

Package ‘JMbayes2’

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Type Package

Title Extended Joint Models for Longitudinal and Time-to-Event Data

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BugReports <https://github.com/drizopoulos/JMbayes2/issues>

Description Fit joint models for longitudinal and time-to-event data under the Bayesian approach. Multiple longitudinal outcomes of mixed type (continuous/categorical) and multiple event times (competing risks and multi-state processes) are accommodated. Rizopoulos (2012, ISBN:9781439872864).

Suggests lattice, knitr, rmarkdown, pkgdown

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Depends survival, nlme, GLMMadaptive, splines

Imports coda, Rcpp, parallel, matrixStats, ggplot2, gridExtra

LinkingTo Rcpp, RcppArmadillo

LazyLoad yes

LazyData yes

License GPL (>= 3)

URL <https://drizopoulos.github.io/JMbayes2/>,
<https://github.com/drizopoulos/JMbayes2>

NeedsCompilation yes

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| | |
|-------------------|--|
| Accuracy Measures | <i>Time-Dependent ROCs and AUCs for Joint Models</i> |
|-------------------|--|

Description

Using the available longitudinal information up to a starting time point, this function computes an estimate of the ROC and the AUC at a horizon time point based on joint models.

Usage

```
tvROC(object, newdata, Tstart, ...)

## S3 method for class 'jm'
tvROC(object, newdata, Tstart, Thoriz = NULL,
      Dt = NULL, ...)

tvAUC(object, newdata, Tstart, ...)

## S3 method for class 'jm'
tvAUC(object, newdata, Tstart, Thoriz = NULL,
      Dt = NULL, ...)

## S3 method for class 'tvROC'
tvAUC(object, ...)

calibration_plot(object, newdata, Tstart, Thoriz = NULL,
  Dt = NULL, df_ns = 3, plot = TRUE, add_density = TRUE,
  col = "red", lty = 1, lwd = 1,
  col_dens = "grey", xlab = "Predicted Probabilities",
  ylab = "Observed Probabilities", main = "", ...)

calibration_metrics(object, newdata, Tstart, Thoriz = NULL,
```

```
Dt = NULL, df_ns = 3, ...)
```

```
tvBrier(object, newdata, Tstart, Thoriz = NULL, Dt = NULL, ...)
```

Arguments

| | |
|---|---|
| object | an object inheriting from class <code>jm</code> , except for <code>tvAUC.tvROC()</code> where this is an object of class <code>tvROC</code> . |
| newdata | a <code>data.frame</code> that contains the longitudinal and covariate information for the subjects for which prediction of survival probabilities is required. The names of the variables in this <code>data.frame</code> must be the same as in the <code>data.frames</code> that were used to fit the linear mixed effects and the event process model that were supplied as the two first argument of <code>jm</code> . |
| Tstart | numeric scalar denoting the time point up to which longitudinal information is to be used to derive predictions. |
| Thoriz | numeric scalar denoting the time point for which a prediction of the survival status is of interest; <code>Thoriz</code> must be later than <code>Tstart</code> and either <code>Dt</code> or <code>Thoriz</code> must be specified. If <code>Thoriz</code> is <code>NULL</code> is set equal to <code>Tstart + Dt</code> . |
| Dt | numeric scalar denoting the length of the time interval of prediction; either <code>Dt</code> or <code>Thoriz</code> must be specified. |
| df_ns | the degrees of freedom for the natural cubic spline of the cloglog transformation of the predicted probabilities used in the Cox model that assess calibration. |
| plot | logical; should a plot be produced. If <code>FALSE</code> , a list is returned with the observed and predicted probabilities. |
| add_density | logical; should the kernel density estimation of the predicted probabilities be superimposed in the calibration plot. |
| col, lwd, lty, col_dens, xlab, ylab, main | graphical parameters. |
| ... | additional arguments passed to <code>predict.jm()</code> . |

Value

A list of class `tvAUC` with components:

| | |
|-------------|--|
| auc | a numeric scalar denoting the estimated prediction error. |
| Tstart | a copy of the <code>Tstart</code> argument. |
| Thoriz | a copy of the <code>Thoriz</code> argument. |
| nr | a numeric scalar denoting the number of subjects at risk at time <code>Tstart</code> . |
| classObject | the class of object. |
| nameObject | the name of object. |

A list of class `tvROC` with components:

`TP`, `FP`, `nTP`, `nFN`, `nTN`, `qSN`, `qSP`, `qOverall`
accuracy indexes.

| | |
|-----------------|---|
| F1score, Youden | numeric scalars with the optimal cut-point using the F1 score and the Youden index. |
| thr | numeric vector of thresholds. |
| Tstart | a copy of the Tstart argument. |
| Thoriz | a copy of the Thoriz argument. |
| nr | a numeric scalar denoting the number of subjects at risk at time Tstart. |
| classObject | the class of object. |
| nameObject | the name of object. |

Author(s)

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References

- Antolini, L., Boracchi, P., and Biganzoli, E. (2005). A time-dependent discrimination index for survival data. *Statistics in Medicine* **24**, 3927–3944.
- Harrell, F., Kerry, L. and Mark, D. (1996). Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Statistics in Medicine* **15**, 361–387.
- Heagerty, P. and Zheng, Y. (2005). Survival model predictive accuracy and ROC curves. *Biometrics* **61**, 92–105.
- Rizopoulos, D. (2016). The R package JMbayes for fitting joint models for longitudinal and time-to-event data using MCMC. *Journal of Statistical Software* **72(7)**, 1–45. doi:10.18637/jss.v072.i07.
- Rizopoulos, D. (2012) *Joint Models for Longitudinal and Time-to-Event Data: with Applications in R*. Boca Raton: Chapman and Hall/CRC.
- Rizopoulos, D. (2011). Dynamic predictions and prospective accuracy in joint models for longitudinal and time-to-event data. *Biometrics* **67**, 819–829.
- Rizopoulos, D., Molenberghs, G. and Lesaffre, E.M.E.H. (2017). Dynamic predictions with time-dependent covariates in survival analysis using joint modeling and landmarking. *Biometrical Journal* **59**, 1261–1276.

See Also

[predict, jm](#)

Examples

```
# We fit a multivariate joint model
pbc2.id$status2 <- as.numeric(pbc2.id$status != 'alive')
CoxFit <- coxph(Surv(years, status2) ~ sex, data = pbc2.id)
fm1 <- lme(log(serBilir) ~ ns(year, 3) * sex, data = pbc2,
          random = ~ ns(year, 3) | id, control = lmeControl(opt = 'optim'))
fm2 <- lme(prothrombin ~ ns(year, 2) * sex, data = pbc2,
```

```
random = ~ ns(year, 2) | id, control = lmeControl(opt = 'optim'))
fm3 <- mixed_model(ascites ~ year * sex, data = pbc2,
                  random = ~ year | id, family = binomial())

jointFit <- jm(CoxFit, list(fm1, fm2, fm3), time_var = "year", n_chains = 1L)

roc <- tvROC(jointFit, newdata = pbc2, Tstart = 4, Dt = 3, cores = 1L)
roc
tvAUC(roc)
plot(roc, legend = TRUE, optimal_cutoff = "Youden")
```

aids

Didanosine versus Zalcitabine in HIV Patients

Description

A randomized clinical trial in which both longitudinal and survival data were collected to compare the efficacy and safety of two antiretroviral drugs in treating patients who had failed or were intolerant of zidovudine (AZT) therapy.

Format

A data frame with 1408 observations on the following 9 variables.

`patient` patients identifier; in total there are 467 patients.

`Time` the time to death or censoring.

`death` a numeric vector with 0 denoting censoring and 1 death.

`CD4` the CD4 cells count.

`obstime` the time points at which the CD4 cells count was recorded.

`drug` a factor with levels `ddC` denoting zalcitabine and `ddI` denoting didanosine.

`gender` a factor with levels `female` and `male`.

`prevOI` a factor with levels `AIDS` denoting previous opportunistic infection (AIDS diagnosis) at study entry, and `noAIDS` denoting no previous infection.

`AZT` a factor with levels `intolerance` and `failure` denoting AZT intolerance and AZT failure, respectively.

Note

The data frame `aids.id` contains the first CD4 cell count measurement for each patient. This data frame is used to fit the survival model.

References

- Goldman, A., Carlin, B., Crane, L., Launer, C., Korvick, J., Deyton, L. and Abrams, D. (1996) Response of CD4+ and clinical consequences to treatment using ddI or ddC in patients with advanced HIV infection. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* **11**, 161–169.
- Guo, X. and Carlin, B. (2004) Separate and joint modeling of longitudinal and event time data using standard computer packages. *The American Statistician* **58**, 16–24.

 crisk_setup

Transform Competing Risks Data in Long Format

Description

In a competing risks setting this function expands the data frame with a single row per subject to a data frame in the long format in which each subject has as many rows as the number of competing events.

Usage

```
crisk_setup(data, statusVar, censLevel,
            nameStrata = "strata", nameStatus = "status2")
```

Arguments

- | | |
|------------|---|
| data | the data frame containing the competing risk data with a single row per subject. |
| statusVar | a character string denoting the name of the variable in data that identifies the status variable which equals 1 if the subject had any of the competing events and 0 otherwise. |
| censLevel | a character string or a scalar denoting the censoring level in the statusVar variable of data. |
| nameStrata | a character string denoting the variable that will be added in the long version of data denoting the various causes of event. |
| nameStatus | a character string denoting the variable that will be added in the long version of data denoting if the subject experience any of the competing events. |

Value

A data frame in the long format with multiple rows per subject.

Author(s)

Dimitris Rizopoulos <d.rizopoulos@erasmusmc.nl>

References

Rizopoulos, D. (2012) *Joint Models for Longitudinal and Time-to-Event Data: with Applications in R*. Boca Raton: Chapman and Hall/CRC.

Putter, H., Fiocco, M., and Geskus, R. (2007). Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* **26**, 2389–2430.

Examples

```
head(crisk_setup(pbc2.id, "status", "alive"))
```

 jm

Joint Models for Longitudinal and Time-to-Event Data

Description

Fits multivariate joint models for longitudinal and time-to-event data.

Usage

```
jm(Surv_object, Mixed_objects, time_var, recurrent = FALSE,
   functional_forms = NULL, data_Surv = NULL, id_var = NULL, priors = NULL,
   control = NULL, ...)
```

```
value(x)
slope(x, eps = 0.001, direction = "both")
area(x)
```

```
vexpit(x)
Dexpit(x)
```

```
vexp(x)
Dexp(x)
```

```
vlog(x)
vlog2(x)
vlog10(x)
```

```
vsqrt(x)
poly2(x)
poly3(x)
poly4(x)
```

```
tv(x, knots = NULL, ord = 2L)
```

Arguments

| | |
|------------------|--|
| Surv_object | <p>an object:</p> <ul style="list-style-type: none"> • of class 'coxph' fitted by function <code>coxph()</code> from package survival, or • of class 'survreg' fitted by function <code>survreg()</code> from package survival. |
| Mixed_objects | <p>a list of objects or a single object. Objects may be:</p> <ul style="list-style-type: none"> • of class 'lme' fitted by function <code>lme()</code> from package nlme, or • of class 'MixMod' fitted by function <code>mixed_model()</code> from package GLM-Madaptive. |
| time_var | a character string indicating the time variable in the mixed-effects model(s). |
| recurrent | a character string indicating "calendar" or "gap" timescale to fit a recurrent event model. |
| functional_forms | a list of formulas. Each formula corresponds to one longitudinal outcome and specifies the association structure between that outcome and the survival submodel as well as any interaction terms between the components of the longitudinal outcome and the survival submodel. See Examples . |
| data_Surv | the <code>data.frame</code> used to fit the Cox/AFT survival submodel. |
| id_var | a character string indicating the id variable in the survival submodel. |
| priors | <p>a named list of user-specified prior parameters:</p> <p><code>mean_betas_HC</code> the prior mean vector of the normal prior for the regression coefficients of the covariates of the longitudinal model(s), which were hierarchically centered.</p> <p><code>Tau_betas_HC</code> the prior precision matrix of the normal prior for the regression coefficients of the longitudinal model(s), which were hierarchically centered.</p> <p><code>mean_betas_nHC</code> a list of the prior mean vector(s) of the normal prior(s) for the regression coefficients of the covariates of the longitudinal model(s), which were not hierarchically centered.</p> <p><code>Tau_betas_nHC</code> a list of the prior precision matrix(ces) of the normal prior(s) for the regression coefficients of the longitudinal model(s), which were not Hierarchically Centered.</p> <p><code>mean_bs_gammas</code> the prior mean vector of the normal prior for the B-splines coefficients used to approximate the baseline hazard.</p> <p><code>Tau_bs_gammas</code> the prior precision matrix of the normal prior for the B-splines coefficients used to approximate the baseline hazard.</p> <p><code>A_tau_bs_gammas</code> the prior shape parameter of the gamma prior for the precision parameter of the penalty term for the B-splines coefficients for the baseline hazard.</p> <p><code>B_tau_bs_gammas</code> the prior rate parameter of the gamma prior for the precision parameter of the penalty term for the B-splines coefficients for the baseline hazard.</p> |

- `rank_Tau_bs_gammas` the prior rank parameter for the precision matrix of the normal prior for the B-splines coefficients used to approximate the baseline hazard.
- `mean_gammas` the prior mean vector of the normal prior for the regression coefficients of baseline covariates.
- `Tau_gammas` the prior precision matrix of the normal prior for the regression coefficients of baseline covariates.
- `penalty_gammas` a character string with value 'none', 'ridge', or 'horseshoe' indicating whether the coefficients of the baseline covariates included in the survival submodel should not be shrunk, shrunk using ridge prior, or shrunk using horseshoe prior, respectively.
- `A_lambda_gammas` the prior shape parameter of the gamma prior for the precision parameter of the local penalty term for the baseline regression coefficients. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `B_lambda_gammas` the prior rate parameter of the gamma prior for the precision parameter of the local penalty term for the baseline regression coefficients. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `A_tau_gammas` the prior shape parameter of the gamma prior for the precision parameter of the global penalty term for the baseline regression coefficients. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `B_tau_gammas` the prior rate parameter of the gamma prior for the precision parameter of the global penalty term for the baseline regression coefficients. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `A_nu_gammas` the prior shape parameter of the gamma prior for the variance hyperparameter for the precision parameter of the local penalty term for the baseline regression coefficients. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `B_nu_gammas` the prior rate parameter of the gamma prior for the variance hyperparameter for the precision parameter of the local penalty term for the baseline regression coefficients. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `A_xi_gammas` the prior shape parameter of the gamma prior for the variance hyperparameter for the precision parameter of the global penalty term for the baseline regression coefficients. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `B_xi_gammas` the prior rate parameter of the gamma prior for the variance hyperparameter for the precision parameter of the global penalty term for the baseline regression coefficients. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `mean_alphas` the prior mean vector of the normal prior for the association parameter(s).
- `Tau_alphas` the prior mean vector of the normal prior for the association parameter(s).

- `penalty_alphas` a character string with value 'none', 'ridge', 'horseshoe' indicating whether the coefficients association parameters should not be shrunk, shrank using ridge prior, or shrank using horseshoe prior, respectively.
- `A_lambda_alphas` the prior shape parameter of the gamma prior for the precision parameter of the local penalty term for the association parameters. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `B_lambda_alphas` the prior rate parameter of the gamma prior for the precision parameter of the local penalty term for the association parameters. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `A_tau_alphas` the prior shape parameter of the gamma prior for the precision parameter of the global penalty term for the association parameters. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `B_tau_alphas` the prior rate parameter of the gamma prior for the precision parameter of the global penalty term for the association parameters. Only relevant when `penalty_gammas = 'ridge'` or `penalty_gammas = 'horseshoe'`.
- `A_nu_alphas` the prior shape parameter of the gamma prior for the variance hyperparameter for the precision parameter of the local penalty term for the association parameters. Only relevant when `penalty_gammas = 'ridge'`, or `penalty_gammas = 'horseshoe'`.
- `B_nu_alphas` the prior rate parameter of the gamma prior for the variance hyperparameter for the precision parameter of the local penalty term for the association parameters. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `A_xi_alphas` the prior shape parameter of the gamma prior for the variance hyperparameter for the precision parameter of the global penalty term for the association parameters. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `B_xi_alphas` the prior rate parameter of the gamma prior for the variance hyperparameter for the precision parameter of the global penalty term for the association parameters. Only relevant when `penalty_gammas = 'ridge'` or when `penalty_gammas = 'horseshoe'`.
- `gamma_prior_D_sds` logical; if TRUE, a gamma prior will be used for the standard deviations of the D matrix (variance-covariance matrix of the random effects). Defaults to TRUE
- `D_sds_df` the prior degrees of freedom parameter for the half-t prior for the standard deviations of the D matrix (variance-covariance matrix of the random effects).
- `D_sds_sigma` the prior sigma parameter vector for the half-t prior for the standard deviations of the D matrix (variance-covariance matrix of the random effects).
- `D_sds_shape` the prior shape parameter for the gamma prior for the standard deviations of the D matrix (variance-covariance matrix of the random effects).
- `D_sds_mean` the prior mean parameter vector for the gamma prior for the standard deviations of the D matrix (variance-covariance matrix of the random effects).

| | | |
|-----------|----------------------|--|
| | D_L_etaLKJ | the prior eta parameter for the LKJ prior for the correlation matrix of the random effects. |
| | sigmas_df | the prior degrees of freedom parameter for the half-t prior for the error term(s). |
| | sigmas_sigma | the prior sigma parameter for the half-t prior for the error term(s). |
| control | | a list of control values with components: |
| | GK_k | the number of quadrature points for the Gauss Kronrod rule; options 15 and 7. |
| | Bsplines_degree | the degree of the splines in each basis; default quadratic splines. |
| | base_hazard_segments | the number of segments to split the follow-up period. Defaults to 10. |
| | diff | the order of the difference used in the penalty matrix for the B-splines for h_0. Defaults to 2. |
| | n_chains | an integer specifying the number of chains for the MCMC. Defaults to 3. |
| | n_burnin | an integer specifying the number of burn-in iterations. Defaults to 500. |
| | n_iter | an integer specifying the number of total iterations per chain. Defaults to 3500. |
| | n_thin | an integer specifying the thinning of the chains. Defaults to 1. |
| | seed | the seed used in the sampling procedures. Defaults to 123. |
| | MALA | a logical; if TRUE, the MALA algorithm is used when updating the elements of the Cholesky factor of the D matrix. Defaults to FALSE. |
| | save_random_effects | a logical; if TRUE, the full MCMC results of the random effects will be saved and returned with the jm object. Defaults to FALSE. |
| | cores | an integer specifying the number of cores to use. Defaults to the available cores minus one. |
| x | | a numeric input variable. |
| knots | | a numeric vector of knots. |
| ord | | an integer denoting the order of the spline. |
| eps | | numeric scalar denoting the step-size for the finite difference approximation. |
| direction | | character string for the direction of the numerical derivative, options are "both", and "backward". |
| ... | | arguments passed to control. |

Details

The mathematical details regarding the definition of the multivariate joint model, and the capabilities of the package can be found in the vignette in the doc directory.

Value

A list of class `jm` with components:

| | |
|-----------------------------|--|
| <code>mcmc</code> | a list of the MCMC samples for each parameter. |
| <code>acc_rates</code> | a list of the acceptance rates for each parameter. |
| <code>logLik</code> | a matrix of dimensions $[(n_iter - n_burnin)/n_thin] * n_thin$, number of individuals], with element $[i, j]$ being the conditional log-Likelihood value of the i^{th} iteration for the j^{th} individual. |
| <code>mlogLik</code> | a matrix of dimensions $[(n_iter - n_burnin)/n_thin] * n_thin$, number of individuals], with element $[i, j]$ being the marginal log-Likelihood value of the i^{th} iteration for the j^{th} individual. |
| <code>running_time</code> | an object of class <code>proc_time</code> with the time used to run <code>jm</code> . |
| <code>statistics</code> | a list with posterior estimates of the parameters (means, medians, standard deviations, standard errors, effective sample sizes, tail probabilities, upper and lower bounds of credible intervals, etc.). |
| <code>fit_stats</code> | a list of lists with fit statistics (DIC, pD, LPML, CPO, WAIC) for both conditional and marginal formulations. |
| <code>model_data</code> | a list of data used to fit the model. |
| <code>model_info</code> | a list of components of the fit useful to other functions. |
| <code>initial_values</code> | a list with the initial values of the parameters. |
| <code>control</code> | a copy of the control values used to fit the model. |
| <code>priors</code> | a copy of the priors used to fit the model. |
| <code>call</code> | the matched call. |

Author(s)

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See Also

[methods.jm](#), [coda_methods.jm](#)

Examples

```
#####

#####
# Univariate joint model for serum bilirubin #
# 1 continuous outcome                       #
#####

# [1] Fit the mixed model using lme().
fm1 <- lme(fixed = log(serBilir) ~ year * sex + I(year^2) +
           age + prothrombin, random = ~ year | id, data = pbc2)
```

```

# [2] Fit a Cox model, specifying the baseline covariates to be included in the
# joint model.
fCox1 <- coxph(Surv(years, status2) ~ drug + age, data = pbc2.id)

# [3] The basic joint model is fitted using a call to jm() i.e.,
joint_model_fit_1 <- jm(fCox1, fm1, time_var = "year",
  n_chains = 1L, n_iter = 11000L, n_burnin = 1000L)
summary(joint_model_fit_1)
traceplot(joint_model_fit_1)

#####

#####
# Multivariate joint model for serum bilirubin, hepatomegaly and ascites #
# 1 continuous outcome, 2 categorical outcomes #
#####

# [1] Fit the mixed-effects models using lme() for continuous
# outcomes and mixed_model() for categorical outcomes.
fm1 <- lme(fixed = log(serBilir) ~ year * sex,
  random = ~ year | id, data = pbc2)

fm2 <- mixed_model(hepatomegaly ~ sex + age + year, data = pbc2,
  random = ~ year | id, family = binomial())

fm3 <- mixed_model(ascites ~ year + age, data = pbc2,
  random = ~ year | id, family = binomial())

# [2] Save all the fitted mixed-effects models in a list.
Mixed <- list(fm1, fm2, fm3)

# [3] Fit a Cox model, specifying the baseline covariates to be included in the
# joint model.
fCox1 <- coxph(Surv(years, status2) ~ drug + age, data = pbc2.id)

# [4] The joint model is fitted using a call to jm() i.e.,
joint_model_fit_2 <- jm(fCox1, Mixed, time_var = "year",
  n_chains = 1L, n_iter = 11000L, n_burnin = 1000L)
summary(joint_model_fit_2)
traceplot(joint_model_fit_2)

#####

#####
# Slope & Area Terms #
#####

# We extend model 'joint_model_fit_2' by including the value and slope term for
# bilirubin, the area term for hepatomegaly (in the log-odds scale), and the
# value and area term for spiders (in the log-odds scale).
# To include these terms into the model, we specify the 'functional_forms'
# argument. This should be a list of right side formulas. Each component of the
# list should have as name the name of the corresponding outcome variable. In

```

```

# the right side formula we specify the functional form of the association using
# functions 'value()', 'slope()' and 'area()'.
# Notes: (1) For terms not specified in the 'functional_forms' list, the default
# value functional form is used.

# [1] Fit the mixed-effects models using lme() for continuous outcomes
# and mixed_model() for categorical outcomes.
fm1 <- lme(fixed = log(serBilir) ~ year * sex, random = ~ year | id, data = pbc2)

fm2 <- mixed_model(hepatomegaly ~ sex + age + year, data = pbc2,
                  random = ~ year | id, family = binomial())

fm3 <- mixed_model(ascites ~ year + age, data = pbc2,
                  random = ~ year | id, family = binomial())

# [2] Save all the fitted mixed-effects models in a list.
Mixed <- list(fm1, fm2, fm3)

# [3] Fit a Cox model, specifying the baseline covariates to be included in the
# joint model.
fCox1 <- coxph(Surv(years, status2) ~ drug + age, data = pbc2.id)

# [4] Specify the list of formulas to be passed to the functional_forms argument
# of jm().
fForms <- list("log(serBilir)" = ~ value(log(serBilir)) + slope(log(serBilir)),
              "hepatomegaly" = ~ area(hepatomegaly),
              "ascites" = ~ value(ascites) + area(ascites))

# [5] The joint model is fitted using a call to jm() and passing the list
# to the functional_forms argument.
joint_model_fit_2 <- jm(fCox1, Mixed, time_var = "year",
                      functional_forms = fForms, n_chains = 1L,
                      n_iter = 11000L, n_burnin = 1000L)
summary(joint_model_fit_2)

```

Description

Methods for an object of class "jm" for diagnostic functions.

Usage

```
traceplot(object, ...)
```

```
## S3 method for class 'jm'
```

```
traceplot(object,
  parm = c("all", "betas", "sigmas", "D", "bs_gammas",
    "tau_bs_gammas", "gammas", "alphas"), ...)

ggtraceplot(object, ...)

## S3 method for class 'jm'
ggtraceplot(object,
  parm = c("all", "betas", "sigmas", "D", "bs_gammas",
    "tau_bs_gammas", "gammas", "alphas"),
  size = 1, alpha = 0.8,
  theme = c('standard', 'catalog', 'metro',
    'pastel', 'beach', 'moonlight', 'goo', 'sunset', 'custom'),
  grid = FALSE, gridrows = 3, gridcols = 1, custom_theme = NULL, ...)

gelman_diag(object, ...)

## S3 method for class 'jm'
gelman_diag(object,
  parm = c("all", "betas", "sigmas", "D", "bs_gammas",
    "tau_bs_gammas", "gammas", "alphas"), ...)

densplot(object, ...)

## S3 method for class 'jm'
densplot(object,
  parm = c("all", "betas", "sigmas", "D", "bs_gammas",
    "tau_bs_gammas", "gammas", "alphas"), ...)

ggdensityplot(object, ...)

## S3 method for class 'jm'
ggdensityplot(object,
  parm = c("all", "betas", "sigmas", "D", "bs_gammas",
    "tau_bs_gammas", "gammas", "alphas"),
  size = 1, alpha = 0.6,
  theme = c('standard', 'catalog', 'metro', 'pastel',
    'beach', 'moonlight', 'goo', 'sunset', 'custom'),
  grid = FALSE, gridrows = 3, gridcols = 1, custom_theme = NULL, ...)

cumuplot(object, ...)

## S3 method for class 'jm'
cumuplot(object,
  parm = c("all", "betas", "sigmas", "D", "bs_gammas",
    "tau_bs_gammas", "gammas", "alphas"), ...)
```

Arguments

| | |
|--------------|---|
| object | an object inheriting from class "jm". |
| parm | a character string specifying which parameters of the joint model to plot. Possible options are 'all', 'betas', 'alphas', 'sigmas', 'D', 'bs_gammas', 'tau_bs_gammas', or 'gammas'. |
| size | the width of the traceplot line in mm. Defaults to 1. |
| alpha | the opacity level of the traceplot line. Defaults to 0.8. |
| theme | a character string specifying the color theme to be used. Possible options are 'standard', 'catalog', 'metro', 'pastel', 'beach', 'moonlight', 'goo', or 'sunset'. Note that this option supports fitted objects with three chains. If the object was fitted using a different number of chains then the colors are either automatically chosen, or can be specified by the user via the argument custom_theme. |
| grid | logical; defaults to FALSE. If TRUE, the plots are returned in grids split over multiple pages. For more details see the documentation for gridExtra::marrangeGrob() . |
| gridrows | number of rows per page for the grid. Only relevant when using grid = TRUE. Defaults to 3. |
| gridcols | number of columns per page for the grid. Only relevant when using grid = TRUE. Defaults to 1. |
| custom_theme | A named character vector with elements equal to the number of chains (n_chains). The name of each element should be the number corresponding to the respective chain. Defaults to NULL. |
| ... | further arguments passed to the corresponding function from the coda package. |

Value

traceplot() Plots the evolution of the estimated parameter vs. iterations in a fitted joint model.

ggtraceplot() Plots the evolution of the estimated parameter vs. iterations in a fitted joint model using **ggplot2**.

gelman_diag() Calculates the potential scale reduction factor for the estimated parameters in a fitted joint model, together with the upper confidence limits.

densplot() Plots the density estimate for the estimated parameters in a fitted joint model.

ggdensityplot() Plots the evolution of the estimated parameter vs. iterations in a fitted joint model using **ggplot2**.

cumuplot() Plots the evolution of the sample quantiles vs. iterations in a fitted joint model.

Author(s)

Dimitris Rizopoulos <d.rizopoulos@erasmusmc.nl>

See Also[jm](#)**Examples**

```
# linear mixed model fits
fit_lme1 <- lme(log(serBilir) ~ year:sex + age,
              random = ~ year | id, data = pbc2)

fit_lme2 <- lme(prothrombin ~ sex,
              random = ~ year | id, data = pbc2)

# cox model fit
fit_cox <- coxph(Surv(years, status2) ~ age, data = pbc2.id)

# joint model fit
fit_jm <- jm(fit_cox, list(fit_lme1, fit_lme2), time_var = "year", n_chains = 1L)

# trace plot for the fixed effects in the linear mixed submodels
traceplot(fit_jm, parm = "betas")

# density plot for the fixed effects in the linear mixed submodels
densplot(fit_jm, parm = "betas")

# cumulative quantile plot for the fixed effects in the linear mixed submodels
cumuplot(fit_jm, parm = "betas")

# trace plot for the fixed effects in the linear mixed submodels
ggtraceplot(fit_jm, parm = "betas")
ggtraceplot(fit_jm, parm = "betas", grid = TRUE)
ggtraceplot(fit_jm, parm = "betas", custom_theme = c('1' = 'black'))

# trace plot for the fixed effects in the linear mixed submodels
ggdensityplot(fit_jm, parm = "betas")
ggdensityplot(fit_jm, parm = "betas", grid = TRUE)
ggdensityplot(fit_jm, parm = "betas", custom_theme = c('1' = 'black'))
```

Description

Methods for object of class "jm" for standard generic functions.

Usage

```

coef(object, ...)

## S3 method for class 'jm'
coef(object, ...)

fixef(object, ...)

## S3 method for class 'jm'
fixef(object, outcome = Inf, ...)

ranef(object, ...)

## S3 method for class 'jm'
ranef(object, outcome = Inf, post_vars = FALSE, ...)

terms(x, ...)

## S3 method for class 'jm'
terms(x, process = c("longitudinal", "event"),
      type = c("fixed", "random"), ...)

model.frame(formula, ...)

## S3 method for class 'jm'
model.frame(formula, process = c("longitudinal", "event"),
            type = c("fixed", "random"), ...)

model.matrix(object, ...)

## S3 method for class 'jm'
model.matrix(object, ...)

family(object, ...)

## S3 method for class 'jm'
family(object, ...)

compare_jm(..., type = c("marginal", "conditional"),
           order = c("WAIC", "DIC", "LPML", "none"))

```

Arguments

object, x, formula object inheriting from class "jm".

outcome the index of the linear mixed submodel to extract the estimated fixed effects. If

| | |
|-----------|--|
| | greater than the total number of submodels, extracts from all of them. |
| post_vars | logical; if TRUE, returns the variance of the posterior distribution. |
| process | which submodel(s) to extract the terms: <ul style="list-style-type: none"> • if "longitudinal", the linear mixed model(s), or • if "event", the survival model. |
| type | in terms() and model.frame(), which effects to select in the longitudinal process: <ul style="list-style-type: none"> • if "fixed", the fixed-effects, or • if "random", the random-effects. in compare_jm(), which log-likelihood function use to calculate the criteria: <ul style="list-style-type: none"> • if "marginal", the marginal log-likelihood, or • if "conditional", the conditional log-likelihood. |
| ... | further arguments; currently, none is used. in compare_jm(), a series of jm objects. |
| order | which criteria use to sort the models in the output. |

Details

coef() Extracts estimated fixed effects for the event process from a fitted joint model.

fixef() Extracts estimated fixed effects for the longitudinal processes from a fitted joint model.

ranef() Extracts estimated random effects from a fitted joint model.

terms() Extracts the terms object(s) from a fitted joint model.

model.frame() Creates the model frame from a fitted joint model.

model.matrix() Creates the design matrices for linear mixed submodels from a fitted joint model.

family() Extracts the error distribution and link function used in the linear mixed submodel(s) from a fitted joint model.

compare_jm() Compares two or more fitted joint models using the criteria WAIC, DIC, and LPML.

Value

coef() a list with the elements:

- gammas: estimated baseline fixed effects, and
- association: estimated association parameters.

fixef() a numeric vector of the estimated fixed effects for the outcome selected. If the outcome is greater than the number of linear mixed submodels, it returns a list of numeric vectors for all outcomes.

ranef() a numeric matrix with rows denoting the individuals and columns the random effects. If postVar = TRUE, the numeric matrix has the extra attribute "postVar".

`terms()` if `process = "longitudinal"`, a list of the terms object(s) for the linear mixed model(s).
 if `process = "event"`, the terms object for the survival model.
`model.frame()` if `process = "longitudinal"`, a list of the model frames used in the linear mixed model(s).
 if `process = "event"`, the model frame used in the survival model.
`model.matrix()` a list of the design matrix(ces) for the linear mixed submodel(s).
`family()` a list of family objects.
`compare_jm()` a list with the elements:

- `table`: a table with the criteria calculated for each joint model, and
- `type`: the log-likelihood function used to calculate the criteria.

Author(s)

Dimitris Rizopoulos <d.rizopoulos@erasmusmc.nl>

See Also

[jm](#)

Examples

```

# linear mixed model fits
fit_lme1 <- lme(log(serBilir) ~ year:sex + age,
               random = ~ year | id, data = pbc2)

fit_lme2 <- lme(prothrombin ~ sex,
               random = ~ year | id, data = pbc2)

# cox model fit
fit_cox <- coxph(Surv(years, status2) ~ age, data = pbc2.id)

# joint model fit
fit_jm <- jm(fit_cox, list(fit_lme1, fit_lme2), time_var = "year",
            n_chains = 1L, n_iter = 11000L, n_burnin = 1000L)

# coef(): fixed effects for the event process
coef(fit_jm)

# fixef(): fixed effects for the first linear mixed submodel
fixef(fit_jm, outcome = 1)

# ranef(): random effects from all linear mixed submodels
head(ranef(fit_jm))

# terms(): random effects terms for the first linear mixed submodel
terms(fit_jm, process = "longitudinal", type = "random")[[1]]

# mode.frame(): model frame for the fixed effects in the second

```

```
# linear mixed submodel
head(model.frame(fit_jm, process = "longitudinal", type = "fixed")[[2]])

# model.matrix(): fixed effects design matrix for the first linear
# mixed submodel
head(model.matrix(fit_jm)[[1]])

# family(): family objects from both linear mixed submodels
family(fit_jm)

# compare_jm(): compare two fitted joint models
fit_lme1b <- lme(log(serBilir) ~ 1,
                random = ~ year | id, data = pbc2)

fit_jm2 <- jm(fit_cox, list(fit_lme1b, fit_lme2), time_var = "year",
             n_chains = 1L, n_iter = 11000L, n_burnin = 1000L)

compare_jm(fit_jm, fit_jm2)
```

JMbayes2

Extended Joint Models for Longitudinal and Time-to-Event Data

Description

Fit joint models for longitudinal and time-to-event data under the Bayesian approach. Multiple longitudinal outcomes of mixed type (continuous/categorical) and multiple event times (competing risks and multi-state processes) are accommodated.

Details

Package: JMbayes2
Type: Package
Version: 0.2-0
Date: 2021-02-10
License: GPL (>=3)

This package fits joint models for longitudinal and time-to-event data. It can accommodate multiple longitudinal outcomes of different type (e.g., continuous, dichotomous, ordinal, counts), and assuming different distributions, i.e., Gaussian, Student's-t, Gamma, Beta, unit Lindley, censored Normal, Binomial, Poisson, Negative Binomial, and Beta-Binomial. For the event time process, right, left and interval censored data can be handled, while competing risks and multi-state processes are also covered.

JMbayes2 fits joint models using Markov chain Monte Carlo algorithms implemented in C++. The package also offers several utility functions that can extract useful information from fitted joint models. The most important of those are included in the **See also** Section below.

Author(s)

Dimitris Rizopoulos, Grigorios Papageorgiou, Pedro Miranda Afonso
 Maintainer: Dimitris Rizopoulos <d.rizopoulos@erasmusmc.nl>

References

Rizopoulos, D. (2012). Joint Models for Longitudinal and Time-to-Event Data With Applications in R. Boca Raton: Chapman & Hall/CRC.

See Also

[jm](#), [methods.jm](#), [coda_methods.jm](#)

pbc2

Mayo Clinic Primary Biliary Cirrhosis Data

Description

Follow up of 312 randomised patients with primary biliary cirrhosis, a rare autoimmune liver disease, at Mayo Clinic.

Format

A data frame with 1945 observations on the following 20 variables.

`id` patients identifier; in total there are 312 patients.

`years` number of years between registration and the earlier of death, transplantation, or study analysis time.

`status` a factor with levels `alive`, `transplanted` and `dead`.

`drug` a factor with levels `placebo` and `D-penicil`.

`age` at registration in years.

`sex` a factor with levels `male` and `female`.

`year` number of years between enrollment and this visit date, remaining values on the line of data refer to this visit.

`ascites` a factor with levels `No` and `Yes`.

`hepatomegaly` a factor with levels `No` and `Yes`.

`spiders` a factor with levels `No` and `Yes`.

`edema` a factor with levels `No edema` (i.e., no edema and no diuretic therapy for edema), `edema no diuretics` (i.e., edema present without diuretics, or edema resolved by diuretics), and `edema despite diuretics` (i.e., edema despite diuretic therapy).

`serBilir` serum bilirubin in mg/dl.

`serChol` serum cholesterol in mg/dl.

`albumin` albumin in g/dl.

alkaline alkaline phosphatase in U/liter.
 SGOT SGOT in U/ml.
 platelets platelets per cubic ml / 1000.
 prothrombin prothrombin time in seconds.
 histologic histologic stage of disease.
 status2 a numeric vector with the value 1 denoting if the patient was dead, and 0 if the patient was alive or transplanted.

Note

The data frame `pb2.id` contains the first measurement for each patient. This data frame is used to fit the survival model.

References

Fleming, T. and Harrington, D. (1991) *Counting Processes and Survival Analysis*. Wiley, New York.
 Therneau, T. and Grambsch, P. (2000) *Modeling Survival Data: Extending the Cox Model*. Springer-Verlag, New York.

 Predictions

Predictions from Joint Models

Description

Predict method for object of class "jm".

Usage

```
## S3 method for class 'jm'
predict(object, newdata = NULL, newdata2 = NULL, times = NULL,
  process = c("longitudinal", "event"),
  type_pred = c("response", "link"),
  type = c("subject_specific", "mean_subject"),
  level = 0.95, return_newdata = FALSE, return_mcmc = FALSE,
  n_samples = 200L, n_mcmc = 55L, cores = NULL, seed = 123L,
  ...)

## S3 method for class 'predict_jm'
plot(x, x2 = NULL, subject = 1, outcomes = 1,
  fun_long = NULL, fun_event = NULL, CI_long = TRUE, CI_event = TRUE,
  xlab = "Follow-up Time", ylab_long = NULL, ylab_event = "Cumulative Risk",
  main = "", lwd_long = 2, lwd_event = 2, ylim_long_outcome_range = TRUE,
  col_line_long = "#0000FF",
```

```
col_line_event = c("#FF0000", "#03BF3D", "#8000FF"), pch_points = 16,
col_points = "blue", cex_points = 1, fill_CI_long = "#0000FF4D",
fill_CI_event = c("#FF00004D", "#03BF3D4D", "#8000FF4D"), cex_xlab = 1,
cex_ylab_long = 1, cex_ylab_event = 1, cex_main = 1, cex_axis = 1,
col_axis = "black", pos_ylab_long = c(0.1, 2, 0.08), bg = "white",
...)
```

Arguments

| | |
|---------------------|--|
| object | an object inheriting from class "jm". |
| newdata, newdata2 | data.frames. |
| times | a numeric vector of future times to calculate predictions. |
| process | for which process to calculation predictions, for the longitudinal outcomes or the event times. |
| type_pred | type of predictions; options are "response" using the inverse link function in GLMMs, and "link" that correspond to the linear predictor. |
| type | level of predictions; only relevant when type_pred = "longitudinal". Option type = "subject_specific" combines the fixed- and random-effects parts, whereas type = "mean_subject" uses only the fixed effects. |
| level | the level of the credible interval. |
| return_newdata | logical; should predict() return the predictions as extra columns in newdata and newdata2. |
| return_mcmc | logical; if TRUE the mcmc sample for the predictions is returned. It can be TRUE only in conjunction with return_newdata being FALSE. |
| n_samples | the number of samples to use from the original MCMC sample of object. |
| n_mcmc | the number of Metropolis-Hastings iterations for sampling the random effects per iteration of n_samples; only the last iteration is retained. |
| cores | how many number of cores to use. If there more than 20 subjects in newdata, parallel computing is invoked with four cores by default. |
| seed | an integer denoting the seed. |
| x, x2 | objects returned by predict.jm() with argument return_data set to TRUE. |
| subject | when multiple subjects are included in the data.frames x and x2, it selects which one to plot. Only a single subject can be plotted each time. |
| outcomes | when multiple longitudinal outcomes are included in the data.frames x and x2, it selects which ones to plot. A maximum of three outcomes can be plotted each time. |
| fun_long, fun_event | function to apply to the predictions for the longitudinal and event outcomes, respectively. When multiple longitudinal outcomes are plotted, fun_long can be a list of functions; see examples below. |
| CI_long, CI_event | logical; should credible interval areas be plotted. |

`xlab`, `ylab_long`, `ylab_event`
 character strings or a character vector for `ylab_long` when multiple longitudinal outcomes are considered with the labels for the horizontal axis, and the two vertical axes.

`lwd_long`, `lwd_event`, `col_line_long`, `col_line_event`, `main`, `fill_CI_long`, `fill_CI_event`, `cex_xlab`, `cex_yl`
 graphical parameters; see `par`.

`pos_ylab_long` controls the position of the y-axis labels when multiple longitudinal outcomes are plotted.

`ylim_long_outcome_range`
 logical; if TRUE, the range of the y-axis spans across the range of the outcome in the data used to fit the model; not only the range of values of the specific subject being plotted.

... extra arguments; currently none is used.

Details

A detailed description of the methodology behind these predictions is given here: https://drizopoulos.github.io/JMbayes2/articles/Dynamic_Predictions.html.

Value

Method `predict()` returns a list or a data.frame (if `return_newdata` was set to TRUE) with the predictions.

Method `plot()` produces figures of the predictions from a single subject.

Author(s)

Dimitris Rizopoulos <d.rizopoulos@erasmusmc.nl>

See Also

[jm](#)

Examples

```
# We fit a multivariate joint model
pbc2.id$status2 <- as.numeric(pbc2.id$status != 'alive')
CoxFit <- coxph(Surv(years, status2) ~ sex, data = pbc2.id)
fm1 <- lme(log(serBilir) ~ ns(year, 3) * sex, data = pbc2,
          random = ~ ns(year, 3) | id, control = lmeControl(opt = 'optim'))
fm2 <- lme(prothrombin ~ ns(year, 2) * sex, data = pbc2,
          random = ~ ns(year, 2) | id, control = lmeControl(opt = 'optim'))
fm3 <- mixed_model(ascites ~ year * sex, data = pbc2,
                  random = ~ year | id, family = binomial())

jointFit <- jm(CoxFit, list(fm1, fm2, fm3), time_var = "year", n_chains = 1L)

# we select the subject for whom we want to calculate predictions
# we use measurements up to follow-up year 3; we also set that the patients
```

```

# were alive up to this time point
t0 <- 3
ND <- pbc2[dbc2$id %in% c(2, 25), ]
ND <- ND[ND$year < t0, ]
ND$status2 <- 0
ND$years <- t0

# predictions for the longitudinal outcomes using newdata
predLong1 <- predict(jointFit, newdata = ND, return_newdata = TRUE)

# predictions for the longitudinal outcomes at future time points
# from year 3 to 10
predLong2 <- predict(jointFit, newdata = ND,
                    times = seq(t0, 10, length.out = 51),
                    return_newdata = TRUE)

# predictions for the event outcome at future time points
# from year 3 to 10
predSurv <- predict(jointFit, newdata = ND, process = "event",
                  times = seq(t0, 10, length.out = 51),
                  return_newdata = TRUE)

plot(predLong1)
# for subject 25, outcomes in reverse order
plot(predLong2, outcomes = 3:1, subject = 25)

# prediction for the event outcome
plot(predSurv)

# combined into one plot, the first longitudinal outcome and cumulative risk
plot(predLong2, predSurv, outcomes = 1)

# the first two longitudinal outcomes
plot(predLong1, predSurv, outcomes = 1:2)

# all three longitudinal outcomes, we display survival probabilities instead
# of cumulative risk, and we transform serum bilirubin to the original scale
plot(predLong2, predSurv, outcomes = 1:3, fun_event = function(x) 1 - x,
     fun_long = list(exp, identity, identity),
     ylab_event = "Survival Probabilities",
     ylab_long = c("Serum Bilirubin", "Prothrombin", "Ascites"),
     pos_ylab_long = c(1.9, 1.9, 0.08))

```

prothro

Prednisone versus Placebo in Liver Cirrhosis Patients

Description

A randomized trial on 488 liver cirrhosis patients.

Format

Two data frames with the following variables.

id patients identifier; in total there are 467 patients.

pro prothrombin measurements.

time for data frame prothro the time points at which the prothrombin measurements were taken;
for data frame prothros the time to death or censoring.

death a numeric vector with 0 denoting censoring and 1 death.

treat randomized treatment; a factor with levels "placebo" and "prednisone".

Source

<http://www.gllamm.org/books/readme.html#14.6>.

References

Andersen, P. K., Borgan, O., Gill, R. D. and Keiding, N. (1993). *Statistical Models Based on Counting Processes*. New York: Springer.

rc_setup

Combine Recurring and Terminal Event Data in Long Format

Description

This function combines two data frames, the recurring event and terminal event datasets, into one. Each subject has as many rows in the new data frame as the number of recurrent risk periods plus one for the terminal event.

Usage

```
rc_setup(rc_data, trm_data,
         rc_idVar = "id", rc_statusVar = "status",
         rc_startVar = "start", rc_stopVar = "stop",
         trm_idVar = "id", trm_statusVar = "status",
         trm_stopVar = "stop",
         nameStrata = "strata", nameStatus = "status")
```

Arguments

| | |
|--------------|---|
| rc_data | the data frame containing the recurring event data with multiple rows per subject. |
| trm_data | the data frame containing the terminal event data with a single row per subject. |
| rc_idVar | a character string denoting the name of the variable in rc_data that identifies the subject. |
| rc_statusVar | a character string denoting the name of the variable in rc_data that identifies the status variable which equals 1 if the subject had an event and 0 otherwise. |

| | |
|----------------------------|--|
| <code>rc_startVar</code> | a character string denoting the name of the variable in <code>rc_data</code> that identifies the starting time for the interval. |
| <code>rc_stopVar</code> | a character string denoting the name of the variable in <code>rc_data</code> that identifies the stopping time for the interval. |
| <code>trm_idVar</code> | a character string denoting the name of the variable in <code>trm_data</code> that identifies the subject. |
| <code>trm_statusVar</code> | a character string denoting the name of the variable in <code>trm_data</code> that identifies the status variable which equals 1 if the subject had the event and 0 otherwise. |
| <code>trm_stopVar</code> | a character string denoting the name of the variable in <code>trm_data</code> that identifies the follow up time. |
| <code>nameStrata</code> | a character string denoting the variable that will be added in the long version of data denoting the various causes of event. |
| <code>nameStatus</code> | a character string denoting the variable that will be added in the long version of data denoting if the subject had an event. |

Value

A data frame in the long format with multiple rows per subject.

Author(s)

Pedro Miranda Afonso <p.mirandaafonso@erasmusmc.nl>

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