BIOM 895 – Special Topics: Systems Bioengineering: multi-scale models in biology

Instructors: Shayn Peirce-Cottler and Jason Papin

Pre-requisites

1. BIOM 601/602: Physiology (or equivalent)
2. One of the following courses in cellular and/or molecular biology:
   . BIOM 204: Cell and Molecular Biology for Engineers
   . BIOM 706: Genetic Engineering
   . BIOM 823: Cell Mechanics, Adhesion, and Locomotion
   . BIOM 891: Molecular Bioengineering
3. Programming experience in Matlab
4. SEAS graduate student status*
5. Knowledge of mathematical techniques, including:
   • Partial Differential Equations
   • Ordinary Differential Equations
   • Linear Algebra
6. Or instructor permission

* Undergraduate students who have met pre-requisites #1, #2, and #3 and who are interested in taking this course may contact the instructors and obtain approval for enrollment on a case-by-case basis

BME Graduate Requirements met by this course: This course counts as an upper-level biomedical engineering course or a math intensive course.

Course Philosophy: The next generation of biomedical researchers has the opportunity to make a significant impact in biology and medicine through computational modeling, but only if they possess a quantitative mindset, critical thinking skills, hands-on programming experience, a baseline math competency, creativity, and an appreciation of the value and caveats associated with applying their techniques to biological questions. To this end, graduate students in this course will not only understand how and when different computational/mathematical modeling approaches can be used to address biological questions effectively, but they will also obtain hands-on experience in different simulation environments to fully appreciate the benefits and drawbacks of different techniques and how they compare to one another (a “learning through doing” approach). This is achieved through a combination of lectures, readings, discussions, and team projects, in which students apply their knowledge to real scientific questions by developing computational/mathematical models, producing results, verifying their results using published experimental data, and critically analyzing the validity, robustness, novelty, and utility of their models. This multi-faceted didactic approach will strengthen students’ quantitative capabilities, improve their critical analysis skills, and enable them to access a variety of different computational modeling tools, all of which will provide them with the skills necessary to create
new computational/mathematical techniques and apply them in novel and useful ways to biomedical problem solving.

**Course Description:** This graduate level course introduces techniques for constructing mathematical and computational models of biological processes at many levels of organizational scale—from genome to whole-tissue. Students will rotate through several modules where they will hear lectures, read literature, and participate in discussions focused on the various modeling techniques. In each module, students will learn:

- Which modeling techniques are best suited for addressing biological problems of different scales
- Quantitative characterization of biological properties (e.g., robustness)
- What constitutes a valid assumption and how can complex problems in biology be simplified while maintaining biological relevance?

Specific modules will teach computational techniques for:

1) genome bioinformatics (e.g., genome-scale protein sequence comparisons),
2) genome network analysis (e.g., metabolic network reconstruction & analysis),
3) multi-cellular simulations (e.g., agent-based modeling of tissue patterning),
4) whole-organ analysis (e.g., finite element analysis of heart function).

Corresponding mathematical techniques will include:

- Partial Differential Equations
- Ordinary Differential Equations
- Linear Algebra

In each module, students will also work in teams to complete group modeling projects that utilize the modeling techniques specific to the particular module. This will provide students with hands-on experience in the different simulation environments while allowing them to address relevant biological problems of different length scales using appropriate modeling techniques.

A pallet of possible projects will be provided by the Module Instructor on the first day of the module, and student teams will be invited to select a project from the pallet. Alternatively, students may define their own projects based on their familiarity with the modeling technique and their own research interests. Student teams, consisting of 3-5 students, will be assembled so that they maintain diversity with respect to computational, mathematical, and biological knowledge and skills, and therefore, students will also teach one another as they work together on their team to complete their projects. Although the detail and complexity of the models generated in each module may be very limited, the complete experience of identifying a problem, conceptual design of a model, execution of the design, and critical analysis will be beneficial in teaching students all of the components of the computational model-building process.

Students will present their projects to the class on the final day of the module. Throughout the module, peer critique of team projects will be encouraged in order to teach critical evaluation of computational models. Apart from the team projects in each module, there will be no additional homework assignments, other than reading assignments, and there will be no final project or exam. A sample timeline for a single module is provided below.
Outline for a single module
(Assuming that there will be 2 classes per week, each lasting 1.25 hours.)

Week 1:

Class 1 ~ Lecture: “Overview of Modeling Technique, and Project Selection”

The Module Instructor will provide an overview of the theory behind the modeling technique, emphasizing the scope and applicability, necessary assumptions, types of conclusions drawn from this approach, model validation techniques, and robustness of this technique. In this class the instructor will provide students with a pallet of possible team projects to choose from, and as the first homework assignment, students will also select/define their team project.

Class 2 ~ Workshop: “Modeling Technique Basics”

By now, students will have selected their team projects, and in this workshop the Module Instructor will provide an introductory tutorial about how to use the modeling software or modeling interface (NetLogo, MatLab, etc.) The Module Instructor will assign a reading assignment (published journal article) that utilizes a computational technique(s) presented in this module.

Week 2:

Class 3 ~ Discussion: “Modeling Technique Example”

The instructor will review the assigned journal article, and the class will discuss the significance and contribution of the work, model assumptions, validity, deficiencies, and possibilities for future work.

Class 4 ~ Discussion: “Modeling Technique Example”

The instructor will review the assigned journal article, and the class will discuss the significance and contribution of the work, model assumptions, validity, deficiencies, and possibilities for future work.

Week 3:

Class 5 ~ Discussion: “Generation of Results and Critical Analysis”

Student teams will have generated preliminary data using their model and this class will provide an open forum for critical analysis of the different team projects (instructor and peer critique). Suggestions made during this class will be incorporated into the final models which will be presented in the last class of the module.

Class 6 ~ Student Presentations and Discussion: “Final Model Conclusions”

Teams will present their models, results, and validation approaches, and students in the class along with the Module Instructor will openly discuss each project, in turn. The Module Instructor will also summarize the main points of this module and relate them to the context of the entire course.
**Grading**

4 group design projects (20% each – 80% of total)
4, 2-page paper reviews (5% each – 20% of total)

**Syllabus**

**Introduction**

Jan. 19 – Introduction - Why build models in biology/what models can ‘buy’ you that you can’t get using other approaches? How to know when a building a model is a suitable approach for answering your scientific question; Review of Matlab and overview of numerical methods and general programming/coding techniques

Jan. 24 – Multi-scale biology: genomes → cells → tissues → organ; Appreciating the different temporal & spatial scales in play at each level of organization; recognizing the challenges of interfacing across scales, especially when it comes to modeling; dealing with the magnitude of complexities inherent at each level of scale (compartmentalization, simplification strategies, etc.)

Jan. 26 – Experimental techniques for probing at each biological scale

**Module 1 – Genome Bioinformatics**

Jan. 31 – Theory & numerical techniques for genome sequence data: genome sequence assembly, multiple sequence alignment, BLAST, FASTA, signal finding techniques, Hidden Markov Models, BLOSUM; project selection

Feb. 2 – Modeling and analysis techniques for ‘omic data: microarray analysis, clustering algorithms, singular value decomposition of large data sets, interaction networks and graph theory techniques

Feb. 7 – Modeling example

Feb. 9 – Modeling example

Feb. 14 – Preliminary results & critical analysis of models in group projects

Feb. 16 – Final model conclusions
Module 2 – Genome-scale network analysis

Feb. 21 – Overview of network analysis tools & challenges at modeling intracellular networks; concerns with network reconstruction, stoichiometric matrices, defining system boundaries; project selection
Feb. 23 – Theory & numerical techniques for intracellular network analysis; ODEs & PDEs of chemical reaction systems, Bayesian networks, constraint-based modeling techniques
Feb. 28 – Modeling example

Mar. 2 – Modeling example

Mar. 7 – Spring Break
Mar. 9 – Spring Break
Mar. 14 – Preliminary results & critical analysis of models in group projects
Mar. 16 – Final model conclusions

Module 3 – Multi-cellular simulations

Mar. 21 – Overview of tools for tissue-level modeling (SWARM, NetLogo, CompuCell, Cellerator, etc.), requisite assumptions, challenges of modeling biological phenomena at this level, what types of processes can be modeled using this technique, what types of questions can be well addressed by this technique, what one can conclude about the systems-level behaviors from these types of models, what constitute appropriate boundary conditions, what kind of output can your models generate and what data is available for validation of models at this level; project selection
Mar. 23 – Theory & numerical techniques for multi-cellular models (e.g., agent-based models): how agent-based models work, introduction to coding in Netlogo
Mar. 28 – Modeling examples to familiarize students with agent-based models and examples from the ecology field where their usage has been traditionally more widespread
Mar. 30 – Modeling example of agent-based model applied to a biological patterning problem

Apr. 4 – Preliminary results & critical analysis of multi-cellular models in group projects
Apr. 6 – Final model conclusions (presentation by teams and discussion)

Module 4 – Whole-organ analysis

Apr. 11 – Overview of tools for tissue-level modeling, requisite assumptions & what theory is available for models to draw on at this level, what it means to take a continuum approach at the organ level, challenges of modeling biological phenomena at this level, what types of processes can be modeled using this technique, what types of questions can be well addressed by this technique, what one can conclude about the systems-level behaviors from these types of models, what type of outputs these models can generate and what data is available for validation of models at this level; project selection
Apr. 13 – Theory & numerical techniques for organ-level models (e.g., finite element analysis): how to develop a finite element model of an organ-level system, how to define nodes and elements and what the implications of this definition are, how to select appropriate boundary conditions
Apr. 18 – Modeling examples
Apr. 20 – Modeling examples

Apr. 25 – Preliminary results & critical analysis of whole-organ analysis
Apr. 27 – Final model conclusions (presentation by teams and discussion)

Conclusions

May 2 – Wrap-up discussion; general principles in modeling in biology