

Package ‘GeneReg’

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Type Package

Title Construct time delay gene regulatory network

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Description GeneReg is an R package for inferring time delay gene regulatory network using time course gene expression profiles. The main idea of time delay linear model is to fit a linear regression model using a set of putative regulators to estimate the transcription pattern of a specific target gene.

Depends splines, igraph

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BMC Res Notes 2010, 3(1):142.

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GeneReg-package	<i>Construct time delay gene regulatory network</i>
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Description

GeneReg is an R package for inferring time delay gene regulatory network using time course gene expression data.

Details

The goal of time delay linear model is to fit a linear regression model using a set of putative regulators to estimate the transcription pattern of a specific target gene.

$$Eg = a1 * Etf1(-t1) + a2 * Etf2(-t2) + \dots + ai * Etfi(-ti) + \dots + an * Etn(-tn)$$

Where Eg is the relative expression level of target gene, $Etfi$ is the relative expression level of TF i , ti is time delay of TF i , ai is the regression coefficient of TF i .

The regression models were optimized by the AIC forward selection procedure.

In the following example, we will demonstrate how to use this package to analysis a cell cycle datasets which is publicly available at GEO <http://www.ncbi.nlm.nih.gov/geo> under accession number GSE8799. The data set included the gene expression profiles of wild-type cells and cyclin-mutant cells with 15 time points during two cell cycles. 1271 periodic genes acquired from wild-type cells were analyzed to investigate how yeast regulators regulate target gene expression. These periodic genes formed the list of target genes. Then, a candidate pool of potential regulators of target genes was constructed by intersecting the periodic genes and the transcription factors in YEASTRACT <http://www.yeasttract.com/>.

First, B spline interpolation was applied to estimate 100 time points according to the original 15 time points.

```
> data(wt.expr.data)

> wt.bspline.data<- ts.bspline(wt.expr.data,
+ ts.point=as.numeric(colnames(wt.expr.data)), data.predict=100)
```

Then, the time delay linear model was carried out based on the interpolated expression data. `single.adj.r.squared` and `multiple.adj.r.squared` were the cutoffs of adjusted R squared of single regulator regression and multiple regulator regression, respectively. `tfs.list` were the candidate pool of regulators. `min.coef` means the regression coefficient should be larger than 1/4 and smaller than 4. `maxdelay` means the time points delay should not exceed 1/4 of all time points.

```
> data(tf.list)
> dir.create('wt.model')
> setwd('wt.model')
> wt.models<-timedelay.lm.batch(bspline.data=wt.bspline.data,
+ expr.data=wt.expr.data, regulator.list=tf.list,
+ target.list=rownames(wt.bspline.data),
+ single.adj.r.squared=0.8, multiple.adj.r.squared=0.9,
+ maxdelay=ncol(wt.bspline.data)*0.1, min.coef=0.25, max.coef=4,
+ output=T, topdf=T, xlab='Time point (lifeline)',
+ ylab='Relative expression level (in log ratio)')
> setwd('..')
```

Finally, the gene regulatory network can be plotted according to the series of time delay linear models.

```
> pdf('wt.network.pdf',width=70, height=70)
> plot.GeneReg(wt.models,vertex.size=2,layout=layout.fruchterman.reingold)
> dev.off()
```

The analysis of cyclin-mutant cells is similar.

Author(s)

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References

Tao Huang, Lei Liu, Ziliang Qian, Kang Tu, Yixue Li, Lu Xie: Using GeneReg to construct time delay gene regulatory networks. *BMC Res Notes* 2010, 3(1):142. <http://www.biomedcentral.com/1756-0500/3/142>

mut.expr.data	<i>Time course cell cycle dataset of cyclin-mutant cells</i>
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Description

mut.expr.data is from a yeast cell cycle datasets which is publicly available at GEO <http://www.ncbi.nlm.nih.gov/geo> under accession number GSE8799. The time course gene expression profiles included 15 time points at 16 min resolution in cyclin-mutant *Saccharomyces cerevisiae*.

Usage

```
data(mut.expr.data)
```

Format

1267 genes expression profiles at 15 time points

Source

<http://www.biology.duke.edu/haaselab/publicData/index.html>

References

Orlando, D.A., Lin, C.Y., Bernard, A., Wang, J.Y., Socolar, J.E., Iversen, E.S., Hartemink, A.J. and Haase, S.B. (2008) Global control of cell-cycle transcription by coupled CDK and network oscillators, *Nature*, 453, 944-947.

plot	<i>Plot gene regulatory network</i>
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Description

Plot gene regulatory network based on a series of time delay linear models.

Usage

```
plot(edge, ...)
```

Arguments

edge	output of <code>timedelay.lm.batch</code> , which has 4 columns. The first column is the regulator, the second column is the target gene, the third column is the regression coefficient, the fourth column is time delay.
...	Additional arguments, passed to <code>plot.igraph</code> .

plot.GeneReg	<i>Plot gene regulatory network</i>
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Description

Plot gene regulatory network based on a series of time delay linear models.

Usage

```
## S3 method for class 'GeneReg'  
plot(edge, ...)
```

Arguments

edge	output of timedelay.lm.batch, which has 4 columns. The first column is the regulator, the second column is the target gene, the third column is the regression coefficient, the fourth column is time delay.
...	Additional arguments, passed to plot.igraph.

References

Tao Huang, Lei Liu, Ziliang Qian, Kang Tu, Yixue Li, Lu Xie: *Using GeneReg to construct time delay gene regulatory networks*. *BMC Res Notes* 2010, 3(1):142. <http://www.biomedcentral.com/1756-0500/3/142>

tf.list	<i>The candidate pool of potential regulators</i>
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Description

tf.list was constructed by intersecting the periodic genes and the transcription factors in YEAS-TRACT <http://www.yeasttract.com/>.

Usage

```
data(tf.list)
```

Format

A list of potential regulators

Source

<http://www.biology.duke.edu/haaselab/publicData/index.html>

<http://www.yeasttract.com/>

References

Orlando, D.A., Lin, C.Y., Bernard, A., Wang, J.Y., Socolar, J.E., Iversen, E.S., Hartemink, A.J. and Haase, S.B. (2008) Global control of cell-cycle transcription by coupled CDK and network oscillators, *Nature*, 453, 944-947.

Teixeira, M.C., Monteiro, P., Jain, P., Tenreiro, S., Fernandes, A.R., Mira, N.P., Alenquer, M., Freitas, A.T., Oliveira, A.L. and Sa-Correia, I. (2006) The YEASTRACT database: a tool for the analysis of transcription regulatory associations in *Saccharomyces cerevisiae*, *Nucleic acids research*, 34, D446-451.

timedelay.lm	<i>time delay linear model</i>
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Description

timedelay.lm is for time delay linear model.

Usage

```
timedelay.lm(bspline.data, expr.data, target, regulator,
maxdelay=ncol(bspline.data)*0.25, single.adj.r.squared=0.8,
multiple.adj.r.squared=0.9, min.coef=0.25, max.coef=4,
output=FALSE, topdf=FALSE, xlab='time point', ylab='log ratio')
```

Arguments

bspline.data	an interpolated expression matrix with genes in the rows, predicted time points in the columns
expr.data	an observed expression matrix with genes in the rows, predicted time points in the columns
target	target gene
regulator	potential regulators
maxdelay	max time points delay
single.adj.r.squared	the cutoff of adjusted R squared of univariate regression
multiple.adj.r.squared	the cutoff of adjusted R squared of multivariate regression
min.coef	the regression coefficient should be larger than min.coef
max.coef	the regression coefficient should be smaller than max.coef
output	whether the model should be plotted
topdf	whether the model should be plotted into a pdf file
xlab	xlab of the plot
ylab	ylab of the plot

References

Tao Huang, Lei Liu, Ziliang Qian, Kang Tu, Yixue Li, Lu Xie: Using GeneReg to construct time delay gene regulatory networks. *BMC Res Notes* 2010, 3(1):142. <http://www.biomedcentral.com/1756-0500/3/142>

timedelay.lm.batch *time delay linear model batch*

Description

Batch usage of time delay linear model.

Usage

```
timedelay.lm.batch(bspline.data, expr.data, regulator.list,  
target.list=rownames(bspline.data), ...)
```

Arguments

bspline.data	output of ts.bspline, an interpolated expression matrix with genes in the rows, predicted time points in the columns
expr.data	an observed expression matrix with genes in the rows, predicted time points in the columns
regulator.list	a candidate pool of potential regulators
target.list	the list of target genes that will be investigated
...	Additional arguments, passed to timedelay.lm

References

Tao Huang, Lei Liu, Ziliang Qian, Kang Tu, Yixue Li, Lu Xie: Using GeneReg to construct time delay gene regulatory networks. *BMC Res Notes* 2010, 3(1):142. <http://www.biomedcentral.com/1756-0500/3/142>

timedelay.univariate.lm
Internal function for time delay linear model

Description

timedelay.univariate.lm is an internal function for time delay linear model.

Usage

```
timedelay.univariate.lm(bspline.data, target, regulator,
maxdelay=ncol(bspline.data)*0.25,
single.adj.r.squared=0.8, min.coef=0.25, max.coef=4)
```

Arguments

bspline.data	an interpolated expression matrix with genes in the rows, predicted time points in the columns
target	target gene
regulator	potential regulators
maxdelay	max time points delay
single.adj.r.squared	the cutoff of adjusted R squared of univariate regression
min.coef	the regression coefficient should be larger than min.coef
max.coef	the regression coefficient should be smaller than max.coef

References

Tao Huang, Lei Liu, Ziliang Qian, Kang Tu, Yixue Li, Lu Xie: *Using GeneReg to construct time delay gene regulatory networks*. *BMC Res Notes* 2010, 3(1):142. <http://www.biomedcentral.com/1756-0500/3/142>

ts.bspline	<i>B spline interpolation</i>
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Description

ts.bspline is for B spline interpolation.

Usage

```
ts.bspline(expr,ts.point=NULL, data.predict=100, df=round(ncol(expr)*0.8))
```

Arguments

expr	an expression matrix with genes in the rows, time points in the columns
ts.point	time points
data.predict	the number of time points to be predicted
df	degrees of freedom, used in B-Spline Basis for Polynomial Splines

`wt.expr.data`*Time course cell cycle dataset of wild-type cells*

Description

wt.expr.data is from a yeast cell cycle datasets which is publicly available at GEO <http://www.ncbi.nlm.nih.gov/geo> under accession number GSE8799. The time course gene expression profiles included 15 time points at 16 min resolution in wild type *Saccharomyces cerevisiae*.

Usage

```
data(wt.expr.data)
```

Format

1267 genes expression profiles at 15 time points

Source

<http://www.biology.duke.edu/haaselab/publicData/index.html>

References

Orlando, D.A., Lin, C.Y., Bernard, A., Wang, J.Y., Socolar, J.E., Iversen, E.S., Hartemink, A.J. and Haase, S.B. (2008) Global control of cell-cycle transcription by coupled CDK and network oscillators, *Nature*, 453, 944-947.

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