IBI* SERIES WINNER

Learning Biology by Recreating and Extending Mathematical Models

Dynamics of Biological Systems, the IBI Prize–winning module, brings mathematics into the biology laboratory.

Hillel J. Chiel,[1,2,3]† Jeffrey P. Gill,[1] Jeffrey M. McManus,[1] Kendrick M. Shaw[1]

Biological systems are dynamic. Proteins fold into three-dimensional shapes to serve as catalysts, motors, or regulators. A fertilized egg divides exponentially, and gradients and internal cell states choreograph fetus formation. Neurons become active or are inhibited in shifting spatial and temporal patterns as an animal moves through its environment. Flocks of birds migrate together, and schools of fish form and disperse to avoid predators and forage for food. The only constant in biological systems is change.

Although biological systems generate beautiful patterns that unfold in space and time, most students are taught biology as static lists of names. Names of species, anatomical structures, cellular structures, and molecules dominate, and sometimes overwhelm, the curriculum and the student. Cookbook labs may demonstrate advanced techniques but have a foregone conclusion. Not surprisingly, students often conclude that biology is boring.

In contrast, students who participate in research discover that biological systems can be understood by developing a "feeling for the organism," a qualitative sense of the system (*1*). Successful students learn the skill of asking the right question with the right technique to find the key elements that make biological systems work.

Can biology be taught by focusing on unfolding patterns in space and time? Can one also reach students who are repelled by details; are more comfortable with abstractions and clear principles; and who often become mathematicians, physicists, or engineers? The divide between the cultures of biology and the more quantitative sciences is unfortunate because interdisciplinary opportunities are expanding. Engineers are fascinated by self-assembling, self-repairing, and self-replicating nanomachines (*2*), exemplified by proteins. How can these nanomachines be combined into cell-like modular reorganizing components? What is the basis for multifunctional designs that allow biological organisms to use the same neural control and periphery to flexibly switch among multiple behaviors (*3*)? How do many agents use distributed computing and cooperation to solve common goals (*4*)? Can we further enhance evolutionary algorithms (*5*) to solve otherwise intractable problems? Life is an alien technology whose mastery would create novel approaches to hard problems.

Classroom setup. Each of the six hexagonal tables in the classroom has power outlets and connections to the CWRU fiber optic network for students' laptops.

These considerations are the basis for the inquiry-based module Dynamics of Biological Systems, developed at Case Western Reserve University (CWRU) (*6*, *7*). The module's learning goals are as follows: construct and extend mathematical models of biological phenomena, analyze these models using the concepts and tools of nonlinear dynamical systems theory, and write clearly about the modeling process and the results obtained from the model.

During the module's first half, students work in teams (see the photo) to solve increasingly complex problems by creating mathematical models using a programming language (*Mathematica*) and to analyze these models using nonlinear dynamical systems theory. After being shown how to find modeling papers, each team selects a peer-reviewed paper that describes a mathematical model of a biological system. They spend the second half of the module using the skills gained in the first half to reconstruct, analyze, and then modify and extend the published model. At the module's end, each student submits a final term paper (*7*).

Biology students develop an intuition for mathematical descriptions of biological phenomena and how to program them as they work on concrete biological problems and systems. Engineers see how the details of a biological system can be fit together into a quantitative model that can be analyzed mathematically, which helps them master biological complexity. The course provides students experience in teamwork, in solving difficult problems that allow them to pursue independent inquiry, and in writing clearly about their results (*7*).

[1]Department of Biology, Case Western Reserve University, Cleveland, OH 44106, USA. [2]Department of Neurosciences, Case Western Reserve University, Cleveland, OH 44106, USA. [3]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH 44106, USA.
*IBI, Science Prize for Inquiry-Based Instruction; www.sciencemag.org/site/feature/data/prizes/inquiry/.
†Author for correspondence. E-mail: hjc@case.edu

CREDIT: JEFFREY P. GILL

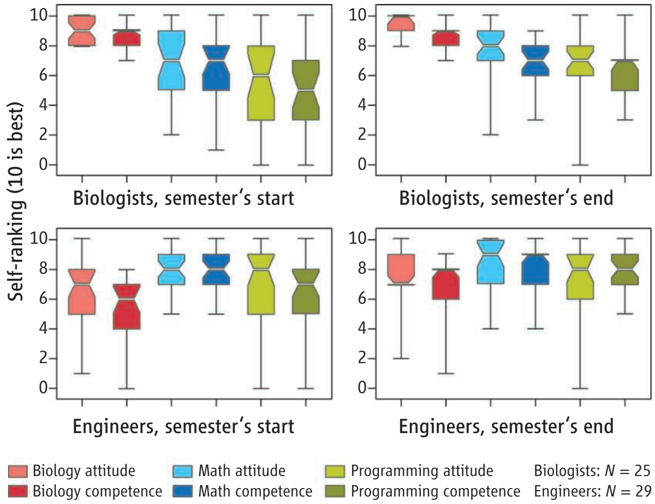
Students test their hypotheses by manipulating their models and comparing the results with published data or by doing additional mathematical analysis of the model that suggests further biological experiments. Model extensions fall into four general categories: exploring the effects of novel patterns of input to the model; exploring different, biologically based parameter values on the model predictions; changing the form of a model; and identifying and exploring qualitative changes in the dynamics of the model that can be triggered by a small change in parameters (i.e., performing a bifurcation analysis).

The interactive textbook for the course is provided free of charge (http://biol300.case.edu/). All students need a licensed copy of *Mathematica* to use this textbook. If their home institution does not have a *Mathematica* site license, students can purchase a 6-month license for $44.95. Thus, if one assumes that a student has a laptop that can run *Mathematica*, the cost in supplies and other expendables per student is less than $50.

Student assessment, like student progress, is continuous. The instructors talk with team members during class to see the progress they are making on the problems, to provide helpful hints, to evaluate how teammates are interacting with one another, and to ask them questions to determine their level of understanding. After class, the instructors meet to review student progress, providing continuously updated information on how well the students are grasping the material, potential problems in comprehension, and/or friction between teammates.

During the module, students are given attitude and concept assessments (see the charts). At the outset, biology majors have a significantly better attitude toward and sense of competence in biology relative to engineering majors ($P < 0.0001$). At the end of the semester, engineers show a significantly higher view of their competence in computer programming and in biology ($P < 0.006$), and biology majors show a strong trend to feel more competent in computer programming. The entire class shows a highly significant increase in the number of correct answers to the conceptual exam ($P < 0.0001$).

The module has taught us important lessons about education and students. First, switching from lectures to a continuous progress approach has improved students' comprehension and skill levels. Second, reinforcing material through application is important. Material from the first half of the module provides students the key tools to reproduce, analyze, and extend models. Third, having students rebuild models provides them with the depth of understanding needed to further extend and analyze their models. Indeed, students often find that the original papers have errors, ranging from minor to serious, which are only revealed as they reconstruct the model. This teaches them the importance, and the limitations, of peer review. Fourth, relating assessment directly to the educational goals ensures that students understand the purpose of everything they do. In particular, specific rubrics guide them as they write each component of their term paper. Fifth, assessing and providing feedback on a continuous basis helps students track their current mastery of the material and learn how to master it better. Finally, when instructors and students are allowed to continuously interact as students build a working model, the process creates solidarity and enthusiasm that makes teaching a pleasure.



Improved attitudes. Data shown are pooled from the attitudes questionnaire. Results are divided by major and are shown for the beginning and end of the semester. Students rate how much they like and how competent they feel they are in biology, mathematics, or computer programming on a scale from 0 to 10 (best). Box and whisker charts showing (in order): maximum value (top whisker), 75th percentile (top of box), median (white line, location of notch), 25th percentile (bottom of box), and minimum value (bottom whisker).

About the authors

Authors are pictured from left to right. **Hillel J. Chiel** received an English B.A. from Yale University and a Ph.D. from M.I.T. in Neural and Endocrine Regulation and did postdoctoral fellowships in Columbia University's Center for Neurobiology and Behavior and in AT&T Bell Labs Molecular Biophysics Department. He is currently Professor of Biology, Neurosciences, and Biomedical Engineering at CWRU. His research focuses on the neuromechanical basis of adaptive behavior in the marine mollusk *Aplysia californica*. **Kendrick M. Shaw** received his B.S. and M.S. from CWRU in Computer Science, worked for Microsoft, and is currently in the Medical Scientist Training Program at CWRU. He focuses on the mathematical and experimental analysis of pattern generation. **Jeffrey M. McManus** received his B.S. in Biology from CWRU and focuses on the experimental analysis of the neuromechanics of multifunctionality in *Aplysia*. **Jeffrey P. Gill** received his B.S. from CWRU in Systems Biology and studies modeling of biological systems. All three are working on their Ph.D. degrees with Dr. Chiel.

References and Notes

1. E. F. Keller, *A Feeling for the Organism: The Life and Work of Barbara McClintock* (W. H. Freeman, San Francisco, 1983).
2. L. M. Smith, *Nature* **465**, 167 (2010).
3. H. J. Chiel, L. H. Ting, O. Ekeberg, M. J. Z. Hartmann, *J. Neurosci.* **29**, 12807 (2009).
4. M. Dorigo, M. Birattari, *Scholarpedia* **2**, 1462 (2007).
5. K. Deb, *Multi-Objective Optimization Using Evolutionary Algorithms* (Wiley, Chichester, UK, 2001).
6. The latest version of the course Web site is at http://biol300.case.edu/. The course policies, syllabus, and the textbook chapters (as *Mathematica* notebooks) are freely available at this site. Notebooks can be read using the *Mathematica* reader, available at http://www.wolfram.com/products/player/. Student surveys and grades require an official student login and password, and thus are only available to students taking the course.
7. H. J. Chiel, J. M. McManus, K. M. Shaw, *CBE Life Sci. Educ.* **9**, 248 (2010); www.lifescied.org/content/9/3/248.full.

Acknowledgments: H.J.C. is supported by NSF grants DMS-10100434 and IIS-1065489 and J.P.G. by the Graduate Assistance in Areas of National Need program (P200A090191-11). K.M.S.'s training is partially supported by NIH grant T32-GM007250. We gratefully acknowledge the encouragement of the previous Chairs of the Department of Biology at CWRU (N. Rushforth and J. Koonce), the current Chair (C. Cullis), the previous Chair of the Department of Biomedical Engineering, P. Crago, and the helpful feedback and suggestions from the students in the module, who have helped us steadily improve both the module and our teaching.

Supplementary Materials

www.sciencemag.org/cgi/content/full/336/6084/993/DC1

10.1126/science.1214192

PHOTO CREDIT: JEFFREY P. GILL