Seminar in Statistics: Survival Analysis
Chapter 6

Extension of the Cox Proportional Hazards Model for Time-Dependent Variables

Tulasi Agnihotram, Gaby Binder, Fabian Frei
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1 Review

Cox PH-Model: \( h(t, X) = h_0(t) \cdot \exp[\sum_{i=1}^{p} \beta_i X_i] \)

Hazard ratio: \( \hat{HR}(t) = \frac{\hat{h}(t,X^*(t))}{\hat{h}(t,X(t))} = \exp[\sum_{i=1}^{p} \hat{\beta}_i [X_i^* - X_i]] \)

PH assumption: The hazard ratio is independent of time: \( \frac{h(t,X^*)}{h(t,X)} = \theta \)

Methods for checking the PH assumption:

- Graphical
- Time-dependent covariates
- Goodness-of-fit test

What can be done if the PH assumption is not met:

- Use a stratified Cox procedure
- Use an extended Cox model

2 Time-dependent Variables

Definition: Any variable whose values differ over time.

Example:

- Race: time-independent
  Race \( \times \) t: time-dependent

There are 3 types of variables:

- Defined variables
- Internal variables
- Ancillary variables
3 The Extended Cox Model for Time-dependent Variables

\[ h(t, X(t)) = h_0(t) \cdot \exp\left[ \sum_{i=1}^{p_1} \beta_i X_i + \sum_{i=1}^{p_2} \delta_i X_i(t) \right] \]

\( X(t) = (X_1, \ldots, X_{p_1}, X_{1}(t), \ldots, X_{p_2}(t)) \) denotes all predictors
\( X_i \) denotes the \( i^{th} \) time-independent variable
\( X_i(t) \) denotes the \( i^{th} \) time-dependent variable

- The ML procedure is used to estimate the regression coefficients
- The model assumes that the hazard at time \( t \) depends on the value of \( X_i(t) \) at the SAME time \( t \)
- We can modify the model to allow lag-time

4 The Hazard Ratio for the Extended Cox Model

Extended hazard ratio:
\[ \hat{HR}(t) = \frac{\hat{h}(t, X^*(t))}{\hat{h}(t, X(t))} = \exp\left[ \sum_{i=1}^{p_1} \hat{\beta}_i [X_i^* - X_i] + \sum_{i=1}^{p_2} \hat{\delta}_i [X_i^*(t) - X_i(t)] \right] \]

The HR depends on time. That’s why the PH assumption is not satisfied.

5 Assessing Time-independent Variables that do not satisfy the PH Assumption

General formula for assessing the PH assumption:
\[ h(t, X(t)) = h_0(t) \cdot \exp\left[ \sum_{i=1}^{p_1} \beta_i X_i + \sum_{i=1}^{p_2} \delta_i X_i g_i(t) \right] \]

Here the \( g_i(t) \) is a function of time. It is important which form we choose for \( g_i(t) \) in the model.

We do a test for assessing the PH assumption using the Likelihood ratio test
\[ LR = -2 \log(L_{PH \text{ model}}) - (-2 \log(L_{ext. Cox \text{ model}})) \sim \chi^2_p \text{ under } H_0 \]

Null hypothesis \( H_0: \delta_1 = \cdots = \delta_p = 0 \)

If the test is significant then the extended Cox model is preferred.

We can choose \( g_i(t) \) as a heaviside function
\[ g_i(t) = \begin{cases} 1 & \text{if } t \geq t_0 \\ 0 & \text{if } t < t_0 \end{cases} \]

In a model, we can use one or more heaviside functions. If we use heaviside functions, the HR yields constant values for different time intervals.
6 An Application of the Extended Cox Model: Treatment of Heroin Addiction

We compare two methadone maintenance clinics. Clinic 2 has always higher retention probabilities than clinic 1. The difference is very significant after one year of treatment. Because the two curves in the -ln(-ln(S)) plot are not parallel, the variable clinic doesn’t satisfy the PH assumption. Two extended Cox models were considered:

- Heaviside functions to obtain two distinct hazard ratios. One for less than one year and the other for greater than one year
- A time-dependent variable that allows for the two survival curves to diverge over time

7 The Extended Cox Likelihood

Example:

<table>
<thead>
<tr>
<th>TIME</th>
<th>STATUS</th>
<th>SMOKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barry</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Gary</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Harry</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Larry</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

Cox PH model: \( h(t) = h_0(t)e^{β_1SMOKE} \)

Cox Likelihood:

\[
L = \frac{h_0(2)e^{β_1}}{h_0(2)e^{β_1} + h_0(2)e^0 + h_0(2)e^0 + h_0(2)e^{β_1}} \times \frac{h_0(3)e^0}{h_0(3)e^0 + h_0(3)e^0 + h_0(3)e^{β_1}} \times \frac{h_0(8)e^{β_1}}{h_0(8)e^{β_1}}
\]

Cox extended model: \( h(t) = h_0(t)e^{β_1SMOKE+β_2SMOKE×TIME} \)

Extended Cox Likelihood:

\[
L = \frac{h_0(2)e^{β_1+2β_2}}{h_0(2)e^{β_1+2β_2} + h_0(2)e^0 + h_0(2)e^0 + h_0(2)e^{β_1+2β_2}} \times \frac{h_0(3)e^0}{h_0(3)e^0 + h_0(3)e^0 + h_0(3)e^{β_1+4β_2}} \times \frac{h_0(8)e^{β_1+8β_2}}{h_0(8)e^{β_1+8β_2}}
\]
References

