

Package ‘frailtypack’

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Title General Frailty models using a semi_parametrical penalized likelihood estimation or a parametrical estimation

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Description Frailtypack now fits several classes of frailty models using a penalized likelihood estimation on the hazard function but also a parametrical estimation. 1) A shared gamma frailty model and Cox proportional hazard model. 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. 2) Additive frailty models for proportional hazard models with two correlated random effects (intercept random effect with random slope). 3) Nested frailty models for hierarchically clustered data (with 2 levels of clustering) by including two iid gamma random effects. 4) Joint frailty models in the context of joint modelling of recurrent events with terminal event. Prediction values are available. The package includes concordance measures for Cox proportional hazards models and for shared frailty models.

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frailtypack-package	<i>General Frailty models using a semi-parametrical penalized likelihood estimation or a parametrical estimation</i>
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Description

Frailtypack now fits several classes of frailty models using a penalized likelihood estimation on the hazard function but also a parametrical estimation. 1) A shared gamma frailty model and Cox proportional hazard model. 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. 2) Additive frailty models for proportional hazard models with two correlated random effects (intercept random effect with random slope). 3) Nested frailty models for hierarchically clustered data (with 2 levels of clustering) by including two iid gamma

random effects. 4) Joint frailty models in the context of joint modelling of recurrent events with terminal event. Prediction values are available. The package includes concordance measures for Cox proportional hazards models and for shared frailty models.

Details

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Author(s)

Virginie Rondeau, Juan R. Gonzalez, Yassin Mazroui, Audrey Mauguen and Amadou Diakite

References

- V. Rondeau, Y. Mazroui and J. R. Gonzalez (2012). Frailtypack: An R package for the analysis of correlated survival data with frailty models using penalized likelihood estimation or parametrical estimation. *Journal of Statistical Software* **47**, 1-28.
- V. Rondeau and J. R. Gonzalez. Frailtypack: A computer program for the analysis of correlated failure time data using penalized likelihood estimation. *Computer Methods and Programs in Biomedicine*, *80*(2): **154-164**, 2005.
- V. Rondeau, S. Michiels, B. Liqueur, and J. P. Pignon (2008). Investigating trial and treatment heterogeneity in an individual patient data meta-analysis of survival data by mean of the maximum penalized likelihood approach. *Statistics in Medicine*, **27**, 1894-1910.
- V. Rondeau, S. Mathoulin-Pellissier, H. Jacqmin-Gadda, V. Brouste, P. Soubeyran (2007). Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events. *Biostatistics*, **8**,4, 708-721.
- V. Rondeau, D. Commenges, and P. Joly (2003). Maximum penalized likelihood estimation in a gamma-frailty model. *Lifetime Data Analysis* **9**, 139-153.

D. Marquardt (1963). An algorithm for least-squares estimation of nonlinear parameters. *SIAM Journal of Applied Mathematics*, 431-441.

V. Rondeau, L. Filleul, P. Joly (2006). Nested frailty models using maximum penalized likelihood estimation. *Statistics in Medecine*, **25**, 4036-4052.

See Also

[frailtyPenal](#), [additivePenal](#),

Examples

```
## Not run:
### Additive model with 1 covariate ###

data(dataAdditive)
modAdd<-additivePenal(Surv(t1,t2,event)~cluster(group)+var1+slope(var1),
                      correlation=TRUE,data=dataAdditive,n.knots=8,kappa1=10000,
                      hazard="Splines")

### Joint model (recurrent and terminal events) with 2 covariates ###
### on a simulated dataset ###

data(readmission)
modJoint_gap<-frailtyPenal(Surv(time,event)~cluster(id)+sex+as.factor(dukes)
                          +as.factor(charlson)+terminal(death),
                          formula.terminalEvent=~sex+as.factor(dukes)+as.factor(charlson),
                          data=readmission,n.knots=14,kappa1=9550000000,kappa2=141000000000,
                          Frailty=TRUE, joint=TRUE, recurrentAG=FALSE, hazard="Splines")

### Nested model (or hierarchical model) with 2 covariates ###

data(dataNested)
modClu<-frailtyPenal(Surv(t1,t2,event)~cluster(group)+
                    subcluster(subgroup)+cov1+cov2,Frailty=TRUE,data=dataNested,
                    n.knots=8,kappa1=50000,hazard="Splines")

### Semi-parametrical Shared model ###

data(readmission)
frailtyPenal(Surv(t.start,t.stop,event)~as.factor(sex)+as.factor(dukes)+
             as.factor(charlson)+cluster(id),data=readmission, Frailty=TRUE,
             n.knots=6,kappa1=5000, recurrentAG=TRUE, cross.validation=TRUE,
             hazard="Splines")

### Parametrical Shared model ###

data(readmission)
frailtyPenal(Surv(t.start,t.stop,event)~as.factor(sex)+as.factor(dukes)+
             as.factor(charlson)+cluster(id),data=readmission, Frailty=TRUE,
             hazard="Piecewise-per",nb.int1=6)
```

```
## End(Not run)
```

additivePenal	<i>Fit an Additive Frailty model using a semi-parametrical penalized likelihood estimation or a parametrical estimation</i>
---------------	-----------------------------------------------------------------------------------------------------------------------------

Description

Fit an additive frailty model using a semi-parametrical penalized likelihood estimation or a parametrical estimation. The main issue in a meta-analysis study is how to take into account the heterogeneity between trials and between the treatment effects across trials. Additive models are proportional hazard model with two correlated random trial effects that act either multiplicatively on the hazard function or in interaction with the treatment, which allows studying for instance meta-analysis or multicentric datasets. Right-censored data are allowed, but not the left-truncated data. A stratified analysis is possible (maximum number of strata: 2). This approach is different from the shared gamma frailty models.

In an additive model, the hazard function for the j^{th} subject in the i^{th} trial with random trial effect u_i as well as the random treatment-by-trial interaction v_i is:

$$\begin{cases} \lambda_{ij}(t|u_i, v_i) = \lambda_0(t) \exp(u_i + v_i X_{ij1} + \sum_{k=1}^p \beta_k X_{ijk}) \\ \mathbf{cov}(u_i, v_i) = \rho \sigma \tau \\ u_i \sim \mathcal{N}(0, \sigma^2), v_i \sim \mathcal{N}(0, \tau^2) \end{cases}$$

where $\lambda_0(t)$ is the baseline hazard function, β_k the fixed effect associated to the covariate X_{ijk} ($k=1, \dots, p$), β_1 is the treatment effect and X_{ij1} the treatment variable. ρ is the corresponding correlation coefficient for the two frailty terms.

Usage

```
additivePenal(formula, data, correlation = FALSE, recurrentAG =
  FALSE, cross.validation = FALSE, n.knots, kappa1,
  kappa2, maxit = 350, hazard, nb.int1)
```

Arguments

formula	a formula object, with the response on the left of a \sim operator, and the terms on the right. The response must be a survival object as returned by the 'Surv' function like in survival package. The slope() function is required.
data	a 'data.frame' in which to interpret the variables named in the 'formula'.
correlation	Logical value. Are the random effects correlated? If so, the correlation coefficient is estimated. The default is FALSE.
recurrentAG	Always FALSE for additive models (left-truncated data are not allowed).
cross.validation	Logical value. Is cross validation procedure used for estimating smoothing parameter in the penalized likelihood estimation? If so a search of the smoothing parameter using cross validation is done, with kappa1 as the seed. The cross validation is not implemented for two strata. The default is FALSE.

n.knots	integer giving the number of knots to use. Value required in the penalized likelihood estimation. 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. (See Note)
kappa1	positive smoothing parameter in the penalized likelihood estimation. The coefficient kappa of the integral of the squared second derivative of hazard function in the fit. To obtain an initial value for kappa1 (or kappa2), a solution is to fit the corresponding shared frailty model using cross validation (See cross.validation). 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. (See Note)
kappa2	Positive smoothing parameter in the penalized likelihood estimation for the second stratum when data are stratified. See kappa1.
maxit	maximum number of iterations for the Marquardt algorithm. Default is 350
hazard	Type of hazard functions: "Splines" for semi-parametrical hazard functions with the penalized likelihood estimation, "Piecewise-per" for piecewise constant hazards functions using percentile, "Piecewise-equi" for piecewise constant hazard functions using equidistant intervals, "Weibull" for parametrical weibull functions. Default is "Splines".
nb.int1	Number of intervals (between 1 and 20) for the parametrical hazard functions ("Piecewise-per", "Piecewise-equi").

Details

The estimated parameter are obtained by maximizing the penalized log-likelihood or by a simple log-likelihood (in the parametrical case) using the robust Marquardt algorithm (Marquardt,1963). The parameters are initialized with values obtained with Cox proportional hazard model. The iterations are stopped when the difference between two consecutive loglikelihoods was small ($< 10^{-4}$), the estimated coefficients were stable (consecutive values ($< 10^{-4}$), and the gradient small enough ($< 10^{-3}$). To be sure of having a positive function at all stages of the algorithm, the spline coefficients were reparametrized to be positive at each stage. The variance space of the two random effects is reduced, so the variances are positive, and the correlation coefficient values are constrained to be between -1 and 1. The marginal log-likelihood depends on integrations that are approximated by using the Laplace integration technique with a first order approximation. The smoothing parameter can be fixed or estimated by maximizing likelihood cross-validation criterion. The usual squared Wald statistic was modified to a mixture of two χ^2 distribution to get significance test for the variance of the random effects.

INITIAL VALUES

The splines and the regression coefficients are initialized to 0.1. An adjusted Cox model is fitted, it provides new initial values for the splines coefficients and the regression coefficients. The variances of the frailties are initialized to 0.1. Then an additive frailty model with independent frailties is fitted. At last, an additive frailty model with correlated frailties is fitted.

Value

An additive model or more generally an object of class 'additivePenal'. Methods defined for 'additivePenal' objects are provided for print, plot and summary.

b	sequence of the corresponding estimation of the splines coefficients, the random effects variances and the regression coefficients.
call	The code used for fitting the model.
coef	the regression coefficients.
cov	covariance between the two frailty terms ($cov(u_i, v_i)$)
cross.Val	Logical value. Is cross validation procedure used for estimating the smoothing parameters in the penalized likelihood estimation?
correlation	Logical value. Are the random effects correlated?
DoF	degrees of freedom associated with the "kappa".
formula	the formula part of the code used for the model.
groups	the maximum number of groups used in the fit.
kappa	A vector with the smoothing parameters in the penalized likelihood estimation corresponding to each baseline function as components.
lam	matrix of hazard estimates and confidence bands.
lam2	the same value as lam for the second stratum.
loglikPenal	the complete marginal penalized log-likelihood in the semi-parametrical case.
loglik	the marginal log-likelihood in the parametrical case.
n	the number of observations used in the fit.
n.events	the number of events observed in the fit.
n.iter	number of iterations needed to converge.
n.knots	number of knots for estimating the baseline functions.
n.strat	number of stratum.
rho	the corresponding correlation coefficient for the two frailty terms.
sigma2	Variance for the random intercept (the random effect associated to the baseline hazard functions).
surv	matrix of baseline survival estimates and confidence bands.
surv2	the same value as surv for the the second stratum.
tau2	Variance for the random slope (the random effect associated to the treatment effect across trials).
varH	the variance matrix of all parameters before positivity constraint transformation (Sigma2, Tau2, the regression coefficients and the spline coefficients). Then after, the delta method is needed to obtain the estimated variance parameters.
varHIH	the robust estimation of the variance matrix of all parameters (Sigma2, Tau2, the regression coefficients and the spline coefficients).
varSigma2	The variance of the estimates of "sigma2".
varTau2	The variance of the estimates of "tau2".
varcov	Variance of the estimates of "cov".
x1	vector of times where both survival and hazard functions for the recurrent events are estimated. By default $seq(0, \max(\text{time}), \text{length}=99)$, where time is the vector of survival times.

x2	vector of times for the second stratum (see x1 value).
type.of.hazard	Type of hazard functions (0:"Splines", "1:Piecewise", "2:Weibull").
type.of.Piecewise	Type of Piecewise hazard functions (1:"percentile", 0:"equidistant").
nbintervR	Number of intervals (between 1 and 20) for the parametrical hazard functions ("Piecewise-per", "Piecewise-equi").
npar	number of parameters.
nvar	number of explanatory variables.
noVar	indicator of explanatory variable.
LCV	the approximated likelihood cross-validation criterion in the semi-parametrical case (with H minus the converged hessian matrix, and l(.) the full log-likelihood).

$$LCV = \frac{1}{n}(\text{trace}(H_{pl}^{-1}H) - l(.))$$

AIC	the Akaike information Criterion for the parametrical case.
-----	-------------------------------------------------------------

$$AIC = \frac{1}{n}(np - l(.))$$

n.knots.temp	initial value for the number of knots.
shape.weib	shape parameter for the weibull hazard function.
scale.weib	scale parameter for the weibull hazard function.
martingale.res	martingale residuals for each cluster.
frailty.pred	empirical Bayes prediction of the first frailty term.
frailty.pred2	empirical Bayes prediction of the second frailty term.
linear.pred	linear predictor: uses simply "Beta*X + u_i + v_i * X_1" in the additive Frailty models.
global_chisq	a vector with the values of each multivariate Wald test.
dof_chisq	a vector with the degree of freedom for each multivariate Wald test.
global_chisq.test	a binary variable equals to 0 when no multivariate Wald is given, 1 otherwise.
p.global_chisq	a vector with the p_values for each global multivariate Wald test.
names.factor	Names of the "as.factor" variables.
Xlevels	vector of the values that factor might have taken.
contrasts	type of contrast for factor variable.

Note

"Kappa" (kappal and kappa2) and "n.knots" are the arguments that the user have to change if the fitted model does not converge. "n.knots" takes integer values between 4 and 20. But with n.knots=20, the model would take a long time to converge. So, usually, begin first with n.knots=7, and increase it step by step until it converges. "Kappa" only takes positive values. So, choose a value for Kappa (for instance 10000), and if it does not converge, multiply or devide this value by 10 or 5 until it converges.

References

V. Rondeau, Y. Mazroui and J. R. Gonzalez (2012). Frailtypack: An R package for the analysis of correlated survival data with frailty models using penalized likelihood estimation or parametrical estimation. *Journal of Statistical Software* **47**, 1-28.

V. Rondeau, S. Michiels, B. Liqueur, and J. P. Pignon (2008).

Investigating trial and treatment heterogeneity in an individual patient data meta-analysis of survival data by mean of the maximum penalized likelihood approach. *Statistics in Medicine*, **27**, 1894-1910.

See Also

[print.additivePenal](#), [plot.additivePenal](#), [summary.additivePenal](#), [cluster](#), [slope](#), [strata](#), [Surv](#)

Examples

```
### Additive model with 1 covariate ###

## Not run:
data(dataAdditive)
modAdd<-additivePenal(Surv(t1,t2,event)~cluster(group)+var1+slope(var1),
                      correlation=TRUE,data=dataAdditive,n.knots=8,kappa1=10000)

# It takes around 4 minutes to converge. Var1 is boolean as a treatment variable. #

print(modAdd)
summary(modAdd)
plot(modAdd)

## End(Not run)
```

Cmeasures

Concordance measures in shared frailty and Cox models

Description

Compute concordance probability estimation for Cox models or shared frailty models in case of grouped data (Mauguen et al. 2012). Concordance is given at different levels of comparison, taking into account the cluster membership: between-groups, within-groups and an overall measure, being a weighted average of the previous two. Can also compute the c-index (Harrell et al. 1996) at these three levels. It is possible to exclude tied pairs from concordance estimation (otherwise, account for 1/2).

Usage

```
Cmeasures(fitc, ties = 1, marginal = 0, cindex = 0, Nboot = 0)
```

Arguments

fitc	A frailtyPenal object , for a shared frailty model. If the fit is a Cox model (Frailty=FALSE), no clustering membership is taken into account and only marginal concordance probability estimation is provided. Only an overall measure is given, where all patients are compared two by two. If a counting process formulation is used to performed the fit, with 't.start' and 't.stop', the gap-times (t.stop-t.start) are used in the concordance estimation.
ties	Indicates if the tied pairs on prediction value must be included (ties=1) or excluded (ties=0) from the concordance estimation. Default is ties=1. When included, tied pairs account for 1/2 in the concordance.
marginal	Indicates if the concordance based on marginal predictions must be given (marginal=1) in addition to conditional ones or not (marginal=0). Marginal predictions do not include the frailty estimation in the linear predictor computation: uses "'Beta'X" instead of "Beta'X + log z_i". Default is marginal=0.
cindex	Indicates if the c-index (Harrell et al. 1996) must be computed (cindex=1) in addition to the concordance probability estimation or not (cindex=0). C-index is also given at the three comparison levels (between, within and overall). Default is cindex=0.
Nboot	Number of bootstrap resamplings to compute standard-error of the concordances measures, as well as a percentile 95% confidence interval. Nboot=0 indicates no bootstrap procedure. Maximum admitted is 1000. Minimum admitted is 2. Default is 0. Resampling is done at the group level. If Cox model is used, resampling is done at individual level.

Value

call	The shared frailty model evaluated.
Frailty	Logical value. Was model with frailties fitted.
frequencies	Numbers of patients, events and groups used to fit the model.
Nboot	Number of bootstrap resamplings required.
Nbproblem	Number of bootstrap resamplings in which the model did not converge. Those are excluded when computing the standard-error and the percentile 95% confidence interval.
ties	A binary, indicating if the tied pairs on prediction were used to compute the concordance.
CPEcond	Values of the Concordance Probability Estimations (conditional) and the number of pairs used. If Nboot>0, give SE, the standard-error of the parameters evaluated by bootstrap, IC.low and IC.high, the lower and upper bounds of the percentile confidence interval evaluated by bootstrap (2.5% and 97.5% percentiles).
marginal	A binary, indicating if the marginal values were computed.
CPEmarg	Values of the Concordance Probability Estimations (marginal) and the number of pairs used, if marginal=1. If Nboot>0, give SE, the standard-error of the parameters evaluated by bootstrap, IC.low and IC.high, the lower and upper bounds of the percentile confidence interval evaluated by bootstrap (2.5% and 97.5% percentiles).

cindex	A binary, indicating if the c-indexes were computed.
cindexcond	Values of the C-index (conditional) and the number of pairs used. If Nboot>0, give SE, the standard-error of the parameters evaluated by bootstrap, IC.low and IC.high, the lower and upper bounds of the percentile confidence interval evaluated by bootstrap (2.5% and 97.5% percentiles).
cindexmarg	Values of the C-index (marginal) and the number of pairs used, if marginal=1. If Nboot>0, give SE, the standard-error of the parameters evaluated by bootstrap, IC.low and IC.high, the lower and upper bounds of the percentile confidence interval evaluated by bootstrap (2.5% and 97.5% percentiles).

References

Concordance measures in shared frailty models: application to multicenter data in cancer prognosis. Mauguen A, Collette S, Pignon JP, Collette L and Rondeau V. (submitted 2012).

Harrell FE et al. Tutorial in biostatistics: multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Statistics in Medicine* 1996; 15:361-387.

Gonen M, Heller G. Concordance probability and discriminatory power in proportional hazards regression. *Biometrika* 2005; 92:965-970.

See Also

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

Examples

```
## load data
data(readmission)

## a frailtypenal fit
fit.frailtypenal <- frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id)+
as.factor(charlson)+as.factor(chemo),data=readmission,Frailty=TRUE,
cross.validation=FALSE,n.knots=10,kappa1=1,hazard="Splines")

## a Cmeasures call
fit.Cmeasures <- Cmeasures(fit.frailtypenal)
fit.Cmeasures.noties <- Cmeasures(fit.frailtypenal, ties=0)

## a short summary
fit.Cmeasures
fit.Cmeasures.noties
```

Description

This contains simulated samples of 100 clusters with 100 subjects in each cluster, like a gathering of clinical trials databases. Two correlated centered gaussian random effects are generated with the same variance fixed at 0.3 and the covariance at -0.2. The regression coefficient β is fixed at -0.11. The percentage of right-censored data is around 30 percent which are generated from a uniform distribution on [1,150]. The baseline hazard function is considered as a simple Weibull.

Usage

```
data(dataAdditive)
```

Format

This data frame contains the following columns:

- group** identification variable
- t1** start of interval (=0, because left-truncated data are not allowed)
- t2** end of interval (death or censoring time)
- event** censoring status (0:alive, 1:death, as acensoring indicator)
- var1** dichotomous covariate (=0 or 1,as a treatment variable)
- var2** dichotomous covariate (=0 or 1,as a treatment variable)

Source

V. Rondeau, S. Michiels, B.Liquet, and J.P. Pignon (2008). Investigating trial and treatment heterogeneity in an individual patient data meta-analysis of survival data by mean of the maximum penalized likelihood approach. *Statistics in Medecine*, **27**, 1894-1910.

See Also

[additivePenal](#)

dataJoint

Simulated data with recurrent events and informative terminal event

Description

This contains simulated data with recurrent events and time until last follow-up that is related to the recurrent process. This data set is useful to illustrate how to fit a joint model where the censoring mechanism is informative about the recurring process. This database combines different observations for each subject (sample size=500, number of lines=1053 so in average more than two recurrent events per subject). The right-censored case is treated only and the calendar timescale representation is used with delayed entry. Exponential death times and recurring times are generated using a gamma frailty model. The common frailty term is iid $\Gamma(2, 2)$ and α , the coefficient associated with the frailty term in the death time hazard function, is set at 0. The right-censoring variable is set at 0.8 and the two covariates are generated from a Bernoulli distribution (p=0.5).

Usage

```
data(dataJoint)
```

Format

This data frame contains the following columns:

id identification variable (ex: subject number)
time.entry start of interval (0 or previous recurrence time)
time.end end of interval (recurrence or censoring time)
status censoring status for recurrent events (1:event, 0: censored or dead)
status.terminal censoring status for terminal events (0:alive, 1:death)
var1 dichotomous covariate (0,1)
var2 dichotomous covariate (0,1)

Source

V. Rondeau, S. Mathoulin-Pellissier, H. Jacqmin-Gadda, V. Brouste, P. Soubeyran (2007). Joint frailty models for recurring events and death using maximum penalized likelihood estimation:application on cancer events. *Biostatistics*, **8**,4, 708-721.

See Also

[frailtyPenal for Joint frailty models](#)

dataNested

Simulated data with two levels of grouping

Description

This contains a simulated sample of 400 observations which allow establishing 20 clusters with 4 subgroups and 5 subjects in each subgroup, in order to obtain two levels of grouping. This data set is useful to illustrate how to fit a nested model. Two independent gamma frailty parameters with a variance fixed at 0.1 for the cluster effect and at 0.5 for the subcluster effect were generated. Independent survival times were generated from a simple Weibull baseline risk function. The percentage of censoring data was around 30 per cent. The right-censoring variables were generated from a uniform distribution on [1,36] and a left-truncating variable was generated with a uniform distribution on [0,10]. Observations were included only if the survival time is greater than the truncated time.

Usage

```
data(dataNested)
```

Format

This data frame contains the following columns:

group group identification variable
subgroup subgroup identification variable
t1 start of interval (0 or truncated time)
t2 end of interval (death or censoring time)
event censoring status (0:alive, 1:death)
cov1 dichotomous covariate (0,1)
cov2 dichotomous covariate (0,1)

Source

V. Rondeau, L. Filleul, P. Joly (2006). Nested frailty models using maximum penalized likelihood estimation. *Statistics in Medicine*, **25**, 4036-4052.

See Also

[frailtyPenal for Nested frailty models](#)

ForInternalUse

For internal use only ...

Description

For internal use only ...

frailtyPenal for Joint frailty models

Fit Joint Frailty model for recurrent and terminal events using semi-parametrical penalized likelihood estimation or a parametrical estimation

Description

Fit a joint frailty model for recurrent and terminal events using a penalized likelihood estimation on the hazard function or a parametrical estimation. Left-truncated and right-censored data are allowed. Stratified analysis is not possible. Joint frailty models allow studying, jointly, survival processes of recurrent and terminal events, by considering the terminal event as an informative censoring. A common frailty term (ω_i) for the two rates will take into account the heterogeneity in the data, associated with unobserved covariates. The frailty term acts differently for the two rates (ω_i for the recurrent rate and ω_i^α for death rate). The covariates could be different for the recurrent rate and death rate.

The joint model for the hazard function for recurrent event $r_i(\cdot)$ and death $\lambda_i(\cdot)$ is :

$$\begin{cases} r_i(t|\omega_i) = \omega_i r_0(t) \exp(\beta_1' \mathbf{Z}_i(t)) \\ \lambda_i(t|\omega_i) = \omega_i^\alpha \lambda_0(t) \exp(\beta_2' \mathbf{Z}_i(t)) \end{cases}$$

where $r_0(t)$ (resp. $\lambda_0(t)$) is the recurrent (resp. terminal) event baseline hazard function, β_1 (resp. β_2) the regression coefficient vector, $\mathbf{Z}_i(t)$ the covariate vector. And where $\omega_i \sim \Gamma(\frac{1}{\theta}, \frac{1}{\theta})$ is iid.

Usage

```
frailtyPenal(formula, formula.terminalEvent, data, Frailty = FALSE,
             joint = FALSE, recurrentAG = FALSE, cross.validation =
             FALSE, n.knots, kappa1, kappa2, maxit = 350, hazard, nb.int1, nb.int2)
```

Arguments

formula	a formula object, with the response on the left of a \sim operator, and the terms on the right. The response must be a survival object as returned by the 'Surv' function like in survival package.
formula.terminalEvent	a formula object, only requires terms on the right to indicate which variables are modelling the terminal event.
data	a 'data.frame' in which to interpret the variables named in the 'formula' and 'formula.terminalEvent'.
Frailty	Logical value. Is model with frailties fitted? If so, variance of frailty parameter is estimated. The default is FALSE
joint	Logical value. Is joint model fitted? If so, 'formula.terminalEvent' is required. The default is FALSE
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 in the penalized likelihood estimation? If so a search of the smoothing parameter using cross validation is done, with kappa1 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 in the penalized likelihood estimation. 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. (See Note)

kappa1	positive smoothing parameter in the penalized likelihood estimation. The coefficient kappa of the integral of the squared second derivative of hazard function in the fit (penalized log likelihood). To obtain a good value for kappa1, a solution is to fit the corresponding shared frailty model using cross validation (See cross.validation) with the event indicator as the event of interest. 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.(See Note)
kappa2	positive smoothing parameter in the penalized likelihood estimation for the terminal event rate. To obtain a good value for kappa2, a solution is to fit the corresponding Cox model using cross-validation (See cross.validation) with the death indicator as the event of interest. See kappa1. Stratification is not allowed here.
maxit	maximum number of iterations for the Marquardt algorithm. Default is 350
hazard	Type of hazard functions: "Splines" for semi-parametrical hazard functions with the penalized likelihood estimation, "Piecewise-per" for piecewise constant hazard function using percentile, "Piecewise-equi" for piecewise constant hazard function using equidistant intervals, "Weibull" for parametrical weibull function. Default is "Splines".
nb.int1	Number of intervals (between 1 and 20) for the recurrent parametrical hazard functions ("Piecewise-per", "Piecewise-equi").
nb.int2	Number of intervals (between 1 and 20) for the death parametrical hazard functions ("Piecewise-per", "Piecewise-equi").

Details

The estimated parameter are obtained by maximizing the semi-parametrical penalized loglikelihood estimation or a parametrical estimation 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. The inverse of the hessian matrix is the variance estimator and to deal with the positivity constraint of the variance component, a squared transformation is used and the Standard errors are computed by the Δ -method (Knight & Xekalaki, 2000). The smooth parameter can be chosen by maximizing a likelihood cross validation criterion (Joly and other, 1998). The integrations in the full log likelihood were evaluated using Gaussian quadrature. Laguerre polynomials with 20 points were used to treat the integrations on $[0, \infty[$.

INITIAL VALUES

The splines and the regression coefficients are initialized to 0.5. The program fits an adjusted Cox model to have new initial values for the regression and the splines coefficients. The variance of the frailty term θ and the coefficient α associated in the death hazard function are initialized to 1. Then, it fits a joint frailty model.

Value

Parameters estimates of a joint frailty model, more generally a 'frailtyPenal' object. Methods defined for 'frailtyPenal' objects are provided for print, plot and summary. The following components are included in a 'frailtyPenal' object for Joint frailty models.

b	sequence of the corresponding estimation of the splines coefficients, the random effects variances, the power of the frailties and the regression coefficients.
alpha	the coefficient associated with the frailty parameter in the terminal hazard function.
call	The code used for fitting the model.
coef	the regression coefficients.
cross.Val	Logical value. Is cross validation procedure used for estimating the smoothing parameters in the penalized likelihood estimation?
formula	the formula part of the code used for the model.
groups	the maximum number of groups used in the fit.
kappa	A vector with the smoothing parameters in the penalized likelihood estimation corresponding to each baseline function as components.
lam	matrix of hazard estimates and confidence bands.
lam2	the same value as lam for the second stratum.
loglikPenal	the complete marginal penalized log-likelihood in the semi-parametrical case.
loglik	the marginal log-likelihood in the parametrical case.
n	the number of observations used in the fit.
n.events	the number of events observed in the fit.
n.knots	number of knots for estimating the baseline functions.
n.iter	number of iterations needed to converge.
surv	matrix of baseline survival estimates and confidence bands.
surv2	the same value as surv for the the second stratum.
theta	variance of the frailty parameter ($Var(\omega_i)$)
varH	the variance matrix of all parameters before positivity constraint transformation (theta, the regression coefficients and the spline coefficients). Thenafter, the delta method is needed to obtain the estimated variance parameters.
varHIH	the robust estimation of the variance matrix of all parameters (theta, the regression coefficients and the spline coefficients).
x1	vector of times where both survival and hazard functions for the recurrent events are estimated. By default seq(0,max(time),length=99), where time is the vector of survival times.
x2	vector of times for the second stratum (see x1 value).
type.of.hazard	Type of hazard functions (0:"Splines", "1:Piecewise", "2:Weibull").
type.of.Piecewise	Type of Piecewise hazard functions (1:"percentile", 0:"equidistant").
nbintervR	Number of intervals (between 1 and 20) for the recurrent parametrical hazard functions ("Piecewise-per", "Piecewise-equi").
nbintervDC	Number of intervals (between 1 and 20) for the death parametrical hazard functions ("Piecewise-per", "Piecewise-equi").
npar	number of parameters.

nvar	A vector with the number of covariates of each type of hazard function as components.
nvarRec	number of recurrent explanatory variables.
nvarEnd	number of death explanatory variables.
noVar1	indicator of recurrent explanatory variables.
noVar2	indicator of death explanatory variables.
LCV	the approximated likelihood cross-validation criterion in the semi parametrical case (with H minus the converged hessian matrix, and l(.) the full log-likelihood.

$$LCV = \frac{1}{n}(\text{trace}(H_{pl}^{-1}H) - l(.))$$

AIC	the Akaike information Criterion for the parametrical case.
-----	-------------------------------------------------------------

$$AIC = \frac{1}{n}(np - l(.))$$

n.knots.temp	initial value for the number of knots.
shape.weib	shape parameters for the weibull hazard function.
scale.weib	scale parameters for the weibull hazard function.
martingale.res	martingale residuals for each cluster (recurrent).
martingaledeath.res	martingale residuals for each cluster (death).
frailty.pred	empirical Bayes prediction of the frailty term.
frailty.var	variance of the empirical Bayes prediction of the frailty term.
linear.pred	linear predictor: uses "Beta'X + log w_i" in the joint Frailty models.
lineardeath.pred	linear predictor for the terminal part from the joint model: "Beta'X + alpha.log w_i".
global_chisq	a vector with the values of each multivariate Wald test.
dof_chisq	a vector with the degree of freedom for each multivariate Wald test.
global_chisq.test	a binary variable equals to 0 when no multivariate Wald is given, 1 otherwise.
p.global_chisq	a vector with the p_values for each global multivariate Wald test.
names.factor	Names of the "as.factor" variables.
Xlevels	vector of the values that factor might have taken for the recurrent part.
contrasts	type of contrast for factor variable for the recurrent part.
Xlevels2	vector of the values that factor might have taken for the death part.
contrasts2	type of contrast for factor variable for the death part.

Note

"Kappa" (kappa1 and kappa2) and "n.knots" are the arguments that the user have to change if the fitted model does not converge. "n.knots" takes integer values between 4 and 20. But with n.knots=20, the model would take a long time to converge. So, usually, begin first with n.knots=7, and increase it step by step until it converges. "Kappa" only takes positive values. So, choose a value for Kappa (for instance 10000), and if it does not converge, multiply or divide this value by 10 or 5 until it converges.

References

- V. Rondeau, Y. Mazroui and J. R. Gonzalez (2012). Frailtypack: An R package for the analysis of correlated survival data with frailty models using penalized likelihood estimation or parametrical estimation. *Journal of Statistical Software* **47**, 1-28.
- V. Rondeau, S. Mathoulin-Pellissier, H. Jacqmin-Gadda, V. Brouste, P. Soubeyran (2007). Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events. *Biostatistics*, **8**,4, 708-721.
- V. Rondeau, D Commenges, and P. Joly (2003). Maximum penalized likelihood estimation in a gamma-frailty model. *Lifetime Data Analysis* **9**, 139-153.
- D. Marquardt (1963). An algorithm for least-squares estimation of nonlinear parameters. *SIAM Journal of Applied Mathematics*, 431-441.

See Also

[summary.jointPenal](#), [print.jointPenal](#), [plot.jointPenal](#), [readmission](#), [terminal](#), [cluster](#)

Examples

```
### Joint model (recurrent and terminal events) with 2 covariates ###
### on a simulated dataset ###

## Not run:

data(readmission)

## Gap-time ##

modJoint_gap<-frailtyPenal(Surv(time,event)~cluster(id)+sex+as.factor(dukes)
+as.factor(charlson)+terminal(death),
formula.terminalEvent=~sex+as.factor(dukes)+as.factor(charlson),
data=readmission,n.knots=14,kappa1=9550000000,kappa2=141000000000,
Frailty=TRUE,joint=TRUE,recurrentAG=FALSE)

## Calendar time ##

modJoint_calendar<-frailtyPenal(Surv(t.start,t.stop,event)~cluster(id)+sex
+as.factor(dukes)+as.factor(charlson)+terminal(death),
formula.terminalEvent=~sex+as.factor(dukes)+as.factor(charlson),
data=readmission,n.knots=10,kappa1=9550000000,kappa2=141000000000,
```

```

    Frailty=TRUE,joint=TRUE,recurrentAG=TRUE)

print(modJoint_gap)
summary(modJoint_gap)
plot(modJoint_gap)

print(modJoint_calendar)
summary(modJoint_calendar)
plot(modJoint_calendar)

## End(Not run)

# A model takes around 1 minute to converge #

```

frailtyPenal for Nested frailty models

Fit a Nested Frailty model using a semi-parametrical penalized likelihood estimation or a parametrical estimation

Description

Fit a nested frailty model using a Penalized Likelihood on the hazard function or using a parametrical estimation. Nested frailty models allow survival studies for hierarchically clustered data by including two iid gamma random effects. Left truncated and censored data are allowed. Stratification analysis is allowed(maximum of strata=2).

The hazard function conditional on the two frailties v_i and w_{ij} for the k^{th} individual of the j^{th} subgroup of the i^{th} group is :

$$\begin{cases} \lambda_{ijk}(t|v_i, w_{ij}) = v_i w_{ij} \lambda_0(t) \exp(\beta' \mathbf{X}_{ijk}) \\ v_i \sim \Gamma\left(\frac{1}{\alpha}, \frac{1}{\alpha}\right) \text{ i.i.d. } \mathbf{E}(v_i) = 1 \quad \mathbf{Var}(v_i) = \alpha \\ w_{ij} \sim \Gamma\left(\frac{1}{\eta}, \frac{1}{\eta}\right) \text{ i.i.d. } \mathbf{E}(w_{ij}) = 1 \quad \mathbf{Var}(w_{ij}) = \eta \end{cases}$$

where $\lambda_0(t)$ is the baseline hazard function, \mathbf{X}_{ijk} denotes the covariate vector and β the corresponding vector of regression parameters.

Usage

```

frailtyPenal(formula, formula.terminalEvent, data, Frailty = FALSE,
             joint = FALSE, recurrentAG = FALSE, cross.validation =
             FALSE, n.knots, kappa1, kappa2, maxit = 350, hazard, nb.int1, nb.int2)

```

Arguments

formula	a formula object, with the response on the left of a \sim operator, and the terms on the right. The response must be a survival object as returned by the 'Surv' function like in survival package. The subcluster() function is required.
formula.terminalEvent	Not required.
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 hazardfunction. The default is FALSE.
joint	Not required
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 in the penalized likelihood estimation? If so a search of the smoothing parameter using cross validation is done, with kappa1 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 in the penalized likelihood estimation. 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. (See Note)
kappa1	positive smoothing parameter. The coefficient kappa of the integral of the squared second derivative of hazard function in the fit (penalized log likelihood). To obtain an initial value for kappa1 (or kappa2), a solution is to fit the corresponding shared frailty model using cross validation (See cross.validation). 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.(See Note)
kappa2	positive smoothing parameter in the penalized likelihood estimation for the second stratum, when data are stratified. See kappa1.
maxit	maximum number of iterations for the Marquardt algorithm. Default is 350
hazard	Type of hazard functions: "Splines" for semi-parametrical hazard function with the penalized likelihood estimation, "Piecewise-per" for piecewise constant hazard function using percentile, "Piecewise-equi" for piecewise constant hazard function using equidistant intervals, "Weibull" for parametrical weibull functions. Default is "Splines".
nb.int1	Number of intervals (between 1 and 20) for the parametrical hazard functions ("Piecewise-per", "Piecewise-equi")

Details

The estimated parameter are obtained by maximizing the penalized loglikelihood 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. The smoothing parameter can be fixed a priori or chosen by maximizing a likelihood cross validation criterion. The iterations are stopped when the difference between two consecutive loglikelihoods was small ($< 10^{-4}$), the estimated coefficients were stable (consecutive values ($< 10^{-4}$), and the gradient small enough ($< 10^{-3}$). To be sure of having a positive function at all stages of the algorithm, the spline coefficients were reparametrizes to be positive at each stage. The variance space of the two random effects is reduced, so the variances are positive, and the correlation coefficient values are constrained to be between -1 and 1. The integrations in the full log likelihood werre evaluated using Gaussian quadrature. Laguerre polynomials with 10 points were used to treat the integrations on $[0, \infty[$.

INITIAL VALUES

The splines and the regression coefficients are initialized to 0.1. The program fits an adjusted Cox model to provide new initial values for the regression and the splines coefficients. The variances of the frailties are initialized to 0.1. Then, a shared frailty model with covariates with only subgroup frailty is fitted to give a new initial value for the variance of the subgroup frailty term. Then, a shared frailty model with covariates and only group frailty terms is fitted to give a new initial value for the variance of the group frailties. In a last step, a nested frailty model is fitted.

Value

a Nested frailty model or more generally an object of class 'frailtyPenal'. Methods defined for 'frailtyPenal' objects are provided for print, plot and summary. The following components are included in a 'frailtyPenal' object for nested frailty models.

b	sequence of the corresponding estimation of the splines coefficients, the random effects variances and the regression coefficients.
alpha	variance of the cluster effect ($\mathbf{Var}(v_i)$)
call	The code used for fitting the model.
coef	the regression coefficients.
cross.Val	Logical value. Is cross validation procedure used for estimating the smoothing parameters?
DoF	degrees of freedom.
eta	variance of the subcluster effect ($\mathbf{Var}(w_{ij})$)
formula	the formula part of the code used for the model.
groups	the maximum number of groups used in the fit.
subgroups	the maximum number of subgroups used in the fit.
kappa	A vector with the smoothing parameters corresponding to each baseline function as components.

lam	matrix of hazard estimates and confidence bands.
lam2	the same value as lam for the second stratum.
loglikPenal	the complete marginal penalized log-likelihood in the semi-parametrical case.
loglik	the marginal log-likelihood in the parametrical case.
n	the number of observations used in the fit.
n.events	the number of events observed in the fit.
n.iter	number of iterations needed to converge.
n.knots	number of knots for estimating the baseline functions.
n.strat	A vector with the number of covariates of each type of hazard function as components.
surv	matrix of baseline survival estimates and confidence bands.
surv2	the same value as surv for the second stratum.
varH	the variance matrix of all parameters before positivity constraint transformation (alpha, eta, the regression coefficients and the spline coefficients). Thenafter, the delta method is needed to obtain the estimated variance parameters.
varHIH	the robust estimation of the variance matrix of all parameters (alpha, eta, the regression coefficients and the spline coefficients).
x1	vector of times where both survival and hazard functions are estimated. By default seq(0,max(time),length=99), where time is the vector of survival times.
x2	vector of times for the second stratum (see x1 value).
type.of.hazard	Type of hazard functions (0:"Splines", "1:Piecewise", "2:Weibull").
type.of.Piecewise	Type of Piecewise hazard functions (1:"percentile", 0:"equidistant").
nbintervR	Number of intervals (between 1 and 20) for the parametrical hazard functions ("Piecewise-per", "Piecewise-equi").
npar	number of parameters.
nvar	number of explanatory variables.
noVar	indicator of explanatory variables.
LCV	the approximated likelihood cross-validation criterion in the semi-parametrical case (with H minus the converged hessian matrix, and l(.) the full log-likelihood).
	$LCV = \frac{1}{n}(\text{trace}(H_{pl}^{-1}H) - l(.))$
AIC	the Akaike information Criterion for the parametrical case.
	$AIC = \frac{1}{n}(np - l(.))$
n.knots.temp	initial value for the number of knots.
shape.weib	shape parameters for the weibull hazard function.
scale.weib	scale parameters for the weibull hazard function.
martingale.res	martingale residuals for each cluster.

frailty.pred.group	empirical Bayes prediction of the frailty term by group.
frailty.pred.subgroup	empirical Bayes prediction of the frailty term by subgroup.
linear.pred	linear predictor: uses "Beta'X + log v_i.w_ij" in the Nested Frailty models.
subgbyg	subgroup by group.
global_chisq	a vector with the values of each multivariate Wald test.
dof_chisq	a vector with the degree of freedom for each multivariate Wald test.
global_chisq.test	a binary variable equals to 0 when no multivariate Wald is given, 1 otherwise.
p.global_chisq	a vector with the p_values for each global multivariate Wald test.
names.factor	Names of the "as.factor" variables.
Xlevels	vector of the values that factor might have taken.
contrasts	type of contrast for factor variable.

Note

"Kappa" (kappa1 and kappa2) and "n.knots" are the arguments that the user have to change if the fitted model does not converge. "n.knots" takes integer values between 4 and 20. But with n.knots=20, the model would take a long time to converge. So, usually, begin first with n.knots=7, and increase it step by step until it converges. "Kappa" only takes positive values. So, choose a value for Kappa (for instance 10000), and if it does not converge, multiply or divide this value by 10 or 5 until it converges.

References

- V. Rondeau, Y. Mazroui and J. R. Gonzalez (2012). Frailtypack: An R package for the analysis of correlated survival data with frailty models using penalized likelihood estimation or parametrical estimation. *Journal of Statistical Software* **47**, 1-28.
- V. Rondeau, L. Filleul, P. Joly (2006). Nested frailty models using maximum penalized likelihood estimation. *Statistics in Medecine*, **25**, 4036-4052.
- V. Rondeau, D Commenges, and P. Joly (2003). Maximum penalized likelihood estimation in a gamma-frailty model. *Lifetime Data Analysis* **9**, 139-153.
- D. Marquardt (1963). An algorithm for least-squares estimation of nonlinear parameters. *SIAM Journal of Applied Mathematics*, 431-441.

See Also

[print.nestedPenal](#), [summary.nestedPenal](#), [plot.nestedPenal](#), [cluster](#), [subcluster](#), [strata](#)

Examples

```
### Nested model (or hierarchical model) with 2 covariates ###
## Not run:
```

```

data(dataNested)
modClu<-frailtyPenal(Surv(t1,t2,event)~cluster(group)+
subcluster(subgroup)+cov1+cov2,Frailty=TRUE,data=dataNested,
n.knots=8,kappa1=50000)

# It takes around 24 minutes to converge (depends on the processor)#

print(modClu)
summary(modClu)
plot(modClu)

modClu.str<-frailtyPenal(Surv(t1,t2,event)~cluster(group)+
subcluster(subgroup)+cov1+strata(cov2),Frailty=TRUE,data=dataNested,
n.knots=8,kappa1=20000,kappa2=20000)

# It takes around 8 minutes to converge (depends on the processor)#

print(modClu.str)
summary(modClu.str)
plot(modClu.str)

## End(Not run)

```

frailtyPenal for Shared frailty models

Fit a Shared Gamma Frailty model using a semi-parametrical penalized likelihood estimation or parametrical estimation

Description

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

The hazard function, conditionnal on the frailty term z_i , of a shared frailty model for the j^{th} subject in the i^{th} group:

$$\lambda_{ij}(t|z_i) = \lambda_0(t)z_i \exp(\beta' \mathbf{X}_{ij})$$

$$z_i \sim \Gamma\left(\frac{1}{\theta}, \frac{1}{\theta}\right) \quad \mathbf{E}(z_i) = 1 \quad \mathbf{Var}(z_i) = \theta$$

where $\lambda_0(t)$ is the baseline hazard function, β the vector of the regression coefficient associated to the covariate vector \mathbf{X}_{ij} for the j^{th} individual in the i^{th} group.

Usage

```
frailtyPenal(formula, formula.terminalEvent, data, Frailty = FALSE,
             joint = FALSE, recurrentAG = FALSE, cross.validation =
             FALSE, n.knots, kappa1, kappa2, maxit = 350, hazard,
             nb.int1, nb.int2)
```

Arguments

formula	a formula object, with the response on the left of a \sim operator, and the terms on the right. The response must be a survival object as returned by the 'Surv' function like in survival package.
formula.terminalEvent	Not required.
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 hazard model is estimated using Penalized Likelihood on the hazard function. The default is TRUE
joint	Not required.
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 in the penalized likelihood estimation? If so a search of the smoothing parameter using cross validation is done, with kappa1 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 in the penalized likelihood estimation. 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. (See Note)
kappa1	positive smoothing parameter in the penalized likelihood estimation. The coefficient kappa of the integral of the squared second derivative of hazard function in the fit (penalized log likelihood). To obtain an initial value for kappa1 (or kappa2), a solution is to fit the corresponding shared frailty model using cross validation (See cross.validation). 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.(See Note)
kappa2	positive smoothing parameter in the penalized likelihood estimation for the second stratum, when data are stratified. See kappa1.
maxit	maximum number of iterations for the Marquardt algorithm. Default is 350

hazard	Type of hazard functions: "Splines" for semi-parametrical hazard functions with the penalized likelihood estimation, "Piecewise-per" for piecewise constant hazard function using percentile, "Piecewise-equi" for piecewise constant hazard function using equidistant intervals, "Weibull" for parametrical weibull functions. Default is "Splines".
nb.int1	Number of intervals (between 1 and 20) for the parametrical hazard functions ("Piecewise-per", "Piecewise-equi").
nb.int2	Argument used only for the Joint frailty model.

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.

INITIAL VALUES

The splines and the regression coefficients are initialized to 0.1. The program fits, firstly, an adjusted Cox model to give new initial values for the splines and the regression coefficients. The variance of the frailty term θ is initialized to 0.1. Then, a shared frailty model is fitted.

Value

The following components are included in a 'frailtyPenal' object for shared frailty models.

b	sequence of the corresponding estimation of the coefficients for the hazard functions (parametrical or semi-parametrical), the random effects variances and the regression coefficients.
call	The code used for the model.
coef	the regression coefficients.
cross.Val	Logical value. Is cross validation procedure used for estimating the smoothing parameters in the penalized likelihood estimation?
DoF	Degrees of freedom associated with the "kappa".
formula	the formula part of the code used for the model.
groups	the maximum number of groups used in the fit.
kappa	A vector with the smoothing parameters in the penalized likelihood estimation corresponding to each baseline function as components.
lam	matrix of hazard estimates and confidence bands.
lam2	the same value as lam for the second stratum.
loglikPenal	the complete marginal penalized log-likelihood in the semi-parametrical case.
loglik	the marginal log-likelihood in the parametrical case.
n	the number of observations used in the fit.
n.events	the number of events observed in the fit.

n.iter	number of iterations needed to converge.
n.knots	number of knots for estimating the baseline functions in the penalized likelihood estimation.
n.strat	number of stratum.
surv	matrix of baseline survival estimates and confidence bands.
surv2	the same value as surv for the second stratum.
theta	variance of frailty parameter.
varH	the variance matrix of all parameters before positivity constraint transformation (theta, the regression coefficients and the spline coefficients). Thenafter, the delta method is needed to obtain the estimated variance parameters.
varHIH	the robust estimation of the variance matrix of all parameters (theta, the regression coefficients and the spline 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.
x2	vector of times for the second stratum (see x1 value).
type.of.hazard	Type of hazard functions (0:"Splines", "1:Piecewise", "2:Weibull").
type.of.Piecewise	Type of Piecewise hazard functions (1:"percentile", 0:"equidistant").
nbintervR	Number of intervals (between 1 and 20) for the parametrical hazard functions ("Piecewise-per", "Piecewise-equi").
npar	number of parameters.
nvar	number of explanatory variables.
noVar	indicator of explanatory variables.
LCV	the approximated likelihood cross-validation criterion in the semi-parametrical case (with H minus the converged hessian matrix, and l(.) the full log-likelihood). $LCV = \frac{1}{n}(\text{trace}(H_{pl}^{-1}H) - l(.))$
AIC	the Akaike information Criterion for the parametrical case. $AIC = \frac{1}{n}(np - l(.))$
n.knots.temp	initial value for the number of knots.
shape.weib	shape parameter for the weibull hazard function.
scale.weib	scale parameter for the weibull hazard function.
martingale.res	martingale residuals for each cluster.
martingaleCox	martingale residuals for observation in the Cox model.
Frailty	Logical value. Was model with frailties fitted.
frailty.pred	empirical Bayes prediction of the frailty term (ie, using conditional posterior distributions).
frailty.var	variance of the empirical Bayes prediction of the frailty term.

frailty.sd	standard error of the frailty empirical Bayes prediction.
linear.pred	linear predictor: uses simply "Beta'X" in the cox proportional hazard model or "Beta'X + log z_i" in the shared Frailty models.
global_chisq	a vector with the values of each multivariate Wald test.
dof_chisq	a vector with the degree of freedom for each multivariate Wald test.
global_chisq.test	a binary variable equals to 0 when no multivariate Wald is given, 1 otherwise.
p.global_chisq	a vector with the p_values for each global multivariate Wald test.
names.factor	Names of the "as.factor" variables.
Xlevels	vector of the values that factor might have taken.
contrasts	type of contrast for factor variable.

Note

"Kappa" (kappa1 and kappa2) and "n.knots" are the arguments that the user have to change if the fitted model does not converge. "n.knots" takes integer values between 4 and 20. But with n.knots=20, the model would take a long time to converge. So, usually, begin first with n.knots=7, and increase it step by step until it converges. "Kappa" only takes positive values. So, choose a value for Kappa (for instance 10000), and if it does not converge, multiply or divide this value by 10 or 5 until it converges.

References

- V. Rondeau, Y. Mazroui and J. R. Gonzalez (2012). Frailtypack: An R package for the analysis of correlated survival data with frailty models using penalized likelihood estimation or parametrical estimation. *Journal of Statistical Software* **47**, 1-28.
- 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.
- D. Marquardt (1963). An algorithm for least-squares estimation of nonlinear parameters. *SIAM Journal of Applied Mathematics*, 431-441.

See Also

[print.frailtyPenal](#), [summary.frailtyPenal](#), [plot.frailtyPenal](#), [cluster](#), [strata](#), [Surv](#)

Examples

```
### Shared model ###

data(kidney)
frailtyPenal(Surv(time,status)~ cluster(id)+sex+age,
             n.knots=12,kappa1=10000,data=kidney,Frailty=TRUE)

### COX proportional hazard model (SHARED without frailties) ###
```

```

### estimated with penalized likelihood ###

frailtyPenal(Surv(time,status)~sex+age+cluster(id),
             n.knots=12,kappa1=10000,data=kidney,Frailty=FALSE)

### Shared model with truncated data ###

# Here is created 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,kappa1=10000,data=kidney,Frailty=TRUE)

### Shared model - stratified analysis ###

data(readmission)
frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id)+strata(sex),
             n.knots=10,kappa1=10000,kappa2=10000,data=readmission,
             Frailty=TRUE)

### Shared model - recurrentAG=TRUE ###

frailtyPenal(Surv(t.start,t.stop,event)~as.factor(sex)+as.factor(dukes)+
             as.factor(charlson)+cluster(id),data=readmission,Frailty=TRUE,
             n.knots=6,kappa1=100000,recurrentAG=TRUE)

### Shared model - cross.validation=TRUE ###

## Not run:
frailtyPenal(Surv(t.start,t.stop,event)~as.factor(sex)+as.factor(dukes)+
             as.factor(charlson)+cluster(id),data=readmission, Frailty=TRUE,
             n.knots=6,kappa1=5000,recurrentAG=TRUE,cross.validation=TRUE)

## End(Not run)

```

hazard

Hazard function.

Description

Let t be a continuous variable, we determine the value of the hazard function to t after run fit.

Usage

```
hazard(t, ObjFrailty)
```

Arguments

t time for hazard function.
ObjFrailty an object from the frailtypack fit.

Value

return the value of hazard function in t.

Author(s)

V. Rondeau

Examples

```
### a fit Shared
data(readmission)
fit.shared <- frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id)+strata(sex),
                          n.knots=10,kappa1=10000,kappa2=10000,data=readmission,
                          Frailty=TRUE)

### calling survival
hazard(20,fit.shared)
```

plot.additivePenal *Plot Method for an Additive frailty model.*

Description

Plots estimated baseline survival and hazard functions of an additive frailty model, more generally of a class ‘additivePenal’ object. Confidence bands are allowed.

Usage

```
## S3 method for class 'additivePenal'
plot(x, ...)
```

Arguments

x An fitted additive frailty model (output from calling additivePenal
... Other graphical parameters like those in [plot.frailtyPenal](#)

Value

Print a plot of HR and survival function of a class additivePenal object

See Also

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

Examples

```
## Not run:

data(dataAdditive)
modAdd<-additivePenal(Surv(t1,t2,event)~cluster(group)+var1+slope(var1),
  correlation=TRUE,data=dataAdditive,n.knots=8,kappa1=862,
  hazard="Splines")

# It takes around 4 minutes to converge. 'var1' is boolean as a treatment variable. #

plot(modAdd)

## End(Not run)
```

plot.frailtyPenal *Plot Method for a Shared frailty model.*

Description

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

Usage

```
## S3 method for class 'frailtyPenal'
plot(x, type.plot = "hazard", conf.bands=TRUE, pos.legend="topright",
  cex.legend=0.7, main, ...)
```

Arguments

x	A shared frailty model, more generally a frailtyPenal class object (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.
pos.legend	The location of the legend can be specified by setting this argument to a single keyword from the list "bottomright", "bottom", "bottomleft", "left", "topleft", "top", "topright", "right" and "center". The default is "topright"
cex.legend	character expansion factor <i>relative</i> to current 'par("cex")'. Default is 0.7
main	title of plot
...	Other graphical parameters

Value

Print a plot of a shared frailty model.

See Also

[print.frailtyPenal](#), [summary.frailtyPenal](#), [frailtyPenal](#) for Shared frailty models

Examples

```
data(readmission)

# /*** Shared frailty model ***/

modSha<-frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id),
                    n.knots=10,kappa1=10000,data=readmission,Frailty=TRUE,
                    hazard="Splines")

plot(modSha,type="surv",conf=FALSE)

# /*** Cox proportional hazard model using Penalized likelihood ***/

modCox<-frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id),
                    n.knots=10,kappa1=10000,data=readmission,Frailty=FALSE,
                    hazard="Splines")
plot(modCox)

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

plot.jointPenal

Plot Method for a Joint frailty model.

Description

Plots estimated baseline survival and hazard functions of a joint frailty model (output from an object of class 'frailtyPenal' for joint frailty models) for each type of event (terminal or recurrent). Confidence bands are allowed.

Usage

```
## S3 method for class 'jointPenal'
plot(x, event = "both", type.plot = "hazard", conf.bands = FALSE,
     pos.legend="topright", cex.legend=0.7, ylim, main, ...)
```

Arguments

x	A joint model, or more generally an object of class frailtyPenal for Joint frailty model (output from calling frailtyPenal function).
event	a character string specifying the type of curve. Possible value are "terminal", "recurrent", or "both". The default is "both".
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.
pos.legend	The location of the legend can be specified by setting this argument to a single keyword from the list "bottomright", "bottom", "bottomleft", "left", "topleft", "top", "topright", "right" and "center". The default is "topright"
cex.legend	character expansion factor <i>relative</i> to current 'par("cex")'. Default is 0.7
ylim	y-axis limits
main	plot title
...	Other graphical parameters

Value

Print a plot of the baseline survival or hazard functions for each type of event or both with the confidence bands or not (conf.bands argument)

See Also

[print.jointPenal](#), [summary.jointPenal](#), [frailtyPenal](#) for Joint frailty models

Examples

```
## Not run:

data(readmission)

## Gap-time ##
modJoint_gap<-frailtyPenal(Surv(time,event)~cluster(id)+sex+as.factor(dukes)
+as.factor(charlson)+terminal(death),
```

```

formula.terminalEvent=~sex+as.factor(dukes)+as.factor(charlson),
data=readmission,n.knots=14,kappa1=9550000000,
kappa2=1410000000000,Frailty=TRUE, joint=TRUE, recurrentAG=FALSE
,hazard="Splines")

# It takes around 1 minute to converge. #

plot(modJoint_gap,type.plot="haz",event="recurrent",conf.bands=TRUE)
plot(modJoint_gap,type.plot="haz",event="terminal",conf.bands=TRUE)
plot(modJoint_gap,type.plot="haz",event="both",conf.bands=TRUE))
plot(modJoint_gap,type.plot="su",event="recurrent",conf.bands=TRUE))
plot(modJoint_gap,type.plot="su",event="terminal",conf.bands=TRUE))
plot(modJoint_gap, event="terminal",type.plot="su",conf.bands=TRUE))
plot(modJoint_gap,type.plot="su","terminal",conf.bands=TRUE))

## End(Not run)

```

plot.nestedPenal *Plot Method for a Nested frailty model.*

Description

Plots estimated baseline survival and hazard functions (output from an object of class ‘frailtyPenal’ for nested frailty models). Confidence bands are allowed.

Usage

```

## S3 method for class 'nestedPenal'
plot(x, ...)

```

Arguments

x A nested model, more generally an object of class frailtyPenal for Nested frailty models (output from calling frailtyPenal function).

... Other graphical parameters like those in [plot.frailtyPenal](#)

Value

Print a plot of the baseline survival or hazard functions with the confidence bands or not (conf.bands argument)

See Also

[print.nestedPenal](#), [summary.nestedPenal](#), [frailtyPenal](#) for Nested frailty models

Examples

```
## Not run:

data(dataNested)
modNested<-frailtyPenal(Surv(t1,t2,event)~cluster(group)+
  subcluster(subgroup)+cov1+cov2,data=dataNested,
  n.knots=8,kappa1=50000,hazard="Splines")

# It takes around 90 minutes to converge (depends on the processor) #

plot(modNested,conf.bands=FALSE)

## End(Not run)
```

```
print.additivePenal Print a Short Summary of parameter estimates of an additive frailty model
```

Description

Prints a short summary of the parameter estimates of an additive frailty model or more generally of an 'additivePenal' object

Usage

```
## S3 method for class 'additivePenal'
print(x, digits = max(options()$digits - 4, 6), ...)
```

Arguments

x	the result of a call to the additivePenal function
digits	number of digits to print
...	other unused arguments

Value

n	the number of observations used in the fit.
n.groups	the maximum number of groups used in the fit
n.events	the number of events observed in the fit

coef	the coefficients of the linear predictor, which multiply the columns of the model matrix.
SE(H)	the standard error deduced from the variance matrix of theta and of the coefficients.
SE(HIH)	the standard error deduced from the robust estimation of the variance matrix of theta and of the coefficients.
z	quantile of the χ^2 mixture distribution
p	p-value
Variance for the random intercept	Variance for the random effect associated to the baseline risk function
Variance for the random slope	Variance for the random effect associated to the treatment effects across trials

See Also

[summary.additivePenal](#), [additivePenal](#), [plot.additivePenal](#)

Examples

```
# /*** Additive frailty model with 1 covariate ***/
## Not run:

data(dataAdditive)
modAdd<-additivePenal(Surv(t1,t2,event)~cluster(group)+var1+slope(var1),
                      correlation=TRUE,data=dataAdditive,n.knots=8,kappa1=862,
                      hazard="Splines")

# It takes around 4 minutes to converge. 'var1' is boolean as a treatment variable. #

print(modAdd)

## End(Not run)
```

```
print.Cmeasures      Print a short summary of results of Cmeasure function.
```

Description

Print a short summary of results of the concordance measure estimated by the Cmeasure function.

Usage

```
## S3 method for class 'Cmeasures'
print(x, digits = 3, ...)
```

Arguments

<code>x</code>	a Cmeasures object.
<code>digits</code>	Number of digits to print
<code>...</code>	Other unused arguments

Value

<code>call</code>	The shared frailty model evaluated.
<code>frequencies</code>	Numbers of patients, events and groups used to fit the model.
<code>Nboot</code>	Number of bootstrap resamplings required.
<code>Nbproblem</code>	Number of bootstrap resamplings in which the model did not converge. Those are excluded when computing the standard-error and the percentile 95% confidence interval.
<code>ties</code>	A binary, indicating if the pairs tied on prediction were used to compute the concordance.
<code>CPEcond</code>	Values of the Concordance Probability Estimations (conditional) and the number of pairs used. If <code>Nboot>0</code> , give SE, the standard-error of the parameters evaluated by bootstrap, <code>IC.low</code> and <code>IC.high</code> , the lower and upper bounds of the percentile confidence interval evaluated by bootstrap (2.5% and 97.5% percentiles).
<code>marginal</code>	A binary, indicating if the marginal values were computed.
<code>CPEmarg</code>	Values of the Concordance Probability Estimations (marginal) and the number of pairs used, if <code>marginal=1</code> . If <code>Nboot>0</code> , give SE, the standard-error of the parameters evaluated by bootstrap, <code>IC.low</code> and <code>IC.high</code> , the lower and upper bounds of the percentile confidence interval evaluated by bootstrap (2.5% and 97.5% percentiles).
<code>cindex</code>	A binary, indicating if the c-indexes were computed.
<code>cindexcond</code>	Values of the C-index (conditional) and the number of pairs used. If <code>Nboot>0</code> , give SE, the standard-error of the parameters evaluated by bootstrap, <code>IC.low</code> and <code>IC.high</code> , the lower and upper bounds of the percentile confidence interval evaluated by bootstrap (2.5% and 97.5% percentiles).
<code>cindexmarg</code>	Values of the C-index (marginal) and the number of pairs used, if <code>marginal=1</code> . If <code>Nboot>0</code> , give SE, the standard-error of the parameters evaluated by bootstrap, <code>IC.low</code> and <code>IC.high</code> , the lower and upper bounds of the percentile confidence interval evaluated by bootstrap (2.5% and 97.5% percentiles).

Examples

```
## load data
data(readmission)

## a frailtypenal fit
fit.frailtypenal <-frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id)+
as.factor(charlson)+strata(sex)+as.factor(chemo),data=readmission,Frailty=TRUE,
cross.validation=FALSE,n.knots=10,kappa1=1,kappa2=1,hazard="Splines")
```

```
## a Cmeasures call
fit.Cmeasures <- Cmeasures(fit.frailtypenal)

## a short summary
print(fit.Cmeasures)
```

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

Description

Prints a short summary of parameter estimates of a 'frailtyPenal' object

Usage

```
## S3 method for class 'frailtyPenal'
print(x, digits = max(options()$digits - 4, 6), ...)
```

Arguments

x	the result of a call to the frailtyPenal function.
digits	number of digits to print.
...	other unusued arguments.

Value

n	the number of observations used in the fit.
n.groups	the maximum number of groups used in the fit
n.events	the number of events observed in the fit
theta	variance of frailty parameter
coef	the coefficients of the linear predictor, which multiply the columns of the model matrix.
SE(H)	the standard error of the estimates deduced from the variance matrix of theta and of the coefficients.
SE(HIH)	the standard error of the estimates deduced from the robust estimation of the variance matrix of theta and of the coefficients.
p	p-value

See Also

[summary.frailtyPenal](#), [frailtyPenal](#) for Shared frailty models, [plot.frailtyPenal](#)

Examples

```

data(readmission)

# /** Shared frailty model */
modSha<-frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id),
                    n.knots=10,kappa1=10000,data=readmission,Frailty=TRUE,
                    hazard="Splines")

print(modSha,type="surv",conf=FALSE)

# /** Cox proportional hazard model using Penalized likelihood */
modCox<-frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id),
                    n.knots=10,kappa1=10000,data=readmission,Frailty=FALSE,
                    hazard="Splines")
print(modCox)

```

```
print.jointPenal      Print a Short Summary of parameter estimates of a joint frailty model
```

Description

Prints a short summary of parameter estimates of a joint frailty model, or more generally an object of class 'frailtyPenal' for joint frailty models.

Usage

```
## S3 method for class 'jointPenal'
print(x, digits = max(options()$digits - 4, 6), ...)
```

Arguments

x	the result of a call to the jointPenal function
digits	number of digits to print
...	other unused arguments

Value

Print, separately for each type of event (recurrent and terminal), the parameter estimates of the survival or hazard functions.

n	the number of observations used in the fit.
---	---------------------------------------------

n.groups	the maximum number of groups used in the fit
n.events	the number of events observed in the fit
theta	variance of the common frailty term
alpha	the coefficient associated with the frailty parameter terminal event hazard function
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.
SE(H)	the standard error of the estimates deduced from the variance matrix of theta and of the coefficients.
SE(HIH)	the standard error of the estimates deduced from the robust estimation of the variance matrix of theta and of the coefficients.
p	p-value

See Also

[summary.jointPenal](#), [frailtyPenal](#) for Joint frailty models, [plot.jointPenal](#)

Examples

```
# /*** Joint frailty model ***/

## Not run:

  data(readmission)

## Gap-time ##
modJoint_gap<-frailtyPenal(Surv(time,event)~cluster(id)+sex+as.factor(dukes)
  +as.factor(charlson)+terminal(death),
  formula.terminalEvent=~sex+as.factor(dukes)+as.factor(charlson),
  data=readmission,n.knots=14,kappa1=9550000000,kappa2=1410000000000,
  Frailty=TRUE,joint=TRUE,recurrentAG=FALSE,hazard="Splines")

# It takes around 1 minute to converge.#

print(modJoint_gap)

## End(Not run)
```

print.nestedPenal	<i>Print a Short Summary of parameter estimates of a nested frailty model</i>
-------------------	-------------------------------------------------------------------------------

Description

Prints a short summary of parameter estimates of a nested frailty model

Usage

```
## S3 method for class 'nestedPenal'
print(x, digits = max(options()$digits - 4, 6), ...)
```

Arguments

x	the result of a call to the frailtyPenal function for nested frailty models
digits	number of digits to print
...	other unused arguments

Value

n	the number of observations used in the fit.
n.groups	the maximum number of groups used in the fit
n.events	the number of events observed in the fit
eta	variance of the subcluster effect ($Var(w_{ij})$)
)	
theta	variance of the cluster effect ($Var(v_i)$)
)	
coef	the coefficients of the linear predictor, which multiply the columns of the model matrix.
SE(H)	the standard error of the estimates deduced from the variance matrix of theta and of the coefficients.
SE(HIH)	the standard error of the estimates deduced from the robust estimation of the variance matrix of theta and of the coefficients.
p	p-value

See Also

[summary.nestedPenal](#), [frailtyPenal](#) for Nested frailty models, [plot.nestedPenal](#),

Examples

```
# /*** Nested frailty model ***/

## Not run:

data(dataNested)

modNested<-frailtyPenal(Surv(t1, t2, event)~cluster(group)+subcluster(subgroup)+
  cov1+cov2, Frailty=TRUE, data=dataNested, n.knots=8, kappa1=50000,
  kappa2=50000, hazard="Splines")

# It takes around 24 minutes to converge (depends on the processor) #

print(modNested)

## End(Not run)
```

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 rehospitalization 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
death death indicator. 1:dead and 0:alive

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.

slope

Identify variable associated with the random slope

Description

This is a special function used in the context of survival additive models. It identifies the variable which is in interaction with the random slope (v_i). Generally, this variable is the treatment variable. Using `interaction()` in a formula implies that an additive frailty model is fitted.

Usage

`slope(x)`

Arguments

`x` A factor, a character or a numerical variable

Value

`x` The variable in interaction with the random slope

Note

It is necessary to specify which variable is in interaction with the random slope, even if only one explanatory variable is included in the model.

See Also

[additivePenal](#), [print.additivePenal](#), [plot.additivePenal](#), [summary.additivePenal](#)

Examples

```
## Not run:

library(frailtypack)
data(dataAdditive)

# Additive with one covariate #

modAdd1cov<-additivePenal(Surv(t1,t2,event)~cluster(group)+var1+slope(var1)
, data=dataAdditive, n.knots=8, kappa1=10000, hazard="Splines")
```

```

# Additive with two covariates #

set.seed(1234)
dataAdditive$var2<-rbinom(nrow(dataAdditive),1,0.5)

modAdd2cov<-additivePenal(Surv(t1,t2,event)~cluster(group)+var1+var2+
  slope(var1),data=dataAdditive,n.knots=8,kappa1=10000,hazard="Splines")

# Additive with 2 covariates and stratification #

dataAdditive$var2<-rbinom(nrow(dataAdditive),1,0.5)

modAddstrat<-additivePenal(Surv(t1,t2,event)~cluster(group)+strata(var2)+var1+
  slope(var1),data=dataAdditive,n.knots=8,kappa1=10000,kappa2=10000,
  hazard="Splines")

## End(Not run)

```

subcluster

Identify subclusters

Description

This is a special function used in the context of survival nested models. It identifies correlated groups of observations within other groups defined by using 'cluster' function from 'survival' package, and is used on the right hand side of a formula of a 'frailtyPenal' object for fitting a nested model. Using `subcluster()` in a formula implies that a nested frailty model is estimated.

Usage

```
subcluster(x)
```

Arguments

x	A character, factor, or numeric variable which is supposed to indicate the variable subgroup
---	----------------------------------------------------------------------------------------------

Value

x	A variable identified as a subcluster
---	---------------------------------------

See Also

[frailtyPenal for Nested frailty models](#), [print.nestedPenal](#), [plot.nestedPenal](#), [summary.nestedPenal](#)

Examples

```
## Not run:

data(dataNested)
modClu<-frailtyPenal(Surv(t1,t2,event)~cluster(group)+
  subcluster(subgroup)+cov1+cov2,Frailty=TRUE,data=dataNested,
  n.knots=8,kappa1=50000,kappa2=50000,hazard="Splines")

print(modClu)

# It takes aound 24 minutes to converge (depends on the processor) #

## End(Not run)
```

summary.additivePenal *summary of parameter estimates of an additive frailty model*

Description

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

Usage

```
## S3 method for class 'additivePenal'
summary(object, level = 0.95, len = 6, d = 2, lab="hr", ...)
```

Arguments

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

Value

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

See Also

[additivePenal](#), [print.additivePenal](#), [plot.additivePenal](#)

Examples

```
## Not run:

data(dataAdditive)
modAdd<-additivePenal(Surv(t1,t2,event)~cluster(group)+var1+slope(var1),
                      correlation=TRUE,data=dataAdditive,n.knots=8,kappa1=862,
                      hazard="Splines")

# It takes around 4 minutes to converge. 'var1' is boolean as a treatment variable.

summary(modAdd)

## End(Not run)
```

summary.frailtyPenal *summary of parameter estimates of a shared frailty model*

Description

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

Usage

```
## S3 method for class 'frailtyPenal'
summary(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%.
d	the desired number of digits after the decimal point. Default of 6 digits is used.
len	the total field width. Default is 6.
lab	label of printed results.
...	other unused arguments.

Value

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

See Also

[frailtyPenal](#) for Shared frailty models, [plot.frailtyPenal](#), [summary.frailtyPenal](#)

Examples

```

data(kidney)

# /** Shared frailty model */

modSha<-frailtyPenal(Surv(time,status)~age+sex+cluster(id),
                    Frailty=TRUE,n.knots=8,kappa1=10000,data=kidney,
                    hazard="Splines")

# /** Cox proportional hazard model using Penalized likelihood */

modCox<-frailtyPenal(Surv(time,status)~age+sex+cluster(id),
                    n.knots=8,kappa1=10000,data=kidney,Frailty=FALSE,
                    hazard="Splines")

# /** confidence interval at 95% level (default) */

summary(modSha)
summary(modCox)

# /** confidence interval at 99% level */

summary(modSha,level=0.99)
summary(modCox,level=0.99)

```

summary.jointPenal *summary of parameter estimates of a joint frailty model*

Description

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

Usage

```

## S3 method for class 'jointPenal'
summary(object, level = 0.95, len = 6, d = 2, lab="hr", ...)

```

Arguments

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

Value

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

See Also

[frailtyPenal](#) for Joint frailty models, [plot.jointPenal](#), [print.jointPenal](#),

Examples

```
## Not run:

  data(readmission)

## Gap-time ##
modJoint_gap<-frailtyPenal(Surv(time,event)~cluster(id)+sex+as.factor(dukes)
  +as.factor(charlson)+terminal(death),
  formula.terminalEvent=~sex+as.factor(dukes)+as.factor(charlson),
  data=readmission,n.knots=14,kappa1=9550000000,kappa2=1410000000000,
  Frailty=TRUE,joint=TRUE,recurrentAG=FALSE,hazard="Splines")

## Calendar time ##
modJoint_calendar<-frailtyPenal(Surv(t.start,t.stop,event)~cluster(id)+sex
  +as.factor(dukes)+as.factor(charlson)+terminal(death),
  formula.terminalEvent=~sex+as.factor(dukes)+as.factor(charlson),
  data=readmission,n.knots=10,kappa1=9550000000,
  kappa2=1410000000000,Frailty=TRUE,joint=TRUE,recurrentAG=TRUE
  ,hazard="Splines")

# It takes around 1 minute to converge

  summary(modJoint_gap)
  summary(modJoint_calendar)

## End(Not run)
```

summary.nestedPenal *summary of regression coefficient estimates of a nested frailty model*

Description

This function returns hazard ratios (HR) and its confidence intervals for each regression coefficient

Usage

```
## S3 method for class 'nestedPenal'
summary(object, level = 0.95, len = 6, d = 2, lab="hr", ...)
```

Arguments

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

Value

Prints HR and its confidence intervals for each regression coefficient. Confidence level is allowed (level argument)

See Also

[frailtyPenal](#) for Nested frailty models, [plot.nestedPenal](#), [print.nestedPenal](#)

Examples

```
## Not run:

data(dataNested)
modNested<-frailtyPenal(Surv(t1,t2,event)~cluster(group)+
  subcluster(subgroup)+cov1+cov2,Frailty=TRUE,
  data=dataNested,n.knots=8,kappa1=50000,kappa2=50000,
  hazard="Splines")

# It takes 90 minutes to converge (depends on processor)

summary(modNested)

## End(Not run)
```

survival

Survival function

Description

Let t be a continuous variable, we determine the value of the survival function to t after run fit.

Usage

```
survival(t, ObjFrailty)
```

Arguments

t time for survival function.
ObjFrailty an object from the frailtypack fit.

Value

return the value of survival function in t.

Author(s)

V. Rondeau

Examples

```
### a fit Shared
data(readmission)
fit.shared <- frailtyPenal(Surv(time,event)~as.factor(dukes)+cluster(id)+strata(sex),
                          n.knots=10,kappa1=10000,kappa2=10000,data=readmission,
                          Frailty=TRUE)

### calling survival
survival(20,fit.shared)
```

terminal

Identify terminal indicator

Description

This is a special function used in the context of recurrent event models with terminal event (e.g., censoring variable related to recurrent events). It contains the status indicator, normally 0=alive, 1=dead, and is used on the right hand side of a formula of a 'frailtyPenal' object. Using terminal() in a formula implies that a joint frailty model for recurrent events and terminal events is fitted.

Usage

```
terminal(x)
```

Arguments

x A numeric variable but should be a Boolean which equals 1 if the subject is dead and 0 if he is alive or censored, as a death indicator.

Value

x a death indicator

See Also

[frailtyPenal](#) for Joint frailty models, [plot.jointPenal](#), [print.jointPenal](#), [summary.jointPenal](#)

Examples

```
## Not run:

data(dataJoint)

modJoint<-frailtyPenal(Surv(time.entry,time.end,status)~cluster(id)+var1+var2
                      +terminal(status.terminal),
                      formula.terminalEvent=~var1,
                      data=dataJoint,n.knots=7,Frailty=TRUE,
                      kappa1=1, kappa2=1, joint=TRUE, recurrentAG=TRUE)

print(modJoint)

## End(Not run)
```

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