USC Mann
Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences

PSCI 518: Introduction to PBPK Modeling
2 units
Spring 2024—Thu—1:00 PM-3:00 PM
Location: PSC B13

Course Coordinator(s):
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Office Hours:
By appointment

Communication:
By email. Coordinators will generally respond in <24 hours.

IT Help:
Blackboard is the Learning Management System (LMS) used at the USC Mann School of Pharmacy and Pharmaceutical Sciences. For 24/7 help with Blackboard:

- Call (213) 740-5555 and choose Option 2.
- Send an e-mail to blackboard@usc.edu.
- Visit USC's Blackboard Online Help site for how-to videos and guides.
- Access additional Blackboard training videos on LinkedIn Learning at https://itservices.usc.edu/linkedin-learning/.
- **Zoom and Panopto may be used for lecture capture and delivery, Zoom and Poll Everywhere may be used as an audience response system, and Blackboard and ExamSoft may be used to administer quizzes and examinations.**
- For help with Zoom, visit https://itservices.usc.edu/zoom/.
- For help with Panopto, call the 24/7 Panopto support team at (855) 765-2341 or e-mail support@panopto.com
- For help with ExamSoft, call the 24/7 ExamSoft support team at (866) 429-8889, e-mail support@examsoft.com , or visit https://help.examsoft.com/.
- You may also visit our Technical Support Specialists in PSC 302B, M-F from 8:00 AM-5:00 PM, call (323) 442-0002, or e-mail mannit@usc.edu.
- **For all other technology-related questions, call USC Information Technology Services at (213) 740-5555.**

Course Description

This course will introduce students to physiologically-based pharmacokinetic (PBPK) Modeling. This will include both lecture content and hands-on experience using the GastroPlus software package. Students will learn the principles underlying PBPK modelling, learn to how to create and refine a PBPK model in GastroPlus, and apply this model to a drug-development project. The course will include presentations of students' projects and submission of a project report.

Course Learning Objectives

- Navigate the screens of GastroPlus
- Identify the physicochemical, biochemical and physiological components of a complete PBPK model
- Make qualitative predictions of the effects of the components on the simulated output from the model
- Describe how each component of a PBPK model affects model output
- Explain methods for predicting or calculating physicochemical and physiologic parameters
- Create a systemic PBPK model (IV delivery) using predicted or calculated physicochemical and physiologic parameters
- Assess the accuracy of a PBPK model using in vitro and in vivo data, and explain potential causes for any discrepancies
- Refine a PBPK model by incorporating in vitro and in vivo data and natural physiologic variance
- Introduce oral absorption into the systemic PBPK model and repeat the assessment and refinement steps for the oral and systemic PBPK model
- Apply a refined PBPK model to a drug development project to make specific predictions on ADMET and/or bioequivalence
- Present a complete model to an audience, including model creation, model refinement, model application, and interpretation of results

Course Notes

Course will consist of didactic lectures with accompanying hands-on application activities, group project work and presentations. Students will use GastroPlus software to create a working PBPK model for their assigned drug, refine the model using experimental data from the literature, and run simulations on this model.

Student will have access to GastroPlus software for the duration of the course. Software is provided courtesy of Simulations Plus Inc. through the University+ Program.

Technology requirements: Access to remote desktop connection (standard on Windows 10/11, downloadable app for Mac). Basic Excel skills.

Required Readings and Supplementary Materials

- Articles will be assigned in class
  Articles will be retrieved from literature searches
  Background material on biopharmaceutics will be made available

Description and Assessment of Assignments

The course project will be performed in groups of two or three

This course will include the following assignments most weeks (details under course schedule):

- Project work: Incorporation of lecture topics into model
- Analysis: One-page report each week on data and simulation results from developing model

The following assessments will be used:

- Weekly 5-minute question
- One-page reports (feedback as formative assessment) (one submission per group)
- Three project presentations (systemic model, oral model, application)

Methods

Teaching Methods

Before Event

- Assigned reading (journal or papers)

During Event

- Classroom lecture
- Small group discussion
- Laboratory
- Group activity
- Student presentation

After Event

- Recorded lecture

Not Associated with an Event

- Group project
- Experiential learning

Assessment Methods

Examination

- Multiple choice
- Oral
- Short answer

In Class

- Oral presentation
- Small group evaluation
- Attendance and Participation

Longer term

- Group assignment
- Term paper

Grading Breakdown

Assignment	Percent
Weekly Questions and Class Discussion (Individual)	20
Weekly Reports (Group)	10
Present Systemic PBPK Model (Group)	20
Present Oral PBPK Model (Group)	20
Present Application of PBPK Model (Individual)	20
Pre- and Post Survey Completion (Individual)	10

Grading Scale

Will be announced.

Additional Policies

Policy Regarding Class Recordings

All class recordings (Zoom, Panopto, etc.) are accessible only to students currently enrolled in the class, instructors, and TAs. These recordings may not be shared or used for purposes outside of this course. Students are also not permitted to record or distribute any course materials or activities on their own without the instructor's permission.

Recording a university class without the express permission of the instructor and announcement to the class, or unless conducted pursuant to an Office of Student Accessibility Services (OSAS) accommodation. Recording can inhibit free discussion in the future, and thus infringe on the academic freedom of other students as well as the instructor. (Living our Unifying Values: The USC Student Handbook, page 13).

Distribution or use of notes, recordings, exams, or other intellectual property, based on university classes or lectures without the express permission of the instructor for purposes other than individual or group study. This includes but is not limited to providing materials for distribution by services publishing course materials. This restriction on unauthorized use also applies to all information, which had been distributed to students or in any way had been displayed for use in relationship to the class, whether obtained in class, via email, on the internet, or via any other media. (Living our Unifying Values: The USC Student Handbook, page 13).

Policy Regarding Assignments and Examinations

The following actions are all violations of academic integrity and subject to disciplinary action:

a. Any use or attempted use of external assistance in the completion of an academic assignment and/or during an examination, or any behavior that defeats the intent of an examination or other classwork or assignment, unless expressly permitted by the instructor.
b. The following are examples of unacceptable behaviors: communicating with fellow students during an exam, copying or attempting to copy material from another student's exam; allowing another student to copy from an exam or assignment; possession or use of unauthorized notes, calculator, or other materials during exams and/or unauthorized removal of exam materials.
c. Other examples of academic misconduct have been and will be considered.

For more information about academic integrity see the student handbook or the Office of Academic Integrity's website.

Policy Regarding Missed Examinations

The policy for this course will follow the policy contained within the Academic Policies and Procedures section of the Student Handbook located on the USC Mann School of Pharmacy and Pharmaceutical Sciences Intranet. Students who miss an examination are referred to this policy.

Technological Requirements and Software Updates

Students may be required to bring an internet-enabled device with browser capabilities, such as a cell phone, tablet, or laptop to class. During class time, it is expected that students will use their devices only to participate in activities guided by the instructor. Use of devices for other purposes is not permitted during class time.

The USC Mann School of Pharmacy and Pharmaceutical Sciences recommends that students purchase a computer that meets, at minimum, the "medium" level hardware requirements that are also recommended for faculty and staff: https://itservices.usc.edu/recommendations/.

Students who use Zoom should be running the latest version of Zoom available at https://zoom.us/download.

Students who use ExamSoft will also be required to have the latest version of Examplify installed on their laptops at all times compatible with their operating system. Occasional updates to the software may be asked of you throughout the year. It is your responsibility to read your USC e-mails regarding Examplify and follow the instructions as listed.

Policy on Learning & Assessment Feedback (LAF)

Feedback on examinations/assessments will be provided using the following methods.

- Return breakdown of scores in areas using ExamSoft
- Feedback on assignments will be provided during the class

Learning Experience Evaluation Notes:

Time will be provided during final course session

University Policy on Absences

University policy grants students excused absences from class for observance of religious holy days. Faculty are asked to be responsive to requests when students contact them IN ADVANCE to request such an excused absence. The student should be given an opportunity to make up missed work because of religious observance. Students are advised to scan their syllabi at the beginning of each course to detect potential conflicts with their religious observances. Please note that this applies only to the sort of holy day that necessitates absence from class and/or whose religious requirements clearly conflict with aspects of academic performance. For additional program-specific absence policies, please refer to the Student Handbook on the USC Mann School of Pharmacy and Pharmaceutical Sciences Intranet.

USC Mann School Policy for Written Assignments Regarding Citation Style

All written assignments in the course should use the uniform style of the USC Mann School of Pharmacy and Pharmaceutical Sciences for formatting in-text citations and reference lists. This style corresponds to the AMA (American Medical Association) format and can be found through this following guide https://libguides.usc.edu/ama11 and handout https://libguides.usc.edu/ld.php?content_id=54130825. The complete AMA Manual of Style is also available as an e-book at tinyurl.com/bdh8amka .

Statement on Academic Conduct and Support Systems

Academic Integrity:

The University of Southern California is a learning community committed to developing successful scholars and researchers dedicated to the pursuit of knowledge and the dissemination of ideas. Academic misconduct, which includes any act of dishonesty in the production or submission of academic work, comprises the integrity of the person who commits the act and can impugn the perceived integrity of the entire university community. It stands in opposition to the university's mission to research, educate, and contribute productively to our community and the world.

All students are expected to submit assignments that represent their own original work, and that have been prepared specifically for the course or section for which they have been submitted. You may not submit work written by others or "recycle" work prepared for other courses without obtaining written permission from the instructor(s).

Other violations of academic integrity include, but are not limited to, cheating, plagiarism, fabrication (e.g., falsifying data), collusion, knowingly assisting others in acts of academic dishonesty, and any act that gains or is intended to gain an unfair academic advantage.

The impact of academic dishonesty is far-reaching and is considered a serious offense against the university. All incidences of academic misconduct will be reported to the Office of Academic Integrity and could result in

outcomes such as failure on the assignment, failure in the course, suspension, or even expulsion from the university.

For more information about academic integrity see the student handbook or the Office of Academic Integrity's website, and university policies on Research and Scholarship Misconduct.

Please ask your instructor if you are unsure what constitutes unauthorized assistance on an exam or assignment, or what information requires citation and/or attribution.

Student Accessibility Services:

USC welcomes students with disabilities into all of the University's educational programs. The Office of Student Accessibility Services (OSAS) is responsible for the determination of appropriate accommodations for students who encounter disability-related barriers. Once a student has completed the OSAS process (registration, initial appointment, and submitted documentation) and accommodations are determined to be reasonable and appropriate, an OSAS letter will be available to generate for each course. The LOA must be given to each course instructor by the student and followed up with a discussion. This should be done as early in the semester as possible as accommodations are not retroactive. More information can be found at osas.usc.edu. You may contact OSAS at (213) 740-0776 or via email at osasfrontdesk@usc.edu.

Support Systems:

Counseling and Mental Health - (213) 740-9355 – 24/7 on call
Free and confidential mental health treatment for students, including short-term psychotherapy, group counseling, stress fitness workshops, and crisis intervention.

At USC Mann, we acknowledge being a student can be difficult at times while managing all personal life matters. Having an accessible mental health and wellness staff member on campus is intended to provide direct supportive services for our students.

Veronica Acosta, LCSW, Wellness Counselor, offers coping tools to reduce stress and anxiety and offers insight from a wellness perspective on how to adjust accordingly to life while being a student. Email: vaacosta@usc.edu; Office: Seaver Residence Hall (SRH) room 307; Appointments: https://engage.usc.edu/meetings/2569802/wellnessmeet

988 Suicide and Crisis Lifeline - 988 for both calls and text messages – 24/7 on call
The 988 Suicide and Crisis Lifeline (formerly known as the National Suicide Prevention Lifeline) provides free and confidential emotional support to people in suicidal crisis or emotional distress 24 hours a day, 7 days a week, across the United States. The Lifeline is comprised of a national network of over 200 local crisis centers, combining custom local care and resources with national standards and best practices. The new, shorter phone number makes it easier for people to remember and access mental health crisis services (though the previous 1 (800) 273-8255 number will continue to function indefinitely) and represents a continued commitment to those in crisis.

Relationship and Sexual Violence Prevention Services (RSVP) - (213) 740-9355(WELL) – 24/7 on call
Free and confidential therapy services, workshops, and training for situations related to gender- and power-based harm (including sexual assault, intimate partner violence, and stalking).

Office for Equity, Equal Opportunity, and Title IX (EEO-TIX) - (213) 740-5086
Information about how to get help or help someone affected by harassment or discrimination, rights of protected classes, reporting options, and additional resources for students, faculty, staff, visitors, and applicants.

Reporting Incidents of Bias or Harassment - (213) 740-5086 or (213) 821-8298
Avenue to report incidents of bias, hate crimes, and microaggressions to the Office for Equity, Equal Opportunity, and Title for appropriate investigation, supportive measures, and response.

The Office of Student Accessibility Services (OSAS) - (213) 740-0776
OSAS ensures equal access for students with disabilities through providing academic accommodations and auxiliary aids in accordance with federal laws and university policy.

USC Campus Support and Intervention - (213) 740-0411
Assists students and families in resolving complex personal, financial, and academic issues adversely affecting their success as a student.

Diversity, Equity and Inclusion - (213) 740-2101
Information on events, programs and training, the Provost's Diversity and Inclusion Council, Diversity Liaisons for each academic school, chronology, participation, and various resources for students.

USC Emergency - UPC: (213) 740-4321, HSC: (323) 442-1000 – 24/7 on call
Emergency assistance and avenue to report a crime. Latest updates regarding safety, including ways in which instruction will be continued if an officially declared emergency makes travel to campus infeasible.

USC Department of Public Safety - UPC: (213) 740-6000, HSC: (323) 442-1200 – 24/7 on call
Non-emergency assistance or information.

Office of the Ombuds - (213) 821-9556 (UPC) / (323-442-0382 (HSC)
A safe and confidential place to share your USC-related issues with a University Ombuds who will work with you to explore options or paths to manage your concern.

Occupational Therapy Faculty Practice - (323) 442-2850 or otfp@med.usc.edu
Confidential Lifestyle Redesign services for USC students to support health promoting habits and routines that enhance quality of life and academic performance.

Summary of Course Schedule

Date	Lecturer	Event
Tue 01/09/24 01:00p - 02:00p	Noam Morningstar-Kywi Ian Haworth	Pre-Class Technology Check (Online)
Wed 01/10/24	Noam Morningstar-Kywi Ian Haworth	Pre-Class Pre-Course Survey
Thu 01/11/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Physicochemical Properties / Cheminformatics / GastroPlus Operation
Thu 01/18/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Introduction to GastroPlus
Thu 01/25/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Intro to PBPK Model / PKplus / Non-Compartmental Analysis
Thu 02/01/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Mechanistic Distribution

Date	Lecturer	Event
Thu 02/08/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Mechanistic Clearance: Metabolism and Transport
Thu 02/15/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Systemic Model Refinement: Mechanistic Distribution and Clearance
Thu 02/22/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Group Presentation of Systemic PBPK Model
Thu 02/29/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	ACAT Model: Solubility and Dissolution
Thu 03/07/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	ACAT Model: Partitioning and Permeability
Thu 03/14/24		Spring Break
Thu 03/21/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Oral Absorption Model Refinement
Thu 03/28/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Group Presentation of Oral Absorption PBPK Model
Thu 04/04/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Model Application: Using GastroPlus for Drug Development
Thu 04/11/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Model Application
Thu 04/18/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Model Application
Thu 04/25/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Individual Presentation of Model Application

Expanded Course Schedule

Date	Lecturer	Event
Tue 01/09/24 01:00p - 02:00p	Noam Morningstar-Kywi Ian Haworth	Pre-Class Technology Check (Online) This session is optional. It will be online. A link will be available in Blackboard. Make sure that Remote Desktop is working Confirm access to cloud server hosting Simulations Plus software. Students will be provided with credentials prior to course start. Ensure proper access prior to the first day of class on Thursday, January 11th Pre-Course survey will be discussed (information will also be sent by e-mail)
Wed 01/10/24	Noam Morningstar-Kywi Ian Haworth	Pre-Class Pre-Course Survey This is not a session that requires attendance, Information on completion of the survey will be sent by e-mail on or before Monday, January 8th Completed Pre-Course Survey due on Blackboard by 11:59 pm Wednesday, January 10th Due: Wed 01/10/24 11:59 PM
Thu 01/11/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Physicochemical Properties / Cheminformatics / GastroPlus Operation In class: What is a PBPK model? Flow of material in the course (45 min) In class: Cheminformatics, physicochemical properties (pKa, LogP), calculation vs. prediction (15 min) In class: Software: GastroPlus structure import and physicochemical properties (30 min) Post-class: Find literature data for pKa, LogP. Judge accuracy of predictions of pKa, LogP Post-class: One-page report due Wednesday 1/17, 11.59 pm
Thu 01/18/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Introduction to GastroPlus In class: GastroPlus software introduction (45 min) In class: Simulation in GastroPlus (45 min) Post-class: Examine results from GastroPlus, compare with observed CP-time data for IV and oral administration Post-class: Consider reasons for lack of fit with observed data Post-class: One-page report due Wednesday 1/25, 11.59 pm

Date	Lecturer	Event
Thu 01/25/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Intro to PBPK Model / PKplus / Non-Compartmental Analysis In class: Create PEAR physiology in GastroPlus, predict Kp values for tissue partitioning (15 min) In class: Make an initial PBPK model for IV administration (15 min) In class: PK principles: ADME, volume of distribution, clearance, rate constants, half life (30 min) In class: Make support files (.ipd, etc.); fit non-compartmental parameters to IV data (PKplus) (30 min) In class: PBPK modeling, effects of physiology on drug distribution and clearance Post-class: List study demographics (age, weight, BMI, sex, health status) Post-class: Start PBPK model for clinical study population for assigned drug Post-class: Make .ipd file, evaluate fit of predicted to experimental IV Post-class: Consider reasons for lack of fit Post-class: One-page report due Wednesday 1/31, 11.59 pm
Thu 02/01/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Mechanistic Distribution In class: Explore options for distribution in PBPK model (Kp, tissue models, Rbp, Fup) In-class: Run simulations for IV administration Post-class: Evaluate fit of predicted to experimental IV Post-class: Consider reasons for lack of fit (should match reasonably well, but no mechanistic clearance yet) Post-class: One-page report due Wednesday 2/7, 11.59 pm
Thu 02/08/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Mechanistic Clearance: Metabolism and Transport In class: Metabolic enzymes and drug transporters, physiological protein distributions, effects on drug ADME In class: Enzyme and transporter tables in GastroPlus In class: In vitro/in vivo extrapolation considerations Post-class: Find enzyme and transporter data (Km, vmax) for the assigned drug Post-class: Start enzyme & transporter table for the assigned drug (will continue next week) Post-class: One-page report due Wednesday 2/14, 11.59 pm

Date	Lecturer	Event
Thu 02/15/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Systemic Model Refinement: Mechanistic Distribution and Clearance In class: Complete enzyme and transporter table In class: Generate Cp-time curves for IV administration to understand effects of inclusion of enzyme and transporter data on both distribution and clearance Post-class: Evaluate fit of predicted to observed IV data Post-class: Consider reasons for lack of fit Post-class: One-page report due Wednesday, 2/21, 11.59 pm
Thu 02/22/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Group Presentation of Systemic PBPK Model In class: Presentation of systemic PBPK model (15 min per group) Post-class: Review feedback on current model (given in class) No one-page report due
Thu 02/29/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	ACAT Model: Solubility and Dissolution In class: ACAT (Advanced Compartmental Absorption and Transit) model for oral absorption, including GI tract physiology (30 min) In class: Mechanistic dissolution: effects of formulation and pH on solubility (30 min) In class: Run an oral simulation in GastroPlus (30 min) Post-class: Create and organize drug records for multiple oral doses Post-class: Run simulations for oral doses in GastroPlus and compare with observed data Post-class: Consider reasons for lack of fit Post-class: One-page report due Wednesday, 3/6, 11.59 pm
Thu 03/07/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	ACAT Model: Partitioning and Permeability In class: Mechanistic absorption: transcellular, paracellular, transpoter-mediated (30 min) In class: Inclusion of transporters and enzymes in the gut in GastroPlus (30 min) In class: Run an oral simulation in GastroPlus (30 min) Post-class: Run simulations for oral doses in GastroPlus and compare with observed data Post-class: Consider reasons for lack of fit Post-class: One-page report due Wednesday, 3/20, 11.59 pm
Thu 03/14/24		Spring Break No Class - Spring Break

Date	Lecturer	Event
Thu 03/21/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Oral Absorption Model Refinement In class: Modify enzyme and transporter table, adjust absorption parameters In class: Generate Cp-time curves for oral administration Post-class: Evaluate fit of predicted to observed data Post-class: Consider reasons for lack of fit Post-class: One-page report due Wednesday, 3/27, 11.59 pm
Thu 03/28/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Group Presentation of Oral Absorption PBPK Model In class: Presentation of oral PBPK model (15 min per group) Post-class: Review feedback on current model (given in class) Post-class: Reading on PBPK model No one-page report due
Thu 04/04/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Model Application: Using GastroPlus for Drug Development In class: Introduction to model application in GastroPlus In class: Start to examine new formulation, food effect, different patient populations, etc. Post-class: Formulate an approach to a question (conceptually and in GastroPlus) Post-class: One-page report due Wednesday 4/10, 11.59 pm
Thu 04/11/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Model Application In class: Project work and troubleshooting, ad hoc presentations & group discussions In class: New formulation, food effect, different patient populations, etc. Post-class: Continue project work Post-class: One-page report due Wednesday 4/17, 11.59 pm
Thu 04/18/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Model Application In class: Project work and troubleshooting, ad hoc presentations & group discussions In class: New formulation, food effect, different patient populations, etc. Post-class: Complete project work Post-class: Prepare presentations No one-page report due
Thu 04/25/24 01:00p - 03:00p	Noam Morningstar-Kywi Ian Haworth	Individual Presentation of Model Application In class: Presentation of model application (5 minutes) Post-Class: Post-Class Survey Due Sunday, May 5th, 2024, 11.59 pm