Chapter 1

The Art of Modeling

Drawn by my eager wish, desirous of seeing the great confusion of the various strange forms created by ingenious nature, I wandered for some time among the shadowed cliffs, and came to the entrance of a great cavern. I remained before it for a while, stupefied, and ignorant of the existence of such a thing, with my back bent and my left hand resting on my knee, and shading my eyes with my right, with lids lowered and closed, and often bending this way and that to see whether I could discern anything within; but that was denied me by the great darkness inside. And after I stayed a while, suddenly there arose in me two things, fear and desire—fear because of the menacing dark cave, and desire to see whether there were any miraculous things within.

—Leonardo da Vinci (1452–1519), Renaissance scientist and philosopher

INTRODUCTION

The focus of this book is primarily on the development of pharmacokinetic and pharmacokinetic-pharmacodynamic models. Models that are reported in the literature are not picked out of thin air. Useful models take time and effort and what is rarely shown is the process that went into developing that model. The purpose of this chapter is to discuss model development, to explain the process, and to introduce concepts that will be used throughout this book. Those criteria used to select a model extend to whether the model is a linear model or a nonlinear mixed effects model and that is why this material is provided first. If the reader can understand what makes a good or validated model, then the particular type of model is irrelevant.

WHAT IS A MODEL AND WHY ARE THEY MADE?

A system is a collection of objects that interact to create a unified whole, such as a cell culture system, a rat, or a human. The type of models that are of interest in this book are mathematical models that represent the system of interest and "*can be used to explore the structure and behavior of the system*" (Wastney et al., 1997). A more simplistic definition might be that a mathematical model defines how you think your data were generated. Most famous mathematical models can be found in chemistry and physics, such as:

- Boyle's law, PV = constant, which states that for a given mass at fixed temperature the pressure (P) times the volume (V) of a gas is a constant;
- Newton's second law of motion, F = ma, which states that the force (F) acting on an object is equal to its mass (m) times its acceleration (a); and
- $E = mc^2$, perhaps the most famous equation of the last century, which most people believe has to do with Einstein's theory of relativity, but in actuality has nothing to do with it. This equation is founded on the basis that matter and energy are really different forms of the same thing and states that that the amount of energy (E) that could be produced is equal to the mass (m) of an atom times the speed of light (c) squared.

Mathematical models in biology tend to be more complex, but are all based on the same foundations used to develop models in the more physically oriented sciences.

In defining a mathematical model it is helpful to distinguish between the various components of the model. Models are built using experimentally derived data. This so-called data generating process is dependent on system inputs, system dynamics, and the device used to measure the output from a system (Fig. 1.1). But in addition to these systematic processes are the sources of error that confound our measurements. These errors may be measurement errors but also include process noise that is part of the system. One goal of mathematical modeling is to differentiate the "information" or systematic component in the system from the noise or random components in the system, i.e.,

$$\text{DATA} = \text{SYSTEMATIC COMPONENT} + \text{ERROR}.$$

Hence, models usually consist of a structural model or systematic component plus a statistical model that describes the error component of the model. Early in the modeling process the focus may lie with the systematic component and then move to a more holistic approach involving the error components. For example, the 1-compartment model after bolus administration is

$$C = \frac{D}{V}\exp\left(-\frac{CL}{V}t\right)+\varepsilon. \tag{1.1}$$

The first term on the right hand side of Eq. (1.1) is the structural model having two inputs (also called independent variables), D (dose) and t (time), and one output (also called the dependent variable), C (concentration). The variables V (volume of distribution) and CL (clearance) are referred to as model parameters which must be estimated from the observed concentration data. The second term in Eq. (1.1) is the error component (also called the variance model). ε represents the deviation between model predicted concentrations and observed concentrations.

Modeling is done for a number of reasons depending on the point of view. Scientifically, modeling "provides a systematic way of organizing data and observations of a system at the cell, tissue, organ, or whole animal (human) levels" and "affords the opportunity to better understand and predict physiological phenomena" (Epstein, 1994). Financially, companies utilize modeling as a way to better leverage business decisions and this has been shown to result in substantial cost savings over traditional experiments (Van Buskirk, 2000). And on a personal level, modelers model because it's fun and challenging.

Beyond characterizing data, once a model is developed, it can be used to answer "what if" questions—a process known as simulation. Hence, modeling and simulation (M&S) are often used in the same breath by modelers. But there are many important differences between modeling and simulation. A model looks back in time. Given a set of outputs (data), the model attempts to find a set of parameters that explain the data generating process. Simulation looks forward in time. Given a model and a set of parameters, what happens if the inputs are varied. In simulation, the model is fixed and the inputs are varied. In modeling, the inputs and outputs are fixed, but what happens in between is varied. More about the differences between M&S will become evident using examples throughout the book.

The implementation of mathematics into biology, physiology, pharmacology, and medicine is not new, but its use has grown in the last three decades as computer speeds have increased and scientists have begun to see the power of modeling to answer scientific questions. A conference was held in 1989 at the National Institutes of Health called "Modeling in Biomedical Research: An Assessment of Current and Potential Approaches." One conclusion from that conference was that "*biomedical research will be most effectively advanced by the continued application of a combination of models—mathematical, computer, physical, cell, tissue culture and animal—in a complementary and interactive manner*."

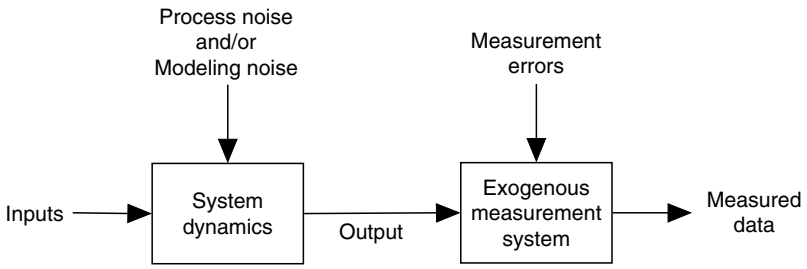

Figure 1.1 Diagram of the system under study. Redrawn with from DiStefano and Landaw (1984). Reprinted with permission from The American Physiological Society, Copyright 1984.