Package ‘HiLDA’

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Type Package

Title Conducting statistical inference on comparing the mutational exposures of mutational signatures by using hierarchical latent Dirichlet allocation

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Suggests knitr, rmarkdown, testthat, BiocStyle

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Description A package built under the Bayesian framework of applying hierarchical latent Dirichlet allocation. It statistically tests whether the mutational exposures of mutational signatures (Shiraishi-model signatures) are different between two groups. The package also provides inference and visualization.

License GPL-3

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boundaryTurbo_F

Check whether the parameter $F$ is within the appropriate range

**Description**

Check whether the parameter $F$ is within the appropriate range

**Usage**

```r
boundaryTurbo_F(turboF, fdim, signatureNum)
```

**Arguments**

- `turboF`: $F$ (converted for turboEM)
- `fdim`: a vector specifying the number of possible values for each mutation signature
- `signatureNum`: the number of mutation signatures

**Value**

a logical value

boundaryTurbo_Q

Check whether the parameter $Q$ is within the appropriate range

**Description**

Check whether the parameter $Q$ is within the appropriate range

**Usage**

```r
boundaryTurbo_Q(turboQ, signatureNum, sampleNum)
```

**Arguments**

- `turboQ`: $Q$ (converted for turboEM)
- `signatureNum`: the number of mutation signatures
- `sampleNum`: the number of cancer genomes

**Value**

a logical value
**calcPMSLikelihood**  
*A function for calculating the log-likelihood from the data and parameters*

**Description**
A function for calculating the log-likelihood from the data and parameters

**Usage**
calcPMSLikelihood(p, y)

**Arguments**
pthis variable includes the parameters for mutation signatures and membership parameters  
ythis variable includes the information on the mutation features, the number of mutation signatures specified and so on

**Value**
a value

**convertFromTurbo_F**  
*Restore the converted parameter F for turboEM*

**Description**
Restore the converted parameter F for turboEM

**Usage**
convertFromTurbo_F(turboF, fdim, signatureNum, isBackground)

**Arguments**
turboF  
F (converted for turboEM)  
fdim  
a vector specifying the number of possible values for each mutation signature  
signatureNum  
the number of mutation signatures  
isBackground  
the logical value showing whether a background mutation features is included or not

**Value**
a vector
**convertFromTurbo_Q**

*Description*

Restore the converted parameter Q for turboEM

*Usage*

```
convertFromTurbo_Q(turboQ, signatureNum, sampleNum)
```

*Arguments*

- `turboQ` : Q (converted for turboEM)
- `signatureNum` : the number of mutation signatures
- `sampleNum` : the number of cancer genomes

*Value*

a vector

**convertToTurbo_F**

*Description*

Convert the parameter F so that turboEM can treat

*Usage*

```
convertToTurbo_F(vF, fdim, signatureNum, isBackground)
```

*Arguments*

- `vF` : F (converted to a vector)
- `fdim` : a vector specifying the number of possible values for each mutation signature
- `signatureNum` : the number of mutation signatures
- `isBackground` : the logical value showing whether a background mutaition features is included or not

*Value*

a vector
convertToTurbo_Q

Convert the parameter Q so that turboEM can treat

Description

Convert the parameter Q so that turboEM can treat

Usage

convertToTurbo_Q(vQ, signatureNum, sampleNum)

Arguments

vQ Q (converted to a vector)
signatureNum the number of mutation signatures
sampleNum the number of cancer genomes

Value

a vector

EstimatedParameters-class

An S4 class representing the estimated parameters

Description

An S4 class representing the estimated parameters

Slots

sampleList a list of sample names observed in the input mutation data
signatureNum the number of mutation signatures specified at the time of estimation
isBackGround the flag showing whether the background signature data is used or not.
backGroundProb the background signatures
signatureFeatureDistribution estimated parameters for mutation signatures
sampleSignatureDistribution estimated parameters for memberships of mutation signatures for each sample
loglikelihood the log-likelihood value for the estimated parameters
getLogLikelihoodC

Calculate the value of the log-likelihood for given parameters

Description
Calculate the value of the log-likelihood for given parameters

Usage
getLogLikelihoodC(
    vPatternList,  
    vSparseCount,  
    vF,             
    vQ,             
    fdim,           
    signatureNum,   
    sampleNum,      
    patternNum,     
    samplePatternNum,  
    isBackground,  
    vF0
)

Arguments
vPatternList  The list of possible mutation features (converted to a vector)
vSparseCount  The table showing (mutation feature, sample, the number of mutation) (converted to a vector)
vF            F (converted to a vector)
vQ            Q (converted to a vector)
fdim          a vector specifying the number of possible values for each mutation signature
signatureNum  the number of mutation signatures
sampleNum     the number of cancer genomes
patternNum    the number of possible combinations of all the mutation features
samplePatternNum  the number of possible combination of samples and mutation patterns
isBackground  the logical value showing whether a background mutation features is included or not
vF0           a background mutation features

Value
a value
getMutationFeatureVector

Get mutation feature vector from context sequence data and reference and alternate allele information

Description

Get mutation feature vector from context sequence data and reference and alternate allele information

Usage

getMutationFeatureVector(
  context,
  ref_base,
  alt_base,
  strandInfo = NULL,
  numBases,
  type
)

Arguments

context the context sequence data around the mutated position. This should be Biostrings::DNAStringSet class
ref_base the reference bases at the mutated position.
alt_base the alternate bases at the mutated position.
strandInfo transcribed strand information at the mutated position. (this is optional)
umBases the number of flanking bases around the mutated position.
type the type of mutation feature vector (should be "independent" or "full").

Value

a mutation feature vector

hildaBarplot

Read the raw mutation data with the mutation feature vector format, estimate and plot both mutation signatures and their fractions

Description

Read the raw mutation data with the mutation feature vector format, estimate and plot both mutation signatures and their fractions
Usage

    hildaBarplot(
        inputG,  
        hildaResult,  
        sigOrder = NULL,  
        refGroup,  
        sortSampleNum = TRUE,  
        refName = "Control",  
        altName = "Case",  
        charSize = 3  
    )

Arguments

inputG a MutationFeatureData S4 class output by the pmsignature.
hildaResult a rjags class output by HiLDA.
sigOrder the order of signatures if needed (default: NULL).
refGroup the samples in the reference group (default: NULL).
sortSampleNum whether to sort plots by number of mutations (default: TRUE).
refName the name of reference group (default: Control)
altName the name of the other group (default: Case)
charSize the size of the character on the signature plot (default: 3)

Value

a list of a signature plot and a barplot of mutational exposures

Examples

    load(system.file("extdata/sample.rdata", package="HiLDA"))
    inputFile <- system.file("extdata/hildaLocal.rdata", package="HiLDA")
    hildaLocal <- readRDS(inputFile)

    hildaBarplot(G, hildaLocal, refGroup=1:4)

hildaDiffPlot Read the raw mutation data with the mutation feature vector format, estimate and plot both mutation signatures and their fractions

Description

Read the raw mutation data with the mutation feature vector format, estimate and plot both mutation signatures and their fractions
Usage

hildaDiffPlot(inputG, hildaResult, sigOrder = NULL, charSize = 3)

Arguments

inputG a MutationFeatureData S4 class output by the pmsignature.
hildaResult a rjags class output by HiLDA.
sigOrder the order of signatures if needed (default: NULL).
charSize the size of the character on the signature plot (default: 3)

Value

a list of the signature plot and the mean difference plot.

Examples

load(system.file("extdata/sample.rdata", package="HiLDA"))
inputFile <- system.file("extdata/hildaLocal.rdata", package="HiLDA")
hildaLocal <- readRDS(inputFile)

hildaDiffPlot(G, hildaLocal)

hildaGlobalResult

Compute the Bayes factor

Description

Compute the Bayes factor

Usage

hildaGlobalResult(jagsOutput, pM1 = 0.5)

Arguments

jagsOutput the output jags file generated by the jags function from the R2jags package.
pM1 the probability of sampling the null (default: 0.5)

Value

a number for the Bayes factor
Examples

```r
load(system.file("extdata/sample.rdata", package="HiLDA"))
hildaGlobal <- hildaTest(inputG=G, numSig=3, refGroup=1:4, nIter=1000,
localTest=TRUE)
hildaGlobalResult(hildaGlobal)
```

**hildaLocalResult**

Extract the posterior distributions of the mean differences in muational exposures

**Description**

Extract the posterior distributions of the mean differences in muational exposures

**Usage**

```r
hildaLocalResult(jagsOutput)
```

**Arguments**

- **jagsOutput**
  
  the output jags file generated by the jags function from the R2jags package.

**Value**

a data frame that contains the posterior distributions of difference.

**Examples**

```r
inputFile <- system.file("extdata/hildaLocal.rdata", package="HiLDA")
hildaLocal <- readRDS(inputFile)
hildaLocalResult(hildaLocal)
```

**hildaPlotSignature**

Plot mutation signatures from HiLDA output

**Description**

Plot mutation signatures from HiLDA output

**Usage**

```r
hildaPlotSignature(hildaResult, sigOrder = NULL, colorList = NULL, ...)
```
hildaReadMPFile

Arguments

- `hildaResult`: a rjags class output by HiLDA
- `sigOrder`: the order of signatures if needed (default: NULL)
- `colorList`: a vector of color for mutational exposures barplots
- `...`: additional arguments passed on to visPMS

Value

A plot object containing all mutational signatures

Examples

```r
inputFile <- system.file("extdata/hildaLocal.rdata", package="HiLDA")
hildaLocal <- readRDS(inputFile)
hildaPlotSignature(hildaLocal)
```

Description

The mutation position format is tab-delimited text file, where the 1st-5th columns shows sample names, chromosome names, coordinates, reference bases (A, C, G, or T) and the alternate bases (A, C, G, or T), respectively. An example is as follows:

```
sample1 chr1 100 A C
sample1 chr1 200 A T
sample1 chr2 100 G T
sample2 chr1 300 T C
sample3 chr3 400 T C
```

Also, this function usually can accept compressed files (e.g., by gzip, bzip2 and so on) when using recent version of R.

Usage

```r
hildaReadMPFile(  
  inFile,  
  numBases = 3,  
  trDir = FALSE,  
  bs_genome = NULL,  
  txdb_transcript = NULL  
)
```
hildaRhat

Arguments

infile the path for the input file for the mutation data of Mutation Position Format.
numBases the number of upstream and downstream flanking bases (including the mutated base) to take into account.
trDir the index representing whether transcription direction is considered or not. The gene annotation information is given by UCSC knownGene (TxDb.Hsapiens.UCSC.hg19.knownGene object) When trDir is TRUE, the mutations located in intergenic region are excluded from the analysis.
bs_genome this argument specifies the reference genome (e.g., B Sgenome.Mmusculus.UCSC.mm10 can be used for the mouse genome). See https://bioconductor.org/packages/release/bioc/html/BSgenome.html for the available genome list
txdb_transcript this argument specified the transcript database (e.g., TxDb.Mmusculus.UCSC.mm10.knownGene can be used for the mouse genome). See https://bioconductor.org/packages/release/bioc/html/AnnotationDbi.html for details.

Value

The output is an instance of MutationFeatureData S4 class (which stores summarized information on mutation data). This will be typically used as the initial values for the global test and the local test.

Examples

inputFile <- system.file("extdata/esophageal.mp.txt.gz", package="HiLDA")
G <- hildaReadMPFile(inputFile, numBases=5, trDir=TRUE)

hildaRhat Output the maximum potential scale reduction statistic of all parameters estimated

Description

Output the maximum potential scale reduction statistic of all parameters estimated

Usage

hildaRhat(jagsOutput)

Arguments

jagsOutput the output jags file generated by the jags function from the R2jags package.
Value

A number for the Rhat statistic.

Examples

```r
inputFile <- system.file("extdata/hildaLocal.rdata", package="HiLDA")
hildaLocal <- readRDS(inputFile)
hildaRhat(hildaLocal)
```

**hildaTest**

*Apply HiLDA to statistically testing the global difference in burdens of mutation signatures between two groups*

Description

Apply HiLDA to statistically testing the global difference in burdens of mutation signatures between two groups

Usage

```r
hildaTest(
  inputG,  # a MutationFeatureData S4 class output by pmsignature.
  numSig,  # an integer number of the number of mutational signatures.
  refGroup,  # the indice indicating the samples in the reference group.
  useInits = NULL,  # a EstimatedParameters S4 class output by pmsignature (default: NULL).
  sigOrder = NULL,  # the order of the mutational signatures.
  nIter = 2000,  # number of total iterations per chain (default: 2000).
  nBurnin = 0,  # length of burn (default: 0).
  pM1 = 0.5,  # the probability of sampling the null (default: 0.5).
  localTest = TRUE,  # a logical value (default: TRUE).
  ...  # Other arguments passed on to methods.
)
```

Arguments

- **inputG**: a MutationFeatureData S4 class output by pmsignature.
- **numSig**: an integer number of the number of mutational signatures.
- **refGroup**: the indice indicating the samples in the reference group.
- **useInits**: a EstimatedParameters S4 class output by pmsignature (default: NULL).
- **sigOrder**: the order of the mutational signatures.
- **nIter**: number of total iterations per chain (default: 2000).
- **nBurnin**: length of burn (default: 0).
- **pM1**: the probability of sampling the null (default: 0.5).
- **localTest**: a logical value (default: TRUE).
- **...**: Other arguments passed on to methods.
MetaInformation-class

Value

the output jags file

Examples

load(system.file("extdata/sample.rdata", package="HiLDA"))

## with initial values
hildaLocal <- hildaTest(inputG=G, numSig=3, refGroup=1:4, nIter=1000,
localTest=TRUE)
hildaGlobal <- hildaTest(inputG=G, numSig=3, refGroup=1:4, nIter=1000,
localTest=FALSE)

MutationFeatureData-class

An S4 class representing the mutation data

Description

An S4 class representing the mutation data

Slots

featureVectorList a list of feature vectors actually observed in the input mutation data
sampleList a list of sample names observed in the input mutation data
countData a matrix representing the number of mutations and samples. The (1st, 2nd, 3rd) columns are for (mutation pattern index, sample index, frequencies).
mutationPosition a data frame containing position and mutations
mySquareEM  
A function for estimating parameters using Squared EM algorithm

Description

A function for estimating parameters using Squared EM algorithm

Usage

mySquareEM(p, y, tol = 1e-04, maxIter = 10000)

Arguments

p this variable includes the parameters for mutation signatures and membership parameters
y this variable includes the information on the mutation features, the number of mutation signatures specified and so on
tol tolerance for the estimation (when the difference of log-likelihoods become below this value, stop the estimation)
maxIter the maximum number of iteration of estimation

Value

a list

pmBarplot  
Plot both mutation signatures and their mutational exposures from pm-signature output

Description

Plot both mutation signatures and their mutational exposures from pm-signature output

Usage

pmBarplot(
  inputG,  
  inputParam,  
  sigOrder = NULL,  
  refGroup = NULL,  
  sortSampleNum = TRUE,  
  refName = "Control",  
  altName = "Case",  
  charSize = 3  
)
pmgetSignature

Arguments

inputG: a MutationFeatureData S4 class output by the pmsignature.
inputParam: a estimatedParameters S4 class output by the pmsignature.
sigOrder: the order of signatures if needed (default: NULL).
refGroup: the samples in the reference group (default: NULL).
sortSampleNum: whether to sort by number of mutations (default: TRUE).
refName: the name of reference group (default: Control).
altName: the name of the other group (default: Case).
charSize: the size of the character on the signature plot (default: 3).

Value

a list of a signature plot and a barplot of mutational exposures

Examples

load(system.file("extdata/sample.rdata", package="HiLDA"))
Param <- pmgetSignature(G, K = 3)

pmPlots <- pmBarplot(G, Param, refGroup=1:4)
cowplot::plot_grid(pmPlots$sigPlot, pmPlots$propPlot, rel_widths = c(1,3))
Arguments

- **mutationFeatureData**: the mutation data (MutationFeatureData class (S4 class)) by the hildaReadMPFile.
- **K**: the number of mutation signatures
- **numInit**: the number of performing calculations with different initial values
- **tol**: tolerance for the estimation (when the difference of log-likelihoods become below this value, stop the estimation)
- **maxIter**: the maximum number of iteration of estimation

Value

The output is an instance of EstimatedParameters S4 class, which stores estimated parameters and other meta-information, and will be used for saving parameter values and visualizing the mutation signatures and memberships

Examples

```r
## After obtaining G (see e.g., hildaReadMPFile function)
load(system.file("extdata/sample.rdata", package="HiLDA"))
Param <- pmgetSignature(G, K = 3)
```

---

**pmMultiBarplot**

Plot both mutation signatures and their mutational exposures from pm-signature output for more than two groups

Description

Plot both mutation signatures and their mutational exposures from pmsignature output for more than two groups

Usage

```r
pmMultiBarplot(
  inputG, inputParam, sigOrder = NULL, groupIndices, sortSampleNum = TRUE, charSize = 3
)
```
pmPlotSignature

Arguments

inputG  a MutationFeatureData S4 class output by the pmsignature.
inputParam  a estimatedParameters S4 class output by the pmsignature.
sigOrder  the order of signatures if needed (default: NULL).
groupIndices  a vector of group indicators.
sortSampleNum  an indictor variable on whether samples are sorted by the number of mutations (default: TRUE).
charSize  the size of the character on the signature plot (default: 3)

Value

a list of the signature plot and the mean difference plot.

Examples

load(system.file("extdata/sample.rdata", package="HiLDA"))
Param <- pmgetSignature(G, K = 3)

pmPlots <- pmMultiBarplot(G, Param, groupIndices=c(1, rep(2,3), rep(3,6)))
cowplot::plot_grid(pmPlots$sigPlot, pmPlots$propPlot, rel_widths = c(1,3))

pmPlotSignature  
Plot mutation signatures from pmsignature output

Description

Plot mutation signatures from pmsignature output

Usage

pmPlotSignature(inputParam, sigOrder = NULL, colorList = NULL, ...)

Arguments

inputParam  a estimatedParameters S4 class output by the pmsignature.
sigOrder  the order of signatures if needed (default: NULL).
colorList  a list of color to highlight the signatures (default: NULL).
...  additional arguments passed on to visPMS.

Value

a plot object containing all mutational signatures
Examples

```r
load(system.file("extdata/sample.rdata", package="HiLDA"))
Param <- pmgetSignature(G, K = 3)
pmPlotSignature(Param)
```

PMSboundary

A functional for generating the function checking the parameter (p) is within the restricted conditions or not

Description

A functional for generating the function checking the parameter (p) is within the restricted conditions or not

Usage

```r
PMSboundary(y)
```

Arguments

- `y`: this variable includes the information on the mutation features, the number of mutation signatures specified and so on

Value

a functional

updateMstepFQC

Update the parameter F and Q (M-step in the EM-algorithm)

Description

Update the parameter F and Q (M-step in the EM-algorithm)

Usage

```r
updateMstepFQC(
  vPatternList,
  vSparseCount,
  nTheta,
  fdim,
  signatureNum,
  sampleNum,
  patternNum,
  samplePatternNum,
  isBackground
)
```
**Arguments**

- `vPatternList` - The list of possible mutation features (converted to a vector)
- `vSparseCount` - The table showing (mutation feature, sample, the number of mutation) (converted to a vector)
- `nTheta` - The parameters in the distribution
- `fdim` - A vector specifying the number of possible values for each mutation signature
- `signatureNum` - The number of mutation signatures
- `sampleNum` - The number of cancer genomes
- `patternNum` - The number of possible combinations of all the mutation features
- `samplePatternNum` - The number of possible combination of samples and mutation patterns
- `isBackground` - The logical value showing whether a background mutation features is included or not

**Value**

A vector

---

**updatePMSParam**

A function for updating parameters using EM-algorithm

**Description**

A function for updating parameters using EM-algorithm

**Usage**

`updatePMSParam(p, y)`

**Arguments**

- `p` - This variable includes the parameters for mutation signatures and membership parameters
- `y` - This variable includes the information on the mutation features, the number of mutation signatures specified and so on

**Value**

A value
updateTheta_NormalizedC

Update the auxiliary parameters theta and normalize them so that the summation of each group sums to 1 (E-step), also calculate the current log-likelihood value

Description

Update the auxiliary parameters theta and normalize them so that the summation of each group sums to 1 (E-step), also calculate the current log-likelihood value

Usage

updateTheta_NormalizedC(
  vPatternList,
  vSparseCount,
  vF,
  vQ,
  fdim,
  signatureNum,
  sampleNum,
  patternNum,
  samplePatternNum,
  isBackground,
  vF0
)

Arguments

vPatternList The list of possible mutation features (converted to a vector)
vSparseCount The table showing (mutation feature, sample, the number of mutation) (converted to a vector)
vF F (converted to a vector)
vQ Q (converted to a vector)
fdim a vector specifying the number of possible values for each mutation signature
signatureNum the number of mutation signatures
sampleNum the number of cancer genomes
patternNum the number of possible combinations of all the mutation features
samplePatternNum the number of possible combination of samples and mutation patterns
isBackground the logical value showing whether a background mutaiton features is included or not
vF0 a background mutaiton features
Value

a value for theta

---

visPMS  
*visualize probabilistic mutation signature for the independent model*

Description

Generate visualization of mutation signatures for the model with substitution patterns and flanking bases represented by the independent representation.

Usage

```r
visPMS(
  vF,
  numBases,
  baseCol = NA,
  trDir = FALSE,
  charSize = 5,
  isScale = FALSE,
  alpha = 2,
  charLimit = 0.25
)
```

Arguments

- `vF`  
a matrix for mutation signature
- `numBases`  
the number of flanking bases
- `baseCol`  
the colour of the bases (A, C, G, T, plus/minus strand)
- `trDir`  
the index whether the strand direction is plotted or not
- `charSize`  
the size of the character
- `isScale`  
the index whether the height of the flanking base is changed or not
- `alpha`  
the parameter for the Renyi entropy (applicable only if the isScale is TRUE)
- `charLimit`  
the limit of char size

Value

a plot of the input mutational signature

Examples

```r
load(system.file("extdata/sample.rdata", package="HiLDA"))
Param <- pmgetSignature(G, K = 3)

sig <- slot(Param, "signatureFeatureDistribution")[1,,]
visPMS(sig, numBases = 5, isScale = TRUE)
```
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