

Package ‘PLIS’

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Type Package

Title Multiplicity Control using Pooled LIS Statistic

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Description A multiple testing procedure for testing several groups of hypotheses is implemented. Linear dependency among the hypotheses within the same group is modeled by using hidden Markov Models. It is noted that a smaller p value does not necessarily imply more significance due to the dependency. A typical application is to analyze genome wide association studies datasets, where SNPs from the same chromosome are treated as a group and exhibit strong linear genomic dependency. See Wei Z, Sun W, Wang K, Hakonarson H (2009) <[doi:10.1093/bioinformatics/btp476](https://doi.org/10.1093/bioinformatics/btp476)> for more details.

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PLIS-package

PLIS

Description

PLIS is a multiple testing procedure for testing several groups of hypotheses. Linear dependency is expected from the hypotheses within the same group and is modeled by hidden Markov Models. It is noted that, for PLIS, a smaller p value does not necessarily imply more significance because of dependency among the hypotheses. A typical application of PLIS is to analyze genome wide association studies datasets, where SNPs from the same chromosome are treated as a group and exhibit strong linear genomic dependency.

Details

Package: PLIS
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main functions: em.hmm & plis

Author(s)

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References

Wei Z, Sun W, Wang K and Hakonarson H, Multiple Testing in Genome-Wide Association Studies via Hidden Markov Models, Bioinformatics, 2009

See Also

p.adjust(), in which the traditional procedures are implemented. The adjustment made by p.adjust will not change the original ranking based on the given p values. However, taking into account dependency, PLIS may generate a ranking different from that by p value.

bfffw.hmm

*backward and forward inferences***Description**

When $L > 1$, calculate values for backward, forward variables, probabilities of hidden states. A supporting function called by em.hmm.

Usage

```
bfffw.hmm(x, pii, A, pc, f0, f1)
```

Arguments

x	the observed Z values
pii	(prob. of being 0, prob. of being 1), the initial state distribution
A	$A=(a_{00} \ a_{01} \ \dots \ a_{10} \ a_{11})$, transition matrix
pc	(c[1], ..., c[L])—the probability weights in the mixture for each component
f0	(mu, sigma), the parameters for null distribution
f1	(mu[1], sigma[1] \ \dots \ \mu[L], sigma[L])—an L by 2 matrix, the parameter set for the non-null distribution

Details

calculates values for backward, forward variables, probabilities of hidden states,
 –the lfd variables and etc.
 –using the forward-backward procedure (Rabiner 89)
 –based on a sequence of observations for a given hidden markov model $M=(pii, A, f)$
 –see Sun and Cai (2009) for a detailed instruction on the coding of this algorithm

Value

alpha	rescaled backward variables
beta	rescaled forward variables
lfd	lfd variables
gamma	probabilities of hidden states
dgamma	rescaled transition variables
omega	rescaled weight variables

Author(s)

Wei Z, Sun W, Wang K and Hakonarson H

References

- Multiple Testing in Genome-Wide Association Studies via Hidden Markov Models, Bioinformatics, 2009
- Large-scale multiple testing under dependence, Sun W and Cai T (2009), JRSSB, 71, 393-424
- A Tutorial on Hidden Markov Models and Selected Applications in Speech Recognition, Rabiner L (1989), Proceedings of the IEEE, 77, 257-286.

 bwfw1.hmm

backward and forward inferences

Description

When $L=1$, calculate values for backward, forward variables, probabilities of hidden states. A supporting function called by em.hmm.

Usage

```
bwfw1.hmm(x, pii, A, f0, f1)
```

Arguments

x	the observed Z values
pii	(prob. of being 0, prob. of being 1), the initial state distribution
A	$A=(a_{00} \ a_{01} \ \dots \ a_{10} \ a_{11})$, transition matrix
f0	(mu, sigma), the parameters for null distribution
f1	(mu[1], sigma[1] \ \dots \ mu[L], sigma[L])—an L by 2 matrix, the parameter set for the non-null distribution

Details

- calculates values for backward, forward variables, probabilities of hidden states, —the lfd variables and etc.
- using the forward-backward procedure (Rabiner 89)
- based on a sequence of observations for a given hidden markov model $M=(pii, A, f)$
- see Sun and Cai (2009) for a detailed instruction on the coding of this algorithm

Value

alpha	rescaled backward variables
beta	rescaled forward variables
lfd	lfd variables
gamma	probabilities of hidden states
dgamma	rescaled transition variables
omega	rescaled weight variables

Author(s)

Wei Z, Sun W, Wang K and Hakonarson H

References

Multiple Testing in Genome-Wide Association Studies via Hidden Markov Models, Bioinformatics, 2009
 Large-scale multiple testing under dependence, Sun W and Cai T (2009), JRSSB, 71, 393-424
 A Tutorial on Hidden Markov Models and Selected Applications in Speech Recognition, Rabiner L (1989), Proceedings of the IEEE, 77, 257-286.

 em.hmm

EM algorithm for HMM to estimate LIS statistic

Description

em.hmm calculates the MLE for a HMM model with hidden states being 0/1. the distribution of observed Z values given state 0 is assumed to be normal and given state 1, is assumed to be a normal mixture with L components

Usage

```
em.hmm(x, L=2, maxiter = 1000, est.null = FALSE)
```

Arguments

x	the observed Z values
L	the number of components in the non-null mixture, default value=2
maxiter	the maximum number of iterations, default value=1000
est.null	logical. If FALSE (the default) set the null distribution as N(0,1), otherwise will estimate the null distribution.

Details

None.

Value

pii	the initial state distribution, pii=(prob. of being 0, prob. of being 1)
A	transition matrix, A=(a00 a01\ a10 a11)
f0	the null distribution
pc	probability weights of each component in the non-null mixture
f1	an L by 2 matrix, specifying the dist. of each component in the non-null mixture
LIS	the LIS statistics

ni	the number of iterations executed
logL	log likelihood
BIC	BIC score for the estimated model
converged	Logic, Convergence indicator of the EM procedure

Author(s)

Wei Z, Sun W, Wang K and Hakonarson H

References

Multiple Testing in Genome-Wide Association Studies via Hidden Markov Models, Bioinformatics, 2009

See Also

plis

Examples

```
##(1) Example for analyzing simulated data
grp1.nonNull.loci=c(21:30, 51:60); grp2.nonNull.loci=c(41:60)
grp1.theta<-grp2.theta<-rep(0,200)
grp1.theta[grp1.nonNull.loci]=2; grp2.theta[grp2.nonNull.loci]=2

grp1.zval=rnorm(n=length(grp1.theta),mean=grp1.theta)
grp2.zval=rnorm(n=length(grp2.theta),mean=grp2.theta)
##Group 1
#Use default L=2
grp1.L2rlts=em.hmm(grp1.zval)
#Use true value L=1
grp1.L1rlts=em.hmm(grp1.zval,L=1)
#Choose L by BIC criteria
grp1.Allrlts=sapply(1:3, function(k) em.hmm(grp1.zval,L=k))
BICs=c()
for(i in 1:3) {
  BICs=c(BICs,grp1.Allrlts[[i]]$BIC)
}
grp1.BICrlts=grp1.Allrlts[[which(BICs==max(BICs))]]

rank(grp1.BICrlts$LIS)[grp1.nonNull.loci]
rank(-abs(grp1.zval))[grp1.nonNull.loci]

##Group 2
grp2.Allrlts=sapply(1:3, function(k) em.hmm(grp2.zval,L=k))
BICs=c()
for(i in 1:3) {
  BICs=c(BICs,grp2.Allrlts[[i]]$BIC)
}
grp2.BICrlts=grp2.Allrlts[[which(BICs==max(BICs))]]
```

```

rank(grp2.BICrlts$LIS)[grp2.nonNull.loci]
rank(-abs(grp2.zval))[grp2.nonNull.loci]

##PLIS: control global FDR
states=plis(c(grp1.BICrlts$LIS,grp2.BICrlts$LIS),fdr=0.1,adjust=FALSE)$States
#0 accept; 1 reject under fdr level 0.1

##(2) Example for analyzing Genome-Wide Association Studies (GWAS) data
#Information in GWAS.SampleData can be obtained by using PLINK
#http://pngu.mgh.harvard.edu/~purcell/plink/

#not running
#please uncomment to run
#
#data(GWAS.SampleData)
#
#chr1.data=GWAS.SampleData[which(GWAS.SampleData[, "CHR"]==1),]
#chr6.data=GWAS.SampleData[which(GWAS.SampleData[, "CHR"]==6),]
#
##Make sure SNPs in the linear physical order
#chr1.data<-chr1.data[order(chr1.data[, "BP"]),]
#chr6.data<-chr6.data[order(chr6.data[, "BP"]),]
#
##convert p values by chi_sq test to z values; odds ratio (OR) is needed.
#chr1.zval<-rep(0, nrow(chr1.data))
#chr1.ors=(chr1.data[, "OR"]>1)
#chr1.zval[chr1.ors]<-qnorm(chr1.data[chr1.ors, "P"]/2, 0, 1, lower.tail=FALSE)
#chr1.zval[!chr1.ors]<-qnorm(chr1.data[!chr1.ors, "P"]/2, 0, 1, lower.tail=TRUE)
#chr1.L2rlts=em.hmm(chr1.zval)
#
#chr6.zval<-rep(0, nrow(chr6.data))
#chr6.ors=(chr6.data[, "OR"]>1)
#chr6.zval[chr6.ors]<-qnorm(chr6.data[chr6.ors, "P"]/2, 0, 1, lower.tail=FALSE)
#chr6.zval[!chr6.ors]<-qnorm(chr6.data[!chr6.ors, "P"]/2, 0, 1, lower.tail=TRUE)
#chr6.L2rlts=em.hmm(chr6.zval)
#
##Note that for analyzing a chromosome in real GWAS dataset, em.hmm can take as long as 10+ hrs
##L=2 or 3 is recommended for GWAS based on our experience
##em.hmm can be run in parallel for different chromosomes before applying the PLIS procedure
#plis.rlts=plis(c(chr1.L2rlts$LIS,chr6.L2rlts$LIS),fdr=0.01)
#all.Rlts=cbind(rbind(chr1.data,chr6.data), LIS=c(chr1.L2rlts$LIS,chr6.L2rlts$LIS),
#gFDR=plis.rlts$aLIS, fdr001state=plis.rlts$States)
#all.Rlts[order(all.Rlts[, "LIS"])[1:10],]

```

GWAS.SampleData

Sample GWAS Dataset

Description

Sample GWAS Dataset with 400 SNPs from Chromosome 1 and 6 (200 SNPs each).

Usage

```
data(GWAS.SampleData)
```

Format

A data frame with 400 observations on the following 6 variables.

CHR Chromosome ID

SNP rs Id

BP Physical Position

OR Odds Ratio

CHISQ 1 d.f. Chi Square test Statistic

P P value of 1 d.f. Chi Square test Statistic

Details

The required values (Odds ratio and P value) can be calculated by using PLINK

References

Supplementary Material of Multiple Testing in Genome-Wide Association Studies via Hidden Markov Models, Bioinformatics, 2009

Examples

```
data(GWAS.SampleData)
```

plis

A multiple testing procedure based on pooled LIS statistics

Description

It controls the global FDR for the pooled hypotheses from different groups

Usage

```
plis(lis, fdr = 0.001, adjust = TRUE)
```

Arguments

lis	pooled LIS statistics estimated from different groups
fdr	nominal fdr level you want to control
adjust	logical. If TRUE (the default), will calculate and return "adjusted" LIS value—the corresponding global FDR if using the LIS statistic as the significance cutoff. It may take hours if you have hundreds of thousands LISs to adjust.

Value

States state sequence indicating if the hypotheses should be rejected or not: 0 accepted
, 1 rejected
aLIS the corresponding global FDR if using the LIS statistic as the significance cutoff

Author(s)

Wei Z, Sun W, Wang K and Hakonarson H

References

Multiple Testing in Genome-Wide Association Studies via Hidden Markov Models, Bioinformatics, 2009

See Also

see em.hmm for examples

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