THE CHALLENGE OF BIOLOGICAL ORGANIZATION TO MATHEMATICAL DESCRIPTION

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To gain knowledge about the internal organization of living systems is the goal of every research biologist and is especially tantalizing to those who work in my field—the neurophysiology of the brain. It is only comparatively recently that the approach through mathematical models and artificial simulation has been added to the classical scientific methods of analysis and synthesis, of stimulus and response (with the brain in between as a black box).

Much is owed to the influence of such figures as Norbert Wiener with their insistence on similarities between living and nonliving systems in terms of information transmission and control, and it is not mere chance that the evolution of this type of biological research should develop in the age of computers. It is easy to forget that only 15 years ago it was rare for a biologist to have access to a computer, let alone to have thought out his problems in the form of questions that could be put to a computer.

Successful modeling requires a close symbiosis of mathematician and biologist, each with his special knowledge and with a common language that allows them to understand each other exactly. For the biologist the practical test of a model is matching it to some aspect of physiological reality, yet often the material the mathematician is given to work with is not physiological reality at all—but the hypothetical concept of the biologist, a hypothesis that may be erroneous.

There have been, and still continue to be, many intriguing mathematical models proposed for various facets of neuronal mechanisms. Possibly the most widely used model in neurophysiology is the one for the conduction of the nerve impulse which we owe to Hodgkin and Huxley. Their mathematical model was originally published in 1952 [13] and more explicitly stated in 1958 [14].

This is a model which describes the movements of potassium out of, and sodium ions into, the nerve when impulses pass along the fiber in the form of electrical action potentials. These ionic fluxes result from a sequence of changes in permeability of the membrane of the nerve to potassium and sodium ions [15].

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The mathematical treatment developed by these workers is based on the probabilities that these charged particles are concentrated at the relevant place on the membrane at the critical time. The equations developed from this model for expression of the membrane current density and the velocity of the propagated action potential along a nerve fiber will be found in their publications. Essentially they consist of a partial differential equation describing the current distribution along the nerve fiber and some additional differential equations describing the current-voltage time characteristics of the nerve membrane. Hodgkin and Huxley have published an example comparing a curve calculated numerically with one recorded experimentally from a biological preparation, in this case the nerve axon of a squid, an animal which has an unusually large nerve fiber that has proved a delight to the neurophysiologist.

The Hodgkin-Huxley equations for propagation of nerve signals along the axon, although they have met their challengers from time to time, have been used very extensively by others in the field, and have in some cases been treated to further refinements bringing them closer to biological reality (some quite recent models bringing in the spatial element are, for example, those of Dodge and Cooley [9], and of Harris and Weaver [12]).

Now the model just discussed is only for the initiation of the nerve impulse in the shaft of the neuron. It is not intended to apply to the cell body or its dendrites, and is not intended to encompass the organization of any complex of neurons or nerve net. It represents one important link in the propagation of activity but does not, and is not intended to describe how impulses are transmitted across junctions, that is, across synapses, between different neurons.

There are many types of these synapses within a nerve net, that is, within a biological nerve net, and the universally descriptive mathematical model has proved elusive to its searchers.

When the first model for a nerve net that made any great impact was proposed, the McCulloch-Pitts model [19] of 1943, physiologists had not yet realized that all parts of the neuron did not share the same properties of conduction and transmission as those that had been found for the long fiber.

Twenty three years ago, when that model was first proposed, physiologists really knew very little about the behavior of neurons in the brain, and were basing their concepts on the hypothesis that the brain shared the same electrical properties as the long axons of the peripheral nerves in the limbs. About the latter a great deal of information had been gathering for over a century, in fact, ever since Du Bois-Reymond had finally provided incontrovertible evidence that the nerve impulse was accompanied by an electrical signal, the action potential. In his famous book [10] on animal electricity, published in 1848, he said: "If I do not greatly deceive myself, I have succeeded in realizing in full actuality (albeit under a slightly different aspect) the hundred years' dream of physicists and physiologists, to wit, the identification of the nervous principle with electricity."

The outstanding electrical property of the long nerve shaft of a peripheral neuron is that it either fires or it doesn't—a beautiful digital signal and one

which lends itself to the logical notation: "if and only if." This property, christened by Adrian [1] in 1914 the "all-or-none principle," states that provided an impulse is strong enough to be propagated at all, the amplitude of its action potential and the velocity of its conduction will be independent of the strength of the stimulus. The occurrence of an all-or-none action potential in the conductile part of the neuron carries the message that an adequate stimulus has been received, but is not in itself proportional in size to the stimulus strength.

At the time when the McCulloch-Pitts model was first formulated, the hypothesis generally held was that this was how neurons in the brain worked, and it was to match logic based on this hypothesis that their model was originally designed. In other words, it was an expression in logical notation, not of factual events but of a conceptual model. Unfortunately, to this day, many biomathematicians, not in close symbiosis with neurophysiologists, pursue this same concept in designing models for nerve nets (though the originators are among those who have recognized that a two-state switch cannot mimic a neuron [20]). The scope and limitations of neural network models based on all-or-none behavior and stereotyped refractory periods have been well summarized by Minsky [21].

In 1943, when the model was first proposed, neurophysiologists were only just beginning to get their electrodes in contact with the nerve cells of the brain and only later were they successful in penetrating the cell bodies with ultrafine electrodes through which they could record the potential changes associated with activity actually within the cell itself.

Hypotheses of transmission between neurons in the brain then began to give way to direct observation, and one of the more important revelations for the model maker was the fact that the digital nature of impulse transmission is a characteristic only of the long shaft of the neuron and that at both ends, at the input and at the output, the electrical events are graded, that is, analog in form and presumably should be represented in mathematics by continuous functions. A schematic representation of these characteristics is shown in figure 1. The direct electrophysiological evidence for this came from many laboratories, including that of Bishop, who has summarized it well in a review written in 1956 [4]. That the nervous system was a "mixed" system with both analog and digital characteristics was recognized by von Neumann in his Silliman lectures on "The Computer and the Brain" [27]. One should realize that computer development owes much to von Neumann's interest in the field of brain science, a fact which we neurophysiologists are proud to recognize.

The demonstration that ultimate activity, that is, output, was influenced and modulated by graded changes in levels of polarization in multiple neuronal units (that did not necessarily lead to a discharge in these units themselves) has led several workers to an exploration of probabilistic models—ones in which the concept that the probability of units firing as a result of these multiple influences is the computation one should seek. In fact, the evidence that the change in state (not necessarily firing) may influence the activity of neighboring neurons,

imposes on us the necessity for recognizing not only the probability of a neuron firing but also the probability that a subthreshold change in its state may influence the ensemble.

One must realize, therefore, that the ingenious model of McCulloch and Pitts in its original form was based on so extreme a simplification of neuronal inter-
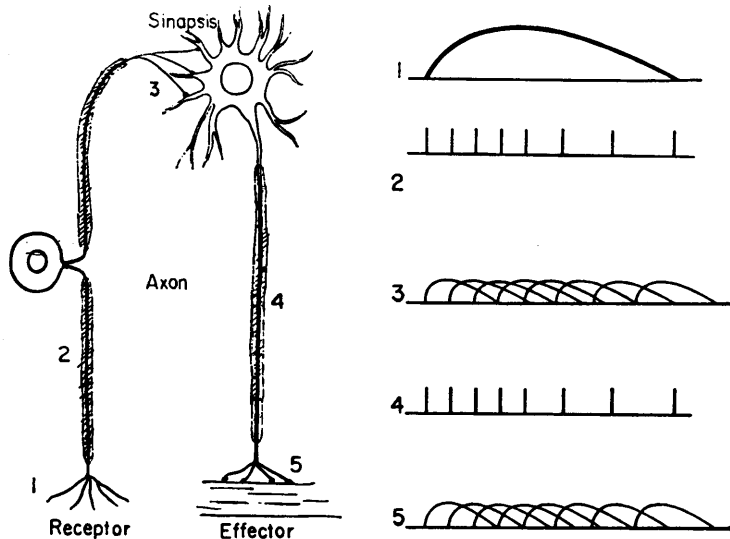

FIGURE 1

A schematic diagram of a neuron to illustrate the graded nature
of the signal at the receptor (1), at the synapse (3) and the
neuromuscular junction (5). Only in the axons of the neurons
is an all-or-none action potential propagated. The afferent
neuron (2) is represented here as one of the bipolar cells of
the dorsal root of the spinal cord and the efferent (4) as the
innervating axon to a muscle.
(Modified from Bishop [4] by E. de Robertis [23], p. 7.)

action as to be misleading to both physiologists and mathematicians. It had, however, the valuable effect of stimulating the interest of mathematicians in the operations of the central nervous system.

The challenges that remain and which succeeding generations of biomathematicians have begun to tackle are for models of information flow in the brain that are not restricted to interactions based on a stereotyped concept of synaptic transmission rigidly determined by the refractory period of the nerve. Among the other influences at work are the time-varying nature of the threshold of discharge for a neuron, the lack of uniformity between the individual neurons composing a net, and the possible field effect of activity in neuronal aggregates in the neighborhood, not necessarily concerned with the particular information

flow under study. And of course there are the many environmental and extra-neuronal influences brought by the bloodstream, the hormones, the transmitter substances and the glial cells.

It would be absurd to demand from our mathematical colleagues a model which encompassed all these properties in one package, and this is not the purpose of a model but it is a reminder that the frequently used term "a model of the brain" is a misnomer.

In any case models, whether conceptual, mathematical, or three dimensional, should be thought of as one in a series of steps towards more accurate and appropriate models, each of which may be an approximation to some facet of nervous activity and each of which may suggest a new hypothesis or a new experiment. The McCulloch-Pitts model for a nervous net, essentially a finite automaton expressed in logical notation, has now been rejected by neurophysiologists, though it has led to the development of other constructs each attempting to correct for one or more of its failings.

To give only three examples from many that might be cited, there is Beurle's [3] model in which the connections between neurons are considered statistically instead of deterministically and in which the threshold for discharge of a neuron is lowered sequentially each time it fires. A second is implied by Chapman's [7] mathematical model of a self-organizing classification system in which the degree of connection between units is a function of the past use of the net. Conditional probability as part of a model for a net has been considered by many people and notably by Uttley [25] who built a hardware version capable of counting, storing and acting on the various sequences of connections that occurred and thus calculating the probability of activity in any one or more parts of the net. The importance of this model is the introduction of conditional probability. The application of probabilistic theory to neural nets has received extensive consideration from Rapoport in a series of papers [22]. Many other examples could be cited were there a necessity to give an all inclusive list, which is not the intention here.

A whole other field of model making that has invaded neurophysiology is represented by the approach through the study of information processing. One great advantage for the novice entering this interface between neurophysiology and mathematics is that the language is couched in terms generally more familiar to the biologist than is the logical notation used by many for models of neural nets.

This approach has led directly to a wealth of investigation of the coding systems used by the sensory systems of the brain in receiving information and rather less, as yet, of the codes by which it sends out its signals to the peripheral effector mechanisms. The coded message in the input as represented by activity in neurons, undergoes many transformations before it results in output—transformations which, in neurophysiological terms, are imposed by the properties of synapses and by convergence and divergence of the multiple neuronal pathways within the brain as well as by the fact that the message does not enter a passive

network but one which is continually active and unpredictably variable. Information is being processed, not only sequentially, but in parallel circuits that may have different properties. It is presumably through these parallel circuits that associations are mediated and, ultimately one supposes, memory traces. Some idea of the convergence of nerve endings onto a neuron is given by figure 2, reproduced here by permission of Dr. de Robertis.
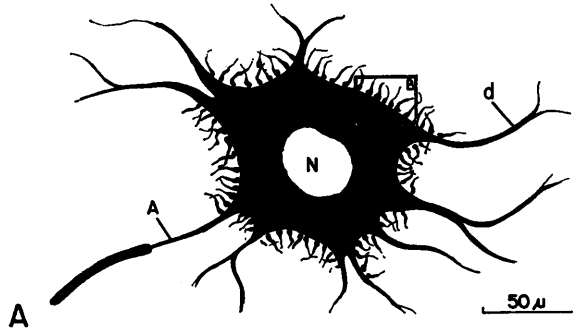

FIGURE 2

Drawing by de Robertis of a nerve cell illustrating the great
number of synaptic endings on a single cell body as seen in one
plane only. Bouton-like endings, such as those shown make
synaptic contact on all surfaces of the cell body as well as on
its branching dendrites (d) and on its axon (A) [23], p. 31.

As neurophysiologists came more and more to realize that the one-to-one kind of connection of a purely deterministic sort is largely foreign to the nervous system, the multiplicity of chain reactions set up by a stimulus began to receive attention. Some of these chains may well contain weak links, components rendered unreliable by some transient state of the organism such as waning of alertness or loss of attention which shut off some of the physiologically demonstrated parallel paths for input to the brain.

This need for the nervous system to be able to assess the reliability in the input channels is one of the factors that have led to concepts of the neurons reacting on a basis of probability, for failure of a neuron in a deterministic model would be disastrous. For example it has been suggested that in a multiple routed input, when the ratio of messages received to those lost exceeds a critical value, the probability of the stimulus having occurred is recognized by the nervous system and processed as an input on the basis of a statistical decision.

Models that recognize probability of failure of individual elements in the net and the need for error correction have been designed by several workers, including the well known one of von Neumann [26] which essentially made use of redundancy.

The brain has to deal not only with the assessment of arrival or nonarrival of

a signal, but with the arrival of noise simultaneously with the signal and the presence always of background activity. Again there would appear to be a probabilistic assessment of significance based on stored associations.

It is well known now that the neuronal mechanisms for selection of messages at the level of input at the sense receptor, for example, the eye or the ear, exist in anatomical form as feedback routes from the brain [5]. The initiation in the brain of controlling impulses flowing out to the receptors implies a matching, on a probabilistic basis, of the significance of the signal at the expense of the noise.

Now let us consider briefly the problem of coding in the nervous system. Mention has been made of transformations in the message reaching the brain caused by convergence and divergence at synapses, that is, at the junction points between neurons in the pathway. This is only one of the complications that defeats any attempt at a simple wiring diagram.

A few biological facts may be quoted as examples. In the visual system, for example, excitation in the mammalian retina has to pass through at least two synapses before it reaches the cell body of the neuron whose fiber reaches into the brain. It is only at this last stage that the message, originating as a graded potential, is passed on in a digital, all-or-none code. This coded message reaches another relay station in the thalamus where it has to cross yet another synapse to continue on to the cortex.

The point to be emphasized is that neurophysiologists who have explored the response of single units have found individual neurons that respond in the same way to wavelength changes as they do to changes in position of a stimulus in the receptive field. Thus the coding in single units, as MacNichol [18], [28] expresses it, is ambiguous although the total message obviously is not.

It is findings such as this that have led neurophysiologists to conceptual models in which the code is envisaged as being carried, not by one-to-one connections, but by patterns of excitation formed by the combined responses of several, or even very many units. The challenge to the model makers is that this patterning is both temporally and spatially distributed [6].

Baffled as one may be by this evidence for ambiguity of message coded in single neuronal units when derived from the same receptor organ, an even greater challenge is presented by the evidence for multisensory convergence onto cortical neurons.

It has been known for some time that several sensory modalities (visual, auditory, tactile and so on) converge onto individual neurons in the nonspecific systems of the depths of the brain (for example in the reticular formation [24] in the nucleus centre median of the thalamus [2] and in the hypothalamus [8], as well as in the hippocampus [11]) but more complicating still, in terms of coding, is the more recent evidence in the primary receiving areas of the cortex for convergence from different sense modalities onto the same neurons [16].

It is not so surprising to the electrophysiologist to find long latency responses from a second modality evoked in a neuron in an area of the cortex primarily specific to a different modality, for they may have traveled by a long poly-

synaptic route, though even this must complicate the decoding process. More puzzling are the clearly bisensory neurons which give similar short latency immediate responses to two different modalities, for example, visual and acoustic, or visual and vestibular, or vestibular and acoustic. All of these bisensory neurons have been found by Jung and his colleagues [16] in Freiburg, who have even found (but more rarely) trisensory neurons responding with short and constant latencies to visual, acoustic and vestibular stimuli.

Possibly the existence of neurons in primary cortex that are multisensory in their responses may be one of the causes underlying what is usually called "spontaneous" activity by the experimenter who is controlling only one modality of sensory input. Spontaneity has always seemed rather a mystical term for a scientist to use.

In presenting a biologist's view of some of the problems encountered when attempting mathematical descriptions of biological systems, it is not the intention to disparage these; in fact the exact opposite is intended. What is needed is a closer symbiosis of the biologist with the mathematician.

It will be noticed that allusion has been made to only a few of the many constructive models that the mathematicians have contributed to neurophysiology. This is only because there are too many. Anyone who is familiar with this field must realize that even to give an adequate list of the references is an impossibility for this is currently an area of great activity.

And indeed the mathematician is probably going to find the neurophysiologist turning to him more and more often, especially as he faces up more courageously than he has in the past to the nonlinearity of the nervous system. A step in this direction is consideration of quasilinear models, possibly along the lines of those suggested by Licklider [17] for manual tracking by the human operator. This is not to say that no linear relationships have been found in the biological preparations. Within a considerable range of normal physiological activity, linear functions are found, but there is little doubt that the physiologist will present the mathematician with more nonlinear than linear examples for which he desires a solution. Biological systems do not give identical responses to identical stimuli. They are not time invariant. And study of the nervous system makes it clear that it is not a network of linear components.

What we ultimately need for the mathematics of the central nervous system is a nonlinear statistical theory. Perception, to use the psychologists' word, is the result of the decoding process. Clearly the earlier concepts of point to point connections from receptor to cortex were oversimplifications and fell far short of explaining "perception." Data are now available from deeply implanted electrodes in the brain of man, an experimental subject who can report the result of his decoding of the message. From such observations it becomes clear that many regions of the brain at considerable distances from the primary receiving cortex are involved in perception of the stimulus.

To extract significant information from the multitude of signals entering the brain through noisy channels there would appear to be the need for some proba-

bilistic selection process based on comparisons made with previously encountered messages and their associations. The amount of storage equipment required for such a system would be immense, but not beyond the capacity of the human brain.

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