

Using Animal

Using **icenReg** for interval censored data in **R**
v1.3.0

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Chapter 1

Introduction

This manual is meant to provide an introduction to using **icenReg** to analyze interval censored data. It is written with expectation that the reader is familiar with basic survival analysis methods. Familiarity with the Kaplan Meier curves and Cox proportional hazards model should be sufficient.

1.1 Interval Censoring

Interval censoring occurs when a response is known only up to an interval. A classic example is testing for diseases at a doctor's clinic; if a subject tests negative at t_1 and positive at t_2 , all that is known is that the subject acquired the disease in (t_1, t_2) , rather than an exact time. Other classic examples include examining test mice for tumors after sacrifice (results in *current status* or *case I* interval censored data, in which all observations are either left or right censored, as opposed to the more general *case II*, which allows for any interval), customer choice models in economics (customers are presented a price for a product and chose to purchase or not, researcher wants to know distribution of maximum spending amount; this results in current status data again), data reduction methods for sensor analyses (to reduce load on sensor system, message is intentionally suppressed if outcome is in an expected region) and data binning (responses reported only up to an interval, in some cases to keep the subjects anonymous, in some cases to reduce size of data).

Often interval censoring is ignored in analysis. For example, age is usually reported only up to the year, rather than as a continuous variable; when a subject reports that their age is 33, the information we have is really that their age is in the interval $[33, 34)$. In the case that these intervals are very

short relative to the question of interest, such as with reported age when the scientific question is about age of onset of type II diabetes, the bias introduced by ignoring the interval censoring may be small enough to be safely ignored. However, in the case that the width of intervals is non-trivial, statistical methods that account for this should be used for reliable analysis.

Standard notation for interval censoring is that each observation contains a response interval $[l_i, r_i]$ such that the true event time is known to have occurred within. Note that this allows for uncensored observations ($l_i = r_i$), right censored ($r_i = \infty$), left censored ($l_i = 0$) or none of the above ($0 < l_i < r_i < \infty$).

In **icenReg**, the response value is allowed to be interval censored. If our data contains the values **L** and **R**, representing the left and right sides of the response interval, we can pass our response to a regression model using either

```
cbind(L, R)
Surv(L, R, type = "interval2")
```

It is worth noting that other R packages, specifically for non-parametric estimation, allow you to declare whether the response intervals are open, closed or a combination of partially opened, for example $[l_i, r_i)$. In **icenReg**, it is always assumed that the intervals are closed.

1.2 Classic Estimators

The topic of interval censoring began in the field of survival analysis. Although it is now considered in other fields of study (such as tobit regression), at this time **icenReg** focusses on survival models.

One of the earliest models is the Non-Parametric Maximum Likelihood Estimator (NPMLE), also referred to as Turnbull's Estimator. This is a generalization of the Kaplan Meier curves (which is a generalization of the empirical distribution function) that allows for interval censoring. Unlike the Kaplan Meier curves, the solution is not in closed form and several algorithms have been proposed for efficient computation. A special topic regarding the NPMLE is the bivariate NPMLE; this is for the special case of two interval censored outcomes, in which the researcher wants a non-parametric estimator of the joint distribution. This is especially computationally intense as the number of parameters can be up to n^2 .

Semi-parametric models exist in the literature as well; two classic regression models fit by **icenReg** are the Cox-PH model and the proportional odds model. The well known Cox-PH, or proportional hazards regression model, has the property that

$$h(t|X, \beta) = h_o(t)e^{X^T \beta}$$

where $h(t|X, \beta)$ is the hazard rate conditional on covariates X and regression parameters β , with h_o as the baseline hazard function. This relation is equivalent to

$$S(t|X, \beta) = S_o(t)e^{X^T \beta}$$

where $S(t|X, \beta)$ is the conditional survival and $S_o(t)$ is the baseline survival function.

The less known proportional odds model can be expressed as

$$\text{Odds}(S(t|X, \beta)) = e^{X^T \beta} \text{Odds}(S_o(t))$$

or

$$\frac{S(t|X, \beta)}{1 - S(t|X, \beta)} = e^{X^T \beta} \frac{S_o(t)}{1 - S_o(t)}$$

Unlike the special example of the Cox PH model with right-censored data, the baseline parameters *must* be estimated concurrently with the regression parameters. The model can be kept semi-parametric (i.e. no need to decide on a parametric baseline distribution) by using the Turnbull estimator, modified to account for the given regression model, as the baseline distribution. The semi-parametric model can be computationally very difficult, as the number of baseline parameters can be quite high (up to n), which must follow shape constraints (i.e. either a set of probability masses or a cumulative hazard function, which must be strictly increasing) and there is no closed form solution to either regression or baseline parameters.

Fully parametric models exist as well and can be calculated using fairly standard algorithms. There are slight complications in that the interval censoring can cause the log likelihood function to be non-concave. However, for reasonable sized data, the log likelihood function is usually locally concave near the mode and only slight modifications are required to address this issue. In practice, fully-parametric models should be used with caution; the lack of observed values means that model inspection can be quite difficult; there are no histograms, etc., to be made. As such, even if fully parametric models are to be used for the final analysis, it is strongly encouraged

to use semi-parametric models at least for model inspection. **icenReg** fits both fully parametric proportional odds and proportional hazard models for interval censored data.

Another common regression model for survival data is the accelerated failure time model (AFT). At this time, this option is not available for interval censored data. However, this model can be fit for interval censored data using **survival**'s **survreg** function.

1.3 Models fit with icenReg

At this time, the following set of models can be fit (name in parentheses is function call in **icenReg**):

- NPMLE (**ic_sp** can fit univariate NPMLE, **ICNPMLE** can fit univariate or bivariate NPMLE)
- Semi-parametric model (**ic_sp**, with options **model** = "ph" for proportional hazards, "po" for proportional odds)
- Fully parametric model (**ic_par**, in addition to **model** option, also have a choice of **dist**, with options "exponential", "gamma", "weibull", "lnorm", "loglogistic" and "generalgamma")

In addition, **icenReg** includes various diagnostic tools. These include

- Plots for diagnosing baseline distribution (**diag_baseline**)
- Plots for diagnosing covariate effects (**diag_covar**)
- Cross validation via multiple imputations (**icenReg_cv**)

1.4 Data Examples in icenReg

The package includes 4 sources of example data: two functions that simulate data and two sample data sets. The simulation functions are **simIC_weib**, which simulates interval censored regression data with a Weibull baseline distribution and **simBVCen**, which simulates bivariate interval censored data. The sample data sets are **miceData**, which contains current status data regarding lung tumors from two groups of mice and **essIncData**, which includes data from the European Social Survey. In this case, wages were only recorded up to an interval to protect the identity of the subjects. The dataset

`essIncData_small` is a smaller subset of `essIncData` ($n = 500$ instead of 6,712), which is used in many of the examples only so that CRAN's testing of the package runs quicker. In practice, using all these models on $n = 6,712$ is trivial to do, rarely taking more than a few seconds even on a slower laptop.

Chapter 2

Fitting Models using **icenReg**

An important note about **icenReg** is that in all models, it is assumed that the response interval is **closed**, i.e. the event is known to have occurred within $[t_1, t_2]$, compared with $[t_1, t_2)$, (t_1, t_2) , etc. This is of no consequence for fully parametric models, but does mean the solutions may differ somewhat in comparison with semi- and non-parametric models that allow different configurations of open and closed response intervals.

2.1 Non-parametric models

As noted earlier, for univariate interval censored data, the model may be fit with either **ic_sp** or **ICNPMLE**. For large datasets (i.e. $n > 50,000$), **ic_sp** will become faster than **ICNPMLE**. In addition, **ic_sp** can readily be provided to the **plot** method. For bivariate data, **ICNPMLE** is currently the only choice.

If the data set is relatively small and the user is interested in non-parametric tests, such as the log-rank statistic, we actually advise using the **interval** package, as this provides several testing functions. However, **icenReg** is several fold faster than **interval**, so if large datasets are used (i.e. $n > 1,000$), the user may have no choice but to use **icenReg**.

To fit an NPMLE model for interval censored data, we will consider the **miceData** provided in **icenReg**. This dataset contains three variables: **l**, **u** and **grp**. **l** and **u** represent the left and right side of the interval containing the event time (note: data is current status) and **grp** is a group indicator with two categories.

If we separate the data into two datasets, i.e.

```
ge.data <- miceData[miceData$grp == "ge", ]
```

```
ce.data <- miceData[miceData$grp == "ce", ]
```

We can then fit the NPMLE by calling the interval censored semi-parametric model, but supplying no covariates. This can be done by

```
ge.fit <- ic_sp(cbind(1, u) ~ 0, data = ge.data)
ce.fit <- ic_sp(cbind(1, u) ~ 0, data = ce.data)
```

Because the objects returned by `ic_sp` are intended to describe semi-parametric models and thus focus on the regression parameters. For the NPMLE, we need the information about the survival curve. We can extract the estimated survival curves by `getSCurves`

```
ge.sc <- getSCurves(ge.fit)
ce.sc <- getSCurves(ce.fit)
```

We can then plot and examine the NPMLE's for the two different groups using `plot` and `lines`

```
plot(ge.sc, xlab = 'Time',
     ylab = 'Estimated Survival', col = 'blue')
lines(ce.sc, col = 'red')
legend('bottomleft', legend = c('ge', 'ce'),
      col = c('blue', 'red'), lty = 1)
```

Looking at figure 2.1, we can see a unique feature about the NPMLE for interval censored data. That is, there are *two* lines used to represent the survival curve. This is because with interval censored data, the NPMLE is not always unique (in fact, it usually is not); any curve that lies between the two lines has the same likelihood. For example, any curve that lies between the two blues lines in figure 2.1 maximizes the likelihood associated with "ge" group of mice.

Formal statistical tests using the NPMLE are not currently supported by **icenReg**. We recommend using the **interval** package for this.

As noted earlier, **ICNPMLE** can be used to fit the univariate or bivariate NPMLE. However, there currently are no methods for plotting or testing on these fits. Because of this, we will not cover the use of this function here. The curious user is welcome to view `?ICNPMLE`.

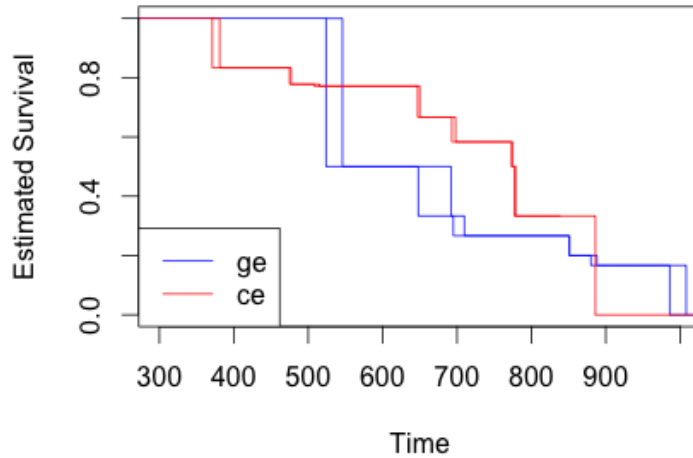


Figure 2.1: NPMLE's for both groups in miceData

2.2 Semi-parametric models

Semi-parametric models can be fit with `ic_sp` function. This function follows standard regression syntax. As an example, we will fit the `essIncData` dataset. In this dataset, we have income from the European Social Survey, which includes income reported up to an interval (to preserve the identity of the subjects). Within each country, the intervals are disjoint, but between countries there is plenty of overlap.

We fit the model below. Note that this may be time consuming, as the semi-parametric model is somewhat computationally intense and we are taking `bs_samples` bootstrap samples of the estimator.

```
fit_ph <- ic_sp(cbind(inc_l, inc_u) ~ cntry + eduLevel,
               bs_samples = 500, data = essIncData)
```

```
fit_po <- ic_sp(cbind(inc_l, inc_u) ~ cntry + eduLevel,
               bs_samples = 500, model = "po", data = essIncData)
```

The first model by default fits a Cox-PH model, while the second fits

a proportional odds model. We can look at the results using either the `summary` function, or just directly looking at the results (what is displayed is the same).

```
> fit_po
```

```
Model: Proportional Odds
```

```
Baseline: semi-parametric
```

```
Call: ic_sp(formula = cbind(inc_l, inc_u) ~ cntry + eduLevel,
  data = essIncData, model = "po", bs_samples = 500)
```

	Estimate	Exp(Est)	Std.Error	z-value	p
cntryPoland	2.6190	13.730	0.05724	45.760	0
cntryRussia	0.7940	2.212	0.05450	14.570	0
cntrySlovakia	0.6351	1.887	0.06766	9.387	0
eduLevel[12,16)	1.0050	2.732	0.05186	19.380	0
eduLevel[16,Inf)	1.8550	6.390	0.05875	31.570	0

```
final llk = -12483.03
```

```
Iterations = 18
```

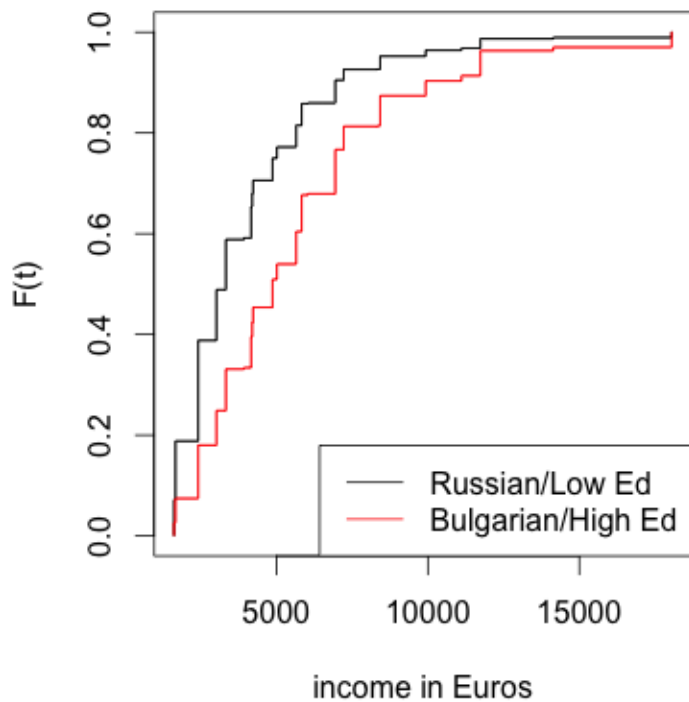
```
Bootstrap Samples = 500
```

For the semi-parametric models, bootstrap samples are used for inference on the regression parameters. The reason for this is that as far as we know, the limiting distribution of the baseline distribution is currently not characterized. In fact, to our knowledge, even using the bootstrap error estimates for the baseline distribution is not valid. Because the regression parameters cannot be separated in the likelihood function, using the negative inverse of the Hessian for the regression standard errors is not generally valid. However, it has been shown that using the bootstrap for inference *on the regression parameters* leads to valid inference.

We can use these fits to create plots as well. The `plot` function will plot the estimated survival curves or CDF for subjects with the set of covariates provided in the `newdata` argument. If `newdata` is left equal to `NULL`, the baseline survival function will be plotted.

If we wanted to plot the estimated CDF for an individual with between zero and 12 years of school from Russia against the estimated CDF for an individual from Bulgaria with 16+ years of school, this can be done with

```
newdata <- data.frame(cntry = c("Russia", "Bulgaria"),
```



```
eduLevel = c("[0,12)", "[16,Inf)") )

rownames(newdata) <- c("Russian/Low Ed",
  "Bulgarian/High Ed")

plot(fit_po, newdata, fun = "cdf",
  lgdLocation = "bottomright", xlab = "income in Euros")
```

2.3 Parametric Models

We can fit parametric models in **icenReg** using the `ic_par` function. The syntax is essentially the same as above, except that the user needs to spec-

ify `dist`, the parametric family that the baseline distribution belongs to. The current choices are "exponential", "weibull" (default), "gamma", "lnorm", "loglogistic" and "generalgamma" (generalized gamma distribution). The user must also select `model = "ph"` or `"po"`, just as in the semi-parametric model.

It is not necessary to specify `bs_samples` for parametric models, as inference is done using the asymptotic normality of the estimators. Fitting a parametric model is typically faster than the semi-parametric model, even if no bootstrap samples are taken for the semi-parametric model. This is because the fully-parametric model is of lower dimensional space without constraints.

Suppose we wanted to fit a proportional odds model to the `essIncData` data with a log-normal distribution. This could be fit by

```
fit_po_ln <- ic_par(cbind(inc_l, inc_u) ~ eduLevel + cntry,
  data = essIncData, model = "po", dist = "lnorm")
```

We can examine the regression coefficients in the same way as with the semi-parametric model.

```
> fit_po_ln
```

```
Model: Proportional Odds
```

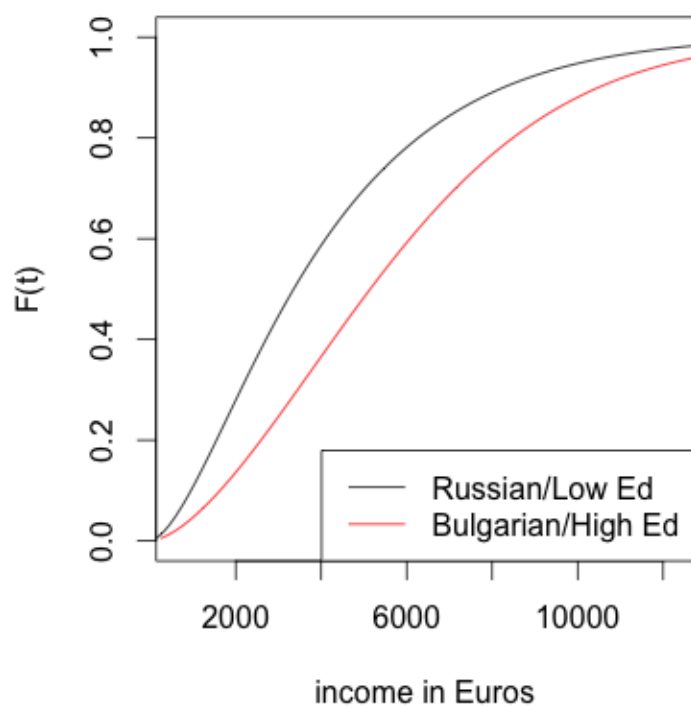
```
Baseline: lnorm
```

```
Call: ic_par(formula = cbind(inc_l, inc_u) ~ eduLevel + cntry,
  data = essIncData, model = "po", dist = "lnorm")
```

	Estimate	Exp(Est)	Std.Error	z-value	p
mu	8.3780	4350.0000	0.007509	1116.00	0
log_s	-0.4880	0.6138	0.010240	-47.65	0
eduLevel[12,16)	1.0150	2.7590	0.048860	20.77	0
eduLevel[16,Inf)	1.8550	6.3910	0.064710	28.66	0
cntryPoland	2.5860	13.2800	0.066930	38.64	0
cntryRussia	0.8493	2.3380	0.055360	15.34	0
cntrySlovakia	0.7928	2.2090	0.062990	12.58	0

```
final llk = -14413.81
```

```
Iterations = 11
```



We can also examine the survival/cdf plots in the same way.

```
plot(fit_po_ln, newdata, fun = "cdf",  
     lgdLocation = "bottomright", xlab = "income in Euros")
```

Chapter 3

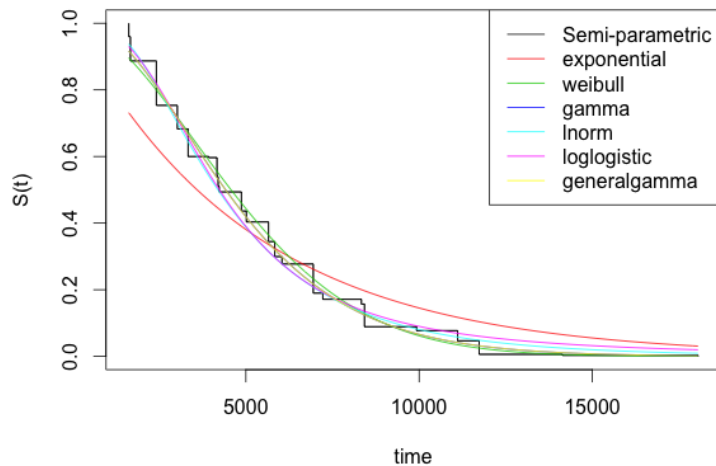
Inspecting model fit

3.1 Examining Baseline Distribution

Although the semi-parametric model is more flexible, and thus more robust to unusual baseline distributions, there are many reasons one may decide to use a parametric model instead. One reason is that, as stated earlier, we are not aware of any general distributional theory regarding the baseline distribution, outside of the univariate case with case I interval censored data. Even in this case, the estimator is highly inefficient, observing convergence rates of $n^{1/3}$ instead of the more standard $n^{1/2}$. Because of this, making inference about values that directly require the baseline distribution, such as creating a confidence interval for the median for subjects with a given set of covariates, cannot be done with the semi-parametric model. Secondly, we have found that when it comes to cross-validation (to be described shortly), we often found the semi-parametric estimator to be overly optimistic for some loss functions in comparison with a parametric model.

However, even if a parametric model is used for final inference, the semi-parametric model is still useful for assessing model fit. This is especially important for interval censored data, as we do not have the option of examining typical residuals or histograms as we would if the outcome was uncensored. **icenReg** has the function `diag_baseline` that plots several choices of parametric baseline distributions against the semi-parametric estimate. If the parametric distribution shows no systematic deviations from the semi-parametric fit, this implies the choice of parametric family may do a reasonable job of describing the underlying distribution. If there are clear deviations, this model should not be trusted.

To use `diag_baseline`, you must provide either a fitted model, or a



formula, data and model. You then select the parametric families that you would like plotted against the non-parametric estimate (default is to fit all available). As an example, suppose we wanted to examine the different parametric fits for the `essIncData` dataset. This could be done with

```
diag_baseline(cbind(inc_l, inc_u) ~
  eduLevel + cntry,
  model = "po",
  data = essIncData,
  lgdLocation = "topright")
```

Alternatively, using the fits from earlier, we can just call

```
diag_baseline(fit_po, lgdLocation = "topright")
```

Visual diagnostics are always subjective, but in this case we definitively know that the exponential fit is not appropriate and we believe the log-normal baseline is most appropriate for the proportional odds model.

3.2 Examining Covariate Effect

Although semi-parametric models do not make assumptions about the parametric family of the baseline distribution, both fully-parametric and semi-parametric models make assumptions about the form of the covariate effect, akin to the link function in generalized linear models.

A rule of thumb for identifying gross violations of proportional hazards is to check if the Kaplan Meier curves cross; if they do, and this cross appears not purely by chance, the proportional hazards assumption seems inappropriate.

This can naturally extend to the case of interval censored data by replacing the Kaplan Meier curves with the NPMLE. Also, this informal test can be generalized to the proportional odds model; the proportional odds assumption also implies that survival curves that differ only by a constant factor of the odds of survival should not cross.

Another method of assessing involves transforming your survival estimates such that if the assumptions are met, the difference in transformed survival will be constant. For the proportional hazards model, this is the complementary log-log transformation (i.e. $\log(-\log(s))$). For the proportional odds model, this is the logit transformation (i.e. $\log(s/(1-s))$).

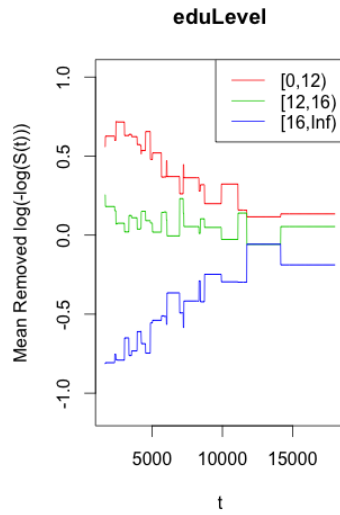
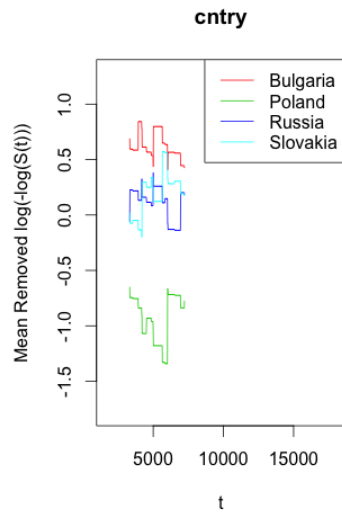
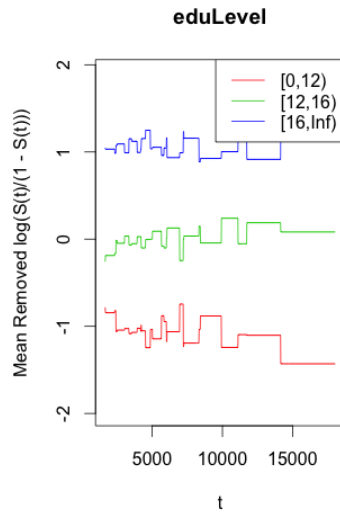
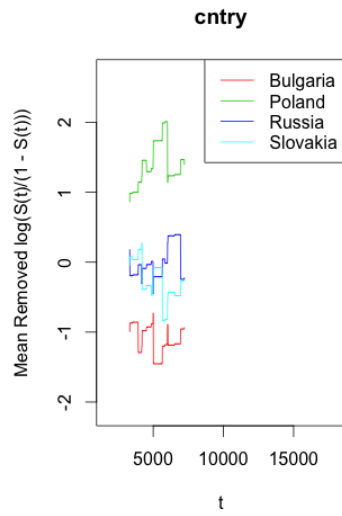
Plotting these functions can be done automatically in **icenReg** using the `diag_covar` function. The basic flow is that function takes in the fit, divides the data up on a covariate of interest. If it is categorical, it simply breaks up by category, if it is numeric, it attempts to find break point to evenly split up the data. Then, for each subset of the data, it fits the corresponding semi-parametric model and plots the transformation of the baseline distribution.

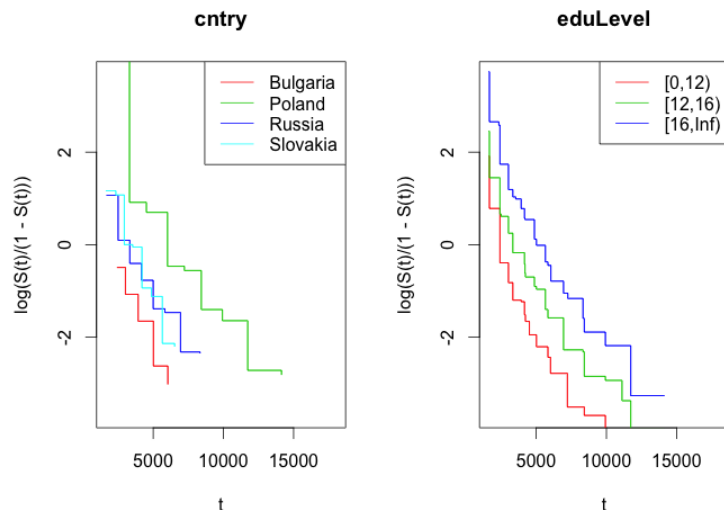
To demonstrate, suppose we wanted to assess whether the Cox-PH or proportional odds model was more appropriate for the `essIncData`. This could be done by

```
diag_covar(fit_po, lgdLocation = "topright")
diag_covar(fit_ph, lgdLocation = "topright")
```

We see that especially for `eduLevel`, the proportional odds seems much more appropriate (the difference between transformed values seems more constant). This agrees with the fact that the likelihood is almost 100 greater for the proportional odds model than Cox-PH.

Note that the plots for `cntry` are very limited. This is because the mean trend is removed from the plots. However, since the cdf for the semi-





parametric model for the Bulgaria subset of the data is defined as exactly 1 around 10,000, the mean of the transformation is not defined.

We can replot the transformation, without the mean removed, by the following call:

```
diag_covar(fit_po, yType = "transform",
            lgdLocation = "topright")
```

3.3 Imputed Cross Validation

Cross validation is a popular method for evaluating how well a model will perform on new data. In general, the idea is simple enough: to get an estimate of some loss function on out of sample data for a given model, we split the data into training and validation datasets. The training dataset is used to fit the model (without touching the validation data). Then an estimate of the out of sample error can be generated by predicting the response in the validation dataset and directly computing the loss function. In K-fold cross validation, K disjoint subsets of the data are used as validation datasets and the process is repeated K-times.

For censored data, this generic recipe is not so simple. In particular, if a value in the validation set is censored, there is typically no direct method

for calculating the contribution to the loss function associated with this observation.

One method to deal with censoring that has appeared in the literature is to calculate likelihood over the validation data set. As an alternative, we offer an imputation based approach. To calculate the average loss function, we take several imputations (or samples) of the interval censored data conditional on the covariates *and censoring interval* (i.e. the distribution is truncated such that the imputation will fall inside the given censoring interval). The average loss across all imputations is then taken as the evaluated loss.

To impute the data, we first take a sample of the posterior parameters and conditional on the parameters and censoring interval, we sample the censored values. An important note is that **icenReg** does *not* sample the baseline parameters, but only the regression parameters for the semi-parametric model. This means that the uncertainty in the baseline parameter is ignored. For the fully parametric model, both the regression and baseline parameters are sampled.

For the prediction, the median value conditional on the parameter estimates is used. This is *not* necessarily the estimate that minimizes the loss function, but it is generally a reasonable estimate.

Cross validation can be done with **icenReg**'s `icenReg_cv` function. This takes a regression model (either from `ic_par` or `ic_sp`), and a loss function to be calculated. CAUTION: When using cross-validation on an `ic_sp` fit, the total number of models fit will be `fold` (default = 10) x `bs_samples`. This can get very expensive very quickly!

The default loss function is `abs_inv`, which is defined as

```
abs_inv <- function(pred, t_val) {
  mean(abs(1/(pred + 1) - 1/(t_val + 1)))
}
```

Although we believe this to be a reasonable loss function for survival data (heavy penalizes for missing subjects that are at high risk, does not heavily penalizing for not being precise with low-risk subjects as long as they are identified as low risk), this function is not the final say in loss functions. A user can write their own loss function, which should take in arguments `pred` and `t_val`, where `pred` is the predicted value and `t_val` is the true response value.

Imputed cross validation can then be used as such:

```
icenReg_cv(fit = fit_po, loss_fun = abs_inv)
```

3.4 Appendix

Both the bootstrap and cross validation statistics can be extremely computationally expensive, yet also are both embarrassingly parallel problems. As such, they are written take advantage of multiple cores via the **doParallel** package. Below is demonstrated how to run the bootstrap and cross validation using four cores.

```
library(doParallel)
myCluster <- makeCluster(4, type = 'FORK')
registerDoParallel(myCluster)
fit <- ic_sp(cbind(inc_l, inc_u) ~ eduLevel + cntry,
             data = essIncData, model = "po",
             bs_samples = 50, useMCores = TRUE)

par_fit <- ic_par(cbind(inc_l, inc_u) ~ eduLevel + cntry,
                  dist = "lnorm", model = "po",
                  data = essIncData)

cv_error <- icenReg_cv(par_fit)
#Fit a parametric model because it is much faster;
#does not need to fit bootstrap samples for each
#training set

stopCluster(myCluster)
```