WATERLOO | PHARMACY

PHARM – 609
Advanced Pharmacokinetics

Winter 2016

Syllabus Last Revised: July 2015

Course Description

This course provides statistical hands-on knowledge for the implementation of nonlinear mixed effects (NLME) models in the analysis of population pharmacokinetic data. In order to provide a foundation for NLME, the content builds from simple to multiple linear regression models and to linear mixed effects models. Exploratory and descriptive analyses, as well as model implementation will be taught in R and Phoenix.

Prerequisite / Corequisite:
Undergraduate course in statistics

Learning Objectives

Upon completion of PHARM 609, students will be able to:

Learning Objectives

1. Construct and interpret descriptive statistics and plots, probability distributions, hypothesis tests and confidence intervals.
2. Perform simple and multiple linear regression modeling and interpret model diagnostics.
3. Perform non linear mixed effects modeling in the context of population pharmacokinetics and interpret model diagnostics.

Contact Information

Course Coordinator:
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Changes to Course Syllabus

The topics addressed in this course, as well as the schedule of topics, may be revised as the course progresses. Any changes will be announced in class and posted on LEARN. **The assessment weights CANNOT be altered.**

Resources

Required Reading

1. Bonate, Peter L. *Pharmacokinetic-Pharmacodynamic Modeling and Simulation*. Springer, Second Edition, New York, 2011. (Online book accessible from the library)
2. Dalgaard, Peter. *Introductory Statistics with R. Second edition.* Springer-Verlag, New York, 2002. (Online book accessible from the library)

Supplemental Reading

1. Montgomery, Douglas C., Peck, Elizabeth A., Vining Geoffrey, G. *Introduction to Linear Regression Analysis.* Wiley, 2012.
2. Pinheiro, Jose C. and Bates, Douglas M. *Mixed Effects Models in S and S-Plus.* Springer-Verlag, New York, 2000.
3. T. A. Durham, J.R. Turner (2008), *Introduction to Statistics in Pharmaceutical Clinical Trials.* Pharmaceutical Press.

Other Required Resources
R freeware, Phoenix will be provided.

Please note that course material will not be available on LEARN after the end of the semester, therefore, students need to download any information that they may require for reference purposes.

Lectures and tutorials may be audio or video recorded only if permission is granted by the lecturer. Any recordings as well as other class materials (either posted in LEARN or distributed in class) are to be used for review purposes only and should not be posted on websites, bulletin boards or distributed via other means without permission of the Course Coordinator and the lecturer if other than the Course Coordinator.

Plagiarism detection software (Turnitin) will be used to screen assignments in this course. This is being done to verify that use of all materials and sources in assignments is documented. Students will be given an option if they do not want to have their assignment screened by Turnitin. In the first week of the term, details will be provided about arrangements and alternatives for the use of Turnitin in this course.

Course Topics

A complete list of activities is available on LEARN.

- Preliminaries:
    - Statistical terms, descriptive statistics and plots.
    - Random variable, Normal, Lognormal, Student's t
    - Sampling distributions and inferential statements under Normality
- Simple and Multiple Linear Regression
    - Estimation goal and interpretation of models coefficients

    - Goodness of fit assessment, hypothesis tests and CI's for individual model coefficients
    - ANOVA F-Test for nested models and Variable Selection
    - The Log-Transformation
    - Collinearity
    - Residual checks and outliers
    - Maximum Likelihood Estimation in Linear Regression
- Random Effects and Non Linear Mixed Effects (NLME) Models
    - Estimation goal and interpretation of model coefficients
    - Model assumptions, correlation structures
    - Goodness of fit assessment and hypothesis testing
    - Residual checks and outliers

Student Assessment

A passing grade for this course is 70 %.

Group work accounts for 0 % of the total mark.

Assessment	Brief Description	Value/100
Assignment #1	Use of R for descriptive analyses and plotting	15
Assignment #2	Implementation of simple and multiple linear regression	35
Assignment #3	Implementation of NLME for population pharmacokinetic analysis.	50

A student will be excused from a mandatory activity only under exceptional and unforeseen circumstances. While it is not possible to list all such circumstances, examples include: death of an immediate family member; significant illness of a family member; serious personal illness or injury requiring medical attention. Please note that student travel plans are not considered acceptable grounds for granting an alternative examination time or altering assignment deadlines.

If an event is missed due to illness, students must complete a Verification of Illness (VIF) form (available online https://uwaterloo.ca/health-services/sites/ca.health-services/files/uploads/files/VIF-online.pdf) and present it to the Pharmacy Undergraduate office. Instructors will then be notified by email that a VIF has been received. In the event that a student unavoidably misses a mandatory activity, a make-up activity will be scheduled for that student at the sole discretion of the coordinator. In the case of a missed exam, a new exam may be administered. This new exam may be the same as the original exam, may be a different exam, may be of a different format (e.g. an oral test), or may be of a different mix of questions (e.g. the percentage of specific topics on the new exam may differ from the original). In any case, the final decision of which exam format and date that it will be administered will rest solely with the course coordinator.

Students may receive a grade of Incomplete (INC) in a course where the student has been unable to complete course work because of verifiable illness or extenuating cicumstances. These students must complete an Incomplete (Inc) Grade Agreement Form. The Incomplete Grade Agreement Form is an agreement between the instructor and student and specifies how and by what date course work will be completed. Failure to complete work by the deadline indicated will result in the INC grade being

changed to FTC (failure to complete). The course will be weighted as a grade of 32 for purposes of calculating the student's average. A link to the Incomplete Grade Agreement Form follows. https://uwaterloo.ca/science/sites/ca.science/files/uploads/files/incomplete-grade-agreement-form.pdf

Students that wish to have an assignment or exam re-graded must submit a written request that details why it should be re-graded. This written request must be delivered to the instructor within one month (see Appendix B of Policy 70) of the date that grade was available, and must contain supporting evidence (e.g. from literature, textbooks, or other sources). Students should note that grades may stay the same, be increased or be decreased after re-grading. Depending upon the request, the instructor may decide to re-grade the whole assignment or test, and not just the question that is being challenged. Students should not mark in any way assignments or tests that they think may warrant a re-examination. Only assignments and tests that are completed in indelible ink are eligible for re-grading.

Unclaimed assignments, reports and tests will be retained for 1 year after term grades become official. After that time, they will be destroyed in compliance with UW's confidential shredding procedures.

Note: Final Exams will be retained for one year from the date the examination was written.

Expectation of Academic Integrity

Academic Integrity:
In order to maintain a culture of academic integrity, members of the University of Waterloo community are expected to promote honesty, trust, fairness, respect and responsibility. Please refer to: http://www.uwaterloo.ca/academicintegrity/Students/index.html

The Office of Academic Integrigty has developed a tutorial that helps students recognize and avoid academic integrity offences https://uwaterloo.ca/academic-integrity/basic-info).

Bringing another student's iClicker® to class to help him/her receive the participation mark is a breach of academic integrity. If you do so, then all students involved will lose the participation mark for the class. Repeated offenses will be dealt with as any other breach in integrity would.

Discipline:
Students are expected to know what constitutes academic integrity, to avoid committing academic offenses, and to take responsibility for their actions. Students who are unsure whether an action constitutes an offense, or who need help in learning how to avoid offenses (e.g., plagiarism, cheating) or about 'rules' for group work/collaboration should seek guidance from the course instructor, academic advisor, or the Associate Dean of Science for Undergraduate Studies. For information on categories of offenses and types of penalties, students should refer to Policy #71, Student Discipline http://www.adm.uwaterloo.ca/infosec/Policies/policy71.htm. For information on typical penalties, students should check Guidelines for the Assessment of Penalties https://uwaterloo.ca/secretariat/policies-procedures-guidelines/guidelines/guidelines-assessment-penalties.

Appeals:
A decision or penalty imposed under Policy 33 (Ethical Behavior), Policy #70 (Student Petitions and Grievances) or Policy #71 (Student Discipline) may be appealed, if there is a ground. Students, who

believe they have a ground for an appeal, should refer to Policy #72 (Student Appeals) http://www.adm.uwaterloo.ca/infosec/Policies/policy72.htm.

Student Grievances

Grievance: A student who believes that a decision affecting some aspect of his/her university life has been unfair or unreasonable may have grounds for initiating a grievance. Read Policy #70, Student Petitions and Grievances, Section 4. https://uwaterloo.ca/secretariat/policies-procedures-guidelines/policy-70 When in doubt, contact the Director of Admissions, Professional Relations & Undergraduate Affairs who will provide further assistance.

Students with Disabilities

AccessAbility Services (https://uwaterloo.ca/disability-services/), located in Needles Hall, room 1132, collaborates with all academic departments to arrange appropriate accommodations for students with disabilities without compromising the academic integrity of the curriculum. If you require academic accommodations to lessen the impact of your disability, please register with AccessAbility Services at the beginning of each academic term.