Package ‘FlexVarJM’

November 20, 2023

Title  Estimate Joint Models with Subject-Specific Variance

Version  0.1.0

Description
Estimation of mixed models including a subject-specific variance which can be time and covari-
ate dependent. In the joint model framework, the package handles left truncation and allows a flex-
ible dependence structure between the competing events and the longitudinal marker. The esti-
mation is performed under the frequentist framework, using the Marquardt-Levenberg algo-

License  GPL (>= 3)

Encoding  UTF-8

RoxygenNote  7.2.3

Imports  ggplot2, lcmm, marqLevAlg, mvtnorm, randtoolbox, Rcpp, stats,
survminer, utils

Depends  R (>= 3.5.0), splines, survival

URL  https://github.com/LeonieCourcoul/FlexVarJM

BugReports  https://github.com/LeonieCourcoul/FlexVarJM/issues

LazyData  true

Suggests  knitr, rmarkdown

VignetteBuilder  knitr

LinkingTo  Rcpp, RcppArmadillo

NeedsCompilation  yes

Author  Léonie Courcoul [aut, cre],
        Antoine Barbieri [aut],
        Hélène Jacqmin-Gadda [aut]

Maintainer  Léonie Courcoul <leonie.courcoul@u-bordeaux.fr>

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**R topics documented:**

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**Description**

Initialisation of Survival Data at Gauss Kronrod time points

**Usage**

```r
data.GaussKronrod(data.id, Time, k = 15)
```

**Arguments**

- `data.id` 
  A database with covariates of interest and 1 line per subject
- `Time` 
  A vector of time event
- `k` 
  The number of Gauss Kronrod points, by default k = 15

**Value**

A list with the following components:

- `K` an integer, the number of points
- `P` a vector, of value Time/2
- `st` a matrix with nrow = number of subjects and ncol = k. The new time to compute the survival function
- `wk` a vector of weights
data.GaussKronrod2

data.id2 a database with K lines per subjects
id.GK the vector of IDs

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Initialisation of Survival Data at Gauss Kronrod time points 2

Description

Initialisation of Survival Data at Gauss Kronrod time points 2

Usage

data.GaussKronrod2(data.id, a, b, k = 15)

Arguments

data.id A database with covariates of interest and 1 line per subject

a First born

b Second born

k The number of Gauss Kronrod points, by default k = 15

Value

A list with the following components :

K an integer, the number of points

P a vector, of value Time/2

st a matrix with nrow = number of subjects and ncol = k. The new time to compute the survival function

wk a vector of weights

data.id2 a database with K lines per subjects

id.GK the vector of IDs
data.manag.long  Management of longitudinal data

Description
Management of longitudinal data

Usage
data.manag.long(formGroup, formFixed, formRandom, data.long1)

Arguments
formGroup       A formula which indicates the group variable
formFixed       A formula which indicates the fixed effects for the longitudinal submodel
formRandom      A formula which indicates the random effects for the longitudinal submodel
data.long1      A dataframe with the longitudinal data

Value
A list with the following components :
data_long  a clean dataframe for the longitudinal data
y.new.prog  the vector of responses variable
X            a matrix with the fixed effects
U            a matrix with the random effects
id           a vector with the identification of individuals
offset      a vector with the number of measurements for each individual
I            an integer, the number of individuals

data.manag.surv  Management of survival data

Description
Management of survival data

Usage
data.manag.surv(formGroup, formSurv, data.long1, formSurv_CompRisk)
**Arguments**

- `formGroup` A formula which indicates the group variable
- `formSurv` A formula which indicates the variables used in the survival submodel
- `data.long1` Database
- `formSurv_CompRisk` A formula which indicates the variables used in the competing survival submodel

**Value**

A list with the following components:

- `tmp` the final database for survival analysis
- `Time` a vector of observed times
- `event1` a vector of first event indicator
- `nTime` length of `Time` vector
- `Z` matrix of covariables of first survival submodel
- `event2` a vector of second event indicator
- `Z_CR` matrix of covariables of second survival submodel

**Description**

Management of data for longitudinal submodel

**Usage**

data.time(data.id, Time, formFixed, formRandom, timeVar)

**Arguments**

- `data.id` A dataframe
- `Time` A vector of Time of events
- `formFixed` A formula for the fixed effects of the longitudinal submodel
- `formRandom` A formula for the random effects of the longitudinal submodel
- `timeVar` The name of the column of time in `data.id`. This variable must appears in `data.id`

**Value**

A list with the following components

- `Xtime` a matrix of fixed effects at each time of measure
- `Utime` a matrix of random effects at each time of measure
Data_toy

Description
A simulated dataset for the example of the FlexVarJM package.

Usage
Data_toy

Format
A data frame with 2076 rows and 5 variables:

- **ID**: the Id of each subject
- **visit**: the time of measurement
- **y**: the value of the marker
- **time**: the time of the first event observed
- **event**: the first event observed: 0 = censoring, 1 = first event, 2 = second event

gaussKronrod

Description
Gauss-Kronrod nodes and weights

Usage
gaussKronrod(k = 15)

Arguments

- **k**: the number of points for Gauss-Kronrod approximation: choice between 7 and 15. 15 by default.

Value
A list with the following components:

- **sk**: A k-vector of nodes
- **wk**: A k-vector of weights
goodness_of_fit

Predictions for the goodness of fit, of the random effects, the current value for each individuals and the cumulative hazard function for both events

Description

Predictions for the goodness of fit, of the random effects, the current value for each individuals and the cumulative hazard function for both events

Usage

```r
goodness_of_fit(object, graph = FALSE, break.times = NULL)
```

Arguments

- `object`: an object of class lsjm
- `graph`: a boolean to indicate to print graphics, False by default
- `break.times`: a vector of times for the time points of longitudinal graphic

Value

A list which contains the following elements:

- `tables`: A list with the table of the predicted random effect, the table of the predicted current value, table(s) of predictive cumulative hazard function(s)
- `graphs`: A list with 2 or 3 graphs: one for the longitudinal adjustment and one for each risk function

Examples

```r
# Fit a joint model with competing risks and subject-specific variability
eexample <- lsjm(formFixed = y~visit,
                 formRandom = ~ visit,
                 formGroup = ~ID,
                 formSurv = Surv(time, event ==1 ) ~ 1,
                 timeVar = "visit",
                 data.long = Data_toy,
                 variability_hetero = TRUE,
                 formFixedVar =~visit,
                 formRandomVar =~visit,
                 correlated_re = TRUE,
                 sharedtype = c("current value", "variability"),
                 hazard_baseline = "Weibull",
                 formSlopeFixed = -1,
```
formSlopeRandom = -1,
indices_beta_slope = c(2),
competing_risk = TRUE,
formSurv_CR = Surv(time, event == 2) - 1,
hazard_baseline_CR = "Weibull",
sharedtype_CR = c("current value", "variability"),
S1 = 100,
S2 = 1000,
nproc = 1,
maxiter = 100,
Comp.Rcpp = TRUE
)

#Assesment of the goodness of fit:
gof <- goodness_of_fit(example, graph = TRUE)
gof$tables
gof$graphs

initial.long  

Initialisation of Longitudinal Submodel

Description
Initialisation of Longitudinal Submodel

Usage
initial.long(formFixed, formRandom, idVar, data.long1, ncX, nproc = nproc)

Arguments

formFixed  
A formula which indicates the fixed effects for the longitudinal submodel

formRandom  
A formula which indicates the random effects for the longitudinal submodel

idVar  
A character, indicates the name of the group variable

data.long1  
A dataframe with the longitudinal data

ncX  
An integer, the number of columns of matrix X, ie, the number of fixed effects

nproc  
An integer, the number of cores for parallel computation

Value

A list with the following components :

long_model  the result of the hlme function

priorMean.beta  the estimated parameters for fixed effects in the linear mixed effects model

sigma  the estimated sigma of the model
log_llh

Log-likelihood computation

Description

Log-likelihood computation

Usage

log_llh(
  param,
  nb.e.a,
  nb_priorMean.beta,
  nb.alpha,
  competing_risk,
  nb.alpha.CR,
  variability_hetero,
  S,
  Zq,
  sharedtype,
  sharedtype_CR,
  hazard_baseline,
  hazard_baseline_CR,
  ord.splines,
  Xtime,
  Utime,
  nb_pointsGK,
  Xs,
  Us,
  Xslope,
  Uslope,
  Xs.slope,
  Us.slope,
  indices_beta_slope,
  Time,
  st_calc,
  B,
  Bs,
  wk,
  Z,
  P,
  left_trunc,
  Z_CR,
  X_base,
  offset,
  U,
  y.new.prog,
event1, event2, Ind, Xs.0, Us.0, Xs.slope.0, Us.slope.0, P.0, st.0, Bs.0, B.CR, Bs.CR, Bs.0.CR, nb.e.a.sigma = nb.e.a.sigma, nb.omega = nb.omega, Otime = Otime, Wtime = Wtime, Os = Os, Ws = Ws, O_base = O_base, W_base = W_base, correlated_re = correlated_re, Os.0 = Os.0, Ws.0 = Ws.0

Arguments

param a vector : parameters to be estimated
nb.e.a integer : number of RE
nb.priorMean.beta integer : number of fixed effects
nb.alpha integer : number of covariates in survival model
competing_risk boolean : allow competing risk or not, FALSE by default
nb.alpha.CR integer : number of covariates in survival model for competing risks
variability_hetero boolean : allow the heterogeneous variability or not
S integer : the number of QMC points
Zq vector : sobol points
sharedtype vector : dependence structure for survival model : "RE" (random effects) or "CV" (current value) or "CVS" (current value and slope) or "S" (slope)
sharedtype_CR vector : dependence structure for competing risk survival model : "RE" (random effects) or "CV" (current value) or "CVS" (current value and slope) or "S" (slope)
hazard_baseline char : baseline hazard function : "Exponential" or "Weibull" or "Splines"
log_llh

hazard_baseline_CR
  char : baseline hazard function, competing risk : "Exponential" or "Weibull" or "Splines"

ord.splines
  integer : the order of splines function for baseline hazard function

Xtime
  matrix : fixed effects at event time

Utime
  matrix : RE at event time

nb_pointsGK
  integer : number of points for Gauss-Kronrod approximation, 7 or 15 (default)

Xs
  matrix : fixed effects at Gauss-Kronrod times

Us
  matrix : RE at Gauss-Kronrod times

Xslope
  matrix : fixed effects of slope at event times

Uslope
  matrix : RE of slope at event times

Xs.slope
  matrix : fixed effects of slope at Gauss-Kronrod times

Us.slope
  matrix : RE of slope at Gauss-Kronrod times

indices_beta_slope
  vector : position of beta which will be used in the slope computation

Time
  vector : observed event times

st_calc
  matrix : Gauss-Kronrod times

B
  matrix : splines for baseline hazard function of event 1

Bs
  matrix : splines for baseline survival function of event 1

wk
  vector : Gauss-Kronrod weights

Z
  matrix : covariates for survival function of event 1

P
  vector : Time/2

left_trunc
  boolean : left truncation indicator

Z_CR
  matrix : covariates for survival function of event 2

X_base
  matrix : fixed effects for longitudinal submodel

offset
  vector : number of lines per subjects

U
  matrix : RE for longitudinal submodel

y.new.prog
  vector : y measures for longitudinal submodel

event1
  vector : event 1 indicator

event2
  vector : event 2 indicator

Ind
  integer : number of subjects

Xs.0
  same for left truncation

Us.0
  same for left truncation

Xs.slope.0
  same for left truncation

Us.slope.0
  same for left truncation

P.0
  same for left truncation

st.0
  same for left truncation

Bs.0
  same for left truncation
B.CR same for left truncation
Bs.CR same for left truncation
Bs.0.CR same for left truncation
nb.e.a.sigma integer : number of RE for variability
nb.omega integer : number of fixed effects for variability
Otime matrix : fixed effects of variability at event time
Wtime matrix : RE of variability at event time
Os matrix : fixed effects of variability at Gauss-Kronrod times
Ws matrix : random effects of variability at Gauss-Kronrod times
O_base matrix : fixed effects for variability
W_base matrix : fixed effects for variability
correlated_re boolean : indicator to allow all the random effects to be correlated
Os.0 matrix : same for left truncation
Ws.0 matrix : same for left truncation

Value

The value of the log-likelihood

---

log_llh_rcpp Log-likelihood computation in RCPP

Description

Log-likelihood computation in RCPP

Usage

log_llh_rcpp(
  param,
  nb.e.a,
  nb.priorMean.beta,
  nb.alpha,
  competing_risk,
  nb.alpha.CR,
  variability_hetero,
  S,
  Zq,
  sharedtype,
  sharedtype_CR,
  hazard_baseline,
  hazard_baseline_CR,
  ord.splines,
Xtime,
Utime,
nb_pointsGK,
Xs,
Us,
Xslope,
Uslope,
Xs.slope,
Us.slope,
indices_beta_slope,
Time,
st_calc,
B,
Bs,
wk,
Z,
P,
left_trunc,
Z_CR,
X_base,
offset,
U,
y.new.prog,
event1,
event2,
Ind,
Xs.0,
Us.0,
Xs.slope.0,
Us.slope.0,
P.0,
st.0,
Bs.0,
B.CR,
Bs.CR,
Bs.0.CR,
nb.e.a.sigma = nb.e.a.sigma,
nb.omega = nb.omega,
Otime = Otime,
Wtime = Wtime,
Os = Os,
Ws = Ws,
Q_base = Q_base,
W_base = W_base,
correlated_re = correlated_re,
Os.0 = Os.0,
Ws.0 = Ws.0
)

Arguments

param a vector : parameters to be estimated
nb.e.a integer : number of RE
nb.priorMean.beta integer : number of fixed effects
nb.alpha integer : number of covariates in survival model
competing_risk boolean : allow competing risk or not, FALSE by default
nb.alpha.CR integer : number of covariates in survival model for competing risks
variability_hetero boolean : allow the heterogeneous variability or not
S integer : the number of QMC points
Zq vector : sobol points
sharedtype vector : dependence structure for survival model : "RE" (random effects) or "CV" (current value) or "CVS" (current value and slope) or "S" (slope)
sharedtype_CR vector : dependence structure for competing risk survival model : "RE" (random effects) or "CV" (current value) or "CVS" (current value and slope) or "S" (slope)
hazard_baseline char : baseline hazard function : "Exponential" or "Weibull" or "Splines"
hazard_baseline_CR char : baseline hazard function, competing risk : "Exponential" or "Weibull" or "Splines"
ord.splines integer : the order of splines function for baseline hazard function
Xtime matrix : fixed effects at event time
Utime matrix : RE at event time
nb_pointsGK integer : number of points for Gauss-Kronrod approximation, 7 or 15 (default)
Xs matrix : fixed effects at Gauss-Kronrod times
Us matrix : RE at Gauss-Kronrod times
Xslope matrix : fixed effects of slope at event times
Uslope matrix : RE of slope at event times
Xs.slope matrix : fixed effects of slope at Gauss-Kronrod times
Us.slope matrix : RE of slope at Gauss-Kronrod times
indices_beta_slope vector : position of beta which will be used in the slope computation
Time vector : observed event times
st_calc matrix : Gauss-Kronrod times
B matrix : splines for baseline hazard function of event 1
Bs matrix : splines for baseline survival function of event 1
wk vector : Gauss-Kronrod weights
**log_llh_rcpp**

- **Z** matrix: covariates for survival function of event 1
- **P** vector: Time/2
- **left_trunc** boolean: left truncation indicator
- **Z_CR** matrix: covariates for survival function of event 2
- **X_base** matrix: fixed effects for longitudinal submodel
- **offset** vector: number of lines per subjects
- **U** matrix: RE for longitudinal submodel
- **y.new.prog** vector: y measures for longitudinal submodel
- **event1** vector: event 1 indicator
- **event2** vector: event 2 indicator
- **Ind** integer: number of subjects
- **Xs.0** same for left truncation
- **Us.0** same for left truncation
- **Xs.slope.0** same for left truncation
- **Us.slope.0** same for left truncation
- **P.0** same for left truncation
- **st.0** same for left truncation
- **Bs.0** same for left truncation
- **B.CR** same for left truncation
- **Bs.CR** same for left truncation
- **Bs.0.CR** same for left truncation
- **nb.e.a.sigma** integer: number of RE for variability
- **nb.omega** integer: number of fixed effects for variability
- **Otime** matrix: fixed effects of variability at event time
- **Wtime** matrix: RE of variability at event time
- **Os** matrix: fixed effects of variability at Gauss-Kronrod times
- **Ws** matrix: random effects of variability at Gauss-Kronrod times
- **O_base** matrix: fixed effects for variability
- **W_base** matrix: fixed effects for variability
- **correlated_re** boolean: indicator to allow all the random effects to be correlated
- **Os.0** matrix: same for left truncation
- **Ws.0** matrix: same for left truncation

**Value**

The value of the log-likelihood
lsjm

lsjm : Estimation of joint model for longitudinal data with a subject-specific time-dependent variability and time-to-event data.

Description

This function fits complex joint models with shared random effects. The longitudinal submodel estimates longitudinal data with a mixed-effects model in which we suppose that the variance of the residual error is time-dependent and subject-specific. The survival submodel handles right-censored and left-truncated time-to-event data and competing risks. The dependence structure between the longitudinal and the survival data can be the random effects from the mixed model or the current value of the marker and/or the slope of the marker. We can also adjust on the current variance of the marker. (See below) Parameters are estimated simultaneously through a maximum likelihood method, using a Marquardt-Levenberg algorithm.

Usage

lsjm(
  formFixed,
  formRandom,
  formGroup,
  formSurv,
  timeVar,
  data.long,
  variability_hetero = TRUE,
  formFixedVar,
  formRandomVar,
  correlated_re = FALSE,
  sharedtype = c("current value", "variability"),
  hazard_baseline = "Exponential",
  formSlopeFixed = NULL,
  formSlopeRandom = NULL,
  indices_beta_slope = NULL,
  nb_pointsGK = 15,
  ord.splines = 3,
  competing_risk = FALSE,
  formSurv_CR = NULL,
  hazard_baseline_CR = "Exponential",
  sharedtype_CR = c("current value", "variability"),
  left_trunc = FALSE,
  Time.0 = NULL,
  S1 = 1000,
  S2 = 5000,
  nproc = 1,
  clustertype = "SOCK",
  maxiter = 100,
  print.info = FALSE,
file = NULL,
cpsa = 0.001,
cpsb = 0.001,
cpsd = 0.001,
binit = NULL,
Comp.Rcpp = TRUE
)

Arguments

formFixed       A formula for the fixed effects of the longitudinal submodel
formRandom      A formula for the random effects of the longitudinal submodel
formGroup       A formula which indicates the group variable
formSurv       A formula which indicates the variables used in the survival submodel
timeVar        The name of the column of time in data.long. This variable must appears in data.long
data.long      A dataframe with the longitudinal data
variability_hetero  A logical to indicate if we suppose a subject specific variability
formFixedVar    A formula for the fixed effects of the variance predictor
formRandomVar   A formula for the random effects of the variance predictor
correlated_re   A logical to indicate if the random effects of the marker and the variance predictors are correlated (By default there are supposed to be independent)
sharedtype      char: dependence structure for survival model: "RE" (random effects) or "CV" (current value) or "CVS" (current value and slope) or "S" (slope)
hazard_baseline char: baseline hazard function: "Exponential" or "Weibull" or "Splines"
formSlopeFixed  A formula for the fixed effects of the slope of the longitudinal submodel: the derivative of the formFixed
formSlopeRandom A formula for the random effects of the slope of the longitudinal submodel: the derivative of the formRandom
indices_beta_slope A vector of index indicating which beta of the formFixed formula is used in the formSlopeFixed formula
nb_pointsGK     the number of points for Gauss-Kronrod approximation: choice between 7 and 15. 15 by default.
ord.splines     A numeric, the order of splines for the baseline risk function (3 by default)
competing_risk   A logical indicating if the model handles with competing risks
formSurv_CR     In case of competing risk A formula which indicates the variables used in the survival submodel for the second event
hazard_baseline_CR In case of competing risk: a character for the baseline hazard function of the second event
sharedtype_CR  In case of competing risk ; a character for the dependence structure
left_trunc  A logical indicating if the model handles with left truncated data
Time.0  In case of left truncation : a vector of entry times
S1  An integer : the number of QMC draws for the first step
S2  An integer : the number of QMC draws for the second step
nproc  An integer : the number of processors for parallel computing
clustertype  one of the supported types from makeCluster function
maxiter  optional maximum number of iterations for the marqLevAlg iterative algorithm.
print.info  logical indicating if the outputs of each iteration should be written
file  optional character giving the name of the file where the outputs of each iteration
epsa  optional threshold for the convergence criterion based on the parameter stability.
epsb  optional threshold for the convergence criterion based on the objective function
epsd  optional threshold for the relative distance to maximum. This criterion has the
binit  optional initials parameters.
Comp.Rcpp  boolean to indicate if the computation is performed with RCPP program or R

Details

A. LONGITUDINAL SUBMODEL

The longitudinal submodel is defined by a linear mixed effects model with the residual variance
which could be supposed to be time-dependent and subject-specific : \[
Y_{ij} = Y_i(t_{ij}) = \tilde{Y}_i(t_{ij}) + \epsilon_{ij} = X_{ij}^T \beta + Z_{ij}^T b_i + \epsilon_{ij}(t_{ij}) \sim \mathcal{N}(0, \sigma_i^2(t_{ij})) \quad \text{with} \quad \log(\sigma_i(t_{ij})) = \mathcal{O}_{ij}^T \mu + \mathcal{M}_{ij}^T \tau_i \]

with \(X_{ij}, O_{ij}, Z_{ij}\) and \(M_{ij}\) four vectors of explanatory variables for subject \(i\) at visit \(j\), respectively associated with the fixed-effect vectors \(\beta\) and \(\mu\), and the subject-specific random-effect vector \(b_i\) and \(\tau_i\), such as \[
\begin{pmatrix}
  b_i \\
  \tau_i
\end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \Sigma_b & \Sigma_{rb} \\ \Sigma_{rb} & \Sigma_{\tau} \end{pmatrix}\right)
\]

\(Y_i(t_{ij}) = \tilde{Y}_i(t_{ij}) + \epsilon_{ij} = X_{ij}^T \beta + Z_{ij}^T b_i + \epsilon_{ij}\)

with \(X_{ij}\) and \(Z_{ij}\) two covariate vectors for subject \(i\) at visit \(j\), respectively associated with the vector of fixed effects \(\beta\) and the vector of subject-specific individual random effects \(b_i\). The vector \(b_i\) is assumed to be normally distributed and a specific-subject random effect on the variance of the measure error can be added: \(\epsilon_{ij} \sim \mathcal{N}(0, \sigma_i^2)\) and \[
\begin{pmatrix}
  \log \sigma_i \\
  \mu_{\sigma}
\end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \Sigma_b & 0 \\ 0 & \Sigma_{\sigma}^2 \end{pmatrix}\right)
\]

B. SURVIVAL SUBMODEL

The risk function for the event \(k = \{1, 2\}\) is defined by: \(\lambda_{ik}(t) = \lambda_{0k}(t) \exp \left(W_i^{\top} \gamma_k + \alpha_{1k} Y_i(t) + \alpha_{2k} Y_i'(t) + \alpha_{\sigma k} \sigma_i(t)\right)\)

with \(\lambda_{0k}(t)\) the baseline risk function, \(W_i\) a vector of baseline covariates associated with the regression coefficient \(\gamma_k\), and \(\alpha_{1k}, \alpha_{2k}\) and \(\alpha_{\sigma k}\) the regression coefficients associated with the
current value $\tilde{y}_i(t)$, the current slope $\tilde{y}_i'(t)$ and the current variability $\sigma_i(t)$ of the marker, respectively. Different parametric forms for the baseline risk function can be considered, such as exponential, Weibull, or, for more flexibility, a B-splines base.

**Value**

A FlexVarJoint object which contains the following elements:

- **result** A marqLevAlg object with the results of the estimation.
- **table.res** The table of results: Estimation and SE
- **time.compute** Computation time
- **control** A list of control elements

**Examples**

```r
# fit a joint model with competing risks and subject-specific variability
example <- lsjm(formFixed = y~visit, 
                 formRandom = ~ visit, 
                 formGroup = ~ID, 
                 formSurv = Surv(time, event ==1 ) - 1, 
                 timeVar = "visit", 
                 data.long = Data_toy, 
                 variability_hetero = TRUE, 
                 formFixedVar =~visit, 
                 formRandomVar =~visit, 
                 correlated_re = TRUE, 
                 sharedtype = c("current value", "variability"), 
                 hazard_baseline = "Weibull", 
                 formSlopeFixed =-1, 
                 formSlopeRandom = -1, 
                 indices_beta_slope = c(2), 
                 competing_risk = TRUE, 
                 formSurv_CR = Surv(time, event ==2 ) - 1, 
                 hazard_baseline_CR = "Weibull", 
                 sharedtype_CR = c("current value", "variability"), 
                 S1 = 100, 
                 S2 = 1000, 
                 nproc = 1, 
                 maxiter = 100, 
                 Comp.Rcpp = TRUE
)

summary(example)
```
Description

This function fits complex mixed effects model with a time and covariate dependent variance. We suppose that the variance of the residual error is time-dependent and subject-specific. Parameters are estimated simultaneously through a maximum likelihood method, using a Marquardt-Levenberg algorithm.

Usage

```r
lsmm(
  formFixed,
  formRandom,
  formGroup,
  timeVar,
  data.long,
  variability_hetero = TRUE,
  formFixedVar,
  formRandomVar,
  correlated_re = FALSE,
  S1 = 1000,
  S2 = 5000,
  nproc = 1,
  clustertype = "SOCK",
  maxiter = 100,
  print.info = FALSE,
  file = NULL,
  epsa = 0.001,
  epsb = 0.001,
  epsd = 0.001,
  binit = NULL
)
```

Arguments

- `formFixed`: A formula for the fixed effects of the longitudinal submodel
- `formRandom`: A formula for the random effects of the longitudinal submodel
- `formGroup`: A formula which indicates the group variable
- `timeVar`: The name of the column of time in data.long. This variable must appear in data.long
- `data.long`: A dataframe with the longitudinal data
- `variability_hetero`: A logical to indicate if we suppose a subject specific variability
A formula for the fixed effects of the variance predictor
A formula for the random effects of the variance predictor
A logical to indicate if the random effects of the marker and the variance predictors are correlated (By default there are supposed to be independent)
An integer : the number of QMC draws for the first step
An integer : the number of QMC draws for the second step
An integer : the number of processors for parallel computing
one of the supported types from makeCluster function
optional maximum number of iterations for the marqLevAlg iterative algorithm.
logical indicating if the outputs of each iteration should be written
optional character giving the name of the file where the outputs of each iteration should be written (if print.info=TRUE)
optional threshold for the convergence criterion based on the parameter stability.
optional threshold for the convergence criterion based on the objective function stability.
optional threshold for the relative distance to maximum. This criterion has the nice interpretation of estimating the ratio of the approximation error over the statistical error, thus it can be used for stopping the iterative process whatever the problem.
optimal initials parameters.

Details

The model is defined by:

\[
\begin{align*}
Y_{ij} &= Y_i(t_{ij}) = \tilde{Y}_i(t_{ij}) + \epsilon_{ij} = X_{ij}^T \beta + Z_{ij}^T b_i + \epsilon_{ij}, \\
\epsilon_{ij}(t_{ij}) &\sim N(0, \sigma_i^2(t_{ij})) \quad \text{with} \quad \log(\sigma_i(t_{ij})) = O_{ij}^T \mu + M_{ij}^T \tau_i
\end{align*}
\]

with \(X_{ij}, O_{ij}, Z_{ij}\) and \(M_{ij}\) four vectors of explanatory variables for subject i at visit j, respectively associated with the fixed-effect vectors \(\beta\) and \(\mu\), and the subject-specific random-effect vector \(b_i\) and \(\tau_i\), such as

\[
\begin{pmatrix}
  b_i \\
  \tau_i
\end{pmatrix} \sim N \left( 
\begin{pmatrix}
  0 \\
  0
\end{pmatrix}, 
\begin{pmatrix}
  \Sigma_b & \Sigma_{\tau b} \\
  \Sigma_{\tau b} & \Sigma_{\tau}
\end{pmatrix}
\right)
\]

\[Y_i(t_{ij}) = \tilde{Y}_i(t_{ij}) + \epsilon_{ij} = X_{ij}^T \beta + Z_{ij}^T b_i + \epsilon_{ij}\]

with \(X_{ij}\) and \(Z_{ij}\) two covariate vectors for subject i at visit j, respectively associated with the vector of fixed effects \(\beta\) and the vector of subject-specific individual random effects \(b_i\). The vector \(b_i\) is assumed to be normally distributed and a specific-subject random effect on the variance of the measure error can be added: \(\epsilon_{ij} \sim N(0, \sigma_i^2)\) and

\[
\begin{pmatrix}
  b_i \\
  \log \sigma_i
\end{pmatrix} \sim N \left( 
\begin{pmatrix}
  0 \\
  \mu_{\sigma}
\end{pmatrix}, 
\begin{pmatrix}
  \Sigma_b & 0 \\
  0 & \Sigma_{\sigma}
\end{pmatrix}
\right)
\]

Value

A FlexVarJoint object which contains the following elements:

result A marqLevAlg object with the results of the estimation.
table.res The table of results: Estimation and SE
time.compute Computation time
control A list of control elements
Examples

```r
# fit a joint model with competing risks and subject-specific variability
example <- lsmm(formFixed = y~visit,
    formRandom = ~ID,
    timeVar = "visit",
    data.long = Data_toy,
    variability_hetero = TRUE,
    formFixedVar =~visit,
    formRandomVar =~visit,
    correlated_re = TRUE,
    S1 = 100,
    S2 = 1000,
    nproc = 1,
    maxiter = 100
)

summary(example)
```

---

**predyn**

*Dynamic prediction for new individuals*

**Description**

Dynamic prediction for new individuals

**Usage**

```r
predyn(
    newdata,
    object,
    s,
    times,
    event = 1,
    IC = 95,
    nb.draws = 500,
    graph = FALSE
)
```

**Arguments**

- `newdata` : data frame : collected data for a new individual
object  lsjm object : estimation of the model
s    numeric : the time to begin prediction
times numeric vector : future times to calculate predictions
event integer (0, 1 or 2) : the event of interest for the prediction
IC integer : percentage of confidence for the interval confidence (between 0 and 100), 95 by default, NULL if no IC
nb.draws integer : the number of simulations to compute the interval confidence (by bootstrap), 500 by default
graph boolean : indicator to plot the graphs or not

Value

A table of dynamic predictions

Examples

#fit a joint model with competing risks and subject-specific variability
example <- lsjm(formFixed = y~visit,
formRandom = ~ visit,
formGroup = ~ID,
formSurv = Surv(time, event ==1 ) - 1,
timeVar = "visit",
data.long = Data_toy,
variability_hetero = TRUE,
formFixedVar = ~visit,
formRandomVar = ~visit,
correlated_re = TRUE,
sharedtype = c("current value", "variability"),
hazard_baseline = "Weibull",
formSlopeFixed = ~1,
formSlopeRandom = ~1,
indices_beta_slope = c(2),
competing_risk = TRUE,
formSurv_CR = Surv(time, event ==2 ) - 1,
hazard_baseline_CR = "Weibull",
sharedtype_CR = c("current value", "variability"),
S1 = 100,
S2 = 1000,
nproc = 1,
maxiter = 100,
Comp.Rcpp = TRUE)

#Prediction for individuals 1 and 3 to experiment the event 1
#at time 1.5, 2, and 3, given their measurements until time 1:
newdata <- Data_toy[which(Data_toy$ID %in% c(1,3)),]
pred.new <- predyn(newdata,example,1, c(1.5,2,2.8,3), event = 1, IC = 95,
pred_s.t.bootstrap.tps

Description
Predictions computation

Usage
pred_s.t.bootstrap.tps(newdata, object, s, window, event = 1, nb.draws)

Arguments
- newdata: data frame : collected data for a new individual
- object: lsjm object : estimation of the model
- s: numeric : the time to begin prediction
- window: numeric : the side of the prediction window
- event: integer (0, 1 or 2) : the event of interest for the prediction
- nb.draws: integer : the number of draws to compute the IC

pred_s.t.ponctuel.tps

Description
Predictions computation

Usage
pred_s.t.ponctuel.tps(newdata, object, s, window, event = 1)

Arguments
- newdata: data frame : collected data for a new individual
- object: lsjm object : estimation of the model
- s: numeric : the time to begin prediction
- window: numeric : the side of the prediction window
- event: integer (0, 1 or 2) : the event of interest for the prediction
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