Package 'mhazard'

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Title Multivariate Survival Function Estimation and Regression **Version** 0.1.2

Description Estimates the survival function and Cox regression parameters for the multivariate survival setting where there are multiple (right-censored) outcome variables. The Volterra, Dabrowska, and Prentice-Cai estimates of the bivariate survival function may be computed as well as the Dabrowska estimate of the trivariate survival function. Bivariate Cox regression estimates can also be computed. Functions are also provided to compute (bootstrap) confidence intervals and plot the estimates of the bivariate survival function. For details, see "The Statistical Analysis of Multivariate Failure Time Data: A Marginal Modeling Approach", Prentice, R., Zhao, S. (2019, ISBN: 978-1-4822-5657-4), CRC Press.

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cox2

Cox regression for a bivariate outcome

Description

Fits a semiparametric Cox regression model for a bivariate outcome. This function computes the regression coefficients, baseline hazards, and sandwich estimates of the standard deviation of the regression coefficients. If desired, estimates of the survival function F and marginal hazard rates Lambda11 can be computed using the cox2.LF function.

Usage

```
cox2(Y1, Y2, Delta1, Delta2, X)
```

Arguments

Y1, Y2 Vectors of event times (continuous).

Delta1, Delta2 Vectors of censoring indicators (1=event, 0=censored).

X Matrix of covariates (continuous or binary).

Value

A list containing the following elements:

Y1, Y2: Original vectors of event times

Delta1, Delta2: Original vectors of censoring indicators

X: Original covariate matrix

n10, n01: Total number of events for the first/second outcome

n11: Total number of double events

beta10, beta11: Regression coefficient estimates

lambda10, lambda01, lambda11: Baseline hazard estimates

SD.beta10, SD.beta01, SD.beta11: Sandwich estimates of the standard deviation of the regression coefficients

SD.beta10.cox, SD.beta01.cox: Standard deviation estimates for the regression coefficients based on a univariate Cox model

cox2.LF

References

Prentice, R., Zhao, S. "The statistical analysis of multivariate failure time data: A marginal modeling approach", CRC Press (2019). Prentice, R., Zhao, S. "Regression models and multivariate life tables", Journal of the American Statistical Association (2020) In press.

See Also

```
cox2.LF
```

Examples

```
x \leftarrow genClaytonReg(1000, 2, 0.5, 1, 1, log(2), log(2), log(8/3), 2, 2)
x.cox2 \leftarrow cox2(x$Y1, x$Y2, x$Delta1, x$Delta2, x$X)
```

cox2.LF

Bivariate regression survival function and marginal hazards estimation

Description

Estimates the survival function F and the marginal hazards Lambda11 for a bivariate Cox regression model. F and Lambda11 are estimated at two specificied values of the covariates. If desired, (bootstrap) confidence intervals or confidence bounds for F and Lambda11 may also be computed.

Usage

```
cox2.LF(
   cox2.obj,
   X0_out,
   X1_out,
   T1_out,
   T2_out,
   confidence = c("none", "CI", "CB"),
   n.boot = 100
)
```

Arguments

cox2.obj	Output from the cox2 function.
X0_out, X1_out	Two possible sets of values for the covariates. F and Lambda will be estimated at $X=X0$ _out and $X=X1$ _out.
T1_out, T2_out	Vector of time points at which F and Lambda11 should be estimated. If confidence="CB", then both vectors must have length 3.
confidence	Type of confidence estimate to be computed. Possible values include "none", "CI" (to compute confidence intervals), and "CB" (to compute confidence bands). Defaults to "none".
n.boot	Number of bootstrap iterations for computing the confidence intervals/bands. Defaults to 100. Ignored if confidence="none".

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Value

A list containing the following elements:

n10, n01: Total number of events for the first/second outcome

n11: Total number of double events

beta10, beta11: Regression coefficient estimates

lambda10, lambda01, lambda11: Baseline hazard estimates

Lambda11_out_Z0, Lambda11_out_Z1: Estimates of Lambda11 at T1_out, T2_out for X=X0_out and X=X1_out

F_out_X0, F_out_X1: Estimates of F at T1_out, T2_out for X=X0_out and X=X1_out

CI_Lambda11_X0.lb, CI_Lambda11_X0.ub: Lower and upper bounds for Lambda11 at X=X0_out

CI_Lambda11_X1.lb, CI_Lambda11_X1.ub: Lower and upper bounds for Lambda11 at X=X1_out

CI_F_X0.lb, CI_F_X0.ub: Lower and upper bounds for F at X=X0_out

CI_F_X1.lb, CI_F_X1.ub: Lower and upper bounds for F at X=X1_out

CB1_Lambda11_X0.lb, CB1_Lambda11_X0.ub, CB2_Lambda11_X0.lb, CB2_Lambda11_X0.ub, CB3_Lambda11_X
Lower and upper bounds for Lambda11 at X=X0_out, at three T1_out, T2_out combinations

CB1_Lambda11_X1.lb, CB1_Lambda11_X1.ub, CB2_Lambda11_X1.lb, CB2_Lambda11_X1.ub, CB3_Lambda11_X

- Lower and upper bounds for Lambda11 at X=X1_out, at three T1_out, T2_out combinations
- CB1_F_X0.lb, CB1_F_X0.ub, CB2_F_X0.lb, CB2_F_X0.ub, CB3_F_X0.lb, CB3_F_X0.ub: Lower and upper bounds for F at X=X0_out, at three T1_out, T2_out combinations
- CB1_F_X1.lb, CB1_F_X1.ub, CB2_F_X1.lb, CB2_F_X1.ub, CB3_F_X1.lb, CB3_F_X1.ub: Lower and upper bounds for F at X=X1_out, at three T1_out, T2_out combinations

Details

If confidence="CI" or confidence="CB", then 95% bootstrap confidence bounds are computed by estimating the standard errors of F/Lambda11 based on n.boot bootstrap iterations. Currently confidence bounds can only be computed at three specified T1out/T2out combinations (meaing that T1out and T2out must both have length 3 if confidencd="CB"). No confidence measures will be returned if confidence="none".

References

Prentice, R., Zhao, S. "The statistical analysis of multivariate failure time data: A marginal modeling approach", CRC Press (2019). Prentice, R., Zhao, S. "Regression models and multivariate life tables", Journal of the American Statistical Association (2020) In press.

See Also

cox2

genClayton2 5

Examples

```
x <- genClaytonReg(1000, 2, 0.5, 1, 1, log(2), log(2), log(8/3), 2, 2)
x.cox2 <- cox2(x$Y1, x$Y2, x$Delta1, x$Delta2, x$X)
x.LF <- cox2.LF(x.cox2, 0, 1, c(0.25, 0.5, 1), c(0.25, 0.5, 1))
x.LF.CI <- cox2.LF(x.cox2, 0, 1, c(0.25, 0.5, 1),
c(0.25, 0.5, 1), confidence="CI")
x.LF.CB <- cox2.LF(x.cox2, 0, 1, c(0.25, 0.5, 1),
c(0.25, 0.5, 1), confidence="CB")</pre>
```

genClayton2

Generates survival data from a bivariate Clayton-Oakes model

Description

Generates simulated survival data from a bivariate Clayton-Oakes model, which can be used to create example data for bivariate survival function estimation. The marginal distributions are exponential with given rate parameters. The joint distribution is defined using a Clayton copula. The censoring times are also exponentially distributed with given rate parameters.

Usage

```
genClayton2(n, theta, lambda10, lambda01, lambdaC1, lambdaC2)
```

Arguments

Sample size for the simulated data set.

theta Parameter for the Clayton copula. Must be -1 or larger.

lambda10, lambda01

Rate parameters for the (marginal) exponential distributions.

lambdaC1, lambdaC2

Rate parameters for the censoring times. No censoring occurs if this parameter is equal to 0.

Value

A data frame containing the following elements:

Y1, Y2: Survival times for the simulated data

Delta1, Delta2: Censoring indicators for the simulated data

Details

This function simulates data with the following survival function: $F(t1,t2) = [F(t1,0)^{-1}(-theta) + F(0,t2)^{-1}(-theta) - 1]^{-1}(-theta)$ (The survival function is defined to be equal to 0 if this quantity is negative.) The marginal survival functions F(t1,0) and F(0,t2) are exponentially distributed with rate parameters lambda10 and lambda01, respectively. After generating survival times Y1 and Y2 (of length n) under this distribution, censoring times C1 and C2 (also of length n) are generated.

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C1/C2 are generated under an exponential distribution with rate parameters lambdaC1 and lambdaC2. If C1[i]<Y1[i] for a given observation i, then observation i is considered to be censored (i.e., Delta1[i]=0). Delta2 is defined in a similar manner. If lambdaC1 or lambdaC2 is equal to 0, then the corresponding variable is uncensored (meaning that Delta[i]=1 for all i).

References

Clayton, D. "Model for association in bivariate life tables and its application in epidemiological studies of familial tendency in chronic disease incidence.", Biometrika (1978) 65:141-151. Prentice, R., Zhao, S. "The statistical analysis of multivariate failure time data: A marginal modeling approach", CRC Press (2019).

Examples

```
x <- genClayton2(1000, 0, 1, 1, 2, 2)
```

genClayton3

Generates survival data from a trivariate Clayton-Oakes model

Description

Generates simulated survival data from a trivariate Clayton-Oakes model, which can be used to create example data for trivariate survival function estimation. The marginal distributions are exponential with rate parameter 1. The joint distribution is defined using a Clayton copula. The censoring times are also exponentially distributed with given rate parameters.

Usage

```
genClayton3(n, theta, lambdaC1, lambdaC2, lambdaC3)
```

Arguments

n Sample size for the simulated data set.

theta Parameter for the Clayton copula. Must be -1 or larger.

lambdaC1, lambdaC2, lambdaC3

Rate parameters for the censoring times. No censoring occurs if this paramter is equal to 0.

Value

A data frame containing the following elements:

Y1, Y2, Y3: Survival times for the simulated data

Delta1, Delta2, Delta3: Censoring indicators for the simulated data

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Details

This function simulates data with the following survival function: $F(t1,t2,t3) = [F(t1,0,0)^{-(theta)} + F(0,t2,0)^{-(theta)} + F(0,0,t3) - 2]^{-(theta)}$ (The survival function is defined to be equal to 0 if this quantity is negative.) The marginal survival functions F(t1,0,0), F(0,t2,0), and F(0,0,t3) are exponentially distributed with rate parameter 1. After generating survival times Y1, Y2, and Y3 (of length n) under this distribution, censoring times C1, C2, and C3 (also of length n) are generated. C1/C2/C3 are generated under an exponential distribution with rate parameters lambdaC1, lambdaC2, lambdaC3, respectively. If C1[i]<Y1[i] for a given observation i, then observation i is considered to be censored (i.e., Delta1[i]=0). Delta2 and Delta3 are defined in a similar manner. If lambdaC1, lambdaC2, and/or lambdaC3 is equal to 0, then the corresponding variable is uncensored (meaning that Delta[i]=1 for all i).

References

Clayton, D. "Model for association in bivariate life tables and its application in epidemiological studies of familial tendency in chronic disease incidence.", Biometrika (1978) 65:141-151. Prentice, R., Zhao, S. "The statistical analysis of multivariate failure time data: A marginal modeling approach", CRC Press (2019).

Examples

```
x \leftarrow genClayton3(200, 0, 0.5, 0.5, 0.5)
```

genClaytonReg

Generates regression data from a bivariate Clayton-Oakes model

Description

Generates simulated survival data from a bivariate Clayton-Oakes model where the hazard depends on a binary coefficient X. This can be used to create example data for bivariate Cox regression. The marginal distributions are exponential with given rate parameters. The joint distribution is defined using a Clayton copula. The censoring times are also exponentially distributed with given rate parameters.

Usage

```
genClaytonReg(
   n,
   theta,
   Xp,
   lambda10,
   lambda01,
   b10,
   b01,
   b11,
   lambdaC1,
   lambdaC2
)
```

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Arguments

n Sample size for the simulated data set.

theta Parameter for the Clayton copula. Must be -1 or larger.

Xp Probability that the covariate is equal to 1. Must satisfy 0<Xp<1.

lambda10, lambda01

Rate parameters for the (marginal) exponential distributions when X=0.

b10, b01, b11 Regression coefficient values.

lambdaC1, lambdaC2

Rate parameters for the censoring times. No censoring occurs if this paramter is equal to 0.

Value

A data frame containing the following elements:

Y1, Y2: Survival times for the simulated data

Delta1, Delta2: Censoring indicators for the simulated data

X Covariate matrix (of dimension n x 1).

Details

This function simulates data with the following survival function: $F(t1,t2) = [F(t1,0)^{-1}](-t1,t2) + F(0,t2)^{-1}](-t1,t2) = [F(t1,0)^{-1}](-t1,t2) = [F(t1,0)^{-1}](-t$

References

Clayton, D. "Model for association in bivariate life tables and its application in epidemiological studies of familial tendency in chronic disease incidence.", Biometrika (1978) 65:141-151. Prentice, R., Zhao, S. "The statistical analysis of multivariate failure time data: A marginal modeling approach", CRC Press (2019).

```
x \leftarrow genClaytonReg(1000, 2, 0.5, 1, 1, log(2), log(2), log(8/3), 2, 2)
```

KM2

Estimates the survival function for a bivariate outcome

Description

Computes the survival function for a bivariate outcome using one of three possible estimators. The survival function for a bivariate outcome is analogous to the Kaplan-Meier estimator for a univariate outcome. Optionally (bootstrap) confidence intervals for the survival function may also be computed.

Usage

```
KM2(
   Y1,
   Y2,
   Delta1,
   Delta2,
   newT1 = NULL,
   newT2 = NULL,
   estimator = c("dabrowska", "volterra", "prentice-cai"),
   conf.int = FALSE,
   R = 1000,
   ...
)
```

Arguments

Y1, Y2	Vectors of event times (continuous).
Delta1, Delta2	Vectors of censoring indicators (1=event, 0=censored).
newT1, newT2	Optional vectors of new times at which to estimate the survival function. Defaults to the unique values in $Y1/Y2$ if not specified.
estimator	Which estimator of the survival function should be used. Possible values include "dabrowska", "volterra", and "prentice-cai". Defaults to "dabrowska".
conf.int	Should bootstrap confidence intervals be computed?
R	Number of bootstrap replicates. This argument is passed to the boot function. Defaults to 1000. Ignored if conf.int is FALSE.
	Additional arguments to the boot function.

Value

A list containing the following elements:

T1: Unique values of Y1 at which Fhat was computed

T2: Unique values of Y2 at which Fhat was computed

Fhat: Estimated survival function (computed at T1, T2)

Fhat.lci: Lower 95% confidence bounds for Fhat **Fhat.uci:** Upper 95% confidence bounds for Fhat

Fmarg1: Estimated marginal survival function for variable 1 (computed at newT1)

Fmarg1.lci: Lower 95% confidence bounds for Fmarg1

Fmarg1.uci: Upper 95% confidence bounds for Fmarg1

Fmarg2: Estimated marginal survival function for variable 2 (computed at newT2)

Fmarg2.lci: Lower 95% confidence bounds for Fmarg2
Fmarg2.uci: Upper 95% confidence bounds for Fmarg2

Fhat_est: Estimated survival function (computed at newT1, newT2)

Fhat_est.lci: Lower 95% confidence bounds for Fhat_est

Fhat_est.uci: Upper 95% confidence bounds for Fhat_est

CR: Estimated cross ratio (computed at T1, T2)

KT: Estimated Kendall\'s tau (computed at T1, T2)

CR_est: Estimated cross ratio (computed at newT1, newT2)

KT_est: Estimated Kendall\'s tau (computed at newT1, newT2)

Details

If conf.int is TRUE, confidence intervals will be computed using the boot function in the boot package. Currently only 95% confidence intervals computed using the percentile method are implemented. If conf.int is FALSE, confidence intervals will not be computed, and confidence bounds will not be returned in the output.

References

Prentice, R., Zhao, S. "Nonparametric estimation of the multivariate survivor function: the multivariate Kaplan–Meier estimator", Lifetime Data Analysis (2018) 24:3-27. Prentice, R., Zhao, S. "The statistical analysis of multivariate failure time data: A marginal modeling approach", CRC Press (2019).

See Also

boot

```
x <- genClayton2(1000, 0, 1, 1, 2, 2)
x.km2 <- KM2(x$Y1, x$Y2, x$Delta1, x$Delta2)
x.km2.ci <- KM2(x$Y1, x$Y2, x$Delta1, x$Delta2, conf.int=TRUE)</pre>
```

KM3

Estimates the survival function for a trivariate outcome

Description

Computes the survival function for a trivariate outcome. The survival function for a trivariate outcome is analogous to the Kaplan-Meier estimator for a univariate outcome. Optionally (bootstrap) confidence intervals for the survival function may also be computed.

Usage

```
KM3(
   Y1,
   Y2,
   Y3,
   Delta1,
   Delta2,
   Delta3,
   newT1 = NULL,
   newT2 = NULL,
   newT3 = NULL,
   conf.int = FALSE,
   R = 1000,
   ...
)
```

Arguments

Value

A list containing the following elements:

T1: Unique values of Y1 at which Fhat was computed

T2: Unique values of Y2 at which Fhat was computed

T3: Unique values of Y3 at which Fhat was computed

Fhat: Estimated survival function (computed at T1, T2, T3)

Fhat.lci: Lower 95% confidence bounds for Fhat **Fhat.uci:** Upper 95% confidence bounds for Fhat

Fmarg1: Estimated marginal survival function for variable 1 (computed at newT1)

Fmarg1.lci: Lower 95% confidence bounds for Fmarg1 **Fmarg1.uci:** Upper 95% confidence bounds for Fmarg1

Fmarg2: Estimated marginal survival function for variable 2 (computed at newT2)

Fmarg2.lci: Lower 95% confidence bounds for Fmarg2 Fmarg2.uci: Upper 95% confidence bounds for Fmarg2

Fmarg3: Estimated marginal survival function for variable 3 (computed at newT3)

Fmarg3.lci: Lower 95% confidence bounds for Fmarg3 Fmarg3.uci: Upper 95% confidence bounds for Fmarg3

Fhat_est: Estimated survival function (computed at newT1, newT2, newT3)

Fhat_est.lci: Lower 95% confidence bounds for Fhat_est
Fhat_est.uci: Upper 95% confidence bounds for Fhat_est
C110: Pairwise marginal cross ratio estimator C110
C101: Pairwise marginal cross ratio estimator C101
C011: Pairwise marginal cross ratio estimator C011

C111: Trivariate dependency estimator C111

Details

If conf.int is TRUE, confidence intervals will be computed using the boot function in the boot package. Currently only 95% confidence intervals computed using the percentile method are implemented. If conf.int is FALSE, confidence intervals will not be computed, and confidence bounds will not be returned in the output.

References

Prentice, R., Zhao, S. "Nonparametric estimation of the multivariate survivor function: the multivariate Kaplan–Meier estimator", Lifetime Data Analysis (2018) 24:3-27. Prentice, R., Zhao, S. "The statistical analysis of multivariate failure time data: A marginal modeling approach", CRC Press (2019).

See Also

boot

```
x <- genClayton3(200, 0, 0.5, 0.5, 0.5)
x.km3 <- KM3(x$Y1, x$Y2, x$Y3, x$Delta1, x$Delta2, x$Delta3)
x.km3.ci <- KM3(x$Y1, x$Y2, x$Y3, x$Delta1, x$Delta2,
x$Delta3, conf.int=TRUE, R=500)</pre>
```

plotKM2.3D

plotKM2.3D

Uses a 3D perspective plot to visualize a bivariate survival function

Description

Plots a 3D perspective plot of an estimated bivariate survival function. This function is a wrapper for the persp3D function from the plot3D package with default parameters chosen to make the data easier to visualize.

Usage

```
plotKM2.3D(
   km2.obj,
   col = "grey",
   shade = 0.25,
   theta = 120,
   xlab = "T1",
   ylab = "T2",
   zlab = "Fhat",
   ...
)
```

Arguments

km2.obj	Output of the KM2 function.
col	Color palette to be used for the plot. Defaults to "grey". See persp3D.
shade	The degree of shading of the surface facets. Defaults to 0.25. See persp.
theta	The azimuthal viewing direction. See persp.
xlab	The x-axis label. Defaults to "T1".
ylab	The y-axis label. Defaults to "T2".
zlab	The z-axis label. Defaults to "Fhat".
	Additional parameters to the persp3D function.

See Also

```
KM2, persp3D
```

```
x <- genClayton2(1000, 0, 1, 1, 2, 2)
x.km2 <- KM2(x$Y1, x$Y2, x$Delta1, x$Delta2)
plotKM2.3D(x.km2)

x2 <- genClayton2(1000, 2, 1, 1, 2, 2)
x2.km2 <- KM2(x2$Y1, x2$Y2, x2$Delta1, x2$Delta2)
plotKM2.3D(x2.km2)</pre>
```

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plotKM2.HM

Uses a heat map to visualize a bivariate survival function

Description

Plots a heat map of an estimated bivariate survival function. This function is a wrapper for the image function with default parameters chosen to make the data easier to visualize.

Usage

```
plotKM2.HM(
   km2.obj,
   contour = TRUE,
   col = terrain.colors(100),
   xlab = "T1",
   ylab = "T2",
   ...
)
```

Arguments

km2.obj	Output of the KM2 function.
contour	Should contour lines be added to the plot? Defaults to TRUE.
col	List of colors for the heat map. Defaults to terrain.colors(100).
xlab	The x-axis label. Defaults to "T1".
ylab	The y-axis label. Defaults to "T2".
	Additional parameters to the image function.

See Also

```
KM2, image
```

```
x <- genClayton2(1000, 0, 1, 1, 2, 2)
x.km2 <- KM2(x$Y1, x$Y2, x$Delta1, x$Delta2)
plotKM2.HM(x.km2)

x2 <- genClayton2(1000, 2, 1, 1, 2, 2)
x2.km2 <- KM2(x2$Y1, x2$Y2, x2$Delta1, x2$Delta2)
plotKM2.HM(x2.km2)</pre>
```

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