Chapter 1

THE QUANTIFICATION OF NEUROELECTRIC ACTIVITY

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Throughout the history of science experimenters from different fields have dealt with the problem of the quantification of their data in a variety of ways. Technological necessities and the prevailing theoretical structure of a given field determine to a high degree the techniques of measurement that are developed and the choice of variables that are quantified. Experimenters concerned with problems of "organized complexity"[1] often made little effort to report their observations in quantitative or even systematic form. They were too aware of the limited range of experimental facts that they could ascertain with a sufficient degree of invariance and of the narrow realm in which they could actually verify predictions from mathematical models.

These difficulties and an overly narrow interpretation of Lord Kelvin's doctrine* may be largely responsible for the fact that neurophysiologists, for instance, have often been hesitant to go beyond reporting raw data in a somewhat phenomenological manner. Such an attitude renders communication with fellow scientists hazardous. If verbal statements alone are made to carry the informational burden of large bodies of data, friendly model-makers from the physical sciences are tempted to construct theories of "how the brain works" on the basis of a few isolated and easily mathematized facts.

But it was just not caprice or lack of farsightedness among the data-rich and theory-poor scientists that produced this mismatch between their vast labors and the relatively small amount of theoretically integrable knowledge that became available. They were handicapped by a lack of adequate data-processing facilities and by the fact that the mathematical models of classical physics (and certainly those of quantum physics) had little to offer to the student of the nervous system or of human behavior. Hence, many

* "I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of Science, whatever the matter may be." Contrast this view of Lord Kelvin's with Gödel's contention[2] according to which "it is purely an historical accident that it [mathematics] developed along quantitative lines."

among them were interested by cybernetics, which emerged as the philosophical expression of the communications technology of the postwar period. It was under cybernetics' influence that many problems relating to the behavior of complex living systems were reconsidered. Only too often these reconsiderations turned out to be not only suggestive but also frustrating. At that stage a search for general principles of the behavior of the nervous system could not help but be somewhat superficial. The neuroanatomical, the neurophysiological, and the behavioral data extant were not in a form that made theorizing at a fairly general level meaningful.

1.1 Problems of Measurement and Analysis in Electrophysiology

For more than two centuries - thanks to various species of electric fish - men have been aware of the existence of "animal electricity." [3] More than a century ago Helmholtz measured the conduction velocity of nerve, and throughout the second half of the nineteenth century an appreciable amount of knowledge concerning brain potentials accumulated. A recent review article on the "Rise of Neurophysiology in the 19th Century" [4] summarized the situation at the end of that century as follows: "It was known that the brain had "spontaneous" electric activity, that potential shifts could be elicited in the appropriate cortical areas by sensory stimulation, that these potentials could be recorded from the skull and that anesthesia abolished them." However, electrophysiology entered its period of rapid growth only after the technology of the vacuum tube gave us amplifiers and oscilloscopes. These two instruments permitted electrophysiologists to increase the sensitivity of their observations and to display even rapid fluctuations in voltages as a function of time.

The characteristic deflections or patterns in voltage-versus-time-displays constitute the electrophysiologist's basic data. But how are these characteristics of a waveform to be assessed? As long as scientists deal with DC potentials or sinusoids, an instrument that yields one or two characteristic numbers is perfectly satisfactory, but when they attempt to assess arbitrary waveforms containing sharp "transients" and "noise," several questions arise. Is the voltmeter (even the vacuum-tube voltmeter) the appropriate instrument of measurement? Is it necessary to display the complete waveform by photographing it from the face of an oscilloscope? Can we find selective transformations upon the data that yield meaningful descriptions while reducing the total amount of information displayed?

A further discussion of appropriate methods for the quantification of electrophysiological data leads us to consider issues that the physical sciences have faced - sometimes quite explicitly and sometimes less so - throughout their history. Before we make measurements reflecting the behavior of complex systems, it may

be wise to ask ourselves two sets of questions. Why do we make a particular measurement? What conclusions (regarding the phenomena under investigation) shall we be able to draw on the basis of the measurement?

The first set of questions inquires into the purposes of the experimenting electrophysiologist: Is he interested in relating the electrical events that he records from an isolated nerve fiber to the physico-chemical processes that occur in the transmission of a nerve impulse? Is he using the electrical events in order to trace certain pathways in the nervous system? Is he trying to study the responses of certain neural structures to carefully controlled sensory stimuli? Is he investigating the behavior of neural structures in relation to a mathematical model that he has formulated? Is he studying the way in which certain chemical substances affect synaptic transmission? Is he trying to relate changes in an organism's electrical activity to conditioning or learning? Or is he concerned with the presence or absence of certain patterns in this activity, with a view towards clinical diagnosis? Neurophysiology includes all of these experiments. The experimenter's purpose determines the choice of his variables, the display technique for his data, and affects the very definition of what constitutes an experiment: Which parameters are to be held constant, how replicable must a phenomenon be, ... ? Neurophysiology - which has, compared to the physical sciences, little theoretical structure of its own - is thus characterized by an aggregate of techniques for the study of the nervous system or of its component parts. As a science it stands in close relation to fields such as neuroanatomy, sensory physiology, biochemistry, psychology, biophysics, and medicine, and the significance of neurophysiological findings is often assessed in terms of their relevance to the neighboring fields.

The second set of questions deals with the inferences that can be drawn from electrophysiological "pointer readings." It is here that our lack of understanding of the organizational principles and of the mechanisms of the nervous system is felt most seriously. The organizational structure of this nonhomogeneous medium that consists of large numbers of highly specific elements has so far defied useful description in terms of the over-all physical properties of the medium. Much effort has gone into analyzing the fine structure of its various components in terms of current biophysical and biochemical knowledge, but up to the present these efforts have not yielded an approach that is capable of dealing with the unique properties that characterize the nervous system of higher animals. Here is a system that is composed of many interacting units (all of which are by no means alike), that is organized both flexibly and hierarchically, that consists of subsystems (enjoying various degrees of autonomy) that are capable of fulfilling specific and/or nonspecific functions. Here is a system that reacts

more reliably and predictably to informationally rich stimuli than to "simple" ones. Here is a system that is capable of learning and of giving reasonably reliable performance throughout an extended period of time, with all the safety factors and maintenance and repair requirements that such performance demands.

If we want to understand the "systems neurophysiology" that underlies the behavior of information-processing organisms, what is the type of electrical activity that we should study? What type of strategy should we adopt in dealing with the signals that we record from the nervous system - signals whose code is known so incompletely? Should we attempt to isolate a single neuron and study its behavior in great detail, hoping that we will pick the "right" (representative) one out of a not-too-well defined population? Should we at the other extreme, work only with the muffled polyneural roar that is able to make itself "heard" through man's thick skull? Should we limit ourselves to studying recordings of "spontaneous" activity of a neuron (or of neuronal populations), that is, the activity that we can still observe when we have turned off all the stimulus generators that are under our control? Or should we study stimulus-response relations, that is, those response events whose occurrence is by some criterion (usually a temporal one) linked to the delivery of a definable stimulus? Can we assume that these latter stimulus-evoked events will always simply add to the "spontaneous background activity," or must we study their interaction in different physiological states of the organism?

Are the biggest voltages, especially when recorded at the outside of the skull, the most important ones to study? If we compare this situation with the facts of speech communication, we find that it is the vowels (yea, their first formants) that carry most of the energy among the speech sounds, although - in English at least - it is the consonants (whose clamor for attention is much less loud) that carry most of the linguistic information. There are perhaps other lessons to be drawn from the study of speech communication. When a Fourier analysis of speech signals is carried out, the vowels (whose duration is of the order of 1/10 second) seem to be represented much more meaningfully by Fourier components than the consonants. The latter can be viewed as "transients" or "transitionals," whose spectral composition depends much more upon the vowels that precede or follow them. The problem of where the vowels end and the consonants start (technically known as the segmentation problem) presents a challenge all of its own, comparable perhaps to that of defining the duration of an evoked response. An "ah" will exhibit rather different spectral components when pronounced by a man, a woman, or a child; it will even exhibit appreciable differences when pronounced repeatedly, and in different context, by the same individual. And yet there is something invariant about it that makes it recognizable as an "ah." This "ah"-ness is not anything that is easily characterizable by absolute numbers, but rather by distinctive features or parametrically defined patterns, by certain relations among the components of a sound, especially in relation to

other sounds that might have been emitted. Lest this analogy be carried too far, let us not pretend that we are waiting for somebody to break "the" code of the nervous system. Let us realize that we are trying to discover the units of analysis, the distinctive features of neural signals, that will help us order the innumerable data of the nervous system.

What are the techniques of analysis that are readily available to electrophysiologists when they record data to deal with the range of experimental problems that we have mentioned above? Let us briefly mention some sample techniques that have been used. The mathematics of circuit analysis (at least in its simpler forms) assumes that the circuits and their components are linear, lumped, finite, passive, and bilateral.[5] It would, of course, be absurd to pretend that the nervous system has these properties, though it may be possible to find, by applying circuit theory, in what manner the behavior of a sensory system, for instance, deviates from this model.

If we restrict ourselves to dealing with whatever waveforms may have been recorded, we must ask whether the specific techniques such as Fourier analysis or correlation analysis are actually appropriate to the particular experimental question. Such techniques imply that the time series analyzed satisfy certain conditions.

Obviously, the assumptions implicit in these analytical techniques are a price that we have to pay for their use. Physical scientists also pay this price. They, however, know so much more about the processes that underlie the phenomena they study than we know about the mechanisms that underlie neuroelectric phenomena. Thus, in physical science there is a better chance of adjusting and correcting models than there is in neurophysiology. And yet the student of the nervous system has little choice until more appropriate techniques of analysis have been developed. He must utilize those that are available in order to find out where they cease to fit. It may, nevertheless, be wise to take the precaution of assembling a sufficient body of apparently consistent data before getting involved in ambitious computations.

Is there a moral that imposes itself on the basis of the preceding tedious and yet incomplete enumerations of problems that one faces in this type of research? We believe that there is, and we believe that it can be stated in a single word: pluralism. Only a pluralistic strategy guarantees, at this stage of our knowledge of the nervous system, that we shall not blind ourselves to useful approaches because we have oversold ourselves on one of them. The very multiplicity of purposes precludes our prescribing experimental design or methods of data processing and analysis too rigidly on intrinsic grounds. We must, rather, be prepared to make our choice on the basis of extrinsic values or influences: Given the biases of interest that we - as a group - have, given the physical and intellectual surroundings in which we work, we have developed certain methods of data processing and certain types of mathematical

models. We believe that these techniques are capable of coming to grips with the statistical character of neural activity which is one of the essential features of the nervous system. We have, furthermore, a preference for packaging our results in a form that is reasonably quantitative; that is, we try to express as many of our findings as we can in some mathematical representation without always trying to fit our data to analytical functions. Since we are dealing with a multivariate system, we are not surprised that the patterns and relationships that we find are often statistical. Finally, it is fair to say that, while we feel more secure when we have the guiding influence of a mathematico-physiological model in our experiments, we are not so narrow-minded as to ignore the usefulness and even the beauty of a good classification scheme that relates to variables whose importance to the organism is undeniable.

1.2. A Statistical View of Neuroelectric Phenomena

No matter which aspect of the electrical activity of the nervous system we study, we always face the task of defining "typical events" among those we observe experimentally. This task confronts the experimenter, whether his concern is with evoked responses or with the EEG (electroencephalograph). He has to establish certain criteria of judgment. These criteria will be different when he records with the aid of gross electrodes than when he studies the activity of a single cell with the aid of a microelectrode. The electrophysiologist has the further problem of deciding whether two observations are "identical." Here the identity-defining operation may range from identity in one aspect of the event only (such as occurrence or nonoccurrence of a spike potential) to identity in all measurable aspects (average spike latency, distribution of spike latencies, and so on).

In order to decide whether an event is typical or whether two events differ, we really have to know something about the distribution of possible events. This distribution might be obtained by observing responses to a large number of identical stimuli or by repeatedly sampling an EEG (electroencephalographic) trace. Actually, experimenters rarely have such information available to them, and yet, if they are well trained, they choose representative records as illustrations for their papers. It is, nevertheless, necessary to realize that few, if any, systematic studies have been made to assess an experimenter's information-handling capacity as applied to his ability to view oscilloscopic traces or examine film records. In other words, we do not really know how safe the current procedures are.

We have tried to present and review elsewhere [6, 7, 8] some of the available evidence on the statistical character of input-output relations in either single units or for responses from populations of neuronal elements. Here we shall try to summarize the essential arguments only.

We faced this problem first when we tried to find criteria for deciding what constitutes a typical evoked response (a response that is evoked by the presentation of a discrete stimulus, most often a sensory one). There exists, to our knowledge, no generally accepted operational definition of what is meant by an evoked response although the concept has been exceedingly useful in electrophysiological and neuroanatomical studies of the nervous system.

Let us briefly see how evoked responses are recorded. The experimenter usually knows when a stimulus is being presented. He then most often establishes the presence or absence of an evoked response by either of two methods or by the two methods conjointly: (1) In recording with gross electrodes, he detects visually the presence of a characteristic waveform or deflection. (2) In recording with microelectrodes, he detects aurally (and/or visually) a change in the acoustic signals that represent the electrical events "seen" by the microelectrode after these events have been appropriately amplified and transduced.

As should be clear from this description, the experimenter's ability to detect such changes in visual and/or aural displays depends upon how stable these changes are in relation to the patterns of "background activity."* These changes will be most easily detected when they have short latencies (that is, when they occur right after the presentation of the stimuli). The more these changes exceed the experimenter's just-noticeable-difference for the visual or aural displays involved, the more reliable their detection will be.

For responses that are recorded with gross electrodes, there is variability both with respect to amplitude and with respect to time. The evoked responses of the classical afferent pathways exhibit relatively short latencies and little variability in latency. It is this relative stability of the temporal aspects of these responses that makes the use of averaging by computing devices (such as the ERD and the ARC-1) possible and useful. It goes without saying that latencies determined from the average evoked response permit us to say little about the latencies of the individual responses. So far no adequate techniques have been developed to deal with electrical events that have longer and more variable latencies (such as the so-called "blocking of the alpha rhythm").

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* We have already mentioned the problems of the typicality of a response and of the identity of two responses. These problems include in some sense decisions of how typical the background activity is in which these responses are embedded. Amassian and his co-workers emphasized only recently[9] how the presence of spontaneous cell discharges complicates the analysis of the effect of stimulus variables.

For responses that are recorded from single units with the aid of microelectrodes, the variability problem is rather different: Here we are dealing with a set of discrete events that are quite comparable in waveshape and amplitude but that occur at latencies that are governed by both stimulus parameters and the existing sequences of "spontaneous" firings of the cell. The changes in the patterns of "spontaneous" firing that do occur may result in either increases ("excitation") or decreases ("inhibition") in average firing frequency; thus variability may now affect (a) changes in number of firings (how many spikes does a given stimulus elicit or inhibit), (b) "first"-spike latency (latency of the spike whose occurrence is most directly linked to the delivery of the stimulus), (c) interspike intervals, and so on.

An overview of the problem of adequate detection and description of evoked responses leads thus to procedures in which computers are instructed to "look" for changes in patterns of ongoing activity that are somehow linked to the delivery of stimuli. "Looking" for changes in averages, such as means, or for changes in distributions within several time intervals becomes thus a method of search in which the properly instructed computer supplements human capacities.

From all that precedes, it should be clear that we must find ways of dealing with the undeniable fact that repeated presentations of the same stimulus do not yield "identical" neuroelectric responses in many physiological preparations. Instead of abdicating before this fact by declaring that neuroelectric activity is thus not truly quantifiable, one can take advantage of this difficulty.

The variabilities that one observes seem to have their own regularities, which are in turn related to both stimulus and organismic variables. By constructing a model that had relevant statements to make with respect to both mean and variance of population responses, Frishkopf[10] was able to give a much deeper interpretation of neural events at the periphery of the auditory system than had been possible previously.

If we look for an interpretation of this statistical behavior, we must first of all consider the complexity of the system or subsystem under study, the multiplicity of possible interactions,* and the lack of adequate description of the state in which a cell or a neuronal population finds itself at the time when a stimulus is presented.

A recent article of Bullock[12] gives a thoughtful discussion of the present status of the neuron doctrine and suggests several

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*Sholl,[11] who has discussed the quantification of neuronal connectivity, states, for instance, that "Impulses arriving along a single primary visual fibre will be dispersed among the 5000 neurons distributed around its terminal branches."

major revisions. Many of the ideas expressed by Bullock force a reconsideration of what is meant by the state of a neuron and emphasize the necessity for looking beyond the occurrence of the spike potential as the sole indicator of neuronal function.

Although there will undoubtedly become available more adequate descriptions of the state of single neurons or of neuronal populations, there is serious doubt whether we shall, in the foreseeable future, be able to dispense with statistical descriptions of neuroelectric phenomena. Given this prognosis, we shall endeavor to develop and use the most appropriate methods available in order to elucidate the statistical aspects of neuroelectric activity.

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