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Neuroelectric Potentials Derived from an Extended Version of the Hodgkin-Huxley Model

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In 1952, Hodgkin and Huxley and others generated a revolution in our concept of the axon membrane and how it propagates the action potential. In 1959, Bullock described another revolution, a "quiet revolution" in our concept of the functions performed by the remainder of the nerve cell. In this paper we have attempted to show a possible connection between these two revolutions. We have proposed that a single unifying concept, that of the Modern Ionic Hypothesis, can account for almost all of the diverse behavior described by Bullock. In addition, we have attempted to demonstrate the value of electronic analogs in the study of systems as complex as that of the neural membrane.

1. Introduction

In 1959, Bullock described a "quiet revolution in our concepts of how the nerve cells act alone and in concert"; and he proposed four major revisions in the classical concept of the neuron: (1) that the nerve impulse, or spike, is characteristic only of a specialized portion of the neuron, the axon; (2) that many parts of the neuron respond to impinging excitation in a completely graded manner and are incapable of all-or-none conduction; (3) that each of these graded responses does not spread to become a spike directly, but several together determine the firing of impulses in some critical region, and (4) that integrative processes at the unit level are not confined to the synapse but also occur in other regions. Bullock went on to say that up to 1938 the only known form of nerve cell activity was the all-or-none spike. In that year, however, the local potential was discovered; and since that time many types of generator potentials and synaptic potentials have been found. Synaptic potentials themselves exhibit at least three degrees of freedom. First, of course, a synapse may be excitatory or inhibitory. In addition, however, a synapse may be facilitating or antifacilitating. That is, the synaptic response to inputs may be enhanced or diminished by previous activity. Finally,

following a long train of input pulses, the synaptic potential may exhibit after effects, either positive or negative, or both. Still further increasing the complexity of the possible combination of processes is the tendency to spontaneous activity. Spontaneous or pacemaker potentials may or may not be accompanied by a spike. The potential itself may be nearly sinusoidal or it may be more nearly sawtooth and include a marked pre-potential.

Bullock (1959), in his discussion, proposed a "locus" model of the neuron in which the various activities (synaptic, spontaneous, local potentials, spike initiation, etc.) are considered to occur in spatially distinct and localized regions, or loci, in the nerve cell. The properties of a neuron would thus depend, to a great extent, on the spatial distribution of these loci. Bullock went on to say that the present physiological models of the single neuron do not lack degrees of freedom. "On the contrary, the permutations of the half-dozen integrative processes now known within the neuron permit so much complexity that we need to know what restrictions to place on the models." He thus poses a very important question about his own locus model: "What restrictions can we place on this model of the neuron?" A corollary to this question is: "Is there an underlying, unifying basis for the diverse forms of both threshold and subthreshold behavior attributed to the various neural loci?"

In this paper I would like to propose that the underlying basis may be the Modern Ionic Hypothesis. It can be shown that the system of delayed and nonlinearly responding ionic fluxes which is the essence of the Modern Ionic Hypothesis inherently contains mechanisms which can provide all of the synaptic "degrees of freedom", the local potentials and the spontaneity found in neurons. Thus the hypothesis which was put forth to explain the generation and propagation of the all-or-none spike may well explain the diverse forms of subthreshold behavior observed in many neurons. In addition, with this hypothesis as the assumed underlying basis of subthreshold behavior, certain predictions of neuronal behavior were made which have since been verified.

In 1952, Hodgkin & Huxley (1952*a*,*b*,*c*) described "voltage-clamp" experiments on the giant axon of the squid, *Loligo*. In a fourth paper (Hodgkin & Huxley, 1952*d*), they formalized the data into a set of empirical nonlinear differential equations describing the hypothetical time course of events during the generation and propagation of the action potential in the squid axon, laying the foundation of the Modern Ionic Hypothesis. The system which they describe is basically one of dynamic opposition of two opposing ion fluxes, sodium and potassium, across the membrane surrounding the axon. The net flux of either ion species may be thought of as the sum of two components, diffusion down the concentration gradient and drift down the electric potential gradient, both components being limited by the resistance of

the membrane. The potassium ions are in greatest concentration inside the axon with the result that potassium ions tend to diffuse outward, carrying positive charges with them. Sodium ions, on the other hand, are in greatest concentration outside the cell and tend to diffuse inward, again carrying positive charges. The potential across the membrane at any instant is related to the net difference in charge from inside to outside; the rate of change of this potential is related to the relative magnitudes of the ionic fluxes, which are in turn related to the relative permeabilities of the membrane to potassium and sodium ions. The Hodgkin–Huxley equations describe, in essence, the dependence of these permeabilities on the transmembrane potential and time, as they found them to be in the giant axon of the squid. Although the physical properties of the membrane are not well understood, it is generally not to be expected that the sum of the diffusion and drift components for a given ion is linearly related to the sum of the concentration potential for that ion and the actual potential difference across the cell membrane (Mullins, 1956; Ling, 1962; Bruner, 1965). The sum of these two potentials, however, was defined by Hodgkin & Huxley (1952*d*) to be the net driving force.

Nonlinearities occur even in the simple case where the electric field is assumed to be constant across the membrane. In this case, we can write an expression for potassium flux J_K (amps/cm^2) as follows:

$$J_K = q\mu_K[K^+]\frac{V_m}{w} - qD_K\frac{d[K^+]}{dx};$$

where q is the electronic charge; μ_K is the mobility of potassium ions in the membrane; $[K^+]$ is the potassium ion concentration, which varies across the membrane; V_m is the transmembrane potential referred to the inside of the cell; w is the membrane thickness; D_K is the diffusion constant for potassium ions in the membrane; and the x-coordinate is orthogonal to the membrane surface. Taking a steady-state condition where both the transmembrane potential and the potassium ion flux are constant, we obtain

$$\frac{d[K^+]}{\frac{J_K}{qD_K} - \frac{\mu_K}{D_K}[K^+]\frac{V_m}{w}} = -dx.$$

It is generally assumed in a system of fluxes that the resistance to a given species of flux is independent of the force driving that flux. The mobility for a given species is thus directly related to the diffusion constant for that species by a simple expression, the "Einstein" relationship

$$\frac{\mu}{D} = \frac{q}{kT};$$

where k is the Boltzmann constant and T is the absolute temperature.

Substituting the Einstein equation and solving the differential equations, we find

$$J_K = \frac{([K^+]_o - [K^+]_i e^{-qV_m/kT}) q\mu_K \frac{V_m}{w}}{(e^{-qV_m/kT} - 1)}$$

where $[K^+]_o$ is the potassium concentration outside the cell; $[K^+]_i$ is the concentration inside the cell.

If we now set J_K equal to zero, we have an expression for equilibrium between the potassium diffusion and potassium drift fluxes:

$$\frac{[K^+]_o}{[K^+]_i} = e^{-qV_K/kT}$$

where V_K is the transmembrane potential necessary for this equilibrium and is defined to be the potassium concentration potential. This expression is one version of the well-known Nernst equation. If we apply this expression and solve for the potassium ion flux in terms of $(V_K - V_m)$ we obtain

$$J_K = \frac{q\mu_K[K^+]_i\{(V_K - V_m)/w - V_K/w\}\left\{e^{\frac{-q(V_K - V_m)}{kT}} - 1\right\}}{\{e^{-q(V_K - V_m)/kT} - e^{-qV_K/kT}\}}.$$

It can readily be seen that J_K is not a linear function of $(V_K - V_m)$.

Hodgkin & Huxley (1952*d*) found that in addition to the nonlinearities inherent in a system where $(V_K - V_m)$ is defined as the driving force, a more profound nonlinearity existed in the relationship between the potassium ion flux and $(V_K - V_m)$, as well as in the relationship between the sodium ion flux and $(V_{Na} - V_m)$. Under the assumption of a reasonably uniform electric field across the membrane, these additional nonlinearities could only be explained in terms of voltage dependent mobilities. In other words, the permeabilities of the membrane to potassium and sodium ions depend on the transmembrane potential.

Hodgkin & Huxley (1952*d*) described the membrane system of the squid axon in terms of the electrical analog of Fig. 1, which represents 1 cm^2 of membrane. The batteries represent the concentration potentials for each ion species, with the effects of all ions other than potassium and sodium lumped into a single "leakage" potential in series with a constant "leakage" conductance. The effective transmembrane capacitance was found to be essentially constant for the squid axon at 1 $\mu F/cm^2$ of membrane. This was found to be effectively in series with a very small resistor—approximately 7 ohms for 1 cm^2 of membrane. The potassium and sodium conductances are the critical variables in this system and each depends on the transmembrane potential and time.

2. Potassium and Sodium Conductances

Most of the conductance data of Hodgkin & Huxley (1952*a*,*b*,*c*) were inferred from experiments in which the transmembrane potential was suddenly changed and held at a new value, and the time course of the resulting transmembrane current was observed. With the membrane at equilibrium, or at rest, the sodium conductance was extremely low, a few micromhos per square centimeter (a resistance of several hundred thousand ohms in series with V_{Na} in Fig. 1). If the transmembrane potential is suddenly increased and held at

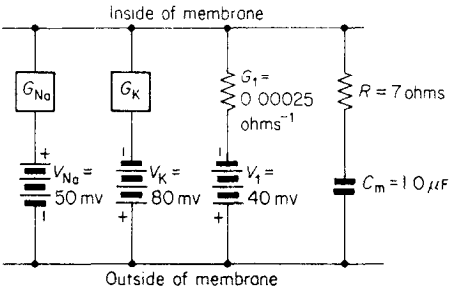

FIG. 1. The Hodgkin–Huxley model of 1 cm^2 of membrane in the squid giant axon.

a value greater than equilibrium, little or no change is observed in the sodium conductance. If, on the other hand, the transmembrane potential is suddenly reduced (depolarized) and held at a value less than the equilibrium potential, two components of change are observable in the sodium conductance, as shown in Fig. 2. One is a transient change in which the sodium conductance rises with a finite time constant and some delay to a peak value, only to fall again with a different time constant. The second component is steady and persists as long as the membrane is held at the non-equilibrium potential. The decline of the transient portion is generally attributed either to inactivation of sodium carriers (Hodgkin & Huxley, 1952*d*) or to clogging of the passages through which the sodium ions flow (Mullins, 1956). Once restored to the equilibrium potential, the membrane recovers from this inactivation or clogging exponentially. If the equilibrium potential is restored instantaneously, both components of sodium conductance fall rapidly to the equilibrium values. For a stepwise depolarization and subsequent repolarization to the resting potential, the change in sodium conductance can be characterized by seven parameters: (1) delay time, which is much less than 1 msec and depends to some extent on the magnitude of depolarization, (2) rise time, which is 1 msec or less and depends on the magnitude of the

depolarizing step, (3) inactivation time constant, which decreases monotonically with increasing depolarization, varying from approximately 10 msec to less than 1 msec, (4) time constant of recovery from inactivation, which was specifically measured for only one case, a 44-mv depolarization; the inactivation time constant was about 1·8 msec, while that for the recovery

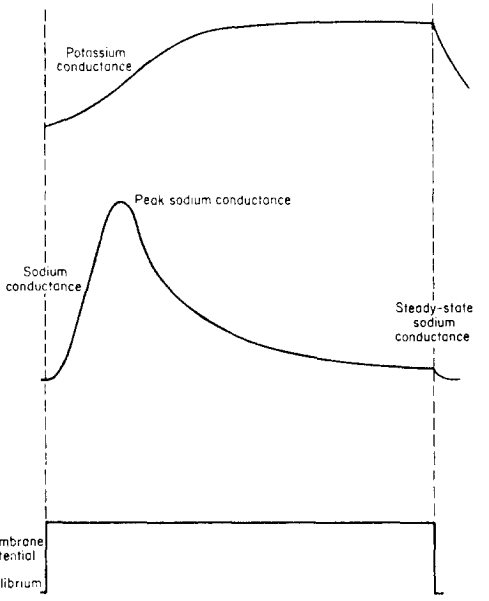

FIG. 2. Generalized responses of the sodium and potassium conductances to a step depolarization from Hodgkin & Huxley (1952*d*).

from inactivation was approximately 12 msec, (5) the peak value of sodium conductance, which increases monotonically and in an extremely nonlinear (cubic to quartic) manner with increasing depolarization and saturates at about 20 mmho/cm^2 for very large depolarizing steps, (6) the steady state sodium conductance which, according to the Hodgkin–Huxley equations (Hodgkin & Huxley, 1952*d*) increases with increasing depolarizations for small depolarizations, then passes through a peak and declines with further increasing depolarizations, (7) fall time on sudden repolarization, which is less than 1 msec.

While these parameters are reasonably inclusive, two important aspects of the sodium conductance have been omitted—namely, its behavior when the sudden depolarization takes place from a non-equilibrium potential, and its behavior when the membrane potential is varied slowly about the equilibrium

value. In one experiment described by Hodgkin & Huxley (1952*c*), the membrane potential was preset and maintained for some time at a non-equilibrium value and then depolarized to a level 44 mv below the equilibrium potential. This was repreated for several values of preset potential, both above and below the equilibrium potential. The peak magnitude of the sodium conductance was observed in each case during the subsequent depolarization. It was found that the peak magnitude decreased as the preset potential was decreased. In other words, if the membrane had originally been hyperpolarized, the peak conductance was greater than that reached from equilibrium, which in turn was greater than that reached from a slightly depolarized state. Hodgkin & Huxley (1952*c*,*d*) and others (e.g. Hoyt, 1963) have interpreted these results in terms of a steady-state "inactivation" as a function of preset potential. For every value of transmembrane potential, Hodgkin and Huxley assume a steady-state inactivation factor (h_∞) which determines not only the steady-state sodium conductance at that point, but also the peak sodium conductance available for depolarization *from* that point. The picture is complicated, however, by another parameter (m_∞) assumed by Hodgkin and Huxley. This parameter is also a factor in determining both the steady state and the transient sodium conductances. The factor m_∞ differs from h_∞, however, in that it only affects the sodium conductance at the membrane potential to which it applies. In other words, at a given transmembrane potential (V_1) we have $m_\infty(V_1)$ and $h_\infty(V_1)$, and the steady state conductance at V_1 is a function of both. The peak sodium conductance for a sudden depolarization from V_1 to V_2, on the other hand, is a function of $m_\infty(V_2)$ and $h_\infty(V_1)$. The factor $m_\infty(V_2)$ thus obscures the relationship between the steady-state conductance at V_1 and the peak conductance on depolarization from V_1 to V_2. Such a relationship may, in fact, be non-existent.

It is interesting to try another assumption, namely that while the steady state sodium conductance depends on the magnitude of the transmembrane potential, the transient or peak sodium conductance is independent of that potential. We will assume instead that the magnitude of the transient sodium conductance depends only on the magnitude of any imposed depolarization, and is independent of the potential from which that depolarization took place. If this assumption is correct, we should be able to plot the Hodgkin–Huxley data with "magnitude of depolarizing step" as the abscissa and find that the data for depolarizations *to* a constant level fall on the same curve as depolarizations *from* a constant level. This has been done in Fig. 3, and it can be seen that the two sets of data almost exactly coincide. The peak sodium conductance appears to be dependent only on the "magnitude of depolarizing step". If we now assume that the transient sodium conductance is not a

function of absolute membrane potential, we must reinterpret another aspect of the Hodgkin–Huxley formulation, namely the inactivation. This now becomes a form of *accommodation*. If the membrane potential is suddenly altered and held at a new value, the transient sodium conductance accommodates in time to that new level. If the change is a depolarization, the time

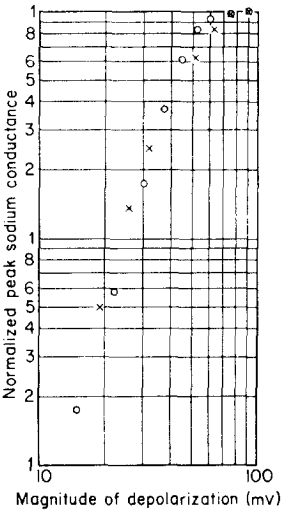

FIG. 3. Comparison of effects of depolarization from a constant level (×) (equilibrium) and depolarization to a constant level (○) (44 mv below equilibrium) (from Hodgkin & Huxley, 1952*c*,*d*.)

constant of accommodation is simply that which Hodgkin & Huxley (1952*c*) call the time constant of inactivation. If, on the other hand, the change is a polarization or hyperpolarization, the time constant of accommodation is simply the time constant of "recovery from inactivation". How does this interpretation affect the Hodgkin–Huxley model? In three ways: first, it allows the same maximum peak sodium conductance to be reached on depolarization from any membrane potential; second, it provides that the peak sodium conductance obtained on sudden depolarization is independent of the steady-state conductance at the level from which depolarization took place; and, third, it contradicts the basis upon which steady-state sodium conductance is calculated with the Hodgkin–Huxley equations for large values of depolarization.

It seems reasonable to generalize from this point that under our new assumption the sodium conductance can be characterized as being composed of two components: a steady-state component whose amplitude depends on

the absolute membrane potential, and a transient component whose magnitude depends on the magnitude and rate of any depolarizations of membrane potential as well as on the recent history of membrane potential fluctuations.

In response to a suddenly applied depolarization, the potassium conductance rises with considerable delay to a steady value which is maintained as long as the membrane remains depolarized (Fig. 2). The rise of the potassium conductance was characterized by Hodgkin & Huxley (1952*d*) as a simple decreasing exponential rise taken to the fourth, fifth, or sixth power:

$$g_K = \{(g_{K\infty})^{1/n} - [(g_{K\infty})^{1/n} - (g_{K0})^{1/n}] \exp [-t/\tau_n]\}^n$$
$$n = 4, 5, \text{or } 6$$

where $g_{k\infty}$ is the final value of conductance; g_{k0} is the value of conductance just prior to the depolarizing step, and τ_n is a time constant which depends on the magnitude of the membrane potential after the step. The exponent, n, simply places an inflection point in what would otherwise be a curve with monotonically decreasing slope. The value of n has very little effect on the general shape of the curve but simply determines the "delay time" or distance along the time axis between the origin and the inflection point (Fig. 2). It can be shown that the inflection point occurs at

$$t = \tau_n \log n.$$

Based on experiments with the giant axon of *Loligo* in which the membrane was first strongly hyperpolarized and then depolarized to the sodium concentration potential, Cole & Moore (1960) revised the Hodgkin–Huxley formulation to read

$$I_K = I_K^*(1 - \exp [-r(t+t_0)])^{25}$$

where r is the rate constant, I_K^* is the final value of potassium current and t_0 is a function of the preset potential from which depolarization takes place. Cole & Moore (1960) found that t_0 was effectively zero for hyperpolarizations of 212 mv. The magnitude of t_0 required to fit the data increases monotonically with decreasing hyperpolarization. In other words, the "delay time" in the rise in potassium conductance is a monotonic function of the membrane potential just prior to the step depolarization. The effect of increasing t_0 is very similar to that of decreasing the exponent, n, so the Hodgkin–Huxley formulation for a step depolarization from equilibrium provides results very similar to those given by the Cole & Moore formulation for the same region. With either formulation, the potassium conductance can be characterized by four parameters: (1) delay time, which decreases monotonically with increasing step depolarizations and which increases monotonically with the magnitude of the membrane potential from which the depolarization takes place; (2) rise time, which decreases monotonically with increasing

depolarization, varying from more than 10 to approximately 1 msec for depolarizations from equilibrium; (3) steady-state potassium conductance which increases monotonically with increasing depolarization (see Fig. 4), and (4) fall time on sudden repolarization which may be 8 msec or more and apparently decreases slightly with increasing depolarization.

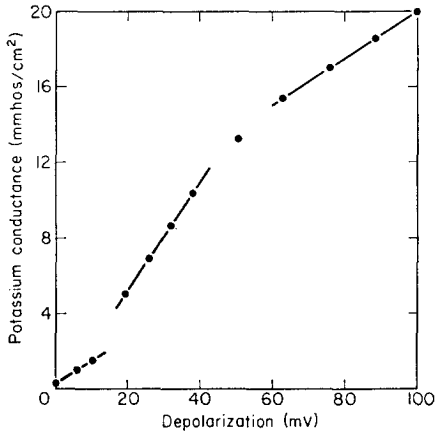

FIG. 4. Potassium conductance as a function of membrane potential, data taken from Hodgkin & Huxley (1952*d*). Note the piecewise-linear appearance of the data.

In addition to the parameters of sodium and potassium conductances, the following details complete the electric analogy of Hodgkin & Huxley (1952*d*):

1. Potassium concentration potential	80 to 85 mv
2. Sodium concentration potential	45 to 50 mv
3. Leakage potential	38 to 43 mv
4. Leakage conductance	approximately 0·25 mmho/cm^2
5. Membrane capacitance	approximately 1·0 μF/cm^2
6. Resting potential	60 to 65 mv inside negative with respect to outside
7. Spike amplitude	approximately 100 mv inside going positive with respect to outside.

The Hodgkin–Huxley model can be summarized as a passive system coupled to a potassium current which is a delayed function of membrane potential, to a transient sodium current related in an extremely nonlinear manner to rate of change of membrane potential as well as the recent history of membrane potential fluctuations, and to a steady-state sodium current related

in a nonlinear and perhaps nonmonotonic manner to membrane potential. Our question is: Can such a system account for the subthreshold behavior described by Bullock (1959)?

3. Use of Electronic Analogs in Studying the Ionic Model

Regardless of the specific, detailed interpretation we give the Hodgkin–Huxley data, the overall system which this data reflects is an extremely complex one; yet this system represents only a small, single patch of cell membrane and does not begin to account for the various distributive effects which one can imagine. The basic system—the single membrane patch—is composed of a set of several nonlinear, interdependent and time dependent variables:

$$V_m(t), I_l(V_m), I_c\left(\frac{dV_m}{dt}\right), I_K(V_m, t), I_{Na}\left(V_m, t, \frac{dV_m}{dt}, \int_{t-\tau}^{t} (t-\tau)V_m\, dt\right).$$

The linear weighting function of $t-\tau$ in I_{Na} may be replaced by an exponential function. A detailed study of this system must include the effects of both steady-state and time-varying perturbations on individual parameters and combinations of parameters.

If, for example, one wished to examine the theoretical properties of this system functioning as subsynaptic membrane at a chemical synapse, one would need to study the effects of time varying conductance perturbations as outlined in the current theories on synaptic transmission (Eccles, 1963, 1964). The currently popular theory of excitatory synaptic transduction is that the transmitter substance effects an increase in the general permeability of the subsynaptic membrane, which is equivalent to a simple shunting conductance across the membrane model of Fig. 1. This synaptically induced conductance is generally thought to be directly proportional to the transmitter concentration in the synapse. If the transmitter is assumed to be injected during a presynaptic spike and then inactivated by a first-order process, the resulting conductance change will rise rapidly during the spike and then fall in a decaying exponential manner. The time variation for inhibitory conductance changes will be similar to those for excitatory changes, but the synaptic transmitter is thought to act specifically on the potassium conductance, the chloride ("leakage") conductance, or both.

In addition to synaptic conductance changes, a detailed study of the system should include the effects of stimuli (voltage or current) applied directly to one side of the membrane model. The results should include, for example, the parametric dependence of strength-duration curves on various system parameters, the effects of sodium inactivation time constants on short-term

accommodation, the effects of stimulus frequency on the all-or-none response of the system, etc. In addition, the Hodgkin–Huxley data apply to the squid (*Loligo*) at 6°C, and the parameters are extremely temperature sensitive (Q_{10}'s of the order of 3). The parameters may also vary from axon to axon in the squid and in other animals, as well as from axon to soma to dendrite in individual neurons. For these reasons, a reasonably complete study of the system should include the effects of systematic parameter changes; so far we have listed 17 potentially independent system parameters. Examination of such a system with classical mathematic techniques would be extremely impractical if not impossible. Even with the aid of high-speed digital computers, examination of such a system is difficult and time consuming. Digital computers are generally designed to attack problems in a serial manner; this problem requires computation of many extremely complicated functions all varying simultaneously. In addition, the effect of any driving function or perturbation would have to be simultaneously computed. If we take the empirical equations of Hodgkin & Huxley (1952*d*), accepting for the moment their formalization of the system, we can estimate the number of computer operations required to evaluate the system variables over a given increment of time. The Hodgkin–Huxley equations are as follows:

$$\alpha_n = 0{\cdot}01\,(V+10)/(\exp\,[(V+10)/10]-1)$$

$$\beta_n = 0{\cdot}125\,\exp\,[V/80]$$

$$\alpha_m = 0{\cdot}1\,(V+25)/(\exp\,[(V+25/10]-1)$$

$$\beta_m = 4\,\exp\,[V/18]$$

$$\alpha_h = 0{\cdot}07\,\exp\,[V/20]$$

$$\beta_h = 1/(\exp\,[(V+30)/10]+1)$$

$$\frac{dn}{dt} = \alpha_n(1-n)-\beta_n n$$

$$\frac{dm}{dt} = \alpha_m(1-m)-\beta_m m$$

$$\frac{dh}{dt} = \alpha_h(1-h)-\beta_h h$$

$$\frac{dv}{dt} = \frac{1}{C_m}\{\bar{G}_K n^4(V-V_K)+\bar{G}_{Na}m^3h(V-V_{Na})+G_l(V-V_l)\}.$$

If we give our program every advantage in speed—constructing in advance tables for all the α's and β's, and not employing any loops, these equations take about 500 μsec on machines with 5 μsec add times. In order to maintain reasonable accuracy, on the other hand, a solution should be made for every 100 μsec of real time in the neuron. Thus, even with modern high-speed

computers and a fairly straightforward, if somewhat rigid, formalization of the system variables, we still suffer a five to one increase in computer time over real time. If, for example, we add auxiliary programs designed to search for certain modes of overall system behavior (spontaneity, facilitation, etc.) and others to explore systematically the parameter space, a more realistic estimate of the time increase would probably be ten to one. With a ten to one increase in computer time over real time and with the current costs of high-speed computer time (approximately $500 per hour), it can be estimated that one hour of neuron time will cost in the neighborhood of $5000. In slower, cheaper machines (with millisecond add times), one hour of system time may take as much as six months of computer time. For problems requiring only a few seconds or even a few minutes of simulated real time, the time increase is probably unimportant. For problems requiring longer simulations, however, it will probably be a major factor

The digital computer contains certain inherent advantages. It provides flexibility: any nonlinear or discontinuous function may be added to the system. It provides means of automating routine experiments: if an experiment is pre-programmable (i.e. if we do not require human feed-back during the running of an experiment), the digital computer can handle it while the researcher is doing more useful tasks. In addition, it provides means for automatic interpretation of data: the data may be processed in many ways automatically (pulse interval histograms, joint interval histograms, etc.) without adding significantly to the computer time. Present-day digital computers, on the other hand, generally have the following disadvantages: on-line experimentation cannot generally be carried out at computer facilities; large changes in the system will often require rewriting of portions of the program or large changes in the tables of values; and the accuracy of the tabled values and the number of tables are both limited by the size of the high-speed (core) memory.

Some of the disadvantages of the digital computer can be avoided by the use of special electronic analog circuits. With nonlinear active filters constructed to provide time- and voltage-dependent functions essentially identical to those of the potassium and sodium conductances, analog circuits can be designed and built to simulate all of the fundamental aspects of the ionic model. The outputs from the filters can be added to any synaptically induced conductance changes and applied to the inputs of multipliers. The function representing potassium conductance is multiplied by $V_m - V_K$, while that representing the sodium conductance is multiplied by $V_m - V_{Na}$. Currents proportional to the products are then formed. The synaptically induced chloride conductance and general shunt conductance can be simulated by two additional multipliers, and the remaining components of the ionic model,

which are passive, linear elements, are very easily simulated with standard electronic components. In addition, through the use of variable resistors, important parameters in the ionic model can be made variable in the electronic analog. Once the analog has been designed and constructed, it costs very little to use. The basic hourly rate is essentially that of the experimenter. The analog approach contains other advantages. On-line or direct experimentation can easily be carried out; so human intuition can be applied with almost no time lag to the search of the parameter space. Real time simulation can readily be achieved, and the output is easily obtained in a natural form (membrane potential, conductance values, etc.) and can be compared with recordings from real neurons. In addition, changes in the system are relatively easy to achieve (by variable resistor adjustments, replacement of capacitors or nonlinear elements, etc.). The analog approach also has its disadvantages, however. Routine or pre-programmed searches of regions of the parameter space cannot easily be automated with presently available equipment. Automatic data reduction equipment is not inherently contained in the apparatus, so such reduction must either be done by hand or a digital computer must be employed. The system model is basically less flexible than in the digital simulation. Not all nonlinear, time-dependent functions are easily realized with electronic analogs; while, in principle, any function can be approximated with numerical techniques.

It is interesting to compare the digital and analog approaches in another respect—namely in the simulation of small systems of neurons based on the ionic model. In the case of the single membrane patch, the digital computer provides more flexibility and greater data reduction but costs about \$5000/hr of simulated membrane time. The analog approach, on the other hand, costs less than \$20/hr and allows on-line experimentation. In a system of 10 membrane patches, the digital simulation cost increases somewhat disproportionally since limitations on the size of the high-speed memory in the fastest current machines force us to abandon the tabled value approach (unless the tables are assumed identical for all patches). The computation time for a single value of V_m across a single patch becomes approximately 1 msec. Adding the time for auxiliary computation brings the new total to approximately 1·5 msec for 100 μsec of real time per patch. If we add synaptically induced, exponentially declining conductance changes, we must add about 50 μsec per synapse to the total. So, for a system of 10 patches and 20 synapses, the computer time is approximately 16 msec for 100 μsec of real time. One hour of simulated system time now requires 160 hours of computer time and costs \$80,000. Ten analog patches, on the other hand, cost very little more than a single analog patch to operate (maintenance may cost a bit more); so the system that costs \$80,000/hr to simulate digitally costs

less than $20/hr to simulate by means of electronic analogs. These cost estimates exclude programming for the digital computer and design and construction for the analog.

In the studies discussed in this paper, the analog system of Fig. 5 was employed. The circuits are reasonably straightforward. They were not built to simulate the Hodgkin–Huxley equations, however, but were designed empirically to match the Hodgkin–Huxley data (Hodgkin & Huxley, 1952*a* to *d*), They were constructed with capacitors, resistors, varistors, variable resistors. transistors and diodes. Several realizations of the system of Fig. 5 have been

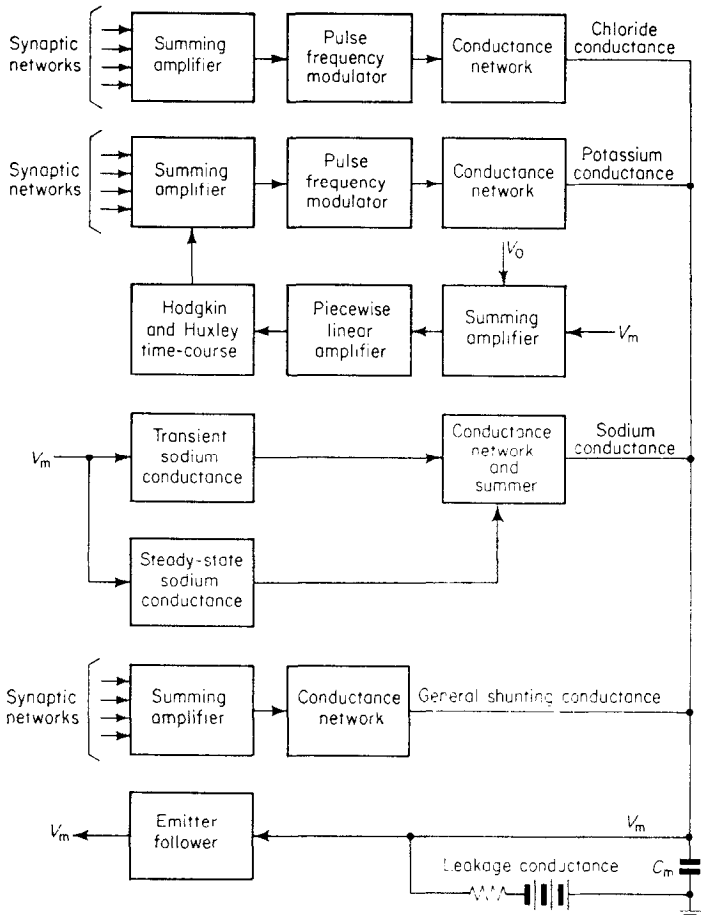

FIG. 5. Block-diagram of the electronic system used to simulate the Hodgkin–Huxley model. The potassium and sodium conductance time course networks are active electronic filters designed to fit the Hodgkin & Huxley data (1952*d*). The pulse-period modulators and conductance networks transform the filter outputs into equivalent conductances.

constructed over the past two years. In that time, the basic designs for the active filters have changed very little. The multiplier circuits, on the other hand, have changed radically. We originally employed "quarter square" analog multipliers in which diodes provided $-(V_1-V_2)^2$ and $(V_1+V_2)^2$. These were added to yield $2V_1V_2$. This scheme was not completely satisfactory, since an accurate product could not be obtained over the required range of inputs (the sodium conductance varies as much as 1000 to 1). In a second version of the system, a pulse-height, pulse-width multiplier was employed. The output was in the form of pulses of amplitude V_1 and width proportional to V_2. This scheme also failed to provide the necessary dynamic range. Finally we employed a pulse frequency modulating network. In this case, the pulse-width was fixed at approximately 1 msec; the amplitude was made equal to V_1; and the frequency varied between approximately 500 pps and 500,000 pps and was proportional to V_2. The latter scheme is particularly well adapted to this system, since the simulated membrane capacitance acts as an integrator for the pulses. Thus, for the potassium conductance, for example, the pulse amplitude is fixed at V_K and the frequency is made proportional to the conductance value. The pulses are applied through a diode and a fixed conductance, G', to the inside of the simulated membrane patch. During a pulse, the current through G' is

$$I = G'(V_m - V_K).$$

The average current over several pulses is:

$$I_K = 10^{-6} f G'(V_m - V_K)$$

where f is the pulse frequency. The effective conductance is thus proportional to the frequency:

$$G_K = 10^{-6} f G'.$$

In our studies with the electronic analog, we have looked for explanations for a number of phenomena. Our basic premise has been as follows: since the soma and dendritic membranes are very likely to be continuous with the axon membrane of a neuron, it seems reasonable that these membranes have electrical properties similar to those of the axon. It therefore seems reasonable that the ionic model or some variation of it should apply to somatic and dendritic membranes. An interesting question then arises: can the various loci and locus properties proposed by Bullock (1959) be explained in terms of the ionic model? In attempting to answer this question, we set out to look for the following in our analog: (1) varying degrees of electrical excitability and how to account for them; (2) spontaneity and how to account for it; (3) facilitation, antifacilitation, or neither and what post-synaptic mechanisms might account for them (this may seem unduly speculative to many physio-

logists since facilitation is almost universally thought to be a presynaptic function), and (4) synaptic after-effects or rebound and how to account for them.

(A) ELECTRICAL EXCITABILITY

While in most neurons the axon membrane responds to electrical stimuli with a spike, or action potential, the somatic and dendritic membranes of many neurons are electrically inexcitable (Bullock, 1959; Hagiwara, 1960; Hagiwara, Watanabe & Saito, 1959; Grundfest, 1957). In other words, these membranes are capable only of completely graded response to applied stimuli and are incapable of all-or-none spike generation. With the aid of our electronic analog we have attempted to discover just what changes in the Hodgkin–Huxley model might account for electrical inexcitability.

Before discussing the question of excitability, however, let us briefly review the regenerative action which, according to the Hodgkin–Huxley model, brings about the all-or-none action potential. Following a brief excitatory stimulus near the spike threshold, the membrane is slightly depolarized. The steady-state sodium conductance increases in response to this depolarization, and the potassium conductance tends to increase but is delayed. The increased sodium conductance induces an inward current which further depolarizes the membrane. This in turn produces a further increase in the steady-state sodium conductance and the process becomes regenerative. Without the transient sodium conductance, however, this regenerative process could not yield an all-or-none spike, since the delayed potassium current would soon overtake the steady-state sodium current and reverse the process. The peak membrane potential obtained before the process reversed would be a function of the stimulus magnitude; the response would be graded. Actually, as the depolarization increases beyond approximately 10 mv, however, the transient sodium conductance becomes significant and adds to the regenerative process. If the excitatory stimulus was above threshold, the added component of sodium conductance makes it impossible for the potassium current to overtake the sodium current until a full spike has been developed.

Following a moderate superthreshold stimulus then, the early part of the regenerative response is due to the steady-state sodium current, while the later part is due to the transient sodium current (Hodgkin & Huxley, 1952*d*). A full all-or-none spike is not possible without the action of the transient sodium current. For large amplitude stimuli, in fact, the steady-state sodium current may not play any significant role in spike generation. Membrane parameters which determine excitability then are those which determine the relative effectiveness of the transient sodium conductance and its antagonist, the potassium current.

In our early studies we found that inexcitability might result from the following changes, taken singly or in combination: decreased sodium current as a function of membrane depolarization, increased rate of sodium conductance inactivation, increased potassium current as a function of membrane depolarization, increased leakage, or chloride conductance, increased membrane capacitance, and finally, changes in a number of less likely candidates such as rates of conductance change (Lewis, in press). Of all these parameters, membrane capacitance now seems to be the most reasonable.

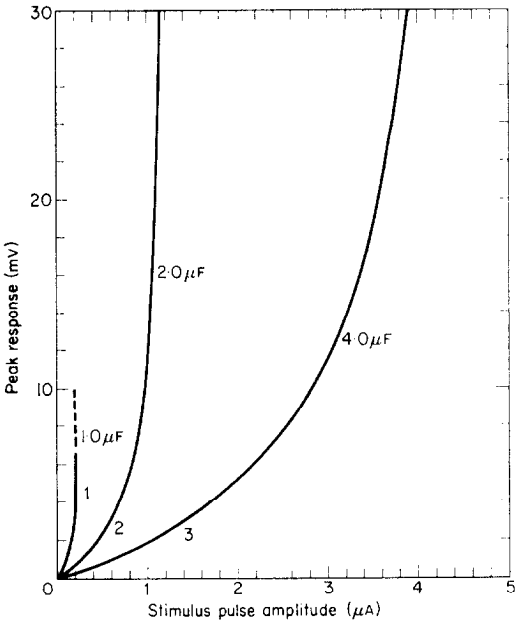

FIG. 6. The peak transmembrane depolarization reached in response to a 5 msec current pulse; the abscissa is the magnitude of the current pulse. The number beside each curve indicates the transmembrane capacitance in $\mu F/cm^2$.

Increasing the membrane capacitance reduces the effectiveness of the transient sodium conductance. This is simply because a given inward current depolarizes the membrane at a rate inversely proportional to the capacitance. As the rate of depolarization is reduced, the resulting transient sodium conductance is reduced.

If we set all the parameters of the analog equal to those specified by Hodgkin & Huxley (1952*d*) and apply 5-msec current pulses of various amplitudes, we obtain the response shown by curve 1 of Fig. 6. The system responds in a graded manner up to a membrane potential of approximately 5 mv. At this point it jumps abruptly to full spike amplitude (100 mv). No

intermediate peak membrane potential is ever observed. If C_m is now doubled (to 2 μF/cm^2) the shape of the response curve becomes completely graded. It is extremely nonlinear, however, and becomes very steep above a membrane potential of 10 mv. If C_m is again doubled (to 4 μF/cm^2) the slope of the response curve is greatly reduced and the curve does not really become steep until the membrane potential is above 40 mv. While the squid giant axon capacitance (Hodgkin, Huxley & Katz, 1952) is approximately 1 μF/cm^2, soma membrane capacitances of 4 μF/cm^2 or more have been measured by several investigators in the puffer, *Spheroider* (Hagiwara, 1960; Hagiwara & Saito, 1959), the lobster cardiac ganglion (Hagiwara, 1960), the cat (Coombs, Eccles & Fatt, 1955), the toad (Araki & Otani, 1955), and others. There is some doubt as to the accuracy of membrane capacitance measurements (Rall, 1960) so a definite correlation between excitability and membrane capacitance cannot be stated at this time. Increased membrane capacitance does appear to be a likely candidate, however, to produce inexcitability. Fitzhugh (1961) has pointed out that completely graded response should be theoretically possible in all cases, but that it cannot always be seen because of lack of fineness in stimulus amplitude adjustment. We can say, however, that the model *appears* to exhibit all-or-none activity for values of membrane capacitance less than 1 μF.

Even with increased capacitance and with the capability of only graded response, the membrane can still respond in an extremely nonlinear manner. In addition, the peak membrane potential in response to a 5-msec current pulse is enhanced by a steady depolarizing current and diminished by a steady hyperpolarizing current. These currents thus affect the excitability of the system. This can be explained in terms of the steady-state sodium conductance. Since it is a nonlinear function of membrane potential, a steady depolarization increases its regenerative effect during the early response phases; this increase is amplified through the remainder of the response. Conversely, a steady hyperpolarization decreases its regenerative effect. A very small depolarization or hyperpolarization can be extremely effective in altering the response.

(B) OSCILLATORY MECHANISMS INHERENT IN THE IONIC MODEL

Many neurons appear to produce periodic spikes or bursts of spikes in the complete absence of external inputs (pacemaker neurons) or in the presence of external stimuli (sensory neurons). Many sensory neurons appear to be pacemakers whose output frequency is altered by external stimuli, but which do not require external stimuli in order to produce spikes. The question which arises is "What mechanisms may account for pacemaker activity?". Early in our work with the analog we tested a rather obvious hypothesis: a depolariz-

ing "leakage" current which prevents establishment of a permanent equilibrium will produce a pacemaker effect. A non-zero sodium flux at what would otherwise be the equilibrium potential would provide such a current; and, with a simulation of the flux, our analog quite readily became unstable and produced periodic spikes. In subsequent experiments, however, we found a number of other mechanisms which produced instability. Pacemaker activity occurred in the following modes: (1) oscillations between the potassium current and the "leakage" ion current; (2) oscillations between the potassium current and the steady-state sodium current; (3) oscillations between the potassium current and the transient sodium current, and (4) oscillations between the potassium current and both sodium currents. These oscillations could be induced in the following ways: (1) introduction of a finite steady-state sodium current at what would otherwise be the equilibrium potential; (2) introduction of an externally applied depolarizing current; (3) alteration of either the potassium or the leakage ion concentration potential; (4) a single excitatory pulse applied to the membrane (in mode 3), and (5) introduction of a general shunting conductance.

The first mode listed above (oscillations between the potassium current and the leakage or chloride current) is of special interest because it can occur without the regenerative action of the sodium current. This is typically a high frequency mode, approximately 20 to 200cs/s for the Hodgkin–Huxley system. Since this system is for the squid giant axon at 6°C, and since Hodgkin and Huxley generally found the system Q_{10} to be about 3 for the various rate constants, we would expect very much higher frequencies at room temperature (180 to 1800cs/s). Since the sodium current does not enter, the depolarizing phase in these oscillations is limited and does not lead to an action potential. While these oscillations occur with an isolated portion of the system and may therefore be of questionable significance, it is important to keep them in mind since they may very well come into play at the subthreshold level and be important in the overall response of membrane systems. One can demonstrate mathematically the potential for oscillations in this mode. Using either Cole & Moore's (1960) formulation or Hodgkin & Huxley's (1952*d*) formulation, we have for a step depolarization:

$$I_K = \Delta I_K(1-\exp[-\alpha(t+t_0)])^n + I_{K0}$$

where t_0, n, and α may all be functions of membrane potential. If we consider the small-signal case where fluctuations in membrane potential are small and t_0, n, and α are essentially constant, we can obtain the Laplace transform of the response:

$$\mathscr{L}[I_K] = \Delta I_K \frac{n!\,\alpha^n \exp[st_0]}{s(s+\alpha)(s+2\alpha)\ldots(s+n\alpha)}.$$

The transform of the step depolarization which produces this current is

$$\mathscr{L}[V_m] = \frac{\Delta V_m}{s}$$

so the transform of the transfer function is

$$\mathscr{L}\left[\frac{I_K}{V_m}\right] = \frac{\Delta I_K}{\Delta V_m} \frac{n!\,\alpha^n \exp[st_0]}{(s+\alpha)(s+2\alpha)\ldots(s+n\alpha)}.$$

Since we are interested in small a/c signals and not step depolarizations, we may substitute

$$(V_K - V_m)\frac{dG_K}{dV_m} \quad \text{for} \quad \Delta I_K/\Delta V_m.$$

Also, since we are interested in small fluctuations about the equilibrium potential, and since the Hodgkin–Huxley and the Cole–Moore formulations are essentially equivalent at this potential, we can eliminate the delay factor (t_0) by choosing the proper exponent (n). Hodgkin & Huxley (1952*d*) settled on 4 for practical computations, but thought 5 or 6 would better fit the data. Cole & Moore (1960) prefered 6. The transfer function is now simply

$$T_1(s) = \frac{I_K(s)}{V_m(s)} = \frac{(V_K - V_m)\dfrac{dG_K}{dV_m} n!\,\alpha^n}{(s+\alpha)(s+2\alpha)\ldots(s+n\alpha)} \tag{1}$$

Unfortunately, this transfer function applies only for increasing I_K. The potassium current in response to a step repolarization decreases in a simple exponential manner, and the transfer function for decreasing I_K is

$$T_2(s) = \frac{I_K(s)}{V_m(s)} = \frac{dI_K}{dV_m}\frac{\alpha'}{s+\alpha'}$$

where α' is not necessarily equal to α. If we eliminate the sodium conductance, and consider only small a/c signals, the Hodgkin–Huxley model of Fig. 1 can be reduced to the system of Fig. 7. If $T(s) = T_1(s)$ this system has two of

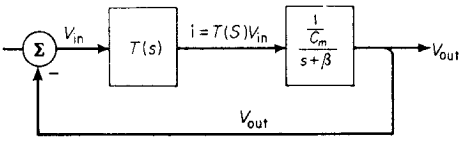

FIG. 7. A small signal equivalent of the Hodgkin–Huxley system without the sodium conductance.

the properties necessary for instability: potential 180° phase shift and negative feedback. If, on the other hand $T(s) = T_2(s)$, the phase shift can only approach 180° and the system is unconditionally stable. Since the latter case is

uninteresting, let us examine the system with $T(s) = T_2(s)$. The overall transfer function is now

$$T' = \frac{n!\,\alpha^n/C_m}{(s+\alpha)(s+2\alpha)\ldots(s+n\alpha)(s+\beta)}$$

where $\beta = G_m/C_m$ and is the reciprocal of the membrane time constant; G_m is the parallel combination of the leakage conductance and the equilibrium potassium conductance. For values of membrane potential near equilibrium, Hodgkin & Huxley (1952*d*) found

$$(V_K - V_m)\frac{dG_K}{dV_m}$$

to be approximately 1 mmho/cm^2. Taking their value of 1 μF/cm^2 for C_m, the open-loop transfer function of the system in Fig. 7 thus becomes

$$\frac{V_{out}}{V_{in}}(s) = \frac{10^3\,n!\,\alpha^n}{(s+\alpha)(s+2\alpha)\ldots(s+n\alpha)(s+\beta)} \tag{2}$$

where α and β are in sec^{-1}. We can find points of potential instability for the open loop transfer function of equation (2) by substituting $j\omega$ for s and solving for the values of ω which provide 180° phase shift. This has been done in a digital computer for values of α from 100 to 1000, β from 100 to 1000 and n equal to 4, 5 and 6. The results are shown in Fig. 8. The contours are those of constant open-loop gain, and constant frequency. The system will be unstable when the open loop gain is greater than unity. The areas below the heavy contour lines thus represent regions in the parameter space where oscillations may occur. It can be seen that this area increases with increasing value of n. Hodgkin & Huxley (1952*d*) found α to be approximately 200 sec^{-1} near equilibrium while their value for β is 500 sec^{-1}. When $n = 4$ or 5, the system is reasonably stable for these values (open loop gain $= 0{\cdot}56$ and $0{\cdot}67$, respectively); when $n = 6$, however, the system is very nearly unstable (open loop gain $= 0{\cdot}76$), and minor fluctuations in system parameters can produce oscillations. The frequency of these oscillations would be approximately 40 cs/s. Thus, if we ignore the discontinuity in the system transfer function (i.e. the shift from T_1 to T_2) we find that very minor parameter changes in the Hodgkin–Huxley system may produce oscillations between the potassium current and the leakage current. Changes which might bring this about are as follows: (1) decreased resting potential or increased potassium potential—a 10% shift in either would suffice; (2) decreased membrane capacitance or increased membrane resistance—a 30% change would suffice; (3) a 30% increase in dG_K/dV_m; (4) a 40% decrease in α. Inclusion of the discontinuity reduces the tendency of our system to oscillate. The extent of such reduction is difficult to assess since

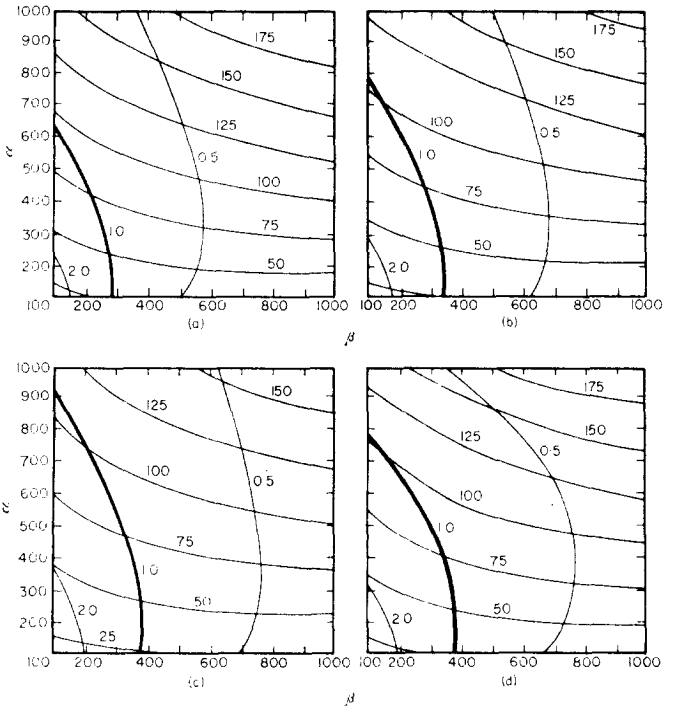

FIG. 8. Contours of constant frequency (25, 50, 75, etc.) and contours of constant open-loop gain ($\frac{1}{2}$, 1, 2, etc.) plotted against system rate constants, α and β.

(a) to (c) The system comprised of the potassium current and the chloride, or leakage ion current. In each case the potassium conductance is taken to be continuous and to respond in the delayed exponential manner ($[1 - \exp(-kT)]^n$). In (a) $n = 4$; (b) $n = 5$; (c) $n = 6$.

(d) Same system as (a) but with the effects of sodium conductance added:

$$\frac{(V_{Na} - V_m)\dfrac{dG_{Na}}{dV_m}}{(V_K - V_m)\dfrac{dG_K}{dV_m}} = \frac{1}{10}.$$

the system is not easily analyzed. Here again, analog techniques are useful. The analog network of Fig. 9, for example, is equivalent to the Hodgkin–Huxley system with

$$T_1(s) = \frac{24\,\alpha^4 A\beta}{(s+\alpha)(s+2\alpha)(s+3\alpha)(s+4\alpha)(s+\beta)}$$

$$T_2(s) = \frac{\gamma A}{s+\gamma}.$$

Studies with this network have led to the following generalizations: inclusion of the discontinuity generally brings about a marked increase in the natural

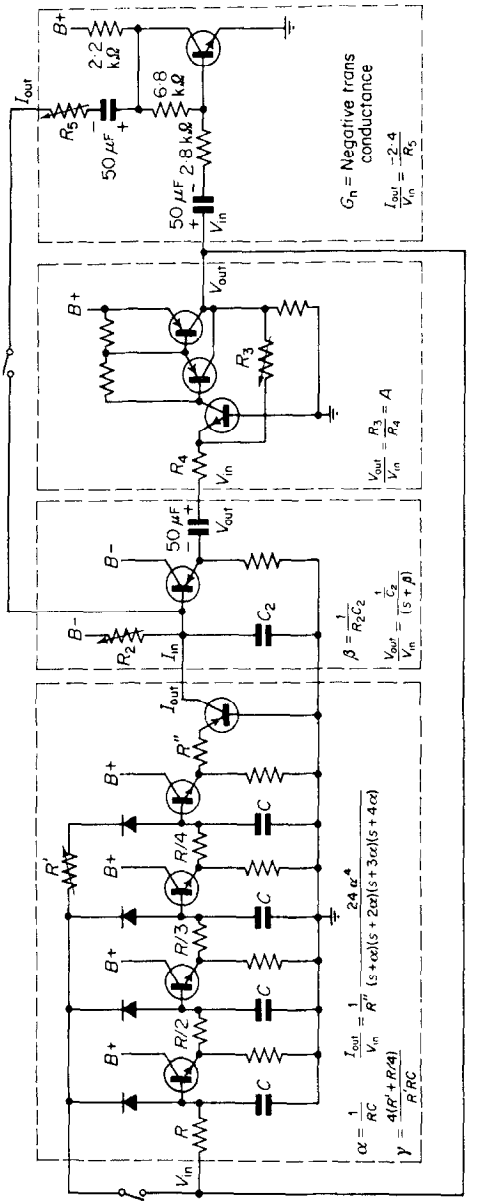

FIG. 9. An electronic realization of the Hodgkin–Huxley model for small signals.

frequency of the system. The frequency becomes strongly dependent on the system gain. It varies from approximately the frequency before inclusion of the discontinuity to almost twice that frequency, increasing monotonically with increasing gain. The gain required for oscillation is approximately doubled, so the system stability is essentially doubled. The variation in open-loop gain as a function of α and β is almost identical to that for the continuous system. The system spends very little time in the mode of $T_2(s)$; so, for the most part, the natural oscillations look like the output of a fullwave rectifier. This probably accounts for the frequency doubling. Table 1 shows

TABLE 1

Results obtained from analog of Fig. 9

$\alpha = 5000$ $\gamma = 2500$ $G_n = 0{\cdot}00003$ ohm^{-1}

	(1) $T = T_1(s)$		(2) $T = T_1(s), T_2(s)$		(3) $T = T_1(s), T_2(s)$	
	No discontinuity in transfer function		Discontinuity in transfer function		Discontinuity in transfer function with negative transconductance in parallel	
β	$A\dagger$	Frequency	A	Frequency	A	Frequency
1000	5·0	42	11·5	72	2·4	35
2000	4·5	49	10·2	86	2·9	54
3000	4·5	53	10·0	93	3·3	67
4000	4·6	56	10·4	100	3·7	77
5000	4·7	59	10·8	106	4·0	83
6000	4·8	60	11·2	112	4·3	88
7000	4·9	61	11·7	115	4·6	93
8000	5·0	62	12·2	118	4·9	95
9000	5·0	63	12·5	119	5·2	95
10,000	5·1	64	13·0	120	5·4	96

$A\dagger$ = gain required for oscillation.

examples of the results obtained with this network, and Plate I shows the waveform of the oscillations obtained from the network.

In the second oscillatory mode mentioned above, the regenerative action of the steady-state sodium conductance is an important factor in the depolarizing phase. As in the previous case, however, the oscillations would not be possible without the delayed potassium current, which produces the hyperpolarizing phase. The depolarizing phase in this case is aided by the steady-state sodium current. The steady-state sodium conductance near the

equilibrium potential increases roughly as the square of depolarization. The steady-state sodium current, which is depolarizing, thus increases in a nonlinear manner with increasing depolarization. The net effect is equivalent to that of a nonlinear negative resistance, providing a regenerative depolarization of the membrane. Repolarization occurs when the delayed potassium current becomes sufficiently strong to overcome the sodium current. As the membrane becomes repolarized, the sodium conductance falls rapidly, but the falling potassium conductance lags the membrane potential enough to allow the membrane to become hyperpolarized. Repolarization is thus regenerative. For small a/c signals superimposed on a slight depolarization, the steady-state sodium conductance is equivalent to a fixed negative transconductance in parallel with $T(s)$ in the system of Fig. 7. The magnitude of the transconductance is simply

$$(V_{Na} - V_m) \frac{dG_{Na-ss}}{dV_m}$$

where V_{Na} is the sodium equilibrium potential and G_{Na-ss} is the steady-state sodium conductance. The system can be analyzed quite easily for $T(s) = T_2(s)$. The solutions were obtained on a digital computer and are shown in Fig. 8. If the discontinuity in $T(s)$ is included, the system again becomes very difficult to analyze. The analog of Fig. 9 can be used, however, to examine the system properties directly. Again several generalizations can be drawn from studies with such an analog. The system with the steady-state sodium conductance becomes more unstable, in fact, a very small negative transconductance will more than overcome the increased stability due to the discontinuity in $T(s)$. The frequency of oscillation is markedly decreased by inclusion of the negative transconductance, and decreases monotonically with increasing magnitude of the transconductance. Data from this analog study are included in Table 1, and Plate I shows the typical waveform resulting from inclusion of the negative transconductance.

One further point should be mentioned: with the parameters of the analog set to the values stipulated by Hodgkin & Huxley for the giant axon of *Loligo* (i.e. $\alpha = 200\ \text{sec}^{-1}$, $\beta = 500\ \text{sec}^{-1}$, $\gamma = 125\ \text{sec}^{-1}$, $n = 4$), and with the open loop gain for $T = T_1(s)$ set at 0·56 (the value computed for those parameter values) the system became unstable when the negative transconductance reached $0{\cdot}54 \times 10^{-3}$ mho. In our representation of the system the transconductance equals $(V_{Na} - V_m) \frac{dG_{Na}}{dV_m}$. The Hodgkin–Huxley value, for $(V_{Na} - V_m)$ is approximately 100 mv; thus for oscillations with the stated parameter values, $\frac{dG_{Na}}{dV_m}$ must be greater than 0·0054 mmho/mv. According

to Hodgkin and Huxley's data (Hodgkin & Huxley, 1952*d*), $\frac{dG_{Na}}{dV_m}$ reaches this value when the membrane is depolarized in the range of 6 to 10 mv. The Hodgkin–Huxley system should thus become unstable in this range of depolarization even without the highly regenerative action of the transient sodium conductance. The system becomes even more unstable with the sixth power formulation for potassium conductance, so it is quite possible, within the framework of the Hodgkin–Huxley model, to have oscillations even when the sodium conductance is in a state of inactivation (e.g. during the relative refractory period).

Like the steady-state sodium conductance, the transient sodium conductance increases nonlinearly with increasing depolarization. Since the sodium current is depolarizing, the transient sodium conductance provides a regenerative process across the membrane. Addition of the transient sodium conductance to our system will thus either enhance any existing oscillations or increase the tendency of the system to oscillate by increasing $\frac{dG_{Na}}{dV_m}$. In addition, the transient sodium conductance may produce all-or-none action potentials on the depolarizing phases. We now come to the complete Hodgkin–Huxley system—including leakage conductance, potassium conductance, and steady-state and transient sodium conductances. From the previous results we can infer several things: (1) the potassium ion flux forms a potentially unstable or oscillatory system when combined with the chloride, or leakage ion flux in the Hodgkin–Huxley model; the sodium ion flux is not required for oscillatory behavior; (2) addition of the effects of steady-state sodium ion flux increases the tendency of the system to oscillate, and the natural frequency of the system tends to be reduced as the sodium ion flux becomes more effective; (3) even with the fourth power formulation for the potassium conductance, the Hodgkin–Huxley system is potentially unstable for values of depolarization slightly more than 6 mv, even without the effects of the transient sodium conductance. Two interesting questions now arise: What results can one expect from the interaction of the various oscillatory and regenerative mechanisms inherent in the Hodgkin–Huxley model? How might these results depend on the various parameters of the model? These questions might be attacked by means of a digital computer, but this seems impractical. The analog of Fig. 5 provides a simple means of examining these questions. By setting the parameters of this analog to correspond to the values of the Hodgkin–Huxley model, and then systematically varying various parameters about those values, we have observed many interesting types of spontaneous behavior. This includes pairing of spontaneous action potentials (i.e. a long interval followed by a short interval, as in Plate II), burst formation (a

spontaneous, periodic burst of action potentials followed by a silent period), and regular, periodic action potentials, essentially identical to the pacemaker potentials observed by Bullock. All of these phenomena can be explained, therefore, in terms of the Ionic Hypothesis, and a single membrane patch.

Another interesting phenomenon was discovered by plotting pulse interval histograms of spontaneous action potentials produced by the analog. Generally, the analog produces regular, periodic action potentials with almost no detectable spread in period. Under certain conditions, however, the spontaneous pulse intervals are distributed as in Fig. 10(a). This figure simply reflects a Poisson process with refractoriness imposed upon it for short intervals. Now, a very slight change in the excitatory state of the system (decreased excitability) can change this histogram to that of Fig. 10(b), 10(c) or 10(d). It is interesting that these multimodal histograms are essentially identical to those observed in units of the cat retina and lateral geniculate by Levick & Williams (1964) and Bishop, Levick & Williams (1964). Thus a form of complex, patterned behavior found in real neurons was found independently in a simulated single membrane patch. The explanation, as far as the analog is concerned, is simple. Following a given spike the analog becomes refractory (i.e. the transient sodium conductance has been inactivated). As shown previously, however, subthreshold oscillations may occur even in the absence of an active transient sodium conductance. In the presence of these oscillations, the next spike will tend to occur during a depolarizing phase of the oscillations. We thus obtain an oscillatory change in excitability superimposed on a Poisson process, and the combination yields the multimodal histograms of Figs 10(b), (c) and (d). The model proposed by Bishop *et al.* (1964) to explain the multimodal histograms includes several nerve cells with statistical pulse outputs. Here we have the same histograms resulting from a model of a single membrane patch.

(c) FACILITATORY MECHANISMS INHERENT IN THE IONIC HYPOTHESIS

One of the important synaptic degrees of freedom mentioned by Bullock (1959) is that of facilitation, antifacilitation, or neither. In the case of facilitation, the response (postsynaptic potential) of the postsynaptic cell to a given presynaptic spike is enhanced by previous spikes in the same presynaptic axon. Antifacilitation is simply the reverse: postsynaptic responses are diminished by previous activity. Facilitation is thus essentially a nonlinear accumulation (or integration) of a series of input pulses from a given channel, the last pulse being much more effective than the first. Antifacilitation, on the other hand, is more like differentiation or rapid accommodation to a series of input pulses, the first pulse being most effective. Both of these effects are generally believed by physiologists to be presynaptic in origin. One popular theory,

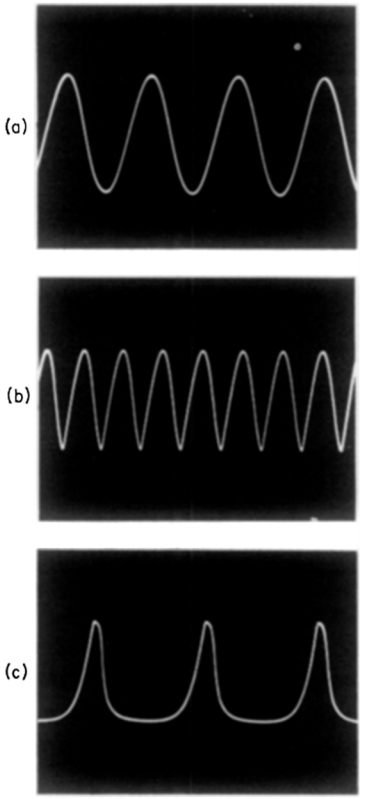

PLATE I. Oscillatory potentials obtained with the circuit of Fig. 8.

(a) Oscillations between potassium current and chloride or leakage ion current, response of potassium conductance taken to be continuous (see text).

(b) Oscillations between potassium current and chloride current with discontinuity in response of potassium conductance.

(c) Same system as Fig. 10(b) with effects of sodium conductance included.

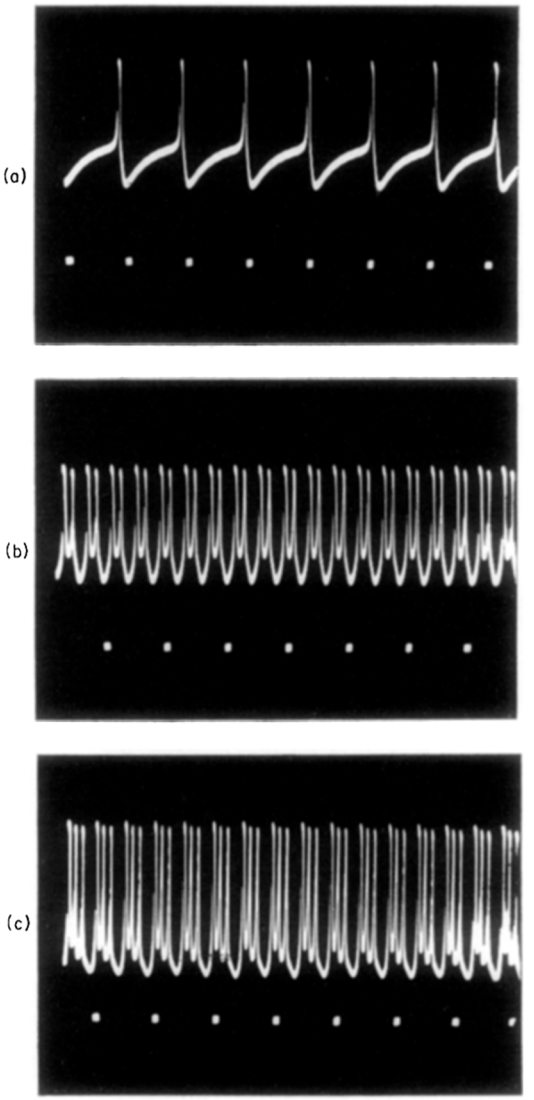

PLATE II. Spontaneous action potentials generated by the model of Fig. 5. (a) Single spikes; (b) spike pairs; (c) spike triplets.

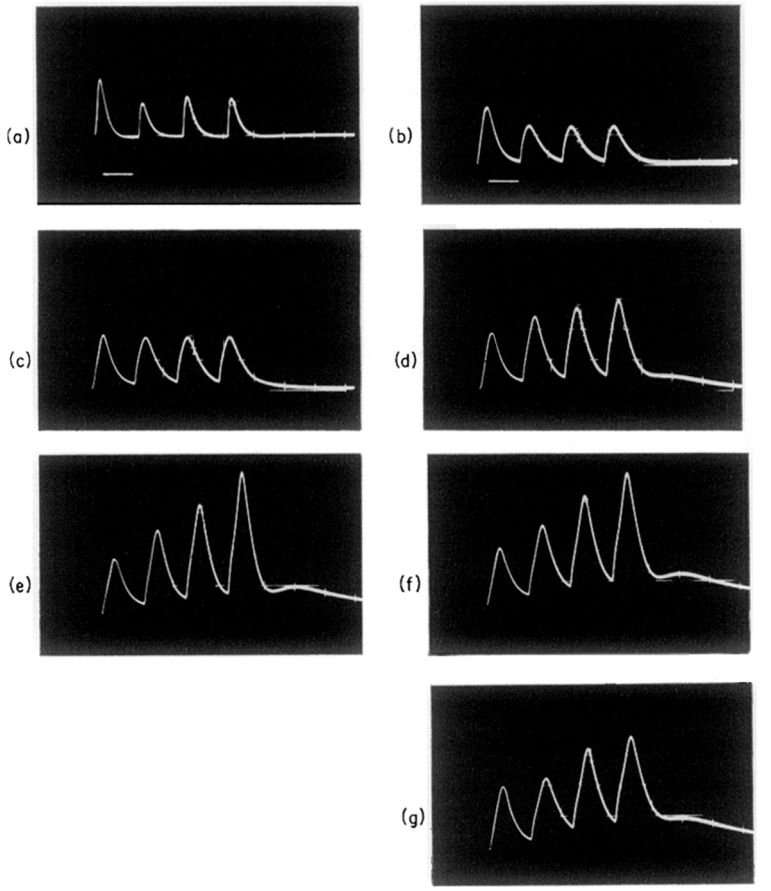

PLATE III. Simulated excitatory postsynaptic potentials from the analog system of Fig. 5. All membrane parameters were held constant at the values stipulated by Hodgkin & Huxley (1952*a–d*). The time constant of recovery from sodium inactivation was set at 10 msec; while the time constant (T) of simulated synaptic transmitter inactivation was varied: (a) $T = 5$ msec, (b) $T = 10$ msec, (c) $T = 15$ msec, (d) $T = 20$ msec, (e) $T = 25$ msec, (f) $T = 35$ msec, (g) $T = 50$ msec. The amplitude of the first epsp in each case corresponds to 5 mv. The horizontal line corresponds to 20 msec.

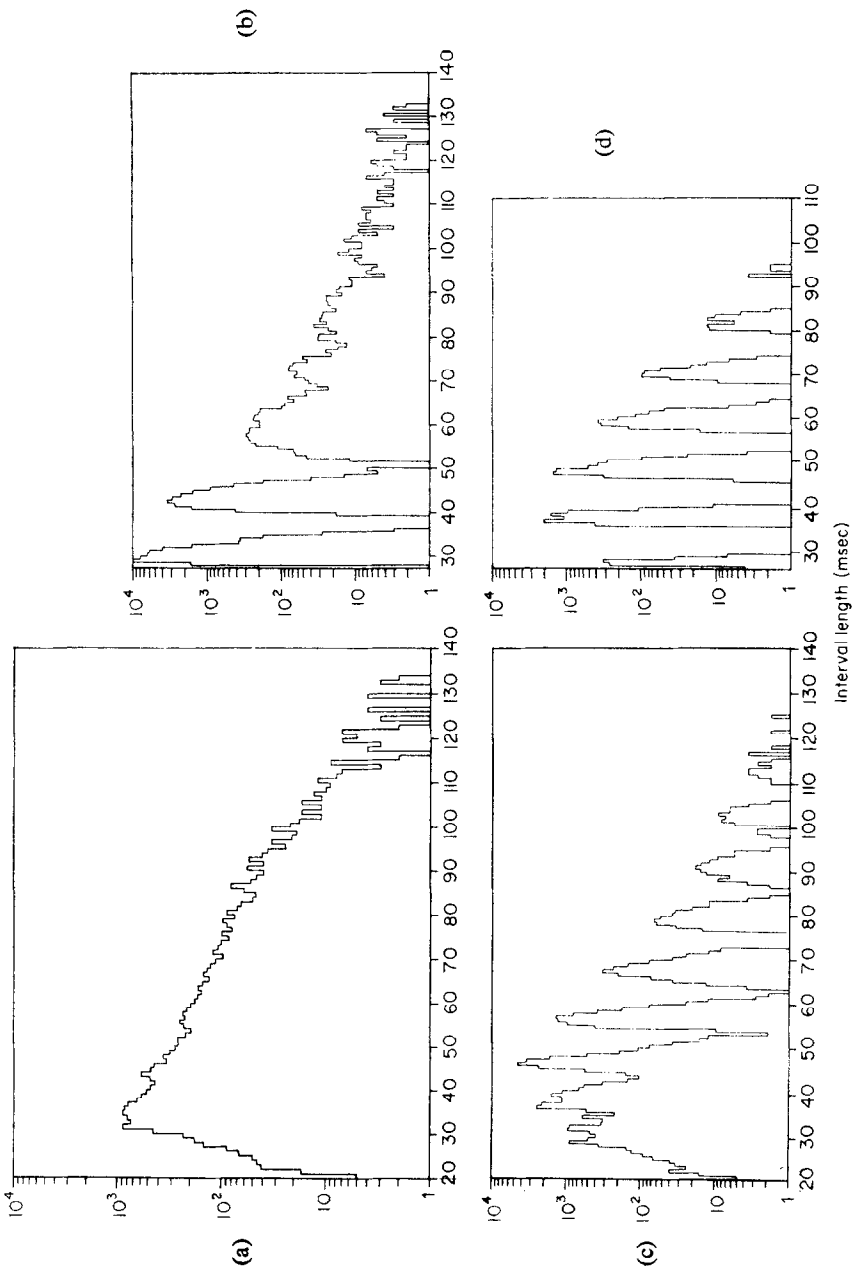

FIG. 10. Spike-interval histograms for spontaneous activity in the analog system of Fig. 5. These histograms resulted when the leakage ion potential was 10 to 20 mv less than the potassium ion potential. The difference is normally nearly 40 mv.

for example, is that facilitation results from enhanced transmitter emission (e.g. acetylcholine emission) as a result of previous synaptic activity (Grundfest, 1957). Another is that more and more terminal knobs of a given fiber become active as activity progresses. This might result, for example, from an accumulation of excitation at low safety factor branchings of the fiber. Antifacilitation can be explained in terms of short-term depletion of available transmitter in the terminal knobs of the presynaptic cell. All of these hypotheses are reasonable, and good evidence exists which supports the general thesis that facilitation and antifacilitation are presynaptic in origin.

There is, however, another possible explanation which appears quite reasonable: that facilitation and antifacilitation may, in some cases, be postsynaptic in origin, that the Ionic Hypothesis inherently provides both facilitatory and antifacilitatory mechanisms, and, finally, that variation in a single parameter (the concentration of transmitter-inactivating enzyme) can change a synapse from facilitatory to antifacilitatory.

According to the currently accepted theories on chemical synaptic transmission (Eccles, 1963,1964) the excitatory synaptic transmitter substance induces a general shunting conductance to all ions across a local region of the cell membrane (subsynaptic membrane), while the inhibitory transmitter induces either an increase in potassium conductance or chloride conductance, or both. In each case the induced conductance is assumed to be proportional to the concentration of transmitter substance at the subsynaptic membrane (Eccles, 1963). The transmitter substance is presumed to be emitted during a presynaptic spike and subsequently either inactivated chemically or diffused away. In either case, the simplest result is a first-order reduction of effective transmitter concentration. The synaptically induced conductance will thus rise rapidly during a presynaptic spike and then fall exponentially toward zero. If we suppose that the subsynaptic membrane is similar in its basic properties to the axon membrane, we can ask an interesting question: What effect will synaptically induced conductance changes have on the system postulated by Hodgkin and Huxley for the axon membrane? Once again we are faced with a problem not well suited to digital computer study. We want to begin with a system with nonlinearly interdependent variables and time varying parameters and impose upon it various series of conductance changes which sum and each of which rises rapidly and decays exponentially. This type of experiment can be accomplished quite easily with the analog of Fig. 5.

When we had completed our first electronic analog of the ionic model, one of the first experiments we performed was a simulation of excitatory synaptic inputs. We immediately observed behavior corresponding to facilitation and, after some parameter changes, behavior corresponding to antifacilitation. We examined this behavior more closely with later, more complete versions of the

analog and found a rather simple explanation (Lewis, 1964). Consider the following sequence in the Hodgkin–Huxley model: A sudden shunting conductance, ΔG, is synaptically induced across the membrane. This in turn allows a depolarizing current to flow which in turn begins to discharge the membrane capacitance. The resulting depolarization induces an immediate increase in both the steady-state and transient sodium conductances and a delayed increase in potassium conductance. The increased sodium conductance allows more depolarizing current to flow and the membrane depolarization becomes regenerative. If the synaptic input is subthreshold, the regenerative process is limited by inactivation of the transient sodium conductance and by the delayed potassium current overcoming sodium current. The original synaptically induced tendency toward depolarization is thus amplified with time by a nonlinear regenerative system until a limiting process sets in (Lewis, 1964). The membrane potential now falls back toward the resting level; it may even overshoot slightly. The excitatory postsynaptic potential has virtually disappeared, but residual effects remain in at least two state variables: the sodium conductance is inactivated and some residual transmitter substance remains at the subsynaptic membrane. A second presynaptic pulse induces emission of more transmitter substance and this is added to that remaining in the synapse. The effect of the newly induced conductance change added to the residual conductance is amplified in an extremely nonlinear manner with time producing a second excitatory postsynaptic potential (epsp). If the sodium conductance has recovered sufficiently from inactivation, the second epsp may be much larger than the first. If, on the other hand, the sodium conductance is still relatively inactive, the regenerative action is reduced; and the second epsp may be much smaller than the first. A simplified analysis of this system showed that a residual transmitter concentration which resulted in a residual depolarization of 3% of the amplitude of the first epsp can facilitate the second epsp by 50% (Lewis, 1964). The residual synaptic transmitter concentration and the residual inactivation of the transient sodium conductance both decay exponentially with time after an epsp. The relative rates of decay determine the nature of the response. If the time constant for recovery from inactivation of the transient sodium conductance is fixed, therefore, the time constant of inactivation of the transmitter substance should determine whether the system is facilitating or antifacilitating. In an experiment with the analog of Fig. 5, the time constant of recovery from inactivation of the transient sodium conductance was fixed at 12 msec (the only value of this variable specifically mentioned by Hodgkin & Huxley, 1952*c*). The membrane capacitance was set at 4 μF and the remaining parameters were given the values and interdependence stipulated by Hodgkin & Huxley (1952*d*). With this configuration,

the system was capable only of graded activity, yet was still able to respond in an extremely nonlinear manner (Fig. 6).

Bursts of simulated synaptic inputs were applied to the system and the value of the transmitter inactivation time constant was varied. The results are shown in Plate III. It can be seen that, as the time constant is increased, epsp's change from marked antifacilitation to marked facilitation. Thus, a single variable can determine the nature of the system; and if the synaptic transmitter is inactivated chemically, that variable is equivalent to the concentration of inactivating enzyme available at the subsynaptic membrane. Facilitation was also observed with simulated inhibitory synaptic inputs but no antifacilitation has been observed (Lewis, 1964, in press). Facilitated ipsp's occur when the membrane is slightly depolarized or when a finite sodium current flows at equilibrium. Facilitation comes about from the nonlinear decrease in sodium current with hyperpolarization.

As previously described, the facilitatory mechanisms inherent in the Ionic Hypothesis are the same mechanisms that effect excitability. One would expect, therefore, that reduction of overall system excitability (e.g. by increased membrane capacitance) would lead to reduction of facilitation. This was found to be the case in the analog: facilitation disappeared as the membrane capacitance was increased beyond approximately 10 μF.

On the basis of these results, one would expect in certain cases facilitation of the response of an excitatory synapse by "priming" activity at another—in other words, one would expect mutual facilitation. If such mutual facilitation occurred, one would expect it to be accompanied by a very slight depolarization, and if it were a fairly long-lived effect, one would expect it to be independent of the state of the postsynaptic membrane at the time of the priming pulse or pulses. Regardless of that state, these pulses would induce the emission of transmitter substance, and the residue of that substance would induce a residual depolarization which would far outlast any effects of the membrane state at the time of the priming pulse. A test pulse at the facilitated synapse would produce the same facilitated epsp. In addition, one would not expect directly induced (nonsynaptically induced) spikes in the postsynaptic cell to produce facilitation since these would not induce presynaptic emission of transmitter. Mutual facilitation has been found in *Aplysia* (Kandel & Tauc, 1964). 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 & Tauc (1964) observed a slight residual depolarization with maximal facilitation. In order to localize the facilitatory mechanism, they: (1) induced spikes directly in the postsynaptic cell 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 in the postsynaptic cell; this did not alter the facilitatory effect. They concluded from this evidence that the facilitatory mechanism was presynaptic and postulated that the priming fiber sends collaterals to the synaptic knob of the facilitated synapse and pulses in this fiber not only induce epsp's and spikes in the postsynaptic cell, but also induce synaptic potentials in the knob. The emission of transmitter from the knob is thus enhanced and we have "heterosynaptic facilitation". This explanation may be correct, but one cannot overlook the fact that a single patch of membrane according to the Hodgkin–Huxley model and including two excitatory synapses can produce the same effect and pass the same tests and, in addition, account for the residual depolarization.

(D) REBOUND MECHANISMS INHERENT IN THE IONIC HYPOTHESIS

Following a prolonged burst of presynaptic spikes, the postsynaptic cell may exhibit positive or negative aftereffects or neither or both. Positive aftereffects are prolonged excitation following otherwise normal epsp's and prolonged inhibition following otherwise normal ipsp's. Negative aftereffects —or rebound, are more commonly known as postexcitatory depression and postinhibitory excitation. All four of these modes have been observed in intracellular potentials; in fact, all four have been observed in one animal—*Aplysia* (Chalazonitis & Arvanitaki, 1961). Both Bullock (1958,1959) and Chalazonitis & Arvanitaki (1961) have observed oscillatory aftereffects with alternating cycles of depression and excitation.

Both the rebound and the oscillatory behavior can be accounted for with the Ionic Hypothesis. Inhibitory rebound is easily explained in terms of the delayed potassium conductance and the mechanisms which also produce the after-hyperpolarization following a spike. Excitatory rebound can be explained in terms of accommodation of the transient sodium conductance and the mechanisms which account for the spike so often observed on anode break. Both of these explanations were offered by Chalazonitis & Arvanitaki (1961) and are familiar to physiologists. The oscillatory aftereffects can easily be accounted for by the oscillatory mechanisms mentioned previously in this paper. It is difficult to imagine, on the other hand, mechanisms strictly inherent in the ionic model which can account for prolonged positive aftereffects. Chalazonitis & Arvanitaki (1961), however, regard positive aftereffects as autochthonous processes. An alternative explanation may be in terms of a long-lived accumulation of synaptic transmitter. In either case, most of the known aftereffects, including rebound, can be explained in terms of the Ionic Hypothesis.

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