Package 'mSigAct'

February 26, 2021

Title mutational Signature Activity analysis ('mSigAct')

Version 2.0.10.9001

```
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Description Analyze the ``activities" of mutational signatures in one or more mutational spectra.
      'mSigAct' stands for mutational Signature Activity. mSigAct can 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. This package does not
      provide all-purpose estimation for signature attribution.
License GPL-3
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 7.1.1
VignetteBuilder knitr
biocViews
Imports dplyr,
      ICAMS,
      ICAMSxtra,
      lsa,
      nloptr,
      PCAWG7,
      philentropy,
      quadprog,
      rlang,
      stats,
      sets,
      tibble,
      utils
```

cossim

2										
Remotes github::steverozen/ICAMS github::steverozen/ICAMS github::steverozen/PCAW	Sxtra@maste									
Suggests BSgenome.Hsapiens.1 devtools, htmlwidgets, knitr, profvis, rmarkdown, testthat (>= 2.1.0), usethis	1000genome	s.hs	37	d5,						
R topics documented	:									
cossim										
LLHSpectrumMAP . LLHSpectrumNegBind										
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cossim

Cosine similarity with useful argument types..

Description

Calls cosine.

Usage

cossim(v1, v2)

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Arguments

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

DefaultManyOpts

Set default options for many functions, especially nloptr.

Description

Set default options for many functions, especially nloptr.

Usage

```
DefaultManyOpts()
```

Value

A list with the following elements

global.opts A sub-list with several options for nloptr, q.v., for the global optimization phase, including eval_f, the objective function.

local.opts A sub-list with several options for nloptr, q.v., for the local optimization phase, including eval_f, the objective function and the inequality constraint function eval_g_ineq

nbinom.size The dispersion parameter for the negative binomial distribution; smaller is more dispersed. See NegBinomial.

trace If > 0 print progress messages.

 ${\tt Exposure Proportions}$

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

```
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.

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.

g_ineq_for_ObjFnBinomMaxLH2

Function to constrain the sum of estimated exposures to the number of mutations in the spectrum.

Description

See nloptr to understand how this function is used.

Usage

```
g_ineq_for_ObjFnBinomMaxLH2(exp, spectrum, sigs, nbinom.size)
```

Arguments

exp A numeric vector of exposures.

spectrum The observed spectrum we are trying to reconstruct.

sigs The signatures with which we are trying to reconstruct the spectrum. (Ignored

in this function but used by nloptr.)

nbinom. size Dispersion parameter. (Ignored in this function but used by nloptr.)

LLHSpectrumMAP 5

LLHSpectrumMAP	Likelihood that 1 observed spectrum was generated from a vector of expected mutation counts using prior information of the signature
	presence proportions

Description

Likelihood that 1 observed spectrum was generated from a vector of expected mutation counts using prior information of the signature presence proportions

Usage

```
LLHSpectrumMAP(
   spectrum,
   expected.counts,
   nbinom.size,
   model,
   sigs.presence.prop,
   verbose = FALSE
)
```

Arguments

spectrum An observed spectrum (a numeric vector).

expected.counts

A vector of (integer) 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 types generates counts according to a negative binomial distribution with the given expected.counts (argument mu to NegBinomial) and dispersion parameter nbinom.size.

nbinom.size

mode1

The dispersion parameter for the negative binomial distribution; smaller is more dispersed. See NegBi nomial

dispersed. See NegBinomial.

sigs.presence.prop

The proportions of samples that contain each signature. A numerical vector

(values between 0 and 1), with names being a superset of model.

Names of sigs present in the MAP exposure. Do not use indices.

verbose If TRUE print messages under some circumstances.

Value

 $\label{log(likelihood(spectrum \mid expected.counts)) + log(probability(model \mid sigs.presence.prop)),} or, in more detail, the sum of the negative binomial likelihoods that each element of the spectrum (i.e., the count for each mutation type e.g. ACT > AAT) was generated from the expected count for that mutation type plus the probability of the signature model used in the reconstruction given the prior sigs.presence.prop.$

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LLHSpectrumNegBinom	Likelihood that 1 observed spectrum was generated from a vector of
	expected mutation counts.

Description

Likelihood that 1 observed spectrum was generated from a vector of expected mutation counts.

Usage

LLHSpectrumNegBinom(spectrum, expected.counts, nbinom.size, verbose = FALSE)

Arguments

spectrum An observed spectrum (a numeric vector)

expected.counts

A vector of (integer) 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 types generates counts according to a negative binomial distribution with the given expected.counts (argument mu to NegBinomial) and dispersion parameter nbinom.size.

The dispersion parameter for the negative binomial distribution; smaller is more dispersed. See NegBinomial.

verbose If TRUE print messages under some circumstances.

Value

log(likelihood(spectrum | expected.counts)), or, in more detail, the sum of the negative binomial likelihoods 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.

MAPAssignActivity Find Maximum A Posteriori (MAP) assignment of signature exposures that explain multiple spectra

Description

Find Maximum A Posteriori (MAP) assignment of signature exposures that explain multiple spectra

```
MAPAssignActivity(
  spectra,
  sigs,
  sigs.presence.prop,
  output.dir,
  max.level = 5,
  p.thresh = 0.05,
  m.opts = DefaultManyOpts(),
```

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```
num.parallel.samples = 5,
mc.cores.per.sample = min(20, 2^max.level),
max.subsets = 1000,
max.presence.proportion = 0.99,
progress.monitor = NULL,
seed = NULL
)
```

Arguments

spectra The spectra (multiple spectra) to be reconstructed.

sigs A numerical matrix, possibly an ICAMS catalog.

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).

output.dir Directory path to save the output file.

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

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.

max.subsets The maximum number of subs

The maximum number of subsets that can be tested for removal from the set of signatures.

max.presence.proportion

The maximum value of the proportion of tumors that must have a given signature

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.)

Value

A list of lists containing output for each sample in spectra. Each sublist has the following elements

MAP A 2-column tibble with the attributions with the highest MAP found. Column 1 contains signature ids; column 2 contains the associated counts.

MAP.row A 1-row tibble with various information on the selected exposure.

best.sparse A 2-column tibble with the most-sparse attributions with the highest MAP, in the same format as element MAP.

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best.sparse.row A 1-row tibble with various information on the most-sparse exposure with the best MAP.

all.tested A tibble of all the search results.

messages Possibly empty character vector with messages.

success TRUE is search was successful, FALSE otherwise.

time.for.MAP.assign Value from system.time for MAPAssignActivityInternal.

MAP.recon Reconstruction based on MAP.

sparse.MAP.recon Reconstruction based on best. sparse.

MAP.distances Various distances and similarities between spect and MAP. recon.

sparse.MAP.distances Various distances and similarities between spect and sparse.MAP.recon.

These elements will be NULL if max. subsets is exceeded.

MAPAssignActivity1

Find a Maximum A Posteriori (MAP) assignment of signature exposures that explain one spectrum.

Description

Find a Maximum A Posteriori (MAP) assignment of signature exposures that explain one spectrum.

Usage

```
MAPAssignActivity1(
   spect,
   sigs,
   sigs.presence.prop,
   max.level = 5,
   p.thresh = 0.05,
   m.opts = DefaultManyOpts(),
   max.mc.cores = min(20, 2^max.level),
   max.subsets = 1000,
   max.presence.proportion = 0.99,
   progress.monitor = NULL,
   seed = NULL
)
```

Arguments

spect A single spectrum.

sigs A numerical matrix, possibly an ICAMS catalog.

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).

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

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

m.opts See DefaultManyOpts.

max.mc.cores The maximum number of cores to use. On Microsoft Windows machines it is

silently changed to 1.

max.subsets The maximum number of subsets that can be tested for removal from the set of

signatures.

max.presence.proportion

The maximum value of the proportion of tumors that must have a given signa-

ture.

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 optimiza-

tion is in two phases; the first, global phase might rarely find different optima

depending on the random seed.)

Value

A list with the elements

MAP A 2-column tibble with the attributions with the highest MAP found. Column 1 contains signature ids; column 2 contains the associated counts.

MAP.row A 1-row tibble with various information on the selected exposure.

best.sparse A 2-column tibble with the most-sparse attributions with the highest MAP, in the same format as element MAP.

best.sparse.row A 1-row tibble with various information on the most-sparse exposure with the best MAP.

all.tested A tibble of all the search results.

messages Possibly empty character vector with messages.

success TRUE is search was successful, FALSE otherwise.

time.for.MAP.assign Value from system. time for MAPAssignActivityInternal.

MAP.recon Reconstruction based on MAP.

sparse.MAP.recon Reconstruction based on best. sparse.

MAP.distances Various distances and similarities between spect and MAP. recon.

sparse.MAP.distances Various distances and similarities between spect and sparse.MAP.recon.

These elements will be NULL if max.subsets is exceeded.

ObjFnBinomMaxLHMustRound

A deprecated negative binomial maximum likelihood objective function.

Description

Use ObjFnBinomMaxLHRound instead.

Usage

ObjFnBinomMaxLHMustRound(exp, spectrum, sigs, nbinom.size)

Arguments

nbinom.size

A vector of exposures ("activities"). exp

The spectrum to assess. spectrum

The matrix of signatures. sigs The dispersion parameter for the negative binomial distribution; smaller is more

dispersed. See NegBinomial.

Details

This function will lead to errors in some situations when the rounded reconstructed signature contains 0s for mutations classes for which the target spectrum is > 0.

ObjFnBinomMaxLHNoRoundOK

A deprecated negative binomial maximum likelihood objective function.

Description

Use ObjFnBinomMaxLHRound instead.

Usage

ObjFnBinomMaxLHNoRoundOK(exp, spectrum, sigs, nbinom.size)

Arguments

A vector of exposures ("activities"). exp

The spectrum to assess. spectrum sigs The matrix of signatures.

The dispersion parameter for the negative binomial distribution; smaller is more nbinom.size

dispersed. See NegBinomial.

Details

This function rounds sometimes, which leads to minor differences in log likelihoods of reconstructed spectra (LLHSpectrumNegBinom) compared to the value returned by this function.

ObjFnBinomMaxLHRound The preferred negative binomial maximum likelihood objective function.

Description

Can be used as the objective function for SparseAssignActivity, SparseAssignActivity1, and SignaturePresenceTest1. (Internally used by by nloptr.)

Usage

```
ObjFnBinomMaxLHRound(exp, spectrum, sigs, nbinom.size)
```

Arguments

exp A vector of exposures ("activities").

spectrum The spectrum to assess.
sigs The matrix of signatures.

nbinom.size The dispersion parameter for the negative binomial distribution; smaller is more

dispersed. See NegBinomial.

Value

-1 * log(likelihood(spectrum | reconstruction))
nloptr minimizes the objective function, so the lower the objective function, the better.

OneMAPAssignTest

Run one test of MAPAssignActivity1.

Description

Run one test of MAPAssignActivity1.

```
OneMAPAssignTest(
   spect,
   reference.exp,
   cancer.type,
   mutation.type,
   exposure.mutation.type,
   max.subsets = 1000,
   max.level = 5,
   max.mc.cores = 100,
   m.opts = DefaultManyOpts(),
   out.dir = NULL,
   p.thresh,
   max.presence.proportion,
   sigs.prop = NULL,
   sigs = NULL
)
```

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Arguments

spect A single spectrum.

reference.exp Compare the inferred exposures to this.

cancer type Character string from a fixed set indicating different cancer types, used to look

up the set of signatures known in that cancer type and the proportion of cancers of that type that have the signature. TODO: provide information on how to find

the allowed cancer types.

mutation.type One of "SBS96", "SBS192", "ID", "DBS78".

exposure.mutation.type

One of "SBS96", "ID", "DBS78".

max.subsets The maximum number of subsets that can be tested for removal from the set of

signatures.

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

max.mc.cores The maximum number of cores to use. On Microsoft Windows machines it is

silently changed to 1.

m.opts See DefaultManyOpts.

out.dir If non-NULL create this directory if necessary and put results there.

p. thresh If the p value for a better reconstruction with than without a set of signatures is

> than p. thresh, then we can use exposures without this set.

max.presence.proportion

The maximum value of the proportion of tumors that must have a given signature. Used so that it is possible to exclude a signature from a spectrum, e.g. perhaps all examples of tumor types have SBS5, but we want to allow a small

chance that SBS5 is not present.

sigs.prop The proportions of samples that contain each signature. A numerical vector

(values between 0 and 1), with names being signature identifiers. Can be the

return value from ExposureProportions.

sigs Matrix of signatures.

OptimizeExposure

Optimize the reconstruction of a spectrum from a set of signatures.

Description

Optimize the reconstruction of a spectrum from a set of signatures.

Usage

```
OptimizeExposure(spectrum, sigs, m.opts, ...)
```

Arguments

spectrum The spectrum to be reconstructed.

sigs The available signatures.

m. opts Options that govern the numerical optimization. For documentation see DefaultManyOpts.

... Additional arguments for eval_f.

OptimizeExposureQP 13

Value

A list with elements

loglh The log likelihood of the best solution (set of exposures) found.

exposure The vector of exposures that generated loglh, i.e. the number of mutations ascribed to each signature.

objective The final value of the objective function.

solution The optimum exposures. Deprecated.

warnings A character vector of warnings.

global.search.diagnostics Diagnostics from nloptr.

local.search.diagnostics Diagnostics from nloptr.

OptimizeExposureQP

Quadratic programming optimization of signature activities

Description

Quadratic programming optimization of signature activities

Usage

OptimizeExposureQP(spectrum, signatures)

Arguments

spectrum Mutational signature spectrum as a numeric vector or single column data frame

or matrix.

signatures Matrix or data frame of signatures from which reconstruct spectrum. Rows

are mutation types and columns are signatures. Should have column names for interpretable results. Cannot be a vector because the column names are needed.

Value

A vector of exposures with names being the colnames from signatures. Code adapted from SignatureEstimation::decomposeQP.

OptimizeExposureQPBootstrap

 ${\it Bootstrap~Optimize Exposure QP~and~filter~exposures~by~confidence~intervals}$

Description

Bootstrap OptimizeExposureQP and filter exposures by confidence intervals

Usage

```
OptimizeExposureQPBootstrap(
  spectrum,
  signatures,
  num.replicates = 10000,
  conf.int = 0.95,
  mc.cores = 10,
  seed = NULL
)
```

Arguments

spectrum Mutational signature spectrum as a numeric vector or single column data frame

or matrix.

signatures Matrix or data frame of signatures from which reconstruct spectrum. Rows

are mutation types and columns are signatures. Should have column names for interpretable results. Cannot be a vector because the column names are needed.

num.replicates Number of bootstrap replicates.

conf.int Discard signatures with conf.int that overlaps 0.

mc.cores The maximum number of cores to use. On MS Windows machines it defaults to

1.

seed Random seed; set this to get reproducible results.

#' @return A list with elements

exposure The vector of exposures that generated loglh, i.e. the number of mutations ascribed to each signature. The names of exposure are a subset of the colnames(signatures).

euclidean.dist The final value of the objective function.

cosine.sim The cosine similarity between spectrum and the reconstruction based on signatures.

If the spectrum has 0 mutations, no bootstrapping is done, and in the return value all signaures have 0 exposures, euclidian.dist is 0, and cosine.sim is NaN.

PCAWGMAPTest 15

PCAWGMAPTest Run MAPAs data set.	signActivity1 on one sample from the PCAWG platinum
----------------------------------	---

Description

Run MAPAssignActivity1 on one sample from the PCAWG platinum data set.

 $Run\ {\tt MAPAssignActivity1}\ on\ one\ sample\ from\ the\ PCAWG\ platinum\ data\ set\ with\ artifact\ signatures\ removed.$

Usage

```
PCAWGMAPTest(
  cancer.type,
  sample.index,
  mutation.type,
  \max.level = 5,
  max.mc.cores,
  out.dir = NULL,
  p.thresh = 0.01,
  m.opts = DefaultManyOpts(),
  max.presence.proportion = 0.99,
  sigs.prop = NULL
)
PCAWGMAPTest(
  cancer.type,
  sample.index,
  mutation.type,
  \max.level = 5,
  max.mc.cores,
  out.dir = NULL,
  p.thresh = 0.01,
  m.opts = DefaultManyOpts(),
  max.presence.proportion = 0.99,
  sigs.prop = NULL
)
```

Arguments

cancer.type	A cancer type from the PCAWG exposures matrix.
sample.index	The index of the sample within the exposures matrix.
mutation.type	One of "SBS96", "SBS192", "ID", "DBS78"
max.level	The maximum number of signatures to try removing.
max.mc.cores	The maximum number of cores to use. On Microsoft Windows machines it is silently changed to 1.
out.dir	If non-NULL create this directory if necessary and put results there.
p.thresh	If the p value for a better reconstruction with than without a set of signatures is > than p. thresh, then we can use exposures without this set.

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m.opts See DefaultManyOpts.

max.presence.proportion

The maximum value of the proportion of tumors that must have a given signature. Used so that it is possible to exclude a signature from a spectrum, e.g. perhaps all examples of tumor types have SBS5, but we want to allow a small chance that SBS5 is not present.

sigs.prop

The proportions of samples that contain each signature. A numerical vector (values between 0 and 1), with names being signature identifiers. Can be the return value from ExposureProportions.

Value

See OneMAPAssignTest.

A list with two elements, each the result for one call to OneMAPAssignTest.

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()

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()

ReconstructSpectrum 17

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 or data frame, with each row one mutation type (g.e. $CCT > CAT$ 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.

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

Description

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

```
SignaturePresenceTest(
  spectra,
  sigs,
  target.sig.index,
  m.opts = 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 and 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.

mc.cores Number of cores to use. Always silently changed to 1 on Microsoft Windows.

SignaturePresenceTest1

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

Description

For backward compatibility. See also AnySigSubsetPresent.

Usage

```
SignaturePresenceTest1(spectrum, sigs, target.sig.index, m.opts)
```

Arguments

spectrum The spectrum to analyze.

sigs A catalog of signatures from which to choose.

 ${\tt target.sig.index}$

The index of the signature the presence of which we want to test.

m.opts For documentation see DefaultManyOpts.

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.

```
SparseAssignActivity(
  spectra,
  sigs,
  max.level = 5,
  p.thresh = 0.05,
  m.opts = NULL,
  num.parallel.samples = 5,
  mc.cores.per.sample = min(20, 2^max.level)
)
```

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Arguments

spectra The spectra (multiple spectra) to be reconstructed. sigs The known signatures to use in reconstruction.

max.level The largest number of signatures to consider discarding in the reconstruction.

p.thresh The maximum p value based on which it is decided to retain a signature in a

reconstruction.

m. opts For documentation see DefaultManyOpts.

num.parallel.samples

The (maximum) number of samples to run in parallel; 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.

Value

A list with the inferred exposure matrix as element exposure.

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