BIST P8110: Applied Regression II

9. Intro to Cox Models

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Regression Models for Hazard Functions

- One form of a regression model for the hazard function is

$$h(t, x, \beta) = h_0(t) r(x, \beta)$$

  - $h_0(t)$: characterizes how the hazard function changes as a function of survival time.
  - $r(x, \beta)$: characterizes how the hazard function changes as a function of subject covariates.
  - $r(x, \beta)$ must be chosen such that $r(x, \beta) > 0$, why?
  - When the function $r(x, \beta)$ is parameterized such that $r(x = 0, \beta) = 1$, $h_0(t)$ is frequently referred to as the **baseline hazard function**.

Hazard Ratio in Regression Models

- The ratio of the hazard functions for two subjects with covariate values denoted as x_1 and x_0 is

$$\begin{aligned} HR(t, x_1, x_0) &= \frac{h(t, x_1, \beta)}{h(t, x_0, \beta)} \\ &= \frac{h_0(t) r(x_1, \beta)}{h_0(t) r(x_0, \beta)} \\ &= \frac{r(x_1, \beta)}{r(x_0, \beta)} \end{aligned}$$

- The HR function depends only on the function $r(x, \beta)$.

Cox Proportional Hazards Model

- Cox (1972) suggested using $r(x, \beta) = \exp(x\beta)$. With this parameterization the hazard function is

  $$h(t, x, \beta) = h_0(t)e^{x\beta}$$

  and the hazard ratio is

  $$HR(t, x_1, x_0) = e^{\beta(x_1 - x_0)}$$

- This model is referred to the **Cox model**, the **Cox proportional hazards model**, or the **proportional hazards model**.

Cox Proportional Hazards Model

- For example, when a covariate is dichotomous, such as gender, with a value of $x_1 = 1$ for males and $x_0 = 0$ for females, the hazard ratio becomes

$$HR(t, x_1, x_0) = e^{\beta}.$$

- If the value of the coefficient is $\beta = \log(2)$, then the interpretation is that males are "dying" at twice ($e^{\beta} = 2$) the rate of females.

Cox Proportional Hazards Model

- An attractive feature of the proportional hazards model is the interpretation of hazard ratio as “relative-risk" type ratio.
- The term **proportional hazards** refers to the fact that the hazard ratio is **constant over survival time.** This is an important assumption for the proportional hazards model.
- The proportional hazards model is a semi-parametric model in that it makes no assumptions about the shape of the control hazard function $h_0(t)$.

Survival Functions under the Cox Model

- Under the proportional hazards model, the survival function is
$$S(t, x, \beta) = [S_0(t)]^{\exp(x\beta)}$$
where, $S_0(t) = e^{-\int_0^t h_0(u)du}$ is the baseline survival function.
- In the example on slide 5,
$$S(t, x_1 = 1) = [S_0(t)]^2$$
$$S(t, x_0 = 0) = S_0(t)$$
Since $0 \leq S_0(t) \leq 1$, we have $S(t, x_1 = 1) \leq S(t, x_0 = 0)$. This is consistent with our conclusion on slide 5 that males are "dying" at a bigger rate than females. What happens if $\beta = -\log(2)$?

Log Partial Likelihood in the Cox Model

- When there are no tied survival times, the regression coefficient β is estimated based on the log partial likelihood function

$$l_p(\beta) = \sum_{j=1}^{m} \left\{ x_j\beta - \log\left(\sum_{k \in R(t_j)} e^{x_k\beta} \right) \right\}$$

where, m is the number of distinct ordered failure times and x_j denotes the value of the covariate for the subject with failure time at t_j. The summation within log is over all subjects at risk at time t_j, denoted by $R(t_j)$.

Estimate β in the Cox Model

- The maximum partial likelihood estimator, $\hat{\beta}$, can be obtained by solving

$$\frac{\partial l_p(\beta)}{\partial \beta} = 0$$

- The estimator of the variance of the estimated coefficient is the inverse of observed information matrix evaluated at $\hat{\beta}$

$$\widehat{var}(\hat{\beta}) = I(\hat{\beta})^{-1}$$

where, the information matrix $I(\beta) = -\frac{\partial^2 l_p(\beta)}{\partial \beta^2}$

- The estimated standard error of $\hat{\beta}$ is $\widehat{SE}(\hat{\beta}) = \sqrt{\widehat{Var}(\hat{\beta})}$ and the 95% CI is $\hat{\beta} \pm 1.96 \times \widehat{SE}(\hat{\beta})$.

Test the Significance of β in the Cox Model

- Three tests to assess the significance of β are
  - The partial likelihood ratio test
  - The Wald test
  - The score test.
- The partial likelihood ratio test:

$$G = 2\{l_p(\hat{\beta}) - l_p(0)\} \sim \chi_1^2$$

where, $l_p(\hat{\beta})$ and $l_p(0)$ are the log partial likelihood (on slide 8) evaluated at $\beta = \hat{\beta}$ and $\beta = 0$, respectively.

Test the Significance of β in the Cox Model

- The Wald test:

$$z = \frac{\hat{\beta}}{\widehat{SE}(\hat{\beta})} \sim N(0,1)$$

- The score test:

$$z^* = \left. \frac{\partial l_p / \partial \beta}{\sqrt{I(\beta)}} \right|_{\beta=0} \sim N(0,1)$$