Package 'SimComp'

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Type Package

Title Simultaneous Comparisons for Multiple Endpoints

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Imports mvtnorm, multcomp, mratios

Description Simultaneous tests and confidence intervals are provided for one-way experimental designs with one or many normally distributed, primary response variables (endpoints). Differences (Hasler and Hothorn, 2011) or ratios (Hasler and Hothorn, 2012) of means can be considered. Various contrasts can be chosen, unbalanced sample sizes are allowed as well as heterogeneous variances (Hasler and Hothorn, 2008) or covariance matrices (Hasler, 2014).

License GPL

LazyLoad yes

NeedsCompilation no

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R topics documented:

`SimComp-package` *Simultaneous Comparisons for Multiple Endpoints*

Description

Simultaneous tests and confidence intervals for one-way experimental designs with one or many normally distributed, primary response variables (endpoints). Means of several groups or dose levels can be compared

- by arbitrary contrasts, like the Dunnett or the Tukey test,
- for balanced or unbalanced sample sizes,
- for a single endpoint or for many endpoints simultaneously,
- for homogeneous or heterogeneous variances/ covariance matrices of the groups, and
- in terms of differences or ratios.

Exact or approximate multivariate *t*-distributions, respectively, are used for the calculation of critical values or (adjusted) *p*-values.

For example, the well-known conventional all-pair comparison of Tukey (1953) can be performed by specifying only a single endpoint and homogeneous (co-)variances. On the other hand, it's also possible to do the same, but for many endpoints simultaneously, with heterogeneous covariance matrices and in terms of ratios.

For multiple comparisons of means of heteroscedastic data, see Hasler and Hothorn (2008). The test procedure for multiple endpoints is described by Hasler and Hothorn (2011,2012). See Hasler (2014) for the case of heterogeneous covariance matrices.

Details

Package:	SimComp
Type:	Package
Version:	2.2
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Author(s)

Mario Hasler

Maintainer: Mario Hasler <hasler@email.uni-kiel.de>

References

Hasler, M. (2014): Multiple contrast tests for multiple endpoints in the presence of heteroscedasticity. *The International Journal of Biostatistics* 10, 17–28.

Hasler, M. and Hothorn, L.A. (2012): A multivariate Williams-type trend procedure. *Statistics in Biopharmaceutical Research* 4, 57–65.

Hasler, M. and Hothorn, L.A. (2011): A Dunnett-type procedure for multiple endpoints. *The International Journal of Biostatistics* 7, Article 3.

Hasler, M. and Hothorn, L.A. (2008): Multiple contrast tests in the presence of heteroscedasticity. *Biometrical Journal* 50, 793–800.

Dilba, G. et al. (2006): Simultaneous confidence sets and confidence intervals for multiple ratios. *Journal of Statistical Planning and Inference* 136, 2640–2658.

See Also

mratios

Examples

```
# Example 1:
# A Dunnett-test for the groups B and H against the standard S, on
# the (single) endpoint Thromb.count, assuming unequal variances for
# the groups. This is the well-known Dunnett-test but in the
# presence of heteroscedasticity.

data(coagulation)

comp1 <- SimTestDiff(data=coagulation, grp="Group", resp="Thromb.count",
  type="Dunnett", base=3, alternative="greater", covar.equal=FALSE)
```

```
comp1

# Example 2:
# A Dunnett-test for the groups B and H against the standard S,
# simultaneously on all endpoints, assuming unequal covariance
# matrices for the groups.

data(coagulation)

comp2 <- SimTestDiff(data=coagulation, grp="Group", resp=c("Thromb.count","ADP","TRAP"),
  type="Dunnett", base=3, alternative="greater", covar.equal=FALSE)
summary(comp2)
```

`coagulation` *Data from a clinical study of three sets of extracorporeal circulation in heart-lung machines*

Description

Three sets of extracorporeal circulation in heart-lung machines: treatments H and B, and standard S. Twelve (S and H each) and eleven (B) male adult patients have been considered. The analysis is based on a set of laboratory parameters restricted to the blood coagulation system, characterized by three primary endpoints (each as quotient from post- and pre-surgery values). Higher values indicate a better treatment effect. For more details, see Kropf et al. (2000).

Usage

```
data(coagulation)
```

Format

A data frame with 35 observations on the following 5 variables.

`Patient` a numeric vector, the patients' number

`Thromb.count` a numeric vector

`ADP` a numeric vector

`TRAP` a numeric vector

`Group` a factor with levels `B`, `H`, `S` specifying the treatments, where `S` is the standard

Source

Kropf, S. et al. (2000): Multiple comparisons of treatments with stable multivariate tests in a two-stage adaptive design, including a test for non-inferiority. *Biometrical Journal* 42, 951-965.

References

Hasler, M. and Hothorn, L.A. (2011): A Dunnett-type procedure for multiple endpoints. *The International Journal of Biostatistics* 7, Article 3.

Examples

```
data(coagulation)
str(coagulation)
```

`DfSattDiff` *Degrees of Freedom Accoding to Satterthwaite (1946) for Differences of Means*

Description

Degrees of freedom accoding to Satterthwaite (1946) for (multivariate) *t*-distributions related to multiple contrast tests or corresponding simultaneous confidence intervals for differences of means. For contrasts representing a two-sample *t*-test, the degree of freedom coincides with the one of Welch (1938).

Usage

```
DfSattDiff(n, sd, type = "Dunnett", base = 1, ContrastMat = NULL)
```

Arguments

`n`	a vector of numbers of observations
`sd`	a vector of standard deviations
`type`	a character string, defining the type of contrast, with the following options: • "Dunnett": many-to-one comparisons • "Tukey": all-pair comparisons • "Sequen": comparisons of consecutive groups • "AVE": comparison of each group with average of all others • "GrandMean": comparison of each group with grand mean of all groups • "Changepoint": differences of averages of groups of higher order to averages of groups of lower order • "Marcus": Marcus contrasts • "McDermott": McDermott contrasts • "Williams": Williams trend tests • "UmbrellaWilliams": Umbrella-protected Williams trend tests note that `type` is ignored if `ContrastMat` is specified by the user (see below)
`base`	a single integer specifying the control group for Dunnett contrasts, ignored otherwise
`ContrastMat`	a contrast matrix, where columns correspond to groups and rows correspond to contrasts

Details

The calculation of critical values or (adjusted) p-values related to multiple contrast tests or corresponding simultaneous confidence intervals is based on a multivariate t-distribution. For homoscedastic data, the respective degree of freedom only depends on the total sample size and the number of groups. A simple and well-known special case ist the usual t-test. If the data are heteroscedastic, however, the degree of freedom of a usual t-test must be decreased according to Welch (1938) to come to an approximate solution. Degrees of freedom according to Satterthwaite (1946) refer to any linear combinations (contrasts) of normal means. They are applied, for example, when doing multiple contrast tests for heteroscedastic data according to Hasler and Hothorn (2008) or Hasler (2014). Like Welch (1938), Satterthwaite (1946) approximated the degree of freedom by matching first and second moments. The resulting degree of freedom then depends on the contrast and on the sample sizes and sample variances per group, respectively.

Value

A vector of degrees of freedom.

Note

The commands `SimTestDiff()` and `SimCiDiff()` use these degrees of freedom automatically if `covar.equal=FALSE` (default). You don't need to apply `DfSattDiff()` additionally.

Author(s)

Mario Hasler

References

Hasler, M. (2014): Multiple contrast tests for multiple endpoints in the presence of heteroscedasticity. *The International Journal of Biostatistics* 10, 17–28.

Hasler, M. and Hothorn, L.A. (2008): Multiple contrast tests in the presence of heteroscedasticity. *Biometrical Journal* 50, 793–800.

Satterthwaite, F.E. (1946): An approximate distribution of estimates of variance components. *Biometrics* 2, 110–114.

Welch, B.L. (1938): The significance of the difference between two means when the population variances are unequal. *Biometrika* 29, 350–362.

See Also

`DfSattRat`

Examples

```
# Example 1:
# Degrees of freedom for a comparison of group two and three against group one, assuming
# unequal standard deviations for the groups. This is an extension for the well-known
# Dunnett-test to the case of heteroscedasticity.

# Either by specifying the type of contrast:
```

```
DfSattDiff(n=c(10,6,6), sd=c(1,3,6), type="Dunnett", base=1)

# Or by specifying the contrast matrix:
DfSattDiff(n=c(10,6,6), sd=c(1,3,6), ContrastMat=rbind(c(-1,1,0),c(-1,0,1)))

# Example 2:
# Degrees of freedom for an all-pair comparison of the groups B, H and S on endpoint ADP,
# assuming unequal standard deviations for the groups. This is an extension for the well-
# known Tukey-test to the case of heteroscedasticity.

data(coagulation)

DfSattDiff(n=tapply(X=coagulation$ADP, INDEX=coagulation$Group, FUN=length),
  sd=tapply(X=coagulation$ADP, INDEX=coagulation$Group, FUN=sd),
  type="Tukey")

# These are the same degrees of freedom as used automatically by command
# \code{SimTestDiff()}:
test <- SimTestDiff(data=coagulation, grp="Group", resp="ADP", type="Tukey",
  covar.equal=FALSE)
test$degr.fr
```

`DfSattRat` *Degrees of Freedom Accoding to Satterthwaite (1946) for Ratios of Means*

Description

Degrees of freedom accoding to Satterthwaite (1946) for (multivariate) *t*-distributions related to multiple contrast tests or corresponding simultaneous confidence intervals for ratios of means.

Usage

```
DfSattRat(n, sd, type = "Dunnett", base = 1, Num.Contrast = NULL, Den.Contrast = NULL,
          Margin = NULL)
```

Arguments

`n`	a vector of numbers of observations
`sd`	a vector of standard deviations
`type`	a character string, defining the type of contrast, with the following options: • "Dunnett": many-to-one comparisons • "Tukey": all-pair comparisons • "Sequen": comparisons of consecutive groups • "AVE": comparison of each group with average of all others • "GrandMean": comparison of each group with grand mean of all groups • "Changepoint": differences of averages of groups of higher order to averages of groups of lower order

- "Marcus": Marcus contrasts
- "McDermott": McDermott contrasts
- "Williams": Williams trend tests
- "UmbrellaWilliams": Umbrella-protected Williams trend tests

note that `type` is ignored if `ContrastMat` is specified by the user (see below)

`base` a single integer specifying the control group for Dunnett contrasts, ignored otherwise

`Num.Contrast` a numerator contrast matrix, where columns correspond to groups and rows correspond to contrasts

`Den.Contrast` a denominator contrast matrix, where columns correspond to groups and rows correspond to contrasts

`Margin` a single numeric value, or a numeric vector with length equal to the number of contrasts, default is 1

Details

The calculation of critical values or (adjusted) *p*-values related to multiple contrast tests or corresponding simultaneous confidence intervals is based on a multivariate *t*-distribution. For homoscedastic data, the respective degree of freedom only depends on the total sample size and the number of groups. A simple and well-known special case ist the usual *t*-test. If the data are heteroscedastic, however, the degree of freedom of a usual *t*-test must be decreased according to Welch (1938) to come to an approximate solution. Degrees of freedom according to Satterthwaite (1946) refer to any linear combinations (contrasts) of normal means. They are applied, for example, when doing multiple contrast tests for heteroscedastic data according to Hasler and Hothorn (2008) or Hasler (2014). Like Welch (1938), Satterthwaite (1946) approximated the degree of freedom by matching first and second moments. The approach of Satterthwaite (1946) is extended here to the case where ratios of means are of interest instead of differences. The resulting degree of freedom then depends on the numerator contrast, the denominator contrast, the (relative) margin which is tested against, and on the sample sizes and sample variances per group, respectively. If `Margin=1` or `Margin=NULL` (default), the result coincides with the result of `DfSattDiff()`.

Value

A vector of degrees of freedom.

Note

The commands `SimTestRat()` and `SimCiRat()` use these degrees of freedom automatically if `covar.equal=FALSE` (default). You don't need to apply `DfSattRat()` additionally.

Author(s)

Mario Hasler

References

Hasler, M. (2014): Multiple contrast tests for multiple endpoints in the presence of heteroscedasticity. *The International Journal of Biostatistics* 10, 17–28.

Hasler, M. and Hothorn, L.A. (2008): Multiple contrast tests in the presence of heteroscedasticity. *Biometrical Journal* 50, 793–800.

Satterthwaite, F.E. (1946): An approximate distribution of estimates of variance components. *Biometrics* 2, 110–114.

See Also

DfSattDiff

Examples

```
# Example 1:
# Degrees of freedom for a non-inferiority test of group two and three against group one,
# assuming unequal standard deviations for the groups. This is an extension for the well-
# known Dunnett-test to the case of heteroscedasticity and in terms of ratios of means
# instead of differences.

# Either by specifying the type of contrast:
DfSattRat(n=c(10,6,6), sd=c(1,3,6), type="Dunnett", base=1, Margin=0.8)

# Or by specifying the contrast matrices:
DfSattRat(n=c(10,6,6), sd=c(1,3,6), Num.Contrast=rbind(c(0,1,0),c(0,0,1)),
           Den.Contrast=rbind(c(1,0,0),c(1,0,0)), Margin=0.8)

# Example 2:
# Degrees of freedom for an all-pair comparison of the groups B, H and S on endpoint ADP,
# assuming unequal standard deviations for the groups. This is an extension for the well-
# known Tukey-test to te case of heteroscedasticity and in terms of ratios of means
# instead of differences.

data(coagulation)

DfSattRat(n=tapply(X=coagulation$ADP, INDEX=coagulation$Group, FUN=length),
  sd=tapply(X=coagulation$ADP, INDEX=coagulation$Group, FUN=sd),
  type="Tukey")

# These are the same degrees of freedom as used automatically by command
# \code{SimTestRat()}:
test <- SimTestRat(data=coagulation, grp="Group", resp="ADP", type="Tukey",
  covar.equal=FALSE)
test$degr.fr
```

ermvnorm *Multivariate Normal Random Numbers with Exact Parameters*

Description

Random numbers of the multivariate normal distribution with EXACT mean vector, EXACT variance vector and approximate correlation matrix. This function is based on the function rmvnorm of the package mvtnorm.

Usage

```
ermvnorm(n, mean, sd, corr = diag(rep(1, length(mean))), mnt = 10000)
```

Arguments

n	a number of observations
mean	a mean vector
sd	a vector of standard deviations
corr	a correlation matrix
mnt	a maximum number of tries for the computation

Details

Unfortunately, it's very common to present only summary statistics in the literature when evaluating real data. This makes it hard to retrace or to verify the related statistical evaluation. Also, the use of such data as an example for other statistical tests is hardly possible. For that reason, ermvnorm allows to reproduce data by simulation. In contrast to rmvnorm of the package mvtnorm, the function ermvnorm produces random numbers which have EXACTLY the same paramer values as specified by mean and sd. The correlation matrix corr is met only approximately.

The simple idea behind ermvnorm is to apply rmvnorm of the package mvtnorm, but only for the first n-2 random numbers. The remaining 2 numbers are obtained by solving a quadratic equation to achieve the specified values for the mean vector and for the vector of standard deviations. Depending on the n-2 random numbers, the underlying quadratic equation can possibly have no solution. In this case, ermvnorm creates a new set of n-2 random numbers until a valid data set is obtained, or until the maximum number of tries mnt is reached.

Value

A matrix of random numbers with dimension n * length(mean).

Note

This function is to be used only with caution. Normally, random numbers with exact mean and standard deviation are not intended to be used. For example, simulations concerning type I error or power of statistical tests cannot be based on ermvnorm.

Author(s)

Gemechis Djira Dilba and Mario Hasler

References

Hothorn, T. et al. (2001): On Multivariate *t* and Gauss Probabilities in R. *R News* 1, 27–29.

See Also

rmvnorm, rcm

Examples

```
# Example 1:
# A dataset representing one endpoint.

set.seed(1234)
dataset1 <- ermvnorm(n=10,mean=100,sd=10)
dataset1
mean(dataset1)
sd(dataset1)

# Example 2:
# A dataset representing two correlated endpoints.

set.seed(5678)
dataset2 <- ermvnorm(n=10,mean=c(10,120),sd=c(1,10),corr=rbind(c(1,0.7),c(0.7,1)))
dataset2
mean(dataset2[,1]); mean(dataset2[,2])
sd(dataset2[,1]); sd(dataset2[,2])
round(cor(dataset2),3)
pairs(dataset2)

# Example 3:
# A dataset representing three uncorrelated endpoints.

set.seed(9101)
dataset3 <- ermvnorm(n=20,mean=c(1,12,150),sd=c(0.5,2,20))
dataset3
mean(dataset3[,1]); mean(dataset3[,2]); mean(dataset3[,3])
sd(dataset3[,1]); sd(dataset3[,2]); sd(dataset3[,3])
pairs(dataset3)

# Example 4:
# A dataset representing four randomly correlated endpoints.

set.seed(1121)
dataset4 <- ermvnorm(n=10,mean=c(2,10,50,120),sd=c(1,4,8,10),corr=rcm(ncol=4))
dataset4
mean(dataset4[,1]); mean(dataset4[,2]); mean(dataset4[,3]); mean(dataset4[,4])
sd(dataset4[,1]); sd(dataset4[,2]); sd(dataset4[,3]); sd(dataset4[,4])
round(cor(dataset4),3)
```

```
pairs(dataset4)
```

`plot.SimCi` *Plot function for SimCi-objects*

Description

A plot of the results of `SimCiDiff` and `SimCiRat`, respectively.

Usage

```
## S3 method for class 'SimCi'
plot(x, xlim, xlab, ylim, ...)
```

Arguments

`x`	an object of class "SimCi" as obtained by calling `SimCiDiff` or `SimCiRat`
`xlim`	a numeric vector of length 2, giving the x coordinate range
`xlab`	a title for the x axis
`ylim`	a numeric vector of length 2, giving the y coordinate range
`...`	arguments to be passed to `plot`

Value

A plot of the confidence intervals of a "SimCi" object.

Author(s)

Christof Kluss and Mario Hasler

See Also

`SimCiDiff`, `SimCiRat`

Examples

```
# Example 1:
# Simultaneous confidence intervals related to a comparison of the groups
# B and H against the standard S, on endpoint Thromb.count, assuming unequal
# variances for the groups. This is an extension of the well-known Dunnett-
# intervals to the case of heteroscedasticity.

data(coagulation)

interv1 <- SimCiDiff(data=coagulation, grp="Group", resp="Thromb.count",
  type="Dunnett", base=3, alternative="greater", covar.equal=FALSE)
interv1
plot(interv1)
```

```
# Example 2:
# Simultaneous confidence intervals related to a comparisons of the groups
# B and H against the standard S, simultaneously on all endpoints, assuming
# unequal covariance matrices for the groups. This is an extension of the well-
# known Dunnett-intervals to the case of heteroscedasticity and multiple
# endpoints.

data(coagulation)

interv2 <- SimCiDiff(data=coagulation, grp="Group", resp=c("Thromb.count","ADP","TRAP"),
  type="Dunnett", base=3, alternative="greater", covar.equal=FALSE)
summary(interv2)
par(mfrow=c(1,3)); plot(interv2)

# Example 3:
# Simultaneous confidence intervals for ratios of means, related to an all-pair
# comparison of the groups B, H and S, simultaneously on all endpoints, assuming unequal
# covariance matrices for the groups. This is an extension of the well-known Tukey-
# intervals to the case of heteroscedasticity and multiple endpoints, and in terms of
# ratios of means instead of differences.

data(coagulation)

interv3 <- SimCiRat(data=coagulation, grp="Group", resp=c("Thromb.count","ADP","TRAP"),
  type="Tukey", alternative="two.sided", covar.equal=FALSE)
summary(interv3)
par(mfrow=c(3,1)); plot(interv3)
```

`print.SimCi` *Print function for SimCi-objects*

Description

A short print out of the results of `SimCiDiff` and `SimCiRat`, respectively.

Usage

```
## S3 method for class 'SimCi'
print(x, digits = 4, ...)
```

Arguments

`x`	an object of class "SimCi" as obtained by calling `SimCiDiff` or `SimCiRat`
`digits`	digits for rounding the results
`...`	arguments to be passed to `print`

Value

A print out containing the estimates, raw and simultaneous confidence intervals computed by `SimCiDiff` or `SimCiRat`, respectively.

Author(s)

Mario Hasler

See Also

`print.SimTest`

`print.SimTest` *Print function for SimTest-objects*

Description

A short print out of the results of `SimTestDiff` and `SimTestRat`, respectively.

Usage

```
## S3 method for class 'SimTest'
print(x, digits = 4, ...)
```

Arguments

`x`	an object of class "SimTest" as obtained by calling `SimTestDiff` or `SimTestRat`
`digits`	digits for rounding the results
`...`	arguments to be passed to `print`

Value

A print out containing the margins, estimates, test statistics, raw and adjusted *p*-values computed by `SimTestDiff` or `SimTestRat`, respectively.

Author(s)

Mario Hasler

See Also

`print.SimCi`

rcm *Random Correlation Matrices*

Description

Correlation matrices with random off-diagonal elements.

Usage

```
rcm(nrow = NULL, ncol = NULL)
```

Arguments

nrow	the desired number of rows
ncol	the desired number of columns

Details

As a correlation matrix is symmetric, only one of nrow or ncol must be specified.

Value

A symmetric correlation matrix with random elements.

Author(s)

Kornelius Rohmeyer and Mario Hasler

References

Holmes, R.B. (1991): On random correlation matrices. *Siam Journal on Matrix Analysis and Applications* 12, 239–272.

See Also

ermvnorm

Examples

```
# Example 1:
# A correlation matrix representing three randomly correlated endpoints.

set.seed(1234)
rcm(nrow=3)

# Example 2:
# A correlation matrix representing five randomly correlated endpoints.

set.seed(5678)
rcm(ncol=5)
```

SimCiDiff *Simultaneous Confidence Intervals for Differences of Means of Multiple Endpoints*

Description

Simultaneous confidence intervals for general contrasts (linear functions) of normal means (e.g., "Dunnett", "Tukey", "Williams" ect.) when there is more than one primary response variable (endpoint). The procedure of Hasler and Hothorn (2011) is applied for differences of means of normally distributed data. The covariance matrices (containing the covariances between the endpoints) may be assumed to be equal or possibly unequal for the different groups (Hasler, 2014). For the case of only a single endpoint and unequal covariance matrices (variances), the procedure coincides with the PI procedure of Hasler and Hothorn (2008).

Usage

```
SimCiDiff(data, grp, resp = NULL, type = "Dunnett", base = 1, ContrastMat = NULL,
          alternative = "two.sided", covar.equal = FALSE, conf.level = 0.95)
```

Arguments

data	a data frame containing a grouping variable and the endpoints as columns
grp	a character string with the name of the grouping variable
resp	a vector of character strings with the names of the endpoints; if resp=NULL (default), all column names of the data frame without the grouping variable are chosen automatically
type	a character string, defining the type of contrast, with the following options: • "Dunnett": many-to-one comparisons • "Tukey": all-pair comparisons • "Sequen": comparisons of consecutive groups • "AVE": comparison of each group with average of all others • "GrandMean": comparison of each group with grand mean of all groups • "Changepoint": differences of averages of groups of higher order to averages of groups of lower order • "Marcus": Marcus contrasts • "McDermott": McDermott contrasts • "Williams": Williams trend tests • "UmbrellaWilliams": Umbrella-protected Williams trend tests note that type is ignored if ContrastMat is specified by the user (see below)
base	a single integer specifying the control group for Dunnett contrasts, ignored otherwise
ContrastMat	a contrast matrix, where columns correspond to groups and rows correspond to contrasts

alternative	a character string specifying the alternative hypothesis, must be one of "two.sided" (default), "greater" or "less"
covar.equal	a logical variable indicating whether to treat the covariance matrices (containing the covariances between the endpoints) for the different groups as being equal; if TRUE then the pooled covariance matrix is used, otherwise the Satterthwaite approximation to the degrees of freedom is used according to Hasler and Hothorn (2008)
conf.level	a numeric value defining the simultaneous confidence level

Details

The interest is in simultaneous confidence intervals for several linear combinations (contrasts) of treatment means in a one-way ANOVA model, and simultaneously for multiple endpoints. For example, corresponding intervals for the all-pair comparison of Tukey (1953) and the many-to-one comparison of Dunnett (1955) are implemented, but allowing for multiple endpoints. Also, the user is free to create other interesting problem-specific contrasts. An approximate multivariate *t*-distribution is used to calculate lower and upper limits (see Hasler and Hothorn, 2011). Simultaneous tests based on these intervals control the familywise error rate in an admissible range and in the strong sense. The covariance matrices of the treatment groups (containing the covariances between the endpoints) can be assumed to be equal (covar.equal=TRUE) or unequal (covar.equal=FALSE). If being equal, the pooled covariance matrix is used, otherwise approximations to the degrees of freedom (Satterthwaite, 1946) are used (see Hasler, 2014). Unequal covariance matrices occure if variances or correlations of some endpoints differ depending on the treatment groups.

Value

An object of class SimCi containing:

estimate	a matrix of estimated differences
lower.raw	a matrix of raw (unadjusted) lower limits
upper.raw	a matrix of raw (unadjusted) upper limits
lower	a matrix of lower limits adjusted for multiplicity
upper	a matrix of upper limits adjusted for multiplicity
CorrMatDat	either the estimated common correlation matrix of the data (covar.equal=TRUE) or the list of the different (one for each treatment) estimated correlation matrices of the data (covar.equal=FALSE)
CorrMatComp	the estimated correlation matrix to be used for the multivariate *t*-distribution
degr.fr	either a single degree of freedom (covar.equal=TRUE) or a vector of degrees of freedom (covar.equal=FALSE) related to the comparisons

Note

All measurement objects of each treatment group must have values for each endpoint. If there are missing values then the procedure stops. If covar.equal=TRUE, then the number of endpoints must not be greater than the total sample size minus the number of treatment groups. If covar.equal=FALSE, the number of endpoints must not be greater than the minimal sample size minus 1. Otherwise the procedure stops.

All intervals have the same direction for all comparisons and endpoints (`alternative="..."`). In case of doubt, use `"two.sided"`.

Author(s)

Mario Hasler

References

Hasler, M. (2014): Multiple contrast tests for multiple endpoints in the presence of heteroscedasticity. *The International Journal of Biostatistics* 10, 17–28.

Hasler, M. and Hothorn, L.A. (2011): A Dunnett-type procedure for multiple endpoints. *The International Journal of Biostatistics* 7, Article 3.

Hasler, M. and Hothorn, L.A. (2008): Multiple contrast tests in the presence of heteroscedasticity. *Biometrical Journal* 50, 793–800.

Satterthwaite, F.E. (1946): An approximate distribution of estimates of variance components. *Biometrics* 2, 110–114.

See Also

SimCiRat, SimTestDiff, SimTestRat

Examples

```
# Example 1:
# Simultaneous confidence intervals related to a comparison of the groups
# B and H against the standard S, on endpoint Thromb.count, assuming unequal
# variances for the groups. This is an extension of the well-known Dunnett-
# intervals to the case of heteroscedasticity.

data(coagulation)

interv1 <- SimCiDiff(data=coagulation, grp="Group", resp="Thromb.count",
  type="Dunnett", base=3, alternative="greater", covar.equal=FALSE)
interv1

# Example 2:
# Simultaneous confidence intervals related to a comparisons of the groups
# B and H against the standard S, simultaneously on all endpoints, assuming
# unequal covariance matrices for the groups. This is an extension of the well-
# known Dunnett-intervals to the case of heteroscedasticity and multiple
# endpoints.

data(coagulation)

interv2 <- SimCiDiff(data=coagulation, grp="Group", resp=c("Thromb.count","ADP","TRAP"),
  type="Dunnett", base=3, alternative="greater", covar.equal=FALSE)
summary(interv2)
```

SimCiRat *Simultaneous Confidence Intervals for Ratios of Means of Multiple Endpoints*

Description

Simultaneous confidence intervals for ratios of contrasts (linear functions) of normal means (e.g., "Dunnett", "Tukey", "Williams" ect.) when there is more than one primary response variable (endpoint). The procedure of Hasler and Hothorn (2012) is applied for ratios of means of normally distributed data. The covariance matrices (containing the covariances between the endpoints) may be assumed to be equal or possibly unequal for the different groups (Hasler, 2014). For the case of only a single endpoint and unequal covariance matrices (variances), the procedure coincides with the PI procedure of Hasler and Hothorn (2008).

Usage

```
SimCiRat(data, grp, resp = NULL, type = "Dunnett", base = 1, Num.Contrast = NULL,
         Den.Contrast = NULL, alternative = "two.sided", covar.equal = FALSE,
         conf.level = 0.95)
```

Arguments

`data`	a data frame containing a grouping variable and the endpoints as columns
`grp`	a character string with the name of the grouping variable
`resp`	a vector of character strings with the names of the endpoints; if `resp=NULL` (default), all column names of the data frame without the grouping variable are chosen automatically
`type`	a character string, defining the type of contrast, with the following options: • "Dunnett": many-to-one comparisons, with control in the denominator • "Tukey": all-pair comparisons • "Sequen": comparisons of consecutive groups, where the group with lower order is the denomniator • "AVE": comparison of each group with average of all others, where the average is taken as denominator • "GrandMean": comparison of each group with grand mean of all groups, where the grand mean is taken as denominator • "Changepoint": ratios of averages of groups of higher order divided by averages of groups of lower order • "Marcus": Marcus contrasts as ratios • "McDermott": McDermott contrasts as ratios • "Williams": Williams contrasts as ratios • "UmbrellaWilliams": Umbrella-protected Williams contrasts as ratios note that `type` is ignored if `Num.Contrast` and `Den.Contrast` are specified by the user (see below)

base	a single integer specifying the control (i.e. denominator) group for Dunnett contrasts, ignored otherwise
Num.Contrast	a numerator contrast matrix, where columns correspond to groups and rows correspond to contrasts
Den.Contrast	a denominator contrast matrix, where columns correspond to groups and rows correspond to contrasts
alternative	a character string specifying the alternative hypothesis, must be one of "two.sided" (default), "greater" or "less"
covar.equal	a logical variable indicating whether to treat the covariance matrices (containing the covariances between the endpoints) for the different groups as being equal; if TRUE then the pooled covariance matrix is used, otherwise the Satterthwaite approximation to the degrees of freedom is used according to Hasler and Hothorn (2008)
conf.level	a numeric value defining the simultaneous confidence level

Details

The interest is in simultaneous confidence intervals for several ratios of linear combinations (contrasts) of treatment means in a one-way ANOVA model, and simultaneously for multiple endpoints. For example, corresponding intervals for the all-pair comparison of Tukey (1953) and the many-to-one comparison of Dunnett (1955) for ratios of means are implemented, but allowing for multiple endpoints. Also, the user is free to create other interesting problem-specific contrasts. An approximate multivariate *t*-distribution is used to calculate lower and upper limits (see Hasler and Hothorn, 2012). Simultaneous tests based on these intervals control the familywise error rate in an admissible range and in the strong sense. The covariance matrices of the treatment groups (containing the covariances between the endpoints) can be assumed to be equal (covar.equal=TRUE) or unequal (covar.equal=FALSE). If being equal, the pooled covariance matrix is used, otherwise approximations to the degrees of freedom (Satterthwaite, 1946) are used (see Hasler, 2014). Unequal covariance matrices occure if variances or correlations of some endpoints differ depending on the treatment groups.

Value

An object of class SimCi containing:

estimate	a matrix of estimated differences
lower.raw	a matrix of raw (unadjusted) lower limits
upper.raw	a matrix of raw (unadjusted) upper limits
lower	a matrix of lower limits adjusted for multiplicity
upper	a matrix of upper limits adjusted for multiplicity
CorrMatDat	either the estimated common correlation matrix of the data (covar.equal=TRUE) or the list of the different (one for each treatment) estimated correlation matrices of the data (covar.equal=FALSE)
CorrMatComp	the estimated correlation matrix to be used for the multivariate *t*-distribution
degr.fr	either a single degree of freedom (covar.equal=TRUE) or a vector of degrees of freedom (covar.equal=FALSE) related to the comparisons

Note

All measurement objects of each treatment group must have values for each endpoint. If there are missing values then the procedure stops. If `covar.equal=TRUE`, then the number of endpoints must not be greater than the total sample size minus the number of treatment groups. If `covar.equal=FALSE`, the number of endpoints must not be greater than the minimal sample size minus 1. Otherwise the procedure stops.

All intervals have the same direction for all comparisons and endpoints (`alternative="..."`). In case of doubt, use `"two.sided"`.

In contrast to simultaneous confidence intervals for differences, the correlation matrix for the multivariate *t*-distribution depends on the unknown ratios. The same problem also arises for the degrees of freedom if the covariance matrices for the different groups are assumed to be unequal (`covar.equal=FALSE`). Both problems are handled by a plug-in approach, see the references therefore.

Author(s)

Mario Hasler

References

Hasler, M. (2014): Multiple contrast tests for multiple endpoints in the presence of heteroscedasticity. *The International Journal of Biostatistics* 10, 17–28.

Hasler, M. and Hothorn, L.A. (2012): A multivariate Williams-type trend procedure. *Statistics in Biopharmaceutical Research* 4, 57–65.

Hasler, M. and Hothorn, L.A. (2008): Multiple contrast tests in the presence of heteroscedasticity. *Biometrical Journal* 50, 793–800.

Dilba, G. et al. (2006): Simultaneous confidence sets and confidence intervals for multiple ratios. *Journal of Statistical Planning and Inference* 136, 2640–2658.

Satterthwaite, F.E. (1946): An approximate distribution of estimates of variance components. *Biometrics* 2, 110–114.

See Also

`SimCiDiff`, `SimTestRat`, `SimTestDiff`

Examples

```
# Example 1:
# Simultaneous confidence intervals for ratios of means, related to a
# comparison of the groups B and H against the standard S, on endpoint
# Thromb.count, assuming unequal variances for the groups. This is an extension
# of the well-known Dunnett-intervals to the case of heteroscedasticity and in
# terms of ratios of means instead of differences.

data(coagulation)

interv1 <- SimCiRat(data=coagulation, grp="Group", resp="Thromb.count",
  type="Dunnett", base=3, alternative="greater", covar.equal=FALSE)
```

```
interv1

# Example 2:
# Simultaneous confidence intervals for ratios of means, related to a
# comparison of the groups B and H against the standard S, simultaneously on
# all endpoints, assuming unequal covariance matrices for the groups. This is an
# extension of the well-known Dunnett-intervals to the case of heteroscedasticity
# and multiple endpoints, and in terms of ratios of means instead of differences.

data(coagulation)

interv2 <- SimCiRat(data=coagulation, grp="Group", resp=c("Thromb.count","ADP","TRAP"),
  type="Dunnett", base=3, alternative="greater", covar.equal=FALSE)
summary(interv2)
```

`SimTestDiff` *Simultaneous Tests for Differences of Means of Multiple Endpoints*

Description

Simultaneous tests for general contrasts (linear functions) of normal means (e.g., "Dunnett", "Tukey", "Williams" ect.) when there is more than one primary response variable (endpoint). The procedure of Hasler and Hothorn (2011) is applied for differences of means of normally distributed data. The covariance matrices (containing the covariances between the endpoints) may be assumed to be equal or possibly unequal for the different groups (Hasler, 2014). For the case of only a single endpoint and unequal covariance matrices (variances), the procedure coincides with the PI procedure of Hasler and Hothorn (2008).

Usage

```
SimTestDiff(data, grp, resp = NULL, type = "Dunnett", base = 1, ContrastMat = NULL,
            alternative = "two.sided", Margin = NULL, covar.equal = FALSE)
```

Arguments

`data`	a data frame containing a grouping variable and the endpoints as columns
`grp`	a character string with the name of the grouping variable
`resp`	a vector of character strings with the names of the endpoints; if `resp=NULL` (default), all column names of the data frame without the grouping variable are chosen automatically
`type`	a character string, defining the type of contrast, with the following options: • "Dunnett": many-to-one comparisons • "Tukey": all-pair comparisons • "Sequen": comparisons of consecutive groups • "AVE": comparison of each group with average of all others • "GrandMean": comparison of each group with grand mean of all groups

- "Changepoint": differences of averages of groups of higher order to averages of groups of lower order
- "Marcus": Marcus contrasts
- "McDermott": McDermott contrasts
- "Williams": Williams trend tests
- "UmbrellaWilliams": Umbrella-protected Williams trend tests

note that `type` is ignored if `ContrastMat` is specified by the user (see below)

`base` a single integer specifying the control group for Dunnett contrasts, ignored otherwise

`ContrastMat` a contrast matrix, where columns correspond to groups and rows correspond to contrasts

`alternative` a character string specifying the alternative hypothesis, must be one of `"two.sided"` (default), `"greater"` or `"less"`

`Margin` a single numeric value, or a numeric vector corresponding to endpoints, or a matrix where columns correspond to endpoints and rows correspond to contrasts, default is 0

`covar.equal` a logical variable indicating whether to treat the covariance matrices (containing the covariances between the endpoints) for the different groups as being equal; if `TRUE` then the pooled covariance matrix is used, otherwise the Satterthwaite approximation to the degrees of freedom is used according to Hasler and Hothorn (2008)

Details

The interest is in simultaneous tests for several linear combinations (contrasts) of treatment means in a one-way ANOVA model, and simultaneously for multiple endpoints. For example, the all-pair comparison of Tukey (1953) and the many-to-one comparison of Dunnett (1955) are implemented, but allowing for multiple endpoints. Also, the user is free to create other interesting problem-specific contrasts. An approximate multivariate *t*-distribution is used to calculate (adjusted) *p*-values (see Hasler and Hothorn, 2011). This approach controls the familywise error rate in an admissible range and in the strong sense. The covariance matrices of the treatment groups (containing the covariances between the endpoints) can be assumed to be equal (`covar.equal=TRUE`) or unequal (`covar.equal=FALSE`). If being equal, the pooled covariance matrix is used, otherwise approximations to the degrees of freedom (Satterthwaite, 1946) are used (see Hasler, 2014). Unequal covariance matrices occure if variances or correlations of some endpoints differ depending on the treatment groups.

Value

An object of class SimTest containing:

`estimate` a matrix of estimated differences

`statistic` a matrix of the calculated test statistics

`p.val.raw` a matrix of raw *p*-values

`p.val.adj` a matrix of *p*-values adjusted for multiplicity

CorrMatDat	either the estimated common correlation matrix of the data (covar.equal=TRUE) or the list of the different (one for each treatment) estimated correlation matrices of the data (covar.equal=FALSE)
CorrMatComp	the estimated correlation matrix to be used for the multivariate *t*-distribution
degr.fr	either a single degree of freedom (covar.equal=TRUE) or a vector of degrees of freedom (covar.equal=FALSE) related to the comparisons

Note

All measurement objects of each treatment group must have values for each endpoint. If there are missing values then the procedure stops. If covar.equal=TRUE, then the number of endpoints must not be greater than the total sample size minus the number of treatment groups. If covar.equal=FALSE, the number of endpoints must not be greater than the minimal sample size minus 1. Otherwise the procedure stops.

All hypotheses are tested with the same test direction for all comparisons and endpoints (alternative="..."). In case of doubt, use "two.sided".

If Margin is a single numeric value or a numeric vector, then the same value(s) are used for the remaining comparisons or endpoints. If Margin is not specified, the default is 0.

Author(s)

Mario Hasler

References

Hasler, M. (2014): Multiple contrast tests for multiple endpoints in the presence of heteroscedasticity. *The International Journal of Biostatistics* 10, 17–28.

Hasler, M. and Hothorn, L.A. (2011): A Dunnett-type procedure for multiple endpoints. *The International Journal of Biostatistics* 7, Article 3.

Hasler, M. and Hothorn, L.A. (2008): Multiple contrast tests in the presence of heteroscedasticity. *Biometrical Journal* 50, 793–800.

Satterthwaite, F.E. (1946): An approximate distribution of estimates of variance components. *Biometrics* 2, 110–114.

See Also

SimTestRat, SimCiDiff, SimCiRat

Examples

```
# Example 1:
# A comparison of the groups B and H against the standard S, on endpoint
# Thromb.count, assuming unequal variances for the groups. This is an
# extension of the well-known Dunnett-test to the case of heteroscedasticity.

data(coagulation)

comp1 <- SimTestDiff(data=coagulation, grp="Group", resp="Thromb.count",
```

```
  type="Dunnett", base=3, alternative="greater", covar.equal=FALSE)
comp1

# Example 2:
# A comparison of the groups B and H against the standard S, simultaneously
# on all endpoints, assuming unequal covariance matrices for the groups. This is
# an extension of the well-known Dunnett-test to the case of heteroscedasticity
# and for multiple endpoints.

data(coagulation)

comp2 <- SimTestDiff(data=coagulation, grp="Group", resp=c("Thromb.count","ADP","TRAP"),
  type="Dunnett", base=3, alternative="greater", covar.equal=FALSE)
summary(comp2)
```

SimTestRat *Simultaneous Tests for Ratios of Means of Multiple Endpoints*

Description

Simultaneous tests for ratios of contrasts (linear functions) of normal means (e.g., "Dunnett", "Tukey", "Williams" ect.) when there is more than one primary response variable (endpoint). The procedure of Hasler and Hothorn (2012) is applied for ratios of means of normally distributed data. The covariance matrices (containing the covariances between the endpoints) may be assumed to be equal or possibly unequal for the different groups (Hasler, 2014). For the case of only a single endpoint and unequal covariance matrices (variances), the procedure coincides with the PI procedure of Hasler and Hothorn (2008).

Usage

```
SimTestRat(data, grp, resp = NULL, type = "Dunnett", base = 1, Num.Contrast = NULL,
           Den.Contrast = NULL, alternative = "two.sided", Margin = NULL,
           covar.equal = FALSE)
```

Arguments

data	a data frame containing a grouping variable and the endpoints as columns
grp	a character string with the name of the grouping variable
resp	a vector of character strings with the names of the endpoints; if resp=NULL (default), all column names of the data frame without the grouping variable are chosen automatically
type	a character string, defining the type of contrast, with the following options: • "Dunnett": many-to-one comparisons, with control in the denominator • "Tukey": all-pair comparisons • "Sequen": comparisons of consecutive groups, where the group with lower order is the denomniator

- "AVE": comparison of each group with average of all others, where the average is taken as denominator
- "GrandMean": comparison of each group with grand mean of all groups, where the grand mean is taken as denominator
- "Changepoint": ratios of averages of groups of higher order divided by averages of groups of lower order
- "Marcus": Marcus contrasts as ratios
- "McDermott": McDermott contrasts as ratios
- "Williams": Williams contrasts as ratios
- "UmbrellaWilliams": Umbrella-protected Williams contrasts as ratios

note that `type` is ignored if `Num.Contrast` and `Den.Contrast` are specified by the user (see below)

`base` a single integer specifying the control (i.e. denominator) group for Dunnett contrasts, ignored otherwise

`Num.Contrast` a numerator contrast matrix, where columns correspond to groups and rows correspond to contrasts

`Den.Contrast` a denominator contrast matrix, where columns correspond to groups and rows correspond to contrasts

`alternative` a character string specifying the alternative hypothesis, must be one of `"two.sided"` (default), `"greater"` or `"less"`

`Margin` a single numeric value, or a numeric vector corresponding to endpoints, or a matrix where columns correspond to endpoints and rows correspond to contrasts, default is 1

`covar.equal` a logical variable indicating whether to treat the covariance matrices (containing the covariances between the endpoints) for the different groups as being equal; if `TRUE` then the pooled covariance matrix is used, otherwise the Satterthwaite approximation to the degrees of freedom is used according to Hasler and Hothorn (2008)

Details

The interest is in simultaneous tests for several ratios of linear combinations (contrasts) of treatment means in a one-way ANOVA model, and simultaneously for multiple endpoints. For example, the all-pair comparison of Tukey (1953) and the many-to-one comparison of Dunnett (1955) for ratios of means are implemented, but allowing for multiple endpoints. Also, the user is free to create other interesting problem-specific contrasts. An approximate multivariate t-distribution is used to calculate (adjusted) p-values (see Hasler and Hothorn, 2012). This approach controls the familywise error rate in an admissible range and in the strong sense. The covariance matrices of the treatment groups (containing the covariances between the endpoints) can be assumed to be equal (`covar.equal=TRUE`) or unequal (`covar.equal=FALSE`). If being equal, the pooled covariance matrix is used, otherwise approximations to the degrees of freedom (Satterthwaite, 1946) are used (see Hasler, 2014). Unequal covariance matrices occure if variances or correlations of some endpoints differ depending on the treatment groups.

Value

An object of class SimTest containing:

`estimate`	a matrix of estimated ratios
`statistic`	a matrix of the calculated test statistics
`p.val.raw`	a matrix of raw *p*-values
`p.val.adj`	a matrix of *p*-values adjusted for multiplicity
`CorrMatDat`	either the estimated common correlation matrix of the data (`covar.equal=TRUE`) or the list of the different (one for each treatment) estimated correlation matrices of the data (`covar.equal=FALSE`)
`CorrMatComp`	the estimated correlation matrix to be used for the multivariate *t*-distribution
`degr.fr`	either a single degree of freedom (`covar.equal=TRUE`) or a vector of degrees of freedom (`covar.equal=FALSE`) related to the comparisons

Note

All measurement objects of each treatment group must have values for each endpoint. If there are missing values then the procedure stops. If `covar.equal=TRUE`, then the number of endpoints must not be greater than the total sample size minus the number of treatment groups. If `covar.equal=FALSE`, the number of endpoints must not be greater than the minimal sample size minus 1. Otherwise the procedure stops.

All hypotheses are tested with the same test direction for all comparisons and endpoints (`alternative="..."`). In case of doubt, use `"two.sided"`.

If `Margin` is a single numeric value or a numeric vector, then the same value(s) are used for the remaining comparisons or endpoints. If `Margin` is not specified, the default is 1.

Author(s)

Mario Hasler

References

Hasler, M. (2014): Multiple contrast tests for multiple endpoints in the presence of heteroscedasticity. *The International Journal of Biostatistics* 10, 17–28.

Hasler, M. and Hothorn, L.A. (2012): A multivariate Williams-type trend procedure. *Statistics in Biopharmaceutical Research* 4, 57–65.

Hasler, M. and Hothorn, L.A. (2008): Multiple contrast tests in the presence of heteroscedasticity. *Biometrical Journal* 50, 793–800.

Dilba, G. et al. (2006): Simultaneous confidence sets and confidence intervals for multiple ratios. *Journal of Statistical Planning and Inference* 136, 2640–2658.

Satterthwaite, F.E. (1946): An approximate distribution of estimates of variance components. *Biometrics* 2, 110–114.

See Also

`SimTestDiff`, `SimCiRat`, `SimCiDiff`

Examples

```
# Example 1:
# A comparison of the groups B and H against the standard S, on endpoint
# Thromb.count, assuming unequal variances for the groups, and for ratios of
# means. This is an extension of the well-known Dunnett-test to the case of
# heteroscedasticity and in terms of ratios of means instead of differences.

data(coagulation)

comp1 <- SimTestRat(data=coagulation, grp="Group", resp="Thromb.count",
  type="Dunnett", base=3, alternative="greater", covar.equal=FALSE)
comp1

# Example 2:
# A comparison of the groups B and H against the standard S, simultaneously on
# all endpoints, assuming unequal covariance matrices for the groups, and for
# ratios of means. This is an extension of the well-known Dunnett-test to the case
# of heteroscedasticity and multiple endpoints, and in terms of ratios of means
# instead of differences.

data(coagulation)

comp2 <- SimTestRat(data=coagulation, grp="Group", resp=c("Thromb.count","ADP","TRAP"),
  type="Dunnett", base=3, alternative="greater", covar.equal=FALSE)
summary(comp2)
```

`summary.SimCi` *Summary function for SimCi-objects*

Description

A detailed print out of the results of `SimCiDiff` and `SimCiRat`, respectively.

Usage

```
## S3 method for class 'SimCi'
summary(object, digits = 4, ...)
```

Arguments

`object`	an object of class "SimCi" as obtained by calling `SimCiDiff` or `SimCiRat`
`digits`	digits for rounding the results
`...`	arguments to be passed to `print`

Value

A print out containing the estimates, raw and simultaneous confidence intervals, estimated covariance and correlation matrices of the data and of the comparisons computed by `SimCiDiff` or `SimCiRat`, respectively.

Author(s)

Mario Hasler

See Also

summary.SimTest

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summary.SimTest *Summary function for SimTest-objects*

Description

A detailed print out of the results of SimTestDiff and SimTestRat, respectively.

Usage

```
## S3 method for class 'SimTest'
summary(object, digits = 4, ...)
```

Arguments

object	an object of class "SimTest" as obtained by calling SimTestDiff or SimTestRat
digits	digits for rounding the results
...	arguments to be passed to print

Value

A print out containing the estimates, test statistics, raw and adjusted p-values, estimated covariance correlation matrices of the data and of the comparisons computed by SimTestDiff or SimTestRat, respectively.

Author(s)

Mario Hasler

See Also

summary.SimCi

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