Package 'MAGAR'

November 12, 2026

Type Package

Title MAGAR: R-package to compute methylation Quantitative Trait Loci (methQTL) from DNA methylation and genotyping data

Version 1.20.0

Date 2024-11-13

Description ``Methylation-Aware Genotype Association in R" (MAGAR) computes methQTL from DNA methylation and genotyping data from matched samples. MAGAR uses a linear modeling stragety to call CpGs/SNPs that are methQTLs. MAGAR accounts for the local correlation structure of CpGs.

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Imports doParallel, igraph, bigstatsr, rjson, plyr, data.table, UpSetR, reshape2, jsonlite, methods, ff, argparse, impute, RnBeads.hg19, RnBeads.hg38, utils, stats

Depends R (>= 4.1), HDF5Array, RnBeads, snpStats, crlmm

Suggests gridExtra, VennDiagram, qqman, LOLA, RUnit, rmutil, rmarkdown, JASPAR2018, TFBSTools, seqLogo, knitr, devtools, BiocGenerics, BiocManager

Encoding UTF-8

RoxygenNote 7.2.3

VignetteBuilder knitr

biocViews Regression, Epigenetics, DNAMethylation, SNP, GeneticVariability, MethylationArray, Microarray, CpGIsland, MethylSeq, Sequencing, mRNAMicroarray, Preprocessing, CopyNumberVariation, TwoChannel, ImmunoOncology, DifferentialMethylation, BatchEffect, QualityControl, DataImport, Network, Clustering, GraphAndNetwork

BugReports https://github.com/MPIIComputationalEpigenetics/MAGAR/issues

URL https://github.com/MPIIComputationalEpigenetics/MAGAR

git_url https://git.bioconductor.org/packages/MAGAR

git_branch RELEASE_3_23

git_last_commit ec09055

git_last_commit_date 2026-04-28

Repository Bioconductor 3.23

Date/Publication 2026-11-11

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`computeCorrelationBlocks`
computeCorrelationBlocks

Description

This function computes CpG correlation blocks from correlations of CpGs across samples by Louvian clustering.

Usage

```
computeCorrelationBlocks(
  meth.data,
  annotation,
  cor.threshold = qtlGetOption("cluster.cor.threshold"),
  sd.gauss = qtlGetOption("standard.deviation.gauss"),
  absolute.cutoff = qtlGetOption("absolute.distance.cutoff"),
  max.cpgs = qtlGetOption("max.cpgs"),
  assembly = "hg19",
  chromosome = "chr1"
)
```

Arguments

`meth.data`	A `data.frame` containing the methylation data with CpGs in the rows and samples in the columns.
`annotation`	The genomic annotations of the CpG positions.
`cor.threshold`	The correlation threshold used to discard edges from the correlation-based network.
`sd.gauss`	Standard deviation of the Gauss distribution used to weight the distance
`absolute.cutoff`	Absolute distance cutoff after which no methQTL interaction is to be considered.
`max.cpgs`	Maximum number of CpGs used in the computation (used to save memory). 40,000 is a reasonable default for machines with ~128GB of main memory. Should be smaller for smaller machines and larger for larger ones.
`assembly`	The assembly used
`chromosome`	The chromosome for which correlation block calling is to be performed

Details

This method performs clustering of the correlation matrix obtaind from the DNA methylation matrix. Correlations are computed for each pair of CpGs across all the samples. We then compute a similarity matrix from this correlation matrix and set correlations lower than the given threshold to 0. In the next step, we weight the correlations by the distance between the CpGs: smaller distances get higher weights according to Gaussian distribution with mean 0 and standard deviation as specified above. Furthermore, similarities of CpGs that are further than `absolute.distance.cutoff` away from one another are discarded.

We then compute the associated weighted, undirected graph from the similarity matrix and execute Louvain clustering on the graph. The resulting clusters of CpGs are returned.

Value

A list representing the clustering of CpGs into correlation blocks. Each element is a cluster, which contains row indices of the DNA methylation matrix that correspond to this cluster.

Author(s)

Michael Scherer

Examples

```
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
meth.data <- getMethData(meth.qtl)
anno.meth <- getAnno(meth.qtl,"meth")
cor.blocks <- computeCorrelationBlocks(meth.data[seq(1,10),],annotation=anno.meth[seq(1,10),])
```

`doImport` *doImport*

Description

Performs input for the given DNA methylation and genotyping data.

Usage

```
doImport(
  data.location,
  s.anno = NULL,
  assembly.meth = "hg19",
  assembly.geno = "hg19",
  tab.sep = ",",
  s.id.col = "sample_id",
  out.folder = tempdir(),
  ...
)
```

Arguments

data.location	Named character vector specifying the data location. The names correspond to: **idat.dir** Path to the DNA methylation data. Can be in the form of IDAT files or in any other format accepted by RnBeads **geno.dir** Path to the genotyping data file directory, either containing PLINK files (i.e. with bed, bim and fam files), imputed, (dosage) files (i.e. with dos and txt files), or idat files
s.anno	Path to the sample annotation sheet. If NULL, the program searches for potential sample annotation sheets in the data location directories.
assembly.meth	Assembly used for the DNA methylation data. Typically is "hg19" for Illumina BeadArray data.
assembly.geno	Assembly used for the genotyping data. If it is not the same as assembly.geno, the positions will be matched using liftOver.
tab.sep	The table separator used for the sample annotation sheet.
s.id.col	The column name of the sample annotation sheet that specifies the sample identifier.
out.folder	The output directory to store diagnostic plots
...	Futher parameters passed to e.g. doGenoImport

Details

Import of DNA methylation and genotyping data is done separately:

DNA methylation data DNA methylation data is imported using the RnBeads package. We use a default option setting commonly used for DNA methylation data obtained from the Illumina BeadArray series. If you want to specify further options, we refer to the rnb.options.

Genotyping data Genotyping data is processed using PLINK. We focus on genotyping data generated with the Illumina BeadArray series and use default options. For further option settings, you should consult the qtlSetOption documentation.

You can specify the import type using qtlSetOption through the options meth.data.type and geno.data.type.

This function internally uses doMethImport and doGenoImport

Value

An object of type MethQTLInput-class with the methylation and genotyping information added.

Author(s)

Michael Scherer

Examples

```
meth.qtl.in <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
meth.qtl.in
```

doMethQTL *doMethQTL*

Description

Function to compute methQTL given DNA methylation and genotyping data.

Usage

```
doMethQTL(
  meth.qtl,
  sel.covariates = NULL,
  p.val.cutoff = 1e-05,
  ncores = 1,
  cluster.submit = FALSE,
  out.dir = getwd(),
  default.options = TRUE
)
```

Arguments

`meth.qtl`	An object of type `MethQTLInput-class` on which methQTL computation is to be performed
`sel.covariates`	Covariates as column names of the sample annotation sheet stored in `meth.qtl` to be used for covariate adjustment.
`p.val.cutoff`	The p-value cutoff used for methQTL calling
`ncores`	The number of cores used.
`cluster.submit`	Flag indicating if jobs are to be distributed among a SGE compute cluster
`out.dir`	Output directory
`default.options`	Flag indicating if default options for `cluster.cor.threshold`, `standard.deviation.gauss`, and `absolute.distance.cutoff` should be loaded for the data set used. See the option settings in `'inst/extdata'`.

Details

The process is split into 4 steps:

1. First the two matrices are split according to the chromosomes.
2. We then compute correlations among the CpGs and compute CpG correlation blocks.
3. In each of the CpG correlation blocks, linear models according to the `linear.model.type` `qtlSetOption` with the CpG methylation state of the reference CpG specified by `representative.cpg.computation` as output and the SNP genotype state and all possible covariates as input are computed.
4. For each of the CpG correlation blocks, we report the p-value of the representative CpG.

Currently, if `qtlGetOption('cluster.architecture')=='sge'` the function does not return a `MethQTLResult` object, but `NULL`, since monitoring finished jobs is hard through SLURM. After the jobs are finished (checked using `squeue`), the results can can be loaded from `out.dir` using `loadMethQTLResult`.

Value

An object of type `MethQTLResult-class` containing the called methQTL interactions.

Author(s)

Michael Scherer

See Also

doMethQTLChromosome

Examples

```
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
meth.qtl.res <- doMethQTL(meth.qtl,p.val.cutoff=0.01)
```

`doMethQTLChromosome` *doMethQTLChromosome*

Description

This functions computes the methQTL interactions for a single chromosome

Usage

```
doMethQTLChromosome(
  meth.qtl,
  chrom,
  sel.covariates = NULL,
  p.val.cutoff = 1e-05,
  out.dir = NULL,
  ncores = 1
)
```

Arguments

`meth.qtl`	An Object of type `MethQTLInput-class`.
`chrom`	Character vector represeting the chromosome to be investigated.
`sel.covariates`	Covariates as column names of the sample annotation sheet stored in `meth.qtl` to be used for covariate adjustment.
`p.val.cutoff`	The p-value used for methQTL calling
`out.dir`	Optional argument specifying the output directory
`ncores`	The number of cores to be used

Value

A data frame with seven columns:

CpGs The CpG ID chosen to be the representative CpG in the methQTL

SNP The SNP ID (as rsNNNNNN) involved in the methQTL

Beta The coefficient estimate of the linear model

P.value The p-value associated with the coefficient estimate

Chromosome The chromosome name

Position.CpG The genomic position of the CpG

Position.SNP The genomic position of the SNP

Distance The distance between the CpG and the SNP

Author(s)

Michael Scherer

See Also

doMethQTL

Examples

```
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
meth.qtl.res <- doMethQTLChromosome(meth.qtl,chrom="chr18",p.val.cutoff=0.01)
```

`filterPval,MethQTLResult-method`
filterPval

Description

This functions filters the methQTL results according to a given p-value cutoff

Usage

```
## S4 method for signature 'MethQTLResult'
filterPval(object, p.val.cutoff = 0.01)
```

Arguments

`object`	The `MethQTLResult-class` object to be filtered
`p.val.cutoff`	The p-value cutoff to be employed

Value

The filtered `MethQTLResult-class` object

Author(s)

Michael Scherer

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
meth.qtl.res <- filterPval(meth.qtl.res)
meth.qtl.res
```

---

getAnno,MethQTLInput-method
getAnno

Description

Returns genomic annotation information for the given dataset.

Usage

```
## S4 method for signature 'MethQTLInput'
getAnno(object, type = "meth")

## S4 method for signature 'MethQTLResult'
getAnno(object, type = "meth")
```

Arguments

object	An object of class MethQTLInput-class or MethQTLResult-class.
type	The type of annotation to be returned. Can either be 'meth' or 'geno' for methylation, and genotyping information, respectively.

Value

The genomic annotation as a data.frame.

Examples

```
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
head(getAnno(meth.qtl,"meth"))
head(getAnno(meth.qtl,"geno"))
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
head(getAnno(meth.qtl.res,"meth"))
head(getAnno(meth.qtl.res,"geno"))
```

getCorrelationBlocks,MethQTLResult-method
getCorrelationBlocks

Description

Returns the correlation blocks defined for the given dataset

Usage

```
## S4 method for signature 'MethQTLResult'
getCorrelationBlocks(object)
```

Arguments

object	An object of class MethQTLResult-class.

Value

A list object containing the correlation blocks.

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
head(getCorrelationBlocks(meth.qtl.res))
```

getGeno,MethQTLInput-method
getGeno

Description

Returns genotyping information for the given dataset.

Usage

```
## S4 method for signature 'MethQTLInput'
getGeno(object, site = NULL, sample = NULL)
```

Arguments

object	An object of class MethQTLInput-class.
site	The sites to be selected either as a numeric or logical vector. If NULL all sites are returned.
sample	The samples to be selected either as a numeric or logical vector. If NULL all samples are returned.

Value

The genotyping matrix either as a matrix of HDF5Matrix.

Examples

```
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
head(getGeno(meth.qtl))
```

`getMethData,MethQTLInput-method`
getMethData

Description

Returns methylation information for the given dataset.

Usage

```
## S4 method for signature 'MethQTLInput'
getMethData(object, site = NULL, sample = NULL)
```

Arguments

`object`	An object of class `MethQTLInput-class`.
`site`	The sites to be selected either as a numeric or logical vector. If `NULL` all sites are returned.
`sample`	The samples to be selected either as a numeric or logical vector. If `NULL` all samples are returned.

Value

The methylation matrix either as a matrix of HDF5Matrix.

Examples

```
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
head(getMethData(meth.qtl))
```

getOverlappingQTL *getOverlappingQTL*

Description

This function merges the QTLs given and returns the methQTL table in a merged format.

Usage

```
getOverlappingQTL(meth.qtl.list, type = "SNP")
```

Arguments

meth.qtl.list	A list of MethQTLResult-class objects to be merged
type	The type of annotation to be overlapped. Needs to be 'SNP', 'CpG' or 'cor.block'

Value

A data.frame with the methQTL interactions and an additional column specifying where the interaction displayed has been found. This value is generated from the names() argument of meth.qtl.list.

Author(s)

Michael Scherer

Examples

```
meth.qtl.res.1 <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
meth.qtl.res.2 <- meth.qtl.res.1
res <- getOverlappingQTL(list(A=meth.qtl.res.1,B=meth.qtl.res.2),type="SNP")
```

getOverlapUniverse *getOverlapUniverse*

Description

This function overlaps results from a list of MethQTLResults and returns the union of all the input data points used.

Usage

```
getOverlapUniverse(meth.qtl.res, type)
```

Arguments

meth.qtl.res	An object of type MethQTLResult-class or a list of such objects
type	The type of annotation to be overlapped. Needs to be 'SNP', 'CpG' or 'cor.block'

Value

A list with two GRanges objects, one containing the overlapped set and the other the union of input data points as elements 'all.qtl' and 'all.input'

Author(s)

Michael Scherer

Examples

```
meth.qtl.res.1 <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
meth.qtl.res.2 <- meth.qtl.res.1
res <- getOverlapUniverse(list(A=meth.qtl.res.1,B=meth.qtl.res.2),type="SNP")
```

---

getPheno,MethQTLInput-method
getPheno

Description

Returns phenotypic information for the given dataset.

Usage

```
## S4 method for signature 'MethQTLInput'
getPheno(object)
```

Arguments

object	An object of class MethQTLInput-class.

Value

The phenotypic data either as a data.frame.

Examples

```
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
head(getPheno(meth.qtl))
```

getResult,MethQTLResult-method *getResult*

Description

Returns the methQTL results stores in the object.

Usage

```
## S4 method for signature 'MethQTLResult'
getResult(object, cor.blocks = NULL, na.rm = FALSE)
```

Arguments

object	An of type MethQTLResult-class.
cor.blocks	Correlation blocks as obtained using getCorrelationBlocks. Please note that the correlation blocks need to contain the CpG identifiers, so the MethQTLInput-class object needs to be provided to getCorrelationBlocks.
na.rm	Flag indicating if rows containing NA values are to be removed from the result.

Value

The methQTL results as a data.frame with each row being a methQTL.

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
head(getResult(meth.qtl.res))
```

getResultGWASMap,MethQTLResult-method *getResultGWASMap*

Description

Returns the methQTL results in the format used as input to GWAS-map and stores in the object.

Usage

```
## S4 method for signature 'MethQTLResult'
getResultGWASMap(object, meth.qtl)
```

Arguments

object	An of type MethQTLResult-class.
meth.qtl	An object of type MethQTLInput-class containing further information about the QTLs

Value

The methQTL results as a data.frame with each row being a methQTL.

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
head(getResultGWASMap(meth.qtl.res,meth.qtl))
```

---

getSamples,MethQTLInput-method
getSamples

Description

Returns the samples of the given dataset.

Usage

```
## S4 method for signature 'MethQTLInput'
getSamples(object)
```

Arguments

object	An object of class MethQTLInput-class.

Value

The samples of the dataset as a character vector.

Examples

```
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
getSamples(meth.qtl)
```

getSpecificQTL *getSpecificQTL*

Description

This function returns the methQTL interactions specific for a result

Usage

```
getSpecificQTL(meth.qtl.res, meth.qtl.background, type = "SNP")
```

Arguments

meth.qtl.res	An object of type MethQTLResult-class for which specific QTLs are to be obtained.
meth.qtl.background	The background set as a list of MethQTLResult-class objects.
type	The type of annotation to be overlapped. Needs to be 'SNP', 'CpG' or 'cor.block'

Value

A data.frame of methQTL interactions sorted by the effect size.

Author(s)

Michael Scherer

Examples

```
meth.qtl.res.1 <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
meth.qtl.res.2 <- meth.qtl.res.1
res <- getSpecificQTL(meth.qtl.res.1,list(A=meth.qtl.res.1,B=meth.qtl.res.2),type="SNP")
```

---

imputeMeth,MethQTLInput-method
imputeMeth

Description

Replaces missing values in the DNA methylation data matrix by imputed values

Usage

```
## S4 method for signature 'MethQTLInput'
imputeMeth(object)
```

Arguments

object	An object of class MethQTLInput-class.

Value

The object with imputed values.

Examples

```
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
meth.qtl.imp <- imputeMeth(meth.qtl)
```

---

joinMethQTLResult *joinMethQTLResult*

Description

This function combines a list of MethQTLResult-class objects.

Usage

```
joinMethQTLResult(obj.list)
```

Arguments

obj.list	A list of MethQTLResult-class objects to be joined

Value

An object of type MethQTLResult-class containing the combined information

Author(s)

Michael Scherer

Examples

```
meth.qtl.res.1 <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
meth.qtl.res.2 <- meth.qtl.res.1
meth.qtl.res <- joinMethQTLResult(list(meth.qtl.res.1,meth.qtl.res.2))
```

loadMethQTLInput *loadMethQTLInput*

Description

This functions load a MethQTLInput-class object from disk.

Usage

```
loadMethQTLInput(path)
```

Arguments

path	Path to the directory that has been created by saveMethQTLInput,MethQTLInput-method.

Value

The object of type MethQTLInput-class that has been stored on disk.

Author(s)

Michael Scherer

Examples

```
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
meth.qtl
```

loadMethQTLResult *loadMethQTLResult*

Description

This functions load a MethQTLResult-class object from disk.

Usage

```
loadMethQTLResult(path)
```

Arguments

path	Path to the directory that has been created by saveMethQTLResult,MethQTLResult-method.

Value

The object of type MethQTLResult-class that has been stored on disk.

Author(s)

Michael Scherer

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
meth.qtl.res
```

`MethQTLInput-class` *MethQTLInput-class*

Description

Class storing methQTL input data, such as DNA methylation and genotyping data, as well as sample metadata

Details

This class is the basis for computing methQTLs in the methQTL-package. It stores all the relevant information including methylation data and genotype data as a matrix or HDF5Matrix, the phenotypic data as a data frame and the genomic annotation of both the methylation sites and the SNP data.

Slots

`meth.data` The methylation data as a numeric matrix of beta values or as an object of type `HDF5Matrix`

`geno.data` The genotyping data as a numeric matrix of SNP genotypes (0=homozygote reference, 1=heterozygote, 2=homozygote alternative allele) or as an object of type `HDF5Matrix`

`pheno.data` Phenotypic data describing the samples used in the study. Matches the dimensions of both `meth.data` and `geno.data`

`anno.meth` Genomic annotation of the methylation sites as a `data.frame`. Has the same number of rows as `meth.data`.

`anno.geno` Genomic annotation of the SNPs as a `data.frame`. Has the same number of rows as `geno.data`.

`samples` The sample identifiers used both for `meth.data` and `geno.data`, and as the rownames of `pheno.data`.

`assembly` The genome assembly used.

`platform` The platform used to compute the methylation data.

`disk.dump` Flag indicating if the matrices are stored on disk rather than in memory.

`imputed` Flag indicating if genotype dataset has been imputed.

Methods

`getMeth` Returns the methylation matrix.

`getGeno` Returns the genotyping matrix.

`getPheno` Returns the phenotypic information.

`getAnno` Returns the genomic annotation.

`saveMethQTLInput` Stores the object on disk.

`imputeMeth` Imputes the DNA methylation data matrix

Author(s)

Michael Scherer

`MethQTLResult-class` *MethQTLResult-class*

Description

Class storing methQTL analysis results and the associated genomic annotations

Details

This class stores the results of the methQTL analysis. It stores a `data.frame` with the methQTL results, and associated genomic annotations for both the methylation sites and SNPs.

Slots

`result.frame` The methQTL results as a `data.frame`

`anno.meth` Genomic annotation of the methylation sites as a `data.frame`.

`anno.geno` Genomic annotation of the SNPs as a `data.frame`.

`correlation.blocks` Correlation blocks determined from the methylation matrix.

`method` The method used to call methQTL.

`rep.type` Method used to determine representative CpGs from correlation blocks.

`chr` Optional argument specifying if methQTL were called on a single chromosome.

Methods

`getResult` Returns the methQTL results.

`getAnno` Returns the genomic annotation.

Author(s)

Michael Scherer

overlapInputs *overlapInputs*

Description

Overlaps the input annotations

Usage

```
overlapInputs(meth.qtl.list, type)
```

Arguments

meth.qtl.list	A list of MethQTLInput-class or MethQTLResult-class objects to be overlapped
type	The type of annotation to be overlapped. Needs to be 'SNP', 'CpG' or 'cor.block'

Value

A data frame containing the annotations of the unique input values.

Author(s)

Michael Scherer

Examples

```
meth.qtl.1 <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
meth.qtl.2 <- meth.qtl.1
res <- overlapInputs(list(A=meth.qtl.1,B=meth.qtl.2),type="SNP")
```

overlapQTLs *overlapQTLs*

Description

This function overlaps a list of methQTLs to determine which interactions are common.

Usage

```
overlapQTLs(meth.qtl.result.list, type)
```

Arguments

`meth.qtl.result.list`	A named list with each entry being an object of type `MethQTLResult-class`. The names are used in the visualization.
`type`	Determines if either the SNP (default), the CpG, or the correlation block `'cor.block'` is to be visualized

Value

A list with `length(meth.qtl.result.list)` elements, containing IDs of methQTL interactions according to the option `type`.

Author(s)

Michael Scherer

Examples

```
meth.qtl.res.1 <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
meth.qtl.res.2 <- meth.qtl.res.1
res <- overlapQTLs(list(A=meth.qtl.res.1,B=meth.qtl.res.2),type="SNP")
```

QTL.OPTIONS *options.R*

Description

This files contains code to generate the options of the methQTL package.

Usage

```
QTL.OPTIONS
```

Format

An object of class `environment` of length 36.

qtlAnnotationEnrichment *qtlAnnotationEnrichment*

Description

This functions performs enrichment analysis using the Fisher's test for the methQTLs detected with respect to different genomic annotations.

Usage

```
qtlAnnotationEnrichment(
  meth.qtl.res,
  type = "SNP",
  annotation = "cpgislands",
  assembly = "hg19"
)
```

Arguments

meth.qtl.res	An object of type MethQTLResult-class or a list of such objects.
type	The type of methQTL to be visualized. Can be either 'SNP', 'CpG', or 'cor.block'
annotation	The genomic annotation to be used. Can be the ones available in rnb.region.types or "ctcf", "distal", "dnase", "proximal", "tfbs", "tss"
assembly	The assembly used. Only "hg19" (default) and "hg38" supported.

Details

We use all data points that have been used to calculate methQTLs as the background and compare the overlaps with the annotation of interest in comparison to the methQTLs that have been computed in case a MethQTLResult-class is provided. If a list of MethQTLResult-class objects is provided, the intersection between the methQTLs from all objects in the list is compared with the union of all interactions that have been tested.

Value

A list of two p-values named 'enrichment' for overrepresentation and 'depletion' for underrepresentation

Author(s)

Michael Scherer

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
res <- qtlAnnotationEnrichment(meth.qtl.res)
```

qtlBaseSubstitutionEnrichment
qtlBaseSubstitutionEnrichment

Description

This function tests for enrichment of a specific base substitution in the methQTL interactions.

Usage

```
qtlBaseSubstitutionEnrichment(meth.qtl.res, merge = FALSE)
```

Arguments

meth.qtl.res	An object of type MethQTLResult-class or a list of such objects.
merge	Flag indicating if 5' and 3' substitutions are to be merged or to be analyzed separately.

Details

The names of the list are e.g. A_G, which refers to a replacement of the reference base A with an A. Enrichment is computed using Fisher's exact test, using all SNP that have been used as input as the background.

Value

A list with one element for each potential base substitution containing the enrichment p-value.

Author(s)

Michael Scherer

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
res <- qtlBaseSubstitutionEnrichment(meth.qtl.res)
```

qtlDistanceScatterplot *qtlDistanceScatterplot*

Description

Computes a scatterplot between CpG-SNP distance with both effect size and p-value

Usage

```
qtlDistanceScatterplot(meth.qtl.result, out.dir = NULL, out.name = NULL)
```

Arguments

meth.qtl.result	An object of type MethQTLResult-class containing called methQTL
out.dir	If specified, the plot is stored as a pdf in this directory
out.name	Optional name for the resulting plot

Value

An object of type ggplot comparing the distance between CpG and SNP. Negative values indicate that the SNP is downstream of the CpG.

Author(s)

Michael Scherer

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
qtlDistanceScatterplot(meth.qtl.res)
```

qtlGetOption *qtlGetOption Print the value of the global option*

Description

qtlGetOption Print the value of the global option

Usage

```
qtlGetOption(names)
```

Arguments

names	string or character vector containing the names of the options to be printed. All options are listed in qtlSetOption

Value

the option for the specified option

Author(s)

Michael Scherer

Examples

```
qtlGetOption("cluster.cor.threshold")
```

---

qtlJSON2options *qtlJSON2options*

Description

This function reads an option setting from a JSON file and applies them to the current session

Usage

```
qtlJSON2options(path)
```

Arguments

path	Path to a JSON file containing the options to be specified

Value

None

Author(s)

Michael Scherer

Examples

```
qtlJSON2options(system.file("extdata","qtl_options_probesEPIC.json",package="MAGAR"))
```

qtlManhattanPlot *qtlManhattanPlot*

Description

This function creates a manhattan plot for the given methQTL result

Usage

```
qtlManhattanPlot(meth.qtl.result, type = "CpG", stat = "p.val.adj.fdr")
```

Arguments

meth.qtl.result	An object of type MethQTLResult-class containing the methQTL
type	Determines if either the CpG (default) or the SNP is to be visualized
stat	Determines the statistic that is to be visualized. Can be either P.value, Beta or p.val.adj.fdr

Details

A plot is shown that contains chromosome-wise interactions.

Value

None

Author(s)

Michael Scherer

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
qtlManhattanPlot(meth.qtl.res)
```

qtlOptions2JSON *qtlOptions2JSON*

Description

This function stores the current options setting as a JSON file at the specified path

Usage

```
qtlOptions2JSON(path = file.path(getwd(), "methQTL_options.json"))
```

Arguments

path	A filename, to which the option setting is to be saved

Value

None

Author(s)

Michael Scherer

Examples

```
qtlSetOption('cluster.cor.threshold'=0.5)
qtlOptions2JSON("my_opts.json")
qtlJSON2options("my_opts.json")
```

qtlPlotBaseSubstitution *qtlPlotBaseSubstitution*

Description

This function returns an enrichment plot for the different base substitutions.

Usage

```
qtlPlotBaseSubstitution(meth.qtl.res, ...)
```

Arguments

meth.qtl.res	An object of type MethQTLResult-class or a list of such objects.
...	Further parameters passed to qtlBaseSubstitutionEnrichment

Value

None

Author(s)

Michael Scherer

See Also

qtlBaseSubstitutionEnrichment

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
qtlPlotBaseSubstitution(meth.qtl.res)
```

---

qtlPlotClusterSize *qtlPlotClusterSize*

Description

This functions returns a histogram comprising the (genomic) sizes of the correlation blocks in the given objet.

Usage

```
qtlPlotClusterSize(meth.qtl.res, type = "count")
```

Arguments

meth.qtl.res	An object of type MethQTLResult-class
type	Either "genomic" or "count", for genomic size of the correlation block in base pairs or as the number of CpGs

Value

An object of type ggplot containing the histogram as a plot

Author(s)

Michael Scherer

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
qtlPlotClusterSize(meth.qtl.res)
```

qtlPlotSNPCpGInteraction *qtlPlotSNPCpGInteraction*

Description

Compares the methylation states of a given CpG for the genotype states availabe at the given SNP

Usage

```
qtlPlotSNPCpGInteraction(
  meth.qtl,
  cpg = NULL,
  snp = NULL,
  out.dir = NULL,
  meth.qtl.res = NULL,
  out.name = NULL
)
```

Arguments

meth.qtl	An object of type MethQTLInput-class containing the methylation and genotype information for the given CpG and the given SNP
cpg	The CpG identifier as a character (e.g. cg12345678)
snp	The SNP identifier as a character (e.g. rs12345678)
out.dir	If specified, the plot is stored as a pdf in this directory
meth.qtl.res	An optional argument of type MethQTLResult-class containing information on the results. If either cpg or snp are NULL, this function sorts the results by increasing p-value and the uses the best results for plotting.
out.name	Optional name for the resulting plot

Value

An object of type ggplot comparing the CpG methylation states as boxplots across the different genotype states

Author(s)

Michael Scherer

Examples

```
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
qtlPlotSNPCpGInteraction(meth.qtl,cpg="cg19565884",snp="rs149871695")
```

qtlSetOption *qtlSetOption*

Description

Change global options for methQTL calculation

Usage

```
qtlSetOption(
  rnbeads.options = NULL,
  meth.data.type = "idat.dir",
  geno.data.type = "plink",
  rnbeads.report = "temp",
  rnbeads.qc = FALSE,
  hdf5dump = FALSE,
  hardy.weinberg.p = 0.001,
  db.snp.ref = NULL,
  minor.allele.frequency = 0.05,
  missing.values.samples = 0.05,
  plink.geno = 0.1,
  impute.geno.data = FALSE,
  n.prin.comp = NULL,
  plink.path = NULL,
  fast.qtl.path = NULL,
  bgzip.path = NULL,
  tabix.path = NULL,
  correlation.type = "pearson",
  cluster.cor.threshold = 0.25,
  standard.deviation.gauss = 250,
  absolute.distance.cutoff = 5e+05,
  linear.model.type = "classial.linear",
  representative.cpg.computation = "row.medians",
  meth.qtl.type = "oneVSall",
  max.cpgs = 40000,
  cluster.architecture = "sge",
  cluster.config = c(h_vmem = "5G", mem_free = "5G"),
  n.permutations = 1000,
  compute.cor.blocks = TRUE,
  recode.allele.frequencies = FALSE,
  vcftools.path = NULL,
  imputation.user.token = NULL,
  imputation.reference.panel = "apps@hrc-r1.1",
  imputation.phasing.method = "shapeit",
  imputation.population = "eur"
)
```

Arguments

`rnbeads.options`
: Path to an XML file specifying the RnBeads options used for data import. The default options are suitable for Illumina Beads Array data sets.

`meth.data.type`
: Type of DNA methylation data used. Choices are listed in `rnb.execute.import`.

`geno.data.type`
: The type of data to be imported. Can be either `'plink'` for `'.bed'`, `'.bim'`, and `'.fam'` or `'.dos'` and `'txt'` files or `'idat'` for raw IDAT files.

`rnbeads.report`
: Path to an existing directory, in which the preprocessing report of RnBeads is to be stored. Defaults to the temporary file.

`rnbeads.qc`
: Flag indicating if the quality control module of RnBeads is to be executed.

`hdf5dump`
: Flag indicating, if large matrices are to be stored on disk rather than in main memory using the `HDF5Array` package.

`hardy.weinberg.p`
: P-value used for the markers to be excluded if they do not follow the Hardy-Weinberg equilibrium as implemented in `PLINK`.

`db.snp.ref`
: Path to a locally stored version of dbSNP[3]. If this option is specified, the reference allele is determined from this file instead of from the allele frequencies of the dataset. This circumvents problems with some imputation methods. If `NULL`(default), recoding will not be performed.

`minor.allele.frequency`
: Threshold for the minor allele frequency of the SNPs to be used in the analysis.

`missing.values.samples`
: Threshold specifying how much missing values per SNP are allowed across the samples to be included in the analyis.

`plink.geno`
: Threshold for missing values per SNP

`impute.geno.data`
: Flag indicating if imputation of genotyping data is to be perfomed using the Michigan imputation server (https://imputationserver.sph.umich.edu/index.html)[2].

`n.prin.comp`
: Number of principal components of the genetic data to be used as covariates in the methQTL calling. `NULL` means that no adjustment is conducted.

`plink.path`
: Path to an installation of PLINK (also comes with the package)

`fast.qtl.path`
: Path to an installation of fastQTL (comes with the package for Linux)

`bgzip.path`
: Path to an installation of BGZIP (comes with the package for Linux)

`tabix.path`
: Path to an installation of TABIX (comes with the package for Linux)

`correlation.type`
: The type of correlation to be used. Please note that for `type='pearson'` (default) the more efficient implementation of correlation in the `bigstatsr` is used. Further available options are `'spearman'` and `'kendall'`.

`cluster.cor.threshold`
: Threshold for CpG methylatin state correlation to be considered as connected in the distance graph used to compute the correlation clustering.

`standard.deviation.gauss`
: Standard deviation of the Gauss distribution used to weight the correlation according to its distance.

absolute.distance.cutoff
: Distance cutoff after which a CpG correlation is not considered anymore.

linear.model.type
: Linear model type to be used. Can be either "categorical.anova" or "classical.linear". If 'meth.qtl.type'='fastQTL', this option is automatically set to 'fastQTL' see callMethQTLBlock for more informations.

representative.cpg.computation
: Option specifying how reference CpGs per correlation block are to be computed. Available options are "row.medians" for the site that is the row median across the samples within the correlation block (for ties a random selection is performed), "mean.center" for an artifical site in the geometric center of the block with the average methylation level or "best.all" for the CpG with the best p-value across all of the CpGs in the correlation block.

meth.qtl.type
: Option specifying how a methQTL interaction is computed. Since the package is based on correlation blocks, a single correlation block can be associated with either one SNP (meth.qtl.type='oneVSall'), with multiple SNPs (meth.qtl.type='allVSall'), or each correlation block can once be positively and once negatively correlated with a SNP genotype (meth.qtl.type='twoVSall'). Additionally, we provide the option to use (FastQTL)[1] as a methQTL mapping tool (option 'fastQTL').

max.cpgs
: Maximum number of CpGs used in the computation (used to save memory). 40,000 is a reasonable default for machines with ~128GB of main memory. Should be smaller for smaller machines and larger for larger ones.

cluster.architecture
: The type of HPC cluster architecture present. Currently supported are 'sge' and 'slurm'

cluster.config
: Resource parameters needed to setup an SGE or SLURM cluster job. Includes h_vmem and mem_free for SGE and clock.limit and mem.size for SLURM. An example configuration for SLURM would be c("clock.limit"="1-0","mem.size"="10G") for 1 day of running time (format days:hours) and 10 GB of maximum memory usage. Additionally, 'n.cpus' can be specified as the SLURM option cpus-per-task

n.permutations
: The number of permutations used to correct the p-values for multiple testing. See (http://fastqtl.sourceforge.net/) for further information.

compute.cor.blocks
: Flag indicating if correlation blocks are to be called. If FALSE, each CpG is considered separately.

recode.allele.frequencies
: Flag indicating if the reference allele is to be redefined according to the frequenciess found in the cohort investigated.

vcftools.path
: Path to the installation of VCFtools. Necessary is the vcf-sort function in this folder.

imputation.user.token
: The user token that is required for authorization with the Michigan imputation server. Please have a look at https://imputationserver.sph.umich.edu, create a user account and request a user token for access in your user profile.

`imputation.reference.panel`
: The reference panel used for imputation. Please see https://imputationserver.readthedocs.io/en/latest/refer panels/ for further information which panels are supported by the Michigan imputation server.

`imputation.phasing.method`
: The phasing method employed by the Michigan imputation server. See https://imputationserver.readthedo for further information.

`imputation.population`
: The population for the phasing method required by the Michigan imputation server. See https://imputationserver.readthedocs.io/en/latest/api/ for further information.

Value

None

Author(s)

Michael Scherer

References

1. Ongen, H., Buil, A., Brown, A. A., Dermitzakis, E. T., & Delaneau, O. (2016). Fast and efficient QTL mapper for thousands of molecular phenotypes. Bioinformatics, 32(10), 1479–1485. https://doi.org/10.1093/bioinformatics/btv722 2. Das S, Forer L, Schönherr S, Sidore C, Locke AE, et al. (2016). Next-generation genotype imputation service and methods. Nature Genetics 48, 1284–1287, https://doi.org/10.1038/ng.3656 3. Sherry, S. T. et al. (2001). dbSNP: the NCBI database of genetic variation. Nucleic Acids Res. 29, 308–311, https://doi.org/10.1093/nar/29.1.308.

Examples

```
qtlGetOption("rnbeads.report")
qtlSetOption(rnbeads.report=getwd())
qtlGetOption("rnbeads.report")
```

`qtlTFBSMotifEnrichment`
qtlTFBSMotifEnrichment

Description

This function performs TFBS enrichment analysis for the methQTL SNPs/CpGs detected and returns overrepresented binding motifs.

Usage

```
qtlTFBSMotifEnrichment(
  meth.qtl.res,
  type = "SNP",
  size = 500,
  assembly = "hg19",
  subsample = 1e+05,
  out.dir = getwd(),
  ...
)
```

Arguments

meth.qtl.res	An object of type MethQTLResult-class or a list of such objects
type	The type of methQTL to be visualized. Can be either 'SNP', 'CpG', or 'cor.block'
size	Motif enrichment is only supported for genomic regions. Therefore, we resize the invididual methQTL to genomic regions using a width of this size around the site of interest.
assembly	The assembly used. Only "hg19" and "hg38" supported
subsample	Integer specifying how many of the regions are to be subsamples from the universe.
out.dir	The output directory in which resulting plots will be stored.
...	Further parameters passed to findMotifFgBg

Details

This function is in part based on the tutorial for Motif discovery in https://compgenomr.github.io/book/motif-discovery.html. We use all data points that have been used to calculate methQTLs as the background and compare the overlaps with the annotation of interest in comparison to the methQTLs that have been computed in case a MethQTLResult-class is provided. If a list of MethQTLResult-class objects is provided, the intersection between the methQTLs from all objects in the list is compared with the union of all interactions that have been tested.

Value

A plot describing the TFB motif enrichment

Author(s)

Michael Scherer

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
res <- qtlTFBSMotifEnrichment(meth.qtl.res)
```

qtlUpsetPlot *qtlUpsetPlot*

Description

This function creates an UpSet plot from the given methQTL results

Usage

```
qtlUpsetPlot(meth.qtl.result.list, type = "SNP", ...)
```

Arguments

meth.qtl.result.list	A named list with each entry being an object of type MethQTLResult-class. The names are used in the visualization.
type	Determines if either the SNP (default), the CpG, or the correlation block 'cor.block' is to be visualized
...	Further argument passed to upset

Details

The plot is directly drawn and can be stored on disk using the known R graphic devices

Value

None

Author(s)

Michael Scherer

Examples

```
meth.qtl.res.1 <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
meth.qtl.res.2 <- meth.qtl.res.1
qtlUpsetPlot(list(A=meth.qtl.res.1,B=meth.qtl.res.2))
```

qtlUpSetPlotCorBlocks *qtlUpSetPlotCorBlocks*

Description

This function overlaps correlation blocks for a list of methQTL results

Usage

```
qtlUpSetPlotCorBlocks(meth.qtl.res.list, ...)
```

Arguments

meth.qtl.res.list	A list of MethQTLResult-class objects, for which correlation blocks are to be overlapped
...	Further argument passed to upset

Details

This function draws an UpSetPlot for the overlaps directly from to the open graphics device

Value

None

Author(s)

Michael Scherer

Examples

```
meth.qtl.res.1 <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
meth.qtl.res.2 <- meth.qtl.res.1
qtlUpSetPlotCorBlocks(list(A=meth.qtl.res.1,B=meth.qtl.res.2))
```

qtlUpSetPlotTagCpGs *qtlUpSetPlotTagCpGs*

Description

This function overlaps the tagCpGs for a list of methQTL results

Usage

```
qtlUpSetPlotTagCpGs(meth.qtl.res.list, ...)
```

Arguments

meth.qtl.res.list	A list of MethQTLResult-class objects, for which correlation blocks are to be overlapped
...	Further argument passed to upset

Details

This function draws an UpSetPlot for the overlaps directly from to the open graphics device

Value

None

Author(s)

Michael Scherer

Examples

```
meth.qtl.res.1 <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
meth.qtl.res.2 <- meth.qtl.res.1
qtlUpSetPlotTagCpGs(list(A=meth.qtl.res.1,B=meth.qtl.res.2))
```

---

qtlVennPlot *qtlVennPlot*

Description

This function creates a venn plot from a list of methQTL results, showing the overlap between the interactions

Usage

```
qtlVennPlot(
  meth.qtl.result.list,
  out.folder,
  type = "SNP",
  out.name = NULL,
  ...
)
```

Arguments

meth.qtl.result.list	A named list with each entry being an object of type MethQTLResult-class. The names are used in the visualization.
out.folder	Required argument specifying the location to store the resulting plot
type	Determines if either the SNP (default), the CpG, or the correlation block 'cor.block' is to be visualized
out.name	Optional argument for the name of the plot on disk (ending needs to be .png)
...	Further argument passed to venn.diagram

Details

The plot can be stored on disk using out.folder and out.name

Value

None

Author(s)

Michael Scherer

Examples

```
meth.qtl.res.1 <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
meth.qtl.res.2 <- meth.qtl.res.1
qtlVennPlot(list(A=meth.qtl.res.1,B=meth.qtl.res.2),out.folder=getwd())
```

---

saveMethQTLInput,MethQTLInput-method
saveMethQTLInput

Description

This functions stores a MethQTLInput object in disk.

Usage

```
## S4 method for signature 'MethQTLInput'
saveMethQTLInput(object, path)
```

Arguments

object	The MethQTLInput-class object to be stored on disk.
path	A path to a non-existing directory for files to be stored.

Value

None

Author(s)

Michael Scherer

Examples

```
meth.qtl <- loadMethQTLInput(system.file("extdata","reduced_methQTL",package="MAGAR"))
saveMethQTLInput(meth.qtl,"MethQTLInput")
```

---

saveMethQTLResult,MethQTLResult-method
saveMethQTLResult

Description

This functions stores a MethQTLInput object in disk.

Usage

```
## S4 method for signature 'MethQTLResult'
saveMethQTLResult(object, path)
```

Arguments

object	The MethQTLResult-class object to be stored on disk.
path	A path to a non-existing directory for files to be stored.

Value

None

Author(s)

Michael Scherer

Examples

```
meth.qtl.res <- loadMethQTLResult(system.file("extdata","MethQTLResult_chr18",package="MAGAR"))
saveMethQTLResult(meth.qtl.res,"MethQTLResult")
```

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