Parametric Survival Models

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Configuring R

Functions from these packages will be used throughout this document:

```
library(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggfortify) # help with graphics
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
library(haven) # import Stata files
library(knitr) # format R output for markdown
library(tidyr) # Tools to help to create tidy data
library(plotly) # interactive graphics
library(dobson) # datasets from Dobson and Barnett 2018
library(parameters) # format model output tables for markdown
library(haven) # import Stata files
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
```

Here are some R settings I use in this document:

```r
rm(list = ls()) # delete any data that's already loaded into R

conflicts_prefer(dplyr::filter)
ggplot2::theme_set(
  ggplot2::theme_bw() +
        # ggplot2::labs(col = "") +
    ggplot2::theme(
      legend.position = "bottom",
      text = ggplot2::element_text(size = 12, family = "serif")))

knitr::opts_chunk$set(message = FALSE)
options('digits' = 6)

panderOptions("big.mark", ",")
pander::panderOptions("table.emphasize.rownames", FALSE)
pander::panderOptions("table.split.table", Inf)
conflicts_prefer(dplyr::filter) # use the `filter()` function from dplyr() by default
legend_text_size = 9
run_graphs = TRUE
```

1.1 Parametric Survival Models

1.1.1 Exponential Distribution

- The exponential distribution is the basic distribution for survival analysis.

$$\begin{aligned}
f(t) &= \lambda e^{-\lambda t} \\
\log f(t) &= \log \lambda - \lambda t \\
F(t) &= 1 - e^{-\lambda t} \\
\text{S}(t) &= e^{-\lambda t} \\
\Lambda(t) &= -\log \text{S}(t) \\
&= \lambda t \\
\lambda(t) &= \lambda \\
\text{E}(T) &= \lambda^{-1}
\end{aligned}$$

1.1.2 Weibull Distribution

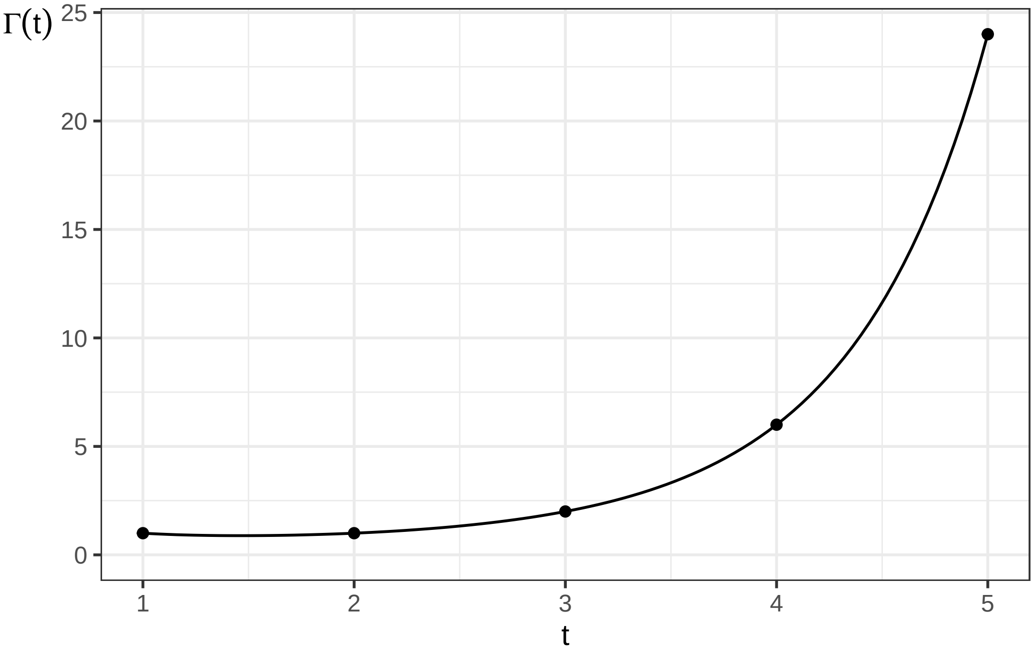
Using the Kalbfleisch and Prentice (2002) notation:

$$\begin{aligned}
f(t) &= \lambda p (\lambda t)^{p-1} e^{-(\lambda t)^p} \\
F(t) &= 1 - e^{-(\lambda t)^p} \\
\text{S}(t) &= e^{-(\lambda t)^p} \\
\lambda(t) &= \lambda p (\lambda t)^{p-1} \\
\Lambda(t) &= (\lambda t)^p \\
\log \Lambda(t) &= p \log \lambda t \\
&= p \log \lambda + p \log t \\
\text{E}(T) &= \lambda^{-1} \cdot \Gamma\left(1 + \frac{1}{p}\right)
\end{aligned}$$

Note

Recall from calculus:

- $\Gamma(t) \overset{\text{def}}{=} \int_{u=0}^{\infty} u^{t-1} e^{-u} du$
- $\Gamma(t) = (t-1)!$ for integers $t \in \mathbb{Z}$
- It is implemented by the `gamma()` function in R.



Here are some Weibull density functions, with $\lambda = 1$ and p varying:

```
library(ggplot2)
lambda = 1
ggplot() +
  geom_function(
    aes(col = "0.25"),
    fun = \(x) dweibull(x, shape = 0.25, scale = 1/lambda)) +
  geom_function(
    aes(col = "0.5"),
    fun = \(x) dweibull(x, shape = 0.5, scale = 1/lambda)) +
  geom_function(
    aes(col = "1"),
    fun = \(x) dweibull(x, shape = 1, scale = 1/lambda)) +
  geom_function(
    aes(col = "1.5"),
    fun = \(x) dweibull(x, shape = 1.5, scale = 1/lambda)) +
  geom_function(
    aes(col = "2"),
    fun = \(x) dweibull(x, shape = 2, scale = 1/lambda)) +
  geom_function(
    aes(col = "5"),
    fun = \(x) dweibull(x, shape = 5, scale = 1/lambda)) +
  theme_bw() +
  xlim(0, 2.5) +
  ylab("f(t)") +
  theme(axis.title.y = element_text(angle=0)) +
  theme(legend.position="bottom") +
  guides(
    col =
      guide_legend(
        title = "p",
        label.theme =
          element_text(
            size = 12)))
```

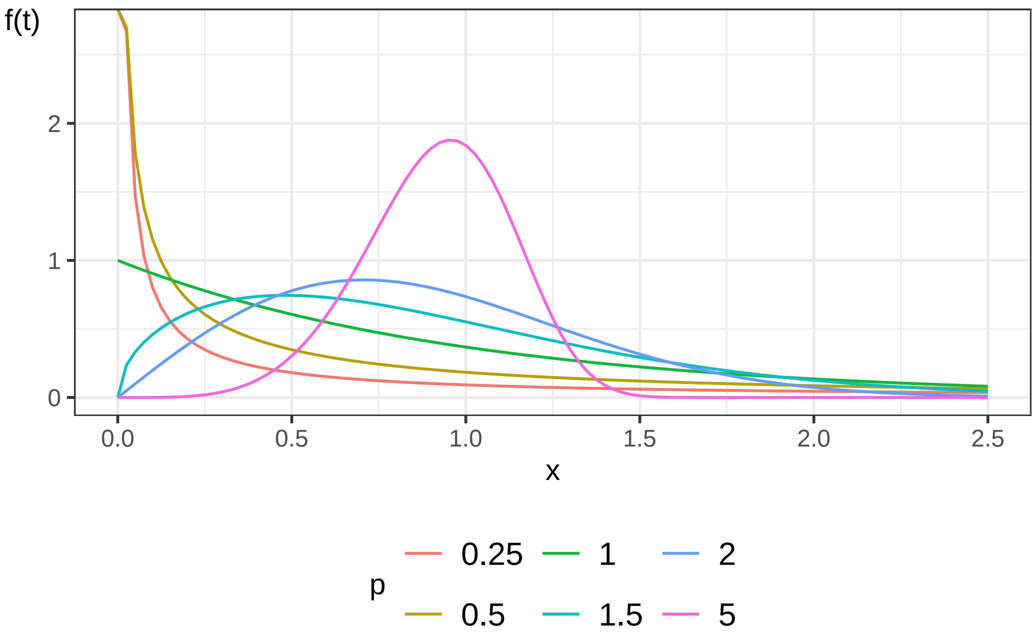


Figure 1: Density functions for Weibull distribution

Properties of Weibull hazard functions

Theorem 1.1. *If T has a Weibull distribution, then:*

- *When $p = 1$, the Weibull distribution simplifies to the exponential distribution*
- *When $p > 1$, the hazard is increasing: $h'(t) > 0$*
- *When $p < 1$, the hazard is decreasing: $h'(t) < 0$*
- $\log \Lambda(t)$ *is a straight line relative to* $\log t$*:* $\log \Lambda(t) = p \log \lambda + p \log t$

Exercise 1.1. Prove Theorem 1.1.

The Weibull distribution provides more flexibility than the exponential. Figure 2 shows some Weibull hazard functions, with $\lambda = 1$ and p varying:

```
library(ggplot2)
library(eha)
lambda = 1

ggplot() +
  geom_function(
    aes(col = "0.25"),
    fun = \(x) hweibull(x, shape = 0.25, scale = 1/lambda)) +
  geom_function(
    aes(col = "0.5"),
    fun = \(x) hweibull(x, shape = 0.5, scale = 1/lambda)) +
  geom_function(
    aes(col = "1"),
    fun = \(x) hweibull(x, shape = 1, scale = 1/lambda)) +
  geom_function(
    aes(col = "1.5"),
    fun = \(x) hweibull(x, shape = 1.5, scale = 1/lambda)) +
  geom_function(
    aes(col = "2"),
    fun = \(x) hweibull(x, shape = 2, scale = 1/lambda)) +
  theme_bw() +
  xlim(0, 2.5) +
  ylab(expr(lambda)) +
  theme(axis.title.y = element_text(angle=0)) +
  theme(legend.position="bottom") +
  guides(
    col =
      guide_legend(
        title = "p",
        label.theme =
          element_text(
            size = 12)))
```

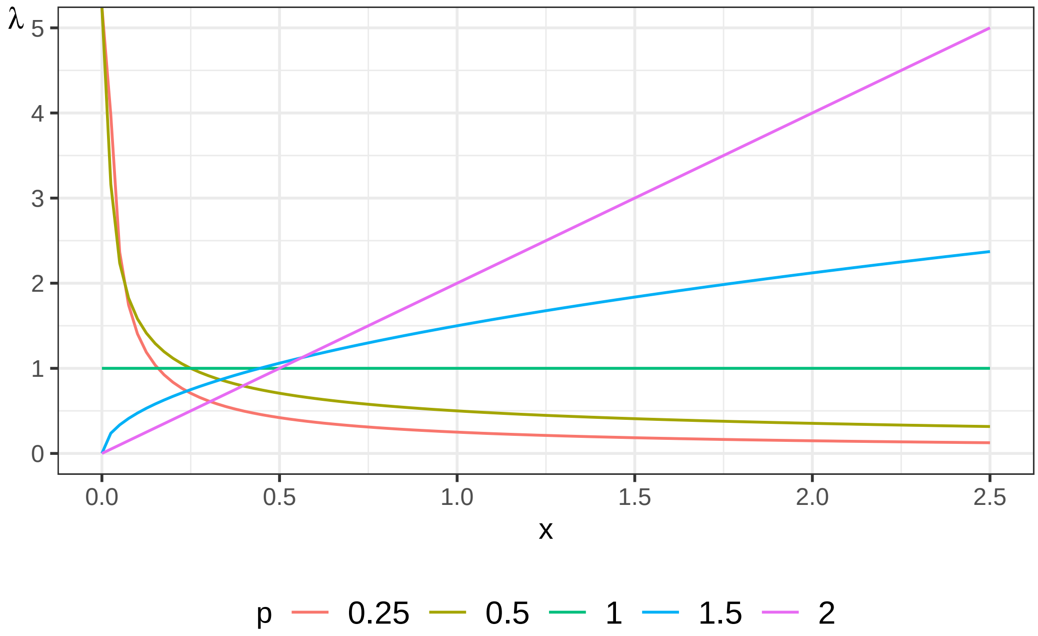


Figure 2: Hazard functions for Weibull distribution

```
library(ggplot2)
lambda = 1

ggplot() +
  geom_function(
    aes(col = "0.25"),
    fun = \(x) pweibull(lower = FALSE, x, shape = 0.25, scale = 1/lambda)) +
  geom_function(
    aes(col = "0.5"),
    fun = \(x) pweibull(lower = FALSE, x, shape = 0.5, scale = 1/lambda)) +
  geom_function(
    aes(col = "1"),
    fun = \(x) pweibull(lower = FALSE, x, shape = 1, scale = 1/lambda)) +
  geom_function(
    aes(col = "1.5"),
    fun = \(x) pweibull(lower = FALSE, x, shape = 1.5, scale = 1/lambda)) +
  geom_function(
    aes(col = "2"),
    fun = \(x) pweibull(lower = FALSE, x, shape = 2, scale = 1/lambda)) +
  theme_bw() +
  xlim(0, 2.5) +
  ylab("S(t)") +
  theme(axis.title.y = element_text(angle=0)) +
  theme(legend.position="bottom") +
  guides(
    col =
      guide_legend(
        title = "p",
        label.theme =
          element_text(
            size = 12)))
```

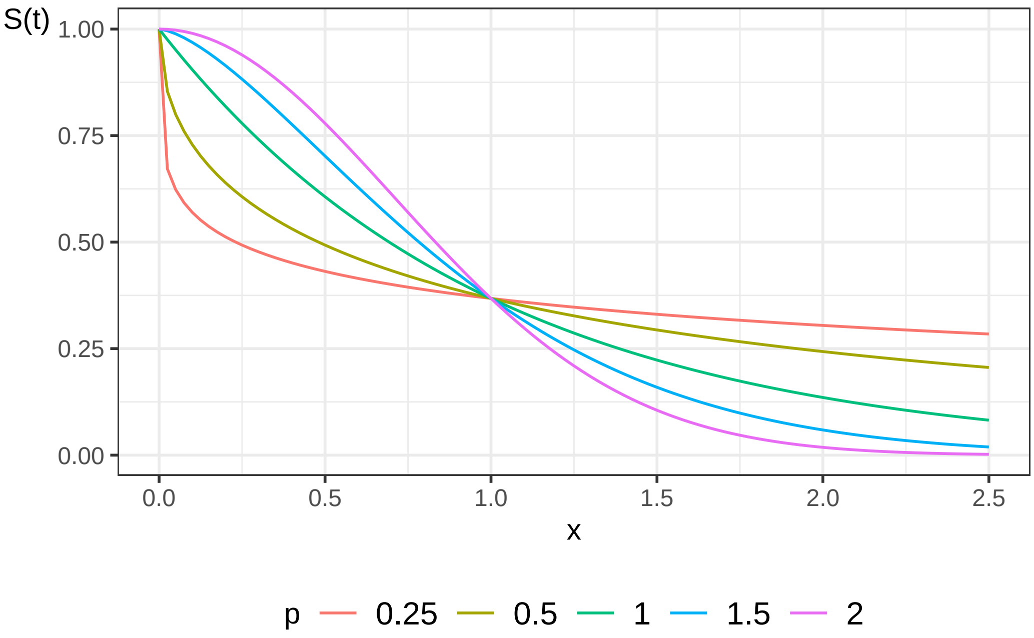


Figure 3: Survival functions for Weibull distribution

1.1.3 Exponential Regression

For each subject i, define a linear predictor:

$$\begin{aligned}
\eta(\tilde{x}) &= \beta_0 + (\beta_1 x_1 + \dots + \beta_p x_p) \\
\lambda(t|\tilde{x}) &= \exp\{\eta(\tilde{x})\} \\
\lambda_0 &\overset{\text{def}}{=} \lambda(t|\tilde{0}) \\
&= \exp\left\{\eta(\tilde{0})\right\} \\
&= \exp\left\{\beta_0 + (\beta_1 \cdot 0 + \dots + \beta_p \cdot 0)\right\} \\
&= \exp\{\beta_0 + 0\} \\
&= \exp\{\beta_0\}
\end{aligned}$$

We let the linear predictor have a constant term, and when there are no additional predictors the hazard is $\lambda = \exp\{\beta_0\}$. This has a log link as in a generalized linear model. Since the hazard does not depend on t, the hazards are (trivially) proportional.

1.1.4 Accelerated Failure Time

Previously, we assumed the hazards were proportional; that is, the covariates multiplied the baseline hazard function:

$$\begin{aligned}
h(T = t|X = x) &\overset{\text{def}}{=} p(T = t|X = x, T \geq t) \\
&= \lambda(t|X = 0) \cdot \exp\{\eta(x)\} \\
&= \lambda(t|X = 0) \cdot \theta(x) \\
&= \lambda_0(t) \cdot \theta(x)
\end{aligned}$$

and correspondingly,

$$\begin{aligned}
\Lambda(t|x) &= \theta(x)\Lambda_0(t) \\
\mathrm{S}(t|x) &= \exp\{-\Lambda(t|x)\} \\
&= \exp\{-\theta(x) \cdot \Lambda_0(t)\} \\
&= (\exp\{-\Lambda_0(t)\})^{\theta(x)} \\
&= (\mathrm{S}_0(t))^{\theta(x)}
\end{aligned}$$

An alternative modeling assumption would be

$$\mathrm{S}(t|X = x) = \mathrm{S}_0(t \cdot \theta(x))$$

where $\theta(x) = \exp\{\eta(x)\}$, $\eta(x) = \beta_1 x_1 + \dots + \beta_p x_p$, and $\mathrm{S}_0(t) = \mathrm{P}(T \geq t|X = 0)$ is the base survival function.

Then

$$\begin{aligned}
\mathrm{E}[T|X = x] &= \int_{t=0}^{\infty} \mathrm{S}(t|x)dt \\
&= \int_{t=0}^{\infty} \mathrm{S}_0(t \cdot \theta(x))dt \\
&= \int_{u=0}^{\infty} \mathrm{S}_0(u)du \cdot \theta(x)^{-1} \\
&= \theta(x)^{-1} \cdot \int_{u=0}^{\infty} \mathrm{S}_0(u)du \\
&= \theta(x)^{-1} \cdot \mathrm{E}[T|X = 0]
\end{aligned}$$

So the mean of T given $X = x$ is the baseline mean divided by $\theta(x) = \exp\{\eta(x)\}$.

This modeling strategy is called an accelerated failure time model, because covariates cause uniform acceleration (or slowing) of failure times.

Additionally:

$$\begin{aligned}\Lambda(t|x) &= \Lambda_0(\theta(x)\cdot t)\\ \lambda(t|x) &= \theta(x)\cdot\lambda_0(\theta(x)\cdot t)\end{aligned}$$

If the base distribution is exponential with parameter λ then

$$\begin{aligned}\mathrm{S}(t|x) &= \exp\{-\lambda\cdot t\theta(x)\}\\ &= [\exp\{-\lambda t\}]^{\theta(x)}\end{aligned}$$

which is an exponential model with base hazard multiplied by $\theta(x)$, which is also the proportional hazards model.

In terms of the log survival time $Y = \log T$ the model can be written as

$$\begin{aligned}Y &= \alpha - \eta + W\\ \alpha &= -\log\lambda\end{aligned}$$

where W has the extreme value distribution. The estimated parameter λ is the intercept and the other coefficients are those of η, which will be the opposite sign of those for coxph.

For a Weibull distribution, the hazard function and the survival function are

$$\begin{aligned}\lambda(t) &= \lambda p(\lambda t)^{p-1}\\ \mathrm{S}(t) &= e^{-(\lambda t)^p}\end{aligned}$$

We can construct a proportional hazards model by using a linear predictor η_i without constant term and letting $\theta_i = e^{\eta_i}$ we have

$$\lambda(t) = \lambda p(\lambda t)^{p-1}\theta_i$$

A distribution with $\lambda(t) = \lambda p(\lambda t)^{p-1}\theta_i$ is a Weibull distribution with parameters $\lambda^* = \lambda\theta_i^{1/p}$ and p so the survival function is

$$\begin{aligned}S^*(t) &= e^{-(\lambda^* t)^p}\\ &= e^{-(\lambda\theta^{1/p}t)^p}\\ &= \mathrm{S}(t\theta^{1/p})\end{aligned}$$

so this is also an accelerated failure time model.

In terms of the log survival time $Y = \log T$ the model can be written as

$$\begin{aligned}Y &= \alpha - \sigma\eta + \sigma W\\ \alpha &= -\log\lambda\\ \sigma &= 1/p\end{aligned}$$

where W has the extreme value distribution. The estimated parameter λ is the intercept and the other coefficients are those of η, which will be the opposite sign of those for `coxph`.

These AFT models are log-linear, meaning that the linear predictor has a log link. The exponential and the Weibull are the only log-linear models that are simultaneously proportional hazards models. Other parametric distributions can be used for survival regression either as a proportional hazards model or as an accelerated failure time model.

1.1.5 Dataset: Leukemia treatments

Remission survival times on 42 leukemia patients, half on new treatment, half on standard treatment.

This is the same data as the `drug6mp` data from KMsurv, but with two other variables and without the pairing.

```r
library(haven)
library(survival)
anderson =
  paste0(
    "http://web1.sph.emory.edu/dkleinb/allDatasets",
    "/surv2datasets/anderson.dta") |>
  read_dta() |>
  mutate(
    status = status |>
      case_match(
        1 ~ "relapse",
        0 ~ "censored"
      ),
    sex = sex |>
      case_match(
        0 ~ "female",
        1 ~ "male"
      ),

    rx = rx |>
      case_match(
        0 ~ "new",
        1 ~ "standard"
      ),

    surv = Surv(time = survt,event = (status == "relapse"))
  )

print(anderson)
```

Cox semi-parametric model

```r
anderson.cox0 = coxph(
  formula = surv ~ rx,
  data = anderson)
summary(anderson.cox0)
#> Call:
#> coxph(formula = surv ~ rx, data = anderson)
#>
#>   n= 42, number of events= 30
#>
#>              coef exp(coef) se(coef)    z Pr(>|z|)
#> rxstandard 1.572     4.817    0.412 3.81  0.00014 ***
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#>            exp(coef) exp(-coef) lower .95 upper .95
#> rxstandard      4.82      0.208      2.15      10.8
#>
#> Concordance= 0.69  (se = 0.041 )
#> Likelihood ratio test= 16.4  on 1 df,   p=5e-05
#> Wald test            = 14.5  on 1 df,   p=1e-04
#> Score (logrank) test = 17.2  on 1 df,   p=3e-05
```

Weibull parametric model

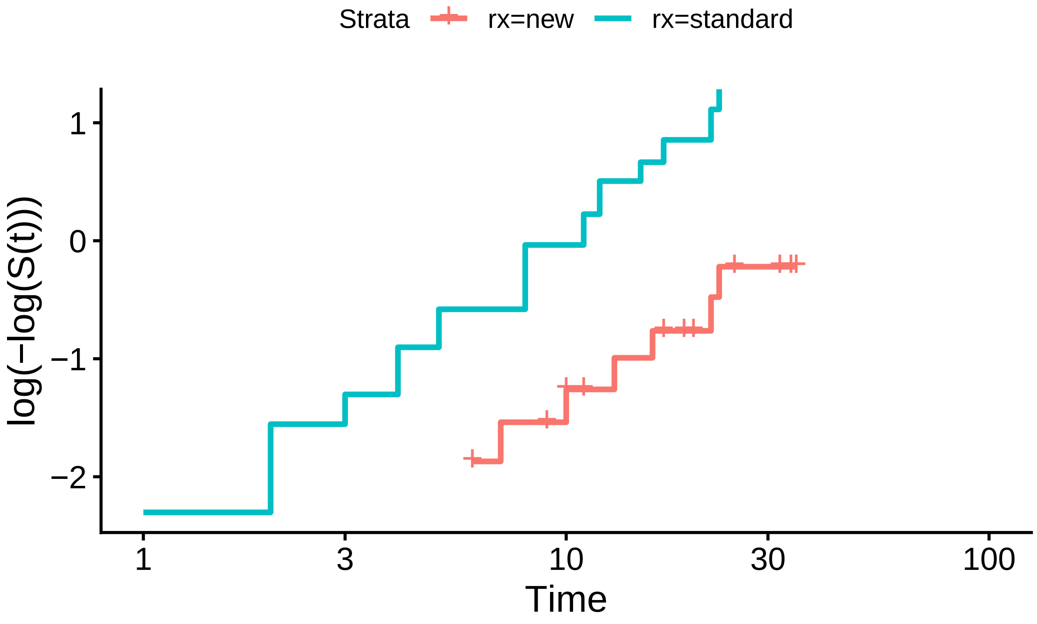
```
anderson.weib <- survreg(
  formula = surv ~ rx,
  data = anderson,
  dist = "weibull")
summary(anderson.weib)
#> 
#> Call:
#> survreg(formula = surv ~ rx, data = anderson, dist = "weibull")
#>              Value Std. Error     z       p
#> (Intercept)  3.516      0.252 13.96 < 2e-16
#> rxstandard  -1.267      0.311 -4.08 4.5e-05
#> Log(scale)  -0.312      0.147 -2.12   0.034
#> 
#> Scale= 0.732 
#> 
#> Weibull distribution
#> Loglik(model)= -106.6   Loglik(intercept only)= -116.4
#>  Chisq= 19.65 on 1 degrees of freedom, p= 9.3e-06 
#> Number of Newton-Raphson Iterations: 5 
#> n= 42
```

Exponential parametric model

```
anderson.exp <- survreg(
  formula = surv ~ rx,
  data = anderson,
  dist = "exp")
summary(anderson.exp)
#> 
#> Call:
#> survreg(formula = surv ~ rx, data = anderson, dist = "exp")
#>              Value Std. Error     z       p
#> (Intercept)  3.686      0.333 11.06 < 2e-16
#> rxstandard  -1.527      0.398 -3.83 0.00013
#> 
#> Scale fixed at 1 
#> 
#> Exponential distribution
#> Loglik(model)= -108.5   Loglik(intercept only)= -116.8
#>  Chisq= 16.49 on 1 degrees of freedom, p= 4.9e-05 
#> Number of Newton-Raphson Iterations: 4 
#> n= 42
```

Diagnostic - complementary log-log survival plot

```
library(survminer)
survfit(
  formula = surv ~ rx,
  data = anderson) |>
  ggsurvplot(fun = "cloglog")
```



If the cloglog plot is linear, then a Weibull model may be ok.

1.2 Combining left-truncation and interval-censoring

From [https://stat.ethz.ch/pipermail/r-help/2015-August/431733.html]:

> coxph does left truncation but not left (or interval) censoring survreg does interval censoring but not left truncation (or time dependent covariates).

- Terry Therneau, August 31, 2015