

# Package ‘joint.Cox’

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**Type** Package

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

**Version** 2.12

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**Description** Perform the Cox regression and dynamic prediction methods under the joint frailty-copula model between tumour progression and death for meta-analysis. A penalized likelihood is employed for estimating model parameters, where the baseline hazard functions are approximated by smoothing splines. The methods are applicable for meta-analytic data combining several studies. The methods can analyze data having information on both terminal event time (e.g., time-to-death) and non-terminal event time (e.g., time-to-tumour progression). See Emura et al. (2015) <doi:10.1177/0962280215604510> and Emura et al. (2017) <doi:10.1177/0962280216688032> for details. Survival data from ovarian cancer patients are also available.

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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 methods under the joint frailty-copula model between tumour progression and death for meta-analysis. A penalized likelihood is employed for estimating model parameters, where the baseline hazard functions are approximated by smoothing splines. The methods are applicable for meta-analytic data combining several studies. The methods can analyze data having information on both terminal event time (e.g., time-to-death) and non-terminal event time (e.g., time-to-tumour progression). See Emura et al. (2015) and Emura et al. (2017) for details. Survival data from ovarian cancer patients are also available.

**Details**

Package: joint.Cox  
Type: Package  
Version: 2.12  
Date: 2017-5-1  
License: GPL-2

**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 (2017), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis

with a joint model Statistical Methods in Medical Research, doi:10.1177/0962280216688032

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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  
PLOD2 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	<i>Data on time-to-death and 128 gene expressions for 912 ovarian cancer patients from 4 independent studies.</i>
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## 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	<i>Prediction of death using the Kaplan-Meier estimator</i>
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---

**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 (2017), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model Statistical Methods in Medical Research, doi:10.1177/0962280216688032

## 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

*Dynamic 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 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 (2017), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model Statistical Methods in Medical Research, doi:10.1177/0962280216688032

**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)
```

---

<i>F.window</i>	<i>Prediction of death</i>
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---

**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 (2017), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model Statistical Methods in Medical Research, doi:10.1177/0962280216688032

## 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 (2017), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model Statistical Methods in Medical Research, doi:10.1177/0962280216688032

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>I-Spline function</i>
----------	--------------------------

---

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  $x_{i1} \leq \text{time} \leq x_{i3}$ . 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 (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**

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)

##### Reproduce the results of Emura et al. (2015) #####
data(data0varian)
t.event=data0varian$t.event
event=data0varian$event
t.death=data0varian$t.death
death=data0varian$death
Z1=as.matrix(data0varian$CXCL12)
group=data0varian$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,
#                  kappa_grid=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. (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 (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**

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**

```
##### Reproduce the results of Emura et al. (2015) #####
data(dataOvarian)
t.event=dataOvarian$t.event
event=dataOvarian$event
t.death=dataOvarian$t.death
death=dataOvarian$death
Z1=as.matrix(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,
#             kappa_grid=kappa_grid,LCV_plot=TRUE,Adj=500)
```

---

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)
```

---

splineCox.reg	<i>Likelihood cross-validation (LCV) for the Cox model with penalized splines</i>
---------------	---

---

**Description**

Calculate likelihood cross-validation (LCV) values for the Cox model when the baseline hazard is modeled via penalized splines.

**Usage**

```
splineCox.reg(t.event, event, Z, xi1 = min(t.event), xi3 = max(t.event),  
kappa_grid = c(seq(10, 1e+17, length = 30)), LCV_plot = TRUE)
```

**Arguments**

t.event	a vector object for time-to-event
event	a vector object for progression indicator (=1 event; =0 censoring)
Z	a matrix object 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_grid	a vector for candidate smoothing parameters in LCV
LCV_plot	Plot the LCV curves if "TRUE"

**Details**

The penalized likelihood approach of Emura et al. (2015) uses the optimal values of the smoothing parameters (kappa) obtained from this function.

**Value**

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**

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**

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

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