# Package 'CoxBoost'

December 11, 2025

<b>Title</b> Cox Models by Likelihood Based Boosting for a Single Survival Endpoint or Competing Risks
Version 1.5.1
<b>Description</b> Provides routines for fitting Cox models by likelihood based boosting for single event survival data with right censoring or in the presence of competing risks. The methodology is described in Binder and Schumacher (2008) <doi:10.1186 1471-2105-9-14=""> and Binder et al. (2009) <doi:10.1093 bioinformatics="" btp088="">.</doi:10.1093></doi:10.1186>
License MIT + file LICENSE
<b>Depends</b> R (>= 3.6.0)
Imports Matrix, survival
Suggests parallel, prodlim, snowfall
Encoding UTF-8
RoxygenNote 7.3.3
NeedsCompilation yes
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Repository CRAN
<b>Date/Publication</b> 2025-12-11 13:30:24 UTC
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# Description

Provides routines for fitting Cox models by likelihood based boosting for single event survival data with right censoring or in the presence of competing risks. The methodology is described in Binder and Schumacher (2008) doi:10.1186/14712105914 and Binder et al. (2009) doi:10.1093/bioinformatics/btp088.

## Author(s)

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coef.CoxBoost

Coeffients from CoxBoost fit

# Description

Extracts the coefficients from the specified boosting steps of a CoxBoost object fitted by CoxBoost.

# Usage

```
## S3 method for class 'CoxBoost'
coef(object, at.step = NULL, scaled = TRUE, ...)
```

## **Arguments**

object	fitted CoxBoost object from a CoxBoost call.
at.step	scalar or vector of boosting step(s) at which prediction is wanted. If no step is given, the final boosting step is used.
scaled	logical value indicating whether coefficients should be returned scaled to be at the level of the original covariate values, or unscaled as used internally when standardize=TRUE is used in the CoxBoost call.
	miscellaneous arguments, none of which is used at the moment.

## Value

For a vector of length p (number of covariates) (at.step being a scalar) or a length(at.step) \* p matrix (at.step being a vector).

# Author(s)

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CoxBoost

Fit a Cox model by likelihood based boosting

# **Description**

CoxBoost is used to fit a Cox proportional hazards model by componentwise likelihood based boosting. It is especially suited for models with a large number of predictors and allows for mandatory covariates with unpenalized parameter estimates.

## Usage

```
CoxBoost(
   time,
   status,
   x,
   unpen.index = NULL,
   standardize = TRUE,
   subset = 1:length(time),
   weights = NULL,
   stratum = NULL,
   stepno = 100,
   penalty = 9 * sum(status[subset] == 1),
   criterion = c("pscore", "score", "hpscore", "hscore"),
   cmprsk = c("sh", "csh", "ccsh"),
   coupled.strata = TRUE,
   stepsize.factor = 1,
   sf.scheme = c("sigmoid", "linear"),
   pendistmat = NULL,
```

```
connected.index = NULL,
  x.is.01 = FALSE,
  return.score = TRUE,
  trace = FALSE
)
```

#### **Arguments**

time vector of length n specifying the observed times.

status censoring indicator, i.e., vector of length n with entries 0 for censored obser-

vations and 1 for uncensored observations. If this vector contains elements not equal to 0 or 1, these are taken to indicate events from a competing risk and a model for the subdistribution hazard with respect to event 1 is fitted (see e.g.

Fine and Gray, 1999; Binder et al. 2009a).

x n \* p matrix of covariates.

unpen.index vector of length p. unpen with indices of mandatory covariates, where parameter

estimation should be performed unpenalized.

standardize logical value indicating whether covariates should be standardized for estima-

tion. This does not apply for mandatory covariates, i.e., these are not standard-

ized

subset a vector specifying a subset of observations to be used in the fitting process.

weights optional vector of length n, for specifying weights for the individual observa-

tions.

stratum vector specifying different groups of individuals for a stratified Cox regression.

In CoxBoost fit each group gets its own baseline hazard.

stepno number of boosting steps (m).

penalty penalty value for the update of an individual element of the parameter vector in

each boosting step.

criterion indicates the criterion to be used for selection in each boosting step. "pscore"

corresponds to the penalized score statistics, "score" to the un-penalized score statistics. Different results will only be seen for un-standardized covariates ("pscore" will result in preferential selection of covariates with larger covariance), or if different penalties are used for different covariates. "hpscore" and "hscore" correspond to "pscore" and "score". However, a heuristic is used for evaluating only a subset of covariates in each boosting step, as described in Binder et al. (2011). This can considerably speed up computation, but may lead

to different results.

cmprsk type of competing risk, specific hazards or cause-specific

coupled.strata logical value indicating whether strata should be coupled during variable se-

lection in each boosting step. If TRUE (default), the same covariate is selected and updated simultaneously across all strata, assuming proportional effects between strata. If FALSE, strata are treated independently during selection, allowing stratum-specific updates (only relevant when multiple strata are defined and

criterion is set to "hscore" or "hpscore").

stepsize.factor

determines the step-size modification factor by which the natural step size of boosting steps should be changed after a covariate has been selected in a boosting step. The default (value 1) implies constant penalties, for a value < 1 the penalty for a covariate is increased after it has been selected in a boosting step, and for a value > 1 the penalty it is decreased. If pendistmat is given, penalty updates are only performed for covariates that have at least one connection to another covariate.

sf.scheme

scheme for changing step sizes (via stepsize.factor). "linear" corresponds to the scheme described in Binder and Schumacher (2009b), "sigmoid" employs a sigmoid shape.

pendistmat

connection matrix with entries ranging between 0 and 1, with entry (i,j) indicating the certainty of the connection between covariates i and j. According to this information penalty changes due to stepsize.factor < 1 are propagated, i.e., if entry (i,j) is non-zero, the penalty for covariate j is decreased after it has been increased for covariate i, after it has been selected in a boosting step. This matrix either has to have dimension (p-p.unpen)\*(p-p.unpen) or the indicices of the p.connected connected covariates have to be given in connected.index, in which case the matrix has to have dimension p.connected p.connected. Generally, sparse matices from package Matrix can be used to save memory.

connected.index

indices of the p.connected connected covariates, for which pendistmat provides the connection information for distributing changes in penalties. No overlap with unpen.index is allowed. If NULL, and a connection matrix is given, all covariates are assumed to be connected.

x.is.01

logical value indicating whether (the non-mandatory part of) x contains just values 0 and 1, i.e., binary covariates. If this is the case and indicated by this argument, computations are much faster.

return.score

logical value indicating whether the value of the score statistic (or penalized score statistic, depending on criterion), as evaluated in each boosting step for every covariate, should be returned. The corresponding element scoremat can become very large (and needs much memory) when the number of covariates and boosting steps is large.

trace

logical value indicating whether progress in estimation should be indicated by printing the name of the covariate updated.

#### Details

In contrast to gradient boosting (implemented e.g. in the glmboost routine in the R package mboost, using the CoxPH loss function), CoxBoost is not based on gradients of loss functions, but adapts the offset-based boosting approach from Tutz and Binder (2007) for estimating Cox proportional hazards models. In each boosting step the previous boosting steps are incorporated as an offset in penalized partial likelihood estimation, which is employed for obtain an update for one single parameter, i.e., one covariate, in every boosting step. This results in sparse fits similar to Lasso-like approaches, with many estimated coefficients being zero. The main model complexity parameter, which has to be selected (e.g. by cross-validation using cv.CoxBoost), is the number of boosting

steps stepno. The penalty parameter penalty can be chosen rather coarsely, either by hand or using optimCoxBoostPenalty.

The advantage of the offset-based approach compared to gradient boosting is that the penalty structure is very flexible. In the present implementation this is used for allowing for unpenalized mandatory covariates, which receive a very fast coefficient build-up in the course of the boosting steps, while the other (optional) covariates are subjected to penalization. For example in a microarray setting, the (many) microarray features would be taken to be optional covariates, and the (few) potential clinical covariates would be taken to be mandatory, by including their indices in unpen.index.

If a group of correlated covariates has influence on the response, e.g. genes from the same pathway, componentwise boosting will often result in a non-zero estimate for only one member of this group. To avoid this, information on the connection between covariates can be provided in pendistmat. If then, in addition, a penalty updating scheme with stepsize.factor < 1 is chosen, connected covariates are more likely to be chosen in future boosting steps, if a directly connected covariate has been chosen in an earlier boosting step (see Binder and Schumacher, 2009b).

#### Value

CoxBoost returns an object of class CoxBoost.

n, p number of observations and number of covariates.

stepno number of boosting steps.

xnames vector of length p containing the names of the covariates. This information is

extracted from x or names following the scheme V1, V2, ...

are used.

coefficients (stepno+1) \* p matrix containing the coefficient estimates for the (standard-

ized) optional covariates for boosting steps 0 to stepno. This will typically be a

sparse matrix, built using package Matrix.

scoremat stepno \* p matrix containing the value of the score statistic for each of the op-

tional covariates before each boosting step.

meanx, sdx vector of mean values and standard deviations used for standardizing the covari-

ates.

unpen.index indices of the mandatory covariates in the original covariate matrix x.

penalty If stepsize.factor != 1, stepno \* (p - p.unpen) matrix containing the penal-

ties used for every boosting step and every penalized covariate, otherwise a vector containing the unchanged values of the penalty employed in each boosting

step.

time observed times given in the CoxBoost call.
status censoring indicator given in the CoxBoost call.

event.times vector with event times from the data given in the CoxBoost call.

linear.predictors

(stepno+1) \* n matrix giving the linear predictor for boosting steps 0 to stepno

and every observation.

Lambda matrix with the Breslow estimate for the cumulative baseline hazard for boosting

steps 0 to stepno for every event time.

logplik partial log-likelihood of the fitted model in the final boosting step.

#### Author(s)

Written by Harald Binder <binderh@uni-mainz.de>.

#### References

Binder, H., Benner, A., Bullinger, L., and Schumacher, M. (2013). Tailoring sparse multivariable regression techniques for prognostic single-nucleotide polymorphism signatures. Statistics in Medicine, doi: 10.1002/sim.5490.

Binder, H., Allignol, A., Schumacher, M., and Beyersmann, J. (2009). Boosting for high-dimensional time-to-event data with competing risks. Bioinformatics, 25:890-896.

Binder, H. and Schumacher, M. (2009). Incorporating pathway information into boosting estimation of high-dimensional risk prediction models. BMC Bioinformatics. 10:18.

Binder, H. and Schumacher, M. (2008). Allowing for mandatory covariates in boosting estimation of sparse high-dimensional survival models. BMC Bioinformatics. 9:14.

Tutz, G. and Binder, H. (2007) Boosting ridge regression. Computational Statistics & Data Analysis, 51(12):6044-6059.

Fine, J. P. and Gray, R. J. (1999). A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association. 94:496-509.

#### See Also

```
predict.CoxBoost, cv.CoxBoost.
```

## **Examples**

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cv.CoxBoost

Determines the optimal number of boosting steps by cross-validation

#### Description

Performs a K-fold cross-validation for CoxBoost in search for the optimal number of boosting steps.

## Usage

```
cv.CoxBoost(
  time,
  status,
  Х,
  subset = 1:length(time),
  weights = NULL,
  stratum = NULL,
  maxstepno = 100,
  K = 10,
  type = c("verweij", "naive"),
  cmprsk = c("sh", "csh", "ccsh"),
  parallel = FALSE,
  upload.x = TRUE,
  multicore = FALSE,
  folds = NULL,
  trace = FALSE,
)
```

## **Arguments**

time vector of length n specifying the observed times.

status censoring indicator, i.e., vector of length n with entries 0 for censored obser-

vations and 1 for uncensored observations. If this vector contains elements not equal to  $\emptyset$  or 1, these are taken to indicate events from a competing risk and a model for the subdistribution hazard with respect to event 1 is fitted (see e.g.

Fine and Gray, 1999).

x n \* p matrix of covariates.

subset a vector specifying a subset of observations to be used in the fitting process.

weights weights to be passed to predict

stratum vector specifying different groups of individuals for a stratified Cox regression.

In CoxBoost fit each group gets its own baseline hazard.

maxstepno maximum number of boosting steps to evaluate, i.e, the returned "optimal" num-

ber of boosting steps will be in the range [0, maxstepno].

K number of folds to be used for cross-validation. If K is larger or equal to the

number of non-zero elements in status, leave-one-out cross-validation is per-

formed.

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type	way of calculating the partial likelihood contribution of the observation in the hold-out folds: "verweij" uses the more appropriate method described in Verweij and van Houwelingen (1996), "naive" uses the approach where the observations that are not in the hold-out folds are ignored (often found in other R packages).
cmprsk	type of competing risk, specific hazards or cause-specific
parallel	logical value indicating whether computations in the cross-validation folds should be performed in parallel on a compute cluster, using package snowfall. Parallelization is performed via the package snowfall and the initialization function of of this package, sfInit, should be called before calling cv.CoxBoost.
upload.x	logical value indicating whether x should/has to be uploaded to the compute cluster for parallel computation. Uploading this only once (using sfExport(x) from library snowfall) can save much time for large data sets.
multicore	indicates whether computations in the cross-validation folds should be performed in parallel, using package parallel. If TRUE, package parallel is employed using the default number of cores. A value larger than 1 is taken to be the number of cores that should be employed.
folds	if not NULL, this has to be a list of length K, each element being a vector of indices of fold elements. Useful for employing the same folds for repeated runs.
trace	logical value indicating whether progress in estimation should be indicated by printing the number of the cross-validation fold and the index of the covariate updated.
	miscellaneous parameters for the calls to CoxBoost

## Value

List with the following components:

mean.logplik	vector of length maxstepno+1 with the mean partial log-likelihood for boosting steps 0 to maxstepno
se.logplik	vector with standard error estimates for the mean partial log-likelihood criterion for each boosting step.
optimal.step	optimal boosting step number, i.e., with minimum mean partial log-likelihood.
folds	list of length K, where the elements are vectors of the indices of observations in the respective folds.

## Author(s)

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derh@uni-mainz.de>

## References

Verweij, P. J. M. and van Houwelingen, H. C. (1993). Cross-validation in survival analysis. Statistics in Medicine, 12(24):2305-2314.

# See Also

CoxBoost, optimCoxBoostPenalty

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## **Examples**

```
Generate some survival data with 10 informative covariates
n <- 200; p <- 100
beta <- c(rep(1,10),rep(0,p-10))
x <- matrix(rnorm(n*p),n,p)</pre>
real.time <- -(\log(\text{runif}(n)))/(10*\exp(\text{drop}(x \%*\% \text{ beta})))
cens.time <- rexp(n,rate=1/10)</pre>
status <- ifelse(real.time <= cens.time,1,0)</pre>
obs.time <- ifelse(real.time <= cens.time,real.time,cens.time)</pre>
# 10-fold cross-validation
cv.res <- cv.CoxBoost(time=obs.time,status=status,x=x,maxstepno=500,</pre>
                        K=10, type="verweij", penalty=100)
# examine mean partial log-likelihood in the course of the boosting steps
plot(cv.res$mean.logplik)
# Fit with optimal number of boosting steps
cbfit <- CoxBoost(time=obs.time,status=status,x=x,stepno=cv.res$optimal.step,</pre>
                   penalty=100)
summary(cbfit)
```

cvcb.control

Control parameters for cross-validation in iCoxBoost

# Description

This function allows to set the control parameters for cross-validation to be passed into a call to iCoxBoost.

## Usage

```
cvcb.control(
  K = 10,
  type = c("verweij", "naive"),
  parallel = FALSE,
  upload.x = TRUE,
  multicore = FALSE,
  folds = NULL
)
```

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# Arguments

K	number of folds to be used for cross-validation. If K is larger or equal to the number of events in the data to be analyzed, leave-one-out cross-validation is performed.
type	way of calculating the partial likelihood contribution of the observation in the hold-out folds: "verweij" uses the more appropriate method described in Verweij and van Houwelingen (1996), "naive" uses the approach where the observations that are not in the hold-out folds are ignored (often found in other R packages).
parallel	logical value indicating whether computations in the cross-validation folds should be performed in parallel on a compute cluster, using package snowfall. Parallelization is performed via the package snowfall and the initialization function of of this package, sfInit, should be called before calling iCoxBoost.
upload.x	logical value indicating whether x should/has to be uploaded to the compute cluster for parallel computation. Uploading this only once (using sfExport(x) from library snowfall) can save much time for large data sets.
multicore	indicates whether computations in the cross-validation folds should be performed in parallel, using package parallel. If TRUE, package parallel is employed using the default number of cores. A value larger than 1 is taken to be the number of cores that should be employed.
folds	if not NULL, this has to be a list of length K, each element being a vector of indices of fold elements. Useful for employing the same folds for repeated runs.

## Value

List with elements corresponding to the call arguments.

# Author(s)

Written by Harald Binder <br/> <br/> derh@uni-mainz.de>.

# References

Verweij, P. J. M. and van Houwelingen, H. C. (1993). Cross-validation in survival analysis. Statistics in Medicine, 12(24):2305-2314.

# See Also

iCoxBoost, cv.CoxBoost

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estimPVal

Estimate p-values for a model fitted by CoxBoost

# Description

Performs permutation-based p-value estimation for the optional covariates in a fit from CoxBoost.

# Usage

```
estimPVal(
  object,
  x,
  permute.n = 10,
  per.covariate = FALSE,
  parallel = FALSE,
  multicore = FALSE,
  trace = FALSE,
  ...
)
```

# Arguments

object	fit object obtained from CoxBoost.
x	$n \star p$ matrix of covariates. This has to be the same that was used in the call to $CoxBoost.$
permute.n	number of permutations employed for obtaining a null distribution.
per.covariate	logical value indicating whether a separate null distribution should be considered for each covariate. A larger number of permutations will be needed if this is wanted.
parallel	logical value indicating whether computations for obtaining a null distribution via permutation should be performed in parallel on a compute cluster. Parallelization is performed via the package snowfall and the initialization function of of this package, sfInit, should be called before calling estimPVal.
multicore	indicates whether computations in the permuted data sets should be performed in parallel, using package parallel. If TRUE, package parallel is employed using the default number of cores. A value larger than 1 is taken to be the number of cores that should be employed.
trace	logical value indicating whether progress in estimation should be indicated by printing the number of the permutation that is currently being evaluated.

miscellaneous parameters for the calls to CoxBoost

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#### **Details**

As p-value estimates are based on permutations, random numbers are drawn for determining permutation indices. Therfore, the results depend on the state of the random number generator. This can be used to explore the variability due to random variation and help to determine an adequate value for permute.n. A value of 100 should be sufficient, but this can be quite slow. If there is a considerable number of covariates, e.g., larger than 100, a much smaller number of permutations, e.g., 10, might already work well. The estimates might also be negatively affected, if only a small number of boosting steps (say <50) was employed for the original fit.

#### Value

Vector with p-value estimates, one value for each optional covariate specificed in the original call to CoxBoost.

## Author(s)

Harald Binder <binderh@uni-mainz.de>

#### References

Binder, H., Porzelius, C. and Schumacher, M. (2009). Rank-based p-values for sparse high-dimensional risk prediction models fitted by componentwise boosting. FDM-Preprint Nr. 101, University of Freiburg, Germany.

## See Also

CoxBoost

## **Examples**

```
p2 <- estimPVal(cbfit,x,permute.n=10)
plot(p1,p2,xlim=c(0,1),ylim=c(0,1),xlab="permute 1",ylab="permute 2")</pre>
```

iCoxBoost

Interface for cross-validation and model fitting using a formula description

## **Description**

Formula interface for fitting a Cox proportional hazards model by componentwise likelihood based boosting (via a call to CoxBoost), where cross-validation can be performed automatically for determining the number of boosting steps (via a call to cv.CoxBoost).

# Usage

```
iCoxBoost(
 formula,
  data = NULL,
 weights = NULL,
 subset = NULL,
 mandatory = NULL,
  cause = 1,
  cmprsk = c("sh", "csh", "ccsh"),
  standardize = TRUE,
  stepno = 200,
  criterion = c("pscore", "score", "hpscore", "hscore"),
 nu = 0.1,
  stepsize.factor = 1,
 varlink = NULL,
  cv = cvcb.control(),
  trace = FALSE,
)
```

#### **Arguments**

formula	A formula describing the model to be fitted, similar to a call to coxph. The response must be a survival object, either as returned by Surv or Hist (in a competing risks application).
data	data frame containing the variables described in the formula.
weights	optional vector, for specifying weights for the individual observations.
subset	a vector specifying a subset of observations to be used in the fitting process.

mandatory vector containing the names of the covariates whose effect is to be estimated

un-regularized.

cause cause of interest in a competing risks setting, when the response is specified by

Hist (see e.g. Fine and Gray, 1999; Binder et al. 2009a).

cmprsk type of competing risk, specific hazards or cause-specific

standardize logical value indicating whether covariates should be standardized for estima-

tion. This does not apply for mandatory covariates, i.e., these are not standard-

ized.

stepno maximum number of boosting steps to be evaluated when determining the num-

ber of boosting steps by cross-validation, otherwise the number of boosting seps

itself.

criterion indicates the criterion to be used for selection in each boosting step. "pscore"

corresponds to the penalized score statistics, "score" to the un-penalized score statistics. Different results will only be seen for un-standardized covariates ("pscore" will result in preferential selection of covariates with larger covariance), or if different penalties are used for different covariates. "hpscore" and "hscore" correspond to "pscore" and "score". However, a heuristic is used for evaluating only a subset of covariates in each boosting step, as described in Binder et al. (2011). This can considerably speed up computation, but may lead

to different results.

(roughly) the fraction of the partial maximum likelihood estimate used for the update in each boosting step. This is converted into a penalty for the call to CoxBoost. Use smaller values, e.g., 0.01 when there is little information in the data, and larger values, such as 0.1, with much information or when the number

of events is larger than the number of covariates. Note that the default for direct

calls to CoxBoost corresponds to nu=0.1.

stepsize.factor

nu

CV

determines the step-size modification factor by which the natural step size of boosting steps should be changed after a covariate has been selected in a boosting step. The default (value 1) implies constant nu, for a value < 1 the value nu for a covariate is decreased after it has been selected in a boosting step, and for a value > 1 the value nu is increased. If pendistmat is given, updates of nu are only performed for covariates that have at least one connection to another

covariate.

varlink list for specifying links between covariates, used to re-distribute step sizes when

stepsize.factor != 1. The list needs to contain at least two vectors, the first containing the name of the source covariates, the second containing the names of the corresponding target covariates, and a third (optional) vector containing weights between 0 and 1 (defaulting to 1). If nu is increased/descreased for one of the source covariates according to stepsize.factor, the nu for the corresponding target covariate is descreased/increased accordingly (multiplied by the weight). If formula contains interaction terms, als rules for these can be set up, using variable names such as V1:V2 for the interaction term between covariates

V1 and V2.

TRUE, for performing cross-validation, with default parameters, FALSE for not performing cross-validation, or list containing the parameters for cross-validation,

as obtained from a call to cvcb.control.

trace logical value indicating whether progress in estimation should be indicated by

printing the name of the covariate updated.

... miscellaneous arguments, passed to the call to cv.CoxBoost.

#### **Details**

In contrast to gradient boosting (implemented e.g. in the glmboost routine in the R package mboost, using the CoxPH loss function), CoxBoost is not based on gradients of loss functions, but adapts the offset-based boosting approach from Tutz and Binder (2007) for estimating Cox proportional hazards models. In each boosting step the previous boosting steps are incorporated as an offset in penalized partial likelihood estimation, which is employed for obtain an update for one single parameter, i.e., one covariate, in every boosting step. This results in sparse fits similar to Lasso-like approaches, with many estimated coefficients being zero. The main model complexity parameter, the number of boosting steps, is automatically selected by cross-validation using a call to cv.CoxBoost). Note that this will introduce random variation when repeatedly calling iCoxBoost, i.e. it is advised to set/save the random number generator state for reproducible results.

The advantage of the offset-based approach compared to gradient boosting is that the penalty structure is very flexible. In the present implementation this is used for allowing for unpenalized mandatory covariates, which receive a very fast coefficient build-up in the course of the boosting steps, while the other (optional) covariates are subjected to penalization. For example in a microarray setting, the (many) microarray features would be taken to be optional covariates, and the (few) potential clinical covariates would be taken to be mandatory, by including their names in mandatory.

If a group of correlated covariates has influence on the response, e.g. genes from the same pathway, componentwise boosting will often result in a non-zero estimate for only one member of this group. To avoid this, information on the connection between covariates can be provided in varlink. If then, in addition, a penalty updating scheme with stepsize.factor < 1 is chosen, connected covariates are more likely to be chosen in future boosting steps, if a directly connected covariate has been chosen in an earlier boosting step (see Binder and Schumacher, 2009b).

## Value

iCoxBoost returns an object of class iCoxBoost, which also has class CoxBoost. In addition to the elements from CoxBoost it has the following elements:

call, formula, terms

call, formula and terms from the formula interface.

cause cause of interest.

cv.res result from cv.CoxBoost, if cross-validation has been performed.

#### Author(s)

Written by Harald Binder <br/>
<br/>
binderh@uni-mainz.de>.

#### References

Binder, H., Benner, A., Bullinger, L., and Schumacher, M. (2013). Tailoring sparse multivariable regression techniques for prognostic single-nucleotide polymorphism signatures. Statistics in Medicine, doi: 10.1002/sim.5490.

Binder, H., Allignol, A., Schumacher, M., and Beyersmann, J. (2009). Boosting for high-dimensional time-to-event data with competing risks. Bioinformatics, 25:890-896.

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Tutz, G. and Binder, H. (2007) Boosting ridge regression. Computational Statistics & Data Analysis, 51(12):6044-6059.

Fine, J. P. and Gray, R. J. (1999). A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association. 94:496-509.

#### See Also

```
predict.iCoxBoost, CoxBoost, cv.CoxBoost.
```

#### **Examples**

```
Generate some survival data with 10 informative covariates
n <- 200; p <- 100
beta <- c(rep(1,2), rep(0,p-2))
x <- matrix(rnorm(n*p),n,p)</pre>
actual.data <- as.data.frame(x)</pre>
real.time <- -(log(runif(n)))/(10*exp(drop(x %*% beta)))</pre>
cens.time <- rexp(n,rate=1/10)</pre>
actual.data$status <- ifelse(real.time <= cens.time,1,0)</pre>
actual.data$time <- ifelse(real.time <= cens.time,real.time,cens.time)</pre>
    Fit a Cox proportional hazards model by iCoxBoost
cbfit <- iCoxBoost(Surv(time,status) ~ .,data=actual.data)</pre>
summary(cbfit)
plot(cbfit)
    ... with covariates 1 and 2 being mandatory
cbfit.mand <- iCoxBoost(Surv(time,status) ~ .,data=actual.data,mandatory=c("V1"))</pre>
summary(cbfit.mand)
plot(cbfit.mand)
```

optimCoxBoostPenalty Coarse line search for adequate penalty parameter

### **Description**

This routine helps in finding a penalty value that leads to an "optimal" number of boosting steps for CoxBoost, determined by cross-validation, that is not too small/in a specified range.

## Usage

```
optimCoxBoostPenalty(
   time,
   status,
   x,
   minstepno = 50,
   maxstepno = 200,
   start.penalty = 9 * sum(status == 1),
   iter.max = 10,
   upper.margin = 0.05,
   parallel = FALSE,
   trace = FALSE,
   ...
)
```

## **Arguments**

time vector of length n specifying the observed times.

status censoring indicator, i.e., vector of length n with entries 0 for censored obser-

vations and 1 for uncensored observations. If this vector contains elements not equal to 0 or 1, these are taken to indicate events from a competing risk and a model for the subdistribution hazard with respect to event 1 is fitted (see e.g.

Fine and Gray, 1999).

x n \* p matrix of covariates.

minstepno, maxstepno

range of boosting steps in which the "optimal" number of boosting steps is

wanted to be.

start.penalty start value for the search for the appropriate penalty.

iter.max maximum number of search iterations.

upper.margin specifies the fraction of maxstepno which is used as an upper margin in which

a cross-validation minimum is not taken to be one. This is necessary because of

random fluctuations of cross-validated partial log-likelihood.

parallel logical value indicating whether computations in the cross-validation folds should

be performed in parallel on a compute cluster. Parallelization is performed via the package snowfall and the initialization function of of this package, sfInit,

should be called before calling cv.CoxBoost.

trace logical value indicating whether information on progress should be printed.

... miscellaneous parameters for cv.CoxBoost.

#### **Details**

The penalty parameter for CoxBoost has to be chosen only very coarsely. In Tutz and Binder (2006) it is suggested for likelihood based boosting just to make sure, that the optimal number of boosting steps, according to some criterion such as cross-validation, is larger or equal to 50. With a smaller number of steps, boosting may become too "greedy" and show sub-optimal performance. This procedure uses a very coarse line search and so one should specify a rather large range of boosting steps.

## Value

List with element penalty containing the "optimal" penalty and cv.res containing the corresponding result of cv.CoxBoost.

## Author(s)

Written by Harald Binder <binderh@uni-mainz.de>.

## References

Tutz, G. and Binder, H. (2006) Generalized additive modelling with implicit variable selection by likelihood based boosting. *Biometrics*, 62:961-971.

#### See Also

```
CoxBoost, cv.CoxBoost
```

# Examples

```
Generate some survival data with 10 informative covariates
n <- 200; p <- 100
beta <- c(rep(1,10),rep(0,p-10))
x <- matrix(rnorm(n*p),n,p)</pre>
real.time <- -(\log(\text{runif}(n)))/(10*\exp(\text{drop}(x \%*\% \text{ beta})))
cens.time <- rexp(n,rate=1/10)</pre>
status <- ifelse(real.time <= cens.time,1,0)</pre>
obs.time <- ifelse(real.time <= cens.time,real.time,cens.time)</pre>
# determine penalty parameter
optim.res <- optimCoxBoostPenalty(time=obs.time,status=status,x=x,</pre>
                                     trace=TRUE, start.penalty=500)
    Fit with obtained penalty parameter and optimal number of boosting
    steps obtained by cross-validation
cbfit <- CoxBoost(time=obs.time,status=status,x=x,</pre>
                   stepno=optim.res$cv.res$optimal.step,
                   penalty=optim.res$penalty)
summary(cbfit)
```

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plot.CoxBoost

Plot coefficient paths from CoxBoost fit

# Description

Plots coefficient paths, i.e. the parameter estimates plotted against the boosting steps as obtained from a CoxBoost object fitted by CoxBoost.

# Usage

```
## $3 method for class 'CoxBoost'
plot(
    x,
    line.col = "dark grey",
    label.cex = 0.6,
    xlab = NULL,
    ylab = NULL,
    xlim = NULL,
    ylim = NULL,
    main = NULL,
    ...
)
```

# **Arguments**

```
x fitted CoxBoost object from a CoxBoost call.

line.col color of the lines of the coefficient path

label.cex scaling factor for the variable labels.

xlab label for the x axis, default label when NULL.

ylab label for the y axis, default label when NULL.

xlim, ylim plotting ranges, default label when NULL.

main a main title for the plot

... miscellaneous arguments, passed to the plot routine.
```

## Value

No value is returned, but a plot is generated.

## Author(s)

Harald Binder <br/>
<br/>
derh@uni-mainz.de>

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predict.CoxBoost

Predict method for CoxBoost fits

## Description

Obtains predictions at specified boosting steps from a CoxBoost object fitted by CoxBoost.

#### Usage

```
## S3 method for class 'CoxBoost'
predict(
  object,
  newdata = NULL,
  newtime = NULL,
  newstatus = NULL,
  subset = NULL,
  weights = NULL,
  stratum = NULL,
  at.step = NULL,
  times = NULL,
  type = c("lp", "logplik", "risk", "CIF"),
  ...
)
```

## **Arguments**

object fitted CoxBoost object from a CoxBoost call.

newdata n.new \* p matrix with new covariate values. If just prediction for the training

data is wanted, it can be omitted.

newtime, newstatus

vectors with observed time and censoring indicator (0 for censoring, 1 for no censoring, and any other values for competing events in a competing risks setting) for new observations, where prediction is wanted. Only required if predicted partial log-likelihood is wanted, i.e., if type="logplik". This can also be omitted when prediction is only wanted for the training data, i.e., newdata=NULL.

subset an optional vector specifying a subset of observations to be used for evaluation.

weights weights for each time.

stratum vector specifying different groups of individuals for a stratified Cox regression.

In CoxBoost fit each group gets its own baseline hazard.

at.step scalar or vector of boosting step(s) at which prediction is wanted. If type="risk"

is used, only one step is admissible. If no step is given, the final boosting step is

used.

times vector with T time points where prediction is wanted. Only needed for type="risk"

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type

type of prediction to be returned: "lp" gives the linear predictor, "logplik" the partial log-likelihood, "risk" the predicted probability of not yet having had the event at the time points given in times, and "CIF" the predicted cumulative incidence function, i.e., the predicted probability of having had the event of interest.

... miscellaneous arguments, none of which is used at the moment.

#### Value

For type="lp" and type="logplik" a vector of length n.new (at.step being a scalar) or a n.new \* length(at.step) matrix (at.step being a vector) with predictions is returned. For type="risk" or type="CIF" a n.new \* T matrix with predicted probabilities at the specific time points is returned.

## Author(s)

Harald Binder <br/>
<br/>
derh@uni-mainz.de>

## **Examples**

```
Generate some survival data with 10 informative covariates
n <- 200; p <- 100
beta <- c(rep(1,10), rep(0,p-10))
x <- matrix(rnorm(n*p),n,p)</pre>
real.time <- -(log(runif(n)))/(10*exp(drop(x %*% beta)))</pre>
cens.time <- rexp(n,rate=1/10)</pre>
status <- ifelse(real.time <= cens.time,1,0)</pre>
obs.time <- ifelse(real.time <= cens.time,real.time,cens.time)</pre>
    define training and test set
train.index <- 1:100
test.index <- 101:200
   Fit CoxBoost to the training data
cbfit <- CoxBoost(time=obs.time[train.index],status=status[train.index],</pre>
                   x=x[train.index,],stepno=300,penalty=100)
    mean partial log-likelihood for test set in every boosting step
step.logplik <- predict(cbfit,newdata=x[test.index,],</pre>
                         newtime=obs.time[test.index],
                         newstatus=status[test.index],
                         at.step=0:300,type="logplik")
plot(step.logplik)
    names of covariates with non-zero coefficients at boosting step
    with maximal test set partial log-likelihood
```

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```
print(cbfit$xnames[cbfit$coefficients[which.max(step.logplik),] != 0])
```

predict.iCoxBoost

Predict method for iCoxBoost fits

# Description

Obtains predictions at specified boosting steps from a iCoxBoost object fitted by iCoxBoost.

## Usage

```
## S3 method for class 'iCoxBoost'
predict(
  object,
  newdata = NULL,
  subset = NULL,
  at.step = NULL,
  times = NULL,
  type = c("lp", "logplik", "risk", "CIF"),
  ...
)
```

# **Arguments**

object	fitted CoxBoost object from a CoxBoost call.
newdata	data frame with new covariate values (for n. new observations). If just prediction for the training data is wanted, it can be omitted. If the predictive partial log-likelihood is wanted (type=logplik), this frame also has to contain the response information.
subset	an optional vector specifying a subset of observations to be used for evaluation.
at.step	scalar or vector of boosting step(s) at which prediction is wanted. If type="risk" is used, only one step is admissible. If no step is given, the final boosting step is used.
times	vector with T time points where prediction is wanted. Only needed for type="risk"
type	type of prediction to be returned: "lp" gives the linear predictor, "logplik" the partial log-likelihood, "risk" the predicted probability of not yet having had the event at the time points given in times, and "CIF" the predicted cumulative incidence function, i.e., the predicted probability of having had the event of interest.
	miscellaneous arguments, none of which is used at the moment.

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## Value

For type="lp" and type="logplik" a vector of length n.new (at.step being a scalar) or a n.new \* length(at.step) matrix (at.step being a vector) with predictions is returned. For type="risk" or type="CIF" a n.new \* T matrix with predicted probabilities at the specific time points is returned.

## Author(s)

Harald Binder <br/>
<br/>
derh@uni-mainz.de>

## **Examples**

```
n <- 200; p <- 100
beta <- c(rep(1,2),rep(0,p-2))
x <- matrix(rnorm(n*p),n,p)</pre>
actual.data <- as.data.frame(x)</pre>
real.time <- -(log(runif(n)))/(10*exp(drop(x %*% beta)))</pre>
cens.time <- rexp(n,rate=1/10)</pre>
actual.data$status <- ifelse(real.time <= cens.time,1,0)</pre>
actual.data$time <- ifelse(real.time <= cens.time,real.time,cens.time)</pre>
    define training and test set
train.index <- 1:100
test.index <- 101:200
   Fit a Cox proportional hazards model by iCoxBoost
cbfit <- iCoxBoost(Surv(time,status) ~ .,data=actual.data[train.index,],</pre>
   stepno=300,cv=FALSE)
   mean partial log-likelihood for test set in every boosting step
step.logplik <- predict(cbfit,newdata=actual.data[test.index,],</pre>
                         at.step=0:300,type="logplik")
plot(step.logplik)
    names of covariates with non-zero coefficients at boosting step
    with maximal test set partial log-likelihood
print(coef(cbfit,at.step=which.max(step.logplik)-1))
```

## **Description**

Print a CoxBoost type

## Usage

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

## **Arguments**

```
x a CoxBoost object ... not used
```

## Value

Invisibly returns NULL. The function is called for its side-effects, printing for each cause-stratum combination:

- the number of boosting steps,
- the number of non-zero coefficients,
- the partial log-likelihood.

resample.CoxBoost

Performs resampling for a stratified weighted Cox model by componentwise likelihood based boosting for developing subgroup covariate signatures

## Description

resample. CoxBoost is used to perform resampling for stratified Cox proportional hazards models by componentwise likelihood based boosting with weights for developing subgroup covariate signatures. Specifically, this weighted Cox regression approach is for performing a subgroup analysis, not for the standard subgroup analysis but for a weighted form of it where the observations of the not analyzed subgroup are down-weighted. resample.CoxBoost calls cv.CoxBoost and CoxBoost.

## Usage

```
resample.CoxBoost(
   time,
   status,
   x,
   rep = 100,
   maxstepno = 200,
   multicore = TRUE,
   mix.list = c(0.001, 0.01, 0.05, 0.1, 0.25, 0.35, 0.5, 0.7, 0.9, 0.99),
   stratum,
```

```
stratnotinfocus = 0,
penalty = sum(status) * (1/0.02 - 1),
criterion = "hscore",
unpen.index = NULL,
trace = FALSE
)
```

#### **Arguments**

time vector of length n with the observed times of each individual.

status vector of length n with entries 0 for censored observations and 1 for observations

having an event.

x n \* p matrix of mandatory and optional covariates.

rep number of resampling data sets used for the evaluation of model stability. Should

be equal to length(iter).

maxstepno maximum number of boosting steps needed for cross-validation in cv.CoxBoost.

So the optimal step number for fitting the componentwise boosting has a range

between zero and maxstepno.

multicore logical value: If TRUE then the cross-validation for selecting the number of opti-

mal boosting steps within each resampling data set is been parallelized, if FALSE

there will be no parallelization.

mix.list vector of different relative weights between zero and one, for specifying weights

for the individual observations for the weighted regression approach. For each

weight, a stratified Cox regression by componentwise boosting is fitted.

stratum vector specifying different groups of individuals for a stratified Cox regression.

In CoxBoost fit each group gets its own baseline hazard.

stratnotinfocus

value for the group which is not analyzed but should be weighted down in the

analysis with the different weights element of mix.list.

penalty penalty value for the covariates for the update of an individual element in each

boosting step. The mandatory covariates should get a penalty value of zero,

which can be realized with unpen.index.

criterion indicates the criterion to be used for selection in each boosting step in CoxBoost.

The default is "hscore" for using a heuristic when evaluating a subset of covari-

ates in each boosting step. For the different other options see CoxBoost.

unpen.index index for mandatory covariates, which should get no penalty value in the log-

partial likelihood function.

trace logical value indicating whether progress in estimation should be indicated by

printing the number of the cross-validation fold and the index of the covariate

updated in the cv.CoxBoost and CoxBoost methods.

#### **Details**

The CoxBoost function can be used for performing variable selection for time-to-event data based on componentwise likelihood based boosting (Binder and Schumacher, 2009; Binder et al., 2013)

for obtaining signatures for high dimensional data, such as gene expression or high throughput methylation measurements. If there is any heterogeneity due to known patient subgroups, it would be interesting for developing subgroup signatures to account for this heterogeneity. To account for heterogeneity in the data a stratified Cox model via stratum can be performed, which allows for different baseline hazards in each subgroup. For performing a stratified CoxBoost for such heterogeneous subgroups the stratum can be set to a subgroup variable, containing also the subgroup for which a subgroup signature should be developed. A standard subgroup analysis may lead to a decreased statistical power. With a weighted approach based on componentwise likelihoodbased boosting one can develop subgroup signatures without losing statistical power as it is the case in standard subgroup analysis. This approach focuses on building a risk prediction signature for a specific stratum by down-weighting the observations (Simon, 2002) from the other strata using a range of weights. The not analyzed subgroup has to be indicated in stratnotinfocus, the observations of this subgroup, which is not in focus but should be retained in the analysis, are weighted down by different relative weights. Binder et al. (2012) propose such a weighting approach for high dimensional data but not for time-to-event endpoints. resample.CoxBoost performs a weighted regression approach for time-to-event data while using resampling over rep resampling data sets, specifically for evaluating the results. The different weights can be entered by mix.list which should be from a range between zero and one. For examining the variable selection stability for specific covariates as a function of the weights the beta coefficients are an output value of resample. CoxBoost, so that resampling inclusion frequencies (Sauerbrei et. al, 2011) can be calculated and visualized via the functions stabtrajec and weightfreqmap. For mandatory variables (Binder and Schumacher, 2008), which are only included for adjusting the model no penalty should be added, these can be indicated by the indices in unpen. index.

#### Value

resample. CoxBoost returns a list of length rep list elements with each list element being further a list of the following two objects:

CV. opt number of optimal boosting steps obtained from cv. CoxBoost for each weight.

beta beta coefficients obtained from CoxBoost as vector for each weight.

#### Author(s)

Written by Veronika Weyer < weyer@uni-mainz.de> and Harald Binder < binderh@uni-mainz.de>.

#### References

Binder, H., Benner, A., Bullinger, L., Schumacher, M. (2013). Tailoring sparse multivariable regression techniques for prognostic single-nucleotide polymorphism signatures. Statistics in medicine 32(10), 1778-1791

Binder, H., Müller, T., Schwender, H., Golka, K., Steffens, M., G., H.J., Ickstadt, K., and Schumacher, M (2012). Cluster-Localized Sparse Logistic Regression for SNP Data. Statistical applications in genetics and molecular biology, 11(4), 1-31

Binder, H. and Schumacher, M. (2009). Incorporating pathway information into boosting estimation of high-dimensional risk prediction models. BMC Bioinformatics. 10:18.

Binder, H. and Schumacher, M. (2008). Allowing for mandatory covariates in boosting estimation of sparse high-dimensional survival models. BMC Bioinformatics. 9:14.

Sauerbrei, W., Boulesteix, A.-L., Binder, H. (2011). Stability investigations of multivariable regression models derived from low- and high-dimensional data. Journal of biopharmaceutical statistics 21(6), 1206-31

Simon, R. (2002). Bayesian subset analysis: application to studying treatment-by-gender interactions. Statistics in medicine 21(19), 2909-16

#### See Also

```
stabtrajec, weightfreqmap.
```

## **Examples**

```
# Generate survival data with five informative covariates for one subgroup
n <- 400; p <- 1000
set.seed(129)
group < -rbinom(n, 1, 0.5)
x \leftarrow matrix(rnorm(n*p,0,1),n,p)
beta.vec1 <- c(c(1,1,1,1,1),rep(0,p-5))
beta.vec0 <- c(c(0,0,0,0,0),rep(0,p-5))
linpred<-ifelse(group==1,x %*% beta.vec1,x %*% beta.vec0)</pre>
set.seed(1234)
real.time<- (-(log(runif(n)))/(1/20*exp(linpred)))</pre>
cens.time <- rexp(n,rate=1/20)</pre>
obs.status <- ifelse(real.time <= cens.time,1,0)
obs.time <- ifelse(real.time <= cens.time,real.time,cens.time)</pre>
# Fit a stratified weighted Cox proportional hazards model
# by \code{resample.CoxBoost}
mix.list=c(0.001, 0.01, 0.05, 0.1, 0.25, 0.35, 0.5, 0.7, 0.9, 0.99)
RIF <- resample.CoxBoost(</pre>
  time=obs.time, status=obs.status, x=x,
  # use more repetitions (eg `rep = 100`) for more stable results
  rep=5,
  maxstepno=200, multicore=FALSE,
  mix.list=mix.list,
  stratum=group, stratnotinfocus=0, penalty=sum(obs.status)*(1/0.02-1),
  criterion="hscore",unpen.index=NULL)
# RIF is a list with number of resampling data sets list objects, each list
# object has further two list objects, the beta coefficients for all
# weights and the selected number of boosting steps.
# For each list object i \code{RIF[[i]]$beta} contains the beta
# coefficients with length mix.list*p for p covariates and with
# \code{RIF[[i]]$CV.opt}
  For getting an insight in the RIF Distribution of different weights
# use the following code:
RIF1<-c()
for (i in 1: length(RIF)){RIF1<-c(RIF1,RIF[[i]][[1]])}</pre>
```

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```
freqmat <-matrix(apply(matrix(unlist(RIF1), ncol=length(RIF))!=0,1,mean),
ncol=length(mix.list))

# freqmat is a matrix with p rows and \code{length(mix.list)} columns
# which contains resampling inclusion frequencies for the different
# covariates and different weights.

# two plotting functions are available for the resulting object:
stabtrajec(RIF)
weightfreqmap(RIF)</pre>
```

stabtrajec

Plots stability trajectories from resCoxBoost fits

## **Description**

Plots the stability trajectories, i.e. the variable selection stability is plotted in form of resampling inclusion frequencies for different weights and a selection of different stably selected genes as obtained from a resCoxBoost object fitted by resample.CoxBoost.

## Usage

```
stabtrajec(
 RIF,
 mix.list = c(0.001, 0.01, 0.05, 0.1, 0.25, 0.35, 0.5, 0.7, 0.9, 0.99)
 plotmix = c(0.001, 0.01, 0.05, 0.1, 0.25, 0.35, 0.5, 0.7, 0.9, 0.99),
 my.colors = grDevices::gray(seq(0.99, 0, len = 10)),
 yupperlim = 1,
  huge = 0.6,
  lowerRIFlimit = 0.6,
 legendval = 4.5
)
weightfreqmap(
 RIF,
 mix.list = c(0.001, 0.01, 0.05, 0.1, 0.25, 0.35, 0.5, 0.7, 0.9, 0.99)
 plotmix = c(0.001, 0.01, 0.05, 0.1, 0.25, 0.35, 0.5, 0.7, 0.9, 0.99),
 lowerRIFlimit = 0.5,
 method = "complete"
)
```

## **Arguments**

RIF list obtained from a resample.CoxBoost call.

mix.list vector of weights which were also entered in the resample.CoxBoost call.

plotmix vector of weights which should be plotted in the stability trajectory plot.

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my.colors vector with length(plotmix) of different colors for plotting the different weights,

default are gray shades.

yupperlim value for the upper y coordinate.

huge size of the labels plottet on the x-axis.

lowerRIFlimit cutoff RIF value: All covariates which have an resampling inclusion frequency

(RIF) greater or equal this lowerRIFlimit value at any weight are presented in

the stability trajectory plot.

legendval space between the last plotted covariate and the legend on the right side of the

plot.

method passed to hclust for the the agglomeration method to be used

#### **Details**

The stabtrajec function produces a visualization tool (stability trajectory plot), which shows the RIFs as a function of weights for stably selected covariates selected via resample. CoxBoost. With this tool it can be shown that with weights between zero and one and so the additional information from the observations of the not analyzed subgroup in comparison to the standard subgroup analysis (weight near zero) can improve the variable selection stability. The number of plotted covariates in this plot depends on lowerRIFlimit. How many weights are plotted which are element of mix.list can be changed with plotmix.

#### Value

No value is returned, but the stability trajectory plot is generated.

## Author(s)

Veronika Weyer <weyer@uni-mainz.de> and Harald Binder <binderh@uni-mainz.de>

summary.CoxBoost  $S\iota$ 

Summary of a CoxBoost type

## Description

Summary of a CoxBoost type

## Usage

```
## S3 method for class 'CoxBoost'
summary(object, ...)
```

### Arguments

object a CoxBoost object

... not used

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# Value

Invisibly returns NULL. The function is called for its side-effects, printing for each cause-stratum combination:

- the number of boosting steps and non-zero coefficients,
- the partial log-likelihood,
- the covariates with positive coefficients,
- the covariates with negative coefficients,
- and, if applicable, the coefficient estimates of mandatory (unpenalized) covariates.

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