Package ‘birta’

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Description Expression levels of mRNA molecules are regulated by different processes, comprising inhibition or activation by transcription factors and post-transcriptional degradation by microRNAs. birta (Bayesian Inference of Regulation of Transcriptional Activity) uses the regulatory networks of TFs and miRNAs together with mRNA and miRNA expression data to predict switches in regulatory activity between two conditions. A Bayesian network is used to model the regulatory structure and Markov-Chain-Monte-Carlo is applied to sample the activity states.
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birta-package

Joint Bayesian Inference of miRNA and Transcription Factor Activities

Description

Expression levels of mRNA molecules are regulated by different processes, comprising inhibition
or activation by transcription factors and post-transcriptional degradation by microRNAs. birta uses
the regulatory networks of TFs and miRNAs together with mRNA and miRNA expression data
to predict switches in regulatory activity between two conditions. A Bayesian network is used to
model the regulatory structure and Markov-Chain-Monte-Carlo is applied to sample the activity
states.

Details

Package: birta
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Author(s)

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References

B. Zacher, K. Abnaof, S. Gade, E. Younesi, A. Tresch, and H. Frohlich. Joint Bayesian Infer-
ence of Condition Specific miRNA and Transcription Factor Activities from Combined Gene and

birta

Main interface for Bayesian Inference of Regulation of Transcriptional
Activity.

Description

The function estimates parameterization of the model and then executes MCMC sampling to infer
activity states.
Usage

birta(dat.mRNA, dat.miRNA, TFexpr, limmamRNA=NULL, limmamiRNA=NULL, limmaTF=NULL, nrep=NULL, fdr.mRNA=0.05, ... run.pretest=FALSE, condition.specific.inference=TRUE, only_switches=FALSE, weightSampleMean=0, weightSampleVariance=0.01)

Arguments

dat.mRNA mRNA expression data (ExpressionSet or matrix). IMPORTANT: Replicates must be ordered according to nrep!
dat.miRNA miRNA expression data (ExpressionSet or matrix).
TFexpr TF expression data (ExpressionSet or matrix).
limmamRNA Output of limma analysis for mRNA data (list: pvalue.tab, lm.fit).
limmamiRNA Output of limma analysis for miRNA data (list: pvalue.tab, lm.fit).
limmaTF Output of limma analysis for TF expression data (list: pvalue.tab, lm.fit).
nrep Vector containing four integers. Entry 1 and 2 are the number of miRNA measurement replicates for condition 1 and 2. Entry 3 and 4 are the number of mRNA measurement replicates for condition 1 and 2.
fdr.mRNA False discovery rate (FDR) cutoff for significance of the logFC for mRNA data.
fdr.miRNA False discovery rate (FDR) cutoff for significance of the logFC for miRNA data.
lfc.mRNA Additional logFC cutoff for significance in mRNA data.
lfc.miRNA Additional logFC cutoff for significance in miRNA data.
genesets Combined TF / miRNA network. IMPORTANT: Names of TF entries must start with V$.
lambda Regularization parameter for edge weights.
sample.weights Should edge weights be adapted during sampling?
one.regulator.weight Should weights of all edges for a regulator to be the same?
theta_TF Expected fraction of active TFs.
theta_miRNA Expected fraction of active miRNAs.
model Type of model. One out of c("all-plug-in", "weight-plug-in", "no-plug-in").
niter Number of MCMC iterations (AFTER burnin).
nburnin Number of MCMC iterations UNTIL burnin is assumed to be finished.
potential_swaps Pre-computed potential swaps (OPTIONAL, see get_potential_swaps).
run.pretest Initialize miRNA and TF states via the result of a hypergeometric test in order to improve convergence (should be taken with care; advise: only use it in case of observed convergence problems!).
condition.specific.inference Should inference on TF / miRNA activities be made only RELATIVE to a reference condition or independently in both conditions?
thin Thinning of Markov chain: only use every thin’s sample for posterior computation.
only_switches Should only switches be performed?
weightSampleMean Mean for normal distribution used for sampling the omegas.
weightSampleVariance Variance for normal distribution used for sampling the omegas.
The function returns a list containing the following entries:

- **miRNAstates1**: Probability of each miRNA to be active in condition 1 (only for condition specific sampling).
- **miRNAstates2**: Probability of each miRNA to be active in condition 2 (only for condition specific sampling).
- **miRNAActivitySwitch**: Probability of each miRNA switching its activities (non-condition specific sampling).
- **TFstates1**: Probability of each TF to be active in condition 1 (only for condition specific sampling).
- **TFstates2**: Probability of each TF to be active in condition 2 (only for condition specific sampling).
- **miRNAactivitySwitch**: Probability of each TF switching its activities (non-condition specific sampling).
- **log_lik_trace**: Log-likelihood trace of MCMC sampling.
- **TFomega**: Weights of TF-target graph. (effect of a TF on its targets)
- **miRNAomega**: Weights of miRNA-target graph. (effect of a miRNA on its targets)
- **genesetsTF**: TF-target network. This might be different from the network submitted to the function, due to incompatibilities of network and experimental measurements. Check your warnings and command line output!
- **genesetsmiRNA**: miRNA-target network. This might be different from the network submitted to the function, due to incompatibilities of network and experimental measurements. Check your warnings and command line output!
- **mRNAexpr**: mRNA expression data. This might be different from the matrix submitted to the function, due to incompatibilities of network and experimental measurements. Check your warnings and command line output!
- **miRNAexpr**: miRNA expression data. This might be different from the matrix submitted to the function, due to incompatibilities of network and experimental measurements. Check your warnings and command line output!
- **TFexpr**: TF expression data (only if they are specifically included). This might be different from the matrix submitted to the function, due to incompatibilities of network and experimental measurements. Check your warnings and command line output!

**Author(s)**

Holger Frohlich, Benedikt Zacher

**Examples**

data(humanSim)
design = model.matrix(~0+factor(c(rep("control", 5), rep("treated", 5))))
colnames(design) = c("control", "treated")
contrasts = "treated - control"
limmamRNA = limmaAnalysis(sim$dat.mRNA, design, contrasts)
limmamiRNA = limmaAnalysis(sim$dat.miRNA, design, contrasts)
sim_result = birta(sim$dat.mRNA, sim$dat.miRNA, limmamRNA=limmamRNA,
                   limmamiRNA=limmamiRNA, nrep=c(5,5,5,5), genesets=genesets,
                   ...
Methods for Function `birta` in Package `birta`

**Description**

Generic methods for function `birta` in package `birta`. The expression data can be stored in a matrix or an ExpressionSet.

**Methods**

The following signatures make sure, that the arguments, storing the expression data are in the correct format.

- `signature(dat.mRNA = "ExpressionSet", dat.miRNA = "ExpressionSet", TFexpr = "ExpressionSet")`
- `signature(dat.mRNA = "ExpressionSet", dat.miRNA = "missing", TFexpr = "ExpressionSet")`
- `signature(dat.mRNA = "ExpressionSet", dat.miRNA = "missing", TFexpr = "missing")`
- `signature(dat.mRNA = "matrix", dat.miRNA = "matrix", TFexpr = "matrix")`
- `signature(dat.mRNA = "matrix", dat.miRNA = "missing", TFexpr = "matrix")`
- `signature(dat.mRNA = "matrix", dat.miRNA = "missing", TFexpr = "missing")`  

**EColiNetwork**

Example TF-target graph from Regulon DB.

**Description**

This list contains the TF-target graph used in the vignette.

**Usage**

`EColiNetwork`

**Format**

A list containing the target gene sets of 160 TFs.

**Source**

This TF-target graph was taken from (R. Castelo and A. Roverato, 2009). It is a pre-filtered version of RegulonDB 6.1.

**References**

**EColiOxygen**  
*Example data set from E. Coli to sample TF activities.*

**Description**  
This data set gives expression values for three experiments of the E. Coli K12 strain under aerobic and three experiments under aerobic growth. It is used in the vignette to illustrate application of birta to TFs only.

**Usage**  
EColiOxygen

**Format**  
ExpressionSet

**Source**  
The original data comes from (Covert et al., 2004) The normalized data set used here is taken from the qpgraph package by R. Castelo and A. Roverato.

**References**  

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**genesets**  
*TF-target and miRNA-target networks for simulated example.*

**Description**  
For miRNAs we looked at target predictions in human via miRanda (Betel et al., 2008), miRBase (Griffiths-Jones et al., 2008) and miRDB (Wang and Naqa, 2008). Experimentally confirmed targets were retrieved from Tarbase (Papadopoulos et al., 2009). As trustworthy miRNA targets we considered those, which were either experimentally confirmed (i.e. listed in Tarbase) or predicted by at least two of the other three methods. In conclusion we arrived at a network with 583 miRNAs regulating between 1 and 1628 genes (median: 302). A TF-target gene network was compiled by computing TF binding affinities to promoter sequences of all human genes according to the TRAP model (Roiderer et al., 2007) via the author’s R implementation. Upstream sequences of genes were retrieved here from the ENSEMBL database via biomaRt (Haider et al., 2009). We assumed that promoter sequences were located in the range 0 - 2Kbp upstream to the transcription start site of a gene. As trustworthy TF targets we considered those, for which a Holm corrected affinity p-value smaller than 0.001 was reported. In conclusion we arrived at a network with 272 TFs regulating between 1 and 16517 genes (median: 20).

**Usage**  
genesets
get_potential_swaps

Format

A list containing a TF- and miRNA-target graph.

Source

The networks were generated using the TRAP model on TRANSFAC matrices and miRNA-target annotations form different databases.

References


get_potential_swaps  Calculate swap partner for TF-/miRNA-target graph.

Description

Calculates for TF-/miRNA-target graph all potential swap partner.

Usage

get_potential_swaps(genesetsTF=NULL, genesetsmiRNA=NULL, perc.overlap.cutoff = 0.8, integer.id=TRUE, verbose=TRUE)

Arguments

genesetsTF Each entry corresponds to a TF and contains its target genes.

genesetsmiRNA Each entry corresponds to a miRNA and contains its target genes.

perc.overlap.cutoff Percentage cutoff of minimal overlap between two miRNAs or TFs to be possible swap partner.

integer.id If TRUE, the swap partner are not outputted as characters, but as integer indices.

verbose print process or not.

Value

The function returns a list, with the following entries:

T_potential_swaps Contains for each TF all potential swap partner.

S_potential_swaps Contains for each miRNA all potential swap partner.
limmaAnalysis

Perform a limma analysis on expression data.

Description

Needed for the parameterization of the model as well as the Fisher (pre-)test.

Usage

limmaAnalysis(dat, design, contrasts)

Arguments

dat  A matrix or ExpressionSet containing the expression values.
design  A design matrix.
contrasts  Contrast for the linear model.

Value

Returns a list containing the following entries:

pvalue.tab  Containing the result of the topTable function from limma.
lm.fit  Linear fit to the model.
design  The design used.
contrast  The contrasts used.

Author(s)

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References


See Also

lmFit, topTable
Examples

```r
data(humanSim)
design = model.matrix(~0+factor(c(rep("control", 5), rep("treated", 5))))
colnames(design) = c("control", "treated")
contrasts = "treated - control"
limmamRNA = limmaAnalysis(sim$dat.mRNA, design, contrasts)
```

Description

Generic methods for function `limmaAnalysis` in package `birta`. The expression data can be stored in a matrix or an ExpressionSet.

Methods

- `signature(dat = "ExpressionSet", design = "matrix", contrasts = "character")`  Generic function for objects of class ExpressionSet.
- `signature(dat = "matrix", design = "matrix", contrasts = "character")`  Generic function for objects of class matrix.

plotConvergence

Plotting the likelihood along MCMC sampling.

Description

Plots the log likelihood along MCMC sampling.

Usage

```r
plotConvergence(res, nburnin=NULL, title="")
```

Arguments

- `res`  The result from `birta.run` (a list).
- `nburnin`  Number of iterations used for the burn in.
- `title`  Optional title of the plot.

Author(s)

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See Also

`birta`
Examples

data(humanSim)
data(humanSim)
design = model.matrix(~0+factor(c(rep("control", 5), rep("treated", 5))))
colnames(design) = c("control", "treated")
contrasts = "treated - control"
limmamRNA = limmaAnalysis(sim$dat.mRNA, design, contrasts)
limmamiRNA = limmaAnalysis(sim$dat.miRNA, design, contrasts)
sim_result = birta(sim$dat.mRNA, sim$dat.miRNA, limmamRNA=limmamRNA,
   limmamiRNA=limmamiRNA, nrep=c(5,5,5,5), genesets=genesets,
   model="all-plug-in", niter=50000, nburnin=10000,
   sample.weights=FALSE, potential_swaps=potential_swaps)
plotConvergence(sim_result, nburnin=10000, title="simulation")

---

potential_swaps  Potential swap moves for TF-target and miRNA-target networks (see genestes data set).

Description

Potential swap moves for TF-target and miRNA-target networks (see genestes data set) used for the simulation in the vignette.

Usage

potential_swaps

Format

A list containing potential swap moves for the TF- and miRNA-target graph used in the simulation.

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sim  Simulated expression data for mRNAs and miRNAs.

Description

This data set contains simulated expression values of miRNAs and mRNAs, together with the associated TF- and miRNA-target networks.

Usage

sim

Format

A list containing the entries dat.mRNA (mRNA expression), dat.miRNA (miRNA expression), miRNAstates (activity states of miRNAs), TFstates (activity states of TFs, TRANSFAC), genesetsmiRNA (miRNA-target graph, targetScan), genesetsTFs (TF-target graph).
Source

Simulation (see reference for details).

References


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| TFexpr | Transcription factor expression values for the aerobic-anaerobic growth experiment. |

Description

This data set gives expression values for the 160 TF of the TF-target graph EColiNetwork used in the vignette.

Usage

TFexpr

Format

ExpressionSet. Rownames in the assayData correspond to entries in TF-target graph.

Source

See EColiOxygen and EColiNetwork (see reference for details).

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