Package ‘joint.Cox’

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Type Package

Title Joint Frailty-Copula Models for Tumour Progression and Death in Meta-Analysis

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Author Takeshi Emura

Maintainer Takeshi Emura <takeshiemura@gmail.com>

Description Fit survival data and perform dynamic prediction under joint frailty-copula models for tumour progression and death.

Likelihood-based methods are employed for estimating model parameters, where the baseline hazard functions are modeled by the cubic M-spline or the Weibull model.

The methods are applicable for meta-analytic data containing individual-patient information from several studies.

Survival outcomes need information on both terminal event time (e.g., time-to-death) and non-terminal event time (e.g., time-to-tumour progression).

Methodologies were published in


Survival data from ovarian cancer patients are also available.

License GPL-2

Depends survival

NeedsCompilation no

Repository CRAN

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R topics documented:

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Description

Fit survival data and perform dynamic prediction under joint frailty-copula models for tumour progression and death. Likelihood-based methods are employed for estimating model parameters, where the baseline hazard functions are modeled by the cubic M-spline or the Weibull model. The methods are applicable for meta-analytic data containing individual-patient information from several studies. Survival outcomes need information on both terminal event time (e.g., time-to-death) and non-terminal event time (e.g., time-to-tumour progression). Methodologies were published in Emura et al. (2017), Emura et al. (2018), Emura et al. (2019), and Wu et al. (2020). See also the book of Emura et al. (2019). Survival data from ovarian cancer patients are also available.

Details

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cmprskCox.reg

The Competing Risks Version of Penalized Likelihood Estimation under the Joint Cox Models Between Tumour Progression and Death for Meta-Analysis

Description

Perform regression analyses under a copula-based joint Cox proportional hazards model between tumour progression and death for meta-analysis, which is proposed in Section 6.2 of Emura et al. (2017) and Section 5.1 of Emura et al. (2019). This is the competing risks version of "jointCox.reg". To avoid the identifiability problem, the copula parameter (theta) should be given by user, e.g., theta=2. The method is applicable for meta-analysis combining several studies or for cluster survival data.

Usage

cmprskCox.reg(t.event, event1, event2, Z1, Z2, group, theta, alpha = 1, kappa1 = c(seq(10, 1e+17, length = 30)), kappa2 = c(seq(10, 1e+17, length = 30)), LCV.plot = TRUE, Randomize_num = 10, Adj = 500, convergence.par=FALSE)

Arguments

t.event a vector for event tims
event1 a vector for event-type 1 indicators (=1 with event; =0 without event)
etvent2 a vector for event-type 2 indicators (=1 with event; =0 without event)
Z1 a matrix for covariates associated with event-type 1; ncol(Z1)=the number of covariates

References

Z2  a matrix for covariates associated with event-type 2; ncol(Z2)=the number of covariates

group  a vector for a group identification number, like 1,2,3,...

theta  A copula parameter under the Clayton copula (theta > 0)

alpha  A value related to the frailty (e.g., alpha=0 or =1); alpha=1 is default

kappa1  a vector for candidate smoothing parameters

kappa2  a vector for candidate smoothing parameters

LCV.plot  Plot the LCV curves if "TRUE"

Randomize_num  The number of randomizations for the initial p0

Adj  Numerical adjustment to prevent overflow; Adj=500 is recommended

cconvergence.par  If TRUE, the converged estimate, gradient, and Hessian matrix are given (log-transformed)

Details

We employ "nlm" routine to maximize the penalized likelihood function with the initial value described in Emura et al. (2015). If "nlm" does not converge, then we randomize the initial value by adding uniform random variables (Hu and Emura, 2015).

Value

count  Count for event occurrences

beta1  Regression coefficient for Z1

beta2  Regression coefficient for Z2

eta  Frailty parameter (variance)

theta  Copula parameter under the Clayton copula (fixed by user)

tau  Kendall’s tau corresponding to the copula parameter

LCV1  Likelihood cross-validation for event-type 1

LCV2  Likelihood cross-validation for event-type 2

g  M-spline coefficients for event-type 1

h  M-spline coefficients for event-type 2

g_var  Variance of M-spline coefficients for event-type 1

h_var  Variance of M-spline coefficients for event-type 2

cconvergence  convergence results for maximizing penalized likelihood

cconvergence.parameters  converged estimate, gradient, and Hessian matrix (log-transformed)

Error

"Error in integrate(func1, 0.001, 10, stop.on.error = FALSE):non-finite function value", an error occurring when the penalized likelihood is maximized by "nlm". The error may frequently occur during the iterations for maximizing the penalized likelihood, but is not crucial (can simply be ignored).
**Warning**

"NA/Inf replaced by maximum positive value", an error occurring when the penalized likelihood is maximized by "nlm". The error frequently occurs during the iterations for maximizing the penalized likelihood, but is not crucial (can simply be ignored).

**Author(s)**

Takeshi Emura, Shih JH

**References**


**Examples**

```r
data(dataOvarian)
t.event=dataOvarian$t.event
t.death=dataOvarian$t.death
event=dataOvarian$event
dehth=dataOvarian$death
non.event=which(event==1 & death==1 & t.event==t.death)
non.death=which(event==1 & death==1 & t.event<t.death)
event[non.event]=0 ## relapse before death
death[non.death]=0 ## death before relapse (tie is counted as death)
Z=as.matrix(dataOvarian$CXCL12)
group=dataOvarian$group
alpha_given=0
theta=2.35
kappa_grid=seq(10,1e+17,length = 30)

#set.seed(1)
#cmprskCox.reg(t.event=t.event,event1=event,event2=death,
# Z1=Z,Z2=Z,group=group,theta=theta,alpha=alpha_given,
# kappa1=kappa_grid,kappa2=kappa_grid,LCV.plot=TRUE,Adj=500)
```

---

condCox.reg

**Penalized Likelihood Estimation under the Joint Cox Models Between Tumour Progression and Death for Meta-Analysis: A Conditional Copula Approach**
Description

Perform regression analyses under a copula-based joint Cox proportional hazards model between tumour progression and death for meta-analysis, which is proposed by Emura et al. (201x). The method extends the joint frailty copula model of Emura et al. (2017). The method is applicable for meta-analysis combining several studies or for cluster survival data.

Usage

```r
condCox.reg(t.event, event, t.death, death, Z1, Z2, Z12, group, alpha = 1,
            kappa1 = c(seq(10, 1e+17, length = 30)), kappa2 = c(seq(10, 1e+17, length = 30)),
            LCV.plot = TRUE, Randomize_num = 10,
            Adj = 500, convergence.par=FALSE)
```

Arguments

- `t.event` a vector for time-to-tumour progression (TTP)
- `event` a vector for progression indicator (=1 if progression; =0 if not progression)
- `t.death` a vector for overall survival (OS), i.e., time-to-death
- `death` a vector for death indicator (=1 if death; =0 if not death)
- `Z1` a matrix for covariates associated with TTP; ncol(Z1)=the number of covariates
- `Z2` a matrix for covariates associated with OS; ncol(Z2)=the number of covariates
- `Z12` a matrix for covariates associated with copula; ncol(Z12)=the number of covariates
- `group` a vector for group identification numbers, like 1,2,3....
- `alpha` A value related to the frailty (e.g., alpha=0 or =1); alpha=1 is default
- `kappa1` a vector for candidate smoothing parameters
- `kappa2` a vector for candidate smoothing parameters
- `LCV.plot` Plot the LCV curves if "TRUE"
- `Randomize_num` The number of randomizations for the initial p0
- `Adj` Numerical adjustment to prevent overflow; Adj=500 is recommended
- `convergence.par` If TRUE, the converged estimate, gradient, and Hessian matrix are given (log-transformed)

Details

We employ "nlm" routine to maximize the penalized likelihood function with the initial value described in Emura et al. (2017). If "nlm" does not converge, then we randomize the initial value by adding uniform random variables (Hu and Emura, 2015).
condCox.reg

Value
- count: Count for event occurrences
- beta1: Regression coefficient for Z1
- beta2: Regression coefficient for Z2
- eta: Frailty parameter (variance)
- theta: Baseline copula parameter under the Clayton copula
- tau: Kendall’s tau corresponding to the baseline copula parameter
- beta12: Regression coefficient for a copula parameter
- LCV1: Likelihood cross-validation for TTP
- LCV2: Likelihood cross-validation for OS
- g: M-spline coefficients for TTP
- h: M-spline coefficients for OS
- g_var: Variance of M-spline coefficients for TTP
- h_var: Variance of M-spline coefficients for OS
- convergence: Convergence results for maximizing penalized likelihood
- convergence.parameters: Converged estimate, gradient, and Hessian matrix (log-transformed)

Error
"Error in integrate(func1, 0.001, 10, stop.on.error = FALSE):non-finite function value", an error occurring when the penalized likelihood is maximized by "nlm". The error may frequently occur during the iterations for maximizing the penalized likelihood, but is not crucial (can simply be ignored).

Warning
"NA/Inf replaced by maximum positive value", an error occurring when the penalized likelihood is maximized by "nlm". The error frequently occurs during the iterations for maximizing the penalized likelihood, but is not crucial (can simply be ignored).

Author(s)
Takeshi Emura

References
Emura T, Rondeau V (201x), Kendalls tau for individual-level surrogacy for failure time endpoints in meta-analysis (in preparation)
**Examples**

```
##
```

```r
dataOvarian
```

**Description**

The survival data was used to study if the CXCL12 gene expression is a predictive biomarker of survival endpoints in ovarian cancer. The dataset was used in Emura et al. (2017), which is a subset of the curated ovarian data of Ganzfried et al (2013). We prepared the dataset by using "patientselection.config" in "Curated ovarian data" around May 2015 in the analysis of Emura et al. (2017).

**Usage**

```r
data("dataOvarian")
```

**Format**

A data frame with 1003 observations on the following 6 variables.

- `t.event`: time to event in days
- `event`: event indicator (1=recurrence, 0=no recurrence)
- `t.death`: time to death in days
- `death`: death indicator (1=death, 0=alive)
- `group`: study ID; group=4, 8, 11, or 14; see the details below
- `CXCL12`: CXCL12 gene expression

**Details**

The data include individual-patient information on 1003 patients from 4 studies (group=4, 8, 11, and 14). The numbers 4, 8, 11 and 14 corresponds to the study IDs from the original data of Ganzfried et al. (2013). "group=4" corresponds to 110 Japanese patients from the study of Yoshihara et al. (2010) (GEO accession number: GSE17260). Other groupds are the studies of GSE30161 (58 patients), GSE9891 (278 patients), and TCGA (557 patients).

**Source**

References


Examples

data(dataOvarian)
study4=dataOvarian[dataOvarian$group==4,] # extract one study
study4

dataOvarian1

Data on time-to-recurrence and 158 gene expressions for 912 ovarian cancer patients from 4 independent studies.

Description

Meta-analytic data containing 158 gene expressions and time-to-relapse information for ovarian cancer patients. The data include time-to-recurrence, residual tumour size (>=1cm vs. <1cm), and associated 158 gene expressions. The dataset is a subset of the curated ovarian data of Ganzfried et al (2013). We prepared the dataset by using "patientselection.config" in "Curated ovarian data" around October 2016.

Usage

data("dataOvarian1")

Format

A data frame with 912 observations on the following 162 variables.

t.event : time-to-recurrence in days
event : event indicator (1=recurrence, 0=no recurrence)
group : study ID; group=4, 9, 12, or 16
debulk : residual tumour size (>=1cm vs. <1cm)
ABI3BP a numeric vector
ADAM12 a numeric vector
ADORA3 a numeric vector
ANKRD27 a numeric vector
AP2M1 a numeric vector
AP3S1 a numeric vector
ARHGAP28 a numeric vector
ARHGAP29 a numeric vector
ARTN a numeric vector
ASAP3 a numeric vector
B4GALT5 a numeric vector
BCAP31 a numeric vector
BRD4 a numeric vector
C1QTNF3 a numeric vector
CALD1 a numeric vector
CCNE1 a numeric vector
CCNL1 a numeric vector
CDC42 a numeric vector
CDV3 a numeric vector
CEBPB a numeric vector
CLIC4 a numeric vector
COL10A1 a numeric vector
COL11A1 a numeric vector
COL16A1 a numeric vector
COL3A1 a numeric vector
COL5A1 a numeric vector
COL5A2 a numeric vector
COMP a numeric vector
CRISPLD2 a numeric vector
CRYAB a numeric vector
CSE1L a numeric vector
CTSK a numeric vector
CXCL12 a numeric vector
CYR61 a numeric vector
DCUN1D1 a numeric vector
DDX27 a numeric vector
DIAPH3 a numeric vector
DNAJB4 a numeric vector
DNAJC13 a numeric vector
DNAJC8 a numeric vector
DPYSL3 a numeric vector
DVL3 a numeric vector
EFNB2 a numeric vector
dataOvarian1

EIF3K  a numeric vector
ELK1  a numeric vector
ENPP1  a numeric vector
EPYC  a numeric vector
FABP4  a numeric vector
FAM69A  a numeric vector
FAP  a numeric vector
FERMT2  a numeric vector
FGF1  a numeric vector
FN1  a numeric vector
FOSL2  a numeric vector
FSTL1  a numeric vector
GABRG3  a numeric vector
GAS1  a numeric vector
GFRA1  a numeric vector
GFRA3  a numeric vector
GJC1  a numeric vector
GLIPR1  a numeric vector
GPATCH1  a numeric vector
HLTF  a numeric vector
HP1BP3  a numeric vector
HSD17B6  a numeric vector
INHBA  a numeric vector
ITGB1  a numeric vector
JUN  a numeric vector
KIAA0226  a numeric vector
KIAA0355  a numeric vector
KIAA1598  a numeric vector
KIN  a numeric vector
KLHL25  a numeric vector
KPNA6  a numeric vector
KRT7  a numeric vector
KRTAP5.8  a numeric vector
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LGALS1  a numeric vector
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Details

4 studies are combined (group=4, 9, 12, and 16). The numbers 4, 9, 12 and 16 corresponds to the IDs from the original data of Ganzfried et al. (2013).

Source


References


Examples

data(dataOvarian1)

######## univariate Cox ##########

t.event=dataOvarian1$t.event
event=dataOvarian1$event
X.mat=dataOvarian1[,,-c(1,2,3,4)] ## gene expression
Symbol=colnames(dataOvarian1)[-c(1,2,3,4)] ## gene symbol

p=ncol(X.mat)
P_value=coef=NULL
for(j in 1:p){
  res=summary(coxph(Surv(t.event,event)~X.mat[,j]))$coefficients
  P_value=c(P_value,res[5])
  coef=c(coef,res[1])
}
data.frame( gene=Symbol[order(P_value)], P=P_value[order(P_value)],
  coef=round(coef[order(P_value)],3) )

---

dataOvarian2

Data on time-to-death and 128 gene expressions for 912 ovarian cancer patients from 4 independent studies.

Description

Meta-analytic data containing 128 gene expressions and time-to-death information for ovarian cancer patients. The data include time-to-death, residual tumour size (>=1cm> vs. <1cm), and associated 128 gene expressions. The dataset is a subset of the curated ovarian data of Ganzfried et al (2013). We prepared the dataset by using "patientselection.config" in "Curated ovarian data" around October 2016.

Usage

data("dataOvarian2")
Format

A data frame with 912 observations on the following 132 variables.

t.death : time to death in days
death : death indicator (1=death, 0=alive)
group : study ID; group=4, 9, 12, or 16
debulk : residual tumour size (>=1cm> vs. <1cm)
ANKRD27 a numeric vector
AP3S1 a numeric vector
APMAP a numeric vector
ARHGAP28 a numeric vector
ASAP1 a numeric vector
ASAP3 a numeric vector
ASB7 a numeric vector
B4GALT5 a numeric vector
BYSL a numeric vector
C1QTNF3 a numeric vector
CASP8 a numeric vector
CCL18 a numeric vector
CD79A a numeric vector
CDK19 a numeric vector
CLIC4 a numeric vector
COL11A1 a numeric vector
COL16A1 a numeric vector
COL3A1 a numeric vector
COL5A1 a numeric vector
COL5A2 a numeric vector
COMP a numeric vector
COX7A2P2 a numeric vector
CPNE1 a numeric vector
CRISPLD2 a numeric vector
CRYAB a numeric vector
CTNNB1 a numeric vector
CXCL12 a numeric vector
CXCL9 a numeric vector
CYBRD1 a numeric vector
CYR61 a numeric vector
CYTH3 a numeric vector
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</tr>
<tr>
<td>FOXN3</td>
<td>numeric vector</td>
</tr>
<tr>
<td>FSTL1</td>
<td>numeric vector</td>
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<tr>
<td>GABRG3</td>
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</tr>
<tr>
<td>GAS1</td>
<td>numeric vector</td>
</tr>
<tr>
<td>GFRA1</td>
<td>numeric vector</td>
</tr>
<tr>
<td>GJC1</td>
<td>numeric vector</td>
</tr>
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<td>GPATCH1</td>
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<tr>
<td>GZMB</td>
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</tr>
<tr>
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<tr>
<td>HOXA5</td>
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<tr>
<td>HP1BP3</td>
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</tr>
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<td>INHBA</td>
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<td>ITGB1</td>
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<td>ITPKC</td>
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<td>JAM2</td>
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<td>KIAA0355</td>
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<tr>
<td>KIN</td>
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</tr>
<tr>
<td>LEP</td>
<td>numeric vector</td>
</tr>
<tr>
<td>L0X</td>
<td>numeric vector</td>
</tr>
</tbody>
</table>
dataOvarian2

LPL  a numeric vector
LSM14A a numeric vector
LUM a numeric vector
LUZP1 a numeric vector
MAPRE1 a numeric vector
MCL1 a numeric vector
MEOX2 a numeric vector
MMP12 a numeric vector
N4BP2L2 a numeric vector
NCOA3 a numeric vector
NCOA6 a numeric vector
NOTCH2NL a numeric vector
NR1H3 a numeric vector
NUAK1 a numeric vector
OAT a numeric vector
OMD a numeric vector
PAK4 a numeric vector
PCDH9 a numeric vector
PDP1 a numeric vector
PDPN a numeric vector
PHF20 a numeric vector
PLXNA1 a numeric vector
PSMC4 a numeric vector
PSMD8 a numeric vector
RAB13 a numeric vector
RAI14 a numeric vector
RARRES1 a numeric vector
RBM39 a numeric vector
RECQL a numeric vector
RIN2 a numeric vector
RND3 a numeric vector
RPS16 a numeric vector
SACS a numeric vector
SH3PXD2A a numeric vector
SKI a numeric vector
SLAMF7 a numeric vector
SLC37A4 a numeric vector
SMG5 a numeric vector
SOC55 a numeric vector
SPARC a numeric vector
SSR4 a numeric vector
STAU1 a numeric vector
SUPT5H a numeric vector
TBCB a numeric vector
TBCC a numeric vector
TEAD1 a numeric vector
TESK1 a numeric vector
TIMP3 a numeric vector
TJP1 a numeric vector
TP53BP2 a numeric vector
TSPAN9 a numeric vector
TTI1 a numeric vector
TUBB2A a numeric vector
TUBB6 a numeric vector
URI1 a numeric vector
USP48 a numeric vector
YWHAB a numeric vector
ZFP36 a numeric vector
ZFP36L2 a numeric vector
ZNF148 a numeric vector

Details

4 studies are combined (group=4, 9, 12, and 16). The numbers 4, 9, 12 and 16 corresponds to the IDs from the original data of Ganzfried et al. (2013).

Source


References

Examples

data(dataOvarian2)

### # univariate Cox ###

t.death=dataOvarian2$t.death
death=dataOvarian2$death

X.mat=dataOvarian2[,c(1,2,3,4)] ## gene expression
Symbol=colnames(dataOvarian2)[c(1,2,3,4)] ## gene symbol

p=ncol(X.mat)
P_value=coef=NULL

for(j in 1:p){
  res=summary(coxph(Surv(t.death,death)~X.mat[,j]))$coefficients
  P_value=c(P_value,res[5])
  coef=c(coef,res[1])
}
data.frame( gene=Symbol[order(P_value)], P=P_value[order(P_value)],
  coef=round(coef[order(P_value)],3) )

---

**F.KM**

*Prediction of death using the Kaplan-Meier estimator*

**Description**

Dynamic prediction of death using the Kaplan-Meier estimator. Probability of death between $t$ and $t+w$ is calculated. The prediction probability is $F(t,t+w)=1-S(t+w)/S(t)$, where $S$ is the Kaplan-Meier estimator.

**Usage**

F.KM(time, widths, t.death, death)

**Arguments**

- **time**: prediction time ($t$)
- **widths**: length of window ($w$)
- **t.death**: a vector object for overall survival (OS), i.e., time-to-death
- **death**: a vector object for death indicator (1 if death; 0 if not death)

**Details**

Prediction probability of death is calculated without covariates.

**Value**

- **time**: $t$
- **widths**: $w$
- **F**: $F(t,t+w)$
**Author(s)**

Takeshi Emura

**References**


**Examples**

```r
time=1
widths=c(0,0.5,1,1.5,2)
t.death=c(0.5,1,1.5,2,2.5,3)
death=c(1,1,1,1,1,1)
F.KM(time=time,width=widths,t.death=t.death,death=death)
```

**Description**

Dynamic prediction of death using a joint frailty-copula model. Probability of death between \( t \) and \( t+w \) is calculated given a tumour progression time \( X \) and covariates \( Z_1 \) and \( Z_2 \). If \( X \leq t \), the prediction probability is \( F(t,t+w|X=x, Z_1, Z_2) \). If \( X>t \), the prediction probability is \( F(t,t+w|X>t, Z_1, Z_2) \). This function is a simpler version of \( F \).windows. The guide for using this function shall be explained by Emura et al. (2019).

**Usage**

```r
F.prediction(time, widths, X, Z1, Z2, beta1, beta2, eta, theta, alpha, g, h, xi1, xi3, Fplot = TRUE)
```

**Arguments**

- **time**: prediction time (=\( t \))
- **widths**: length of window (=\( w \))
- **X**: time of tumour progression; if tumour progression does not occur before time \( t \), one can set an arbitrary value \( X \) greater than \( t \)
- **Z1**: a vector of covariates for progression
- **Z2**: a vector of covariates for death
- **beta1**: a vector of regression coefficients for progression
- **beta2**: a vector of regression coefficients for death
- **eta**: frailty variance
F.prediction

\theta \text{ copula parameter}

\alpha \text{ parameter related to frailty; usually } \alpha=1

g \text{ parameters related to the baseline hazard for progression}

h \text{ parameters related to the baseline hazard for death}

\xi_1 \text{ lower bound for time-to-event}

\xi_3 \text{ upper bound for time-to-death}

Fplot \text{ if FALSE, the plot is not shown}

Details

Predicted probability of death is calculated given the event status (X<=t or X>t) and covariates (Z1 and Z2).

Value

time \ t

widths \ w

X \ X

F \ F(t,t+w|X=x, Z1, Z2) or F(t,t+w|X>t, Z1, Z2)

Author(s)

Takeshi Emura

References


Examples

w=c(0, 0.5, 1, 1.5, 2)
par(mfrow=c(1,2))
F.prediction(time=1,X=0.8,widths=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
alpha=1,g=rep(1,5),h=rep(1,5),xi1=0,xi3=3)
F.prediction(time=1,X=1.5,widths=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
alpha=1,g=rep(1,5),h=rep(1,5),xi1=0,xi3=3)
Dynamic prediction of death using a joint frailty-copula model. Probability of death between \( t \) and \( t+w \) is calculated given a tumour progression time \( X \) and covariates \( Z_1 \) and \( Z_2 \). If \( X\leq t \), the prediction probability is \( F(t,t+w|X=x, Z_1, Z_2) \). If \( X>t \), the prediction probability is \( F(t,t+w|X>t, Z_1, Z_2) \).

Usage

\[
F\text{-window}(\text{time}, \text{width}, X, Z_1, Z_2, \text{beta1, beta2, eta, theta, alpha, g, h, xi1, xi3, Fplot = TRUE})
\]

Arguments

- \text{time} \quad \text{prediction time (=t)}
- \text{width} \quad \text{length of window (=w)}
- \text{X} \quad \text{time of tumour progression < time}
- \text{Z1} \quad \text{a vector of covariates for progression}
- \text{Z2} \quad \text{a vector of covariates for death}
- \text{beta1} \quad \text{a vector of regression coefficients for progression}
- \text{beta2} \quad \text{a vector of regression coefficients for death}
- \text{eta} \quad \text{frailty variance}
- \text{theta} \quad \text{copula parameter}
- \text{alpha} \quad \text{parameter related to frailty; usually alpha=1}
- \text{g} \quad \text{parameters related to the baseline hazard for progression}
- \text{h} \quad \text{parameters related to the baseline hazard for death}
- \text{xi1} \quad \text{lower bound for time to event}
- \text{xi3} \quad \text{upper bound for time to death}
- \text{Fplot} \quad \text{if FALSE, the plot is not shown}

Details

Predicted probability of death is calculated given the event status (\( X\leq t \) or \( X>t \)) and covariates (\( Z_1 \) and \( Z_2 \)).

Value

\[
\begin{align*}
\text{time} & \quad t \\
\text{width} & \quad w \\
\text{X} & \quad X \\
F\_\text{event\_at\_X} & \quad F(t,t+w|X=x, Z_1, Z_2) \\
F\_\text{noevent} & \quad F(t,t+w|X>t, Z_1, Z_2)
\end{align*}
\]
Author(s)
Takeshi Emura

References

Examples
w=1
par(mfrow=c(1,2))
F.window(time=1,X=0.2,width=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8, alpha=1,g=rep(1,5),h=rep(1,5),xi1=0,xi3=3)
F.window(time=1,X=0.5,width=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8, alpha=1,g=rep(1,5),h=rep(1,5),xi1=0,xi3=3)

Description
Dynamic prediction of death using a joint frailty-copula model. Probability of death between t and t+w is calculated given a tumour progression time X and covariates Z1 and Z2. If X≤t, the prediction probability is F(t,t+w|X=x, Z1, Z2). If X>t, the prediction probability is F(t,t+w|X>t, Z1, Z2).

Usage
F.window.Weibull(time, width, X, Z1, Z2, beta1, beta2, eta, theta, alpha, scale1, shape1,scale2,shape2, xi1, xi3, Fplot = TRUE)

Arguments
time prediction time (=t)
width length of window (=w)
X time of tumour progression < time
Z1 a vector of covariates for progression
Z2 a vector of covariates for death
beta1 a vector of regression coefficients for progression
beta2 a vector of regression coefficients for death
eta frailty variance
theta copula parameter
alpha  parameter related to frailty; usually alpha=1
scale1  scale parameter related to the baseline hazard for progression
shape1  shape parameter related to the baseline hazard for progression
scale2  scale parameter related to the baseline hazard for death
shape2  shape parameter related to the baseline hazard for death
xi1  lower bound for time to event
xi3  upper bound for time to death
Fplot  if FALSE, the plot is not shown

Details

Predicted probability of death is calculated given the event status (X<=t or X>t) and covariates (Z1 and Z2).

Value

time  t
width  w
X  X
F_event_at_X  F(t,t+w|X=x, Z1, Z2)
F_noevent  F(t,t+w|X>t, Z1, Z2)

Author(s)

Sayaka Shinohara, Takeshi Emura

References


Examples

```r
w=1
par(mfrow=c(1,2))
F.window.Weibull(time=1,X=0.2,width=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
alpha=1,scale1=1,shape1=1,scale2=1,shape2=1,xi1=0,xi3=3)
F.window.Weibull(time=1,X=0.8,width=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
alpha=1,scale1=1,shape1=1,scale2=1,shape2=1,xi1=0,xi3=3)
```
F.windows

Dynamic prediction of death under the joint frailty-copula model

Description

Dynamic prediction of death using a joint frailty-copula model. Probability of death between \( t \) and \( t+w \) is calculated given a tumour progression time \( X \) and covariates \( Z_1 \) and \( Z_2 \). If \( X \leq t \), the prediction probability is \( F(t,t+w|X=x, Z_1, Z_2) \). If \( X > t \), the prediction probability is \( F(t,t+w|X>t, Z_1, Z_2) \). This is a vector version of F.window.

Usage

F.windows(time, widths, X, Z1, Z2, beta1, beta2, eta, theta, alpha, g, h, xi1, xi3, Fplot = TRUE)

Arguments

time    prediction time (=t)
widths  length of window (=w)
X       time of tumour progression < time
Z1      a vector of covariates for progression
Z2      a vector of covariates for death
beta1   regression coefficients for progression
beta2   regression coefficients for death
eta     frailty variance
theta   copula parameter
alpha   parameter related to frailty; usually alpha=1
eg      parameters related to the baseline hazard for progression
h       parameters related to the baseline hazard for death
xi1     lower bound for time to event
xi3     upper bound for time to death
Fplot   if FALSE, the plot is not shown

Details

Predicted probability of death is calculated given the event status (\( X \leq t \) or \( X > t \)) and covariates (\( Z_1 \) and \( Z_2 \)).

Value

time        t
widths      w
X            X
F_event_at_X \( F(t,t+w|X=x, Z_1, Z_2) \)
F_noevent   \( F(t,t+w|X>t, Z_1, Z_2) \)
Author(s)
Takeshi Emura

References

Examples
```r
w=c(0,0.5,1,1.5,2)
par(mfrow=c(1,2))
F.windows(time=1,X=0.2,widths=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
alpha=1,g=rep(1,5),h=rep(1,5),xi1=0,xi3=3)
F.windows(time=1,X=0.8,widths=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
alpha=1,g=rep(1,5),h=rep(1,5),xi1=0,xi3=3)
```

F.windows.Weibull  Dynamic prediction of death under the joint frailty-copula model (the Weibull baseline hazard functions)

Description
Dynamic prediction of death using a joint frailty-copula model. Probability of death between \( t \) and \( t+w \) is calculated given a tumour progression time \( X \) and covariates \( Z_1 \) and \( Z_2 \). If \( X \leq t \), the prediction probability is \( F(t,t+w|X=x, Z_1, Z_2) \). If \( X > t \), the prediction probability is \( F(t,t+w|X>t, Z_1, Z_2) \). This is a vector version of F.window.Weibull.

Usage
```r
F.windows.Weibull(time, widths, X, Z1, Z2, beta1, beta2, eta, theta, alpha,
scale1, shape1,scale2,shape2, xi1, xi3, Fplot = TRUE)
```

Arguments
- `time`: prediction time (=\( t \))
- `widths`: length of window (=\( w \))
- `X`: time of tumour progression < time
- `Z1`: a vector of covariates for progression
- `Z2`: a vector of covariates for death
- `beta1`: a vector of regression coefficients for progression
- `beta2`: a vector of regression coefficients for death
- `eta`: frailty variance
- `theta`: copula parameter
alpha parameter related to frailty; usually alpha=1
scale1 scale parameter related to the baseline hazard for progression
shape1 shape parameter related to the baseline hazard for progression
scale2 scale parameter related to the baseline hazard for death
shape2 shape parameter related to the baseline hazard for death
xi1 lower bound for time to event
xi3 upper bound for time to death
fplot if FALSE, the plot is not shown

Details

Predicted probability of death is calculated given the event status (X<=t or X>t) and covariates (Z1 and Z2).

Value

time t
widths w
X X
F_event_at_X F(t,t+w|X=x, Z1, Z2)
F_noevent F(t,t+w|X>t, Z1, Z2)

Author(s)

Sayaka Shinohara, Takeshi Emura

References


Examples

w=c(0, 0.5, 1, 1.5, 2)
par(mfrow=c(1,2))
F.windows.Weibull(time=1,X=0.2,widths=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
alpha=1, scale1=1, shape1=1, scale2=1, shape2=1, xi1=0, xi3=3)
F.windows.Weibull(time=1,X=0.8,widths=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
alpha=1, scale1=1, shape1=1, scale2=1, shape2=1, xi1=0, xi3=3)
**Description**

Calculate the I-spline basis functions (the integrals of the M-spline basis functions).

**Usage**

```r
I.spline(time, xi1, xi3)
```

**Arguments**

- `time`: a vector of time points
- `xi1`: lower bound of time points
- `xi3`: upper bound of time points

**Details**

The output shows the values of the 5 basis functions at "time", giving a matrix with nrow=length(time) and ncol=5. The five basis functions were originally given in the Supplementary Material of Emura et al. (2017). More details can be found in Emura and Chen (2018), Emura et al. (2019), and Shih and Emura (2020-). The "time" argument should be a vector satisfying the contraints xi1<=time<=xi3. If "time" does not meet the constraints, error messages are shown.

**Value**

```r
NULL
```

A matrix with nrow=length(time) and ncol=5, containing the values of the 5 I-spline basis functions at "time".

**Author(s)**

Takeshi Emura

**References**


Examples

\[ I.spline(time=c(1,2,3),xi1=1,xi3=3) \]

Description

Perform regression analyses under a joint Cox proportional hazards model between tumour progression and death for meta-analysis, which is proposed by Rondeau et al. (2015). The method is applicable for meta-analysis combining several studies or for cluster survival data.

Usage

```
jointCox.indep.reg(t.event, event, t.death, death, Z1, Z2, group, alpha = 1, kappa1 = c(seq(10, 1e+17, length = 30)), kappa2 = c(seq(10, 1e+17, length = 30)), LCV.plot = TRUE, Randomize_num = 10, Adj = 500, convergence.par = FALSE)
```

Arguments

- `t.event`: a vector for time-to-tumour progression (TTP)
- `event`: a vector for progression indicator (=1 if progression; =0 if not progression)
- `t.death`: a vector for overall survival (OS), i.e., time-to-death
- `death`: a vector for death indicator (=1 if death; =0 if not death)
- `Z1`: a matrix for covariates associated with TTP; ncol(Z1)=the number of covariates
- `Z2`: a matrix for covariates associated with OS; ncol(Z2)=the number of covariates
- `group`: a vector for group identification numbers, like 1,2,3....
- `alpha`: A value related to the frailty (e.g., alpha=0 or =1); alpha=1 is default
- `kappa1`: a vector for candidate smoothing parameters
- `kappa2`: a vector for candidate smoothing parameters
- `LCV.plot`: Plot the LCV curves if "TRUE"
- `Randomize_num`: The number of randomizations for the initial p0
- `Adj`: Numerical adjustment to prevent overflow; Adj=500 is recommended
- `convergence.par`: If TRUE, the converged estimate, gradient, and Hessian matrix are given (log-transformed)

Details

We employ "nlm" routine to maximize the penalized likelihood function with the initial value described in Emura et al. (2015). If "nlm" does not converge, then we randomize the initial value by adding uniform random variables (Hu and Emura, 2015).
Value

count Count for event occurrences
beta1 Regression coefficient for Z1
beta2 Regression coefficient for Z2
eta Frailty parameter (variance)
LCV1 Likelihood cross-validation for TTP
LCV2 Likelihood cross-validation for OS
g M-spline coefficients for TTP
h M-spline coefficients for OS
g_var Variance of M-spline coefficients for TTP
h_var Variance of M-spline coefficients for OS
convergence convergence results for maximizing penalized likelihood
convergence.parameters converged estimate, gradient, and Hessian matrix (log-transformed)

Error

"Error in integrate(func1, 0.001, 10, stop.on.error = FALSE):non-finite function value", an error occurring when the penalized likelihood is maximized by "nlm". The error may frequently occur during the iterations for maximizing the penalized likelihood, but is not crucial (can simply be ignored).

Warning

"NA/Inf replaced by maximum positive value", an error occurring when the penalized likelihood is maximized by "nlm". The error frequently occurs during the iterations for maximizing the penalized likelihood, but is not crucial (can simply be ignored).

Author(s)

Takeshi Emura

References


Examples

######## Reproduce the results of Emura et al. (2015) ########

data(dataOvarian)
t.event=dataOvarian$t.event
event=dataOvarian$event
t.death=dataOvarian$t.death
death=dataOvariandeath
Z1=dataOvarian$CXCL12
group=dataOvarian$group
alpha_given=0
kappa_grid=seq(10,1e+17,length=30)
set.seed(1)
#jointCox.indep.reg(t.event=t.event,event=event,t.death=t.death,death=death,
# Z1=Z1,Z2=Z1,group=group,alpha=alpha_given,
# kappa1=kappa_grid,kappa2=kappa_grid,LCV.plot=TRUE,Adj=500)

jointCox.reg  
Penalized Likelihood Estimation under the Joint Cox Models Between Tumour Progression and Death for Meta-Analysis

Description

Perform regression analyses under a copula-based joint Cox proportional hazards model between tumour progression and death for meta-analysis, which is proposed by Emura et al. (2017). The methodological details can be found in Emura et al. (2019). The method is applicable for meta-analysis combining several studies or for cluster survival data.

Usage

jointCox.reg(t.event, event, t.death, death, Z1, Z2, group, alpha = 1,
   kappa1 = c(seq(10, 1e+17, length = 30)),kappa2 = c(seq(10, 1e+17, length = 30)),
   LCV.plot = TRUE, Randomize_num = 10,
   Adj = 500,convergence.par=FALSE)

Arguments

t.event a vector for time-to-tumour progression (TTP)
event a vector for progression indicator (=1 if progression; =0 if not progression)
t.death a vector for overall survival (OS), i.e., time-to-death
death a vector for death indicator(=1 if death; =0 if not death)
Z1 a matrix for covariates associated with TTP; ncol(Z1)=the number of covariates
Z2 a matrix for covariates associated with OS; ncol(Z2)=the number of covariates
group a vector for group identification numbers, like 1,2,3....
alpha A value related to the frailty (e.g., alpha=0 or =1); alpha=1 is default
kappa1  a vector for candidate smoothing parameters
kappa2  a vector for candidate smoothing parameters
LCV.plot  Plot the LCV curves if "TRUE"
Randomize_num  The number of randomizations for the initial p0
Adj  Numerical adjustment to prevent overflow; Adj=500 is recommended
convergence.par  If TRUE, the converged estimate, gradient, and Hessian matrix are given (log-transformed)

Details

We employ "nlm" routine to maximize the penalized likelihood function with the initial value described in Emura et al. (2017). If "nlm" does not converge, then we randomize the initial value by adding uniform random variables (Hu and Emura, 2015).

Value

count  Count for event occurrences
beta1  Regression coefficient for Z1
beta2  Regression coefficient for Z2
eta  Frailty parameter (variance)
theta  Copula parameter under the Clayton copula
tau  Kendall’s tau corresponding to the copula parameter
LCV1  Likelihood cross-validation for TTP
LCV2  Likelihood cross-validation for OS
g  M-spline coefficients for TTP
h  M-spline coefficients for OS
g_var  Variance of M-spline coefficients for TTP
h_var  Variance of M-spline coefficients for OS
convergence  convergence results for maximizing penalized likelihood
convergence.parameters  converged estimate, gradient, and Hessian matrix (log-transformed)

Error

"Error in integrate(func1, 0.001, 10, stop.on.error = FALSE): non-finite function value", an error occurring when the penalized likelihood is maximized by "nlm". The error may frequently occur during the iterations for maximizing the penalized likelihood, but is not crucial (can simply be ignored).

Warning

"NA/Inf replaced by maximum positive value", an error occurring when the penalized likelihood is maximized by "nlm". The error frequently occurs during the iterations for maximizing the penalized likelihood, but is not crucial (can simply be ignored).
**Author(s)**

Takeshi Emura

**References**


**Examples**

```
############################################################################## Reproduce the results of Emura et al. (2017) ##############################################################################
data(dataOvarian)
t.event=dataOvarian$t.event
event=dataOvarian$event	.death=dataOvarian$t.death
death=dataOvarian$death
Z1=dataOvarian$CXCL12
group=dataOvarian$group
alpha_given=0
kappa_grid=seq(10,1e+17,length=30)
set.seed(1)
#jointCox.reg(t.event=t.event,event=event,t.death=t.death,death=death,
# Z1=Z1,Z2=Z1,group=group,alpha=alpha_given,
# kappa1=kappa_grid,kappa2=kappa_grid,LCV.plot=TRUE,Adj=500)
```

---

**jointCox.Weibull.reg**

*Weibull-based Likelihood Estimation under the Joint Cox Models Between Tumour Progression and Death for Meta-Analysis*

**Description**

Perform Weibull regression analyses under a copula-based joint Cox proportional hazards model between tumour progression and death for meta-analysis, which is proposed by Wu et al. (2020).

**Usage**

```
jointCox.Weibull.reg(t.event, event, t.death, death, Z1, Z2, group, alpha = 1, Randomize_num = 10, Adj = 500, convergence.par=FALSE)
```
Arguments

t.event  a vector for time-to-tumour progression (TTP)
etvent  a vector for progression indicator (=1 if progression; =0 if not progression)
t.death a vector for overall survival (OS), i.e., time-to-death
death  a vector for death indicator(=1 if death; =0 if not death)
Z1  a matrix for covariates associated with TTP; ncol(Z1)=the number of covariates
Z2  a matrix for covariates associated with OS; ncol(Z2)=the number of covariates
group  a vector for group identification numbers, like 1,2,3,...
alpha A value related to the frailty (e.g., alpha=0 or =1); alpha=1 is default
Randomize_num  The number of randomizations for the initial p0
Adj  Numerical adjustment to prevent overflow; Adj=500 is recommended
convergence.par  If TRUE, the converged estimate, gradient, and Hessian matrix are given (log-transformed)

Details

We employ "nlm" routine to maximize the penalized likelihood function with the initial value described in Wu et al. (2020). If "nlm" does not converge, then we randomize the initial value by adding uniform random variables (Hu and Emura, 2015).

Value

count  Count for event occurrences
beta1  Regression coefficient for Z1
beta2  Regression coefficient for Z2
eta  Frailty parameter (variance)
theta  Copula parameter under the Clayton copula
tau  Kendall’s tau corresponding to the copula parameter
scale1  Scale parameter for the Weibull model of TTP
shape1  Shape parameter for the Weibull model of TTP
scale2  Scale parameter for the Weibull model of OS
shape2  Shape parameter for the Weibull model of OS
convergence  convergence results for maximizing penalized likelihood
convergence.parameters  converged estimate, gradient, and Hessian matrix (log-transformed)

Error

"Error in integrate(func1, 0.001, 10, stop.on.error = FALSE):non-finite function value", an error occurring when the penalized likelihood is maximized by "nlm". The error may frequently occur during the iterations for maximizing the penalized likelihood, but is not crucial (can simply be ignored).
Warning

"NA/Inf replaced by maximum positive value", an error occurring when the penalized likelihood is maximized by "nlm". The error frequently occurs during the iterations for maximizing the penalized likelihood, but is not crucial (can simply be ignored).

Author(s)

Takeshi Emura

References


Examples

data(dataOvarian)
t.event=dataOvarian$t.event
event=dataOvarian$event
t.death=dataOvarian$t.death
death=dataOvarian$death
Z1=dataOvarian$CXCL12
group=dataOvarian$group
alpha_given=0
kappa_grid=seq(10,1e+17,length=30)

t.event[t.event == 0] = 1 ## data can not be zero ##
t.death[t.death == 0] = 1 ## data can not be zero ##

#set.seed(1)
#jointCox.Weibull.reg(t.event=t.event,event=event,t.death=t.death,death=death,
# Z1=Z1,Z2=Z1,group=group,alpha=alpha_given,Adj=500)

M.spline

M-spline basis function

Description

Calculate the M-spline basis functions (a M-spline basis is a B-spline basis normalized so that the integral is 1).

Usage

M.spline(time, x1, x3)
Arguments

time  a vector of time points
xi1   lower bound of time points
xi3   upper bound of time points

Details

The output shows the values of the 5 basis functions at "time", giving a matrix with nrow=length(time) and ncol=5. The five basis functions were originally given in the Supplementary Material of Emura et al. (2017). More details can be found in Emura and Chen (2018), Emura et al. (2019), and Shih and Emura (2020-). The "time" argument should be a vector satisfying the contraints xi1<=time<=xi3. If "time" does not meet the constraints, error messages are shown.

Value

NULL A matrix with nrow=length(time) and ncol=5, containing the values of the 5 spline basis functions at "time".

Author(s)

Takeshi Emura

References


Examples

M.spline(time=c(1,2,3),xi1=1,xi3=3)
**Description**

Fitting the Cox proportional hazards model when the baseline hazard function is specified by a five-parameter spline model.

**Usage**

```r
splineCox.reg(t.event, event, Z, xi1 = min(t.event), xi3 = max(t.event),
             kappa = c(seq(10, 1e+17, length = 30)), LCV.plot = TRUE, p0=rep(0,5+p))
```

**Arguments**

- `t.event`: a vector for time-to-event
- `event`: a vector for event indicator (=1 event; =0 censoring)
- `Z`: a matrix for covariates; `nrow(Z)`=sample size, `ncol(Z)`=the number of covariates
- `xi1`: lower bound for the hazard function; the default is `min(t.event)`
- `xi3`: upper bound for the hazard function; the default is `max(t.event)`
- `kappa`: a vector for candidate smoothing parameters. Only positive values are allowed. Values too close to zero may yield errors (see below).
- `LCV.plot`: Plot the LCV curves if "TRUE". This plot is used to find the optimal value from the candidate smoothing parameters given by "kappa".
- `p0`: Initial values to maximize the penalized likelihood (5+p parameters; five M-spline coefficients and p regression coefficients)

**Details**

One can perform Cox-type regression for censored survival data with covariates. The method is essentially the same as Cox regression (Cox 1972) expect for the models of the baseline hazard function. Unlike the nonparametric model of Cox (1972), the method applies a five-parameter spline model as originally proposed by Emura et al. (2017). The method is detailed in Section 2.4 of Emura et al. (2019). See also Shih and Emura (2020-) for more details. This method is also used as a subroutine for computing the optimal smoothing parameter (kappa1 and kappa2) for many advanced functions, such as "jointCox.reg" and "cmprskCox.reg". The definition of LCV is given in Section 3.7 of Emura et al. (2019). See also Shih and Emura (2020-). The error message "Error in nlm(l.func, p = rep(0, 5 + p), hessian = TRUE):non-finite value supplied by 'nlm'" may imply that some candidate parameters for kappa are too close to zero; please exclude such values from kappa. The output values are usually similar to those given by "coxph(Surv(t.event,event)~Z)". Unreasonable output values are usually caused by a wrong choice of "kappa" and occasionary caused by a wrong choice of p0.
Value

- beta: Regression coefficient for Z
- h: M-spline coefficients
- h_var: Variance of M-spline coefficients
- kappa: Smoothing parameter at the optimal LCV
- DF: Degree of freedom at the optimal LCV
- LCV: The optimal LCV (= logL - DF)

Author(s)

Takeshi Emura

References


Examples

```r
data(dataOvarian)
t.event=dataOvarian$t.event
event=dataOvarian$event
t.death=dataOvarian$t.death
death=dataOvarian$death
Z=dataOvarian$CXCL12
#splineCox.reg(t.event,event,Z,kappa=c(seq(10,1e+17,length=30)))
```

---

**Weibull.simu**

Simulating data from the Weibull joint frailty-copula model

Description

Simulating data from the Weibull joint frailty-copula model.

Usage

```r
Weibull.simu(G,N,scale1,scale2,shape1,shape2,beta1,beta2,eta,theta,alpha,beta12=0,C.max,Z.dist=runif,...)
```
Arguments

- G: The number of studies or groups
- N: The number of patients within each study
- scale1: scale parameter related to the baseline hazard for progression
- scale2: scale parameter related to the baseline hazard for death
- shape1: shape parameter related to the baseline hazard for progression
- shape2: shape parameter related to the baseline hazard for death
- beta1: regression coefficients for progression
- beta2: regression coefficients for death
- eta: frailty variance
- theta: copula parameter
- alpha: parameter related to frailty; usually alpha=1
- beta12: regression coefficients for copula
- C.max: the upper bound for the censoring distribution
- Z.dist: the distribution of a covariate Z
- ...: parameters for Z.dist

Details

See Wu et al. (2020) for the algorithms.

Value

- X: time to event
- D: time to death
- C: independent censoring time
- t.event: time to event (censored)
- event: event indicator (1=event, 0=no event)
- t.death: time to death (censored)
- death: death indicator (1=death, 0=alive)
- group: study ID (1~G)
- Z: covariate

Author(s)

Takeshi Emura

References

Examples

\[
\text{Weibull.simu}(G=5,N=2, \text{scale}1=1, \text{scale}2=1, \text{shape}1=1, \text{shape}2=1, \\
\beta_1=1, \beta_2=1, \eta=0.5, \theta=2, \alpha=1, C.\max=5)
\]

\[
\text{Weibull.simu}(G=5,N=2, \text{scale}1=1, \text{scale}2=1, \text{shape}1=1, \text{shape}2=1, \\
\beta_1=1, \beta_2=1, \eta=0.5, \theta=2, \alpha=1, C.\max=5, Z.\text{dist=runif}, \text{size}=1, \text{prob}=0.5)
\]
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