Biological Dynamics, APC/EEB/MOL 514
Fall 2002

Important Information

Lectures: Tuesdays, Thursdays, 2:40-4:00PM, starting Sept. 12
Lewis Thomas Laboratory Room 118

Computer Labs: Thursdays 1:00-2:30PM, starting Sept. 19
Course Lounge (Guyot Room 9B)

Course Webpage: http://www.math.princeton.edu/~jmoehlis/APC514

Questions? Contact (email preferred):

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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:

- Action Potentials and Simple Neural Circuits, D. W. Tank (Mol. Bio., Physics)
- Dynamics of Disease, J. B. Plotkin (PACM, IAS Prog. Theor. Bio.)
- Intracellular Chemical Networks, W. S. Bialek (Physics)
- Spatial Patterns in Development, E. C. Cox (Mol. Bio.), S. Y. Shvartsman (Chem. Eng.)

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

Prerequisites

No background in the relevant biology is required. However, a solid preparation in mathematics, including differential equations, integral calculus, and linear algebra is essential, as is some experience in using mathematics to model the real world. Graduate students with undergraduate degrees in mathematics, physics, electrical engineering, mathematical biology, and biophysics will have such backgrounds, as should Princeton seniors with these 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. (Items listed as "requested" have be requested to be put on reserve, but are not there yet as of 9/10/02.) The APC/EEB/MOL 514 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, as listed.

- B. Alberts *et al*, *Molecular biology of the cell*, 3rd edition, Reserve APC/EEB/MOL 514
- R. M. Anderson and R. M. May, *Infectious diseases of humans: dynamics and control*, Reserve APC/EEB/MOL 514 (requested)
- H. C. Berg, *Random walks in biology*, Reserve APC/EEB/MOL 514
- F. Brauer and C. Castillo-Chavez, *Mathematical models in population biology and epidemiology*, Reserve APC/EEB/MOL 514
- L. Edelstein-Keshet, *Mathematical models in biology*, Reserve APC/EEB/MOL 514
- A. Goldbeter, *Biochemical oscillations and cellular rhythms*, Reserve APC/EEB/MOL 514
- T. G. Hallam and S. A. Levin, eds *Mathematical ecology: an introduction*, Reserve APC/EEB/MOL 514 (requested)
- D. C. Hanselman, B. Littlefield *Mastering MATLAB 6: a comprehensive tutorial and reference*, Reserve APC/EEB/MOL 514 (requested)
- N. J. Higham and D. J. Higham, *MATLAB guide*, Reserve APC/EEB/MOL 514
- D. Johnston and S. M-S. Wu, *Foundations of cellular neurophysiology*, Reserve APC/EEB/MOL 514
- J. P. Keener and J. Sneyd, *Mathematical physiology*, Reserve APC/EEB/MOL 514
- R. H. Kessin, *Dictyostelium: evolution, cell biology, and the development of multicellularity*, Reserve APC/EEB/MOL 514 (requested)
- C. Koch, *Biophysics of computation: information processing in single neurons*, Reserve APC/EEB/MOL 514
- S. A. Levin, T. G. Hallam, and L. J. Gross (ed.) *Applied mathematical ecology*, Reserve EEB321
- J. D. Murray, *Mathematical biology*, 2nd edition, Reserve APC/EEB/MOL 514
- M. Nowak and R. M. May, *Virus dynamics: mathematical foundations of immunology and virology*, Reserve APC/EEB/MOL 514
- R. Pratap, *Getting started with MATLAB 5: a quick introduction for scientists and engineers*, Reserve APC/EEB/MOL 514 (requested)
- M. Ptashne, *A genetic switch*, Reserve MOL505

- D. Purves *et al*, *Neuroscience*, Reserve APC/EEB/MOL 514
- S. H. Strogatz, *Nonlinear dynamics and chaos: with applications in physics, biology, chemistry, and engineering*, Reserve APC/EEB/MOL 514 (requested)
- G. H. Weiss, *Aspects and applications of the random walk*, Reserve APC/EEB/MOL 514 (requested)

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 distributed in class or made 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!*

- During the second part of the term, small groups will be formed and independent projects assigned. In a final meeting of the class, the projects will be presented in 30 minute presentations and the results for each project posted on the class web site.

Grading

Students will have the option of taking the course on a letter grade or pass/fail basis. Note, however, that pass/fail does not correspond to a "free ride," and students are expected to complete all homework assignments in order to pass. Overall, 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 on Thursdays from 4:00-5:00PM. Office hours will start after lectures in the lecture room (Lewis Thomas Laboratory 118), and will move to the course lounge (Guyot Room 9B) if necessary. 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 lecturers will also be available for consultation by appointment.

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 Labs

Attendance of the computer labs is optional, but encouraged. Computer labs will meet Thursdays 1:00-2:30PM, starting Sept. 19, in the course lounge (Guyot Room 9B). The computer labs will cover supplemental material to the lectures, and will typically focus on tutorials to be posted on the Course Webpage. Students are also encouraged to ask questions about the lectures and homework assignments during the computer labs.

Computer Accounts and Programs

Each registered student will get a computer account on the Linux computers in the course lounge (Guyot Room 9B), details of which will be sent in an email.

The computers in the course lounge have MATLAB installed, which is an integrated technical computing environment that combines numeric computation, advanced graphics and visualization, and a high-level programming language. You will find MATLAB useful for the homework assignments and the computer tutorials. MATLAB is also available on the CIT arizona UNIX cluster, and many other computers around campus, including the computers in Room 106 Schultz - if you have never logged in before, try the last 8 digits of your social security number as a password. A MATLAB primer is available from the Course Webpage, and several books on MATLAB have been put on reserve in the Math/Biology library.

Another computer program which may be of interest is XPP, a tool for solving differential equations, difference equations, delay equations, functional equations, boundary value problems, and stochastic equations. XPP is not installed on the computers mentioned above, but can be downloaded from

http://www.math.pitt.edu/~bard/xpp/xpp.html

Note that this website has a nice tutorial for learning to use XPP; the author of this program, Bard Ermentrout, has also recently published a book called *Simulating, Analyzing, and Animating Dynamical Systems: A Guide to Xppaut for Researchers and Students*, SIAM, 2002.

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

Schedule for APC/EEB/MOL 514, Fall 2002 (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: Action Potentials Generation and Simple Neural Circuits

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

Sept. 12th, 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 APC/EEB/MOL 514

Sept. 17th, 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).
- 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 APC/EEB/MOL 514

Sept. 19th, Lecture 3 (Tank): Generalization of Hodgkin/Huxley and simplified models of spiking neurons.

Sept. 24th, 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. 26th, Lecture 5 (Hopfield): Action potential synchrony and its significance to neural computation

- 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
- C. D. Brody and J. J. Hopfield. Simple networks for spike-timing based computation. Preprint. Web
- J. J. Hopfield and C. D. Brody. Simple networks and learning rules for spike-timing based computation: learning rules. Preprint. Web
- Vol. 24, issue 1 of the journal *Neuron*, 1999: many individual articles on synchrony occupying one entire issue. Link to this issue on the Course Webpage. Extreme examples in this ongoing debate are:
    - W. Singer. Neuronal synchrony: a versatile code for the definition of relations. *Neuron* 24:49-65 (1999). Web
    - M. N. Shadlen and J. A. Movshon. Synchrony unbound: A critical evaluation of the temporal binding hypothesis. *Neuron* 24:66-77 (1999). Web

Oct. 1st, Lecture 6 (Hopfield): Action potential synchrony and its significance to neural computation, continued

Unit 2: Dynamics of Disease

Main Lecturer: J. B. Plotkin (PACM, IAS Prog. Theor. Bio.)
Guest Lecturer: J. G. Dushoff (EEB)
Guest Lecturer: A. L. Lloyd (IAS, Prog. Theor. Bio.)

Oct. 3, Lecture 1 (Plotkin): Introduction to the dynamics of disease

Overview of pathogens, large questions in theoretical epidemiology. Classical 3-stage ODE model without birth and death. Stability and periodicity in 3-stage ODE model with demographics.

Oct. 8, Lecture 2 (Plotkin): Stochastic dynamics of epidemics

The Poisson process and exponential distribution. The Markov version of the 3-stage epidemic model. How to simulate a stochastic model. The quasi-stationary state and the mean time to disease extinction.

Oct. 10, Lecture 3 (Plotkin): Influenza dynamics and vaccination strategies

Overview of the epidemiological and evolutionary patterns of Influenza A. A PDE model in disease dynamics and evolution. Quasispecies and clustering of Influenza RNA sequences. Viral epitopes. Vaccine choice.

Oct. 15, Lecture 4 (Dushoff): Multi-group models of epidemics

R_0 as a bifurcation diagram. Endemic curves. Host heterogeneity. Multi-group gonorrhea model with random mixing, assortative mixing.

Oct. 17, Lecture 5 (Dushoff): Global dynamics and stability

Poincare-Bendixon theorem. Dulac's condition. Lyapunov functions. Transcritical bifurcations. Forward/backward bifurcations.

Oct. 22, Lecture 6 (Lloyd): Spatial heterogeneity in epidemic models

Reading List

- R. M. May, "Population Biology of Microparasitic Infections", pp.405-442 of *Mathematical Ecology*, ed. Hallam and Levin, Reserve APC/EEB/MOL 514 (requested)
- M. A. Nowak and R. M. May, *Virus Dynamics*, Oxford University Press, 2000, Reserve APC/EEB/MOL 514
- A. S. Perelson and G. Weisbuch, Immunology for Physicists. *Rev. Mod. Physics*, 69:1219–1267, 1997. Web
- H. W. Hethcote, The mathematics of infectious diseases. *SIAM Rev.*, 42:599–653, 2000. Web
- F. Brauer and C. Castillo-Chavez, *Mathematical models in population biology and epidemiology*, Springer, 2000, Reserve APC/EEB/MOL 514
- A. L. Lloyd and R. M. May. Spatial heterogeneity in epidemic models. *J. Theor. Biol.* 179: 1-11 (1996). Web
- J. B. Plotkin, J. Dushoff, S. A. Levin. Hemagglutinin sequence clusters and the antigenic evolution of influenza A. *Proc. Nat. Acad. Sci.* 99: 6263-6268 (2002). Web
- I. Nasell. On the time to extinction in recurrent epidemics. *J. Roy. Statist. Soc.* 61: 309-320 (1999). Web
- C. Castillo-Chavez, H. W. Hethcote, V. Andreasen, S. A. Levin, and W. M. Liu. Epidemiological models with age structure, proportionate mixing and cross-immunity. *J. Math. Biol.* 27: 233–258 (1989).

- V. Andreasen, J. Lin, and S. A. Levin, The dynamics of cocirculating influenza strains conferring partial cross-immunity. (1997) *J. Math. Biol.* 35: 825–842. Web
- R. Ross *The Prevention of Malaria*, E.P. Dutton and Co., 1910.
- R. M. Anderson and R. M. May, *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press, 1991. APC/EEB/MOL 514 (requested)

Unit 3: Intracellular Networks

Main Lecturer: W. S. Bialek (Physics)

Statement from Professor Bialek: I will draw heavily on two examples: the phototransduction network in rod visual receptors and the chemotaxis network in bacteria. In each case I think we know a great deal about the components, although we'll see that this isn't sufficient to understand how things work. More significantly, in each case we can place the network in the context of experiments that characterize its function, even to the point of saying that function is optimal or near optimal in some quantitative sense. I will distribute lecture notes and a collection of papers to support what we do in class. If time permits I will go on to discuss oscillators (e.g., the cell cycle) and switches (e.g., in genetic regulation and synaptic plasticity). I would like to respond a bit to student interests and background, so I won't fix the agenda in too much detail.

Oct. 24, Lecture 1

Oct. 29, Oct. 31: Fall Recess

Nov. 5, Lecture 2

Nov. 7, Lecture 3

Nov. 12, Lecture 4

Nov. 14, Lecture 5

Nov. 19, Lecture 6

Reading List

- TBA

Unit 4: Spatial Patterns in Development

Main Lecturer #1: E. C. Cox (Mol. Bio.)
Main Lecturer #2: S. Y. Shvartsman (Chem. Eng.)

Nov. 21, Lecture 1 (Cox): What kinds of spatial patterns do we see and what needs to be explained?
In this lecture I plan to cover the kinds of spatial patterns that we find in living systems. These range from crystal-like patterns in the cortex of single-celled diatoms, the spatial patterns in chains of nitrogen fixing bacteria, large scale patterns of bacterial colonies on Petri dishes, branching patterns in the cellular slime mold *Polysphondylium pallidum*, the arrangement of sensory organs in *Drosophila*, and the origin of the invertebrate and vertebrate body plan. This first part of the lecture will emphasize the richness of the phenomena in a wide variety of organisms. Next, I will outline the kinds of questions we will later address in a quantitative way: how are symmetries broken as patterns evolve during development? What are the minimum formal requirements for spatial patterning? How are periodic structures selected from a noisy background? How is the accuracy of a spatial pattern maintained (if it is maintained)? And is there feedback, both internal and external, acting both to select and sharpen or maintain a given pattern?

Nov. 26, Lecture 2 (Cox): Order from disorder in simple systems, and patterns from prepatterns in complex systems.
One way to characterize patterning systems is to group them into those that are entirely self-organizing, such as the cellular slime molds and many examples of collective behavior in bacteria, and those whose coordinates already exist in the young embryo or egg before there is any external evidence for patterning. Here I shall discuss one well-studied case in a multicellular organism, *P. pallidum*, a cellular slime mold, where free living randomly located cells behave cooperatively to form a highly patterned multicellular organism consisting of dead stalk and live spore cells. We shall see that a prepattern, on which the final pattern is built, arises from an initial random and noisy state. The essential features of the patterning mechanism can be captured by a reaction diffusion mechanism first described by Alan Turing.

I will then turn to examples in higher organisms, insects and vertebrates, where there is abundant evidence for prepatterns in the unfertilized egg. Here we can ask how many prepatterns (or coordinates) are required for a three dimensional organism, how the information is read out during development, what kinds of feedback are used, and how early noisy prepatterns can give rise to successively more detailed and refined adult patterns. Because it is not easy to reproducibly establish patterns in three dimensions, the dimensionality of the mature organism, we will ask how this might be accomplished.

Nov. 28: Thanksgiving Recess

Dec. 3, Lecture 3 (Cox): Long range order in dynamical systems.
Many of the examples discussed in the previous two lectures produce essentially static one and two dimensional structures, although the early patterning events are strong functions of time. There are many examples of spatially extended systems where waves propagate through cell layers over surprisingly large distances, heart rhythms, calcium fertilization waves, and territories of slime mold cells being three examples. All three systems are

said to be excitable, which is to say a suprathreshold stimulus can propagate through the system. The class will be familiar with one such system described by Hodgkin and Huxley for nerve propagation in one dimension. I will discuss a second well-studied example in two dimensions, the propagation of cyclic AMP waves in excitable layers of slime mold cells for which there are well worked out models and some experiments which test the models.

Dec. 5, Lecture 4 (Shvartsman): Microscopic origins of diffusion and transport mechanisms.
Random motion of molecules and microorganisms. Single particle and population-level description. Random walks and fluxes. Two simple models: position and velocity jump processes. Cell communication by diffusing signals. Ranges of communication mechanisms.

Dec. 10, Lecture 5 (Shvartsman): Cell communication mechanisms in development.
Dynamics of morphogen gradients. Interaction of prepatterns with secondary refinement processes. Positive and negative feedback loops in cell communication networks. Interaction of nonlinear feedback and transport, generation of spatial patterns. Examples from fruit fly development. Phenomenological and mechanistic models.

Dec. 12, Lecture 6 (Shvartsman): Pattern formation is paracrine and autocrine networks.
Receptor dynamics in specifying morphogen gradients. Induction and secondary refinement processes. Eggshell morphogenesis in Drosophila egg develpoment. Robustness and versatility of patterning networks. Continuum and discrete mathematical models of patterning networks.

Reading List

- TBA