# Package 'icenReg'

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Type Package

Title Regression Models for Interval Censored Data

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<b>Author</b> Clifford Anderson-Bergman; the Eigen team for Eigen library included; uses Maarloes Maathius's HeightMap algorithm (MLEcens::reduc)
Depends survival, MLEcens
Imports foreach, methods
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<b>Description</b> Regression models for interval censored data. Currently supports Cox-PH and proportional odds models. Allows for both semi and fully parametric models. Includes functions for easy visual diagnostics of model fits. Includes functions for fitting both the univariate and bivariate NPMLE.
<b>License</b> LGPL (>= 2.0, < 3)
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diag_baseline	Compare baseline	parametric	baseline	distributions	with	semi-parametric

## Description

Creates plots to diagnosis fit of different choices of parametric baseline model. Plots the semi parametric model (which only uses up to max\_n\_use subjects from the dataset for speed) against different choices of parametric models.

## Usage

## **Arguments**

object	Either a formula or a model fit with ic_sp or ic_par
data	data. Unnecessary if object is a fit
model	type of model. Choices are 'ph' or 'po'
dists	parametric baseline fits
max_n_use	maximum number of observations used to fit semi-parametric model
cols	colors of baseline distributions
weights	case weights
lgdLocation	where legend will be placed. See ?legend for more details
useMidCovars	Should the distribution plotted be for covariates = mean values instead of $0$

#### **Details**

If useMidCovars = T, then the survival curves plotted are for fits with the mean covariate value, rather than 0. This is because often the baseline distribution (i.e. with all covariates = 0) will be far away from the majority of the data.

For larger datasets (n > 10,000), the semi-parametric model can be become slow. Because of this, diag\_covar allows the user to select  $\max_n$ use samples from their data to assess the fit of their models.

## Author(s)

Clifford Anderson-Bergman

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#### **Examples**

diag\_covar

Evaluate covariate effect for regression model

#### **Description**

Creates plots to diagnosis fit of covariate effect in a regression model. For a given variable, stratifies the data across different levels of the variable and adjusts for all the other covariates included in fit and then plots a given function to help diagnosis where covariate effect follows model assumption (i.e. either proportional hazards or proportional odds). See details for descriptions of the plots.

If varName is not provided, will attempt to figure out how to divide up each covariate and plot all of them, although this may fail.

## Usage

## **Arguments**

object Either a formula or a model fit with ic\_sp or ic\_par

varName covariate to split data on. If left blank, will split on each covariate

data data. Unnecessary if object is a fit model type of model. Choices are 'ph' or 'po'

weights case weights

yType type of plot created. See details

factorSplit Should covariate be split as a factor (i.e. by levels)

numericCuts If fractorSplit == FALSE, cut points of covariate to stratify data on

col colors of each subgroup plot. If left blank, will auto pick colors

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xlab label of x axis ylab label of y axis main title of plot

max\_n\_use maximum number of observations used to fit semi-parametric model

lgdLocation where legend should be placed. See details

#### **Details**

For the Cox-PH and proportional odds models, there exists a transformation of survival curves such that the difference should be constant for subjects with different covariates. In the case of the Cox-PH, this is the  $\log(-\log(S(t|X)))$  transformation, for the proportional odds, this is the  $\log(S(t|X))$  (1 - S(t|X))) transformation.

The function diag\_covar allows the user to easily use these transformations to diagnosis whether such a model is appropriate. In particular, it takes a single covariate and stratifies the data on different levels of that covariate. Then, it fits the semi-parametric regression model (adjusting for all other covariates in the data set) on each of these stratas and extracts the baseline survival function. If the stratified covariate does follow the regression assumption, the difference between these transformed baseline survival functions should be approximately constant.

To help diagnosis, the default function plotted is the transformed survival functions, with the overall means subtracted off. If the assumption holds true, then the difference between the plotted lines should be approximately constant. Other choices of yType, the function to plot, are "transform", which is the transformed functions without the means subtracted and "survival", which is the baseline survival distribution is plotted for each strata.

Currently does not support stratifying covariates that are involved in an interaction term.

For variables that are factors, it will create a strata for each level of the covariate, up to 20 levels. If factorSplit == FALSE, will divide up numeric covariates according to the cuts provided to numericCuts.

For larger datasets (n > 10,000), the semi-parametric model can become slow. Because of this, diag\_covar allows the user to select  $max_n$ use samples from their data to assess the fit of their models.

lgdLocation is an argument placed to legend dictating where the legend will be placed. If lgdLocation = NULL, will use standard placement given yType. See ?legend for more details.

## Author(s)

Clifford Anderson-Bergman

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essIncData

Interval Censored Income Data from European Social Survey

## Description

Dataset containing a sample from the European Social Survey.

In the European Social Survey, income is reported up a to discrete intervals. Within each country, these intervals are disjoint (i.e. [0, 1k), [1k,2k)...). However, across countries, the intervals are not disjoint and so interval censored methods should be used to compare subjects across different countries.

## Usage

```
data(essIncData)
```

#### **Format**

A data frame with 6712 rows and 4 variables

- cntry Country
- eduLevel Categorical variable for number of years of reported education
- inc\_1 Lower limit of reported income level (in Euros)
- inc\_u Upper limit of reported income level (in Euros)

#### Source

ESS Round 5: European Social Survey Round 5 Data (2010). Data file edition 3.2. Norwegian Social Science Data Services, Norway\- Data Archive and distributor of ESS data.

```
# Not run

# data(essIncData)
#
# lnormFit <- ic_par(Surv(inc_l, inc_u, type = 'interval2') ~ eduLevel * cntry,
# data = essIncData,
# model = 'po',
# dist = 'loglogistic')
#
# summary(lnormFit)</pre>
```

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essIncData\_small

Interval Censored Income Data from European Social Survey

## **Description**

Dataset containing a sample from the European Social Survey. This is a small subsample from the dataset essIncData, used only to run the example very quickly for CRAN. Using the full dataset, running the examples should still be fairly fast; at most a few seconds.

In the European Social Survey, income is reported up a to discrete intervals. Within each country, these intervals are disjoint (i.e. [0, 1k), [1k,2k)...). However, across countries, the intervals are not disjoint and so interval censored methods should be used to compare subjects across different countries.

## Usage

```
data(essIncData_small)
```

#### **Format**

A data frame with 500 rows and 4 variables

- cntry Country
- eduLevel Categorical variable for number of years of reported education
- inc\_1 Lower limit of reported income level (in Euros)
- inc\_u Upper limit of reported income level (in Euros)

#### **Source**

ESS Round 5: European Social Survey Round 5 Data (2010). Data file edition 3.2. Norwegian Social Science Data Services, Norway\- Data Archive and distributor of ESS data.

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Get Estimates from icenReg Regression Model

#### **Description**

Gets estimates from a ic\_par or ic\_sp object. Provided estimates conditional on regression parameters found in newdata.

## Usage

```
getFitEsts(fit, newdata, p, q)
```

### **Arguments**

fit	model fit with ic_par or ic_sp
newdata	data.frame containing covariates
р	percentiles
q	quantiles

#### **Details**

If newdata is left blank, baseline estimates will be returned (i.e. all covariates = 0). If p is provided, will return the estimated  $F^{-1}(p \mid x)$ . If q is provided, will return the estimated  $F(q \mid x)$ . If neither p nor q are provided, the estimated conditional median is returned.

For ic\_par fits, it is worth noting that  $F^{-1}(p \mid x)$  is approximated using R's optimize function, so there may be some numerical error.

In the case of ic\_sp, the MLE of the baseline survival is not necessarily unique, as probability mass is assigned to disjoint Turnbull intervals, but the likelihood function is indifferent to how probability mass is assigned within these intervals. In order to have a well defined estimate returned, we assume probability is assigned uniformly in these intervals. In otherwords, we return \*a\* maximum likelihood estimate, but don't attempt to characterize \*all\* maximum likelihood estimates with this function. If that is desired, all the information needed can be extracted with getSCurves.

#### Author(s)

Clifford Anderson-Bergman

getSCurves

getSCurves	Get Estimated Survival Curves from Semi-parametric Model for Interval Censored Data

#### **Description**

Extracts the estimated survival curve(s) from a ic\_sp model for interval censored data. Output will be a list with two elements: the first item will be \$Tbull\_ints, which is the Turnbull intervals. This is a k x 2 matrix, with the first column being the beginning of the Turnbull interval and the second being the end. This is necessary due to the *representational non-uniqueness*; any survival curve that lies between the survival curves created from the upper and lower limits of the Turnbull intervals will have equal likelihood. See example for proper display of this. The second item is \$S\_curves, or the estimated survival probability at each Turnbull interval for individuals with the covariates provided in newdata. Note that multiple rows may be provided to newdata, which will result in multiple S\_curves.

## Usage

```
getSCurves(fit, newdata)
```

#### **Arguments**

fit model fit with ic\_sp

newdata data.frame containing covariates for which the survival curve will be fit to. Row-

names from newdata will be used to name survival curve. If left blank, baseline

covariates will be used

#### Author(s)

Clifford Anderson-Bergman

```
set.seed(1)
sim_data <- simIC_weib(n = 500, b1 = .3, b2 = -.3,
                      shape = 2, scale = 2,
                      inspections = 6, inspectLength = 1)
fit <- ic_sp(Surv(l, u, type = 'interval2') \sim x1 + x2, data = sim_data, bs_samples = 0)
new_data <- data.frame(x1 = c(0,1), x2 = c(1, 1))
#want to fit survival curves with above covariates
rownames(new_data) <- c('group 1', 'group 2')</pre>
#getSCurves will name the survival curves according to rownames
curveInfo <- getSCurves(fit, new_data)</pre>
xs <- curveInfo$Tbull_ints</pre>
#Extracting Turnbull intervals
sCurves <- curveInfo$S_curves
#Extracting estimated survival curves
plot(xs[,1], sCurves[[1]], xlab = 'time', ylab = 'S(t)',
     type = 's', ylim = c(0,1),
```

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```
xlim = range(as.numeric(xs), finite = TRUE))
#plotting upper survival curve estimate
lines(xs[,2], sCurves[[1]], type = 's')
#plotting lower survival curve estimate
lines(xs[,1], sCurves[[2]], col = 'blue', type = 's')
lines(xs[,2], sCurves[[2]], col = 'blue', type = 's')
#plotting upper and lower survival curves for group 2
# Actually, all this plotting is a unnecessary:
# plot(fit, new_data) will bascially do this all
# But this is more of a tutorial in case custom
# plots were desired
```

**ICNPMLE** 

Computes the NPMLE for Univariate or Bivariate Interval Censored Data

### **Description**

Computes the MLE for a Interval Censored Data with a squeezing EM algorithm (*much* faster than the standard EM). Accepts either univariate interval censored data (where times is an n x 2 matrix with times[,1] being the left side of the interval and times[,2] is the right side), or bivariate interval censored data (where times is an n x 4 matrix with times[,1:2] being left and right side of the interval for event 1 and times[,3:4] being the left and right side of the interval for event 2).

#### Usage

```
ICNPMLE(times, B = c(1,1), max.inner = 100, max.outer = 100, tol = 1e-10)
```

#### **Arguments**

times	either an n x 2 or n x 4 data. frame or matrix of censoring intervals
В	A vector indicating whether each end of the intervals are open (0) or closed (1). Alternatively, this could be an n x 2 or n x 4 matrix of indicators for each individual interval
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max.inner	number of inner loops used in optimization algorithm
max.outer	number of outer loops used in optimization algorithm
tol	numerical tolerance

#### Author(s)

Clifford Anderson-Bergman

Also uses Marloes Maathius's MLEcens::reduc function for calculation of the clique matrix.

#### References

Anderson-Bergman, C., (2014) Semi- and non-parametric methods for interval censored data with shape constraints, Ph.D. Thesis

Yu, Y., (2010), Improved EM for Mixture Proportions with Applications to Nonparametric ML Estimation for Censored Data, *preprint* 

Maathuis, M., (2005). Reduction algorithm for the NPMLE for the distribution function of bivariate interval censored data. *Journal of Computational and Graphical Statistics* Vol 14 pp 252\- 262

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#### **Examples**

```
simData <- simBVCen(500)
fit <- ICNPMLE(simData)
fit</pre>
```

ic\_par

Parametric Regression Models for Interval Censored Data

#### **Description**

Fits a parametric regression model for interval censored data. Can fit either a Cox-PH model or a proportional odds model.

## Usage

```
ic_par(formula, data, model = 'ph', dist = 'weibull', weights = NULL)
```

#### **Arguments**

formula	regression formula. Response must be a Surv object of type 'interval2'
data	dataset
model	What type of model to fit. Current choices are "ph" (Cox PH) or "po" (proportional odds)
dist	What baseline parametric distribution to use. See details for current choices
weights	vector of case weights. Not standardized; see details

#### **Details**

Currently supported distributions choices are "exponential", "weibull", "gamma", "lnorm" and "loglogistic".

Does not allow uncensored data points at t = 0 (i.e. where left side of interval == right side == 0), as this will lead to a degenerate estimator for most parametric families. Unlike the current implementation of survreg, does allow left side of intervals of positive length to 0 and right side to be Inf.

In regards to weights, they are not standardized. This means that if weight[i] = 2, this is the equivalent to having two observations with the same values as subject i.

For numeric stability, if abs(right - left) < 10^-6, observation is considered uncensored rather than interval censored with an extremely small interval.

## Author(s)

Clifford Anderson-Bergman

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#### **Examples**

ic\_sp

Semi-Parametric models for Interval Censored Data

## Description

Fits a semi-parametric model for interval censored data. Can fit either a Cox-PH model or a proportional odds model.

The covariance matrix for the regression coefficients is estimated via bootstrapping. For large datasets, this can become slow so parallel processing can be used to take advantage of multiple cores via the foreach package.

## Usage

```
ic_sp(formula, data, model = 'ph', weights = NULL,
    bs_samples = 0, useMCores = F, seed = NULL,
    useGD = T, maxIter = 500)
```

#### **Arguments**

formula	regression formula. Response must be a Surv object of type 'interval2'
data	dataset
model	What type of model to fit. Current choices are "ph" (Cox PH) or "po" (proportional odds) $$
weights	Vector of case weights. Not standardized; see details
bs_samples	Number of bootstrap samples used for estimation of standard errors
useMCores	Should multiple cores be used for bootstrap sample? Does not register cluster (see example)
seed	Seed for bootstrap. If seed == NULL, a random seed is still used. See details
useGD	Should a gradient ascent step be used in addition to an icm? See details
maxIter	Maximum iterations

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#### **Details**

In regards to weights, they are not standardized. This means that if weight[i] = 2, this is the equivalent to having two observations with the same values as subject i.

It is very important to note that a random seed is \*always\* set if bs\_samples > 0 (via set.seed(seed)), which can create problems in simulation studies if the same seed is set in every call to ic\_sp during a simulation study. If seed == NULL, then the starting seed will be round(runif(0, max = 10^8)), which should be approximately equivalent to not setting a seed.

The algorithm used is inspired by the extended ICM algorithm from Wei Pan 1999. However, it uses a conditional Newton Raphson step and an ICM step, rather than one single ICM step. In addition, a gradient ascent can also be used to update the baseline parameters. This step is necessary if the data contains many uncensored observations, very similar to how the EM algorithm greatly accelerates the ICM algorithm for the NPMLE (gradient ascent is used rather than the EM, as the M step is not in closed form for semi-parametric models). However, if the data contains no uncensored observations, the gradient ascent step is likely to be unhelpful. It also worth noting that for each step of the algorithm, 1 conditional Newton Raphson step, 1 gradient ascent step (if selected) and up to 10 icm steps are taken.

#### Author(s)

Clifford Anderson-Bergman

#### References

Pan, W., (1999), Extending the iterative convex minorant algorithm to the Cox model for intervalcensored data, *Journal of Computational and Graphical Statistics*, Vol 8(1), pp109-120

Wellner, J. A., and Zhan, Y. (1997) A hybrid algorithm for computation of the maximum likelihood estimator from censored data, *Journal of the American Statistical Association*, Vol 92, pp945-959

```
set.seed(1)
sim_data <- simIC_weib(n = 500, inspections = 5, inspectLength = 1)</pre>
ph_fit <- ic_sp(Surv(1, u, type = 'interval2') ~ x1 + x2, data = sim_data)</pre>
# Default fits a Cox-PH model
summary(ph_fit)
# Regression estimates close to true 0.5 and -0.5 values
new_data <- data.frame(x1 = c(0,1), x2 = c(1, 1))
rownames(new_data) <- c('group 1', 'group 2')</pre>
plot(ph_fit, new_data)
# plotting the estimated survival curves
po_fit <- ic_sp(Surv(1, u, type = 'interval2') ~ x1 + x2, data = sim_data,</pre>
                model = 'po')
# fits a proportional odds model
summary(po_fit)
# Not run: how to set up multiple cores
# library(doParallel)
# myCluster <- makeCluster(2, type = 'FORK')</pre>
```

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```
# registerDoParallel(myCluster)
# fit <- ic_sp(Surv(l, u, type = 'interval2') ~ x1 + x2,
# data = sim_data, useMCores = TRUE
# bs_samples = 500)
# stopCluster(myCluster)</pre>
```

miceData

Lung Tumor Interval Censored Data from Hoel and Walburg 1972

## **Description**

RFM mice were sacrificed and examined for lung tumors. This resulted in current status interval censored data: if the tumor was present, this implied left censoring and if no tumor was present this implied right censoring. Mice were placed in two different groups: conventional environment or germ free environment.

## Usage

```
data(miceData)
```

#### **Format**

A data frame with 144 rows and 3 variables

- 1 left side of observation interval
- u right side of observation interval
- grp Group for mouse. Either ce (conventional environment) or ge (grem-free environment)

## Source

Hoel D. and Walburg, H.,(1972), Statistical analysis of survival experiments, *The Annals of Statistics*, 18, 1259-1294

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optCliq

Computes the MLE for a Binary Mixture Model.

## **Description**

Computes the MLE for a Binary Mixture Model. Used internally for ICNPMLE, but may be useful in other problems. In the abstraction, solves the problem

$$\arg\max_{p} \sum_{i=1}^{n} \log \left( \sum_{j=1} p_{j} C_{ij} \right)$$

where  $C_{ij}$  is an indicator of whether the i-th observation could have come from the j-th source. C is referred to as the *clique matrix*.

#### Usage

#### **Arguments**

cliqMat  $n \times m$  clique matrix. n = number of observations, m = number of components

tol numerical tolerance

## Examples

```
testData <- simBVCen()
#simulate bivariate interval censored data

cliqMat <- MLEcens::reduc(testData, cm = TRUE)$cm
#computes the cliqMat associated with data

cliqFit <- optCliq(cliqMat)
#optimizes the component weights for clique matrix
cliqFit</pre>
```

simBVCen

Simulates Bivariate Interval Censored Data

#### **Description**

Simulates Bivariate Interval Censored Data

#### Usage

```
simBVCen(n = 1000)
```

simIC\_weib

#### **Arguments**

n number of observations simulated

## **Examples**

```
testData <- simBVCen()
#simulate bivariate interval censored data
bvcenFit <- ICNPMLE(testData)
bvcenFit</pre>
```

simIC\_weib

Simulates interval censored data from regression model with a Weibull baseline

## **Description**

Simulates interval censored data from a regression model with a weibull baseline distribution. Used for demonstration

## Usage

```
simIC_weib(n = 100, b1 = 0.5, b2 = -0.5, model = "ph", shape = 2, scale = 2, inspections = 2, inspectLength = 2.5, rndDigits = NULL)
```

## Arguments

n	Number of samples simulated
b1	Value of first regression coefficient
b2	Value of second regression coefficient
model	Type of regression model. Options are 'po' (prop. odds) and 'ph' (Cox PH)
shape	shape parameter of baseline distribution
scale	scale parameter of baseline distribution
inspections	number of inspections times of censoring process
inspectLength	max length of inspection interval
rndDigits	number of digits to which the inspection time is rounded to, creating a discrete inspection time. If rndDigits = NULL, the inspection time is not rounded, resulting in a continuous inspection time

## **Details**

Exact event times are simulated according to regression model: covariate x1 is distributed rnorm(n) and covariate x2 is distributed 1 - 2 \* rbinom(n, 1, 0.5). Event times are then censored with a case II interval censoring mechanism with inspections different inspection times. Time between inspections is distributed as runif(min = 0, max = inspectLength). Note that the user should be careful in simulation studies not to simulate data where nearly all the data is right censored (or more over, all the data with x2 = 1 or -1) or this can result in degenerate solutions!

simIC\_weib

## Author(s)

Clifford Anderson-Bergman

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