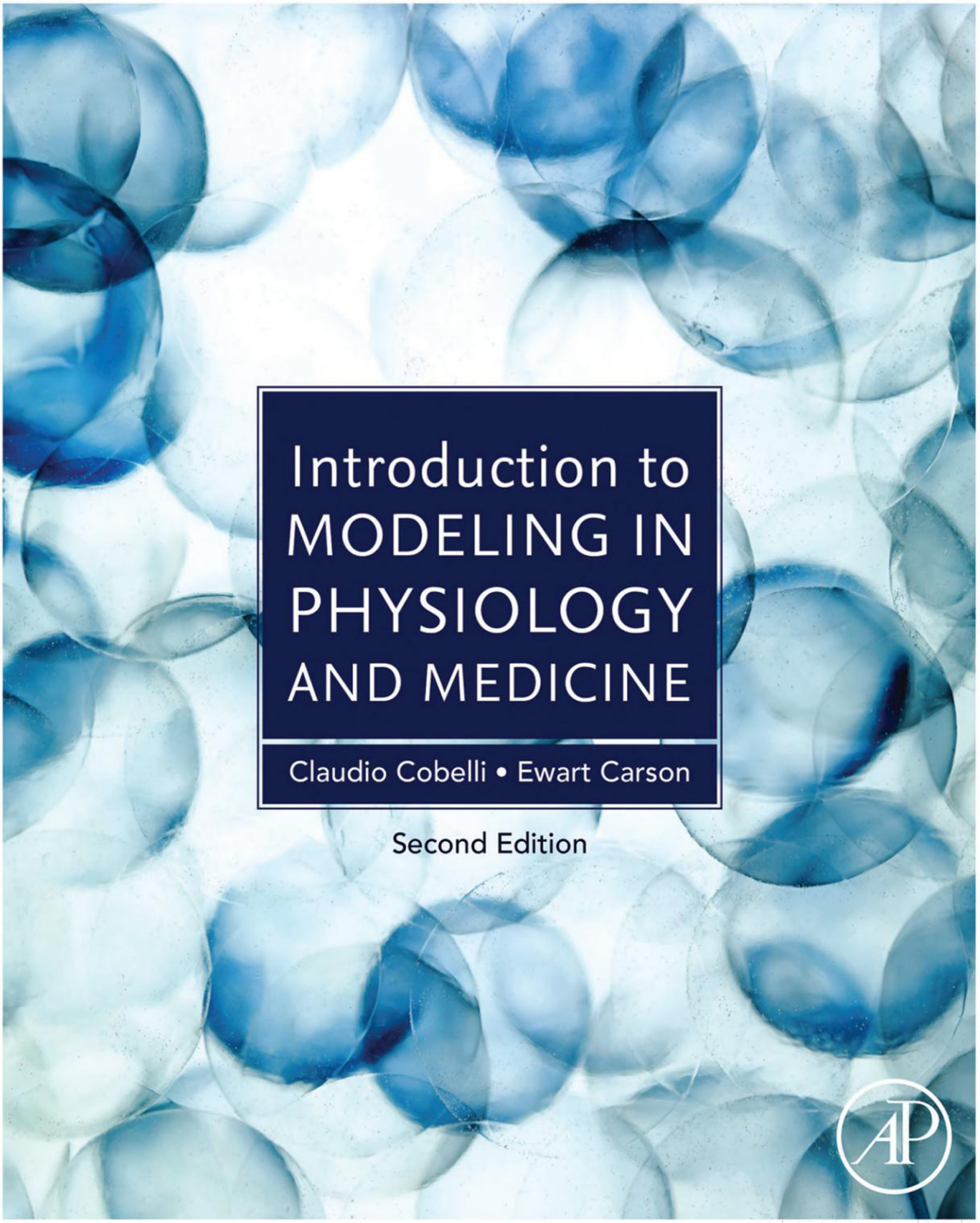
Introduction to
MODELING IN
PHYSIOLOGY
AND MEDICINE
Claudio Cobelli • Ewart Carson
Second Edition

Introduction to Modeling in Physiology and Medicine

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Preface to the second edition

A number of changes have been introduced in this second edition. First, clearer guidance is provided regarding the mathematical prerequisites in order to achieve the maximum benefit from the material, particularly in the later chapters. The basic structure of the book remains unchanged, while a number of the chapters providing details of the basic approaches to modeling have been enhanced. In the light of developments over recent years, the range of case study material included in this book has been substantially increased, including two new extensive examples drawn from recent research experience.

Our thanks go to Martina Negretto for assistance with preparation of the manuscript.

We would also like to thank members of the Elsevier team who have encouraged and helped us in bringing this second edition into fruition, particularly Leticia Lima and Mara Conner.

Claudio Cobelli and Ewart Carson
Padova, Italy and Ludlow, United Kingdom
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Preface to the first edition

Mathematical modeling is now widely applied in physiology and medicine to support life scientists and clinical workers. Our aim in writing this book is to provide an introduction to this topic, presenting the underlying principles of good modeling methodology together with numerous examples, indicating the way in which such modeling is finding application in physiology and medicine.

Mathematical modeling finds application in medical research, in education, and in supporting clinical practice. In the research context, the use of models can, for example, yield quantitative insights into the manner in which physiological systems are controlled. In the educational setting, medical students can use computer model simulation to explore the dynamic effects of pathophysiological processes or of drug therapy. In the clinical arena, mathematical models can enable estimates to be made of physiological parameters that are not directly measurable—useful for example in diagnosis, as well as enabling predictions to be made as to how changes in drug therapy will impact on variables of clinical importance, such as blood pressure or blood glucose concentration.

This book is directed at a broad readership across a wide range of student and practitioner backgrounds. In terms of the student readership, it is designed to appeal to biomedical engineers and to those studying physical and engineering sciences, and biological and life sciences. It should also appeal to medical students who wish to enhance their quantitative understanding of the physical and chemical processes that underpin physiology and medicine. Further, this book should be of interest to practitioners of all professions who have an interest in quantitative aspects of physiology and medicine.

This book begins by exploring some of the complexities of physiology that lend themselves to modeling in order that their quantitative features may be better understood. The concepts of mathematical modeling are then introduced, showing that models can be used for a wide range of purposes: to gain insights, to support processes of measurement, to make predictions of future behavior, and in a variety of ways assist in enhancing clinical research and practice. A number of approaches to developing mathematical models are then considered, with each being illustrated by a range of examples. The remainder of the text then focuses on issues associated with making estimates of model parameters and addressing the problem of ensuring that a mathematical model is valid; that is to say fit for its intended purpose. The final chapter comprises a number of case studies which demonstrate, in detail, how the modeling concepts, methods, and techniques that have been described and discussed earlier can be applied to real-world problems in physiology and medicine.

Lastly, we wish to express our thanks to a number of our colleagues who have worked with us in developing the examples and case studies, including: Alessandra Bertoldo, Chiara Dalla Man, Giovanni Sparacino, Gianna Toffolo, and Peter Weller; and to Andy Morrison for

his assistance in the preparation of the figures. We are also indebted to those who over many years have offered us encouragement and support in our modeling ventures, including Riccardo Bonadonna, Derek Cramp, Ludwik Finkelstein, Roman Hovorka, David Kelley, Antonio Lepschy, Robert Rizza, Abdul Roudsari, and Peter Sönksen. Finally, we should like to express our gratitude to Jonathan Simpson and all his colleagues at Academic Press/Elsevier for their encouragement, support, and tolerance during the lengthy gestation of this book.

Claudio Cobelli, Ewart Carson

1 Introduction

1.1 Introduction

Over the past few decades there has been a considerable increase in the application of quantitative methods to the study of physiological systems. New techniques for making physiological measurements are being constantly developed and applied, and there has been a corresponding increase in the methods available for the analysis and interpretation of such experimental data.

Improvements have occurred in both the quality and quantity of experimental data that are now available from studies in the intact organism and on the isolated organ. Advances in instrument technology and biochemical laboratory methods have significantly contributed to these improvements.

In parallel, there have been substantial advances in terms of concepts, methods, and techniques for the study of dynamic systems; advances that have originated in control and systems theory. These are increasingly finding their way into physiological investigations, and in associated investigations in the clinical sciences and medicine. An additional driver for all of this is, of course, the availability of more computing power. Harnessing all of these together results in an increase in the use of mathematical modeling techniques in physiological investigations.

The increasing application of modeling and dynamic systems analysis offers benefits for the physiology, control and systems science, and biomedical engineering. For control and systems science there is opportunity to examine the structure and behavior of complex physiological systems which function effectively. Moreover, such systems provide a test bed for examining the merits and limitations of techniques of modeling and dynamic systems analysis, originally developed largely for technological applications.

For the physiologist, the appropriate use of mathematical models offers many potential benefits. They provide a concise description of complex dynamic processes, indicate ways in which improved experimental design could be achieved, and enable hypotheses concerning physiological structure to be tested. Furthermore, they allow estimates to be made of parameters (physiological quantities) that are otherwise not directly accessible to measurement. Although initially most modeling applications have been in the areas of physiological and medical research, they are now increasingly being used as aids in the diagnosis and treatment of disease.

If these benefits are to be realized, there is clearly a need for a greater awareness and understanding of modeling methodology and techniques, together with their strengths and limitations. This book has been devised to address those issues, provide insight into the why

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and how of modeling, the need for models, what they can do, how to build them, and how to use them.

The concepts, problems, and approaches are illustrated with examples and case studies drawn both from literature within the field and from our own extensive experiences gained over many years of endeavor. The illustrations cover a broad range of physiological topics, demonstrating the wide applicability of the approaches being described.

1.2 The book in context

This book forms a part of the series of volumes in *Biomedical Engineering*. However, physiological modeling is very much an interdisciplinary subject. Hence the topic is also central to a range of related disciplines including biomathematics, medical and health informatics, and systems physiology.

Significant activity in the field of mathematical modeling of physiological systems stretches back more than 100 years. Texts in the field have been produced for more than 50 years. Milsum (1966) and Milhorn (1966) were among the first to produce such texts. Additionally, an early, biomathematics classic was created by Riggs (1963), while Talbot and Gessner (1973) produced a definitive text having a systems physiology focus. Since then dynamic modeling of physiological systems has been a major component of many biomedical engineering texts. Examples include Bronzino (2000), and Enderle, Blanchard, and Bronzino (2000), Keener and Sneyd (1998), Hoppensteadt and Peskin (2002), Edelstein-Kehset (2004), Ottesen *et al.* (2004), and DiStefano (2013). For a more advanced treatment of modeling methodology, the reader should consult Carson and Cobelli (2014).

Other volumes have focused on particular approaches to modeling or on specific areas of physiology. For example, volumes on compartmental modeling have been produced by Atkins (1969) and Godfrey (1983), among others. The analysis of data yielded by dynamic tracer experiments has been the subject of volumes by Jacquez (1972, 1996) and Cobelli *et al.* (2000). The modeling of metabolic and endocrine systems has been described by McIntosh and McIntosh (1980) and by Carson *et al.* (1983). The related subject of physiological modeling and control has been dealt with extensively by authors such as Carson and Cramp (1985), Khoo (2000), and Northrop (2000).

In addition to textbooks on the subject, there are readily available modeling software packages. Some such as MATLAB and SIMULINK are generic modeling packages for dynamic systems. Others have been designed for a specific physiological application. Examples include SAAM II, NONMEM, and Jsim which is extensively used in the physiome project.

However, there have been remarkably few attempts to produce entry-level texts on the topic of modeling of physiological systems; the earlier volume by Finkelstein and Carson (1985) being one of the few. The focus of this present volume is to provide a comprehensive introduction to the modeling of dynamic, physiological systems. The emphasis is placed firmly on developing sound modeling methodology, with numerous examples and case studies being included as illustrations.

1.3 The major ingredients

In general terms, a model is a representation of reality. However, it is also an approximation of that reality since not all the ingredients of that reality can be incorporated into any model. Hence the models that we are concerned with in the chapters that follow will all, in their various ways, provide approximate representations of the particular physiological systems under consideration. What is crucial is that the form of model developed is appropriate for its purpose. As already hinted at, there can be a wide range of possible purposes for modeling. For instance, the form of a model adopted for the purpose of understanding some of the complexities of the control of breathing might be different from one adopted as an aid for weaning an intensive care unit patient off a ventilator. This is the case even though in both examples the physiological focus is the respiratory system.

The way in which we develop a model will be dependent on our knowledge of the relevant physiology and the availability of relevant experimental data. So in essence the process of building a model can be regarded as a mapping of physiological knowledge and experimental data into the model. In the case of a model that is essentially a representation of the experimental data available; it is those data that dominate in this mapping process. On the other hand, if the model is designed to provide a representation of the physiology more explicitly, then it will be the physical and chemical knowledge of that physiological system that dominates in the building of the model.

The overall process of modeling involves a number of interrelated ingredients. These are model building, model identification, simulation, and model validation. Used appropriately in conjunction with each other, they provide a methodology for developing a model that will be fit for its intended purpose.

Model building involves formulating equations that provide an adequate representation of either the experimental data (in the case of a data-driven model) or the underlying physiology (in the case of a model that explicitly represents the underlying physiology). Once the model has been built, identification can take place which includes making estimates of those parameters (physiological quantities) in the model that cannot be measured directly, using the available input/output experimental data.

Simulation involves solving the model equations to predict output behavior. Such computer simulation might, for instance, be used to predict the time course of a patient's blood glucose concentration in the case of a model designed to explore relationships between insulin dosage and blood glucose in a diabetic patient. The fourth ingredient is that of model validation; this involves examining (in the case of two or more competing models) which is the best in relation to the modeling purpose. In the case of a single model it involves examining whether that model is good enough in relation to its purpose. This validation process involves the use of statistical tests as well as examining other features of the behavior of the model.

All are vital ingredients of the modeling exercise and are very much interrelated. One point that will be stressed in the following chapters is the iterative nature of the modeling process. Just as any design process is very much iterative in nature—only very rarely will it

be right first time—the same applies with modeling. Usually, several iterations through the cycle of ingredients will be needed before an acceptable end product is produced.

1.4 Readership and prerequisites

This book describes the development of models of physiological systems; models that can be used in a variety of ways, including as aids to understanding, as means of supporting clinical processes, and for educational purposes among others. Given that the level of this text is essentially an introductory guidebook, it is aimed at students of biomedical engineering and related disciplines. Such students may be undergraduates, or may be following more specialized master's programs in the subject.

However, one of the fascinations of the subject of physiological modeling is its very interdisciplinary nature. As such, it is an activity undertaken not only by those with technical backgrounds in biomedical engineering and health informatics, but also by many in the clinical and life sciences. Thus this text will also be relevant to the needs of physiologists, biologists, and clinical scientists and practitioners interested in quantitative approaches and results.

In terms of prerequisites for those with a clinical or life sciences background, it is helpful to have a basic understanding of the fundamental concepts of dynamic systems and their representation by differential equations. In Chapter 2, Physiological complexity and the need for models, some examples are included which offer a resume of the dynamics of first-order systems; showing how such systems can be represented mathematically, and the nature of the solutions of such equations.

1.5 Organization of the book

As indicated above, the aim of this book is to provide an introduction to the modeling of physiological systems. However, before proceeding to the actual modeling process, it is worth understanding a little about the fundamentals of physiology itself. This is important if modeling is to be undertaken successfully. In the normal healthy individual, the physiological systems provide an almost incredible array of functions necessary for the maintenance of life. In doing so, they exhibit a variety of forms of complexity. Chapter 2, Physiological complexity and the need for models, thus provides some insights into the nature of physiological complexity.

Physiological complexity is discussed in terms of function and behavior (which we wish to access), and measurements (which are available). Complexity manifests itself in terms of concepts such as hierarchy and feedback, and each is considered in the physiological context. As a result of complexity it is often not possible to directly measure (*in vivo*) the quantities of interest. Only indirect measures of such quantities may be possible. This complexity of physiological systems, coupled with limitations in measurement means that models have to be adopted as a means to aid understanding.

Chapter 3, Models and the modeling process, introduces the concepts of model and modeling process. It describes what is meant by a model, the variety of models, why modeling (i.e., modeling purpose), and the nature of the modeling process. There are many possible purposes for modeling. These can range from investigating the physical or chemical structure and associated parameters of the physiological system in question to the development of clinical models for either diagnosis or patient management. This is followed by a description of the modeling process, stressing the need for good modeling methodology. The basic ingredients of model formulation, model identification, model validation, and model simulation are described.

Following on from the first three introductory chapters, Chapter 4, Modeling the data, starts the detailed examination of approaches to modeling. Here the focus is modeling the data. The aim of this chapter is to describe data modeling approaches as representations of physiological dynamics. The chapter describes what we mean by modeling the data, when such approaches are applicable and how it should be done (i.e., a description of the principal types of data-driven (black box) models). Approaches include modeling both continuous and discrete time signals, adopting both time domain and frequency domain methods.

In contrast, Chapter 5, Modeling the system, focuses on modeling the system. The aim of the chapter is to describe approaches to modeling the physiology, showing that it can be done at different levels and that the approach adopted depends on available *a priori* knowledge and assumptions made. The approaches adopted compare and contrast the following cases: static versus dynamic, deterministic versus stochastic, time-invariant versus time-varying, lumped versus distributed, linear versus nonlinear and continuous versus discrete. As with the previous chapter, extensive examples are included as illustrations of the approaches available, demonstrating how modeling can be carried out for a wide range of physiological processes and situations.

We need a complete model of the physiological system under consideration. By this stage we shall have at least one candidate model, but possibly more than one with the need to choose between them. Focusing on a single model, if it is incomplete this will be due to some of the parameter values being unknown. This is true whether the modeling approach has been data driven or driven by the physiology of the system. We may be dealing with the whole model or just part of it. Chapter 6, Model identification, aims to provide a framework for dealing with this situation (whether the model is data driven or physiologically based). To solve this problem we need data. Data sometimes occur from the intrinsic dynamics of the system (e.g., spontaneous oscillations or noise), but usually we must design experiments. Chapter 6, Model identification, discusses what experiments need to be designed to yield appropriate data.

Chapter 7, Parametric modeling—the identifiability problem, and Chapter 8, Parametric models—the estimation problem, address the problem of identifying models that include parameters, whether these are input/output models or models that explicitly correspond to the physiology of the system under investigation. Chapter 7, Parametric modeling—the identifiability problem, considers the problem of identifiability. That is, whether it is theoretically possible to make unique estimates of all the unknown parameters of the model on the basis

of those input/output experiments, which it is proposed to perform as a means of acquiring experimental data. Having addressed this problem of identifiability, techniques for estimating the unknown parameters are then discussed in Chapter 8, Parametric models—the estimation problem. Emphasis is placed upon linear least squares and nonlinear least squares techniques, though brief reference is made to maximum likelihood and Bayesian estimation.

The focus of Chapter 9, Nonparametric models—signal estimation, is nonparametric models. These are defined and methods are outlined for estimating functions, rather than parameters. Available techniques include raw deconvolution and deterministic regularization.

Chapter 10, Model validation, considers the issue of model validation, that is to say whether a particular model is good enough for its intended purpose, or in the case of a number of competing models, which of them is best. Having defined what is meant by model validity, an overall framework, together with associated methods, for the validation process is presented. The chapter ends with some recommendations for good modeling practice. Finally Chapter 11, Case studies, illustrates the methods and techniques that have been discussed in relation to validation through a series of case studies.

Throughout the text, numerous illustrations, examples, and case studies are included; demonstrating how the methodology and techniques described can be applied across a wide range of physiological examples. All of these illustrations are appropriately referenced. With regard to the basic methodology described in this book, only essential references are included. Readers who wish to engage in a deeper study of modeling methodology are encouraged to consult our companion volume (Carson & Cobelli, 2014), which includes extensive referencing to all methodological issues and detail.

2

Physiological complexity and the need for models

2.1 Introduction

Before moving on to the modeling activity that forms the bulk of this book, it is worth devoting attention to the nature of the physiological systems that we shall be modeling. In various ways all physiological systems are characterized by their complexity. In this chapter we shall examine the nature of this complexity in physiology. It is important to understand this complexity, since by definition any model that we create will be a simplification, an approximation of that complex reality. By understanding something of this complexity we shall be in a better position to make the simplifying assumptions that correspond to the particular model formulation that we shall adopt. In essence, the model that we develop needs to have taken into account both the inherent complexity that we have simplified and the availability of measurement data which will be used in estimating the parameters of our model.

Fig. 2−1 shows a schematic representation of the human organism. In effect, this is a conceptual model that gives a flavor of the complexity of human physiology. Although quite a complex figure, it is clearly a very simplified and approximate representation of all the physiological detail. Nevertheless, it does capture the essence of the dynamic processes that are present within the living organism. It depicts the human organism as a complex multi-input, multi-output system, with linkages involving an array of physicochemical processes. Finally, it includes many of the standard functions found in any complex control system; that is sensing, decision making and control, actuating or effecting, and the feeding back of information. Some of the ingredients of complexity in this physiological context are considered in later sections of this chapter. However, let us first examine some of the attributes of complexity in a more general sense.

2.2 Complexity

Complexity manifests itself in a number of ways. First, in general, the greater the number of components or elements there are in a system, the greater its complexity will be. The greater the number of neurons in a central nervous system or the larger the number of intermediate substances in a metabolic pathway, the greater the complexity will be. However, complexity is associated not only with the number of elements, but also with their interconnectivity (Flood & Carson, 1993). In the case of the central nervous system this would correspond to the number of interconnections between neurons.

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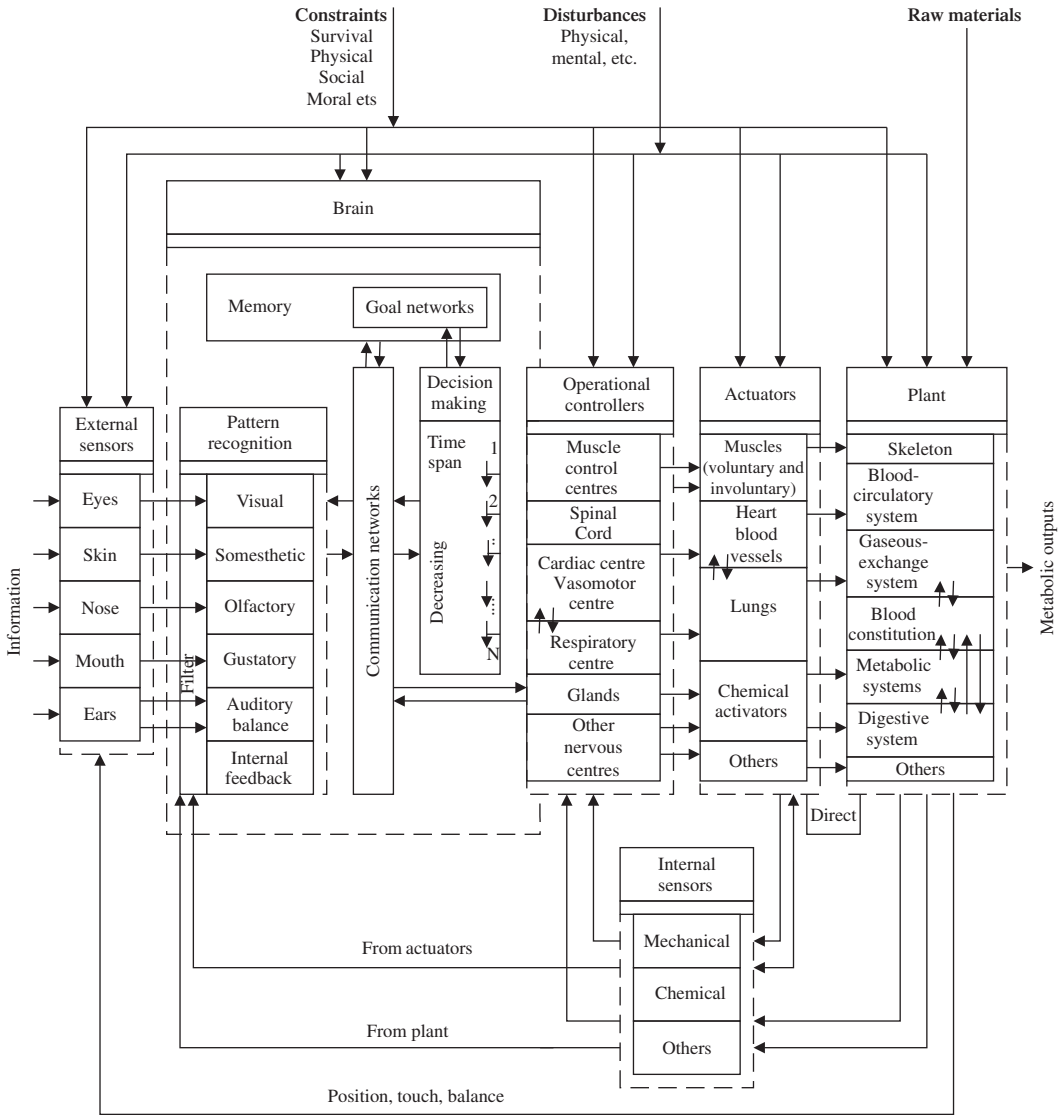

FIGURE 2–1 The human organism as a complex system. *Source: Adapted from Janes, F. R., & Carson, E. R. (1971). Modelling biological systems.* IEE Electronics and Power, 17, *110–116.*

These concepts of numbers of elements and interactions form part of a framework for complexity that has been proposed by Yates (1978). Yates suggested that complexity arises when one or more of five attributes are found which, in addition to the two already referred to, include nonlinearity, asymmetry, and nonholonomic constraints.

Nonlinear systems occur when at least one element in the system relates to and varies in a nonlinear way with another. It would be represented graphically by a curved rather than a straight line. Nonlinear systems are, in general, much more difficult to analyze and comprehend than linear systems; that is, they are more complex. Almost all physiological systems are inherently nonlinear, even if from a modeling perspective it may be possible, and indeed reasonable, to treat them as if they were linear under specific conditions. This is a concept that will be considered in detail later in the book.

Asymmetry occurs when symmetry in a system's relationships no longer holds. Consider the following example. A single cell after fertilization multiplies to become two cells, and then four, and then eight, and so on. Eventually, this produces an organism in the mold of its parents. During the developmental process, the single cell becomes a distinct organism or creature due to organization and differential growth. Differential growth is a type of asymmetry, and without it the process of growth described above would result in nothing more than a very large number of cells. Due to the differential growth, the results in the specialization give rise to the emergence of specific organs within the overall organism, such as the liver.

Holonomics relate to the integrity of systems, so that holonomic constraints are constraints that relate to laws affecting an entire organism. The obverse of this is nonholonomic constraints. These relate to parts of a system that are temporarily outside central control and which, in essence, go off and do their own thing. This applies significantly in the physiological context. The central nervous system would not be able to cope with the myriad of regulatory functions that take place within the human organism, for instance. As such, the human organism has evolved and adapted in such a manner that there is very considerable local regulation and control. For example, large numbers of metabolic processes are regulated at the local level (as will be described later), without recourse to centralized neural control. Complexity arises in situations where there is a high degree of freedom in parts of a system. In other words, the behavior and control of the parts cannot easily be predicted just on the basis of knowledge of the overall system characteristics.

Complexity also arises as a consequence of stochastic and time-varying dynamic effects. These will be considered in later chapters. Three key concepts that will aid our understanding of physiological complexity are feedback, control, and hierarchy and these will be discussed in later sections of this chapter. However, before doing so a review some of the basic concepts of dynamic systems and their mathematical representation which will underpin much of the modeling to be described later in the book.

2.3 System dynamics

To gain an understanding of the nature and behavior of dynamic systems, such as are to be found throughout the human organism, it is convenient at the outset to examine the simplest type of system, namely those modeled by first-order differential equations with constant, or time-invariant coefficients. As an approximation, many real systems can be represented satisfactorily by such simple models. Moreover, these simple models exhibit clearly some of the basic phenomena of system dynamic behavior.

2.3.1 First-order linear time-invariant systems

Fundamentally, a first-order linear time-invariant dynamic system is one in which the rate of change of the response variable is, in the absence of a forcing input, directly proportional to the instantaneous value of the variable itself. The nature of such systems can be illustrated by deriving the equations in the examples that follow. Other examples will be presented in Chapter 5, Modeling the system, in the context of modeling the system. Here the intention is to use two examples to illustrate the nature of the mathematical representation and the solution of the relevant differential equations.

2.3.2 The dynamic behavior of first-order linear time-invariant systems—solution by integration

By the behavior of a dynamic system we mean the variation of the response variable with time, resulting either from the application of a forcing input or from starting from some initial state, which is not an equilibrium state. To analyze the behavior it is necessary to solve the appropriate differential equation to obtain the response variable as a function of time. Consider first a simple system in the absence of any forcing function. The equation of such a system can be solved by simple integration.

As an example consider a population, the magnitude of which is measured at convenient time intervals, Δt apart (see Fig. 2–2). If P_{n-1} and P_n are the levels of population at times t_{n-1} and t_n respectively.

$$\frac{(P_n - P_{n-1})}{\Delta t} = \frac{\Delta P}{\Delta t} \tag{2.1}$$

As the time interval $\Delta t = t_n - t_{n-1}$ becomes very small, $\Delta P/\Delta t$ approximates more closely to the instantaneous rate of change of the population with respect to time, dP/dt.

The rate of change of population dP/dt is equal to the difference between the birth rate N_b and the death rate N_d. Hence:

$$\frac{dP}{dt} = N_b - N_d \tag{2.2}$$

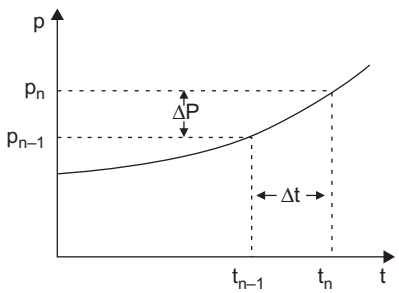

FIGURE 2–2 Graph of population, P, as a function of time.

Suppose that both birth rate and death rate are proportional to the existing population, but with different constants of proportionality k_b and k_d such that $N_b = k_b\ P$ and $N_d = k_d\ P$. Therefore:

$$N_b - N_d = k_b\ P - k_d\ P = (k_b - k_d)\ P = kP \tag{2.3}$$

Substituting for $N_b - N_d$ in (2.2)

$$\frac{dP}{dt} = kP \tag{2.4}$$

Rearranging (2.4) we have:

$$\frac{dP}{P} = k \times dt \tag{2.5}$$

Integrating both sides of this equation:

$$\begin{aligned} &\int (1/P) \cdot dP = \int k \cdot\ dt, \quad \text{that is} \\ &\log_e P = k\ t + C \end{aligned} \tag{2.6}$$

where C is the constant of integration. When $t = 0$, $P = P_0$. Therefore $C = \log_e P_0$. Hence:

$$\log_e P - \log_e P_0 = k\ t \tag{2.7}$$

Rearranging: $\log_e (P/P_0) = k\ t$. Hence:

$$\frac{P}{P_0} = e^{kt} \text{ or } P = P_0 e^{kt} \tag{2.8}$$

So the solution is an exponential function of time, the magnitude of which depends on P_0, the initial value of P.

The general form of response is dependent upon k, the rate constant. The two real forms of solution are those with P_0 being positive and k being either positive or negative. With k positive, the birth rate is greater than the death rate, and the plot of P against time results in a positive exponential (see Fig. 2–3). With k negative, the death rate is greater than the birth rate, and the plot gives a negative (decreasing) exponential. The time constant T, which is the reciprocal of the rate constant k governs the speed of the system response. For example, if k is small, there is a slow response since T is then large. As shown in Fig. 2–3, the time constant may be found graphically by drawing the tangent to the curve at any point Z and measuring the distance between the point where the tangent cuts the time axis and the point where the vertical projection through Z cuts the time axis.

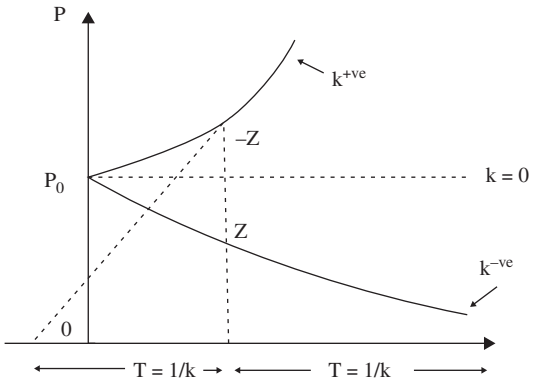

FIGURE 2–3 Graph depicting the dynamics of population as a function of the value of the population rate constant, k.

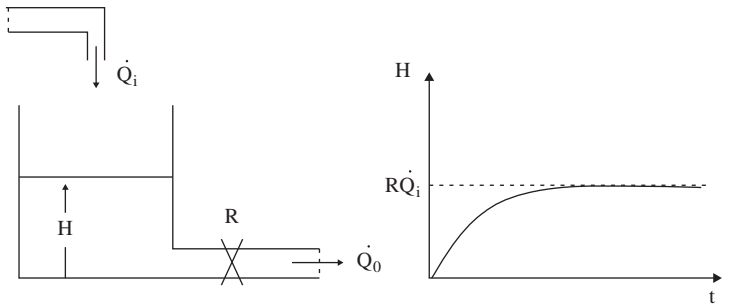

FIGURE 2–4 Representation of a first-order tank system, including the dynamics of the head of liquid in the tank, H, as a function of time in response to a step change in flow input, F_i.

2.3.3 The classical solution for a first-order system

Consider now the dynamic response of a first-order, linear time-invariant system, subjected to a forcing input. To illustrate the classical method of analyzing such a problem consider the tank system shown diagrammatically in Fig. 2−4. This example is a useful analog of many important biological systems, such as a compartment, loss from which is a function of the substance contained.

The flow rate of liquid into the tank is F_i, with an output flow rate of F_o through a valve of resistance R. It is assumed that the valve has a linear characteristic such that F_o is proportional to the head of water H. The rate of change of volume of liquid in the tank, V, is thus:

$$\frac{dV}{dt} = F_i - F_o \tag{2.9}$$

But,

$$F_o = \frac{H}{R} \tag{2.10}$$

and,

$$\frac{dV}{dt} = A\,\frac{dH}{dt} \tag{2.11}$$

where A is the cross sectional area of the tank. Substituting (2.10) and (2.11) in (2.9) gives

$$A\,\frac{dH}{dt} = F_i - \left(\frac{H}{R}\right) \tag{2.12}$$

which is first-order linear differential equation relating H to F_i.

Let the tank initially be empty, such that H, the height of the liquid in the tank is zero at $t = 0$.

Further, let a step input of flow rate, F_i, be applied at $t = 0$, that is, let the input rate of liquid be zero for $t < 0$ and F_i (a constant value) for $t \geq 0$. Eq. (2.12) can then be solved to determine the response of H to the input F_i. The solution has two parts; a free or natural response H_n, and a forced response H_f. The total solution or response is the sum of these two, $H = H_n + H_f$. The natural response is the response exhibited in the absence of a forcing function, as a result of a disturbance from equilibrium. This is given by the solution of

$$A\left(\frac{dH}{dt}\right) + \frac{H}{R} = 0 \tag{2.13}$$

which can be rewritten as

$$\frac{dH}{dt} = -\frac{H}{AR} \tag{2.14}$$

From the previous discussion it can be seen that the solution is an exponential form. This can also be seen from the fact that the solution must be a function that remains in the same form when differentiated. Let us try the solution

$$H = C\,e^{at} \tag{2.15}$$

Substituting for H and dH/dt in (2.13) we have

$$a\,C\,e^{at} + \left(\frac{1}{AR}\right) C\,e^{at} = 0 \tag{2.16}$$

Hence,

$$a + \left(\frac{1}{AR}\right) = 0 \tag{2.17}$$

Therefore $H = C\ e^{at}$ is a solution of (2.13) if a is a root of (2.16) which is known as the auxiliary equation, that is if $a = -1/(AR)$

We can write $T = 1/(AR)$, so that $a = -1/T$. The natural response is thus

$$H_n = C\ e^{-t/T} \tag{2.18}$$

Since the exponential function decays with time, the free response can, in this case, be described as a transient response.

We can now write the complete solution as

$$H = H_f + C\ e^{-t/T} \tag{2.19}$$

The response H_f can now be seen as the ultimate steady-state response, the part which remains after the transient response has decayed, in other words when $dH/dt = 0$.

Substituting $dH/dt = 0$ in (2.12) we have

$$H_f = R\ F_i \tag{2.20}$$

so that

$$H = RF_i + C\ e^{-t/T} \tag{2.21}$$

To evaluate C, which determines the magnitude of the natural response, it is necessary to consider initial conditions. When $t = 0$, $H = 0$, and substituting this in (2.21) we have

$$0 = RF_i + C \tag{2.22}$$

Hence,

$$C = -RF_i \tag{2.23}$$

The total response is then, as shown in Fig. 2—4

$$H = R\ F_i(1 - e^{-t/T}) \tag{2.24}$$

2.3.4 General case of a first-order linear system

Let us apply this approach to the general first-order system, as shown in Fig. 2—5, which can be described by the first-order, time-invariant differential equation:

$$T \cdot \left(\frac{dy}{dt}\right) + y = m(t) \tag{2.25}$$

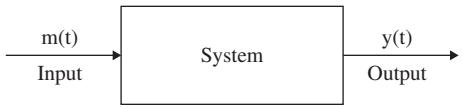

FIGURE 2–5 General representation of a first-order system with input m(t) and output y(t).

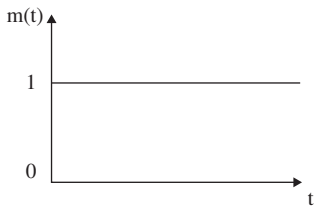

FIGURE 2–6 Forced component of response of a first-order system with a step input.

The natural or free response, y_n, depends upon the dynamics of the system itself and is found by solving (2.25) with the input equal to zero:

$$T \cdot \left(\frac{dy}{dt}\right) = -y \tag{2.26}$$

The solution, derived in a manner parallel to that developed in Section 2.3.2 is:

$$y_t = C\, e^{-t/T} \tag{2.27}$$

For a physical system the constant T is generally positive, so that the natural response is transient. The constant C depends on the initial conditions of the system as shown below.

The forced response, y_i, depends upon the particular input of the system and is usually the same form as the input for the case where the input is a unit step function (see Fig. 2—6). The forced response is obtained by finding a value of y which satisfies the equation:

$$T \cdot \left(\frac{dy}{dt}\right) + y = 1 \tag{2.28}$$

where the right-hand side of the equation is the particular input applied. The solution (cf. (2.20)) is:

$$y_t = 1 \tag{2.29}$$

The complete response is found by adding the natural and forced responses:

$$y = y_f + y_n = 1 + C\, e^{-t/T} \tag{2.30}$$

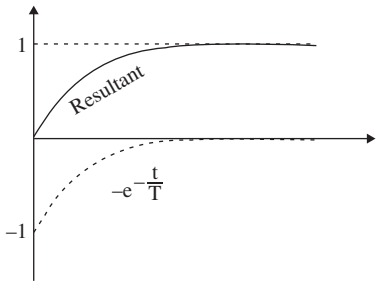

FIGURE 2–7 Resultant response (free + forced) of a first-order system to a unit step input.

The constant C can be found from the initial conditions. If at $t = 0$, $y = 0$, then from (2.30) $C = -1$. Therefore as shown in Fig. 2–7:

$$y = 1 - e^{-t/T} \tag{2.31}$$

The response of the system will vary depending on the specific form of the input applied. The most commonly used input, in addition to the step, is the impulse, which can be regarded as the first derivative of the step. In the context of this book, the injection of a drug could be regarded as an impulse input, whilst a constant infusion could be regarded as a step input.

For a system that can be described by a first-order, linear time-invariant differential equation, the rate at which the process proceeds is completely described by specifying the value of the time constant, rate constant, or half-life of that process.

The time constant is the value of time that makes the power to which the number e is raised equal to -1 in (2.31). For a step input it is the time taken to reach 63.2% of the final value.

That is in (2.31), let $t = T$. Then,

$$y = 1 - e^{-1} = 0.632 \tag{2.32}$$

The time constant is the reciprocal of the rate constant (which therefore has the dimension of time^{-1}).

Alternatively, a first-order linear process may be characterized by its half-life. This is particularly appropriate when examining the exponential decrease observed in the output variable of a first-order linear process following the application of an impulse input. The half-life is the time required for the output variable to be reduced to half of its initial value. Consider the output variable which is characterized by

$$y(t) = y_0\, e^{-t/T} = y_0\, e^{-kt} \tag{2.33}$$

where T is the time constant of the process and k is the corresponding rate constant.

Starting at time $t_0 = 0$, there is a time $t_{½}$ at which y has decayed to half its initial value, that is:

$$y(t_{½}) = ½\, y_0.$$

Substituting for $t_{½}$ in (2.33):

$$y\,(t_{½}) = ½\, y_0 = y_0\, e^{-t^{½}/T} = y_0\, e^{-kt^{½}}$$

Solving for $t_{½}$ by taking logarithms to the base e yields:

$$t_{½} = T\, \ell n\, 2 = \frac{1}{k}\, \ell n\, 2 \tag{2.34}$$

The half-life, $t_{½}$, depends only upon the time constant of the system and is independent of the magnitude of the initial value. Hence for any general time, t_1, on the response curve with a value of y_1, the value of y at time $(t = t_1 + t_{½})$ will be $½\, y_1$.

2.4 Feedback

Feedback is a fundamental feature of all physiological systems. It is vital in terms of ensuring physiological regulation and control. It is an ingredient of the complexity that characterizes physiological systems.

At its simplest, feedback can be regarded as a mutual causality, whereby variable X has an effect on variable Y, and in turn variable Y has an effect on variable X. If an increase in variable X brings about an increase in variable Y, and that increase in variable Y brings about a decrease in variable X, the process is referred to as negative feedback.

2.4.1 Negative feedback

Glucose metabolism provides us with examples of such negative feedback. For instance, in a normal individual, an increase in blood glucose concentration (variable X), brought about by the ingestion of the carbohydrate component of a meal, causes an increase in the secretion of insulin (variable Y). The effect of this increased insulin level is to bring about a reduction in the blood glucose concentration toward a normal value. This negative feedback process is inherently regulatory, seeking to enhance the control of blood glucose concentration. Physiologically the effects of insulin on glucose are achieved by processes that include the chemical conversion of glucose into glycogen that is stored in the liver.

2.4.2 Positive feedback

On the other hand, positive feedback corresponds to the situation in which variable X causes an increase in variable Y, which in turn, brings about a further increase in X. An example

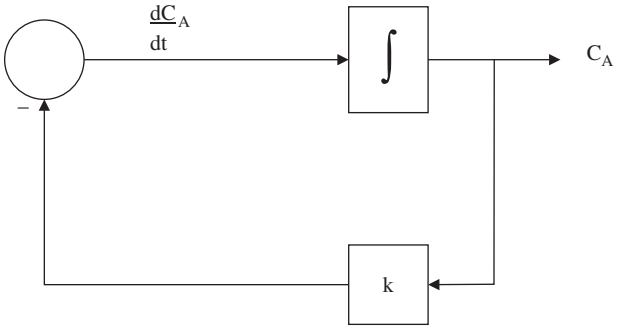

FIGURE 2–8 Signal flow diagram illustrating inherent negative feedback.

outside the physiological domain is the wage-price spiral. An increase in wages causes price increases that in turn act as a catalyst for further wage increases. This is clearly a destabilizing phenomenon.

2.4.3 Inherent feedback

The examples of feedback considered above relate to control systems in which the feedback link takes the form of a flow of material or information. There is, however, a further form of feedback that needs to be considered, namely inherent feedback.

Consider the case of a metabolic system. Suppose that in a simple chemical reaction, it can be assumed that the rate of concentration decrease of chemical A, taking part in the reaction, is directly proportional to its concentration. Mathematically this can be expressed as:

$$\frac{dC_A}{dt} = -k\,C_A \tag{2.35}$$

where C_A is the concentration of chemical A, and k is the rate constant for the reaction. Eq. (2.35) can be expressed in the form of a signal flow diagram (see Fig. 2−8). This shows the integration of dC_A/dt to yield C_A. This is then fed back, being multiplied by k and by -1 to yield dC_A/dt. This is effectively a negative feedback connection. In other words, there is an inherent regulatory effect exhibited in this chemical reaction despite the fact that there is no physical feedback link. This phenomenon of inherent feedback that has been revealed is contained in any dynamic process that can be described mathematically in this way in differential equation form.

2.4.4 Combining negative and positive feedback

Both positive and negative feedback can be seen in a simple model of population dynamics, as already considered in terms of the mathematics involved in Section 2.3.2. This is a model that could apply, for instance, in relation to the number of humans or animals in a particular location, or equally in the context of cell populations within an organism.