Package: gMCP (via r-universe)

October 28, 2026

Type Package

Title Graph Based Multiple Comparison Procedures

Version 0.8-17

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Description Functions and a graphical user interface for graphical described multiple test procedures.

Depends R (>= 3.0.0), methods

Imports MASS, PolynomF, multcomp (>= 1.1), mvtnorm, Matrix, CommonJavaJars (>= 1.1.0), rJava (>= 0.6-3), JavaGD, xlsxjars (>= 0.6.1), stats4

Suggests RUnit, knitr, graph (>= 1.20), mutoss, boot, coin

VignetteBuilder knitr

SystemRequirements Java (>= 5.0)

License GPL (>= 2)

URL https://github.com/kornl/gMCP

BugReports https://github.com/kornl/gMCP/issues

Encoding UTF-8

RoxygenNote 7.2.3

Collate 'analysis.R' 'calcPower.R' 'graphMCP.R' 'closure.R' 'convertFromOldClassDefinition.R' 'doRUnitTests.R' 'exampleGraphs.R' 'gACT-internal.R' 'gMCP.R' 'gMCP.extended.R' 'gPAD.R' 'generateBounds.R' 'generatePvals.R' 'generateTest.R' 'generateWeights.R' 'graph2latex.R' 'graphTest.R' 'helperGUI.R' 'initJava.R' 'matrix2graph.R' 'misc.R' 'modifyGraphs.R' 'onLoad.R' 'plotCI.R' 'powerPlot.R' 'rqmvnorm.R' 'sampSize.R' 'startGUIs.R' 'subVariables.R'

NeedsCompilation yes

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Config/pak/sysreqs default-jdk

Repository https://cran.r-universe.dev

Date/Publication 2024-03-26 02:33:53 UTC

RemoteUrl https://github.com/cran/gMCP

RemoteRef HEAD

RemoteSha ed5d11cb052fe412d5da1bb65d889a6455939623

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gMCP-package *Graphical described Multiple Comparison Procedures*

Description

This package provides functions and graphical user interfaces for graphical described multiple comparison procedures.

Details

Package:	gMCP
Type:	Package
License:	GPL (>= 2)

The package gMCP helps with the following steps of performing a multiple test procedure:

1. Creating a object of `graphMCP` that represents a sequentially rejective multiple test procedure. This can be either done directly via the `new` function or converter functions like `matrix2graph` at the R command line or by using a graphical user interface started with function `graphGUI`.

2. Calling `gMCP` or `graphGUI`.

3. Exporting the results (optional with all sequential steps) as LaTeX or Word report.

Note

We use the following Java libraries:

- Apache Commons Logging under the Apache License, Version 2.0, January 2004, `https://commons.apache.org/logging/`, Copyright 2001-2007 The Apache Software Foundation
- Apache jog4j under Apache License 2.0, `https://logging.apache.org/log4j/`, Copyright 2007 The Apache Software Foundation
- Apache Commons Lang under Apache License 2.0, `https://commons.apache.org/lang/`, Copyright 2001-2011 The Apache Software Foundation
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- JRI under Lesser General Public License (LGPL) 2.1, https://www.rforge.net/rJava/, Copyright 2004-2007 Simon Urbanek
- iText 2.1.4 under LGPL, https://itextpdf.com/, Copyright by Bruno Lowagie
- SwingWorker under LGPL, from java.net/projects/swingworker/, Copyright (c) 2005 Sun Microsystems
- JXLayer under BSD License, from java.net/projects/jxlayer/, Copyright 2006-2009, Alexander Potochkin
- JGoodies Forms under BSD License, https://www.jgoodies.com/freeware/libraries/forms/, Copyright JGoodies Karsten Lentzsch
- AFCommons under BSD License, https://web.archive.org/web/20180828002833/http://www.algorithm-forge.com/afcommons/, Copyright (c) 2007-2014 by Kornelius Rohmeyer and Bernd Bischl
- JHLIR under BSD License, https://jhlir.r-forge.r-project.org/, Copyright (c) 2008-2014 by Bernd Bischl and Kornelius Rohmeyer

Author(s)

Kornelius Rohmeyer, R code for correlated tests and adaptive designs from Florian Klinglmueller.

Maintainer: Kornelius Rohmeyer <rohmeyer@small-projects.de>

References

Frank Bretz, Martin Posch, Ekkehard Glimm, Florian Klinglmueller, Willi Maurer, Kornelius Rohmeyer (2011): Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes or parametric tests. Biometrical Journal 53 (6), pages 894-913, Wiley. doi:10.1002/bimj.201000239

Frank Bretz, Willi Maurer, Werner Brannath, Martin Posch: A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine 2009 vol. 28 issue 4 page 586-604. https://www.meduniwien.ac.at/fwf_adaptive/papers/bretz_2009_22.pdf

Examples

```
g5 <- BonferroniHolm(5)
## Not run:
graphGUI("g5")
## End(Not run)
gMCP(g5, pvalues=c(0.1,0.2,0.4,0.4,0.4))
```

---

bdiagNA *Create a Block Diagonal Matrix with NA outside the diagonal*

Description

Build a block diagonal matrix with NA values outside the diagonal given several building block matrices.

Usage

```
bdiagNA(...)
```

Arguments

`...`	individual matrices or a `list` of matrices.

Details

This function is usefull to build the correlation matrices, when only partial knowledge of the correlation exists.

Value

A block diagonal matrix with NA values outside the diagonal.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

See Also

gMCP

Examples

```
bdiagNA(diag(3), matrix(1/2,nr=3,nc=3), diag(2))
```

---

bonferroni.test *Weighted Bonferroni-test*

Description

Weighted Bonferroni-test

Usage

```
bonferroni.test(
  pvalues,
  weights,
  alpha = 0.05,
  adjPValues = TRUE,
  verbose = FALSE,
  ...
)
```

Arguments

pvalues	A numeric vector specifying the p-values.
weights	A numeric vector of weights.
alpha	A numeric specifying the maximal allowed type one error rate. If adjPValues==TRUE (default) the parameter alpha is not used.
adjPValues	Logical scalar. If TRUE (the default) an adjusted p-value for the weighted Bonferroni-test is returned. Otherwise if adjPValues==FALSE a logical value is returned whether the null hypothesis can be rejected.
verbose	Logical scalar. If TRUE verbose output is generated.
...	Further arguments possibly passed by gMCP which will be used by other test procedures but not this one.

Examples

```
bonferroni.test(pvalues=c(0.1,0.2,0.05), weights=c(0.5,0.5,0))
bonferroni.test(pvalues=c(0.1,0.2,0.05), weights=c(0.5,0.5,0), adjPValues=FALSE)
```

---

bonferroni.trimmed.simes.test

Trimmed Simes test for intersections of two hypotheses and otherwise weighted Bonferroni-test

---

Description

Trimmed Simes test for intersections of two hypotheses and otherwise weighted Bonferroni-test

Usage

```
bonferroni.trimmed.simes.test(
  pvalues,
  weights,
  alpha = 0.05,
  adjPValues = FALSE,
  verbose = FALSE,
  ...
)
```

Arguments

pvalues	A numeric vector specifying the p-values.
weights	A numeric vector of weights.
alpha	A numeric specifying the maximal allowed type one error rate. If adjPValues==TRUE (default) the parameter alpha is not used.

adjPValues	Logical scalar. If TRUE (the default) an adjusted p-value for the weighted test is returned. Otherwise if adjPValues==FALSE a logical value is returned whether the null hypothesis can be rejected.
verbose	Logical scalar. If TRUE verbose output is generated.
...	Further arguments possibly passed by gMCP which will be used by other test procedures but not this one.

References

Brannath, W., Bretz, F., Maurer, W., & Sarkar, S. (2009). Trimmed Weighted Simes Test for Two One-Sided Hypotheses With Arbitrarily Correlated Test Statistics. Biometrical Journal, 51(6), 885-898.

Examples

```
bonferroni.trimmed.simes.test(pvalues=c(0.1,0.2,0.05), weights=c(0.5,0.5,0))
bonferroni.trimmed.simes.test(pvalues=c(0.1,0.2,0.05), weights=c(0.5,0.5,0), adjPValues=FALSE)
```

---

calcPower *Calculate power values*

Description

Given the distribution under the alternative (assumed to be multivariate normal), this function calculates the power to reject at least one hypothesis, the local power for the hypotheses as well as the expected number of rejections.

Usage

```
calcPower(
  weights,
  alpha,
  G,
  mean = rep(0, nrow(corr.sim)),
  corr.sim = diag(length(mean)),
  corr.test = NULL,
  n.sim = 10000,
  type = c("quasirandom", "pseudorandom"),
  f = list(),
  upscale = FALSE,
  graph,
  ...
)
```

Arguments

weights	Initial weight levels for the test procedure (see graphTest function). Alternatively a graphMCP object can be given as parameter graph.
alpha	Overall alpha level of the procedure, see graphTest function. (For entangled graphs alpha should be a numeric vector of length equal to the number of graphs, each element specifying the partial alpha for the respective graph. The overall alpha level equals sum(alpha).)
G	Matrix determining the graph underlying the test procedure. Note that the diagonal need to contain only 0s, while the rows need to sum to 1. When multiple graphs should be used this needs to be a list containing the different graphs as elements. Alternatively a graphMCP object can be given as parameter graph.
mean	Mean under the alternative
corr.sim	Covariance matrix under the alternative.
corr.test	Correlation matrix that should be used for the parametric test. If corr.test==NULL the Bonferroni based test procedure is used. Can contain NAs.
n.sim	Monte Carlo sample size. If type = "quasirandom" this number is rounded up to the next power of 2, e.g. 1000 is rounded up to $1024 = 2^10$ and at least 1024.
type	What type of random numbers to use. quasirandom uses a randomized Lattice rule, and should be more efficient than pseudorandom that uses ordinary (pseudo) random numbers.
f	List of user defined power functions (or just a single power function). If one is interested in the power to reject hypotheses 1 and 3 one could specify: f=function(x) {x[1] && x[3]}. If the power of rejecting hypotheses 1 and 2 is also of interest one would use a (optionally named) list: f=list(power1and3=function(x) {x[1] && x[3]}, power1and2=function(x) {x[1] && x[2]}). If the list has no names, the functions will be referenced to as "func1", "func2", etc. in the output.
upscale	Logical. If upscale=FALSE then for each intersection of hypotheses (i.e. each subgraph) a weighted test is performed at the possibly reduced level alpha of sum(w)*alpha, where sum(w) is the sum of all node weights in this subset. If upscale=TRUE all weights are upscaled, so that sum(w)=1.
graph	A graph of class graphMCP.
...	For backwards compatibility. For example up to version 0.8-7 the parameters corr.model and corr.test were called sigma and cr. Also instead of supplying a graph object one could supply a parameter weights and a transition matrix G.
test	In the parametric case there is more than one way to handle subgraphs with less than the full alpha. If the parameter test is missing, the tests are performed as described by Bretz et al. (2011), i.e. tests of intersection null hypotheses always exhaust the full alpha level even if the sum of weights is strictly smaller than one. If test="simple-parametric" the tests are performed as defined in Equation (3) of Bretz et al. (2011).

Value

A list containg three elements

`LocalPower` A numeric giving the local powers for the hypotheses

`ExpRejections` The expected number of rejections

`PowAtlst1` The power to reject at least one hypothesis

References

Bretz, F., Maurer, W., Brannath, W. and Posch, M. (2009) A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine, 28, 586–604

Bretz, F., Maurer, W. and Hommel, G. (2010) Test and power considerations for multiple endpoint analyses using sequentially rejective graphical procedures, to appear in Statistics in Medicine

Examples

```
## reproduce example from Stat Med paper (Bretz et al. 2010, Table I)
## first only consider line 2 of Table I
## significance levels
graph <- simpleSuccessiveII()
## alternative (mvn distribution)
corMat <- rbind(c(1, 0.5, 0.5, 0.5/2),
                c(0.5,1,0.5/2,0.5),
                c(0.5,0.5/2,1,0.5),
                c(0.5/2,0.5,0.5,1))
theta <- c(3, 0, 0, 0)
calcPower(graph=graph, alpha=0.025, mean=theta, corr.sim=corMat, n.sim= 100000)


## now reproduce all 14 simulation scenarios
## different graphs
weights1 <- c(rep(1/2, 12), 1, 1)
weights2 <- c(rep(1/2, 12), 0, 0)
eps <- 0.01
gam1 <- c(rep(0.5, 10), 1-eps, 0, 0, 0)
gam2 <- gam1
## different multivariate normal alternatives
rho <- c(rep(0.5, 8), 0, 0.99, rep(0.5,4))
th1 <- c(0, 3, 3, 3, 2, 1, rep(3, 7), 0)
th2 <- c(rep(0, 6), 3, 3, 3, 3, 0, 0, 0, 3)
th3 <- c(0, 0, 3, 3, 3, 3, 0, 2, 2, 2, 3, 3, 3, 3)
th4 <- c(0,0,0,3,3,3,0,2,2,2,0,0,0,0)

## function that calculates power values for one scenario
simfunc <- function(nSim, a1, a2, g1, g2, rh, t1, t2, t3, t4, Gr){
  al <- c(a1, a2, 0, 0)
  G <- rbind(c(0, g1, 1-g1, 0), c(g2, 0, 0, 1-g2), c(0, 1, 0, 0), c(1, 0, 0, 0))
 corMat <- rbind(c(1, 0.5, rh, rh/2), c(0.5,1,rh/2,rh), c(rh,rh/2,1,0.5), c(rh/2,rh,0.5,1))
  mean <- c(t1, t2, t3, t4)
  calcPower(weights=al, alpha=0.025, G=G, mean=mean, corr.sim=corMat, n.sim = nSim)
}
```

```
## calculate power for all 14 scenarios
outList <- list()
for(i in 1:14){
  outList[[i]] <- simfunc(10000, weights1[i], weights2[i],
                    gam1[i], gam2[i], rho[i], th1[i], th2[i], th3[i], th4[i])
}

## summarize data as in Stat Med paper Table I
atlst1 <- as.numeric(lapply(outList, function(x) x$PowAtlst1))
locpow <- do.call("rbind", lapply(outList, function(x) x$LocalPower))

round(cbind(atlst1, locpow), 5)
```

`corMatWizard` *Graphical User Interface for the creation of correlation matrices*

Description

Starts a graphical user interface for the correlation matrices.

Usage

```
corMatWizard(n, matrix, names, envir = globalenv())
```

Arguments

`n`	Square root of the dimension of the quadratic $n \times n$-Matrix.
`matrix`	Variable name of matrix of dimension $n \times n$ to start with.
`names`	Row and column names. (Default will be H1,H2,...,Hn.)
`envir`	Environment where the object *matrix* is located and/or it should be saved (default is the global environment).

Value

The function itself returns NULL. But with the dialog a symmetric matrix of dimension $n \times n$ can be created or edited that will be available in R under the specified variable name after saving.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

Examples

```
## Not run:
corMatWizard(5) # is equivalent to
corMatWizard(matrix=diag(5))
corMatWizard(names=c("H1", "H2", "H3", "E1", "E2"))
C <- cor(matrix(rnorm(100),10), matrix(rnorm(100),10))
corMatWizard(matrix="C") # or
corMatWizard(matrix=C)

## End(Not run)
```

`doInterim` *EXPERIMENTAL: Evaluate conditional errors at interim for a pre-planned graphical procedure*

Description

Computes partial conditional errors (PCE) for a pre-planned graphical procedure given information fractions and first stage z-scores. - Implementation of adaptive procedures is still in an early stage and may change in the near future

Usage

```
doInterim(graph, z1, v, alpha = 0.025)
```

Arguments

`graph`	A graph of class `graphMCP`.
`z1`	A numeric vector giving first stage z-scores.
`v`	A numeric vector giving the proportions of pre-planned measurements collected up to the interim analysis. Will be recycled of length different than the number of elementary hypotheses.
`alpha`	A numeric specifying the maximal allowed type one error rate.

Details

For details see the given references.

Value

An object of class `gPADInterim`, more specifically a list with elements

`Aj` a matrix of PCEs for all elementary hypotheses in each intersection hypothesis

`BJ` a numeric vector giving sum of PCEs per intersection hypothesis

`preplanned` Pre planned test represented by an object of class `graphMCP`

Author(s)

Florian Klinglmueller <float@lefant.net>

References

Frank Bretz, Willi Maurer, Werner Brannath, Martin Posch: A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine 2009 vol. 28 issue 4 page 586-604. https://www.meduniwien.ac.at/fwf_adaptive/papers/bretz_2009_22.pdf

Frank Bretz, Martin Posch, Ekkehard Glimm, Florian Klinglmueller, Willi Maurer, Kornelius Rohmeyer (2011): Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes or parametric tests. Biometrical Journal 53 (6), pages 894-913, Wiley. doi:10.1002/bimj.201000239

Posch M, Futschik A (2008): A Uniform Improvement of Bonferroni-Type Tests by Sequential Tests JASA 103/481, 299-308

Posch M, Maurer W, Bretz F (2010): Type I error rate control in adaptive designs for confirmatory clinical trials with treatment selection at interim Pharm Stat 10/2, 96-104

See Also

graphMCP, secondStageTest

Examples

```
## Simple successive graph (Maurer et al. 2011)
## two treatments two hierarchically ordered endpoints
a <- .025
G <- simpleSuccessiveI()
## some z-scores:

p1=c(.1,.12,.21,.16)
z1 <- qnorm(1-p1)
p2=c(.04,1,.14,1)
z2 <- qnorm(1-p2)
v <- c(1/2,1/3,1/2,1/3)

intA <- doInterim(G,z1,v)

## select only the first treatment
fTest <- secondStageTest(intA,c(1,0,1,0))
```

`entangledMCP-class` *Class entangledMCP*

Description

A entangledMCP object describes ... TODO

Slots

`subgraphs`: A list of graphs of class graphMCP.

`weights`: A numeric.

`graphAttr`: A list for graph attributes like color, etc.

Methods

print `signature(object = "entangledMCP")`: A method for printing the data of the entangled graph to the R console.

getMatrices `signature(object = "entangledMCP")`: A method for getting the list of transition matrices of the entangled graph.

getWeights `signature(object = "entangledMCP")`: A method for getting the matrix of weights of the entangled graph.

getRejected `signature(object = "entangledMCP")`: A method for getting the information whether the hypotheses are marked in the graph as already rejected. If a second optional argument `node` is specified, only for these nodes the boolean vector will be returned.

getXCoordinates `signature(object = "entangledMCP")`: A method for getting the x coordinates of the graph. If a second optional argument `node` is specified, only for these nodes the x coordinates will be returned. If x coordinates are not yet set, `NULL` is returned.

getYCoordinates `signature(object = "entangledMCP")`: A method for getting the y coordinates of the graph If a second optional argument `node` is specified, only for these nodes the x coordinates will be returned. If y coordinates are not yet set, `NULL` is returned.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

See Also

graphMCP

Examples

```
g1 <- BonferroniHolm(2)
g2 <- BonferroniHolm(2)

graph <- new("entangledMCP", subgraphs=list(g1,g2), weights=c(0.5,0.5))
```

```
getMatrices(graph)
getWeights(graph)
```

---

exampleGraphs *Functions that create different example graphs*

Description

Functions that creates example graphs, e.g. graphs that represents a Bonferroni-Holm adjustment, parallel gatekeeping or special procedures from selected papers.

Usage

```
BonferroniHolm(n, weights = rep(1/n, n))

BretzEtAl2011()

BauerEtAl2001()

BretzEtAl2009a()

BretzEtAl2009b()

BretzEtAl2009c()

HommelEtAl2007()

HommelEtAl2007Simple()

parallelGatekeeping()

improvedParallelGatekeeping()

fallback(weights)

fixedSequence(n)

simpleSuccessiveI()

simpleSuccessiveII()

truncatedHolm(gamma)

generalSuccessive(weights = c(1/2, 1/2), gamma, delta)

HuqueAloshEtBhore2011()
```

```
HungEtWang2010(nu, tau, omega)

MaurerEtAl1995()

cycleGraph(nodes, weights)

improvedFallbackI(weights = rep(1/3, 3))

improvedFallbackII(weights = rep(1/3, 3))

FerberTimeDose2011(times, doses, w = "\\nu")

Ferber2011(w)

Entangled1Maurer2012()

Entangled2Maurer2012()

WangTing2014(nu, tau)
```

Arguments

n	Number of hypotheses.
weights	Numeric vector of node weights.
gamma	An optional number in [0,1] specifying the value for variable gamma.
delta	An optional number in [0,1] specifying the value for variable delta.
nu	An optional number in [0,1] specifying the value for variable nu.
tau	An optional number in [0,1] specifying the value for variable tau.
omega	An optional number in [0,1] specifying the value for variable omega.
nodes	Character vector of node names.
times	Number of time points.
doses	Number of dose levels.
w	Further variable weight(s) in graph.

Details

We are providing functions and not the resulting graphs directly because this way you have additional examples: You can look at the function body with body and see how the graph is built.

list("BonferroniHolm") Returns a graph that represents a Bonferroni-Holm adjustment. The result is a complete graph, where all nodes have the same weights and each edge weight is $\frac{1}{n-1}$.

list("BretzEtAl2011") Graph in figure 2 from Bretz et al. See references (Bretz et al. 2011).

list("HommelEtAl2007") Graph from Hommel et al. See references (Hommel et al. 2007).

list("parallelGatekeeping") Graph for parallel gatekeeping. See references (Dmitrienko et al. 2003).

list("improvedParallelGatekeeping") Graph for improved parallel gatekeeping. See references (Hommel et al. 2007).

list("HungEtWang2010") Graph from Hung et Wang. See references (Hung et Wang 2010).

list("MaurerEtAl1995") Graph from Maurer et al. See references (Maurer et al. 1995).

list("cycleGraph") Cycle graph. The weight `weights[i]` specifies the edge weight from node i to node $i+1$ for $i = 1, \ldots, n-1$ and `weight[n]` from node n to node 1.

list("improvedFallbackI") Graph for the improved Fallback Procedure by Wiens & Dmitrienko. See references (Wiens et Dmitrienko 2005).

list("improvedFallbackII") Graph for the improved Fallback Procedure by Hommel & Bretz. See references (Hommel et Bretz 2008).

list("Ferber2011") Graph from Ferber et al. See references (Ferber et al. 2011).

list("FerberTimeDose2011") Graph from Ferber et al. See references (Ferber et al. 2011).

list("Entangled1Maurer2012") Entangled graph from Maurer et al. TODO: Add references as soon as they are available.

Value

A graph of class `graphMCP` that represents a sequentially rejective multiple test procedure.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

References

Holm, S. (1979). A simple sequentally rejective multiple test procedure. Scandinavian Journal of Statistics 6, 65-70.

Dmitrienko, A., Offen, W., Westfall, P.H. (2003). Gatekeeping strategies for clinical trials that do not require all primary effects to be significant. Statistics in Medicine. 22, 2387-2400.

Bretz, F., Maurer, W., Brannath, W., Posch, M.: A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine 2009 vol. 28 issue 4 page 586-604. https://www.meduniwien.ac.at/fwf_adaptive/papers/bretz_2009_22.pdf

Bretz, F., Maurer, W. and Hommel, G. (2011), Test and power considerations for multiple endpoint analyses using sequentially rejective graphical procedures. Statistics in Medicine, 30: 1489–1501.

Hommel, G., Bretz, F. und Maurer, W. (2007). Powerful short-cuts for multiple testing procedures with special reference to gatekeeping strategies. Statistics in Medicine, 26(22), 4063-4073.

Hommel, G., Bretz, F. (2008): Aesthetics and power considerations in multiple testing - a contradiction? Biometrical Journal 50:657-666.

Hung H.M.J., Wang S.-J. (2010). Challenges to multiple testing in clinical trials. Biometrical Journal 52, 747-756.

W. Maurer, L. Hothorn, W. Lehmacher: Multiple comparisons in drug clinical trials and preclinical assays: a-priori ordered hypotheses. In Biometrie in der chemisch-pharmazeutischen Industrie, Vollmar J (ed.). Fischer Verlag: Stuttgart, 1995; 3-18.

Maurer, W., & Bretz, F. (2013). Memory and other properties of multiple test procedures generated by entangled graphs. Statistics in medicine, 32 (10), 1739-1753.

Wiens, B.L., Dmitrienko, A. (2005): The fallback procedure for evaluating a single family of hypotheses. Journal of Biopharmaceutical Statistics 15:929-942.

Wang, B., Ting, N. (2014). An Application of Graphical Approach to Construct Multiple Testing Procedures in a Hypothetical Phase III Design. Frontiers in public health, 1 (75).

Ferber, G. Staner, L. and Boeijinga, P. (2011): Structured multiplicity and confirmatory statistical analyses in pharmacodynamic studies using the quantitative electroencephalogram, Journal of neuroscience methods, Volume 201, Issue 1, Pages 204-212.

Examples

```
g <- BonferroniHolm(5)

gMCP(g, pvalues=c(0.1, 0.2, 0.4, 0.4, 0.7))

HungEtWang2010()
HungEtWang2010(nu=1)
```

`extractPower` *Calculate power values*

Description

Calculates local power values, expected number of rejections, the power to reject at least one hypothesis and the power to reject all hypotheses.

Usage

```
extractPower(x, f = list())
```

Arguments

`x`	A matrix containing the rejected hypothesis, as produces by the graphTest function.
`f`	List of user defined power functions. If one is interested in the power to reject hypotheses 1 and 3 one could specify `function(x) {x[1] && x[3]}`. If f is a named list, the result will contain corresponding items with the same names (among the default elements described in the following).

Value

A list containg at least the following four elements and an element for each element in the parameter `f`.

`LocPower` A numeric giving the local powers for the hypotheses

`ExpNrRej` The expected number of rejections

`PowAtlst1` The power to reject at least one hypothesis

`RejectAll` The power to reject all hypotheses

`generateBounds` *generateBounds*

Description

compute rejection bounds for z-scores of each elementary hypotheses within each intersection hypotheses

Usage

```
generateBounds(
  g,
  w,
  cr,
  al = 0.05,
  hint = generateWeights(g, w),
  upscale = FALSE
)
```

Arguments

`g`	graph defined as a matrix, each element defines how much of the local alpha reserved for the hypothesis corresponding to its row index is passed on to the hypothesis corresponding to its column index
`w`	vector of weights, defines how much of the overall alpha is initially reserved for each elementary hypothesis
`cr`	correlation matrix if p-values arise from one-sided tests with multivariate normal distributed test statistics for which the correlation is partially known. Unknown values can be set to NA. (See details for more information)
`al`	overall alpha level at which the family error is controlled
`hint`	if intersection hypotheses weights have already been computed (output of `generateWeights`) can be passed here otherwise will be computed during execution
`upscale`	if `FALSE` (default) the parametric test is performed at the reduced level alpha of sum(w)*alpha. (See details)

Details

It is assumed that under the global null hypothesis $(\Phi^{-1}(1-p_1), ..., \Phi^{-1}(1-p_m))$ follow a multivariate normal distribution with correlation matrix `cr` where Φ^{-1} denotes the inverse of the standard normal distribution function.

For example, this is the case if $p_1, ..., p_m$ are the raw p-values from one-sided z-tests for each of the elementary hypotheses where the correlation between z-test statistics is generated by an overlap in the observations (e.g. comparison with a common control, group-sequential analyses etc.). An application of the transformation $\Phi^{-1}(1 - p_i)$ to raw p-values from a two-sided test will not in general lead to a multivariate normal distribution. Partial knowledge of the correlation matrix is supported. The correlation matrix has to be passed as a numeric matrix with elements of the form: $correlation[i, i] = 1$ for diagonal elements, $correlation[i, j] = \rho_{ij}$, where ρ_{ij} is the known value of the correlation between $\Phi^{-1}(1 - p_i)$ and $\Phi^{-1}(1 - p_j)$ or NA if the corresponding correlation is unknown. For example correlation[1,2]=0 indicates that the first and second test statistic are uncorrelated, whereas correlation[2,3] = NA means that the true correlation between statistics two and three is unknown and may take values between -1 and 1. The correlation has to be specified for complete blocks (ie.: if cor(i,j), and cor(i,k) for i!=j!=k are specified then cor(j,k) has to be specified as well) otherwise the corresponding intersection null hypotheses tests are not uniquely defined and an error is returned.

The parametric tests in (Bretz et al. (2011)) are defined such that the tests of intersection null hypotheses always exhaust the full alpha level even if the sum of weights is strictly smaller than one. This has the consequence that certain test procedures that do not test each intersection null hypothesis at the full level alpha may not be implemented (e.g., a single step Dunnett test). If `upscale` is set to `FALSE` (default) the parametric tests are performed at a reduced level alpha of sum(w) * alpha and p-values adjusted accordingly such that test procedures with non-exhaustive weighting strategies may be implemented. If set to `TRUE` the tests are performed as defined in Equation (3) of (Bretz et al. (2011)).

Value

Returns a matrix of rejection bounds. Each row corresponds to an intersection hypothesis. The intersection corresponding to each line is given by conversion of the line number into binary (eg. 13 is binary 1101 and corresponds to (H1,H2,H4))

Author(s)

Florian Klinglmueller

References

Bretz F, Maurer W, Brannath W, Posch M; (2008) - A graphical approach to sequentially rejective multiple testing procedures. - Stat Med - 28/4, 586-604

Frank Bretz, Martin Posch, Ekkehard Glimm, Florian Klinglmueller, Willi Maurer, Kornelius Rohmeyer (2011): Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes or parametric tests. Biometrical Journal 53 (6), pages 894-913, Wiley. doi:10.1002/bimj.201000239

Examples

```
## Define some graph as matrix
g <- matrix(c(0,0,1,0,
              0,0,0,1,
              0,1,0,0,
              1,0,0,0), nrow = 4,byrow=TRUE)
## Choose weights
```

```
w <- c(.5,.5,0,0)
## Some correlation (upper and lower first diagonal 1/2)
c <- diag(4)
c[1:2,3:4] <- NA
c[3:4,1:2] <- NA
c[1,2] <- 1/2
c[2,1] <- 1/2
c[3,4] <- 1/2
c[4,3] <- 1/2

## Boundaries for correlated test statistics at alpha level .05:
generateBounds(g,w,c,.05)
```

`generatePvals` *generatePvals*

Description

compute adjusted p-values either for the closed test defined by the graph or for each elementary hypotheses within each intersection hypotheses

Usage

```
generatePvals(
  g,
  w,
  cr,
  p,
  adjusted = TRUE,
  hint = generateWeights(g, w),
  upscale = FALSE
)
```

Arguments

`g`	graph defined as a matrix, each element defines how much of the local alpha reserved for the hypothesis corresponding to its row index is passed on to the hypothesis corresponding to its column index
`w`	vector of weights, defines how much of the overall alpha is initially reserved for each elementary hypothesis
`cr`	correlation matrix if p-values arise from one-sided tests with multivariate normal distributed test statistics for which the correlation is partially known. Unknown values can be set to NA. (See details for more information)
`p`	vector of observed unadjusted p-values, that belong to test-statistics with a joint multivariate normal null distribution with (partially) known correlation matrix `cr`

adjusted	logical, if TRUE (default) adjusted p-values for the closed test are returned, else a matrix of p-values adjusted only for each intersection hypothesis is returned
hint	if intersection hypotheses weights have already been computed (output of generateWeights) can be passed here otherwise will be computed during execution
upscale	if FALSE (default) the p-values are additionally adjusted for the case that non-exhaustive weights are specified. (See details)

Details

It is assumed that under the global null hypothesis $(\Phi^{-1}(1-p_1), ..., \Phi^{-1}(1-p_m))$ follow a multivariate normal distribution with correlation matrix cr where Φ^{-1} denotes the inverse of the standard normal distribution function.

For example, this is the case if $p_1, ..., p_m$ are the raw p-values from one-sided z-tests for each of the elementary hypotheses where the correlation between z-test statistics is generated by an overlap in the observations (e.g. comparison with a common control, group-sequential analyses etc.). An application of the transformation $\Phi^{-1}(1-p_i)$ to raw p-values from a two-sided test will not in general lead to a multivariate normal distribution. Partial knowledge of the correlation matrix is supported. The correlation matrix has to be passed as a numeric matrix with elements of the form: $cr[i,i] = 1$ for diagonal elements, $cr[i,j] = \rho_{ij}$, where ρ_{ij} is the known value of the correlation between $\Phi^{-1}(1-p_i)$ and $\Phi^{-1}(1-p_j)$ or NA if the corresponding correlation is unknown. For example cr[1,2]=0 indicates that the first and second test statistic are uncorrelated, whereas cr[2,3] = NA means that the true correlation between statistics two and three is unknown and may take values between -1 and 1. The correlation has to be specified for complete blocks (ie.: if cor(i,j), and cor(i,k) for i!=j!=k are specified then cor(j,k) has to be specified as well) otherwise the corresponding intersection null hypotheses tests are not uniquely defined and an error is returned.

The parametric tests in (Bretz et al. (2011)) are defined such that the tests of intersection null hypotheses always exhaust the full alpha level even if the sum of weights is strictly smaller than one. This has the consequence that certain test procedures that do not test each intersection null hypothesis at the full level alpha may not be implemented (e.g., a single step Dunnett test). If upscale is set to FALSE (default) the parametric tests are performed at a reduced level alpha of sum(w) * alpha and p-values adjusted accordingly such that test procedures with non-exhaustive weighting strategies may be implemented. If set to TRUE the tests are performed as defined in Equation (3) of (Bretz et al. (2011)).

Value

If adjusted is set to true returns a vector of adjusted p-values. Any elementary null hypothesis is rejected if its corresponding adjusted p-value is below the predetermined alpha level. For adjusted set to false a matrix with p-values adjusted only within each intersection hypotheses is returned. The intersection corresponding to each line is given by conversion of the line number into binary (eg. 13 is binary 1101 and corresponds to (H1,H2,H4)). If any adjusted p-value within a given line falls below alpha, then the corresponding intersection hypotheses can be rejected.

Author(s)

Florian Klinglmueller

References

Bretz F, Maurer W, Brannath W, Posch M; (2008) - A graphical approach to sequentially rejective multiple testing procedures. - Stat Med - 28/4, 586-604 Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K; (2011) - Graphical approaches for multiple endpoint problems using weighted Bonferroni, Simes or parametric tests - to appear

Examples

```
## Define some graph as matrix
g <- matrix(c(0,0,1,0, 0,0,0,1, 0,1,0,0, 1,0,0,0), nrow = 4, byrow=TRUE)
## Choose weights
w <- c(.5,.5,0,0)
## Some correlation (upper and lower first diagonal 1/2)
c <- diag(4)
c[1:2,3:4] <- NA
c[3:4,1:2] <- NA
c[1,2] <- 1/2
c[2,1] <- 1/2
c[3,4] <- 1/2
c[4,3] <- 1/2
## p-values as Section 3 of Bretz et al. (2011),
p <- c(0.0121,0.0337,0.0084,0.0160)

## Boundaries for correlated test statistics at alpha level .05:
generatePvals(g,w,c,p)

g <- Entangled2Maurer2012()
generatePvals(g=g, cr=diag(5), p=rep(0.1,5))
```

`generateTest` *generateTest*

Description

generates a test function for the multiple comparison procedure with correlated test statistics defined by a graph

Usage

```
generateTest(g, w, cr, al, upscale = FALSE)
```

Arguments

g	graph defined as a matrix, each element defines how much of the local alpha reserved for the hypothesis corresponding to its row index is passed on to the hypothesis corresponding to its column index
w	vector of weights, defines how much of the overall alpha is initially reserved for each elementary hypothesis

cr	correlation matrix if p-values arise from one-sided tests with multivariate normal distributed test statistics for which the correlation is partially known. Unknown values can be set to NA. (See details for more information)
al	overall alpha level at which the family error is controlled
upscale	if FALSE (default) the parametric tests are performed at a reduced level alpha of sum(w) * alpha. (See details)

Details

It is assumed that under the global null hypothesis $(\Phi^{-1}(1-p_1), ..., \Phi^{-1}(1-p_m))$ follow a multivariate normal distribution with correlation matrix cr where Φ^{-1} denotes the inverse of the standard normal distribution function.

For example, this is the case if $p_1, ..., p_m$ are the raw p-values from one-sided z-tests for each of the elementary hypotheses where the correlation between z-test statistics is generated by an overlap in the observations (e.g. comparison with a common control, group-sequential analyses etc.). An application of the transformation $\Phi^{-1}(1-p_i)$ to raw p-values from a two-sided test will not in general lead to a multivariate normal distribution. Partial knowledge of the correlation matrix is supported. The correlation matrix has to be passed as a numeric matrix with elements of the form: $cr[i,i] = 1$ for diagonal elements, $cr[i,j] = \rho_{ij}$, where ρ_{ij} is the known value of the correlation between $\Phi^{-1}(1-p_i)$ and $\Phi^{-1}(1-p_j)$ or NA if the corresponding correlation is unknown. For example cr[1,2]=0 indicates that the first and second test statistic are uncorrelated, whereas cr[2,3] = NA means that the true correlation between statistics two and three is unknown and may take values between -1 and 1. The correlation has to be specified for complete blocks (ie.: if cor(i,j), and cor(i,k) for i!=j!=k are specified then cor(j,k) has to be specified as well) otherwise the corresponding intersection null hypotheses tests are not uniquely defined and an error is returned.

The parametric tests in (Bretz et al. (2011)) are defined such that the tests of intersection null hypotheses always upscale the full alpha level even if the sum of weights is strictly smaller than one. This has the consequence that certain test procedures that do not test each intersection null hypothesis at the full level alpha may not be implemented (e.g., a single step Dunnett test). If upscale is set to FALSE (default) the parametric tests are performed at a reduced level alpha of sum(w) * alpha. If set to TRUE the tests are performed as defined in Equation (3) of (Bretz et al. (2011)).

Value

Returns a function that will take a vector of z-scores to which the test will be applied. This function in turn will return a boolean vector with elements false if the particular elementary hypothesis can not be rejected and true otherwise.

Author(s)

Florian Klinglmueller

References

Bretz F, Maurer W, Brannath W, Posch M; (2008) - A graphical approach to sequentially rejective multiple testing procedures. - Stat Med - 28/4, 586-604 Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K; (2011) - Graphical approaches for multiple endpoint problems using weighted Bonferroni, Simes or parametric tests - to appear

Examples

```
## Define some graph as matrix
g <- matrix(c(0,0,1,0,
              0,0,0,1,
              0,1,0,0,
              1,0,0,0), nrow = 4,byrow=TRUE)
## Choose weights
w <- c(.5,.5,0,0)
## Some correlation (upper and lower first diagonal 1/2)
c <- diag(4)
c[1:2,3:4] <- NA
c[3:4,1:2] <- NA
c[1,2] <- 1/2
c[2,1] <- 1/2
c[3,4] <- 1/2
c[4,3] <- 1/2

## Test function for further use:
myTest <- generateTest(g,w,c,.05)
myTest(c(3,2,1,2))
```

---

generateWeights *generateWeights*

Description

compute Weights for each intersection Hypotheses in the closure of a graph based multiple testing procedure

Usage

```
generateWeights(g, w)
```

Arguments

g	Graph either defined as a matrix (each element defines how much of the local alpha reserved for the hypothesis corresponding to its row index is passed on to the hypothesis corresponding to its column index), as graphMCP object or as entangledMCP object.
w	Vector of weights, defines how much of the overall alpha is initially reserved for each elementary hypthosis. Can be missing if g is a graphMCP object (in which case the weights from the graph object are used). Will be ignored if g is an entangledMCP object (since then the matrix of weights from this object is used).

Value

Returns matrix with each row corresponding to one intersection hypothesis in the closure of the multiple testing problem. The first half of elements indicate whether an elementary hypotheses is in the intersection (1) or not (0). The second half of each row gives the weights allocated to each elementary hypotheses in the intersection.

Author(s)

Florian Klinglmueller <float@lefant.net>, Kornelius Rohmeyer <rohmeyer@small-projects.de>

References

Bretz F, Maurer W, Brannath W, Posch M; (2008) - A graphical approach to sequentially rejective multiple testing procedures. - Stat Med - 28/4, 586-604 Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K; (2011) - Graphical approaches for multiple endpoint problems using weighted Bonferroni, Simes or parametric tests - to appear

Examples

```
g <- matrix(c(0,0,1,0,
              0,0,0,1,
              0,1,0,0,
              1,0,0,0), nrow = 4,byrow=TRUE)
## Choose weights
w <- c(.5,.5,0,0)
## Weights of conventional gMCP test:
generateWeights(g,w)

g <- Entangled2Maurer2012()
generateWeights(g)
```

---

getJavaInfo *Get Memory and Runtime Info from JVM*

Description

Get Memory and Runtime Info from JVM

Usage

```
getJavaInfo(memory = TRUE, filesystem = TRUE, runtime = TRUE)
```

Arguments

memory	Logical whether to include memory information + number of available cores
filesystem	Logical whether to include filesystem information (Total, free and usable space)
runtime	Logical whether to include runtime information (Class Path, Library Path, Input Arguments)

Value

character vector of length 1 containing the memory and runtime info.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

Examples

```
## Not run:
cat(getJavaInfo())

## End(Not run)
```

---

gMCP *Graph based Multiple Comparison Procedures*

Description

Performs a graph based multiple test procedure for a given graph and unadjusted p-values.

Usage

```
gMCP(
  graph,
  pvalues,
  test,
  correlation,
  alpha = 0.05,
  approxEps = TRUE,
  eps = 10^(-3),
  ...,
 upscale = ifelse(missing(test) && !missing(correlation) || !missing(test) && test ==
    "Bretz2011", TRUE, FALSE),
  useC = FALSE,
  verbose = FALSE,
  keepWeights = FALSE,
  adjPValues = TRUE
)
```

Arguments

graph	A graph of class graphMCP.
pvalues	A numeric vector specifying the p-values for the graph based MCP. Note the assumptions in the details section for the parametric tests, when a correlation is specified.

test	Should be either "Bonferroni", "Simes" or "parametric". If not specified by default the Bonferroni-based test procedure is used if no correlation is specified or the algorithm from Bretz et al. 2011 if a correlation is specified. If test is set to "Simes" the weighted Simes test will be performed for each subset of hypotheses.
correlation	Optional correlation matrix. If the weighted Simes test is performed, it is checked whether type I error rate can be ensured and a warning is given if this is not the case. For parametric tests the p-values must arise from one-sided tests with multivariate normal distributed test statistics for which the correlation is (partially) known. In that case a weighted parametric closed test is performed (also see generatePvals). Unknown values can be set to NA. (See details for more information)
alpha	A numeric specifying the maximal allowed type one error rate.
approxEps	A boolean specifying whether epsilon values should be substituted with the value given in the parameter eps.
eps	A numeric scalar specifying a value for epsilon edges.
...	Test specific arguments can be given here.
upscale	Logical. If upscale=FALSE then for each intersection of hypotheses (i.e. each subgraph) a weighted test is performed at the possibly reduced level alpha of sum(w)*alpha, where sum(w) is the sum of all node weights in this subset. If upscale=TRUE all weights are upscaled, so that sum(w)=1. For backward comptibility the default value is TRUE if a the parameter test is missing, but parameter correlation is specified or if test=="Bretz2011".
useC	Logical scalar. If TRUE neither adjusted p-values nor intermediate graphs are returned, but the calculation is sped up by using code written in C. THIS CODE IS NOT FOR PRODUCTIVE USE YET! If approxEps is FALSE and the graph contains epsilon edges, a warning is thrown and useC will be ignored.
verbose	Logical scalar. If TRUE verbose output is generated.
keepWeights	Logical scalar. If FALSE the weight of a node without outgoing edges is set to 0 if it is removed. Otherwise it keeps its weight.
adjPValues	Logical scalar. If FALSE no adjusted p-values will be calculated. Especially for the weighted Simes test this will result in significantly less calculations in most cases.

Details

For the Bonferroni procedure the p-values can arise from any statistical test, but if you improve the test by specifying a correlation matrix, the following assumptions apply:

It is assumed that under the global null hypothesis $(\Phi^{-1}(1-p_1), ..., \Phi^{-1}(1-p_m))$ follow a multivariate normal distribution with correlation matrix correlation where Φ^{-1} denotes the inverse of the standard normal distribution function.

For example, this is the case if $p_1, ..., p_m$ are the raw p-values from one-sided z-tests for each of the elementary hypotheses where the correlation between z-test statistics is generated by an overlap in the observations (e.g. comparison with a common control, group-sequential analyses etc.). An application of the transformation $\Phi^{-1}(1-p_i)$ to raw p-values from a two-sided test will not in

general lead to a multivariate normal distribution. Partial knowledge of the correlation matrix is supported. The correlation matrix has to be passed as a numeric matrix with elements of the form: $correlation[i,i] = 1$ for diagonal elements, $correlation[i,j] = \rho_{ij}$, where ρ_{ij} is the known value of the correlation between $\Phi^{-1}(1-p_i)$ and $\Phi^{-1}(1-p_j)$ or NA if the corresponding correlation is unknown. For example correlation[1,2]=0 indicates that the first and second test statistic are uncorrelated, whereas correlation[2,3] = NA means that the true correlation between statistics two and three is unknown and may take values between -1 and 1. The correlation has to be specified for complete blocks (ie.: if cor(i,j), and cor(i,j') for i!=j!=j' are specified then cor(j,j') has to be specified as well) otherwise the corresponding intersection null hypotheses tests are not uniquely defined and an error is returned.

For further details see the given references.

Value

An object of class `gMCPResult`, more specifically a list with elements

`graphs` list of graphs

`pvalues` p-values

`rejected` logical whether hyptheses could be rejected

`adjPValues` adjusted p-values

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

References

Frank Bretz, Willi Maurer, Werner Brannath, Martin Posch: A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine 2009 vol. 28 issue 4 page 586-604. https://www.meduniwien.ac.at/fwf_adaptive/papers/bretz_2009_22.pdf

Bretz F., Posch M., Glimm E., Klinglmueller F., Maurer W., Rohmeyer K. (2011): Graphical approaches for multiple endpoint problems using weighted Bonferroni, Simes or parametric tests. Biometrical Journal 53 (6), pages 894-913, Wiley. doi:10.1002/bimj.201000239

Strassburger K., Bretz F.: Compatible simultaneous lower confidence bounds for the Holm procedure and other Bonferroni based closed tests. Statistics in Medicine 2008; 27:4914-4927.

Hommel G., Bretz F., Maurer W.: Powerful short-cuts for multiple testing procedures with special reference to gatekeeping strategies. Statistics in Medicine 2007; 26:4063-4073.

Guilbaud O.: Simultaneous confidence regions corresponding to Holm's stepdown procedure and other closed-testing procedures. Biometrical Journal 2008; 50:678-692.

See Also

`graphMCP` `graphNEL`

Examples

```
g <- BonferroniHolm(5)
gMCP(g, pvalues=c(0.01, 0.02, 0.04, 0.04, 0.7))
# Simple Bonferroni with empty graph:
g2 <- matrix2graph(matrix(0, nrow=5, ncol=5))
gMCP(g2, pvalues=c(0.01, 0.02, 0.04, 0.04, 0.7))
# With 'upscale=TRUE' equal to BonferroniHolm:
gMCP(g2, pvalues=c(0.01, 0.02, 0.04, 0.04, 0.7), upscale=TRUE)

# Entangled graphs:
g3 <- Entangled2Maurer2012()
gMCP(g3, pvalues=c(0.01, 0.02, 0.04, 0.04, 0.7), correlation=diag(5))
```

---

gMCP.extended *Graph based Multiple Comparison Procedures*

Description

Performs a graph based multiple test procedure for a given graph and unadjusted p-values.

Usage

```
gMCP.extended(
  graph,
  pvalues,
  test,
  alpha = 0.05,
  eps = 10^(-3),
  upscale = FALSE,
  verbose = FALSE,
  adjPValues = TRUE,
  ...
)
```

Arguments

graph	A graph of class graphMCP.
pvalues	A numeric vector specifying the p-values for the graph based MCP. Note the assumptions in the description of the selected test (if there are any - for example test=bonferroni.test has no further assumptions, but test=parametric.test assumes p-values from a multivariate normal distribution).
test	A weighted test function. The package gMCP provides the following weighted test functions: **bonferroni.test** Bonferroni test - see ?bonferroni.test for details.

parametric.test Parametric test - see ?parametric.test for details.

simes.test Simes test - see ?simes.test for details.

bonferroni.trimmed.simes.test Trimmed Simes test for intersections of two hypotheses and otherwise Bonferroni - see ?bonferroni.trimmed.simes.test for details.

simes.on.subsets.test Simes test for intersections of hypotheses from certain sets and otherwise Bonferroni - see ?simes.on.subsets.test for details.

To provide your own test function see ?weighted.test.function.

alpha	A numeric specifying the maximal allowed type one error rate.
eps	A numeric scalar specifying a value for epsilon edges.
upscale	Logical. If upscale=FALSE then for each intersection of hypotheses (i.e. each subgraph) a weighted test is performed at the possibly reduced level alpha of sum(w)*alpha, where sum(w) is the sum of all node weights in this subset. If upscale=TRUE all weights are upscaled, so that sum(w)=1.
verbose	Logical scalar. If TRUE verbose output is generated during sequentially rejection steps.
adjPValues	Logical scalar. If FALSE no adjusted p-values will be calculated. Especially for the weighted Simes test this will result in significantly less calculations in most cases.
...	Test specific arguments can be given here.

Value

An object of class gMCPResult, more specifically a list with elements

graphs list of graphs

pvalues p-values

rejected logical whether hyptheses could be rejected

adjPValues adjusted p-values

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

References

Frank Bretz, Willi Maurer, Werner Brannath, Martin Posch: A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine 2009 vol. 28 issue 4 page 586-604. https://www.meduniwien.ac.at/fwf_adaptive/papers/bretz_2009_22.pdf

Bretz F., Posch M., Glimm E., Klinglmueller F., Maurer W., Rohmeyer K. (2011): Graphical approaches for multiple endpoint problems using weighted Bonferroni, Simes or parametric tests. Biometrical Journal 53 (6), pages 894-913, Wiley. doi:10.1002/bimj.201000239

Strassburger K., Bretz F.: Compatible simultaneous lower confidence bounds for the Holm procedure and other Bonferroni based closed tests. Statistics in Medicine 2008; 27:4914-4927.

Hommel G., Bretz F., Maurer W.: Powerful short-cuts for multiple testing procedures with special reference to gatekeeping strategies. Statistics in Medicine 2007; 26:4063-4073.

Guilbaud O.: Simultaneous confidence regions corresponding to Holm's stepdown procedure and other closed-testing procedures. Biometrical Journal 2008; 50:678-692.

See Also

graphMCP graphNEL

Examples

```
g <- BonferroniHolm(5)
gMCP(g, pvalues=c(0.01, 0.02, 0.04, 0.04, 0.7))
# Simple Bonferroni with empty graph:
g2 <- matrix2graph(matrix(0, nrow=5, ncol=5))
gMCP(g2, pvalues=c(0.01, 0.02, 0.04, 0.04, 0.7))
# With 'upscale=TRUE' equal to BonferroniHolm:
gMCP(g2, pvalues=c(0.01, 0.02, 0.04, 0.04, 0.7), upscale=TRUE)

# Entangled graphs:
g3 <- Entangled2Maurer2012()
gMCP(g3, pvalues=c(0.01, 0.02, 0.04, 0.04, 0.7), correlation=diag(5))
```

---

gMCPReport *Automatic Generation of gMCP Reports*

Description

Creates a LaTeX file with a gMCP Report.

Usage

```
gMCPReport(object, file = "", ...)
```

Arguments

object	A graph of class graphMCP or an object of class gMCPResult.
file	A connection, or a character string naming the file to print to. If "" (the default), the report is printed to the standard output connection (the console unless redirected by sink). If it is "|cmd", the output is piped to the command given by cmd, by opening a pipe connection [taken from the manual page of cat, which is called in this function].
...	Arguments to be passed to method graph2latex like package and scale.

Details

This function uses cat and graph2latex.

Value

None (invisible NULL).

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

References

The TikZ and PGF Packages Manual for version 2.00, Till Tantau, https://www.ctan.org/pkg/pgf/

See Also

cat graph2latex

Examples

```
g <- BretzEtAl2011()

result <- gMCP(g, pvalues=c(0.1, 0.008, 0.005, 0.15, 0.04, 0.006))

gMCPReport(result)
```

---

gMCPResult-class *Class gMCPResult*

Description

A gMCPResult object describes an evaluated sequentially rejective multiple test procedure.

Slots

graphs: Object of class list.

alpha: A numeric specifying the maximal type I error rate.

pvalues: The numeric vector of pvalues.

rejected: The logical vector of rejected null hypotheses.

adjPValues: The numeric vector of adjusted pvalues.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

See Also

gMCP

gPADInterim-class *Class gPADInterim*

Description

A gPADInterim object describes an object holding interim information for an adaptive procedure that is based on a preplanned graphical procedure.

Slots

`Aj`: Object of class `numeric`. Giving partial conditional errors (PCEs) for all elementary hypotheses in each intersection hypothesis

`BJ`: A `numeric` specifying the sum of PCEs per intersection hypothesis.

`z1`: The `numeric` vector of first stage z-scores.

`v`: A `numeric` specifying the proportion of measurements collected up to interim

`preplanned`: Object of class `graphMCP` specifying the preplanned graphical procedure.

`alpha`: A `numeric` giving the alpha level of the pre-planned test

Author(s)

Florian Klinglmueller <float@lefant.net>

See Also

`gMCP`, `doInterim`, `secondStageTest`

graph2latex *Graph2LaTeX*

Description

Creates LaTeX code that represents the given graph.

Usage

```
graph2latex(
  graph,
  package = "TikZ",
  scale = 1,
  showAlpha = FALSE,
  alpha = 0.05,
  pvalues,
  fontsize,
  nodeTikZ,
```

```
  labelTikZ = "near start,above,fill=blue!20",
  tikzEnv = TRUE,
  offset = c(0, 0),
  fill = list(reject = "red!80", retain = "green!80"),
  fig = FALSE,
  fig.label = NULL,
  fig.caption = NULL,
  fig.caption.short = NULL,
  nodeR = 25,
  scaleText = TRUE
)
```

Arguments

graph	A graph of class graphMCP.
package	A character string specifying the LaTeX package that should be used. Up to now only TikZ is available.
scale	A numeric scalar specifying a possible scaling of the graph. It is only used if tikzEnv==TRUE. Note that this does only effect the fontsize of the graph if scaleText==FALSE. (Coordinates are interpreted in big points: 72 bp = 1 inch).
showAlpha	Logical whether local alpha levels or weights should be shown.
alpha	An optional numeric argument to specify the type I error rate.
pvalues	If the optional numeric argument pvalues is given, nodes that can be rejected, will be marked.
fontsize	An optional character vector specifying the fontsize for the graph, must be one of "tiny", "scriptsize", "footnotesize", "small", "normalsize", "large", "Large", "LARGE", "huge" or "Huge".
nodeTikZ	A character string with additional arguments for the TikZ node command like for example nodeTikZ="minimum size=2cm".
labelTikZ	A character string with arguments for the TikZ node command within an edge.
tikzEnv	Logical whether the LaTeX code should be wrapped in a TikZ environment.
offset	A numeric of length 2 specifying the x and y offset in the TikZ environment.
fill	A list containing 2 elements reject and retain specifying node fill colour of rejected and retained (or not yet rejected) nodes.
fig	Logical whether a figure environment should be created.
fig.label	Label for figure environment (if fig==TRUE).
fig.caption	Caption for figure environment (if fig==TRUE).
fig.caption.short	Optional short version of fig.caption for list of figures (if fig==TRUE).
nodeR	Radius of nodes (pixel in Java, bp in LaTeX).
scaleText	Only used if scale is unequal 1 and tikzEnv==TRUE. If scaleText is TRUE (the default) a scalebox environment is used. If it is FALSE the optional parameter scale from the tikzpicture environment is used and font size will not change.

Note that while you easily can change the scale in the scalebox environment, it is more problematic to adjust the scale in the tikzpicture environment afterwards in the LaTeX document, since for curved edges the parameters are calculated for a certain relative node size which changes if the graph is scaled but the text size stays the same.

Details

For details see the given references.

Value

A character string that contains LaTeX code representing the given graph.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

References

The TikZ and PGF Packages Manual for version 2.00, Till Tantau, https://www.ctan.org/pkg/pgf/

See Also

graphMCP, gMCPReport

Examples

```
g <- BonferroniHolm(5)

graph2latex(g)
```

---

graphAnalysis *Analysis of a gMCP-Graph*

Description

Creates LaTeX code that represents the given graph.

Usage

```
graphAnalysis(graph, file = "")
```

Arguments

graph	A graph of class graphMCP.
file	A connection, or a character string naming the file to print to. If "" (the default), the analysis is printed to the standard output connection (the console unless redirected by sink). If it is "|cmd", the output is piped to the command given by cmd, by opening a pipe connection [taken from the manual page of cat, which is called in this function].

Details

In the moment it is only tested whether each node is accessible from each other node. Further analysis will be added in future versions.

Value

A character string that contains the printed analysis.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

See Also

graphMCP

Examples

```
g <- BonferroniHolm(5)

graphAnalysis(g)
```

---

graphGUI *Graphical User Interface for graphical described multiple comparison procedures*

Description

Starts a graphical user interface for the creation/modification of directed weighted graphs and applying graphical described multiple comparison procedures.

Usage

```
graphGUI(
  graph = "createdGraph",
  pvalues = numeric(0),
  grid = 0,
  debug = FALSE,
  experimentalFeatures = FALSE,
  envir = globalenv()
)
```

Arguments

graph	Either a variable name for the graph, given as a character string. (If it is not a syntactically valid name, make.names is called to change it to a valid one.) Or an object of class graphMCP. If the object is modified (even just by updating the class definition or arranging the nodes) it will be saved in the specified environment (default is the global environment).
pvalues	Numeric value that optionally specifies the p-values.
grid	Positive integer that sets the grid size for easier placement of nodes. (Therefore grid size 1 allows unrestricted placement and disables the grid.) The default grid=0 uses the last used grid value or if the GUI is started the first time a value of 50.
debug	Logical. If TRUE debug output is printed to the R console.
experimentalFeatures	Logical. If TRUE some unfinished / insufficiently tested experimental features are available in the GUI.
envir	Environment where the object *graph* is located and/or it should be saved (default is the global environment).

Details

See the vignette of this package for further details, since describing a GUI interface is better done with a lot of nice pictures.

The GUI can save result files if asked to, can look for a new version on CRAN (if this behaviour has been approved by the user), will change the random seed in the R session if this is specified by the user in the options (default: no) and could send bug reports if an error occurs and the user approves it.

Value

The function itself returns NULL. But with the GUI a graph can be created or edited that will be available in R under the specified variable name after saving in the specified environment.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

Examples

```
## Not run:
graphGUI()
pvalues <- c(9.7, 1.5, 0.5, 0.6, 0.4, 0.8, 4)/100
graphGUI(HommelEtAl2007(), pvalues=pvalues)

x <- new.env()
assign("graph", BonferroniHolm(3), envir=x)
graphGUI("graph", envir=x)
## End(Not run)
```

---

graphMCP-class *Class graphMCP*

Description

A graphMCP object describes a sequentially rejective multiple test procedure.

Slots

`m`**:** A transition matrix. Can be either `numerical` or `character` depending whether the matrix contains variables or not. Row and column names will be the names of the nodes.

`weights`**:** A numeric.

`edgeAttr`**:** A list for edge attributes.

`nodeAttr`**:** A list for node attributes.

Methods

getMatrix `signature(object = "graphMCP")`: A method for getting the transition matrix of the graph.

getWeights `signature(object = "graphMCP")`: A method for getting the weights. If a third optional argument `node` is specified, only for these nodes the weight will be returned.

setWeights `signature(object = "graphMCP")`: A method for setting the weights. If a third optional argument `node` is specified, only for these nodes the weight will be set.

getRejected `signature(object = "graphMCP")`: A method for getting the information whether the hypotheses are marked in the graph as already rejected. If a second optional argument `node` is specified, only for these nodes the boolean vector will be returned.

getXCoordinates `signature(object = "graphMCP")`: A method for getting the x coordinates of the graph. If a second optional argument `node` is specified, only for these nodes the x coordinates will be returned. If x coordinates are not set yet `NULL` is returned.

getYCoordinates `signature(object = "graphMCP")`: A method for getting the y coordinates of the graph If a second optional argument `node` is specified, only for these nodes the x coordinates will be returned. If y coordinates are not set yet `NULL` is returned.

setEdge `signature(from="character", to="character", graph="graphNEL", weights="numeric")`:
A method for adding new edges with the given weights.

setEdge `signature(from="character", to="character", graph="graphMCP", weights="character")`:
A method for adding new edges with the given weights.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

Examples

```
m <- rbind(H11=c(0,   0.5, 0,   0.5, 0,   0  ),
   H21=c(1/3, 0,   1/3, 0,   1/3, 0  ),
   H31=c(0,   0.5, 0,   0,   0,   0.5),
   H12=c(0,   1,   0,   0,   0,   0  ),
   H22=c(0.5, 0,   0.5, 0,   0,   0  ),
   H32=c(0,   1,   0,   0,   0,   0  ))

weights <- c(1/3, 1/3, 1/3, 0, 0, 0)

# Graph creation
graph <- new("graphMCP", m=m, weights=weights)

# Visualization settings
nodeX <- rep(c(100, 300, 500), 2)
nodeY <- rep(c(100, 300), each=3)
graph@nodeAttr$X <- nodeX
graph@nodeAttr$Y <- nodeY

getWeights(graph)

getRejected(graph)

pvalues <- c(0.1, 0.008, 0.005, 0.15, 0.04, 0.006)
result <- gMCP(graph, pvalues)

getWeights(result@graphs[[4]])
getRejected(result@graphs[[4]])
```

`graphTest` *Multiple testing using graphs*

Description

Implements the graphical test procedure described in Bretz et al. (2009). Note that the gMCP function in the gMCP package performs the same task.

Usage

```
graphTest(
  pvalues,
  weights = NULL,
  alpha = 0.05,
  G = NULL,
  cr = NULL,
  graph = NULL,
  verbose = FALSE,
  test,
  upscale = FALSE
)
```

Arguments

pvalues	Either a vector or a matrix containing the local p-values for the hypotheses in the rows.
weights	Initial weight levels for the test procedure, in case of multiple graphs this needs to be a matrix.
alpha	Overall alpha level of the procedure. For entangled graphs alpha should be a numeric vector of length equal to the number of graphs, each element specifying the partial alpha for the respective graph. The overall alpha level equals sum(alpha).
G	For simple graphs G should be a numeric matrix determining the graph underlying the test procedure. Note that the diagonal need to contain only 0s, while the rows need to sum to 1. For entangled graphs it needs to be a list containing the different graph matrices as elements.
cr	Correlation matrix that should be used for the parametric test. If cr==NULL the Bonferroni based test procedure is used.
graph	As an alternative to the specification via weights and G one can also hand over a graphMCP object to the code. graphMCP objects can be created for example with the graphGUI function.
verbose	If verbose is TRUE, additional information about the graphical rejection procedure is displayed.
test	In the parametric case there is more than one way to handle subgraphs with less than the full alpha. If the parameter test is missing, the tests are performed as described by Bretz et al. (2011), i.e. tests of intersection null hypotheses always exhaust the full alpha level even if the sum of weights is strictly smaller than one. If test="simple-parametric" the tests are performed as defined in Equation (3) of Bretz et al. (2011).
upscale	Logical. If upscale=FALSE then for each intersection of hypotheses (i.e. each subgraph) a weighted test is performed at the possibly reduced level alpha of sum(w)*alpha, where sum(w) is the sum of all node weights in this subset. If upscale=TRUE all weights are upscaled, so that sum(w)=1.

Value

A vector or a matrix containing the test results for the hypotheses under consideration. Significant tests are denoted by a 1, non-significant results by a 0.

References

Bretz, F., Maurer, W., Brannath, W. and Posch, M. (2009) A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine, 28, 586–604

Bretz, F., Maurer, W. and Hommel, G. (2010) Test and power considerations for multiple endpoint analyses using sequentially rejective graphical procedures, to appear in Statistics in Medicine

Examples

```
#### example from Bretz et al. (2010)
weights <- c(1/3, 1/3, 1/3, 0, 0, 0)
graph <- rbind(c(0,       0.5, 0,     0.5, 0,      0),
               c(1/3,     0,   1/3,    0,   1/3,    0),
               c(0,       0.5, 0,     0,   0,      0.5),
               c(0,       1,   0,     0,   0,      0),
               c(0.5,     0,   0.5,   0,   0,      0),
               c(0,       1,   0,     0,   0,      0))
pvals <- c(0.1, 0.008, 0.005, 0.15, 0.04, 0.006)
graphTest(pvals, weights, alpha=0.025, graph)

## observe graphical procedure in detail
graphTest(pvals, weights, alpha=0.025, graph, verbose = TRUE)

## now use many p-values (useful for power simulations)
pvals <- matrix(rbeta(6e4, 1, 30), ncol = 6)
out <- graphTest(pvals, weights, alpha=0.025, graph)
head(out)

## example using multiple graphs (instead of 1)
G1 <- rbind(c(0,0.5,0.5,0,0), c(0,0,1,0,0),
            c(0, 0, 0, 1-0.01, 0.01), c(0, 1, 0, 0, 0),
            c(0, 0, 0, 0, 0))
G2 <- rbind(c(0,0,1,0,0), c(0.5,0,0.5,0,0),
            c(0, 0, 0, 0.01, 1-0.01), c(0, 0, 0, 0, 0),
            c(1, 0, 0, 0, 0))
weights <- rbind(c(1, 0, 0, 0, 0), c(0, 1, 0, 0, 0))
pvals <- c(0.012, 0.025, 0.005, 0.0015, 0.0045)
out <- graphTest(pvals, weights, alpha=c(0.0125, 0.0125), G=list(G1, G2), verbose = TRUE)

## now again with many p-values
pvals <- matrix(rbeta(5e4, 1, 30), ncol = 5)
out <- graphTest(pvals, weights, alpha=c(0.0125, 0.0125), G=list(G1, G2))
head(out)
```

hydroquinone *Hydroquinone Mutagenicity Assay*

Description

This data set gives the number of micronuclei per animal and 2000 scored cells for six different groups of differently treated male mice: The negative control (C-), four doses (30, 50, 75, 100 mg hydroquinone / kg) of hydroquinone and an active control (C+) (with 25 mg/kg cyclophosphamide).

Usage

```
data(hydroquinone)
```

Format

A data frame with 31 observations on the following 2 variables:

group A factor with levels "C-", "30 mg/kg", "50 mg/kg", "75 mg/kg", "100 mg/kg" and "C+" specifying the groups.

micronuclei A numeric vector, giving the counts of micronuclei per animal and 2000 scored cells after 24h.

Source

Adler, I.-D. and Kliesch, U. (1990): *Comparison of single and multiple treatment regimens in the mouse bone marrow micronucleus assay for hydroquinone and cyclophosphamide*. Mutation Research 234, 115-123.

References

Bauer, P., Roehmel, J., Maurer, W., and Hothorn, L. (1998): *Testing strategies in multi-dose experiments including active control*. Statistics in Medicine 17, 2133-2146.

Examples

```
data(hydroquinone)
boxplot(micronuclei~group, data=hydroquinone)
```

joinGraphs *Joins two graphMCP objects*

Description

Creates a new graphMCP object by joining two given graphMCP objects.

Usage

```
joinGraphs(graph1, graph2, xOffset = 0, yOffset = 200)
```

Arguments

graph1	A graph of class graphMCP.
graph2	A graph of class graphMCP.
xOffset	A numeric specifying an offset (on the x-axis) for placing the nodes and edge labels of the second graph.
yOffset	A numeric specifying an offset (on the y-axis) for placing the nodes and edge labels of the second graph.

Details

If graph1 and graph2 have duplicates in the node names, the nodes of the second graph will be renamed.

If and only if the sum of the weights of graph1 and graph2 exceeds 1, the weights are scaled so that the sum equals 1.

A description attribute of either graph will be discarded.

Value

A graphMCP object that represents a graph that consists of the two given graphs.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

See Also

graphMCP

Examples

```
g1 <- BonferroniHolm(2)
g2 <- BonferroniHolm(3)

joinGraphs(g1, g2)
```

`matrix2graph` *Matrix2Graph and Graph2Matrix*

Description

Creates a graph of class `graphMCP` from a given transition matrix or vice versa.

Usage

```
matrix2graph(m, weights = rep(1/dim(m)[1], dim(m)[1]))

graph2matrix(graph)
```

Arguments

`m`	A transition matrix.
`weights`	A numeric for the initial weights.
`graph`	A graph of class `graphMCP`.

Details

The hypotheses names are the row names or if these are `NULL`, the column names or if these are also `NULL` of type H1, H2, H3, ...

If the diagonal of the matrix is unequal zero, the values are ignored and a warning is given.

Value

A graph of class `graphMCP` with the given transition matrix for matrix2graph. The transition matrix of a `graphMCP` graph for graph2matrix.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

Examples

```
# Bonferroni-Holm:
m <- matrix(rep(1/3, 16), nrow=4)
diag(m) <- c(0, 0, 0, 0)
graph <- matrix2graph(m)
print(graph)
graph2matrix(graph)
```

`parametric.test` *Weighted parametric test*

Description

It is assumed that under the global null hypothesis $(\Phi^{-1}(1-p_1), ..., \Phi^{-1}(1-p_m))$ follow a multivariate normal distribution with correlation matrix `correlation` where Φ^{-1} denotes the inverse of the standard normal distribution function.

Usage

```
parametric.test(
  pvalues,
  weights,
  alpha = 0.05,
  adjPValues = TRUE,
  verbose = FALSE,
  correlation,
  ...
)
```

Arguments

`pvalues`	A numeric vector specifying the p-values.
`weights`	A numeric vector of weights.
`alpha`	A numeric specifying the maximal allowed type one error rate. If `adjPValues==TRUE` (default) the parameter `alpha` is not used.
`adjPValues`	Logical scalar. If `TRUE` (the default) an adjusted p-value for the weighted parametric test is returned. Otherwise if `adjPValues==FALSE` a logical value is returned whether the null hypothesis can be rejected.
`verbose`	Logical scalar. If `TRUE` verbose output is generated.
`correlation`	Correlation matrix. For parametric tests the p-values must arise from one-sided tests with multivariate normal distributed test statistics for which the correlation is (partially) known. In that case a weighted parametric closed test is performed (also see `generatePvals`). Unknown values can be set to NA. (See details for more information)

... Further arguments possibly passed by gMCP which will be used by other test procedures but not this one.

Details

For example, this is the case if $p_1, ..., p_m$ are the raw p-values from one-sided z-tests for each of the elementary hypotheses where the correlation between z-test statistics is generated by an overlap in the observations (e.g. comparison with a common control, group-sequential analyses etc.). An application of the transformation $\Phi^{-1}(1 - p_i)$ to raw p-values from a two-sided test will not in general lead to a multivariate normal distribution. Partial knowledge of the correlation matrix is supported. The correlation matrix has to be passed as a numeric matrix with elements of the form: $correlation[i, i] = 1$ for diagonal elements, $correlation[i, j] = \rho_{ij}$, where ρ_{ij} is the known value of the correlation between $\Phi^{-1}(1 - p_i)$ and $\Phi^{-1}(1 - p_j)$ or NA if the corresponding correlation is unknown. For example correlation[1,2]=0 indicates that the first and second test statistic are uncorrelated, whereas correlation[2,3] = NA means that the true correlation between statistics two and three is unknown and may take values between -1 and 1. The correlation has to be specified for complete blocks (ie.: if cor(i,j), and cor(i,j') for i!=j!=j' are specified then cor(j,j') has to be specified as well) otherwise the corresponding intersection null hypotheses tests are not uniquely defined and an error is returned.

For further details see the given references.

References

Bretz F., Posch M., Glimm E., Klinglmueller F., Maurer W., Rohmeyer K. (2011): Graphical approaches for multiple endpoint problems using weighted Bonferroni, Simes or parametric tests. Biometrical Journal 53 (6), pages 894-913, Wiley. doi:10.1002/bimj.201000239

`placeNodes` *Placement of graph nodes*

Description

Places the nodes of a graph according to a specified layout.

Usage

```
placeNodes(graph, nrow, ncol, byrow = TRUE, topdown = TRUE, force = FALSE)
```

Arguments

graph	A graph of class graphMCP or class entangledMCP.
nrow	The desired number of rows.
ncol	The desired number of columns.
byrow	Logical whether the graph is filled by rows (otherwise by columns).
topdown	Logical whether the rows are filled top-down or bottom-up.
force	Logical whether a graph that has already a layout should be given the specified new layout.

Details

If one of nrow or ncol is not given, an attempt is made to infer it from the number of nodes of the graph and the other parameter. If neither is given, the graph is placed as a circle.

Value

The graph with nodes placed according to the specified layout.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

See Also

graphMCP, entangledMCP

Examples

```
g <- matrix2graph(matrix(0, nrow=6, ncol=6))

g <- placeNodes(g, nrow=2, force=TRUE)

## Not run:
graphGUI(g)


## End(Not run)
```

---

plotSimCI *Plot confidence intervals*

Description

A function for convenient plotting of confidence intervals.

Usage

```
plotSimCI(ci)
```

Arguments

ci	a (named) matrix containing the lower confidence bounds in the first column, the point estimates in the second and the upper confidence bounds in the third column.

Author(s)

Code adapted from plotCII from Frank Schaarschmidt

Examples

```
est <- c("H1"=0.860382, "H2"=0.9161474, "H3"=0.9732953)
# Sample standard deviations:
ssd <- c("H1"=0.8759528, "H2"=1.291310, "H3"=0.8570892)

pval <- c(0.01260, 0.05154, 0.02124)/2

ci <- simConfint(BonferroniHolm(3), pvalues=pval,
   confint="t", df=9, estimates=est, alpha=0.025, alternative="greater")

plotSimCI(ci)
```

---

rejectNode *Rejects a node/hypothesis and updates the graph accordingly.*

Description

Rejects a node/hypothesis and updates the graph accordingly.

Usage

```
rejectNode(graph, node, upscale = FALSE, verbose = FALSE, keepWeights = FALSE)
```

Arguments

graph	A graph of class graphMCP or entangledMCP.
node	A character string specifying the node to reject.
upscale	Logical. If upscale=TRUE then the weights of all non-rejected nodes are scaled so that the sum is equal to 1. This forces keepWeights=FALSE to reduce confusion, since otherwise the sum of weights could become bigger than 1.
verbose	Logical scalar. If TRUE verbose output is generated during sequentially rejection steps.
keepWeights	Logical scalar. If FALSE the weight of a node without outgoing edges is set to 0 if it is removed. Otherwise it keeps its weight.

Details

For details see the given references.

Value

An updated graph of class graphMCP or entangledMCP.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

References

Frank Bretz, Willi Maurer, Werner Brannath, Martin Posch: A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine 2009 vol. 28 issue 4 page 586-604. https://www.meduniwien.ac.at/fwf_adaptive/papers/bretz_2009_22.pdf

See Also

graphMCP

Examples

```
g <- BonferroniHolm(5)

rejectNode(g, "H1")
```

---

replaceVariables *Replaces variables in a general graph with specified numeric values*

Description

Given a list of variables and real values a general graph is processed and each variable replaced with the specified numeric value.

Usage

```
replaceVariables(
  graph,
  variables = list(),
  ask = TRUE,
  partial = FALSE,
  expand = TRUE,
  list = FALSE
)
```

Arguments

graph	A graph of class graphMCP or class entangledMCP.
variables	A named list with one or more specified real values, for example list(a=0.5, b=0.8, "tau"=0.5) or list(a=c(0.5, 0.8), b=0.8, "tau"=0.5). If ask=TRUE and this list is missing at all or single variables are missing from the list, the user is asked for the values (if the session is not interactive an error is thrown). For interactively entered values only single numbers are supported.
ask	If FALSE all variables that are not specified are not replaced.
partial	IF TRUE only specified variables are replaced and parameter ask is ignored.
expand	Used internally. Don't use yourself.
list	If TRUE the result will always be a list, even if only one graph is returned in this list.

Value

A graph or a matrix with variables replaced by the specified numeric values. Or a list of theses graphs and matrices if a variable had more than one value.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

See Also

graphMCP, entangledMCP

Examples

```
graph <- HungEtWang2010()
## Not run:
replaceVariables(graph)

## End(Not run)
replaceVariables(graph, list("tau"=0.5,"omega"=0.5, "nu"=0.5))
replaceVariables(graph, list("tau"=c(0.1, 0.5, 0.9),"omega"=c(0.2, 0.8), "nu"=0.4))
```

---

rqmvnorm *Random sample from the multivariate normal distribution*

Description

Draw a quasi or pseudo random sample from the MVN distribution. For details on the implemented lattice rule for quasi-random numbers see Cools et al. (2006).

Usage

```
rqmvnorm(
  n,
  mean = rep(0, nrow(sigma)),
  sigma = diag(length(mean)),
  type = c("quasirandom", "pseudorandom")
)
```

Arguments

n	Number of samples, when type = "quasirandom" is used this number is rounded up to the next power of 2 (e.g. 1000 to 1024=2^10) and at least 1024.
mean	Mean vector
sigma	Covariance matrix
type	What type of random numbers to use. quasirandom uses a randomized Lattice rule, and should be more efficient than pseudorandom that uses ordinary (pseudo) random numbers.

Value

Matrix of simulated values

Author(s)

We thank Dr. Frances Kuo for the permission to use the generating vectors (order 2 lattice rule) obtained from her website https://web.maths.unsw.edu.au/~fkuo/lattice/.

References

Cools, R., Kuo, F. Y., and Nuyens, D. (2006) Constructing embedded lattice rules for multivariate integration. SIAM Journal of Scientific Computing, 28, 2162-2188.

Examples

```
sims <- rqmvnorm(100, mean = 1:2, sigma = diag(2))
plot(sims)
```

---

sampSize *Sample size calculations*

Description

Sample size calculations

Usage

```
sampSize(
  graph,
  esf,
  effSize,
  powerReqFunc,
  target,
  corr.sim,
  alpha,
  corr.test = NULL,
  type = c("quasirandom", "pseudorandom"),
  upscale = FALSE,
  n.sim = 10000,
  verbose = FALSE,
  ...
)
```

Arguments

graph	A graph of class graphMCP.
esf	...
effSize	...
powerReqFunc	One power requirement function or a list of these. If one is interested in the power to reject hypotheses 1 and 3 one could specify: f=function(x) {x[1] && x[3]}. If the power of rejecting hypotheses 1 and 2 is also of interest one would use a (optionally named) list: f=list(power1and3=function(x) {x[1] && x[3]}, power1and2=function(x) {x[1] && x[2]}). If the list has no names, the functions will be referenced to as "func1", "func2", etc. in the output.
target	Target power that should be at least achieved. Either a numeric scalar between 0 and 1 or if parameter powerReqFunc is a list a numeric vector of the same length as powerReqFunc.
corr.sim	Covariance matrix under the alternative.
alpha	...
corr.test	Correlation matrix that should be used for the parametric test. If corr.test==NULL the Bonferroni based test procedure is used. Can contain NAs.
type	What type of random numbers to use. quasirandom uses a randomized Lattice rule, and should be more efficient than pseudorandom that uses ordinary (pseudo) random numbers.
upscale	Logical. If upscale=FALSE then for each intersection of hypotheses (i.e. each subgraph) a weighted test is performed at the possibly reduced level alpha of sum(w)*alpha, where sum(w) is the sum of all node weights in this subset. If upscale=TRUE all weights are upscaled, so that sum(w)=1.
n.sim	...

verbose	Logical, whether verbose output should be printed.
...	...
test	In the parametric case there is more than one way to handle subgraphs with less than the full alpha. If the parameter `test` is missing, the tests are performed as described by Bretz et al. (2011), i.e. tests of intersection null hypotheses always exhaust the full alpha level even if the sum of weights is strictly smaller than one. If `test="simple-parametric"` the tests are performed as defined in Equation (3) of Bretz et al. (2011).

Value

...

Examples

```
## Not run:
graph <- BonferroniHolm(4)
powerReqFunc <- function(x) { (x[1] && x[2]) || x[3] }
#TODO Still causing errors / loops.
#sampSize(graph, alpha=0.05, powerReqFunc, target=0.8, mean=c(6,4,2) )
#sampSize(graph, alpha=0.05, powerReqFunc, target=0.8, mean=c(-1,-1,-1), nsim=100)
sampSize(graph, esf=c(1,1,1,1), effSize=c(1,1,1,1),
         corr.sim=diag(4), powerReqFunc=powerReqFunc, target=0.8, alpha=0.05)
powerReqFunc=list('all(x[c(1,2)])'=function(x) {all(x[c(1,2)])},
                  'any(x[c(0,1)])'=function(x) {any(x[c(0,1)])})
sampSize(graph=graph,
         effSize=list("Scenario 1"=c(2, 0.2, 0.2, 0.2),
                      "Scenario 2"=c(0.2, 4, 0.2, 0.2)),
         esf=c(0.5, 0.7071067811865476, 0.5, 0.7071067811865476),
         powerReqFunc=powerReqFunc,
         corr.sim=diag(4), target=c(0.8, 0.8), alpha=0.025)

## End(Not run)
```

`sampSizeCore` *Function for sample size calculation*

Description

Function for sample size calculation

Usage

```
sampSizeCore(
  upperN,
  lowerN = floor(upperN/2),
  targFunc,
  target,
```

```
  tol = 0.001,
  alRatio,
  Ntype = c("arm", "total"),
  verbose = FALSE,
  ...
)
```

Arguments

upperN	targFunc(upperN) should be bigger than target (otherwise upperN is doubled until this is the case).
lowerN	targFunc(lowerN) should be smaller than target (otherwise lowerN is halfed until this is the case).
targFunc	The target (power) function that should be monotonically increasing in n.
target	The target value. The function searches the n with targFunc(n)-target<tol and targFunc(n)>target.
tol	Tolerance: The function searches the n with targFunc(n)-target<tol and targFunc(n)>target.
alRatio	Allocation ratio.
Ntype	Either "arm" or "total".
verbose	Logical, whether verbose output should be printed.
...	...

Details

For details see the manual and examples.

Value

Integer value n (of type numeric) with targFunc(n)-target<tol and targFunc(n)>target.

Author(s)

This function is taken from package DoseFinding under GPL from Bjoern Bornkamp, Jose Pinheiro and Frank Bretz

Examples

```
f <- function(x){1/100*log(x)}
gMCP:::sampSizeCore(upperN=1000, targFunc=f, target=0.008, verbose=TRUE, alRatio=1)
```

secondStageTest *EXPERIMENTAL: Construct a valid level alpha test for the second stage of an adaptive design that is based on a pre-planned graphical MCP*

Description

Based on a pre-planned graphical multiple comparison procedure, construct a valid multiple level alpha test that conserves the family wise error in the strong sense regardless of any trial adaptations during an unblinded interim analysis. - Implementation of adaptive procedures is still in an early stage and may change in the near future

Usage

```
secondStageTest(
  interim,
  select,
  matchCE = TRUE,
  zWeights = "reject",
  G2 = interim@preplanned
)
```

Arguments

interim	An object of class gPADInterim.
select	A logical vector giving specifying which hypotheses are carried forward to the second stage
matchCE	Logical specifying whether second stage weights should be computed proportional to corresponding PCEs
zWeights	Either "reject","accept", or "strict" giving the rule what should be done in cases where none of the selected hypotheses has positive second stage weight.
G2	An object of class graphMCP laying down the rule to compute second stage weights. Defaults to pre-planned graph.

Details

For details see the given references.

Value

A function of signature `function(z2)` with arguments `z2` a numeric vector with second stage z-scores (Z-scores of dropped hypotheses should be set no `NA`) that returns objects of class gMCPResult.

Author(s)

Florian Klinglmueller <float@lefant.net>

References

Frank Bretz, Willi Maurer, Werner Brannath, Martin Posch: A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine 2009 vol. 28 issue 4 page 586-604. https://www.meduniwien.ac.at/fwf_adaptive/papers/bretz_2009_22.pdf

Bretz F., Posch M., Glimm E., Klinglmueller F., Maurer W., Rohmeyer K. (2011): Graphical approaches for multiple endpoint problems using weighted Bonferroni, Simes or parametric tests - to appear.

Posch M, Futschik A (2008): A Uniform Improvement of Bonferroni-Type Tests by Sequential Tests JASA 103/481, 299-308

Posch M, Maurer W, Bretz F (2010): Type I error rate control in adaptive designs for confirmatory clinical trials with treatment selection at interim Pharm Stat 10/2, 96-104

See Also

graphMCP, doInterim

Examples

```
## Simple successive graph (Maurer et al. 2011)
## two treatments two hierarchically ordered endpoints
a <- .025
G <- simpleSuccessiveI()
## some z-scores:

p1=c(.1,.12,.21,.16)
z1 <- qnorm(1-p1)
p2=c(.04,1,.14,1)
z2 <- qnorm(1-p2)
v <- c(1/2,1/3,1/2,1/3)

intA <- doInterim(G,z1,v)

## select only the first treatment
fTest <- secondStageTest(intA,c(1,0,1,0))
```

---

simConfint *Simultaneous confidence intervals for sequentially rejective multiple test procedures*

Description

Calculates simultaneous confidence intervals for sequentially rejective multiple test procedures.

Usage

```
simConfint(object, pvalues, confint, alternative=c("less", "greater"),
           estimates, df, alpha=0.05, mu=0)
```

Arguments

object	A graph of class graphMCP.
pvalues	A numeric vector specifying the p-values for the sequentially rejective MTP.
confint	One of the following: A character string "normal", "t" or a function that calculates the confidence intervals. If confint=="t" the parameter df must be specified. If confint is a function it must be of signature ("character", "numeric"), where the first parameter is the hypothesis name and the second the marginal confidence level (see examples).
alternative	A character string specifying the alternative hypothesis, must be "greater" or "less".
estimates	Point estimates for the parameters of interest.
df	Degree of freedom as numeric.
alpha	The overall alpha level as numeric scalar.
mu	The numerical parameter vector under null hypothesis.

Details

For details see the given references.

Value

A matrix with columns giving lower confidence limits, point estimates and upper confidence limits for each parameter. These will be labeled as "lower bound", "estimate" and "upper bound".

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

References

Frank Bretz, Willi Maurer, Werner Brannath, Martin Posch: A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine 2009 vol. 28 issue 4 page 586-604. http://www.meduniwien.ac.at/fwf_adaptive/papers/bretz_2009_22.pdf

See Also

graphMCP

Examples

```
est <- c("H1"=0.860382, "H2"=0.9161474, "H3"=0.9732953)
# Sample standard deviations:
ssd <- c("H1"=0.8759528, "H2"=1.291310, "H3"=0.8570892)

pval <- c(0.01260, 0.05154, 0.02124)/2

simConfint(BonferroniHolm(3), pvalues=pval,
  confint=function(node, alpha) {
   c(est[node]-qt(1-alpha,df=9)*ssd[node]/sqrt(10), Inf)
  }, estimates=est, alpha=0.025, mu=0, alternative="greater")

# Note that the sample standard deviations in the following call
# will be calculated from the pvalues and estimates.
ci <- simConfint(BonferroniHolm(3), pvalues=pval,
  confint="t", df=9, estimates=est, alpha=0.025, alternative="greater")
ci

plotSimCI(ci)
```

---

simes.on.subsets.test *Simes on subsets, otherwise Bonferroni*

Description

Weighted Simes test introduced by Benjamini and Hochberg (1997)

Usage

```
simes.on.subsets.test(
  pvalues,
  weights,
  alpha = 0.05,
  adjPValues = TRUE,
  verbose = FALSE,
  subsets,
  subset,
  ...
)
```

Arguments

pvalues	A numeric vector specifying the p-values.
weights	A numeric vector of weights.
alpha	A numeric specifying the maximal allowed type one error rate. If adjPValues==TRUE (default) the parameter alpha is not used.

adjPValues	Logical scalar. If TRUE (the default) an adjusted p-value for the weighted test is returned. Otherwise if adjPValues==FALSE a logical value is returned whether the null hypothesis can be rejected.
verbose	Logical scalar. If TRUE verbose output is generated.
subsets	A list of subsets given by numeric vectors containing the indices of the elementary hypotheses for which the weighted Simes test is applicable.
subset	A numeric vector containing the numbers of the indices of the currently tested elementary hypotheses.
...	Further arguments possibly passed by gMCP which will be used by other test procedures but not this one.

Details

As an additional argument a list of subsets must be provided, that states in which cases a Simes test is applicable (i.e. if all hypotheses to test belong to one of these subsets), e.g. subsets <- list(c("H1", "H2", "H3"), c("H4", "H5", "H6")) Trimmed Simes test for intersections of two hypotheses and otherwise weighted Bonferroni-test

Examples

```
simes.on.subsets.test(pvalues=c(0.1,0.2,0.05), weights=c(0.5,0.5,0))
simes.on.subsets.test(pvalues=c(0.1,0.2,0.05), weights=c(0.5,0.5,0), adjPValues=FALSE)

graph <- BonferroniHolm(4)
pvalues <- c(0.01, 0.05, 0.03, 0.02)

gMCP.extended(graph=graph, pvalues=pvalues, test=simes.on.subsets.test, subsets=list(1:2, 3:4))
```

---

simes.test *Weighted Simes test*

Description

Weighted Simes test introduced by Benjamini and Hochberg (1997)

Usage

```
simes.test(
  pvalues,
  weights,
  alpha = 0.05,
  adjPValues = TRUE,
  verbose = FALSE,
  ...
)
```

Arguments

pvalues	A numeric vector specifying the p-values.
weights	A numeric vector of weights.
alpha	A numeric specifying the maximal allowed type one error rate. If adjPValues==TRUE (default) the parameter alpha is not used.
adjPValues	Logical scalar. If TRUE (the default) an adjusted p-value for the weighted Simes test is returned. Otherwise if adjPValues==FALSE a logical value is returned whether the null hypothesis can be rejected.
verbose	Logical scalar. If TRUE verbose output is generated.
...	Further arguments possibly passed by gMCP which will be used by other test procedures but not this one.

Examples

```
simes.test(pvalues=c(0.1,0.2,0.05), weights=c(0.5,0.5,0))
simes.test(pvalues=c(0.1,0.2,0.05), weights=c(0.5,0.5,0), adjPValues=FALSE)
```

---

simvastatin *Simvastatin and Colesevelam Treatment in Patients with Primary Hypercholesterolemia*

Description

This data set gives the results from a study investigating the efficacy and safety of simvastatin and colesevelam treatment in patients with primary hypercholesterolemia. It shows the sample sizes, the mean LDL cholesterol levels and the number of patients with adverse events after 6 weeks. The treatment groups are: The Placebo control, two doses 10 mg and 20 mg of simvastatin and an combined treatment 20 mg + 2.3 g colesevelam.

Usage

```
data(simvastatin)
```

Format

A data frame with a summary table for ...:

group A factor with levels "Placebo", "10 mg", "20 mg", "20 mg + 2.3 g Colesevelam" specifying the groups.

sampleSize A numeric vector, giving the number of patients in the groups.

means A numeric vector, giving the mean LDL cholesterol levels.

sd A numeric vector, giving the standard deviation of the LDL cholesterol levels.

adverseEvents An integer vector, giving the number of patients with adverse events after 6 weeks.

Source

Knapp, H.H. and Schrott, H. and Ma, P. and Knopp, R. and Chin, B. and Gaziano, J.M. and Donovan, J.M. and Burke, S.K. and Davidson, M.H. (2001): *Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia* The American journal of medicine 110, 352-360.

References

Bretz, F., Hothorn, L. A. and Hsu, J. C. (2003): *Identifying effective and/or safe doses by stepwise confidence intervals for ratios* Statistics in Medicine 22, 847-858.

Examples

```
data(simvastatin)
barplot(simvastatin$means, names.arg=simvastatin$group)
```

---

subgraph *Get a subgraph*

Description

Given a set of nodes and a graph this function creates the subgraph containing only the specified nodes.

Usage

```
subgraph(graph, subset)
```

Arguments

graph	A graph of class graphMCP.
subset	A logical or character vector specifying the nodes in the subgraph.

Value

A subgraph containing only the specified nodes.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

See Also

graphMCP

Examples

```
graph <- improvedParallelGatekeeping()
subgraph(graph, c(TRUE, FALSE, TRUE, FALSE))
subgraph(graph, c("H1", "H3"))
```

`substituteEps` *Substitute Epsilon*

Description

Substitute Epsilon with a given value.

Usage

```
substituteEps(graph, eps = 10^(-3))
```

Arguments

`graph`	A graph of class `graphMCP` or class `entangledMCP`.
`eps`	A numeric scalar specifying a value for epsilon edges.

Details

For details see the given references.

Value

A graph where all epsilons have been replaced with the given value.

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

See Also

`graphMCP`, `entangledMCP`

Examples

```
graph <- improvedParallelGatekeeping()
graph
substituteEps(graph, eps=0.01)
```

`unitTestsGMCP` *Run the R unit (and optional the JUnit) test suite for gMCP*

Description

Runs the R unit (and optional the JUnit) test suite for gMCP and prints the results.

Usage

```
unitTestsGMCP(
  extended = FALSE,
  java = FALSE,
  interactive = FALSE,
  junitLibrary,
  outputPath
)
```

Arguments

`extended`	If `TRUE` (or if the environment variable GMCP_UNIT_TESTS equals "extended" or "all") an extended version of the R unit test suite for gMCP will be used. The run will take significantly longer time.
`java`	If `TRUE` (or if the environment variable GMCP_UNIT_TESTS equals "java" or "all") the GUI and its logic is tested with JUnit tests. You need JUnit 4 classes in the classpath or specify the path to a JUnit 4 jar file via the parameter junitLibrary.
`interactive`	If `TRUE` (or if the environment variable GMCP_UNIT_TESTS equals "interactive" or "all") the interactive part of the RUnit tests is run. The user have to look at results and answer questions.
`junitLibrary`	A character String specifying the path to a JUnit 4 jar file to run the JUnit tests. You can download it from `https://junit.org/`. Alternatively you can use the environment variable GMCP_JUNIT_LIBRARY to specify the path.
`outputPath`	During the RUnit tests files maybe produced at this location. If missing the current working directory is used if nothing else is specified in the environment variable GMCP_UNIT_TEST_OPATH. Also the log of the results of the test suite is saved in this place.

Details

The environment variable GMCP_UNIT_TESTS may be used to specify which unit tests should run: "extended", "interactive", "java" or a combination of these separated by comma (without blanks). A short cut for all three is "all".

Value

None of interest so far - the function prints the results to the standard output. (Perhaps in future versions a value will be returned that can be processed by the GUI.)

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

Examples

```
## Not run:
unitTestsGMCP()
unitTestsGMCP(extended=TRUE, java=TRUE, interactive=TRUE, outputPath="~/RUnitTests")


## End(Not run)
```

---

weighted.test.functions

Weighted Test Functions for use with gMCP

Description

The package gMCP provides the following weighted test functions:

bonferroni.test Bonferroni test - see ?bonferroni.test for details.

parametric.test Parametric test - see ?parametric.test for details.

simes.test Simes test - see ?simes.test for details.

bonferroni.trimmed.simes.test Trimmed Simes test for intersections of two hypotheses and otherwise Bonferroni - see ?bonferroni.trimmed.simes.test for details.

simes.on.subsets.test Simes test for intersections of hypotheses from certain sets and otherwise Bonferroni - see ?simes.on.subsets.test for details.

Details

Depending on whether adjPValues==TRUE these test functions return different values:

- If adjPValues==TRUE the minimal value for alpha is returned for which the null hypothesis can be rejected. If that's not possible (for example in case of the trimmed Simes test adjusted p-values can not be calculated), the test function may throw an error.
- If adjPValues==FALSE a logical value is returned whether the null hypothesis can be rejected.

To provide your own test function write a function that takes at least the following arguments:

pvalues A numeric vector specifying the p-values.

weights A numeric vector of weights.

alpha A numeric specifying the maximal allowed type one error rate. If adjPValues==TRUE (default) the parameter alpha should not be used.

adjPValues Logical scalar. If TRUE an adjusted p-value for the weighted test is returned (if possible - if not the function should call stop). Otherwise if adjPValues==FALSE a logical value is returned whether the null hypothesis can be rejected.

... Further arguments possibly passed by gMCP which will be used by other test procedures but not this one.

Further the following parameters have a predefined meaning:

verbose Logical scalar. If TRUE verbose output should be generated and printed to the standard output

subset

correlation

Author(s)

Kornelius Rohmeyer <rohmeyer@small-projects.de>

Examples

```
# The test function 'bonferroni.test' is used in by gMCP in the following call:
graph <- BonferroniHolm(4)
pvalues <- c(0.01, 0.05, 0.03, 0.02)
alpha <- 0.05
r <- gMCP.extended(graph=graph, pvalues=pvalues, test=bonferroni.test, verbose=TRUE)

# For the intersection of all four elementary hypotheses this results in a call
bonferroni.test(pvalues=pvalues, weights=getWeights(graph))
bonferroni.test(pvalues=pvalues, weights=getWeights(graph), adjPValues=FALSE)

# bonferroni.test function:
bonferroni.test <- function(pvalues, weights, alpha=0.05, adjPValues=TRUE, verbose=FALSE, ...) {
  if (adjPValues) {
    return(min(pvalues/weights))
  } else {
    return(any(pvalues<=alpha*weights))
  }
}
```

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