Package 'PTC'

May 20, 2020

Type Package

Title Pseudo-temporal Causality Approach

Version 1.0.0

Description PTC package provides tools find miRNA-mRNA causal regulatory relationships during
biological processes. Causal inference is made by assuming a linear dependence model between
the predictors (miRNAs) and a target mRNA (response variable). This model is assumed invariant
throughout the whole process.
The model is created from gene expression sequential data. PTC transforms static gene expression
datasets to sequential data (via a Pseudotime analysis). PTC identifies causal regulatory
relationships by testing violations to the invariance property (Peters et al., 2015; Pfister et
al., 2018) for those sets that contains only miRNAs that biologically can interact with each tar-
get gene.

License GPL-3.0

Encoding UTF-8

LazyData true

Imports miRBaseConverter,
CancerSubtypes,
seqICP,
miRBaseConverter

RoxygenNote 7.1.0

R topics documented:

1

Index   **17**

Extract.Parents   *Extract.Parents*

Description

Uses the outcomes of PTC.GeneSel and PTC.TestInvariance to create a list of all mRNAs with at
least one causal parent.

Usage

```
Extract.Parents(PTC.outcome, Predictors)
```

Arguments

PTC.outcome   A list containing the results of the function PTC.TestInvariance. Each element
                 of the list must have the following form:

- name: mRNA name
- data: indexes indicating the position of the inferred miRNAs in the vector
  of plausible parents.

Predictors   A list containing the set of miRNAs to be used as predictors (plausible parents)
                 of each mRNA, obtained from PTC.GeneSel.

Value

A list of 3 elements.

Index   Indexes of miRNAs inferrred as causal parents of each mRNA. The indexes
                 correspond to miRNAs position in the set of plausible parents of each mRNA.

Names   A list where each element corresponds to a mRNA and contains the names of
                 the miRNAs that are inferred as causal parents of that mRNA.

genes   Names of all mRNAs with at least one parent inferred by PTC.

Examples

```
## Not run:
data(TCGA_BRCAdata)
data(TScan)
seqData<-PTC.ptime(TCGA_BRCAdata,TCGA_BRCAdata$mRNAs[,"VIM"])
SelData<-PTC.GeneSel(seqData, nmiR = 30, nmR = 1500)
PParents<-PTC.findPP(TScan, miRs=SelData$miRs, mRs="SORCS1")
temp <-SelData$PParents[["SORCS1"]]
SORCS1.X.TScan=SelData$d[,temp]
SORCS1.Parents<-PTC.TestInvariance(Y=SelData$d[,"SORCS1", drop = F], X=SORCS1.X.TScan)
names(SORCS1.Parents)<-"SORCS1"
SORCS1.Parents<-Extract.Parents(SORCS1.Parents,SelData$PParents["SORCS1"])

## End(Not run)
```

Find.Confirmed   *Find.Confirmed*

Description

Returns a `list` with all experimentally confirmed interactions inferred by PTC.

Usage

```
Find.Confirmed(miRNAsList, GroundT)
```

Arguments

miRNAsList   A `list` where each element has the following structure:

- `name`: mRNA name.
- `data`: Names of the miRNAs inferred as parents by PTC.

GroundT   A `list` where each element has the following structure:

- `name`: mRNA name.
- `data`: Names of the miRNAs whose interactions with the mRNA have been experimentally confirmed.

Value

A `list` where each element has the following structure:

name   Name of a mRNA inferred by PTC with at least one confirmed interaction.

data   Names of the miRNAs whose miRNA-mRNA interactions are in the `GroundT`.

See Also

PTC, GroundT

Examples

```
## Not run:
data(TCGA_BRCAdata)
data(GroundT)
test1<-PTC(miRNAs=TCGA_BRCAdata$miRs,mRNAs=TCGA_BRCAdata$mRNAs, VIM=TCGA_BRCAdata$mRNAs[,"VIM"])
t1.Confirmed<-Find.Confirmed(test1$Plist$Names,GroundT)

## End(Not run)
```

getDatabyMAD   *getDatabyMAD*

Description

Given a gene expression matched data including miRNAs-mRNAs, finds the `nmiR` miRNAs and the `nmR` mRNAs with the largest Median Absolute Deviation (MAD).

Usage

```
getDatabyMAD(seqData, nmiR, nmR)
```

Arguments

seqData   A list with two elements:

                 • A matrix with miRNAs gene expression.
                 • A matrix with mRNAs gene expression.

                 Columns represent miRNAs/mRNAs and rows represent time samples. Columns
                 names must correspond to miRNAs/mRNAs names.

nmiR   Number of miRNAs to be selected as predictor candidates.

nmR   Number of mRNAs to be selected as target variables.

Value

A `list` containing samples of miRs and mRs. The elements of the `list` are:

d   The data with rows being samples and columns being miRs and mRs.

miRs   The names of the selected miRs.

mRs   The names of the selected mRs.

Author(s)

Vu VH Pham <vu_viet_hoang.pham@mymail.unisa.edu.au>, Taosheng Xu <taosheng.x@gmail.com>

References

Taosheng Xu, Thuc Duy Le, Lin Liu, Ning Su, Rujing Wang, Bingyu Sun, Antonio Colaprico, Gianluca Bontempi, Jiuyong Li. CancerSubtypes: an R/Bioconductor package for molecular cancer subtype identification, validation, and visualization. Bioinformatics 33(19): 3131–3133 (2017). https://doi.org/10.1093/bioinformatics/btx378

See Also

[FSbyMAD](#)

Examples

```
TCGA_BRCAdata
nmiR <- 30
nmR <- 1500
l <- getDatabyMAD(TCGA_BRCAdata, nmiR, nmR)
```

GroundT   *Confirmed interactions in miR-Tarbase 6.1, Tarbase 7.0 and miRWalk*
                            2.0

Description

File containing a `list` containing the experimentally confirmed miRNA-mRNA interactions from the databases described above.

Usage

```
GroundT
```

Format

A `list` where each element has the following structure:

- `name` mRNA name.
- `data` names of miRNAs whose interactions with the mRNA can be founded in at least one of the databases described above.

References

Chou, C.-H.; Chang, N.-W.; Shrestha, S.; Hsu, S.-D.; Lin, Y.-L.; Lee, W.-H.; Yang, C.-D.; Hong, H.-C.; Wei, T.-Y.; Tu, S.-J. & others miRTarBase 2016: updates to the experimentally validated miRNA-target interactions database Nucleic acids research, Oxford University Press , 2015, 44, D239-D247

Vlachos, I. S.; Paraskevopoulou, M. D.; Karagkouni, D.; Georgakilas, G.; Vergoulis, T.; Kanellos, I.; Anastasopoulos, I.-L.; Maniou, S.; Karathanou, K.; Kalfakakou, D. & others DIANA-TarBase v7. 0: indexing more than half a million experimentally supported miRNA: mRNA interactions Nucleic acids research, Oxford University Press, 2014, 43, D153-D159

Dweep, H.and Gretz, N. miRWalk2. 0: a comprehensive atlas of microRNA-target interactions Nature methods, Nature Publishing Group, 2015, 12, 697

InterList.toMatrix   *InterList.toMatrix*

Description

Given a `list` of mRNAs containing the set of their inferred parents (the output of [Extract.Parents](#)), it returns a `matrix` with the miRNA-mRNA interactions. Each row represents an interaction. The first column contains miRNAs. The second column contains mRNAs

Usage

```
InterList.toMatrix(miRNAsList)
```

Arguments

miRNAsList   A `list` where each element has the following structure:

- `name`: mRNA name.
- `data`: Names of the miRNAs inferred as parents by PTC.

Value

A matrix with 2 columns containing the miRNA-mRNA interactions.

Examples

```
## Not run:
data(TCGA_BRCAdata)
data(TScan)
seqData<-PTC.ptime(TCGA_BRCAdata,TCGA_BRCAdata$mRNAs[,"VIM"])
SelData<-PTC.GeneSel(seqData, topk_miR = 30, topk_mR = 1500)
PParents<-PTC.findPP(TScan, miRs=SelData$miRs, mRs="SORCS1")
temp <-SelData$PParents[["SORCS1"]]
SORCS1.X.TScan=SelData$d[,temp]
SORCS1.Parents<-PTC.TestInvariance(Y=SelData$d[,"SORCS1"], X=SORCS1.X.TScan)
SORCS1.Parents<-Extract.Parents(SORCS1.Parents,SelData$PParents[["SORCS1"]])
SORCS1.relMatrix<-na.omit(InterList.toMatrix(SORCS1.Parents$Plist$Names))

## End(Not run)
```

PTC   *PTC*

Description

PTC estimates the causal parents of a set of `nmR` mRNAs, given a set of `nmiR` predictors (miRNAs). This estimation assumes a linear model

$$Y_t = \beta X_t + \epsilon$$

With Y_t, X_t the sequential data of a target and predictors respectively, and ϵ independent and identically distributed errors for the n time points in the time series. Y_t, X_t are the sequential data obtained after a pseudotime analysis.

Usage

```
PTC(miRNAs, mRNAs, VIM, nmiR=30, nmR=1500 , ngrid=2, alpha=0.02, complements = TRUE
, explore.all=TRUE, silent=TRUE)
```

Arguments

miRNAs   A matrix containing gene expression data of miRNAs. A total of `nmiR` miRNAs from this matrix are selected to be used as predictors candidates. Columns represent miRNAs, rows represent samples.

mRNAs   A `matrix` containing gene expression data from mRNAs. A total of `nmR` mRNAs from this matrix are selected to be used as response variables. Columns represent mRNAs, rows represent samples.

VIM	VIM expression to be used for calculating VIM_Time.
nmiR	Number of miRNAs to be selected as predictor candidates.
nmR	Number of mRNAs to be selected as target variables.
ngrid	Number of segments of the time series data used for creating the different enviroments required for the statistical test. ngrid=2 by default.
alpha	Significance level for the statistical test. alpha=0.2 by default.
complements	If TRUE (default), each environment is compared against its complement. If FALSE all environments are compared pairwise.
explore.all	If TRUE(default), PTC explores all combinations of predictors and returns the union set of all combinations that does not violate the invariance property. If FALSE PTC returns the first set that does not violate the invariance property. Exploration is made starting from the set of all predictors and reducing the size of the set by one predictor at a time.
silent	If TRUE (default), PTC displays the currently evaluated set. If FALSE, PTC only displays the number of sets to be explored in the current iteration.

Value

A list consisting of the following elements:

PList A list of three elements:

- Index: A list. For each target gene with at least one parent. The index of the parents.
- names: For each target gene with at least one parent. The names of the parents.
- genes: The names of all target genes with at least one parent.

Summary A matrix representing miRNA-mRNA regulatory interactions inferred by PTC. The columns of the matrix are:

1. rank: Rank of the inferred interaction
2. miR: Names of miRNA (Parent)
3. mR: Names of mRNA (Child)
4. Score: Score as calculated by PTC.RankByContext

Author(s)

Andres Mauricio Cifuentes_Bernal, Vu VH Pham, Xiaomei Li, Lin Liu, JiuyongLi and Thuc Duy Le

See Also

PTC.ptime, PTC.GeneSel, PTC.TestInvariance.

Examples

```
## Not run:
   data(TCGA_BRCAdata)
   test1<-PTC(miRNAs=TCGA_BRCAdata$miRs, mRNAs=TCGA_BRCAdata$mRNAs
         , VIM=TCGA_BRCAdata$mRNAs[,"VIM"])

## End(Not run)
```

PTC.ConfirmedInTopK   *This fuction finds the number of confirmed interactions, given a matrix of interacions miR-mR, and a Ground Truth*

Description

This fuction finds the number of confirmed interactions, given a matrix of interacions miR-mR, and a Ground Truth

Usage

```
PTC.ConfirmedInTopK(
  GT,
  relationshipsM,
  topK,
  GT_miR_EMT = NULL,
  GT_mR_EMT = NULL
)
```

Arguments

GT: a list where each element has name=gene, data= confirmed miRs able to bind that gene

relationshipsM:
                        A matrix [n,2]

topK: a vector including all topK

Value

A matrix [n,3], where the additional column has a score calculated as the mean of all context score of each miR-mR pair

---

PTC.findPP   *PTC.findPP*

Description

For each mRNA, creates a set of miRNAs (plausible parents) that can biologically target that mRNA. A total of `nmiR` miRNAs and `nmR` mRNAs with the largest gene expression Median Absolute Deviation (MAD) are selected as predictor candidates and target mRNAs respectively.
The set of plausible parents of each gene is a subset of the predictor candidates and contains those miRNA that can bind the gene as predicted by TargetScan 7.0. miRNAs names are converted to `miRBase v.21` during selection process.

Usage

```
PTC.findPP(TScan, miRs, mRs)
```

Arguments

TScan   A `matrix` containing miRNA-mRNA interactions predicted by TargetScan 7.0. The first and second columns contain miRNAs names from miRBase versions 18 and 17 respectively. The third column contains the names of the target mRNAs.

miRs   A vector containing the names of miRNAs to be verified. These names corresponds to the names of predictor candidates.

mRs   A vector containing the names of mRNAs to be verified. These names corresponds to the names of target genes (response variables).

Value

A list containing the set of miRNAs that can bind each target mRNA:

See Also

PTC,PTC.GeneSel, TScan

Examples

```
## Not run:
data(TCGA_BRCAdata)
data(TScan)
seqData<-PTC.ptime(TCGA_BRCAdata,TCGA_BRCAdata$mRNAs[,"VIM"])
SelData<-PTC.GeneSel(seqData, topk_miR = 30, topk_mR = 1500)
PParents<-PTC.findPP(TScan, miRs=SelData$miRs, mRs=SelData$mRs)

## End(Not run)
```

PTC.GeneSel   *PTC.GeneSel*

Description

Creates a set of miRNAs (plausible parents) for each mRNA among `nmR` mRNAs that can biologically target that mRNA. A total of `nmiR` miRNAs and `nmR` mRNAs with the largest gene expression Median Absolute Deviation (MAD) are selected as predictor candidates and target mRNAs respectively.
The set of plausible parents of each gene is a subset of the predictor candidates and contains those miRNA that can bind the gene as predicted by TargetScan 7.0. miRNAs names are converted to `miRBase v.21` during selection process

Usage

```
PTC.GeneSel(seqData, nmiR = 30, nmR = 1500)
```

Arguments

seqData   A list with two elements:

- A matrix with miRNAs gene expression.
- A matrix with mRNAs gene expression.

Columns represent miRNAs/mRNAs and rows represent time samples. Columns names must correspond to miRNAs/mRNAs names.

nmiR   Number of miRNAs to be selected as predictor candidates.

nmR   Number of mRNAs to be selected as target variables.

Value

A list containing four elements:

miRs   nmiR miRNAs names (version `miRBase v.21`) selected by MAD

mRs   nmR mRNAs names selected by MAD

d   A matrix with `nmiR + nmR` columns, containing miRNAs:mRNAs gene expression. Columns [1 : nmiR] correspond to miRNAs data. Columns [nmiR+1 : nmiR+nmR]

correspond to mRNAs data. Rows correspond to samples.

PParents   A list containing the set of miRNAs to be used as predictors (plausible parents) of each mRNA. This set contains the miRNAs among the predictor candidates that can bind the target gene as predicted by TargetScan 7.0

See Also

PTC, getDatabyMAD, miRNAVersionConvert, PTC.findPP

Examples

```
## Not run:
seqData<-PTC.ptime(TCGA_BRCAdata,TCGA_BRCAdata$mRNAs[,"VIM"])
SelData<-PTC.GeneSel(seqData, nmiR = 30, nmR = 1500)

## End(Not run)
```

PTC.miRv21   *PTC.miRv21*

Description

Takes a vector containing miRNAs names and returns the `miRBase v.21` version of them.

Usage

```
PTC.miRv21(miRs)
```

Arguments

miRs   miRNAs names to be changed to version `miRBase v.21`

Value

nmiR A vector with the miRNAs names (version `miRBase v.21`)

See Also

[PTC](), [miRNAVersionConvert](), [PTC.GeneSel]()

Examples

```
## Not run:
data(TCGA_BRCAdata)
miRnamesv21<-PTC.miRv21(colnames(TCGA_BRCAdata$miRs))

## End(Not run)
```

PTC.ptime	*PTC.ptime*

Description

Orders the gene expression by VIM_Time order. miRNAs names are changed to `miRBase v.21`

Usage

```
PTC.ptime(matchedData, VIM)
```

Arguments

matchedData	A List with two matrices. miRNA gene expressions (1st element) and mRNA gene expressions (2nd element). Columns represent miRNAs and rows represent samples.
VIM	VIM expression to be used for calculating VIM_Time.

Value

Pseudotime ordered matched data.

See Also

[PTC]()

Examples

```
## Not run:
  data(TCGA_BRCAdata)
  Time_series<-PTC.ptime(TCGA_BRCAdata, TCGA_BRCAdata$mRNAs[,"VIM"])

## End(Not run)
```

PTC.RankByContext   *PTC.RankByTScontext*

Description

This fuction uses TS70 Conserved_Site_Context_Scores (from http://www.targetscan.org/cgi-bin/targetscan/data_download.cgi?db=vert_70 to rank a matrix of inferred miRNA-mRNA relationships.

Usage

```
PTC.RankByContext(TS70context, relationshipsM)
```

Arguments

TS70context: A `matrix` containing conserved site context++ scores. The headers of the matrix from TargetScan must be conserved when the file is imported into R.

relationshipsM:
                  A matrix with two columns containing miRNAs and mRNAs names. First column represents miRNAs and second column mRNAs (e.g the output of [InterList.toMatrix](#)).

Value

A relationship matrix with four columns [Rank, miRNA, mRNA, Score]. The more negative the score, the best the rank of the corresponding miRNA-mRNA pair.

See Also

[PTC](#)

Examples

```
## Not run:
data(TCGA_BRCAdata)
data(TScan)
data(TS7.0_Conserved_Site_Context_Scores)
seqData<-PTC.ptime(TCGA_BRCAdata,TCGA_BRCAdata$mRNAs[,"VIM"])
SelData<-PTC.GeneSel(seqData, topk_miR = 30, topk_mR = 1500)
PParents<-PTC.findPP(TScan, miRs=SelData$miRs, mRs="SORCS1")
temp <-SelData$PParents[["SORCS1"]]
SORCS1.X.TScan=SelData$d[,temp]
SORCS1.Parents<-PTC.TestInvariance(Y=SelData$d[,"SORCS1"], X=SORCS1.X.TScan)
SORCS1.Parents<-Extract.Parents(SORCS1.Parents,SelData$PParents[["SORCS1"]])
SORCS1.relMatrix<-na.omit(InterList.toMatrix(SORCS1.Parents$Plist$Names))
SORCS1.Summary<-PTC.RankByContext(TS7.0_Conserved_Site_Context_Scores
                               ,SORCS1.relMatrix)

## End(Not run)
```

PTC.TestInvariance   *PTC.TestInvariance*

Description

Finds a set of miRNAs (predictors) that are causal parents of a target gene. This set is defined as the union of sets that are invariant. Invariance is determined by using the decoupled test from [seqICP]seqICP.s.

Usage

```
PTC.TestInvariance(
  Y,
  X,
  ngrid = 2,
  alpha = 0.02,
  explore.all = TRUE,
  silent = TRUE,
  complements = TRUE
)
```

Arguments

Y	[nx1] A vector containing the sequential gene expression of a target gene Y.
X	[nxp] A matrix containing the sequential gene expression of p plausible parents (miRNAs that can bind the target mRNA).
ngrid	Number of segments of the time series data used for creating the different enviroments required for the statistical test. ngrid=2 by default.
alpha	Significance level for the statistical test. alpha=0.2 by default.
explore.all	If TRUE(default), PTC explores all combinations of predictors and returns the union set of all combinations that does not violate the invariance property. If FALSE PTC returns the first set that does not violate the invariance property. Exploration is made starting from the set of all predictors and reducing the size of the set by one predictor at a time.
silent	If TRUE (default), PTC displays the currently evaluated set. If FALSE, PTC only displays the number of sets to be explored in the current iteration.
complements	If TRUE (default), each environment is compared against its complement. If FALSE all environments are compared pairwise.

Value

Parents	A set containing the indexes of the parents inferred by PTC. These indexes correspond to the indexes of the miRNAs in the set of Plausible Parents. The Plausible Parents are the miRNAs obtained from PTC.GeneSel

See Also

PTC, seqICP.s

Examples

```
## Not run:
data(TCGA_BRCAdata)
data(TScan)
seqData<-PTC.ptime(TCGA_BRCAdata,TCGA_BRCAdata$mRNAs[,"VIM"])
SelData<-PTC.GeneSel(seqData, topk_miR = 30, topk_mR = 1500)
PParents<-PTC.findPP(TScan, miRs=SelData$miRs, mRs="SORCS1")
temp <-SelData$PParents[["SORCS1"]]
SORCS1.X.TScan=SelData$d[,temp]
SORCS1.Parents<-PTC.TestInvariance(Y=SelData$d[,"SORCS1"], X=SORCS1.X.TScan)

## End(Not run)
```

SC_miRNAsdata   *Original miRNAs dataset from GSE114071*

Description

File containing miRNA normalized and log2 transformed gene expresion of 2822 miRNAs from 21 samples.

Usage

```
SC_miRNAsdata
```

Format

A `matrix` with 2822 rows and 23 columns. samples are represented in rows. Columns contains miRNAs names, description and samples

References

Wang, N., Zheng, J., Chen, Z. et al. "Single-cell microRNA-mRNA co-sequencing reveals non-genetic heterogeneity and mechanisms of microRNA regulation." Nat Commun 10, 95 (2019). https://doi.org/10.1038/s41467-018-07981-6

SC_mRNAsdata   *Original mRNAs dataset from GSE114071*

Description

File containing mRNA gene expresion of 23284 mRNAs from 22 samples.

Usage

```
SC_mRNAsdata
```

Format

A `matrix` with 23285 rows and 24 columns. samples are represented in rows (from row 2). Columns contains miRNAs names, description and samples

References

Wang, N., Zheng, J., Chen, Z. et al. "Single-cell microRNA-mRNA co-sequencing reveals non-genetic heterogeneity and mechanisms of microRNA regulation." Nat Commun 10, 95 (2019). https://doi.org/10.1038/s41467-018-07981-6

TCGA_BRCAdata   *miRNA-mRNA matched bulk data from TCGA BRCA project*

Description

File containing BRCA gene expresion matched data of 518 miRNAs and 17403 mRNAs from 503 samples.

Usage

```
TCGA_BRCAdata
```

Format

A `list` object with 2 elements: miRs and mRNAs

References

Pham, V., Zhang, J., Liu, L. et al. "Identifying miRNA-mRNA regulatory relationships in breast cancer with invariant causal prediction." BMC Bioinformatics 20, 143 (2019). https://doi.org/10.1186/s12859-019-2668-x

---

TS7.0_Conserved_Site_Context_Scores
                    TargetScan 7.0 Conserved Site Context Scores.

Description

File containing a `matrix` with the TargetScan 7.0 Context++ scores and contributions for all conserved miRNA sites, downloaded from http://www.targetscan.org/cgi-bin/targetscan/data_download.cgi?db=vert_70

Usage

```
TS7.0_Conserved_Site_Context_Scores
```

Format

A `matrix` with TargetScan 7.0 Conserved Site Context Scores data.

References

Agarwal, V.; Bell, G. W.; Nam, J.-W. & Bartel, D. P. Predicting effective microRNA target sites in mammalian mRNAs eLife, eLife Sciences Publications, Ltd, 2015, 4

TScan   *TargetScan 7.0*

Description

File containing a `matrix` with miRNAs and predicted targets from TargetScan Release 7.0

Usage

    TScan

Format

A `matrix` with 3 columns

- miRNAs names v18
- miRNAs names v17
- predicted target (mRNA)

References

Agarwal, V.; Bell, G. W.; Nam, J.-W. & Bartel, D. P. Predicting effective microRNA target sites in mammalian mRNAs eLife, eLife Sciences Publications, Ltd, 2015, 4

Index