Preface

The molecular revolution in the 20th century has provided biological sciences with an abundance of factual information but with no more insight to the biochemical processes at work in biological organisms. In a 2009 report entitled *A New Biology for 21st Century* <http://www.nap.edu/catalog/php?record_id=12764>, the National Research Council (NRC) recommends a new approach to biology that "depends on greater integration within biology, and closer collaboration with physical, computational, and earth scientists, mathematicians and engineers be used to find solutions ...". Given the centrality of mathematical modeling in these areas designated for collaboration, it is implicit in the NRC recommendation that it be exploited for significant advances in biology.

Prompted by their own experience, faculty at the University of California, Irvine (UCI) independently recognized the same needs for interdisciplinary collaboration and initiated in 2007 a gateway graduate program in Mathematical and Computational Biology (MCB) <http://mcsb.bio.uci.edu/> to educate a new generation of researchers in the life sciences capable of such collaboration. The MCB program was made possible with an award from the Howard Hughes Medical Institute (HHMI)-National Institute of Biomedical Imaging and Bioengineering (NIBIB) Interface Initiative and has also been sustained by subsequent NIH training grants and a P50 Center Grant <http://ccbs.uci.edu/> for the last ten years. A new option of stand-alone interdisciplinary Ph.D. degree program in Mathematical and Computational Systems Biology was established in 2015 to provide more flexibility to our educational effort in this area. Several dozen MCB students have received their Ph.D. degrees since the Program's inception.

For the core curriculum of the MCB Program, the Mathematics Department at UCI introduced in 2007 a three-quarter course sequence on Mathematical and Computational Biology, Math 227A,B,C, to acquaint interested students with mathematical modeling of biological phenomena and the attendant mathematical and computational techniques for extracting useful information from mathematical models. This volume grew out of the course notes for the first quarter of the three-quarter course sequence, focusing on models involving *ordinary differential equations* (ODE). Models involving *partial differential equations* (PDE) are studied in

Math 227B while Math 227C is concerned with differential equation models involving uncertainty (stochastic differential equations, SDE). While differential equations (DE), ordinary, partial or stochastic, are known to be important in the quantitative understanding of life science phenomena, teaching DE modeling is much more challenging than teaching the mathematics of DE for a number of reasons including the following:

- There is no recipe or algorithm for the development of a mathematical model for any specific phenomenon.
- The undergraduate training of students in our program is diverse: Those majored in the biological sciences are often deficient in the needed training in mathematics and computing. Those majored in non-biological sciences are usually deficient in their knowledge of biology.
- Even among life science majors, the amount of background science needed for the teaching of a relatively comprehensive set of models is too extensive to have been covered in an undergraduate curriculum in biology.

In order for students to be more or less similarly prepared for the MCB curriculum, the Program requires attendance of a three-week pre-program boot camp, one week in mathematics and computational software and two weeks on basic biology. The math and computing week provides all participants a working knowledge of MatLab and Mathematica while using them to review undergraduate mathematics relevant to the MCB core curriculum. Even so, experience in teaching nearly ten groups of program students suggested that only a working knowledge of basic calculus and minimal matrix computation can be expected of the students in general. To accommodate the need of such a group of students for gradual acquisition of more mathematical knowledge and computational skills, the course starts with the simplest of growth models for a single population but forces them to face the challenge of parameter estimation in order to obtain a meaningful and realistic solution of the problem. As models evolve to provide different information, students are led to consider more and more complex models that require them to learn more sophisticated mathematics and computational skills. This volume culminates in some rather challenging discussion and applications of Pontryagin's Maximum Principle for constrained optimal control problems.

On the teaching of mathematical modeling, courses and textbooks on mathematical models typically consist of 1) case studies of specific phenomena, or 2) exposition of different mathematical methods with discussion of specific mathematical models as examples of their applications. While the MCB curriculum for mathematical modeling needs both approaches, it specifically organizes the teaching of modeling around what we want to know about the phenomenon of interest. Typically, we group the development of course material around mathematically expressed scientific issues such as

- How does a phenomenon of interest evolves with time (evolution)?

- Does it tend to a time-independent or time-varying steady state (equilibrium or periodic motion)?
- Is a steady state sensitive to small external perturbation (stability)?
- Does a small change of the system characteristics cause a catastrophic change in the steady states and/or their stability (bifurcation)?
- Does a biological organism maintain its normal functions or developments after environmental or genetic changes (robustness)?
- What is the mechanism for an organism to maintain robustness (feedback, redundancy)?
- etc.

Different mathematical models are needed for different issues about the same phenomenon. Different analytical and computational requirements relevant to the different models are then identified. Appropriate mathematical and computational tools are then introduced as needed for extracting from these models the information sought at the start.

Analysis and numerical simulations of mathematical models require knowledge of mathematical methods and computational techniques for differential equations. With the mixed background of MCB students, some having had minimal training in quantitative methods, it is necessary to introduce the mathematical and computational techniques needed for studying the models being investigated throughout the course. In terms of mathematical techniques, this first volume on ODE models is divided into the following three related parts:

(1) *Initial Value Problems* (IVP) for which **all** the auxiliary conditions supplementing the ODE are prescribed at the same value of the independent variable, usually the initial value t_0 of the interval of the independent variable t (giving rise to the term initial value problem or *IVP* for short) or the terminal value t_T (known as terminal value problem) but may be some point in between.
(2) *Boundary Value Problems* (BVP) for which some of the auxiliary conditions are prescribed at the initial point t_0 while the remaining ones prescribed at the end point t_T resulting in what is known as two-point boundary value problems.
(3) *Calculus of Variations* (CoV) *and Optimal Control* which reduce two important classes of optimization problems to solving BVP.

Phenomena in the biological sciences and the corresponding mathematical models are generally rather complex and require extensive computation. Fortunately, much of the computing involved can be relegated to user friendly mathematical software such as Mathematica, MatLab and Maple. Still, a working knowledge of basic ODE is so critical to mathematical modeling that we take every opportunity to work out the mathematical details whenever possible. For an exposure to a variety of ODE systems, we work in this volume with a wide range of mathematical models for a diverse group of biological phenomena. These range from the efficacy of cocktail treatment of AID, to the mechanism for effective regenerative biology, to the level of genetic instability for carcinogenesis. In the process, the volume introduce readers to frontier research on ODE models for biological phenomena of current interest. Nevertheless, the principal goal of this volume is not teaching mathematics of ODE or an exposition of current research in mathematical and computational biology. The principal new elements of the volume is on mathematical modeling of biological phenomena with an emphasis on the kind of scientific issues (evolution, stability, bifurcation, robustness, etc.) of interest pertaining to the particular phenomenon.

There is no text on mathematical biology that meets the intended purposes and the planned curriculum indicated above. In the absence of an appropriate text, MCB students are provided with a set of course notes for a coherent coverage of the prescribed course material. Experience from more than 40 years of teaching suggests that students are best served by continuous engagement in an active learning process. To provide an active learning environment (short of engaging students in research projects, which the MCB Program does concurrently through three quarterly lab rotations), the course notes for each quarter course are accompanied by nine sets of required weekly exercises on the course material in addition to the suggested exercises sprinkled throughout these notes. To incentivize students for punctual completion of the assigned exercises, their homework assignments are graded and their overall performance on the assignments constitutes 35% of their final course grade. The course is reputed to have a fast pace and the weekly exercises are by and large not straightforward. Optional discussion sessions are offered to help students with the exercises; however they are never provided with written solutions for the homework assignments, mid term or final examination.

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