STAT 6390: Analysis of Survival Data

Textbook coverage: Chapter 8

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Parametric models

- Methods described previously are *non-parametric*; no distributional assumptions were made.
- Non-parametric (and semi-parametric) methods have the flexibility to accommodate a wide range of applications.
- If the assumption of a particular probability distribution for the data is valid, inferences based on such an assumption will be more precise.
- The validity of the parametric methods depends heavily on the appropriateness of the distributional assumption.
- Parametric models are often much easier to work with.

Maximum likelihood estimation

- Suppose *actual survival times* observed for n individuals are $\{t_1, \ldots, t_n\}$.
- If the probability density function of the random variable associated with theos survival times is $f(t)$, the likelihood of the n observations is

$$\prod_{i=1}^{n} f(t_i).$$

- If a distributional assumption is made (e.g., $f(t) = \lambda e^{-t\lambda}$.), the unkonwon parameters (λ) can be estimated by maximzing the likelihood.

Maximum likelihood estimation

- Now suppose the survival data includes (right) censored data.
- In this case, n pairs of observations are observed $(\tilde{t}_i, \Delta_i), i = 1, \ldots, n$, where $\tilde{T}_i$ is the observed survival time.
- When $\Delta_i = 0$, t_i is right-censored.
- The likelihood then takes the form

$$L = \prod_{i=1}^{n} [f_T(t_i)]^{\Delta_i} \cdot [S_T(t_i)]^{1-\Delta_i} = \prod_{i=1}^{n} [h_T(t_i)]^{\Delta_i} \cdot S_T(t_i). \quad (1)$$

- The last equation follows from the property $h(t) = f(t)/S(t)$.
- Note that the derivation of of L does not require a distributional assumption.

Maximum likelihood estimation

- A more careful derivation of the likelihood function in (1) is to assume the censoring times to be random.
- Let C_i be the random variable associated with the censoring time.
- Let $\tilde{T}_i$ be the observed survival time, $\tilde{T}_i = \min(C_i, T_i)$.
- We will consider censored and uncensored cases separately.
- For the censored observation:

$$\mathrm{P}(\tilde{T}_i = t, \Delta_i = 0) = \mathrm{P}(C_i = t, T_i > t).$$

- For the uncensored observation:

$$\mathrm{P}(\tilde{T}_i = t, \Delta_i = 1) = \mathrm{P}(T_i = t, C_i > t).$$

- The likelihood is then

$$L^* = \prod_{i=1}^{n} [\mathrm{P}(T_i = t, C_i > t)]^{\Delta_i} \cdot [\mathrm{P}(C_i = t, T_i > t)]^{1-\Delta_i}.$$

Maximum likelihood estimation

- Under the assumption that C_i and T_i are independent, L^* becomes

$$L^* = \prod_{i=1}^{n} [f_T(t_i)S_C(t_i)]^{\Delta_i} \cdot [f_C(t_i)S_T(t_i)]^{1-\Delta_i}.$$

- If the interest is in the parameter estimation in $f_T(\cdot)$, e.g., the λ in the exponential assumption, $f_C(\cdot)$ and $S_C(\cdot)$ can be considered as constant in the maximum likelihood estimation and L^* reduces to L.
- This construction shows the relevance of the assumption of independent censoring.

Exponential model

- If a random variable, T, follows an exponential distribution with rate λ, then
$$f(t) = \lambda e^{-\lambda t}, S(t) = e^{-\lambda t}, \text{ and } h(t) = \lambda.$$
- If we are willing to assumption $\{t_1, \ldots, t_n\}$ are iid samples from an exponential distribution with rate λ, then the likelihood $L(\lambda)$ is
$$L(\lambda) = \prod_{i=1}^{n} \left[\lambda e^{-\lambda t_i}\right]^{\Delta_i} \cdot \left[e^{-\lambda t_i}\right]^{1-\Delta_i} = \prod_{i=1}^{n} \lambda^{\Delta_i} \cdot e^{-\lambda t_i}.$$
- The log-likelihood is
$$\log L(\lambda) = \ell(\lambda) = \log(\lambda)\left(\sum_{i=1}^{n} \Delta_i\right) - \lambda \sum_{i=1}^{n} t_i.$$

Exponential model

- Solving for
$$\frac{\mathrm{d}\log L(\lambda)}{\mathrm{d}\lambda} = \ell'(\lambda) = 0 \text{ gives } \hat{\lambda} = \frac{\sum_{i=1}^{n} \Delta_i}{\sum_{i=1}^{n} t_i}.$$
- The maximum likelihood estimator (MLE), $\hat{\lambda}$, is the *number of deaths* divides by the total survival time (*number of person-years*).
- The MLE for the average survival time is $1/\hat{\lambda}$, which is the total survival time divides by the number of deaths.
- With $\hat{\lambda}$, other quantities like the MLE for median survival times, can be derived.

Exponential model

- The second derivative of $\ell(\lambda)$ gives the *information*.
- In the exponential model, we have

$$\ell''(\lambda) = -\frac{1}{\lambda^2}\sum_{i=1}^{n}\Delta_i.$$

- The standard MLE theory implies

$$\mathrm{Var}(\hat{\lambda}) \approx \frac{\hat{\lambda}^2}{\sum_{i=1}^{n}\Delta_i}.$$

- The $100(1-\alpha)\%$ confidence interval can be constructed accordingly.
- The Delta method can be applied to obtain standard errors for $g(\lambda)$, e.g., average survival time, median survival time, etc.

Weibull model

- The simplicity of the exponential distribution makes it attractive for some specialized applications.
- A more flexibility alternative is modeling with the Weibull distribution.
- If T follows a Weibull distribution with scale parameters λ and shape parameter γ, then

$$f(t) = \lambda\gamma t^{\gamma-1} e^{-\lambda t^{\gamma}}, S(t) = e^{-\lambda t^{\gamma}}, \text{ and } h(t) = \lambda\gamma t^{\gamma-1}.$$

- It is easy to see that when $\gamma = 1$, Weibull reduces to an exponential distribution with rate λ.

Weibull model

- Following the similar procedure as before, the likelihood $L(\lambda, \gamma)$ is

$$\prod_{i=1}^{n} \left\{ \lambda\gamma t_i^{\gamma-1} \right\}^{\Delta_i} e^{-\lambda t_i^{\gamma}}.$$

- Let $\ell(\lambda, \gamma) = \log L(\lambda, \gamma)$, the MLE for λ turns out to be

$$\hat{\lambda} = \frac{\sum_{i=1}^{n} \Delta_i}{\sum_{i=1}^{n} t_i^{\hat{\gamma}}},$$

but there is no close-form solution for $\hat{\gamma}$.

Weibull model

- The MLE $\hat{\theta} \equiv (\hat{\lambda}, \hat{\gamma})$ can be obtained directly implementing the likelihood and optimized with `optim`.
- Numerical method like the Newton-Raphson procedure can also be used.
- The basic idea of the Newton-Raphson procedure iterates

$$\hat{\theta}_{n+1} = \hat{\theta}_n + \left(-\frac{\mathrm{d}^2\ell(\hat{\theta}_n)}{\mathrm{d}\theta^2}\right)^{-1} \cdot \frac{\mathrm{d}\ell(\hat{\theta}_n)}{\mathrm{d}\theta}.$$

- The variance-covariance matrix comes as a by-product.

Weibull model

- Since parametric models are sensitive to the distributional assumption, it is important to have a diagnostic tool.
- A diagnostic tool for Weibull model is derived from its survival curve.
- The log-log transformation of the Weibull survival function gives

$$\log[-\log S(t)] = \log(\lambda) - \gamma \log(t).$$

- This suggest that if $\log[-\log S(t)]$ is plotted against $\log(t)$, we would expect to see a straight line if the Weibull assumption is valid.
- $S(t)$ can be replaced with $\widehat{S}_{KM}(t)$ or $\widehat{S}_{NA}(t)$.

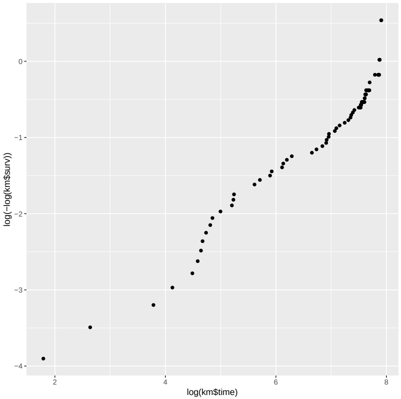
Weibull model

- Recall that $\widehat{S}_{KM}(t)$ for the `whas100` can be obtained with the `survfit`:

```
> km <- survfit(Surv(lenfol, fstat) ~ 1, whas100)
```

- We plot $\log[-\log S(t)]$ against $\log(t)$ via the `qplot` function of **ggplot2**:

```
> qplot(log(km$time), log(-log(km$surv)))
```



- The Weibull assumption might be questionable.

Weibull model

- An alternative way is to select λ and γ to match the survival data at two specified time points.
- This approach is motivated by the linear relationship between $\log\left[-\log S(t)\right]$ and $\log(t)$.
- Suppose we have (t_1, s_1), and (t_2, s_2) that are two time points on a estimated survival curve (e.g., set $s_i = \widehat{S}_{KM}(t_i)$ for $i = 1, 2$).
- Then $\hat{\lambda}$ and $\hat{\gamma}$ can be obtained by solving the system of equation

$$\begin{cases} \log\left(-\log s_1\right) = \log(\lambda) - \gamma \log(t_1) \\ \log\left(-\log s_2\right) = \log(\lambda) - \gamma \log(t_2) \end{cases},$$

for λ and γ.

Weibull model

- The `Weibull2` function in the **Hmisc** package can be used to produce a Weibull function that matches the two points (t_1, s_1), and (t_2, s_2).
- Suppose we want to find a Weibull distribution that matches the KM estimator at the 1st and the 6th year ($t = 365$ and $t = 2190$).

```
> summary(km, time = c(365, 2190))
Call: survfit(formula = Surv(lenfol, fstat) ~ 1, data = whas100)

 time n.risk n.event survival std.err lower 95% CI upper 95% CI
  365     80      20    0.800  0.0400        0.725        0.882
 2190     15      27    0.505  0.0537        0.410        0.622
```

- The two points we what the Weibull curve to pass through are $(365, 0.8)$ and $(2190, 0.505)$.

Weibull model

- Matching the two points with

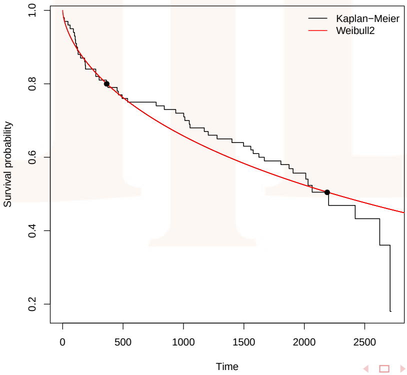
```
> weiSurv <- Weibull2(c(365, 2190), c(.8, .505))
> str(weiSurv)
function (times = NULL, alpha = 0.00560289516761242, gamma = 0.624507785991088)
> class(weiSurv)
[1] "function"
```

- `Weibull2` returns a function.
- The parameters are $\lambda = 0.006$ and $\gamma = 0.625$.
- The "`alpha`" used in `Weibull2` is equivalent to our λ.

Weibull model

- `weiSurv` returns survival probability depending on inputs.

```
> weiSurv(365)
[1] 0.8
> weiSurv(2190)
[1] 0.505
> weiSurv(0:13)
 [1] 1.0000000 0.9944128 0.9913993 0.9889347 0.9867714 0.9848084 0.9829920
 [8] 0.9812894 0.9796788 0.9781448 0.9766759 0.9752633 0.9739001 0.9725807
```



Exponential regression model

- Recall that if T follows an exponential distribution with rate λ, T has the hazard function $h(t) = \lambda$.
- If one wants to construct a regression model under the exponential assumption, it is natural to model the exponential parameter λ.
- Suppose a covariates vector $X = (X_1, \ldots, X_p)'$ is available for an individual.
- The hazard at time t for an individual can be written as

$$\lambda(t; x) = \lambda \cdot r(X'\beta),$$

where $\beta = (\beta_1, \ldots, \beta_p)'$ is the regression coefficient, λ is a constant, and $r(\cdot)$ is a specified functional form.

Exponential regression model

- A few choices of $r(\cdot)$ have been proposed:
  1. $r(u) = u$
  2. $r(u) = u^{-1}$
  3. $r(u) = e^u$
- The first two forms suffer from the disadvantage that $\underset{\sim}{4}ta$ must be restricted to guarantee $r(X'\beta) > 0$ for all possible X.
- The third form is commonly considered and will be used here.

Exponential regression model

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- The third form is commonly considered and will be used here, but we should keep in mind that there may be more appropriate forms in specific settings.

Exponential regression model

- Working with model with hazard function

$$\lambda(t; x) = \lambda e^{X'\beta}. \tag{2}$$

- This model specifies that log failure rate is a linear function of X.
- Setting $Y = \log(T)$, the model (2) implies

$$Y = \alpha - X'\beta + \epsilon, \tag{3}$$

  where $\alpha = -\log(\lambda)$ and ϵ follows an extreme value distribution.
- The model (3) is a log-linear model.

Exponential regression model

- The model (2) also implies

$$S(t;x) = \lambda t e^{X'\beta},$$

and the conditional density function of T given X is then

$$f(t;x) = \lambda e^{X'\beta} \cdot e^{\{-\lambda t e^{X'\beta}\}}.$$

- Parameters can be solved by maximizing the likelihood.

Weibull regression model

- The similar idea can be applied to Weibull assumption.

$$\lambda(t; x) = \lambda\gamma t^{\gamma-1} e^{X'\beta}. \tag{4}$$

- Setting $Y = \log(T)$, model 4 implies

$$Y = \alpha - X'\beta^* + \sigma\epsilon, \tag{5}$$

  where $\alpha = -\log(\lambda)/\gamma$, $\beta^* = \beta/\gamma$, $\sigma = 1/\gamma$, and ϵ is an extreme value distribution.
- The (Weibull) relationship suggests the effect of the covariates
  1. act multiplicatively on the hazard function.
  2. act additively on Y; the general model has a log-linear models.
- The conditional density function and the survival function can be derived for likelihood estimation

Weibull regression model

- The `survreg` function in **`survival`** package covers a large family of parametric models.

```
> library(survival)
> args(survreg)
function (formula, data, weights, subset, na.action, dist = "weibull",
    init = NULL, scale = 0, control, parms = NULL, model = FALSE,
    x = FALSE, y = TRUE, robust = FALSE, score = FALSE, ...)
NULL
```

- Suppose we want to fit a parametric model using covariates:
  - gender
  - age
  - gender-age interaction
  - body mass index (BMI)
- We can create a `Surv` formula as

```
> fm <- Surv(lenfol, fstat) ~ (age + gender)^2 + bmi
```

Weibull regression model

- Exponential regression model:

```
> fit.exp <- survreg(fm, data = whas100, dist = "exp")
> summary(fit.exp)

Call:
survreg(formula = fm, data = whas100, dist = "exp")
              Value Std. Error     z       p
(Intercept)  9.2897     1.6200  5.73 9.8e-09
age         -0.0532     0.0157 -3.39  0.0007
gender      -3.9324     1.8098 -2.17  0.0298
bmi          0.0935     0.0376  2.49  0.0128
age:gender   0.0498     0.0241  2.06  0.0394

Scale fixed at 1

Exponential distribution
Loglik(model)= -444.4   Loglik(intercept only)= -458.5
Chisq= 28.25 on 4 degrees of freedom, p= 1.1e-05
Number of Newton-Raphson Iterations: 5
n= 100
```

- This is equivalent to the Weibull regression model when λ (scale) = 1.
- The same result is presented in Table 8.2.

Weibull regression model

- Since Weibull relationship suggests two kinds of covariates effects (see page 23), the regression coefficient can be interpret in two ways.
- For one unit increase in `bmi` ($\hat{\beta}_{\text{bmi}} = 0.0935$):
  - the risk of death is expected to increase by $e^{0.0935} = 1.098$ times.
  - the log of survival time is expected to decrease by 0.0935 (days).
- For one unit increase in `age` among females (`gender = 1`):
  - the risk of death is expected to increase by $e^{-0.0532+0.0498} = 0.997$ times.
  - the log of survival time is expected to decrease by $-0.0532 + 0.0498 = -0.0034$.
  - The Wald p-value of $\hat{\beta}_{\text{age}} + \hat{\beta}_{\text{gender}=1}$ can be computed as following

```
> name <- c("age", "age:gender")
> 2 - 2 * pnorm(abs(sum(coef(fit.exp)[name])) /
+                 sqrt(sum(fit.exp$var[name, name])))
[1] 0.8584273
```

Weibull regression model

- Since the exponential distribution is a special case of the Weibull distribution, fitting a exponential regression model is equivalent to fitting a Weibull regression model with $\gamma = 1$.
- The intercept defines the exponential parameter, λ.
- The likelihood, `Loglik(model)`, is available because we are fitting a parametric model.
- `Chisq` is likelihood ratio statistics:

```
> 2 * log(exp(-444.4) / exp(-458.5))
[1] 28.2
```

- The likelihood ratio test gives a *p*-value of

```
> 1 - pchisq(28.25, 4)
[1] 1.109905e-05
```

Weibull regression model

- Weibull regression model:

```
> summary(survreg(fm, data = whas100))

Call:
survreg(formula = fm, data = whas100)
               Value Std. Error     z       p
(Intercept)   9.8727     2.0470  4.82 1.4e-06
age          -0.0639     0.0206 -3.10  0.0019
gender       -4.6895     2.2848 -2.05  0.0401
bmi           0.1055     0.0465  2.27  0.0232
age:gender    0.0592     0.0304  1.94  0.0518
Log(scale)    0.2254     0.1242  1.81  0.0695

Scale= 1.25

Weibull distribution
Loglik(model)= -442.6   Loglik(intercept only)= -455.3
Chisq= 25.36 on 4 degrees of freedom, p= 4.3e-05
Number of Newton-Raphson Iterations: 5
n= 100
```

- The same result is presented in Table 8.5.

Weibull regression model

- The interpretation of the regression parameters is similar to that in exponential regression model.
- In addition to the intercept and parameter estimates, `survreg` also gives `Log(scale)`, which corresponds to $\log(\gamma)$.
- The *p*-value for `Log(scale)` is at the borderline of $\alpha = 0.05$, suggesting that adding an extra parameter (γ) to the model does not improve the overall fit significantly.

Log-normal regression model

- Suppose we have a common form

$$Y = X'\beta + \epsilon,$$

  different parametric model can be specified through the distribution of ϵ.
- Another common parametric model is when ϵ follows a standard normal, this also implies the survival times follow a log-normal distribution.

Log-normal regression model

- In the log-normal case, the parameters are not in the form of a proportional hazards model.

```
> summary(survreg(fm, data = whas100, dist = "lognormal"))

Call:
survreg(formula = fm, data = whas100, dist = "lognormal")
              Value Std. Error     z       p
(Intercept) 10.3193     2.2278  4.63 3.6e-06
age         -0.0737     0.0233 -3.16  0.0016
gender      -4.9028     2.5880 -1.89  0.0582
bmi          0.0969     0.0500  1.94  0.0525
age:gender   0.0626     0.0354  1.77  0.0774
Log(scale)   0.6871     0.1066  6.44 1.2e-10

Scale= 1.99

Log Normal distribution
Loglik(model)= -446.5   Loglik(intercept only)= -457.1
Chisq= 21.22 on 4 degrees of freedom, p= 0.00029
Number of Newton-Raphson Iterations: 4
n= 100
```

Other parametric models

- Here is a list of distributions ϵ can be specified via `survreg.distributions`.

```
> names(survreg.distributions)
 [1] "extreme"     "logistic"    "gaussian"    "weibull"     "exponential"
 [6] "rayleigh"    "loggaussian" "lognormal"   "loglogistic" "t"
```