

Wednesday, April 8

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.

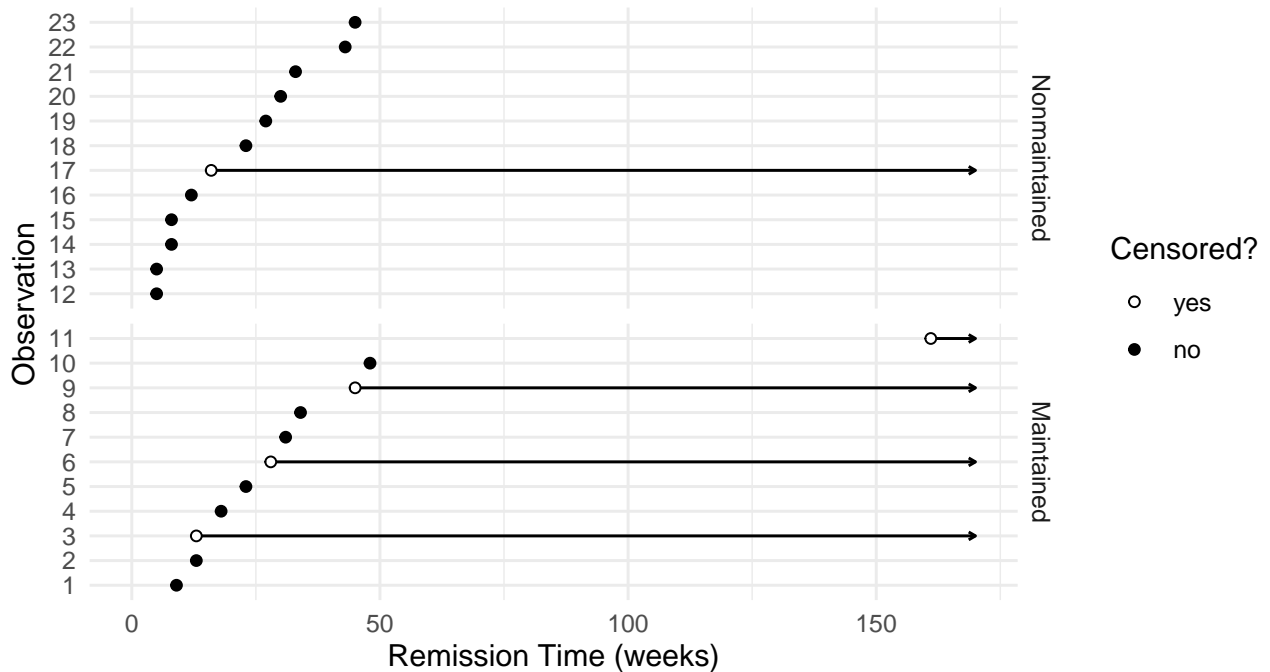
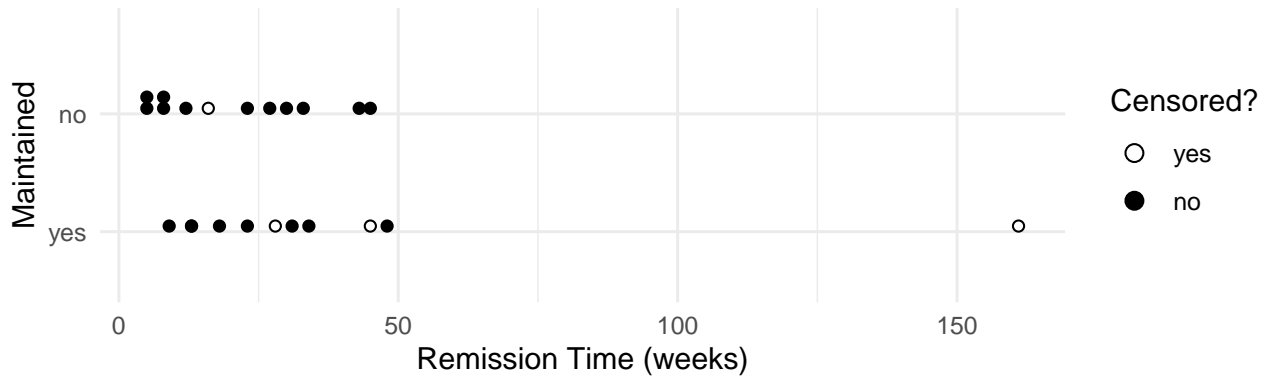
Example: Consider the following data from a study of the effect of normal versus extended chemotherapy on the survival (length of remission) of patients with acute myelogenous leukemia.

```
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



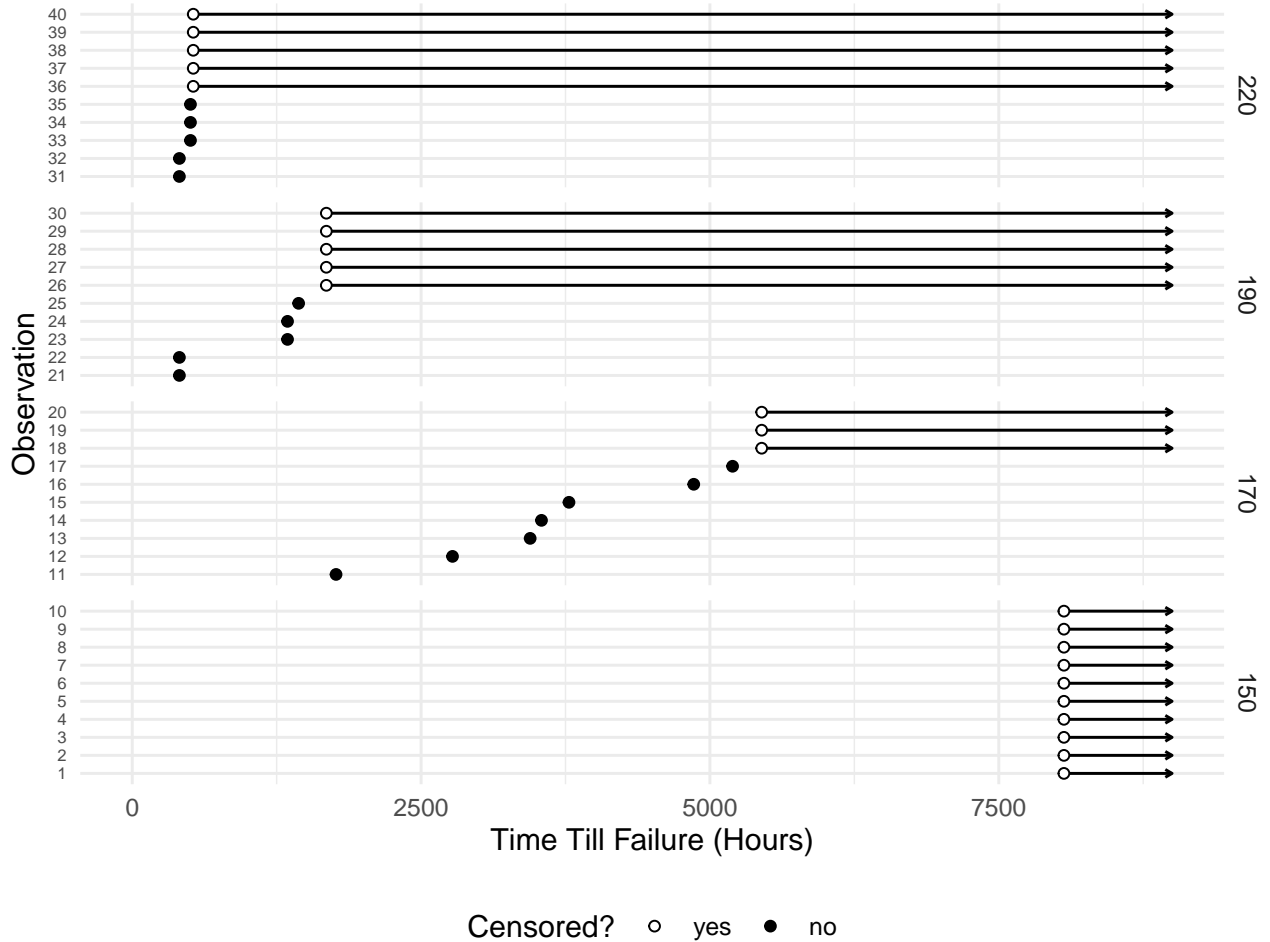
Example: Consider the following data from a study on the effect of temperature on the operational time of motors.

```
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

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

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).

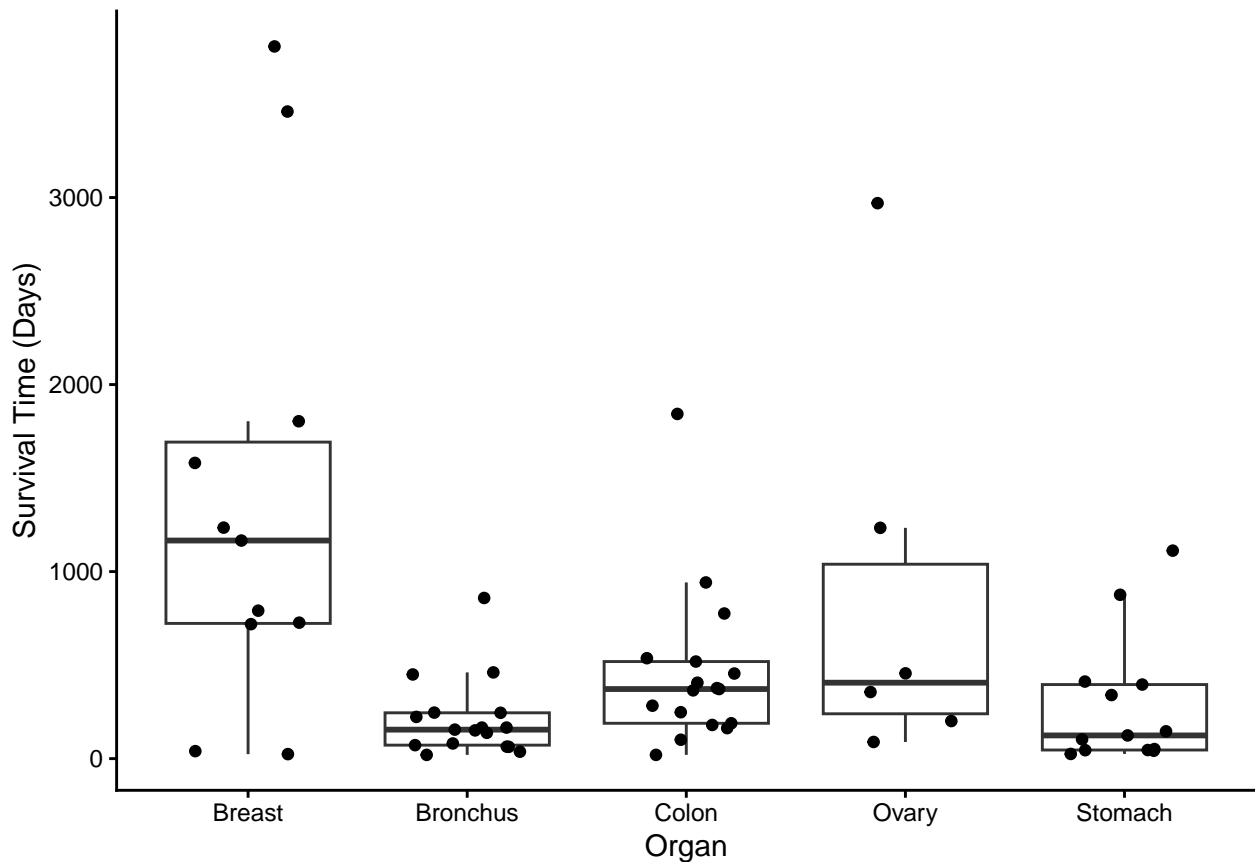
Note that a AFT is essentially a *linear* model where the response variable is $Y_i = \log T_i$ is a transformation of T_i . This is **not** the same as a GLM using a log link function. That would be

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

However in practice the two kinds of models can produce similar results, and can be interpreted similarly.

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

Other functions for estimating an AFT model are `survreg` from the `survival` package and `flexsurvreg` from the `flexsurv` package. In both cases we can specify the distribution of T_i 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 from `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 $\beta_1, \beta_2, \dots, \beta_k$. 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

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

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

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

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

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

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

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

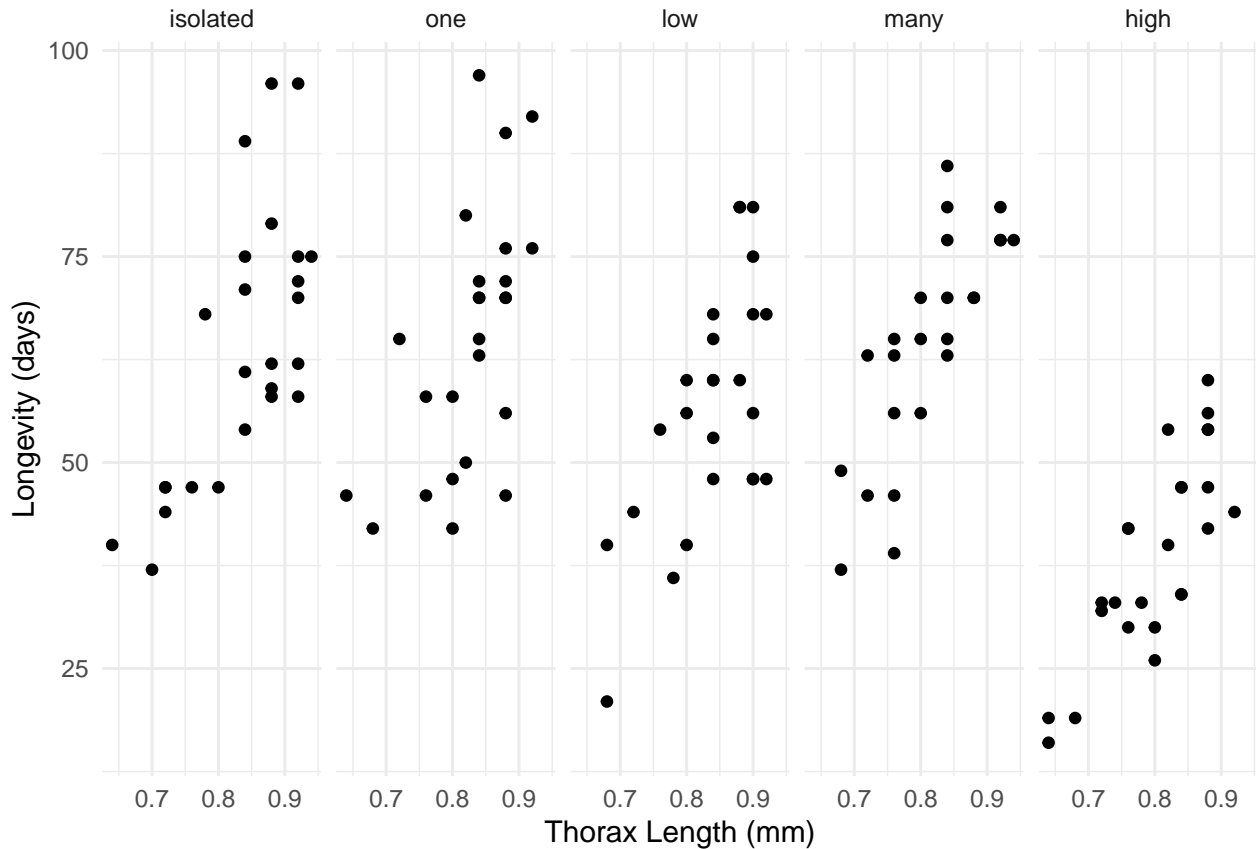
and

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

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? We can do this by changing the units to *tenths of a mm*. One mm is ten tenths of a mm so multiplying length by 10 will put the units into tenths of a 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

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

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

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

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^{β_1}). 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

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

so

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

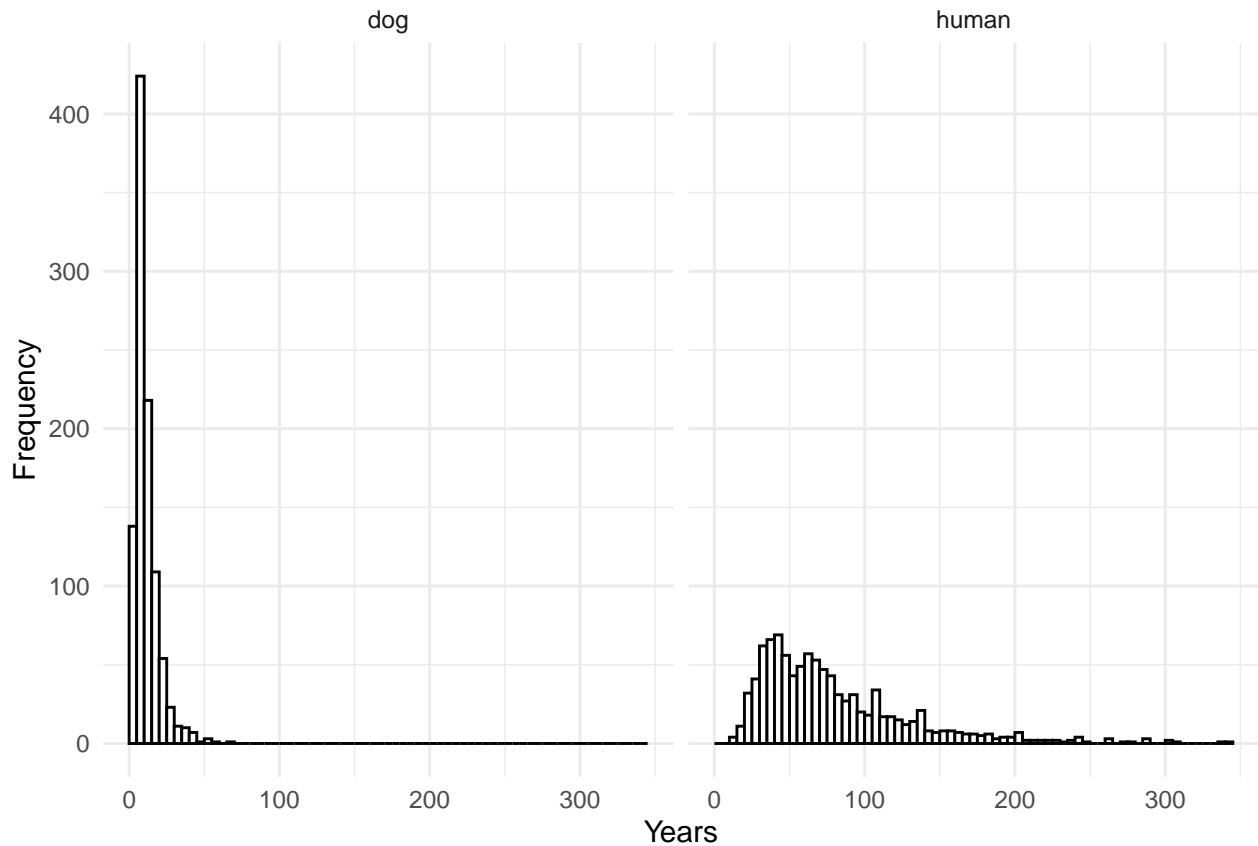
Again, the interpretation is like that for GLMs with the log link function.

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) +
  geom_histogram(boundary = 0, binwidth = 5, color = "black", fill = "white") +
  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
speciesthuman	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
speciesthuman	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 = 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 <0.0001
```

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 = 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 <0.0001
```

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 = TRUE)
```

```
contrast          ratio      SE  df lower.CL upper.CL null t.ratio p.value  
isolated / one    0.950 0.0506 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 <0.0001  
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 <0.0001  
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 <0.0001  
many / high       1.661 0.0895 117    1.492    1.848    1  9.407 <0.0001
```

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 = 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	0.0354	117	0.591	0.732	1	-7.777	<0.0001
high / one	0.624	0.0335	117	0.561	0.694	1	-8.787	<0.0001
high / low	0.744	0.0402	117	0.669	0.828	1	-5.473	<0.0001
high / many	0.602	0.0325	117	0.541	0.670	1	-9.407	<0.0001

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

Here is how we can estimate this effect using the **emmeans** package.

```
m <- survreg(Surv(longevity) ~ activity * thorax, dist = "lognormal", data = fruitfly)
pairs(emmeans(m, ~thorax|activity, at = list(thorax = c(0.5,0.4)),
  type = "response"), infer = TRUE)
```

activity = isolated:

contrast	ratio	SE	df	lower.CL	upper.CL	null	t.ratio	p.value
thorax0.5 / thorax0.4	1.27	0.0562	113	1.16	1.38	1	5.323	<0.0001

activity = one:

contrast	ratio	SE	df	lower.CL	upper.CL	null	t.ratio	p.value
thorax0.5 / thorax0.4	1.24	0.0662	113	1.11	1.38	1	3.977	0.0001

activity = low:

contrast	ratio	SE	df	lower.CL	upper.CL	null	t.ratio	p.value
thorax0.5 / thorax0.4	1.34	0.0709	113	1.20	1.48	1	5.473	<0.0001

activity = many:

contrast	ratio	SE	df	lower.CL	upper.CL	null	t.ratio	p.value
thorax0.5 / thorax0.4	1.27	0.0643	113	1.15	1.40	1	4.728	<0.0001

activity = high:

contrast	ratio	SE	df	lower.CL	upper.CL	null	t.ratio	p.value
thorax0.5 / thorax0.4	1.46	0.0695	113	1.32	1.60	1	7.864	<0.0001

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

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

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