Package 'HEM'

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Title Heterogeneous error model for identification of differentially expressed genes under multiple conditions

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Depends R (>= 2.1.0)

Imports Biobase, grDevices, stats, utils

Description This package fits heterogeneous error models for analysis of microarray data

License GPL (>= 2)

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`am.tran` *AM transformation for LPE*

Description

Computes AM for LPE

Author(s)

HyungJun Cho and Jae K. Lee

`am.tran.half` *AM transformation for LPE*

Description

Computes AM for LPE

Author(s)

HyungJun Cho and Jae K. Lee

base.ASE.Olig *Baseline ASE estimation for oligonucleotide arrays*

Description

Estimates baseline error for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

base.error.Olig *Baseline error estimation for oligonucleotide arrays*

Description

Estimates baseline error for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

base.error.Olig.quanOnly
Baseline error estimation for oligonucleotide arrays

Description

Estimates baseline error for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

base.PSE.Olig *Baseline PSE estimation for oligonucleotide arrays*

Description

Estimates baseline error for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

`boot.base.ASE.Olig` *Baseline error bootstrap estimation for oligonucleotide arrays*

Description

Estimates baseline error using bootstrap samples for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

`boot.base.error.Olig` *Baseline error bootstrap estimation for oligonucleotide arrays*

Description

Estimates baseline error using bootstrap samples for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

`boot.base.PSE.Olig` *Baseline error bootstrap estimation for oligonucleotide arrays*

Description

Estimates baseline error using bootstrap samples for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

`fixbound.predict.smooth.spline`
Prediction using smoothing spine

Description

Makes predictions using smoothing spine

Author(s)

HyungJun Cho and Jae K. Lee

hem *Heterogeneous Error Model for Identification of Differential Expressed Genes Under Multiple Conditions*

Description

Fits an error model with heterogeneous experimental and biological variances.

Usage

```
hem(dat, probe.ID=NULL, n.layer, design, burn.ins=1000, n.samples=3000,
    method.var.e="gam", method.var.b="gam", method.var.t="gam",
    var.e=NULL, var.b=NULL, var.t=NULL, var.g=1, var.c=1, var.r=1,
    alpha.e=3, beta.e=.1, alpha.b=3, beta.b=.1, alpha.t=3, beta.t=.2,
    n.digits=10, print.message.on.screen=TRUE)
```

Arguments

dat	data
probe.ID	a vector of probe set IDs
n.layer	number of layers; 1=one-layer EM, 2=two-layer EM
design	design matrix
burn.ins	number of burn-ins for MCMC
n.samples	number of samples for MCMC
method.var.e	prior specification method for experimental variance; "gam"=Gamma(alpha,beta), "peb"=parametric EB prior specification, "neb"=nonparametric EB prior specification
method.var.b	prior specification method for biological variance; "gam"=Gamma(alpha,beta), "peb"=parametric EB prior specification
method.var.t	prior specification method for total variance; "gam"=Gamma(alpha,beta), "peb"=parametric EB prior specification, "neb"=nonparametric EB prior specification
var.e	prior estimate matrix for experimental variance
var.b	prior estimate matrix for biological variance
var.t	prior estimate matrix for total variance
var.g	N(0, var.g); prior parameter for gene effect
var.c	N(0, var.c); prior parameter for condition effect
var.r	N(0, var.r); prior parameter for interaction effect of gene and condition
alpha.e, beta.e	Gamma(alpha.e,alpha.e); prior parameters for inverse of experimental variance
alpha.b, beta.b	Gamma(alpha.b,alpha.b); prior parameters for inverse of biological variance
alpha.t, beta.t	Gamma(alpha.b,alpha.b); prior parameters for inverse of total variance
n.digits	number of digits
print.message.on.screen	if TRUE, process status is shown on screen.

Value

n.gene	numer of genes
n.chip	number of chips
n.cond	number of conditions
design	design matrix
burn.ins	number of burn-ins for MCMC
n.samples	number of samples for MCMC
priors	prior parameters
m.mu	estimated mean expression intensity for each gene under each condition
m.x	estimated unobserved expression intensity for each combination of genes, conditions, and individuals (n.layer=2)
m.var.b	estimated biological variances (n.layer=2)
m.var.e	estimated experiemental variances (n.layer=2)
m.var.t	estimated total variances (n.layer=1)
H	H-scores

Author(s)

HyungJun Cho and Jae K. Lee

References

Cho, H. and Lee, J.K. (2004) Bayesian Hierarchical Error Model for Analysis of Gene Expression Data, Bioinformatics, 20: 2016-2025.

See Also

hem.eb.prior, hem.fdr

Examples

```
#Example 1: Two-layer HEM

data(pbrain)

##construct a design matrix
cond <- c(1,1,1,1,1,1,2,2,2,2,2,2) #condition
ind  <- c(1,1,2,2,3,3,1,1,2,2,3,3) #biological replicate
rep  <- c(1,2,1,2,1,2,1,2,1,2,1,2) #experimental replicate
design <- data.frame(cond,ind,rep)

##normalization
pbrain.nor <- hem.preproc(pbrain[,2:13])

##fit HEM with two layers of error
##using the small numbers of burn-ins and MCMC samples for a testing purpose;
```

```
##but increase the numbers for a practical purpose
#pbrain.hem <- hem(pbrain.nor, n.layer=2, design=design,
#                  burn.ins=10, n.samples=30)

##print H-scores
#pbrain.hem$H


#Example 2: One-layer HEM

data(mubcp)

##construct a design matrix
cond <- c(rep(1,6),rep(2,5),rep(3,5),rep(4,5),rep(5,5))
ind  <- c(1:6,rep((1:5),4))
design <- data.frame(cond,ind)

##construct a design matrix
mubcp.nor <- hem.preproc(mubcp)

#fit HEM with one layers of error
#using the small numbers of burn-ins and MCMC samples for a testing purpose;
#but increase the numbers for a practical purpose
#mubcp.hem <- hem(mubcp.nor, n.layer=1,design=design, burn.ins=10, n.samples=30)

##print H-scores
#mubcp.hem$H


###NOTE: Use 'hem.fdr' for FDR evaluation
###NOTE: Use 'hem.eb.prior' for Empirical Bayes (EB) prior sepecification
###NOTE: Use EB-HEM ('hem' after 'hem.eb.prior') for small data sets
```

---

hem.eb.prior *Empirical Bayes (EB) Prior Specification*

Description

Estimates experimental and biological variances by LPE and resampling

Usage

```
hem.eb.prior(dat,  n.layer, design,
             method.var.e="neb", method.var.b="peb", method.var.t="neb",
             rep=TRUE, baseline.var="LPE", p.remove=0, max.chip=4,
             q=0.01, B=25, n.digits=10, print.message.on.screen=TRUE)
```

Arguments

dat	data
n.layer	number of layers
design	design matrix
method.var.e	prior specification method for experimental variance; "peb"=parametric EB prior specification, "neb"=nonparametric EB prior specification
method.var.b	prior specification method for biological variance; "peb"=parametric EB prior specification
method.var.t	prior specification method for total variance; "peb"=parametric EB prior specification, "neb"=nonparametric EB prior specification
rep	no replication if FALSE
baseline.var	baseline variance estimation method: LPE for replicated data and BLPE, PSE, or ASE for unreplicated data
p.remove	percent of removed rank-variance genes for BLPE
max.chip	maximum number of chips to estimate errors
q	quantile for paritioning genes based on expression levels
B	number of iterations for resampling
n.digits	number of digits
print.message.on.screen	if TRUE, process status is shown on screen.

Value

var.b	prior estimate matrix for biological variances (n.layer=2)
var.e	prior estimate matrix for experiemtnal variances (n.layer=2)
var.t	prior estimate matrix for total variances (n.layer=1)

Author(s)

HyungJun Cho and Jae K. Lee

See Also

hem, hem.fdr

Examples

```
#Example 1: Two-layer HEM with EB prior specification

data(pbrain)

##construct a design matrix
cond <- c(1,1,1,1,1,1,2,2,2,2,2,2)
ind  <- c(1,1,2,2,3,3,1,1,2,2,3,3)
rep  <- c(1,2,1,2,1,2,1,2,1,2,1,2)
```

```
design <- data.frame(cond,ind,rep)

##normalization
pbrain.nor <- hem.preproc(pbrain[,2:13])

##take a subset for a testing purpose;
##use all genes for a practical purpose
pbrain.nor <- pbrain.nor[1:1000,]

##estimate hyperparameters of variances by LPE
#pbrain.eb  <- hem.eb.prior(pbrain.nor, n.layer=2,  design=design,
#                           method.var.e="neb", method.var.b="peb")

#fit HEM with two layers of error
#using the small numbers of burn-ins and MCMC samples for a testing purpose;
#but increase the numbers for a practical purpose
#pbrain.hem <- hem(pbrain.nor, n.layer=2,  design=design,burn.ins=10, n.samples=30,
#              method.var.e="neb", method.var.b="peb",
#              var.e=pbrain.eb$var.e, var.b=pbrain.eb$var.b)


#Example 2: One-layer HEM with EB prior specification

data(mubcp)

##construct a design matrix
cond <- c(rep(1,6),rep(2,5),rep(3,5),rep(4,5),rep(5,5))
ind  <- c(1:6,rep((1:5),4))
design <- data.frame(cond,ind)

##normalization
mubcp.nor <- hem.preproc(mubcp)

##take a subset for a testing purpose;
##use all genes for a practical purpose
mubcp.nor <- mubcp.nor[1:1000,]

##estimate hyperparameters of variances by LPE
#mubcp.eb  <- hem.eb.prior(mubcp.nor, n.layer=1, design=design,
#             method.var.t="neb")

#fit HEM with two layers of error
#using the small numbers of burn-ins and MCMC samples for a testing purpose;
#but increase the numbers for a practical purpose
#mubcp.hem <- hem(mubcp.nor, n.layer=1, design=design,  burn.ins=10, n.samples=30,
#             method.var.t="neb", var.t=mubcp.eb$var.t)
```

---

hem.fdr *FDR Evaluation*

Description

Computes resampling-based False Discovery Rate (FDR)

Usage

```
hem.fdr(dat, n.layer, design, rep=TRUE, hem.out, eb.out=NULL, n.iter=5, q.trim=0.9,
       target.fdr=c(0.001, 0.005, 0.01, 0.05, 0.1, 0.15, 0.20, 0.30, 0.40, 0.50),
        n.digits=10, print.message.on.screen=TRUE)
```

Arguments

dat	data
n.layer	number of layers: 1=one-layer EM; 2=two-layer EM
design	design matrix
rep	no replication if FALSE
hem.out	output from hem function
eb.out	output from hem.eb.prior function
n.iter	number of iterations
q.trim	quantile used for estimtaing the proportion of true negatives (pi0)
target.fdr	Target FDRs
n.digits	number of digits
print.message.on.screen	if TRUE, process status is shown on screen.

Value

fdr	H-values and corresponding FDRs
pi0	estimated proportion of true negatives
H.null	H-scores from null data
targets	given target FDRs, corrsponding critical values and numbers of significant genes are provided

Author(s)

HyungJun Cho and Jae K. Lee

See Also

hem.eb.prior hem

Examples

```
data(pbrain)

##construct a design matrix
cond <- c(1,1,1,1,1,1,2,2,2,2,2,2)
ind  <- c(1,1,2,2,3,3,1,1,2,2,3,3)
rep  <- c(1,2,1,2,1,2,1,2,1,2,1,2)
design <- data.frame(cond,ind,rep)

##normalization
pbrain.nor <- hem.preproc(pbrain[,2:13])

##take a subset for a testing purpose;
##use all genes for a practical purpose
pbrain.nor <- pbrain.nor[1:1000,]

##estimate hyperparameters of variances by LPE
#pbrain.eb  <- hem.eb.prior(pbrain.nor, n.layer=2,  design=design,
#                           method.var.e="neb", method.var.b="peb")

##fit HEM with two layers of error
##using the small numbers of burn-ins and MCMC samples for a testing purpose;
##but increase the numbers for a practical purpose
#pbrain.hem <- hem(pbrain.nor, n.layer=2,  design=design,burn.ins=10, n.samples=30,
#              method.var.e="neb", method.var.b="peb",
#              var.e=pbrain.eb$var.e, var.b=pbrain.eb$var.b)

##Estimate FDR based on resampling
#pbrain.fdr <- hem.fdr(pbrain.nor, n.layer=2,  design=design,
#                 hem.out=pbrain.hem, eb.out=pbrain.eb)
```

`hem.null.no` *Generation of null data*

Description

Generates null data by resampling

Author(s)

HyungJun Cho and Jae K. Lee

hem.null.one *Generation of null data*

Description

Generates null data by resampling

Author(s)

HyungJun Cho and Jae K. Lee

hem.null.two *Generation of null data*

Description

Generates null data by resampling

Author(s)

HyungJun Cho and Jae K. Lee

hem.preproc *Preprocessing*

Description

Performs IQR normalization, thesholding, and log2-transformation

Usage

```
hem.preproc(x, data.type = "MAS5")
```

Arguments

x	data
data.type	data type: MAS5 or MAS4

Author(s)

HyungJun Cho and Jae K. Lee

See Also

hem, hem.eb.prior, hem.fdr

Examples

```
data(pbrain)
pbrain.nor <- hem.preproc(pbrain[,2:13])
```

---

mubcp *Gene expression data for mouse B cell development*

Description

This data set consists of gene expression of the five consecutive stages (pre-B1, large pre-B2, small pre-B2, immature B, and mature B cells) of mouse B cell development. The data were obtained with high-density oligonucleotide arrays, Affymetrix Mu11k GeneChips, from flow-cytometrically purified cells.

Usage

```
data(mubcp)
```

Format

A matrix containing 13,207 probe sets and 26 chips; first 6 chips for pre-B1 cell and next 20 chips for other stages (5 chips for each)

Source

Hoffmann, R., Seidl, T., Neeb, M., Rolink, A. and Melchers, F. (2002). Changes in gene expression profiles in developing B cells of murine bone marrow, Genome Research 12:98-111.

---

nonpar.error.Olig *Baseline error nonparametric estimation for oligonucleotide arrays*

Description

Estimates baseline error for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

nonpar.no.error.Olig *Baseline error nonparametric estimation for oligonucleotide arrays*

Description

Estimates baseline error for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

nonpar.rep.error.Olig *Baseline error nonparametric estimation for oligonucleotide arrays*

Description

Estimates baseline error for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

par.error.Olig *Baseline error parametric estimation for oligonucleotide arrays*

Description

Estimates baseline error for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

par.no.error.Olig *Baseline error parametric estimation for oligonucleotide arrays*

Description

Estimates baseline error for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

par.rep.error.Olig *Baseline error parametric estimation for oligonucleotide arrays*

Description

Estimates baseline error for oligonucleotide arrays

Author(s)

HyungJun Cho and Jae K. Lee

pbrain *Gene expression data for primate brains*

Description

This data set consists of gene expression of primate brains (Affymetrix U95A GeneChip). The frozen brains of three humans (H1, H2, H3) and three chimpanzees (C1, C2, C3) were used to take the postmortem tissue samples, and two independent tissue samples for each individual were taken.

Usage

```
data(pbrain)
```

Format

A matrix containing 12,600 probe sets and 12 chips (H1,H1,H2,H2,H3,H3,C1,C1,C2,C2,C3,C3); the first column is probe set ID

Source

Enard, W., Khaitovich, P., Klose, J., Zollner, S., Heissig, F., Giavalisco, P., Nieselt-Struwe, K., Muchmore, E., Varki, A., Ravid, R., Doxiadis, G.M., Bontrop, R.R., and Paabo, S. (2002) Intra- and interspecific variation in primate gene expression patterns, Science 296:340-343

permut *Permutation*

Description

Permute

Author(s)

HyungJun Cho and Jae K. Lee

quant.norm *Quantile normalization*

Description

Performs quantile normalization

Author(s)

HyungJun Cho and Jae K. Lee

quant.normal *Normalization*

Description

Normalization

Author(s)

HyungJun Cho and Jae K. Lee

quant.normal2 *Normalization*

Description

Normalization

Author(s)

HyungJun Cho and Jae K. Lee

quant.normalize *Quantile normalization*

Description

Performs quantile normalization

Author(s)

HyungJun Cho and Jae K. Lee

`remove.sig.genes` *Remove significant genes*

Description

Remove significant genes

Author(s)

HyungJun Cho and Jae K. Lee

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