1

Introduction

In medicine, one must pay attention not to plausible theorizing (λογισμος) but to experience and reason (λογος) together. I agree that theorizing is to be approved, provided that it is based on facts and is systematically induced from what is observed; but conclusions drawn by the unaided reason can hardly be serviceable, only those drawn from observed facts.

—Hippocrates, "Precepts," Athens, 5th Century B.C.

1.1 PURPOSE OF THIS BOOK

The purpose of this book is to bring to the attention of the biomedical community the fact that an effective methodology exists for quantifying the dynamic interrelationships among physiological variables of interest from natural observations (data).

The book presents the conceptual framework and the mathematical foundation of this methodology that render it *general* in its application and *rigorous* in its approach. This methodology yields mathematical models of the dynamic interrelationships among the observed variables in a *nonlinear and nonstationary* context that is appropriate for physiological systems. Unlike many previous approaches, the advocated approach resists the temptation of simplifying the model to fit the method but retains, instead, the full complexity depicted in the data.

The book is focused on the modeling of nonlinear time-invariant physiological systems, unlike most modeling studies to date, which have focused on the limited class of linear time-invariant systems, due to the relative simplicity of the methods of estimation and analysis associated with the latter. Nonlinearities are ubiquitous in physiology and often essential in subserving critical aspects of physiological function. Although few will argue with the importance and necessity of addressing the nonlinear and dynamic aspects of physiological systems, most will view this task as a daunting challenge owing to its

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considerable complexity. The purpose of this book is to alter this confining view, so prevalent in the scientific community, by removing the perceived methodological barriers and offering the practicable prospect of analyzing nonlinear physiological systems within the prevailing experimental and computational constraints.

We seek to achieve this goal by presenting recently developed methodologies in a clear and reasoned manner that is rigorous but not unduly burdened by mathematical formalism. The emphasis is on key operational issues that allow the practical application of the advocated approach by interested investigators in a manner that avoids critical pitfalls and enhances the understanding of the physiological function of the system under study. Illustrative examples are used extensively to elucidate important methodological points and to assist the reader in understanding *why* and *how* the method works. The examples also instruct the reader in the manner through which the utility of the obtained results can be realized by elucidating their physiological interpretation.

The mathematical models are derived *inductively* (from the data) using a general and rigorous mathematical framework in order to secure methodological rigor and fidelity to the data. Unlike *deductive* methods previously used, the advocated methodology does not require *a priori* model postulates and avoids the potential pitfall of (possibly inaccurate) preconceived notions that may unduly constrain the achievable model form.

This point is most critical when limited experimental or natural data are used for the estimation and validation of the model, thereby limiting the modeling task to a portion of the operating space of the system. The advocated approach espouses the fundamental requirement of a broad ensemble of input–output data that covers as densely as possible the entire operating space of the system. Therefore, in the advocated approach, the inductively derived models are *"true to the data"* that are collected under broad experimental or natural operating conditions, and not *ad hoc* mathematical postulates (reflecting specific preconceived notions) fitted to experimental data that may probe only part of the total operating space of the system. Essential for the inductive approach is a general methodological framework (such as the one advocated herein) that does not constrain the possible form of the emerging model.

It is evident that the advocated methodology departs from the conventional way of thinking and practice in the study of physiological systems with regard to the undesirability of *a priori* model postulates and specialized/experimental input waveforms. It challenges the established deductive approach, especially when limited experimental data are used, as potentially misleading and inherently incapable of exploring the full complexity of the system. It rejects the notion that practical necessity dictates the simplification of the employed model to stay within the "tractable boundaries" of linear, stationary or static analysis as unjustifiable in light of recent developments that make nonlinear, nonstationary, and dynamic analysis feasible. It insists on the use of a broad repertoire of data (be they experimental or natural, although the latter are preferable) instead of limited experimental data using specialized waveforms (e.g., pulses, sinusoids) that are often contrived to "simplify" the experiment and facilitate its interpretation. The risks of such experimental or methodological "simplifications" cannot be overstated, since they are likely to create the illusion of knowledge while providing results that have limited utility (at best) or are potentially misleading. For instance, the response to a pulse or sinusoidal stimulus cannot be used to extrapolate or infer the response of nonlinear dynamic systems to any other stimulus.

The validity of the aforementioned arguments rests on whether physiological systems (which have been shown to be almost always nonlinear and dynamic) can be represented

meaningfully by approximate linear and/or static models. The definitive answer to this question can be given *only after* performing the complete nonlinear dynamic analysis of the system under broad operating conditions and, subsequently, assessing the adequacy of linear/static analysis. In other words, the linear/static analysis is inherently incapable of answering this question because it does not probe the nonlinear/dynamic alternative (i.e., it does not contain explicit information about the possible nonlinear dynamic characteristics of the system). Note that the assessment of the adequacy (or lack thereof) of the linear/static model depends on the specific data ensemble used and the prevailing ambient noise. Therefore, nonlinear dynamic analysis with a broad data repertoire is the only way to reach the correct assessment of the adequacy of the linear/static model and obtain globally valid models (even if the latter end up being static and/or linear).

The expressed views seem almost self-evident but represent a strong challenge to the status quo. They seek to facilitate the advent of a new era in systems physiology that constitutes a quantum leap in the way physiological systems are modeled and understood. They are not meant to denigrate the efforts of past investigators who did not follow the advocated approach, since a review of history establishes the fact that the process of scientific progress requires a multitude of viewpoints and reveals that even unsuccessful efforts contribute to the advancement of knowledge by identifying dead ends.

The advocated approach cannot be the definitive view on the subject of physiological system modeling, since it simply represents another stage in the evolution of knowledge (with many improvements and refinements certain to follow). Nonetheless, it can advance the state of the art by a "quantum leap," since it represents a drastic departure from conventional thinking and practice. It is interesting to note that the advocated approach is consistent with the basic tenets of the Hippocratic teachings that formed the foundation of medicine as a scientific discipline, separated from priestcraft and groundless speculation, in the 5th century B.C. (see Historical Note #1).

Hippocrates first asserted the cardinal importance of clinical observation against "theorizing" (speculation not supported by data) and established the fundamental concept of the "unity of organism" against the fragmented approach of the "Empiricists" and the "Anatomists." The latter distinction remains the key issue underpinning the ongoing debate between the integrative systems approach advocated herein and the reductionist approach prevalent in the physical and biological sciences to date. The static view of the Anatomists and the Empiricists was countered by the Hippocratic dynamic view of the "disease process" and the "recuperative faculties" of living organisms (an early version of the concepts of homeostasis and system dynamics). The Hippocratic views survived the challenge of the Empiricists, as well as the "Methodists" and the "Atomicists" of antiquity (all espousing reductionist views), and were restored to their rightful place of universal acceptance by the great Greek physician, scientist, and philosopher, Galen of Pergamos (Galenos or Γαληνος in Greek) in the 2nd century A.D. Galenos' extensive writings on human physiology defined medicine until the 16th century when William Harvey founded modern physiology with his seminal experiments in Padua (building on earlier seminal anatomical contributions by Vesalius and others in northern Italy).

Galenos fully espoused the key Hippocratic views on the "unity of the organism" and the cardinal importance of clinical observation of the "disease process" (as opposed to the static view of examining the composing parts and the isolated symptoms, espoused by all other schools of thought at his time) that led him to an *integrative* and *dynamic* view of physiology. These basic tenets form the foundation of the advocated approach of *dynamic system physiology* under natural operating conditions.

This approach stands in contrast to the reductionist and static viewpoints that remain dominant in biological sciences, and questions the validity (or even the purpose) of the oversimplified experimental preparations often used in designing experiments for conventional "hypothesis-driven" research. These strong statements do not seek to invalidate the significant contributions made by hypothesis-driven research or to reject the valuable knowledge acquired over the centuries through the reductionist approach that have advanced scientific progress. The advocated viewpoint simply seeks to establish the proper balance between the two approaches in pursuing scientific knowledge, so that their synergistic contributions serve scientific progress and prevent the establishment of a mutually impeding antagonism so often fostered in the past by an unwise inclination for polarized thinking.

It is the ambitious goal of this book to contribute to a new movement (with ancient roots) that will restore the key Hippocratic–Galenic tenets to their rightful position in scientific thinking and practice through adoption of the dynamic systems viewpoint, in order to bring about the desirable leap of progress in physiology and medicine.

1.2 ADVOCATED APPROACH

The advocated approach offers the effective methodological framework for obtaining reliable and objective (i.e., devoid of subjective modeling notions) descriptors of the system nonlinear dynamics based on the available experimental or natural data. This approach employs general model forms that do not require specific model postulates and yield inductively "data-true" models in the stochastic broadband context of natural operating conditions.

Due to the complexity of this fundamental problem, we have taken a gradualist step-by-step approach, building on the rigorous and general mathematical foundation of the Volterra–Wiener approach as extended and modified for various applications over the last thirty years. It is gratifying to note that our efforts have succeeded in developing a solid foundation for a general modeling approach capable of tackling this problem in a practical context.

This novel modeling methodology has been tested in pilot applications from the nervous, cardiovascular, renal, respiratory and metabolic/endocrine systems. These applications have showcased the efficacy of the developed methodology and have allowed important advances in systems physiology by assigning physiological significance to the obtained model components in a manner that deepens the scientific understanding of the system under study. This demonstrates the potential benefits of the advocated approach that are expected to enable improvements in diagnostic as well as therapeutic procedures.

Standing on this solid foundation, we are poised to address the next generation of challenges that pertain to the *multivariate* and *highly interconnected* nature of physiological systems. This direction represents the natural extension of our efforts in reaching our ultimate objective of modeling the *true* physiological systems, and not their simplified "surrogates" born of methodological inadequacy. This forward-looking task is commenced with the important case of multiple inputs and multiple outputs that is discussed in Chapter 8. The complexity that emerges from the interconnections among multiple physiological variables of interest (often in *closed-loop* or *nested-loop* configurations) must be placed in a nonlinear dynamic context, with possible nonstationarities. Since we seek to study the physiological system under "natural" operating conditions (i.e., exposed to an

ensemble of natural stimuli and unconstrained by arbitrary experimental manipulations), the ultimate modeling task must be placed in a multivariate stochastic broadband context, without artificially imposed constraints (e.g., fixed operating points or specialized input waveforms), in order to achieve a globally valid model of the *real* system.

A measure of the posed challenge is attained when we note that proper study of the *real* physiological systems requires reliable modeling methods that are capable of dealing with:

- Nonlinear dynamics (of arbitrary order)
- Multiple variables of interest (observable/measurable)
- Multiple interconnections (possibly closed-loop)
- Possible nonstationarities in system dynamics
- Broadband stochastic input/output signals
- Considerable measurement noise and systemic interference

Last, but not least, the obtained models must be amenable to meaningful physiological interpretation and offer the prospect of achieving significant diagnostic and/or therapeutic improvements.

The critical task of meaningful interpretation of the obtained models and their proper utilization in clinical practice is formidable, as much as it is important, because the wealth of information contained within these complicated models may be overwhelming and difficult to harness. Nonetheless, it is incumbent on us to perform this task in order to realize the benefits of the advocated new approach and achieve the ambitious goal of a quantum leap in the state of the art.

Interpretation of the obtained models will focus on relating their characteristics to specific physiological mechanisms that are either known qualitatively or can be explored experimentally. It will also examine the effects of changes in certain physiological variables (in a dynamic context) and the robustness of the overall system in the event of internal or external perturbations (homeostasis). The latter study may demarcate the bounds of normal versus pathological states.

Utilization of the obtained models in a clinical context will seek to examine their use for improved diagnosis of disease (i.e., more and better clinically relevant information) and for the quantitative assessment of pharmaceutical treatment or therapeutic intervention. The latter will allow optimization of treatment (with regard to specific clinical goals) and the design of improved therapeutic procedures, consistent with the key Hippocratic exhortation: "*first, do no harm. . . .*"

The progress made to date in the development of effective methodologies for nonlinear and/or nonstationary modeling of physiological systems is summarized in this book and has given rise to a new generation of issues associated with the study of greater system complexity and the analysis of expanded experimental/clinical databases—both direct consequences of advances in the state of the art—consistent with Socrates' aphorism: "*the more I learn, the more I realize how much I do not know.*"

The advocated approach stands on the confluence of methodological (nonlinear and nonstationary) and technological (computational and experimental) advancements, and seeks to leverage on their synergistic utilization in order to tackle the formidable challenges in physiological system modeling from natural (i.e., random broadband) data. Pilot applications are selected from physiological domains that exhibit essential nonlineari-

ties/nonstationarities (neural, cardiovascular, respiratory, renal, endocrine, and metabolic systems) in order to demonstrate the wide applicability and unique capabilities of the advocated novel methodologies. In this sense, the advocated approach is at the cutting edge of scientific developments and has a universal appeal to all physiological domains in terms of scientific advancement, as well as potential impact across a broad swath of clinical applications.

The immense variety of nonlinear behavior makes it desirable that the developed methodologies retain a high degree of generality and the ability to gracefully transition into interpretable models for each particular application.

The complexity of nonlinear behavior also makes it imperative that the ensemble of input signals used for probing/observing the system behavior be spectrally and temporally rich, so that the maximum possible interactions among different values or frequencies of the input signal be observed at the recorded output. This is the fundamental reason why we favor *random broadband input signals* over specialized deterministic signals, following on the pivotal suggestion of Norbert Wiener regarding the use of Gaussian white noise inputs that is discussed in Section 2.2. For instance, the customary use of rectangular pulses or sinusoids as stimuli by experimental physiologists may be appealing to the eye of the observer and offer a comprehensible response waveform, but they are very poor probing signals in terms of the extracted amount of information for given experimentation time duration. This important point will be elaborated in Sections 2.1.5, 2.2.1, and 5.1.

In addition, the practical modeling task is complicated by the fact that the observed operating conditions are often burdened by severe interference and noise, as well as nonstationarities in the system behavior. Since we will mainly address the case of stationary (time-invariant) models, the issue of systemic and measurement nonstationarities should be borne in mind as a complicating factor that may compromise the quality of the results or limit the record length of the data used for model estimation. The subject of explicit nonstationary modeling will be discussed in Chapter 9.

The practical challenge posed by the ubiquitous presence of noise and/or interference necessitates robust estimation algorithms that minimize the effect of noise/interference on the obtained model estimates for a given data record length. Increasing the data record length will normally improve the model estimates unless possible nonstationarities degrade the benefits of the extended data record. Repetition of identical experiments and proper averaging may mitigate the effects of noise/interference even for certain types of systemic nonstationarity but is more time-consuming and vulnerable to lack of ergodicity (see Chapter 5). In all cases, intelligent design of experiments can maximize the output signal-to-noise ratio by putting more input signal power at those frequency bands that are most critical for the system dynamics and are less contaminated by noise/interference. This is an important practical issue that has not received adequate attention in the literature and will be discussed in Chapter 5.

1.3 THE PROBLEM OF SYSTEM MODELING IN PHYSIOLOGY

The purpose of physiological system modeling is to advance our quantitative understanding of biological function and improve medical science and practice by utilizing the acquired quantitative knowledge. In modeling physiological systems, we seek to summarize all available experimental evidence about the functional characteristics of a system in the

form of mathematical relations among variables of physiological interest. The resulting mathematical models ought to emulate the observed functional behavior of the system under natural operating conditions when simulated on the computer.

Ideally, such a model must be *accurate* (i.e., reproduce precisely the observed data), *global* (i.e., be accurate under all natural operating conditions), *compact* (i.e., have the minimum mathematical and computational complexity), and *interpretable* (i.e., be amenable to physiological interpretation that advances our understanding of the mechanisms subserving the system function). Implicit in the first attribute is the *robustness* of the model, which provides for stable behavior in the face of internal or external random perturbations. The latter, and the omnipresence of noise, require that our modeling efforts be cast in a stochastic context. Furthermore, the development of a global model (valid under all natural operating conditions) presumes our ability to observe and measure the spontaneous activity of the variables of interest with sufficient accuracy and sampling resolution over representative time intervals. These variables can be viewed as inputs, outputs, or internal state variables depending on our specific modeling goals.

Such an "ideal" model would offer a succinct quantitative representation of the functional characteristics of the system and would allow the study of its behavior under arbitrary conditions through computer simulations (thus maximizing the "yield" of physiological research). In addition to being a complete "capsule of knowledge" that advances scientific understanding of how and why physiological systems function in the way they do, such a model can improve clinical diagnosis (by providing better and more relevant information) and treatment (by properly guiding therapeutic procedures and assessing their effects). The implications are immense and promise to usher a new era of advanced medical care.

The development of such an "ideal" model is a formidable task, because of the functional complexity of physiological systems, which are typically dynamic, nonlinear, nonstationary, highly interconnected (often in closed-loop configurations), and subject to stochastic perturbations and noise. Furthermore, the modeling process has been constrained in practice by limitations of the available experimental, computational, and analytical methods, leading heretofore to the development of "less than ideal" models in the sense defined above, that is, inability to reach the desired attributes of accuracy, globality, compactness, and interpretability.

This sobering reality is put in perspective when one notes that many of the current modeling efforts are still confined to rudimentary methods of static and linear analysis. The course of methodological evolution started with static linear analysis (linear regression among variables of interest) and gradually progressed into dynamic (differential or integral equations) and nonlinear analysis. Although linear dynamic analysis has been increasingly used, the use of nonlinear dynamic analysis remains rather limited due to the scarcity of practical methods and the intrinsic complexity of the problem. This shortcoming would not be alarming, if it were not for the fact that most physiological systems exhibit significant and essential dynamic nonlinearities. This problem is compounded by the fact that physiological systems are also often nonstationary (i.e., their functional characteristics vary with time) necessitating models whose parameters also change with time. The need for proper modeling methodologies in this realistic context is increasingly pressing and provides the motivation for this book.

Physiological system modeling provides the means of summarizing vast amounts of experimental data into relatively compact mathematical (or computational) forms that allow the formulation and testing of scientific hypotheses regarding the functional proper-

ties of the system—an iterative process that should lead to successive refinement and evolution of the system model. Thus, system modeling attains a central role in the scientific process of generation and dissemination of knowledge, consistent with the credo "model or muddle." Models can be applied to arbitrary levels of system decomposition or integration depending on the availability of appropriate data, hence providing the conceptual and methodological means for developing a hierarchical understanding of integrative systems physiology.

The fundamental question of the functional relationships between observed physiological variables drives the system modeling effort. The variables are observed experimentally over time (occasionally over space or wavelength) and are viewed as signals (or datasets) that are linked by a causal relationship. The direction of this causal relationship (cause-to-effect sequence) defines some of them as inputs and some of them as outputs of a conceptual operator (the system) that transforms the inputs into the outputs (Figure 1.1). This transformation is generally dynamic in the sense that the present values of the outputs depend not only on the present but also on the past values of the inputs. Another way of describing the same (defining) characteristic of dynamic systems is to state that the effect of an input change upon the output signal spreads over time.

It is worth noting that the system is defined by means of its inputs and outputs (and not by a physical entity). Thus, we may define many different systems using the same physical entity by altering the selected inputs and outputs, as long as causality is not violated. This point is illustrated in Figure 1.2, where a physical entity is comprised of five components (A, B, C, D, and E) and the designated connections (arrows) represent directional causal relationships. If we stimulate component A with input $x_A(t)$ and record output $y_C(t)$ from component C, then we define the system S_{AC} as the signal transformation from A to C. However, if we record from another component [e.g., $y_D(t)$ out of component D] and stimulate another component [e.g., $x_B(t)$ into component B], then we define a different system S_{BD} representing the signal transformation from input B to output D, even though the underlying physical entity remains the same.

The input–output signal transformation describes the functional properties of the system and may be linear or nonlinear, time-invariant (stationary) or time-varying (nonstationary), and deterministic or stochastic. A mathematical expression describing quantitatively this input–output signal transformation is the sought model of the system. For our purposes, the sought model will be deterministic, implying that possible stochastic variations of the system characteristics will be relegated to the status of systemic noise or modeling errors and will be incorporated in the stochastic error term of the model. The latter will also incorporate other modeling errors and possible measurement noise or external/systemic interference.

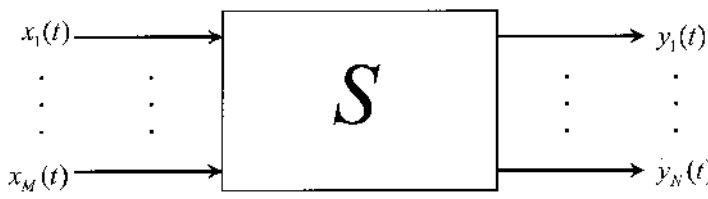
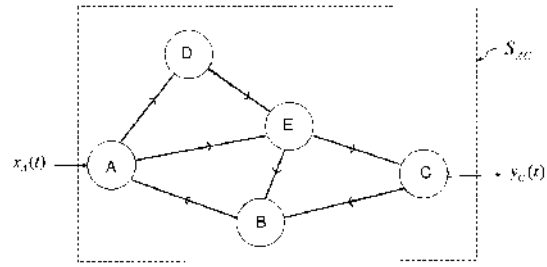
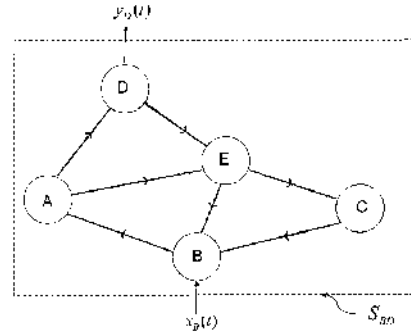


Figure 1.1 Schematic of a "black-box" system operator S transforming M input signals $\{x_1(t), \ldots, x_M(t)\}$ into N output signals $\{y_1(t), \ldots, y_N(t)\}$.



(a)



(b)

Figure 1.2 Schematic diagram of causal connections (denoted by arrows) among five physical variables (A, B, C, D, E). The selected input(s) and output(s) define the particular system operator. For instance, an input $x_A(t)$ stimulating A and an output $y_C(t)$ recorded from C define a system operator S_{AC} (a) or an input $x_B(t)$ stimulating B and an output $y_D(t)$ recorded from D define a different system operator S_{BD} (b).

If we limit ourselves, at first, to the single-input/single-output case, we can use the convenient mathematical notation of a functional $S[\cdot]$ to denote the causal relationship between past and present values of the input x and the present value of the output y as

$$y(t) = S[x(t'), t' \leq t] + \varepsilon(t) \tag{1.1}$$

where the functional $S[\cdot]$ represents the deterministic system as it maps the input past and present values onto the output present value, and $\varepsilon(t)$ represents the stochastic error term. The error term is assumed to be stochastic and additive—the latter is a common assumption that simplifies the estimation task but may not correspond to reality in some cases where the error may have a multiplicative or other modulatory effect on the input/output signals. The error term is also called the "residual" and may contain modeling errors (including possible stochastic variations of the system characteristics), systemic noise or interference, and measurement noise. For analysis and estimation purposes, the residual is usually treated as a stationary random process (with zero mean) that is statistically independent from the input and the noise-free output signals (although it is contained in the output data measurements). Note that deviation from this assumption regarding the residual term may cause significant estimation errors.

The convenient mathematical notation of Equation (1.1) can be extended to the case of causal systems with multiple inputs and multiple outputs by adopting a vector notation (shown in bold) for the input/output signals, the residual terms, and the functionals:

$$\boldsymbol{y}(t) = \boldsymbol{S}[\boldsymbol{x}(t'), t' \leq t] + \boldsymbol{\varepsilon}(t) \tag{1.2}$$

Clearly each output signal must have its own distinct functional, implicating (potentially) all inputs. The case of multiinput/multioutput systems is discussed extensively in Chapter 8. However, the main methodological developments are presented in Chapters 2–5 for the single-input/single-output case to avoid the burden of the inevitably increased complexity of mathematical expressions resulting from the multiple inputs and outputs.

1.3.1 Model Specification and Estimation

The goal of mathematical modeling is to obtain an explicit mathematical expression for the functional $S[\cdot]$ using experimental or natural input–output data and all other available knowledge about the system. This goal is generally achieved in two steps. At first, a suitable mathematical form is selected for $S[\cdot]$, containing unknown parameters and/or functions, which are subsequently estimated by use of input–output data in the second step. This two-step procedure is often referred to as "system identification" in the engineering literature, and the two steps are termed "model specification" and "model estimation," respectively.

The *model specification* task is generally more challenging and the critical step to successful modeling. It utilizes all prior knowledge and information regarding the system under study and seeks to select the appropriate model form in each case. Typically, the selection is made from among four classes of models: nonparametric, parametric, modular, and connectionist (see Table 1.1). The criteria for selection of the appropriate model class are discussed in Chapters 2–5 and constitute a critical issue.

The *model estimation* task employs estimation methods suitable for the specific characteristics of each case and seeks to maximize the accuracy of the resulting model prediction for given data types and noise conditions. Various measures and norms of model prediction accuracy can be used, but the most common is the mean-square error of the output prediction (the sum of the squared residuals).

The model estimation task is important because it yields the desired result, but it is meaningful only when the model specification task is performed successfully. The highly technical nature of the model estimation task has attracted most of the attention in the en-

Table 1.1 Nonlinear System Modeling Methodologies

	Strengths (+) and Weaknesses (–)			
	Nonparametric	Parametric	Modular	Connectionist
Model specification	+	–	±	±
Interpretability	±	+	+	–
Robustness to noise	+	–	+	±
Compactness	–	+	+	–
Adaptable to time variance	+	±	±	+

gineering literature, and the contents of this book reflect this fact by delving into the many technical details of the various estimation methods. Nonetheless, it is useful to remember that, although the estimation methods are necessary tools for accomplishing the modeling task, the art of modeling and the impact of its scientific applications hinge primarily on the successful performance of the model specification task and the meaningful interpretation of the obtained model. It is for this reason that the overall modeling philosophy advocated by this book places the emphasis on securing first the best possible model specification results and then performing accurate model estimation.

Since system modeling seeks to find and quantify the causal functional relationships among observed variables, it occupies a central position in the process of scientific discovery. Although it addresses only the functional aspects of the system under study, structural information can be used to assist the model specification task by properly constraining the postulated model. Conversely, system models can be used to examine alternative hypotheses regarding the structural composition of a given system (e.g., interconnections of neuronal circuitry) and thus can advance our structural knowledge of physiological systems.

It is critical to note that the selection of the model form must not constrain unduly the range of functional possibilities of a system, lest it lead to biased and inaccurate results. Thus extreme care must be taken to avoid such inappropriate constraining of the model either in terms of its mathematical form or in terms of its operational range (i.e., dynamic range and bandwidth). At the same time, the efficiency of the employed estimation methods and the utility of the obtained model in terms of scientific interpretability are compromised when the model is not adequately constrained. This key trade-off between model parsimony and its global validity pervades all modeling studies and is of fundamental importance, as discussed later in connection with the various classes of model forms.

Related to the model specification task is the issue of inductive versus deductive model development, discussed in Section 1.5. Deductive modeling is possible only in those rare occasions where sufficient knowledge exists about the detailed functional properties of the system, so that its internal workings can be described accurately by use of first physical and/or chemical principles. In these fortunate, but rare, occasions the system model can be reliably postulated in the form of precise mathematical expressions using a deductive process. The complexity of physiological systems rarely affords this kind of opportunity and, consequently, modeling of physiological systems is usually inductive (i.e., it is based on accumulated empirical evidence from experimental data). This distinction between inductive and deductive modeling has been made before with the use of the terms “empirical or external” and “axiomatic or internal” models respectively [Arbib et al., 1969; Astrom & Eykhoff, 1971; Bellman & Astrom, 1969; Rosenblueth & Wiener, 1945; Yates, 1973; Zadeh, 1956].

Although prior knowledge about the system can be used to assist the model specification task, the modeling approaches presented herein are based entirely on experimental or natural input–output data and exclude the favorable (but rare) occasions where the model form can be derived from first principles or can be reliably postulated on the basis of prior knowledge about the system. Therefore, our approach to physiological system modeling is inductive and data driven.

The necessity of inductive modeling for most physiological systems elevates the importance of the type and quality of experimental or natural data needed for our modeling purposes. It is imperative, for instance, that the data cover the entire functional space of the system (e.g., the entire bandwidth and dynamic range of interest) and that the noise

levels remain low relative to the power of the signal of interest. It must be noted in this connection that the systemic noise or interference (which is prevalent in physiological systems) is usually more harmful for the estimation process than the measurement noise.

1.3.2 Nonlinearity and Nonstationarity

A critical issue that complicates the modeling task is the presence of nonlinearities in the physiological system. Since this is the focus of the book, it is discussed in detail in the following section and in Chapters 2–7. Here, we limit ourselves to the definition of nonlinearities and nonstationarities with regard to the functional notation of Equation (1.1). A note should be made about static nonlinearities, whereby $y(t)$ depends only on the value of $x(t)$ and the functional $S[\cdot]$ reduces to a function. Static nonlinearities are easy to model (graphically or with simple numerical fitting procedures), leaving dynamic nonlinearities as the true challenge.

With reference to the functional notation of Equation (1.1), linearity of the system implies that $S[\cdot]$ obeys the "*superposition principle,*" which states that if $y_1(t)$ and $y_2(t)$ are the system outputs for inputs $x_1(t)$ and $x_2(t)$, respectively, then for an input $x(t) = \lambda_1 x_1(t) + \lambda_2 x_2(t)$ the output is: $y(t) = \lambda_1 y_1(t) + \lambda_2 y_2(t)$. This can be expressed by the mathematical condition

$$S[\lambda_1 x_1(t) + \lambda_2 x_2(t)] = \lambda_1 S[x_1(t)] + \lambda_2 S[x_2(t)] \tag{1.3}$$

where $x_1(t)$ and $x_2(t)$ are linearly independent signals, and λ_1 and λ_2 are nonzero scalar coefficients. The above condition can be tested experimentally with any pair of linearly independent inputs and scalar coefficients, and it must be satisfied by all such pairs. This condition for linear superposition can be extended to any number of linearly independent signals and remains by practical necessity a *necessary,* but not sufficient, condition (since all possible combinations cannot be practically tested). Appendix I provides the definition of linear independence between two or more signals. Elaboration on the experimental testing of system linearity is given in Section 5.2.4.

Returning to the functional notation of Equation (1.1), we can point out that stationarity (or time-invariance) of the system implies that the input–output mapping rule represented by $S[\cdot]$ remains invariant through time. It should be stressed that $S[\cdot]$ denotes the rule by which the system constructs the output at time t using the input values at time t and before. Thus, nonstationarity (or time-variance) should not be confused with the inevitable temporal changes in the output signal caused by temporal changes in the input signal that occur whether the system is stationary or not. Experimental testing of the stationarity of a system requires the repetition of identical experiments at different times and the comparison of the obtained results. The test for stationarity of a system can be based on the following conditional statement: if the system output for input $x(t)$ is $y(t)$ then the output for input $x(t - \sigma)$ is $y(t - \sigma)$ for every time shift σ. Since all experimental studies are subject to random influences and disturbances, this assessment is not straightforward in practice and requires statistical analysis of sufficient data, as discussed in Section 5.2.3 and in Chapter 9.

An experimental complication, often encountered in physiological systems, is the presence of possible nonstationarities in the experimental preparation caused by inadvertent injuries in surgical procedures. Thus an important distinction must be made between nonstationarties that are intrinsic to the system operation (e.g., endocrine/hormonal cycles or biological rhythms) and pertain to the actual physiological function of the system, and

those that affect our measurement but are of no interest vis-à-vis the physiological function of the system under study. The former type of nonstationarity ought to be incorporated into the estimated model by proper methodological means, as discussed in Chapter 9. The latter type of nonstationarity degrades the quality of the data and, although it can be often viewed as low-frequency noise, it may not have a simple additive effect on the observed output data (e.g., it may have a multiplicative or modulatory effect). Therefore, it is important to remember that the employed modeling methodologies for physiological systems must be robust in the presence of noise or systemic interference and must not require very long experimentation time over which measurement nonstationarities may develop or have significant effect.

Since the input–output data are collected and processed in sampled digital form, it is evident that the actual implementation of these modeling approaches takes place in discrete time. Thus, the continuous-time, input–output signals $x(t)$ and $y(t)$ must be converted into discrete-time signals $x(n)$ and $y(n)$ using a fixed sampling interval T, where n denotes the discrete-time index (i.e., $t = nT$). Provided that proper attention is paid to the issue of aliasing (by sampling at a sufficiently high rate that secures a Nyquist frequency greater than the bandwidth of the sampled input–output signals, as discussed in Section 5.1.3), the presented mathematical methods generally transfer to the discrete-time case with minor modifications (e.g., converting an integral into a summation). Both discrete and continuous cases are presented throughout the book, and we make special note of the few cases where the transition from continuous to discrete time requires special attention (e.g., from nonlinear differential to difference equations).

1.3.3 Definition of the Modeling Problem

With all these considerations in mind, the physiological system modeling problem is defined as:

Given a set of input–output experimental or natural data, find a mathematical model that describes the dynamic input–output relationship with sufficient accuracy (using a mean-square-error criterion for the output model prediction) under the following conditions:

- *No prior knowledge is available about the internal workings of the system*
- *Nonlinearities and/or nonstationarities may be present in the system*
- *Extraneous noise and/or systemic interference may be present in the data*
- *The obtained model must be amenable to physiological interpretation*
- *Experimentation time and computational requirements may not be excessive*

A practical guide for the solution of the modeling problem in the context of physiological systems is provided in Chapter 5.

1.4 TYPES OF NONLINEAR MODELS OF PHYSIOLOGICAL SYSTEMS

The challenge of modeling nonlinear physiological systems derives from the immense variety of nonlinearities in living systems and the complex interactions among multiple mechanisms linked together within these systems.

We summarize in Table 1.1 the four main nonlinear modeling approaches and class-

es of nonlinear models used to date: nonparametric, parametric, modular, and connectionist.

In the *nonparametric* approach, the input–output relation is represented either analytically in integral equation form where the unknown quantities are kernel functions (e.g., Volterra–Wiener expansions) or computationally as input–output mapping combinations (e.g., look-up tables or operational surfaces/subspaces in phase space). Nonparametric models are easy to postulate (because of their generality) but typically lack parsimony of representation. Of the various nonparametric approaches, the discrete-time Volterra–Wiener (kernel) formulation has been used most extensively for nonlinear modeling of physiological systems and will form the mathematical foundation of this book, along with its relations to the other modeling approaches.

In the *parametric* approach, algebraic or differential/difference equation models are typically used to represent the input–output relation for static or dynamic systems, respectively. These models typically contain a small number of unknown parameters that may be constant or time-varying depending on whether the model is stationary or nonstationary. The specific form of these parametric models is usually postulated *a priori* but the selection of certain structural parameters (e.g., degree/order of equation) are guided by the data.

The *modular* approach is a hybrid between the parametric and the nonparametric approaches that makes use of *block-structured* models composed of parametric and/or nonparametric components properly connected to represent the input–output relation in a manner that reflects our evolving understanding of the functional organization of the system. The model specification task for this class of models is more demanding and may utilize previous parametric and/or nonparametric modeling results. A promising variant of this approach, which derives from the general Volterra–Wiener formulation, employs *principal dynamic modes* as a minimum set of filters to represent parsimoniously a nonlinear dynamic system of the broad Volterra class (see Section 4.1.1).

The *connectionist* approach has recently acquired considerable popularity and makes use of generic model configurations/architectures known as *artificial neural networks* to represent input–output nonlinear mappings in discrete time. These connectionist models are fully parameterized, making this approach akin to parametric modeling, although typically lacking the parsimony and interpretability of parametric models. A hybrid nonparametric/connectionist approach is at the core of the modeling methodology that is advocated as the best overall option at present.

The relations among these four approaches are of critical practical importance, since considerable benefits may accrue from the combined use of these approaches in a cooperative manner. This synergistic use aims at securing the full gamut of advantages specific to each approach. The relative advantages and disadvantages in practical applications of the four modeling approaches will be discussed in Chapters 2–4.

The ultimate selection of a particular methodology (or combinations thereof) hinges upon the specific characteristics of the application at hand and the prioritization of objectives by the individual investigator. Nonetheless, it is appropriate to state that no single methodology is globally superior to all others (i.e., excelling with regard to all criteria and under all possible circumstances) and much can be gained by the synergistic use of the various modeling approaches in a combination that takes into account the specific characteristics/requirements of each application. Judgment must be exercised in each individual case to select the combination of methods that yields the greatest insight within the given experimental constraints. Since the general nonlinear system identification problem re-

mains a challenge of considerable complexity, one must not be lulled into the risk-prone complacency of blind algorithmic processing. Many challenging issues remain that require vigilant attention, since there is no substitute for intelligence and educated judgment in resolving these issues. Four examples are given below to illustrate the various model forms employed by these approaches in different physiological domains.

Example 1.1. Vertebrate Retina

The early stage of the vertebrate visual system (retina) is chosen as the first illustrative example to honor the historical fact that this was the first physiological system extensively studied with the Volterra–Wiener approach. A schematic of the neuronal architecture of the retina is shown in Figure 1.3. The natural input to the retina is light intensity (photon flux per unit surface) impinging on the photoreceptor cells that convert the photon energy into intracellular potential through a chain of photochemical and biochemical reactions. The generated photoreceptor potential is synaptically transferred to downstream horizontal cells and bipolar cells through triadic synapses in the photoreceptor pedicle. The intracellular potentials thus generated within horizontal and bipolar cells are synaptically transferred to the postsynaptic ganglion cells and to the interneurons of the inner plexiform layer (various types of amacrine cells).

Thus, visual information conveyed by the time variations of light intensity is converted (encoded) into sequences of action potentials by the ganglion cells and transmitted to higher levels of the visual system via the optic nerve. This "encoding" process represents cascaded signal transformations effected by the various retinal neurons and their multiple interconnections. Therefore, one "system of interest" can be defined by considering as input signal the variations of light intensity impinging on the photoreceptors and as output

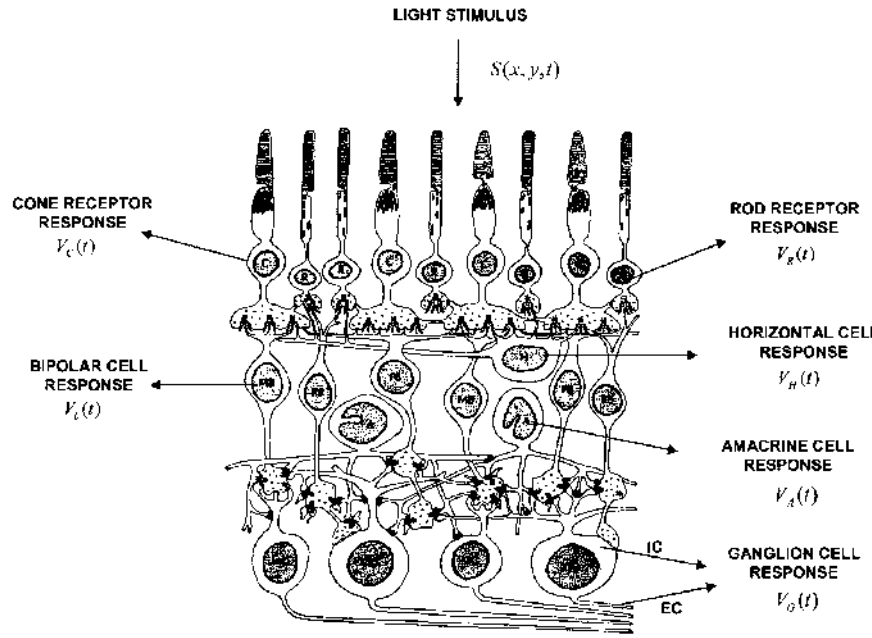


Figure 1.3 Schematic of the neuronal organization of the retina (after Dowling & Boycott, 1966).

signal the resulting sequence of action potentials generated by the ganglion cells. The induced intracellular potential in any other retinal neuron along this cascade of signal transformations can be used as an output signal in order to define a different "system of interest." A block diagram depicting the main neuronal interconnections in the retina is shown in Figure 1.4, suggesting many different possibilities for defining input/output signals and the corresponding "systems of interest."

In the foregoing, we described briefly the temporal sequence of causal effects from input photons impinging on the photoreceptor cell to the output action potentials generated by the ganglion cells. However, it is clear that complicated causal effects also occur in space through the multiple lateral interconnections among retinal neurons and interneurons. Thus, space can be viewed as another independent variable (in addition to time) to define retinal input–output signal transformations. This leads to the advanced spatiotemporal analysis of the visual system discussed in Section 7.4.1. Note that the wavelength of the input photons can be viewed as yet another independent variable in studies of color vision.

The first successful application of the cross-correlation technique of nonparametric modeling (see Section 2.2.3) on visual neuronal pathways using band-limited Gaussian white noise (GWN) test inputs was performed on the catfish retina [Marmarelis & Naka, 1972]. The recorded output signal was the sequence of action potentials generated by a ganglion cell (actually the "probability of firing" measured by superimposing the outputs of repeated trials with the same GWN input, also called the "peristimulus histogram"). The obtained nonparametric model took the form of a discrete-time, second-order Wiener model:

$$y(n) = h_0 + \sum_m h_1(m)x(n-m) + \sum_{m_1}\sum_{m_2} h_2(m_1, m_2)x(n-m_1)x(n-m_2) - P\sum_m h_2(m, m) \quad (1.4)$$

where h_0, h_1, and h_2 denote the discretized Wiener kernels of zeroth, first, and second order, P is the power level of the discretized GWN input $x(n)$ (light intensity), and the sum-

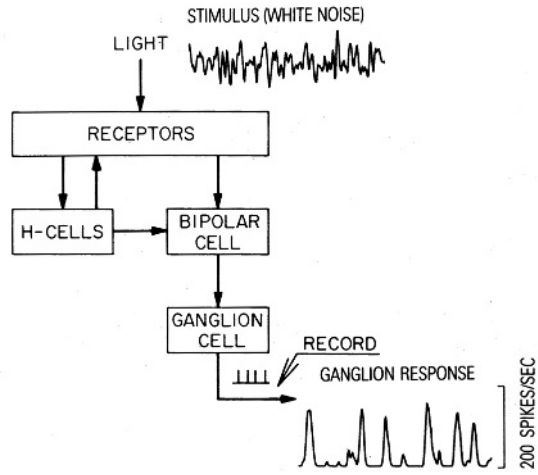


Figure 1.4 A block diagram depicting the main signal-flow pathways in the vertebrate retina and a light stimulus with the resulting ganglion cell response. Other stimulus–response pairs can be chosen experimentally (after Marmarelis & Marmarelis, 1978).

mation over m, m_1, and m_2 covers the entire memory of the system kernels. The discretized output $y(n)$ represents the probability of firing an action potential by a single ganglion cell at discrete-time index n ($t = nT$, where T is the sampling interval).

The first-order and second-order Wiener kernels of the horizontal-to-ganglion neuronal pathway, estimated through the cross-correlation technique, are shown in Figure 1.5. The interpretation of these kernels became a key issue from the very beginning, instigating intensive debates regarding the potential utility of this approach. Many arguments were voiced for and against this approach, some of which remain the fodder of lively debate to date. However, the fact remains that this general nonparametric approach represents a quantum leap of improvement over any other method used heretofore and, although some interpretation issues remain open, it has already elucidated immensely our understanding of retinal function. For instance, it is evident from the waveform of h_1 that the system is encoding both intensity and rate-of-change information (discussed further in Section 6.1.1). It is also evident from the form of h_2 that the system exhibits rectifying nonlinearities, consistent with the presence of a threshold for the generation of action potentials (see the contribution of h_2 to the model prediction in Figure 1.6). The validation for this model is provided by its ability to predict the output signal to any given input signal, as demonstrated in Figure 1.6.

Many other "systems of interest" have been defined in the retina by considering the outputs of other retinal neurons (e.g., horizontal, bipolar, amacrine) and/or other inputs (e.g., light intensity, current injected into various cells, or light stimuli of different wavelengths). Extensive modeling studies have been reported for these systems by Naka and his associates following the nonparametric approach (see Section 6.1.1).

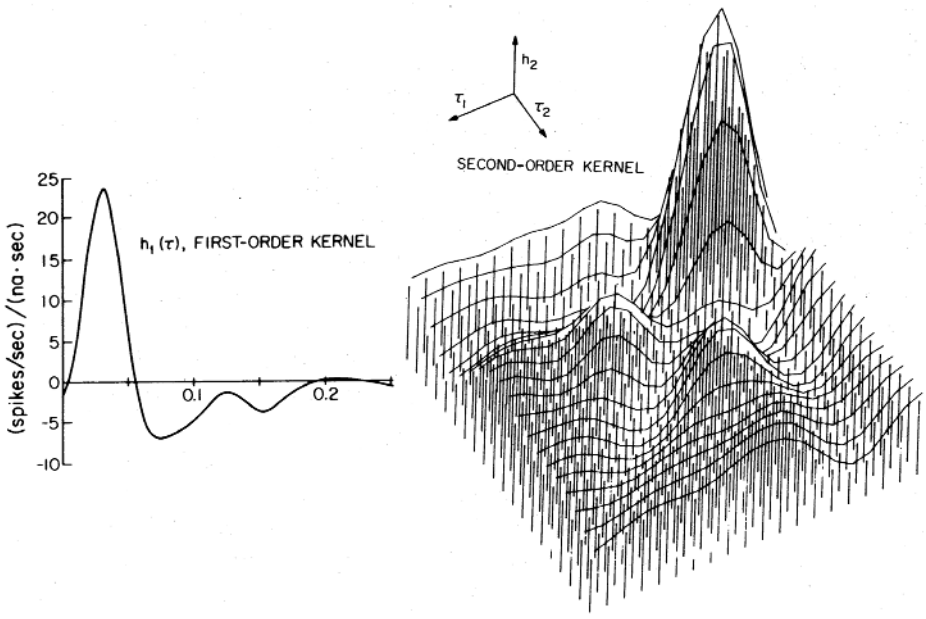


Figure 1.5 The first- and second-order Wiener kernel estimates of the horizontal-to-ganglion cell system in the catfish retina, obtained via the cross-correlation technique using band-limited GWN stimuli of current injected into the horizontal cell layer (after Marmarelis & Naka, 1972).

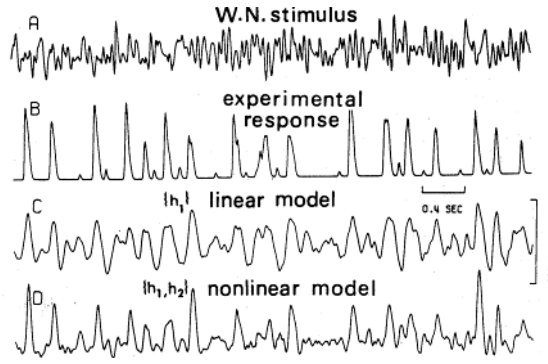


Figure 1.6 The recorded experimental response of the ganglion cell (second trace) represented as "frequency of firing" (or peristimulus histogram) for repeated trials of the band-limited GWN current stimulus shown in the top trace. The predictions of the linear (i.e., first-order) model and of the nonlinear (i.e., second-order) model using the Wiener kernels of Figure 1.5 are shown in the third and fourth traces, respectively (after Marmarelis & Naka, 1972).

Example 1.2. Invertebrate Photoreceptor

As a second illustrative example, we consider the modular (block-structured) model derived for the photoreceptor of the fly eye (retinula cells 1–6 in an ommatidium of the composite eye of the fly *Calliphora erythrocephala*) using CSRS quasiwhite stimuli under light-adapted conditions [Marmarelis & McCann, 1977]. We have found that the input–output relation of this system can be described by means of a modular model comprised of the cascade of a linear filter L followed by a quadratic static nonlinearity N (see Figure 1.7). If the impulse response function of the filter L is denoted by $g(m)$ and the static nonlinearity N is the quadratic function: $y = c_1 v + c_2 v^2$, then the equivalent discrete-time nonparametric model takes the form of a discrete Volterra model similar to the Wiener model of Equation (1.4), except for the first and last terms of the right-hand side, which become zero in the Volterra model (see Section 2.2.1). The first- and second-order discrete Volterra kernels of this model (all other kernels are zero) are given by the expressions

$$\tilde{k}_1(m) = c_1 g(m)\tilde{u}(m) \tag{1.5}$$

$$\tilde{k}_2(m_1, m_2) = c_2 g(m_1)g(m_2)\tilde{u}(m_1)\tilde{u}(m_2) \tag{1.6}$$

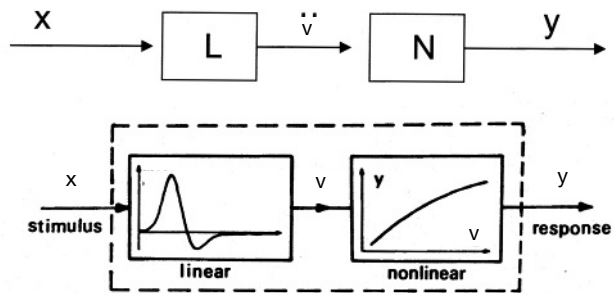


Figure 1.7 The *L–N* cascade model (a linear filter *L* followed by a static nonlinearity *N*) obtained for the photoreceptor of the fly *Calliphora erythrocephala* (after Marmarelis & McCann, 1977).

where $\tilde{u}(m)$ denotes the discrete step function (zero for $m < 0$ and 1 for $m \geq 0$) manifesting the causality of the model, and $g(m)$ is shown in Figure 1.7 (for the proof, see Section 4.1.2).

We can obtain the equivalent parametric discrete-time model through "parametric realization" of $g(m)$ (see Section 3.4), given by the two equations

$$v(n) = \alpha_1 v(n-1) + \ldots + \alpha_K v(n-K) + \beta x(n) \tag{1.7}$$

$$y(n) = c_1 v(n) + c_2 v^2(n) \tag{1.8}$$

where the linear difference equation (1.7) describes the linear filter L (for properly chosen order K) and the algebraic equation (1.8) describes the static nonlinearity N. It is evident that if we seek to substitute v in terms of y in Equation (1.7) by solving Equation (1.8) with respect to v, we arrive at an irrational expression in terms of y (i.e., this system cannot be represented by a single rational nonlinear difference equation). In control engineering terminology, Equation (1.7) can be viewed as a "state equation" and Equation (1.8) as the "output equation." This parametric model is also isomorphic to the L–N modular model in this case.

The equivalent connectionist model for this system requires an infinite number of hidden units if the conventional sigmoidal activation functions are used (see Section 4.2.1). However, the use of polynomial activation functions allows for an equivalent connectionist model with a single hidden unit, as discussed in Section 4.2.1.

Example 1.3. Volterra Analysis of Riccati Equation
The third example is chosen to be a parametric model of a nonlinear differential system described by the well-studied Riccati equation:

$$\frac{dy}{dt} + ay + by^2 = cx \tag{1.9}$$

where $x(t)$ is viewed as the input and $y(t)$ as the output of the system. This model exhibits a squared-output nonlinearity and can be also written as

$$L(D)y = cx - by^2 \tag{1.10}$$

where $L(D)$ represents the differential operator $D + a$, with D denoting differentiation over time. The form of Equation (1.10) implies that this model can be also viewed as a nonlinear feedback model with a linear feedforward component $cL^{-1}(D)$ and a static nonlinear (square) negative feedback, as shown in Figure 1.8. This negative feedback formulation represents a modular (block-structured) model, equivalent to the parametric model of Equation (1.9). In Figure 1.8, we also show an equivalent "circuit model," since this type of equivalent model form has been used extensively in physiology for parametric models described by differential equations. We consider the equivalent circuit model as another form of a parametric model (since it can be directly converted into a system of differential equations, and vice versa).

The equivalent nonparametric model for the Riccati equation is derived in Section 3.2 and corresponds to an infinite-order Volterra series. However, if we assume that $|b|$ is very small, then the higher-order Volterra functional terms (higher than second order) can

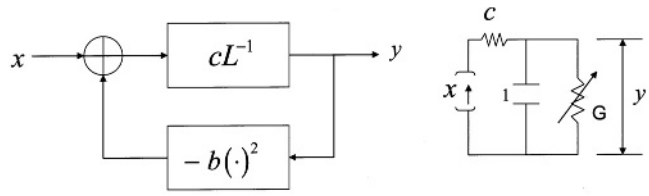


Figure 1.8 Equivalent modular (block-structured) model for the parametric model defined by the Riccati equation (1.9), depicting linear dynamic feedforward and nonlinear static feedback components (left panel). The equivalent "circuit model" (right panel) has a current source x flowing through a fixed conductance c, and the output is represented by the voltage y applied to a unit capacitance and a voltage-dependent conductance: $G = a + by$.

be neglected and the equivalent nonparametric Volterra model becomes approximately of second order, expressed in continuous time as

$$y(t) \cong k_0 + \int_0^\infty k_1(\tau)x(t-\tau)d\tau + \int_0^\infty \int k_2(\tau_1, \tau_2)x(t-\tau_1)x(t-\tau_2)d\tau_1 d\tau_2 \qquad (1.11)$$

where $x(t)$ and $y(t)$ denote the input and output signals, respectively, and the Volterra kernels are given by the expressions

$$k_0 = 0 \qquad (1.12)$$

$$k_1(\tau) = ce^{-a\tau}u(\tau) \qquad (1.13)$$

$$k_2(\tau_1, \tau_2) = -\frac{bc^2}{a}\, e^{-a(\tau_1+\tau_2)}[1 - e^{a\,\cdot\,\min(\tau_1,\tau_2)}]u(\tau_1)u(\tau_2) \qquad (1.14)$$

where $u(\tau)$ denotes the continuous-time step function (0 for $\tau < 0$, 1 for $\tau \geq 0$). Note that the Volterra kernels depend on the Riccati parameters (as expected), but terms of order b^2 or higher have been neglected. In practice, these Volterra kernels are estimated from sampled input–output data (i.e., discretized signals) and they yield a discrete-time Volterra model. An equivalent continuous-time model can be obtained subsequently (if needed) by means of the "kernel invariance method" presented in Section 3.5.

The discrete-time Volterra kernels of first order and second order can be obtain by discretization of their continuous-time counterparts of Equations (1.13) and (1.14):

$$\tilde{k}_1(m) = \gamma\alpha^m\tilde{u}(m) \qquad (1.15)$$

$$\tilde{k}_2(m_1, m_2) = \frac{\beta\gamma^2}{\ln\alpha}\alpha^{m_1+m_2}[1 - \alpha^{-\min(m_1,m_2)}]\tilde{u}(m_1)\tilde{u}(m_2) \qquad (1.16)$$

where the discrete-time parameters (α, β, γ) of the equivalent discrete-time parametric model that takes the form of a first-order nonlinear difference equation,

$$\tilde{y}(n) + \alpha\tilde{y}(n-1) + \beta\tilde{y}(n-1)^2 = \gamma\tilde{x}(n) \qquad (1.17)$$

are distinct from the continuous-time parameters (a, b, c) and expressed in terms of the continuous parameters of the Riccati equation as $\alpha = \exp[-aT]$, $\beta = bT$, $\gamma = cT$, where T is the sampling interval.

The mathematical analysis of the equivalence between nonlinear differential and difference equation models is based on the "kernel invariance method" presented in Section 3.5. We note that the nonparametric model is not as compact as its parametric counterpart. On the other hand, the model specification task is greatly simplified in the nonparametric approach, and the estimation of the kernels of the nonparametric model can be accomplished by various methods using input–output data, as described in Chapter 2.

Example 1.4. Glucose–Insulin Minimal Model

The fourth example is drawn from the metabolic/endocrine system and concerns the extensively studied dynamic interrelationship between blood glucose and insulin. The widely accepted "minimal model," used in connection with glucose tolerance tests, is a good example of a parametric model for this nonlinear dynamic interrelationship [Bergman et al., 1981; Carson et al., 1983; Cobelli & Mari, 1983]. This model is comprised of the following two first-order differential equations:

$$\frac{dG(t)}{dt} = -p_1[G(t) - G_b] - X(t)G(t) \tag{1.18}$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3[I(t) - I_b] \tag{1.19}$$

where $G(t)$ is the glucose plasma concentration (in *mg/dl*), $X(t)$ is the insulin action (in min^{-1}), $I(t)$ is the insulin plasma concentration (in μU/ml), G_b is the basal glucose plasma concentration (in mg/dl), I_b is the basal insulin plasma concentration (in μU/ml), p_1 and p_2 are two characteristic parameters describing the kinetics of glucose and insulin action, respectively, (in min^{-1}), and p_3 (in min^{-2} ml/μU) is a parameter determining the modulatory influence of insulin action on glucose uptake dynamics. It should be noted that this model does not take into consideration the pancreatic secretion of insulin induced by changes in glucose plasma concentration or the production of new glucose from internal organs (e.g., liver in response to elevation of plasma insulin), which can be described by separate differential equations (although this is far from a trivial task). The physiological parameters of glucose effectiveness $S_G = p_1$ (in min^{-1}) and insulin sensitivity $S_I = p_3/p_2$ (in *ml* min^{-1}/μU) have been defined and used extensively in the literature for physiological/clinical purposes.

The above system is nonlinear, due to the bilinear term present in Equation (1.18), which gives rise to an equivalent nonparametric Volterra model of infinite order. However, it can be shown that, for the physiological range of the parameter values, a second-order Volterra model approximation is adequate for all practical purposes. Considering the variations of $I(t)$ around I_b as the input of the system and $G(t)$ as the output, we can derive the Volterra kernels of the system analytically using the generalized harmonic balance method (see Section 3.2). The resulting expressions for the zeroth-, first-, and second-order kernels are (in first approximation, for $p_3 \ll p_1$):

$$k_0 = G_b \tag{1.20}$$

$$k_1(\tau) = -p_3 G_b h(\tau) \tag{1.21}$$

$$k_2(\tau_1, \tau_2) = \frac{G_b p_3^2}{2}\left\{h(\tau_1)h(\tau_2) + p_1 \int_0^{\min(\tau_1, \tau_2)} \exp(-p_1\lambda)h(\tau_1 - \lambda)h(\tau_2 - \lambda)d\lambda\right\} \tag{1.22}$$

where

$$h(\tau) = \frac{1}{p_2 - p_1}[\exp(-p_1\tau) - \exp(-p_2\tau)] \tag{1.23}$$

The rth-order Volterra kernel is proportional to p_3^r and can be neglected if $|p_3|$ is very small. Many other parametric models have been proposed for this system, typically comprising a larger number of "compartments" [Cobelli & Pacini, 1988; Vicini et al., 1999]. The equivalent first- and second-order Volterra kernels of the "minimal model" are shown in Figure 1.9 for typical parameters: $p_1 = 0.023$, $p_2 = 0.033$, $p_3 = 1.783 \cdot 10^{-5}$, and $G_b = 80.25$. An equivalent modular model is shown in Figure 1.10, utilizing two linear filters, a multiplier, an adder, and a feedback pathway. This modular (block-structured) model depicts the fact that the minimum model can be viewed as expressing a nonlinear (modulatory) control mechanism implemented by the feedback pathway into the multiplier.

Example 1.5. Cerebral Autoregulation

The fifth example is drawn from the cardiovascular system and concerns cerebral autoregulation. This is a challenging example of a physiological system with multiple closed (nested) loops that involve biomechanical, neural, endocrine and metabolic mechanisms interacting with each other. A simplified schematic of the protagonists in cerebral autoregulation is shown in Figure 1.11. A modular model obtained from real data is shown in Figure 1.12, depicting three parallel branches that correspond to the "principal dynamic modes" of this system (see Section 4.1.1). This modular model was obtained via

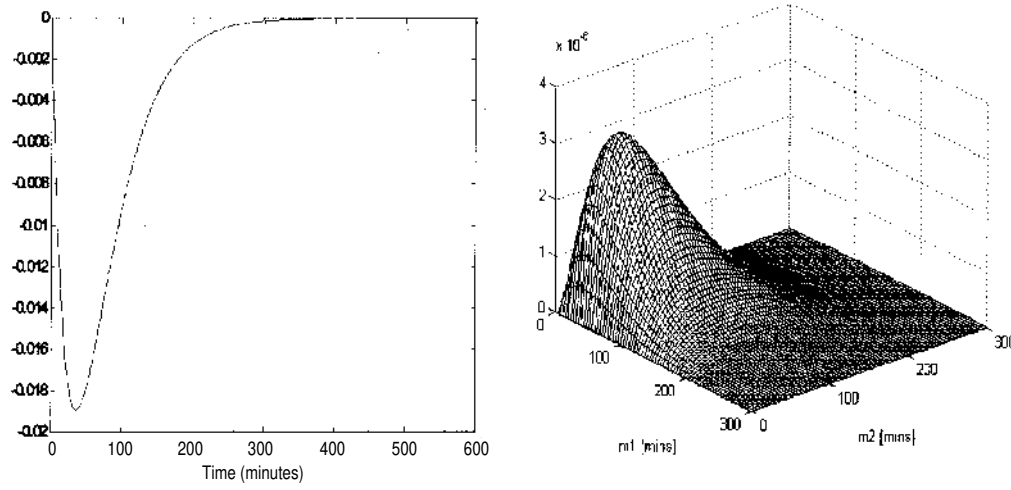


Figure 1.9 The equivalent first- and second-order Volterra kernels given by the Equations (1.21) and (1.22) for the insulin–glucose "minimal" model defined by Equations (1.18)–(1.19).

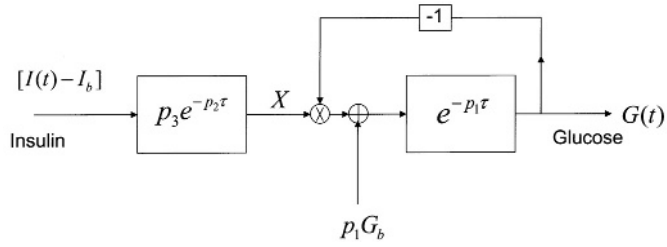


Figure 1.10 Equivalent modular (block-structured) model for insulin–glucose minimal model, utilizing two linear filters with impulse response functions: $p_3 \exp(-p_2\tau)$ and $\exp(-p_1\tau)$, an adder, and a multiplier for negative multiplicative (modulatory) feedback (p_1G_b is a fixed-reference level defined by the basal glucose value).

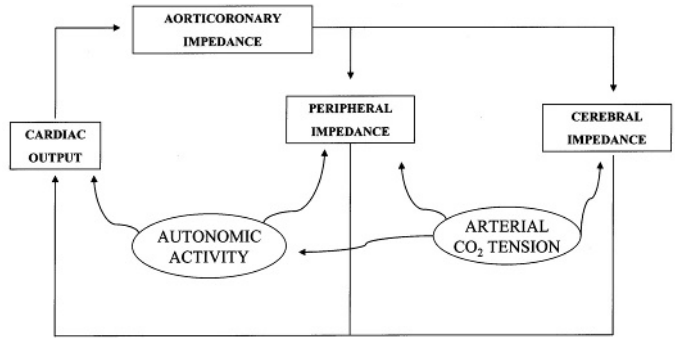


Figure 1.11 Schematic of the main protagonists in cerebral flow autoregulation.

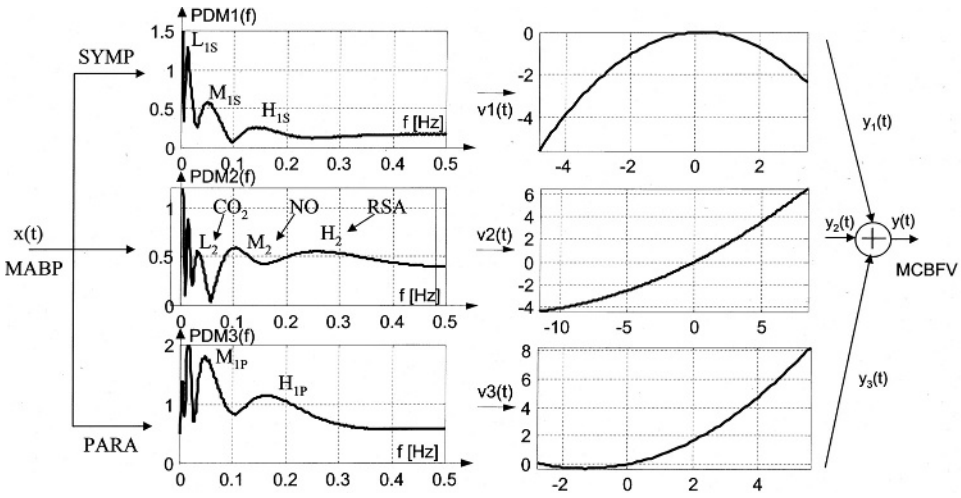


Figure 1.12 Modular model of cerebral flow autoregulation in a normal human subject, using the advocated methodology that starts with the general Volterra model and derives an equivalent "principal dynamic mode" model of lower complexity. Each of the three branches is composed of a linear filter (a "principal dynamic mode" of the system) followed by a static nonlinearity. The model was obtained from 6 min long data of mean arterial blood pressure (input) and mean cerebral blood flow velocity (output) sampled every 1 sec (for details, see Section 6.2).

the Laguerre–Volterra network approach presented in Section 4.3, using mean arterial blood pressure data as input and mean cerebral blood flow velocity data as output. The model reveals the presence of (at least) three nonlinear dynamic mechanisms of cerebral autoregulation (see Section 6.2). Equivalent parametric, connectionist, and nonparametric models can be obtained from this modular model (see Chapter 4).

The many technical details surrounding the derivation of these equivalent model forms are discussed in Chapters 2–4, along with the corresponding estimation methods and their relative performance characteristics. Important practical considerations for the successful application of these modeling methodologies and the required preliminary testing and error analysis in actual modeling applications are given in Chapter 5.

1.5 DEDUCTIVE AND INDUCTIVE MODELING

The hypothesis-driven approach to scientific research offers a time-honored *deductive* path to scientific discovery that has been proven effective in the development of the physical sciences, closely associated with the reductionist viewpoint (i.e., proceeding deductively from first principles). However, this traditional approach encounters difficulties as the complexity of the problem under study increases, making the effective use of first principles unwieldy. This fact has given rise to a complementary approach that follows an *inductive* method based on the available data. In the inductive (data-driven) approach, priority is given to the data and the research effort is directed toward developing rigorous and robust mathematical and computational methods that extract the relevant information (models in our case) in a general context. This general context minimizes the *a priori* assumptions made about the system under study and, therefore, avoids possible "biasing" of the results by preconceived (and possibly restrictive) notions of the individual investigator. To the extent that "unbiased knowledge" is acquired by this data-true inductive process, it can be incorporated in subsequent hypothesis-driven research to answer specific questions of interest and ultimately derive "general laws" that can be used deductively to advance scientific knowledge.

A synergistic approach is advocated in this book that commences with inductive (data-driven) modeling, following the methodologies presented in this book, and then formulates specific hypotheses that can be tested to unambiguously answer specific scientific questions of interest. In this manner, we secure the advantages of both approaches (inductive and deductive) and avoid their mutual shortcomings. In addition, this synergistic approach is time-efficient and cost-effective, because the inductive method places us quickly in the "neighborhood" of the correct model that can be further elaborated with regard to specific scientific questions of interest by use of hypothesis-driven research. The specific hypotheses depend, of course, on the goals of the study and, therefore, cannot be prescribed beforehand, other than to indicate that they will be structured in a manner compatible with the available models.

Examples of the advocated synergistic approach are given in Chapter 6, where specific parametric or modular (block-structured) models are examined along with the previously obtained (data-true) nonparametric models in order to answer specific scientific questions and assist in the interpretation of the models. Another class of examples pertains to the effects caused by the experimental change of a key controlling variable and the assessment of the resulting quantitative changes in the model characteristics (e.g., effect of various drugs on cardiovascular, neural, or metabolic function).

The advocated synergistic approach is appropriate for complex systems (because it obviates the need for vast reductionist/hierarchical structures) and protects the investigator from possible misleading results (when the assumptions made are restrictive or the testing conditions are not "natural"). It is hard to imagine a "downside" to this synergistic approach. In the worst case, when it is not necessary because the investigator is able to construct "perfect" hypothesis-driven tests, then we get definitive validation of the hypothesis-based results—hardly a useless outcome. In all other cases, where existing reductionist knowledge and subjective intuition are either limited or yield unwieldy model postulates, the initial use of the data-driven approach can protect from potentially misleading results and can accelerate the pace of progress by placing us in the "neighborhood" of the correct answer. Further refinements/elaborations using the hypothesis-driven approach are subsequently possible and desirable.

One may wonder, then, why the advocated data-driven approach has not been used more extensively. The answer is that appropriate methodologies capable of tackling the *true complexity* of the problem (i.e., nonlinear, dynamic, nonstationary, multivariate, nested-loop) have not been available heretofore. Lack of such methodologies forces investigators to use inadequate (restrictive) methods that are often unable to achieve the intended goals (i.e., the results are "biased" and often obtained under restrictive experimental conditions that do not place us in the "neighborhood" of the correct answer). As a result, the data-driven approach has not yet "proven" itself for lack of appropriate practicable methodologies, and investigators have seen no compelling reason yet to depart from the traditional hypothesis-driven approach. The overall goal of this book is to make available such appropriate methodologies to the biomedical research community at large to help usher in a new era of advanced research on the *true* physiological systems—and help the peer community avoid unrealistic simplifications, born of perceived necessity, that may breed misconceptions and perpetuate a state of studious confusion.

It is useful to remind the reader that the long debate between the reductionist and the integrative viewpoints (originating with Hippocrates in the 5th century B.C. and lasting with undiminished intensity until the present time) is intertwined with the issue of hypothesis-driven research. The latter fosters a tendency toward fragmentation and static inquiry in a legitimized effort to construct and test clear and comprehensible hypotheses. This approach has borne considerable benefits but also has placed serious limitations on those cases in which multipart dynamic interactions are of critical importance. For instance, when Erasistratus and the Anatomists were generating a wealth of anatomic knowledge in Alexandria in the 3rd century B.C., they were inadvertently diverting medical thought away from the fundamental Hippocratic concepts of the unity of organism and the dynamic disease process. This fact should not detract from the indisputable contributions of the Anatomists to medical science but should serve as a constructive reminder of the balance required in pursuing scientific research. Advancing knowledge is a multifaceted endeavor and requires a multiprong approach.

This point is not a mere historical curiosity, because a similar debate is taking place in our times (only on a much larger scale) between the reductionist approach espoused by molecular biology and the integrative approach advocated by systems biology/physiology. Nor is this debate an idle intellectual exercise, since it affects critically the direction of future research efforts. Although the integrative approach may follow either hypothesis-driven or data-driven methods, this book argues for a synergistic approach that gives priority to the data-driven methods in order to avoid self-entrapment within the comfortable confines of established viewpoints. A synergistic approach is also sensible in order to

combine the benefits of the reductionist and integrative viewpoints. Although the desirability of this combination is self-evident, the historical record shows that even the best human minds have a tendency toward polarized binary thinking. The reasons for this tendency toward "binary thinking" are beyond the scope of this book, but certainly the root causes must be searched for in the psychophilosophical plexus of the human mind. The reader is urged to contemplate a way out of this "failing of the human mind" by taking into consideration the Galenic philosophical exhortations (see Historical Note #1 below).

HISTORICAL NOTE #1: HIPPOCRATIC AND GALENIC VIEWS OF INTEGRATIVE PHYSIOLOGY*

Hippocrates is considered the founder of the medical profession, since he was the first to separate medicine from priestcraft and give it the independent status of a scientific discipline in Greece in the 5th century B.C. He was affiliated with the Asclepeion of Cos (a Greek island in the southeast Aegean) but also lived and worked in post-Periclean Athens. By providing a rational basis for medical practice and emphasizing the importance of clinical observation, Hippocrates did to medical thought what his contemporary, Socrates, did to thought in general: separated it from cosmological speculation. He gave the physician an independent status but held him to a high professional standard embodied in the "Hippocratic oath" that still defines the elevated duties of physicians worldwide.

Hippocrates observed that the human organism responds to external stresses/assaults (including disease) in a homeostatic manner (recuperation, in the case of disease); that is, the living organism possesses self-preserving powers and tends to maintain stable operation through complicated intrinsic mechanisms. He observed that each disease tends to follow a specific course through time and, therefore, it is a dynamic process (as opposed to a static state, which was the prevailing view at the time). Consequently, he emphasized *prognosis* over *diagnosis* and believed in the recuperative powers of the living organism. He advocated "giving nature a chance" to effect over time the adjustments that will cure the disease and restore health in most cases.

This broadly defined homeostatic view led Hippocrates to the notion of the "unity of organism" that underpins integrative systems physiology to the present day. This integrative view tended to overlook the importance of the constituent parts and set him apart from the "reductionist" viewpoint espoused by the Anatomists of Alexandria. The labors of the latter in the 3rd century B.C. (especially Erasistratus) made outstanding contributions to medicine and gave rise to the sect of the Empiricists, who proclaimed their concern with "the cure, and not the cause, of disease."

The reductionist viewpoint promulgated by the Empiricists was reinforced by the atomic theory of Leucippus and Democritus, as adapted to medicine by Asclepiades (1st century B.C.), who introduced Greek medicine to Rome. A man of forceful personality and broad education, Asclepiades combined flamboyance with sharp intellect to achieve professional success and promote the view that physiological processes depend upon the particular way in which the indivisible particles of atomic theory come together. Although the validity of this fundamental view is indisputable (and self-evident), it did not lead to any constructive proposition for medical practice but served only as a public-rela-

*Following A. J. Brock's introductory comments in his translation of Galen's "On the Natural Faculties," Harvard University Press, 1979 (first printed in 1916).

tions vehicle for self-promotion in the intellectually shallow and "faddish prone" society of 1st-century Rome—a phenomenon that is frequently recurring in history and all too familiar in our times as well. In fact, it can be argued that the disbelief of Asclepiades in the self-maintaining powers of the living organism and the intrinsic obstructionism of his maximalist approach caused a serious regression in the progress of medicine at that time. His views gave rise to the "Methodists" (founded by his pupil Themison), who espoused the simplistic pathological theory that all diseases belonged to two classes: one caused by constricted and the other by dilated pores traversing the molecular groups that compose all tissues. Another dubious trait established by the Methodists (and still prevalent to present time) is the tendency to invent a label for a perceived "disease" and then "treat the label" with no regard to the actual physiological processes that underpin the perceived disease.

The Empiricists and the Methodists were dominating Graeco-Roman medicine when Galen was born (circa 131 A.D.) as Claudius Galenos in Pergamos (a major Greek cultural center in Asia Minor during the Roman period). Galen, or more appropriately, Galenos ($\Gamma\alpha\lambda\eta\nu o\varsigma$, meaning "tranquil" in Greek) had a benevolent and well-educated father, Nicon, who was a distinguished architect, mathematician, and philosopher. Galenos received an eclectic liberal education and studied the four main philosophical systems: Platonic, Aristotelian, Stoic, and Epicurean. He pursued medical studies under the best teachers in Pergamos and afterward in the other Hellenic centers of medical studies: Smyrna, Corinth, and Alexandria. At the age of 27, he returned to Pergamos and was appointed surgeon to the gladiators. Four years later, driven by professional ambition, he went to Rome, where he quickly achieved high distinction, rising to the coveted position of physician to the emperor Marcus Aurelius. Despite his broad acceptance and popularity, Galenos made no effort to conceal his contempt for the ignorance and charlatanism of most physicians in Rome. His courageous stand against corrupt medical practice, combined with professional envy, earned him many enemies in the medical circles of Rome, who conspired against his life. To save his life, he fled Rome secretly at the age of 37 and retuned to his old home in Pergamos, where he settled down to a literary life of philosophical contemplation and medical research. Even an imperial mandate a year later was not able to summon him back to Italy. Galenos pleaded vigorously to be excused and the emperor eventually consented, while trusting to his care the young prince Commodus. During the remaining 30 years of his life, Galenos wrote extensively on physiology, anatomy, and logic, providing the foundation for medieval medicine as the supreme authority (he was called the "Medical Pope of the Middle Ages") until Vesalius and Harvey disproved some of Galenos' basic cardiovascular premises with their seminal experiments and laid the foundation of modern anatomy and physiology, respectively, in the 16th and 17th centuries A.D.

In the six centuries that elapsed between Hippocrates and Galenos, the big debate in medicine revolved around the interrelated issues of the integrative versus reductionist viewpoints of physiology (Hippocrates' view of the unity of organism vs. the Atomists' view of decomposition into indivisible particles) and the dynamic versus static views of disease (Hippocrates' view of disease as a process vs. the anatomical view of the Empiricists). Galenos managed to put this debate to rest for 14 centuries by convincingly making the Hippocratic case. He reestablished the Hippocratic ideas of the unity of the organism, the dynamic interdependence of its parts, and its interaction with the environment (homeostasis). This constitutes the common conceptual foundation with our contemporary view of *integrative systems physiology* in a dynamic and homeostatic context that is espoused

by this book. *The living system can only be understood as a dynamic whole* and not by static isolation of its component parts.

This fundamental principle is in direct opposition to the widespread view (even in our own times) that the whole can be understood by careful summation of the elaborated parts (reductionist viewpoint). The key difference concerns the emerging physiological properties from the dynamic interactions of the component parts and the interaction of the whole living system with its environment. In this, we stand today with Hippocrates and Galenos in uncompromising solidarity.

Galenos was not only a man of great intellect but also possessed a strong moral constitution. In his book "That the best Physician is also a Philosopher," he stipulated that a physician should have perfect self-control, should live laborious days, and should be disinterested in money and the weak pleasures of the senses. Clearly, he would be a "hard sell" today. He calls on the physicians to be versed in: (a) *logic,* the science of how to think; (b) *physics,* the science of what is nature; and (c) *ethics,* the science of what to do. We must always remain aware of his concerns that medicine should not be allowed to fall into the hands of competing specialists without any organizing scientific, philosophical, and moral principles. His recorded thoughts remain an inspiration forever and guide the constant evolution of medical science and practice.