Package 'cox.rvph'

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Type Package

Title Remedy the Violation of the Proportional Hazards Assumption in Cox Proportional Hazards Models

Version 0.1.4

Description Remedying proportional hazards assumption violations of a Cox proportional hazards model using stepwise changepoint and time-varying coefficient methods based on Cox (1972) <doi:10.1111/j.2517-6161.1972.tb00899.x> and Klein and Moeschberger (1997) <doi:10.1007/978-1-4757-2728-9>.

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Encoding UTF-8

RoxygenNote 7.3.3

Imports survival

Suggests KMsurv

NeedsCompilation no

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cox.rvph *cox.rvph (Remedy for Violations of the Proportional Hazards Assumption in Cox Proportional Hazards Models)*

Description

Stepwise or time-varying remedies for proportional hazards assumption violations in Cox Proportional Hazards Models

Usage

```
cox.rvph(
  data,
  time,
  event,
  covariate,
  adjust_vars = NULL,
  method = c("step", "timev"),
  g_candidates = NULL,
  max_K = 4,
  p_threshold = 0.05,
  verbose = TRUE
)
```

Arguments

data	a data frame
time	the survival time variable
event	event indicator variable coded as 0 = right-censored and 1 = event
covariate	covariate that violates the proportional hazards assumption
adjust_vars	the variables to be included as adjustment covariates
method	the method to be applied ("step" or "timev")
g_candidates	a list of candidate time functions used in the time-varying coefficient method. If NULL, a default set of candidate functions (linear, log, sqrt, quadratic, inverse, and scaled) is used. Users may also supply custom transformation functions. If supplied, the user-provided functions replace the default candidate set.
max_K	maximum number of segments
p_threshold	threshold for PH test
verbose	logical; whether to print progress messages

Details

The event indicator specified by `event` must be binary, with 0 indicating a right-censored observation and 1 indicating that the event of interest occurred. Other event codings must be recoded before using `cox.rvph()`.

Additionally, users should verify that the survival time variable does not contain negative values. For the `step` method, observations with a survival time of 0 should be handled using an appropriate preprocessing strategy based on the scientific context. For the `timev` method, the specified time-transformation functions should be defined over the observed range of survival times.

Users should first assess the proportional hazards (PH) assumption using `cox.zph()` before applying `cox.rvph()`. Variables showing evidence of non-proportional hazards may then be modeled using stepwise or time-varying remedies.

Currently, only a single continuous variable can be specified in `covariate`. Categorical variables may still be included in `adjust_vars` as adjustment covariates.

The `step` method performs segmented modeling by searching for optimal cut points in time by maximizing the partial likelihood. The selected cut points are incorporated into the Cox model through time-dependent interval-specific covariates using the counting-process formulation. If the resulting model satisfies the PH assumption with relatively few cut points, hazard ratios (HRs) may be interpreted within each estimated time interval.

However, if many cut points are required or PH violations persist, a smooth time-varying effect may be more appropriate. In such cases, the `timev` method compares the base Cox model with time-varying coefficient models based on several candidate time-transformation functions using AIC, and selects the model with the smallest AIC. By default, the following candidate functions are evaluated: linear (t), log ($\log(t+1)$), sqrt ($\sqrt{t}$), quadratic (t^2), inverse ($1/(t+1)$), and scaled ($t/\max(t)$). Users may alternatively provide their own candidate functions through the `g_candidates` argument.

For the selected time-varying model, the hazard ratio at time t is given by:

$$HR(t) = \exp(\beta + \gamma g(t))$$

where β is the coefficient of the covariate and γ represents the time-varying interaction effect. Users may evaluate this expression at clinically relevant time points to interpret how the hazard ratio changes over time.

Example output (method: step):

```
$K
[1] 2

$tau
[1] 24.8

$p_value

[1] 0.2529169

$zph
                chisq df    p
```

```
covariate_seg1 0.0813  1 0.78
covariate_seg2 3.8528  1 0.05
variable       0.3214  1 0.57
GLOBAL         4.0804  3 0.25

$fit
Call:
survival::coxph(formula = as.formula(f_str_final), data = final_data)

                   coef exp(coef) se(coef)      z        p
covariate_seg1  0.27052   1.31065  0.07944  3.405 0.000661
covariate_seg2  0.05550   1.05707  0.09677  0.574 0.566284
.
.
```

Interpretation (method: step):

For the `step` method, hazard ratios are interpreted separately within each estimated time interval.

```
covariate_seg1  HR = 1.31
covariate_seg2  HR = 1.06
```

If the estimated cut point is $\tau = 24.8$, this indicates that the hazard ratio associated with a one-unit increase in age is approximately 1.31 before time 24.8 and decreases to approximately 1.06 after time 24.8.

Example output (method: timev):

```
$selected_g
[1] "sqrt"

$AIC
    base    linear       log      sqrt quadratic   inverse    scaled
30935.70  30917.65  30923.49  30916.70  30922.30  30935.77  30917.65

$fit
Call:
survival::coxph(formula = as.formula(f_str), data = data, tt = tt_fun)

                     coef exp(coef)  se(coef)      z        p
covariate       0.0737807 1.0765707 0.0057407 12.852  < 2e-16
tt(covariate)   0.0005973 1.0005974 0.0001298  4.602 4.19e-06
variable        0.1640114 1.1782278 0.0194412  8.436  < 2e-16
.
.
```

Interpretation (method: timev):

For the `timev` method, hazard ratios vary continuously over time.

Example model:

$$HR(t) = \exp(0.0737807 + 0.0005973 \times \sqrt{t})$$

In this example, the square-root time transformation indicates that the hazard ratio changes continuously over time. Users may substitute clinically meaningful values of t to estimate hazard ratios at specific time points.

Value

a list containing the fitted model and related results

Examples

```
if (requireNamespace("KMsurv", quietly = TRUE)) {
  data(psych, package = "KMsurv")

  psych$sex <- factor(psych$sex)

  cox.rvph(
    data = psych,
    time = "time",
    event = "death",
    covariate = "age",
    adjust_vars = "sex",
    method = "step"
  )
}

## Not run:

  data(flchain, package = "survival")

  cox.rvph(
    data = flchain,
    time = "futime",
    event = "death",
    covariate = "age",
    adjust_vars = c("lambda", "flc.grp", "creatinine"),
    method = "timev"
  )

## End(Not run)
```

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