Package 'jocre'

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Type Package

Title Joint Confidence Regions

Version 0.3.3

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Description Computing and plotting joint confidence regions and intervals. Regions include classical ellipsoids, minimum-volume or minimum-length regions, and an empirical Bayes region. Intervals include the TOST procedure with ordinary or expanded intervals and a fixed-sequence procedure. Such regions and intervals are useful e.g., for the assessment of multiparameter (bio-)equivalence. Joint confidence regions for the mean and variance of a normal distribution are available as well.

License GPL-2

Imports boot, KernSmooth, plyr, TSP

Suggests mvtnorm

BugReports https://github.com/PhilipPallmann/jocre/issues

NeedsCompilation no

Author Philip Pallmann [aut, cre]

Maintainer Philip Pallmann <p.pallmann@lancaster.ac.uk>

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R topics documented:

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jocre-package   *Joint confidence regions*

Description

This package provides functions for computing and plotting joint confidence regions as well as (simultaneous) confidence intervals, with a focus on multivariate normal parameter vectors and parameters of the normal distribution i.e., mean and variance.

Details

Package:	jocre
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License:	GPL-2

`cset` computes joint confidence regions and (simultaneous) confidence intervals around multivariate normal means. The parameter estimates and interval bounds (in the case of confidence regions their boundaries are projected onto the axes) are displayed with `print` or `summary`, and `plot` generates a graph of the estimate and region or intervals and allows for some fine tuning e.g., shading of an equivalence region.

`csetMV` computes joint confidence regions for the mean and variance (or standard deviation) of a normal distribution. `plot`, `print`, and `summary` produce the corresponding graphics and summaries.

Insights into the conservativeness of the two one-sided test procedure can be obtained with `iutsize`.

Confidence levels of a joint ellipse and marginal intervals can be "translated" back and forth with `translate`.

Author(s)

Philip Pallmann (<p.pallmann@lancaster.ac.uk>)

References

Philip Pallmann (2017) Joint confidence regions with the R package jocre. In preparation.

Examples

```
## Not run:
data("marzo")
plot(cset(dat=marzo, method="limacon"))

data("wires")
plot(csetMV(dat=wires, method="mood"))
```

```
## End(Not run)
```

---

cset   *Confidence regions and intervals around multivariate normal means*

Description

Computes boundaries of (simultaneous) confidence regions and intervals around multivariate normal means using different methods.

Usage

```
cset(dat, method, alpha=0.1, steps=NULL, nboot=1e4, TsengBrownA=1, TsengBrownB=1)
```

Arguments

dat	A matrix or data.frame with independent units in rows and multivariate outcomes in columns.
method	A character string specifying the method to be used. See details for available methods.
alpha	A numeric value giving the type I error level to be controlled. Default is 0.1.
steps	An integer setting the initial number of steps for the search algorithm. Default is NULL, which chooses 300 for two-dimensional and 50 for higher-dimensional problems.
nboot	A numeric giving the number of bootstrap replications to be used when method="bootkern" (ignored otherwise). Default is 1e4.
TsengBrownA	A numeric giving the parameter A to be used when method="tseng.brown" (ignored otherwise). Default is 1.
TsengBrownB	A numeric giving the parameter B to be used when method="tseng.brown" (ignored otherwise). Default is 1.

Details

Available methods for confidence regions are: boot.kern for the nonparametric bootstrap method using kernel density estimation described in Pallmann & Jaki (2017); emp.bayes for the empirical Bayes region described in Casella & Hwang (1983); hotelling for the Hotelling-type region described in Wang et al (1999); limacon.asy for the limacon-shaped mimimum expected volume region described in Brown et al (1995); limacon.fin for the finite-sample variant of the minimum expected volume region described in Berger & Hsu (1996); standard.cor for the standard region incorporating correlation between parameters described in Chew (1966); standard.ind for the standard region ignoring correlation between parameters; tost for the two one-sided test (TOST) intervals described in Schuirmann (1987); tseng for the mimimum expected interval length region described in Tseng (2002); tseng.brown for the pseudo-empirical Bayes region described in Tseng & Brown (1997).

Available methods for confidence intervals are: expanded for the two one-sided test (TOST) procedure (Schuirmann 1987) using the expanded intervals described e.g., in Bofinger (1992) and Hsu

et al. (1994); `fix.seq` for the fixed sequence intervals described in Maurer et al (1995) and Hsu & Berger (1999); `tost` for the two one-sided test (TOST) intervals described in Schuirmann (1987).

See also an overview and comparison of all methods in Pallmann & Jaki (2017).

Value

An object of class `JOC`.

Note

Warning: please use with care! Some of the functionality has not yet been thoroughly tested.

Author(s)

Philip Pallmann (`<p.pallmann@lancaster.ac.uk>`)

References

Roger L. Berger & Jason C. Hsu (1996) Bioequivalence trials, intersection-union tests and equivalence confidence sets. Statistical Science, 11(4), 283–319.

Eve Bofinger (1992) Expanded confidence intervals, one-sided tests, and equivalence testing. Journal of Biopharmaceutical Statistics, 2(2), 181–188.

Lawrence D. Brown, George Casella, J. T. Gene Hwang (1995) Optimal confidence sets, bioequivalence, and the limacon of Pascal. Journal of the American Statistical Association, 90(431), 880–889.

George Casella & Jiunn T. Hwang (1983) Empirical Bayes confidence sets for the mean of a multivariate normal distribution. Journal of the American Statistical Association, 78(383), 688–698.

Victor Chew (1966) Confidence, prediction, and tolerance regions for the multivariate normal distribution. Journal of the American Statistical Association, 61(315), 605–617.

Jason C. Hsu & Roger L. Berger (1999) Stepwise confidence intervals without multiplicity adjustment for dose-response and toxicity studies. Journal of the American Statistical Association, 94(446), 468–482.

Jason C. Hsu, J. T. Gene Hwang, Hung-Kung Liu, Stephen J. Ruberg (1994) Confidence intervals associated with tests for bioequivalence. Biometrika, 81(1), 103–114.

Willi Maurer, Ludwig A. Hothorn, Walter Lehmacher (1995) Multiple comparisons in drug clinical trials and preclinical assays: a priori ordered hypotheses. In: Joachim Vollmar (editor), Biometrie in der Chemisch-Pharmazeutischen Industrie, vol. 6, pp. 3–18. Fischer-Verlag, Stuttgart, Germany.

Philip Pallmann & Thomas Jaki (2017) Simultaneous confidence regions and intervals for multivariate bioequivalence. Submitted to Statistics in Medicine.

Donald J. Schuirmann (1987) A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. Journal of Pharmacokinetics and Biopharmaceutics, 15(6), 657–680.

Yu-Ling Tseng (2002) Optimal confidence sets for testing average bioequivalence. Test, 11(1), 127–141.

Yu-Ling Tseng & Lawrence D. Brown (1997) Good exact confidence sets for a multivariate normal mean. The Annals of Statistics, 25(5), 2228–2258.

Weizhen Wang, J. T. Gene Hwang, Anirban DasGupta (1999) Statistical tests for multivariate bioe-quivalence. Biometrika, 86(2), 395–402.

bootkern not included so far

See Also

csetMV for (simultaneous) confidence regions for normal mean and variance.

Examples

```
## Not run:
# Example 1: simultaneous 90% confidence intervals for trivariate data

trivar <- mvtnorm::rmvnorm(n=20, mean=rep(0.05, 3), sigma=toeplitz(c(0.05, 0.04, 0.03)))
colnames(trivar) <- c("AUCinf", "AUCt", "Cmax")

tost <- cset(dat=trivar, method="tost", alpha=0.1)
summary(tost)

# Example 2: simultaneous 90% confidence regions for bivariate data

bivar <- mvtnorm::rmvnorm(n=20, mean=rep(0.05, 2), sigma=toeplitz(c(0.05, 0.04)))
colnames(bivar) <- c("AUC", "Cmax")

hotelling <- cset(dat=bivar, method="hotelling", alpha=0.1)
summary(hotelling)
plot(hotelling, main="90% Hotelling Region")

limacon <- cset(dat=bivar, method="limacon.asy", alpha=0.1)
summary(limacon)
plot(limacon, main="90% Limacon Region")

tseng <- cset(dat=bivar, method="tseng", alpha=0.1)
summary(tseng)
plot(tseng, main="90% Tseng Region")

## End(Not run)
```

---

csetMV   *Confidence regions and intervals for a normal mean and variance*

Description

Computes boundaries of (simultaneous) confidence regions for the mean and variance of a normal distribution using different methods.

Usage

```
csetMV(dat, n, method, alpha=0.1, scale="var", steps=500)
```

Arguments

dat	A vector of numeric values assumed to follow a normal distribution. Not required for method="cheng.iles" or "min.area".
n	A numeric value giving the sample size. Only required for method="cheng.iles" or "min.area".
method	A character string specifying the method to be used. See details for available methods.
alpha	A numeric value giving the type I error level to be controlled. Default is 0.1.
scale	A character string specifying whether the variance (var) or standard deviation (sd) is to be plotted on the y axis. Not required for method="cheng.iles" or "min.area".
steps	An integer setting the initial number of steps for the search algorithm. Default is 800.

Details

Available methods are: mood for the classical region described in Mood (1950); large for the large-sample approximation region described in section 4.1 of Arnold & Shavelle (1998); plugin for a plug-in variant of the large-sample approximation region described in section 4.2 of Arnold & Shavelle (1998); pluginF for the plug-in variant of the large-sample approximation region described in section 4.3 of Arnold & Shavelle (1998) using an asymptotic F distribution as in Douglas (1993); lrt for the likelihood ratio test region described in section 4.4 of Arnold & Shavelle (1998); cheng.iles for the region described in Cheng & Iles (1983); min.area for the minimum-area region described in Frey et al. (2009).

Value

An object of class JOCMV.

Note

Warning: please use with care! Some of the functionality has not yet been thoroughly tested.

Author(s)

Philip Pallmann (<p.pallmann@lancaster.ac.uk>)

References

Barry C. Arnold & Robert M. Shaville (1998) Joint confidence sets for the mean and variance of a normal distribution. The American Statistician, 52(2), 133–140.

R. C. H. Cheng & T. C. Iles (1983) Confidence bands for cumulative distribution functions of continuous random variables. Technometrics, 25(1), 77–86.

J. B. Douglas (1993) Confidence regions for parameter pairs. The American Statistician, 47(1), 43–45.

Jesse Frey, Osvaldo Marrero, Douglas Norton (2009) Minimum-area confidence sets for a normal distribution. Journal of Statistical Planning and Inference, 139(3), 1023–1032.

Alexander M. Mood (1950) Introduction to the Theory of Statistics. McGraw-Hill, New York, NY.

See Also

cset for (simultaneous) confidence regions and intervals around multivariate normal means.

Examples

```
## Not run:
# Simultaneous 90% confidence regions for the mean and variance or sd of univariate normal data

univar <- rnorm(n=50)

moodvar <- csetMV(dat=univar, method="mood", alpha=0.1, scale="var")
summary(moodvar)
plot(moodvar)

moodsd <- csetMV(dat=univar, method="mood", alpha=0.1, scale="sd")
summary(moodsd)
plot(moodsd)

## End(Not run)
```

---

  helpers   *Different generic functions for classes* JOC *and* JOCMV

Description

Generic functions for summarising and plotting objects of class JOC or JOCMV.

Usage

```
## S3 method for class 'JOC'
plot(x, equi=log(c(0.8, 1.25)), axnames=NULL, main=NULL, xlim=log(c(0.77, 1.3)),
     ylim=log(c(0.77, 1.3)), col="black", convexify=FALSE, ...)

## S3 method for class 'JOC'
print(x, digits=max(3, getOption("digits") - 4), ...)

## S3 method for class 'JOC'
summary(object, digits=max(3, getOption("digits") - 4), ...)

## S3 method for class 'JOCMV'
plot(x, axnames=NULL, main=NULL, xlim=NULL, ylim=NULL, col="black", ...)

## S3 method for class 'JOCMV'
print(x, digits=max(3, getOption("digits") - 4), ...)

## S3 method for class 'JOCMV'
summary(object, digits=max(3, getOption("digits") - 4), ...)
```

Arguments

x	An output object of class JOC or JOCMV.
object	An output object of class JOC or JOCMV.
digits	A numeric value giving the number of significant digits to be printed.
equi	A numeric vector of length 2 specifying the equivalence region (lower and upper equivalence threshold) to be shaded in grey. When set to NULL no equivalence region is drawn. Default is log(c(0.8, 1.25)).
axnames	A vector of two character strings giving the x and y axis labels. For plot.JOC, when set to NULL the column names of dat are used as axis labels. Default is NULL.
main	A character string giving the plot title. Default is NULL.
xlim	A numeric vector of length two specifying the plotting range on the x-axis. Default is log(c(0.77, 1.3)) for plot.JOC and NULL for plot.JOCMV.
ylim	A numeric vector of length two specifying the plotting range on the y-axis. Default is log(c(0.77, 1.3)) for plot.JOC and NULL for plot.JOCMV.
col	A character string specifying the colour of the plotted region or intervals.
convexify	A logical specifying whether the convex hull around a non-convex region should be plotted instead of the region itself. Ignored unless method="limacon.fin" or method="limacon.asy" for the JOC object. Default is FALSE.
...	Further plotting arguments to be passed to methods. Type ?plot for details.

Details

print and summary summarise the estimates and confidence set boundaries of an object of class JOC or JOCMV that was created with cset or csetMV, respectively. plot displays a (simultaneous) confidence region or intervals when applied to an object of class JOC or JOCMV.

Value

An on-screen summary or graphical display.

Note

Warning: please use with care! Some of the functionality has not yet been thoroughly tested.

Author(s)

Philip Pallmann (<p.pallmann@lancaster.ac.uk>)

References

Philip Pallmann & Thomas Jaki (2017) Simultaneous confidence regions and intervals for multivariate bioequivalence. Submitted to Statistics in Medicine.

See Also

[cset](#) and [csetMV](#) for computing (simultaneous) confidence regions and intervals.

Examples

```
## Not run:
# Example 1: simultaneous 90% confidence region for bivariate data

bivar <- mvtnorm::rmvnorm(n=100, mean=rep(0.05, 2), sigma=diag(2) * 0.05)

hotelling <- cset(dat=bivar, method="hotelling", alpha=0.1)
summary(hotelling)
plot(hotelling, main="90% Hotelling Region")

# Example 2: simultaneous 90% confidence region for the mean and variance of univariate normal data

univar <- rnorm(n=50)

moodvar <- csetMV(dat=univar, method="mood", alpha=0.1, scale="var")
summary(moodvar)
plot(moodvar, main="90% Mood Region")

## End(Not run)
```

| iutsize | *Size of intersection union tests derived from confidence sets* |

Description

Computes the actual size of a intersection union test procedure that corresponds to a (1 – alpha) confidence set.

Usage

```
iutsize(p, n, alpha=0.1, sim=1e6)
```

Arguments

p	An integer giving the number of dimensions.
n	An integer giving the sample size.
alpha	A numeric value specifying the type I error level to be controlled. Default is 0.1.
sim	An integer giving the number of simulations to be carried out. Default is 1 million.

Details

A (1 – alpha) confidence set can be used to derive a two one-sided tests (TOST) procedure (Schuirmann 1987) whereby type I error rate control is ensured at level alpha due to the intersection union principle (Berger 1982). The actual test size, however, is often substantially lower than alpha i.e., the approach is conservative. It is well known for the one-dimensional case that the TOST corresponding to a (1 – alpha) confidence interval has size (1 – alpha/2). This function computes the achieved test size with dimension p and n according to the formula on p. 399 of Wang et al (1999).

Value

A numeric value giving the actual size of the test.

Author(s)

Philip Pallmann (<p.pallmann@lancaster.ac.uk>)

References

Roger L. Berger (1982) Multiparameter hypothesis testing and acceptance sampling. Technometrics, 24(4), 295–300.

Donald J. Schuirmann (1987) A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. Journal of Pharmacokinetics and Biopharmaceutics, 15(6), 657–680.

Weizhen Wang, J. T. Gene Hwang, Anirban DasGupta (1999) Statistical tests for multivariate bioequivalence. Biometrika, 86(2), 395–402.

Examples

```
# For p=1 we get the well-known result that the 90% CI corresponds to the TOST at 5%:

#iutsize(p=1, n=20)

# With increasing dimension the test gets conservative:

#iutsize(p=2, n=20)
#iutsize(p=3, n=20)

# For p>1 the conservativeness also depends on sample size:

#iutsize(p=2, n=10)
#iutsize(p=2, n=1000)
```

---

marzo   *Bioequivalence study of ticlopidine hydrochloride*

Description

Pharmacokinetic data from a study on the bioequivalence of a test and a reference formulation of ticlopidine hydrochloride in 24 healthy male volunteers, using a randomised crossover design (Marzo et al. 2002).

Usage

```
data("marzo")
```

Format

A data frame with 24 observations on the following 8 variables.

Volunteer A numeric vector giving the volunteer ID.

Sequence A factor with levels RT and TR specifying the sequence a volunteer was randomised to (R=reference, T=test).

Cmax_T A numeric vector of the maximum concentration (Cmax) with the test product.

Cmax_R A numeric vector of the maximum concentration (Cmax) with the reference product.

AUC_T A numeric vector of the area under the concentration-time curve (AUC) from zero to the last observed time point with the test product.

AUC_R A numeric vector of the area under the concentration-time curve (AUC) from zero to the last observed time point with the reference product.

AUCinf_T A numeric vector of the area under the concentration-time curve AUC) from zero to infinity with the test product.

AUCinf_R A numeric vector of the area under the concentration-time curve AUC) from zero to infinity with the reference product.

Details

The pharmacokinetic parameters (Cmax and AUC) were calculated using a non-compartmental approach. The data were taken from Tables I and II of Marzo et al. (2002).

Source

Antonio Marzo, Lorenzo Dal Bo, Antonio Rusca, Pierangelo Zini (2002) Bioequivalence of ticlopidine hydrochloride administered in single dose to healthy volunteers. Pharmacological Research, 46(5), 401–407.

References

Philip Pallmann & Thomas Jaki (2017) Simultaneous confidence regions and intervals for multivariate bioequivalence. Submitted to Statistics in Medicine.

Examples

```
data(marzo)

## An example analysis of Cmax assuming log-normality

# Difference of log(Cmax)
marzo$deltalogCmax <- log(marzo$Cmax_T) - log(marzo$Cmax_R)

# Estimated mean treatment effect with SE
mean(marzo$deltalogCmax)
sd(marzo$deltalogCmax) / sqrt(nrow(marzo))

# Two one-sided test (TOST) p-values
t.test(x=marzo$deltalogCmax, alternative="less", mu=log(1.25))$p.value
```

```
t.test(x=marzo$deltalogCmax, alternative="greater", mu=log(0.80))$p.value

# 90% TOST confidence interval
t.test(x=marzo$deltalogCmax, conf.level=0.9)$conf.int[1:2]
```

---

translate   *Conversion of confidence levels between intervals and ellipses*

Description

Translates the confidence level of a joint $100(1 - \text{alpha})\%$ confidence ellipse into that of the corresponding marginal confidence interval when projecting the ellipse's boundary onto the axes. Also does the "inverse operation" i.e., calculates the confidence level of a joint confidence ellipse so that its perpendicular shadows onto the axes are $100(1 - \text{alpha})\%$ confidence intervals.

Usage

```
translate(level=0.95, ddf, direction)
```

Arguments

level	A numeric value giving the confidence level.
ddf	An integer specifying the denominator degrees of freedom. Setting this to `0` enforces an asymptotic computation.
direction	A character string indicating what is to be computed. Choose either `ci2cr` or `cr2ci` (see details).

Details

Setting `direction="ci2cr"` calculates the confidence level of a confidence interval generating ellipse (CIGE) whose perpendicular shadows onto the axes are $100(1 - \text{alpha})\%$ confidence intervals with a marginal confidence level $(1 - \text{alpha})$ as specified in `level`; see p. 205 of Fox (2008).

On the other hand, setting `direction="cr2ci"` computes the marginal confidence level of the intervals obtained by projecting a joint $100(1 - \text{alpha})\%$ confidence ellipse with $(1 - \text{alpha})$ as specified in `level`; see p. 254 of Monette (1990). These marginal intervals can be viewed as including a Scheffe penalty (Scheffe 1953).

For `ddf=0` the F-distribution used for calculating the confidence levels is replaced with an asymptotic chi-square distribution.

Value

A numeric value giving the calculated confidence level.

Author(s)

Philip Pallmann (<p.pallmann@lancaster.ac.uk>)

References

John Fox (2008) Applied Linear Regression and Generalized Linear Models. Second Edition. SAGE, Thousand Oaks, CA.

Georges Monette (1990). Geometry of multiple regression and interactive 3-D graphics. In: John Fox & J. Scott Long (eds.) Modern Methods of Data Analysis. SAGE, Newbury Park, CA.

Henry Scheffe (1953) A method for judging all contrasts in the analysis of variance. Biometrika, 40(1–2), 87–104.

Examples

```
# Get CIGE level
translate(0.95, ddf=1, "ci2cr")
translate(0.95, ddf=9999, "ci2cr")
translate(0.95, ddf=0, "ci2cr")

# Get Scheffe CI level
translate(0.95, ddf=1, "cr2ci")
translate(0.95, ddf=9999, "cr2ci")
translate(0.95, ddf=0, "cr2ci")
```

---

wires	*Quality control study of wire connections*

Description

Data from a study in quality control assessing the breaking strengths of 20 wire connections between a semiconductor wafer and a terminal post (King 1971).

Usage

```
data("wires")
```

Format

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

Strength A numeric vector giving the strength at which the connection failed.

Failure A factor with levels b and w specifying whether the bond or wire failed.

Details

The data were taken from Table 4.1 of Nelson (1982).

Source

James R. King (1971) Probability Charts for Decision Making. Industrial Press, New York, NY.

References

Wayne B. Nelson (1982) Applied Life Data Analysis. Wiley, Hoboken, NJ.

Examples

```
## Not run:
data(wires)

# Simultaneous 90% confidence regions for the mean and variance
plot(csetMV(wires$Strength, method="mood"), main="Mood")
plot(csetMV(wires$Strength, method="lrt"), main="LRT")

## End(Not run)
```

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