Package 'cuRe'

October 12, 2022

Type Package
Title Parametric Cure Model Estimation
Version 1.1.0
Date 2022-05-16
Maintainer Lasse Hjort Jakobsen <lahja@math.aau.dk></lahja@math.aau.dk>
Description Contains functions for estimating generalized parametric mixture and non-mixture cure models, loss of lifetime, mean residual lifetime, and crude event probabilities.
<pre>URL https://github.com/LasseHjort/cuRe</pre>
<pre>BugReports https://github.com/LasseHjort/cuRe/issues</pre>
License GPL (>= 2)
Encoding UTF-8
Depends R (>= 3.5.0), survival, rstpm2, date
Imports numDeriv, statmod, relsurv, reshape2
LazyData Yes
RoxygenNote 7.1.2
NeedsCompilation no
Author Lasse Hjort Jakobsen [aut, cre], Mark Clements [cph], Rasmus Kuhr Jensen [ctb], Lars Klingen Gjærde [ctb]
Repository CRAN
Date/Publication 2022-05-16 18:20:02 UTC
R topics documented:
AIC.cm

2 AIC.cm

bsx	4
calc.Crude	5
calc.Crude.quantile	8
calc.cure.quantile	10
calc.LL	11
calc.LL.quantile	13
cb	15
cbc	16
colonDC	17
fit.cure.model	17
general.haz	20
GenFlexCureModel	22
lrtest	25
lts	26
plot.crude	28
plot.cuRe	29
Provide the first term of the	30
plot.lts	30
predict.cm	31
F0	
survexp.dk	34
	35

AIC.cm

Index

Akaike information criterion

Description

This function computes the AIC for a fitted parametric cure model.

Usage

```
## S3 method for class 'cm'
AIC(object, ..., k = 2)
```

Arguments

object	Object of class cm or gfcm.
	Additionally arguments. Not currently used
k	Number to control if either AIC or BIC is to be computed (default is 2 equal to AIC).

AIC.gfcm 3

Description

This function computes the AIC for a fitted parametric cure model.

Usage

```
## S3 method for class 'gfcm' AIC(object, ..., k = 2)
```

Arguments

object	Object of class cm or gfcm.
	Additionally arguments. Not currently used
k	Number to control if either AIC or BIC is to be computed (default is 2 equal to AIC).

BIC.cm Bayesian information criterion	BIC.cm	Bayesian information criterion	
---------------------------------------	--------	--------------------------------	--

Description

This function computes the BIC for a fitted parametric cure model.

Usage

```
## S3 method for class 'cm'
BIC(object, ...)
```

Arguments

object Object of class cm or gfcm.

... Some methods for this generic function may take additional, optional arguments.
At present none do.

4 bsx

BIC.gfcm

Bayesian information criterion

Description

This function computes the BIC for a fitted parametric cure model.

Usage

```
## S3 method for class 'gfcm'
BIC(object, ...)
```

Arguments

object

Object of class cm or gfcm.

. . .

Some methods for this generic function may take additional, optional arguments.

At present none do.

bsx

Polynomial B-splines with eXtensions

Description

Generate the B-spline basis matrix for a polynomial spline with derivative restrictions at the boundary knots.

Usage

```
bsx(
    x,
    df = NULL,
    knots = NULL,
    degree = 3,
    intercept = FALSE,
    Boundary.knots = range(x),
    deriv = NULL
)
```

Arguments

x the predictor variable. Missing values are allowed.

df

degrees of freedom; one can specify df rather than knots; bs() then chooses df-degree (minus one if there is an intercept) knots at suitable quantiles of x (which will ignore missing values). The default, NULL, corresponds to no inner knots, i.e., degree-intercept.

calc.Crude 5

knots the internal breakpoints that define the spline. The default is NULL, which results

in a basis for ordinary polynomial regression. Typical values are the mean or median for one knot, quantiles for more knots. See also Boundary.knots.

degree degree of the piecewise polynomial—default is 3 for cubic splines.

intercept if TRUE, an intercept is included in the basis; default is FALSE.

Boundary knots boundary points at which to anchor the B-spline basis (default the range of the

non-NA data). If both knots and Boundary, knots are supplied, the basis parameters do not depend on y. Data can extend beyond Boundary, knots

rameters do not depend on x. Data can extend beyond Boundary.knots.

deriv an integer vector of length 2 with values between 0 and degree + 1 giving the

derivative constraint order at the left and right boundary knots; an order of 2 constrains the second derivative to zero (f''(x)=0); an order of 1 constrains the first and second derivatives to zero (f'(x)=f''(x)=0); an order of 0 constrains the zero, first and second derivatives to zero (f(x)=f''(x)=f''(x)=0) An order of

degree + 1 computes the basis matrix similarly to bs.

Value

A matrix with containing the basis functions evaluated in x.

calc.Crude

Crude event probabilities

Description

Function for computing crude event probabilties based on relative survival models.

Usage

```
calc.Crude(
  object,
  newdata = NULL,
  type = c("disease", "other", "condother"),
  time = NULL,
  tau = 100,
  reverse = FALSE,
  var.type = c("ci", "se", "n"),
  exp.fun = NULL,
  ratetable = cuRe::survexp.dk,
  rmap,
  scale = ayear.
  smooth.exp = FALSE,
  pars = NULL,
  link = "loglog",
  n = 100
)
```

6 calc.Crude

Arguments

_		
	object	Fitted model to do predictions from. Possible classes are gfcm, cm, stpm2, and pstpm2.
	newdata	Data frame from which to compute predictions. If empty, predictions are made on the the data which the model was fitted on.
	type	Probability to compute. Possible values are disease (default), other, and condother (see details).
	time	Time points at which to compute predictions. If empty, a grid of 100 time points between 0 and tau is selected.
	tau	Upper bound of the integral used to compute the probability of disease-related death (see details). The argument is only used for type = condother. Default is 100.
	reverse	Logical. If TRUE, 1 - probability is provided (default is FALSE). Only applicable for type = condother.
	var.type	Character. Possible values are "ci" (default) for confidence intervals, "se" for standard errors, and "n" for neither.
	exp.fun	Object of class list containing functions for the expected survival of each row in newdata. If not specified, the function computes the expected survival based on newdata using the survival::survexp function. If newdata is not provided, the expected survival is based on the data which the model was fitted on.
	ratetable	Object of class ratetable used to compute the general population survival. Default is $survexp.dk$.
	rmap	List to be passed to survexp from the survival package if exp.fun = NULL. Detailed documentation on this argument can be found by ?survexp.
	scale	Numeric. Passed to the survival::survexp function and defaults to 365.24. That is, the time scale is assumed to be in years.
	smooth.exp	Logical. If TRUE, the general population survival function is smoothed by the function smooth. $spline$ using the the argument all.knots = TRUE.
	pars	\boldsymbol{A} vector of parameter values for the model given in object. Currently not used.
	link	Link function for computing variance in order to restrict confidence intervals to $[0, 1]$. Default is loglog.
	n	Number of knots used for the Gauss-Legendre quadrature.

Details

The function estimates crude probabilities by using the relative survival, expected survival, and the cause-specific hazard function. The crude cumulative incidence of disease-related death (type = "disease") is

$$P(T \leq t, D = disease) = \int_0^t S^*(u) R(u) \lambda(u) du.$$

The crude cumulative incidence of death from other causes (type = "other") is

$$P(T \le t, D = other) = \int_0^t S^*(u)R(u)h^*(u)du.$$

calc.Crude 7

The conditional probability of eventually dying from other causes than disease (type = "condother") is

$$P(D = other | T > t) = \frac{P(D = disease) - P(T \le t, D = disease)}{P(T > t)}$$

The probability of disease-related death, P(D = disease), can be computed by using type = "disease" and choosing a sufficiently large time point. For P(D = other| T>t), the argument tau controls this time point (default is 100).

Value

A list containing the crude probability estimates of each individual in newdata.

Examples

```
##Use data cleaned version of the colon disease data from the rstpm2 package
data("colonDC")
set.seed(2)
colonDC <- colonDC[sample(1:nrow(colonDC), 1000), ]</pre>
##Extract general population hazards
colonDC$bhaz <- general.haz(time = "FU", rmap = list(age = "agedays", sex = "sex", year= "dx"),</pre>
                            data = colonDC, ratetable = survexp.dk)
##Spline-base cure model
#Fit cure model
fit <- rstpm2::stpm2(Surv(FUyear, status) ~ 1, data = colonDC, df = 6,
                     bhazard = colonDC$bhaz, cure = TRUE)
#Compute the probability of disease-related death
res <- calc.Crude(fit, time = seq(0, 20, length.out = 50),
                  rmap = list(age = agedays, sex = sex, year = dx),
                  var.type = "n")
plot(res)
#Compute the conditional probability of dying from other causes than disease
res <- calc.Crude(fit, time = seq(0, 20, length.out = 50), type = "condother",
                  rmap = list(age = agedays, sex = sex, year = dx), var.type = "n")
plot(res)
#Simple parametric cure model
#Fit cure model
fit <- fit.cure.model(Surv(FUyear, status) ~ 1, data = colonDC, bhazard = "bhaz",</pre>
                      type = "mixture", dist = "weibull", link = "logit")
#Compute the probability of disease-related death
res <- calc.Crude(fit, time = seq(0, 20, length.out = 50),
                  rmap = list(age = agedays, sex = sex, year = dx),
                  var.type = "n")
plot(res)
#Compute the conditional probability of disease-related death
```

8 calc.Crude.quantile

calc.Crude.quantile Compute the time to statistical cure using the conditional probability of disease-related death

Description

The following function estimates the time to statistical cure using the conditional probability of disease-related death.

Usage

```
calc.Crude.quantile(
   fit,
   q = 0.05,
   newdata = NULL,
   max.time = 20,
   exp.fun = NULL,
   var.type = c("ci", "se", "n"),
   rmap,
   ratetable = cuRe::survexp.dk,
   tau = 100,
   reverse = TRUE,
   scale = ayear
)
```

Arguments

fit	Fitted model to do predictions from. Possible classes are gfmc, cm, stpm2, and pstpm2.
q	Threshold to estimate statistical cure according to.
newdata	Data frame from which to compute predictions. If empty, predictions are made on the data which the model was fitted on.
max.time	Upper boundary of the interval [0, max.time] in which to search for solution (see details). Default is 20.
exp.fun	Object of class list containing functions for the expected survival of each row in newdata. If not specified, the function computes the expected survival based on newdata using the survival::survexp function. If newdata is not provided, the expected survival is based on the data which the model was fitted on.
var.type	Character. Possible values are "ci" (default) for confidence intervals, "se" for standard errors, and "n" for neither.

calc.Crude.quantile 9

rmap	List to be passed to survexp from the survival package if exp.fun = NULL. Detailed documentation on this argument can be found by ?survexp.
ratetable	Object of class ratetable used to compute the general population survival. Default is survexp.dk
tau	Upper bound of integral (see ?calc.Crude). Default is 100.
reverse	$\label{logical} Logical\ passed\ on\ to\ {\tt calc.Crude.}\ If\ {\tt TRUE}\ (default),\ 1\ -\ probability\ is\ provided.$ Only applicable for type = condother.
scale	Numeric. Passed to the survival::survexp function and defaults to 365.24. That is, the time scale is assumed to be in years.

Details

The cure point is calculated as the time point at which the conditional probability of disease-related death reaches the threshold, q. If q is not reached within max.time, no solution is reported.

Value

The estimated cure point.

Examples

```
##Use data cleaned version of the colon cancer data from the rstpm2 package
data("colonDC")
set.seed(2)
colonDC <- colonDC[sample(1:nrow(colonDC), 500), ]</pre>
##Extract general population hazards
colonDC$bhaz <- general.haz(time = "FU", rmap = list(age = "agedays", sex = "sex", year= "dx"),</pre>
                             data = colonDC, ratetable = survexp.dk)
#Fit cure model and estimate cure point
fit <- rstpm2::stpm2(Surv(FUyear, status) ~ 1, data = colonDC, df = 6,</pre>
                     bhazard = colonDC$bhaz, cure = TRUE)
cp <- calc.Crude.quantile(fit, q = 0.05,</pre>
                           rmap = list(age = agedays, sex = sex, year = dx))
#Compare the result with the trajectory of the conditional probability of disease-related death
res <- calc.Crude(fit, type = "condother", time = seq(0, 20, length.out = 100),
                  var.type = "n",
                  rmap = list(age = agedays, sex = sex, year = dx), reverse = TRUE)
plot(res)
abline(h = 0.05, v = cp$Estimate)
```

10 calc.cure.quantile

calc.cure.quantile	Compute the time to statistical cure using the conditional probability of cure
--------------------	--

Description

The following function estimates the time to statistical cure using the conditional probability of cure.

Usage

```
calc.cure.quantile(
  fit,
  q = 0.05,
  newdata = NULL,
  max.time = 20,
  var.type = c("ci", "n"),
  reverse = TRUE,
  bdr.knot = NULL
)
```

Arguments

fit	Fitted model to do predictions from. Possible classes are gfcm, cm, and stpm2.
q	Threshold to estimate statistical cure according to.
newdata	Data frame from which to compute predictions. If empty, predictions are made on the the data which the model was fitted on.
max.time	Upper boundary of the interval [0, max.time] in which to search for solution (see details). Default is 20.
var.type	Character. Possible values are "ci" (default) for confidence intervals, "se" for standard errors, and "n" for neither.
reverse	Logical. Whether to use the conditional probability of not being cured (default) or the conditional probability of cure.
bdr.knot	Time point from which cure is assumed. Only relevant for class stpm2.

Details

The cure point is calculated as the time point at which the conditional probability of disease-related death reaches the threshold, q. If q is not reached within max.time, no solution is reported.

Value

The estimated cure point.

calc.LL 11

Examples

calc.LL

Loss of lifetime estimation

Description

Function for computing mean residual lifetime and loss of lifetime estimates based on relative survival models.

Usage

```
calc.LL(
  object,
  newdata = NULL,
  type = c("ll", "mrl"),
  time = NULL,
  tau = 100,
  var.type = c("ci", "se", "n"),
  exp.fun = NULL,
  ratetable = cuRe::survexp.dk,
  rmap,
  smooth.exp = FALSE,
  scale = ayear,
  pars = NULL,
  n = 100
)
```

Arguments

object

Fitted model to do predictions from. Possible classes are gfcm, cm, stpm2, and

newdata

Data frame from which to compute predictions. If empty, predictions are made on the the data which the model was fitted on.

12 calc.LL

type	Type of life expectation estimate. Possible values are 11 (default) which gives the loss of lifetime, and mr1 which gives the mean residual lifetime.
time	Time points at which to compute predictions. If empty, a grid of 100 time points between 0 and tau is selected.
tau	The upper limit of the integral (see details). Default is 100.
var.type	Character. Possible values are "ci" (default) for confidence intervals, "se" for standard errors, and "n" for neither.
exp.fun	Object of class list containing functions for the expected survival of each row in newdata. If not specified, the function computes the expected survival based on newdata using the survival::survexp function. If newdata is not provided, the expected survival is based on the data which the model was fitted on.
ratetable	Object of class ratetable used to compute the general population survival. Default is survexp.dk.
rmap	List to be passed to survexp from the survival package if exp.fun = NULL. Detailed documentation on this argument can be found by ?survexp.
smooth.exp	Logical. If TRUE, the general population survival function is smoothed by the function smooth.spline using the the argument all.knots = TRUE.
scale	Numeric. Passed to the survival::survexp function and defaults to 365.24. That is, the time scale is assumed to be in years.
pars	A vector of parameter values for the model given in object. Currently not used.
n	Number of knots used for the Gauss-Legendre quadrature.

Details

The mean residual lifetime function and loss of lifetime function are based on numerical integration of the area under the observed and expected conditional survival functions. If type = "11", the function computes

$$\frac{\int_t^{\infty} S^*(u)}{S^*(t)} - \frac{\int_t^{\infty} S(u)}{S(t)}.$$

If type = "mrl", the function computes

$$\frac{\int_{t}^{\infty} S(u)}{S(t)},$$

for a given t. The function $S^*(t)$ is the general population survival function and S(t) is the observed survival function. Integration to infinity is not required in studies of human mortality, so an upper limit, tau, is chosen instead. As most humans die before they 100 years, this is the default setting of the function. The integral is computed by Gauss-Legendre quadrature and the point wise variance is estimated using the delta method and numerical differentiation.

Value

An object of class le containing the life expectancy estimates of each individual in newdata.

calc.LL.quantile

Examples

```
##Use data cleaned version of the colon cancer data from the rstpm2 package
data("colonDC")
set.seed(2)
colonDC <- colonDC[sample(1:nrow(colonDC), 1000), ]</pre>
##Extract general population hazards
colonDC$bhaz <- general.haz(time = "FU", rmap = list(age = "agedays", sex = "sex", year= "dx"),
                            data = colonDC, ratetable = survexp.dk)
##Spline-base cure model
#Fit cure model
fit <- rstpm2::stpm2(Surv(FUyear, status) ~ 1, data = colonDC,</pre>
                     df = 6, bhazard = colonDC$bhaz, cure = TRUE)
#Compute and plot the loss of lifetime function
res <- calc.LL(fit, time = seq(0, 20, length.out = 50),
               rmap = list(age = agedays, sex = sex, year = dx),
               var.type = "n")
plot(res)
#Compute and plot the mean residual lifetime
res <- calc.LL(fit, time = seq(0, 20, length.out = 50), type = "mrl",
               rmap = list(age = agedays, sex = sex, year = dx),
               var.type = "n")
plot(res)
#Simple parametric cure model
#Fit cure model
fit <- fit.cure.model(Surv(FUyear, status) ~ 1, data = colonDC, bhazard = "bhaz",</pre>
                      type = "mixture", dist = "weibull", link = "logit")
#Compute and plot the loss of lifetime function
res <- calc.LL(fit, time = seq(0, 20, length.out = 50),
               rmap = list(age = agedays, sex = sex, year = dx),
               var.type = "n")
plot(res)
#Compute and plot the mean residual lifetime
res <- calc.LL(fit, time = seq(0, 20, length.out = 50), type = "mrl",
               rmap = list(age = agedays, sex = sex, year = dx),
               var.type = "n")
plot(res)
```

14 calc.LL.quantile

Description

The following function estimates the time to statistical cure using the loss of lifetime function.

Usage

```
calc.LL.quantile(
  fit,
  q = 1,
  newdata = NULL,
  max.time = 20,
  var.type = c("ci", "n"),
  exp.fun = NULL,
  rmap = NULL,
  ratetable = cuRe::survexp.dk,
  tau = 100,
  type = "ll",
  scale = ayear
)
```

Arguments

fit	Fitted model to do predictions from. Possible classes are gfcm, cm, stpm2, and pstpm2.
q	Threshold to estimate statistical cure according to.
newdata	Data frame from which to compute predictions. If empty, predictions are made on the the data which the model was fitted on.
max.time	Upper boundary of the interval [0, max.time] in which to search for solution (see details). Default is 20.
var.type	Character. Possible values are "ci" (default) for confidence intervals, "se" for standard errors, and "n" for neither.
exp.fun	Object of class list containing functions for the expected survival of each row in newdata. If not specified, the function computes the expected survival based on newdata using the survival::survexp function. If newdata is not provided, the expected survival is based on the data which the model was fitted on.
rmap	List to be passed to survexp from the survival package if exp.fun = NULL. Detailed documentation on this argument can be found by ?survexp.
ratetable	Object of class ratetable used to compute the general population survival. Default is survexp.dk
tau	Upper bound of integral (see ?calc.LL). Default is 100.
type	Type of life expectancy measure. Possible values are type = "11" for the loss of lifetime and type = "mrl" for the mean residual lifetime.
scale	Numeric. Passed to the survival::survexp function and defaults to 365.24. That is, the time scale is assumed to be in years.

cb 15

Value

The estimated cure point.

Examples

cb

Restricted cubic splines

Description

Function for computing the basis matrix for restricted cubic splines

Usage

```
cb(x, df = NULL, knots = NULL, ortho = FALSE, R.inv = NULL, intercept = FALSE)
```

Arguments

X	Values to evaluate the basis functions in.
df	Degrees of freedom. One can supply df rather than knots; cb then chooses df + 1 knots at suitably chosen quantiles of x (which will ignore missing values).
knots	Chosen knots for the spline.
ortho	Logical. If TRUE orthogonalization of the basis matrix is carried out.
R.inv	Matrix or vector containing the values of the R matrix from the QR decomposition of the basis matrix. This is used for making new predictions based on the initial orthogonalization. Therefore the default is NULL.
intercept	Logical. If FALSE, the intercept of the restricted cubic spline is removed.

Value

A matrix with containing the basis functions evaluated in x.

16 cbc

References

Royston P. and Parmar M.K. (2002) Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Statistics in Medicine*, 21:15.

cbc

Restricted cubic splines with cure

Description

Function for computing the basis matrix for restricted cubic splines which are constant beyond the last knot

Usage

```
cbc(x, df = NULL, knots = NULL, ortho = FALSE, R.inv = NULL, intercept = FALSE)
```

Arguments

Х	Values to evaluate the basis functions in.
df	Degrees of freedom. One can supply df rather than knots; cbc then chooses df $+$ 1 knots at suitably chosen quantiles of x (which will ignore missing values) and adds an additional knot at the 95th quantile of x.
knots	Chosen knots for the spline.
ortho	Logical. If TRUE orthogonalization of the basis matrix is carried out.
R.inv	Matrix or vector containing the values of the R matrix from the QR decomposition of the basis matrix. This is used for making new predictions based on the initial orthogonalization. Therefore the default is NULL.
intercept	Logical. If FALSE, the intercept of the restricted cubic spline is removed.

Value

A matrix with containing the basis functions evaluated in x.

References

Andersson T.M.-L., et al. (2011) Estimating and modelling cure in population-based cancer studies within the framework of flexible parametric survival models. *BMC Medical Research Methodology*, 11:96.

colonDC 17

colonDC

Colon cancer data

Description

A dataset containing the individual baseline and follow-up data on more than 15,000 colon cancer patient. The data is a cleaned version of the rstpm2::colon data set.

Usage

data(colonDC)

Format

A data frame with 15564 rows and 11 variables

Details

- sex. Either female or male
- age. Diagnostic age
- stage. Clinical stage at diagnosis (either unknown, localised, regional, or distant)
- statusDC. Alive indicator with cause of death
- subsite. Anatomical subsite of tumour (either coecum and ascending, transverse, descending and sigmoid, or other and NOS)
- dx. Date of diagnosis
- exit. Date of study exit
- status. Alive indicator (0 = alive, 1 = dead)
- FU. Follow-up time measured in days
- FUyear. Follow-up time measured in years
- agedays. Diagnostic age in days.

fit.cure.model

Parametric cure model

Description

This function fits parametric cure models using simple parametric distributions.

18 fit.cure.model

Usage

```
fit.cure.model(
  formula,
  data,
  formula.surv = NULL,
  type = c("mixture", "nmixture"),
  dist = c("weibull", "exponential", "lognormal", "weiwei", "weiexp", "gmw"),
  link = c("logit", "loglog", "identity", "probit"),
  bhazard = NULL,
  covariance = TRUE,
  link.mix = c("logit", "loglog", "identity", "probit"),
  control = list(maxit = 10000),
  method = "Nelder-Mead",
  init = NULL
)
```

Arguments

formula	Formula for modelling the cure proportion. The left hand side has to be of the form Surv(time, status).
data	Data frame in which to interpret the variable names in formula and formula. surv.

formula. surv List of formulas for each parameter in the parametric distribution (see details).

type A character indicating the type of cure model. Possible values are mixture

(default) and nmixture.

The parametric distribution of the survival of the uncured.

Character. Specifies the link function of the cure proportion.

bhazard Background hazard.

covariance Logical. If TRUE (default), the covariance matrix is computed.

link.mix Character. Specifies the link function for the mixture parameter in a weibull-

weibull mixture model and weibull-exponential model.

Only used when dist = "weiwei" and dist = "weiexp".

control List of control parameters passed to optim.

method Optimization method passed to optim.

init Initial values for the maximum likelihood optimization. If not provided, the

optimization will start in 0.

Details

If type = "mixture", the function fits the model,

$$S(t|z) = \pi(z) + [1 - \pi(z)]S_u(t|z),$$

and if type = "nmixture", the function fits the model,

$$S(t|z) = \pi(z)^{\widetilde{F}(t)},$$

fit.cure.model 19

where z is a vector of covariates. The formula. surv argument is used to model $S_u(t)$ (1 - $\widetilde{F}(t)$). It is a list of formulas with as many entries as there are parameters in the chosen parametric distribution. If not specified, all formulas are assumed to be ~1. The ith formula, i.e., formula. surv[[i]] refers to θ_i in the below survival functions.

Exponential model:

$$S_u(t) = \exp(-t\theta_1)$$
.

Weibull model:

$$S_u(t) = \exp\left(-\theta_1 t^{\theta_2}\right).$$

Log-normal model:

$$S_u(t) = 1 - \Phi\left(\frac{\log(t) - \theta_1}{\theta_2}\right).$$

Weibull-exponential mixture model:

$$S_u(t) = \theta_1 \exp\left(-\theta_2 t^{\theta_3}\right) + (1 - \theta_1) \exp\left(-\theta_4 t\right).$$

Weibull-Weibull mixture model:

$$S_u(t) = \theta_1 \exp\left(-\theta_2 t^{\theta_3}\right) + (1 - \theta_1) \exp\left(-\theta_4 t^{\theta_5}\right).$$

Generalized modified Weibull distribution:

$$S_u(t) = 1 - \left(1 - \exp\left(-\theta_1 t_2^{\theta} \exp(\theta_3 t)\right)\right)_4^{\theta}.$$

In the Weibull-exponential and Weibull-Weibull mixture models, the link function for the mixture component is controlled by link.mix. The remaining parameters are modelled using an exponential link function except θ_1 in the log-normal model, which is modelled using the identity. Parameters are not transformed back to the original scale in the outputted object and related print.cm and summary.cm functions

Value

An object of class cm containing the estimated parameters of the cure model. The appropriate link functions taken on π and the θ_i 's are linear in the covariates corresponding to their respective parameter estimates.

Examples

20 general.haz

```
fit.wei <- fit.cure.model(Surv(FUyear, status) ~ 1, data = colonDC, bhazard = "bhaz",</pre>
                          type = "mixture", dist = "weibull", link = "logit")
##Plot various summaries of the model (see ?predict.cm)
plot(fit.wei)
plot(fit.wei, time = seq(0, 40, length.out = 100))
plot(fit.wei, type = "hazard")
plot(fit.wei, type = "survuncured")
plot(fit.wei, type = "probcure")
#Fit a weibull-weibull mixture cure model
fit.weiwei <- fit.cure.model(Surv(FUyear, status) ~ 1, data = colonDC, bhazard = "bhaz",
                          type = "mixture", dist = "weiwei", link = "logit")
#Compare to the weibull model
plot(fit.wei, ci = FALSE)
plot(fit.weiwei, add = TRUE, col = 2, ci = FALSE)
###With covariates
##Fit weibull mixture cure model with age effect for both components of the Weibull model
fit <- fit.cure.model(Surv(FUyear, status) ~ age, data = colonDC, bhazard = "bhaz",</pre>
                      formula.surv = list(~ age, ~ age),
                      type = "mixture", dist = "weibull", link = "logit")
##Plot model for age 50 and 60
plot(fit, newdata = data.frame(age = 60),
     time = seq(0, 15, length.out = 100), ci = FALSE)
plot(fit, newdata = data.frame(age = 50),
     time = seq(0, 15, length.out = 100), ci = FALSE, add = TRUE, col = 2)
plot(fit, newdata = data.frame(age = 60),
     time = seq(0, 15, length.out = 100), ci = FALSE, type = "hazard")
plot(fit, newdata = data.frame(age = 50),
    time = seq(0, 15, length.out = 100), ci = FALSE, type = "hazard", add = TRUE, col = 2)
```

general.haz

Extract general population hazard

Description

Yearly general population hazards matched on age, gender, and calendar year is extracted from a ratetable.

Usage

```
general.haz(
  time,
  rmap,
  data = NULL,
  ratetable = cuRe::survexp.dk,
```

general.haz 21

```
scale = 365.24
)
```

Arguments

time

Either a numeric vector of follow-up times (in days) or a character indicating the variable containing the follow-up times in the data.

rmap

A named list. The names must match the dimension names of the ratetable input. The elements should be given as vectors containing the relevant variables in the data or a character indicating the name of the variable in the data. Elements in the list named 'age' and 'year' are transformed such that the age and year of the event/censoring time is used. 'age' must be a numeric vector given as age in days or a character indicating the variable containing the patient ages in the data. 'year' must be of class Date with the calendar time points or a character indicating the variable containing the calendar times in the data. Other variables should be coded as characters in the data.

data

The data from which to extract variables from. If time, age, sex, or year are not characters, this will not be used.

ratetable

Object of class ratetable to extract background hazards from. Defaults to

survexp.dk.

scale

Numeric to adjust the scale of the outputted hazard values. If the ratetable provides daily hazards and scale = 365.24 (default), the outputted hazard values are yearly.

Value

An object of class numeric containing the yearly expected hazards.

Examples

22 GenFlexCureModel

GenFlexCureModel

Fit generalized mixture cure model

Description

The following function fits a generalized mixture or non-mixture cure model using a link function for the cure rate and for the survival of the uncured. For a mixture cure model, the model is specified by

$$S(t|z) = \pi(z) + [1 - \pi(z)]S_u(t|z),$$

where

$$g_1[S_u(t|z)] = \eta_1(t,z)$$
 and $g_2[\pi(z)] = \eta_2(z)$.

The function implements multiple link functions for both g_1 and g_2 . The default time-effect is natural cubic splines, but the function allows for the use of other smoothers.

Usage

```
GenFlexCureModel(
  formula,
  data,
  smooth.formula = NULL,
  smooth.args = NULL,
  df = 3,
  tvc = NULL,
  tvc.formula = NULL,
  bhazard = NULL,
  cr.formula = ~1,
  type = "mixture",
  link.type.cr = c("logit", "loglog", "identity", "probit"),
 link.type = c("PH", "PO", "probit"),
  init = NULL,
  baseoff = FALSE,
  timeVar = "",
  time0Var = ""
  covariance = T,
  verbose = T,
  control = list(maxit = 10000),
 method = "Nelder-Mead",
 constraint = TRUE,
  ini.types = c("cure", "flexpara")
)
```

Arguments

formula

Formula for modelling the survival of the uncured. Reponse has to be of the form Surv(time, status).

GenFlexCureModel 23

data	Data frame in which to interpret the variables names in formula, smooth.formula, tvc.formula, and $cr.formula$.
smooth.formula	Formula for describing the time-effect of the survival of the uncured. If NULL (default), the function uses the natural cubic splines modelled on the log-time scale.
smooth.args	List. Optional arguments to the time-effect of the survival of the uncured (default is NULL).
df	Integer. Degrees of freedom (default is 3) for the time-effect of the survival of the uncured. Is not used if smooth. formula is provided.
tvc	Named list of integers. Specifies the degrees of freedom for time-varying covariate effects. For instance, $tvc = list(x = 3)$ creates a time-varying spline-effect of the covariate "x" with 3 degrees of freedom using the rstpm2::nsx function.
tvc.formula	Formula for the time-varying covariate effects. For time-varying effects, a linear term of the covariate has to be included in formula.
bhazard	Background hazard.
cr.formula	Formula for the cure proportion. The left hand side of the formula is not used and should therefore not be specified.
type	A character indicating the type of cure model. Possible values are mixture for mixture cure models (default) and nmixture for non-mixture cure models.
link.type.cr	Character providing the link function for the cure proportion. Possible values are logit (default), loglog, identity, and probit.
link.type	Character providing the link function for the survival of the uncured. Possible values are PH for a proportional hazards model (default), PO for a proportion odds model, and probit for a probit model.
init	Initial values for the optimization procedure. If not specified, the function will create initial values internally.
baseoff	Logical. If TRUE, the time-effect is modelled only using tvc.formula rather than merging with smooth.formula.
timeVar	Optional character giving the name of the variable specifying the time component of the Surv object. Should currently not be used.
time0Var	Optional character giving the name of the variable specifying the time start time component used for delayed entry. Should currently not be used.
covariance	Logical. If TRUE (default), the covariance matrix is computed.
verbose	Logical. If TRUE status messages of the function is outputted.
control	Named list with control arguments passed to optim.
method	Character passed to optim indicating the method for optimization. See ?optim for details.
constraint	Logical. Indicates whether non-negativity constraints should be forced upon the hazard of the uncured patients (see details).
ini.types	Character vector denoting the executed schemes for computing initial values (see details).

24 GenFlexCureModel

Details

The default smoother is natural cubic splines established by the rstpm2::nsx function. Functions such as ns, bs are readily available for usage. Also the cb function in this package can be used. Initial values are calculated by two procedures and the model is fitted under each set of initial values. The model producing the highest likelihood is selected.

```
Using link.type = 'PH', the link function g_1(x) = \log(-\log(x)) is used. Using link.type = 'PO', the link function g_1(x) = \log(\frac{x}{1-x}) is used.
```

If constraint = TRUE, a non-negative hazard of the uncured is ensured by a general penalization scheme. If constraint = FALSE, penalization is still employed, but on the all-cause hazard instead.

Value

An object of class gfcm.

Examples

```
##Use data cleaned version of the colon cancer data from the rstpm2 package
data("colonDC")
set.seed(2)
colonDC <- colonDC[sample(1:nrow(colonDC), 400), ]</pre>
##Extract general population hazards
colonDC$bhaz <- general.haz(time = "FU", rmap = list(age = "agedays", sex = "sex", year= "dx"),</pre>
                             data = colonDC, ratetable = survexp.dk)
###Without covariates
##Fit mixture cure model
fit <- GenFlexCureModel(Surv(FUyear, status) ~ 1, data = colonDC, df = 4, bhazard = "bhaz")</pre>
##Plot model
plot(fit)
plot(fit, time = seq(0.001, 40, length.out = 100))
plot(fit, type = "hazard")
plot(fit, type = "survuncured")
plot(fit, type = "probcure")
##Predict cure proportion
predict(fit, type = "curerate")
##Fit non-mixture cure model
fit <- GenFlexCureModel(Surv(FUyear, status) ~ 1, data = colonDC, df = 4,</pre>
                         bhazard = "bhaz", type = "nmixture")
##Plot relative survival
plot(fit)
##Predict cure proportion
```

Irtest 25

```
predict(fit, type = "curerate")
###With covariates
##Fit mixture cure model
fit <- GenFlexCureModel(Surv(FUyear, status) ~ sex, data = colonDC, df = 4,</pre>
                        bhazard = "bhaz", cr.formula = ~ sex)
##Plot model
plot(fit, newdata = data.frame(sex = factor("female", levels = c("male", "female"))),
     time = seq(0.001, 15, length.out = 100), ci = FALSE)
plot(fit, newdata = data.frame(sex = factor("male", levels = c("male", "female"))),
     time = seq(0.001, 15, length.out = 100), col = 2, ci = FALSE, add = TRUE)
plot(fit, newdata = data.frame(sex = factor("female", levels = c("male", "female"))),
     time = seq(0.001, 15, length.out = 100), ci = FALSE, type = "survuncured")
plot(fit, newdata = data.frame(sex = factor("male", levels = c("male", "female"))),
     time = seq(0.001, 15, length.out = 100), col = 2, ci = FALSE,
     add = TRUE, type = "survuncured")
predict(fit, type = "curerate",
        data.frame(sex = factor(c("male", "female"),
                                levels = c("male", "female"))))
##Fit mixture cure model with time-varying covariates
colonDC$gender <- as.numeric(colonDC$sex) - 1</pre>
fit <- GenFlexCureModel(Surv(FUyear, status) ~ gender, data = colonDC, df = 6,</pre>
                        bhazard = "bhaz", cr.formula = ~ gender, tvc = list(gender = 2))
##Plot model
plot(fit, newdata = data.frame(gender = 0))
plot(fit, newdata = data.frame(gender = 1), add = TRUE, col = 2)
plot(fit, type = "hazard", newdata = data.frame(gender = 0), ci = FALSE)
plot(fit, type = "hazard", newdata = data.frame(gender = 1),
     add = TRUE, col = 2, ci = FALSE)
#Predict cure proportions for a male and female patients
predict(fit, type = "curerate", newdata = data.frame(gender = 0))
predict(fit, type = "curerate", newdata = data.frame(gender = 1))
```

1rtest

Likelihood ratio tests for comparing nested cure models

Description

Function for doing likelihood ratio tests for class cuRe.

26 lts

Usage

```
lrtest(model1, model2)
```

Arguments

Model fitted by the fit.cure.model or the GenFlexCureModel function

Another model fitted by the fit.cure.model or the GenFlexCureModel function for comparison.

Details

One of the models must be nested within the other model, and both models must be fitted to the same data set.

Value

An object of class "anova" containing the degrees of freedom and log-likelihoods of the two models, the difference in degrees of freedom, the likelihood ratio Chi-squared statistic (twice the difference in log-likelihoods), and the p-value for the asymptotic likelihood ratio test.

lts

Long term survival predictions

Description

Function for computing survival estimates using a relative survival model and the expected general population survival.

Usage

```
lts(
   fit,
   type = c("surv", "hazard", "cumhaz", "loghaz", "fail"),
   newdata = NULL,
   time = NULL,
   var.type = c("ci", "se", "n"),
   exp.fun = NULL,
   ratetable = cuRe::survexp.dk,
   rmap,
   scale = 365.24,
   smooth.exp = FALSE,
   link = NULL,
   mean = FALSE
)
```

Its 27

Arguments

fit	Fitted model to do predictions from. Possible classes are gfcm, stpm2, pstpm2, and cm.
type	Prediction type (see details). The default is surv.
newdata	Data frame from which to compute predictions. If empty, predictions are made on the the data which the model was fitted on.
time	Optional time points at which to compute predictions. If empty, a grid of 100 time points between 0 and the maximum follow-up time is selected.
var.type	Character. Possible values are "ci" (default) for confidence intervals, "se" for standard errors, and "n" for neither.
exp.fun	Object of class list containing functions for the expected survival of each row in newdata. If not specified, the function computes the expected survival based on newdata using the survival::survexp function. If newdata is not provided, the expected survival is based on the data which the model was fitted on.
ratetable	Object of class ratetable used to compute the general population survival. Default is survexp.dk.
rmap	List to be passed to survexp from the survival package if exp.fun = NULL. Detailed documentation on this argument can be found by ?survexp.
scale	Numeric. Passed to the survival::survexp function and defaults to 365.24. That is, the time scale is assumed to be in years.
smooth.exp	Logical. If TRUE, the general population survival function is smoothed by the function smooth.spline using the the argument all.knots = TRUE.
link	Character, indicating the link function for the variance calculations. Possible values are "log", "cloglog" for $log(-log(x))$, "mlog" for $-log(x)$, and "I" for the indentity.
mean	Logical. If TRUE, the function outputs the average estimate across the rows in newdata. If newdata = NULL, the argument is not used. The default is FALSE.

Details

Possible values for argument type are:

surv: Survival function computed by $S(t)=R(t)S^*(t)$ hazard: Hazard function computed by $h(t)=\lambda(t)+h^*(t)$

cumhaz: The cumulative hazard function computed by $H(t) = \Lambda(t) + H^*(t)$

loghazard: The log-hazard function computed by $\log(\lambda(t) + h^*(t))$

fail: The distribution function computed by $1 - R(t)S^*(t)$

Value

An object of class 1ts containing the predictions of each individual in newdata.

28 plot.crude

Examples

plot.crude

Plot crude event probabilities

Description

Plot function for the computed crude event probabilties.

Usage

Arguments

X	Object of class crude in which crude probabilities are stored.
ylim	Limits of y-axis.
xlim	Limits of x-axis.
ci	Logical. If TRUE (default), confidence intervals are added to the plot.
col	Colour of each curve.
ylab	Label of the y-axis. If NULL, the function uses its default labels depending on object $type$.
xlab	Label of the x-axis (default is "Time").
add	Logical indicating wether the cruves should be added to the current plot window (default is FALSE).
	Further arguments passed to plot and lines.

plot.cuRe 29

plot.cuRe	Plot function for Flexible mixture cure model

Description

Plot function associated with the classes gfcm and cm

Usage

Arguments

X	Object of class cuRe.
newdata	Data frame from which to compute predictions. If empty, predictions are made on the the data which the model was fitted on.
type	Character. Defines the desired scale to plot. See ?predict.gfcm for possible values.
time	Optional time points at which to compute predictions. This argument is not used if type is curerate.
xlim	Limits of the x-axis.
ylim	Limits of the y-axis.
xlab	Label of the x-axis. Default is "Time".
ylab	Label of the y-axis. If NULL, the function uses its default y-labels depending on object\$type and object\$excess.
col	Colour of each line.
ci	Logical. If TRUE (default), confidence intervals are added to the plot.
add	Loglca. If TRUE the curve is added to the existing plot.
	Further arguments passed to plot and lines.

Value

A plot containing the predictions of each observation in newdata.

30 plot.lts

plot.le

Plot the loss of lifetime function

Description

Plot function for the class le

Usage

Arguments

x	Object of class le.
ylim	Limit of the y-axis.
xlim	Limit of x-axis.
ci	Logical. If TRUE (default), confidence intervals are added to the plot.
col	Numeric or character indicating the colours of the curves.
ylab	Label to be written on the y-axis.
xlab	Label to be written on the x-axis.
add	Logical. If TRUE, the curve is added to the current plot window.
	Further argument passed to plot and lines.

plot.lts

Plot the long term survival

Description

Plot function for the class 1ts.

Usage

predict.cm 31

Arguments

х	Object of class 1ts.
ylim	Limit of the y-axis.
xlim	Limit of x-axis.
ci	Logical. If TRUE (default), confidence intervals are added to the plot.
col	Numeric or character indicating the colours of the curves.
ylab	Label to be written on the y-axis. If NULL, this is based on type.
xlab	Label to be written on the x-axis.
add	Logical indicating whether to add to current plot window (default is FALSE).
	Further argument passed to plot and lines.

predict.cm Predict function for flexible mixture cure model

Description

Function for doing predictions for class cm.

Usage

Arguments

object	Object of class cm to do predictions from.
newdata	Data frame from which to compute predictions. If empty, predictions are made on the data which the model was fitted on.
type	Prediction type (see details). The default is surv.
time	Optional time points at which to compute predictions. This argument is not used if type is curerate.
var.type	Character. Possible values are "ci" (default) for confidence intervals, "se" for standard errors, and "n" for neither.
pars	Numerical vector containing the parameters values of the model. In general, this argument can be ignored by the user.
link	Character, indicating the link function for the variance calculations. Possible values are "log", "cloglog" for $log(-log(x))$, "mlog" for -log(x), and "I" for the indentity. If NULL (default), the function will determine link from type.

32 predict.gfcm

keep.attributes

Logical. If TRUE, newdata will be added to the attributes of the output.

. . . Additional arguments. Currently not used.

Details

Possible values for argument type are:

surv: Survival function curerate: The cure fraction

probcure: The conditional probability of being cured

survuncured: The survival of the uncured

hazarduncured: The hazard function of the uncured cumhazuncured: The cumulative hazard of the uncured densityuncured: The density function of the uncured

failuncured: The distribution function of the uncured, i.e., 1 - survuncured oddsuncured: Odds of the uncured, i.e., (1 - survuncured) / survuncured

loghazarduncured: The log-hazard of the uncured

hazard: The hazard function density: The density function fail: The distribution function loghazard: The log-hazard function odds: The odds, i.e., (1 - surv) / surv cumhaz: The cumulative hazard function

Value

A list containing the predictions of each individual in newdata.

predict.gfcm

Predict function for flexible mixture cure model

Description

Function for doing predictions for class gfcm.

Usage

predict.gfcm 33

Arguments

object Object of class gfcm to do predictions from.

newdata Data frame from which to compute predictions. If empty, predictions are made

on the data which the model was fitted on.

type Prediction type (see details). The default is surv.

indi Logical. If TRUE, each line in newdata is treated as an individual observations.

This functionality allows predictions for each observation at more than one time

point.

time Optional time points at which to compute predictions. This argument is not used

if type is curerate.

var.type Character. Possible values are "ci" (default) for confidence intervals, "se" for

standard errors, and "n" for neither.

pars Numerical vector containing the parameters values of the model. In general, this

argument can be ignored by the user.

link Character, indicating the link function for the variance calculations. Possible

values are "log", "cloglog" for log(-log(x)), "mlog" for -log(x), and "I" for the indentity. If NULL (default), the function will determine link from type.

keep.attributes

Logical. If TRUE, newdata will be added to the attributes of the output.

... Additional arguments. Currently not used.

Details

Possible values for argument type are:

surv: Survival function curerate: The cure fraction

probcure: The conditional probability of being cured

survuncured: The survival of the uncured

hazarduncured: The hazard function of the uncured cumhazuncured: The cumulative hazard of the uncured densityuncured: The density function of the uncured

failuncured: The distribution function of the uncured, i.e., 1 - survuncured oddsuncured: Odds of the uncured, i.e., (1 - survuncured) / survuncured

loghazarduncured: The log-hazard of the uncured

hazard: The hazard function density: The density function fail: The distribution function loghazard: The log-hazard function odds: The odds, i.e., (1 - surv) / surv cumhaz: The cumulative hazard function

Value

A list containing the predictions of each individual in newdata.

34 survexp.dk

survexp.dk

Ratetable of the Danish general population

Description

Object of class ratetable containing the daily hazards in the Danish general population as reported by the Human Mortality Database (www.mortality.org).

Usage

survexp.dk

Format

An object of class ratetable of dimension 111 x 180 x 2.

Details

The ratetable was generated by using the relsurv::transrate.hmd function. The data were downloaded on 15-09-2017 seperately for male and female Danish citizens.

The data can be accessed through:

Female: http://www.mortality.org/hmd/DNK/STATS/fltper_1x1.txt Male: http://www.mortality.org/hmd/DNK/STATS/mltper_1x1.txt

Index

```
* datasets
    colonDC, 17
    survexp.dk, 34
AIC.cm, 2
AIC.gfcm, 3
BIC.cm, 3
BIC.gfcm, 4
bsx, 4
calc.Crude, 5
{\tt calc.Crude.quantile,8}
\verb|calc.cure.quantile|, 10
calc.LL, 11
calc.LL.quantile, 13
cb, 15
cbc, 16
colonDC, 17
fit.cure.model, 17
\texttt{general.haz}, \textcolor{red}{20}
GenFlexCureModel, 22
1rtest, 25
1ts, 26
plot.crude, 28
plot.cuRe, 29
plot.le, 30
plot.lts, 30
predict.cm, 31
predict.gfcm, 32
survexp.dk, 34
```