SUBTHRESHOLD OSCILLATORY RESPONSES OF THE HODGKIN-HUXLEY CABLE MODEL FOR THE SQUID GIANT AXON

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ABSTRACT The classical cable equation, in which membrane conductance is considered constant, is modified by including the linearized effect of membrane potential on sodium and potassium ionic currents, as formulated in the Hodgkin-Huxley equations for the squid giant axon. The resulting partial differential equation is solved by numerical inversion of the Laplace transform of the voltage response to current and voltage inputs. The voltage response is computed for voltage step, current step, and current pulse inputs, and the effect of temperature on the response to a current step input is also calculated.

The validity of the linearized approximation is examined by comparing the linearized response to a current step input with the solution of the nonlinear partial differential cable equation for various subthreshold current step inputs.

All the computed responses for the squid giant axon show oscillatory behavior and depart significantly from what is predicted on the basis of the classical cable equation. The linearization procedure, coupled with numerical inversion of the Laplace transform, proves to be a convenient approach which predicts at least qualitatively the subthreshold behavior of the nonlinear system.

INTRODUCTION

In the derivation of cable equations for membranes, it is usually assumed that the membrane conductance is constant, i.e. the conductance does not vary with membrane potential or with time (Hodgkin and Rushton, 1946; Taylor, 1963; Hellerstein, 1968). In the case of excitable membranes, it is clear that this assumption cannot be strictly valid. For example, the application of small amplitude, long-duration current pulses to a space-clamped squid giant axon causes the membrane voltage to oscillate before settling to a steady value (Hodgkin and Huxley, 1952). If this oscillatory behavior is accepted as characteristic of each patch of membrane, then it should have a significant effect on the cable response, although the oscillations might be damped somewhat by removing the constraint of the space clamp. Yet, under these conditions the classical cable equation, which is commonly used to describe subthreshold behavior of axons, has only nonoscillatory solutions. It is of interest, therefore, to examine more closely the validity of the classical cable equation when applied to such situations and to determine how it could be modified to account for oscillatory responses.

The subthreshold, nonpropagated response of the squid giant axon has been computed by Hodgkin and Huxley for the space clamp condition (Hodgkin and Huxley, 1952). Cooley and Dodge have developed a computer program for calculating both the subthreshold and nondecremental responses (Cooley and Dodge, 1966). Their computer program, however, is rather elaborate and expensive to run f one is only concerned with subthreshold responses. It would be useful, therefore, to have an alternative approach that is relatively simple and which gives at least a good qualitative picture of the subthreshold response of the membrane model under consideration. This has the additional advantage that the influence of membrane parameters on the response, i.e. whether it is oscillatory or not, becomes more easily apparent. The existence of purely passive nerve membranes, even in dendrites and some fibers which do not sustain all or none spikes has been in doubt for some time and it has recently again been questioned (Leibovic and Sabah, 1969). The considerations of this paper are also relevant to the proper description of signals in active dendrites and nerve fibers.

In what follows, the subthreshold response of an active fiber is examined, using the data of the squid giant axon. The treatment is based on a linearization technique coupled with a greatly simplified numerical procedure for inversion of Laplace transforms (Bellman et al., 1966).

SYMBOLS AND NUMERICAL VALUES

a	radius of axon = 0.0238 cm
C	membrane capacitance per unit area = 1μF/cm^2
G_{K}°, G_{Na}°	constants in the Hodgkin-Huxley expressions for potassium and sodium conductances per unit area; $G_{\mathrm{K}}^{\circ} = 36$ mmho/cm^2, $G_{\mathrm{Na}}^{\circ} = 120$ mmho/cm^2
$G_{\mathrm{K}r}$, $G_{\mathrm{Na}r}$, G_L	resting state conductances per unit area of the three ionic paths in the Hodgkin-Huxley equivalent circuit; $G_{\mathrm{K}r} = 0.3667$ mmho/cm^2, $G_{\mathrm{Na}r} = 0.0106$ mmho/cm^2, $G_L = 0.3$ mmho/cm^2
G_{cr}	total membrane conductance per unit area in the resting state (instantaneous) = $G_{\mathrm{K}r} + G_{\mathrm{Na}r} + G_L = 0.6773$ mmho/cm^2
G_{nr}, G_{mr}, G_{hr}	series conductances per unit area of the three inductive branches in the complex frequency equivalent circuit derived by linearizing the Hodgkin-Huxley equations about the resting state (Fig. 1 and equations 16, 17 and 18 of the Appendix); $G_{nr} = 0.8489$ mmho/cm^2, $G_{mr} = -0.4316$ mmho/cm^2 $G_{hr} = 0.0716$ mmho/cm^2
G_{tr}	total membrane conductance per unit area (steady state) for perturbations of the linearized system about the resting state; $G_{tr} = G_{cr} + G_{nr} + G_{mr} + G_{hr} = 1.1662$ mmho/cm^2
I_{K}, I_{Na}, I_L	current density in the three ionic paths of the Hodgkin-Huxley membrane equivalent circuit, μa/cm^2

I_{Kr}, I_{Nar}, I_{Lr}	resting state values of I_K, I_{Na} and I_L; $I_{Kr} = 4.3997$ μa/cm^2, $I_{Nar} = -1.2200$ μa/cm^2 $I_{Lr} = -3.1797$ μa/cm^2 (outward current positive)
I_p	amplitude of current step input, μa
i_i	current in axoplasm, μa
i_0, $\bar{i}_0$	input current, μa, and its Laplace transform, respectively
k	temperature factor equivalent to a Q_{10} of 3
m, n, h	dimensionless parameters of the Hodgkin-Huxley equations
m_r, n_r, h_r	resting state values of m, n, and h; $m_r = 0.0529$, $n_r = 0.3177$, $h_r = 0.5961$
$\left\{\begin{matrix}\delta m, \delta n, \delta h,\\ \overline{\delta m}, \overline{\delta n}, \overline{\delta h},\end{matrix}\right\}$	small signal variations, and their Laplace transforms, of m, n, and h about their resting state values
N	order of shifted Legendre polynomial
q	complex frequency propagation constant (equation 1)
r_i, r_e	internal and external resistances per unit length, respectively, of the cylindrical cable model. r_e is considered to be zero, $r_i = 19.893$ Kohm/cm
s	complex frequency
T	temperature, °C
t	time, msec
V	membrane potential, mv (depolarization positive)
V_K, V_{Na}, V_L	ionic equilibrium potentials in the three branches of the Hodgkin-Huxley membrane equivalent circuit; $V_K = -12$ mv, $V_{Na} = 115$ mv, $V_L = 10.5989$ mv
V_p	amplitude of voltage step input, mv
v, $\bar{v}$	small signal membrane voltage for perturbations about the resting state, mv, and its Laplace transform, respectively
v_0, $\bar{v}_0$	input voltage, mv, and its Laplace transform, respectively
x	distance along the cable, cm
X	normalized distance $= x/\lambda$
λ	space constant of the linearized cable model $= 1/\sqrt{2\pi a G_{tr}(r_i + r_e)} =$ 0.5369 cm for $r_e = 0$
τ_{cr}	membrane time constant in the resting state calculated on the basis of total conductance in the resting state $= C/G_{cr} = 1.4766$ msec
τ_{nr}, τ_{mr}, τ_{hr}	resting state time constants of potassium activation, sodium activation and sodium inactivation; $\tau_{nr} = 5.4586$ msec, $\tau_{mr} = 0.2368$ msec, $\tau_{hr} =$ 8.5160 msec
w	time scaling factor

The Linearized Cable Model

Linearization of the Hodgkin-Huxley equations leads to a complex frequency equivalent circuit with three inductive branches (Chandler et al., 1962), as outlined in the Appendix. For linearization about the resting state, the branches accounting for potassium activation and sodium inactivation have components with positive values, whereas the branch accounting for sodium activation has components with negative values, due to the fact that sodium activation gives rise to a current component which flows in a direction opposite that of a passive current. If this equivalent circuit is used as the shunt element of the cable model for a uniform cylindrical axon, Fig. 1, the cable equation, in terms of the Laplace transform of

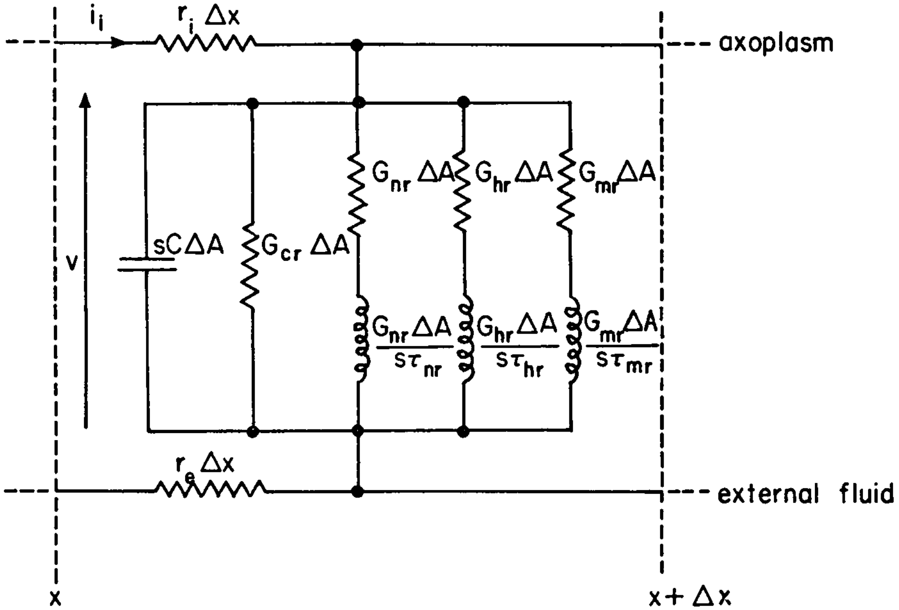

FIGURE 1 Equivalent circuit of element of length Δx of modified cable; $\Delta A = 2\pi a \Delta x$, where "$a$" is the axon radius.

the voltage at any point along the cable, assumes the form (Equation 19 of the Appendix)

$$\frac{1}{2\pi a(r_i + r_e)} \frac{d^2\bar{v}}{dx^2} = \left[G_{cr}(1 + s\tau_{cr}) + \frac{G_{nr}}{1 + s\tau_{nr}} + \frac{G_{hr}}{1 + s\tau_{hr}} + \frac{G_{mr}}{1 + s\tau_{mr}}\right]\bar{v}.$$

In terms of the normalized space coordinate this equation may be written as

$$\frac{d^2\bar{v}}{dX^2} = q^2\bar{v} \tag{1}$$

where

$$q^2 = \frac{1}{G_{tr}}\left[G_{cr}(1 + s\tau_{cr}) + \frac{G_{nr}}{1 + s\tau_{nr}} + \frac{G_{hr}}{1 + s\tau_{hr}} + \frac{G_{mr}}{1 + s\tau_{mr}}\right]$$

and

$$G_{tr} = G_{cr} + G_{nr} + G_{hr} + G_{mr}\,.$$

For an infinite cable, extending from $X = -\infty$ to $X = +\infty$, the general solution to this equation is of the form (Taylor, 1963)

$$\bar{v} = Ee^{-qX}, \qquad X \geqq 0$$

$$\bar{v} = Ee^{+qX}, \qquad X \leqq 0.$$

where E is a constant to be determined from input conditions.

If a voltage input, v_0, is applied to the cable between inside and outside at $X = 0$, then,

$$\bar{v} = \bar{v}_0 e^{-qX}, \qquad X \geqq 0. \tag{2}$$

Alternatively, if a current input, i_0, is applied in the same way, then E can be determined using the relation $i_i = -\frac{1}{(r_i + r_e)\lambda}\frac{\partial v}{\partial X}$. It follows that

$$\bar{v} = \frac{\lambda(r_i + r_e)}{2q}\,\bar{i}_0 e^{-qX}, \qquad X \geqq 0. \tag{3}$$

For a given voltage or current input, therefore, the voltage response is obtained as the inverse Laplace transform of $\bar{v}$ in equations 2 or 3. In this paper, the responses interest are those to step inputs, with the resistance of the external fluid neglected. Equations 2 and 3 then become

$$\bar{v} = V_p \frac{e^{-qX}}{s}, \qquad X \geqq 0 \tag{4}$$

$$\bar{v} = \frac{\lambda r_i}{2} I_p \frac{e^{-qX}}{qs}, \qquad X \geqq 0 \tag{5}$$

where V_p and I_p are the amplitudes of the voltage and current input steps, respectively.

Numerical Inversion of the Laplace Transform

Since the inverse Laplace transforms of equations 4 and 5 are not tabulated, a numerical inversion method was employed based on a Gauss quadrature formula using shifted Legendre polynomials (Bellman et al., 1966). The procedure reduces simply to matrix multiplication, so that given a Laplace transform, $F(s)$, its inverse may be determined as follows:

(i) $f(s) = (F[s/w])/w$ is formed, where "w" is a constant whose value is chosen according to the time range of interest; this step corresponds to replacing "t" by "wt" in the inverse time function.

(ii) $f(i)$ is calculated for $i = 1, 2, \cdots, N$, where N is the order of the shifted Legendre polynomial being employed.

(iii) the matrix product is determined: $[g(x_i)] = [I][f(i)]$, where $[f(i)]$ is the column matrix of order N formed from $f(i)$, $i = 1, 2, \cdots, N$, and $[I]$ is an $N \times N$ inverse matrix given in Appendix V of Bellman et al.

(iv) the elements of the column matrix $[g(x_i)]$ are the values of the inverse Laplace transform at $t_i = -w \ln x_i$, where x_i, $i = 1, 2, \cdots, N$ are the zeros of the shifted Legendre polynomial of order N. The values of $-\ln x_i$ are tabulated in Appendix VI of Bellman et al.

The step responses presented in this paper were computed using matrices of order 7, 8, 9 and 10 for each curve and choosing w to be 10 or 5.5, according to the time range required. The four matrices give 34 points per curve covering, for $w = 10$, the time range 0.13–43.4 msec.

The above numerical procedure is a convenient method for inverting Laplace transforms and works well for computing the types of step response presented in this paper. Small-amplitude numerical oscillations may occur in some cases but can be eliminated by the methods described by Bellman et al.

Response to Current Step Input

The response of the infinite cable to a current step input of 0.2 μa amplitude is shown in Fig. 2 *a* as a function of time for various values of X and in Fig. 2 *b* as a function of X for various values of time. The numerical values used are those appropriate to the squid giant axon at the standard temperature of 6.3°C.

The response curves of Fig. 2 *a* show oscillatory behavior at a frequency of about 50 Hz. As X increases, the peaks of these curves shift slightly in the direction of increasing time and the percentage overshoot increases. It can be easily verified from equation 5 that

$$\begin{aligned}\lim_{t\to 0}\frac{\partial v}{\partial t} = \lim_{s\to\infty} s^2\bar{v} &= \infty \quad \text{if} \quad X = 0 \\ &= 0 \quad \text{if} \quad X \neq 0.\end{aligned}$$

Moreover, the larger the value of X, the slower is the rise of membrane potential at small values of time.

This behavior is a consequence of the fact that the voltage across a capacitor does not change instantaneously for any finite change in the magnitude of the current through the capacitor (Guillemin, 1953). It follows that at the instant following the application of a step current to the cable:

(i) v remains zero all along the cable

(ii) since a point current source is assumed, all the applied current will be drawn by an infinitesimally small capacitive element at $X = 0$. This makes $\partial v/\partial t$ approach infinity at $X = 0$; moreover, i_i will be zero all along the cable, so that i_m and $\partial v/\partial t$ will vanish for $X \neq 0$.

The series current, i_i, in the infinite cable is equal to $i_0/2$ at $X = 0$ and decreases continuously as X increases, due to the presence of the shunt paths. Since $\partial v/\partial X = -\lambda r_i i_i$, the response curves of Fig. 2 *b* will have their largest negative slope at $X = 0$ and the response will decrease monotonically with X. It is interesting to note that for a current step input of amplitude I_p, $\partial v/\partial X\,|_{X=0} = -\lambda r_i I_p/2$ independently of time, so that all the response curves of Fig. 2 *b* will have the same slope at $X = 0$.

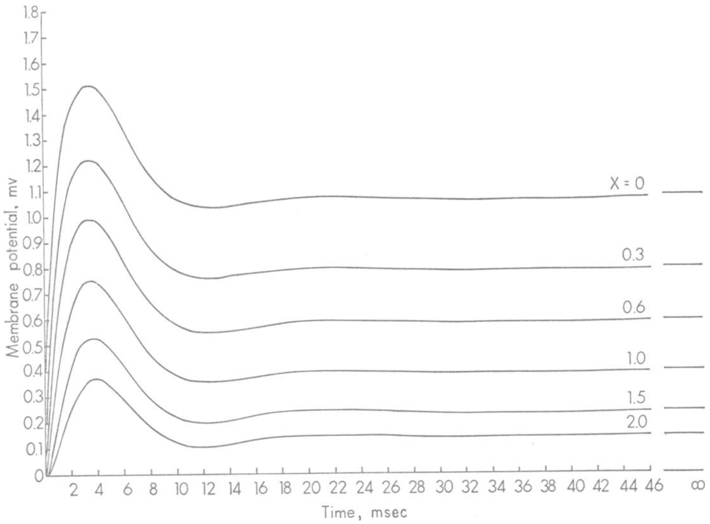

FIGURE 2 *a* Response of linearized Hodgkin-Huxley cable of infinite length to a current step input of 0.2 μa amplitude at a temperature of 6.3°C. Response as a function of time. The values at $t = \infty$ were calculated from the analytical expression.

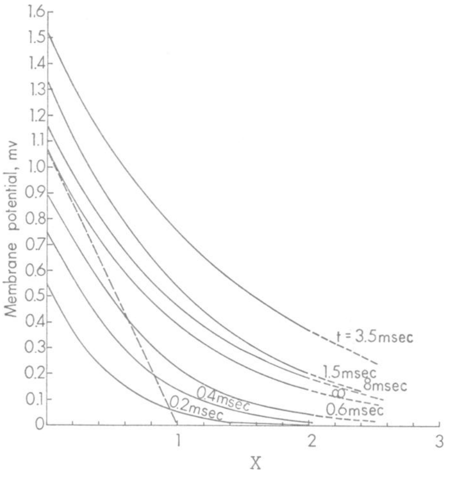

FIGURE 2 *b* Response of linearized Hodgkin-Huxley cable of infinite length to a current step input of 0.2 μa amplitude at a temperature of 6.3°C. Response as a function of distance.

From equation 5

$$\lim_{t\to\infty} v = \lim_{s\to 0} s\bar{v} = \frac{\lambda r_i}{2} I_p e^{-X}$$

so that the $t = \infty$ curve in Fig. 2 *b* is a simple exponential.

Response to Current Pulse Input

The voltage response at $X = 0$ and $X = 1$ to current pulses of 0.2 μa amplitude and 6 ms and 2 ms durations are shown in Fig. 3. These curves were drawn by appropriately superimposing the corresponding step responses of Fig. 2. The curves for $X = 0$ are discontinuous in $\partial v/\partial t$ at the trailing edge of the pulse, since at $X = 0$,

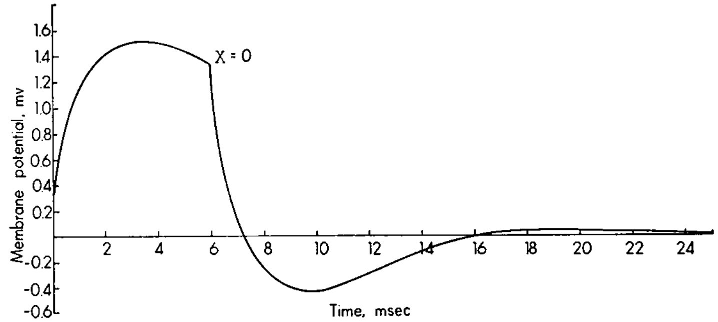

FIGURE 3 *a* Response of linearized Hodgkin-Huxley cable of infinite length to a current pulse of 0.2 μa amplitude at 6.3°C. (*a*) $X = 0$, pulse duration 6 msec.

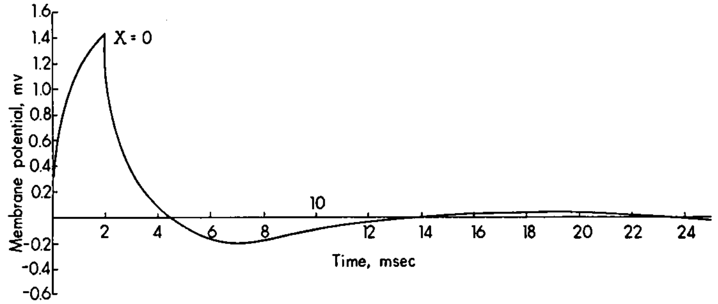

FIGURE 3 b X = 0, pulse duration 2 msec.

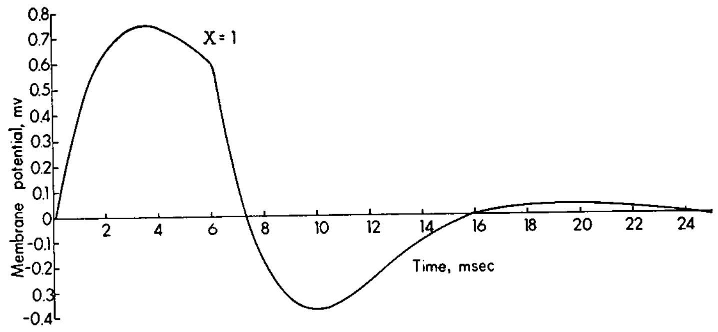

FIGURE 3 *c* X = 1, pulse duration 6 msec. (*Fig. 3 d on following page.*)

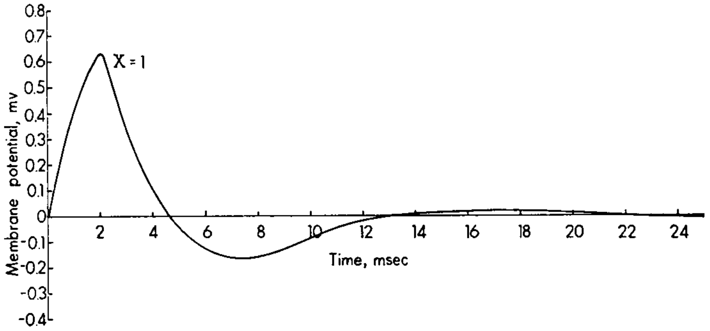

FIGURE 3 *d* X = 1, pulse duration 2 msec.

$\partial v/\partial t \rightarrow \infty$ at the instant of application of a current step input. For $X = 1$, $\partial v/\partial t = 0$ at this instant so that the slopes of the response curves is not discontinuous at the trailing edge of the pulse.

All response curves show oscillatory behavior following the termination of the pulse. Moreover, when the duration of the pulse is longer than the time for the first peak in the step response, as is the case with the 6 msec pulse, this peak appears in the pulse response.

Effect of a Rise in Temperature

A rise in temperature from 6.3°C to T°C is considered to have the effect of multiplying all the α's and β's in the Hodgkin-Huxley equations by a factor $k = 3^{\frac{T-6.3}{10}}$ corresponding to a Q_{10} of 3; there is also a small effect on the magnitude of the ionic conductances which is neglected (Hodgkin and Huxley, 1952). It follows from the expressions for the conductances and time constants of the complex frequency equivalent circuit, as given in the Appendix, that the inductances will be reduced by a factor of k while the conductances in series with the inductances remain unchanged. Raising the temperature should decrease the amplitude of oscillation, increase the frequency and shift the first peak towards smaller values of time. If the temperature is raised to 20°C the frequency of oscillation increases to about 125 Hz, Fig. 4 *a*, and the rate of rise at small values of time is slightly increased. Raising the temperature to 30°C makes the response almost critically damped, as in Fig. 4 *b*, which also shows the response of the same cable with the three inductances reduced to zero.

Response to Voltage Step Input

The response to a voltage step input of 1 mv, obtained by numerical inversion of equation 4, is shown in Fig. 5 for various values of X. The voltage response at $X = 0$ is, of course, the applied voltage step. As to be expected from the damping

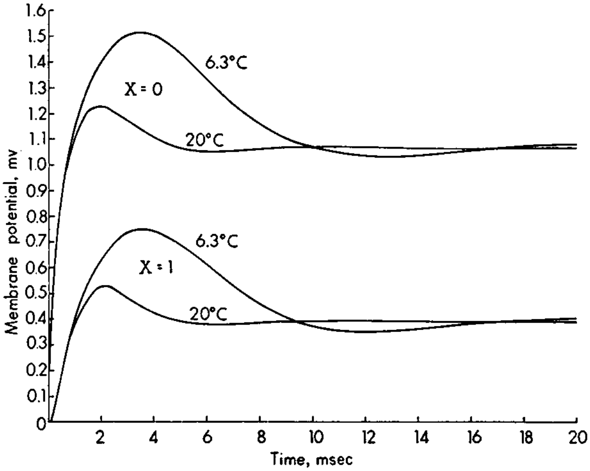

FIGURE 4 *a* Effect of temperature on the response of linearized Hodgkin-Huxley cable of infinite length to a current step input of 0.2 μa amplitude. Response at 20°C.

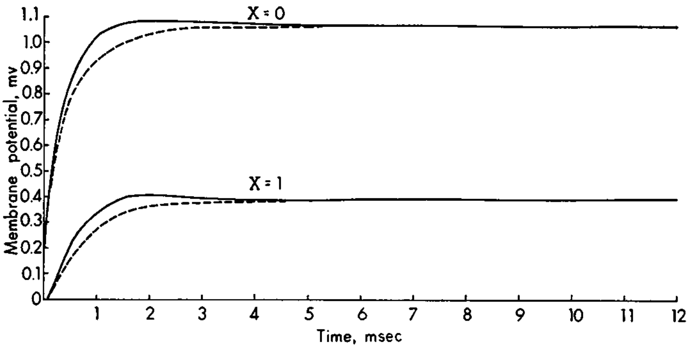

FIGURE 4 *b* Effect of temperature on the response of linearized Hodgkin-Huxley cable of infinite length to a current step input of 0.2 μa amplitude. Response at 30°C. Dotted line is the response with inductances at zero.

effect of the constant voltage source, the oscillatory behavior is less pronounced for small values of X. But, as X increases the percentage overshoot increases and the peaks of the curves shift in the direction of increasing time.

It follows from equation 4 that, as for the response to current step inputs

$$\lim_{t\to 0} \frac{\partial v}{\partial t} = \lim_{s\to\infty} s^2 \bar{v} = 0 \quad \text{if} \quad X \neq 0$$

the physical interpretation for this being analogous to that given above for the response to current step inputs.

It is interesting to note that for this type of cable, with only resistance in the

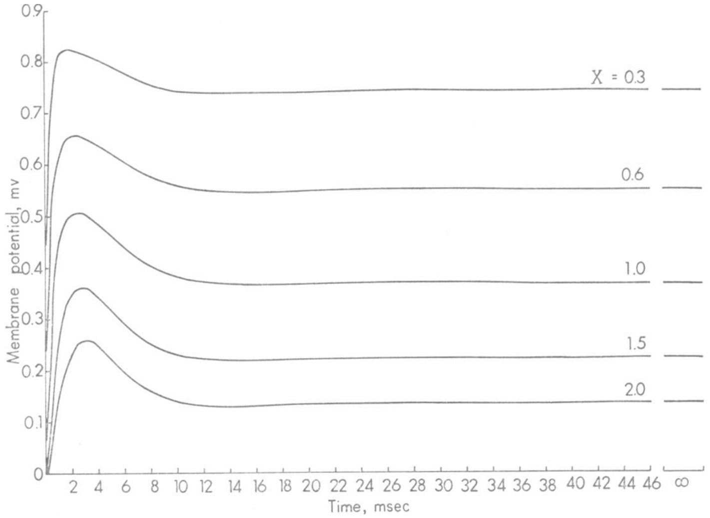

FIGURE 5 Response of linearized Hodgkin-Huxley cable of infinite length to a voltage step input of 1 mv amplitude at 6.3°C. The values at $t = \infty$ were calculated from the analytical expression.

series branch, the response to a voltage source input can be derived from that to a current source input. Thus, from equation 3

$$\frac{d\bar{v}}{dX} = -\frac{\lambda(r_i + r_e)}{2}\,\bar{i}_0 e^{-qX}. \qquad (6)$$

Comparing equation 6 with equation 2, it follows that the response to a voltage input, v_0, is identical to the normalized space derivative of the response to a current input $i_0 = -2v_0/\lambda(r_i + r_e)$.

Comparison with Nonlinear Response

In order to investigate the validity of the linear approximation, and as an additional check on the accuracy of the numerical inversion of the Laplace transform, the response of the linearized model was compared with that obtained from the numerical solution of the nonlinear partial differential equation (Cooley and Dodge, 1966). It was found that for current step inputs of very small amplitude, for example 0.02μa, the two responses were identical. For an amplitude of 0.2μa, the two responses deviate somewhat, Fig. 6 *a*, the maximum deviation being about 5%. When the amplitude is increased to 1μa the nonlinear response becomes more oscillatory, Fig. 6 *b*, and shows a higher initial rise, due to sodium activation, and a lower steady response, due to potassium activation or "delayed rectification", (Hodgkin and Huxley, 1952). The response of the nonlinear system to a current pulse of 1μa amplitude and 3 msec duration is shown in Fig. 7. It is seen to be qualitatively of similar shape to that of the linearized model.

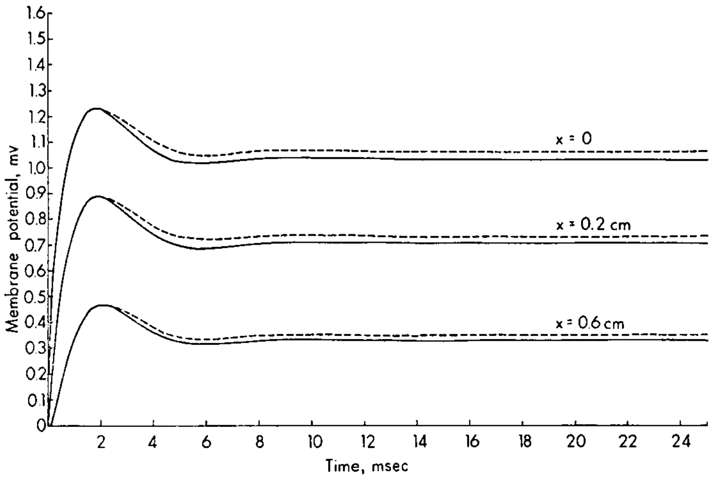

FIGURE 6 *a* Response of Hodgkin-Huxley cable of infinite length at 20°C to current step inputs of amplitude 0.2 μa. Response of nonlinear cable is shown solid and that of linearized model shown dotted.

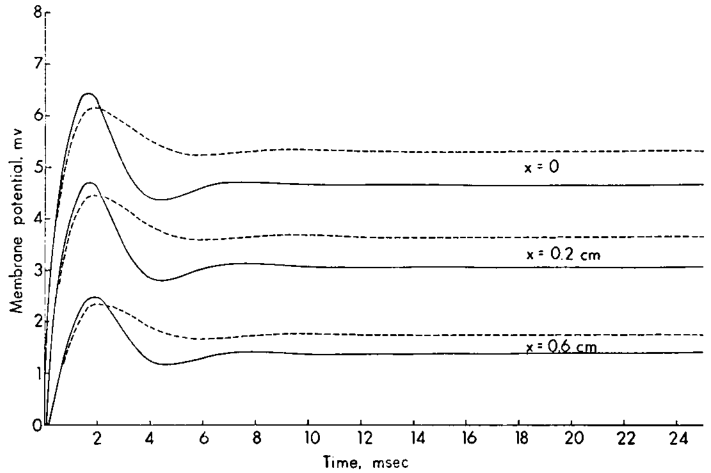

FIGURE 6 *b* Response of Hodgkin-Huxley cable of infinite length at 20°C to current step inputs of amplitude 1 μa. Response of nonlinear cable is shown solid and that of linearized model is shown dotted.

DISCUSSION

Excitable membranes are characterized by a membrane conductance having voltage-dependent, time-variant components which give rise to the regenerative and recovery phases of the action potential. Such voltage-dependent, time-variant conductances have inherent reactive properties which may be capacitive or inductive

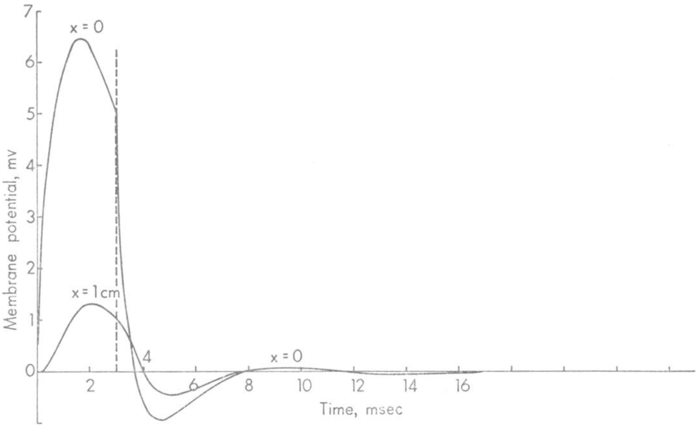

Figure 7 Response of Hodgkin-Huxley cable of infinite length, at $x = 0$ and $x = 1$ cm, to a current pulse input of 1 μa amplitude and 3 msec duration. Temperature 20°C.

(Mauro, 1961; Cole, 1968). It can be shown that excitatory conductance changes give rise to a capacitive reactance whereas conductance changes that aid in membrane recovery give rise to an inductive reactance (Cole, 1968). This explains why positive inductances appear in those branches of the equivalent circuit of Fig. 1 which account for potassium activation and sodium inactivation, whereas the negative series conductance and inductance of the sodium activation branch are formally equivalent to a negative conductance in parallel with a series combination of positive capacitance and conductance (Chandler et al., 1962).

As is well known, the presence of capacitive and inductive reactances in a circuit can give rise, in general, to overdamped, critically damped, or oscillatory type responses depending on the values of the circuit parameters. At a temperature of 20°C or less, the squid giant axon characteristically has an oscillatory response, but this need not be generally true of all excitable membranes. For example, Hodgkin and Rushton, in their classical paper on the electrical constants of a crustacean nerve fiber, cite the example of an axon having a membrane resistance of 700 Ωcm^2, which gave oscillatory responses with an overshoot of 5%, whereas axons with a membrane resistance of the order of 2300 Ωcm^2 did not oscillate, and the response in this case was very close to that predicted by the classical cable equation (Hodgkin and Rushton, 1946). This can also be seen in Fig. 4 *b* where raising the temperature to 30°C makes the response of the squid giant axon approach that predicted on the basis of the classical cable equation.

The initial rise of membrane voltage following current or voltage step inputs confirms that a true latency does not occur; although the larger the distance from the source, the slower is the rise of membrane potential. A true latency cannot occur if the series element is a pure resistance, which therefore establishes continuity all along the cable at all times. By contrast, a cable structure having inductance in the series branch, as is the case with cables ordinarily considered by electrical engineers (Ryder, 1955), does show a true latency. It is interesting to note that the series inductance in such a cable is due to the magnetic field associated with longitudinal current flow and which, in general, is stored largely in the dielectric separating the two conductors and, to a certain extent, in the conductors themselves. Such a series inductance can be neglected in deriving the cable model for an axon because

(i) the magnitude of the inductance will be relatively small due to the small thickness of the membrane,

(ii) the emf induced in this inductance will be small in comparison with the voltage drop across the relatively large longitudinal resistance of the axon.

The computed response to current pulses bears some resemblance to the recordings from the presynaptic membrane of the stellate ganglion of the squid, following the application of a current pulse (Katz and Miledi, 1967), in that both responses, at least to large current pulses, show a peak before the termination of the stimulus; this cannot be explained in terms of the classical cable model.

Oscillatory responses are often observed in electrophysiological recordings. The analysis presented in this paper would indicate that, where nonpassive membranes are involved, such oscillations may be due, at least in part, to the variation of the ionic conductances with membrane potential.

APPENDIX

The conventional cable equation may be written as (Hodgkin and Huxley, 1952)

$$\frac{1}{2\pi a(r_i + r_e)} \frac{\partial^2 V}{\partial x^2} = C\frac{\partial V}{\partial t} + I_{\mathrm{K}} + I_{\mathrm{Na}} + I_L \tag{7}$$

where V is the membrane potential, I_{K}, I_{Na} and I_L are the ionic current densities given by the Hodgkin-Huxley equations

$$\left.\begin{aligned} I_{\mathrm{K}} &= \overset{\circ}{G}_{\mathrm{K}} n^4(V - V_{\mathrm{K}}) \\ I_{\mathrm{Na}} &= \overset{\circ}{G}_{\mathrm{Na}} m^3 h(V - V_{\mathrm{Na}}) \\ I_L &= G_L(V - V_L). \end{aligned}\right\} \tag{8}$$

For linearization about the resting state

$$\left.\begin{aligned} I_{\mathrm{K}} &= I_{\mathrm{K}r} + \left(\frac{\partial I_{\mathrm{K}}}{\partial V}\right)_r \delta V + \left(\frac{\partial I_{\mathrm{K}}}{\partial n}\right)_r \delta n \\ I_{\mathrm{Na}} &= I_{\mathrm{Na}r} + \left(\frac{\partial I_{\mathrm{Na}}}{\partial V}\right)_r \delta V + \left(\frac{\partial I_{\mathrm{Na}}}{\partial m}\right)_r \delta m + \left(\frac{\partial I_{\mathrm{Na}}}{\partial h}\right)_r \delta h \\ I_L &= I_{Lr} + \left(\frac{\partial I_L}{\partial V}\right)_r \delta V. \end{aligned}\right\} \tag{9}$$

From equation 8

$$\left.\begin{aligned}\left(\frac{\partial I_{\mathrm{K}}}{\partial V}\right)_r &= G^{\circ}_{\mathrm{K}} n_r^4 = G_{\mathrm{K}r}\\ \left(\frac{\partial I_{\mathrm{Na}}}{\partial V}\right)_r &= G^{\circ}_{\mathrm{Na}} m_r^3 h_r = G_{\mathrm{Na}r}\\ \left(\frac{\partial I_L}{\partial V}\right)_r &= G_L.\end{aligned}\right\} \tag{10}$$

Substituting equations 9 and 10 in 7, noting that $I_{\mathrm{K}r} + I_{\mathrm{Na}r} + I_{Lr} = 0$, replacing V and δV by v, since only small deviations from the resting state $V = 0$ are being considered, and taking the Laplace transform

$$\frac{1}{2\pi a(r_i + r_e)} \frac{d^2\bar{v}}{dx^2} = (sC + G_{cr})\bar{v} + \left(\frac{\partial I_{\mathrm{K}}}{\partial n}\right)_r \overline{\delta n} + \left(\frac{\partial I_{\mathrm{Na}}}{\partial m}\right)_r \overline{\delta m} + \left(\frac{\partial I_{\mathrm{Na}}}{\partial h}\right)_r \overline{\delta h} \tag{11}$$

where $G_{cr} = G_{\mathrm{K}r} + G_{\mathrm{Na}r} + G_L$, and $\bar{v}$, $\overline{\delta n}$, $\overline{\delta m}$, and $\overline{\delta h}$ are the Laplace transforms of the corresponding functions.

In order to express the partial derivatives in equation 11 in terms of $\bar{v}$, consider the potassium term as an example. From equation 8

$$\left(\frac{\partial I_{\mathrm{K}}}{\partial n}\right)_r = -4G^{\circ}_{\mathrm{K}} n_r^3 V_{\mathrm{K}}. \tag{12}$$

From the Hodgkin-Huxley first-order differential equation for n

$$\frac{dn}{dt} = \alpha_n - (\alpha_n + \beta_n)n \tag{13}$$

dn/dt may be regarded as a function of n and V, since α_n and β_n are functions of V only. Thus

$$\delta\dot{n} = \frac{d}{dt}(\delta n) = \left(\frac{\partial \dot{n}}{\partial V}\right)_r \delta V + \left(\frac{\partial \dot{n}}{\partial n}\right)_r \delta n \tag{14}$$

where $\dot{n} \equiv dn/dt$. Taking the Laplace transform of equation 14, noting that the initial value of δn is zero

$$s\overline{\delta n} = \left(\frac{\partial \dot{n}}{\partial V}\right)_r \bar{v} + \left(\frac{\partial \dot{n}}{\partial n}\right)_r \overline{\delta n}. \tag{15}$$

From equation 13:

$$\left(\frac{\partial \dot{n}}{\partial V}\right)_r = \left(\frac{d\alpha_n}{dV}\right)_r - \left[\left(\frac{d\alpha_n}{dV}\right)_r + \left(\frac{d\beta_n}{dV}\right)_r\right] n_r \quad \text{and,} \quad \left(\frac{\partial \dot{n}}{\partial n}\right)_r = -(\alpha_{nr} + \beta_{nr}).$$

Substituting in equation 15, solving for $\overline{\delta n}$, and multiplying by equation 12

$$\left(\frac{\partial I_{\mathrm{K}}}{\partial n}\right)_r \overline{\delta n} = \frac{G_{nr}}{1 + s\tau_{nr}} \bar{v} \tag{16}$$

where,

$$G_{nr} = 4G^{\circ}_{\mathrm{K}} n_r^3 \tau_{nr} \; V_{\mathrm{K}} \left\{ \left[\left(\frac{d\alpha_n}{dV} \right)_r + \left(\frac{d\beta_n}{dV} \right)_r \right] n_r - \left(\frac{d\alpha_n}{dV} \right)_r \right\}$$

$$n_r = \frac{\alpha_{nr}}{\alpha_{nr} + \beta_{nr}} \qquad , \tau_{nr} = \frac{1}{\alpha_{nr} + \beta_{nr}}$$

Similarly,

$$\left(\frac{\partial I_{\mathrm{Na}}}{\partial m} \right)_r \overline{\delta m} = \frac{G_{mr}}{1 + s\tau_{mr}} \mathfrak{v} \tag{17}$$

where

$$G_{mr} = 3G^{\circ}_{\mathrm{Na}} \, m_r^2 \, h_r \, \tau_{mr} \, V_{\mathrm{Na}} \left\{ \left[\left(\frac{d\alpha_m}{dV} \right)_r + \left(\frac{d\beta_m}{dV} \right)_r \right] m_r - \left(\frac{d\alpha_m}{dV} \right)_r \right\}$$

$$m_r = \frac{\alpha_{mr}}{\alpha_{mr} + \beta_{mr}}, \qquad \tau_{mr} = \frac{1}{\alpha_{mr} + \beta_{mr}}$$

and

$$\left(\frac{\partial I_{\mathrm{Na}}}{\partial h} \right)_r \overline{\delta h} = \frac{G_{hr}}{1 + s\tau_{hr}} \mathfrak{v} \tag{18}$$

where

$$G_{hr} = G^{\circ}_{\mathrm{Na}} \, m_r^3 \tau_{hr} V_{Na} \left\{ \left[\left(\frac{d\alpha_h}{dV} \right)_r + \left(\frac{d\beta_h}{dV} \right)_r \right] h_r - \left(\frac{d\alpha_h}{dV} \right)_r \right\}$$

$$h_r = \frac{\alpha_{hr}}{\alpha_{hr} + \beta_{hr}}, \qquad \tau_{hr} = \frac{1}{\alpha_{hr} + \beta_{hr}}.$$

Substituting equations 16, 17, and 18 in equation 11

$$\frac{1}{2\pi a(r_i + r_e)} \frac{d^2 \mathfrak{v}}{dx^2} = \left[G_{cr} \, (1 + s\tau_{cr}) + \frac{G_{nr}}{1 + s\tau_{nr}} + \frac{G_{hr}}{1 + s\tau_{hr}} + \frac{G_{mr}}{1 + s\tau_{mr}} \right] \mathfrak{v} \tag{19}$$

where $\tau_{cr} = C/G_{cr}$.

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