# Package 'coxinterval'

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Title Cox-Type Models for Interval-Censored Data Version 1.2 Date 2015-04-30 Author Audrey Boruvka and Richard J. Cook Maintainer Audrey Boruvka <audrey.boruvka@gmail.com> Description Fits Cox-type models based on interval-censored data from a survival or illness-death process. SystemRequirements GNU make **Depends** R (>= 2.15.2), survival, timereg Imports Matrix LazyData yes LazyLoad yes NeedsCompilation yes **License** GPL ( $\geq 2$ ) URL https://github.com/aboruvka/coxinterval BugReports https://github.com/aboruvka/coxinterval/issues **Repository** CRAN Date/Publication 2015-05-02 14:14:36

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const2lin

Accumulate values from a piecewise constant function of time

## Description

A utility function for coxdual that integrates values from a piecewise constant function of time.

## Usage

const2lin(const, time = "time", stratum = NULL)

## Arguments

const	a matrix whose columns give the (possibly multivariate) piecewise constant function values, corresponding time points and strata.
time	an integer or character value indicating the column index or name of the time variable in the matrix const. Defaults to "time".
stratum	integer or character value for the column index or name of the stratifying variable in the matrix const. If stratum is NULL (default), const is presumed unstratified.

## Value

A matrix of the same dimension as const.

## See Also

lin2const

cosmesis

#### Description

Interval-censored times to cosmetic deterioration for breast cancer patients undergoing radiation or radiation plus chemotherapy.

## Usage

data(cosmesis)

#### Format

A data frame with 94 observations on the following 3 variables.

left left endpoint of the censoring interval in months

right right endpoint of the censoring interval in months

treat a factor with levels RT and RCT representing radiotherapy-only and radiation plus chemotherapy treatments, respectively

#### Source

Finkelstein, D. M. and Wolfe, R. A. (1985) A semiparametric model for regression analysis of interval-censored failure time data. *Biometrics* **41**, 933–945.

#### References

Finkelstein, D. M. (1986) A proportional hazards model for interval-censored failure time data. *Biometrics* **42**, 845–854.

## Examples

data(cosmesis)

coxaalen

Cox-Aalen model for interval-censored survival data

## Description

Fit a Cox-Aalen model to interval-censored survival data with fixed covariates.

## Usage

#### Arguments

formula	an expression of the form response $\sim$ terms, where response is an object returned by the Surv function and terms contains at least one multiplicative term identified by the prop function from the <b>timereg</b> package.
data	an optional data frame in which to interpret the variables named in the arguments formula and formula.timereg.
subset	expression specifying which rows of data should be used in the fit. All observations are included by default.
init	a list with elements named coef and basehaz. The coef element should be a scalar or vector specifying the initial values of the multiplicative regression coefficient. If init = NULL or coef = NULL, this coefficient will be initialized to zero. The element basehaz should be a matrix or data frame whose columns represent time and the corresponding value for the cumulative baseline hazard function and any remaining additive cumulative coefficients. Initial values are obtained by linear interpolation or extrapolation at observation times relevant in the data. If init = NULL or basehaz = NULL, the cumulative baseline hazard function is initialized to a linear function of time and any cumulative coefficients are started at zero.
formula.timereg	5
	an optional formula object specifying a model to fit with the <b>timereg</b> package's cox.aalen function using right-censored observations. Here the shorthand $\sim$ .refers to the same terms given in formula. Multiple formula objects can be provided as a list.
init.timereg	a logical value indicating that init should be overrided by estimates based on the cox.aalen fit to the first model in formula.timereg.
control	a named list of parameters controlling the model fit, as returned by the function coxaalen.control. This defaults to coxaalen.control().
	additional arguments to be passed to coxaalen.control.

#### Details

A valid response in the formula argument can be expressed as

```
Surv(<left>, <right>, type = "interval2")
```

where (<left>, <right>] is the censoring interval for the survival time. Following the **survival** package's type = "interval2" censoring for the Surv function, we use the convention that any right-censoring times are provided in the variable <left> and <right> is set to the NA value.

Terms in formula have either time-varying additive effects on the survival hazard as in Aalen's additive regression model, or fixed multiplicative effects as in the Cox model. Multiplicative terms are distinguished by applying **timereg**'s prop function to each corresponding variable.

coxaalen depends on libraries that are loaded only if coxinterval is installed from source on a system with IBM ILOG CPLEX Optimization Studio. Refer to the package's INSTALL file for detailed instructions.

## coxaalen

## Value

An object of the class "coxinterval" and "coxaalen", which is a list with the following components.

call	the matched call to coxaalen.
n	size of the sample used in the model fit.
р	number of (multiplicative) regression coefficients.
coef	a named p vector of regression coefficients.
var	a named p by p covariance matrix of the regression coefficients.
basehaz	a data frame giving the cumulative regression functions evaluated at time points given by the right endpoints of the maximal intersections among the censoring intervals.
init	list of initial values used in the model fit.
loglik	a vector giving the log-likelihood at initiation and each iteration.
iter	number of iterations needed to meet the stopping criteria.
maxnorm	the maximum norm of the difference between the penultimate and final parameter values.
gradnorm	the inner product between the final parameter value and the score function.
cputime	the processing time for parameter and variance estimation.
fit.timereg	the cox.aalen fit to any models specified by the formula.timereg argument. If formula.timereg is a list of formula objects, fit.timereg is an unnamed list following the same order.
na.action	the "na.action" attribute of the model frame.
censor.rate	a vector giving the rates of exact, left-censored, interval-censored and right- censored observations used in the model fit.
control	a named list of arguments passed to coxaalen.control.
data	a list containing the maximal intersections among the censoring intervals and model matrices for the multiplicative and additive terms in formula. This component is returned only if the coxaalen.control argument data is true.

#### References

Boruvka, A. and Cook, R. J. (2015) A Cox-Aalen model for interval-censored data. *Scandinavian Journal of Statistics* **42**, 414–426.

Martinussen, T. and Scheike, T. H. (2006) Dynamic Regression Models for Survival Data. New York: Springer.

Scheike, T. H. and Zhang, M.-J. (2002) An additive-multiplicative Cox-Aalen regression model. *Scandinavian Journal of Statistics* **29**, 75–88.

## See Also

cox.aalen, prop, Surv

## Examples

coxaalen.control Control a Cox-Aalen model fit

## Description

Set parameters controlling the model fit returned by coxaalen.

#### Usage

## Arguments

eps	threshold value for the norm used to measure convergence in the parameter estimates.
eps.norm	a character string identifying the norm to use in the convergence criteria— either the maximum norm between the current and previous parameter values (eps.norm = "max") or the absolute inner product between the current value and the score (eps.norm = "grad").
iter.max	maximum number of iterations to attempt. This ensures that coxaalen will eventually exit, even when the convergence criteria is not met. A warning is issued whenever the estimation routine has stopped before converging on a final parameter value.
armijo	a scale factor in (0, 1/2) for Armijo's (1966) rule—a line search used to ensure that each iteration achieves an adequate increase in the log-likelihood. The model fit is typically not very sensitive to this value.
var.coef	a logical value indicating that standard errors for the multiplicative regression coefficients should be estimated. This is done via profile likelihood—an ap- proach that can require an inordinate amount of processing time under many regression coefficients and larger sample size.
coef.typ	a scalar or vector of typical (absolute) values for the multiplicative regression coefficient.

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#### coxdual

coef.max	a scalar or vector of probable upper bounds for the multiplicative regression coefficient. This and the coef.typ arguments tune variance estimation via the curvature in the profile log-likelihood.
trace	a logical value indicating that CPLEX should print its results to the screen.
thread.max	maximum number of CPU threads to allocate to CPLEX. The default value disables multithreading. A value of zero allows CPLEX to set the number of threads automatically. The actual number of threads used is limited by the number of available processors and the CPLEX license.
data	a logical value indicating that the object returned by coxaalen should contain an element data that gives the maximal intersections and the model matrix split into multiplicative and additive terms.

#### Value

A list of the above arguments with their final values.

#### References

Boruvka, A. and Cook, R. J. (2015) A Cox-Aalen model for interval-censored data. *Scandinavian Journal of Statistics* **42**, 414–426.

Armijo, L. (1966) Minimization of functions having Lipschitz continuous first partial derivatives. *Pacific Journal of Mathematics* **16**, 1–3.

#### See Also

coxaalen

#### Examples

coxdual

Cox model for a Markov illness-death process under dual censoring

#### Description

Fit a Cox model to a progressive Markov illness-death process observed under right-censored survival times and interval- or right-censored progression times.

#### Usage

#### Arguments

formula	an expression of the form response $\sim$ terms, where response is anobject returned by the Surv function and terms contain clustering and state-transition variables identified by the cluster and trans functions, respectively.
data	an optional data frame in which to interpret the variables named in the arguments formula and formula.coxph.
subset	expression specifying which rows of data should be used in the fit. All observations are included by default.
init	a named list of the vector coef, specifying the initial coefficient values, and ma- trix or data frame basehaz, used to the initialize the cumulative baseline transi- tion intensities. The basehaz element should contain columns representing the cumulative transition intensity, time and transition type. If the columns do not appear in this order, they should be indicated by the column names "hazard", "time" and "trans", respectively. The sorted values used to represent the tran- sition types should respectively denote the initial to intermediate, initial to ter- minal, and intermediate to terminal state transitions. The NULL value for init or its components enables default values. For coef the default is zero. For basehaz the default corresponds to linear functions of time with an upper bound of one. Under any alternatives arising from this or the init.coxph arguments, basehaz is interpreted as a step function of time and the initial value is its piecewise linear approximation.
formula.coxph	an optional formula specifying a model to fit with coxph using singly right- censored observations. The shorthand ~ . indicates the same terms given in formula, with the function strata in place by trans. Under dual right cen- soring and init.coxph = TRUE, formula.coxph defaults to same model in formula, which is fit to observations singly-right-censored at the earlier cen- soring time. Multiple formula objects can be provided as a list.
init.coxph	a logical value indicating that init should be overrided by estimates based on the coxph fit to the (first) model specified in formula.coxph.
control	a named list of parameters controlling the model fit, returned by the function coxdual.control. This defaults to coxdual.control().
	additional arguments to be passed to coxdual.control.

## Details

A valid formula argument can be expressed as

where (<start>, <stop>] is largest *known* time interval over which individual <id> is at risk for a transition between the states <from> and <to>. The variable <status> indicates whether or not a transition is observed to occur at <stop>.

Under dual censoring (Boruvka and Cook, 2014), both the originating state and the left endpoint of an at-risk interval may be unknown. This case is handled with <start> = NA, <from> = NA, <to> equal to the index of the terminal state, and any transition-type–specific covariates taking on the

#### coxdual

values assumed when <from> is equal to the intermediate state index. Under discrete observation of non-terminal events, the right-endpoint of some at-risk intervals may be unknown. For these <start> is the initial observation time (zero, unless left-truncated), <stop> = NA and <from> is equal to the initial state index. Missing values are retained by the NA action na.coxdual. The default NA action is used to handle any missing values passed to coxph via the arguments formula.coxph or init.coxph.

Dual censoring typically arises in two scenarios: (1) dual right-censoring, where intermediate events are right-censored before terminal events, and (2) interval-censored intermediate events. For examples of these refer to dualrc and dualic, respectively.

A consequence of dual censoring is that any discrete maximum likelihood estimator has ambiguous support at any failure times associated with these NA values. To resolve this, the cumulative baseline transition intensities are restricted to piecewise linear functions on a sieve partition with size controlled by arguments passed to coxdual.control. This approach requires that both types of transitions to the terminal state are, at least for some subjects, observed exactly.

#### Value

An object of the classes "coxinterval" and "coxdual", which is a list with the following components.

call	the matched call to coxdual.
censor	a string indicating the dual censoring type. The value "right" corresponds to strictly dual-right–censored data. All other cases return "interval".
n	size of the sample used in the model fit.
m	number of at-risk intervals used in the model fit.
р	number of regression coefficients.
coef	a named p vector of regression coefficients.
var	a named p by p covariance matrix of the regression coefficients.
basehaz	a data frame giving the cumulative baseline transition intensities evaluated over the sieve partition.
init	list of initial values used in the model fit.
loglik	a vector giving the log-likelihood at initiation and each iteration.
iter	number of iterations needed to reach the stopping criteria.
gradnorm	the maximum norm of the score scaled by the parameter value at the final itera- tion.
maxnorm	the maximum norm of the difference between the penultimate and final parameter values.
cputime	the processing time used for parameter and variance estimation.
fit.coxph	the coxph fit to any models specified by the formula.coxph argument. If formula.coxph is a list of formula objects, fit.coxph is an unnamed list following the same order.
na.action	the "na.action" attribute of the model frame. Here this corresponds to the result from the custom NA action na.coxdual.
censor.rate	a named vector of censoring rates.

control	a list of arguments passed to coxdual.control.
data	a list containing the data relevant to the model fit, if the coxdual.control ar-
	gument data is true.

#### References

Boruvka, A. and Cook, R. J. (2014) Sieve estimation in a Markov illness-death process under dual censoring.

#### See Also

cluster, dualic, dualrc, Surv, trans

#### Examples

```
# Fit Cox model to dual-right--censored data
fit <- coxdual(Surv(start, stop, status) ~ cluster(id) + trans(from, to)</pre>
               + I(z * (to == 1)) + I(z * (from %in% 0 & to == 2))
               + I(z * (from %in% c(NA, 1) & to == 2)), data = dualrc,
               sieve.rate = 2/5)
fit
par(mfrow = c(1, 3))
by(fit$basehaz, fit$basehaz$trans, function(x) plot(x[, 2:1],
   type = "1", main = paste(x[1, 3]), xlim = c(0, 2), ylim = c(0, 4)))
# Fit Cox model to data with interval-censored progression times
fit <- coxdual(Surv(start, stop, status) ~ cluster(id) + trans(from, to)</pre>
               + I(z * (to == 1)) + I(z * (from %in% 0 & to == 2))
               + I(z * (from %in% c(NA, 1) & to == 2)), data = dualic)
fit
par(mfrow=c(1, 3))
by(fit$basehaz, fit$basehaz$trans, function(x) plot(x[, 2:1],
   type = "l", main = paste(x[1, 3]), xlim = c(0, 2), ylim = c(0, 4)))
```

coxdual.control Control Cox model fit

#### Description

Set parameters controlling the model fit returned by coxdual.

#### Usage

#### coxdual.control

#### Arguments

eps	threshold value for the norm used to measure convergence in the parameter estimates.
iter.max	maximum number of iterations to attempt. This ensures that coxdual will even- tually exit, even when the convergence criteria are not met.
coef.typ	a scalar or vector of typical (absolute) values for the regression coefficient.
coef.max	a scalar or vector of probable upper bounds for the regression coefficient. This and the coef.typ arguments tune variance estimation via the curvature in the profile log-likelihood.
sieve	a logical value indicating that the sieve rather than the semiparametric maximum likelihood estimator should be fit to the data. The default TRUE is recommended to avoid issues with support finding and convergence.
sieve.const	a constant factor that, in part, determines the sieve size. The factor can be made specific to the transition type with sieve.const a vector of length three. Indexing the states from zero, this vector's components correspond to the state 0 to state 1, 0 to 2, and 1 to 2 transition types, respectively.
sieve.rate	a scalar in $(1/8, 1/2)$ determining the rate at which the sieve increases with the sample size.
risk.min	a positive integer giving the minimum size of risk set for support points defining the sieve.
data	a logical value indicating that the object returned by coxdual should contain an element data that gives the known support points, corresponding size of the risk set, left and right endpoints of censoring intervals for the progression time, first and last observation times, likelihood contribution type (0 progression status unknown, 1 positive status, 2 negative status), survival time observed, and type-specific covariates.

## Details

For a given sample size n, the resulting sieve has size at most sieve.const\*nsieve.rate. Any reduction in size from this value is applied to ensure that each subinterval in the sieve's time partition captures at least one support point from the semiparametric maximum likelihood estimator based on the subsample with known progression status (Boruvka and Cook, 2014).

## Value

A list of the above arguments with their final values.

## References

Boruvka, A. and Cook, R. J. (2014) Sieve estimation in a Markov illness-death process under dual censoring.

#### See Also

coxdual

dualic

#### Examples

```
dualic
```

Simulated dual-censored data from an illness-death process

## Description

Data from a Markov illness-death process with interval-censored progression times, simulated according to the initial scenario described in Boruvka and Cook (2014).

#### Usage

data(dualic)

#### Format

A data frame with 723 observations on the following 7 variables.

id subject identifier.

- from originating state index with 0 denoting the initial state, 1 the intermediate state, 2 the terminal state and NA an unknown state.
- to subsequent state index.
- start left endpoint of the time interval at which the subject is known to be at risk for a transition between state from and state to.
- stop right endpoint of the at-risk interval.

status indicator that a transition between state from and state to was observed at stop.

z a binary covariate.

## References

Boruvka, A. and Cook, R. J. (2014) Sieve estimation in a Markov illness-death process under dual censoring.

#### See Also

coxdual

#### Examples

data(dualic)

dualrc

## Description

Data from a Markov illness-death process with progression and death observed under dual right censoring, simulated according to the initial scenario described in Boruvka and Cook (2014).

#### Usage

data(dualrc)

#### Format

A data frame with 644 observations on the following 7 variables.

id subject identifier.

from originating state index with 0 denoting the initial state, 1 the intermediate state, 2 the terminal state and NA an unknown state.

to subsequent state index.

start left endpoint of the time interval at which the subject is known to be at risk for a transition between state from and state to.

stop right endpoint of the at-risk interval.

status indicator that a transition between state from and state to was observed at stop.

z a binary covariate.

## References

Boruvka, A. and Cook, R. J. (2014) Sieve estimation in a Markov illness-death process under dual censoring.

#### See Also

coxdual

#### Examples

data(dualrc)

jump2step

## Description

A utility function for coxdual that returns values from a step function given its increments over time.

## Usage

```
jump2step(jump, time = "time", stratum = NULL)
```

#### Arguments

jump	a matrix whose columns give increments in the (possibly multivariate) step func- tion, corresponding time points and strata.
time	an integer or character value indicating the column index or name of the time variable in the matrix jump. Defaults to "time".
stratum	integer or character value for the column index or name of the stratifying variable in the matrix jump. If stratum is NULL (default), jump is presumed unstratified.

## Value

A matrix of the same dimension as jump.

#### See Also

step2jump

lin2const

## Description

A utility function for coxdual that gives the slope corresponding to values from a piecewise linear function of time.

#### Usage

lin2const(lin, time = "time", stratum = NULL)

## Arguments

lin	a matrix whose columns give the (possibly multivariate) piecewise linear function values, time points and strata.
time	an integer or character value indicating the column index or name of the time variable in the matrix lin. Defaults to "time".
stratum	integer or character value for the column index or name of the stratifying variable in the matrix lin. If stratum is NULL (default), lin is presumed unstratified.

## Details

This is a utility function for coxdual.

## Value

A matrix of the same dimension as lin.

#### See Also

const2lin

linapprox

#### Description

Perform linear interpolation or extrapolation

## Usage

linapprox(xyin, xout)

#### Arguments

xyin	a matrix whose rows give the coordinate pairs of the points to be interpolated or extrapolated.
xout	a vector of numeric values at which interpolation or extrapolation should take place.

## Value

A vector of interpolated or extrapolated values.

#### See Also

approx const2lin lin2const

## Examples

maximalint

Find maximal intersections from an interval-type survival object

#### Description

A utility function that returns the "maximal intersections" from a set of censoring intervals in a given type = "interval" or type = "interval2" Surv object.

#### Usage

maximalint(x, eps = 1e-7)

#### print.coxinterval

#### Arguments

x	a two-column matrix or data frame giving the left- and right-endpoints of the censoring intervals or, alternatively, a type = "interval" or type = "interval2" Surv object. Following the type = "interval2" format, any NA-valued right endpoints are considered the same as Inf.
eps	a small value used to break ties in maximal intersection endpoints. Note that a large time scale requires a larger epsilon in order to ensure that $t = t + eps$ for a given time value t.

## Details

Each censoring interval is assumed to exclude its left endpoint. Analogous to Maathuis (2005, Section 2.1) ties between the unique (open) left and (closed) right endpoints among the censoring intervals are broken by subtracting a small value from the right endpoint value before constructing the maximal intersections.

#### Value

int	a two-column matrix whose rows give the maximal intersections (Wong and Yu, 1999) of the censoring intervals represented in ${\sf x}$
ind	a nrow(x) by nrow(int) matrix that indicates overlap between each maximal intersection and censoring interval

#### References

Maathuis, MH (2005) Reduction algorithm for the NPMLE for the distribution function of bivariate interval-censored data. *Journal of Computational and Graphical Statistics* **14**, 352–362.

Wong, GYC. and Yu, Q. (1999) Generalized MLE of a joint distribution function with multivariate interval-censored data. *Journal of Multivariate Analysis* **69**, 155–166.

#### Examples

```
s <- with(cosmesis[1:10, ], Surv(left, right, type = "interval2"))
s
maximalint(s)</pre>
```

print.coxinterval Print method for model fit

## Description

Prints an object the class "coxinterval".

## Usage

```
## S3 method for class 'coxinterval'
print(x, ...)
```

#### Arguments

Х	an object returned by coxaalen or coxdual.
	further arguments for other methods.

## See Also

summary.coxinterval

step2jump

Increments from a step function of time

## Description

A utility function for coxdual that returns increments from values of a step function over time.

#### Usage

step2jump(step, time = "time", stratum = NULL)

## Arguments

step	a matrix whose columns give the (possibly multivariate) step function values, corresponding time points and strata.
time	an integer or character value indicating the column index or name of the time variable in the matrix step. Defaults to "time".
stratum	integer or character value for the column index or name of the stratifying vari- able in the matrix step. If stratum is NULL (default), step is presumed unstrat- ified.

## Value

A matrix of the same dimension as step.

## See Also

jump2step

step2stepfun

#### Description

A utility function for that returns a step function given cumulative increments over time.

#### Usage

step2stepfun(step, time = "time", stratum = NULL)

#### Arguments

step	a matrix whose columns give the (possibly multivariate) step function values, corresponding time points and strata.
time	an integer or character value indicating the column index or name of the time variable in the matrix step. Defaults to "time".
stratum	integer or character value for the column index or name of the stratifying variable in the matrix step. If stratum is NULL (default), step is presumed unstratified.

#### Value

A function that returns cumulative increments for given times. If stratified, a list of such functions given in the same order as the strata.

## See Also

jump2step step2jump

Summary method for Cox model fit summary.coxinterval

## Description

summary method for the class "coxinterval".

#### Usage

```
## S3 method for class 'coxinterval'
summary(object, conf.int = 0.95, scale = 1, ...)
```

## Arguments

object	an object returned by coxaalen or coxdual.
conf.int	level for confidence intervals. If FALSE, no confidence intervals are provided.
scale	scale factor for the confidence intervals, whose limits represent the change in risk associated with one scale unit increase in the corresponding variable.
	further arguments for other methods.

## Value

An object of the class "summary.coxinterval".

#### Examples

```
# Fit Cox model to dual-right--censored data
fit <- coxdual(Surv(start, stop, status) ~ cluster(id) + trans(from, to)</pre>
               + I(z * (to == 1)) + I(z * (from %in% 0 & to == 2))
               + I(z* (from %in% c(NA, 1) & to == 2)), data = dualrc,
               sieve.rate = 2/5)
```

fit

Identify	transition	type in	n model	terms
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#### Description

trans

A special function for coxdual that identifies formula terms specifying the state-transition type.

## Usage

trans(from, to)

## trans

## Arguments

from	a variable representing the originating state.
to	a variable representing the subsequent state.

## Value

A combination of the from and to arguments by column with two attributes:

"states"	a vector giving the unique non-missing values in the from and to arguments ordered so that the initial state appears first, the intermediate state second, and the terminal state last.
"types"	a vector of transition type labels in terms of the values in the from and to ar- guments ordered so that the intermediate transition appears first, the terminal transition directly from the initial state second, and the terminal transition from the intermediate state last.

## See Also

coxdual

## Examples

with(dualrc[1:10, ], trans(from, to))

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