USCViterbi

BME 430: Principles and Applications of Systems Biology
Units: 3
Fall 2017 — Mon/Wed: 2:00 - 3:20pm

Location: KAP 164

Instructor: Professor Stacey D. Finley
Office Location: DRB 172
Office Hours: Tuesdays and Wednesdays: 9:00 – 10:00 am
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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 signaling pathways, metabolic systems, and gene regulatory networks.

Learning Objectives, Specific Outcomes of Instruction, and Relationship to Program Outcomes

1. *Learning objectives*
   - Understand the principles and concepts of computational systems biology tools and analysis
   - Construct and analyze mathematical models of biological systems
   - Summarize and critique papers from the literature describing systems biology approaches and analyses

2. *Course outcomes*
   - Outcome 1: Apply principles and concepts of computational systems biology tools and analysis.
   - Outcome 2: Construct and analyze mathematical models of biological systems.
   - Outcome 3: Summarize and apply computational theories and techniques used in systems biology.
   - Outcome 4: Critically read and summarize journal articles selected from published papers in systems biology and prepare structured write-ups and oral presentations of the articles.
   - Outcome 5: As part of a team, design a computational project to extend the research of a published work. Present experimental results in writing and orally.

3. *Relationship between course outcomes and student outcomes*

The BME Student Outcomes (a-k):

(a) an ability to apply knowledge of mathematics, science, and engineering
(b) an ability to design and conduct experiments, as well as to analyze and interpret data
(c) an ability to design a system, component, or process to meet desired needs within realistic constraints such as economic, environmental, social, political, ethical, health and safety, manufacturability, and sustainability
(d) an ability to function on multi-disciplinary teams

(e) an ability to identify, formulate, and solve engineering problems
(f) an understanding of professional and ethical responsibility
(g) an ability to communicate effectively
(h) the broad education necessary to understand the impact of engineering solutions in a global, economic, environmental, and societal context
(i) a recognition of the need for, and an ability to engage in life-long learning
(j) a knowledge of contemporary issues
(k) an ability to use the techniques, skills, and modern engineering tools necessary for engineering practice

Course outcomes↓ Student Outcomes →	a	b	c	d	e	f	g	h	i	j	k
Outcome 1:	X				X						
Outcome 2:					X						X
Outcome 3:	X				X						
Outcome 4:							X		X	X	
Outcome 5:				X			X		X		X
All course outcomes	X			X	X		X		X	X	X

Course Preparation

Prerequisite: BME 210 or CHE 205; MATH 245
Recommended preparation: BISC 220

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 Backboard 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 should feel 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 an in-class computer session, tentatively scheduled for August 30, 2017 Students should bring their laptops, with Matlab installed. Matlab is available from the university: https://software.usc.edu/index.aspx#DISTRIBUTED.

Required Readings and Supplementary Materials

Mathematical modeling in systems biology by Brian P. Ingalls, MIT Press, 2013 (ISBN 9780262018883). Professor Finley will provide electronic copies of supplemental readings and make them available on the course website.

Description and Assessment of Assignments

Homework. Students will be responsible for six 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.

***Journal club articles*.** Students will critically read several journal articles, selected from a list of published papers, and individually prepare a short write-up of the articles. The articles will be selected from 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., < 20 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 Krishna, *et al.*, "Minimal model of spiky oscillations in NF-κB signaling", *PNAS*, **103**, 10840–10845 (2006), which models an important transcription factor using three nonlinear ordinary differential equations.

Students will sign up for two papers to review. The write-ups are due by the beginning of class on October 16, 2017 (submit electronic version online and hard copy in class). The write-ups are intended to encourage discussion during the group journal club presentations (described below), and class participation is incorporated into your grade. The write-up must consist of: 1) An overview paragraph stating the purpose of the work, the main methods, and the findings; 2) A one-paragraph description of one results figure from the paper and the methods used to generate the results in the figure; and 3) Two questions or discussion subjects regarding some component of the paper. Combined, the two write-ups should be no more than one single-sided page.

Group project. Students will critically read and evaluate one of the journal club articles and individually prepare a summary and critique of the paper. Then, teams involving 2-4 students will work to present their journal article in class. Prior to the presentation, I will meet with each group individually to answer any questions regarding the model, its significance, and its broader implications.

Each team will work to reproduce the results from their journal club article and propose and execute a project to extend the published work. Examples of appropriate proposals for future work include: extending the model to include new species or reactions (to make the mode 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, and all propsals should address the items listed in the rubric (see **Attachment A**

below). A successful proposal will clearly explain two specific aims that follow logically from a limitation or gap in the existing work presented in the assigned journal article, present the methods used to complete the aims, and describe expected results (see **Attachment B** below, which is an example of a successful proposal from Fall 2014).

The research proposal, including results from reproducing the published work ("preliminary results"), will be submitted in written form. Results from the group project will be presented orally on the Final Examination date (Friday, December 8, 2017; 2:00 – 4:00 pm). 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. The rubrics for the written critique and presentations are provided on the Blackboard course site (also, see **Attachments C and D** below).

Grading Breakdown

Grades will be based on the individual assignments (homework, exams, journal club write-ups, paper summary/critique) and the group project (journal club and final presentations, and research proposal).

The weighting scheme for the final grade is below:

Exams	**25%**
Homework assignments	**20%**
Written paper summary/critique	**15%**
Journal club write-ups and Participation	**10%**
Group research project:	
Journal club presentation	**10%**
Research proposal	**10%**
Final presentation	**10%**
Total:	**100%**

Assignment Submission Policy

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. 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 for code that does not run. Additional directions for code submission may be provided.

Electronic versions of the research proposal and final report should be submitted via Blackboard. Hard copies are due in class on the due date.

Additional Policies

***Email communication*.** Please do not email Professor Finley with questions regarding course content or homework. It is not possible to answer all questions via email, and these questions are better explained face-to-face. Therefore, you must utilize office hours and in-class interactions rather than 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. Otherwise, points will be reduced by 10% for each day it is late. There are no make-up days for presentations or exams.

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

Course Schedule *(The timeline is subject to change, at the instructor's discretion.)*

Date	Topics	Reading*	Activity
8/21/17 8/23/17	**Overview and Biology in a nutshell** Introduction to systems biology and mathematical models Dynamic models, Mass-action kinetics	Appendix A 2.1	**Form groups, HW 1 assigned**
8/28/17 8/30/17	**Modeling biochemical reaction networks** Timescale separation, Enzyme kinetics Tutorial: Modeling ODE systems in MATLAB	2.2, 3.1 – 3.2	**Assign papers**
9/4/17 9/6/17	**Modeling biochemical reaction networks** **NO CLASS** in observance of Labor Day Regulation of enzyme activity, Cooperativity	3.2	**HW 1 due, HW 2 assigned**
9/11/17 9/13/17	**Aanlysis of dynamic mathematical models** Phase planes, Direction fields, Nullclines Stability analysis	3.3 – 3.4, Appendix C.2	**HW 2 due, HW 3 assigned**
9/18/17 9/20/17	**EXAM 1** Stability analysis, Bifurcation analysis	4.1 – 4.2	**EXAM**
9/25/17 9/27/17	**Analysis of dynamic mathematical models** Bifurcation analysis Sensitivity analysis, Parameter fitting	4.4	
10/2/17 10/4/17	**Model analysis and Metabolic networks** Metabolic networks: Graph theory Graph theory, Stoichiometric network analysis	4.5 – 4.6	**HW 3 due, HW 4 assigned**
10/9/17 10/11/17	**Metabolic networks** Stoichiometric network analysis Modeling metabolic networks	5.4	**Paper critique due**
10/16/17 10/18/17	**JOURNAL CLUB PRESENTATIONS**		**Paper write-ups due, Presentations**
10/23/17 10/25/17	**Metabolic and Signaling networks** Network motifs of signaling systems Network motifs of signaling systems	5.1 – 5.3	**HW 4 due, HW 5 assigned**
10/30/17 11/1/17	**Signaling systems** *NO CLASS* Signal amplification, Ultrasensitivity	6.1 – 6.4	
11/6/17 11/8/17	**Signaling and Gene regulatory systems** Simple regulation Autoregulation	Alon handout, 7.1 – 7.4	**HW 5 due, HW 6 assigned**

11/13/17 11/15/17	**Gene regulatory systems** Feed-forward loops Feed-forward loops	Alon handout, 7.5	**Research proposal due**
11/20/17 11/22/17	**Gene regulatory systems** Regulatory motifs Stochastic modeling	7.5, 7.6	**HW 6 due**
11/27/17 11/29/17	**REVIEW SESSION** **EXAM 2**		**EXAM**
12/8/17	**FINAL PRESENTATIONS (during Final Examination Period)**		

** Indicates section(s) from textbook and/or additional handouts provided by Prof. Finley made available via the course website on Blackboard.*

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 Section 11, *Behavior Violating University Standards* https://scampus.usc.edu/1100-behavior-violating-university-standards-and-appropriate-sanctions. Other forms of academic dishonesty are equally unacceptable. See additional information in *SCampus* and university policies on scientific misconduct, http://policy.usc.edu/scientific-misconduct.

Discrimination, sexual assault, and harassment are not tolerated by the university. You are encouraged to report any incidents to the *Office of Equity and Diversity* http://equity.usc.edu or to the *Department of Public Safety* http://capsnet.usc.edu/department/department-public-safety/online-forms/contact-us. This is important for the safety of the whole USC community. Another member of the university community – such as a friend, classmate, advisor, or faculty member – can help initiate the report, or can initiate the report on behalf of another person. *The Center for Women and Men* http://www.usc.edu/student-affairs/cwm/ provides 24/7 confidential support, and the sexual assault resource center webpage http://sarc.usc.edu describes reporting options and other resources.

Support Systems

A number of USC's schools provide support for students who need help with scholarly writing. Check with your advisor or program staff to find out more. Students whose primary language is not English should check with the *American Language Institute* http://dornsife.usc.edu/ali, which sponsors courses and workshops specifically for international graduate students. *The Office of Disability Services and Programs* http://sait.usc.edu/academicsupport/centerprograms/dsp/home_index.html provides certification for students with disabilities and helps arrange the relevant accommodations. If an officially declared emergency makes travel to campus infeasible, *USC Emergency Information* *http://emergency.usc.edu* will provide safety and other updates, including ways in which instruction will be continued by means of blackboard, teleconferencing, and other technology.

ATTACHMENT A

BME 430: Principles and Applications of Systems Biology
Rubric for Research Proposals

Each team will write a research proposal that includes specific biological questions for future work that can be accomplished 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: 3 pages, single-spaced includes figure(s), references limited to one additional page
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.* *Cite pertinent sources from different research groups that have studied this system, and describe their results.* *Background information and previous work should logically lead to the specific aims* *Provide smooth transition into the specific aims.*	
10	**Specific aims** *Clearly state two well-defined, original specific aims.* *The aims should be built on the introduction.*	
20	**Research methods** *Clearly describe methods and tools needed to accomplish the aims.* *Present the required equations and/or theory.*	
10	**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 from introduction section.*	
20	**Preliminary results** *Reproduce at least one data figure from the assigned paper.* *Properly label the axes and curves.* *Provide figure legend that describes the results.* *Matlab code used to generate the results will be submitted separately.*	
10	**Conclusions** *Summarize the proposed work.* *Highlight the novelty and importance of the proposed work.*	
10	**Grammar and style** *Clear, concise writing with good flow.* *Complete sentences and proper grammar.* *Proper headings for the sections*	
	Total Points	___ ***/100***

BME 499 Research Proposal (Fall 2014)

Introduction

Amoxicillin is a commonly prescribed broad spectrum antibiotic is used to treat a variety of ailments including pneumonia, skin infections, urinary tract infections, Salmonella, Lyme disease, sickle cell anemia, and bacterial endocarditis. Amoxicillin is a 4-membered ß-lactam ring, which enables it to prevent the synthesis of bacterial walls - making it a highly efficient treatment for a wide variety of bacterial infections [1]. Currently, pneumonia is the leading cause of death in children under 5, particularly in Africa and Southeast Asia. Of the 97 million pneumonia cases recorded annually, roughly 80% of the children receive improper or no treatment [2]. Our hope is that, in determining a more efficient method of producing amoxicillin, we can increase its accessibility for children with pneumonia and other bacterial infections.

In addition to amoxicillin's wide application, other advantages of this synthetic compound include high solubility and absorption properties, and stability in acidic conditions. However, the current industrial chemical process has disadvantages such as high energy costs, toxic solvents, and high waste production [3]. Instead, a milder enzyme-catalyzed pathway, which produces amoxicillin and methanol from p-hydroxyphenylglycine methyl ester (POH-PGME) and 6-aminopenicillanic acid (6-APA) using the enzyme penicillin G acylase (PGA) from Escherichia coli bacteria, was developed [3]. As shown in Figure 1, PGA catalyzes the main synthesis reaction (Vs) as well as two side hydrolysis reactions of the substrate and product (Vh1 and Vh2 respectively). To achieve its catalytic activity, PGA works in conjunction with ester side chains that function as acylating agents [4]. Therefore, varying the acylating agent has the potential to influence the enzymatic activity of PGA.

Goncalves et al has done extensive work in determining a model that accurately represents the reaction network for the semi-batch fed production of amoxicillin. For the purposes of their work - to determine optimal operational conditions for a single set of inputs and initial conditions - they used a hybrid neural-network model and found their input equations and parameters capable of accurately fitting experimental data. As a result, we feel confident in basing our model of amoxicillin synthesis off of their findings [3],[5].

The inspiration for our proposal comes from the work of Fernández-Lafuente et al, who observed a dual enhancing/inhibitory interaction between the methanol byproduct of amoxicillin synthesis (Figure 1) and PGA, depending on the acylating agent used [4]. Methanol has a contradictory effect when POH-PGME is the acylating agent, by increasing the synthesis/hydrolysis activity ratio of PGA with amoxicillin (vs: vh2) but decreasing the synthesis/hydrolysis activity with the POH-PGME (vs: vh1). However, methanol increases both activity ratios when mandelic acid is the acylating agent. According to Fernández-Lafuente et al., these effects can be modulated based on the PGA enzyme derivative used [4].

Specific aims

Because of the global importance of amoxicillin, our team believes further research on the dynamics of its enzymatic synthesis worthwhile. Our goal is to establish a better understanding of the reaction network and potentially elucidate conditions to maximize production of the antibiotic. To achieve this goal, our team has set forth two primary aims.

The first aim is to generate a dynamic model for the semi-batch, enzymatic synthesis of amoxicillin. To accomplish this, we will use the collection of ordinary differential equations and associated parameters generated by Goncalves et al, who previously established the quality of fit for the set of differential equations describing amoxicillin synthesis to experimental data. Using Matlab, we will simultaneously solve the differential equations for the metabolite concentrations and the sensitivity values by applying numerical differentiation methods and variable-step, variable order Taylor series methods - similar to Shirashi et al [6]. This computation also yields the dynamic logarithmic gains for the enzyme catalyzed pathway [6].

The second aim of this proposal is to apply the methodology for finding the bottleneck enzyme, as described by Shirashi et al, for the synthesis of amoxicillin [6]. Shirashi et al created their bottleneck enzyme methodology for the fermentation of Penicillin V (Pen V), which is catalyzed by three different enzymes. While PGA is the sole catalyst for amoxicillin synthesis, it has two distinct roles - as a synthetase for amoxicillin, and hydrolase for both the amoxicillin and the acylating agent (Figure 1). Because of this dual enzymatic action across three elementary reactions, we believe the techniques outlined by Shirashi et al for determining the effects of multiple enzymes on the output of a reaction network can be applied here to determine the effects of varying derivatives of PGA on amoxicillin output.

Our goal is to find the combination of PGA enzyme derivative and conditions that is the "bottleneck" - the combination to which amoxicillin production is most sensitive - using the methods set out by Shirashi et al [6]. While they analyzed a multiple-enzyme catalyzed network, the overall goal was to observe how changes in enzyme activity affected the overall output of Pen V. We are asking a similar question here: changes in which enzyme derivative have the most profound impact on amoxicillin production? If we can establish which combination results in the greatest changes in amoxicillin production, we can offer insight into how the enzymatic synthesis of amoxicillin can be optimized.

To accomplish this aim, we will vary the combination of acylating substrate (phenylglycine methyl ester or mandelic acid) and PGA derivatives (3 total) to generate parallel simulations of amoxicillin synthesis. These will be done for the non-steady state case, with infinitesimal and finite changes in enzyme activity. Using the computational methods in Shirashi et al, we will ultimately calculate the time-averaged logarithmic gains of amoxicillin production for each simulation [6]. In ranking the calculated gains of each enzyme derivative for the infinitesimal and finite changes in enzyme activity, we hope to determine the bottleneck enzyme derivative/acylating agent combination.

Research Methods

In varying the combination of acylating agent and PGA derivative, we will run a total of 6 different variations of amoxicillin synthesis. Each of these six variations will be run twice at non-steady state conditions, the first with infinitesimal changes in enzyme derivative activity and the second with finite changes. We will use equations and parameter values for amoxicillin synthesis established by Gonclaves, which apply for a semi-batch reactor at pH 6.5 and 25 C [3]. Input concentrations of PGA derivatives and acylating agents will be taken from Fernández-Lafuente et al, and methanol concentrations will be fixed at 20% in order to observe the effects of the byproduct on the catalytic activity of PGA [4].

Using the reaction model just described, we would follow the procedure outlined by Shirashi et al for determining the bottleneck enzyme [6]. First, we would calculate time-course metabolite concentrations and logarithmic gains for each simulation. Then we would compute and rank the time-averaged logarithmic gains of each simulation, for both infinitesimal and finite changes in enzyme activity. Lastly, we would assess the correlation between rankings for infinitesimal and finite changes in activity, and follow the prescribed next steps from Shirashi et al for determining the bottleneck enzyme derivative [6].

Expected outcomes and potential results

The primary outcome of the proposed study would be to ascertain if proposed methods for determining the bottleneck enzyme of a multiple-enzyme catalyzed pathway could be extended to parallel simulations of a single-enzyme catalyzed pathway. The simulation with highest ranking time-averaged logarithmic gain could be identified as the "bottleneck" enzyme derivative/acylating agent combination – meaning the combination that, when enzyme activity is changed, results in the greatest fluctuations in amoxicillin production. In order for this to occur, we expect to find some distinct variation of amoxicillin output between the different combinations of acylating agents and derivatives. This ideally would lead to a clear ranking of the time-averaged logarithmic gains for

each simulation, and therefore a clear bottleneck candidate. As seen in Shirashi et al, there may be some disagreement between infinitesimal and finite enzyme changes [6]. To rectify the inconsistency, we would have to take the further steps prescribed by Shirashi et al to see if this remedies the discrepancy [6]. Ideally, our results would establish one PGA derivative/acylating agent combination as superior to the others. However, a more reasonable outcome is eliminating less effective combinations. Further simulations and testing could be done to optimize the production of amoxicillin with this narrowed scope of useful enzyme derivatives/acylating agent combinations.

Conclusions

Our novel proposal involves two key steps: modeling the kinetic synthesis of amoxicillin and applying the methods of Shirashi et al to analyze how varying derivatives of PGA and acylating agents impact overall amoxicillin production. Rather than applying the methods for finding the bottleneck enzyme to a multi-enzyme catalyzed network, we aim to extend them to studying the impact of varying enzyme derivatives in a single enzyme catalyzed network.

The bottleneck enzyme derivative would correlate to the simulation involving the combination of acylating agent and the enzyme derivative to which the production of amoxicillin is most sensitive. By establishing this combination, it could give a target for manipulation in the large-scale enzymatic synthesis of amoxicillin that would optimize production and increase the availability of the crucial medication.

The results of the study also have the potential to inspire further research. If the validity of this extension of Shirashi et al is established, it may pertain to other single enzyme catalyzed synthesis reactions. Furthermore, establishing a functioning model of amoxicillin synthesis allows for further exploration of the system. Performing extended analyses - including sensitivity analyses and varying catalytic as well as other input parameters - will increase our understanding of the overall dynamics of amoxicillin synthesis as catalyzed by PGA.

1. $\frac{dCAB}{dt} = -vAN - vAOH + FAB$
2. $\frac{dCAN,I}{dt} = vAN$
3. $\frac{dCAOH,I}{dt} = vAOH$
4. $\frac{dCNH}{dt} = -vAN + FNH$
5. $\frac{dCAN,I}{dt} = 0$
6. $\frac{dCAN,S}{dt} = vAN$
7. $\frac{dCAOH,L}{dt} = 0$
8. $\frac{dCAOH,S}{dt} = vAOH$
9. $vh2 = \frac{Kcat2 * Ce * Can}{Km2\left(1 + \left(\frac{Cab}{Kab}\right) + (Cnh/knh) + (Caoh/kaoh)\right) + Can}$
10. $vs = \frac{Kcat1 * Ce * Cab}{Km1\left(1 + \left(\frac{Can}{Kan}\right) + (Cnh/knh) + Caoh/kaoh)\right) + Cab} * \frac{Cnh}{Ken + Cnh} * Tmax$
11. $vab = \frac{Kcat1 * Ce * Cab}{Km1\left(1 + \left(\frac{Can}{Kan}\right) + (Cnh/knh) + Caoh/kaoh)\right) + Cab}$

Shirashi, F., and Suzuki, Y. (2009). Method for Determination of the Main Bottleneck Enzyme in a Metabolic Reaction Network by Dynamic Sensitivity Analysis. *Ind. Eng. Chem. Res.* 48: 415-423.

Parameter	Value	Parameter	Value
Kcat1	(0.18+-0.2)*10^-1	Ken	14.4+-2.1
Kcat2	(0.33+-0.3)*10^-1	Kab	3.78+-0.7
Kas1	7.91+-3.6	Kan	9.17+-2.1
Kas2	12.5+-3.2	Kaoh	10.9+-2.1
Tmax	(0.61+-)*10^-1	Knh	62+-7.2

Shirashi, F., and Suzuki, Y. (2009). Method for Determination of the Main Bottleneck Enzyme in a Metabolic Reaction Network by Dynamic Sensitivity Analysis. *Ind. Eng. Chem. Res.* 48: 415-423.

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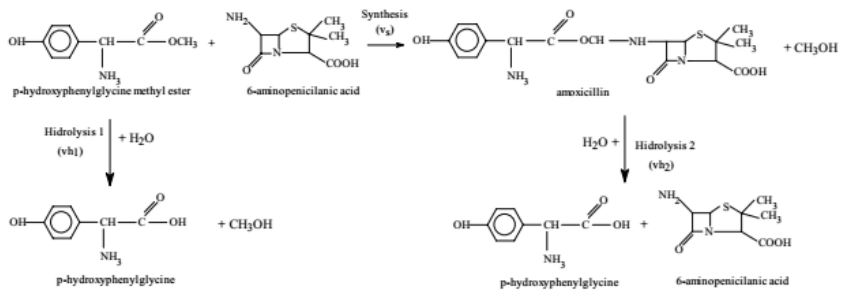

Goncalves, L.R.B, Giordano R.L.C., and Giordano R.C. (2005). Mathematical modeling of batch and semibatch reactors for the enzymic synthesis of amoxicillin. *Process Biochemistry.* 40: 247-256

References

[1] Blum, J. K., Deaguero, A. L., Perez, C. V., & Bommarius, A. S. (2010). Ampicillin Synthesis Using a Two-Enzyme Cascade with Both α-Amino Ester Hydrolase and Penicillin G Acylase. *ChemCatChem*, *2*(8), 987–991. doi:10.1002/cctc.201000135

[2] Gates Foundation (2014). The Growing Market for Amoxicillin Dispersible Tablets. *US AID*: 1-21.

[3] Goncalves, L.R.B, Giordano R.L.C., and Giordano R.C. (2005). Mathematical modeling of batch and semibatch reactors for the enzymic synthesis of amoxicillin. *Process Biochemistry.* 40: 247-256.

[4] Fernández-Lafuente, R., Rossel, C.M., and Guisan, J.M. (1998). The presence of methanol exerts a strong and complex modulation of the synthesis of different antibiotics by immobilized penicillin G acylase. *Enzyme and Microbial Tech.* 23: 305-310.

[5] Goncalves, L.R.B., Fernandez-Lafuente, R., Guisan, J.M., and Giordano, R.L.C. (2002). The role of 6-aminopenicillanic acid on the kinetics of amoxicillin enzymatic synthesis catalyzed by penicillin G acylase immobilized on glyoxyl agarose. *Enzyme and Microbial Technology*. 31: 464-471.

[6] Shirashi, F., and Suzuki, Y. (2009). Method for Determination of the Main Bottleneck Enzyme in a Metabolic Reaction Network by Dynamic Sensitivity Analysis. *Ind. Eng. Chem. Res.* 48: 415-423.

ATTACHMENT C

BME 430: Principles and Applications of Systems Biology
2017 Fall Semester
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* *Identify the problems and limitations of the selected methods* *Explain the assumptions made*	
30	**Results and discussion** *Clearly describe and explain results* *Describe importance and biological significance of the results* *State the limitations of the study*	
20	**Issues identified** *State the limitations of the study identified by the authors* *State the limitations of the study identified by you*	
10	**Path forward** *Propose ideas about refining study and / or new applications of the model*	
10	**Writing style** *Clear, well-organized, easy to follow* *Proper grammar*	
	Total Points	___ ***/100***

Additional comments and feedback:

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_____

ATTACHMENT D

BME 430: Principles and Applications of Systems Biology
2017 Fall Semester
Rubric for Research Proposal Presentations

Name of group members: _____

Paper assigned: _____

Points possible	***Item***	***Points assigned***
20	**Introduction** *Describe the biological system being studied and its importance.* *Describe results from other research groups that have studied this system.* *Clearly explain the background information and previous work so that there is a logical progression into the specific aims.*	
20	**Specific aims** *Clearly state two well-defined, original specific aims.* *Answer the questions: what will you do and why is it important?* *The aims should be built on the introduction.*	
20	**Research methods** *Clearly describe the methods and tools needed to accomplish the aims.* *Present the required equations and/or theory.*	
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.*	
10	**Conclusions** *Summarize the proposed work.* *Highlight the novelty and importance of the proposed work.*	
10	**Presentation style and Questions** *Clear, concise slides with proper grammar and good flow.* *Presentation should be organized and appear to have been rehearsed in advance.* *Points will be deducted if presenters rely too heavily on note cards.* *The group should be able to adequately answer questions.*	
		___ ***/100***

Additional comments and feedback:

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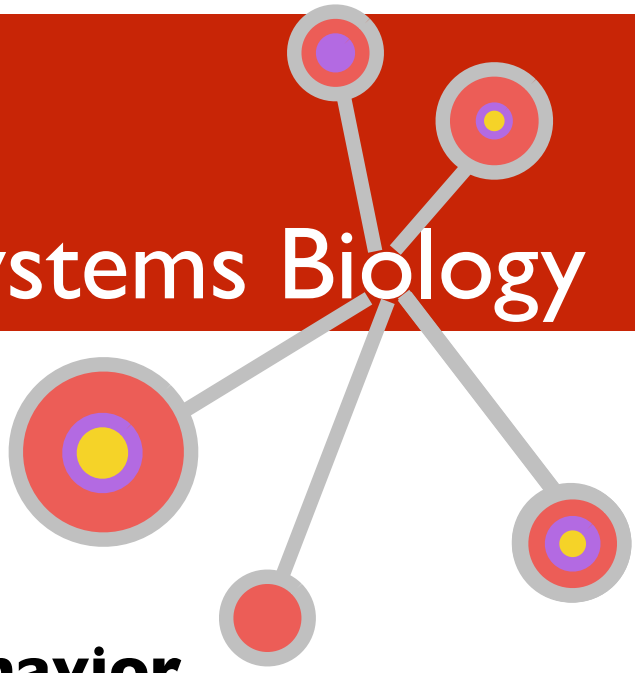
BME 430:
Principles and Applications of Systems Biology



Systems Biology:

A dynamic, integrative analysis of all the components of a biological system in order to explain and understand its behavior

- **This course will explore many of the computational tools and analyses used in Drug Development and the Pharmaceutical Industry!**
- **Apply engineering concepts in real biomedical applications**
- **Study biological systems that influence human health and disease**
- **Construct mathematical models**
- **Critique papers from the literature**
- **Develop a research project**

Fall 2018

Mondays & Wednesdays at 2pm