

# Package ‘EnMCB’

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**Type** Package

**Title** Predicting Disease Progression Based on Methylation Correlated Blocks using Ensemble Models

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**VignetteBuilder** knitr

**Suggests** SummarizedExperiment, testthat, Biobase, survminer, affycoretools, knitr, plotROC, prognosticROC

**Description** Creation of the correlated blocks using DNA methylation profiles. A stacked ensemble of machine learning models, which combined the support vector machine and elastic-net regression model, can be constructed to predict disease progression.

**License** GPL-2

**BugReports** <https://github.com/whirlsyu/EnMCB/issues>

**biocViews** Normalization, DNAMethylation, MethylationArray, SupportVectorMachine

**LazyData** FALSE

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create_demo	<i>create demo matrix</i>
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### Description

Demo matrix for methylation matrix.

### Usage

```
create_demo(model = c("all", "short")[1])
```

### Arguments

model            Two options, 'all' or 'short' for creating full dataset or very brief demo.

### Value

This function will generate a demo data.

### Author(s)

Xin Yu

### Examples

```
demo_set<-create_demo()
```

---

demo_data	<i>Expression matrix of demo dataset.</i>
-----------	---

---

### Description

A Expression matrix containing the 10020 CpGs beta value of 455 samples in TCGA lung Adeno-carcinoma dataset. This will call form create\_demo() function.

### Usage

```
data(demo_data)
```

### Format

ExpressionSet:

**rownames** rownames of 10020 CpG features

**colnames** colnames of 455 samples

**realdata** Real data matrix for demo.

---

demo_MCBinformation	<i>MCB information.</i>
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---

### Description

A dataset containing the number and other attributes of 94 MCBs; This results was created by the identification function IdentifyMCB. This data used for metricMCB function.

### Usage

```
data(demo_MCBinformation)
```

### Format

A data frame with 94 rows and 8 variables:

**MCB\_no** MCB code

**start** Start point of this MCB in the chromosome.

**end** End point of this MCB in the chromosome.

**CpGs** All the CpGs probe names in the MCB.

**location** Start, end point and the chromosome number of this MCB.

**chromosomes** the chromosome number of this MCB.

**length** the length of bps of this MCB in the chromosome.

**CpGs\_num** number of CpG probes of this MCB.

---

demo\_survival\_data      *Survival data of demo dataset.*

---

### Description

A Surv containing survival value of 455 samples in TCGA lung Adenocarcinoma dataset.

### Usage

```
data(demo_survival_data)
```

### Format

Surv data created by Surv() function in survival package. This data have two unnamed arguments, they will match time and event.

---

draw\_survival\_curve      *draw survival curve*

---

### Description

Draw a survival curve based on survminer package. This is a wrapper function of ggsurvplot.

### Usage

```
draw_survival_curve(
  exp,
  living_days,
  living_events,
  write_name,
  title_name = "",
  threshold = NA
)
```

### Arguments

exp	expression level for gene.
living_days	The survival time (days) for each individual.
living_events	The survival event for each individual, 0 indicates alive and 1 indicates death. Other choices are TRUE/FALSE (TRUE = death) or 1/2 (2=death). For interval censored data, the status indicator is 0=right censored, 1=event at time, 2=left censored, 3=interval censored.
write_name	The name for pdf file which contains the result figure.
title_name	The title for the result figure.
threshold	Threshold used to indicate the high risk or low risk.

**Value**

This function will generate a pdf file with 300dpi which compare survival curves using the Kaplan-Meier (KM) test.

**Author(s)**

Xin Yu

**Examples**

```
data(demo_survival_data)
library(survival)
demo_set<-create_demo()
draw_survival_curve(demo_set[1,],
  living_days = demo_survival_data[,1],
  living_events =demo_survival_data[,2],
  write_name = "demo_data" )
```

---

 ensemble\_model

*Training stacking ensemble model for Methylation Correlation Block*


---

**Description**

Method for training a stacking ensemble model for Methylation Correlation Block.

**Usage**

```
ensemble_model(single_res, training_set, Surv_training, testing_set, Surv_testing)
```

**Arguments**

single_res	Methylation Correlation Block information returned by the IdentifyMCB function.
training_set	methylation matrix used for training the model in the analysis.
Surv_training	Survival function contain the survival information for training.
testing_set	methylation matrix used for testing the model in the analysis.
Surv_testing	Survival function contain the survival information for testing.

**Value**

Object of class list with elements (XXX represents the model you choose):

cox	Model object for the cox model at first level.
svm	Model object for the svm model at first level.
lasso	Model object for the lasso model at first level.
stacking	Model object for the stacking model.

**Author(s)**

Xin Yu

**References**

Xin Yu et al. 2019 Predicting disease progression in lung adenocarcinoma patients based on methylation correlated blocks using ensemble machine learning classifiers (under review)

**Examples**

```
#import datasets
library(survival)
data(demo_survival_data)
datamatrix<-create_demo()
data(demo_MCBinformation)
#select MCB with at least 3 CpGs.
demo_MCBinformation<-demo_MCBinformation[demo_MCBinformation[, "CpGs_num"]>2,]
trainingset<-colnames(datamatrix) %in% sample(colnames(datamatrix),0.6*length(colnames(datamatrix)))
select_single_one=1
em<-ensemble_model(t(demo_MCBinformation[select_single_one,]),
  training_set=datamatrix[,trainingset],
  Surv_training=demo_survival_data[trainingset])
```

---

ensemble\_prediction    *fitting function using stacking ensemble model for Methylation Correlation Block*

---

**Description**

predict is a generic function for predictions from the results of stacking ensemble model fitting functions. The function invokes particular methods which is the ensemble model described in the reference.

**Usage**

```
ensemble_prediction(ensemble_model, prediction_data)
```

**Arguments**

ensemble\_model    ensemble model which built by ensemble\_model() function

prediction\_data    A vector, matrix, list, or data frame containing the predictions (input).

**Value**

Object of numeric class double

**References**

Xin Yu et al. 2019 Predicting disease progression in lung adenocarcinoma patients based on methylation correlated blocks using ensemble machine learning classifiers (under review)

**Examples**

```

library(survival)
#import datasets
data(demo_survival_data)
datamatrix<-create_demo()
data(demo_MCBinformation)
#select MCB with at least 3 CpGs.
demo_MCBinformation<-demo_MCBinformation[demo_MCBinformation[, "CpGs_num"]>2,]
trainingset<-colnames(datamatrix) %in% sample(colnames(datamatrix),0.6*length(colnames(datamatrix)))
testingset<-!trainingset
#select one MCB
select_single_one=1
em<-ensemble_model(t(demo_MCBinformation[select_single_one,]),
  training_set=datamatrix[,trainingset],
  Surv_training=demo_survival_data[trainingset])

em_prediction_results<-ensemble_prediction(ensemble_model = em,
  predition_data = datamatrix[,testingset])

```

---

fast\_roc\_calculation *Fast calculation of AUC for ROC using parallel strategy*

---

**Description**

This function is used to create time-dependent ROC curve from censored survival data using the Kaplan-Meier (KM) or Nearest Neighbor Estimation (NNE) method of Heagerty, Lumley and Pepe, 2000

**Usage**

```
fast_roc_calculation(test_matrix, y_surv, predict_time = 5, roc_method = "NNE")
```

**Arguments**

test_matrix	Test matrix used in the analysis. Colmuns are samples, rows are markers.
y_surv	Survival information created by Surv function in survival package.
predict_time	Time point of the ROC curve, default is 5 year.
roc_method	Method for fitting joint distribution of (marker,t), either of KM or NNE, the default method is NNE.

**Value**

This will retrun a numeric vector contains AUC results for each row in test\_matrix.

**Author(s)**

Xin Yu

**Examples**

```
data(demo_survival_data)
data('demo_data', package = "EnMCB")
demo_set<-demo_data$realdata
res<-fast_roc_calculation(demo_set[1:2,], demo_survival_data)
```

IdentifyMCB

*Identification of methylation correlated blocks***Description**

This function is used to partition the genome into blocks of tightly co-methylated CpG sites, Methylation correlated blocks. This function calculates Pearson correlation coefficients  $r^2$  between the beta values of any two CpGs  $r^2 < \text{CorrelationThreshold}$  was used to identify boundaries between any two adjacent markers indicating uncorrelated methylation. Markers not separated by a boundary were combined into MCB. Pearson correlation coefficients between two adjacent CpGs were calculated.

**Usage**

```
IdentifyMCB(
  MethylationProfile,
  method = c("pearson", "spearman", "kendall")[1],
  CorrelationThreshold = 0.8,
  PositionGap = 1000,
  platform = "Illumina Methylation 450K"
)
```

**Arguments**

MethylationProfile	Methylation matrix is used in the analysis.
method	method used for calculation of correlation, should be one of "pearson", "spearman", "kendall". Default is "pearson".
CorrelationThreshold	coef correlation threshold is used for define boundaries.
PositionGap	CpG Gap between any two CpGs positioned CpG sites less than 1000 bp (default) will be calculated.
platform	This parameter indicates the platform used to produce the methylation profile.

**Details**

Currently, only illumina 450k platform is supported, the methylation profile need to convert into matrix format.

**Value**

Object of class list with elements:

MCBsites	Character set contains all CpG sites in MCBs.
MCBinformation	Matrix contains the information of results.



**Author(s)**

Xin Yu

**References**

Xin Yu et al. 2019 Predicting disease progression in lung adenocarcinoma patients based on methylation correlated blocks using ensemble machine learning classifiers (under review)

**Examples**

```
data('demo_data',package = "EnMCB")

#import the demo TCGA data with 10000+ CpGs site and 455 samples
#remove # to run
res<-IdentifyMCB(demo_data$realdata)
demo_MCBinformation<-res$MCBinformation
```

metricMCB

*Calculation of the metric matrix for Methylation Correlation Block***Description**

To enable quantitative analysis of the methylation patterns within individual Methylation Correlation Blocks across many samples, a single metric to define the methylated pattern of multiple CpG sites within each block. Compound scores which calculated all CpGs within individual Methylation Correlation Blocks by SVM model were used as the compound methylation values of Methylation Correlation Blocks.

**Usage**

```
metricMCB(MCBset,training_set,Surv,testing_set,Surv.new,Method,silent)
```

**Arguments**

MCBset	Methylation Correlation Block information returned by the IdentifyMCB function.
training_set	methylation matrix used for training the model in the analysis.
Surv	Survival function contain the survival information for training.
testing_set	methylation matrix used in the analysis. This can be missing then training set itself will be used as testing set.
Surv.new	Survival function contain the survival information for testing.
Method	model used to calculate the compound values for multiple Methylation correlation blocks. Options include "svm" "cox" and "lasso". The default option is SVM method.
silent	Ture indicates that processing information and progress bar will be shown.

**Value**

Object of class list with elements (XXX will be replaced with the model name you choose):

MCB_XXX_matrix_training	Prediction results of model for training set.
MCB_XXX_matrix_test_set	Prediction results of model for test set.
XXX_auc_results	AUC results for each model.
best_XXX_model	Model object for the model with best AUC.
maximum_auc	Maximum AUC for the whole generated models.

### Author(s)

Xin Yu

### References

Xin Yu et al. 2019 Predicting disease progression in lung adenocarcinoma patients based on methylation correlated blocks using ensemble machine learning classifiers (under review)

### Examples

```
#import datasets
data(demo_survival_data)
datamatrix<-create_demo()
data(demo_MCBinformation)
#select MCB with at least 3 CpGs.
demo_MCBinformation<-demo_MCBinformation[demo_MCBinformation[, "CpGs_num"]>2,]

trainingset<-colnames(datamatrix) %in% sample(colnames(datamatrix),0.6*length(colnames(datamatrix)))
testingset<-!trainingset
#create the results using Cox regression.
mcb_cox_res<-metricMCB(MCBset = demo_MCBinformation,
  training_set = datamatrix[,trainingset],
  Surv = demo_survival_data[trainingset],
  testing_set = datamatrix[,testingset],
  Surv.new = demo_survival_data[testingset],
  Method = "cox"
)
```

---

metricMCB.cv

*Calculation of model AUC for Methylation Correlation Blocks using cross validation*

---

### Description

To enable quantitative analysis of the methylation patterns within individual Methylation Correlation Blocks across many samples, a single metric to define the methylated pattern of multiple CpG sites within each block. Compound scores which calculated all CpGs within individual Methylation Correlation Blocks by SVM model were used as the compound methylation values of Methylation Correlation Blocks.

### Usage

```
metricMCB.cv(MCBset,data_set,Surv,nfold,Method,seed,silent)
```

**Arguments**

MCBset	Methylation Correlation Block information returned by the IdentifyMCB function.
data_set	methylation matrix used for training the model in the analysis.
Surv	Survival function contain the survival information for training.
nfold	fold used in the cross validation procedure.
Method	model used to calculate the compound values for multiple Methylation correlation blocks. Options include "svm" "cox" and "lasso". The default option is "svm" for SVR method.
seed	an integer vector, containing the random number generator (RNG) state for random number generation.
silent	Ture indicates that processing information and progress bar will be shown.

**Value**

Object of class list with elements (XXX will be replaced with the model name you choose):

MCB_matrix	Prediction results of model.
auc_results	AUC results for each model.

**Author(s)**

Xin Yu

**References**

Xin Yu et al. 2019 Predicting disease progression in lung adenocarcinoma patients based on methylation correlated blocks using ensemble machine learning classifiers (under review)

**Examples**

```
#import datasets
data(demo_survival_data)
datamatrix<-create_demo()
data(demo_MCBinformation)
#select MCB with at least 3 CpGs.
demo_MCBinformation<-demo_MCBinformation[demo_MCBinformation[, "CpGs_num"]>2,]
trainingset<-colnames(datamatrix) %in% sample(colnames(datamatrix),0.6*length(colnames(datamatrix)))
testingset<-!trainingset
#create the results using Cox regression.
mcb_cox_res<-metricMCB.cv(MCBset = demo_MCBinformation,
                          data_set = datamatrix,
                          Surv = demo_survival_data,
                          Method = "cox")
```

---

```
pre_process_methylation
```

*Preprocess the Beta value matrix*

---

### Description

This process is optional for the pipeline. This function pre-process the Beta matrix and transform the Beta value into M value.

### Usage

```
pre_process_methylation(met, Mvalue, constant_offset, remove_na, remove_percentage)
```

### Arguments

`met`                    methylation matrix for CpGs. Rows are the CpG names, columns are samples.

`Mvalue`                Boolean value, TRUE for the M transformation.

`constant_offset`        the constant offset used in the M transformation formula.

`remove_na`            Boolean value, if TRUE ,CpGs with NA values will be removed.

`remove_percentage`     If percentage of NA value exceed the threshold(percentage), the whole CpG probe will be removed. Otherwise, the NA values are replaced with rowmeans.

### Value

Object of class `matrix`.

### Examples

```
demo_set<-create_demo()
pre_process_methylation(demo_set, Mvalue=FALSE)
```

---

```
univ_coxph
```

*Batch test for variables using coxph*

---

### Description

Batch test for variables using coxph

### Usage

```
univ_coxph(dataframe, y_surv, digits = 4, asnumeric = TRUE)
```

**Arguments**

<code>dataframe</code>	Clinic data and covariates ready to be tested. Rows are variables and columns are samples.
<code>y_surv</code>	Survival function contain survival data, usually are obtained form <code>Surv()</code> function in survival package.
<code>digits</code>	Integer indicating the number of decimal places.
<code>asnumeric</code>	indicator that the data will be (True) / not (False) transformed into numeric. Default is true.

**Value**

Object of class `matrix` with results.

**Author(s)**

Xin Yu

**Examples**

```
data(demo_survival_data)
data('demo_data', package = "EnMCB")
demo_set<-demo_data$realdata
res<-univ_coxph(demo_set,demo_survival_data)
```

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