

Package ‘WCE’

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Type Package

Title Weighted Cumulative Exposure Models

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Description A flexible method for modeling cumulative effects of time-varying exposures, weighted according to their relative proximity in time, and represented by time-dependent covariates. The current implementation estimates the weight function in the Cox proportional hazards model. The function that assigns weights to doses taken in the past is estimated using cubic regression splines.

License GPL (>= 2)

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wce-package	<i>Weighted Cumulative Exposure Models</i>
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Description

Fit proportional hazards models with a weighted cumulative exposure, based on a weight function estimated from cubic regression b-splines. This implementation of WCE assumes that the dataset is in the interval format with one line per unit of time.

Details

Package: WCE
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Author(s)

Authors: Marie-Pierre Sylvestre, Marie-Eve Beauchamp, Ryan Patrick Kyle, Michal Abrahamowicz

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References

Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. *Stat Med.* 2009;28(27):3437-53.

Abrahamowicz M, Beauchamp M-E, Sylvestre M-P. Comparison of alternative models for linking drug exposure with adverse effects. *Stat Med.* 2012;31(11-12):1014-1030.

checkWCE	<i>Verify that the arguments passed to the WCE function are in correct format</i>
----------	---

Description

This function checks whether the arguments passed to the WCE function are in the correct format. If at least one argument is incorrectly specified, the function returns an error message specifying what needs to be fixed.

Usage

```
checkWCE(data, id, event, start, stop, expos)
```

Arguments

data	A data frame in the long (interval) format with one line per unit of time.
id	The name of the variable in data that identifies subjects.
event	The name of the variable in data that identifies the events (must be 0 or 1).
start	The name of the variable in data that identifies the beginning of the interval.
stop	The name of the variable in data that identifies the end of the interval.
expos	The name of the variable in data that represents the exposure of interest.

Details

The arguments passed to WCE must be exactly those passed to WCE.

Value

checkWCE returns a message on the screen indicating whether the arguments are correctly specified or not.

Author(s)

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Examples

```
checkWCE(drugdata, id = "Id", event = "Event", start = "Start", stop = "Stop",  
expos = "dose")
```

coef.WCE	<i>Obtain estimated coefficients from WCE object</i>
----------	--

Description

This function extracts the estimated coefficients from a WCE object.

Usage

```
## S3 method for class 'WCE'
coef(object, ...)
```

Arguments

object	A WCE object.
...	Optional. Additional arguments to be passed to coef (none currently used).

Value

The function returns a list with one element if the WCE object was fitted without covariates and two if the WCE object was fitted with covariates. The first element is a matrix of estimated coefficients for the artificial D variables (see Sylvestre and Abrahamowicz, 2009). Each row of the matrix corresponds to a model with the number of knots specified in WCE. The second element of the list is a matrix of estimated covariate coefficients. Similarly, each row of the matrix corresponds to a model with the number of knots specified in WCE.

WCEest	Matrix of estimated coefficients of the artificial D variables.
covariates	Matrix of estimated coefficients of the covariates (optional).

Author(s)

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References

Sylvestre, M. P., & Abrahamowicz, M. (2009). Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. *Statistics in medicine*, 28(27), 3437-3453.

Examples

```
checkWCE(drugdata, id = "Id", event = "Event", start = "Start",
  stop = "Stop", expos = "dose")

wce <- WCE(drugdata, "Cox", 1, 90, constrained = "R", id = "Id",
  event = "Event", start = "Start", stop = "Stop", expos = "dose",
  covariates = c("age", "sex"))

coef(wce)
```

`drugdata`*Sample dataset for use with WCE package*

Description

Data to illustrate the use of WCE.

Usage

```
data("drugdata")
```

Format

A data frame with 77038 observations from 500 individuals. The data frame is formatted in an interval format. Contains 7 variables.

`Id` a numeric vector to identify observations that belong to the same individual (`Id`).

`Event` a numeric vector representing the event of interest. Takes the value of 1 in the interval during which the event occurs and is 0 otherwise.

`Start` a numeric vector indicating the beginning of the interval.

`Stop` a numeric vector indicating the end of the interval.

`sex` a numeric vector indicating males (0) and females (1).

`age` a numeric vector representing age at baseline.

`dose` a numeric vector representing time-dependent doses of a drug.

Details

The variables `sex` and `age` are covariates. They are optional and illustrate the inclusion of adjustment variables. Covariates can be numeric or factors.

Source

This dataset was simulated using the `PermAlgo` package (<https://cran.r-project.org/package=PermAlgo>).

References

Sylvestre, MP, & Abrahamowicz, M. (2008). Comparison of algorithms to generate event times conditional on time-dependent covariates. *Statistics in Medicine*, 27(14), 2618-2634.

Examples

```
data(drugdata)
```

HR.WCE	<i>Obtain a hazard ratio (HR) from a WCE Cox proportional hazards model</i>
--------	---

Description

This function calculates the hazard ratio (HR) from an estimated model in a WCE object to compare two scenarios of time-dependent exposures.

Usage

```
HR.WCE(x, vecnum, vecdenom, allres = FALSE)
```

Arguments

x	A WCE object.
vecnum	A vector of time-dependent exposures corresponding to a scenario of interest (numerator of the HR).
vecdenom	A vector of time-dependent exposures corresponding to a scenario for the reference category (denominator of the HR).
allres	Logical. If FALSE, prints the results using the best model from the WCE object, i.e. among the models fitted with the different numbers of interior knots requested by nknots, based on AIC or BIC as specified in the WCE call. If TRUE, prints the results for all the estimated models available from the WCE object. Default to FALSE.

Details

Both vecnum and vecdenom need to be of the same length as the weight function cutoff argument used in the call to WCE. The first value of each vector represents the exposure today (t1) and subsequent values represent the exposures in the past. The hazard ratio computed by HR.WCE corresponds to the ratio of the weighted cumulative exposures for the scenario of interest (vecnum) and the reference scenario (vecdenom). It corresponds to equation (8) of Sylvestre and Abrahamowicz (2009).

Value

Returns one or several hazard ratios. Inference may be obtained by bootstrap and has to be coded separately (please see WCE for an example).

Author(s)

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References

Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. *Stat Med.* 2009 Nov 30;28(27):3437-53.

Examples

```
wce <- WCE(drugdata, "Cox", 1, 90, constrained = "R", id = "Id", event = "Event",
  start = "Start", stop = "Stop", expos = "dose",
  covariates = c("age", "sex"))

# Exposed at a dose of 1 (constant) vs. unexposed over the time window of 90 days
scenario1 <- rep(1, 90)
scenario2 <- rep(0, 90)
HR.WCE(wce, vecnum = scenario1, vecdenom = scenario2)
```

knotsWCE

Obtain the placement of the knots used for splines in WCE models

Description

This function extracts the knots placement for the spline function used to fit the WCE models.

Usage

```
knotsWCE(x)
```

Arguments

x A WCE object returned by WCE.

Value

Returns a list of vectors indicating the placement of the knots used in the spline function of each of the models fitted in the WCE object.

Author(s)

Marie-Pierre Sylvestre
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References

Sylvestre, M. P., & Abrahamowicz, M. (2009). Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. *Statistics in medicine*, 28(27), 3437-3453.

Examples

```
wce <- WCE(drugdata, "Cox", 1, 90, constrained = "R", id = "Id", event = "Event",
  start = "Start", stop = "Stop", expos = "dose",
  covariates = c("age", "sex"))

knotsWCE(wce)
```

plot.WCE

Plot of the weight function(s) estimated by WCE

Description

Method to plot the weight function(s) of a WCE object. Can plot the best estimated weight function or all the estimated functions simultaneously.

Usage

```
## S3 method for class 'WCE'
plot(x, allres = FALSE, ...)
```

Arguments

x	A WCE object
allres	Logical. If TRUE, then all the weight functions from the WCE object are plotted simultaneously. If FALSE, then only the best function, determined by AIC or BIC, is plotted. Default to FALSE.
...	Optional. Additional arguments to be passed to plot (none currently used).

Author(s)

Marie-Pierre Sylvestre
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References

Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. *Stat Med.* 2009 Nov 30;28(27):3437-53.

Examples

```
wce <- WCE(drugdata, "Cox", 1, 90, constrained = "R", id = "Id", event = "Event",
  start = "Start", stop = "Stop", expos = "dose", covariates = c("age", "sex"))

plot(wce)
```

`summary.WCE`*Method to summarize the results of a WCE object*

Description

This is a method to summarize the results from either the best fitting or all of the estimated models from a WCE object.

Usage

```
## S3 method for class 'WCE'  
summary(object, allres = FALSE, ...)
```

Arguments

<code>object</code>	A WCE object
<code>...</code>	Optional; other parameters to be passed through to <code>summary</code> .
<code>allres</code>	Logical. If TRUE, then a summary is produced for every model from the WCE object. If FALSE, then a summary is produced only for the best fitting model, as determined by AIC or BIC. Default to FALSE.

Value

The `summary` method prints to screen the estimated coefficients, standard errors and p-values for the coefficients (if any) included in the WCE model. It also provides the partial likelihood and AIC or BIC value, and the number of events used in the estimation of the model.

Author(s)

Marie-Pierre Sylvestre
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References

Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. *Stat Med*. 2009 Nov 30;28(27):3437-53.

Examples

```
wce <- WCE(drugdata, "Cox", 1, 90, constrained = "R", id = "Id", event = "Event",  
          start = "Start", stop = "Stop", expos = "dose", covariates = c("age", "sex"))  
  
summary(wce)
```

`vcov.WCE`*Obtain variance-covariance matrix from WCE models*

Description

The `vcov` method returns the variance-covariance matrix of the estimated regression coefficients from a WCE model.

Usage

```
## S3 method for class 'WCE'  
vcov(object, ...)
```

Arguments

<code>object</code>	A WCE object.
<code>...</code>	Optional; other parameters to be passed through to <code>vcov</code> (none currently used).

Value

The function returns variance-covariance matrices with the estimated regression coefficients for the supplied WCE model object. The number of matrices returned is equivalent to the length of the `nknots` vector (or one matrix, if `nknots` is a scalar) passed to the WCE function when fitting the model.

Author(s)

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References

Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. *Stat Med.* 2009 Nov 30;28(27):3437-53.

Examples

```
wce <- WCE(drugdata, "Cox", 1, 90, constrained = "R", id = "Id", event = "Event",  
  start = "Start", stop = "Stop", expos = "dose",  
  covariates = c("age", "sex"))  
  
vcov(wce)
```

WCE *Fit weighted cumulative exposure models*

Description

WCE implements a flexible method for modeling cumulative effects of time-varying exposures, weighted according to their relative proximity in time, and represented by time-dependent covariates. The current implementation estimates the weight function in the Cox proportional hazards model. The function that assigns weights to doses taken in the past is estimated using cubic regression splines.

Usage

```
WCE(data, analysis, nknots, cutoff, constrained = FALSE, aic = FALSE, MatchedSet = NULL,
id, event, start, stop, expos, covariates = NULL, controls = NULL, ...)
```

Arguments

data	A data frame in an interval (long) format, in which each line corresponds to one and only one time unit for a given individual.
analysis	Character string. One of 'Cox', 'NCC' or 'CC' for Cox proportional hazards model, conditional logistic regression for nested case controls (NCC) or logistic regression for case-controls (CC). Currently only 'Cox' for the Cox proportional hazards model is implemented, calling the <code>coxph</code> function of the <code>survival</code> package.
nknots	A scalar or a vector. Corresponds to the number(s) of interior knots for the cubic splines to estimate the weight function. For example, if <code>nknots</code> is set to 2, then a model with two interior knots is fitted. If <code>nknots</code> is set to 1:3 or alternatively <code>c(1,2,3)</code> then three models with 1, 2, and 3 interior knots, respectively, are fitted.
cutoff	Integer. Time window over which the WCE model is estimated. Corresponds to the length of the estimated weight function.
constrained	Controls whether the weight function should be constrained to smoothly go to zero. Set to <code>FALSE</code> for unconstrained models, to 'Right' or 'R' to constrain the weight function to smoothly go to zero for exposure remote in time, and to 'Left' or 'L' to constrain the weight function to start a zero for the current values.
aic	Logical. If <code>TRUE</code> , then the AIC is used to select the best fitting model among those estimated for the different numbers of interior knots requested with <code>nknots</code> . If <code>FALSE</code> , then the BIC is used instead of the AIC. Default to <code>FALSE</code> (BIC). Note that the BIC implemented in WCE is the version suggested by Volinsky and Raftery in <i>Biometrics</i> (2000), which corresponds to $BIC = 2 * \log(PL) + p * \log(d)$ where PL is the model's partial likelihood, p is the number of estimated parameters and d is the number of uncensored events. See Sylvestre and Abrahamowicz (2009) for more details.
MatchedSet	Argument required for 'NCC' analysis only. Corresponds to the variable in data that specifies the matched sets for the conditional logistic regression. Currently not implemented.

<code>id</code>	Name of the variable in data corresponding to the identification of subjects.
<code>event</code>	Name of the variable in data corresponding to event indicator. Must be coded 1 = event and 0 = no event.
<code>start</code>	Name of the variable in data corresponding to the starting time for the interval. Corresponds to <code>time</code> argument in function <code>Surv</code> in the <code>survival</code> package.
<code>stop</code>	Name of the variable in data corresponding to the ending time for the interval. Corresponds to <code>time2</code> argument in function <code>Surv</code> in the <code>survival</code> package.
<code>expos</code>	Name of the variable in data corresponding to the exposure variable.
<code>covariates</code>	Optional. Vector of characters corresponding to the name(s) of the variable(s) in data corresponding to the covariate(s) to be included in the model. Default to <code>NULL</code> , which corresponds to fitting model(s) without covariates.
<code>controls</code>	List corresponding to the control parameters to be passed to the <code>coxph</code> function. See <code>coxph.control</code> for more details.
<code>...</code>	Optional; other parameters to be passed through to <code>WCE</code> .

Details

The current implementation of the `WCE` function does not allow missing values in the `Id`, `event`, `start`, `stop`, `expos` variables. Intervals in data determined by `start` and `stop` are assumed to be open on the left and closed on the right, $(start, stop]$. Intervals for a given individual (`Id`) must not overlap, and must cover the entire follow-up for the individual. The `start` and `stop` values for a given interval must not be equal. Delayed entry is not implemented in this version of the `WCE` function so all of the `Id` must start their follow-up at the same `start` value. The interior knots are placed at quantiles of the exposure variable distribution.

Value

A list of 14 items:

<code>knotsmat</code>	List of vectors of knots used for the spline modelling of the weight function(s).
<code>WCEmat</code>	Matrix of the estimated weight function. Each row corresponds to an estimated weight function. The number of columns in the <code>WCEmat</code> corresponds to the value of the argument <code>nknots</code> .
<code>loglik</code>	Partial likelihood for each estimated model.
<code>est</code>	List of vectors of estimated coefficients for the artificial time-dependent variables used to fit the <code>WCE</code> model(s).
<code>vcovmat</code>	List of variance-covariance matrices estimated for each model.
<code>SED</code>	List of vectors of estimated standard errors of the estimated coefficients of the artificial time-dependent variables used to fit each <code>WCE</code> model.
<code>beta.hat.covariates</code>	List of vectors of estimated coefficients for the covariates.
<code>se.covariates</code>	List of vectors of standard errors of the estimated coefficients for the covariates.
<code>covariates</code>	Names of the covariates used in the estimation.
<code>constrained</code>	Indicator of whether the model(s) was(were) unconstrained, right-constrained or left-constrained.

nevents	Number of events.
aic	Logical value corresponding to the aic argument.
info.criterion	Value of the AIC or BIC for each model estimated.
analysis	Value of the analysis argument.
...	Potentially, additional arguments (as required by generic).

Note

Note that the print method for a WCE object returns the estimated WCE function(s), the number of events, the partial likelihoods, the AIC or BIC values, the matrix of coefficients estimates for the covariates (if any) and the matrix of standard error estimates for the covariates (if any).

Author(s)

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References

Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. *Stat Med.* 2009 Nov 30;28(27):3437-53.

See Also

See also [checkWCE](#), a function to check whether the arguments passed to WCE are correctly specified.

Examples

```
wce <- WCE(drugdata, "Cox", 1, 90, constrained = "R", id = "Id", event = "Event",
  start = "Start", stop = "Stop", expos = "dose", covariates = c("age", "sex"))

## Not run:
# Confidence intervals for HR, as well as pointwise confidence bands
# for the estimated weight function can be obtained via bootstrap.

# Set the number of bootstrap resamples
#(set to 5 for demonstration purposes, should be higher)
B <- 5

# Obtain the list of ID for sampling
ID <- unique(drugdata$Id)

# Prepare vectors to extract estimated weight function and HR
# for the best-fitting model for each bootstrap resample
boot.WCE <- matrix(NA, ncol = 90, nrow=B)
boot.HR <- rep(NA, B)

# Sample IDs with replacement
for (i in 1:B){
  ID.resamp <- sort(sample(ID, replace=T))
```

```

datab <- drugdata[drugdata$Id

# deal with duplicated Id and assign them new Id
step <- 1
repeat {
  ID.resamp <- ID.resamp[duplicated(ID.resamp)==TRUE] # select duplicated Id in ID.resamp
  if (length(ID.resamp)==0) break # stop when no more duplicated Id to deal with
  subset.dup <- drugdata[drugdata$Id
  # assign new Id to duplicates
  subset.dup$Id <- subset.dup$Id + step * 10^ceiling(log10(max(drugdata$Id)))
  # 10^ceiling(log10(max(drugdata$Id)) is the power of 10
  # above the maximum Id from original data
  datab <- rbind(datab, subset.dup)
  step <- step+1
}

mod <- WCE(data = datab, analysis = "Cox", nknots = 1:3, cutoff = 90,
  constrained = "R", aic = FALSE, MatchedSet = NULL,
  id = "Id", event = "Event", start = "Start", stop = "Stop",
  expos = "dose", covariates = c("sex", "age"))

# return best WCE estimates and corresponding HR
best <- which.min(mod$info.criterion)
boot.WCE[i,] <- mod$WCEmat[best,]
boot.HR[i] <- HR.WCE(mod, rep(1, 90), rep(0, 90))
}

# Summarize bootstrap results using percentile method
apply(boot.WCE, 2, quantile, p = c(0.05, 0.95))
quantile(boot.HR, p = c(0.05, 0.95))

## End(Not run)

```

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