

Package ‘joint.Cox’

October 30, 2016

Type Package

Title Penalized Likelihood Estimation and Dynamic Prediction under the Joint Frailty-Copula Models Between Tumour Progression and Death for Meta-Analysis

Version 2.10

Date 2016-10-30

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Description Perform the Cox regression and dynamic prediction under the joint frailty-copula model between tumour progression and death for meta-analysis. The method is applicable for meta-analytic data combining several studies. The data should have information on both terminal event time (e.g., time-to-death) and non-terminal event time (e.g., time-to-tumour progression).

License GPL-2

Depends survival

NeedsCompilation no

Repository CRAN

Date/Publication 2016-10-30 11:39:33

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joint.Cox-package	<i>Penalized Likelihood Estimation and Dynamic Prediction under the Joint Frailty-Copula Models Between Tumour Progression and Death for Meta-Analysis</i>
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Description

Perform the Cox regression and dynamic prediction under the joint frailty-copula model between tumour progression and death for meta-analysis. The method is applicable for meta-analytic data combining several studies. The data should have information on both terminal event time (e.g., time-to-death) and non-terminal event time (e.g., time-to-tumour progression).

Details

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Author(s)

Takeshi Emura Maintainer: Takeshi Emura <takeshiemura@gmail.com>

References

Emura T*, Nakatochi M, Murotani K, Rondeau V (2015), A joint frailty-copula model between tumour progression and death for meta-analysis, *Statistical Methods in Medical Research*, doi: 10.1177/0962280215604510

Emura T*, Nakatochi M, Matsui S, Michimae H, Rondeau V (2016), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model, in revision, *Statistical Methods in Medical Research*.

dataOvarian	<i>Meta-analytic data of ovarian cancer patients combining 4 independent studies.</i>
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Description

Meta-analytic data for studying the CXCL12 gene expression as a predictive biomarker of survival in ovarian cancer. 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 May 2015.

Usage

```
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
CXCL12  : CXCL12 expression
```

Details

4 studies are combined (group=4, 8, 11, and 14). The numbers 4, 8, 11 and 14 corresponds to the IDs from the original data of Ganzfried et al. (2013).

Source

Ganzfried BF et al. (2013), Curated ovarian data: clinically annotated data for the ovarian cancer transcriptome, Database, Article ID bat013, doi:10.1093/database/bat013.

References

Ganzfried BF et al. (2013), Curated ovarian data: clinically annotated data for the ovarian cancer transcriptome, Database, Article ID bat013, doi:10.1093/database/bat013.

Examples

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

dataOvarian1	<i>Data on time-to-recurrence and 158 gene expressions for 912 ovarian cancer patients from 4 independent studies.</i>
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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 ($\geq 1\text{cm}$ vs. $< 1\text{cm}$), 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 ($\geq 1\text{cm}$ vs. $< 1\text{cm}$)

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
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
L2HGDH a numeric vector
LGALS1 a numeric vector
LOX a numeric vector
LPP a numeric vector
LUM a numeric vector
LUZP1 a numeric vector
MAP7D1 a numeric vector
MAPRE1 a numeric vector
MCL1 a numeric vector
MEOX2 a numeric vector
METTL9 a numeric vector
MFN1 a numeric vector
MICAL2 a numeric vector
MMP12 a numeric vector
MRPS22 a numeric vector
MXD1 a numeric vector
MXRA8 a numeric vector
N4BP2L2 a numeric vector
NCOA3 a numeric vector
NDRG3 a numeric vector
NINJ1 a numeric vector
NNMT a numeric vector
NOTCH2 a numeric vector
NPY a numeric vector
NTM a numeric vector
NUAK1 a numeric vector

OAT a numeric vector
OLFML2B a numeric vector
PARD3 a numeric vector
PCYT1A a numeric vector
PDE1A a numeric vector
PDGFD a numeric vector
PDPN a numeric vector
PGRMC1 a numeric vector
PLAU a numeric vector
PLOC2 a numeric vector
PLSCR4 a numeric vector
POSTN a numeric vector
PPIC a numeric vector
PRDM2 a numeric vector
PSMC4 a numeric vector
RAB22A a numeric vector
RAB31 a numeric vector
RAB32 a numeric vector
RARRES1 a numeric vector
RPS16 a numeric vector
SERPINE1 a numeric vector
SGK1 a numeric vector
SH3PXD2A a numeric vector
SKIL a numeric vector
SLC12A8 a numeric vector
SPARC a numeric vector
SPHK1 a numeric vector
STAU1 a numeric vector
SULF1 a numeric vector
SUPT5H a numeric vector
TAGLN a numeric vector
TBCB a numeric vector
TEAD1 a numeric vector
TESK1 a numeric vector
TGM5 a numeric vector
THEMIS2 a numeric vector
TIMP2 a numeric vector

TIMP3 a numeric vector
TJP1 a numeric vector
TP73.AS1 a numeric vector
TPM2 a numeric vector
TPM4 a numeric vector
TSC22D2 a numeric vector
TUBB2A a numeric vector
TUBB6 a numeric vector
TUFT1 a numeric vector
URI1 a numeric vector
USP48 a numeric vector
VCAN a numeric vector
VSIG4 a numeric vector
YWHAB a numeric vector
ZFP36 a numeric vector
ZFP36L2 a numeric vector
ZMYM1 a numeric vector
ZNF148 a numeric vector
ZNF79 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

Ganzfried BF et al. (2013), Curated ovarian data: clinically annotated data for the ovarian cancer transcriptome, Database, Article ID bat013, doi:10.1093/database/bat013.

References

Ganzfried BF et al. (2013), Curated ovarian data: clinically annotated data for the ovarian cancer transcriptome, Database, Article ID bat013, doi:10.1093/database/bat013.

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 ($\geq 1\text{cm}$ vs. $< 1\text{cm}$), 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 ($\geq 1\text{cm}$ vs. $< 1\text{cm}$)
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
CTNBL1 a numeric vector
CXCL12 a numeric vector
CXCL9 a numeric vector
CYBRD1 a numeric vector
CYR61 a numeric vector
CYTH3 a numeric vector
DDX27 a numeric vector
DLGAP4 a numeric vector
DNAJC13 a numeric vector
DYNLRB1 a numeric vector
EFNB2 a numeric vector
EIF3K a numeric vector
ELN a numeric vector
EMP1 a numeric vector
ENPP1 a numeric vector
FABP4 a numeric vector
FAP a numeric vector
FBL a numeric vector
FGF1 a numeric vector
FOXN3 a numeric vector
FSTL1 a numeric vector
GABRG3 a numeric vector

GAS1 a numeric vector
GFRA1 a numeric vector
GJC1 a numeric vector
GPATCH1 a numeric vector
GZMB a numeric vector
HLA.D0B a numeric vector
HOXA5 a numeric vector
HP1BP3 a numeric vector
HSD17B6 a numeric vector
IL2RG a numeric vector
INHBA a numeric vector
ITGB1 a numeric vector
ITPKC a numeric vector
JAM2 a numeric vector
JUN a numeric vector
KCNH4 a numeric vector
KDELC1 a numeric vector
KIAA0355 a numeric vector
KIN a numeric vector
LEP a numeric vector
LOX a numeric vector
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
SOCS5 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

Ganzfried BF et al. (2013), Curated ovarian data: clinically annotated data for the ovarian cancer transcriptome, Database, Article ID bat013, doi:10.1093/database/bat013.

References

Ganzfried BF et al. (2013), Curated ovarian data: clinically annotated data for the ovarian cancer transcriptome, Database, Article ID bat013, doi:10.1093/database/bat013.

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 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

Emura T*, Nakatochi M, Matsui S, Michimae H, Rondeau V (2016), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model, in revision, *Statistical Methods in Medical Research*.

Examples

```
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)
```

F.prediction	<i>Dynamic prediction of death</i>
--------------	------------------------------------

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 $X \leq t$, the prediction probability is $F(t, t+w|X=x, Z1, Z2)$. If $X > t$, the prediction probability is $F(t, t+w|X>t, Z1, Z2)$. This function is a simpler version of `F.windows`.

Usage

```
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	event time occurred
Z1	a vector of covariates
Z2	a vector of covariates
beta1	regression coefficients for progression
beta2	regression coefficients for death
eta	frailty variance
theta	copula parameter
alpha	parameter related to frailty; usually alpha=1
g	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 ($Z1$ 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

Emura T*, Nakatochi M, Matsui S, Michimae H, Rondeau V (2016), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model, in revision, *Statistical Methods in Medical Research*.

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,Fplot=FALSE)
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,Fplot=FALSE)
```

F.window

*Prediction of 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 $Z1$ and $Z2$. If $X \leq t$, 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(time, width, X, Z1, Z2, beta1, beta2, eta, theta, alpha,
         g, h, xi1, xi3, Fplot = TRUE)
```

Arguments

time	prediction time (=t)
width	length of window (=w)
X	event time occurred < time
Z1	a vector of covariates
Z2	a vector of covariates; usually $Z1=Z2$
beta1	regression coefficients for progression
beta2	regression coefficients for death
eta	frailty variance
theta	copula parameter
alpha	parameter related to frailty; usually $\alpha=1$

g	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 ($Z1$ 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)

Takeshi Emura

References

Emura T*, Nakatochi M, Matsui S, Michimae H, Rondeau V (2016), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model, in revision, Statistical Methods in Medical Research.

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=0.8,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.windows

*Prediction of 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 $Z1$ and $Z2$. If $X \leq t$, the prediction probability is $F(t, t+w | X=x, Z1, Z2)$. If $X > t$, the prediction probability is $F(t, t+w | X > t, Z1, Z2)$. 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	event time occurred < time
Z1	a vector of covariates
Z2	a vector of covariates; usually $Z1=Z2$
beta1	regression coefficients for progression
beta2	regression coefficients for death
eta	frailty variance
theta	copula parameter
alpha	parameter related to frailty; usually $\alpha=1$
g	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 ($Z1$ 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)

Takeshi Emura

References

Emura T*, Nakatochi M, Matsui S, Michimae H, Rondeau V (2016), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model, in revision, *Statistical Methods in Medical Research*.

Examples

```
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)
```

I.spline

*I-Spline function***Description**

Calculate I-Spline bases (5 bases) suggested in Emura et al. (2015).

Usage

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

Arguments

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

Details

The "time" argument is a vector satisfying the constraints $xi1 \leq time \leq xi3$. Otherwise, error messages will be produced.

Value

NULL I-Spline bases (5 bases) evaluated at "time".

Author(s)

Takeshi Emura

References

Supplementary Material to: Emura T*, Nakatochi M, Murotani K, Rondeau V (2015), A joint frailty-copula model between tumour progression and death for meta-analysis, *Statistical Methods in Medical Research*, doi: 10.1177/0962280215604510

Examples

```
I.spline(c(1,1.5,2,2.5,3),xi1=1,xi3=3)
```

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

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,
  kappa_grid = c(seq(10, 1e+17, length = 30)), LCV_plot = TRUE,
  Randomize_num = 10, Adj = 500, convergence.par=FALSE)
```

Arguments

t.event	a vector object for time-to-tumour progression (TTP)
event	a vector object for progression indicator (=1 if progression; =0 if not progression)
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)
Z1	a matrix object for covariates associated with TTP; ncol(Z1)=the number of covariates
Z2	a matrix object for covariates associated with OS; ncol(Z2)=the number of covariates
group	a vector object for a group identification number, like 1,2,3....
alpha	A value related to the frailty (e.g., alpha=0 or =1); alpha=1 is default
kappa_grid	a vector for candidate smoothing parameters in likelihood cross-validation (LCV)
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
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)

Author(s)

Takeshi Emura

References

Rondeau V, Pignon JP, Michiels S (2015). A joint model for dependence between clustered times to tumour progression and deaths: A meta-analysis of chemotherapy in head and neck cancer. *Statistical Method in Medical Research* 24(6):711-729.

Hu YH, Emura T* (2015), Maximum likelihood estimation for a special exponential family under random double-truncation, *Computational Statistics*, 30 (No. 4): 1199-1229

Examples

```
G=5
N=20
theta_true=2 ## copula parameter ##

beta1_true=2
beta2_true=2
r1_true=1
r2_true=1
eta_true=1
alpha_true=1
```

```

t.event=t.death=event=death=Z1=group=NULL

ij=0

set.seed(1)

for(i in 1:G){

  u_i=rgamma(1,shape=1/eta_true,scale=eta_true)
  for(j in 1:N){

    ij=ij+1

    group[ij]=i
    Z1[ij]=runif(1)
    r1_ij=r1_true*u_i*exp(beta1_true*Z1[ij])
    r2_ij=r2_true*(u_i^alpha_true)*exp(beta2_true*Z1[ij])
    V1=runif(1)
    V2=runif(1)
    X_ij=-1/r1_ij*log(1-V1);W=(1-V1)^(-theta_true)
    D_ij=1/theta_true/r2_ij*log( 1-W+W*(1-V2)^(-theta_true/(theta_true+1)) )
    C_ij=runif(1,min=0,max=10)
    t.event[ij]=min(X_ij,D_ij,C_ij)
    t.death[ij]=min(D_ij,C_ij)
    event[ij]=as.numeric( t.event[ij]==X_ij )
    death[ij]=as.numeric( t.death[ij]==D_ij )
  }
}

Z1=as.matrix(Z1)

jointCox.indep.reg(t.event=t.event,event=event,t.death=t.death,
  death=death,Z1=Z1,Z2=Z1,group=group,alpha=alpha_true,
  kappa_grid=seq(10,5000,length=10),LCV_plot=TRUE)

```

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. (2015). The method extends the joint frailty model of Rondeau et al. (2015) such that intra-subject dependence is modeled via the Clayton copula. 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,
  kappa_grid = c(seq(10, 1e+17, length = 30)), LCV_plot = TRUE, Randomize_num = 10,
  Adj = 500, convergence.par=FALSE)
```

Arguments

t.event	a vector object for time-to-tumour progression (TTP)
event	a vector object for progression indicator (=1 if progression; =0 if not progression)
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)
Z1	a matrix object for covariates associated with TTP; ncol(Z1)=the number of covariates
Z2	a matrix object for covariates associated with OS; ncol(Z2)=the number of covariates
group	a vector object for a group identification number, like 1,2,3....
alpha	A value related to the frailty (e.g., alpha=0 or =1); alpha=1 is default
kappa_grid	a vector for candidate smoothing parameters in likelihood cross-validation (LCV)
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
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)

Author(s)

Takeshi Emura

References

Emura T*, Nakatochi M, Murotani K, Rondeau V (2015), A joint frailty-copula model between tumour progression and death for meta-analysis, *Statistical Methods in Medical Research*, doi: 10.1177/0962280215604510

Hu YH, Emura T* (2015), Maximum likelihood estimation for a special exponential family under random double-truncation, *Computational Statistics*, 30 (No. 4): 1199-1229

Examples

```

G=3
N=10
theta_true=3 ## copula parameter ##

beta1_true=1
beta2_true=1
r1_true=1
r2_true=1
eta_true=1
alpha_true=1

t.event=t.death=event=death=Z1=group=NULL

ij=0

set.seed(1)

for(i in 1:G){

  u_i=rgamma(1,shape=1/eta_true,scale=eta_true)
  for(j in 1:N){

    ij=ij+1

    group[ij]=i
    Z1[ij]=runif(1)
    r1_ij=r1_true*u_i*exp(beta1_true*Z1[ij])
    r2_ij=r2_true*(u_i^alpha_true)*exp(beta2_true*Z1[ij])
    V1=runif(1)
  }
}

```



```

V2=runif(1)
X_ij=-1/r1_ij*log(1-V1);W=(1-V1)^(-theta_true)
D_ij=1/theta_true/r2_ij*log( 1-W+W*(1-V2)^(-theta_true/(theta_true+1)) )
#C_ij=runif(1,min=0,max=20)
C_ij=20
t.event[ij]=min(X_ij,D_ij,C_ij)
t.death[ij]=min(D_ij,C_ij)
event[ij]=as.numeric( t.event[ij]==X_ij )
death[ij]=as.numeric( t.death[ij]==D_ij )
}
}

Z1=as.matrix(Z1)

jointCox.reg(t.event=t.event,event=event,t.death=t.death,
             death=death,Z1=Z1,Z2=Z1,group=group,alpha=alpha_true,
             kappa_grid=seq(10,5000,length=2),LCV_plot=TRUE,convergence.par=TRUE)

```

M.spline

*M-Spline function***Description**

Calculate M-Spline bases (5 bases) suggested in Emura et al. (2015).

Usage

```
M.spline(time, xi1, xi3)
```

Arguments

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

Details

The "time" argument is a vector satisfying the constraints $xi1 \leq time \leq xi3$. Otherwise, error messages will be produced.

Value

NULL M-Spline bases (5 bases) evaluated at "time".

Author(s)

Takeshi Emura

References

Supplementary Material to: Emura T*, Nakatochi M, Murotani K, Rondeau V (2015), A joint frailty-copula model between tumour progression and death for meta-analysis, *Statistical Methods in Medical Research*, doi: 10.1177/0962280215604510

Examples

```
M.spline(c(1,1.5,2,2.5,3),xi1=1,xi3=3)
```

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