N. Estimation, Confidence Intervals for Various Quantities

1. Estimate Parameters and Standard Errors Via Likelihood

   a. Likelihood is \( L(\beta, \alpha, \sigma) = \prod_{j=1}^{n} f_U \left( \frac{\log(T_j) - \alpha - \beta z_j}{\sigma} \right)^{\delta_j} \sigma^{-\delta_j} S_U \left( \frac{\log(T_j) - \alpha - \beta z_j}{\sigma} \right)^{1-\delta_j} \)

   b. Maximizer gives estimate

   c. Simplest example is Weibull

      i. \( W \) has unit exponential distribution.

      ii. \( S_W(w) = \exp(-w) \)

      iii. \( S_U(u) = P[U > u] = P[W > \exp(u)] = \exp(-\exp(u)) \).

      iv. \( f_U(u) = \exp(-\exp(u)) \exp(u) \).

   d. For location and scale families, can fit regression model with only intercept to estimate \( \eta \) by residual variation, \( \lambda \) as exponential of intercept.

      i. ex. Weibull, Log Normal.

   e. Some distributions have additional parameters estimable similarly.

      i. ex. generalized gamma

   f. Get approximate covariance matrix \( \Sigma \) of \( (\hat{\alpha}, \hat{\beta}, \hat{\sigma}) \) using \( \ell'' \)
1. \[ \Sigma = \text{Var} \left[ (\hat{\alpha}, \hat{\beta}, \hat{\sigma}, \ldots) \right] \approx [\ell'']^{-1} \]

2. Estimate derived quantities via maximum likelihood

a. \[ \hat{S}(t) \] with covariates \( \mathbf{z} \) is \( \hat{p} = S_U([\log(t) - \hat{\alpha} - \hat{\beta}\mathbf{z}]/\hat{\sigma}) \)

i. \[ \frac{d\hat{p}}{d\alpha} = -f_U(\cdots)/\hat{\sigma} \]

ii. \[ \frac{d\hat{p}}{d\beta} = -f_U(\cdots)\mathbf{z}/\hat{\sigma} \]

iii. \[ \frac{d\hat{p}}{d\sigma} = f_U(\cdots)/\hat{\sigma}^2 \]

iv. Let \( \mathbf{v} = \left( \frac{d\hat{p}}{d\alpha}, \frac{d\hat{p}}{d\beta}, \frac{d\hat{p}}{d\sigma} \right) \)

v. \[ \text{Var} \left[ g(\hat{\alpha}, \hat{\beta}, \hat{\sigma}, \ldots) \right] = (g')^\top \text{Var} \left[ (\hat{\alpha}, \hat{\beta}, \hat{\sigma}, \ldots) \right] g' \]

- Delta method, lecture 2.

vi. \[ \text{SE} [\hat{p}] = \sqrt{\mathbf{v}^\top \Sigma \mathbf{v}} \]

vii. \[ \text{SE} [\log(\hat{p})] = \text{SE} [\hat{p}] / \hat{p} \]

b. acceleration factor \( \exp((\mathbf{z}_k - \mathbf{z}_j)\hat{\beta}) \)

i. Let \( \mathbf{v} = (0, \mathbf{z}_k - \mathbf{z}_j, 0) \)

ii. SE on log scale is \( \sqrt{\mathbf{v}^\top \Sigma \mathbf{v}} \)

c. relative risk \( \exp((\mathbf{z}_k - \mathbf{z}_j)/\hat{\sigma}) \)

i. Let \( \mathbf{v} = (0, (\mathbf{z}_k - \mathbf{z}_j)/\hat{\sigma}, -1/\hat{\sigma}^2) \)

ii. SE on log scale is \( \sqrt{\mathbf{v}^\top \Sigma \mathbf{v}} \)

d. CI’s best on log scale

e. Can fit hazard ratios and acceleration factors.
3. Interpretation:
   a. Scale gives shape parameter for exponential family
   b. Intercept gives location parameter (sort of).

KM: 12.5

O. Diagnostics for Accelerated Failure Models

1. One-Sample:
   a. If you want to diagnose family with specific member unspecified,
      i. $S(t) = S_0(\exp((\log(t) - \psi)/\phi))$ for
      ii. $S_0$ known
      iii. $\psi, \phi$ unknown,
   b. Cumulative hazard estimated without using model should agree with model
      i. $H(t) = H_0(\exp((\log(t) - \psi)/\phi))$ for $H_0 = -\log(S_0)$
      ii. $\log(H_0^{-1}(H(t))) = (\log(t) - \psi)/\phi$, linear in $\log(t)$
      iii. Hence $\log(H_0^{-1}(\hat{H}(t)))$ approx. linear in $\log(t)$.
         • $\hat{H}$ is Nelson-Allen estimator
   iv. Slope is dispersion parameter
   c. Form depends on specific family:
i. Weibull:
   - Easiest member is exponential
   - \( \log(H_0^{-1}(s)) = \log(s) \)
   - Plot \( \log(\hat{H}(t)) vs \log(t) \)
   - Exponential if slope is 1

ii. Log normal:
   - Easiest member is standard normal
   - \( H_0(t) = -\log(\Phi(-\log(t))) \)
   - \( H_0^{-1}(s) = \exp(-\Phi^{-1}(\exp(-s))) \)
   - Plot \( -\Phi^{-1}(\exp(-\hat{H}(t))) vs \log(t) \)

iii. Log logistic:
   - \( H_0(t) = \log(1 + t) \)
   - \( H_0^{-1}(s) = \exp(s) - 1 \)
   - \( \log(H_0^{-1}(s)) = \log(\exp(s) - 1) \)
   - Plot \( \log(\exp(\hat{H}(t)) - 1) vs \log(t) \)

2. Multiple Sample:
   a. Counterpart to Anderson Plots:
   b. Plot \( \hat{S}^{-1}(p) \) computed group-wise against each other
   c. \( \hat{S} \) computed nonparametrically
3. Regression Case:

a. Calculate Cox and Snell Residuals

i. This time $\hat{H}$ computed parametrically

ii. Weibull:

- $P[T_i > t] = \exp(-\exp((\log(t) - \alpha - z_i\beta)/\sigma))$.
- Cumulative hazard $-\log(P[T_i > t]) = \exp((\log(t) - \alpha - z_i\beta)/\sigma)$.
- CS residual is fitted $\text{CH} \exp((\log(t) - \hat{\alpha} - z_i\hat{\beta})/\hat{\sigma})$.

iii. Log normal:

- $P[T_i > t] = \Phi((\log(t) - \alpha/\sigma - z_i\beta)/\sigma)$.
- Cumulative hazard $-\log(\Phi((\log(t) - \alpha - z_i\beta)/\sigma))$.
- CS residual is fitted $\text{CH} - \log(\Phi((\log(t) - \hat{\alpha} - z_i\hat{\beta})/\hat{\sigma}))$.

iv. Log logistic:

- $P[T_i > t] = 1/(1 + \exp((\log(t) - \alpha/\sigma - z_i\beta)/\sigma))$.
- Cumulative hazard $\log(1 + \exp((\log(t) - \alpha/\sigma - z_i\beta)/\sigma))$
- CS residual is fitted $\text{CH} \log(1 + \exp((\log(t) - \hat{\alpha} - z_i\hat{\beta})/\hat{\sigma}))$.

b. $\hat{H}$ for residuals should be approximately 45° line

c. Simulation shows that this technique can identify correct model.
4. Summary

a. Comparison of interpretations of different models:

<table>
<thead>
<tr>
<th>Event</th>
<th>Model</th>
<th>Interp. of $z_j \hat{\beta} &gt; 0$ (compared to baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Proportional Hazards</td>
<td>Better</td>
</tr>
<tr>
<td>Bad</td>
<td>Proportional Hazards</td>
<td>Worse</td>
</tr>
<tr>
<td>Good</td>
<td>Accelerated Failure</td>
<td>Worse</td>
</tr>
<tr>
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<td>Accelerated Failure</td>
<td>Better</td>
</tr>
</tbody>
</table>

P. Estimation with interval censoring:

1. Notation for interval censoring:
   a. patients are screened at fixed intervals $t_0, t_1, t_2, \ldots, t_J$ for $t_{J+1} = \infty$.
   b. know that event happened within $(L_i, R_i]$ for $L_i, R_i \in \{t_1, \ldots, t_J\}$.
      i. $R_i = \infty$ reflects right censoring.
      ii. $L_i = R_i$ reflects observation without censoring
           - (not withstanding $(L_i, R_i]$ is empty if $L_i = R_i$).
   c. Because times are fixed, the profiling argument putting all weight on times doesn’t apply.
   d. Data format similar to life-table approach.

2. Likelihood for interval censoring
a. Likelihood \( L = \prod_{i=1}^{n} [S_i(L_i) - S_i(R_i)] \).
   
i. \( n \) is the number of observations.
   
ii. Assume observations are independent, and so contributions multiply.
   
iii. \( S_i(t) = S_0(t) \exp(z_i\beta) \)
   
iv. Estimate \( \beta \) and \( S_0(t_j) \) for all \( j \).

b. If \( L_i \) and \( R_i \) are all consecutive times from \( t_0, t_1, t_2, \ldots, t_J \) for \( t_{J+1} = \infty \).
   
i. \( L = \prod_{j=1}^{J+1} [S_i(t_j) - S_i(t_{j-1})]^N \)
   
ii. \( N_j \) are the number of observations in interval \( (t_{j-1}, t_j] \).

c. More complicated if \( L_i \) and \( R_i \) are not consecutive items from \( t_0, t_1, t_2, \ldots, t_J \) for \( t_{J+1} = \infty \).
   
i. Ex., if potential visits are Jan, Apr, Jul, Oct, but visits are 6 mo apart, then we need to split an event that happens between Apr and Oct to Apr-Jul or Aug-Oct.
   
ii. Iterative procedure for splitting events over sub-intervals.
   
iii. Issue does not arise in the fully-parametric case.  

3. Case with all subjects having the same assessment times
a. Let $\pi_{ij} = P[T_i \leq t_j | T_i > t_{j-1}]$

b. $P[T_i > t_j] = \prod_{l=1}^{j}(1 - \pi_{il})$

c. Let $J_i$ be index such that $T_i \in (t_{J_i}, t_{J_i+1}]$.

d. $Y_{ij}$ indicate which interval subject $i$ has event in.
   i. 1 if subject $i$ had the event in interval $(t_j, t_{j+1}]$,
   ii. $Y_{iJ+1} = 1$ if item not observed to fail,
   iii. 0 otherwise.

e. Likelihood is $\prod_{i=1}^{n} \pi_i J_i \prod_{l=1}^{J_i-1}(1 - \pi_{il}) = \prod_{i=1}^{n} Y_{iJ_i} \prod_{l=1}^{J_i-1}(1 - \pi_{il})^{1-Y_{il}},$

i. Likelihood for Bernoulli trials $Y_{ij}$ with successs probabilities $\pi_{ij}$

ii. Likelihood contributions multiply through conditioning rather than through independence.

4. Proportional hazards

a. $P[T_i > t_j] = P[T_m > t_j]^{\exp((z_i-z_m)\beta)} \forall i, j, m$

b. $\prod_{l=1}^{j}(1 - \pi_{il}) = \prod_{l=1}^{j}(1 - \pi_{ml})^{\exp((z_i-z_m)\beta)} \forall i, j, m$

c. $(1 - \pi_{ij}) = (1 - \pi_{mj})^{\exp((z_i-z_m)\beta)} \forall i, j, m$

d. $\log(1 - \pi_{ij}) = \exp(\alpha_j + z_i\beta)) \forall i, j$

e. $\log(\log(1 - \pi_{ij})) = \alpha_j + z_i\beta \forall i, j$
f. Gives complimentary log log link for regression model for $\pi_{ij}$