Nonparametric and Semi-parametric Methods

• Estimate a survivor function without covariates:
  - Kaplan-Meier (product-limit) Estimator
  - Nelson-Aalen Estimator
  - Life table estimator

• Estimate a survivor function with covariates: Cox proportional hazards model

Kaplan-Meier Estimator

- Also called the product-limit estimator
- Most commonly used estimator
- Suppose \( t_1 < t_2 < \ldots < t_r \) are the ordered failure times.
  - Let \( n_j \) denote the number of individuals alive (at risk) just before time \( t_j \), including those who will die at time \( t_j \)
  - If an observation is censored at the same time \( t_j \) that one or more failures occur, then censoring is assumed to occur after any failures and \( n_j \) includes the censored observations
  - Let \( d_j \) denote the number of failures (deaths) at time \( t_j \)

- The conditional probability that an individual dies in the time interval from \( t_j - \Delta \) to \( t_j \), given survival up to time \( t_j - \Delta \), is estimated as \( \frac{d_j}{n_j} \)
- The conditional probability that an individual survives beyond \( t_j - \Delta \), given survival up to time \( t_j - \Delta \), is estimated as \( \frac{n_j - d_j}{n_j} \)
- In the limit as \( \Delta \to 0 \), \( \frac{n_j - d_j}{n_j} \) becomes an estimate of the conditional probability of surviving beyond \( t_j \) given survival up to \( t_j \).

- For \( t_{(k)} \leq t < t_{(k+1)} \), the probability of surviving beyond time \( t \) is
  \[
  S(t) = P\{T > t\} = P\{T > t \text{ and } T > t_{(k)}\} \\
  = P\{T > t|T > t_{(k)}\}P\{T > t_{(k)}\} \\
  = P\{T > t|T > t_{(k)}\}P\{T > t_{(k-1)}\} \\
  = P\{T > t|T > t_{(k)}\} \times \frac{P\{T > t_{(k)}\}}{P\{T > t_{(k-1)}\}} \\
  = P\{T > t|T > t_{(k)}\} \times \frac{P\{T > t_{(k-1)}\}}{P\{T > t_{(k-2)}\}} \\
  \ldots \times \frac{P\{T > t_{(1)}\}}{P\{T > t_{(0)}\}} \\
  \approx \prod_{j=1}^{k} \frac{P\{T > t_j\}}{P\{T > t_{(j-1)}\}}
  \]
  where \( t_{(0)} = 0 \) and \( t_{(r+1)} = \infty \)
The Kaplan-Meier estimator of the survivor function at time \( t \), for \( t_1 \leq t < t_{k+1} \), is

\[
\hat{S}(t) = \prod_{j=1}^{k} \frac{n_j - d_j}{n_j}
\]

**Example:**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Time</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>1</td>
</tr>
</tbody>
</table>

**Order with respect to failure times**

<table>
<thead>
<tr>
<th>( j )</th>
<th>( t(j) )</th>
<th>( n_j )</th>
<th>( d_j )</th>
<th>( (n_j - d_j)/n_j )</th>
<th>( \hat{S}(t) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 6 0</td>
<td>1.0000</td>
<td>1.0000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 6 1</td>
<td>0.8333</td>
<td>0.8333</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 5 1</td>
<td>0.8000</td>
<td>0.6667</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12 3 2</td>
<td>0.3333</td>
<td>0.2222</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>21 1 1</td>
<td>0.0000</td>
<td>0.0000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Variance of the Kaplan-Meier estimator (Greenwood’s formula)**

For \( t_1 \leq t < t_{k+1} \),

\[
Var(\hat{S}(t)) = (\hat{S}(t))^2 \sum_{j=1}^{k} \frac{d_j}{n_j(n_j - d_j)}
\]

**Derivation:**

- **Start with**

\[
\log(\hat{S}(t)) = \log\left( \prod_{j=1}^{k} \frac{n_j - d_j}{n_j} \right)
\]

\[
= \sum_{j=1}^{k} \log((n_j - d_j)/n_j)
\]

\[
= \sum_{j=1}^{k} \log(p_j)
\]

- **Then**

\[
Var(\log(\hat{S}(t))) = Var\left( \sum_{j=1}^{k} \log(p_j) \right)
\]

\[
= \sum_{j=1}^{k} Var(\log(p_j))
\]

- **Apply the delta method**

\[
Var(\log(p_j)) \approx \left( \frac{1}{\pi_j} \right)^2 \frac{\pi_j(1 - \pi_j)}{n_j}
\]

\[
= \left( \frac{1}{\pi_j} \right)^2 \frac{1 - \pi_j}{n_j}
\]

- **Then**

\[
Var(\log(\hat{S}(t)) \approx \sum_{j=1}^{k} \left( \frac{1}{\pi_j} \right)^2 \frac{1 - \pi_j}{n_j}
\]
Apply the delta method a second time to get

\[ \text{Var}(\hat{S}(t)) \approx [S(t)]^2 \text{Var}(\log(\hat{S}(t))) \]

\[ = [S(t)]^2 \sum_{j=1}^{k} \frac{1}{\pi_j} \frac{1 - \pi_j}{n_j} \]

The Greenwood formula, obtained by substituting \( p_j = (n_j - d_j)/n_j \) for \( \pi_j \), is

\[ \text{Var}(\hat{S}(t)) = (\hat{S}(t))^2 \sum_{j=1}^{k} \frac{d_j}{n_j(n_j - d_j)} \]

A large sample standard error for \( \hat{S}(t) \) is

\[ \text{se}(\hat{S}(t)) = \hat{S}(t) \frac{\sum_{j=1}^{k} d_j}{\sum_{j=1}^{k} n_j(n_j - d_j)} \]

Confidence intervals

- Large sample normal distribution for \( \hat{S}(t) \)

\[ \hat{S}(t) \pm \frac{Z_{\alpha/2}}{\sqrt{\sum_{j=1}^{k} \frac{d_j}{n_j(n_j - d_j)}}} \]

potential problems:
- endpoints outside 0 or 1
- normality if sample size is not large

- CI based on the large sample normal distribution of \( \log(\frac{-\log(\hat{S}(t))}{\hat{S}(t)}) \) with

\[ \text{Var}(\log(\frac{-\log(\hat{S}(t))}{\hat{S}(t)})) = \left(\frac{1}{\log(\hat{S}(t))}\right)^2 \sum_{j=1}^{k} \frac{d_j}{n_j(n_j - d_j)} \]

for \( t(k) \leq t \leq t(k+1) \)

Kaplan-Meier Estimator in SAS

/* SAS code for Kaplan-Meier estimation of survivor functions to times from the VA lung cancer trial of 137 male patients with inoperable lung cancer. This code is posted as vakm.sas */

/* Variables */
- Treatment: 1=standard, 2=test (chemotherapy)
- Celltype: 1=squamous, 2=smallcell, 3=adenocarcinoma, 4=large
- Survival in days
- Status: 1=dead, 0=censored
- Karnofsky score
- Months from Diagnosis
- Age in years
- Prior therapy: 0=no, 10=yes

*/
data va;
  infile 'c:\stat565\va.dat';
  input rx cellt time status karno months
    age prior_rx;
  prior_rx = prior_rx/10;
  if (cellt=1) then celltype= 'squamous';
  if (cellt=2) then celltype= 'smallcell';
  if (cellt=3) then celltype= 'adenocarcinoma';
  if (cellt=4) then celltype= 'large';
proc lifetest method=KM plots=(s) graphics
  outa=su data=va;
  time time*status(0);
  strata rx;
  symbol1 v=none color=black line=1;
  symbol2 v=none color=black line=2;
run;
proc print data=su; run;

/* Delete censored cases */
data su2;
set su;
  if _CENSOR_=0;
run;
goptions rotate=landscape;
axis1 label=(f=swiss h=1.2 a=90 r=0 "Survival Probability")
  order = 0 to 1 by 0.1
  length = 4.3in w=3
  value=(f=swiss h=1.0);
axis2 label=(f=swiss h=1.2 "Time(days)")
  order = 0 to 1000 by 100
  length = 6. in;
proc gplot data=su2; by rx;
  plot (SURVIVAL SDF_LCL SDF_UCL)*time/
  overlay vaxis=axis1 haxis=axis2;
  symbol1 v=none interpol=join color=black
  line=1 w=4;
  symbol2 v=none interpol=join color=black
  line=3 w=4;
  symbol3 v=none interpol=join color=black
  line=3 w=4;
  title l=0.4 H=2.0 F=swiss
    "Estimated Survivor Function";
run;

The LIFETEST Procedure
Stratum 1: rx = 1
Product-Limit Survival Estimates

<table>
<thead>
<tr>
<th>time</th>
<th>Survival</th>
<th>Failure</th>
<th>Standard Error</th>
<th>Number</th>
<th>Number Failed</th>
<th>Number Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000</td>
<td>1.0000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>3.000</td>
<td>0.9855</td>
<td>0.0145</td>
<td>0.0144</td>
<td>1</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>4.000</td>
<td>0.9710</td>
<td>0.0290</td>
<td>0.0202</td>
<td>2</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>7.000</td>
<td>0.9565</td>
<td>0.0435</td>
<td>0.0246</td>
<td>3</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>8.000</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>4</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>8.000</td>
<td>0.9275</td>
<td>0.0725</td>
<td>0.0312</td>
<td>5</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>10.000</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>6</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>10.000</td>
<td>0.8986</td>
<td>0.1014</td>
<td>0.0363</td>
<td>7</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>11.000</td>
<td>0.8841</td>
<td>0.1159</td>
<td>0.0385</td>
<td>8</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>12.000</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>9</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>12.000</td>
<td>0.8551</td>
<td>0.1449</td>
<td>0.0424</td>
<td>10</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>13.000</td>
<td>0.8406</td>
<td>0.1594</td>
<td>0.0441</td>
<td>11</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>16.000</td>
<td>0.8261</td>
<td>0.1739</td>
<td>0.0456</td>
<td>12</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>18.000</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>13</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>18.000</td>
<td>0.7971</td>
<td>0.2029</td>
<td>0.0484</td>
<td>14</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>20.000</td>
<td>0.7826</td>
<td>0.2174</td>
<td>0.0497</td>
<td>15</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>21.000</td>
<td>0.7681</td>
<td>0.2319</td>
<td>0.0508</td>
<td>16</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>22.000</td>
<td>0.7536</td>
<td>0.2464</td>
<td>0.0519</td>
<td>17</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>25.000</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>18</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>27.000</td>
<td>0.7388</td>
<td>0.2612</td>
<td>0.0529</td>
<td>18</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>30.000</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>411.000</td>
<td>0.0177</td>
<td>0.9823</td>
<td>0.0175</td>
<td>63</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>553.000</td>
<td>0</td>
<td>1.0000</td>
<td>0</td>
<td>64</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: The marked survival times are censored observations.
The LIFETEST Procedure

Summary Statistics for Time Variable time

Quartile Estimates

<table>
<thead>
<tr>
<th>Percent</th>
<th>Point</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>162.000</td>
<td>132.000 - 250.000</td>
</tr>
<tr>
<td>50</td>
<td>103.000</td>
<td>54.000 - 126.000</td>
</tr>
<tr>
<td>25</td>
<td>27.000</td>
<td>16.000 - 54.000</td>
</tr>
</tbody>
</table>

Mean Standard Error

123.928 14.961

The LIFETEST Procedure

Stratum 2: rx = 2

Product-Limit Survival Estimates

<table>
<thead>
<tr>
<th>time</th>
<th>Survival</th>
<th>Failure</th>
<th>Error</th>
<th>Failed</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000</td>
<td>1.0000</td>
<td>0</td>
<td>0</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>1.000</td>
<td>0.9706</td>
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<td>0.0205</td>
<td>2</td>
<td>66</td>
</tr>
<tr>
<td>2.000</td>
<td>0.9559</td>
<td>0.0441</td>
<td>0.0249</td>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>7.000</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>7.000</td>
<td>0.9285</td>
<td>0.0715</td>
<td>0.0317</td>
<td>5</td>
<td>63</td>
</tr>
<tr>
<td>8.000</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>62</td>
</tr>
<tr>
<td>8.000</td>
<td>0.8971</td>
<td>0.1029</td>
<td>0.0369</td>
<td>7</td>
<td>61</td>
</tr>
<tr>
<td>13.000</td>
<td>0.8824</td>
<td>0.1176</td>
<td>0.0391</td>
<td>8</td>
<td>60</td>
</tr>
<tr>
<td>15.000</td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>59</td>
</tr>
<tr>
<td>15.000</td>
<td>0.8529</td>
<td>0.1471</td>
<td>0.0429</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td>18.000</td>
<td>0.8382</td>
<td>0.1618</td>
<td>0.0447</td>
<td>11</td>
<td>57</td>
</tr>
</tbody>
</table>

NOTE: The marked survival times are censored observations.

Summary Statistics for Time Variable time

Quartile Estimates

<table>
<thead>
<tr>
<th>Percent</th>
<th>Point</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>140.000</td>
<td>95.000 - 283.000</td>
</tr>
<tr>
<td>50</td>
<td>52.500</td>
<td>44.000 - 90.000</td>
</tr>
<tr>
<td>25</td>
<td>24.500</td>
<td>19.000 - 36.000</td>
</tr>
</tbody>
</table>

Mean Standard Error

142.061 27.023

Summary of the Number of Censored and Uncensored Values

<table>
<thead>
<tr>
<th>Stratum</th>
<th>rx</th>
<th>Total</th>
<th>Failed</th>
<th>Censored</th>
<th>Censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>69</td>
<td>64</td>
<td>5</td>
<td>7.25</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>68</td>
<td>64</td>
<td>4</td>
<td>5.88</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>137</td>
<td>128</td>
<td>9</td>
<td>6.57</td>
</tr>
</tbody>
</table>
Testing Homogeneity of Survival Curves over Strata

Rank Statistics

rx | Log-Rank | Wilcoxon |
---|---------|---------|
1 | -0.50020 | -447.00 |
2 | 0.50020 | 447.00 |

Test of Equality over Strata

<table>
<thead>
<tr>
<th>Test</th>
<th>Chi-Square</th>
<th>DF</th>
<th>Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-Rank</td>
<td>0.0082</td>
<td>1</td>
<td>0.9277</td>
</tr>
<tr>
<td>Wilcoxon</td>
<td>0.9608</td>
<td>1</td>
<td>0.3270</td>
</tr>
<tr>
<td>-2Log(LR)</td>
<td>0.2758</td>
<td>1</td>
<td>0.5995</td>
</tr>
</tbody>
</table>

Estimated Survivor Function

rx = 1

Estimated Survivor Function

rx = 2
Kaplan-Meier Estimation in R or S-Plus

# R code to estimate the survivor
# function for the VA lung cancer trial
# of 137 male patients with inoperable
# lung cancer. This code is posted as
# vakm.ssc

# Variables
# Treatment: 1=standard, 2=test (chemotherapy)
# Celltype: 1=squamous, 2=smallcell,
# 3=adenocarcinoma, 4=large
# Survival in days
# Status: 1=dead, 0=censored
# Karnofsky score
# Months from Diagnosis
# Age in years
# Prior therapy: 0=no, 10=yes

# Enter the data into a data frame.

va <- read.table("c:/va.dat",
 header=F, col.names=c("rx", "cellt", "time",
 "status", "karno", "months", "age",
 "prior_rx"))

va$prior_rx <- va$prior_rx/10;
va

rx cellt time status karno months age prior_rx
11 1 7 2 1 6 0 76 9 0
2 1 1 411 1 70 5 64 10
3 1 1 228 1 60 3 38 0
4 1 1 126 1 60 9 63 10
5 1 1 118 1 70 11 65 10
.
.
.
134 2 4 111 1 60 5 64 0
135 2 4 231 1 70 18 67 10
136 2 4 378 1 80 4 65 0
137 2 4 49 1 30 3 37 0

vafit <- survfit(Surv(time, status) ~ rx,
 data = va,
 conf.int=.95, conf.type="log-log",
 type="kaplan-meier", se.fit=T)

# Specify the type of survival curve estimator.
# Possible values are
# "kaplan-meier", "fleming-harrington" or "fh2"
# if a formula is given and
# "aalen" or "kaplan-meier"
# if the first argument is a coxph object (only the
# first two characters are necessary). The default
# is "aalen" when a coxph object is given, and
# it is "kaplan-meier" otherwise.

# conf.type: specifies the confidence interval
# type. Possible values are:
# "none" for no confidence intervals
# "plain" for standard intervals,
# "curve <- k*se(curve)", where k
# is determined from conf.int,
# "log" for intervals based on the cumulative
# hazard or log(survival) (the default)

# Print out estimates of median survival times
vafit

Call: survfit(formula = Surv(time, status) ~ rx, 
 data = va, conf.int = 0.95, 
 conf.type = "log-log", 
 type = "kaplan-meier", se.fit = T)

m events mean se(mean) median 0.95LCL 0.95UCL
rx=1 69 64 124 14.8 103 54 126
rx=2 68 64 142 26.8 52 43 90

# Print out estimates of survivor curve and
# confidence limits
summary(vafit)
Life-Table Estimator

- Grouped data (interval censoring)
  analog of the Kaplan-Meier estimator

- Survival data generally presented in calendar time units (monthly, semiannually, etc.)

- Suppose we use 6 month intervals, \([t, t+6)\): \(n\) = number of subjects at risk of dying at time \(t\); \(d\) subjects die in the interval; \(c\) subjects are censored during the interval

- Conditional probability of surviving during the interval is

\[
\hat{S} = \frac{(n - (c/2) - d)}{(n - (c/2))}
\]

- Example:

<table>
<thead>
<tr>
<th>Interval</th>
<th>Enter</th>
<th>Die</th>
<th>Censored</th>
<th>(\hat{S})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0, 6)</td>
<td>100</td>
<td>41</td>
<td>10</td>
<td>.5684</td>
</tr>
<tr>
<td>(6, 12)</td>
<td>49</td>
<td>21</td>
<td>3</td>
<td>.3171</td>
</tr>
<tr>
<td>(12, 18)</td>
<td>25</td>
<td>6</td>
<td>2</td>
<td>.2378</td>
</tr>
<tr>
<td>(18, 24)</td>
<td>17</td>
<td>1</td>
<td>1</td>
<td>.2234</td>
</tr>
</tbody>
</table>
Nelson-Aalen Estimator

- Recall, \( S(t) = \exp(-H(t)) \)
- Obtain an estimator for \( S(t) \) from an estimator for \( H(t) \), \( \tilde{H}(t) = \sum_{i(t) \leq t} d_i / n_i \)
- When risk sets are large relative to the number of events, KM and NA are essentially the same
- Larger differences when ties are present in the data (ties have no effect on K-M estimator)
- Biased upward when estimates are close to zero
- Smaller MSE than K-M for \( S(t) \geq .20 \) and larger otherwise

• Easier to extend to more complicated situations than K-M
• Standard error in presence of ties (revisit later in context of the Cox model)

# Fit the Fleming-Harrington estimator
# for the survivor function
fit <- survfit(Surv(time, status) ~ rx, data = va, conf.int=.95, conf.type="log-log", se.fit=T, type="fleming-harrington")
plot(fit, lty = 2:3,
     main="Fleming-Harrington Estimator",
     xlab="Time(days)",
     ylab="Survival Function")
legend(400, .8, c("Standard", "Chemotherapy"), lty = 2:3)
summary(fit)

Comparing Survivor Functions

- Form contingency tables of group by status at each observed survival time

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Die</th>
<th>Not Die</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>( d_{1i} )</td>
<td>( n_{1i} - d_{1i} )</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>( d_{2i} )</td>
<td>( n_{2i} - d_{2i} )</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>( d_i )</td>
<td>( n_i - d_i )</td>
</tr>
</tbody>
</table>

- compute expected number of deaths in Group 1, \( \hat{e}_{1i} = n_{1i}d_i / n_i \)
- compute variance
  \[ \hat{V}_{1i} = n_{1i}n_{2i}d_i(n_i - d_i)/(n_i^2(n_i - 1)) \]
  (based on hypergeometric distribution)
- Logrank test:
  \[ LR = \left( \sum_{i=1}^{r} (d_{1i} - \hat{e}_{1i}) \right)^2 / \sum \hat{V}_{1i} \sim \chi^2_1 \]
  under \( H_0 \) (no difference between groups)
Generalization of log-rank test

- Weighted test statistic:
  \[ GL = \left( \sum_{i=1}^{n} w_i (d_{1i} - \hat{e}_{1i}) \right)^2 / \sum w_i^2 \hat{V}_{1i} \sim \chi_1^2 \]
  under \( H_0 \) (no difference between groups)

- \( w_i = 1 \), log rank (Mantel-Haenszel) test (Peto and Peto): good power against proportional hazards alternatives

- \( w_i = n_i \), (Generalized) Wilcoxon test (Gehan, Breslow): depends on number at risk; good power against early differences in the survival curves (where there are more data)

- \( w_i = \sqrt{n_i} \), (Taron and Ware): good power against early differences

• You can easily extend these tests to more than two groups

Log-Rank and Wilcoxon Tests in SAS

The LIFETEST Procedure

Summary of the Number of Censored and Uncensored Values

<table>
<thead>
<tr>
<th>Stratum</th>
<th>rx</th>
<th>Total Failed</th>
<th>Censored</th>
<th>Censored Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>69</td>
<td>5</td>
<td>7.25</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>68</td>
<td>4</td>
<td>5.86</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>137</td>
<td>9</td>
<td>6.57</td>
</tr>
</tbody>
</table>
Testing Homogeneity of Survival Curves over Strata

**LOG RANK AND WILCOXON STATISTICS FOR EACH GROUP**

<table>
<thead>
<tr>
<th>Numerator of Test Statistic</th>
<th>Rank Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Log-Rank</td>
</tr>
<tr>
<td>1</td>
<td>-0.50020</td>
</tr>
<tr>
<td>2</td>
<td>0.50020</td>
</tr>
</tbody>
</table>

For two strata the values are perfectly correlated, they sum to zero.

**Covariance Matrix for the Log-Rank Statistics**

<table>
<thead>
<tr>
<th>rx</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30.4104</td>
<td>-30.4104</td>
</tr>
<tr>
<td>2</td>
<td>-30.4104</td>
<td>30.4104</td>
</tr>
</tbody>
</table>

**Covariance Matrix for the Wilcoxon Statistics**

<table>
<thead>
<tr>
<th>rx</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>207972</td>
<td>-207972</td>
</tr>
<tr>
<td>2</td>
<td>-207972</td>
<td>207972</td>
</tr>
</tbody>
</table>

**Test of Equality over Strata**

<table>
<thead>
<tr>
<th>Test</th>
<th>Chi-Square</th>
<th>DF</th>
<th>Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-Rank</td>
<td>0.0082</td>
<td>1</td>
<td>0.9277</td>
</tr>
<tr>
<td>Wilcoxon</td>
<td>0.9608</td>
<td>1</td>
<td>0.3270</td>
</tr>
<tr>
<td>-2Log(LR)</td>
<td>0.2758</td>
<td>1</td>
<td>0.5995</td>
</tr>
</tbody>
</table>

Note: The likelihood ratio test assumes an exponential distribution.

**Log-Rank Tests in R and SPlus**

```r
library(survival)
survdiff(Surv(time, status) ~ rx, data=va, rho=0)
```

This function implements the G-rho family of Harrington and Fleming (1982), with weights on each death of \((S(t))^\rho\), where \(S\) is the Kaplan-Meier estimate of the survivor function.

When \(\rho = 0\) this is the log-rank or Mantel-Haenszel test, and when \(\rho = 1\) it is equivalent to the Peto & Peto modification of the Gehan-Wilcoxon test.
> survdiff(Surv(time, status) ~ rx, 
  data=va, rho=1)

Call:
  survdiff(formula = Surv(time, status) ~ rx, 
            data = va, rho = 1)

N Observed Expected (O-E)^2/E (O-E)^2/V
rx=1 69 32.2 35.4 0.279 0.871
rx=2 68 35.2 32.1 0.308 0.871

Chisq= 0.9 on 1 degrees of freedom, p= 0.351

Kaplan-Meier: For \( t(j) < t < t(j+1) \)

\[
\hat{h}(t) = \frac{d_j}{n_j(t_{j+1}) - t_{(j)}}
\]

Kernel smoothed estimate

\[
\hat{h}^*(t) = b^{-1} \sum_{j=1}^{r} 0.75 \left[ 1 - \frac{(t - t_{(j)})}{b} \right]^2 \frac{d_j}{n_j}
\]

where \( b \) is called the bandwidth.

%macro smooth(data=_last_, time=, width=, survival=survival);
/**********************************************
MACRO SMOOTH produces graphs of smoothed hazard
functions using output from either PROC LIFETEST
or PROC PHREG. With PROC LIFETEST, it uses the
data set produced by the OUTSURV option in the
PROC statement. With PROC PHREG, it uses the data
set produced by the BASELINE statement. SMOOTH
employs a kernel smoothing method described by
Process Intensities by Means of Kernel Functions,"
The Annals of Statistics 11, 453-466. If there
is more than one survival curve in the input
data set, SMOOTH will produce multiple smoothed
hazard curves on the same axes.
There are four parameters:
DATA is the name of the data set containing
survivor function estimates. The default is the most recently created data set.
TIME is name of the variable containing event
times.
SURVIVAL is the name of a variable containing
survivor function estimates (the default is SURVIVAL, which is the automatic name
in PROC LIFETEST).
WIDTH is bandwidth of smoothing function. The
default is 1/5 of the range of event times.
**********************************************

Example of usage:
%smooth(data=my.data,time=duration,width=8,survival=s)

Author: Paul D. Allison, University of Pennsylvania
allison@ssc.upenn.edu
*******************************************************************************/

%macro smooth(data=_last_, time=, width=, survival=survival);
%if %ne %then %let w2=%width;
%else %let w2=(max(time)-min(time))/5;
\newpage

width=8;
\setin setin=

proc iml;
use _inset_;
read all var {t _grp_}
\nif \&width ne %then \let w2=\width;
\else \let w2=(max(t)-min(t))/5;
w=w2;
\r=char(w,8,2);
call sympyt(‘width’,z);
nunset=max(_grp_);
create _plt_ var{ lambda s group};
setin _inset_;
do m=1 to numset;
read all var {t survival _grp_} where (_grp_=m);
num=numrow(survival);
lo=t[1] + w;
hi=t[num] - w;
inc=(hi-lo)/npt;
s=lo+(1:npt)'*inc;
group=j(npt,1,m);
slag=1/survival[1:n-1];
b=1-survival/slag;
x = (j(npt,1,1)*t' - s*j(1,n,1))/w;
k=1.75*(1-x##2)##(abs(x)<=1);
lambda=k*h/w;
append;
end;
quit;
%if &nset = yes %then %let c==group;
%else %let c=;
proc gplot data=_plt_
plot lambda*s &c / vaxis=axis1
vzero haxis=axis2;
axis1 label=(angle=90 f=swiss h=2.5
'Hazard Function' ) minor=none ;
axis2 label=(f=swiss h=2.5
'Time (bandwidth=&width)') minor=none;
symbol1 i=join color=black line=1;
symbol2 i=join color=red line=2;
symbol3 i=join color=green line=3;
symbol4 i=join color=blue line=4;
run;
quit;
%mend smooth;

Hazard Estimation with R

# R code to estimate the survivor function for the VA lung cancer trial of 137 male patients with inoperable lung cancer. This code is posted as vakm.smooth.R

# Variables
# Treatment: 1=standard, 2=test (chemotherapy)
# Celltype: 1=squamous, 2=smallcell, 3=adenocarcinoma, 4=large
# Survival in days
# Status: 1=dead, 0=censored
# Karnofsky score
# Months from Diagnosis
# Age in years
# Prior therapy: 0=no, 1=yes

va <- read.table("c:/stat565/va.dat", header=F, col.names=c("rx", "cellt", "time", "status", "karno", "months", "age", "prior_rx"))

# Fit the Kaplan-Meier estimator
# for the survivor function
fit <- survfit(Surv(time, status) ~ rx,
data = va, conf.int=.95,
conf.type="log-log", se.fit=T,
type="kaplan-meier")
plot(fit, lty = 2:3,
main="Kaplan-Meier Estimator",
lab="Time(days)",
ylab="Survival Function")
legend(400, .8, c("Standard", "Chemotherapy"),
lty = 2:3)
# Check for fit of the Weibull model

fit$logs <- -1.*log(fit$surv)
m1 <- fit$strata[1]
m2 <- fit$strata[2]

plot(log(fit$time[1:m1]), log(logs[1:m1]),
     main="VA Cancer Study",
     ylab="Log(-Log(surv))",
     xlab="Log(time)", pch=1, cex=1.5,
     xlim=c(0,7), ylim=c(-4,2))

points(log(fit$time[(m1+1):(m1+m2)]),
      log(logs[(m1+1):(m1+m2)]),
      pch=16, cex=1.5)

legend(0.1, 2, c("Standard", "Chemotherapy"),
       marks=c(1, 16), cex=0.9)

# Smoothed estimates for hazard functions
# First delete the censored cases

e1 <- fit$n.event[1:m1]
n1 <- m1 - length(e1[e1<1])
e2 <- fit$n.event[(m1+1):(m1+m2)]
n2 <- m2 - length(e2[e2<1])

time <- fit$time[fit$n.event>0]
event <- fit$n.event[fit$n.event>0]
risk <- fit$n.risk[fit$n.event>0]

den <- event[1:(n1+n2-1)]/risk[1:(n1+n2-1)]/
      (time[2:(n1+n2)]-time[1:(n1+n2-1)])

plot(time[1:(n1+n2-1)], den, type="n",
     xlab="Time(days)", ylab="Hazard", cex=1.5,
     xlim=c(0,600), ylim=c(0,0.04),
     main="Smoothed Hazard Estimation 

Gaussian Kernel Smoothers 
")

lines(ksmooth(time[1:(n1-2)], den[1:(n1-2)],
            kernel="normal",
            bandwidth=150), lty=1, lwd=3)
lines(ksmooth(time[(n1+1):(n1+n2-2)],
              den[(n1+1):(n1+n2-2)],
              kernel="normal", bandwidth=300),
       lty=3, lwd=3)

legend(50, 0.035, c("Standard", "Chemotherapy"),
       lty=c(1, 3))
Comparison of Parametric and Non-parametric Estimation

- Parametric methods are biased if the parametric model is incorrect
- Non-parametric methods can be much less efficient than parametric methods

\[
\text{efficiency} = \frac{E[\hat{S}_{\text{Weibull}}(t) - S(t)]^2}{E[\hat{S}_{\text{KM}}(t) - S(t)]^2} = \frac{\text{Var}(\hat{S}_{\text{Weibull}}(t)) + \text{Bias}^2_{\text{Weibull}}}{\text{Var}(\hat{S}_{\text{KM}}(t)) + \text{Bias}^2_{\text{KM}}}
\]

Randomization Tests

- The accuracy of the p-value produced by the chi-square approximation to the distribution of the log-rank or Wilcoxon tests depends on
  - sample sizes
  - number of deaths
  * length of follow-up
  * level of censoring
• “Exact” p-values from permutation distributions

• Consider all possible random assignments of subjects to treatment groups (PERM_GEN and TEST macros)

• Consider a random sample from the possible random assignments of subjects to treatment groups (RAND_GEN and TEST macros)

• Alan B. Cantor, SAS Survival Techniques for Medical Research, 2nd edition

• STAT EXACT: add on to SAS

*/ SAS code to for premutation tests to compare two survival functions. Applied to data from the VA lung cancer trial of 137 male patient with inoperable lung cancer. This code is posted as va.perm.sas /*

/* Variables 
Treatment: 1=standard, 2=test (chemotherapy) 
Celltype: 1=squamous, 2=smallcell, 3=adeno, 4=large 
Survival in days 
Status: 1=dead, 0=censored 
Karnofsky score 
Months from Diagnosis 
Age in years 
Prior therapy: 0=no, 10=yes  */

data va;
  infile 'c:\st565\data\va.dat';
  input rx cellt time status karno months age prior_rx;
proc lifetest method=KM plots=(s) graphics 
  outs=su data=va;
  time time*status(0);
  strata rx;
  symbol1 v=none color=black line=1 w=3;
  symbol2 v=none color=black line=2 w=3;
run;

The LIFETEST Procedure
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>0.0082</td>
<td>1</td>
<td>0.9277</td>
</tr>
<tr>
<td>Wilcoxon</td>
<td>0.9608</td>
<td>1</td>
<td>0.3270</td>
</tr>
<tr>
<td>-2Log(LR)</td>
<td>0.2758</td>
<td>1</td>
<td>0.5996</td>
</tr>
</tbody>
</table>

%include "c:\st565\sas\randgen.macro.sas";
%include "c:\st565\sas\test.macro.sas";

%RAND_GEN(indata=va, time=time, cens=status, numreps=1000, group=rx, seed=0);
%TEST(time=time, cens=status, censval=0, test=logrank, group=rx, type=rand);
%TEST(time=time, cens=status, censval=0, test=gehan, group=rx, type=rand);
Randomization

logrank Test

<table>
<thead>
<tr>
<th>Estimated P-Value</th>
<th>Lower 95 Pct</th>
<th>Upper 95 Pct</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2-sided) stderr</td>
<td>Bound Bound</td>
<td>Bound Bound</td>
</tr>
<tr>
<td>0.925</td>
<td>0.008329166</td>
<td>0.90867</td>
</tr>
</tbody>
</table>

Number of Asymptotic Replicates: 1000

P-Value: 0.92798

Randomization
gehan Test

<table>
<thead>
<tr>
<th>Estimated P-Value</th>
<th>Lower 95 Pct</th>
<th>Upper 95 Pct</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2-sided) stderr</td>
<td>Bound Bound</td>
<td>Bound Bound</td>
</tr>
<tr>
<td>0.358</td>
<td>0.015160</td>
<td>0.32829</td>
</tr>
</tbody>
</table>

Number of Asymptotic Replicates: 1000

P-Value: 0.34869

Power Analysis

Power of the log-rank and Wilcoxon (Gehan) tests for comparing two groups depends on

- Type I error level ($\alpha$)
- Survival distributions of the two groups
  - Length of accrual period
  - Accrual rate
  - Length of follow-up times
  - Distributions of loss to follow-up

References

- No literature for more than two groups
Power Analysis

- Length of accrual period is $T_0$ units
- Recruit $r$ individuals per time unit
- Randomly assign a proportion $\pi$ to group 1
  - Expected sample size for group 1: $N_1 = rT_0\pi$
  - Expected sample size for group 2: $N_2 = rT_0(1 - \pi)$
- Exponential distributions (constant hazard) for time to loss to follow-up
- Additional right censoring at end of study period

The SURVPOW macro:

The code appears on page 103 in *SAS(R) Survival Analysis Techniques for Medical Research, Second Edition* by Alan B. Cantor

```
%survpow(s1= , s2= , nsub=365,
actime= ,futime= ,rate= ,p=.5,
loss1=0, loss2=0, w=1, siglevel=.05) ;
```

s1 and s2 Data files that describe the survival distributions for groups 1 and 2, respectively
- Each line has a pair of values $t$ for time, $s$ for the survival probability at $t$
- The first line has $t = 0$ and $s = 1$
- The values of $t$ must be increasing
- The values of $s$ must be decreasing
- The last value of $t$ must be the end of the study $T = T_0 + T_1$

nsub Number of subintervals per time unit. The default is 365.
actime Number of accrual time units
futime Number of time post-accrual time units
rate Accrual rate (individuals per unit time)
p Proportion assigned to group 1 (default is 0.5)
loss1 Loss to follow-up rate for group1 (default is 0)
loss2 Loss to follow-up rate for group2 (default is 0)
Specify weights for the linear rank test

- \( w=1 \): log-rank test
- \( w=n \): Wilcoxon (Gehan) test
- \( w=(n^{.5}) \): Tarone and Ware test

Type I error level (default is .05)

**Example:**

Suppose you are designing a randomized clinical trial to compare survival distributions for a new prostate cancer treatment to a standard treatment.

- It will be a seven year study
- During the first three years, the hospitals involved in the study will recruit about 60 participants per year
- Participants will be randomly assigned to treatments with probability 0.5 of receiving the new treatment
- The log-rank test will be used with Type I error level 0.05

**Projected survival probabilities**

<table>
<thead>
<tr>
<th>Standard Treatment</th>
<th>New Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>t</td>
<td>s</td>
</tr>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>0.88</td>
</tr>
<tr>
<td>2</td>
<td>0.70</td>
</tr>
<tr>
<td>3</td>
<td>0.60</td>
</tr>
<tr>
<td>4</td>
<td>0.48</td>
</tr>
<tr>
<td>5</td>
<td>0.39</td>
</tr>
<tr>
<td>6</td>
<td>0.30</td>
</tr>
<tr>
<td>7</td>
<td>0.24</td>
</tr>
</tbody>
</table>

What is the power of the log-rank test to detect a difference in the survival distributions for these two treatments?

```sas
/* Code for estimating power of weighted linear rank tests.
Posted as spower1.sas */

%include "c:\st565\survpow.macro.sas";

data group1;
  input t s;
datalines;
  0 1
  0 1
  2 0.70
  3 0.60
  4 0.48
  5 0.39
  6 0.30
  7 0.24
run;
```
data group2;
input t s;
datalines;
0 1.00
1 0.95
2 0.89
3 0.77
4 0.65
5 0.53
6 0.40
7 0.30
run;

/* Estimate power for the log-rank test
for a single recruitment rate */
%survpow(s1=group1, s2=group2, actime=3,
futime=4, rate=60, p=.5,
loss1=0.10, loss2=0.10, w=1, siglevel=.05);

Accrual Followup Accrual
Time Time Rate N alpha
3 4 60 180 .05

Prop in Loss Loss
Grp 1 Rate 1 Rate 2 Weights Power
.5 0.10 0.20 1 0.56776

/* Cycle through a set accrual rates and
several test statistics */
data data;
input w $;
datalines;
(n**.5)
n 1
run;

/* Create macro variables from weight functions */
data _null_; set data; i=_n_; call symput('w'||left(i), w);
run;

/* Create macro to loop across accrual
rates and weight functions */
%macro loop;
%do arate=60 %to 100 %by 5;
%do jj=1 %to 3;
%survpow(s1=group1, s2=group2, actime=3,
futime=4, rate=&arate, p=0.5,
loss1=.10, loss2=.20, w&&w&jj,
siglevel=0.05 );
%end;
%end;
%mend;
%loop;
runcorruptions
<table>
<thead>
<tr>
<th>Accrual Time</th>
<th>Followup Time</th>
<th>Accrual Rate</th>
<th>N alpha</th>
<th>Gpr1 Rate1</th>
<th>Rate2 Weights</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 4 60 180 0.05 0.5</td>
<td>.10 .20</td>
<td>(n**.5)</td>
<td>0.6890</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 4 60 180 0.05 0.5</td>
<td>.10 .20</td>
<td>n</td>
<td>0.7392</td>
<td></td>
<td></td>
<td></td>
</tr>
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