IT’S TIME TO REASSESS TRADITIONAL TIME-DEPENDENT REGRESSION METHODS

Christopher M. Blanchette, PhD, IMS Health
Alex Exuzides, PhD, ICON Late Phase & Outcomes Research
Roger Luo, PhD, IMS Health

Agenda

• Traditional Time Dependent Models – Christopher Blanchette
• Marginal Structural Models as an Alternative to Cox-proportional Hazard Model – Roger Luo
• Prediction of Mortality in the Presence of Time-Depended Covariates: An Application – Alex Exuzides

EU ISPOR: W8; Nov 6, 2012
A Typical Longitudinal Data Structure

- **At baseline (t=0):**
  - Time-invariant covariates, e.g., demographic information
  - Time-variant covariates measured at baseline
  - Initial treatment

- **During follow-up period (t>0):**
  - Time-variant covariates
  - Time-variant treatments
  - Time-variant outcomes (survival type of outcome can be treated as repeated indicators of outcome)
Research Question

• What is the true effect of treatment on outcome
  – Example: whether taking long-acting beta2-adrenergic agonist (LABA) lower the risk of hospitalization among chronic obstructive pulmonary disease (COPD) patients.
  – Example: estimate the causal effort of zidovudine on the survival of human immuno-deficiency virus-positive patients.

Research Questions (cont’d)

• Straightforward, if treatment does not change over time, i.e., static treatment
• However, estimates would be biased if treatment changes over time:
  • Intermediate confounding effects are not fully controlled if ignoring time-varying components
  • The true treatment effect cannot be unbiasedly estimated from the total effects on the outcomes.
Cox Proportional Hazards Model

- A popular model for survival type of outcomes
- A model for the hazard rate \( h(t) \), i.e., the ratio of the probability density function \( f(t) \) to the survival function \( S(t) \)
  \[ h(t) = \frac{f(t)}{S(t)} \]
- Model \( h(t) \) as a function of covariates
  \[ h(t) = h_0(t)\exp(X\beta), \] in which \( h_0(t) \) is the baseline hazard rate, i.e., the hazard rate when \( X = 0 \)

Cox Proportional Hazards Model (cont’d)

- A key assumption is the proportional hazards assumption
  - For two subjects with covariate \( X_1 \) and \( X_2 \), the hazards ratio is
    \[ \frac{h_1(t)}{h_2(t)} = \frac{h_0(t)\exp(X_1\beta)}{h_0(t)\exp(X_2\beta)} = \exp((X_1-X_2)\beta), \] which does not change over time
- Test of proportional hazards assumption
  - Plot \( \log(-\log(\text{survival})) \) versus log of survival time graph
    - Parallel lines if assumption is satisfied
  - Including treatment by time interaction in the model
    - Significant interaction term indicates violation of the assumption
  - Test and graph based on the Schoenfeld residuals
    - A non-zero slope of the residuals over time indicates violation of the assumption
Benefit of Cox Proportional Hazards Model

- Handle censoring naturally compared to generalized linear models
  - Assume random censoring, i.e., censoring is random conditioning on the covariates
- Appropriate for estimating the effects in the next time-period

Cox Proportional Hazards Model with time-varying components

- An improvement to the static Cox model is to include time-updated covariates in the model
  - The time-updated covariate information has to be incorporated through the programming statement within the Cox model procedure, i.e., PROC PHREG.
- Alternatively, can fit discrete time logistic regression model
  - Model the outcome at each time point and repeat over time
- Limitation: still cannot estimate the joint effect of treatments over an extended time period
Alternatives to Cox Proportional Hazard Models

- Marginal Structural Models
- Incorporation of Accelerated Failure Time Models (Weibull)

Marginal Structural Models as an Alternative to Cox Proportional Hazard Models

Roger Luo, PhD
IMS Health
Time-dependent Confounding

- Time dependent confounding occurs if
  - CD4 count confounds the association between Zidovudine2 and mortality3
  - CD4 is also on the causal pathway between Zidovudine1 and mortality3

- Standard regression methods are biased when estimating the joint effects of Zidovudine1 and Zidovudine2 on mortality3 whether or not controlling for CD4 count

Marginal Structural Models

- Generalize standard regressions (e.g., proportional hazards/repeated measures linear regression)
- Use inverse probability weighting to control for confounding
- Models can be fit in two steps using standard software
  - First step is to fit a model for treatment and get the estimated probability of treatment received
  - Second step is to fit the outcome model in a sample weighted by inverse probability of treatment received
- Limitation:
  - MSM doesn’t control for unmeasured confounders
  - Often have large weights due to small estimated probability of treatment received
    - Weight truncation is often required to improve efficiency
    - Bias and variance trade off
**Data: Structural Tree Graph**

- **Zidovudine 1**: On 4,000
  - **CD4: Low 3,000**
  - **CD4: High 1,000**
  - **Zidovudine 2**: On 2,000
    - **Zidovudine 2**: Off 1,000
  - **Zidovudine 2**: On 500
    - **Zidovudine 2**: Off 500

- **Zidovudine 2**: Off 500
  - **CD4: Low 1,000**
  - **CD4: High 3,000**
  - **Zidovudine 2**: On 500
    - **Zidovudine 2**: Off 500

- **Mortality Risk**
  - 0.15
  - 0.20
  - 0.35
  - 0.40
  - 0.10
  - 0.15
  - 0.30
  - 0.35

**Traditional Cox Model without CD4 Count variables**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Traditional Cox</th>
<th>Cox with CD4</th>
<th>MSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.3100</td>
<td>0.1500</td>
<td>0.3000</td>
</tr>
<tr>
<td>tx1</td>
<td>-0.0433</td>
<td>0.0500</td>
<td>-0.0500</td>
</tr>
<tr>
<td>tx2</td>
<td>-0.0767</td>
<td>-0.0500</td>
<td>-0.0500</td>
</tr>
</tbody>
</table>
Revised Structural Tree Graph

- Calculate the probability of receiving the treatment at each time point

Revised Structural Tree Graph (cont’d)

- The weight for each subject is one over the multiplication of the probability of receiving treatment at each time point
Weighted Data Table

<table>
<thead>
<tr>
<th>Zidovudine&lt;sub&gt;1&lt;/sub&gt;</th>
<th>CD4</th>
<th>Zidovudine&lt;sub&gt;2&lt;/sub&gt;</th>
<th>N</th>
<th>wt</th>
<th>Wtd N</th>
<th>% Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Low</td>
<td>Yes</td>
<td>2,000</td>
<td>3</td>
<td>6,000</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>1,000</td>
<td>6</td>
<td>6,000</td>
<td>20</td>
</tr>
<tr>
<td>High</td>
<td>Yes</td>
<td>500</td>
<td>4</td>
<td></td>
<td>2,000</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>500</td>
<td>4</td>
<td></td>
<td>2,000</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Yes</td>
<td>500</td>
<td>4</td>
<td>2,000</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>500</td>
<td>4</td>
<td>2,000</td>
<td>10</td>
</tr>
<tr>
<td>High</td>
<td>Yes</td>
<td>1,000</td>
<td>6</td>
<td></td>
<td>6,000</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>2,000</td>
<td>3</td>
<td></td>
<td>6,000</td>
<td>35</td>
</tr>
</tbody>
</table>

- Each subject contributes multiple copies in the weighted sample
- In the weighted sample, CD4 count is not associated with Zidovudine<sub>2</sub> so that it is not a confounder anymore

Marginal Table in Weighted Sample

<table>
<thead>
<tr>
<th>Zidovudine&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Zidovudine&lt;sub&gt;2&lt;/sub&gt;</th>
<th>N</th>
<th>% Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>8,000</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>8,000</td>
<td>25</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>8,000</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>8,000</td>
<td>30</td>
</tr>
</tbody>
</table>

- Zidovudine at time 1 is associated with 5% decreased risk of death
  - $(20\%-25\%)*0.5+(25\%-30\%)*0.5=-5\%$
- Zidovudine at time 2 is associated with 5% decreased risk of death
  - $(20\%-25\%)*0.5+(25\%-30\%)*0.5=-5\%$
Summary

- Standard Cox proportional hazards model is appropriate to estimate the effect of static or initial treatment assignment on outcome
- Estimating joint treatment effects requires to adjust for time-dependent confounding
- MSM can properly adjust for time-dependent confounding through inverse probability of treatment weighting

Prediction of Mortality in the Presence of Time-Depended Covariates: An Application

Alex Exuzides, PhD
ICON Late Phase & Outcomes Research
Research Goal

• Based on data from an observational study of disease D:
  – Develop a parametric model to predict mortality for future patients with disease D that have specific demographic and clinical characteristics.
  – Take into account patient trajectories over time for biomarkers $B_1, \ldots, B_k$ that are important predictors of disease progression.

Background

• In time-to-event studies, longitudinal measures are collected for important disease progression markers:
  – CD4 cell counts at different time points among HIV patients are related to time of death.
  – FEV1 and exacerbations measures among COPD patients are important predictors of disease progression.
• Using only the last available value of these measures in survival models discards important information from the longitudinal evolution.
Implementation Challenge

- The Cox Proportional Hazards model in SAS (PHREG) allows for longitudinal covariates to model survival:
  - Nonparametric, not suitable for mortality predictions.

- The Accelerated Failure Time model in SAS (LIFEREG) does not allow for longitudinal covariates to model survival:
  - A family of parametric models, suitable for mortality predictions.
Implementation Solution

- Use the Cox Proportional Hazards model in SAS (PHREG) with longitudinal covariates for $B_1, \ldots, B_k$ to estimate the coefficients for each covariate.

- Use the Weibull Accelerated Failure Time model in SAS (LIFEREG) to estimate the scale of the parametric distribution.

- In developing the prediction model for mortality, use the covariate coefficients from the PHREG and the scale from LIFEREG to compute the probability of survival.

### Results from the Weibull Model

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Parameter Estimate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B_1$</td>
<td>-0.0605</td>
<td>0.0201</td>
</tr>
<tr>
<td>$B_2$</td>
<td>-0.0528</td>
<td>0.0618</td>
</tr>
<tr>
<td>$B_3$</td>
<td>0.0024</td>
<td>0.0001</td>
</tr>
<tr>
<td>$B_4$</td>
<td>0.0103</td>
<td>0.0278</td>
</tr>
<tr>
<td>Age</td>
<td>-0.0442</td>
<td>0.0454</td>
</tr>
<tr>
<td>BMI</td>
<td>0.0807</td>
<td>0.0539</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>-0.0815</td>
<td>0.0507</td>
</tr>
<tr>
<td>Scale</td>
<td>0.8211</td>
<td></td>
</tr>
</tbody>
</table>
Results from the Cox Model

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Parameter Estimate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B_1$ (time-dependent)</td>
<td>-0.0805</td>
<td>0.1021</td>
</tr>
<tr>
<td>$B_2$ (time-dependent)</td>
<td>-0.0432</td>
<td>0.3451</td>
</tr>
<tr>
<td>$B_3$ (time-dependent)</td>
<td>0.0034</td>
<td>0.0001</td>
</tr>
<tr>
<td>$B_4$ (time-dependent)</td>
<td>0.0235</td>
<td>0.0363</td>
</tr>
<tr>
<td>Age</td>
<td>-0.0522</td>
<td>0.0472</td>
</tr>
<tr>
<td>BMI</td>
<td>0.0901</td>
<td>0.0639</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>-0.0632</td>
<td>0.0235</td>
</tr>
<tr>
<td>Scale</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Weibull Survival Function

$$S(t) = \exp\{-[te^{-\sum\beta X}]^{1/\sigma}\}$$
Weibull Model

Hybrid Cox/Weibull Model
Summary

- Ignoring the additional variability of patient trajectories over time when modeling survival can lead to biased estimates.

- Implement a hybrid approach:
  - A Cox Proportional Hazards model with time-dependent covariates to estimate all covariate effects.
  - A parametric survival model to estimate the scale/shape of the distribution for projections.
  - A combination of these estimates for projecting survival time.

Q & A