Survival Analysis
Bios 662

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Outline

• Intro to survival data/analysis
• KM estimator, SE, CI
• Log-rank test
Survival Analysis

- Chapter 16 text; BIOS 680/780

- Survival analysis: response is time to event

- Measure time from beginning of follow-up until an event such as incident disease, death, or relapse

- Examples:
  - time from kidney transplant until death
  - time from leukemia treatment to remission
  - time from release from jail to rearrest
Survival Analysis: Notation

• Let $T^*$ denote the survival time; assume $T^* > 0$

• Define the survival function

$$S(t) = \Pr[T^* > t] = 1 - \Pr[T^* \leq t] = 1 - F(t)$$

where $F(t)$ is CDF of $T^*$

• Properties

$$S(0) = 1; S(\infty) = 0$$

If $t_1 \leq t_2$, then $S(t_1) \geq S(t_2)$
Example Survival Curve/Function
Censoring

- Often do not know the exact time of failure

- Reasons for right censoring:
  - subject does not experience event before the end of the study
  - subject is lost to follow-up during the study (eg withdraws from study, moves, death from something other than event of interest)

- Failure times can also be left or interval censored
Right Censoring

![Diagram of right censoring in survival analysis]

- **Study begins**
- **Study ends**
- **No event under study**
- **Event occurs**
- **Loss-to-follow-up**
- **Withdrews from study**

**t**
Survival Data

- Let $T_i^*$ and $C_i$ denote the survival and right censoring times for the $i^{th}$ individual.
- Observe $T_i = \min\{T_i^*, C_i\}$
- Censoring indicator
  $$\delta_i = \begin{cases} 
  1 & \text{if failure i.e. } T_i = T_i^* \\
  0 & \text{if right censored i.e. } T_i = C_i 
  \end{cases}$$
- Observe $(T_i, \delta_i)$ for $i = 1, 2, \ldots, N$
Example

- Remission time in weeks for leukemia patients ($N = 21$)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$(T_i, \delta_i)$</td>
<td>$(T_i, \delta_i)$</td>
<td>$(T_i, \delta_i)$</td>
</tr>
<tr>
<td>(6,1)</td>
<td>(6,1)</td>
<td>(6,1)</td>
</tr>
<tr>
<td>(6,0)</td>
<td>(7,1)</td>
<td>(9,0)</td>
</tr>
<tr>
<td>(10,1)</td>
<td>(10,0)</td>
<td>(11,0)</td>
</tr>
<tr>
<td>(13,1)</td>
<td>(16,1)</td>
<td>(17,0)</td>
</tr>
<tr>
<td>(19,0)</td>
<td>(20,0)</td>
<td>(22,1)</td>
</tr>
<tr>
<td>(23,1)</td>
<td>(25,0)</td>
<td>(32,0)</td>
</tr>
<tr>
<td>(32,0)</td>
<td>(34,0)</td>
<td>(35,0)</td>
</tr>
</tbody>
</table>
Estimation

• How do we estimate $S(t)$ w/ minimal assumptions?
• Answer 1: In the absence of censoring, use 1-EDF
• Answer 2: Otherwise, use Kaplan-Meier estimator
Tabular Summary of Data

- Let \( t(1), t(2), \ldots, t(k) \) be the distinct ordered failure times

<table>
<thead>
<tr>
<th>Ordered failures</th>
<th>No. of failures</th>
<th>No. censored in ([t(j), t(j+1)))</th>
<th>Risk set</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T(j) )</td>
<td>( m_j )</td>
<td>( q_j )</td>
<td>( R(T(j)) )</td>
</tr>
<tr>
<td>( t(0) = 0 )</td>
<td>( m_0 = 0 )</td>
<td>( q_0 )</td>
<td>( R(t(0)) = N )</td>
</tr>
<tr>
<td>( t(1) )</td>
<td>( m_1 )</td>
<td>( q_1 )</td>
<td>( R(t(1)) )</td>
</tr>
<tr>
<td>( t(2) )</td>
<td>( m_2 )</td>
<td>( q_2 )</td>
<td>( R(t(2)) )</td>
</tr>
<tr>
<td>( \ldots )</td>
<td>( \ldots )</td>
<td>( \ldots )</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>( t(k) )</td>
<td>( m_k )</td>
<td>( q_k )</td>
<td>( R(t(k)) )</td>
</tr>
</tbody>
</table>

- \( R(T(j)) = R(T(j-1)) - m_{j-1} - q_{j-1} \)
## Leukemia Example

<table>
<thead>
<tr>
<th>( t(j) )</th>
<th>( m_j )</th>
<th>( q_j )</th>
<th>( R(t(j)) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>22</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>23</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
Kaplan-Meier estimator of $S(t)$

- For $t \in [0, t(1))$
  \[ \hat{S}(t) = 1 \]

- For $t \in [t(j), t(j+1))$
  \[ \hat{S}(t) = \hat{S}(t(j-1)) \hat{\Pr}[T > t(j) | T \geq t(j)] \]
  \[ = \hat{S}(t(j-1)) \left\{ \frac{R(t(j)) - m_j}{R(t(j))} \right\} \]
Kaplan-Meier

- KM is a NPMLE (nonparametric maximum likelihood estimator)
- Assumes independent censoring
- Aka product limit estimator
- If no censoring, KM equals 1-EDF
- Alternative: life-table or actuarial method
Leukemia Example

<table>
<thead>
<tr>
<th>$t_{(j)}$</th>
<th>$m_j$</th>
<th>$q_j$</th>
<th>$R(t_{(j)})$</th>
<th>$\hat{S}(t_{(j)})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>1</td>
<td>21</td>
<td>$18/21 = .857$</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1</td>
<td>17</td>
<td>$.857(16/17) = .807$</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>2</td>
<td>15</td>
<td>$.807(14/15) = .753$</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>$.753(11/12) = .690$</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>3</td>
<td>11</td>
<td>$.690(10/11) = .627$</td>
</tr>
<tr>
<td>22</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>$.627(6/7) = .538$</td>
</tr>
<tr>
<td>23</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>$.538(5/6) = .448$</td>
</tr>
</tbody>
</table>
Kaplan-Meier Estimate for Leukemia Example

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Survival Analysis
Kaplan-Meier Estimate: R code

```r
> library("survival")

> fit <- survfit(Surv(t, delta), conf.type="plain")

> plot(fit, xlab="t", ylab="S(t)")

> summary(fit)
Call: survfit(formula = Surv(t, delta))

time n.risk n.event survival std.err

   6    21      3   0.857  0.0764
   7    17      1   0.807  0.0869
  10    15      1   0.753  0.0963
  13    12      1   0.690  0.1068
  16    11      1   0.627  0.1141
  22     7      1   0.538  0.1282
  23     6      1   0.448  0.1346
```
Kaplan-Meier Estimate: SAS code

```
proc lifetest; time t*delta(0);
```

The LIFETEST Procedure
Product-Limit Survival Estimates

<table>
<thead>
<tr>
<th>t</th>
<th>Survival</th>
<th>Failure</th>
<th>Standard Error</th>
<th>Number Failed</th>
<th>Number Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0000</td>
<td>1.0000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>6.0000</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>6.0000</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>6.0000</td>
<td>0.8571</td>
<td>0.1429</td>
<td>0.0764</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>6.0000*</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>7.0000</td>
<td>0.8067</td>
<td>0.1933</td>
<td>0.0869</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>9.0000*</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>10.0000</td>
<td>0.7529</td>
<td>0.2471</td>
<td>0.0963</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>10.0000*</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>11.0000*</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>5</td>
<td>12</td>
</tr>
</tbody>
</table>
Derivation of Greenwood SE/CI of KM

• Let $n_j = R(t_{(j)})$

• Write KM as

$$\hat{S}(t) = \prod_{j=1}^{i} \hat{p}_j \text{ for } t \in [t_{(j)}, t_{(j+1)}),$$

where $\hat{p}_j = (n_j - m_j)/n_j$ is the estimated probability of surviving interval $[t_{(j)}, t_{(j+1)})$ conditional on survival up to $t_{(j)}$. 
Derivation of Greenwood

• Take logs

$$\log \hat{S}(t) = \sum_{j=1}^{i} \log \hat{p}_j$$

such that

$$V\{\log \hat{S}(t)\} = \sum_{j=1}^{i} V\{\log \hat{p}_j\}$$

• Binomial argument

$$\hat{V}(\hat{p}_j) = \hat{p}_j(1 - \hat{p}_j)/n_j$$
Derivation of Greenwood

- Taylor series approximation

\[ \hat{V}\{g(X)\} \approx \{g'(\mu)\}^2 \hat{V}(X) \]

implies

\[ \hat{V}(\log \hat{p}_j) \approx \frac{1 - \hat{p}_j}{n_j\hat{p}_j} = \frac{m_j}{n_j(n_j - m_j)} \]

- Thus

\[ \hat{V}\{\log \hat{S}(t)\} \approx \sum_{j=1}^{i} \frac{m_j}{n_j(n_j - m_j)} \]
Greenwood SE/Ci

- Additional application of Taylor series approximation

\[ \hat{V}\{\log \hat{S}(t)\} \approx \{\hat{S}(t)\}^{-2} \hat{V}\{\hat{S}(t)\} \]

implying

\[ \hat{V}\{\hat{S}(t)\} \approx \{\hat{S}(t)\}^2 \sum_{j=1}^{i} \frac{m_j}{n_j(n_j - m_j)} \]

- Thus

\[ \hat{SE}(\hat{S}(t)) \approx \hat{S}(t) \sqrt{\sum_{j=1}^{i} \frac{m_j}{n_j(n_j - m_j)}} \]

for \( t_{(i)} \leq t < t_{(i+1)} \)
Greenwood SE/CI

• For Leukemia example,

\[ \hat{SE}(\hat{S}(6)) = .8571 \sqrt{\frac{3}{21 \times 18}} = 0.0764 \]

\[ \hat{SE}(\hat{S}(7)) = .8067 \sqrt{\frac{3}{21 \times 18} + \frac{1}{17 \times 16}} = 0.0869 \]

• Approx \((1 - \alpha) \times 100\%\) CI

\[ \hat{S}(t) \pm z_{1-\alpha/2} \hat{SE}(\hat{S}(t)) \]
Greenwood CIs

- Greenwood based CIs are symmetric
- Problematic when survivor function near 0 or 1; can have CI lie outside (0,1)
- Pragmatic solution: set equal to 0 or 1 in this case
- Many other methods exist to estimate standard error and obtain confidence intervals
- All have pointwise interpretation; different methods exist to obtain *confidence bands*
Testing

• How do we test if two survival functions are different under minimal assumptions?

• For example: leukemia patients are randomized to treatment or placebo. Are the survival functions the same between the two groups?

• Without censoring, use a rank test (e.g., Wilcoxon rank sum)

• In the presence of right censoring, use logrank test
Logrank test

- Data from two samples

\((T_{ij}, \delta_{ij})\)

for \(i = 1, 2\) and \(j = 1, 2, \ldots, n_i\)

- Want to test

\(H_0 : S_1(t) = S_2(t)\)

where

\(S_j(t) = \Pr[T_j^* > t] \text{ for } j = 1, 2\)
Logrank test

- Let \( t(1), t(2), \ldots, t(k) \) be the distinct ordered failure times in the two groups combined.

- At each time \( t(j) \), construct the table:

<table>
<thead>
<tr>
<th>Group</th>
<th>Event</th>
<th>Survive</th>
<th>At risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( m_{1j} )</td>
<td>( R_1(t(j)) - m_{1j} )</td>
<td>( R_1(t(j)) )</td>
</tr>
<tr>
<td>2</td>
<td>( m_{2j} )</td>
<td>( R_2(t(j)) - m_{2j} )</td>
<td>( R_2(t(j)) )</td>
</tr>
<tr>
<td></td>
<td>( m_j )</td>
<td>( R(t(j)) - m_j )</td>
<td>( R(t(j)) )</td>
</tr>
</tbody>
</table>
Logrank Test

- Under $H_0$, the expected number of deaths in group 1 is
  \[ E_{1j} = R_1(t_{(j)}) \frac{m_j}{R(t_{(j)})} \]

- The hypergeometric variance is
  \[ V_{1j} = \frac{R_1(t_{(j)})R_2(t_{(j)})m_j\{R(t_{(j)}) - m_j\}}{R(t_{(j)})^2\{R(t_{(j)}) - 1\}} \]
Logrank Test

• The logrank (Mantel-Haenszel) statistic:

\[
E_1 = \sum_{j=1}^{k} E_{1j}, \quad O_1 = \sum_{j=1}^{k} m_{1j}, \quad V_1 = \sum_{j=1}^{k} V_{1j}
\]

• Under \( H_0 \): \( S_1(t) = S_2(t) \) for all \( t \),

\[
X = \frac{(O_1 - E_1)^2}{V_1} \sim \chi_1^2
\]
### Logrank Test

- **Leukemia Example**

<table>
<thead>
<tr>
<th>Treatment ($n = 21$)</th>
<th>Placebo ($n = 21$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6, 6, 6, 6+</td>
<td>6, 6, 6, 6</td>
</tr>
<tr>
<td>7, 9+, 10, 10+</td>
<td>6, 6, 7, 7</td>
</tr>
<tr>
<td>11+, 13, 16, 17+</td>
<td>7, 10, 10, 12+, 13</td>
</tr>
<tr>
<td>19+, 20+, 22, 23</td>
<td>13, 15+, 16, 17+</td>
</tr>
<tr>
<td>25+, 32+, 32+ 34+, 35+</td>
<td>22, 23, 23, 23+</td>
</tr>
</tbody>
</table>
Logrank Test: Leukemia Example
Code for Plotting Kaplan-Meier Curves

- **R**

```r
library("survival")
fit <- survfit(Surv(t, delta)~rx, conf.type="none")
pdf("surv_leuk1.pdf", width=11, height=8.5)
plot(fit, xlab="t", ylab="S(t)", lwd=c(1,3))
legend(25,1, c("Treatment", "Placebo"), lwd=c(3,1))
dev.off()
```

- **SAS**

```sas
proc lifetest plot=(s) graphics;
```
Logrank test “by hand”: Leukemia Example

<table>
<thead>
<tr>
<th>$t_{(j)}$</th>
<th>$m_{1j}$</th>
<th>$R_1(t_{(j)})$</th>
<th>$m_{2j}$</th>
<th>$R_2(t_{(j)})$</th>
<th>$m_j$</th>
<th>$R(t_{(j)})$</th>
<th>$E_{1j}$</th>
<th>$V_{1j}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>3</td>
<td>21</td>
<td>6</td>
<td>21</td>
<td>9</td>
<td>42</td>
<td>4.50</td>
<td>1.81</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>17</td>
<td>3</td>
<td>15</td>
<td>4</td>
<td>32</td>
<td>2.13</td>
<td>0.90</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>15</td>
<td>2</td>
<td>12</td>
<td>3</td>
<td>27</td>
<td>1.67</td>
<td>0.68</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>12</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>21</td>
<td>1.71</td>
<td>0.66</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>11</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>17</td>
<td>1.29</td>
<td>0.43</td>
</tr>
<tr>
<td>22</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>11</td>
<td>1.27</td>
<td>0.42</td>
</tr>
<tr>
<td>23</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>2.00</td>
<td>0.50</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.57</td>
<td>5.4</td>
</tr>
</tbody>
</table>
Logrank test: Leukemia Example

• Therefore

\[ X = \frac{(9 - 14.57)^2}{5.4} = 5.75 \]

\[ \Pr[\chi^2_1 > 5.75] = 0.0165 \]

• R code:

Call:
survdiff(formula = Surv(t, delta) ~ rx)

    N  Observed Expected (O-E)^2/E (O-E)^2/V
rx=p 21     17      11.4       2.72   5.75
rx=t 21      9      14.6       2.13   5.75

Chisq= 5.8 on 1 degrees of freedom, p= 0.0165
Logrank test: Leukemia Example

- SAS code

```sas
proc lifetest;
  time t*delta(0);
  strata trt;
```

Test of Equality over Strata

<table>
<thead>
<tr>
<th>Test</th>
<th>Chi-Square</th>
<th>DF</th>
<th>Pr &gt; Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-Rank</td>
<td>5.7507</td>
<td>1</td>
<td>0.0165</td>
</tr>
<tr>
<td>Wilcoxon</td>
<td>4.3357</td>
<td>1</td>
<td>0.0373</td>
</tr>
<tr>
<td>-2Log(LR)</td>
<td>6.0441</td>
<td>1</td>
<td>0.0140</td>
</tr>
</tbody>
</table>
Logrank test: SAS

data;
  input time group death wt;
cards;
  6 1 1 3
  6 1 0 18
  6 2 1 6
  6 2 0 15
  7 1 1 1
  7 1 0 16
  7 2 1 3
  7 2 0 12
  .
  .
  .

proc freq order=data;
  tables time*group*death/chisq cmh;
  weight wt;
Logrank test: SAS

The FREQ Procedure

Summary Statistics for group by death
Controlling for time

Cochran-Mantel-Haenszel Statistics (Based on Table Scores)

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Alternative Hypothesis</th>
<th>DF</th>
<th>Value</th>
<th>Prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nonzero Correlation</td>
<td>1</td>
<td>5.7507</td>
<td>0.0165</td>
</tr>
<tr>
<td>2</td>
<td>Row Mean Scores Differ</td>
<td>1</td>
<td>5.7507</td>
<td>0.0165</td>
</tr>
<tr>
<td>3</td>
<td>General Association</td>
<td>1</td>
<td>5.7507</td>
<td>0.0165</td>
</tr>
</tbody>
</table>