Package ‘TargetScore’

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Type Package
Title TargetScore: Infer microRNA targets using microRNA-overexpression data and sequence information
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Author Yue Li
Maintainer Yue Li <yueli@cs.toronto.edu>
Description Infer the posterior distributions of microRNA targets by probabilistically modelling the likelihood microRNA-overexpression fold-changes and sequence-based scores. Variational Bayesian Gaussian mixture model (VB-GMM) is applied to log fold-changes and sequence scores to obtain the posteriors of latent variable being the miRNA targets. The final targetScore is computed as the sigmoid-transformed fold-change weighted by the averaged posteriors of target components over all of the features.
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TargetScore-package .................................................. 2
bsxfun.se ................................................................. 3
dot.ext ................................................................. 4
getTargetScores ....................................................... 5
initialization ............................................................ 6
logmvgamma ............................................................. 7
logsumexp ............................................................... 8
sort_components ....................................................... 9
targetScore ........................................................... 9
Description

Infer the posterior distributions of microRNA targets by probabilistically modeling the likelihood microRNA-overexpression fold-changes and sequence-based scores. Variational Bayesian Gaussian mixture model (VB-GMM) is applied to log fold-changes and sequence scores to obtain the posteriors of latent variable being the miRNA targets. The final targetScore is computed as the sigmoid-transformed fold-change weighted by the averaged posteriors of target components over all of the features.

Details

Package: TargetScore
Type: Package
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The front-end main function `targetScore` should be used to obtain the probabilistic score of miRNA target. The workhorse function is `vbgmm`, which implementates multivariate variational Bayesian Gaussian mixture model.

Author(s)

Yue Li <yueli@cs.toronto.edu>

References


See Also

`targetScore`
Examples

library(TargetScore)
ls("package:TargetScore")

bsxfun.se

bsxfun with single expansion (real Matlab style) (Internal function)

Description

Depending on the dimension of x, repeat y in either by row or by column and apply element-wise operation defined by func.

Usage

bsxfun.se(func, x, y, expandByRow = TRUE)

Arguments

func  function with two or more input parameters.
x, y  two vectors, matrices, or arrays
expandByRow  expand by row or by column of x when nrow(x)==ncol(x)==length(y)

Details

The function is used by vbgmm.

Value

func(x,y)  A matrix of having the same dimension of x.

Note

Internal function.

Author(s)

Yue Li

See Also

bsxfun

Examples

bsxfun.se("*", matrix(c(1:10), nrow=2), matrix(c(1:5), nrow=5))
dot.ext

Elementwise dot product (modified dot function) (Internal function)

Description

Same as dot but handle single row matrix differently by multiplying each value but not sum them up

Usage

dot.ext(x, y, mydim)

Arguments

x numeric vector or matrix
y numeric vector or matrix
mydim Elementwise product (if 1); otherwise defined by dot

Details

Returns the 'dot' or 'scalar' product of vectors or columns of matrices. Two vectors must be of same length, two matrices must be of the same size. If x and y are column or row vectors, their dot product will be computed IF mydim is 1 (only difference from dot).

Value

A scalar or vector of length the number of columns of x and y.

Author(s)

Yue Li

See Also

dot

Examples

dot.ext(1:5, 1:5)
dot.ext(1:5, 1:5, 1)
**getTargetScores**  

*Compute targetScore of an overexpressed human microRNA*

**Description**

Obtain for each gene the targetScore using pre-computed (logFC) TargetScan context score and PCT as sequence score. TargetScanData package is needed.

**Usage**

```r
getTargetScores(mirID, logFC, ...)
```

**Arguments**

- `mirID`  
  A character string of microRNA ID (e.g., hsa-miR-1)

- `logFC`  
  N x D numeric vector or matrix of logFC with D replicates for N genes.

- `...`  
  Parameters passed to `vbgmm`

**Details**

This is a convenient function for computing targetScore for a human miRNA using user-supplied or pre-computed logFC and (if available) two pre-computed sequence scores namely TargetScan context score and PCT (probability of conserved targeting). The function also searches for any validated targets from the MirTarBase human validated target list. The function requires TargetScanData to be installed first.

**Value**

```r
targetScores  
numeric matrix of probabilistic targetScores together with the input variable and a binary vector indicating whether each gene is a validated target (if available).
```

**Author(s)**

Yue Li

**References**


**See Also**

`targetScore`
Examples

if(interactive()) {
  library(TargetScoreData)
  library(Biobase)
  library(GEOquery)

  # compute targetScore from pre-computed logFC and sequence scores
  # for hsa-miR-1
  mir1.score <- getTargetScores("hsa-miR-1", tol=1e-3, maxiter=200)

  # download fold-change data from GEO for hsa-miR-124 overexpression in HeLa
  gset <- getGEO("GSE2075", GSEMatrix =TRUE, AnnotGPL=TRUE)
  if (length(gset) > 1) idx <- grep("GPL1749", attr(gset, "names")) else idx <- 1
  gset <- gset[[idx]]
  sampleinfo <- as.character(pData(gset)$title)
  geneInfo <- fData(gset)

  # only 24h data are used (discard 12h data)
  logfc.mir124 <- as.matrix(exprs(gset)[, grep("HeLa transfected with miR-1 versus control transfected HeLa, 24 hours", sampleinfo)])
  rownames(logfc.mir124) <- geneInfo$'Gene symbol'
  mir124.score <- getTargetScores("hsa-miR-124", logfc.mir124, tol=1e-3, maxiter=200)

  head(mir124.score)
}

initialization

Initialization of latent variable assignments (responsibility) of the VB-GMM (Internal function)

Description

Initialize latent variables based on the number of components. The function is run before the VB-EM iteration in vbgmm.

Usage

initialization(X, init)

Arguments

X D x N numeric vector or matrix of observations
init Based on the dimension, init is expected to be one of the followings: scalar: number of components; vector: intial class labels; matrix: initialize with a D x K matrix for D variables and K components.
logmvgamma

Details
The function is expected to be used by vbgmm to initialize assignments of latent variables before VM-EM iterations.

Value
R  N by K matrix for N observations and K latent components (defined by init)

Author(s)
Yue Li

References

See Also
vbgmm

Examples
tmp <- initialization(matrix(c(rnorm(100,mean=2), rnorm(100,mean=3)),nrow=1), init=2)

logmvgamma  Logarithmic multivariate Gamma function (Internal function)

Description
Compute logarithm multivariate Gamma function.

Usage
logmvgamma(x, d)

Arguments
x  numeric vector or matrix
d  dimension

Details
Gamma_p(x) = pi^(p(p-1)/4) prod_(j=1)^p Gamma(x+(1-j)/2)
log Gamma_p(x) = p(p-1)/4 log pi + sum_(j=1)^p log log Gamma(x+(1-j)/2)

Value
Matrix of the same dimension as x.
logsumexp

Author(s)
Yue Li

References

See Also
lgamma

Examples
logmvgamma(matrix(c(1:5)), 2)

logsumexp(x, margin = 1)

Arguments
x numeric vector or matrix
margin dimension to apply summation

Value
numeric vector or matrix of the same columns or rows (depending on margin) as x

Author(s)
Yue Li

References

Examples
logsumexp(matrix(c(1:5)), 2)
sort_components

**Sort mixture components in increasing order of averaged means (Internal function)**

**Description**
Sort Gaussian mixture components with model parameters in increasing order of averaged means of d variables.

**Usage**
```
sort_components(model)
```

**Arguments**
- `model`: A list containing trained parameters of the Bayesian GMM (see Value section in vbgmm).

**Value**
VB-GMM model list in increasing order of averaged means.

**Author(s)**
Yue Li

**See Also**
vbgmm

**Examples**
```
tmp <- vbgmm(c(rnorm(100,mean=2), rnorm(100,mean=3)), tol=1e-3)
tmp$mu
```

targetScore

*Probabilistic score of genes being the targets of an overexpressed microRNA*

**Description**
Given the overexpression fold-change and sequence-scores (optional) of all of the genes, calculate for each gene the TargetScore as a probability of miRNA target.

**Usage**
```
targetScore(logFC, seqScores, ...)
```
Arguments

logFC numeric vector of log fold-changes of N genes in treatment (miRNA overexpression) vs control (mock).

seqScores N x D numeric vector or matrix of D sequence-scores for N genes. Each score vector is expected to be equal to or less than 0. The more negative the scores, the more likely the corresponding target.

Details

Given expression fold-change (due to miRNA transfection), we use a three-component VB-GMM to infer down-regulated targets accounting for genes with little or positive log fold-change (due to off-target effects (Khan et al., 2009). Otherwise, two-component VB-GMM is applied to unsigned sequence scores (seqScores). The parameters for the VB-GMM are optimized using Variational Bayesian Expectation-Maximization (VB-EM) algorithm. Presumably, the mixture component with the largest absolute means of observed negative fold-change or sequence score is associated with miRNA targets and denoted as “target component”. The other components correspond to the “background component”. It follows that inferring miRNA-mRNA interactions most likely explained by the observed data is equivalent to inferring the posterior distribution of the target component given the observed variables. The targetScore is computed as the sigmoid-transformed fold-change weighted by the averaged posteriors of target components over all of the features. Specifically, we define the targetScore as a composite probabilistic score of a gene being the target t of a miRNA:

$$\text{sigmoid}(-\text{logFC}) \cdot \frac{1}{K+1} \sum_{x \in \{x_f, x_1, ..., x_L\}} p(t | x),$$

where sigmoid(-logFC) = 1/(1 + exp(logFC)) and p(t | x) is the posterior of the first component computed by vbgmm.

Value

targetScore numeric vector of probabilistic targetScores for N genes

Author(s)

Yue Li

References


See Also

vbgmm
Examples

# A toy example:
# 10 down-reg, 1000 unchanged, 90 up-reg genes
# due to overexpressing a miRNA
trmt <- c(rnorm(10, mean=0.01), rnorm(1000, mean=1), rnorm(90, mean=2)) + 1e3
ctrl <- c(rnorm(1000, mean=1)) + 1e3
logFC <- log2(trmt) - log2(ctrl)

# 8 out of the 10 down-reg genes have prominent seq score A
seqScoreA <- c(rnorm(8, mean=-2), rnorm(1092, mean=0))

# 10 down-reg genes plus 10 more genes have prominent seq score B
seqScoreB <- c(rnorm(20, mean=-2), rnorm(1080, mean=0))
seqScores <- cbind(seqScoreA, seqScoreB)
p.targetScore <- targetScore(logFC, seqScores, tol=1e-3)

vbgmm

Variational Bayesian Gaussian mixture model (VB-GMM)

Description

Given a N x D matrix of N observations and D variables, compute VB-GMM via VB-EM.

Usage

vbgmm(data, init = 2, prior, tol = 1e-20, maxiter = 2000, mirprior = TRUE, expectedTargetFreq = 0.01, verbose = FALSE)

Arguments

data N x D numeric vector or matrix of N observations (rows) and D variables (columns)
init Based on the dimension, init is expected to be one of the followings: scalar: number of components; vector: initial class labels; matrix: initialize with a D x K matrix for D variables and K components.
prior A list containing the hyperparameters including alpha (Dirichlet), m (Gaussian mean), kappa (Gaussian variance), v (Wishart degree of freedom), M (Wishart precision matrix).
tol Threshold that defines termination/convergence of VB-EM when abs(L[t] - L[t-1]) / abs(L[t]) < tol
maxiter Scalar for maximum number of EM iterations
mirprior Boolean to indicate whether to use expectedTargetFreq to initialize alpha0 for the hyperparameters of Dirichlet.
expectedTargetFreq Expected target frequency within the gene population. By default, it is set to 0.01, which is consistent with the widely accepted prior knowledge that 200/20000 targets per miRNA.
verbose Boolean indicating whether to show progress in terms of lower bound (vbound) of VB-EM (default: FALSE)
**Details**

The function implements variation Bayesian multivariate GMM described in Bishop (2006). Please refer to the reference below for more details. This is the workhorse of `targetScore`. Alternatively, user can choose to apply this function to other problems other than miRNA target prediction.

**Value**

A list containing:

- `label`: a vector of maximum-a-posteriori (MAP) assignments of latent discrete values based on the posteriors of latent variables.
- `R`: N x D matrix of posteriors of latent variables
- `mu`: Gaussian means of the latent components
- `full.model`: A list containing posteriors R, logR, and the model parameters including alpha (Dirichlet), m (Gaussian mean), kappa (Gaussian variance), v (Wishart degree of freedom), M (Wishart precision matrix)
- `L`: A vector of variational lower bound at each EM iterations (should be strictly increasing)

**Author(s)**

Yue Li

**References**


**See Also**

`targetScore`

**Examples**

```r
X <- c(rnorm(100,mean=2), rnorm(100,mean=3))
tmp <- vbgmm(X, tol=1e-3)
names(tmp)
```

---

**vbound**

**Variational Lower Bound Evaluation**

**Description**

Evaluate variational lower bound to determine when to stop VB-EM iteration (convergence).

**Usage**

`vbound(X, model, prior)`
vexp

Arguments

X  D x N numeric vector or matrix of N observations (columns) and D variables (rows)
model  List containing model parameters (see vbglm)
prior  numeric vector or matrix containing the hyperparameters for the prior distributions

Value
A continuous scalar indicating the lower bound (the higher the more converged)

Note
X is expected to be D x N for N observations (columns) and D variables (rows)

Author(s)
Yue Li

References

See Also
vbglm

Examples
X <- c(rnorm(100,mean=2), rnorm(100,mean=3))
tmp <- vbglm(X, tol=1e-3)
head(tmp$L) # lower bound should be strictly increasing
Arguments

X
D x N numeric vector or matrix of N observations (columns) and D variables (rows)

model
List containing model parameters (see `vbgmm`)

Value

model
A list containing the updated model parameters including alpha (Dirichlet), m (Gaussian mean), kappa (Gaussian variance), v (Wishart degree of freedom), M (Wishart precision matrix).

Note

X is expected to be D x N for N observations (columns) and D variables (rows)

Author(s)

Yue Li

References


See Also

`vbgmm`

Examples

```r
X <- c(rnorm(100, mean=2), rnorm(100, mean=3))
tmp <- vbgmm(X, tol=1e-3)
dim(tmp$R); head(tmp$R)
```
Arguments

- **X**: D x N numeric vector or matrix of N observations (columns) and D variables (rows)
- **model**: List containing model parameters (see `vbgmm`)
- **prior**: List containing the hyperparameters defining the prior distributions

Value

- **model**: A list containing the updated model parameters including alpha (Dirichlet), m (Gaussian mean), kappa (Gaussian variance), v (Wishart degree of freedom), M (Wishart precision matrix).

Note

- X is expected to be D x N for N observations (columns) and D variables (rows)

Author(s)

Yue Li

References


See Also

- `vbgmm`

Examples

```r
X <- c(rnorm(100,mean=2), rnorm(100,mean=3))
tmp <- vbgmm(X, tol=1e-3)
names(tmp$full.model)
```
Index

*Topic microRNA target prediction
  TargetScore-package, 2
*Topic package
  TargetScore-package, 2
*Topic
  TargetScore-package, 2
bsxfun, 3
bsxfun.se, 3
dot, 4
dot.ext, 4
getTargetScores, 5
initialization, 6
lgamma, 8
logmvgamma, 7
logsumexp, 8
sort_components, 9
TargetScore (TargetScore-package), 2
targetScore, 2, 5, 9, 12
TargetScore-package, 2
vbgmm, 2, 5, 7, 9, 10, 11, 13–15
vbound, 11, 12
vexp, 13
vmax, 14