

Package ‘MetaDE’

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MetaDE-package	<i>MetaDE: Microarray meta-analysis for differentially expressed gene detection</i>
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Description

MetaDE package implements 12 major meta-analysis methods for differential expression analysis : Fisher (Rhodes, et al., 2002), Stouffer (Stouffer, 1949), adaptively weighted Fisher (AW) (Li and Tseng, 2011), minimum p-value (minP), maximum p-value (maxP), rth ordered p-value (rOP) (Song and Tseng, 2012), fixed effects model (FEM), random effects model (REM) (Choi, et al., 2003), rank product (rankProd) (Hong, et al., 2006), naive sum of ranks and naive product of ranks (Dreyfuss, et al., 2009). Detailed algorithms, pros and cons of different methods have been discussed in a recent review paper (Tseng, et al., 2012). In addition to selecting a meta-analysis method, two additional considerations are involved in the implementation: (1) Choice of test statistics: Different test statistics are available in the package for each type of outcome variable (e.g. t-statistic or moderated t-statistic for binary outcome, F-statistic for multi-class outcome, regression or correlation for continuous outcome and Cox proportional hazard model for survival outcome). Additionally, a minimum multi-class correlation (min-MCC) has been included for multi-class outcome to only capture concordant expression patterns that F-statistic often fails (Lu, et al., 2010); (2) One-sided test correction: When combining two-sided p-values for binary outcomes, DE genes with discordant DE direction may be identified and the results are difficult to interpret (e.g. up-regulation in one study but down-regulation in another study). One-sided test correction is helpful to guarantee identification of DE genes with concordant DE direction. For example, Pearson's correction has been proposed for Fisher's method (Owen, 2009). In addition to the choices above, MetaDE also provides options for gene matching across studies and gene filtering before meta-analysis. Outputs of the meta-analysis results include DE gene lists with corresponding raw p-value, q-values and various visualization tools. Heatmaps can be plotted across studies.

The `ind.analysis` Function

This function is used to perform individual analysis and calculate the p-values frequently used in meta-analysis. Based on the type of outcome variable,

The `ind.cal.ES` Function

This function is used for calculating the effect sizes (standardized mean difference) frequently used in meta-analysis.

The `MetaDE.rawdata` Function

With the raw gene expression datasets, all the methods combining the options of `ind.method` and `meta.method` can be implemented by function `MetaDE.rawdata`.

The `MetaDE.pvalue` and `MetaDE.ES` Function

If p-values or effect sizes (and corresponding variances) have been calculated already, for example by other methods not used in functions, `ind.analysis` or `ind.cal.ES`, with the help of other software, then the meta-analysis can be implemented by function `MetaDE.pvalue` or `MetaDE.ES`.

Author(s)

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References

Jia Li and George C. Tseng. (2011) An adaptively weighted statistic for detecting differential gene expression when combining multiple transcriptomic studies. *Annals of Applied Statistics*. 5:994-1019.

Shuya Lu, Jia Li, Chi Song, Kui Shen and George C Tseng. (2010) Biomarker Detection in the Integration of Multiple Multi-class Genomic Studies. *Bioinformatics*. 26:333-340. (PMID: 19965884; PMID: PMC2815659)

Xingbin Wang, Yan Lin, Chi Song, Etienne Sibille and George C Tseng. (2012) Detecting disease-associated genes with confounding variable adjustment and the impact on genomic meta-analysis: with application to major depressive disorder. *BMC Bioinformatics*. 13:52.

George C. Tseng, Debashis Ghosh and Eleanor Feingold. (2012) Comprehensive literature review and statistical considerations for microarray meta-analysis. *Nucleic Acids Research* accepted

Xingbin Wang, Dongwan Kang, Kui Shen, Chi Song, Lunching Chang, Serena G. Liao, Zhiguang Huo, Naftali Kaminski, Etienne Sibille, Yan Lin, Jia Li and George C. Tseng. (2012) A Suite of R Packages for Quality Control, Differentially Expressed Gene and Enriched Pathway Detection in Microarray Meta-analysis. In press.

count.DENumber	<i>Count the number of differentially expressed (DE) genes</i>
----------------	--

Description

a function to summary the number of DE genes at given p-value or FDR thresholds.

Usage

```
count.DENumber(result, p.cut, q.cut)
```

Arguments

result	A p-value matrix or an object file from metaDE.pvalue,metaDE.minMCC, metaDE.ES
p.cut	a numeric vector to specify the p-value thresholds at which the DE number is counted.
q.cut	a numeric vector to specify the FDR thresholds at which the DE number is counted.

Details

To count the DE number at FDR thresholds, the p-values were corrected by Benjamini-Hochberg procedure.

Value

a list with components:

pval.table a table contains the DE numbers counted at given p-value thresholds.
 FDR.table a table contains the DE numbers counted at given FDR thresholds.

Author(s)

Jia Li and Xingbin Wang

References

Benjamini Y, Hochberg Y: Controlling the False Discovery Rate - a Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society Series B-Methodological 1995, 57(1):289-300.

See Also

[draw.DEnumber](#)

Examples

```
#---example 1: Meta analysis of Differentially expressed genes between two classes-----#
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
exp1<-cbind(matrix(rnorm(5*200),200,5),matrix(rnorm(5*200,2),200,5))
exp2<-cbind(matrix(rnorm(5*200),200,5),matrix(rnorm(5*200,1.5),200,5))
x<-list(list(exp1,label1),list(exp2,label2))

# here I used modt to generate p-values.
DEgene<-ind.analysis(x,ind.method=rep("regt",2),tail="abs",nperm=100)

#--then you can use Fisher's method to combine the above p-values
res<-MetaDE.pvalue(DEgene,meta.method='Fisher')
draw.DEnumber(res,FDR=TRUE,maxcut=0.1)
count.DEnumber(res,p.cut=c(0.01,0.05),q.cut=c(0.01,0.05))
```

draw.DEnumber	<i>A function to plot the number of DE genes against FDR obtained from the Meta-analysis.</i>
---------------	---

Description

draw.DEnumber(result,maxcut,m1ty=NULL,mcol=NULL,m1wd=NULL,mpch=NULL,FDR=TRUE) plot the number of DE genes against FDR obtained from the Meta-analysis.

Usage

```
draw.DEnumber(result,maxcut,mpty=NULL,mcol=NULL,mldw=NULL,mpch=NULL,FDR=TRUE)
```

Arguments

result	A p-value matrix or an object file from metaDE.rawdata.pvalue,metaDE.pvalue,metaDE.minMCC, metaDE.ES
FDR	use FDR for cutpoints if true, p-value otherwise
maxcut	The maximum cut point for FDR or P-value
mpty	line type for each line. default is set
mcol	line colour. default is set
mldw	line width for each line. default is set
mpch	symbol for each line. default is set

Value

A figure containing:

figure	p-value(or FDR) vs numberof detected genes for individual analysis as well as meta analysis.
--------	--

References

Li and Tseng (2011) and Lu, Li and Tseng (2009).

See Also

[count.DEnumber](#)

Examples

```
#---example 1: Meta analysis of Differentially expressed genes between two classes-----#
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
exp1<-cbind(matrix(rnorm(5*200),200,5),matrix(rnorm(5*200,2),200,5))
exp2<-cbind(matrix(rnorm(5*200),200,5),matrix(rnorm(5*200,1.5),200,5))
x<-list(list(exp1,label1),list(exp2,label2))

# here I used modt to generate p-values.
DEgene<-ind.analysis(x,ind.method=rep("regt",2),tail="abs",nperm=100)

#--then you can use Fisher's method to combine the above p-values
res<-MetaDE.pvalue(DEgene,meta.method='Fisher')
draw.DEnumber(res,FDR=TRUE,maxcut=0.1)
```

heatmap.sig.genes	<i>A function to plot the heatmap of DE genes detected at a given FDR threshold from the Meta-analysis.</i>
-------------------	---

Description

heatmap.sig.genes, a function to draw the Heatmap of DE genes given a FDR cut point obtained from the Meta-analysis.

Usage

```
heatmap.sig.genes(result, meta.method, fdr.cut=0.2, color="GR")
```

Arguments

result	The object file from MetaDE.pvalue, MetaDE.ES or metaDE.minMCC.
meta.method	If multiple methods were chosen for the meta analysis, the user needs to specify which which method is to be used for plotting.
fdr.cut	cut off for FDR for the meta analysis result.
color	The color scheme for the heatmap. "GR" is the default. "GR" stands for green, black, red. "BY" stands for blue, black and yellow.

Value

A figure shows the standardized expression levels for the DE genes detected by meta analysis across studies/datasets.

References

Jia Li and George C. Tseng. (2011) An adaptively weighted statistic for detecting differential gene expression when combining multiple transcriptomic studies. *Annals of Applied Statistics*. 5:994-1019.

Shuya Lu, Jia Li, Chi Song, Kui Shen and George C Tseng. (2010) Biomarker Detection in the Integration of Multiple Multi-class Genomic Studies. *Bioinformatics*. 26:333-340. (PMID: 19965884; PMID: PMC2815659)

Examples

```
#-----example 2: -----#
# here I generate two pseudo datasets
set.seed(123)
label1<-rep(0:1, each=5)
label2<-rep(0:1, each=5)
exp1<-cbind(matrix(rnorm(5*200), 200, 5), matrix(rnorm(5*200, 2), 200, 5))
exp2<-cbind(matrix(rnorm(5*200), 200, 5), matrix(rnorm(5*200, 1.5), 200, 5))

#the input has to be arranged in lists
```

```
x<-list(list(exp1,label1),list(exp2,label2))

#here I used the modt test for individual study and used Fisher's method to combine results
#from multiple studies.
meta.res2<-MetaDE.rawdata(x=x,ind.method=c('modt','modt'),meta.method=c('Fisher',"maxP"),nperm=200)
heatmap.sig.genes(meta.res2, meta.method="maxP",fdr.cut=1,color="GR") #plot all genes
heatmap.sig.genes(meta.res2, meta.method="Fisher",fdr.cut=0.05,color="GR")
```

ind.analysis

Identify differentially expressed genes in each individual dataset

Description

ind.analysis is a function to perform individual analysis. The outputs are measures (p-values) for meta-analysis.

Usage

```
ind.analysis(x, ind.method = c("f", "regt", "modt", "pairedt",
                              "pearsonr", "spearmnr", "F", "logrank"), miss.tol =
0.3, nperm = NULL, tail, ...)
```

Arguments

x	a list of studies. Each study is a list with components: <ul style="list-style-type: none"> • x: the gene expression matrix. • y: the outcome variable. For a binary outcome, 0 refers to "normal" and 1 to "diseased". For a multiple class outcome, the first level being coded as 0, the second as 1, and so on. For survival data, it is the survival time of the patients. • censoring.status: 0 refers to individual who did not experimented the outcome while 1 is used for patients who develop the event of interest.
miss.tol	The maximum percent missing data allowed in any gene (default 30 percent).
nperm	The number of permutations. If nperm is NULL,the results will be based on asymptotic distribution.
ind.method	a character vector to specify the statistical test to test if there is association between the variables and the labels (i.e. genes are differentially expressed in each study). see "Details".
tail	a character string specifying the alternative hypothesis,must be one of "abs" (default), "low" or "high".
...	Additional arguments.

Details

The available statistical tests for argument, `ind.method`, are:

- "regt": Two-sample t-statistics (unequal variances).
- "modt": Two-sample t-statistics with the variance is modified by adding a fudging parameter. In our algorithm, we choose the penalized t-statistics used in Efron et al.(2001) and Tusher et al. (2001). The fudge parameter `s0` is chosen to be the median variability estimator in the genome.
- "pairedt": Paired t-statistics for the design of paired samples.
- "pearsonr": Pearson's correlation. It is usually chosen for quantitative outcome.
- "spearmanr": Spearman's correlation. It is usually chosen for quantitative outcome.
- "F": the test is based on F-statistics. It is usually chosen where there are 2 or more classes.

For the argument, `miss.tol`, the default is 30 percent. For those genes with less than `miss.tol * 100` percent missing are imputed using KNN method in package, `impute`; for those genes with more than or equal `miss.tol * 100` percent missing are ignored for the further analysis.

Value

a list with components:

<code>stat</code>	the value of test statistic for each gene
<code>p</code>	the p-value for the test for each gene
<code>bp</code>	the p-value from <code>nperm</code> permutations for each gene. It will be used for the meta analysis. It can be NULL if you chose asymptotic results.

References

Jia Li and George C. Tseng. (2011) An adaptively weighted statistic for detecting differential gene expression when combining multiple transcriptomic studies. *Annals of Applied Statistics*. 5:994-1019.

Shuya Lu, Jia Li, Chi Song, Kui Shen and George C Tseng. (2010) Biomarker Detection in the Integration of Multiple Multi-class Genomic Studies. *Bioinformatics*. 26:333-340. (PMID: 19965884; PMCID: PMC2815659)

See Also

[MetaDE.Read](#), [MetaDE.match](#), [MetaDE.merge](#), [MetaDE.filter](#), [MetaDE.pvalue](#) and [MetaDE.rawdata](#)

Examples

```
#--generate two pseudo datasets----#
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
exp1<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,2),20,5))
exp2<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,1.5),20,5))
```



```

#the input has to be arranged in lists
x<-list(list(x=exp1,y=label1),list(x=exp2,y=label2))

# start individual analysis for each study:
#find genes whose expression is higher in class 2 vs class 1 using moderated t test for both studies
test1<-ind.analysis(x,ind.method=c("modt","modt"),tail="high",nperm=100)
#here I want to use two-sample t test for study 1 and moderated t test for study 2.
test2<-ind.analysis(x,ind.method=c("regt","modt"),tail="abs",nperm=100)

#-----time to event-----#
#--generate three pseudo datasets----#
exp1<-matrix(rnorm(20*10),20,10)
time1=c(4,3,1,1,2,2,3,10,5,4)
event1=c(1,1,1,0,1,1,0,0,0,1)
#study 2
exp2<-matrix(rnorm(20*10,1.5),20,10)
time2=c(4,30,1,10,2,12,3,10,50,2)
event2=c(0,1,1,0,0,1,0,1,0,1)
#study 3
exp3<-matrix(rnorm(20*15),20,15)
time3=c(1,27,40,10,2,6,1,10,50,100,20,5,6,8,50)
event3=c(0,1,1,0,0,1,0,1,0,1,1,1,1,0,1)

#the input has to be arranged in lists
test3<-list(list(x=exp1,y=time1,censoring.status=event1),list(x=exp2,y=time2,censoring.status=event2),
list(x=exp3,y=time3,censoring.status=event3))

# start individual analysis for each study: i use log rank test for all studies
test3.res<-ind.analysis(test3,ind.method=rep("logrank",3),nperm=100,tail='abs')

```

ind.cal.ES

Calculate the effect sizes

Description

The function can be used to calculate various effect sizes (and the corresponding sampling variances) that are commonly used in meta-analyses.

Usage

```
ind.cal.ES(x, paired, nperm = NULL, miss.tol=0.3)
```

Arguments

x	a list of data sets and their labels. The first list is a list of datasets, the second list is a list of their labels
paired	A vector of logical values to specify the design patterns of studies. see 'Details'.

nperm	an integer to specify the number of permutations.
miss.tol	The maximum percent missing data allowed in any gene (default 30 percent).

Details

This function is used to calculate the effect size, standardized mean difference, often used in meta-analysis.

The argument `paired` is a vector of logical values to specify whether the corresponding study is paired design or not. If the study is pair-designed, the effect sizes (corresponding variances) are calculated using the formula in Morris's paper, otherwise calculated using the formulas in Choi *et al.*

Value

ES	The observed effect sizes.
Var	The observed variances corresponding to ES
perm.ES	The effect sizes calculated from permutations, perm.ES is NULL if the argument <code>nperm</code> is set as NULL.
perm.Var	The corresponding variances calculated from permutations. perm.Var is NULL if the argument <code>nperm</code> is set as NULL.

Author(s)

Jia Li and Xingbin Wang

References

Morris SB: Distribution of the standardized mean change effect size for meta-analysis on repeated measures. *Br J Math Stat Psychol* 2000, 53 (Pt 1):17-29.

Choi et al, Combining multiple microarray studies and modeling interstudy variation. *Bioinformatics*,2003, 18:84-90.

See Also

[MetaDE.ES](#)

Examples

```
#---example 1: Meta analysis of Differentially expressed genes between two classes-----#
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
exp1<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,2),20,5))
exp2<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,1.5),20,5))
x<-list(list(exp1,label1),list(exp2,label2))
ind.res<-ind.cal.ES(x,paired=rep(FALSE,2),nperm=100)
MetaDE.ES(ind.res,meta.method='REM')
```

 MetaDE.ES

Identify differentially expressed genes by combining effect sizes

Description

Function to fit the meta-analytic fixed- and random-effects models. The data consists of effect sizes and corresponding variances from your own method/calculations.

Usage

```
MetaDE.ES(x, meta.method = c("FEM", "REM"))
```

Arguments

x	a list with components. <ul style="list-style-type: none"> • ES: The observed effect sizes. • Var: The observed variances corresponding to ES • perm.ES: The effect sizes calculated from permutations, perm.ES is NULL if the argument nperm is set as NULL. • perm.Var: The corresponding variances calculated from permutations. perm.Var is NULL if the argument nperm is set as NULL.
meta.method	a character string specifying whether a fixed- or a random/mixed-effects model should be fitted. A fixed-effects model is fitted when using meta.method="FEM". Random-effects model is fitted by setting meta.method equal to "REM". See "Details".

Details

The function can be used to combine any of the usual effect size used in meta-analysis, such as standardized mean differences. Simply specify the observed effect sizes via the `x$ES` and the corresponding variances via `x$Var`. If the effect sizes and corresponding variances calculated from permutation are available, then specify them by `x$perm.ES` and `x$perm.Var`, respectively.

The argument `paired` is a vector of logical values to specify whether the corresponding study is paired design or not. If the study is pair-designed, the effect sizes (corresponding variances) are calculated using the formula in Morris's paper, otherwise calculated using the formulas in Choi *et al.*

In addition, if the components of `x`, `perm.ES` and `perm.Var`, are not "NULL", the p-values are calculated using permutation method, otherwise, the p-values are calculated using parametric method by assuming the z-scores following a standard normal distribution.

Value

The object is a list containing the following components:

zval	test statistics of the aggregated value.
pval	p-values for the test statistics.
FDR	A matrix with one column which has the corrected p-values using Benjamini and Hochberg method (see references).
Qval	test statistics for the test of heterogeneity.
Qpval	p-values for the test of heterogeneity.
tau2	estimated amount of (residual) heterogeneity.

Author(s)

Jia Li and Xingbin Wang

References

Choi et al, Combining multiple microarray studies and modeling interstudy variation. *Bioinformatics*, 2003, i84-i90.

Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B*, 57, 289:300.

See Also

[ind.cal.ES](#)

Examples

```
#---example 1: Meta analysis of Differentially expressed genes between two classes-----#
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
exp1<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,2),20,5))
exp2<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,1.5),20,5))
x<-list(list(exp1,label1),list(exp2,label2))
ind.res<-ind.cal.ES(x,paired=rep(FALSE,2),nperm=100)
MetaDE.ES(ind.res,meta.method='REM')
```

MetaDE.filter

A function to filter genes

Description

MetaDE.filter filters genes in the gene expression data sets.

Usage

```
MetaDE.filter(x, DelPerc)
```

Arguments

- `x` a list of studies. Each study is a list with components:
- `x`: the gene expression matrix.
 - `y`: the outcome variable. For a binary outcome, 0 refers to "normal" and 1 to "diseased". For a multiple class outcome, the first level being coded as 0, the second as 1, and so on. For survival data, it is the survival time of the patients.
 - **`censoring.status`**: 0 refers to individual who did not experimented the outcome while 1 is used for patients who develop the event of interest. This object is NULL for binary, multiclass and continuous outcome.
- `DelPerc` a numeric vector of size 2, which specify the percentage of genes to be filtered in the two sequential steps of gene filtering. see "Details".

Details

Two sequential steps of gene filtering were performed in `MetaDE.filter`. In the first step, we filtered out genes with very low gene expression that were identified with small average expression values across majority of studies. Specifically, mean intensities of each gene across all samples in each study were calculated and the corresponding ranks were obtained. The sum of such ranks across five studies of each gene was calculated and genes with the lowest alpha percent rank sum were considered un-expressed genes (i.e. small expression intensities) and were filtered out. Similarly, in the second step, we filtered out non-informative (small variation) genes by replacing mean intensity in the first step with standard deviation. Genes with the lowest beta percent rank sum of standard deviations were filtered out.

Value

a list of studies. Each study is a list with components:

- `x`: the gene expression matrix.
- `y`: the outcome.
- **`censoring.status`**: the censoring status. This only for survival data.

Author(s)

Jia Li and Xingbin Wang

References

Xingbin Wang, Yan Lin, Chi Song, Etienne Sibille* and George C Tseng*. (2012) Detecting disease-associated genes with confounding variable adjustment and the impact on genomic meta-analysis: with application to major depressive disorder. BMC Bioinformatics. tentatively accepted.

See Also

[MetaDE.Read](#), [MetaDE.match](#), [MetaDE.rawdata](#), [ind.analysis](#) and [MetaDE.rawdata](#)

Examples

```
#####Example Test Filter.gene#####
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
exp1<-cbind(matrix(rnorm(5*200),200,5),matrix(rnorm(5*200,2),200,5))
exp2<-cbind(matrix(rnorm(5*300),300,5),matrix(rnorm(5*300,1.5),300,5))
rownames(exp1)<-paste("g1",1:200,sep="_")
rownames(exp2)<-paste("g2",1:300,sep="_")
symbol1<-sample(paste("symbol_",1:20,sep=""),200,replace=TRUE)
symbol2<-sample(paste("symbol_",1:20,sep=""),300,replace=TRUE)
study1<-cbind(c(NA,symbol1),rbind(label1,exp1))
study2<-cbind(c(NA,symbol2),rbind(label2,exp2))
setwd(tempdir())
write.table(study1,"study1.txt",sep="\t")
write.table(study2,"study2.txt",sep="\t")
mydata<-MetaDE.Read(c("study1","study2"),via="txt",skip=c(2,1),log=FALSE)
mydata.matched<-MetaDE.match(mydata,"IQR")
mydata.Merged<-MetaDE.merge(mydata.matched)
mydata.filtered<-MetaDE.filter(mydata.Merged,DelPerc=c(0.1,0.2))
ind.res<-ind.analysis(mydata.filtered,ind.method=c("regt","regt"),tail="abs",nperm=10)
meta.res<-MetaDE.rawdata(mydata.filtered,ind.method=c("regt","regt"),meta.method="Fisher",ind.tail="abs",nperm=10)
```

MetaDE.match

Match the probeIds to gene symbol

Description

When multiple probes (or probe sets) matched to an identical gene symbol, these functions are used to match them into a single gene symbol.

Usage

```
Match.gene(x, pool.replicate = c("average", "IQR"))
MetaDE.match(x,pool.replicate = c("average", "IQR"))
```

Arguments

x a list of studies. Each study is a list with components:

- **x**: the gene expression matrix.
- **y**: the outcome.
- **censoring.status**: the censoring status. This only for survival data.
- **symbol**: the gene symbols.

pool.replicate a character to specify the method to match multiple probeIds to a single gene symbol. see "Details".

Details

To be able to be combined, Probes (or probe sets) in each study need to be matched to official gene symbols. When multiple probes (or probe sets) matched to an identical gene symbol, the probe that presented the greatest inter-quartile range (IQR) was selected to represent the target gene symbol. Larger IQR represents greater variability (and thus greater information content) in the data and this probe matching method has been recommended in Bioconductor. Another matching method is to take average across genes.

Function, `Match.gene`, is used to perform matching on a single study; `MetaDE.match` is used to apply on multiple study sets.

Value

A list with components:

<code>data</code>	a list of gene expression datasets.
<code>l</code>	a list of labels.

Author(s)

Jia Li and Xingbin Wang

References

Gentleman R, Carey V, Huber W, Irizarry R, Dudoit S (eds.): Bioinformatics and Computational Biology Solutions Using R and Bioconductor: Springer; 2005.

See Also

[MetaDE.Read](#), [MetaDE.filter](#)

Examples

```
#####example simulate data sets#####
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
time1=c(4,3,1,1,2,2,3,10,5,4)
event1=c(1,1,1,0,1,1,0,0,0,1)
exp1<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,2),20,5))
exp2<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,1.5),20,5))
rownames(exp1)<-paste("g1",1:20,sep="_")
rownames(exp2)<-paste("g2",1:20,sep="_")
symbol1<-sample(c("SST","VGF","CNP"),20,replace=TRUE)
symbol2<-sample(c("SST","VGF","CNP"),20,replace=TRUE)
study1<-cbind(c(NA,NA,symbol1),rbind(rbind(time1,event1),exp1))
study2<-cbind(c(NA,symbol2),rbind(label2,exp2))
setwd(tempdir())
write.table(study1,"study1.txt",sep="\t")
write.table(study2,"study2.txt",sep="\t")
mydata<-MetaDE.Read(c("study1","study2"),via="txt",skip=c(2,1),log=FALSE)
```

```
#-----Test MetaDE.match-----#
mydata.matched2<-MetaDE.match(mydata, "IQR")
```

MetaDE.merge *Merge microarray data sets*

Description

Merge microarray data sets in possibly irregular order.

Usage

```
MetaDE.merge(x, MVperc=0)
```

Arguments

x a list of studies. Each study is a list with components:

- **x**: the gene expression matrix.
- **y**: the outcome variable. For a binary outcome, 0 refers to "normal" and 1 to "diseased". For a multiple class outcome, the first level being coded as 0, the second as 1, and so on. For survival data, it is the survival time of the patients.
- **censoring.status**: 0 refers to individual who did not experimented the outcome while 1 is used for patients who develop the event of interest. This object is NULL for binary, multiclass and continuous outcome.

MVperc a threshold to specificity which genes are remained for further analysis. The default is zero.

Details

The gene expression data sets may be in possibly irregular order with different numbers of genes. This function is used to extract the common genes across studies. The merged data sets have the same genes in the same order.

When we combine a large of number of studies, the number of common genes may be very small, so we allow to include some gene appearing in most studies and missing in few studies. The default is zero which means that we only include genes appearing in all the studies.

Value

a list of studies. Each study is a list with components:

- **x**: the gene expression matrix.
- **y**: the outcome.
- **censoring.status**: the censoring status. This only for survival data.

Author(s)

Jia Li and Xingbin Wang

See Also[MetaDE.Read](#), [MetaDE.filter](#), [ind.analysis](#) and [MetaDE.rawdata](#)**Examples**

```
#####example test MetaDE.merge#####
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
time1=c(4,3,1,1,2,2,3,10,5,4)
event1=c(1,1,1,0,1,1,0,0,0,1)
exp1<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,2),20,5))
exp2<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,1.5),20,5))
rownames(exp1)<-paste("g1",1:20,sep="_")
rownames(exp2)<-paste("g2",1:20,sep="_")
symbol1<-sample(c("SST","VGF","CNP","LPA"),20,replace=TRUE)
symbol2<-sample(c("SST","VGF","CNP","APOE"),20,replace=TRUE)
study1<-cbind(c(NA,NA,symbol1),rbind(rbind(time1,event1),exp1))
study2<-cbind(c(NA,symbol2),rbind(label2,exp2))
setwd(tempdir())
write.table(study1,"study1.txt",sep="\t")
write.table(study2,"study2.txt",sep="\t")
mydata.raw<-MetaDE.Read(c("study1","study2"),via="txt",skip=c(2,1),log=FALSE)

mydata.matched<-MetaDE.match(mydata.raw,"IQR")
mydata.merged<-MetaDE.merge(mydata.matched)
```

MetaDE.minMCC

*Identify differentially expressed genes by integrating multiple studies(datasets) using minMCC approach***Description**

MetaDE.minMCC Identify differentially expressed genes with the same pattern across studies/datasets.

Usage

MetaDE.minMCC(x,nperm=100,miss.tol=0.3)

Arguments

x	a list of data sets and their labels. The first list is a list of datasets, the second list is a list of their labels. see examples for details.
nperm	The number of permutations. If nperm is NULL,the results will be based on asymptotic distribution.
miss.tol	The maximum percent missing data allowed in any gene (default 30 percent).

Value

A list containing:

```
meta.analysis$meta.stat
    the statistics for the chosen meta analysis method
meta.analysis$pval
    the p-value for the above statistic. It is calculated from permutation.
meta.analysis$FDR
    the FDR of the p-value.
meta.analysis$AW.weight
    The optimal weight assigned to each dataset/study for each gene if the 'AW' or
    'AW.OC' method was chosen.
raw.data
    the raw data of your input. That's x. This part will be used for plotting.
```

References

Jia Li and George C. Tseng. (2011) An adaptively weighted statistic for detecting differential gene expression when combining multiple transcriptomic studies. *Annals of Applied Statistics*. 5:994-1019.

Shuya Lu, Jia Li, Chi Song, Kui Shen and George C Tseng. (2010) Biomarker Detection in the Integration of Multiple Multi-class Genomic Studies. *Bioinformatics*. 26:333-340. (PMID: 19965884; PMID: PMC2815659)

See Also

[MetaDE.rawdata](#) [MetaDE.pvalue](#) [MetaDE.ES](#) [draw.DENumber](#)

Examples

```
label1<-rep(0:2,each=5)
label2<-rep(0:2,each=4)
exp1<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,2),20,5),matrix(rnorm(5*20,2.5),20,5))
exp2<-cbind(matrix(rnorm(4*20),20,4),matrix(rnorm(4*20,1.5),20,4),matrix(rnorm(4*20,2.5),20,4))
x<-list(list(exp1,label1),list(exp2,label2))
```

```
MetaDE.minMCC(x,nperm=100)
```

MetaDE.pvalue

Identify differentially expressed genes by combining p-values

Description

MetaDE.pvalue Identify differentially expressed genes by integrating multiple studies(datasets). The data consists of p-values from your own method/calculations.

Usage

```
MetaDE.pvalue(x, meta.method = c("maxP", "maxP.OC", "minP",
                                "minP.OC", "Fisher", "Fisher.OC", "AW", "AW.OC",
                                "roP", "roP.OC", "Stouffer", "Stouffer.OC", "SR",
                                "PR"), rth = NULL, miss.tol = 0.3, asymptotic = FALSE)
```

Arguments

x	a list with components: <ul style="list-style-type: none"> • p: a list of p values for each dataset. • bp: a list of p values calculated from permutation for each dataset. This part can be NULL if you just have the p-values from your own method.
meta.method	a character to specify the type of Meta-analysis methods to combine the p-values or effect sizes. See "Details".
rth	this is the option for roP and roP.OC method. rth means the rth smallest p-value.
miss.tol	The maximum percent missing data allowed in any gene (default 30 percent).
asymptotic	A logical values to specify whether the parametric methods is chosen to calculate the p-values in meta-analysis. The default is FALSE.

Details

The options for argument,meta.method,are listed below:

- **"maxP"**: the maximum of p value method.
- **"maxP.OC"**: the maximum of p values with one-sided correction.
- **"minP"**: the minimum of p values from "test" across studies.
- **"minP.OC"**: the minimum of p values with one-sided correction.
- **"Fisher"**: Fisher's method (Fisher, 1932),the summation of $-\log(\text{p-value})$ across studies.
- **"Fisher.OC"**: Fisher's method with one-sided correction (Fisher, 1932),the summation of $-\log(\text{p-value})$ across studies.
- **"AW"**: Adaptively-weighted method (Li and Tseng, 2011).
- **"AW.OC"**: Adaptively-weighted method with one-sided correction (Li and Tseng, 2011).
- **"roP"**: rth p-value method.
- **"roP.OC"**: rth p-value method with one-sided correction.
- **"Stouffer"**: the minimum of p values from "test" across studies.
- **"Stouffer.OC"**: the minimum of p values with one-sided correction.
- **"SR"**: the naive sum of the ranks method.
- **"PR"**: the naive product of the ranks method.

For those genes with less than $\text{miss.tol} * 100$ percent missing,the p-values are calculated using parametric metod if asymptotic is TRUE. Otherwise, , the p-values for genes without missing values are calculated using permutation method.

Value

A list containing:

stat	a matrix with rows representing genes. It is the statistic for the selected meta analysis method of combining p-values.
pval	the p-value from meta analysis for each gene for the above stat.
FDR	the FDR of the p-value for each gene for the above stat.
AW.weight	The optimal weight assigned to each dataset/study for each gene if the 'AW' or 'AW.OC' method was chosen.

References

Jia Li and George C. Tseng. (2011) An adaptively weighted statistic for detecting differential gene expression when combining multiple transcriptomic studies. *Annals of Applied Statistics*. 5:994-1019.

Shuya Lu, Jia Li, Chi Song, Kui Shen and George C Tseng. (2010) Biomarker Detection in the Integration of Multiple Multi-class Genomic Studies. *Bioinformatics*. 26:333-340. (PMID: 19965884; PMID: PMC2815659)

See Also

MetaDE.minMCC, MetaDE.pvalue, MetaDE.ES, plot.FDR, heatmap.sig.genes

Examples

```
#---example 1: Meta analysis of Differentially expressed genes between two classes-----#
# here I generate two pseudo datasets
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
exp1<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,2),20,5))
exp2<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,1.5),20,5))

#the input has to be arranged in lists
x<-list(list(exp1,label1),list(exp2,label2))

# start individual analysis for each dataset: here I used modt to generate p-values.
DEgene<-ind.analysis(x,ind.method=c("modt","modt"),tail="high",nperm=100)
#you don't have to use our ind.analysis for the analysis for individual study. you can input
#p-values to MetaDE.pvalue for meta analysis only. But the input has to be specified in the
# same format as the DEgene in the example above

#--then you can use meta analysis method to combine the above p-values:here I used the Fisher's method
MetaDE.pvalue(DEgene,meta.method='Fisher')
```

MetaDE.rawdata	<i>Identify differentially expressed genes by integrating multiple studies(datasets)</i>
----------------	--

Description

MetaDE.rawdata Identify differentially expressed genes by integrating multiple studies(datasets).

Usage

```
MetaDE.rawdata(x, ind.method = c("modt", "regt", "pairedt", "F",
  "pearsonr", "spearmanr", "logrank"), meta.method =
  c("maxP", "maxP.OC", "minP", "minP.OC", "Fisher",
  "Fisher.OC", "AW", "AW.OC", "roP", "roP.OC",
  "Stouffer", "Stouffer.OC", "SR", "PR", "minMCC",
  "FEM", "REM", "rankProd"), paired = NULL, miss.tol =
  0.3, rth = NULL, nperm = NULL, ind.tail = "abs",
  asymptotic = FALSE, ...)
```

Arguments

x	a list of studies. Each study is a list with components: <ul style="list-style-type: none"> • x: the gene expression matrix. • y: the outcome variable. For a binary outcome, 0 refers to "normal" and 1 to "diseased". For a multiple class outcome, the first level being coded as 0, the second as 1, and so on. For survival data, it is the survival time of the patients. • censoring.status: 0 refers to individual who did not experimented the outcome while 1 is used for patients who develop the event of interest.
ind.method	a character vector to specify the statistical test to test whether there is association between the variables and the labels (i.e. genes are differentially expressed in each study). see "Details".
ind.tail	a character string specifying the alternative hypothesis, must be one of "abs" (default), "low" or "high".
meta.method	a character to specify the type of Meta-analysis methods to combine the p-values or effect sizes. See "Details".
paired	a vector of logical values to specify that whether the design of ith study is paired or not. If the ith study is paired-design , the corresponding element of paired should be TRUE otherwise FALSE.
miss.tol	The maximum percent missing data allowed in any gene (default 30 percent).
rth	this is the option for roP and roP.OC method. rth means the rth smallest p-value.
nperm	The number of permutations. If nperm is NULL,the results will be based on asymptotic distribution.

asymptotic A logical values to specify whether the parametric methods is chosen to calculate the p-values in meta-analysis. The default is FALSE.

... Additional arguments.

Details

The available statistical tests for argument, `ind.method`, are:

- "regt": Two-sample t-statistics (unequal variances).
- "modt": Two-sample t-statistics with the variance is modified by adding a fudging parameter. In our algorithm, we choose the penalized t-statistics used in Efron et al.(2001) and Tusher et al. (2001). The fudge parameter s_0 is chosen to be the median variability estimator in the genome.
- "pairedt": Paired t-statistics for the design of paired samples.
- "pearsonr": Pearson's correlation. It is usually chosen for quantitative outcome.
- "spearmanr": Spearman's correlation. It is usually chosen for quantitative outcome.
- "F": the test is based on F-statistics. It is usually chosen where there are 2 or more classes.

The options for argument, `mete.method`, are listed below:

- "maxP": the maximum of p value method.
- "maxP.OC": the maximum of p values with one-sided correction.
- "minP": the minimum of p values from "test" across studies.
- "minP.OC": the minimum of p values with one-sided correction.
- "Fisher": Fisher's method (Fisher, 1932), the summation of $-\log(p\text{-value})$ across studies.
- "Fisher.OC": Fisher's method with one-sided correction (Fisher, 1932), the summation of $-\log(p\text{-value})$ across studies.
- "AW": Adaptively-weighted method (Li and Tseng, 2011).
- "AW.OC": Adaptively-weighted method with one-sided correction (Li and Tseng, 2011).
- "SR": the naive sum of the ranks method.
- "PR": the naive product of the ranks methods.
- "minMCC": the minMCC method.
- "FEM": the Fixed-effect model method.
- "REM": the Random-effect model method.
- "roP": rth p-value method.
- "roP.OC": rth p-value method with one-sided correction.
- "rankProd": rank Product method.

For the argument, `miss.tol`, the default is 30 percent. In individual analysis, for those genes with less than `miss.tol * 100` percent, missing values are imputed using KNN method in package, `impute`; for those genes with more than or equal `miss.tol * 100` percent missing are ignored for the further analysis. In meta-analysis, for those genes with less than `miss.tol * 100` percent missing, the p-values are calculated if `asymptotic` is TRUE.

Value

A list with components:

<code>meta.analysis</code>	a list of the results of meta-analysis with components: <ul style="list-style-type: none"> • <code>meta.stat</code>: the statistics for the chosen meta analysis method • <code>pval</code>: the p-value for the above statistic. It is calculated from permutation. • <code>FDR</code>: the p-values corrected by Benjamini-Hochberg. • <code>AW.weight</code>: The optimal weight assigned to each dataset/study for each gene if the 'AW' or 'AW.OC' method was chosen.
<code>ind.stat</code>	the statistics calculated from individual analysis. This is for <code>meta.method</code> expecting "REM", "FEM", "minMCC" and "rankProd".
<code>ind.p</code>	the p-value matrix calculated from individual analysis. This is for <code>meta.method</code> expecting "REM", "FEM", "minMCC" and "rankProd".
<code>ind.ES</code>	the effect size matrix calculated from individual analysis. This is only <code>meta.method</code> , "REM" and "FEM".
<code>ind.Var</code>	the corresponding variance matrix calculated from individual analysis. This is only <code>meta.method</code> , "REM" and "FEM".
<code>raw.data</code>	the raw data of your input. That's x. This part will be used for plotting.

References

Jia Li and George C. Tseng. (2011) An adaptively weighted statistic for detecting differential gene expression when combining multiple transcriptomic studies. *Annals of Applied Statistics*. 5:994-1019.

Shuya Lu, Jia Li, Chi Song, Kui Shen and George C Tseng. (2010) Biomarker Detection in the Integration of Multiple Multi-class Genomic Studies. *Bioinformatics*. 26:333-340. (PMID: 19965884; PMID: PMC2815659)

See Also

[MetaDE.minMCC](#), [MetaDE.pvalue](#), [MetaDE.ES](#), [draw.DENumber](#) ,

Examples

```
#---example 1: Meta analysis of Differentially expressed genes between two classes-----#
# here I generate two pseudo datasets
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
exp1<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,2),20,5))
exp2<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,1.5),20,5))

#the input has to be arranged in lists
x<-list(list(exp1,label1),list(exp2,label2))

#here I used the modt test for individual study and used Fisher's method to combine results
#from multiple studies.
```

```

meta.res1<-MetaDE.rawdata(x=x,ind.method=c('modt','modt'),meta.method='Fisher',nperm=20)

#-----example 2: genes associated with survival-----#
# here I generate two pseudo datasets
exp1<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,2),20,5))
time1=c(4,3,1,1,2,2,3,10,5,4)
event1=c(1,1,1,0,1,1,0,0,0,1)
exp2<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,1.5),20,4))
time2=c(4,30,1,10,2,12,3,10,50)
event2=c(0,1,1,0,0,1,0,1,0)

#again,the input has to be arranged in lists
test2 <-list(list(x=exp1,y=time1,censoring.status=event1),list(x=exp2,y=time2,censoring.status=event2))

#here I used the log-rank test for individual study and used Fisher's method to combine results
#from multiple studies.
meta.res2<-MetaDE.rawdata(x=test2,ind.method=c('logrank','logrank'),meta.method='Fisher',nperm=20)

#-----example 3: Fixed effect model for two studies from paired design-----#
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
exp1<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,2),20,5))
exp2<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,1.5),20,5))
x<-list(list(x=exp1,y=label1),list(x=exp2,y=label2))
test<- MetaDE.rawdata(x,nperm=1000, meta.method="FEM", paired=rep(FALSE,2))

```

MetaDE.Read

Read data sets into R

Description

Function to import data set(s) into R and reformat it (them) to form required for other functions in MetaDE package.

Usage

```
MetaDE.Read(filenamees, via = c("txt", "csv"), skip,matched=FALSE, log = TRUE)
```

Arguments

filenamees	a character vector specifying the names of data sets to read data values from. Should be a tab-separated or comma-separated text file, with one row per gene set.
via	a character to specify the type of data sets. "txt" means tab delimited files and "csv" means comma-delimited files.
skip	a vector of size K (the number of data sets) composes of 1 or 2. see 'Details'.
matched	a logical to specify whether the gene ProbeIDs have been matched into gene symbols in each data set.
log	a logical to specify wheter data sets need to be log2-transformed.

Details

The files to be read in should be prepared strictly according following format:
 If `matched` is `FALSE`, column 1 has gene ProbeIds, column 2 has gene symbols, remaining columns are samples. If `matched` is `TRUE`, column 1 has gene symbols, remaining columns are samples.
 If the data set is a survival data, the second row should has the survival time, and third row should have the status of events, and remaining rows are gene expression files. otherwise, the second row should has the labels of samples and remaining rows are gene expression profiles.

If the `i`th file is a survival data, the corresponding element of `skip` should be 2, otherwise, 1.

The user can prepare the files according the structure of files wrote out using the example file.

Value

a list of studies. Each study is a list with components:

- `x`: the gene expression matrix.
- `y`: the outcome.
- `censoring.status`: the censoring status. This only for survival data.
- `symbol`: the gene symbols. This is only for un-matched raw data.

Author(s)

Jia Li and Xingbin Wang

References

Xingbin Wang, Jia Li and George C Tseng. Conducting Meta-analysis in R with the MetaDE package. <http://xxxxx/MetaDE.pdf>

See Also

[MetaDE.match](#), [MetaDE.rawdata](#)

Examples

```
#####example test MetaDE.Read #####
setwd(tempdir())
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
exp1<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,2),20,5))
exp2<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,1.5),20,5))
rownames(exp1)<-paste("g1",1:20,sep="_")
rownames(exp2)<-paste("g2",1:20,sep="_")
study1<-rbind(label1,exp1)
study2<-rbind(label2,exp2)
write.table(study1,"study1.txt",sep="\t")
write.table(study2,"study2.txt",sep="\t")
mydata<-MetaDE.Read(c("study1","study2"),via="txt",skip=rep(1,2),matched=TRUE,log=FALSE)
#####Non-matched #####
```

```
label1<-rep(0:1,each=5)
label2<-rep(0:1,each=5)
exp1<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,2),20,5))
exp2<-cbind(matrix(rnorm(5*20),20,5),matrix(rnorm(5*20,1.5),20,5))
rownames(exp1)<-paste("g1",1:20,sep="_")
rownames(exp2)<-paste("g2",1:20,sep="_")
symbol1<-sample(c("SST","VGF","CNP"),20,replace=TRUE)
symbol2<-sample(c("SST","VGF","CNP"),20,replace=TRUE)
study1<-cbind(c(NA,symbol1),rbind(label1,exp1))
study2<-cbind(c(NA,symbol2),rbind(label2,exp2))
setwd(tempdir())
write.table(study1,"study1.txt",sep="\t")
write.table(study2,"study2.txt",sep="\t")
mydata<-MetaDE.Read(c("study1","study2"),via="txt",skip=rep(1,2),log=FALSE)
```

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