Package: MEAT (via r-universe)

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Title Muscle Epigenetic Age Test

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Description This package estimates epigenetic age in skeletal muscle, using DNA methylation data generated with the Illumina Infinium technology (HM27, HM450 and HMEPIC).

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`BMIQcalibration` *Calibrate methylation data to a gold standard.*

Description

`BMIQcalibration` uses an adapted version of the BMIQ algorithm to calibrate the beta-matrix stored in the input SummarizedExperiment object `SE` to the gold standard dataset used in the muscle clock (GSE50498).

Usage

```
BMIQcalibration(SE, version = "MEAT2.0")
```

Arguments

`SE`	A `SummarizedExperiment-class` object. The "assays" component of `SE` should contain a beta-matrix of DNA methylation beta-values called "beta" that has been cleaned with `clean_beta`. `SE` may optionally contain annotation information on the CpGs stored in "rowData" and sample phenotypes stored in "colData".
`version`	A character specifying which version of the epigenetic clock you would like to use. Dy default, `version` is set to "MEAT2.0" for the second version of the epigenetic clock. If you would like to use the original version, set `version` to "MEAT".

Details

BMIQcalibration was created by Steve Horvath, largely based on the BMIQ function from Teschendorff (2013) to adjust for the type-2 bias in Illumina HM450 and HMEPIC arrays. BMIQ stands for beta mixture quantile normalization. Horvath fixed minor errors in the v_1.2 version of the BMIQ algorithm and changed the optimization algorithm to make the code more robust. He used method = "Nelder-Mead" in optim since the other optimization method sometimes gets stuck. Toward this end, the function blc was replaced by blc2. SE needs to be a SummarizedExperiment object containing a matrix of beta-values that has been cleaned using clean_beta. Each sample in SE is iteratively calibrated to the gold standard values, so the time it takes to run BMIQcalibration is directly proportional to the number of samples in SE. This step is essential to estimate epigenetic age with accuracy.

Value

A calibrated version of the input SE calibrated to the gold standard dataset GSE50498.

See Also

clean_beta to get the DNA methylation matrix ready for calibration, BMIQ for the original BMIQ algorithm and https://genomebiology.biomedcentral.com/articles/10.1186/gb-2013-14-10-r115 for the original paper describing Horvath's adapted BMIQ algorithm, and SummarizedExperiment-class for more details on how to create and manipulate SummarizedExperiment objects.

Examples

```
# Load matrix of beta-values of two individuals from dataset GSE121961
data("GSE121961", envir = environment())
# Load phenotypes of the two individuals from dataset GSE121961
data("GSE121961_pheno", envir = environment())

# Create a SummarizedExperiment object to coordinate phenotypes and
# methylation into one object.
library(SummarizedExperiment)
GSE121961_SE <- SummarizedExperiment(assays=list(beta=GSE121961),
colData=GSE121961_pheno)

# Run clean_beta() to clean the beta-matrix
GSE121961_SE_clean <- clean_beta(SE = GSE121961_SE, version = "MEAT2.0")

# Run BMIQcalibration() to calibrate the clean beta-matrix
GSE121961_SE_calibrated <- BMIQcalibration(SE = GSE121961_SE_clean, version = "MEAT2.0")
```

---

clean_beta *Clean beta-matrix.*

Description

clean_beta reduces the beta-matrix stored in the input SummarizedExperiment object SE to the right CpGs, imputes missing values if any, and replaces 0 and 1 with min and max values.

Usage

```
clean_beta(SE = NULL, version = "MEAT2.0")
```

Arguments

SE	A SummarizedExperiment-class object. The "assays" component of SE should contain a beta-matrix of DNA methylation beta-values called "beta", with samples in columns and CpGs in rows. SE may optionally contain annotation information on the CpGs stored in "rowData" and sample phenotypes stored in "colData".
version	A character specifying which version of the epigenetic clock you would like to use. Dy default, version is set to "MEAT2.0" for the second version of the epigenetic clock. If you would like to use the original version, set version to "MEAT".

Details

clean_beta will transform the the beta-matrix stored in SE by:

1. reducing it to the CpGs used to calibrate DNA methylation profiles to the gold standard. By default, clean_beta will reduce your beta-matrix to the 18,747 CpGs used in the updated version of MEAT (MEAT 2.0). If you would like to use the original version of MEAT, clean_beta will reduce your data to the 19,401 CpGs that are in common between the 12 datasets from the original publication.
2. checking whether it contains missing values, and impute them with impute.knn,
3. check whether it contains 0 and 1 values, and if any, change them to the minimum non-0 and maximum non-1 values in the beta-matrix.

Value

A clean version of the input SE reduced to the right CpGs, with missing values imputed, and without 0 or 1 values.

See Also

impute.knn for imputation of missing values, and SummarizedExperiment-class for more details on how to create and manipulate SummarizedExperiment objects.

Examples

```
# Load matrix of beta-values of two individuals from dataset GSE121961
data("GSE121961", envir = environment())
# Load phenotypes of the two individuals from dataset GSE121961
data("GSE121961_pheno", envir = environment())
```

```
# Create a SummarizedExperiment object to coordinate phenotypes and
# methylation into one object.
library(SummarizedExperiment)
GSE121961_SE <- SummarizedExperiment(assays=list(beta=GSE121961),
colData=GSE121961_pheno)

# Run clean_beta() to clean the beta-matrix
GSE121961_SE_clean <- clean_beta(SE = GSE121961_SE, version = "MEAT2.0")
```

`CpGs_in_MEAT` *Description of the CpGs used in MEAT*

Description

Detailed information on the 200 CpGs automatically selected by the elastic net model.

Usage

```
CpGs_in_MEAT
```

Format

A data frame with 201 rows and 6 variables:

CpG CpG name

Coefficient Weight given by the elastic net model to the CpG

Chromosome Chromosome where the CpG is located

Position Position in bp where the CpG is located (human genome build version hg38)

Gene Gene annotated to the CpG. Each CpG was annotated to one or more genes using the annotation file from Zhou et al. to which we added annotation to long-range interaction promoters using chromatin states in male skeletal muscle from the Roadmap Epigenomics Project and GeneHancer information from the Genome Browser (hg38).

Chromatin_state_male_SM Chromatin state in male skeletal muscle from the the Roadmap Epigenomics Project)

Source

https://onlinelibrary.wiley.com/doi/full/10.1002/jcsm.12556

CpGs_in_MEAT2.0 *Description of the CpGs used in MEAT2.0*

Description

Detailed information on the 156 CpGs automatically selected by the elastic net model.

Usage

```
CpGs_in_MEAT2.0
```

Format

A data frame with 157 rows and 6 variables:

CpG CpG name

Coefficient Weight given by the elastic net model to the CpG

Chromosome Chromosome where the CpG is located

Position Position in bp where the CpG is located (human genome build version hg38)

Gene Gene annotated to the CpG. Each CpG was annotated to one or more genes using the annotation file from Zhou et al. to which we added annotation to long-range interaction promoters using chromatin states in male skeletal muscle from the Roadmap Epigenomics Project and GeneHancer information from the Genome Browser (hg38).

Chromatin_state_male_SM Chromatin state in male skeletal muscle from the the Roadmap Epigenomics Project)

Chromatin_state_female_SM Chromatin state in female skeletal muscle from the the Roadmap Epigenomics Project)

Source

https://onlinelibrary.wiley.com/doi/full/10.1002/jcsm.12741

elasticnet_model_MEAT *Elastic net model used in the original muscle clock (MEAT).*

Description

An object with S3 class "glmnet","elnet" generated by training 682 skeletal muscle DNA methylation profiles on a tranformed version of age. This elastic net model can take in any skeletal muscle DNA methylation profile that has been cleaned and calibrated to the GSE50498 gold standard dataset, to estimate epigenetic age in the sample.

Usage

```
elasticnet_model_MEAT
```

Format

An elastic net model

See Also

glmnet

`elasticnet_model_MEAT2.0` *Elastic net model used in the updated muscle clock (MEAT 2.0).*

Description

An object with S3 class "glmnet","elnet" generated by training 1,053 skeletal muscle DNA methylation profiles on a tranformed version of age. This elastic net model can take in any skeletal muscle DNA methylation profile that has been cleaned and calibrated to the GSE50498 gold standard dataset, to estimate epigenetic age in the sample.

Usage

```
elasticnet_model_MEAT2.0
```

Format

An elastic net model

See Also

glmnet

`epiage_estimation` *Estimates age in skeletal muscle from calibrated DNA methylation profiles.*

Description

`epiage_estimation` takes as input a `SummarizedExperiment-class` object whose assays contain a beta-matrix called "beta". This beta-matrix should contain DNA methylation profiles in skeletal muscle that have been cleaned with `clean_beta` and calibrated with `BMIQcalibration`. `epiage_estimation` will use the muscle clock to estimate epigenetic age in each sample.

Usage

```
epiage_estimation(SE = NULL, version = "MEAT2.0", age_col_name = NULL)
```

Arguments

SE	A SummarizedExperiment-class object. The "assays" component of SE should contain a beta-matrix of DNA methylation beta-values called "beta" that has been cleaned with clean_beta and calibrated with BMIQcalibration. SE may optionally contain annotation information on the CpGs stored in "rowData" and sample phenotypes stored in "colData".
version	A character specifying which version of the epigenetic clock you would like to use. Dy default, version is set to "MEAT2.0" for the second version of the epigenetic clock. If you would like to use the original version, set version to "MEAT".
age_col_name	The name of the column in colData from SE that contains age (in years).

Details

epiage_estimation estimates epigenetic age for each sample in the input SE based on DNA methylation profiles. SE needs to be a SummarizedExperiment-class object containing a matrix of beta-values called "beta" in assays. Beta must have been calibrated to the gold standard GSE50498 using BMIQcalibration to obtain good estimates of epigenetic age.

Value

A SummarizedExperiment-class object identical to the input SE, with components added to colData. If no phenotypes were provided in the colData of the input SE, epiage_estimation will put in colData a tibble containing a single column called "DNAmage", corresponding to epigenetic age (in years) for each sample. If phenotypes were provided in the colData of the input SE, epiage_estimation will add to the existing colData three columns:

1. DNAmage epigenetic age (in years)
2. AAdiff the difference between predicted and actual age (in years).
3. AAresid the residuals of a linear model (using lm) of DNAmage against actual age. AAresid is only returned if the number of samples is > 2, as AAresid cannot be calculated with < 2 samples.

See Also

BMIQ for the original BMIQ algorithm, https://genomebiology.biomedcentral.com/articles/10.1186/gb-2013-14-10-r115 for the adapted version of the BMIQ algorithm, and https://onlinelibrary.wiley.com/doi/full/10.1002/jcsm.12556 for the elastic net model of the muscle clock.

Examples

```
# Load matrix of beta-values of two individuals from dataset GSE121961
data("GSE121961", envir = environment())
# Load phenotypes of the two individuals from dataset GSE121961
data("GSE121961_pheno", envir = environment())

# Create a SummarizedExperiment object to coordinate phenotypes and
# methylation into one object.
```

```
library(SummarizedExperiment)
GSE121961_SE <- SummarizedExperiment(assays=list(beta=GSE121961),
colData=GSE121961_pheno)

# Run clean_beta() to clean the beta-matrix
GSE121961_SE_clean <- clean_beta(SE = GSE121961_SE,
version = "MEAT2.0")

# Run BMIQcalibration() to calibrate the clean beta-matrix
GSE121961_SE_calibrated <- BMIQcalibration(SE = GSE121961_SE_clean,
version = "MEAT2.0")

# Run epiage_estimation() to obtain DNAmage + optionally AAdiff and AAresid
GSE121961_SE_epiage <- epiage_estimation(SE = GSE121961_SE_calibrated,
version = "MEAT2.0",
age_col_name = "Age")
colData(GSE121961_SE_epiage)
```

`gold.mean.MEAT` *Mean methylation in dataset GSE50498 reduced to the 19,401 CpGs of MEAT*

Description

Gold standard dataset GSE50498 containing the mean methylation across 24 young and 24 old individuals at the 19,401 CpGs used to calibrate DNA methylation profiles.

Usage

```
gold.mean.MEAT
```

Format

A data frame with 19,401 rows and 2 variables:

CpGs CpG name

gold.mean mean methylation across all samples at the corresponding CpG (between 0 and 1)

Source

ftp://ftp.ncbi.nlm.nih.gov/geo/series/GSE50nnn/GSE50498/matrix/

`gold.mean.MEAT2.0` *Mean methylation in dataset GSE50498 reduced to the 18,747 CpGs of MEAT 2.0*

Description

Gold standard dataset GSE50498 containing the mean methylation across 24 young and 24 old individuals at the 18,747 CpGs used to calibrate DNA methylation profiles.

Usage

```
gold.mean.MEAT2.0
```

Format

A data frame with 18,747 rows and 2 variables:

CpGs CpG name

gold.mean mean methylation across all samples at the corresponding CpG (between 0 and 1)

Source

ftp://ftp.ncbi.nlm.nih.gov/geo/series/GSE50nnn/GSE50498/matrix/

`GSE121961` *GSE121961 methylation data*

Description

GSE121961 dataset containing 2 DNA methylation profiles generated with the HMEPIC technology, and used here as a test dataset.

Usage

```
GSE121961
```

Format

A data frame with 866,091 CpGs (rows) and 2 individuals (columns)

Source

ftp://ftp.ncbi.nlm.nih.gov/geo/series/GSE121nnn/GSE121961/matrix/

GSE121961_pheno *GSE121961 phenotypes*

Description

GSE121961_pheno contains information on sex, age (missing for the controls), and group (Control, or SELENON/RYR mutant) for the 2 samples in the GSE121961 DNA methylation dataset.

Usage

```
GSE121961_pheno
```

Format

A data frame with 2 samples (rows) and 4 phenotypes (columns).

Source

https://onlinelibrary.wiley.com/doi/abs/10.1002/humu.23745

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