# Chapter 10

# Parametric Survival Analysis

So far, we have focused primarily on nonparametric and semi-parametric approaches to survival analysis, with heavy emphasis on the Cox proportional hazards model:

$$\lambda(t, \mathbf{Z}) \quad = \quad \lambda_0(t) \;\exp(\beta \mathbf{Z})$$

We used the following estimating approach:

- We estimated $\lambda_0(t)$ nonparametrically, using the Kaplan-Meier estimator, or using the Kalbfleisch/Prentice estimator under the PH assumption
- We estimated $\beta$ by assuming a linear model between the log HR and covariates, under the PH model

Both estimates were based on maximum likelihood theory.

**Reading:** for parametric models see Collett.

There are several reasons why we should consider some alternative approaches based on parametric models:

- The assumption of proportional hazards might not be appropriate (based on major departures)
- If a parametric model actually holds, then we would probably gain efficiency

- We may want to handle non-standard situations like
  - interval censoring
  - incorporating population mortality
- We may want to make some connections with other familiar approaches (e.g. use of the Poisson likelihood)
- We may want to obtain some estimates for use in designing a future survival study.

## 10.1 Exponential Regression

**Observed data:** $(X_i, \delta_i, \mathbf{Z}_i)$ for individual $i$,

$\mathbf{Z}_i = (Z_{i1}, Z_{i2}, ..., Z_{ip})$ represents a set of $p$ covariates.

**Right censoring:** Assume that $X_i = \min(T_i, U_i)$

**Survival distribution:** Assume $T_i$ follows an exponential distribution with a parameter $\lambda$ that depends on $\mathbf{Z}_i$, say $\lambda_i = \Psi(\mathbf{Z}_i)$.

Then we can write:

$$T_i \sim exponential(\Psi(\mathbf{Z}_i))$$

First, let's review some facts about the exponential distribution (from our first survival lecture):

$$\begin{aligned}
f(t) &= \lambda e^{-\lambda t} \qquad \text{for } t \geq 0 \\
S(t) &= P(T \geq t) = \int_t^\infty f(u)du = e^{-\lambda t} \\
F(t) &= P(T < t) = 1 - e^{-\lambda t} \\
\lambda(t) &= \frac{f(t)}{S(t)} = \lambda \qquad \text{constant hazard!} \\
\Lambda(t) &= \int_0^t \lambda(u)\, du = \int_0^t \lambda\, du = \lambda t
\end{aligned}$$

Now, we say that $\lambda$ is a constant *over time* $t$, but we want to let it depend on the covariate values, so we are setting

$$\lambda_i = \Psi(\mathbf{Z}_i)$$

The hazard rate would therefore be the same for any two individuals with the same covariate values.

Although there are many possible choices for $\Psi$, one simple and natural choice is:

$$\Psi(\mathbf{Z}_i) = \exp[\beta_0 + Z_{i1}\beta_1 + Z_{i2}\beta_2 + ... + Z_{ip}\beta_p]$$

**WHY?**

- ensures a positive hazard
- for an individual with $\mathbf{Z} = \mathbf{0}$, the hazard is $e^{\beta_0}$.

The model is called **exponential regression** because of the natural generalization from regular linear regression

### 10.1.1 Exponential regression for the 2-sample case

Assume we have only a single covariate $\mathbf{Z} = Z$,
i.e., $(p = 1)$.

<u>**Hazard Rate:**</u>

$$\Psi(\mathbf{Z}_i) = \exp(\beta_0 + Z_i\beta_1)$$

Define: $\begin{array}{ll} Z_i = 0 & \text{if individual } i \text{ is in group 0} \\ Z_i = 1 & \text{if individual } i \text{ is in group 1} \end{array}$

**What is the hazard for group 0?**

**What is the hazard for group 1?**

**What is the hazard ratio of group 1 to group 0?**

**What is the interpretation of $\beta_1$?**

### 10.1.2 Likelihood for Exponential Model

Under the assumption of right censored data, each person has one of two possible contributions to the likelihood:

(a) they have an **event** at $X_i$ $(\delta_i = 1) \Rightarrow$ contribution is

$$L_i = \underbrace{S(X_i)}_{\text{survive to } X_i} \cdot \underbrace{\lambda(X_i)}_{\text{fail at } X_i} = e^{-\lambda X_i}\,\lambda$$

(b) they are **censored** at $X_i$ ($\delta_i = 0$) $\Rightarrow$ contribution is

$$L_i = \underbrace{S(X_i)}_{\text{survive to } X_i} = e^{-\lambda X_i}$$

The **likelihood** is the product over all of the individuals:

$$\begin{aligned}
\mathcal{L} &= \prod_i L_i \\
&= \prod_i \underbrace{\left(\lambda e^{-\lambda X_i}\right)^{\delta_i}}_{\text{events}} \underbrace{\left(e^{-\lambda X_i}\right)^{(1-\delta_i)}}_{\text{censorings}} \\
&= \prod_i \lambda^{\delta_i} \left(e^{-\lambda X_i}\right)
\end{aligned}$$

### 10.1.3 Maximum Likelihood for Exponential

**How do we use the likelihood?**

- first take the log
- then take the partial derivative with respect to $\beta$
- then set to zero and solve for $\widehat{\beta}$
- this gives us the **maximum likelihood estimators**

The log-likelihood is:

$$\begin{aligned}
\log \mathcal{L} &= \log\left[\prod_i \lambda^{\delta_i} \left(e^{-\lambda X_i}\right)\right] \\
&= \sum_i \left[\delta_i \log(\lambda) - \lambda X_i\right] \\
&= \sum_i \left[\delta_i \log(\lambda)\right] - \sum_i \lambda X_i
\end{aligned}$$

For the case of exponential regression, we now substitute the hazard $\lambda = \Psi(\mathbf{Z}_i)$ in the above log-likelihood:

$$\log \mathcal{L} = \sum_i \left[\delta_i \log(\Psi(\mathbf{Z}_i))\right] - \sum_i \Psi(\mathbf{Z}_i) X_i \tag{10.1}$$

**General Form of Log-likelihood for Right Censored Data**

In general, whenever we have right censored data, the likelihood and corresponding log likelihood will have the following forms:

$$\begin{aligned}\mathcal{L} &= \prod_i [\lambda_i(X_i)]^{\delta_i}\ S_i(X_i)\\ \log\mathcal{L} &= \sum_i [\delta_i \log(\lambda_i(X_i))] - \sum_i \Lambda_i(X_i)\end{aligned}$$

where

- $\lambda_i(X_i)$ is the hazard for the individual $i$ who fails at $X_i$
- $\Lambda_i(X_i)$ is the cumulative hazard for an individual at their failure <u>or</u> censoring time

For example, see the derivation of the likelihood for a Cox model on p.11-13 of Lecture 4 notes. We started with the likelihood above, then substituted the specific forms for $\lambda(X_i)$ under the PH assumption.

Consider our model for the hazard rate:

$$\lambda = \Psi(\mathbf{Z}_i) = \exp[\beta_0 + Z_{i1}\beta_1 + Z_{i2}\beta_2 + ... + Z_{ip}\beta_p]$$

We can write this using vector notation, as follows:

$$\begin{aligned}\text{Let}\quad \mathbf{Z}_i &= (1, Z_{i1}, ...Z_{ip})^T\\ \text{and}\quad \beta &= (\beta_0, \beta_1, ...\beta_p)\end{aligned}$$

(Since $\beta_0$ is the intercept (i.e., the log hazard rate for the baseline group), we put a "1" as the first term in the vector $\mathbf{Z}_i$.)

Then, we can write the hazard as:

$$\Psi(\mathbf{Z}_i) = \exp[\beta\mathbf{Z}_i]$$

Now we can substitute $\Psi(\mathbf{Z}_i) = \exp[\beta\mathbf{Z}_i]$ in the log-likelihood shown in (10.1):

$$\log\mathcal{L} = \sum_{i=1}^{n} \delta_i(\beta\mathbf{Z}_i) - \sum_{i=1}^{n} X_i \exp(\beta\mathbf{Z}_i)$$

### 10.1.4 Score Equations

Taking the derivative with respect to $\beta_0$, the score equation is:

$$\frac{\partial \log \mathcal{L}}{\partial \beta_0} = \sum_{i=1}^{n} [\delta_i - X_i \exp(\beta \mathbf{Z}_i)]$$

For $\beta_k$, $k = 1, ...p$, the equations are:

$$\begin{aligned} \frac{\partial \log \mathcal{L}}{\partial \beta_k} &= \sum_{i=1}^{n} [\delta_i Z_{ik} - X_i Z_{ik} \exp(\beta \mathbf{Z}_i)] \\ &= \sum_{i=1}^{n} Z_{ik} [\delta_i - X_i \exp(\beta \mathbf{Z}_i)] \end{aligned}$$

To find the MLE's, we set the above equations to 0 and solve (simultaneously). The equations above imply that the MLE's are obtained by setting the weighted number of failures ($\sum_i Z_{ik}\delta_i$) equal to the weighted cumulative hazard ($\sum_i Z_{ik}\Lambda(X_i)$). To find the variance of the MLE's, we need to take the second derivatives:

$$-\frac{\partial^2 \log \mathcal{L}}{\partial \beta_k \partial \beta_j} = \sum_{i=1}^{n} Z_{ik} Z_{ij} X_i \exp(\beta \mathbf{Z}_i)$$

Some algebra (see Cox and Oakes section 6.2) reveals that

$$Var(\widehat{\beta}) = I(\beta)^{-1} = \left[\mathbf{Z}(\mathbf{I} - \Pi)\mathbf{Z}^T\right]^{-1}$$

where

- $\mathbf{Z} = (\mathbf{Z}_1, \ldots, \mathbf{Z}_n)$ is a $(p+1) \times n$ matrix
  ($p$ covariates plus the "1" for the intercept $\beta_0$)

- $\Pi = diag(\pi_1, \ldots, \pi_n)$ (this means that $\Pi$ is a diagonal matrix, with the terms $\pi_1, \ldots, \pi_n$ on the diagonal)

- $\pi_i$ is the probability that the $i$-th person is censored, so $(1 - \pi_i)$ is the probability that they failed.

- **Note:** The information $I(\beta)$ (inverse of the variance) is proportional to the number of failures, not the sample size. This will be important when we talk about study design.

### 10.1.5 The Single Sample Problem ($Z_i = 1$ for everyone)

First, what is the MLE of $\beta_0$?

We set $\frac{\partial \log \mathcal{L}}{\partial \beta_0} = \sum_{i=1}^n [\delta_i - X_i \exp(\beta_0 Z_i)]$ equal to 0 and solve:

$$\begin{aligned} \Rightarrow \sum_{i=1}^n \delta_i &= \sum_{i=1}^n [X_i \exp(\beta_0)] \\ d &= \exp(\beta_0) \sum_{i=1}^n X_i \\ \exp(\widehat{\beta_0}) &= \frac{d}{\sum_{i=1}^n X_i} \\ \hat{\lambda} &= \frac{d}{t} \end{aligned}$$

where $d$ is the total number of deaths (or events), and $t = \sum X_i$ is the total person-time contributed by all individuals.

**If $d/t$ is the MLE for $\lambda$, what does this imply about the MLE of $\beta_0$?**

Using the previous formula $Var(\hat{\beta}) = \left[\mathbf{Z}(\mathbf{I} - \Pi)\mathbf{Z}^T\right]^{-1}$,
what is the variance of $\widehat{\beta_0}$?:

With some matrix algebra, you can show that it is:

$$Var(\widehat{\beta_0}) = \frac{1}{\sum_{i=1}^n (1 - \pi_i)} = \frac{1}{d}$$

**What about $\hat{\lambda} = e^{\hat{\beta}_0}$?**

By the delta method,

$$\begin{aligned} Var(\hat{\lambda}) &= \hat{\lambda}^2 \, Var(\widehat{\beta_0}) \\ &= ? \end{aligned}$$

### 10.1.6 The Two-Sample Problem

| | $Z_i$ | Subjects | Events | Follow-up |
|---|---|---|---|---|
| **Group 0:** | $Z_i = 0$ | $n_0$ | $d_0$ | $t_0 = \sum_{i=1}^{n_0} X_i$ |
| **Group 1:** | $Z_i = 1$ | $n_1$ | $d_1$ | $t_1 = \sum_{i=1}^{n_1} X_i$ |

**The log-likelihood**

$$\log \mathcal{L} = \sum_{i=1}^{n} \delta_i(\beta_0 + \beta_1 Z_i) - \sum_{i=1}^{n} X_i \exp(\beta_0 + \beta_1 Z_i)$$

$$\text{so} \quad \frac{\partial \log \mathcal{L}}{\partial \beta_0} = \sum_{i=1}^{n} [\delta_i - X_i \exp(\beta_0 + \beta_1 Z_i)]$$

$$= (d_0 + d_1) - (t_0 e^{\beta_0} + t_1 e^{\beta_0 + \beta_1})$$

$$\frac{\partial \log \mathcal{L}}{\partial \beta_1} = \sum_{i=1}^{n} Z_i [\delta_i - X_i \exp(\beta_0 + \beta_1 Z_i)]$$

$$= d_1 - t_1 e^{\beta_0 + \beta_1}$$

This implies: $\hat{\lambda}_1 = e^{\hat{\beta}_0 + \hat{\beta}_1} = ?$

$$\hat{\lambda}_0 = e^{\hat{\beta}_0} = ?$$

$$\hat{\beta}_0 = ?$$

$$\hat{\beta}_1 = ?$$

**Important Result:**

> **The maximum likelihood estimates (MLE's) of the hazard rates under the exponential model are the number of events divided by the person-years of follow-up!**

(this result will be relied on heavily when we discuss study design)

### 10.1.7 Exponential Regression: Means and Medians

**Mean Survival Time**

For the exponential distribution, $E(T) = 1/\lambda$.

- **Control Group:**

$$\overline{T}_0 = 1/\hat{\lambda}_0 = 1/\exp(\hat{\beta}_0)$$

- **Treatment Group:**

$$\overline{T}_1 = 1/\hat{\lambda}_1 = 1/\exp(\hat{\beta}_0 + \hat{\beta}_1)$$

**Median Survival Time**

This is the value $M$ at which $S(t) = e^{-\lambda t} = 0.5$, so $M = \text{median} = \frac{-\log(0.5)}{\lambda}$

- **Control Group:**

$$\hat{M}_0 = \frac{-\log(0.5)}{\hat{\lambda}_0} = \frac{-\log(0.5)}{\exp(\hat{\beta}_0)}$$

- **Treatment Group:**

$$\hat{M}_1 = \frac{-\log(0.5)}{\hat{\lambda}_1} = \frac{-\log(0.5)}{\exp(\hat{\beta}_0 + \hat{\beta}_1)}$$

### 10.1.8 Exponential Regression: Variance Estimates and Test Statistics

We can also calculate the variances of the MLE's as simple functions of the number of failures:

$$\begin{aligned} var(\hat{\beta}_0) &= \frac{1}{d_0} \\ var(\hat{\beta}_1) &= \frac{1}{d_0} + \frac{1}{d_1} \end{aligned}$$

So our test statistics are formed as:

**For testing $H_o : \beta_0 = 0$:**

$$\begin{aligned} \chi^2_w &= \frac{\left(\hat{\beta}_0\right)^2}{var(\hat{\beta}_0)} \\ &= \frac{[\log(d_0/t_0)]^2}{1/d_0} \end{aligned}$$

**For testing $H_o : \beta_1 = 0$:**

$$\begin{aligned} \chi^2_w &= \frac{\left(\hat{\beta}_1\right)^2}{var(\hat{\beta}_1)} \\ &= \frac{\left[\log(\frac{d_1/t_1}{d_0/t_0})\right]^2}{\frac{1}{d_0} + \frac{1}{d_1}} \end{aligned}$$

**How would we form confidence intervals for the hazard ratio?**

### 10.1.9 The Likelihood Ratio Test Statistic: An alternative to the Wald test

A likelihood ratio test is based on 2 times the log of the ratio of the likelihoods under the null and alternative. We reject $H_0$ if 2 log(LR) $> \chi^2_{1,0.05}$, where

$$LR = \frac{\mathcal{L}(H_1)}{\mathcal{L}(H_0)} = \frac{\mathcal{L}(\widehat{\lambda}_0, \widehat{\lambda}_1)}{\mathcal{L}(\widehat{\lambda})}$$

For a sample of n independent exponential random variables with parameter $\lambda$, the Likelihood is:

$$\begin{aligned} L &= \prod_{i=1}^{n} [\lambda^{\delta_i} \exp(-\lambda x_i)] \\ &= \lambda^d \exp(-\lambda \sum x_i) \\ &= \lambda^d \exp(-\lambda n \bar{x}) \end{aligned}$$

where $d$ is the number of deaths or failures. The log-likelihood is

$$\ell = d \log(\lambda) - \lambda n \bar{x}$$

and the MLE is

$$\widehat{\lambda} = d/(n\bar{x})$$

**Two-Sample Case: LR test calculations**

**Data:**

| | |
|---|---|
| Group 0: | $d_0$ failures among the $n_0$ females<br>mean failure time is $\bar{x}_0 = (\sum_i^{n_0} X_i)/n_0$ |
| Group 1: | $d_1$ failures among the $n_1$ males<br>mean failure time is $\bar{x}_1 = (\sum_i^{n_1} X_i)/n_1$ |

Under the **alternative hypothesis**:

$$\begin{aligned} \mathcal{L} &= \lambda_1^{d_1} \exp(-\lambda_1 n_1 \bar{x}_1) \times \lambda_0^{d_0} \exp(-\lambda_0 n_0 \bar{x}_0) \\ \log(\mathcal{L}) &= d_1 \log(\lambda_1) - \lambda_1 n_1 \bar{x}_1 + d_0 \log(\lambda_0) - \lambda_0 n_0 \bar{x}_0 \end{aligned}$$

The MLE's are:

$$\begin{aligned} \widehat{\lambda}_1 &= d_1/(n_1\bar{x}_1) && \text{for males} \\ \widehat{\lambda}_0 &= d_0/(n_0\bar{x}_0) && \text{for females} \end{aligned}$$

Under the **null hypothesis**:

$$\begin{aligned} \mathcal{L} &= \lambda^{d_1+d_0}\exp[-\lambda(n_1\bar{x}_1+n_0\bar{x}_0)] \\ \log(\mathcal{L}) &= (d_1+d_0)\log(\lambda)-\lambda[n_1\bar{x}_1+n_0\bar{x}_0] \end{aligned}$$

The corresponding MLE is

$$\widehat{\lambda} = (d_1+d_0)/[n_1\bar{x}_1+n_0\bar{x}_0]$$

A likelihood ratio test can be constructed by taking twice the difference of the log-likelihoods under the alternative and the null hypotheses:

$$-2\left[(d_0+d_1)\log\left(\frac{d_0+d_1}{t_0+t_1}\right)-d_1\log[d_1/t_1]-d_0\log[d_0/t_0]\right]$$

### 10.1.10 Nursing home example

**For the females:**

- $n_0 = 1173$
- $d_0 = 902$
- $t_0 = 310754$
- $\bar{x}_0 = 265$

**For the males:**

- $n_1 = 418$
- $d_1 = 367$
- $t_1 = 75457$
- $\bar{x}_1 = 181$

Plugging these values in, we get a LR test statistic of 64.20.

**Hand Calculations using events and follow-up**

By adding up "LOS" for males to get $t_1$ and for females to get $t_0$, I obtained:

- $d_0 = 902$ (females)
  $d_1 = 367$ (males)
- $t_0 = 310754$ (female follow-up)
  $t_1 = 75457$ (male follow-up)

This yields an estimated log HR:

$$\hat{\beta}_1 = \log\left[\frac{d1/t1}{d0/t0}\right] = \log\left[\frac{367/75457}{902/310754}\right] = \log(1.6756) = 0.5162$$

The estimated standard error is:

$$\sqrt{var(\hat{\beta}_1)} = \sqrt{\frac{1}{d_1} + \frac{1}{d_0}} = \sqrt{\frac{1}{902} + \frac{1}{367}} = 0.06192$$

So the Wald test becomes:

$$\chi^2_W = \frac{\hat{\beta}_1^2}{var(\hat{\beta}_1)} = \frac{(0.51619)^2}{0.061915} = 69.51$$

We can also calculate $\hat{\beta}_0 = log(d_0/t_0) = -5.842$,
along with its standard error $se(\hat{\beta}_0) = \sqrt{(1/d0)} = 0.0333$

### 10.1.11 Exponential Regression in R

We use the `survreg` command with the `dist="exp"` option:

```
Call:
survreg(formula = Surv(losyr, fail) ~ gender, data = nurshome,
    dist = "exp")
              Value Std. Error     z        p
(Intercept) -0.0578     0.0333 -1.73 8.28e-02
gender      -0.5162     0.0619 -8.34 7.62e-17

Scale fixed at 1

Exponential distribution
```

```
Loglik(model)= -1006.3   Loglik(intercept only)= -1038.4
Chisq= 64.2 on 1 degrees of freedom, p= 1.1e-15
Number of Newton-Raphson Iterations: 5
n= 1591
```

Since $Z = 8.337$, the chi-square test is $Z^2 = 69.51$.

## 10.2 The Weibull Regression Model

At the beginning of the course, we saw that the survivorship function for a Weibull random variable is:

$$S(t) \quad = \quad \exp[-\lambda(t^{\kappa})]$$

and the hazard function is:

$$\lambda(t) \quad = \quad \kappa\,\lambda\,t^{(\kappa-1)}$$

The Weibull regression model assumes that for someone with covariates $\mathbf{Z}_i$, the survivorship function is

$$S(t;\mathbf{Z}_i) = \exp[-\Psi(\mathbf{Z}_i)(t^{\kappa})]$$

where $\Psi(\mathbf{Z}_i)$ is defined as in exponential regression to be:

$$\Psi(\mathbf{Z}_i) = \exp[\beta_0 + Z_{i1}\beta_1 + Z_{i2}\beta_2 + ...Z_{ip}\beta_p]$$

For the 2-sample problem, we have:

$$\Psi(\mathbf{Z}_i) = \exp[\beta_0 + Z_{i1}\beta_1]$$

### 10.2.1 Weibull MLEs for the 2-sample problem

**Log-likelihood:**

$$\log\mathcal{L} \quad = \quad \sum_{i=1}^{n}\delta_i\log\left[\kappa\exp(\beta_0+\beta_1 Z_i)X_i^{\kappa-1}\right] - \sum_{i=1}^{n}X_i^{\kappa}\exp(\beta_0+\beta_1 Z_i)$$

$$\Rightarrow \qquad \exp(\hat\beta_0) = d_0/t_0\kappa \qquad \exp(\hat\beta_0+\hat\beta_1) = d_1/t_1\kappa$$

where

$$t_{j\kappa} = \sum_{i=1}^{n_j}X_i^{\hat\kappa} \quad \text{among } n_j \text{ subjects}$$

$$\hat\lambda_0(t) = \hat\kappa\ \exp(\hat\beta_0)\ t^{\hat\kappa-1}\ \ \hat\lambda_1(t) = \hat\kappa\ \exp(\hat\beta_0+\hat\beta_1)\ t^{\hat\kappa-1}$$

$$\begin{aligned}\widehat{HR} \quad &= \quad \hat\lambda_1(t)/\hat\lambda_0(t) = \exp(\hat\beta_1)\\ &= \quad \exp\left(\frac{d_1/t_1\kappa}{d_0/t_0\kappa}\right)\end{aligned}$$

### 10.2.2 Weibull Regression: Means and Medians

**Mean Survival Time**

For the Weibull distribution, $E(T) = \lambda^{(-1/\kappa)}\Gamma[(1/\kappa) + 1]$.

- **Control Group:**

$$\overline{T}_0 = \hat{\lambda}_0^{(-1/\hat{\kappa})}\ \Gamma[(1/\hat{\kappa}) + 1]$$

- **Treatment Group:**

$$\overline{T}_1 = \hat{\lambda}_1^{(-1/\hat{\kappa})}\ \Gamma[(1/\hat{\kappa}) + 1]$$

**Median Survival Time**

For the Weibull distribution, $M = \text{median} = \left[\frac{-\log(0.5)}{\lambda}\right]^{1/\kappa}$

- **Control Group:**

$$\hat{M}_0 = \left[\frac{-\log(0.5)}{\hat{\lambda}_0}\right]^{1/\hat{\kappa}}$$

- **Treatment Group:**

$$\hat{M}_1 = \left[\frac{-\log(0.5)}{\hat{\lambda}_1}\right]^{1/\hat{\kappa}}$$

where $\hat{\lambda}_0 = \exp(\hat{\beta}_0)$ and $\hat{\lambda}_1 = \exp(\hat{\beta}_0 + \hat{\beta}_1)$.

Note: the symbol $\Gamma$ is the "gamma" function. If $x$ is an integer, then

$$\Gamma(x) = (x - 1)!$$

In cases where $x$ is not an integer, this function has to be evaluated numerically. In homework and labs, I will supply this value to you.

The Weibull regression model is very easy to fit:

- In STATA: Just specify `dist(weibull)` instead of `dist(exp)` within the `streg` command
- In SAS: use model option `dist=weibull` within the `proc lifereg` procedure
- In R: we use the `survreg` command with the `dist="weibull"` option.

Note: to get more information on these modeling procedures, use the online help facilities.

### 10.2.3 Fitting the Weibull model in R

**The nursing home data example**

```
Call:
survreg(formula = Surv(losyr, fail) ~ gender, data = nurshome,
    dist = "weibull")
             Value Std. Error     z        p
(Intercept) -0.143     0.0542 -2.65 8.13e-03
gender      -0.673     0.1011 -6.66 2.67e-11
Log(scale)   0.487     0.0232 20.99 8.94e-98

Scale= 1.63

Weibull distribution
Loglik(model)= -731.1   Loglik(intercept only)= -751.9
Chisq= 41.73 on 1 degrees of freedom, p= 1e-10
Number of Newton-Raphson Iterations: 5
n= 1591
```

## 10.3 Comparison of parametric and nonparametric models

### 10.3.1 Comparison of Exponential with Kaplan-Meier

We can see how well the Exponential model fits by comparing the survival estimates for males and females under the exponential model, i.e., $P(T \geq t) = e^{(-\hat{\lambda}_z t)}$, to the Kaplan-Meier survival estimates:

### 10.3.2 Comparison of Weibull with Kaplan-Meier

We can see how well the Weibull model fits by comparing the survival estimates, $P(T \geq t) = e^{(-\hat{\lambda}_z t^{\hat{\kappa}})}$, to the Kaplan-Meier survival estimates. **Which do you think fits best?**

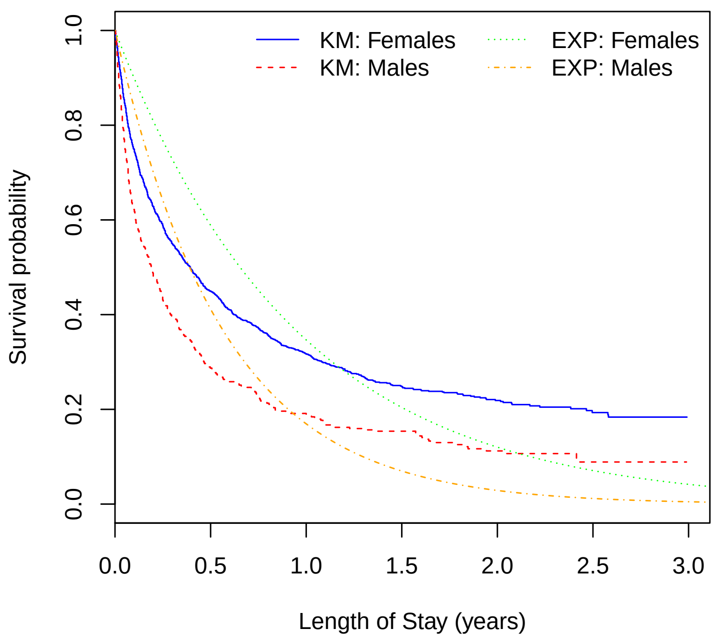
### 10.3.3 Other useful plots for evaluating goodness of fit

Other visual tests of goodness of fit are as follows:

- $-\log(\hat{S}(t))$ vs $t$
- $\log[-\log(\hat{S}(t))]$ vs $\log(t)$

Why are these useful?

Figure 10.1: Comparison of exponential with Kaplan Meier




**If T is exponential**, then $S(t) = \exp(-\lambda t))$

$$\begin{array}{rrcl} \text{so} & \log(S(t)) & = & -\lambda t \\ \text{and} & \Lambda(t) & = & \lambda\, t \end{array}$$

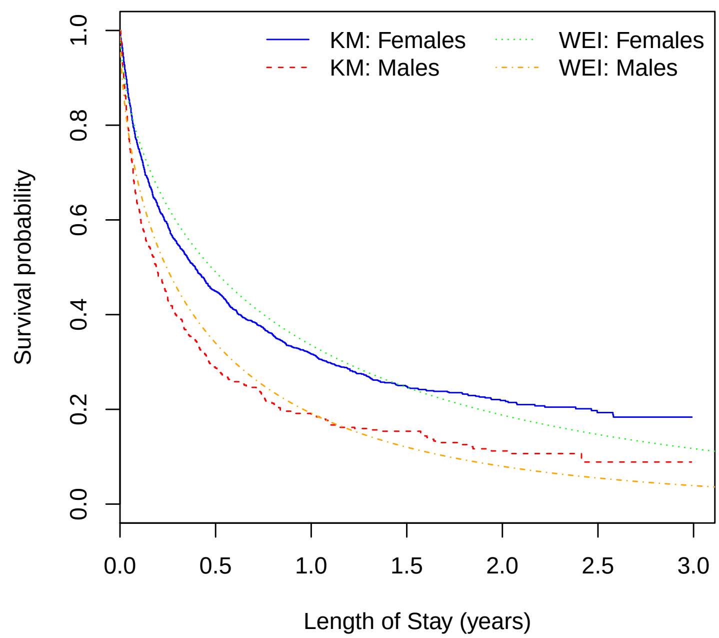
a straight line in $t$ with slope $\lambda$ and intercept=0

**If T is Weibull**, then $S(t) = \exp(-(\lambda t)^\kappa)$

$$\begin{array}{rrcl} \text{so} & \log(S(t)) & = & -\lambda t^\kappa \\ \text{then} & \Lambda(t) & = & \lambda t^\kappa \\ \text{and} & \log(-\log(S(t))) & = & \log(\lambda) + \kappa * \log(t) \end{array}$$

a straight line in $\log(t)$ with slope $\kappa$ and intercept $\log(\lambda)$. So we can calculate our estimated $\Lambda(t)$ and plot it versus $t$, and if it seems to form a straight line, then the exponential distribution is probably appropriate for our dataset.

Figure 10.2: Comparison between Weibull and Kaplan Meier




Or we can plot $\log \hat{\Lambda}(t)$ versus $\log(t)$, and if it seems to form a straight line, then the Weibull distribution is probably appropriate for our dataset.

### 10.3.4 Comparison of Methods for the two-sample problem:

**Data:**

| | $Z_i$ | Subjects | Events | Follow-up |
|---|---|---|---|---|
| **Group 0:** | $Z_i = 0$ | $n_0$ | $d_0$ | $t_0 = \sum_{i=1}^{n_0} X_i$ |
| **Group 1:** | $Z_i = 1$ | $n_1$ | $d_1$ | $t_1 = \sum_{i=1}^{n_1} X_i$ |

**In General:**

$$\lambda_z(t) \quad = \quad \lambda(t, Z = z) \qquad \text{for } z = 0 \text{ or } 1.$$

The hazard rate depends on the value of the covariate $Z$. In this case, we are assuming that we only have a single covariate, and it is binary ($Z = 1$ or $Z = 0$)

Figure 10.3: Log-log plot of the exponential model

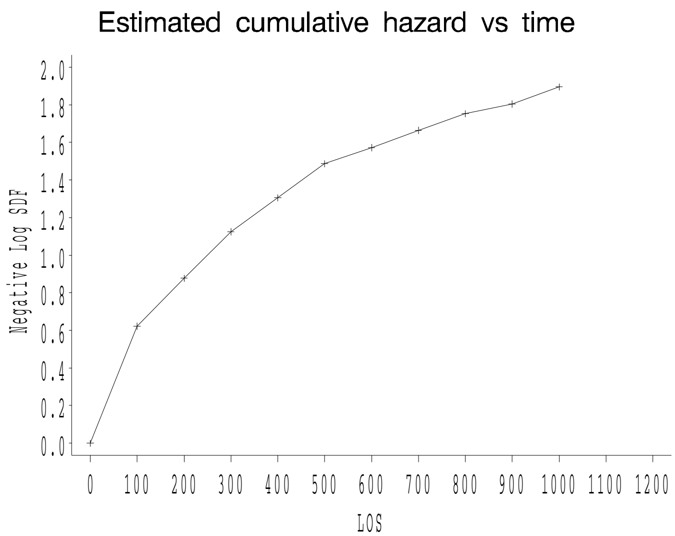
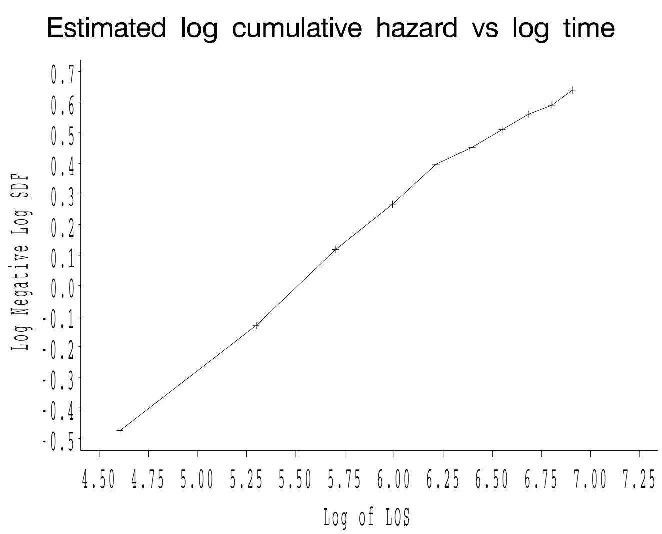



Figure 10.4: Log-log plot of the Weibull model



## 10.4 Models

### 10.4.1 Exponential Regression

$$\begin{aligned} \lambda_z(t) &= \exp(\beta_0 + \beta_1 Z) \\ \Rightarrow \lambda_0 &= \exp(\beta_0) \\ \lambda_1 &= \exp(\beta_0 + \beta_1) \\ HR &= \exp(\beta_1) \end{aligned}$$

### 10.4.2 Weibull Regression:

$$\begin{aligned} \lambda_z(t) &= \kappa\ \exp(\beta_0 + \beta_1 Z)\ t^{\kappa-1} \\ \Rightarrow \lambda_0 &= \kappa\ \exp(\beta_0)\ t^{\kappa-1} \\ \lambda_1 &= \kappa\ \exp(\beta_0 + \beta_1)\ t^{\kappa-1} \\ HR &= \exp(\beta_1) \end{aligned}$$

### 10.4.3 Proportional Hazards Model:

$$\begin{aligned} \lambda_z(t) &= \lambda_0(t) \exp(\beta_1) \\ \Rightarrow \lambda_0 &= \lambda_0(t) & \text{KM?} \\ \lambda_1 &= \lambda_0(t) \exp(\beta_1) \\ HR &= \exp(\beta_1) \end{aligned}$$

### 10.4.4 Remarks

Exponential model is a special case of the Weibull model with $\kappa = 1$ (note: Collett uses $\gamma$ instead of $\kappa$)

Exponential and Weibull models are both special cases of the Cox PH model.

**How can you show this?**

If either the exponential model or the Weibull model is valid, then these models will tend to be more efficient than PH (smaller s.e.'s of estimates). This is because they assume a particular form for $\lambda_0(t)$, rather than estimating it at every death time.

For the Exponential model, the hazards are constant over time, given the value of the covariate $Z_i$:

$$\begin{aligned} Z_i = 0 \Rightarrow \quad \hat{\lambda}_0 &= \exp(\hat{\beta}_0) \\ Z_i = 1 \Rightarrow \quad \hat{\lambda}_0 &= \exp(\hat{\beta}_0 + \hat{\beta}_1) \end{aligned}$$

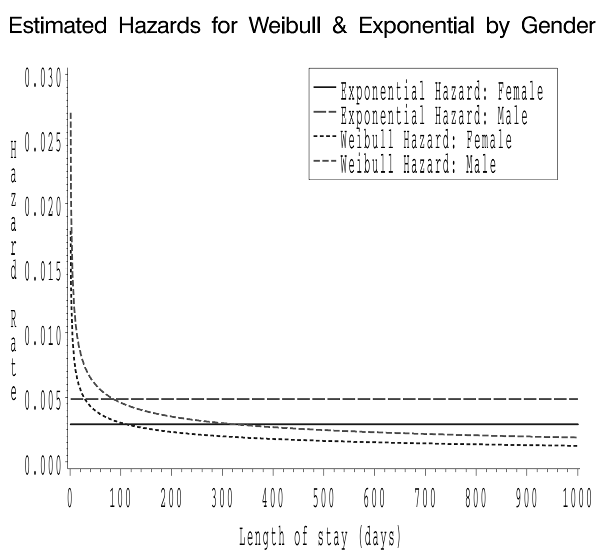
For the Weibull model, we have to estimate the hazard as a function of time, given the estimates of $\beta_0, \beta_1$ and $\kappa$:

$$\begin{aligned} Z_i = 0 \Rightarrow \quad \hat{\lambda}_0(t) &= \hat{\kappa}\ \exp(\hat{\beta}_0)\ t^{\hat{\kappa}-1} \\ Z_i = 1 \Rightarrow \quad \hat{\lambda}_1(t) &= \hat{\kappa}\ \exp(\hat{\beta}_0 + \hat{\beta}_1)\ t^{\hat{\kappa}-1} \end{aligned}$$

However, the ratio of the hazards is still just $\exp(\hat{\beta}_1)$, since the other terms cancel out.

**Here's what the estimated hazards look like for the nursing home data:**

Figure 10.5: Comparison of the Weibull and Exponential hazards



### 10.4.5 Proportional Hazards Model:

To get the MLE's for this model, we have to maximize the Cox partial likelihood iteratively. There are not closed form expressions like above.

$$
\begin{aligned}
L(\beta) &= \prod_{i=1}^{n} \left[ \frac{e^{\beta \mathbf{Z}_i}}{\sum_{\ell \in \mathcal{R}(X_i)} e^{\beta \mathbf{Z}_\ell}} \right]^{\delta_i} \\
&= \prod_{i=1}^{n} \left[ \frac{e^{\beta_0 + \beta_1 Z_i}}{\sum_{\ell \in \mathcal{R}(X_i)} e^{\beta_0 + \beta_1 Z_\ell}} \right]^{\delta_i}
\end{aligned}
$$

#### Comparison with Proportional Hazards Model

For the PH model, $\hat{\beta}_1 = 0.394$ and $\widehat{HR} = e^{0.394} = 1.483$.

#### Comparison with the Logrank and Wilcoxon Tests

```
\begin{verbatim}
Call:
survdiff(formula = Surv(losyr, fail) ~ gender, data = nurshome)

            N Observed Expected (O-E)^2/E (O-E)^2/V
gender=0 1173      902      995      8.76      41.1
gender=1  418      367      274     31.88      41.1

 Chisq= 41.1  on 1 degrees of freedom, p= 1.46e-10
```

The Gehan-Wilcoxon test. Note that this is fit by adding `rho=1` in R:

```
Call:
survdiff(formula = Surv(losyr, fail) ~ gender, data = nurshome,
    rho = 1)

            N Observed Expected (O-E)^2/E (O-E)^2/V
gender=0 1173      529      592      6.66      41.8
gender=1  418      236      173     22.73      41.8

 Chisq= 41.8  on 1 degrees of freedom, p= 9.94e-11
```

### 10.4.6 Comparison of Hazard Ratios and Test Statistics

**For effect of Gender**

| Model/Method | $\lambda_0$ | $\lambda_1$ | HR | log(HR) | se(log HR) | Wald Statistic |
|---|---|---|---|---|---|---|
| **Exponential** | 0.0029 | 0.0049 | 1.676 | 0.5162 | 0.0619 | 69.507 |
| **Weibull** | | | | | | |
| $t = 50$ | 0.0040 | 0.0060 | 1.513 | 0.4138 | 0.0636 | 42.381 |
| $t = 100$ | 0.0030 | 0.0046 | 1.513 | | | |
| $t = 500$ | 0.0016 | 0.0025 | 1.513 | | | |
| **Logrank** | | | | | | 41.085 |
| **Wilcoxon** | | | | | | 41.468 |
| **Cox PH** | | | | | | |
| Ties=Breslow | | | 1.483 | 0.3944 | 0.0621 | 40.327 |
| Ties=Discrete | | | 1.487 | 0.3969 | 0.0623 | 40.565 |
| Ties=Efron | | | 1.486 | 0.3958 | 0.0621 | 40.616 |
| Ties=Exact | | | 1.486 | 0.3958 | 0.0621 | 40.617 |
| Score (Discrete) | | | | | | 41.085 |

**Comparison of Mean and Median Survival Times by Gender**

| | Mean Survival | | Median Survival | |
|---|---|---|---|---|
| Model/Method | Female | Male | Female | Male |
| **Exponential** | 344.5 | 205.6 | 238.8 | 142.5 |
| **Weibull** | 461.6 | 235.4 | 174.2 | 88.8 |
| **Kaplan-Meier** | 318.6 | 200.7 | 144 | 70 |
| **Cox PH** (Kalbfleisch/Prentice) | | | 131 | 72 |