Modeling and Control of Biomolecular Machines

EGM 5586 Section 1309
Spring 2026, M W F, 6th Period, 12:50 PM – 1:40 PM
LAR 0239

Modifications to this syllabus may be required during the semester. Any changes that are made will be reflected in a posted version of the syllabus and announced in class.

Instructor

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WERT 489
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Any emails to ufl email address must include EGM 5586 in the subject line

Office Hours

- M W, 2:00 PM – 3:00 PM, WERT 489
- Or via confirmed written appointment

Course Description

Course Catalog: "Overview of biomolecular systems engineering. Introduction to cell processes, biochemical kinetics, models of biological macromolecules, analyses of biomolecular dynamics, simulation of stochastic behaviors, common gene regulatory network motifs, and the design of synthetic biology circuits." (Credits: 3)

Course Pre-Requisites

Undergraduate course in ordinary differential equations (e.g., MAP 2302) with a minimum grade of C, or instructor permission.

Course Objectives

By the end of this course, you should be able to do the following:

- Describe biomolecular machine behaviors using kinetic and thermodynamic concepts;
- Construct phenomenological and mechanistic models of these behaviors and machine interactions;
- Predict the dynamics of biomolecular and cellular networks using analysis and design tools from dynamical systems theory and control;
- Deploy models, analysis, and design tools from dynamical systems theory and control to alter the predicted dynamics of biomolecular and cellular networks, in simulation; and
- Recognize the state-of-the-art in biomolecular control systems, and identify the next research steps that will advance the field.

Materials and Supply Fees

None.

Recommended Textbooks, Software, and Hardware

- Brian P. Ingalls, "Mathematical Modelling in Systems Biology: An Introduction," MIT Press, 1st Ed., ISBN: 9780262545822, 2022
- MATLAB (MathWorks), any recent release.
- Various handout materials provided digitally on Canvas.
- Scientific calculator (not your phone).
- It is important that you have your own laptop/mobile computer. Details are provided at:
  https://it.ufl.edu/get-help/student-computer-recommendations/
  https://www.eng.ufl.edu/students/advising/fall-semester-checklist/computer-requirements/

Alternate (Reference) Textbooks

- Uri Alon, *An Introduction to Systems Biology: Design Principles of Biological Circuits*, 2nd Ed., 2020
- Geoff Baldwin et al., *Synthetic Biology - A Primer (Revised Edition)*, 2016
- Carlo Cosentino and Declan Bates, *An Introduction to Feedback Control in Systems Biology*, 2012
- Domitilla Del Vecchio and Richard M. Murray, *Biomolecular Feedback Systems*, 2015
- Leah Edelstein-Keshet, *Mathematical Models in Biology*, 2005
- Terrell Hill, *Free Energy Transduction and Biochemical Cycle Kinetics*, 2004
- Pablo Iglesias and Brian Ingalls, *Control Theory and Systems Biology*, 2010
- Eric Klavins, *BioCircuits: A Systems Approach to Synthetic Biology,* 2019
- John Kuriyan et al., *The Molecules of Life: Physical and Chemical Principles*, 2013
- J. D. Murray, *Mathematical Biology*, Vols. I and II, 3rd Ed., 2007
- Rob Phillips et al., *Physical Biology of the Cell*, 2nd Ed., 2013
- Steven Strogatz, *Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemistry, and Engineering*, 2nd Ed., 2015

Important Dates

- Classes Begin: Jan 12 (Monday)
- Holidays/Reading Days: Jan 19 (Monday), Mar 16 – 20 (Monday – Friday), Apr 23, 24 (Thursday, Friday)
- Classes End: Apr 22 (Wednesday)
- Classes Canceled: Mar 27 (Friday)
- Project Presentations: Apr 30 (Thursday)
- Homework, reading assignment, and project due dates stated in this syllabus will be confirmed in class

Requirements for class attendance, make-up exams, assignments, and other work in this course are consistent with university academic policies: https://go.ufl.edu/syllabuspolicies

Attendance Policy

- Students are expected to attend all lectures and final project presentations.
- **Make-up Policy:** Homework / reading assignment / project presentation absences may be excused with appropriate documentation. See https://care.dso.ufl.edu/instructor-notifications. Note that "Instructors have the right to accept or reject the Instructor Notification."

Class Expectations

- The student is solely responsible for their education. The instructor is the guide to their understanding of the field.
- Cell phones, laptops, etc.: **under no circumstances will disruptions from electronic devices be tolerated. Students are expected to take either handwritten notes with pen/pencil and paper, or electronic notes with stylus and tablet.**
- **Electronic notes must be printed out if used as reference material on examinations.**

- **No Artificial Intelligence (AI):** The learning that takes place in this course requires your unique perspective and human experience. Use of AI would make it harder to evaluate your work. It is not permitted to use any generative AI tools in this course, and the use of AI will be treated as an academic integrity issue.

- Respect and disruption: the instructor and students will be always respectful. Classroom disruption of any kind will not be tolerated.
- **The principles of the Honor Code must be always adhered to.** Individual effort is required on homework assignments, quizzes, and exams. Groups will be treated as individuals for projects. Students are bound by the Honor Pledge which states, "We, the members of the University of Florida community, pledge

to hold ourselves and our peers to the highest standards of honor and integrity by abiding by the Honor Code." On all work submitted for credit, the following statement is either required or implied:

On my honor, I have neither given nor received unauthorized aid in doing this homework/quiz/report/exam.

The Conduct Code (https://sccr.dso.ufl.edu/process/student-conduct-code/) specifies behaviors that are in violation of this code and the possible sanctions. You are obligated to report any academic misconduct to appropriate personnel. If you have any questions or concerns, please consult with the instructor or TA.

Course Zero-Tolerance Policy: *Any* violation or suspected violation of the Honor Code by a student may result in that student receiving a grade of E for the course.

Homework

The purpose of homework is to learn and understand the material. **Students are responsible for performing and understanding the homework problems and solutions on their own.**

Software and Copyrighted Material Use

All faculty, staff, and students of the University are required and expected to obey the laws and legal agreements governing the use of software and the use of copyrighted material. Failure to do so can lead to monetary damages and/or criminal penalties for the individual violator. Because such violations are also against University policies and rules, disciplinary action will be taken as appropriate. We, the members of the University of Florida community, pledge to uphold ourselves and our peers to the highest standards of honesty and integrity.

Exams

Honorlock: Consistent with UF policy, Honorlock may be used for course assessments and will be confirmed by the instructor in advance. Please see https://distance.ufl.edu/proctoring/ for more information.

Students Requiring Accommodations

Students with disabilities who experience learning barriers and would like to request academic accommodations should connect with the Disability Resource Center (https://disability.ufl.edu/students/get-started/). Students should share their accommodation letter with their instructor and discuss their access needs as early as possible in the semester.

Commitment to a Positive Learning Environment

The Herbert Wertheim College of Engineering values varied perspectives and lived experiences within our community and is committed to supporting the University's core values.

If you feel like your performance in class is being impacted by discrimination or harassment of any kind, please contact your instructor or any of the following:

- Your academic advisor or Graduate Coordinator
- HWCOE Human Resources, 352-392-0904, student-support-hr@eng.ufl.edu
- Professor Pam Dickrell, Associate Dean of Student Affairs, 352-392-2177, pld@ ufl.edu

Evaluation of Grades and Grading Policy

Evaluation Mechanism on a Percent Basis

Homeworks (6)	30%
Reading Assignments (8)	40%
Final Project, Project Attendance	30%

Homework

Students will submit solutions of the homework problems only via the course website. Students who turn in homework before the due date and time will have their homework graded. Not all homework problems may be graded, and a selection of problems may be randomly chosen for grading after the homework due date and time. Submitted homework that is partially- or fully-missing solutions to these chosen problems will not be eligible for full or partial credit for those problems, respectively, even if other non-chosen homework problems were completed. **Grading may be on completeness or on correctness.** However, it is the student's responsibility to check their solutions against posted homework solutions.

Reading Assignment

For each assignment, students will submit a document that includes the signed Honor Code, a list of the assigned papers that they attest to have finished reading, and for each of these papers, a few bullet points that summarize the paper's key results / methodological advance / significance / errors (if any). **Grading may be on completeness or on correctness.**

Project

All students are expected to undertake the final project and present in their assigned timeslot. If a student is unable to present in this timeslot for unforeseeable reasons, then the other assignments will count toward the percentage of the grade that makes up the project if an appropriate DSO instructor notification is accepted.

Final Grade

Final grades may be calculated by the following table. For example, if a student earns 86.60% (Percent Grade Earned %GE = 86.60) then their grade point will be 3.33 (B+). %GE are rounded to the hundredths decimal place. For example, if a student earns 77.995% (Percent Grade Earned %GE = 77.995) it will be rounded up to 78.00%, and their grade point will be 2.67 (B-). Shifts in the grading table are at the discretion of the instructor.

Table 1. Grading Table. *%GE = Percent Grade Earned.*

Percentage Range	Grade Point
92.00 ≤ %GE < 100.00 ⟹ A	4.00
88.00 ≤ %GE < 92.00 ⟹ A-	3.67
85.00 ≤ %GE < 88.00 ⟹ B+	3.33
81.00 ≤ %GE < 85.00 ⟹ B	3.00
78.00 ≤ %GE < 81.00 ⟹ B-	2.67
74.00 ≤ %GE < 78.00 ⟹ C+	2.33
71.00 ≤ %GE < 74.00 ⟹ C	2.00
67.00 ≤ %GE < 71.00 ⟹ C-	1.67
64.00 ≤ %GE < 67.00 ⟹ D+	1.33
61.00 ≤ %GE < 64.00 ⟹ D	1.00
60.00 ≤ %GE < 61.00 ⟹ D-	0.67
00.00 ≤ %GE < 60.00 ⟹ E	0.00

Grade Corrections

Grade corrections should be submitted promptly in writing within three business days of the grade posting. Include a concise statement of why you believe that there has been an error. The instructor has the final determination in the assigned grade; if a grade change is made, the grade may be lower or higher.

Final Project

There are two components to the final project:

1. A written report on a topic that you choose (sample topics are in the list below). This report should be at least three pages of content in an IEEE-style double-column conference paper (this includes figures and abstract, but not references); and

2. A presentation with slides highlighting the findings of your report. Your presentation will be ~20 minutes long. The goal of the presentation is to educate the class on the topic that you have now become expert in.

Report and presentations are due on April 30 (Thursday), 10:00 AM. Project topics need to be substantive enough to justify a half-conference paper write-up. There are two options:

Option 1

A literature review on a topic from the list below or some other topic that relates to the modeling and control of biomolecular machines. You must have at least three primary-literature source papers on this topic. Instructor permission for the project topic is required, to ensure topic uniqueness among students. You will need supporting literature on top of your three main papers to write your report and produce explanatory figures. Figures can be produced in MATLAB and confirm published modeling results in new ways, and/or provide sensitivity analyses.

Option 2

Any novel research advance from your ongoing graduate studies, or a design problem that you would like to tackle (sample problems in the list below) that relates to the modeling and control of biomolecular machines, and uses or builds upon class-presented material. Instructor permission for the project topic is required, to ensure topic uniqueness among students. In this option, the project introduction and relevant literature will be on page 1+, theoretical background and advances will be on page 2, results/discussion/conclusions will be on page 3+, and references will be on page 4.

Potential Final Project Topics

- CRISPR-Cas dynamical/biophysical models.
- Resource burden of synthetic biological circuits.
- Detailed models of transcription and/or translation.
- Effects of cell-free experimental systems on dynamical/biophysical biomolecular models.
- Dynamic metabolic engineering.
- Methods to analyze metabolic dynamics (e.g., flux balance analysis, modal analysis).
- Whole-cell models of a cell you choose.
- Evolutionary trade-offs, Pareto optimality, biomolecular multi-objective optimization.
- Fitness landscapes, organism evolution and adaptation in environments, epigenetic inheritance, developmental plasticity, etc., using statistical physics, information theory, and machine learning.
- Design of a biological system that can memorize the order of N inputs.
- Design of a biological system that can self-organize into a two-layer onion structure.
- Design of a bacterial stem cell that "buds" off a daughter in a different physiological state, both terminally, and another that relaxes ultimately back to the same state as the mother cell.
- Development of a parts family for synthetic biology. Argue in favor of your family – is it: Scalable? Designable? Connectable? Composable? Predictable? Functionally homogeneous? Turing complete?
- Creation of the most compact, biologically plausible circuit that can take three environmental inputs and based on their "ON and OFF" values turn on each of eight different response systems. Create the system that is easiest to construct out of known parts that have already been used in synthetic biological circuits or parts that function similarly to these. Compare their operational properties such as speed, signal rectification, susceptibility to intrinsic noise and fluctuations on the input.
- Design of a biological system in which different cell types search for partner cells and upon encountering the right one irreversibly adheres to it. Make this system "addressable" in that one can "program" a large number of different cell types derived from the same common chassis. Can we do cellular "origami" with this?
- Design of a biological system with a form of simple associative learning.
- Design of a bacterium that can circulate safely in blood, recognize arterial plaque, and degrade it. Ensure that it can survive long enough to have an effect but that it can be cleared from the system on demand.
- Design of a tumor-targeting/tumor-killing bacterium when the presence of a tumor is sensed.

- Design of a biological system to optimize nitrogen fixation for a plant.
- Design of a biological system to sense or record or manipulate a human gut microbiome.
- Analysis of various oscillator designs (single cell and/or population synchronized).
- Spatiotemporal modeling of bacterial quorum sensing, including hysteresis.
- Detailed models of bacterial chemotaxis.
- Modeling segmentation in *Drosophila* embryogenesis.
- Design and spatiotemporal simulation of wave-propagation using BZ reaction-diffusion system (also, investigate propagation only in a particular direction).
- Modeling synthetic emergent pattern formation systems (e.g. stripes and spirals with a Turing system).
- Analysis of Conway's Game of Life: emergence of global patterns from local rules of interaction based on neighborhood density and cell life/death.
- Modeling 3D tissue structuring with a sheet of epithelial cells.
- Analysis of noise propagation for network topologies and transcription factor interactions with DNA / RNAp.
- Modeling DNA computing approach based on gel electrophoresis.
- Modeling DNA self-assembly and tiling that form large scale patterns.
- Design and simulate a system to treat Type I Diabetes: control stem cell to pancreatic beta cell differentiation.
- Design of gene circuit motifs that involve master regulator genes of stem cell differentiation.
- Simulation of a phosphorylation-only toggle switch.
- Design and simulation of an emergent pattern forming system that uses three signals.
- Design and spatiotemporal simulation of a predator-prey ecosystem.
- Design and simulation of a cell division counter.
- Simulation of programmed cell motility (synthesis of chemical attractants and repellants by "leaders" and movement based on these chemicals by "followers") – can be used as a component for modeling injury repair.
- Design of a synthetic biological system that is robust to mutations (as long as they are below a certain threshold) or that kills itself upon mutation occurrence.
- A multiscale Computer Aided Design (CAD) tool "bio-compiler" that translates a program written in a high-level language to a low-level genetic circuit implementing that program.
- Design of a genetic "bandpass filter" – assuming an oscillating input signal, only propagate certain frequencies to output of the genetic circuit.
- Design and spatiotemporal simulation of a multicellular branching system.
- Simulation and analysis of RNAi circuits for cancer therapy.
- Hydrophobic effect strength at high temperatures.
- Myosin walking on actin via a hand-over-hand mechanism.
- How proteins find their recognition sites on DNA: 1D diffusion vs. intrinsic 3D diffusion rate limits.
- Turing's reaction/diffusion mechanism applied to animal morphogenesis.
- Kinetic proofreading to explain how a T-cell discriminates self peptides from non-self peptides.
- Out-of-equilibrium 'proofreading' effects to prevent cross-talk in eukaryotic gene regulation.
- Do effective molarities achieved by enzyme scaffolds approach 10^{8} M?
- Is it possible to carry out computation with zero energy input?
- Are the tightest binding affinities that are achievable by a protein for a nucleotide 10^{-23} M?
- Can enzymes achieve k_{cat}/k_{m} beyond the diffusion-limit of 10^{7} $M^{-1}s^{-1}$?
- Is it true that the rate-limiting step is not generally well-defined for an enzyme's free energy diagram?

Course Schedule

The course content is approximately:

Lectures 02-15	Deterministic modeling of biomolecular machines (14 lectures)
Lectures 16-21	Stochastic modeling of biomolecular machines (6 lectures)
Lectures 22-28	Dynamical systems theory to control biomolecular machines (7 lectures)
Lectures 29-39	Control of biomolecular machines (11 lectures)

Course Schedule, Approximately by Lecture Number (1/2 Modeling, 1/2 Control)

1 Jan 12 Systems Biology and Synthetic Biology
2 Jan 14 Biomolecular Systems Modeling
3 Jan 16 Cell Processes
4 Jan 21 Cell Processes for Synthetic Biology
5 Jan 23 Passive and Active Transport, Biological Macromolecules
Reading Assignment 1 Due Jan 23 (Friday), 11:59 PM
6 Jan 26 Strong and Weak Forces
Approximate End of Coverage for Homework 1
7 Jan 28 Ligand-Receptor Binding, Intro to Chemical Reaction Networks (CRNs)
8 Jan 30 CRNs: Conversion, Binding
Homework 1 Due Jan 30 (Friday), 11:59 PM
9 Feb 2 Binding Isotherm
10 Feb 4 CRNs: (Non-)Exponential Decay, Stoichiometry
11 Feb 6 CRNs: Cooperative Binding and Allostery
Reading Assignment 2 Due Feb 6 (Friday), 11:59 PM
12 Feb 9 CRNs: Feedback Inhibition, Competitive Binding
Approximate End of Coverage for Homework 2
13 Feb 11 CRNs: Enzyme Kinetics, Michaelis-Menten
14 Feb 13 CRNs: Quasi-steady-state, Briggs-Haldane, Post-Translational Regulation
Homework 2 Due Feb 13 (Friday), 11:59 PM
15 Feb 16 Linear Transforms, Monod Kinetics, Statistical Mechanics
16 Feb 18 Microstates, Macrostates, Boltzmann Distribution
17 Feb 20 Thermodynamic Entropy, Gibbs Entropy, Free Energy
Reading Assignment 3 Due Feb 20 (Friday), 11:59 PM
18 Feb 23 Stochastic Behavior, Chemical Master Equation
19 Feb 25 Stochastic Modeling, Fokker-Planck Equation
20 Feb 27 Langevin Equation, Monte Carlo Methods
Reading Assignment 4 Due Feb 27 (Friday), 11:59 PM
21 Mar 2 Gillespie Algorithm, Flux Balance Analysis
Approximate End of Coverage for Homework 3
22 Mar 4 Glycolysis, Limit Cycles, Stability
23 Mar 6 Phase Portraits, Negative Autoregulation
Homework 3 Due Mar 6 (Friday), 11:59 PM
24 Mar 9 Linearization, Nonlinear System Equilibria
Approximate End of Coverage for Homework 4
25 Mar 11 Repressilator, Dulac's Criterion, Poincaré-Bendixson Theorem
26 Mar 13 Cyclic Feedback Systems, Glycolytic Oscillations
Homework 4 Due Mar 13 (Friday), 11:59 PM
27 Mar 23 Bifurcations
28 Mar 25 Hopf Bifurcation, Glycolytic Oscillations, Positive Systems Theory
Approximate End of Coverage for Homework 5
Reading Assignment 5 Due Mar 27 (Friday), 11:59 PM
29 Mar 30 Genetic Circuit Design, Negative Autoregulation
30 Apr 1 Sequestration, Subtraction, Quorum Sensing, Ultrasensitivity
Homework 5 Due Apr 1 (Wednesday), 11:59 PM

31	Apr 3	Digital vs. Analog Genetic Circuits, Positive Autoregulation, Genetic Toggle Switch
32	Apr 6	Review of Classical Control, Integral Control, Disturbance Rejection

Reading Assignment 6 Due Apr 6 (Monday), 11:59 PM

33	Apr 8	Bacterial Chemotaxis, Adaptation
34	Apr 10	Biomolecular Network Motifs, Relationship to Control
35	Apr 13	Biomolecular Integral Control, Plasmid Copy Number Control

Reading Assignment 7 Due Apr 13 (Monday), 11:59 PM

36	Apr 15	Activator-Repressor Clock
37	Apr 17	Hasty Oscillator, Oscillator-Based Control

Approximate End of Coverage for Homework 6

38	Apr 20	Turing Patterns, Oscillator-Driven Turing Patterns

Reading Assignment 8 Due Apr 20 (Monday), 11:59 PM

39	Apr 22	Optogenetics, Model Predictive Control

Homework 6 Due Apr 22 (Wednesday), 11:59 PM

Project Presentations on Apr 30 (Thursday), 10:00 AM