

Wednesday, Apr 5

## 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.

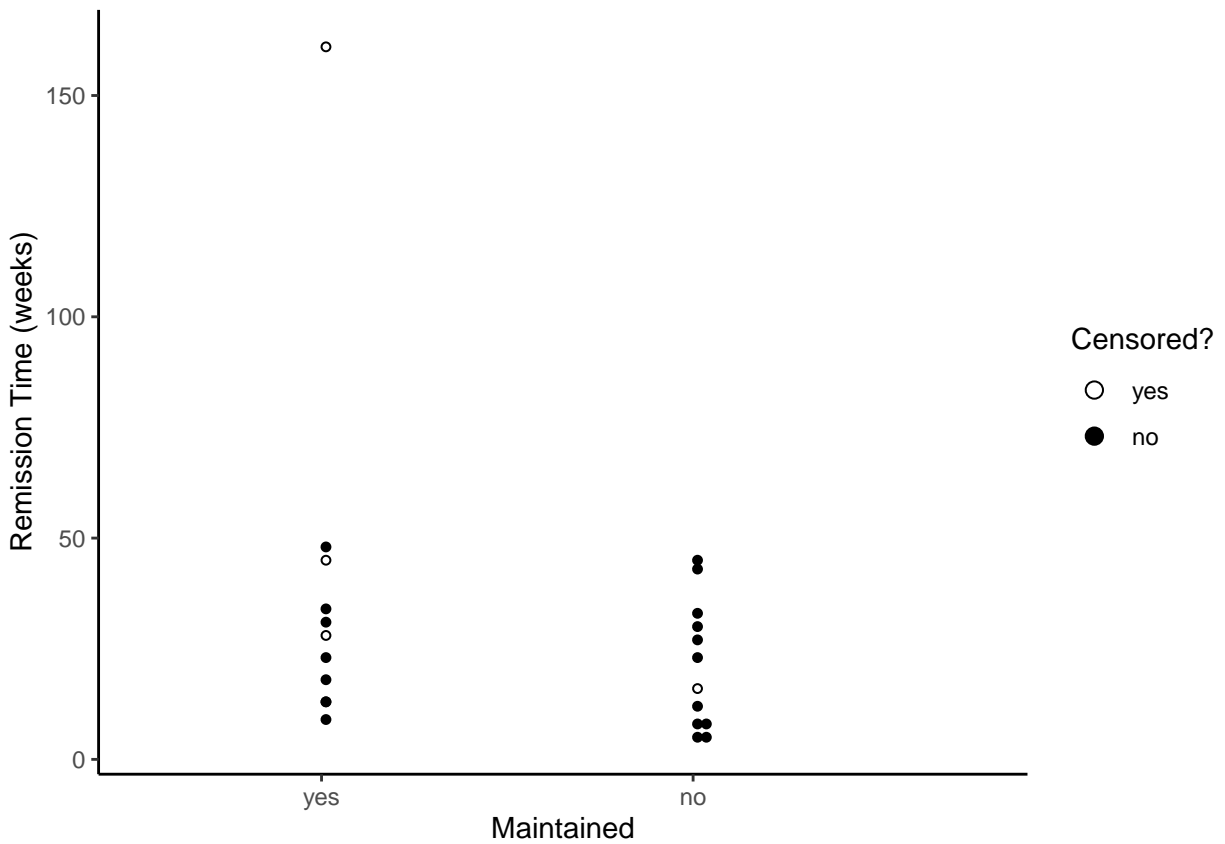
Note that censoring can occur for variables other than time to event. **Example:** Consider the following data from a study of the effect of normal versus extended chemotherapy on the survival of patients with acute myelogenous leukemia.

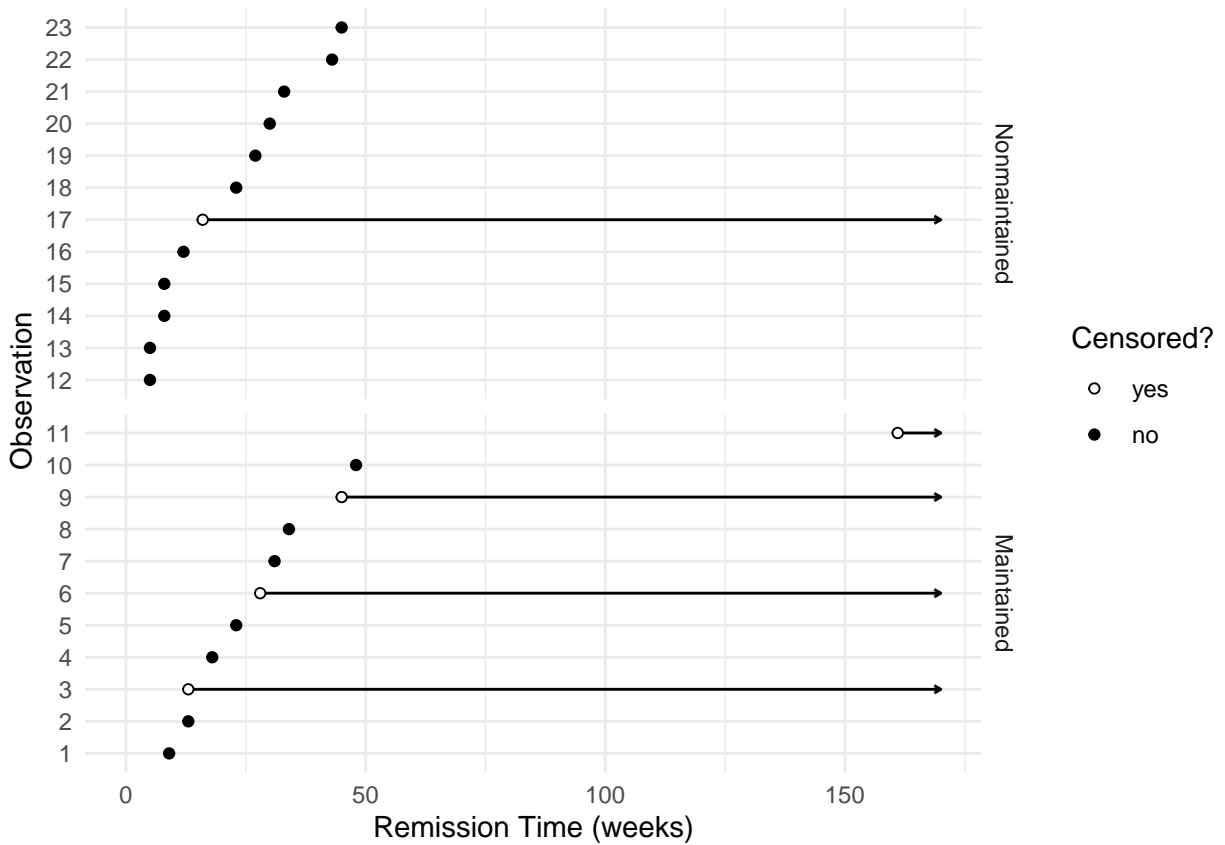
```
library(survival)

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





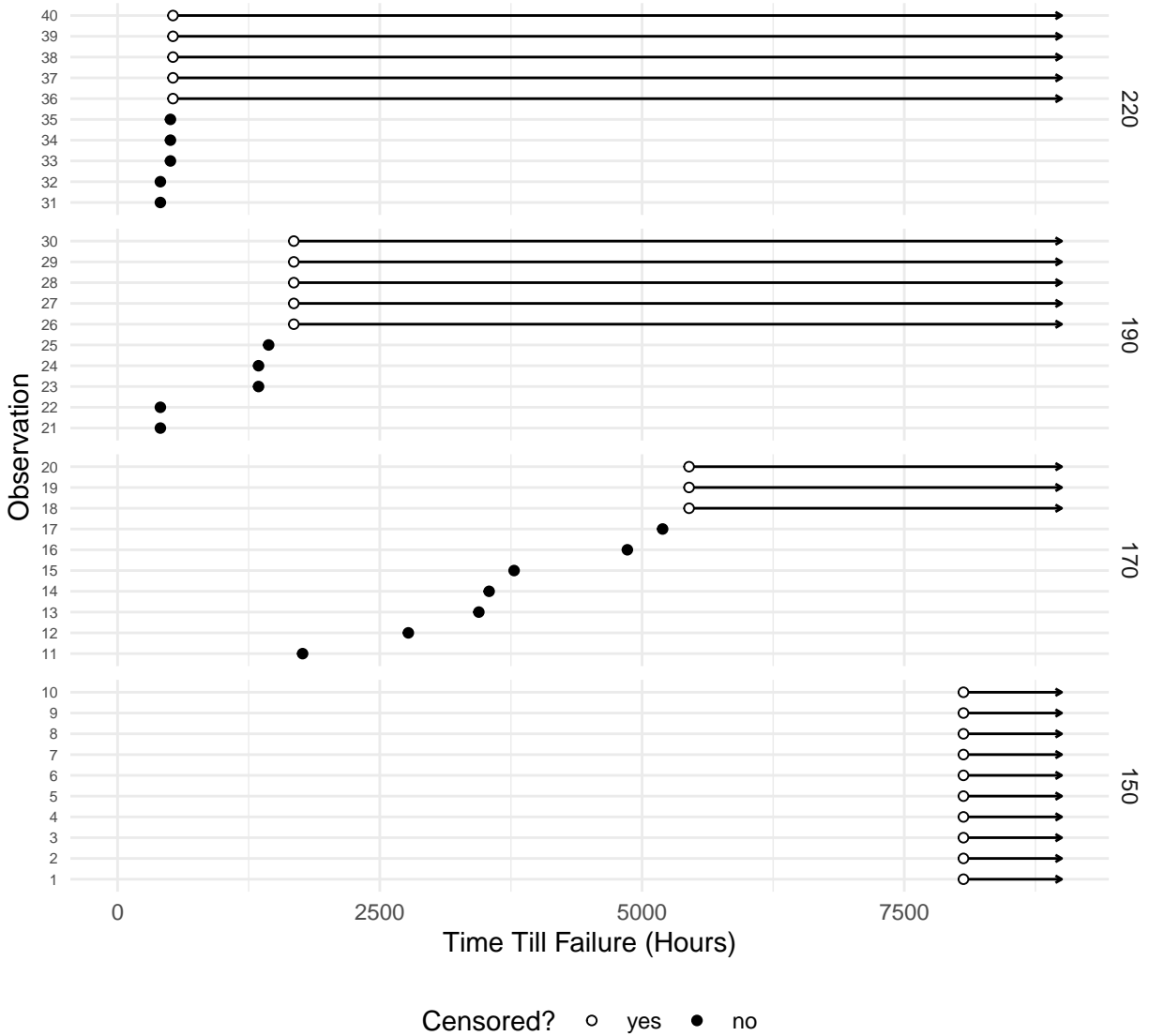
**Example:** Consider the following data from a study on the effect of temperature on the operational time of motors.

```
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  $\sigma$  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  $\epsilon_i$ ), or a distribution for  $\epsilon_i$  (which implies a distribution for  $T_i$ ).

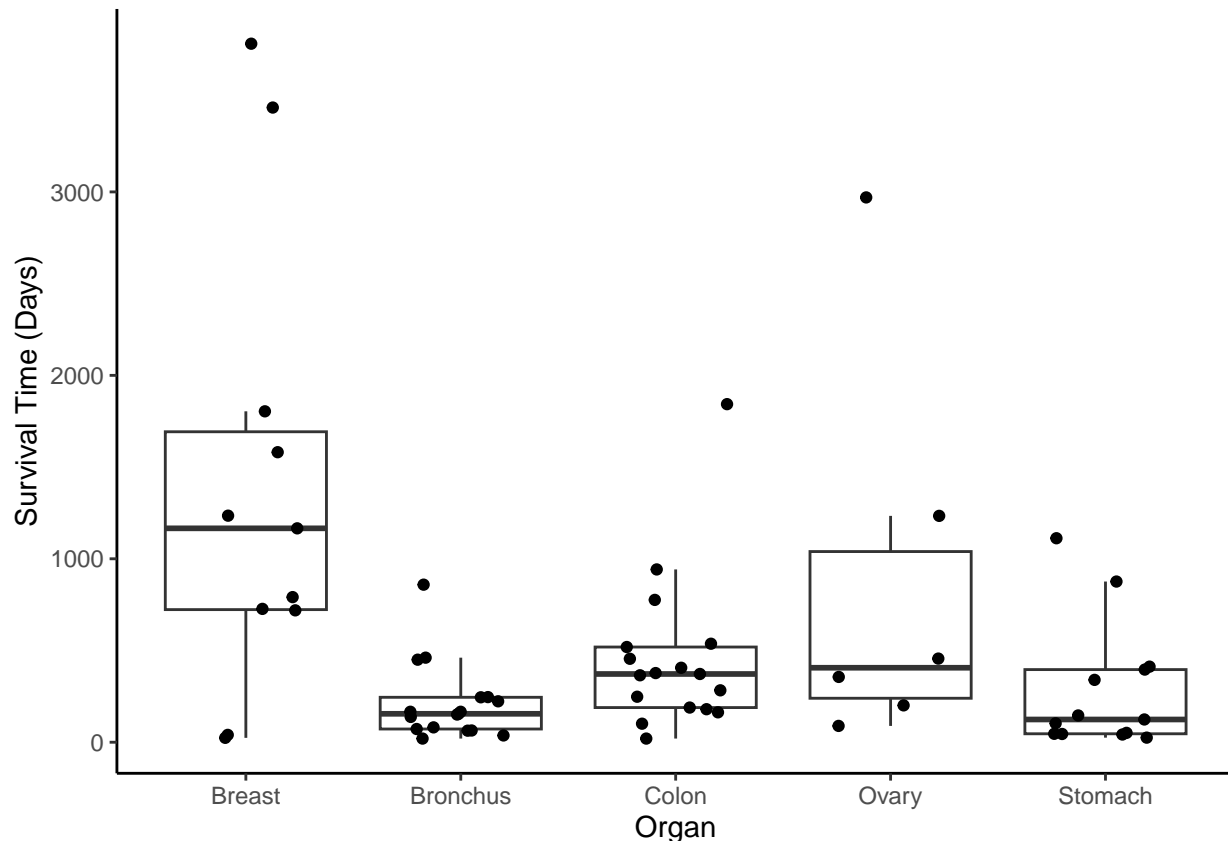
Note that a AFT is essentially a *linear* model where the response variable is  $Y_i = \log T_i$  is a transformation of  $T_i$ . This is **not** the same as a GLM using a log link function. That would be

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

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  $\sigma$ , 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 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  $\sigma$ . 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  $\sigma$ , and `meanlog` corresponds to  $\beta_0$ . 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  $e^{\beta_1}$ . We could also say that increasing  $x_1$  by one unit reduces time-till-event by a factor of  $e^{\beta_1}$ , 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  $e^{\beta_1}$ . We could also say that increasing  $x_1$  by one unit increases time-till-event by a factor of  $e^{\beta_1}$ , 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

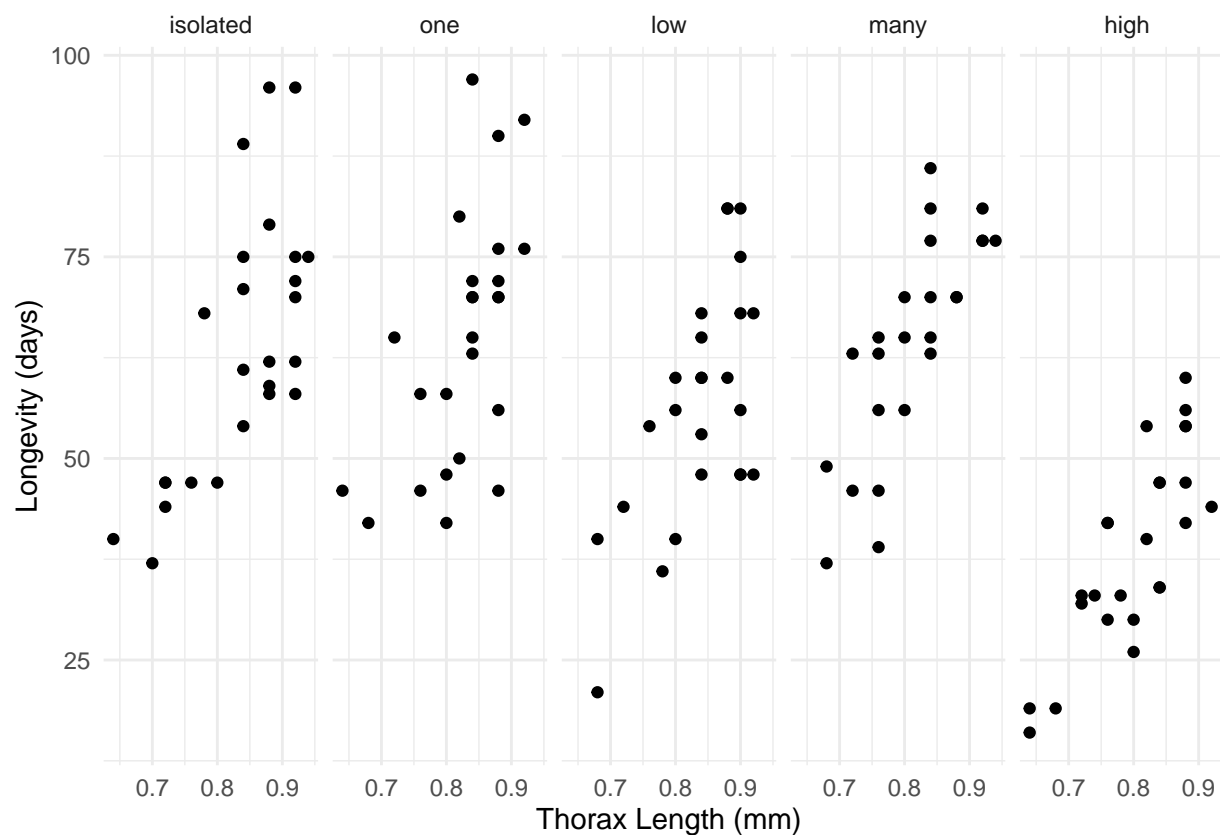
$$E(T_a) = e^{\beta_0} e^{\beta_1(x_1+1)} e^{\beta_2 x_2} \dots e^{\beta_p x_p} E(e^{\sigma \epsilon}) = e^{\beta_1} \underbrace{e^{\beta_0} e^{\beta_1 x_1} e^{\beta_2 x_2} \dots e^{\beta_p x_p} E(e^{\sigma \epsilon})}_{E(T_b)},$$

so we can interpret  $e^{\beta_1}$  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  $e^{\beta_1}$  (i.e., progression to the event is *faster* at level  $a$  than at level  $b$  by a factor of  $e_1^\beta$ ). 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  $e^{\beta_1}$  (i.e., progression to the event is *slower* at level  $a$  than at level  $b$  by a factor of  $e^{\beta_1}$ ). 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  $e^{\beta_1}$  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

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

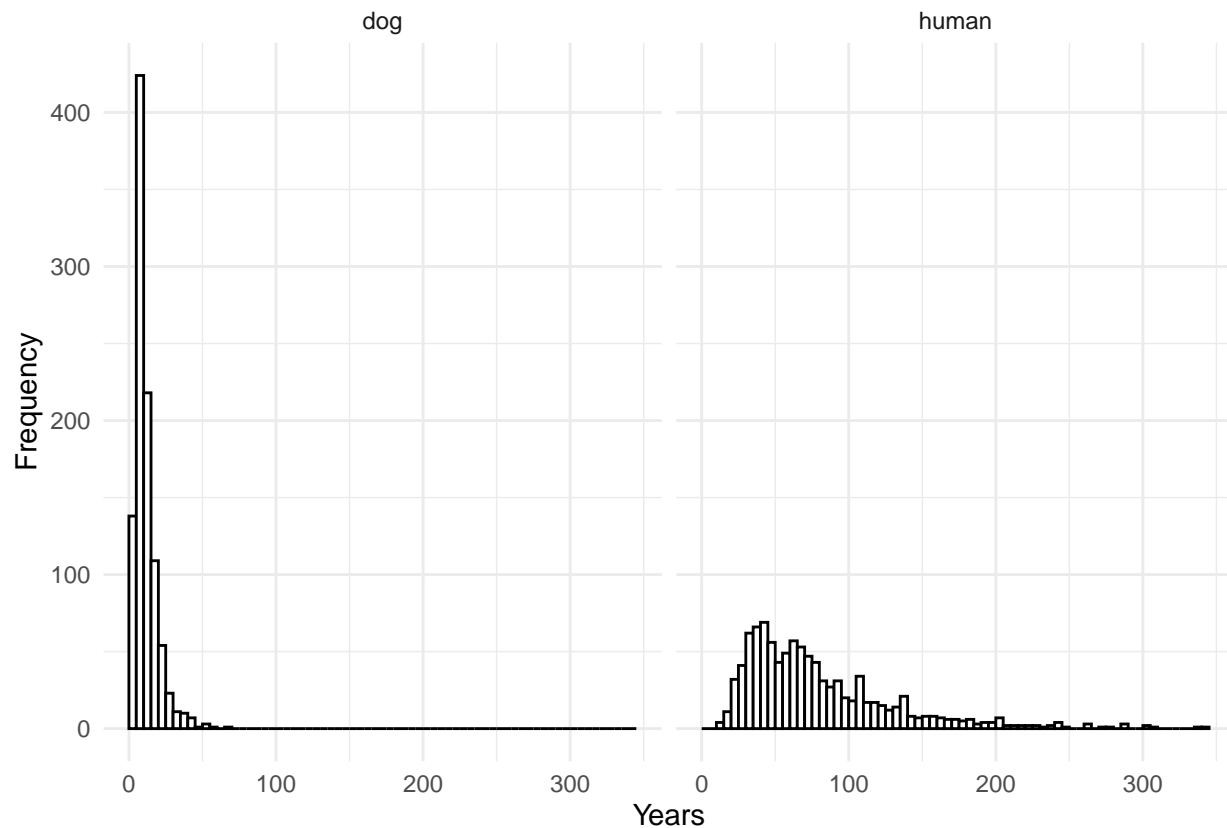
Again, the interpretation is like that for GLMs with the log link function.

**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)
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	9.846
specieshuman	7.001	6.642

```
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
speciesdog	0.1428	0.1355

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	I(thorax*10).trend	SE	df	lower.CL	upper.CL	t.ratio	p.value
isolated	0.236	0.0444	113	0.148	0.324	5.323	<.0001
one	0.213	0.0535	113	0.107	0.319	3.977	0.0001
low	0.290	0.0530	113	0.185	0.395	5.473	<.0001
many	0.239	0.0506	113	0.139	0.340	4.728	<.0001
high	0.376	0.0478	113	0.281	0.470	7.864	<.0001

Confidence level used: 0.95

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)	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