Special Topics in Biological Dynamics, APC 591
Fall 2001

Important Information

Lectures: Tuesdays, Thursdays, 2:40-4:00PM, starting Sept. 13
Lewis Thomas Laboratory Room 118

Computer labs: Wednesdays 2:40-4:00PM, Fridays 2:40-4:00PM, starting Sept. 19
Schultz Lab Room 106

Course Webpage: http://www.math.princeton.edu/~jmoehlis/APC591

Course Lounge: Guyot Room 9B, available soon (?)

Questions? Contact (email preferred):

Jeff Moehlis, Course TA
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John Hopfield, Course Coordinator
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Course Description

This course is an introduction to the methods used to describe and understand biological dynamics using mathematical models and computer simulation. There will be four main units:

- Models of Action Potential Generation and Neural Circuits, D. W. Tank (Mol. Bio., Physics)
- Biological Pattern Formation, E. C. Cox (Mol. Bio.)
- Dynamics of Disease, S. A. Levin (EEB)
- Intracellular Networks, W. S. Bialek (Physics)

Each unit will have a lecture component (taught by the main lecturer given above, and perhaps guest lecturers) and a computer laboratory component.

Prerequisites

A preparation in mathematics, including integral calculus, differential equations, and linear algebra is expected, as is some experience in using mathematics to model the real world. Graduate students with undergraduate majors or minors in physics, biophysics, mathematics (pure or applied), engineering, and evolutionary biology will have such backgrounds, as will Princeton seniors with these or similar majors. Much of the material is best explored through computer simulations, and problem sets are an important component of the course. Instruction and help will be available in a computer simulation laboratory. Previous experience with computers is not essential, but the student will need to learn useful aspects of Matlab and other programs for scientific computation.

Reading Materials

There is no single book which covers all of the topics in this course. The following general books, which will be useful at various times, have been placed on reserve at the Math/Biology library. The APC591 Reserve materials are on the lower right side of the shelf behind the circulation desk, to the right of PHYS and MATH and to the left of EEB and MOL Reserve materials. Some of these books are on reserve for other classes, and may be in multiple locations, as listed.

- B. Alberts *et al*, *Molecular biology of the cell*, 3rd edition, Reserve APC591, MOL504
- H. C. Berg, *Random walks in biology*, Reserve APC591
- L. Edelstein-Keshet, *Mathematical models in biology*, Reserve APC591, EEB324
- A. Goldbeter, *Biochemical oscillations and cellular rhythms*, Reserve APC591 (on order)
- T. G. Hallam and S. A. Levin, editors. *Mathematical ecology: an introduction*, Reserve APC591
- D. Johnston and S. M-S. Wu, *Foundations of cellular neurophysiology*, Reserve APC591
- J. P. Keener and J. Sneyd, *Mathematical physiology*, Reserve APC591 (on order)
- R. H. Kessin, *Dictyostelium: evolution, cell biology, and the development of multicellularity*, Reserve APC591
- C. Koch, *Biophysics of computation: information processing in single neurons*, Reserve APC591
- J. D. Murray, *Mathematical biology*, 2nd edition, Reserve APC591, EEB324
- M. Nowak and R. M. May, *Virus dynamics: mathematical foundations of immunology and virology*, Reserve APC591, EEB524
- M. Ptashne, *A genetic switch*, Reserve MOL505
- D. Purves *et al*, *Neuroscience*, Reserve MOL508
- G. H. Weiss, *Aspects and applications of the random walk*, Reserve APC591 (on order)

A copy of Johnston and Wu will also be made available to the students, location TBA.

The lectures will often draw upon material in specific research articles, many of which are listed in the schedule. These articles can typically be downloaded off the web, with website address given on the Course Webpage. Where appropriate, a paper copy will be available to be photocopied, location TBA.

Homework

- There will be two homework sets per unit. These will often involve computer simulations, and the necessary background will be provided in the lectures and in the computer labs taught by the Course TA. Assignments will be put on the Course Webpage.

  The homework will be due at the time given on the assignments, typically Friday at 5:00PM. Completed homework should be turned into the Course TA's mailbox, which is located in **Room 205 Fine Hall**. *Because solution sets will be posted on the Course Webpage shortly after the due date, please get the assignments in on time!*

- Tentatively, each student will be expected to complete a final project. This will involve both a written and oral report on research done on modeling a specific biological system. More information will be made available later in the semester.

Grading

The course is only offered on a Pass/Fail basis. However, this does not mean that it will be a "free ride." Students are expected to complete all homework assignments (and, tentatively, the final project) in order to pass. Doing the assignments is *necessary* for learning the material, and this is the type of course which will be most rewarding to students who devote appropriate effort.

Office Hours

In addition to the computer labs, the Course TA will be available to answer questions, tentatively on Thursdays from 4:00-6:00PM, location TBA. Office hours are a good opportunity to obtain clarification and tips on doing the homework. Also, feel free to email the Course TA with questions.

The main lecturers will also be available for consultation at times TBA.

Email List

A roster including email addresses will be compiled at the first few lectures so that students can be contacted with important announcements and homework tips. (If you have a suggestion which you feel should be circulated to fellow students, please contact the Course TA, who will do so at his discretion.)

Computer Accounts

Regular CIT accounts will allow access to the computers in Room 106 Schultz (if you have never logged in before, try the last 8 digits of your SSN as a password). These computers will have the necessary programs to complete the problem sets, namely:

- MATLAB - *an integrated technical computing environment that combines numeric computation, advanced graphics and visualization, and a high-level programming*

language. MATLAB is also available on the CIT arizona UNIX cluster, and many other computers around campus. MATLAB primer available from Course Webpage.

- XPP - *a tool for solving differential equations, difference equations, delay equations, functional equations, boundary value problems, and stochastic equations.* XPP can also be downloaded from http://www.math.pitt.edu/~bard/xpp/xpp.html and installed on other computers. Note that this website also has a nice tutorial for learning to use XPP.

Students with access to other computers with these or equivalent programs are welcome to use them to complete the homework sets.

Schedule for APC 591, Fall 2001 (subject to change)

Locations for the reading materials are included where possible. If given as "Web", please access the article through the Course Webpage. It might be necessary to be on a princeton.edu computer to access some articles.

Unit 1: Models of Action Potential Generation and Neural Circuits

Main Lecturer: D. W. Tank (Mol. Bio., Physics)
Guest Lecturer: J. J. Hopfield (Mol. Bio.)

Sept. 13th, Lecture 1 (Tank): Overview of nervous system organization and electrochemical signaling in neurons.

- D. Purves, G. J. Augustine, D. Fitzpatrick, L. C. Katz, A. S. LaMantia, J. O. McNamara, S. M. Williams. *Neuroscience*, 2nd Edition, Sinauer Associates, 2001 (Chapters 1,2). Reserve MOL 508

Sept. 18th, Lecture 2 (Tank): The Hodgkin/Huxley model of the action potential.

- A. L. Hodgkin and A. F. Huxley. A quantitative description of membrane current and its application to conduction and excitation in nerve, J. Physiol. 117:500-544 (1952). Web
- A. L. Hodgkin. The Croonian Lecture: Ionic Movements and Electrical Activity in Giant Nerve Fibres, Proceedings of the Royal Society of London, Series B, Biological Sciences, 148(930):1-37 (1958). Web
- D. Johnston and S. M-S. Wu. Foundations of Cellular Neurophysiology, MIT Press, 1995. (Chapter 6) Reserve APC591

Sept. 20th, Lecture 3 (Tank): Generalization of Hodgkin/Huxley and simplified models of spiking neurons.

Sept. 25th, Lecture 4 (Tank): Neural circuit models of persistent neural activity and short term memory.

- H. S. Seung, D. D. Lee, B. Y. Reis, and D. W. Tank. Stability of the Memory of Eye Position in a Recurrent Network of Conductance-Based Model Neurons. Neuron 26:259-271 (2000). Web
- H. S. Seung, D. D. Lee, B. Y. Reis, and D. W. Tank. The autapse: a simple illustration of short-term analog memory storage by tuned synaptic feedback. Journal of Computational Neuroscience 9:171-85 (2000). Web
- E. Aksay, G. Gamkrelidze, H. S. Seung, R. Baker, and D. W. Tank. In vivo intracellular recording and perturbation of persistent activity in a neural integrator. Nature Neuroscience 4:184-93 (2001). Web

Sept. 27th, Lecture 5 (Hopfield): Neural computation through action potential synchrony

- J. J. Hopfield and C. Brody. What is a moment? "Cortical" sensory integration over a brief interval. Proc Natl Acad Sci USA. 97(25):13919-24 (2000). Web
- J. J. Hopfield and C. Brody. What is a moment? Transient synchrony as a collective mechanism for spatiotemporal integration. Proc Natl Acad Sci USA. 98(3):1282-7 (2001). Web

Oct. 2th, Lecture 6 (Hopfield): Neural computation through action potential synchrony, continued

Unit 2: Biological Pattern Formation

Main Lecturer: E. C. Cox (Mol. Bio.)
Guest Lecturer: S. Y. Shvartsman (Chem. Eng.)

Oct. 4, Lecture 1: How bacteria find their food

- H. C. Berg and D. A. Brown. (1972) Chemotaxis in *E. coli* analyzed by three-dimensional tracking. Nature 239:500-504
- R. M. Macnab and D. E. Koshland Jr. (1972) The gradient-sensing mechanism in bacterial chemotaxis. Proc Natl Acad Sci USA 69:2509-2512
- D. A. Brown and H. C. Berg.(1974) Temporal stimulation of chemotaxis in *Escherichia coli*. Proc Natl Acad Sci USA 71:1388-1392
- G. L. Hazelbauer, R. E. Mesibov, and J. Adler. (1969) *Escherichia coli* mutants defective in chemotaxis toward specific chemicals. Proc Natl Acad Sci USA 64:1300-1307
- S. M. Block and H. C. Berg. (1984) Successive incorporation of force-generating units in the bacterial rotary motor. Nature 1984 309:470-472
- General reference: H. C. Berg, *Random Walks in Biology*, Princeton University Press, 1983, Reserve APC591

Oct. 9, Lecture 2: Order from disorder in the cellular slime molds

- R. H. Kessin, *Dictyostelium: evolution, cell biology, and the development of multicellularity*, Cambridge University Press, 2001, Chapters 1 and 2. Reserve APC591

- E. Pálsson, K. J. Lee, R. E. Goldstein, J. Franke, R. H. Kessin, and E. C. Cox. (1997) Selection for spiral waves in the social amoebae *Dictyostelium*. Proc. Natl. Acad. Sci. USA 94:13719-13723
- K. L. Lee, R. E. Golstein, and E. C. Cox. (2001) Resetting wave forms in *Dictyostelium* territories. Phys. Rev. Letters 87:068101

- G. Byrne and E. C. Cox. (1987) Genesis of a spatial pattern in the cellular slime mold *Polysphondylium pallidum*. Proc. Natl. Acad. Sci. USA 84:4140-4144

Oct. 11, Lecture 3: Random walks and diffusion of molecules and microorganisms:
Introduction to transport equations for Brownian particles, one dimensional model for chemotaxis: derivation and associated approximation.

- G. H. Weiss, *Aspects and applications of the random walk*, Reserve APC591
- E. F. Keller and L. A. Segel. A model for chemotaxis, J. Theor. Biol., 30(2):225, 1971
- H. G. Othmer, S. R. Dunbar, and W. Alt. Models of dispersal in biological systems. J. Math. Biol. 26(3):263-298, 1988

Oct. 16, Lecture 4: Modeling the cAMP relay system in the slime molds.
Excitability and oscillations in the binding induced release model, phase plane analysis and bifurcation techniques.

- J. L. Martiel and A. Goldbeter. A model based on receptor desensitization for cyclic-AMP signaling in *Dictyostelium* cells. Biophys. J. 52(5):807-828, 1987.
- A. Goldbeter, *Biochemical oscillations and cellular rhythms*, Reserve APC591

Oct. 18, Lecture 5: The importance of being spiral.

Oct. 23, Lecture 6: Random walks and feedback loops in models for slime mold aggregation.
Three variable model, formation of spiral waves, numerical analysis of the coupled system, summary of existing modeling approaches

Unit 3: Dynamics of Disease

Main Lecturer: S. A. Levin (EEB)
Guest Lecturer: M. A. Nowak (IAS, Prog. Theor. Bio.)
Guest Lecturer: J. G. Dushoff (EEB)

Oct. 25, Lecture 1 (Levin): Introduction to the dynamics of disease

Oct. 30, Nov. 1: *Fall Recess*

Nov. 6, Lecture 2: (Nowak) Virus dynamics I

Nov. 8, Lecture 3 (Nowak) : Virus dynamics II

Nov. 13, Lecture 4 (Levin): Influenza dynamics and vaccination strategies

Nov. 15, Lecture 5 (Dushoff): Influenza dynamics

Nov. 20, Lecture 6 (Dushoff): Influenza dynamics, continued

Nov. 23: *Thanksgiving Recess*

Reading List

- R. M. May, "Population Biology of Microparasitic Infections", pp.405-442 of *Mathematical Ecology*, ed. Hallam and Levin, Reserve APC591
- M. A. Nowak and R. M. May, *Virus Dynamics*, Oxford University Press, 2000, Reserve APC591, EEB524
- Perelson and Weisbuch, "Immunology for Physicists", *Rev. Mod. Physics*, 69:1219–1267, 1997

Unit 4: Intracellular Networks

Main Lecturer: W. S. Bialek (Physics)

Nov. 27, Lecture 1: What are we trying to explain?
Networks in biochemical reactions in cells perform many different functions, and before launching into models we should try understand what functional behaviors these models must reproduce. This will be a somewhat qualitative introduction, with examples (to which we return) of amplification, adaptation, switching and oscillation. A theme that runs through all of these examples is that functions often are accomplished with surprisingly small numbers of molecules.

Nov. 29, Lecture 2: Building blocks
The "elementary" pieces of biochemical networks are already protein machines of some sophistication. In this lecture I will try to give an impression of what is known about catalysis, specificity, cooperativity and the patterns of regulation. The goal is both to know what is plausible (what are we allowed to write in our models?) and to highlight some open questions one level below the analysis of networks themselves.

Dec. 4, Lecture 3: Bacterial chemotactic behavior
Bacterial chemotaxis is an excellent "model system" for the analysis of intracellular networks, and the chemotactic behavior itself provides an interesting example of biological dynamics, apparently implementing a stochastic optimization algorithm. In this lecture I will focus on the behavior itself. Models for the behavior offer a chance to think about the connections between the description of individual trajectories and generalized diffusion or Fokker-Planck dynamics for distributions, as well as the relation of these physical pictures to the computational task facing the bacterium. Understanding the physical constraints under which the bacterium operates also gives us a chance to introduce methods for describing fluctuations and noise in chemical kinetics.

Dec. 6, Lecture 4: Networks for chemotactic computation
We are close to knowing all of the protein components that are involved in the biochemical computations of chemotaxis. On the other hand, we may never know all of the parameters that describe interactions in this network. This lecture will review efforts to make models in the face of this uncertainty. Important (and probably universal) issues include sensitivity, adaptation and robustness. The same system which is sensitive to single molecular

events at the cell surface maintains functional (if individualistic) behavior in the face of order of magnitude changes in the concentrations of crucial components. I will try to make the unviersality of the issues more concrete by drawing analogies to problems that have been addressed in models of individual neurons (cf. the lectures by Tank), neural networks, and other sensory receptor systems (next lecture).

Dec. 11, Lecture 5: Counting photons and molecules
Receptor cells in the eyes and noses of different animals use a variety of biochemical networks for detection, amplification and signal processing. Conveniently these cells provide an electrical output signal that can be measured with considerable precision; other signal transduction networks use analogous protein components but the outputs (eg., modulations in gene expression) are harder to quantify. In this lecture we will look at the facts regarding particular transduction systems, especially in vertebrate vision where quantitative models are most advanced, and at attempts to identify universalities in strategies for amplification and adaptation.

Dec. 13, Lecture 6: Switches, oscillators and (maybe) state machines
Many aspects of biological function, from the regulation of gene expression in bacteria to the storage of memories in the brain, involve the construction of multistable "switches" in which the different stable states are fixed points in the dynamics of a biochemical reaction network. In other cases the system can cycle through these states, as in the cell cycle or circadian rythyms, and there is even the possibility of using the multiple states to perform computations. The systems that we understand best have an interesting interplay of sophisticated machinery in the individual molecules plus patterns of network connectivity use collective dynamics to achieve function. Again small numbers of molecules are relevant, so there are questions of noise and its impact on stability.

Reading List

- TBA