20.320 Design Project 1. Receptor Tyrosine Kinase signaling and endocytosis modeling.

Assigned: 9/25.
Due: 10/16.

Teams of 4-5 students. Find a balance between dividing the work evenly within your group while also attempting the requirements together. Email 320staff@mit.edu about an issue.

Objective: The goal of this project is to develop a quantitative model predicting the temporal response of a receptor tyrosine kinase to cell stimulation under different conditions.

Model Implementation:
Working together with colleagues in the class, develop an ODE-based model of EGFR activation, signaling, and endocytosis. Your model should include the following steps:

1. Ligand binding
2. Receptor dimerization
3. Receptor signaling (this can be simplified -- for instance, recruitment and phosphorylation of an adaptor protein)
4. Receptor endocytosis
5. Activated receptor (complex/dimer depending on your model) endocytosis
6. Receptor synthesis
7. Receptor and/or complex recycling
8. Receptor and/or complex degradation
9. Any other steps you deem necessary for your model to function correctly

Many of the parameters for this model can be found in the literature, while others will have to be based on estimates and model fitting.

Using this model, provide plots for number of receptors, complexes, and dimers on the cell surface to answer the following questions:

1. How does the model perform under basal conditions (e.g. in the absence of ligand)
2. How does the model respond to low-dose ligand stimulation (e.g., 0.1 nM ligand)
3. How does the model respond to high-dose ligand stimulation (e.g., 5 nM ligand)

The EGFR / HER-family of receptors is often aberrantly activated in cancer. From the literature, identify a mechanism of altered EGFR / HER-family signaling and adapt your model accordingly.

Demonstrate the performance of your altered system under the same three conditions. Does your alteration lead to increased EGFR signaling, or alter the duration of EGFR activation?

As part of submission, provide the following details.

Part 1: Conceptual design

a. Draw a schematic of the proposed biological system and label all system components.
b. Clearly describe and motivate any assumptions you have made.

Part 2: Mathematical design

a. Write out the system of ODEs.
b. Provide realistic values for rate constants and other parameters. Don't forget to include units.
c. Input the system in MATLAB/Python to build a model.

Part 3: Model analysis

a. Provide plots for number of receptors, complexes, and dimers on the cell surface
b. Discuss the response dynamics of EGFR signaling under following conditions.
    1. How does the model perform under basal conditions (e.g. in the absence of ligand)
    2. How does the model respond to low-dose ligand stimulation (e.g., 0.1 nM ligand)
    3. How does the model respond to high-dose ligand stimulation (e.g., 5 nM ligand)

Part 4: Aberrant system

The EGFR / HER-family of receptors is often aberrantly activated in cancer. From the literature, identify a mechanism of altered EGFR / HER-family signaling and adapt your model accordingly. Demonstrate the performance of your altered system under the same three conditions. Does your alteration lead to increased EGFR signaling, or alter the duration of EGFR activation?

a. Provide a schematic for altered system.
b. Provide ODEs, rate constants and assumptions.
c. Provides plots number of receptors, complexes, and dimers on the cell surface for the altered system
d. Discuss the effect of altered EGFR signaling in the context of cancer and potential therapeutics for patients with aberrant EGFR signaling.