calcTNullFast  Compute Null T Distribution for Each Gene

Description
Computes a null t distribution for each gene by permuting the phenotypes.

Usage
calcTNullFast(tab, phenotype, nsim, ngroups = 2)

Arguments
- **tab**: a numeric matrix of expression values, with the rows and columns representing probe sets and sample arrays, respectively
- **phenotype**: a numeric vector indicating the phenotype
- **nsim**: an integer indicating the number of permutations to use
- **ngroups**: an integer indicating the number of groups in the expression matrix

Details
Similar to calcTStatFast but calculates t-statistics over permuted phenotypes. Please refer to the help file of calcTStatFast for more details.

Value
A matrix with nsim rows and nrow(tab) columns.

Author(s)
Weil Lai

calcTStatFast  Compute T-Statistics and Corresponding P-Values

Description
Computes t-statistics and corresponding p-values.

Usage
calcTStatFast(tab, phenotype, ngroups = 2)
Arguments

- **tab**: A numeric matrix of expression values, with the rows and columns representing probe sets and sample arrays, respectively.
- **phenotype**: A numeric vector indicating the phenotype.
- **ngroups**: An integer indicating the number of groups in the expression matrix.

Details

- If there are two groups in the matrix, then the phenotype vector should only consist of 0 and 1 to denote which sample columns belong to which group.
- If **ngroups** = 2, the t-test done here is equivalent to a unpaired two-sample t-test, assuming unequal variances. The sign of the t-statistic is positive if the mean of group 0 is greater than group 1.
- If there is only one group in the matrix (e.g., Alzheimer’s data set as reanalyzed in Tian et al. (2005)), then the phenotype vector should consist of continuous values. In this case, the association between phenotype and expression values is first calculated as Pearson correlation coefficients, transformed to Fisher’s z, and then rescaled so that its variance is 1:
  \[ z = 0.5 \log((1+\rho)/(1-\rho)) \times \sqrt{(n-3)} \]
  where \( n \) is the number of phenotypes.

Value

- **pval**: A vector of unadjusted p-values.
- **tstat**: A vector of t-statistics (\( \text{ngroups} = 2 \)) or rescaled Fisher’s z (\( \text{ngroups} = 1 \)).
- **rho**: (Also returned when \( \text{ngroups} = 1 \)) A vector of Pearson correlation coefficients.

Author(s)

Weil Lai

Examples

```r
## Load inflammatory myopathy data set
data(MuscleData)

## Create appropriate variables for
tab <- MuscleData[, c(index.IBM, index.NORM)]
phenotype <- c(rep(0, length(index.IBM)), rep(1, length(index.NORM)))
statList <- calcTStatFast(tab, phenotype, ngroups = 2)

## Generate histogram of p-values
hist(statList$pval, xlab = "Unadjusted p-values", ylab = "Frequency")
```
**calculate.GSEA**  
*Calculate 2-sided statistics based on the GSEA algorithm*

**Description**

Calculates the 2-sided statistics based on the GSEA algorithm.

**Usage**

```r
calculate.GSEA(tab, phenotype, gsList, nsim = 1000, verbose = FALSE)
```

**Arguments**

- `tab` a numeric matrix of expression values, with the rows and columns representing probe sets and sample arrays, respectively
- `phenotype` a numeric vector indicating the phenotype
- `gsList` a list containing three vectors from the output of the `selectGeneSets` function
- `nsim` an integer indicating the number of permutations to use
- `verbose` a boolean to indicate whether to print debugging messages to the R console

**Details**

This function calculates a variant of the GSEA statistics (Mootha et al.) with the following modifications: (a) GSEA was changed from a 1-sided to a 2-sided approach. (b) The 2-group t-statistics is used as the difference metric.

The function also normalizes the GSEA statistic and calculates the corresponding q-values for each gene set as described in Tian et al. (2005) The function’s output can be used for further analysis in other functions such as `rankPathways.NGSk` or `getPathwayStatistics.NGSk`.

**Value**

A list containing

- `ngs` number of gene sets
- `nsim` number of permutations performed
- `t.set` a numeric vector of Tk statistics
- `t.set.new` a numeric vector of NTk statistics
- `p.null` the proportion of nulls
- `p.value` a numeric vector of p-values
- `q.value` a numeric vector of q-values
Author(s)
Lu Tian and Peter Park, with contributions from Weil Lai

References


http://www.pnas.org/cgi/doi/10.1073/pnas.0506577102

calculate.NGSk

*Calculate NGSk (NTk-like) statistics with gene label permutation*

Description
Calculates the NGSk (NTk-like) statistics with gene label permutation and the corresponding p-values and q-values for each selected pathway.

Usage
`calculate.NGSk(statV, gsList, nsim = 1000, verbose = FALSE)`

Arguments
- `statV`: a numeric vector of test statistic (not p-values) for each individual probe/gene
- `gsList`: a list containing three vectors from the output of the `selectGeneSets` function
- `nsim`: an integer indicating the number of permutations to use
- `verbose`: a boolean to indicate whether to print debugging messages to the R console

Details
This function is a generalized version of NTk calculations; `calculate.NTk` calls this function internally. To use this function, the user must specify a vector of test statistics (e.g., t-statistic, Wilcoxon). Pathways from this function can be ranked with `rankPathways.NGSk` or with `rankPathways` when combined with results from another pathway analysis algorithm (e.g., `calculate.NEk`).
Value

A list containing

- `ngs` number of gene sets
- `nsim` number of permutations performed
- `t.set` a numeric vector of Tk/Ek statistics
- `t.set.new` a numeric vector of NTk/NEk statistics
- `p.null` the proportion of nulls
- `p.value` a numeric vector of p-values
- `q.value` a numeric vector of q-values

Author(s)

Lu Tian and Peter Park, with contributions from Weil Lai

References


http://www.pnas.org/cgi/doi/10.1073/pnas.0506577102

Examples

```r
## Load in expression data and select the probe sets have expression
## values greater than the trimmed mean in at least 1 out of 49 arrays
data(MuscleData)
sf <- apply(MuscleData, 2, mean, tr = 0.025)
temp <- sweep(MuscleData, 2, sf, FUN = '/')
ind.pskeep <- which(rowSums(temp > 1) > 0)
tabMD <- MuscleData[ind.pskeep, ]
probeID <- rownames(tabMD)
rm(temp)

## Select the data to study: IBM vs. NORM or DM vs. NORM
compIBM <- TRUE
if( compIBM == TRUE ) {
tab <- tabMD[,c(index.NORM, index.IBM)]
phenotype <- c(rep.int(0,length(index.NORM)), rep.int(1,length(index.IBM)))
} else {
tab <- tabMD[,c(index.NORM, index.DM)]
phenotype <- c(rep.int(0,length(index.NORM)), rep.int(1,length(index.DM)))
}

## Prepare the pathways to analyze
data(GenesetsU133a)
gsList <- selectGeneSets(G, probeID, 20, 500)
```
nsim <- 1000
groups <- 2
verbose <- TRUE
weightType <- "constant"
methodNames <- c("NTk", "NEk")
npath = 25
allpathways <- FALSE

statV <- calcTStatFast(tab, phenotype, ngroups)$tstat
res.NGSk <- calculate.NGSk(statV, gsList, nsim, verbose)
res.NEk <- calculate.NEk(tab, phenotype, gsList, nsim, weightType, ngroups, verbose)

## Summarize top pathways from NGSk
res.pathways.NGSk <- rankPathways.NGSk(res.NGSk, G, gsList, methodName = "NGSk", npath)
print(res.pathways.NGSk)

res.pathways <- rankPathways(res.NGSk, res.NEk, G, tab, phenotype, gsList, ngroups, methodNames, npath, allpathways)
print(res.pathways)

## Get more information about the probe sets' means and other statistics
## for the top pathway in res.pathways

res.topPathway.NGSk <- getPathwayStatistics.NGSk(statV, probeID, G, topIndex, FALSE, NULL)
print(res.topPathway.NGSk[[1]])

res.topPathway <- getPathwayStatistics(tab, phenotype, G, topIndex, ngroups, NULL, FALSE, NULL)
print(res.topPathway[[1]])


calculatePathwayStatistics

*Calculate the NTk and NEk statistics*

**Description**

Calculates the NTk and NEk statistics and the corresponding p-values and q-values for each selected pathway.

**Usage**

calculate.NTk(tab, phenotype, gsList, nsim = 1000,
ngroups = 2, verbose = FALSE)
calculate.NEk(tab, phenotype, gsList, nsim = 1000,
weightType = c("constant", "variable"),
ngroups = 2, verbose = FALSE)

Arguments

- **tab**: a numeric matrix of expression values, with the rows and columns representing probe sets and sample arrays, respectively
- **phenotype**: a numeric vector indicating the phenotype
- **gsList**: a list containing three vectors from the output of the `selectGeneSets` function
- **nsim**: an integer indicating the number of permutations to use
- **weightType**: a character string specifying the type of weight to use when calculating NEk statistics
- **ngroups**: an integer indicating the number of groups in the matrix
- **verbose**: a boolean to indicate whether to print debugging messages to the R console

Details

These functions calculate the NTk and NEk statistics and the corresponding p-values and q-values for each selected pathway. The output of both functions should be together to rank top pathways with the `rankPathways` function.

Value

A list containing

- **ngs**: number of gene sets
- **nsim**: number of permutations performed
- **t.set**: a numeric vector of Tk/Ek statistics
- **t.set.new**: a numeric vector of NTk/NEk statistics
- **p.null**: the proportion of nulls
- **p.value**: a numeric vector of p-values
- **q.value**: a numeric vector of q-values

Author(s)

Lu Tian and Peter Park, with contributions from Weil Lai

References


http://www.pnas.org/cgi/doi/10.1073/pnas.0506577102
Examples

## Load in expression data and select the probe sets have expression
## values greater than the trimmed mean in at least 1 out of 49 arrays

data(MuscleData)
sf <- apply(MuscleData, 2, mean, tr = 0.025)
temp <- sweep(MuscleData, 2, sf, FUN = "/")
ind.pskeep <- which(rowSums(temp > 1) > 0)
tabMD <- MuscleData[ind.pskeep, ]
probeID <- rownames(tabMD)
rm(temp)

## Select the data to study: IBM vs. NORM _or_ DM vs. NORM

compIBM <- TRUE
if( compIBM == TRUE ) {
  tab <- tabMD[,c(index.NORM, index.IBM)]
  phenotype <- c(rep.int(0,length(index.NORM)), rep.int(1,length(index.IBM))))
} else {
  tab <- tabMD[,c(index.NORM, index.DM)]
  phenotype <- c(rep.int(0,length(index.NORM)), rep.int(1,length(index.DM))))
}

## Prepare the pathways to analyze

data(GenesetsU133a)
gsList <- selectGeneSets(G, probeID, 20, 500)

## Calculate NTk and weighted NEk for each gene set
## * Use a higher nsim (e.g., 2500) value for more reproducible results

nsim <- 1000
ngroups <- 2
verbose <- TRUE
weightType <- "constant"
methodNames <- c("NTk", "NEk")
npath = 25
allpathways <- FALSE

res.NTk <- calculate.NTk(tab, phenotype, gsList, nsim, ngroups, verbose)
res.NEk <- calculate.NEk(tab, phenotype, gsList, nsim, weightType, ngroups, verbose)

## Summarize results

res.pathways <- rankPathways(res.NTk, res.NEk, G, tab, phenotype, gsList, ngroups, methodNames, npath, allpathways)
print(res.pathways)

## Get more information about the probe sets' means and other statistics
## for the top pathway in res.pathways

topIndex <- res.pathways$IndexG[1]
res.topPathway <- getPathwayStatistics(tab, phenotype, G, topIndex, ngroups, NULL, FALSE, NULL)
print(res.topPathway[[1]])
GenesetsU133a  
*Collection of Human Pathways from Gene Ontology, BioCyc, BioCarta, KEGG, and SuperArray*

**Description**

In this data set, the list $G$ contain annotations for most human pathways as described in Gene Ontology, BioCyc, BioCarta, KEGG, and SuperArray. Each pathway in $G$ contains the lookup ID ($src$), the Entrez Gene IDs ($locusID$), the pathway title ($title$), and the probe set IDs represented in the pathway ($probes$).

**Usage**

```r
data(GenesetsU133a)
```

**Format**

A nested list

**Source**

[http://www.chip.org/~ppark/PNAS05/](http://www.chip.org/~ppark/PNAS05/)

**References**


---

**getPathwayStatistics.NGSk**

*Give the statistics for the probe sets in a pathway*

**Description**

Gives the statistics for the probe sets associated with a pathway.

**Usage**

```r
getPathwayStatistics.NGSk(statV, probeID, G, index,  
    keepUnknownProbes = FALSE, annotpkg = NULL)
```
Arguments

- **statV**: a numeric vector of test statistic (not p-values) for each individual probe/gene
- **probeID**: a character vector containing the names of probe sets associated with a matrix of expression values
- **G**: a list containing the source, title, and probe sets associated with each curated pathway
- **index**: an integer vector specifying the pathway(s) to summarize in G
- **keepUnknownProbes**: a boolean indicating whether to keep the names of probe sets not represented in tab in the summary data frame
- **annotpkg**: a character vector specifying the name of the BioConductor annotation package to use to fetch accession numbers, Entrez Gene IDs, gene name, and gene symbols

Details

This function gives the test statistic for each probe in the pathway as indicated in G[[index]].

Value

A list containing data frames (1 per pathway) with the probes’ name and the corresponding test statistic.

If a valid annotpkg is specified, the probes’ accession numbers, Entrez Gene IDs, gene name, and gene symbols are also returned.

Note

See the help page for calculate.NGSk for example code that uses getPathwayStatistics.NGSk

Author(s)

Weil Lai

gPathwayStatistics  Give the statistics for the probe sets in a pathway

Description

Gives the statistics for the probe sets associated with a pathway.

Usage

```
gPathwayStatistics(tab, phenotype, G, index, ngroups = 2, statList = NULL, keepUnknownProbes = FALSE, annotpkg = NULL)
```
Arguments

- **tab**: a numeric matrix of expression values, with the rows and columns representing probe sets and sample arrays, respectively.
- **phenotype**: a numeric vector indicating the phenotype.
- **G**: a list containing the source, title, and probe sets associated with each curated pathway.
- **index**: an integer vector specifying the pathway(s) to summarize in G.
- **ngroups**: an integer indicating the number of groups in the expression matrix.
- **statList**: a list containing results from `calcTStatFast`.
- **keepUnknownProbes**: a boolean indicating whether to keep the names of probe sets not represented in tab in the summary data frame.
- **annotpkg**: a character vector specifying the name of the BioConductor annotation package to use to fetch accession numbers, Entrez Gene IDs, gene name, and gene symbols.

Details

This function gives the mean, standard deviation, and test statistic for each probe in the pathway as indicated in `G[[index]]`.

Value

A list containing data frames (1 per pathway) with the probes' name, mean, standard deviation, the test statistic (e.g., t-test), and the corresponding unadjusted p-value.

- If `ngroups = 1`, the Pearson correlation coefficient is also returned.
- If a valid `annotpkg` is specified, the probes' accession numbers, Entrez Gene IDs, gene name, and gene symbols are also returned.

Note

See the help page of `calculate.NTk` or `calculate.NEk` for example code that uses `getPathwayStatistics`.

Author(s)

Weil Lai
MuscleData

Inflammatory Myopathy Dataset

Description

MuscleData is a R workspace containing MuscleData, index.DM, index.IBM, and index.NORM. The MuscleData object contains data from 49 samples hybridized onto Affymetrix HG-U133A arrays; the row names for the data frame contain the corresponding probe set IDs. The ‘index’ objects contain indices that describe the phenotype for the sample columns in MuscleData.

Usage

data(MuscleData)

Format

1 data frame and 3 vectors

Source

http://www.chip.org/~ppark/PNAS05

References


rankPathways.NGSk

Summarizes Top Pathways from One of the Pathway Analyses

Description

Summarizes top pathways from one of the pathway analyses (i.e., calculate.NTk, calculate.NEk, calculate.NGSk, or calculate.GSEA)

Usage

rankPathways.NGSk(res.NGSk, G, gsList, methodName = "NGSk", npath = 25)
Arguments

- `res.NGSk`: a list from the output of `calculate.NGSk`, `calculate.NTk`, `calculate.NEk`, or `calculate.GSEA`.
- `G`: a list containing the source, title, and probe sets associated with each curated pathway.
- `gsList`: a list containing three vectors from the output of the `selectGeneSets` function.
- `methodName`: a character vector of length 1 giving the name of the pathway analysis used in making `res.NGSk`.
- `npath`: an integer indicating the number of top gene sets to consider when ranking the top pathways.

Details

This function ranks the statistics given in `res.NGSk` and summarizes the top gene sets in a tabular format similar to Table 2 in Tian et al. (2005).

Value

A data frame showing the pathways' indices in `G`, gene set category, pathway title, set size, `res.NGSk`'s statistics, the corresponding q-values, and the numerical ranks for the top gene sets.

Note

See the help page for `calculate.NGSk` for example code that uses `rankPathways.NGSk`.

Author(s)

Lu Tian and Peter Park, with contributions from Weil Lai.

References


---

rankPathways: Summarizes Top Pathways from Pathway Analyses

Description

Summarizes top pathways from pathway analyses.

Arguments

res.A  a list from the output of calculate.NTk or calculate.NEk
res.B  a list from the output of calculate.NTk or calculate.NEk
G  a list containing the source, title, and probe sets associated with each curated pathway
tab  a numeric matrix of expression values, with the rows and columns representing probe sets and sample arrays, respectively
phenotype  a numeric vector indicating the phenotype
gsList  a list containing three vectors from the output of the selectGeneSets function
ngroups  an integer indicating the number of groups in the matrix
methodNames  a character vector of length 2 giving the names for res.A and res.B
npath  an integer indicating the number of top gene sets to consider from each statistic when ranking the top pathways
allpathways  a boolean to indicate whether to include the top npath pathways from each statistic or just consider the top npath pathways (sorted by the sum of ranks of both statistics) when generating the summary table

Details

This function ranks together the statistics given in res.A and res.B and summarizes the top gene sets in a tabular format similar to Table 2 in Tian et al. (2005)

Value

A data frame showing the pathways' indices in G, gene set category, pathway title, set size, res.A's statistics, res.B's statistics, the corresponding q-values, and the ranks for the top gene sets.

Note

See the help page for calculate.NTk or calculate.NEk for example code that uses rankPathways

Author(s)

Lu Tian and Peter Park, with contributions from Weil Lai

References

http://www.pnas.org/cgi/doi/10.1073/pnas.0506577102
runSigPathway  

Perform pathway analysis

Description

Performs pathway analysis

Usage

```r
runSigPathway(G, minNPS = 20, maxNPS = 500,
               tab, phenotype, nsim = 1000,
               weightType = c("constant", "variable"), ngroups = 2,
               npath = 25, verbose = FALSE, allpathways = FALSE)
```

Arguments

- **G**: a list containing the source, title, and probe sets associated with each curated pathway
- **minNPS**: an integer specifying the minimum number of probe sets in `tab` that should be in a gene set
- **maxNPS**: an integer specifying the maximum number of probe sets in `tab` that should be in a gene set
- **tab**: a numeric matrix of expression values, with the rows and columns representing probe sets and sample arrays, respectively
- **phenotype**: a numeric vector indicating the phenotype
- **nsim**: an integer indicating the number of permutations to use
- **weightType**: a character string specifying the type of weight to use when calculating NEk statistics
- **ngroups**: an integer indicating the number of groups in the matrix
- **npath**: an integer indicating the number of top gene sets to consider from each statistic when ranking the top pathways
- **verbose**: a boolean to indicate whether to print debugging messages to the R console
- **allpathways**: a boolean to indicate whether to include the top `npath` pathways from each statistic or just consider the top `npath` pathways (sorted by the sum of ranks of both statistics) when generating the summary table

Details

`runSigPathway` is a wrapper function that

1. Selects the gene sets to analyze using `selectGeneSets`
2. Calculates NTk and NEk statistics using `calculate.NTk` and `calculate.NEK`
3. Ranks the top `npath` pathways from each statistic using `rankPathways`
4. Summarizes the means, standard deviation, and individual statistics of each probe set in each of the above pathways using `getPathwayStatistics`
Value

A list containing

gsList a list containing three vectors from the output of the `selectGeneSets` function
list.NTk a list from the output of `calculate.NTk`
list.NEk a list from the output of `calculate.NEk`
df.pathways a data frame from `rankPathways` which contains the top pathways’ indices in `G`, gene set category, pathway title, set size, NTk statistics, NEk statistics, the corresponding q-values, and the ranks.
list.gPS a list from `getPathwayStatistics` containing `nrow(df.pathways)` data frames corresponding to the pathways listed in `df.pathways`. Each data frame contains the name, mean, standard deviation, the test statistic (e.g., t-test), and the corresponding unadjusted p-value. If `ngroups = 1`, the Pearson correlation coefficient is also returned.

Author(s)

Lu Tian and Peter Park, with contributions from Weil Lai

References


Examples

```r
## Load in expression data and select the probe sets have expression
## values greater than the trimmed mean in at least 1 out of 49 arrays
data(MuscleData)
sf <- apply(MuscleData, 2, mean, tr = 0.025)
temp <- sweep(MuscleData, 2, sf, FUN = '/')
ind.pskeep <- which(rowSums(temp > 1) > 0)
tabMD <- MuscleData[ind.pskeep,]
rm(temp)

## Select the data to study: IBM vs. NORM _or_ DM vs. NORM
compIBM <- TRUE
if( compIBM == TRUE ) {
tab <- tabMD[,c(index.NORM, index.IBM)]
phenotype <- c(rep.int(0,length(index.NORM)), rep.int(1,length(index.IBM)))
}else {
tab <- tabMD[,c(index.NORM, index.DM)]
phenotype <- c(rep.int(0,length(index.NORM)), rep.int(1,length(index.DM)))
}
```

16
## Prepare the pathways to analyze
data(GenesetsU133a)

nsim <- 1000
groups <- 2
verbose <- TRUE
weightType <- "constant"
npath = 25
allpathways <- FALSE

res.muscle <- runSigPathway(G, 20, 500, tab, phenotype, nsim,
weightType, groups, npath, verbose, allpathways)

## Summarize results
print(res.muscle$df.pathways)

## Get more information about the probe sets' means and other statistics
## for the top pathway in res.pathways
print(res.muscle$list.gPS[[1]])

---

selectGeneSets  

Select gene sets to be analyzed in pathway analysis

---

### Description

Selects gene sets to be analyzed in pathway analysis based on minimum and maximum number of probe sets to consider per pathway.

### Usage

```r
selectGeneSets(G, probeID, minNPS = 20, maxNPS = 500)
```

### Arguments

- **G**
a list containing the source, title, and probe sets associated with each curated pathway
- **probeID**
a character vector containing the names of probe sets associated with a matrix of expression values
- **minNPS**
an integer specifying the minimum number of probe sets in `probeID` that should be in a gene set
- **maxNPS**
an integer specifying the maximum number of probe sets in `probeID` that should be in a gene set

### Details

This function selects the appropriate pathways from a large, curated list based on the minimum and maximum number of probe sets that should be considered in a gene set. It creates three vectors: `nprobesV` and `indexV` representing a sparse indicator matrix and `indGused` indicating which gene sets were selected from `G`. 

17
Value

A list containing

nprobesV an integer vector indicating the number of probe sets in `probeID` that is in each selected gene set

indexV an integer vector containing positions for each 1s in the sparse indicator matrix

indGused an integer vector indicating which pathways in `G` were chosen

Note

See the help page for `calculate.NTk` or `calculate.NEk` for example code that uses `getPathwayStatistics`

Author(s)

Lu Tian and Peter Park, with contributions from Weil Lai

References
