Friday, April 4

Censoring Specification

Without much loss of generality we will limit the discussion here to right-censoring. We define an indicator variable D_i such that

$$D_i = \begin{cases} 1, & \text{if the } i\text{-th observation is not censored,} \\ 0, & \text{if the } i\text{-th observation is censored.} \end{cases}$$

The variable D_i can be viewed as another response variable which depends on the actual time to event, T_i, as well as whatever is responsible for the censoring. In what follows we will let t_i and d_i denote observed values of T_i and D_i respectively.

Let t_i be the actual time-till-event if $d_i = 1$, and the *lower-bound* on the time-till-event if $d_i = 0$ so that the *actual* time-till-event is *greater than or equal to* t_i. Under certain assumptions about how censoring occurs, the likelihood function is

$$L = \prod_{i=1}^{n} f(t_i)^{d_i} P(T_i \ge t_i)^{1-d_i}.$$

where $f(t_i)$ is the *probability density function* of T_i, and $P(T_i \ge t_i)$ is the probability that T_i is *at least* t_i (this is also called the *survival function*). Note that

$$f(t_i)^{d_i} P(T_i \ge t_i)^{1-d_i} = \begin{cases} f(t_i), & \text{if } d_i = 1 \text{ (i.e., not censored),} \\ P(T_i \ge t_i), & \text{if } d_i = 0 \text{ (i.e., censored),} \end{cases}$$

so the indicator variable d_i simply selects the appropriate term for computing the likelihood of an observation depending on whether or not it was censored.

Specification of Right-Censoring in `Surv`

For *right-censoring*, the response variable can be specified as `Surv(t,d)` where `t` is (a) the actual time to event if there is no censoring or (b) the lower bound on time to event if the observation is right-censored, and `d` is either an indicator variable (i.e., `0` or `1`) or a logical variable (i.e., `FALSE` or `TRUE`) where we have `d = 1` or `d = TRUE` if the observation is *not* censored.

Example: Consider an AFT model for the `leukemia` data.

```r
library(survival) # for leukemia and survreg
head(leukemia) # status=1 if remission ended at that time, status=0 if right-censored
```

```
  time status          x censored treatment ysurv
1    9      1 Maintained       no       yes     9
2   13      1 Maintained       no       yes    13
3   13      0 Maintained      yes       yes   13+
4   18      1 Maintained       no       yes    18
5   23      1 Maintained       no       yes    23
6   28      0 Maintained      yes       yes   28+
```

```r
m <- survreg(Surv(time, status) ~ x, dist = "lognormal", data = leukemia)
summary(m)$table
```

```
              Value Std. Error      z        p
(Intercept)  2.854      0.254 11.242 2.55e-29
xMaintained  0.724      0.380  1.905 5.68e-02
Log(scale)  -0.145      0.170 -0.858 3.91e-01
```

Alternatively suppose we had a variable `censored` that told us if the observation was censored or not.

```
leukemia$censored <- factor(leukemia$status, labels = c("yes","no"))
head(leukemia)
```

```
  time status          x censored treatment ysurv
1    9      1 Maintained       no       yes     9
2   13      1 Maintained       no       yes    13
3   13      0 Maintained      yes       yes   13+
4   18      1 Maintained       no       yes    18
5   23      1 Maintained       no       yes    23
6   28      0 Maintained      yes       yes   28+
```

Then we specify the censoring as follows.

```
m <- survreg(Surv(time, censored == "no") ~ x, dist = "lognormal", data = leukemia)
summary(m)$table
```

```
              Value Std. Error      z        p
(Intercept)  2.854      0.254 11.242 2.55e-29
xMaintained  0.724      0.380  1.905 5.68e-02
Log(scale)  -0.145      0.170 -0.858 3.91e-01
```

It is useful to note that we can see how `Surv` codes the response variable for censoring. This is useful if you want to verify that you have used `Surv` correctly.

```
leukemia$ysurv <- Surv(leukemia$time, leukemia$censored == "no")
head(leukemia)
```

```
  time status          x censored treatment ysurv
1    9      1 Maintained       no       yes     9
2   13      1 Maintained       no       yes    13
3   13      0 Maintained      yes       yes   13+
4   18      1 Maintained       no       yes    18
5   23      1 Maintained       no       yes    23
6   28      0 Maintained      yes       yes   28+
```

As before, interpretation is facilitated by applying the exponential function to the parameter estimates.

```
exp(cbind(coef(m),confint(m)))
```

```
                   2.5 % 97.5 %
(Intercept) 17.36 10.556  28.56
xMaintained  2.06  0.979   4.35
```

```
leukemia$x <- relevel(leukemia$x, ref = "Nonmaintained")
m <- survreg(Surv(time, status) ~ x, dist = "lognormal", data = leukemia)
summary(m)$table
```

```
              Value Std. Error      z        p
(Intercept)  2.854      0.254 11.242 2.55e-29
xMaintained  0.724      0.380  1.905 5.68e-02
Log(scale)  -0.145      0.170 -0.858 3.91e-01
```

```r
exp(cbind(coef(m),confint(m)))
```

```
                    2.5 % 97.5 %
(Intercept) 17.36 10.556  28.56
xMaintained  2.06  0.979   4.35
```

Interval-Censoring

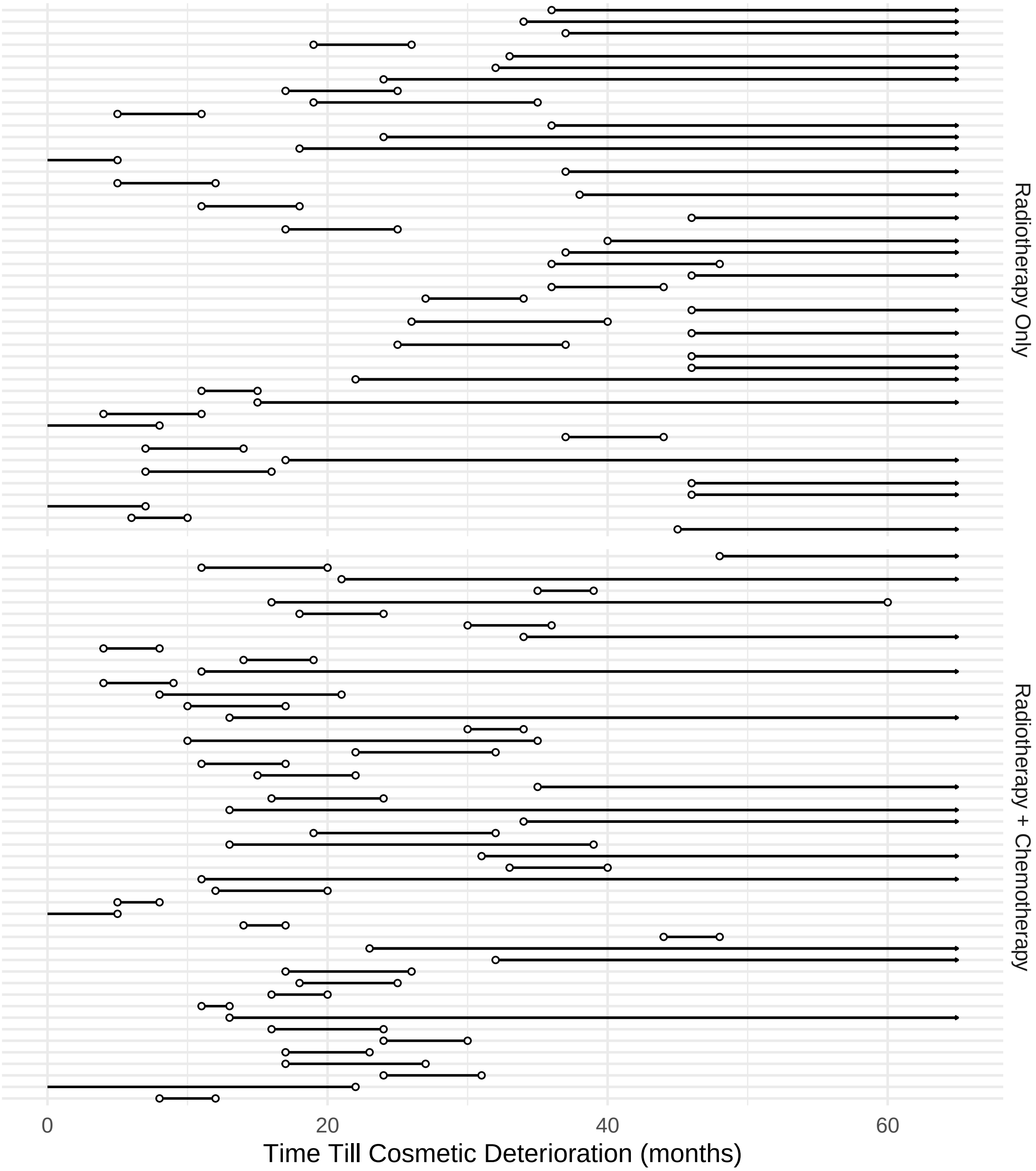
Interval censoring occurs when T_i is only known to be between two numbers such that $a < T_i < b$ where $0 \le a < b \le \infty$. Note that right-censoring is a special case where $b = \infty$, and left-censoring is a special case where $a = 0$.

Example: Consider the following data from a study of the time till cosmetic deterioration for breast cancer patients undergoing radiotherapy alone versus radiotherapy and chemotherapy.

```r
library(mable)
head(cosmesis, 10)
```

```
   left right treat
1    45    NA    RT
2     6    10    RT
3     0     7    RT
4    46    NA    RT
5    46    NA    RT
6     7    16    RT
7    17    NA    RT
8     7    14    RT
9    37    44    RT
10    0     8    RT
```

Note that these data include left-censoring, interval-censoring, and right-censoring).



Using the **Surv** function to specify censoring requires that lower bounds of 0 and upper bounds of ∞ be replaced with `NA`.

```
cosmesis$left <- ifelse(cosmesis$left == 0, NA, cosmesis$left)
head(cosmesis, 10)
```

```
  left right treat
1   45    NA    RT
2    6    10    RT
3   NA     7    RT
4   46    NA    RT
5   46    NA    RT
```

```
6     7    16    RT
7    17    NA    RT
8     7    14    RT
9    37    44    RT
10   NA     8    RT
```

```
tail(cosmesis, 10)
```

```
   left right treat
85   14    19   RCT
86    4     8   RCT
87   34    NA   RCT
88   30    36   RCT
89   18    24   RCT
90   16    60   RCT
91   35    39   RCT
92   21    NA   RCT
93   11    20   RCT
94   48    NA   RCT
```

It is also useful to note that you can accommodate an observation that is *not* censored by specifying *equal* left and right interval endpoints.

We can verify the censoring specification by looking at what `Surv` produces.

```
cosmesis$y <- with(cosmesis, Surv(left, right, type = "interval2"))
head(cosmesis, 10)
```

```
   left right treat        y
1    45    NA    RT      45+
2     6    10    RT [ 6, 10]
3    NA     7    RT       7-
4    46    NA    RT      46+
5    46    NA    RT      46+
6     7    16    RT [ 7, 16]
7    17    NA    RT      17+
8     7    14    RT [ 7, 14]
9    37    44    RT [37, 44]
10   NA     8    RT       8-
```

Now we can estimate an AFT model.

```
m <- survreg(Surv(left, right, type = "interval2") ~ treat,
  dist = "lognormal", data = cosmesis)
summary(m)$table
```

```
             Value Std. Error     z         p
(Intercept)  3.548      0.154 23.01 3.45e-117
treatRCT    -0.421      0.203 -2.07  3.83e-02
Log(scale)  -0.125      0.109 -1.15  2.52e-01
```

Applying the exponential function helps interpret the effect of the treatment.

```
exp(cbind(coef(m), confint(m)))
```

```
                   2.5 % 97.5 %
(Intercept) 34.739 25.680 46.995
treatRCT     0.656  0.441  0.978
```

Using `flexsurvreg` produces the same information but in one output.

```r
library(flexsurv)
m <- flexsurvreg(Surv(left, right, type = "interval2") ~ treat,
  dist = "lognormal", data = cosmesis)
print(m)
```

```
Call:
flexsurvreg(formula = Surv(left, right, type = "interval2") ~ 
    treat, data = cosmesis, dist = "lognormal")

Estimates: 
          data mean  est      L95%     U95%     se       exp(est)  L95%     U95%   
meanlog        NA     3.5479   3.2457   3.8500   0.1542       NA        NA        NA
sdlog          NA     0.8821   0.7118   1.0933   0.0966       NA        NA        NA
treatRCT   0.5106    -0.4210  -0.8192  -0.0228   0.2032   0.6564    0.4408    0.9775

N = 94,  Events: 0,  Censored: 94
Total time at risk: 2089
Log-likelihood = -147, df = 3
AIC = 299
```

Again, it is sometimes helpful for interpretation to change the reference level when dealing with categorical explanatory varaibles.

```r
cosmesis$treat <- relevel(cosmesis$treat, ref = "RCT")
m <- flexsurvreg(Surv(left, right, type = "interval2") ~ treat,
  dist = "lognormal", data = cosmesis)
print(m)
```

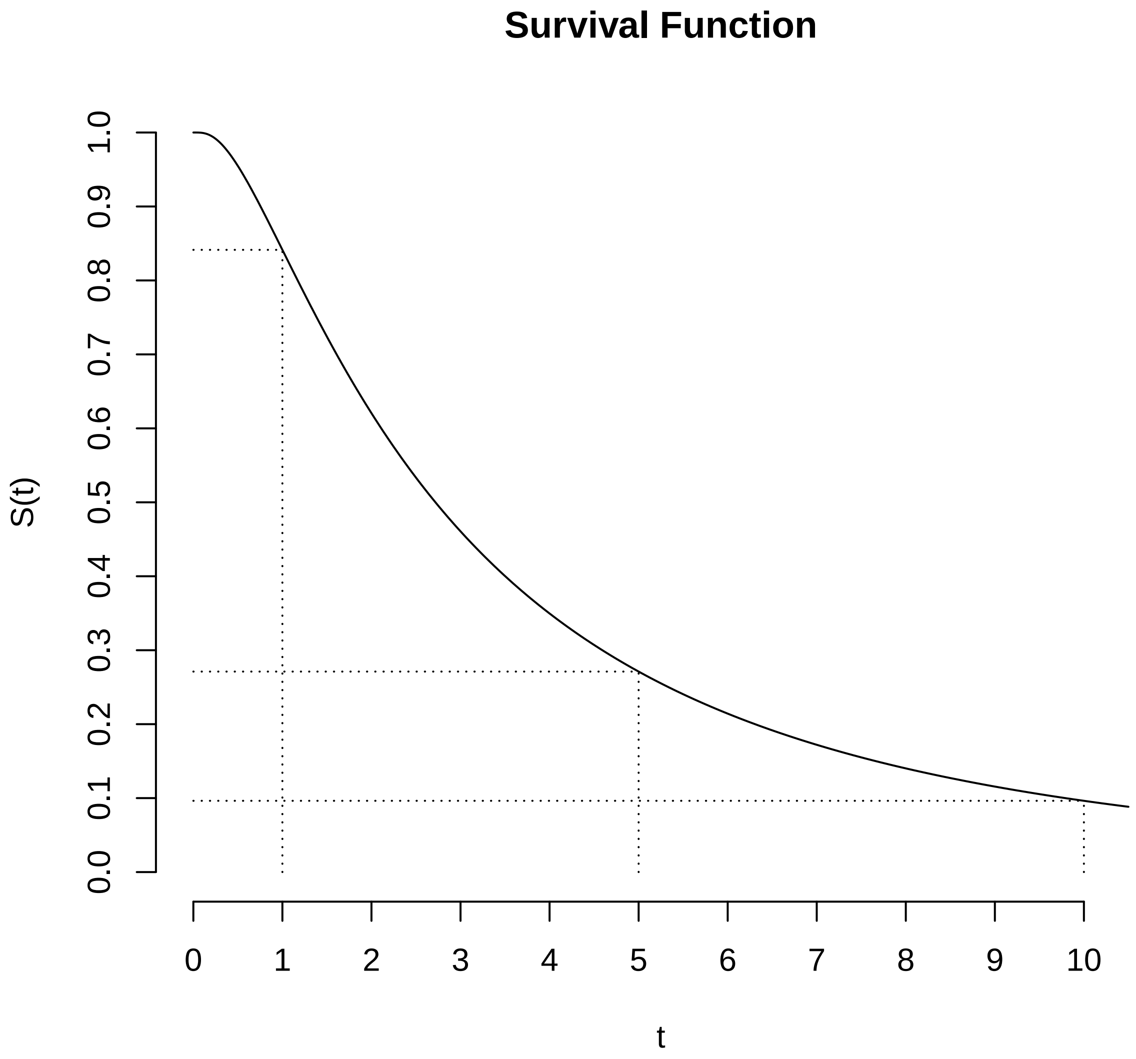
```
Call:
flexsurvreg(formula = Surv(left, right, type = "interval2") ~ 
    treat, data = cosmesis, dist = "lognormal")

Estimates: 
         data mean  est     L95%    U95%    se      exp(est)  L95%    U95%  
meanlog      NA     3.1269  2.8558  3.3980  0.1383      NA        NA      NA
sdlog        NA     0.8821  0.7118  1.0933  0.0966      NA        NA      NA
treatRT  0.4894     0.4210  0.0228  0.8192  0.2032  1.5235    1.0230  2.2688

N = 94,  Events: 0,  Censored: 94
Total time at risk: 2089
Log-likelihood = -147, df = 3
AIC = 299
```

Survival Functions

The *survival function* is

$$S(t) = P(T \geq t),$$

i.e., the probability of a survival time of *at least* t. It is sometimes defined as $S(t) = P(T > t)$ rather than $S(t) = P(T \geq t)$, but if time is modeled as a continuous random variable this distinction does not matter.



Another useful property of survival functions is that the area under the survival curve equals the expected survival time $E(T_i)$, assuming $S(0) = 0$ (i.e., no events have happened at time zero) and $S(\infty) = 1$ (i.e., events eventually do happen).

Survival Functions and AFT Models

Technical Explanation: Accelerated failure time models can be interpreted in terms of effects on survival functions. Let

$$T_b = e^{\beta_0} e^{\beta_1 x_1} e^{\beta_2 x_2} \cdots e^{\beta_k x_k} e^{\sigma \epsilon},$$

and let $T_a = e^{\beta_1} T_b$ as before where T_a and T_b are the survival times when the first explanatory variable assumes values of x_a and x_b, respectively. The survival functions for T_a and T_b are then

$$S_a(t) = P(T_a \geq t) \;\; \text{and} \;\; S_b(t) = P(T_b \geq t),$$

respectively. These survival functions are related because

$$S_b(t) = P(T_b \geq t) = P(e^{\beta_1} T_b \geq e^{\beta_1} t) = P(T_a \geq e^{\beta_1} t) = S_a(e^{\beta_1} t).$$

That is, $S_b(t) = S_a(e^{\beta_1} t)$ and also $S_b(t/e^{\beta_1}) = S_a(t)$. So we can say the following.

1. The probability of survival past t at x_b equals the probability of survival past $e^{\beta_1}t$ at x_a.
2. The probability of survival past t at x_a equals the probability of survival past t/e^{β_1} at x_b.

It can also be shown that we can "order" the survival functions/probabilities from an AFT model because

$$\beta_j > 0 \Leftrightarrow e^{\beta_j} > 1 \Leftrightarrow S_b(t) < S_a(t),$$
$$\beta_j < 0 \Leftrightarrow e^{\beta_j} < 1 \Leftrightarrow S_b(t) > S_a(t).$$

Note that with an AFT model the survival functions at two different values of an explanatory variable do not cross.

In an AFT model the explanatory variables can be viewed as "compressing" or "stretching" time which has the effect of "horizontally compressing/stretching" the survival function. Assume $T_i = e^{\beta_0}e^{\beta_1 x_{i1}} \cdots e^{\beta_k x_{ik}} e^{\sigma\epsilon_i}$ and let $S_i(t)$ be the survival function of T_i. Then

$$S_i(t) = P(T_i \geq t) = P(e^{\beta_0}e^{\beta_1 x_{i1}} \cdots e^{\beta_k x_{ik}} e^{\sigma\epsilon_i} \geq t) = P[e^{\beta_0}e^{\sigma\epsilon_i} \geq t/(e^{\beta_1 x_{i1}} \cdots e^{\beta_k x_{ik}})].$$

If all $x_{ij} = 0$ then $T_i = e^{\beta_0}e^{\sigma\epsilon_i}$ with a "baseline" survival function $S_0(t) = P(e^{\beta_0}e^{\sigma\epsilon_i} \geq t)$. Then

$$S_i(t) = S_0[t/(e^{\beta_1 x_{i1}} \cdots e^{\beta_k x_{ik}})] \quad \text{and} \quad S_i(te^{\beta_1 x_{i1}} \cdots e^{\beta_k x_{ik}}) = S_0(t).$$

So the explanatory variables effectively "horizontally" compress or stretch a (hypothetical) baseline survival function. Also in terms of the actual times, if $T_0 = e^{\beta_0}e^{\sigma\epsilon}$ represents a "baseline" survival time when all $x_{ij} = 0$, the

$$T_i = e^{\beta_1 x_{i1}} \cdots e^{\beta_k x_{ik}} T_0,$$

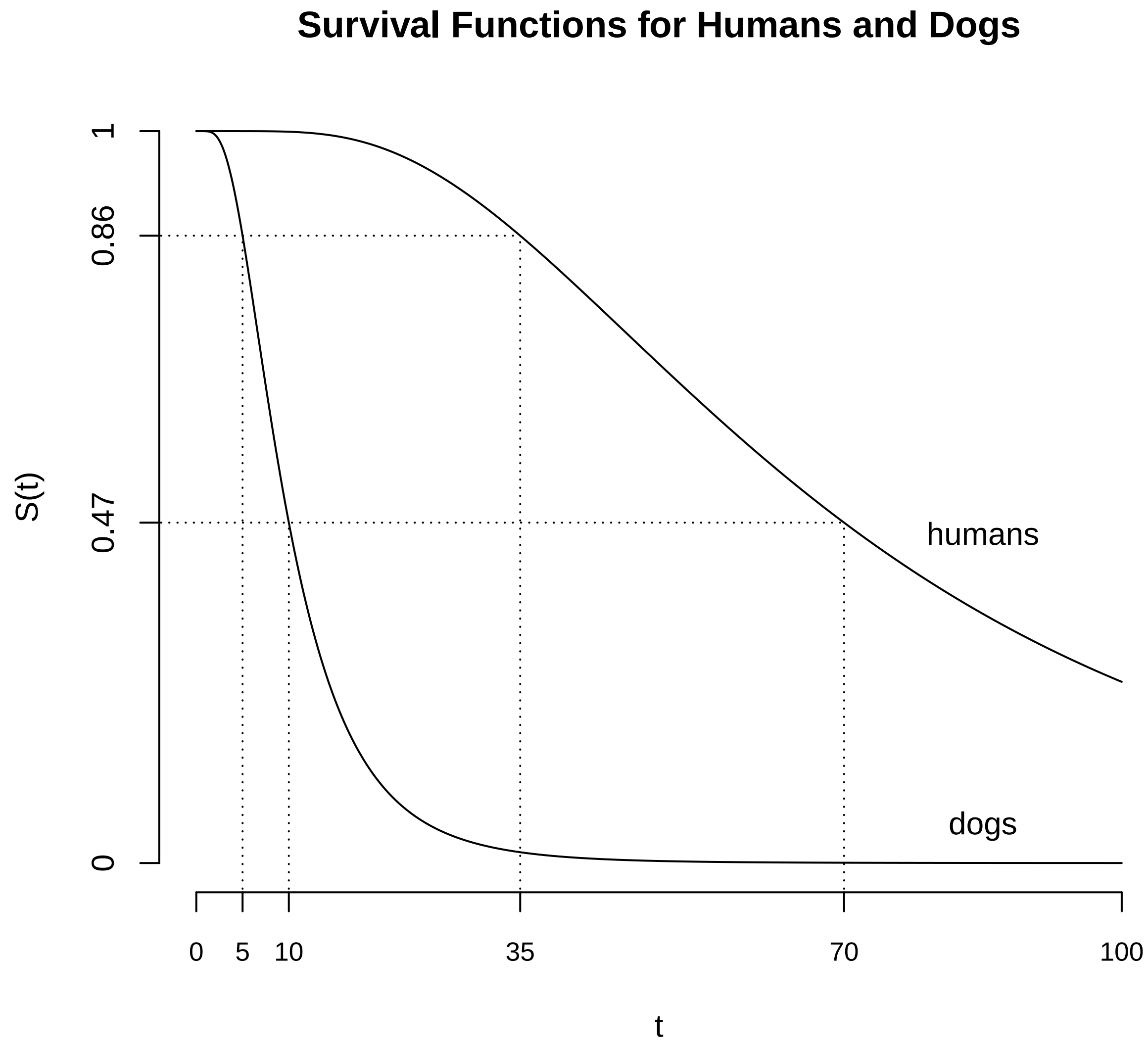
so that again the values of the explanatory variables have the effect of "stretching" or "compressing" time time scale.

Example: Recall the AFT model for the `lifespan` data where the model is

$$\log T_i = \beta_0 + \beta_1 x_i,$$

where x_i is an indicator variable such that $x_i = 1$ if the species is human (so $x_a = 1$ in the above discussion), and $x_i = 0$ if the species is dog (so $x_b = 0$ in the above discussion). The estimate of β_1 was $\hat{\beta}_1 \approx 1.946$ so that $e^{\hat{\beta}_1} \approx 7$. The "baseline" survival function is the survival function for dogs, which we can write as $S_d(t)$. The survival function for humans is then $S_h(7t)$. For example, we estimate that the probability that a dog lives for 10 or more years equals the probability that a human will live for 70 or more years because $S_d(t) = S_h(7t)$ where $t = 10$. The survival function of a human is obtained by "stretching" the survival function of a dog by a factor of 7.

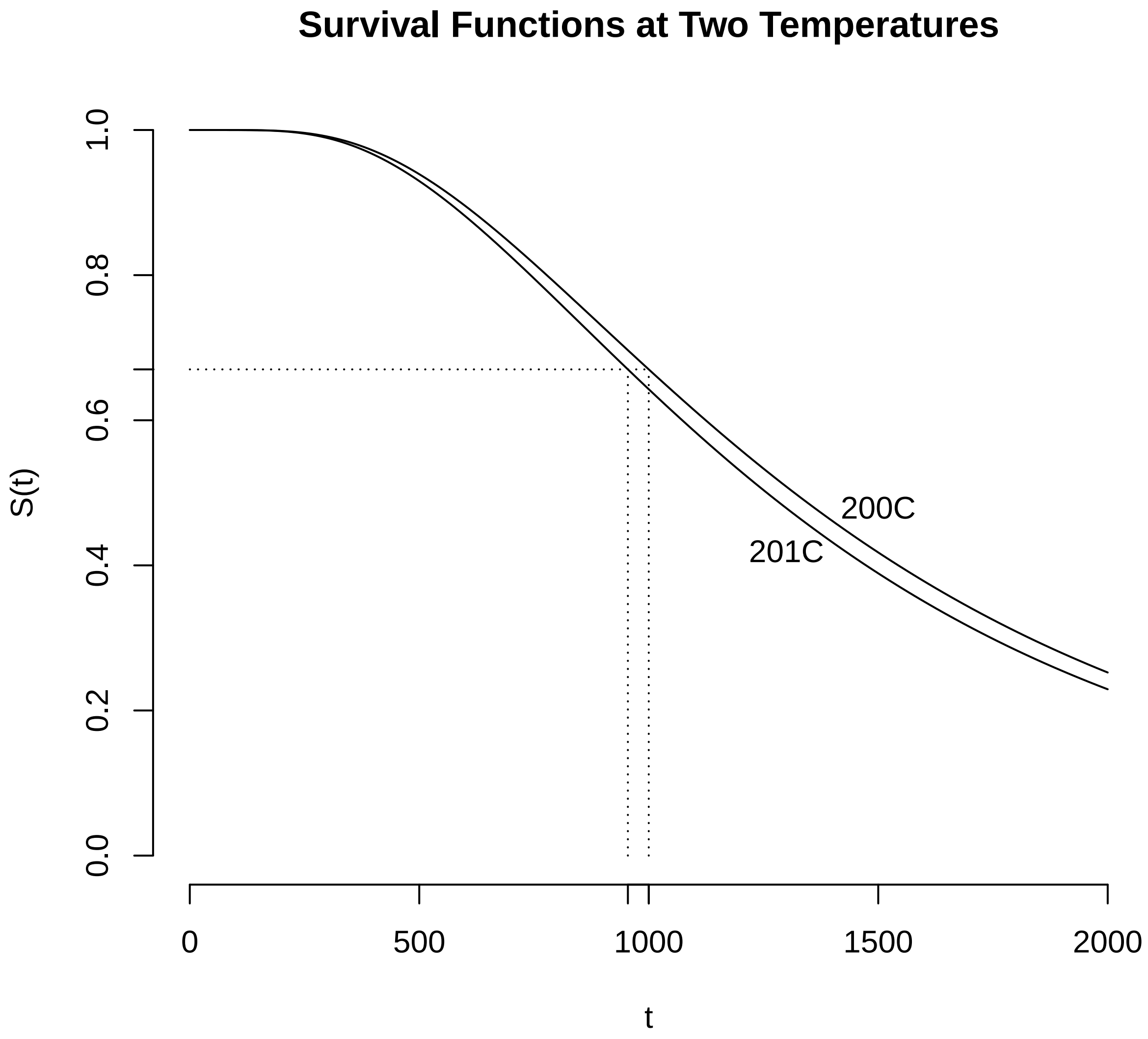
If we re-parameters the model so that $x_i = 1$ if the species is *dog*, then we have that $\hat{\beta}_1 \approx 1/7$, so that the "baseline" survival function is for humans, and we have that $S_h(t) = S_d(t/7)$. We can also say that we estimate that the probability that a human lives to be 35 or more equals the probability that a dog lives to be 5 or more because $S_d(t/7) = S_h(t)$ where $t = 35$. The survival function of a dog is obtained by "compressing" the survival function of a human by a factor of 1/7.



Example: Recall the AFT model for the `motors` data where the model is

$$\log T_i = \beta_0 + \beta_1 x_i,$$

where x_i is temperature. The estimate of β_1 was $\hat{\beta}_1 \approx$ -0.047 so that $e^{\hat{\beta}_1} \approx 0.95$. Thus $S_{x+1}(0.95t) = S_x(t)$ where the subscript of x represents temperature. Increasing by one degree "compresses" the survival function by a factor of about 0.95 (i.e., 5%).



Plotting Estimated Survival Functions

Estimating and plotting survival functions is relatively easy using `flexsurvreg` objects. Here the `summary` function behaves more like `predict` for other model objects produced by `lm`, `nls`, and `glm`.

Example: The estimated survival functions for the AFT model for the `lifespan` data can be computed/plotted as follows.

```
library(trtools) # for lifespan data
m <- flexsurvreg(Surv(years) ~ species, dist = "lognormal", data = lifespan)

d <- data.frame(species = c("dog","human"))
d <- summary(m, newdata = d, t = seq(0, 100, by = 0.5), type = "survival", tidy = TRUE)
head(d)
```

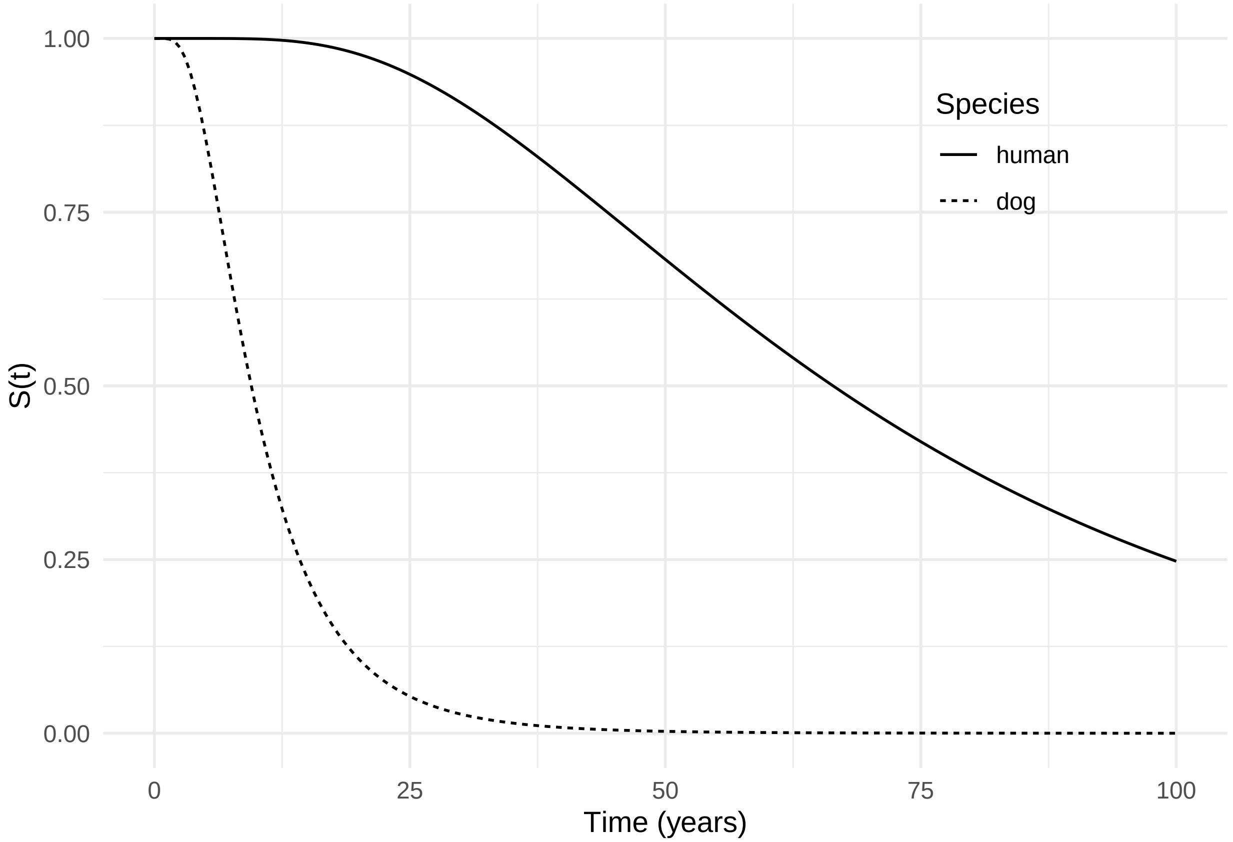
```
  time   est   lcl   ucl species
1  0.0 1.000 1.000 1.000     dog
2  0.5 1.000 1.000 1.000     dog
```

```
3   1.0 1.000 1.000 1.000     dog
4   1.5 0.999 0.998 0.999     dog
5   2.0 0.995 0.994 0.997     dog
6   2.5 0.987 0.983 0.990     dog
```

```r
tail(d)
```

```
     time   est   lcl   ucl species
397  97.5 0.261 0.240 0.281   human
398  98.0 0.258 0.237 0.278   human
399  98.5 0.256 0.235 0.275   human
400  99.0 0.253 0.232 0.272   human
401  99.5 0.250 0.229 0.269   human
402 100.0 0.248 0.227 0.267   human
```

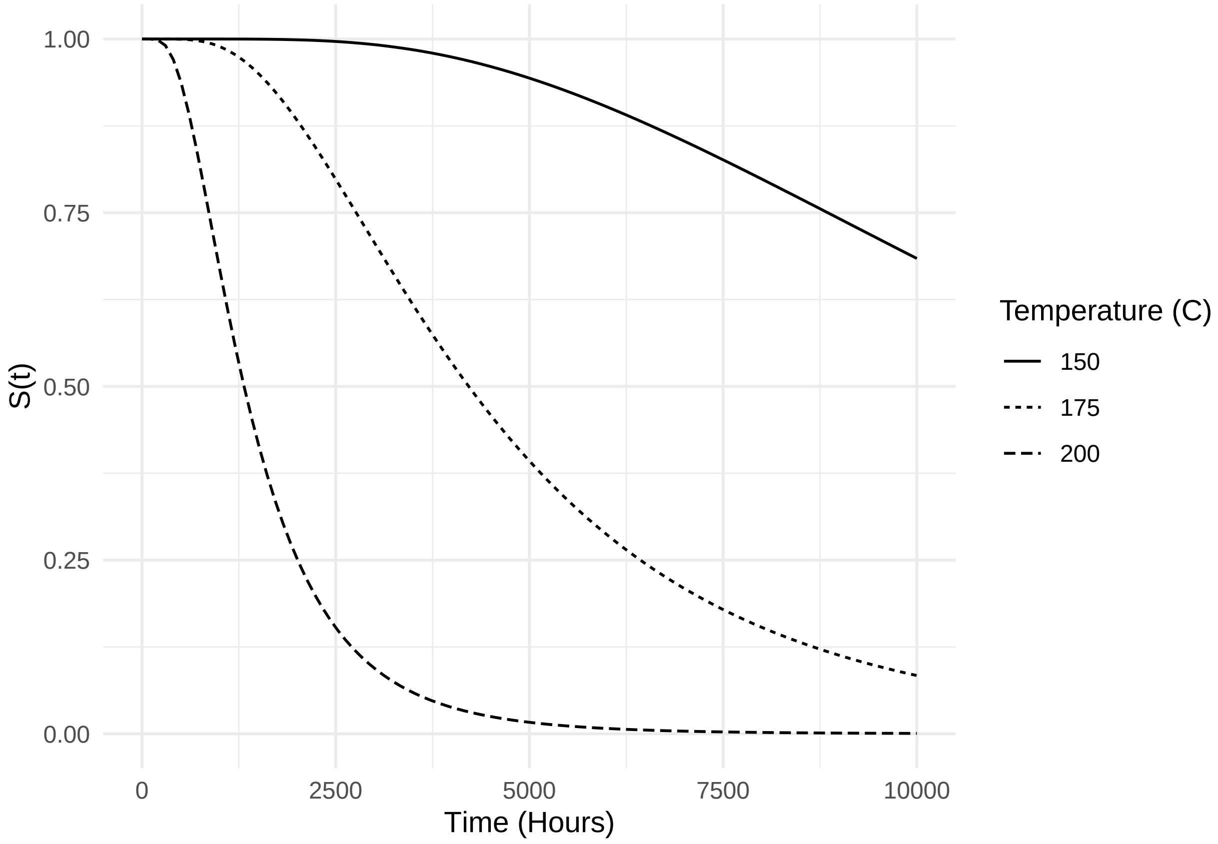
```r
p <- ggplot(d, aes(x = time, y = est)) +
  geom_line(aes(linetype = species)) +
  labs(x = "Time (years)", y = "S(t)", linetype = "Species") +
  theme_minimal() +
  theme(legend.position = "inside", legend.position.inside = c(0.8,0.8))
plot(p)
```



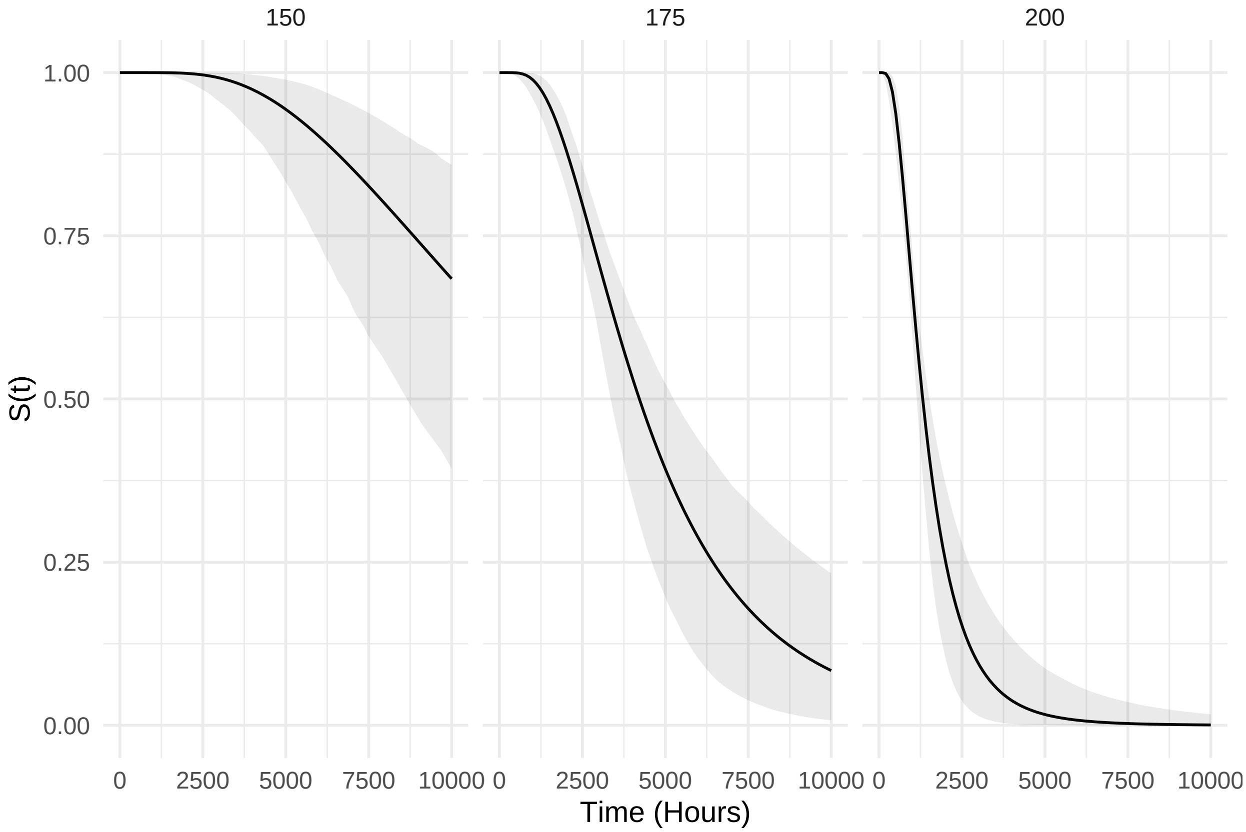
Example: Survival functions at different temperatures based on the AFT model for the `motors` data can be computed/plotted as follows.

```r
library(MASS) # for motors data frame
m <- flexsurvreg(Surv(time, cens) ~ temp, dist = "lognormal", data = motors)
```

```
d <- data.frame(temp = c(150,175,200))
d <- summary(m, newdata = d, t = seq(0, 10000, length = 100),
 type = "survival", tidy = TRUE)

p <- ggplot(d, aes(x = time, y = est, linetype = factor(temp))) +
  geom_line() + theme_minimal() +
  labs(x = "Time (Hours)", y = "S(t)", linetype = "Temperature (C)")
plot(p)
```



```
p <- ggplot(d, aes(x = time, y = est)) +
  geom_line() + facet_wrap(~ temp, nrow = 1) +
  geom_ribbon(aes(ymin = lcl, ymax = ucl), alpha = 0.1) +
  labs(x = "Time (Hours)", y = "S(t)") + theme_minimal()
plot(p)
```


150
175
200
S(t)
1.00
0.75
0.50
0.25
0.00
0
2500
5000
7500
10000
Time (Hours)