USCViterbi

BME 530: Introduction to Systems Biology

Units: 4
Lecture: TBD (two 100-minute lectures per week)
Discussion: TBD (one 50-minute discussion per week)

Location: TBD

Instructor: Professor Stacey D. Finley
Office Location: MCB 356
Office Hours: TBD
Contact Info: Email: sfinley@usc.edu; Phone: 213-740-8788; Emails will be replied to within 36 hours.

Teaching Assistant: TBD
Office: TBD
Office Hours: TBD
Contact Info: TBD

Course Description

Systems biology attempts to identify interactions between the components of biological systems and understand how these interactions give rise to the physiological function of the system. This course will focus on the computational tools designed to investigate and analyze various molecular systems, including metabolic systems, signaling pathways, and gene regulatory networks.

Learning Objectives

After completing this course, you should be able to:

- Construct and analyze computational models of biological systems
- Understand common mathematical approaches to study biological problems
- Apply computational analyses to explore the behavior of biological systems
- Summarize and critique papers from the literature describing systems biology approaches and analysis

Course Notes

This course is designed to introduce you to different aspects of systems biology. Through homework assignments, exams, critical reading of primary literature, class presentations and a collaborative project, students will learn how systems biology approaches can be applied to address important biological questions. The timeline on which the material will be covered is provided below and is subject to change, at the instructor's discretion.

Resources

Web page: A class website will be setup on Blackboard containing information about the course: syllabus, reading handouts, homework assignments, grades, information about class activities, solutions to the

homework sets, and an email directory of all students in the class. Use it as much as you find it useful. The web page can be accessed at: https://Blackboard.usc.edu.

Office Hours: Professor Finley will hold office hours every week. This is for your benefit, and you are welcome to attend office hours as much as you need assistance. Time and location for office hours are at the beginning of the syllabus.

Technological Proficiency and Hardware/Software Required

Several practical modeling examples will be discussed, including hands-on tutorial sessions held in the Discussion period during the first two weeks of the course. Students are asked to bring their laptops, with MATLAB installed. MATLAB is available from USC: https://software.usc.edu/index.aspx#DISTRIBUTED

Required Readings and Supplementary Materials

Systems biology by Edda Klipp, et. al, Wiley-Blackwell, 2016, ISBN 978-3-527-33636-4. Additionally, Professor Finley will provide electronic copies of supplemental readings.

Description and Assessment of Assignments

Overview. Studenst should expect, on average, approximately 8 hours of outside-of-class work per week. This includes completing homework assignments, studying for exams, reading and evaluating journal club articles, identifying questions to raise during discussion of journal articles, working on the research project (establishing aims and completing the proposed work), and preparing oral presentations. These different aspects of the course are described in detail below.

Homework. Students will be responsible for homework sets that incorporate the computational modeling techniques and derivations discussed in class. These assignments are to be completed individually. Homework should be prepared on paper sheets and written legibly. Each problem must start on a new page. Units must be indicated for all numerical results. All derivations must be included with symbols before numbers are "plugged in". Homework sheets must be stapled together. The instructor is not responsible for sheets lost due to not being stapled.

Exams. The course exams will be closed-book tests consisting of quantitative problems and short essay questions. No make ups will be given. Students who are not able to attend an examination due to medical or other emergency must notify the instructor **before** the exam via phone message at 213-740-8788 or email at sfinley@usc.edu. Proper documentation for medical emergencies is required.

Journal club articles. Students will critically read several journal articles, selected from a list of published papers. The articles will be foundational papers in systems biology describing mathematical models that are relevant to human health and disease, while still manageable for students to understand and work with (i.e., < 30 differential equations that are described in detail and can be implemented in MATLAB to reproduce the results presented in the paper). A representative example of a paper is Kholodenko, *et al.*, "Quantification of short term signaling by the epidermal growth factor receptor", *Journal of Biological Chemistry* **74**, 30169-30181 (1999), which models an important signaling pathway using 22 nonlinear ordinary differential equations.

Each student will evaluate one of the journal club articles and write a summary and critique of the article. The written assignment deadline is listed in the weekly course schedule below. The rubric for the summary/critique is provided on the Blackboard course site (also, see **Attachment A** below).

Students are required to participate in discussion of the papers following each presentation. Thus, students should review the paper and identify 2-3 questions that can be mentioned during the discussion of each paper. Participation in journal article discussions will be assessed by submitting the list of questions and by raising those questions during the discussion. Specifically, students will receive points for asking questions and engaging in the discussion.

Group project. Students will be divided into teams of 2-3 members and select a journal article that will be the basis of their research project. Student teams will present their article in class and lead a discussion of the merits and limitations of the paper (follow rubric in **Attachment A** below). There are typically 20 students in the class; thus, with teams of 3-4 students, we will have a maximum of 5 teams. Journal article presentations are scheduled for three lecture periods (see Weekly Schedule listed below). By giving each team a total of ~25 minutes for their presentation (20 minutes, plus 5 minutes for questions), we can easily accommodate two presentations in the 80-minute class period.

The teams will then reproduce the results from their journal article, propose two specific aims to extend the work based on concepts from the class, and work to complete the proposed aims. **Each group must schedule time to meet with the instructor individual to review their proposed aims by the end of Week 9**.

Examples of appropriate proposals for the final project include: extending the model to include new species or reactions (to make the model more physiological); performing a sensitivity analysis of the model parameters; performing bifurcation analysis on key model parameters. The rubric for the proposal is provided on the Blackboard course site (also, see **Attachment B** below), and all propsals should address the items listed in the rubric. A successful proposal will clearly explain two specific aims that follow logically from a limitation or gap in the work presented in the assigned journal article, present the methods used to complete the aims, and describe expected results (See **Attachment C** below, which is an example of a successful proposal from Spring 2015).

The research proposal will be submitted in typed form. Results from the group project will be presented in typed form and orally on the Final Examination date (**TBA, according to the University's Final Examination Schedule**). The rubric for the written proposal and final project presentation is provided on the Blackboard course site (also, see **Attachment D** below).

For the oral presentation, each student in the team must give a portion of the presentation, and the group will be evaluated as a whole, sharing the same grade. The teams will have up to 15 minutes for their presentations and an additional three minutes to answer questions. There are typically 20 students in the class; thus, with teams of 3-4 students, we will have a maximum of 5 teams. By giving each team a total of ~20 minutes for their presentation (15 minutes, plus 3 minutes for questions), we can easily accommodate all presentations in the 120-minute period reserved for the final exam.

Discussions

The discussion section aims to achieve three primary goals: (1) provide the opportunity to emphasize MATLAB programming concepts and their application to the systems biology principles and problems presented in the lectures; (2) provide additional time to complete more in-depth problems for which there is limited time to cover in class; and (3) enable discussion of the journal articles presented in class in greater depth.

Grading Breakdown

Grades will be based on the written critiques and presentations of one journal article and a research proposal, project, and presentation. The weighting scheme for the final grade is below:

Homework assignments	**20%**
Exams	**20%**
Journal article critique	**15%**
Participation during journal club presentations	**5%**
Group research project:	
Journal club presentation	**10%**
Written proposal	**10%**
Final report and presentation	**20%**
Total:	**100%**

Assignment Rubrics

Rubrics are provided as **Attachments A through D** at the end of the syllabus.

Assignment Submission Policy

Homework. Hard copy results of the homework assignments will be due by the indicated due date. MATLAB code should be submitted via Blackboard by the deadline. MATLAB code must be submitted as a zipped folder with all required dependencies directly in that folder. Name the script that produces the results as "Main.m" and the folder name as "LASTNAME_HW<X>.zip". **Make sure the code works as a stand-alone before submitting it**. Points will be deducted from the homework score if the code does not work as submitted.

Group projects. Electronic versions of the research proposal and final report should be submitted via Blackboard.

Grading Timeline

Graded homework assignments will be returned one week after the due date. Other assignments (presentations, research proposal) will be graded and returned within two weeks of submission.

Additional Policies

***Email communication*.** Please refrain from email Professor Finley with questions regarding course content or homework. Email is not the best platform to answer questions, as typically, questions will require a face-to-face eplanation. Therefore, students are urged to utilize office hours and in-class interactions rather an relying solely on email.

Late policy. Late reports and homework will only be accepted without penalty if special circumstances exist (i.e., medical emergencies) and permission is given before the deadline. Proper documentation for medical emergencies is required. Otherwise, points will be reduced by 10% for each 24-hour period it is late, starting immediately after the deadline. There are no make-up days for presentations or exams.

Electronic devices. Electronic communication devices (i.e., phones, laptops, tablets) must be turned off or put away during lectures. Students are prohibited from using messaging apps/programs during class.

Course Schedule

**Schedule subject to change, at the Professor's discretion*

***Readings refer to main text*

Week	Topics	Readings**	Activity	Discussion topics
1	**Overview** Introduction to systems biology and mathematical models Mass-action kinetics	Chapters 1, 2 Section 4.1	**HW 1 assigned**	Introduction to MATLAB Plotting data in MATLAB
2	**Modeling biochemical reaction networks** Timescale separation Enzyme-catalyzed reactions	Section 6.3 Section 4.1	**Sign up for journal articles**	Simulating systems biology models in MATLAB
3	**Modeling biochemical reaction networks** Regulation of enzyme activity, Cooperativity **Cooperativity, Alternative reaction mechanisms**	Section 4.1 Chapter 5	**HW 1 due,** **HW 2 assigned**	Simulating systems biology models in MATLAB
4	**Analysis of dynamic mathematical models** Phase planes, Direction fields, Nullclines Linear stability analysis	Sections 15.1, 15.2		Performing phase plane analysis in MATLAB
5	**Analysis of dynamic mathematical models** Linear stability analysis, Bifurcation analysis Bifurcation analysis, Sensitivity analysis	Section 10.1 Sections	**HW 2 due,** **HW 3 assigned**	Exam review
6	**Analysis of dynamic mathematical models** **Parameter fitting** MIDTERM EXAM #1	Section 6.1	**EXAM**	Performing bifurcation analysis, Sensitivity analysis, and Parameter estimation in MATLAB
7	**Metabolic networks** Graph theory Graph theory, Stoichiometric analysis	Section 8.1 Chapter 3		**Visualizing and analyzing graphs using Cytoscape**
8	**Signaling systems** Stoichiometric analysis, **Modeling metabolism** **Signaling motifs**	Sections 4.2, 12.1	**HW 3 due**	**Evaluating published literature** **Presenting journal articles**
9	**Signaling systems and Gene regulation** **Signaling motifs** Signal amplification, Ultrasensitivity	Sections 12.2 to 12.4	**HW 4 assigned** **Journal club summary/critiques due**	**Models of the MAPK pathway**

	SPRING RECESS (NO CLASS)			
10	**Signaling and Gene regulatory systems** Simple regulation JOURNAL ARTICLE PRESENTATIONS	Section 8.2 PAPERS	**HW 4 due,** **HW 5 assigned**	**Student-led discussion of journal articles**
11	**Signaling and Gene regulatory systems** Autoregulation JOURNAL ARTICLE PRESENTATIONS	Section 8.2 HANDOUT	**Research proposal due**	**Student-led discussion of journal articles**
12	**Signaling and Gene regulatory systems** Feed-forward loops JOURNAL ARTICLE PRESENTATIONS	HANDOUT PAPERS	**HW 5 due**	**Student-led discussion of journal articles**
13	**Signaling and Gene regulatory systems** Feed-forward loops Regulatory motifs	Section 8.2		Interactive activity for review of regulatory motifs and Exam review
14	**Signaling and Gene regulatory systems** Regulatory motifs MIDTERM EXAM #2	PAPERS	**EXAM**	**Oscillators and cell cycle control**
15	**Signaling and Gene regulatory systems** **Stochastic modeling** **Stochastic modeling**	Section 15.4 Section 7.2		**Implementing Gillespie's algorithm in MATLAB**
Finals week	**FINAL PRESENTATIONS, 2 – 4pm**			

Statement on Academic Conduct and Support Systems

Academic Conduct:

Plagiarism – presenting someone else's ideas as your own, either verbatim or recast in your own words – is a serious academic offense with serious consequences. Please familiarize yourself with the discussion of plagiarism in SCampus in Part B, Section 11, "Behavior Violating University Standards" policy.usc.edu/scampus-part-b. Other forms of academic dishonesty are equally unacceptable. See additional information in SCampus and university policies on scientific misconduct, policy.usc.edu/scientific-misconduct.

Support Systems:

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

National Suicide Prevention Lifeline - 1 (800) 273-8255 – 24/7 on call
suicidepreventionlifeline.org
Free and confidential emotional support to people in suicidal crisis or emotional distress 24 hours a day, 7 days a week.

Relationship and Sexual Violence Prevention and Services (RSVP) - (213) 740-9355(WELL), press "0" after hours – 24/7 on call
studenthealth.usc.edu/sexual-assault
Free and confidential therapy services, workshops, and training for situations related to gender-based harm.

Office of Equity and Diversity (OED)- (213) 740-5086 | Title IX – (213) 821-8298
equity.usc.edu, titleix.usc.edu
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. The university prohibits discrimination or harassment based on the following *protected characteristics*: race, color, national origin, ancestry, religion, sex, gender, gender identity, gender expression, sexual orientation, age, physical disability, medical condition, mental disability, marital status, pregnancy, veteran status, genetic information, and any other characteristic which may be specified in applicable laws and governmental regulations. The university also prohibits sexual assault, non-consensual sexual contact, sexual misconduct, intimate partner violence, stalking, malicious dissuasion, retaliation, and violation of interim measures.

Reporting Incidents of Bias or Harassment - (213) 740-5086 or (213) 821-8298
usc-advocate.symplicity.com/care_report
Avenue to report incidents of bias, hate crimes, and microaggressions to the Office of Equity and Diversity |Title IX for appropriate investigation, supportive measures, and response.

The Office of Disability Services and Programs - (213) 740-0776
dsp.usc.edu
Support and accommodations for students with disabilities. Services include assistance in providing readers/notetakers/interpreters, special accommodations for test taking needs, assistance with architectural barriers, assistive technology, and support for individual needs.

USC Support and Advocacy - (213) 821-4710
uscsa.usc.edu

Assists students and families in resolving complex personal, financial, and academic issues adversely affecting their success as a student.

Diversity at USC - (213) 740-2101
diversity.usc.edu
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
dps.usc.edu, emergency.usc.edu
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) 442-120 – 24/7 on call
dps.usc.edu
Non-emergency assistance or information.

ATTACHMENT A **BME 530: Introduction to Systems Biology**

Rubric for Journal Club Summary/Critique

Name: _____ Date: _____

Paper evaluated: _____

Points possible	***Item***	***Points assigned***
10	**Biology** *Provide background information about the system* *Describe the importance and broader impact of the system*	
10	**Questions / problems addressed** *Clearly describe the questions being studied* *Explain the rationale and justification for studying the question(s)*	
10	**Methods** *Clearly describe the methods* *Explain the assumptions made* *Identify the problems and limitations of the selected methods*	
30	**Results and discussion** *Clearly describe and explain results* *Describe importance and biological significance of the results*	
20	**Issues identified** *State the limitations of the study identified by the authors* *State the limitations of the study you identified*	
10	**Path forward** *Propose ideas about refining study and / or new applications*	
10	**Writing style** *Clear, well-organized, easy to follow* *Proper grammar*	
	Total Points	___ ***/100***

Additional comments and feedback:

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ATTACHMENT B **BME 530: Introduction to Systems Biology**

Rubric for Research Proposal

Each team will write a specific aims page that proposes specific biological questions that can be addressed with mathematical analyses. The proposed work should use concepts described in class. Examples of appropriate proposals include: extending the model to include new species or reactions; performing a sensitivity analysis of the model parameters; performing bifurcation analysis on key model parameters.

Formatting requirements
Page limit: 1 page, single-spaced
Margins: No less than 0.75" around page
Font size: Arial 11pt or Times New Roman 12pt

Pts possible	***Item***	***Pts assigned***
20	**Introduction** *Describe the biological system being studied and its importance.* *Describe results from previous studies of this system.* *Identify the gap in the field or limitations of previous work.* *Background information and previous work should logically lead to the specific aims.*	
25	**Specific aims** *Clearly state two well-defined, original specific aims.* *The aims should be built on the introduction.*	
25	**Research methods** *Concisely describe the approaches you will take to accomplish the aims.*	
20	**Expected outcomes and potential results** *Describe the reasonable results expected.* *Describe what you expect to learn from completing the aims.* *Tie the expected results to previous work described in the introduction section.*	
10	**Grammar and style** *Clear, concise writing with good flow.* *Complete sentences and proper grammar.*	
	Total Points	___ ***/100***

Additional comments and feedback:

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ATTACHMENT C **Example of Successful Research Proposal**

BME 599 Research Proposal (Spring 2015; *assigned a grade of 98/100*)

In industrial fermentation processes, maximizing the production of the desired compound is crucial in terms of economics and efficiency. An article published by Shiraishi *et al.* in 2009 elucidates the importance of identifying the bottleneck enzyme in the penicillin V (PenV) fed-batch fermentation process as a means of expediting the synthesis of PenV. This system is utilized because the mathematical model accurately fits previously studied experimental results with enzymatic reaction kinetics. The bottleneck enzyme is the key enzyme in a metabolic reaction network that most strongly controls reactions in producing the desired metabolite, in which increasing its activity will increase the amount of product output. The results from the paper showed that the logarithmic value gains changed over time, thus implying that the bottleneck enzyme can change during the course of the fermentation process. However, the paper does not verify the bottleneck enzymes by testing multiple initial conditions nor does it further investigate the impact that the bottleneck enzymes have on PenV production. In order to mediate these issues, we aim to finitely change various parameters to verify the predicted bottleneck enzyme over the entire time course and to change the level of the bottleneck enzyme's activity.

Aim#1: In order to study the dynamics of the system, we will verify the predicted bottleneck enzymes proposed by Shiraishi et al. with a local sensitivity analysis involving finite change in various parameters. In particular, we will alter three parameters of interest: the liquid volume in the fermenter (X12), the initial cell concentration (X13), and the extracellular glucose concentration (X14). We will incrementally increase and decrease the values by 1% up until 10% change from the set value, and also observe changes of even 25% and 50% from the set value. For each change, we will generate metabolite concentration profiles and the corresponding logarithmic gain time courses. During the periods in which one enzyme exhibits bottleneck characteristics, we will observe whether the enzyme continues to have the largest dynamic logarithmic gain in response to finite changes in the parameters. If the same enzyme maintains the largest dynamic logarithmic gain in response to all the finite parameter changes, then we can verify that the enzyme is the bottleneck.

Aim#2: In order to explore the sensitivity of the system to changes in the activity of the bottleneck enzyme, we will alter each enzyme's activity during the time it exhibits bottleneck properties. The work conducted by Shiraishi et al. demonstrated that the bottleneck enzyme changes over the time course of the fermentation process. The work, however, does not investigate further the implications of this finding. By increasing and decreasing an enzyme's activity in finite steps (1% to 10%, 25%, and 50%) when it becomes the bottleneck, we hope to characterize the change in system PenV output due to this enzymatic change. This characterization would have far reaching implications, especially in the industrial production of PenV. If our model were to demonstrate that specifically targeting bottleneck enzymes during the batch fermentation process significantly increases the yield, the efficiency of industrial fermentation processes could be improved.

By accomplishing these specific aims, we hope to better understand the PenV fed-batch fermentation process. From Aim#1, we expect to learn if the bottleneck enzymes described by Shiraishi et al. are characteristic of the system, or a result of the initial conditions and parameters selected by the experimenters. We expect to find that changing system parameters does not drastically alter the bottleneck enzymes of the system, although it may alter the yield. From Aim#2, we expect to learn the impact that the bottleneck enzymes can have on the yield of the system. We expect to find that increasing the activity of the bottleneck enzyme will have a significant impact on the yield of the system and could point to methods that would increase the effectiveness of industrial batch fermentation techniques. By successfully performing these aims, we will better characterize the system explored by Shiraishi *et al.* and provide a practical industrial application for their findings.

Rubric for Group Project Report and Presentation

Group members names:_____

Title of original paper: _____

Points possible	Item	Points assigned
10	**Background and motivation** Provide background information about the biological system Describe the motivating factors for studying this system (*importance and broader impacts*)	
20	**Specific aims of the study** Clearly describe the specific aims (*What did you set out to do? What is the gap or question being addressed?*) Explain the rationale and justification for each of the aims (*Why?*)	
20	**Methods** Clearly describe methods used to address the specific aims (*How?*) Identify limitations of the selected methods Explain the assumptions made	
20	**Results and discussion** Clearly describe and explain results Describe importance and biological significance of the results State the limitations of the study	
10	**Conclusions** Clearly describe the take-away message of the study	
10	**Path forward** Describe what additional work you would complete, given more time (*Provide at least one example of future work.*)	
10	**Style** Report: clearly written; flows well and is easy to read; good grammar Presentation: clear, well-organized, and polished presentation; able to answer questions from the audience	
	Total Points	**___ /100**

Additional comments and feedback:

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