

# 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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**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) <[doi:10.1177/0962280215604510](https://doi.org/10.1177/0962280215604510)>, Emura et al. (2018) <[doi:10.1177/0962280216688032](https://doi.org/10.1177/0962280216688032)>, Emura et al. (2020) <[doi:10.1177/0962280219892295](https://doi.org/10.1177/0962280219892295)>, Shinohara et al. (2020) <[doi:10.1080/03610918.2020.1855449](https://doi.org/10.1080/03610918.2020.1855449)> and Wu et al. (2020) <[doi:10.1007/s00180-020-00977-1](https://doi.org/10.1007/s00180-020-00977-1)>. See also the book of Emura et al. (2019) <[doi:10.1007/978-981-13-3516-7](https://doi.org/10.1007/978-981-13-3516-7)>. Survival data from ovarian cancer patients are also available.

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joint.Cox-package	<i>Joint Frailty-Copula Models for Tumour Progression and Death in Meta-Analysis</i>
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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. (2020), Wu et al. (2020), and Shinohara et al. (2020). See also the book of Emura et al. (2019). Survival data from ovarian cancer patients are also available.

## Details

Package:	joint.Cox
Type:	Package
Version:	3.14
Date:	2021-07-03
License:	GPL-2

**Author(s)**

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

**References**

Emura T, Nakatochi M, Murotani K, Rondeau V (2017), A joint frailty-copula model between tumour progression and death for meta-analysis, *Stat Methods Med Res* 26(6):2649-66

Emura T, Nakatochi M, Matsui S, Michimae H, Rondeau V (2018), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model, *Stat Methods Med Res* 27(9):2842-58

Emura T, Matsui S, Rondeau V (2019), Survival Analysis with Correlated Endpoints, *Joint Frailty-Copula Models*, JSS Research Series in Statistics, Springer

Emura T, Shih JH, Ha ID, Wilke RA (2020), Comparison of the marginal hazard model and the sub-distribution hazard model for competing risks under an assumed Copula, *Stat Methods Med Res* 29(8):2307-27

Emura T, Sofeu C, Rondeau V (2021), Conditional copula models for correlated survival endpoints in meta-analyses of randomized controlled trials, in revision

Shinohara S, Lin YH, Michimae H, Emura T (2020), Dynamic lifetime prediction using a Weibull-based bivariate failure time model: a meta-analysis of individual-patient data, *Comm Stat-Simul*, DOI:10.1080/03610918.2020.1855449

Wu BH, Michimae H, Emura T (2020), Meta-analysis of individual patient data with semi-competing risks under the Weibull joint frailty-copula model, *Comp Stat* 35(4):1525-52

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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*

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**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 indentifiability 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 times
event1	a vector for event-type 1 indicators (=1 with event; =0 without event)
event2	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
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 $p_0$
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 (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
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, Shih JH

**References**

Emura T, Nakatochi M, Murotani K, Rondeau V (2017), A joint frailty-copula model between tumour progression and death for meta-analysis, *Stat Methods Med Res* 26(6): 2649-66

Emura T, Shih JH, Ha ID, Wilke RA (2019), Comparison of the marginal hazard model and the sub-distribution hazard model for competing risks under an assumed copula, *Stat Methods Med Res*, doi.org/10.1177/0962280219892295

Hu YH, Emura T (2015), Maximum likelihood estimation for a special exponential family under random double-truncation, *Compu Stat* 30 (4): 1199-1229

**Examples**

```
data(dataOvarian)
t.event=dataOvarian$t.event
t.death=dataOvarian$t.death
event=dataOvarian$event
death=dataOvarian$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)
```

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condCox.reg	<i>Penalized Likelihood Estimation under the Joint Cox Models Between Tumour Progression and Death for Meta-Analysis; A Conditional Copula Approach</i>
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## 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

```
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, u.min = 0.001, u.max = 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
u.min	the lower bound of the numerical integration for the frailty term
u.max	the upper bound of the numerical integration for the frailty term
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	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)
- Emura T, Nakatochi M, Murotani K, Rondeau V (2017), A joint frailty-copula model between tumour progression and death for meta-analysis, *Stat Methods Med Res* 26(6): 2649-66
- Hu YH, Emura T (2015), Maximum likelihood estimation for a special exponential family under random double-truncation, *Computational Stat* 30 (4): 1199-1229

## Examples

```
##
```

---

```
dataOvarian      Survival data of 1003 ovarian cancer patients from 4 independent studies.
```

---

## Description

The data consist of 1003 surgically treated ovarian cancer patients from four studies (N1=110, N2=58, N3=278, N4=557). Survival outcomes are given to study if the CXCL12 gene expression is a prognostic factor 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

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

## Format

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

t.event : time to event (days from surgery to tumour recurrence)  
 event : event indicator (1=recurrence, 0=no recurrence)  
 t.death : time to death (days from surgery to death due to any cause)  
 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 groups are the studies of GSE30161 (58 patients), GSE9891 (278 patients), and TCGA (557 patients).



**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**

Emura T, Nakatochi M, Murotani K, Rondeau V (2017), A joint frailty-copula model between tumour progression and death for meta-analysis, Stat Methods Med Res 26(6): 2649-66

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.

Yoshihara K et al. (2010) Gene expression profile for predicting survival in advanced-stage serous ovarian cancer across two independent datasets. PLoS One 12;5(3):e9615

**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 of gene expressions. The CXCL12 gene expression is a predictive biomarker of survival in ovarian cancer (Poppo et al. 2012). It has been known that CXCL12 promotes tumour growth, participates in tumour metastasis, and suppresses tumour immunity (Kryczek et al. 2007). The statistical significance of the CXCL12 expression on survival is first examined by Poppo et al. (2012), and is further confirmed by Ganzfried et al. (2013) based on the meta-analysis of 14 independent studies. A meta-analysis using a joint model further confirmed that the expression of CXCL12 gene is predictive of both cancer relapse and death (Emura et al. 2017; 2018).  
CVR61 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 of gene expressions. The NCOA3 gene encodes a nuclear receptor coactivator, and amplification of the gene occurs in breast and ovarian cancers (Anzick et al. 1997). The overexpression of NCOA3 is associated with tumor size (Spears et al. 2012) and tamoxifen resistance (Osborne et al. 2003), which are involved in the progression. Yoshida et al. (2005) reported that NCOA3 could contribute to ovarian cancer progression by promoting cell migration. In Emura et al. (2018), the overexpression of the gene was highly associated with time-to-relapse (Coefficient=0.194, P-value<0.00001) and time-to-death (Coefficient=0.237, P-value<0.00001). This result is consistent with the function of these reports.  
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 of gene expressions. The PDPN gene encodes the podoplanin protein. It is reported that cancer cells with higher PDPN expression have higher malignant potential due to enhanced platelet aggregation, which promotes alteration of metastasis, cell motility, and epithelial-mesenchymal transition (Shindo et al. 2013). Zhang et al. (2011) reported that over-expression of PDPN in fibroblasts is significantly associated with a poor prognosis in ovarian carcinoma. In Emura et al. (2018), the overexpression of the gene was highly associated with time-to-relapse (Coefficient=0.222, P-value<0.00001) and time-to-death (Coefficient=0.161, P-value<0.0001).

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 of gene expressions. TEAD1 encodes a ubiquitous transcriptional enhancer factor that is a member of the TEA/ATTS domain family. It is reported that the protein level of TEAD1 was associated with poor prognosis in prostate cancer patients (Knight et al. 2008). In Emura et al. (2018), the overexpression of the gene was highly associated with time-to-relapse (Coefficient=0.195, P-value<0.00001) and time-to-death (Coefficient=0.223, P-value<0.00001).

TESK1 a numeric vector

TGM5 a numeric vector

THEMIS2 a numeric vector

TIMP2 a numeric vector of gene expressions. TIMP2 is a member of the TIMP gene family. The proteins encoded by this gene family are natural inhibitors of the matrix metalloproteinases (MMPs). MMPs and their inhibitors (TIMP gene family) play an important regulatory role in the homeostasis of the extracellular matrix (Halon et al. 2012). In addition to inhibitors of MMPs, TIMP2 has additional functions that are associated with cell proliferation and survival (Bourbouliia et al., 2011). In Emura et al. (2018), the overexpression of the gene was highly associated with time-to-relapse (Coefficient=0.235, P-value<0.00001).

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 of gene expressions. YWHAB encodes a protein belonging to the 14-3-3 family of proteins, members of which mediate signal transduction by binding to phosphoserine-containing proteins. It is reported that the protein of YWHAB can regulate cell survival, proliferation, and motility (Tzivion 2006). Actually, it is reported that overexpression of this gene promotes tumor progression and was associated with extrahepatic metastasis and worse survival in hepatocellular carcinoma (Liu et al. 2011). In Emura et al. (2018), the overexpression of the gene was highly associated with time-to-relapse (Coefficient=0.169, P-value<0.0001) and time-to-death (Coefficient=0.263, P-value<0.00001)

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.

## References

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- Shindo K, et al. (2013), Podoplanin expression in cancer-associated fibroblasts enhances tumor progression of invasive ductal carcinoma of the pancreas. *Mol Cancer* 12:168
- Tzivion G, et al. (2006), 14-3-3 proteins as potential oncogenes. *Semin Cancer Biol* 16:203-13
- Yoshida H, et al. (2005), Steroid receptor coactivator-3, a homolog of Taiman that controls cell migration in the *Drosophila* ovary, regulates migration of human ovarian cancer cells. *Mol Cell Endocrinol* 245:77-85
- Zhang Y, et al. (2011), Ovarian cancer-associated fibroblasts contribute to epithelial ovarian carcinoma metastasis by promoting angiogenesis, lymphangiogenesis and tumor cell invasion. *Cancer Lett* 303:47-55

**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 of gene expressions. The CXCL12 gene expression is a predictive biomarker of survival in ovarian cancer (Popple et al. 2012). It has been known that CXCL12 promotes tumour growth, participates in tumour metastasis, and suppresses tumour immunity (Kryczek et al. 2007). The statistical significance of the CXCL12 expression on survival is first examined by Popple et al. (2012), and is further confirmed by Ganzfried et al. (2013) based on the meta-analysis of 14 independent studies. A meta-analysis using a joint model further confirmed that the expression of CXCL12 gene is predictive of both cancer relapse and death (Emura et al. 2017; 2018)  
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  
KDEL1C1 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 of gene expressions. The NCOA3 gene encodes a nuclear receptor coactivator, and amplification of the gene occurs in breast and ovarian cancers (Anzick et al. 1997). The overexpression of NCOA3 is associated with tumor size (Spears et al. 2012) and tamoxifen resistance (Osborne et al. 2003), which are involved in the progression. Yoshida et al. (2005) reported that NCOA3 could contribute to ovarian cancer progression by promoting cell migration. In Emura et al. (2018), the overexpression of the gene was highly associated with time-to-relapse (Coefficient=0.194, P-value<0.00001) and time-to-death (Coefficient=0.237, P-value<0.00001). This result is consistent with the function of these reports.

NCOA6 a numeric vector of gene expressions

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 of gene expressions. The PDPN gene encodes the podoplanin protein. It is reported that cancer cells with higher PDPN expression have higher malignant potential due to enhanced platelet aggregation, which promotes alteration of metastasis, cell motility, and epithelial-mesenchymal transition (Shindo et al. 2013). Zhang et al. (2011) reported that overexpression of PDPN in fibroblasts is significantly associated with a poor prognosis in ovarian carcinoma. In Emura et al. (2018), the overexpression of the gene was highly associated with time-to-relapse (Coefficient=0.222, P-value<0.00001) and time-to-death (Coefficient=0.161, P-value<0.0001).

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 of gene expressions. TEAD1 encodes a ubiquitous transcriptional enhancer factor that is a member of the TEA/ATTS domain family. It is reported that the protein level of TEAD1 was associated with poor prognosis in prostate cancer patients (Knight et al. 2008). In Emura et al. (2018), the overexpression of the gene was highly associated with time-to-relapse (Coefficient=0.195, P-value<0.00001) and time-to-death (Coefficient=0.223, P-value<0.00001).  
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 of gene expressions. YWHAB encodes a protein belonging to the 14-3-3 family of proteins, members of which mediate signal transduction by binding to phosphoserine-containing proteins. It is reported that the protein of YWHAB can regulate cell survival, proliferation, and motility (Tzivion 2006). Actually, it is reported that overexpression of this gene promotes tumor progression and was associated with extrahepatic metastasis and worse survival in hepatocellular carcinoma (Liu et al. 2011). In Emura et al. (2018), the overexpression of the gene was highly associated with time-to-relapse (Coefficient=0.169, P-value<0.0001) and time-to-death (Coefficient=0.263, P-value<0.00001).  
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

## References

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- Shindo K, et al. (2013), Podoplanin expression in cancer-associated fibroblasts enhances tumor progression of invasive ductal carcinoma of the pancreas. *Mol Cancer* 12:168
- Tzivion G, et al. (2006), 14-3-3 proteins as potential oncogenes. *Semin Cancer Biol* 16:203-13
- Yoshida H, et al. (2005), Steroid receptor coactivator-3, a homolog of Taiman that controls cell migration in the Drosophila ovary, regulates migration of human ovarian cancer cells. *Mol Cell Endocrinol* 245:77-85
- Zhang Y, et al. (2011), Ovarian cancer-associated fibroblasts contribute to epithelial ovarian carcinoma metastasis by promoting angiogenesis, lymphangiogenesis and tumor cell invasion. *Cancer Lett* 303:47-55

## 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 (2018), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model, *Stat Methods Med Res* 27(9):2842-58

## 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`. The guide for using this function shall be explained by Emura et al. (2019).

## 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	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
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 (2018), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model, *Stat Methods Med Res* 27(9):2842-58

Emura T, Michimae H, Matsui S (2019-), A clinician's guide for dynamic risk prediction of death using an R package joint.Cox, submitted for publication.

### 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)
```



F.window

*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  $Z1$  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	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
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 (2018), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model, *Stat Methods Med Res* 27(9):2842-58

**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.window.Weibull	<i>Dynamic prediction of death under the joint frailty-copula model (the Weibull baseline hazard functions)</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  $F(t,t+w|X>t, Z1, Z2)$ .

**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 ( $X \leq t$  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)

Sayaka Shinohara, Takeshi Emura

### References

Emura T, Nakatochi M, Matsui S, Michimae H, Rondeau V (2018), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model, *Stat Methods Med Res* 27(9):2842-58

Shinohara S, Lin YH, Michimae H, Emura T (2020), Dynamic lifetime prediction using a Weibull-based bivariate failure time model: a meta-analysis of individual-patient data, *Comm Stat Simul*, DOI:10.1080/03610918.2020.1855449

### Examples

```
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  $Z1$  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	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
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 (2018), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model, *Stat Methods Med Res* 27(9):2842-58

**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)
```

---

F.windows.Weibull	<i>Dynamic prediction of death under the joint frailty-copula model (the Weibull baseline hazard functions)</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 is a vector version of `F.window.Weibull`.

**Usage**

```
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 ( $X \leq t$  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)

Sayaka Shinohara, Takeshi Emura

### References

Emura T, Nakatochi M, Matsui S, Michimae H, Rondeau V (2018), Personalized dynamic prediction of death according to tumour progression and high-dimensional genetic factors: meta-analysis with a joint model, *Stat Methods Med Res* 27(9):2842-58

Shinohara S, Lin YH, Michimae H, Emura T (2020), Dynamic lifetime prediction using a Weibull-based bivariate failure time model: a meta-analysis of individual-patient data, *Comm Stat Simul*, DOI:10.1080/03610918.2020.1855449

### 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)
```

---

I.spline	<i>I-spline basis function</i>
----------	--------------------------------

---

**Description**

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

**Usage**

```
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 constraints  $xi1 \leq time \leq xi3$ . If "time" does not meet the constraints, error messages are shown.

**Value**

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

**Author(s)**

Takeshi Emura

**References**

- Emura T, Chen YH (2018). Analysis of Survival Data with Dependent Censoring, Copula-Based Approaches, JSS Research Series in Statistics, Springer, Singapore.
- Emura T, Matsui S, Rondeau V (2019), Survival Analysis with Correlated Endpoints; Joint Frailty-Copula Models, JSS Research Series in Statistics, Springer
- Emura T, Nakatochi M, Murotani K, Rondeau V (2017), A joint frailty-copula model between tumour progression and death for meta-analysis, Stat Methods Med Res 26(6): 2649-66: Supplementary Material.
- Shih JH, Emura T (2020-), Penalized Cox regression with a five-parameter spline model, Commun Stat-Theor, in revision.

**Examples**

```
I.spline(time=c(1,2,3),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,
  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**

- 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. *Stat Methods Med Res* 24(6):711-729.
- Hu YH, Emura T (2015), Maximum likelihood estimation for a special exponential family under random double-truncation, *Computational Statist* 30(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=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, u.min = 0.001, u.max = 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
u.min	the lower bound of the numerical integration for the frailty term
u.max	the upper bound of the numerical integration for the frailty term
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**

Emura T, Nakatochi M, Murotani K, Rondeau V (2017), A joint frailty-copula model between tumour progression and death for meta-analysis, *Stat Methods Med Res* 26(6): 2649-66

Emura T, Matsui S, Rondeau V (2019), Survival Analysis with Correlated Endpoints; Joint Frailty-Copula Models, *JSS Research Series in Statistics*, Springer

Hu YH, Emura T (2015), Maximum likelihood estimation for a special exponential family under random double-truncation, *Computational Stat* 30 (4): 1199-1229

**Examples**

```
##### Reproduce the results of Emura et al. (2017) #####
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)
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, u.min = 0.001, u.max = 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
Randomize_num	The number of randomizations for the initial p0
u.min	the lower bound of the numerical integration for the frailty term
u.max	the upper bound of the numerical integration for the frailty term
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**

Wu BH, Michimae H, Emura T (2020), Meta-analysis of individual patient data with semi-competing risks under the Weibull joint frailty-copula model. *Comp Stat* 35(4):1525-52

Emura T, Nakatochi M, Murotani K, Rondeau V (2017), A joint frailty-copula model between tumour progression and death for meta-analysis, *Stat Methods Med Res* 26(6): 2649-66

Hu YH, Emura T (2015), Maximum likelihood estimation for a special exponential family under random double-truncation, *Comp Stat* 30 (4): 1199-1229

**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

#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, 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 constraints `xi1<=time<=xi3`. If "time" does not meet the constraints, error messages are shown.

**Value**

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

**Author(s)**

Takeshi Emura

**References**

- Emura T, Chen YH (2018). Analysis of Survival Data with Dependent Censoring, Copula-Based Approaches, JSS Research Series in Statistics, Springer, Singapore.
- Emura T, Matsui S, Rondeau V (2019), Survival Analysis with Correlated Endpoints; Joint Frailty-Copula Models, JSS Research Series in Statistics, Springer
- Emura T, Nakatochi M, Murotani K, Rondeau V (2017), A joint frailty-copula model between tumour progression and death for meta-analysis, Stat Methods Med Res 26(6): 2649-66: Supplementary Material.
- Shih JH, Emura T (2020-), Penalized Cox regression with a five-parameter spline model, Commun Stat-Theor, in revision.

**Examples**

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

splineCox.reg

*Fitting the Cox model for survival data using a penalized spline model***Description**

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

**Usage**

```
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 yeild 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 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**

Cox DR (1972), Regression models and life-tables, JRSS(B) 34(2):187-202.

Emura T, Matsui S, Rondeau V (2019), Survival Analysis with Correlated Endpoints: Joint Frailty-Copula Models, JSS Research Series in Statistics, Springer

Emura T, Nakatochi M, Murotani K, Rondeau V (2017), A joint frailty-copula model between tumour progression and death for meta-analysis, Stat Methods Med Res 26(6): 2649-66: Supplementary Material.

Shih JH, Emura T (2020-), Penalized Cox regression with a five-parameter spline model, Commun Stat-Theor, in revision.

**Examples**

```
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. The form of copulas can be the Clayton (default), Frank, Gumbel, or BB1.

**Usage**

```
Weibull.simu(G,N,scale1,scale2,shape1,shape2,beta1,beta2,
eta,copula="Clayton",theta,d=0,alpha,beta12=0,C.max,tau=FALSE,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
copula	copula function; either "Clayton" (default) or "Gumbel"
theta	copula parameter
d	BB1 copula's departure parameter from the Clayton (d=0 is default)
alpha	parameter related to frailty, e.g., alpha=1
beta12	regression coefficients for copula
C.max	the upper bound for the censoring distribution
tau	if TRUE, conditional Kendall's tau given Z is shown
Z.dist	the distribution of a covariate Z
...	parameters for Z.dist

**Details**

See Wu et al. (2020) for the algorithms for the Clayton copula. The model has been extended by including the covariate effect on a copula (beta12). See the conditional copula model of Emura et al. (2021). The Frank, Gumbel, and BBB1 copulas are also available.

**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
tau	: Kendall's tau

**Author(s)**

Takeshi Emura

**References**

Wu BH, Michimae H, Emura T (2020), Meta-analysis of individual patient data with semi-competing risks under the Weibull joint frailty-copula model. *Comp Stat* 35(4):1525-52

Emura T, Sofeu C, Rondeau V (2021), Conditional copula models for correlated survival endpoints in meta-analyses of randomized controlled trials, in revision

**Examples**

```
Weibull.simu(G=5,N=2,scale1=1,scale2=1,shape1=1,shape2=1,  
            beta1=1,beta2=1,eta=0.5,theta=2,alpha=1,C.max=5)
```

```
Weibull.simu(G=5,N=2,scale1=1,scale2=1,shape1=1,shape2=1,  
            beta1=1,beta2=1,eta=0.5,copula="Gumbel",theta=2,alpha=1,C.max=5)
```

```
Weibull.simu(G=5,N=2,scale1=1,scale2=1,shape1=1,shape2=1,  
            beta1=1,beta2=1,eta=0.5,theta=2,alpha=1,C.max=5,Z.dist=rbinom,size=1,prob=0.5)
```

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