Thresholds and Plateaus in the Hodgkin-Huxley Nerve Equations

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ABSTRACT Phase space methods and an analog computer are used to analyze the Hodgkin-Huxley non-linear differential equations for the squid giant axon membrane. V is the membrane potential, m the Na^+ activation, h the Na^+ inactivation, and n the K^+ activation. V and m change rapidly, relative to h and n. The (V, m) phase plane of a reduced system of equations, with h and n held constant at their resting values, has three singular points: a stable resting point, a threshold saddle point, and a stable excited point. When h and n are allowed to vary, recovery and refractoriness result from the movement with subsequent disappearance of the threshold and excited points. Multiplying the time constant of n by 100 or more, and that of h by one-third, reproduces the experimental plateau action potentials obtained with tetraethylammonium by Tasaki and Hagiwara, including the phenomena of abolition and of refractoriness of the plateau duration. The equations have, transiently, two stable states, as found in the real axon by these authors. Since the theoretical membrane conductance curves differ significantly from the experimental ones, further experimental analysis of ionic currents with tetraethylammonium is needed to decide whether the Hodgkin-Huxley model can be generalized to explain these experiments completely.

INTRODUCTION

Although the differential equations of Hodgkin and Huxley (1952) have not been universally accepted as a valid model of the squid giant axon membrane, they do successfully reproduce many experimental results. Aside from questions about the basic physical assumptions of the model, which can be answered only by further experiments, there has been some misunderstanding of the rather complex mathematical properties which form the basis for the model's "physiological" behavior, but which are not at all obvious on a first examination of the equations.

The usefulness of an equation to an experimental physiologist (like the usefulness of his amplifier) depends on his understanding of how it works. The aim of this paper is to expose to view part of the inner working mechanism of the Hodgkin-Huxley (H-H) equations. A knowledge of their mathe-

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matical properties can provide a guide for making future modifications of the model to match improved experimental data. Such modifications must be made with careful regard for the desired mathematical properties, which may change suddenly at critical values of certain parameters.

A general conclusion of this analysis is that many of the physiologically important properties of the Hodgkin-Huxley model arise from certain qualitative mathematical properties of their equations; but that a model with different equations and physical assumptions, but with similar qualitative properties, might appear to be just as good an analog of the real axon. A result which illustrates this distinction is the partial duplication of Tasaki and Hagiwara's (1957) results obtained from squid axons injected with tetraethylammonium chloride (TEA). The plateau, its abolition, and subsequent refractoriness are well reproduced by the equations, after suitable modification. On the other hand, the corresponding theoretical curves of membrane conductance disagree significantly from the experimental measurements, but these latter curves are more dependent on the exact form of the equations and the physical assumptions than are the action potential curves.

Goodall and Martin (1958) have also used an analog computer to solve a set of differential equations which, for greater convenience in adjusting parameters, were slightly different from the Hodgkin-Huxley equations. Using a chloride current and a sixth instead of a fourth power in their potassium conductance, they have obtained action potentials like those of muscle, and by altering the potassium time constant, an oscillating plateau. Their work overlaps that of this paper to some extent, but had a rather different purpose, that of empirical exploration rather than of theoretical analysis.

Methods of Computation

The Hodgkin-Huxley model is based on four ordinary non-linear differential equations with time as the independent variable. No explicit general solution of these equations is known, but they have been solved approximately by three methods: (1) the numerical method of Hartree, with a desk calculator, used by Hodgkin and Huxley in their original paper (1952), (2) the Runge-Kutta method used with automatic digital computers (Cole, Antosiewicz, and Rabinowitz (1955); Cole (1958); FitzHugh and Antosiewicz (1959)), and (3) solution by electronic analog computer as described here. Method (1) is very time-consuming for the desired degree of accuracy. The digital computer (2) has a much higher accuracy than an analog computer (3), but proved to be very slow to use, involving a week or more for a solution, including time for relaying instructions to the programming and operating personnel, scheduling time on the computer, and receiving back the results. The delay was often much longer, if unforeseen changes in the program were required. As a result, the digital computer has been useful only for solutions which can be planned well in advance. However, exploratory studies of the equations, as made in this paper,

require that the solutions be overseen by the investigator as they are run so that he can continually decide what to do next. For this purpose, an analog computer, operated by the investigator himself, has proved to be most useful.

A Berkeley EASE analog computer having 40 operational amplifiers, 6 diode function generators, and 5 servo multipliers was used. The accuracies of the various components were as follows: computing resistors and capacitors, 0.1 per cent; function generators, 0.3 volt; multipliers, 0.6 volt (dynamic), compared with an operating range of ± 100 volts. The computing block diagram was similar to that worked out by Bekey and Paxson (1957) for use in this problem, except that servo instead of electronic multipliers were used here, both because of the convenience of the former in generating third and fourth powers, and because of their low drift.

Because the Hodgkin-Huxley equations taxed the accuracy of this computer in certain respects, special precautions were needed. As can be seen in Figs. 2 and 3, two singular points, A and B, are located where two curves (the nullclines) intersect at small angles. Slight computing errors can shift the nullclines enough to move the two singular points markedly, or even to make them disappear if the nullclines do not intersect at all. Therefore, frequent manual corrections were made with trimming potentiometers to those voltages representing the four time derivatives, in order to locate point A as exactly as possible at its theoretical resting position. The straight line segment approximation to a smooth curve given by the diode function generators was smoothed according to the method of Stone (Peretz (1956); Witsenhausen (1956)): by spacing the X values of the break-points 10 v. apart, adding a 10 v. peak-to-peak zigzag wave at 1200 cycles per sec. to the input of the function generator, and then filtering out the zigzag component from the function generator output. The sodium current is the product of three factors, not all of which are large at the same time, so that the product on the computer never exceeds 5 v. This voltage is subsequently amplified times 20, with the result that both noise and the resolution from wire to wire in the single-turn multiplier potentiometers can distort the solution. It is expected that this trouble will be eliminated by using multipliers with multi-turn potentiometers.

Random inaccuracies of the computer are noticeable as an unevenness in the level of the plateau, which is very sensitive to small fluctuations in the equations (Figs. 10 to 13).

Mathematical Analysis

LIST OF SYMBOLS

I = membrane current density, positive inward (μa./cm.^{2})*
V = membrane potential difference, outside relative to inside (mv.)*
m = sodium activation (dimensionless, varying between 0 and 1)
h = sodium inactivation (dimensionless, varying between 0 and 1)
n = potassium activation (dimensionless, varying between 0 and 1)

* Hodgkin and Huxley's original sign convention for V and I has been kept in this paper, to avoid confusion, although Hodgkin (1958, p. 10, footnote) has later adopted the opposite one.

$\dot{V} = dV/dt$, etc., t = time in msec.
C = membrane capacitance = 1 μf./cm.^{2}
$\phi = 3^{(T-6.3)/10}$
T = temperature (°C.)

$$\alpha_m(V) = 0.1(V + 25)\left[\exp\left(\frac{V + 25}{10}\right) - 1\right]^{-1}, \beta_m(V) = 4 \exp(V/18)$$

$$\alpha_h(V) = 0.07 \exp(V/20), \beta_h(V) = \left[\exp\left(\frac{V + 30}{10}\right) + 1\right]^{-1}$$

$$\alpha_n(V) = 0.01(V + 10)\left[\exp\left(\frac{V + 10}{10}\right) - 1\right]^{-1}, \beta_n(V) = 0.125 \exp(V/80)$$

$\bar{g}_{Na} = 120$, $\bar{g}_K = 36$, $\bar{g}_L = 0.3$ (all in mmho/cm.^{2})
g_m = total membrane conductance = $\bar{g}_{Na}m^3h + \bar{g}_K n^4 + \bar{g}_L$
$V_{Na} = -115$, $V_K = 12$, $V_L = -10.5989$ (ionic equilibrium potentials—all in millivolts).

HODGKIN-HUXLEY EQUATIONS

These are the H-H equations (Hodgkin and Huxley (1952); Cole, Antosiewicz, and Rabinowitz (1955)):

$$I = C\dot{V} + \bar{g}_{Na}m^3h(V + 115) + \bar{g}_K n^4(V - 12) + \bar{g}_L(V + 10.5989) \quad (1)$$

$$\dot{m} = \phi[(1 - m)\alpha_m(V) - m\beta_m(V)], \quad (2)$$

$$\dot{h} = \phi[(1 - h)\alpha_h(V) - h\beta_h(V)], \quad (3)$$

$$\dot{n} = \phi[(1 - n)\alpha_n(V) - n\beta_n(V)]. \quad (4)$$

The coefficient ϕ provides the three conductance variables with a Q_{10} of 3, and equals 1 at Hodgkin and Huxley's standard temperature of 6.3°.

An additional space-clamp condition has been assumed throughout; longitudinal currents are eliminated by the use of internal axial and external guard electrodes, and the state of the membrane is always spatially uniform. Three principal external circuit conditions have been used. The *voltage clamp*, in which V is specified as an arbitrary function of t, then m, h, and n are found by solving the differential equations (2) to (4), and finally I is found from (1). The *current clamp*, in which I is specified as an arbitrary function of t, and equations (1) to (4) are solved for V, m, h, and n as functions of t. The *resistive clamp*, described by the equation $E = V + RI$, in which R ($\neq 0$) and E are the equivalent resistance and E.M.F., (according to Thévenin's theorem; Harnwell (1949); M.I.T. Staff (1940)), of the external clamping circuit; E is an arbitrary function of t. Using this last equation, I can be eliminated from (1), and equations (1) to (4) solved for V, m, h, n as functions

of t. The "arbitrary functions" are usually steps or rectangular pulses starting at $t = 0$.

Another case, which will not be treated here, is the non–space-clamp case in which longitudinal currents circulate through the axoplasm and the external medium, and impulse propagation can occur (Hodgkin and Huxley (1952); FitzHugh and Antosiewicz (1959)).

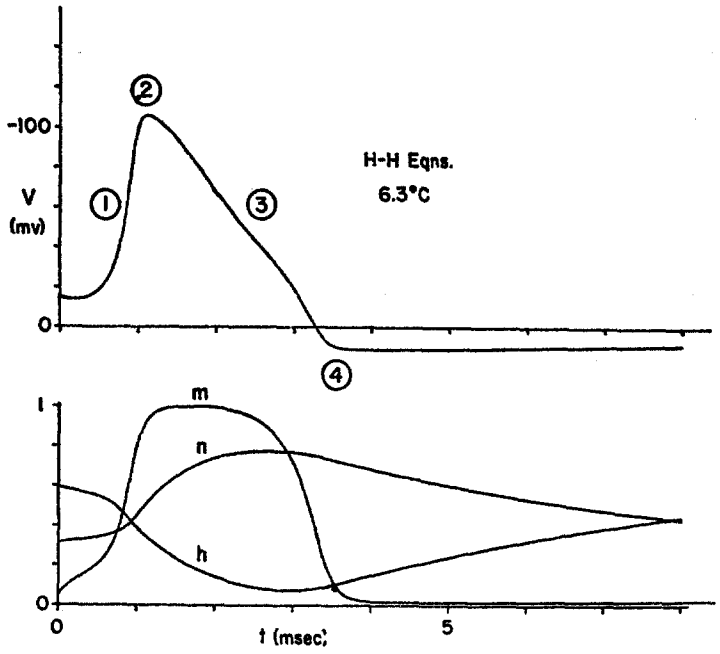

FIGURE 1 Action potential of normal Hodgkin-Huxley equations following instantaneous cathodal current shock at $t = 0$, and corresponding time courses of their three conductance variables. $I = 0$ for $t > 0$. Circled numbers correspond to stages of excitation cycle similarly marked in Fig. 9. All curves in this and succeeding figures were drawn with an ink-writing X-Y plotter by an analog computer. A few lines have been retouched for clearer reproduction.

For the voltage-clamp case in which V is a step function, changing discontinuously from V_0 to V_1 at $t = 0$, the differential equations can be solved explicitly. For $t > 0$, equation (2) is linear with constant coefficients and has the solution $m(t) = m_\infty(V_1) + [m(0) - m_\infty(V_1)] \exp [-t/\tau_m(V_1)]$, in which $m_\infty = \alpha_m/(\alpha_m + \beta_m)$ is the steady-state value of m, and $\tau_m = 1/(\alpha_m + \beta_m)$ is the "time constant" of m, both actually being functions of V. The initial condition $m(0)$, if the system is in a steady state for $t < 0$, equals $m_\infty(V_0)$. The solutions of equations (3) and (4) are analogous. Then I can be found by substituting these solutions for m, h, n into equation (1), $\dot{V}$ being

zero everywhere, except for an instantaneous impulse (proportional to a delta function) in V at $t = 0$.

The set of values $V = 0$, $m = m_\infty(0)$, $h = h_\infty(0)$, $n = n_\infty(0)$ are called the resting values of the variables and correspond to the stable resting state when $I = 0$.

Although the Hodgkin-Huxley equations were originally based on experimental voltage-clamp data, it was found that when they were solved under current-clamp conditions, the important physiological properties of excitation were reproduced (Hodgkin and Huxley (1952); Cole, Antosiewicz, and Rabinowitz (1955); FitzHugh and Antosiewicz (1959)). In the current-clamp case, the equations cannot be solved explicitly, but require the use of a numerical method or an analog computer; Fig. 1 shows an action potential (V *versus* t) plotted with the analog computer, and the simultaneous time courses of m, h, n.

The resistive-clamp case will be considered in a later paper, in connection with the occurrence of oscillations.

PHASE SPACE METHODS

Basic to what follows are those mathematical techniques for the study of ordinary non-linear differential equations which have been called non-linear mechanics by applied mathematicians (Andronow and Chaikin (1949); Minorsky (1947)), and the geometric or qualitative theory of differential equations by pure mathematicians (Lefschetz (1957); Nemickii and Stepanov (1949)). These techniques are applicable to all ordinary differential equations including those for which no explicit solutions in closed form are obtainable, although solutions defined by a limiting process can be proved to exist. The solutions are considered to describe curves called *paths* in an Euclidean *phase space* having as coordinates the dependent variables of the equations. Time does not appear as a coordinate of the space, but units of time may be thought of as plotted along any path starting from a chosen initial condition. The state of the physical system described by the differential equations can be represented by a *phase point* which travels along a path in a phase space. An over-all qualitative description of the solutions is sought through a study of certain special paths (singular points, separatrices, and limit cycles) which determine the topological behavior of all the paths in the phase space. When the phase space is a plane, the paths can be drawn on paper and their topological properties easily visualized. When the space has three or more dimensions, it can be represented graphically only by taking sections or projections onto a plane, but its properties can still be described mathematically in qualitative terms. Even without solving a non-linear differential equation, one can often discover by these methods much useful information about the over-

all qualitative behavior of the solutions, such as the presence of stable and unstable states, threshold phenomena, and oscillations.

An acquaintance with these methods will help in the understanding of what follows, although all necessary terms will be defined. Certain purely mathematical details of this theory as applied to the Hodgkin-Huxley equations will be given cursorily in fine print for completeness.

Since the four-dimensional phase space of the Hodgkin-Huxley equations with coordinates V, m, h, n cannot be visualized, it is best to study first the properties of lower dimensional phase spaces obtained by omitting one or two coordinates, as described in the next section.

REDUCED SYSTEMS

As an aid to understanding the current-clamp case, it has been found helpful to build up the system of equations conceptually step by step from its component parts. The variables are divided into two pairs according to the orders of magnitudes of their "time constants," the "time constant" of V being C/g_m (see List of symbols). V and m change relatively rapidly, and h and n change relatively slowly. For brief periods of time, during which h and n change very little, V and m vary markedly. The behavior of V and m can therefore be studied, to a first approximation, by arbitrarily setting h and n constant and equal to their resting values, and solving the resulting "V, m reduced system," defined by equations (1) and (2), with $I = 0$. Next, the effect on the behavior of this reduced system produced by changing h and n to other constant values, or by changing I, is investigated. Then h and n are reintroduced (separately or together) as variables to give the V, m, h and V, m, n reduced systems and finally the complete V, m, h, n, system for the current-clamp case. This synthetic process, carried out with the aid of the analog computer, leads to a better understanding of the complete system than can be obtained by considering all the variables at once, and suggests how modifications in the separate equations will affect the behavior of the complete system. In particular, it becomes obvious how plateau-type action potentials can be produced, resembling those obtained experimentally from heart (Weidmann (1957)), frog node (Spyropoulos (1956)), frog muscle (Falk and McGrath (1958)), and squid axon (Tasaki and Hagiwara (1957)).

V, m Reduced System For this system equations (3) and (4) can be replaced by:

$$\dot{h} = 0, \; h = \text{constant} \qquad (3R)$$

$$\dot{n} = 0, \; n = \text{constant} \qquad (4R)$$

Once constant values of I, h, and n have been specified, the state of this re-

duced system is completely defined at any time by the values of V and m, and can be represented by a phase point on the (V, m) phase plane. Figs. 2 and 3 show this phase plane, with $I = 0$, $n = n_\infty(0)$, $h = h_\infty(0)$. The solutions are represented as paths, with time increasing in the direction of the arrow heads. Particularly important landmarks in this plane are the V and m *nullclines* (Cole, Antosiewicz, and Rabinowitz (1955); often called the vertical and horizontal isoclines), which are the curves on which $\dot{V}$ and $\dot{m}$ are zero, respectively.

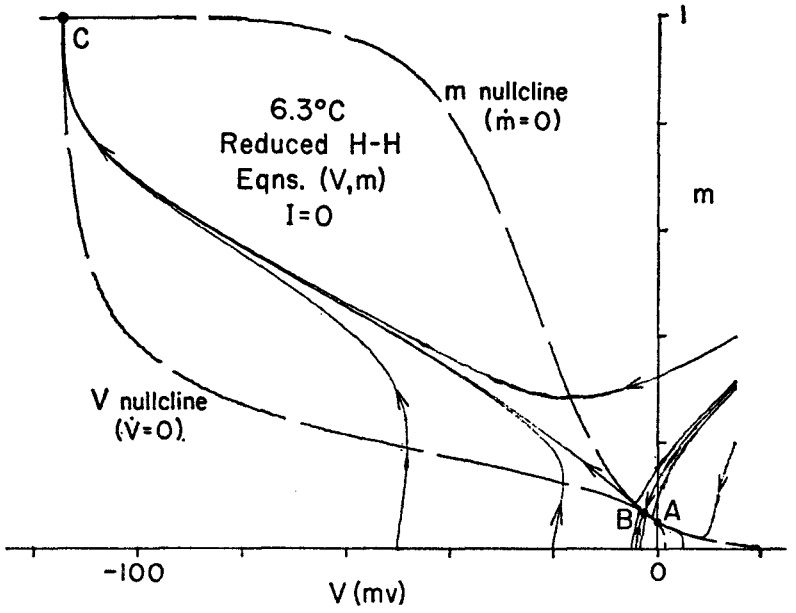

FIGURE 2. Phase plane of V, m reduced Hodgkin-Huxley system, with h and n fixed at their resting values and $I = 0$. Solutions of equations follow paths marked with arrowheads. Three singular points occur at intersections of nullclines (curves on which $\dot{V} = 0$ and $\dot{m} = 0$ respectively). Threshold phenomenon appears at saddle point B. Stimulus displaces phase point from resting singular point A, and is followed by either return to A or passage to singular point C (excitation), depending on shock strength.

The m nullcline is simply the graph of $m_\infty(V)$. The V nullcline gives the steady-state value of V as a function of m; when $I = 0$ this is the same as the equivalent Thévenin E.M.F., the P.D.M. (potential demand of the membrane) of Polissar (Johnson, Eyring, and Polissar (1954)), or the intrinsic E.M.F. of the membrane (Shanes (1958)). Fig. 2 in fact resembles the phase plane of Polissar's nerve membrane model, but inverted (FitzHugh (1955) Fig. 7).

The three intersections A, B, and C of the two nullclines are called the *singular points* (equilibrium, or steady-state points) where $\dot{V} = \dot{m} = 0$. A and C are *stable*, that is, they are approached, as $t \to +\infty$, by all nearby solutions.

B is a *saddle point*; there are two paths, called the *stable separatrices* (singular: *separatrix*), along which solutions approach B as $t \to +\infty$; and two others, the unstable separatrices, along which solutions approach B as $t \to -\infty$. All other nearby solutions follow approximately hyperbolic paths, first approaching, then turning away from B. The stable separatrices, which can be called *threshold separatrices*, together form a boundary in the phase plane at which a threshold phenomenon occurs (FitzHugh (1955)). Paths on opposite sides of

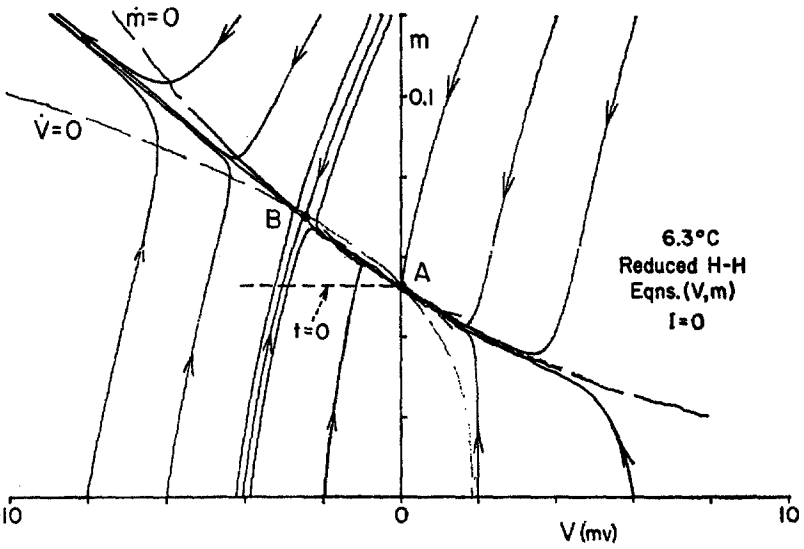

FIGURE 3. Enlarged detail of Fig. 2 to show singular points A and B. Instantaneous cathodal shock displaces phase point horizontally from A along line labeled "$t = 0$."

this boundary diverge from each other. Any path to the right of the threshold separatrices eventually approaches A, and any to the left, C. The singular point A corresponds to the stable resting state, and C to a stable excited state. This reduced system therefore shows no recovery to the resting state, for which changes in h and n are required.

An instantaneous negative (cathodal) current pulse (brief enough to be considered as instantaneous or proportional to a delta function) at $t = 0$ will displace the phase point of the resting system from A to some point on the locus of initial points labeled "$t = 0$" in Fig. 3. This displacement in V will be denoted ΔV; it is equal to Cq, in which C is the membrane capacitance and q is the charge crossing the membrane during the current pulse. The threshold value ΔV_θ of ΔV is that which brings the state point to rest on the threshold separatrix. If $\Delta V \neq \Delta V_\theta$, the phase point will eventually approach either C or A, resulting in an "all" or a "none" response.

With the analog computer one can systematically investigate the effects of

changing the constant parameters h, n, and I. Setting $\dot{V} = 0$ in equation (1) and solving for m, one obtains the equation of the V nullcline:

$$m = \left[\frac{I - \bar{g}_K n^4(V - V_K) - \bar{g}_L(V - V_L)}{\bar{g}_{Na} h(V - V_{Na})}\right]^{1/3}, (0 < m < 1). \quad (5)$$

According to this equation, for any fixed V ($-115 < V < 12$ mv.), m is increased by a positive change of I or of n, or by a negative change of h. Any

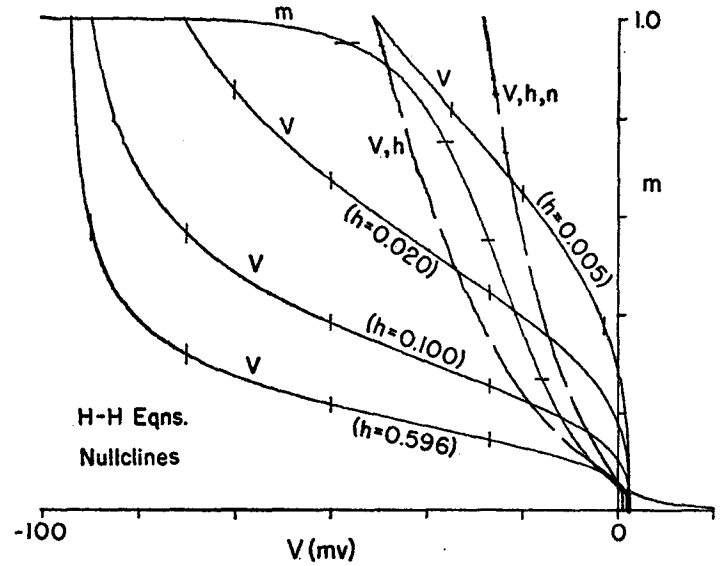

FIGURE 4. Solid lines are V and m nullclines. With decreasing h, the V nullcline rises and two of its intersections with the m nullcline (singular points) vanish, leaving only the resting singular point. Also shown as broken lines are the V, h nullcline ($\dot{V} = \dot{h} = 0$ in the V, m, h reduced system), which has three intersections with the m nullcline, and the V, h, n nullcline (complete system), which has only one.

of these changes therefore raise the V nullcline, although not uniformly over the whole V axis. The V nullcline is lowered by opposite changes of I, n, or h. The m nullcline is not changed. The solid curves in Fig. 4 are the V nullclines, for several values of h, and the stationary m nullcline. The resting value of h is 0.596. The dashed curves in Fig. 4 will be explained below.

Because of the small angles between the nullclines at their two lower intersections (labeled A and B in Fig. 3), the locations of these intersections are very sensitive to slight movements of the V nullcline. If the V nullcline is lowered, A moves to the left and B to the right, so that A and B approach each other. This changes the resting potential (the value of V at A) negatively, and, in decreasing the separation of A and B, decreases the magnitude of ΔV_θ. As a critical value of I (or h or n) is passed, A and B coalesce and then vanish as

in Fig. 5, where the nullclines no longer intersect in this region. *C*, which is the only remaining singular point, is approached by all solutions, including those starting at the original resting point. One result of this is that a step change I_0 of I at $t = 0$ will have a negative threshold value for excitation, or rheobase, at which the nullclines are just tangent. Fig. 5 shows a phase plane for I negative and beyond rheobase. Similar results are found when h or n are changed instead of I. Changing any one of the parameters I, h, or n can modify the effect of another so that, for instance, a decrease of h or an increase of n will increase the magnitude of the rheobase. These changes of excitability in

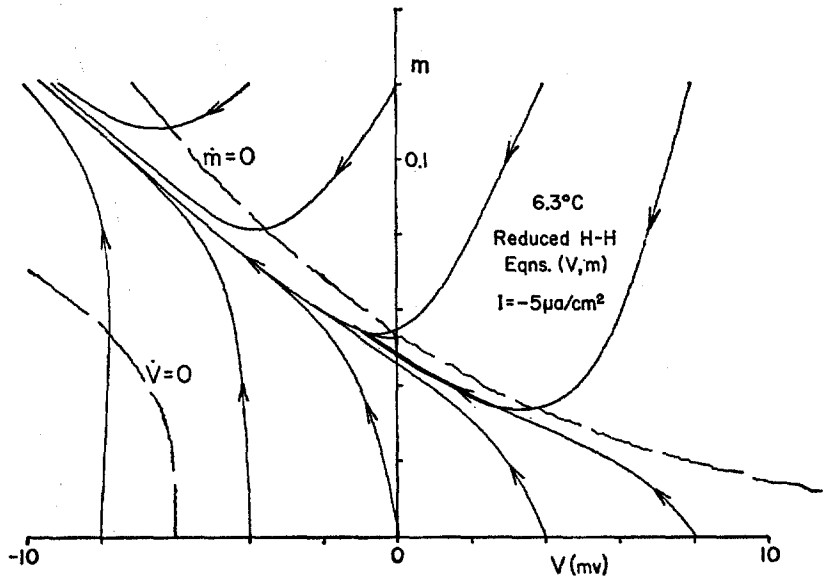

FIGURE 5. Like Fig. 3 except that constant negative (cathodal) current I exceeds rheobase. V nullcline is lowered, singular points A and B have vanished, and excitation occurs.

the V, m reduced system are also what one would expect qualitatively from the physical significance of the variables I, h, and n in the H-H model.

Conversely, when the V nullcline is raised, by changing I, h, or n in opposite directions from those considered above, A and B move apart, changing the resting potential positively and increasing the magnitude of the shock threshold ΔV_θ (Fig. 6). Eventually points B and C approach, coalesce, and vanish, leaving A as the only singular point, as in Fig. 4 for decreasing h. The system is now inexcitable, and each parameter (I, h, n) has a critical value at which this happens.

For the V, m reduced system, the action potential ($-V$ plotted against t), with h and n at their resting values, shows a rising phase similar to that of a real nerve, followed by a permanent plateau with V about equal to V_{Na}

(−115 mv.). The plateau potentials of Tasaki and Hagiwara (1957) are, however, not at this level, but are in the neighborhood of −50 mv. To get such lower plateau levels following the spike, it is necessary to reintroduce h (or n) as a third variable.

V, m, h Reduced System In this case only n is held constant. V, m, and h are the coordinates of a three-dimensional phase space in which the solutions of equations (1), (2), (3), and (4R) appear as paths. However, h changes more slowly than V and m, that is, its time constant τ_h is roughly of an order of

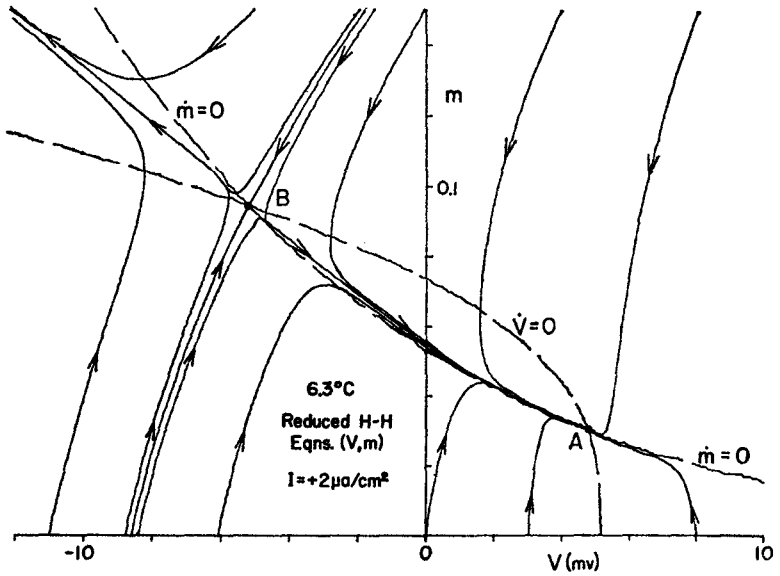

FIGURE 6. Like Fig. 3 except that I is positive (anodal current). V nullcline is raised and singular points A and B have moved farther apart, increasing the shock threshold.

magnitude (× 10) larger than both τ_m and the electrical time constant C/g_m for V, at 6.3°C. (See Tables 1 and 2 of Hodgkin and Huxley (1952).)

As described in the previous subsection, changes in h make the V nullcline, the singular points, and the other paths move about in the (V, m) phase plane. For the moment, consider the (V, m, h) phase space to be projected onto the (V, m) plane. At any instant, the projected phase point will be moving in time along some path of the (V, m) phase plane corresponding to the value of h at that instant. It should be pointed out, however, that the idea of a phase point moving "along" paths which are themselves moving about in a phase plane is not mathematically rigorous and is only used as an aid to the imagination. Strictly speaking, the path determines only the vector of motion of the phase point in the (V, m) plane at any instant, and thus adds no information not provided by the original differential equations themselves. Nevertheless, a description of this sort has been found to be useful for making the qualitative

behavior of these systems more vivid and should therefore be considered as a useful heuristic device.

The function $h_\infty(V)$ is a monotonically increasing sigmoid curve (Fig. 10 of Hodgkin and Huxley (1952)). Therefore, when V goes negative, as during the rising phase of the membrane action potential, $h_\infty(V)$ decreases, and h pursues it. Consider first the case of stimulation of the V, m, h reduced system by an instantaneous shock producing an initial displacement ΔV. If ΔV is just threshold for the V, m reduced system the phase point lies initially on the threshold separatrix. Initially, $h = h_\infty(0)$ and the (V, m) phase plane is as shown in Fig. 2. However, as t increases, since $V < 0$, h decreases, the V nullcline in the (V, m) plane moves upward, and saddle point B moves to the left, carrying the threshold separatrix with it away from the moving phase point. At any instant $t > 0$, therefore, the phase point finds itself no longer on the threshold separatrix, but on a subthreshold path, so that it returns toward A. If ΔV is made more negative by increasing the shock strength, the phase point will initially lie beyond the threshold separatrix and may get so far as to cross the V nullcline and start moving to the left and upward toward the excited point C. But the threshold separatrix is also moving to the left, and whether excitation actually takes place will depend on whether the phase point is overtaken by the separatrix and forced to turn back toward A. In a slightly subthreshold case, V will start decreasing, reach a minimum, and then turn back to zero, having lost the race. This minimum is the active subthreshold potential (Shanes (1958)).

In the case of stimulation by a negative step current, the rheobase also is increased when changes in h are allowed. I must be greater than for the V, m system in order to allow the phase point to pass between the two nearly tangent nullclines before these have had a chance to collide and produce a saddle point B with a threshold separatrix, which can then pursue the phase point, head it off, and turn it back toward A. Thus the effect of allowing h to vary is to produce accommodation; *i.e.*, an increase of rheobase or shock threshold.

The introduction of h as a variable produces an action potential having a distinct peak, followed by a lower plateau which may be looked on as the result of partial recovery. The rather complex process of interaction between the variables can be described as follows. By the time the phase point has nearly reached C, C has started to move to the right, as a result of the decrease in h. As C continues to move to the right, the phase point follows it closely. As V simultaneously turns and starts to become more positive again, $h_\infty(V)$ reverses its decreasing trend and begins to increase again toward h. The latter therefore begins to decrease even more slowly than before. This slows down the motion of C to the right, and the behavior of the system from now on will depend very much on whether C finally stops moving before it can meet B,

which is approaching it along the m nullcline. If B and C do meet and vanish, the phase point must return to A. It happens that the addition of the third variable h to the V, m system does not change the number of the singular points, but it will be shown below that the addition of the fourth variable n does do so.

In order to find out what does finally become of C it is necessary to consider all three dimensions of the phase space at once. If the derivatives $\dot{V}$, $\dot{m}$, and $\dot{h}$ are set equal to zero in equations (1), (2), and (3), these equations define three two-dimensional curved *nullclinal surfaces* in the (V, m, h) space, and the points where all three surfaces intersect are the singular points. Equation (2) defines the m nullclinal ruled surface which is projected parallel to the h axis onto the (V, m) plane as the m nullcline. Equations (1) and (3) together define a curve, the intersection of the V and h nullclinal surfaces. This line will be called the V, h nullcline, and is shown projected onto the (V, m) plane as a dashed curve in Fig. 4. Like the V nullcline, it intersects the m nullcline in three singular points, A, B, and C. A is again the stable resting state. C may be called the *stable plateau point* and represents physiologically a stable excited state following partial recovery. B is a generalized saddle point at which there is a threshold phenomenon (FitzHugh (1955)).

Theoretically, there must be at least one other singular point in addition to A and C. A generalization of the Poincaré index of a singular point in a phase plane to phase spaces of higher dimensions is the Kronecker index (Alexandroff and Hopf (1945)). If M is the matrix of the coefficients of the linearized set of differential equations at a singular point, and if the determinant D of M is not zero, then the index of the singular point equals $\pm$ 1, with the same sign as D. Equivalently, the index is $(-1)^r$, in which r is the number of characteristic roots of M having negative real parts. In an N-dimensional phase space, let R be an N-cell such that the vector of motion points inward everywhere on its boundary. Such an R can be defined for the H-H equations (Cole, Antosiewicz, and Rabinowitz (1955)). Then the sum of the indexes of all singular points in R is $(-1)^N$. The stable points A and C in the V, m, h space each have the index -1. There must then be at least one other singular point with index $+1$ to give a total sum of $(-1)^3$ or -1. B in fact has one positive characteristic root and two with negative real parts, and therefore establishes a threshold phenomenon.

The nullclines and the locations of the singular points are independent of temperature. The solutions shown in Figs. 7 and 8 are for $T = 22°C.$, since the experimental plateau action potentials discussed below were done at this temperature. Also, this helps to eliminate certain troublesome oscillations in the plateau potential level which appear at 6.3°. Fig. 7 shows an infinitely long lasting plateau of the action potential for the V, m, h reduced system. A positive (anodal) instantaneous shock during this plateau causes a return to the resting state, if the potential displacement V is greater than a certain threshold value. On the (V, m) plane (Fig. 8), this threshold phenomenon for abolition of the

plateau occurs at the saddle point B, which is now approached from above, rather than from below, as in the original excitation. In Fig. 8, the moving saddle point cannot be labeled, but it lies somewhere between the two oppositely pointing arrowheads to the left of A.

The plateau abolition phenomenon just described resembles those obtained experimentally by Tasaki and Hagiwara, but before their action potential curves can be duplicated, it is necessary to produce a plateau which terminates after 20 or 30 msec. by introducing a slow change in n.

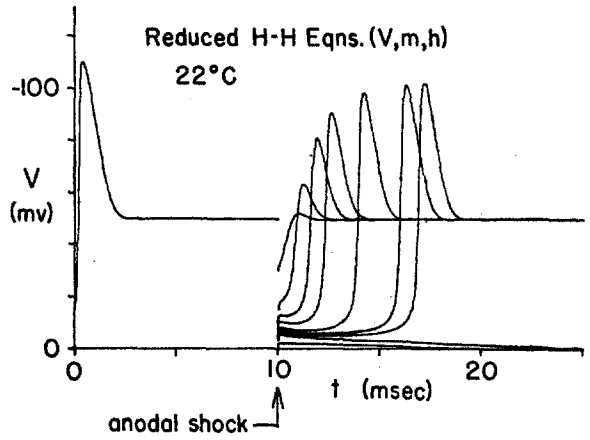

FIGURE 7. Infinite plateau of V, m, h reduced system, and its abolition by an anodal shock.

Complete V, m, h, n System If n is reintroduced as a variable, the complete H-H equations are obtained. A plateau no longer occurs, since when both h and n vary normally, the V nullcline in the (V, m) phase plane rises farther during the action potential than in the V, m, h system, with the result that the stable excited point C and the threshold saddle point B disappear. It will be shown below how these two points can be made to disappear later than in the normal equations (1) to (4), by effectively increasing τ_h or τ_n, so that a terminating plateau occurs. In the normal equations, however, B and C disappear so soon that V falls smoothly to form the descending phase of the action potential (Fig. 1). The slight hump low on the descending phase at 6.3°C. is actually a vestige of the plateau, but disappears when the temperature is raised. It may be that modifying the time constants at 6.3°C. would make the action potential curve agree better with experiment.

Fig. 9 shows solutions projected onto the (V, m) plane, for $I = 0$, following instantaneous shocks of different strengths at $t = 0$. (The circled numbers in Fig. 9 indicate stages in the excitability cycle corresponding to those in Fig. 1, similarly labeled.) By the time B and C have disappeared during the action

potential, point A has moved positively in V nearly to $V_K(+12$ mv.). As the phase point approaches A, which is now the only singular point in the (V, m) plane, V swings positively to form the positive after-potential. From here on, the phase point remains nearly at the slowly moving stable singular point A. Since V is now positive, $\dot{h}$ and $\dot{n}$ reverse sign, h and n approach new resting values, the V nullcline falls again, and A returns slowly to its original resting position. This last process appears as the decay of the positive after-potential.

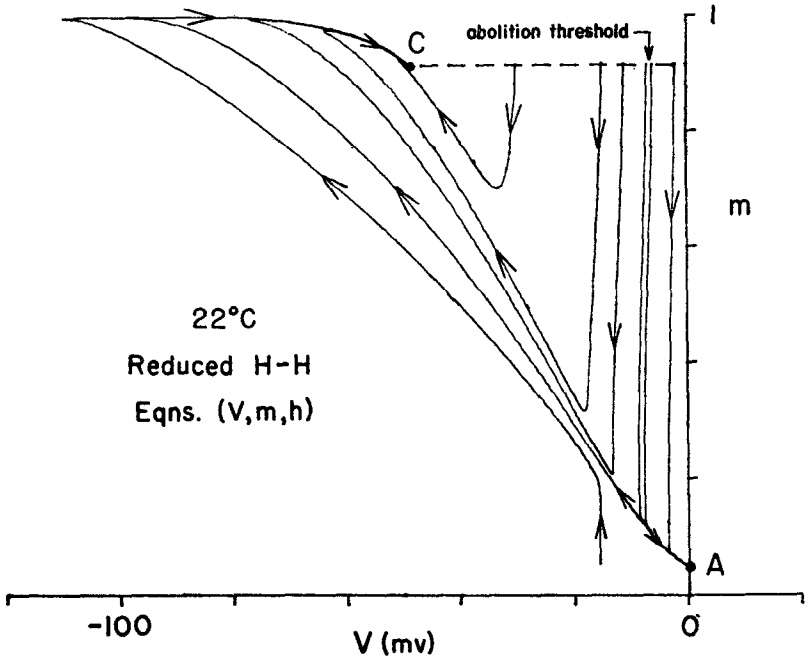

FIGURE 8. (V, m) phase plane corresponding to Fig. 7.

The time interval during which B is absent is the absolute refractory period. When B finally returns, it is far away from A (where the phase point now is, approximately), and therefore the threshold value of V necessary for a second excitation is larger than in the resting state. As long as this is true, the system is relatively refractory. This is the mathematical basis of refractoriness in the H-H equations.

The entire (V, m, h, n) phase space can be examined for the presence of singular points. In Fig. 4 is plotted the V, h, n nullcline as a dashed curve, representing the projection onto the (V, m) plane of the curve of intersection of the three nullclinal three-dimensional hypersurfaces for V, h, and n in the (V, m, h, n) space. This curve intersects the m nullcline only at $V = 0$, so that in the V, m, h, n system there is only one singular point A. The fact that the complete equations have no saddle point

made it difficult to understand why they had such a sharp threshold (Cole, Antosiewicz, and Rabinowitz (1955); FitzHugh (1955); FitzHugh and Antosiewicz (1959)). This sharp threshold can now be explained by the saddle point B which does exist for h and n near their resting values in the V, m reduced system.

According to a classification of mathematical threshold phenomena previously proposed (FitzHugh (1955)), the V, m and V, m, h and V, m, n reduced systems each have a singular point threshold phenomenon (STP), while the complete V, m, h, n

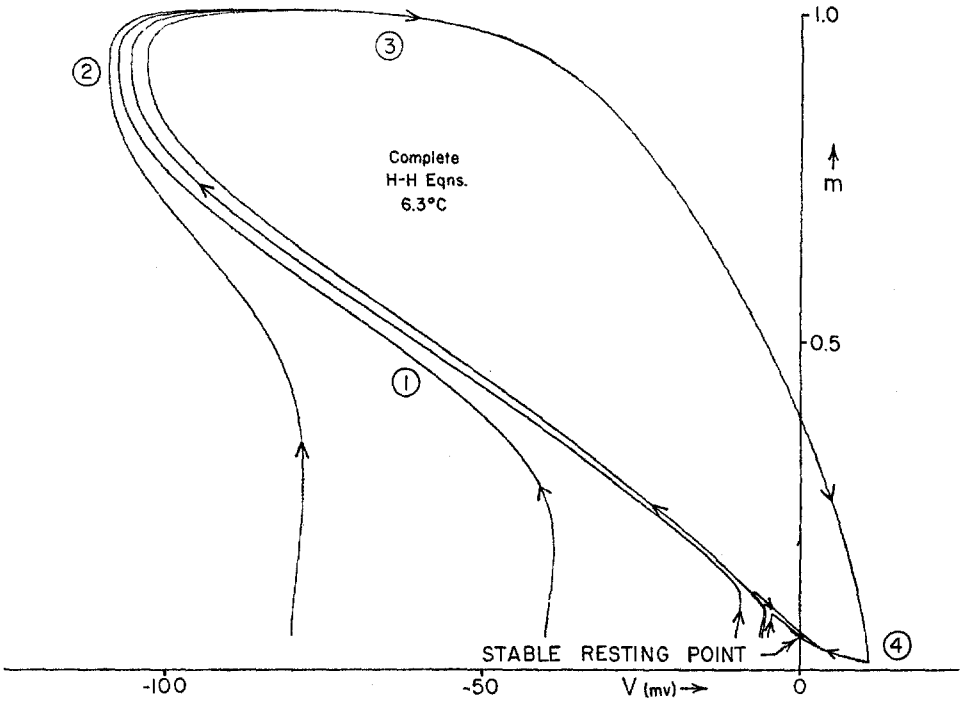

FIGURE 9. (V, m) plane showing paths corresponding to solutions of complete equations following instantaneous current shocks of various strengths at $t = 0$. $I = 0$ for $t > 0$. All conditions the same as in Fig. 1 except for the shock strength. Circled numbers correspond to those in Fig. 1.

system has a quasi-threshold phenomenon (QTP). In a QTP, there is no saddle point in the complete system, and any intermediate response between "all" and "none" is obtainable by an accurate enough adjustment of the stimulus intensity. This property of the complete H-H equations has been discussed elsewhere (FitzHugh and Antosiewicz (1959)). The present analysis gives an example of how a QTP in a four-dimensional phase space can be represented by an STP in a moving two-dimensional subspace. This is related to Lotka's (1925) interpretation of a quasi-equilibrium state which has a slowly changing non-equilibrium variable as a "moving (stable) equilibrium." A QTP could be described from this point of view as one type of "moving unstable equilibrium."

Plateaus with "TEA"

In this section a comparison will be made between the computations of a modified H-H system and the experimental results of Tasaki and Hagiwara (1957) obtained from squid axons injected with TEA (tetraethylammonium chloride). The computed curves for the plateau action potential, its abolition, and the refractoriness following a plateau, agree well with experiment, although the corresponding conductance changes do not.

Equations (3) and (4) were modified by dividing their right hand sides by constants K_h and K_n as follows:—

$$\dot{h} = (\phi/K_h)[(1 - h)\,\alpha_h(V) - h\beta_h(V)] \qquad (3K)$$

$$\dot{n} = (\phi/K_n)[(1 - n)\,\alpha_n(V) - n\beta_n(V)] \qquad (4K)$$

This change is equivalent to multiplying τ_h by K_h and τ_n by K_n. The case $K_h = K_n = 1$ corresponds to the normal equations (1) to (4).

An infinitely long lasting, or "permanent," plateau was obtained earlier for the V, m, h reduced system (Fig. 7). The condition that n be constant is equivalent to setting $K_n = \infty$ in equation (4K). If, instead, K_n is made finite but large compared to one then τ_n is very long, and during the first few milliseconds of the action potential the complete system behaves nearly the same as the V, m, h system. Then, however, as n slowly increases, the V, h nullcline rises. When n reaches a critical value, the singular points B and C meet and vanish, and the plateau ends, with V swinging to a positive value. This positive level decays much more slowly than the normal positive after-potential, since it is governed by an increased τ_n. A second effect of increasing τ_n is to broaden and heighten the initial peak of the action potential, in disagreement with experiment; TEA actually lowered the peak height slightly. However, when τ_h is arbitrarily shortened by letting K_h = one-third, the resulting curve (Fig. 10, upper, *cf.* Fig. 1) resembles those of Tasaki and Hagiwara more closely, especially those with linearly descending plateaus (their Figs. 4, 7, and 8—their Figs. 3 and 6 show plateaus which are more convex upward than the computed ones). Empirically shortening τ_h to one-third its normal value (at each value of V) made the upward movement of the V nullcline in the V, m subsystem more rapid initially, thus lowering and shortening the peak, while the increase of τ_n slowed the later movement, producing the long plateau. The experimental plateaus start about 10 mv. farther from the resting potential than the computed ones, and K_h was arbitrarily adjusted so as to make the fall of potential from the peak to the plateau agree with experiment; the computed peak heights are therefore also about 10 mv. lower than the experimental ones. The duration of the plateau is approximately proportional to

K_n; for $K_n = 100$, the plateau lasts 20 msec. A (V, m) phase plane for this case looks very much like Fig. 9, except that in the plateau region the phase point moves very much more slowly than in the normal action potential.

When an instantaneous positive (anodal) current pulse is added experimentally during the plateau, the latter is abolished if the pulse amplitude is

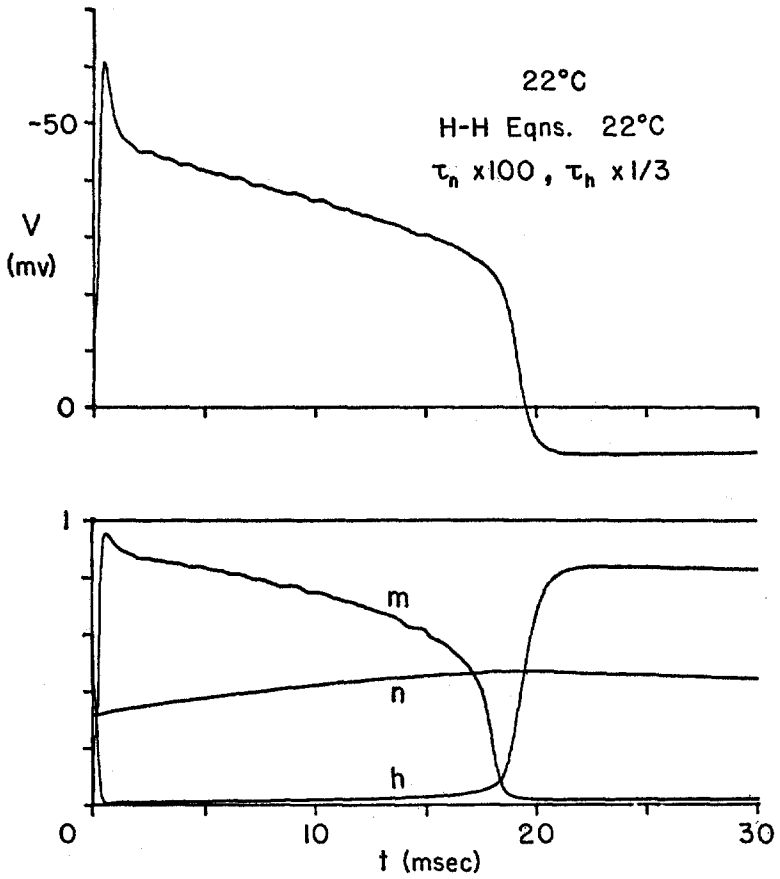

FIGURE 10. Modified h and n "time constants" give an imitation of Tasaki and Hagiwara's (1957) TEA action potentials with finite plateau.

above a certain threshold level (Fig. 11). The threshold level of V, following the pulse, becomes more negative (upward) as the plateau potential is moving positively (downward). The experimental curves in Tasaki and Hagiwara's Fig. 7, illustrating this phenomenon, are rather well duplicated by the computed curves of Fig. 11. They describe this phenomenon by saying that following a current pulse near threshold, V stayed "at an approximately constant level for a variable length of time and then it went either up or down to reach one of 'two stable potential levels,' " and later, that "between the upper and

lower stable states, there is an 'unstable state' at which the membrane current may vanish for a short period of time but the membrane potential is extremely labile." They suggest further that the "natural termination of an action potential is the result of the impingement of the membrane potential upon the abolition threshold." *This is in fact an excellent description of how the modified H-H equations work.* Their two stable states correspond to the stable singular points A and C of the V, m subsystem, and the "unstable state" to the saddle point B. Their "threshold membrane potential for abolition" is the value of V of that point on the threshold separatrix of the saddle point B which is

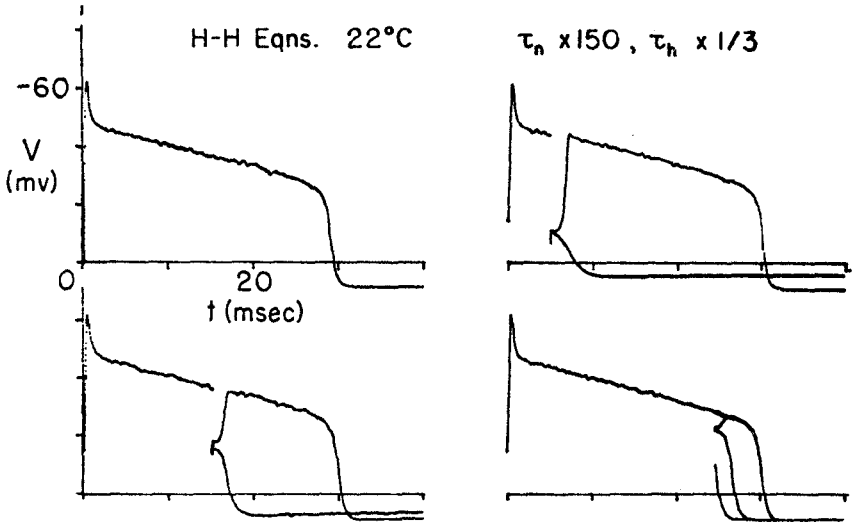

FIGURE 11. Abolition of finite plateaus by anodal shocks. Threshold repolarization decreases as t increases.

reached for a just threshold current pulse (*cf.* Fig. 8). During the plateau, as B moves to the left and upward along the m nullcline in the (V, m) plane, the separatrix of B moves to the left too, and the threshold potential for abolition becomes more negative. At the same time the plateau potential is becoming more positive. These two potentials meet and the plateau ends when B and C touch, but in the equations this is not the primary event, but is rather the result of n reaching a critical value. The rate of change of the potassium activation n is the limiting factor which determines the duration of the plateau. Thus, these properties of the membrane as interpreted by Tasaki and Hagiwara can be duplicated by the H-H equations, suitably modified.

Abolition is also obtained with the normal H-H equations, if an anodal shock is applied during the falling phase of the action potential as mentioned by Dodge and Frankenhaeuser (1958); (this result has been checked with the analog computer). The mathematical basis of this abolition is the same as for

the modified equations, but the threshold phenomenon (QTP) is less sharp. Dodge and Frankenhaeuser have already criticized Tasaki and Hagiwara's conclusions on the H-H equations in this connection.

Tasaki and Hagiwara also found refractoriness, in that a second stimulus following soon after a plateau action potential produces a shorter plateau than the first one. If the first one is abolished, then this refractory effect is less. Fig. 12 shows computed curves which duplicate Tasaki and Hagiwara's Fig. 8 rather well. The explanation of the refractoriness in the equations is that at the second stimulus following the plateau, n has decreased only part of the way back to its resting value, so that during the second plateau it reaches its critical value for termination of the plateau sooner than it did in the first

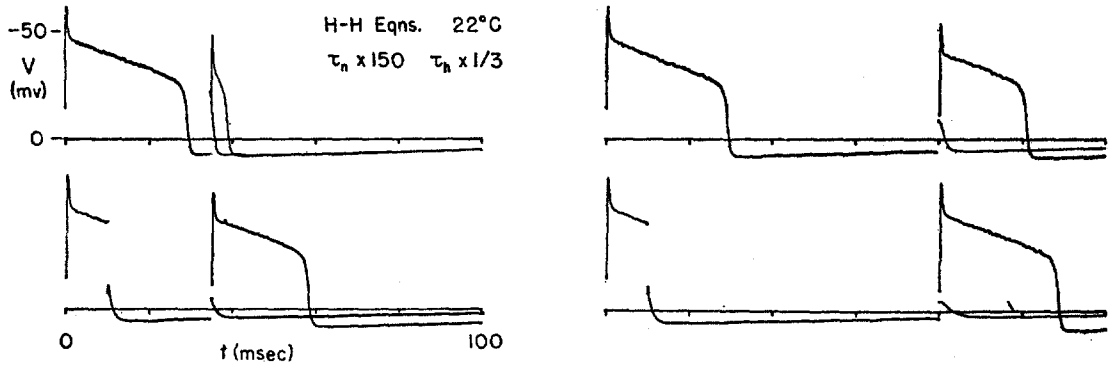

FIGURE 12. Upper, refractoriness reduces duration of a second plateau. Lower, abolition of plateau decreases refractoriness.

one. This effect is less if the second shock comes later. However, if the first plateau is abolished, n is smaller by the time the second shock is applied, with the result that the second plateau is longer than it is when the first plateau is not abolished.

There are some significant quantitative differences between the computed and experimental results. Besides the minor discrepancies in the membrane potential curves already mentioned, there are disagreements in the time course of the membrane conductance.

Tasaki and Hagiwara measured membrane conductance changes in two ways, with rather long pulses of constant current and with an A.C. impedance bridge. Tasaki and Hagiwara show in their Figs. 4 and 5 the effect of 5 msec. rectangular current pulses of constant amplitude on the time course of the membrane potential. They assumed that the latter was displaced during the pulse by an amount proportional to the membrane *resistance* at the time. Their Fig. 5 shows that the experimental membrane *conductances* measured in this way at three times—before, during, and after the plateau—were approxi-

mately in the ratios 1:1.4:1.1. Fig. 13 (lower) shows an attempt to reproduce their Fig. 5 by computation of the modified H-H equations; the corresponding conductance ratios are 1:5:2.5. The theoretical conductances, as measured during and after the plateau by the current pulse method, are therefore too large, relative to the resting value.

It is worth mentioning, moreover, that the theoretical "membrane conductance" as measured by the current pulse method can differ from the actual

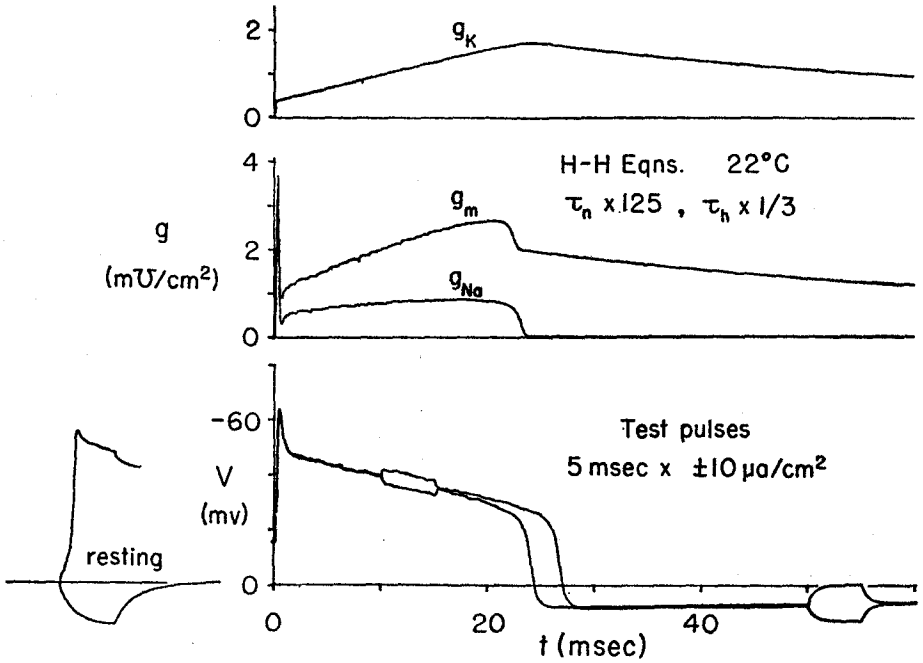

FIGURE 13. Upper, time course of Na^+ and K^+ conductances (g_{Na} and g_K), and of total membrane conductance (g_m) in mmho/cm². $g_{Na} = 120\ m^3h$, $g_K = 36\ n^4$. Lower, conductance measurements by test pulse method. Rectangular current test pulses applied to resting membrane, and during and after plateau, produce potential pulses as shown.

membrane conductance g_m as defined above in the List of symbols. This is because the changes of n, m, and h, during and resulting from the pulse, make V differ from what it would be if n, m, and h were unaffected by the pulse. Fig. 13 (upper) shows curves of g_m from which the ratios of conductance at the three times are 1:2.9:2.3. The differences between these ratios and the ratios 1:5:2.5 (mentioned above) show that the current pulse method may give only a roughly accurate measure of the true membrane conductance, even when the potential is changing slowly and neither excitation nor abolition results from the pulse.

Tasaki and Hagiwara also measured membrane impedance by recording the imbalance of a Wheatstone bridge, by the method of Cole and Curtis

(1939). They found, again, that after a sharp decrease of impedance during the spike, the impedance rose nearly to the resting value during the plateau. During the turning off of the plateau, there was a transient increase of impedance followed by a return to approximately the resting level, which was maintained during the positive after-potential. The bridge and band-pass filter used by Tasaki and Hagiwara were simulated on the analog computer (slowed by a factor of 5000) but the noise level in the computer was too high to obtain satisfactory curves by this method.

In Fig. 13, g_m is seen to rise steadily during the plateau, mostly due to the steady rise of the K^+ conductance $g_K(= g_K n^4)$. This is in contrast to the experimental results, in which the conductance as measured by the bridge method fell steadily during the plateau. The computed g_m drops suddenly during the turning off of the plateau, due to a rapid decrease in m, and then continues to drop more slowly. The experimental curves of bridge imbalance, in contrast, show only a transient decrease in conductance at this moment.

Finally, Tasaki and Hagiwara show experimental curves of membrane current during voltage clamp with TEA, including curves for low external sodium. A few such voltage-clamp curves were obtained with the analog computer. Those for the modified H-H system differ from the TEA curves in sea water in one important respect. In the normal axon, there is an initial surge of current, either positive or negative, depending on the potential level at which the membrane is clamped. There is one borderline potential value at which amplitude of this peak is zero; in the H-H formulation, this is identified with the sodium equilibrium potential, $V_{Na}(= -115$ mv.). In the experimental curves, this potential was shifted by the injection of TEA from about -110 mv. to about -88 mv. In the modified H-H model, however, V_{Na} was not changed from its normal value of -115 mv., so that the potential for a reversal of the initial peak did not change. An attempt was made to change V_{Na} to -90 mv. in the equations, but this caused a lowering of the plateau potential level even further below the experimental values than with the modified model described. Several other changes were tried, in order to compensate for this discrepancy, but these had other deleterious effects. It was decided therefore, not to try further *ad hoc* modifications, the possibilities for which are many. However, one feature of the experimental voltage-clamp current curves was matched rather well by the computed curves. In the experimental curves with TEA, the current level just following the initial surge was very small compared with that for the normal axon. Hodgkin and Huxley interpret this steady-state current as being principally potassium current and Hodgkin (1958) suggests that these TEA voltage-clamp curves of Tasaki and Hagiwara indicate that the rise in g_K is either absent or greatly delayed. The multiplication of τ_n by 100 in the H-H model does not change the steady-state level of the potassium current, but it

slows its rise so much that for time intervals of about 5 msec. only a low, very slowly rising level of current appears. An examination of the experimental curves shows that in them also the final current level is rising detectably. This suggests that it would be worthwhile to record experimentally the current for longer time intervals, say up to 50 msec., for both the normal and the TEA-injected axon, in order to see whether the steady level of current keeps on rising with a greatly prolonged time constant.

Current—Voltage Representation

The foregoing division of the H-H equations into a rapid excitatory and a slow inhibitory subsystem can be used to show the mathematical significance of certain current-voltage curves obtained experimentally. If m, h, and n are all held constant at their resting values, the following single differential equation obtained from equation (1) describes a V reduced system:

$$I = C\dot{V} + g_m V,$$

in which the resting membrane conductance $g_m = 0.67725$ mmho/cm.[2] The steady-state current-voltage characteristic of the membrane is found from this equation by setting $\dot{V} = 0$ and is a straight line in the (V, I) plane with slope g_m (Fig. 14, broken line labeled "V," with ordinate magnified 10 times). This line may be considered, from another point of view, to be the locus of all possible singular points of the V reduced system, and the actual singular point is the intersection of this line and a second line representing the external experimental circuit to which the membrane is connected at the two electrodes. The latter characteristic, or "load line" is parallel to the I axis for a voltage clamp or to the V axis for a current clamp, and has a negative slope for a resistive clamp with positive clamping resistance.

Now, if we reintroduce m as a variable according to equation (2), set $\dot{V} = \dot{m} = 0$ in equations (1) and (2), and eliminate m, we obtain an N-shaped steady-state characteristic, or locus of singular points for the V, m reduced system. This locus is shown in Fig. 14 (solid curve labeled V, m) and intersects the V axis at three points, which are simply the singular points A, B, and C already found for the V, m reduced system when $I = 0$. Unfortunately, the intersections A and B cannot be distinguished in Fig. 14, because the curve is nearly tangent to the horizontal axis there, but if the vertical scale were increased greatly, they would be evident. Clamping I at a sufficiently negative value, that is, beyond rheobase, makes A and B disappear and the phase point passes spontaneously toward C.

This N-shaped curve is a "dynatron characteristic" such as characterizes various types of excitable and oscillatory electrical systems (Franck (1956)).

The very similar dynatron characteristic which appears shortly after excitation in the squid axon can be measured (Cole (1949); Hodgkin, Huxley, and Katz (1949, 1952)). In the light of the present analysis, it seems reasonable to think of this characteristic, with its three intersections with the V axis, as

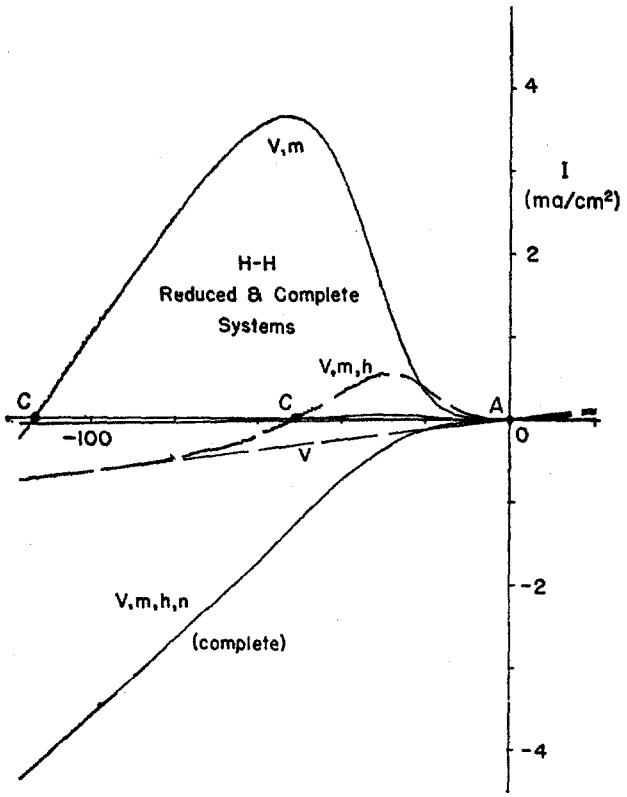

FIGURE 14. Solid curves, steady-state current-voltage characteristics (loci of singular points) for reduced and complete systems. Curves for the V and V, m, h reduced systems are too small to distinguish easily, and are therefore also shown with ordinate magnified 10 times (broken curves). Horizontal axis intersects the V and V, m, h, n curves only at the origin (A), but the V, m and V, m, h curves in two additional places each (points C shown, points B near A but indistinguishable).

corresponding approximately to the steady-state characteristic of the V, m reduced system, which shows bi-stable behavior and a threshold phenomenon. The only difference is that the experimentally measured curves do not represent an actual steady state, but only a transient state. The slower inhibitory h, n subsystem then reacts upon the V, m subsystem so as to remove its excited stable state and its threshold phenomenon, thereby causing recovery.

Finally, Fig. 14 shows the steady state characteristics of the V, m, h and V, m, h, n systems. The former intersects the V axis in three singular points

(not visible even at the magnified scale shown) and the latter in one, in agreement with the phase plane analysis given above.

DISCUSSION

Why should the modified H-H equations duplicate the experimental action potential curves of the TEA squid axon rather well, and the conductance measurements rather poorly? The former depend largely on the qualitative properties of the equations, *i.e.* on the topological properties of their phase space, and it is doubtless possible to devise many other models, mathematically but not physically resembling the H-H model, which would give satisfactory potential curves. The quantitative duplication of experimental conductance curves is, however, a more stringent test, and it is obvious that the modified H-H equations presented above do not completely explain the TEA axon.

Tasaki and Hagiwara's (1957) objections to H-H equations on the basis of their conductance measurements of the TEA axon still have some validity for the modified H-H equations solved here. However, in view of the remarkably good agreement for the plateau action potential curves, and of abolition and refractoriness, it may still be worthwhile to look for better modifications of the equations capable of reproducing the experimental membrane conductance measurements. The H-H equations were, after all, not designed to explain the TEA plateau action potential, and it may be that with TEA there are slow conductance changes, with time constants tens of milliseconds long at 22°C., which the equations omit. If so, the H-H equations may still adequately describe the principal events which take place during the normal action potential, but require further modification for the TEA case. It is interesting that in crustacean muscle fibers soaked in TEA there is an increase of Ca^{++} conductance (which is not represented at all in the H-H equations), and Ca^{++} replaces Na^{+} in its role of producing an action potential (Fatt and Ginsborg (1958)).

Alternately, the slow negative change of the potassium equilibrium potential as a result of the accumulation of K^{+} in a space external to the membrane (Frankenhaeuser and Hodgkin (1956)) may play a role here, and might prolong the plateau. Nevertheless, there would seem to be little point in trying to make further changes in the equations until more voltage-clamp experiments are available for the TEA case, especially ones using long voltage pulses up to 50 msec. long. It may be concluded, then, that the H-H equations can be modified easily so as to give plateau action potentials, with abolition and refractoriness, like those caused by TEA, but that without more fundamental revisions in the kinetics of the ionic conductances they cannot match the experimental conductance measurements.

Exploratory attempts were made to produce long lasting but suddenly terminating plateaus by several other modifications tending to oppose recovery

in the H-H equations. Satisfactory plateaus were obtained by increasing τ_h instead of τ_n, but not by any other means. (In this case the conductance curves were much worse.) It is therefore suggested that the most reasonable general explanation of such plateaus is the existence of some slowly changing variable of state which, when it reaches a critical value, causes the disappearance of the stable excited state. Such a slow recovery process might be revealed by voltage-clamp experiments in which long lasting potential pulses were applied to the membrane and the ionic currents separated. There must also be a fast recovery process in addition to the slow one, in order to provide a distinct initial spike followed by the lower plateau level of potential. These two separate recovery processes are provided in the H-H equations by n and h, but a pair of variables of state with different physiological meanings might play the same role in the TEA axon. The exact changes in the equations used in this paper to duplicate the TEA results are therefore not as important as the fact that the equations can be slightly modified so as to permit such a duplication.

Tasaki and Hagiwara describe their results in terms of two stable states of the membrane, which in fact is a good description of the two stable singular points of the V, m reduced system in the H-H model. They interpret this concept rather differently, however. They postulate in addition that "when the membrane is in an unstable intermediate condition, some part of the membrane is in state I and the remaining part in state II . . . there is a continuous flow of eddy currents between the spots or patches in state I and those in state II." They assume further that "each of these two states is characterized by the effective membrane—E.M.F. and its conductance . . . denoted by E_{I}, g_{I}, E_{II}, and g_{II}. During activity E's and g's undergo continuous relatively slow changes . . . Transitions between these two stable states are induced by changes in the membrane potential."

The present results show that the assumption of separate patches, some in each of the two stable states, is not *necessary* in order to give plateau-type action potentials, since spatial uniformity for all variables has been assumed. Tasaki and Hagiwara state that the E.M.F. of their active state E_{II} corresponds to a sodium equilibrium potential of the H-H type "which has lost its original physical meaning and is modified during the course of activity to fit the observed data." But a potential answering this description exists in the H-H model—the value of V for the stable excited singular point C in the V, m reduced system. One other difference is that Tasaki and Hagiwara do not mention the disappearance of the possibility for stable state II following an impulse, which, however, would have to occur to produce an absolutely refractory period.

It appears, then, that the difference between these two points of view is not great, and that the principal qualitative features of Tasaki and Hagiwara's

theoretical interpretation can be derived from the H-H model. Quantitative differences do exist in the kinetics of the conductance changes, but it may be that these could still be improved by a suitable modification of the H-H model.

The study of the nerve membrane has advanced to the point at which mathematical formulations can be made on the basis of physicochemical models. At the same time, mathematicians studying non-linear differential equations have become concerned with their qualitative or topological properties, as distinct from techniques of solution. Now if investigators in these two fields are sometimes talking about the same things, though in different languages, this fact is worth knowing for the physiologist, because he can then make a better use of mathematics in developing theoretical models of excitable membranes.

In this paper the parallelisms between physiological concepts and the mathematical properties of the H-H equations have been emphasized. The mathematical properties in question are not peculiar to these equations, but have appeared several times in different theoretical models of excitable systems (summarized by FitzHugh (1955)) although the H-H equations are the most complete formulation of this kind to appear so far. These properties are therefore of physiological importance and worth considering as factors in future models of the nerve membrane. They include the stability of the resting state, transient stability of the plateau, the threshold phenomena for excitation and for recovery from the plateau, and the appearance of trains of impulses. (This last property is now being analyzed by phase space methods.)

It is hoped, in conclusion, that this conceptual separation of the physical and mathematical properties of the Hodgkin-Huxley model will provide its supporters with ammunition for its defense, and its opponents with a more clearly defined target at which to fire.

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