Package ‘BEclear’

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Title Correction of batch effects in DNA methylation data
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Description Provides functions to detect and correct for batch effects in DNA methylation data. The core function is based on latent factor models and can also be used to predict missing values in any other matrix containing real numbers.

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Correction of batch effects in DNA methylation data

Description

Provides some functions to detect and correct for batch effects in DNA methylation data. The core function `correctBatchEffect` is based on Latent Factor Models and can also be used to predict missing values in any other matrix containing real numbers.
Details

BEclear-package

**correctBatchEffect**: The function combines most functions of the **BEclear-package** to one. This function performs the whole process of searching for batch effects and automatically correct them for a matrix of beta values stemming from DNA methylation data.

**correctBatchEffect**: This function predicts the missing entries of an input matrix (NA values) through the use of a Latent Factor Model.

**calcBatchEffects**: Compares the median value of all beta values belonging to one batch with the median value of all beta values belonging to all other batches. Returns a matrix containing this median difference value for every gene in every batch, columns define the batch numbers, rows the gene names.

And compares the distribution of all beta values corresponding to one batch with the distribution of all beta values corresponding to all other batches and returns a p-value which defines if the distributions are the same or not.

**calcSummary**: Summarizes the results of the **calcBatchEffects** function

**calcScore**: Returns a table with the number of found genes with found p-values less or equal to 0.01 and median values greater or equal to 0.05. A score is calculated depending on the number of found genes as well as the magnitude of the median difference values, this score is divided by the overall number of genes in the data and returned as "BEscore". See the methods details for further information and details about the score calculation.

**makeBoxplot**: A simple boxplot is done with boxes either separated by batches or by samples and describe the five number summary of all beta values corresponding to a batch or a sample, respectively. The batch_ids are shown on the x-axis with a coloring corresponding to the BEscore.

**clearBEgenes**: A function that simply sets all values to NA which were previously found by median value comparison and p-value calculation and are stored in a summary. The summary defines which values in the data matrix are set to NA.

**countValuesToPredict**: Simple function that counts all values in a matrix which are NA

**findOutsideValues**: A method which lists values below 0 or beyond 1 contained in the input matrix. These entries are stored in a data.frame together with the corresponding row and column position of the matrix.

**replaceOutsideValues**: A method which replaces values below 0 or beyond 1 contained in the input matrix. These entries outside the boundaries are replaced by 0 or 1, respectively.

Author(s)

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References


See Also

Useful links:

- [https://github.com/uds-helms/BEclear](https://github.com/uds-helms/BEclear)
- Report bugs at [https://github.com/uds-helms/BEclear/issues](https://github.com/uds-helms/BEclear/issues)
Examples

```r
data(BEclearData)
## Calculate the batch effects
batchEffects <- calcBatchEffects(data = ex.data, samples = ex.samples,
                                  adjusted = TRUE, method = "fdr")
med <- batchEffects$med
pvals <- batchEffects$pval

## Summarize p-values and median differences for batch affected genes
sum <- calcSummary(medians = med, pvalues = pvals)

## Calculates the score table
score.table <- calcScore(data = ex.data, samples = ex.samples, summary = sum)

## Simple boxplot for the example data separated by batch
makeBoxplot(
  data = ex.data, samples = ex.samples, score = score.table,
  bySamples = FALSE, main = "Some box plot"
)

## Simple boxplot for the example data separated by samples
makeBoxplot(
  data = ex.data, samples = ex.samples, score = score.table,
  bySamples = TRUE, main = "Some box plot"
)

## Sets assumed batch affected entries to NA
cleared <- clearBEgenes(data = ex.data, samples = ex.samples, summary = sum)
## Counts and stores number of entries to predict
numberOfEntries <- countValuesToPredict(data = cleared)
## Not run:
## Predicts the missing entries
predicted <- imputeMissingData(data = cleared)

## Find predicted entries outside the boundaries
outsideEntries <- findOutsideValues(data = predicted)

## Replace predicted entries outside the boundaries
corrected <- replaceOutsideValues(data = predicted)

## End(Not run)
```

BEclear example methylation data

Example data set for the BEclear-package

Description

Example data set for the BEclear-package
**Usage**

data(BEclearData)

**Format**

An example data frame containing a column for the sample id and a column for the corresponding batch id, stemming from breast cancer data from the TCGA portal [1].

**References**

calcBatchEffects  

*Calculate the Batch Effects in a given data set*

**Description**

Calculates for each gene in every batch the median distance to the other batches and the p-value resulting from the Kolmogorov-Smirnov test.

**Usage**

```r
calcBatchEffects(data, samples, adjusted=TRUE, method="fdr", BPPARAM=SerialParam())
```

**Arguments**

- **data**: a data.table with one column indicating the sample, one the features and a value column indicating the beta value or a matrix with rows as features and columns as samples.
- **samples**: data frame with two columns, the first column has to contain the sample numbers, the second column has to contain the corresponding batch number. Column names have to be named as "sample_id" and "batch_id".
- **adjusted**: should the p-values be adjusted or not, see "method" for available adjustment methods.
- **method**: adjustment method for p-value adjustment (if TRUE), default method is "false discovery rate adjustment", for other available methods see the description of the used standard R package p.adjust.
- **BPPARAM**: An instance of the BiocParallelParam-class that determines how to parallelisation of the functions will be evaluated.

**Details**

`calcBatchEffects`

1. **medians**: Compares the median value of all beta values belonging to one batch with the median value of all beta values belonging to all other batches. Returns a matrix containing this median difference value for every gene in every batch, columns define the batch numbers, rows the gene names.
2. **p-values**: Compares the distribution of all beta values corresponding to one batch with the distribution of all beta values corresponding to all other batches and returns a p-value which defines if the distributions are the same or not. Standard two sided Kolmogorov-Smirnov test is used to calculate the (adjusted) p-values.

**Value**

a matrix containing medians and p-values for all genes in all batches
See Also

ks.test
p.adjust
correctBatchEffect

Examples

## Shortly running example. For a more realistic example that takes
## some more time, run the same procedure with the full BEclearData
## dataset.

## Calculate fdr-adjusted p-values in non-parallel mode
data(BEclearData)
ex.data <- ex.data[31:90, 7:26]
ex.samples <- ex.samples[7:26, ]

res <- calcBatchEffects(data = ex.data, samples = ex.samples, method = "fdr")

## How to handle data-sets without defined batches
## https://github.com/Livia-Rasp/BEclear/issues/22
library(data.table)
data(BEclearData)

DT <- data.table(ex.samples)[, .(sample_id)]

## set the batch_id equal to the sample_id
## this way samples are treated as batches
DT[, batch_id := sample_id]

res <- calcBatchEffects(data = ex.data, samples = DT)

Description

function to calculate batch effects for every gene in a batch

Usage

calcBatchEffectsForBatch(batch, samples, data, BPPARAM = SerialParam())

Value

the medians p-values for genes in a batch
calcBlockFrame

**Description**

Calculates every start and stop position for every block.

**Usage**

```r
calcBlockFrame(rowPositions, colPositions, rowBlockSize, colBlockSize)
```

**Value**

A data.frame containing the start and stop positions for each block.

calcPositions

**Description**

calcPositions

**Usage**

```r
calcPositions(num, blockSize)
```

**Value**

Returns a vector with the number of blocks, start - and stop position of last 2 blocks.

calcScore

**calculate batch effect score**

**Description**

Returns a table with the number of found genes with found p-values less or equal to 0.01 and median values greater or equal to 0.05. A score is calculated depending on the number of found genes as well as the magnitude of the median difference values, this score is divided by the overall number of genes in the data and returned as "BEscore". See details for further information and details about the score calculation. The returned data.frame is also stored in the specified directory as .RData file.

**Usage**

```r
calcScore(data, samples, summary, saveAsFile=FALSE, dir=getwd())
```
### Arguments

- **data**
  any matrix filled with beta values, column names have to be sample_ids corresponding to the ids listed in "samples", row names have to be gene names.

- **samples**
  data frame with two columns, the first column has to contain the sample numbers, the second column has to contain the corresponding batch number. Column names have to be named as "sample_id" and "batch_id".

- **summary**
  a summary data.table containing the columns "gene", "batch", median" and "p-value" and consists of all genes which were found in the median and p-value calculations, see calcSummary function for more details.

- **saveAsFile**
  determining if the data.frame should also be saved as a file

- **dir**
  set the path to a directory the returned data.frame should be stored. The current working directory is defined as default parameter.

### Details

**calcScore**

The returned data frame contains one column for the batch numbers, 11 columns containing the number of genes found in a certain range of the median difference value and a column with the calculated BEscore. These found genes are assumed to be batch affected due to their difference in median values and their different distribution of the beta values. The higher the found number of genes and the more extreme the median difference is, the more severe is the assumed batch effect supposed to be. We suggest that there is no need for a batch effect correction if the BEscore for a batch is less than 0.02. BEscores between 0.02 and 0.1 are lying in a "gray area" for which we assume a not severe batch effect, and values beyond 0.1 certainly describe a batch effect and should definitely be corrected.

The 11 columns containing the numbers of found genes count the median difference values which are ranging from >= 0.05 to < 0.1 ; >= 0.1 to < 0.2; >= 0.2 to < 0.3 and so on up to a limit of 1.

The BEscore is calculated by the sum of the weighted number of genes divided by the number of genes. Weightings are calculated by multiplication of the number of found genes between 0.05 and 0.1 by 1, between 0.1 and 0.2 by 2, between 0.2 and 0.3 by 4, between 0.3 and 0.4 by 6 and so on.

### Value

A data.frame is returned containing the number of found genes assumed to be batch affected separated by batch and a BEscore for every batch. Furthermore there’s a column dixonPval giving you a p-value regarding each BEscore according to a Dixon test. The data.frame is also stored in the specified directory as .RData file, if saveAsFile is TRUE.

### References


See Also

calcBatchEffects
calcSummary
correctBatchEffect

Examples

```r
## Shortly running example. For a more realistic example that takes
## some more time, run the same procedure with the full BEclearData
## dataset.

## Whole procedure that has to be done to use this function.
data(BEclearData)
ex.data <- ex.data[31:90, 7:26]
ex.samples <- ex.samples[7:26, ]
## Calculate the batch effects
batchEffects <- calcBatchEffects(data = ex.data, samples = ex.samples,
adjusted = TRUE, method = "fdr")
med <- batchEffects$med
pvals <- batchEffects$pval

# Summarize p-values and median differences for batch affected genes
sum <- calcSummary(medians = med, pvalues = pvals)

# Calculates the score table
score.table <- calcScore(data = ex.data, samples = ex.samples, summary = sum)
```

calcSummary Summarize median comparison and p-value calculation results

Description

Summarizes the results of the `calcBatchEffects` function

Usage

calcSummary(medians, pvalues, mediansTreshold, pvaluesTreshold)
calcSummary

Arguments

medians a matrix containing median difference values calculated by the calcBatchEffects function. For further details look at the documentation of this function.

pvalues a matrix containing p-values calculated by the calcBatchEffects function. For further details look at the documentation of this function.

mediansThreshold the threshold above or equal median values are regarded as batch effected, when the criteria for p-values is also met.

pvaluesThreshold the threshold below or equal p-values are regarded as batch effected, when the criteria for medians is also met.

Details

calcSummary
All genes with a median comparison value >= 0.05 and a p-value of <= 0.01 are summarized into a data.frame. These genes are assumed to contain a batch effect

Value

Null if there are no batch effects detected, else a data.table with the columns "gene" containing the gene name, "batch" containing the batch number from which the gene was found, "median" and "p-value" containing the calculated median difference values and the p-values, respectively.

See Also

calcBatchEffects
correctBatchEffect

Examples

## Shortly running example. For a more realistic example that takes
## some more time, run the same procedure with the full BEclearData
## dataset.

## Whole procedure that has to be done to use this function.
data(BEclearData)
ex.data <- ex.data[31:90, 7:26]
ex.samples <- ex.samples[7:26,]

## Calculate the batch effects
batchEffects <- calcBatchEffects(data = ex.data, samples = ex.samples,
adjusted = TRUE, method = "fdr")
med <- batchEffects$med
pvals <- batchEffects$pval

## Summarize p-values and median differences for batch affected genes
sum <- calcSummary(medians = med, pvalues = pvals)
clearBEgenes

Prepare a data matrix for the BEclear function

Description

A function that simply sets all values to NA which were previously found by median value comparison and p-value calculation and are stored in a summary. The summary defines which values in the data matrix are set to NA.

Usage

clearBEgenes(data, samples, summary)

Arguments

data any matrix filled with beta values, column names have to be sample_ids corresponding to the ids listed in "samples", row names have to be gene names.
samples data frame with two columns, the first column has to contain the sample numbers, the second column has to contain the corresponding batch number. Colnames have to be named as "sample_id" and "batch_id".
summary a summary data.frame containing the columns "gene", "batch", "median" and "p-value" and consists of all genes which were found in the median and p-value calculations, see calcSummary function for more details.

Details

clearBEgenes

All entries belonging to genes stated in the summary are set to NA for the corresponding batches in the data matrix. Please look at the descriptions of calcBatchEffects for more detailed information about the data which should be contained in the summary data.frame.

Value

A data matrix with the same dimensions as well as the same column and row names as the input data matrix is returned, all entries which are defined in the summary are now set to NA.

See Also

calcBatchEffects
calcSummary
correctBatchEffect
Examples

## Shortly running example. For a more realistic example that takes
## some more time, run the same procedure with the full BEclearData
## dataset.

## Whole procedure that has to be done to use this function.
data(BEclearData)
ex.data <- ex.data[31:90, 7:26]
ex.samples <- ex.samples[7:26, ]

## Calculate the batch effects
batchEffects <- calcBatchEffects(data = ex.data, samples = ex.samples,
adjusted = TRUE, method = "fdr")
mads <- batchEffects$med
pvals <- batchEffects$pval

## Summarize p-values and median differences for batch affected genes
sum <- calcSummary(medians = mads, pvalues = pvals)

## Set values for summarized BEgenes to NA
clearedMatrix <- clearBEgenes(data = ex.data, samples = ex.samples, summary = sum)

combineBlocks

Description

load and combine blocks

Usage

combineBlocks(blockFrame, rowPos, colPos, dir)

Value

the combined matrix consisting of the individual blocks

correctBatchEffect

Correct a batch effect in DNA methylation data

Description

This method combines most functions of the BEclear-package to one. The method performs the
whole process of searching for batch effects and automatically correct them for a matrix of beta
values stemming from DNA methylation data.
correctBatchEffect

Usage

correctBatchEffect(data, samples, adjusted=TRUE, method="fdr",
mediansTreshold = 0.05, pvaluesTreshold = 0.01, rowBlockSize=60,
colBlockSize=60, epochs=50, lambda = 1, gamma = 0.01, r = 10,
outputFormat="", dir=getwd(), BPPARAM=SerialParam())

Arguments

data any matrix filled with beta values, column names have to be sample_ids corresponding to the ids listed in "samples", row names have to be gene names.
samples data frame with two columns, the first column has to contain the sample numbers, the second column has to contain the corresponding batch number. Column names have to be named as "sample_id" and "batch_id".
adjusted should the p-values be adjusted or not, see "method" for available adjustment methods.
method adjustment method for p-value adjustment, default method is "false discovery rate adjustment", for other available methods see the description of the used standard R package p.adjust. See calcBatchEffects for more information.
mediansTreshold the threshold above or equal median values are regarded as batch effected, when the criteria for p-values is also met.
pvaluesTreshold the threshold below or equal p-values are regarded as batch effected, when the criteria for medians is also met.
rowBlockSize the number of rows that is used in a block if the function is run in parallel mode and/or not on the whole matrix. Set this, and the "colBlockSize" parameter to 0 if you want to run the function on the whole input matrix. See imputeMissingData and especially the details section of See imputeMissingData for more information about this feature.
colBlockSize the number of columns that is used in a block if the function is run in parallel mode and/or not on the whole matrix. Set this, and the "rowBlockSize" parameter to 0 if you want to run the function on the whole input matrix. See imputeMissingData and especially the details section of See imputeMissingData for more information about this feature.
epochs the number of iterations used in the gradient descent algorithm to predict the missing entries in the data matrix. See imputeMissingData for more information.
lambda constant that controls the extent of regularization during the gradient descent
gamma constant that controls the extent of the shift of parameters during the gradient descent
r length of the second dimension of variable matrices R and L
outputFormat you can choose if the finally returned data matrix should be saved as an .RData file or as a tab-delimited .txt file in the specified directory. Allowed values are "RData" and "txt". See imputeMissingData for more information.
**correctBatchEffect**

*dir* set the path to a directory the predicted matrix should be stored. The current working directory is defined as default parameter.

**BPPARAM** An instance of the `BiocParallelParam-class` that determines how to parallelisation of the functions will be evaluated.

**Details**

**correctBatchEffect**

The function performs the whole process of searching for batch effects and automatically correct them for a matrix of beta values stemming from DNA methylation data. Thereby, the function is running most of the functions from the `BEclear-package` in a logical order.

First, median comparison values are calculated by the `calcBatchEffects` function, followed by the calculation of p-values also by the `calcBatchEffects` function. With the results from the median comparison and p-value calculation, a summary data frame is build using the `calcSummary` function, and a scoring table is established by the `calcScore` function. Now, found entries from the summary are set to NA in the input matrix using the `clearBEgenes` function, then the `imputeMissingData` function is used to predict the missing values and at the end, predicted entries outside the boundaries (values lower than 0 or greater than 1) are corrected using the `replaceOutsideValues` function.

**Value**

A list containing the following fields (for detailed information look at the documentations of the corresponding functions):

- **medians** A `data.frame` containing all median comparison values corresponding to the input matrix.
- **pvalues** A `data.frame` containing all p-values corresponding to the input matrix.
- **summary** The summarized results of the median comparison and p-value calculation.
- **score.table** A `data.frame` containing the number of found genes and a BEscore for every batch.
- **cleared.data** the input matrix with all values defined in the summary set to NA.
- **predicted.data** the input matrix after all previously NA values have been predicted.
- **corrected.predicted.data** the predicted matrix after the correction for predicted values outside the boundaries.

**References**


See Also

calcBatchEffects
calcSummary
calcScore
clearBEgenes
imputeMissingData
replaceOutsideValues

Examples

## Shortly running example. For a more realistic example that takes
## some more time, run the same procedure with the full BEclearData
## dataset.

## Whole procedure that has to be done to use this function.
## Correct the example data for a batch effect
data(BEclearData)
ex.data <- ex.data[31:90, 7:26]
ex.samples <- ex.samples[7:26, ]

# Note that row- and block sizes are just set to 10 to get a short runtime.
# To use these parameters, either use the default values or please note the
# description in the details section of \code{\link{imputeMissingData}}
result <- correctBatchEffect(
  data = ex.data, samples = ex.samples,
  adjusted = TRUE, method = "fdr", rowBlockSize = 10, colBlockSize = 10,
  epochs = 50, outputFormat = "RData", dir = getwd()
)

# Unlist variables
medians <- result$medians
pvals <- result$pvals
summary <- result$summary
score <- result$score.table
cleared <- result$clearedData
predicted <- result$predictedData
corrected <- result$correctedPredictedData

countValuesToPredict  Count NA entries in a matrix

Description

Simple function that counts all values in a matrix which are NA

Usage

countValuesToPredict(data)
countValuesToPredict

Arguments

data any kind of matrix

Details

countValuesToPredict

Value

Returns a data frame with the number of NA entries per column. Since the function is mainly written for the usage in batch effect correction of DNA methylation data, the column names of the data frame are set to "sample" and "num_pred_values". Nevertheless, the function can be used with any other matrix containing anything but beta values.

See Also

clearBEgenes
correctBatchEffect
correctBatchEffect

Examples

## Shortly running example. For a more realistic example that takes ## some more time, run the same procedure with the full BEclearData ## dataset

## Whole procedure that has to be done to use this function.
data(BEclearData)
ex.data <- ex.data[31:90, 7:26]
ex.samples <- ex.samples[7:26, ]

## Calculate the batch effects
batchEffects <- calcBatchEffects(data = ex.data, samples = ex.samples, adjusted = TRUE, method = "fdr")
meds <- batchEffects$med
pvals <- batchEffects$pval

## Summarize p-values and median differences for batch affected genes
sum <- calcSummary(medians = meds, pvalues = pvals)
clearedMatrix <- clearBEgenes(data = ex.data, samples = ex.samples, summary = sum)
numberOfEntries <- countValuesToPredict(data = clearedMatrix)
findOutsideValues

---

**ex.corrected.data**  
Example matrix of corrected data for the BEclear-package

---

**Description**

Example matrix containing a already batch effect corrected sample matrix of beta values from breast invasive carcinoma TCGA methylation data.[1] The matrix contains a small amount of predicted beta values outside of the boundaries to show the operating principles of some of the methods from the BEclear package.

**Usage**

data(BEclearCorrected)

**Format**

A matrix containing already corrected beta values of some samples from the breast invasive carcinoma TCGA methylation data. The colnames denote samples, rownames denote gene names.

**References**


---

**findOutsideValues**  
Find DNA methylation values out of the boundaries

---

**Description**

A method which lists values below 0 or beyond 1 contained in the input matrix. These entries are stored in a data.frame together with the corresponding row and column position of the matrix. Note that this method is especially designed for DNA methylation data.

**Usage**

findOutsideValues(data)

**Arguments**

data  
any matrix filled with values that normally should be bounded between 0 and 1.
Details

findOutsideValues

Note that this method is especially designed to run after the batch effect correction of DNA methylation data, e.g. with the correctBatchEffect method. It can happen, that the predicted values are lying slightly below the lower bound of 0 or beyond the upper bound of 1. This method finds these inaccurately predicted entries. Another method called replaceOutsideValues replaces these values either by 0 or 1, respectively.

Value

A data frame containing the columns "level", "row", "col" and "value" defining if the value is below 0 or beyond 1 (level = 0 or level = 1), the row position and the column position in the input matrix and the value itself, respectively.

See Also

replaceOutsideValues

correctBatchEffect

Examples

data(BEclearCorrected)
# Find predicted values outside of the boundaries
outsideEntries <- findOutsideValues(data = ex.corrected.data)
**Description**

This function predicts the missing entries of an input matrix (NA values) through the use of a Latent Factor Model. You can run the function also in parallel mode and split up the matrix to a certain number of smaller matrices to speed up the prediction process. If you set the `rowBlockSize` and `colBlockSize` both to 0, the function is running on the whole matrix. Take a look at the details section for some deeper information about this. The default parameters are chosen with the intention to make an accurate prediction within an affordable time interval.

**Usage**

```r
imputeMissingData(data, rowBlockSize=60, colBlockSize=60, epochs=50, lambda = 1, gamma = 0.01, r = 10, outputFormat="", dir = tempdir(), BPPARAM=SerialParam())
```

**Arguments**

data: any matrix filled e.g. with beta values. The missing entries you want to predict have to be set to NA.

rowBlockSize: the number of rows that is used in a block if the function is run in parallel mode and/or not on the whole matrix. Set this and the "colBlockSize" parameter to 0 if you want to run the function on the whole input matrix. We suggest to use a block size of 60 but you can also use any other block size, but the size has to be bigger than the number of samples in the biggest batch. Look at the details section for more information about this feature.

colBlockSize: the number of columns that is used in a block if the function is run in parallel mode and/or not on the whole matrix. Set this, and the "rowBlockSize" parameter to 0 if you want to run the function on the whole input matrix. We suggest to use a block size of 60 but you can also use any other block size, but the size has to be bigger than the number of samples in the biggest batch. Look at the details section for more information about this feature.

epochs: the number of iterations used in the gradient descent algorithm to predict the missing entries in the data matrix.

lambda: constant that controls the extent of regularization during the gradient descent.

gamma: constant that controls the extent of the shift of parameters during the gradient descent.

r: length of the second dimension of variable matrices R and L.

outputFormat: you can choose if the finally returned data matrix should be saved as an .RData file or as a tab-delimited .txt file in the specified directory. Allowed values are "RData" and "txt".

dir: set the path to a directory the predicted matrix should be stored. The current working directory is defined as default parameter.
Details

imputeMissingData

The method used to predict the missing entries in the matrix is called "latent factor model". In the following sections, the method itself is described as well as the correct usage of the parameters. The parameters are described in the same order as they appear in the usage section.

The method originally stems from recommender systems where the goal is to predict user ratings of products. It is based on matrix factorization and uses a discrete gradient descent (GDE) algorithm that stepwise predicts two matrices L and R with matching dimensions to the input matrix. These two matrices are initialized with random numbers and stepwise adjusted towards the values of the input matrix through the GDE algorithm. After every adjustment step, the global loss is calculated and the parameters used for the adjustment are possibly also adjusted so that the global loss is getting minimized and the prediction is getting accurate. After a predefined number of steps (called epochs) are executed by the GDE algorithm, the predicted matrix is calculated by matrix multiplication of L and R. Finally, all missing values in the input matrix are replaced with the values from the predicted matrix and the already known values from the input matrix are maintained. The completed input matrix is then returned at the end.

Description of the parameters:

• data: simply the input matrix with missing values set to NA

• rowBlockSize and colBlockSize: Here you can define the dimensions of the smaller matrices, the input matrix is divided into if the function is working in parallel mode. For details about these so called blocks, see the section "About the blocks" below.

• epochs: Defines the number of steps the gradient descent algorithm performs until the prediction ends. Note that the higher this number is, the more precisely is the prediction and the more time is needed to perform the prediction. If the step size is too small, the prediction would not be very good. We suggest to use a step size of 50 since we did not get better predictions if we took higher step sizes during our testing process.

About the blocks: You have the possibility to change the size of the blocks in which the input matrix can be divided. If you choose e.g. the rowBlockSize = 50 and the colBlockSize = 60 your matrix will be cut into smaller matrices of the size approximately 50x60. Note that this splitting algorithm works with every possible matrix size! If both size parameters do not fit to the dimensions of the input matrix, the remaining rows and columns of the input matrix are distributed over some blocks, so that the block sizes are roughly of the same size. All blocks are saved at the specified directory after the processing of a block has been done within an RData file. These RData files are continuously numbered and contain the row and column start and stop positions in their name. Next, these blocks are assembled into the returned matrix and this matrix is saved in the specified directory. Finally, single blocks are deleted. To see how this is done, simply run the example at the end of this documentation. We suggest to use the block size of 60 (default) but you can also use any other block size, as far as it is bigger than the number of samples in the biggest batch. This avoids having an entire row of NA values in a block which leads to a crash of the imputeMissingData method. In order to process the complete matrix without dividing into blocks, specify rowBlockSize = 0 and colBlockSize = 0. But if the input matrix is large (more than 200x200), it is not recommended due to exponential increase of computation time required.
Note that the size of the blocks affect the prediction accuracy. In case of very small blocks, the information obtained from neighbor entries is not sufficient. Thus, the larger the size of the block is, the more accurately those entries are predicted. Default size 60 is enough to have accurate prediction in a reasonable amount of time.

Value

Returns a data matrix with the same dimensions as well as same row and column names as the input matrix. According to the "outputFormat" parameter, either a .RData file containing only the returned matrix or a tab-delimited .txt file containing the content of the returned matrix is saved in the specified directory.

References


Examples

```r
##Shortly running example. For a more realistic example that takes
##some more time, run the same procedure with the full BEclearData
##dataset.

##Whole procedure that has to be done to use this function.
data(BEclearData)
ex.data <- ex.data[31:90, 7:26]
ex.samples <- ex.samples[7:26, ]

## Calculate the batch effects
batchEffects <- calcBatchEffects(data = ex.data, samples = ex.samples,
adjusted = TRUE, method = "fdr")
meds <- batchEffects$med
pvals <- batchEffects$pval

## Summarize p-values and median differences for batch affected genes
sum <- calcSummary(medians = meds, pvalues = pvals)

## Set entries defined by the summary to NA
clearedMatrix <- clearBEgenes(data = ex.data, samples = ex.samples, summary = sum)

# Predict the missing entries with standard values, row- and block sizes are
# just set to 10 to get a short runtime. To use these parameters, either use
# the default values or please note the description in the details section
# above
```
imputeMissingDataForBlock

predicted <- imputeMissingData(
  data = clearedMatrix, rowBlockSize = 10,
  colBlockSize = 10
)

---

**imputeMissingDataForBlock**

**Description**

imputeMissingDataForBlock

**Usage**

imputeMissingDataForBlock(block, dir, epochs, lambda = 1, gamma = 0.01, r = 10)

**Arguments**

fixedSeed
determines if they seed should be fixed, which is important for testing

**Value**

number of the block processed

---

**localLoss**

*Calculating the Local Loss*

**Description**

Calculates the gradient dR and dL for the current epoch.

**Usage**

localLoss(L, R, is, js, error_matrix)

**Value**

a list containing two matrices containing the local loss
Description

computation of the loss of factorization LR

Usage

loss(L, R, lambda, D)

Arguments

L a matrix describing the effects of the features
R a matrix describing the effects of the samples
lambda constant that controls the extent of regularization during the gradient descent
D a matrix containing the measured values

Value

a list containing the loss calculated and the error matrix

makeBoxplot produce simple predefined boxplot for methylation data

Description

A simple boxplot is done with boxes either separated by batches or by samples and describe the five number summary of all beta values corresponding to a batch or a sample, respectively. The batch_ids are shown on the x-axis with a coloring corresponding to the BEscore.

Usage

makeBoxplot(data, samples, score, bySamples=FALSE, col="standard", main="", xlab="Batch", ylab="Beta value", scoreCol=TRUE, log = FALSE)

Arguments

data any matrix filled with beta values, column names have to be sample_ids corresponding to the ids listed in "samples", row names have to be gene names.
samples data frame with two columns, the first column has to contain the sample numbers, the second column has to contain the corresponding batch number. Col-names have to be named as "sample_id" and "batch_id".
**makeBoxplot**

The color code for the batch_ids on the x-axis provides a simple "traffic light" the user can use to decide if he wants to correct for an assumed batch effect or not. Green means no batch effect, yellow a possibly existing not severe batch effect and red stands for an obviously existing batch effect that should be corrected. The traffic light colors are set according to the BEscore from the `calcScore` function, values from 0 to 0.02 are colored in green, from 0.02 to 0.1 in yellow and values over 0.1 are colored in red.

**Value**

Returns a boxplot on the graphic device with the features explained above.

**See Also**

- `calcScore`
- `boxplot`
- `correctBatchEffect`

**Examples**

```r
## Shortly running example. For a more realistic example that takes
## some more time, run the same procedure with the full BEclearData
## dataset.

## Whole procedure that has to be done to use this function.
data(BEclearData)
ex.data <- ex.data[31:90, 7:26]
ex.samples <- ex.samples[7:26, ]

## Prepare the data for the box plots
```
## Calculate the batch effects
batchEffects <- calcBatchEffects(data = ex.data, samples = ex.samples,
adjusted = TRUE, method = "fdr")
meds <- batchEffects$med
pvals <- batchEffects$pval

## Summarize p-values and median differences for batch affected genes
sum <- calcSummary(medians = meds, pvalues = pvals)

# Calculate the BEscore for the batch_id colorings of the x-axis
score <- calcScore(data = ex.data, samples = ex.samples, summary = sum)

## Simple boxplot for the example data separated by batch
makeBoxplot(
  data = ex.data, samples = ex.samples, score = score, bySamples = FALSE,
  main = "Some box plot"
)

## Simple boxplot for the example data separated by samples
makeBoxplot(
  data = ex.data, samples = ex.samples, score = score, bySamples = TRUE,
  main = "Some box plot"
)

---

**Description**

This method does some preprocessing steps for the later methods like removing rows containing only missing values.

**Usage**

```r
preprocessBEclear(data, samples)
```

**Arguments**

- `data`: any matrix filled with beta values, column names have to be sample_ids corresponding to the ids listed in "samples", row names have to be gene names.
- `samples`: data frame with two columns, the first column has to contain the sample numbers, the second column has to contain the corresponding batch number. Column names have to be named as "sample_id" and "batch_id".

**Details**

Here we describe the preprocessing steps in the order they are executed:

- Values below 0 or above 1 are set to NA, as the other methods expect methylation beta values
replaceOutsideValues

- columns that only contain NAs are removed
- rows that only contain NAs are removed
- samples that are present in the data, but are not annotated in the samples are removed. If this is the case with your data-set, please check those samples.
- samples that are annotated but not in the data matrix are removed
- if there are duplicate sample names in the data matrix, all sample names get replaced through a new unique ID. In this case a data.table containing the mapping is returned as well.

Value

a list containing the processed data and samples and a data.table containing mappings from the original sample names to the new ones. If sample names weren’t changed this third object is NULL.

Examples

data(BEclearData)
res <- preprocessBEclear(ex.data, ex.samples)

Details

A method which replaces values below 0 or beyond 1 contained in the input matrix. These wrong entries are replaced by 0 or 1, respectively. Note that this method is especially designed for DNA methylation data.

Usage

replaceOutsideValues(data)

Arguments

data any matrix filled with values that normally should be bounded between 0 and 1.

Note that this method is especially designed to run after the batch effect correction of DNA methylation data, e.g. with the imputeMissingData method. It can happen, that the predicted values are lying slightly below the lower bound of 0 or beyond the upper bound of 1. This method finds these inaccurately predicted entries. Another method called replaceOutsideValues replaces these values either by 0 or 1, respectively. Another method called findOutsideValues returns a list of existing wrong values and can be run before the replacement.
Value

Returns the input matrix with every value previously below 0 changed to 0 and every value previously beyond 1 changed to 1.

See Also

findOutsideValues
correctBatchEffect

Examples

data(BEclearCorrected)
# Replace wrongly predicted values
corrected <- replaceOutsideValues(data = ex.corrected.data)

runGradientDescent

Description

Runner for gradient descent (or stochastic gradient descent) for the specified number of epoch

Usage

runGradientDescent(L, R, lambda, epochs, gamma = 0.01, blockNr, is, js, D, r)

Value

a list containing two matrices generated by the gradient descent
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