.sample = 30,  
seed = 2561)  
  
## End(Not run)
```

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