Package ‘limorhyde2’

January 26, 2023

Type Package
Title Quantify Rhythmicity and Differential Rhythmicity in Genomic Data
Version 0.1.0
Description Fit linear models based on periodic splines, moderate model coefficients using multivariate adaptive shrinkage, then compute properties of the moderated curves.
License GPL-2
Encoding UTF-8
LazyData true
RoxygenNote 7.2.3
Depends R (>= 3.6)
Imports abind (>= 1.4-5), ashr (>= 2.2-54), checkmate (>= 2.0.0), data.table (>= 1.12.8), DESeq2 (>= 1.30.0), foreach (>= 1.5.0), HDInterval (>= 0.2.2), iterators (>= 1.0.12), limma (>= 3.42.2), mashr (>= 0.2.50), pbs (>= 1.1), zeallot (>= 0.1.0)
Suggests cowplot (>= 1.1.1), knitr, doParallel (>= 1.0.15), ggplot2 (>= 3.3.5), glue (>= 1.6.1), qs (>= 0.24.1), rmarkdown, testthat (>= 3.0.0)
Config/testthat/edition 3
VignetteBuilder knitr
NeedsCompilation no
Author Jake Hughey [aut, cre], Dora Obodo [aut], Elliot Outland [aut]
Maintainer Jake Hughey <jakejhughey@gmail.com>
Repository CRAN
Date/Publication 2023-01-26 20:30:02 UTC
getDiffRhythmStats

Description

This function computes differences in rhythmicity between fitted curves for a given pair of conditions.

Usage

getDiffRhythmStats(fit, rhyStats, conds = fit$conds, dopar = TRUE)

Arguments

fit
A limorhode2 object containing data from multiple conditions.

rhyStats
A data.table of rhythmic statistics, as returned by getRhythmStats(), for fitted models in fit.

conds
A character vector indicating the conditions to compare pairwise, by default all conditions in fit.

dopar
Logical indicating whether to run calculations in parallel if a parallel backend is already set up, e.g., using doParallel::registerDoParallel(). Recommended to minimize runtime.

Value

A data.table containing the following differential rhythm statistics:

- mean_mesor
- mean_peak_trough_amp
- mean_rms_amp (only calculated if rms to getRhythmStats() was TRUE)
- diff_mesor
getExpectedMeas

• diff_peak_trough_amp
• diff_rms_amp (only calculated if rms to getRhythmStats() was TRUE)
• diff_peak_phase: circular difference between -fit$period/2 and fit$period/2
• diff_trough_phase: circular difference between -fit$period/2 and fit$period/2
• diff_rhy_dist: Euclidean distance between polar coordinates (peak_trough_amp, peak_phase)
• rms_diff_rhy: root mean square difference in mean-centered fitted curves (only calculated if rms to getRhythmStats() was TRUE)

The stats will be based on the value for cond2 minus the value for cond1. The rows of the data.table depend on the 'fitType' attribute of rhyStats:

• 'fitType' is 'posterior_mean' or 'raw': one row per feature per pair of conditions.
• 'fitType' is 'posterior_samples': one row per feature per posterior sample per pair of conditions.

See Also

getAddress(), getStatsIntervals()

Examples

library('data.table')

# rhythmicity in one condition
y = GSE54650$y
metadata = GSE54650$metadata

fit = getModelFit(y, metadata)
fit = getPosteriorFit(fit)
rhyStats = getRhythmStats(fit, features = c('13170', '13869'))

# rhythmicity and differential rhythmicity in multiple conditions
y = GSE34018$y
metadata = GSE34018$metadata

fit = getModelFit(y, metadata, nKnots = 3L, condColname = 'cond')
fit = getPosteriorFit(fit)
rhyStats = getRhythmStats(fit, features = c('13170', '12686'))
diffRhyStats = getDiffRhythmStats(fit, rhyStats)

getExpectedMeas  Compute expected measurements from fitted models

Description

This function computes expected measurements (corresponding to the fitted curves) for the specified times and features in all combinations of conditions and covariates (if they exist).
Usage

getExpectedMeas(
  fit,
  times,
  fitType = c("posterior_mean", "posterior_samples", "raw"),
  features = NULL,
  dopar = TRUE
)

Arguments

fit A 'limorhyde2' object.
times Numeric vector of times, in units of fit$metadata[[fit$timeColname]].
fitType String indicating which fitted models to use to compute the expected measurements. A typical analysis using limorhyde2 will be based on 'posterior_mean', the default.
features Vector of names, row numbers, or logical values for subsetting the features. NULL indicates all features.
dopar Logical indicating whether to run calculations in parallel if a parallel backend is already set up, e.g., using doParallel::registerDoParallel(). Recommended to minimize runtime.

Value

A data.table.

See Also

getModelFit(), getPosteriorFit(), getPosteriorSamples(), getExpectedMeasIntervals()

Examples

library('data.table')

y = GSE34018$y
metadata = GSE34018$metadata

fit = getModelFit(y, metadata)
fit = getPosteriorFit(fit)

measObs = mergeMeasMeta(y, metadata, features = c('13170', '12686'))
measFitMean = getExpectedMeas(
  fit, times = seq(0, 24, 0.5), features = c('13170', '12686'))
getExpectedMeasIntervals

*Compute credible intervals for expected measurements*

**Description**

This function uses posterior samples to quantify uncertainty in the expected measurements from fitted models.

**Usage**

```r
getExpectedMeasIntervals(expectedMeas, mass = 0.9, method = c("eti", "hdi"))
```

**Arguments**

- **expectedMeas** A `data.table` of expected measurements for posterior samples, as returned by `getExpectedMeas()`.
- **mass** Number between 0 and 1 indicating the probability mass for which to calculate the intervals.
- **method** String indicating the type of interval: 'eti' for equal-tailed using `stats::quantile()`, or 'hdi' for highest density using `HDInterval::hdi()`.

**Value**

A `data.table` containing lower and upper bounds of the expected measurement for each combination of feature, time, and possibly condition and covariate.

**See Also**

`getExpectedMeas()`, `getStatsIntervals()`

**Examples**

```r
library('data.table')

y = GSE34018$y
metadata = GSE34018$metadata

fit = getModelFit(y, metadata)
fit = getPosteriorFit(fit)
fit = getPosteriorSamples(fit, nPosteriorSamples = 10L)

measFitSamps = getExpectedMeas(
    fit, times = seq(0, 24, 0.5), fitType = 'posterior_samples',
    features = c('13170', '12686'))
measFitInts = getExpectedMeasIntervals(measFitSamps)
```
getModelFit  

Fit linear models for rhythmicity in one or more conditions

Description

This is the first step in an analysis using limorhyde2, the second is to moderate the fits using getPosteriorFit().

Usage

getModelFit(
  y, 
  metadata, 
  period = 24, 
  nKnots = 3L, 
  degree = if (nKnots > 2) 3L else 2L, 
  sinusoid = FALSE, 
  timeColname = "time", 
  condColname = NULL, 
  covarColnames = NULL, 
  sampleColname = "sample", 
  nShifts = 3L, 
  method = c("trend", "voom", "deseq2"), 
  lmFitArgs = list(), 
  eBayesArgs = if (method == "trend") list(trend = TRUE) else list(), 
  DESeqArgs = list(), 
  keepLmFits = FALSE
)

Arguments

y  
Matrix-like object of measurements, with rows corresponding to features and columns to samples.

metadata  
data.frame containing experimental design information for each sample. Rows of metadata must correspond to columns of y. Row names are ignored.

period  
Number specifying the period for the time variable, in the same units as the values in the timeColname column.

nKnots  
Number of internal knots for the periodic spline for the time variable.

degree  
Integer indicating degree of the piecewise polynomial for the spline.

sinusoid  
Logical indicating whether to fit a cosinor-based model instead of a spline-based model.

timeColname  
String indicating the column in metadata containing the time at which each sample was acquired.
condColname String indicating the column in metadata containing the condition in which each sample was acquired. NULL indicates all samples came from the same condition. If not NULL, the model will include main effects and interactions with the terms for time.

covarColnames Character vector indicating the columns in metadata containing covariates to include in the model. NULL indicates no covariates.
sampleColname String indicating the column in metadata containing the name of each sample, which must correspond to the column names of y.
nShifts Number of shifted models to fit. Only used for periodic splines, not for cosinor. Do not change from the default unless you know what you’re doing.

method String indicating method to estimate model coefficients. For microarray data, use ’trend’. For RNA-seq count data, use ’voom’ or ’deseq2’.

lmFitArgs List of arguments passed to limma::lmFit().
eBayesArgs List of arguments passed to limma::eBayes().
DESeqArgs List of arguments passed to DESeq2::DESeq().
keepLmFits Logical indicating whether to keep the complete fit objects from limma or DESeq2. Not needed by any functions in limorhyde2.

Value

A limorhyde2 object with elements:

• metadata: As supplied above, converted to a data.table.
• timeColname: As supplied above.
• condColname: As supplied above.
• covarColnames: As supplied above.
• coefficients: Matrix with rows corresponding to features and columns to model terms, including all shifted models.
• shifts: Numeric vector indicating amount by which timepoints were shifted for each shifted model.
• period: As supplied above.
• conds: If condColname is not NULL, a vector of unique values of the condition variable.
• nKnots: Number of knots.
• degree: As supplied above.
• sinusoid: As supplied above.
• nConds: Number of conditions.
• nCovs: Number of covariates.
• lmFits: If keepLmFits is TRUE, a list of objects from limma or DESeq2, with length equal to length of the shifts element.

See Also

getPosteriorFit()
Examples

```r
library('data.table')

# rhythmicity in one condition
y = GSE54650$y
metadata = GSE54650$metadata

fit = getModelFit(y, metadata)
fit = getPosteriorFit(fit)
rhyStats = getRhythmStats(fit, features = c('13170', '13869'))

# rhythmicity and differential rhythmicity in multiple conditions
y = GSE34018$y
metadata = GSE34018$metadata

fit = getModelFit(y, metadata, nKnots = 3L, condColname = 'cond')
fit = getPosteriorFit(fit)
rhyStats = getRhythmStats(fit, features = c('13170', '12686'))
diffRhyStats = getDiffRhythmStats(fit, rhyStats)
```

---

**getPosteriorFit**

*Compute posterior fit for linear models for rhythmicity*

**Description**

This is the second step in an analysis using limorhyde2, the first is to fit linear models using `getModelFit()`. This function obtains posterior estimates of coefficients using multivariate adaptive shrinkage (mash), which learns patterns in the data and accounts for noise in the original fits. The defaults for arguments should work well in most cases, so only change them if you know what you're doing.

**Usage**

```r
getPosteriorFit(
  fit,
  covMethod = c("data-driven", "canonical", "both"),
  getSigResArgs = list(),
  npc = fit$nKnots,
  covEdArgs = list(),
  overwrite = FALSE,
  ...
)
```

**Arguments**

- **fit** A limorhyde2 object.
- **covMethod** String indicating the type(s) of covariance matrices to use for the mash fit.
getPosteriorFit

getSigResArgs List of arguments passed to `mashr::get_significant_results()`. Only used if covMethod is 'data-driven' or 'both'.

npc Number of principal components passed to `mashr::cov_pca()`. Only used if covMethod is 'data-driven' or 'both'.

covEdArgs List of arguments passed to `mashr::cov_ed()`. Only used if covMethod is 'data-driven' or 'both'.

overwrite Logical for whether to recompute the mash fit if it already exists.

... Additional arguments passed to `mashr::mash()`. 

Value

A limorhyde2 object containing everything in fit with added or updated elements:

- mashData: list of mash data objects
- mashFits: list of mash fit objects
- mashCoefficients: Matrix of posterior mean coefficients, with rows corresponding to features and columns to model terms.
- mashIdx: Vector indicating which model terms were included in the mash fit.

See Also

`getModelFit()`, `getRhythmStats()`, `getExpectedMeas()`

Examples

```r
library('data.table')

# rhythmicity in one condition
y = GSE54650$y
metadata = GSE54650$metadata

fit = getModelFit(y, metadata)
fit = getPosteriorFit(fit)
rhyStats = getRhythmStats(fit, features = c('13170', '13869'))

# rhythmicity and differential rhythmicity in multiple conditions
y = GSE34018$y
metadata = GSE34018$metadata

fit = getModelFit(y, metadata, nKnots = 3L, condColname = 'cond')
fit = getPosteriorFit(fit)
rhyStats = getRhythmStats(fit, features = c('13170', '12686'))
diffRhyStats = getDiffRhythmStats(fit, rhyStats)
```
getPosteriorSamples  Draw samples from posterior distributions of fitted models

Description

This is an optional step in an analysis using limorhyde2, and is useful for quantifying uncertainty in posterior estimates of fitted curves and rhythmic statistics. The function calls `mashr::mash_compute_posterior_matrices`.

Usage

```r
getPosteriorSamples(fit, nPosteriorSamples = 200L, overwrite = FALSE)
```

Arguments

- `fit`  
  A `limorhyde2` object containing posterior fits.
- `nPosteriorSamples`  
  Number of samples to draw from each posterior distribution.
- `overwrite`  
  Logical indicating whether to recompute posterior samples if they already exist.

Value

A `limorhyde2` object containing everything in `fit` with added or updated element:

- `mashPosteriorSamples`: a three-dimensional array of coefficients, with dim 1 corresponding to features, dim 2 to model terms, and dim 3 to posterior samples.

See Also

`getPosteriorFit(), getRhythmStats(), getExpectedMeas(), getStatsIntervals()`

Examples

```r
library('data.table')

y = GSE54650$y
metadata = GSE54650$metadata

fit = getModelFit(y, metadata)
fit = getPosteriorFit(fit)
fit = getPosteriorSamples(fit, nPosteriorSamples = 10L)

rhyStatsSamps = getRhythmStats(  
  fit, features = c('13170', '13869'), fitType = 'posterior_samples')
rhyStatsInts = getStatsIntervals(rhyStatsSamps)
```
getRhythmStats

Compute rhythm statistics from fitted models

Description
This function uses stats::optim() to compute various properties of fitted curves with respect to time, potentially in each condition and for each posterior sample, and adjusting for any covariates.

Usage
getRhythmStats(
  fit,
  fitType = c("posterior_mean", "posterior_samples", "raw"),
  features = NULL,
  dopar = TRUE,
  rms = FALSE
)

Arguments
- **fit**: A limorhyde2 object.
- **fitType**: String indicating which fitted models to use to compute the rhythmic statistics. A typical analysis using limorhyde2 will be based on 'posterior_mean', the default.
- **features**: Vector of names, row numbers, or logical values for subsetting the features. NULL indicates all features.
- **dopar**: Logical indicating whether to run calculations in parallel if a parallel backend is already set up, e.g., using doParallel::registerDoParallel(). Recommended to minimize runtime.
- **rms**: Logical indicating whether to calculate rms_amp.

Value
A data.table containing the following rhythm statistics:
- **peak_phase**: time between 0 and fit$period at which the peak or maximum value occurs
- **peak_value**
- **trough_phase**: time between 0 and fit$period at which the trough or minimum value occurs
- **trough_value**
- **peak_trough_amp**: peak_value - trough_value
- **rms_amp**: root mean square difference between fitted curve and mean value between time 0 and fit$period (only calculated if rms is TRUE)
- **mesor**: mean value between time 0 and fit$period
getStatsIntervals

The rows of the data.table depend on the fit object and fitType:

- fit contains data from one condition and fitType is 'posterior_mean' or 'raw': one row per feature.
- fit contains data from one condition and fitType is 'posterior_samples': one row per posterior sample.
- fit contains data from multiple conditions and fitType is 'posterior_mean' or 'raw': one row per feature per condition.
- fit contains data from multiple conditions and fitType is 'posterior_samples': one row per feature per condition per posterior sample.

See Also

gModelFit(), getPosteriorFit(), getPosteriorSamples(), getDiffRhythmStats(), getStatsIntervals()

Examples

library('data.table')

# rhythmicity in one condition
y = GSE54650$y
metadata = GSE54650$metadata

fit = gModelFit(y, metadata)
fit = getPosteriorFit(fit)
rhyStats = getRhythmStats(fit, features = c('13170', '13869'))

# rhythmicity and differential rhythmicity in multiple conditions
y = GSE34018$y
metadata = GSE34018$metadata

fit = gModelFit(y, metadata, nKnots = 3L, condColname = 'cond')
fit = getPosteriorFit(fit)
rhyStats = getRhythmStats(fit, features = c('13170', '12686'))
diffRhyStats = getDiffRhythmStats(fit, rhyStats)

getStatsIntervals

Compute credible intervals for rhythm or differential rhythm statistics

Description

This function uses posterior samples to quantify uncertainty in the properties of fitted curves.

Usage

ggetStatsIntervals(posteriorStats, mass = 0.9, method = c("eti", "hdi"))
Arguments

posteriorStats A data.table of statistics for posterior samples, as returned by `getRhythmStats()` or `getDiffRhythmStats()`.

mass Number between 0 and 1 indicating the probability mass for which to calculate the intervals.

method String indicating the type of interval: 'eti' for equal-tailed using `stats::quantile()`, or 'hdi' for highest density using `HDInterval::hdi()`.

Value

A data.table containing lower and upper bounds of various statistics for each feature or each feature-condition pair. For `peak_trough_amp` and `rms_amp`, a negative lower bound indicates a rhythm of the opposite phase.

See Also

`getRhythmStats()`, `getDiffRhythmStats()`, `getExpectedMeasIntervals()`

Examples

```r
library('data.table')

y = GSE54650$y
metadata = GSE54650$metadata

fit = getModelFit(y, metadata)
fit = getPosteriorFit(fit)
fit = getPosteriorSamples(fit, nPosteriorSamples = 10L)

rhyStatsSamps = getRhythmStats(
  fit, features = c('13170', '13869'), fitType = 'posterior_samples')
rhyStatsInts = getStatsIntervals(rhyStatsSamps)
```
Format
A list with two elements:

- y: Matrix of normalized, log-transformed expression values. Rows correspond to genes (row-names are Entrez Gene IDs) and columns to samples.
- metadata: data.table with one row per sample. time is in hours.

Source

See Also
GSE54650, getModelFit()

GSE54650 Gene expression data for GSE54650

Description
Data are based on total RNA, measured by microarray, obtained from livers of wild-type mice at various times after transfer to constant darkness. To save space and time, the data include only a subset of genes, and so are mainly useful for examples of how to use limorhyde2.

Usage
GSE54650

Format
A list with two elements:

- y: Matrix of normalized, log-transformed expression values. Rows correspond to genes (row-names are Entrez Gene IDs) and columns to samples.
- metadata: data.table with one row per sample. time is in hours.

Source

See Also
GSE34018, getModelFit()
mergeMeasMeta

Merge measurements and metadata

Description

This function is useful for plotting time-courses for individual features.

Usage

mergeMeasMeta(y, metadata, features = NULL, sampleColname = "sample")

Arguments

- **y**: Matrix-like object of measurements, with rows corresponding to features and columns to samples.
- **metadata**: data.frame containing experimental design information for each sample. Rows of metadata must correspond to columns of y. Row names are ignored.
- **features**: Vector of names, row numbers, or logical values for subsetting the features. NULL indicates all features.
- **sampleColname**: String indicating the column in metadata containing the name of each sample, which must correspond to the column names of y.

Value

A data.table with one row for each sample-feature pair.

See Also

getExpectedMeas()

Examples

library('data.table')

y = GSE34018$y
metadata = GSE34018$metadata

fit = getModelFit(y, metadata)
fit = getPosteriorFit(fit)

measObs = mergeMeasMeta(y, metadata, features = c('13170', '12686'))
measFitMean = getExpectedMeas(
    fit, times = seq(0, 24, 0.5), features = c('13170', '12686'))
Index

* datasets
  GSE34018, 13
  GSE54650, 14
  DESeq2::DESeq(), 7
  doParallel::registerDoParallel(), 2, 4, 11
  getDiffRhythmStats, 2
  getDiffRhythmStats(), 12, 13
  getExpectedMeas, 3
  getExpectedMeas(), 5, 9, 10, 15
  getExpectedMeasIntervals, 5
  getExpectedMeasIntervals(), 4, 13
  getModelFit, 6
  getModelFit(), 4, 8, 9, 12, 14
  getPosteriorFit, 8
  getPosteriorFit(), 4, 6, 7, 10, 12
  getPosteriorSamples, 10
  getPosteriorSamples(), 4, 12
  getRhythmStats, 11
  getRhythmStats(), 2, 3, 9, 10, 13
  getStatsIntervals, 12
  getStatsIntervals(), 3, 5, 10, 12
  GSE34018, 13, 14
  GSE54650, 14, 14
  HDInterval::hdi, 5, 13
  limma::eBayes(), 7
  limma::lmFit(), 7
  mashr::cov_ed, 9
  mashr::cov_pca(), 9
  mashr::get_significant_results(), 9
  mashr::mash(), 9
  mashr::mash_compute_posterior_matrices(), 10
  mergeMeasMeta, 15
  stats::optim(), 11
  stats::quantile, 5, 13