Package 'MultiMed'

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Title Testing multiple biological mediators simultaneously

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Depends R (>= 3.1.0)

Suggests RUnit, BiocGenerics

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Description Implements methods for testing multiple mediators

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`medTest` *Permutation test for multiple mediators which uses a joint correction*

Description

Implements Boca et al. 2014 method of testing multiple biological mediators simultaneously, which uses a permutation test with a joint correction based on the maximal test statistics.

Usage

```
medTest(E, M, Y, Z = NULL, useWeightsZ = TRUE, nperm = 100, w = 1)
```

Arguments

`E`	Exposure: numerical vector of length n or numerical n x 1 matrix, where n is the number of samples or subjects.
`M`	Mediators: numerical matrix of dimension n x p, where p is the number of mediators.
`Y`	Outcome: numerical vector of length n or numerical n x 1 matrix
`Z`	Additional covariates: NULL or numerical matrix having n rows. If it is not NULL, then the exposure, mediators, and outcome will all be initially regressed on Z, with the residuals being used in the mediation analysis.
`nperm`	Number of permutations performed. One of the permutations always consists of the observed data.
`w`	Weight assigned to each subject or sample for the E-M associations. Useful for case-control sampling.
`useWeightsZ`	If TRUE, use the weights in w for the initial regression of E and M on Z, in the case where Z is not null. If FALSE, use equal weights.

Details

See Boca et al. 2014 paper for a more in-depth description of this method.

Value

Matrix with p rows and 2 columns, where the first column (labeled "S") gives the S-statistics and the second column (labeled "p") gives the p-values for each mediator, where the mediators correspond to the rows. For each mediator, the S-statistic is the absolute value of the product of the correlation between the exposure and the mediator and the conditional (or partial) correlation between the mediator and the outcome conditional on the exposure. Thus, the larger the S-statistic is, the smaller the p-value is, and the more likely it is that the mediator is statistically significant.

Author(s)

Simina M. Boca, Joshua N. Sampson

References

Boca SM, Sinha R, Cross AJ, Moore SC, Sampson JN. Testing multiple biological mediators simultaneously. *Bioinformatics*, 2014, 30(2), 214-220.

See Also

NavyAdenoma

Examples

```
##More details on this example are given in the accompanying vignette.

data(NavyAdenoma)

##the exposure of interest is the daily intake of fish
##the possible mediators are 149 normalized serum metabolite values
##the outcome of interest is colorectal adenoma case-control status

##get weights needed due to retrospective sampling, to use for all regressions
##that do not have adenoma status as the outcome
prev <- 0.228
p <- sum(NavyAdenoma$Adenoma==1)/nrow(NavyAdenoma)
w <- rep(NA, nrow(NavyAdenoma))
w[NavyAdenoma$Adenoma == 1] <- prev/p
w[NavyAdenoma$Adenoma == 0] <- (1-prev)/(1-p)

##perform the test of mediation, adjusting for the covariates
##BMI, gender, age, and current smoking status
##(only running 10 permutations in this example - would need to
##perform more to get an accurate p-value)
set.seed(840218)
medsFish <- medTest(E=NavyAdenoma$Fish,
                    M=NavyAdenoma[, 6:154],
                    Y=NavyAdenoma$Adenoma,
                    Z=NavyAdenoma[, 2:5],
                    nperm=10, w=w)

##get metabolite with lowest p-value
medsFish[which.min(medsFish[,"p"]),]
colnames(NavyAdenoma[,-(1:5)])[which.min(medsFish[,"p"])]
```

---

medTest.SBMH — *Test for multiple mediators which uses the Bogomolov and Heller approach*

Description

Implements Heller/Sampson method of testing multiple biological mediators simultaneously, controlling either FWER or FDR.

Usage

```
medTest.SBMH(pEM,pMY,MCP.type="FWER",t1=0.05,t2=0.05,lambda=0)
```

Arguments

pEM	Vector of size m (where m = number of mediators). Entries are the p-values for the E,M_j relationship.
pMY	Vector of size m (where m = number of mediators). Entries are the p-values for the M_j,Y|E relationship.
MCP.type	Multiple comparison procedure - either "FWER" or "FDR".
t1	Threshold for determining the cutoff to be one of the top S_1 E/M_j relationships.
t2	Threshold for determining the cutoff to be one of the top S_2 M_j/Y relationships.
lambda	Threshold for estimating the proportion of false positives.

Details

See Heller/Sampson paper for a more in-depth description of this method.

Value

m x 1 matrix of either p-values (if MCP.type = "FWER") or q-values (if MCP.type = "FDR").

Author(s)

Ruth Heller, Joshua N. Sampson

References

Sampson JN, Boca SM, Moore SC, Heller R. FWER and FDR control when testing multiple mediators. *Bioinformatics*, 2018, 34(14), 2418-2424.

Examples

```
##load dataset - details are given in the accompanying vignette

data(NavyAdenoma)

##the exposure of interest is the daily intake of fish
##the possible mediators are 149 normalized serum metabolite values
##the outcome of interest is colorectal adenoma case-control status

##get all metabolites
metabs <- colnames(NavyAdenoma)[6:154]

##get exposure/mediator relationships
pEM <- sapply(NavyAdenoma[,metabs],
              function(m,e){coef(summary(lm(m ~ e)))[2,4]},
```

```
              e=NavyAdenoma$Fish)

##get mediator/outcome relationship (conditional on exposure)
pMY <- sapply(NavyAdenoma[,metabs],
              function(m,y,e){coef(summary(glm(y ~ m + e, family=binomial)))[2,4]},
              y=NavyAdenoma$Adenoma, e=NavyAdenoma$Fish)

##perform mediation test for both FWER and FDR procedures
medTest.FWER <- medTest.SBMH(pEM, pMY, MCP.type="FWER")
##get smallest p-value and corresponding metabolite
min(medTest.FWER)
metabs[which.min(medTest.FWER)]

medTest.FDR <- medTest.SBMH(pEM, pMY, MCP.type="FDR")
##get smallest p-value and corresponding metabolite
min(medTest.FDR)
metabs[which.min(medTest.FDR)]
```

NavyAdenoma *Data from the Sinha et al. 1999 and Boca et al. 2014 studies concerning the Navy Colorectal Adenoma case-control study.*

Description

The data consists of a dietary exposures of interest (daily intake of fish in grams/day), the outcome of interest (colorectal adenoma status), and 149 serum metabolites which are possible mediators between either of the exposures and the outcome. Four other additional covariates of interest are included (body mass index, gender, age, current smoking status.)

Usage

```
data(NavyAdenoma)
```

Format

Data frame with 258 rows, representing 129 cases and 129 controls in the Navy Colorectal Adenoma study. There are 155 columns, ordered as follows: fish intake (*Fish*), body mass index (*BMI*), gender (*Female* - coded as 0 for male, 1 for female), age in years (*Age*), current smoking status (*Smoking* - coded as 0 for non-smoker, 1 for current smoker), 149 serum metabolites (values were previously batch normalized and log transformed), and case-control status for adenoma (*Adenoma* - coded as 0 for control, 1 for case.)

References

Sinha, R, Chow WH, Kulldorff M, Denobile J, Butler J, Garcia-Closas M, Weil R, Hoover RN, Rothman N. Well-done, grilled red meat increases the risk of colorectal adenomas. *Cancer Res.*, 1999, 59(17), 4320-4324.

Boca SM, Sinha R, Cross AJ, Moore SC, Sampson JN. Testing multiple biological mediators simultaneously. *Bioinformatics*, 2014, 30(2), 214-220.

See Also

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