

Package ‘metaplus’

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Type Package

Title Robust meta-analysis and meta-regression.

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Description Performs meta-analysis using standard and robust methods with confidence intervals from profile likelihood.

Depends R(>= 3.1.0), bbmle, metafor

Imports boot, methods, numDeriv

License GPL (>= 2)

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metaplus-package	<i>Fits random effects meta-analysis models including robust models</i>
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Description

Allows fitting of random effects meta-analysis producing confidence intervals based on profile likelihood (Hardy and Thompson, 1996). Two methods of robust meta-analysis are included, based on either the t -distribution (Baker and Jackson (2008) and Lee and Thompson (2008)) or normal-mixture distribution (Beath, 2014). Tests can be performed for the need for a robust model, using a parametric bootstrap, and for the normal-mixture the identity of the outliers using the posterior probability. Plots are produced allowing a comparison between the results of each method. Where possible use has been made of the metafor package.

Future enhancements include the addition of binary meta-analysis using a likelihood approach with confidence intervals from profile likelihood.

The metaplus function

This is the main function that allows fitting the models.metaplus objects may be plotted, using plot, tested for outliers using test.outliers. The results of tests.outliers may also be plotted.

Author(s)

Ken Beath <ken.beath@mq.edu.au>

References

- Baker, R., & Jackson, D. (2008). A new approach to outliers in meta-analysis. *Health Care Management Science*, 11(2), 121-131. doi:10.1007/s10729-007-9041-8
- Beath, K. J. (2014). A finite mixture method for outlier detection and robustness in meta-analysis. *Research Synthesis Methods*, (in press). doi:10.1002/jrsm.1114
- Hardy, R. J., & Thompson, S. G. (1996). A likelihood approach to meta-analysis with random effects. *Statistics in Medicine*, 15, 619-629.
- Lee, K. J., & Thompson, S. G. (2008). Flexible parametric models for random effects distributions. *Statistics in Medicine*, 27, 418-434. doi:10.1002/sim

Examples

```
## Not run:
data(marinho)
# fit standard normal random effects model
marinho1 <- metaplus(marinho$meaneffect,marinho$seeffect,plotci=TRUE,slab=marinho$study)
summary(marinho1)
# fit t-distribution random effects model
marinho2 <- metaplus(marinho$meaneffect,marinho$seeffect,plotci=TRUE,slab=marinho$study,
  random="t-dist")
summary(marinho2)
# test for presence of outliers
summary(test.outliers(marinho2))
# fit mixture normal random effects model
marinho3 <- metaplus(marinho$meaneffect,marinho$seeffect,plotci=TRUE,slab=marinho$study,
  random="mixture")
summary(marinho3)
# test for presence of outliers
summary(test.outliers(marinho3))
# obtain posterior probability of each study being an outlier and plot
marinho3.outlier.probs <- outlier.probs(marinho3)
plot(marinho3.outlier.probs)
# produce forest plot including all 3 fitted models to compare
plot(marinho1,extrameta=list(marinho2,marinho3))

## End(Not run)
```

AIC

*AIC for metaplus object***Description**

Returns AIC for a metaplus object.

Usage

```
## S3 method for class 'metaplus'
AIC(object, ...)
```

Arguments

object	metaplus object
...	additional argument; currently none are used.

Value

AIC of fitted model

Author(s)

Ken Beath

BIC	<i>BIC for metaplust object</i>
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Description

Returns BIC for a metaplust object.

Usage

```
## S3 method for class 'metaplust'
BIC(object, ...)
```

Arguments

object	metaplust object
...	additional argument; currently none are used.

Value

BIC of fitted model

Author(s)

Ken Beath

cdp	<i>CDP meta-analysis data</i>
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Description

Data for the meta-analysis by Fioravanti and Yanagi (2005) of cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly.

Usage

```
data(cdp)
```

Format

A data frame with 10 observations on the following 3 variables.

study study authors and date

yi study effect estimate

sei study standard error

Source

Fioravanti and Yanagi (2005)

References

Fioravanti, M., & Yanagi, M. (2005). Cytidinediphosphocholine (CDP choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly (Review). The Cochrane Database of Systematic Reviews. Retrieved from <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000269>

Examples

```
## Not run:
data(cdp)
cdp1 <- metaplust(cdp$yi, cdp$sei, plotci=TRUE, slab=cdp$study)

## End(Not run)
```

exercise

Exercise meta-analysis data

Description

Lawlor & Hopker (2001) performed a meta-analysis of trials of exercise in the management of depression, which was subsequently analysed using meta-regression (Higgins & Thompson 2004) with duration of treatment as a covariate. There is a possible outlier, the study by Reuter. While there are additional predictors, it seems excessive to use them given the small number of studies.

Usage

```
data(exercise)
```

Format

A data frame with 10 observations on the following 9 variables.

```
study study author
smd study effect estimate
varsmd study effect variance
sesmd study effect standard error
abstract study available as abstract only?
duration length of study in weeks
itt intention to treat analysis?
alloc outcome assessor blinded
phd phd thesis?
```

Source

Higgins and Thompson (2004)

References

Higgins, J. P. T., & Thompson, S. G. (2004). Controlling the risk of spurious findings from meta-regression. *Statistics in Medicine*, 23(11), 1663-1672. doi:10.1002/sim.1752

Lawlor, D. A., & Hopker, S. W. (2001). The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *BMJ*, 322(31 March), 18.

Examples

```
## Not run:
data(exercise)
exercise1 <- metaplustest(exercise$smd, sqrt(exercise$varsmd), mods=exercise[,c("duration"), drop=FALSE],
  slab=exercise$study)

## End(Not run)
```

logLik

log Likelihood for metaplustest object

Description

Returns the log Likelihood for a metaplustest object.

Usage

```
## S3 method for class 'metaplustest'
logLik(object, ...)
```

Arguments

object metaplustest object
... additional argument; currently none are used.

Value

The loglikelihood of the fitted model.

Author(s)

Ken Beath

mag

Magnesium meta-analysis data

Description

Data for a meta-analysis of intravenous magnesium in acute myocardial infarction. An interesting question is whether the ISIS4 study is an outlier.

Usage

```
data(mag)
```

Format

A data frame with 16 observations on the following 3 variables.

study study author

yi study effect estimate

sei study standard error

Source

Sterne et al (2001)

References

Sterne, J. A. C., Bradburn, M. J., & Egger, M. (2001). Meta-analysis in Stata. In M. Egger, G. D. Smith, & D. G. Altman (Eds.), *Systematic Reviews in Health Care: Meta-Analysis in Context* (pp. 347-369). BMJ Publishing Group.

Examples

```
## Not run:  
data(mag)  
mag1 <- metaplot(mag$yi,mag$sei,plotci=TRUE,slab=mag$study)  
  
## End(Not run)
```

marinho

Marinho meta-analysis data

Description

Data for the meta-analysis by Marinho et al (2009) to determine the effectiveness of fluoride tooth-pastes on caries in children.

Usage

```
data(marinho)
```

Format

A data frame with 70 observations on the following 11 variables.

```
study study authors and date
nfluor number in fluoride group
meanfluor mean effect in fluoride group
sdfluor standard deviation of effect in fluoride group
nplacebo number in placebo group
meanplacebo mean effect in placebo group
sdplacebo standard deviation of effect in placebo group
meaneffect mean effect difference
seeffect standard error of effect difference
```

Source

Marinho et al (2009)

References

Marinho, V. C. C., Higgins, J. P. T., Logan, S., & Sheiham, A. (2009). Fluoride toothpastes for preventing dental caries in children and adolescents (Review). The Cochrane Database of Systematic Reviews. Retrieved from <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002278/pdf>

Examples

```
## Not run:
data(marinho)
marinho1 <- metaplot(marinho$meaneffect,marinho$seeffect,plotci=TRUE,slab=marinho$study)

## End(Not run)
```

metaplus	<i>Fits random effects meta-analysis models, using either a standard normal distribution, a t-distribution or a mixture of normals for the random effect.</i>
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Description

Allows fitting of random effects meta-analysis producing confidence intervals based on profile likelihood. Two methods of robust meta-analysis are included, based on either the t -distribution or normal-mixture distribution.

Usage

```
metaplus(yi, sei, mods=NULL, random="normal",
         label=switch(random, "normal"="Random Normal", "t-dist"="Random t-distribution",
                     "mixture"="Random mixture"),
         plotci=FALSE, justfit=FALSE, slab=1:length(yi))
```

Arguments

<code>yi</code>	vector of observed effect size
<code>sei</code>	vector of observed standard errors
<code>mods</code>	data frame of covariates corresponding to each study
<code>random</code>	The type of random effects distribution. One of "normal", "t-dist", "mixture", for standard normal, t -distribution or mixture of normals respectively.
<code>label</code>	The label to be used for this model when plotting
<code>plotci</code>	Should profile be plotted for each confidence interval?
<code>justfit</code>	Should model only be fitted? If <code>justfit=TRUE</code> then profiling and likelihood ratio statistics are not calculated. Useful for when bootstrapping.
<code>slab</code>	Vector of character strings corresponding to each study.

Details

As well as standard normal random effects meta-analysis, fitting of robust models incorporating either a t -distribution random effect (Lee and Thompson, 2008) or a mixture of normals (Beath, 2014) may be fitted. For all models the profile log-likelihood (Hardy and Thoismpson, 1996) is used to determine the confidence intervals for the parameters, with corresponding p values calculated using the likelihood ratio test, to give consistency between the confidence intervals and p values. The profile log-likelihood produces confidence intervals with better properties than REML or Der Simonian-Laird method (Brockwell and Gordon 2001, Jackson et al 2010)

For the mixture normal model, multiple starting values are used. This is achieved by starting with the no outlier model, then all possible single outlier models and choosing the model with the maximum likelihood. The process is repeated by adding all possible outliers to obtain the two outlier models and the maximum likelihood chosen. The process is repeated until the likelihood is not further maximised by adding outliers. This method gives a faster fitting time and is more reliable than using random assignments, as we have usually only a small number of outliers.

Value

results	Matrix containing columns for estimate, lower 95%, upper 95% and p value, or if justfit=TRUE then only the parameter estimates
yi	Effect sizes
sei	Standard error of effect sizes
mods	Modifiers for meta-regression
slab	Study labels
justfit	Value of justfit passed to the method.
fittedmodel	final model returned by mle2
outlier.prob	Outlier probabilities for robust mixture model only

Author(s)

Ken Beath <ken.beath@mq.edu.au>

References

- Beath, K. J. (2014). A finite mixture method for outlier detection and robustness in meta-analysis. *Research Synthesis Methods*, (January), n/a-n/a. doi:10.1002/jrsm.1114
- Brockwell, S. E., & Gordon, I. R. (2001). A comparison of statistical methods for meta-analysis. *Statistics in Medicine*, 20, 825-840.
- Hardy, R. J., & Thompson, S. G. (1996). A likelihood approach to meta-analysis with random effects. *Statistics in Medicine*, 15, 619-629.
- Jackson, D., Bowden, J., & Baker, R. (2010). How does the DerSimonian and Laird procedure for random effects meta-analysis compare with its more efficient but harder to compute counterparts? *Journal of Statistical Planning and Inference*, 140, 961-970. doi:10.1016/j.jspi.2009.09.017
- Lee, K. J., & Thompson, S. G. (2008). Flexible parametric models for random effects distributions. *Statistics in Medicine*, 27, 418-434. doi:10.1002/sim

Examples

```
data(cdp)
cdp.meta <- metaplus(cdp$yi, cdp$sei)
summary(cdp.meta)
```

outlier.probs

Calculate outlier probabilities for each study.

Description

For the normal mixture random effect calculates the probability that each study is an outlier based on the posterior probability of it being an outlier.

Usage

```
outlier.probs(object)
```

Arguments

object A metaplust object with a mixture (robust) random effects distribution.

Details

The outlier probabilities are obtained as the posterior probabilities of each study being an outlier based on the fitted mixture model.

Value

outlier.prob Posterior probability that each study is an outlier
slab Labels corresponding to each study

Author(s)

Ken Beath <ken.beath@mq.edu.au>

Examples

```
## Not run:
data(cdp)
cdp3 <- metaplust(cdp$yi, cdp$sei, plotci=TRUE, slab=cdp$study, random="mixture")
cdp3.outlier.probs <- outlier.probs(cdp3)
plot(cdp3.outlier.probs)

## End(Not run)
```

plot.metaplust *Produces forest plot for the studies together with the meta-analysis results.*

Description

Produces a forest plot for the studies in the meta-analysis and the result of the meta-analysis. Allows the inclusion of extra results of alternative meta-analyses, to allow, for example comparison between standard and robust methods of meta-analysis. Makes extensive use of the metafor package to produce the forest plot.

Usage

```
## S3 method for class 'metaplust'
plot(x, ..., extrameta = NULL)
```

Arguments

x	metaplust object to be plotted
...	additional parameters to plot
extrameta	Additional metaplust objects to be plotted. Only the summary statistic is plotted at the end of the plot. This is useful for comparing standard and robust methods, or meta-regressions for various values of the predictor.

Value

Plot

Author(s)

Ken Beath <ken.beath@mq.edu.au>

Examples

```
## Not run:
# produce all 3 models for the CDP data and plot them all
data(cdp)
cdp1 <- metaplust(cdp$yi,cdp$sei,plotci=TRUE,slab=cdp$study)
cdp2 <- metaplust(cdp$yi,cdp$sei,plotci=TRUE,slab=cdp$study,random="t-dist")
cdp3 <- metaplust(cdp$yi,cdp$sei,plotci=TRUE,slab=cdp$study,random="mixture")
plot(cdp1,extrameta=list(cdp2,cdp3))

# plot effect of exercise on depression at 4, 8 and 12 weeks
data(exercise)
exercise$duration4 <- exercise$duration-4
exercise$duration8 <- exercise$duration-8
exercise$duration12 <- exercise$duration-12

exercise.wk4 <- metaplust(exercise$smd,sqrt(exercise$varsmd),mods=exercise[,c("duration4"),
  drop=FALSE],label="Random Mixture (Week 4)",slab=exercise$study,random="mixture")
exercise.wk8 <- metaplust(exercise$smd,sqrt(exercise$varsmd),mods=exercise[,c("duration8"),
  drop=FALSE],label="Random Mixture (Week 8)",slab=exercise$study,random="mixture")
exercise.wk12 <- metaplust(exercise$smd,sqrt(exercise$varsmd),mods=exercise[,c("duration12"),
  drop=FALSE],label="Random Mixture (Week 12)",slab=exercise$study,random="mixture")

exercise.nodurn <- metaplust(exercise$smd,sqrt(exercise$varsmd),plotci=TRUE,
  label="Random Mixture (No Duration)",slab=exercise$study,random="mixture")

plot(exercise.nodurn,extrameta=list(exercise.wk4,exercise.wk8,exercise.wk12))

## End(Not run)
```

plot.outlier.probs *Plot outlier probabilities.*

Description

Plots the outlier probability for each study, from an outlier.probs object.

Usage

```
## S3 method for class 'outlier.probs'  
plot(x, ...)
```

Arguments

x outlier.probs object to be plotted
... additional parameters to plot

Value

Plot

Author(s)

Ken Beath <ken.beath@mq.edu.au>

Examples

```
## Not run:  
data(cdp)  
cdp.mix <- metaplus(cdp$yi, cdp$sei, plotci=TRUE, slab=cdp$study, random="mixture")  
cdp.mix.outlier.probs <- outlier.probs(cdp.mix)  
plot(cdp.mix.outlier.probs)  
  
## End(Not run)
```

summary *Summary of a metaplus object.*

Description

Summarises the meta-analysis, giving the parameter estimates and goodness of fit statistics. For the robust methods this includes the values of the parameters relating to robustness.

Usage

```
## S3 method for class 'metaplus'  
summary(object, ...)
```

Arguments

object metaplus object to summarise.
 ... Additional parameters to summary.

Value

results Matrix containing parameter estimates, confidence intervals and p values
 fitstats List containing logLikelihood, AIC and BIC

Author(s)

Ken Beath <ken.beath@mq.edu.au>

Examples

```
data(cdp)
cdp1 <- metaplus(cdp$yi,cdp$sei,plotci=TRUE,slab=cdp$study)
summary(cdp1)
```

test.outliers *Tests for the presence of outliers.*

Description

For the t -distribution models this is a test that the degrees of freedom is infinite, or equivalently that its inverse is zero. For the mixture-normal model it is a test that the proportion of outliers is zero. As both tests involve a parameter on the boundary of the parameter space, asymptotic theory does not apply, so a parametric bootstrap is performed to determine the empirical distribution of the test statistic under the null hypothesis. The observed likelihood ratio statistic is then compared to this distribution to determine the p value.

Usage

```
test.outliers(object, R = 999)
```

Arguments

object The meta-analysis for which the presence of outliers is to be tested.
 R Number of simulations (parametric bootstraps) used in testing the hypothesis. Initially, it may be useful to set this to a smaller value, to allow faster execution time.

Value

```
pvalue=pvalue,observed=meta.boot$T[1],sims
```

pvalue p value obtained from parametric bootstrap
 observed Observed value of the likelihood ratio test statistic
 sims Simulated values of the test statistic under the null hypothesis

Author(s)

Ken Beath <ken.beath@mq.edu.au>

Examples

```
## Not run:  
data(cdp)  
cdp3 <- metaplus(cdp$yi,cdp$sei,plotci=TRUE,slab=cdp$study,random="mixture")  
summary(test.outliers(cdp3))
```

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

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