Package 'metaplus'

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Type Package

Title Robust Meta-Analysis and Meta-Regression

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Description Performs meta-analysis and meta-regression using standard and robust methods with confidence intervals based on the profile likelihood. Robust methods are based on alternative distributions for the random effect, either the t-distribution (Lee and Thompson, 2008 <doi:10.1002/sim.2897> or Baker and Jackson, 2008 <doi:10.1007/s10729-007-9041-8>) or mixtures of normals (Beath, 2014 <doi:10.1002/jrsm.1114>).

Depends R(>= 3.2.0)

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VignetteBuilder R.rsp

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Contents

metaplus-package   *Fits random effects meta-analysis models including robust models*

Description

Allows fitting of random effects meta-analysis producing confidence intervals based on the 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.

The metaplus function

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

Author(s)

Ken Beath <ken@kjbeath.id.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

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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

Examples

```
data(mag)
mag1 <- metaplus(yi, sei, plotci = TRUE, slab = study, cores = 1, data = mag)
print(AIC(mag1))
```

BIC *BIC for metaplus object*

Description

Returns BIC for a metaplus object.

Usage

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

Arguments

object   metaplus object

...   additional argument; currently none are used.

Value

BIC of fitted model

Author(s)

Ken Beath

Examples

```
data(mag)
mag1 <- metaplus(yi, sei, plotci = TRUE, slab = study, cores = 1, data = mag)
print(BIC(mag1))
```

---

cdp *CDP meta-analysis data*

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

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

```
data(cdp)
cdp1 <- metaplus(yi, sei, plotci = TRUE, slab = study, cores = 1, data = cdp)
```

---

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

```
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), 166382. 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

```
exercise1 <- metaplus(smd, sqrt(varsmd), mods = duration, slab = study,
    cores = 1, data = exercise)
exercise2 <- metaplus(smd, sqrt(varsmd), mods = cbind(duration, itt), slab = study,
    cores = 1, data = exercise)
```

---

logLik   *log Likelikelihood for metaplus object*

Description

Returns the log Likelihood for a metaplus object.

Usage

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

Arguments

object   metaplus object

...   additional argument; currently none are used.

Value

The loglikelihood of the fitted model.

Author(s)

Ken Beath

Examples

```
data(mag)
mag1 <- metaplus(yi, sei, plotci = TRUE, slab = study, cores = 1, data = mag)
print(logLik(mag1))
```

---

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

```
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

```
data(mag)
mag1 <- metaplus(yi, sei, plotci = TRUE, slab = study, cores = 1, data = mag)
plot(mag1)
```

---

marinho   *Marinho meta-analysis data*

Description

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

Usage

```
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

```
data(marinho)
marinho1 <- metaplus(meaneffect, seeffect, plotci = TRUE, slab = study, cores = 1, data = marinho)
```

---

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

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),
 useAGQ = FALSE, quadpoints = 21, notrials = 20,
 cores = max(detectCores()%/%2, 1), data)
```

Arguments

yi	vector of observed effect size
sei	vector of observed standard errors (note: not standard errors squared)
mods	data frame of covariates corresponding to each study
random	The type of random effects distribution. One of "normal", "t-dist", "mixture", for standard normal, t-distribution or mixture of normals respectively.

label	The label to be used for this model when plotting
plotci	Should profile be plotted for each confidence interval?
justfit	Should model only be fitted? If justfit = TRUE then profiling and likelihood ratio statistics are not calculated. Useful for when bootstrapping.
slab	Vector of character strings corresponding to each study.
useAGQ	Deprecated. No longer used.
quadpoints	Deprecated. No longer used.
notrials	Number of random starting values to use for mixture models.
cores	Number of rcores to use for parallel processing of .
data	Optional data frame containing some or all other data.

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 Baker and Jackson, 2008) or a mixture of normals (Beath, 2014) may be fitted. For all models the profile log-likelihood (Hardy and Thompson, 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
profile	profile likelihood returned as described in bbmle
random	Type of random effect
outlier.prob	Outlier probabilities for robust mixture model only

Note

I have used cores = 1 in the examples, as this is required by some of the checking procedures but it can, and should be, be removed for your own use for faster execution.

Author(s)

Ken Beath <ken@kjbeath.id.au>

References

Baker, R., & Jackson, D. (2008). A new approach to outliers in meta-analysis. Health Care Management Science, 11(2), 121131.

Beath, K. J. (2014). A finite mixture method for outlier detection and robustness in meta-analysis. Research Synthesis Methods, 5, 285-293. 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

```
library(metaplus)

# perform meta-analysis for mag studies, which have no outliers
# fit standard normal random-effect model and print summary
mag.meta <- metaplus(yi, sei, slab = study, data = mag)
summary(mag.meta)
# repeat, but this time plot the profile likelihood diagnostic plot using plotci
mag.meta <- metaplus(yi, sei, slab = study, plotci = TRUE, cores = 1, data = mag)
# plot a forest plot with exponential transform, so that the odds ratios are plotted
plot(mag.meta, atransf = exp, at = log(c(.01, .1, 1, 10, 100)), xlab = "Odds Ratio",
 cex = 0.75)
# repeat for t-distribution random effects
mag.tdist <- metaplus(yi, sei, slab = study,
 random = "t-dist", cores = 1, data = mag)
summary(mag.tdist)
# use parametric bootstrap to test for presence of outliers
summary(testOutliers(mag.tdist, cores = 1))
# repeat for robust mixture random effects
mag.mix <- metaplus(yi, sei, slab = study,
 random = "mixture", cores = 1, data = mag)
summary(mag.mix)
# use parametric bootstrap to test for presence of outliers
summary(testOutliers(mag.mix, cores = 1))


# perform meta-analysis for CDP studies
# where there is one outlier
cdp.meta <- metaplus(yi, sei, slab = study, cores = 1, data = cdp)
```

```
summary(cdp.meta)
cdp.tdist <- metaplus(yi, sei, slab = study,
 random = "t-dist", cores = 1, data = cdp)
summary(cdp.tdist)
summary(testOutliers(cdp.tdist, cores = 1))
cdp.mix <- metaplus(yi, sei, slab = study,
 random = "mixture", cores = 1, data = cdp)
summary(cdp.mix)
summary(testOutliers(cdp.mix, cores = 1))

# extract and plot outlier probabilities
cdp.mix.outlierProbs <- outlierProbs(cdp.mix)
plot(cdp.mix.outlierProbs)

# produce forest plot with summary for all 3 models, showing narrower confidence
# intervals for robust models
plot(cdp.meta, extrameta = list(cdp.tdist, cdp.mix), xlab = "Standardised Mean Difference")


# effect of exercise on depression with covariate of length of study
# fit the 3 models
exercise.meta <- metaplus(smd, sqrt(varsmd),
 mods = duration, slab = study, cores = 1, data = exercise)
summary(exercise.meta)
exercise.mix <- metaplus(smd, sqrt(varsmd),
 mods = duration, slab = study, random = "mixture",
 cores = 1, data = exercise)
summary(exercise.mix)
exercise.testOutliers <- testOutliers(exercise.mix, cores = 1)
summary(exercise.testOutliers)

# identify possible outliers
exercise.outlierProbs <- outlierProbs(exercise.mix)
plot(exercise.outlierProbs)

# centre duration at different values to obtain predictions at 4, 8 and 12 weeks
exercise$duration4 <- exercise$duration-4
exercise$duration8 <- exercise$duration-8
exercise$duration12 <- exercise$duration-12

# fit the different models, giving each an appropriate label
exercise.nodurn <- metaplus(smd, sqrt(varsmd),
 label = "Random Mixture (No Duration)", slab = study,
 random = "mixture", cores = 1, data = exercise)
exercise.wk4 <- metaplus(smd, sqrt(varsmd),
 mods = duration4, label = "Random Mixture (Week 4)",
 slab = study, random = "mixture", cores = 1, data = exercise)
exercise.wk8 <- metaplus(smd, sqrt(varsmd),
 mods = duration8, label = "Random Mixture (Week 8)",
 slab = study, random = "mixture", cores = 1, data = exercise)
exercise.wk12 <- metaplus(smd, sqrt(varsmd),
 mods = duration12, label = "Random Mixture (Week 12)",
 slab = study, random = "mixture", cores = 1, data = exercise)
```

```
# produce forest plot with summary for each model with robust mixture model at different weeks
plot(exercise.nodurn, extrameta = list(exercise.wk4, exercise.wk8,
 exercise.wk12), xlab = "Standardised mean difference")
```

---

outlierProbs   *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

```
## S3 method for class 'metaplus'
outlierProbs(object)
```

Arguments

object   A metaplus 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@kjbeath.id.au>

Examples

```
data(mag)
mag3 <- metaplus(yi, sei, plotci = TRUE, slab = study, random = "mixture", cores = 1, data = mag)
mag3.outlierProbs <- outlierProbs(mag3)
plot(mag3.outlierProbs)
```

---

plot.metaplus	*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 'metaplus'
plot(x, ..., extrameta = NULL)
```

Arguments

x	metaplus object to be plotted
...	additional parameters to plot
extrameta	Additional metaplus 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

Note

On some systems the alignment of characters in the CI may be poor when saving the plots to pdf. A solution is to use the extrafont package and a fixed width font, for eample Courier New. Then if creating the plot using pdf() the parameter family = "Courier New" will use this font and fonts = "Courier New" will add it to the pdf.

An alternative is to use pdf.options() with the same parameters before the plot, and pdf.options(reset = TRUE) will produce the same effect.

Author(s)

Ken Beath <ken@kjbeath.com.au>

Examples

```
data(cdp)
# produce all 3 models for the CDP data and plot them all
cdp1 <- metaplus(yi, sei, plotci = TRUE, slab = study, cores = 1, data = cdp)
cdp2 <- metaplus(yi, sei, plotci = TRUE, slab = study, random = "t-dist", cores = 1, data = cdp)
```

```
cdp3 <- metaplus(yi, sei, plotci = TRUE, slab = study, random = "mixture", cores = 1, data = cdp)
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 <- metaplus(smd, sqrt(varsmd), mods = duration4,
 label = "Random Mixture (Week 4)", slab = study, random = "mixture", cores = 1, data = exercise)
exercise.wk8 <- metaplus(smd, sqrt(varsmd), mods = duration8,
 label = "Random Mixture (Week 8)", slab = study, random = "mixture", cores = 1, data = exercise)
exercise.wk12 <- metaplus(smd, sqrt(varsmd), mods = duration12,
 label = "Random Mixture (Week 12)", slab = study, random = "mixture", cores = 1, data = exercise)

exercise.nodurn <- metaplus(smd, sqrt(varsmd), plotci = TRUE,
 label = "Random Mixture (No Duration)", slab = study, random = "mixture",
 cores = 1, data = exercise)

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

---

plot.outlierProbs   *Plot outlier probabilities.*

Description

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

Usage

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

Arguments

x	outlierProbs object to be plotted
...	additional parameters to plot

Value

Plot

Author(s)

Ken Beath <ken@kjbeath.id.au>

Examples

```
data(mag)
mag.mix <- metaplus(yi, sei, plotci = TRUE, slab = study, random = "mixture", cores = 1, data = mag)
mag.mix.outlierProbs <- outlierProbs(mag.mix)
plot(mag.mix.outlierProbs)
```

---

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. In the summary the 95% confidence intervals are calculated using the profile likelihood method. To produce corresponding p-values these are obtained from the likelihood ratio test statistic.

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@kjbeath.id.au>

Examples

```
data(mag)
mag1 <- metaplus(yi, sei, plotci = TRUE, slab = study, cores = 1, data = mag)
summary(mag1)
```

---

testOutliers   *Tests for the presence of outliers.*

Description

For the t-distribution models this is a test that the degrees of freedom is infinitite, or equivalently that it's 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

```
## S3 method for class 'metaplus'
testOutliers(object, R = 999, cores = max(detectCores()%/%2, 1))
```

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.
cores	Number of cores used to simultaneously perform simulations.

Value

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

Note

Running the default number of bootstrap samples may take considerable time, of the order of hours. Use of the parallel options will improve these times. For a preliminary guide to whether there are outliers, this is indicated by a reduction in AIC or BIC with the robust model, and a change in the estimated mean effect.

Author(s)

Ken Beath <ken@kjbeath.id.au>

Examples

```
data(cdp)
cdp3 <- metaplus(yi, sei , plotci = TRUE, slab = study, random = "mixture", cores = 1, data = cdp)
summary(testOutliers(cdp3, cores = 1))
```

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