BIO/AMS 332: Computational Modeling of Physiological Systems — Project 3

Instructions

This project is to be completed using MATLAB. MATLAB is a powerful environment for mathematical modeling — allowing quite sophisticated models to be implemented without requiring a lot of knowledge about programming. In this project, you will learn the basics of how to use MATLAB, using as examples some of the models that we have discussed in class. MATLAB is available on most SINC site computers, and for installation on your own computer via SoftWeb. Please read through the "Introduction to Matlab" appendix in the class notes for a basic introduction to MATLAB commands.

The solutions to the problems should be presented as a computer-formatted document with answers given in full sentences. All figures should be integrated into the document, and should include a brief descriptive caption. All plots should include a title and axes labels (with units), and a legend where appropriate. An appendix including all Matlab scripts should be included. A final copy of the report should be submitted electronically as a single PDF document through BlackBoard.

All MATLAB work presented in your answers must be consistent with your submitted M-files. Separate M-files should be used for each part of the project; for the various questions within a part, you may either create a single M-file that solves all the sub-problems or split your work among multiple M-files. Regardless, a single "zip" file containing all Matlab scripts (M-file) should be submitted at the same time as the project PDF document. The zip file should contain the executable M-files (as unformatted text); this is NOT a substitute for including the code as an appendix to your report.

You are encouraged to work in groups, both in discussing how to implement the problems in MATLAB and in the interpretation of your results, and to use online resources. However, simply copying the work of a fellow student (or directly copying any material found online) is forbidden. All projects must include a statement that explains all resources that were used in the completion of all aspects of the project and lists all collaborators involved. A few examples are given below:

- *I worked on implementing the Matlab code with Tom Hanks and Brad Pitt; Tom really knew how to solve the problems, and Brad and I largely followed his guidance. However, I wrote the program myself, based on Tom's help. Tom, Brad and I also discussed the answers to the questions together, using Wikipedia for guidance on question 2, but we all made equal contributions. The written work is all my own. Signed: Sam Jackson*

- *I did the project completely on my own; I did not discuss any of the problems with anyone in the class, and did not share any of my work with others. However, I did make extensive use of both Wikipedia and MatlabCentral. Signed: Katy Perry*

Part A: A diffusing autoregulatory gene.

In Project 1, we implemented a ODE-based model for a simple autoregulatory gene; that is, a gene that encodes a protein whose function (or part of whose function) is to activate the transcription of itself. The reaction-diffusion model for this system is:

$$\frac{\partial[X_{rna}]}{\partial t} = \frac{\mu[X_{prot}]^2}{K_{1/2}^2 + [X_{prot}]^2} - \chi_{rna}[X_{rna}] + D_{rna}\nabla^2[X_{rna}]$$

$$\frac{\partial[X_{prot}]}{\partial t} = \omega[X_{rna}] - \chi_{prot}[X_{prot}] + D_{prot}\nabla^2[X_{prot}]$$

Consider a one dimensional model of this system, in which $[X_{rna}]$ and $[X_{prot}]$ are functions of a position variable r and time t; in this model $\nabla^2 c = \frac{\partial^2 c}{\partial r^2}$.

For all the questions below, use the parameters $\mu = \omega = \chi_{prot} = \chi_{rna} = 1\ s^{-1}$, $K_{1/2} = 0.33$ mM, and $D_{prot} = D_{rna} = 1 \times 10^{-4}\ \mu\text{m} \cdot s^{-1}$

1. Implement a Finite Difference/Forward Euler approach to integrating this system to determine the concentration of both RNA and protein over space and time. Use a time step of 0.01 s, a total time of 30 s, a distance step of 0.02 μm and a total distance of 3.0 μm. For initial conditions, set the concentration of both RNA and protein to 0.5 mM everywhere in space. Plot the concentration of both protein and RNA at the first three positions in space as functions of concentration versus time. Also plot the concentration of both protein and RNA versus distance at both the first and last points in time.

2. Repeat the simulation from (a), but this time set the initial concentration of both RNA and protein to 0.5 mM only in the first position in space, with the initial concentrations zero everywhere else.

3. Repeat the simulation from (b), but this time increase the initial concentration of both RNA and protein to 1.0 mM (again only in the first position in space, with initial concentrations set to zero everywhere else).

4. Repeat the simulation from (c), but with the total time set to 50, 100 and 200 and 400 s.

5. Write a paragraph explaining your observations, and how they are related to the steady states of the ODE-based system studied in Project 1.

Part B: A diffusing pair of mutually-inhibiting genes.

In Project 2, we implemented an ODE-based model of the cro/cI pair of mutually inhibitory genes. Here will consider a simplified version of that system with symmetric parameters, in a reaction-diffusion model:

$$\frac{\partial[X_{rna}]}{\partial t} = \mu\left(1 - \frac{[Y_{prot}]^2}{K_{1/2}^2 + [Y_{prot}]^2}\right) - \chi_{rna}[X_{rna}] + D_{rna}\nabla^2[X_{rna}]$$

$$\frac{\partial[X_{prot}]}{\partial t} = \omega[X_{rna}] - \chi_{prot}[X_{prot}] + D_{prot}\nabla^2[X_{prot}]$$

$$\frac{\partial[Y_{rna}]}{\partial t} = \mu\left(1 - \frac{[X_{prot}]^2}{K_{1/2}^2 + [X_{prot}]^2}\right) - \chi_{rna}[X_{rna}] + D_{rna}\nabla^2[Y_{rna}]$$

$$\frac{\partial[Y_{prot}]}{\partial t} = \omega[Y_{rna}] - \chi_{prot}[Y_{prot}] + D_{prot}\nabla^2[Y_{prot}]$$

One again we will consider a one dimensional model of this system, using the parameters $\mu = \omega = \chi_{prot} = \chi_{rna} = 1\ s^{-1}$, $K_{1/2} = 0.33$ mM, and $D_{prot} = D_{rna} = 1 \times 10^{-4}\ \mu\text{m} \cdot s^{-1}$

1. Modify your model from Part A to represent this system. Once again, use a time step of 0.01 s, a distance step of 0.02 μm and a total distance of 3.0 μm.

2. Simulate the system for a total time of 5 seconds, with the following initial conditions: At the first position in space, set the initial concentration of both protein and RNA for gene X to 1.0 mM, while setting the initial concentrations for gene Y to zero; at the last position in space, set the initial concentration of both protein and RNA for gene Y to 1.0 mM, while setting the initial concentrations for gene X to zero; for all other points, set the initial concentrations of all species to zero. Plot the protein and RNA concentrations of both X and Y versus time at the first, last and middle points in space. Also plot the protein and RNA concentrations versus distance at both the first, last and middle points in time.

3. Repeat the simulation from (b), but with the total time set to 50, 100 and 200 and 400 s.

4. Repeat (c) with a different set of initial conditions: At both the first and last positions in space, set the initial concentration of both protein and RNA for gene X to 1.0 mM, while setting the initial concentrations for gene Y to zero; at the central position in space, set the initial concentration of both protein and RNA for gene Y to 1.0 mM, while setting the initial concentrations for gene X to zero; for all other points, set the initial concentrations of all species to zero.

5. Write a paragraph explaining your observations.

Helpful hints.

1-D Finite Differences and Forward Euler: To integrate a reaction-diffusion in 1 dimension, we may loop over both time and the single spatial dimension, updating concentrations for the next time point at each postion using the Forward Euler update:

$$x(t + \Delta t) \approx x(t) + \left(\frac{\partial x(t)}{\partial t} \right) \Delta t$$

To compute $\frac{\partial x(t)}{\partial t}$ requires $\frac{\partial^2 c}{\partial r^2}$, which can be calculated by finite differences:

$$\frac{\partial^2 c(i,t)}{\partial r^2} \approx \frac{c(i+1,t) + c(i-1,t) - 2(c(i,t))}{(\Delta r)^2}$$

Absorbing Boundary Conditions: The finite difference calculation of the Laplacian (∇^2) requires additional information at the boundaries; that is, what to do with $i-1$ or $i+1$ are outside the range of grid points. With absorbing boundary conditions we set these boundary values to zero, so that we have the special cases:

$$\frac{\partial^2 c(1,t)}{\partial r^2} \approx \frac{c(2,t) - 2(c(1,t))}{(\Delta r)^2}$$

and

$$\frac{\partial^2 c(i_{max},t)}{\partial r^2} \approx \frac{c(i_{max}-1,t) - 2(c(i_{max},t))}{(\Delta r)^2}$$

