Package 'ipdmeta'

February 20, 2015

Type Package

Title Tools for subgroup analyses with multiple trial data using aggregate statistics

Version 2.4

Date 2012-08-10

Author S. Kovalchik

Maintainer S. Kovalchik <s.a.kovalchik@gmail.com>

Description This package provides functions to estimate an IPD linear mixed effects model for a continuous outcome and any categorical covariate from study summary statistics. There are also functions for estimating the power of a treatment-covariate interaction test in an individual patient data meta-analysis from aggregate data.

License GPL-2

Depends nlme, methods

LazyLoad yes

Repository CRAN

Date/Publication 2012-09-04 19:06:36

NeedsCompilation no

R topics documented:

`confint` *Compute confidence intervals for population effects of an* `ipdlme` *object*

Description

Computes Wald-type confidence intervals for all fixed effects of the fit of an IPD LME model.

Usage

```
confint(object,parm,level=0.95,...)
```

Arguments

`object`	object of the `ipdlme` class
`parm`	term names, currently ignored
`level`	numeric value of confidence level to be used
`...`	additional arguments, currently not implemented

Value

Matrix of the estimate, lower and upper confidence intervals for the fixed effects of the IPD LME model.

See Also

`ipdlme-class`

Examples

```
data(regress_chol)

confint(ipdlme(n, Y, S2))
```

converged *Extract the convergence status for an* ipdlme *object*

Description

Extract the convergence status for the fit of an IPD LME model.

Usage

```
converged(object)
```

Arguments

object	object of the ipdlme class

Value

Logical value indicating whether convergence was achieved.

See Also

ipdlme-class

Examples

```
data(regress_chol)

converged(ipdlme(n, Y, S2))
```

convergence *Extract the convergence trace for an* ipdlme *object*

Description

Extract the convergence trace for the fit of an IPD LME model.

Usage

```
convergence(object)
```

Arguments

object	object of the ipdlme class

Value

List of the trace for every parameters of the IPD LME fitted model.

See Also

ipdlme-class

Examples

```
data(regress_chol)

convergence(ipdlme(n, Y, S2))
```

`fixef` *Extract the population (fixed effect) estimates for an* `ipdlme` *object*

Description

Extract fixed effects estimates of the fit of an IPD LME model.

Usage

```
fixef(object,...)
```

Arguments

`object`	object of the `ipdlme` class
`...`	additional arguments, currently not implemented

Value

Numeric vector of the fitted fixed effects of an IPD LME model.

See Also

ipdlme-class

Examples

```
data(regress_chol)

fixef(ipdlme(n, Y, S2))
```

ipd.sep *IPD meta-analysis Subgroup Effect Power Estimator*

Description

The function estimates the power of an IPD meta-analysis to detect a specified subgroup effect (covariate-treatment interaction) based on summary statistics.

Usage

```
ipd.sep(
      effect,
               event0=NULL,
               event1=NULL,
               mean0=NULL,
               mean1=NULL,
               var0=NULL,
               var1=NULL,
               x0=NULL,
               x1=NULL,
               s20=NULL,
               s21=NULL,
               n0=NULL,
               n1=NULL,
       data,
               alpha=.05
       )
```

Arguments

effect	scalar, subgroup effect under alternative hypothesis
event0	vector, for binary outcome, events in group 0
event1	vector, for binary outcome, events in group 1
mean0	vector, for continuous outcome, mean in group 0
mean1	vector, for continuous outcome, mean in group 1
var0	vector, for contunuous outcome, sample variances for responses in group 0
var1	vector, for contunuous outcome, sample variances for responses in group 1
x0	vector of subgroup covariate means for group 0
x1	vector of subgroup covariate means for group 1
s20	vector of covariate sample variances for control group
s21	vector of covariate sample variances for treatment group
n0	vector of number of subjects for group 0
n1	vector of number of subjects for group 1
data	data frame containing the objects specified in response or covariate arguments
alpha	scalar significance level of Wald test (two-sided)

Details

If a data frame is supplied, then the object indicated in each vector argument is looked for in `data`.

For a patient-level binary outcome, `mean0`, `mean1`, `var0` and `var1` should not be specified. Zero event counts will be corrected with a 0.5 factor. For a continuous response, `event0` and `event1` should not be specified.

For a covariate that is a mean proportion, such as proportion male, no sample variances need to be specified. If no values are given for the sample variances `s20` and `s21` it will be assumed that the covariate is a mean proportion and the sample variances will be determined from the proportions.

The SEP for the IPD meta-analysis is based on a generalized linear mixed model for the patient-level analysis. The model has intercept, treatment, covariate and interaction fixed effects and independent random effects for the baseline and treatment by study. Under this model, an estimator for the subgroup effect variance, that is, the variance for the estimate of the covariate-treatment interaction, for either an identity or logistic GLMM, can be obtained from the study sample statistics. This variance is then used to estimate the power of the IPD meta-analysis for a specified subgroup effect based on a two-sided Wald test.

Value

A list with the following named components:

`esimated.power`	The estmated IPD meta-analysis interactive effect power
`power.lower`	Lower bound for `level` CI
`power.upper`	Upper bound for `level` CI
`estimated.se`	Estimated standard error of IPD meta-analysis interaction effect
`se.lower`	Lower bound for `level` CI
`se.upper`	Upper bound for `level` CI
`sigma`	The mean of the study residual variance
`sigma0`	Estimate of intercept random effect variance from simple RE meta-analysis with DSL estimator
`sigma1`	Estimate of treatment random effect variance simple RE meta-analysis with DSL estimator
`level`	confidence level for Wald test

Author(s)

S. Kovalchik <s.a.kovalchik@gmail.com>

Examples

```
data(poynard)

#AGE SEP FOR IPD META-ANALYSIS OF BETA-ANTAGONISTS TO PREVENT GI BLEEDING EVENTS

#ALTERNATIVE HYPOTHESIS FOR AGE-TREATMENT EFFECT
#WITH 10 YEARS CHANGE TO OR TREATMENT EFFECT exp(beta*10)
#EFFECT MODIFIER CHANGES TREATMENT EFFECT BY 30%

beta = log(1.3)/10

age.sep <-
```

```
ipd.sep(
 effect=beta,
 event0=bleed0,
 event1=bleed1,
 n0=n0,
 n1=n1,
 x0=age0,
 x1=age1,
 s20=age.s20,
 s21=age.s21,
 data=poynard
)

age.sep

#GENDER SUBGROUP EFFECT; 30% OR CHANGE BY GENDER

beta <- log(1.3)

gender.sep <-

ipd.sep(
 effect=beta,
 event0=bleed0,
 event1=bleed1,
 n0=n0,
 n1=n1,
 x0=male0,
 x1=male1,
 data=poynard
)

gender.sep
```

---

ipdlme *IPD Linear Mixed-Effects Models from Aggregate Data*

Description

Fits the IPD linear mixed-effects model for a treatment and single categorical covariate and their interaction using study-level summary statistics.

Usage

```
ipdlme(n, y, s2, max.iter = 100, tol = 1e-10,equal.residual.var=TRUE)
```

Arguments

n	a list ordered by trial with each element a data frame having the columns trt and ctrl and the row the sample sizes in each group for the covariate of interest, e.g. males/females, never/former/current smokers.
y	a list ordered by trial with each element a data frame having the columns trt and ctrl and the row the average outcome (the response variable of the model) in each group for the covariate of interest.
s2	A vector of the study overall sample variances for the outcome or a list of the treatment-subgroup sample variances following the structure of n and y.
max.iter	An integer indicating the maximum number of iterations to perform in the optimization algorithm
tol	A numeric value that is used for the termination rule (see details).
equal.residual.var	logical, indicates whether the residual variances for the outcomes are assumed constant between studies or are heterogeneous

Details

The last group in the covariates, designated by the final row in the list arguments, will be treated as the reference variable.

The order of the list components should agree for all arguments.

The optimization algorithm performs maximum likelihood estimation for the IPD LME model. Given the treatment indicator z the factor x and the study variable study, the fitted model is equivalent to y~x*z+(z|study) fitted with lmer with the option REML=FALSE.

The termination rule looks at the percentage change for the fixed and study random effects after the first iteration. Convergence is declared at the first iteration for which the maximum percentage change is less than tol.

Value

An object of class ipdlme-class, for which a number of methods are available.

Author(s)

Stephanie A. Kovalchik <kovalchiksa@nih.gov>

See Also

The ipdlme-class

Examples

```
data(regress_age)

# Homogeneous residual variance
metafit <- ipdlme(n,Y,S2)
```

```
summary(metafit)

fixef(metafit)
confint(metafit)

ranef(metafit)

labs <- paste("Center",c(1,10,11,2:9))
plot(metafit, y=labs)

#Heterogeneous residual variance
metafit <- ipdlme(n,Y,S2,equal=FALSE)

summary(metafit)

fixef(metafit)
confint(metafit)

ranef(metafit)

labs <- paste("Center",c(1,10,11,2:9))
plot(metafit, y=labs)
```

`ipdlme-class` *Class for representing ipdlme objects*

Description

The `ipdlme` class represents the fit of a linear mixed-effects model of individual patient data meta-analysis of multiple parallel group clinical trials, based on aggregate data estimation methods.

Objects from the Class

Objects can be created by calls of the form `new("ipdlme", ...)` or via the function `ipdlme`.

Slots

The class `"ipdlme"` represents a linear mixed model to assess effect modification of multiple clinical trials and contains the slots:

`fixef`**:** The vector of the population effect estimates.

`ranef`**:** The matrix of the study-specific intercept and treatment random effects.

`vcov.fixef`**:** The variance-covariance matrix for inference with the population effects.

`vcov.ranef`**:** The variance-covariance matrix for inference with the study random effects.

`sigma2`**:** Estimate of the residual variance.

`VarCorr`**:** Covariance-variance matrix for bivariate normal random effects.

`convergence.trace`**:** A list of the values of each of the effects and variance components at each iteration in the maximization algorith.

converged: Logical value indicating whether the convergence criterion was met.

n.iter: The total number of iterations used in the optimization algorithm.

max.iter: The maximum number of iterations specified for the optimization algorithm.

tol: The tolerance level on which the termination rule for convergence is based.

df: The degrees of freedom of the model fit.

Methods

The following methods are extractors for the component that shares the method's name:

```
fixef signature(object = "ipdlme")
ranef signature(object = "ipdlme")
coef signature(object = "ipdlme")
vcov signature(object = "ipdlme")
Var signature(object = "ipdlme")
sigma2 signature(object = "ipdlme")
vcov.fixef signature(object = "ipdlme")
vcov.ranef signature(object = "ipdlme")
convergence signature(object = "ipdlme")
converged signature(object = "ipdlme")
n.iter signature(object = "ipdlme")
tol signature(object = "ipdlme")
max.iter signature(object = "ipdlme")
```

`print signature(x = "ipdlme")`: print information about the fitted model.

`show signature(object = "ipdlme")`: Same as the `print` method.

`confint signature(object = "ipdlme",parm, level = 0.95, ...)`Returns the specified confidence interval for all the population parameters.

`plot signature(x = "ipdlme",y,...)`: Displays a forest plot of the study intercept and treatment effects with the option of user-defined labels for the studies.

`summary signature(object = "ipdlme")`:Summary table of standard error and Wald tests for the population effects. A list of the study random effects and estimates of the variance components are also displayed.

See Also

ipdlme

Examples

```
data(regress_chol)

metafit <- ipdlme(n,Y,S2)

converged(metafit)

summary(metafit)

confint(metafit)
```

`ipdmeta` *Tools for subgroup analyses with multiple trial data using aggregate statistics*

Description

This package provides functions to estimate an IPD linear mixed effects model for a continuous outcome and any categorical covariate from study summary statistics. There are also functions for estimating the power of a treatment-covariate interaction test in an individual patient data meta-analysis from aggregate data.

Details

Package:	ipdmeta
Type:	Package
Version:	2.3
Date:	2012-11-06
License:	GPL 2
LazyLoad:	yes

Author(s)

Maintainer: Stephanie A. Kovalchik <kovalchiksa@nih.gov>

`MaxIter` *Extract the maximum number of iterations specified for an* `ipdlme` *object*

Description

Extract the maximum number of iterations specified for the fit of an IPD LME model.

Usage

```
MaxIter(object,...)
```

Arguments

object	object of the ipdlme class
...	additional arguments, currently not implemented

Value

Setting for the maximum possible iterations performed in fitting the IPD LME model.

See Also

ipdlme-class

Examples

```
data(regress_chol)

MaxIter(ipdlme(n, Y, S2))
```

---

n.iter *Extract the number of iterations for an* ipdlme *object*

Description

Extract the number of iterations for the fit of an IPD LME model.

Usage

```
n.iter(object)
```

Arguments

object	object of the ipdlme class

Value

Number of iterations of maximization alogrithm perfomed in fitting IPD LME model.

See Also

ipdlme-class

Examples

```
data(regress_chol)

n.iter(ipdlme(n, Y, S2))
```

`plot` *Forest plot of study random effects for an* `ipdlme` *object*

Description

Forest plot of the study random effects.

Usage

```
plot(x,y,...)
```

Arguments

`x`	object of the `ipdlme` class
`y`	vector of label names for studies. This will be used for labels along the y-axis.
`...`	additional arguments passed to `graphics` `plot` function

Value

Side-by-side forest plots with intercept effects on the left and treatment effects on the right.

See Also

`ipdlme-class`

Examples

```
data(regress_chol)

plot(ipdlme(n, Y, S2))
```

`poynard` *Meta-analysis data set for Poynard et al. review of beta-adrenergic-antagonist drugs*

Description

Meta-analytic dataset of 4 trials of Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices.

Dataset used to illustrate power estimator `ipd.sep`

Format

study	Name of trial
n0	Control group sample size
n1	Beta-adrenergic-antagonist group sample size
bleed0	Control group number of bleeding events at 2 year follow-up
bleed1	Beta-adrenergic-antagonist group number of bleeding events at 2 year follow-up
age0	Control group mean age
age1	Beta-adrenergic-antagonist group mean age
age.s20	Control group variance age
age.s21	Beta-adrenergic-antagonist group variance age
male0	Control group sample proportion male
male1	Beta-adrenergic-antagonist sample proportion male
drug	Beta-adrenergic-antagonist studied

Author(s)

S. Kovalchik <s.a.kovalchik@gmail.com>

References

Poynard, T, Cales, P, Pasta, L, Ideo, G, Pascal, J P, Pagliaro, L, Lebrec, D, (1991), Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. Franco-Italian Multicenter Study Group, *NEJM*, 324, 1532-8.

Qt *Measures of covariate heterogeneity*

Description

Measures of covariate heterogeneity proposed by Simmonds and Higgins (2007) for assessing the power of a meta-regression

Usage

```
Qt(m,n,sigma2)
```

Arguments

m	vector of study-level covariate means
n	vector of study sample sizes
sigma2	vector of covariate sample variances

Value

A list with the following named components: t, Qd, Qe, bar.Qd,bar.Qe, tilde.Qd, tilde.Qe

Author(s)

S. Kovalchik <s.a.kovalchik@gmail.com>

References

Simmonds, M. C., Higgins, J. P. T., (2007), Covariate heterogeneity in meta-analysis: criteria for deciding between meta-regression and individual patient data, *Statistics in Medicine*, 26 (15): 2982-99.

Examples

```
data(poynard)

#COVARIATE HETEROGENEITY FOR AGE

m <- (poynard$n0*poynard$age0+poynard$n1*poynard$age1)/(poynard$n0+poynard$n1)
n <- poynard$n0+poynard$n1
sigma2 <- ((poynard$n0-1)*poynard$age.s20+(poynard$n1-1)*poynard$age.s21)/(poynard$n0+poynard$n1-2)


Q <- Qt(m,n,sigma2)

lapply(Q,function(x){x/Q$t})
```

---

ranef *Extract the study random effects for an* ipdlme *object*

Description

Extract random effects estimates of the fit of an IPD LME model.

Usage

```
ranef(object,...)
```

Arguments

object	object of the ipdlme class
...	additional arguments, currently not implemented

Value

Numeric vector of the fitted random effects of an IPD LME model.

See Also

ipdlme-class

Examples

```
data(regress_chol)

ranef(ipdlme(n, Y, S2))
```

`regress_age` *Aggregated data set of REGRESS trial outcomes for IPD meta-analysis of treatment covariate effect*

Description

The data come from the Regression Growth Evaluation Statin Study (REGRESS) which was a double-blind, placebo-controlled multicenter study to assess the effects of 2 years of treatment with the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor pravastatin on progression and regression of coronary atherosclerosis in male patients with a serum cholesterol level between 4 and 8 mmol/L (155 and 310 mg/dL) by quantitative coronary arteriography. The primary end point of the trial was the average mean segment diameter per patient.

These data are used to demonstrate how a patient-level meta-analysis to estimate the effect modificaton of a categorical factor can be estimated from aggregate data. In this case centers of REGRESS are treated as trials and the categorical factor is baseline age (<50, 50-59, 60+).

Because the data are for demonstrative purposes only, observations have been permuted within treatment group and trial so that the summary statistics are not equivalent to the outcomes of the original study.

Format

The data are formatted as needed for use with `ipdlme`. Note that the treatment group columns of each data frame must be named `trt` and `ctrl`.

`Y`	List of trial specific data frames containing the mean outcome (change is mean segment diameter) within each
`n`	List of trial specific data frames containing the sample sizes of each treatment-age subgroup.
`S2`	Vector of trial sample variances in change in mean segment diameter.
`S2.subgroup`	List of trial specific data frames containing the sample variance of each treatment-age subgroup.

Author(s)

S. Kovalchik <s.a.kovalchik@gmail.com>

References

Jukema JW, Bruschke AVG, van Boven AJ, Reiber JHC, Bal ET, Zwinderman AH, et al. on behalf of the REGRESS Study Group Interuniversity Cardiology Institute Utrecht Netherlands. Effects of Lipid Lowering by Pravastatin on Progression and Regression of Coronary Artery Disease in Symptomatic Men With Normal to Moderately Elevated Serum Cholesterol Levels *Circulation.* 1995;91:2528-2540.

Examples

```
data(regress_age)

n[1:3]

Y[1:3]

S2[1:3]
```

`regress_chol` *Aggregated data set of REGRESS trial outcomes for IPD meta-analysis of treatment covariate effect*

Description

The data come from the Regression Growth Evaluation Statin Study (REGRESS) which was a double-blind, placebo-controlled multicenter study to assess the effects of 2 years of treatment with the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor pravastatin on progression and regression of coronary atherosclerosis in male patients with a serum cholesterol level between 4 and 8 mmol/L (155 and 310 mg/dL) by quantitative coronary arteriography. The primary end point of the trial was the average mean segment diameter per patient.

These data are used to demonstrate how a patient-level meta-analysis to estimate the effect modificaton of a categorical factor can be estimated from aggregate data. In this case centers of REGRESS are treated as trials and the categorical factor is baseline cholesterol (<=6 or 6+ mmol/L).

Because the data are for demonstrative purposes only, observations have been permuted within treatment group and trial so that the summary statistics are not equivalent to the outcomes of the original study.

Format

The data are formatted as needed for use with `ipdlme`. Note that the treatment group columns of each data frame must be named `trt` and `ctrl`.

`Y`	List of trial-specific data frames containing the mean outcome (change is mean segment diameter) within eacl
`n`	List of trial specific data frames containing the sample sizes of each treatment-cholesterol subgroup.
`S2`	Vector of trial sample variances in change in mean segment diameter.
`S2.subgroup`	List of trial specific data frames containing the sample variance of each treatment-cholesterol subgroup.

Author(s)

S. Kovalchik <s.a.kovalchik@gmail.com>

References

Jukema JW, Bruschke AVG, van Boven AJ, Reiber JHC, Bal ET, Zwinderman AH, et al. on behalf of the REGRESS Study Group Interuniversity Cardiology Institute Utrecht Netherlands. Effects of Lipid Lowering by Pravastatin on Progression and Regression of Coronary Artery Disease in Symptomatic Men With Normal to Moderately Elevated Serum Cholesterol Levels *Circulation.* 1995;91:2528-2540.

Examples

```
data(regress_chol)

n[1:3]

Y[1:3]

S2[1:3]
```

`sigma2` *Extract the estimated residual variance for an* `ipdlme` *object*

Description

Extract the estimated residual variance for the fit of an IPD LME model.

Usage

```
sigma2(object)
```

Arguments

`object`	object of the `ipdlme` class

Value

Numeric, maximum likelihood estimate for the residual variance of the fitted IPD LME model.

See Also

`ipdlme-class`

Examples

```
data(regress_chol)

sigma2(ipdlme(n, Y, S2))
```

tol *Extract the convergence criterion for an* ipdlme *object*

Description

Extract the convergence criterion for the fit of an IPD LME model.

Usage

```
tol(object)
```

Arguments

object	object of the ipdlme class

Value

Numeric convergence threshold for max percentage change in population and study effect estimates that must be met to declare convergence.

See Also

ipdlme-class

Examples

```
data(regress_chol)

tol(ipdlme(n, Y, S2))
```

Var *Extract the random effect variance parameters*

Description

Extract the estimates of study-level baseline and intercept variance parameters for the bivariate normal random effects of the IPD LME model.

Usage

```
Var(object)
```

Arguments

object	object of the ipdlme class

Value

The matrix of the two-by-two covariance-variance for the random effects.

See Also

ipdlme-class

Examples

```
data(regress_chol)

Var(ipdlme(n, Y, S2))
```

VcovFixef — *Extract the variance-covariance for the population (fixed effect) estimates for an* ipdlme *object*

Description

Extract the variance-covariance for the fixed effects estimates of the fit of an IPD LME model.

Usage

```
VcovFixef(object,...)
```

Arguments

object	object of the ipdlme class
...	additional arguments, currently not implemented

Value

Matrix of the variance-covariance for the fitted fixed effects of an IPD LME model.

See Also

ipdlme-class

Examples

```
data(regress_chol)

VcovFixef(ipdlme(n, Y, S2))
```

VcovRanef *Extract the variance-covariance matrix for study random effect estimates for an* ipdlme *object*

Description

Extract the variance-covariance for the estimated BLUPs for the study baseline and treatment terms for the fit of an IPD LME model.

Usage

```
VcovRanef(object,...)
```

Arguments

object	object of the ipdlme class
...	additional arguments, currently not implemented

Value

Matrix of the variance-covariance for the study randoms effects of an IPD LME model.

See Also

ipdlme-class

Examples

```
data(regress_chol)

VcovRanef(ipdlme(n, Y, S2))
```

Index