What to do this week (March 21 and 23, 2023)?

Part I. Introduction
Part II. Epidemiologic Concepts and Designs
Part III. Clinical Trials

Part IV. Modern Biostatistical Approaches

Part IV.1 Incomplete Data Analysis

Part IV.2 Some Other Important Topics (Chp 8 - 18, Koepsell and Weiss, 2003)

Part IV.3 Selected Widely-Used Algorithms

Part IV.4 Lifetime Data Analysis

IV.4.1 Parametric Inference
IV.4.2 Nonparametric Inference: Estimation
IV.4.3 Nonparametric Inference: Testing
IV.4.4 Semiparametric Inference
IV.4.5 An Overview by A.A. Tsiatis

IV.4.4 Semiparametric Inference: Cox Proportional Hazards Model

- Recall the two-sample problem $\rightarrow$ testing on $H_0 : h_1(\cdot) = h_0(\cdot)$
  - $Z = \begin{cases} 1 & \textit{treatment} \\ 0 & \textit{placebo} \end{cases}$,
    to study event time $T|Z = z$?
  - with general covariates Z, to explore event time $T|Z = z$?
    $\Longrightarrow$ regression modeling?

- Feigl and Zelen (1965)
  $T|Z = z \sim NE(\lambda_z)$: $h(t|z) = \lambda_z = \lambda_0 e^{\beta z}$
  $\beta = 0 \rightarrow$ no effect of Z

$\Longrightarrow$ **Cox Proportional Hazards Model** (Cox, JRSSB 1972)

Cox Proportional Hazards Model: (Cox, JRSSB 1972)
The hazard function of event time $T|Z = z$ is

$$h(t|z) = h_0(t)e^{\beta z}, \quad t > 0$$

The conditional survivor function is

$$S(t|z) = \exp(-\int_0^t h_0(u)e^{\beta z}du) = \exp(-H_0(t)e^{\beta z}), \quad t > 0$$

Remarks

- the hazard ratio $h(t|Z = z_1)/h(t|Z = z_0) = e^{\beta(z_1 - z_0)}$ for all $t > 0$ *proportional*!

- $Z = \begin{cases} 1 & \textit{treatment} \\ 0 & \textit{placebo} \end{cases}$, e^{β}: treatment effect

- $Z_1 = \begin{cases} 1 & \textit{treatment} \\ 0 & \textit{placebo} \end{cases}$, $Z_2 = \begin{cases} 1 & \textit{male} \\ 0 & \textit{female} \end{cases}$, $\boldsymbol{\beta} = \begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix}$, $\mathbf{Z} = \begin{pmatrix} Z_1 \\ Z_2 \end{pmatrix}$, $h(t|\mathbf{Z}) = h_0(t)e^{\boldsymbol{\beta}'\mathbf{Z}}$: relative impacts of the treatment to female and male are the same.

Cox Proportional Hazards Model: Estimation of β

Often is interested to estm β in the Cox PH model, for comparison/evaluate/assess effect ... ...

With right-censored event times along with the covariates

$$\left\{(U_i, \delta_i, Z_i) : i = 1, \ldots, n\right\}$$

from n indpt subjects and indpt censoring $T_i \perp\!\!\!\perp C_i$

$$L(\beta, h_0(\cdot) \big| data) = \prod_{i=1}^{n} \left(h_0(u_i) e^{\beta z_i}\right)^{\delta_i} \exp(-H_0(u_i) e^{\beta z_i})$$

$$L(\beta, h_0(\cdot) \big| data) = L_1(\beta \big| data) L_2(\beta, h_0(\cdot) \big| data)$$

$\Longrightarrow$ **the Cox partial likelihood function** (Cox, Biometrika 1975)

the Cox partial likelihood function (Cox, Biometrika 1975)

$$L_1(\beta \big| data) = \prod_{i=1}^{n} \Big(\frac{e^{\beta z_i}}{\sum_{l \in \mathcal{R}_i} e^{\beta z_l}} \Big)^{\delta_i}$$

the risk set at time u_i: $\mathcal{R}_i = \{j : u_j \geq u_i\}$

$\Longrightarrow$ the MPLE (maximum partial likelihood estimator) of β:

$$\hat{\beta} = argmax_{all\ \beta} L_1(\beta \big| data)$$

With some conditions, as $n \to \infty$

- $\hat{\beta} \to \beta$ a.s.
- $\sqrt{n}(\hat{\beta} - \beta) \to N(0, ?)$ in distn

Example. $n = 5$ indpt subjects and $Z = \begin{cases} 1 & \textit{treatment} \\ 0 & \textit{placebo} \end{cases}$

$(u_i, \delta_i, z_i):\ (16, 1, 1),\ (13, 0, 0),\ (21, 1, 1),\ (11, 1, 0),\ (12, 1, 1)$

Remarks

- *implementation*
  - to use $\log L_1(\beta) = \sum_{i=1}^{n} \delta_i \{\beta z_i - \log(\sum_{l \in \mathcal{R}_i} e^{\beta z_l})\}$

    or $U(\beta) = \partial \log L_1(\beta)/\partial\beta = \sum_{i=1}^{n} \delta_i \{ z_i - \frac{\sum_{l \in \mathcal{R}_i} z_l e^{\beta z_l}}{\sum_{l \in \mathcal{R}_i} e^{\beta z_l}} \} = 0$
  - e.g. *R: coxph*

Remarks (cont'd)

- *interpretation*
  - recall *likelihood, marginal likelihood, conditional likelihood, partial likelihood*
  - **the Cox partial likelihood function** of β
    - conditional arguments
    - the marginal distn of the rank statistic when no tie, no censored observation, cfs: Kalbfleisch and Prentice (1980, 2011)

Cox Proportional Hazards Model: Testing on β

Consider $H_0 : \beta = 0$ vs $H_1 : \beta \neq 0$

the partial score test

$$U(\beta) = \partial \log L_1(\beta)/\partial\beta = \sum_{i=1}^{n} \delta_i \left[z_i - \frac{\sum_{l \in \mathcal{R}_i} z_l e^{\beta z_l}}{\sum_{l \in \mathcal{R}_i} e^{\beta z_l}} \right]$$

Based on $U(\beta)/\sqrt{n} \sim AN(0, ??)$ as $n \to \infty$ with some conditions,

$\Longrightarrow$ the partial score testing procedure ...

Remarks.

- e.g. when $Z = \begin{cases} 1 & treatment \\ 0 & placebo \end{cases}$

  $U(\beta)\big|_{\beta=0} = \sum_{l=1}^{L} \left(O_l - n_{.l} \frac{N_{1l}}{N_{.l}} \right) = O - E$, the numerator of the logrank test statistic

- the Wald-type, using the MPLE of β and its asymptotic normality?

- the PLRT, using the structure of LRT?

IV.4.5 An Overview by A.A. Tsiatis

What to do next?

- Individual meetings: Project A-II; Homework 2; Project B-I
  - March 28 (Tuesday) 3:30 - 4:00
  - March 28 (Tuesday) 4:00 - 4:30
  - March 28 (Tuesday) 4:30 - 5:00
  - March 28 (Tuesday) 5:00 - 5:30
  - March 30 (Thursday) 3:30 - 4:00
  - March 30 (Thursday) 4:00 - 4:30
  - March 30 (Thursday) 4:30 - 5:00
  - March 30 (Thursday) 5:00 - 5:30
- Project B-II (Class presentations)
  - April 4 (Tuesday) 3:30 - 4:00 *Tong-Wei Lin*
  - April 4 (Tuesday) 4:10 - 4:40 *Quang Vuong*
  - April 6 (Thursday) 3:30 - 4:00 *Nadia Enhaili*
  - April 6 (Thursday) 4:10 - 4:40 *So-Yeon Park*
  - April 6 (Thursday) 4:50 - 5:20 *Quinn Forzley*
  - April 11 (Tuesday) 3:30 - 4:00 *David Lai*
  - April 11 (Tuesday) 4:10 - 4:40 *Sashini Silva*
  - April 11 (Tuesday) 4:50 - 5:20 *Niwanthi Ruwan*
- Project C The final report is due on April 21 by 5:00pm.