**Math 490 Project presentations**

April 23 (Friday) Bifurcation diagrams of equilibrium solutions of nonlinear-diffusion models
Young He Lee, Lena Sherbakov and Jacky Taber

April 26 (Monday) Animal aggregation and nonlinear diffusion models
Michael Deal, Brian Van Hise and David Pluim

April 28 (Wednesday) Numerical computations of reaction-diffusion systems
Zayd Khoury, Chris Leonetti and Andrew Todd

April 30 (Friday) Two-patch diffusive fishery harvesting model
Victoria Dyer, Eileen Tschetter and David Weissenberger

**Modeling of Biological Systems** A Workshop at the National Science Foundation March 14 and 15, 1996

`http://www.nsf.gov/bio/pubs/mobs/mobs.htm`

**Panel Members**:
Chair Peter Kollman, University of California, San Francisco,
Co-Chair Simon Levin, Princeton University,
Alberto Apostolico, University of Padova,
Marjorie Asmussen, University of Georgia
Bruce L. Bush, Merck Research Labs,
Carlos Castillo-Chavez, Cornell University,
Robert Eisenberg, Rush Medical College,
Bard Ermentrout, University of Pittsburgh,
Christopher Fields, Santa Fe Institute,

John Guckenheimer, Cornell University,
Alan Hastings, University of California,
Davis Michael Hines, Yale University,
Barry Honig, Columbia University,
Lynn Jelinski, Cornell University,
Nancy Kopell, Boston University,
Don Ludwig, University of British Columbia,
Terry Lybrand, University of Washington,
George Oster, University of California, Berkeley,
Alan Perelson, Los Alamos National labs
Charles Peskin, Courant Institute of Mathematical Sciences,
Greg Petsko, Brandeis University,
John Rinzel, National Institutes of Health,
Robert Silver, Marine Biological Laboratory,
Sylvia Spengler, Lawrence Berkeley Labs,
DeWitt Sumners, Florida State University,
Carla Wofsy, University of New Mexico

The common theme of this report is the tremendous potential of mathematical and computational approaches in leading to fundamental insights and important practical benefits in research on biological systems. Mathematical and computational approaches have long been appreciated in physics and in the last twenty years have played an ever-increasing role in chemistry. In our opinion, they are just coming into their own in biology.

Our report also highlights computational issues that are common across biology, from the molecular to the ecosystem. Computers are getting more powerful at a prodigious rate and, in parallel, the potential for computational methods to ever more complex systems is also increasing. Thus, it is essential that the next generation of biological scientists have a strong training in mathematics and computation from kindergarten through graduate school.

# I. MOLECULAR AND CELLULAR BIOLOGY

A central organizing theme in Molecular and Cellular Biology is the relationship between structure of molecules and high level complexes of molecules and their function, both in normal and aberrant biological contexts. The connection between structure and function was most clearly illustrated in the paper that began Molecular Biology, the elucidation of the structure of DNA by Watson and Crick.

**1. GENOME** Since 1990 genomic sequence information has continued its exponential growth. Sequencing technology is being applied directly to sequence diversity analysis and gene expression analysis via high throughput, chip-based, automated assay systems. This influx has changed both the questions that are asked, as well as the range of the interactions considered.

Significant work is required to develop data management systems to make these data not just retrievable, but usable as input to computations and amenable to complex, ad hoc queries across multiple data types. Significant work is also required on techniques for integrating data obtained for multiple observables, at different scales, with different uncertainties (data fusion) and for formulating meaningful queries against such heterogeneous data (data mining).

For example, it should be possible in the future to ask what differences to expect in the kinetic efficiencies of a signal-transduction pathway across multiple individuals, given the differences in the sequences of the proteins involved in the pathway. Answering such queries will require improvements in data models, heterogeneous database management systems, multivariate correlation analysis, molecular structure prediction, constrained-network modeling, and uncertainty management.

## 2. PROTEIN STRUCTURE AND FUNCTION

As the amount of genomic data grows, three dimensional structure will provide an increasingly important means for exploiting and organizing this information. Structure provides a unique yet largely unexplored vehicle for deducing gene function from sequence data. Structure also links genomic information to biological assays and serves as a basis for rational development of bioactive compounds, including drugs and vaccines.

Research opportunities in this area can be divided into four distinct categories: experimental structure determination, structure prediction, structure exploitation of globular proteins, and modeling of membrane proteins, where the determination of high resolution structures is much more difficult.

**3. SIMULATIONS** Simulations of molecules of biological interest use computational representations that range from simple lattice models to full quantum mechanical wave functions of nuclei and electrons. If one has access to a macromolecular structure derived from NMR or X-ray crystallography, then one can begin with a full atom representation and fruitfully examine "small changes" in the system such as ligand binding or site specific mutation. Again, the goal is to reproduce and predict structure, dynamics and thermodynamics.

Developments in both hardware and software for parallel computing have played a major role. However, the longest time simulations that have been carried out are still 9 orders of magnitude away from the typical time scale for experimental protein folding. Simplified but realistic models, for example using a

continuum treatment of the solvent (Gilson et al, 1995), could increase the time scale by 1-2 orders of magnitude. Continuum representations may more readily incorporated into Monte Carlo methods and thus allow large movements of the molecule during simulation (Senderowitz et al, 1996). In some cases, the use of Langevin and Brownian dynamics and multiple time step algorithms (Humphreys et al, 1994) may be warranted. The simulation of biological molecules at the molecular level has generated much excitement and these approaches have become an increasingly important partner with experimental studies of these complex systems.

## 4. BIO-INSPIRED MATERIALS

Bio-inspired materials represent a special area of opportunity for developing new high-performance engineering materials based on ideas inferred from Nature (Tirrell et al, 1994). For example, the proteins derived from spider silk serve as the inspiration for high-strength fibers (Simmons et al, 1996); the adhesives from barnacles suggest how to produce glues that cure and function underwater; and the complex protein-inorganic interactions in mollusk shells supply ideas for producing ceramics that are less brittle than current ones. It is likely that ultimate bio-inspired materials will be chimeric, that is, they will be produced as a hybrid between biological and synthetic components. Consequently, these materials represent a special class of the protein folding problem and of polymer physics.

## II. ORGANISMAL BIOLOGY

The central organizing theme for Cells and Cell Systems is how behavior and function at one level of organization emerges from the structure and interactions of components at lower levels. In the set of topics described in this section the lower level of organization is subcellular or cellular. Though some of the subcellular components that play a role in these models are molecular, the focus is not on the structure of those molecules, but on the part that they play in cellular and multicellular function.

**1. CELL SIGNALING** Control of cellular processes, mediated by interactions of signaling molecules and their cell surface receptors, is a central and unifying theme in current experimental

cell biology. Within the past five years, techniques of molecular biology have revealed many of the kinases, phosphatases and other molecules involved in signal transduction pathways, as well as molecular sub-domains and sequence motifs that determine distinct functions. New techniques for measuring phosphorylation, calcium fluxes, and other early biochemical responses to receptor interactions are being applied to study many cell signaling systems (e.g., chemotactic bacteria, neurons and lymphocytes). Genetically engineered experimental systems consisting of homogeneous cell lines, transfected with homogeneous populations of wild type and mutant receptors and effector molecules, have facilitated acquisition of much of the new information about the intracellular molecules that mediate signal transduction. Improved measurement and experimental design make mathematical modeling an increasingly feasible tool for testing ideas about the interactions of these molecules.

## 2. MECHANICS AND EMBRYOLOGY

Recent advances in instrumentation have made it possible to measure motions and mechanical forces at the molecular scale (Svoboda and Block, 1994). Concomitant with these new mechanical measurements are crystallographic and x-ray diffraction techniques that have revealed the atomic structure and molecular geometry of mechanochemical enzymes to angstrom resolutions (Rayment and Holden, 1994). Together, these techniques have begun to supply data that has revived interest in cellular mechanics, and reinvigorated the view of enzymes as mechanochemical devices. It is now possible to make realistic models of molecular mechanochemical processes that can be related directly to experimentally observable, and controllable, parameters (Peskin and Oster, 1995). These advances in experimental technology

have initiated a renaissance in theoretical efforts to readdress the central question: how do protein machines work? More precisely, how is chemical energy transduced into directed mechanical forces that drive so many cellular events?

Embryology has also moved beyond descriptive observation to encompass genetic control of development and localization of protein effectors. The stress and strain measurements that are now possible at the cellular scale promise to unite the genetics, biochemistry and biomechanics of development (Oliver et al, 1995). By characterizing the mechanical properties of embryonic cells and tissues, mathematical models can be used to discriminate between various possible mechanisms for driving morphogenesis (Davidson et al, 1995).

# 3. BIOFLUID DYNAMICS

Because of the ongoing revolution in computer technology, we can now solve fluid dynamics problems in the three spatial dimensions and time (Ellington and Pedley, 1995). This opens up biological opportunities on many different scales of size. On the organ scale, for example, one can now perform fluid dynamics simulations of the embryonic and fetal heart at different stages of development. Such models will help to elucidate the role of fluid forces in shaping the developing heart. The swimming mechanics of microorganisms are also accessible to computer simulation. A particularly challenging problem in this field concerns the intense hydrodynamic interaction among the different flagella of the same bacterium: When the flagella are spinning so that their helical waves propagate away from the cell body,

they wrap around each other to form a kind of superflagellum that propels the bacterium steadily along; when their motors are reversed and the flagella spin the other way, the superflagellum unravels and the bacterium tumbles in place. Because of the difficulty of measuring microscopic fluid flows, hydrodynamics within cells is a much neglected aspect of cellular and intracellular biomechanics. Indeed, computation provides our only window onto this important aspect of cellular physiology. The incompressibility and viscosity of water have the effect of coupling motions along different axes, and between objects quite distant from one another; biomolecular processes are also modulated by the necessity of moving water out of the way. A new feature in this realm of micro and nano hydrodynamics is the importance of Brownian motion and the related significance of osmotic mechanics (including sol-gel transformations) for controlling fluid motions.

# 3. IMMUNOLOGY AND VIROLOGY

During the last two years mathematical modeling has had a major impact on research in immunology and virology. Serious collaborations between theorists and experiment provided breakthroughs by viewing experiments in which AIDS patients were given potent anti-retroviral drugs as perturbations of a dynamical system. Mathematical modeling combined with analysis of data obtained during drug clinical trials established for the first time that HIV is rapidly cleared from the body and that approximately 10 billion virus particles are produced daily (Ho et al, 1995). This work had tremendous impact on the AIDS community and has, for the first time, given them a quantitative picture of the disease process. The impact of this type of analysis has extended beyond AIDS, and opportunities exist for developing realistic and useful

models of many viral diseases. Challenges remain in studying drug therapy as a nonlinear control problem, and the issue of how rapidly viruses mutate and become drug resistant under different therapeutic regimes needs to be considered. Such issues also apply to the development of antibiotic resistance in bacterial disease.

## 4. NEUROSCIENCES

The fundamental challenge in neuroscience is to understand how behavior emerges from properties of neurons and networks of neurons. Advances in experimental methodologies are providing detailed information on ionic channels, their distribution over the dendritic and axonal membranes of cells, their regulation by modulatory agents, and the kinetics of synaptic interactions.

The development of fast computing, sophisticated simulation tools, and improved numerical algorithms has enabled the development of detailed biophysically-based computational models that reproduce the complex dynamic firing properties of neurons and networks. Such computations provide a two-fold opportunity for advancing our knowledge: (1) they both explain and drive new experiments, (2) they provide the basis for new mathematical theories that enable one to obtain reduced models that retain the quantitative essence of the detailed models. These reduced models, which allow the bridging of multiple spatial and temporal scales, are the building blocks for higher level models.

Modeling tools and mathematical analysis allow us to address the central question: What are the cellular bases for neural computations and tasks such as sensory processing, motor behavior and

cognition? (Koch and Segev, 1989; Bower, 1992) More specifically, how do intrinsic properties of neurons combine in networks with synaptic properties, connectivity, and the cable properties of dendrites to produce our interaction with the world? Neural modulators affect both the intrinsic currents and the synaptic interactions between neurons. (Harris-Warrick et al, 1992) The effects of these changes at the network level are difficult to work out even for small networks. The largest challenge in this area is to understand how systems with enormous numbers of degrees of freedom and large numbers of different modulators combine to produce flexible but stable behavior. The geometry and electrical cable properties of the branching dendrites of neurons also affect network activity. (Stuart and Sakmann, 1994) Mathematical analysis is needed to interpret the results of massive computations, and to incorporate the insights into network models.

# III. ECOLOGY AND EVOLUTIONARY BIOLOGY

Evolution is the central organizing theme in biology (e.g. Roughgarden,1979), and its manifestation in the relationships among types of organisms spans levels of organization, and reaches out from biology to earth and social sciences. Thus, the core problems in ecology and evolution run the gamut from those that address fundamental biological issues to those that address the role of science in human affairs. Fundamental challenges facing ecologists and evolutionary biologists relate to the threats of the loss of biological diversity, global change, and the search for a sustainable future, as well as to the continued search for an understanding of the biological world and how it came to assume its present form. To what extent is the organization of the biological world the predictable and unique playing out of the fundamental

rules governing its evolution, and to what extent has it been constrained by historical accident? How are the interactions among species, ranging from the tight interdependence of host and parasite to the more diffuse connections among plant species in a forest, manifested in their coevolutionary patterns and life history evolution? What are the evolutionary relationships among closely related species, in terms of their shared phylogenetic histories? How do human influences, such as the use of antibiotics and pesticides, exploitation of fisheries and land, and accelerated patterns of global change, influence the evolutionary dynamics of species and patterns of invasion? To what extent can an evolutionary perspective help us to prepare for the future, in terms of understanding what species might be best suited to new environments? The latter is important both in terms of natural patterns of change, and deliberate manipulations through breeding and species introductions.

## 1. **Conservation biology, the preservation of biodiversity**

What factors maintain biodiversity? How can new approaches to phylogenetic analyses, in clarifying the evolutionary relationships within and among species, help us to understand how we should measure biodiversity? How are ecosystems organized into functional groups, ecologically and evolutionarily, and how does that organization translate into the maintenance of critical ecosystem processes, such as productivity and biogeochemical cycles, as well as climate mediation, sequestering of toxicants, and other issues of importance to human life on earth.

## 2. Global change

What are the connections between the physical and biological parts of the global biosphere, and the multiple scales of space, time and organizational complexity on which critical processes are played out? (Bolker et al, 1995) In particular, how are individual plants influenced by changes in atmospheric patterns; and, more difficult, how do those effects on individual plants feed back to influence regional and global patterns of climate and biological diversity? How do effects on phytoplankton and zooplankton relate to each other, and to the broader patterns that may be observed?

## 3. Emerging disease

How do patterns of population growth and resource use, as well as the profligate use of antibiotics, contribute to the emergence and reemergence of deadly new diseases, many of them antibiotic resistant? (Ewald, 1995) Are there approaches to management of the diversity of those diseases, guided by both an evolutionary and an ecosystem perspective, that can reduce the threat and provide new strategies for mitigation?

## 4. Resource management

The history of the management of our sources of food and fiber is not one of unmitigated successes, and many of these crucial resources are threatened to a level that they will be unable to support the needs of humanity in the coming decades. The prospect of large-scale alterations of the earth's physical and biological systems creates a potential conflict between human needs, desires and capabilities. (Walters and Parma, 1996; Walters and Maguire, 1996) This situation is further complicated by the limitations of our understanding and ability to control complex biological systems. We must develop methods for decision-making and management that are appropriate for an uncertain future. (Hilborn et al, 1995)

## A. POPULATION GENETICS

With the rapid accumulation of sequence data for entire genomes, we are now poised to analyze the set of genes, their order and organization, codon usage, etc. across taxa (Griffiths and Tavare, 1996) and how and perhaps why this has evolved over time. (Thorne et al, 1992) This requires an increased ability to model how information is represented and acted upon in biological systems (Griffiths and Tavare, 1996) based on tools from such fields as discrete mathematics, combinatorics, and formal languages. Novel, perhaps ad-hoc formulations are needed to form the mathematical basis of genomic analyses because classical quantitative formulations of notions such as information, similarity, and classification - all inextricably related to biology - are inadequate. Correspondingly, methods for organizing vast sequence data into

data structures and databases suited for the most efficient data storage and access are needed, along with improved algorithms for sequence analysis and the identification of homologies among sequences.

## B. CONSERVATION BIOLOGY

Virtually all important questions in conservation biology require making predictions, so theory and mathematical methods have played and will continue to play a central role. Although many of the underlying scientific issues have been defined during the past decade, many questions remain to be resolved. What species would be lost in the wake of an invasion, and what are the effects on ecosystem function? For example, what are the consequences of the replacement of native fish species by introduced species? Substantial progress is likely (and needed) in the near future in understanding the dynamics of invading exotic species, determining more carefully the role genetics plays in the dynamics of rare or endangered species, and in the ecological dynamics of threatened species.

## C. MANAGEMENT OF NATURAL SYSTEMS

In recent years there has been an abrupt shift in management philosophy. (Hiborn et al, 1995) The old goal of managing individual species in order to reach and maintain optimal conditions has been replaced by a new goal of maintaining ecosystem function and adapting to new conditions or changes in the system. This shift reflects a more mature attitude towards nature that recognizes the limitations of our knowledge and capabilities, the importance of interactions between species and an appreciation of the dangers of a command and control mode of operation.

This new approach to management makes it possible to apply elements of the scientific method in a new and significant context: we may design experimental management schemes to

provide information that is required to improve the management process and adapt to changes, even unforeseen changes. This new approach challenges our mathematical and statistical skills. Successful adaptation requires effective and timely organization of data through estimation of parameters that affect system dynamics, including the dynamics of our learning. That information then must be translated into an assessment of the likely consequences of management strategies and actions.

## D. GLOBAL CHANGE AND BIODIVERSITY

Climate change and associated changes in greenhouse gases have made imperative the examination of the potential impacts on natural systems, and associated feedbacks. Advances in computational capabilities have made possible the construction of detailed individual-based models that take account of the responses of individual trees to changes in environmental conditions, and their mutual effects. Yet such models are tremendously data-hungry, and have great potential for error propagation. To make their predictions robust, and to allow those predictions to be interfaced with the much broader scale predictions of climate models, and the masses of broad scale information that are becoming available from remote sensing, we must find ways to reduce dimensionality and simplify those overly detailed models. Similar comments apply to models of other systems, such

as the aggregation of social organisms from cellular slime molds to marine and terrestrial invertebrates and vertebrates. Methods such as moment closure and hydrodynamic limits, borrowed from other disciplines, are proving remarkably promising, especially when coupled with experimental approaches (Levin and Pacala, 1996).

This represents one of the most challenging and important issues in ecosystem science. At the same time, masses of data are becoming available from global observation systems, and critical experiments are providing understanding of the linkages between ecosystem structure and function, and in particular the role of biodiversity in maintaining system processes. The next 5-10 years hold remarkable potential for integrated theoretical, empirical and computational approaches to elucidate profound and important issues (Field, 1992; Bolker, 1995).

## E. THE DYNAMICS OF INFECTIOUS DISEASES

The subject of infectious disease dynamics has been one of the oldest and most successful in mathematical biology for a century, and has seen powerful advances in recent years in mathematical theory, and in the application of that theory to management strategies (see, for example, Anderson and May, 1991). Much of the literature has assumed homogeneous mixing, so that every individual is equally likely to infect every other individual; but such models are inadequate to describe the central qualitative features of most diseases, especially those that are sexually transmitted, or for which spatial or socioeconomic structure localizes interactions. The classical work of Hethcote and Yorke (1984) on core-group dynamics highlighted the importance of such effects, and formed the basis upon which much recent work rests.

Such work, involving spatial structure, frequency and density dependence, and behavioral factors have not only forced us to revise old paradigms, but have reenergized the interplay among nonlinear dynamics, ecology and epidemiology.

## Professor Donald Knuth on Bioinformatics

Professor Donald Knuth, of the Stanford Computer Science Department was once interviewed and had some comments on issues related to Bioinformatics:

CLB: If you were a soon-to-graduate college senior or Ph.D. and you didn't have any "baggage", what kind of research would you want to do? Or would you even choose research again?

Knuth: I think the most exciting computer research now is partly in robotics, and partly in applications to biochemistry. Robotics, for example, that's terrific. Making devices that actually move around and communicate with each other. Stanford has a big robotics lab now, and our plan is for a new building that will have a hundred robots walking the corridors, to stimulate the students. It'll be two or three years until we move in to the building. Just seeing robots there, you'll think of neat projects. These projects also

suggest a lot of good mathematical and theoretical questions. And high level graphical tools, there's a tremendous amount of great stuff in that area too. Yeah, I'd love to do that... only one life, you know, but...

CLB: Why do you mention biochemistry?

Knuth: There's millions and millions of unsolved problems. Biology is so digital, and incredibly complicated, but incredibly useful. The trouble with biology is that, if you have to work as a biologist, it's boring. Your experiments take you three years and then, one night, the electricity goes off and all the things die! You start over. In computers we can create our own worlds. Biologists deserve a lot of credit for being able to slug it through.

It is hard for me to say confidently that, after fifty more years of explosive growth of computer science, there will still be a lot of fascinating unsolved problems at peoples' fingertips, that it won't be pretty much working on

refinements of well-explored things. Maybe all of the simple stuff and the really great stuff has been discovered. It may not be true, but I can't predict an unending growth. I can't be as confident about computer science as I can about biology. Biology easily has 500 years of exciting problems to work on, it's at that level.

## Graduate study in Mathematical Biology

University of British Columbia

`http://www.math.ubc.ca/people/faculty/keshet/mathbio/mathbio.html`

RESEARCH AREAS INCLUDE: Ecology, Animal Behaviour; Evolutionary Genetics; Cellular and Molecular Biology; Excitable Cells, Neurobiology; Morphogenesis, Pattern Formation, Self-Organization; Nonlinear Dynamics, Chaos

FACULTY: *Leah Keshet*: Cytoskeleton and actin dynamics, swarming and aggregation behaviour in animal societies; *Yue Xian Li*: Calcium dynamics, signal transduction in cells, biophysics, neuroscience; *Michael Doebeli*: mathematical models of evolution; *Fred Brauer* Mathematical epidemiology and ecology.

University of Washington

http://www.amath.washington.edu/

RESEARCH AREAS: Our interest lies in understanding the spatial and temporal patterns that arise in dynamic biological systems. Our mathematical activities range from reaction-diffusion equations, to nonlinear and chaotic dynamics, to optimization. We employ a variety of tools and models to study problems that arise in development, epidemiology, ecology, resource management, and biomechanics.

FACULTY: Mark Kot, J. D. Murray, H. Qian

Princeton University

http://www.eeb.princeton.edu/index.html

RESEARCH AREAS: Ecology, evolution and behavior.

FACULTY:

Simon A. Levin, Dynamics of populations and communities; spatial heterogeneity and problems of scale; evolutionary ecology; theoretical and mathematical ecology; biodiversity and ecosystem processes.

Stephen W. Pacala, Population biology and community ecology of plants; theoretical and mathematical ecology; global interactions among the biosphere, atmosphere, and hydrosphere.

New York University

`http://www.cns.nyu.edu/`

RESEARCH AREAS: The research interests of the faculty span a broad range of topics in neural science, and utilize techniques ranging from molecular and cellular analyses to fully integrated systems, computational, and cognitive studies.

FACULTY: John Rinzel, Biophysical mechanisms and theoretical foundations of neural computations; Charles S. Peskin, Mathematical biology; Michael J. Shelley, Professor of Mathematics and Neural Science; Michael J. Shelley, Applied Mathematics, Modeling, and Large-Scale Computation; Vision and Computational Neuroscience

University of Pittsburgh

`http://www.math.pitt.edu/`

G. Bard Ermentrout, Dynamical systems, nonlinear differential and integral equations, mathematical biology, neuroscience; Carson C. Chow, Applied mathematics, biological mathematics, nonlinear dynamics; Jonathan Rubin, (W & M graduate) Dynamical systems, computational neuroscience.

Boston University

http://math.bu.edu/

Univ of Tennessee

http://www.math.utk.edu/

Duke University

http://www.math.duke.edu/cmclm/

NC State University

http://www.stat.ncsu.edu/programs/bma.html

University of Utah

http://www.math.utah.edu/grad/mathbiol/index.html

University of Arizona

http://appliedmath.arizona.edu/

Arizona State

http://lifesciences.asu.edu/irceb/stoichiometry/

http://www.eas.asu.edu/~sserc/index.html

UC Davis

http://www-eve.ucdavis.edu/Popbio.htm

UCLA

http://www.biomath.medsch.ucla.edu/