HODGKIN-HUXLEY AXON

INCREASED MODULATION AND LINEARITY OF
RESPONSE TO CONSTANT CURRENT STIMULUS

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ABSTRACT   Repetitive response patterns resembling those of tonic receptors were
obtained by increasing the potassium system time constant in the Hodgkin-Huxley
(H-H) equations. The increase in time constant varied with membrane potential.
Calculated spike frequencies varied linearly with the magnitude of the constant
current stimulus; in addition, minimum frequencies were greatly reduced, and the
frequency range increased. Modification of the maximum ionic conductances, mem-
brane capacitance, and rate constant voltage dependence was found to vary the
minimum frequency, current at that frequency, slope, and over-all modulation of the
modified responses.

INTRODUCTION

Neurons exhibit great diversity in the nature of their responses to stimuli. Ulti-
mately the explanation of this diversity can only be obtained empirically. In the
absence of sufficiently detailed data on the causes of this variation it is useful to
develop models which approximate the behavior of the different classes of neurons.

One model of neuron function is the system of differential equations known as
the H-H axon (Hodgkin and Huxley, 1952). This model is based on a wealth of
experimental data and fits the data very closely. The data was derived from voltage
clamp studies on the squid giant axon; hence it models events in a rapidly conducting,
nonmyelinated axon. The theory accurately reproduces many typical properties of
the action potential, threshold strength-duration relations, all-or-none propagation,
temperature effects, and ionic fluxes. Since the original model was developed from
squid data, however, it clearly cannot be expected to reproduce response characteris-
tics of neurons which differ in some important respect. Nevertheless, it has been
possible to extend the range of applicability of the theory, with relatively minor
modifications, to myelinated axons (Frankenhaeuser and Huxley, 1964), cardiac
muscle fibers (Noble, 1966), and striated muscle fibers (Adrian et al., 1970).

A major type of nerve cell whose behavior has not yet been duplicated satisfactorily is the sensory receptor. Receptors transduce the time variation of some stimulus magnitude into a time varying instantaneous frequency of response. If the coding is such that a constant stimulus evokes a constant response frequency, the cell is called "tonic." The stimulus appears to reduce the membrane impedance of specialized portions of the receptor cell and leads to a shunt depolarization called the receptor potential. This potential is then thought to spread electrotonically to an initiating site at the somatic end of the receptor axon. The receptor potential depends primarily on the strength of the applied stimulus, since the action potential cannot in general propagate into the depolarized transducing region. Hence, at least to a first approximation, a constant stimulus causes a constant depolarizing current to flow across the membrane at the impulse initiating site.

If an analogous constant current stimulus is applied to a space-clamped H-H axon, the calculated response is a long train of constant frequency spikes. The variation of frequency with current magnitude, however, differs from sensory receptors in three major respects. First, a discontinuity is observed in the response frequency as the applied current is increased. Below approximately $0.8 \ \mu amp/cm^2$, there is no repetitive response. At higher intensities, the cell suddenly begins firing a train of impulses at a relatively high rate (≈ 50 Hz). Second, the variation of frequency with current is highly nonlinear, increasing rapidly at first and leveling off at high current strengths. Finally, partly as a consequence of the first two points, there is relatively little modulation range in the response (ratio of maximum to minimum frequency).

In contrast to this behavior the majority of tonic receptors which have been studied (Fuortes and Mantegazzini, 1962) show repetitive firing to small currents, linear frequency variations over a considerable range, and extensive modulation capabilities. Similar responses are also seen in a variety of other cell types (e.g., cat motoneurons, in Granit et al., 1963) which subserve different roles than the stereotyped, nonrepetitive squid giant axon.

There is little doubt, however, that the areas (encoding regions) of sensory cells responsible for converting generator potentials to repetitive spikes are similar in their membrane characteristics to the squid giant axon. The action potentials in both cells are blocked by tetrodotoxin (Loewenstein et al., 1963). To get regenerative, selfterminating potentials something like the squid giant axon system would be expected. There is no reason to believe that the special membrane characteristics necessary to encode potential changes as changes in frequency extend to the soma or the remainder of the sensory axons. Axons need only follow the encoding region with a 1:1 firing ratio. For this, classic H-H parameters are sufficient. Somas probably do not play a large role in spike generation. Because of the location of the encoding region in the initial axonal region (Nakajima and Onodera, 1969) it is not feasible to voltage clamp it. With present techniques a good space clamp of the encoding region, with the test membrane confined to that region, would be extremely

difficult. Because of the difficulty in obtaining voltage clamp data from the encoding region we instead tried to model the behavior with a system of equations. Since this region is tetrodotoxin sensitive and very possibly similar to the squid giant axon in its behavior, we took the H-H equations as our starting system. The successful extension of the H-H approach to other systems is another reason for taking this approach. We then tried to find some minor modifications which would make the membrane give a current-frequency curve which more closely resembles that of a sensory axon. The emphasis was on keeping the changes in the H-H equations to a minimum.

METHODS

Equations

The H-H equations were the same as those developed in 1952 (Hodgkin and Huxley, 1952). Unless otherwise specified the space-clamped condition was investigated. The constants (at a temperature of 6.3°C) are g_{Na}, 120 mmho/cm²; g_L, 0.3 mmho/cm²; g_K, 36 mmho/cm²; C_m, 1.0 μF/cm²; V_L, -10.6 mv; V_{Na}, -115 mv; V_K, 12 mv.

It seemed to us that one of the most critical factors in achieving a low firing frequency and improving the frequency-current function is the rate of repolarization after the spike undershoot (hyperpolarization). In the squid giant axon this is nonlinear and rapid whereas in sensory cells, such as the crayfish slowly adapting stretch receptor, it is slow and moderately linear. An important factor in determining the rate of repolarization is the time constant of potassium activation, T_n. If T_n is increased over the entire voltage range, however, the action potentials become greatly prolonged (FitzHugh, 1960). Although this might produce very low repetitive rates it is doubtful that they could ever get very high. In order to keep the increase in duration to a minimum T_n was multiplied by a voltage dependent function. Thus

$$T_n^* = 1/\gamma \, T_n \,,$$

where T_n^* is the new function in our modified H-H equations, and γ is a function of voltage. γ varies linearly with voltage such that

$$\gamma = \frac{1}{\gamma_0} - \frac{(1 - 1/\gamma_0)V}{115} \,.$$

When $V = 0$, $\gamma = 1/\gamma_0$; when $V = V_{Na} = (-115$ mv), then $\gamma = 1$.

Thus, for $\gamma_0 > 1$, as the membrane becomes more depolarized T_n^* approaches T_n. They are equal at V_{Na}, and for even greater depolarizations $T_n^* < T_n$. Since such potentials, however, are never achieved $T_n^* \geq T_n$.

In the H-H equations $T_n = 1/(\alpha_n + \beta_n)$ and the steady-state value, $n_\infty = \alpha_n/(\alpha_n +$

β_n). In order to assume that all steady-state values of the modified H-H equations are identical with those in the original H-H equations, we made

$$\alpha_n^* = \gamma \alpha_n ,$$

$$\beta_n^* = \gamma \beta_n ,$$

where α_n^* and β_n^* are the new voltage dependent n variable rate constants for the modified H-H equations. When $\gamma_0 = 1$, the equations are in the unmodified H-H form.

Modeling

Solutions to the equations were calculated on an EAI 680 analogue computer. Values of the rate constants as functions of the membrane potential were obtained from three variable diode function generators and three fixed exponential generators. The frequency of oscillations was measured on a digital frequency meter.

It was soon established that the modified axon ($\gamma_0 > 1$) resembled the encoding region more closely than did the unmodified one. The effect on the frequency-current plot of the modified axon of alterations in other membrane parameters was investigated. Reductions in g_{Na}, g_K, or g_L and the voltage shifts of certain rate constants (see below), however, produced a change in resting ionic conductances. Although the axon could be allowed to depolarize or hyperpolarize to a new steady-state ("resting") level, for the most part we introduced a small voltage bias into the integrating amplifier whose output represented membrane voltage. The bias was so adjusted that the initial conditions were always $V = 0$, $dV/dt = 0$.

RESULTS

Potassium Time Constant Factor

The variation of repetitive response frequency with stimulus current is shown in Fig. 1 for six levels of potassium time constant factor ($\gamma_0 = 1, 2, 3, 5, 7$, and 10). A low stimulus (0.6 μamp/cm^2) corresponds approximately to the repetitive threshold; at this point the unmodified axon began suddenly to fire at about 50 impulses per second. As γ_0 increased, the threshold frequency was progressively reduced, reaching 2.0 Hz at $\gamma_0 = 10$. The highest stimulus was somewhat arbitrarily chosen to be 120 μamp/cm^2. This represents a relatively intense current density probably near the limit of the physiological range. Slowing the potassium system again gradually reduced the response frequency from 152 Hz with $\gamma_0 = 1$–61 Hz with $\gamma_0 = 10$. Hence, the observed modulation capability of the model, f_{max}/f_{min} for the 100-fold range of stimulus current was increased from 3.02 to 30.5, or more than 9 times.

The unmodified axon exhibited negative deviation from linearity as previously reported (Agin, 1964), above its discontinuity the relationship to applied current was
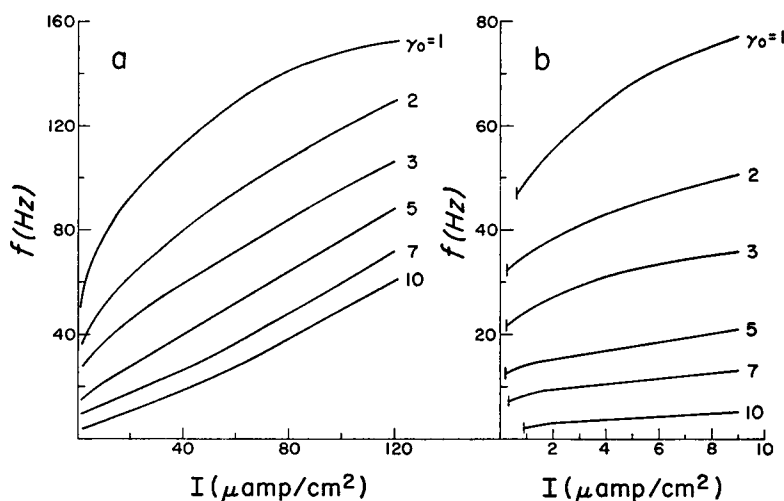
FIGURE 1 (*a*) Repetitive firing in model axons as a function of amplitude of constant current. Values in this and subsequent figures are steady-state frequencies. Curves drawn for various values of γ_0, the reciprocal of the voltage intercept of the linear function γ (see text). When $\gamma_0 = 1$ the model is identical with the original H-H axon. Other values of γ_0 represent various degrees of modification of the H-H equations. (*b*) Same data on an expanded scale. Vertical bars represent the limits of repetitive firing. Currents below these values will not produce infinite trains of action potentials.

approximately logarithmic. The response became more linear as γ_0 increased up to $\gamma_0 = 5$ or 7. Additional slowing of the potassium system resulted in a small positive deviation from linearity, with a very small positive curvature developing.

A comparison of normal and modified action potentials is given in Fig. 2. In Figs. 2 *a* and *b* the response to a brief superthreshold shock of unmodified and modified axons can be seen. The differences are slight and confined to the last half of the falling phase and, most markedly, to the undershoot and repolarization. Figs. 2 *c* and *e* show the response of the unmodified and modified axons to a constant current density of 9 μamp/cm². Note the marked difference in frequency. The H-H axon fires at a frequency which is almost limited by its refractory period. In contrast the modified axon fires at a low frequency determined by the slow nearly linear repolarization after each spike. Figs. 2 *d* and *f* show such potentials on a different time scale. Note the slightly greater amplitude of action potential in the modified axon, due to the lower firing frequency and hence higher value of h.

The changes in spike height as a function of firing frequency have previously been observed experimentally (Eyzaguirre and Kuffler, 1955). For high frequencies the oscillations cease to resemble action potentials and may shrink to less than 20 mv. Since the model is space clamped it is impossible to say at what currents and frequencies propagation would cease. Establishment of some arbitrary criterion (e.g., 40 mv, $p - p$) shows that different conditions, such as changes in γ_0, C, g_{Na}, result
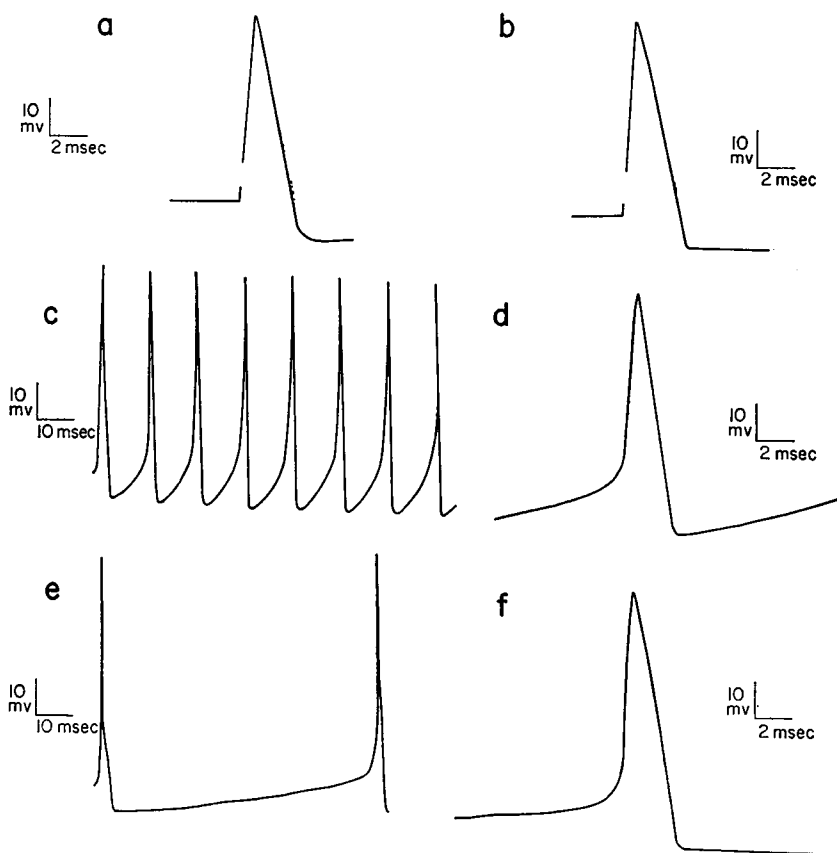
FIGURE 2 Sample action potentials from the computer output. (a) Response of the H-H axon to a brief superthreshold shock. (b) Same as (a) but for modified axon (γ_0 = 7). (c) Repetitive firing of H-H axon in response to a constant current of 9 μamp/cm^2. (d) Same as (c) but faster sweep. (e) Repetitive firing of modified axon (γ_0 = 7) to a constant current of 9 μamp/cm^2. (f) Same as (e) but faster sweep.

in frequency-current curves which reach this criterion at different frequencies and currents. Thus, there is no generally applicable maximum current or frequency for repetitive firing. As noted below, however, under some conditions when the parameter changes cause a change primarily in the slope of the frequency-current curve, there appears to be an approximate frequency maximum.

Maximum Conductances

The results described above were considered successful in that they reproduced the continuous, linear, highly modulated behavior characteristic of many sensory neurons. The effect of employing the original values of all the other constants in the H-H axon, however, was to produce an axon with roughly a 10 Hz response at threshold and 100 Hz limit with maximum stimulus. In an effort to duplicate a

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greater range of receptor-like responses and to investigate the interaction of the γ function with other changes, the effects of alterations in several other parameters was investigated.

Fig. 3 shows the observed frequency-current characteristics when maximum potassium conductance is varied. The effect of reduced g_K was to increase the slope of the curves without greatly affecting linearity. This increased rate of modulation or gain led eventually to damping of the responses to strong stimuli. That is, as currents increased the amplitude of oscillations decreased and above a certain level the rate of decrease was very marked, a damping point. The response frequency at which damping occurred was moderately constant but did decrease slightly as g_K was reduced. This means that the maximum modulation range probably decreased slightly with decreasing g_K .

Reduction in g_K caused small depolarization and this was routinely balanced by a bias voltage added to an integrating amplifier. If, however, no bias was added the initial, steady-state potential changed. At this potential the cell could fire spontaneously at a low rate (Fig. 3 b). The rate varied with the reduction in g_K and ranged from about 12 to 20 Hz for reductions of g_K down to 0.25 nominal. It is particularly interesting that the firing frequency of the spontaneously firing model axons can be modulated in either direction. As is apparent in Fig. 3 b, passage of hyperpolarizing current reduces the frequency. Although the maximum reduction is much smaller than the increase, it is significant nevertheless. Such behavior is reminiscent of the encoding region in the lateral line organs of certain elasmobranch and bony fishes (Murray, 1965; Hagiwara and Morita, 1963).

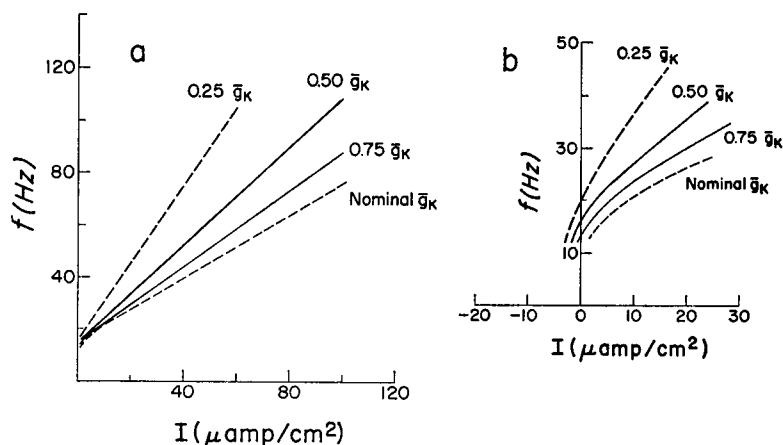The effect of changes in sodium conductance is shown in Fig. 4 b. Reduction in

FIGURE 3   Frequency-current plots for modified axons ($\gamma_0 = 5$). Potassium conductance constants, $\bar{g}_K$, varied from nominal (H-H) values to 0.25 times nominal. (a) Voltage rebalanced to H-H steady-state resting level. Note that for $\bar{g}_{K}$, only 0.25 nominal, currents above 60 μamp/cm² produce small repetitive oscillations. (b) Voltage not rebalanced. Model axons can fire spontaneously. Such cells can be modulated by outwardly directed current.
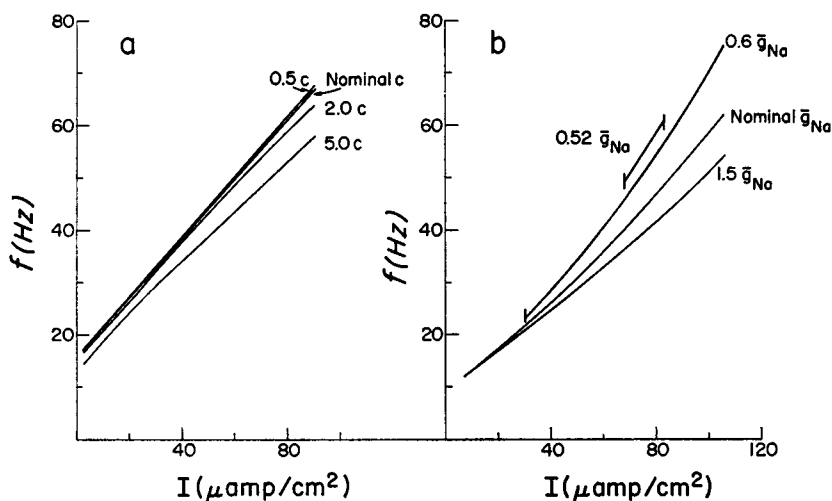
FIGURE 4   (a) Effect of membrane capacitance changes on frequency-current characteristics of a modified axon ($\gamma_0 = 5$). Capacitance varied from 0.50 nominal to 5.0 nominal. (b) Effect of changes in sodium conductance constant ($\bar{g}_{Na}$), on frequency-current characteristics of modified axon ($\gamma_0 = 7$). Note the narrow range of the curve for 0.52 $\bar{g}_{Na}$. Currents outside of the range do not produce infinite trains of action potentials.

g_{Na} by 48 % led to a loss of repetitive excitability except over a narrow middle range of stimuli. With lower currents the modified axon fired singly or, for currents just below the indicated threshold, in finite trains. For currents larger than maximum the trains first became finite and then, for slightly larger current densities, the oscillations were extremely small. The effect of increased conductance was similar to that found with potassium, reducing the observed frequency of response.

The effect of a 50 % reduction in leakage conductance was found to be negligible for all values of γ_0 and g_K. This was to be expected, since the rebalance procedure described above effectively canceled the change in leakage current near resting potential.

Membrane Capacitance

The results of modifying membrane capacitance proved to be surprising. It might be anticipated that higher capacitance would lead to a significantly lower response frequency, since a depolarizing stimulus would have to supply more charge to bring the axon to threshold. As may be seen in Fig. 4 a, however, the effect is very small. Only large changes in membrane capacitance affect the frequency to a significant extent. This effect is larger for larger currents and higher frequencies. Inspection of the wave forms during repetitive firing of axons with nominal or 5 times nominal capacitance shows that most of the difference in frequency of firing is due to differences in the spike duration rather than differences in the slow interspike depolarization.

Rate Constant Voltage Shifts

Frankenhaeuser and Hodgkin (1957) discovered that the effects of low external calcium concentration (increased repetitive behavior with single shocks) could be modeled by shifting the six rate constants with respect to the potential axis. Stein (1967) found, however, that shifting α_h and β_h did not significantly increase the modulation achievable with constant current stimuli. This result was confirmed in the present study. In contrast, however, the modified axon (Fig. 5) was found to be quite sensitive to voltage shifts of the h rate constants. 60% higher response frequencies resulted when the resting value of h was reduced by a 10 mv shift of the voltage axis.

Note that for both modified and unmodified axons a voltage shift of the h/V curve such as to reduce h_∞ at rest increased the minimum current necessary to produce repetitive firing. As can be seen from Fig. 5, this effect was greater the smaller the value of γ_0. When $\gamma_0 = 1$, i.e. the axon is in the unmodified H-H form, currents of greater than 22 μamp/cm² are necessary to produce infinite trains. Below that only single spikes or brief finite trains are seen. For such an axon, as currents are increased above 60 μamp/cm² the spike height is severely reduced; and oscillations of less than 5 mv occur at currents above 67 μamp/cm². Thus, this axon has an extremely small modulation range. Taken with the data from Fig. 4 b it appears that reduction in the sodium currents of the modified axon leads to severe reduction of the modulation range.

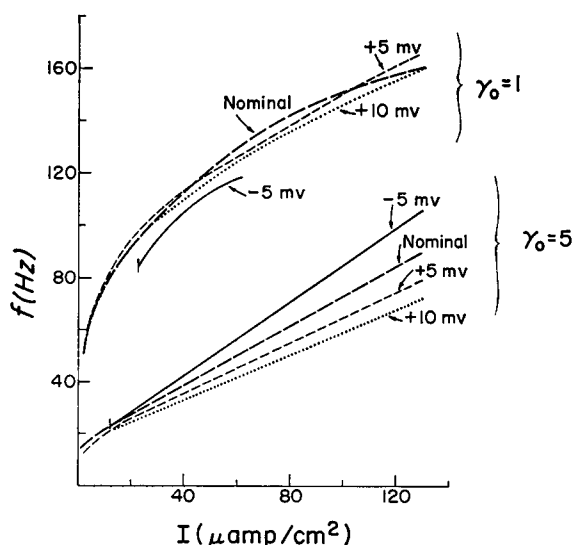
FIGURE 5   Effect of shifting the h rate constants along the voltage axis on the frequency-current characteristics of an unmodified ($\gamma_0 = 1$) and modified ($\gamma_0 = 5$) axon. Positive voltage shifts increase the resting value of h. Solid lines, -5 mv; long dashes, nominal values; short dashes, $+5$ mv; dots, $+10$ mv.

The effects of voltage shifts on the n parameters (Fig. 6) were similar; response frequencies increased approximately 35% with a 10 mv shift in the direction of reducing the resting value of n. Responses to weak stimuli were, however, less affected in this case.

Axon Gain

It is possible to combine several parameter changes and produce a modified axon with a wide range of gain. Such an axon can still fire at frequencies below 20 Hz and display a linear frequency-current plot with a large modulation range. The effects of the other parameters are roughly additive, so that a modified axon ($\gamma_0 = 5$) with $g_K = 0.5$ nominal, $\Delta V_h = -5$ mv, and $\Delta V_n = -10$ mv has a slope of about 3 Hz/mamp per cm². On the other hand a modified axon ($\gamma_0 = 10$) with $\Delta V_h = 10$ mv and $g_{Na} = 1.5$ nominal has a slope of only 0.10 Hz/mamp per cm².
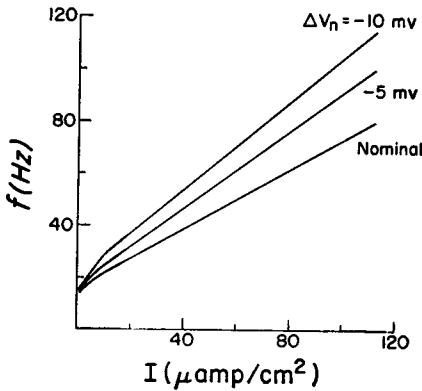

FIGURE 6 Effect of shifting the n rate constants along the voltage axis on the frequency-current characteristics of a modified axon ($\gamma_0 = 5$). The shifts shown reduce the resting value of n.
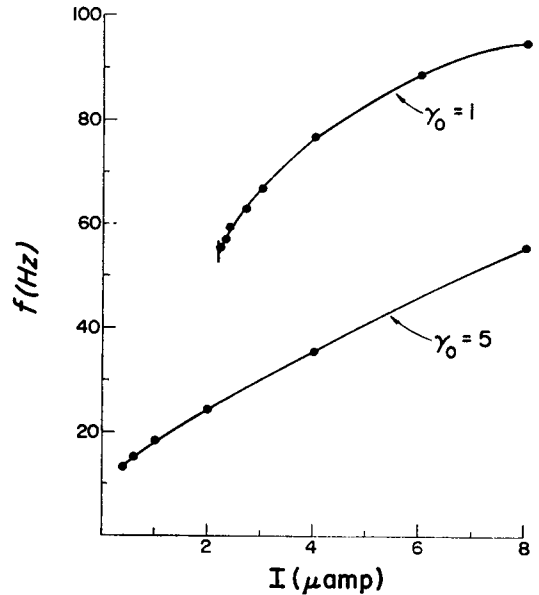
FIGURE 7 Frequency-current plots for the propagating spikes in an infinite cable of uniform characteristics. The current is applied by a point source in the middle of the cable. Digital solutions are obtained by methods of Cooley and Dodge (1966). Points show instantaneous frequencies and both finite and infinite trains are plotted. Currents outside the range give either single spikes or none at all. (Data courtesy of J. W. Cooley and F. A. Dodge.)

Modified Infinite Cable

Cooley and Dodge (1966) showed that the repetitive firing in a propagating infinite cable is even more frequency invariant than in the space-clamped model. They have repeated this for an axon at 6.3°C. For the unmodified axon ($\gamma_0 = 1$) total range is from 15 to 25 Hz, even including finite trains. The frequency-current function is clearly nonlinear. Doctors Dodge and Cooley have also run their digital program for modified axon ($\gamma_0 = 5$). As in their 1966 paper, constant currents are applied from a point source in the middle of an infinite cable. Propagation is in both directions. The cable was uniform in its membrane properties and had a diameter of 350 μ. Their results are plotted in Fig. 7. Note that the range is markedly increased as is the linearity. The slight deviation from linearity at low currents is similar to that seen for modified space-clamped axons.

DISCUSSION

Only the potassium system rate constant modification significantly affected the linearity of the observed frequency-current curve. The greatest over-all linearity occurred with $\gamma_0 = 5$; $\gamma_0 = 10$ was slightly superior in the very low current region. Receptor-like behavior is therefore obtained from the H-H model if a potassium time constant of about 30 msec at resting potential is substituted for the original value.

The resulting linear frequency-current relations are defined by four independent factors, namely the threshold frequency f_θ, the repetitive current threshold I_θ, the modulation gain df/dI, and the achievable modulation f_{max}/f_θ. The qualitative effects of deviations from nominal H-H axon values on these parameters are summarized in Table I. The ultimate modulation capability cannot be calculated for several axons with large effective stimulus ranges. These cases have been indicated by question marks; weak effects have been enclosed in parentheses. Although only the modified axon was studied in detail, qualitatively similar trends were also observed for the original unmodified responses.

Two correlations are evident in the data of Table I. First, the frequency at the threshold for repetitive firing was highly correlated with gain, i.e., a larger discontinuity in most cases was accompanied by a higher gain. Second, the modulation appeared to be negatively correlated with gain, i.e. as gain increased, over-all frequency variation was generally reduced.

These correlations may be taken to define two extreme classes of repetitive response, the first with a more pronounced discontinuity at repetitive threshold, with high initial gain but limited modulation, and the second with lower gain but greater over-all modulation. Axons of the first class are characterized by a low γ_0 value, high g_K, low g_{Na}, and decreased resting values of h and n, while those of the continuous class possess values deviating in the opposite direction. Intermediate types of behavior would of course be obtained from cells with mixed characteristics.

TABLE I
EFFECTS OF CHANGES IN PARAMETERS

Factor	Change	Threshold frequency	Threshold current	Gain	Modulation
γ_0	1–5	−	(−)	−	+
	5–10	−	+	−	+?
$\bar{g}_K$	Increase	+	+	−	?
	Decrease	(+)	0	+	−
$\bar{g}_{Na}$	Increase	(−)	0	(−)	?
	Decrease	+	+	+	−
$\bar{g}_L$	Decrease	0	0	0	0
C_m	Increase	0	0	(−)	?
	Decrease	0	0	(+)	?
ΔV_h	Decrease h_0	+	+	+	−?
	Increase h_0	(−)	0	−	?
ΔV_n	Decrease n_0	(+)	0	+	?

The H-H axon represents an extreme case of the first group. It fires singly or at rather high frequencies, with high initial gain. Presumably, fine control of the squid axon's firing rate is not necessary for its proper functioning. The axon mediates an escape response which does not require sensitive gradation.

In contrast linearity and continuity of response seem desirable characteristics for any quantitative signaling device such as a receptor unit. As Mountcastle (1967) has pointed out the nervous system appears to have recognized this point by lumping any required nonlinearity "upstream" of the frequency coding process in the events leading to the generator potential.

A possible conclusion from the present data in this regard is that the cell with a linear frequency-current relation will tend to possess reduced gain and greater over-all modulation. Since reasonable gain may be desirable the cell might be expected to modify other factors which increase gain without increasing discontinuity. Thus, according to Table I, the most suitable changes would be a decrease in g_K ; in fact, many receptors are known to possess lower potassium conductances than that of the squid giant axon. Another method of obtaining a more continuous, high gain function might be a moderate depolarization of the cell, which would shift the discontinuity of an intrinsically high gain cell outside the physiological range. Other factors are important, such as the size of the synaptic or generator conductance changes, the location of the sites of increase, the resistance of the cell soma, and the

cell geometry, particularly near the encoding region. All of these would affect the efficacy of a synaptic or sensory stimulus in producing a given current density at the encoding region.

It is interesting that the solutions for the infinite cable fire repetitively over a narrower frequency range than those for a nonpropagating space-clamped cell. This is true for both modified and unmodified axons although the unmodified axon's range is diminished much more. The modified axon still fires nearly linearly over a fourfold range. This is another example of the robustness of the modification: the linearity and range of the repetitive response is fairly insensitive to changes in other parameters and conditions. The infinite uniform cable is not necessarily a better model than the space-clamped axon. The best model would probably involve at least four compartments: a dendritic segment serving as a current source and possibly incapable of spiking; a somatic segment of large diameter and high spike threshold; an encoding region of small diameter and low spiking threshold; an axonal section of small diameter, slightly higher threshold, and infinite extent. Only the encoding region would have modified H-H properties. A solution of this model is required, and clearly the frequency-current characteristics would depend greatly on the geometry, extent of the encoding region, and H-H parameters of all segments.

The modified axon is a much better approximation of the behavior of the frequency encoding region of sensory cells than is the classical H-H axon. The introduction of the linear function γ is undoubtedly only one of a large number of alterations of the H-H equations which would improve the frequency-current relation. Yet it is a minor change and probably one of the simplest changes which will yield a reasonable approximation to sensory behavior. In view of the difficulties associated with voltage clamping an encoding region the model outlined above presents an alternative approach and suggests that it might be fruitful to look for certain peculiarities of the encoding region. If the model is even approximately accurate the most obvious characteristic would be a relatively long time constant of potassium rectification around the resting level, and a more conventionally brief time constant for large depolarizing pulses. For example, whereas for an H-H axon T_n at resting potential and 0 mv would be about 5 and 1.5 msec, respectively, for a modified axon ($\gamma_0 = 5$) the time constants at these potentials would be 25 and 4 msec, thus the ration of T_n at these two potentials would be more than 6:1 in the modified case rather than a little over 3:1 in the unmodified case.

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