Package 'cox.rvph'

July 17, 2026

Type Package

Title Remedy the Violation of the Proportional Hazards Assumption of Cox Regression

Version 0.1.3

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 Grambsch and Therneau (1994) <doi:10.1093/biomet/81.3.515>.

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Encoding UTF-8

RoxygenNote 7.3.3

Imports survival

Suggests KMsurv

NeedsCompilation no

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Repository CRAN

Date/Publication 2026-07-17 12:40:08 UTC

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`cox.rvph` *cox.rvph (Remedy for Violations of the Proportional Hazards Assumption of Cox regression)*

Description

Stepwise or time-varying remedies for proportional hazards assumption violations of a cox regression model

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`	dataset
`time`	time variable
`event`	event indicator
`covariate`	covariate that violates the proportional hazards assumption
`adjust_vars`	optional adjustment variables
`method`	"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

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 continuous variables 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 fits several candidate time-transformation functions $g(t)$ 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 baseline coefficient 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
1519.300  1508.827  1508.895  1507.789  1512.190  1516.242  1508.827

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

                   coef exp(coef)  se(coef)      z        p
covariate      0.693216  2.000137  0.132824  5.219 1.80e-07
tt(covariate) -0.013456  0.986634  0.003959 -3.399 0.000677
variable       0.118716  1.126050  0.012860  9.231  < 2e-16
.
.
```

Interpretation (method: timev):

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

Example model:

$$HR(t) = \exp(0.693 - 0.013\sqrt{t})$$

This indicates that the hazard ratio decreases gradually over time. Users may substitute clinically meaningful values of t to estimate hazard ratios at specific time points.

Value

list containing model 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"
  )
}

if (requireNamespace("survival", quietly = TRUE)) {

  data(pbc, package = "survival")

  pbc$event <- ifelse(pbc$status == 2, 1, 0)
  pbc <- na.omit(pbc[, c("time","event","bili","albumin","protime","age")])

  cox.rvph(
    data = pbc,
    time = "time",
    event = "event",
    covariate = "protime",
    adjust_vars = c("bili","albumin","age"),
    method = "timev"
  )
}
```

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