Package ‘multxpert’

May 9, 2026

Title Common Multiple Testing Procedures and Gatekeeping Procedures

Version 0.1.1

Date 2010-10-31

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Description Implementation of commonly used p-value-based and parametric multiple testing procedures (computation of adjusted p-values and simultaneous confidence intervals) and parallel gatekeeping procedures based on the methodology presented in the book ``Multiple Testing Problems in Pharmaceutical Statistics'' (edited by Alex Dmitrienko, Ajit C. Tamhane and Frank Bretz) published by Chapman and Hall/CRC Press 2009.

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Depends R (>= 2.1.0), stats, mvtnorm (>= 0.9)

URL http://multxpert.com/wiki/MultXpert_package

LazyLoad yes

License GPL-2

Repository CRAN

Date/Publication 2019-10-02 15:54:00 UTC

NeedsCompilation no

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paradjp *Common parametric procedures: Adjusted p-values*

Description

Computation of adjusted p-values for commonly used parametric multiple testing procedures (single-step and step-down Dunnett procedures).

Usage

```
paradjp(stat,n,proc)
```

Arguments

`stat`	Vector of test statistics.
`n`	Common sample size in each treatment group.
`proc`	Vector of character strings containing the procedure name. This vector should include any of the following: `"Single-step Dunnett"`, `"Step-down Dunnett"`.

Details

This function computes adjusted p-values for the single-step Dunnett procedure (Dunnett, 1955) and step-down Dunnett procedure (Naik, 1975; Marcus, Peritz and Gabriel, 1976) in one-sided hypothesis testing problems with a balanced one-way layout and equally weighted null hypotheses. For more information on the algorithms used in the function, see Dmitrienko et al. (2009, Section 2.7).

Value

A list with the following components:

`proc`	Name of procedure used.
`result`	A data frame with columns for the test statistics, one-sided raw p-values, and one-sided adjusted p-values for the specified procedure.

Source

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References

Dmitrienko, A., Bretz, F., Westfall, P.H., Troendle, J., Wiens, B.L., Tamhane, A.C., Hsu, J.C. (2009). Multiple testing methodology. *Multiple Testing Problems in Pharmaceutical Statistics*. Dmitrienko, A., Tamhane, A.C., Bretz, F. (editors). Chapman and Hall/CRC Press, New York.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *Journal of the American Statistical Association*. 50, 1096–1121.

Marcus, R. Peritz, E., Gabriel, K.R. (1976). On closed testing procedures with special reference to ordered analysis of variance. *Biometrika*. 63, 655–660.

Naik, U.D. (1975). Some selection rules for comparing p processes with a standard. *Communications in Statistics. Series A*. 4, 519–535.

See Also

pvaladjp

Examples

```
# Consider a clinical trial conducted to evaluate the effect of three
# doses of a treatment compared to a placebo with respect to a normally
# distributed endpoint

# Three null hypotheses of no effect are tested in the trial:
# Null hypothesis H1: No difference between Dose 1 and Placebo
# Null hypothesis H2: No difference between Dose 2 and Placebo
# Null hypothesis H3: No difference between Dose 3 and Placebo

# Treatment effect estimates (mean  dose-placebo differences)
est<-c(2.3,2.5,1.9)

# Pooled standard deviation
sd<-9.5

# Study design is balanced with 180 patients per treatment arm
n<-180

# Standard errors
stderror<-rep(sd*sqrt(2/n),3)

# T-statistics associated with the three dose-placebo tests
stat<-est/stderror

# Compute one-sided adjusted p-values for the single-step Dunnett procedure
paradjp(stat, n, proc="Single-step Dunnett")

# Compute one-sided adjusted p-values for the single-step and
# step-down Dunnett procedures
paradjp(stat, n, proc=c("Single-step Dunnett", "Step-down Dunnett"))
```

`parci` *Common parametric procedures: Simultaneous confidence intervals*

Description

Computation of simultaneous confidence intervals for commonly used parametric multiple testing procedures (single-step and step-down Dunnett procedures).

Usage

```
parci(stat, n, est, stderror, covprob, proc)
```

Arguments

`stat`	Vector of test statistics.
`n`	Common sample size in each treatment group.
`est`	Vector of point estimates.
`stderror`	Vector of standard errors associated with the point estimates.
`covprob`	Simultaneous coverage probability (default is 0.975).
`proc`	Vector of character strings containing the procedure name. This vector should include any of the following: `"Single-step Dunnett"`, `"Step-down Dunnett"`.

Details

This function computes lower one-sided simultaneous confidence limits for the single-step Dunnett procedure (Dunnett, 1955) and step-down Dunnett procedure (Naik, 1975; Marcus, Peritz and Gabriel, 1976) in one-sided hypothesis testing problems with a balanced one-way layout and equally weighted null hypotheses.

The simultaneous confidence intervals are computed using the methods developed in Bofinger (1987) and Stefansson, Kim and Hsu (1988). For more information on the algorithms used in the function, see Dmitrienko et al. (2009, Section 2.7).

Value

A data frame `result` with columns for the test statistics, point estimates, standard errors, adjusted p-values, and lower simultaneous confidence limits for the specified procedure.

Source

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References

Bofinger, E. (1987). Step-down procedures for comparison with a control. *Australian Journal of Statistics*. 29, 348–364.

Dmitrienko, A., Bretz, F., Westfall, P.H., Troendle, J., Wiens, B.L., Tamhane, A.C., Hsu, J.C. (2009). Multiple testing methodology. *Multiple Testing Problems in Pharmaceutical Statistics*. Dmitrienko, A., Tamhane, A.C., Bretz, F. (editors). Chapman and Hall/CRC Press, New York.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *Journal of the American Statistical Association*. 50, 1096–1121.

Marcus, R. Peritz, E., Gabriel, K.R. (1976). On closed testing procedures with special reference to ordered analysis of variance. *Biometrika*. 63, 655–660.

Naik, U.D. (1975). Some selection rules for comparing p processes with a standard. *Communications in Statistics. Series A*. 4, 519–535.

Stefansson, G., Kim, W.-C., Hsu, J.C. (1988). On confidence sets in multiple comparisons. *Statistical Decision Theory and Related Topics IV*. Gupta, S.S., Berger, J.O. (editors). Academic Press, New York, 89–104.

See Also

parci

Examples

```
# Consider a clinical trial conducted to evaluate the effect of three
# doses of a treatment compared to a placebo with respect to a normally
# distributed endpoint

# Three null hypotheses of no effect are tested in the trial:
# Null hypothesis H1: No difference between Dose 1 and Placebo
# Null hypothesis H2: No difference between Dose 2 and Placebo
# Null hypothesis H3: No difference between Dose 3 and Placebo

# Treatment effect estimates (mean  dose-placebo differences)
est<-c(2.3,2.5,1.9)

# Pooled standard deviation
sd<-9.5

# Study design is balanced with 180 patients per treatment arm
n<-180

# Standard errors
stderror<-rep(sd*sqrt(2/n),3)

# T-statistics associated with the three dose-placebo tests
```

```
stat<-est/stderror

# Compute lower one-sided simultaneous confidence limits
# for the single-step Dunnett procedure
parci(stat,n,est,stderror,covprob=0.975,proc="Single-step Dunnett")

# Compute lower one-sided simultaneous confidence limits
# for the single-step and step-down Dunnett procedures
parci(stat,n,est,stderror,covprob=0.975,proc=c("Single-step Dunnett", "Step-down Dunnett"))
```

`pargateadjp` *Multistage parallel gatekeeping procedures: Adjusted p-values*

Description

Computation of adjusted p-values for multistage parallel gatekeeping procedures.

Usage

```
pargateadjp(gateproc, independence, alpha, printDecisionRules)
```

Arguments

`gateproc` List of gatekeeping procedure parameters in each family of null hypotheses, including the family label, vector of raw p-values, procedure name and procedure parameter (`pargateadjp` function supports truncated and regular versions of the Bonferroni, Holm, Hommel, Hochberg and fallback procedures).

`independence` Boolean indicator (TRUE, Independence condition is imposed (i.e., inferences in earlier families are independent of inferences in later families); FALSE, Independence condition is not imposed).

`alpha` Global family-wise error rate (default is 0.05). Note that this argument is not needed if the function is called to compute adjusted p-values, i.e., if `printDecisionRules=FALSE`.

`printDecisionRules` Boolean indicator for printing the decision rules for the gatekeeping procedure (default is FALSE).

Details

This function computes adjusted p-values and generates decision rules for multistage parallel gatekeeping procedures in hypothesis testing problems with multiple families of null hypotheses (null hypotheses are assumed to be equally weighted within each family) based on the methodology presented in Dmitrienko, Tamhane and Wiens (2008) and Dmitrienko, Kordzakhia and Tamhane (2011). For more information on parallel gatekeeping procedures (computation of adjusted p-values, independence condition, etc), see Dmitrienko and Tamhane (2009, Section 5.4).

Value

A data frame `result` with columns for the family labels, procedures, procedure parameters (truncation parameters), raw p-values, and adjusted p-values.

Source

http://multxpert.com/wiki/MultXpert_package

References

Dmitrienko, A., Tamhane, A., Wiens, B. (2008). General multistage gatekeeping procedures. *Biometrical Journal*. 50, 667–677.

Dmitrienko, A., Tamhane, A.C. (2009). Gatekeeping procedures in clinical trials. *Multiple Testing Problems in Pharmaceutical Statistics*. Dmitrienko, A., Tamhane, A.C., Bretz, F. (editors). Chapman and Hall/CRC Press, New York.

Dmitrienko, A., Kordzakhia, G., Tamhane, A.C. (2011). Multistage and mixture parallel gatekeeping procedures in clinical trials. *Journal of Biopharmaceutical Statistics*. To appear.

Examples

```
# Consider a clinical trial with two families of null hypotheses

# Family 1: Primary null hypotheses (one-sided p-values)
# H1 (Endpoint 1), p1=0.0082
# H2 (Endpoint 2), p2=0.0174

# Family 2: Secondary null hypotheses (one-sided p-values)
# H3 (Endpoint 3), p3=0.0042
# H4 (Endpoint 4), p4=0.0180

# Define family label and raw p-values in Family 1
label1<-"Primary endpoints"
rawp1<-c(0.0082,0.0174)

# Define family label and raw p-values in Family 2
label2<-"Secondary endpoints"
rawp2<-c(0.0042,0.0180)

# Independence condition is imposed (Families 1 and 2 are tested
# sequentually from first to last and thus adjusted p-values
# in Family 1 do not depend on inferences in Family 2)
independence<-TRUE

# Define a two-stage parallel gatekeeping procedure which
# utilizes the truncated Holm procedure in Family 1 (truncation
# parameter=0.5) and regular Holm procedure in Family 2 (truncation
# parameter=1)
```

```
# Create a list of gatekeeping procedure parameters
family1<-list(label=label1, rawp=rawp1, proc="Holm", procpar=0.5)
family2<-list(label=label2, rawp=rawp2, proc="Holm", procpar=1)
gateproc<-list(family1,family2)

# Compute adjusted p-values
pargateadjp(gateproc, independence)

# Generate decision rules using a one-sided alpha=0.025
pargateadjp(gateproc, independence, alpha=0.025, printDecisionRules=TRUE)
```

`pvaladjp` *Common p-value-based procedures: Adjusted p-values*

Description

Computation of adjusted p-values for commonly used multiple testing procedures based on univariate p-values (Bonferroni, Holm, Hommel, Hochberg, fixed-sequence and fallback procedures).

Usage

```
pvaladjp(rawp, weight, alpha, proc, printDecisionRules)
```

Arguments

`rawp`	Vector of raw p-values.
`weight`	Vector of hypothesis weights whose sum is equal to 1 (default is a vector of equal weights).
`alpha`	Familywise error rate (default is 0.05). Note that this argument is not needed if the function is called to compute adjusted p-values, i.e., if `printDecisionRules=FALSE`.
`proc`	Vector of character strings containing the procedure name. This vector should include any of the following: `"Bonferroni"`, `"Holm"`, `"Hommel"`, `"Hochberg"`, `"Fixed-sequence"`, `"Fallback"`.
`printDecisionRules`	Boolean indicator for printing the decision rules for each of the procedures specified in `"proc"` (default is FALSE).

Details

This function computes adjusted p-values and generates decision rules for the Bonferroni, Holm (Holm, 1979), Hommel (Hommel, 1988), Hochberg (Hochberg, 1988), fixed-sequence (Westfall and Krishen, 2001) and fallback (Wiens, 2003; Wiens and Dmitrienko, 2005) procedures.

The adjusted p-values are computed using the closure principle (Marcus, Peritz and Gabriel, 1976) in general hypothesis testing problems (equally or unequally weighted null hypotheses). The decision rules are generated only in hypothesis testing problems with equally weighted null hypotheses. For more information on the algorithms used in the function, see Dmitrienko et al. (2009, Section 2.6).

Value

A data frame `result` with columns for the raw p-values, weights, and adjusted p-values for each of the procedures.

Source

http://multxpert.com/wiki/MultXpert_package

References

Dmitrienko, A., Bretz, F., Westfall, P.H., Troendle, J., Wiens, B.L., Tamhane, A.C., Hsu, J.C. (2009). Multiple testing methodology. *Multiple Testing Problems in Pharmaceutical Statistics*. Dmitrienko, A., Tamhane, A.C., Bretz, F. (editors). Chapman and Hall/CRC Press, New York.

Hochberg, Y. (1988). A sharper Bonferroni procedure for multiple significance testing. *Biometrika*. 75, 800–802.

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

Hommel, G. (1988). A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika*. 75, 383–386.

Marcus, R. Peritz, E., Gabriel, K.R. (1976). On closed testing procedures with special reference to ordered analysis of variance. *Biometrika*. 63, 655–660.

Westfall, P. H., Krishen, A. (2001). Optimally weighted, fixed sequence, and gatekeeping multiple testing procedures. *Journal of Statistical Planning and Inference*. 99, 25–40.

Wiens, B. (2003). A fixed-sequence Bonferroni procedure for testing multiple endpoints. *Pharmaceutical Statistics*. 2, 211–215.

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

See Also

`paradjp`

Examples

```
# Consider a clinical trial conducted to evaluate the effect of three
# doses of a treatment compared to a placebo with respect to a normally
# distributed endpoint

# Three null hypotheses of no effect are tested in the trial:
# Null hypothesis H1: No difference between Dose 1 and Placebo
```

```
# Null hypothesis H2: No difference between Dose 2 and Placebo
# Null hypothesis H3: No difference between Dose 3 and Placebo

# Null hypotheses of no treatment effect are equally weighted
weight<-c(1/3,1/3,1/3)

# Treatment effect estimates (mean  dose-placebo differences)
est<-c(2.3,2.5,1.9)

# Pooled standard deviation
sd<-9.5

# Study design is balanced with 180 patients per treatment arm
n<-180

# Standard errors
stderror<-rep(sd*sqrt(2/n),3)

# T-statistics associated with the three dose-placebo tests
stat<-est/stderror

# Compute degrees of freedom
nu<-2*(n-1)

# Compute raw one-sided p-values
rawp<-1-pt(stat,nu)

# Compute adjusted p-values for the Bonferroni procedure
pvaladjp(rawp, weight, proc="Bonferroni")

# Compute adjusted p-values for the Hommel and Fallback procedures
pvaladjp(rawp, weight, proc=c("Hommel", "Fallback"))

# Generate decision rules for the Holm procedure
# using a one-sided alpha=0.025
pvaladjp(rawp, weight, alpha=0.025, proc="Holm", printDecisionRules=TRUE)
```

`pvalci` *Common p-value-based procedures: Simultaneous confidence intervals*

Description

Computation of simultaneous confidence intervals for selected multiple testing procedures based on univariate p-values (Bonferroni, Holm and fixed-sequence procedures).

Usage

```
pvalci(rawp, est, stderror, weight, covprob, proc)
```

Arguments

`rawp`	Vector of raw p-values.
`est`	Vector of point estimates.
`stderror`	Vector of standard errors associated with the point estimates.
`weight`	Vector of hypothesis weights whose sum is equal to 1 (default is a vector of equal weights).
`covprob`	Simultaneous coverage probability (default is 0.975).
`proc`	Vector of character strings containing the procedure name. This vector should include any of the following: `"Bonferroni"`, `"Holm"`, `"Fixed-sequence"`.

Details

This function computes one-sided simultaneous confidence limits for the Bonferroni, Holm (Holm, 1979) and fixed-sequence (Westfall and Krishen, 2001) procedures in in general one-sided hypothesis testing problems (equally or unequally weighted null hypotheses).

The simultaneous confidence intervals are computed using the methods developed in Hsu and Berger (1999), Strassburger and Bretz (2008) and Guilbaud (2008). For more information on the algorithms used in the function, see Dmitrienko et al. (2009, Section 2.6).

Value

A data frame `result` with columns for the raw p-values, point estimates, standard errors, weights, adjusted p-values, and simultaneous confidence limits for each of the procedures.

Source

http://multxpert.com/wiki/MultXpert_package

References

Dmitrienko, A., Bretz, F., Westfall, P.H., Troendle, J., Wiens, B.L., Tamhane, A.C., Hsu, J.C. (2009). Multiple testing methodology. *Multiple Testing Problems in Pharmaceutical Statistics*. Dmitrienko, A., Tamhane, A.C., Bretz, F. (editors). Chapman and Hall/CRC Press, New York.

Guilbaud, O. (2008). Simultaneous confidence regions corresponding to Holm's stepdown procedure and other closed-testing procedures. *Biometrical Journal*. 5, 678–692.

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

Hsu, J.C., Berger, R.L. (1999). Stepwise confidence intervals without multiplicity adjustment for dose-response and toxicity studies. *Journal of the American Statistical Association*. 94, 468–482.

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

Westfall, P. H., Krishen, A. (2001). Optimally weighted, fixed sequence, and gatekeeping multiple testing procedures. *Journal of Statistical Planning and Inference*. 99, 25–40.

See Also

parci

Examples

```
# Consider a clinical trial conducted to evaluate the effect of three
# doses of a treatment compared to a placebo with respect to a normally
# distributed endpoint

# Three null hypotheses of no effect are tested in the trial:
# Null hypothesis H1: No difference between Dose 1 and Placebo
# Null hypothesis H2: No difference between Dose 2 and Placebo
# Null hypothesis H3: No difference between Dose 3 and Placebo

# Null hypotheses of no treatment effect are equally weighted
weight<-c(1/3,1/3,1/3)

# Treatment effect estimates (mean  dose-placebo differences)
est<-c(2.3,2.5,1.9)

# Pooled standard deviation
sd<-9.5

# Study design is balanced with 180 patients per treatment arm
n<-180

# Standard errors
stderror<-rep(sd*sqrt(2/n),3)

# T-statistics associated with the three dose-placebo tests
stat<-est/stderror

# Compute degrees of freedom
nu<-2*(n-1)

# Compute raw one-sided p-values
rawp<-1-pt(stat,nu)

# Compute lower one-sided simultaneous confidence limits
# for the Bonferroni procedure
pvalci(rawp,est,stderror,weight,covprob=0.975,proc="Bonferroni")

# Compute lower one-sided simultaneous confidence limits
# for the Holm and Fixed-sequence procedures
pvalci(rawp,est,stderror,weight,covprob=0.975,proc=c("Holm", "Fixed-sequence"))
```

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