

# Investigating Biological Systems Using Modeling

Strategies  
and  
Software

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# Investigating Biological Systems Using Modeling

## Strategies and Software

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# **Investigating Biological Systems Using Modeling**

**Strategies and Software**



*Loren Zech, B.E. (Elect. Eng.), M.D.*  
*1943–1997*

This book is dedicated to the memory of Dr. Loren Zech who was a senior investigator at the National Institutes of Health, Bethesda, for over 20 years. Following the death of Dr. Mones Berman, the instigator of SAAM in 1982, Loren became the guiding force in the continued development of the software while maintaining his work as a clinician and active researcher in the areas of lipoprotein and trace element metabolism, endocrinology, and pharmacokinetics. He was the author of over 100 papers, most of which involved modeling. He was dedicated, enthusiastic, and knowledgeable in the areas of mathematics, engineering, computer science, and biology. Most of all, he was a patient teacher and a gentle guide. Each of the authors of this book benefitted from his wisdom and experience. He was a teacher, colleague, and friend to each of us, and we dedicate this book to his memory and to his lifelong love of modeling.

# Preface

Ample evidence now exists that complex biological systems can only be progressively understood with the aid of mathematical models. Mathematical modeling requires an understanding of several disciplines: biology, computing, kinetics, mathematics, and statistics. While many texts cover these topics individually, previous textbooks do not integrate this information to enable an investigator without a strong mathematical background to apply modeling for hypothesis testing. This textbook is an attempt to meet this need. References are made to material covered in other textbooks.

The approach described in this textbook is often called the “SAAM (simulation, analysis, and modeling) approach” or “Berman approach” to mathematical modeling. Briefly, it involves the process of mathematical modeling on a computer as an aid to understanding biological system behavior [1]. This approach has guided the development of the WinSAAM (Windows SAAM) modeling software. The SAAM program and its conversational version, CONSAM, have been under development at the Laboratory of Experimental and Computational Biology, National Institutes of Health, since the late 1950s. WinSAAM evolved from the SAAM and CONSAM programs. It was designed for use by biologists. For example, compartmental models to describe experiments performed on biological systems can be set up and changed by simply specifying differential equation parameters and providing the initial conditions for the experiment. Models can also be solved by entering explicit equations. Parameter values can be changed during a solution to simulate variable experimental conditions. Data can be fitted by ordinary, generalized, or weighted least-squares regression techniques. Plotting and statistical measures of fit make it easy to compare and evaluate mathematical or compartmental models. WinSAAM incorporates Windows features for interapplication communication, making interacting through WinSAAM with other software as simple as Select|Copy|Paste.

Section I is a general introduction to the field of modeling biological systems. Section II describes modeling software and compares several packages. Section III explains the tools for modeling and illustrates them using examples. Section IV covers topics related to the design of experimental studies and the steps involved in modeling biological data. Finally, Section V describes how to evaluate and use published models.

The book is designed for students (all sections), experimentalists who have data to analyze (Sections II–IV) or who are planning kinetic studies (Sections IV and V), and for modelers as a resource (Section III). Models contain a plethora of information about a system, and the book is also designed for those who wish to access information inherent in models for designing experiments, for assessing the state of knowledge in a particular area, or for teaching complex biophysical principles (Section V). There is some repetition in the book as the description of topics focuses more on theoretical aspects in some sections and practical approaches in others.

The principles of developing models to interpret kinetic data apply across disciplines, and examples in the text are chosen from many fields, including chemistry, biochemistry, physiology, pharmacology, animal science, medicine, and agriculture. Modeling is part art and part science and is best understood by a hands-on approach. The CD supplied with this book includes the latest version of WinSAAM as well as the examples that have been used in the text. Readers are encouraged to use and adapt the models for their own areas of interest and to incorporate modeling as a routine tool for data analysis and in experimental design.

We acknowledge the contributions made by our families and colleagues during the writing of this book, and specifically Dr. Janet Novotny for proofing some of the chapters.

*Without data models can't exist . . .*

*Without models data can't be used . . .*

*R. Boston, 1998*

## Reference

1. Berman M. (1963). The formulation and testing of models. *Ann. N.Y. Acad. Sci.* **108**, 182–194.

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# **SECTION I**

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## **Introduction**



## WHAT IS MODELING ?

This chapter will provide an introduction to modeling by defining terms and discussing modeling philosophy. Modeling straddles the fields of biology and mathematics. Therefore, it could be termed 'Biomodeling'. However, it differs from, but is related to, the fields of Biomathematics, Biostatistics, and Bioengineering where mathematics, statistics, and engineering are applied to the study of biological systems. Biomodeling involves the use of these scientific tools, a knowledge of biology, intuition, imagination, and creativity to answer the question, what biological process could explain these data? Modeling is therefore part art and part science. The approaches, concepts, and tools can be taught to some extent, but the art of modeling can only be acquired through practice and experience.

### I. Definitions

**Models** are simplified representations of systems. They can be physical such as scale models of airplanes, or abstract such as mathematical models. Mathematical models are used widely in the fields of engineering, physics, economics, business, and meteorology where models are routinely used in weather prediction. Models are useful for studying complex systems where many processes occur simultaneously. In the case of weather forecasting, such processes might include temperature changes, precipitation patterns and expected movement of high and low pressure systems. The processes and their interactions can be represented mathematically by a set of equations (or model). Then, by solving the equations simultaneously, the solution of the model will mimic the behavior of the system (e.g., the path of a hurricane). As evident from this example, models are developed because it may not be possible, or it may be too costly, to probe the real system. Mathematical models therefore predict the response or behavior of a system. They can be also be used to predict the response of a system prior to an experiment on the actual system.

Models are used in all fields of biology. Specific examples are: 1) to calculate nutrient intake for optimal growth, 2) to represent blood circulation, 3) to predict the pharmacological response to a drug, 4) to determine the rate of uptake of compounds by cells, and 5) to calculate enzyme kinetics.

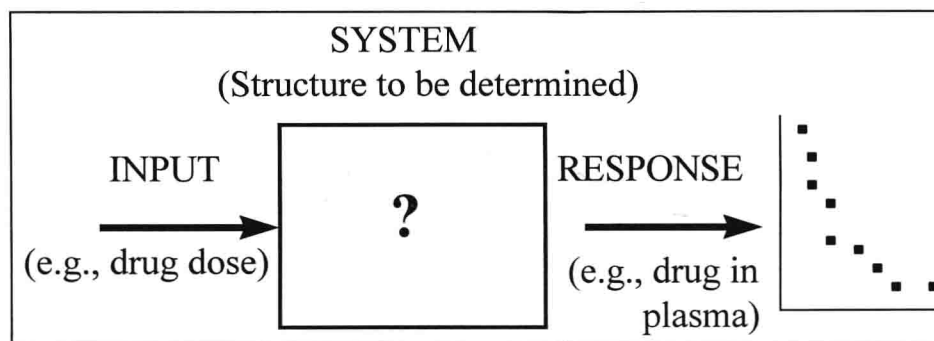
**Modeling** is the process of developing a model or set of equations to simultaneously represent the structure and behavior of a system. Modeling biological systems differs fundamentally from modeling physical systems because the structure of physical systems is usually known, whereas, the structure of biological systems is generally not known. Models of biological systems are based on observations of the system (Fig 1.1). This process of determining the structure of a system based on its behavior is called the inverse problem. There are a number of limitations in modeling biological compared to physical systems; data are often incomplete due to the limitations on sampling sites; sampling times and number of studies that can be performed; data are imprecise; constraints related to the biology and the experimental techniques must be embedded in the analysis (3, 4).

Because the structure of a biological system is not known, a model developed to fit data from the system also represents a hypothesis of the system. Models therefore



are not static, but evolve over time as studies provide new information that extend and refine the model. A good example is the development of models that describe lipoprotein kinetics (5).

**Tip:** The aim of modeling is to create a mathematical 'likeness' of a system so that the model behaves in the same way as the system.



**Fig 1.1** Biological modeling is the process of determining the structure of a system from its response.

## II. Approaches to modeling

There are three general approaches to modeling biological systems. They relate to whether the model is defined before or after a study, whether the model parameters are related to the structure (physiology or chemistry) of a system, and the complexity of the model. The approach chosen by an investigator depends on the purpose for modeling the system.

### 1) *A priori* versus *post priori*:

*A priori* (or theoretical) models are developed based on existing information about a system. For example, a model for glucose metabolism could be based on *in vitro* studies of the individual enzyme reactions. An example of this approach is described by Garfinkel et al (11). By contrast, *post priori* (or empirical) models are based on new observations. With this approach, a model for glucose metabolism would be developed by injecting labeled glucose *in vivo*, measuring its disappearance from blood, and proposing a model to fit the data. An example of this approach is described by Foster et al. (10).

### 2) Descriptive versus mechanistic

Descriptive models consist of mathematical functions or equations that fit the observed data. Parameters in the equations generally have no relationship to entities in the system. An example is an equation that is the sum of exponentials. Although descriptive models are usually simpler than mechanistic models (described below),