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Volume 14

Mathematical Biology

Mark A. Lewis
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IAS/Park City Mathematics Institute runs mathematics education programs that bring together high school mathematics teachers, researchers in mathematics and mathematics education, undergraduate mathematics faculty, graduate students, and undergraduates to participate in distinct but overlapping programs of research and education. This volume contains the lecture notes from the Graduate Summer School program.

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Mathematical
Biology

Preface

The IAS/Park City Mathematics Institute (PCMI) was founded in 1991 as part of the "Regional Geometry Institute" initiative of the National Science Foundation. In mid 1993 the program found an institutional home at the Institute for Advanced Study (IAS) in Princeton, New Jersey.

The IAS/Park City Mathematics Institute encourages both research and education in mathematics and fosters interaction between the two. The three-week summer institute offers programs for researchers and postdoctoral scholars, graduate students, undergraduate students, high school teachers, undergraduate faculty, and researchers in mathematics education. One of PCMI's main goals is to make all of the participants aware of the total spectrum of activities that occur in mathematics education and research: we wish to involve professional mathematicians in education and to bring modern concepts in mathematics to the attention of educators. To that end the summer institute features general sessions designed to encourage interaction among the various groups. In-year activities at the sites around the country form an integral part of the High School Teachers Program.

Each summer a different topic is chosen as the focus of the Research Program and Graduate Summer School. Activities in the Undergraduate Summer School deal with this topic as well. Lecture notes from the Graduate Summer School are being published each year in this series. The first fourteen volumes are:

- Volume 1: *Geometry and Quantum Field Theory* (1991)
- Volume 2: *Nonlinear Partial Differential Equations in Differential Geometry* (1992)
- Volume 3: *Complex Algebraic Geometry* (1993)
- Volume 4: *Gauge Theory and the Topology of Four-Manifolds* (1994)
- Volume 5: *Hyperbolic Equations and Frequency Interactions* (1995)
- Volume 6: *Probability Theory and Applications* (1996)
- Volume 7: *Symplectic Geometry and Topology* (1997)
- Volume 8: *Representation Theory of Lie Groups* (1998)
- Volume 9: *Arithmetic Algebraic Geometry* (1999)
- Volume 10: *Computational Complexity Theory* (2000)
- Volume 11: *Quantum Field Theory, Supersymmetry, and Enumerative Geometry* (2001)
- Volume 12: *Automorphic Forms and their Applications* (2002)
- Volume 13: *Geometric Combinatorics* (2004)
- Volume 14: *Mathematical Biology* (2005)

Volumes are in preparation for subsequent years.

Some material from the Undergraduate Summer School is published as part of the Student Mathematical Library series of the American Mathematical Society. We hope to publish material from other parts of the IAS/PCMI in the future. This will include material from the High School Teachers Program and publications documenting the interactive activities which are a primary focus of the PCMI. At the summer institute late afternoons are devoted to seminars of common interest to all participants. Many deal with current issues in education, while others treat mathematical topics at a level which encourages broad participation. The PCMI has also spawned interactions between universities and high schools at a local level. We hope to share these activities with a wider audience in future volumes.

John C. Polking
Series Editor
October 2008

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M. A. Lewis and J. Keener

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Introduction

M. A. Lewis and J. Keener

Mathematical Biology is a rapidly growing field that defies definition. In simplest terms it is the use of mathematics to study and understand problems of biology. In fact, there is no area of mathematics that is precluded from use and no area of biology that is beyond reach. Obviously, then, an introduction to Mathematical Biology can only begin to scratch the surface of this field. However, if there is a unifying theme to these lecture notes it is that the study of biology is the study of how things change, that is, it is the study of dynamics. So in the introductory lectures of Jim Keener and Mark Lewis, we are given a brief overview of dynamical systems analysis that has been proven to be widely useful in the study of biology.

Chemical reactions, whether in the test tube or in the cell, are a natural place to begin when modeling biological dynamics. Jim Keener builds up the tools and theory of chemical reaction dynamics from first principles, and shows how bistability, thresholds and excitability can arise from simple chemical reactions, and how the resulting dynamics can give rise to biologically significant behavior, such as switches, oscillations and quorum sensing.

Spatial dynamics, whether in an ecosystem, a growing tumor, or in developing tissue patterns, is an area central to mathematical biology. The mathematical problems are challenging, as they involve both time and space components. Mark Lewis and coauthors introduce the theory pattern formation and traveling waves in biology using the so-called stream paradox of spatial ecology as a motivating example. How do species persist in streams while being constantly washed down-river by the current?

The lectures of the main speakers each emphasize a specific biological problem. The lectures of Jim Cushing show how discrete dynamical systems have been used to model the population dynamics of flour beetles; those of David Earn show how the SARS epidemic can be studied using SIR models; Leon Glass uses topological arguments to study the behavior of oscillatory biological dynamics; Helen Byrne shows how populations of cancer cells can be modeled and studied; Paul Bressloff describes the dynamics of neural systems;

Jim Cushing's chapter applies nonlinear matrix models to the study of population dynamics. Matrix population models have a long and distinguished history in mathematical biology — their application to ecological systems goes back more than half a century and they are widely applied by biologists to understand dynamics of structured populations. However, Cushing's work brings new excitement to this well-established subject. In his study of insect populations he includes specific nonlinearities that describe overcompensation and cannibalism in structured populations. These give rise to very complex dynamics, which are influenced by chaotic attractors. Part of Cushing's chapter focuses on understanding the bifurcation structure and qualitative dynamics using mathematical tools. Another part focuses on analyzing data from experimental case studies from real laboratory populations of flour beetles, and on relating these data to the nonlinear dynamical systems using maximum likelihood methods. This coupling of complex nonlinear dynamics and large biological data sets brings a level of biological realism that moves the mathematics from "understanding the theory" to "testing the hypotheses."

David Earn's chapter introduces the reader to the science and art of modeling diseases using dynamical systems. He introduces the dynamical systems from a refreshingly data-oriented perspective. Starting with time series data for real epidemics, Earn asks how we can tease out patterns for infection levels, using statistics. Which diseases persist? Which oscillate? Are there characteristic scales for outbreaks? He then introduces mechanistic models for disease, based on ordinary differential equations, which can connect the dynamical outbreak behaviors to underlying mechanisms. The mechanisms, in turn are depicted as terms in the equations. He adds increasing layers of realism to the models, with the inclusion of stochasticity and environmental forcing, and shows that these factors can have a major influence on observed dynamics.

Leon Glass explores topological approaches to biological dynamics. His approach exploits the topologies common to many physiological systems: a heart cell beats, forming a time-periodic signal; travel far enough around a developing limb bud and you may return to the same spot on the limb bud; a wave of excitation on a spherical surface, such as a whole heart, can travel over the entire surface, returning to the spot where it started; and a network of genes can repeatedly cycle through a variety of different states. What happens when the heart cell is over-stimulated, when a right limb bud is transplanted onto a left stump, when dead region on the excitable surface of the heart is formed, or when the gene network is perturbed or damaged? The result, in a very general sense, is a perturbation of the dynamical system, described on a particular topology (such as a circle or a sphere). Glass develops mathematical tools for studying fixed points, limit cycles, entrainment, and phase resetting in a topological setting, and applies these to understanding the nonlinear dynamical properties to a broad spectrum of biological systems.

Our understanding of cancer tumor growth is rapidly expanding through the application of mathematics and computer modeling to study tumor dynamics. Helen Byrne weaves a framework of dynamical systems models for the various stages of cancer solid tumor dynamics. These stages progress from avascular (little blood supply) through angiogenesis (formation of new blood vessels) to vascular (supplied with blood). Progression from avascular to vascular mirrors an increase in the size and seriousness of tumors, and a detailed understanding of the processes governing the progression may eventually be key to medical treatments, including optimal radiotherapy and chemotherapy. Byrne's dynamical models address the growth, size, shape and the complex movement patterns of tumors and their cells. A mixture of analysis and numerical simulation is used to understand the processes from first principles.

The brain and its neurons remains a source of fascination for many modelers. How can we understand the overwhelming complexity exhibited by the brain, based on the chemical and cellular processes that describe individual brain cells, or neurons? Paul Bressloff's chapter takes on this daunting challenge, starting at the level of a single neuron, and building up to neural pattern formation in the visual cortex of the brain. One of the mathematical challenges lies in the nonlocal nature of interactions between nerves: excitation or inhibition can occur over distant spatial scales as one part of the brain signals to another. The resulting models, coupling nonlinear dynamics to nonlocal interactions, provide insight as to the form and function of the brain.

While the first two chapters are designed as introductory material, each of the remaining chapters of the book stand alone, as snapshots of in-depth research within sub-areas of mathematical biology. In this respect, the volume sacrifices breadth for depth; many other important sub-areas, ranging from cell structure to evolution to immunology are not covered. While these could fill several more volumes, we trust that the excitement and richness of research topics shown here will encourage the reader to explore these other areas on their own.

Introduction to Dynamics of Biological Systems

James P. Keener