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Description Newly developed methods for the estimation of several probabilities in an illness-death model. The package can be used to obtain nonparametric and semiparametric estimates for: transition probabilities, occupation probabilities, cumulative incidence function and the sojourn time distributions. Additionally, it is possible to fit proportional hazards regression models in each transition of the Illness-Death Model. Several auxiliary functions are also provided which can be used for marginal estimation of the survival functions.

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survidm-package

survidm: Inference and Prediction in an Illness-Death Model

Description

Newly developed methods for the estimation of several probabilities in an illness-death model. The package can be used to obtain nonparametric and semiparametric estimates for: transition probabilities, occupation probabilities, cumulative incidence function and the sojourn time distributions. Additionally, it is possible to fit proportional hazards regression models in each transition of the Illness-Death Model. Several auxiliary functions are also provided which can be used for marginal estimation of the survival functions.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

Maintainer: Marta Sestelo, sestelo@uvigo.es

References

Aalen O. O., Johansen S. (1978) An Empirical Transition Matrix for Nonhomogeneous Markov Chains Based on Censored Observations. Scandinavian Journal of Statistics, 5(3), 141–150.

Cao R., Lopez-de Ullibarri I., Janssen P., Veraverbeke N. (2005) Presmoothed kaplan-meier and nelsonaalen estimators. Journal of Nonparametric Statistics, 17, 31–56.

de Una-Alvarez J. and Meira-Machado L. (2015). Nonparametric estimation of transition probabilities in a non-Markov illness-death model: a comparative study. Biometrics, 71, 364–375. Geskus R.B. (2011). Cause-specific cumulative incidence estimation and the fine and gray model under both left truncation and right censoring. Biometrics, 67, 39–49.

Meira-Machado L. F., de Una-Alvarez J. and Cadarso-Suarez C. (2006). Nonparametric estimation of transition probabilities in a non-Markov illness-death model. Lifetime Data Anal 12(3), 325–344.

Satten G.A. and Datta S. (2002) Marginal estimation for multi-stage models: waiting time distributions and competing risks analyses. Statistics in Medicine, 21, 3–19.

autoplot.survIDM Visualization of objects of class survIDM with ggplot2 graphics.

Description

It draws the estimated probabilities.

Usage

```
## S3 method for class 'survIDM'
autoplot(
  object = object,
 y = NULL,
  trans = "all",
  func = "distribution",
  conf = NULL,
  type = NULL,
  conftype = NULL,
  col = 1:6,
  confcol = 1:6,
  lty = 1,
  conflty = 2,
  xlab = "Time",
 ylab = NULL,
 ylim = NULL,
 xlim = NULL,
  interactive = FALSE,
  . . .
)
```

Arguments

object	Object of survIDM class.
У	NULL
trans	The transition probabilities plotted. It is used only when the object is of class "AJ", "LIDA" "LM", "PLM", "LMAJ", "PLMAJ", "PAJ" and "tpIPCW". Possible options are "all" (default), "00", "01", "02", "11" or "12".
func	It is used only when the object is of class "soj" or "sojIPCW". The type of curve to be drawn ("distribution" or "survival"). Default to "distribution".

conf	Draw the confidence intervals into the plot. By default it is NULL, they are drawn if the "surv" object contains them.
type	The type of plot that should be drawn. See details par for possible options. Defaults to "s" for the draw be stair steps.
conftype	The type of plot that should be drawn for confidence intervals. See details par for possible options. Defaults to "s" for the draw be stair steps.
col	Vector of colors. Colors are used cyclically.
confcol	Vector of colors for the confidence intervals. Colors are used cyclically.
lty	The line type. Line types can either be specified as an integer $(0 = blank, 1 = solid (default), 2 = dashed, 3 = dotted, 4 = dotdash, 5 = longdash, 6 = twodash).$ See details in par.
conflty	The line type for confidence intervals. Line types can either be specified as an integer ($0 = blank$, $1 = solid$ (default), $2 = dashed$, $3 = dotted$, $4 = dotdash$, $5 = longdash$, $6 = twodash$).
xlab	A title for the x axis: see title.
ylab	A title for the y axis: see title.
ylim	The y limits of the plot.
xlim	The x limits of the plot.
interactive	Logical flag indicating if an interactive plot with plotly is produced.
	Other options.

Value

A ggplot object, so you can use common features from ggplot2 package to manipulate the plot.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

Beran

autoplot(res3)

Beran	Estimation of the conditional distribution function of the response,
	given the covariate under random censoring.

Description

Computes the conditional survival probability P(T > y|Z = z)

Usage

Beran(time, status, covariate, delta, x, y, kernel = "gaussian", bw, lower.tail = FALSE)

Arguments

time	The survival time of the process.
status	Censoring indicator of the total time of the process; 0 if the total time is censored and 1 otherwise.
covariate	Covariate values for obtaining estimates for the conditional probabilities.
delta	Censoring indicator of the covariate.
X	The first time (or covariate value) for obtaining estimates for the conditional probabilities. If missing, 0 will be used.
У	The total time for obtaining estimates for the conditional probabilities.
kernel	A character string specifying the desired kernel. See details below for possible options. Defaults to "gaussian" where the gaussian density kernel will be used.
bw	A single numeric value to compute a kernel density bandwidth.
lower.tail	logical; if FALSE (default), probabilities are $P(T > y Z = z)$ otherwise, $P(T \le y Z = z)$.

Details

Possible options for argument window are "gaussian", "epanechnikov", "tricube", "boxcar", "triangular", "quartic" or "cosine".

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho

References

R. Beran. Nonparametric regression with randomly censored survival data. Technical report, University of California, Berkeley, 1981.

Examples

```
obj <- with(colonIDM, survIDM(time1, event1, Stime, event))
obj0 <- obj

#P(T>y|age=45)
library(KernSmooth)
h <- dpik(colonIDM$age)
Beran(time = obj0$Stime, status = obj0$event, covariate = colonIDM$age,
x = 45, y = 730, bw = h)

#P(T<=y|age=45)
Beran(time = obj0$Stime, status = obj0$event, covariate = colonIDM$age,
x = 45, y = 730, bw = h, lower.tail = TRUE)</pre>
```

bladderIDM

Bladder Cancer Recurrences.

Description

bladderIDM is a data frame with 8 variables and 85 observations. Data on recurrences of bladder cancer, used by many people to demonstrate methodology for recurrent event modelling.

Usage

data("bladderIDM")

Format

A data frame with 85 observations on the following 8 variables. Below a brief description is given for some of these variables.

- t1 Time to first recurrence/censoring, whichever occurs first.
- e1 Recurrence/censoring indicator (first recurrence=1) for the first time (t1).
- t2 Time to second recurrence/censoring, whichever occurs first.
- e2 Recurrence/censoring indicator (second recurrence=1) for the second time (t2)
- t3 Time to recurrence/censoring, whichever occurs first.
- e3 Recurrence/censoring indicator (third recurrence=1) for the third time (t3)
- t4 Time to fourth recurrence/censoring, whichever occurs first.
- e4 Recurrence/censoring indicator (fourth recurrence=1) for the fourth time (t4)

References

CIF

Byar, D. (1980) Veterans administration study of chemoprophylaxis for recurrent stage i bladder tumors: Comparisons of placebo, pyridoxine and topical thiotepa. Bladder Tumors and Other Topics in Urological Oncology, 18:363–370.

Examples

data(bladderIDM)
head(bladderIDM)

CIF

Nonparametric estimation of the Cumulative Incident Functions in the illness-death model

Description

This function is used to obtain nonparametric estimates of the cumulative incidence probabilities in the illness-death model. They represent the probability of one individual's being or having been in state j at time t.

Usage

```
CIF(
   formula,
   s,
   data,
   conf = FALSE,
   n.boot = 199,
   conf.level = 0.95,
   z.value,
   bw = "dpik",
   window = "gaussian",
   method.weights = "NW",
   cluster = FALSE,
   ncores = NULL,
   presmooth = FALSE
)
```

Arguments

formula	A formula object, which must have a survIDM object as the response on the left of the \sim operator and, if desired, a term on the right. The term may be a qualitative or quantitative variable. Without covariates, the right hand side should be ~ 1 .
S	The first time for obtaining estimates for the cumulative incidence functions. If missing, 0 will be used.

data	A data.frame including at least four columns named time1, event1, Stime and event, which correspond to disease free survival time, disease free survival indicator, time to death or censoring, and death indicator, respectively.
conf	Provides pointwise confidence bands. Defaults to FALSE.
n.boot	The number of bootstrap replicates to compute the variance of the estimator. Default is 199.
conf.level	Level of confidence. Defaults to 0.95 (corresponding to 95%).
z.value	The value of the covariate on the right hand side of formula at which the cumu- lative incidence probabilities are computed. For quantitative covariates, i.e. of class integer and numeric.
bw	A single numeric value to compute a kernel density bandwidth. Use "dpik" for the KernSmooth package based selector or "np" for the 'npudensbw' function of the np package.
window	A character string specifying the desired kernel. See details below for possible options. Defaults to "gaussian" where the gaussian density kernel will be used.
method.weights	A character string specifying the desired weights method. Possible options are "NW" for the Nadaraya-Watson weights and "LL" for local linear weights. Defaults to "NW".
cluster	A logical value. If TRUE (default), the bootstrap procedure for the confidence in- tervals is parallelized. Note that there are cases (e.g., a low number of bootstrap repetitions) that R will gain in performance through serial computation. R takes time to distribute tasks across the processors also it will need time for binding them all together later on. Therefore, if the time for distributing and gathering pieces together is greater than the time need for single-thread computing, it does not worth parallelize.
ncores	An integer value specifying the number of cores to be used in the parallelized procedure. If NULL (default), the number of cores to be used is equal to the number of cores of the machine - 1.
presmooth	A logical value. If TRUE, the presmoothed landmark estimator of the cumulative incidence function is computed.

Details

Possible options for argument window are "gaussian", "epanechnikov", "tricube", "boxcar", "triangular", "quartic" or "cosine".

Value

An object of class "survIDM" and one of the following two classes: "CIF" (Cumulative Incidence Function), and "cifIPCW" (Inverse Probability of Censoring Weighting for the Cumulative Incidence Function). Objects are implemented as a list with elements:

est	data.frame with estimates of the cumulative incidence probabilities.
CI	data.frame with the confidence intervals of the cumulative incidence probabili- ties.
conf.level	Level of confidence.

S	The first time for obtaining estimates for the cumulative incidence probabilities.
t	The time for obtaining the estimates of cumulative incidence probabilities.
conf	logical; if FALSE (default) the pointwise confidence bands are not given.
callp	The expression of the estimated probability.
Nlevels	The number of levels of the covariate. Provides important information when the covariate at the right hand side of formula is of class factor.
levels	The levels of the qualitative covariate (if it is of class factor) on the right hand side of formula.
formula	A formula object.
call	A call object.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

References

Geskus, R.B. (2011). Cause-specific cumulative incidence estimation and the fine and gray model under both left truncation and right censoring. Biometrics, 67, 39–49.

Kalbeisch, J. D. and Prentice R. L. (1980) The statistical analysis of failure time data. John Wiley & Sons, New York.

```
# Cumulative Incidence Function (CIF)
res <- CIF(survIDM(time1, event1, Stime, event) ~ 1, data = colonIDM,</pre>
conf = FALSE)
res
summary(res, time=365*1:7)
plot(res, ylim=c(0, 0.6))
res01 <- CIF(survIDM(time1, event1, Stime, event) ~ 1, data = colonIDM,</pre>
conf = FALSE, presmooth = TRUE)
res01
summary(res01, time=365*1:7)
plot(res01, ylim=c(0, 0.6))
# CIF for those in State 1 at time s=365, Y(s)=0
res1 <- CIF(survIDM(time1, event1, Stime, event) ~ 1, data = colonIDM,</pre>
s = 365, conf = FALSE)
summary(res1, time=365*1:7)
plot(res1, ylim=c(0, 0.6))
# Conditional CIF (with a factor)
res2 <- CIF(survIDM(time1, event1, Stime, event) ~ factor(sex),</pre>
data = colonIDM, s = 365, conf = FALSE)
```

colonIDM

```
summary(res2, time=365*1:5)
plot(res2)
res2.1 <- CIF(survIDM(time1, event1, Stime, event) ~ factor(sex), #new
data = colonIDM, s = 365, conf = FALSE, presmooth = TRUE)
summary(res2.1, time=365*1:5)
plot(res2.1)
# Conditional CIF (with continuous covariate)
res3 <- CIF(survIDM(time1, event1, Stime, event) ~ age, data = colonIDM,
z.value = 56, conf = FALSE)
summary(res3, time=365*1:6)
plot(res3)</pre>
```

colonIDM

Chemotherapy for Stage B/C colon cancer.

Description

These are data from one of the first successful trials of adjuvant chemotherapy for colon cancer. Levamisole is a low-toxicity compound previously used to treat worm infestations in animals; 5-FU is a moderately toxic (as these things go) chemotherapy agent.

Usage

data("colonIDM")

Format

A data frame with 929 observations on the following 15 variables. Below a brief description is given for some of these variables.

time1 Time to recurrence/censoring/death, whichever occurs first.

event1 Recurrence/censoring indicator (recurrence=1, alive=0).

Stime Time to censoring/death, whichever occurs first.

event Death/censoring indicator (death=1, alive=0).

rx Treatment - Obs(ervation), Lev(amisole), Lev(amisole)+5-FU.

sex Sex indicator (male=1, female=0).

age Age in years.

obstruct Obstruction of colon by tumour.

perfor Perforation of colon.

adhere Adherence to nearby organs.

nodes Number of lymph nodes with detectable cancer.

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coxidm

differ Differentiation of tumour (1=well, 2=moderate, 3=poor).

extent Extent of local spread (1=submucosa, 2=muscle, 3=serosa, 4=contiguous structures).

surg Time from surgery to registration (0=short, 1=long).

node4 More than 4 positive lymph nodes.

Source

The study is originally described in Laurie (1989). The main report is found in Moertel (1990). This data set is closest to that of the final report in Moertel (1991). A version of the data with less follow-up time was used in the paper by Lin (1994).

References

JA Laurie, CG Moertel, TR Fleming, HS Wieand, JE Leigh, J Rubin, GW McCormack, JB Gerstner, JE Krook and J Malliard. Surgical adjuvant therapy of large-bowel carcinoma: An evaluation of levamisole and the combination of levamisole and fluorouracil: The North Central Cancer Treatment Group and the Mayo Clinic. Journal of Clinical Oncology, 7:1447-1456, 1989.

DY Lin. Cox regression analysis of multivariate failure time data: the marginal approach. Statistics in Medicine, 13:2233-2247, 1994.

CG Moertel, TR Fleming, JS MacDonald, DG Haller, JA Laurie, PJ Goodman, JS Ungerleider, WA Emerson, DC Tormey, JH Glick, MH Veeder and JA Maillard. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. New England Journal of Medicine, 332:352-358, 1990.

CG Moertel, TR Fleming, JS MacDonald, DG Haller, JA Laurie, CM Tangen, JS Ungerleider, WA Emerson, DC Tormey, JH Glick, MH Veeder and JA Maillard. Fluorouracil plus Levamisole as and effective adjuvant therapy after resection of stage II colon carcinoma: a final report. Annals of Internal Medicine, 122:321-326, 1991.

Examples

data(colonIDM)
head(colonIDM)

coxidm

Fit proportional hazards regression model in each transition of the Illness-Death Model.

Description

Fits a Cox proportional hazards regression model for each transition.

Usage

coxidm(formula, data, semiMarkov = FALSE)

Arguments

formula	A formula object, which must have a survIDM object as the response on the left of the \sim operator and, if desired, a term on the right. The term may be a qualitative or quantitative variable. Without covariates, the right hand side should be ~ 1 .
data	A data.frame including at least four columns named time1, event1, Stime and event, which correspond to disease free survival time, disease free survival indicator, time to death or censoring, and death indicator, respectively.
semiMarkov	By default, FALSE.

Value

A data frame or a list containing the following components:

coef	Estimated coeficients.
exp(coef)	Exponent of the estimated coefficients.
lower0.95	Lower limit of the confidence interval.
upper 0.95	Upper limit of the confidence interval.
pvalue	obtained pvalue testing that the coefficient is equals to zero.

Other data frames or lists:

anova	Analysis of Deviance for the Cox Regression models.
zph	Test the Proportional Hazards Assumption of the Cox Regression models.
term	Predicted values of splines and partial residual for the terms of the model.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

Description

This function provides survival estimates using the product-limit Kaplan-Meier estimator.

Usage

KM(time, status, t)

Arguments

time	Survival time of the process.
status	Censoring indicator of the survival time of the process; 0 if the survival time is censored and 1 otherwise.
t	The time for obtaining survival estimates.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

References

E. Kaplan and P. Meier. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association, 53:457-481, 1958.

See Also

PKM

Examples

```
require(survival)
obj <- with(colonIDM, survIDM(time1, event1, Stime, event))
KM(time = obj$Stime, status = obj$event, t = 1095)
fit <- survfit(Surv(obj$Stime, obj$event) ~ 1, data = obj)
summary(fit, time = 1095)$surv</pre>
```

ΚM

KMW

Description

This function returns a vector with the Kaplan-Meier weights.

Usage

KMW(time, status)

Arguments

time	Survival time of the process.
status	Censoring indicator of the survival time of the process; 0 if the survival time is
	censored and 1 otherwise.

Value

Vector with Kaplan-Meier weights.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

References

E. Kaplan and P. Meier. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association, 53:457-481, 1958.

See Also

PKMW

```
obj <- with(colonIDM, survIDM(time1, event1, Stime, event))
kmw <- KMW(time = obj$Stime, status = obj$event)</pre>
```

```
require(survival)
colon.surv <- survfit(Surv(Stime, event) ~ 1, obj)
times <- summary(colon.surv)$time
surv <- summary(colon.surv)$surv
nevent <- summary(colon.surv)$n.event
p <- match(obj$Stime, times)
kmw2 <- -diff(c(1, surv))/nevent
kmw2 <- kmw2[p]*obj$event
kmw2[is.na(kmw2)] <- 0
all.equal(kmw, kmw2)</pre>
```

LLW

Description

Computes local linear weights based on Kernel smoothing.

Usage

LLW(x, kernel = "gaussian", bw, t1)

Arguments

х	Covariate values for obtaining estimates for the conditional probabilities. If missing, unconditioned probabilities will be computed.
kernel	A character string specifying the desired kernel. See details below for possible options. Defaults to "gaussian" where the gaussian density kernel will be used.
bw	A single numeric value to compute a kernel density bandwidth.
t1	Covariate value to compute the weight at.

Details

Possible options for argument window are "gaussian", "epanechnikov", "tricube", "boxcar", "triangular", "quartic" or "cosine".

Value

A vector with local linear weights.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

See Also

NWW

Examples

LLW(x = colonIDM\$age, bw = 3, t1 = 60)

markov.test

Description

The markov assumption may be tested including the sojourn time in the initial state, "times1", and other covariates in the Cox model.

Usage

markov.test(formula, s, nm.method = "LM", data)

Arguments

formula	A formula object, which must have a survIDM.
S	The first time for obtaining a graphical test of markovianity by comparison of the estimates for transition probabilities. If missing, first quartile of the sojourn time in the initial state has been considered for the graphical test.
nm.method	The non-markov method used to compute the transition probabilities. Defaults to "LM".
data	A data.frame including at least four columns named time1, event1, Stime and event, which correspond to disease free survival time, disease free survival indicator, time to death or censoring, and death indicator, respectively.

Details

The markov assumption may be tested including the sojourn time in the initial state, "times1", and other covariates in the Cox model. A graphical test for Markovianity is also available.

Value

cox.markov.test	
	An object of class coxph representing the fit. See coxph.object for details.
TPestimates	Dataframe with estimates of the transition probabilities for Aalen-Johansen es- timator (markovian) and for non-markov estimator. Confidence intervals for the transition probability from State 1 to State 2 are also available.
nm.method	The non-markov method used to compute the transition probabilities.
S	The first time for obtaining a graphical test of markovianity by comparison of the estimates for transition probabilities.
call	A call object.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

nevents

References

L. Meira-Machado, J. de Una-Alvarez, C. Cadarso-Suarez, and P. Andersen. Multi-state models for the analysis of time to event data. Statistical Methods in Medical Research, 18:195-222, 2009.

J. de Una-Alvarez and L. Meira-Machado. Nonparametric estimation of transition probabilities in the non-markov illness-death model: A comparative study. Biometrics, 71(2):364-375, 2015.

L. Meira-Machado and M. Sestelo. Estimation in the progressive illness-death model: A nonexhaustive review. Biometrical Journal, 2018.

Examples

```
mk <- markov.test(survIDM(time1,event1,Stime,event)~1, s=365, nm.method = "LM", data=colonIDM)
mk$cox.markov.test
mk$TPestimates
mk$nm.method
plot(mk)</pre>
```

nevents

Count number of observed transitions.

Description

Given a dataset of class "survIDM", this function counts the number of observed transitions in the multi-state model.

Usage

```
nevents(dataidm, state.names=NULL)
```

Arguments

dataidm	A dataframe including at least four columns named time1, event1, Stime and
	event, which correspond to disease free survival time, disease free survival in-
	dicator, time to death or censoring, and death indicator, respectively.
state.names	Names for the transition states. If NULL (default), transition states are named by "healthy", "illness" and "death".
	neartny, iiiness and death.

Details

The colums of the dataset needs to have the format of class "survIDM", which holds the transition matrix of the multi-state model. The arguments time1 and Stime must be numeric and nonnegative; event1 and event must be 0 or 1 if numeric and TRUE or FALSE if logical. Stime must be greater or equal to argument arguments time1. Stime and time1 must be equal when argument event1 equals 0 or FALSE. Argument event must be equal to 0 or FALSE when argument event1 equals 0 or FALSE. When arguments Stime and time1 are equal and argument event1 equals 1 or TRUE, argument event must be equal to 1 or TRUE.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

References

L. Meira-Machado, J. de Una-Alvarez, C. Cadarso-Suarez, and P. Andersen. Multi-state models for the analysis of time to event data. Statistical Methods in Medical Research, 18:195-222, 2009.

J. de Una-Alvarez and L. Meira-Machado. Nonparametric estimation of transition probabilities in the non-markov illness-death model: A comparative study. Biometrics, 71(2):364-375, 2015.

L. Meira-Machado and M. Sestelo. Estimation in the progressive illness-death model: A nonexhaustive review. Biometrical Journal, 2018.

Examples

nevents(colonIDM)

nevents(colonIDM, c('State0', 'State1', 'State2'))

NWW

Nadaraya-Watson weights.

Description

Computes the Nadaraya-Watson weights.

Usage

```
NWW(covariate, x, kernel = "gaussian", bw)
```

Arguments

covariate	Covariate values for obtaining weights.
х	Covariate value to compute the weight at.
kernel	A character string specifying the desired kernel. See details below for possible options. Defaults to "gaussian" where the gaussian density kernel will be used.
bw	A single numeric value to compute a kernel density bandwidth.

Details

Possible options for argument window are "gaussian", "epanechnikov", "tricube", "boxcar", "triangular", "quartic" or "cosine".

Value

A vector with Nadaraya-Watson weights.

РКМ

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

See Also

LLW

Examples

```
NWW(covariate = colonIDM$age, x=40, kernel = "gaussian", bw = 3)
```

PKM

Presmoothed Kaplan-Meier product-limit estimate of survival

Description

This function provides survival estimates using the presmoothed product-limit Kaplan-Meier estimator.

Usage

PKM(time, status, t)

Arguments

time	Survival time of the process.
status	Censoring indicator of the survival time of the process; 0 if the survival time is censored and 1 otherwise.
t	The time for obtaining survival estimates.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

References

R. Cao, I. Lopez-de Ullibarri, P. Janssen, and N. Veraverbeke. Presmoothed kaplan-meier and nelsonaalen estimators. Journal of Nonparametric Statistics, 17:31-56, 2005.

G. Dikta. On semiparametric random censorship models. Journal of Statistical Planning and Inference, 66:253-279, 1998.

E. Kaplan and P. Meier. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association, 53:457-481, 1958.

See Also

KΜ

Examples

```
obj <- with(colonIDM, survIDM(time1, event1, Stime, event))
PKM(time = obj$Stime, status = obj$event, t = 1095)</pre>
```

PKMW

Presmoothed Kaplan-Meier weights

Description

This function returns a vector with the presmoothed Kaplan-Meier weights.

Usage

PKMW(time, status)

Arguments

time	Survival time of the process.
status	Censoring indicator of the survival time of the process; 0 if the survival time is censored and 1 otherwise.

Value

Vector with presmoothed Kaplan-Meier weights.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

References

R. Cao, I. Lopez-de Ullibarri, P. Janssen, and N. Veraverbeke. Presmoothed kaplan-meier and nelsonaalen estimators. Journal of Nonparametric Statistics, 17:31-56, 2005.

G. Dikta. On semiparametric random censorship models. Journal of Statistical Planning and Inference, 66:253-279, 1998.

E. Kaplan and P. Meier. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association, 53:457-481, 1958.

See Also

KMW

Examples

```
obj <- with(colonIDM, survIDM(time1, event1, Stime, event))
PKMW(time = obj$Stime, status = obj$event)</pre>
```

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plot.survIDM

Description

It draws the estimated probabilities.

Usage

```
## S3 method for class 'survIDM'
plot(x = object, y = NULL, trans = "all",
func = "distribution", conf = NULL,
type = NULL, conftype = NULL, col = 1:6, confcol = 1:6, lty = 1, conflty = 2,
xlab = "Time (years)", ylab = NULL, ylim = NULL, xlim = NULL, ...)
```

Arguments

x	An object of class "survIDM".
У	NULL
trans	The transition probabilities plotted. It is used only when the object is of class "AJ", "LIDA" "LM", "PLM", "LMAJ", "PLMAJ", "PAJ" and "tpIPCW". Possible options are "all" (default), "00", "01", "02", "11" or "12".
func	It is used only when the object is of class "soj" or "sojIPCW". The type of curve to be drawn ("distribution" or "survival"). Default to "distribution".
conf	Draw the confidence intervals into the plot. By default it is NULL, they are drawn if the "surv" object contains them.
type	The type of plot that should be drawn. See details par for possible options. Defaults to "s" for the draw be stair steps.
conftype	The type of plot that should be drawn for confidence intervals. See details par for possible options. Defaults to "s" for the draw be stair steps.
col	Vector of colors. Colors are used cyclically.
confcol	Vector of colors for the confidence intervals. Colors are used cyclically.
lty	The line type. Line types can either be specified as an integer $(0 = blank, 1 = solid (default), 2 = dashed, 3 = dotted, 4 = dotdash, 5 = longdash, 6 = twodash).$ See details in par.
conflty	The line type for confidence intervals. Line types can either be specified as an integer ($0 = blank$, $1 = solid$ (default), $2 = dashed$, $3 = dotted$, $4 = dotdash$, $5 = longdash$, $6 = twodash$).
xlab	A title for the x axis: see title.
ylab	A title for the y axis: see title.
ylim	The y limits of the plot.
xlim	The x limits of the plot.
	Other options.

Value

No value is returned.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

Examples

```
res <- tprob(survIDM(time1, event1, Stime, event) ~ 1, s = 0,
method = "AJ", conf = FALSE, data = colonIDM)
plot(res)
plot(res)
plot(res, trans = "02")
res1 <- tprob(survIDM(time1, event1, Stime, event) ~ factor(sex), s = 365,
method = "AJ", conf = FALSE, data = colonIDM)
plot(res1, trans="02", ylim=c(0,0.5))
res2 <- CIF(survIDM(time1, event1, Stime, event) ~ age, data = colonIDM,
z.value = 56, conf = FALSE)
plot(res2)
res3 <- sojourn(survIDM(time1, event1, Stime, event) ~ factor(sex),
data = colonIDM, conf = FALSE, conf.level = 0.95)
plot(res3)
```

sojourn

Nonparametric estimation of the Sojourn time distributions in the recurrence state in the illness-death model

Description

This function is used to obtain nonparametric estimates of of the sojourn probabilities in the recurrence state in the illness-death model.

Usage

```
sojourn(
  formula,
  data,
  conf = FALSE,
```

sojourn

```
n.boot = 199,
conf.level = 0.95,
z.value,
bw = "dpik",
window = "gaussian",
method.weights = "NW",
method = "LM",
presmooth = FALSE,
cluster = FALSE,
ncores = NULL
)
```

Arguments

formula	A formula object, which must have a survIDM object as the response on the left of the \sim operator and, if desired, a term on the right. The term may be a qualitative or quantitative variable. Without covariates, the right hand side should be ~ 1 .
data	A data.frame including at least four columns named time1, event1, Stime and event, which correspond to disease free survival time, disease free survival indicator, time to death or censoring, and death indicator, respectively.
conf	Provides pointwise confidence bands. Defaults to FALSE.
n.boot	The number of bootstrap replicates to compute the variance of the non-Markovian estimator. Default is 199.
conf.level	Level of confidence. Defaults to 0.95 (corresponding to 95%).
z.value	The value of the covariate on the right hand side of formula at which the sojourn probabilities are computed. For quantitative covariates, i.e. of class integer and numeric.
bw	A single numeric value to compute a kernel density bandwidth. Use "dpik" for the KernSmooth package based selector or "np" for the 'npudensbw' function of the np package.
window	A character string specifying the desired kernel. See details below for possible options. Defaults to "gaussian" where the gaussian density kernel will be used.
method.weights	A character string specifying the desired weights method. Possible options are "NW" for the Nadaraya-Watson weights and "LL" for local linear weights. Defaults to "NW".
method	The method used to compute the sojourn estimates. Possible options are "LM" and "Satten-Datta". Defaults to "LM".
presmooth	- A logical value. If TRUE, the presmoothed landmark estimator of the sojourn function is computed. Only valid for method = "LM".
cluster	A logical value. If TRUE (default), the bootstrap procedure for the confidence in- tervals is parallelized. Note that there are cases (e.g., a low number of bootstrap repetitions) that R will gain in performance through serial computation. R takes time to distribute tasks across the processors also it will need time for binding them all together later on. Therefore, if the time for distributing and gathering

	pieces together is greater than the time need for single-thread computing, it does not worth parallelize.
ncores	An integer value specifying the number of cores to be used in the parallelized procedure. If NULL (default), the number of cores to be used is equal to the number of cores of the machine - 1. #'

Details

Possible options for argument window are "gaussian", "epanechnikov", "tricube", "boxcar", "triangular", "quartic" or "cosine".

Value

An object of class "survIDM" and one of the following two classes: "soj" (Sojourn Time Distribution), and "sojIPCW" (Inverse Probability of Censoring Weighting for the Sojourn Time Distribution). Objects are implemented as a list with elements:

est	data.frame with estimates of the sojourn probabilities.
CI	data.frame with the confidence intervals of the sojourn probabilities.
conf.level	Level of confidence.
t	The time for obtaining the estimates of sojourn probabilities.
conf	logical; if FALSE (default) the pointwise confidence bands are not given.
callp	The expression of the estimated probability.
Nlevels	The number of levels of the covariate. Provides important information when the covariate at the right hand side of formula is of class factor.
levels	The levels of the qualitative covariate (if it is of class factor) on the right hand side of formula.
formula	A formula object.
call	A call object.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

References

Satten, G.A. and Datta, S. (2002) Marginal estimation for multi-stage models: waiting time distributions and competing risks analyses. Statistics in Medicine, 21, 3–19.

```
res <- sojourn(survIDM(time1, event1, Stime, event) ~ 1,
data = colonIDM, conf = FALSE, conf.level = 0.95)
res
summary(res, time=365*1:6)
```

summary.cmm

```
plot(res)
res1 <- sojourn(survIDM(time1, event1, Stime, event) ~ 1,</pre>
data = colonIDM, conf = FALSE, conf.level = 0.95, method = "LM",
presmooth = TRUE)
res1
summary(res1, time=365*1:6)
plot(res1)
# not run:
#res2 <- sojourn(survIDM(time1, event1, Stime, event) ~ 1,</pre>
#data = colonIDM, conf = FALSE, conf.level = 0.95, method = "Satten-Datta")
#res2
# with a factor
res3 <- sojourn(survIDM(time1, event1, Stime, event) ~ factor(sex),</pre>
data = colonIDM, conf = FALSE, conf.level = 0.95)
res3
summary(res3, time=365*1:6)
plot(res3)
# with a qualitative covariate
res4 <- sojourn(survIDM(time1, event1, Stime, event) ~ age, data = colonIDM,</pre>
z.value = 56, conf = FALSE, conf.level = 0.95)
res4
summary(res4, time=365*1:6)
plot(res4)
```

summary.cmm

Summarizing fits of cmm class

Description

Produces a summary of a fitted coxidm model (proportional hazards regression model in each transition of the Illness-Death Model.

Usage

```
## S3 method for class 'cmm'
summary(object, type=NULL, conf.level = 0.95, ...)
```

Arguments

object A fitted cmm object as produced by coxidm().

type	Type of summary of the Cox model. Default value is "NULL" that produces a summary of a fitted coxidm model. Possible choices are "anova" and "ph". The "anova" option provides the Analysis of Deviance of the regression model. The "ph" option computes the tests of the proportional hazards assumption of the Cox Regression models.
conf.level	Level for computation of the confidence intervals. If set to FALSE no confidence intervals are printed.
	Other options.

Value

A data frame or a list containing the following components:

coef	Estimated coeficients.
exp(coef)	Exponent of the estimated coefficients.
lower0.95	Lower limit of the confidence interval.
upper 0.95	Upper limit of the confidence interval.
pvalue	obtained pvalue testing that the coefficient is equals to zero.

Other data frames with the Analysis of Deviance or the tests of the Proportional Hazards Assumption of the Cox Regression models.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

summary.survIDM Summarizing fits of survIDM class

Description

Returns a a data.frame or list containing the estimates of the probabilities, its confidence limits and other information.

Usage

```
## S3 method for class 'survIDM'
summary(object, times = NULL, ...)
```

Arguments

object	A fitted survIDM object as produced by tprob(), CIF() or sojourn().
times	Vector of times; the returned data frame will contain 1 row for each time. Miss- ing values are not allowed.
	For future methods.

Value

A data frame or a list containing the following components:

У	The total time for obtaining the estimates of the probabilities.
est	Estimates of the probability.
lower 95% CI	The lower probabilities of the interval.
upper 95% CI	The upper probabilities of the interval.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

```
fit <- tprob(survIDM(time1,event1,Stime, event) ~ 1, s = 365,
method = "AJ", conf = TRUE, conf.level = 0.95,
conf.type = "linear", n.boot = 50, data = colonIDM)
summary(fit)
summary(fit, times = c(400, 1000, 2900))
```

survIDM

Description

Creates a "survIDM" object, usually used as a response variable in a model formula.

Usage

survIDM(time1, event1, Stime, event, ...)

Arguments

time1	First time or censoring time.
event1	Indicator of the first time; 0 if the first time is censored and 1 otherwise.
Stime	The total time of the process.
event	Censoring indicator of the survival time of the process; 0 if the total time is censored and 1 otherwise.
	Other options.

Details

Arguments in this function must be introduced in the following order: time1, event1, Stime and event, where time1 and Stime are the sojourn time in the initial state and the total time, respectively. event1 and event denote their corresponding indicator statuses. This function checks the following conditions: (i) the arguments time1 and Stime must be numeric and nonnegative; event1 and event must be 0 or 1 if numeric and TRUE or FALSE if logical. Stime must be greater or equal to argument arguments time1. Stime and time1 must be equal when argument event1 equals 0 or FALSE. Argument event must be equal to 0 or FALSE when argument event1 equals 0 or FALSE. When arguments Stime and time1 are equal and argument event1 equals 1 or TRUE, argument event must be equal to 1 or TRUE.

Value

An object of class "survIDM". "survIDM" objects are implemented as a single dataframe.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

```
with(colonIDM, survIDM(time1, event1, Stime, event))
```

tprob

Nonparametric estimation of transition probabilities in the illnessdeath model

Description

This function is used to obtain nonparametric estimates of the transition probabilities in the illnessdeath model.

Usage

```
tprob(
  formula,
  s,
 method = "AJ",
 conf = FALSE,
 conf.level = 0.95,
 conf.type = "log",
 n.boot = 199,
 data,
 z.value,
 bw = "dpik",
 window = "gaussian",
 method.weights = "NW",
 cluster = FALSE,
 ncores = NULL,
 na.rm = TRUE
)
```

Arguments

formula	A formula object, which must have a survIDM object as the response on the left of the \sim operator and, if desired, a term on the right. The term may be a qualitative or quantitative variable. Without covariates, the right hand side should be ~ 1 .
S	The first time for obtaining estimates for the transition probabilities. If missing, 0 will be used.
method	The method used to compute the transition probabilities. Possible options are "AJ", "LIDA" "LM", "PLM", "LMAJ", "PLMAJ", "PAJ", "IPCW" and "breslow". Defaults to "AJ". The "IPCW" method is recommended to obtain conditional transition probabilities (i.e., with a quantitative term on the right hand side of formula). The "breslow" method is based on a Cox's regression model (Cox, 1972) fitted marginally to each allowed transition, with the corresponding baseline hazard function estimated by the Breslow's method (Breslow, 1972).
conf	Provides pointwise confidence bands. Defaults to FALSE.
conf.level	Level of confidence. Defaults to 0.95 (corresponding to 95%).

conf.type	Method to compute the confidence intervals. Depends on the choice of the es- timation method of the transition probabilities. For Aalen-Johansen type es- timators ("AJ", "LMAJ", "PAJ" and "PLMAJ") possible choices are "linear", "log" and "log-log". Default method is "log". The "linear" option pro- vides the standard intervals curve +-k *se(curve), where k is determined from "conf.int". The "log" option calculates the intervals based on the cumulative hazard or -log(survival). The "log-log" option uses the log hazard function or log(-log(survival)). For the remaining estimation methods ("LIDA", "LM", "PLM", "IPCW" and "breslow") the percentile bootstrap which resamples each datum with probability 1/n is used.
n.boot	The number of bootstrap replicates to compute the variance of the non-Markovian estimator. Default is 199.
data	A data.frame including at least four columns named time1, event1, Stime and event, which correspond to disease free survival time, disease free survival indicator, time to death or censoring, and death indicator, respectively.
z.value	The value of the covariate on the right hand side of formula at which the transi- tion probabilities are computed. For quantitative covariates, i.e. of class integer and numeric.
bw	A single numeric value to compute a kernel density bandwidth. Use "dpik" for the KernSmooth package based selector or "np" for the 'npudensbw' function of the np package.
window	A character string specifying the desired kernel. See details below for possible options. Defaults to "gaussian" where the gaussian density kernel will be used.
method.weights	A character string specifying the desired weights method. Possible options are "NW" for the Nadaraya-Watson weights and "LL" for local linear weights. Defaults to "NW".
cluster	A logical value. If TRUE (default), the bootstrap procedure for the confidence intervals is parallelized. Note that there are cases (e.g., a low number of bootstrap repetitions) that R will gain in performance through serial computation. R takes time to distribute tasks across the processors also it will need time for binding them all together later on. Therefore, if the time for distributing and gathering pieces together is greater than the time need for single-thread computing, it does not worth parallelize.
ncores	An integer value specifying the number of cores to be used in the parallelized procedure. If NULL (default), the number of cores to be used is equal to the number of cores of the machine - 1.
na.rm	A logical value indicating whether NA values should be stripped in the compu- tation.

Details

Possible options for argument window are "gaussian", "epanechnikov", "tricube", "boxcar", "triangular", "quartic" or "cosine". The LIDA estimator was labelled according to the acronym of the Lifetime Data Analysis journal in which the estimator was described for the first time (Meira-Machado, U?a-?lvarez and Cadarso-Su?rez, 2006).

Possible methods are:

- AJ Aalen-Johansen estimator
- PAJ Presmoothed Aalen-Johansen estimator
- LIDA LIDA estimator
- LM Landmark approach estimator
- PLM Presmoothed Landmark approach estimator
- LMAJ Landmark approach Aalen-Johansen estimator
- · PLDAJ Presmoothed Landmark approach Aalen-Johansen estimator
- tpIPCW Inverse Probability of Censoring Weighting for Transition Probabilities
- tpBreslow Breslow method

Value

An object of class "survIDM" and one of the following five classes: "AJ", "LIDA", "LM", "PLM", "LMAJ", "PAJ", "PAJ", "tpIPCW" and "tpBreslow". Objects are implemented as a list with elements:

est	data.frame with estimates of the transition probabilities.
CI	data.frame with the confidence intervals of the transition probabilities.
conf.level	Level of confidence.
S	The first time for obtaining estimates for the transition probabilities.
t	The time for obtaining the estimates of transition probabilities.
conf	logical; if FALSE (default) the pointwise confidence bands are not given.
conf.type	Type of the confidence interval.
callp	The expression of the estimated probability.
Nlevels	The number of levels of the covariate. Provides important information when the covariate at the right hand side of formula is of class factor.
levels	The levels of the qualitative covariate (if it is of class factor) on the right hand side of formula.
formula	A formula object.
call	A call object.

Author(s)

Luis Meira-Machado, Marta Sestelo and Gustavo Soutinho.

References

Aalen O. O., Johansen S. (1978) An Empirical Transition Matrix for Nonhomogeneous Markov Chains Based on Censored Observations. Scandinavian Journal of Statistics 5(3), 141–150.

Meira-Machado L. F., de Una-Alvarez J. and Cadarso-Suarez C. (2006). Nonparametric estimation of transition probabilities in a non-Markov illness-death model. Lifetime Data Anal 12(3), 325–344. de Una-Alvarez J. and Meira-Machado L. (2015). Nonparametric estimation of transition probabilities in a non-Markov illness-death model: a comparative study. Biometrics 71, 364–375.

Cox, DR (1972). Regression models and life tables (with discussion). Journal of the Royal Statistical Society, Series B 34, 187-200.

Breslow, N. (1972). Discussion of paper by dr cox. Journal of Royal Statistical Society, Series B 34, 216-217.

```
## Not run:
# Aalen-Johansen
res <- tprob(survIDM(time1, event1, Stime, event) ~ 1, s = 0,</pre>
method = "AJ", conf = FALSE, data = colonIDM)
summary(res, time=365*1:6)
plot(res)
# Transition Probabilities Pij(t)=Pij(365,t)
# LIDA
res1 <- tprob(survIDM(time1, event1, Stime, event) ~ 1, s = 365,</pre>
             method = "LIDA", conf = FALSE, data = colonIDM)
summary(res1, time=365*1:6)
plot(res1)
plot(res1, trans="01", ylim=c(0,0.15))
# Landmark (LM)
res2 <- tprob(survIDM(time1, event1, Stime, event) ~ 1, s = 365,</pre>
              method = "LM", conf = FALSE, data = colonIDM)
summary(res2, time=365*1:6)
plot(res2)
# Presmoothed LM
res3 <- tprob(survIDM(time1, event1, Stime, event) ~ 1, s = 365,</pre>
              method = "PLM", conf = TRUE, data = colonIDM)
summary(res3, time=365*1:6)
autoplot(res3, interactive = TRUE)
# Conditional transition probabilities
# With factor
res4 <- tprob(survIDM(time1, event1, Stime, event) ~ factor(sex), s = 365,</pre>
              method = "AJ", conf = TRUE, data = colonIDM)
summary(res4, time=365*1:6)
plot(res4, trans="02", ylim=c(0,0.5))
res5 <- tprob(survIDM(time1, event1, Stime, event) ~ rx, s =365,</pre>
              method = "breslow", z.value='Lev', conf = TRUE, data =colonIDM)
summary(res5, time=365*1:6)
plot(res5,trans="02", ylim=c(0,0.5))
# with continuous covariate (IPCW and Breslow Method)
res6 <- tprob(survIDM(time1, event1, Stime, event) ~ age, s = 365,</pre>
              method = "IPCW", z.value = 48, conf = FALSE, data = colonIDM,
              bw = "dpik", window = "gaussian", method.weights = "NW")
summary(res6, time=365*1:6)
plot(res6)
res7 <- tprob(survIDM(time1, event1, Stime, event) ~ age, s =365,</pre>
              method = "breslow", z.value=60, conf = FALSE, data =colonIDM)
summary(res7, time=365*1:6)
autoplot(res7, interactive=TRUE)
res8 <- tprob(survIDM(time1, event1, Stime, event) ~ age, s =365,</pre>
```

```
method = "breslow", conf.type='bootstrap', z.value=60, conf = TRUE, data =colonIDM)
summary(res8, time=365*1:6)
plot(res8)
res9 <- tprob(survIDM(time1, event1, Stime, event) ~ rx, s =365,</pre>
              method = "breslow", conf.type='bootstrap', conf = TRUE, data =colonIDM)
summary(res9, time=365*1:6)
plot(res9, trans="02", ylim=c(0,0.5))
# more than a covariate (Breslow Method)
res10<- tprob(survIDM(time1, event1, Stime, event) ~ nodes + factor(rx), s =365,</pre>
              method = "breslow", conf = TRUE, data =colonIDM)
summary(res10,t=365*1:5)
autoplot(res10)
res11<- tprob(survIDM(time1, event1, Stime, event) ~ nodes + factor(rx), s =365,
              method = "breslow", z.value=c(10, 'Obs'), conf = TRUE, data =colonIDM)
summary(res11,t=365*1:5)
autoplot(res11)
# more than a covariate for Non Linear Models (Breslow Method)
res12<- tprob(survIDM(time1, event1, Stime, event) ~ pspline(age)+ nodes + factor(rx), s =365,</pre>
              method = "breslow", conf = TRUE, data =colonIDM)
summary(res12,t=365*1:5)
autoplot(res12)
# Confidence intervals
res13 <- tprob(survIDM(time1, event1, Stime, event) ~ 1, s = 365,</pre>
               method = "AJ", conf = TRUE, n.boot = 5, conf.level = 0.95,
               conf.type = "log", data = colonIDM)
summary(res13, time=365*1:7)
autoplot(res13)
```

End(Not run)

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