

Package: PathwayVote (via r-universe)

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Title Robust Pathway Enrichment for DNA Methylation Studies Using Ensemble Voting

Version 0.1.3

Description Performs pathway enrichment analysis using a voting-based framework that integrates CpG–gene regulatory information from expression quantitative trait methylation (eQTM) data. For a grid of top-ranked CpGs and filtering thresholds, gene sets are generated and refined using an entropy-based pruning strategy that balances information richness, stability, and probe bias correction. In particular, gene lists dominated by genes with disproportionately high numbers of CpG mappings are penalized to mitigate active probe bias—a common artifact in methylation data analysis. Enrichment results across parameter combinations are then aggregated using a voting scheme, prioritizing pathways that are consistently recovered under diverse settings and robust to parameter perturbations.

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Depends R (>= 4.0.0)

Imports harmonicmeanp, AnnotationDbi, clusterProfiler, future, furr, methods, parallelly

Suggests GO.db, org.Hs.eg.db, reactome.db, openxlsx

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create_eQTM	<i>Create an expression quantitative trait methylation (eQTM) object</i>
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Description

Create an expression quantitative trait methylation (eQTM) object

Usage

```
create_eQTM(data, metadata = list())
```

Arguments

data	A data.frame containing eQTM data with columns: cpg, statistics, p_value, distance, and at least one of entrez or ensembl.
cpg	Character. CpG probe ID (e.g., "cg00000029"), representing a methylation site.
statistics	Numeric. Test statistic from eQTM association analysis (e.g., correlation coefficient, r-square, regression coefficient, or t-statistic). Can be positive or negative.
p_value	Numeric. P-value associated with the test statistic, must be between 0 and 1.
distance	Numeric. Genomic distance (in base pairs) between the CpG and the associated gene's transcription start site (TSS). Must be non-negative.
entrez	Character. Entrez gene ID of the associated gene. At least one of entrez or ensembl must be provided.
ensembl	Character. Ensembl gene ID of the associated gene. At least one of entrez or ensembl must be provided.
metadata	A list of metadata (optional).

Value

An eQTM object.

Examples

```

data <- data.frame(
  cpg = c("cg000001", "cg000002"),
  statistics = c(2.5, -1.8),
  p_value = c(0.01, 0.03),
  distance = c(50000, 80000),
  entrez = c("673", "1956")
)
eqtm_obj <- create_eQTM(data)

```

eQTM-class

*Expression quantitative trait methylation (eQTM) Class***Description**

A class to store eQTM data for pathway analysis. eQTM stands for Expression Quantitative Trait Methylation.

Slots

data A data.frame containing eQTM data with columns: cpg, statistics, p_value, distance, and at least one of entrez or ensembl.

metadata A list of metadata (e.g., data source, time point). Reserved for future use.

getData

*Get expression quantitative trait methylation (eQTM) Data***Description**

Retrieve the eQTM data.frame from an eQTM object.

Usage

```

getData(object)

## S4 method for signature 'eQTM'
getData(object)

```

Arguments

object An eQTM object.

Value

A data.frame stored in the object.

getMetadata	<i>Get expression quantitative trait methylation (eQTM) Metadata</i>
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Description

Retrieve the metadata list from an eQTM object.

Usage

```
getMetadata(object)

## S4 method for signature 'eQTM'
getMetadata(object)
```

Arguments

object An eQTM object.

Value

A list containing metadata.

pathway_vote	<i>Pathway Voting-Based Enrichment Analysis</i>
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Description

Performs pathway enrichment analysis using a voting-based framework that integrates CpG-gene regulatory information from expression quantitative trait methylation (eQTM) data. For a grid of top-ranked CpGs and filtering thresholds, gene sets are generated and refined using an entropy-based pruning strategy that balances information richness, stability, and probe bias correction. In particular, gene lists dominated by genes with disproportionately high numbers of CpG mappings are penalized to mitigate active probe bias, a common artifact in methylation data analysis. Enrichment results across parameter combinations are then aggregated using a voting scheme, prioritizing pathways that are consistently recovered under diverse settings and robust to parameter perturbations.

Usage

```
pathway_vote(
  cpg_input,
  eQTM,
  databases = c("Reactome"),
  k_grid = NULL,
  stat_grid = NULL,
  distance_grid = NULL,
```

```

    grid_size = 5,
    overlap_threshold = 0.7,
    fixed_prune = NULL,
    min_genes_per_hit = 2,
    readable = FALSE,
    workers = NULL,
    verbose = FALSE
)

```

Arguments

<code>cpg_input</code>	A data.frame containing CpG-level results or identifiers. The first column must contain CpG IDs, which can be Illumina probe IDs (e.g., "cg00000029") for array-based data, or genomic coordinates (e.g., "chr1:10468" or "chr1:10468:") for sequencing-based data. These IDs will be matched against the eQTM object. Optionally, a second column may provide a ranking metric. If supplied, this must be: (i) the complete set of raw p-values from association tests (required for automatic <code>k_grid</code> generation), or (ii) an alternative metric such as t-statistics or feature importance scores, in which case <code>k_grid</code> must be specified manually. If no ranking information is provided, all input CpGs are used directly and <code>k_grid</code> is ignored.
<code>eQTM</code>	An eQTM object containing CpG-gene linkage information, created by the <code>create_eQTM()</code> function. This object provides the CpG-to-gene mapping used for pathway inference. Please make sure the CpG IDs used here match those in <code>cpg_input</code> .
<code>databases</code>	A character vector of pathway databases. Supporting: "Reactome", "KEGG", and "GO".
<code>k_grid</code>	A numeric vector specifying the top-k CpGs used for gene set construction. If NULL, the grid is inferred automatically, but this requires that <code>cpg_input</code> contains: (i) the complete set of CpGs tested (first column), and (ii) raw p-values from the association test (second column). If these conditions are not satisfied, or if alternative ranking metrics are provided (e.g., t-statistics, feature importance scores), then <code>k_grid</code> must be specified manually.
<code>stat_grid</code>	A numeric vector of eQTM statistic thresholds. If NULL, generated based on quantiles of the observed distribution.
<code>distance_grid</code>	A numeric vector of CpG-gene distance thresholds (in base pairs). If NULL, generated based on quantiles of the observed distribution.
<code>grid_size</code>	Integer. Number of values in each grid when auto-generating. Default is 5.
<code>overlap_threshold</code>	Numeric between 0 and 1. Controls the maximum allowed Jaccard similarity between gene lists during redundancy filtering. Default is 0.7, which provides robust and stable results across a variety of simulation scenarios.
<code>fixed_prune</code>	Integer or NULL. Minimum number of votes to retain a pathway. If NULL, will use $\text{cuberoot}(N)$ where N is the number of total enrichment runs.
<code>min_genes_per_hit</code>	Minimum number of genes a pathway must include to be considered. Default is 2.

readable	Logical. Whether to convert Entrez IDs to gene symbols in enrichment results.
workers	Optional integer. Number of parallel workers. If NULL, use 2 logical cores.
verbose	Logical. Whether to print progress messages.

Value

A named list of data.frames containing:

- Enrichment results for each selected database (e.g., 'Reactome', 'KEGG', 'GO'). Each data.frame contains columns: 'ID', 'p.adjust', 'Description', and 'geneID'.
- 'CpG_Gene_Mapping': A data.frame showing the CpG-Gene relationships for genes identified in the significantly enriched pathways, limited to the CpGs present in the input 'cpg_input'.

Examples

```
set.seed(123)

# Simulated EWAS result: a mix of signal and noise
n_cpg <- 500
ewas <- data.frame(
  cpg = paste0("cg", sprintf("%08d", 1:n_cpg)),
  p_value = c(runif(n_cpg*0.1, 1e-9, 1e-5), runif(n_cpg*0.2, 1e-3, 0.05), runif(n_cpg*0.7, 0.05, 1))
)

# Corresponding eQTM mapping (some of these CpGs have gene links)
signal_genes <- c("5290", "673", "1956", "7157", "7422")
background_genes <- as.character(1000:9999)
entrez_signal <- sample(signal_genes, n_cpg * 0.1, replace = TRUE)
entrez_background <- sample(setdiff(background_genes, signal_genes), n_cpg * 0.9, replace = TRUE)

eqtm_data <- data.frame(
  cpg = ewas$cpg,
  statistics = rnorm(n_cpg, mean = 2, sd = 1),
  p_value = runif(n_cpg, min = 0.001, max = 0.05),
  distance = sample(1000:100000, n_cpg, replace = TRUE),
  entrez = c(entrez_signal, entrez_background),
  stringsAsFactors = FALSE
)
eqtm_obj <- create_eQTM(eqtm_data)

# Run pathway voting with minimal settings
## Not run:
results <- pathway_vote(
  cpg_input = ewas,
  eQTM = eqtm_obj,
  databases = c("GO", "KEGG", "Reactome"),
  readable = TRUE,
  verbose = TRUE
)
head(results$GO)
head(results$KEGG)
```

```
head(results$Reactome)

# Export results to Excel (optional)
library(openxlsx)
write_enrich_results_xlsx(results, "pathway_vote_results.xlsx")

## End(Not run)
```

write_enrich_results_xlsx

Export Enrichment Results to Excel

Description

Exports the results from ‘pathway_vote’ to a multi-sheet Excel file. Validates that the input is a list, checks for the ‘openxlsx’ package, and handles sheet naming to comply with Excel limitations.

Usage

```
write_enrich_results_xlsx(results, file = "enrich_results.xlsx")
```

Arguments

results	A named list of data.frames (e.g., output from ‘pathway_vote’).
file	Character. Output file path (e.g., "enrich_results.xlsx").

Value

Invisible. The path to the saved file.

Examples

```
## Not run:
# Assuming `res` is the output from pathway_vote(...)
write_enrich_results_xlsx(res, "my_results.xlsx")

## End(Not run)
```

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