Package ‘joint.Cox’

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Type Package

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

Version 3.16

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Author Takeshi Emura

Maintainer Takeshi Emura <takeshiemura@gmail.com>

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

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

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

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

Methodologies were published in


Survival data from ovarian cancer patients are also available.

License GPL-2

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joint.Cox-package ................................................................. 2
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), Shinohara et al. (2020), and Emura et al. (2021). 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:** 3.16
- **Date:** 2022-2-4
- **License:** GPL-2
Author(s)

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

References


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 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 p0

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

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

Details

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

Value

count Count for event occurrences

beta1 Regression coefficient for Z1

beta2 Regression coefficient for Z2

eta Frailty parameter (variance)

theta Copula parameter under the Clayton copula (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


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 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


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 groups are the studies of GSE30161 (58 patients), GSE9891 (278 patients), and TCGA (557 patients).

Source


References


Examples

data(dataOvarian)
study4=dataOvarian[dataOvarian$group==4,] # extract one study
study4
**dataOvarian1**

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

**Description**

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

**Usage**

```r
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
dataOvarian1

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
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<thead>
<tr>
<th>Gene</th>
<th>Description</th>
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<tr>
<td>FGF1</td>
<td>a numeric vector</td>
</tr>
<tr>
<td>FN1</td>
<td>a numeric vector</td>
</tr>
<tr>
<td>FOSL2</td>
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<tr>
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<td>GABRG3</td>
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<tr>
<td>GAS1</td>
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<td>GLIPR1</td>
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</tr>
<tr>
<td>GPATCH1</td>
<td>a numeric vector</td>
</tr>
<tr>
<td>HLTFS</td>
<td>a numeric vector</td>
</tr>
<tr>
<td>HP1BP3</td>
<td>a numeric vector</td>
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<td>HSD17B6</td>
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<tr>
<td>INHBA</td>
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<tr>
<td>ITGB1</td>
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<tr>
<td>JUN</td>
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<td>KPNA6</td>
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<td>L2HGDH</td>
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</tr>
<tr>
<td>MAPRE1</td>
<td>a numeric vector</td>
</tr>
<tr>
<td>MCL1</td>
<td>a numeric vector</td>
</tr>
<tr>
<td>MEOX2</td>
<td>a numeric vector</td>
</tr>
</tbody>
</table>
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
**dataOvarian1**

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)

**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**


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


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


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)],1) )
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
DYNL1B1 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
KDEL.C1 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


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


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


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) )
Description

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

Usage

\[
F.KM(time, widths, t.death, death)
\]

Arguments

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

Details

Prediction probability of death is calculated without covariates.

Value

- **time**: \( t \)
- **widths**: \( w \)
- **F**: \( F(t, t+w) \)

Author(s)

Takeshi Emura

References


Examples

\[
\begin{align*}
time &= 1 \\
widths &= c(0,0.5,1,1.5,2) \\
t.death &= c(0.5,1.5,2.5,3) \\
death &= c(1,1,1,1,1) \\
F.KM(time=time, width=widths, t.death=t.death, death=death)
\end{align*}
\]
**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 \( Z_1 \) and \( Z_2 \). If \( X\leq t \), the prediction probability is \( F(t,t+w|X=x, Z_1, Z_2) \). If \( X>t \), the prediction probability is \( F(t,t+w|X>t, Z_1, Z_2) \). This function is a simpler version of \( F\text{-windows} \). The guide for using this function shall be explained by Emura et al. (2019).

**Usage**

\[
F\text{.prediction}(\text{time}, \text{widths}, \text{X}, \text{Z1}, \text{Z2}, \text{beta1}, \text{beta2}, \text{eta}, \text{theta}, \text{alpha}, \text{g}, \text{h}, \text{xi1}, \text{xi3}, \text{Fplot} = \text{TRUE})
\]

**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 \((X\leq t \text{ or } X>t)\) and covariates \((Z_1 \text{ and } Z_2)\).
Value

- **time**: \( t \)
- **widths**: \( w \)
- **X**: \( X \)
- **F**: \( F(t, t+w|X=x, Z1, Z2) \) or \( F(t, t+w|X>t, Z1, Z2) \)

Author(s)

Takeshi Emura

References


Examples

```r
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)
```

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

```r
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

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

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

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

Value

<table>
<thead>
<tr>
<th>time</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>width</td>
<td>w</td>
</tr>
<tr>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>F_event_at_X</td>
<td>F(t,t+w</td>
</tr>
<tr>
<td>F_noevent</td>
<td>F(t,t+w</td>
</tr>
</tbody>
</table>

Author(s)

Sayaka Shinohara, Takeshi Emura

References


Examples

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

Description

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

**Examples**

```r
w=c(0,0.5,1,1.5,2)
pair(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**

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

**Arguments**

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

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

Value

<table>
<thead>
<tr>
<th>time</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>widths</td>
<td>w</td>
</tr>
<tr>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>F_event_at_X</td>
<td>F(t,t+w</td>
</tr>
<tr>
<td>F_noevent</td>
<td>F(t,t+w</td>
</tr>
</tbody>
</table>

Author(s)

Sayaka Shinohara, Takeshi Emura

References


Examples

```r
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,shape1=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,shape1=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

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

time a vector of time points

xi1 lower bound of time points

xi3 upper bound of time points

Details

The output shows the values of the 5 basis functions at "time", giving a matrix with nrow=length(time) and ncol=5. The five basis functions were originally given in the Supplementary Material of Emura et al. (2017). More details can be found in Emura and Chen (2018), Emura et al. (2019), and Shih and Emura (2021). 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 nrow=length(time) and ncol=5, containing the values of the 5 I-spline basis functions at "time".

Author(s)

Takeshi Emura

References


Examples

I.spline(time=c(1,2,3),xi1=1,xi3=3)
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 initial p0
- `Adj`: Numerical adjustment to prevent overflow; Adj=500 is recommended
- `convergence.par`: If TRUE, the converged estimate, gradient, and Hessian matrix are given (log-transformed)

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

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

Error

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

Warning

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

Author(s)

Takeshi Emura

References


Examples

Reproduce the results of Emura et al. (2015)

```r
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)
```

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

```r
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
              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 de-
scribed 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
              converged estimate, gradient, and Hessian matrix (log-transformed)
convergence.parameters

Error

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

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

**Author(s)**

Takeshi Emura

**References**


**Examples**

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

**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)
**M.spline**

**Error**

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

**Warning**

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

**Author(s)**

Takeshi Emura

**References**


**Examples**

```r
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**

<table>
<thead>
<tr>
<th>M-spline basis function</th>
</tr>
</thead>
</table>

**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


Examples

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

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

**Arguments**

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

**Details**

One can perform Cox-type regression for censored survival data with covariates. The method is essentially the same as 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**


**Examples**

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

---

**Weibull.simu**  
Simulating data from the Weibull joint frailty-copula model

**Description**

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.
Weibull.simu

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))
Weibull.simu

**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**

**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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