Package 'bcmixed'

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Type Package

Title Mixed Effect Model with the Box-Cox Transformation

Version 0.1.4

Description Inference on the marginal model of the mixed effect model with
the Box-Cox transformation and on the model median differences between
treatment groups for longitudinal randomized clinical trials. These
statistical methods are proposed by Maruo et al. (2017)
<doi:10.1002/sim.7279>.

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R topics documented:

aidscd4   *CD4 Cells Count Data in Aids Randomized Controlled Clinical Trial.*

Description

The data are from a randomized, double-blind study of acquired immune deficiency syndrome (AIDS) patients with advanced immune suppression (cluster of differentiation 4 (CD4) cells count of less than or equal to 50 cells/mm3) (Henry et al., 1998; Fitzmaurice et al., 2011). Patients in the AIDS Clinical Trial Group Study 193A were randomized to dual or triple combinations of human immunodeficiency virus-1 reverse transcriptase inhibitors. Specifically, patients were randomized to one of four daily regimens.

Format

A data frame with 4708 observations on the following 7 variables:

id patient identifier; in total there are 1177 patients.

weekc nominal visit variable (weeks 8, 16, 24, 32).

treatment allocated treatment regimens; 1 = zidovudine alternating monthly with 400mg didanosine, 2 = zidovudine plus 2.25mg of zalcitabine, 3 = zidovudine plus 400mg of didanosine, and 4 = zidovudine plus 400mg of didanosine plus 400mg of nevirapine.

age patients' age (years).

sex patients' sex (1 = male, 0 = female)

cd4.bl baseline value of CD4 cells count + 1.

cd4 CD4 cells count + 1.

Source

https://www.hsph.harvard.edu/fitzmaur/ala/

References

• Henry, K., Erice, A., Tierney, C., Balfour, H.H. Jr., Fischl, M.A., Kmack, A., Liou, S.H., Kenton, A., Hirsch, M.S., Phair, J., Martinez, A., Kahn, J.O., for the AIDS Clinical Trial Group 193A Study Team. (1998). A randomized, controlled, double-blind study comparing the survival benefit of four different reverse transcriptase inhibitor therapies (three-drug, two-drug, and alternating drug) for the treatment of advanced AIDS. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*, 19, 339-349, https://doi.org/10.1097/00042560-199812010-00004.

- Fitzmaurice, G.M., Laird, N.M., and Ware, J.H. (2011). *Applied Longitudinal Analysis 2nd ed.*, Wiley, New York, https://doi.org/10.1002/9781119513469.

Examples

```
data(aidscd4)
```

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bcmarg	*Marginal Model of the Mixed Effect Model with the Box-Cox Transformation.*

Description

`bcmarg` returns the inference results the parameters of the marginal model of the linear mixed effect model with the Box-Cox transformation proposed by Maruo et al. (2017). If time and id are not specified, inference results reduce to the results for the context of linear regression model provided by Maruo et al. (2015).

Usage

```
bcmarg(
  formula,
  data,
  time = NULL,
  id = NULL,
  structure = "UN",
  lmdint = c(-3, 3)
)
```

Arguments

formula	a two-sided linear formula object describing the model, with the response on the left of a ~ operator and the terms, separated by + operators, on the right.
data	a data frame containing the variables used in the model.
time	time variable name for repeated measurements. The default is NULL.
id	subject id variable name for repeated measurements. The default is NULL.
structure	specify the covariance structure from c("UN", "CS", "AR(1)"). The default is "UN".
lmdint	a vector containing the end-points of the interval to be searched for a transformation parameter. The default is c(-3, 3).

Value

an object of class "bcmarg". Objects of this class have methods for the generic functions coef, logLik, print, and summary. The object includes following components for the marginal model parameter inference:

lambda a numeric value of the estimate of the transformation parameter.

beta a vector with the estimates of the regression parameters.

alpha a vector with the estimates of the covariance parameters.

V variance-covariance matrix for any subject with no missing values.

betainf a matrix containing the inference results for beta under the assumption that lambda is known. Note that standard errors might be underestimated although statistical tests would be asymptotically valid.

Vtheta.mod model-based variance-covariance matrix for MLE of the vector of all parameters: c(lambda, beta, alpha).

Vtheta.rob robust variance-covariance matrix for MLE of the vector of all parameters.

logLik a numeric value of the maximized likelihood.

adj.prm a vector with parameters used for the empirical small sample adjustment in bcmmrm: c(number of subjects, number of completed subjects, number of outcome observations, number of missing observations).

glsObject an object of "gls" (or "lm" when time and id are not specified) containing results of gls (or lm) function on the transformed scale.

References

- Maruo, K., Isogawa, N., Gosho, M. (2015). Inference of median difference based on the Box-Cox model in randomized clinical trials. *Statistics in Medicine*, 34, 1634-1644, https://doi.org/10.1002/sim.6408.

- Maruo, K., Yamaguchi, Y., Noma, H., Gosho, M. (2017). Interpretable inference on the mixed effect model with the Box-Cox transformation. *Statistics in Medicine*, 36, 2420-2434, https://doi.org/10.1002/sim.7279.

See Also

bcmmrm gls

Examples

```
data(aidscd4)
bcmarg(cd4 ~ as.factor(treatment) * as.factor(weekc) + age,
       data = aidscd4, time = weekc, id = id, structure = "AR(1)")
```

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bcmixed | *bcmixed: A package for mixed effect models with the Box-Cox transformations.*

Description

The bcmixed package provides two categories of important functions: [bcmarg](#) and [bcmmrm](#). The [bcmarg](#) function provides inferences on the marginal model of the mixed effect model with the Box-Cox transformation and the [bcmmrm](#) provides inferences on the model median differences between treatment groups for longitudinal randomized clinical trials. These statistical methods are proposed by Maruo et al. (2017, <https://doi.org/10.1002/sim.7279>).

Details

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Author(s)

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bcmmrm | *Model Median Inference for Longitudinal Data in Randomized Clinical Trials.*

Description

`bcmmrm` provides inference results for the model median differences between treatment groups proposed by Maruo et al. (2017), which focuses on continuous and positive longitudinally observed outcomes and a situation where the efficacy of some treatments is compared based on a randomized, parallel group clinical trial. If `time` and `id` are not specified, inference results reduce to the results for the context of linear regression model provided by Maruo et al. (2015).

Usage

```
bcmmrm(
  outcome,
  group,
  data,
```

```
    time = NULL,
    id = NULL,
    covv = NULL,
    cfactor = NULL,
    structure = "UN",
    conf.level = 0.95,
    lmdint = c(-3, 3),
    glabel = NULL,
    tlabel = NULL
)
```

Arguments

outcome	a name of positive outcome (dependent) variable included in `data`.
group	a name of treatment group variable included in `data`.
data	a data frame that may include `outcome`, `group`, `time`, `id`, and specified covariate variables.
time	a name of time variable for repeated measurements included in `data`. The default is NULL.
id	a name of subject id variable for repeated measurements included in `data`. The default is NULL.
covv	a character vector with names of covariate variables included in `data`. The default is NULL.
cfactor	an integer vector including nominal variable indicators for covariate variables. Nominal variable: 1, continuous variable: 0. The default is NULL.
structure	specify the covariance structure from `c("UN", "CS","AR(1)")`. The default is `"UN"`.
conf.level	a numeric value of the confidence level for the confidence intervals. The default is 0.95.
lmdint	a vector containing the end-points of the interval to be searched for a transformation parameter. The default is `c(-3, 3)`.
glabel	a vector of length number of treatment groups containing the labels of `group` variable. The default is NULL and the levels of `group` variable in `data` are used.
tlabel	a vector of length number of repeated measures containing the labels of `time` variable. The default is NULL and the levels of `time` variable in `data` are used.

Value

an object of class `"bcmmrm"` representing the results of model median inference based on the Box-Cox transformed MMRM model. Generic functions such as `print`, `plot`, and `summary` have methods to show the results of the fit. See [bcmmrmObject](#) for the components of the fit.

Note

If baseline observation for the outcome variable is available, Box-Cox transformed baseline should be included as a covariate for accuracy of estimation.

Although this function can be applied to non-randomized trial data, performances of the above approach have not evaluated in context of non-randomized trials.

References

- Maruo, K., Isogawa, N., Gosho, M. (2015). Inference of median difference based on the Box-Cox model in randomized clinical trials. *Statistics in Medicine*, 34, 1634-1644, https://doi.org/10.1002/sim.6408.

- Maruo, K., Yamaguchi, Y., Noma, H., Gosho, M. (2017). Interpretable inference on the mixed effect model with the Box-Cox transformation. *Statistics in Medicine*, 36, 2420-2434, https://doi.org/10.1002/sim.7279.

See Also

bcmarg, bcmmrmObject

Examples

```
data(aidscd4)

# covariate: Box-Cox transformed baseline (continuous) and sex (nominal),
# covariance structure: AR(1) structure
# *Note: The UN structure is preferred although the AR(1)
#        structure is used in this example to reduce calculation time

# Box-Cox transformation for the baseline
aidscd4$cd4.bl.tr <- bct.v(aidscd4$cd4.bl)$transformed

# Median inference for each group and week
bcmmrm(outcome = cd4, group = treatment, data = aidscd4, time = weekc,
       id = id, covv = c("cd4.bl.tr", "sex"), cfactor = c(0, 1),
       structure = "AR(1)", glabel = c("Zid/Did", "Zid+Zal", "Zid+Did",
       "Zid+Did+Nev"))
```

---

bcmmrmObject   *Fitted bcmmrm Object*

Description

An object returned by the bcmmrm function, inheriting from class "bcmmrm" and representing the Box-Cox transformed MMRM analysis. Objects of this class have methods for the generic functions boxplot, coef, logLik, plot, print, and summary.

Value

The following components must be included in a legitimate "bcmmrm" object.

call a list containing an image of the bcmmrm call that produced the object.

median.mod, median.rob, median.mod.adj, median.rob.adj lists including inference results for
the model medians for all groups. Levels of the list are time points, where correspondence ta-
ble is given as time.tbl$code. mod: model-based inference, rob: robust inference, adj: with
empirical small sample adjustment.

meddif.mod, meddif.rob, meddif.mod.adj, meddif.rob.adj lists including inference results for
the for the model median differences between all pairs of groups (group1 - group0). Levels
of the list are time points, where correspondence table is given as time.tbl$code. mod:
model-based inference, rob: robust inference, adj: with empirical small sample adjustment.

lambda a numeric value of estimates of the transformation parameter.

R a correlation matrix for transformed outcomes.

betainf inference results for beta under the assumption that lambda is known. Note that standard
errors might be underestimated although statistical tests would be asymptotically valid.

time.tbl a data frame of a correspondence table for the timepoints.

group.tbl a data frame of a correspondence table for treatment groups.

inf.marg a list with results of [bcmarg](#) function.

outdata a data frame where the transformed outcome (ytr), the fitted values on the transformed
scale (ytr.fitted), and the residuals on the transformed scale (res.tr) are added to input
data.

conf.level a numeric value of the specified confidence level.

See Also

[bcmmrm](#)

---

  bcreg   *Linear regression model with the Box-Cox Transformation.*

Description

bcreg returns the maximum likelihood estimates for parameters of the linear regression models
with the Box-Cox transformation (Box and Cox, 1964).

Usage

```
bcreg(formula, data, lmdint = c(-3, 3))
```

Arguments

formula	a two-sided linear formula object describing the model, with the response on the left of a ~ operator and the terms, separated by + operators, on the right.
data	a data frame in which to interpret the variables named in the formula.
lmdint	a vector containing the end-points of the interval to be searched for a transformation parameter. Default is c(-3, 3).

Value

bcreg returns a list including following components:

lambda a numeric value with the estimate of the transformation parameter.

beta a vector with the estimates of the regression parameters.

sigma a numeric value with the estimate of the scale parameter.

betainf a data frame with inference results for beta under the assumption that lambda is known.

lik a numeric value with the maximized likelihood.

lmObject an object of "lm" containing the results of lm function on the transformed scale

References

Box, G.E.P. and Cox, D.R. (1964). An analysis of transformations (with discussion). *Journals of the Royal Statistical Society, Series B*, 26, 211-246, https://doi.org/10.1111/j.2517-6161.1964.tb00553.x.

See Also

lm

Examples

```
data(aidscd4)
#Transformation of baseline observation for aid.cd4 data
bcreg(cd4.bl ~ 1, aidscd4[aidscd4$weekc == 8, ])
```

---

bct	*Applying the Box-Cox Transformation.*

Description

bct returns the Box-Cox transformed numeric vector (Box and Cox, 1964).

Usage

```
bct(y, lambda)
```

Arguments

y	a positive real number vector.
lambda	a scalar transformation parameter.

Value

bct returns the Box-Cox transformed numeric vector, z = log(y) for lambda = 0, z = (y ^ lambda - 1) / lambda for lambda ne 1.

References

Box, G.E.P. and Cox, D.R. (1964). An analysis of transformations (with discussion). *Journals of the Royal Statistical Society, Series B*, 26, 211-246, https://doi.org/10.1111/j.2517-6161.1964.tb00553.x.

Examples

```
y <- exp(rnorm(10))
z <- bct(y, 0) #log transformation
```

---

  bct.v   *Applying the Box-Cox Transformation to a numeric vector.*

Description

bct.v returns the Box-Cox transformed numeric vector (Box and Cox, 1964).

Usage

```
bct.v(y, lmdint = c(-3, 3))
```

Arguments

y	a positive real number vector.
lmdint	a vector containing the end-points of the interval to be searched for a transformation parameter. Default is c(-3, 3).

Value

bct.v returns the Box-Cox transformed numeric vector and estimated transformation parameter.

transformed The Box-Cox transformed numeric vector.

lambda a numeric value of the estimate of the transformation parameter.

References

Box, G.E.P. and Cox, D.R. (1964). An analysis of transformations (with discussion). *Journals of the Royal Statistical Society, Series B*, 26, 211-246, `https://doi.org/10.1111/j.2517-6161.1964.tb00553.x`.

Examples

```
y <- exp(rnorm(50))
bct.v(y)
```

---

boxplot.bcmmrm   *Box-whisker plot for a bcmmrm Object.*

Description

Box-whisker plot for the transformed residuals of each treatment groups at a specified time point with error bar plot (mean +- SD) using `bcmmrmObject`.

Usage

```
## S3 method for class 'bcmmrm'
boxplot(
  x,
  timepoint = NULL,
  xlab = NULL,
  ylab = NULL,
  main = TRUE,
  sub = NULL,
  verbose = FALSE,
  ...
)
```

Arguments

x	an object inheriting from class "`bcmmrm`", representing the Box-Cox transformed MMRM analysis.
timepoint	an numeric value of a specified level of `time` variable. The default is `NULL` and the last level is specified.
xlab	a title for the x axis. The default is `NULL` and the name of `time` or `group` variable is used.
ylab	a title for the y axis. The default is `NULL` and the default title is "Transformed residuals".
main	a main title for the plot. The default is `TRUE` and default title is "Box-whisker plot for transformed residuals".
sub	a sub title for the plot. The default is `NULL`.

verbose   a logical optional value specifying to print the detailed plot information in the
                 console. The default is FALSE.

...   some methods for this generic require additional arguments.

Value

a box-whisker plot for transformed residual.

See Also

[bcmmrm](), [bcmmrmObject]()

Examples

```
data(aidscd4)
lmd.bl <- bcreg(cd4.bl ~ 1, data = aidscd4[aidscd4$weekc == 8, ])$lambda
aidscd4$cd4.bl.tr <- (aidscd4$cd4.bl ^ lmd.bl - 1) / lmd.bl
resar <- bcmmrm(outcome = cd4, group = treatment, data = aidscd4,
                time = weekc, id = id, covv = c("cd4.bl.tr", "sex"),
                cfactor = c(0, 1), structure = "AR(1)", glabel =
                c("Zid/Did", "Zid+Zal", "Zid+Did", "Zid+Did+Nev"))
boxplot(resar, xlab = "Treatment", col = 1:4)
```

---

plot.bcmmrm   *Plot a bcmmrm Object.*

Description

Plot for the model medians of each treatment groups with the 95 percent confidence intervals stored
in bcmmrmObject.

Usage

```
## S3 method for class 'bcmmrm'
plot(
  x,
  robust = TRUE,
  ssadjust = TRUE,
  dt = 1,
  timepoint = NULL,
  tnom = TRUE,
  xlab = NULL,
  ylab = NULL,
  xlim = NULL,
  ylim = NULL,
  lwd = 2,
  col = NULL,
  lty = NULL,
```

```
    main = TRUE,
    sub = NULL,
    legend = TRUE,
    loc = "topright",
    verbose = FALSE,
    ...
)
```

Arguments

x	an object inheriting from class "bcmmrm", representing the Box-Cox transformed MMRM analysis.
robust	an optional logical value used to specify whether to apply the robust inference. The default is TRUE.
ssadjust	an optional logical value used to specify whether to apply the empirical small sample adjustment. The default is TRUE.
dt	an numeric value indicating shift length between groups in the longitudinal median plot. A multiplying factor for the default settings specified (e.g. if 2 is specified, shift length is twice longer than that for the default setting). The default is 1.
timepoint	an numeric value of a specified level of time variable at which median plot is created. When timepoint is NULL and number of time points is not 1, longitudinal median plot (x axis is time) is created. Otherwise, median plot where x axis is group is created. The default is NULL.
tnom	a optional logical value indicating the scale of x axis of the longitudinal median plot. When tnom is TRUE, nominal scale is used and widths between any combinations of neighbor time points are same. When tnom is FALSE, actual scale of time variable is used. The default is TRUE.
xlab	a title for the x axis. The default is NULL and the name of time or group variable is used.
ylab	a title for the y axis. The default is NULL and the name of outcome variable is used.
xlim	a numeric vector with length of 2 indicating limits of x axis. The default is NULL and limits are calculated automatically.
ylim	a numeric vector with length of 2 indicating limits of y axis. The default is NULL and limits are calculated automatically.
lwd	an optional positive numeric value indicating line width. The default is 2.
col	an integer or a character vector with length of the number of groups indicating colors of lines for each treatment group. The default is NULL and all of colors are black.
lty	an optional integer or a character vector with length of the number of groups indicating line types of lines for each treatment group. The default is NULL and 1:ng is used, where ng is number of groups.
main	a main title for the plot. The default is TRUE and default title is "(Longitudinal) Plot for median of each group".

sub	a sub title for the plot. The default is NULL.
legend	a logical optional value specifying to add legends to plots. When legend is TRUE legends are added to the plot. Otherwise, legends are not added. The default is TRUE.
loc	a character value indicating the location of the legends. The location can be specified by setting loc to a single keyword from the list "bottomright", "bottom", "bottomleft", "left", "topleft", "top", "topright", "right", and "center". The default is "topright".
verbose	a logical optional value specifying to print the detailed analysis information in the console. The default is FALSE.
...	some methods for this generic require additional arguments.

Value

a median plot.

See Also

[bcmmrm](#), [bcmmrmObject](#)

Examples

```
data(aidscd4)
resar <- bcmmrm(outcome = cd4, group = treatment, data = aidscd4,
                time = weekc, id = id, structure = "AR(1)", glabel =
                c("Zid/Did", "Zid+Zal", "Zid+Did", "Zid+Did+Nev"))
plot(resar, xlab = "Week", ylab = "CD4+1", col = 1:4, main = NULL)
plot(resar, timepoint = 32, xlab = "Treatment", ylab = "CD4+1")
```

---

summary.bcmmrm   *Summarize a bcmmrm Object.*

Description

Additional information about the Box-Cox transformed MMRM analysis represented by object is extracted and included as components of object.

Usage

```
## S3 method for class 'bcmmrm'
summary(object, robust = TRUE, ssadjust = TRUE, ...)
```

Arguments

object	an object inheriting from class "bcmmrm", representing the Box-Cox transformed MMRM analysis.
robust	an optional logical value used to specify whether to apply the robust inference. The default is TRUE.
ssadjust	an optional logical value used to specify whether to apply the empirical small sample adjustment. The default is TRUE.
...	some methods for this generic require additional arguments. None are used in this method.

Value

an object inheriting from class summary.bcmmrm with all components included in object (see [glsObject](#) for a full description of the components) plus the following components:

median a list including inference results of the model median for specified values of robust and ssadjust.

meddif a list including inference results of the model median difference for specified values of robust and ssadjust.

robust a specified value of robust.

ssadjust a specified value of ssadjust.

See Also

[bcmmrm](#), [bcmmrmObject](#), [summary](#)

Examples

```
data(aidscd4)
resar <- bcmarg(cd4 ~ as.factor(treatment), aidscd4, weekc, id, "AR(1)")
summary(resar)
```

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