# The mratios Package

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**Type** Package

**Title** Inferences for ratios of coefficients in the general linear model

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**Depends** R (>= 2.2.0), mvtnorm

**Suggests** multcomp

**Description** With this package, it is possible to perform (simultaneous) inferences for ratios of linear combinations of coefficients in the general linear model. In particular, tests and confidence interval estimations for ratios of treatment means in the normal one-way layout and confidence interval estimations like in (multiple) slope ratio and parallel line assays can be carried out. Moreover, it is possible to calculate the sample sizes required in comparisons with a control based on relative margins. For the simple two-sample problem, functions for a t-test for ratio-formatted hypotheses and the corresponding Fieller confidence interval are provided assuming homogeneous or heterogeneous group variances.

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## R topics documented:

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`AP` *Angina pectoris data*

---

## Description

A data set is generated (from normal distribution) to imitate the summary statistics in Table II of Bauer et al. (1998). In the experiment, patients with chronic stable angina pectoris were randomized to five treatment arms (placebo, three doses of a new compound, and an active control). The primary endpoint is the difference in the duration of an exercise test before and after treatment.

## Usage

```
data(AP)
```

## Format

A data frame with 303 observations on the following 2 variables.

**`pre_post`** a numeric vector

**`treatment`** a factor with levels `AC`the active control, `D0` the zero dose (placebo), and `D50` `D100`, `D150` the three dose groups of the new compound.

## Source

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

```
library(mratios)

data(AP)
boxplot(pre_post ~ treatment, data=AP)
by(AP,AP$treatment, function(x){mean(x$pre_post)})
by(AP,AP$treatment, function(x){sd(x$pre_post)})
```

ASAT *ASAT data*

## Description

Data from a toxicity study: ASAT values of the serum of female Wistar rats six months after application

## Usage

```
data(ASAT)
```

## Format

A data frame with 34 observations on the following 2 variables.

**group** a factor with two levels KON TREAT, where KON is the control group consisting of 19 subjects and TREAT is the treatment group consisting of only 15 subjects due to mortality

**ASAT** a numeric vector containing values of the response variable

## Details

The objective is to test that ASAT values of treatment group are not relevantly heightened compared to the control group, where average ASAT value which is more than 25 percent higher than the average of the control group is defined as relevant.

## Source

Hauschke, D. (1999): Biometrische Methoden zur Auswertung und Planung von Sicherheitsstudien. Habilitationsschrift, Fachbereich Statistik, Universtaet Dortmund.

## Examples

```
library(mratios)

data(ASAT)
boxplot(ASAT~group, data=ASAT)
```

## BW *Body weights measured in a toxicological study*

### Description

Body weights of a 90-day chronic toxicological study on rats with a control and three dose groups.

### Usage

```
data(BW)
```

### Format

A data frame with 60 observations on the following 2 variables.

**`Weight`** a numeric vector containing the bodyweights of rats

**`Dose`** a factor with levels `1` `2` `3` `4`, specifying the dose groups, where `1` is the control group

### Source

Hothorn, L.A. (2004): Statistische Auswerteverfahren. In: Regulatorische Toxikologie (Reichl, F.X., ed.). Springer Verlag Heidelberg, pp. 167-181.

### References

### Examples

```
library(mratios)

data(BW)
boxplot(Weight~Dose, data=BW)
```

## Mutagenicity *Mutagenicity assay*

### Description

Mutagenicity assay for 4 doses of a compound (hydroquinone) against a negative (vehicle) control and a positive (active) control (cyclophosphamide). Hydroquinone was applied in doses of 30, 50, 70, 100 mg/kg, positive control was applied with 25mg/kg. Counts of micronuclei in polychromatic erythrocytes after 24h are taken as a measure for the potency to induce chromosome damage. Data of male mice are presented (Hauschke et al., 2005).

### Usage

```
data(Mutagenicity)
```

### Format

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

**`Treatment`** a factor with levels `Cyclo25` `Hydro100` `Hydro30` `Hydro50` `Hydro75` `Vehicle`

**`MN`** a numeric vector, giving the counts of micronuclei after 24h

### Details

### Source

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

### References

Hauschke, D, Slacik-Erben, R, Hansen, S, Kaufmann,R (2005): Biostatistical Assessment of mutagenicity studies by including the positive control. Biometrical Journal 47, 82-87.

### Examples

```
data(Mutagenicity)

boxplot(MN~Treatment, data=Mutagenicity)
```

---

## `Penicillin` *Comparing 6 strains with respect to production of antibiotics*

---

### Description

The production of antibiotics of 6 strains (mutants of the same micro organism) was compared. MO were put to holes in agar infected with Bacteria. The diameter of Baceria-free areas around the colonies of the MO was recorded. Each strain was repeated 8 times.

### Usage

```
data(Penicillin)
```

## Format

A data frame with 48 observations on the following 2 variables.

**strain** a numeric veactor, the number identifying the strains

**diameter** a numeric vector, size of the diameter of Bacteria-free area around each colony

## Source

Horn, M, Vollandt, R (1995): Multiple Tests und Auswahlverfahren in Biomtrie (Lorenz, RJ, Vollmar, J, eds). Gustav Fischerverlag, Stuttgart Jena New York.

## Examples

```
library(mratios)

data(Penicillin)
## str(Penicillin) ; plot(Penicillin) ...
```

---

# SRAssay *Slope ratio assay of panthotenic acid contents in plant tissues*

---

## Description

Content of panthotenic acid in a standard and three unknown samples were measured. The response variable is the titer of a sample to pH 6.8.

## Usage

```
data(SRAssay)
```

## Format

A data frame with 34 observations on the following 3 variables.

**Response** a numeric vector, containing the response variable (titer to pH 6.8)

**Treatment** a factor with levels `St` `U1` `U2` `U3`, specifying the standard and 3 unknown samples

**Dose** a numeric vector

## Details

## Source

Jensen, D.R. (1989): Joint confidence sets in multiple dilution assays. Biometrical Journal 31, 841-853.

## References

Data originally from Bliss, C.I. (1952): The Statistics of Bioassay. Academic Press, New York.

## Examples

```
library(mratios)

data(SRAssay)

plot(Response~Dose, data=SRAssay)

# library(lattice)
# xyplot(Response~Dose|Treatment, data=SRAssay)

# see ?sci.ratio.gen for  the analysis of this dataset
```

---

# angina *The angina data set from 'multcomp' package*

---

## Description

Dose response study of an angina drug; data set taken from Westfall et al. (1999, p. 164).

## Usage

```
data(angina)
```

## Format

A data frame with 50 observations on the following 2 variables.

**dose** a factor with levels `0 1 2 3 4`

**response** a numeric vector giving the change from pretreatment as measured in minutes of pain-free walking.

## Details

See Westfall et al. (1999, p. 164)

## Source

P. H. Westfall, R. D. Tobias, D. Rom, R. D. Wolfinger, Y. Hochberg (1999). Multiple Comparisons and Multiple Tests Using the SAS System. Cary, NC: SAS Institute Inc.

## References

angina(multcomp)

## Examples

```
library(mratios)

data(angina)

plot(response~dose, data=angina)
```

---

`contrMatRatio` *Creates numerator and denominator contrast matrices for ratio-based hypotheses for common multiple comparison and trend test problems*

---

## Description

Creates numerator and denominator contrast matrices for some common multiple comparison and trend test problems. These matrices are internally used by the sci.ratio and simtest.ratio functions. The contrMatRatio function is a modification of the function contrMat (multcomp).

Whether the given definitions of contrast matrices for trend test problems in terms of ratios make sense and how they are to be interpreted is to be discussed.

## Usage

```
contrMatRatio(n, type = "Tukey", base = 1)
```

## Arguments

| | |
|---|---|
| `n` | integer vector of sample sizes |
| `type` | the type of multiple contrasts<br>• **"Dunnett":** many to one comparisons, with the control group in the denominator<br>• **"Tukey":** all-pair comparisons<br>• **"Sequen":** comparison of consecutive groups, where the groups of lower order is the denominator<br>• **"AVE":** comparison of each group with average of all others, where the average is taken as denominator<br>• **"GrandMean":** comparison of each group with grand mean of all groups, where the grand mean is taken as denominator<br>• **"Changepoint":** ratio of averages of groups of higher order divided by averages of groups of lower order<br>• **"Marcus":** Marcus contrasts defined for ratios<br>• **"McDermott":** McDermott contrasts for ratios<br>• **"Williams":** Williams contrasts for ratios<br>• **"UmbrellaWilliams":** Umbrella-protected Williams contrasts for ratios, i.e.a sequence of Williams-type contrasts with groups of higher order stepwise omitted |

| | |
|---|---|
| base | a single integer specifying the control (i.e. denominator) group for "Dunnett"-type contrasts for calculating the ratios to the control |

## Details

This is a simple adaption of the contrMat function in the package multcomp for ratio hypotheses.

## Value

A list containing:

| | |
|---|---|
| numC | the (named) numerator contrast where rows correspond to contrasts |
| denC | the (named) denominator contrast where rows correspond to contrasts |
| rnames | a character vector with names of the contrasts |

and the type of contrast as attr.

## Author(s)

Frank Schaarschmidt and Daniel Gerhard by modifying the code of contrMat(multcomp)

## See Also

contrMat(multcomp)

## Examples

```
library(mratios)

n=c(A=10,B=20,Z=10,D=10)

contrMatRatio(n=n, type="Dunnett", base=1)
contrMatRatio(n=n, type="Dunnett", base=3)

contrMatRatio(n=n, type="Tukey")
contrMatRatio(n=n, type="Sequen")
contrMatRatio(n=n, type="AVE")
contrMatRatio(n=n, type="GrandMean")
contrMatRatio(n=n, type="Williams")
contrMatRatio(n=n, type="UmbrellaWilliams")
```

mratios-package *mratios*

## Description

With this package, it is possible to perform (simultaneous) inferences for ratios of linear combinations of coefficients in the general linear model. In particular, tests and confidence interval estimations for ratios of treatment means in the normal one-way layout and confidence interval estimations like in (multiple) slope ratio and parallel line assays can be carried out. Moreover, it is possible to calculate the sample sizes required in comparisons with a control based on relative margins. For the simple two-sample problem, functions for a t-test for ratio-formatted hypotheses and Fieller confidence intervals are provided assuming homogeneous or heterogeneous group variances.

## Author(s)

Gemechis Dilba, Frank Schaarschmidt

Maintainer: Frank Schaarschmidt <schaarschmidt@biostat.uni-hannover.de>

## References

Dilba, G., Bretz, F., and Guiard, V. (2006): Simultaneous confidence sets and confidence intervals for multiple ratios. Journal of Statistical Planning and Inference 136, 2640-2658.

Dilba, G., Guiard, V., and Bretz, F.: On the efficiency of ratio formatted hypotheses (submitted).

Kieser, M. and Hauschke, D. (2000): Statistical methods for demonstrating equivalence in crossover trials based on the ratio of two location parameters. Drug Information Journal 34, 563-568.

Tamhane, A.C. and Logan, B.R. (2004): Finding the maximum safe dose level for heteroscedastic data. Journal of Biopharmaceutical Statistics 14, 843-856.

## See Also

Multiple comparisons for differences of means: <multcomp>

## Examples

```
library(mratios)

# # # t.test.ratio:
# Two-sample test and confidence interval
# for comparison of means, allowing for heteroscedasticity

data(ASAT)
ASAT
t.test.ratio(ASAT~group, data=ASAT, alternative="less", base=1,
 rho=1.25, var.equal=TRUE)

data(Mutagenicity)
```

```
boxplot(MN~Treatment, data=Mutagenicity)
# It seems to be inappropriate to assume homogeneous variances:

# 1) comparing whether the active control is more effective
# than vehicle control

t.test.ratio(MN~Treatment,
 data=subset(Mutagenicity, Treatment=="Cyclo25"|Treatment=="Vehicle"),
 alternative="greater", rho=1, var.equal=FALSE)

# 2) lowest dose vs. vehicle control

t.test.ratio(MN~Treatment,
 data=subset(Mutagenicity, Treatment=="Hydro30"|Treatment=="Vehicle"),
 alternative="greater", rho=1, var.equal=FALSE)

############################################################

# # # sci.ratio:
# Calculation of simultaneous confidence intervals for ratios
# of linear combinations of treatment means in a one-way ANOVA model

data(BW)
boxplot(Weight~Dose, data=BW)

# Body weights of a 90-day chronic toxicology study on rats
# with a control (1) and three dose groups (2,3,4).

# Calculate upper confidence limits for the ratio of means
# of the three dose groups vs. the control group:
# Which of the doses lead to not more than 90 percent weight loss
# compared to the control group:

m21 <- sci.ratio(Weight~Dose, data=BW, type="Dunnett",
 alternative="greater")

summary(m21)

plot(m21, rho0=0.9)

############################################################

# # # simtest.ratio: Simultaneous tests for ratios of means

data(AP)

boxplot(pre_post~treatment, data=AP)

# Test whether the differences of doses 50, 100, 150 vs. Placebo
# are non-inferior to the difference Active Control vs. Placebo

NC <- rbind(
"(D100-D0)" = c(0,-1,1,0,0),
```

```
"(D150-D0)" = c(0,-1,0,1,0),
 "(D50-D0)" = c(0,-1,0,0,1))

DC <- rbind(
"(AC-D0)" = c(1,-1,0,0,0),
"(AC-D0)" = c(1,-1,0,0,0),
"(AC-D0)" = c(1,-1,0,0,0))

NC
DC

simtest.ratio(pre_post ~ treatment, data=AP,
 Num.Contrast=NC, Den.Contrast=DC, Margin.vec=c(0.9,0.9,0.9))

summary( simtest.ratio(pre_post ~ treatment, data=AP,
 Num.Contrast=NC, Den.Contrast=DC, Margin.vec=c(0.9,0.9,0.9)) )

# Comparisons vs. Control (default type of comparisons):

many21 <- simtest.ratio(pre_post ~ treatment, data=AP,
 type="Dunnett")

summary(many21)


######################################################################

# # # sci.ratio.gen:
# Simultaneous confidence intervals for ratios of coefficients
# in the general linear model:

# Slope-ratio assay, data from Jensen(1989), Biometrical Journal 31,
# 841-853.

data(SRAssay)
SRAssay

# In this problem, the interest is in simultaneous estimation
# of the ratios of slopes relative to the slope of the standard
# treatment.

# First it is needed to carefully define the vector of responses
# and the design matrix of th general linear model:
# The design matrix can be constructed using model.matrix,
# and the vector of the response variable can be extracted
# from the dataframe.

X <- model.matrix(Response~Treatment:Dose, data=SRAssay)
Response <- SRAssay[,"Response"]

# The response vector and the design matrix are:

X
```

```
Response

# The following coefficients result:

lm(Response~0+X)

# where the last four coefficients are the estimated slopes
# of the control treatment and the three new treatments

# Contrasts for the ratios of the slopes of the three new treatments
# vs. the control are then defined as:

Num.Contrast <- matrix(c(0,0,1,0,0,
                         0,0,0,1,0,
                         0,0,0,0,1),nrow=3,byrow=TRUE)
Den.Contrast <- matrix(c(0,1,0,0,0,
                         0,1,0,0,0,
                         0,1,0,0,0),nrow=3,byrow=TRUE)

summary(sci.ratio.gen(Y=Response, X=X,
 Num.Contrast=Num.Contrast, Den.Contrast=Den.Contrast))

#########################################################################

# # # n.ratio: Sample size computations in comparisons with a
#     control based on relative margins.

  #
  #  Example 1: Sample size calculation in tests for non-inferiority
  #  (two-sample case)(Laster and Johnson (2003),
  #  Statistics in Medicine 22:187-200)

     n.ratio(m=1, rho=0.8, Power=0.8, CV0=0.75, rho.star=1,
     alpha=0.05)

  #
  #  Example 2: Sample size calculation in simultaneous tests for
  #  non-inferiority
  #  (Dilba et al. (2006), Statistics in Medicine 25: 1131-1147)

     n.ratio(m=3, rho=0.7, Power=0.8, CV0=0.5, rho.star=0.95,
     alpha=0.05)
```

---

`n.ratio` *Sample size computation in simultaneous tests for ratios of means*

---

## Description

Computes the sample sizes required in simultaneous tests for non-inferiority (or superiority) based on relative margins in multiple comparisons with a control.

## Usage

```
n.ratio(m, rho, Power, CV0, rho.star, alpha, Min.power = TRUE)
```

## Arguments

| | |
|---|---|
| m | number of comparisons with a control group |
| rho | relative non-inferiority (or superiority) margin |
| Power | given power (1-beta) |
| CV0 | coefficient of variation of the control group |
| rho.star | the percentage (of the mean of the control group) to be detected |
| alpha | familywise error rate |
| Min.power | if set to TRUE (by default), the minimal power will be controlled, otherwise complete power |

## Details

The sample sizes are computed at the least favourable configurations, based on the assumption of no prior information regarding the true configuration of the ratios under the alternative hypotheses. The formula is

$n = ((C_1 + C_2)^2)(1 + \rho^2)/((\rho - \rho^*)^2)CV0^2$,

where $C_1$ is the lower $1 - \alpha$ equi-coordinate percentage point of an m-variate normal distribution and $C_2$ is the quantile of univariate (multivariate) normal distribution depending on the type of power controlled. In tests for non-inferiority (or superiority) with large response values indicating better treatment benefit, $\rho < \rho^*$, where $\rho < 1$ for non-inferiority and $\rho > 1$ for superiority testing. Whereas, if small response values indicate better treatment benefit, $\rho^* < \rho$, where $\rho > 1$ for non-inferiority and $\rho < 1$ for superiority testing.

## Author(s)

Gemechis Dilba

## References

Dilba, G., Bretz, F., Hothorn, L.A., and Guiard, V. (2006): Power and sample size computations in simultaneous tests for non-inferiority based on relative margins. Statistics in Medicine 25, 1131-1147.

## Examples

```
#
#  Example 1: Sample size calculation in tests for non-inferiority
#  (two-sample case)(Laster and Johnson (2003),
#  Statistics in Medicine 22:187-200)

   n.ratio(m=1, rho=0.8, Power=0.8, CV0=0.75, rho.star=1,
   alpha=0.05)
```

```
#
#  Example 2: Sample size calculation in simultaneous tests for
#  non-inferiority
#  (Dilba et al. (2006), Statistics in Medicine 25:1131-1147)

   n.ratio(m=3, rho=0.7, Power=0.8, CV0=0.5, rho.star=0.95,
   alpha=0.05)

#
#  Example 3: Controlling complete power
#

   n.ratio(m=5, rho=1.2, Power=0.8, CV0=0.2, rho.star=1.40,
       alpha=0.05, Min.power=FALSE)
```

---

`plot.sci.ratio` *Plot output for sci.ratio and sci.ratio.gen*

---

## Description

Plot the intervals returned by sci.ratio

## Usage

```
## S3 method for class 'sci.ratio':
plot(x, rho0 = 1, rho0lty=2, rho0lwd=1, rho0col="black",
 CIvert = FALSE, CIlty = 1, CIlwd = 1, CIcex = 1,
 main = NULL, ylab = NULL, xlab = NULL, sub = NULL, ...)
```

## Arguments

| | |
|---|---|
| `x` | an object of class "sci.ratio" as can be obtained by calling the function sci.ratio |
| `rho0` | a single numeric value or vector of values defining the hypothesized ratio |
| `rho0lty` | integer values to specify the line type for the rho0 line(s) |
| `rho0lwd` | integer values to specify the line width for the rho0 line(s) |
| `rho0col` | character vector to specify the colour for the rho0 line(s) |
| `CIvert` | logical, CI are plotted horizontal if CIvert=FALSE and vertical otherwise |
| `CIlty` | numeric value, giving the line type of the plotted confidence interval, see argument lty in ?par |
| `CIlwd` | numeric value, giving the line width of the plotted confidence interval, see argument lwd in ?par |
| `CIcex` | a single numeric value: by which amount the symbols in the CI shall be scaled relative to the default (see argument cex in ?par) |
| `main` | character string to be plotted as main title of the plot |

| | |
|---|---|
| ylab | character string, label of the y axis (ignored if CIvert=TRUE) |
| xlab | character string, label of the x axis (ignored if CIvert=FALSE) |
| sub | as in plot |
| ... | further arguments from plot or par, e.g. cex.axis |

## Details

Too long names of the contrasts/comparisons should be avoided, otherwise use par() to change plot parameters.

## Value

A plot of the confidence intervals in the sci.ratio object.

## Author(s)

Frank Schaarschmidt

## References

plot.hmtest(multcomp)

## Examples

```
library(mratios)

data(angina)
aCI<-sci.ratio(response~dose, data=angina, type="Dunnett",
 alternative="greater")

# Visualize testing for superiority

plot(aCI, rho0=1.25, rho0lty=3)
```

---

# print.sci.ratio *Print function for sci.ratio objects*

---

## Description

A short print out of the value of a sci.ratio object.

## Usage

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

### Arguments

| | |
|---|---|
| x | an object of class "sci.ratio" as can be obtained by calling the function sci.ratio |
| digits | digits for rounding the output |
| ... | arguments to be passed to print |

### Value

A print out of the confidence intervals computed by sci.ratio.

### Author(s)

Frank Schaarschmidt

### See Also

plot.sci.ratio, summary.sci.ratio

---

## print.simtest.ratio

*Print out the results of simtest.ratio*

---

### Description

A short print out of the results of simtest.ratio

### Usage

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

### Arguments

| | |
|---|---|
| x | An object of class "simtest.ratio" as obtained by calling simtest.ratio |
| digits | digits for rounding of the results |
| ... | arguments to be passed to print |

### Value

A print out, containing the margins, estimates, teststatistics, and p.values computed by simtest.ratio.

### Author(s)

Frank Schaarschmidt

`rat.weight` *Body weight of rats in a toxicity study*

## Description

Body weights of male rats were compared between a control group and a group which had received a high dose of a chemical in a toxicity study after a period of recovery

## Usage

```
data(rat.weight)
```

## Format

A data frame with 20 observations on the following 2 variables.

**`group`** a factor with two levels `Dosis Kon`, where Dosis is the high dose group, consisiting of ten individulas and Kon is the control group, consisting of ten individuals

**`weight`** a numeric vector containing the values of response variable, final body weight in gramm

## Details

Aim was to test that application of the chemical does not lead to a relevantly lowered or heightened body weight after a time of recovery. 0.8 and 1.25 were defined as relevance boundaries compared to the mean of control group

## Source

Hauschke, D. (1999): Biometrische Methoden zur Auswertung und Planung von Sicherheitsstudien. Habilitationsschrift, Fachbereich Statistik, Universtaet Dortmund.

## Examples

```
library(mratios)

data(rat.weight)
boxplot(weight~group, data=rat.weight)

boxplot(weight~group, data=rat.weight)
```

`sci.ratio` *Simultaneous confidence intervals for ratios of linear combinations of means*

## Description

This function constructs simultaneous confidence intervals for ratios of linear combinations of normal means in a one-way ANOVA model. Different methods are available for multiplicity adjustment.

## Usage

```
sci.ratio(formula, data, type = "Dunnett", base = 1,
 method = "Plug", Num.Contrast = NULL, Den.Contrast = NULL,
 alternative = "two.sided", conf.level = 0.95, names=TRUE)
```

## Arguments

| | |
|---|---|
| `formula` | A formula specifying a numerical response and a grouping factor as e.g. `response ~ treatment` |
| `data` | A dataframe containing the response and group variable |
| `type` | type of contrast, with the following options:<br>• **"Dunnett":** many-to-one comparisons, with the control group in the denominator<br>• **"Tukey":** all-pair comparisons<br>• **"Sequen":** comparison of consecutive groups, where the group with lower order is the denominator<br>• **"AVE":** comparison of each group with average of all others, where the average is taken as denominator<br>• **"GrandMean":** comparison of each group with grand mean of all groups, where the grand mean is taken as denominator<br>• **"Changepoint":** ratio of averages of groups of higher order divided by averages of groups of lower order<br>• **"Marcus":** Marcus contrasts as ratios<br>• **"McDermott":** McDermott contrasts as ratios<br>• **"Williams":** Williams contrasts as ratios<br>• **"UmbrellaWilliams":** Umbrella-protected Williams contrasts as ratios<br>Note: `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 the Dunnett contrasts, ignored otherwise |
| `method` | character string specifying the method to be used for confidence interval construction: |

- **"Plug":** Plug-in of ratio estimates in the correlation matrix of the multivariate t distribution. This method is the default.
- **"Bonf":** Simple Bonferroni-adjustment of Fieller confidence intervals for the ratios
- **"MtI":** Sidak or Slepian- adjustment for two-sided and one-sided confidence intervals, respectively
- **"Unadj":** Unadjusted Fieller confidence intervals for the ratios (i.e. with comparisonwise confidence level = conf.level)

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

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

`alternative` a character string: "two.sided" for two-sided intervals, "less" for upper confidence limits, "greater" for lower confidence limits

`conf.level` simultaneous confidence level in case of method="Plug","Bonf", or "MtI", and comparisonwise confidence level in case of method="Unadj"

`names` logical, indicating whether rownames of the contrast matrices shall be retained in the output

## Details

Given a one-way ANOVA model, the interest is in simultaneous confidence intervals for several ratios of linear combinations of the treatment means. It is assumed that the responses are normally distributed with homogeneous variances. Unlike in multiple testing for ratios, the joint distribution of the likelihood ratio statistics has a multivariate t-distribution the correlation matrix of which depends on the unknown ratios. This means that the critical point needed for CI calculations also depends on the ratios. There are various methods of dealing with this problem (for example, see Dilba et al., 2006). The methods include (i) the unadjusted intervals (Fieller confidence intervals without multiplicity adjustments), (ii) Bonferroni (Fieller intervals with simple Bonferroni adjustments), (iii) MtI (a method based on Sidak and Slepian inequalities for two- and one-sided confidence intervals, respectively), and (iv) plug-in (plugging the maximum likelihood estimates of the ratios in the unknown correlation matrix). The latter method is known to have good simultaneous coverage probabilities. The MtI method consists of replacing the unknown correlation matrix of the multivariate t by an identity matrix of the same dimension.

See the examples for the usage of Numerator and Denominator contrasts. Note that the argument names Num.Contrast and Den.Contrast need to be specified. If numerator and denominator contrasts are plugged in without their argument names, they will not be recognized.

## Value

An object of class "sci.ratio", containing a list with elements:

`estimate` point estimates of the ratios

`CorrMat.est` estimate of the correlation matrix (for the plug-in approach)

`Num.Contrast`
matrix of contrasts used for the numerator of ratios

`Den.Contrast`
: matrix of contrasts used for the denominator of ratios

`conf.int`
: confidence interval estimates of the ratios

And some further elements to be passed to print and summary functions.

## Author(s)

Gemechis Dilba, Frank Schaarschmidt

## References

Dilba, G., Bretz, F., and Guiard, V. (2006): Simultaneous confidence sets and confidence intervals for multiple ratios. Journal of Statistical Planning and Inference 136, 2640-2658.

## See Also

`glht(multcomp)` for simultaneous CI of differences of means, `plot.sci.ratio` for a plotting function of the intervals

## Examples

```
# # #

# Antibiotic activity of 8 different strains of a micro organisms.
# (Horn and Vollandt, 1995):

data(Penicillin)

boxplot(diameter~strain, data=Penicillin)

allpairs<-sci.ratio(diameter~strain, data=Penicillin, type="Tukey")
plot(allpairs)
summary(allpairs)

# Comparison to the grand mean of all strains:

CGM<-sci.ratio(diameter~strain, data=Penicillin, type="GrandMean")
plot(CGM)
summary(CGM)

# # #

# A 90-days chronic toxicity assay:
# Which of the doses (groups 2,3,4) do not show a decrease in
# bodyweight more pronounced than 90 percent of the bodyweight
# in the control group?

data(BW)

boxplot(Weight~Dose,data=BW)
```

```
BWnoninf <- sci.ratio(Weight~Dose, data=BW, type="Dunnett",
 alternative="greater")

plot(BWnoninf, rho0=0.9)
```

---

`sci.ratio.gen` *Simultaneous confidence intervals for ratios of coefficients in the general linear models*

---

## Description

Constructs simultaneous confidence intervals for multiple ratios of linear combinations of coefficients in the general linear model.

## Usage

```
sci.ratio.gen(Y, X, Num.Contrast, Den.Contrast,
 alternative = "two.sided", conf.level = 0.95,
 method="Plug")
```

## Arguments

| | |
|---|---|
| `Y` | A numerical vector, containing the values of the response variable |
| `X` | A design matrix for the the linear model, defining the parameters to be estimated, must have same number of rows as Y |
| `Num.Contrast` | Numerator contrast matrix |
| `Den.Contrast` | Denominator contrast matrix |
| `alternative` | one of "two.sided", "less", or "greater" |
| `conf.level` | simultaneous confidence levels |
| `method` | character string, specifying the method for confidence interval calculation: |

- **"Plug":** Plug-in of ratio estimates in the correlation matrix of the multivariate t distribution. This method is the default.
- **"Bonf":** Simple Bonferroni-adjustment of Fieller confidence intervals for the ratios
- **"MtI":** Sidak or Slepian- adjustment for two-sided and one-sided confidence intervals, respectively
- **"Unadj":** Unadjusted Fieller confidence intervals for the ratios (i.e. with comparisonwise confidence level = conf.level)

## Details

Given a general linear model, the interest is in simultaneous confidence intervals for several ratios of linear combinations of the coefficients in the model. It is assumed that the responses are normally distributed with homogeneous variances. In this problem, the joint distribution of the likelihood ratio statistics has a multivariate t-distribution the correlation matrix of which depends on the unknown ratios. This means that the critical point needed for CI calculations also depends on the ratios. There are various methods of dealing with this problem (for example, see Dilba et al., 2006). The methods include (i) the unadjusted intervals (Fieller confidence intervals without multiplicity adjustments), (ii) Bonferroni (Fieller intervals with simple Bonferroni adjustments), (iii) MtI (a method based on Sidak and Slepian inequalities for two- and one-sided confidence intervals, respectively), and (iv) plug-in (plugging the maximum likelihood estimates of the ratios in the unknown correlation matrix). The MtI method consists of replacing the unknown correlation matrix by an identity matrix of the same dimension.

Applications include relative potency estimations in multiple parallel line or slope-ratio assays. Users need to define the design matrix of the linear model and the corresponding contrast matrices in an appropriate way.

## Value

A list containing

| | |
|---|---|
| `estimate` | point estimates for the ratios |
| `CorrMat.est` | estimates of the correlation matrix (for the plug-in approach) |
| `Num.Contrast` | matrix of contrasts used for the numerator of ratios |
| `Den.Contrast` | matrix of contrasts used for the denominator of ratios |
| `conf.int` | confidence interval estimates of the ratios |
| `Y` | response vector |
| `X` | design matrix |
| `fit` | the model fit, an object of class "lm" |

and some further input arguments, to be passed to print and summary functions.

## Note

## Author(s)

Gemechis Dilba, Frank Schaarschmidt

## References

Dilba, G., Bretz, F., and Guiard, V. (2006): Simultaneous confidence sets and confidence intervals for multiple ratios. Journal of Statistical Planning and Inference 136, 2640-2658.

## See Also

glht(multcomp) for multiple comparisons of parameters from lm, glm,..., `sci.ratio` for confidence intervals for ratios of means in a one-way-layout, `simtest.ratio` for simultaneous tests for ratios of means in a one-way-layout, `plot.sci.ratio` for plotting the confidence intervals.

## Examples

```
# Slope-ratio assay on data from Jensen(1989),
# Biometrical Journal 31, 841-853.

# Definition of the vector of responses and
# the design matrix can be done directly as
# follows:

Y0 <- scan()
1.3 1.7 2.4 2.7 3.6 3.6 4.7 5.0 6.1 6.3

Y1 <- scan()
2.8 2.9 4.1 3.7 5.5 5.5 6.4 6.7

Y2 <- scan()
2.2 2.1 3.2 3.2 3.8 3.9 4.7 4.9

Y3 <- scan()
2.3 2.3 3.2 3.0 4.2 4.2 4.6 5.1

Y <- c(Y0,Y1,Y2,Y3) # the response vector

xi <- rep(1,34)
x0 <- c(0,0, gl(4,2),rep(0,8*3))
x1 <- c(rep(0,10),gl(4,2), rep(0,8*2))
x2 <- c(rep(0,18),gl(4,2), rep(0,8))
x3 <- c(rep(0,26),gl(4,2))

X <- cbind(xi,x0,x1,x2,x3) # the design matrix

# Have a look at the response vector:
Y

# and the design matrix:

X

# In this problem, interest is simultaneous estimation of
# the ratios of slopes relative to the slope of the standard
# treatment. Therefore, the appropriate contrast matrices are:

Num.Contrast <- matrix(c(0,0,1,0,0,
                         0,0,0,1,0,
                         0,0,0,0,1),nrow=3,byrow=TRUE)
Den.Contrast <- matrix(c(0,1,0,0,0,
```

```
                          0,1,0,0,0,
                          0,1,0,0,0),nrow=3,byrow=TRUE)


SlopeRatioCI <- sci.ratio.gen(Y=Y, X=X,
 Num.Contrast=Num.Contrast, Den.Contrast=Den.Contrast)

SlopeRatioCI

# Further details of the fitted model and the contrasts used:

summary(SlopeRatioCI)

plot(SlopeRatioCI)

# # #

# If one starts with a dataframe, the function model.matrix
# can be used to create the design matrix:

data(SRAssay)
SRAssay

# Create the design matrix using model.matrix

X <- model.matrix(Response~Treatment:Dose, data=SRAssay)
Response <- SRAssay[,"Response"]

# The response vector and the design matrix are now:

X
Response

# The following coefficients result from fitting this model:

lm(Response~0+X)

# The same contrasts as above are used:

Num.Contrast <- matrix(c(0,0,1,0,0,
                          0,0,0,1,0,
                          0,0,0,0,1),nrow=3,byrow=TRUE)
Den.Contrast <- matrix(c(0,1,0,0,0,
                          0,1,0,0,0,
                          0,1,0,0,0),nrow=3,byrow=TRUE)

summary(sci.ratio.gen(Y=Response, X=X, Num.Contrast, Den.Contrast))
```

---

`simtest.ratio` *Simultaneous tests for ratios of normal means*

---

## Description

Performs simultaneous tests for several ratios of linear combinations of treatment means in the normal one-way ANOVA model with homogeneous variances.

## Usage

```
simtest.ratio(formula, data, type = "Dunnett", base = 1,
 alternative = "two.sided", Margin.vec = NULL, FWER = 0.05,
 Num.Contrast = NULL, Den.Contrast = NULL, names = TRUE)
```

## Arguments

| | |
|---|---|
| formula | A formula specifying a numerical response and a grouping factor (e.g., response treatment) |
| data | A dataframe containing the response and group variable |
| type | type of contrast, with the following options:<br>• **"Dunnett":** many-to-one comparisons, with control in the denominator<br>• **"Tukey":** all-pair comparisons<br>• **"Sequen":** comparison of consecutive groups, where the group with lower order is the denomniator<br>• **"AVE":** comparison of each group with average of all others, where the average is taken as denominator<br>• **"GrandMean":** comparison of each group with grand mean of all groups, where the grand mean is taken as denominator<br>• **"Changepoint":** ratio of averages of groups of higher order divided by averages of groups of lower order<br>• **"Marcus":** Marcus contrasts as ratios<br>• **"McDermott":** McDermott contrasts as ratios<br>• **"Williams":** Williams contrasts as ratios<br>• **"UmbrellaWilliams":** Umbrella-protected Williams contrasts as ratios<br>Note: 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 the Dunnett contrasts, ignored otherwise |
| alternative | a character string:<br>• **"two.sided":** for two-sided tests<br>• **"less":** for lower tail tests<br>• **"greater":** for upper tail tests |
| Margin.vec | a single numerical value or vector of Margins under the null hypotheses, default is 1 |
| FWER | a single numeric value specifying the family-wise error rate to be controlled |
| Num.Contrast | Numerator contrast matrix, where columns correspond to groups and rows correspond to contrasts |

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

`names` a logical value: if TRUE, the output will be named according to names of user defined contrast or factor levels

## Details

Given a one-way ANOVA model, the interest is in simultaneous tests for several ratios of linear combinations of the treatment means. Let us denote the ratios by $\gamma_i, i = 1, ..., r$, and let $\psi_i, i = 1, ..., r$, denote the relative margins against which we compare the ratios. For example, upper-tail simultaneous tests for the ratios are stated as

$$H_0 i : \gamma_i <= \psi_i$$

versus

$$H_1 i : \gamma_i > \psi_i, i = 1, ..., r$$

.

The associated likelihood ratio test statistic $T_i$ has a t-distribution. For multiplicity adjustments, we use the joint distribution of the $T_i$ , $i = 1, ..., r$, which under the null hypotheses follows a central r-variate t-distribution. Adjusted p-values can be calculated by adapting the results of Westfall et al. (1999) for ratio formatted hypotheses.

## Value

An object of class simtest.ratio containing:

`estimate` a (named) vector of estimated ratios

`teststat` a (named) vector of the calculated test statistics

`Num.Contrast` the numerator contrast matrix

`Den.Contrast` the denominator contrast matrix

`CorrMat` the correlation matrix of the multivariate t-distribution calculated under the null hypotheses

`critical.pt` the equicoordinate critical value of the multi-variate t-distribution for a specified FWER

`p.value.raw` a (named) vector of unadjusted p-values

`p.value.adj` a (named) vector of p-values adjusted for multiplicity

`Margin.vec` the vector of margins under the null hypotheses

and some other input arguments.

## Author(s)

Gemechis Dilba, Frank Schaarschmidt

## References

Dilba, G., Bretz, F., and Guiard, V. (2006): Simultaneous confidence sets and confidence intervals for multiple ratios. Journal of Statistical Planning and Inference 136, 2640-2658.

Westfall, P.H., Tobias, R.D., Rom, D., Wolfinger, R.D., and Hochberg, Y. (1999): Multiple comparisons and multiple tests using the SAS system. SAS Institute Inc. Cary, NC, 65-81.

## See Also

While `print.simtest.ratio` produces a small default print-out of the results,

`summary.simtest.ratio` can be used to produce a more detailed print-out, which is recommended if user-defined contrasts are used,

`sci.ratio` for constructing simultaneous confidence intervals for ratios in oneway layout

See `summary.glht(multcomp)` for multiple tests for parameters of `lm`, `glm`.

## Examples

```
library(mratios)

# # #

# User-defined contrasts for comparisons
# between Active control, Placebo and three dosage groups:

data(AP)
AP
boxplot(pre_post~treatment, data=AP)

# Test whether the differences of doses 50, 100, 150 vs. Placebo
# are non-inferior to the difference of Active control vs. Placebo

# User-defined contrasts:

# Numerator Contrasts:

NC <- rbind(
"(D100-D0)" = c(0,-1,1,0,0),
"(D150-D0)" = c(0,-1,0,1,0),
 "(D50-D0)" = c(0,-1,0,0,1))

# Denominator Contrasts:

DC <- rbind(
"(AC-D0)" = c(1,-1,0,0,0),
"(AC-D0)" = c(1,-1,0,0,0),
"(AC-D0)" = c(1,-1,0,0,0))

NC
DC
```

```
noninf <- simtest.ratio(pre_post ~ treatment, data=AP,
 Num.Contrast=NC, Den.Contrast=DC, Margin.vec=c(0.9,0.9,0.9),
 alternative="greater")

summary( noninf )

# # #

# Some more examples on standard multiple comparison procedures
# stated in terms of ratio hypotheses:

# Comparisons vs. Control:

many21 <- simtest.ratio(pre_post ~ treatment, data=AP,
 type="Dunnett")

summary(many21)

# Let the Placebo be the control group, which is the second level
# in alpha-numeric order. A simultaneous test for superiority of
# the three doses and the Active control vs. Placebo could be
# done as:

many21P <- simtest.ratio(pre_post ~ treatment, data=AP,
 type="Dunnett", base=2, alternative="greater", Margin.vec=1.1)
summary(many21P)

# All pairwise comparisons:

allpairs <- simtest.ratio(pre_post ~ treatment, data=AP,
 type="Tukey")

summary(allpairs)

# # #

# Comparison to grand mean of all strains
# in the Penicillin example:

data(Penicillin)

CGM <- simtest.ratio(diameter~strain, data=Penicillin, type="GrandMean")
CGM
summary(CGM)
```

---

`summary.sci.ratio` *Summary function for sci.ratio*

---

### Description

Detailed print out for sci.ratio objects.

### Usage

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

### Arguments

| | |
|---|---|
| object | an object of class "sci.ratio" or "sci.ratio.gen" as can be obtained by calling the function sci.ratio |
| digits | digits for rounding the output |
| ... | arguments to be passed to print |

### Value

A more detailed print output of the results and some computational steps used in sci.ratio.

### Author(s)

Frank Schaarschmidt

### See Also

print.sci.ratio, plot.sci.ratio

### Examples

---

## summary.simtest.ratio

*Summary function for simtest.ratio*

---

### Description

A detailed print out of the results of simtest.ratio

### Usage

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

### Arguments

| | |
|---|---|
| object | An object of class "simtest.ratio" as obtained by calling simtest.ratio |
| digits | digits for rounding of the results |
| ... | arguments to be passed to print |

### Value

A print out, containing the numerator and denominator contrast matrices, the correlation under the null-hypothesis, margins, estimates, teststatistics, and p.values computed by simtest.ratio.

### Author(s)

Frank Schaarschmidt

---

## t.test.ratio *t-test for the ratio of two means*

---

### Description

Performs t-test for the ratio of means of independent samples from two gaussian distributions. In case of heterogeneous variances a Satterthwaite approximation of the degrees of freedom is used (Tamhane & Logan, 2004).

### Usage

```
t.test.ratio(x, ...)
## Default S3 method:
t.test.ratio(x, y, alternative = "two.sided",
 rho = 1, var.equal = FALSE, conf.level = 0.95, ...)
## S3 method for class 'formula':
t.test.ratio(formula, data, base=2, ...)
```

### Arguments

| | |
|---|---|
| x | A numeric vector (group in the numerator of the ratio) |
| y | A numeric vector (group in the denominator of the ratio) |
| formula | A two-sided `formula` specifying a numeric response variable and a factor with two levels |
| data | A dataframe containing the variables specified in formula. Note: the first group in alpha-numeric order will appear in the denominator of the ratio |
| alternative | character string defining the alternative hypothesis, one of "two.sided", "less" or "greater" |
| rho | a single numeric value: the margin or ratio under the null hypothesis |
| var.equal | logical, if set TRUE, a ratio-t-test assuming equal group variances is performed, otherwise (default) unequal variances are assumed |

| | |
|---|---|
| `conf.level` | confidence level of Fieller's interval for the ratio of two means |
| `base` | if formula is used: a single numeric value specifying whether the first or second group (according to alpha-numeric order) is to be used as denominator |
| `...` | arguments to be passed to t.test.ratio.default |

## Details

## Value

An object of class "htest"

## Author(s)

Frank Schaarschmidt

## References

Kieser, M., Hauschke, D. (2000): Statistical methods for demonstrating equivalence in crossover trials based on the ratio of two location parameters. Drug Information Journal 34, 563-568.

Tamhane, A.C., Logan, B.R. (2004): Finding the maximum safe dose level for heteroscedastic data. Journal of Biopharmaceutical Statistics 14, 843-856.

## Examples

```
library(mratios)

# # # ASAT values of female rats in a toxicity study
#     (Hauschke, 1999).

data(ASAT)
ASAT

t.test.ratio(ASAT~group, data=ASAT, alternative="less",
 base=1, rho=1.25, var.equal=TRUE)

# # # Bodyweights of male rats in a toxicity study.
# Objective was to show equivalence between the high
# dose group (Dosis) and the control group (Kon).
# Equivalence margins are set to 0.8 and 1.25. The
# type-I-error to show equivalence is set to alpha=0.05.

data(rat.weight)

# two one-sided tests:

t.test.ratio(weight~group, data=rat.weight, alternative="less",
 rho=1.25, var.equal=TRUE)
```

```
t.test.ratio(weight~group, data=rat.weight, alternative="greater",
 rho=0.8, var.equal=TRUE)


# For rho=1, t.test.ratio corresponds to a simple t.test
# with the difference of means under the null set to zero
# (,i.e. mu=0).

t.test.ratio(ASAT~group, data=ASAT, alternative="less",
 rho=1, var.equal=TRUE)

t.test(ASAT~group, data=ASAT, alternative="less",
 mu=0, var.equal=TRUE)
```

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