

Theoretical Effect of Temperature on Threshold in the Hodgkin-Huxley Nerve Model

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ABSTRACT In the squid giant axon, Sjodin and Mullins (1958), using 1 msec duration pulses, found a decrease of threshold with increasing temperature, while Guttman (1962), using 100 msec pulses, found an increase. Both results are qualitatively predicted by the Hodgkin-Huxley model. The threshold vs. temperature curve varies so much with the assumptions made regarding the temperature-dependence of the membrane ionic conductances that quantitative comparison between theory and experiment is not yet possible. For very short pulses, increasing temperature has two effects. (1) At lower temperatures the decrease of relaxation time of Na activation (m) relative to the electrical (RC) relaxation time favors excitation and decreases threshold. (2) For higher temperatures, effect (1) saturates, but the decreasing relaxation times of Na inactivation (h) and K activation (n) favor accommodation and increased threshold. The result is a U-shaped threshold-temperature curve. R. Guttman has obtained such U-shaped curves for 50 μ sec pulses. Assuming higher ionic conductances decreases the electrical relaxation time and shifts the curve to the right along the temperature axis. Making the conductances increase with temperature flattens the curve. Using very long pulses favors effect (2) over (1) and makes threshold increase monotonically with temperature.

I. INTRODUCTION

Experimental studies on the effect of temperature on the threshold stimulating current of the squid giant axon have been made by Sjodin and Mullins (1958) and Guttman (1962, 1966). Sjodin and Mullins, using stimulating pulses of 1 msec duration, found that the threshold decreased with increasing temperature, while Guttman (1962), using 100 msec pulses, found that it increased. Guttman (1966), using 50 μ sec pulses, finds that some fibers give a U-shaped curve with a minimum in the neighborhood of 15°C.

All the above results are predicted qualitatively by computations of the effect of temperature on threshold, using the Hodgkin-Huxley model (Hodgkin and Huxley, 1952). However, since the exact shape of the curve of threshold vs. temperature varies markedly, both experimentally with the condition

of the axon, and theoretically according to the assumptions made regarding the effect of temperature on ionic conductances of the membrane, a quantitative agreement cannot yet be made between theory and experiment.

II. EQUATIONS

Temperature is assumed to affect the Hodgkin-Huxley (HH) equations in two ways. The first (which was the only one assumed originally by Hodgkin and Huxley) is to multiply the rates of change of the conductance variables m , h , and n by a factor ϕ :

$$\phi = 3^{(T-6.3)/10} \quad (1)$$

where T is the temperature in degrees centigrade. This formula gives to m , h , and n a Q_{10} of 3.

The second way is to assume changes in the ionic conductances in accordance with Moore's experiments (1958). Moore found that the Na and K conductances increased linearly with temperature at a rate per degree centigrade which was about 4% of their values at 15°C. Moreover, his values of conductance were greater than Hodgkin and Huxley's at their reference temperature of 6.3°C. Both effects are provided for by multiplying the conductance constants \bar{g}_{Na} , \bar{g}_K , and, for mathematical simplicity, also g_L ,¹ by the following factor η :

$$\eta = A[1 + B(T - 6.3)]. \quad (2)$$

A is the ratio between the ionic conductances of the axon at 6.3°C and the values used by Hodgkin and Huxley (which they assumed to be independent of temperature). A depends on the condition of the axon. Recent experiments by my colleagues have shown that at 6.3°C an axon in very good condition may be about four times as powerful ($A = 4$) as those used by Hodgkin and Huxley.

The parameter B determines the rate of change of conductance with temperature. For the above figure of 4% quoted from Moore (1958), $B = 0.061$. FitzHugh and Cole (1964) use the values $A = 1.1389$ and $B = 0.05853$, which were taken from a representative axon in Moore's original data. Since the values of A and B vary considerably from axon to axon, computations are made here only for $A = 1$ and 4, $B = 0$ and 0.061, in order to show how changing A and B affects the temperature-threshold relation.

¹ Note that this assumption makes the resting potential independent of temperature. Hodgkin and Katz (1949) and Guttman (1965) actually found no change of resting potential below 25°C, and only a slight decrease above 25°C.

III. RESULTS OF COMPUTATION

The stimulus assumed was a rectangular pulse of membrane current I and duration D . Two limiting cases are of importance, because they are mathematically simpler than the general case. The first is the case of an instantaneous shock ($D \rightarrow 0$), in which I is proportional to a unit impulse or Dirac delta function, and the second is a step current ($D \rightarrow \infty$).

The first case is equivalent to displacing V from its resting value by an amount proportional to the amplitude of the stimulus (the displacement being simply the potential change of the membrane capacitor resulting from instantaneously applying a certain charge per unit area to the membrane) and keeping $I = 0$ thereafter. The value of charge which is just threshold is denoted as Q . Fig. 1 shows Q as a function of temperature T , for the four assumed combinations of values of A and B . This curve has a minimum at an optimal value T_0 of T .

It is shown below (section V) that if $B = 0$, increasing A simply moves the whole curve to the right along the T axis without changing its shape. For a given value of A , increasing B flattens the curve, and also (if $A > 1$) increases the optimal temperature. For all curves the minimum value of Q is the same, $6.51 \text{ nCoul cm}^{-2}$.

Fig. 2 shows the result of stimulating with step currents. The threshold intensity (rheobase) of I , denoted as R , is plotted against temperature for the same four cases as in Fig. 1. These curves have no minimum; R is an increasing function of T . For $B = 0$, increasing A raises the curve and shifts it toward the right without otherwise changing its shape. For a given value of A , increasing B tends to increase the slope of the curve.

A qualitative explanation in physiological terms can be given for the different shapes of the curves in Figs. 1 and 2. For the instantaneous shock, there are two effects of increasing temperature. (1) For low temperatures, below T_0 , the relaxation times τ_m , τ_h , and τ_n of m , h , and n , are all large compared to τ_v , the electrical (RC) relaxation time of the membrane. Increasing T decreases all these relaxation times, but, since τ_m is less than the other two by a factor of about ten, the effect of its decrease appears first. Decreasing τ_m speeds up the sodium activation process, and therefore the excitation process which depends on it. This decreases the amount of stimulus necessary to cause excitation, giving the curve of Q vs. T a negative slope. In this region of the T axis, ($T < T_0$), τ_h and τ_n are still both so large that they have little effect on excitation. (2) For $T > T_0$, τ_m is so small compared with τ_v that effect 1 saturates and a second process becomes important. τ_h and τ_n are here small enough to affect excitation; the accommodative processes of sodium inactivation and potassium activation, which tend to raise

the threshold, are accelerated with increasing temperature. Thus in this region the curve has a positive slope. The resulting value of T_0 , where the minimum occurs, is determined by these two antagonistic processes. If A is increased, the resultant increase of conductance at all temperatures decreases τ_V and shifts the transition point between effect 1 and effect 2 to higher temperatures, where the other relaxation times are correspondingly decreased. Increasing B makes τ_V progressively smaller for higher temperatures, thus slowing the progress of effects 1 and 2 as T is increased and flattening the curve.

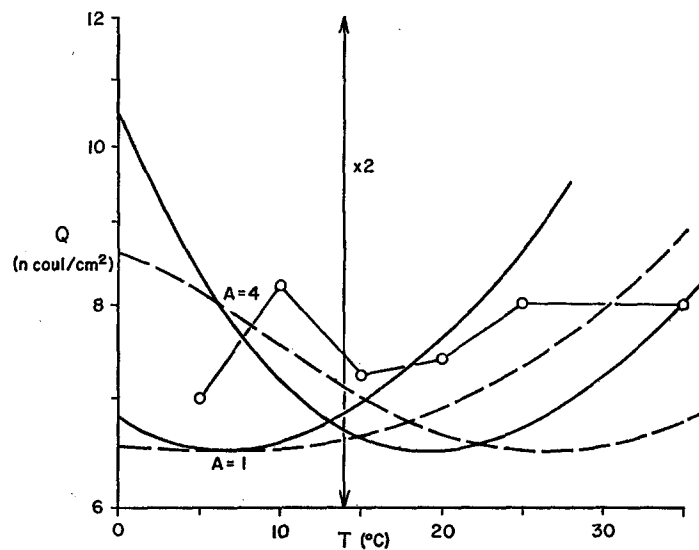


FIGURE 1. The charge Q contained in a threshold instantaneous current stimulating pulse, plotted on a logarithmic scale as a function of temperature T , for the Hodgkin-Huxley equations. Solid curves, $B = 0$ in equation (2). Broken curves, $B = 0.061$. A as labeled. Vertical line represents the logarithmic increase for a factor-of-two change in the ordinate. Circles, experimental data of Guttman (1966), reduced by one-half.

For a step current, which is a weaker but longer lasting stimulus than an instantaneous pulse, effect 2 always has long enough to act and overshadows effect 1 for all temperatures. The curve thus has a positive slope everywhere. Increasing A , and therefore the conductances, tends to short-circuit the applied current, which must therefore be increased to excite (curve raised). Increasing B progressively strengthens this effect as T is increased, and makes the curve steeper.

Using an intermediate pulse duration produces curves (Fig. 3) which are intermediate in form between those of Figs. 1 and 2. Stimulating with rectangular current pulses of different duration D and threshold amplitude I gives a strength-duration curve of customary shape, as shown in Fig. 4. Both

axes are logarithmic. For small D , the curve approaches the (broken) straight line with slope -1 . This line corresponds to a fixed value of total charge (Q) contained in the pulse, as shown in the following equations:

$$Q = ID$$

$$\log I = \log Q - \log D \tag{3}$$

In the limit, as D approaches zero, I approaches infinity, and Q is the charge contained in a threshold instantaneous pulse. The fact that the curve is nearly

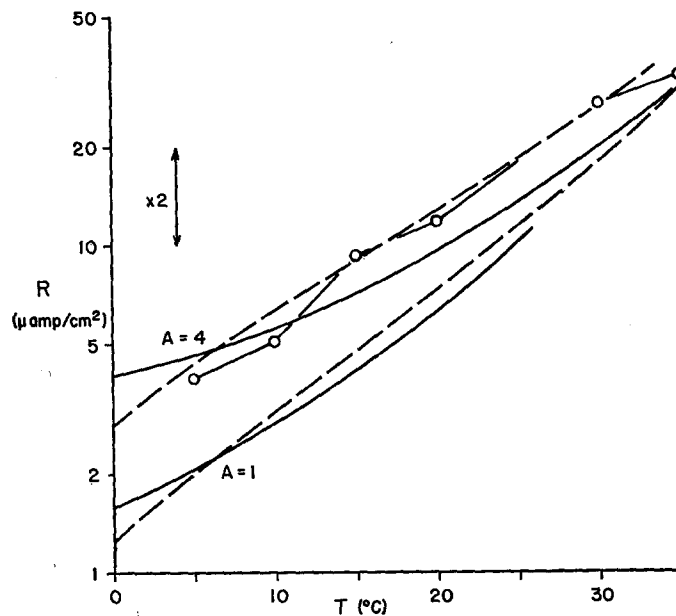


FIGURE 2. Threshold value of a step stimulating current (rheobase R), plotted against temperature. Curves and vertical line as in Fig. 1. Circles, data of Guttman (1966).

a straight line for D sufficiently small is expressed in the “constant quantity law” of nerve excitation. Q may be measured with sufficient accuracy by using a pulse of duration of 0.1τ or less (τ is defined below).

For large D , the curve approaches the horizontal (broken) line at $I = R$. The intersection point of the two broken lines is at $D = \tau$. Substituting $D = \tau$ and $I = R$ into (3) gives:

$$R\tau = ID = Q \tag{4}$$

τ is the duration which a pulse of rheobasic amplitude would have to have in order to deliver the same total charge as given by the constant-quantity law. Such a pulse (duration τ , amplitude R) is, however, subthreshold, because the

actual strength-duration curve lies above the intersection point by a factor denoted here as σ .

The four parameters R , Q , T , and σ help to determine the strength-duration curve.² The effect of temperature change on R , Q , and τ is shown in Figs. 1, 2, and 5. How σ changes with temperature has not been investigated.

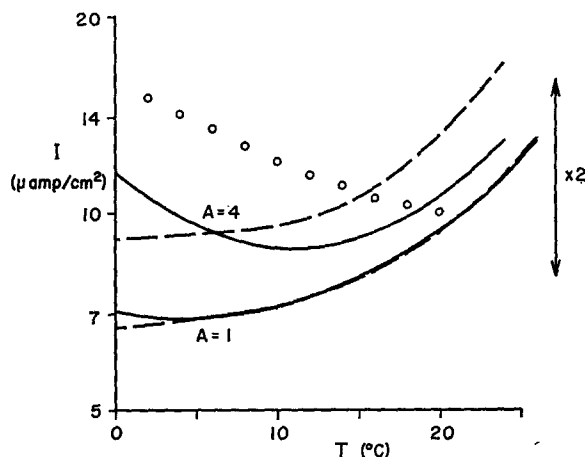


FIGURE 3. Threshold current for a stimulating pulse of 1 msec duration, plotted against temperature. Curves and vertical line as in Fig. 1. Circles, data of Sjodin and Mullins (1958), with arbitrary vertical position (see text).

IV. COMPARISON WITH EXPERIMENTAL DATA

Average values of experimental measurements by Guttman (1966) have been plotted in Figs. 1, 2, and 5 for comparison with the theoretical curves.

In Fig. 1, the values of threshold charge, averaged from six experiments (Guttman, personal communication) have been reduced by a factor of two to bring them on to the diagram. These points do not lie along a smooth curve of the theoretical shape, but the scatter of points may only reflect experimental error on the enlarged vertical scale. The vertical arrow shows the logarithmic difference of ordinate corresponding to a factor of two. The data from one experiment (Guttman, 1966, Fig. 5), not plotted in Fig. 1, do suggest the U shape predicted theoretically. In Fig. 2, the experimental values of rheobase (Guttman, 1966, Fig. 8) lie close to the theoretical curve for $A = 4$, $B = 0.061$. If, however, these points were lowered by a factor of two (vertical arrow), as in Fig. 1, they would lie closer to the curve for $A = 1$,

² Two other classical parameters, the utilization time and the chronaxie, do not seem to be so useful for this purpose.

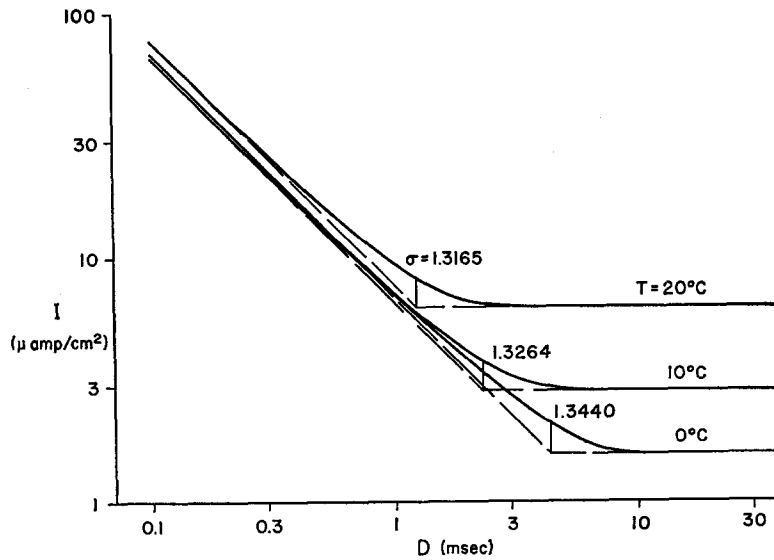


FIGURE 4. Strength-duration curves, showing threshold current I plotted against pulse duration D , for three temperatures. Both scales logarithmic. Each curve approaches a straight line with a slope of -1 , for very short pulses, and a horizontal straight line for very long pulses. The vertical position of the first line is determined by Q (Fig. 1), that of the second by R (Fig. 2). The two lines intersect for $D = \tau$, the characteristic time of excitation. See text for meaning of τ .

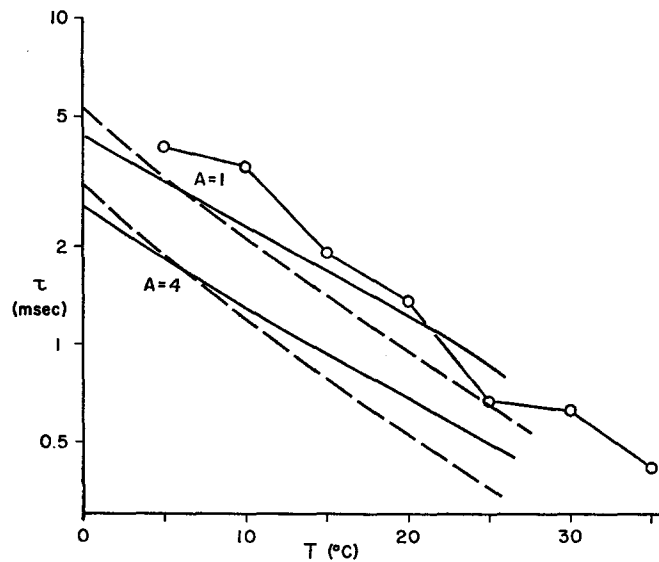


FIGURE 5. Characteristic time of excitation (τ) as a function of temperature. Vertical scale logarithmic. Curves as in Fig. 1. Broken straight lines fit curves over part of their range. Circles, data of Guttman (1966).

$B = 0$. In Fig. 5, the experimental points for τ (Guttman, 1966, Fig. 7) lie close to the two curves for $A = 1$.

Although only an approximate agreement between theory and experiment in Figs. 1, 2, and 5 is obtained, it does not seem advisable to try to obtain a better fit, because of the difficulties of choosing between similar curves obtained by various combinations of the parameters A and B . Both in order of magnitude and general shape of the curves, the computed curves in Figs. 1, 2, and 5 strongly resemble the experimental data and account for the general differences in shape seen with stimulation using long and short pulse durations. A closer comparison would require further experimental study of the conductance values and temperature-dependence of the squid giant axon, preferably on those which are known to be in similar condition to those used for the threshold measurements.

In Fig. 3, the data of Sjodin and Mullins (1958) have been plotted as circles. Since their published threshold values are not absolute, but relative to the threshold at 20°C, the vertical position of the curve of circles in Fig. 3 is arbitrary. In comparison with the theoretical curves, their curve appears to tend toward a minimum well to the right of the theoretical ones. With $B = 0$, increasing A raises the curve and moves the optimum value to the right. It is possible that their axons, which were not in sucrose, were in a different condition than Guttman's and had a still higher value of A . However, since their axons were not space-clamped (as in both Guttman's experiments and the computations), it is not certain how close an agreement one would expect with the computations.

In Fig. 4 are shown strength-duration curves for $A = 1$, $B = 0$, at three temperatures. The values of σ do not differ widely from each other (1.31 to 1.34). Guttman's (1966) value of σ , 1.38, is not greatly different.

As shown in the Appendix, theoretical upper and lower bounds for σ can be calculated from Young's excitation model, the most general one for which an explicit formula for the strength-duration curve is available. The bounds depend on whether the eigenvalues of the characteristic equation of the model are real or complex; i.e., whether the potential transient is nonoscillatory or oscillatory. As shown in Table I, the lower bound for σ (1.445) for the case of real roots (e.g., in Hill's (1936) model) is significantly above early experimental and theoretical results (see Guttman, 1965, for discussion). The lower bound for the oscillatory cases is, however, much lower.

The values for the Hodgkin-Huxley model (1.31–1.34) and from Guttman's experiments (1.38) lie within the range for complex eigenvalues, which is to be expected, since this model has a pair of complex eigenvalues (as well as a pair of real ones) and shows an oscillatory or underdamped response to small stimuli (Hodgkin and Huxley, 1952). An underdamped response is expected when the inductive reactance of the membrane predominates over the resistance (Cole, 1941).

V. DETAILS OF COMPUTATION

The computations were done with a Honeywell 800 digital computer. The differential equations were solved using Gill's modification of the fourth-order Runge-Kutta process (Gill, 1951; Romanelli, 1960). For a given step in t , the equations are solved once for a full step and a second time for two half-steps. The two results are combined (1) to estimate the truncation error and (2) to improve the values of the dependent variables at the end of the full step. The step size is continually adjusted by Anderson's (1960) method to provide an approximately constant accumulated truncation error per unit time. This method uses less computing time for a given accuracy than does

TABLE I
BOUNDS FOR σ IN YOUNG'S MODEL

<i>Eigen values</i>	Bound for σ	Accommodation	
		Incomplete	Complete
Real	Upper	1.582	1.582
	Lower	1.445	1.445
Complex	Upper	1.582	1.445
	Lower	1.188	1.188

specifying a constant step size in advance. A maximum step size, determined by trial and error, is specified to prevent instability in the numerical method (Carr, 1958). To prevent excessive accumulation of round-off error when very short steps are used, a minimum step size is also specified, calculated by a formula of Gorn and Moore (1954). The threshold is found to the desired accuracy by a convergent process in which repeated solutions of the equations are tested to determine whether each stimulus tried is above or below threshold; i.e., whether the resulting peak value of V is above or below 50 mv.

The function $x/[\exp(x) - 1]$, used to compute Hodgkin and Huxley's functions α_m and α_n , is indeterminate at $x = 0$. For $|x| < 1$, this function was computed using the expansion in Bernoulli numbers (Knopp, 1951), as suggested by Gorn (1962).

Most of the threshold determinations took between 5 and 10 min of machine time. The following parameter values were used for most of the computations:

Maximum relative threshold error	0.5%
Maximum step size in t	1 msec
Minimum step size in t	0.001 msec
Allowable truncation error for V	0.001 mv/msec
Allowable truncation error for m, h, n	0.01/msec

Considerable computing time was saved, in the cases of zero and infinite

pulse durations, by making use of a transformation of time. The HH equations, with the two factors defined by (1) and (2) included, are called here the *original equations*:

$$C dV/dt = I - \eta I_i \quad (5)$$

$$dm/dt = \phi[(1 - m)\alpha_m - m\beta_m], \text{ etc.} \quad (6)$$

where I_i , the expression for the total ionic current, is a function of m , h , and n , and "etc." means that the equations for h and n are similar in form to that for m (Hodgkin and Huxley, 1952).

To transform the time variable, define

$$u = \eta t. \quad (7)$$

Then $d/dt = \eta d/du$. Substitute and rewrite (5) and (6) as the *transformed equations*:

$$C dV/du = I' - I_i \quad (8)$$

$$dm/du = \phi'[(1 - m)\alpha_m - m\beta_m], \text{ etc.}, \quad (9)$$

where, by definition,

$$I' = I/\eta \quad (10)$$

$$\phi' = \phi/\eta = 3^{(T' - 6.3)/10} \quad (11)$$

For every solution of the original equations, there is a solution of the transformed equations, and vice versa; either one can be obtained from the other by use of the transformations (7), (10), (11). The transformed equations do not contain η ; they are of the same form as given by Hodgkin and Huxley (1952). If the transformed equations are solved for a number of different values of T' in (11), solutions of the original equations can be obtained for any combination of values of A and B in (2). From (1) and (11) comes the relation:

$$T = T' + \frac{10 \log \eta}{\log 3} \quad (12)$$

For every value of T' , one can calculate, using (12), the corresponding value of temperature T in the original equations, as described below.

For the case of an instantaneous stimulus pulse, the threshold is measured as Q , the total charge delivered by the pulse. This quantity is not changed by the transformation, since, by (7) and (10),

$$\int I' du = \int I dt = Q \quad (13)$$

After solving the transformed equations and computing threshold, express Q as a function of T' :

$$Q = f(T') \quad (14)$$

For the case $A = 1$ and $B = 0$, one has $\eta = 1$ and $T = T'$, therefore $Q = f(T)$. The function $f(T)$ is plotted in Fig. 1 for this case. For $A = 4$ and $B = 0$, one has $\eta = 4$ by (2), and, by (12) and (14),

$$Q = f(T - 12.619) \quad (15)$$

The corresponding curve in Fig. 1 differs from the first one only in that it is shifted 12.619°C to the right.

For $B = 0.061$, η varies with T , and (12) becomes

$$T' = T - 20.959[\log A + \log(0.061 T + 0.6159)] \quad (16)$$

For a given value of T' , T is the root of the transcendental equation (16), which was solved both graphically and then, for greater accuracy, numerically with a digital computer by an iteration method. There are either two roots or none. However, no more than one root is positive, and, since the HH equations are here assumed to be valid only for temperatures greater than or equal to zero, only the positive root was used.

By using the values of T obtained in this way, one plots the two curves in Fig. 1 for $B = 0.061$, $A = 1$ and 4 . Since only the temperature values are transformed, not those of Q , all curves in Fig. 1 have the same minimum value.

For the case of stimulation by step currents, the threshold is measured as I , which transforms according to (10). From the solutions of the transformed equations, I is computed as a function of T' :

$$I' = g(T') \quad (17)$$

From (10),

$$I = \eta I' = \eta g(T') \quad (18)$$

For $A = 1$ and $B = 0$, one has $\eta = 1$, $T = T'$, and, therefore, $I = g(T)$. The curve of $g(T)$ is plotted in Fig. 2 for this case. For $A = 4$ and $B = 0$, one has $\eta = 4$, and, by (10), (12), and (17):

$$I = 4g(T - 12.619) \quad (19)$$

For $B = 0.061$, T is found from T' as before, by finding positive roots of (16), $\eta(T)$ is calculated from (2), and $I = \eta I'$.

Because the ranges of T and T' are not identical, the points of all curves

could not be obtained by this method for the desired range of T . The additional points needed were obtained by direct computation from the original equations. Because the transformation changes the pulse duration this method cannot be used to obtain the values in Fig. 3.

Appendix

Since no exact formula is known for the general solution of the Hodgkin-Huxley equations, strength-duration curves can be obtained only by computation of specific cases. An explicit formula can, however, be obtained for the mathematically simpler model of Young (1937), from which upper and lower bounds for the parameter σ can be computed. Young's model, though less complete than later ones, is still useful, and its connection with the HH and BVP (Bonhoeffer-Van der Pol) models is shown elsewhere (FitzHugh, 1966).

The two variables of state of Young's model are called here V , the membrane potential, and U , the accommodation variable. I is the stimulating current applied to the membrane. Young's differential equations are:

$$\begin{aligned}\dot{V} &= k_{11}(V - V_0) + k_{12}(U - U_0) + aI \\ \dot{U} &= k_{21}(V - V_0) + k_{22}(U - U_0) + abI\end{aligned}\quad (20)$$

V_0 and U_0 are the resting values of V and U (steady-state values for zero I), and $V_0 < U_0$. Excitation occurs when $V = U$ for the first time after the application of a stimulus. The time course of the impulse and its recovery are not described by Young's model.

To make Young's model a useful description of a nerve membrane, according to present ideas as embodied in the Hodgkin-Huxley model, restrictions are placed on the constants in (20). Assume that a positive I is cathodal and increases V , but does not act directly on U . The processes represented by V and U , if isolated from each other, would be stable. The cross-effect of increasing U is to decrease V ; that of increasing V is to increase U . All these properties are expressed in the following relations:

$$\begin{aligned}a > 0, & \quad b = 0, & \quad k_{11} < 0, \\ k_{12} < 0, & \quad k_{21} > 0, & \quad k_{22} < 0.\end{aligned}\quad (21)$$

Let

$$Y = \frac{(V - V_0) - (U - U_0)}{U_0 - V_0}\quad (22)$$

$Y = 0$ in the resting state. When $Y = 1$, excitation occurs. Y obeys the differential equation

$$\ddot{Y} + P\dot{Y} + DY = EI + F\dot{I}\quad (23)$$

where

$$\begin{aligned} P &= -k_{11} - k_{22} > 0 \\ M &= k_{11}k_{22} - k_{12}k_{21} > 0 \\ F &= a/(U_0 - V_0) > 0 \\ E &= -F(k_{21} + k_{22}) \end{aligned} \quad (24)$$

Let p_1, p_2 be the eigenvalues, or roots of the characteristic equation corresponding to (23):

$$p^2 + Pp + M = 0 \quad (25)$$

p_1 and p_2 are either both real or a complex conjugate pair. Real eigenvalues correspond to an overdamped, complex ones to an underdamped response to a sub-threshold stimulus. In either case, since, by (24), P and M are positive, the real parts of p_1 and p_2 are negative, and the singular point of (23) for constant I is stable.

Let I be the amplitude of a step current starting at $t = 0$. Then

$$Y(t) = I[E/M - C_1 \exp(p_1 t) + C_2 \exp(p_2 t)] \quad (26)$$

where

$$C_1 = \frac{Ep_2/M + F}{p_2 - p_1}, \quad C_2 = \frac{Ep_1/M + F}{p_2 - p_1} \quad (27)$$

Now let I be the amplitude of a just threshold rectangular current pulse of duration D starting at $t = 0$. Then, from (26) and (27):

$$Y(D) = 1 = I\{C_1[1 - \exp(p_1 D)] - C_2[1 - \exp(p_2 D)]\} \quad (28)$$

Solve for I to get the strength-duration relation for rectangular current pulses:

$$I(D) = \frac{1}{C_1[1 - \exp(p_1 D)] - C_2[1 - \exp(p_2 D)]} \quad (29)$$

Equation (29) holds only for values of D less than the time at which Y reaches 1 for the first time; i.e., for $D < D_0$, where D_0 is the time of the first maximum in Y in (26):

$$\exp[(p_2 - p_1)D_0] = C_1 p_1 / C_2 p_2 \quad (30)$$

D_0 is the utilization time, and $I(D_0)$ is the rheobase. For $D \geq D_0$, $I(D) = I(D_0)$.

Suppose that I is constant and below rheobase, and Y is at its steady-state value EI/M . To this constant current add a just threshold instantaneous shock $Q_I \delta(t)$. Then, by (23), Y jumps by an amount FQ_I and

$$Y(+0) = 1 = EI/M + FQ_I \quad (31)$$

Solve (31) for Q_I and let Q_0 be its value for $I = 0$. From (27),

$$Q_0 = 1/F = 1/(C_2 p_2 - C_1 p_1) > 0 \quad (32)$$

Define a new parameter Z :

$$Z = (Q_0 - Q_I)/Q_0 I = E/M \quad (33)$$

Z is a measure of the steady-state accommodation to a constant current, as measured by the change of threshold to an instantaneous added shock. If $Z = 0$, the accommodation is complete, as in Hill's (1936) model. If $Z > 0$, it is incomplete. Assume that $Z \geq 0$. Then $E \geq 0$, and in addition to (21) there is, from (24), the assumption:

$$k_{21} + k_{22} \leq 0 \quad (34)$$

If p_1, p_2 are both real and negative, assume that $p_1 \leq p_2 < 0$. Then C_1, C_2 are real, by (27). Assume that the utilization time D_0 is positive and finite. Define $p = p_1/p_2 \geq 1$ and $\mu = C_1/C_2$. Then, by (30), $1 < \mu p = C_1 p_1/C_2 p_2 < \infty$ and $C_2 \neq 0$. If $C_2 < 0$, then $C_1 p_1 > C_2 p_2$, contradicting (32). Therefore $C_2 > 0$. Since $\mu p > 1$, $\mu > 0$ and $C_1 = \mu C_2 > 0$. Since $p_1 \leq p_2 < 0$, (27) gives the result $0 < C_2 \leq C_1$, and $\mu \leq 1$. If $Z = 0$, $E = 0$, $C_1 = C_2$, and $\mu = 1$. If $Z > 0$, $E > 0$, $C_1 \neq C_2$; therefore $\mu > 1$.

The value of D at which the two straight line asymptotes in Fig. 4 intersect is

$$\tau = Q_0/I(D_0) \quad (35)$$

The parameter σ is defined as follows:

$$\sigma = I(\tau)/I(D_0) \quad (36)$$

Define the parameters

$$\theta = (\mu\rho)^{\frac{1}{1-\rho}}, \quad \eta = \theta \left(1 - \frac{1}{\rho}\right) + \mu - 1 \quad (37)$$

Then, from (24), (30), (32), (35), (37), and earlier definitions,

$$\begin{aligned} \exp(p_2 D_0) &= \theta, & \exp(p_1 D_0) &= \theta/\mu\rho, \\ I(D_0) &= \frac{1}{C_2[\mu(1 - \theta/\mu\rho) - (1 - \theta)]} \\ Q_0 &= \frac{1}{C_2 p_2(1 - \mu\rho)}, & \tau &= \frac{\eta}{p_2(1 - \mu\rho)} \end{aligned} \quad (38)$$

$$I(\tau) = \frac{1}{C_2\{\exp[\eta/(1 - \mu\rho)] - \mu \exp[\rho\eta/(1 - \mu\rho)] + \mu - 1\}}$$

Then, from (36):

$$\sigma = \frac{\eta}{\exp [\eta/(1 - \mu\rho)] - \mu \exp [\rho\eta/(1 - \mu\rho)] + \mu - 1} \quad (39)$$

Table I gives upper and lower bounds on σ as obtained by digital computation for $\rho \geq 1$. The bounds are the same for $\mu = 1$ (complete accommodation) and for $\mu > 1$ (incomplete accommodation).

For the case of complex conjugate roots of (25), let

$$p_1 = -\alpha - i\beta, \quad p_2 = -\alpha + i\beta \quad (40)$$

From (24) and (25),

$$\alpha = P/2 > 0, \quad \beta = \sqrt{M - P^2/4} > 0 \quad (41)$$

From (27), $C_2 = -C_1^*$. Then

$$C_1 = A - iB, \quad C_2 = -A - iB \quad (42)$$

$$A = E/2M \geq 0, \quad B = \left(F - \frac{E\alpha}{M} \right) / 2\beta \quad (43)$$

Consider the quantity $\dot{Y}(0)$ obtained from (26):

$$\begin{aligned} \dot{Y}(0) &= I(C_2 p_2^2 - C_1 p_1^2) \\ &= -2I \operatorname{Re}(C_1 p_1^2) \end{aligned} \quad (44)$$

Then from (40) and (42),

$$\operatorname{Re}(C_1 p_1^2) = A(\alpha^2 - \beta^2) + 2B\alpha\beta \quad (45)$$

From (21), (24), (41), (43), (45),

$$\operatorname{Re}(C_1 p_1^2) = (F/2)(k_{21} - k_{11}) > 0 \quad (46)$$

Let $\chi = \beta/\alpha > 0$. Then from (45) and (46),

$$A(1 - \chi^2) + 2B\chi > 0 \quad (47)$$

Let $H = B/A$. If $A > 0$,

$$H > (\chi - \chi^{-1})/2 \quad (48)$$

If $A = 0$, let $H = +\infty$, and (48) is still true.

Define:

$$\begin{aligned}
 \gamma &= 1/\chi = \alpha/\beta, & G &= 1/H = A/B \\
 \phi &= \arctan \chi, & 0 < \phi < \pi/2, \\
 \Phi &= \operatorname{arccot} H, & 0 \leq \Phi < \pi, \\
 r &= (1 + \gamma^2)^{1/2}, & R &= (1 + G^2)^{1/2}.
 \end{aligned} \tag{49}$$

From (30), (40), (42), (49):

$$p_1 p_2 = \exp(2i\phi), \quad C_1 C_2 = \exp(2i\Phi) \tag{50}$$

$$D_0 = (\phi + \Phi)/\beta \tag{51}$$

D_0 , the time of the first maximum in $I(D)$, is positive. Then $\cos \Phi = (\operatorname{sgn} G)/R$, $\sin \Phi = G(\operatorname{sgn} G)/R$, where $\operatorname{sgn} G = 1$ if $G \geq 0$, $\operatorname{sgn} G = -1$ if $G < 0$. From (29), (42), (50):

$$\begin{aligned}
 I(D_0) &= 1/[C_1 - C_2 - 2 \operatorname{Re}(C_1 \exp p_1 D_0)] \\
 &= 1/2B\lambda,
 \end{aligned} \tag{52}$$

where

$$\begin{aligned}
 \lambda &= \{G - [G \cos(\phi + \Phi) - \sin(\phi + \Phi)] \exp[-\gamma(\phi + \Phi)]\}^{-1} \\
 &= \left\{ G - \frac{G(\gamma - G) - (1 + \gamma G)}{rR} (\operatorname{sgn} G) \exp[-\gamma(\phi + \Phi)] \right\}^{-1} \\
 &= \{G + R(\operatorname{sgn} G) \exp[-\gamma(\phi + \Phi)]/r\}^{-1}
 \end{aligned} \tag{53}$$

Then, by (32), (35), (40), (42)

$$\begin{aligned}
 \tau &= \frac{2B\lambda}{C_2 p_2 - C_1 p_1} = \frac{B\lambda}{A\alpha + B\beta} = \frac{\psi}{\beta}, \\
 \psi &= \frac{\lambda}{G\gamma + 1}
 \end{aligned} \tag{54}$$

By (29):

$$I(\tau) = \frac{1}{2B[G - (G \cos \psi - \sin \psi) \exp(-\gamma\psi)]} \tag{55}$$

The formula for σ , by (36), is:

$$\sigma = \frac{\lambda}{G - (G \cos \psi - \sin \psi) \exp(-\gamma\psi)} \tag{56}$$

For complete accommodation, $E = 0$, $A = 0$, and therefore $G = 0$. Computed bounds for σ in the case of complex roots of (25), for $\chi > 0$ and assuming condition (48), are given in Table I.

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