Neural Modeling

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I. INTRODUCTION

A. Modeling Philosophy

The making of models is universal in the search for a consistent and instructive picture of nature. This review examines the history, accomplishments, and promises

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of overt neural models. We use the term *model* synonomously with *analog* to mean that which is similar in function but differs in structure and origin from that which is modeled. By *overt* modeling we mean studies explicitly designed to complement experimental neurophysiology, not the tacit modeling that always accompanies experimental design, measurement, description, and interpretation of results.

With growing emphasis being placed on the information-processing aspects of nervous systems, theoretical studies assume increasing importance. The use of models to help elucidate neural behavior has thus expanded rapidly during the last decade. Theoretical neurophysiologists have used a wide assortment of tools and techniques to study realistic analogs of membrane, single-unit, and network action. In some instances there are questions that appear to be unanswerable by present experimental techniques; in such cases, models can usefully augment direct physiological experimentation. Some of the tangible progress in the applications of models is documented in this review. The advances so far obtained suggest that neural modeling may be expected to exert increasing influence on the course of neurophysiological research.

An important part of the utility of a model lies in its ability to focus disparate evidence and interpretations into one coherent view; parsimony of explanation often leads to revealing unity. Models are also valuable to the extent that they raise new questions and suggest new relationships, perhaps leading to new experiments that might not otherwise have been considered. Worthwhile models are predictive; that is, new relevant properties are deducible from them. Further, a model often suggests constraints that may exist in the system being modeled. If these constraints are valid, they can serve to guide subsequent experimental interpretation. To thus reveal, test, compute, extrapolate, and predict is to accelerate the process of learning about the real world.

Models are a necessary ingredient of scientific method: as deductively manipulatable constructs they are essential to the evolution of theory from observation. But the role of models and modeling is often controversial and ill understood.

Several illuminating treatises on models are available, offering insight from rather disparate points of view. Bremermann (295), for example, develops the concept of an "eigen model," which is essentially a model of the environment built into any system that responds actively to environmental changes. Fogel (297) discusses the relationships between models and reality and the crucial role of models in scientific method. Rosenblueth and Wiener (305) develop utility criteria for models in science. Lillie (52), Schmitt (72), Harmon (300), and Perkel and Moore (303) examine the virtues and flaws of models in neurophysiology. Many aspects of the philosophy and practice of modeling are discussed in a multidiscipline symposium on biological models (292) and in one on information processing in nervous systems (299).

Criticism of modeling has taken many forms. One interesting accusation denies the value of any model that is not "primary" (i.e., a *direct* representation of the real world). It is said that no "model of a model" can really add anything valid to scientific knowledge. However, it is difficult to conceive of a genuinely primary

model. It seems clear that all models as we know them are secondary (i.e., that they are models of models); our conceptions of our environment are themselves models and, indeed, are structured from more basic models [Bremermann (295); Fogel (297)].

Once past the doubt that modeling is at all possible, we encounter criticisms of specific models. Two neural analogs that often are strongly criticized are the "Lillie iron-wire model" and the "formal neuron" of McCulloch and Pitts. Rosenblueth and Wiener (305) delivered the *coup de grâce* to the iron-wire analog in 1945, pointing out that measurements on this model were more difficult than on nerve itself and that the underlying physical mechanisms of propagation were perhaps even more obscure in the model than in the modeled. They deplored the fact that physiologists had paid so much attention to the iron-wire model in years past.

In a similar manner the formal neuron is presently deprecated as being an extremely unrealistic simplification of a biological neuron and thus insufficient as a model. Many modelers have particularly emphasized the contrasts between their analogs and the "simple" McCulloch-Pitts variety.

In view of the obvious validity of such criticisms we sometimes forget the importance of these models in their own time. The iron-wire model proved that a purely physicochemical system could conduct a disturbance without attenuation, and it provided strong early support for the membrane theory [Adrian (1)]. Similarly, the formal neuron played an important role in its demonstration of the theretofore unknown logical power of simple nerve nets. While the present utility of both of these models can be doubted, their historical value cannot. Man's knowledge of nature is evolving. Admittedly, a model or a theory that leads to a dead end is of limited interest, but one that forms a link in the continuing chain is extremely valuable, regardless of whether or not subsequent events far outreach it.

The history of neural modeling is one of many false starts, dead ends, and continual groping. Progress has seldom been rapid and has often been frustrating. The advance, nonetheless, is measurable. We hope to show that the advance has, in fact, been substantial.

B. Modeling Rationale

In its ideal role of providing a coherent, parsimonious description of nature, a model is necessarily a simplified representation of the prototype. Were this reduced representation useless, complete *replication* of the thing modeled would be necessary, and the idea of "model" would lose all meaning. Thus, systems are usefully modeled by constructs that have some functional equivalence but are not identical in detail; the essential properties of the original are represented while the obscuring irrelevancies are ignored. However, this imposes a need for selection that lies at the heart of the modeler's problems.

There are two distinct philosophies in the selection of parameters in neural modeling, each with important application. In one, a very large number of neural properties is reproduced with high accuracy. Initially the model is presumed to

have been overspecified to some extent, and the tacit intention is to simplify if and when it seems *reasonable* to do so. In the other approach a more restricted set of properties is used, but the restrictions have been made on the basis of an *a priori* set of assumptions as to the most significant ones. It is assumed in such "minimum-parameter" models that the essential features have been retained, and the tacit intention is to introduce more complication if it becomes *necessary* to do so.[2]

There are of course advantages and disadvantages to each approach. Models of the first type are more complete but are more difficult to realize and are more costly. Models of the second type are more amenable to analysis but are in greater danger of important omissions. Although one of the more nearly complete models can contain the features of several minimum-parameter models, the addition of accessories to the latter is equivalent to the changing of parameters in the former (to model different situations).

Both kinds of models must always be open to question. It is essential in each approach to test and modify unceasingly to obtain convergent qualitative and quantitative agreement between analog and prototype. So long as there is continual testing for appropriateness and so long as neither seriously violates physiological evidence, the choice depends largely on the nature of the functions to be modeled.

Once a model is realized there are three kinds of action to be taken. The first, which is mandatory, consists of preliminary validation by testing the model's accuracy. This is done by matching the model's behavior with physiological observation. Successive refinements of the model may then lead to convergence to an accurate and revealing abstraction.

Second, with validity tentatively established, one may attempt to discover new properties of the model (i.e., operations not explicitly considered in the original design). Although such "discovered" properties are implicit, owing to the choice of parameters, it is most unlikely that all of them will have been foreseen. If these new properties also match those known to exist for the biological system, or if on subsequent physiological testing they are shown to have successfully predicted functions not previously known, then the model's validity is given additional support.

The third course of action is more speculative but can have great value. It consists of testing hypotheses and exploring their consequences more rapidly and economically than direct physiological measurement permits. In this way a large number of theoretical ideas can be tested and evaluated. Further, such preliminary observations can reveal the necessary consequences of a particular hypothesis; these in turn can be used as a basis for planning more effective physiological experiments.

Although the kinds of models to be reviewed are diverse, one purpose lies behind their selection. This is the question of understanding the information-processing aspects of neural action, that is, the input-output signal relationships, sensory and motor coding and decoding, and logical or computer-like operations.

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[2] Berman (293) describes an interesting technique for parameter manipulation to develop unique models. He discusses the quantitative aspects of minimal system-perturbation experiments that can lead to constrained models in situations where the available experimental data are inadequate for a full quantitative description.

One may profitably explore the information-processing aspects of neural activity at several levels. One may seek understanding at the subcellular level, dealing with molecular organization, ionic dynamics, and membrane mechanics. At another level, one may consider questions pertaining to cellular input-output functions, seeking understanding of information transfer in single-unit action; this is the domain of signal integration and transmission. At a still higher level it is useful to explore the function of cell assemblies and networks. Further, one might wish to investigate the holistic properties of signal generation, interaction, and propagation by viewing gross electrical activity. Finally, it is important to attempt to understand the entire organism from a behavioral point of view.

Undoubtedly there would be considerable utility in achieving understanding at each of these levels. However, though there seems to be little question that phenomena from each level are causally related, it is not clear that one can readily extrapolate from one level to another. Membrane kinetics may be as uselessly remote from the physiology of visual *Gestalt* as is particle physics from celestial mechanics. In each case, of course, there are direct causal relationships, but there may be little reason (or possibility) for establishing explicit functional dependencies.

Yet another level in the understanding of any information-processing system is the elucidation of the information flow per se, without explication of the underlying mechanisms. Thus one can comprehend the essential nature of a system such as a computer from its logical block diagram; in this case the machine's information-processing functions can be understood even though no reference is made to physical devices underlying those functions. Such operational abstraction is an important ultimate goal of many who wish to understand nervous systems.

It is essential to note that there are two radically distinct research areas to which the term "neural modeling" has been applied. In one the intent is to represent the physiological phenomena. It is the purpose of this review to document the salient aspects of such modeling.

In the other research area, often euphemistically called neural modeling, the network properties of systems of quasi-neural elements are explored. The intent often is to build automata whether or not they replicate in realistic detail any actual physiological functions. Such is the province of "adaptive systems" and "self-organizing systems." In most cases only a few selected neural properties are adopted simply to see what can be done by applying mathematical or computer concepts to neuron-like elements. The present review does not deal with such studies except for brief mention to sharpen the distinctions between the two kinds of "neural modeling."

Temptations are ever present in neural modeling as in all fields of science, and some modelers have yielded. One of these temptations is to design ingenious circuits that simulate some aspects of a neuron and then quietly edge away, leaving the model for others to apply.

Another failing of some modelers is evidenced by what one might describe as the "reminiscence syndrome." Early in a paper the author may describe some outputs from models that are "reminiscent" of this or that neural phenomenon, such as conditioning, slow potentials, or epilepsy. Toward the middle of the paper "reminiscent" is omitted in the apparent hope that the reader will infer equality

between the model's performance and the neural phenomenon. By the end of the paper equality is overtly implied.

Deft use of the excluded middle is often seen. Consider, for instance, the implication found in one neuron-modeling paper where it was stated that it is possible to construct artificial neurons which are, as far as input-output relations are concerned, complete analogs of their biological counterpart. It was then said that the networks shown in the figures in the report were assembled and tested using artificial neurons. The implication, to the unwary reader, is that the "artificial neurons" used were realistic analogs, whereas in fact they were but extremely vestigial.

In this review we have attempted to include those models associated with more than a hope, a circuit, or a reminiscence.

C. Modeling Techniques

Neural analogs take a variety of forms, ranging from informal, verbal models to highly elaborate physical and mathematical constructs. Most models that have appeared during the last half century or so have taken the form of chemical systems, electronic circuits, mathematical formulations, or computer simulations.

Considerable advantages and serious shortcomings are found in each, although for a given modeling problem there is generally little difficulty in selecting the most appropriate technique. Since mathematical, electronic, and computer-simulation models comprise the majority of contemporary analogs, it is of interest to examine some of their intrinsic merits and deficiencies.

Mathematical models have great utility in limited domains. They are invaluable in cases where the number of variables is reasonably limited and nonlinearities do not present severe analytical difficulties. An outstanding application is found in the analyses of membrane biophysics. Formal mathematical description, however, is simply unable in its present state of development to deal adequately with the multivariable nonlinear complexities of entire neurons; complete network analysis is even more formidable.

In certain special cases, however, mathematical models of network behavior are extremely well qualified. This is particularly true for statistical treatment of large ensembles and for the analysis of large-scale electrical activity such as wave formation and propagation.

Electronic models can simulate continuous-variable nonlinear operations accurately and economically. Providing real-time signals that may be observed while experimental conditions are manipulated, they permit a rapid and effective kind of observer-model interaction not easily achieved by other techniques. There is considerable advantage to direct observation of waveforms, phase relationships, modulations, and time-dependent interactions while stimuli and model parameters are changed. Such advantage is most effective for the modeling of one or a few interconnected units. For large networks, however, both observation and manipulation of parameters and connections become very difficult.

Analog computers have advantages similar to those of electronic models, but

tend to be slow and cumbersome. Both have the advantage over mathematical models that they do not tend to compel oversimplification.

The growing speed and storage capabilities of digital computers carry great promise for flexible, realistic modeling. The special problems that arise with large-network simulation are more readily handled by digital computation than by other techniques. It should be noted that serial digital processing intrinsically does not permit economical representation of continuous-variable nonlinear interactions; however, contemporary advances in speed, storage capacity, and parallel operation point to alleviation of such problems in the future. It seems likely that high-speed digital computers will ultimately provide one of the most satisfactory means for modeling complex neural systems.

An additional powerful advantage of computer simulation is that the models can be made to work faster than their prototypes, and many more experiments can be run. Finally, an important asset of digital simulation is that the use of discrete symbols permits complete control and observation of assigned variables. It is advantageous, for example, to be able to obtain a precise "snapshot" of the state of an entire network at an arbitrary time, and such accurate, multiple-state representations are not easily obtained from either analog computers or electronic models.

D. Coverage of This Review

This review is representative rather than exhaustive. We attempt to delineate the main streams of activity in neural modeling and to emphasize what seem to us the important directions and achievements. Both the references given in the modeling studies cited and the reviews listed in the reference section indicate the enormous extent of this field.

It should be noted, however, that the examples we consider are restricted to models of fixed properties of membranes, single units, and relatively small networks. There has been no attempt to include models of information storage, i.e., analogs of memory, conditioning, or learning. Emphasis throughout is on the dynamic information-processing aspects of nervous systems.

II. A BRIEF HISTORY OF NEURAL MODELING

The earliest models of nervous systems arose from considerations of neuromuscular action. The fact that nerves activate muscles was known as long ago as the Ptolemaic period, but only in the past hundred years has man begun to resolve two mysteries inherent in this knowledge: how does nerve conduct, and how does muscle contract? For many centuries these two questions were dealt with as one, so that an early nerve model was usually one-half of a nerve-muscle model.

At least from the time of the pre-Galenic physician, Erasistratus, until well after the time of Glisson in the seventeenth century, the contraction of muscle was thought to be a result of swelling or increase in muscle volume. The commonly

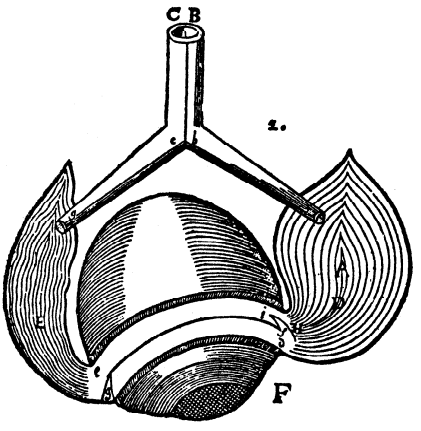


FIG. 1. A model of reciprocal innervation of two muscles of the human eye. For details see text. [From Descartes (17)]

viewed picture was that of a long, inflatable tube whose ends came closer together as the tube was pumped up. The postulated role of nerve was to induce this swelling. The theory of nervous conduction, therefore, held that a liquid or gas flowed through pipe-like nerves to inflate the muscles, a concept that probably culminated with Descartes's theories in the seventeenth century.

Descartes (16) compared the nerves of animals with the water pipes in the hydraulic machines and automata of his time. This comparison was not simply metaphorical; Descartes considered these machines to be good models of conduction in nerve. In fact, he used these machines to demonstrate the plausibility of his theories of nervous conduction and muscular contraction. Among these theories, by the way, are some of the earliest discussions of involuntary reflexes and reciprocal innervation of muscle.

Cartesian philosophy viewed life as mechanistic. To Descartes all lower animals were automatons, and their every action could be explained in terms of the laws of nature [Cohen (15)]. Of all the animals only man had a rational element, the soul, and it was located in the pineal gland. The human body, like the animal body, was a machine; however, since it was partially controlled by the rational soul ("*l'âme raisonnable*"), it was not an automaton.

According to Descartes, "The animal spirits resemble a very subtle fluid, or rather a very pure and lively flame" [Fulton (29)]. These spirits were continuously generated in the heart and ascended to cavities of the brain, which served as a reservoir. (This naive notion was an inheritance from Galen 1400 years earlier, but still was a notable advance over Aristotle's view that the function of the brain is to cool the blood.) From the brain the spirits passed through the hollow nerves to the muscles, causing contraction or relaxation depending on their quantity. The flow of animal spirits in a nerve was controlled by valves located at each junction. The valves were either under the direct control of the pineal gland or indirectly controlled by it through flow and pressure differences in different nerves. When the muscles were filled with animal spirits they swelled in the middle and the ends contracted; when emptied they relaxed.

As an example of Descartes's schemes, consider Figure 1, which is his representation of two reciprocally innervated, antagonistic muscles of the eye (17). Animal spirits flow through hollow nerves into the muscles *D* and *E*. There is a one-way valve at the base of each muscle. Valve *g* (at the bottom of muscle *E*) regulates flow from *D* to *E*, and valve *f* (at the bottom of muscle *D*) regulates flow from *E* to *D*. If the flow in both nerves were equal, both muscles would be equally tense. In the figure, however, the flow in the right branch is assumed to be greater than that in the left; this has two effects. It causes muscle *D* to become inflated, and it causes valve *f* to open and valve *g* to close. With this valve arrangement the spirits flowing through *g* are not held in muscle *E* but flow on into muscle *D*. Muscle *E* thus relaxes as *D* contracts. Valves *f* and *g* are controlled by pressure differential. After the eye motion has been completed, other valves (not shown) are adjusted to equalize the forces in the two branches. Valves *f* and *g* will then both be half open, and the pressures in muscles *D* and *E* will equalize. The animal spirits do not flow centripetally through the nerves, but are eventually lost through pores in the muscles.

Descartes questioned whether or not a subtle fluid flowing through small tubes could be responsible for the rapid, powerful, coordinated actions typical of animals. He relied on previously existing hydraulic automata as models of his system to settle this issue. These machines had been contrived by engineers to do such things as playing musical instruments, pronouncing words, or moving in a human- or animal-like way; they were actuated by water flowing through small tubes controlled by systems of valves. Descartes compared the tubes of these machines with nerves, the hydraulic engines and springs with muscles, the water sources or fountains with the heart, and the central reservoirs with the cavities of the brain.

The mechanistic views of Descartes influenced many seventeenth-century scientists. Among these was Borelli, who was not only a staunch mechanist but was also a champion of the theory that muscles contract by swelling. Borelli (10) proposed a number of mechanical models of muscle, most of which were based on the rhombohedron. If the edges of a rhombohedron are fixed in length, the distance between opposite vertices will decrease over a considerable range of increasing volume. He used this analogy to show the consistency between swelling and contraction and to calculate the forces necessary for muscle contraction under load.

In the last half of the seventeenth century at least three physiologists, Glisson, Lower, and Swammerdam, independently demonstrated that muscle volume did not increase during contractions. In spite of these results the so-called "Balloon Theory" persisted into the eighteenth century. Analogies were still drawn between the heart as a pump for blood and the brain as a pump for nervous spirits [Brazier (12)]. Glisson, on the other hand, had postulated that muscle contracted as a result of intrinsic irritability, a concept that was finally made popular by Haller in the eighteenth century. A muscle was no longer considered simply a passive device waiting to be inflated or swollen by some action of nervous fluid; it was now thought to contain all the components necessary for contraction, needing only a stimulus to set it off.

A new question arose: how could nerves transmit the stimulus to the muscle

with the apparently great velocities such as those observed in reflex action? Haller himself proposed several interesting possibilities. One of these was in the form of an analogy; one might call it the croquet model of nerve. Suppose nerve were constructed of a long row of spheres—each in contact with both of its neighbors. If one were to rap the first sphere sharply, the last one would fly off almost instantaneously and would stimulate the muscle, inducing contraction [Hoff (42)].

Another view was quite prevalent in the eighteenth century. In two very short paragraphs (Queries 23 and 24, included in the second edition of Opticks) Newton (58) postulated that nerves were solid but transparent and that excitation was propagated as optical vibrations through them, exactly as he supposed light was propagated in the "æther." In this, as in most matters, Newton's influence was very strong, and these postulates dominated early eighteenth-century concepts of nervous transmission.

Toward the end of the eighteenth century, however, the concept of "Animal Electricity" began to emerge. Even before Galvani published the results of his frog experiments, electricity was accepted as the cause of discomfort when one touched fish such as *Torpedo* or *Electrophorus*. In 1776 Cavendish (14) published "An account of some attempts to imitate the effects of the *Torpedo* by electricity." This contains a description of what must certainly rank as one of the earliest devices actually constructed and tested as a physiological model. Cavendish built an electric model of the ray, *Torpedo*, and with that model he was able to convince a previously skeptical scientific community that the shock of the ray could indeed be caused by electricity.

The ability of *Torpedo* to produce a shock had been known from very early times [Walker (79)]. Aristotle, for example, wrote about this phenomenon. Redi and Lorenzini investigated the ray and published accounts of the investigation in 1675 and 1678. Lorenzini postulated that the shock was due to corpuscles or "effluvia" that entered the hand when it touched the ray. Réaumer proposed in 1714 that the shock was due to the sharp contraction of the ray's muscles, which he supposed produced a sharp mechanical blow on the person touching the fish; a similar theory had been proposed earlier by Borelli [Grundfest (33)].

By 1772 several scientists had independently proposed that the shocks of the ray were due to electricity, and Walsh tested the new hypothesis [Walker (79)]. He determined that the shock was conducted only through electrical conductors. He also found that the shock was diminished as the number of circuits through which it passed was increased. Unfortunately, he could observe no spark across gaps introduced in the circuit and no electrostatic attraction or repulsion, even with the most sensitive electrometers of the day. Many scientists were ready to accept the theory that the shock was the result of electricity, but these two negative results left them in doubt. Another disturbing point was the fact that *Torpedo* could deliver shocks in salt water, a known conductor, and that these shocks were not significantly increased when the fish was in air.

While Walsh continued his attempts to obtain a spark from the discharge of the real *Torpedo*, Cavendish (14) began a series of experiments with artificial torpedoes. First by reasoning and then by means of these experiments, Cavendish

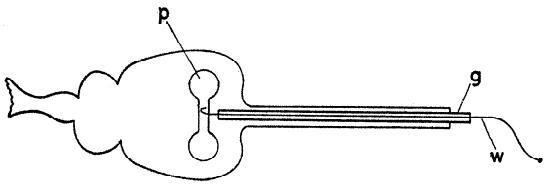


FIG. 2. A model of the electric ray (*Torpedo*). The body was made of wood or leather, with electrodes (*p*) mounted on both sides, each connected to a wire (*w*) that passed through a glass tube (*g*) on the handle. [Redrawn from Cavendish (14)]

satisfied himself and the scientific community that there was "nothing in the phenomena of the *Torpedo* at all incompatible with electricity." His first model ray, shown in Figure 2, consisted of laminated wood in the shape of a *Torpedo* with a long handle. Pewter plates were attached to the top and bottom of the model, and insulated wires led from these plates to the end of the handle. The entire model was covered with sheepskin and was soaked for several days in salt water to increase the conductance of the wood.

Cavendish submerged the artificial torpedo in a trough of salt water and then placed one hand over each pewter plate while an assistant touched the wires to a battery of charged Leyden jars. He repeated this experiment, varying the charges on the individual jars as well as the total number of series- and parallel-connected jars in the battery. He found that he received a greater shock from a large number of weakly charged jars (low voltage, high capacitance) than from a small number of strongly charged jars (high voltage, low capacitance). If he used enough jars, the shock was equivalent to that of *Torpedo* even when the "force of the current" (i.e., voltage) was not enough to jump even the smallest gap in the circuit. In addition, the discharge was completed so rapidly that even the most sensitive electrometers of the day were not deflected. Thus the first two objections to Walsh's results were answered.

The third objection proved more difficult. With the jars charged so that the shock of the artificial ray in salt water was equivalent to that of the real ray, the shock in air was much too great. Reasoning that the conductance of water-soaked leather would be greater than that of water-soaked wood and, in fact, closer to the conductance of *Torpedo*, Cavendish constructed another model made of laminated leather. The Leyden jars now required more charge to produce a shock equivalent to that of the wooden model, but the shock in air was no longer greatly dissimilar to that in water. Thus, with the aid of his model, Cavendish answered all of the major objections to the hypothesis of electricity in *Torpedo* and *Electrophorus* [Lewis (47)].

Fifteen years later, in 1791, Galvani (31) published the results of two experiments: the first showed that electricity could induce contraction in muscle, and the second purportedly demonstrated the presence of electricity in muscle. A third experiment (published anonymously in 1794) is now thought to have definitely proved the existence of electricity in muscle (32).

All three experiments were discredited, however, by Volta, who attributed the results of the second and third experiments to electricity generated by contacts between dissimilar metals and dissimilar tissues, respectively. Both Volta and Galvani discussed analogies between living tissues and electric devices. Galvini com-

pared muscle to a Leyden jar, or capacitor, which was discharged by nerve, causing contraction. Volta, who denied the presence of electricity in muscle, compared his Voltaic cell with the electric organs of fish. The controversy between Volta and Galvani left the scientific world in a state of confusion [Fulton and Cushing (30)]; it remained for du Bois-Reymond to settle the issue once and for all.

Between 1840 and 1850, du Bois-Reymond (18, 19) constructed a pair of very sensitive galvanometers. With them he was able to measure electric currents associated with both nerve and muscle activity. He performed experiments not only with living nerve and muscle, but also with electrochemical analogs of both.

Du Bois-Reymond used these models to extend his thinking and to test his own hypotheses on animal electricity. He used electrochemical analogs, in fact, to develop his "peripolar molecular" theory, which is said to be the forerunner of ionic hypotheses [Brazier (12)]. The analogs themselves were the predecessors of a long series of electrochemical neural models, many of which are still in use today.

Du Bois-Reymond observed what he called the "electrical antagonism between the longitudinal and the transverse sections of muscle," the former being positive with respect to the latter. In reality what he saw was an injury current, but he interpreted his results to mean that an intact muscle has a gross resting potential between its belly (longitudinal section) and its tendons (transverse section). With more refined measurements he found that there were potential differences even within a given section. He attempted to model this potential distribution with a solid copper cylinder, with the cylindrical surface coated with zinc and the ends left bare. The ends represented the transverse section of a muscle and the cylindrical surface represented the longitudinal section. If he applied one end of a wet electrolytic conductor to the zinc and the other end to the copper, a current flowed between the zinc and the copper.

In this configuration, however, the model provided no potential gradations over either the zinc suface or the copper. The cylinder was subsequently submerged in spring water, causing steady currents to flow from zinc to copper. The maximum negativity occurred on the cylinder axis, and the potential was graded from that point to the point of maximum positivity on the cylindrical surface. Du Bois-Reymond measured the currents flowing about this cylinder and found them spatially arranged in a manner similar to the currents in whole muscles.

A flaw still existed in this model. In real muscle the "electric antagonism" existed even in the smallest dissected parts. Thus, if the muscle were cut apart, the smallest obtainable pieces still exhibited a transverse section that was negative to the longitudinal section. This would obviously not be true in the cylinder model. If it were cut in half, parallel to the cylindrical axis, a portion of the zinc suface would be cut away, and part of the longitudinal section would be negative.

Next, du Bois-Reymond (18, 20) proposed a "peripolar molecular" model. In order that every transverse section should always be negative with respect to every longitudinal section (no matter how finely divided the muscle), he assumed that the interior of the muscle was composed of polarized molecules. These "peripolar" molecules, he assumed, were negative at both ends and positive in the center, the negative ends pointing toward the ends of the muscle.

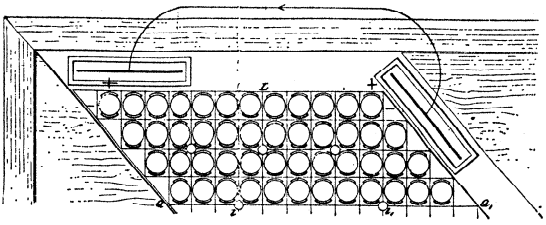


FIG. 3. An electrochemical model designed to test the peripolar molecular theory, consisting of 48 short cylinders (seen on end) with zinc strips mounted on two sides. The entire array was submerged in spring water. [From du Bois-Reymond (20)].

This hypothesis was tested with other zinc-and-copper models. The new models consisted of up to 72 small, hollow, copper cylinders with zinc strips soldered to their sides (Fig. 3 shows a 48-cylinder version). The inside of each cylinder was insulated with varnish. All the cylinders were evenly spaced in a box with the zinc strips oriented in the same direction. The box was filled with an electrolytic solution, and the resulting currents were measured with platinum electrodes.

Du Bois-Reymond was satisfied that these measurements justified his "peripolar molecular" hypothesis. A further justification was found in what he called the "negative variation." During a tetanizing stimulus, the muscle current diminished; the "electric antagonism" had vanished. Du Bois-Reymond felt that this could be adequately explained only in terms of very small polar centers that could rapidly be reoriented.

Electrotonic spread was a mystery at first to the mid-nineteenth-century physiologists who observed it. They were unable to explain how a current applied between two points on a nerve could induce potential changes beyond the region bounded by the points. Du Bois-Reymond attempted to explain this phenomenon also in terms of his peripolar molecule. He supposed that each peripolar molecule might be made up of two dipoles with their poles together. Each molecule would thus be electrostatically neutral and there would be no net polarization of the nerve. He then assumed that an applied current would cause all the individual dipoles to align in its direction of flow, resulting in polarization of the nerve. He further assumed that the polarization between electrodes would induce alignment of dipoles in the regions beyond and thus result in electrotonic spread. This explanation was fairly well accepted until Matteucci discredited it by means of another electrochemical model, one of the first "*Kernleiter*," or "core conductors."

Matteucci (53), in 1863, decided to see if electrotonus was strictly a biological phenomenon. To determine whether or not it could be duplicated in nonliving electrochemical systems, he stretched a platinum wire with a cloth sheath in an electrolytic solution and applied a current between two points on the sheath. He then examined the regions beyond the points of current application and indeed found potentials in these regions. The molecular theory of du Bois-Reymond had hinged on the presence of a pre-existing voltage in nerve—a concept that was then in doubt and later was completely discredited because of the confusion between injury potential and resting potential [Biedermann (294)]. Matteucci had now shown that electrotonus was possible in a system having no pre-existing electromotive force (emf); du Bois-Reymond's theory of electrotonus was superfluous. Matteucci (53, 54) proposed a simpler explanation: electrotonus was due to the

spread of electrolysis by diffusion. This explanation, however, was soon replaced by that of Hermann, who also relied on electrochemical models as analogs of nerve.

Hermann (37, 38) greatly extended the experiments of Matteucci, working not only with cloth-sheathed wires, but also with bare wires immersed in electrolytic solutions. He showed that the electrotonic spread in such models was a result of polarization of the wire surface.

In 1883, Hermann worked with a core model (platinum in zinc sulphate) 2 m long, stimulated at one end with repetitive current pulses. He found electrotonic currents that sometimes attained their maximum value only after the polarizing current was off. As in nerve there were two successive, unequal phases of current, the first being in the same direction as the polarizing current, the second opposite. He attributed the second phase to recovery from polarization.

Whereas Hermann was careful not to draw too strong an analogy between these phenomena and propagation in nerve, Boruttau (11) was not. He experimented with applied alternating current in very long core models of platinum or palladium wire in sodium chloride and found rapid transmission of the negative phase but not of the positive phase. Boruttau equated this with the propagating "negative variation" (spike) in nerve. Most physiologists did not accept this theory, however. Biedermann (294), for example, put forth a very strong argument against it by pointing out that the propagated negative variation in real nerve followed mechanical and chemical stimuli as well as electrical stimuli, which was not the case with the wire.

In addition to Matteucci, Hermann, and Boruttau, a number of physiologists were employing core models to aid in their understanding of the properties of nerve [cf. Taylor (77) and Weinberg (81)]. Some of the simplest of these models were devised by Hering (36). He simply filled hollow grass stems or the exoskeletons of crayfish antennae with saline solution. These models exhibited electrotonic spread even without the central metallic conductor and its progressive polarization. This electrotonus was not analogous to that of nerve, however, in that the polarity gradients within the cylinder were not radially symmetrical, but rather changed sign across the axis of the cylinder.

Most nerve physiologists of the period 1870–1900 were well aware of the *Kernleiter* models. Bernstein (4) and Biedermann (294) both discussed *Kernleiter* in detail in their texts; more modern reviews are to be found in Clark and Plonsey (296) and Taylor (77). Between 1900 and 1910, however, the membrane theory began to command the attention of physiologists [see Nernst (57)], and the popularity of core conductors began to wane. *Kernleiter* models were applicable to electrotonic spread, but the newly postulated mechanisms of action-potential propagation were much more exciting. One of the explanations was Bernstein's ionic hypothesis [see Offner et al. (59)]. Along with it came a new electrochemical model, the iron-wire model.

Not long after Bernstein proposed the ionic hypothesis, Lillie (48–52) became a proponent and introduced into his arguments the first of a long series of discussions of electrochemical models. In 1915 he developed an analog of the injury potential, using a galvanized iron wire immersed in dilute sulfuric acid (49). When

the zinc surface was intact, no chemical or electrical effect was seen. When the outer layer of zinc was removed at some point, a continuous current would flow from the iron to the zinc, and one could observe an "injury potential" that diminished with distance from the point of damage. Lillie drew an analogy between the zinc coat of the wire and the plasma membrane of the nerve fiber.

Lillie's first mention of the analogy between neural propagation and the spread of excitation over "passivated" (oxidized) iron appeared in 1916 (50), although Ostwald had pointed it out in 1900 [Bonhoeffer (7)], and Heathcote (35) had subsequently explored it in detail. If an iron wire is immersed in concentrated nitric acid, its surface is oxidized and becomes insensitive to further attack, even when the wire is transferred to dilute nitric acid. If part of the wire is artificially activated (e.g., if the oxide surface is broken by scratching) the activation spreads, and the wire eventually dissolves in the dilute acid. In nitric acid of the proper concentration, however, a local reaction accompanied by bubbles and a darkening of the metal surface propagates over the wire and is followed by complete recovery (return to passivation) of the wire surface. Immediately after repassivation the wire is resistant to activation, recovering its excitability gradually over a period of about 1 min. The passive wire can be activated (stimulated) mechanically, electrically, or chemically. Subthreshold stimuli may be temporally summed to produce activation, but a slowly rising electrical stimulus is not nearly so effective as one suddenly applied. Lillie showed that in these and many other ways the iron wire behaves like the nerve fiber, and he concluded from this that the basic mechanisms of response were the same.

One of the strongest objections to Lillie's model came from Hill (39), who felt that complete reduction of a passive oxide film was too drastic to be a direct analog of nerve transmission. Hill pointed out that the energy released per square centimeter of iron wire during propagation had to be orders of magnitude greater than the energy released during propagation in nerve. Hill did believe, though, that the iron wire was a good nerve model in many other respects and that much could be learned from it—providing its limitations were realized.

Despite the objections raised by Hill, by Rosenblueth and Wiener (see p. 515), and others, there was very considerable continued development of Lillie's electrochemical analogs. Bishop (5) and Bonhoeffer and his colleagues (6–9) were responsible for many new experiments and analyses; Franck (28, 298) modeled saltatory conduction; Yamagiwa (82–84), attempting to model synaptic activity, examined interactions among contiguous iron-wire models. In a sustained program at Gunma University in Japan, many variants of the iron-wire model were explored (e.g. 2, 3, 44, 86).

Further diversity is found in the voltage-clamp experiments of Tasaki and Bak (76) and in the relaxation-oscillation studies of Carricaburu (13). Other electrochemical systems have provided analogs similar to the iron-nitric acid one; the mercury-hydrogen peroxide model [Vis (78)] and the cobalt-chromic acid model [Tasaki (75)] are representative.

Electrochemical models represent only one of many classes of neural models to appear since the time of du Bois-Reymond. Some of these models were pedagogical,

used by their designers to clarify concepts for students or readers of papers. Pflüger [60, p. 480; cf. Biedermann (294)], Hill (40), and Franck (298) used complicated hydraulic models to illustrate their ideas about excitation. Later authors such as Rushton (69, 70), Katz (301), Hodgkin and Huxley (41), and Grundfest (34) used electrical circuit analogs for this purpose. Rushton (69) also developed an interesting device that was essentially a mechanical neural analog.

Other models were used for exploring or predicting consequences of specific theories of excitation or conduction. Sutherland (73, 74), for example, proposed a gyroscopic model to test his theory that nervous conduction was due to torsional vibrations traveling along a fiber. A row of gyroscopes, fastened to a flexible bar, permitted a mechanical disturbance (twist) at one end to be propagated along the bar; each gyroscope in turn was deflected by the propagating disturbance, passed the deflection on to the next gyroscope, and through its restoring force ultimately recovered its resting position. A traveling wave was thus propagated along the line.

Fabre (21, 22) and Schmitt (71, 72) constructed electronic models in the late 1930's to explore theories of excitation. (As part of his model, in fact, Schmitt invented the electronic circuit now commonly used for many applications and universally known as the "Schmitt Trigger.") These neuron models probably were the first to be made with electronic circuits, and they demonstrated a new kind of flexibility and simplicity in model making.

During the 1930's another type of neural model appeared, the mathematical model [Katz (301), Rashevsky (304)]. The earliest of these, proposed by Rashevsky (67), was based on the proposition that processes of excitation in nerve could be described completely by two time factors (parameters). Monnier (55) and Hill (40) followed with similar, independently constructed theories. The two time factors are time constants in two ordinary, first-order, linear differential equations. The dependent variables of the equations either are membrane potential and threshold potential (Hill) or excitation and inhibition (Rashevsky). The time factor for each variable relates its rate of change to its displacement from equilibrium. The two-time-factor models were all similar; Young (85) showed that Rashevsky's and Hill's models were equivalent.

In addition to mathematical models of excitation there appeared several mathematical models of conduction. In this case they were based on linear partial differential equations. Rashevsky (67, 68) and Rushton (70) both proposed such models. Weinberg (80) later demonstrated their equivalence.

Encouraged by the success of differential equations as representations of nervous activity, Rashevsky (173), Householder (149), and Landahl (155) attempted to extend this form of mathematics to large systems of nerves, treating (without much success) problems of perception and discrimination.

Then in 1943 McCulloch and Pitts (160) published a revolutionary concept in mathematical neural modeling. Viewing the all-or-none behavior of neurons as of first-order importance, they proposed to treat neural systems with discrete rather than continuous mathematics. McCulloch and Pitts applied Boolean algebra and set theory rather than differential equations. They were able to prove that the behavior of all networks of nerve-like threshold elements (now known as "formal

neurons") can be treated by the propositional calculus, and that given any logical expression a net of such elements having corresponding function can be found.

The impact of the McCulloch-Pitts theory was stated well by von Neumann (194): "It has been attempted to show that such specific functions, logically, completely described, are *per se* unable of mechanical, neural realization. The McCulloch-Pitts result puts an end to this. It proves that anything that can be exhaustively and unambiguously described, anything that can be completely and and unambiguously put into words, is *ipso facto* realizable by a suitable finite neural network."

Modeling studies with the formal neuron expanded in several directions. Minsky (163, 164) used the McCulloch-Pitts model to examine learning; whereas McCulloch and Pitts had been interested in deterministically connected nets, Minsky examined the properties of random nets. Kleene (154) went on to build a theory of finite automata around the McCulloch-Pitts model, showing the restrictions on classes of events that could be represented by states in a net of formal neurons. Von Neumann (195) examined the role of error in such finite-state automata, studying the problem of constructing reliable systems from unreliable elements. This prompted McCulloch (158, 159) to look into this problem in more detail, and Verbeek (193), Cowan and Winograd (133), and others have since studied extensively the theoretical stability aspects of networks of formal neurons, analyzing those properties leading to reliable operation despite threshold and connection changes. A survey by Pierce (167) of reliability in networks of computing elements, though primarily related to digital computers, discusses a number of topics that bear on the stability and reliability of neural networks.

A new kind of mathematical model appeared in 1952; it provided analysis rather than mere description of excitation in nerve. Hodgkin and Huxley (261–263) had placed microelectrodes inside the giant axon of the squid and measured changes in axon membrane current in response to stepwise changes in membrane voltage. They were able to distinguish two important components of change in the current: *1*) a rapidly rising component that immediately passes through maximum and declines to a low level (and which they associated with sodium ions flowing into the axon), and *2*) a component that exhibits slower, delayed rise and a very slow subsequent decline (and which they associated with potassium flowing out of the axon).

From their data Hodgkin and Huxley derived four simultaneous differential equations. They showed that the solutions to these equations accounted accurately for the spike potential as well as for its aftereffects.

These four equations constitute the most well known of all neural models. Owing to this fact we have not described the model in detail, but chose instead to emphasize its importance by showing (in following sections) how it underlies many of the subsequently developed models.

This work of Hodgkin and Huxley caused a resurgence of interest in the use of continuous mathematics to describe and analyze excitation in nerve. The studies by Mueller (56) and Hoyt (43) exemplify the continuing development of such techniques. This trend, intensified by continuing discovery of many continuously vari-

able (graded) subthreshold properties, led, in subsequent models of many kinds, to the inclusion of continuous properties as well as the discrete ones that the formal neurons had employed.

The advent of digital- and analog-computer concepts and technology, well established by the mid-1950's, added new dimensions to the foundations on which neurophysiological research is based. Nervous systems began to be considered more and more explicitly as processors of information, literally as biological computers. Also, increasingly more conceptual and technical tools became available to meet the accelerating demands of neurophysiological study. So, too, models of many kinds began to come of age. Let us examine some of them.

III. CONTEMPORARY NEURAL MODELS

A. Excitation and Conduction

1) Passive dendritic trees [*Rall (61–66)*]. From published histological data on dendritic trees Rall (61) concluded that the contributions of the dendrites to the electrical properties of whole neurons had been greatly underestimated. In defending this thesis he used two mathematical models of dendritic trees. The first, an "equivalent-cylinder" model (63–66), was used in cases where excitation was assumed to arise in the soma and spread into symmetrical dendritic trees. In these cases the entire tree structure could be reduced to a single, mathematically equivalent cylinder that had distributed electrical properties (see Fig. 4).

An early version of the equivalent-cylinder model was applied in an examination of the "standard motoneurone" of Eccles. Basing his arguments on anatomical evidence as well as on this plausible model of dendrites, Rall (62) showed that Eccles's estimates of dendritic contributions to whole-neuron conductance were too small, perhaps by as much as a factor of ten. Rall's dendritic model as an improvement on the standard motoneuron led to consistency among anatomical data, membrane resistivity estimates, and whole-neuron conductance data.

Rall (61, 63) also applied his dendrite model to the problem of estimating membrane time constants. Eccles and others (247) had postulated that excitatory synaptic activation resulted in a brief active phase of depolarization that was followed by passive repolarization of the membrane. From the observed passive decay of postsynaptic potentials, the membrane time constant had been taken to be from 3 to 5 msec for cat motoneurons. However, in subsequent studies (247, 251), where steps of current were passed through the soma membrane, faster transients were observed. Time constants of 1–2.5 msec were estimated from the data. In an attempt to provide consistency between the time courses of synaptic potentials and the newly calculated membrane time constants, a prolonged residual phase of synaptic activity was postulated to follow the brief early phase. Thus the earlier concept of a single active phase was replaced by a two-phase active process.

Rall's model disclosed that electrotonic spread into the dendritic tree could account for the newly found rapid transients and that the older estimates of mem-

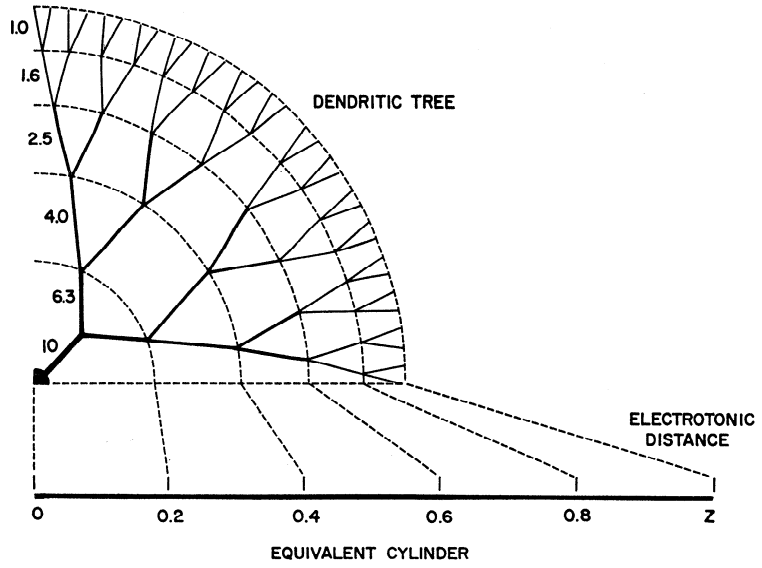


FIG. 4. A particular symmetric dendritic tree and its equivalent-cylinder representation. "Electrotonic distance" between two points is proportional to the time required for electrotonic conduction between them. *Dashed lines* connect points having the same electrotonic distance in both the tree and equivalent cylinder. [From Rall (66)]

brane time constant did not have to be abandoned. It was thus demonstrated that consistency between the observed synaptic potentials and the rapid transients did not have to depend on an assumption of a prolonged active phase of synaptic current so long as one took into account the distributed electrical properties of the dendritic tree. The model thus provided consistency among anatomical data, the transient response of the soma potential, and Eccles's older, simpler model of synaptic activation; it made possible the subsequent reacceptance of the old single-active-phase concept.

For asymmetric trees or for asymmetric disturbances arising in dendritic trees, Rall (66) used a second, more general model. Here the dendritic tree was represented by a series of discrete elements, hence the model was lumped rather than distributed. Each of the elements or "compartments" represents a region of the tree. In applying the model Rall used the mathematics of compartmental systems analysis.

This "compartmental model" can, in principle, be used to handle any specified dendritic structure. One example is shown in Figure 5.

Rall (66) used the compartmental model to study spatial and temporal summation of synaptic potentials generated in various parts of a dendritic tree (see Fig. 5). In calculating the soma-membrane depolarizations resulting from excitatory synaptic inputs at various locations in the dendritic tree, Rall found rather sharp differences between the effects of synapses close to the soma and those of more remote synapses.

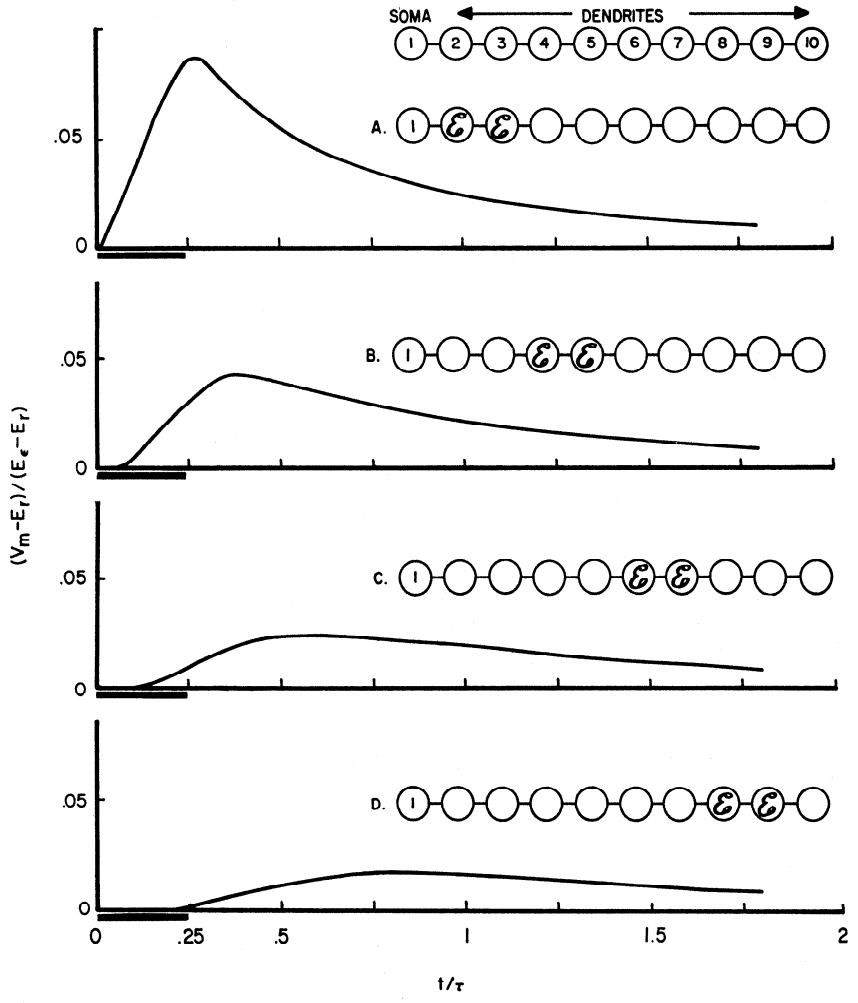


FIG. 5. A sample of results from Rall's compartmental model: time courses of soma potentials in response to excitatory stimuli at various positions on the dendritic tree. Circles (2–10) are compartments representing regions of the dendritic tree. The ascending numerical order of the compartments indicates increasing electrotonic distance from the soma. The *script E* shows the location of the stimulus in each case; the *heavy line* along the time axis shows stimulus duration. [From Rall (66)]

The variations in epsp time course found by Rall in his model are similar to those reported by Fadiga and Brookhart (249) for monosynaptic activation of different portions of a spinal motoneuron in the frog and to those reported by Fatt and Katz (250) for muscle end-plate potentials.

2) *Membrane excitation phenomena* [*Lewis* (*45*, *46*)]. Although the ionic hypothesis, culminating with the Hodgkin-Huxley model, satisfactorily explained the axon

spike potential, no coherent view of subthreshold phenomena existed. Lewis (45, 46) postulated that many of the subthreshold effects found in somatic and dendritic regions should be explicable in terms of the same ionic hypothesis used to explain suprathreshold phenomena. This postulate was based on the assumption that since the dendritic and somatic membranes presumably are continuous with the axon membrane, the basic electrical properties of all three should be similar.

To test these ideas, Lewis developed an electronic analog that simulated the ionic currents of squid giant axon. The model was designed to reproduce the physiological data of Hodgkin and Huxley (261–263) with emphasis on the subthreshold data (the emphasis of the Hodgkin-Huxley model having been primarily on suprathreshold phenomena).

The model consists of a set of active, nonlinear electronic circuits connected in parallel. Each circuit is designed to match the data of Hodgkin and Huxley for the time- and voltage-dependence of a particular ionic conductance across the squid axon membrane.

In addition to the voltage-dependent conductances, the model includes conductances that are synaptically controlled, so that the results of synaptic inputs may also be studied. Presynaptic spikes result in emission of a fixed quantity of simulated transmitter substance. The resulting transmitter concentration is then allowed to decay exponentially, corresponding to a diffusion process or to a first-order enzymatic inactivation. Two synaptic parameters are thus available in the analog—the quantum of transmitter per presynaptic spike and the transmitter inactivation rate. The simulated transmitter concentrations are transformed into directly proportional conductance changes (potassium conductance or chloride conductance or both for inhibitory inputs and a general shunting conductance for excitatory inputs).

Bullock (238, 239) had observed that there are at least three degrees of freedom in synaptic response: a series of synaptic potentials may *1*) be excitatory or inhibitory, *2*) be facilitatory, antifacilitatory, or neither, and *3*) exhibit excitatory or inhibitory aftereffects, or neither, or both. By varying two synaptic parameters (quantity of transmitter per presynaptic spike and transmitter inactivation rate), and by selecting a particular conductance (either potassium, chloride, or general shunt), Lewis obtained synaptic potentials that had precisely the degrees of freedom specified by Bullock.

With the simulated membrane parameters adjusted to the values stipulated by Hodgkin and Huxley, and with a simulated synaptically induced shunt conductance imposed on it, the analog exhibited excitatory postsynaptic potentials (epsp's) with either facilitation, antifacilitation, or neither. The particular mode of response depended on the magnitude of a single parameter—the time constant of inactivation of the transmitter substance. When the time constant was long, facilitation resulted; when it was short, antifacilitation resulted; when it was intermediate, neither occurred.

The occurrence of facilitation in the analog was the result of the simulated regenerative electrical properties of the membrane. The amplitude of individual epsp's was determined not only by the synaptic current but also by a limited, regen-

erative amplification of that current through the voltage-dependent sodium conductance. A regenerative process of this type can provide extremely nonlinear amplification. Thus a slight residual depolarization can greatly enhance the effects of synaptically induced current. Lewis (45) showed, in fact, that a residual depolarization of 3 % of the peak amplitude of the first epsp could result in a 50 % increase in the peak amplitude of the second epsp.

After an epsp, however, the regenerative effects are reduced by a residual inactivation of the sodium conductance. The occurrence of facilitation or antifacilitation in the analog depends, therefore, on whether or not the residual depolarization (resulting from residual transmitter substance) is sufficient to overcome the residual sodium inactivation. This in turn depends on the time constant of inactivation of the transmitter substance. A single variable thus determines the nature of the system, and if the synaptic transmitter is assumed to be inactivated chemically, that variable is equivalent to the concentration of inactivating enzyme available at the subsynaptic membrane.

On the basis of these results Lewis (45, 46) postulated that facilitation may in some cases be the result of postsynaptic mechanisms. This is contrary to the generally accepted belief that facilitation is presynaptic in origin [Grundfest (34)]. One consequence of the postulated postsynaptic mechanisms is the possibility of mutual facilitation or antifacilitation between completely separate presynaptic pathways. If the residual depolarization from excitation at one synapse or synaptic region could spread to another, it would tend to enhance synaptic excitation there. Likewise, an epsp spreading to the other synaptic region would leave a temporary inactivation that would tend to diminish synaptic response there. Depending on which effect dominated, one would expect mutual facilitation or antifacilitation between the two regions.

If mutual facilitation of this type were observed, one would expect it to be accompanied by a slight residual depolarization. If it were a fairly long-lived effect it should be independent of the state of the postsynaptic membrane at the time of the initial (priming) excitation. Regardless of that state, the presynaptic spikes in the priming pathway would induce emission of transmitter substance, and the residue of that transmitter would induce residual depolarization. Furthermore, since this type of facilitation depends on the presence of transmitter substance, one would not expect antidromic spikes in the postsynaptic cell to produce long-term facilitation.

Mutual facilitation of the type predicted by the model was found in *Aplysia* by Kandel and Tauc (270). They observed that a burst of presynaptic spikes in the priming fiber produces *1*) spikes in the postsynaptic cell and *2*) long-lived facilitation of the postsynaptic response to inputs at a completely different synapse. In addition, Kandel and Tauc observed a slight residual depolarization with maximal facilitation. In order to localize the facilitatory mechanism, they *1*) induced spikes by stimulating the postsynaptic cell directly and observed no facilitation and *2*) hyperpolarized the postsynaptic cell during the priming stimulus so that the synaptically induced conductance changes could not produce spikes. This did not alter the facilitatory effect.

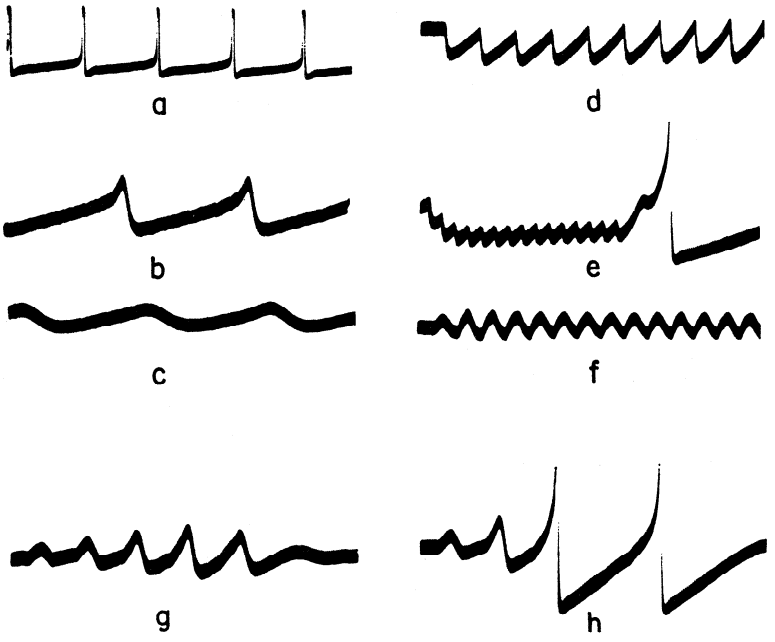


FIG. 6. Waveforms from Lewis's electronic model. Trace *a* shows simulated spontaneous spikes that occurred at 100-msec intervals (spikes are truncated at zero membrane potential). The remaining traces, which depict subthreshold events, are shown with the same time scale as trace *a*, but with the amplitude expanded by a factor of 5. Traces *b* and *c* show pacemaker potentials. Traces *d* and *e* show ipsp's resulting from simulated synaptic activation of potassium conductance (*e* showing excitatory rebound developing into a spike on cessation of inhibitory input). In *f*, inverted ipsp's appear; these result from activation of leakage conductance. Facilitating epsp's are shown in *g* and *h*. Facilitation in *h* was sufficient to produce spikes (4th epsp in *h* is apparently obscured by refractoriness).

Kandel and Tauc believed that these results precluded the presence of postsynaptic facilitation, and they postulated heterosynaptic facilitation. That is, they assumed that a collateral of the priming fiber made synaptic connection to the presynaptic fiber of the facilitated pathway; excitation in the priming pathway would thus spread synaptically to the facilitated pathway, producing long-lived enhancement of transmission in the latter. There was no independent evidence to support this premise, however, and furthermore heterosynaptic facilitation does not account for the observed residual depolarization.

Lewis's model, on the other hand, showed that the results of Kandel and Tauc did not preclude postsynaptic facilitation. Although the model did not rule out presynaptic facilitation, it predicted the physiologically observed mutual facilitation and the test results of Kandel and Tauc, and it accounted for the observed residual depolarization as well, all on the basis of postsynaptic facilitation.

In another class of experiments with the model, weak steady depolarizing currents produced subthreshold oscillations of the membrane potential. These

oscillations were nearly sinusoidal for very weak depolarizing currents and were nearly sawtooth in shape for stronger currents. Still stronger currents produced periodic spikes. These were the three possibilities mentioned by Bullock (238, 239) for spontaneous potentials in single cells; typical results from the model are shown in Figure 6.

In another series of experiments Lewis varied slightly the simulated potassium-ion equilibrium potential. Depending on the value of that potential, he observed periodic pulse pairs or triplets (or even pulse bursts) similar to those observed in some spontaneous neurons. If the simulated potassium potential was reduced to a value somewhat below the leakage-ion potential, periodic inverted spikes similar to those described by Hoyle (265) and Tasaki (289) were sometimes observed.

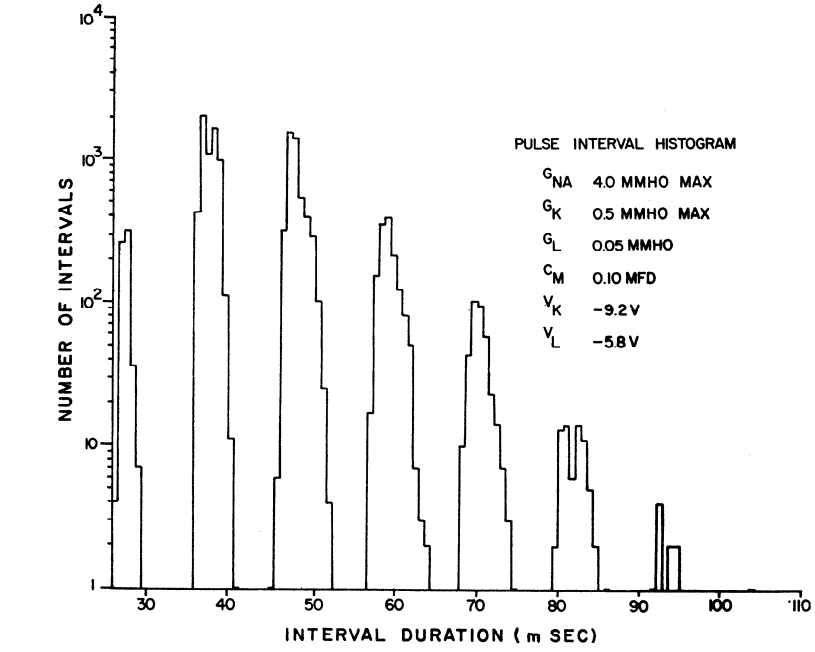
In examining interval histograms for spontaneous spikes in the model, Lewis found a wide variety of distributions as the simulated ionic potentials and the steady depolarizing currents were varied. Of particular interest were multimodal histograms of the type derived by Bishop et al. (236) for cat lateral geniculate units. In the model, relationships of this sort resulted from a tendency for subthreshold oscillations of the membrane potential.

Lewis showed mathematically how the oscillations can result from the Hodgkin-Huxley model. The spontaneous spikes tend to occur on the depolarizing phases of these oscillations, leading to multimodal histograms such as the one shown in Figure 7*A*. The basic form, the variety, and such quantitative measures as the ranges of mode intervals and the variances about mode peaks were all essentially identical to the results of Bishop et al. (236), as illustrated in Figure 7*B*.

Problems of electrical excitability were also explored with this model. The membrane capacitance measured by Hodgkin and Huxley for the squid giant axon was 1 $\mu f/cm^2$. However, capacitances of up to ten times that value have been measured for neural somata that were electrically inexcitable [cf. Araki and Otani (231), Hagiwara and Saito (257), Coombs et al. (242)]. In the model, increasing the capacitance greatly diminished excitability. In fact, totally graded, nonregenerative response was found over the range of physiologically measured capacitance values for electrically inexcitable membrane. Although moderate increases of capacitance in the model decreased excitability to the extent of producing only continuously variable (graded) response, the many varieties of subthreshold response were not altered.

These results lead to two significant conclusions. *1*) It is not necessary to postulate different membrane structure or function to account for electrical inexcitability. The differences between electrically excitable and inexcitable membrane may be viewed simply as arising from different values of capacitance in the same type of active membrane. *2*) The entire gamut of subthreshold responses may be expected to arise independently of whether the membrane is electrically excitable or inexcitable.

This model thus demonstrated that the Hodgkin-Huxley model could be extended in a simple manner to provide consistency between the mechanisms postulated for axonal spike generation and the many diverse forms of subthreshold phenomena found in the often less excitable soma and dendrites.



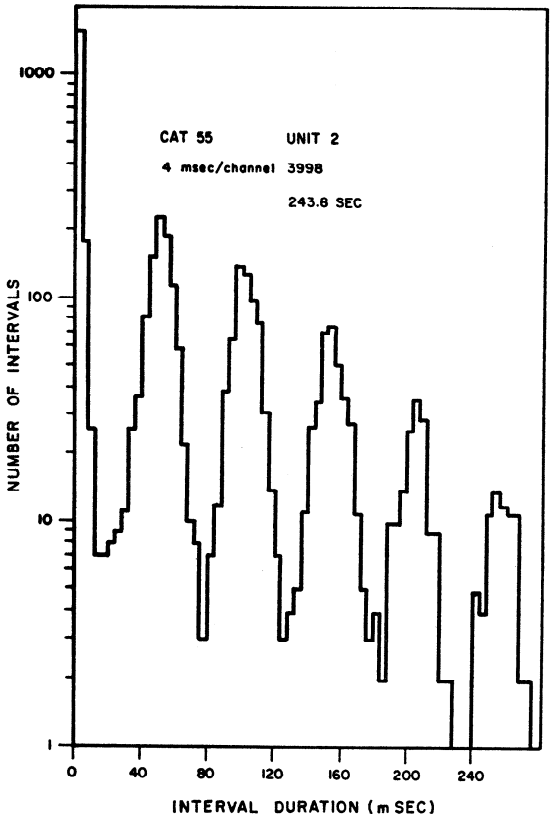


FIG. 7. Comparison of spike-interval histograms from Lewis's model and from lateral geniculate of a cat. *Upper figure* (*A*) shows a sample of data from the model, while *lower left figure* (*B*) shows an example of results of Bishop et al. (236). *Abscissas* in both histograms represent spike intervals; *ordinates* indicate the numbers of occurrences of spike intervals. [From Lewis (46)]

3) Threshold phenomena in axons [FitzHugh (23–27)]. Analysis techniques analogous to those used in nonlinear mechanics were successfully applied by FitzHugh (24, 25) in order to elucidate some of the consequences of the Hodgkin-Huxley equations. In addition, he extracted from those equations a minimum-parameter analog (see p. 515) that he calls the Bonhoeffer-van der Pol model. This model was not intended to be a quantitatively accurate model of squid axon membrane but rather to represent in the simplest mathematical form those interactions responsible for basic axonal properties.

FitzHugh and Antosiewicz (23, 26), initially attempted to use a digital computer to solve the Hodgkin-Huxley equations but found this procedure too slow. They went on to solve the equations on an analog computer, which proved to be considerably more satisfactory. The basic method for evaluating the equation is what was called the "phase-space" technique. The phase-space coordinates are the dependent variables of the differential equations. Since Hodgkin and Huxley specified four simultaneous differential equations, one for each postulated state-variable in the axon membrane, the corresponding phase space is four-dimensional. Solutions to the set of equations are represented in FitzHugh's model by paths through this space. The analog computer was used to find these paths.

Each point on a path represents a specific set of values of the four state-variables of the system. A given set of initial conditions (one for each of the four states) places the system on a particular solution path or "trajectory." The system then follows this trajectory in time until it reaches either a position of equilibrium or a cyclic equilibrium path.

In this treatment of differential equations the independent variable (time, in the Hodgkin-Huxley equations) is included only as a parameterization. For the Hodgkin-Huxley model each solution path has a direction associated with it representing the direction of system change with time.

Many characteristics of a system can be evaluated by phase-plane techniques, even though the time-dependent solution may not be obtained. These characteristics include stability and response maxima and minima. It should be noted that graphical representations of a four-dimensional phase plane must be two-dimensional projections. As will be seen later, FitzHugh was ultimately able to demonstrate adequate representation with only a two-dimensional model.

FitzHugh's examination of the Hodgkin-Huxley equations with phase-plane techniques led to several interesting new conclusions. First, implicit in these equations is what FitzHugh (24) calls a "quasi-threshold phenomenon." This means that the system is capable of apparent all-or-none response, but in principle any response between "all" and "none" can be observed if the stimulus magnitude is precisely controlled.

A second implication of the equations is that the system is potentially unstable but has stable limit cycles in phase space. This means that rather than returning to an equilibrium position, the trajectory approaches a closed path, cycling around and around ever closer to that path. This represents oscillatory behavior or, more specifically, periodic pulse trains in the Hodgkin-Huxley model. FitzHugh used the analysis to show how such periodic pulse trains could result from a steady depolarizing current.

Finally, FitzHugh used phase-plane methods to demonstrate the possibility of metastable plateaus in the Hodgkin-Huxley model. By varying two time constants in the model, for example, he found behavior very similar to that found in the squid axon by Tasaki and Hagiwara (290) after injection of tetraethylammonium chloride; on being stimulated the treated axon produces an action potential that is nearly normal up to the repolarization phase. Rather than subsequently returning through a hyperpolarizing phase to equilibrium, however, the membrane potential returns to a value intermediate between the full spike potential and the equilibrium potential. It remains at this plateau for 20 or 30 msec and then passes through a prolonged phase of hyperpolarization to equilibrium. While the membrane potential was at the plateau level, the recovery processes could be initiated by a brief anodal stimulus. To be effective, however, this stimulus had to be above a certain threshold.

In the model the potentials computed for the modified Hodgkin-Huxley system exhibited the initial peak of depolarization, the intermediate plateau of 20–30 msec, the prolonged phase of hyperpolarization, and the abolition of the plateau by anodal stimulation above a certain threshold. The quantitative results of the computations agreed well with the physiological measurements for the plateau potential, its abolition, and the time course and magnitude of the refractoriness that followed a plateau.

The conductance values computed for the model during and after a plateau were considerably larger, however, than the physiologically measured values. Thus the Hodgkin-Huxley model did not completely fit Tasaki and Hagiwara's data. Nonetheless, the geometrical properties of that model in phase space accounted for almost all of the measured behavior of the squid axon under the influence of tetraethylammonium chloride.

FitzHugh pointed out that many other models may exhibit geometrical properties equivalent to those of the Hodgkin-Huxley model. He decided to represent this entire class of models with a single minimum-parameter model. This was derived by combining the equations of van der Pol (228) for nonlinear oscillators with those of Bonhoeffer (6, 7) for the iron wire in nitric acid. This "Bonhoeffer-van der Pol model" (BvP model) was expressed as two simultaneous differential equations and had two variables of state. The phase space was thus only two-dimensional and could be completely represented graphically (see Fig. 8). FitzHugh demonstrated the similarities between the BvP and the Hodgkin-Huxley models by comparing their phase-space geometries as well as their responses to various types of stimuli. He used the more tractable BvP model to examine both single-pulse and pulse-train activity and found the results to be qualitatively and quantitatively equivalent to those obtained with the more complicated Hodgkin-Huxley model.

B. Pulse Processing in Single Neurons

1)Inhibitory driving of a pacemaker [Perkel et al. (114)]. Examining intracellular records from *Aplysia,* Moore and Segundo (108) noticed that certain pacemaker cells apparently make inhibitory or excitatory synaptic contact with other pace-

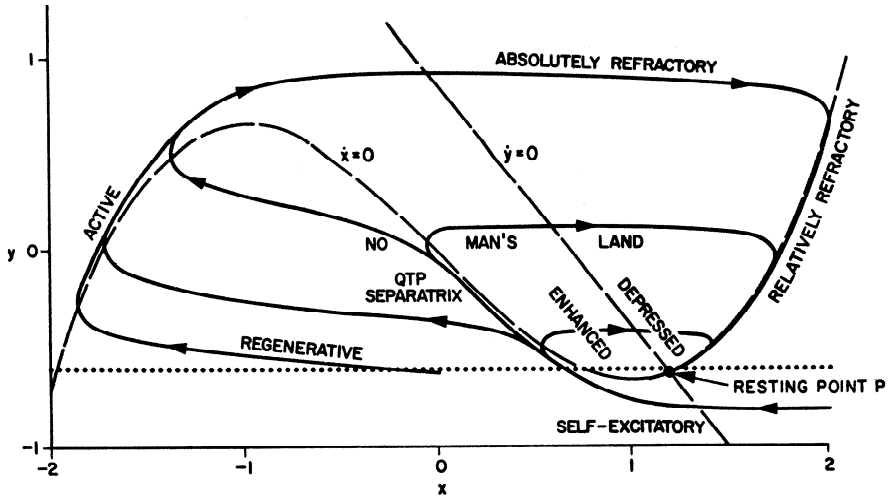


FIG. 8. "Phase-plane" representation of FitzHugh's BvP model. Coordinates x and y are state variables and are analogous to excitation and refractoriness (or accommodation), respectively. Each *dashed line* represents positions of rest for one of the state variables, so the intersection (P) of these lines is a point of equilibrium for the entire system. If a set of initial conditions (e.g., those after a stimulus) correspond to a set of coordinates other than those of P, the model follows the appropriate trajectory (shown as a directed path) until it reaches P. The various phases of the trajectories are labeled with the names of analogous physiological states. The large trajectory loops passing through the phase labeled "active" represent spikes. The smaller loops indicate graded or subthreshold potentials. [From FitzHugh (24)]

maker cells, such that periodic ipsp's or epsp's are produced in those cells. An ipsp would lengthen the natural interval of the receiving cell, while an epsp would shorten it. Occasionally there was seen a receiving pacemaker cell whose spike interval was lengthened to the extent that the cell fired in a one-to-one ratio with the ipsp's. Thus Moore and Segundo had observed stable interaction of two cells brought about by open-loop inhibitory coupling. Perkel (110–112) studied this stable interaction by means of a digital computer simulation of a pacemaker neuron [see also Perkel et al. (113)].

It is interesting to note that Perkel's model had an advantage not present in many other digital computer simulations of neural elements [e.g. Farley and Clark (139), Josephson et al. (153)]. In this model, time was not quantized but was treated as a continuous variable. Rather than sampling at fixed time intervals for events in the model, the computer was programed to calculate, after each event, the time to the next "interesting" event. This was done by simultaneous solution of continuous equations for the state variables in the model. A similar technique had been employed by Reiss (175) in the simulation of a "neuromuscular organism."

Perkel's model was a fairly simple minimum-parameter model. It included only those characteristics he believed to be essential. After a spike, the model had an absolute refractory period followed by hyperpolarization that decayed exponentially, the membrane potential returning toward equilibrium. If the threshold level

was below the equilibrium potential, the cell would fire again on its return toward equilibrium. If threshold was above the equilibrium potential, the cell would reach equilibrium and come to rest. For each presynaptic input, a potential was instantaneously added to the membrane potential; the membrane potential then returned from this new value toward equilibrium with the same rate constant as that for recovery from a spike. The added potential was positive for epsp's and negative for ipsp's.

Perkel adjusted the parameters of his model so that it simulated the spontaneous activity of pacemaker cells in *Aplysia*. To induce spontaneity he set the threshold below the equilibrium potential. Applying periodic ipsp's with an interval just slightly longer than the natural pacemaker interval, he observed the same sort of stable interaction that had been seen in *Aplysia*; the pacemaker spikes occurred in a one-to-one ratio with the ipsp's. Other stable modes of synchronization in the model were discovered, and the range of stability was established for each case. The results are presented in Figure 9 in the form of a plot of mean pacemaker firing frequency as a function of inhibitory input frequency.

These results brought to light two interesting implications. First, several stable modes of interaction were predicted by the model. These modes corresponded to "higher-order interactions" (such as one ipsp for every two pacemaker spikes), and "fractional-order interactions" (such as two ipsp's for every spike). Second, in a region of stability, an apparently anomalous relationship occurs; the firing frequency of the pacemaker cell *increases* with increasing inhibitory input frequency. These findings were then confirmed independently with a more general mathematical model of the ipsp-pacemaker interaction.

A further check of the *Aplysia* recordings was instigated as a result of the simulation studies. This revealed higher-order and fractional-order stability modes—just as predicted by the computer model. In addition, some predictions from the more general mathematical model were verified from the recordings. These were predictions of stability range boundaries and stable phase relationships between ipsp's and pacemaker spikes. The latter were predicted with great accuracy (114).

Because of incomplete data, a curve similar to that of Figure 9 could not be obtained for *Aplysia*. This type of curve had been obtained independently, however, by Schulman for a monosynaptically inhibited stretch receptor cell in the crayfish and appears in the Perkel et al. report (114). It is reproduced here as Figure 10.

Under the influence of stretch, the crayfish cell acts like a pacemaker, producing regular periodic spikes. This fact, together with the accessibility of a presynaptic inhibiting fiber, provided an experimental advantage not present in *Aplysia*. Schulman was able to partially control the average spike frequency by varying the degree of stretch, and he had complete control over timing of the ipsp's. It can be seen that the curve of Figure 10 is almost identical to that predicted by Perkel (Fig. 9) and that the results include verification of the predicted "anomalous" increase in pacemaker frequency with increasing inhibitory input frequency.

2) *Input-output relations in motoneurons* [*Jenik and Küpfmüller* (101–103, 105)].

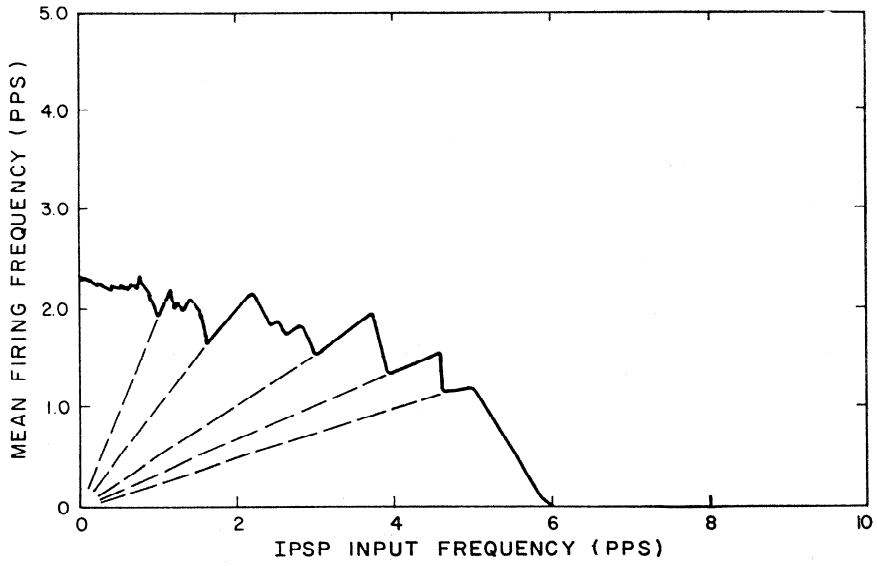


FIG. 9. Data from simulated inhibitory firing of a pacemaker neuron. *Dashed lines* are drawn from the origin to segments of the data showing stable interaction between pacemaker spikes and incoming ipsp's. Increased inhibitory input over these segments results in increased output spike frequency. In the other segments of data, stable interaction is absent, and increased inhibitory input results in reduced output frequency. [From Perkel et al. (114)]

Küpfmüller and Jenik developed electronic neuron models specifically designed to be analogs of mammalian motoneurons. These models were intended primarily for studies of pulse processing in single cells and small nerve nets.

Preliminary explorations employed a digital computer simulation that extended the Hodgkin-Huxley model to include synaptically induced currents (103). It was found that this extended system behaved very much like the giant synapse of the squid *Loligo*. Both the squid giant synapse and the model exhibited very similar nonlinear relationships between input intensity and epsp amplitude; also, epsp's in both had hyperpolarizing overshoot before returning to the resting potential.

Nonlinearity and overshoot are not normally found in the epsp's of mammalian motoneurons, so Küpfmüller and Jenik (102, 103) modified the extended Hodgkin-Huxley model in designing their subsequent electronic analog. Above threshold it behaves very much like the Hodgkin-Huxley model. However, two important distinctions must be noted: *1*) the Küpfmüller-Jenik model responds linearly to most subthreshold stimuli or synaptic inputs (as in motoneurons, epsp's are proportional in magnitude to the intensity of the presynaptic input, while ipsp's are proportional to input intensity for low-intensity values, saturating at the potassium potential as input intensities become high), and *2*) the time constants and other parameters were chosen to simulate mammalian motoneurons. Consequently the model exhibits epsp's, ipsp's, and action potentials essentially identical to those found in many motoneurons.

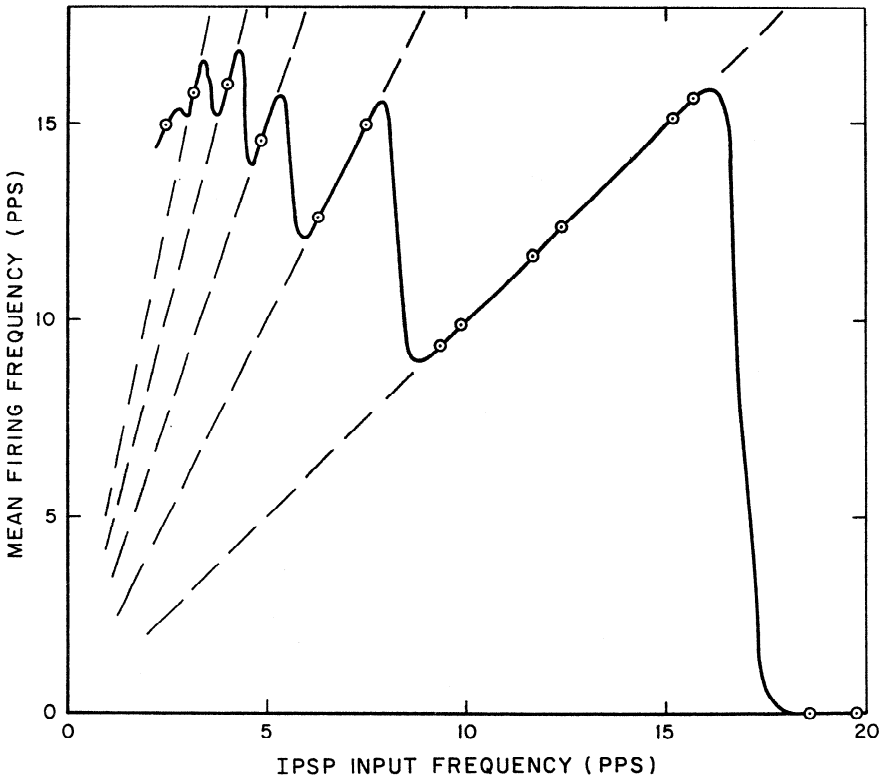


FIG. 10. Data showing inhibitory driving of a crayfish stretch receptor. Two regions of stable interaction are apparent at ipsp frequencies greater than 5 pps. Other regions of stability were inferred from single points of data. Data on right exhibit wide segments over which increased inhibitory input results in increased output spike frequency, as predicted by Perkel's model. [From Perkel et al. (114)]

As a result of their early modeling studies, Küpfmüller and Jenik (105) proposed a new graphical method for characterizing neurons with regard to their pulse-processing characteristics. They call this the "ν-Diagram," which is based on the response of a neuron or a neural model to a periodic input-pulse train (a train of evenly spaced pulses). It is basically a map showing areas of constant ratio between average output-pulse frequency and input-pulse frequency. This map is drawn with log input frequency as the abscissa and relative input intensity as the ordinate. Figure 11 shows a typical ν-Diagram for Jenik's electronic model. Küpfmüller and Jenik (102, 103, 105) interpret these diagrams in terms of neuronal pulse processing.

Jenik developed a detailed classification scheme for pulse trains. In addition, he defined two ranges of operation according to the ratio of pulse duration to pulse interval in a given train of input pulses. The region where pulse interval is comparable to pulse duration is the "integrating range," where the effect of any single

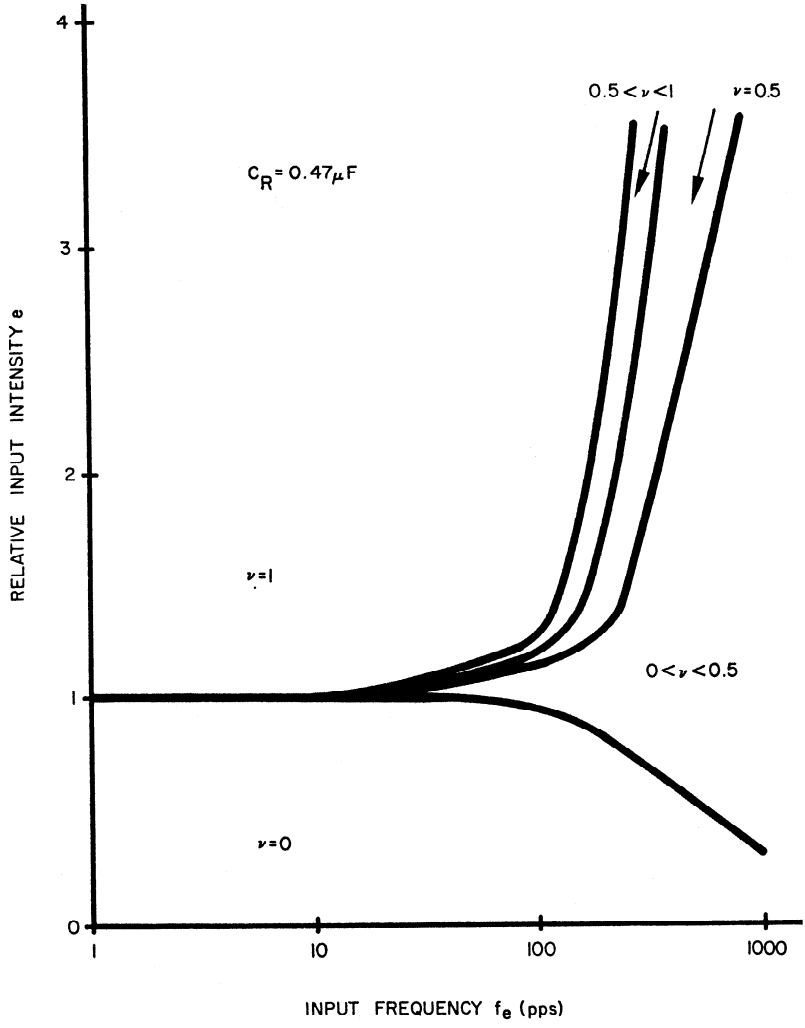


FIG. 11. A ν-diagram for one of Jenik's model neurons. The bounded regions have constant ratio (ν) of output spike frequency to input stimulus frequency. *Ordinate* is the ratio of input pulse amplitude to the resting threshold. Contours are plotted for periodic stimulus-pulse trains. [From Jenik (103)]

pulse is lost. In the other range, called the "switching range," the pulse interval is long, and individual pulses are important.

Jenik was primarily concerned with the switching range. He was able to demonstrate mathematically as well as with the electronic model that neurons in the switching range should be able to perform not only the basic arithmetic operations of addition and subtraction but also that of multiplication. This is particularly sig-

nificant, since many investigators of biological control systems have postulated the need for some sort of multiplication [e.g., Fender (208), Reichardt (218), Stark et al. (224)]. The multiplication that Jenik found was between two noncoherent, periodic, subthreshold pulse trains converging on and exciting a single model neuron. The average output frequency is proportional to the product of the two input frequencies.

Rapoport (115) had also demonstrated addition and multiplication of average frequencies for two pulse-train inputs to a single mathematical neuron model. His treatment was very similar to that of Jenik, but he considered the case of Poisson spike-interval distributions in the two input channels. Jenik's treatment took into account noncoherent periodic pulse trains.

In addition to multiplication and ν-Diagrams, Jenik examined several other forms of pulse processing with his models. In two cases he confirmed results of other modelers working essentially simultaneously and independently with other types of models. He found, for example, that his model could act as a coincidence filter with a very narrow (temporal) bandwidth and that the bandwidth was very strongly dependent on input intensity. These results are similar to those of Reiss and of Schief (see p. 570).

In another instance Jenik attempted to store temporal pulse patterns in loops of model neurons. He found, as did Crane with his neuristor lines (see following section), that the original pulse patterns vanish in a relatively short time.

Jenik's model lies between a minimum-parameter analog and a complete membrane simulation, being somewhat closer to the latter. Jenik (102) pointed out, however, that many of the experiments performed on his models could be repeated with qualitatively equivalent results on minimum-parameter models. He shows, for example, that one can obtain addition, subtraction, and multiplication with Harmon's *neuromime* [electronic analog of a single neuron; see van Bergeijk (120)]. In addition, Reiss's model (see p. 569), which yielded equivalent results for coincidence-filter experiments, is a minimum-parameter model. The important point here is the demonstration that additional complexity did not fundamentally alter the basic results obtainable from minimum-parameter models.

3) Idealized axon models [*Crane (88–90)*]. For many years axons, submarine cables, and iron-wire models were classified under the general heading of "core conductors" or "*Kernleiter*," and much was learned about axonal conduction simply by analogy with conduction in the other two. Core conductors were classified as such by virtue of their structure. A core conductor was any cylindrical conductor surrounded by an insulating or semi-insulating sheath and immersed in a conducting medium.

More recently a new class of devices appeared that may also be useful in studying the axon by model or analogy. First proposed by Crane (88, 89), *neuristors* are identified by their properties of conduction rather than by their structure. A neuristor is any device in which a one-dimensional channel propagates signals in the form of discharges and exhibits *1*) a stimulus threshold, *2*) attenuationless propagation, *3*) uniform velocity of propagation (assuming uniform geometry), and *4*) an absolute refractory period at any point after passage of a discharge.

Neuristors are thus characterized by a functional rather a physical description.

Two basic types of junctions are defined for neuristors: T-junctions, where coupling is excitatory through the trigger mechanisms, and R-junctions, where coupling is inhibitory through the inactivation or refractory mechanism.

Crane (88, 89) has shown how a large family of logical functions may be derived using combinations of T-junctions and R-junctions. In addition, with different experimental neuristor models built with electric relays and tunnel diodes, Crane and Green (90, 95) observed several quite interesting transmission phenomena. If, for example, two pulses are traveling on the same neuristor line, one of three things can happen. First, the trailing pulse may be repelled by the leading pulse, regardless of the magnitude of separation. This results from a monotonic recovery from refractoriness after the first pulse. Second, the pulses may assume a fixed, stable spacing owing to an oscillatory recovery process. Crane calls this effect "pulse locking." Finally, the pulses may coalesce owing, for example, to structural discontinuities in the line. This effect is called "rear-end collision."

Another phenomenon, "pulse trapping," occurs when two neuristor lines are connected side by side in a manner allowing sharing of refractoriness. If the two lines have different propagation velocities, a pulse in the faster line, upon catching up with a pulse in the slower line, may be trapped slightly behind it so that the two pulses travel together at the lower velocity. This phenomenon has been observed in axons [Katz and Schmitt (271)].

Although he does not intend the neuristor as a neural model, Crane has documented many similarities between neuristors and axons. He shows how various neural phenomena (such as accommodation and pacemaking) can be simulated with neuristor lines (95). He also compares various neuristor lines with the Hodgkin-Huxley model, showing where analogies exist. Considering the analogous properties of neuristors and axons, along with the fact that logically complete systems can be constructed from neuristors, Crane has postulated that axon interactions themselves may provide powerful information-processing capabilities, even without complicated synaptic interactions or other integrative processes. Some of the evidence for axonal interaction such as that adduced by Arvanitaki (233), Bullock (238), and Grundfest (254) gives support to Crane's conjectures and suggests the possible neurophysiological utility of neuristor concepts.

A similar technique for obtaining axon-like signal generation and propagation was developed by Hamilton (97). He explored gas-ion axon models based on analogies between the discharges of low-pressure gases in electric fields and the action potentials of neurons.

Hamilton (97) and Vinetz (124) examined two basic classes of gas-ion models, two-electrode arrays and three-electrode arrays. Only the two-electrode array is considered here. Electrical energy is stored along the array in the capacitances that exist between the electrode pairs. The space between the electrodes is filled with a gas, such as argon, at low pressure. The electric field strength is set at a value just below that required to break down the gas.

A stimulus in the form of a slight increase in field strength at one end of the array will cause a discharge between the electrodes at that end. The resulting gas

ions and the distortion of the local field lines will cause a breakdown at the neighboring electrode pair, and the discharge will propagate in an all-or-none manner along the array, leaving a wake of refractoriness. In addition to all-or-none activity, graded responses have been obtained at individual electrode pairs. Subthreshold stimuli can be linearly or nonlinearly summed in time, and an array may also be adjusted to produce spontaneous or pacemaker activity.

4) Nonintegral frequency division [*Harmon* (*99*)]. During the course of cataloguing the input-output properties of a neuromime, it was of interest to investigate the variations in firing pattern of a single unit as a function of excitation amplitude for a constant-frequency train of stimulus pulses. It is well known, of course, that in some preparations frequency division occurs for diminished excitation amplitude. In such cases every *nth* stimulus pulse succeeds in evoking a response spike, owing presumably to temporal summation of postsynaptic membrane responses, each of which alone is insufficient to exceed threshold. The ratio of input to output frequencies for such action will always be integral (i.e., 1:1, 2:1, 3:1 . . .) over the effective range of temporal summation.

In the modeling experiments (99) a single neuromime was stimulated with pulses whose frequency was constant and whose amplitudes were progressively reduced (as in the case of presynaptic inhibition or, equivalently, with increasing threshold). Besides the anticipated integral ratios of input/output frequencies, a surprising class of nonintegral ratios was observed (e.g., 5:4, 3:2, 14:3, etc.).

These nonintegral ratios were not explicable simply on the basis of temporal summation or of recovery from refractoriness alone. It was found that this behavior depends on the relative time courses of excitation and of threshold recovery and on the phase relationships between the stimulus-induced excitatory pulses and the response spikes. Since the time course of recovery of threshold is not necessarily phase-locked to the stimulus pulses, the recovering threshold may intersect the stimulus-induced excitatory potential at progressively later phases until it misses altogether, and there is no response. Recovery from refractoriness is complete by the time the next stimulus pulse arrives so that intersection occurs quite early. Phase recession starts again and continues until another pulse is missed. Thus single stimuli are repetitively and regularly missed, resulting in nonintegral input-output ratios.

Of course, in the presence of noise in threshold or in prespike amplitude, missing can occur. In general, however, that missing will be irregular, and the ratio of pulse-stimulation frequency to spike-response frequency will be on the average nonintegral [see, for example, Bullock and Chichibu (240)]. In contrast the phenomenon examined in the modeling study was for the noise-free case where missing is perfectly regular.

A neurophysiological study prompted by the modeling results disclosed that nonintegral firing ratios, previously unknown, do in fact exist. Wilson (291) identified the phenomenon in the locust flight motor system, finding 3:2 and 8:5 firing ratios. An example of one of the nonintegral ratios found in the locust is shown in Figure 12.

In concurrent experiments using the models, Wilson demonstrated a second

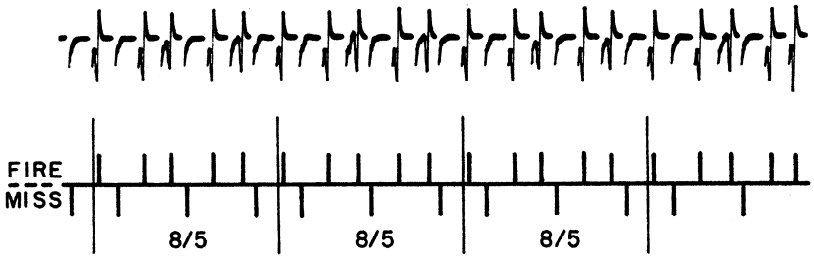


FIG. 12. Nonintegral frequency division predicted by Harmon's modeling experiments and found by Wilson in locust flight motor neurons. Five thoracic ganglion responses occur for every eight evenly spaced stimuli. This series of three 8:5 stimulus-response ratios arises from repetitively missed spikes owing to accumulating refractoriness. A regular progression in phase of response spikes with respect to stimulus artifacts can be seen. [From Wilson (291)]

mechanism that produces equivalent results. This alternative process depends on accumulating refractoriness, and Wilson concluded that both mechanisms may operate together in locust nervous systems.

5) *Reverberation in cortical neurons* [*Burns* (*87*)]. Though the many important questions regarding long-lasting facilitation and elementary learning phenomena remain largely unanswered, several studies have suggested some interesting possibilities for underlying mechanism. Some of these studies are intended to elucidate the nature of normal synchronized activity in neural tissue and of abnormal massive discharge such as epileptiform behavior. In each case the mechanisms by which single units or cell ensembles can be triggered into self-synchrony are of great interest.

Burns (241) showed that a few strong stimuli applied to the cortex of cat can produce a repetitive burst response that considerably outlasts the stimulus. These so-called "afterbursts," observed in neurologically isolated cortex, may persist for as long as an hour. Local radially directed current flow can either enhance or eliminate afterbursts, depending on the direction of the flow. It was proposed that the mechanism underlying the triggered, sustained afterburst activity had to do with differential repolarization of neurons, the deep somatic ends repolarizing more slowly than the superficial ends. Burns supposed that the consequent current flow between the two ends during postfiring recovery led to re-excitation. Thus, once started, such activity could be cyclic and self-supporting.

Burns (87) used electronic analogs of type-B cortical neurons in order to test quantitatively the consequence of the mechanism he had assumed responsible for afterbursts. The major assumption on which the model rests is that, after firing, a neuron recovers its resting membrane potential in two phases; the first is rapid, the second is relatively slow. The slow phase is assumed to have different time courses for the two ends of a given cortical neuron; the recovery of the deep end lags that of the superficial end. When a sufficient number of properly spaced conditioning stimuli are applied, the potential difference between these two recovering ends can accumulate to the point where the resultant current flow is suprathreshold.

The results obtained with the electronic model having the appropriate temporal parameters closely approximated the physiological observations. In response to a single stimulus, a pair of linked units produced a prolonged burst resembling the actual cortical response in great detail, including afterpositivity, which increased with burst length. For multiple stimuli, the relationships among their number, their frequency, and the number of afterbursts produced were qualitatively and quantitatively similar in model and prototype. Analytical consideration of the model also permitted estimates of two time constants that were postulated for the physiological system, but experimental confirmation of these time constants has not yet been made.

An interesting result of this model is that simple mechanisms are proposed that permit relatively long-lasting, reverberating, and patterned activity in cell assemblies that can be abolished by transient interruptions caused by extrinsic neural signals. Similar studies, relating to dynamic stability in large nets, are discussed in section *C, Networks.*

6) Temporal resolution in sensory systems [*Harmon et al.* (*100, 107*)]. The actions implicit in perceptual or behavioral data often raise important questions concerning the neurophysiological substrates that may in turn lead to explicit, testable models of nervous action.

It seems important to concentrate on problems such as these where behavior and underlying mechanism can readily be studied in common. As Jung (269) cogently put it ". . . the coordination of psychophysiological and neurophysiological experiments will lead us further than either of these approaches alone. The combination of the two may indicate a *via regia* to the exploration of human sensory information. The unilateral pursuit of only one method without regard to the other risks either blind neurophysiological recording or fancy psychological hypotheses, and either of them may lead to minor sidetracks and end in a jungle of barren facts or luxuriantly growing speculations."

Two examples of models designed to integrate physiological and psychophysical knowledge are given in this section. Both were prompted by psychophysical findings, and both relate to temporal discrimination properties of sensory systems; one concerns audition, the other pertains to vision.

An experiment performed by Guttman et al. (256) showed that human binaural resolution of separate clicks in closely spaced pairs improves as repetition rate is increased. In this experiment click pairs are presented to one ear while a single "probe" click is delivered to the other ear. This triad is repetitively presented, and the subject, having control over the relative timing of the probe click, is required to adjust it until he perceives a "fused" binaural image. If the two clicks of the pair presented to one ear are widely separated in time, the subject has no difficulty in aligning the probe click with either member of the click pair, thus obtaining two separate fused images. However, if the two clicks of the pair are very closely spaced, temporal resolution is lost, and only one fused image can be found. Now if the repetition rate of the click triads is *increased,* separate resolution of the two clicks is again obtained. Thus the curious result is that the minimum resolution interval is inversely related to the repetition rate.

Guttman, van Bergeijk, and David proposed a model based on the statistical behavior of a population of neurons. Although that model provided a qualitative fit to the data, no attempt was made to obtain a quantitative fit, and owing to its statistical nature, physiological verification would be difficult.

An alternative hypothetical model to account for the phenomenon, based on cochlear-nucleus action, was proposed by Harmon et al. (100), and experimental data were derived from an electronic analog arranged to simulate single units of the cochlear nucleus. This model related more directly to the available neurophysiological evidence, and it was made to fit the psychophysical data quantitatively. It emphasized the information-processing power implicit in the action of a single neuron.

The central postulate of the model is that neural responses of the auditory nerve to single clicks are transformed into burst responses by cochlear nucleus neurons and that burst length varies inversely with repetition rate. The changes in burst length are assumed to be accomplished by recurrent collateral inhibition, which acts to quench bursts. Increasing repetition rate serves to increase inhibition level, which progressively shortens burst length; thus two sequential bursts that at a lower repetition rate would have merged together can be separately resolved.

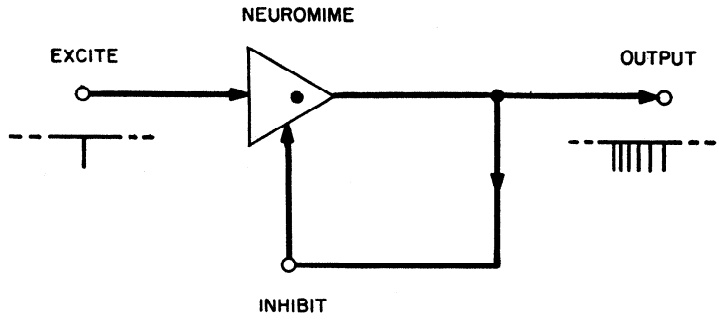
The presumed properties of cochlear nuclear units were based on previously observed firing characteristics for neurons in which bursts are found for single click stimuli (286) and where burst length varies with stimulus repetition rate (281).

The configuration of the model is schematized in Figure 13*A*. Its basic action, depicted in Figure 13*B*, is as follows. In the fused case, excitatory potential is increased in response to the first stimulus pulse (S_1), decays until the arrival of the second pulse (S_2) when it again is increased, and then it decays back to resting level. Meanwhile, when the excitatory potential crosses threshold, an output burst is initiated. Threshold is changed during this burst, owing to self-inhibition; it increases until it crosses the excitatory potential. Firing then ceases, and the threshold slowly decays to resting by the time the next stimulus pulse pair arrives. Since the excitatory potential exceeds threshold over the entire period between pulses (δt), the two output bursts due to S_1 and S_2 are effectively fused into a single, protracted burst.

In the unfused case δt is held constant, and the pulse-pair repetition rate is higher than in the fused case (thus in Fig. 13*B*, $P_2 < P_1$). The threshold decay time is now relatively long compared to the shortened repetition period. Consequently threshold has not yet returned to its resting value by the time a new pulse pair arrives. In thus starting from an increased level, threshold attains a greater maximum value than in the fused case. It becomes sufficiently great to intersect the decaying excitatory potential in the S_1-S_2 interval, whereupon firing ceases; as a result the output bursts are sufficiently shortened to separate clearly the S_1 and S_2 responses.

The electronic model produced temporal discrimination effects that quantitatively replicated the significant aspects of the psychophysical data; as stimulus repetition rate was increased by a factor of 16, the minimum detectable interval between two input pulses diminished by a factor of 2.

The model's action also fitted the results of another series of psychoacoustic



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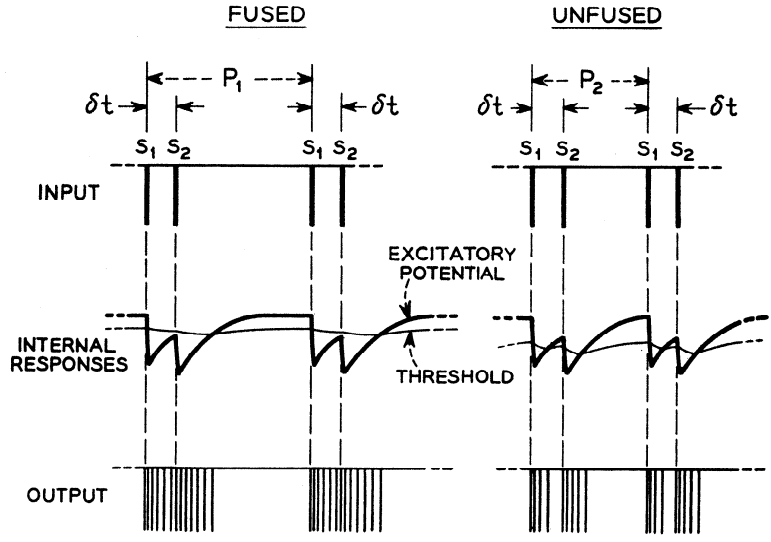

B

FIG. 13. *A:* configuration of neuromime with self-inhibition. Output burst is used to provide quenching inhibitory feedback. *B:* schematically represented action of self-inhibiting neural model to obtain burst-length variation as a function of pulse-pair repetition rate. *Left:* pulse pairs S_1S_2 repeating with period P_1 are not separately resolved in resultant output bursts. *Right:* shortening the repetition period to P_2 results in each pulse in pair S_1S_2 being separately represented in output bursts. See text for details. [From Harmon et al. (100)]

experiments in which the addition of a small amount of noise *enhanced* temporal resolution. Hall (259) had found that at a click-pair repetition rate of 20 pps the effect of adding a small amount of white noise was to *reduce* the minimum interval for 50% detection of the second clicks by 0.5 msec. This behavior was also observed in the model.

Another result of these experiments is that the model predicts one time constant associated with excitatory decay in a cochlear nucleus single unit and another

time constant associated with recurrent inhibitory feedback. Both provide explicit bases for subsequent physiological verification. Further, the precise nature of burst responses to specified classes of stimuli is predicted.

In another modeling study of sensory processing, problems relating to visual flicker-fusion were explored. The inability of visual systems to follow the changes in intensity of a flickering light has been voluminously documented for over 200 years. Yet as Landis (272) pointed out ". . . there is no comprehensive theory of flicker. Even such a simple point as whether the flicker-fusion threshold is dependent on retinal function limitations or on limitations imposed by the central nervous system has never been clearly answered."

Here is a prime example of an area where both physiological and psychophysical knowledge not only are incomplete but are almost totally unrelated. Intriguingly, however, the phenomena of flicker-fusion seem to be well suited to a combined attack using both disciplines.

In flicker-fusion, problems pertaining to frequency-dependent characteristics are paramount. The fundamental aspect of flicker-fusion is that when a light of constant maximum intensity is turned on and off with increasingly greater frequency, a critical frequency is found above which the illumination no longer appears to flicker but seems to be steady. It thus seems that the visual system in effect attenuates high frequencies.

As long ago as 1922, Ives (150) pointed out that high-frequency attenuation might be distributed among successive stages in the visual system. It has since become clear that there are at least two fundamental questions: *1*) which stages are linear, and *2*) how many decibels-per-octave attenuation does each stage contribute to the over-all high-frequency loss?

Experiments by de Lange (244, 245) show that as the frequency of a sinusoidally-modulated light is increased, the amplitude of modulation must be increased in a disproportionate manner for a human to perceive flicker. That is, the slope of the curve relating flicker intensity to the minimum frequency required for fusion grows steeper with frequency. At the highest perceptible flicker frequencies, de Lange's results indicate that response falls at 50–60 db/octave.

Enroth (248) measured the responses of cat retinal ganglion cells to light whose intensity was modulated by a square wave of variable frequency and constant maximum amplitude. She found that the ganglion cells fire with bursts in response to half of each cycle of the square wave, the number of spikes per burst decreasing with increasing square-wave frequency. Enroth measured the latency of the first spike of the ganglion cell burst as a function of frequency; its constancy with increasing frequency implied an increasing phase lag (on a per-cycle-of-stimulus basis).

Kelly (104) used a model neuron as a nonlinear element to provide the high-frequency attenuation observed by de Lange, but he did not consider the latency data of Enroth.

Levinson and Harmon (107) postulated that the psychophysical results of de Lange and the physiological results of Enroth were complementary. The high-frequency attenuation measured by de Lange closely resembles that of a low-pass

filter. The ganglion cell phase-lag characteristics found by Enroth closely resemble the phase relationships in low-pass filters. Levinson and Harmon constructed a model consisting of a generator-potential source, a five-stage low-pass filter, and a neuromime. The latter was intended to simulate a retinal ganglion cell.

The criterion for fusion in the model was the spacing and regularity of the neuromime's spikes; flicker response was taken to be present as long as the spikes followed individual cycles of the input stimulus. Fusion was said to occur when the spike response became irregular. With this criterion, Levinson and Harmon were able to reproduce the essential features of de Lange's psychophysical results. In addition, responses similar to the physiological data of Enroth were obtained, including the decreasing numbers of spikes per cycle of flicker and the increasing phase lag as fusion was approached.

The model provided quantitative demonstration of the possible relationships between physiological and psychophysical flicker-fusion phenomena. It was further tested against other psychophysical results relating to the nonlinearity of visual response. Levinson (273) had presented a human subject with light modulated by the sum of two sinusoids, a fundamental and its second harmonic. The subject was required to set the amplitude of each modulation component separately to the fusion threshold. When the two signals were added, flicker was again apparent. Fusion was re-established by a simultaneous reduction of both amplitudes. It was found that with different relative phases between the fundamental and the harmonic modulation components, different amplitude reductions were required to re-establish fusion.

In subsequent modeling experiments Levinson and Harmon found excellent agreement between results from the analog and those from the two-component psychophysical experiments.

Investigating a problem similar to flicker-fusion, Fuortes and Hodgkin (252) analyzed generator potentials that had been measured in *Limulus* ommatidial receptor cells. They proposed a model requiring ten stages of low-pass filtering in order to account for the measured phase and frequency response. They used a multiple resistive-capacitive filter analog (as did Levinson and Harmon) but added the feature of variable resistance dependent on filter output. This kind of nonlinearity is difficult, though not impossible, to model electronically; in this case the action of the model for various inputs was found by digital computation, that is, by employing a computer-simulation model.

Levinson (106) has recently proposed an alternative model in which a single process rather than a many-stage filter can account for all of the observed temporal response characteristics. It is based on the statistical behavior of particles passing through a permeable membrane, and it is consistent with the Fuortes and Hodgkin results, which imply that all of the low-pass filtering may occur within a single receptor cell.

7) Stochastic processes [*Viernstein and Grossman* (*123*)*; Gerstein and Mandelbrot* (*93, 94*)*; ten Hoopen et al.* (*118, 119*)]. Spikes and spike trains observed in individual axons invariably exhibit some probabilistic aspects. The most commonly described are fluctuations in the temporal relationship between a spike and some other event.

Verveen et al. (119, 122), for example, examined the distributions of spike latencies in an isolated axon after essentially identical stimuli. Viernstein and Grossman (123) discussed a similar problem in neurons in the intact auditory system of the cat, where irregular discharge patterns in response to constant stimuli were observed. In order to explain these and other fluctuating neuronal responses, a number of investigators have constructed neural models that include hypothetical noise. These stochastic unit models are distinguished from the probabilistic nerve-net models (see pp. 571–577) by the fact that they are concerned with random properties of single neurons and not with the properties of randomly connected networks.

One of the first stochastic unit models was proposed by Hagiwara (96) to account for fluctuations in motor unit discharges. In his model, Hagiwara introduced noise in the form of Gaussian-distributed fluctuations of the membrane potential. This model, along with many others, is discussed in a review of statistical spike-data-analysis techniques by Moore et al. (302). Since these authors have included an extensive discussion of stochastic unit models in their review, the discussion here is limited to brief descriptions and comparisons of four models that are representative of the entire class.

Viernstein and Grossman (123) examined spike-interval histograms for single neurons in various sensory pathways in the cat. They found that in general the spike-interval distribution exhibited a prolonged tail on the long-interval side of the mode; so the mean interval was greater than the mode. As excitation was increased, however, the tail was reduced, the mean moving closer to the mode, and the distribution exhibited less variance.

In order to explain these statistical characteristics, Viernstein and Grossman proposed a simple stochastic model of a neuron. In it they assumed a constant threshold and a noisy membrane potential. After a spike, the membrane was assumed to be hyperpolarized, the potential then falling with an exponential mean back toward an asymptote that is a level determined by the steady stimulus. "Noise" was introduced as step changes in membrane potential at fixed frequency, with Gaussian amplitude distribution.

The model was simulated by means of two tables. One contained the values of membrane potential at fixed increments of time for smooth exponential recovery; the other table represented the noise and consisted of numbers randomly selected from a Gaussian distribution with a mean of zero. A number was taken from each table, and the two were added. When the sum exceeded the threshold, a spike was assumed to occur. The preceding interval was simply the number of pairs selected from the tables before threshold was reached. After a spike, the procedure was repeated from the beginning of the smooth recovery table but with a new sequence from the noise table.

Viernstein and Grossman found qualitative agreement between the results from the model and those from the cat. The spike-interval histograms in the model exhibited a tail in the long-interval region, and the variance decreased with increasing excitation. As an interesting sidelight they observed that increasing the frequency of the noise signal had an effect similar to increasing excitation; it reduced both the modal interval and the variance.

In an earlier investigation of stochastic neural events, Pecher (109) had found that an axon stimulated at a low rate with identical, short electrical pulses of about threshold intensity responds with an action potential only in a fraction of all trials. Apparently the axon's excitability varies from moment to moment in an irregular way. This fluctuation in excitability is accompanied by a fluctuation in latency; that is, for those stimuli that manage to elicit response, the interval between stimulus onset and subsequent action potential is variable. Pecher's statistical investigation showed these fluctuations to be inherent properties of nerve fiber and that the sequence of spike responses to low-frequency equal-energy pulse stimulation is randomly distributed; the relationship of the probability of response to stimulus intensity is described by a symmetrical sigmoid curve. The source of fluctuation is apparently Gaussian, and the firing-latency distribution is highly skewed.

A number of mathematical models were developed to account for these fluctuations in response. Those of Rashevsky (116) and Verveen (121) provided quite accurate approximations to Pecher's data but were not completely satisfactory.

Verveen found that in axons the standard deviation of the probability-of-response distribution depends on stimulus duration but that the coefficient of variation (i.e., the relative spread of the deviation) is independent of stimulus duration. He suggested that the underlying causes of the statistical parameters that cause excitability fluctuations are threefold: *1*) the nature of stimulus-induced depolarization, *2*) the presence of a threshold potential difference, and *3*) a Gaussian distribution of fluctuations of this threshold potential difference.

One of the principal inadequacies of the early mathematical models was brought about by the assumption that excitability did not fluctuate during the time over which a stimulus was applied. Though reasonable for stimuli of quite short duration, this assumption is inappropriate for relatively long-lasting stimuli. Excitability fluctuations that occur whether or not a stimulus is present are difficult to model mathematically, so ten Hoopen and Verveen (119) used an electronic model of a single unit [an early version of the neuromime—see Harmon (98)] to investigate the phenomena more thoroughly. The model made possible the elimination of the earlier constraints on stimulus rate and duration. It was assumed that the fluctuations were comparable to band-limited white noise, and a number of parametric variations of such noise were employed to test the model.

These modeling studies produced firing statistics in close agreement with physiological data. The parametric constraints in the model under which that agreement could be obtained disclosed two conditions that must hold in the physiological case. It was shown that for membrane fluctuations to be effective, the equivalent band-limited white noise must have a maximum upper limit of 2000 cycles/sec and a likely upper limit of about 500 cycles/sec. Although the lower limit of fluctuation frequency in the model was held to 20 cycles/sec, slow long-term threshold instabilities were also found. This drift arose from fortuitous thermal variations, but its presence accounted for effects in the model that paralleled effects observed in the physiological preparations.

The model satisfactorily accounted for intensity- and duration-dependent properties of single-fiber firing fluctuations. Latency distributions obtained from the analog also fitted the physiological data well.

Whereas the modeling results implied that the effective noise spectrum in axon membrane should extend to somewhat less than 2000 cycles/sec, a calculation based on the membrane time constant of single nodes of Ranvier in frog axon implied that the spectrum should extend to about 2800 cycles/sec. This discrepancy prompted Verveen and Derksen[3] (122) to examine more closely the nature of the physiological excitability fluctuations and the underlying noise processes. In doing so they developed a new and productive approach to the measurement and analysis of voltage fluctuations that in turn is leading to a better comprehension of membrane ionic conductance mechanisms.

In subsequent studies, ten Hoopen et al. (118) developed mathematical models to explain further the isolated axon data of Pecher (109) and Verveen (121). They proposed two models, one suited to direct solution of the equations and the other suited to solution by Monte Carlo techniques. Both models had noise in the threshold rather than in the membrane potential, and both included the two-time-factor theory of Rashevsky (see p. 528). After a near-threshold stimulus, a quantity labeled "activation" first increased, then passed through a maximum, and finally decreased toward zero. The time course of activation was described by the difference between two negative exponentials with different time constants (the two time factors).

While the activation proceeds through its course, the threshold varies about a mean value close to the peak of activation. If the activation curve crosses the threshold, a spike is assumed to occur. Two types of threshold fluctuation were considered. In one case, the threshold was assumed to vary from one value to another in stepwise manner, the magnitudes of the steps having a Gaussian distribution and the times of occurrence having a Poisson distribution. This model was studied by direct solution of the equations. The second model was identical to the first in all but one detail; the stepwise changes in threshold occurred at equal time intervals. This model was simulated by Monte Carlo techniques similar to those used by Viernstein and Grossman with their tables of values.

Results from the two mathematical models were very similar, agreeing quantitatively with results obtained from isolated frog axon [Verveen (121)] as well as with results obtained with the earlier electronic model studies of ten Hoopen and Verveen. Poststimulus latency distributions from both models exhibited prolonged tails in the long-latency region as well as variance that decreased with increasing stimulus magnitude. These distributions were thus qualitatively similar to the spike-interval distributions obtained by Viernstein and Grossman.

Rodieck et al. (285), like Viernstein and Grossman, were interested in spike patterns in the mammalian auditory system. Their approach to the problem was somewhat different, however. They began by developing a set of statistical measurements that were applied to the data. In addition to the spike-interval histogram and the poststimulus-time histogram, this set included the joint-interval histogram and the scaled-interval histogram.

The joint-interval histogram provides information about the statistical rela-

[3] Though Derksen has been predominantly concerned with direct neurophysiological experiments (122, 246), he has also made excellent contributions to the design of electronic single-unit models (91).

tionship between two successive spike intervals in a train produced by a single unit. This type of histogram is generated by plotting, for every pair of intervals, a point whose abscissa is proportional to the first interval and whose ordinate is proportional to the second interval. The results are usually displayed either as a scatter diagram or as a set of contours of constant occurrence density.

The scaled-interval histogram shows the distribution of specific sums of successive spike intervals. The number of intervals in each sum is an integral power of two, and that power is denoted as the "order" of the histogram. The second-order-scaled-interval histogram is thus a histogram of the sums of four successive intervals. The scaled intervals are mutually exclusive, so that any single interval is a member of only one sequence. Note that the zero-order-scaled-interval histogram is identical to the simple spike-interval histogram.

Applying these measurements to their data, Rodieck, Kiang, and Gerstein were able to classify spike trains according to their statistical properties. Gerstein (93) was then able to propose plausible limits on the classes of generating mechanisms. From these limits Gerstein and Mandelbrot (94) went on to develop a series of stochastic unit models based on "random-walk" statistics. They used these in an attempt to relate spike-train statistics to fluctuations in membrane potential.

In a specific class of spike trains considered by Gerstein, all of the lower orders of scaled-interval histograms had the same shape. From the fact that there was only one known distribution function that had this stability property and at the same time was readily interpreted in physiological terms, Gerstein used that function in particularizing his model.

The applicable probability density function happens to describe the distribution of first passage times in a particular random walk toward an absorbing barrier, and Gerstein adapted his model to that random walk. The membrane potential was assumed to change *only* on the occurrence of a postsynaptic potential (no decay was assumed in these models). An epsp was assumed to move the membrane potential one unit toward the threshold, and an ipsp moved it one unit away from threshold. When threshold was reached, a spike was assumed to occur, and the potential was reset to zero level, from which the process of accumulation or "walking" was repeated. The probabilities of occurrence were assumed equal for both excitatory and inhibitory postsynaptic potentials.

Applying this model and several modifications of it, Gerstein and Mandelbrot were able to account for many quantitative details of both single-interval histograms and scaled-interval histograms of spike trains from single units. They were able, for example, to reproduce the stability properties exhibited in the scaled-interval histograms. Consistency with experimental data was once again obtained with a minimum-parameter model. The basic random-walk model has one parameter, the number of steps between the zero level (reset potential) and the threshold; and it has one state variable, the membrane potential. In a slightly more complicated version, Gerstein and Mandelbrot added one additional parameter, the ratio of the number of excitatory inputs to the number of inhibitory inputs. With two parameters the model accounted for an even wider variety of spike-train observations in cat cochlear nucleus neurons.

Fetz and Gerstein (92) expanded the model further by including exponential

decay of the membrane potential toward equilibrium. This new version was difficult to handle mathematically, so they employed a resistor-capacitor network simulation.

By varying the ratio of the number of incoming epsp's to the number of incoming ipsp's as well as the threshold, Fetz and Gerstein were then able to simulate almost all the spontaneous spike trains found in the neurons of the cat cochlear nucleus.

Stevens (117) subsequently showed that a different model, based on a diffusion process, leads to precisely the same spike-interval statistics as those in the random-walk models and can thus account for the same variety of spike trains.

Ambiguities of this kind in which analogs are nonunique present a problem in all areas of neural modeling, particularly in the modeling of stochastic action. Continuing physiological measurements on noise in axons [e.g., Verveen and Derksen (122, 246)], however, are rapidly leading to more constraints. The stochastic models are constantly being re-evaluated and revised, and they have been useful in suggesting new and more meaningful statistical measures for spike trains [see Moore et al. (302) and Poggio and Viernstein (282)].

C. Networks

1) Input-output relations in a motoneuron pool [Rall and Hunt (169, 170, 283)]. In the monosynaptic reflex pathway of the gastrocnemius nerve of the cat, a single shock stimulus induces a nearly synchronous volley of spikes in a fraction of the afferent fibers. Some proportion of those fibers have synaptic terminations directly on the motoneurons of the pathway.

The intensity of excitation delivered to a given motoneuron in response to the single shock stimulus has been thought to depend not only on the number of activated synaptic knobs but also on the distribution of these knobs over the motoneuron surface (274, 275). The complex geometric dependencies were, in fact, thought to preclude any simple definition of threshold in such a system. In addition, simply defined thresholds seemed insufficient to explain the observed input-output relations in these systems.

With a simple statistical model, however, Rall (169) was able to demonstrate the adequacy of a threshold defined just in terms of the number of active synaptic knobs required to trigger a given motoneuron. In his basic model, Rall assumed that the effective input intensity to the motoneuron pool in the reflex pathway was proportional to the number of synchronously activated knobs (which were assumed to be randomly distributed over the pool). The resting thresholds for individual motoneurons were assumed to be randomly distributed and independent of activated knobs. The distributions of thresholds and knobs were taken to be normal.

Developing his model from these assumptions, Rall showed that regardless of the values of the important model parameters, the fraction of motoneurons in the model firing in response to a given stimulus was given by the area under the portion of a normal distribution curve that exceeded a certain "critical" value. The firing fraction was thus completely determined by the critical value.

Further, the model predicted that the critical value would be linearly related to the fraction of afferent synaptic knobs activated by the stimulus. From the results of subsequent experiments on the gastrocnemius reflex in cat, Rall (169, 283) estimated the effective number of activated synaptic knobs and the firing fraction of the motoneuron pool. These estimates supported the prediction of linearity.

Rall's model, together with his experimental results, thus showed that a simple definition of threshold in terms of the numbers of activated synaptic knobs was sufficient for the prediction of relations previously assumed to be incompatible with such a simple definition. In addition, the model produced excellent quantitative consistency with other aspects of the data from the cat and predicted many of the observed relationships among sets of data. This included the effects of posttetanic potentiation as well as the input-output relations for various combinations of inputs to synergic systems.

These studies were extended by Rall and Hunt (170) to include uncorrelated fluctuations in excitability (which affected only individual neurons) and correlated fluctuations (which affected the entire motoneuron pool). By separating the fluctuations into these two independent classes, Rall and Hunt were able to predict accurately the probability of spikes in individual neurons during discharges of the pool.

2) *Coelenterate nerve net* [*Josephson et al.* (*152*, *153*)]. Current physiological evidence indicates that although coelenterates have the most simply organized of all nervous systems, their neurons operate very much like those of higher animals. The neurons conduct impulses in an all-or-nothing manner, they usually interact synaptically exhibiting both inhibition and excitation, and they are sometimes spontaneously active. In spite of the fact that coelenterate nerve nets appear to be randomly connected, they are often capable of integrative activity. This is particularly apparent in the case of repetitive stimuli in so-called "local conducting" nets. In these nets the response to a single stimulus does not spread to the boundaries of the system but is limited to a local area. If a second stimulus is applied shortly after the first, the response area increases. The distance to which excitation spreads in a local system is thus usually a function of the frequency and total number of stimuli (264).

Horridge (264) distinguished three types of increases in response area during repetitive stimulation at constant frequency. In some species the radius of the response area would increase with approximately equal increments; in other species the increments would be progressively smaller; in still other species the increments would increase, resulting in an acceleration of the spread of excitation.

Horridge used two models in attempts to explain his observations. The first was a mechanical model, but the results from it were not consistent, so he discarded it in favor of a mathematical model. With this model he was able to explain many of the characteristics of spread in a coelenterate nerve net, but he had to make a number of assumptions that could not be justified.

Josephson et al. (153) designed a flexible digital-simulation model and with it were able to relate many of the integrative properties of coelenterate nerve nets to the known or suspected properties of coelenterate neurons. The nerve-net ge-

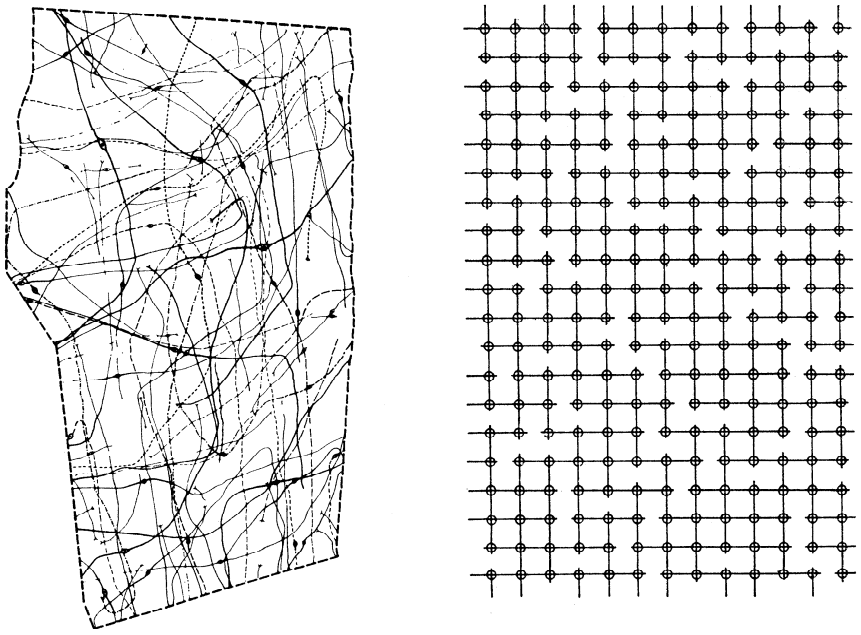

FIG. 14. Comparison of geometries of real and modeled coelenterate nerve nets. *A:* drawing of nerve net in mesentery of the anemone, *Metridium*. For clarity some neurons are shown as *dashed lines*. [From Batham et al. (235)] *B:* schematic representation of a coelenterate nerve-net model. *Circles* represent possible junctions between fibers. [From Josephson et al. (153)]

ometry was represented by a two-dimensional array of idealized fibers. Figure 14 shows a comparison of such an array with a portion of a nerve net from the coelenterate *Metridium*.

The model may be viewed as a grid of horizontal and vertical lines with randomly selected segments missing. The remaining line segments represent fibers of various lengths intersecting with one another at right angles. Each intersection forms two unidirectional synaptic junctions, and each of those may be either through-conducting (T-type) or facilitating (F-type) junctions. A pulse arriving at a T-junction is transmitted to the intersecting fiber. A pulse arriving at an F-junction facilitates the intersecting fiber so that a second pulse arriving soon after the first will be transmitted. The first pulse, however, is not transmitted. Facilitation decays linearly with time and may accumulate.

Their proportion having been specified, the T-junctions in the model are distributed randomly; the remainder of the crossings are F-junctions. A mixture of junctions of these types was first proposed by Horridge and is consistent with physiological evidence. Each time a net was formulated in the computer, the experimenter would specify the proportion of T-junctions, the mean fiber length (in grid units), and the facilitation decay-time distributions. The computer would then

construct a simulated net with random distributions of fiber lengths and of T-junction locations.

Conduction was assumed to be all-or-nothing in a given fiber, and the conduction velocity was assumed constant. In contrast to the model of Perkel (described on p. 539), time in the present model was quantized, with basic increments equal to the assumed time of travel for an impulse over one unit of grid length.

Josephson (152) performed a number of experiments with the simulation model, but he was most interested in the effects of repetitive stimulation. He found that by varying the proportion of T-junctions and the ratio of the number of facilitated F-junctions to the number of unfacilitated F-junctions, the spread of excitation could be changed from that of decreasing increment to that of equal increment or even increasing increment—all the types found by Horridge. When the proportion of T-junctions was high and the fraction of F-junctions remaining sufficiently facilitated to pass the next pulse was low, the spread increased in decreasing increments. When the proportion of T-junctions was low and the fraction of F-junctions remaining facilitated was high, the increase was in equal increments. Finally, when the proportion of T-junctions and the fraction of facilitated F-junctions both were high, the increase was in increasing increments.

The modeling results showing spread in decreasing increments and equal increments were consistent with results from coelenterate nerve nets, but two problems existed with respect to increasing increments. First, Josephson did not believe that the simulation data showing increasing increments were sufficient to be statistically significant. Second, the increase in size of successive increments was small in the model, and such increases would not readily be noticed in physiological experiments. Liu (156) resolved the first problem by showing that spread in increasing increments occurs consistently over statistically significant samples; but the problem of the size of increment increase remains.

A second observation of Josephson and his colleagues is worth noting. With higher proportions of T-junctions, the response of the model net to a single pulse propagates over large areas, but the extent of this propagation becomes increasingly variable. Thus there must be a compromise between distance of conduction in the net and the uniformity of response to a given stimulus. One way to avoid this compromise in the model is to allow a single stimulus to evoke a train of pulses. A net with a low proportion of T-junctions can thus have a large but consistent area of response to a single stimulus. Josephson, Reiss, and Worthy point out that repetitive firing is quite normal in coelenterates in response to a mechanical stimulus.

Liu (156) recently revived the model studies begun by Josephson, Reiss, and Worthy and improved the digital program in several ways. He included manual input and visual output (oscilloscope) so that the experimenter can easily interrupt the program at will in order to change parameters. In addition to demonstrating the statistical significance of increasing increments of response in the model, Liu also performed a number of other experiments that verify and extend the earlier results. He has, for example, included electrotonic spread in the model and performed experiments with various cuts or blocks simulated in the net.

These coelenterate nerve-net studies provide another example of minimum-parameter modeling. Both the individual neuron model and the modes of inter-

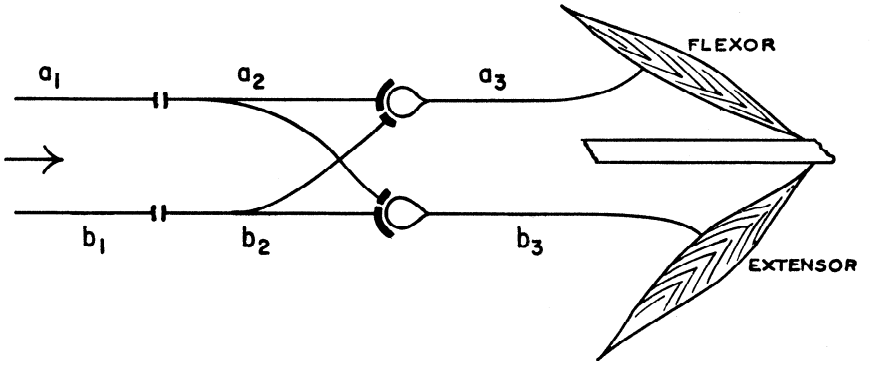

FIG. 15. Reciprocal inhibition for control of antagonistic muscles. According to McDougall's 1903 theory, this configuration allowed alternation of flexion and extension for steady, nearly equal activity in both afferent neurons (a_1 and b_1). During flexion, "resistance" of synapse a_2-a_3 is low, and excitation passes from afferent a_1 through central neuron a_2 to efferent a_3 and onto the flexor. The low resistance of synapse a_2-a_3 is transferred to its "cosynapse" b_2-a_3 (formed by the collateral of b_2 terminating on a_3), and excitation from b_1 is diverted to a_3. This diversion of excitation "inhibits" extension and "enhances" flexion. Fatigue soon increases the resistances of synapse a_2-a_3 and its cosynapse b_2-a_3, so excitation from b_1 is no longer completely diverted. Increased excitation is thus available to lower the resistance of synapse b_2-b_3 and its cosynapse a_2-b_3. Extension becomes dominant, and flexion is inhibited. The cycle repeats, and alternation results. [Redrawn from McDougall (161)]

connection are extremely simple. In spite of this the results are neither simple nor obvious.

3) *Two-unit reciprocal inhibition* [*Reiss* (176), *Harmon* (146)]. It has long been conjectured that the alternating rhythmic behavior of muscular antagonists may arise from reciprocally inhibiting neurons. More than half a century ago McDougall (161) postulated a system for nervous control of muscular alternation (shown in Fig. 15). Though inaccurate in the light of subsequent knowledge, it was a notable first attempt to explain antagonism and alternating dominance in terms of relatively modern neurophysiology.

Aside from the reciprocal innervation, recurrent axonal collaterals, and inhibitory interneurons now well known in neuromuscular systems, the ubiquity of crossed inhibition in visual and auditory peripheral sensory systems suggests that reciprocal inhibition may play an important and widespread role in neural information processing.

Reiss (176) studied a number of models of two-neuron interaction using both digital computer simulation and electronic analogs. He showed that a relatively constant-frequency stream of impulses exciting in common a pair of mutually inhibiting units can produce rhythmic, alternating bursts of pulses. Although the input pulse train provides common excitation to both units, if the units' temporal parameters are properly adjusted only one fires at a time; the other unit is inhibited by the one firing. As the active unit fatigues, however, its output rate declines, and the silent unit is released from inhibition. The second unit begins to fire and becomes dominant, inhibiting the first.

In this alternating dominance of one unit over the other, which produces alternating bursts of pulses in the two units, Reiss found that the rate of alternation is an almost monotonic function of the input, or driving frequency. At very low input frequencies, one unit dominated completely. As the frequency was increased, low-frequency alternations occurred. The frequency of alternation would then increase with increasing drive frequency until, at very high rates, one unit would again dominate.

This dominance was often not complete, however; while the dominant unit remained on, the other fired in rapidly recurring bursts. These patterns of response are identical to those observed by Hoyle (266) in reciprocally innervated flexor and extensor muscles in the legs of locusts. As the locust walks faster and faster, the alternation rate increases. Finally, when the walking becomes quite rapid, the extensor is continuously excited (dominant neural control) and provides an elastic band against which the flexor can work differentially (via rhythmic burst input). Reiss thus demonstrated a simple mechanism that not only provides this apparently complicated behavior but does so with an extremely simple driving source.[4]

These studies were completed with experimental determinations and analyses of the effects of threshold and recovery asymmetry in the two units, extents of reciprocal firing periods, mean frequencies, limits of input-controllable stable activity, and noise immunity.

In a related study Harmon (146) explored the modes of action available to a pair of reciprocally inhibited electronic single-unit analogs excited in common by a constant-frequency pulse train. The model was initially arranged to replicate spike patterns observed by Wilson (291) in locust flight motor systems; it accounted in a simple way for alternating spike-pair patterns seen in the locust's thoracic ganglion. The model's time courses of excitatory and inhibitory potentials and of accommodation were very much shorter than those employed by Reiss, resulting in quite different modes of action.

Extended experimentation with this model led to a disclosure of several novel phenomena. With variation of stimulus frequency, the output firing patterns of the two units changed in discrete steps, progressing through a number of different patterns, some quite intricate. The effect of increasing stimulus frequency over a large range was to change the output firing activity in the dominant unit from patterned and phasic to tonic, while the nondominant unit changed from patterned and phasic firing to ultimate quiescence. Typical examples of the patterned response are shown in Figure 16.

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[4] A similar study by Szekely (184) used electronic single-unit analogs to replicate prolonged-discharge alternating bursts of the kind presumed to be responsible for coordinated limb movements in salamanders. Szekely's network of 8 units simulated 4 motoneurons and 4 inhibitory (Renshaw) interneurons in spinal cord segments. The model produced rhythmic outputs for nonrhythmic inputs with an arrangement suggested by neurohistological and neurophysiological data. A simpler, mathematical model of 2-unit interaction developed by Pavlidis (166) permitted detailed analysis and was tested by analog computer simulation. Two units, connected by crossed excitation, produced alternating bursts of the kind often seen in insect flight motor systems. The model was also used to show how spontaneous and seemingly random firing can arise from excitatory cross-coupling rather than from internal noise as is generally considered to be the case (see p. 554).

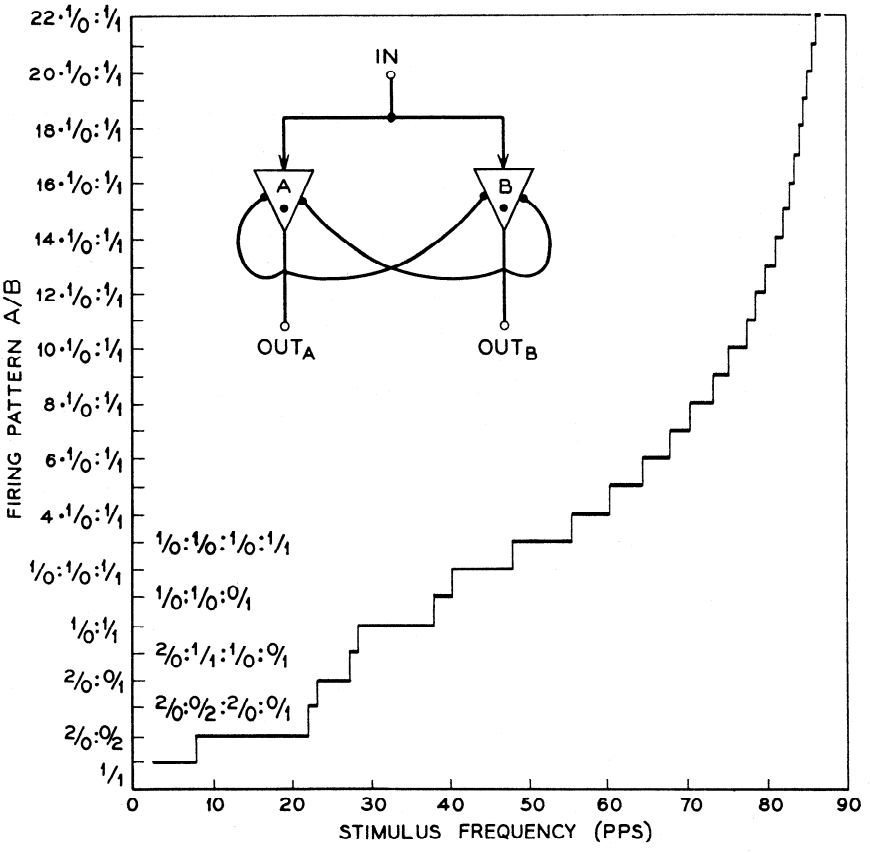

FIG. 16. Family of firing patterns obtained by reciprocally inhibiting neuromime pair as common stimulus frequency is increased. Each pattern, which repeats indefinitely, is stable over a range of frequencies, discontinuously changing at the extremes of the range. The notation for the patterns represents sequential firing in the two units; each ratio represents the response to a single stimulus pulse. For example, 1/0:1/0:1/1 indicates unit A fires once and unit B is silent for the 1st pulse in the input train; this repeats for the 2nd pulse; both units fire simultaneously in response to the 3rd, and then the entire pattern repeats. The patterns range from 1/1, in which both units fire synchronously with the input, through a series of more intricate patterns, to a set of responses in which unit A, following synchronously, increases its dominance as unit B, firing less and less frequently, is finally suppressed completely. For example, in the last pattern shown, unit A repeats 22 times before B responds once. [From Harmon (146)]

A rather surprising phenomenon arising from the direction of stimulus frequency change was found. Patterns exhibited hysteresis. That is, the pattern elicited by a given stimulus frequency depends on whether that frequency is approached from above or below. For example, suppose a particular patterned output from the two reciprocally inhibited units is observed for a given driving frequency. While that frequency is *increased* the pattern remains stable until a critical frequency is reached, at which time there is an abrupt change to a new pattern, as

illustrated in any one of the steps shown in Figure 16. However, if the drive frequency is now *decreased*, the original path is not retraced. Instead, the new pattern persists, quite stably, over the range of drive frequencies that before had elicited the old pattern. The "captured" pattern continues until the stimulus frequency is lowered to the point where the original pattern had first appeared with increasing drive frequency. At that time the original pattern reappears, and a complete hysteresis loop has been traced. This is illustrated in Figure 17.

A concomitant of this hysteretic action is that output pattern selection can be controlled by the injection or deletion of a single pulse in the stimulus pulse train. That is, in order for a given driving frequency to produce one or the other of the two patterns traced by the hysteresis loop, smooth frequency change is unessential; a single control pulse will suffice.

Aside from the alternating patterns described for locust flight control by Wilson (291), no clear physiological demonstration yet exists for the actions or mechanisms documented in this study. There are, however, several suggestive bits of evidence. Blaschko et al. (237) described a trigger (hysteresis) effect in crustacean claw where a given muscular tension produced by a background stimulus of constant frequency applied to a single nerve fiber can be triggered into a sustained state of increased tension simply by intercalating a single extra shock. Further, Pantin (280) was able to abolish this state by injection of inhibitory spikes.

The action of the model to produce alternate firing of a mutually inhibitory pair of units excited by a common stimulus of constant frequency appears similar to that of cicada motoneurons. Hagiwara and Watanabe (258) found that alternating activation of the two main sound-producing muscles typically may occur at a 100-pulse/sec rate for each while a preceding internuncial unit fires at a 200-pulse/sec rate. Interestingly, this pattern corresponds to one of the simplest found in the model's family of patterns. Hagiwara and Watanabe postulated the possibility of mutual inhibitory interaction of the motor centers. The model not only demonstrates the feasibility of that suggestion, but it also indicates the anatomical and temporal parametric conditions under which the phenomenon may be expected to occur.

4) Dynamic-range extension in the cochlea [*van Bergeijk (189)*]. In 1961 van Bergeijk initiated a modeling study of the properties of the external spiral nerves of the cochlea. The morphology and connections of these nerve fibers were reasonably well known, but no observations or theory of their function existed.

Although primate audition extends over a stimulus sound-pressure range of more than 100 db, a single neuron typically exhibits a dynamic range (threshold stimulus to that required for maximum firing rate) of little more than 25 db. The question arises as to how a system of neurons may achieve a far greater dynamic response range than that of a single unit.

Van Bergeijk postulated that the convergent arborization of the cochlea's spiral innervation could account for at least part of the discrepancy in the following way. At low stimulus intensities the density of signals traversing the fibers is low, and thus the probability that two signals will simultaneously reach a junction of two converging fibers is also low. However, as stimulus intensity is increased, the likeli-

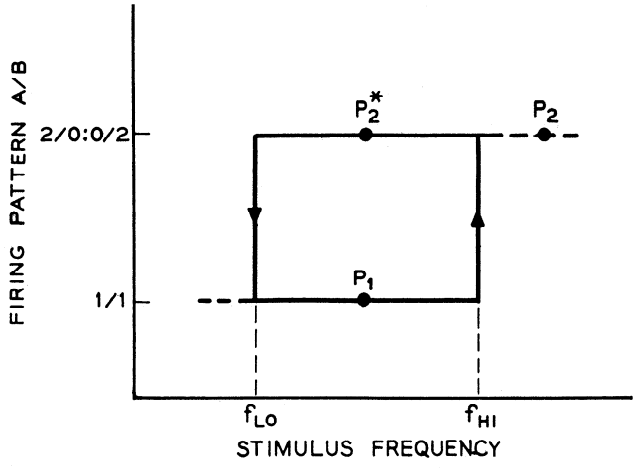

FIG. 17. Hysteresis of patterned response. Consider one of the steps in Fig. 16. If pattern P_1 is present (for example 1/1), and the stimulus frequency is increased to f_{HI}, there is a discontinuous jump to a new pattern P_2 (in this case 2/0:0/2, double alternate firings). If the stimulus frequency is then decreased, the new pattern remains, and it persists, say, at P_2^*, for which stimulus frequency the old pattern P_1 had originally been elicted. The new pattern remains "captured" even though the frequency is lowered almost to f_{LO}. At f_{LO} there is an abrupt switch to the original pattern. A separate hysteresis loop of this kind exists for each pattern step shown in Fig. 16. [From Harmon (146)]

hood of destructive interference of signals arriving at a node via different branches increases owing to the increased temporal density of the signals. That is, as more and more signals converge on a single node, it becomes increasingly likely either that several of them arrive simultaneously and cause only a single output, or that several arrive nearly simultaneously and, running into a refractory zone, are ineffective. The postnodal fiber thus saturates slowly. With very high stimulus intensities there is, of course, saturation of the prenodal fibers located at the place of maximum basilar membrane displacement, but other neighboring fibers now come more and more into play. Thus the postnodal fiber responds to a continual build-up of activity from the family of prenodal fibers serving it until it ultimately saturates.

By driving a convergent branched network of neuromimes by an electrical analog of the cochlea, van Bergeijk demonstrated that the more branches his artificial fibers had, the larger was the dynamic range of the system. That is, while a single neuromime might respond over a stimulus intensity range of only 20 db, a simulated spiral fiber array with 19 side branches was able to respond to a range of more than 40 db.

On the strength of these observations van Bergeijk proposed that the function of the spiral arrangement in the auditory nerve is to extend the dynamic range of the ear. To test this hypothesis it would be necessary to record from the nerve fibers of the cochlea under conditions where side branches of the spiral nerves are progres-

sively eliminated. Van Bergeijk suggested that, since the location of maximum displacement on the basilar membrane is a function of input acoustic frequency, a frequency can be found such that a maximal portion of a particular convergent arbor is exposed to stimulation. Changing the frequency of stimulation then would effectively eliminate side branches from the nerve as the displacement envelope on the basilar membrane retreats to either end of the cochlea, thus leaving more and more branches unexcited. When the stimulus pattern exerts its maximum influence, the slope of the curve relating output response (in impulses/sec) to input intensity should be rather low, increasing in steepness as more and more branches are deactivated at frequencies other than this maximally effective one.

The test of this hypothesis was carried out by Nomoto et al. in 1964 (279), and van Bergeijk's prediction was effectively confirmed. The test consisted of measuring the thresholds and firing frequencies of eighth-nerve fibers as auditory stimuli were varied in intensity and frequency. Slopes of input intensity versus output frequency were established. Nomoto et al. found one class of units that exhibited low slopes at their "best frequencies" but showed steeper slopes at other frequencies of stimulation. On the basis of this theoretically expected behavior, together with the low threshold expected from nerve fibers emanating from the outer hair cells, they took such "crossed-ramp" units (as they term them) to be external spiral fibers. Two other classes of units, "parallel ramp with low threshold" and "parallel ramp with high threshold," show rather steep slopes; thus on the basis of van Bergeijk's theory they may be inferred to be *unbranched* nerves. They would correspond to the *radial* nerve fibers.

On the basis of this inference and, again, on the threshold difference expected between inner and outer hair cells, these two classes of units are classified by Nomoto et al. as external radial and internal radial fibers, respectively.[5] This marks the first instance in which neurophysiological measurements suggest a plausible distinction between external spiral, external radial, and internal radial fibers, a distinction long known anatomically, but never seen physiologically.

On the basis of the same modeling experiments, van Bergeijk (192) also proposed a new theory to account for the pathological phenomenon of "loudness recruitment." This phenomenon is diagnostic for damage to the sensory elements in the cochlea; it is characterized by a markedly reduced dynamic range caused by an elevated threshold and, above threshold, an accelerated increase of loudness. Random elimination of sensory cells would result in spiral fibers with less than the normal complement of side branches and thus in decreased dynamic range.

5) *Auditory binaural interaction* [*van Bergeijk (190, 191)*]. The model described here evolved in successive stages on the basis of results from related physiological and psychophysical experiments.

In the auditory phenomenon of time-intensity trade, if a given signal arrives slightly earlier at one ear than at the other, the perceived spatial location of the

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[5] Through an unfortunate printing error, the summary of Nomoto et al. (279) indicates the reverse of what is discussed on pp. 782–783 of their paper; in the last 2 lines of paragraph 3 of the summary, the words "radial" and "spiral" should be interchanged.

signal is toward the early ear; increasing the intensity of the lagging signal at the other ear can offset the effect and center the image; i.e., time and intensity can be traded in binaural spatial perception.

Psychophysical studies of this phenomenon in humans had led David et al. (243) to an *ad hoc* black-box model, although it was not intended to represent in any detail the neural pathways along which binaural interactions take place. The gross anatomy of these pathways is known, however. Each of the two accessory nuclei of the superior olivary complex consists of neurons that receive inputs from both ears via the respective cochlear nuclei. Moreover, each accessory nucleus neuron is known to receive bilateral innervation from the cochlear nuclei (288). Further, Galambos et al. (253) have described binaural interactions at the single-unit level in the accessory nucleus.

Van Bergeijk (190) put the various pieces together into a neurophysiological model designed to account for the psychophysical data without violating the known anatomical and physiological constraints.

There are three essential propositions in the model. First, each accessory nucleus receives inhibitory afferents from the ipsilateral cochlear nucleus and excitatory afferents from the contralateral one, and each neuron in the accessory nucleus receives contralateral excitatory together with ipsilateral inhibitory inputs. Second, the first-arriving input to a neuron determines its state; i.e., if an excitatory input arrives first, the neuron becomes excited, and subsequent inhibitory inputs are ineffective, or if an inhibitory input arrives first, the neuron remains unexcited despite later excitatory inputs. Thus if one ear receives the stimulus earlier than the other, it produces a dominantly inhibitory state in the ispsilateral accessory nucleus and a dominantly excitatory state in the contralateral one; the resultant excess of excited neurons in the contralateral accessory nucleus then forms the basis of the spatial perception. The third proposition holds that if one ear is more intensely stimulated, more afferents from that ear are active, producing an excess of excited units in the contralateral accessory nucleus (this fact, by itself, would again form the basis for a spatial percept). Thus temporal advantage of one ear can be cancelled by an intensity advantage of the other, resulting in time-intensity trade.

The major objection to the model from a neurophysiological point of view is the assumption of an exclusive response of the accessory neurons with respect to the first-arriving input; in the light of what is known of neuronal behavior, this hypothesis is unlikely. This, indeed, turned out to be the first modification of the model required by new data resulting from a physiological test. The test was carried out almost immediately by Hall (260) in a microelectrode study of the accessory nucleus in cat. Hall found that every neuron he tested would do a certain amount of time-intensity trading; that is to say, the *probability* that the neuron will fire in response to a binaural stimulus pair can be affected by changes in interaural time difference as well as by changes in interaural intensity difference. This interaction is, moreover, affected to some extent by the over-all level of stimulation.

With his data and van Bergeijk's hypothesis, Hall was able to derive neural time-intensity trading ratios that, after allowance for the cat's smaller head size, quantitatively match the human psychophysical data. The conditions of time and

intensity differences that produce centered images in human perception produce equal numbers of excited units in the two accessory nuclei of the cat; this is just what would be expected on the basis of the model.

In his most recent paper on the subject, van Bergeijk (191) modified his model to accommodate Hall's data on continuous (probabilistic) trading by each neuron; the innervation diagram of the accessory nucleus that he deduced from the new data (191, fig. 4B) begins to bear a striking resemblance to Ramón y Cajal's classic picture (284, fig. 344).

An important criticism of van Bergeijk's model was made by Moushegian et al. (278). They found, as had Galambos et al. (253) earlier, that there are a number of accessory-nucleus units that appear to have ipsilateral excitation and contralateral inhibition. The behavior of these units with respect to time and intensity differences between the ears seems to be indistinguishable from the ipsi-inhibited, contra-excited units that van Bergeijk assumed and Hall investigated. However, as Moushegian et al. pointed out, the model is incomplete if it does not account for them. Evolution, both of the model and experiment, is continuing.

6) Spike-pattern detection [Reiss (177)]. One of the most important problems one encounters in attempting to understand the information-processing capabilities of nervous systems concerns the repertoire of behavior available to small groups of neurons. The accumulating physiological evidence for great functional complexity, even at the single-unit level, makes it imperative to examine, both experimentally and theoretically, the range of activity available to one or a few interconnected neurons. The evidence already developed showing considerable sensitivity to simple spatio-temporal patterns of excitation and inhibition suggests that the characterization of a single neuron as a simple logical element may be insufficient. Very likely the signal-processing capabilities of small nerve networks go far beyond transmission, integration, or elementary logical operations.

The idea that small neural nets could act as "property filters," responding uniquely to well-specified input patterns, is not new. As early as 1947, Pitts and McCulloch (168) hypothesized neural mechanisms that could lead to *Gestalt* perception. They proposed networks that could provide invariant detection of visual and auditory forms despite changes in operating conditions of individual neurons. The theoretical networks developed to explain recognition of chords regardless of pitch, and of shapes regardless of size, were plausibly defined on the basis of known neuroanatomy. Though the detailed propositions have been neither proved nor disproved, the fundamental idea that neural nets having quite regular structure can classify input signals underlies all of the later models for peripheral sensory information processing.

Motivated similarly, Uttley (187, 188) attempted to derive from perceptual behavior a hypothesis of signal classification and to deduce from it mechanisms that could underlie that behavior. Uttley's discussion of the geometry and action of small nets to extract invariances in spatio-temporal patterns was one of the first to demonstrate how arbitrarily long sequences of stimulus tones or temporal intervals could be recognized by neuron-like networks.

Babcock et al. (127, 128) contributed theoretical studies of how small assem-

blies and multiple-layered networks might be arranged to produce unique response to patterns of visual or auditory information. Sutherland's review of stimulus-analyzing mechanisms (183) examines similar problems in the light of physiologically relevant evidence. In extensive studies by Martin et al. (157), using electronic models, it was shown how structured arrays of minimum-parameter neurons could extract significant features of speech.

The plausibility and predictive significance of models such as these are supported by recent physiological observation of similar kinds of property filters. For example, the work of Maturana et al. (277), Hubel and Wiesel (267), Barlow and Hill (234), Arden (232), Maturana and Frenck (276), Grüsser-Cornehls et al. (255), and Schipperheyn (287) shows related types of property filtering in frog, rabbit, cat, and pigeon. In each case there is reason to believe that the invariances may be extracted by rather simple network configurations of single units whose essential properties for these operations are just those of the minimum-parameter units employed by the modelers.

A provocative example of neural network pattern detection is found in the conceptual experiments of Reiss (177). Using paper-and-pencil analysis only, he studied the behavior of "resonant networks." The idea was to examine the actions of small networks of neuron-like elements (minimum parameter) using variable-frequency stimulus pulses, temporal summation, threshold, and axon delay to produce frequency-selective responsiveness. The question of what constitutes the language of neural action is, of course, totally unsettled; it is likely that nervous systems employ spike interval, average frequency, frequency modulation, and intensity coding separately and in combination. Reiss's aim was to investigate the kinds of simple neural network detectors that may conceivably operate to decode some of these messages.

Schief (180) had previously shown how neuron-like elements could be made to behave as "coincidence filters" that possess sharp frequency discrimination. His models demonstrated possible mechanisms for cochlear pitch discrimination that suggested how a neurological narrow-band filter could be achieved that is free of the concomitant long build-up times encountered in conventional electrical circuits. The essential feature of this approach was to use transmission delay and coincidental arrival of two signals at a single unit to sense particular intervals in a pulse train. This is in contrast to other proposals to achieve sharply tuned frequency-selective response from the action of mutually inhibiting units, briefly mentioned by Rapoport (171), Tarjan (185), and Heydemann (148). More extensive analysis of mutual-inhibition sharpening was made by Huggins and Licklider (268), Zwicker (197), and Furman and Frishkopf (142), though only in the last two cases was there an explicit attempt to show how the model can be tested by physiological experiment.

Reiss extended Schief's work to include a variety of frequency- and interval-discriminating filters that, while entirely hypothetical at present, conceivably may be physiologically valid.

The basic "resonant" network analyzed by Reiss is responsive to specific periodic regularities in an incoming train of pulses. It consists of three neurons; an input

unit delivers pulses both to an interneuron and to an output unit. When the incoming train contains pulses whose spacing corresponds to the delay introduced by the interneuron, the output unit coincidentally receives both the direct and the delayed pulses. The output neuron fires if and only if two stimuli arrive within a small, critical summation time; hence, response occurs whenever the input train contains properly spaced pulses. For an input train of constant frequency, the network responds continuously when the frequency is appropriate; that is, it acts as a sharply tuned filter. (Since such a network responds both to the fundamental frequency and to all harmonics, it acts as a "comb" filter.)

Reiss examined the consequences of regular and irregular (noisy) input trains and of changing network characteristics owing to facilitation and accommodation. Interesting symmetries were found in which, for example, the effect of substituting inhibition for excitation by the interneuron is to change period or frequency-band response from detection to suppression. Other relatively simple network elaborations permit band detection with harmonic suppression, phase detection, and harmonic analysis.

Reiss concluded his analysis with an examination of what neural temporal parameters would be required that are realistically possible and what spatial configurations might be expected. Explicit guides for relevant neurophysiological experimentation and data analysis were suggested.

An important framework is provided by this study for the formal description of temporal-pattern behavior in nervous systems. As Reiss put it, "There is an urgent theoretical need for a rich and flexible classification scheme that can be applied to pulse trains, a 'taxonomy of pulse patterns' as it were. It seems reasonable to suppose that such a taxonomy would not only facilitate the development of nerve-net theory, but would also sharpen the observational powers of the experimental biologist. Even if it turns out that the types of resonant networks discussed here do not exist in nature, they will have served a useful purpose if they stimulate biologists to take some steps toward developing a pulse-pattern taxonomy."

In a continuation of this work, Jenik and Adolphs (151) analyzed extensively the characteristics of coincidence filters using nonrectangular impulses. Employing waveforms that more closely approximate motoneuron epsp signals, they developed relationships among realizable functional bandwidth (neurally realistic), variational tolerances on that bandwidth, and the error-producing effects of amplitude and threshold variations (noise) on performance.

7) Discrete representations of nets [*Rochester et al. (178); Farley and Clark (136, 137, 139)*]. In sharp distinction to the matter of information processing by single units and explicitly arrayed networks are questions relating to the holistic behavior of large pools of neurons. Whether or not one believes that significant discrete information-processing actions can be taken by large masses of cells acting in some unified way, interesting considerations of gross-signal propagation and of stability arise.

Hebb (147) postulated that significant aspects of neural action could emerge from "cell assemblies." These assemblies might be simultaneously aroused and, through selective synchronization, could be expected to play an important role

(albeit statistical) in perception and learning. A central idea in Hebb's view of nervous action is that when one neuron succeeds in firing another neuron, synaptic efficiency is enhanced such that the subsequent probability of the firing sequence is increased. This hypothesized action, though still not demonstrated physiologically, plays a central role in many network models.

With Milner's observation (162) that inhibitory function would be vital to the successful operation of such a system, the stage was set for investigation of just which factors might be expected to influence the stability of large neural networks, for quite obviously sustained or even disruptive oscillation is possible.

Burns' earlier physiological modeling investigation of reverberatory afterbursts (see p. 548) treated oscillation and its control locally, assigning primary importance to the excitation and recovery functions of single neurons. However, some years before that Rapoport (172) analyzed the effects of neural threshold and of axon density on the ability of a large, randomly connected network to "ignite" (i.e., become active), and Trucco (186), extending this work, developed additional constraints on ignition threshold.

Allanson (125), in further mathematical analysis, showed how randomly connected neuron-like[6] nets could oscillate continuously, remain quiescent, or exhibit damped oscillations as a function of the various network parameters.

Frankel (140) contributed a thoughtful discussion of the significance of Hebb's network proposals and briefly described exploratory computer-simulation experiments, the first so reported.

The earliest constructed network to be explored and reported in detail was that of Rochester et al. (178). Computer-simulation experiments were run on a quasi-randomly connected net of 512 "neurons" to test the postulates of Hebb and Milner. The network elements were simplified axon models that had both excitatory and inhibitory synapses. Synaptic efficiency was continually changed as a function of the firings of the neural elements they mediated, and adaptation of threshold under repeated stimulation was included. The network was connected in a many-to-many fashion. The firing of a particular neuron at each instant depended on the summated excitatory and inhibitory influences relative to the value of its refractory recovery function at that instant.

Preliminary experiments were run with a simplified prototype network of 64 units in which synaptic transmission could be both enhanced and diminished but, following Hebb's postulate, no explicit inhibitory action was included. (In the Hebb model, the network, though lacking inhibition, can suppress reverberatory activity owing to relatively long refractory periods.)

Two interesting results were obtained. First, the system exhibited what was called "diffuse reverberation"; aperiodic firing patterns persistently circulated through the net. Curiously, virtually undamped oscillations could persist for some

[6] It should be noted (as Allanson was careful to point out) that the representations of neurons in this study were extremely reduced. However, the parameters used, plus the fact that a given cell could be fired either by external stimuli or by other cells, or could be spontaneously active, constituted a much more realistic model than the earlier ones.

while, then all activity would cease abruptly. Rochester et al. believed that the phenomenon offers a plausible explanation for short-term memory. Second, with six units acting as receptors to which external stimuli were applied, no characteristic responses developed for particular classes of stimuli, and no "cell assemblies" developed. (Hebb had postulated that diffuse reverberation in cortical networks takes place in cell assemblies—specific active subsets of units that are developed and aroused by certain classes of stimulation and prior activity.) It was found, at least for the particular networks tried, that with a very slight change in the threshold of just one unit (introduced at an arbitrary time), subsequent firing patterns changed markedly, and the network activity diverged rapidly from its original behavior. That is, the system was acutely sensitive to small perturbations.

It was concluded that although sustained reverberatory action that satisfied some requirements for short-term memory had been demonstrated, additional mechanisms or structure would be required to demonstrate the cell-assembly action that Hebb had postulated.

In the second series of experiments run by Rochester and his colleagues, inhibitory synapses were added, and the number of simulated neurons in the network was increased to 512. Owing to the limitations of the computer then available (IBM 704), it was necessary to abandon precise knowledge of when a unit fired and instead work with average-frequency-of-firing parameters. A further change was that interconnections were given more coherence; the probability of connection between two elements in the network diminished with the distance between them; i.e., near neighbors were more likely to be coupled than remote ones. Sixteen units, arranged in four separate blocks of four units each, were used to supply input stimuli.

It is unfortunate that so many variables were simultaneously changed in going to the revised network since the effects of each could not be properly assessed. The new results, however, were rewarding. Cell assemblies formed around each of the receptor areas. The intercellular connections became largely excitatory while the interassembly connections became principally inhibitory. The Hebb-Milner requirements for "fractionation" and "recruitment" were seen. In time particular neurons changed allegiance from one cell assembly to another. There was some tendency, though quite weak, for one cell assembly to arouse another; the tendency was insufficiently strong for spontaneous network activity.

These experiments represent an interesting start in a significant area of network modeling but, unfortunately, they were not continued. In contrast, the work of Farley and Clark, beginning along similar lines, has continued to develop over a period of years.

In preliminary studies Farley and Clark (139) explored the activity of large planar nets (1296 elements) where the interconnections were specified by two-dimensional probability distributions; the probability of connection between two elements varied inversely with the distance between them. The neuron-like elements were defined by parameters that included spatial and temporal summation, threshold, all-or-none output, and absolute and relative refractoriness. Synaptic connec-

tions were excitatory only. These parameters were quasi-continuous (time was quantized into relatively small increments), hence the elements were effectively analog rather than digital, and firing was not forced to be synchronous.

In typical experiments, momentary excitation was applied to a selected subset of cells, and the resultant activity was observed on a cathode-ray-tube display as patterns of bright spots propagating through the network. Patterns of firing activity would either pass through the entire net, saturating it (i.e., a propagating wave activated all cells it passed), or else the activity would decrease with distance and time, dying out prematurely. The network elements' threshold settings determined which mode existed. External control over threshold setting could also be made to influence whether and when particular cells or sets of cells fired. The results were similar to those obtained by Beurle (see p. 576), who used a continuous rather than a discrete formulation of a network.

Farley and Clark also observed that with low threshold settings and repetitive stimulation, sustained oscillatory patterns occurred. Further, patterns of activity from simultaneous excitation of several groups of cells propagated as waves that, on collision, interacted nonlinearly.

These results were obtained from "tightly connected" nets, that is, nets where the network connectivity, delay times, and refractory time constants were such as to produce well-defined, dense wave fronts of activity. In a subsequent study of "loosely connected" nets, Farley (136) used connection and timing parameters such that backfiring occurred in cells lying in the refractory trough of a wave. In this case, wave fronts tended to become fuzzy, and scattered activity over the entire net was seen. Under some conditions the whole network would oscillate diffusely, either continuing indefinitely or else stopping spontaneously after a few cycles.

Several different oscillatory modes were observed. In one, activity might spread evenly over the entire net so that large-amplitude, in-phase oscillation was everywhere present. In another mode, activity could transfer from one part of the net to another. In this case the total number of active units at any time would be approximately constant, but observation of a particular section might disclose irregular bursts of rhythmic oscillations.

Farley also observed a "resonance" phenomenon in which the net could be driven by a repetitive external stimulus at or near the natural period of the net (synchronized oscillation). A related effect, "augmented" responses, occurred when the second external stimulus of a pair, properly timed, could enhance the network activity over a number of successive periods.

All these effects were attributed primarily to the refractory characteristics of the network units. Farley (137) noted that some of the phenomena were at least qualitatively similar to slow-wave, augmenting, and recruiting responses of EEG, and in discussing possible relationships of the modeling studies to neurophysiology, he suggested some new interpretations of slow potentials.

Smith and Davidson (181, 182) modeled networks similar to those of Farley and Clark but took the additional step of providing inhibitory connections among elements. They complemented their computer-simulation studies with mathematical analysis, developing expressions for steady-state activity. Although the level of activity maintained in the simulated nets was generally higher than that pre-

dicted analytically, the mathematical treatment permitted the visualization of several interesting explicit relationships among network parameters. Both in stable steady-state activity and in oscillatory behavior it was shown that identical subsets of elements could fire periodically, despite widely differing element parameters. Smith and Davidson examined the effects of the proportion of inhibitory interconnections on oscillation stability and on the transient time required for the network to reach steady-state activity. Though little relevance to neurological behavior was demonstrated, the study is significant in its extended treatment of inhibitory as well as excitatory interconnections in modeling investigations of large networks.

In concluding this section on discrete networks it is interesting to note that the influence of Hebb's (147) speculations on cell assemblies had a strong effect in quite another direction. These ideas prompted not only the network propagation and stability modeling studies cited above, but they also were largely responsible for initiating interest in "self-organizing" systems, These are the quasi-neural models briefly mentioned in the INTRODUCTION.

Several years before the work of Farley and Clark just described, the same authors (132, 138) addressed themselves to the problem of how randomly connected networks of active, nonlinear threshold elements could "adapt" or "learn." Although there had been some interest prior to 1954 in computer-programed learning and adaptive machines, this work of Farley and Clark was the first explicitly designed to represent neuron-like elements in self-organizing networks where the connections among the elements could be appropriately modified in the synaptic sense that Hebb had postulated.

Though they obtained some measure of success in getting these computer-simulated networks to exhibit a kind of learning (network self-modification to classify simple input signals), Farley and Clark were diffident about claiming relevance to neurophysiological systems. They observed that their system bore some casual resemblance to actual nerve networks and pointed out that further study might reveal more germane relationships, but emphasized that the work was principally of interest for further investigation of large complex systems in general.

This modest beginning, however, marked the start of a new kind of "neural modeling." In the ensuing decade tremendous interest was generated in the analysis and design of self-organizing systems. As fervor waxed, diligence in taking care to note lack of relevance to neurophysiological systems waned. Most if not all of the proposed systems employ elements that are simple, time stationary, formal neurons, that is, threshold elements that lack the many temporal dependencies of biological neurons. Terms like "neuron" and "synapse" are used loosely and irrelevantly. Further, in clear distinction to real nerve nets, these systems start with completely chaotic (random) connection patterns. Finally, the mechanisms for network change are based on Hebb's still unproven postulate of synaptic change for memory and functional modification.

It is not, as we have stated, within the province of this review to document this field of endeavor. A wealth of literature, easily found, is available to the interested reader. Perhaps the most representative work is that of Rosenblatt (179). Some interesting defenses and objections to the work may be found in the survey of Daly et al. (134), and a number of telling criticisms are made by Offner (165) and espe-

cially by White (196). The fundamental problems being addressed by self-organizing systems research are certainly interesting, but appear to be neurophysiologically irrelevant. Perhaps in time neural modeling will be better served by such approaches, but their applicability for now at least is unclear.

8) Continuous representations of networks [Beurle (129–131), Griffith (143–145)]. Since the representation of large nerve nets by discrete models has often proven extremely difficult, many modelers have begun to rely on continuous representations. One of the first to do this was Beurle, who used a continuous formulation to study propagation of activity in large cell masses. More recent applications have been those of Dewan (135), who has compared EEG data with the output of a nonlinear oscillator, and Freeman (141), who derived a continuous control-theory model for portions of the cat prepyriform cortex, using the model to study stability.

At approximately the same time that Rochester et al. (178) were conducting empirical studies on a large, simulated network of quasi-randomly connected discrete elements, Beurle (129) formulated a continuous mathematical representation of such a net. His primary aim was to determine whether or not organized activity could arise from a network of randomly connected cells. Beurle was not concerned with activity in individual cells, but rather with the proportion of cells becoming active in any given region per unit time. A basic simplification was achieved by statistical treatment of activity. An additional simplification, for mathematical convenience, was that variation of activity in one dimension only was considered.

The specifications for elements comprising the array, similar to those used in most of the network studies, were principally axonal; they included spatial and temporal summation, absolute refractoriness, delay, and all-or-none output. As in the case of the first of the discrete network simulations by Rochester and his colleagues, inhibition was excluded. Beurle's network specifications included distributions of cell dimensions and packing densities, fiber counts, and dendrite and axon densities. Characteristically the analysis obtained quantitative measures of threshold distributions, proportions of active and inactive units, propagated wave pattern and velocity, wave interaction, and reverberatory behavior.

Beurle examined the propagation of plane waves of activity through a mass of cells and found that one of three things happened. If a wave was of *precisely* the critical amplitude for the system, it would propagate without change throughout the entire network. If a wave was of less than the critical amplitude, it would be attenuated as it progressed and would eventually disappear. Alternatively, a wave having greater than critical amplitude would increase until all units in its path became active when it passed; the net would thus become saturated, and the wave amplitude would no longer increase.

Beurle found that this was a general property of his model; it could not maintain sustained activity at an intermediate level except under an unrealistically precise set of initial conditions. In general, either activity died out or the net became saturated. Beurle later postulated (130, 131) that inclusion of inhibition would allow for sustained intermediate behavior [which was later proved by Griffith (143)].

In 1962 Ashby et al. (126) attempted to examine with another mathematical model the question of stability in a large net, again looking for stable, submaximal

activity. In their model they represented the activity of the entire net by a single variable, the probability of firing of a unit in a given interval of time. As in the case of Beurle, Ashby and his colleagues did not include inhibition, and they were unable to find sustained intermediate activity with their model. They concluded that natural brains, which normally operate at an intermediate level of activity, present a moderate "paradox."

Carrying on these studies, Griffith (143) added inhibition to the model. Using the same single-variable representation, he was able to show sustained oscillations of the net through various degrees of activity. Griffith thus eliminated the apparent paradox (144, 145) and went on to develop alternate representations of nets using continuous mathematics and the notation of field theory. He is continuing to examine the problem of stability of nonsaturating activity.

In the continuous models of nerve nets, the general underlying assumption is that of random connectivity among the units. In response to a recent paper by Beurle, Sperry pointed out that many examples of central-nervous-system cell masses have at first appeared random to observers but were subsequently found to be connected in a highly specific manner [see discussion following Beurle (130)]. The preponderance of evidence suggests, in fact, that above minute, local levels, few, if any, neural structures are randomly connected. Until the structure of some real net has been completely specified, however, the only tractable approach for modeling such nets may be the statistical one, and indeed the studies cited above have been very useful.

D. Systems

An economical and effective way to characterize systems is to define them in terms of functional operators. This treats a system as a collection of black boxes whose input-output (transfer) functions are specified together with the transmission paths (generally including feedback) among the boxes. Control systems engineering developed for this purpose contains analysis and synthesis techniques for dealing with complex information-processing and control networks. It has provided particularly useful tools for examination of some important aspects of living systems.

The models described in this section reflect extensive use of control systems engineering. Postulates derived from behavioral experiments on organisms are used in the design of networks of functional black boxes, accounting for that behavior and predicting other (theretofore unobserved) behavior. The black boxes evolved in this process carry implications of certain internal neural functions (each box represents an underlying neural network), and they suggest possible mechanisms responsible for certain classes of sensory-motor phenomena. Models of this kind, while not neural per se, can indicate with precision the information-processing nature of a nervous system; in so doing they help to establish very useful links between behavior and nervous system function.

Mach [see Ratliff (174)] must certainly rank as one of the first to apply these

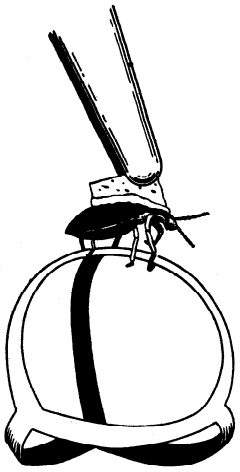

FIG. 18. *Chlorophanus* beetle on a Y-maze globe. As the beetle walks he must continually choose between left and right turns. [From Reichardt (218)]

techniques to a biological control system. Beginning in 1865, he developed a mathematical model to account for a psychophysical phenomenon he discovered and which now bears his name, *Mach bands.* This model included effects of reciprocal action of neighboring areas of the retina upon each other, and it was the forerunner of modern theories of lateral and reciprocal inhibition. The following discussion concerns some of the more modern examples of systems analysis applications.

1) Optomotor responses and orientation [*Hassenstein and Reichardt (212, 218)*]. Reichardt applied control systems engineering techniques to develop a model for the optomotor response in a beetle. Most of the elements of the model were linear, but it required two nonlinear elements in the form of multipliers. Once the model had been designed and its parameters specified, it was used to predict responses to classes of stimuli that had not yet been presented to the beetle. These predictions were then verified, supporting the validity of the model.

The basic experiments with the beetle were performed with a device called the "Y-maze globe," shown in Figure 18. The beetle was held in position by a piece of cardboard glued to its back while it held the Y-maze globe with its feet. As the beetle walked it actually remained fixed while the globe moved. Every few steps the beetle had to choose between two alternative paths at a Y-junction. Hassenstein and Reichardt (212) observed the distribution of turning choices as various patterns of vertical lines were revolved around the beetle on a rotating cylinder.

The first experiments used three concentric cylinders with the beetle and his Y-maze globe suspended at the center. The inner cylinder was fixed and had vertical slits cut in its surface. The outer cylinder, striped alternately white and black, was also fixed and provided either a black or a white background for each slit. The middle cylinder, consisting of separated gray screens (broad with respect to slit width and spacing), was rotated at various constant velocities. When the gray screen moved across a slit with a white background, it provided a moving change from light to dark; when the screen moved across a slit with a black background,

the change was from dark to light. From these experiments, Hassenstein and Reichardt concluded that a succession of light levels on adjacent ommatidia or on ommatidia once removed is required to elicit an optomotor response.

To account for the observed stimulus-response characteristics, Hassenstein and Reichardt proposed what they called a minimum mathematical model. Since an optomotor response was elicited by stimuli on adjacent ommatidia, but not by stimuli on a single ommatidium, the minimum model included information-processing channels for two adjacent ommatidia and took into account the effects of the nearest neighbors. It was assumed that the correlative effects between channels were due to multiplicative interconnections; these were included in the model along with linear filter functions equivalent to those found in control systems. Once the general mathematical operations had been specified for the model, it was necessary to fill in the parametric details (time constants, weighting factors, etc.). This was accomplished by means of additional experiments performed with sinusoidal light patterns on a single rotating cylinder; the turning response was observed as a function of cylinder velocity.

With the parameters specified, Hassenstein and Reichardt used the model to predict responses to previously untested patterns. The predictions proved to be extremely accurate. In addition to specific pattern-response predictions, an even more profound prediction was made from the model. The response of the model was determined by the amplitude of the Fourier components of the rotating pattern, not by the pattern itself. In addition, the model was insensitive to phase relations among the Fourier components. Hassenstein and Reichardt set out to test the beetle optomotor response for this property. They constructed two seemingly different cylinder patterns, both having the same Fourier amplitude components, but with different phase relations (see top and middle drawings in Fig. 19). As predicted by the model, the beetle responded identically to both patterns. Its response to a similar pattern with different Fourier components (bottom of Fig. 19), on the other hand, was very different, both qualitatively and quantitatively.

As a final test of their model, Hassenstein and Reichardt used it to predict the beetle optomotor response to a random pattern of gray and black vertical lines. Among other things, the model predicted that for low pattern velocities the response would be in the direction opposite to pattern motion. Not only was this prediction verified, but the beetle's responses matched the predicted response curve for all low and moderate cylinder velocities. The predictions failed at higher velocities since the pattern was no longer effectively random, being repeated every 360 deg.

Having successfully applied systems engineering concepts to the beetle optomotor response, Reichardt (219) has gone on to similar studies of the compound eye in *Limulus*, and Fermi and Reichardt (211) have analyzed optomotor response in the fly *Musca*. In addition, Bliss (200, 201) and Thorson (226, 227) have extended the insect optomotor-response studies to include the beetle *Lixus* and the locust *Schistocerca*, and Kunze (213) has applied the same techniques to study eye-stalk reaction in the ghost crab *Ocypode*. Thorson has shown several interesting alternatives to Reichardt's model. A number of other workers have used control systems engineering techniques in the analysis of invertebrate systems. Mittelstaedt (215, 216), for

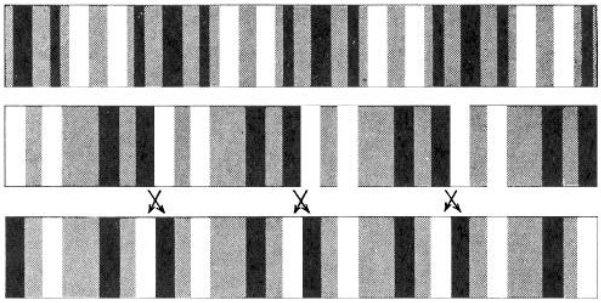

FIG. 19. Stripe patterns used to elicit turning responses in *Chlorophanus*. As predicted by Reichardt's model, the beetle's responses to the top two patterns were identical. The bottom pattern, with only two stripes interchanged, produced a completely different response, as predicted. [From Reichardt (218)]

example, applied them to orientation in insects, and Varjú (229) has used them in studies of the eye of *Limulus*.

2) *Pupillary reflex* [*Stark and Sherman* (*222*, *223*)]. Stark modeled the human pupillary reflex, viewing it as a servomechanism or error-actuated control device, and used the mathematics of control theory to predict conditions of instability in that reflex. Further experiments then verified the predicted instability.

Stark began by assuming that in the presence of very small light-intensity variations the pupillary reflex system could be considered to be a linear, proportional-error control system. The error in this case was presumed to be the difference between the level of light energy actually reaching the retina and some preferred or reference energy level. If these assumptions are correct, one should be able to measure the changes in pupil area as a function of the frequency and magnitude of light energy fluctuations at the retina and to characterize the system completely from these data. In control theory such data provide the so-called open-loop gain characteristics (the feedback path has been removed, or "opened").

In order to obtain the open-loop characteristics of the pupil reflex, Stark had to bypass the effects of pupil size on retinal illumination level. He did this by using a short-focal-length lens to focus a broad beam of parallel light rays to a point at the center of the pupil; this prevented the iris from intercepting any of the light. Since the lens had a short focal length, the rays diverged rapidly inside the eye, and a large area of the retina was illuminated.

Stark sinusoidally modulated the intensity of the light and measured the resulting fluctuations in pupil area. Both the amplitude and the phase of the response as a function of frequency of light modulation were measured.

From these open-loop response data, Stark derived the mathematical form of the open-loop transfer function. Applying his assumption of a linear, proportional-error system, he then calculated the closed-loop or complete system transfer function. From this he predicted the frequency dependence of the amplitude and phase response of the complete pupil-reflex system to sinusoidally modulated illumination.

To test these predictions it was necessary to include effects of pupil size in the system. This was accomplished by presenting a light beam of uniform intensity that was broad enough in diameter always to cover the pupil as well as a portion of the adjacent iris. The light energy impinging on the retina in this case was directly proportional to pupil area. Repeating his phase and amplitude measurements with this system, Stark found that the data matched the predictions very well.

Encouraged by the verification of his predictions for the closed-loop system, Stark went on to examine the question of stability. From the open-loop transfer function, he estimated that with considerably increased gain, the pupil-reflex system should become unstable and oscillate. He predicted that the frequency of oscillation would be approximately 1.5 cycles/sec. By again applying a focused beam, but with the spot of light moved to the boundary between the pupil and the iris, Stark was able to increase artificially the system gain. With the spot in this position, small changes in pupil diameter were much more effective in changing total light energy at the retina. Not only did a steady, unmodulated beam in this position produce oscillations as predicted, but these oscillations were almost exactly at the predicted frequency.

Several years after Stark first published the results of his tests and modeling with sinusoidal light modulation, Clynes (205, 206) tested pupillary response to transient light changes. He found that the pupil diameter decreased, not only in response to a brief flash of increased light intensity, but also in response to a "flash" of decreased light intensity; in other words, the pupil area momentarily *decreased* in response to a *dark* flash. Clynes concluded that the transient pupillary response in each case was elicited by the positive rate of change of light intensity (i.e., the leading edge of the light flash and the trailing edge of the dark flash).

He proceeded to postulate a new model for the pupil reflex system. This model included two input channels for light intensity, one sensitive to the steady light level, the other sensitive to positive light changes but not to negative changes. He thus introduced an asymmetry in the transfer function and cautioned investigators that a linear model may not be adequate for such a system, even for small signals. Clynes (206, 207) then proceeded to study the more general properties of such "unidirectional rate sensitive" systems.[7]

In further studies Sobel and Stark (221) found that the linearized model was indeed adequate for small-amplitude sinusoidal light changes, as one might judge from the fact that this model had accurately predicted pupillary response. Sandberg and Stark (220, 222) subsequently included nonlinearites in the model, however, to account for transients. In addition, Stark employed more sophisticated control-systems techniques to analyze the pupillary system, evaluating, for example, some of the noise mechanisms as well as the nonlinearities for large signal amplitudes. Applying these results along with his small-signal model, Stark deduced a very detailed model of the pupillary reflex. Stark and his colleagues (224, 225)

[7] An interesting analogy is found in membrane physiology. Lewis (46) compared stability criteria for unilateral and linear models in connection with the potassium conductance in nerve membrane. In that particular case, the inclusion of a discontinuity did indeed alter the conditions for stability as well as the frequency of oscillations in the case of instability.

used these modeling studies as a starting point for the investigation of several other classes of human tracking and coordination systems; one of these is discussed in the following section.

3) Tracking control systems [*Mittelstaedt (214, 215), Fender and Nye (208–210), Stark et al. (224)*]. Several biological tracking systems involving visual input and motor output have been studied in great detail. Recently, sophisticated systems analysis techniques have been extensively applied to the human manual control system and the eye-movement control system. In addition, studies of invertebrate systems have been illuminating, Some of the latter were discussed under *Optomotor responses and orientation,* but another, the prey-capture system of mantids, is analogous to the manual control system in humans and is therefore discussed in this section.

Investigating prey tracking and capture by the mantid (*Parastagmatoptera*), Mittelstaedt (214) observed that the stroke of the forelegs during capture has a time duration of 10–30 msec, indicating that, in this stage of capture, the system operates without visual feedback. Prior to the foreleg stroke, however, the mantid tracks the prey with apparent error control or visual feedback. Mittelstaedt pointed out the analogy between this method of prey capture and certain manual tasks performed by humans. If, for example, a person is shown the position of a pencil, then asked to shut his eyes and reach for it, he can readily perform the task; clearly he does so without visual feedback, using only the visual information obtained before beginning his arm motion. So it is with the mantid.

Generally the mantid tends to bring its head and prothorax (which bears the forelegs) into one line with the prey; it can, however, strike a target that has considerable deviation from the median plane of the prothorax. In the latter case, the head, which tends to track the prey, is rotated relative to the prothorax, and so the strike must be based not only on visual information about the position of the prey relative to the head but also on proprioceptive information about the position of the head relative to the median plane of the prothorax.

From his early experimental results, Mittelstaedt postulated a model for the prey-tracking and capture system. He assumed that the head movement during tracking was proportional to the difference between an optical error signal and the proprioceptor signal indicating the position of the head. In steady-state tracking, then, the optical error signal would be proportional to the deviation of the head from the median plane of the prothorax. The strike could be determined by that signal.

To test this model, Mittelstaedt observed the deviation of the mantid's optical axis from the prey. As predicted, he found the deviation to be proportional to the angle between the median plane of the prothorax and a line joining the prey to the head-prothorax joint. In addition, and as predicted, the deviation was diminished by proprioceptive deafferentation.

In Mittelstaedt's continuation of work on animal control systems (216), he has concentrated on orientation and navigation in bees and orientation in fish. His models, being more verbal than mathematical, offer an interesting contrast to those of the Reichardt school. They have, however, provided considerable insight into the systems they represent.

Fender and Nye (208, 210) and Stark et al. (224) have applied control systems theory to the human visual tracking system. Construction of satisfactory models for visual tracking has been difficult, however, owing to the complexity of the system. Typically, a subject is asked to follow a target (such as a spot of light) with his eye. The target is then moved, and the motion of the eye in attempting to follow the target is observed. The open-loop characteristics of the tracking system are studied by using either optical or optical and electronic systems to stabilize the target field with respect to the retina. The position of the target on the retina is therefore not changed by any movement of the eye. The feedback loop is open because the subject cannot detect the effects of his corrective eye movements during tracking. Closed-loop tracking is studied with a system in which the target field is not stabilized with respect to the retina.

In both cases sinusoidal target motion has been used. Comparison of the open- and closed-loop characteristics indicates that the visual feedback pathway has a gain of unity and essentially no phase shift (208).

Up to this point the eye-movement system appears to be relatively simple, but this is deceptive. Discrepancies were found immediately in the experimentally determined curves of gain and phase shift of eye motion as functions of frequency of the sinusoidal target motion. The time lag for tracking was much less than it would be in any linear mechanical system having the same gain characteristics.

The eye tracking system was soon found to be predictive; i.e., it anticipates target position (224). Stark et al. (224) isolated the nonpredictive aspects of the eye-movement system simply by presenting a target moving in an unpredictable manner (more complicated than simple sinusoidal). In addition, Rashbass (217) showed that two separate systems are involved in eye movement. One system controls smooth tracking, the other controls saccadic, or rapid corrective movements. Feedback loops other than the visual path were found, complicating matters even more (208). There is apparently proprioceptive feedback from the eye muscles, as well as several loops in the central nervous system.

Besides eye-movement control studies, Stark and Young (225), Chase and his colleagues (202–204), Bekey (199), and others have applied control systems theory to the human manual-control system. Adolph (198) used similar techniques for analysis of the flexor-extensor system of the leg. A comprehensive review of this subject has recently been published [Young and Stark (230)].

IV. SUMMARY

Overt neural modeling has proven valuable in neurophysiology, and it seems certain that it will continue to do so. The purposes of modeling that are significant to physiologists are threefold: facilitation of preliminary testing of pertinent hypotheses, provision of tractable means of synthesizing disparate physiological data into unified consistent pictures, and generation of guidelines to crucial physiological experiments. In this review we have shown how numerous models have fulfilled one or more of these goals, contributing concrete knowledge to neurophysiology.

Contemporary neural models are playing an important role in complementing direct neurophysiological investigation. While their accomplishments have been

substantial, their utility certainly has by no means been fully exploited. The increasingly close liaison between theoretical and experimental neurophysiology made possible by modeling presents an intriguing challenge for the future.

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REFERENCES

The references are divided into six sections. The first four (A–D) reflect the organization of the text with respect to contemporary neural modeling; the remaining two sections (E and F) cover more general topics.

The selection of citations, based on a considerably more extensive literature search than the number of entries indicates, is meant to be representative rather than exhaustive. This bibliography, like the text, is intended primarily to be a guide for the student of neural modeling.

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