What to do this week (2022/02/08, 02/10)?

Part I. Preliminaries

Part II. Parametric Inference

Part III. Nonparametric/Semi-parametric Inference

- *Part III.1. Introduction and Overview: Motivation*
- **Part III.2. Kaplan-Meier Estimator**
- **Part III.3. Nonparametric Tests**
- *Part III.4. Cox Proportional Hazards Model*

Part III.2. Kaplan-Meier Estimator

Consider r.v. $T \sim F(\cdot)$ with the goal to estm $F(\cdot)$ without any strong model assumption.

- If only right-censored event times $\{(U_i, \delta_i) : i = 1, \ldots, n\}$ available, provided indpt censoring,
  $\Longrightarrow$ the Kaplan-Meier estimator (left-continuous)

$$\hat{S}(t) = \prod_{j:V_j<t} \left(1 - \frac{n_j}{N_j}\right) = \begin{cases} 1 & t \le V_1 \\ \prod_{l=1}^{j}(1 - \hat{h}_j) & V_j < t \le V_{j+1} \\ ? & t > V_{J+1} \end{cases}$$

  the distinct observed event times: $0 = V_0 \le V_1 < \ldots < V_J \le V_{J+1}$
  - $\{V_j : j = 1, \ldots, J\} = \{U_i : i = 1, \ldots, n\}$
  - $S(t) = P(T \ge t) = \prod_{l=1}^{j}(1 - h_l)$ if $t \in (V_j, V_{j+1}]$.
  - the nonparametric MLE
  - the general case vs the discrete case

Part III.2. Kaplan-Meier Estimator: Applications

- for comparing two populations' distn with censored data e.g. $\sup_{t>0} |\hat{S}_{1,KM}(t) - \hat{S}_{2,KM}(t)|$? an extension of the Kolmogorov-Smirnov test statistic $\sup_{t>0} |F_{1,n}(t) - F_{2,m}(t)|$ *no need to specify the population distributions into parametric models*

- for justifying actuarial life table

Part III.2. Kaplan-Meier Estimator: Applications

- for assessing parametric goodness-of-fit with censored data
  - e.g. is $T \sim NE(\lambda)$ $(H(t) = \lambda t)$?
    $\Longrightarrow$ to check if $\log S(t) = -\lambda t$?
    using the scatter plot of $\log \hat{S}(t)$ vs t: is $\log \hat{S}(t)$ linear function of t?
  - e.g. is $T \sim \mathit{Weibull}(\lambda, \rho)$ $(H(t) = \lambda t^{\rho})$?
    $\Longrightarrow$ to check if $\log\big(-\log S(t)\big) = \log \lambda + \rho \log t$?
    using the scatter plot of $\log\big(-\log \hat{S}(t)\big)$ vs $\log t$: look for linearity?

Part III.3. Nonparametric Tests: Introduction

Consider to compare two groups wrt the event time distns ... ...

For example,

- in the placebo group, iid $T_{0i} \sim F_0(\cdot)$: $i = 1, \ldots, n$
- in the treatment group, iid $T_{1j} \sim F_1(\cdot)$: $j = 1, \ldots, m$

$\Longrightarrow H_0 : F_0(\cdot) = F_1(\cdot)$

... Many different ways to differ: any UMP?

- *directional tests*: designated/oriented to a specific type of difference between the two population distns
  e.g. $S_1(t) = S_0(t)^c$
- *omnibus tests*: there is power to detect all or most types of differences but not with great power for a specific difference

Part III.3. Nonparametric Tests: Introduction

Early work with censored data ... ...

- Gehan (1965, Biometrika): modifying rank tests to allow censoring
- Mantel (1966, Cancer Chem): adapting data to use methods for several 2×2 tables
- Application of the Cox partial likelihood approach (Cox, 1975)*

Part III.3. Nonparametric Tests: Gehan Test

Recall that, without censoring and provided the two populations are indpt, the Wilcoxon sign test:

$$\Phi(T_{1i}, T_{0j}) = \begin{cases} 1 & T_{0j} > T_{1i} \\ -1 & T_{0j} < T_{1i} \\ 0 & T_{0j} = T_{1i} \end{cases}$$

$W = \sum_{i=1}^{n} \sum_{j=1}^{m} \Phi(T_{1i}, T_{0j})$

- $E_{H_0}(W) = 0$
- $W/SE(W) \sim N(0,1)$ in distn as $n, m \to \infty$

$\Longrightarrow$ the Wilcoxon sign test

Part III.3. Nonparametric Tests: Gehan Test

- efficiency?
- what if $T_1 \not\perp T_0$?
- what if the data are right-censored?
  $\left\{(U_{1i}, \delta_{1i}) : i = 1, \ldots, n\right\} \bigcup \left\{(U_{0j}, \delta_{0j}) : j = 1, \ldots, m\right\}$

Part III.3. Nonparametric Tests: Gehan Test

With the right-cenosred data
$\left\{(U_{1i}, \delta_{1i}) : i = 1, \ldots, n\right\} \bigcup \left\{(U_{0j}, \delta_{0j}) : j = 1, \ldots, m\right\}$:

$$\Phi(U_{1i}, \delta_{1i}; U_{0j}, \delta_{0j}) = \begin{cases} 1, & U_{0j} > U_{1i}; \delta_{1i} = 1 \\ -1, & U_{0j} < U_{1i}; \delta_{0j} = 1 \\ 0, & otherwise \end{cases}$$

$GW = \sum_i \sum_j \Phi(U_{1i}, \delta_{1i}; U_{0j}, \delta_{0j})$ provided indpt censoring,

- $E_{H_0}(GW) = 0$
- $GW/SE(GW) \sim N(0,1)$ in distn as $n, m \to \infty$

$\Longrightarrow$ Wilcoxon-Gehan testing procedure ...

Part III.3. Nonparametric Tests: Gehan Test

- efficiency?
- what if $T_1 \not\perp\!\!\!\perp T_0$?
- how is it compared to the extended Kolmogorov-Smirnov test based on the KM estm?

Part III.3. Nonparametric Tests: Mantel Test

with all observed distinct event times: $0 < V_1 < \ldots, V_K$

First, consider what happens at time $t = V_l$ ...

	at $t = V_l$		
Group	failure	not	at risk
placebo	n_{0l}	–	N_{0l}
treatment	n_{1l}	–	N_{1l}
total	$n_{.l}$	–	$N_{.l}$

The number of observed failures at time V_l from the treatment group $O_l = n_{1l} \sim$ Hypergeometric distn under $H_0 : S_0(\cdot) = S_1(\cdot)$

$$P(O_l = a) = \frac{\begin{pmatrix} N_{1l} \\ a \end{pmatrix} \begin{pmatrix} N_{0l} \\ n_{.l} - a \end{pmatrix}}{\begin{pmatrix} N_{.l} \\ n_l \end{pmatrix}}$$

Part III.3. Nonparametric Tests: Mantel Test

with all observed distinct event times: $0 < V_1 < \ldots, V_K$

First, consider what happens at time $t = V_l$ ...

	at $t = V_l$		
Group	failure	not	at risk
placebo	n_{0l}	–	N_{0l}
treatment	n_{1l}	–	N_{1l}
total	$n_{.l}$	–	$N_{.l}$

- the expected number of failures from treatment group $E_l = E(O_l) = n_l \frac{N_{1l}}{N_l}$ under H_0
- $V(O_l) = \frac{N_l - N_{1l}}{N_l - 1} N_{1l} \left(\frac{n_l}{N_l}\right)\left(1 - \frac{n_l}{N_l}\right)$ under H_0

Part III.3. Nonparametric Tests: Mantel Test

Now, pull together the information at all the observed failure times ...

$$Z = \frac{\sum_{l=1}^{K}(O_l - E_l)}{\sqrt{\sum_{l=1}^{K} V(O_l)}} \sim N(0,1)$$

approximately under H_0
$\Longrightarrow$ the Mantel (logrank) testing procedure ...

- $Z^2 \sim \chi^2(1)$ under H_0
- $Z = (\sum_l O_l - \sum_l E_l)/SE(O)$

Part III.3. Nonparametric Tests: Mantel Test

Example. Group 0: $3.1,\ 6.8^+,\ 9,\ 9,\ 11.3^+,\ 16.2$

Group 1: $8.7,\ 9,\ 10.1^+,\ 12.1^+,\ 18.7,\ 23.1^+$

Part III.3. Nonparametric Tests: Mantel Test

Remarks

- similar to the techniques for combining 2×2 tables across strata to test for independence
- efficiency?
- Mantel (logrank) test vs Gehan test?
- oriented towards $S_1(t) = S_0(t)^c$, a directional test

Part III.3. Nonparametric Tests: Variants of Logrank Test

What if the subjects are stratified according to a factor, say, gender?

Stratified Logrank Test with the factor of K levels

$$Z = \frac{\sum_{k=1}^{K}(O^{(k)} - E^{(k)})}{\left(\sum_k V^{(k)}\right)^{1/2}} \sim N(0,1)$$

approximately under H_0.

$\Longrightarrow$ the testing procedure ... ...

Part III.3. Nonparametric Tests: Variants of Logrank Test

What if there is a need to weight the information at different times differently?

Weighted Logrank Test

$$Z_W = \frac{\sum_{l=1}^{L} w_l(O_l - E_l)}{\left(\sum_l w_l^2 V_l\right)^{1/2}} \sim N(0,1)$$

approximately under H_0.

$\Longrightarrow$ the testing procedure ... ...

How to choose the weights in general?

- If $w_l = N_{.l}$, the test is similar to Gehan test.

Part III.3. Nonparametric Tests: Variants of Logrank Test

What if to compare p treatment groups with the placebo group?
$H_0 : S_0(\cdot) = S_1(\cdot) = \ldots = S_p(\cdot)$
Given all the distinct failure times are $0 < V_1 < \ldots < V_L < \infty$,

	at $t = V_l$		
Group	failure	not	at risk
placebo	n_{0l}	...	N_{0l}
treatment 1	n_{1l}	...	N_{1l}
$\vdots$	$\vdots$	$\vdots$	$\vdots$
treatment p	n_{pl}	...	N_{pl}
total	$n_{.l}$	...	$N_{.l}$

$$\mathbf{O}_l = \begin{pmatrix} n_{1l} \\ \vdots \\ n_{pl} \end{pmatrix};\ \mathbf{E}_l = E\{\mathbf{O}_l\} = \begin{pmatrix} N_{1l} \\ \vdots \\ N_{pl} \end{pmatrix} \frac{n.l}{N_{.l}};\ \mathbf{V}_l = Var\{\mathbf{O}\}$$

Part III.3. Nonparametric Tests: Variants of Logrank Test

$\tilde{\mathbf{O}} = \sum_{l=1}^{L} \mathbf{O}_l$, $\tilde{\mathbf{E}} = \sum_{l=1}^{L} \mathbf{E}_l$, $\tilde{\mathbf{V}} = \sum_{l=1}^{L} \mathbf{V}_l$

$$\left(\tilde{\mathbf{O}} - \tilde{\mathbf{E}}\right)' \tilde{\mathbf{V}}^{-1} \left(\tilde{\mathbf{O}} - \tilde{\mathbf{E}}\right) \sim \chi^2(p)$$

approximately under H_0, provided the sample size is large.

$\Longrightarrow$ the testing procedure ... ...

- The test is *omnibus*.
- If a trend test is intended?
  to consider $\mathbf{c}' \left(\tilde{\mathbf{O}} - \tilde{\mathbf{E}}\right) \sim N(0, \mathbf{c}'\tilde{\mathbf{V}}\mathbf{c})$?

What to study next?

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Part II. Parametric Inference

Part III. Nonparametric/Semi-parametric Inference

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Part IV. Advanced Topics