

# Package ‘GEM’

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**Type** Package

**Title** GEM: fast association study for the interplay of Gene,  
Environment and Methylation

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**Description** Tools for analyzing EWAS, methQTL and GxE genome widely.

**License** Artistic-2.0

**biocViews** MethylationSeq, MethylationArray, GenomeWideAssociation,  
Regression, DNAMethylation, SNP, GeneExpression, GUI

**Depends** R (>= 3.3)

**VignetteBuilder** knitr

**Suggests** knitr, RUnit, testthat, BiocGenerics, rmarkdown, markdown

**Imports** tcltk, ggplot2, methods, stats, grDevices, graphics, utils

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| GEM-package | <i>GEM: Fast association study for the interplay of Gene, Environment and Methylation</i> |
|-------------|-------------------------------------------------------------------------------------------|

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## Description

The GEM package provides a highly efficient R tool suite for performing epigenome wide association studies (EWAS). GEM provides three major functions named [GEM\\_Emodel](#), [GEM\\_Gmodel](#) and [GEM\\_GxEmodel](#) to study the interplay of Gene, Environment and Methylation (GEM). Within GEM, the existing "Matrix eQTL" package is utilized and extended to study methylation quantitative trait loci (methQTL) and the interaction of genotype and environment (GxE) to determine DNA methylation variation, using matrix based iterative correlation and memory-efficient data analysis. GEM can facilitate reliable genome-wide methQTL and GxE analysis on a standard laptop computer within minutes.

## Author(s)

Hong Pan

## References

<https://github.com/fastGEM/GEM>

## See Also

[GEM\\_GUI](#)

## Examples

```
## Launch GEM GUI
#GEM_GUI() # remove the hash symbol for running

## Checking the vignettes for more details
if(interactive()) browseVignettes(package = 'GEM')
```

**Description**

GEM\_Emodel is to find the association between methylation and environmental factor genome widely.

**Usage**

```
GEM_Emodel(env_file_name, covariate_file_name, methylation_file_name, Emodel_pv,
            output_file_name, qqplot_file_name, savePlot = TRUE)
```

**Arguments**

`env_file_name` Text file with rows representing environment factor and columns representing samples, such as the example data file "env.txt".

`covariate_file_name` Text file with rows representing covariate factors and columns representing samples, such as the example data file "cov.txt".

`methylation_file_name` Text file with rows representing methylation profiles for CpGs, and columns representing samples, such as the example data file "methylation.txt".

`Emodel_pv` The pvalue cut off. Associations with significances at Emodel\_pv level or below are saved to output\_file\_name, with corresponding estimate of effect size (slope coefficient), test statistics and p-value. Default value is 1.0.

`output_file_name` The result file with each row presenting a CpG and its association with environment, which contains CpGID, estimate of effect size (slope coefficient), test statistics, pvalue and FDR at each column.

`qqplot_file_name` Image file name to present the QQ-plot for all p-value distribution.

`savePlot` If save the plot.

**Details**

GEM\_Emodel finds the association between methylation and environment genome-wide by performing matrix based iterative correlation and memory-efficient data analysis instead of millions of linear regressions ( $N = \text{number\_of\_CpGs}$ ). The methylation data are the measurements for CpG probes, for example, 450,000 CpGs from Illumina Infinium HumanMethylation450 Array. The environmental factor can be a particular phenotype or environment factor from, for example, birth outcomes, maternal conditions or disease traits. The output of GEM\_Emodel for particular environmental factor is a list of CpGs that are potential epigenetic biomarkers. GEM\_Emodel runs linear regression like  $\text{lm}(M \sim E + \text{covt})$ , where  $M$  is a matrix with methylation data,  $E$  is a matrix with environment factor and  $\text{covt}$  is a matrix with covariates, and all read from the formatted text data file.

**Value**

save results automatically

**Examples**

```

DATADIR = system.file('extdata',package='GEM')
RESULTDIR = getwd()
env_file = paste(DATADIR, "env.txt", sep = .Platform$file.sep)
covariate_file = paste(DATADIR, "cov.txt", sep = .Platform$file.sep)
methylation_file = paste(DATADIR, "methylation.txt", sep = .Platform$file.sep)
Emodel_pv = 1
output_file = paste(RESULTDIR, "Result_Emodel.txt", sep = .Platform$file.sep)
qqplot_file = paste(RESULTDIR, "QQplot_Emodel.jpg", sep = .Platform$file.sep)
GEM_Emodel(env_file, covariate_file, methylation_file, Emodel_pv, output_file, qqplot_file)

```

---

GEM\_Gmodel

*GEM\_Gmodel Analysis*


---

**Description**

GEM\_Gmodel creates a methQTL genome-wide map.

**Usage**

```
GEM_Gmodel(snp_file_name, covariate_file_name, methylation_file_name, Gmodel_pv,
output_file_name)
```

**Arguments**

**snp\_file\_name** Text file with rows representing genotype encoded as 1,2,3 or any three distinct values for major allele homozygote (AA), heterozygote (AB) and minor allele homozygote (BB) and columns representing samples, such as the example data file "snp.txt".

**covariate\_file\_name** Text file with rows representing covariate factors and columns representing samples, such as the example data file "cov.txt".

**methylation\_file\_name** Text file with rows representing methylation profiles for CpGs, and columns representing samples, such as the example data file "methylation.txt".

**Gmodel\_pv** The pvalue cut off. Associations with significances at Gmodel\_pv level or below are saved to output\_file\_name, with corresponding estimate of effect size (slope coefficient), test statistics and p-value. Default value is 5.0E-08.

**output\_file\_name** The result file with each row presenting a CpG and its association with SNP, which contains CpGID, SNPID, estimate of effect size (slope coefficient), test statistics, pvalue and FDR at each column.

## Details

GEM\_Gmodel creates a methQTL genome-wide map by performing matrix based iterative correlation and memory-efficient data analysis instead of millions of linear regressions ( $N = \text{number\_of\_CpGs} \times \text{number\_of\_SNPs}$ ) between methylation and genotyping. Polymorphisms close to CpGs in the same chromosome (cis-) or different chromosome (trans-) often form methylation quantitative trait loci (methQTLs) with CpGs. In GEM\_Gmodel, MethQTLs can be discovered by correlating single nucleotide polymorphism (SNP) data with CpG methylation from the same samples, by linear regression  $\text{lm}(M \sim G + \text{covt})$ , where  $M$  is a matrix with methylation data,  $G$  is a matrix with genotype data and  $\text{covt}$  is a matrix with covariates, and all read from the formatted text data file. The methylation data are the measurements for CpG probes, for example, 450,000 CpGs from Illumina Infinium HumanMethylation450 Array. The genotype data are encoded as 1,2,3 or any three distinct values for major allele homozygote (AA), heterozygote (AB) and minor allele homozygote (BB). The linear regression is adjusted by covariates read from covariate data file. The output of GEM\_Gmodel is a list of CpG-SNP pairs, where the SNP is the best fit to explain the particular CpG. The significant association between CpG-SNP pair suggests the methylation driven by genotyping variants, which is so called methylation quantitative trait loci (methQTL).

## Value

save results automatically

## Examples

```
DATADIR = system.file('extdata',package='GEM')
RESULTDIR = getwd()
snp_file = paste(DATADIR, "snp.txt", sep = .Platform$file.sep)
covariate_file = paste(DATADIR, "cov.txt", sep = .Platform$file.sep)
methylation_file = paste(DATADIR, "methylation.txt", sep = .Platform$file.sep)
Gmodel_pv = 1e-04
output_file = paste(RESULTDIR, "Result_Gmodel.txt", sep = .Platform$file.sep)
GEM_Gmodel(snp_file, covariate_file, methylation_file, Gmodel_pv, output_file)
```

---

GEM\_GUI

*Graphical User Interface (GUI) for GEM*

---

## Description

The user friendly GUI for running GEM package easily and quickly

## Usage

GEM\_GUI()

**Details**

The GEM package provides a highly efficient R tool suite for performing epigenome wide association studies (EWAS). GEM provides three major functions named [GEM\\_Emodel](#), [GEM\\_Gmodel](#) and [GEM\\_GxEmodel](#) to study the interplay of Gene, Environment and Methylation (GEM). Within GEM, the pre-existing "Matrix eQTL" package is utilized and extended to study methylation quantitative trait loci (methQTL) and the interaction of genotype and environment (GxE) to determine DNA methylation variation, using matrix based iterative correlation and memory-efficient data analysis. GEM can facilitate reliable genome-wide methQTL and GxE analysis on a standard laptop computer within minutes.

**Value**

GEM model analysis results

**See Also**

[GEM-package](#)

**Examples**

```
interactive()
#GEM_GUI() ## remove the hash symbol to run
```

---

GEM\_GWASmodel

*GEM\_GWASmodel*

---

**Description**

GEM\_GWASmodel performs genome wide association study (GWAS).

**Usage**

```
GEM_GWASmodel(env_file_name, snp_file_name, covariate_file_name, GWASmodel_pv,
  output_file_name, qqplot_file_name)
```

**Arguments**

|                                  |                                                                                                                                                                                                                                                         |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>env_file_name</code>       | Text file with rows representing environment factor and columns representing samples, such as the example data file "env.txt".                                                                                                                          |
| <code>snp_file_name</code>       | Text file with rows representing genotype encoded as 1,2,3 or any three distinct values for major allele homozygote (AA), heterozygote (AB) and minor allele homozygote (BB) and columns representing samples, such as the example data file "snp.txt". |
| <code>covariate_file_name</code> | Text file with rows representing covariate factors, and columns representing samples, such as the example data file "cov.txt".                                                                                                                          |

|                  |                                                                                                                                                                                                                                          |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| GWASmodel_pv     | The pvalue cut off. Associations with significances at GWASmodel_pv level or below are saved to output_file_name, with corresponding estimate of effect size (slope coefficient), test statistics and p-value. Default value is 5.0E-08. |
| output_file_name | The result file with each row presenting a SNP and its association with environment, which contains SNPID, estimate of effect size (slope coefficient), test statistics, pvalue and FDR at each column.                                  |
| qqplot_file_name | Output QQ plot for all pvalues.                                                                                                                                                                                                          |

### Details

GEM\_GWASmodel finds the association between genetic variants and environment genome-wide by performing matrix based iterative correlation and memory-efficient data analysis instead of millions of linear regressions ( $N = \text{number\_of\_SNPs}$ ). The environmental factor can be a particular phenotype or environment factor from, for example, birth outcomes, maternal conditions or disease traits. The genotype data are encoded as 1,2,3 or any three distinct values for major allele homozygote (AA), heterozygote (AB) and minor allele homozygote (BB). The linear regression is adjusted by covariates read from covariate data file. The output of GEM\_GWASmodel is a list of SNPs and their association with environment. GEM\_GWASmodel runs linear regression like  $\text{lm}(E \sim G + \text{covt})$ , where  $G$  is a matrix with genotype data,  $E$  is a matrix with environment factor and  $\text{covt}$  is a matrix with covariates, and all read from the formatted text data file.

### Value

save results automatically

### Examples

```
DATADIR = system.file('extdata',package='GEM')
RESULTDIR = getwd()
snp_file = paste(DATADIR, "snp.txt", sep = .Platform$file.sep)
covariate_file = paste(DATADIR, "cov.txt", sep = .Platform$file.sep)
env_file = paste(DATADIR, "env.txt", sep = .Platform$file.sep)
GWASmodel_pv = 1e-5
output_file = paste(RESULTDIR, "Result_GxEmodel.txt", sep = .Platform$file.sep)
qqplot_file = paste(RESULTDIR, "Result_GxEmodel.jpeg", sep = .Platform$file.sep)
GEM_GWASmodel(env_file, snp_file, covariate_file, GWASmodel_pv, output_file, qqplot_file)
```

---

GEM\_GxEmodel

*GEM\_GxEmodel*

---

### Description

GEM\_GxEmodel tests the ability of the interaction of gene and environmental factor to predict DNA methylation level.

**Usage**

```
GEM_GxEmodel(snp_file_name, covariate_file_name, methylation_file_name,
             GxEmodel_pv, output_file_name, topKplot = 10, savePlot = TRUE)
```

**Arguments**

|                       |                                                                                                                                                                                                                                                         |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| snp_file_name         | Text file with rows representing genotype encoded as 1,2,3 or any three distinct values for major allele homozygote (AA), heterozygote (AB) and minor allele homozygote (BB) and columns representing samples, such as the example data file "snp.txt". |
| covariate_file_name   | Text file with rows representing covariate factors and the environment value, and the environment value should be put in the last row, and columns representing samples, such as the example data file "gxe.txt".                                       |
| methylation_file_name | Text file with rows representing methylation profiles for CpGs, and columns representing samples, such as the example data file "methylation.txt".                                                                                                      |
| GxEmodel_pv           | The pvalue cut off. Associations with significances at GxEmodel_pv level or below are saved to output_file_name, with corresponding estimate of effect size (slope coefficient), test statistics and p-value. Default value is 5.0E-08.                 |
| output_file_name      | The result file with each row presenting a CpG and its association with SNPx-Env, which contains CpGID, SNPID, estimate of effect size (slope coefficient), test statistics, pvalue and FDR at each column.                                             |
| topKplot              | The top number of topKplot CpG-SNP-Env triplets will be presented into charts to demonstrate how environment values segregated by SNP groups can explain methylation.                                                                                   |
| savePlot              | if save the plot.                                                                                                                                                                                                                                       |

**Details**

GEM\_GxEmodel explores how the genotype can work in interaction with environment (GxE) to influence specific DNA methylation level, by performing matrix based iterative correlation and memory-efficient data analysis among methylation, genotyping and environment. This has greatly released the computational burden for GxE study from billions of linear regression ( $N = \text{number\_of\_CpGs} \times \text{number\_of\_SNPs} \times \text{number\_of\_environment}$ ) and made it possible to be accomplished in an efficient way. The linear regression is  $\text{lm}(M \sim G \times E + \text{covt})$ , where  $M$  is a matrix with methylation data,  $G$  is a matrix with genotype data,  $E$  is environment data and  $\text{covt}$  is covariate matrix.  $E$  values is combined into covariate file as the last row, and all read from the formatted text data file. The output of GEM\_GxEmodel is a list of CpG-SNP-Env triplets, where the environment factor segregated in genotype group fits to explain the particular CpG. The significant association suggests the association between methylation and environment can be better explained by segregation in genotype groups (GxE).

**Value**

save results automatically

**Examples**

```

DATADIR = system.file('extdata',package='GEM')
RESULTDIR = getwd()
snp_file = paste(DATADIR, "snp.txt", sep = .Platform$file.sep)
covariate_file = paste(DATADIR, "gxe.txt", sep = .Platform$file.sep)
methylation_file = paste(DATADIR, "methylation.txt", sep = .Platform$file.sep)
GxEmodel_pv = 1e-4
output_file = paste(RESULTDIR, "Result_GxEmodel.txt", sep = .Platform$file.sep)
GEM_GxEmodel(snp_file, covariate_file, methylation_file, GxEmodel_pv, output_file)

```

SlicedData-class

*Class SlicedData for storing large matrices***Description**

This class is created for fast and memory efficient manipulations with large datasets presented in matrix form. It is used to load, store, and manipulate large datasets, e.g. genotype and gene expression matrices. When a dataset is loaded, it is sliced in blocks of 1,000 rows (default size). This allows imputing, standardizing, and performing other operations with the data with minimal memory overhead.

**Usage**

```

# x[[i]] indexing allows easy access to individual slices.
# It is equivalent to x$GetSlice(i) and x$SetSlice(i,value)
## S4 method for signature 'SlicedData'
x[[i]]
## S4 replacement method for signature 'SlicedData'
x[[i]] <- value

# The following commands work as if x was a simple matrix object
## S4 method for signature 'SlicedData'
nrow(x)
## S4 method for signature 'SlicedData'
ncol(x)
## S4 method for signature 'SlicedData'
dim(x)
## S4 method for signature 'SlicedData'
rownames(x)
## S4 method for signature 'SlicedData'
colnames(x)
## S4 replacement method for signature 'SlicedData'
rownames(x) <- value
## S4 replacement method for signature 'SlicedData'
colnames(x) <- value

# SlicedData object can be easily transformed into a matrix

```

```

# preserving row and column names
## S4 method for signature 'SlicedData'
as.matrix(x)

# length(x) can be used in place of x$nSlices()
# to get the number of slices in the object
## S4 method for signature 'SlicedData'
length(x)

```

### Arguments

|       |                                                      |
|-------|------------------------------------------------------|
| x     | SlicedData object.                                   |
| i     | Number of a slice.                                   |
| value | New content for the slice / new row or column names. |

### Value

check the results

### Extends

SlicedData is a reference classes ([envRefClass](#)). Its methods can change the values of the fields of the class.

### Fields

**dataEnv:** environment. Stores the slices of the data matrix. The slices should be accessed via `getSlice()` and `setSlice()` methods.

**nSlices1:** numeric. Number of slices. For internal use. The value should be access via `nSlices()` method.

**rowNameSlices:** list. Slices of row names.

**columnNames:** character. Column names.

**fileDelimiter:** character. Delimiter separating values in the input file.

**fileSkipColumns:** numeric. Number of columns with row labels in the input file.

**fileSkipRows:** numeric. Number of rows with column labels in the input file.

**fileSliceSize:** numeric. Maximum number of rows in a slice.

**fileOmitCharacters:** character. Missing value (NaN) representation in the input file.

### Methods

**initialize(mat):** Create the object from a matrix.

**nSlices():** Returns the number of slices.

**nCols():** Returns the number of columns in the matrix.

**nRows():** Returns the number of rows in the matrix.

**Clear():** Clears the object. Removes the data slices and row and column names.

Clone(): Makes a copy of the object. Changes to the copy do not affect the source object.

CreateFromMatrix(mat): Creates SlicedData object from a [matrix](#).

LoadFile(filename, skipRows = NULL, skipColumns = NULL, sliceSize = NULL, omitCharacters = NULL, delimiter): Loads data matrix from a file. filename should be a character string. The remaining parameters specify the file format and have the same meaning as file\* fields. Additional rowNamesColumn parameter specifies which of the columns of row labels to use as row names.

SaveFile(filename): Saves the data to a file. filename should be a character string.

getSlice(sl): Retrieves sl-th slice of the matrix.

setSlice(sl, value): Set sl-th slice of the matrix.

ColumnSubsample(subset): Reorders/subsets the columns according to subset.  
Acts as  $M = M[ , subset]$  for a matrix M.

RowReorder(ordr): Reorders rows according to ordr.  
Acts as  $M = M[ordr, ]$  for a matrix M.

RowMatrixMultiply(multiplier): Multiply each row by the multiplier.  
Acts as  $M = M \%*\% multiplier$  for a matrix M.

CombineInOneSlice(): Combines all slices into one. The whole matrix can then be obtained via `$getSlice(1)`.

IsCombined(): Returns TRUE if the number of slices is 1 or 0.

ResliceCombined(sliceSize = -1): Cuts the data into slices of sliceSize rows. If sliceSize is not defined, the value of fileSliceSize field is used.

GetAllRowNames(): Returns all row names in one vector.

RowStandardizeCentered(): Set the mean of each row to zero and the sum of squares to one.

SetNanRowMean(): Impute rows with row mean. Rows full of NaN values are imputed with zeros.

RowRemoveZeroEps(): Removes rows of zeros and those that are nearly zero.

FindRow(rowname): Finds row by name. Returns a pair of slice number and row number within the slice. If no row is found, the function returns NULL.

rowMeans(x, na.rm = FALSE, dims = 1L): Returns a vector of row means. Works as [rowMeans](#) but requires dims to be equal to 1L.

rowSums(x, na.rm = FALSE, dims = 1L): Returns a vector of row sums. Works as [rowSums](#) but requires dims to be equal to 1L.

colMeans(x, na.rm = FALSE, dims = 1L): Returns a vector of column means. Works as [colMeans](#) but requires dims to be equal to 1L.

colSums(x, na.rm = FALSE, dims = 1L): Returns a vector of column sums. Works as [colSums](#) but requires dims to be equal to 1L.

**Author(s)**

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**References**

The package website: [http://www.bios.unc.edu/research/genomic\\_software/Matrix\\_eQTL/](http://www.bios.unc.edu/research/genomic_software/Matrix_eQTL/)

**Examples**

```
# Create a SlicedData variable
```

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