School of Chemical and Biomolecular Engineering

Cornell University

ChemE 7770: Advanced Principles of Biomolecular Engineering

Project Guidelines

General Objectives:

- Provide a setting where physical and engineering principles can be applied intelligently to a biological phenomenon.
- Provide concrete, "hands-on" experience on open-ended problems.
- Develop skills for critical reading and analysis of technical literature.
- Give students the opportunity to be active participants in the learning process by teaching themselves and the class a particular subject of interest.

Specific Objectives:

- Demonstrate ability for critical interpretation and analysis of current literature.
- Demonstrate ability to *apply* concepts, methods, and lessons learned throughout the course to specific problems (beyond what may be given in a selected publication).

The second specific objective entails the pursuit of some aspect of a problem that is new, even if incrementally so. The novelty of the project may be due to features of the system of interest which are different from those treated in the literature, or due to distinctive features of the method of analysis. The project may emphasize theoretical, computational modeling, or experimental aspects (e.g., experimental design and quantitative analysis) of a problem. Projects should not involve actual experimental work.

Output:

Deliverable I – Selection of project (**Recommended delivery on April 16th by 5 PM**): Students are expected to select a project topic from a list of available projects or propose a project of their own design that can be ***related to their MS or PHD thesis work***, but should not be work already in progress under direct supervision of a research mentor. The proposed projects consist of key papers and/or modeling ideas with suggested open-ended questions for further inquiry. By April 16th, students should communicate their selected topic and project goals in one paragraph summary sent by email to the course instructors (mjp31 and jdv27).

Deliverable II – Project update (**Due April 30th by 5 PM; Penalty imposed for late submissions**): Students should submit a 2-page progress report (12-point font, single spaced, 1-inch margins) with optional figures and equations to communicate preliminary

results related to construction of their model, execution of code, and/or analyses. Deliverable III – Project presentation (**To be delivered on May 14th during a special Zoom session, 9 AM – 12 PM**): Students will give a 15-min presentation on their project to the class to communicate the goals and accomplishments of their project. Students are expected to present background information (including from other literature sources), rational of the modeling approach and/or quantitative analyses, and key findings. Feedback by instructors and peers will be provided during the session.

Deliverable IV – Final report (**Due May 21st by 5 PM; No late submissions can be accepted**): Students should prepare a final written report on the project. The final written paper should contain the typical sections of peer-reviewed papers, e.g., title, abstract, introduction, methodology, results-discussion, conclusions, acknowledgements, references, and appendix. The paper should be concise, making sure to stress the most important points and results. Any additional materials, including extended modeling details and equations, can be included in appendices. Slides from the May 14th presentation should be included as one appendix. New calculations and analyses not discussed in the May 14th presentation are allowed. Any model source code should be released on GitHub with a README document. Formatting guidelines:

a. The main text (title, abstract, introduction, methodology, results, figures, conclusions, and acknowledgements) should not exceed 7 pages, 12-point font, single spaced, 1-inch margins. The bibliography and appendices do not count toward the page limit.
b. References should be provided throughout the text with a bibliography included at the end of the document. Free reference managers, such as Zotero, can be used to insert references directly into Microsoft Word documents (cite-and-write feature) and automatically compile a bibliography. American Chemical Society would be one recommended citation style for formatting the bibliography.
c. A LaTeX template will be provided if you would like to explore a professional typesetting program as an alternative to word processing programs, like Word (this is optional).
d. Appendices should be numbered and referenced in the main text. An appendix with your slides from the May 14th presentation is required. Any additional appendices are optional.
e. Figures should be numbered and referenced in order in the main text.
f. All model source code should be released on GitHub (with a README document) as part of the deliverable.

Projects ideas:

Project 1: COVID-19 circuit design challenge

Olin Therapeutics has been contracted to develop a synthetic gene expression system for COVID-19 genes using a commercial *E. coli* TX-TL cell free protein synthesis

(CFPS) system (myTXTL). Toward this contract, Olin wants to better understand what they might see in the experiments. Your tasks are:

i) develop a simulation of integration between the central gene amplification loop for key COVID-19 genes with metabolism assuming a sigma factor based regulatory network structure. The simulation should consider:

   1. expression of the RNA-directed RNA polymerase (RdRp) protein
   2. expression of the host translation inhibitor protein nsp1
   3. at least one other COVID-19 protein to study the amplification

ii) Study the effect of the host translation inhibitor protein nsp1 on the expression of non-COVID-19 proteins. Toward this objective:

   1. Simulate the expression of ssrA-tagged Green Fluorescent Protein (GFP-ssrA) and estimate how GFP-ssrA expression changes with different levels of nsp1

Demonstrate the proof-of-principle of your circuit design using sequence specific constraint based modeling of *E. coli* TX-TL CFPS.

information of COVID-19 genes: https://zhanglab.ccmb.med.umich.edu/C-I-TASSER/2019-nCov/

Assume*:* (i) you can use all currently available genetic parts in your design (both RNA and protein parts are fine); (ii) your circuit operates in a well-mixed continuous steady-state bioreactor on a chip (with working volume of V = 15μL). The chip has two inputs and a single output:

Input 1: an infinite reservoir of TX-TL reaction extract (with no glucose or amino acid supplementation). Assume commercial *E. coli* myTXTL extract.

Input 2: an infinite reservoir containing the genetic material for the circuit;

(iii) ignore reactor startup; (iv) amino acids, oxygen and maltodextrin from myTXTL power the circuit. i)

Your project presentation should include a description of your circuit design (biology and model equations), and an analysis of the performance of your circuit (simulations).

Project 2: Synthetic Pancreas Circuit Design Challenge

Olin Therapeutics has been contracted to develop synthetic gene expression circuits for the production of proteins using the *E. coli* TX-TL cell free protein synthesis (CFPS) system. Your task is to develop a glucose responsive switch that:

i) produces ssrA-tagged Green Fluorescent Protein (GFP-ssrA) in the presences of high glucose levels, and

ii) produces ssrA-tagged Red Fluorescent Protein (RFP-ssrA) in the presence of low glucose levels.

Demonstrate the proof-of-principle of your circuit design using sequence specific constraint based modeling of *E. coli* TX-TL CFPS. In particular, estimate which model parameters influence the selectivity of the switch.

Assume*:* (i) you can use all currently available genetic parts in your design (both RNA and protein parts are fine); (ii) your circuit operates in a well-mixed continuous steady-state bioreactor on a chip (with working volume of V = 15μL). The chip has three inputs and a single output:

Input 1: infinite blood draws from either normal or diabetic volunteers.

Input 2: an infinite reservoir of TX-TL reaction extract (with no glucose or amino acid supplementation). Assume commercial *E. coli* myTXTL extract.

Input 3: an infinite reservoir containing the genetic material for the circuit;

(iii) ignore reactor startup; (iv) amino acids, oxygen in the blood stream and maltodextrin from myTXTL power the circuit.

Your project presentation should include a description of your circuit design (biology and model equations), and an analysis of the performance of your circuit (simulations).

Project 3: SARS-CoV-2 infection model with detailed docking kinetics

Goverment agencies are rapidly mobilizing funding and efforts to develop predictive models for the spread of SARS-CoV-2. Recent reports have now identified that Spike glycoprotien on SARS-CoV-2 docks to ACE-2 receptors on the surface of target cells (Zhou et al.). Your goal in this project is to develop a detailed kinetic model for SARS-CoV-2 binding to the cell surface and incorporate into a broader model of infection spread. Multivalent binding interactions between virus and cell-surface ACE-2 should be considered, for instance, through approaches descibed in Lauffenburger chapter 4.3. You may want to addtionally consider (optional) peneration of viral particles through the cell-surface glycocalyx. For example, you could assume that the glycocalyx and entering virus behaves as a polymer brush with a nano-inclusion (Kim and O'Shaughnessy, 2006). Other possibilities exist. Your project should extend a relevant model of viral infection to include your more detailed description of binding kinetics (See Boianelli et al., 2015 and Nowak et al., 1996 for viral infection models).

References:

1. Zhou et al. (2020), A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, DOI: 10.1038/s41586-020-2012-7

2. Kim and O'Shaughnessy (2006), Nanoinclusions in dry polymer brushes, Macromoelcules, DOI: 10.1021/ma050817i

3. Boianelli et al. (2015), Modeling influenza virus infection: a roadmap for influenza research, Viruses, DOI: 10.3390/v7102875

4. Nowak and Bangham (1996), Population dynamics of immune responses to persistent viruses, Science, DOI: 10.1126/science.272.5258.74

Project 4: Kinetic Monte Carlo simulation of traction force dynamics

Cells tug on their extracellular environment and utilize molecular stress sensors or strain gauges to measure physical properties of the microenvironment. This information is used in decision making for critical cell processes, including movement, morphogenesis, and differentiation. In this project, you will investigate the underlying principles of force generation and mechanosensing through analysis and extension of some recent kinetic Monte Carlo simulations of traction force generation.

Proposed strategy:

i. Explain the concept of a molecular clutch and how it works according to Chan and Odde.
ii. Consider what force transduction (i.e. mechanotransduction) entails molecularly and what are the key elements of a force-transducing network. Describe how the dynamics of the molecular clutch can dictate force transduction. Reconstruct the simulation of Chan and Odde to confirm their key results.
iii. Choose an extension of Chan and Odde to explore further through new simulations and analyses. For instance, how would the response to a viscoelastic substrate differ from the response to an elastic substrate? Alternatively, would the model benefit from additional molecular details, such as those included in Elosequi-Artola and colleagues?

References:

1. Chan and Odde (2008), Traction dynamics of filopodia on compliant substrates, Science, DOI: 10.1126/science.1163595

2. Elosegui-Artola et al. (2016), Mechanical regulation of a molecular clutch defines force transmission and transduction in response to matrix rigidity, Nature Cell Biology, doi:10.1038/ncb3336

Project 5: Programmable sorting dynamics

The ability to program organized multicellular biological structures on demand is a grand challenge in the manufacturing of synthetic tissues and organs for regenerative medicine. Recent work by Toda et al. suggests that the SynNotch system, coupled with rationally designed intracellular circuits, may provide a powerful approach for programming self-organization of cells. Computational models are now under development to test and analyze new circuit designs in silico. The goal of this project is to develop an agent-based model **OR** cellular pots model for investigation of cellular self-organization.

Proposed strategy:

Select either an agent-based model or cellular pots model for your project. Explain the fundamental principles, advantages and limitations of your selected approach. Why is your selected approach attractive for modeling cellular spatial patterning?

If you selected an **agent based model**, build and run an agent-based model of contract inhibition by Notch and Delta. One approach would be to use a multi-agent programmable modeling environment called NetLogo. Example code for the Notch-Delta system is provided in the supplement of Reynolds et al. Extend your code to analyze one or more of the circuits proposed in Todo et al. Consider adding movement rules (For examples, see: http://modelingcommons.org/browse/one_model/6224#model_tabs_browse_procedures and http://modelingcommons.org/browse/one_model/6246#model_tabs_browse_info)

If you selected a **cellular potts model**,consider the recently published model by the Morsut lab that captured some of the dynamics observed in Toda et al. (Lam and Morsut 2019). Reproduce some of the key aspects and analyses of the model in Lam and Morsut using CompuCell3D. Note that this model has not completed peer-review yet. Are the modeling results of Lam and Morsut reproducible? Consider extending the Lam and Morsut model to consider a modified circuit network of your choosing.

References:

1. Toda et al. (2018), Programming self-organizing multicellular structures with synthetic cell-cell signaling, Science, DOI: 10.1126/science.aat0271
2. Elaine R. Reynolds et al (2019), An agent-based model of the Notch signaling pathway elucidates three levels of complexity in the determination of developmental patterning, BMC Systems Biology, DOI: 10.1186/s12918-018-0672-9
3. Lam and Morsut (2019), A modular computation framework for the rational design and exploration of synthetic development, BioRXiv, DOI: 10.1101/784496