Monday, Apr 4

Survival Analysis

In survival analysis the response variable is time-till-event defined as

$$T_i = T_i^{(E)} - T_i^{(0)} \geq 0,$$

where $T_i^{(0)}$ is the starting time and $T_i^{(E)}$ is the time of the event, so that T_i is the time-till-event.

Issues with modeling time-to-event:

1. Distribution of T_i tends to be right-skewed and heteroscedastic with the variance increasing with $E(T_i)$.
2. Times may be *censored*. Right-censoring and interval-censoring are particularly common.
3. Time-varying covariates. Explanatory variables may change values over time.

Censored Observations

Censoring of a variable occurs when we only know that the response variable is within a set or range of values. Common types of censoring are right-censoring, left-censoring, and interval-censoring.

Right-Censoring: We only know that $T > c$ for some constant c. This is very common in survival analysis. It often occurs when the event has not yet happened when observations are stopped, or when the researchers lose track of an observation unit.

Left-Censoring: We only know that $T < c$ for some constant c. This may happen because the event had already happened prior to when we started observation.

Interval-Censoring: We only know that $a < T < b$ for some constants $a < b$. Note that right-censoring can be viewed as a special case where $b = \infty$ and left-censoring can be viewed as a special case where $a = 0$. Interval censoring occurs in survival analysis when units are only periodically observed.

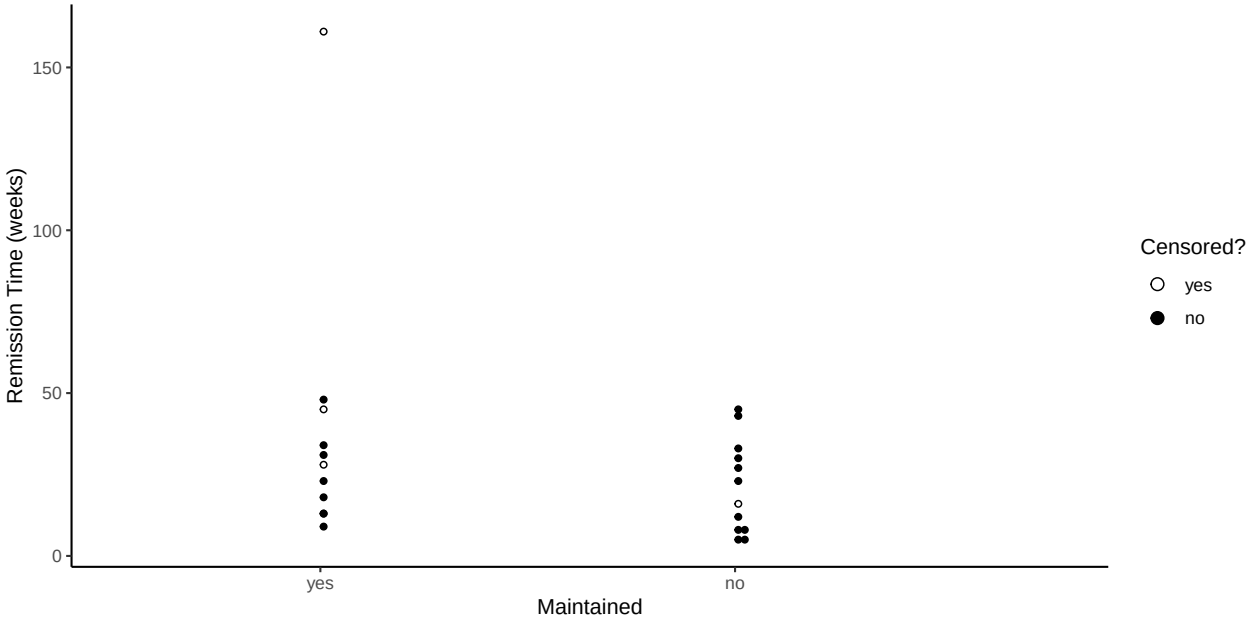
Note that censoring can occur for variables other than time to event. **Example**: Consider the following data from a study of the effect of normal versus extended chemotherapy on the survival of patients with acute myelogenous leukemia.

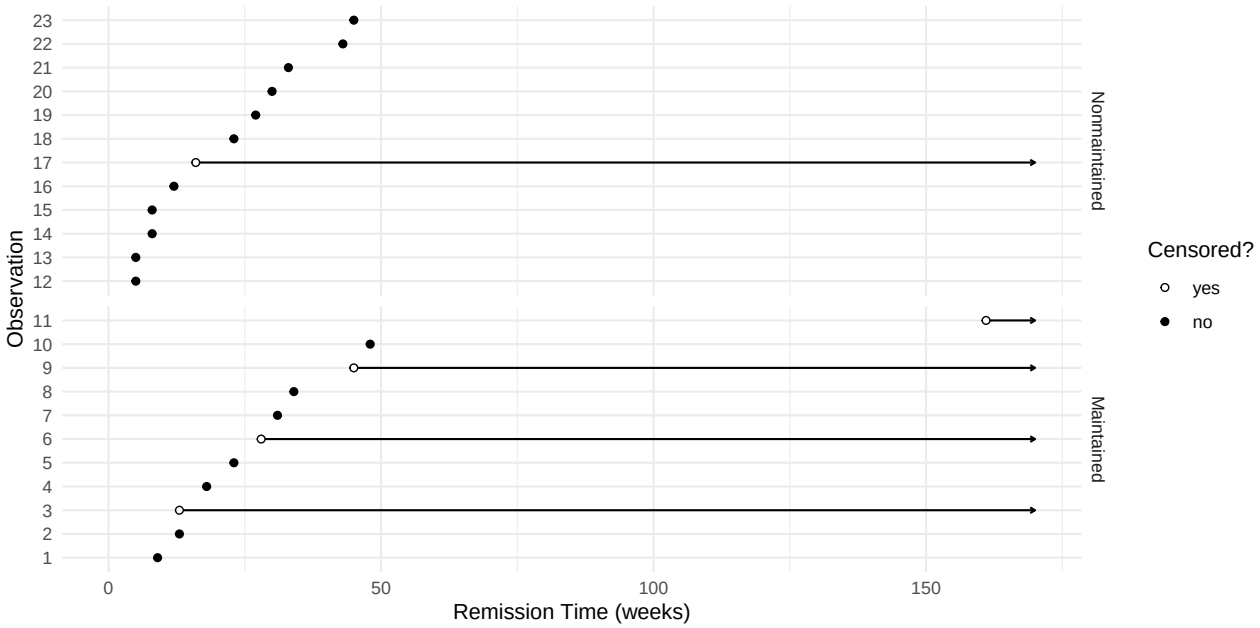
```
library(survival)

leukemia$censored <- factor(leukemia$status, levels = c(0,1),
  labels = c("yes","no")) # right-censored?
leukemia
```

```
   time status             x censored
1     9      1    Maintained       no
2    13      1    Maintained       no
3    13      0    Maintained      yes
4    18      1    Maintained       no
5    23      1    Maintained       no
6    28      0    Maintained      yes
7    31      1    Maintained       no
8    34      1    Maintained       no
9    45      0    Maintained      yes
```

```
10   48      1    Maintained       no
11  161      0    Maintained      yes
12    5      1 Nonmaintained       no
13    5      1 Nonmaintained       no
14    8      1 Nonmaintained       no
15    8      1 Nonmaintained       no
16   12      1 Nonmaintained       no
17   16      0 Nonmaintained      yes
18   23      1 Nonmaintained       no
19   27      1 Nonmaintained       no
20   30      1 Nonmaintained       no
21   33      1 Nonmaintained       no
22   43      1 Nonmaintained       no
23   45      1 Nonmaintained       no
```





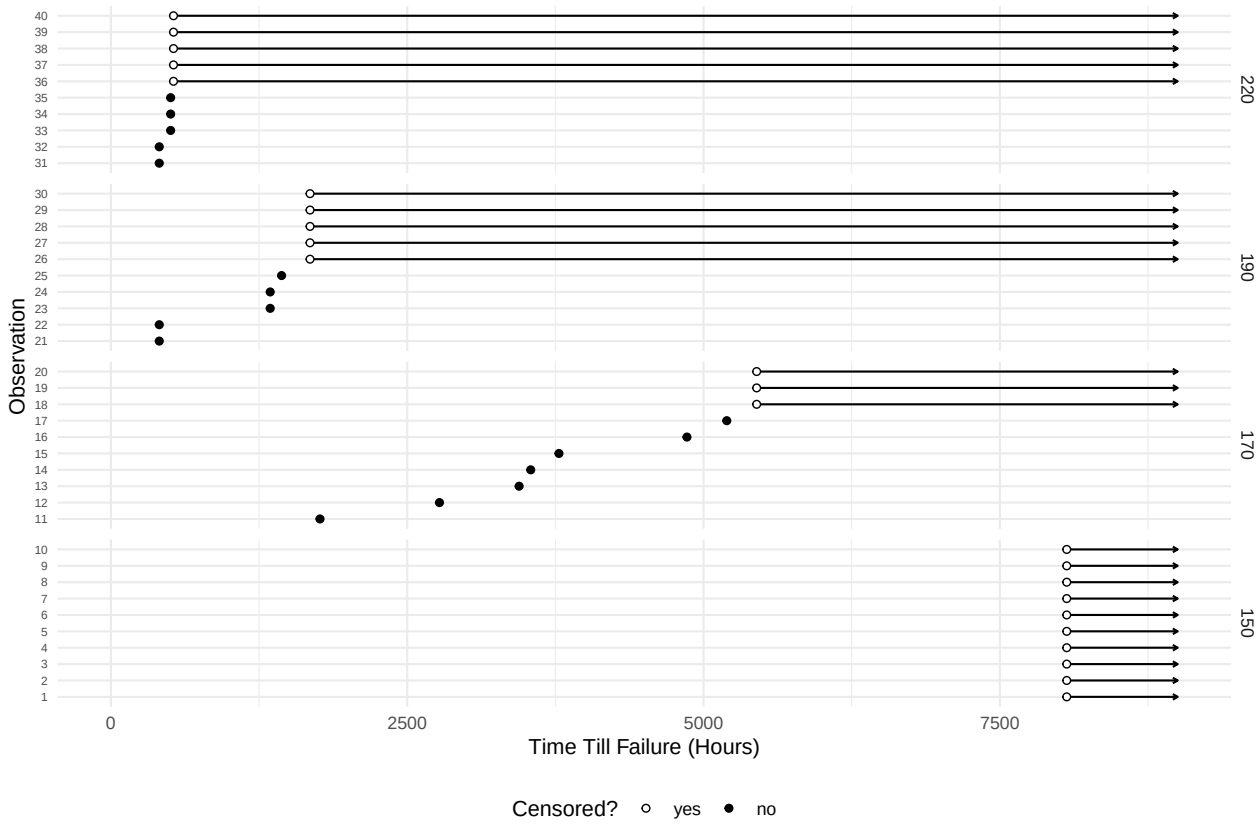
Example: Consider the following data from a study on the effect of temperature on the operational time of motors.

```
library(MASS)
head(motors) # note: cens = 0 if observation IS censored
```

```
  temp time cens
1  150 8064    0
2  150 8064    0
3  150 8064    0
4  150 8064    0
5  150 8064    0
6  150 8064    0
```

```
tail(motors)
```

```
   temp time cens
35  220  504    1
36  220  528    0
37  220  528    0
38  220  528    0
39  220  528    0
40  220  528    0
```



Approaches to Modeling of Survival Data

Most regression models for *continuous* survival time can be classified as follows.

1. *Parametric models.* A specific distribution is assumed/specified for T_i. One or more parameters of the distribution can then be a function of one or more explanatory variables. Examples include *accelerated failure time models*, *parametric proportional hazards models*, and *parametric proportional odds models.*
2. *Semi-parametric models.* A specific distribution is not assumed/specified for T_i, but certain relationships between the properties of the distribution and one or more explanatory variables are assumed. Examples include *semi-parametric (Cox) proportional hazards models*, and *semi-parametric proportional odds models.*
3. *Non-parametric methods.* No or negligible assumptions, but largely limited to categorical explanatory variables.

We will also discuss *discrete* survival models where time is either divided into consecutive intervals of time, or we are modeling progression through discrete stages.

Accelerated Failure Time (AFT) Model

An accelerated failure time model can be written as

$$\log T_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_k x_{ik} + \sigma\epsilon_i,$$

where σ is a *scale* parameter that determines the variability of $\log T_i$. This can also be written as

$$T_i = e^{\beta_0} e^{\beta_1 x_{i1}} e^{\beta_2 x_{i2}} \cdots e^{\beta_k x_{ik}} e^{\sigma\epsilon_i}.$$

To complete the model specification we assume a distribution for T_i (which implies a distribution for ϵ_i), or a distribution for ϵ_i (which implies a distribution for T_i).

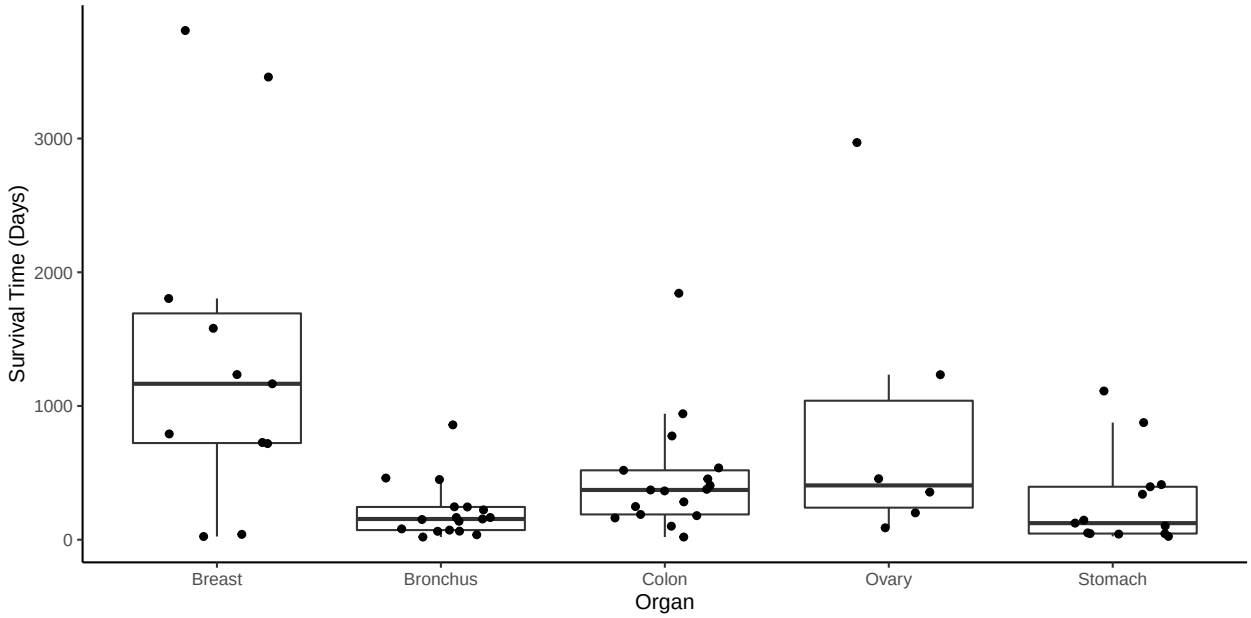
Note that a AFT is essentially a *linear* model where the response variable is $Y_i = \log T_i$ is a transformation of T_i. This is **not** the same as a GLM using a log link function. That would be

$$\log E(T_i) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_k x_{ik}.$$

However in practice the two kinds of models can produce similar results.

Example: Consider the following data on survival time after administration of ascorbate.

```
library(Stat2Data)
data(CancerSurvival)
p <- ggplot(CancerSurvival, aes(x = Organ, y = Survival)) +
  geom_boxplot(outlier.shape = NA) +
  geom_jitter(width = 0.25, height = 0) +
  ylab("Survival Time (Days)") +
  theme_classic()
plot(p)
```



Suppose we assume that $\log T_i$ has a *normal* distribution. Then we can estimate an AFT as follows.

```
m <- lm(log(Survival) ~ Organ, data = CancerSurvival)
summary(m)
```

```
Call:
lm(formula = log(Survival) ~ Organ, data = CancerSurvival)

Residuals:
   Min     1Q Median     3Q    Max
-3.381 -0.661  0.102  0.821  2.046

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)     6.559      0.360   18.20  < 2e-16 ***
OrganBronchus  -1.605      0.462   -3.47  0.00097 ***
OrganColon     -0.809      0.462   -1.75  0.08525 .
OrganOvary     -0.408      0.607   -0.67  0.50380
```

```
OrganStomach    -1.591      0.490   -3.25  0.00191 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1.2 on 59 degrees of freedom
Multiple R-squared:  0.225, Adjusted R-squared:  0.173
F-statistic: 4.29 on 4 and 59 DF,  p-value: 0.00412
```

Here the `residual standard error` is the estimate of σ, computed as

$$\hat{\sigma} = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n-k-1}},$$

where $\hat{y}_i = \hat{\beta}_0 + \hat{\beta}_1 x_{i1} + \cdots + \hat{\beta}_k x_{ik}$.

Other functions for estimating an AFT model are `survreg` from the **survival** package and `flexsurvreg` from the **flexsurv** package. In both cases the distribution of T_i is specified as *log-normal* (a random variable Y_i has a log-normal distribution if its logarithm has a normal distribution).

```
library(survival)
m <- survreg(Surv(Survival) ~ Organ, dist = "lognormal", data = CancerSurvival)
summary(m)
```

```
Call:
survreg(formula = Surv(Survival) ~ Organ, data = CancerSurvival,
    dist = "lognormal")
                Value Std. Error     z       p
(Intercept)    6.5586     0.3460 18.96 < 2e-16
OrganBronchus -1.6054     0.4440 -3.62 0.00030
OrganColon    -0.8095     0.4440 -1.82 0.06829
OrganOvary    -0.4080     0.5824 -0.70 0.48357
OrganStomach  -1.5907     0.4701 -3.38 0.00071
Log(scale)     0.1376     0.0884  1.56 0.11961

Scale= 1.15

Log Normal distribution
Loglik(model)= -455.2   Loglik(intercept only)= -463.3
    Chisq= 16.33 on 4 degrees of freedom, p= 0.0026
Number of Newton-Raphson Iterations: 4
n= 64
```

```
confint(m)
```

```
                2.5 %   97.5 %
(Intercept)    5.880  7.23671
OrganBronchus -2.476 -0.73517
OrganColon    -1.680  0.06078
OrganOvary    -1.549  0.73343
OrganStomach  -2.512 -0.66932
```

Note the use of the function `Surv` to define the response variable. This is necessary to communicate any censoring to the function (although here there is no censoring). Note also that the `Scale` is the estimate of scale parameter σ. The reason why it is different from what was obtained form `lm` is that it is a maximum likelihood estimate computed as

$$\hat{\sigma} = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}}.$$

Using `flexsurvreg` produces comparable results.

```
library(flexsurv)
m <- flexsurvreg(Surv(Survival) ~ Organ, dist = "lognormal", data = CancerSurvival)
print(m) # summary behaves differently for flexsurvreg objects --- use print instead
```

```
Call:
flexsurvreg(formula = Surv(Survival) ~ Organ, data = CancerSurvival,
    dist = "lognormal")

Estimates:
               data mean  est      L95%     U95%     se       exp(est)  L95%     U95%
meanlog             NA     6.5586   5.8805   7.2367   0.3460       NA        NA       NA
sdlog               NA     1.1475   0.9650   1.3645   0.1014       NA        NA       NA
OrganBronchus   0.2656    -1.6054  -2.4757  -0.7352   0.4440   0.2008    0.0841   0.4794
OrganColon      0.2656    -0.8095  -1.6797   0.0608   0.4440   0.4451    0.1864   1.0627
OrganOvary      0.0938    -0.4080  -1.5494   0.7334   0.5824   0.6650    0.2124   2.0822
OrganStomach    0.2031    -1.5907  -2.5120  -0.6693   0.4701   0.2038    0.0811   0.5121

N = 64,  Events: 64,  Censored: 0
Total time at risk: 35752
Log-likelihood = -455.2, df = 6
AIC = 922.4
```

Here `sdlog` corresponds to the scale parameter σ, and `meanlog` corresponds to β_0. The `est` column gives the estimates of $\beta_1, \beta_2, \ldots, \beta_k$. The `se` column is the standard error of each estimator, and the first set of columns `L95%` and `U95%` give the confidence interval of each parameter.

Note that we can obtain the same estimates (although slightly different standard errors) using a linear model for $\log T_i$.

Interpretation of Model Parameters in AFT Models

Recall that with an AFT model we can write time-till-event as

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

We can interpret parameters and linear combinations thereof by applying the exponential function in much the same way as we do with a GLM that has a log link function.

Quantitative Explanatory Variable

Let

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

be time-till-event at given values of the explanatory variables. If we increase x_1 by one unit to $x_1 + 1$ then we get

$$T_a = e^{\beta_0} e^{\beta_1 (x_1+1)} e^{\beta_2 x_2} \cdots e^{\beta_p x_p} e^{\sigma\epsilon} = e^{\beta_1} \underbrace{e^{\beta_0} e^{\beta_1 x_1} e^{\beta_2 x_2} \cdots e^{\beta_p x_p} e^{\sigma\epsilon}}_{T_b},$$

so $T_a/T_b = e^{\beta_1}$ and $T_a = e^{\beta_1} T_b$.

1. If $\beta_1 < 0$ then $e^{\beta_1} < 1$ and increasing x_1 will "compress" time-till-event (i.e., "accelerate the passage through time") by a factor of e^{β_1}. We could also say that increasing x_1 by one unit reduces time-till-event by a factor of e^{β_1}, or by $(1 - e^{\beta_1}) \times 100\%$.

2. If $\beta_1 > 0$ then $e^{\beta_1} > 1$ and increasing x_1 will "stretch" time-till-event (i.e., "decelerate the passage through time") by a factor of e^{β_1}. We could also say that increasing x_1 by one unit increases time-till-event by a factor of e^{β_1}, or by $(e^{\beta_1} - 1) \times 100\%$. Also note that

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

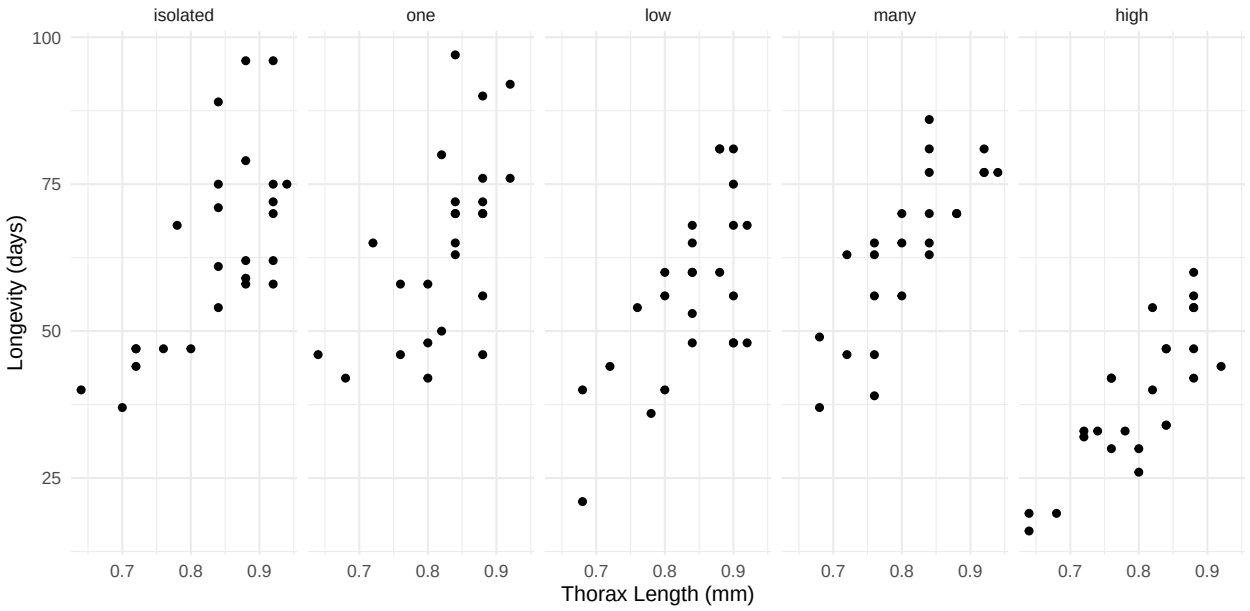
and

$$E(T_a) = e^{\beta_0} e^{\beta_1 (x_1+1)} e^{\beta_2 x_2} \cdots e^{\beta_p x_p} E(e^{\sigma\epsilon}) = e^{\beta_1} \underbrace{e^{\beta_0} e^{\beta_1 x_1} e^{\beta_2 x_2} \cdots e^{\beta_p x_p} E(e^{\sigma\epsilon})}_{E(T_b)},$$

so we can interpret e^{β_1} in the same way that we do for GLMs with a log link function in terms of what happens to the expected time-till-event.

Example: Consider the following data from a study of the longevity of male fruit flies in five experimental conditions.

```
library(faraway)
p <- ggplot(fruitfly, aes(x = thorax, y = longevity)) +
  geom_point() + facet_wrap(~ activity, ncol = 5) +
  labs(x = "Thorax Length (mm)", y = "Longevity (days)") +
  theme_minimal()
plot(p)
```




```
m <- survreg(Surv(longevity) ~ activity + thorax, dist = "lognormal", data = fruitfly)
summary(m)$table
```

```
               Value Std. Error        z          p
(Intercept)  1.84421    0.19395   9.5088  1.929e-21
activityone  0.05174    0.05334   0.9701  3.320e-01
activitylow -0.12387    0.05329  -2.3245  2.010e-02
activitymany 0.08791    0.05410   1.6248  1.042e-01
activityhigh -0.41925    0.05391  -7.7765  7.455e-15
thorax       2.72146    0.22758  11.9585  5.861e-33
Log(scale)  -1.66921    0.06350 -26.2867 2.721e-152
```

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

```
                    2.5 %  97.5 %
(Intercept)    6.3231 4.3236  9.2474
activityone    1.0531 0.9486  1.1692
activitylow    0.8835 0.7959  0.9808
activitymany   1.0919 0.9820  1.2140
activityhigh   0.6575 0.5916  0.7308
thorax        15.2025 9.7320 23.7480
```

```
m <- flexsurvreg(Surv(longevity) ~ activity + thorax, dist = "lognormal", data = fruitfly)
print(m)
```

```
Call:
flexsurvreg(formula = Surv(longevity) ~ activity + thorax, data = fruitfly,
    dist = "lognormal")

Estimates:
              data mean  est      L95%     U95%     se       exp(est)  L95%     U95%
meanlog            NA     1.8442   1.4641   2.2243   0.1939       NA        NA       NA
sdlog              NA     0.1884   0.1663   0.2134   0.0120       NA        NA       NA
activityone    0.2016     0.0517  -0.0528   0.1563   0.0533   1.0531    0.9486   1.1692
activitylow    0.2016    -0.1239  -0.2283  -0.0194   0.0533   0.8835    0.7959   0.9808
activitymany   0.1935     0.0879  -0.0181   0.1940   0.0541   1.0919    0.9820   1.2140
activityhigh   0.2016    -0.4193  -0.5249  -0.3136   0.0539   0.6575    0.5916   0.7308
thorax         0.8224     2.7215   2.2754   3.1675   0.2276  15.2025    9.7320  23.7480

N = 124,  Events: 124,  Censored: 0
Total time at risk: 7145
Log-likelihood = -465, df = 7
AIC = 944
```

A 1mm increase in thorax length is *huge*. How about a 0.1 mm increase in thorax length? One way to consider this is to change the units of thorax length from cm to mm.

```
m <- flexsurvreg(Surv(longevity) ~ activity + I(thorax*10), dist = "lognormal", data = fruitfly)
print(m)
```

```
Call:
flexsurvreg(formula = Surv(longevity) ~ activity + I(thorax *
    10), data = fruitfly, dist = "lognormal")

Estimates:
                data mean  est      L95%     U95%     se       exp(est)  L95%     U95%
meanlog              NA     1.8442   1.4641   2.2243   0.1939       NA        NA       NA
sdlog                NA     0.1884   0.1663   0.2134   0.0120       NA        NA       NA
activityone      0.2016     0.0517  -0.0528   0.1563   0.0533   1.0531    0.9486   1.1692
activitylow      0.2016    -0.1239  -0.2283  -0.0194   0.0533   0.8835    0.7959   0.9808
activitymany     0.1935     0.0879  -0.0181   0.1940   0.0541   1.0919    0.9820   1.2140
activityhigh     0.2016    -0.4193  -0.5249  -0.3136   0.0539   0.6575    0.5916   0.7308
I(thorax * 10)   8.2242     0.2721   0.2275   0.3167   0.0228   1.3128    1.2555   1.3727

N = 124,  Events: 124,  Censored: 0
Total time at risk: 7145
Log-likelihood = -465, df = 7
AIC = 944
```

Example: Consider a AFT for the `motors` data.

```
m <- survreg(Surv(time, cens) ~ temp, dist = "lognormal", data = motors)
summary(m)$table
```

```
               Value Std. Error      z         p
(Intercept) 16.49155   0.929144 17.749 1.749e-70
temp        -0.04654   0.004853 -9.589 8.866e-22
Log(scale)  -0.46838   0.184519 -2.538 1.114e-02
```

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

```
                          2.5 %    97.5 %
(Intercept) 1.453e+07 2.351e+06 8.976e+07
temp        9.545e-01 9.455e-01 9.636e-01
```

Note: We will discuss the specification of the censoring in the next lecture.

Categorical Explanatory Variable

Suppose that x_1 is an indicator variable such that $x_1 = 1$ at a level a, and $x_1 = 0$ at the *reference level* b. Then we have that

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

noting that if $x_1 = 1$ then $e^{\beta_1 x_1} = e^{\beta_1}$ and if $x_1 = 0$ then $e^{\beta_1 x_1} = 1$. So

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

Similarly, $T_b/T_a = 1/e^{\beta_1} = e^{-\beta_1}$.

1. If $\beta_1 < 0$ then $e^{\beta_1} < 1$ and so the time-till-event at level a is "compressed" (accelerated) relative to that at level b by a factor of e^{β_1} (i.e., progression to the event is *faster* at level a than at level b by a factor of e_1^{β}). We could also say that time-till-event at level a is $(1 - e^{\beta_1}) \times 100\%$ that of time-till-event at level b, or that time-till-event at level b is $(e_1^{\beta} - 1) \times 100\%$ that of time-till-event at level a.
2. If $\beta_1 > 0$ then $e^{\beta_1} > 1$ and so the time-till-event at level a is "stretched" (decelerated) relative to that at level b by a factor of e^{β_1} (i.e., progression to the event is *slower* at level a than at level b by a factor of e^{β_1}). We could also say that time-till-event at level a is $(e^{\beta_1} - 1) \times 100\%$ that of time-till-event at level b, or that time-till-event at level b is $(1 - e_1^{\beta}) \times 100\%$ that of time-till-event at level a.

Furthermore, we can interpret e^{β_1} in terms of expected values. We have that

$$E(T_a) = e^{\beta_0} e^{\beta_1 x_1} e^{\beta_2 x_2} \cdots e^{\beta_k x_k} E(e^{\sigma\epsilon}) \quad \text{and} \quad E(T_b) = e^{\beta_0} e^{\beta_2 x_2} \cdots e^{\beta_k x_k} E(e^{\sigma\epsilon}),$$

so

$$\frac{E(T_b)}{E(T_a)} = \frac{e^{\beta_0} e^{\beta_1 x_1} e^{\beta_2 x_2} \cdots e^{\beta_k x_k} E(e^{\sigma\epsilon})}{e^{\beta_0} e^{\beta_2 x_2} \cdots e^{\beta_k x_k} E(e^{\sigma\epsilon})} = e^{\beta_1}.$$

Again, the interpretation is like that for GLMs with the log link function.

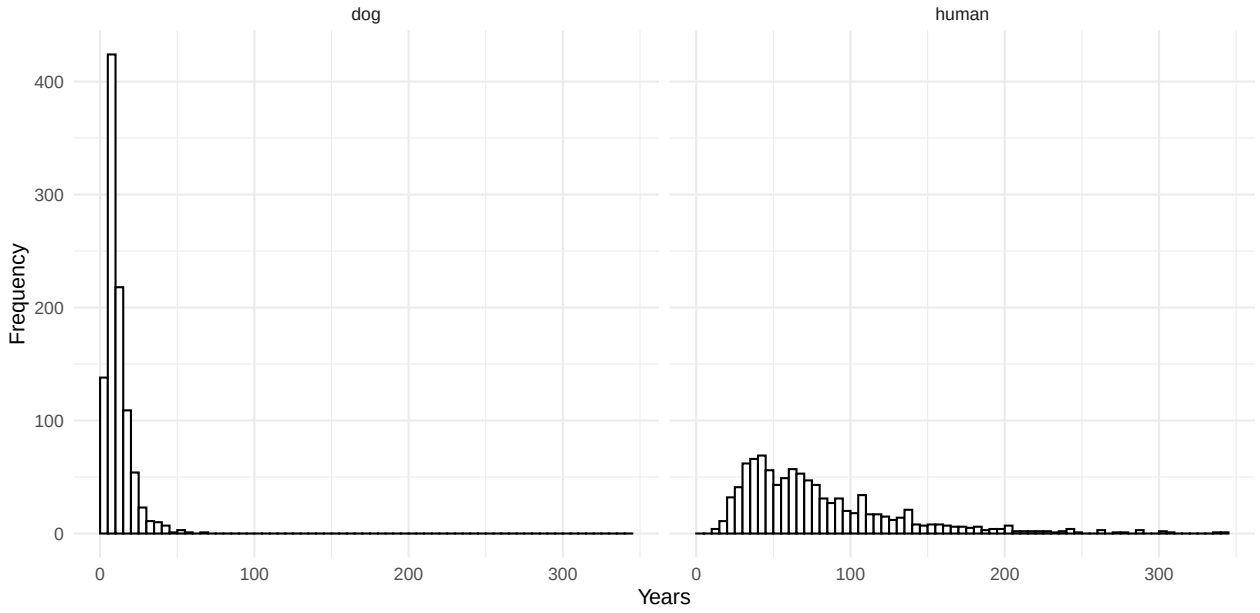
Example: Consider a model for some fictional lifespan data.

```
library(trtools)
head(lifespan)
```

```
  years species
1  36.5   human
2   5.6     dog
3  30.5   human
```

```
4  39.1   human
5   6.7     dog
6   1.8     dog
```

```
p <- ggplot(lifespan, aes(x = years)) + facet_wrap(~ species)
p <- p + geom_histogram(boundary = 0, binwidth = 5, color = "black", fill = "white")
p <- p + labs(x = "Years", y = "Frequency") + theme_minimal()
plot(p)
```




```
m <- survreg(Surv(years) ~ species, dist = "lognormal", data = lifespan)
summary(m)$table
```

```
              Value Std. Error      z          p
(Intercept)   2.250    0.01897 118.60  0.000e+00
specieshuman  1.946    0.02683  72.54  0.000e+00
Log(scale)   -0.511    0.01581 -32.32 3.897e-229
```

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

```
                 2.5 % 97.5 %
(Intercept)  9.486 9.140  9.846
specieshuman 7.001 6.642  7.379
```

```
lifespan$species <- relevel(lifespan$species, ref = "human")
m <- survreg(Surv(years) ~ species, dist = "lognormal", data = lifespan)
summary(m)$table
```

```
             Value Std. Error      z          p
(Intercept)  4.196    0.01897 221.18  0.000e+00
speciesdog  -1.946    0.02683 -72.54  0.000e+00
Log(scale)  -0.511    0.01581 -32.32 3.897e-229
```

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

```
                    2.5 %  97.5 %
(Intercept) 66.4132 63.9892 68.9290
speciesdog   0.1428  0.1355  0.1505
```

For *categorical* explanatory variables (i.e., factors) we can use the **emmeans** package to obtain inferences concerning effects on time (but only for models estimated using `survreg`).

```
library(emmeans)
pairs(emmeans(m, ~species), type = "response", infer = c(TRUE,TRUE))
```

```
 contrast    ratio    SE   df lower.CL upper.CL null t.ratio p.value
 human / dog     7 0.188 1997     6.64     7.38    1  72.540  <.0001

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

```
pairs(emmeans(m, ~species), type = "response", reverse = TRUE, infer = c(TRUE,TRUE))
```

```
 contrast    ratio      SE   df lower.CL upper.CL null t.ratio p.value
 dog / human 0.143 0.00383 1997    0.136    0.151    1 -72.540  <.0001

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

Here we can compare the treatment conditions of the fruit fly experiment.

```
m <- survreg(Surv(longevity) ~ activity + thorax, dist = "lognormal", data = fruitfly)
pairs(emmeans(m, ~activity, at = list(thorax = 0.8)),
  type = "response", adjust = "none", infer = c(TRUE,TRUE))
```

```
 contrast        ratio     SE  df lower.CL upper.CL null t.ratio p.value
 isolated / one  0.950 0.0507 117    0.854    1.055    1  -0.970  0.3340
 isolated / low  1.132 0.0603 117    1.018    1.258    1   2.324  0.0218
 isolated / many 0.916 0.0495 117    0.823    1.019    1  -1.625  0.1069
 isolated / high 1.521 0.0820 117    1.367    1.692    1   7.777  <.0001
 one / low       1.192 0.0636 117    1.072    1.325    1   3.291  0.0013
 one / many      0.965 0.0520 117    0.867    1.073    1  -0.671  0.5037
 one / high      1.602 0.0858 117    1.440    1.781    1   8.787  <.0001
 low / many      0.809 0.0438 117    0.727    0.901    1  -3.912  0.0002
 low / high      1.344 0.0725 117    1.207    1.495    1   5.473  <.0001
 many / high     1.661 0.0895 117    1.492    1.848    1   9.407  <.0001

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

```
pairs(emmeans(m, ~activity, at = list(thorax = 0.8)),
  type = "response", adjust = "none", reverse = TRUE, infer = c(TRUE,TRUE))
```

```
 contrast        ratio     SE  df lower.CL upper.CL null t.ratio p.value
 one / isolated  1.053 0.0562 117    0.948    1.170    1   0.970  0.3340
 low / isolated  0.883 0.0471 117    0.795    0.982    1  -2.324  0.0218
 low / one       0.839 0.0448 117    0.755    0.932    1  -3.291  0.0013
 many / isolated 1.092 0.0591 117    0.981    1.215    1   1.625  0.1069
 many / one      1.037 0.0559 117    0.932    1.154    1   0.671  0.5037
 many / low      1.236 0.0669 117    1.110    1.376    1   3.912  0.0002
 high / isolated 0.657 0.0355 117    0.591    0.732    1  -7.777  <.0001
 high / one      0.624 0.0335 117    0.561    0.694    1  -8.787  <.0001
 high / low      0.744 0.0402 117    0.669    0.828    1  -5.473  <.0001
```

```
 high / many     0.602 0.0325 117    0.541    0.670    1  -9.407  <.0001

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

Note that since there is no interaction between activity and thorax the value of thorax that we use does not matter.

Suppose there was an interaction between thorax length (in 0.1 mm units) and the treatment condition.

```
m <- survreg(Surv(longevity) ~ activity * I(thorax*10), dist = "lognormal", data = fruitfly)
summary(m)$table
```

```
                               Value Std. Error         z          p
(Intercept)                 2.144272    0.37286   5.75083  8.881e-09
activityone                 0.241387    0.57929   0.41670  6.769e-01
activitylow                -0.574782    0.58097  -0.98935  3.225e-01
activitymany                0.054618    0.55635   0.09817  9.218e-01
activityhigh               -1.546499    0.53509  -2.89016  3.850e-03
I(thorax * 10)              0.236253    0.04438   5.32282  1.022e-07
activityone:I(thorax * 10) -0.023422    0.06953  -0.33689  7.362e-01
activitylow:I(thorax * 10)  0.053903    0.06914   0.77963  4.356e-01
activitymany:I(thorax * 10) 0.003059    0.06732   0.04545  9.638e-01
activityhigh:I(thorax * 10) 0.139291    0.06520   2.13649  3.264e-02
Log(scale)                 -1.697073    0.06350 -26.72553 2.378e-157
```

The `emtrends` function from the **emmeans** package can be used here to estimate the effect of thorax size (per 0.1 mm increase) on longevity.

```
emtrends(m, ~activity, var = "I(thorax*10)",
   type = "response", tran = "log", infer = c(TRUE,TRUE))
```

```
 activity response     SE  df lower.CL upper.CL null t.ratio p.value
 isolated     1.27 0.0562 113     1.16     1.38    1   5.323  <.0001
 one          1.24 0.0662 113     1.11     1.38    1   3.977  0.0001
 low          1.34 0.0709 113     1.20     1.48    1   5.473  <.0001
 many         1.27 0.0643 113     1.15     1.40    1   4.728  <.0001
 high         1.46 0.0695 113     1.32     1.60    1   7.864  <.0001

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

Note that the `type = "response"` and `tran = "log"` options are necessary here to get `emtrends` to estimate the multiplicative effect of thorax length. Unfortunately the **emmeans** package function cannot be used with a `flexsurvreg` object, but we can get the effects of thorax length through clever re-parameterization.

```
m <- flexsurvreg(Surv(longevity) ~ activity + activity:I(thorax*10),
   dist = "lognormal", data = fruitfly)
print(m)
```

```
Call:
flexsurvreg(formula = Surv(longevity) ~ activity + activity:I(thorax *
    10), data = fruitfly, dist = "lognormal")

Estimates:
                                data mean  est      L95%     U95%     se       exp(est)
```

```
meanlog                              NA     2.1443   1.4135   2.8751   0.3729       NA
sdlog                                NA     0.1832   0.1618   0.2075   0.0116       NA
activityone                      0.2016     0.2414  -0.8940   1.3768   0.5793   1.2730
activitylow                      0.2016    -0.5748  -1.7135   0.5639   0.5810   0.5628
activitymany                     0.1935     0.0546  -1.0358   1.1450   0.5564   1.0561
activityhigh                     0.2016    -1.5465  -2.5953  -0.4977   0.5351   0.2130
activityisolated:I(thorax * 10)  1.6855     0.2363   0.1493   0.3232   0.0444   1.2665
activityone:I(thorax * 10)       1.6645     0.2128   0.1079   0.3177   0.0535   1.2372
activitylow:I(thorax * 10)       1.6887     0.2902   0.1863   0.3941   0.0530   1.3366
activitymany:I(thorax * 10)      1.5726     0.2393   0.1401   0.3385   0.0506   1.2704
activityhigh:I(thorax * 10)      1.6129     0.3755   0.2819   0.4691   0.0478   1.4558
                                 L95%     U95%
meanlog                              NA       NA
sdlog                                NA       NA
activityone                      0.4090   3.9621
activitylow                      0.1802   1.7575
activitymany                     0.3549   3.1426
activityhigh                     0.0746   0.6079
activityisolated:I(thorax * 10)  1.1610   1.3816
activityone:I(thorax * 10)       1.1140   1.3740
activitylow:I(thorax * 10)       1.2047   1.4830
activitymany:I(thorax * 10)      1.1504   1.4029
activityhigh:I(thorax * 10)      1.3257   1.5986

N = 124,  Events: 124,  Censored: 0
Total time at risk: 7145
Log-likelihood = -461.6, df = 11
AIC = 945.1
```