Workshop on Modeling Biological Systems

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1 About the workshop

Biological systems often have many interacting components, and describing them mathematically allows us to formalize our (often pathetic) description of a given system. The mathematical model can then be used to make predictions or develop a better intuition about the biological system's behavior. This workshop will teach you to utilize simple numerical tools from computational physics and chemistry to mechanistically model processes seen in biological systems. The

material covered will include modelling well-mixed biochemical reactions, microscopic diffusion, macroscopic diffusion, and reaction-diffusion systems. There will be a total of three sessions and each session will last around 3 hours. We will use the programming language MATLAB to execute all simulations, but if you feel confident about replicating MATLAB's matrix and rendering capabilities on another platform that you are more comfortable with, feel free to do so. Prerequisites: Some familiarity with differential equations, matrix algebra, molecular biology, and programming. You will need to bring your own laptop to run simulations (you can get a licensed version through Duke). If you are new to programming with MATLAB, the MATLAB onRamp course is an excellent resource: https://matlabacademy.mathworks.com.

2 A single diffusing molecule

2.1 Microscopic diffusion, characteristics of a diffusing particle, and particle movement on different geometries

Diffusion plays an important role in conveying biochemical signals. Hence, diffusing particles often form the backbone for a variety of biophysical models. Let's watch a diffusing particle in action and study its properties.

1. Simulate a particle that performs a random walk in two dimensions with a step length of $0.6325\mu m$ per $0.1s$. Plot its path of travel starting from the origin $(0, 0)$ over a span of 5 minutes. Do the same for twenty more particles and plot all the paths of travel on the same graph. What do you notice about these plots?

2. We need to make sure that we are actually simulating diffusion. Plot the mean squared displacement (msd) of your particles' movement vs time. Does it look linear? Find the slope of the curve and use the formula $D = \frac{\Delta msd}{2k\Delta t}$ to infer the diffusion constant from the data ($D-$ Diffusion constant, $msd-$ Mean squared displacement, $k-$ Dimensions (here, it is 2), and $t-$ Time).

3. Feeling reckless? Simulate a diffusing particle that travels along the surface of a sphere.

3 Well-mixed biochemical reactions

3.1 Using ordinary differential equations (ODEs) to model protein interactions, explicit methods to solve differential equations, and emergent behavior from protein interactions in biological systems

When a biochemical system is composed of numerous molecules that are homogeneously distributed, we can use ordinary differential equations to model it. Simulating these differential equations can provide important insights into the emergent properties of these biochemical systems.

1. Consider a first-order chemical decay: $A \rightarrow B$, where A is some chemical that gets converted into B at rate k. Thus, $\frac{dA(t)}{dt} = -k[A(t)]$. Use forward Euler and Runge-Kutta methods to observe how this system evolves with time, and compare your numerical output to the analytical solution. Simulation parameters: $A(0) = 100\mu M$; $k = 0.8s^{-1}$; $dt = 0.01s$.

2. Model a ligand-receptor interaction of the form: $P + R \rightleftharpoons PR$. Here P is a chemical signal, R is a receptor that can bind with the signal, and PR is the complex formed when P binds with R. The forward rate constant is k_{on} and backward rate constant is k_{off}.

   The differential equations that govern this system are:

$$\frac{d[PR]}{dt} = k_{on}[P][R] - k_{off}[PR]$$

$$\frac{d[P]}{dt} = -k_{on}[P][R] + k_{off}[PR]$$

$$\frac{d[R]}{dt} = -k_{on}[P][R] + k_{off}[PR]$$

   Let's say the ligand-receptor interaction happens in the context of pheromone signaling in yeast. Simulate the system shown above, where your initial conditions are $k_{on} = 0.1667s^{-1}\mu M^{-1}, k_{off} = 0.001s^{-1}$([1]), $[P] = 1\mu M, s[R] = 1\mu M, and[PR] = 0$ Plot the change in concentration of

each of these chemicals over time. Just by looking at your graphs (and perhaps carrying out multiple simulations in case you don't reach steady state), can you determine what the (approximate) steady state values are? Compare your final steady state values with theoretical results.

3. Building a biochemical switch [2]: Assume a signaling molecule A is converted into its activated state B by a stimulus enzyme S (at rate k_1), and B is converted to A by an inactivating enzyme I (at rate k_2).

   - Simulate a system with different starting conditions for A and B, such that $A + B$ is a constant $T = 1$. Assume that S and I are far from saturation. Use the following parameters: $k_1 = 0.08$, $k_2 = 0.05$, $S = 1$, and $I = 1$.
   - Add a linear feedback with strength k_f so that B promotes its own formation. Set $k_f = 0.5$ and $S = 0$.
   - Make the feedback sigmoidal and see what happens to your steady state. (E.g. $\frac{k_f B^n}{B^n + K_m^n}$; set $n = 3$ and $K_m = 1$).

4 Diffusion of many molecules and reaction-diffusion systems

4.1 Macroscopic diffusion and its characteristics, using partial differential equations (PDEs) to model diffusion, explicit methods to solve PDEs, and coupling reaction with diffusion

Earlier, we studied properties of individual diffusing particles. When there are many such particles diffusing at once, we can treat them as a continuous distribution. The evolution of this distribution can modeled with partial-differential equations [3].

1. Simulate the diffusion of a chemical V along two dimensions on a 100x100 grid with periodic boundary conditions. Use an impulse function of height 1000 in the middle your domain as your initial condition. Set step sizes $dx = 0.01$ and $dt = 1$, and diffusion constant $D_v = 10^{-5}$. Verify that your

diffusion solver is working properly by comparing your simulated result with theoretical predictions.

2. Simulate the following reaction-diffusion equation:

$$\frac{\partial U}{\partial t} = D_u \nabla^2 U - UV^2 + F(1 - U)$$

$$\frac{\partial V}{\partial t} = D_v \nabla^2 U + UV^2 - (F + k)V$$

with $D_u = 2 \times 10^{-5}$. Explore the parameter space for $F \in [0, 0.07]$ and $k \in [0.04, 0.065]$ to see what patterns emerge. For each simulations, start with $U = 1$ and $V = 0$. After some time passes (say ≈ 100 steps), introduce a 10×10 square perturbation where $U = 1/2$ and $V = 1/4$ with about 5% noise to break symmetry.

References

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[2] J. E. Ferrell Jr and W. Xiong, "Bistability in cell signaling: How to make continuous processes discontinuous, and reversible processes irreversible," *Chaos: An Interdisciplinary Journal of Nonlinear Science*, vol. 11, no. 1, pp. 227–236, 2001.

[3] J. E. Pearson, "Complex patterns in a simple system," *Science*, vol. 261, no. 5118, pp. 189–192, 1993.