Package 'hdcuremodels'

July 22, 2025

Title Penalized Mixture Cure Models for High-Dimensional Data

Version 0.0.1

Date 2024-06-11

Description Provides functions for fitting various penalized parametric and semi-parametric mixture cure models with different penalty functions, testing for a significant cure fraction, and testing for sufficient follow-up as described in Fu et al (2022)<doi:10.1002/sim.9513> and Archer et al (2024)<doi:10.1186/s13045-024-01553-6>. False discovery rate controlled variable selection is provided using model-X knock-offs.

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Encoding UTF-8

Depends R (>= 4.2.0)

Imports doParallel, flexsurv, flexsurvcure, foreach, ggplot2, ggpubr, glmnet, knockoff, mvnfast, parallel, plyr, methods, survival

RoxygenNote 7.3.1

Suggests knitr, rmarkdown

VignetteBuilder knitr

LazyData true

NeedsCompilation no

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Maintainer Kellie J. Archer <archer.43@osu.edu>

Repository CRAN

Date/Publication 2024-06-13 10:10:06 UTC

Contents

`amltest` *AML test data*

Description

Duration of complete response for 40 cytogenetically normal AML patients and a subset of 320 transcript expression from RNA-sequencing.

Usage

```
amltest
```

Format

A data frame with 40 rows (subjects) and 322 columns:

cryr duration of complete response in years

relapse.death censoring indicator: 1 = relapsed or died; 0 = alive at last follow=up

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ENSG00000005249 normalized expression for indicated transcript

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Source

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11068580/

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amltrain *AML training data*

Description

Duration of complete response for 306 cytogenetically normal AML patients and a subset of 320 transcript expression from RNA-sequencing.

Usage

```
amltrain
```

Format

A data frame with 306 rows (subjects) and 322 columns:

cryr duration of complete response in years

relapse.death censoring indicator: 1 = relapsed or died; 0 = alive at last follow=up

ENSG00000001561 normalized expression for indicated transcript

ENSG00000005249 normalized expression for indicated transcript

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ENSG00000241489 normalized expression for indicated transcript
ENSG00000241529 normalized expression for indicated transcript
ENSG00000244405 normalized expression for indicated transcript
ENSG00000247627 normalized expression for indicated transcript
ENSG00000249592 normalized expression for indicated transcript
ENSG00000250116 normalized expression for indicated transcript

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ENSG00000251079 normalized expression for indicated transcript

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ENSG00000259276 normalized expression for indicated transcript

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ENSG00000261377 normalized expression for indicated transcript

ENSG00000264885 normalized expression for indicated transcript

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ENSG00000267136 normalized expression for indicated transcript

ENSG00000267551 normalized expression for indicated transcript

ENSG00000267702 normalized expression for indicated transcript

ENSG00000268001 normalized expression for indicated transcript

ENSG00000268573 normalized expression for indicated transcript

ENSG00000270554 normalized expression for indicated transcript

ENSG00000270562 normalized expression for indicated transcript

ENSG00000271646 normalized expression for indicated transcript

ENSG00000273018 normalized expression for indicated transcript

ENSG00000273033 normalized expression for indicated transcript

Source

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11068580/

AUC *AUC for cure prediction using mean score imputation*

Description

This function calculates the AUC for cure prediction using the mean score imputation (MSI) method proposed by Asano et al.

Usage

```
AUC(object, newdata, cure_cutoff = 5, model.select = "AIC")
```

Arguments

object	a mixturecure object resulting from curegmifs, cureem, cv_curegmifs, cv_cureem.
newdata	an optional data.frame that minimally includes the incidence and/or latency variables to use for predicting the response. If omitted, the training data are used.
cure_cutoff	cutoff value for cure, used to produce a proxy for the unobserved cure status; default is 5.
model.select	for models fit using curegmifs or cureem any step along the solution path can be selected. The default is model.select = "AIC" which calculates the predicted values using the coefficients from the model having the lowest AIC. Other options are model.select = "mAIC" for the modified AIC, model.select = "cAIC" for the corrected AIC, model.select = "BIC", model.select = "mBIC" for the modified BIC, model.select = "EBIC" for the extended BIC, model.select = "logLik" for the step that maximizes the log-likelihood, or any numeric value from the solution path. This option has no effect for objects fit using cv_curegmifs or cv_cureem.

Value

Returns the AUC value for cure prediction using the mean score imputation (MSI) method.

References

Asano, J., Hirakawa, H., Hamada, C. (2014) Assessing the prediction accuracy of cure in the Cox proportional hazards cure model: an application to breast cancer data. *Pharmaceutical Statistics*, **13**:357–363.

See Also

concordance_mcm

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 100, J = 10, nTrue = 10, A = 1.8)
training <- temp$Training
testing <- temp$Testing
fit <- curegmifs(Surv(Time, Censor) ~ .,
                 data = training, x.latency = training,
                 model = "weibull", thresh = 1e-4, maxit = 2000,
                 epsilon = 0.01, verbose = FALSE)
AUC(fit)
AUC(fit, newdata = testing)
```

`coef.mixturecure` *Extract model coefficients from a fitted mixture cure object*

Description

`coef.mixturecure` is a generic function which extracts the model coefficients from a fitted mixture cure model object fit using `curegmifs`, `cureem`, `cv_curegmifs`, or `cv_cureem`.

Usage

```
## S3 method for class 'mixturecure'
coef(object, model.select = "AIC", ...)
```

Arguments

`object`	a `mixturecure` object resulting from `curegmifs`, `cureem`, `cv_curegmifs`, or `cv_cureem`.
`model.select`	for models fit using `curegmifs` or `cureem` any step along the solution path can be selected. The default is `model.select = "AIC"` which calculates the predicted values using the coefficients from the model having the lowest AIC. Other options are `model.select = "mAIC"` for the modified AIC, `model.select = "cAIC"` for the corrected AIC, `model.select = "BIC"`, `model.select = "mBIC"` for the modified BIC, `model.select = "EBIC"` for the extended BIC, `model.select = "logLik"` for the step that maximizes the log-likelihood, or any numeric value from the solution path. This option has no effect for objects fit using `cv_curegmifs` or `cv_cureem`.
`...`	other arguments.

Value

a list of estimated parameters extracted from the model object using the model selection criterion

See Also

`curegmifs`, `cureem`, `summary.mixturecure`, `plot.mixturecure`, `predict.mixturecure`

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 100, J = 10, nTrue = 10, A = 1.8)
training <- temp$Training
fit <- curegmifs(Surv(Time, Censor) ~ .,
                     data = training, x.latency = training,
                     model = "weibull", thresh = 1e-4, maxit = 2000, epsilon = 0.01,
                     verbose = FALSE)
coef(fit)
```

concordance_mcm *C-statistic for mixture cure models*

Description

This function calculates the C-statistic using the cure status weighting (CSW) method proposed by Asano and Hirakawa.

Usage

```
concordance_mcm(object, newdata, cure_cutoff = 5, model.select = "AIC")
```

Arguments

object	a mixturecure object resulting from curegmifs, cureem, cv_curegmifs, cv_cureem.
newdata	an optional data.frame that minimally includes the incidence and/or latency variables to use for predicting the response. If omitted, the training data are used.
cure_cutoff	cutoff value for cure, used to produce a proxy for the unobserved cure status; default is 5.
model.select	for models fit using curegmifs or cureem any step along the solution path can be selected. The default is model.select = "AIC" which calculates the predicted values using the coefficients from the model having the lowest AIC. Other options are model.select = "mAIC" for the modified AIC, model.select = "cAIC" for the corrected AIC, model.select = "BIC", model.select = "mBIC" for the modified BIC, model.select = "EBIC" for the extended BIC, model.select = "logLik" for the step that maximizes the log-likelihood, or any numeric value from the solution path. This option has no effect for objects fit using cv_curegmifs or cv_cureem.

Value

value of C-statistic for the cure models.

References

Asano, J. and Hirakawa, H. (2017) Assessing the prediction accuracy of a cure model for censored survival data with long-term survivors: Application to breast cancer data. *Journal of Biopharmaceutical Statistics*, **27**:6, 918–932.

See Also

AUC

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 100, J = 10, nTrue = 10, A = 1.8)
training <- temp$Training
testing <- temp$Testing
fit <- curegmifs(Surv(Time, Censor) ~ .,
                 data = training, x.latency = training,
                 model = "weibull", thresh = 1e-4, maxit = 2000,
                 epsilon = 0.01, verbose = FALSE)
concordance_mcm(fit)
concordance_mcm(fit, newdata = testing)
```

`cureem` *Fit penalized mixture cure model using the E-M algorithm*

Description

Fits a penalized parametric and semi-parametric mixture cure model (MCM) using the E-M algorithm with user-specified penalty parameters. The lasso (L1), MCP, and SCAD penalty is supported for the Cox MCM while only lasso is currently supported for parametric MCMs.

Usage

```
cureem(
  formula,
  data,
  subset,
  x.latency = NULL,
  model = "cox",
  penalty = "lasso",
  penalty.factor.inc = NULL,
  penalty.factor.lat = NULL,
  thresh = 0.001,
  scale = TRUE,
  maxit = NULL,
  inits = NULL,
  lambda.inc = 0.1,
  lambda.lat = 0.1,
  gamma.inc = 3,
  gamma.lat = 3,
  ...
)
```

Arguments

`formula`	an object of class "`formula`" (or one that can be coerced to that class): a symbolic description of the model to be fitted. The response must be a survival

object as returned by the Surv function while the variables on the right side of the formula are the covariates that are included in the incidence portion of the model.

`data` a data.frame in which to interpret the variables named in the `formula` or in the `subset` argument.

`subset` an optional expression indicating which subset of observations to be used in the fitting process, either a numeric or factor variable should be used in subset, not a character variable. All observations are included by default.

`x.latency` specifies the variables to be included in the latency portion of the model and can be either a matrix of predictors, a model formula with the right hand side specifying the latency variables, or the same data.frame passed to the `data` parameter. Note that when using the model formula syntax for `x.latency` it cannot handle `x.latency = ~ .`.

`model` type of regression model to use for the latency portion of mixture cure model. Can be "cox", "weibull", or "exponential" (default is "cox").

`penalty` type of penalty function. Can be "lasso", "MCP", or "SCAD" (default is "lasso").

`penalty.factor.inc`
vector of binary indicators representing the penalty to apply to each incidence coefficient: 0 implies no shrinkage and 1 implies shrinkage. If not supplied, 1 is applied to all incidence variables.

`penalty.factor.lat`
vector of binary indicators representing the penalty to apply to each latency coefficient: 0 implies no shrinkage and 1 implies shrinkage. If not supplied, 1 is applied to all latency variables.

`thresh` small numeric value. The iterative process stops when the differences between successive expected penalized complete-data log-likelihoods for both incidence and latency components are less than this specified level of tolerance (default is 10^-3).

`scale` logical, if TRUE the predictors are centered and scaled.

`maxit` integer specifying the maximum number of passes over the data for each lambda. If not specified, 100 is applied when `penalty = "lasso"` and 1000 is applied when `penalty = "MCP"` or `penalty = "SCAD"`.

`inits` an optional list specifiying the initial value for the incidence intercept (`itct`), a numeric vector for the unpenalized incidence coefficients (`b_u`), and a numeric vector for unpenalized latency coefficients (`beta_u`). For parametric models, it should also include a numeric value for the rate parameter (`lambda`) when `model = "weibull"` or `model = "exponential"`, and a numeric value for the shape parameter (`alpha`) when `model = "weibull"`. When `model = "cox"`, it should also include a numeric vector for the latency survival probabilities $S_u(t_i|w_i)$ for i=1,...,N (`survprob`). Penalized coefficients are initialized to zero. If `inits` is not specified or improperly specified, initialization is automatically provided by the function.

`lambda.inc` numeric value for the penalization parameter λ for variables in the incidence portion of the model.

`lambda.lat` numeric value for the penalization parameter λ for variables in the latency portion of the model.

`gamma.inc` numeric value for the penalization parameter γ for variables in the incidence portion of the model when `penalty = "MCP"` or `penalty = "SCAD"` (default is 3).

`gamma.lat` numeric value for the penalization parameter γ for variables in the latency portion of the model when `penalty = "MCP"` or `penalty = "SCAD"` (default is 3).

`...` additional arguments.

Value

`b_path` Matrix representing the solution path of the coefficients in the incidence portion of the model. Row is step and column is variable.

`beta_path` Matrix representing the solution path of lthe coefficients in the latency portion of the model. Row is step and column is variable.

`b0_path` Vector representing the solution path of the intercept in the incidence portion of the model.

`logLik.inc` Vector representing the expected penalized complete-data log-likelihood for the incidence portion of the model for each step in the solution path.

`logLik.lat` Vector representing the expected penalized complete-data log-likelihood for the latency portion of the model for each step in the solution path.

`x.incidence` Matrix representing the design matrix of the incidence predictors.

`x.latency` Matrix representing the design matrix of the latency predictors.

`y` Vector representing the survival object response as returned by the `Surv` function

`model` Character string indicating the type of regression model used for the latency portion of mixture cure model ("weibull" or "exponential").

`scale` Logical value indicating whether the predictors were centered and scaled.

`method` Character string indicating the EM alogoritm was used in fitting the mixture cure model.

`rate_path` Vector representing the solution path of the rate parameter for the Weibull or exponential density in the latency portion of the model.

`alpha_path` Vector representing the solution path of the shape parameter for the Weibull density in the latency portion of the model.

`call` the matched call.

References

Archer, K. J., Fu, H., Mrozek, K., Nicolet, D., Mims, A. S., Uy, G. L., Stock, W., Byrd, J. C., Hiddemann, W., Braess, J., Spiekermann, K., Metzeler, K. H., Herold, T., Eisfeld, A.-K. (2024) Identifying long-term survivors and those at higher or lower risk of relapse among patients with cytogenetically normal acute myeloid leukemia using a high-dimensional mixture cure model. *Journal of Hematology & Oncology*, **17**:28.

See Also

cv_cureem

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 80, J = 100, nTrue = 10, A = 1.8)
training <- temp$Training
fit <- cureem(Surv(Time, Censor) ~ ., data = training, x.latency = training,
                model = "cox", penalty = "lasso",
                lambda.inc = 0.1, lambda.lat = 0.1, gamma.inc = 6, gamma.lat = 10)
```

---

curegmifs *Fit penalized parametric mixture cure model using the GMIFS algorithm*

Description

Fits a penalized Weibull or exponential mixture cure model using the generalized monotone incremental forward stagewise (GMIFS) algorithm and yields solution paths for parameters in the incidence and latency portions of the model.

Usage

```
curegmifs(
  formula,
  data,
  subset,
  x.latency = NULL,
  model = "weibull",
  penalty.factor.inc = NULL,
  penalty.factor.lat = NULL,
  epsilon = 0.001,
  thresh = 1e-05,
  scale = TRUE,
  maxit = 10000,
  inits = NULL,
  verbose = TRUE,
  ...
)
```

Arguments

formula	an object of class "formula" (or one that can be coerced to that class): a symbolic description of the model to be fitted. The response must be a survival object as returned by the Surv function while the variables on the right side of the formula are the covariates that are included in the incidence portion of the model.

data	a data.frame in which to interpret the variables named in the formula or in the subset argument.
subset	an optional expression indicating which subset of observations to be used in the fitting process, either a numeric or factor variable should be used in subset, not a character variable. All observations are included by default.
x.latency	specifies the variables to be included in the latency portion of the model and can be either a matrix of predictors, a model formula with the right hand side specifying the latency variables, or the same data.frame passed to the data parameter. Note that when using the model formula syntax for x.latency it cannot handle x.latency = ~ ..
model	type of regression model to use for the latency portion of mixture cure model. Can be "weibull" or "exponential"; default is "weibull".
penalty.factor.inc	vector of binary indicators representing the penalty to apply to each incidence coefficient: 0 implies no shrinkage and 1 implies shrinkage. If not supplied, 1 is applied to all incidence variables.
penalty.factor.lat	vector of binary indicators representing the penalty to apply to each latency coefficient: 0 implies no shrinkage and 1 implies shrinkage. If not supplied, 1 is applied to all latency variables.
epsilon	small numeric value reflecting the incremental value used to update a coefficient at a given step (default is 0.001).
thresh	small numeric value. The iterative process stops when the differences between successive expected penalized complete-data log-likelihoods for both incidence and latency components are less than this specified level of tolerance (default is 10^-5).
scale	logical, if TRUE the predictors are centered and scaled.
maxit	integer specifying the maximum number of steps to run in the iterative algorithm (default is 10^4).
inits	an optional list specifiying the initial value for the incidence intercept (itct), a numeric vector for the unpenalized incidence coefficients (b_u), and a numeric vector for unpenalized latency coefficients (beta_u), a numeric value for the rate parameter (lambda), and a numeric value for the shape parameter (alpha) when model = "weibull". If not supplied or improperly supplied, initialization is automatically provided by the function.
verbose	logical, if TRUE running information is printed to the console (default is FALSE).
...	additional arguments.

Value

b_path	Matrix representing the solution path of the coefficients in the incidence portion of the model. Row is step and column is variable.
beta_path	Matrix representing the solution path of lthe coefficients in the latency portion of the model. Row is step and column is variable.

b0_path	Vector representing the solution path of the intercept in the incidence portion of the model.
rate_path	Vector representing the solution path of the rate parameter for the Weibull or exponential density in the latency portion of the model.
logLik	Vector representing the log-likelihood for each step in the solution path.
x.incidence	Matrix representing the design matrix of the incidence predictors.
x.latency	Matrix representing the design matrix of the latency predictors.
y	Vector representing the survival object response as returned by the Surv function
model	Character string indicating the type of regression model used for the latency portion of mixture cure model ("weibull" or "exponential").
scale	Logical value indicating whether the predictors were centered and scaled.
alpha_path	Vector representing the solution path of the shape parameter for the Weibull density in the latency portion of the model.
call	the matched call.

References

Fu, H., Nicolet, D., Mrozek, K., Stone, R. M., Eisfeld, A. K., Byrd, J. C., Archer, K. J. (2022) Controlled variable selection in Weibull mixture cure models for high-dimensional data. *Statistics in Medicine*, **41**(22), 4340–4366.

See Also

cv_curegmifs

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 100, J = 10, nTrue = 10, A = 1.8)
training <- temp$Training

fit <- curegmifs(Surv(Time, Censor) ~ .,
         data = training, x.latency = training,
         model = "weibull", thresh = 1e-4, maxit = 2000, epsilon = 0.01,
         verbose = FALSE)
```

---

cure_estimate *Estimate cured fraction*

Description

Estimates the cured fraction using a Kaplan-Meier fitted object.

Usage

```
cure_estimate(object)
```

Arguments

object	a survfit object.

Value

estimated proportion of cured observations

See Also

survfit, sufficient_fu_test, nonzerocure_test

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 100, J = 10, nTrue = 10, A = 1.8)
training <- temp$Training
km.fit <- survfit(Surv(Time, Censor) ~ 1, data = training)
cure_estimate(km.fit)
```

---

cv_cureem *Fit penalized mixture cure model using the E-M algorithm with cross-validation for parameter tuning*

Description

Fits a penalized parametric and semi-parametric mixture cure model (MCM) using the E-M algorithm with with k-fold cross-validation for parameter tuning. The lasso (L1), MCP and SCAD penalty are supported for the Cox MCM while only lasso is currently supported for parametric MCMs. When FDR controlled variable selection is used, the model-X knockoffs method is applied and indices of selected variables are returned.

Usage

```
cv_cureem(
  formula,
  data,
  subset,
  x.latency = NULL,
  model = "cox",
  penalty = "lasso",
  penalty.factor.inc = NULL,
  penalty.factor.lat = NULL,
  fdr.control = FALSE,
```

```
  fdr = 0.2,
  grid.tuning = FALSE,
  thresh = 0.001,
  scale = TRUE,
  maxit = NULL,
  inits = NULL,
  lambda.inc.list = NULL,
  lambda.lat.list = NULL,
  nlambda.inc = NULL,
  nlambda.lat = NULL,
  gamma.inc = 3,
  gamma.lat = 3,
  lambda.min.ratio.inc = 0.1,
  lambda.min.ratio.lat = 0.1,
  n_folds = 5,
  measure.inc = "c",
  one.se = FALSE,
  cure_cutoff = 5,
  parallel = FALSE,
  seed = NULL,
  verbose = TRUE,
  ...
)
```

Arguments

formula	an object of class "formula" (or one that can be coerced to that class): a symbolic description of the model to be fitted. The response must be a survival object as returned by the Surv function while the variables on the right side of the formula are the covariates that are included in the incidence portion of the model.
data	a data.frame in which to interpret the variables named in the formula or in the subset argument.
subset	an optional expression indicating which subset of observations to be used in the fitting process, either a numeric or factor variable should be used in subset, not a character variable. All observations are included by default.
x.latency	specifies the variables to be included in the latency portion of the model and can be either a matrix of predictors, a model formula with the right hand side specifying the latency variables, or the same data.frame passed to the data parameter. Note that when using the model formula syntax for x.latency it cannot handle x.latency = ~ ..
model	type of regression model to use for the latency portion of mixture cure model. Can be "cox", "weibull", or "exponential" (default is "cox").
penalty	type of penalty function. Can be "lasso", "MCP", or "SCAD" (default is "lasso").
penalty.factor.inc	vector of binary indicators representing the penalty to apply to each incidence coefficient: 0 implies no shrinkage and 1 implies shrinkage. If not supplied, 1 is applied to all incidence variables.

penalty.factor.lat
: vector of binary indicators representing the penalty to apply to each latency coefficient: 0 implies no shrinkage and 1 implies shrinkage. If not supplied, 1 is applied to all latency variables.

fdr.control
: logical, if TRUE, model-X knockoffs are used for FDR-controlled variable selection and indices of selected variables are returned (default is FALSE).

fdr
: numeric value in (0, 1) range specifying the target FDR level to use for variable selection when fdr.control=TRUE (default is 0.2).

grid.tuning
: logical, if TRUE a 2-D grid tuning approach is used to select the optimal pair of λ_b and λ_β penalty parameters for the incidence and latency portions of the model, respectively. Otherwise the λ_b and λ_β are selected from a 1-D sequence and are equal to one another (default is FALSE).

thresh
: small numeric value. The iterative process stops when the differences between successive expected penalized complete-data log-likelihoods for both incidence and latency components are less than this specified level of tolerance (default is 10^-3).

scale
: logical, if TRUE the predictors are centered and scaled.

maxit
: maximum number of passes over the data for each lambda. If not specified, 100 is applied when penalty = "lasso" and 1000 is applied when penalty = "MCP" or penalty = "SCAD".

inits
: an optional list specifiying the initial value for the incidence intercept (itct), a numeric vector for the unpenalized incidence coefficients (b_u), and a numeric vector for unpenalized latency coefficients (beta_u). For parametric models, it should also include a numeric value for the rate parameter (lambda) when model = "weibull" or model = "exponential", and a numeric value for the shape parameter (alpha) when model = "weibull". When model = "cox", it should also include a numeric vector for the latency survival probabilities $S_u(t_i|w_i)$ for i=1,...,N (survprob). Penalized coefficients are initialized to zero. If inits is not specified or improperly specified, initialization is automatically provided by the function.

lambda.inc.list
: a numeric vector used to search for the optimal λ_b tuning parameter. If not supplied, the function computes a λ_b sequence based on nlambda.inc and lambda.min.ratio.inc. If grid.tuning=FALSE, the same sequence should be used for both λ_b and λ_β.

lambda.lat.list
: a numeric vector used to search for the optimal λ_β tuning parameter. If not supplied, the function computes a λ_β sequence based on nlambda.lat and lambda.min.ratio.lat. If grid.tuning=FALSE, the same sequence should be used for both λ_b and λ_β.

nlambda.inc
: an integer specifying the number of values to search for the optimal λ_b tuning parameter; default is 10 if grid.tuning=TRUE and 50 otherwise.

nlambda.lat
: an integer specifying the number of values to search for the optimal λ_β tuning parameter; default is 10 if grid.tuning=TRUE and 50 otherwise.

gamma.inc
: numeric value for the penalization parameter γ for variables in the incidence portion of the model when penalty = "MCP" or penalty = "SCAD" (default is 3).

`gamma.lat` numeric value for the penalization parameter γ for variables in the latency portion of the model when `penalty = "MCP"` or `penalty = "SCAD"` (default is 3).

`lambda.min.ratio.inc` numeric value in (0,1) representing the smallest value for λ_b as a fraction of `lambda.max.inc`, the data-derived entry value at which essentially all penalized variables in the incidence portion of the model have a coefficient estimate of 0 (default is 0.1).

`lambda.min.ratio.lat` numeric value in (0.1) representing the smallest value for λ_β as a fraction of `lambda.max.lat`, the data-derived entry value at essentially all penalized variables in the latency portion of the model have a coefficient estimate of 0 (default is 0.1).

`n_folds` an integer specifying the number of folds for the k-fold cross-valiation procedure (default is 5).

`measure.inc` character string specifying the evaluation criterion used in selecting the optimal λ_b. Can be "c" or "auc"; default is "c". If `measure.inc="c"`, the C-statistic using the cure status weighting (CSW) method proposed by Asano and Hirakawa (2017) is used to select both λ_b and λ_β. If `measure.inc="auc"`, the AUC for cure prediction using the mean score imputation (MSI) method proposed by Asano et al. (2014) is used to select λ_b while the C-statistic with CSW is used for λ_β.

`one.se` logical, if TRUE then the one standard error rule is applied for selecting the optimal parameters. The one standard error rule selects the most parsimonious model having evaluation criterion no more than one standard error worse than that of the best evaluation criterion (default is FALSE).

`cure_cutoff` numeric value representing the cutoff time value that represents subjects not experiencing the event by this time are cured. This value is used to produce a proxy for the unobserved cure status when calculating C-statistic and AUC (default is 5 representing 5 years). Users should be careful to note the time scale of their data and adjust this according to the time scale and clinical application.

`parallel` logical. If TRUE, parallel processing is performed for K-fold CV using `foreach` and the **doMC** package is required.

`seed` optional integer representing the random seed. Setting the random seed fosters reproducibility of the results.

`verbose` logical, if TRUE running information is printed to the console (default is FALSE).

`...` additional arguments.

Value

`b0` Estimated intercept for the incidence portion of the model.

`b` Estimated coefficients for the incidence portion of the model.

`beta` Estimated coefficients for the latency portion of the model.

`alpha` Estimated shape parameter if the Weibull model is fit.

`rate` Estimated rate parameter if the Weibull or exponential model is fit.

`logLik.inc` Expected penalized complete-data log-likelihood for the incidence portion of the model.

`logLik.lat` Expected penalized complete-data log-likelihood for the latency portion of the model.

`selected.lambda.inc` Value of λ_b selected using cross-validation. NULL when fdr.control is TRUE.

`selected.lambda.lat` Value of λ_β selected using cross-validation. NULL when fdr.control is TRUE.

`max.c` Maximum C-statistic achieved.

`max.auc` Maximum AUC for cure prediction achieved; only output when `measure.inc="auc"`.

`selected.index.inc` Indices of selected variables for the incidence portion of the model when `fdr.control=TRUE`. If no variables are selected, `int(0)` will be returned.

`selected.index.lat` Indices of selected variables for the latency portion of the model when `fdr.control=TRUE`. If no variables are selected, `int(0)` will be returned.

`call` the matched call.

References

Archer, K. J., Fu, H., Mrozek, K., Nicolet, D., Mims, A. S., Uy, G. L., Stock, W., Byrd, J. C., Hiddemann, W., Braess, J., Spiekermann, K., Metzeler, K. H., Herold, T., Eisfeld, A.-K. (2024) Identifying long-term survivors and those at higher or lower risk of relapse among patients with cytogenetically normal acute myeloid leukemia using a high-dimensional mixture cure model. *Journal of Hematology & Oncology*, **17**:28.

See Also

`cureem`

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 200, J = 25, nTrue = 5, A = 1.8)
training <- temp$Training
fit.cv <- cv_cureem(Surv(Time, Censor) ~ ., data = training,
                x.latency = training, fdr.control = FALSE,
                grid.tuning = FALSE, nlambda.inc = 10, nlambda.lat = 10,
                n_folds = 2, seed = 23, verbose = TRUE)
fit.cv.fdr <- cv_cureem(Surv(Time, Censor) ~ ., data = training,
                x.latency = training, model = "weibull", penalty = "lasso",
                fdr.control = TRUE, grid.tuning = FALSE, nlambda.inc = 10,
                nlambda.lat = 10, n_folds = 2, seed = 23, verbose = TRUE)
```

`cv_curegmifs` *Fit a penalized parametric mixture cure model using the GMIFS algorithm with cross-validation for model selection*

Description

Fits a penalized Weibull or exponential mixture cure model using the generalized monotone incremental forward stagewise (GMIFS) algorithm with k-fold cross-validation to select the optimal iteration step along the solution path. When FDR controlled variable selection is used, the model-X knockoffs method is applied and indices of selected variables are returned.

Usage

```
cv_curegmifs(
  formula,
  data,
  subset,
  x.latency = NULL,
  model = "weibull",
  penalty.factor.inc = NULL,
  penalty.factor.lat = NULL,
  fdr.control = FALSE,
  fdr = 0.2,
  epsilon = 0.001,
  thresh = 1e-05,
  scale = TRUE,
  maxit = 10000,
  inits = NULL,
  n_folds = 5,
  measure.inc = "c",
  one.se = FALSE,
  cure_cutoff = 5,
  parallel = FALSE,
  seed = NULL,
  verbose = TRUE,
  ...
)
```

Arguments

`formula`	an object of class "`formula`" (or one that can be coerced to that class): a symbolic description of the model to be fitted. The response must be a survival object as returned by the `Surv` function while the variables on the right side of the formula are the covariates that are included in the incidence portion of the model.
`data`	a data.frame in which to interpret the variables named in the `formula` or in the `subset` argument.

`subset` an optional expression indicating which subset of observations to be used in the fitting process, either a numeric or factor variable should be used in subset, not a character variable. All observations are included by default.

`x.latency` specifies the variables to be included in the latency portion of the model and can be either a matrix of predictors, a model formula with the right hand side specifying the latency variables, or the same data.frame passed to the `data` parameter. Note that when using the model formula syntax for `x.latency` it cannot handle `x.latency = ~ .`.

`model` type of regression model to use for the latency portion of mixture cure model. Can be "weibull" or "exponential"; default is "weibull".

`penalty.factor.inc`
vector of binary indicators representing the penalty to apply to each incidence coefficient: 0 implies no shrinkage and 1 implies shrinkage. If not supplied, 1 is applied to all incidence variables.

`penalty.factor.lat`
vector of binary indicators representing the penalty to apply to each latency coefficient: 0 implies no shrinkage and 1 implies shrinkage. If not supplied, 1 is applied to all latency variables.

`fdr.control` logical, if TRUE, model-X knockoffs are used for FDR-controlled variable selection and indices of selected variables are returned (default is FALSE).

`fdr` numeric value in (0, 1) range specifying the target FDR level to use for variable selection when `fdr.control=TRUE` (default is 0.2).

`epsilon` small numeric value reflecting incremental value used to update a coefficient at a given step (default is 0.001).

`thresh` small numeric value. The iterative process stops when the differences between successive expected penalized complete-data log-likelihoods for both incidence and latency components are less than this specified level of tolerance (default is 10^-5).

`scale` logical, if TRUE the predictors are centered and scaled.

`maxit` integer specifying the maximum number of steps to run in the iterative algorithm (default is 10^4).

`inits` an optional list specifiying the initial value for the incidence intercept (`itct`), a numeric vector for the unpenalized incidence coefficients (`b_u`), and a numeric vector for unpenalized latency coefficients (`beta_u`), a numeric value for the rate parameter (`lambda`), and a numeric value for the shape parameter (`alpha`) when `model = "weibull"`. If not supplied or improperly supplied, initialization is automatically provided by the function.

`n_folds` an integer specifying the number of folds for the k-fold cross-valiation procedure (default is 5).

`measure.inc` character string specifying the evaluation criterion used in selecting the optimal λ_b. Can be "c" or "auc"; default is "c". If `measure.inc="c"`, the C-statistic using the cure status weighting (CSW) method proposed by Asano and Hirakawa (2017) is used to select both λ_b and λ_β. If `measure.inc="auc"`, the AUC for cure prediction using the mean score imputation (MSI) method proposed by Asano et al. (2014) is used to select λ_b while the C-statistic with CSW is used for λ_β.

one.se	logical, if TRUE then the one standard error rule is applied for selecting the optimal parameters. The one standard error rule selects the most parsimonious model having evaluation criterion no more than one standard error worse than that of the best evaluation criterion (default is FALSE).
cure_cutoff	numeric value representing the cutoff time value that represents subjects not experiencing the event by this time are cured. This value is used to produce a proxy for the unobserved cure status when calculating C-statistic and AUC (default is 5 representing 5 years). Users should be careful to note the time scale of their data and adjust this according to the time scale and clinical application.
parallel	logical. If TRUE, parallel processing is performed for K-fold CV using `foreach` and the **doMC** package is required.
seed	optional integer representing the random seed. Setting the random seed fosters reproducibility of the results.
verbose	logical, if TRUE running information is printed to the console (default is FALSE).
...	additional arguments.

Value

b0	Estimated intercept for the incidence portion of the model.
b	Estimated coefficients for the incidence portion of the model.
beta	Estimated coefficients for the latency portion of the model.
alpha	Estimated shape parameter if the Weibull model is fit.
rate	Estimated rate parameter if the Weibull or exponential model is fit.
logLik	Log-likelihood value.
selected.step.inc	Iteration step selected for the incidence portion of the model using cross-validation. NULL when fdr.control is TRUE.
selected.step.lat	Iteration step selected for the latency portion of the model using cross-validation. NULL when fdr.control is TRUE.
max.c	Maximum C-statistic achieved
max.auc	Maximum AUC for cure prediction achieved; only output when `measure.inc="auc"`.
selected.index.inc	Indices of selected variables for the incidence portion of the model when `fdr.control=TRUE`. If none selected, `int(0)` will be returned.
selected.index.lat	Indices of selected variables for the latency portion of the model when `fdr.control=TRUE`. If none selected, `int(0)` will be returned.
call	the matched call.

References

Fu, H., Nicolet, D., Mrozek, K., Stone, R. M., Eisfeld, A. K., Byrd, J. C., Archer, K. J. (2022) Controlled variable selection in Weibull mixture cure models for high-dimensional data. *Statistics in Medicine*, **41**(22), 4340–4366.

See Also

curegmifs

curegmifs

Examples

```
library(survival)
set.seed(123)
temp <- generate_cure_data(N = 100, J = 15, nTrue = 3, A = 1.8, rho = 0.2)
training <- temp$Training

fit.cv <- cv_curegmifs(Surv(Time, Censor) ~ ., data = training,
                       x.latency = training, fdr.control = FALSE,
                       maxit = 450, epsilon = 0.01,
                       n_folds = 2, seed = 23, verbose = TRUE)
```

---

generate_cure_data *Simulate data under a mixture cure model*

Description

Simulate data under a mixture cure model

Usage

```
generate_cure_data(
  N = 400,
  J = 500,
  nonp = 2,
  train.prop = 3/4,
  nTrue = 10,
  A = 1,
  rho = 0.5,
  itct_mean = 0.5,
  cens_ub = 20,
  alpha = 1,
  lambda = 2,
  same_signs = FALSE,
  model = "weibull"
)
```

Arguments

N	an integer denoting the total sample size.
J	an integer denoting the number of penalized predictors which is the same for both the incidence and latency portions of the model.

nonp	an integer less than J denoting the number of unpenalized predictors (which is the same for both the incidence and latency portions of the model.
train.prop	a numeric value in 0, 1 representing the fraction of N to be used in forming the Training dataset.
nTrue	an integer denoting the number of variables truly associated with the outcome (i.e., the number of covariates with nonzero parameter values) among the penalized predictors.
A	a numeric value denoting the effect size which is the same for both the incidence and latency portions of the model.
rho	a numeric value in 0, 1 representing the correlation between adjacent covariates in the same block. See details below.
itct_mean	a numeric value representing the expectation of the incidence intercept which controls the cure rate.
cens_ub	a numeric value representing the upper bound on the censoring time distribition which follows a uniform distribution on 0, cens_ub.
alpha	a numeric value representing the shape parameter in the Weibull density.
lambda	a numeric value representing the rate parameter in the Weibull density.
same_signs	logical, if TRUE the incidence and latency coefficients have the same signs.
model	type of regression model to use for the latency portion of mixture cure model. Can be "weibull", "GG", "Gompertz", "nonparametric", or "GG_baseline".

Value

Training	Training data.frame which includes Time, Censor, and covariates.
Testing	Testing data.frame which includes Time, Censor, and covariates.
parameters	A list including: the indices of true incidence signals (nonzero_b), indices of true latency signals (nonzero_beta), unpenalized incidence parameter values (b_u), unpenalized latency parameter values (beta_u), parameter values for the true incidence signals among penalized covariates (b_p_nz), parameter values for the true latency signals among penalized covariates (beta_p_nz), parameter value for the incidence intercept (itct)

Examples

```
library(survival)
set.seed(1234)
data <- generate_cure_data(N = 200, J = 50, nTrue = 10, A = 1.8, rho = 0.2)
training <- data$Training
testing <- data$Testing
fit <- cureem(Surv(Time, Censor) ~ ., data = training,
              x.latency = training, model = "cox", penalty = "lasso",
              lambda.inc = 0.05, lambda.lat = 0.05,
              gamma.inc = 6, gamma.lat = 10)
```

nonzerocure_test *Non-parametric pest for a non-zero cured fraction*

Description

Tests the null hypothesis that the proportion of observations susceptible to the event = 1 against the alternative that the proportion of observations susceptible to the event is < 1. If the null hypothesis is rejected, there is a significant cured fraction.

Usage

```
nonzerocure_test(object, Reps = 1000, seed = NULL, plot = FALSE, B = NULL)
```

Arguments

object	a survfit object.
Reps	number of simulations on which to base the p-value (default = 1000).
seed	optional random seed.
plot	logical. If TRUE a histogram of the estimated susceptible proportions over all simulations is produced.
B	optional. If specified the maximum observed time for the uniform distribution for generating the censoring times. If not specified, an exponential model is used for generating the censoring times (default).

Value

proportion_susceptible
: estimated proportion of susceptibles

proportion_cured
: estimated proportion of those cured

p.value
: p-value testing the null hypothesis that the proportion of susceptibles = 1 (cured fraction = 0) against the alternative that the proportion of susceptibles < 1 (non-zero cured fraction)

time_95_percent_of_events
: estimated time at which 95% of events should have occurred

References

Maller, R. A. and Zhou, X. (1996) *Survival Analysis with Long-Term Survivors*. John Wiley & Sons.

See Also

survfit, cure_estimate, sufficient_fu_test

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 100, J = 10, nTrue = 10, A = 1.8)
training <- temp$Training
km.fit <- survfit(Surv(Time, Censor) ~ 1, data = training)
nonzerocure_test(km.fit)
```

`plot.mixturecure` *Plot fitted mixture cure model*

Description

This function plots either the coefficient path, the AIC, the cAIC, the BIC, or the log-likelihood for a fitted `curegmifs` or `cureem` object. This function produces a lollipop plot of the coefficient estimates for a fitted `cv_curegmifs` or `cv_cureem` object.

Usage

```
## S3 method for class 'mixturecure'
plot(x, type = "trace", xlab = NULL, ylab = NULL, main = NULL, ...)
```

Arguments

`x`	a `mixturecure` object resulting from `curegmifs` or `cureem`, `cv_curegmifs` or `cv_cureem`.
`type`	default is `"trace"` which plots the coefficient path for the fitted object. Also available are `"AIC"`, `"cAIC"`, `"mAIC"`, `"BIC"`, `"mBIC"`, `"EBIC"`, and `"logLik"`. This option has no effect for objects fit using `cv_curegmifs` or `cv_cureem`.
`xlab`	a default x-axis label will be used which can be changed by specifying a user-defined x-axis label.
`ylab`	a default y-axis label will be used which can be changed by specifying a user-defined y-axis label.
`main`	a default main title will be used which can be changed by specifying a user-defined main title. This option is not used for `cv_curegmifs` or `cv_cureem` fitted objects.
`...`	other arguments.

Value

this function has no returned value but is called for its side effects

See Also

`curegmifs`, `cureem`, `coef.mixturecure`, `summary.mixturecure`, `predict.mixturecure`

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 100, J = 10, nTrue = 10, A = 1.8)
training <- temp$Training
fit <- curegmifs(Surv(Time, Censor) ~ .,
                  data = training, x.latency = training,
                  model = "weibull", thresh = 1e-4, maxit = 2000,
                  epsilon = 0.01, verbose = FALSE)
plot(fit)
```

---

predict.mixturecure *Predicted probabilities for susceptibles, linear predictor for latency, and risk class for latency for mixture cure fit*

Description

This function returns a list the includes the predicted probabilities for susceptibles as well as the linear predictor for the latency distribution and a dichotomous risk for latency for a `curegmifs`, `cureem`, `cv_curegmifs` or `cv_cureem` fitted object.

Usage

```
## S3 method for class 'mixturecure'
predict(object, newdata, model.select = "AIC", ...)
```

Arguments

`object`	a `mixturecure` object resulting from `curegmifs`, `cureem`, `cv_curegmifs`, `cv_cureem`.
`newdata`	an optional data.frame that minimally includes the incidence and/or latency variables to use for predicting the response. If omitted, the training data are used.
`model.select`	for models fit using `curegmifs` or `cureem` any step along the solution path can be selected. The default is `model.select = "AIC"` which calculates the predicted values using the coefficients from the model having the lowest AIC. Other options are `model.select = "mAIC"` for the modified AIC, `model.select = "cAIC"` for the corrected AIC, `model.select = "BIC"`, `model.select = "mBIC"` for the modified BIC, `model.select = "EBIC"` for the extended BIC, `model.select = "logLik"` for the step that maximizes the log-likelihood, or any numeric value from the solution path. This option has no effect for objects fit using `cv_curegmifs` or `cv_cureem`.
`...`	other arguments

Value

p.uncured	a vector of probabilities from the incidence portion of the fitted model representing the P(uncured).
linear.latency	a vector for the linear predictor from the latency portion of the model.
latency.risk	a dichotomous class representing low (below the median) versus high risk for the latency portion of the model.

See Also

curegmifs, cureem, coef.mixturecure, summary.mixturecure, plot.mixturecure

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 100, J = 10, nTrue = 10, A = 1.8)
training <- temp$Training
fit <- curegmifs(Surv(Time, Censor) ~ .,
                 data = training, x.latency = training,
                 model = "weibull", thresh = 1e-4, maxit = 2000,
                 epsilon = 0.01, verbose = FALSE)
predict.train <- predict(fit)
names(predict.train)
testing <- temp$Testing
predict.test <- predict(fit, newdata = testing)
```

---

print.mixturecure *Print the contents of a mixture cure fitted object*

Description

This function prints the names of the list objects from a curegmifs, cureem, cv_cureem, or cv_curegmifs fitted model.

Usage

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

Arguments

x	a mixturecure object resulting from curegmifs, cureem, cv_cureem, or cv_curegmifs.
...	other arguments.

Value

names of the objects in a mixturecure object fit using cureem, curegmifs, cv_cureem, or cv_curegmifs.

Note

The contents of an mixturecure fitted object differ depending upon whether the EM (cureem) or GMIFS (curegmifs) algorithm is used for model fitting. Also, the output differs depending upon whether x.latency is specified in the model (i.e., variables are included in the latency portion of the model fit) or only terms on the right hand side of the equation are included (i.e., variables are included in the incidence portion of the model).

See Also

curegmifs, cureem, coef.mixturecure, summary.mixturecure, plot.mixturecure, predict.mixturecure

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 100, J = 10, nTrue = 10, A = 1.8)
training <- temp$Training
fit <- curegmifs(Surv(Time, Censor) ~ .,
                      data = training, x.latency = training,
                      model = "weibull", thresh = 1e-4, maxit = 2000,
                      epsilon = 0.01, verbose = FALSE)
print(fit)
```

---

sufficient_fu_test *Test for sufficient follow-up*

Description

Tests for sufficient follow-up using a Kaplan-Meier fitted object.

Usage

```
sufficient_fu_test(object)
```

Arguments

object	a survfit object.

Value

p.value	p-value from testing the null hypothesis that there was not sufficient follow-up against the alternative that there was sufficient follow-up
Nn	total number of events that occurred at time > pmax(0, 2*(last observed event time)-(last observed time)) and < the last observed event time
N	number of observations in the dataset

References

Maller, R. A. and Zhou, X. (1996) *Survival Analysis with Long-Term Survivors*. John Wiley & Sons.

See Also

survfit, cure_estimate, nonzerocure_test

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 100, J = 10, nTrue = 10, A = 1.8)
training <- temp$Training
km.fit <- survfit(Surv(Time, Censor) ~ 1, data = training)
sufficient_fu_test(km.fit)
```

---

summary.mixturecure *Summarize a Fitted Mixture Cure Object.*

Description

summary method for a mixturecure object fit using curegmifs, cureem, cv_curegmifs, or cv_cureem.

Usage

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

Arguments

object	a mixturecure object resulting from curegmifs, cureem, cv_curegmifs, or cv_cureem.
...	other arguments.

Value

prints the following items extracted from the object fit using curegmifs or cureem: the step and value that maximizes the log-likelihood; the step and value that minimizes the AIC, modified AIC (mAIC), corrected AIC (cAIC), BIC, modified BIC (mBIC), and extended BIC (EBIC). Returns log-likelihood, AIC, and BIC if the object was fit using cv_curegmifs or cv_cureem at the optimal cross-validated values if no FDR control; the number of non-zero incidence and latency variables is returned when cross-validation is used together with FDR control.

See Also

curegmifs, cureem, coef.mixturecure, plot.mixturecure, predict.mixturecure

Examples

```
library(survival)
set.seed(1234)
temp <- generate_cure_data(N = 100, J = 10, nTrue = 10, A = 1.8)
training <- temp$Training
fit <- curegmifs(Surv(Time, Censor) ~ .,
                      data = training, x.latency = training,
                      model = "weibull", thresh = 1e-4, maxit = 2000,
                      epsilon = 0.01, verbose = FALSE)
summary(fit)
```

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