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An Introduction to Dynamical Systems

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Abstract

This Teaching Resource provides lecture notes, slides, and a problem set that can assist in teaching concepts related to dynamical systems tools for the analysis of ordinary differential equation (ODE)-based models. The concepts are applied to familiar biological problems, and the material is appropriate for graduate students or advanced undergraduates. The lecture explains how equations describing biochemical signaling networks can be derived from diagrams that illustrate the reactions in graphical form. Because such reactions are most frequently described using systems of ODEs, the lecture discusses and illustrates the principles underlying the numerical solution of ODEs. Methods for determining the stability of steady-state solutions of one or two-dimensional ODE systems are covered and illustrated using standard graphical methods. The concept of a bifurcation, a condition at which a system's behavior changes qualitatively, is also introduced. A problem set is included that (i) requires students to implement an ODE model of biochemical reactions using MATLAB and (ii) allows them to explore dynamical systems concepts.

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Educational Details

Learning Resource Type: Lecture notes, assignment, PowerPoint presentation

Context: Graduate

Intended Users: Teacher, learner

Intended Educational Use: Learn, plan, teach

Discipline: Biochemistry, biophysics, cell biology, education, physiology, theoretical biology

Technical Details

Format: PowerPoint (.ppt)

Size: 2.12 MB

Requirements: Microsoft PowerPoint

Format: MATLAB (.m)

Requirements: Mathworks MATLAB

Format: PDF (.pdf)

Requirements: Adobe PDF Reader

Supplementary Materials

<http://stke.sciencemag.org/cgi/content/full/sigtrans;4/191/tr6/DC1>

Slides. Introduction to dynamical systems.

Problem set MATLAB code. One MATLAB program that implements Euler's method; used as a template to model yeast glycolytic oscillations.

Answer key. MATLAB code and PDF of the answers is available upon request

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Keywords

Dynamical systems; mathematical modeling; numerical methods; simulation; computer programming; MATLAB; cardiac myocytes; glycolytic oscillations

Lecture Notes

Modeling Using Systems of Ordinary Differential Equations (ODEs)

Many biological processes can be represented mathematically using systems of ODEs (Slide 2). A signaling pathway, for instance, may consist of several coupled biochemical reactions. In this case, each ODE represents the change in concentration with time of a particular chemical species. The lecture begins by demonstrating how to obtain the ODEs appropriate for a given system. The law of mass action is introduced, and the simple example of ligand binding to a receptor is discussed (Slides 3 to 5). Enzyme-catalyzed reactions are covered next (Slides 6 to 15). Because mathematical models frequently employ the Michaelis-Menten equation to describe such reactions, this equation is derived, and the assumptions underlying it, such as the assumption of excess substrate, are discussed (Slides 7 to 12). To illustrate how Michaelis-Menten assumptions are translated into ODEs, a model of a biochemical oscillator that uses Michaelis-Menten kinetics is described (Slides 13 to 15) (1, 2). In certain cases, however, a diagram provided in a paper or textbook provides insufficient information for the relevant ODEs to be derived from the diagram (3). For instance, important intermediate steps may be eliminated when the diagram is simplified for easier display (Slides 16 and 17).

Numerical Solution of ODEs

The lecture next covers the principles underlying the numerical solution of ODEs and illustrates how to implement such solutions in the scientific programming language MATLAB (Slides 18 to 23). The slides explain Euler's method for solving differential equations (Slide 18), which uses a numerical approximation of the derivative to compute the next value of a function based on its current value, the time step, and the value of the function's derivative. A simple MATLAB program that solves an ODE using this method is presented and discussed (Slide 19 and 20). Students can use this program as a template for the numerical solution of more complicated models. Numerical errors that can potentially arise in the implementation of Euler's method, such as artificial fluctuations when the time step is too large (Slides 21), are discussed, as are extensions of the method to systems of ODEs (Slide 22). Because numerically challenging ODE models are frequently solved using more sophisticated algorithms, such as the Runge-Kutta method, which computes function derivatives at intermediate time points, methods for using such solvers in MATLAB are then described (Slides 23 to 28).

Next the lecture covers principles of dynamical systems analysis, specifically how to determine whether steady-state values in ODE systems are stable or unstable (Slides 29 to 40). By definition, a steady state is defined as the set of values at which all derivatives are equal to zero. In an ODE system, the steady state is also referred to as a "fixed point." When the system variables are close to steady-state values, however, one of two things can happen.

The variable values can move toward the steady-state values and eventually settle there, or they can move away. The former situation describes a stable fixed point; the latter describes an unstable fixed point. Graphical methods for determining whether fixed points are stable or unstable are explained and illustrated with examples. For instance, the process of electrical excitation in models of cardiac myocytes (4, 5) can be simplified and analyzed using intuitive graphs that plot voltage on the abscissa and the derivative of voltage with respect to time on the ordinate (Slides 31 and 32). Stability in two-variable systems can be examined using phase plane techniques, in which one variable is plotted versus the other variable rather than plotting variables versus time. These techniques are illustrated using the example of yeast glycolytic oscillations (Slide 33) (6), as mathematically represented in a simple model by Bier *et al.* (Slide 34) (7, 8). The Bier *et al.* model (8) contains two variables, the intracellular concentrations of glucose and adenosine 5'-triphosphate (ATP), and the model simulates transport of glucose into the cell, conversion of glucose to ATP via glycolysis, and conversion of ATP to adenosine diphosphate (ADP) via energy-consuming enzymes.

Principles that are illustrated through the analysis of model output include the following: (i) plotting one variable versus the other in a phase plane (Slide 35); (ii) computing and plotting a nullcline, the set of points at which one derivative is equal to zero (Slides 36 to 38); and (iii) calculating fixed-point stability analytically. This last procedure involves: (i) calculating the Jacobian, a matrix whose elements consist of the partial derivatives of each equation with respect to each variable; (ii) evaluating the Jacobian at the fixed point; and then (iii) solving for the eigenvalues of this matrix (Slides 39 and 40). The lecture concludes by briefly introducing the concept of a bifurcation, or a parameter value at which the behavior of the system changes qualitatively (Slide 41).

Slide 42 shows an example of model output generated with MATLAB that the students must reproduce as part of the homework assignment.

Problem Set

Introductory Details

The homework assignment consists of two parts. The first requires the students to implement a simple model of yeast glycolytic oscillations (8). This model calculates the concentrations of two chemical species, glucose ([G]) and [ATP], according to the following ODEs:

$$\begin{aligned}\frac{d[ATP]}{dt} &= 2k_1 [G] [ATP] - \frac{k_p [ATP]}{[ATP] + K_m} \\ \frac{d[G]}{dt} &= V_{in} - k_1 [G] [ATP]\end{aligned}$$

The Supplementary Materials contain a MATLAB script (euler.m) that can assist the students in completing the homework assignment.

Student Assignment: Part 1

The MATLAB script “euler.m” uses Euler's method to integrate the differential equation $dx/dt = a - bx$, $x(0) = c$. Using this script as a template, implement the model of yeast glycolytic oscillations (Slide 34) (8). Step-by-step hints for how to achieve this are as follows:

1. Change the parameters defined at the top of the script from a , b , and c to those relevant to the Bier *et al.* model: V_{in} , k_1 , k_p , and K_m . Control values are given on Slide 34.
2. Replace the statement defining the initial condition for x with statements that assign initial conditions of $[G]$ and $[ATP]$. Good initial values are $[ATP] = 4$; $[G] = 3$.
3. Replace the differential equation describing dx/dt with two equations describing $d[ATP]/dt$ and $d[G]/dt$.
4. Replace the statement that updates x at each time step with statements that update $[ATP]$ and $[G]$.
5. Alter the code so that it keeps track of values of $[G]$ and $[ATP]$ at all points in time.
6. Change the time of the simulation to one that is long enough to observe oscillations. This is best determined by trial and error.
7. Remember that Euler's method can “blow up” if the time step is too large. You may need to adjust the time step to make sure you have a stable solution. One way to verify this is to start with a time step that gives “reasonable” output, then reduce the time step by a factor of 2. If this gives the same output as the larger time step, then the time step is small enough. (A mathematician might contend that this statement cannot be proven correct, but it works in practice).
8. Plot $[G]$ and $[ATP]$ versus time in different colors on the same plot.
9. Visualize the trajectory in the phase plane—i.e., generate a plot of $[ATP]$ versus $[G]$.

Student Assignment: Part 2

Once the model is working, you can simulate biologically meaningful changes to the system. For instance, results presented in class showed the effects of changes in the Michaelis constant (K_m). Here, we will simulate a potentially important perturbation and investigate how this alters the behavior of the model.

Simulate increases and decreases in the activity of phosphofructokinase (PFK). How do these changes affect the amplitude and frequency of glycolytic oscillations? How do you interpret these results?

If PFK activity becomes large enough, oscillations will cease. Plot time courses, and trajectories in the phase plane, under both oscillating and nonoscillating conditions. How large does PFK activity need to become to stop oscillations?

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and Notes

1. Igoshin OA, Goldbeter A, Kaiser D, Oster G. A biochemical oscillator explains several aspects of *Myxococcus xanthus* behavior during development. *Proc. Natl. Acad. Sci. U.S.A.* 2004; 101:15760–15765. [PubMed: 15496464]
2. Mogilner A, Wollman R, Marshall WF. Quantitative modeling in cell biology: What is it good for? *Dev. Cell.* 2006; 11:279–287. [PubMed: 16950120]
3. Kamrava M, Simpkins F, Alejandro E, Michener C, Meltzer E, Kohn EC. Lysophosphatidic acid and endothelin-induced proliferation of ovarian cancer cell lines is mitigated by neutralization of granulinepithelin precursor (GEP), a prosurvival factor for ovarian cancer. *Oncogene.* 2005; 24:7084–7093. [PubMed: 16044162]
4. Luo CH, Rudy Y. A model of the ventricular cardiac action potential. Depolarization, repolarization, and their interaction. *Circ. Res.* 1991; 68:1501–1526. [PubMed: 1709839]
5. Wang LJ, Sobie EA. Mathematical model of the neonatal mouse ventricular action potential. *Am. J. Physiol. Heart Circ. Physiol.* 2008; 294:H2565–H2575. [PubMed: 18408122]
6. Tu BP, Kudlicki A, Rowicka M, McKnight SL. Logic of the yeast metabolic cycle: temporal compartmentalization of cellular processes. *Science.* 2005; 310:1152–1158. [PubMed: 16254148]
7. Bier M, Teusink B, Kholodenko BN, Westerhoff HV. Control analysis of glycolytic oscillations. *Biophys. Chem.* 1996; 62:15–24. [PubMed: 8962468]
8. Bier M, Bakker BM, Westerhoff HV. How yeast cells synchronize their glycolytic oscillations: A perturbation analytic treatment. *Biophys. J.* 2000; 78:1087–1093. [PubMed: 10692299]