THE EFFECT OF MEMBRANE PARAMETERS ON THE PROPERTIES OF THE NERVE IMPULSE

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ABSTRACT The effect of varying membrane capacitance, conductance, and rate constants on the properties of the nerve impulse is considered in terms of the degree of regeneration in the Hodgkin-Huxley model for the squid giant axon. It is shown through computer simulation that reducing regeneration generally increases the duration of the action potential and decreases its amplitude, rate of rise, and conduction velocity. The threshold becomes much less sharp and the amplitude of the response of a patch of membrane grades with stimulus strength. A second stimulus, applied shortly after a first stimulus, considerably perturbs the membrane potential from its original time-course. Under certain conditions, the nerve signal can propagate with a small decrement.

INTRODUCTION

Discussion of nerve signals in the literature has been almost exclusively limited to two types of signal: the axonal "all-or-none" spike and electrotonic spread. Unit responses that do not quite fall into either of these categories have long been observed, such as the response of the narcotized axon (Lorento de Nó and Condouris, 1959) and the "partial spike" responses reported for a variety of neurons (see Purpura, 1967, for references). Nonetheless, no systematic study has apparently been made of the genesis and properties of these intermediate signals. The purpose of the present paper is to explore the effect of varying some membrane parameters on the properties of the nerve impulse. The investigation is based on computer simulation of the Hodgkin-Huxley equations for the squid giant axon, including variations in membrane capacitance, conductances, and the rates of change of n, m, and h. These parameter changes are dimensionally related (Appendix and Huxley, 1959) and largely independent of the details of the Hodgkin-Huxley formulation. It is shown that by reducing the degree of regeneration in the excitable membrane, the character of the nerve signal can be smoothly changed from that of the axonal spike to essentially electrotonic spread, with all gradations in between. The reduction in the degree of regeneration can be brought about in a variety of ways, the simplest perhaps being a decrease in the density of active membrane patches.

Previous studies (Leibovic and Sabah, 1969; Sabah and Leibovic, 1969 *a*) have

dealt with particular examples of graded responses, their propagation, and some of their refractory and integrative properties. The present account extends our previous work and unifies it through the notion of degree of regeneration.

All computer simulation was performed on the CDC 6400 using a program essentially similar to that described by Cooley and Dodge (1966).

PRINCIPAL SYMBOLS

$\beta = \eta/\gamma\phi$.

γ Factor multiplying membrane capacitance.

η Factor multiplying the conductance constants G^0_{Na} and G^0_K and the leakage conductance G_L in the Hodgkin-Huxley equations.

ϕ Factor multiplying dn/dt, dm/dt, and dh/dt in the Hodgkin-Huxley equations.

Degree of Regeneration in the Hodgkin-Huxley Model

It is shown in the Appendix that if the rates of change of n, m, and h with respect to time are altered by a factor ϕ, and membrane capacitance and conductances are

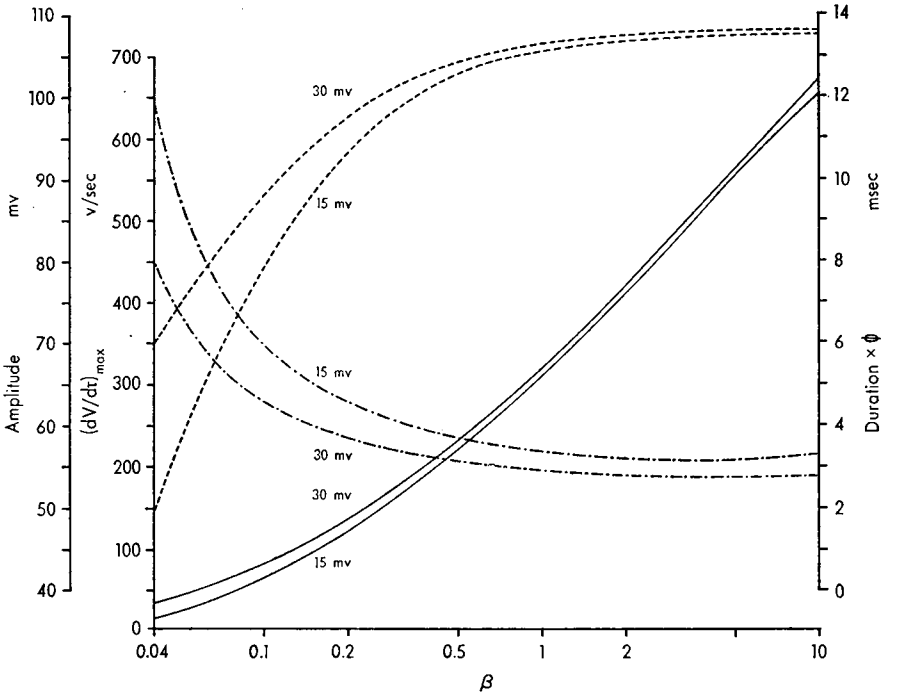

FIGURE 1 Variation of the maximum rate of rise of the action potential (solid lines), its amplitude (dotted lines), and duration (dash-dotted lines) with β for two strengths of stimulus applied to the Hodgkin-Huxley model for a space-clamped squid giant axon. The stimulus is a current pulse of 5 μsec duration and delivers a charge that causes an initial membrane depolarization equal to 15 or 30 mv as indicated for each curve. Duration is measured from the time of application of stimulus to the time the membrane potential first crosses the zero level. Time is expressed in units of $\tau = \phi t$.

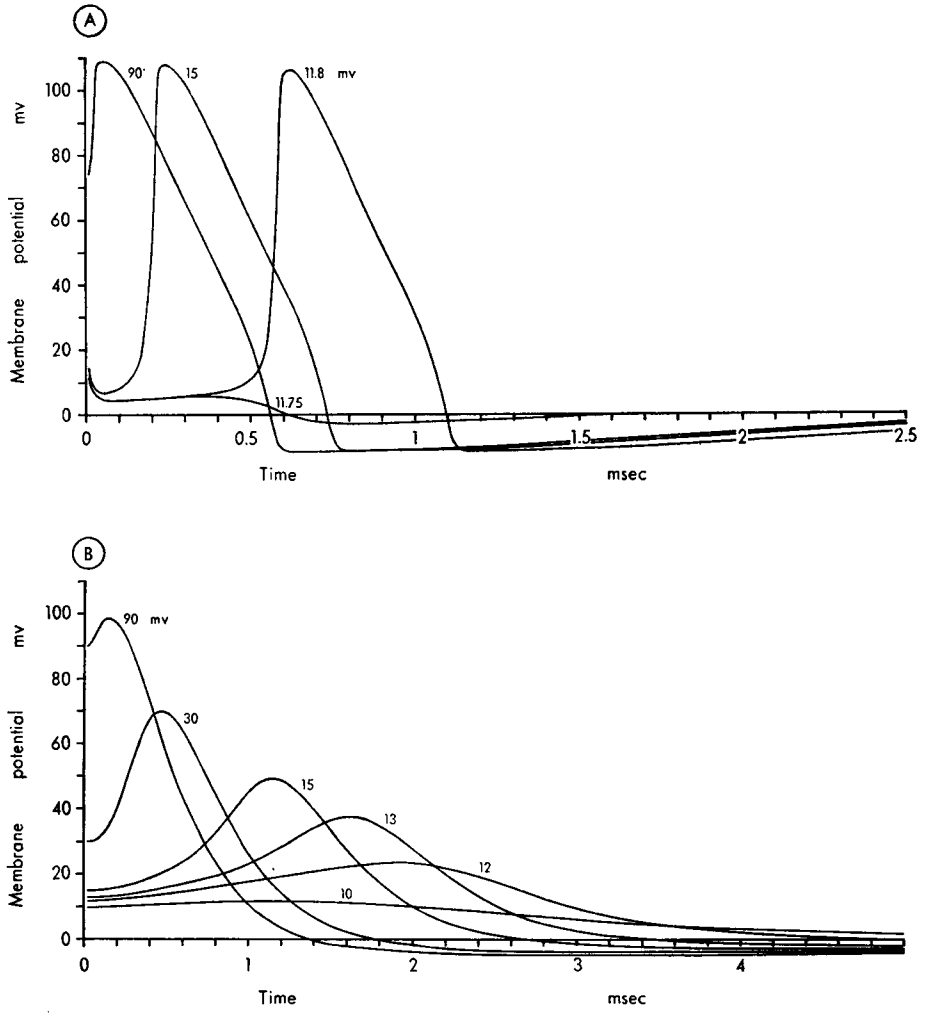

FIGURE 2 Responses of the Hodgkin-Huxley model for a squid giant axon to various initial depolarizations at 20°C. Membrane conductances were modified to make β equal 10 in A and 0.04 in B. The applied stimulus is a current pulse of 5 μsec duration and area equal in nanocoulombs per square centimeter to the initial depolarization given for each curve.

multiplied by γ and η, respectively, then for a given type of stimulus applied to a space-clamped axon or patch of membrane, any characteristic of the action potential can be considered as some function of $\beta = \eta/\gamma\phi$ (Huxley, 1959). Fig. 1 illustrates the variation of the maximum rate of rise of the action potential, its amplitude, and its duration with respect to β for two intensities of a current pulse stimulus of short duration. Time is expressed in units of $\tau = \phi t$. If the Hodgkin-Huxley model is viewed in terms of the well-known regenerative and degenerative processes (Ruch et al., 1965; Sabah and Spangler, 1970), then the monotonic increase of the maximum

rate of rise of the action potential and its amplitude with β, for a given stimulus intensity, is seen to be associated with greater regeneration in the system. Substituting $\xi = \gamma/\eta$, gives $\beta = 1/\xi\phi$; in other words, β is the reciprocal of the product of the factors by which n, m, h, and the membrane time constant are multiplied. An increase in β arises from a reduced membrane time constant, a slower rate of change of n, m, and h, or both. Under standard conditions ($\eta = \gamma = \phi = 1$), $\tau_n = 5.46$ msec, $\tau_m = 0.237$ msec, $\tau_h = 8.52$ msec, and the membrane time constant equals 1.477 msec (Sabah and Leibovic, 1969 *b*), so that the regenerative rate of change of membrane potential is limited by the membrane time constant. An increase in β mitigates this effect and therefore enhances regeneration in the system. Conversely, a decrease in β not only limits the regenerative rate of change of membrane potential, but will eventually bring the degenerative processes into closer temporal correspondence with the regenerative process, thereby reducing the degree of regeneration in the system.

It will be noted from Fig. 1 that the amplitude of the action potential is much more sensitive to stimulus intensity at low values of β than at high values, as is further illustrated in Figs. 2 A and B. This emphasizes that for small β the action potential

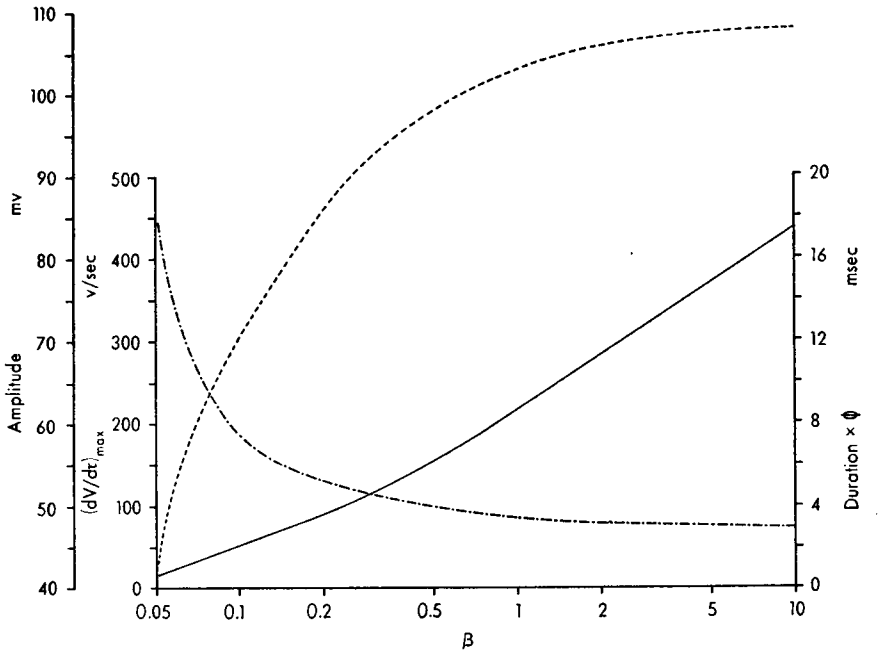

FIGURE 3 Variation of the maximum rate of rise of the action potential (solid line), its amplitude (dotted line), and duration (dash-dotted line) with β for an action potential propagating steadily along an infinite Hodgkin-Huxley cable model for the squid giant axon. Duration is measured from the time the membrane potential reaches 1% of the amplitude of the action potential to the time it first crosses the zero level. Time is expressed in units of $\tau = \phi t$. Steady propagation is not possible for β less than about 0.05.

of a uniform patch of membrane grades with stimulus strength and the transition between subthreshold and suprathreshold responses become less sharp.

Similar considerations apply to a propagated action potential. The maximum rate of rise and the amplitude increase monotonically with β, as illustrated in Fig. 3, so that β is again an index of the degree of regeneration in the system. In this case the duration of the action potential, expressed in units of $\tau = \phi t$, decreases monotonically with β.

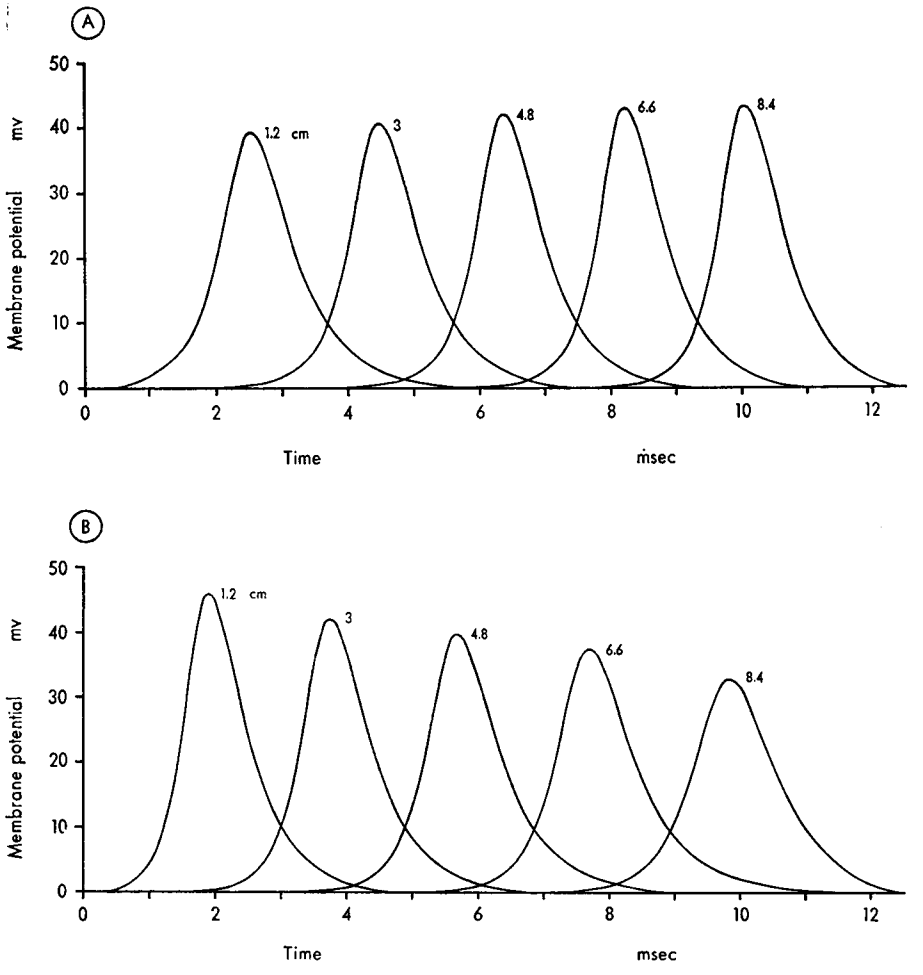

FIGURE 4 Responses of an infinite Hodgkin-Huxley cable model for the squid giant axon at 20°C. Membrane conductances were multiplied by a factor of 0.227 ($\beta = 0.0505$) in A and 0.217 ($\beta = 0.0483$) in B. The stimulus is a current pulse of 1 msec duration applied at $t = 0$, $x = 0$, the amplitude being 3.8 μamp/cm^2 in A and 6 μamp/cm^2 in B. The responses are shown for the indicated values of x, hyperpolarizations being omitted. The conduction velocity is about 10 m/sec for the nondecremental response in A (see Fig. 8).

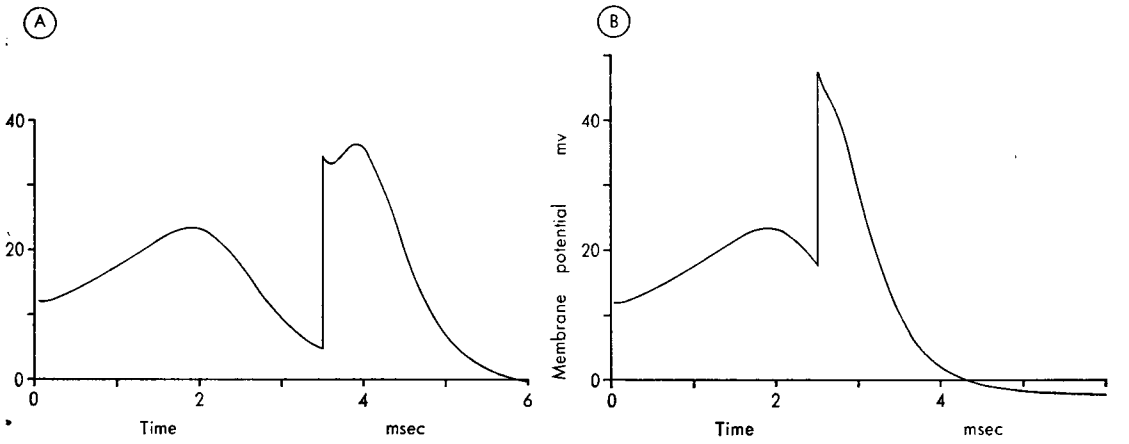

FIGURE 5 Refractoriness in the response of the Hodgkin-Huxley model for the squid giant axon at $T = 20°C$, with membrane conductances reduced so as to make $\beta = 0.04$. Two stimuli are applied having amplitudes of 2.4 mamp/cm² and 6 mamp/cm², respectively, and a duration of 5 μsec. The stimuli are applied at 0 and 3.5 msec in A and at 0 and 2.5 msec in B. The responses to the two stimuli applied singly are shown in Fig. 2 B (12 and 30 mv initial depolarization).

Nondecremental and Decremental Responses

The propagated response for the case $T = 20°C$, $\eta = 0.227$, $\beta = 0.0505$, is illustrated in Fig. 4 A. The stimulus intensity was chosen in this case so that the response increased gradually to its steady-state form.Since the amplitude of response never decreases with distance, there can be no doubt that this is a nondecrementally propagated response. Compared with an action potential under standard conditions, the response of Fig. 4 A is bell shaped, has a smaller amplitude, and is of longer duration. Additional examples of this type of response have previously been given (Leibovic and Sabah, 1969).

Fundamentally, there exists in a regenerative mode of propagation under steady-state conditions a stable wave form, determined by the properties of the membrane, for which the energy input just balances the total dissipation during the cycle (Fitzhugh, 1969). As β is reduced past some transitional value $\beta_r \simeq 0.05$ the regeneration in the system becomes insufficient to maintain this balance and steady, nondecremental propagation is no longer possible. For $\beta \ll \beta_r$ the response decrements very rapidly and approaches electrotonic spread. It will be observed from Fig. 1 that as β is reduced past β_r patches of membrane remain excitable without any discontinuities in the properties of the generated action potential. For β only slightly less than β_r, the net energy loss per cycle will be small, and the decrement will be small. This is illustrated in Fig. 4 B for $T = 20°C$, $\eta = 0.217$, $\beta = 0.0483$. Under these conditions the space constant is 1.51 cm, so that the span between $x = 2.5$ cm and $x = 7.0$ cm is approximately three space constants. Over this distance, the amplitude of the re-

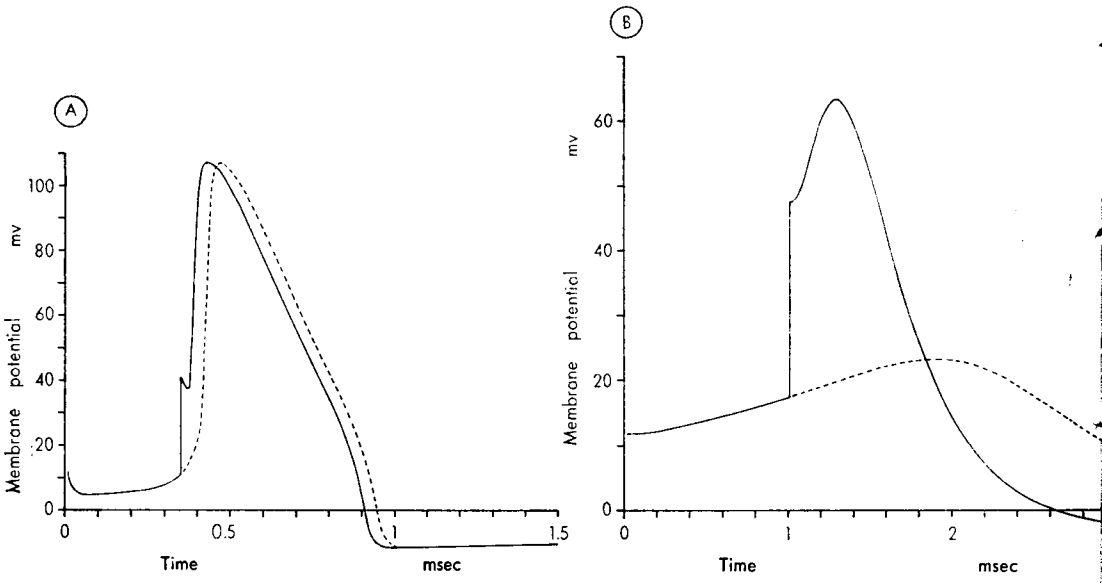

FIGURE 6 Response of the Hodgkin-Huxley model for the squid giant axon to twin-pulse stimulation at 20°C. Membrane conductances were modified to make β equal 10 in A and 0.04 in B. Two stimuli are applied, having amplitudes of 2.4 mamp/cm² and 6 mamp/cm², respectively, and a duration of 5 μsec. The stimuli are applied at 0 and 0.35 msec in A and at 0 and 1 msec in B. The dotted line represents the response to the first stimulus alone.

sponse decreases by about 13.5%. In principle, the decrement can be arbitrarily small if β is sufficiently close to β_r. According to a previously used terminology (Leibovic and Sabah, 1969), the responses of Figs. 4 A and B may be referred to, respectively, as nondecremental and decremental graded pulses or G-pulses.

Twin-Pulse Stimulation

Since for low values of β the graded responses of a membrane patch are still regenerative in nature, they would be expected to have relatively and absolutely refractory properties as illustrated in Figs. 5 A and B. A striking difference is observed, however, between the responses at high and low values of β when the intervals between the two stimuli is further reduced. At high values of β a second stimulus, applied before the response to the first stimulus develops appreciably, has only a small effect on the time-course of the response to the first stimulus (Fig. 6 A). At low values of β, on the other hand, the second stimulus considerably perturbs the response from its original time-course (Fig. 6 B). Such behavior is to be expected from the reduced regeneration at low values of β and the ensuing gradation of the response with stimulus strength.

In the case of a decremental response, if β is only slightly less than β_r, then the amplitude of the response, at a given distance from the point of stimulation, increases

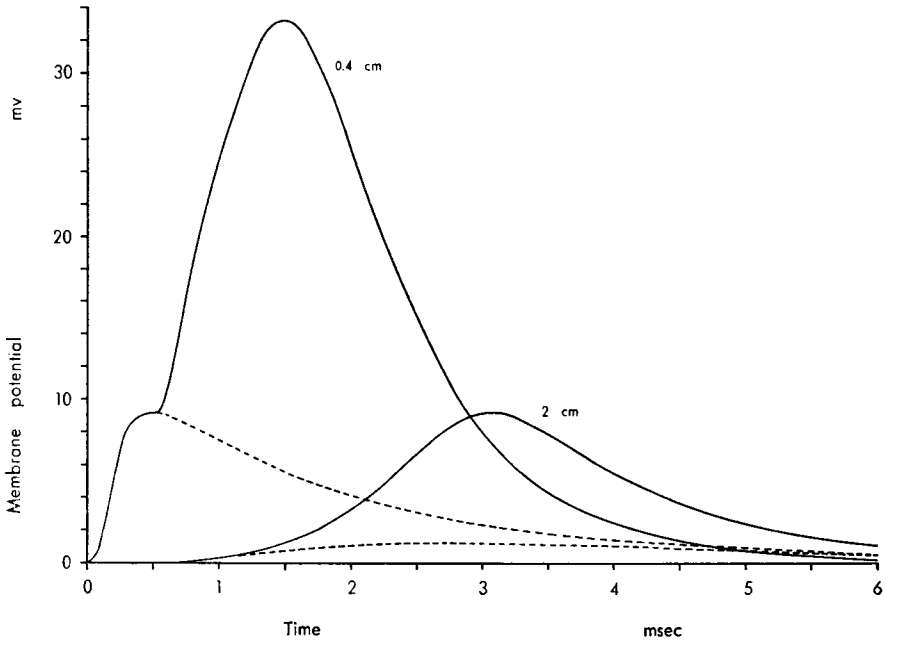

FIGURE 7 Response of an infinite Hodgkin-Huxley cable model of the squid giant axon to twin-pulse stimulation at 20°C. Membrane conductances were modified to make β equal to 0.04. The first and second stimuli have a duration of 200 μsec, an amplitude of 10 μamps/cm^2 and are 0.5 msec apart. The response is shown at distances of 0.4 and 2 cm from the point of stimulation. The dotted line represents the response to the first stimulus alone.

rapidly with stimulus intensity. A similar effect is observed with twin-pulse stimuli applied closely in time, as illustrated in Fig. 7 for the case $T = 20°C$, $\eta = 0.18$, $\beta = 0.04$. The response to the two stimuli is seen to be more than double the response to the first stimulus alone. Such behavior is of course attributable to the residual regeneration in the system.

DISCUSSION

It follows from the above results that by reducing the degree of regeneration in the membrane the character of the nerve signal can be changed continuously from an axonal spike to a nondecremental graded pulse, to a decremental graded pulse, eventually to approach electrotonic spread. That axonal spikes and electrotonic spread are but two opposite extremes of a continuum of responses has been noted by Schmitt and Schmitt (1940) from their experiments on partial blocks in squid giant axons at the points where branches of the giant axon were severed.

In the context of the variation in membrane parameters considered above, regeneration may be reduced by any combination of decreased membrane conductance, increased capacitance, and faster rates of change with respect to time of the voltage-

dependent permeability changes. Variations in membrane capacitance of neuronal membranes may be excluded on the general grounds that a capacitance of about 1 μF/cm^2 seems to be a universal constant determined by membrane structure (Cole, 1968). If it is accepted that membrane excitability is due to a certain density of active patches (Moore and Narahashi, 1967), then membrane conductance may be reduced by decreasing this density without changing the properties of the active patches. It is of course also possible to change the degree of regeneration by means other than those considered in this paper, as by selective attenuation or slowing down of the sodium activation process (Leibovic and Sabah, 1969). Cooley and Dodge (1966) obtained a slowly decrementing response by multiplying G^0_{Na} and G^0_K by a factor of 0.25, while adjusting G_L and V_L to compensate for the changes in resting potential and membrane conductance.

In general, the character of the nerve impulse, after any changes in membrane parameters, may be expected to depend fundamentally upon the degree of regeneration in the membrane. For the type of parameter changes considered in this paper, it was argued above that β serves as an index of the degree of regeneration; but for other more general changes in membrane parameters it would be necessary to derive a more direct and fundamental measure of the degree of regeneration. This is a rather complex problem which will not be pursued in the present paper.

The effect of temperature on the form of the action potential and its propagation velocity, as computed from the Hogkin-Huxley equations, is in good agreement with the experimental data on the squid giant axon (Chapman, 1967; Cole, 1968; Hodgkin and Katz, 1949; Huxley, 1959; Spyropoulos, 1965). Fitzhugh (1966) has shown that the effect of temperature on the threshold of the action potential in the squid giant (Guttman, 1966; Sjodin and Mullins, 1958) is qualitatively predicted by the Hodgkin-Huxley model. In the present analysis, temperature variation is implicitly included in the quantity β, and temperature effects are thereby incorporated in the more general context of the degree of regeneration.

The types of nerve signal considered above are relevant to understanding the nature of dendritic signals and the responses of neurons that do not generate spikes. In the retina of *Necturus*, for example, horizontal and bipolar cells were found to respond with graded potentials that were hyperpolarizing in the case of the former and either hyperpolarizing or depolarizing for the latter, whereas amacrine cells exhibited a spikelike response superimposed upon a wave of depolarization (Werblin, 1970; Werblin and Dowling, 1969). As regards dendritic signals, it is probably a gross oversimplification to consider the dendritic membrane as inexcitable (Eccles, 1960). Rather, it seems more likely that the dendritic membrane is in general excitable, but that the degree of regeneration present, and therefore the type of response observed experimentally, is primarily determined by the functional role of the neuron under observation and to some extent depends upon the physiological state of the preparation. A well-documented case has been reported of dendritic spikes in Purkinje cells of alligator cerebellar cortex (Llinás and Nicholson, 1969). These examples illus-

trate the variety of neuronal signals and emphasize the hazards of adhering to too rigid and categoric a view of these signals.

APPENDIX

Dimensional Aspects

The Hodgkin-Huxley equations (Hodgkin and Huxley, 1952) may be written as:

$$C\frac{dV}{dt} + I_i(V, t) = I_s(t), \tag{1}$$

where $I_s(t)$ is the current stimulus for a uniform patch of membrane, and

$$I_i(V, t) = G_K^0 n^4(V - V_K) + G_{Na}^0 m^3 h(V - V_{Na}) + G_L(V - V_L),$$

$$\frac{dk}{dt} = \alpha_k(1 - k) - \beta_k k, \qquad (k = n, m, h),$$

with α_k, β_k being functions of V alone. If the rates of change of n, m, and h with respect to time are altered by a factor ϕ, and membrane capacitance and conductances are multiplied by γ and η, respectively (Huxley, 1959), then equation 1 becomes:

$$\gamma C\frac{dV}{dt} + \eta I_i(V, \phi t) = I_s(t).$$

Substituting $\tau = \phi t$:

$$\frac{C}{\beta}\frac{dV}{d\tau} + I_i(V, \tau) = \frac{I_s}{\eta}\left(\frac{\tau}{\phi}\right), \tag{2}$$

where

$$\beta = \frac{\eta}{\gamma\phi}.$$

Any characteristic of the action potential can be considered as some function of β and the right-hand side of equation 2. In particular, threshold values for a given type of stimulus must be a function of β. Two types of stimuli are of interest: a current step of amplitude I_p, and a current impulse, or delta function, equivalent to a charge Q_d. For a current step stimulus equation 2 becomes:

$$\frac{C}{\beta}\frac{dV}{d\tau} + I_i = \frac{I_p}{\eta}, \qquad \tau > 0.$$

It follows that the threshold value I_{pthr}, or rheobase, is given by:

$$I_{pthr}/\eta = f_p(\beta),$$

where $f_p(\beta)$ is a function of β. This function was evaluated through numerical computation of the Hodgkin-Huxley equations and is plotted in Fig. 8. In the case of a current impulse

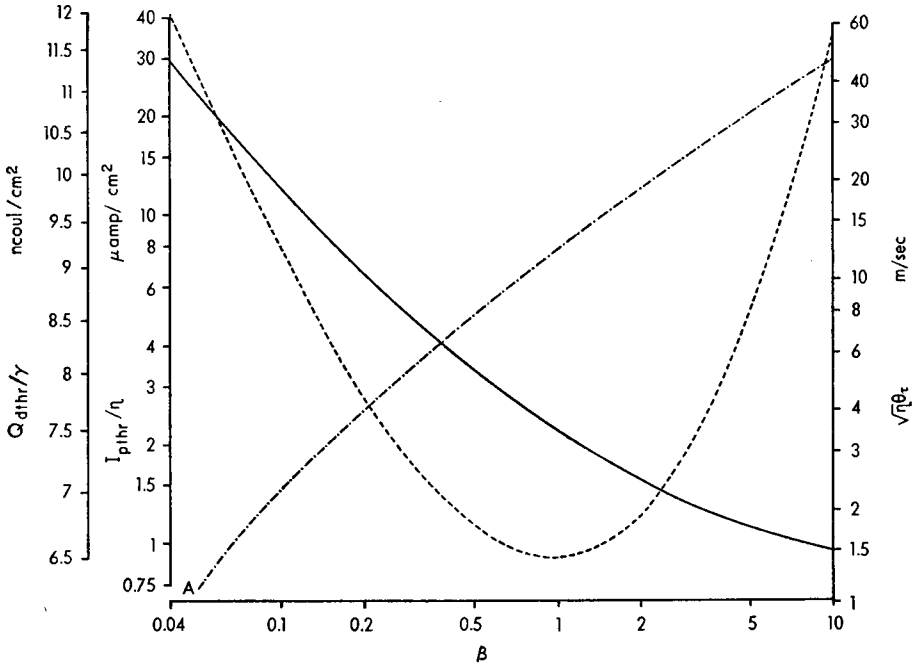

FIGURE 8 The variation with respect to β of $1/\eta$ times the rheobase (solid line), and $1/\gamma$ times a threshold current pulse stimulus of 5 μsec duration (dotted line), for the Hodgkin-Huxley space-clamped model for the squid giant axon. The dash-dotted line represents the variation with respect to β of $\sqrt{\eta}\theta_\tau$ for an action potential propagating steadily along an infinite Hodgkin-Huxley cable model for the squid giant axon. θ_τ is the conduction velocity expressed in units of time $\tau = \phi t$, so that $\theta_\tau = \phi \times \theta$, where θ is the actual conduction velocity in meters per second.

stimulus equation 2 becomes:

$$\frac{C}{\beta}\frac{dV}{d\tau} + I_i = 0 \qquad \tau > 0,$$

with $V = Q_d/\gamma C$ at $\tau = 0$. The threshold value Q_{dthr} is given by:

$$\frac{Q_{dthr}}{\gamma} = f_d(\beta),$$

where $f_d(\beta)$ is a function of β. Computed values of this function are also plotted in Fig. 8.

It will be noted that whereas $f_p(\beta)$ is monotonic, $f_d(\beta)$ exhibits a minimum. This type of behavior has been noted with respect to changes in temperature both in computations and experiments on the space-clamped squid giant axon (Fitzhugh, 1966; Guttman, 1966; Sjodin and Mullins, 1958). A large β implies a small ϕ or a reduced membrane time constant. Excitation will therefore have to take place on a relatively faster falling membrane potential as can be seen by comparing the responses shown in A and B of Fig. 2. Presumably, this accounts for the increase in $f_d(\beta)$ for large β.

For a uniform axon in a highly conducting medium, equation 1 becomes (Hodgkin and Huxley, 1952):

$$C\frac{\partial V}{\partial t} + I_i(V, t) = K\frac{\partial^2 V}{\partial x^2}, \tag{3}$$

where $K = a/2\rho$, a is the radius of the axon and ρ the resistivity of the axoplasm. For a uniformly propagated action potential: $\partial^2 V/\partial x^2 = 1/\theta^2(\partial^2 V/\partial t^2)$, where θ is the conduction velocity. If the membrane capacitance, conductances and the rates of change of n, m, and h are modified as for the space-clamped axon, equation 3 becomes:

$$\frac{C}{\beta}\frac{\mathrm{d}V}{\mathrm{d}\tau} + I_i = \frac{K}{\eta\theta_\tau^2}\frac{\mathrm{d}^2 V}{\mathrm{d}\tau^2}, \tag{4}$$

where $\theta_\tau = \theta/\phi$ is the conduction velocity measured in units of time $\tau = \phi t$. Following the argument of Hodgkin and Huxley (1952) and Huxley (1959), there corresponds to every value of β for which propagation is possible, a value of $\eta\theta_\tau^2$ for which the solution of equation 4 becomes finite for all time. Hence

$$\theta_\tau\sqrt{\eta} = f_\theta(\beta),$$

where $f_\theta(\beta)$ is some function of β. Computed values of this function are plotted in Fig. 8. Steady propagation is not possible for values of β less than about 0.05 (point A on the curve).

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