Package 'EpiMix'

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Title EpiMix: an integrative tool for the population-level analysis of DNA methylation

Version 1.8.0

Description
EpiMix is a comprehensive tool for the integrative analysis of high-throughput DNA methylation data and gene expression data. EpiMix enables automated data downloading (from TCGA or GEO), preprocessing, methylation modeling, interactive visualization and functional annotation.To identify hypo- or hypermethylated CpG sites across physiological or pathological conditions, EpiMix uses a beta mixture modeling to identify the methylation states of each CpG probe and compares the methylation of the experimental group to the control group.The output from EpiMix is the functional DNA methylation that is predictive of gene expression. EpiMix incorporates specialized algorithms to identify functional DNA methylation at various genetic elements, including proximal cis-regulatory elements of protein-coding genes, distal enhancers, and genes encoding microRNAs and lncRNAs.

Depends R (>= 4.2.0), EpiMix.data (>= 1.2.2)

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Encoding UTF-8

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.extractPriMiRNA *The extractPriMiRNA function*

Description

Utility function to convert mature miRNA names to pri-miRNA names

Usage

```
.extractPriMiRNA(str)
```

Arguments

str	a character string for a mature miRNA name (e.g. "hsa-miR-34a-3p")

Value

a character string for the corresponding pri-miRNA name (e.g. "hsa-mir-34a")

.getComp *The .getComp function*

Description

Helper function to get a string indicating the comparison made for gene expression

Usage

```
.getComp(state)
```

Arguments

state	character string indicating the methylation state, can be either "Hyper", "Hypo", "Dual"

Value

a list of sample names split by methylation group

.getMetGroup *The .getMetGroup function*

Description

Helper function to get sample names split by methylation group based on DM values

Usage

```
.getMetGroup(state, DM_values)
```

Arguments

state	character string indicating the methylation state, can be either "Hyper", "Hypo", "Dual"
DM_values	a vector of DM values for the probe. The names of the vector are sample names.

Value

a list of sample names split by methylation group

.mapProbeGene *The .mapProbeGene function*

Description

since in the original probe annotation, a specific probe can be mapped to multiple genes, this function splits the rows and maps each probe to a signle gene in a row.

Usage

```
.mapProbeGene(df.annot)
```

Arguments

df.annot	a dataframe with probe annotation, can be the object returned from the convertAnnotToDF function.

Value

a dataframe with 1:1 mapping of probe and gene

.splitMetData *The .splitMetData function*

Description

Helper function to split the methylation data matrix into the experimental group and the control group

Usage

```
.splitMetData(methylation.data, sample.info, group.1, group.2)
```

Arguments

methylation.data	methylation data matrix
sample.info	sample information matrix
group.1	name of group.1
group.2	name of group.2

Value

a list with methylation data of group.1 and group.2

addDistNearestTSS *Calculate the distance between probe and gene TSS*

Description

Calculate the distance between probe and gene TSS

Usage

```
addDistNearestTSS(data, NearGenes, genome, met.platform, cores = 1)
```

Arguments

data	A multi Assay Experiment with both DNA methylation and gene Expression objects
NearGenes	A list or a data frame with the pairs gene probes
genome	Which genome build will be used: hg38 (default) or hg19.
met.platform	DNA methyaltion platform to retrieve data from: EPIC or 450K (default)
cores	Number fo cores to be used. Deafult: 1

Value

a dataframe of nearest genes with distance to TSS.

addGeneNames *The addGeneNames function*

Description

Given a dataframe with a column of probe names, add the gene names

Usage

```
addGeneNames(df_data, ProbeAnnotation)
```

Arguments

df_data	a dataframe with a column named Probe
ProbeAnnotation	a dataframe with ProbeAnnotation, including one column named 'probe' and another column named 'gene'

Value

a dataframe with added gene names

BatchCorrection_Combat *The BatchCorrection_Combat function*

Description

The BatchCorrection_Combat function

Usage

```
BatchCorrection_Combat(GEN_Data, BatchDataSelected)
```

Arguments

GEN_Data	matrix with methylation.data or gene.expression.data
BatchDataSelected	BatchData after filtering out the small batches and selecting for overlapped samples

Details

correct batch effects with Combat

Value

corrected data matrix

BatchCorrection_Seurat *The BatchCorrection_Seurat function*

Description

The BatchCorrection_Seurat function

Usage

```
BatchCorrection_Seurat(GEN_Data, BatchDataSelected)
```

Arguments

GEN_Data	matrix with methylation.data or gene.expression.data
BatchDataSelected	BatchData after filtering out the small batches and selecting for overlapped samples.

Details

correct batch effects with the Seurat data integration functions.

Value

corrected data matrix

betaEst_2 *The betaEst_2 function*

Description

Internal. Estimates a beta distribution via Maximum Likelihood. Adapted from RPMM package.

Usage

```
betaEst_2(Y, w, weights)
```

Arguments

Y	data vector.
w	posterior weights.
weights	Case weights.

Value

(a,b) parameters.

blc_2 *The blc_2 function*

Description

Internal. Fits a beta mixture model for any number of classes. Adapted from RPMM package.

Usage

```
blc_2(Y, w, maxiter = 25, tol = 1e-06, weights = NULL, verbose = TRUE)
```

Arguments

Y	Data matrix (n x j) on which to perform clustering.
w	Initial weight matrix (n x k) representing classification.
maxiter	Maximum number of EM iterations.
tol	Convergence tolerance.
weights	Case weights.
verbose	Verbose output.

Value

A list of parameters representing mixture model fit, including posterior weights and log-likelihood.

calcDistNearestTSS *Calculate distance from region to nearest TSS*

Description

Idea For a given region R linked to X genes G merge R with nearest TSS for G (multiple) this will increse nb of lines i.e R1 - G1 - TSS1 - DIST1 R1 - G1 - TSS2 - DIST2 To vectorize the code: make a granges from left and onde from right and find distance collapse the results keeping min distance for equals values

Usage

```
calcDistNearestTSS(links, TRange, tssAnnot)
```

Arguments

links	Links to calculate the distance
TRange	Genomic coordinates for Tartget region
tssAnnot	TSS annotation

Value

dataframe of genomic distance from TSS

Author(s)

Tiago C. Silva

`ClusterProbes` *The ClusterProbes function*

Description

This function uses the annotation for Illumina methylation arrays to map each probe to a gene. Then, for each gene, it clusters all its CpG sites using hierchical clustering and Pearson correlation as distance and complete linkage. If data for normal samples is provided, only overlapping probes between cancer and normal samples are used. Probes with SNPs are removed. This function is prepared to run in parallel if the user registers a parallel structure, otherwise it runs sequentially. This function also cleans up the sample names, converting them to the 12 digit format.

Usage

```
ClusterProbes(MET_data, ProbeAnnotation, CorThreshold = 0.4)
```

Arguments

`MET_data`	data matrix for methylation.
`ProbeAnnotation`	GRange object for probe annoation.
`CorThreshold`	correlation threshold for cutting the clusters.

Value

List with the clustered data sets and the mapping between probes and genes.

`ComBat_NoFiles` *The ComBat_NoFiles function*

Description

Internal. Performs batch correction.

Usage

```
ComBat_NoFiles(
  dat,
  saminfo,
  type = "txt",
  write = FALSE,
  covariates = "all",
  par.prior = FALSE,
  filter = FALSE,
  skip = 0,
  prior.plots = TRUE
)
```

Arguments

dat	dat
saminfo	saminfo
type	currently supports two data file types 'txt' for a tab-delimited text file and 'csv' for an Excel .csv file (sometimes R handles the .csv file better, so use this if you have problems with a .txt file!).
write	if 'T' ComBat writes adjusted data to a file, and if 'F' and ComBat outputs the adjusted data matrix if 'F' (so assign it to an object! i.e. NewData <- ComBat('my expression.xls','Sample info file.txt', write=F)).
covariates	'covariates=all' will use all of the columns in your sample info file in the modeling (except array/sample name), if you only want use a some of the columns in your sample info file, specify these columns here as a vector (you must include the Batch column in this list).
par.prior	if 'T' uses the parametric adjustments, if 'F' uses the nonparametric adjustments– if you are unsure what to use, try the parametric adjustments (they run faster) and check the plots to see if these priors are reasonable.
filter	'filter=value' filters the genes with absent calls in > 1-value of the samples. The defaut here (as well as in dchip) is .8. Filter if you can as the EB adjustments work better after filtering. Filter must be numeric if your expression index file contains presence/absence calls (but you can set it >1 if you don't want to filter any genes) and must be 'F' if your data doesn't have presence/absence calls;
skip	is the number of columns that contain probe names and gene information, so 'skip=5' implies the first expression values are in column 6
prior.plots	if true will give prior plots with black as a kernal estimate of the empirical batch effect density and red as the parametric estimate.

Value

Results.

---

combineForEachOutput *The combineForEachOutput function*

Description

Internal. Function to combine results from the foreach loop.

Usage

```
combineForEachOutput(out1, out2)
```

Arguments

out1	result from one foreach loop.
out2	result from another foreach loop.

Value

List with the combined results.

convertAnnotToDF *The convertAnnotToDF function*

Description

convert the probe annotation from the GRange object to a dataframe

Usage

```
convertAnnotToDF(annot)
```

Arguments

annot	a GRange object of probe annotation, can be the object returned from the getInfiniumAnnotation function.

Value

a dataframe with chromosome, beginning and end position, mapped gene information for each CpG probe

convertGeneNames *The convertGeneNames function*

Description

auxiliary function to translate ensembl_gene_ids or ensembl_transcript_ids to human gene symbols (HGNC)

Usage

```
convertGeneNames(gene.expression.data)
```

Arguments

gene.expression.data	gene expression data matrix with the rownames to be the ensembl_gene_ids or ensembl_transcript_ids

Value

gene expression matrix with rownames translated to human gene symbols (HGNC)

`CorrectBatchEffect` *The CorrectBatchEffect function*

Description

top-level wrapper function for batch correction.

Usage

```
CorrectBatchEffect(
  GEN_Data,
  BatchData,
  batch.correction.method,
  MinInBatch = 5,
  featurePerSet = 50000
)
```

Arguments

`GEN_Data`	matrix with methylation.data or gene.expression.data with genes in rows and samples in columns
`BatchData`	dataframe with two columns: the first column indicates the sample names, and the second column indicates the batch ids.
`batch.correction.method`	character string. Should be either 'Seurat' or 'Combat'.
`MinInBatch`	integer indicating the batch size threshold. Batches smaller than this threshold will be removed. Default: 5
`featurePerSet`	integer indicating the row numbers to split the GEN_Data into small subsets. Default: 50,000

Details

(1) filters the batch data and the molecular data to keep only the overlapped samples. (2) removes extremely small batches. (3) if the molecular data have over 50,000 features (rows), it splits the data into subsets, with 50,000 features in each subset, and perform batch correction on each subset. (4) identify overlapped samples in batch corrected subsets, and merge the subsets into one matrix.

Value

matrix with corrected data

EpiMix *The EpiMix function*

Description

EpiMix uses a model-based approach to identify functional changes DNA methylation that affect gene expression.

Usage

```
EpiMix(
  methylation.data,
  gene.expression.data,
  sample.info,
  group.1,
  group.2,
  mode = "Regular",
  promoters = FALSE,
  correlation = "negative",
  met.platform = "HM450",
  genome = "hg38",
  cluster = FALSE,
  listOfGenes = NULL,
  filter = TRUE,
  raw.pvalue.threshold = 0.05,
  adjusted.pvalue.threshold = 0.05,
  numFlankingGenes = 20,
  roadmap.epigenome.groups = NULL,
  roadmap.epigenome.ids = NULL,
  chromatin.states = c("EnhA1", "EnhA2", "EnhG1", "EnhG2"),
  NoNormalMode = FALSE,
  cores = 1,
  MixtureModelResults = NULL,
  OutputRoot = "."
)
```

Arguments

`methylation.data`	Matrix of the DNA methylation data with CpGs in rows and samples in columns.
`gene.expression.data`	Matrix of the gene expression data with genes in rows and samples in columns.
`sample.info`	Dataframe that maps each sample to a study group. Should contain two columns: the first column (named 'primary') indicates the sample names, and the second column (named 'sample.type') indicating which study group each sample belongs to (e.g.,"Cancer" vs. "Normal", "Experiment" vs. "Control"). Sample names in the 'primary' column must coincide with the column names of the methylation.data.
`group.1`	Character vector indicating the name(s) for the experiment group.
`group.2`	Character vector indicating the names(s) for the control group.

`mode` Character string indicating the analytic mode to model DNA methylation. Should be one of the followings: 'Regular', 'Enhancer', 'miRNA' or 'lncRNA'. Default: 'Regular'. See details for more information.

`promoters` Logic indicating whether to focus the analysis on CpGs associated with promoters (2000 bp upstream and 1000 bp downstream of the transcription start site). This parameter is only used for the Regular mode.

`correlation` Character vector indicating the expected correlation between DNA methylation and gene expression. Can be either 'negative' or 'positive'. Default: 'negative'.

`met.platform` Character string indicating the microarray type for collecting the DNA methylation data. The value should be either 'HM27', 'HM450' or 'EPIC'. Default: 'HM450'

`genome` Character string indicating the genome build version to be used for CpG annotation. Should be either 'hg19' or 'hg38'. Default: 'hg38'.

`cluster` Logic indicating whether to cluster CpG site based on methylation levels using hierarchical clustering

`listOfGenes` Character vector used for filtering the genes to be evaluated.

`filter` Logic indicating whether to use a linear regression filter to pre-filter the CpGs whose methyhlation correlates with gene expression. Used in the Regular mode. Default: TRUE.

`raw.pvalue.threshold`
Numeric value indicating the threshold of the raw P value for selecting the functional CpG-gene pairs. Default: 0.05.

`adjusted.pvalue.threshold`
Numeric value indicating the threshold of the adjusted P value for selecting the function CpG-gene pairs. Default: 0.05.

`numFlankingGenes`
Numeric value indicating the number of flanking genes whose expression is to be evaluated for selecting the functional enhancers. Default: 20.

`roadmap.epigenome.groups`
(parameter used for the 'Enhancer' mode) Character vector indicating the tissue group(s) to be used for selecting the enhancers. See details for more information. Default: NULL.

`roadmap.epigenome.ids`
(parameter used for the 'Enhancer' mode) Character vector indicating the epigenome ID(s) to be used for selecting the enhancers. See details for more information. Default: NULL.

`chromatin.states`
(parameter used for the 'Enhancer' mode) Character vector indicating the chromatin states to be used for selecting the enhancers. To get the available chromatin states, please run the list.chromatin.states() function. Default: c('EnhA1', 'EnhA2', 'EnhG1', 'EnhG2').

`NoNormalMode` Logical indicating if the methylation states found in the experiment group should be compared to the control group. Default: FALSE.

`cores` Number of CPU cores to be used for computation. Default: 1.

`MixtureModelResults`
Pre-computed EpiMix results, used for generating functional probe-gene pair matrix. Default: NULL

`OutputRoot` File path to store the EpiMix result object. Default: '.' (current directory)

Details

mode: EpiMix incorporates four alternative analytic modes for modeling DNA methylation: "Regular," "Enhancer", "miRNA" and "lncRNA". The four analytic modes target DNA methylation analysis on different genetic elements. The Regular mode aims to model DNA methylation at proximal cis-regulatory elements of protein-coding genes. The Enhancer mode targets DNA methylation analysis on distal enhancers. The miRNA or lncRNA mode focuses on methylation analysis of miRNA- or lncRNA-coding genes.

roadmap.epigenome.groups & roadmap.epigenome.ids:

Since enhancers are cell-type or tissue-type specific, EpiMix needs to know the reference tissues or cell types in order to select the proper enhancers. EpiMix identifies enhancers from the RoadmapEpigenomic project (Nature, PMID: 25693563), which enhancers were identified by ChromHMM in over 100 tissue and cell types. Available epigenome groups (a group of relevant cell types) or epigenome ids (individual cell types) can be obtained from the original publication (Nature, PMID: 25693563, figure 2). They can also be retrieved from the list.epigenomes() function. If both roadmap.epigenome.groups and roadmap.epigenome.ids are specified, EpiMix will select all the epigenomes from the combination of the inputs.

Value

The results from EpiMix is a list with the following components:

`MethylationDrivers`
: CpG probes identified as differentially methylated by EpiMix.

`NrComponents`
: The number of methylation states found for each driver probe.

`MixtureStates`
: A list with the DM-values for each driver probe. Differential Methylation values (DM-values) are defined as the difference between the methylation mean of samples in one mixture component from the experiment group and the methylation mean in samples from the control group, for a given probe.

`MethylationStates`
: Matrix with DM-values for all driver probes (rows) and all samples (columns).

`Classifications`
: Matrix with integers indicating to which mixture component each sample in the experiment group was assigned to, for each probe.

`Models`
: Beta mixture model parameters for each driver probe.

`group.1`
: sample names in group.1 (experimental group).

`group.2`
: sample names in group.2 (control group).

`FunctionalPairs`
: Dataframe with the prevalence of differential methyaltion for each CpG probe in the sample population, and fold change of mRNA expression and P values for each signifcant probe-gene pair.

Examples

```
data(MET.data)
data(mRNA.data)
data(microRNA.data)
data(lncRNA.data)
data(LUAD.sample.annotation)

# Example #1: Regular mode
EpiMixResults <- EpiMix(methylation.data = MET.data,
```

```
                        gene.expression.data = mRNA.data,
                        sample.info = LUAD.sample.annotation,
                        group.1 = 'Cancer',
                        group.2 = 'Normal',
                        met.platform = 'HM450',
                        OutputRoot = tempdir())

# Example #2: Enhancer mode
EpiMixResults <- EpiMix(methylation.data = MET.data,
                        gene.expression.data = mRNA.data,
                        sample.info = LUAD.sample.annotation,
                        mode = 'Enhancer',
                        group.1 = 'Cancer',
                        group.2 = 'Normal',
                        met.platform = 'HM450',
                        roadmap.epigenome.ids = 'E096',
                        OutputRoot = tempdir())

# Example #3: miRNA mode
EpiMixResults <- EpiMix(methylation.data = MET.data,
                        gene.expression.data = microRNA.data,
                        sample.info = LUAD.sample.annotation,
                        mode = 'miRNA',
                        group.1 = 'Cancer',
                        group.2 = 'Normal',
                        met.platform = 'HM450',
                        OutputRoot = tempdir())

# Example #4: lncRNA mode
EpiMixResults <- EpiMix(methylation.data = MET.data,
                        gene.expression.data = lncRNA.data,
                        sample.info = LUAD.sample.annotation,
                        mode = 'lncRNA',
                        group.1 = 'Cancer',
                        group.2 = 'Normal',
                        met.platform = 'HM450',
                        OutputRoot = tempdir())
```

`EpiMix_getInfiniumAnnotation`

The EpiMix_getInfiniumAnnotation function

Description

fetch the Infinium probe annotation from the AnnotationHub

Usage

```
EpiMix_getInfiniumAnnotation(plat = "EPIC", genome = "hg38")
```

Arguments

`plat`	character string indicating the methylation platform.
`genome`	character string indicating the version of genome build

Value

a GRange object of probe annotation

Examples

```
annot <- EpiMix_getInfiniumAnnotation(plat = "EPIC", genome = "hg38")
```

`EpiMix_PlotGene` *The EpiMix_PlotGene function*

Description

plot the genomic coordinate, DM values and chromatin state for each CpG probe of a specific gene.

Usage

```
EpiMix_PlotGene(
  gene.name,
  EpiMixResults,
  met.platform = "HM450",
  roadmap.epigenome.id = "E002",
  left.gene.margin = 10000,
  right.gene.margin = 10000,
  gene.name.font = 0.7,
  show.probe.name = TRUE,
  probe.name.font = 0.6,
  plot.transcripts = TRUE,
  plot.transcripts.structure = TRUE,
  y.label.font = 0.8,
  y.label.margin = 0.1,
  axis.number.font = 0.5,
  chromatin.label.font = 0.7,
  chromatin.label.margin = 0.02
)
```

Arguments

`gene.name`	character string indicating the name of the gene to be plotted.
`EpiMixResults`	the resulting list object returned from the function of EpiMix.
`met.platform`	character string indicating the type of the microarray where the DNA methylation data were collected. The value should be either 'HM27', 'HM450' or 'EPIC'. Default: 'HM450'
`roadmap.epigenome.id`	character string indicating the epigenome id (EID) for a reference tissue or cell type. Default: 'E002'. If the value is empty (""), no histone modifications plot will show.\ Note: Keep this value empty if using the Windows system, since this feature is not supported in Windows.
`left.gene.margin`	numeric value indicating the number of extra nucleotide bases to be plotted on the left side of the target gene. Default: 10000.

`right.gene.margin`
: numeric value indicating the number of extra nucleotide bases to be plotted on the right side of the target gene. Default: 10000.

`gene.name.font`
: numeric value indicating the font size for the gene name. Default: 0.7.

`show.probe.name`
: logic indicating whether to show the name(s) for each differentially methylated CpG probe. Default: TRUE

`probe.name.font`
: numeric value indicating the font size of the name(s) for the differentially methylated probe(s) in pixels. Default: 0.6.

`plot.transcripts`
: logic indicating whether to plot each individual transcript of the gene. Default: TRUE. If False, the gene will be plotted with a single rectangle, without showing the structure of individual transcripts.

`plot.transcripts.structure`
: logic indicating whether to plot the transcript structure (introns and exons). Non-coding exons are shown in green and the coding exons are shown in red. Default: TRUE.

`y.label.font`
: font size of the y axis label

`y.label.margin`
: distance between y axis label and y axis

`axis.number.font`
: font size of axis ticks and numbers

`chromatin.label.font`
: font size of the labels of the histone proteins

`chromatin.label.margin`
: distance between the histone protein labels and axis

Details

this function requires R package dependencies: karyoploteR, TxDb.Hsapiens.UCSC.hg19.knownGene, org.Hs.eg.db

roadmap.epigenome.id: since the chromatin state is tissue or cell-type specific, EpiMix needs to know the reference tissue or cell type in order to retrieve the proper DNase-seq and histone ChIP-seq data. Available epigenome ids can be obtained from the Roadmap Epigenomic study (Nature, PMID: 25693563, figure 2). They can also be retrieved from the list.epigenomes() function.

Value

plot of the genomic coordinate, DM values and chromatin state for each CpG probe of a specific gene.

Examples

```
library(karyoploteR)
library(TxDb.Hsapiens.UCSC.hg19.knownGene)
library(org.Hs.eg.db)
library(regioneR)

data(Sample_EpiMixResults_Regular)

gene.name = 'CCND2'
```

```
roadmap.epigenome.id = 'E096'

EpiMix_PlotGene(gene.name = gene.name,
                EpiMixResults = Sample_EpiMixResults_Regular,
                met.platform = 'HM450',
                roadmap.epigenome.id = roadmap.epigenome.id)
```

`EpiMix_PlotModel` *The EpiMix_PlotModel function.*

Description

Produce the mixture model and the gene expression plots representing the EpiMix results.

Usage

```
EpiMix_PlotModel(
  EpiMixResults,
  Probe,
  methylation.data,
  gene.expression.data = NULL,
  GeneName = NULL,
  axis.title.font = 20,
  axis.text.font = 16,
  legend.title.font = 18,
  legend.text.font = 18,
  plot.title.font = 20
)
```

Arguments

`EpiMixResults`	resulting list object from the EpiMix function.
`Probe`	character string indicating the name of the CpG probe for which to create a mixture model plot.
`methylation.data`	Matrix with the methylation data with genes in rows and samples in columns.
`gene.expression.data`	Gene expression data with genes in rows and samples in columns (optional). Default: NULL.
`GeneName`	character string indicating the name of the gene whose expression will be ploted with the EpiMix plot (optional). Default: NULL.
`axis.title.font`	font size for the axis legend.
`axis.text.font`	font size for the axis label.
`legend.title.font`	font size for the legend title.

`legend.text.font`
: font size for the legend label.

`plot.title.font`
: font size for the plot title.

Details

The violin plot and the scatter plot will be NULL if the gene expression data or the GeneName is not provided

Value

A list of EpiMix plots:

`MixtureModelPlot`
: a histogram of the distribution of DNA methylation data

`ViolinPlot`
: a violin plot of gene expression levels in different mixutures in the MixtureModelPlot

`CorrelationPlot`
: a scatter plot between DNA methylation and gene expression

Examples

```
{
data(MET.data)
data(mRNA.data)
data(Sample_EpiMixResults_Regular)

probe = "cg14029001"
gene.name = "CCND3"
plots <- EpiMix_PlotModel(
                          EpiMixResults = Sample_EpiMixResults_Regular,
                          Probe = probe,
                          methylation.data = MET.data,
                          gene.expression.data = mRNA.data,
                          GeneName = gene.name
                           )
plots$MixtureModelPlot
plots$ViolinPlot
plots$CorreilationPlot
}
```

EpiMix_PlotProbe *The EpiMix_PlotProbe function*

Description

plot the genomic coordinate and the chromatin state of a specific CpG probe and the nearby genes.

Usage

```
EpiMix_PlotProbe(
  probe.name,
  EpiMixResults,
  met.platform = "HM450",
  roadmap.epigenome.id = "E002",
  numFlankingGenes = 20,
  left.gene.margin = 10000,
  right.gene.margin = 10000,
  gene.name.pos = 2,
  gene.name.size = 0.5,
  gene.arrow.length = 0.05,
  gene.line.width = 2,
  plot.chromatin.state = TRUE,
  y.label.font = 0.8,
  y.label.margin = 0.1,
  axis.number.font = 0.5,
  chromatin.label.font = 0.7,
  chromatin.label.margin = 0.02
)
```

Arguments

probe.name	character string indicating the CpG probe name.
EpiMixResults	resulting list object returned from EpiMix.
met.platform	character string indicating the type of micro-array where the DNA methylation data were collected.Can be either 'HM27', 'HM450' or 'EPIC'. Default: 'HM450'
roadmap.epigenome.id	character string indicating the epigenome id (EID) for a reference tissue or cell type. Default: 'E002'. If the value is empty (""), no histone modifications plot will show.\ Note: Keep this value empty if using the Windows system, since this feature is not supported in Windows.
numFlankingGenes	numeric value indicating the number of flanking genes to be plotted with the CpG probe. Default: 20 (10 gene upstream and 10 gene downstream).
left.gene.margin	numeric value indicating the number of extra nucleotide bases to be plotted on the left side of the image. Default: 10000.
right.gene.margin	numeric value indicating the number of extra nucleotide bases to be plotted on the right side of the image. Default: 10000.
gene.name.pos	integer indicating the position for plotting the gene name relative to the gene structure. Should be 1 or 2 or 3 or 4, indicating bottom, left, top, and right, respectively.
gene.name.size	numeric value indicating the font size of the gene names in pixels.
gene.arrow.length	numeric value indicating the size of the arrow which indicates the positioning of the gene.

`gene.line.width`
: numeric value indicating the line width for the genes.

`plot.chromatin.state`
: logical indicating whether to plot the DNase-seq and histone ChIP-seq signals. Warnings: If the 'numFlankingGenes' is a larger than 15, plotting the chromatin state may flood the internal memory.

`y.label.font`
: font size of the y axis label.

`y.label.margin`
: distance between y axis label and y axis.

`axis.number.font`
: font size of axis ticks and numbers.

`chromatin.label.font`
: font size of the labels of the histone proteins.

`chromatin.label.margin`
: distance between the histone protein labels and axis.

Details

this function requires additional dependencies: karyoploteR, TxDb.Hsapiens.UCSC.hg19.knownGene, org.Hs.eg.db

roadmap.epigenome.id: since the chromatin state is tissue or cell-type specific, EpiMix needs to know the reference tissue or cell type in order to retrieve the proper DNase-seq and histone ChIP-seq data. Available epigenome ids can be obtained from the Roadmap Epigenomic study (Nature, PMID: 25693563, figure 2). They can also be retrieved from the list.epigenomes() function.

Value

plot with CpG probe and nearby genes. Genes whose expression is significantly negatively associated with the methylation of the probe are shown in red, while the others are shown in black.

Examples

```
library(karyoploteR)
library(TxDb.Hsapiens.UCSC.hg19.knownGene)
library(org.Hs.eg.db)
library(regioneR)

data(Sample_EpiMixResults_Regular)

# The CpG site to plot
probe.name = 'cg00374492'

# The number of adjacent genes to be plotted
numFlankingGenes = 10

# Set up the reference cell/tissue type
roadmap.epigenome.id = 'E096'

# Generate the plot
EpiMix_PlotProbe(probe.name = probe.name,
                 EpiMixResults = Sample_EpiMixResults_Regular,
                 met.platform = 'HM450',
                 roadmap.epigenome.id = roadmap.epigenome.id,
                 numFlankingGenes = numFlankingGenes)
```

EpiMix_PlotSurvival *EpiMix_PlotSurvival function*

Description

function to plot Kaplan-meier survival curves for patients with different methylation state of a specific probe.

Usage

```
EpiMix_PlotSurvival(
  EpiMixResults,
  plot.probe,
  TCGA_CancerSite = NULL,
  clinical.df = NULL,
  font.legend = 16,
  font.x = 16,
  font.y = 16,
  font.tickslab = 14,
  legend = c(0.8, 0.9),
  show.p.value = TRUE
)
```

Arguments

EpiMixResults	List of objects returned from the EpiMix function
plot.probe	Character string with the name of the probe
TCGA_CancerSite	TCGA cancer code (e.g. 'LUAD')
clinical.df	(If the TCGA_CancerSite parameter has been specified, this parameter is optional) Dataframe with survival information. Must contain at least three columns: 'sample.id', 'days_to_death', 'days_to_last_follow_up'.
font.legend	numeric value indicating the font size of the figure legend. Default: 16
font.x	numeric value indicating the font size of the x axis label. Default: 16
font.y	numeric value indicating the font size of the y axis label. Default: 16
font.tickslab	numeric value indicating the font size of the axis tick label. Default: 14
legend	numeric vector indicating the x,y coordinate for positioning the figure legend. c(0,0) indicates bottom left, while c(1,1) indicates top right. Default: c(0.8,0.9). If 'none', legend will be removed.
show.p.value	logic indicating whether to show p value in the plot. P value was calculated by log-rank test. Default: TRUE.

Value

Kaplan-meier survival curve showing the survival time for patients with different methylation states of the probe.

Examples

```
library(survival)
library(survminer)

data(Sample_EpiMixResults_miRNA)

EpiMix_PlotSurvival(EpiMixResults = Sample_EpiMixResults_miRNA,
                    plot.probe = 'cg00909706',
                    TCGA_CancerSite = 'LUAD')
```

`filterLinearProbes` *The filterLinearProbes function*

Description

use a linear regression filter to screen for probes that were negatively associated with gene expression.

Usage

```
filterLinearProbes(
  methylation.data,
  gene.expression.data,
  ProbeAnnotation,
  cores,
  filter,
  cluster,
  correlation = "negative"
)
```

Arguments

`methylation.data`	methylation data matrix.
`gene.expression.data`	gene expression data matrix.
`ProbeAnnotation`	dataframe of probe annotation
`cores`	number of CPU cores used for computation
`filter`	logical indicating whether to perform a linear regression to select functional probes
`cluster`	logical indicating whether the CpGs were clustered using hierarchical clustering
`correlation`	Character vector indicating the expected correlation between DNA methylation and gene expression. Can be either 'negative' or 'positive'. Default: 'negative'.

Value

a character vector of probe names.

filterMethMatrix *The filterMethMatrix function*

Description

The filterMethMatrix function

Usage

```
filterMethMatrix(MET_matrix, control.names, gene.expression.data)
```

Arguments

MET_matrix	a matrix of methylation states from the EpiMix results
control.names	a character vector of control sample names
gene.expression.data	a matrix with gene expression data

Details

This function filters methylation states from the beta mixture modeling for each probe. The filtered probes can be used to model gene expression by Wilcoxon test.

Value

a matrix of methylation states for each differentially methylated probe with probes in rows and patient in columns.

filterProbes *The filterProbes function*

Description

filter CpG sites based on user-specified conditions

Usage

```
filterProbes(
  mode,
  gene.expression.data,
  listOfGenes,
  promoters,
  met.platform,
  genome
)
```

Arguments

mode	analytic mode
gene.expression.data	matrix of gene expression data
listOfGenes	list of genes of interest
promoters	logic indicating whether to filter CpGs on promoters
met.platform	methylation platform
genome	genome build version

Value

filtered ProbeAnnotation

---

find_miRNA_targets *The find_miRNA_targets function*

Description

Detection potential target protein-coding genes for the differentially methylated miRNAs using messenger RNA expression data

Usage

```
find_miRNA_targets(
  EpiMixResults,
  geneExprData,
  database = "mirtarbase",
  raw.pvalue.threshold = 0.05,
  adjusted.pvalue.threshold = 0.2,
  cores = 1
)
```

Arguments

EpiMixResults	List of the result objects returned from the EpiMix function.
geneExprData	Matrix of the messenger RNA expression data with genes in rows and samples in columns.
database	character string indicating the database for retrieving miRNA targets. Default: "mirtarbase".
raw.pvalue.threshold	Numeric value indicating the threshold of the raw P value for selecting the miRNA targets based on gene expression. Default: 0.05.
adjusted.pvalue.threshold	Numeric value indicating the threshold of the adjusted P value for selecting the miRNA targets based on gene expression. Default: 0.2.
cores	Number of CPU cores to be used for computation. Default: 1.

Value

Matrix indicating the miRNA-target pairs, with fold changes of target gene expression and P values.

Examples

```
library(multiMiR)
library(miRBaseConverter)

data(mRNA.data)
data(Sample_EpiMixResults_miRNA)

miRNA_targets <- find_miRNA_targets(
 EpiMixResults = Sample_EpiMixResults_miRNA,
 geneExprData = mRNA.data
)
```

`functionEnrich` *The functionEnrich function*

Description

Perform functional enrichment analysis for the differentially methylated genes occurring in the significant CpG-gene pairs.

Usage

```
functionEnrich(
  EpiMixResults,
  methylation.state = "all",
  enrich.method = "GO",
  ont = "BP",
  simplify = TRUE,
  cutoff = 0.7,
  pvalueCutoff = 0.05,
  pAdjustMethod = "BH",
  qvalueCutoff = 0.2,
  save.dir = "."
)
```

Arguments

`EpiMixResults`	List of the result objects returned from the EpiMix function.
`methylation.state`	character string indicating whether to use all the differentially methylated genes or only use the hypo- or hyper-methylated genes for enrichment analysis. Can be either 'all', 'Hyper' or 'Hypo'.
`enrich.method`	character string indicating the method to perform enrichment analysis, can be either 'GO' or 'KEGG'.

ont	character string indicating the aspect for GO analysis. Can be one of 'BP' (i.e., biological process), 'MF' (i.e., molecular function), and 'CC' (i.e., cellular component) subontologies, or 'ALL' for all three.
simplify	boolean value indicating whether to remove redundancy of enriched GO terms.
cutoff	if simplify is TRUE, this is the threshold for similarity cutoff of the ajusted p value.
pvalueCutoff	adjusted pvalue cutoff on enrichment tests to report
pAdjustMethod	one of 'holm', 'hochberg', 'hommel', 'bonferroni', 'BH', 'BY', 'fdr', 'none'
qvalueCutoff	qvalue cutoff on enrichment tests to report as significant. Tests must pass i) pvalueCutoff on unadjusted pvalues, ii) pvalueCutoff on adjusted pvalues and iii) qvalueCutoff on qvalues to be reported.
save.dir	path to save the enrichment table.

Value

a clusterProfiler enrichResult instance

Examples

```
library(clusterProfiler)
library(org.Hs.eg.db)

data(Sample_EpiMixResults_Regular)

enrich.results <- function.enrich(
 EpiMixResults = Sample_EpiMixResults_Regular,
 enrich.method = 'GO',
 ont = 'BP',
 simplify = TRUE,
 save.dir = ''
)
```

---

generateFunctionalPairs

The generateFunctionalPairs function

Description

Wrapper function to get functional CpG-gene pairs, used for Regular, miRNA and lncRNA modes

Usage

```
generateFunctionalPairs(
  MET_matrix,
  control.names,
  gene.expression.data,
  ProbeAnnotation,
  raw.pvalue.threshold,
  adjusted.pvalue.threshold,
```

```
  cores,
  mode = "Regular",
  correlation = "negative"
)
```

Arguments

MET_matrix	matrix of methylation states
control.names	character vector indicating the samples names in the control group
gene.expression.data	matrix of gene expression data
ProbeAnnotation	dataframe of probe annotation
raw.pvalue.threshold	raw p value threshold
adjusted.pvalue.threshold	adjusted p value threshold
cores	number of computational cores
mode	character string indicating the analytic mode
correlation	the expected relationship between DNAme and gene expression

Value

a dataframe of functional CpG-gene matrix

GEO_Download_DNAMethylation

The GEO_Download_DNAmethylation function

Description

Download the methylation data and the associated sample phenotypic data from the GEO database.

Usage

```
GEO_Download_DNAMethylation(
  AccessionID,
  targetDirectory = ".",
  DownloadData = TRUE
)
```

Arguments

AccessionID	character string indicating GEO accession number. Currently support the GEO series (GSE) data type.
targetDirectory	character string indicting the file path to save the data. Default: '.' (current directory).
DownloadData	logical indicating whether the actual data should be downloaded (Default: TRUE). If False, the desired directory where the downloaded data should have been saved is returned.

Value

a list with two elements. The first element ('$MethylationData') indicating the file path to the downloaded methylation data. The second element ('$PhenotypicData') indicating the file path to the sample phenotypic data.

Examples

```
METdirectories <- GEO_Download_DNAMethylation(AccessionID = 'GSE114134',
                                              targetDirectory = tempdir())
```

`GEO_Download_GeneExpression`

The GEO_Download_GeneExpression function

Description

Download the gene expression data and the associated sample phenotypic data from the GEO database.

Usage

```
GEO_Download_GeneExpression(
  AccessionID,
  targetDirectory = ".",
  DownloadData = TRUE
)
```

Arguments

`AccessionID`	character string indicating the GEO accession number. Currently support the GEO series (GSE) data type.
`targetDirectory`	character string indicting the file path to save the data. Default: '.' (current directory)
`DownloadData`	logical indicating whether the actual data should be downloaded (Default: TRUE). If False, the desired directory where the downloaded data should have been saved is returned.

Value

a list with two elements. The first element ('$GeneExpressionData') indicating the file path to the downloaded methylation data. The second element ('$PhenotypicData') indicating the file path to the sample phenotypic data.

Examples

```
GEdirectories <- GEO_Download_GeneExpression(AccessionID = 'GSE114065',
                                             targetDirectory = tempdir())
```

GEO_EstimateMissingValues_Methylation

The GEO_EstimateMissingValues_Methylation function

Description

Internal. Removes samples and probes with more missing values than the MissingValueThreshold, and imputes remaining missing values using Tibshirani's KNN method.

Usage

```
GEO_EstimateMissingValues_Methylation(
  MET_Data,
  MissingValueThresholdGene = 0.3,
  MissingValueThresholdSample = 0.3
)
```

Arguments

MET_Data	methylation data or gene expression data matrix.
MissingValueThresholdGene	threshold for missing values per gene. Genes with a percentage of NAs greater than this threshold are removed. Default is 0.3.
MissingValueThresholdSample	threshold for missing values per sample. Samples with a percentage of NAs greater than this threshold are removed. Default is 0.1.

Value

the dataset with imputed values and possibly some genes or samples deleted.

GEO_EstimateMissingValues_Molecular

The GEO_EstimateMissingValues_Molecular function

Description

Internal. Removes samples and genes with more missing values than the MissingValueThreshold, and imputes remaining missing values using Tibshirani's KNN method.

Usage

```
GEO_EstimateMissingValues_Molecular(
  MET_Data,
  MissingValueThresholdGene = 0.3,
  MissingValueThresholdSample = 0.1
)
```

Arguments

MET_Data	methylation data or gene expression data matrix.
MissingValueThresholdGene	threshold for missing values per gene. Genes with a percentage of NAs greater than this threshold are removed. Default is 0.3.
MissingValueThresholdSample	threshold for missing values per sample. Samples with a percentage of NAs greater than this threshold are removed. Default is 0.1.

Value

the dataset with imputed values and possibly some genes or samples deleted.

GEO_GetSampleInfo *The GEO_GetSampleInfo function*

Description

auxiliary function to generate a sample information dataframe that indicates which study group each sample belongs to.

Usage

```
GEO_GetSampleInfo(METdirectories, group.column, targetDirectory = ".")
```

Arguments

METdirectories	list of the file paths to the downloaded DNA methylation data, which can be the output from the GEO_Download_DNAMethylation function.
group.column	character string indicating the column in the phenotypic data that defines the study group of each sample. The values in this column will be used to split the experiment and the control group.
targetDirectory	file path to save the output. Default: '.' (current directory)

Value

a dataframe with two columns: a 'primary' column indicating the actual sample names, a 'sample.type' column indicating the study group for each sample.

GEO_getSampleMap *the GEO_getSampleMap function*

Description

auxiliary function to generate a sample map for DNA methylation data and gene expression data

Usage

```
GEO_getSampleMap(METdirectories, GEdirectories, targetDirectory = ".")
```

Arguments

METdirectories	list of the file paths to the downloaded DNA methylation datasets, which can be the output from the GEO_Download_DNAMethylation function.
GEdirectories	list of the file paths to the downloaded gene expression datasets, which can be the output from the GEO_Download_GeneExpression function.
targetDirectory	file path to save the output. Default: '.' (current directory)

Value

dataframe with three columns: $assay (character string indicating the type of the experiment, can be either 'DNA methylation' or 'Gene expression'), $primary(character string indicating the actual sample names), $colnames (character string indicating the actual column names for each samples in DNA methylation data and gene expression data)

get.chromosome *The get.chromosome function*

Description

given a list of genes, get the chromosomes of these genes.

Usage

```
get.chromosome(genes, genome)
```

Arguments

genes	character vector with the gene names
genome	character string indicating the genome build version, can be either 'hg19' or 'hg38'

Value

a dataframe for the mapping between genes and their chromosomes.

get.prevalence *The get.prevalence function*

Description

Helper function to get the methylation state and the prevalence of the differential methylation of a CpG sites in the study population.

Usage

```
get.prevalence(MethylMixResults)
```

Arguments

MET_matrix	matrix of methylation states

Value

a list of prevalence for the abnormal methylation

Get.Pvalue.p *Calculate empirical Pvalue*

Description

Calculate empirical Pvalue

Usage

```
Get.Pvalue.p(U.matrix, permu)
```

Arguments

U.matrix	A data.frame of raw pvalue from U test. Output from .Stat.nonpara
permu	data frame of permutation. Output from .Stat.nonpara.permu

Value

A data frame with empirical Pvalue.

getFeatureProbe *getFeatureProbe to select probes within promoter regions or distal regions.*

Description

getFeatureProbe is a function to select the probes falling into distal feature regions or promoter regions.

This function selects the probes on HM450K that either overlap distal biofeatures or TSS promoter.

Usage

```
getFeatureProbe(
  feature = NULL,
  TSS,
  genome = "hg38",
  met.platform = "HM450",
  TSS.range = list(upstream = 2000, downstream = 2000),
  promoter = FALSE,
  rm.chr = NULL
)
```

Arguments

feature	A GRange object containing biofeature coordinate such as enhancer coordinates. If NULL only distal probes (2Kbp away from TSS will be selected) feature option is only usable when promoter option is FALSE.
TSS	A GRange object contains the transcription start sites. When promoter is FALSE, Union.TSS in **ELMER.data** will be used for default. When promoter is TRUE, UCSC gene TSS will be used as default (see detail). User can specify their own preference TSS annotation.
genome	Which genome build will be used: hg38 (default) or hg19.
met.platform	DNA methyaltion platform to retrieve data from: EPIC or 450K (default)
TSS.range	A list specify how to define promoter regions. Default is upstream =2000bp and downstream=2000bp.
promoter	A logical.If TRUE, function will ouput the promoter probes. If FALSE, function will ouput the distal probes overlaping with features. The default is FALSE.
rm.chr	A vector of chromosome need to be remove from probes such as chrX chrY or chrM

Details

In order to get real distal probes, we use more comprehensive annotated TSS by both GENCODE and UCSC. However, to get probes within promoter regions need more accurate annotated TSS such as UCSC. Therefore, there are different settings for promoter and distal probe selection. But user can specify their own favorable TSS annotation. Then there won't be any difference between promoter and distal probe selection. @return A GRanges object contains the coordinate of probes which locate within promoter regions or distal feature regions such as union enhancer from REMC and FANTOM5. @usage getFeatureProbe(feature, TSS, TSS.range = list(upstream = 2000, downstream = 2000), promoter = FALSE, rm.chr = NULL)

Value

A GRange object containing probes that satisfy selecting critiria.

`getFunctionalGenes` *The getFunctionalGenes function*

Description

Helper function to assess if the methylation of a probe is reversely correlated with the expression of its nearby genes.

Usage

```
getFunctionalGenes(
  target.probe,
  target.genes,
  MET_matrix,
  gene.expression.data,
  ProbeAnnotation,
  correlation = "negative",
  raw.pvalue.threshold = 0.05,
  adjusted.pvalue.threshold = 0.01
)
```

Arguments

`target.probe`	character string indicating the probe to be evaluated.
`target.genes`	character vector indicating the nearby genes of the target probe.
`MET_matrix`	methylation data matrix for CpGs from group.1 and group.2.
`gene.expression.data`	gene expression data matrix.
`ProbeAnnotation`	GRange object of CpG probe annotation.
`raw.pvalue.threshold`	raw p value from testing DNA methylation and gene expression
`adjusted.pvalue.threshold`	adjusted p value from testing DNA methylation and gene expression

Details

This function is probe-centered, which is used in the enhancer mode and the miRNA mode of EpiMix.

Value

dataframe with functional probe-gene pair and p values from the Wilcoxon test for methylation and gene expression.

Examples

```
data(Sample_EpiMixResults_Enhancer)
data(mRNA.data)
EpiMixResults <- Sample_EpiMixResults_Enhancer
target.probe <- EpiMixResults$FunctionalPairs$Probe[1]
target.genes <- EpiMixResults$FunctionalPairs$Gene
MET_matrix <- EpiMixResults$MethylationStates
ProbeAnnotation <- ExperimentHub::ExperimentHub()[["EH3675"]]
res <- getFunctionalGenes(target.probe, target.genes, MET_matrix, mRNA.data, ProbeAnnotation)
```

---

getLncRNAData *The getLncRNAData function*

Description

Helper function to retrieve the lncRNA expression data from Experiment Hub

Usage

```
getLncRNAData(CancerSite)
```

Arguments

CancerSite	TCGA cancer code

Value

local file path where the lncRNA expression data are saved

---

getMethStates *The getMethStates function*

Description

Helper function that adds a methyaltion state label to each driver probe

Usage

```
getMethStates(MethylMixResults, DM.probes)
```

Arguments

MethylMixResults	the list object returned from the EpiMix function
DM.probes	character vector of differentially methylated probes.

Value

a character vector with the methylation state ('Hypo', 'Hyper' or 'Dual') for each probe. The names for the vector are the probe names and the values are the methylation state.

getMethStates_Helper *The getMethStates_Helper function*

Description

helper function to determine the methylation state based on DM values

Usage

```
getMethStates_Helper(DMValues)
```

Arguments

DMValues	a character vector indicating the DM values of a CpG site

Value

a character string incdicating the methylation state of the CpG

GetNearGenes *GetNearGenes to collect nearby genes for one locus.*

Description

GetNearGenes is a function to collect equal number of gene on each side of one locus. It can receite either multi Assay Experiment with both DNA methylation and gene Expression matrix and the names of probes to select nearby genes, or it can receive two granges objects TRange and geneAnnot.

Usage

```
GetNearGenes(
  data = NULL,
  probes = NULL,
  geneAnnot = NULL,
  TRange = NULL,
  numFlankingGenes = 20
)
```

Arguments

data	A multi Assay Experiment with both DNA methylation and gene Expression objects
probes	Name of probes to get nearby genes (it should be rownames of the DNA methylation object in the data argument object)
geneAnnot	A GRange object or Summarized Experiment object that contains coordinates of promoters for human genome.
TRange	A GRange object or Summarized Experiment object that contains coordinates of a list of targets loci.

numFlankingGenes
: A number determines how many gene will be collected totally. Then the number devided by 2 is the number of genes collected from each side of targets (number shoule be even) Default to 20.

Value

A data frame of nearby genes and information: genes' IDs, genes' symbols, distance with target and side to which the gene locate to the target.

References

Yao, Lijing, et al. "Inferring regulatory element landscapes and transcription factor networks from cancer methylomes." Genome biology 16.1 (2015): 1.

---

getProbeAnnotation *The getProbeAnnotation function*

Description

Helper function to get the probe annotation based on mode

Usage

```
getProbeAnnotation(mode, met.platform, genome)
```

Arguments

mode	analytic mode
met.platform	methylation platform
genome	genome build version

Value

a ProbeAnnotation dataframe consisting of two columns: probe, gene

---

getRandomGenes *The getRandomGenes function*

Description

Helper function to get a set of random genes located on different chromosomes of the target CpG.

Usage

```
getRandomGenes(
  target.probe,
  gene.expression.data,
  ProbeAnnotation,
  genome = "hg38",
  perm = 1000
)
```

Arguments

target.probe	character string indicating the target CpG for generating the permutation p values.
gene.expression.data	a matrix of gene expression data.
ProbeAnnotation	GRange object of probe annotation.
genome	character string indicating the genome build version, can be either 'hg19' or 'hg38'.
perm	the number of permutation tests. Default: 1000

Value

a dataframe for the permutation genes and p values for the target CpG site.

---

getRegionNearGenes *Identifies nearest genes to a region*

Description

Auxiliary function for GetNearGenes This will get the closest genes (n=numFlankingGenes) for a target region (TRange) based on a genome of refenrece gene annotation (geneAnnot). If the transcript level annotation (tssAnnot) is provided the Distance will be updated to the distance to the nearest TSS.

Usage

```
getRegionNearGenes(
  TRange = NULL,
  numFlankingGenes = 20,
  geneAnnot = NULL,
  tssAnnot = NULL
)
```

Arguments

TRange	A GRange object contains coordinate of targets.
numFlankingGenes	A number determine how many gene will be collected from each
geneAnnot	A GRange object contains gene coordinates of for human genome.
tssAnnot	A GRange object contains tss coordinates of for human genome.

Value

A data frame of nearby genes and information: genes' IDs, genes' symbols,

Author(s)

Tiago C Silva (maintainer: tiagochst@usp.br)

getRoadMapEnhancerProbes *getRoadMapEnhancerProbes*

Description

getRoadMapEnhancerProbes

Usage

```
getRoadMapEnhancerProbes(
  met.platform = "EPIC",
  genome = "hg38",
  functional.regions = c("EnhA1", "EnhA2"),
  listOfEpigenomes = NULL,
  ProbeAnnotation
)
```

Arguments

met.platform	character string indicating the methylation platform, can be either 'EPIC' or 'HM450'
genome	character string indicating the genome build version, can be either 'hg19' or 'hg38'
functional.regions	character vector indicating the MNEMONIC chromatin states that will be retrieved from the Roadmap epigenomics. Default values are the active enhancers:'EnhA1', 'EnhA2'.
listOfEpigenomes	character vector indicting which epigenome(s) to use for finding enhancers.
ProbeAnnotation	GRange object of probe annotation.

Details

get the CpG probes that locate at the enhancer regions identified by the Roadmap epigenomics project

Value

a dataframe with enhancer probes and their chromosome coordinates

Examples

```
met.platform = 'EPIC'
genome = 'hg38'
listOfEpigenomes = c('E034', 'E045', 'E047')
functional.regions = c('EnhA1', 'EnhA2', 'EnhG1', 'EnhG2')
df.enhancer.probes <-  getEnhancerProbes(met.platform = met.platform,
                                         genome = genome,
                                         functional.regions = functional.regions,
```

```
                                    listOfEpigenomes = listOfEpigenomes)
```

`GetSurvivalProbe` *The GetSurvivalProbe function*

Description

Get probes whose methylation state is predictive of patient survival

Usage

```
GetSurvivalProbe(
  EpiMixResults,
  TCGA_CancerSite = NULL,
  clinical.data = NULL,
  raw.pval.threshold = 0.05,
  p.adjust.method = "none",
  adjusted.pval.threshold = 0.05,
  OutputRoot = ""
)
```

Arguments

`EpiMixResults`	List of objects returned from the EpiMix function
`TCGA_CancerSite`	String indicating the TCGA cancer code (e.g. 'LUAD')
`clinical.data`	(If the TCGA_CancerSite is specified, this parameter is optional) Dataframe with survival information. Must contain at least three columns: 'sample.id', 'days_to_death', 'days_to_last_follow_up'.
`raw.pval.threshold`	numeric value indicting the raw p value threshold for selecting the survival predictive probes. Survival time is compared by log-rank test. Default: 0.05
`p.adjust.method`	character string indicating the statistical method for adjusting multiple comparisons, can be either of 'holm', 'hochberg', 'hommel', 'bonferroni', 'BH', 'BY', 'fdr', 'none'. Default: 'fdr'
`adjusted.pval.threshold`	numeric value indicting the adjusted p value threshold for selecting the survival predictive probes. Default: 0.05
`OutputRoot`	path to save the output. If not null, the return value will be saved as 'Survival)Probes.csv'.

Value

a dataframe with probes whose methylation state is predictive of patient survival and the p value.

Examples

```
library(survival)

data('Sample_EpiMixResults_miRNA')

survival.CpGs <- GetSurvivalProbe(EpiMixResults = Sample_EpiMixResults_miRNA,
                                  TCGA_CancerSite = 'LUAD')
```

`getTSS` *getTSS to fetch GENCODE gene annotation (transcripts level) from Bioconductor package biomaRt If upstream and downstream are specified in TSS list, promoter regions of GENCODE gene will be generated.*

Description

getTSS to fetch GENCODE gene annotation (transcripts level) from Bioconductor package biomaRt If upstream and downstream are specified in TSS list, promoter regions of GENCODE gene will be generated.

Usage

```
getTSS(genome = "hg38", TSS = list(upstream = NULL, downstream = NULL))
```

Arguments

`genome`	Which genome build will be used: hg38 (default) or hg19.
`TSS`	A list. Contains upstream and downstream like TSS=list(upstream, downstream). When upstream and downstream is specified, coordinates of promoter regions with gene annotation will be generated.

Value

GENCODE gene annotation if TSS is not specified. Coordinates of GENCODE gene promoter regions if TSS is specified.

Author(s)

Lijing Yao (maintainer: lijingya@usc.edu)

get_firehoseData *The get_firehoseData function*

Description

Gets data from TCGA's firehose.

Usage

```
get_firehoseData(
  downloadData = TRUE,
  saveDir = "./",
  TCGA_acronym_uppercase = "LUAD",
  dataType = "stddata",
  dataFileTag = "mRNAseq_Preprocess.Level_3",
  FFPE = FALSE,
  fileType = "tar.gz",
  gdacURL = "https://gdac.broadinstitute.org/runs/",
  untarUngzip = TRUE,
  printDisease_abbr = FALSE
)
```

Arguments

downloadData	logical indicating if data should be downloaded (default: TRUE). If false, the url of the desired data is returned.
saveDir	path to directory to save downloaded files.
TCGA_acronym_uppercase	TCGA's cancer site code.
dataType	type of data in TCGA (default: 'stddata').
dataFileTag	name of the file to be downloaded (the default is to download RNAseq data, but this can be changed to download other data).
FFPE	logical indicating if FFPE data should be downloaded (default: FALSE).
fileType	type of downloaded file (default: 'fileType', other type not admitted at the moment).
gdacURL	gdac url.
untarUngzip	logical indicating if the gzip file downloaded should be untarred (default: TRUE).
printDisease_abbr	if TRUE data is not downloaded but all the possible cancer sites codes are shown (default: FALSE).

Value

DownloadedFile path to directory with downloaded files.

`mapTranscriptToGene` *mapTranscriptToGene*

Description

map the miRNA precursor names to HGNC

Usage

```
mapTranscriptToGene(transcripts)
```

Arguments

`transcripts`	vector with the name of miRNA precursors

Value

a dataframe with two columns: 'Transcript' indicating the miRNA precursor names, 'Gene_name' indicating the actual human gene names (HGNC)

`MethylMix_MixtureModel` *The MethylMix_MixtureModel function*

Description

Internal. Prepares all the structures to store the results and calls in a foreach loop a function that fits the mixture model in each gene.

Usage

```
MethylMix_MixtureModel(
  METcancer,
  METnormal = NULL,
  FunctionalGenes,
  NoNormalMode = FALSE
)
```

Arguments

`METcancer`	matrix with methylation data for cancer samples (genes in rows, samples in columns).
`METnormal`	matrix with methylation data for normal samples (genes in rows, samples in columns). If NULL no comparison to normal samples will be done.
`FunctionalGenes`	vector with genes names to be considered for the mixture models.
`NoNormalMode`	logical, if TRUE no comparison to normal samples is performed. Defaults to FALSE.

Value

MethylationStates matrix of DM values, with driver genes in the rows and samples in the columns.

NrComponents matrix with the number of components identified for each driver gene.

Models list with the mixture model fitted for each driver gene.

MethylationDrivers character vector with the genes found by MethylMix as differentially methylated and transcriptionally predictive (driver genes).

MixtureStates a list with a matrix for each driver gene containing the DM values.

Classifications a vector indicating to which component each sample was assigned.

MethylMix_ModelSingleGene

The MethylMix_ModelSingleGene function

Description

Internal. For a given gene, this function fits the mixture model, selects the number of components and defines the respective methylation states.

Usage

```
MethylMix_ModelSingleGene(
  GeneName,
  METdataVector,
  METdataNormalVector = NULL,
  NoNormalMode = FALSE,
  maxComp = 3,
  PvalueThreshold = 0.01,
  MeanDifferenceTreshold = 0.1,
  minSamplesPerGroup = 1
)
```

Arguments

GeneName	character string with the name of the gene to model
METdataVector	vector with methylation data for cancer samples.
METdataNormalVector	vector with methylation data for normal samples. It can be NULL and then no normal mode will be used.
NoNormalMode	logical, if TRUE no comparison to normal samples is performed. Defaults to FALSE.
maxComp	maximum number of mixture components admitted in the model (3 by default).
PvalueThreshold	threshold to consider results significant.
MeanDifferenceTreshold	threshold in beta value scale from which two methylation means are considered different.
minSamplesPerGroup	minimum number of samples required to belong to a new mixture component in order to accept it. Defaul is 1 (not used). If -1, each component has to have at least 5% of all cancer samples.

Details

maxComp, PvalueThreshold, METDiffThreshold, minSamplesPerGroup are arguments for this function but are fixed in their default values for the user because they are not available in the main MethylMix function, to keep it simple. It would be easy to make them available to the user if we want to.

Value

NrComponents number of components identified.

Models an object with the parameters of the model fitted.

MethylationStates vector with DM values for each sample.

MixtureStates vector with DMvalues for each component.

Classifications a vector indicating to which component each sample was assigned.

FlipOverState FlipOverState

`MethylMix_Predict` *The MethylMix_Predict function*

Description

Given a new data set with methylation data, this function predicts the mixture component for each new sample and driver gene. Predictions are based on posterior probabilities calculated with MethylMix'x fitted mixture model.

Usage

```
MethylMix_Predict(newBetaValuesMatrix, MethylMixResult)
```

Arguments

`newBetaValuesMatrix`
: Matrix with new observations for prediction, genes/cpg sites in rows, samples in columns. Although this new matrix can have a different number of genes/cpg sites than the one provided as METcancer when running MethylMix, naming of genes/cpg sites should be the same.

`MethylMixResult`
: Output object from MethylMix

Value

A matrix with predictions (indices of mixture component), driver genes in rows, new samples in columns

`MethylMix_RemoveFlipOver` *The MethylMix_RemoveFlipOver function*

Description

Internal. The estimated densities for each beta component can overlap, generating samples that look like being separated from their group. This function re classifies such samples.

Usage

```
MethylMix_RemoveFlipOver(
  OrigOrder,
  MethylationState,
  classification,
  METdataVector,
  NrComponents,
  UseTrainedFlipOver = FALSE,
  FlipOverState = 0
)
```

Arguments

`OrigOrder`	order of sorted values in the methylation vector.
`MethylationState`	methylation states for this gene.
`classification`	vector with integers indicating to wich component each sample was classified into.
`METdataVector`	vector with methylation values from the cancer samples.
`NrComponents`	number of components in this gene.
`UseTrainedFlipOver`	.
`FlipOverState`	.

Value

Corrected vectors with methylation states and classification.

`predictOneGene` *The predictOneGene function*

Description

Auxiliar function. Given a new vector of beta values, this function calculates a matrix with posterior prob of belonging to each mixture commponent (columns) for each new beta value (rows), and return the number of the mixture component with highest posterior probabilit

Usage

```
predictOneGene(newVector, mixtureModel)
```

Arguments

newVector	vector with new beta values
mixtureModel	beta mixture model object for the gene being evaluated.

Value

A matrix with predictions (indices of mixture component), driver genes in rows, new samples in columns

---

Preprocess_CancerSite_Methylation27k

The Preprocess_CancerSite_Methylation27k function

Description

Internal. Pre-processes DNA methylation data from TCGA from Illymina 27k arrays.

Usage

```
Preprocess_CancerSite_Methylation27k(
  CancerSite,
  METdirectory,
  doBatchCorrection,
  batch.correction.method,
  MissingValueThreshold
)
```

Arguments

CancerSite	character of length 1 with TCGA cancer code.
METdirectory	character with directory where a folder for downloaded files will be created. Can be the object returned by the Download_DNAmethylation function.
MissingValueThreshold	threshold for removing samples or genes with missing values.

Value

List with pre processed methylation data for cancer and normal samples.

`Preprocess_DNAMethylation` *The Preprocess_DNAMethylation function*

Description

Preprocess DNA methylation data from the GEO database.

Usage

```
Preprocess_DNAMethylation(
  methylation.data,
  met.platform = "EPIC",
  genome = "hg38",
  sample.info = NULL,
  group.1 = NULL,
  group.2 = NULL,
  sample.map = NULL,
  rm.chr = c("chrX", "chrY"),
  MissingValueThresholdGene = 0.2,
  MissingValueThresholdSample = 0.2,
  doBatchCorrection = FALSE,
  BatchData = NULL,
  batch.correction.method = "Seurat",
  cores = 1
)
```

Arguments

`methylation.data`	matrix of DNA methylation data with CpG in rows and sample names in columns.
`met.platform`	character string indicating the type of the Illumina Infinium BeadChip for collecting the methylation data. Should be either 'HM450' or 'EPIC'. Default: 'EPIC'
`genome`	character string indicating the genome build version for retrieving the probe annotation. Should be either 'hg19' or 'hg38'. Default: 'hg38'.
`sample.info`	dataframe that maps each sample to a study group. Should contain two columns: the first column (named: 'primary') indicating the sample names, and the second column (named: 'sample.type') indicating which study group each sample belongs to (e.g., "Experiment" vs. "Control", "Cancer" vs. "Normal"). Sample names in the 'primary' column must coincide with the column names of the methylation.data. Please see details for more information. Default: NULL.
`group.1`	character vector indicating the name(s) for the experiment group. The values must coincide with the values in the 'sample.type' of the sample.info dataframe.Please see details for more information. Default: NULL.
`group.2`	character vector indicating the names(s) for the control group. The values must coincide with the values in the 'sample.type' of the sample.info dataframe. Please see details for more information. Default: NULL.

`sample.map` dataframe for mapping the GEO accession ID (column names) to the actual sample names. Can be the output from the GEO_getSampleMap function. Default: NULL.

`rm.chr` character vector indicating the probes on which chromosomes to be removed. Default: 'chrX', 'chrY'.

`MissingValueThresholdGene` threshold for missing values per gene. Genes with a percentage of NAs greater than this threshold are removed. Default: 0.3.

`MissingValueThresholdSample` threshold for missing values per sample. Samples with a percentage of NAs greater than this threshold are removed. Default: 0.1.

`doBatchCorrection` logical indicating whether to perform batch correction. If TRUE, the batch data need to be provided.

`BatchData` dataframe with batch information. Should contain two columns: the first column indicating the actual sample names, the second column indicating the batch. Users are expected to retrieve the batch information from the GEO on their own, but this can also be done using the GEO_getSampleInfo function with the 'group.column' as the column indicating the batch for each sample. Defualt': NULL.

`batch.correction.method` character string indicating the method that will be used for batch correction. Should be either 'Seurat' or 'Combat'. Default: 'Seurat'.

`cores` number of CPU cores to be used for batch effect correction. Defaut: 1.

Details

The data preprocessing pipeline includes: (1) eliminating samples and genes with too many NAs, imputing NAs. (2) (optional) mapping the column names of the DNA methylation data to the actual sample names based on the information from 'sample.map'. (3) (optional) removing CpG probes on the sex chromosomes or the user-defined chromosomes. (4) (optional) doing Batch correction. If both sample.info and group.1 and group.2 information are provided, the function will perform missing value estimation and batch correction on group.1 and group.2 separately. This will ensure that the true difference between group.1 and group.2 will not be obscured by missing value estimation and batch correction.

Value

DNA methylation data matrix with probes in rows and samples in columns.

Examples

```
{
data(MET.data)
data(LUAD.sample.annotation)

Preprocessed_Data <- Preprocess_DNAMethylation(MET.data,
                                               met.platform = 'HM450',
                                               sample.info = LUAD.sample.annotation,
                                               group.1 = 'Cancer',
                                               group.2 = 'Normal')

}
```

Preprocess_GeneExpression
The Preprocess_GeneExpression function

Description

Preprocess the gene expression data from the GEO database.

Usage

```
Preprocess_GeneExpression(
  gene.expression.data,
  sample.info = NULL,
  group.1 = NULL,
  group.2 = NULL,
  sample.map = NULL,
  MissingValueThresholdGene = 0.3,
  MissingValueThresholdSample = 0.1,
  doBatchCorrection = FALSE,
  BatchData = NULL,
  batch.correction.method = "Seurat",
  cores = 1
)
```

Arguments

gene.expression.data	a matrix of gene expression data with gene in rows and samples in columns.
sample.info	dataframe that maps each sample to a study group. Should contain two columns: the first column (named: 'primary') indicating the sample names, and the second column (named: 'sample.type') indicating which study group each sample belongs to (e.g., "Experiment" vs. "Control", "Cancer" vs. "Normal"). Sample names in the 'primary' column must coincide with the column names of the methylation.data. Please see details for more information. Default: NULL.
group.1	character vector indicating the name(s) for the experiment group. The values must coincide with the values in the 'sample.type' of the sample.info dataframe.Please see details for more information. Default: NULL.
group.2	character vector indicating the names(s) for the control group. The values must coincide with the values in the 'sample.type' of the sample.info dataframe. Please see details for more information. Default: NULL.
sample.map	dataframe for mapping the GEO accession ID (column names) to the actual sample names. Can be the output from the GEO_getSampleMap function. Default: NULL.
MissingValueThresholdGene	threshold for missing values per gene. Genes with a percentage of NAs greater than this threshold are removed. Default is 0.3.
MissingValueThresholdSample	threshold for missing values per sample. Samples with a percentage of NAs greater than this threshold are removed. Default is 0.1.

doBatchCorrection
: logical indicating whether to perform batch correction. If TRUE, the batch data need to be provided.

BatchData
: dataframe with batch information. Should contain two columns: the first column indicating the actual sample names, the second column indicating the batch. Users are expected to retrieve the batch information from GEO on their own, but this can also be done using the GEO_getSampleInfo function with the 'group.column' as the column indicating the batch for each sample. Defualt': NULL.

batch.correction.method
: character string indicating the method that be used for batch correction. Should be either 'Seurat' or 'Combat'. Default: 'Seurat'.

cores
: number of CPU cores to be used for batch effect correction. Default: 1

Details

The preprocessing pipeline includes: (1) eliminating samples and genes with too many NAs and imputing NAs. (2) if the gene names (rownames) in the gene expression data are ensembl_gene_ids or ensembl_transcript_ids, translate the gene names or the transcript names to human gene symbols (HGNC). (3) mapping the column names of the gene expression data to the actual sample names based on the information from 'sample.map'. (4) doing batch correction.

Value

gene expression data matrix with genes in rows and samples in columns.

Examples

```
{
data(mRNA.data)
data(LUAD.sample.annotation)
Preprocessed_Data <- Preprocess_GeneExpression(gene.expression.data = mRNA.data,
                                                sample.info = LUAD.sample.annotation,
                                                group.1 = 'Cancer',
                                                group.2 = 'Normal')
}
```

Preprocess_MAdata_Cancer

The Preprocess_MAdata_Cancer function

Description

Internal. Pre-process gene expression data for cancer samples.

Usage

```
Preprocess_MAdata_Cancer(
  CancerSite,
  Directory,
  File,
  MissingValueThresholdGene = 0.3,
  MissingValueThresholdSample = 0.1,
```

```
  doBatchCorrection,
  batch.correction.method,
  BatchData
)
```

Arguments

CancerSite	TCGA code for the cancer site.
Directory	Directory.
File	File.
MissingValueThresholdGene	threshold for missing values per gene. Genes with a percentage of NAs greater than this threshold are removed. Default is 0.3.
MissingValueThresholdSample	threshold for missing values per sample. Samples with a percentage of NAs greater than this threshold are removed. Default is 0.1.

Value

The data matrix.

Preprocess_MAdata_Normal

The Preprocess_MAdata_Normal function

Description

Internal. Pre-process gene expression data for normal samples.

Usage

```
Preprocess_MAdata_Normal(
  CancerSite,
  Directory,
  File,
  MissingValueThresholdGene,
  MissingValueThresholdSample,
  doBatchCorrection,
  batch.correction.method,
  BatchData
)
```

Arguments

CancerSite	TCGA code for the cancer site.
Directory	Directory.
File	File.
MissingValueThresholdGene	threshold for missing values per gene. Genes with a percentage of NAs greater than this threshold are removed. Default is 0.3.
MissingValueThresholdSample	threshold for missing values per sample. Samples with a percentage of NAs greater than this threshold are removed. Default is 0.1.

Value

The data matrix.

`removeDuplicatedGenes` *The removeDuplicatedGenes function*

Description

sum up the transcript expression values if a gene has multiple transcripts

Usage

```
removeDuplicatedGenes(GEN_data)
```

Arguments

`GEN_data`	gene expression data matrix

Value

gene expression data matrix with duplicated genes removed

`splitmatrix` *The splitmatix function*

Description

The splitmatix function

Usage

```
splitmatrix(x, by = "row")
```

Arguments

`x`	A matrix
`by`	A character specify if split the matrix by row or column.

Value

A list each of which is the value of each row/column in the matrix.

TCGA_Download_DNAmethylation
The TCGA_Download_DNAmethylation function

Description

Download DNA methylation data from TCGA.

Usage

```
TCGA_Download_DNAmethylation(CancerSite, TargetDirectory, downloadData = TRUE)
```

Arguments

CancerSite	character of length 1 with TCGA cancer code.
TargetDirectory	character with directory where a folder for downloaded files will be created.
downloadData	logical indicating if data should be downloaded (default: TRUE). If false, the url of the desired data is returned.

Value

list with paths to downloaded files for both 27k and 450k methylation data.

Examples

```
METdirectories <- TCGA_Download_DNAmethylation(CancerSit = 'OV', TargetDirectory = tempdir())
```

TCGA_Download_GeneExpression
The TCGA_Download_GeneExpression function

Description

Download gene expression data from TCGA.

Usage

```
TCGA_Download_GeneExpression(
  CancerSite,
  TargetDirectory,
  mode = "Regular",
  downloadData = TRUE
)
```

Arguments

CancerSite	character string indicating the TCGA cancer code.
TargetDirectory	character with directory where a folder for downloaded files will be created.
mode	character string indicating whether we should download the gene expression data for miRNAs or lncRNAs, instead of for protein-coding genes. See details for more information.
downloadData	logical indicating if the data should be downloaded (default: TRUE). If False, the url of the desired data is returned.

Details

mode: when mode is set to 'Regular', this function downloads the level 3 RNAseq data (file tag 'mRNAseq_Preprocess.Level_3'). Since there is not enough RNAseq data for OV and GBM, the micro array data is downloaded. If you plan to run the EpiMix on miRNA- or lncRNA-coding genes, please specify the 'mode' parameter to 'miRNA' or 'lncRNA'.

Value

list with paths to downloaded files for gene expression.

Examples

```
# Example #1 : download regular gene expression data for ovarian cancer
GEdirectories <- TCGA_Download_GeneExpression(CancerSite = 'OV', TargetDirectory = tempdir())

# Example #2 : download miRNA expression data for ovarian cancer
GEdirectories <- TCGA_Download_GeneExpression(CancerSite = 'OV',
                                              TargetDirectory = tempdir(),
                                              mode = 'miRNA')

# Example #3 : download lncRNA expression data for ovarian cancer
GEdirectories <- TCGA_Download_GeneExpression(CancerSite = 'OV',
                                               TargetDirectory = tempdir(),
                                               mode = 'lncRNA')
```

TCGA_EstimateMissingValues_MolecularData

The TCGA_EstimateMissingValues_MolecularData function

Description

Internal.Deletes samples and genes with more NAs than the respective thresholds. Imputes other NAs values.

Usage

```
TCGA_EstimateMissingValues_MolecularData(
  MET_Data,
  MissingValueThresholdGene = 0.3,
  MissingValueThresholdSample = 0.1
)
```

Arguments

MET_Data	matrix of gene expression data
MissingValueThresholdGene	threshold for missing values per gene. Genes with a percentage of NAs greater than this threshold are removed. Default is 0.3.
MissingValueThresholdSample	threshold for missing values per sample. Samples with a percentage of NAs greater than this threshold are removed. Default is 0.1.

Value

gene expression data with no missing values.

TCGA_GENERIC_CheckBatchEffect

The TCGA_GENERIC_CheckBatchEffect function

Description

Internal. Checks if batch correction is needed.

Usage

```
TCGA_GENERIC_CheckBatchEffect(GEN_Data, BatchData)
```

Arguments

GEN_Data	matrix with data to be corrected for batch effects.
BatchData	Batch data.

Value

the p value from ANOVA test on PCA values.

TCGA_GENERIC_CleanUpSampleNames
The TCGA_GENERIC_CleanUpSampleNames function

Description

Internal. Cleans the samples IDs into the 12 digit format and removes doubles.

Usage

```
TCGA_GENERIC_CleanUpSampleNames(GEN_Data, IDlength = 12)
```

Arguments

GEN_Data	data matrix.
IDlength	length of samples ID.

Value

data matrix with cleaned sample names.

TCGA_GENERIC_GetSampleGroups
The TCGA_GENERIC_GetSampleGroups function

Description

Internal. Looks for the group of the samples (normal/cancer).

Usage

```
TCGA_GENERIC_GetSampleGroups(SampleNames)
```

Arguments

SampleNames	vector with sample names.

Value

a list.

TCGA_GENERIC_LoadIlluminaMethylationData

The TCGA_GENERIC_LoadIlluminaMethylationData function

Description

Internal. Read in an illumina methylation file with the following format: header row with sample labels, 2nd header row with 4 columns per sample: beta-value, geneSymbol, chromosome and GenomicCoordinate. The first column has the probe names.

Usage

```
TCGA_GENERIC_LoadIlluminaMethylationData(Filename)
```

Arguments

Filename	name of the file with the data.

Value

methylation data.

TCGA_GENERIC_MergeData

The TCGA_GENERIC_MergeData function

Description

Internal.

Usage

```
TCGA_GENERIC_MergeData(NewIDListUnique, DataMatrix)
```

Arguments

NewIDListUnique	unique rownames of data.
DataMatrix	data matrix.

Value

data matrix.

TCGA_GENERIC_MET_ClusterProbes_Helper_ClusterGenes_with_hclust *The TCGA_GENERIC_MET_ClusterProbes_Helper_ClusterGenes_with_hclust function*

Description

Internal. Cluster probes into genes.

Usage

```
TCGA_GENERIC_MET_ClusterProbes_Helper_ClusterGenes_with_hclust(
  Gene,
  ProbeAnnotation,
  MET_Cancer,
  MET_Normal = NULL,
  CorThreshold = 0.4
)
```

Arguments

Gene	gene.
ProbeAnnotation	data set matching probes to genes.
MET_Cancer	data matrix for cancer samples.
MET_Normal	data matrix for normal samples.
CorThreshold	correlation threshold for cutting the clusters.

Value

List with the clustered data sets and the mapping between probes and genes.

TCGA_GetData *The TCGA_GetData function*

Description

This function wraps the functions for downloading, pre-processing and analysis of the DNA methylation and gene expression data from the TCGA project.

Usage

```
TCGA_GetData(
  CancerSite,
  mode = "Regular",
  outputDirectory = ".",
  doBatchCorrection = FALSE,
  batch.correction.method = "Seurat",
```

```
  roadmap.epigenome.ids = NULL,
  roadmap.epigenome.groups = NULL,
  forceUse450K = FALSE,
  cores = 1
)
```

Arguments

CancerSite	character string indicating the TCGA cancer code. The information can be found at: https://gdc.cancer.gov/resources-tcga-users/tcga-code-tables/tcga-study-abbreviations
mode	character string indicating the analytic mode to model DNA methylation. Should be one of the followings: 'Regular', 'Enhancer', 'miRNA' or 'lncRNA'. Default: 'Regular'. See details for more information.
outputDirectory	character string indicating the file path to save the output.
doBatchCorrection	logical indicating whether to do batch effect correction during preprocessing. Default: False.
batch.correction.method	character string indicating the method to perform batch effect correction. The value should be either 'Seurat' or 'Combat'. Seurat is much fatster than the Combat. Default: 'Seurat'.
roadmap.epigenome.ids	character vector indicating the epigenome ID(s) to be used for selecting enhancers. See details for more information. Default: NULL.
roadmap.epigenome.groups	character vector indicating the tissue group(s) to be used for selecting enhancers. See details for more information. Default: NULL.
forceUse450K	logic indicating whether force to use only 450K methylation data. Default: FALSE
cores	Number of CPU cores to be used for computation.

Details

mode: EpiMix incorporates four alternative analytic modes for modeling DNA methylation: "Regular," "Enhancer", "miRNA" and "lncRNA". The four analytic modes target DNA methylation analysis on different genetic elements. The Regular mode aims to model DNA methylation at proximal cis-regulatory elements of protein-coding genes. The Enhancer mode targets DNA methylation analysis on distal enhancers. The miRNA or lncRNA mode focuses on methylation analysis of miRNA- or lncRNA-coding genes.

roadmap.epigenome.groups & roadmap.epigenome.ids:

Since enhancers are cell-type or tissue-type specific, EpiMix needs to know the reference tissues or cell types in order to select proper enhancers. EpiMix identifies enhancers from the RoadmapEpigenomic project (Nature, PMID: 25693563), in which enhancers were identified by ChromHMM in over 100 tissue and cell types. Available epigenome groups (a group of relevant cell types) or epigenome ids (individual cell types) can be obtained from the original publication (Nature, PMID: 25693563, figure 2). They can also be retrieved from the list.epigenomes() function. If both roadmap.epigenome.groups and roadmap.epigenome.ids are specified, EpiMix will select all the epigenomes from the combination of the inputs.

Value

The results from EpiMix is a list with the following components:

`MethylationDrivers`
: CpG probes identified as differentially methylated by EpiMix.

`NrComponents`
: The number of methylation states found for each driver probe.

`MixtureStates`
: A list with the DM-values for each driver probe. Differential Methylation values (DM-values) are defined as the difference between the methylation mean of samples in one mixture component from the experiment group and the methylation mean in samples from the control group, for a given probe.

`MethylationStates`
: Matrix with DM-values for all driver probes (rows) and all samples (columns).

`Classifications`
: Matrix with integers indicating to which mixture component each sample in the experiment group was assigned to, for each probe.

`Models`
: Beta mixture model parameters for each driver probe.

`group.1`
: sample names in group.1 (experimental group).

`group.2`
: sample names in group.2 (control group).

`FunctionalPairs`
: Dataframe with the prevalence of differential methyaltion for each CpG probe in the sample population, and fold change of mRNA expression and P values for each signifcant probe-gene pair.

Examples

```
# Example #1 - Regular mode
EpiMixResults <- TCGA_GetData(CancerSite = 'LUAD',
                              outputDirectory = tempdir(),
                              cores = 8)

# Example #2 - Enhancer mode
EpiMixResults <- TCGA_GetData(CancerSite = 'LUAD',
                              mode =  'Enhancer',
                              roadmap.epigenome.ids = 'E097',
                              outputDirectory = tempdir(),
                              cores = 8)

Example #3 - miRNA mode
EpiMixResults <- TCGA_GetData(CancerSite = 'LUAD',
                              mode = 'miRNA',
                              outputDirectory = tempdir(),
                              cores = 8)

#' Example #4 - lncRNA mode
EpiMixResults <- TCGA_GetData(CancerSite = 'LUAD',
                              mode = 'lncRNA',
                              outputDirectory = tempdir(),
                              cores = 8)
```

TCGA_GetSampleInfo *The TCGA_GetSampleInfo function*

Description

The TCGA_GetSampleInfo function

Usage

```
TCGA_GetSampleInfo(METProcessedData, CancerSite = "LUAD", TargetDirectory = "")
```

Arguments

METProcessedData	Matrix of preprocessed methylation data.
CancerSite	Character string of TCGA study abbreviation.
TargetDirectory	Path to save the sample.info. Default: ".

Details

Generate the 'sample.info' dataframe for TCGA data.

Value

A dataframe for the sample groups. Contains two columns: the first column (named: 'primary') indicating the sample names, and the second column (named: 'sample.type') indicating whether each sample is a Cancer or Normal tissue.

Examples

```
{
data(MET.data)
sample.info <- TCGA_GetSampleInfo(MET.data, CancerSite = 'LUAD')
}
```

TCGA_Load_MethylationData *The TCGA_Load_MethylationData function*

Description

The TCGA_Load_MethylationData function

Usage

```
TCGA_Load_MethylationData(METdirectory, ArrayType)
```

Arguments

METdirectory	path to the 27K or 450K data
ArrayType	character string indicating the array type, can be either '27K' or '450K'

Details

load 27K or 450K methyaltion data into memory

Value

matrix of methylation data with probes in rows and patient in columns

---

TCGA_Load_MolecularData

The TCGA_Load_MolecularData function

Description

Internal. Reads in gene expression data. Deletes samples and genes with more NAs than the respective thresholds. Imputes other NAs values.

Usage

```
TCGA_Load_MolecularData(Filename)
```

Arguments

Filename	name of the file with the data.
MissingValueThresholdGene	threshold for missing values per gene. Genes with a percentage of NAs greater than this threshold are removed. Default is 0.3.
MissingValueThresholdSample	threshold for missing values per sample. Samples with a percentage of NAs greater than this threshold are removed. Default is 0.1.

Value

gene expression data.

TCGA_Preprocess_DNAmethylation *The TCGA_Preprocess_DNAmethylation function*

Description

Pre-processes DNA methylation data from TCGA.

Usage

```
TCGA_Preprocess_DNAmethylation(
  CancerSite,
  METdirectories,
  doBatchCorrection = FALSE,
  batch.correction.method = "Seurat",
  MissingValueThreshold = 0.2,
  cores = 1,
  use450K = FALSE
)
```

Arguments

CancerSite	character string indicating the TCGA cancer code.
METdirectories	character vector with directories with the downloaded data. It can be the object returned by the TCGA_Download_DNAmethylation function.
doBatchCorrection	logical indicating whether to perform batch correction. Default: False.
batch.correction.method	character string indicating the method to perform batch correction. The value should be either 'Seurat' or 'Combat'. Default: 'Seurat'. Note: Seurat is much faster than the Combat.
MissingValueThreshold	numeric values indicating the threshold for removing samples or genes with missing values.Default: 0.2.
cores	integer indicating the number of cores to be used for performing batch correction with Combat.
use450K	logic indicating whether to force use 450K, instead of 27K data.

Details

Pre-process includes eliminating samples and genes with too many NAs, imputing NAs, and doing Batch correction. If there are samples with both 27k and 450k data, the 27k data will be used only if the sample number in the 27k data is greater than the 450k data and there is more than 50 samples in the 27k data. Otherwise, the 450k data is used and the 27k data is discarded.

Value

pre-processed methylation data matrix with CpG probe in rows and samples in columns.

Pre-processed methylation data matrix with CpG probe in rows and samples in columns.

Examples

```
METdirectories <- TCGA_Download_DNAmethylation(CancerSite = 'OV', TargetDirectory = tempdir())
METProcessedData <- TCGA_Preprocess_DNAmethylation(CancerSite = 'OV',
                                                   METdirectories = METdirectories)
```

`TCGA_Preprocess_GeneExpression`
The TCGA_Preprocess_GeneExpression function

Description

Pre-processes gene expression data from TCGA.

Usage

```
TCGA_Preprocess_GeneExpression(
  CancerSite,
  MAdirectories,
  mode = "Regular",
  doBatchCorrection = FALSE,
  batch.correction.method = "Seurat",
  MissingValueThresholdGene = 0.3,
  MissingValueThresholdSample = 0.1,
  cores = 1
)
```

Arguments

`CancerSite`	character string indicating the TCGA cancer code.
`MAdirectories`	character vector with directories with the downloaded data. It can be the object returned by the GEO_Download_GeneExpression function.
`mode`	character string indicating whether the genes in the gene expression data are miRNAs or lncRNAs. Should be either 'Regular', 'Enhancer', 'miRNA' or 'lncRNA'. This value should be consistent with the same parameter in the TCGA_Download_GeneExp function. Default: 'Regular'.
`doBatchCorrection`	logical indicating whether to perform batch effect correction. Default: False.
`batch.correction.method`	character string indicating the method to perform batch correction. The value should be either 'Seurat' or 'Combat'. Default: 'Seurat'. Seurat is much fatster than the Combat.
`MissingValueThresholdGene`	threshold for missing values per gene. Genes with a percentage of NAs greater than this threshold are removed. Default is 0.3.
`MissingValueThresholdSample`	threshold for missing values per sample. Samples with a percentage of NAs greater than this threshold are removed. Default is 0.1.
`cores`	integer indicating the number of cores to be used for performing batch correction with Combat

Details

Pre-process includes eliminating samples and genes with too many NAs, imputing NAs, and doing Batch correction. If the rownames of the gene expression data are ensembl ENSG names or ENST names, the function will convert them to the human gene symbol (HGNC).

Value

pre-processed gene expression data matrix.

Examples

```
# Example #1: Preprocessing gene expression for Regular mode

 GEdirectories <- TCGA_Download_GeneExpression(CancerSite = 'OV',
                                               TargetDirectory = tempdir())
 GEProcessedData <- TCGA_Preprocess_GeneExpression(CancerSite = 'OV',
                                                   MAdirectories = GEdirectories)

# Example #2: Preprocessing gene expression for miRNA mode

 GEdirectories <- TCGA_Download_GeneExpression(CancerSite = 'OV',
                                               TargetDirectory = tempdir(),
                                               mode = 'miRNA')

 GEProcessedData <- TCGA_Preprocess_GeneExpression(CancerSite = 'OV',
                                                   MAdirectories = GEdirectories,
                                                   mode = 'miRNA')

# Example #3: Preprocessing gene expression for lncRNA mode

 GEdirectories <- TCGA_Download_GeneExpression(CancerSite = 'OV',
                                               TargetDirectory = tempdir(),
                                               mode = 'lncRNA')

 GEProcessedData <- TCGA_Preprocess_GeneExpression(CancerSite = 'OV',
                                                   MAdirectories = GEdirectories,
                                                   mode = 'lncRNA')
```

TCGA_Process_EstimateMissingValues

The TCGA_Process_EstimateMissingValues function

Description

Internal. Removes patients and genes with more missing values than the MissingValueThreshold, and imputes remaining missing values using Tibshirani's KNN method.

Usage

```
TCGA_Process_EstimateMissingValues(MET_Data, MissingValueThreshold = 0.2)
```

Arguments

MET_Data	data matrix.
MissingValueThreshold	threshold for removing samples and genes with too many missing values.

Value

the data set with imputed values and possibly some genes or samples deleted.

TCGA_Select_Dataset *The TCGA_Select_Dataset function*

Description

internal function to select which MET dataset to use

Usage

```
TCGA_Select_Dataset(CancerSite, MET_Data_27K, MET_Data_450K, use450K)
```

Arguments

CancerSite	TCGA cancer code
MET_Data_27K	matrix of MET_Data_27K
MET_Data_450K	matrix of MET_Data_450K
use450K	logic indicating whether to force use 450K data

Value

the selected MET data set

---

test_gene_expr *The test_gene_expr function*

Description

Helper function to test whether the expression levels of a gene is reversely correlated with the methylation state of a probe.

Usage

```
test_gene_expr(
  gene,
  probe,
  DM_values,
  gene.expr.values,
  correlation = "negative"
)
```

Arguments

gene	character string indicating a target gene to be modeled.
probe	character string indicating a probe mapped to the target gene.
DM_values	a vector of DM values for the probe. The names of the element should be sample names.
gene.expr.values	a vector of gene expression values for the tested gene. The names of the vector are sample names.
correlation	character indicating the direction of correlation between the methylation state of the CpG site and the gene expression levels. Can be either 'negative' or 'positive'.
raw.pvalue.threshold	raw p value from testing DNA methylation and gene expression
adjusted.pvalue.threshold	adjusted p value from testing DNA methylation and gene expression

Value

dataframe with functional probe-gene pairs and corresponding p values obtained from the Wilcoxon test for gene expression and methylation.

---

translateMethylMixResults

The translateMethylMixResults function

Description

unfold clustered MethylMix results to single CpGs

Usage

```
translateMethylMixResults(MethylMixResults, probeMapping)
```

Arguments

MethylMixResults	list of MethylMix output
probeMapping	dataframe of probe to gene-cluster mapping

Value

list of unfolded MethylMix results

validEpigenomes *The validEpigenomes function*

Description

check user input for roadmap epigenome groups or ids

Usage

```
validEpigenomes(roadmap.epigenome.groups, roadmap.epigenome.ids)
```

Arguments

roadmap.epigenome.groups	epigenome groups
roadmap.epigenome.ids	epigenome ids

Value

a character vector of selected epigenome ids

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