Package ‘MetaCycle’

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Type Package

Title Evaluate Periodicity in Large Scale Data

Version 1.1.0

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Description Provides two functions-meta2d and meta3d for detecting
rhythmic signals from time-series datasets. For analyzing
time-series datasets without individual information, 'meta2d' is
suggested, which could incorporates multiple methods from ARSER,
JTK_CYCLE and Lomb-Scargle in the detection of interested rhythms. For
analyzing time-series datasets with individual information, 'meta3d' is
suggested, which takes use of any one of these three methods to analyze
time-series data individual by individual and gives out integrated values
based on analysis result of each individual.

Depends R (>= 3.0.2)

Imports gnm

Suggests knitr, rmarkdown, diagram, shape

VignetteBuilder knitr

License GPL (>= 2)

LazyData true

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R topics documented:

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### cycHumanBloodData

**Description**

This data set lists time-series profiles of 10 transcripts sampled from multiple individuals under different sleep conditions.

**Usage**

```r
cycHumanBloodData
```

**Format**

A dataframe containing 439 columns (column 1 = transcript name, column 2 to 439 = samples from individuals at different time points and sleep conditions).

**Source**


---

### cycHumanBloodDesign

**Description**

This data set describes individual information, sleep condition and sampling time corresponding to each sample in 'cycHumanBloodData'.

**Usage**

```r
cycHumanBloodDesign
```

**Format**

A dataframe containing 4 columns described as below:

- `cycHumanBloodDesign`
- `cycMouseLiverProtein`
- `cycMouseLiverRNA`
- `cycSimu4h2d`
- `cycVignettesAMP`
- `cycYeastCycle`
- `meta2d`
- `meta3d`
- `MetaCycle`
**cycMouseLiverProtein**

<table>
<thead>
<tr>
<th>.1</th>
<th>sample_library</th>
<th>character</th>
<th>sample ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>.2</td>
<td>subject</td>
<td>character</td>
<td>individual ID</td>
</tr>
<tr>
<td>.3</td>
<td>group</td>
<td>character</td>
<td>sleep condition</td>
</tr>
<tr>
<td>.4</td>
<td>time_hoursawake</td>
<td>numeric</td>
<td>hours after awake</td>
</tr>
</tbody>
</table>

**Source**


---

**cycMouseLiverProtein**

**Description**

This data set lists expression profiles of 5 circadian proteins with 3h-resolution covering two days.

**Usage**

cycMouseLiverProtein

**Format**

A dataframe containing 49 columns (column 1 = protein name, column 2 to 49 = time points from CT0 to CT45 with three replicates at each time point).

**Source**


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**cycMouseLiverRNA**

**Description**

This data set lists expression profiles of 20 circadian transcripts with 1h-resolution covering two days.

**Usage**

cycMouseLiverRNA
**Format**

A dataframe containing 49 columns (column 1 = transcript name, column 2 to 49 = time points from CT18 to CT65).

**Source**


---

**Description**

This data set lists 20 simulated profiles (periodic and non-periodic) with 4h-resolution covering two periods.

**Usage**

cycSimu4h2d

**Format**

A dataframe containing 13 columns (column 1 = curve ID, column 2 to 13 = time points from 0 to 44).

**Source**


---

**Description**

This data set lists meta2d’s analysis results of three circadian transcripts selected from the same source dataset used by cycMouseLiverRNA.

**Usage**

cycVignettesAMP

**Format**

A dataframe containing 71 columns described as below:
| .[1] | CycID | character | transcript name |
| .[2] | ARS_pvalue | numeric | pvalue from ARS |
| .[3] | ARS_BH.Q | numeric | FDR from ARS |
| .[4] | ARS_period | numeric | period from ARS |
| .[5] | ARS_adjphase | numeric | adjusted phase from ARS |
| .[6] | ARS_amplitude | numeric | amplitude from ARS |
| .[7] | JTK_pvalue | numeric | pvalue from JTK |
| .[8] | JTK_BH.Q | numeric | FDR from JTK |
| .[9] | JTK_period | numeric | period from JTK |
| .[10] | JTK_adjphase | numeric | adjusted phase from JTK |
| .[11] | JTK_amplitude | numeric | amplitude from JTK |
| .[12] | LS_pvalue | numeric | pvalue from LS |
| .[13] | LS_BH.Q | numeric | FDR from LS |
| .[14] | LS_period | numeric | period from LS |
| .[15] | LS_adjphase | numeric | adjusted phase from LS |
| .[16] | LS_amplitude | numeric | amplitude from LS |
| .[17] | meta2d_pvalue | numeric | integrated pvalue |
| .[18] | meta2d_BH.Q | numeric | FDR based on integrated pvalue |
| .[19] | meta2d_period | numeric | averaged period of three methods |
| .[20] | meta2d_phase | numeric | integrated phase |
| .[21] | meta2d_Base | numeric | baseline value given by meta2d |
| .[22] | meta2d_AMP | numeric | amplitude given by meta2d |
| .[23] | meta2d_rAMP | numeric | relative amplitude |
| .[24:71] | CT18 to CT65 | numeric | sampling time point |

**Source**


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**cycYeastCycle**

**Description**

This data set lists expression profiles of 10 cycling transcripts with 16-minutes resolution covering about two yeast cell cycles.

**Usage**

cycYeastCycle

**Format**

A dataframe containing 12 columns(column 1 = transcript name, column 2 to 12 = time points from 2 minutes to 162 minutes after recovery phase).
Source

---

**meta2d**
Detect rhythmic signals from time-series datasets with multiple methods

**Description**
This is a function that incorporates ARSER, JTK_CYCLE and Lomb-Scargle to detect rhythmic signals from time-series datasets.

**Usage**
```
meta2d(infile, outdir = "metaout", filestyle, timepoints, minper = 20,
maxper = 28, cycMethod = c("ARS", "JTK", "LS"),
analysisStrategy = "auto", outputFile = TRUE, outIntegration = "both",
adjustPhase = "predictedPer", combinePvalue = "fisher",
weightedPerPha = FALSE, ARSmlle = "auto", ARSdefaultPer = 24,
outRawData = FALSE, releaseNote = TRUE, outSymbol = "")
```

**Arguments**
- **infile**
  a character string. The name of input file containing time-series data.
- **outdir**
  a character string. The name of directory used to store output files.
- **filestyle**
  a character vector(length 1 or 3). The data format of input file, must be "txt", or "csv", or a character vector containing field separator character(sep), quoting character (quote), and the character used for decimal points(dec, for details see `read.table`).
- **timepoints**
  a numeric vector corresponding to sampling time points of input time-series data; if sampling time points are in the first line of input file, it could be set as a character string-"Line1" or "line1".
- **minper**
  a numeric value. The minimum period length of interested rhythms. The default is 20 for circadian rhythms.
- **maxper**
  a numeric value. The maximum period length of interested rhythms. The default is 28 for circadian rhythms.
- **cycMethod**
  a character vector(length 1 or 2 or 3). User-defined methods for detecting rhythmic signals, must be selected as any one, any two or all three methods(default) from "ARS"(ARSER), "JTK"(JTK_CYCLE) and "LS"(Lomb-Scargle).
- **analysisStrategy**
  a character string. The strategy used to select proper methods from cycMethod for analyzing input time-series data, must be "auto"(default), or "selfUSE". See Details part for more information.
**outputFile** logical. If TRUE, analysis results will be wrote in the output files. If FALSE, analysis results will be returned as an R list.

**outIntegration** a character string. This parameter controls what kinds of analysis results will be outputted, must be one of "both" (default), "onlyIntegration" (only output integration file), or "noIntegration" (not output integration file).

**adjustPhase** a character string. The method used to adjust original phase calculated by each method in integration file, must be one of "predictedPer" (adjust phase with predicted period length) or "notAdjusted" (not adjust phase).

**combinePvalue** a character string. The method used to integrate multiple p-values, must be one of "bonferroni" (Bonferroni correction), or "fisher" (Fisher's method).

**weightedPerPhase** logical. If TRUE, weighted scores based on p-value given by each method will be used to calculate the integrated period length and phase.

**ARSmle** a character string. The strategy of using MLE method in ar fit of "ARS", must be one of "auto" (use MLE depending the number of time points), "mle" (always use MLE), or "nomle" (never use MLE).

**ARSGlobalPer** a numeric value. The expected period length of interested rhythm, which is a necessary parameter for ARS. The default is 24 (for circadian rhythms). Set it to another proper numeric value for other rhythms.

**outRawData** logical. If TRUE, raw time-series data will be added in the output files.

**releaseNote** logical. If TRUE, reminding or warning notes during the analysis will be released on the screen.

**outSymbol** a character string. A common prefix exists in the names of output files.

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**Details**

**ARSE** (Yang, 2010), **JTK_CYCLE** (Hughes, 2010), and **Lomb-Scargle** (Glynn, 2006) are three popular methods of detecting rhythmic signals. ARS can not analyze unevenly sampled datasets, or evenly sampled datasets but with missing values, or with replicate samples, or with non-integer sampling interval. JTK is not suitable to analyze unevenly sampled datasets or evenly sampled datasets but with non-integer sampling interval. If set **analysisStrategy** as "auto" (default), meta2d will automatically select proper method from **cycMethod** for each input dataset. If the user clearly know that the dataset could be analyzed by each method defined by **cycMethod** and do not hope to output integrated values, **analysisStrategy** can be set as "selfUSE".

ARS used here is translated from its python version which always uses "yule-walker", "burg", and "mle" methods (see ar) to fit autoregressive models to time-series data. Fitting by "mle" will be very slow for datasets with many time points. If **ARSmle** = "auto" is used, meta2d will only include "mle" when number of time points is smaller than 24. In addition, one evaluation work (Wu, 2014) indicates that ARS shows relative high false positive rate in analyzing high-resolution datasets (1h/2days and 2h/2days). JTK (version 3) used here is the latest version, which improves its p-value calculation in analyzing datasets with missing values.

The power of detecting rhythmic signals for an algorithm is associated with the nature of data and interested periodic pattern (Deckard, 2013), which indicates that integrating analysis results from multiple methods may be helpful to rhythmic detection. For integrating p-values, Bonferroni correction("bonferroni") and Fisher's method("fisher") (Fisher, 1925; implementation code from MADAM) could be selected, and "bonferroni" is usually more conservative than "fisher".
The integrated period is arithmetic mean of multiple periods. For integrating phase, meta2d takes use of mean of circular quantities. Integrated period and phase is further used to calculate the baseline value and amplitude through fitting a constructed periodic model.

Phases given by JTK and LS need to be adjusted with their predicted period (adjustedPhase = "predictedPer") before integration. If adjustedPhase = "notAdjusted" is selected, no integrated phase will be calculated. If set weightedPerPha as TRUE, weighted scores will be used in averaging periods and phases. Weighted scores for one method are based on all its reported p-values, which means a weighted score assigned to any one profile will be affected by all other profiles. It is always a problem of averaging phases with quite different period lengths (eg. averaging two phases with 16-hours’ and 30-hours’ period length). Currently, setting minper, maxper and ARSdefaultPer to a same value may be the only way of completely eliminating such problem.

This function is originally aimed to analyze large scale periodic data (eg. circadian transcriptome data) without individual information. Please pay attention to data format of input file (see Examples part). Except the first column and first row, others are time-series experimental values (setting missing values as NA).

Value

meta2d will write analysis results in different files under outdir if set outputFile = TRUE. Files named with "ARSResult", "JTKResult" and "LSresult" store analysis results from ARS, JTK and LS respectively. The file named with "meta2d" is the integration file, and it stores integrated values in columns with a common name tag-"meta2d". The integration file also contains p-value, FDR value, period, adjusted phase if adjustedPhase = "predictedPer") and amplitude values calculated by each method. If outputFile = FALSE is selected, meta2d will return a list containing the following components:

ARS analysis results from ARS method
JTK analysis results from JTK method
LS analysis results from LS method
meta the integrated analysis results as mentioned above

References


### Examples

```r
# write 'cycMouseLiverProtein' into a 'txt' file
write.table(cycMouseLiverProtein, file="cycMouseLiverProtein.txt", sep="\t", quote=FALSE, row.names=FALSE)
# write 'cycSimu4h2d' and 'cycYeastCycle' into two 'csv' files
write.csv(cycSimu4h2d, file="cycSimu4h2d.csv", row.names=FALSE)
write.csv(cycYeastCycle, file="cycYeastCycle.csv", row.names=FALSE)

# analyze 'cycMouseLiverProtein.txt' with JTK_CYCLE and Lomb-Scargle
meta2d(infile="cycMouseLiverProtein.txt", filestyle="txt",
        outdir="example", timepoints=rep(seq(0, 45, by=3), each=3),
        cycMethod=c("JTK"), outIntegration="noIntegration")

# analyze 'cycSimu4h2d.csv' with ARSER, JTK_CYCLE and Lomb-Scargle and
# output integration file with analysis results from each method
meta2d(infile="cycSimu4h2d.csv", filestyle="csv", outdir="example",
        timepoints="Line1")

# analyze 'cycYeastCycle.csv' with ARSER, JTK_CYCLE and Lomb-Scargle to
# detect transcripts associated with cell cycle, and return analysis
# results instead of output them into files

cyc <- meta2d(infile="cycYeastCycle.csv", filestyle="csv",
               minper=80, maxper=96, timepoints=seq(2, 162, by=16),
               outputFile=FALSE, ARSdefaultPer=85, outrawData=TRUE)
head(cyc$ARS)
head(cyc$JTK)
head(cyc$LS)
head(cyc$meta)
```

---

**meta3d**

*Detect rhythmic signals from time-series datasets with individual information*

### Description

This is a function that takes use of any one method from ARSER, JTK_CYCLE and Lomb-Scargle to detect rhythmic signals from time-series datasets containing individual information.

### Usage

```r
meta3d(datafile, designfile, outdir = "metaout", filestyle, design_libColm,
        design_subjectColm, minper = 20, maxper = 28, cycMethodOne = "JTK",
        timeUnit = "hour", design_hrColm, design_dayColm = NULL,
        design_minColm = NULL, design_secColm = NULL, design_groupColm = NULL,
        design_libIDrename = NULL, adjustPhase = "predictedPer",
```
```
combinePvalue = "fisher", weightedMethod = TRUE,
outIntegration = "both", ARSmle = "auto", ARSdefaultPer = 24,
dayZeroBased = FALSE, outSymbol = "")
```

**Arguments**

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><code>datafile</code></td>
<td>a character string. The name of data file containing time-series experimental values of all individuals.</td>
</tr>
<tr>
<td><code>designfile</code></td>
<td>a character string. The name of experimental design file, at least containing the library ID(column names of <code>datafile</code>), subject ID(the individual corresponding to each library ID), and sampling time information of each library ID.</td>
</tr>
<tr>
<td><code>outdir</code></td>
<td>a character string. The name of directory used to store output files.</td>
</tr>
<tr>
<td><code>filestyle</code></td>
<td>a character vector(length 1 or 3). The data format of input files, must be &quot;txt&quot;, or &quot;csv&quot;, or a character vector containing field separator character(sep), quoting character(quote), and the character used for decimal points(dec, for details see <code>read.table</code>).</td>
</tr>
<tr>
<td><code>design_libColm</code></td>
<td>a numeric value. The order index(from left to right) of the column storing library ID in <code>designfile</code>.</td>
</tr>
<tr>
<td><code>design_subjectColm</code></td>
<td>a numeric value. The order index(from left to right) of the column storing subject ID in <code>designfile</code>.</td>
</tr>
<tr>
<td><code>minper</code></td>
<td>a numeric value. The minimum period length of interested rhythms. The default is 20 for circadian rhythms.</td>
</tr>
<tr>
<td><code>maxper</code></td>
<td>a numeric value. The maximum period length of interested rhythms. The default is 28 for circadian rhythms.</td>
</tr>
<tr>
<td><code>cycMethodOne</code></td>
<td>a character string. The selected method for analyzing time-series data of each individual, must be one of &quot;ARS&quot;(ARSER), &quot;JTK&quot;(JTK_CYCLE), or &quot;LS&quot;(Lomb-Scargle).</td>
</tr>
<tr>
<td><code>timeUnit</code></td>
<td>a character string. The basic time-unit, must be one of &quot;day&quot;, &quot;hour&quot;(default for circadian study), &quot;minute&quot;, or &quot;second&quot; depending on specific experimental design.</td>
</tr>
<tr>
<td><code>design_hrColm</code></td>
<td>a numeric value. The order index(from left to right) of the column storing time point value-sampling hour information in <code>designfile</code>. If there is no such column in <code>designfile</code>, set it as NULL.</td>
</tr>
<tr>
<td><code>design_dayColm</code></td>
<td>a numeric value. The order index(from left to right) of the column storing time point value-sampling day information in <code>designfile</code>. If there is no such column in <code>designfile</code>, set it as NULL(default).</td>
</tr>
<tr>
<td><code>design_minColm</code></td>
<td>a numeric value. The order index(from left to right) of the column storing time point value-sampling minute information in <code>designfile</code>. If there is no such column in <code>designfile</code>, set it as NULL(default).</td>
</tr>
<tr>
<td><code>design_secColm</code></td>
<td>a numeric value. The order index(from left to right) of the column storing time point value-sampling second information in <code>designfile</code>. If there is no such column in <code>designfile</code>, set it as NULL(default).</td>
</tr>
</tbody>
</table>
**design_groupColm**

A numeric value. The order index (from left to right) of the column storing experimental group information of each individual in **designfile**. If there is no such column in **designfile**, set it as NULL (default) and take all individuals as one group.

**design_libIDrename**

A character vector (length 2) containing a matchable character string in each library ID of **designfile**, and a replacement character string. If it is not necessary to replace characters in library ID of **designfile**, set it as NULL (default).

**adjustPhase**

A character string. The method used to adjust each calculated phase before getting integrated phase, must be one of "predictedPer" (adjust phase with predicted period length) or "notAdjusted" (not adjust phase).

**combinePvalue**

A character string. The method used to integrate p-values of multiple individuals, currently only "fisher" (Fisher's method) could be selected.

**weightedMethod**

Logical. If TRUE (default), weighted score based on p-value of each individual will be used to integrate period, phase and amplitude values of multiple individuals.

**outIntegration**

A character string. This parameter controls what kinds of analysis results will be outputted, must be one of "both", "onlyIntegration", or "noIntegration". See `meta2d` for more information.

**ARSmle**

A character string. The strategy of using MLE method in "ARS", must be one of "auto", "mle", or "nomle". See `meta2d` for more information.

**ARSdefaultPer**

A numeric value. The expected period length of interested rhythm, which is a necessary parameter for ARS. See `meta2d` for more information.

**dayZeroBased**

Logical. If TRUE, the first sampling day is recorded as day zero in the **designfile**.

**outSymbol**

A character string. A common prefix exists in the names of output files.

## Details

This function is originally aimed to analyze large scale periodic data with individual information. Please pay attention to the data format of **datafile** and **designfile** (see Examples part). Time-series experimental values (missing values as NA) from all individuals should be stored in **datafile**, with the first row containing all library ID (unique identification number for each sample) and the first column containing all detected molecular names (e.g., transcript or gene name). The **designfile** should at least have three columns—library ID, subject ID and sampling time column. Experimental group information of each subject ID may be in another column. In addition, sampling time information may be stored in multiple columns instead of one column. For example, sampling time-"36 hours" may be recorded as "day 2" (sampling day column, **design_dayColm**) plus "12 hours" (sampling hour column, **design_hrColm**). The library ID in **datafile** and **designfile** should be same. If there are different characters between library ID in these two files, try `design_libIDrename` to keep them same.

ARS, JTK or LS could be used to analyze time-series profiles individual by individual. `meta3d` requires that all individuals should be analyzed by the same method before integrating calculated p-value, period, phase, baseline value, amplitude and relative amplitude values group by group. However, the sampling pattern among individuals may be different and the requirement of sampling pattern for each method is not same (see more information about these methods and their limitations.
Please carefully select a proper method for the specific dataset. meta3d also help users select the suitable method through warning notes.

P-values from different individuals are integrated with Fisher’s method (“fisher”) (Fisher, 1925; implementation code from MADAM). For short time-series profiles (e.g., 10 time points or less), p-values given by Lomb-Scargle may be over conservative, which will also lead to conservative integrated p-values. The integrated period, baseline, amplitude and relative amplitude values are arithmetic mean of multiple individuals, respectively. The phase is mean of circular quantities (adjustPhase = "predictedPer") or a arithmetic mean (adjustPhase = "notAdjusted") of multiple individual phases. For completely removing the potential problem of averaging phases with quite different period length (also mentioned in meta2d), setting minper, maxper and ARSdefaultPer to a same value may be the only known way. If weightedMethod = TRUE is selected, weighted scores (− log10(p-values)) will be taken into account in integrating period, phase, baseline, amplitude and relative amplitude.

Value

meta3d will write analysis results to outdir instead of returning them as objects. Output files with "meta3dSubjectID" in the file name are analysis results for each individual. Files named with "meta3dGroupID" store integrated p-values, period, phase, baseline, amplitude and relative amplitude values from multiple individuals of each group and calculated FDR values based on integrated p-values.

References


Examples

```r
# write 'cycHumanBloodData' and 'cycHumanBloodDesign' into two 'csv' files
write.csv(cycHumanBloodData, file="cycHumanBloodData.csv", row.names=FALSE)
write.csv(cycHumanBloodDesign, file="cycHumanBloodDesign.csv", row.names=FALSE)

# detect circadian transcripts with JTK in studied individuals
meta3d(datafile="cycHumanBloodData.csv", cycMethodOne="JTK", 
designfile="cycHumanBloodDesign.csv", outdir="example", 
filestyle="csv", design_libColm=1, design_subjectColm=2, 
design_hrColm=4, design_groupColm=3)
```
MetaCycle

| MetaCycle | MetaCycle Evaluate periodicity in large scale data |

**Description**

MetaCycle Evaluate periodicity in large scale data

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