Analysis of Physiological Systems

The White-Noise Approach

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Preface

In studying physiological systems bioscientists are continually faced with the problem of providing descriptions of cause–effect relationships. This task is usually carried out through the performance of stimulus–response experiments. In the past, the design of such experiments has been ad hoc, incomplete, and certainly inefficient. Worse yet, bioscientists have failed to take advantage of advances in fields directly related to their problems (specifically, advances in the area of systems analysis). The raison d'être of this book is to rectify this deficiency by providing the physiologist with methodological tools that will be useful to him or her in everyday laboratory encounters with physiological systems.

The book was written so that it would be practical, useful, and up-to-date. With this in mind, parts of it give step-by-step descriptions of systematic procedures to be followed in the laboratory. It is hoped that this will increase the usefulness of the book to the average research physiologist and, perhaps, reduce the need for in-depth knowledge of some of the associated mathematics. Even though the material deals with state-of-the-art techniques in systems and signal analysis, the mathematical level has been kept low so as to be comprehensible to the average physiologist with no extensive training in mathematics. To this end, mathematical rigor is often sacrificed readily to intuitive simple arguments.

The main theme treated is the use of white-noise signals in identifying physiological systems. The reason for this emphasis is the plethora of advantages that these signals provide. However, other, more traditional methods are also covered—sine wave analysis, describing functions, etc. In general, the state of the art in system identification is adapted to the idiosyncrasies of physiological systems in a way that should be very useful to graduate students and researchers grappling with physiological systems. The book could also be used as a graduate-level textbook for courses in systems physiology, bioengineering, and biosignal analysis.

Chapter 1 discusses the problem of systems analysis in physiology, including the various philosophical as well as analytical approaches to it.

Chapter 2 discusses issues related to the analysis of physiological signals. Thus, it forms the background necessary for the developments in the following chapters. Both the time-domain and frequency-domain descriptions are covered, with emphasis on the statistical approach.

Chapter 3 covers the traditional approaches to system identification in physiology: gain and phase measurements, describing functions, spectral analysis, and feedback systems.

Chapter 4 introduces the Volterra–Wiener theory and related methodology. It also includes an exposition on the interpretation of Wiener kernels, the extension of the theory to multi-input systems, and a comparative discussion of other approaches.

Chapter 5 presents certain practical variants of the white-noise method (quasiwhite test signals) and their applicability. It also presents various methods of designing noise generators for use in experiments and the tests necessary to assess their suitability for system identification.

Chapter 6 discusses various computational approaches to the efficient estimation of the system kernels. Both time-domain and frequency-domain (fast Fourier transform) computer techniques are presented.

Chapter 7 discusses the various sources of error inherent in the identification process and how they may be minimized. These include effects of record length, system noise, bandwidth, system nonlinearity, etc.

Chapter 8 discusses the preliminary tests and considerations prior to the execution of the identification experiment, e.g., system stationarity, response drift removal, system memory, etc.

Chapter 9 concerns itself with the synthesis problem, i.e., how to identify interconnections between linear and nonlinear subsystems, e.g., cascade, feedback, etc.

Chapter 10 presents several applications of the white-noise method to physiological systems. These include the catfish retina, the fly visual system, the semicircular canal of the guitarfish, the abdominal ganglion of the seahare, and the lobster cardiac ganglion.

Chapter 11 covers various classes of physiological systems that require special treatment, e.g., neural systems with point process (action potentials) inputs and outputs, nonstationary systems, systems with spatiotemporal inputs, etc.

The final chapter is an exposition in dialogue form on specific aspects of the identification process. These points have often been a matter of lively discussion between us and our colleagues.

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The Problem of System Identification in Physiology

> Words ought to be a little wild
> for they are the assault of
> thoughts on the unthinking.
>
> *John Maynard Keynes*

Introduction

Even though the epistemology of the life sciences has a distinctly hierarchical organization—extending from the subcellular level to the behavioral—the main thrust of research up to now has focused on each particular level of this organization, e.g., at the molecular, cellular, or behavioral level. The relationships and interdependences between the various levels have been relatively neglected. This latter endeavor belongs to the realm of systems analysis. In addition, a great part of the methodology employed within each particular level (and being equally applicable to all of them) belongs to systems analysis. Thus, systems analysis, as a methodological tool, has both a "vertical" and a "horizontal" component in the hierarchy of physiological systems.

The decade of the sixties saw massive application of engineering, mathematical, and computer techniques to problems in the life sciences; however, the significant results produced were far below expectations, given the magnitude of this effort. Accordingly, the early seventies justifiably witnessed a developing skepticism as to the usefulness of this large-scale invasion of the methodology of the physical sciences into biology and medicine. In spite, however, of any sins of overenthusiasm committed during the sixties, the inescapable conclusion was reached—and emphasized—that living systems, including the human body, are such complex collections of dynamically interacting components that their efficient study could not be accomplished in piecemeal fashion, but required their treatment as an organic whole; this necessitated the employment of sophisticated systems analysis techniques.

1.1. The Problem of Systems Analysis in Physiology

In talking about physiological systems we will employ repeatedly the concepts of *system, element,* and *signal.*

A *system* is a set of connected and interacting "elements," conceived as a whole, and intended to achieve a certain objective. For example, the retina, at a certain level of approach, can be conceived as a set of connected and interacting neurons whose objective is to translate light patterns cast onto it into the matrix of ganglion responses that are sent to the brain.

An *element* is a conceptual entity that exhibits some measurable dimensions. The mathematical representation of such a measure is realized through a "variable." Continuing on the same example as before, a neuron is an element and its electrical activity is the variable.

A *signal* is the mathematical description of some quantity changing in time, e.g., in the example of the retina, the time history of a neuron potential is a signal. The change in the measurement of an element within a system may proclaim a change in the measure of another element of the system *if and only if* an interconnection exists between these two elements, e.g., the existence of a synaptic (or other) connection between two neurons. In this sense, *interconnection* between two elements of a system can be considered as the "path" that allows the flow of a "physiological change in time," i.e., a signal, from one element to another in the system.

It is evident that a system always has interconnections with elements (or systems) not belonging to itself. The possible signals "flowing" through such "boundary interconnections" are the so-called "inputs" and "outputs" of the system, according to the corresponding *direction of flow of the signal* at each "boundary interconnection": When the "flow" is directed inward to the system the "signal" is called "*input*" (stimulus); if the "flow" is directed outward it is called "*output*" (response).

According to this conceptualization of a system we can represent it as shown in Fig. 1.1. In general, the system will have many inputs (and therefore stimuli) and many outputs (i.e., possible recordable responses) in most cases. From the cause–effect point of view, however, and with regard to describing the transformations (by the system) of the stimuli $x_i(t)$ into the responses $y_i(t)$, we may consider each response separately. That is, we have

$$y_k(t) = F[x_1(t), x_2(t), \ldots, x_n(t)] \tag{1.1}$$

i.e., any of the responses could be a function of (may be due to) all the inputs. Following again the example of the retina mentioned above, the response of the ganglion cell can conceivably be described in terms of all the inputs impinging upon the "retina" (light, temperature, circulatory effects, other neuronal inputs from outside the retina, etc.), and so could all

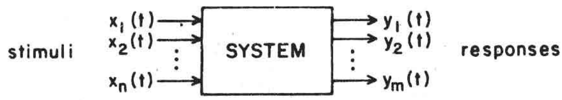

Fig. 1.1. Multi-input–multi-output system.

the other retinal neural responses. Alternatively, we could, of course, describe the ganglion responses in terms of the photoreceptor responses plus all these other inputs. However, the photoreceptor responses can in turn be described in terms of these retinal inputs (light, temperature, etc.); therefore, the ganglion responses are describable solely in terms of these inputs to the "retinal system." This should clarify our conceptualization of a system in terms of Eq. (1.1).

In the study of a system we seek to identify the functional transformation F depicted in Eq. (1.1). Experimentally this entails the measurement of all extrinsic variables (inputs) affecting the system (e.g., in the case of the retina, light, temperature, blood flow, etc.). Clearly, this is infeasible or extremely difficult in practice. Therefore, what is done is to simply ignore most of the inputs and concentrate on the few major ones with respect to their effect on each particular response. The relative effect of the ignored inputs can often be assessed approximately. These "minor" inputs are termed *noise* and are simply ignored in practice.

The first motivation in the study of a physiological system is our concern with the system's "expected" behavior, i.e., response to a known excitation. The justification of such a concern is something that the authors consider self-evident.

For example, in studying the retina the researcher will be concerned with the behavior of the retinal neurons and other retinal elements in such a way that he or she can *predict* their responses under normal or abnormal physiological operation.

The above comments apply quite generally to the analysis of systems. Our concern however is with *physiological* systems and the special problems associated with *their* analysis. Relative to physical and artificial systems, living systems are "great unknowns" to us. We are relatively ignorant of their function, structure, and modes of operations. Part of our problem is due to the fact that, experimentally, we are usually unable to break them up into their fundamental components and study them separately and/or while these are interacting. Thus, we are called upon, from the beginning of our efforts, to understand and describe phenomena that are quite complex. This forces us to take a *phenomenological approach* at the start of the study, which leads us directly and logically to the *functional identification* problem for the system—as posed in the next section. In short, this is the task of describing, as completely as possible, the system response to any given stimulus, i.e., identifying the function of the system in processing physiological signals from its inputs to its outputs. In conclusion, our relative ignorance about the workings of a physiological system is why this task—functional identification—is a first objective in approaching physiological systems through the systems analysis methodology.

The next question concerns the special conditions—experimental and other—that have to be dealt with in carrying out the functional identification task on physiological systems, i.e., the constraints and idiosyncracies of such systems as a set that will be encountered in practice (in experimental situations) during the identification process. This is discussed in the next sections.

1.2. Functional and Structural Identification of Physiological Systems

Bound by both inductive and deductive reasoning in our logic, we approach the study of physiological systems in terms of cause–effect relationships. These relationships are often manifested as stimulus–response relationships, where the stimulus is either applied externally by the experimenter or is simply observed as it occurs naturally during the operation of the physiological system.

Given this conceptualization in terms of stimulus–response relationships, two questions face the researcher immediately. The first is "What does the system do? That is, how does the system respond to various stimuli?" To answer this question in the absence of detailed information about the system's inner structure, we must perform stimulus–response experiments. From the results of these experiments we aim to deduce a complete description of the system, which will allow us to describe its response to each arbitrary stimulus. This task is the so-called *functional identification* of the system.

A natural question, following the functional identification question and a logical sequel to it, is "How does the system do this? That is, how are the various components of the system interconnected and how do they interact so as to produce the observed responses?" Obviously, this question concerns the structure of the system, and we, therefore, term it *structural identification* of the system. In practice, it is usually carried out by performing anatomy, that is, breaking open the "black box" and looking inside at the various components. Another way is to develop the ability to measure new system state variables, i.e., responses from points within the black box. However, this may prove to be a difficult task in practice for certain biological systems, for example, aggregates of neurons.

The system identification objectives, as outlined above, imply, up to a point, a "black box" approach, because they aim at the determination of the transfer characteristics at one approach level and largely ignore issues at underlying levels. For example, in studying a neuron network we would aim at the description of the transformation of incoming spike trains and/or continuous potentials into outgoing spike trains and/or continuous potentials while ignoring to a great extent the underlying physicochemical, molecular transformations. This is not a "limitation," as sometimes is mistakenly thought, but a necessary methodological feature. First, the analysis of a system into its "ultimate" components is a necessary but not a sufficient step for understanding thoroughly its operation and role; it may, in fact, be illusory to think that the smaller the pieces into which a system is dissected the better we will understand it. Second, in practice any investigator selects a certain approach level and deals with variables therein as with elementary quantities, as dictated by practical considerations (experimental observability) as well as conceptual ones. In any case, for any choice of an approach level, there would be an infinite number of more basic ones underlying it; description of the system's functioning at these lower levels may often becloud the issues involved at the higher levels of functioning by simply deflecting attention from these latter ones. Third, and most important, the system identification approach is compatible with our desire (this desire is clearly motivated again by the cause–effect nature of our logic) to explain higher-level functioning through descriptions at lower levels; in fact, it is a natural way to achieve it and the ones employed in practice *anyway*. Let us explain this statement: The system identification approach results in the determination of the system transfer characteristics without specifying its internal topological structure. However, as the experimental ability is developed to measure more "state variables," some heretofore "hidden" in the "black box," the system is broken up into smaller subsystems whose organization reflects more and more closely its topological structure. In spite of current common belief (more accurately, misconception), it should be stressed that no stimulus–response experiment can reveal the "internal structure" of a system without making assumptions about certain alternative configurations; that is, a stimulus–response experiment could conceivably, in certain cases, distinguish between two or more possible structural configurations but usually cannot determine precisely the system structure without *a priori* information about it. The task of *decomposing* a system into smaller component subsystems can be accomplished through the combination (and interplay) of functional identification (through stimulus–response experiments) and structural identification (through histology and anatomy).

To concretize the above general comments, let us consider a specific example, as it would be encountered in experimental research: the study and modeling of the vertebrate retina. The actual model to be described below is not necessarily accurate (even though it might be plausible), but it