# Package 'reda'

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<b>Description</b> Functions that fit gamma frailty model with spline or piecewise constant baseline rate function for recurrent event data, compute and plot parametric mean cumulative function (MCF) from a fitted model as well as nonparametric sample MCF (Nelson-Aalen estimator) are provided. Most functions are S4 methods that produce S4 class objects.
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## **Description**

The package reda mainly provides function rateReg to fit parametric gamma frailty model with spline or piecewise constant baseline rate function. Another main function mcf computes and plots the parametric mean cumulative function (MCF) from a fitted model as well as the nonparametric sample MCF (Nelson-Aelson estimator) for recurrent event data.

## **Details**

See vignettes for introduction and demonstration.

AIC, rateReg-method

Akaike Information Criterion (AIC)

## **Description**

AIC, rateReg-method is an S4 class method calculating Akaike information criterion (AIC) for one or several rateReg-class objects, according to the formula - 2 \* log-likelihood + 2 \* nPar, where nPar represents the number of parameters in the fitted model.

## Usage

```
## S4 method for signature 'rateReg'
AIC(object, ..., k = 2)
```

## **Arguments**

object	An object used to dispatch a method.
	Optionally more fitted model objects.
k	An optional numeric value used as the penalty per parameter. The default $k = 2$ is the classic AIC.

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#### **Details**

When comparing models fitted by maximum likelihood to the same data, the smaller the AIC, the better the fit. help(AIC, stats) for other details.

#### Value

If just one object is provided, a numeric value representing calculated AIC. If multiple objects are provided, a data frame with rows corresponding to the objects and columns df and AIC, where df means degree of freedom, which is the number of parameters in the fitted model.

#### See Also

 $\verb|rateReg| for model fitting; summary, \verb|rateReg| - method for summary of a fitted model; \verb|BIC|, \verb|rateReg| - method for BIC|. \\$ 

## **Examples**

```
## See examples given in function rateReg.
```

baseRate

Estimated Coefficients of Baseline Rate Function

## **Description**

An S4 class generic function that returns the estimated coefficients of baseline rate function. For rateReg-class object, it returns either coefficients of pieceswise (including one piece) constant rate function or coefficients of B-spline bases.

#### Usage

```
baseRate(object, ...)
## S4 method for signature 'rateReg'
baseRate(object, ...)
```

## **Arguments**

object An object used to dispatch a method.
... Other arguments for future usage.

#### Value

A named numeric vector.

#### Methods (by class)

• rateReg: Extract estiamted coefficients of baseline rate function from rateReg-class object.

#### See Also

rateReg for model fitting; summary, rateReg-method for summary of a fitted model.

BIC,rateReg-method

#### **Examples**

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```
## See examples given in function rateReg.
```

BIC, rateReg-method

Bayesian Information Criterion (BIC)

## **Description**

BIC, rateReg-method is an S4 class method calculating Bayesian information criterion (BIC) or so-called Schwarz's Bayesian criterion (SBC) for one or several rateReg-class objects, according to the formula - 2 \* log-likelihood + ln(nObs) \* nPar, where nPar represents the number of parameters in the fitted model and nObs is the number of observations.

## Usage

```
## S4 method for signature 'rateReg'
BIC(object, ...)
```

## **Arguments**

object An object used to dispatch a method.
... Optionally more fitted model objects.

#### **Details**

When comparing models fitted by maximum likelihood to the same data, the smaller the BIC, the better the fit. help(BIC, stats) for other details.

#### Value

If just one object is provided, a numeric value representing calculated BIC. If multiple objects are provided, a data frame with rows corresponding to the objects and columns df and BIC, where df means degree of freedom, which is the number of parameters in the fitted model.

## See Also

rateReg for model fitting; summary, rateReg-method for summary of a fitted model; AIC, rateReg-method for AIC.

```
## See examples given in function rateReg.
```

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coef,rateReg-method

Estimated Coefficients of Covariates

## **Description**

coef, rateReg-method is a S4 class method that extracts estimated coefficients of covariates from rateReg-class object produced by function rateReg.

## Usage

```
## S4 method for signature 'rateReg'
coef(object, ...)
```

#### **Arguments**

```
object rateReg-class object.
... Other arguments for future usage.
```

#### Value

A named numeric vector.

## See Also

rateReg for model fitting; confint, rateReg-method for confidence intervals for covariate coefficients; summary, rateReg-method for summary of a fitted model.

## **Examples**

```
## See examples given in function rateReg.
```

```
confint,rateReg-method
```

Confidence Intervals for Covariate Coefficients

## **Description**

confint, rateReg-method is a S4 class method for rateReg object, which returns approximate confidence intervals for all or specified covariates.

## Usage

```
## S4 method for signature 'rateReg'
confint(object, parm, level = 0.95, ...)
```

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### **Arguments**

object rateReg-class object. parm A specification of which parameters are to be given confidence intervals, either a vector of numbers or a vector of names. If missing, all parameters are consid-An optional numeric value to specify the confidence level required. By default, level the value is 0.95, which produces 95% confidence intervals.

Other arguments for future usage.

#### **Details**

Under regularity condition (Shao, 2003, Theorem 4.16 and Theorem 4.17, page 287, 290), the approximate confidence intervals are constructed loosely based on Fisher information matrix and estimates of coefficients. See Fu et al. (2014) for details also.

#### Value

A numeric matrix with rownames and colnames.

#### References

Fu, H., Luo, L., & Qu Y. (2014). Hypoglycemic Events Analysis via Recurrent Time-to-Event (HEART) Models. Journal of biopharmaceutical statistics, Epub 2014 Dec 1.

Shao, J. (2003), Mathematical statistics, Springer texts in statistics, New York: Springer, 2nd Edition.

#### See Also

rateReg for model fitting; coef, rateReg-method for point estimates of covariate coefficients; summary, rateReg-method for summary of a fitted model.

## **Examples**

## See examples given in function rateReg.

Mean Cumulative Function (MCF) mcf

## **Description**

An S4 class generic function that estimates mean cumulative function (MCF) from a fitted model or computing the sample nonparametric MCF (also called Nelson-Aalen estimator) from data.

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#### Usage

```
mcf(object, ...)
## S4 method for signature 'formula'
mcf(object, data, subset, na.action, level = 0.95, ...)
## S4 method for signature 'rateReg'
mcf(object, newdata, groupName, groupLevels, level = 0.95,
    na.action, control = list(), ...)
```

#### Arguments

object An object used to dispatch a method.
... Other arguments for future usage.

data An optional data frame, list or environment containing the variables in the model.

If not found in data, the variables are taken from environment (formula), usu-

ally the environment from which the function is called.

subset An optional vector specifying a subset of observations to be used in the fitting

process.

na.action A function that indicates what should the procedure do if the data contains NAs.

The default is set by the na.action setting of options. The "factory-fresh" default is na.omit. Other possible values inlcude na.fail, na.exclude, and

na.pass. help(na.fail) for details.

level An optional numeric value indicating the confidence level required. The default

value is 0.95.

newdata An optional data frame. If specified, the data frame should have the same col-

umn names as the covariate names appearing in the formula of original fitting.

groupName An optional length-one character vector to specify the name for grouping each

unique row in newdata, such as "gender" for "male" and "female". The default

value is "group".

groupLevels An optional character vector to specify the levels for each unique row in newdata,

such as "treatment" and "control". The default values are capital letters starting

from "A".

control An optional list to specify the time grid where the MCF are estimated. The

availble elements of the control list include grid, length.out, from and to. The time grid can be directly specified via element grid. A dense time grid is suggested. Element length.out represents the length of grid points. The dafault value is 1,000. Element from means the starting point of grid with default 0. Element to represents the endpoint of grid with the right boundary knot as default. When grid is missing, the grid will be generated by seq (from package

base) with arguments from, to and length.out.

#### **Details**

For formula object with Survr object as response, the covariate specified at the right hand side of the formula should be either 1 or any one factor variable in the data. The former computes the overall sample MCF. The latter computes the sample MCF for each level of the factor variable specified, respectively. The sample MCF is also called Nelson-Aalen nonparametric estimator (Nelson, 2003) and computed on each time point from sample data. The point estimate of sample MCF at each time point does not assume any particular underlying model. The variance of estimated MCF (ReliaWiki,

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2012) at each time point is estimated and the approximate confidence intervals are provided as well, which are constructed based on the asymptotic normality of log mean cumulative function.

For rateReg-class object, mcf estimates the baseline MCF and its confidence interval at each time grid if argument newdata is not specified. Otherwise, mcf estimates MCF and its confidence interval for the given newdata based on Delta-method.

#### Value

sampleMcf-class or rateRegMcf-class object. Their slots include

- level: Confidence level specified.
- MCF: Mean cumulative function at each time point.
- multiGroup: A logical value indicating whether MCF is estimated for different specified group.
- newdata: Given dataset used to estimate MCF.

For the meaning of other slots, see rateReg.

#### Methods (by class)

- formula: Sample MCF from data.
- rateReg: Estimated MCF from a fitted model.

#### References

Nelson, W. B. (2003). Recurrent events data analysis for product repairs, disease recurrences, and other applications (Vol. 10). SIAM.

ReliaWiki. (2012, March 19). Recurrent Event Data Analysis. Retrieved November 23, 2015, from http://reliawiki.org/index.php/Recurrent\_Event\_Data\_Analysis

#### See Also

rateReg for model fitting; plotMcf for plotting MCF.

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plotMcf Plot Mean Cumulative Function (MCF)	
---	--

#### **Description**

An S4 class generic function dispatched to a certain method to plot mean cumulative function by using ggplot2 plotting system. The plots generated are able to be further customized properly.

## Usage

```
plotMcf(object, conf.int = FALSE, ...)
## S4 method for signature 'sampleMcf'
plotMcf(object, conf.int = FALSE, mark.time = FALSE,
    lty, col, ...)
## S4 method for signature 'rateRegMcf'
plotMcf(object, conf.int = FALSE, lty, col, ...)
```

#### **Arguments**

object	An object used to dispatch a method.
conf.int	A logical value indicating whether to plot confidence interval. The default value is FALSE.
	Other arguments for further usage.
mark.time	A logical value with default FALSE. If TRUE, each censoring time is marked by "+" on the MCF curves. Otherwise, the censoring time would not be marked.
lty	An optional numeric vector indicating line types specified to different groups: $0 = \text{blank}$ , $1 = \text{solid}$ , $2 = \text{dashed}$ , $3 = \text{dotted}$ , $4 = \text{dotdash}$ , $5 = \text{longdash}$ , $6 = \text{twodash}$ .
col	An optional character vector indicating line colors specified to different groups.

#### Value

A ggplot object.

## Methods (by class)

- sampleMcf: Plot sample MCF from data.
- rateRegMcf: Plot estimated MCF from a fitted model.

#### See Also

```
mcf for estimation of MCF; rateReg for model fitting.
```

```
\mbox{\tt \#\#} See examples given in function mcf and rateReg.
```

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rateReg	Fit Recurrent Events Regression Based on Counts and Rate Function

## Description

The default model is the gamma frailty model with one piece constant baseline rate function, which is equivalent to negative binomial regression of the same shape and rate parameter in gamma prior. Spline and piecewise constant baseline rate function can be specified and applied to model fitting instead. rateReg returns the fitted model through a rateReg-class object.

## Usage

```
rateReg(formula, df = NULL, knots = NULL, degree = 0L, data, subset,
  na.action, start = list(), control = list(), contrasts = NULL, ...)
```

## Arguments

formula	Survr object produced by function Survr.
df	An optional nonnegative integer to specify the degree of freedom of baseline rate function. If argument knots or degree are specified, df will be neglected whether it is specified or not.
knots	An optional numeric vector that represents all the internal knots of baseline rate function. The default is NULL, representing no any internal knots.
degree	An optional nonnegative integer to specify the degree of spline bases.
data	An optional data frame, list or environment containing the variables in the model. If not found in data, the variables are taken from environment(formula), usually the environment from which function rateReg is called.
subset	An optional vector specifying a subset of observations to be used in the fitting process.
na.action	A function that indicates what should the procedure do if the data contains NAs. The default is set by the na.action setting of options. The "factory-fresh" default is na.omit. Other possible values inlcude na.fail, na.exclude, and na.pass. help(na.fail) for details.
start	An optional list of starting values for the parameters to be estimated in the model. See more in section details.
control	An optional list of parameters to control the maximization process of negative log likelihood function and adjust the baseline rate function. See more in section details.
contrasts	An optional list, whose entries are values (numeric matrices or character strings naming functions) to be used as replacement values for the contrasts replacement function and whose names are the names of columns of data containing factors. See contrasts.arg of model.matrix.default for details.
	Other arguments for future usage.

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#### **Details**

Function Survr in the formula response first checks the dataset and will report an error if the dataset does not fall into recurrent event data framework. Subject's ID is pinpointed if its observation violates any checking rule. See Survr for all the checking rules.

Function rateReg first constructs the design matrix from the specified arguments: formula, data, subset, na.action and constrasts before model fitting. The constructed design matrix will be checked again to fit the recurrent event data framework if any observation with missing covariates is removed.

The model fitting process involves minimization of negative log likelihood function, which calls function nlm from package **stats** internally. help(nlm) for more details.

The argument start is an optional list that allows users to specify the initial guess for the parameter values for the minimization of negative log likelihood function. The available numeric vector elements in the list include

- beta: Coefficient(s) of covariates, set to be 0.1 by default.
- theta: Parameter of frailty random effect, set to be 0.5 by default.
- alpha: Coefficient(s) of baseline rate function, set to be 0.05 by default.

The argument control is an optional list that allows users to control the process of minimization of negative log likelihood function and to specify the boundary knots, intercept for baseline rate function. The available elements in the list include

- gradtol: A positive scalar giving the tolerance at which the scaled gradient is considered close enough to zero to terminate the algorithm. The default value is 1e-6.
- stepmax: A positive scalar that gives the maximum allowable scaled step length. The default value is 1e5.
- steptol: A positive scalar providing the minimum allowable relative step length. The default value is 1e-6.
- iterlim: A positive integer specifying the maximum number of iterations to be performed before the program is terminated. The default value is 1e2.
- Boundary.knots: A length-two numeric vector to specify the boundary knots for baseline rate funtion. By default, the left boundary knot is zero and the right one takes the largest censoring time from data.
- intercept: A logical value specifying whether intercept is included in spline baseline rate function. For piecewise constatu baseline (df=0), the specified value would be neglected. The default value is TRUE, i.e. the intercept is included.

#### Value

A rateReg-class object, whose slots include

- call: Function call of rateReg.
- formula: Formula used in the model fitting.
- n0bs: Number of observations.
- knots: Internal knots specified for the baseline rate function.
- Boundary.knots: Boundary knots specified for the baseline rate function.
- degree: Degree of spline bases specified in baseline rate function.
- df: Degree of freedom of the model specified.

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• estimates: Estimated coefficients of covariates and baseline rate function, and estimated rate parameter of gamma frailty variable.

- control: The control list specified for model fitting.
- start: The initial guess specified for the parameters to be estimated.
- na.action: The procedure specified to deal with missing values in the covariate.
- xlevels: A list that records the levels in each factor variable.
- contrasts: Contrasts specified and used for each factor variable.
- convergCode: code returned by function nlm, which is an integer indicating why the optimization process terminated. help(nlm) for details.
- logL: Log likelihood of the fitted model.
- fisher: Observed Fisher information matrix.

#### References

Fu, H., Luo, L., & Qu Y. (2014). Hypoglycemic Events Analysis via Recurrent Time-to-Event (HEART) Models. *Journal of biopharmaceutical statistics*, Epub 2014 Dec 1.

#### See Also

summary, rateReg-method for summary of fitted model; coef, rateReg-method for estimated covariate coefficients; confint, rateReg-method for confidence interval of covariate coefficients; baseRate, rateReg-method for estimated coefficients of baseline rate function; mcf, rateReg-method for estimated MCF from a fitted model; plotMcf, rateRegMcf-method for plotting estimated MCF.

```
library(reda)
## constant rate function
constFit <- rateReg(Survr(ID, time, event) ~ group + x1,</pre>
                    data = simuDat, subset = ID %in% 1:50)
## 6 pieces' piecewise constant rate function
piecesFit <- rateReg(Survr(ID, time, event) ~ group + x1,</pre>
                      data = simuDat, subset = ID %in% 1:50,
                      knots = seq(28, 140, by = 28))
## fit rate function with cubic spline
splineFit <- rateReg(Survr(ID, time, event) ~ group + x1,</pre>
                      data = simuDat, subset = ID %in% 1:50,
                      knots = c(56, 84, 112), degree = 3)
## brief summary of fitted models
constFit
piecesFit
splineFit
## more specific summary
summary(constFit)
summary(piecesFit)
summary(splineFit)
## model selection based on AIC or BIC
```

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```
AIC(constFit, piecesFit, splineFit)
BIC(constFit, piecesFit, splineFit)
## estimated covariate coefficients
coef(piecesFit)
coef(splineFit)
## confidence intervals for covariate coefficients
confint(piecesFit)
confint(splineFit, "x1", 0.9)
confint(splineFit, 1, 0.975)
## estimated coefficients for baseline rate function
baseRate(piecesFit)
baseRate(splineFit)
## estimated baseline mean cumulative function (MCF) from a fitted model
piecesMcf <- mcf(piecesFit)</pre>
plotMcf(piecesMcf, conf.int = TRUE, col = "blueviolet") +
    ggplot2::xlab("Days") + ggplot2::theme_bw()
## estimated MCF for given new data
newDat <- data.frame(x1 = rep(0, 2), group = c("Treat", "Contr"))
splineMcf <- mcf(splineFit, newdata = newDat, groupName = "Group",</pre>
                 groupLevels = c("Treatment", "Control"))
plotMcf(splineMcf, conf.int = TRUE, lty = c(1, 5)) +
    ggplot2::xlab("Days") + ggplot2::theme_bw()
```

rateReg-class

An S4 Class to Represent a Fitted Model

#### **Description**

rateReg-class is an S4 class that represents a fitted model. rateReg produces objects of this class. See "Slots" for details.

#### **Slots**

```
call Function call.
formula Formula.
n0bs A positive integer
knots A numeric vector.
Boundary.knots A numeric vector.
degree A nonnegative integer.
df A list of nonnegative numeric vectors.
estimates A list.
control A list.
start A list.
na.action A length-one character vector.
```

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```
xlevels A list.
```

contrasts A list.

convergCode A nonnegative integer.

logL A numeric value.

fisher A numeric matrix.

## See Also

rateReg for details of slots.

rateRegMcf-class

An S4 Class to Respresent Estimated MCF from a Fitted Model

## Description

An S4 class that represents estimated mean cumulative function (MCF) from Models. mcf produces objects of this class.

## **Slots**

call Function call.

formula Formula.

knots A numeric vector.

degree A nonnegative integer.

Boundary.knots A numeric vector.

newdata A numeric matrix.

MCF A data frame.

level A numeric value between 0 and 1.

na.action A length-one character vector.

control A list.

multiGroup A logical value.

## See Also

mcf,rateReg-method for details of slots.

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sampleMcf-class

An S4 Class to Represent Sample MCF

## **Description**

An S4 class that represents sample mean cumulative function (MCF) from data. mcf produces objects of this class.

#### **Slots**

```
call Function call
formula Formula.
na.action A length-one character vector.
level A numeric value.
MCF A data frame.
multiGroup A logical value.
```

#### See Also

mcf, formula-method for details of slots.

show-method

Show an object.

## **Description**

An S4 class generic function that displays certain object.

## Usage

```
## S4 method for signature 'rateReg'
show(object)

## S4 method for signature 'summaryRateReg'
show(object)

## S4 method for signature 'sampleMcf'
show(object)

## S4 method for signature 'rateRegMcf'
show(object)
```

## **Arguments**

object

An object used to dispatch a method.

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#### **Details**

- For rateReg-class object, it prints out brief summary of the fitted model.
- For summaryRateReg-class object, it prints out summary of the fitted model.
- For sampleMcf-class object, it prints out the function call, formula and the sample MCF data frame.
- For rateRegMcf-class object, it prints formula, new data, confidence level, and the estimated MCF data frame.

#### See Also

rateReg for model fitting; summary, rateReg-method for summary of a fitted model; mcf for estimation of MCF.

simuDat

Simulated Sample Dataset for Demonstration

## **Description**

A simulated data frame with covariates named ID, time, event, group and x1, where

- ID: Subjects identification;
- time: Event or censoring time;
- event: Event indicator, 1 = event, 0 = censored;
- group: Treatment group indicator;
- x1: Continuous variable.

#### **Format**

A data frame with 500 rows and 5 variables.

## **Details**

The sample dataset is originally simulated by the thinning method developed by Lewis and Shedler (1979) and further processed for a better demonstration purpose. See Fu et al. (2014) for details also.

#### References

Lewis, P. A., & Shedler, G. S. (1979). Simulation of nonhomogeneous Poisson processes by thinning. *Naval Research Logistics Quarterly*, 26(3), 403–413.

Fu, H., Luo, L., & Qu Y. (2014). Hypoglycemic Events Analysis via Recurrent Time-to-Event (HEART) Models. *Journal of biopharmaceutical statistics*, Epub 2014 Dec 1.

```
summary, rateReg-method
```

Summarizing a Fitted Model

## **Description**

Summary of estimated coefficients of covariates, rate function bases, and estimated rate parameter of frailty random variable, etc., which can be printed out by show.

## Usage

```
## S4 method for signature 'rateReg'
summary(object, showCall = TRUE, showKnots = TRUE, ...)
```

#### **Arguments**

object	rateReg-class object.
showCall	A logic value with dafault TRUE, indicating whether function show prints out the original call information of rateReg. It may be helpful for a more concise printout.
showKnots	A logic value with default TRUE, indicating whether function show prints out the internal and boundary knots. Similar to argument showCall, It may be helpful for a more concise printout.
	Other arguments for future usage.

## **Details**

summary, rateReg-method returns a summaryRateReg-class object, whose slots include

- covarCoef: Estimated covariate coefficients.
- frailtyPar: Estimated rate parameter of gamma frailty.
- baseRateCoef: Estimated coeffcients of baseline rate function.

For the meaning of other slots, see rateReg.

## Value

summaryRateReg-class object

## See Also

rateReg for model fitting; coef, rateReg-method for point estimates of covariate coefficients; confint, rateReg-method for confidence intervals of covariate coefficients; baseRate, rateReg-method for coefficients of baseline rate function.

```
## See examples given in function rateReg.
```

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summaryRateReg-class An S4 Class to Represent Summary of a Fitted Model

## Description

summaryRateReg-class is an S4 class with selective slots of rateReg-class object. See "Slots" for details. summary, rateReg-method produces objects of this class.

## **Slots**

call Function call.

knots A numeric vector.

Boundary.knots A numeric vector.

covarCoef A numeric matrix.

frailtyPar A numeric matrix.

degree A nonnegative integer.

baseRateCoef A numeric matrix.

logL A numeric value.

#### See Also

summary, rateReg-method for details of slots.

Survr

Formula Response for Recurrent Event Data

## Description

Survr is an S3 class that represents formula response for recurrent event data modeled by methods based on counts and rate function. The last letter 'r' in 'Survr' represents 'rate'.

## Usage

```
Survr(ID, time, event)
```

## **Arguments**

ID Identificator of each subject.

time Time of reccurence event or censoring.

event The status indicator, 0 = censored, 1 = event.

#### **Details**

This is a similar function to Survr in package **survrec** but with a better embedded checking procedure for recurrent event data modeled by methods based on counts and rate function. The checking rules include that

- Identification of each subject cannot be missing.
- Event indicator must be coded as 0 (censored) or 1 (event).
- Event time and censoring time cannot be missing.
- Each subject must have one and only one censoring time.
- Event time cannot not be later than censoring time.

## See Also

rateReg for model fitting.

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