A Conceptual Approach to Survival Analysis

Laura Lee Johnson, Ph.D.
Statistician
National Center for Complementary and Alternative Medicine
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johnslau@mail.nih.gov
Submit your ideas for December 7 lecture!

- As of 13 November only a few verbal questions, no emailed examples or questions
- Examples due by Monday, 23 November 2009 to johnslau@mail.nih.gov
- Studies you want used as an example for study development
- Might be from the popular press, a protocol you are working on, from a journal (but I need to be able to research it)
Objectives

• “Conceptual Approach”
• Recognize some vocabulary used in survival analysis and a few commonly used statistical methods for time to event data in medical research
• Interpret Kaplan Meier graph
• Interpret a covariate from a Cox model
• Understand a few of the assumptions for basic types of survival models
Why Survival (Time to Event) Analysis

• New cancer treatment
  – Want to know if it extends a person’s life 5 months longer than current treatments
• Survival is about events and when they happen
  – Death, infection, MI, hospitalization
  – Recurrence of cancer after treatment
  – Marriage, soccer goal
  – Light bulb fails, computer crashes
  – Balloon filling with air bursts
Why Survival Analysis? Hypertension

- Treat it
  - Lower/Normal blood pressure (BP)
  - Want to extend healthy life, prevent heart attacks...events in time
- Follow people, see how many die and have events like MI and when
- What if Intervention lowers blood pressure but after 20+ years people die two years before a similar person not on medicine?
  - Goal accomplished?
  - COX 2 inhibitors
People with lower X live longer!

• Many times from an observational study
• Instigate a change in blood pressure, weight, something
  – Do you get a similar change in outcome?
  – Perhaps
People live too long to follow!

- We can only hope (and that they live well and feel great, are productive, and all that)

- Many surrogates
- Even more surrogates for events (in particular death)
- Sometimes follow people a long time
What is Survival

- Survival analysis deals with making inference about EVENT RATES
- Rate at $t = \text{Rate among those at risk at } t$
- Look at Median survival (50%) not Mean survival
  - Mean: need everyone to have an event
Outline

- How to Measure Time and Events
  - Truncation and Censoring
  - Survival and Hazard Functions
  - Competing Risks
  - Models and Hypothesis Testing
  - Example
  - Conclusions
What is a Model?

• Basic

\[ Y = \beta_0 + \beta_1 X_1 + \ldots + \beta_p X_p \]

– \( Y \) = outcome or response variable
– \( \beta \) = coefficient
– \( X \) = covariate, variable

• Survival

\[ \lambda(t) = \lambda_0(t) \exp\{ \beta_1 X_1 + \ldots + \beta_p X_p \} \]

– \( \lambda_0(t) \) = baseline hazard
– \( \beta_1, \ldots, \beta_p \) = regression coefficients
– \( X_1, \ldots, X_p \) = prognostic factors
Vocabulary

• Survival vs. time-to-event
• Outcome variable = event time
• Examples of events:
  – HIV positive test, AIDS defining event, Mother-Infant HIV transmission
  – Systolic blood pressure or Cholesterol below a cut
• BMJ 17 October 2009 article on follow-up of MIST trial: incidence of pregnancy
  – Time in years to first live birth after index miscarriage
Time Notation

- $t$: for time axis
  - $t = 0$ is the time origin
- $T$: random outcome variable
  - time at which event occurs
Vocabulary

- $t =$ time
  - Baseline = 0 months
  - 6, 12, 18, 24 months, etc.
- $S(t) =$ Survival at time $t$
- $P[ T \geq t ] =$ Probability Time of event is greater than time $t$
Define the Outcome Variable

• What is the event? (Death?)
• Where is the time origin? (Diagnosis?)
• What is the time scale? (Weeks? Years?)

• Then what?
  – Need to know the time the event occurs
  – May or may not use covariates
• Could do a logistic regression model
  – Yes/No outcome
  – Not focus of lecture
<table>
<thead>
<tr>
<th>Scale</th>
<th>Origin</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study time</td>
<td>Dx or Rx</td>
<td>Clinical Trials</td>
</tr>
<tr>
<td></td>
<td>First Exposure</td>
<td>(Occupational)</td>
</tr>
<tr>
<td>Age</td>
<td>Birth (subject)</td>
<td>Epidemiology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidemiology</td>
</tr>
</tbody>
</table>
Treatment for a Cancer

- Event = death
- Time origin = date of surgery
- Time scale = time (months)
- $T = \text{time from surgical treatment to death}$
- Graph = $P[T \geq t]$ vs $t$
Months since surgery

Proportion Alive
Example Numbers

• $S(9) = P[T \geq 9] = 0.25$
• 25% is the probability the time from surgical treatment to death is greater than 9 months
• “9 month post-resection survival is 25%” = Plain English
• $0 \leq S(t) \leq 1$
Herpes Example

- Recurrence of Herpes Lesions After Treatment for a Primary Episode
- Event = recurrence
  - needs well defined criteria
- Time origin = end of primary episode
- Time scale = months from end of primary episode
- $T = \text{time from end of primary episode to first recurrence}$
Toxin Effect on Lung Cancer Risk

- Occupational exposure at nickel refinery
- Event = death from lung cancer
- Origin = first exposure
  - Employment at refinery
- Scale = years since first exposure
- $T =$ time: first employed to death from LC
Population Mortality

- Event = death
- Time origin = date of birth
- Time scale = age (years)
- T = age at death
Volume of Air a Balloon Can Tolerate

- Event = balloon bursts
- $t = \text{ml of air infused}$
- Origin = 0 ml of air in the balloon
- $T = \text{ml of air in balloon when it bursts}$
Unique Features of Survival Analysis

- Event involved
- Progression on a dimension (usually time) until the event happens
- Length of progression may vary among subjects
- Event might not happen for some subjects
Sample Size Considerations

• Event may not ever happen for some subjects
  – Sample sizes based on number of events
  – Work backwards to figure out # of subjects
• Covariates must be considered (age, total exposure, etc)
Notation

- $T =$ event time
- $T^* =$ observation time
  - $T$ if event occurs
  - Follow-up time otherwise
- $\partial =$ failure indicator
  - 1 if $T^* = T$
  - 0 if $T^* < T$
  - “censor” or “censor indicator”
Outline

✓ How to Measure Time and Events

➢ Truncation and Censoring
  • Survival and Hazard Functions
  • Competing Risks
  • Models and Hypothesis Testing
  • Example
  • Conclusions
Truncation and Censoring

- **Truncation** is about *entering* the study
  - Right: Only sample those with Event of interest (cancer registry) (underestimate)
  - Left: short survival may be overlooked (>65 years of age) (overestimate)
- **Censoring** is about *leaving* the study
  - Right: Incomplete follow-up (common)
  - Left: Observed time > survival time (know the subject exists)
- Independence is key
Left Truncation

• Mention more in epi vs medical studies
  – Medical: zero-out at time of dx/tx
• Key Assumption
  – Those who enter the study at time t are a random sample of those in the population still at risk at t
  – Allows one to estimate the hazard function \( \lambda(t) \) in a valid way
• Who is the audience
Censoring

- Incomplete observations
- Right
  - Incomplete follow-up
  - Common and Easy to deal with
- Left
  - Event has occurred before $T_0$, but exact time is unknown
  - Not easy to deal with
Left Censoring

- Age smoking starts
  - Data from interviews of 12 year olds
  - 12 year old reports regular smoking
  - Does not remember when he started smoking regularly
- Study of incidence of CMV infection in children
  - Two subjects already infected at enrollment
One Form of Right Censoring: Withdrawals

- Must be unrelated to the subsequent risk of event for ‘independent censoring’ to hold
- Accidental death is usually ok
- Moves out of area (moribund unlikely to move)
Types of Censoring

- **Type I censoring**
  - $T^*$ same for all subjects
  - Everyone followed for 1 year

- **Type II censoring**
  - Stop observation when a set number of events have occurred
  - Replace all light bulbs when 4 have failed

- **Random censorship**
  - Our focus, more general than Type I
Key Assumption: Independent Censoring

- Those still at risk at time t in the study are a random sample of the population at risk at time t, for all t

- This assumption means that the hazard function ($\lambda(t)$) can be estimated in a fair/unbiased/valid way
Independent Censoring: If you have Covariates

• Censoring must be independent *within* group
  – Censoring must be ‘independent’ given X
  – Censoring can depend on X
• Among those with the same values of X, censored subjects must be at similar risk of subsequent events as subjects with continued follow-up
• Censoring can be different across groups
Age Example

• Early in trial older subjects are not enrolled
• Condition on age: ok
• Do not condition on age: the estimates will be biased because censoring is not independent
Take Away: Study Types

- **Clinical studies**
  - Time origin = enrollment, treatment begins
  - Time axis = time on study
  - Right censoring common

- **Epidemiological studies**
  - Time axis = age
  - Right censoring common
  - Left truncation common
Bottom Line

• Standard methods to deal with right censoring and left truncation
• Key assumption is that those at risk at t are a random sample from the population of interest at risk at t
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Survival Function

- \( S(t) = P[T \geq t] = 1 - P[T < t] \)
- Plot: Y axis = % alive, X axis = time
- Proportion of population still without the event \textit{by time t}
Survival Curve

Proportion Alive

Months since surgery
Survival Function in English

• Event = death, scale = months since Rx
• “$S(t) = 0.3$ at $t = 60$”
• “The 5 year survival probability is 30%”
• “70% of patients die within the first 5 years”

• Everyone dies $\rightarrow S(\infty) = 0$
Hazard Function

- Incidence rate, instantaneous risk, force of mortality
- $\lambda(t)$ or $h(t)$
- Event rate at $t$ among those at risk for an event
- Key function
- Estimated in a straightforward way
  - Censored
  - Truncated
Hazard Function in English

- Event = death, scale = months since Rx
- “$\lambda(t) = 1\%$ at $t = 12$ months”
- “At 1 year, patients are dying at a rate of 1\% per month”
- “At 1 year the chance of dying in the following month is 1\%”
Hazard Function: Instantaneous

- 120,000 die in 1 year
- 10,000 die in 1 month
- 2,500 die in a week
- 357 die in a day
- Instantaneous: move one increment in time
Survival Analysis

• Models mostly for the hazard function
• Accommodates incomplete observation of T
• Censoring
  – Observation of T is ‘right censored’ if we observed only that T > last follow-up time for a subject
Typical Intervention Trial

- Accrual into the study over 2 years
- Data analysis at year 3
- Reasons for exiting a study
  - Died
  - Alive at study end
  - Withdrawal for non-study related reasons (LTFU)
  - Died from other causes
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Competing Risks

- Multiple causes of death/failure
- Special considerations of competing risk events described in the literature
- Example:
  - event = cancer
  - death from MI = competing risk
- No basis for believing the independence assumption
Competing Risks

- Interpretation of $\lambda(t) = \text{"risk of cancer at } t\text{ when the risk of death from MI does not exist"}$ isn’t practically meaningful.
- Rather, interpret $\lambda(t) = \text{"risk of cancer among those at risk of cancer at } t\text{"}$
  - This will exclude MI deaths (if you are dead from an MI you are not at risk of cancer) and that is ok.
Polar Bear Club Death Rates (fiction)

• Annual death rates
  – 3% taking dip 1Jan in Lake Michigan
  – 2% Males all other causes
  – 1% Female all other causes

• Over a decade
  – 25% of women died from taking a dip in Lake Michigan 1 Jan
  – 24% of men died from taking a dip in Lake Michigan 1 Jan
Polar Bear Club Death Rates (fiction)

• Why does it harm women?
• Over a decade
  – 33.5% of women died from all other causes
  – 40% of men died from all other causes
• There are more women to harm
• People die of something
  – Which means they cannot die from something else
Bottom Line

• We make inference about $\lambda^{\text{obs}}(t) = \text{event rate among subjects under observation at } t$

• We can interpret it as $\lambda(t) = \text{event rate among subjects with } T \geq t$, if censoring is independent
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Kaplan Meier

- One way to estimate survival
- Nice, simple, can compute by hand
- Can add stratification factors
- Cannot evaluate covariates like Cox model
- No sensible interpretation for competing risks
### Kaplan Meier

- Multiply together a series of conditional probabilities

<table>
<thead>
<tr>
<th>Time $t_i$</th>
<th># at risk</th>
<th># events</th>
<th>Est. survival = $\hat{S}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>0</td>
<td>$1.00$</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>2</td>
<td>$[1-(2/20)]*1.00=0.90$</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>0</td>
<td>$[1-(0/18)]*0.90=0.90$</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>1</td>
<td>$[1-(1/15)]*0.90=0.84$</td>
</tr>
<tr>
<td>13</td>
<td>14</td>
<td>2</td>
<td>$(1-(2/14)]*0.84=0.72$</td>
</tr>
</tbody>
</table>
Kaplan Meier Curve
Kaplan Meier Estimator

• One estimate of S(t)
  – Use the same idea when looking at 1- S(t)
• Need independent censoring
  – If high risk subjects enter the study late then early on the K-M curve will come down faster than it should
• Censored observations provide information about risk of death while on study
• What are those little hash marks on the curves? Mark times people were censored
Kaplan Meier

- Just the outcome is in many models
- One or more stratification variables may be added
  - Intervention
  - Gender
  - Age categories
- Quick and Dirty
How to Test? At a Given Time

- $H_0: S_1(t) = S_2(t)$
- Form test statistic

$$Z = \frac{\hat{S}_1(t) - \hat{S}_2(t)}{\sqrt{\sigma^2 \hat{S}_1(t) + \sigma^2 \hat{S}_2(t)}}$$

- “Arbitrary time” – choosing $t$ post hoc
- Not using all of the data
Inference

• For single event data inference about rates → inference for \( S(t) \)
  – No time dependent covariates, no recurrent events, no competing risk events
• Logrank statistics compare event rates and allow the same generality as right censoring, left truncation
Log Rank

- $H_0: S_1(.) = S_2(.)$
- Test overall survival
- 2 independent samples from the same population
- Observed # events vs. Expected #
- Software; statistician should check
- Some variations and some assumptions
Log Rank

- Confounding
- Are prognostic factors balanced between treatment groups?
- Can see a difference using logrank, but just bias
Stratified Log Rank

- Compare survival within each stratum
- Essentially perform test within each stratum
- Can prognostic factor be categorized?
- Enough people per stratum?
- Loss of power
- Significance test, no estimates of difference
Preventing Mother-Infant HIV Transmission (D.O. Dixon, NIAID)

- Zidovudine slowed progression of HIV in adults with advanced disease
- AIDS Clinical Trials Group Protocol 076 designed to assess safety and efficacy of Zidovudine in preventing transmission of HIV from infected (not advanced) women to their babies
- Powered to detect 33% reduction in transmission rate through 78wk of baby’s life (projected rate=30%)
At First Interim Analysis
(1/3 of projected infant infections)

P = 0.00006

Weeks

Placebo
Zidovudine

0 24 48 72

Probability of Transmission (%)
Proportional Hazards: Cox

- Cox Proportional Hazards model
  \[ \lambda(t) = \lambda_0(t) \exp\{ \beta_1 X_1 + \ldots + \beta_p X_p \} \]
- \( \lambda_0(t) \) = baseline hazard
- \( \beta_1, \ldots, \beta_p \) = regression coefficients
- \( X_1, \ldots, X_p \) = prognostic factors
- \( \beta = 0 \rightarrow \) hazard ratio = 1
  - Two groups have the same survival experience
- \( e^{\beta} \) = relative rate (relative risk) (RR)
Cox Proportional Hazards Model

- Add covariates to the model
- No need to stratify
- Change in a prognostic factor → proportional change in the hazard (on the log scale)
- Statistical software
- Can test the effect of the prognostic factor as in linear regression - $H_0: \beta=0$
Cox Model for Event Rates

• Provides a framework for making inference about covariate effects
• Semi-parametric
  – $\lambda_0(t)$ completely unspecified
• Multiplicative - $e^{\beta x}$
  – Effect of covariate is to multiply the rate by a factor
Cox cont.

- Requires either that
  - RR is constant over time (proportional hazards), or
  - That we model RR over time
- Allows time-dependent covariates and stratification factors
Age Example

• Early in trial older subjects are not enrolled
• If age is not in the Kaplan Meier then the KM estimate is biased because censoring is not independent
• Put age in the Cox model – conditioned on age; ok
Age Example (cont.)

• If I follow everyone for 1 year, am I ok?
• Not necessarily
  – The study is not proportional by age to the population risk set
  – Could try to over sample older people later in the study to make the final study more correctly proportional
    • Easier to condition on age?
Testing Proportional Hazards

- $\lambda(t) = \lambda_0(t) \exp\{ \beta_1 \text{age} + \beta_2 \text{drug} \}$
- $\exp\{ \beta_1 \text{age} + \beta_2 \text{drug} + \beta_3 \text{age} \times \ln(t) + \beta_4 \text{drug} \times \ln(t) \}$
- Look at p-values associated with $\beta_3$ and $\beta_4$ (Wald tests)
- Do a partial likelihood ratio test comparing the two models
- Look at Schoenfeld residual plots
# Testing Proportional Hazards

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coef</th>
<th>SE</th>
<th>P-value</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>0.58</td>
<td>0.25</td>
<td>0.020</td>
<td>(0.09, 1.1)</td>
</tr>
<tr>
<td>Age</td>
<td>0.18</td>
<td>0.03</td>
<td>&lt;0.001</td>
<td>(0.12, 0.25)</td>
</tr>
<tr>
<td>Drug</td>
<td>0.57</td>
<td>0.25</td>
<td>0.023</td>
<td>(0.08, 1.1)</td>
</tr>
<tr>
<td>Age</td>
<td>0.19</td>
<td>0.03</td>
<td>&lt;0.001</td>
<td>(0.12, 0.26)</td>
</tr>
<tr>
<td>Drug*ln(t)</td>
<td>0.002</td>
<td>0.16</td>
<td>0.988</td>
<td>(-0.32, 0.31)</td>
</tr>
<tr>
<td>Age*ln(t)</td>
<td>0.007</td>
<td>0.02</td>
<td>0.716</td>
<td>(-0.03, 0.05)</td>
</tr>
</tbody>
</table>
### Testing Proportional Hazards

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coef</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>4.24</td>
<td>0.61</td>
<td>&lt;0.001</td>
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<tr>
<td>Age</td>
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<td>0.03</td>
<td>&lt;0.001</td>
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<tr>
<td>Drug</td>
<td>8.98</td>
<td>1.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.19</td>
<td>0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug*ln(t)</td>
<td>2.71</td>
<td>0.84</td>
<td>0.001</td>
</tr>
<tr>
<td>Age*ln(t)</td>
<td>0.01</td>
<td>0.02</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Time-Dependent Survival Curves

• Failure to account for change in exposure/treatment over time
  – Usually assume there is no change
  – Think about HAART example
• Stanford Heart Transplant Study (1971)
  – End-stage heart disease
  – Not responding
  – Seeking transplant
Heart Transplant Study

- N=100
- 27 / 31 (87%) without transplant died
- 45 / 69 (65%) with transplant died
- Exposure: Transplant yes/no
- Outcome: time to death
- Time origin: study entry
Fixed-Effect or Time Independent

- Patients classified as ever/never receiving transplant during study

![Time-Invariant KM Plot](chart.png)
Kaplan Meier

Proportion Surviving

Survival Time

Ever received transplant

Never received transplant
Timing of the Transplant?

Sample of Patients from Stanford Heart Transplant Study

Patient ID

Follow-up Time (days)

0 20 40 60 80 100 120 140 160

No Transplant

Transplant

NCCAM
Problem: Time Dependent Dataset

- Total follow-up time (days)
- Time of transplant (days)
  - Missing = no transplant
- Transplant status (0=no, 1=transplant)
- End of time interval for given transplant status (days)
- Censoring (0=alive, 1=dead)
- Patient ID
Effect of Transplant on Survival?

Time-Varying KM Plot

At risk:

No transplant: 99 6 2 1 1 1 1 1
Transplant: 0 33 24 18 14 8 6 4

Probability

Follow-up Time (days)

transplant = No transplant  transplant = Transplant
Take Home

- Choose the right method and test
- Kaplan Meier – simple
- Logrank tests – useful, potentially misleading
- Cox Proportional Hazards – workhorse
- Not everything is proportional – check
- Time matters
- Changes in protocol matter
Outline

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➢ Example

• Conclusions
Example

- Randomized clinical trial at Mayo: survival of patients with liver cirrhosis (NEJM 1982)
- Two year survival probability of 0.88, calculated with Kaplan Meier
- Compare a new treatment, D-penicillamine with placebo
Trial Information

- Data collected at randomization
  - Presence/absence of ascites
  - Prothrombin time in seconds -10
- Cox model
- \( \lambda(t) = \lambda_0(t) \exp\{-0.135 X_{\text{TRT}} + 1.737 X_A + 0.346 X_P\} \)
How to say it in English

- $\lambda(t) = \lambda_0(t) \exp\{-0.135 X_{\text{TRT}} + 1.737 X_A + 0.346 X_P\}$
- $X_{\text{TRT}}$: 1 = D-penicillamine, 0 = placebo
- $X_A$: 1 = ascites, 0 = no ascites
- $X_P$: Prothrombin time – 10
  – Continuous, in seconds
- $\lambda_0(t)$ is the event rate at time $t$ in the placebo arm for subjects without ascites with a prothrombin time of 10 seconds
$\lambda(t) = \lambda_0(t) \exp\{-0.135 \times X_{TRT} + 1.737 \times X_A + 0.346 \times X_P\}$

- Relative rate of death two years post randomization for a subject on this trial who received the new treatment, had ascites at randomization and a prothrombin time of 10 seconds compared to a similar subject who received placebo?
- $RR = \exp\{-0.135\} = 0.87$
\[ \lambda(t) = \lambda_0(t) \exp\{-0.135 \, X_{\text{TRT}} + 1.737 \, X_A + 0.346 \, X_P\} \]

\[ \frac{\lambda_{\text{person1}}(t)}{\lambda_{\text{person2}}(t)} = \frac{\lambda_0(t) \exp\{-0.135 \times 1 + 1.737 \times 1 + 0.346 \times 0\}}{\lambda_0(t) \exp\{-0.135 \times 0 + 1.737 \times 1 + 0.346 \times 0\}} = \]

\[ e^{\frac{-0.135 \times 1.737}{0 \times 1.737}} = \]

\[ \exp\{-0.135\} = 0.87 \text{ is the relative rate of death for subjects who received treatment compared to those who received placebo} \]
RR at Three Years?

- Relative rate does not vary with time according to the proportional hazards model.
- At the years the previously described RR is also $\exp\{ -0.135 \}$
- Can work out RR for lots of other subject comparisons
But…

- Physicians were initially reluctant to enter patients with ascites on the trial because of potential toxicity concerns.
- After about a year and a half recruitment became more representative of the clinic population.
How does this Effect the Validity of the Kaplan Meier Estimator?

• Censoring is not independent
• At large $t$, the risk sets will not include patients with ascites because they were not recruited early enough and therefore are censored early.
• The hazard function will be biased too small for larger $t$ and so $\hat{S}$ will be larger than the population survival function at large $t$. 
In Short, What If

• From first participant entered until the end of study: 4 years
• Enroll for 3 years
  – Can be on study at least 1 year and up to 4 years
• Followed enrollment to end of study
• Do not start fully enrolling ascites until year 1.5
Ascites Participants

- On study at least 1 yr and up to 2.5 yr
- Do not have full population/risk set information at time $t > 2.5$ years
- At time points $t > 2.5$ the study does not include a representative population
  - Ascites $\rightarrow$ worse prognosis
  - KM estimate at $t > 2.5$ too high
  - Hazard is too small at larger $t$
Cox Model: Doomed Regression Coefficient Estimates?

- No bias because conditional on covariates (including $X_A$)
- Censoring must be independent GIVEN $X$
- Censoring is independent and that is all that is required for consistency of the partial likelihood estimator (i.e. the coefficients)
MIST RCT Follow-up
(BMJ article 13 Oct 2009)

- 3 management methods for early miscarriage
  - Outcome was gyn infection
- Effect of management method on
  subsequent fertility over the next 5-10 years?
  - Intervention randomized to (what received)
  - Age
  - Previous miscarriage (yes/no, #)
  - Previous birth history?
- KM plots and log rank tests (stratified)
- Proportional hazards regression
Outline

✓ How to Measure Time and Events
✓ Truncation and Censoring
✓ Survival and Hazard Functions
✓ Competing Risks
✓ Models and Hypothesis Testing
✓ Example
➢ Conclusions
Survival Analysis

- Survival analysis deals with making inference about EVENT RATES
- Rate at t = Rate among those at risk at t
- Look at Median survival (50%) not Mean survival
  - Mean: need everyone to have an event
- Cox Regression is the most robust method
- Kaplan Meier curves do not have sensible interpretations for competing risks
Survival Analysis Can Handle

- Right censoring
- Left truncation
- Recurrent events
- Competing risks, etc.

- Because we have available representative risk sets at t which allow us to estimate/model event rates.
Kaplan Meier

• One way to estimate survival
• Nice, simple, can compute by hand
• Can add stratification factors
• Cannot evaluate covariates like Cox model
• No sensible interpretation for competing risks
Inference: Log Rank

- Logrank statistics compare event rates and allow the same generality as right censoring, left truncation
- For single event data inference about rates $\rightarrow$ inference for $S(t)$
  - No time dependent covariates, no recurrent events, no competing risk events
Cox Model for Event Rates

- Provides a framework for making inference about covariate effects
- Semi-parametric
  - $\lambda_0(t)$ completely unspecified
- Multiplicative - $e^{\beta x}$
  - Effect of covariate is to multiply the rate by a factor
Cox cont.

• Requires either that
  – RR is constant over time (proportional hazards), or
  – That we model RR over time
• Allows time-dependent covariates and stratification factors
Truncation and Censoring

• Independence is key
• Truncation is about *entering* the study
  – Right: Event has occurred (e.g. cancer registry)
  – Left: Have the event and fall out of view before they can enter to be counted
• Censoring is about *leaving* the study
  – Right: Incomplete follow-up (common)
  – Left: Observed time > survival time
Analysis Follows Design

Questions → Hypotheses → Experimental Design → Samples → Data → Analyses → Conclusions

• Take all of your design information to a statistician early and often
  – Guidance
  – Assumptions
Questions?

• Thanks!
• Please fill out the course evaluations
• Please email me with specific examples or suggestions to further improve the course
• johnslau@mail.nih.gov