Package 'joint.Cox'

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Type Package

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

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

License GPL-2

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`joint.Cox-package` *Penalized Likelihood Estimation and Dynamic Prediction under the Joint Frailty-Copula Models Between Tumour Progression and Death for Meta-Analysis*

Description

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

Details

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Type:	Package
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Date:	2016-10-22
License:	GPL-2

Author(s)

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

References

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

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

`dataOvarian` *Meta-analytic data of ovarian cancer patients combining 4 independent studies.*

Description

Meta-analytic data for studying the CXCL12 gene expression as a predictive biomarker of survival in ovarian cancer. The dataset is a subset of the curated ovarian data of Ganzfried et al (2013). We prepared the dataset by using "patientselection.config" in "Curated ovarian data" around May 2015.

Usage

```
data("data0varian")
```

Format

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

`t.event` : time to event in days

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

`t.death` : time to death in days

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

`group` : study ID; group=4, 8, 11, or 14

`CXCL12` : CXCL12 expression

Details

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

Source

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

References

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

Examples

```
data(data0varian)
study4=data0varian[data0varian$group==4,] # extract one study
study4
```

F.KM *Prediction of death using the Kaplan-Meier estimator*

Description

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

Usage

```
F.KM(time, widths, t.death, death)
```

Arguments

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

Details

Prediction probability of death is calculated without covariates.

Value

time	t
widths	w
F	F(t,t+w)

Author(s)

Takeshi Emura

References

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

Examples

```
time=1
widths=c(0,0.5,1,1.5,2)
t.death=c(0.5,1,1.5,2,2.5,3)
death=c(1,1,1,1,1,1)
F.KM(time=time,width=widths,t.death=t.death,death=death)
```

F.prediction *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.

Usage

```
F.prediction(time, widths, X, Z1, Z2, beta1, beta2, eta, theta, alpha,
 g, h, xi1, xi3, Fplot = TRUE)
```

Arguments

time	prediction time (=t)
widths	length of window (=w)
X	event time occurred
Z1	a vector of covariates
Z2	a vector of covariates
beta1	regression coefficients for progression
beta2	regression coefficients for death
eta	frailty variance
theta	copula parameter
alpha	parameter related to frailty; usually alpha=1
g	parameters related to the baseline hazard for progression
h	parameters related to the baseline hazard for death
xi1	lower bound for time-to-event
xi3	upper bound for time-to-death
Fplot	if FALSE, the plot is not shown

Details

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

Value

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

Author(s)

Takeshi Emura

References

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

Examples

```
w=c(0,0.5,1,1.5,2)
par(mfrow=c(1,2))
F.prediction(time=1,X=0.8,widths=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
         alpha=1,g=rep(1,5),h=rep(1,5),xi1=0,xi3=3,Fplot=FALSE)
F.prediction(time=1,X=1.5,widths=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
         alpha=1,g=rep(1,5),h=rep(1,5),xi1=0,xi3=3,Fplot=FALSE)
```

`F.window` *Prediction of death*

Description

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

Usage

```
F.window(time, width, X, Z1, Z2, beta1, beta2, eta, theta, alpha,
 g, h, xi1, xi3, Fplot = TRUE)
```

Arguments

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

Details

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

Value

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

Author(s)

Takeshi Emura

References

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

Examples

```
w=1
par(mfrow=c(1,2))
F.window(time=1,X=0.2,width=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
         alpha=1,g=rep(1,5),h=rep(1,5),xi1=0,xi3=3)
F.window(time=1,X=0.8,width=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
         alpha=1,g=rep(1,5),h=rep(1,5),xi1=0,xi3=3)
```

F.windows *Prediction of death*

Description

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

Usage

```
F.windows(time, widths, X, Z1, Z2, beta1, beta2, eta, theta, alpha,
 g, h, xi1, xi3, Fplot = TRUE)
```

Arguments

time	prediction time (=t)
widths	length of window (=w)
X	event time occurred < time
Z1	a vector of covariates
Z2	a vector of covariates; usually Z1=Z2
beta1	regression coefficients for progression
beta2	regression coefficients for death
eta	frailty variance
theta	copula parameter
alpha	parameter related to frailty; usually alpha=1
g	parameters related to the baseline hazard for progression
h	parameters related to the baseline hazard for death
xi1	lower bound for time to event
xi3	upper bound for time to death
Fplot	if FALSE, the plot is not shown

Details

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

Value

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

Author(s)

Takeshi Emura

References

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

Examples

```
w=c(0,0.5,1,1.5,2)
par(mfrow=c(1,2))
F.windows(time=1,X=0.2,widths=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
         alpha=1,g=rep(1,5),h=rep(1,5),xi1=0,xi3=3)
F.windows(time=1,X=0.8,widths=w,Z1=1,Z2=1,beta1=1,beta2=1,eta=0.5,theta=8,
         alpha=1,g=rep(1,5),h=rep(1,5),xi1=0,xi3=3)
```

I.spline *I-Spline function*

Description

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

Usage

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

Arguments

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

Details

The "time" argument is a vector satisfying the contraints xi1<=time<=xi3. Otherwise, error messages will be produced.

Value

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

Author(s)

Takeshi Emura

References

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

Examples

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

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

Arguments

`t.event`	a vector object for time-to-tumour progression (TTP)
`event`	a vector object for progression indicator (=1 if progression; =0 if not progression)
`t.death`	a vector object for overall survival (OS), i.e., time-to-death
`death`	a vector object for death indicator(=1 if death; =0 if not death)
`Z1`	a matrix object for covariates associated with TTP; ncol(Z1)=the number of covariates
`Z2`	a matrix object for covariates associated with OS; ncol(Z2)=the number of covariates
`group`	a vector object for a group identification number, like 1,2,3....
`alpha`	A value related to the frailty (e.g., alpha=0 or =1); alpha=1 is default
`kappa_grid`	a vector for candidate smoothing parameters in likelihood cross-validation (LCV)
`LCV_plot`	Plot the LCV curves if "TRUE"
`Randomize_num`	The number of randomizations for the 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
LCV1	Likelihood cross-validation for TTP
LCV2	Likelihood cross-validation for OS
g	M spline coefficients for TTP
h	M spline coefficients for OS
g_var	Variance of M spline coefficients for TTP
h_var	Variance of M spline coefficients for OS
convergence	convergence results for maximizing penalized likelihood
convergence.parameters	converged estimate, gradient, and Hessian matrix (log-transformed)

Author(s)

Takeshi Emura

References

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

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

Examples

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

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

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

ij=0

set.seed(1)
```

```
for(i in 1:G){

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

    ij=ij+1

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

}

Z1=as.matrix(Z1)

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

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

Description

Perform regression analyses under a copula-based joint Cox proportional hazards model between tumour progression and death for meta-analysis, which is proposed by Emura et al. (2015). The method extends the joint frailty model of Rondeau et al. (2015) such that intra-subject dependence is modeled via the Clayton copula. The method is applicable for meta-analysis combining several studies or for cluster survival data.

Usage

```
jointCox.reg(t.event, event, t.death, death, Z1, Z2, group, alpha = 1,
 kappa_grid = c(seq(10, 1e+17, length = 30)), LCV_plot = TRUE, Randomize_num = 10,
 Adj = 500,convergence.par=FALSE)
```

Arguments

t.event	a vector object for time-to-tumour progression (TTP)
event	a vector object for progression indicator (=1 if progression; =0 if not progression)
t.death	a vector object for overall survival (OS), i.e., time-to-death
death	a vector object for death indicator(=1 if death; =0 if not death)
Z1	a matrix object for covariates associated with TTP; ncol(Z1)=the number of covariates
Z2	a matrix object for covariates associated with OS; ncol(Z2)=the number of covariates
group	a vector object for a group identification number, like 1,2,3....
alpha	A value related to the frailty (e.g., alpha=0 or =1); alpha=1 is default
kappa_grid	a vector for candidate smoothing parameters in likelihood cross-validation (LCV)
LCV_plot	Plot the LCV curves if "TRUE"
Randomize_num	The number of randomizations for the 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
theta	Copula parameter under the Clayton copula
tau	Kendall's tau corresponding to the copula parameter
LCV1	Likelihood cross-validation for TTP
LCV2	Likelihood cross-validation for OS
g	M spline coefficients for TTP
h	M spline coefficients for OS
g_var	Variance of M spline coefficients for TTP
h_var	Variance of M spline coefficients for OS
convergence	convergence results for maximizing penalized likelihood
convergence.parameters	converged estimate, gradient, and Hessian matrix (log-transformed)

Author(s)

Takeshi Emura

References

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

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

Examples

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

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

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

ij=0

set.seed(1)

for(i in 1:G){

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

    ij=ij+1

    group[ij]=i
    Z1[ij]=runif(1)
    r1_ij=r1_true*u_i*exp(beta1_true*Z1[ij])
    r2_ij=r2_true*(u_i^alpha_true)*exp(beta2_true*Z1[ij])
    V1=runif(1)
    V2=runif(1)
    X_ij=-1/r1_ij*log(1-V1);W=(1-V1)^(-theta_true)
    D_ij=1/theta_true/r2_ij*log(  1-W+W*(1-V2)^(-theta_true/(theta_true+1))  )
    #C_ij=runif(1,min=0,max=20)
    C_ij=20
    t.event[ij]=min(X_ij,D_ij,C_ij)
    t.death[ij]=min(D_ij,C_ij)
    event[ij]=as.numeric( t.event[ij]==X_ij )
    death[ij]=as.numeric( t.death[ij]==D_ij )
```

```
  }

}

Z1=as.matrix(Z1)

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

`M.spline` *M-Spline function*

Description

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

Usage

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

Arguments

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

Details

The "time" argument is a vector satisfying the contraints xi1<=time<=xi3. Otherwise, error messages will be produced.

Value

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

Author(s)

Takeshi Emura

References

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

Examples

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

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