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By Stephen W. Brady *

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TABLE OF CONTENTS

I. INTRODUCTION

In 1952 A. L. Hodgkin and A. F. Huxley, Professors of Biophysics at Cambridge University, published a now famous series of papers [1, 2, 3, 4, 5] concerning the flow of electric current through the surface membrane of a giant nerve fiber of the squid Loligo. For this work they received the Nobel Prize (shared with J. C. Eccles) in Physiology and Medicine in 1963. In part of their concluding paper [5] they constructed a mathematical model describing the propagation of electrical impulses along the squid's axon. This model was a nonlinear system of differential equations consisting of one second order partial differential equation of parabolic type and three subsidiary first order differential equations. Not wishing to contend with the partial differential equation and desiring to deal only with the fully developed impulses (the so-called "steady state" or "propagated action potential"), they altered the model by assuming, based on clear empirical evidence, that the voltage v satisfies the wave equation

$$v_{xx} - \frac{1}{\theta^2} v_{tt} = 0$$

where x denotes distance along the axon, t is time, and θ is the propagation rate of an impulse. This enabled them to transform the partial differential equation into a second order ordinary differential equation. Unfortunately, numerical "solutions" to the new system were highly sensitive to θ.

Rather than impulse type solutions, grossly unbounded solutions appeared to be produced in such a way that for one given value of θ the solution v of the second order equation would appear to tend toward plus infinity while for extremely small variations of this value the solution v would appear to tend toward minus infinity. This discontinuous dependence on the parameter θ and the apparent occurrence of unbounded solutions created, in numerical practice, a need for very unusual numerical methods of solution of the system. Bounded "solutions" were extricated from the system by averaging unbounded solutions at slightly different values of θ.

In formulating their equations, Hodgkin and Huxley did not include the effects of core capacitance or inductance when they related axon current to membrane current and voltage. In 1966 H. M. Lieberstein, while Professor of Mathematics at Indiana University, found that these important effects could be included in the model without introducing any new parameters [6]. He formulated a new model which utilizes the same (empirical) equation for membrane current density and the same three subsidiary equations which Hodgkin and Huxley developed, but which gives rise to a hyperbolic partial differential equation of second order which accompanies the subsidiary equations. Dr. Lieberstein showed numerically that a "steady state" satisfying the wave equation developed asymptotically with time so that recourse to empirical evidence for this behavior as a separate *ad hoc* condition, as utilized by Hodgkin and Huxley, could be avoided. For this steady state formulation the new model yields a first order ordinary differential equation for voltage (instead of second order as formerly), and thus forms an autonomous system of four first order ordinary differential equations. The solutions to the equations, which now can be handled by entirely standard means, were shown numerically to be bounded and no longer sensitive to variations in the propagation rate. Furthermore, the agreement of the numerical solutions of this new system when compared to numerical solutions of the Hodgkin-Huxley system and the empirical evidence is excellent.

In a later paper [7, Part II] Lieberstein investigated the extent to which his modified Hodgkin-Huxley model of nerve cells could be used as a general model of other membranous cells such as skeletal muscle fibers, pacemakers, receptors, and heart cells with a plateau type behavior. This research involved the investigation of the accommodation of the model to the application of a sustained constant membrane current density I_o. He showed numerically that the gross behavior of the electrical properties of such cells can be imitated by choosing appropriate values of the parameters which occur in the model. By varying the I_o it was shown that the model exhibits the threshold "on-off" phenomenon observed in nerves, the plateau type behavior of certain heart cells, and the phenomena of repetitive firing of potential spikes as seen in both pacemaker cells in the heart and receptor cells. Any desired (finite) number of potential spikes could be achieved by applying the required sustained constant membrane current density, and numerical evidence strongly indicated a value of I_o, termed the limit of thresholds, which if applied to the model would initiate an infinite chain of impulses. All this, of course, depended on a numerical justification given for using the steady (or asymptotic) state approximately to treat the local stimulation effects.

The present paper considers this last model discussed, that of Lieberstein's modified Hodgkin-Huxley equation, altered so as to accept application of a sustained constant membrane current density, together with Hodgkin and Huxley's three subsidiary equations. This model is an initial value problem for a highly nonlinear autonomous system of four first order ordinary differential equations. The independent variable is time, and the four dependent variables are v, n, m, and h where v is membrane voltage and n, m, and h relate to membrane conductances.

We first prove an existence and uniqueness theorem for solutions of the system of differential equations in a neighborhood of the initial point and then extend this solution to the right maximal interval of existence which until we show that the solutions are bounded will be either

$[0,\infty)$ or $[0,b]$, where b would be the time when the solutions leave the closed domain that is specified in the theorem. It is shown that the system is analytic, implying that the solutions will be analytic, a property that is found to be valuable in limiting the behavior of the solutions. The fact that solutions exist and are unique allows us to prove several results that provide a preview of the behavior of the solutions. In order to determine additional information, we next prove that the solutions are bounded, a fact which proves the existence of the solutions for all nonnegative time.

Boundedness is proved in steps. First, it is proved that n, m, and h are all bounded by zero and one. Then three new functions are introduced whose behavior depends solely on the solution v and which help to determine the behavior of n, m, and h. Using these three functions and subsequent propositions which follow from their use, we prove lower boundedness and then upper boundedness of the solution v. For the upper boundedness it was necessary to include an assumption which is justified by the original intent of the model as described in the writings of Hodgkin and Huxley, by a proposition which we prove, and by some of the new numerical work which we have undertaken. In the course of our investigations a second proof of lower boundedness was discovered which uses an extension of an elementary comparison theorem from the theory of Ordinary

Differential Equations. This method of proof is also included in this paper. Because of a certain convention on sign of voltage adopted in the original Hodgkin-Huxley work (which we preserve, but which is apparently no longer popular), lower bound considerations are by far the more critical, and lower bounds are established without resort to any assumptions that are extraneous to the system of differential equations.

The boundedness of the solutions, as mentioned above, guarantees the existence of a unique solution for all time t greater than or equal to zero. The boundedness of v also enabled us to find new bounds for n, m, and h. But probably the most important contribution of boundedness was that the solutions must now be continuously dependent on any and all parameters which occur in the system. We thus have a mathematical proof that the extreme sensitivity of the solution v to the propagation rate θ, inherent in the original Hodgkin-Huxley model, has been completely removed in the model as Lieberstein has reformulated it.
Dr. Lieberstein's numerical work [7] of altering the equations by varying the maximum values of the conductances is now mathematically justified. Thus, one is now entirely justified in freely testing the equations by varying parameters to see whether they can model pacemaker cells, smooth muscle fibers, heart cells with plateau type behavior, etc., provided, of course, that one of the

standard numerical methods is used which is known to be free of numerical instabilities. We use Runge-Kutta.

In the chapter concerning threshold phenomena we examine the mathematical possibilities which when considered in the perspective of continuous dependence could still govern the threshold phenomena demonstrated numerically in [7]. Then we present some new numerical work by altering the parameter I_o (the sustained constant applied membrane current density) which shows that the threshold phenomenon occuring in the model is an extremely rapid (but continuous) change of potential from what has been called an "off" curve to an "on" curve. For values of I_o intermediate to the values which provide "off" and "on" curves, we exhibit "intermediate" solutions for v. It should be remarked, however, that some of those who are thoroughly experienced in scientific calculations have proclaimed that they have never seen such sensitivity to a parameter in a stable process. To "hit" halfway between a subthreshold and a suprathreshold curve, it has been necessary to vary I_o in the seventeenth digit and to perform concomitant high accuracy calculations. Thus there is a genuine threshold phenomenon involved appearing to give sharply discontinous behavior at the three digit level or higher; that is, to stimulation changes of one tenth of a percent or less.

Much has been written in the past hinting or hoping that singular (or stationary) points are involved in the mechanism governing the threshold phenomenon. This is probably because the extremely rapid change of potential from subthreshold to suprathreshold looked when graphed like the graphs of solutions of equations in which a stationary point does appear. We prove a theorem that provides an equation which determines the stationary points in terms of the value of I_o. Then the equation is (successively) solved numerically and these results are found to indicate that the v coördinate of a stationary point is a strictly decreasing function of the parameter I_o. It is shown that for the values of I_o concerned with the threshold phenomenon, stationary points are not involved. They do, however, seem to be involved in the behavior of the solutions as t approaches infinity. This fact is of primary importance for cells of plateau type behavior for, as will be seen, it is possible to choose the value of voltage which the plateau will "rest" on.

Finally, in the Appendix we present a theorem which proves the equivalence of the system of four differential equations and one first order integro-differential equation. Although this equivalence was not used in the present paper, it is closely related and may be used in subsequent investigations.

II. BACKGROUND

In order to present background material necessary for an understanding of this paper and also to introduce the numerous parameters and notations that are used, we begin by summarizing the equations and models developed by Hodgkin and Huxley and modified by Lieberstein.

1. The Hodgkin-Huxley (H-H) Excitation Equation

Hodgkin and Huxley [1, 2, 3, 4, 5] separated the membrane current density I into two parts: the capacitive current given by

$$C_M \frac{\partial v}{\partial t},$$

and the ionic current with components

$\bar{g}_K n^4 (v - v_K)$, the potassium current,

$\bar{g}_{Na} m^3 h(v - v_{Na})$, the sodium current,

and

$\bar{g}_\ell (v - v_\ell)$, the leakage current (chloride and other ions),

where C_M is the membrane capacitance per unit area; v denotes membrane potential difference (positive voltage is given by outside potential minus inside potential); v_K, v_{Na}, v_ℓ are the equilibrium potentials of the ions; and $\bar{g}_K$, $\bar{g}_{Na}$, $\bar{g}_\ell$ are the maximal values of the specific conductances corresponding to the ionic currents. The n, m, and h are dimensionless variables which Hodgkin and Huxley used to describe the specific conductances g_K and g_{Na}; i.e.,

$$g_K = \bar{g}_K n^4 ,$$

$$g_{Na} = \bar{g}_{Na} m^3 h.$$

The variables n, m, h satisfy the equations

$$\frac{\partial n}{\partial t} = \left[\alpha_n(v) \cdot (1 - n)\right] - \left[\beta_n(v) \cdot n\right]$$

$$(2.1) \qquad \frac{\partial m}{\partial t} = \left[\alpha_m(v) \cdot (1 - m)\right] - \left[\beta_m(v) \cdot m\right]$$

$$\frac{\partial h}{\partial t} = \left[\alpha_h(v) \cdot (1 - h)\right] - \left[\beta_h(v) \cdot h\right]$$

where

$$\alpha_n(v) = \begin{cases} (0.1)\dfrac{[(v + 10)/10]}{\{-1 + \exp[(v + 10)/10]\}} & \text{if } v \neq -10 \\ 0.1 & \text{if } v = -10, \end{cases}$$

$$\beta_n(v) = 0.125 \exp\left(\frac{v}{80}\right),$$

$$\alpha_m(v) = \begin{cases} \dfrac{[(v + 25)/10]}{\{-1 + \exp[(v + 25)/10]\}} & \text{if } v \neq -25 \\ 1 & \text{if } v = -25, \end{cases}$$

$$\beta_m(v) = 4 \exp\left(\frac{v}{18}\right),$$

$$\alpha_h(v) = 0.07 \exp\left(\frac{v}{20}\right),$$

$$\beta_h(v) = \left(1 + \exp\left[\frac{(v + 30)}{10}\right]\right)^{-1} .$$

The (H-H) excitation equation is

$$(2.2) \qquad I = C_M \frac{\partial v}{\partial t} + \bar{g}_K n^4 (v - v_K) + \bar{g}_{Na} m^3 h(v - v_{Na}) + \bar{g}_\ell (v - v_\ell)$$

where I, v, n, m, h are functions of time; C_M, $\bar{g}_K$, v_K, $\bar{g}_{Na}$, v_{Na}, $\bar{g}_\ell$, v_ℓ are constants; and I is positive when directed inward.

In this paper the values of these constants are the ones given by Hodgkin and Huxley for the 6.3° Centigrade case, and are the ones used by Lieberstein [6, 7] and also in [8], [9]. We will use these values exclusively. For the 6.3° Centigrade case

$$C_M = 1\ \mu\text{Farad/cm}^2 = 10^{-3}\ \text{msec/ohm cm}^2,$$

$$\bar{g}_K = 36\ \text{mmho/cm}^2 = .036\ \text{mho/cm}^2,$$

$$\bar{g}_{Na} = 120\ \text{mmho/cm}^2 = .120\ \text{mho/cm}^2,$$

$$\bar{g}_\ell = .3\ \text{mmho/cm}^2 = .0003\ \text{mho/cm}^2,$$

$$v_K = 12\ \text{mvolts},$$

$$v_{Na} = -115\ \text{mv},$$

and

$v_\ell = -10.5989$ mv (value chosen so that when the membrane voltage $v = 0$ and $\frac{\partial v}{\partial t} = 0$, the membrane current density I will also be zero).

To give I in terms of mamp/cm², we would have

$$(2.2\text{a}) \qquad I = 10^{-3} \frac{\partial v}{\partial t} + .036\, n^4 (v - 12) + .120\, m^3 h(v + 115) + .0003\, (v + 10.5989).$$

The voltage v is measured in mv; the time t is measured in msec; and α_J and β_J, where J = n, m, or h, are measured in reciprocal msec. We also include here the values for other parameters which will be used later:

$$a = .0238 \text{ cm},$$

$$R = 35.4 \text{ ohm cm}.$$

These give

$$\left(\frac{2}{a}\right)R = 2974.789915966\cdots \text{ ohm.}^1$$

We shall also use the symbol $\hat{K}$ for $(2/a)R\theta^2 C$. (In [5], [8], and [9], $\hat{K}$ = K and is given by $4.51084055 < K < 4.51084060$ in [9].)

2. <u>The Transmission Equation, the Equation for Membrane Voltage, and the Steady State Equation</u>

As mentioned in the Introduction, Hodgkin and Huxley did not include the effects of core capacitance or inductance. The equation they used [5, p. 522] to relate axon current to membrane current and voltage was

$$i = \left(\frac{1}{r}\right)\frac{\partial^2 v}{\partial x^2}$$

where i is the membrane current per unit length; r is the internal resistance per unit length (the external resistance

---

[1] It should be noted that there is a technical error in [6]. The value there for (2/a)R is 2974.8991, the second 7 having been omitted. This error causes a slight error in the propagation rate θ used in [6]. However, the error in (2/a)R is of the magnitude of 3.7 times 10^{-6}. This extremely small error does not noticeably affect the equations; hence, the values 2974.8991 for (2/a)R and 1.23138148 for θ will be used in this paper whenever data from [6] is used. These values give $\hat{K}$ to be 4.51084054....

is considered negligible); and x is the distance along the fiber. Setting

$$I = \frac{i}{2\pi a}$$

and

$$R = \pi a^2 r$$

where a is the axon radius and, therefore, I is membrane current density and R is the specific resistance of the axon; and substituting into the excitation equation (2.2) for I, they obtained their second order differential equation of parabolic type.

Lieberstein [6] used the more general equations relating axon current to membrane current and voltage

$$(2.3) \qquad -\partial i_a/\partial x = i + (\pi a^2 C_a)\partial v/\partial t$$

$$(2.4) \qquad -\partial v/\partial x = ri_a + \left[(1/\pi a^2)L\right]\partial i_a/\partial t$$

where i_a is axon current; C_a is axon self-capacitance per unit area per unit length; and L is axon specific self-inductance. After combining (2.3) and (2.4) and introducing I and R, the new transmission equation is given by

$$(2.5) \qquad \frac{\partial^2 v}{\partial x^2} - LC_a \frac{\partial^2 v}{\partial t^2} = RC_a \frac{\partial v}{\partial t} + \left(\frac{2}{a}\right)RI + \left(\frac{2}{a}\right)L\frac{\partial I}{\partial t}.$$

Substituting equation (2.2) for I and using $\theta = (a/2LC)^{\frac{1}{2}}$, where θ is the steady state propagation rate and C is the membrane capacitance (actually $C = (a/2)C_a + C_M$, but $(a/2)C_a$ is negligible), the new equation for membrane voltage is

$$\frac{\partial^2 v}{\partial x^2} - \left(\frac{1}{\theta^2}\right)\frac{\partial^2 v}{\partial t^2} = \left[\left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)(\bar{g}_K n^4 + \bar{g}_{Na} m^3 h + \bar{g}_\ell)\right]\frac{\partial v}{\partial t}$$

$$+ \bar{g}_K\left[\left(\frac{2}{a}\right)Rn^4 + \left(\frac{1}{\theta^2 C}\right)4n^3\frac{\partial n}{\partial t}\right](v - v_K)$$

(2.6)

$$+ \bar{g}_{Na}\left[\left(\frac{2}{a}\right)Rm^3 h + \left(\frac{1}{\theta^2 C}\right)\left(3m^2 h\frac{\partial m}{\partial t} + m^3\frac{\partial h}{\partial t}\right)\right](v - v_{Na})$$

$$+ \bar{g}_\ell\left(\frac{2}{a}\right)R(v - v_\ell).$$

For the steady state equation it is assumed that

$$\frac{\partial^2 v}{\partial x^2} - \left(\frac{1}{\theta^2}\right)\frac{\partial^2 v}{\partial t^2} = 0$$

which means that (2.6) becomes

$$\frac{dv}{dt} = -\left\{\left[\left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)(\bar{g}_K n^4 + \bar{g}_{Na} m^3 h + \bar{g}_\ell)\right]^{-1}\right\}$$

$$\cdot\left\{\bar{g}_K\left[\left(\frac{2}{a}\right)Rn^4 + \left(\frac{4}{\theta^2 C}\right)n^3\frac{dn}{dt}\right](v - v_K)\right.$$

(2.7)

$$+ \bar{g}_{Na}\left[\left(\frac{2}{a}\right)Rm^3 h + \left(\frac{1}{\theta^2 C}\right)\left(3m^2 h\frac{dm}{dt} + m^3\frac{dh}{dt}\right)\right](v - v_{Na})$$

$$\left. + \bar{g}_\ell\left(\frac{2}{a}\right)R(v - v_\ell)\right\}.$$

Hodgkin and Huxley's subsidiary equations (2.1) now become the ordinary differential equations

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

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

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

Also, the (H-H) excitation equation (2.2) now becomes

$$(2.9) \qquad I = C\frac{dv}{dt} + \bar{g}_K n^4 (v - v_K) + \bar{g}_{Na} m^3 h(v - v_{Na}) + \bar{g}_\ell (v - v_\ell).$$

The initial values for the original Hodgkin-Huxley steady state model are

$$(2.10) \qquad \begin{aligned} v(t_o) &= v(0) = 0, \\ J(t_o) &= J(0) = \frac{\alpha_J(0)}{\alpha_J(0) + \beta_J(0)} \end{aligned}$$

where J = n, m, or h. They are left unchanged. We shall refer to the system consisting of equations (2.7) and (2.8) together with the initial conditions (2.10) as the reformulated Hodgkin-Huxley model.

3. Application of a Sustained Constant Membrane Current Density

In order to adapt the reformulated model to a study of the gross behavior observed in pacemaker cells, receptor cells, etc.; or physically speaking, in order to apply a sustained constant membrane current density I_o to an active part of the membrane, Lieberstein [7] found that he had only to add I_o to the new (H-H) excitation equation (2.9). Equation (2.9) then becomes

$$(2.11) \qquad \begin{aligned} I = {} & C\frac{dv}{dt} + \bar{g}_K n^4 (v - v_K) + \bar{g}_{Na} m^3 h(v - v_{Na}) \\ & + \bar{g}_\ell (v - v_\ell) + I_o. \end{aligned}$$

Carrying out the processes described in II.2 with the new value for I, the singular perturbation equation attained is

$$
\begin{aligned}
\frac{dv}{dt} = -&\left\{\left[\left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)(\bar{g}_K n^4 + \bar{g}_{Na} m^3 h + \bar{g}_{\ell})\right]^{-1}\right\} \\
&\cdot \left\{ \bar{g}_K\left[\left(\frac{2}{a}\right)Rn^4 + \left(\frac{1}{\theta^2 C}\right) 4n^3 \frac{dn}{dt}\right](v - v_K) \right. \\
&\quad + \bar{g}_{Na}\left[\left(\frac{2}{a}\right)Rm^3 h + \left(\frac{1}{\theta^2 C}\right)\left(3m^2 h\frac{dm}{dt} + m^3\frac{dh}{dt}\right)\right](v - v_{Na}) \\
&\quad \left. + \bar{g}_{\ell}\left(\frac{2}{a}\right)R(v - v_{\ell}) + \left(\frac{2}{a}\right)RI_o \right\} \qquad (2.12) \\
= \; & H_1(v,n,m,h).
\end{aligned}
$$

This equation (2.12) together with the equations (2.8) and the initial conditions (2.10) make up the system and initial values that will be studied in this paper; i.e., we shall consider the initial value problem

$$
\begin{aligned}
\frac{dv}{dt} &= H_1(v,n,m,h) \\
\frac{dn}{dt} &= H_2(v,n) = \alpha_n(v)(1 - n) - \beta_n(v)n \\
\frac{dm}{dt} &= H_3(v,m) = \alpha_m(v)(1 - m) - \beta_m(v)m \qquad (2.13) \\
\frac{dh}{dt} &= H_4(v,h) = \alpha_h(v)(1 - h) - \beta_h(v)h
\end{aligned}
$$

where

$$
\begin{aligned}
v(t_o) &= v(0) = 0 \\
J(t_o) &= J(0) = \frac{\alpha_J(0)}{\alpha_J(0) + \beta_J(0)}, \qquad J = n, m, h.
\end{aligned}
$$

Note: For a complete discussion and numerical justification of the physical basis for the assumptions in Sections II.2 and II.3, see [6, 7].

III. EXISTENCE AND UNIQUENESS OF THE SOLUTIONS OF SYSTEM (2.13)

As stated in the Introduction, we wish to prove existence and uniqueness of solutions to (2.13) for all time greater than or equal to zero. To do this we need boundedness of the solutions. Therefore, we will be able for the present to establish only an existence and uniqueness theorem which holds up to a possibly finite time b.

1. Preliminary Properties of the System

The goal of this present section is to prove that H_2, H_3, and H_4 are each entire functions of the four real variables v, n, m, and h and that H_1 is analytic in the region in which solutions are sought. Therefore we first state some properties of the various functions of which H_1, H_2, H_3, and H_4 are composed.

Proposition 3.1. *α_n, α_m, α_h, β_n, β_m, and β_h are entire functions of v.*

Proof.

Let

$$f(x) = \begin{cases} \dfrac{x}{-1 + \exp(x)} & \text{if } x \neq 0 \\ 1 & \text{if } x = 0. \end{cases}$$

For $x \neq 0$, since f is the quotient of two entire functions and the denominator is different from zero, we have that f is analytic at every real $x \neq 0$. It is well known that there is a neighborhood of zero such that f is represented by a power series in x. In fact, the coefficients B_n in the power series representing f ($f(x) = \sum_{n=0}^{\infty} B_n x^n/n!$) are simply the Bernoulli numbers. The B_n ($= f^{(n)}(0)$) have properties:

$$B_0 = 1; \; B_1 = -\tfrac{1}{2}; \; B_2 = \tfrac{1}{6}; \sum_{K=0}^{n-1} \binom{n}{K} B_K = 0 \text{ if } n = 2, 3, \ldots.$$

Also

$$B_{2n+1} = 0 \text{ if } n = 1, 2, 3, 4, \ldots.$$

A direct proof that f is analytic at zero follows from considering $g(x) = \left[-1 + \exp(x)\right]/x$ which is represented by the power series $1 + \sum_{n=1}^{\infty} x^n/(n+1)!$ that is absolutely convergent for every real x. The proof is established by using the following theorem: <u>Theorem</u>. If $p(z) = \sum_{n=0}^{\infty} p_n z^n$ for $z \in N(0;h)$ (neighborhood about zero of radius h) and if $p(0) \neq 0$, then there exists a neighborhood $N(0;\delta)$ in which the reciprocal of p has the power series expansion of the form $(1/p(z)) = \sum_{n=0}^{\infty} q_n z^n$. Furthermore, $q_o = (1/p_o)$. (In our case $p = g$, $(1/p) = f$.) Thus f is analytic at every real number x. If we now define

$$g_1(v) = \frac{(v + 10)}{10}$$

and

$$g_2(v) = \frac{(v + 25)}{10},$$

then since g_1 and g_2 are analytic at every real v, it follows that the compositions

$$\hat{\alpha}_n = f \circ g_1 \text{ and } \alpha_m = f \circ g_2$$

are analytic at every real v and therefore

$$\alpha_n = \frac{1}{10}\hat{\alpha}_n$$

is analytic at every real v.

Since $1 + \exp\left[(v + 30)/10\right]$ is analytic at every real v and is never zero, the reciprocal β_h is analytic at every real v. Finally since exponential functions are analytic at every real v, we have that β_n, β_m, and α_h are analytic at every real v. This completes the proof.

It now follows immediately that

$$H_2(v,n,m,h) = \alpha_n(v)(1 - n) - \beta_n(v)n$$
$$H_3(v,n,m,h) = \alpha_m(v)(1 - m) - \beta_m(v)m$$
$$H_4(v,n,m,h) = \alpha_h(v)(1 - h) - \beta_h(v)h$$

are entire functions of the four variables v, n, m, and h; i.e., they are analytic functions of the four real variables v, n, m, and h at every point of four dimensional space.

We next show that the numerator and denominator of H_1 are entire functions of v, n, m, and h. Let

$$K(v,n) = \bar{g}_K\left[\left(\frac{2}{a}\right)Rn^4 + \left(\frac{1}{\theta^2 C}\right)\left(4n^3\frac{dn}{dt}\right)\right] \tag{3.1}$$

and

$$Na(v,m,h) = \bar{g}_{Na}\left[\left(\frac{2}{a}\right)Rm^3h + \left(\frac{1}{\theta^2 C}\right)\left(3m^2h\frac{dm}{dt} + m^3\frac{dh}{dt}\right)\right]. \tag{3.2}$$

Since $dn/dt = H_2(v,n,m,h)$, $dm/dt = H_3(v,n,m,h)$, and $dh/dt = H_4(v,n,m,h)$; it is clear that K and Na are entire functions in their variables and it follows immediately that the numerator of H_1

$$-[K(v,n)(v - 12) + Na(v,m,h)(v + 115) + \bar{g}_\ell(2/a)R(v + 10.5989) + (2/a)RI_o] \tag{3.3}$$

is entire. Furthermore the denominator

$$(2/a)RC + (1/\theta^2 C)(\bar{g}_K n^4 + \bar{g}_{Na} m^3 h + \bar{g}_\ell) \tag{3.4}$$

of H_1, being a polynomial in n, m, and h is an entire function of n, m, and h and hence of v, n, m, and h. Therefore H_1 will be analytic in any region in which the denominator (3.4) is not zero.

Proposition 3.2. *Let E be any region (open connected set) in (v,n,m,h) space such that $mh \geq 0$. Then the denominator (3.4) of H_1 is greater than zero.*

Proof. All terms in the expression are nonnegative and $(2/a)RC > 0$.

Remark 1.

$$\begin{aligned}(2/a)RC + (1/\theta^2 C)\bar{g}_\ell &= (2/a)R(C + \bar{g}_\ell/\hat{K}) \\ &> 2974.7899(.001 + .0003/4.5108406) \\ &> 2974.7899(.0010665064) \\ &> 3.17263246\ .\end{aligned}$$ [2]

[2] In this paper strict inequalities are used in remarks and proofs involving computations. The inequalities are valid because they refer to truncation of real numbers. Usual usage would require an equality sign because the numbers are equal to the number of digits quoted.

Therefore the denominator (3.4) > 3.17263246 for all v, n, m, and h such that $mh \geqq 0$.

Remark 2. In any region where

$$n > n(0) = \frac{\alpha_n(0)}{\alpha_n(0) + \beta_n(0)}$$

and

$$mh \geqq 0,$$

we have that (3.4) is greater than $(2/a)R\delta$ where $\delta = .0011477816$.

Proof.

$$\left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)(\bar{g}_K n^4 + \bar{g}_{Na} m^3 h + \bar{g}_\ell) \geqq \left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)(\bar{g}_K n^4 + \bar{g}_\ell)$$

$$> \left(\frac{2}{a}\right)R\left[C + \left(\frac{1}{\hat{K}}\right)(\bar{g}_K n^4(0) + \bar{g}_\ell)\right]$$

$$> \left(\frac{2}{a}\right)R\left[.001 + \frac{(.036)(.010184565) + .0003}{4.5108406}\right]$$

$$> \left(\frac{2}{a}\right)R\left[.001 + \frac{(.00036664434 + .0003)}{4.5108406}\right]$$

$$= \left(\frac{2}{a}\right)R(.00114778716\ldots)$$

$$> \left(\frac{2}{a}\right)R\delta.$$

Remark 3. In Remark 2 above we used the inequality

$$n^4(0) > .010184565.$$

In order to justify this inequality and also to become familiar with the values of n(0), m(0), and h(0) we will here give upper and lower bounds for each of the real numbers n(0), m(0), and h(0). Recall from (2.10) that

$$J(0) = \frac{\alpha_J(0)}{\alpha_J(0) + \beta_J(0)}$$

where J = n, m, or h. Letting J be n, m, and h successively, and performing elementary operations, we have

$$n(0) = \frac{4}{-1 + 5\exp(1)},$$

$$m(0) = \frac{5}{-3 + 8\exp(2.5)},$$

and

$$h(0) = \frac{7[1 + \exp(3)]}{7[1 + \exp(3)] + 100}.$$

Using [10] we obtain the values

$$.3176769141 < n(0) < .31767691411,^3$$

$$.0529324850 < m(0) < .0529324852,$$

and

$$.5961207534 < h(0) < .596120754.$$

The inequality $n^*(0) > .010184565$ follows.

2. An Existence and Uniqueness Theorem

Let $I_o > 0$ be given. Let $\omega = \min\{-115, v_\ell - (I_o/\bar{g}_\ell)\}$. Let $D = \{(v,n,m,h) \mid \omega < v < 12, 0 < n < 1, 0 < m < 1, 0 < h < 1\}$ and $D_t = \{(t,v,n,m,h) \mid t \text{ arbitrary}, (v,n,m,h) \in D\}$.

Theorem 3.3. *Let* $x_o \in D$, *let* $H = (H_1,H_2,H_3,H_4)$, *and let* $x = (v,n,m,h)$. *Then the system*

$$\frac{dx}{dt} = H(x)$$

---

[3] See footnote 2.

has a unique solution x(t) satisfying the initial condition $x(t_0) = x_0$ and defined on an interval $t_0 \leq t < b$ ($b \leq \infty$) such that, if $b < \infty$, then x(t) approaches the boundary of D as t approaches b.

Proof. We show that the system satisfies the hypotheses of Theorem 10 [11, p. 122]. This theorem states: "Let X(x,t) be defined and of class C^1 in an open region R of (x,t) space. For any point (c,a) in the region R, the DE(2) [differential system dx/dt = X(x,t)] has a unique solution x(t) satisfying x(**a**) = **c** and defined for an interval $\mathbf{a} \leq t < b$ ($b \leq \infty$) such that, if $b < \infty$, either x(t) approaches the boundary of the region or x(t) is unbounded as $t \to b$." Such a time interval is called a right maximal interval of existence. First of all, D_t is open. In D, by Proposition 3.2, the denominator of H_1 is positive. Therefore H_1 is analytic in D. Hence H is analytic in D_t and is thus certainly defined and of class C^1 in D_t. Therefore by the theorem, dx/dt = H(x) has a unique solution $x(t) = (v(t),n(t),m(t),h(t))$ satisfying $x(t_0) = x_0$ and defined on a right maximal interval of existence $[t_0,b)$. Since D is bounded, x(t) cannot be unbounded as $t \to b$ if $b < \infty$. Hence $b = \infty$ or x approaches the boundary of D as $t \to b$.

Remark 1. Since $(v(0),n(0),m(0),h(0)) \in D$ we have the existence and uniqueness of system (2.13) from time $t_0 = 0$ up until the time that the solution approaches the boundary of D.

Remark 2. If we consider $\bar{D}$, the closure of **D**, then we have that the right maximal interval of existence is either $[t_o,\infty)$ or is $[t_o,b]$, if $b < \infty$, where $x(b) \in \partial D$ (the boundary of D). Therefore when we prove that $\omega < v(t) < 12$, $0 < n(t) < 1$, $0 < m(t) < 1$, and $0 < h(t) < 1$ for any time interval in which the solution exists, we will at the same time prove that a unique solution of (2.13) exists for $t \in [0,\infty)$.

Remark 3. Since H_1, H_2, H_3, and H_4 are analytic functions, the solution $(v(t),n(t),m(t),h(t))$ is composed of analytic functions according to the theory of Ordinary Differential Equations.

Remark 4. From the theory of Ordinary Differential Equations (see [12, p. 15]) it follows that since $(0,n(0),m(0),h(0))$ is in D_t (which is open) then the solution $(v(t),n(t),m(t),h(t))$ of (2.13) may be continued to the left of the initial value $(0,n(0),m(0),h(0))$. Therefore the differential equations (2.13) are satisfied at the initial value.

3. Properties of α_n, α_m, α_h, β_n, β_m, and β_h

In later propositions, lemmas, and theorems we shall need the following properties of α_J and β_J, where $J = n$, m, or h.

Property 3.a. $\alpha_J > 0$, $\beta_J > 0$ where $J = n$, m, or h.

Proof. β_n, β_m, and α_h are positive since they are exponential functions. Consider

$$f(x) = \begin{cases} \dfrac{x}{-1 + \exp(x)} & \text{if } x \neq 0 \\ 1 & \text{if } x = 0. \end{cases}$$

If $x \neq 0$, then $x > 0$ implies $\exp(x) > 1$ which implies $-1 + \exp(x) > 0$ and therefore $f(x) > 0$. If $x = 0$, then $f(x) = 1 > 0$. Therefore $f(x) > 0$ for all x. It follows that α_n and α_m are both greater than zero for all v. Since $\exp[(v + 30)/10] > 0$, it follows that

$$\beta_h = \left[1 + \exp\left(\frac{v + 30}{10}\right)\right]^{-1} > 0.$$

Property 3.b. $\alpha_J + \beta_J > 0$ where J = n, m, or h.

Proof. The proof follows from Property 3.a.

Property 3.c. α_n, α_m, and β_h are strictly decreasing with respect to v. β_n, β_m, and α_h are strictly increasing with respect to v.

Proof. β_n, β_m, and α_h are exponential functions of v and are, of course, strictly increasing with respect to v. Consider

$$f(x) = \begin{cases} \dfrac{x}{-1 + \exp(x)} & \text{if } x \neq 0 \\ 1 & \text{if } x = 0. \end{cases}$$

If $x \neq 0$, then

$$f'(x) = \frac{-1 + (1 - x)\exp(x)}{[-1 + \exp(x)]^2}.$$

We claim that $f'(x) < 0$. Let

$$g(x) = -1 + (1 - x)\exp(x).$$

Then

$$g'(x) = -x\exp(x).$$

Therefore, g is decreasing if $x > 0$ and is increasing if $x < 0$ which implies that g has a maximum at $x = 0$. Now $g(0) = 0$. Therefore $g(x) < 0$ for all $x \neq 0$. This implies $f'(x) = g(x)/[-1 + \exp(x)]^2 < 0$ for all $x \neq 0$. Now f' exists and is continuous everywhere. Therefore

$$f'(0) = \lim_{x \to 0} \frac{-1 + (1 - x)\exp(x)}{[-1 + \exp(x)]^2}$$

$$= \lim_{x \to 0} \frac{-x}{2[-1 + \exp(x)]}$$

$$= -\frac{1}{2}$$

by L'Hospital's rule, and we have $f'(x) < 0$ for all x.

Now let

$$x = p(v) = \frac{(v + 10)}{10}.$$

Then

$$\alpha_n = \frac{1}{10}(f \circ p)$$

which implies

$$\alpha_n'(v) = \frac{1}{10}f'(p(v))p'(v) = \frac{1}{100}f'(x) < 0.$$

Let

$$x = q(v) = \frac{(v + 25)}{10}.$$

Then

$$\alpha_m = f \bullet q$$

which implies

$$\alpha_m'(v) = f'(q(v))q'(v) = \frac{1}{10}f'(x) < 0.$$

Therefore α_n and α_m are strictly decreasing with respect to v. We now look at β_h.

Consider

$$f(x) = \frac{1}{1 + \exp(x)}$$

so that

$$f'(x) = \frac{-\exp(x)}{[1 + \exp(x)]^2} < 0.$$

Let

$$x = s(v) = \frac{(v + 30)}{10}.$$

Then

$$\beta_h = f \circ s$$

which implies

$$\beta_h'(v) = f'(s(v))s'(v) = \frac{1}{10}f'(x) < 0.$$

Therefore β_h is strictly decreasing with respect to v.

<u>Property</u> 3.d. α_n, α_m, α_h, β_n, <u>and</u> β_m <u>are convex (concave upward) functions of</u> v. β_h <u>is convex if</u> $v > -30$, <u>concave if</u> $v < -30$, <u>and has a point of inflection at</u> $v = -30$.

<u>Proof</u>. β_n, β_m, and α_h are exponential functions and hence are convex. For α_n and α_m, consider

$$f(x) = \begin{cases} \dfrac{x}{-1 + \exp(x)} & \text{if } x \neq 0 \\ 1 & \text{if } x = 0. \end{cases}$$

Then

$$f''(x) = \begin{cases} \dfrac{\exp(x)[(x + 2) + (x - 2)\exp(x)]}{[-1 + \exp(x)]^3} & \text{if } x \neq 0 \\ \dfrac{1}{6} & \text{if } x = 0. \end{cases}$$

We claim that $f''(x) > 0$ for all x. Let

$$g(x) = (x + 2) + (x - 2)\exp(x)$$

and let

$$k(x) = (x - 1)\exp(x).$$

Then

$$k'(x) = x \exp(x)$$

which implies that k has a minimum at zero. Now $k(0) = -1$ and therefore $k(x) \geqq -1$ for all x. This implies that

$$g'(x) = 1 + (x - 1)\exp(x) = k(x) + 1 \geqq 0$$

for all x. Also, $g'(x) = 0$ if and only if $x = 0$. So g has a point of inflection at $x = 0$. Since $g(0) = 0$, we have $x > 0$ implies $g(x) > 0$, and $x < 0$ implies $g(x) < 0$. Therefore,

$$f''(x) = \frac{g(x)\exp(x)}{[-1 + \exp(x)]^3}$$

is greater than zero if $x \neq 0$. Let

$$x = p(v) = \frac{(v + 10)}{10}.$$

Then

$$\alpha_n = \frac{1}{10}(f \circ p)$$

which implies

$$\alpha_n''(v) = \frac{1}{100}f''(x)p'(v) = \frac{1}{1000}f''(x) > 0.$$

If

$$x = q(v) = \frac{v + 25}{10},$$

then

$$\alpha_m''(v) = \frac{1}{10}f''(x)q'(v) = \frac{1}{100}f''(x) > 0.$$

Therefore, α_n and α_m are convex functions with respect to v. For β_h, consider

$$f(x) = \left[1 + \exp(x)\right]^{-1}.$$

Then

$$f''(x) = \frac{-\exp(x)\left[1 - \exp(x)\right]}{\left[1 + \exp(x)\right]},$$

Therefore, the sign of $f''(x)$ is the same as the sign of x. Let

$$x = s(v) = \frac{v + 30}{10}.$$

Then

$$\beta_h''(v) = \frac{1}{100}f''(x)$$

which implies that the sign of β_h'' is the same as the sign of x. Hence β_h is convex if $v > -30$, is concave if $v < -30$, and has a point of inflection if $v = -30$.

<u>Property</u> 3.e. <u>Let</u> $S = [-115, 12]$. <u>Then</u>

$$\max_{v \in S} (\alpha_m(v) + \beta_m(v)) = \alpha_m(-115) + \beta_m(-115)$$

<u>Proof</u>. By Property 3.d., $\alpha_m''(v) > 0$ and $\beta_m''(v) > 0$ for all v which implies that

$$(\alpha_m + \beta_m)''(v) = \alpha_m''(v) + \beta_m''(v) > 0.$$

Therefore $\alpha_m + \beta_m$ is a convex function of v which implies that if there is a $\hat{v}$ such that $(\alpha_m + \beta_m)'(\hat{v}) = 0$, then there is only one such $\hat{v}$ and it is a minimum for $\alpha_m + \beta_m$. Now

$$(\alpha_m + \beta_m)'(-25) = -\left(\frac{1}{20}\right) + 4\exp\left(-\frac{25}{18}\right) > -.05 + \left(\frac{2}{9}\right)\exp(-1.3889)$$

$$> -.05 + \left(\frac{2}{9}\right)(.249) > -.05 + .055 > 0;^{4}$$

$$(\alpha_m + \beta_m)'(-30) < \frac{(.1)[(1.5)(.60653066) - 1]}{(.60653066 - 1)^2} + \left(\frac{4}{18}\right)(.1690264614)$$

$$= \frac{(.1)(.90979599 - 1)}{(.30346934)^2} + \left(\frac{1}{9}\right)(.3380529228)$$

$$= -\frac{.009020401}{.0920936403200356} + .03756143586667$$

$$< -\frac{.009020401}{.1} + .03756144$$

$$= -.09020401 + .03756144$$

$$< 0.$$

Therefore $(\alpha_m + \beta_m)'$ has a zero between -25 and -30 which implies that

$$\max_{v \in S} (\alpha_m + \beta_m)(v) = \max\left\{(\alpha_m + \beta_m)(-115), (\alpha_m + \beta_m)(12)\right\}.$$

Now

$$(\alpha_m + \beta_m)(-115) > 9.0011107 + .0067183972 = 9.0078291342;$$

$$(\alpha_m + \beta_m)(12) < .0937961 + 7.7911960 = 7.8849921.$$

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[4] See footnote 2.

Therefore

$$\max_{v \in S} (\alpha_m + \beta_m)(v) = \alpha_m(-115) + \beta_m(-115)$$
$$< 9.0011108271 + .0067210854$$
$$= 9.0078319125$$
$$< 9.0078320.$$

Property 3.f. $(\alpha_h + \beta_h)(v) < 1.07$ for all $v < 0$.

Proof. Since $0 < \exp[(v + 30)/10]$ implies $1 > (1 + \exp[(v + 30)/10])^{-1}$, we have $\beta_h(v) < 1$. Since $v < 0$ implies $\exp(v/20) < 1$ and therefore $.07 \exp(v/20) < .07$, we have $\alpha_h(v) < .07$. Therefore $\alpha_h(v) + \beta_h(v) < 1.07$ for all $v < 0$.

4. First Consequences of the Existence and Uniqueness Theorem

Now that we know that a solution to the initial value problem (2.13) exists for the region D in at least some neighborhood of $t_o = 0$, we can prove four propositions that give us a first glimpse at the behavior of the solutions.

Let $(v(t),n(t),m(t),h(t))$ be the solution to the initial value problem (2.13) where $t_o = 0$, $v(t_o) = v(0) = 0$, and $J(t_o) = \alpha_J(0)/[\alpha_J(0) + \beta_J(0)]$ for $J = n$, m, or h. Then we have:

Proposition 3.4. $\frac{dn}{dt}(0) = \frac{dm}{dt}(0) = \frac{dh}{dt}(0) = 0$;

Proposition 3.5. If $I_o = 0$, *then* $\frac{dv}{dt}(0) = 0$, *while if* $I_o > 0$, *then* $\frac{dv}{dt}(0) < 0$;

Proposition 3.6. At $t = 0$, *the solutions* n *and* m *are concave upward while* h *is concave downward for* $I_o > 0$.

Proof of Proposition 3.4. Let $J = n, m$, or h. The differential equations (2.8) are satisfied at $t_o = 0$ according to Remark 4 following Theorem 3.3. Therefore

$$\frac{dJ}{dt}(0) = \alpha_J(v(0)) - \left[\alpha_J(v(0)) + \beta_J(v(0))\right]J(0).$$

By (2.10),

$$\begin{aligned}\frac{dJ}{dt}(0) &= \alpha_J(0) - \left\{\left[\alpha_J(0) + \beta_J(0)\right] \frac{\alpha_J(0)}{\alpha_J(0) + \beta_J(0)}\right\} \\ &= \alpha_J(0) - \alpha_J(0) \\ &= 0.\end{aligned}$$

Proof of Proposition 3.5. Let $I_o \geq 0$. Then the differential equation $dv/dt = H_1(v,n,m,h)$ is satisfied at $t_o = 0$ according to Remark 4 following Theorem 3.3. Therefore, using (3.1) and (3.2), we have

$$\begin{aligned}\frac{dv}{dt}(0) = -&\left\{\left[\left(\frac{2}{a}\right)RC + \frac{1}{\theta^2 C}\left(\bar{g}_K n^4(0) + \bar{g}_{Na} m^3(0)h(0) + \bar{g}_\ell\right)\right]^{-1}\right\} \\ &\cdot \Big\{K(v(0),n(0))(v(0) - v_K) \\ &\quad + Na(v(0),m(0),h(0))(v(0) - v_{Na}) \\ &\quad + \bar{g}_\ell\left(\frac{2}{a}\right)R(v(0) - v_\ell) + \left(\frac{2}{a}\right)RI_o\Big\}.\end{aligned}$$

By Proposition 3.4

$$K(v(0),n(0)) = \bar{g}_K\left(\frac{2}{a}\right)Rn^4(0)$$

and

$$Na(v(0),m(0),h(0)) = \bar{g}_{Na}\left(\frac{2}{a}\right)Rm^3(0)h(0).$$

Therefore, by (2.10)

$$\frac{dv}{dt}(0) = -\left\{\left[\left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)(\bar{g}_K n^4(0) + \bar{g}_{Na} m^3(0)h(0) + \bar{g}_\ell)\right]^{-1}\right\}$$
$$\cdot \left(\frac{2}{a}\right)R\Big[\bar{g}_K n^4(0)(-v_K) + \bar{g}_{Na} m^3(0)h(0)(-v_{Na})$$
$$+ \bar{g}_\ell(-v_\ell) + I_o\Big].$$

Now recall from II.1. that v_ℓ was chosen so that

$$\bar{g}_K n^4(0)(-v_K) + \bar{g}_{Na} m^3(0)h(0)(-v_{Na}) + \bar{g}_\ell(-v_\ell) = 0.$$

This implies that

$$\frac{dv}{dt}(0) = -\left\{\left[\left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)(\bar{g}_K n^4(0) + \bar{g}_{Na} m^3(0)h(0) + \bar{g}_\ell)\right]^{-1}\right\}$$
$$\cdot \left(\frac{2}{a}\right)RI_o.$$

Therefore, if $I_o = 0$, $\frac{dv}{dt}(0) = 0$. If $I_o > 0$, since Proposition 3.2 implies that the denominator is positive, we have $\frac{dv}{dt}(0) < 0$.

<u>Proof of Proposition</u> 3.6. Let $J = n$, m, or h. Let $I_o > 0$. Then

$$\frac{d^2 J}{dt^2} = \left[\alpha_J'(v)(1 - J) - \beta_J'(v)J\right]\frac{dv}{dt} - \left[\alpha_J(v) + \beta_J(v)\right]\frac{dJ}{dt}.$$

Proposition 3.4 and (2.10) imply that

$$\frac{d^2 J}{dt^2}(0) = \left[\alpha_J'(0)(1 - J(0)) - \beta_J'(0)J(0)\right]\frac{dv}{dt}(0)$$
$$- \left[\alpha_J(0) + \beta_J(0)\right]\frac{dJ}{dt}(0)$$
$$= \left[\alpha_J'(0)(1 - J(0)) - \beta_J'(0)J(0)\right]\frac{dv}{dt}(0).$$

Now for $J = n$ or m, Property 3.c implies that $\alpha_J'(v) < 0$ and $\beta_J'(v) > 0$ for all v; for $J = h$, Property 3.c implies that $\alpha_J'(v) > 0$ and $\beta_J'(v) < 0$ for all v. From Remark 3 following Proposition 3.2 we see that $0 < J(0) < 1$ for $J = n, m$, or h which implies $0 < 1 - J(0) < 1$. Therefore for $J = n$ or m,

$$\alpha_J'(0)(1 - J(0)) - \beta_J'(0)J(0) < 0$$

and for $J = h$,

$$\alpha_J'(0)(1 - J(0)) - \beta_J'(0)J(0) > 0.$$

Since $I_o > 0$, Proposition 3.5 says that $\frac{dv}{dt}(0) < 0$. Combining these results we have that for $J = n$ or m, $\frac{d^2J}{dt^2}(0) > 0$; for $J = h$, $\frac{d^2J}{dt^2}(0) < 0$. This result gives us the conclusion.

Remark 1. These three propositions say that for $I_o > 0$ the solution $v(t)$ starts out strictly decreasing (from the initial point $t_o = 0$), and hence is negative for some positive time interval $(0,t_1)$; the solutions $n(t)$ and $m(t)$ are strictly increasing for some time intervals $(0,t_2)$ and $(0,t_3)$ respectively; and $h(t)$ is strictly decreasing for some time interval $(0,t_4)$ where t_1, t_2, t_3, and t_4 are greater than zero. Also $n(t) > n(0)$, $m(t) > m(0)$, and $h(t) < h(0)$ for some time interval $(0,t_5)$ where $t_5 > 0$.

Remark 2. It could also be shown that there exists a $t_6 > 0$ such that m^3h is strictly increasing for all $t \in (0,t_6)$, and that $(m^3h)'(0) = 0$.

Remark 3. If we call a point $x = (v,n,m,h)$ such that

$$H_k(v,n,m,h) = 0 \qquad \text{for } k = 1, 2, 3, 4$$

a stationary point[5] of the system

$$\frac{dx}{dt} = H(x)$$

where $H = (H_1,H_2,H_3,H_4)$, then Proposition 3.4 and Proposition 3.5 show that $(0,n(0),m(0),h(0))$ is a stationary point for the system (2.13) if and only if $I_o = 0$. Furthermore, for $I_o = 0$, the unique solution to system (2.13) is, for any time t,

$$v(t) = 0$$
$$n(t) = n(0)$$
$$m(t) = m(0)$$
$$h(t) = h(0) \ .$$

Proposition 3.7. Let $I_o > 0$. Let $(v(t),n(t),m(t),h(t))$ be the solution of (2.13) in $\bar{D}$, and let $[0,b]$ be the right maximal interval of existence of the solution. Then the zeros of the functions v', n', m', and h' are isolated in $[0,b]$.

Proof. According to Remark 3 following Proposition 3.3, v, n, m, and h are analytic functions of t. Therefore the first derivatives v', n', m', and h' are analytic functions of t in $[0,b]$. Now if a function f is analytic (real or complex) on an open region S, if $f(z_o) = 0$ for

[5] The terms singular point and critical point are also used to describe such a value.

some z_o ε S, and if f is not identically zero on any neighborhood of z_o, then there is a deleted neighborhood $N'(z_o) \subset S$ on which f does not assume the value zero. Furthermore, a function f analytic on S cannot be zero on any non-empty open subset of S without being identically zero throughout S. By hypothesis $I_o > 0$. Therefore, by Proposition 3.5 and Proposition 3.6, there is a neighborhood of zero in which the functions v, n, m, and h are non-constant which implies that v', n', m', and h' cannot be identically zero throughout (0,b). Since each is analytic on (0,b), it follows that none of v', n', m', or h' can be zero on any non-empty open subset of (0,b). So for any time t_1 such that any one of v', n', m', or h' is zero, we have that there exists a deleted neighborhood $N'(t_1)$ in which that function is different from zero. Thus the zeros of v', n', m', and h' are isolated on (0,b) and therefore on [0,b].

Remark 1. Proposition 3.7 says that none of the functions v, n, m, or h can become constant on any open subinterval of [0,b]. Therefore any time t_1 ε [0,b] that v', n', m', or h' is zero can be at most a relative maximum, relative minimum, or stationary inflection point of v, n, m, or h respectively.

IV. BOUNDEDNESS

We shall prove here the boundedness of the solutions $(v(t),n(t),m(t),h(t))$ of (2.13). After a preliminary section in which three new functions are introduced, it will be shown that the solutions n, m, and h are bounded. We shall then show that the solution v is bounded for any given fixed $I_o > 0$. A theorem numbered 4.11 will prove lower boundedness and a theorem numbered 4.13 will prove upper boundedness. These results are significant since they prove, among other things, that the initial value problem (2.13) cannot have the unbounded difficulties (mentioned in the Introduction) that the solutions of the original Hodgkin-Huxley equations appeared to have. Theorem 4.13 will provide an upper bound of twelve for v which is the best possible upper bound that the method of proof used in the theorem can provide. The numerical evidence in [7] also indicates that twelve is a good upper bound for v. However, such is not the case for the lower bound given by Theorem 4.11 for large values of I_o. The numerical evidence indicates that -115 mv is a lower bound for v for all $I_o \leqq 500$ $\mu A/cm^2$ (The case run for $I_o = 600$ $\mu A/cm^2$ yielded a lower bound of v = -116.5 mv. No cases were run between $I_o = 500$ $\mu A/cm^2$ and $I_o = 600$ $\mu A/cm^2$.). Even a value for I_o of 4120.8 $\mu A/cm^2$ produced numerically a lower bound for v of -167 mv. However, the lower bound for

$I_0 = 500\ \mu A/cm^2$ given by Theorem 4.11 is approximately $v = -1680$ mv, so that the usefulness of Theorem 4.11 for large I_0 ($I_0 \geqq 80\ \mu A/cm^2$) will be in showing existence of a lower bound, not in finding the value of a lower bound; such a value could be a major consideration for cells that have a plateau type behavior, but Theorem 4.11 will not provide it.

Since for the threshold phenomenon and the phenomena of repetitive firings the relevant values of I_0 indicated by the numerical evidence [7, Part II] are between $0\ \mu A/cm^2$ and $7\ \mu A/cm^2$, we present additional theorems which provide a lower bound for v of -115 mv for all such I_0. Corollary 4.12, using the method of proof of Theorem 4.11 establishes a lower bound for v of -115 mv for $0 \leqq I_0 \leqq 31\ \mu A/cm^2$ whereas Theorem 4.25 using a completely different method, will establish a lower bound for v of -115 mv for $0 \leqq I_0 \leqq 72 \mu A/cm^2$ in the first time interval in which the voltage v is negative. Actually, Theorem 4.25 yields a curve u(t) which passes through the initial value $v(0) = 0$, which is bounded below by -115, and which has the property that $u(t) \leqq v(t)$ for all times t in the first time interval in which $v < 0$.

The following notations consistent with those used in II and III, will be used throughout IV: for I_0 given, let $\omega = \min\{-115,\ v_\ell - (I_0/\bar{g}_\ell)\}$; let $D = \{(v,n,m,h) \mid \omega < v < 12,\ 0 < J < 1 \text{ where } J = n, m, \text{ or } h\}$; let $\bar{D}$ be the closure of D;

and let $[0,b]$ be the right maximal interval of existence of solutions $(v(t),n(t),m(t),h(t))$ of (2.13) corresponding to $\overline{D}$. Finally, let d denote the first positive time that the solution v equals either -115 or 0 unless v is neither -115 or 0 for any positive time; let $d = \infty$ in that case.

1. The Functions ν, μ, and η

We now introduce the functions ν, μ, and η which will play a primary role in the study of the solutions $(v(t),n(t),m(t),h(t))$ of (2.13). These three functions are connected with the solution v(t) in such a way that the curve $(v(t),\nu(t),\mu(t),\eta(t))$ determines to a large extent the behavior of the solution $(v(t),n(t),m(t),h(t))$. In this section we state some of the properties of these functions.

Definition. Let $(v(t),n(t),m(t),h(t))$ *be the solution of* (2.13) *in* $[0,b]$. *Define* $\nu : [0,b] \longrightarrow R^1$, $\mu : [0,b] \longrightarrow R^1$, *and* $\eta : [0,b] \longrightarrow R^1$ *by*

$$\nu = \alpha_n \circ v / [\alpha_n \circ v + \beta_n \circ v],$$

$$\mu = \alpha_m \circ v / [\alpha_m \circ v + \beta_m \circ v],$$

and

$$\eta = \alpha_h \circ v / [\alpha_h \circ v + \beta_h \circ v].$$

The domain of ν, μ, and η equals the domain of v equals $[0,b]$ since by Property 3.b the denominators of the functions

ν, μ, and η are greater than zero for all v.

Note. If v were a constant function, then ν, μ, and η would be the same as n_∞, m_∞, and h_∞ respectively, which were used by Hodgkin and Huxley in [5].

Proposition 4.1. Let $t \in [0,b]$. *Let* $\rho = \nu, \mu$, *or* η *and let* $J = n, m$, *or* h *in the same order*; i.e., $\rho = \nu$ *if and only if* $J = n$, $\rho = \mu$ *if and only if* $J = m$, *and* $\rho = \eta$ *if and only if* $J = h$. *Then*

(i) $\frac{dJ}{dt}(t) > 0$ *if and only if* $\rho(t) > J(t)$;

(ii) $\frac{dJ}{dt}(t) = 0$ *if and only if* $\rho(t) = J(t)$;

(iii) $\frac{dJ}{dt}(t) < 0$ *if and only if* $\rho(t) < J(t)$.

Proof. By definition of dJ/dt,

$$\frac{dJ}{dt}(t) > 0$$

if and only if

$$\alpha_J(v(t))[1 - J(t)] - \beta_J(v(t))J(t) > 0$$

if and only if

$$\alpha_J(v(t)) - [\alpha_J(v(t)) + \beta_J(v(t))]J(t) > 0$$

if and only if

$$\left(\alpha_J(v(t))/[\alpha_J(v(t)) + \beta_J(v(t))]\right) > J(t)$$

by Property 3.b. Therefore by definition of ρ

$$\frac{dJ}{dt}(t) > 0 \text{ if and only if } \rho(t) > J(t).$$

Thus (i) is proved; (ii) and (iii) can be proved similarly by using the appropriate signs.

Proposition 4.2. Let J = n, m, or h. Define the function $f_J: R^1 \longrightarrow R^1$ by

$$f_J(v) = \alpha_J(v)/[\alpha_J(v) + \beta_J(v)].$$

Then $f_J'(v) < 0$ for all v if J = n or m; if J = h, then $f_J'(v) > 0$ for all v.

Proof. f_J is an entire function of v by Proposition 3.1 and Property 3.b. Therefore f_J' exists and is continuous.

$$f_J' = \frac{(\alpha_J + \beta_J)\alpha_J' - \alpha_J(\alpha_J' + \beta_J')}{(\alpha_J + \beta_J)^2} = \frac{\beta_J\alpha_J' - \alpha_J\beta_J'}{(\alpha_J + \beta_J)^2} .$$

Let J = n or m. Then by Property 3.a and Property 3.c, $\beta_J > 0$ and $\alpha_J' < 0$. Also $\alpha_J > 0$ and $\beta_J' > 0$. These results imply $\beta_J\alpha_J' < 0$ and $\alpha_J\beta_J' > 0$. Hence $\beta_J\alpha_J' - \alpha_J\beta_J' < 0$.
Let J = h. Then by Property 3.a and Property 3.c, $\beta_h > 0$, $\alpha_h' > 0$, $\alpha_h > 0$, and $\beta_h' < 0$. Therefore $\beta_h\alpha_h' > 0$ and $\alpha_h\beta_h' < 0$ which imply $\beta_h\alpha_h' - \alpha_h\beta_h' > 0$. Thus, for J = n or m, $f_J'(v) < 0$ for all v; for J = h, $f_J'(v) > 0$ for all v.

Proposition 4.3.

(i) v is increasing if and only if ν is decreasing if and only if μ is decreasing if and only if η is increasing;

(ii) v is decreasing if and only if ν is increasing if and only if μ is increasing if and only if η is decreasing;

(iii) v _is at a relative maximum if and only if_ ν _is at a relative minimum if and only if_ μ _is at a relative minimum if and only if_ η _is at a relative maximum;_

(iv) v _is at a relative minimum if and only if_ ν _is at a relative maximum if and only if_ μ _is at a relative maximum if and only if_ η _is at a relative minimum;_

(v) _None of the four functions_ v, ν, μ, _or_ η _can have a stationary inflection point at any time_ t^* _without the other three having a stationary inflection point at_ t^*.

Proof. We have $\nu = f_n \circ v$, $\mu = f_m \circ v$, and $\eta = f_h \circ v$. Therefore

$$\nu'(t) = f_n'(v(t))\frac{dv}{dt}(t),$$

$$\mu'(t) = f_m'(v(t))\frac{dv}{dt}(t),$$

and

$$\eta'(t) = f_h'(v(t))\frac{dv}{dt}(t).$$

(i), (ii), (iii), and (iv) now follow from Proposition 4.2. (v) follows from

$$\nu''(t) = f_n''(v(t))\left(\frac{dv}{dt}(t)\right)^2 + f_n'(v(t))\frac{d^2 v}{dt^2}(t),$$

$$\mu''(t) = f_m''(v(t))\left(\frac{dv}{dt}(t)\right)^2 + f_m'(v(t))\frac{d^2 v}{dt^2}(t),$$

$$\eta''(t) = f_h''(v(t))\left(\frac{dv}{dt}(t)\right)^2 + f_h'(v(t))\frac{d^2 v}{dt^2}(t),$$

and (i), (ii), and (iii).

Remark. It can be seen from the proof that "strictly" may be inserted into the hypotheses if desired.

Proposition 4.4. *If* $t^* > 0$ *is such that* $v(t^*) < v(t)$ *for all* $t \in [0,t^*)$, *then for all* $t \in [0,t^*)$ *we have*

$$\nu(t^*) > \nu(t),$$

$$\mu(t^*) > \mu(t),$$

and

$$\eta(t^*) < \eta(t).$$

Proof. Let $t \in [0,t^*)$. Now $v(t^*) < v(t)$. Therefore, by Proposition 4.2, since f_n and f_m are strictly decreasing and f_h is strictly increasing, we have $f_n(v(t^*)) > f_n(v(t))$, $f_m(v(t^*)) > f_m(v(t))$, and $f_h(v(t^*)) < f_h(v(t))$. This implies $\nu(t^*) > \nu(t)$, $\mu(t^*) > \mu(t)$, and $\eta(t^*) < \eta(t)$.

Remark. Dual results (inequalities reversed) also hold by the same arguments. Also, if the inequalities are replaced by equations, the proposition holds.

Proposition 4.5. *Let* $t_1, t_2 \in [0,b]$ *such that* $v(t_1) < v(t_2)$. *Then*

$$\nu(t_1) > \nu(t_2),$$

$$\mu(t_1) > \mu(t_2),$$

and

$$\eta(t_1) < \eta(t_2).$$

Proof. The proof is the same as the proof of Proposition 4.4.

In order to illustrate the utility of ν, μ, and η we prove two simple propositions which concern the relationship between v and n, m, or h.

Proposition 4.6. *If n is nondecreasing (nonincreasing) in some interval $[t_1,t_2]$ and has a stationary point at $t_3 \varepsilon (t_1,t_2)$, then either v has a stationary inflection point at t_3 or a relative maximum (minimum) at t_3.*

Proof. If n is nondecreasing (nonincreasing) in $[t_1,t_2]$, then $\frac{dn}{dt}(t) \geq 0$ $(\frac{dn}{dt}(t) \leq 0)$ for all $t \varepsilon [t_1,t_2]$ which implies by Proposition 4.1 that $n(t) \leq \nu(t)$ $(n(t) \geq \nu(t))$ for all $t \varepsilon [t_1,t_2]$. If n has a stationary point at some $t_3 \varepsilon (t_1,t_2)$, then $n(t_3) = \nu(t_3)$ by Proposition 4.1. Also it follows that n has an inflection point at t_3. These results together imply that ν has either a relative minimum (maximum) at t_3 or a stationary inflection point at t_3. If ν has a stationary inflection point at t_3 then ν is nondecreasing (nonincreasing) at t_3. By Proposition 4.3 v therefore has either a relative maximum (minimum) at t_3 or a stationary inflection point at t_3.

Remark. The same type of results hold for m and h.

Proposition 4.7. *Let $[a_1,a_2]$ be any interval in which the function v is nonincreasing and for which* $\frac{dn}{dt}(a_1) \geq 0$, $\frac{dm}{dt}(a_1) \geq 0$, *and* $\frac{dh}{dt}(a_1) \leq 0$. *Then* $\frac{dn}{dt}(t) \geq 0$,

$\frac{dm}{dt}(t) \geq 0$, <u>and</u> $\frac{dh}{dt}(t) \leq 0$ <u>for all</u> $t \in [a_1,a_2]$.

Proof. We show $\frac{dm}{dt}(t) \geq 0$ for all $t \in [a_1,a_2]$. Now v is nonincreasing on $[a_1,a_2]$, so $\frac{dv}{dt}(t) \leq 0$ for all $t \in [a_1,a_2]$. This implies by Proposition 4.3 that $\frac{d\mu}{dt}(t) \geq 0$ for all $t \in [a_1,a_2]$. Now m is a continuous function and is nondecreasing at a_1. Therefore if we assume that $\frac{dm}{dt}(\hat{t}) < 0$ at some $\hat{t} \in (a_1,a_2]$, then there exists a $t' \in (a_1,\hat{t})$ such that $\frac{dm}{dt}(t') = 0$ where $m(t') > m(\hat{t})$. Now $\frac{d\mu}{dt}(t) \geq 0$ for all $t \in [a_1,a_2]$ implies $\mu(t') \leq \mu(\hat{t})$. But $\frac{dm}{dt}(t') = 0$ which implies $m(t') = \mu(t')$ (Proposition 4.1). Therefore $m(\hat{t}) < m(t') = \mu(t') \leq \mu(\hat{t})$ implying $\frac{dm}{dt}(\hat{t}) > 0$ (Proposition 4.1) which is a contradiction. Therefore $\frac{dm}{dt}(t) \geq 0$ for all $t \in [a_1,a_2]$. Similar results **hold** for n and h.

Remark. The dual result (inequalities reversed) also holds by the same arguments.

2. Boundedness of n, m, and h

The theorem and proof to be presented in this section are similar to the statement and proof of Lemma 1 in [8, p.157]. Since the system of differential equations here is different from that in [8], the proof is given.

Theorem 4.8. <u>Let</u> $(v(t),n(t),m(t),h(t))$ <u>denote the solution of</u> (2.13) <u>corresponding to</u> $\bar{D}$. <u>Then for all</u>

$t \in [0,b]$ <u>we</u> <u>have</u>

$$0 < n(t) < 1,$$
$$0 < m(t) < 1,$$

<u>and</u>

$$0 < h(t) < 1.$$

<u>Proof</u>. Let $J = n, m$, or h. Suppose there exists a time $t \in (0,b]$ such that $J(t) = 0$. Since $J(0) > 0$ and any solution J is continuous, there must be a first such time. Call it t^*. Then $J(t^*) = 0$ and $J(t) > 0$ for all $t \in [0,t^*)$. Now

$$\begin{aligned}\frac{dJ}{dt}(t^*) &= \alpha_J(v(t^*))(1 - J(t^*)) - \beta_J(v(t^*))J(t^*)\\ &= \alpha_J(v(t^*)).\end{aligned}$$

Since $\alpha_J > 0$ by Property 3.a, we have $\frac{dJ}{dt}(t^*) > 0$. Therefore, J is strictly increasing at t^* which implies that there exists a neighborhood N of t^* such that if $t \in N \cap (0,t^*)$, then $J(t) < J(t^*) = 0$. This contradicts the fact that $J(t) > 0$ for all $t \in [0,t^*)$. Therefore, for all $t \in [0,b]$ we have $J(t) > 0$ where $J = n, m$, or h.

Now suppose that there exists a time $t \in (0,b]$ such that $J(t) = 1$. Since $J(0) < 1$ and any solution J is continuous, there must be a first such time. Call it t^*. Then $J(t^*) = 1$ and $J(t) < 1$ for all $t \in [0,t^*)$. Now

$$\begin{aligned}\frac{dJ}{dt}(t^*) &= \alpha_J(v(t^*))(1 - J(t^*)) - \beta_J(v(t^*))J(t^*)\\ &= - \beta_J(v(t^*)).\end{aligned}$$

Since by Property 3.a we have $\beta_J > 0$, it follows that $\frac{dJ}{dt}(t^*) < 0$ which implies that J is strictly decreasing at t^*. This implies that there exists a neighborhood N of t^* such that if $t \in N \cap (0,t^*)$ then $J(t) > J(t^*) = 1$ contradicting the fact that $J(t) < 1$ for all $t \in [0,t^*)$. Therefore, for all $t \in [0,b]$ we have $J(t) < 1$ where $J = n$, m, or h.

Remark 1. Note that it follows from the definitions of ν, μ, and η that for all $t \in [0,b]$

$$0 < \nu(t) < 1,$$

$$0 < \mu(t) < 1,$$

and

$$0 < \eta(t) < 1.$$

Remark 2. Since α_J and β_J (where J = n, m, or h) are analytic functions of v for all v, if v is bounded then so are α_J and β_J. If v is a given bounded function, then the three equations $dn/dt = H_2(v,n)$, $dm/dt = H_3(v,m)$, and $dh/dt = H_4(v,h)$ become linear equations and solutions will exist for all time if the given bounded region is sufficiently large to include v for all time. Using Theorem 4.8 and $\bar{D}$, we can now extend the results of Theorem 3.3 to the statement: the solution x(t) exists and is unique on an interval $t_o \leq t \leq b$ $(b \leq \infty)$ such that if $b < \infty$, then $\lim_{t \to b} x(t) = (\omega, n(b), m(b), h(b))$ or

$\lim_{t \to b} x(t) = (12, n(b), m(b), h(b))$. In order to make a further extension we must show that v is bounded. This we do next.

3. Lower Boundedness of v

Lemma 4.9. Let $I_0 > 0$. Then for any $t^* \varepsilon (0,b]$ such that $v(t^*) < v(t)$ for all $t \varepsilon [0,t^*)$ we have $\frac{dn}{dt}(t^*) \geq 0$, $\frac{dm}{dt}(t^*) \geq 0$, and $\frac{dh}{dt}(t^*) \leq 0$.

Proof. Let $t^* \varepsilon (0,b]$ be such that $v(t^*) < v(t)$ for all $t \varepsilon [0,t^*)$. Such a t^* exists by Proposition 3.5 and Remark 1 following Proposition 3.6. By Proposition 4.4, $\nu(t^*) > \nu(t)$ for all $t \varepsilon [0,t^*)$. We claim that $n(t^*) \leq \nu(t^*)$. Assume that this is not the case; i.e., assume $n(t^*) > \nu(t^*)$. Then by Proposition 4.1 (iii), $\frac{dn}{dt}(t^*) < 0$ so n is strictly decreasing at t^*. Now since ν and η are both continuous, since $n(t^*) > \nu(t^*) > \nu(0)$ (by Proposition 4.5), since $\nu(0) = n(0)$ by definition of ν and $n(0)$, and, since near $t = 0^+$ we have $\frac{dn}{dt} > 0$ (Proposition 3.6 and Remark 1 following), there exists a $t^{**} \varepsilon (0,t^*)$ such that $\frac{dn}{dt}(t^{**}) = 0$ where $n(t^{**}) > n(t^*)$. But $\frac{dn}{dt}(t^{**}) = 0$ implies $n(t^{**}) = \nu(t^{**})$ by Proposition 4.1 (ii). Therefore $\nu(t^{**}) > n(t^*) > \nu(t^*)$. This contradicts the fact that $\nu(t^*) > \nu(t)$ for all $t \varepsilon [0,t^*)$. Therefore, $n(t^*) \leq \nu(t^*)$ which implies by Proposition 4.1 that $\frac{dn}{dt}(t^*) \geq 0$. Similar arguments imply $\frac{dm}{dt}(t^*) \geq 0$ and $\frac{dh}{dt}(t^*) \leq 0$.

Remark 1. The dual result for all three functions n, m, and h (with the inequalities reversed) can also be proved similarly if it is assumed that there exists $\hat{t} \varepsilon (0,b]$ such that $v(\hat{t}) > 0$.

Remark 2. If it is assumed, in addition to the hypotheses of Lemma 4.9, that v is strictly decreasing at t^* then the conclusion can be changed to $\frac{dn}{dt}(t^*) > 0$, $\frac{dm}{dt}(t^*) > 0$, and $\frac{dh}{dt}(t^*) < 0$.

Proposition 4.10. Let $(v(t),n(t),m(t),h(t))$ be the solution of (2.13). Then for any $t^* > 0$ such that

(i) $v(t^*) < 0$

and

(ii) $v(t^*) < v(t)$ for all $t \varepsilon [0,t^*)$,

we have $K(v(t^*),n(t^*)) > 0$ and $Na(v(t^*),m(t^*),h(t^*)) > 0$.

Note. For definitions of the functions K and Na, see (3.1) and (3.2).

Proof. Let $t^* > 0$ satisfy (i) and (ii). Such a t^* exists by Remark 1 following Proposition 3.6. By Property 3.f, $\alpha_h(v) + \beta_h(v) < 1.07$ for all $v < 0$. This implies

$$\hat{K} - (\alpha_h(v) + \beta_h(v)) > 0 \text{ for all } v < 0.$$

Therefore,

$$\begin{aligned} 0 &< [\hat{K} - (\alpha_h(v(t^*)) + \beta_h(v(t^*)))]h(t^*) \\ &< [\hat{K} - (\alpha_h(v(t^*)) + \beta_h(v(t^*)))]h(t^*) + \alpha_h(v(t^*)) \\ &= \hat{K}h(t^*) + \frac{dh}{dt}(t^*). \end{aligned}$$

Hence

$$0 < \left(\frac{1}{K}\right)\bar{g}_{Na}\left(\frac{2}{a}\right)Rm^3(t^*)\left[\hat{K}h(t^*) + \frac{dh}{dt}(t^*)\right].$$

From Lemma 4.9 we have $\frac{dm}{dt}(t^*) \geq 0$. This implies

$$0 < \left(\frac{1}{K}\right)\bar{g}_{Na}\left(\frac{2}{a}\right)Rm^3(t^*)\left[\hat{K}h(t^*) + \frac{dh}{dt}(t^*)\right]$$

$$+ \left(\frac{1}{\theta^2 C}\right)\bar{g}_{Na}3m^2(t^*)h(t^*)\frac{dm}{dt}(t^*)$$

$$= \bar{g}_{Na}\left\{\left(\frac{2}{a}\right)Rm^3(t^*)h(t^*)\right.$$

$$\left. + \left(\frac{1}{\theta^2 C}\right)\left[3m^2(t^*)h(t^*)\frac{dm}{dt}(t^*) + m^3(t^*)\frac{dh}{dt}(t^*)\right]\right\}$$

$$= Na(v(t^*),m(t^*),h(t^*)).$$

For the proof that $K(v(t^*),n(t^*)) > 0$, Lemma 4.9 implies that $\frac{dn}{dt}(t^*) \geq 0$. Therefore

$$0 < \bar{g}_K\left(\frac{2}{a}\right)Rn^4(t^*)$$

$$\leq \bar{g}_K\left[\left(\frac{2}{a}\right)Rn^4(t^*) + \left(\frac{1}{\theta^2 C}\right)4n^3(t^*)\frac{dn}{dt}(t^*)\right]$$

$$= K(v(t^*),n(t^*)).$$

Theorem 4.11. *Let* $I_o > 0$ *be given. Let* $\omega = \min\{-115, v_\ell - (I_o/\bar{g}_\ell)\}$. *Let* $(v(t),n(t),m(t),h(t))$ *be the solution of the initial value problem* (2.13) *in the region* $\bar{D}$. *Then* $v(t) > \omega$ *for all* $t \in [0,b]$.

Proof. Suppose there is a time t such that $v(t) = \omega$. Then since $v(0) = 0$ and v is continuous, there must be a first such time. Call it t^*. Therefore,

$$v(t^*) = \omega, \text{ and } v(t) > \omega \text{ for all } t \in [0,t^*).$$

Thus

$$v(t^*) < v(t) \text{ for all } t \in [0,t^*).$$

Therefore, from Proposition 4.10 we have $K(v(t^*),n(t^*)) > 0$ and $Na(v(t^*),m(t^*), h(t^*)) > 0$. Since

$$\begin{aligned} v(t^*) - v_K &= \omega - v_K \\ &\leqq -115 - 12 \\ &= -127 \\ &< 0, \end{aligned}$$

we have

$$K(v(t^*),n(t^*))[v(t^*) - v_K] < 0.$$

Since

$$\begin{aligned} v(t^*) - v_{Na} &= \omega - v_{Na} \\ &\leqq -115 + 115 \\ &= 0, \end{aligned}$$

we have

$$Na(v(t^*),m(t^*),h(t^*))[v(t^*) - v_{Na}] \leqq 0.$$

Also,

$$\begin{aligned} v(t^*) - v_\ell &= \omega - v_\ell \\ &\leqq -115 + 10.5989 \\ &< 0 \end{aligned}$$

which implies

$$\left(\frac{2}{a}\right)R\bar{g}_\ell(v(t^*) - v_\ell) < 0.$$

Putting these terms together we have, since the denominator of $H_1(v,n,m,h)$ is greater than zero (Proposition 3.2);

$$\frac{dv}{dt}(t^*) = -\left\{\left[\left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)\left(\bar{g}_K n^4(t^*) + \bar{g}_{Na} m^3(t^*)h(t^*) + \bar{g}_\ell\right)\right]^{-1}\right\}$$
$$\cdot \left\{K(v(t^*),n(t^*))\left[v(t^*) - v_K\right]\right.$$
$$+ Na(v(t^*),m(t^*),h(t^*))\left[v(t^*) - v_{Na}\right]$$
$$\left. + \bar{g}_\ell\left(\frac{2}{a}\right)R\left(v(t^*) - v_\ell\right) + \left(\frac{2}{a}\right)RI_o\right\}$$
$$> -\left\{\left[\left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)\left(\bar{g}_K n^4(t^*) + \bar{g}_{Na} m^3(t^*)h(t^*) + \bar{g}_\ell\right)\right]^{-1}\right\}$$
$$\cdot \left(\frac{2}{a}\right)R\left[\bar{g}_\ell(v(t^*) - v_\ell) + I_o\right].$$

Now $v(t^*) = \omega \leqq v_\ell - (I_o/\bar{g}_\ell)$ by hypothesis. Therefore

$$\bar{g}_\ell(v(t^*) - v_\ell) + I_o \leqq 0$$

which implies $\frac{dv}{dt}(t^*) > 0$. Thus we have shown that if there is a time such that $v = \omega$, then v must be strictly increasing at the first such time t^*. However, $v(t) > \omega$ for all $t \in [0,t^*)$ which implies that v must be nonincreasing at t^*. Therefore, the assumption must be false and we conclude that there is no time such that $v = \omega$. Since v is continuous and $v(0) = 0$, we have $v(t) > \omega$ for all $t \in [0,b]$.

Corollary 4.12. Let $0 < I_o < 31.32033$ µA/cm². Then $v(t) > -115$ for all $t \in [0,b]$.

Proof. $0 < I_o < 31.32033$ µA/cm² implies $0 < I_o < .03132033$ mA/cm² which makes the units consistent. Then

$$v_\ell - (I_o/\bar{g}_\ell) > v_\ell - \left(\frac{.03132033}{.0003}\right) = v_\ell - 104.4011$$
$$= -(10.5989 + 104.4011) = -115.$$

Therefore $\omega = -115$ and the conclusion follows from Theorem 4.11.

Remark 1. It is crucial to the proof of Theorem 4.11 that the lower bound be less than or equal to -115. Otherwise the proof would not work since if $v > -115$, the inequality involving the dropping of the sodium term $Na\cdot(v + 115)$ would go the wrong way. In this sense -115 is the best available lower bound for v.

Remark 2. The 31.32033 $\mu A/cm^2$ of Corollary 4.12 is not necessarily the largest I_0 which gives a lower bound of -115 mv for v. The value of I_0 could be increased in this proof if it were desired, by neglecting fewer terms than we did. However, since these other terms involve values of n, m, and h, we would have to restrict the time interval involved. Instead of doing that here, we will wait until Section IV.5 where a lower bound of -115 mv for v will be proved that holds for larger values of I_0 in the time interval in which a first threshold appears.

4. Upper Boundedness of v

Theorem 4.13. *Let* $I_0 > 0$. *Let* $(v(t),n(t),m(t),h(t))$ *be the solution of the initial value problem (2.13) in the region* $\bar{D}$. *Assume that for any time interval* $[t_1,t_2]$ *in which* $v \geq 0$, *there is some* $v^* \varepsilon (0,12)$ *with the* *property that for any* $t \in [t_1, t_2]$ *such that* $v(t) \geq v^*$ *we have* $m(t) \leq m(0)$. *Then* $v(t) < 12$ *for all* $t \in [0,b]$.

Proof. Suppose that $v(t) = 12$ for some $t \in [0,b]$. Then v continuous and $v(0) = 0$ imply that there is a first such time. Call it t^*. Then $v(t^*) = 12$ and $v(t) < 12$ for all $t \in [0,t^*)$. The function v being continuous and $\frac{dv}{dt}(0) < 0$ (Proposition 3.5) imply that there exists a $t_1 > 0$ such that for all $t \in [t_1, t^*]$ we have $v(t) \geq 0$. Now by hypothesis there is a $v^* \in (0,12)$ such that $t \in [t_1, t^*]$ and $v(t) \geq v^*$ imply $m(t) \leq m(0)$. Therefore

$$m(t^*) \leq m(0). \tag{4.1}$$

We now claim that

$$Na(v(t^*), m(t^*), h(t^*)) > -.15. \tag{4.2}$$

$$Na(v(t^*), m(t^*), h(t^*)) = \bar{g}_{Na}\left\{\left(\frac{2}{a}\right)Rm^3(t^*)h(t^*) + \left(\frac{1}{\theta^2 C}\right)\left[3m^2(t^*)h(t^*)\frac{dm}{dt}(t^*) + m^3(t^*)\frac{dh}{dt}(t^*)\right]\right\}$$

$$> \bar{g}_{Na}\left(\frac{1}{\theta^2 C}\right)\left[\hat{K}m(t^*) + 3\frac{dm}{dt}(t^*)\right]m^2(t^*)h(t^*) \tag{4.3}$$

since $\hat{K} = \left(\frac{2}{a}\right)R\theta^2 C$ and $\frac{dh}{dt}(t^*) \geq 0$ by Remark 1 following Lemma 4.9. Now

$$\hat{K}m(t^*) + 3\frac{dm}{dt}(t^*) = 3\alpha_m(v(t^*)) + m(t^*)\left\{\hat{K} - 3\left[\alpha_m(v(t^*)) + \beta_m(v(t^*))\right]\right\}$$

which implies

$$\hat{K}m(t^*) + 3\frac{dm}{dt}(t^*) = 3\alpha_m(12) + m(t^*)\left\{\hat{K} - 3\left[\alpha_m(12) + \beta_m(12)\right]\right\}$$ [6]

$$> 3\alpha_m(12) + m(t^*)(4.51 - 23.66)$$

$$= 3\alpha_m(12) - m(t^*)(19.15)$$

$$> .28 - 19.15m(t^*)$$

(4.4) $$> .28 - 19.15m(0)$$

since by (4.1) $m(t^*) \leqq m(0)$. Combining (4.3) and (4.4) we have

$Na(v(t^*),m(t^*),h(t^*))$

$$> \bar{g}_{Na}\left(\frac{1}{\theta^2 C}\right)m^2(t^*)h(t^*)\left[.28 - 19.15m(0)\right]$$ [6]

$$> (120)\left(\frac{1}{\theta^2}\right)m^2(t^*)h(t^*)\left[.28 - 19.15(.053)\right]$$

$$> (120)(.28 - 1.02)\left(\frac{1}{\theta^2}\right)m^2(t^*)h(t^*)$$

$$= (120)(-.74)\left(\frac{1}{\theta^2}\right)m^2(t^*)h(t^*)$$

$$> (120)(-.74)(1/\theta^2)m^2(0)\eta(t^*) \qquad (4.5)$$

by (4.1) and Proposition 4.1. Continuing, since $(1/\theta^2) < .6595$, since $m(0) < .052932486$ implies $m^2(0) < .0028018481$, and since $\eta(t^*) < .89619325$ we have by (4.5)

$Na(v(t^*),m(t^*),h(t^*))$

$$> (120)(-.74)(.6595)(.0028018481)(.89619325)$$ [6]

$$> (.6595)(-120)(.74)(.0025109974)$$

$$= (.6595)(-120)(.001858138076)$$

[6] See footnote 2.

$$> (.6595)(-120)(.0018581381)$$
$$= -(.6595)(.2229765720)$$
$$> -(.6595)(.22297658)$$
$$= -.147053054510$$
$$> -.15 .$$

Since

$$K(v(t^*),n(t^*))\left(v(t^*) - v_K\right) = K(v(t^*),n(t^*))(12 - 12) = 0,$$

we have

$$\frac{dv}{dt}(t^*) = -\left\{\left[\left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)\left(\bar{g}_K n^4(t^*) + \bar{g}_{Na} m^3(t^*)h(t^*) + \bar{g}_\ell\right)\right]^{-1}\right\}$$
$$\cdot \left\{Na(v(t^*),m(t^*),h(t^*))\left(v(t^*) - v_{Na}\right) + \bar{g}_\ell\left(\frac{2}{a}\right)R(v(t^*) - v_\ell) + \left(\frac{2}{a}\right)RI_o\right\}$$
$$< -\left\{\left[\left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)\left(\bar{g}_K n^4(t^*) + \bar{g}_{Na} m^3(t^*)h(t^*) + \bar{g}_\ell\right)\right]^{-1}\right\}$$
$$\cdot \left[(-.15)(127) + \left(\frac{2}{a}\right)R(.0003)(22.5989)\right].$$

Now $\left(\frac{2}{a}\right)R > 2974.7899$ which implies

$$\left(\frac{2}{a}\right)R(.0003)(22.5989) > 20.16 .$$

Also $(-.15)(127) = -19.05$. Therefore

$$\frac{dv}{dt}(t^*) < -\left\{\left[\left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)\left(\bar{g}_K n^4(t^*) + \bar{g}_{Na} m^3(t^*)h(t^*) + \bar{g}_\ell\right)\right]^{-1}\right\}$$
$$\cdot (-19.05 + 20.16)$$
$$< 0.$$

But since $v(0) = 0$ and t^* is the first time that $v = 12$, we must have $\frac{dv}{dt}(t^*) \geqq 0$. This contradiction establishes the conclusion; i.e., $v(t) < 12$ for all $t \in [0,b]$.

Some remarks should perhaps be made regarding the assumption in the last theorem. The inclusion of the derivative of m^3h in the sodium terms

$$Na(v,m,h) = \bar{g}_{Na}\left[\left(\frac{2}{a}\right)Rm^3h + \left(\frac{1}{\theta^2 C}\right)(m^3h)'\right]$$

presents the mathematical possibility that the derivative of m^3h is a large negative number in any region in which the voltage v is positive (called the <u>refractory period</u>). Also, unlike the potassium terms,

$$K(v,n) = \bar{g}_K\left[\left(\frac{2}{a}\right)Rn^4 + \left(\frac{1}{\theta^2 C}\right)(n^4)'\right],$$

where even a rough calculation shows that

$$\left(\frac{2}{a}\right)Rn^4 > -\left(\frac{1}{\theta^2 C}\right)(n^4)' ,$$

the best estimate made on the size of $(m^3h)'$ allowed the possibility that $(2/a)Rm^3h$ might be much smaller than $(-1/\theta^2 C)(m^3h)'$ during any refractory period. If it were the case that $\left|\frac{d(m^3h)}{dt}\right|$ is very large in some refractory period, then the methods employed to prove upper boundedness for v in Theorem 4.13 would no longer apply. However, in nature the various conductances return to the normal levels (those where n is near n(0), m is near m(0), and h is near h(0)) during any refractory period. In [4, p. 505] Hodgkin and Huxley make the statement: " A membrane in the refractory or inactive condition resembles one in the resting state in having a low sodium conductance." In [5, p. 530] when discussing the manner in which the various conductances affect the change of total conductance in their model, they state: " ...but after the peak [of the total conductance] the potassium conductance takes a progressively larger share until, by the beginning of the positive phase [of the voltage], the sodium conductance has become negligible." On page 532, when discussing the refractory period and speaking about the behavior of g_K ($g_K = \bar{g}_K n^4$) and h, they state: " Both curves reach their normal levels again near the end of the positive phase...." For our case the model is different, but since the numerical solution for v(t) closely follows the H-H solution for v(t) and since the equations for dn/dt, dm/dt, and dh/dt depend explicitly only on v, n, m, and h, and are the equations that Hodgkin and Huxley used, their statements above should remain true.

If m is to reach its normal level in any region in which the voltage is positive, it is necessary for m to be near m(0) and also for the first derivative of m to become positive. Since when v enters its positive phase (the first time) we have $dm/dt < 0$, m must cross the curve μ in order for dm/dt to become positive. Now v positive implies that $\mu(t) < \mu(0) = m(0)$, so m would, in its descent, have to attain the value m(0). Furthermore, in the proposition below it will be shown that: For any t such that $v(t) > 0$, either $m(t) < m(0)$ or $\frac{dm}{dt}(t) < 0$. We assumed slightly more, **namely that there is a value** v^*

of voltage ($v^* \varepsilon$ (0,12)) in each refractory period such that any time t that $v(t) > v^*$ we definitely have $m(t) < m(0)$. This hypothesis could be weakened if it could be shown, as the numerical evidence suggests, that v has no non-negative minima. Then it would suffice to assume that in any refractory period there is a value v^* of voltage ($v^* \varepsilon$ (0,12)) such that if there is some time t such that $v(t) = v^*$, then $m(t) = m(0)$. Since the empirical evidence also strongly suggests that v has no nonnegative minima, one may regard our assumption as a part of the model to be addended to (2.13).

Proposition 4.14. For any t such that $v(t) > 0$ we have either $m(t) < m(0)$ or $\frac{dm}{dt}(t) < 0$.

Proof. Let t be such that $v(t) > 0$. Then $v(t) > 0 = v(0)$ implies $\mu(t) < \mu(0) = m(0)$ by Proposition 4.5. If $m(t) < m(0)$, we are done; if not, then $m(t) \geqq m(0)$ implies $m(t) \geqq m(0) = \mu(0) > \mu(t)$. Therefore, by Proposition 4.1 (iii), $\frac{dm}{dt}(t) < 0$.

Remark. Similar results hold for n and h but are not relevant to the discussion above.

In order to substantiate further the assumption of Theorem 4.13, the initial value problem (2.13) was solved numerically using the IBM 1130 digital computer at Wichita State University. (This and other numerical work will be discussed in VI and VII.) Numerical solutions were obtained for various values of I_o. In every case run the assumption of Theorem 4.13 was found to be satisfied although for cases with large I_o, approaching plateau behavior, the assumption was vacuously satisfied (see VI,1).

Table 1 gives the approximate values of v^* for some of the cases which appear in [7] along with others which do not. The number of refractory periods listed in each case is the total number which appeared in the time interval for which the equations were solved. These time intervals are also listed.

TABLE 1. Numerical Substantiation of the Assumption of Theorem 4.13

I_o ($\mu A/cm^2$)	v^* (mv) Refractory Period 1st	2nd	3rd	4th	Time Interval (ms)
2.27	.48				100
2.28	8.7				100
2.879	8.7				10.5
5.97	8.5	.48			100
5.98	8.5	8.2			100
6.22	8.5	8.2			25
6.23	8.5	8.2	8.2	8.2 (4th through 7th)	200
7.0	8.5	8.2	8.2	8.2 (4th through 12th)	200
10.	8.2	7.9	7.9	7.9 (4th through 7th)	100
50.	4.8	3.4	3.1	3.0 (4th through 12th)	100
80.	1.7				100

5. A Second Proof of the Lower Boundedness of v

Before we discuss the results of these three boundedness theorems, we wish to present a second proof of lower boundedness. The method of proof to be presented represents a different approach to understanding the nature of the solutions to the system. It involves an extension of an elementary comparison theorem for first order ordinary differential equations. The following elementary comparison theorem and lemma are found in [11].

Lemma 4.15 ([11, p. 20]). *Let* σ *be a differentiable function satisfying the differential inequality* $\sigma'(x) \leq K\sigma(x)$ *where* $a \leq x \leq b$, K *is a constant. Then* $\sigma(x) \leq \sigma(a)\exp[K(x - a)]$ *for* $a \leq x \leq b$.

Theorem 4.16 ([11, p. 22]). *Let* F *satisfy a Lipschitz condition for* $x \geq a$. *If the function* f *satisfies the differential inequality* $f'(x) \leq F(x,f(x))$ *for* $x \geq a$, *and if* g *is a solution of* $y' = F(x,y)$ *satisfying the initial condition* $g(a) = f(a)$, *then* $f(x) \leq g(x)$ *for* $x \geq a$.

We shall extend this theorem to a system of first order differential equations in the following way:

Theorem 4.17. *Let* E *be a region (open connected set) of x-space where* $x = (x_1, x_2, \cdots, x_n)$. *Let* E_t *denote* the set of all (t,x) such that $t \in [t_o,b_o)$ and $x \in E$ where $b_o > t_o$. Let $F = (F_1,F_2,\cdots,F_n)$ be defined on E_t and satisfy a Lipschitz condition (with respect to x) on E_t. Let $g = (g_1,g_2,\cdots,g_n)$ be a solution of the vector differential equation $\frac{dx}{dt} = F(t,x)$ satisfying the initial condition $g(t_o) = g_o = (g_1^o,g_2^o,\cdots,g_n^o) \in E$. Let $[t_o,b_1)$ be the right maximal interval of existence of g. Finally, suppose that the function $f = (f_1,f_2,\cdots,f_n)$ satisfies:

$$f_1'(t) \leqq F_1(t,f(t)) \text{ for } t \in [t_o,b_o),$$
$$f_2 = g_2,$$
$$\vdots$$
$$f_n = g_n,$$

and the initial condition $f_1(t_o) \leqq g_1^o$. Then $f_1(t) \leqq g_1(t)$ for $t \in [t_o,t_1)$ where $t_1 = \min\{b_o, b_1\}$.

Proof. Suppose not; i.e., suppose there exists a $t_2 \in [t_o,t_1)$ such that $f_1(t_2) > g_1(t_2)$. Note that $t_2 > t_o$ since $f_1(t_o) \leqq g_1^o$. Let S be the set of all $t^* \in [t_o,t_2]$ such that $f_1(t^*) \leqq g_1(t^*)$. S is not empty since $t_o \in S$. Since the set A of all t such that $f_1(t) > g_1(t)$ is open, the complement A^c of A is closed which implies that $A^c \cap [t_o,t_2] = S$ is closed. Since S is clearly bounded, we have that S is compact. Let $t_3 = \max_{t \in S} t$. This maximum exists since S is compact and $t_3 \in S$. Furthermore,

$f_1(t_3) = g_1(t_3)$ since $f_1 - g_1$ is continuous.

Let $\sigma(t) = f_1(t) - g_1(t)$. Then if $t \varepsilon [t_3,t_2]$, $\sigma(t) \geqq 0$. Also, if $t \varepsilon [t_3,t_2]$, then if $\hat{L}$ is the Lipschitz constant (where $\| \ \|$ is the Euclidean norm), we have

$$\begin{aligned}
\sigma'(t) &= f_1'(t) - g_1'(t) \\
&\leqq F_1(t,f(t)) - F_1(t,g(t)) \\
&\leqq \left|F_1(t,f(t)) - F_1(t,g(t))\right| \\
&\leqq \|F(t,f(t)) - F(t,g(t))\| \\
&\leqq \hat{L}\|f(t) - g(t)\| \\
&= \hat{L}\left|f_1(t) - g_1(t)\right| \\
&= \hat{L}(f_1(t) - g_1(t)) \\
&= \hat{L}\sigma(t) \ .
\end{aligned}$$

Therefore, by Lemma 4.15, $\sigma(t) \leqq \sigma(t_3)\exp[\hat{L}(t - t_3)]$ for all $t \varepsilon [t_3,t_2]$. But $\sigma(t_3) = 0$ which implies that $\sigma(t) \leqq 0$ for all $t \varepsilon [t_3,t_2]$. Since we already know that $\sigma(t) \geqq 0$ for all $t \varepsilon [t_3,t_2]$, we conclude that $\sigma \equiv 0$ in $[t_3,t_2]$. Now $\sigma(t) = f_1(t) - g_1(t)$ which implies $0 = f_1(t_2) - g_1(t_2)$. Therefore $f_1(t_2) = g_1(t_2)$. But by assumption, $f_1(t_2) > g_1(t_2)$ giving a contradiction and thus proving the theorem.

Corollary 4.18. *Let $\bar{E}$ be a closed region of x-space where $x = (x_1,x_2,\cdots,x_n)$. Let $\bar{E}_t$ denote the set of all (t,x) such that $t \varepsilon [t_o,b_o]$ and $x \varepsilon \bar{E}$ where $b_o > t_o$.* Let $F = (F_1,F_2,\cdots,F_n)$ be defined on $\bar{E}_t$ and satisfy a

Lipschitz condition (with respect to x) on E_t. Let $g = (g_1, \cdots, g_n)$ be a solution of the vector differential equation $\frac{dx}{dt} = F(t,x)$ satisfying the initial condition $g(t_o) = g^o = (g_1^o, \cdots, g_n^o) \in$ Interior $\bar{E}$. Let $[t_o, b_1]$ be the right maximal interval of existence of g. Finally, suppose that the function $f = (f_1, \cdots, f_n)$ satisfies:

$$f_1'(t) \leqq F_1(t, f(t)) \text{ for } t \in [t_o, b_o],$$
$$f_2 = g_2,$$
$$\vdots$$
$$f_n = g_n,$$

and the initial condition $f_1(t_o) \leqq g_1^o$. Then $f_1(t) \leqq g_1(t)$ for $t \in [t_o, t_1]$ where $t_1 = \min\{b_o, b_1\}$.

For the forthcoming proof of lower boundedness we need several additional preliminary results.

Proposition 4.19. Let $I_o > 0$. Let $t^* \in (0,b]$ such that for all $t \in (0,t^*)$ we have $v(t) < 0$. Let $t \in (0,t^*)$. Then $n(t) > n(0)$, $m(t) > m(0)$, and $h(t) < h(0)$. Furthermore, if $\frac{dv}{dt}(t^*) > 0$ and $v(t^*) = 0$, then $n(t^*) > n(0)$, $m(t^*) > m(0)$, and $h(t^*) < h(0)$.

Proof. Such times t^* exist by Remark 1 following Proposition 3.6. Let t^* be any such time; i.e., let $t^* \in (0,b]$ such that for all $t \in (0,t^*)$, $v(t) < 0$. By the same Remark we know that initially n and m are increasing and h is decreasing (all strictly if $t \neq 0$). Therefore, in order for the first conclusion to be false, there must exist a time $\hat{t}$ such that at least one of n, m, or h equals n(0), m(0), or h(0) respectively; i.e., suppose that there exists $\hat{t} \in (0,t^*)$ such that $m(\hat{t}) = m(0)$. Without loss of generality assume that $m(t) > m(0)$ for all $t \in (0,\hat{t})$. Then m is nonincreasing at $\hat{t}$ which implies $\frac{dm}{dt}(\hat{t}) \leqq 0$. Therefore by Proposition 4.1, $m(\hat{t}) \geqq \mu(\hat{t})$. Since $\hat{t} \in (0,t^*)$ we have by hypothesis $v(\hat{t}) < 0 = v(0)$ which implies, by Proposition 4.5, $\mu(\hat{t}) > \mu(0) = m(0)$. Therefore $m(\hat{t}) > m(0)$ which is a contradiction. Therefore, if $t \in (0,t^*)$, then $m(t) > m(0)$. Similarly, if $n(\hat{t}) = n(0)$ or if $h(\hat{t}) = h(0)$ we can reach a contradiction by the same type of argument. The first conclusion then follows.

Now assume $v(t^*) = 0$ and $\frac{dv}{dt}(t^*) > 0$. Then, by Proposition 4.3 (i), $\frac{d\eta}{dt}(t^*) > 0$, $\frac{d\nu}{dt}(t^*) < 0$, and $\frac{d\mu}{dt}(t^*) < 0$. By what has already been proved, since n, m, and h are continuous, it follows that $n(t^*) \geqq n(0)$, $m(t^*) \geqq m(0)$, and $h(t^*) \leqq h(0)$. Now if say $h(t^*) = h(0)$, then since $h(t) < h(0)$ for all $t \in (0,t^*)$ and h is continuous, there is a neighborhood N_1 of t^* such that for all $t \in N_1 \cap (0,t^*)$, $\frac{dh}{dt}(t) > 0$. This implies, by Proposition 4.1, that for all $t \in N_1 \cap (0,t^*)$ we have $h(t) < \eta(t)$. Now $h(t^*) = h(0)$ implies $h(t^*) = \eta(t^*)$ since $v(t^*) = 0 = v(0)$ implies $\eta(t^*) = \eta(0) = h(0)$ by the Remark after Proposition 4.4. Since $\frac{d\eta}{dt}(t^*) > 0$ and since $\frac{dh}{dt}(t) > 0$ for all $t \in N_1 \cap (0,t^*)$, in order for h to intersect η in a nonzero angle there would have to be a neighborhood N_2 of t^* such that $\frac{dh}{dt}(t) > 0$ for all $t \varepsilon N_2 \cap (t^*,b)$; therefore, there would have to be a neighborhood N_3 of t^* (where $N_3 \cap N_2 \neq \emptyset$) such that $h(t) > \eta(t)$ for all $t \varepsilon N_3 \cap (t^*,b)$. But, by Proposition 4.1, $h(t) < \eta(t)$ for all $t \varepsilon N_2 \cap (t^*,b)$. Since there are points common to N_2 and N_3 this would be nonsense; therefore h cannot intersect η in a nonzero angle. Hence $\frac{dh}{dt}(t^*) = \frac{d\eta}{dt}(t^*)$. But $\frac{dh}{dt}(t^*) = 0$ since $h(t^*) = \eta(t^*)$ above, and $\frac{d\eta}{dt}(t^*) > 0$. So we have shown that $h(t^*) \neq h(0)$ which implies that $h(t^*) < h(0)$ since we already know that $h(t^*) \leqq h(0)$. A similar proof follows for n and m.

<u>Corollary</u> 4.20. <u>Let</u> $I_o > 0$. <u>Let</u> t^* <u>be</u> <u>as</u> <u>in</u> <u>Proposition</u> 4.19. <u>Then</u> <u>if</u> $\frac{dv}{dt}(t^*) = 0$ <u>and</u> $v(t^*) = 0$, <u>at least one of the following statements must hold</u>:

(i) $n(t^*) > n(0)$,

(ii) $m(t^*) > m(0)$,

(iii) $h(t^*) < h(0)$.

<u>Proof</u>. Since we know that $n(t^*) \geqq n(0)$, $m(t^*) \geqq m(0)$, and $h(t^*) \leqq h(0)$, if none of the statements (i) - (iii) hold we would have $n(t^*) = n(0)$, $m(t^*) = m(0)$, and $h(t^*) = h(0)$. Then since $v(t^*) = 0$, we would have

$$\nu(t^*) = \nu(0) = n(0),$$

$$\mu(t^*) = \mu(0) = m(0),$$

and

$$\eta(t^*) = \eta(0) = h(0).$$

This would imply $\nu(t^*) = n(t^*)$, $\mu(t^*) = m(t^*)$, and $\eta(t^*) = h(t^*)$ which would imply $\frac{dJ}{dt}(t^*) = 0$ where $J = n$, m, or h. Thus $(v(t^*), n(t^*), m(t^*), h(t^*)) = (0, n(0), m(0), h(0))$ would be a stationary point of (2.13). But for $I_o > 0$, it has already been shown that $(0, n(0), m(0), h(0))$ is not a stationary point of (2.13). The conclusion follows.

Lemma 4.21. *Let* $\frac{du}{dt} = -(1/\delta)(\lambda u + \psi + I_o)$ *where* $0 < I_o \leq .07272$, $\delta = .00114778716$,

$$\lambda = \bar{g}_K n^4(0)\,\frac{2\hat{K} - 1}{2\hat{K}} + \bar{g}_{Na} h(0)\left\{1 + \left(\frac{1}{\hat{K}}\right)\left[3.9945300 + \frac{\alpha_h(0)}{f_h(-115)}\right]\right\} + \bar{g}_\ell,$$

and

$$\psi = 115\bar{g}_{Na} h(0)\left\{1 + \left(\frac{1}{\hat{K}}\right)\left[3.9945300 + \frac{\alpha_h(0)}{f_h(-115)}\right]\right\} - 12\bar{g}_K n^4(0)\,\frac{2\hat{K} - 1}{2\hat{K}} + 10.5989\bar{g}_\ell .$$

Then

(i) $u(t) = \left[(\psi + I_o)/\lambda\right]\left[-1 + \exp(-\lambda t/\delta)\right]$ *is the unique solution passing through* $u(0) = 0$ *where* t *is any real number*;

(ii) $\inf_{t \in R^1} u(t) > -115.$

Proof. This linear initial value problem has a unique solution by elementary theorems. It is easily verified that u, defined in (i), satisfies the differential equation for all time t. Furthermore, $u(0) = 0$. Now $\exp(-\lambda t/\delta) > 0$ for all t so that $-1 + \exp(-\lambda t/\delta) > -1$. Therefore if it is shown that $(\psi + I_o)/\lambda > 0$, then it follows that $u(t) > -[(\psi + I_o)/\lambda]$. Now $I_o > 0$ by hypothesis. We show that λ and ψ are greater than zero. Since λ is composed of the sum of positive terms, $\lambda > 0$. Since $n^4(0) < .011$ and $(2\hat{K} - 1)/2\hat{K} < .9$, we have by Remark 3 following Proposition 3.2

$$\begin{aligned} &115\bar{g}_{Na}h(0) - 12\bar{g}_K n^4(0)(2\hat{K} - 1)(1/2\hat{K}) \\ &\quad > 115(.120)h(0) - 12(.036)(.011)(.9) \\ &\quad = 12[1.15h(0) - (.036)(.0099)] \\ &\quad > 12(h(0) - .00036) \\ &\quad > 0. \end{aligned}$$

Therefore, $\psi > 0$. So $(\psi + I_o)/\lambda > 0$.

Since $u(t) > -[(\psi + I_o)/\lambda]$, we have

$$\inf_{t \in R^1} u(t) \geqq -[(\psi + I_o)/\lambda].$$

Now $-[(\psi + I_o)/\lambda] \geqq -115$ if and only if $I_o \leqq 115\lambda - \psi$.

We have

$$\begin{aligned} &115\lambda - \psi \\ &= 115\{\bar{g}_K n^4(0)(2\hat{K} - 1)(1/2\hat{K}) + \bar{g}_\ell \\ &\qquad + \bar{g}_{Na}h(0)[1 + (1/\hat{K})(3.9945300 + (\alpha_h(0)/f_h(-115)))]\} \\ &\quad -115\bar{g}_{Na}h(0)[1 + (1/\hat{K})(3.9945300 + (\alpha_h(0)/f_h(-115)))] \\ &\quad + 12\bar{g}_K n^4(0)(2\hat{K} - 1)(1/2\hat{K}) - 10.5989\bar{g}_\ell \end{aligned}$$

which implies

$$115\lambda - \psi = 115\bar{g}_K n^*(0)(2\hat{K} - 1)(1/2\hat{K}) + 115\bar{g}_\ell$$
$$+ 12\bar{g}_K n^*(0)(2\hat{K} - 1)(1/2\hat{K}) - 10.5989\bar{g}_\ell$$
$$= 127\bar{g}_K n^*(0)(2\hat{K} - 1)(1/2\hat{K}) + 104.4011\bar{g}_\ell$$
$$> \frac{127(.036)(.010184565)(8.0216811)}{9.0216811} + .03132033$$ [7]
$$> (127)(.00036664434)(.88915591) + .03132033$$
$$> .04140250 + .03132033$$
$$= .07272283 .$$

Therefore, since $I_o \leqq .07272 < .07272283 < 115\lambda - \psi$, we have $-[(\psi + I_o)/\lambda] > -115.$

Hence

$$\inf_{t \in R^1} u(t) > -115.$$

<u>Proposition</u> 4.22. <u>Let</u> $[t_1, t_2]$ <u>be any interval such that</u> $-115 \leqq v(t) \leqq 0$. <u>Then</u> $m^2(t)\frac{dm}{dt}(t) < 1.3315100.$

<u>Proof</u>.

$$m^2\frac{dm}{dt} = m^2\left[\alpha_m(v) - (\alpha_m(v) + \beta_m(v))m\right]$$
$$= m^2\left[\alpha_m(v) + \beta_m(v)\right]\left\{(\alpha_m(v) / [\alpha_m(v) + \beta_m(v)]) - m\right\}$$
$$= \left[\alpha_m(v) + \beta_m(v)\right]\left[f_m(v)m^2 - m^3\right].$$

Let $S_1 = [-115, 12]$ and $S_2 = [-115, 0]$. Let

$$\phi(m) = \gamma m^2 - m^3$$

where γ is a positive constant. Then ϕ has a maximum at $(2/3)\gamma$. Therefore, if $\gamma = \max_{v(t) \in S_2} f_m(v)$, then

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[7] See footnote 2.

for $t \in [t_1, t_2]$

$$m^2(t)\frac{dm}{dt}(t) \leqq \left[\alpha_m(v(t)) + \beta_m(v(t))\right]\left(\gamma m^2(t) - m^3(t)\right)$$

$$\leqq \left[\alpha_m(v(t)) + \beta_m(v(t))\right]\left(\gamma^3(2/3)^2 - \gamma^3(2/3)^3\right)$$

$$= (4/27)\gamma^3\left[\alpha_m(v(t)) + \beta_m(v(t))\right]$$

$$\leqq (4/27)\gamma^3 \max_{v(t)\, \varepsilon\, S_2}\left[\alpha_m(v(t)) + \beta_m(v(t))\right] . \tag{4.6}$$

By Proposition 4.2, f_m is strictly decreasing with respect to v for all v. Therefore $\gamma \leqq f_m(-115) < .99925418$.

By Property 3.e

$$\max_{v\, \varepsilon\, S_1}\left[\alpha_m(v) + \beta_m(v)\right] = \alpha_m(-115) + \beta_m(-115) .$$

Therefore,

$$\max_{v(t)\, \varepsilon\, S_2}\left[\alpha_m(v(t)) + \beta_m(v(t))\right] \leqq \alpha_m(-115) + \beta_m(-115)$$

$$< 9.0078319125 .$$

So we have by (4.6)

$$m^2\frac{dm}{dt} \leqq (4/27)\gamma^3 \max_{v\, \varepsilon\, S_2}\left[\alpha_m(v) + \beta_m(v)\right]$$

$$< (4/27)(.99925418)^3(9.0078319125) \quad [8]$$

$$< (4/27)(.99776421)(9.0078319125)$$

$$= (.14781692)(9.0078319125)$$

$$< 1.3315100 .$$

[8] See footnote 2.

Proposition 4.23. Let $t^* \varepsilon [0,b]$ be such that for all $t \varepsilon [0,t^*]$, $0 \geqq v(t) \geqq -115$. Then $h(t) \geqq f_h(-115)$ for all $t \varepsilon [0,t^*]$.

Proof. Let t^* satisfy the hypothesis (such times exist by Remark 1 following Proposition 3.6.). Let $t \varepsilon [0,t^*]$ and let $S = [-115,0]$. By Proposition 4.2, $f_h = \alpha_h/(\alpha_h + \beta_h)$ is a strictly increasing function. Therefore

$$\inf_{y \varepsilon S} f_h(y) = \min_{y \varepsilon S} f_h(y) = f_h(-115) > 0 .$$

Since $v(t) \geqq -115$, we have by Proposition 4.2,

$$\eta(t) = f_h(v(t)) \geqq f_h(-115) .$$

Also, since η is initially strictly decreasing (Proposition 4.2 (ii), the Remark following Proposition 4.2, and the Remark following Proposition 3.6) we have

$\inf_{t \varepsilon [0,t^*]} \eta(t) < \eta(0)$. Hence,

$$h(0) > \inf_{t \varepsilon [0,t^*]} \eta(t) \geqq f_h(-115). \tag{4.7}$$

Suppose there exists $\hat{t} \varepsilon [0,t^*]$ such that $h(\hat{t}) = f_h(-115)$. Since we have (4.7), $h(0) = \eta(0) = f_h(0) > f_h(-115)$, and the fact that h is a continuous function, there exists $\bar{t} \leqq \hat{t}$ such that $h(\bar{t}) = \inf_{t \varepsilon [0,t^*]} \eta(t)$, $h(\bar{t}) < h(t)$ for all $t \varepsilon [0,\bar{t}]$, and $\frac{dh}{dt}(\bar{t}) \leqq 0$. But $h(\bar{t}) = \inf_{t \varepsilon [0,t^*]} \eta(t)$ implies $h(\bar{t}) \leqq \eta(t)$ for all $t \varepsilon [0,t^*]$ which implies $h(\bar{t}) \leqq \eta(\bar{t})$. Therefore, $\frac{dh}{dt}(\bar{t}) \geqq 0$ by Proposition 4.1.

Hence $\frac{dh}{dt}(\bar{t}) = 0$. We claim that, for the interval $[0,t^*]$, h has an absolute minimum at $\bar{t}$. If $\bar{t} = t^*$ we are done. So we assume $\bar{t} < t^*$. Let $A \in (0, \inf_{t \in [0,t^*]} \eta(t))$. Then by definition of $\bar{t}$, there does not exist a $t \in [0,\bar{t}]$ such that $h(t) = A$. If there is a $t \in (\bar{t},t^*]$ such that $h(t) = A$, let t^{**} be the first such time. Then $\frac{dh}{dt}(t^{**}) \leqq 0$. But $A < \inf_{t \in [0,t^*]} \eta(t)$ and $h(t^{**}) = A$ implies $h(t^{**}) < \eta(t^{**})$ which implies (Proposition 4.1) $\frac{dh}{dt}(t^{**}) > 0$. This contradiction gives us that there can be no $t \in (\bar{t},t^*]$ such that $h(t) = A$. Therefore, since A was arbitrary we have $h(t) \geqq \inf_{t \in [0,t^*]} \eta(t)$ for all $t \in [0,t^*]$ and h has an absolute minimum at $\bar{t}$ when h is restricted to $[0,t^*]$. Note that this implies that if $\hat{t}$ exists then $\inf_{t \in [0,t^*]} \eta(t)$ equals $f_h(-115)$ which implies there is a time $t \in [0,t^*]$ such that $v(t) = -115$. If no such $\hat{t}$ exists then since $h(0) > f_h(-115)$ and since h is continuous we have $h(t) > f_h(-115)$ for all $t \in [0,t^*]$. In either case $h(t) \geqq f_h(-115)$ for all $t \in [0,t^*]$.

Lemma 4.24. *Let* $I_o > 0$. *Let* $(v(t),n(t),m(t),h(t))$ *be the solution of* (2.13) *in* $\bar{D}$. *Let* $t^* \in (0,b]$ *be such that for all* $t \in (0,t^*)$, $-115 < v(t) < 0$. *As in Lemma* 4.21, *let* $u(t) = [(\psi + I_o)/\lambda][-1 + \exp(-\lambda t/\delta)]$ *where* t *is arbitrary*, $\delta = .00114778716$,

$$\lambda = \bar{g}_K n^4(0)(2\hat{K} - 1)(1/2\hat{K})$$
$$+ \bar{g}_{Na} h(0)\{1 + (1/\hat{K})[3.9945300 + (\alpha_h(0)/f_h(-115))]\} + \bar{g}_\ell ,$$

<u>and</u>

$$\Psi = 115\bar{g}_{Na} h(0)\{1 + (1/\hat{K})[3.9945300 + (\alpha_h(0)/f_h(-115))]\}$$
$$- 12\bar{g}_K n^4(0)(2\hat{K} - 1)(1/2\hat{K}) + 10.5989\bar{g}_\ell .$$

<u>Then</u>, <u>for</u> <u>all</u> $t \in [0,t^*]$,

$$u'(t) \leq H_1(u(t),n(t),m(t),h(t)).$$

<u>Proof</u>. Such values t^* exist by Proposition 3.5 and Remark 1 following Proposition 3.6. Let t^* be any such value. By Proposition 4.19 we have, for all $t \in (0,t^*)$

$$n(t) > n(0),\ m(t) > m(0),\ \text{and}\ h(t) < h(0).$$

Therefore, for all $t \in [0,t^*]$

(4.8) $$n(t) \geq n(0),\ m(t) \geq m(0),\ \text{and}\ h(t) \leq h(0).$$

Let $t \in [0,t^*]$. Consider $\alpha_n(u(t))(1 - n(t)) - \beta_n(u(t))n(t)$. Now β_n is an increasing function which implies

$$\beta_n(u(t)) \leq \beta_n(u(0)) = \beta_n(0) = (1/8)$$

since $u(t) \leq 0 = u(0)$. Therefore by Theorem 4.8

$$\begin{aligned}\frac{dn}{dt}(t) &= \alpha_n(u(t))(1 - n(t)) - \beta_n(u(t))n(t) \\ &> -\beta_n(t)n(t) \\ &\geq -(1/8)n(t) .\end{aligned}$$

Hence $4n^3(t)\frac{dn}{dt}(t) > -(1/2)n^4(t)$ which implies

$$K(u(t),n(t)) = \bar{g}_K\left(\frac{2}{a}\right)R\left[n^4(t) + \left(\frac{1}{\hat{K}}\right)\left(4n^3(t)\frac{dn}{dt}(t)\right)\right]$$
$$\bar{g}_K\left(\frac{2}{a}\right)R\left[n^4(t) - (1/\hat{K})(1/2)n^4(t)\right]$$

which implies

$$(4.9) \qquad K(u(t),n(t)) > \bar{g}_K(2/a)Rn^*(0)(2\hat{K} - 1)(1/2\hat{K}),$$

by (4.8) and the fact that $2\hat{K} - 1 > 0$. Now

$$\begin{aligned} \alpha_h(u(t))(1 - h(t)) - \beta_h(u(t))h(t) &< \alpha_h(u(t)) \\ &\leq \alpha_h(0) \\ (4.10) \qquad &= .07 \end{aligned}$$

since $h(t) < 1$ by Theorem 4.8, since α_h is increasing, and since $u(t) \leq 0$. Therefore by (4.10) and Proposition 4.22

$$\begin{aligned} Na(u(t),m(t),h(t)) &= \bar{g}_{Na}\left(\frac{2}{a}\right)R\left\{m^3(t)h(t) + \left(\frac{1}{\hat{K}}\right)\left[3m^2(t)h(t)\frac{dm}{dt}(t) + m^3(t)\frac{dh}{dt}(t)\right]\right\} \\ &< \bar{g}_{Na}\left(\frac{2}{a}\right)R\left\{m^3(t)h(t) + \left(\frac{1}{\hat{K}}\right)\left[3h(t)(1.3315100) + m^3(t)\alpha_h(0)\right]\right\} \\ &= \bar{g}_{Na}\left(\frac{2}{a}\right)Rh(t)\left\{m^3(t) + \left(\frac{1}{\hat{K}}\right)\left[3.9945300 + \frac{m^3(t)\alpha_h(0)}{h(t)}\right]\right\}. \end{aligned}$$

By (4.8) and Theorem 4.8

$$\begin{aligned} Na(u(t),m(t),h(t)) &< \bar{g}_{Na}\left(\frac{2}{a}\right)Rh(0) \\ (4.11) \qquad &\cdot \left\{1 + \left(\frac{1}{\hat{K}}\right)\left[3.9945300 + (\alpha_h(0)/h(t))\right]\right\}. \end{aligned}$$

By Proposition 4.23, $h(t) \geq f_h(-115)$ for all $t \in [0,t^*]$. Therefore, by (4.11)

$$\begin{aligned} Na(u(t),m(t),h(t)) &< \bar{g}_{Na}\left(\frac{2}{a}\right)Rh(0) \\ (4.12) \qquad &\cdot \left\{1 + \left(\frac{1}{\hat{K}}\right)\left[3.9945300 + (\alpha_h(0)/f_h(-115))\right]\right\}. \end{aligned}$$

Using (4.9) and (4.12) we have, since $0 \geq u(t) > -115$,

$$K(u(t),n(t))(u(t) - 12) + Na(u(t),m(t),h(t))(u(t) + 115)$$
$$+ \left(\frac{2}{a}\right)R\bar{g}_\ell(u(t) + 10.5989) + \left(\frac{2}{a}\right)RI_o <$$
$$< \left(\frac{2}{a}\right)R\bar{g}_K n^4(0)(2\hat{K} - 1)(1/2\hat{K})(u(t) - 12)$$
$$+ \left(\frac{2}{a}\right)R\bar{g}_{Na}h(0)\left\{1 + \left(\frac{1}{\hat{K}}\right)\left[3.9945300 + \frac{\alpha_h(0)}{f_h(-115)}\right]\right\}(u(t) + 115)$$
$$+ \left(\frac{2}{a}\right)R\bar{g}_\ell(u(t) + 10.5989) + \left(\frac{2}{a}\right)RI_o$$
$$= \left(\frac{2}{a}\right)R\left[\lambda u(t) + \psi + I_o\right]. \qquad (4.13)$$

Hence from (4.13) and Remark 2 following Proposition 3.2

$$H_1(u(t),n(t),m(t),h(t))$$
$$> -\left\{\left[\left(\frac{2}{a}\right)RC + \left(\frac{1}{\theta^2 C}\right)(\bar{g}_K n^4(t) + \bar{g}_{Na}m^3(t)h(t) + \bar{g}_\ell)\right]^{-1}\right\}$$
$$\cdot\left(\frac{2}{a}\right)R\left[\lambda u(t) + \psi + I_o\right]$$
$$> -\left[\left(\frac{2}{a}\right)R/\left(\frac{2}{a}\right)R\delta\right]\left[\lambda u(t) + \psi + I_o\right]$$
$$= -(1/\delta)\left[\lambda u(t) + \psi + I_o\right].$$

Since, by Lemma 4.21, $u'(t) = -(1/\delta)\left[\lambda u(t) + \psi + I_o\right]$ we have $H_1(u(t),n(t),m(t),h(t)) > u'(t)$ for all $t \in [0,t^*]$ and the conclusion follows.

Theorem 4.25. Let $0 < I_o \leq 72.72\ \mu A/cm^2$. Let $(v(t),n(t),m(t),h(t))$ be the solution of (2.13) in $\bar{D}$ and let $[0,b]$ be the right maximal interval of existence of the solution in $\bar{D}$. Let d be the first positive time that the solution v attains either -115 or 0 unless v attains neither, then let $d = b$. Then for all $t \in [0,d]$,

$$v(t) > -115 \quad .$$

Proof. We wish to show that v cannot become -115 before it becomes zero a second time ($v(0) = 0$). Suppose it does; i.e., suppose $v(d) = -115$. As in Lemma 4.21, let $u(t) = \left[(\psi + I_o)/\lambda\right]\left[-1 + \exp(-\lambda t/\delta)\right]$ for arbitrary t where

$\delta = .00114778716$,

$$\lambda = \bar{g}_K n^*(0)(2\hat{K} - 1)(1/2\hat{K}) + \bar{g}_{Na} h(0)\left\{1 + (1/\hat{K})\left[3.9945300 + (\alpha_h(0)/f_h(-115))\right]\right\} + \bar{g}_\ell ,$$

and

$$\psi = 115\bar{g}_{Na} h(0)\left\{1 + (1/\hat{K})\left[3.9945300 + (\alpha_h(0)/f_h(-115))\right]\right\} - 12\bar{g}_K n^*(0)(2\hat{K} - 1)(1/2\hat{K}) + 10.5989\bar{g}_\ell \quad .$$

Then u and d satisfy the hypotheses of Lemma 4.24. Therefore, for all $t \in [0,d]$, $u'(t) \leq H_1(u(t),n(t),m(t),h(t))$. Also, since $H = (H_1,H_2,H_3,H_4)$ is analytic in $\bar{D}$, then H satisfies a Lipschitz condition in $\bar{D}$. Now since $d \leq b$, if we let b_o of Corollary 4.18 equal d, then d also equals the t_1 of Corollary 4.18. Then, since $u(0) = v(0)$, if we let u be f_1 and v be g_1, we have that all of the hypotheses of Corollary 4.18 are satisfied. Therefore, by Corollary 4.18, $u(t) \leq v(t)$ for all $t \in [0,d]$. By Lemma 4.21, $\inf_{t \in R^1} u(t) > -115$ if $0 < I_o \leq .07272$. We have $0 < I_o \leq 72.72\ \mu A/cm^2$ which, since the consistent units are mA/cm^2, gives $0 < I_o \leq .07272$. Thus, $u(d) > -115$ which implies $v(d) > -115$ contradicting the assumption.

Therefore v cannot become -115 before it becomes zero a second time. Now if, for positive time, v never attains either zero or -115, then since $v(0) = 0$ we have $d = b$ and $v(t) > -115$ for all $t \in [0,b]$. If there is a time $t \in [0,b]$ such that $v(t) = 0$ then, by the above, d is the first such time and $v(t) > -115$ for all $t \in [0,d]$. In either case $v(t) > -115$ for all $t \in [0,d]$.

V. RESULTS OF THE BOUNDEDNESS THEOREMS

1. Solutions for All Nonnegative Time

The first conclusion is that for $I_o \geqq 0$ we have existence and uniqueness of the solutions of the initial value problem (2.13) for all time $t \geqq 0$. This follows from Theorem 3.3 and Remarks 1 and 2 after Theorem 3.3; i.e., it was proved that the right maximal interval of existence of the unique solution to (2.13) was either $[0,\infty)$ or $[0,b]$ where $(v(b),n(b),m(b),h(b)) \in \partial\bar{D}$ (the boundary of $\bar{D}$). In IV we proved that $0 < J(t) < 1$ where $J = n, m,$ or h, and that $\omega < v(t) < 12$ for any $t \geqq 0$ for which the solution (v,n,m,h) existed. Hence for no time $t \geqq 0$ do we have $(v(t),n(t),m(t),h(t)) \in \partial\bar{D}$ implying $b = \infty$.

2. New Bounds for n, m, and h

From Theorem 4.8 and V.1 we have $0 < J(t) < 1$ for all $t \in [0,\infty)$ where $J = n, m,$ or h. By Proposition 4.16 we have the results $n(t) > n(0)$, $m(t) > m(0)$, and $h(t) < h(0)$ for any nonnegative time t up to the first positive time t^* that $v(t^*) = 0$. So, for all $t \in [0,t^*)$

$$n(t) > .31767689,$$

$$m(t) > .052932485,$$

and

$$h(t) < .59612078 \quad .$$

For any $I_o \geqq 0$ such that $-115 \leqq v(t) \leqq 12$, we can obtain new bounds for n, m, and h which hold for all nonnegative time. Although they are not as good as the above bounds, we do obtain new upper and lower bounds, and at the same time prove that the functions n, m, and h are bounded away from zero and one. Also, it should be noted that if, for some positive time, the value of v were known, then considerably better resolutions on n, m, and h could be achieved by using the functions ν, μ, and η.

For the new upper and lower bounds we have the following proposition:

Proposition 5.1. Let $I_o \geqq 0$ be such that $-115 \leqq v(t) \leqq 12$ for all $t \in [0,\infty)$. Then for all $t \in [0,\infty)$

(i) $f_n(-115) = \dfrac{\alpha_n(-115)}{\alpha_n(-115) + \beta_n(-115)} \geqq n(t) \geqq f_n(12)$,

(ii) $f_m(-115) \geqq m(t) \geqq f_m(12)$,

(iii) $f_h(-115) \leqq h(t) \leqq f_h(12)$.

Proof. By Proposition 4.23, with $b = t^* = \infty$, we have $h(t) \geqq f_h(-115)$ for all $t \in [0,\infty)$. The proofs of the other five inequalities of (i), (ii), and (iii) are similar to the proof of Proposition 4.23.

Remark 1. By substituting in the values of 12 and -115 into the functions f_n, f_m, and f_h, we find that the new bounds are, for all $t \in [0,\infty)$,

$$.158791234 \leqq n(t) \leqq .97250201$$

$$.011895512 \leq m(t) \leq .99925418$$

$$.000222790356 \leq h(t) \leq .89619315 \quad .$$

Remark 2. The method of proof used in Proposition 4.23 will show that h is bounded away from zero for any $I_o \geq 0$ if -115 is replaced by $\omega = \min \{-115, v_\ell - (I_o/\bar{g}_\ell)\}$. Such a proof will also show that n and m are bounded away from one for any $I_o \geq 0$. For a given $I_o \geq 0$, new upper bounds could be calculated for n and m by using $f_n(\omega)$ and $f_m(\omega)$ respectively; likewise, a new lower bound could be calculated for h using $f_h(\omega)$. However, since $\omega < -115$ would imply that $.97250201 < f_n(\omega) < 1$, $.99925418 < f_m(\omega) < 1$, and $0 < f_h(\omega) < .000222790356$, they would probably not have much use in numerical work.

3. Continuous Dependence upon Parameters

The third result that can be derived is the continuous dependence of the system upon parameters. The following theorem and its proof may be found in [14, pp. 44, 45]:

Theorem 5.2. *Assume $\phi(\lambda)$ is defined on a p dimensional rectangle $R = \{\lambda \mid |\lambda - \lambda_o| < r\}$ and is continuous at $\lambda = \lambda_o$, and that if f, f_y, and f are continuous in an (q + p + 1) dimensional region $S = \{(x,y,\lambda) \mid (x,y) \in D$, D a region containing $(x_o, \phi(x_o))$; $\lambda \in R\}$. Consider the initial value problem*

(i) $dy/dx = f(x,y,\lambda)$

(ii) $y = \phi(\lambda)$ for $x = x_0$,

and assume that the solution $y = y(x,\lambda_0)$ for $\lambda = \lambda_0$ exists at least in the closed finite half-interval $x_0 \leqq x \leqq x_0 + b_1 < \infty$. Then for any $\varepsilon > 0$, there exists a $\delta > 0$ such that for $|\lambda - \lambda_0| < \delta$, the (unique) solution $y(x,\lambda)$ exists at least in the same interval, and $|y(x,\lambda) - y(x,\lambda_0)| < \varepsilon$ there.

Since for our purposes $p = 1$, $q = 4$, $\phi: R^1 \longrightarrow R^4$ is the constant function given by $\phi(\lambda) = (0,n_0,m_0,h_0)$, $R = R^1$, $f = (H_1,H_2,H_3,H_4)$ and is autonomous, etc., this theorem can be specialized to:

Theorem 5.3. Let $I_0 \geqq 0$. Let $\omega = \min\{-115, v_\ell - (I_0/\bar{g}_\ell)\}$. Let $D = \{(v,n,m,h) \mid \omega < v < 12, 0 < J < 1$ where $J = n, m,$ or $h\}$. Consider the initial value problem (2.13). Let $[0,b_1]$ be any finite interval and let λ_0 equal any parameter in $H_1(v,n,m,h)$. Let $x(t,\lambda_0) = (v(t),n(t),m(t),h(t))$ be the solution to (2.13) in $[0,b_1]$. Then for any $\varepsilon > 0$, there exists a $\delta > 0$ such that for $|\lambda - \lambda_0| < \delta$, the (unique) solution $x(t,\lambda)$ exists at least in $[0,b_1]$ and $|x(t,\lambda) - x(t,\lambda_0)| < \varepsilon$.

Proof. As stated above, most of Theorem 5.3 follows directly from applying Theorem 5.2 to system (2.13) and D. The fact that $[0,b_1]$ can be any finite interval follows directly from the boundedness theorems.

By allowing λ_o to be the propagation rate θ, Theorem 5.3 provides the mathematical proof that the former extreme sensitivity (see [5], [8], and [9]) to the propagation rate is removed. One can also vary the maximum values of the various conductances, or the radius of the axon, or the resistance without measurably changing the solutions of the system. A thorough discussion and numerical treatment of such possibilities can be found in [7, Part II].

Perhaps the most important parameter in the system is the sustained constant membrane current density I_o. The choice of I_o determines, to a large extent, the membranous cell that is to be modeled. Because of its importance we shall devote Chapter VI to a discussion of I_o and its effects on system (2.13).

VI. THE THRESHOLD PHENOMENON

1. Some Past and Present Numerical Results

H. M. Lieberstein [7] solved the system (2.13) numerically for various values of I_o. He demonstrated numerically the existence of a value of I_o, called a threshold, which exhibits the following behavior: if I_o is chosen below threshold, the first component **v** of the solution, starting at zero, varies slowly in time with small maximum negative and positive slope and is bounded by ±10 mv; if I_o is chosen just above threshold a potential spike develops which falls rapidly to about -93 mv, which then just as rapidly returns to zero, enters the refractory period, and imitates thereafter the v curve for subthreshold values of I_o. Dr. Lieberstein found that $I_o = 2.27$ $\mu A/cm^2$ was below threshold and that $I_o = 2.28$ $\mu A/cm^2$ was above threshold. He also found values of I_o, called successive thresholds, which yield two, three, four, etc. potential spikes before settling down to a subthreshold type behavior. The values of I_o for two, three, and four spikes, are respectively 5.98 $\mu A/cm^2$, 6.16 $\mu A/cm^2$, and 6.20 $\mu A/cm^2$. The numerical evidence also strongly indicated a value of I_o, called the limit of thresholds, for which an infinite sequence of potential spikes is fired.

Using the IBM 1130 digital computer at Wichita

State University, we obtained numerical solutions to the initial value problem (2.13) for various values of I_0. The method used to obtain the numerical solutions was the Runge-Kutta method of $O(\varphi^5)$ accuracy with $\varphi = .05$. Most of the cases which appear in [7] were run and our results coincide with the results in [7] except that we found only seven potential spikes for $I_0 = 6.23\ \mu A/cm^2$. This value of I_0 was the one which was estimated in [7] to be the limit of thresholds. The discrepancy probably lies partly in the small variation of parameters in our system (see footnote 1) and partly in the difficulty of predicting a limit from numerical evidence.

In addition to obtaining the solution component v, we also obtained the numerical solutions for n, m, and h. Representative graphs of these functions are presented in Figures 1 and 2 where (i) I_0 has values 2.27 $\mu A/cm^2$ and 2.28 $\mu A/cm^2$ in Figure 1; (ii) I_0 has values 5.97 $\mu A/cm^2$ and 5.98 $\mu A/cm^2$ in Figure 2. The graphs correspond respectively to Figures 2a and 2b of [7]. In Figures 3 and 4 the functions v and m are graphed for other larger values of I_0. It should be remarked that in our graphs positive potential differences are above the time axis and negative potential differences are below the time axis according to standard mathematical practice.
The graphs of voltage against time will therefore appear to be "upside down" to most of the graphs

which appear in the physiological literature. Hodgkin and Huxley's conventions on sign forced them to reverse the standard mathematical convention and graph positive potential difference "down" and negative potential difference "up". We discontinued this practice because of the confusion which would have resulted between theory and graphs for such concepts as "concave upward", "concave downward", "increasing", "decreasing", etc..

The various graphs represented in Figures 1-4 indicate that the function m has maxima and minima shortly after v has minima and maxima respectively. It can be seen that for any I_o such that v remains positive for a moderate length of time (for I_o less than about 80 $\mu A/cm^2$) m drops below m(0). For these values of I_o, which contain the range in which Hodgkin and Huxley were concerned, the assumption of Theorem 4.13 is substantiated with v^* less than or equal to about .48 mv for subthreshold values and greater than or equal to about 3 mv for suprathreshold values of I_o. The n and h also agree very well with the behavior desired by Hodgkin and Huxley (compare our Figure 1 with Figure 19 of [5]) which provides further evidence of the ability of these equations to model impulse type phenomena. For larger values of I_o, v either never becomes positive or is positive for only a very short period of time. In either case $v < 3$ mv and therefore taking $v^* > 3$ mv satisfies the assumption of Theorem 4.13

vacuously.

2. The Effects of the Theorem on Continuous Dependence

For this section I_o, measured in μA/cm², will be in the interval [2.27,2.28]. Theorem 5.3 specified that for a given fixed finite time interval $[0,\hat{b}]$ and a given $I_o > 0$, say I_o^*, the solution to (2.13) corresponding to any I_o sufficiently close to I_o^* must remain arbitrarily close to the solution of (2.13) corresponding to I_o^* throughout the interval $[0,\hat{b}]$. Since it can be shown that v is concave upward at t = 0 for $I_o > 0$, and since the numerical evidence indicates

(i) for $I_o = 2.27$ μA/cm², v is concave upward whenever v is negative;

(ii) for $I_o = 2.28$ μA/cm², v is concave downward as it starts its rapid decrease to -93 mv,

Theorem 5.3 admits only two mathematical possibilities for a threshold. The first possibility is that as I_o decreases from $I_o = 2.28$ μA/cm² the first time that v becomes concave downward tends to plus infinity. In this way, for a given $[0,\hat{b}]$ the first potential spike would occur at a time $t > \hat{b}$ as I_o is increased from 2.27 μA/cm², no impulses of intermediate size would occur, and the theorem would be satisfied. Since v starts out decreasing and negative for any $I_o > 0$, the fact that near $I_o = 2.27$ μA/cm² v is concave upward whenever v is negative would imply that there is some value of I_o ($2.27 < I_o < 2.28$) such that the solution v corresponding to this I_o would have the property $\lim_{t \to \infty} v'(t) = 0$. As we shall see in VII this would imply that (v,n,m,h) has a stationary point $(\hat{v},\hat{n},\hat{m},\hat{h})$ where $\hat{v}$ is approximately -8 mv. As we shall also see in VII, for $2.27 < I_o < 2.28$ there is no stationary point $(\hat{v},\hat{n},\hat{m},\hat{h})$ where $\hat{v}$ is near -8 mv. Therefore this possibility cannot be the one which explains the threshold phenomenon. For an example which does satisfy the above description, we have:

Example 6.1. Consider $\frac{dy}{dt} = y + \lambda$ with initial condition $y(0) = 0$. It can be readily verified that the solution $y(t) = \lambda(-1 + \exp(t))$ is the unique solution to this linear differential equation and also that the hypotheses of Theorem 5.3 are satisfied, implying that the solution y is continuously dependent upon λ. For $\lambda = -1$, the solution is $y(t) = 1 - \exp(t)$ and is concave downward. For $\lambda = +1$, the solution is $y(t) = -1 + \exp(t)$ and is concave upward. Thus we have seemingly a similar gross behavior as that of the solution v of system (2.13) near the point where the "off" and "on" solutions divide. As λ increases from minus one to plus one it is concave downward for every negative λ and concave upward for every positive λ. The value of λ such that $\lim_{t \to \infty} y'(t) = 0$ is $\lambda = 0$ and note that the solution for $\lambda = 0$ is a stationary value for the differential equation.

The other mathematical possibility and the only one remaining is that as I_o increases from 2.27 $\mu A/cm^2$ to 2.28 $\mu A/cm^2$ the solution **v** assumes intermediate positions between the two curves and has minima at intermediate points between -8 mv and -93 mv. For this case there is no really distinct threshold (as I_o takes on all real number values between 2.27 and 2.28), but only an extremely rapid change from one type of behavior to another which appears to give a jump of voltage when one is varying I_o by letting it assume only terminating decimal values as is necessarily the case in computing and in actual experiments. In the next section we will verify numerically that this continuous change is the behavior which the reformulated Hodgkin-Huxley model exhibits. (This type behavior has been called a quasi-threshold phenomenon in [13].)

It should be noted that in [13], where various past models (good and bad) of the threshold phenomenon have been discussed and classified, we find that these two mathematical possibilities are the only two types of behavior that have been proposed for systems of differential equations consisting of analytic functions. It is made clear that the models discussed in [13] do not involve any applied sustained membrane current density.

However, since the results obtained using the reformulated Hodgkin-Huxley model match the results desired for the original Hodgkin-Huxley model, it is appropriate to point out some differences which are present. There seemed to be some question with the original Hodgkin-Huxley model as to the presence or absence of "saddle points" and their relevance, if any, to the threshold phenomenon. This could perhaps be due in part to the mathematical problem of dealing with a system consisting of one second order equation and three first order equations and the desire to look at only the subspace of the variables v and dv/dt. For the reformulated model we shall show numerically that no singular points of any type are involved in the threshold phenomenon. Furthermore, since the reformulated model is a system of four first order equations, the space with coördinates v and dv/dt has no relevance as a "phase space" or subspace of a "phase space". There also seems to have been, in [13], no evidence then available (1955) indicating any intermediate impulses for the solution v between the "all" and "none" curves. Such evidence was given in [9] (1959), but the extreme instability inherent in the numerical handling of the original Hodgkin-Huxley model completely obviated any possibility for a precision search for a threshold with distinctions fine enough to conclusively exhibit intermediate behavior. Below we present a search for intermediate values of v using an IBM 360 Series, Model 76 computer. As will be seen, seventeen digits were needed to indicate adequately the behavior of v as I_o varied. It is important to note that such accuracy is only meaningful and can only be trusted when the system is continuously dependent on the initial values and parameters.

3. New Numerical Results

As stated in Section 2, an IBM 360 Series, Model 76 computer was used to search for a threshold between $I_o = 2.27\ \mu A/cm^2$ and $I_o = 2.28\ \mu A/cm^2$. In Table 2 we list the cases run, showing the intermediate positions obtained as we varied I_o. The maximum number of digits that could be computed accurately was seventeen. For two values of I_o which differed only in the seventeenth decimal place the intermediate values of a minimum for v were -19.73 mv and -46.06 mv. Note that v = -46.06 mv is approximately half way between the minima of v for the cases $I_o = 2.27\ \mu A/cm^2$ and $I_o = 2.28\ \mu A/cm^2$. Figure 5 shows the graphs for the solution v of some representative cases from Table 2.

Remark. The functions n, m, and h show the same kind of behavior as v concerning the threshold (see Figure 1) although it cannot be so easily seen since they only vary between zero and one.

TABLE 2. Intermediate Values of v Near Threshold

I_o (mA/cm²)	t (ms) at v minimum	v minimum (mv)
.00227	6.65	-7.63
.002271	6.70	-7.71
.002272	6.75	-7.80
.002273	6.85	-7.90
.002274	6.95	-8.01
.002275	7.05	-8.16
.002276	7.20	-8.34
.002277	7.45	-8.60
.002278	7.90	-9.09
.0022781	7.95	-9.17
.0022782	8.05	-9.27
.0022783	8.15	-9.40
.0022784	8.30	-9.57
.0022785	8.55	-9.83
.0022786	9.15	-10.48
.00227861	9.30	-10.65
.00227862	9.60	-10.96
.002278621	9.65	-11.01
.002278622	9.70	-11.07
.002278623	9.75	-11.13
.002278624	9.80	-11.20
.002278625	9.90	-11.30
.002278626	10.00	-11.42
.002278627	10.15	-11.59
.002278628	10.45	-11.91
.0022786281	10.50	-11.97
.0022786282	10.55	-12.03
.0022786283	10.60	-12.11
.0022786284	10.70	-12.20
.0022786285	10.80	-12.33

TABLE 2. continued

I_o (mA/cm²)	t (ms) at v minimum	v minimum (mv)
.0022786286	11.00	-12.52
.0022786287	11.35	-12.94
.00227862871	11.40	-13.02
.00227862872	11.50	-13.14
.00227862873	11.65	-13.31
.00227862874	11.90	-13.62
.002278628741	11.95	-13.68
.002278628742	12.00	-13.74
.002278628743	12.10	-13.82
.002278628744	12.15	-13.92
.002278628745	12.25	-14.05
.002278628746	12.45	-14.27
.002278628747	12.90	-14.86
.0022786287471	13.05	-15.05
.0022786287472	13.35	-15.45
.00227862874721	13.40	-15.53
.00227862874722	13.50	-15.63
.00227862874723	13.55	-15.76
.00227862874724	13.70	-15.96
.00227862874725	14.00	-16.39
.002278628747251	14.05	-16.48
.002278628747252	14.15	-16.58
.002278628747253	14.25	-16.73
.002278628747254	14.40	-16.96
.002278628747255	14.70	-17.49
.0022786287472551	14.75	-17.61
.0022786287472552	14.85	-17.77
.0022786287472553	15.00	-18.03
.0022786287472554	15.30	-18.55
.00227862874725541	15.35	-18.64

TABLE 2. continued

I_o (mA/cm²)	t (ms) at v minimum	v minimum (mv)
.00227862874725542	15.40	-18.78
.00227862874725543	15.55	-19.00
.00227862874725544	15.70	-19.29
.00227862874725545	15.90	-19.73
.00227862874725546	17.85	-46.06
.00227862874725547	17.05	-56.32
.00227862874725548	16.95	-57.56
.00227862874725549	16.80	-58.81
.0022786287472555	16.75	-59.63
.0022786287472556	16.40	-62.54
.0022786287472557	16.25	-63.87
.0022786287472558	16.20	-64.62
.0022786287472559	16.10	-65.26
.002278628747256	16.05	-65.71
.002278628747257	15.75	-67.91
.002278628747258	15.60	-68.86
.002278628747259	15.55	-69.53
.00227862874726	15.45	-70.04
.00227862874727	15.15	-72.17
.00227862874728	15.00	-73.09
.00227862874729	14.90	-73.68
.0022786287473	14.85	-74.04
.0022786287474	14.50	-75.99
.0022786287475	14.35	-76.80
.0022786287476	14.25	-77.32
.0022786287477	14.20	-77.64
.0022786287478	14.10	-77.93
.0022786287479	14.05	-78.16
.002278628748	14.05	-78.41
.002278628749	13.80	-79.63

TABLE 2. continued

I_o (mA/cm²)	t (ms) at v minimum	v minimum (mv)
.00227862875	13.65	-80.27
.00227862876	13.20	-82.29
.00227862877	13.05	-82.96
.00227862878	12.90	-83.42
.00227862879	12.85	-83.78
.0022786288	12.75	-83.96
.0022786289	12.45	-85.31
.002278629	12.30	-85.86
.00227863	11.75	-87.63
.00227864	11.00	-89.95
.00227865	10.80	-90.58
.00227866	10.65	-91.00
.00227867	10.55	-91.26
.00227868	10.45	-91.49
.00227869	10.40	-91.65
.0022787	10.35	-91.75
.0022788	10.00	-92.62
.0022789	9.80	-93.10
.002279	9.65	-93.38
.00228	9.10	-94.59

4. Conclusions

Table 2 and Figure 5 clearly illustrate the remarkable behavior of system (2.13). The threshold phenomenon is clearly present and accurately represented and yet the reformulated model contains none of the mathematical pecularities and unpleasantness inherent in all the earlier models. The system is still complicated and difficult to handle theoretically, but numerical treatment is very straightforward and could hardly be easier to deal with.

Although we did not search between $I_o = 5.97\ \mu A/cm^2$ and $I_o = 5.98\ \mu A/cm^2$ for intermediate potential impulses, it is clear how that could be accomplished and equally clear what the results would be since stationary points are not involved. The same is true for third, fourth, $\cdots$, thresholds. There is still the mathematical question as to what property of the system causes the rapid change of behavior from subthreshold to suprathreshold. It seems probable that there is a closed connected set T of points of six dimensional (t,v,n,m,h,I_o) space such that if at some time t the solutions (v,n,m,h), for a given I_o, reach a point in T, then the second derivative of the solution component v becomes negative and an impulse is initiated. The size of I_o affects the slope of v at $t_o = 0$ (see $\frac{dv}{dt}(0)$ in the proof of Proposition 3.5). As I_o increases, $\frac{dv}{dt}(0)$ gets more and more negative which enables v to take on larger negative values. This in turn allows n and m to take on larger positive values and h to take on smaller positive values. Future work will concentrate on this problem in the hope that once the mathematical property that governs the threshold behavior of (2.13) is known, then a simpler system of differential equations can be developed with the same such property that can replace or at least simplify system (2.13), and still satisfy the experimental data. In that way, perhaps one can even get an insight into the physical mechanism of the membrane.

VII. STATIONARY POINTS

It has been determined numerically that stationary points do actually play an important role in system (2.13) but, as has already been recounted, not a role which is involved with the threshold phenomenon. In order to discuss the role which stationary points do seem to play, it is necessary to include a section of definitions and theorems pertaining to the theory of Autonomous Systems of Differential Equations. We shall use and combine results from [14], [15], and [16].

1. Prerequisites

An autonomous system of differential equations is a system in which the independent variable does not occur explicitly. Let

$$\frac{dx}{dt} = f(x) \tag{7.1}$$

be an autonomous system of p differential equations. For simplicity assume that f is defined and analytic on a compact region $\bar{D}$ in x-space. A point x_0 is called a stationary point of (7.1) if $f(x_0) = 0$. Such a point has the property that the constant function given by $x(t) = x_0$ for all $t \in (-\infty,\infty)$ is a solution of (7.1). Since solutions of (7.1) will be uniquely determined by initial conditions, if there is a time t_0 such that $x(t_0) = x_0$ and if $f(x_0) = 0$, then $x(t) = x_0$ for all $t \varepsilon (-\infty, \infty)$.

Let $x(t)$ be a solution of (7.1). Let $T = \{t \mid b_1 < t < b\}$ denote the maximal interval of existence of that solution. The set of points $\{(t,x(t)) \mid t \varepsilon T\}$ is called a trajectory for that solution. The set of points $\{x(t) \mid t \varepsilon T\}$ is called the orbit for the solution. The whole x-space of dependent variables is called the phase space for (7.1). For autonomous systems every trajectory $\{(t,x(t)) \mid t \varepsilon T\}$ generates a one parameter family of trajectories; i.e., if γ is arbitrary and if $\{(t,x(t)) \mid t \varepsilon T\}$ is a trajectory, then $\{(t,x(t + \gamma)) \mid b_1 - \gamma < t < b - \gamma\}$ is also a trajectory for the solution x. The trajectories of this family all have the same orbit and are called equivalent. From the theory on the existence and uniqueness of solutions to (7.1) if follows that there is one and only one orbit through every point $x_0 \varepsilon \bar{D}$. Since our purposes are mainly concerned with $t \geqq 0$, we introduce the notion of semi-orbit: a semi-orbit for an orbit is that part of an orbit which is described by $t \varepsilon [t_0, b)$ where t_0 is an arbitrary but fixed point of T.

Suppose that $x(t) \varepsilon \bar{D}$ for all $t \varepsilon T$. Then $b = \infty$ and x is bounded. We can then talk about the concept of limit points for a semi-orbit. A point $\zeta \varepsilon \bar{D}$ is called a limit point for the semi-orbit if there exists a sequence $\{t_n\}$ such that $t_n \longrightarrow \infty$ and $x(t_n) \rightarrow \zeta$ as $n \rightarrow \infty$. Let Ω denote the set of limit points of the semi-orbit.

It should be noted that Ω does not depend upon t_0. The set Ω has the following properties (see [14, p. 69], [15, p. 145], or [16, pp. 3-4]):

(i) $\Omega \subset \bar{D}$; $\Omega \neq 0$.

(ii) If Ω consists of a single point ζ, then ζ is a stationary orbit (an orbit that consists of a single point) for the differential equation. In this case $\lim_{t \to \infty} x(t) = \zeta$. (If ζ is interior to $\bar{D}$, then $f(\zeta) = 0$.)

(iii) Ω is the union of orbits; i.e., if $\zeta \in \Omega$, then the entire orbit that passes through ζ also lies in Ω and is defined for all t.

(iv) Ω is compact.

(v) Ω is connected.

Note. Another way to talk about (iii) above is to define what is meant by an invariant set. If M is a set of points in phase space and x is a solution of (7.1), then if we denote the solution x through the initial point x_0 by $x = x(t_0, x_0)$ and if $x(t,M) = \{x(t,x_0) \mid x_0 \in M\}$, then M is said to be invariant if $x(t,M) = M$ for all t. Then (iii) can be stated: Ω is invariant.

For the orbits of an autonomous system there are only three topological possibilities for a phase space of any dimension (see [14, pp. 57-61]). They are:

(a) an orbit may consist of a single point in $\bar{D}$;

(b) an orbit may be homeomorphic to the unit circle in 2-space;

(c) an orbit may be such that any closed finite segment of it is homeomorphic to the closed unit interval between zero and one.

If an orbit consists of a single point then this point is a stationary point for the system. Case (b) corresponds to periodic motion; i.e., if x is a solution of (7.1) and $x(t_1) = x(t_2)$ for some $t_1 \neq t_2$, then x is either a stationary solution or a periodic one. If an orbit is neither periodic nor stationary, the following can be proved ([14, pp. 61-62]): if a representative trajectory approaches an interior point Δ of $\bar{D}$, then $f(\Delta) = 0$ so that Δ is a stationary point of the differential system and therefore cannot belong to the orbit defined by the trajectory. Another important fact is that the periodicity of an orbit needs nowhere to depend continuously on the initial data or parameters. An example is given in [14] which shows that when a parameter in a given system of differential equations is rational the solution is periodic and when the parameter is irrational, the solution never passes through the same point twice, but comes (infinitely often) arbitrarily close to every point in the phase space. In order to elaborate on the possibility of coming arbitrarily close to every point in some point set we shall need some additional definitions and theorems. We shall state several theorems which are, together with their proofs, found in [16]. First we need four definitions. (1) A bounded semi-orbit is said to be Lagrange-stable. (2) A set Σ of points in phase space is said to be minimal if it is nonempty, closed, invariant, and has no proper subset with these properties (Examples of minimal sets are stationary points and orbits of periodic motion.). (3) A solution x such that $x(t_o) = x_o$ is said to be positive (negative) Poisson-stable if, for any $\varepsilon > 0$ and $T > 0$, there exists a $t > T$ ($t < -T$) such that $d(x(t),x_o) < \varepsilon$, where d here signifies distance. A solution that is both positive and negative Poisson-stable is said to be Poisson-stable. (4) A solution x such that $x(t_o) = x_o$ is said to be recurrent if for all $\varepsilon > 0$ there exists a time interval T (depending on ε) such that the entire orbit is approximated (in d) within ε accuracy by any arc whose length corresponds to the time interval T. It follows that any recurrent motion is Poisson-stable.

Theorem 7.1 (Theorem 1.3, [16, p. 5]). *A bounded closed invariant set contains a minimal set.*

Theorem 7.2 (Theorem 1.4, [16, p. 6]). *Any orbit in a bounded minimal set is recurrent.*

Corollary 7.3 (Corollary 1.2, [16, p. 7]). *If a semi-orbit is Lagrange stable, then its set of limit points Ω contains a recurrent orbit.*

An orbit which is contained in Ω and which does not itself contain the semi-orbit is called a limit orbit. If the limit orbit is periodic, it is called a limit cycle.

The results above apply directly to system (2.13) since it is an autonomous system of analytic functions and since we have proved that the solution $(v(t),n(t),m(t),h(t))$ exists and is unique and bounded for each $I_o \geqq 0$ on the time interval $[0,\infty)$. Taking $\bar{D}$ of this section to be the same set $\bar{D}$ which we have used throughout this paper, we have shown that $(v(t),n(t),m(t),h(t)) \varepsilon \bar{D}$ for all $t \varepsilon [0,\infty)$. Therefore we can talk about the set Ω of limit points of the semi-orbit through $(0,n(0),m(0),h(0))$ corresponding to some $I_o \geqq 0$. We know that for each $I_o \geqq 0$, Ω is nonempty, invariant, closed, and connected and that the semi-orbit is Lagrange-stable. Therefore, by Theorems 7.1 and 7.2 and Corollary 7.3, Ω contains a recurrent orbit.

For the remainder of the paper we shall use, consistent with those before, the following notations: $\bar{D}$ shall, as always, be the set $\{(v,n,m,h) | \omega \leqq v \leqq 12, 0 \leqq J \leqq 1$ where $J = n$, m, or $h\}$ where $\omega = \min\{-115, v_\ell - (I_o/\bar{g}_\ell)\}$; for $J = n$, m, or h, $f_J(v) = \alpha_J(v)/[\alpha_J(v) + \beta_J(v)]$ and for $\rho = \nu$, μ, or η, we shall again employ the convention: $\rho = \nu$ if and only if $J = n$, $\rho = \mu$ if and only if $J = m$, and $\rho = \eta$ if and only if $J = h$.

2. A Stationary Point of System (2.13) for Each $I_o \geqq 0$

Theorem 7.4. Let $I_o \geqq 0$ be given. Let $(\hat{v},\hat{n},\hat{m},\hat{h}) \varepsilon \bar{D}$.

Then $(\hat{v},\hat{n},\hat{m},\hat{h})$ is a stationary point for system (2.13) if and only if $\hat{v}$ solves the equation

$$(7.2) \qquad (.036)\left[\frac{\alpha_n(v)}{\alpha_n(v) + \beta_n(v)}\right]^4 (v - 12) + (.120)\left[\frac{\alpha_m(v)}{\alpha_m(v) + \beta_m(v)}\right]^3 \left[\frac{\alpha_h(v)}{\alpha_h(v) + \beta_h(v)}\right](v + 115) + (.0003)(v + 10.5989) + I_o = 0$$

Proof. The point $(\hat{v},\hat{n},\hat{m},\hat{h})$ is a stationary point of system (2.13) if and only if $H_j(\hat{v},\hat{n},\hat{m},\hat{h}) = 0$ for $j = 1, 2, 3, 4$ if and only if

$$K(\hat{v},\hat{n})(\hat{v} - 12) + Na(\hat{v},\hat{m},\hat{h})(\hat{v} + 115) + \left(\frac{2}{a}\right)R\left[\bar{g}_\ell(\hat{v} + 10.5989) + I_o\right] = 0$$

and

$$0 = \alpha_J(\hat{v})(1 - \hat{J}) - \beta_J(\hat{v})\hat{J} \quad \text{for } J = n,\ m, \text{ and } h$$

if and only if

$$K(\hat{v},\hat{n})(\hat{v} - 12) + Na(\hat{v},\hat{m},\hat{h})(\hat{v} + 115) + \left(\frac{2}{a}\right)R\left[\bar{g}_\ell(\hat{v} + 10.5989) + I_o\right] = 0$$

and

$$\hat{J} = f_{\hat{J}}(\hat{v}) \quad \text{for } J = n,\ m, \text{ and } h$$

if and only if

$$\bar{g}_K\hat{n}^4(\hat{v} - 12) + \bar{g}_{Na}\hat{m}^3\hat{h}(\hat{v} + 115) + \bar{g}_\ell(\hat{v} + 10.5989) + I_o = 0$$

and

$$\hat{J} = f_{\hat{J}}(\hat{v}) \quad \text{for } J = n,\ m, \text{ and } h$$

if and only if

$$\bar{g}_K f_n^4(\hat{v})(\hat{v} - 12) + \bar{g}_{Na} f_m^3(\hat{v}) f_h(\hat{v})(\hat{v} + 115) + \bar{g}_\ell(\hat{v} + 10.5989) + I_o = 0$$

if and only if

$\hat{v}$ satisfies (7.2).

Theorem 7.4 gives us an explicit means of determining, for each I_o, the stationary points of system (2.13). We have already seen (see Remarks 1 and 3 following Proposition 3.6) that the initial value (0,n(0),m(0),h(0)) is a stationary point of (2.13) if and only if $I_o = 0$. This can also be verified easily by considering (7.2). However, for $I_o > 0$ the determination of v is not as simple. Note that if $\hat{v}$ is given then there is one and only one value of I_o (which might be negative) such that (7.2) is satisfied. We have not yet been able to prove that for each I_o there is one and only one value of v that solves (7.2). However, the following table, which gives a value of I_o for each integral value of v between v = 12 and v = -115 presents strong numerical evidence that $\hat{v}$ is a strictly decreasing function of I_o and hence indicates that there is a one to one correspondence between I_o and $\hat{v}$ and therefore between I_o and stationary points of (2.13). (We also computed a value of I_o for each tenth between v = 0 and v = -12. The results further justified the conjecture that $\hat{v}$ is a strictly decreasing function of I_o.) The values of $\hat{v}$ for the various values of I_o which have been graphed in Chapter VI also are included in the table. These values of v were determined numerically using the Newton method for each given value of I_o (Both determinations were made on the IBM 1130 computer at Wichita State University.). It should be noted that there is no indication of any connection at all between stationary points and values of I_o which produce thresholds.

TABLE 3. The Relationship Between I_o and Stationary Points $(\hat{v},\hat{n},\hat{m},\hat{h})$ as Determined by Equation (7.2)

$\hat{v}$ (mv)	I_o ($\mu A/cm^2$)	$\hat{v}$ (mv)	I_o ($\mu A/cm^2$)
12	-6.80266	-4	6.51836
11	-6.48290	-5	8.87870
10	-6.14971	-6	11.61228
9	-5.79778	-7	14.76454
8	-5.42033	-8	18.38409
7	-5.00890	-9	22.52306
6	-4.55302	-10	27.23936
5	-4.04008	-11	32.58797
4	-3.45501	-12	38.63987
3	-2.78021	-13	45.46405
2	-1.99534	-14	53.13692
1	-1.07725	-15	61.74044
0	0	-16	71.36159
-1	1.26524	-17	82.09140
-2	2.75003	-18	94.02335
-3	4.48873	-19	107.25123
-3.7445131	5.97	-20	121.86650
-3.7492619	5.98	-21	137.95525
-3.8668821	6.23	-22	155.59505

TABLE 3. continued

$\hat{v}$ (mv)	I_o ($\mu A/cm^2$)	$\hat{v}$ (mv)	I_o ($\mu A/cm^2$)
-23	174.85183	-51	1234.46514
-24	195.77707	-52	1281.13811
-25	218.40459	-53	1327.91609
-26	242.75440	-54	1374.77652
-27	268.82127	-55	1421.69918
-28	296.58581	-56	1468.66587
-28.118960	300	-57	1515.66030
-29	326.01010	-58	1562.66784
-30	357.04047	-59	1609.67539
-31	389.60985	-60	1656.67123
-32	423.64027	-61	1703.64485
-33	459.04562	-62	1750.58691
-34	495.73431	-63	1797.48901
-35	533.61177	-64	1844.34370
-36	572.58270	-65	1891.14437
-36.688485	600	-66	1937.88512
-37	612.55289	-67	1984.56072
-38	653.43079	-68	2031.16656
-39	695.12862	-69	2077.69858
-40	737.56324	-70	2124.15319
-41	780.65665	-71	2170.52727
-42	824.33629	-72	2216.81812
-43	868.53513	-73	2263.02333
-44	913.19159	-73.999980	2309.140
-45	958.24937	-74	2309.14091
-46	1003.65721	-75	2355.16910
-47	1049.36857	-76	2401.10645
-48	1095.34129	-77	2446.95170
-49	1141.53731	-78	2492.70387
-50	1187.92225	-79	2538.36215

TABLE 3. continued

$\hat{v}$ (mv)	I_o ($\mu A/cm^2$)	$\hat{v}$ (mv)	I_o ($\mu A/cm^2$)
-80	2583.92588	-99	3431.66665
-81	2629.39460	-100	3475.36609
-82	2674.76798	-101	3518.97806
-83	2720.04580	-102	3562.50333
-84	2765.22796	-103	3605.94269
-85	2810.31450	-104	3649.29688
-86	2855.30553	-105	3692.56673
-87	2900.20123	-106	3735.75298
-88	2945.00186	-107	3778.85649
-89	2989.70777	-108	3821.87802
-90	3034.31935	-109	3864.81842
-91	3078.83706	-110	3907.67845
-92	3123.26138	-111	3950.45898
-93	3167.59287	-112	3993.16076
-94	3211.83208	-113	4035.78463
-95	3255.97965	-114	4078.33140
-96	3300.03621	-114.99993	4120.800
-97	3344.00244	-115	4120.80190
-98	3387.87901		

The theory presented in Section 1 stated that there are only three topological possibilities for the orbits of an autonomous system. We already know that for $I_o > 0$ the initial point (0,n(0),m(0),h(0)) is not a stationary point of system (2.13). Therefore for any $I_o > 0$ the semi-orbit must consist of more than one point and cannot, because of the uniqueness of an orbit through each point, become a stationary value at any finite time. The last two sections discuss the remaining two possibilities.

3. Periodic Solutions

Our numerical evidence indicates that there are no periodic solutions for the initial value problem (2.13). For any $I_o > 0$ such that the assumption of Theorem 4.13 is nonvacuously satisfied, it can be proved that there are no periodic solutions. The proof hinges on the fact that in order for the solution to be periodic there must be a time $t^* > 0$ such that $\frac{dv}{dt}(t^*) < 0$, $\frac{dJ}{dt}(t^*) = 0$ for $J = n$, m, or h, $v(t^*) = 0$, $n(t^*) = n(0)$, $m(t^*) = m(0)$ and $h(t^*) = h(0)$. Such a t^* would occur at the end of a refractory period of v. But it follows from the assumption of Theorem 4.13 that for any such t^* there is a time $t_1 < t^*$ such that $m(t_1) = m(0)$, $m(t) \leqq m(0)$ for $t \in [t_1, t^*]$ and $v(t) > 0$ for $t \in (t_1, t^*)$. It also follows that there is some t_2, $t_1 < t_2 < t^*$, such that $m(t_2) = \mu(t_2)$ and $m(t) \leqq \mu(t)$ for $t \in [t_2, t^*]$. The only way for $m(t^*)$ to be equal to $m(0)$ is for $m(t^*) = \mu(t^*)$ which cannot happen unless μ is stationary at t^*. But μ stationary at t^* implies v is stationary at t^* and we have already that $\frac{dv}{dt}(t^*) < 0$.

Our numerical computations show that the assumption of Theorem 4.13 is nonvacuously satisfied for I_o less than approximately 80 $\mu A/cm^2$. For larger I_o this assumption is satisfied vacuously. For values of I_o greater than approximately 100 $\mu A/cm^2$ the solution v never returns to zero and the initial point is never taken on a second time, so there can be no periodic solutions. For I_0 in the approximate interval $80\ \mu A/cm^2 < I_0 < 100\ \mu A/cm^2$, the numerical evidence indicates that v is bounded above by about 1 mv and is positive only for one brief period which occurs after the first impulse. In this time interval m is near m(0) but n has values near its maximum and h has values near its minimum, both of them far away from the initial values. Therefore, for any $I_0 > 0$ such that the assumption of Theorem 4.13 is vacuously satisfied, the solution does not appear to be Poisson-stable and hence not periodic. Hence the numerical evidence indicates that there is no periodic solution for any $I_0 > 0$.

4. Stationary Points at Infinity and Recurrent Orbits

The discussions of Sections 2 and 3 indicate that for $I_0 > 0$ the semi-orbit pertaining to the solution of the initial value problem (2.13) is such that any closed finite segment of it is homeomorphic to the closed unit interval [0,1]. It was shown numerically, in [7], that for large I_0 cells with a plateau type behavior could be modeled; i.e., for large I_0 the solution component v appeared to tend to a constant which was an interior point of the interval $(\omega, 12)$. If we knew that this information implied that the semi-orbit tended to an interior point of $\bar{D}$ then this point, by the theory of Section 1, would be a stationary point for the system. The following theorem proves just that.

Theorem 7.5. *Let* $I_o > 0$. *Let* $(v(t),n(t),m(t),h(t))$ *be the solution of* (2.13) *on* $[0,\infty)$ *corresponding to* $\bar{D}$. *Suppose* $\lim_{t\to\infty} v(t) = \hat{v}$ *where* $\hat{v} \in (\omega,12)$. *Then* $\lim_{t\to\infty} J(t) = f_J(\hat{v})$ *for* $J = n$, m, and h.

Proof. Let $\varepsilon > 0$. Let J be one of n, m, or h and ρ be the corresponding function ν, μ, or η. We have seen early in the paper that ρ is an analytic function of t and that f_J is an analytic function of v. Hence both are continuous functions of their variables. Therefore since $\rho = f_J \circ v$ we have

$$\begin{aligned}\lim_{t\to\infty}\rho(t) &= \lim_{t\to\infty}(f_J \circ v)(t)\\ &= \lim_{t\to\infty} f_J(v(t))\\ &= f_J(\lim_{t\to\infty} v(t))\\ &= f_J(\hat{v}) \quad .\end{aligned} \tag{7.3}$$

Now $\hat{v} \in (\omega,12)$ implies by Proposition 4.2 that $f_J(\omega) > f_J(\hat{v}) > f_J(12)$ if J is either n or m, and $f_J(12) > f_J(\hat{v}) > f_J(\omega)$ if J is h. This implies that $f_J(\hat{v})$ is an interior point of $[0,1]$.

Let $T_\rho > 0$ be the time such that $t > T_\rho$ implies $|\rho(t) - f_J(\hat{v})| < \varepsilon$. T_ρ exists by (7.3). Therefore

$$\inf_{t > T_\rho} \rho(t) > f_J(\hat{v}) - \varepsilon$$

and

$$\sup_{t > T_\rho} \rho(t) < f_J(\hat{v}) + \varepsilon.$$

(Case 1.) Suppose there exists $\bar{t} \in (0,\infty)$ such that

$$\inf_{t > T_\rho} \rho(t) \leqq J(\bar{t}) \leqq \sup_{t > T_\rho} \rho(t).$$

Then it follows from Proposition 4.1 that for all $t > \bar{t}$

$$\inf_{t > T_\rho} \rho(t) \leqq J(t) \leqq \sup_{t > T_\rho} \rho(t)$$

and thus

$$|J(t) - f_J(\hat{v})| < \varepsilon.$$

Now suppose such a $\bar{t}$ does not exist. Then for all $t \in (0,\infty)$ we have either

(Case 2.) $$J(t) < \inf_{s > T_\rho} \rho(s)$$

or

(Case 3.) $$J(t) > \sup_{s > T_\rho} \rho(s)$$

In Case 2., we have that $J(t) < \rho(t)$ for all $t > T_\rho$ and therefore by Proposition 4.1 that J is a strictly increasing function in (T_ρ, ∞). J is also bounded above by $\inf_{t > T_\rho} \rho(t)$. Therefore there exists some point $s_J \in (0,1)$ such that

$$\lim_{t \to \infty} J(t) = s_J.$$

Similarly, in Case 3, J is a strictly decreasing function in (T_ρ, ∞) and is bounded below implying that there exists some point $s_J \in (0,1)$ such that

$$\lim_{t \to \infty} J(t) = s_J.$$

In any one of the three possible cases we have that for $J = n, m,$ or h there exist constants s_n, s_m, and s_h such that $\lim_{t \to \infty} J(t) = s_J$. Therefore the solution $(v(t), n(t), m(t), h(t))$ converges to an interior point of $\overline{D}$. By Section 1 this implies that $(\hat{v}, s_n, s_m, s_h)$ is a stationary point of the system which implies, by the proof of Theorem 7.4, that $s_n = f_n(\hat{v})$, $s_m = f_m(\hat{v})$, and $s_h = f_h(\hat{v})$. (This last statement also implies that Cases 2 and 3 are not possible, giving us the same result by Case 1 for each function.)

The case used in [7] to illustrate the plateau behavior used the parameters $I_o = 500\ \mu A/cm^2$, $\bar{g}_{Na} = .192\ mho/cm^2$, and $v_\ell = -8.1588$ mv with the other parameters the standard ones for the 6.3° Centigrade case. For this case equation (7.2) yields the value $\hat{v} = -35.237402$ mv. Solving the system numerically we get that v converges to some interior point. The convergence is very rapid so that when t reached 35.0 ms the numerical value for v was constant to eight digits and was the value v = -35.237400 mv. This result strongly indicates that for these values of the parameters the semi-orbit was tending to a stationary point at infinity. Using this result as a hint we checked the numerical computations for other values of I_o run earlier. The results are that for any I_o below what is called in [7] the <u>limit of thresholds</u> the solution v tended toward a constant after, in some cases, several impulses. We also found the same behavior for any I_o above what is called in [7] the <u>overload value</u> of I_o. Between these two values the solutions were oscillatory for as long as the computations were run. Table 4 shows some of the cases run where the semi-orbit tended to a stationary point. One important result of this discovery is that we can now choose the value of voltage which we wish the plateau to "rest on," because once that value is chosen, (7.2) provides the I_o. The oscillatory numerical solutions exhibited the following behavior: being above threshold, there is first a large negative potential spike followed by the series of smaller impulses. Every impulse after the first for these values of I_o were of consistent height and showed no evidence of damping as the numerical solutions for values of I_o above the "overload value" and below the "limit of thresholds" value.

We conclude the following: in the perspective of Section 1 these numerical results indicate that for I_o below the "limit of thresholds" or above the "overload value" the set of limit points Ω of the semi-orbit consists of only one point. For I_o between these values Ω consists of more than one point and hence is connected, compact, and invariant. Corollary 7.3 would then indicate that Ω contains a recurrent orbit. Evidently, the solution for such I_o approached this recurrent orbit as $t \to \infty$. Because of the difference of size of the first and later impulses the initial point could not be in the minimal set because if it were, Theorem 7.2 would indicate that the whole semi-orbit is recurrent and the first impulse could not be different in size from the later impulses. Further work on this subject will concentrate on providing theorems to substantiate the strong numerical evidence presented here.

TABLE 4. The Asymptotic Approach of the Solutions of (2.13) to the Stationary Values $(\hat{v},\hat{n},\hat{m},\hat{h})$ Given by Equation (7.2)

I_o (mA/cm)	$\hat{v}$	$\hat{n}$ (given by (7.2))	$\hat{m}$	$\hat{h}$	v	n at maximum time of numerical solutions*	m	h
.00227	-1.6937574	.34392137	.06450145	.53593264	-1.6937605	.34392134	.06450148	.53593236
.00228	-1.7002910	.34402360	.06455012	.53569794	-1.7002960	.34402362	.06455017	.53569823
.00597	-3.7445131	.37628111	.08146027	.46231215	-3.7432837	.37627109	.08144714	.46232459
.00598	-3.7492619	.37635654	.08150365	.46214306	-3.7529980	.37639810	.08154789	.46208179
.00623	-3.8668821	.37822534	.08258453	.45795891	-3.8576965	.37819443	.08249357	.45798975
.300	-28.118960	.71116722	.58121622	.03648831	-28.118962	.71116717	.58121627	.03648831
.600	-36.688485	.78397149	.76496364	.01662547	-36.688482	.78397150	.76496361	.01662548
2.30914	-73.999980	.92823025	.98689442	.00174883	-73.999960	.92823034	.98689439	.00174891
4.1208	-114.99993	.97250197	.99925392	.00022279	-114.99995	.97250197	.99925392	.00022340

*The maximum time was: 100 ms for I_o = .00227, .00228, .00597, .00598, and .300; 200 ms for I_o = .00623; 32 ms for I_o = .600; 16 ms for I_o = 2.309143; 14 ms for I_o = 4.1208.

APPENDIX: One Equivalent First Order Integro-differential Equation

Part of the difficulty involved in a mathematical investigation of system (2.13) is that this system consists of four nonlinear equations. It would be convenient if we could express this system in some simpler way. The following theorem proves the equivalence of system (2.13) and one first order integro-differential equation. While one might question whether the resulting equation is much simpler, yet it is one equation and also opens up the possibilities of studying the Hodgkin-Huxley equations using the theory of Integro-differential Equations. Although we have not made use of this theorem, it is certainly closely related and is thus included here.

Theorem A.1. *Let* $(\bar{v}(t), \bar{n}(t), \bar{m}(t), \bar{h}(t))$ *be the solution of the initial value problem* (2.13). *Let*

$$\varphi_J(t,v) = J(0)\exp\left[-\int_0^t (\alpha_J \circ v + \beta_J \circ v)(x)dx\right]$$

$$- \exp\left[-\int_0^t (\alpha_J \circ v + \beta_J \circ v)(x)dx\right]$$

$$\cdot \int_0^t (-\alpha_J \circ v)(s)\exp\left[\int_0^s (\alpha_J \circ v + \beta_J \circ v)(x)dx\right]ds$$

where $J = n, m,$ *or* h *and* v *is an implicit function of* t.

Consider

$$\text{(A.1)} \quad \frac{dv}{dt} = \bar{H}(v,t) = H_1(v,\varphi_n(t,v),\varphi_m(t,v),\varphi_h(t,v))$$

Then if $\tilde{v}$ is a solution of (A.1), then $(\tilde{v}(t),\varphi_n(t,\tilde{v}(t)),\varphi_m(t,\tilde{v}(t)),\varphi_h(t,\tilde{v}(t)))$ is a solution of (2.13). Conversely, if $(\bar{v}(t),\bar{n}(t),\bar{m}(t),\bar{h}(t))$ is a solution of (2.13) then $\bar{v}$ solves (A.1).

Proof. Let $(\bar{v}(t),\bar{n}(t),\bar{m}(t),\bar{h}(t))$ solve (2.13). Then using the function $\bar{v}$ we have that $\alpha_n \circ \bar{v}$, $(\alpha_n + \beta_n) \circ \bar{v}$, $\alpha_m \circ \bar{v}$, $(\alpha_m + \beta_m) \circ \bar{v}$, $\alpha_h \circ \bar{v}$, and $(\alpha_h + \beta_h) \circ \bar{v}$ are all functions of t and hence given $\bar{v}$ the functions H_2, H_3, and H_4 of (2.13) become linear. Therefore we can solve these last three equations by elementary means obtaining

$$J(t) = J(0)\exp\left[-\int_0^t (\alpha_J \circ \bar{v} + \beta_J \circ \bar{v})(x)dx\right]$$

$$- \exp\left[-\int_0^t (\alpha_J \circ \bar{v} + \beta_J \circ \bar{v})(x)dx\right]$$

$$\cdot \int_0^t (-\alpha_J \circ \bar{v})(s)\exp\left[\int_0^s (\alpha_J \circ \bar{v} + \beta_J \circ \bar{v})(x)dx\right]ds$$

for J = n, m, and h as the solutions of the second, third, and fourth equations of the system respectively. Since the solution of the system is unique, we have $n = \bar{n}$, $m = \bar{m}$, and $h = \bar{h}$. Therefore since $n(t)$ is just $\varphi_n(t,\bar{v})$, $m(t) = \varphi_m(t,\bar{v})$, and $h(t) = \varphi_h(t,\bar{v})$ we have that $d\bar{v}/dt = H_1(\bar{v},\bar{n},\bar{m},\bar{h}) = H_1(\bar{v},\varphi_n(t,\bar{v}),\varphi_m(t,\bar{v}),\varphi_h(t,\bar{v})) = H_1(\bar{v},t)$ which implies that $\bar{v}$ solves (A.1). Conversely, let $\tilde{v}$ be a solution of (A.1). We claim that $(\tilde{v}(t),\varphi_n(t,\tilde{v}),\varphi_m(t,\tilde{v}),\varphi_h(t,\tilde{v}))$ is a solution of (2.13) satisfying the initial conditions. Consider

$$\frac{dn}{dt} = H_2(v,n).$$

Let n be defined by $n(t) = \varphi_n(t,\tilde{v})$. Then if we let

$$G(t) = (\alpha_n \circ \tilde{v} + \beta_n \circ \tilde{v})(t) \text{ and } F(t) = \exp\left[-\int_0^t G(x)dx\right],$$

we have

$$\begin{aligned}
\frac{dn}{dt}(t) = \frac{d\varphi_n}{dt}(t) &= n(0)(-1)G(t)F(t) \\
&\quad - (-1)G(t)F(t)\int_0^t\left[(-\alpha_n \circ \tilde{v})(s)/F(s)\right]ds \\
&\quad - F(t)\left[(-\alpha_n \circ \tilde{v})(t)/F(t)\right] \\
&= -n(0)G(t)F(t) \\
&\quad + G(t)F(t)\int_0^t\left[(-\alpha_n \circ \tilde{v})(s)/F(s)\right]ds \\
&\quad + \alpha_n(\tilde{v}(t)) \\
&= -G(t)F(t)\left\{n(0) - \int_0^t\left[(-\alpha_n \circ \tilde{v})(s)/F(s)\right]ds\right\} \\
&\quad + \alpha_n(\tilde{v}(t)) \\
&= \alpha_n(\tilde{v}(t)) - (\alpha_n(\tilde{v}(t)) + \beta_n(\tilde{v}(t)))n(t) \\
&= H_2(\tilde{v},n)
\end{aligned}$$

Thus the second equation is solved. The third and fourth are solved similarly and the initial conditions are satisfied trivially. Therefore if $(\tilde{v},n,m,h)$ solves the first equation, we are done. Now

$$\frac{d\tilde{v}}{dt}(t) = \bar{H}(\tilde{v},t) = H_1(\tilde{v},\varphi_n(t,\tilde{v}),\varphi_m(t,\tilde{v}),\varphi_h(t,\tilde{v}))$$

$$= H_1(\tilde{v},n,m,h),$$

so $(\tilde{v},n,m,h)$ is a solution of (2.13).

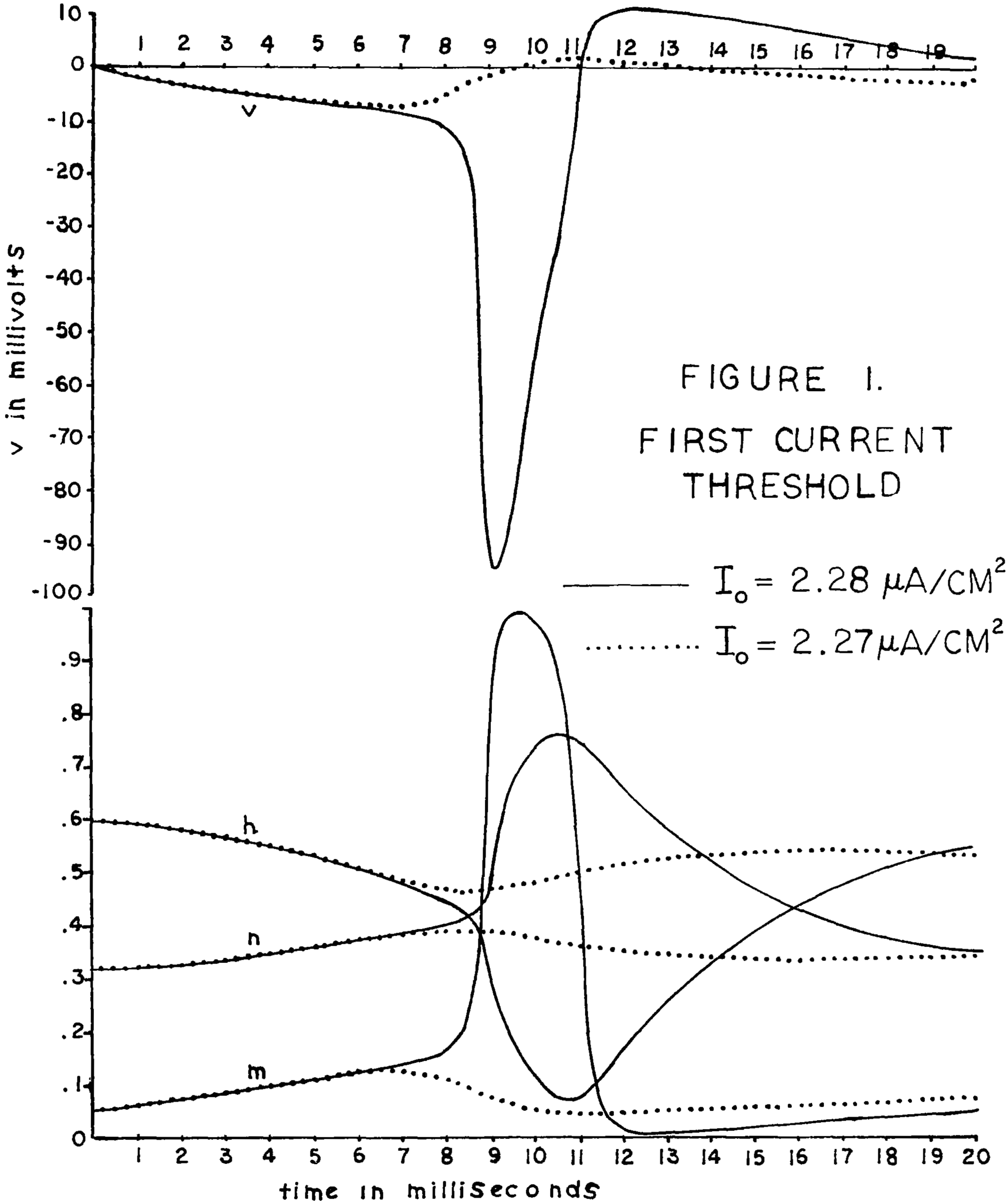


FIGURE 1.
FIRST CURRENT THRESHOLD

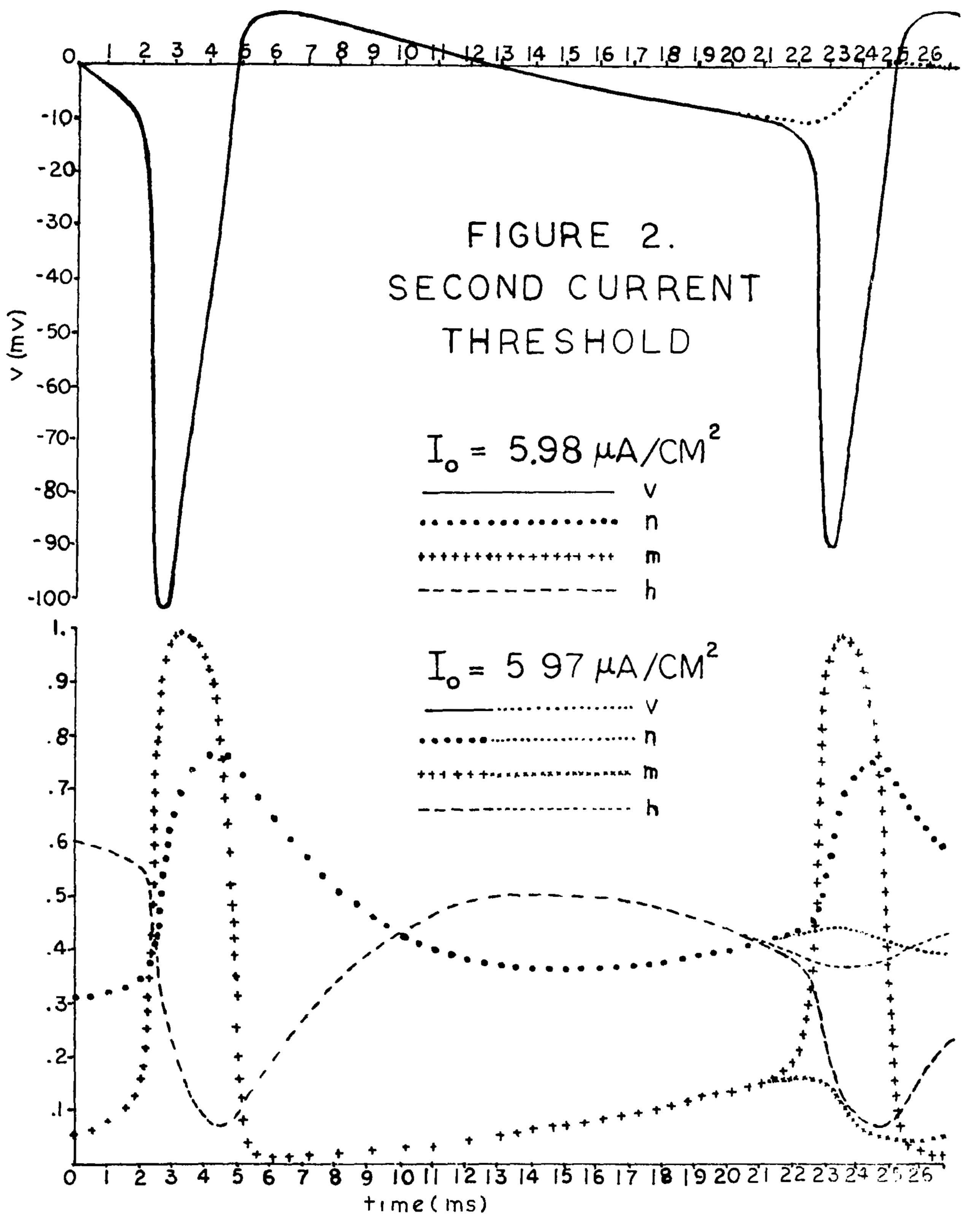


FIGURE 2.
SECOND CURRENT
THRESHOLD
I_o = 5.98 μA/CM^2
v
n
m
h
I_o = 5 97 μA/CM^2
v
n
m
h
v (mv)
time (ms)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
1.
.9
.8
.7
.6
.5
.4
.3
.2
.1
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26

FIGURE 3. v AND m FOR $I_o = 7.\ \mu A/CM^2$ AND $I_o = 50.\ \mu A/CM^2$

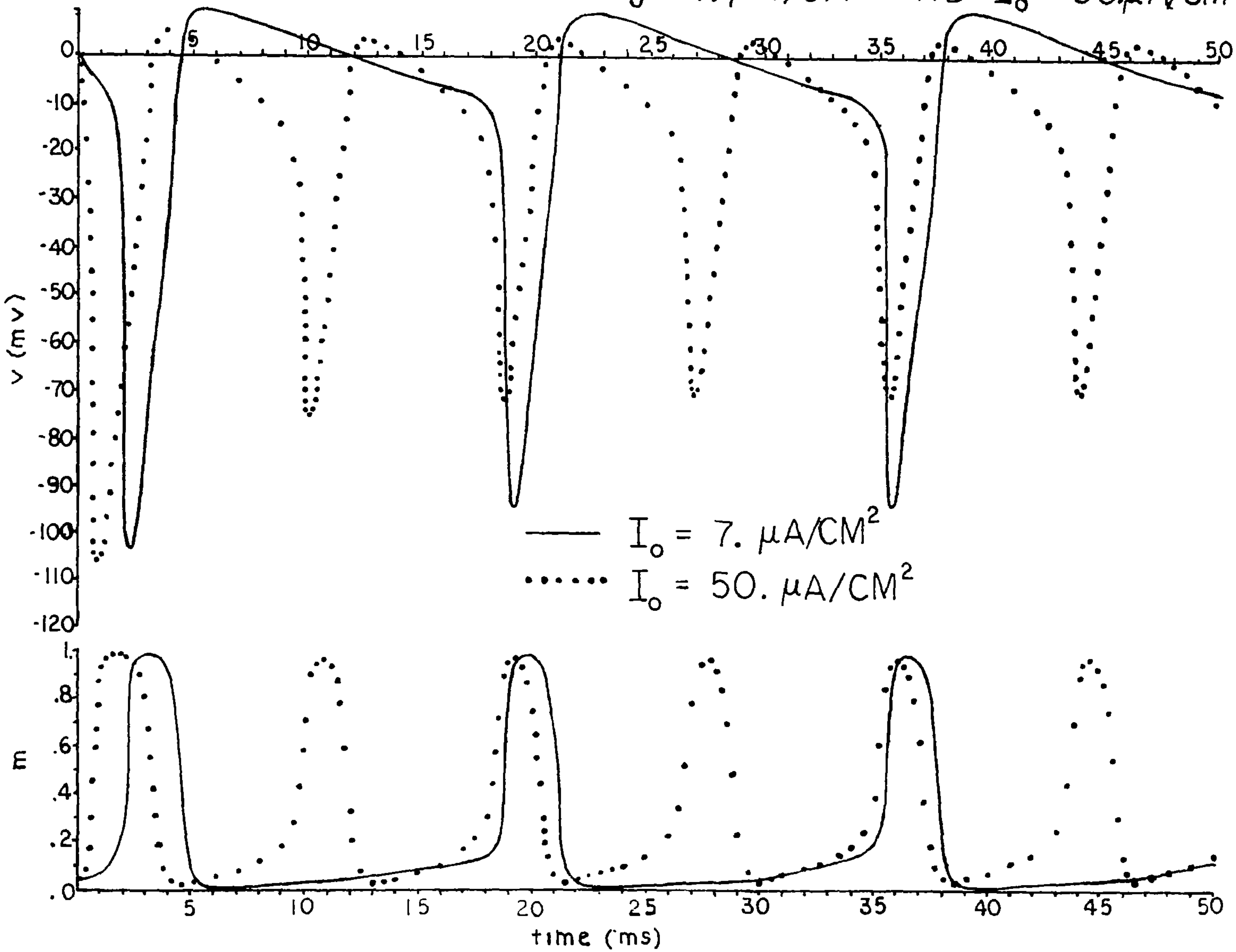


FIGURE 4. v AND m FOR $I_o = 100.\ \mu A/CM^2$ AND $I_o = 600.\ \mu A/CM^2$

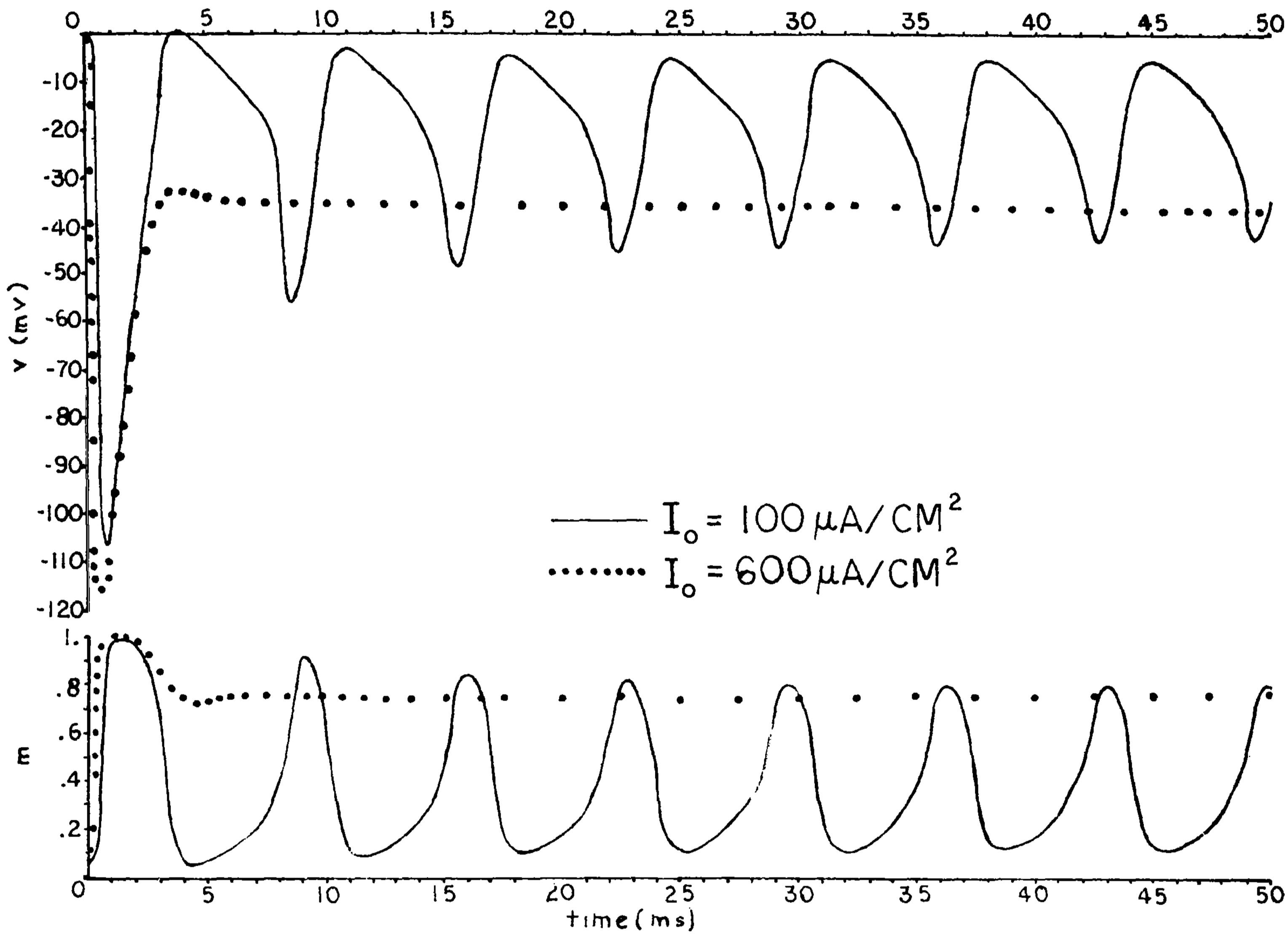
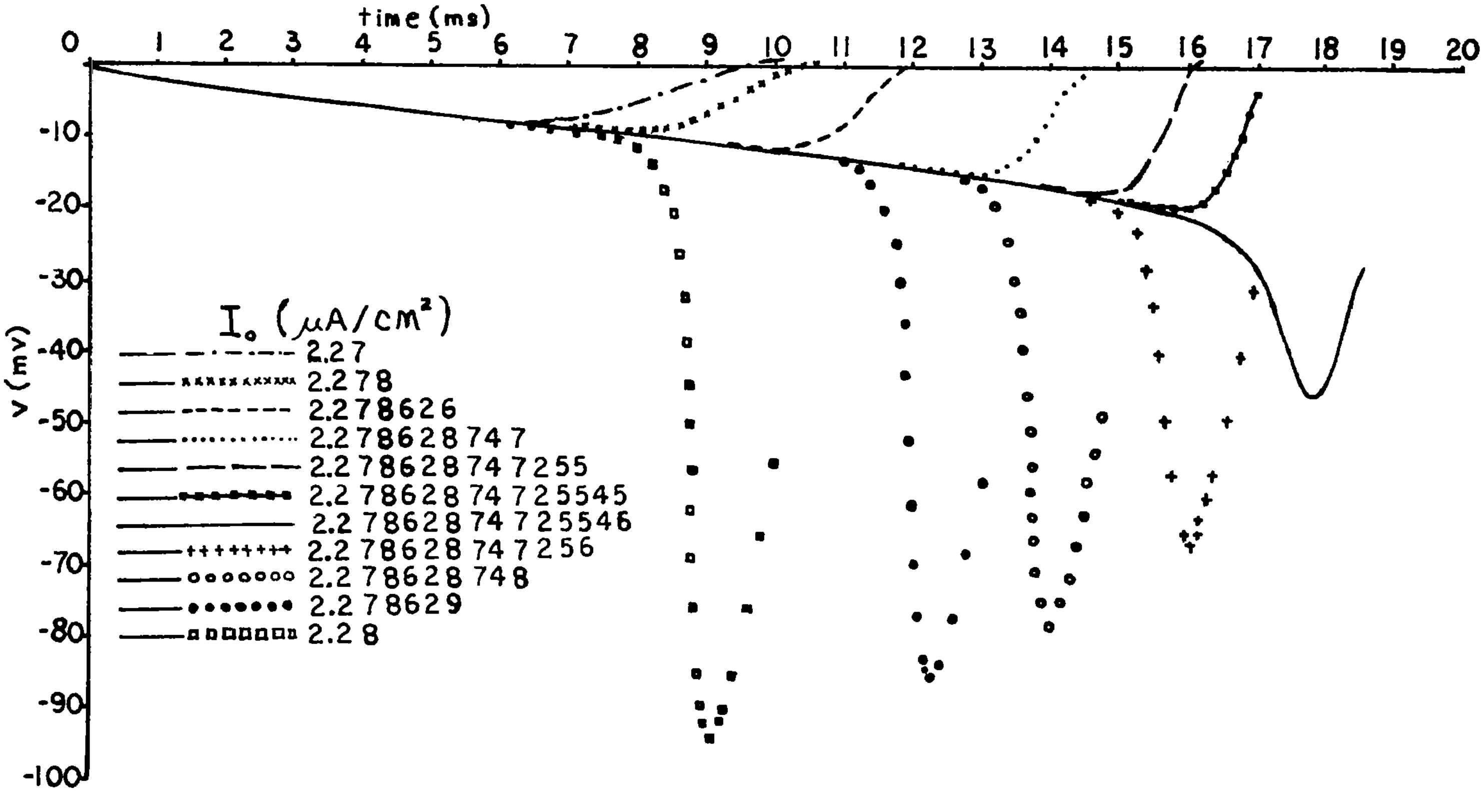


FIGURE 5. "INTERMEDIATE" VALUES OF v NEAR THRESHOLD



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