Package 'COVID'

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Title Evaluating Treatment Efficacy in Hospitalized Covid-19 Patients

Version 1.0

Description Implements the two robust methods described in Lin et al. (2022) to assess the totality of evidence for the treatment effects on the entire clinical course of a patient. The first method specifies marginal proportional hazards models for the time to each level of improvement or deterioration from the clinical status at enrollment. The second method specifies marginal proportional odds models for the clinical status of each day. The two methods are implemented via ph() and po(), respectively.

License GPL-2

Encoding UTF-8

Suggests rmarkdown

VignetteBuilder utils, knitr

RoxygenNote 7.2.1

Imports Rcpp (>= 0.11.0), RcppArmadillo, ggplot2, survival, dplyr, methods, stats

LinkingTo Rcpp, RcppArmadillo

NeedsCompilation yes

Author Jianqiao Wang [aut, cre], Yu Gu [aut]

Maintainer Jianqiao Wang <jianqiao@live.unc.edu>

Collate 'RcppExports.R' 'acttData.R' 'cox_wlw.R' 'imputation.R' 'outcome.R' 'proportional.hazards.modelling.R' 'proportional.odds.modelling.R'

Depends R (>= 3.5.0)

R topics documented:

acttData *Toy Dataset For Illustration*

Description

This data set is provided to illustrate the use of the software. It is a randomly scrambled subset of the actual ACTT-1 trial data.

Usage

```
data(acttData)
```

Format

acttData is a data.frame containing 500 subjects who were followed for up to 29 days. The data.frame contains 8 columns,

subject_id Subject ID.

treatment_arm A binary indicator of treatment arm (0: placebo; 1: remdesivir).

initial_status The initial clinical status at randomization, can be 4, 5, 6, or 7.

clinical_status The clinical status at each examination, can be 1, 2, ..., 8.

examination_time The examination times in days.

baseline_severity The baseline disease severity, Mild-Moderate Disease or Severe Disease.

age Age in years.

sex A binary indicator of sex (F/M).

outcome *Specify Outcome Variables*

Description

This function is used to specify the examination time and the clinical status in the model statement of `ph()` and `po()`.

Usage

```
outcome(examination.time, clinical.status)
```

Arguments

`examination.time`
: The variable for the time when the subject is examined for clinical status. NA if missing.

`clinical.status`
: The variable for the clinical status at each examination. Must be integer and take values among 1, 2, ..., K, where K is the total number of categories. NA if missing.

Value

This function is intended to be used only in the model statement of ph() and po(). The result, a matrix, is used internally.

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ph *Treatment Effects on Changes of Clinical Status Over Time*

Description

Different levels of improvement or deterioration from the clinical status at randomization are viewed as multiple events. Treatment effect on each event is formulated through a Cox proportional hazards model, stratified by the initial status. The covariance matrix of all the estimated treatment effects is estimated using the Wei, Lin and Weissfeld (1989) method. Z-scores are used or combined to test various null hypotheses, including no treatment effect on a particular event, no treatment effect on any improvement or deterioration, and no overall benefits.

Usage

```
ph(formula, data, subject, treatment, init.status, nmin = 5)
```

Arguments

`formula`	A formula object, with all of the outcome variables on the left hand side of a ~ operator and the treatment and covariates on the right. The outcome variables must be specified through the `outcome()` function. See `?outcome` and Details for further information.
`data`	A data.frame object. The data.frame in which to interpret the variable names in formula. Must contain the subject ID, the treatment arm, the initial status, the examination time, the clinical status measured at each examination, and any covariates. See Details.
`subject`	A character string. Name of the variable in data which identifies multiple rows from the same subject.
`treatment`	A character string. Name of the variable in data that corresponds to treatment arm.
`init.status`	A character string. Name of the variable in data that corresponds to initial status.
`nmin`	A positive integer object. The minimum number of cases for an event to be taken into account. Any event with fewer cases than this number will not be modelled. The default value is 5.

Details

The information required for an analysis is

Subject ID: The variable used to identify subjects.

Treatment arm: The binary indicator of the treatment arm, 1 for the treatment group and 0 for the placebo group.

Initial Status: The clinical status at randomization. NA if missing.

Examination Time: The times when the subject is examined for clinical status. NA if missing.

Clinical Status: The clinical status of the subject at each examination. NA if missing.

Covariates: Baseline covariates.

The input data should be in the long format, i.e., each row pertains to one examination of one subject. The subject ID can be numeric or character. The treatment arm must be 0/1, with 0 and 1 representing the placebo and the treatment arms, respectively. The examination time must be non-negative integer. The clinical status must be integer, with values 1, 2, ..., K, where K is the total number of categories. The larger the status, the worse the clinical outcome. The covariates can include categorical variables, for which all other categories are compared to the first category. A model without covariates is also allowed.

The general structure of the formula input is

```
outcome(examination_time, clinical_status) ~ treatment_arm + covariates
```

The left-hand side contains the information about the examination time and the corresponding clinical status. It must be specified through function `outcome()`. Specifically,

```
outcome(examination_time, clinical_status)
```

Value

A matrix containing the estimated hazard ratio for each level of improvement or deterioration from the clinical status at enrollment, the estimate of a common hazard ratio for any level of improvement, the estimate of a common hazard ratio for any level of deterioration, and the estimate of a common hazard ratio summarizing the overall treatment benefit, together with the 95% confidence interval and the two-sided p-value for testing no treatment effect on each of the endpoints.

References

Lin DY, Wang J, Gu Y, Zeng D (2022). Evaluating Treatment Efficacy in Hospitalized Covid-19 Patients. Submitted.

Wei LJ, Lin DY, Weissfeld L (1989). Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. J Am Stat Ass, 84: 1065-1073.

Examples

```
data(acttData)
model <- outcome(examination_time, clinical_status) ~ treatment_arm + baseline_severity
ph(formula = model,
   data = acttData,
   subject = "subject_id",
   treatment = "treatment_arm",
   init.status = "initial_status")
```

po *Treatment Effects on Odds Ratio of Lower Severity over Time*

Description

Treatment effect on the clinical status is characterized by the odds ratio of lower severity under a series of proportional odds models. The overall treatment effect over a time window is captured by a common odds ratio of lower severity over time. A piecewise log-linear odds ratio of lower severity over time can be estimated. Missing values can be imputed internally by carrying the last observation forward.

Usage

```
po(
  formula,
  data,
  subject,
  treatment,
  imputation = F,
  common.odds.ratio = T,
  piecewise.linear = T,
  intercept = T,
  knots = NULL,
 control.ngd = list(learning.rate = 0.1, max.iter = 1000, eps = 1e-06, messages = F),
  start.time = NULL,
  end.time = NULL,
  imputed.score = 7
)
```

Arguments

formula	A formula object, with all of the outcome variables on the left hand side of a ~ operator and the treatment and covariates on the right. The outcome variables must be specified through the outcome() function. See ?outcome and ?ph for further information.
data	A data.frame object. The data.frame in which to interpret the variable names in formula. Must contain the subject ID, the treatment arm, the examination time, the clinical status measured at each examination, and any covariates. The clinical status must contain at least two categories at each examination time. See ?ph for further information.
subject	A character string. Name of the variable in data which identifies multiple rows from the same subject.
treatment	A character string. Name of the variable in data that corresponds to treatment arm.
imputation	Logical. Whether the input data is imputed by carrying the last observation forward. The default value if FALSE.
common.odds.ratio	Logical. Whether the common odds ratio of lower severity over time for treatment versus placebo is estimated. The default value is TRUE.

`piecewise.linear`
: Logical. Whether a piecewise log-linear odds ratio of lower severity over time is estimated and whether daily odds ratios of lower severity are estimated by separate proportional odds models. The default value is TRUE. See Details for further information.

`intercept`
: Logical. Whether intercept is included for the piecewise linear function while assuming a piecewise log-linear odds ratio over time. The default value is TRUE. See Details for further information.

`knots`
: An integer vector or NULL, The potential change points in days of the piecewise log-linear odds ratio. See Details for further information. If NULL, the function will set change points at the start of every week.

`control.ngd`
: List, with hyperparameters for natual gradient ascent algorithm. See Details for further information.

`start.time`
: Non-negative integer or `NULL`. The first examination day included in the analysis. If NULL, the first examination day is day 1 for estimating the common odds ratio and day 0 for estimating the piecewise log-linear odds ratio.

`end.time`
: Non-negative integer or `NULL`. The last examination day included in the analysis. If NULL, the last examination day is day 28 for estimating the common odds ratio and the piecewise log-linear odds ratio.

`imputed.score`
: Integer. The clinical status used for imputation when there are no measurements for a subject. The default value is 7.

Details

The piecewise linear function for the log odds raio is determined by the `intercept` and `knots`. If the intercept is excluded from the piecewise linear function, the model assumes no treatment effect on the odds ratio of lower severity at examination time zero. The knots are the change points in the piecewise linear function. For example, if we assume the treatment effect on log odds ratio of lower severity has change points at examination time 0, 8, 15, 21, the input argument should be `knots = c(0,8,15,21)`.

We use natural gradient ascent algorithm to maximize the log likelihood function of the proportional odds model. The natural gradient ascent algorithm has four hyperparameters

- `learning.rate` determines the step size for natural gradient ascent algorithm. Must be numeric. The default value is 0.1.
- `max.iter` is the maximum number of iterations for natural gradient ascent algorithm. Must be integer. The default value is 1000.
- `eps` is the convergence threshold for natural gradient ascent algorithm. Must be numeric. The default value is `1e-6`.
- `messages` decides whether to print out the coefficient estimates and log likelihood during optimization. Must be logical. The default value is `FALSE`.

Value

A list object with the following elements:

`common.odds.ratio`
: A list object contains common odds ratio estimate of lower severity over time for treatment versus placebo and its 95% confidence interval.

`piecewise.linear`
: A list object contains change points, coefficient estimates, and covariance matrix estimates for piecewise linear model. It also contains a plot showing the estimated piecewise log-linear odds ratios and daily odds ratios, with corresponding 95% confidence intervals.

`separate`
: A data.frame object contains the estimated daily odds ratios of lower severity for treatment versus placebo, together with corresponding 95% confidence intervals, under separate proportional odds models.

References

Lin DY, Wang J, Gu Y, Zeng D (2022). Evaluating Treatment Efficacy in Hospitalized Covid-19 Patients. Submitted.

Examples

```
data(acttData)
model <- outcome(examination_time, clinical_status) ~ treatment_arm + baseline_severity
po(formula = model,
   data = acttData,
   subject = 'subject_id',
   treatment = 'treatment_arm',
   imputation = T,
   knots = c(0, 8, 13, 17, 24),
   start.time = 1,
   end.time = 28)
```

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