Using Stratified Cox Regression to Test Competing Risks

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Objectives

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- Introduce an analytic approach to jointly model the cause-specific hazard for two or more competing events
  - Specifically, the hypothesis testing of differential effects on the competing events
- Demonstrate the implementation of the Cause-specific Joint Model

Outline

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- Survival Analysis Review
  - Stratified Cox Regression
  - Competing Risk Analysis
  - Cause-specific Hazard
- Cause-specific Hazard Joint Modeling
  - Problem Statement
  - Formulation
  - Implementation
- REGARDS Example
- Conclusion

Survival Analysis Review

Survival Analysis Review

Definition: Survival analysis is a way to model time-to-event outcome while accounting for (mostly right) censoring that is non-informative and random.

- censoring: events of interest are not observed over the course of a study

Components:

- Outcome: time-to-event and censoring status (T_i, C_i)
- Survival function: $S(t) = Pr(T > t)$
- Cumulative incidence function: $F(t) = 1 - S(t) = Pr(T \leq t)$
- Hazard function:

$$h(t) = \lim_{\Delta t \to 0} \frac{Pr(t \leq T < t + \Delta t | T \geq t)}{\Delta t}$$

Cox Propotional Hazard Regression

- Assumption: the hazard are proportional
- Formulation:

$$h(t|x_i) = h_0(t)\exp(\beta x_i)$$

where $\exp(\beta)$ is the hazard ratio,
$h_0(t)$ is the baseline hazard function

- Hazard ratio (HR) ranges $(0,\infty)$,
  - HR > 1 means more likely to observe the event
  - HR < 1 means less likely to observe the event

Stratified Cox Proportional Hazard Regression

- Used when stratified analysis are required
- Additional assumption: the risk associated with an exposure are the same across all strata,
- Formulation:

$$h_j(t|x_i) = h_{0j}(t)\exp(\beta x_i),$$

where $h_{0j}(t)$ is the baseline hazard function for the j the strata. $exp(\beta)$ is the hazard ratio across all strata

Stratified Cox Regression Example

Race stratified analysis for CVD outcomes

- Research question: what is the effect of smoking on CVD risk among Blacks and Whites
- The hazard functions for different race groups are different because of the distinct baseline hazard function
- The estimate of hazard ratio associated with smoking is $\exp(\beta)$ for all race groups

Competing Risk Analysis

Definition: Competing risk exists when we have two or more mutually exclusive events of consideration

- either stroke or coronary heart disease (CHD)

Components:

- Outcome:(T_i, C_i, J_i), where $J_i \in \{1, 2(, \dots)\}$ for event types
- Two types of hazard
  - Cause-specific hazard
  - Sub-distribution hazard, AKA Fine-Grey method

Austin, Lee, and Fine (2016) stated "*subdistribution hazards models should be used for developing clinical prediction models and risk-scoring systems for survival outcomes, whereas cause-specific hazard models may be more appropriate for addressing epidemiological questions of etiology.*"

Cause-specific hazard models

- Used when studying etiology of diseases (Lau, Cole, and Gange 2009)
- Fitting Cox models by focusing on the events of primary interest and treating the competing events as censored.
- Formulation:

$$h_J(t|x_i) = h_{0,J}(t)\exp(\beta_J x_i)$$

where J denotes different types of events

- Animated demonstration in PowerPoint

Cause-specific Hazard Joint Modeling

REGARDS Example

- Events of Interest: Stroke / CHD
- Exposure of Interest: Smoking status (at baseline)
- Research Question:
  - How does smoking affect the risk of stroke considering competing risk of CHD?

$$h_{Stroke}(t|x_i) = h_{0,Stroke} \exp(\beta_{Stroke} x_i)$$

  - How does smoking affect the risk of CHD?

$$h_{CHD}(t|x_i) = h_{0,CHD} \exp(\beta_{CHD} x_i)$$

  - Does smoking affect the risk of stroke the same way as the risk of CHD

Problem Statement

How to test if the impact on the risks from an exposure are the same for all events?

- The original cause-specific hazard model requires two models, one for each type of events by treating the other as censored outcome
- Statistically, the hazard ratio of exposures are not directly comparable

Cause-specific Hazard Joint Model

- Lunn and McNeil (1995) proposed a joint modeling approach to estimate the cause specific hazards for both events using stratified Cox regression
- Formulation for two event types:

$$h_J(t|x_i) = h_{0J}(t)\exp(\beta x_i + \beta'\delta_i x_i)$$

where δ is an indicator variable: $\delta_i = 1$ if J=1 and $\delta_i = 0$ if J=2

Implementation

- Basic idea:
  1. Data augmentation
     - Duplicate each event (both types) by treating the duplication as censored outcome
     - Duplicate the censored events
     - Create interaction term of event type & exposure
  2. Stratified Cox model based on event type

$$h_{CHD}(t|x_i) = h_{0,CHD} \exp(\beta x_i + \beta' \delta_i x_i)$$

$$h_{Stroke}(t|x_i) = h_{0,Stroke} \exp(\beta x_i + \beta' \delta_i x_i)$$

  3. Test the interaction term β'
- Animated demonstration in PowerPoint

Toy Example

Toy Example

- Events of Interest: Stroke / CHD
- Exposure of Interest: Smoking status (at baseline)
- Covariates: Age, Race
- Research Question:
  - How does smoking affect the risk of stroke considering competing risk of CHD?
  - How does smoking affect the risk of CHD?
  - Does smoking affect the risk of stroke the same way as the risk of CHD

Cause-specific Hazard for Stroke

Characteristic	**HR**	**95% CI**	**p-value**
Current Smoker	1.57	1.34, 1.84	<0.001
Age (years)	1.07	1.06, 1.07	<0.001
Race (Whites Vs Blacks)	0.85	0.76, 0.95	0.004

Cause-specific Hazard for CHD

Characteristic	**HR**	**95% CI**	**p-value**
Current Smoker	2.07	1.77, 2.42	<0.001
Age (years)	1.06	1.05, 1.07	<0.001
Race (Whites Vs Blacks)	0.97	0.86, 1.10	0.6

Joint Model

Characteristic	**HR**	**95% CI**	**p-value**
Current Smoker	2.07	1.77, 2.42	<0.001
Stroke*Smoker	0.76	0.61, 0.94	0.014
Age	1.06	1.05, 1.07	<0.001
Stroke*Age	1.01	1.00, 1.02	0.066
Race (Whites Vs Blacks)	0.97	0.86, 1.10	0.6
Stroke*Race(Whites Vs Blacks)	0.87	0.74, 1.03	0.11

Experience

- Include the interaction for all variables in the model, including strata-covariates interactions
- Need extra cautious when interpreting the cause-specific hazard ratios
  - Understand which strata is the reference level
- Possible to extend to exposures that are more than 2 levels, or more than two competing events
  - Extra effort to setup the design matrix, i.e. the interaction terms

Conclusion

Conclusion

- Review the basic concepts about survival analysis and competing risk analysis
  - Cause-specific hazard, preferably used in epidemiological study
- Cause-specific hazard joint model proposed by Lunn and McNeil (1995)
  - Simultaneously models two or more competing events
  - Stratified Cox Regression with a data augmentation step
  - Test the effect change in competing risks via statistical interaction
- Demonstrate the implementation
  - Results are the same
  - Cautious about the reference level

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Reference

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