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>, Emura et al. (2018) <doi:10.1177/0962280216688032>,
Emura et al. (2020) <doi:10.1177/0962280219892295>, Shinohara et al. (2020) <doi:10.1080/03610918.2020.1855449>,
Wu et al. (2020) <doi:10.1007/s00180-020-00977-1>, and Emura et al. (2021) <doi:10.1177/09622802211046390>.
See also the book of Emura et al. (2019) <doi:10.1007/978-981-13-3516-7>.
Survival data from ovarian cancer patients are also available.

License GPL-2

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Contents

`joint.Cox-package` *Joint Frailty-Copula Models for Tumour Progression and Death in Meta-Analysis*

Description

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Details

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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: individual patient data meta-analysis of randomized controlled trials, Stat Methods Med Res 30(12):2634-50

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

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

Description

Perform regression analyses under a copula-based joint Cox proportional hazards model between tumour progression and death for meta-analysis, which is proposed in Section 6.2 of Emura et al. (2017) and Section 5.1 of Emura et al. (2020). 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 tims
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 ititial 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 occurences
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 maximizad 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 maximizad 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 (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

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)
```

`condCox.reg` *Penalized Likelihood Estimation under the Joint Cox Models Between Tumour Progression and Death for Meta-Analysis; A Conditional Copula Approach*

Description

An extension of the function "joint.Cox(.)" by regression on a conditional copula. Perform joint 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. (2021). The method extends the joint frailty copula model of Emura et al. (2017) by adding a regression function on a copula parameter. 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 ititial 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 occurences
`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 maximizad 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 maximizad 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, Sofeu C, Rondeau V (2021), Conditional copula models for correlated survival endpoints: individual patient data meta-analysis of randomized controlled trials, Stat Methods Med Res 30(12):2634-50

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

```
data=Weibull.simu(G=10,N=50,scale1=1.5,scale2=1,beta1=-0.2,beta2=-0.2,beta12=0.5,
                    eta=0.5,copula="Clayton",theta=2,alpha=1,
                    C.max=5,Z.dist=rbinom,size=1,prob=0.5)
t.event=data$t.event
event=data$event
t.death=data$t.death
death=data$death
group=data$group
Z1=as.matrix(data$Z)
Z2=Z12=Z1
kappa=seq(1,10000,length=50)

#condCox.reg(t.event=t.event,event=event,t.death=t.death,death=death,
#             Z1=Z1,Z2=Z2,Z12=Z12,group=group,alpha=1,
#             kappa1=kappa,kappa2=kappa,Randomize_num=1,LCV.plot=FALSE,u.max=20)
```

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

Description

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

Usage

```
data("dataOvarian1")
```

Format

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

`t.event` : time-to-recurrence in days

`event` : event indicator (1=recurrence, 0=no recurrence)

`group` : study ID; group=4, 9, 12, or 16

`debulk` : residual tumour size (>=1cm> vs. <1cm)

`ABI3BP` a numeric vector

`ADAM12` a numeric vector

`ADORA3` a numeric vector

`ANKRD27` a numeric vector

`AP2M1` a numeric vector

`AP3S1` a numeric vector

`ARHGAP28` a numeric vector

`ARHGAP29` a numeric vector

`ARTN` a numeric vector

`ASAP3` a numeric vector

`B4GALT5` a numeric vector

`BCAP31` a numeric vector

`BRD4` a numeric vector

`C1QTNF3` a numeric vector

`CALD1` a numeric vector

`CCNE1` a numeric vector

`CCNL1` a numeric vector

CDC42 a numeric vector

CDV3 a numeric vector

CEBPB a numeric vector

CLIC4 a numeric vector

COL10A1 a numeric vector

COL11A1 a numeric vector

COL16A1 a numeric vector

COL3A1 a numeric vector

COL5A1 a numeric vector

COL5A2 a numeric vector

COMP a numeric vector

CRISPLD2 a numeric vector

CRYAB a numeric vector

CSE1L a numeric vector

CTSK a numeric vector

CXCL12 a numeric vector 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).

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 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 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).

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 (Bourboulia 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

Bourboulia D, et al. (2011), Endogenous angiogenesis inhibitor blocks tumor growth via direct and indirect effects on tumor microenvironment. Am J Pathol 179:2589-600

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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

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Knight JF, et al. (2008), TEAD1 and c-Cbl are novel prostate basal cell markers that correlate with poor clinical outcome in prostate cancer. Br J Cancer 99:1849-58

Kryczek I, et al. (2007), Stroma-derived factor (SDF-1/CXCL12) and human tumor pathogenesis. Am J Physiol 292:987-95

Liu TA, et al. (2011), Increased expression of 14-3-3beta promotes tumor progression and predicts extrahepatic metastasis and worse survival in hepatocellular carcinoma. Am J Pathol 179:2698-708

Osborne CK, et al. (2003), Role of the estrogen receptor coactivator AIB1 (SRC-3) and HER-2/neu in tamoxifen resistance in breast cancer. J Natl Cancer Inst 95:353-61

Popple A, et al. (2012), The chemokine, CXCL12, is an independent predictor of poor survival in ovarian cancer. Br J Cancer 106:1306-13

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 (>=1cm> vs. <1cm), and associated 128 gene expressions. The dataset is a subset of the curated ovarian data of Ganzfried et al (2013). We prepared the dataset by using "patientselection.config" in "Curated ovarian data" around October 2016.

Usage

```
data("dataOvarian2")
```

Format

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

`t.death` : time to death in days

`death` : death indicator (1=death, 0=alive)

`group` : study ID; group=4, 9, 12, or 16

`debulk` : residual tumour size (>=1cm> vs. <1cm)

`ANKRD27` a numeric vector

`AP3S1` a numeric vector

`APMAP` a numeric vector

`ARHGAP28` a numeric vector

`ASAP1` a numeric vector

`ASAP3` a numeric vector

`ASB7` a numeric vector

`B4GALT5` a numeric vector

`BYSL` a numeric vector

`C1QTNF3` a numeric vector

`CASP8` a numeric vector

`CCL18` a numeric vector

`CD79A` a numeric vector

`CDK19` a numeric vector

`CLIC4` a numeric vector

`COL11A1` a numeric vector

`COL16A1` a numeric vector

COL3A1 a numeric vector

COL5A1 a numeric vector

COL5A2 a numeric vector

COMP a numeric vector

COX7A2P2 a numeric vector

CPNE1 a numeric vector

CRISPLD2 a numeric vector

CRYAB a numeric vector

CTNNBL1 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.DOB 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 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 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).

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

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

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

Knight JF, et al. (2008), TEAD1 and c-Cbl are novel prostate basal cell markers that correlate with poor clinical outcome in prostate cancer. Br J Cancer 99:1849-58

Kryczek I, et al. (2007), Stroma-derived factor (SDF-1/CXCL12) and human tumor pathogenesis. Am J Physiol 292:987-95

Liu TA, et al. (2011), Increased expression of 14-3-3beta promotes tumor progression and predicts extrahepatic metastasis and worse survival in hepatocellular carcinoma. Am J Pathol 179:2698-708

Osborne CK, et al. (2003), Role of the estrogen receptor coactivator AIB1 (SRC-3) and HER-2/neu in tamoxifen resistance in breast cancer. J Natl Cancer Inst 95:353-61

Popple A, et al. (2012), The chemokine, CXCL12, is an independent predictor of poor survival in ovarian cancer. Br J Cancer 106:1306-13

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` *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<=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<=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<=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<=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` *Dynamic prediction of death under the joint frailty-copula model (the Weibull baseline hazard functions)*

Description

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

Usage

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

Arguments

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

Details

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

Value

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

Author(s)

Sayaka Shinohara, Takeshi Emura

References

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<=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<=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` *Dynamic prediction of death under the joint frailty-copula model (the Weibull baseline hazard functions)*

Description

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

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 (2021). The "time" argument should be a vector satisfying the contraints xi1<=time<=xi3. If "time" does not meet the constraints, error messages are shown.

Value

NULL	A matrix with nrow=length(time) and ncol=5, containing the values of the 5 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 (2021) Penalized Cox regression with a five-parameter spline model, Commun Stat-Theor 50(16):3749-68

Examples

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

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

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 ititial 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 occurences
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 maximizad 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 maximizad 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 ititial 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 occurences
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 maximizad 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 maximizad 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 ititial 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 occurences
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 maximizad 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 maximizad 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 (2021). The "time" argument should be a vector satisfying the contraints xi1<=time<=xi3. If "time" does not meet the constraints, error messages are shown.

Value

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

Author(s)

Takeshi Emura

References

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 (2021) Penalized Cox regression with a five-parameter spline model, Commun Stat-Theor 50(16):3749-68

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 (2021) 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", "cmprskCox.reg", and "condCox.reg". The definition of LCV is given in Section 3.7 of Emura et al. (2019). See also Shih and Emura (2021). 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 (2021) Penalized Cox regression with a five-parameter spline model, Commun Stat-Theor 50(16):3749-68

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

This function generate clustered (grouped) bivariate event times from the joint frailty-copula model with the Weibull baseline hazard functions. Simulating (X_ij,D_ij,C_ij), i=1,2,...,G, and j=1,2,...,N, where G is the number of studies (groups), and N is the number of individuals (patients) within each study. X_ij is time-to-event, D_ij is time-to-death, and C_ij is time-to-censoring. (X_ij, D_ij) and C_ij are independent. Dependence structure on (X_ij, D_ij) is modeled by a copula, which can be the Clayton (default), Frank, Gumbel, or BB1. Covariate effects are specified by the Cox models given a frailty term.

Usage

```
Weibull.simu(G,N,scale1,scale2,shape1,shape2,beta1,beta2,
 eta,copula="Clayton",theta,d=0,alpha,beta12=0,C.max,
 cmprsk=FALSE,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; "Clayton" (default), "Gumbel", "Frank", or "BB1"
theta	copula parameter
d	BB1 copula's departure parameter from the Clayton (d=0 is the default)
alpha	parameter related to frailty, e.g., alpha=1
beta12	regression coefficients for copula
C.max	the upper bound for the censoring distribution
cmprsk	if TRUE, simulated data follow the competing risks setting
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 method was later extended by including covariate effects on a copula (beta12) via the conditional copula model of Emura et al. (2021), The available copulas are the Frank, Gumbel, and BB1 copulas. For the BB1 copula, please see Supplementary Material:Additional simulation studies under the copula misspecification in Emura et al. (2021),

Value

X	: time to event
D	: time to death
C	: time to independent censoring
t.event	: time to event (=min(X,D,C))
event	: event indicator (=I(X<=D,X<=C))

event1	: indicator for Event 1 (=I(X<=D,X<=C))
t.death	: time to death (=min(D,C))
death	: death indicator (=I(D<=C))
event2	: indicator for Event 2 (=I(D<X,D<=C))
group	: study ID (=1,2,...,G)
Z	: covariate
tau	: Conditional Kendall's tau given Z

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, 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: individual patient data meta-analysis of randomized controlled trials, Stat Methods Med Res 30(12):2634-50

Supplementary Material:Additional simulation studies under the copula misspecification in "Emura T, Sofeu C, Rondeau V (2021), Conditional copula models for correlated survival endpoints: individual patient data meta-analysis of randomized controlled trials, Stat Methods Med Res 30(12):2634-50"

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)

## simulated data follow the competing risks setting
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,cmprsk=TRUE)
```

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