

Package ‘frailtypack’

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Title Frailty models using maximum penalized likelihood estimation

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Depends R (>= 2.0.0), survival

Description Fit a shared gamma frailty model and Cox proportional hazards model using a Penalized Likelihood on the hazard function. Left truncated, censored data and strata (max=2) are allowed. Clustered and recurrent survival times can be studied (the Andersen-Gill (1982) approach has been implemented for recurrent events). An automatic choice of the smoothing parameter is possible using an approximated cross-validation procedure.

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frailtyPenal

*Fit Shared Gamma Frailty model using penalized likelihood estimation***Description**

Fit a shared gamma frailty model using a Penalized Likelihood on the hazard function. Left truncated and censored data and strata (max=2) are allowed. It allows to obtain a non-parametric smooth hazard of survival function. This approach is different from the partial penalized likelihood approach of Therneau et al.

Usage

```
frailtyPenal(formula, data, Frailty = TRUE, recurrentAG=FALSE,
             cross.validation=FALSE, n.knots, kappal, kappa2, maxit=350)
```

Arguments

formula	a formula object, with the response on the left of a '~' operator, and the terms on the right. The response must be a survival object as returned by the 'Surv' function like in survival package.
data	a data.frame in which to interpret the variables named in the 'formula'.
Frailty	Logical value. Is model with frailties fitted? If so variance of frailty parameter is estimated. If not, Cox proportional hazards model is estimated using Penalized Likelihood on the hazard function
recurrentAG	Logical value. Is Andersen-Gill model fitted? If so indicates that recurrent event times with the counting process approach of Andersen and Gill is used. This formulation can be used for dealing with time-dependent covariates. The default is FALSE.
cross.validation	Logical value. Is cross validation procedure used for estimating smoothing parameter? If so a search of the smoothing parameter using cross validation is done, with kappal as the seed. The cross validation is not implemented for two strata. The cross validation has been implemented for a Cox proportional hazard model, with no covariates. The default is FALSE.
n.knots	integer giving the number of knots to use. Value required. It corresponds to the (n.knots+2) splines functions for the approximation of the hazard or the survival functions. Number of knots must be between 4 and 20.
kappal	positive smoothing parameter. The coefficient kappa of the integral of the squared second derivative of hazard function in the fit (penalized log likelihood). We advise the user to identify several possible tuning parameters, note their defaults and look at the sensitivity of the results to varying them. Value required.
kappa2	positive smoothing parameter for the second stratum, when data are stratified. See kappal.
maxit	maximum number of iterations for the Marquardt algorithm. Default is 350

Details

The estimated parameter are obtained using the robust Marquardt algorithm (Marquardt, 1963) which is a combination between a Newton-Raphson algorithm and a steepest descent algorithm. When frailty parameter is small, numerical problems may arise. To solve this problem, an alternative formula of the penalized log-likelihood is used (see Rondeau, 2003 for further details). Cubic M-splines of order 4 are used for the hazard function, and I-splines (integrated M-splines) are used for the cumulative hazard function.

PARAMETERS

As frailtypack is written in Fortran 77 some parameters had to be hard coded in. The default values of these parameters are

maximum number of observations: 60000
 maximum number of groups: 5000
 maximum number of subjects: 30000

If these parameters are not large enough (an error message will let you know this), you need to reset them in frailtypack.f and recompile. In particular, the statements defining these parameters are

```
PARAMETER (ndatemax = 60000)
PARAMETER (ngmax = 5000)
PARAMETER (nsujetmax = 30000)
```

Value

an object of class "frailtyPenal". Methods defined for 'frailtyPenal' objects are provided for print and plot. The following components are included in a 'frailtyPenal' object.

n	the number of observations used in the fit.
groups	the maximum number of groups used in the fit
n.events	the number of events observed in the fit
logVerComPenal	the complete marginal penalized log-likelihood
theta	variance of frailty parameter
coef	the coefficients of the linear predictor, which multiply the columns of the model matrix.
varH	the variance matrix of theta and of the coefficients.
varHIH	the robust estimation of the variance matrix of theta and of the coefficients.
x1	vector of times where both survival and hazard function are estimated. By default seq(0,max(time),length=99), where time is the vector of survival times.
lam	matrix of hazard estimates at x1 times and confidence bands.
surv	matrix of baseline survival estimates at x1 times and confidence bands.
x2	see x1 value for the second stratum
lam2	the same value as lam for the second stratum
surv2	the same value as surv for the second stratum

References

- D. Marquardt (1963). An algorithm for least-squares estimation of nonlinear parameters. *SIAM Journal of Applied Mathematics*, 431-441.
- V. Rondeau, D Commenges, and P. Joly (2003). Maximum penalized likelihood estimation in a gamma-frailty model. *Lifetime Data Analysis* **9**, 139-153.
- McGilchrist CA and Aisbett CW (1991). Regression with frailty in survival analysis. *Biometrics* **47**, 461-466.

See Also

[print.frailtyPenal](#), [summary.frailtyPenal](#)

Examples

```
data(kidney)
#Shared frailty model
frailtyPenal(Surv(time,status)~sex+age+cluster(id),
             n.knots=12,kappal=1000,data=kidney)

#model without frailties (e.g., Cox proportional hazards
#                               estimated via penalized likelihood)
frailtyPenal(Surv(time,status)~sex+age+cluster(id),
             n.knots=12,kappal=1000,data=kidney,Frailty=FALSE)

# truncated data

# first, we create a hypothetical truncated data
kidney$tt0<-rep(0,nrow(kidney))
kidney$tt0[1:3]<-c(2,9,13)

# then, we fit the model
frailtyPenal(Surv(tt0,time,status)~sex+age+cluster(id),
             n.knots=12,kappal=1000,data=kidney)

#stratified data. Let's use another dataset
data(readmission)
frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id)+strata(sex),
             n.knots=10,kappal=10000,kappa2=10000,data=readmission)

#Andersen-Gill counting-process approach with time-dependent covariate
frailtyPenal(Surv(t.start,t.stop,event)~as.factor(sex)+as.factor(dukes)+
             as.factor(charlson)+cluster(id),data=readmission, Frail=TRUE,
             n.knots=6,kappal=100000,recurrentAG=TRUE)

# with the use of the cross validation approach, to find the smoothing parameter
frailtyPenal(Surv(t.start,t.stop,event)~as.factor(sex)+as.factor(dukes)+
             as.factor(charlson)+cluster(id),data=readmission, Frail=TRUE,
             n.knots=6,kappal=5000,recurrentAG=TRUE,cross.validation=TRUE)
```

plot.frailtyPenal *Plot Method for an object of class 'frailtyPenal'.*

Description

Plots estimated baseline survival and hazard functions from an object of class 'frailtyPenal'. Confidence bands are allowed.

Usage

```
plot.frailtyPenal(x, type.plot = "hazard", conf.bands=TRUE, ...)
```

Arguments

x	Object of class frailtyPenal (output from calling frailtyPenal function).
type.plot	a character string specifying the type of curve. Possible value are "hazard", or "survival". The default is "hazard". Only the first words are required, e.g "haz", "su"
conf.bands	logical value. Determines whether confidence bands will be plotted. The default is to do so.
...	Other graphical parameters

Value

Print a plot of class frailtyPenal

See Also

[print.frailtyPenal](#)

Examples

```
data(readmission)

# Let's compare shared frailty model with Cox proportional hazards model
mod.sha<-frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id),
                     n.knots=10,kappal=10000,data=readmission)
plot(mod.sha,type="surv",conf=FALSE)
mod.cox<-frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id),
                     n.knots=10,kappal=10000,data=readmission,Frailty=FALSE)
lines(mod.cox,type="surv",conf=FALSE,col=2)

# Stratified model
mod<-frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id)+strata(sex),
```

```
      n.knots=10, kappal=10000, kappa2=10000, data=readmission)
plot(mod)

# no confidence bands
plot(mod, conf.bands=FALSE)
```

`print.frailtyPenal` *Print a Short Summary of parameter estimates of a shared gamma frailty model*

Description

Prints a short summary of 'frailtyPenal' object

Usage

```
print.frailtyPenal(x, digits = max(options()$digits - 4, 3), ...)
```

Arguments

<code>x</code>	the result of a call to the <code>frailtyPenal</code> function
<code>digits</code>	number of digits to print
<code>...</code>	other unused arguments

Value

`x`, with the invisible flag set

See Also

[summary.frailtyPenal](#), [frailtyPenal](#)

Examples

```
data(kidney)
mod<-frailtyPenal(Surv(time, status)~sex+age+cluster(id),
  n.knots=8, kappal=10000, data=kidney)
print(mod)
```

readmission *Rehospitalization colorectal cancer*

Description

This contains rehospitalization times after surgery in patients diagnosed with colorectal cancer

Usage

```
data(readmission)
```

Format

This data frame contains the following columns:

id identifier of each subject. Repeated for each recurrence
enum which readmission
t.start start of interval (0 or previous recurrence time)
t.stop recurrence or censoring time
time interoccurrence or censoring time
event censoring status. All event are 1 for each subject excepting last one that it is 0
chemo Did patient receive chemotherapy? 1: No; 2:Yes
sex gender: 1:Males 2:Females
dukes Dukes' tumoral stage: 1:A-B; 2:C 3:D
charlson Comorbidity Charlson's index. Time-dependent covariate. 0: Index 0; 1: Index 1-2; 3: Index >=3

Source

González, JR., Fernandez, E., Moreno, V. et al. Gender differences in hospital readmission among colorectal cancer patients. *Journal of Epidemiology and Community Health*. In press, 2005.

```
summary.frailtyPenal
```

summary of 'frailtyPenal'

Description

This function returns hazard ratios (HR) and its confidence intervals

Usage

```
summary.frailtyPenal(object, level = 0.95, len = 6, d = 2, lab="hr", ...)
```

Arguments

object	output from a call to frailtyPenal.
level	significance level of confidence interval. Default is 95%.
len	the desired number of digits after the decimal point. Default of 6 digits is used.
d	the total field width. Default is 6.
lab	label of printed results.
...	other unused arguments.

Details

This function calls to intervals.frailtyPenal

Value

Prints HR and its confidence intervals. Confidence level is allowed (level argument)

See Also

[intervals.frailtyPenal](#)

Examples

```
data(kidney)
mod<-frailtyPenal(Surv(time,status)~age+sex+cluster(id),
  data=kidney,n.knots=8,kappa1=1000)
summary(mod)

# confidence interval at 99

summary(mod,level=0.99)
```

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