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 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.

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

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

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github::steverozen/mSigBG

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usethis,
utils

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`AnySigSubsetPresent` *For each combination of several signatures, determine if the combination is plausibly needed to reconstruct a spectrum.*

Description

Please see **Details**.

Usage

```
AnySigSubsetPresent(
  spect,
  all.sigs,
  Ha.sigs.indices,
  eval_f = ObjFnBinomMaxLHRound,
  m.opts,
  max.mc.cores = NULL
)
```

Arguments

`spect`	The spectrum to be reconstructed, as single column matrix or `ICAMS` catalog.
`all.sigs`	The matrix or catalog of all signatures of possible interest, which consist of the signatures for H_0 and for the alternative hypotheses.
`Ha.sigs.indices`	An integer vector of the indices of the signatures that are in the various H_a's.
`eval_f`	Usually `ObjFnBinomMaxLHRound`. For background see `nloptr`.
`m.opts`	Controls the numerical search for maximum likelihood reconstructions of `spect` plus some additional flags; see `DefaultManyOpts`.
`max.mc.cores`	The maximum number of cores to use. If `NULL` defaults to $2^{n_a} - 1$, where n_a is the length of `Ha.sigs.indices` – except on MS Windows machines, where it defaults to 1.

Details

Let H_0 be the likelihood that the signatures specified by `all.sigs[,-Ha.sigs.indicies,drop = FALSE]` generated the observed spectrum, `spect`. For each non-empty subset, S, of `Ha.sigs.indices` let H_a be the likelihood that all the signatures in H_0 plus the signatures specified by S generated `spect`. Return a list with the results of likelihood ratio tests of all H_a's against H_0.

Value

A list with two elements:

`H0.info` contains the sub-elements

- `loglh` The log likelihood associated with H_0.
- `exposure` The signature attributions (exposures) corresponding to the H_0 log likelihood.
- `everything.else` A sub-list with information on the output of the numerical optimization that provided `loglh`.

`all.Ha.info` A list with one sub-element for each non-empty subset of `Ha.sigs.indices`. Each sub-element is a list with elements that include

- `sigs.added` The identifiers of the (additional) signatures tested.
- `p` The p value for the likelihood-ratio test.This this p value can be `NaN` when the likelihoods of (H_0 and H_a) are both `-Inf`. This can occur if there are are mutation classes in the spectra that are > 0 but that have 0 probability in all the available input signatures. This is unlikely to occur, since most spectra have non-0 (albeit very small) probabilities for most mutation classes. This is not an error if using `eval_f = ObjFnBinomMaxLHNoRound`.
- `df` The degrees of freedom of the likelihood-ratio test (equal to the number of signatures in `sigs.added`).

WARNING: tests all non-empty subsets of `Ha.sigs.indices`, so will get very slow for large numbers of `Ha.sigs.indices`.

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

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 Options for nloptr, q.v., for the global optimization phase.

local.opts Options for nloptr, q.v., for the local optimization phase.

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

trace If > 0 print progress messages.

`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
)
```

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.
`drop.sigs.no.info`	If TRUE, drop any not present in the column names of `all.sigs`. There are some signatures that do not have SBS192 versions, including SBS29.

Value

A numerical vector of the proportion of tumors of type `cancer.type` with each signature for those signatures observed in `cancer.types`.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.)

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.
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 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.

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,
  eval_f,
  eval_g_ineq = NULL,
  m.opts,
  max.mc.cores = min(20, 2^max.level),
  max.subsets = 1000,
  max.presence.proportion = 0.99
)
```

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 than without a set of signatures is > than p.thresh, then we can use exposures without this set.
eval_f	See nloptr.
eval_g_ineq	See nloptr.
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 signature.

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.

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

`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`.

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

`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`.

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`.

Usage

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

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.

eval_f	See nloptr.
eval_g_ineq	See nloptr.
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.

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, eval_f, eval_g_ineq = NULL, ...)
```

Arguments

spectrum	The spectrum to be reconstructed.
sigs	The available signatures.
m.opts	Options that govern the numerical optimization. For documentation see DefaultManyOpts.
eval_f	The objective function for nloptr.
eval_g_ineq	See nloptr.
...	Additional arguments for eval_f.

Returns a list with elements

- loglh The log likelihood of the best solution (set of exposures) found. For a more general objective function this might be NULL.
- exposure The vector of exposures that generate loglh, i.e. the number of mutations ascribed to each signature.
- obj.fn.value The objective function value associated with exposure.
- everything.else Everything returned by the function Nloptr1Tumor.

`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`.

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

Description

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

Usage

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

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.
m.opts	See DefaultManyOpts.
eval_f	See nloptr.
eval_g_ineq	See nloptr.
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.

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

Usage

```
SignaturePresenceTest(
  spectra,
  sigs,
  target.sig.index,
  m.opts = NULL,
  eval_f,
  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.
eval_f	See nloptr.
mc.cores	Number of cores to use. Always silently changed to 1 on Microsoft Windows.

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

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.
eval_f	The objective function for nloptr.
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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