Survival Analysis

1 Introduction

Definition: A failure time (survival time, lifetime), T , is a nonnegative-valued random variable.

For most of the applications, the value of T is the time from a certain event to a failure event. For example,

- in a clinical trial, time from start of treatment to a failure event
- Time from birth to death = age at death
- to study an infectious disease, time from onset of infection to onset of disease
- to study a genetic disease, time from birth to onset of a disease = onset age

Definition: Cumulative distribution function

$$F(t) = P(T \leq t)$$

Definition: Survial function S(t).

$$S(t) = Pr(T > t) = 1 - P(T \leq t)$$

Characteristics of $S(t)$:

- $S(t) = 1$ if $t < 0$
- $S(\infty) = \lim_{t\to\infty} S(t) = 0$
- $S(t)$ is non-increasing in t

Density: density function $f(t)$

- if T is discrete then $f(t) = P(T = t)$.
- b) If T is (absolutely) continuous, the density function is

$$f(t) = \frac{dF(t)}{dt} = -\frac{dS(t)}{dt}$$

Definition. Hazard function $\lambda(t)$ is

- If Tis discrete

分子是在t这个节点上死亡的人数
分母是在t这个节点之前没有死的人数

without censoring

$$\lambda(t) = P(T = t | T \geq t) = \frac{P(T = t)}{P(T \geq t)}$$
$$= \frac{f(t)}{S(t-)}$$

If $t_1 < t_2 < t_3 < \ldots$ are the possible values of T and $t_j \leq t < t_{j+1}$, then

$$S(t) = \prod_{i=1}^{j} (1 - \lambda(t_i))$$ 等于 sum_{i=1}^{i=n}I(T_i > t) / n)

this because

$$\begin{aligned} S(t) &= P(T \geq t) \\ &= P(T \geq t_{j+1}) \\ &= \frac{P(T \geq t_2)}{P(T \geq t_1)} \frac{P(T \geq t_3)}{P(T \geq t_2)} \cdots \frac{P(T \geq t_{j+1})}{P(T \geq t_j)} \\ &= \left(1 - \frac{P(T = t_1)}{P(T \geq t_1)}\right) \left(1 - \frac{P(T = t_2)}{P(T \geq t_2)}\right) \cdots \left(1 - \frac{P(T = t_j)}{P(T \geq t_j)}\right) \\ &= \prod_{i=1}^{j} (1 - \lambda(t_i)) \end{aligned}$$

- If T is (absolutely) continuous

$$\begin{aligned} \lambda(t) &= \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t | T \geq t)}{\Delta t} \\ &= \text{Instantaneous failure rate at t given survival up to t} \\ &= \frac{f(t)}{S(t)} \end{aligned}$$

Definition: Cumulative hazard function (chf) $\Lambda(t)$

- If T is discrete

$$\Lambda(t) = \sum_{t_i \leq t} \lambda(t_i)$$

- It T is (absolutely) continuous,

$$\Lambda(t) = \int_0^t \lambda(u)du$$

therefore

$$\lambda(t) = \frac{d\Lambda(t)}{dt}.$$

Also

$$\begin{aligned}\Lambda(t) &= \int_0^t \lambda(u)du \\ &= \int_0^t \frac{-dS(u)/du}{S(u)} \\ &= -\log(S(t))\end{aligned}$$

This implies that

$$S(t) = e^{-\Lambda(t)} = e^{-\int_0^t \lambda(u)du}.$$

in addition, since $S(\infty) = 0$,

$$\int_0^t \lambda(u)du = \infty.$$

- Examples
  - Suppose T has a survival function given by

$$S(t) = \begin{cases} e^{-\lambda t}, & t > 0 \\ 0, & t \leq 0 \end{cases}$$

    In this case T has exponential distribution with parameter λ and

$$\lambda(t) = \frac{f(t)}{S(t)} = \frac{\lambda e^{-\lambda t}}{e^{-\lambda t}} = \lambda.$$

  - Suppose T has a survival function given by

$$S(t) = \begin{cases} e^{-(\lambda t)^\alpha}, & t > 0 \\ 0, & t \leq 0 \end{cases}$$

$\alpha > 0$ and $\lambda > 0$. In this case T has a Weibull distribution with parameters λ and α. and

$$\lambda(t) = \frac{f(t)}{S(t)} = \lambda^\alpha \alpha t^{\alpha-1} = \alpha\lambda(\lambda t)^{\alpha-1}.$$

If $\alpha = 1$, we have exponential (λ).

Type I censoring: Let $T_1, T_2, \ldots, T_n$ be independent, identically distributed random variables. Assume that t_c is some fixed time. Instead of observing $T_1, T_2, \ldots, T_n$, we only observe

$$X_i = \min(T_i, t_c) = \begin{cases} X_i, & \text{if } T_i \le t_c \\ t_c, & \text{if } T_i > t_c \end{cases}.$$

Type II Censoring: Let $r < n$ and lt $T_{(1)} < T_{(2)} < T_{(2)} < \ldots < T_{(n)}$ be the order statistics of $T_1, T_2, \ldots, T_n$. Suppose observations cease after the rth failure and we only observe $T_{(1)}, T_{(2)}, T_{(2)}, \ldots, T_{(r)}$

In Type II Censoring model we have instead t_c the random time $T_{(r)}$

Both the Type I and the Type II censoring arise in engineering applications.

Random Censoring: Let $C_1, C_2, \ldots, C_n$ be iid random variables with cdf G. Here C_i is the censoring time associated with T_i. We observe the pairs

$$(X_1, \delta_1), (X_2, \delta_2), \ldots, (X_n, \delta_n)$$

delta用来表明在特点的时间点上，被测者是否还存活，因为存在这样的情况，在某个时间点之后被测者的数据不可得，可能是因其他原因而去世了，而不是我们想要研究的原因。当delta等于0的时候，表明对于我们想要观测的愿意，他们至少活到了这个点，所以他们的存活时间是大于或者等于这个值的。用+表示

where

$$X_i = \min(T_i, C_i) = \begin{cases} X_i, & \text{if } T_i \le C_i \\ C_i, & \text{if } T_i > C_i \end{cases}.$$

and

$$\delta_i = \begin{cases} 1, & \text{if } T_i \le C_i \\ 0, & \text{if } T_i > C_i \end{cases}.$$

Example: A set of observed survival data is

x_i	25	18	17	22	27
δ_i	1	0	1	0	1

The data can also be presented as

$$25 \quad 18^+ \quad 17 \quad 22^+ \quad 27$$

Notice that

$$\begin{aligned} S_X(x) = P(X > x) &= P(\min(T, C) > x) \\ &= P(T > x, C > x) \\ &= P(T > x)P(C > x) \\ &= S(x)\bar{G}(x) \leq S(x) \end{aligned}$$

where $\bar{G} = 1 - G$ is the survival function corresponding to C.

2 Estimation of S:

- Complete Failure Times: Nonparametric Models Recall that

$$\begin{aligned} S(t) &= P(T > t) \\ &= \text{population fraction surviving beyond t} \end{aligned}$$

The set of the complete data $t_1, t_2, \ldots, t_n$ reflects the structure of population failure times. Thus, we estimate $S(t)$ by the sample fraction surviving beyond t:

$$\hat{S}(t) = \frac{\# t_i > t}{n} = \frac{1}{n}\sum_{i=1}^{n} I(t_i > t).$$

$\hat{S}$ is also called the empirical survival distribution. How to derive confidence interval for $S(t)$?

We have

$$\frac{\sqrt{n}[\hat{S}(t) - S(t)]}{\sqrt{\hat{S}(t)(1 - \hat{S}(t))}} \xrightarrow{d} N(0, 1)$$

that is

$$\frac{\sqrt{n}[\hat{S}(t) - S(t)]}{\sqrt{\hat{S}(t)(1 - \hat{S}(t))}} \overset{App}{\sim} N(0, 1)$$

or

$$\lim_{n\to\infty} P\left(\frac{\sqrt{n}[\hat{S}(t) - S(t)]}{\sqrt{\hat{S}(t)(1 - \hat{S}(t))}} \leq x\right) = \Phi(x).$$

An approximate $100(1-\alpha)\%$ confidence interval for $S(t)$ is

$$\hat{S}(t) \pm z_{\alpha/2}\sqrt{\hat{S}(t)(1-\hat{S}(t))/n}$$

What do we do when we have right censoring?

Kaplan-Meier Estimator: The Kaplan-Meier estimator is a nonparametric estimator for the survival function S. Consider now either random censoring or type I censoring. The data are

$$(x_1, \delta_1), (x_2, \delta_2), \ldots, (x_n, \delta_n)$$

Let $y_{(1)} < y_{(2)} < \ldots < y_{(k)}, k \leq n$, be the distinct, uncensored and ordered failure times. y是δ=1时候对应的x_i并且排序。δ=0的数据上面有一个+号，一个特定的元素只出现一次（unique）

Example. Data: $3, 2, 0, 1, 5^+, 3, 5$ then

$$(y_{(1)}, y_{(2)}, y_{(3)}, y_{(4)}, y_{(5)}) = (0, 1, 2, 3, 5)$$

Suppose $y_{(i-1)} < t \leq y_{(i)}$. A principle of nonparametric estimation of S is to assign positive probability to and only to uncensored failure time. Therefore, we try to estimate

$$S(t) \approx \frac{P(T \geq y_{(2)})}{P(T \geq y_{(1)})}\frac{P(T \geq y_{(3)})}{P(T \geq y_{(2)})}\cdots\frac{P(T \geq y_{(i)})}{P(T \geq y_{(i-1)})}$$

find x_i with delta = 1 表明在这个时间点上没有因为其他的原因停止的数据

How to estimate $S(t)$? Define

R_j 表示的是在y_j这个时间点上，死亡或者存活超过这个时间点的人数
the people at risk

$$\begin{aligned} R_{(j)} &= \{x_k : x_k \geq y_{(j)}\} \\ d_{(j)} &= \#\text{ of failures at } y_{(j)} \\ N_{(j)} &= \#\text{ of individuals at risk at } y_{(j)} = \text{cardinal of } R_{(j)} \end{aligned}$$

d_j 表明确定的在y_j这个时间点上死亡的人数

N_j就是R_j中元素的个数

Example: Using the previous data, we have

$$\begin{aligned} N_{(0)} &= 7, N_{(1)} = 6, N_{(2)} = 5, N_{(3)} = 4, N(5) = 2 \\ d_{(0)} &= 1, d_{(1)} = 1, d_{(2)} = 1, d_{(3)} = 2, d_{(5)} = 1 \end{aligned}$$

R_0={0,1,2,3,3,5,5+} 在计算时候需要把所有的加上，包括不unique的

p(y_j)

We estimate

$$\frac{P(T \geq y_{(j+1)})}{P(T \geq y_{(j)})}$$

by

$$\frac{N_{(j)} - d_{(j)}}{N_{(j)})} = 1 - \frac{d_{(j)}}{N_{(j)})}$$

$j = 1, 2, \ldots, i-1$. The Kaplan-Meier estimator of $S(t)$ is that

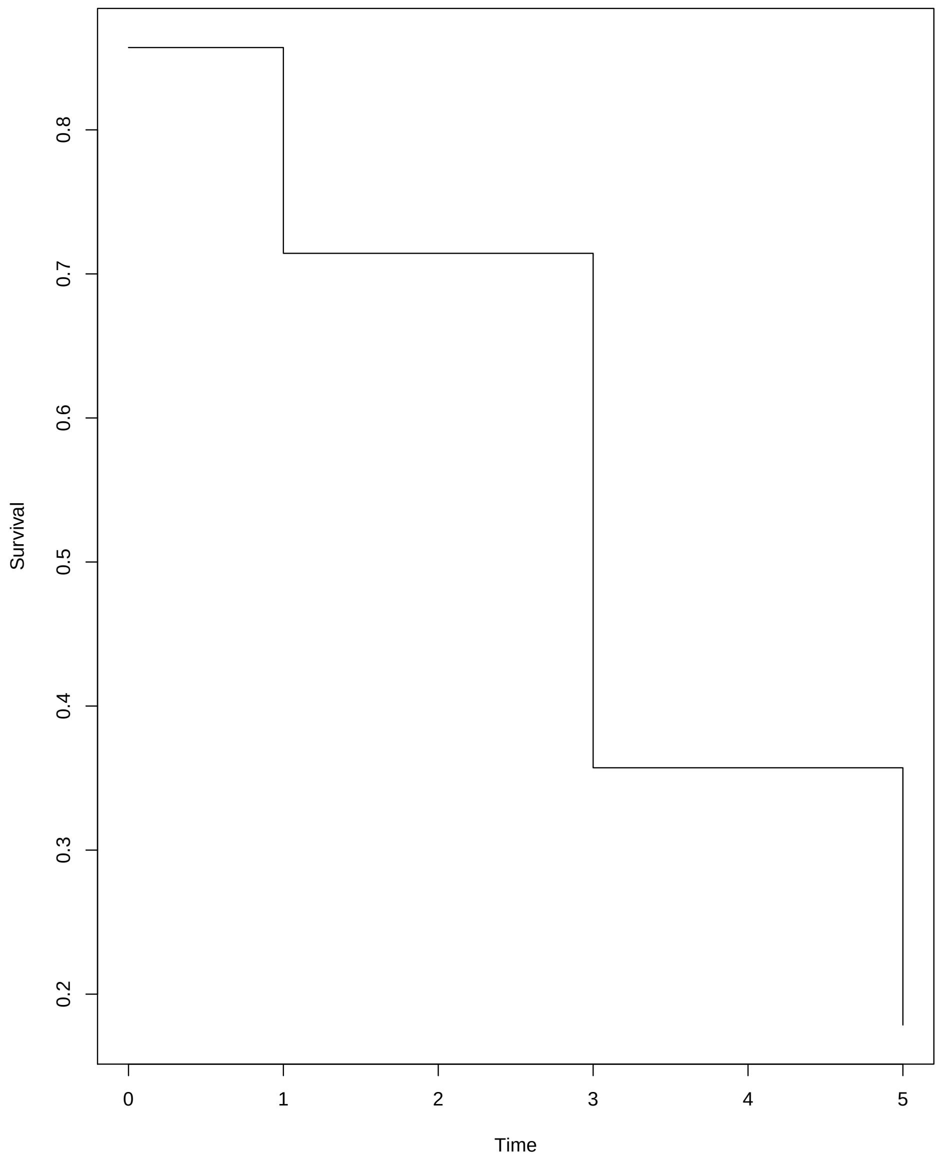
$$\begin{aligned}\hat{S}(t) &= \left(1 - \frac{d_{(1)}}{N_{(1)})}\right)\left(1 - \frac{d_{(2)}}{N_{(2)}}\right)\ldots\left(1 - \frac{d_{(i-1)}}{N_{(i-1)})}\right) \\ &= \prod_{y_{(j)} \leq t} \left(1 - \frac{d_{(j)}}{N_{(j)}}\right)\end{aligned}$$

Example:

Uncensored Times	0	1	2	3	5
$d_{(i)}$	1	1	1	2	1
$N_{(i)}$	7	6	5	4	2

$$\begin{aligned}\hat{S}(0) &= \left(1 - \frac{1}{7}\right) = \frac{6}{7} = 0.857 \\ \hat{S}(1) &= \left(1 - \frac{1}{7}\right)\left(1 - \frac{1}{6}\right) = \frac{5}{7} = 0.714 \\ \hat{S}(2) &= \left(1 - \frac{1}{7}\right)\left(1 - \frac{1}{6}\right)\left(1 - \frac{1}{5}\right) = \frac{4}{7} = 0.571 \\ \hat{S}(3) &= \left(1 - \frac{1}{7}\right)\left(1 - \frac{1}{6}\right)\left(1 - \frac{1}{5}\right)\left(1 - \frac{2}{4}\right) = \frac{2}{7} = 0.286 \\ \hat{S}(5) &= \left(1 - \frac{1}{7}\right)\left(1 - \frac{1}{6}\right)\left(1 - \frac{1}{4}\right)\left(1 - \frac{2}{4}\right)\left(1 - \frac{1}{2}\right) = \frac{1}{7} = 0.143\end{aligned}$$

```
> library(survival)
> time<-c(3, 2,0, 1,5, 3, 5)
> delta<-c(1,1,1, 1, 0, 1, 1)
> library(survival)
> km<-survfit(Surv(time, delta)~1,type="kaplan-meier")
> km$surv
0.8571429 0.7142857 0.5714286 0.2857143 0.1428571
> plot(km$time,km$surv, type="s",xlab="Time",ylab="Survival")
```



It turns out that

$$\sqrt{n}[\hat{S}(t) - S(t)] \xrightarrow{d} N(0, \sigma^2(t))$$

where

$$\sigma^2(t) = S(t)^2 \int_0^t \frac{d\Lambda(t)}{\pi(u)}$$

where $\pi(u) = S(u)\bar{G}(u)$

Un estimate of $\sigma^2(t)$ is

$$\hat{\sigma}^2(t) = \hat{S}(t)^2 \sum_{y_{(j)} \leq t} \frac{d_{(j)}}{N_{(j)}(N_{(j)} - d_{(j)})}$$

An approximate $100(1-\alpha)\%$ confidence interval for $S(t)$ is

$$\hat{S}(t) \pm z_{\alpha/2}\hat{\sigma}(t)$$

```
> summary(km)
Call: survfit(formula = Surv(time, delta) ~ 1, type = "kaplan-meier")

 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    0      7       1    0.857   0.132       0.6334        1.000
    1      6       1    0.714   0.171       0.4471        1.000
    2      5       1    0.571   0.187       0.3008        1.000
    3      4       2    0.286   0.171       0.0886        0.922
    5      2       1    0.143   0.132       0.0233        0.877
```

也可以用KS tests去做这件事。因为KS检验时用于测试是否数据都来自于同一个分布

Group 1: (x_11,δ_11),(x_12,δ_12),...,(x_1n,δ_1n)
Group 2: (x_21,δ_21),(x_22,δ_22),...,(x_2n,δ_2n)

We want to test whether these two distribution is the same:
H0: S_1 = S_2
Ha: S_1 != S_2

Comparing two survival distributions: the logrank statistic

Let $T_1^0 < T_2^0 < \ldots < T_L^0$ denote the odered observed distinct failure 只是observed不是censor的数据 times in the sample made by combining the two groups. Let d_{ik} and $N_{ik}, k = 1, 2, \ldots, L$ denote the number of failures and the number at risk, respectively, in the ith sample at time T_k^0. Let d_k and N_k the corresponding values in the combined sample. The data at T_k^0 can be summarized as follows

Yes表示的是死亡的人数
No表示的是存活的人数

Sample			
Failure	Group 1	Group 2	Total
Yes	d_{1k}	d_{2k}	d_k
No	$N_{1k} - d_{1k}$	$N_{2k} - d_{2k}$	$N_k - d_k$
Total	N_{1k}	N_{2k}	N_k

Total是前面两个数据的和

Given N_{ik}, d_{ik} has a binomial distribution with the number of trials N_{ik} and under the hypothesis of common failure rate λ is the two groups, approximate probability

Under H_0, d_{1k} given d_k has a hypergeometric with mean and variance

$$\begin{aligned} E_{1k} &= d_k \frac{N_{1k}}{N_k} \\ V_{1k} &= d_k \frac{N_{1k} N_{2k}}{N_k^2} \frac{N_k - d_k}{N_k - 1} \end{aligned}$$

Given the margins in each of the L tables at the observed death time

$$\{d_{11} - E_{11}, d_{12} - E_{12}, \ldots, d_{1L} - E_{1L}\}$$

is a vector of observed-minus-conditionally-expected number of failures across the observed failure times, and if we assume these difference are independent

$$Q = \frac{\sum_{k=1}^{L} (d_{1k} - E_{1k})}{\sqrt{\sum_{k=1}^{L} V_{1k}}}$$

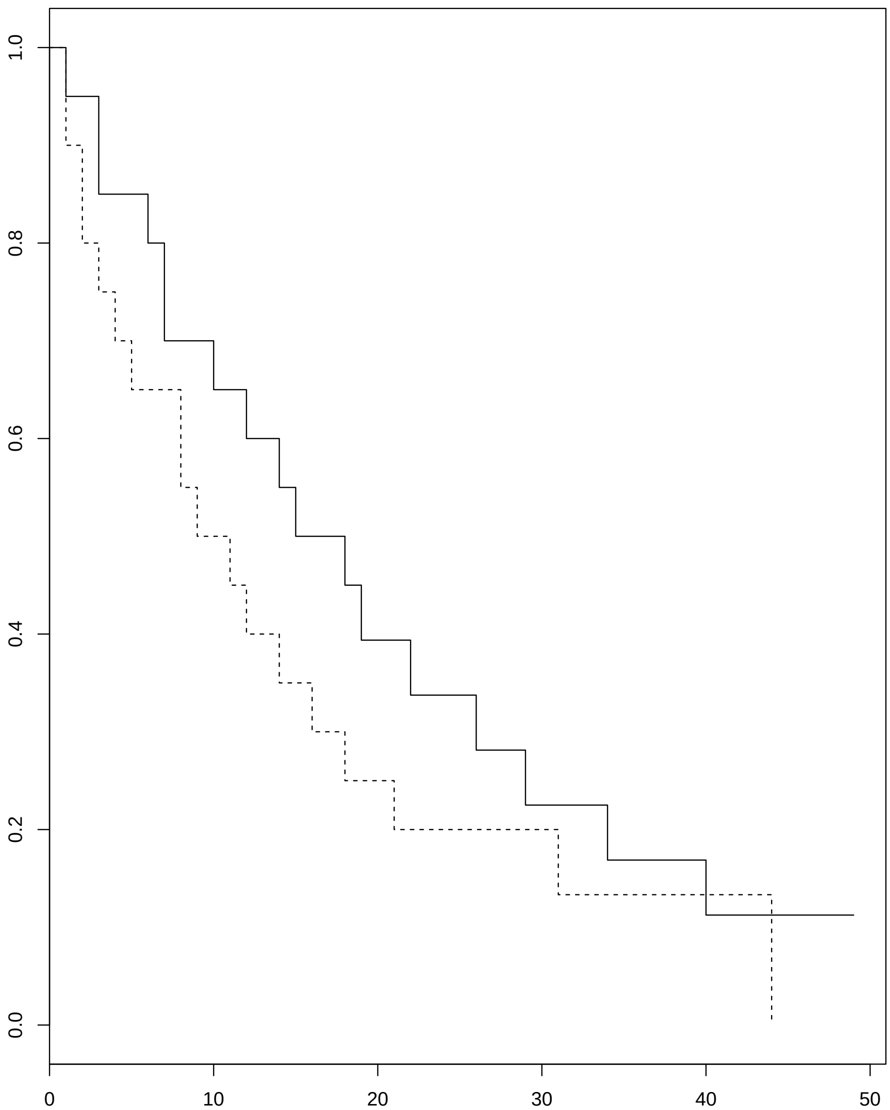
has approximately a standard normal distribution. So Q^2 has approximately χ_1^2.

Example: The data below shows remission times, in weeks, for leukemia patients given two types of treatments. In the study 20 patients were given treatment A and 20 treatment B. Starred observation are censoring time.

$$\begin{aligned} \text{Treatment A} &: 1, 3, 3, 6, 7, 7, 10, 12, 14, 15, 18, 19, 22, 26, 18+, 29, 34, 40, 48+, 49. \\ \text{Treatment B} &: 1, 1, 2, 2, 3, 4, 5, 8, 8, 9, 11, 12, 14, 16, 18, 21, 27+, 31, 38+, 44. \end{aligned}$$

First we create estimate the survival functions. To do this in R we use the package survival

```
> head(data)
   time status group
1     1      1     1
2     3      1     1
3     3      1     1
4     6      1     1
5     7      1     1
>library(survival)
> fit<-survfit(Surv(time,status)~group)
> plot(fit,lty=1:2)
```



To implement the test we use

```
surdiff(Surv(time,status) ~ group, rho=0)
```

```
> survdiff(Surv(time,status)~group, rho=0)
Call:
survdiff(formula = Surv(time, status) ~ group, rho = 0)

         N Observed Expected (O-E)^2/E (O-E)^2/V
group=1 20       17     20.2     0.506      1.24
group=2 20       18     14.8     0.690      1.24

 Chisq= 1.2  on 1 degrees of freedom, p= 0.265
```

The p-value is 0.265, we fail to reject the null hypothesis that the two survival functions are equal.

Example (in detail)

$$\begin{aligned} \text{Treatment A} &: \; 3, 5, 7, 9+, 18 \\ \text{Treatment B} &: \; 12, 19, 20, 20+, 33+ \end{aligned}$$

Here $k = 7$ and $T_1^0 = 2, T_2^0 = 5, T_3^0 = 7, T_4^0 = 12, T_5^0 = 18, T_6^0 = 19, T_7^0 = 19$. at $T_1^0 = 3$, we need to look at the table

	Sample		
Failure	Group 1	Group 2	Total
Yes	1	0	1
No	4	5	9
Total	5	5	10

$d_1 = 1, N_{11} = 5$ and $N_1 = 10$. this gives $E_{11} = 1/2$ and $V_{11} = 1/4$

At $T_1^0 = 5$, we need to look at the table

	Sample		
Failure	Group 1	Group 2	Total
Yes	1	0	1
No	3	5	8
Total	4	5	9

$d_2 = 1, N_{12} = 4$ and $N_2 = 9$. this gives $E_{12} = 4/9$ and $V_{12} = 20/81$

at $T_3^0 = 7$, we need to look at the table

Sample			
Failure	Group 1	Group 2	Total
Yes	1	0	1
No	2	5	7
Total	3	5	8

$d_3 = 1, N_{13} = 3$ and $N_3 = 8$. this gives $E_{13} = 3/8$ and $V_{13} = 15/64$
at $T_4^0 = 12$, we need to look at the table

Sample			
Failure	Group 1	Group 2	Total
Yes	0	1	1
No	1	4	5
Total	1	5	6

$d_4 = 1, N_{14} = 1$ and $N_4 = 6$. this gives $E_{14} = 1/6$ and $V_{14} = 5/36$
at $T_5^0 = 18$, we need to look at the table

Sample			
Failure	Group 1	Group 2	Total
Yes	1	0	1
No	0	4	4
Total	1	4	5

$d_5 = 1, N_{15} = 1$ and $N_5 = 5$. this gives $E_{15} = 1/5$ and $V_{15} = 4/25$
at $T_6^0 = 19$, we need to look at the table

Sample			
Failure	Group 1	Group 2	Total
Yes	0	1	1
No	0	3	3
Total	0	4	4

$d_6 = 1, N_{16} = 0$ and $N_6 = 4$. this gives $E_{16} = 0$ and $V_{16} = 0$
at $T_7^0 = 20$, we need to look at the table

Sample			
Failure	Group 1	Group 2	Total
Yes	0	1	1
No	0	2	2
Total	0	3	3

$d_7 = 1, N_{17} = 0$ and $N_6 = 3$. this gives $E_{17} = 0$ and $V_{17} = 0$

The log-rank statistics is

$$
\begin{aligned}
Q &= \frac{\sum_{k=1}^{L}(d_{1k} - E_{1k})}{\sqrt{\sum_{k=1}^{L} V_{1k}}} \\
&= \frac{(1-1/2)+(1-4/8)+(1-3/8)+(0-1/6)+(1-1/5)+(0-0)+(0-0)}{\sqrt{1/4+20/81+15/64+5/36+4/25}} = 2.26
\end{aligned}
$$

and $Q^2 = 5.108$ the p-value $= 1 - pchisq(5.108, 1) = 0.02381576$. **Generalizations** Use a weighted sum with weights $w_1, w_2, \ldots, w_k$. The test statistic is

$$
Q^2(w_1,, w_2, \ldots, w_k) = \frac{[\sum_{\ell=1}^{k} w_\ell(d_{1\ell} - E_{1\ell})]^2}{\sum_{\ell=1}^{k} w_\ell^2 V_\ell}
$$

Note that if

- $w_1 = w_2 = \ldots = w_k = 1$ we get the logrank test

- $w_\ell = n_\ell, \ell = 1, 2, \ldots, \ell$, we get the Gehan test statistics

- $w_\ell = (n_\ell)^\alpha, \ell = 1, 2, \ldots, \ell, \alpha \in [0, 1]$, we get the Tarone-Ware test statistics

Regression Approach to Survival Analysis

In the presence of covariates, the standard linear regression model formulation is not appropriate for survival time, due to censoring and the skewed nature of the distributions. Before we present the model, we review some results on the types of test that we use in this part.

Cox Proportional Hazard Model (phm)

Let $\mathbf{x} = (x_1, x_2, \ldots, x_p)$ be a vector of covariates and let T be time until failure (failure time)

Define the hazard function for a given individual by

$$\lambda(t, \mathbf{x}) = \lambda_0(t) e^{\beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p}$$

- $\lambda_0(t)$ is some baseline hazard function.
- $\beta_1, \beta_2, \ldots, \beta_p$ are coefficients and they do not include the intercept (the intercept is absorbed in $\lambda_0(t)$)
- $\lambda_0(t)$ does not need to be specified in order to carry out the analysis
- The exponential guarantees that $\lambda(t)$ is positive for any $\beta_1, \beta_2, \ldots, \beta_p$
- The beauty of this model, as observed by Cox, is that if you use a model of this form, and you are interested in the effects of the covariates on survival, then you do not need to specify the form of $\lambda_0(t)$.
- Even without doing so you may estimate $\boldsymbol{\beta}$
- The Cox phm is thus called a semi-parametric model, as some assumptions are made but no form is pre-specified for $\lambda_0(t)$.
- To see why it is called the phm, suppose $p = 1$ and consider two individuals with covariates x_1 and x_2 Then the ratio of their failure rates (or hazard rates) at time t is

  x表示数据源自于哪一组

  $$\frac{\lambda(t, x_1)}{\lambda(t, x_2)} = \frac{e^{\beta_1 x_1}}{e^{\beta_1 x_1}} = e^{\beta_1 (x_1 - x_2)}$$

  that is

  $$\lambda(t, x_1) \propto \lambda(t, x_2)$$

- The hazards rates are proportional to each other and do not depend on time. In particular, the hazard rate for the individual with covariate x_1 is $e^{\beta_1(x_1 - x_2)}$ times that of the individual with covariate x_2
- The term$e^{\beta_1(x_1 - x_2)}$ is called the hazard ratio comparing x_1 to x_2.

- If $\beta_1 = 0$ then the hazard ratio for that covariate is equal to 1, i.e. that covariate doesn?t affect survival. Thus we can use the notion of hazard ratios to test if covariates influence survival.

- The hazard ratio also tells us how much more likely one individual is to die than another at any particular point in time.

- If the hazard ratio comparing men to women were 2, say, it would mean that, at any instant in time, men are twice as likely to die than women.

We need to estimate the beta's in order to assess the effect of the covariates on the survival time.

Let $t_1, t_2, \ldots, t_n$ be the survival time for n indiviuals and $\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_n$ be the corresponding covariates. Let

$$Y_i(t) = \begin{cases} 1, & \text{if the ith person is alive at time t} \\ 0, & \text{otherwise} \end{cases}$$

Suppose a death is observed at time t, the conditional probability that it is subject j is

$$\begin{aligned} L_j(\beta_1, \beta_2, \ldots, \beta_p) &= \frac{\lambda_0(t) e^{\sum_{\ell=1}^{p} x_{\ell j}\beta_j}}{\sum_{i=1}^{n} Y_i(t)\lambda_0(t) e^{\sum_{\ell=1}^{p} x_{\ell i}\beta_\ell}} \\ &= \frac{e^{\sum_{\ell=1}^{p} x_{\ell j}\beta_j}}{\sum_{i=1}^{n} Y_i(t) e^{\sum_{\ell=1}^{p} x_{\ell i}\beta_\ell}} \end{aligned}$$

and this does not depend on $\lambda_0(t)$.

Notice that

- The model depends only on the ranks of the survival times. Therefore, it is nonparamteric in nature

- The parameters my be sensitive to outliers in the covariates

The partial likelihood is defined as

$$L(\beta_1, \beta_2, \ldots, \beta_p) = \prod_{i=1}^{n} L_j(\beta_1, \beta_2, \ldots, \beta_p)$$

The estimates of $\hat{\beta}_1, \hat{\beta}_2, \ldots, \hat{\beta}_p$ of $\beta_1, \beta_2, \ldots, \beta_p$ are obtained by maximizing $L(\beta_1, \beta_2, \ldots, \beta_p)$

To test $H_0 : \beta_\ell = \beta_{\ell 0}, \ell = 1, 2, \ldots, p$ we can use one of the following test statistics

1. Likelihood ratio test

$$LR = -2 \ln \frac{L(\beta_{10}, \beta_{20}, \ldots, \beta_{p0})}{L(\hat{\beta}_1, \hat{\beta}_2, \ldots, \hat{\beta}_p)}$$

   and we reject H_0 is $LR > \chi^2_p(\alpha)$

2. Wald Statistic

$$W = (\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}_0)^T \hat{\Sigma}^{-1} (\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}_0)$$

   where $\hat{\Sigma}$ is an estimate of the covariance of $\hat{\boldsymbol{\beta}}$ and is given by

$$\hat{\Sigma} = I^{-1}(\hat{\boldsymbol{\beta}})$$

   where

$$I(\hat{\boldsymbol{\beta}}) = -\frac{\partial^2}{\partial \boldsymbol{\beta}^2} \ln L(\boldsymbol{\beta})$$

   Under H_0, W has approximately χ^2_p and we reject H_0 if $W > \chi^2_p(\alpha)$. For individual hypotheses, say we want to test $H_0 : \beta_\ell = \beta_{\ell 0}$ against $H_a : \beta_\ell \neq \beta_{\ell 0}$, we use

$$Z = \frac{\hat{\beta}_\ell - \beta_{\ell 0}}{SE(\hat{\beta}_\ell}$$

   and reject H_0 if $|Z| > Z_{\alpha/2}$.

3. Rao's Score Test

$$RS = U'(\boldsymbol{\beta}_0) I(\boldsymbol{\beta}_0) U(\boldsymbol{\beta}_0)$$

   where

$$U(\boldsymbol{\beta}_0) = \frac{\partial}{\partial \boldsymbol{\beta}} \ln L(\boldsymbol{\beta}_0)$$

   Under H_0, RS has approximately χ^2_p and we reject H_0 if $S > \chi^2_p(\alpha)$.

```
Example (cont)
x<-c(rep("1",20),rep("2",20))
> fitphm<-coxph(Surv(time,status)~factor(x))
> fitphm
Call:
coxph(formula = Surv(time, status) ~ factor(x))

             coef exp(coef) se(coef)    z    p
factor(x)2 0.377     1.458    0.340 1.11 0.27

Likelihood ratio test=1.22  on 1 df, p=0.269
n= 40, number of events= 35
```

group two: hazard rate (t|2) = () * e^(0.377)
group one: hazard rate (t|1) = ()

```
> summary(fitphm)
Call:
coxph(formula = Surv(time, status) ~ factor(x))

  n= 40, number of events= 35

             coef exp(coef) se(coef)     z Pr(>|z|)
factor(x)2 0.3769    1.4577   0.3403 1.107    0.268

           exp(coef) exp(-coef) lower .95 upper .95
factor(x)2     1.458      0.686    0.7482      2.84

Concordance= 0.563  (se = 0.05 )
Rsquare= 0.03   (max possible= 0.994 )
Likelihood ratio test= 1.22  on 1 df,   p=0.2686
Wald test            = 1.23  on 1 df,   p=0.2681
Score (logrank) test = 1.24  on 1 df,   p=0.2654
```

Example: The data contains information from an experimental study of recidivism of 432 male prisoners, who were observed for a year after being released from prison The following variables are included in the data; the variable names are those used by Allison (1995), from whom this example and variable descriptions are adapted:

- week : week of first arrest after release, or censoring time.

- arrest : the event indicator, equal to 1 for those arrested during the period of the study and 0 for those who were not arrested.
- fin : a factor, with levels yes if the individual received financial aid after release from prison, and no if he did not; financial aid was a randomly assigned factor manipulated by the researchers.
- age : in years at the time of release.
- race: a factor with levels black and other
- wexp: a factor with levels yes if the individual had full-time work experience prior to incarceration and no if he did not. mar: a factor with levels married if the individual was married at the time of release and not married if he was not.
- paro : a factor coded yes if the individual was released on parole and no if he was not.
- prio : number of prior convictions.
- educ: education, a categorical variable coded numerically, with codes 2 (grade 6 or less), 3 (grades 6 through 9), 4 (grades 10 and 11), 5 (grade 12), or 6 (some post-secondary).

```
> head(data)
  week arrest fin age  race wexp         mar paro prio educ
1   20      1  no  27 black   no not married  yes    3    3
2   17      1  no  18 black   no not married  yes    8    4
3   25      1  no  19 other  yes not married  yes   13    3
4   52      0 yes  23 black  yes     married  yes    1    5
5   52      0  no  19 other  yes not married  yes    3    3
6   52      0  no  24 black  yes not married   no    2    4
```

week 相当于time，arrest相当于status（δ）

```
> fit<-coxph(Surv(week, arrest) ~ fin + age + race + wexp + mar + paro + prio,data
> summary(fit)
```

factor

```
Call:
coxph(formula = Surv(week, arrest) ~ +fin + age + race + wexp +
    mar + paro + prio, data = data)
```

```
  n= 432, number of events= 114

                   coef exp(coef) se(coef)      z Pr(>|z|)
finyes         -0.37942   0.68426  0.19138 -1.983  0.04742 *
age            -0.05744   0.94418  0.02200 -2.611  0.00903 **
raceother      -0.31390   0.73059  0.30799 -1.019  0.30812
wexpyes        -0.14980   0.86088  0.21222 -0.706  0.48029
marnot married  0.43370   1.54296  0.38187  1.136  0.25606
paroyes        -0.08487   0.91863  0.19576 -0.434  0.66461
prio            0.09150   1.09581  0.02865  3.194  0.00140 **
---
Signif. codes:  0 ?***? 0.001 ?**? 0.01 ?*? 0.05 ?.? 0.1 ? ? 1

               exp(coef) exp(-coef) lower .95 upper .95
finyes            0.6843     1.4614    0.4702    0.9957
age               0.9442     1.0591    0.9043    0.9858
raceother         0.7306     1.3688    0.3995    1.3361
wexpyes           0.8609     1.1616    0.5679    1.3049
marnot married    1.5430     0.6481    0.7300    3.2614
paroyes           0.9186     1.0886    0.6259    1.3482
prio              1.0958     0.9126    1.0360    1.1591

Concordance= 0.64  (se = 0.027 )
Rsquare= 0.074   (max possible= 0.956 )
Likelihood ratio test= 33.27  on 7 df,   p=2.362e-05
Wald test            = 32.11  on 7 df,   p=3.871e-05
Score (logrank) test = 33.53  on 7 df,   p=2.11e-05
```

Reduced model

```
> fit<-coxph(Surv(week, arrest) ~ fin + age  + prio,data=Rossi)
> fit
Call:
coxph(formula = Surv(week, arrest) ~ fin + age + prio, data = Rossi)

          coef exp(coef) se(coef)     z       p
finyes -0.3470    0.7068   0.1902 -1.82 0.06820
age    -0.0671    0.9351   0.0209 -3.22 0.00129
```

```
prio    0.0969    1.1017   0.0273  3.56 0.00038

Likelihood ratio test=29.1  on 3 df, p=2.19e-06
n= 432, number of events= 114
```

Test stat = 33.3-29.1= 4.2. The p-value based on a chi-square with 4 df is 0.3796

Asymptotic Likelihood Theory

3 Likelihood function and the maximum likelihood estimator

In general, we have $y_1, y_2, \ldots, y_n$, independent observations, their distribution depending on the parameter $\boldsymbol{\theta}^T = (\theta_1, \theta_2, \ldots, \theta_p)$. Frequently it is the case that $\boldsymbol{\theta}$ is partitioned into two sub-vetors $\boldsymbol{\theta}^T = (\boldsymbol{\theta}_1^T, \theta_2^T)$ where $\boldsymbol{\theta}_1$ is the parameter of interest and $\boldsymbol{\theta}_2$ is a nuisance paramter.

- The likelihood is
$$L(\boldsymbol{\theta}) = \prod_{i=1}^{n} L_i(\boldsymbol{\theta}).$$

  1. Uncensored data:
  $$L_i(\boldsymbol{\theta}) = f(t_i|\boldsymbol{\theta}, x_i)$$
  where $y_i = (t_i, x_i)$
  2. Random censorship data with noninformative censoring:
  $$L_i(\boldsymbol{\theta}) = [\lambda(t_i|\boldsymbol{\theta}, x_i)]^{\delta_i} S(t_i|\boldsymbol{\theta}, x_i)$$
  where $y_i = (t_i, \delta_i, x_i)$

- The score function
$$U(\boldsymbol{\theta}) = \frac{\partial}{\partial \boldsymbol{\theta}} \ln L(\boldsymbol{\theta}) = \begin{pmatrix} \frac{\partial}{\partial \theta_1} \ln L(\boldsymbol{\theta}) \\ \frac{\partial}{\partial \theta_2} \ln L(\boldsymbol{\theta}) \\ \vdots \\ \frac{\partial}{\partial \theta_p} \ln L(\boldsymbol{\theta}) \end{pmatrix}$$

- Under some regularity conditions
$$E(U(\boldsymbol{\theta})) = \mathbf{0} \qquad \text{and} \qquad \mathrm{Var}(U(\boldsymbol{\theta})) = \mathcal{J}(\boldsymbol{\theta})$$

where $\mathcal{I}(\boldsymbol{\theta})$ is the information matrix

$$\begin{aligned}
\mathcal{J}(\boldsymbol{\theta}) = E[U(\boldsymbol{\theta})U^T(\boldsymbol{\theta})] &= -E\left[\frac{\partial^2}{\partial\boldsymbol{\theta}\partial\boldsymbol{\theta}^T}\ln L(\boldsymbol{\theta})\right] \\
&= -E\begin{pmatrix}
\frac{\partial^2}{\partial\theta_1^2}\ln L(\boldsymbol{\theta}) & \frac{\partial^2}{\partial\theta_1\partial\theta_2}\ln L(\boldsymbol{\theta}) & \dots & \frac{\partial^2}{\partial\theta_1\partial\theta_p}\ln L(\boldsymbol{\theta}) \\
\frac{\partial^2}{\partial\theta_2\partial\theta_1}\ln L(\boldsymbol{\theta}) & \frac{\partial^2}{\partial\theta_2^2}\ln L(\boldsymbol{\theta}) & \dots & \frac{\partial^2}{\partial\theta_2\partial\theta_p}\ln L(\boldsymbol{\theta}) \\
\vdots & \vdots & \vdots & \vdots \\
\frac{\partial^2}{\partial\theta_p\partial\theta_1}\ln L(\boldsymbol{\theta}) & \frac{\partial^2}{\partial\theta_2\partial\theta_2}\ln L(\boldsymbol{\theta}) & \dots & \frac{\partial^2}{\partial\theta_p^2}\ln L(\boldsymbol{\theta})
\end{pmatrix}
\end{aligned}$$

- Likelihood Equations

$$U(\boldsymbol{\theta}) = \frac{\partial}{\partial\boldsymbol{\theta}}\ln L(\boldsymbol{\theta}) = \begin{pmatrix} \frac{\partial}{\partial\theta_1}\ln L(\boldsymbol{\theta}) \\ \frac{\partial}{\partial\theta_2}\ln L(\boldsymbol{\theta}) \\ \vdots \\ \frac{\partial}{\partial\theta_p}\ln L(\boldsymbol{\theta}) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ \vdots \\ 0 \end{pmatrix} = \mathbf{0}$$

- The maximum likelihood estimator $\hat{\boldsymbol{\theta}}_{MLE}$ has the property

$$U(\hat{\boldsymbol{\theta}}_{MLE}) = \mathbf{0}.$$

- Under regularity conditions

$$n^{-1/2}U(\boldsymbol{\theta}) \overset{Approx}{\sim} N(\mathbf{0}, \mathcal{J}(\boldsymbol{\theta}))$$

as $n \to \infty$.

4 Hypotheses tests

4.1 The score test

- We can use the result above to test $H_0 : \boldsymbol{\theta} = \boldsymbol{\theta}_0$ against $H_a : \boldsymbol{\theta} \neq \boldsymbol{\theta}_0$.
- The test is the score test and is give by

$$RS = U^T(\boldsymbol{\theta}_0)[\mathcal{J}(\theta_0)]^{-1}U(\boldsymbol{\theta}_0)/n$$

Under H_0,

$$RS \xrightarrow{d} \chi^2_p$$

as $n \to \infty$. We reject H_0 if

$$RS > \chi_p^2(\alpha).$$

- Approximate $100(1-\alpha)$ confidence interval for $\boldsymbol{\theta}$ is

$$\{\boldsymbol{\theta}, U^T(\boldsymbol{\theta})[\mathcal{J}(\boldsymbol{\theta})]^{-1}U(\boldsymbol{\theta}) \leq \chi_p^2(\alpha)\}$$

- To handle the situation with nuisance parameters, partition $\boldsymbol{\theta}^T$ in $(\boldsymbol{\theta}_1^T, \boldsymbol{\theta}_2^T)$ where $\boldsymbol{\theta}_1^T = (\theta_1, \theta_2, \ldots, \theta_k)^T$ and $\boldsymbol{\theta}_2 = (\theta_{k+1}, \theta_{k+2}, \ldots, \theta_p)^T$ and similarly

$$[\mathcal{J}(\boldsymbol{\theta})]^{-1} = \begin{pmatrix} \mathcal{J}^{11}(\boldsymbol{\theta}) & \mathcal{J}^{12}(\boldsymbol{\theta}) \\ \mathcal{J}^{21}(\boldsymbol{\theta}) & \mathcal{J}^{22}(\boldsymbol{\theta}) \end{pmatrix}$$

Where $I^{11}(\boldsymbol{\theta})$ is a k by k matrix. Suppose we want to test

$$H_0 : \boldsymbol{\theta}_1 = \boldsymbol{\theta}_1^0 \quad (\text{ nothing is hypothesized about } \boldsymbol{\theta}_2)$$

against

$$H_0 : \boldsymbol{\theta}_1 \neq \boldsymbol{\theta}_1^0.$$

- Let $\hat{\boldsymbol{\theta}}_2(\boldsymbol{\theta}_1^0)$ be the mle of $\boldsymbol{\theta}_2$ given $\boldsymbol{\theta}_1 = \boldsymbol{\theta}_1^0$, i.e.

$$\hat{\boldsymbol{\theta}}_2(\boldsymbol{\theta}_1^0) = \arg\max L(\boldsymbol{\theta}_1^0, \boldsymbol{\theta}2)$$

- Define

$$U(\boldsymbol{\theta}_1^0) = \frac{\partial}{\partial \boldsymbol{\theta}} \ln L(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2)|_{\boldsymbol{\theta}_1 = \boldsymbol{\theta}_1^0, \boldsymbol{\theta}_2 = \hat{\boldsymbol{\theta}}_2(\boldsymbol{\theta}_1^0)}$$

- The score statistic for testing $H_0 : \boldsymbol{\theta}_1 = \boldsymbol{\theta}_1^0$ is

$$RS = U^T(\boldsymbol{\theta}_1^0)\mathcal{J}^{11}(\boldsymbol{\theta}_1 = \boldsymbol{\theta}_1^0, \boldsymbol{\theta}_2 = \hat{\boldsymbol{\theta}}_2(\boldsymbol{\theta}_1^0))U(\boldsymbol{\theta}_1^0)/n$$

- This test statistic has approximately under H_0 a chi-square distribution with k degrees of freedom. We reject H_0 if

$$RS > \chi_k^2(\alpha)$$

where k is the dimension of $\boldsymbol{\theta}_1$.

4.2 Wald test

- Under regularity conditions

$$\hat{\boldsymbol{\theta}}_{MLE} \overset{Approx}{\sim} N(\boldsymbol{\theta}, \mathcal{J}^{-1}(\boldsymbol{\theta})).$$

- This gives another test called the Wald test for testing $H_0 : \boldsymbol{\theta} = \boldsymbol{\theta}_0$. The test statistic is

$$W = (\hat{\boldsymbol{\theta}}_{MLE} - \boldsymbol{\theta}_0)^T \mathcal{J}(\boldsymbol{\theta}_0)(\hat{\boldsymbol{\theta}}_{MLE} - \boldsymbol{\theta}_0).$$

- Under $H0$

$$W \xrightarrow{d} \chi^2_p$$

  and we reject H_0 if $W > \chi^2_p(\alpha)$

- Approximate $100(1-\alpha)$ confidence interval for $\boldsymbol{\theta}$ is

$$\{\boldsymbol{\theta}, (\hat{\boldsymbol{\theta}}_{MLE} - \boldsymbol{\theta})^T \mathcal{J}(\boldsymbol{\theta})((\hat{\boldsymbol{\theta}}_{MLE} - \boldsymbol{\theta}) \leq \chi^2_p(\alpha)\}$$

- To test $H_0 : \boldsymbol{\theta}_1 = \boldsymbol{\theta}_1^0$, use

$$W = (\hat{\boldsymbol{\theta}}_{1,MLE} - \boldsymbol{\theta}_1^0)^T [\mathcal{J}^{11}(\hat{\boldsymbol{\theta}}_{MLE})]^{-1} (\hat{\boldsymbol{\theta}}_{1,MLE} - \boldsymbol{\theta}_1^0)$$

  and reject H_0 if $W > \chi^2_k(\alpha)$.

- Practical Example ($k = 1$). Suppose we want to test

$$H_0 : \theta_j = \theta_j^0$$

  Here $theta_1 = \theta_j$ and $\boldsymbol{\theta}_2 =$ rest. Let $\imath^{jj}(\boldsymbol{\theta})$ be the (j, j)th element of $[\mathcal{J}(\boldsymbol{\theta})]^{-1}$. Then

$$\frac{(\hat{\theta}_j - \theta_j^0)}{\sqrt{\imath^{jj}(\hat{\boldsymbol{\theta}})}} \overset{Approx}{\sim} N(0,1)$$

- An approximate 95% confidence interval for θ_j is

$$\hat{\theta}_j \pm 1.96 \sqrt{\imath^{jj}(\hat{\boldsymbol{\theta}})}$$

4.3 Likelihood Ratio Test (LRT)

- We have always

$$\frac{L(\boldsymbol{\theta}_0)}{L(\hat{\boldsymbol{\theta}})} \leq 1$$

- When $\boldsymbol{\theta} = \boldsymbol{\theta}_0$, the likeliho od ration $\Lambda = \frac{L(\boldsymbol{\theta}_0)}{L(\hat{\boldsymbol{\theta}})}$ is close to 1.

- For this reason, the LRT for $H_0 : \boldsymbol{\theta} = \boldsymbol{\theta}_0$ rejects H_0 for small value of Λ

- It turns out that under H_0

$$-2 \ln \frac{L(\boldsymbol{\theta}_0)}{L(\hat{\boldsymbol{\theta}})} \xrightarrow{d} \chi^2_p$$

- We reject H_0 if

$$-2 \ln \frac{L(\boldsymbol{\theta}_0)}{L(\hat{\boldsymbol{\theta}})} > \chi^2_p(\alpha).$$

- For testing $H_0 : \boldsymbol{\theta}_1 = \boldsymbol{\theta}_1^0$, again let $\hat{\boldsymbol{\theta}}_2(\boldsymbol{\theta}_1^0)$ be the mle of $\boldsymbol{\theta}_2$ given that $\boldsymbol{\theta}_1 = \boldsymbol{\theta}_1^0$ the test statistic is

$$-2 \ln \frac{L(\boldsymbol{\theta}_1^0, \hat{\boldsymbol{\theta}}_2(\boldsymbol{\theta}_1^0))}{L(\hat{\boldsymbol{\theta}})}$$

  and we reject H_0 if this test statistics is greater than $\chi^2_k(\alpha)$.

4.4 Information Matrix

$I(\theta)$ is called the "Fisher information" or "expected information", But how should one calculate expectation (i.e $-E\left(\frac{\partial^2}{\partial\theta_i\theta_j} \ln L(\boldsymbol{\theta})\right)$.) when there censoring.

In survival analysis, we typically use "observed information"

$$I(\boldsymbol{\theta}) = -\left(\frac{\partial^2}{\partial\theta_1\theta_j} \ln L(\boldsymbol{\theta})\right)_{p\times p}$$

5 Examples

Example 1: Suppose we observe $(t_i, \delta_i), i = 1, 2, \ldots, n$.

$$L(\lambda) = \prod_{i=1}^{n} L_i(\lambda) = \prod_{i=1}^{n} [\lambda e^{-\lambda t_i}]^{\delta_i} [e^{-\lambda t_i}]^{1-\delta_i} = \prod_{i=1}^{n} \lambda^{\delta_i} e^{-\lambda t_i}$$

then

$$\ln L(\lambda) = \sum_{i=1}^{n} \delta_i \ln(\lambda) - \lambda \sum_{i=1}^{n} t_i$$

Then

$$U(\lambda) = \frac{\partial}{\partial \lambda} \ln L(\lambda) = \frac{\sum\limits_{i=1}^{n}}{\lambda} - \sum_{i=1}^{n} t_i = 0 \Rightarrow \hat{\lambda} = \frac{\sum\limits_{i=1}^{n} \delta_i}{\sum\limits_{i=1}^{n} t_i}$$

The observed Fisher information is

$$I(\lambda) = -\frac{\partial^2}{\partial \lambda^2} \ln L(\lambda) = \frac{\sum\limits_{i=1}^{n} \delta_i}{\lambda^2}$$

and

$$\widehat{\text{Var}}(\hat{\lambda}) = I^{-1}(\lambda)|_{\lambda=\hat{\lambda}} = \frac{\hat{\lambda}}{\sum\limits_{i=1}^{n} \delta_i} = \frac{\sum\limits_{i=1}^{n} \delta_i}{\sum\limits_{i=1}^{n} t_i^2}$$

and

$$\sqrt{n}(\hat{\lambda} - \lambda) \xrightarrow{d} N(0, I^{-1}(\lambda))$$

An approximate 95% confidence interval for λ is

$$\hat{\lambda} \pm 1.96 \sqrt{\widehat{\text{Var}}(\hat{\lambda})}$$

that is

$$\frac{\sum\limits_{i=1}^{n} \delta_i}{\sum\limits_{i=1}^{n} t_i} \pm 1.96 \frac{\sqrt{\sum\limits_{i=1}^{n} \delta_i}}{\sum\limits_{i=1}^{n} t_i}$$

Example 2 : Exponential Regression
Data : $(t_i, \delta_i, x_i), \mathbf{x}_i = (x_{1i}, x_{2i}, \ldots, x_{pi})^T, i = 1, 2, \ldots, n$
Hazard Model : $\lambda(t|x) = \lambda e^{\boldsymbol{\beta}^T \mathbf{x}}$ where $\boldsymbol{\beta} = (\beta_1, \beta_2, \ldots, \beta_p)^T$
Likelihood:

$$\begin{aligned} L(\lambda, \boldsymbol{\beta}) &= \prod_{i=1}^{n} [\lambda(t_i|\mathbf{x}_i)]^{\delta_i} S(t_i|\mathbf{x}_i) \\ &= \prod_{i=1}^{n} \lambda^{\delta_i} e^{\delta_i \boldsymbol{\beta}^T \mathbf{x}_i} e^{-\lambda e^{\boldsymbol{\beta}^T \mathbf{x}_i} t_i} \\ &= \lambda^{\sum \delta_i} e^{\boldsymbol{\beta}^T \sum \mathbf{x}_i \delta_i} e^{-\lambda \sum e^{\boldsymbol{\beta}^T \mathbf{x}_i} t_i} \end{aligned}$$

log-likelihood

$$\sum \delta_i \lambda + \boldsymbol{\beta}^T \sum \mathbf{x}_i \delta_i - -\lambda \sum e^{\boldsymbol{\beta}^T \mathbf{x}_i} t_i$$

Likelihood equations:

$$\begin{aligned} \frac{\partial}{\partial \lambda} \ln L &= \frac{\sum \delta_i}{\lambda} - \sum e^{\boldsymbol{\beta}^T \mathbf{x}_i} t_i = 0 \\ \frac{\partial}{\partial \beta_j} \ln L &= \sum \mathbf{x}_{ji} \delta_i - \lambda \sum x_{ji} e^{\boldsymbol{\beta}^T \mathbf{x}_i} t_i = 0, j = 1, 2, \ldots, p. \end{aligned}$$

How do we solve the likelihood equations for $\hat{\lambda}$ and $\hat{\boldsymbol{\beta}}$?

Special Case: Two sample problem

$$p = 1, x_i = \begin{cases} 0, & \text{if i is in group 1} \\ 1, & \text{if i is in group 2} \end{cases}$$

so the hazard rate for goup 1 is λ and for group 2 the hazard rate is λe^{β}.

Suppose

$$\begin{aligned} d_j &= \text{number of individuals who failed in group}\, j, j = 1, 2 \\ V_j &= \text{total observed time under study in group j, } j, j = 1, 2 \end{aligned}$$

that is

$$\begin{aligned} d_1 &= \sum_{1}^{n} \delta_i (1 - x_i), \quad d_1 = \sum_{1}^{n} \delta_i x_i \quad \text{this implies that} \quad \sum \delta_i = d_1 + d_2 \\ V_1 &= \sum_{1}^{n} t_i (1 - x_i), \quad V_1 = \sum_{1}^{n} t_i x_i \end{aligned}$$

Then from above, the likelihood equations are

$$\frac{\partial}{\partial \lambda} \ln L = \frac{d_1 + d_2}{\lambda} - V_1 - e^{\beta} V_2 = 0 \quad (1)$$

$$\frac{\partial}{\partial \beta} \ln L = d_2 - \lambda e^{\beta} V_2 = 0 \quad (2)$$

$$(2) \Rightarrow \hat{\lambda} = e^{-\hat{\beta}} \frac{d_2}{V_2}$$

Substitution into (1) gives

$$(d_1 + d_2) e^{\hat{\beta}} \frac{d_2}{V_1} - V_1 - e^{\hat{\beta}} V_2 = 0$$

this implies that

$$e^{\hat{\beta}} = \frac{V_1/d_1}{V_2/d_2} \quad \text{and} \quad \hat{\lambda} = d_1/V_1$$

Notice that $e^{\hat{\beta}}$ is the ratio of failure rates.

The information matrix in this case is

$$I(\lambda, \beta) = \begin{pmatrix} \lambda^{-2} \sum_i \delta_i & \sum_i x_i t_i e^{\beta x_i} \\ \sum_i x_i t_i e^{\beta x_i} & \lambda \sum_i x_i^2 t_i e^{\beta x_i} \end{pmatrix}$$

Note that

$$\sum_i \delta_i / \hat{\lambda}^2 = \frac{d_1 + d_2}{d_1^2} V_1^2$$

$$\sum_i x_i t_i e^{\hat{\beta} x_i} = e^{\hat{\beta}} V_2 = \frac{V_1 d_2}{d_1 V_2} V_2$$

$$\sum_i x_i^2 t_i e^{\beta x_i} = \sum_i x_i t_i e^{\beta x_i}$$

This implies that

$$I(\hat{\lambda}, \hat{\beta}) = \begin{pmatrix} \frac{d_1 + d_2}{d_1^2} V_1^2 & \frac{V_1 d_2}{d_1} \\ \frac{V_1 d_2}{d_1} & d_2 \end{pmatrix}$$

Therefore

$$\widehat{Var}(\hat{\lambda}, \hat{\beta}) = I^{-1}(\hat{\lambda}, \hat{\beta}) = \begin{pmatrix} \frac{d_1}{V_1^2} & -V_1^{-1} \\ -V_1^{-1} & \frac{d_1 + d_2}{d_1 d_2} \end{pmatrix}$$

We will use the following data to illustrate the mle based procedures. the data is time measured in 100 days

$$\begin{aligned}
\text{Group 1} &: 43, 64, 88, 88, 90, 92, 106, 109, 113, 116, 120, 127, 130, 134, 146, 165, 204, 116+, 144+ \\
\text{Group 2} &: 42, 56, 73, 98, 105, 132, 132, 133, 133, 133, 133, 139, 140, 161, 180, 196, 223, 104+, 244+
\end{aligned}$$

It is easy to see that $d_1 = 17, V_1 = 2195, d_2 = 19, V_2 = 2923$. This implies that

$$\hat{\lambda} = \frac{17}{2195} = 0.007745, \quad \hat{\beta} = \ln\left(\frac{V_1 d_2}{V_2 d_1}\right) = \ln(0.839) = -0.175.$$

To test $H_0 : \beta = 0$, the Wald test is

$$\frac{\hat{\beta}}{\sqrt{\widehat{Var}(\hat{\beta})}} = \frac{\hat{\beta}}{\sqrt{\frac{d_1+d_2}{d_1 d_2}}} = \ln\left(\frac{V_1 d_2}{V_2 d_1}\right)\sqrt{\frac{d_1 d_2}{d_1 + d_2}}$$

This is equal to -0.524 (not significant)

A 95% confidence interval for β is

$$\hat{\beta} \pm 1.96\sqrt{\frac{d_1 + d_2}{d_1 d_2}} = (-0.830, 0.480)$$