
CLRES 2010
Clinical Research Methods

Course instructors:
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Course Summary

Clinical Research Methods (CLRES 2010) covers fundamental concepts and basic analytic methods pertaining to the design, analysis, and interpretation of clinical research studies. The course is broadly divided into three major analytic areas: 1) Basic epidemiology and observational methods, 2) interventional and randomized controlled trials, and 3) Clinical epidemiology and evidence-based medicine. Each section of the course will last 7-9 sessions, and culminate in a short examination. Section 1 will cover concepts of association and outcome, introduce standard epidemiological concepts of incidence and prevalence, define and describe relative risk, absolute risk, attributable risk and the various methods for calculating those quantities in different observational research designs. Definitions of and methods for reducing bias and confounding are major components of this section. The second session introduces interventional trials, including the four phases of drug trials, the importance and effects of randomization, and the analysis and interpretation of controlled trials. Methods for comparing results across trials, as well as an introduction to non-standard trial designs are provided. The final section of the course introduces the concepts of clinical epidemiology, including evidence-based medicine, the interpretation of diagnostic tests, the construction and use of clinical prediction rules, and the evaluation of screening for chronic disease.

Course mechanics: 3 credits; meets on Mondays, Wednesdays and Fridays from 8:30 – 10:15 and on Wednesdays from 3:30 – 5:00 for recitation

Grading: Letter grade based on section exams and class participation.

Location: 305 Parkvale Building (corners of Forbes and Meyran Avenues).

Course requirements:

The course consists of three sections. There will be homework assignments, in-class activities/projects and an exam for each section.

Required Texts:

Neither of the required texts covers all of the material in this course. The Hulley book is more directed toward clinical research and clinical epidemiology; the Gordis book more traditional epidemiology. Where appropriate, we have provided the chapters and pages in each book that correspond to the particular lecture: you only need to read one or the other when both books are referenced. However, there are some days when only one of the texts contains appropriate material, and that should be read.

1. Designing Clinical Research: An Epidemiologic Approach, Third Edition. SB Hulley, SR Cummings, WS Browner, D Grady, and TB Newman. 2007.
2. Epidemiology, Fourth Edition. L Gordis, 2008.

Teaching Fellow:

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Section 1.0: Course Section – Epidemiology

Session 1.1 Introduction to Clinical Research Methods

July 6, 2009

Roberts

Topics:

1. Describe what is meant by “Clinical Epidemiology.”
2. Construct specific research questions that clearly identify a population, an exposure or intervention, and an outcome.
3. Explain what an association is, and the difference between statistical error, epidemiological bias, and true cause-effect relationship.
4. Identify criteria used to evaluate a cause-effect relationship, and be able to apply those criteria to specific examples.
5. Brief introduction to study designs

Readings:

1. Hulley textbook; Chapters 1 and 2.
 2. Gordis textbook; Chapter 1 and 14
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Session 1.2 Quantitative Concepts in Epidemiology

July 8, 2009

Roberts

Topics:

1. Review types of variables, precision and validity.
2. Explain the difference between prevalence and incidence, including their relationship based on duration of illness.
3. Understand the complexities of these measures, including issues related to the numerator and the denominator.
4. Calculate incidence rates and prevalence given data tables with information of disease counts, population, and time.
5. Understand the difference between crude and adjusted rates.
6. Describe a confidence interval and how it applies to rates.

Readings:

1. Gordis textbook; Chapter 3 and 4

Homework: Gordis Chapter 3 and 4 problems at the end of the chapter.

Session 1.3 Research Study Design: Cohort Studies

July 10, 2009

McTigue

Topics:

1. To understand how to use longitudinal cohort data to determine whether there is an association between a factor or a characteristics and the development of a disease using longitudinal (cohort) data.
2. To recognize the advantages and disadvantages of the cohort design and understand when it should be applied.
3. To understand the differences between a retrospective cohort and a prospective cohort.

Readings:

1. Gordis textbook; chapter 9
2. Hulley textbook; chapter 7
3. Article: Mozaffarian D. et al. Cardiac Benefits of Fish Consumption May Depend on the Type of fish Meal Consumed: The Cardiovascular Health Study. *Circulation* 2003;107;1372-1377

Homework: Gordis Chapter 9 review questions (Check your own work)

Topics:

1. Describe the key features that distinguish a case-control study from other types of observational research studies.
2. Be able to identify several possible sources of “control” subjects, and describe potential biases associated with choice of control group.
3. Interpret outcome measures generated from case control studies (e.g. odds ratio with 95% confidence interval).

Readings:

1. Gordis textbook; chapter 10
2. Hulley textbook; chapter 8, pages 112-120
3. Article: Phenylpropanolamine and the risk of hemorrhagic stroke. New England Journal of Medicine 2000; 343:1826-1832.

Homework: Review questions at the end of Gordis Chapter 10 (due at the beginning of session 1.8)

In-class small group exercise: Design a case control study. Response to RFA.

Topics:**Case Series**

1. Describe research questions that would be appropriate for a case series study.
2. Identify the most important potential sources of bias in a case series design, and discuss methods to reduce these biases in the design phase of the study.

Cross-Sectional

1. Describe research questions that would be appropriate for a cross-sectional study.
2. Identify the most important potential sources of bias in a cross-sectional study design, and discuss methods to reduce these biases in the design phase of the study.

Readings:

1. Gordis textbook; chapter 10, pages 195-198
2. Hulley textbook; chapter 8, pages 109-112
3. Article: Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto Area. JAMA 2003; 289:2801-2809.

Homework: Article discussion questions to be distributed in previous class.

In-class small group exercise: Design a cross-sectional study. Response to Request for Applications (RFA).

Topics:

1. To understand the definition and calculation of measures of association, including: Relative Risk, Absolute Risk, Attributable Risk, Odds Ratios, Number needed to treat.
2. To understand the application of the different measures to epidemiologic questions.

Readings (to be done before class):

1. Gordis textbook; chapter 11
2. Epidemiology in Medicine, Chapter 4 (provided on Courseweb)

Homework: Review questions at the end of Gordis Chapter 11 (due at the beginning of Session 1.7)

Problem set to be handed out in class

Topics:

1. To understand the definition and calculation of measures of association, including: Relative Risk, Absolute Risk, Attributable Risk, Odds Ratios, Number needed to treat.
2. To understand the application of the different measures to epidemiologic questions.

Readings:

3. Gordis textbook; chapter 12
4. Epidemiology in Medicine, Chapter 4
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Homework: Review questions at the end of Gordis Chapter 12 and those at the end of Epidemiology in Medicine Chapter 4 (due at the beginning of Session 1.8)

Problem set to be handed out in class

Topics:

1. Define bias in general, and more specifically for different types of selection bias and information bias.
2. Identify general strategies to address bias when planning a new research study.
3. Define confounding, and be able to identify potential confounding variables in the study design phase and the analysis phase.
4. Identify the relationships between variables that must be present in order for a variable to be a confounding variable.
5. Identify general strategies to deal with confounding.
6. Define interaction, and be able to demonstrate interaction using a 2x2 table.

Readings:

1. Gordis textbook; chapter 15
2. Hulley textbook; chapter 4

Homework: Gordis textbook Chapter 15 review questions.

Section 2.0: Course Section - Clinical Trials

Section objectives:

1. Describe the purpose, phases, pros and cons of the RCT.
2. Describe and use basic design concepts important to the validity of a randomized trial.
3. Describe how design decisions affect feasibility and generalizability of a randomized trial.
4. Describe at least five types of intervention maneuvers.
5. Describe threats to blinding in an RCT and methods to overcome them.
6. Discuss the effects of dropouts and missing data on an RCT.
7. Be able to read and plan a CONSORT statement.
8. Describe the purpose and processes of phase I and II drug development trials.
9. Define, give examples, and describe the advantages and disadvantages of quasi-experimental research designs.
10. Describe the purpose, methodology, strengths and limitations of a meta-analysis.

OVERVIEW OF READING ASSIGNMENTS:

Clinical trials are covered in only a very brief way in our two main textbooks, but are covered at too much depth in the texts on Clinical Trials only. Over the period of the four sessions on clinical trials, you should read the chapters about trials in one of the two textbooks (Hulley Chapter 10 and 11 pp 147-182 or Gordis Chapters 7 and 8 pp 131-164) and the CONSORT statement. Specific pages related to each topic are listed below but it may be easier to read the whole chapter at a time.

Optional Textbooks Readings:

1. Fundamentals of Clinical Trials, 3rd edition. Friedman, Furberg and Demets. Springer Publisher, 1998. *This is the best short text on clinical trials.*
2. Clinical Trials: A Methodologic Perspective. S Piantadosi. Wiley Interscience, 1997.
3. Clinical Trials: Design, Conduct and Analysis (Monographs in Epidemiology and Biostatistics Vol 8). CL Meinert. Oxford University Press, 1986.

Session 2.1	RCT I: Overview: Principles and Concepts	July 27, 2009	Studenski
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Topics:

1. Randomized trials as experiments.
2. Advantages and disadvantage of the RCT.
3. Four phases of intervention development.
4. Clinical vs. statistical meaningfulness.
5. Overview of trial goals (efficacy and effectiveness, internal and external validity)
6. The iterative process of RCT development; opportunities for pilot studies.
7. The CONSORT Statement

Readings:

1. Hulley textbook; review Chapter 1; and 147,169.
2. Gordis textbook; pages 153,156-158.
3. D Moher, K Schulz, DG Altman, et al. The CONSORT Statement: Revised Recommendation for Improving the Quality of Reports of Parallel-group Randomized Trials. *Annals of Internal Medicine*; 134(8):657-662.

Supplemental Readings (** means personal favorite):

1. J Concato, N Shah, R Horwitz. Randomized, controlled trials, observational studies and the hierarchy of research designs. *New England Journal of Medicine*, 2000; 342:1887-1892.
2. G Diamond, TA Denton. Alternative perspectives on the biased foundation of medical technology assessment. *Annals of Internal Medicine*, 1993; 118:455-464.
3. B Freedman. Equipoise and the ethics of clinical research. *New England Journal of Medicine*, 1987; 317:141-145.
4. DL Sackett, M Gent. Controversy in counting and attributing events in clinical trials. *New England Journal of Medicine*; 1979; 301:1410-1412.
5. ** DL Sackett. Why randomized controlled trials fail but needn't. *CMAJ*, 2001; 165:1226-1237.
6. D Torgerson, B Sibbald. Understanding controlled trials: what is a patient preference trial? *BMJ*, 1998; 316:360-361.

In Class Activity:

Plan for the three RCT small group sessions to follow. Select one of three publications on RCTs to evaluate in detail using the attached checklists. Prepare checklists in advance and discuss in small groups.

1. JB Moseley, K O'Malley, NJ Peterson, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *New England Journal of Medicine*, 2002; 347:81-88.
2. RM Neer, CD Arnaud, JR Zanchetta, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *New England Journal of Medicine*, 2001; 344:1434-1441.
3. TJ Marrie, CY Lau, SL Wheeler, et al. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. *JAMA*, 2000; 283:749-755.

Session 2.2 RCT II: Intervention

July 29, 2009

Studenski

Topics:

1. Types of interventions.
2. Reproducibility, intensity.
3. Randomizing.
4. Choice of control.
5. Blinding.
6. Adherence and retention, pros and cons of a run-in.
7. Factorial designs- more than one intervention.

Readings:

1. Hulley textbook; pages 147-150,155-159,163-165,170-173
2. Gordis textbook; pages 135-138,139,143-145.

Supplemental Readings:

1. AE Brittain, J Wites. The run-in period in clinical trials. *Controlled Clinical Trials*; 11:327-338.
2. T Chalmers, P Celano, H Sacks, et al. Bias in treatment assignment in controlled clinical trials. *New England Journal of Medicine*, 1983; 309:1358-1361.
3. ** PJ Devereaux, M Bhandari, VM Montori, et al. Double blind, you are the weakest link-goodbye! *ACP Journal Club*, 2002; 136:A11-A14.
4. RI Horwitz, CM Viscoli, L Berkman, RM Donaldson, et al. Treatment adherence and risk of death after a myocardial infarction. *Lancet*, 1990; 336:542-545.
5. FA McAlister, SE Strauss, DL Sackett, DG Altman. Analysis and reporting of factorial trials. *JAMA*, 2003; 289:2545-2553.

6. S Pocock. Current issues in the design and interpretation of clinical trials. *BMJ*, 1985; 296:39-42.

In class activity:

For your study:

1. Complete attached checklist on intervention issues.
2. Propose feasible improvements.
3. Be prepared to discuss in your group.

Session 2.3	RCT III: Samples and Measures	July 31, 2009	Studenski
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Topics:

1. Participants: influence of trial goals, entry criteria, recruitment plan and sample size.
2. Baseline measures: influence of trial goals, types of measures and consistency.

Readings:

1. Hulley textbook; pages 152-155.
2. Gordis textbook; pages 133,147-152

Supplemental Readings:

1. DG Altman, CJ Dore. Randomisation and baseline comparisons in clinical trials. *Lancet*, 1990; 335:149-153.
2. A Fleissig, V Jenkins, L Fallowfield. Result of an intervention study to improve communication about randomized clinical trials of cancer therapy. *European Journal of Cancer*, 2001; 37:322-331.
3. JA Freiman, TC Chalmers, H Smith, RR Kuebler. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. *New England Journal of Medicine*, 1978; 299:690-694.
4. C Schaake-Koning, A Kirkpatrick, R Kroger, et al. The need for immediate monitoring of treatment parameters and uniform assessment of patient data in clinical trials. *European Journal of Cancer*, 1991; 27:615-619.
5. KM Taylor, RG Margolese, CL Soskolne. Physicians' reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer. *New England Journal of Medicine*, 1984; 310:1363-1367.

In Class Activity:

For your study:

1. Complete attached checklist on participants and baseline measures.
2. Propose feasible improvements.
3. Be prepared to discuss in your group.

Session 2.4	RCT I4: Outcome and Analysis	August 3, 2009	Studenski
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Topics:

1. Outcomes: types, number, adjudication and adverse events.
2. Analysis: primary and secondary analyses, event rates and number needed to treat, intention to treat and subgroups.
3. Trial summaries: the CONSORT Statement and flow diagram.

Readings:

1. Hulley textbook; pages 150-151,173-179
2. Gordis textbook; pages 152-153
3. D Moher, A Schulz, DG Altman, et al. The CONSORT Statement: revised recommendations for improving the quality of parallel-group randomized trials. *Annals of Internal Medicine*; 134(8):6578-662.

Supplemental Readings:

1. D Ferguson, SD Aaron, G Guyatt, P Hebert. Post-randomisation exclusion: the intention to treat principal and excluding patients from analysis. *BMJ*, 2002; 325:652-654.
2. ** L Forrow, WC Taylor, RM Arnold. Absolutely relative: how research results are summarized can affect treatment decisions. *American Journal of Medicine*, 1992; 92:121-124.
3. N Freemantle, M Calvert, J Wood, et al. Composite outcomes in randomized trials. *JAMA*, 2003; 289:2554-2559.
4. VM Montori, GH Guyatt. Intention to treat principle. *CMAJ*, 2001: 1339-1341.
5. JH Ware, EM Antman. Equivalence trials. *New England Journal of Medicine*, 1997; 337:1159-1161.

In class activity

For your study:

1. Complete checklist on outcome and analysis issues.
2. Complete CONSORT flow sheet and rest of the CONSORT checklist.
3. Propose feasible improvements.
4. Be prepared to discuss in your group.
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Session 2.5 Meta Analysis I

August 5, 2009

Studenski

Topics:

1. Rationale for studies of pooled data from individual RCTs
2. Elements of a good meta-analysis of clinical trials
3. Issues in statistical analyses of pooled data: summary effects and tests of heterogeneity
4. Graphical presentations of data from meta analysis (Forest, L'Abbe, funnel plots)
5. Sources of heterogeneity: subgroups and sensitivity analyses
6. Publication bias
7. The Cochrane collaboration

Reading:

Hulley 213-218, 219-220

Gordis 342-343

Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Internal Med*. 1997 Nov 1; 127(9):820-6.

Song F, Sheldon TA, Sutton AJ, Abrams KR, Jones DR. Methods for exploring heterogeneity in meta-analysis. *Eval Health Prof* 2001 Jun; 24(2):126-51. focus on pp 134-136 on how to make a L'Abbe plot.

Optional supplemental readings:

Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. *Ann Int Med* 1997:380-387.

Meade MO, Raichardson WS. Selecting and appraising studies for a systematic review. *Ann Int Med* 1997;531-537.

Balk EM, Bonis PA, Moskowitz H, Schmid CH, Ioannidis J, Wang, C, Lau J. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *JAMA* 2002 Jun; 287(22):2973-82.

Lambert PC, Sutton AJ, Abrams KR, Jones DR. A comparison of summary patient-level covariates in meta-regression with individual patient data meta-analysis. *J Clin Epidemiol.* 2002 Jan; 55(1):86-94.

Davey Smith G, Egger M. Meta-analysis. Unresolved issues and future developments. *BMJ* 1998 Jan 17; 316(7126):221-5.

Papanikolaou PN, Ioannidis JP. Availability of large-scale evidence on specific harms from systematic reviews of randomized trials. *Am J Med.* 2004 Oct 15;117(8):582-9

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses *Ann Intern Med.* 2001 Dec 4;135(11):982-9

LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med.* 1997 Aug 21;337(8):536-42.

Assignment:

1. Read article entitled “Meta-Analysis: Antibiotic Prophylaxis reduces mortality in neutropenic patients” *Ann Int Med* 2005: 142:979-995
2. Answer the following questions:
 1. For which analyses did this study use fixed or random effects models? How would use of the each analytic model for pooling data model affect estimates?
 2. Use table 1 and figure 2 to make a L’Abbe plot comparing fluorquinolone studies that used a placebo control to studies that used no treatment as a control.
 - A. What is the range of event rates in the control group?
 - B. What does the plot suggest about the influence of the type of control on the treatment effect?
 3. What are some potential sources of heterogeneity? (consider population, outcomes, intervention)

Session 2.6	Quasi-experimental design	August 7, 2009	Roberts
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Topic:

Not all experimental designs fit well into the rubric of observational or interventional randomized controlled trials. There are a series of study design types that have elements of one or both, and are called *quasi-experimental* designs. The major attribute that quasi-experimental designs usually lack is the random assignment of patients to a therapy. Pre-post interventions, N of one trials, crossover designs, and several other modifications of standard experimental designs are often more practical to institute, but their interpretation requires substantial care to avoid bias and confounding.

Readings:

Be prepared to discuss whether you are convinced of the effect of the particular intervention in the article listed below.

1. DM Rind, C Safran, RS Phillips, et al. Effect of computer-based alerts on the treatment and outcomes of hospitalized patients. *Arch Intern Medicine*, 1994; 154:1511-1517.

Session 2.7	Section Examination	August 10, 2009	Studenski
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Section 3.0: Course section – Clinical Epidemiology

Session 3.1	Introduction and Evidence-Based Medicine-I	August 12, 2009	Roberts
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Topics:

1. Introduction to the EBM Concept
2. The Practice of EBM – General Overview
3. Defining the Question
4. Finding the Evidence

Session 3.2	Evidence Based Medicine-II	August 14, 2009	Roberts
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Topics:

1. Appraising the Evidence – A “thumbnail” approach to appraising evidence
2. Applying the Evidence to Patient Care
3. Controversies in EBM - A review of the major criticisms of Evidence Based Medicine
4. Teaching Evidence-Based Medicine in a clinical setting – A brief review of the major curricular advances

Session 3.3	Diagnostic Tests Part I	August 17, 2009	Roberts
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Topics:

Diagnostic tests are one of the most common mechanisms for obtaining clinical information about the presence or absence of disease. In this session, the basic characteristics of diagnostic tests will be explored, sensitivity, specificity, predictive value will be defined. Characteristics that are necessary for a good screening tests and diagnostic test are reviewed.

Readings:

1. Gordis textbook; chapter 4.
2. Hully textbook chapter 12.

Homework: Problem set: calculating sensitivity, specificity, predictive value and likelihood ratios.

Session 3.4	Diagnostic tests Part II	August 19, 2009	Roberts
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Topics:

Many diagnostic tests have positivity criteria that are “set”: there is no absolute positive or negative. This includes tests such as the Troponin cutoff for the diagnosis of a myocardial infarction and the size of a mediastinal node on CT to be considered pathological adenopathy. This session will examine methods for understanding the tradeoffs between different cut offs for a diagnostic test, and explore the tradeoff between sensitivity and specificity. Receiver Operating Curves (ROC) curves will be described and calculated for several types of test.

Readings:

1. RM Centor. Signal detectability: the use of ROC curves and their analyses. Medical Decision Making, 1991;11(2): 102-106.

Homework: ROC curve construction: examine the CA-19-9 spreadsheet data and construct an ROC curve.

Topics:

1. Identify possible biases in screening studies and how to address them in the design phase.
2. Describe how the natural history of disease may influence the type of screening intervention that may be needed,
3. Identify the strengths and weaknesses of various study design options as they apply to screening studies.

Readings:

1. Gordis textbook; chapter 18.

Homework: Review questions, chapter 18.

Class exercise: Design a screening study. Response to RFA.

Topics:

The purpose of a clinical prediction rule is to make assessments of the risk of a future event based on characteristics of the patient. There is a wide array of clinical prediction rules, from simple scores such as the Ranson criteria in pancreatitis, to the Pneumonia Severity Index which predicts the likelihood of bad outcomes in community acquired pneumonia or the APPACHE (Acute physiology score) which predicts the likelihood of death for patients admitted to the Intensive care unit. This section will describe the development, testing and validation and clinical application of clinical prediction rules.

Readings:

1. Justice AC. Covinsky KE. Berlin JA. Assessing the generalizability of prognostic information. *Annals of Internal Medicine*. 130(6):515-24, 1999
2. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules: applications and methodological standards. *New England Journal of Medicine* 1985;313:793-799
3. Fine MJ. Auble TE. Yealy DM. Hanusa BH. Weissfeld LA. Singer DE. Coley CM. Marrie TJ. Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. *New England Journal of Medicine*. 336(4):243-50, 1997

Homework:

none

Topics:

There are many research questions which cannot practically or ethically be answered by observational or interventional techniques. For example, estimating the mitigation effects of various strategies to respond to an anthrax attack cannot be answered empirically: it would require conduct such an attack. Mathematical models can be used to represent complex biological systems and diseases, and appropriately constructed and validated models have the potential to answer many questions not amenable to standard investigative methods. This lecture will review and provide examples of the following model classes and types:

1. Continuous/Deterministic models
 - a. differential equations (feedback) models
 - b. infectious disease (compartment) models
2. Discrete and stochastic models

- a. Decision Analysis models
- b. Markov Models
- c. Discrete event simulation
- 3. Agent-based models
- 4. Hybrid models

Readings:

None

Homework:

None