Seminar in Statistics: Survival Analysis

Presentation 3:

The Cox Proportional Hazard Model and Its Characteristics

Peter Fabsic, Vakhrushev Evgeny, Kevin Zemmer

March 14, 2011

1 Introduction

Simple Linear Regression

In simple linear regression we examine the relation between a response variable and a **single** predictor. The model is

$$Y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$$

where

- i is the observation number, $i = 1, \ldots, n$;
- Y is the response;
- x is the predictor;
- β_0, β_1 are regression coefficients, called intercept and slope respectively;
- ε is an error term.

Estimates of β_0 and β_1 (denoted by $\hat{\beta}_0$ and $\hat{\beta}_1$ respectively) are determined by a least squares approach. Note that $\hat{\beta}_1$ is the increase in Y corresponding to a 1-unit increase in x.

Multiple Linear Regression

In multiple linear regression there are p predictors. The model in this case is

$$Y_i = \beta_0 + \beta_1 x_{i1} + \ldots + \beta_p x_{ip} + \varepsilon_i.$$

Parameters are again estimated using least squares, but the interpretation is now slightly different: Y increases by $\hat{\beta}_j$ if x_j increases by 1 unit and all other predictors remain constant. Note that if predictors are correlated and their regression coefficients are non-zero, **multiple regression cannot be substituted by many simple regressions**.

Confounding and Interaction

Confounding occurs when an extraneous variable is correlated with both the dependent and the independent variable(s).

Interaction occurs when independent variables combine to affect a dependent variable.

Confounding and interaction may lead to wrong conclusions about causal relationships.

2 The Cox Proportional Hazard Model

The hazard function for the Cox Proportional Hazard (Cox PH) model is

$$h(t, \boldsymbol{X}) = h_0(t) \exp\left(\sum_{i=1}^{p} \beta_i X_i\right)$$

where $\boldsymbol{X} = (X_1, X_2, \ldots, X_p)$ are the predictor variables and $h_0(t)$ is called the baseline hazard. Important characteristics of the Cox PH model are that

- it is a product of a function in t and a function in $\boldsymbol{X}$;
- $\boldsymbol{X}$ is time independent;
- the baseline hazard is an unspecified function, making it a semi-parametric model.

3 The Popularity of the Cox PH Model

Reasons for the popularity of the Cox model:

1. The Cox model is **robust**.
2. The estimated hazards are always non-negative.
3. The β_i's can be estimated and the hazard ratio calculated.
4. $h(t, \boldsymbol{X})$ and $S(t, \boldsymbol{X})$ can be estimated.
5. The Cox model is preferred over the logistic model which ignores survival time and censoring information.

4 Computing the Hazard Ratio

The Hazard Ratio is defined as

$$\widehat{HR} = \frac{\hat{h}(t, \boldsymbol{X}^*)}{\hat{h}(t, \boldsymbol{X})}$$

where $\boldsymbol{X}^*$ is typically the group with the larger hazard (e.g. placebo group) while $\boldsymbol{X}$ is the group with the smaller hazard (e.g. treatment group). In the case of the Cox PH model this simplifies to

$$\widehat{HR} = \exp\left(\sum_{i=1}^{p} \hat{\beta}_i (X_i^* - X_i)\right)$$

which can be easily computed once the $\hat{\beta}_i$ have been determined.

5 The Meaning of the PH Assumption

The PH assumption requires that the hazard ratio is constant over time, or equivalently, that the hazard for one individual is proportional to the hazard for any other individual and the proportionality constant is independent of time. Graphically this means that hazards for different individuals do not cross. The general rule is that if the hazards cross, then the PH assumption cannot be met, so that a Cox PH model is inappropriate. More on the evaluation of PH assumption is to follow in the next presentations.

6 ML Estimation of the Cox PH Model

The full likelihood can be used to derive a formula for the baseline hazard. The Cox model likelihood function L is called a "partial" likelihood function because it only considers probabilities for failed subjects explicitly.

It can be shown that the Cox partial likelihood can be written as

$$L(\boldsymbol{\beta}) = \prod_{j=1}^{k} \frac{\exp\left(\sum_{i=1}^{p} \beta_i X_{[j]i}\right)}{\sum_{l \in R(t_{(j)})} \exp\left(\sum_{i=1}^{p} \beta_i X_{li}\right)}$$

where

- we assume k different failure times $t_{(1)} < t_{(2)} < \cdots < t_{(k)}$ with exactly one failure at each time;
- $[i]$ denotes the subject with event at time $t_{(i)}$;
- $R(t)$ is the risk set at time t.

Properties of Cox likelihood:

- The Cox likelihood is determined by the order of events and censoring and not by the distribution of the outcome variable.
- The baseline hazard cancels out in each term of the likelihood and does not play any role in estimation.
- It is still possible to derive a complete likelihood function.

Once the likelihood is formulated, the goal is to choose values of parameters that maximize the likelihood. The process of maximizing the likelihood is typically carried out by setting the partial derivative of the natural logarithm of the likelihood to zero and then solving the system of equations (called the score equations).

7 Adjusted Survival Curves Using the Cox Proportional Hazard Model

Converting the hazard function for the Cox PH model leads to the following survival function:

$$\hat{S}(t, \boldsymbol{X}) = \left[\hat{S}_0(t)\right]^{\exp\left(\sum_{i=1}^{p} \hat{\beta}_i X_i\right)}$$

Once the estimated quantities $\hat{S}_0(t)$ and $\hat{\beta}_i$ have been obtained this can be plotted as a step function.

References

[1] D. G. Kleinbaum & M. Klein, *Survival Analysis - A Self-Learning Text.* Springer, Second Edition, 2005.

[2] D. R. Cox, *Regression Models and Life-Tables.* Imperial College, London, 1972.

[3] J. Fox, *Applied Regression Analysis, Linear Models, and Related Methods.* Sage Publications, 1997.

[4] J. P. Klein & M. L. Moeschberger, *Survival Analysis: Techniques for Censored and Truncated Data.* Springer, Second Edition, 2003.

[5] M. Dettling, *Lecture Notes on Applied Statistical Regression.* ETH Zürich, 2010. Available at http://stat.ethz.ch/education/semesters/as2010/asr/ASR-HS10-Scriptum.pdf