Introduction
Statistics 255 - Survival Analysis

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Logistics and Contact Information

Lectures: Tuesday and Thursday, 2:00-3:20, Room: MSTB 110

Discussion: Tuesday, 4:00-4:50, Room: MSTB 114


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Office hours: Wednesday 11:00-12:00,
Thursday 11:00-12:00 &
or by appointment
Description and Textbooks

Co-requisites: Statistics 202 or 211 or equivalent, or permission of instructor

Description: This course will provide an introduction to the principles and methods for the analysis of time-to-event data. While some theoretical statistical detail is given (at the level appropriate for a MS student in statistics), the primary focus will be on data analysis.

Description and Textbooks

References:


Examples that are presented in class will use the R statistical software package.

R is free and can be installed on multiple platforms and is available in the ICS computer lab (ICS 364).

I (highly) recommend that you use R but you may choose to use any other software package that allows you to complete the assigned coursework.
Assignments, Exams and Grading

Homework: There will be a total of 5-6 homework assignments. Assignments will typically be due 1-1.5 weeks from the date they are handed out.

Midterm Exam: Tentatively scheduled for Thursday, February 11th. The exam will be in-class (closed-book, closed-note), and will cover material through the Tuesday, February 9th lecture.

Final Exam: The final exam is scheduled for Thursday, March 17th. The final exam will be a take-home handed out on Tuesday, March 8th and due on Thursday, March 17th by 3:30pm.
Assignments, Exams and Grading

Grading: Homework: 35%
Midterm: 30%
Final: 35%
**Stat 255 Course Outline**

*We will study methods (some theory and mostly practice) for censored data*

**Part I - One- and two-sample problems (3 weeks)**

- Introduction to censored data and types of censoring
  - Choice of time scale and reasons for censoring
  - Independence between censoring and failure time assumption
- Summary measures in the censored data setting
  - Survival distribution (Life-table, Kaplan-Meier)
  - Cumulative hazard (Nelson-Aalen)
  - Hazard Function (Life-table, smoothing)
- Comparison of two or more survival distributions
  - The logrank test and weighted versions
  - K-sample logrank statistics and stratified tests
Part II - Proportional hazards regression (3.5 weeks)

- Introduction to the model
  - Partial likelihood
  - Modeling continuous and categorical covariates
  - Model interpretation
  - Survival and cumulative hazard estimation
  - Stratification

- Extensions of the proportional hazards model
  - Time dependent effects / exposures
  - Time dependent stratification

- Model diagnostics
  - Residual diagnostics
  - Influence measures
Part III - Additional survival analysis techniques (3.5 weeks)

- Left truncation
  - Standardized mortality ratios (SMRs)
- Sampling from the risk set
  - Nested case-control designs
  - Nested case-cohort designs
- Multivariate survival data
  - Recurrent events
  - Correlated outcomes
  - Competing risks
- Parametric methods
  - Univariate
  - Regression (AFT)
- Sample size and power calculations for two-sample problems
Time to Event Data

Motivating Examples

- It is often of scientific interest to estimate the length of time to a given event and to determine how factors may be associated with this length of time

1. The Worcester Heart Attack Study considered the length of time from hospital discharge for acute myocardial infarction (MI) to death as a function of cohort year

2. Breslow & Day (Appendix D) considered the time from first employment to death from nasal cancer among Welsh Nickel Refiners as a function of age at first employment

3. Freireich et al (1963) compared the time to relapse between 6-mercaptopurine (6-MP) and placebo among children in remission from acute leukemia

4. The time to access survival among hemodialysis patients as a function of access type and the number of previous accesses
## Time to Event Data

### Choice of Time Scale

- **How do we measure time and when does the clock start ticking?**

- **This should be dictated by the scientific question of interest!**

<table>
<thead>
<tr>
<th>Scale</th>
<th>Origin</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calendar time</td>
<td>Birth of JC</td>
<td>Not usually meaningful</td>
</tr>
<tr>
<td>Study time</td>
<td>Diagnosis or treatment</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>Study time</td>
<td>First exposure</td>
<td>Epidemiology</td>
</tr>
<tr>
<td>Age</td>
<td>Birth (subject specific)</td>
<td>Epidemiology</td>
</tr>
</tbody>
</table>
## Examples: Choice of Time Scale

1. The Worcester Heart Attack Study
   - Time origin: Discharge from hospital

2. Welsh Nickel Refiners
   - Time origin: Date of first employment

3. 6-MP leukemia trial
   - Time origin: Entry into the study (clinical trial)

4. Access survival study
   - Time origin: Placement of access (could be multiple accesses)
Time to Event Data

Examples: Time to event

- Objective of survival analysis: Quantify and make inference about the time, $t$, from the origin to the event of interest

1. The Worcester Heart Attack Study
   - Time origin: Discharge from hospital
   - Event of interest: Mortality
   - Covariate of interest: Year of discharge

2. Welsh Nickel Refiners
   - Time origin: Date of first employment
   - Event of interest: Death from nasal cancer
   - Covariate of interest: Age at first employment
Time to Event Data

Examples: Time to event

3. 6-MP leukemia trial
   - Event of interest: Cancer relapse
   - Covariate of interest: Treatment with 6-MP

4. Access survival study
   - Time origin: Placement of access (could be multiple accesses)
   - Event of interest: Access failure
   - Covariate of interest: Type of access and number of previous accesses
### Censoring

#### Right censored data

- In general, not all subjects can be followed long enough to observe the event of interest on everyone.

  ⇒ Only know the last time at which they were still at risk without having the event.

#### Notation

- \( T = \text{time to failure (from origin)} \)
- \( C = \text{Censoring time} \)

#### Observed Data

- \( X = \min(T, C) \)
- Event indicator, \( \delta \), defined as

\[
\delta = \begin{cases} 
1, & X = T \\
0, & X = C < T 
\end{cases}
\]
Censoring

Right censored data

- Termination of study (funding, need to write report)
- Subject lost to follow-up (moves, refuses participation)
- Termination of treatment due to negative side effects of treatment
- Death due to an unrelated cause

Example

- Consider a clinical trial designed to last 4 years
- Patients enter into the trial at various time points
- Patients are followed to determine if they experience some event of interest (eg. death or stroke)
- At the completion of the trial, some patients will have experienced the event of interest and some will not
Censoring

Example: Administrative censoring

![Graph showing study time vs. patient number with censoring marks.](image-url)
Censoring

Right censored data

- The observed set of data from the previous example would be:

<table>
<thead>
<tr>
<th>(i)</th>
<th>(X_i) (observed survival time)</th>
<th>(\delta_i) (Failure indicator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1.6</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>3.1</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>3.9</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0.8</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>0.8</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>1.0</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1.0</td>
<td>1</td>
</tr>
</tbody>
</table>
## Types of censoring

### Type I censoring

- Refers to right censoring in which the event of interest is observed only if it occurs prior to some prespecified time, $C$

#### Example

A clinical trial designed to follow people for one year may censor each individual after one year of followup

- Censoring times may not all be the same
- For example, the censoring time may be the time between enrollment in a trial (staggered entry) and the fixed end of study (see the previous example on slide 1.17)
- This is often referred to as **administrative censoring** or **generalized Type I censoring**
- One reason why *time on study* is often more relevant than *calendar time*
Types of censoring

Type II censoring

- Refers to censoring that stems from ceasing followup immediately after the $r^{th}$ event has been observed (i.e. sampling to $D$ events)

Example

A clinical trial may be designed (powered) for 100 events, and a hypothesis test is performed at that time
Types of censoring

Random censoring

- Occurs when censoring is due to some unplanned or unexpected cause

Example

In a clinical trial considering the time to cancer progression as the primary endpoint, a patient ‘randomly’ withdraws from the study and refuses further evaluation

Q: Are we sure this is truly random censoring?
Types of censoring

**Left censoring**

- Refers to the case when knowledge of a failure time is less than some value replaces knowledge of the exact time.
- If an event happens before time $C_i$ we only know that the true failure time, $t$, is in the interval $(0, C_i)$.

**Example**

Suppose the primary endpoint for a childhood learning center study is the age at which a child is able to perform a specific task. Some children will already know how to perform the task when they enter the study, which means their learning time will be left censored.
Types of censoring

Double censoring

- Refers to the case when a combination of both left and right censoring may occur

Example

Consider the above example with administrative censoring due to end of study.
Types of censoring

Interval censoring

- Refers to the case where we only know that failure time $t$ in in some interval $(C_l, C_u)$

Example

A study periodically screens women for breast cancer. If a woman tests positive for cancer, we only know that cancer occurred in the interval between the previous screening and the current one.
## Types of censoring

<table>
<thead>
<tr>
<th>Truncation</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Refers to the case where certain subjects omitted from the data set (<em>selection bias</em>)</td>
</tr>
<tr>
<td>▶ <em>Left truncation</em>: May be caused because of delayed entry or because a subject has an event before the study starts</td>
</tr>
<tr>
<td>→ Medicare beneficiaries</td>
</tr>
<tr>
<td>→ $t_i$’s less than 65 years <em>are not observed</em></td>
</tr>
<tr>
<td>▶ <em>Right truncation</em>: Subjects who have not had an event are not recorded</td>
</tr>
<tr>
<td>→ Time from HIV infection to AIDS among blood transfusion recipients</td>
</tr>
<tr>
<td>→ Subjects diagnosed <em>with AIDS</em></td>
</tr>
<tr>
<td>→ $t_i$’s greater than study time <em>are not observed</em></td>
</tr>
</tbody>
</table>
Independence Assumption

**Independence assumption**

- $T$ and $C$ are statistically independent (possibly conditional on other covariates)

  → This assumption underlies (almost) all methods for survival data

**Critical Question**

For subject(s) censored at $C = t_c$, does the risk of failure for $t > t_c$ differ from that of subject(s) not censored at $C = t_c$?
Independence Assumption

Examples: Violation of independence assumption

- Administrative censoring – Independence assumption usually OK unless there are secular (calendar time) trends in survival or accrual

- Withdrawals before the end of the study period – MAY BE A PROBLEM!
  - Accidental deaths usually OK
  - Moves out of area (sicker patients unlikely to move)

- Competing risks (multiple causes of death/failure)
  - No basis for believing independence assumption
  - Recognize that cause specific failure rates pertain to particular set of study conditions and may not be generalizable
  - Not generally possible to remove other causes of death without affecting death rates from cause of interest