**CHL 5424H**

**Advanced Quantitative Methods in Epidemiology**

**Course Information Syllabus and Readings**

**Winter 2016**

**Instructors:**

Melania Pintilie, MSc

Principal Biostatistician, Princess Margaret Cancer Center

Assistant Professor, Dalla Lana School Public Health, University of Toronto

[pintile@uhnresearch.ca](mailto:pintile@uhnresearch.ca)

Brendan Smith, PhD

Scientist, Public Health Ontario

Assistant Professor, Dalla Lana School of Public Health, University of Toronto

[brendant.smith@utoronto.ca](file:///C:\Users\Brendan.Smith.OAHPP\Dropbox\Work%20Computer\CHL5424\2016\brendant.smith@utoronto.ca)

Rinku Sutradhar, PhD

Senior Scientist, Institute for Clinical Evaluative Sciences

Assistant Professor, Dalla Lana School Public Health, University of Toronto

416-480-6091

[rinku.sutradhar@ices.on.ca](mailto:rinku.sutradhar@ices.on.ca)

**Pre/Co Requisites:**

1. Research Methods in Epidemiology I (CHL5404H)

2. Quantitative Methods for Biomedical Research (CHL5406H)

3. Or permission from the course director

**Expectation:**

It is expected that all students in this class have prior experience with data analysis using datasets arising from epidemiological studies. Experience and conceptual understanding of multivariable linear, logistic and proportional hazards regression analysis is assumed. Students should be comfortable with material covered in chapters 1 thru 7 of Regression Methods in Biostatistics by Vittinghoff (ISBN 0-387-20275-7). It is also assumed that students will be comfortable using SAS for data manipulation and analysis. Both SAS and R will be used for presentation of examples in class. SAS is available to University of Toronto students through the licensed software office and on-campus computing laboratories. Assignments can be completed using either program.

**Description:**

This course will provide students with an overview of the theory and applications of advanced quantitative methods in epidemiology. The purpose of the course is to assist students in answering complex etiological research questions in epidemiology. The course includes three modules: 1) introduction to survival analysis; 2) Cox proportional hazards model and it’s extensions; and 3) multi-state models for event history data.

**Evaluation:**

The evaluation for the course will include three assignments (90% of final grade). Each assignment will be based on an existing data set collected from a large cohort study. Students will be provided with a specific question to answer and expected to submit a five page paper presenting their analysis and results. Participation (10% of final grade) will be based on class attendance and involvement in class discussion.

The three homework assignments will be due at the beginning of the lectures identified (i.e. no later than 2:00 pm on the due date). The penalty for late assignments is an automatic 10% of the maximum grade immediately and an additional 10% for each 24 hour period the assignment remains outstanding. You are encouraged to discuss the assignments with other students, to help each other, and/or to form homework study groups. However, each student is responsible for preparing his or her own independent homework assignment for submission.

**Objectives:**

Module 1. Introduction to Survival Analysis

* + 1. Review the basic techniques for survival: definitions (dependent variable, origin of time, study window), censoring, important functions describing survival distribution, life tables and Kaplan-Meier estimation.
    2. Convert person data into person-period data, including how to incorporate time-varying covariates.
    3. Review the basic techniques for discrete-time survival models.

Module 2. Cox proportional hazards model and it’s extensions

1. Review the basic techniques for survival using the Cox proportional hazards model. Understand and analyze the time to event outcome using either parametric models or Cox proportional hazards model.
2. Assess the assumptions for Cox proportional hazards model and understand the bias when they are not fulfilled.
3. Understand parametric models, their use and interpretation. Understand the intricacies of power calculation for survival. Calculate power for a 2 arm randomized study.
4. Be able to identify competing risks and analyze efficiently time to event data in the presence of competing risks. Conduct an analysis for data which has competing risks events.

Module 3. Multi-state models for event history data

1. Introduce definitions and counting process notation for building multistate models (this includes understanding transition intensity functions, transition intensity matrices, and transition probability matrices).
2. Understand likelihood construction and parameter estimation for multistate models under complete observation.
3. Discuss Markov and Semi-Markov multistate model assumptions.
4. Understand how to structure data for conducting multistate analyses.
5. Understand how to incorporate covariates into a multistate model.
6. Understand how multistate models are related to survival models and competing risks models, and be able to conduct a competing risks data analysis using multistate methods.
7. Know how to perform multistate analyses under the presence of intermittent observation.

**Meeting Place and Time:**

Mondays 2-5 pm

Health Sciences Building

155 College Street

HS 790 (computer lab)

**Course Web Site:**

The course web site can be accessed through Blackboard. Course announcements, homework assignments, and other information will be posted on the web site. You can login to the portal at https://weblogin.utoronto.ca/ using your UTORid and password then click on this class under "My Courses."

**Office Hours:**

Office hours for all instructors is by prior appointment.

**Lecture Schedule:**

**Module 1. Introduction to Survival Analysis – Instructor: Brendan Smith**

January 11: Introduction to survival analysis

January 18: Discrete-time survival models

January 25: Laboratory 1: Work on Assignment 1

**Module 2.** Cox proportional hazards model and it’s extensions **– Instructor: Melania Pintilie**

February 1: Review the basic techniques for survival and the assumptions for Cox proportional hazards model.

February 8: Parametric modelling and power calculation for survival

February 15: Family Day – University closed

February 22: Modelling competing risks

February 29: Guest lecture: Prognostic Modeling using time to event data

March 7:Laboratory 2: Work on Assignment 2

**Module 3. Multi-state models for event history data – Instructor: Rinku Sutradhar**

March 14 Introduce definitions and counting process notation for building multistate models; Understand likelihood construction and parameter estimation for multistate models under complete observation

March 21 Discuss Markov and Semi-Markov multistate model assumptions; Understand how to structure data for conducting multistate analyses; Understand how to incorporate covariates into a multistate model

March 28 Understand how multistate models are related to survival models and competing risks models, and conduct a competing risks data analysis using multistate methods; Know how to perform multistate analyses under the presence of intermittent observation

April 4 Laboratory 3: Work on Assignment 3

**Assignment Due Dates**: #1 due February 1, #2 due March 14th, #3 due April 6th

**Required Readings:**

**January 11: Introduction to survival analysis**

1. Kleinbaum, D.G. and Klein, M. Survival Analysis: A Self-Learning Text, Third Edition, Statistics for Biology and Health, New York, NY : Springer, c2012. **Chapters 1 and 2**.

Available:

<http://books1.scholarsportal.info.myaccess.library.utoronto.ca/viewdoc.html?id=/ebooks/ebooks2/springer/2012-05-29/3/9781441966469>

*Optional Readings:*

1. Allison, P.D. Survival analysis using SAS: a practical guide, Second Edition, SAS Institute. © 2010. **Chapters 1, 2 and 3**.

Available: <http://library.books24x7.com.myaccess.library.utoronto.ca/toc.aspx?site=V38VL&bookid=35240>

1. Clark TG, Bradburn MJ, Love SB, Altman DG. (2003) Survival Analysis Part I: Basic concepts and first analyses. British Journal of Cancer 89:232-238.

**January 18: Discrete-time models**

1. Allison, P.D. Survival analysis using SAS: a practical guide, Second Edition, SAS Institute. © 2010. **Chapter 7**.

Available: <http://library.books24x7.com.myaccess.library.utoronto.ca/toc.aspx?site=V38VL&bookid=35240>

1. Singler, J.D. and Willett, J.B. Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence, New York, NY: Oxford University Press, c2003. **Chapter 11**.

Available:

<http://www.oxfordscholarship.com.myaccess.library.utoronto.ca/view/10.1093/acprof:oso/9780195152968.001.0001/acprof-9780195152968>

*Optional Readings:*

1. Singler, J.D. and Willett, J.B. (1993) It’s about time: Using discrete-time survival analysis to study duration and the timing of events. Journal of Educational Statistics, 18:2 155-195.

**January 25: Laboratory**

1. Singler, J.D. and Willett, J.B. Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence, New York, NY: Oxford University Press, c2003. **Chapter 12**.

Available:

<http://www.oxfordscholarship.com.myaccess.library.utoronto.ca/view/10.1093/acprof:oso/9780195152968.001.0001/acprof-9780195152968>

Work on assignment in the lab.

**February 1: Review the basic techniques for survival and the assumptions for Cox proportional hazards model.**

1. Clark TG, Bradburn MJ, Love SB, Altman DG. (2003) Survival Analysis Part I: Basic concepts and first analyses. British Journal of Cancer 89:232-238.
2. Bradburn MJ, Clark TG, Love SB, Altman DG. (2003) Survival Analysis Part II: Multivariate data analysis -an introduction to concepts and methods. British Journal of Cancer 89:431-436.
3. Altman DG, de Stavola BL. (1994) Practical problems in fitting a proportional hazards model to data with updated measurements of the covariates. Statistics in Medicine 13:301-341.

*Optional Readings:*

1. Bradburn MJ, Clark TG, Love SB, Altman DG. (2003) Survival Analysis Part III: Multivariate data analysis -choosing a model and assessing its adequacy and fit. British Journal of Cancer 89:605-611.
2. Clark TG, Bradburn MJ, Love SB, Altman DG. (2003) Survival Analysis Part IV: Further concepts and methods in survival analysis. British Journal of Cancer 89:781-786.
3. Therneau TM, Grambsch PM. (2000). Chapters 5 and 6. Modelling survival data. Extending the Cox Model. Springer. New York.
4. Collett D. (2003). Modelling Survival Data in Medical Research. Chapman & Hall.

**February 8: Parametric modelling and power calculation for survival**

*Required Readings:* See February 1

*Optional Readings:* See February 1

**February 15: Family Day- University closed**

**February 22: Modelling competing risks**

1. Gooley T, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of the old estimators
2. Pintilie M. (2011) An Introduction to Competing Risks Analysis. Revista Espanola de cardiologie. Vol 64. p: 599-605

*Optional Readings:*

1. Pintilie M. (2006). Competing risks – A Practical Perspective. Wiley. Chichester.

**February 29: Prognostic Modeling using time to event data**

1. Harrell FE, Lee KL, Mark DB (1996). Tutorial in biostatistics: multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Statistics in Medicine.15, p.361-387.

**March 7: Laboratory**

Work on assignment in the lab.

**March 14: Introduce definitions and counting process notation for building multistate models; Understand likelihood construction and parameter estimation for multistate models under complete observation**

1. Hougaard P. Multistate models: a review. Lifetime Data Analysis 1999; 5: 239-264.
2. Andersen PK, Keiding N. Multi-state models for event history analysis. Statistical Methods in Medical Research 2002; 11: 91-115.
3. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Statistics in Medicine 2007; 26: 2389-2430. Sections 1, 2, and 4.
4. Meira-Machado L et al. Multistate models for the analysis of time-to-event data. Statistical Methods in Medical Research 2009; 18: 195-222.
5. Broet P et al. Analyzing prognostic factors in breast cancer using a multistate model. Breast Cancer Research and Treatment 1999; 54: 83-89.

*Optional Readings:*

1. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model. New

York: Springer; 2000. Chapter 8.

**March 21: Discuss Markov and Semi-Markov multistate model assumptions; Understand how to structure data for conducting multistate analyses; Understand how to incorporate covariates into a multistate model**

*Required Readings:* See March 14

*Optional Readings:* See March 14

**March 28: Understand how multistate models are related to survival models and competing risks models, and conduct a competing risks data analysis using multistate methods; Know how to perform multistate analyses under the presence of intermittent observation**

1. Schmoor C et al. Competing risks and multistate models. Clinical Cancer Research 2013; 19: 12-21.
2. Jackson CH. Multi-state models for panel data: The msm package for R. Journal of Statistical Software 2011; 38(8).
3. Sutradhar R, Barbera L, Seow H, et al: Multistate analysis of interval-censored longitudinal data: application to a cohort study of performance status among patients diagnosed with cancer. Am J Epidemiol 2011; 173:468-475.

**April 4: Laboratory**

Work on assignment in the lab.