ANODAL EXCITATION IN THE HODGKIN-HUXLEY NERVE MODEL

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ABSTRACT Computations show that cathodal rheobase increases with temperature from 0°C to 30°C. Anodal rheobase (stimulation at the end of an indefinitely long anodal pulse) also increases with temperature, but goes to infinity at a critical temperature 17.13°C, above which such excitation is impossible. For a stimulus consisting of any step change of current from I_0 to I_1, a threshold curve of I_1 is plotted against I_0. As the temperature increases, this curve rises. Its intersection with the horizontal axis, which determines the anodal rheobase, goes to infinity at the critical temperature. This phenomenon is caused by the saturation of the variables m, h, n for strongly hyperpolarized potentials, combined with the relative speeding up of the inhibitory process with increasing temperature. The threshold charge Q in an instantaneous anodal current pulse (of zero duration) goes to infinity at the same temperature, with a similar explanation in terms of threshold curves in the I_1 vs. Q plane. The fact that the critical temperature for both cases is the same is generalized by the conjecture that, for any anodal current waveform whatever, as its amplitude approaches infinity, the trajectory in the phase space following its cessation approaches the same limiting trajectory. This limiting trajectory changes from suprathreshold to subthreshold at the critical temperature.

INTRODUCTION

A space-clamped squid axon membrane can be excited by a sufficiently strong rectangular pulse of applied current of either sign. By present convention, an outward, cathodal, depolarizing current is called positive; an inward, anodal, hyperpolarizing current is called negative. The response to a long-lasting positive current occurs during the stimulus pulse (cathodal make response), but that to a negative current occurs only after the end of the pulse (anodal break response). In both cases there is a positive step change of current, the difference being that it occurs at the beginning of the cathodal pulse, but at the end of the anodal pulse. The nerve impulse is a response to this positive step.

The shorter the duration of the pulse, the higher the current needed to excite the membrane, as shown in a strength-duration curve. Strength-duration curves for both cathodal and anodal pulses have similar shapes, but anodal curves show greater amplitudes than cathodal curves (Fig. 5).

Guttman and Hachmeister (1972) measured strength-duration curves for anodal break excitation in space-clamped squid axons at various temperatures. The present computations with the Hodgkin-Huxley (HH) model were initiated for comparison with their experiments, and some of the preliminary results were published in their paper. The equations used differ from the original ones given by Hodgkin and Huxley (1952) only in that $-V$ and $-I$ have been substituted for V and I everywhere, to agree with the present sign convention for membrane potential and current (see above). The present equations and notation have been published elsewhere (FitzHugh, 1969, Eqs. 4-1 to 4-8) and are not repeated here.

In over twenty years of experimental work on axons, enough data have been collected to permit important revisions in the Hodgkin-Huxley equations (e.g., Goldman and Schauf, 1973; Adelman and FitzHugh, 1975). It may seem unnecessary to make detailed computations on the temperature dependence of the threshold of a model which will probably continue to undergo considerable modification. In an earlier paper (FitzHugh, 1966), the original equations were compared with several modified ones in which the ionic conductances were increased, with and without temperature dependence. This has not been done in the present paper, in the belief that what is eventually needed is a much more thoroughgoing revision of the HH equations, based on the best available experimental data. The present paper attempts only to determine certain properties of the original 1952 HH model.

Anodal and cathodal excitation in the standard HH model are analyzed in this paper and explained in terms of the properties of the equations, in particular the saturation of the conductance variables m, h, n as the membrane potential V approaches minus infinity. This explanation is not mathematically rigorous, but appeals primarily to mathematical intuition of the reader. Such explanations will be relevant to later modifications of the HH equations if, as is likely, the latter also have these mathematical properties.

COMPUTATION TECHNIQUES

The HH equations were solved numerically with a FORTRAN program on a DEC system-10 time-sharing computer. The numerical method was that of C. W. Gear (1971*a*, *b*), whose subroutine DIFSUB provides a choice of two methods, (*1*) an Adams predictor-corrector method with automatically controlled order and step size, and automatic starting, and (*2*) a method designed for stiff equations. Stiff differential equations are those which have a wide range of relaxation times (FitzHugh, 1969). When ordinary methods are used to solve stiff equations, the step size must be decreased so much to maintain accuracy for the fastest variable that excessive computation time is required. The stiff method used only 15–85% as much computation time as the Adams method. For high temperatures and V very negative, τ_m (the relaxation time of the sodium activation) became very small and the equations very stiff. The stiff method was routinely used. The version of DIFSUB used, a later version than those given in the above references, was sent to me by Professor Gear (27 Nov. 1973).

For computation of the response to a step change of current at the end of a long nonzero current pulse, all variables of state were assumed to have reached stationary values at the end of the pulse. These values were computed directly and used as initial conditions at $t = 0$, without actually solving the differential equations during the pulse. This procedure is of course meaningful only if the stationary state is stable. To insure this, the maximum value of the current used was 15 $\mu A/cm^2$.

For reasons described below, the method used for calculating threshold was to search for the inflection point of the stimulus-response curve (SR curve: peak V plotted against stimulus strength). Such a search was started with a pair of bracketing values of stimulus, assuming one to be below and the other above threshold. The peak value V_p of V was computed for each. For a subthreshold stimulus, the active subthreshold response provided a low V_p, while for a suprathreshold one, V_p was at the top of the action potential. A new stimulus midway between the bracketing pair was then tried, and the new peak computed. The slopes of the two straight line segments connecting these three points, one segment on each side of the middle stimulus, approximate the slope of the SR curve. The segment with the smaller slope was discarded, and the endpoints of the other segment retained as the new bracketing pair. This process was continued, halving the separation between the bracketing pair at each step, until the desired separation (usually 0.01 $\mu A \cdot cm^{-2}$) is reached. If, at the end of the search, one of the bracketing stimuli had still been retained, it was possible that the true point of maximum slope lay beyond that bracket and had been missed. To check this, a new search was made with that bracket replaced by one further away on that side. (For such work an interactive program, controlled from a keyboard terminal, is most useful.)

This method requires sufficiently accurate values of V_p. The latter was computed from the polynomial approximation to the solution, produced by the array Y in DIFSUB, using Newton's method to converge to the point of zero slope of V as a function of t.

Gear's program is written to compute in double precision. A single precision version used only 70–75% as much computer time as the double precision one, and was adequate for most threshold searches. With Gear's accuracy parameter EPS set to 10^{-6}, V_p was computed to an accuracy of about ± 0.001 mV. Solutions very near threshold are however particularly unstable, and for these the single precision program produced larger errors, causing irregularities in the SR curve. In such cases, the double precision version was used. Even the single precision program has an accuracy far beyond what is attainable through experimental measurements, but it is still desirable, in studying the properties of the model itself, to be able to diminish the effects of errors in numerical approximation by using increased precision.

For the highest temperatures, the SR curve is so nearly straight near its point of inflection that it was not always possible to locate the latter to the desired accuracy, because of errors in computing V_p, from which the slopes between adjacent stimuli are found. When the estimated error in the difference between the slopes of two adjacent segments of the SR curve, from errors in V_p, became equal to the average slope, it was impossible to choose which slope was greater, and the search was stopped. Since h is near 1 for these solutions, the quantity $1 - h$ was computed directly, instead of h, to obtain greater relative accuracy. The ratio of the estimated error in each variable was compared with the maximum magnitude of that variable, as stored in the array YMAX. In order to ensure proper error control for the variables m, $1 - h$, and n when they were extremely small, it was necessary to reset YMAX to a comparably small value at the start of those solutions which correspond to strong anodal pulses of long duration. As the variables increase, YMAX was automatically increased by DIFSUB to keep pace with them, but never decreased. For solutions following strong pulses of zero duration, in which m, $1 - h$, and n initially decrease to very low levels initially, it was necessary to modify the program to keep adjusting YMAX downward to keep pace.

A magnetic tape containing the FORTRAN programs used in this paper, together with instructions for their use, can be purchased from the National Technical Information Service, Springfield, Va. 22161.[1]

STIMULUS-RESPONSE CURVES AND DEFINITIONS OF THRESHOLD

A stimulus-response (SR) curve shows V_p, the peak value of the membrane potential V, plotted against the stimulus strength. This is the peak potential for the first impulse only; repetitive responses are not considered. Fig. 1 shows SR curves for a stimulus consisting of a step change of total applied membrane current from zero to I, for four temperatures. For the three lower temperatures, there is a part of the curve which rises so sharply that it appears to have an infinite slope. The sudden increase of V_p with increasing stimulus is called a threshold phenomenon, and the value of stimulus at which

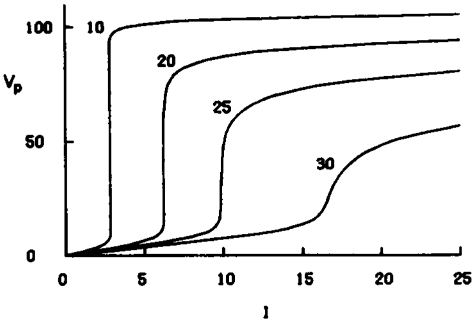

FIGURE 1 Stimulus-response curves for cathodal constant current stimuli at different temperatures (°C). The peak value of V (mV) following the stimulus is plotted against current ($\mu A \cdot cm^{-2}$). Threshold is defined as the current at the inflection point of a curve. The sharpness of the threshold is the (maximum) slope value there.

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[1] Specify NTIS Accession No. PB243847/AS, with title "Nerve Membrane Model." The tape is 9-track, 800 bits per inch, and is written in IBM's EBCDIC character code, for widest use in different computers. The programs are designed for interactive use on a time-sharing DEC system-10 computer, but can be modified for use on other computers, including batch processors if desired. The price is $150 (domestic) or $190 (foreign).

this occurs is the threshold stimulus. Although the curve may appear discontinuous, mathematical considerations indicate that such curves are actually continuous, though with a very high maximum slope (FitzHugh, 1955, 1969; FitzHugh and Antosiewicz, 1959).

The usual method of computing thresholds is to set a critical value V_c of V (e.g. V_c = 50 mV), and define threshold as the stimulus at which the curve of V_p crosses the level V_c. This *level definition* of threshold works well at 10°C. Any value of V_c between 15 and 70 mV would give the same threshold value, to the accuracy of a single-precision computation.

At 30°C, the SR curve has a maximum slope that is clearly finite. This kind of SR curve corresponds to a graded response, rather than what is usually called a threshold phenomenon (Cole et al., 1970). However, the above-mentioned mathematical considerations also indicate that as the temperature is raised, the form of the curve changes in a continuous way, so that the maximum slope decreases continuously as a function of temperature. Since there is no temperature at which one can say that the threshold phenomenon suddenly disappears, it seems more reasonable to consider all the SR curves of Fig. 1 as differing quantitatively rather than qualitatively. The maximum slope of the SR curve provides a convenient parameter for characterizing this quantitative difference between the curves.

If the level definition were used for the 30°C curve, the resulting value of threshold would vary widely, depending on the chosen value of V_c. If the threshold stimulus is defined as that value of stimulus at which the slope is maximum, i.e. the inflection point of the curve, one obtains a unique definition for each temperature. This is called the *inflection definition* of threshold; the maximum slope is the *sharpness*. This method was used to compute the thresholds for this paper, as described in more detail in the previous section.

For the 10°C curve, the search for the maximum slope was continued until the bracketing values of I differed only in the last bit of the 27-bit mantissa of the single-precision floating point number in the DEC system-10. During the final steps of this search, the maximum slope attained was still approximately doubling at each step, as would be expected if the curve were truly discontinuous. A somewhat more convenient parameter is the reciprocal of the sharpness, called the *gradedness* (γ). When the sharpness approaches infinity, the gradedness approaches zero. Expressed in units of $m\mathrm{V}^{-1} \cdot \mu\mathrm{A} \cdot \mathrm{cm}^{-2}$ the last computed value of γ at 10°C was 0.718×10^{-9}. Once the gradedness has fallen below about 10^{-4} in these units, it can be considered for practical purposes to be zero, in comparison with the much larger values at higher temperatures.

At 30°C, the search for threshold was stopped when the errors in computing the slopes made it impossible to decide which slope was greater, as described in the previous section. That part of the curve is so nearly straight that its inflection point cannot be computed accurately. At 30°C the slope appeared to be converging to a finite limit. The final computed value of γ was 0.0564, much larger than at 10°C.

Another possible way to define threshold uniquely for all temperatures is provided by the observation that the latency, the time of occurrence of the peak V, increases as threshold is approached from either above or below. This can be seen in Fig. 2 of FitzHugh and Antosiewicz (1959). A bounded maximum latency is characteristic of a continuous (or quasi) threshold phenomenon, such as is found in the HH equations (FitzHugh, 1955, 1969).

RESPONSE TO A STEP CHANGE OF CURRENT

Assume that a current of amplitude I_0 has been applied to the membrane for so long a time that all variables of state have reached stationary values. At $t = 0$, the current is increased discontinuously to a new value I_1. There are two important special cases. For cathodal make excitation, $I_0 = 0$, and I_1 is varied. The threshold value of I_1 is the rheobase, as usually defined. It is called *cathodal rheobase* here. For anodal break excitation, $I_1 = 0$, and I_0 is varied. The threshold value of I_0 is called the *anodal rheobase.*

Fig. 2 shows curves of cathodal and anodal rheobase (absolute value), computed as functions of temperature. The cathodal curve rises gradually with increasing temperature (FitzHugh, 1966), but the anodal curve rises more sharply and appears to approach infinity at 17.13°C.

This difference in response to anodal and cathodal threshold stimuli can be made clearer by considering the more general case in which both I_0 and I_1 are nonzero. If

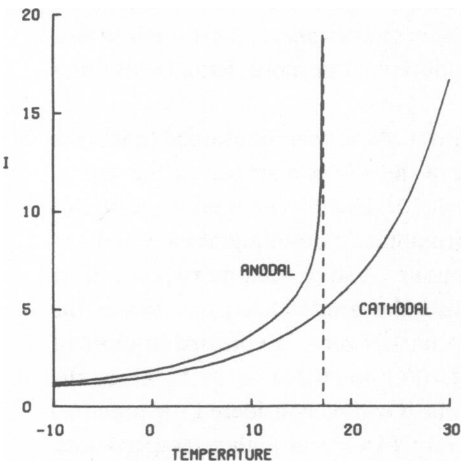

FIGURE 2

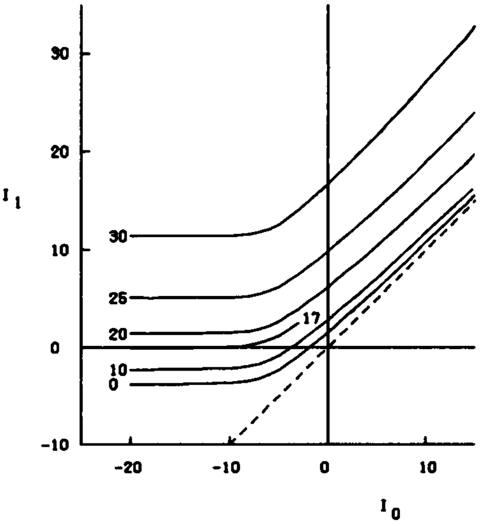

FIGURE 3

FIGURE 2 Threshold rheobasic currents I ($\mu A \cdot cm^{-2}$, absolute values) for cathodal and anodal stimulus pulses as functions of temperature (°C), computed from HH equations.

FIGURE 3 Threshold curves for different temperatures (°C), for a stimulus consisting of a step change of current from I_0 to I_1 ($\mu A \cdot cm^{-2}$). Intersection of each curve with vertical axis gives cathodal rheobase; intersection with horizontal axis gives anodal rheobase.

the threshold value of the difference $I_1 - I_0$ is plotted against I_0, the result is a threshold curve of the type first measured experimentally by Chweitzer (1937). In this paper different coordinates are used; I_1 is plotted against I_0. The Chweitzer diagram can be obtained from this by a linear transformation of axes.

Fig. 3 shows threshold curves computed from the HH equations for different temperatures. The straight broken line through the origin with slope +1 corresponds to $I_0 = I_1$. Since this line is always subthreshold, all curves lie above it. Cathodal and anodal rheobases can be read from this diagram. The cathodal rheobase is given by the intersection of the threshold curve with the vertical axis ($I_0 = 0$). The anodal break rheobase is given by the intersection of the curve with the horizontal axis ($I_1 = 0$).

From Fig. 3 it can be seen that all the curves have the first of these intersection points, but not all have the second one. The higher the temperature, the higher the curve lies in the diagram. As I_0 becomes more negative, each curve approaches, from above, a horizontal straight line asymptote which passes either above or below the origin, depending on the temperature. For 17° and below, the asymptote lies below the origin, and the threshold curve therefore intersects the horizontal axis, determining the anodal break rheobase. For 18° and above, however, the asymptote lies above the horizontal axis and does not intersect it. As the temperature is increased continuously above 17°, the intersection point travels farther and farther to the left, until at a critical temperature (about 17.13°) the asymptote coincides with the horizontal axis, and the rheobase becomes infinite. Above the critical temperature there is no intersection, and anodal break excitation does not occur.

To understand why a critical temperature exists, above which anodal break excitation does not occur, one must explain (*1*) why the threshold curve as a whole is raised by increasing the temperature, and (*2*) why each curve approaches a horizontal asymptote for negative values of I_0.

Consider how the variables of state of the model interact to produce a response to a stimulus (FitzHugh, 1969). Stimulation by a positive change of applied current drives V positively. If the stimulus is strong enough, V and m tend to increase further through mutual interaction, which constitutes the excitatory process. The variables h and n are also changing as a result of the change in V, but more slowly than V and m, and tend to oppose excitation. This is the accommodation-recovery process. Whether an action potential occurs or not depends on the relative strength and rapidity of these two opposed processes. For a weak stimulus, the decrease in h and the increase in n can reverse the rise of V and bring it quickly back down toward its steady-state value. If the stimulus is stronger, V and m are able to escape momentarily from the retarding effect of h and n. V rises nearly to the sodium equilibrium potential, to form the peak of the action potential. Only then are the delayed changes of h and n able to bring V back down again, producing recovery.

As the temperature is increased, the relaxation times τ_m, τ_h, and τ_n decrease with a Q_{10} of 3. This accelerates the accommodation process more than the excitatory process, because the rate of the latter is limited by the electrical relaxation time (C/g) of V, which does not change with temperature. This increase in accommodation can, however, be overcome by simply increasing I_1. Thus the threshold curves tend to rise with increasing temperature. This explains point (*1*) mentioned above.

In explaining point (*2*), the way that the steady-state values of the variables, defined by the functions $m_\infty(V)$, $h_\infty(V)$, and $n_\infty(V)$, depend on V is important. Graphs of these functions can be found in several places (Hodgkin and Huxley, 1952, Figs. 5, 8, 10; Cole, 1968, Fig. 3:32; FitzHugh, 1969, Fig. 4-2). As V changes more and more negatively from its resting value, these steady-state functions tend to saturate: m_∞ and n_∞ approach zero, and h_∞ approaches one. As the initial current I_0 becomes more and more negative, it tends to push h toward one and n toward zero, decreasing their accommodative effects. The sudden increase of the current to a higher value I_1 makes V and also m increase. Since the inhibitory effects of h and n have been decreased by the previous hyperpolarization, an action potential can occur, even though m started from a small value. Making I_0 more negative favors excitation, and the value of I_1 needed to produce excitation at threshold decreases. But, because of saturation, as I_0 becomes more and more negative, it has less effect on excitation, which depends more on I_1 alone. The latter therefore approaches a fixed value from above, which is represented in the threshold diagram by a horizontal line. Thus the threshold curve approaches such a line asymptotically as I_0 approaches minus infinity. This explains point (*2*).

This explanation is of course intuitive; a more rigorous, mathematical treatment might be worth attempting.

The above explanation has a minor flaw. It assumes that there is a single curve in the I_0, I_1 plane which represents threshold for either of two cases: (*1*) I_0 fixed, I_1 varying, or (*2*) I_1 fixed, I_0 varying. If the level criterion of threshold is used, this assumption is true. For the inflection method, however, the two curves, one for fixed I_0 and the other for fixed I_1, do not necessarily coincide exactly. Actually, at temperatures at or below 17.13°C, the two criteria when tested gave identical computed results, since the threshold phenomenon is sufficiently sharp. For another model which had a more graded response, however, it is possible that the above assumption would be less accurate.

RESPONSE TO INSTANTANEOUS SHOCK

Instead of a step change of current, which corresponds to a current pulse of infinite duration, the opposite extreme is a pulse of zero duration (instantaneous shock). Mathematically, an instantaneous shock is proportional to a Dirac delta function in time. It contains an electric charge Q and displaces V by an amount Q/C, where C is the membrane capacitance. (Since in the HH equations $C = 1 \mu F \cdot cm^{-2}$, the displacement of V, in millivolts, is numerically equal to Q in nanocoulombs$\cdot$cm^{-2}).

Fig. 4 shows threshold values of Q (absolute value) plotted against temperature for both cathodal and anodal shocks. The shapes of the curves are similar to those for rheobase (Fig. 2), except that at the lowest temperatures they have negative slopes, and minima appear near 5°C. This is because the stimulating current, being applied all at

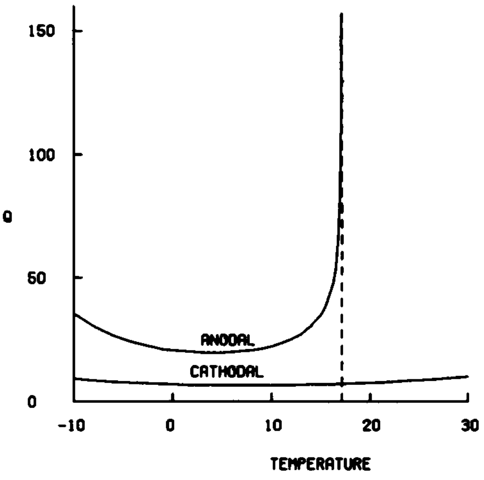

FIGURE 4 Threshold charges ($nC \cdot cm^{-2}$, absolute value) for instantaneous cathodal and anodal stimulus shocks, as functions of temperature (°C).

one instant, instead of continuously for an indefinite period, must produce initially a change of V that lasts long enough to excite. Since the relaxation times of m, h, n increase with decreasing temperature, the initial change of V must be greater, the lower the temperature, in order to do this. Thus the threshold stimulus increases for very low temperatures.

The critical temperature at which the anodal threshold goes to infinity is the same (17.13°C) as for rheobase. At first sight, there seems to be no reason why the threshold charge Q and the rheobase R should go to infinity at the same critical temperature, since the response to an instantaneous anodal pulse has a very different time course from that to an indefinitely long pulse. This result however becomes more reasonable if pulses of intermediate durations are also considered.

STRENGTH-DURATION CURVES

Fig. 5 shows computed strength-duration (SD) curves for both cathodal and anodal stimuli. The threshold amplitude I of a stimulus current pulse of fixed duration D is plotted against D, with logarithmic scales on both axes. As D approaches zero (abscissa approaches minus infinity), the curve approaches a straight line asymptote with slope -1. This agrees with the constant quantity law, which says that the total electric charge contained in a threshold pulse approaches a constant quantity Q, as its duration approaches zero (instantaneous shock). As D increases, the curve approaches a horizontal asymptote; its level is the rheobase R. These two asymptotes are shown as connected broken lines in Fig. 5.

For anodal stimuli, R approaches infinity at the critical temperature (Fig. 2). Since this makes the entire SD curve rise, it is reasonable that Q should also become infinite

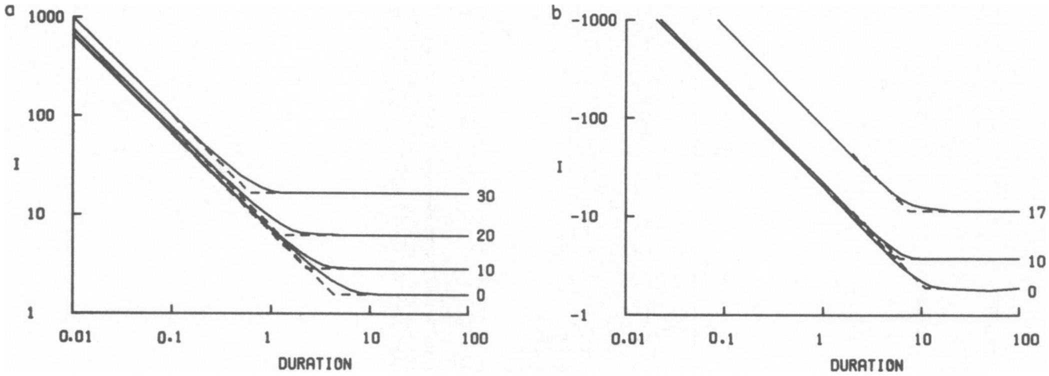

FIGURE 5 Strength-duration curves for different temperatures (°C), for (*a*) cathodal, and (*b*) anodal stimulus pulses. Threshold amplitude ($\mu A \cdot cm^{-2}$) of a rectangular pulse plotted against its duration (ms). Both axes logarithmic.

at the same temperature (Fig. 4). To clarify this problem further, a more complicated stimulus current wave form was tried, as described in the next section.

Besides their temperature dependence, it was noticed also that the anodal curves differ from the cathodal ones in that they fall somewhat below their straight line asymptotes in places. Thus, by choosing appropriate anodal pulse durations, it is possible to stimulate with either a charge smaller than Q or a current smaller than R. This effect is small and was not investigated further.

RESPONSE TO A STEP CURRENT PLUS AN INSTANTANEOUS SHOCK

The stimulus used was a step change of current from zero to I, with an instantaneous shock of charge Q added at the beginning of the step. Fig. 6 shows threshold I plotted

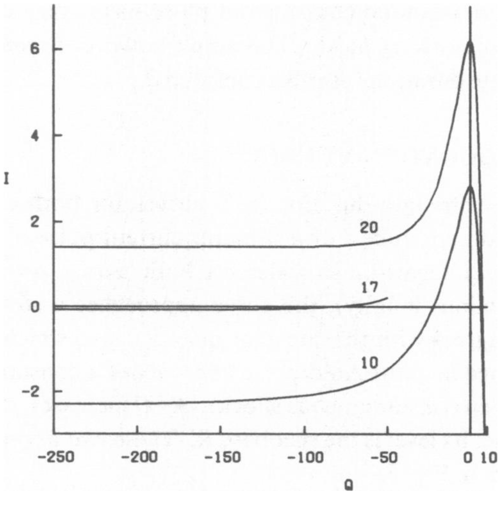

FIGURE 6 Threshold curves for a stimulus consisting of an instantaneous shock of charge Q ($nC \cdot cm^{-2}$) applied at the same time as a step change of current from 0 to 1 ($\mu A \cdot cm^{-2}$).

against Q for different temperatures. The intersection of the threshold curve with the vertical axis is the cathodal rheobase. The intersection with the horizontal axis determines the threshold charge for an instantaneous shock. For 10°C, there are two such intersections, one positive (cathodal) and one negative (anodal). As Q becomes more negative, this curve approaches a horizontal asymptote lying below the horizontal axis. As the temperature increases, the whole curve rises. As in Fig. 3, the asymptote coincides with the horizontal axis at the critical temperature, and the anodal threshold point goes to infinity. Above that temperature anodal excitation by an anodal instantaneous shock is impossible.

As stated above, the computed value of the critical temperature for an anodal instantaneous shock turns out to be the same as that for an infinitely long pulse (17.13°C). The reason for this becomes clearer on examination of the trajectories in phase space.

THE LIMITING TRAJECTORY

Any solution of the HH differential equations can be represented by a curve (trajectory) in the four-dimensional phase space with coordinates V, m, h, n. The following conjecture is proposed. Suppose that the membrane is in its resting state, with zero applied current. An anodal current pulse of long duration and of adjustable amplitude is applied. During the pulse, V approaches a new negative steady-state value, and m, h, and n approach their steady-state values for that value of V. As the amplitude of the pulse approaches minus infinity, the steady-state values of m, h, n approach 0, 1, 0. At the end of the stimulus pulse, when the applied current becomes zero again, the state point, starting from its steady-state position reached during the pulse, returns toward the resting point along some trajectory. Now as the stimulus pulse amplitude is increased, this trajectory is assumed to approach a certain *limiting trajectory*. As the limiting trajectory is followed backward for negative t, V approaches minus infinity, and m, h, n approach 0, 1, 0 on that trajectory. Finally, it is assumed that the same limiting trajectory is approached following increasingly strong anodal stimulus pulses of any duration, whether instantaneous, rectangular, or of any pulse shape whatever, since any such pulse would, if strong enough, make V very negative and have similar effects on m, h, and n. The existence of such a limiting trajectory has not been rigorously proved, but it provides a reasonable and useful working hypothesis for explaining the critical temperature.

With V sufficiently negative on the limiting trajectory, the sodium and potassium conductances are negligible compared to the leakage conductance g_L. The differential equation for V becomes approximately

$$\mathrm{d}V/\mathrm{d}t = -g_L(V - V_L)/C.$$

Its solution is

$$V(t) = V_L - [V_L - V(0)]\exp(-g_L t/C),$$

where $V(0) < V_L$.

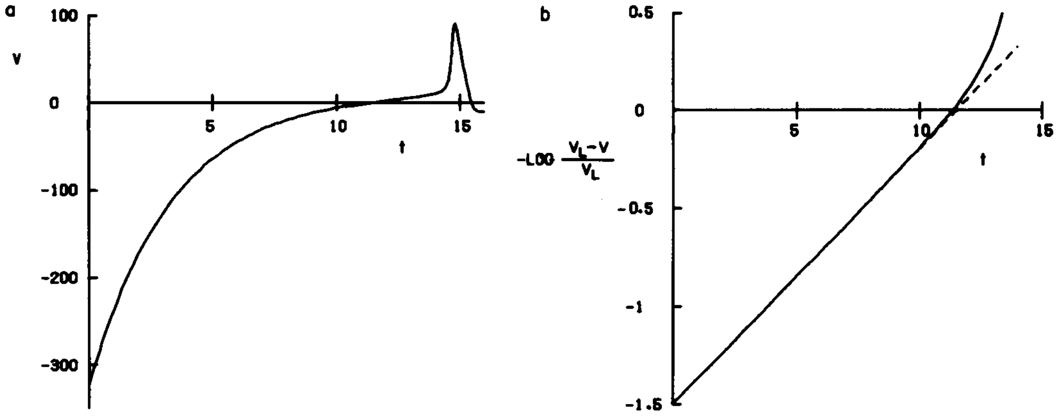

FIGURE 7 Time course of membrane potential for strong anodal stimulus (infinite duration pulse, $-100\ \mu\text{A}\cdot\text{cm}^{-2}$). This solution approximates the limiting trajectory. (*a*) V(mV) plotted against t(ms). (*b*) $-\log(V_L - V)/V_L$ plotted against t. The broken line indicates the exponential approximation given in the text. Temperature 17°C.

An anodal stimulus current pulse of any duration and waveform, if strong enough, sends V very negative. Since the relaxation times τ_m, τ_h, τ_n are small for very negative V, the variables m, h, n come close to their steady states quickly. It is reasonable to expect that the resulting trajectory will lie close to the limiting trajectory, and that the stronger the stimulus, the closer it will lie.

To test this conjecture, solutions were computed with zero current, following strong anodal current pulses of both zero and infinite duration.

Fig. 7*a* shows V plotted against t following a strong anodal stimulus pulse of infinite duration and amplitude $I = -100\ \mu\text{A}\cdot\text{cm}^{-2}$. Two other cases tried were an infinite duration pulse of $-20\ \mu\text{A}\cdot\text{cm}^{-2}$ and a zero duration pulse of -200 nC$\cdot$cm^{-2}. When shifted horizontally along the t axis, these curves nearly coincided with the above curve, and are therefore not shown.

Fig. 7*b* shows the same solution with $-\log[(V_L - V)/V_L]$ plotted (solid curve) on the vertical axis ("log" means logarithm to the base 10). The exponential function of time appears as a broken straight line, which approximates the limiting trajectory well, until V comes close to zero. For V sufficiently negative, the solid curve is indistinguishable from the straight line and the limiting trajectory. As V approaches zero, m and n increase, the sodium and potassium conductances become appreciable, the limiting trajectory diverges from the straight line, and an action potential follows (Fig. 7*a*). This curve was computed for 17°C, just below the critical temperature. Above the critical temperature, there is no action potential. It seems natural to say that the limiting trajectory is suprathreshold below the critical temperature and subthreshold above it. However, in this paper, the term "threshold" has been defined only in terms of the location of an inflection point of an SR curve, that is, for a finite stimulus. On the other hand, a limiting trajectory is defined only in the limit as the

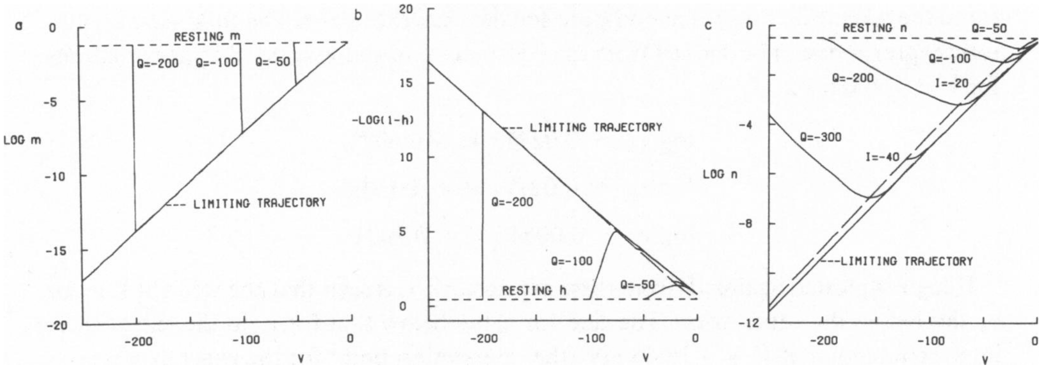

FIGURE 8 Trajectories projected from the four-dimensional HH phase space. Trajectories for increasing current strengths approach a limiting trajectory. Temperature 17°C. Horizontal short-dashed lines show steady-state value as a function of V (mV). (*a*) log m vs. V. (*b*) $-\log(1-h)$ vs. V. (*c*) log n vs. V. Logarithms are to the base 10.

amplitude of the stimulus goes to infinity or, so to speak, for an "infinite stimulus." Below the critical temperature, there is an inflection point in the SR curve, and therefore a finite threshold value of the stimulus. In this case the limiting trajectory shows an action potential and is called "suprathreshold." As the critical temperature is passed, this threshold approaches infinity and disappears; the limiting trajectory then shows no action potential and is called "subthreshold."

Fig. 8 shows the trajectories projected from the four-dimensional phase space (V, m, h, n) onto three different planes, to show m, h, and n each plotted against V. Instead of plotting the three variables directly, logarithmically transformed vertical coordinates were used to make the trajectories more visible.

The separate trajectories can be seen most clearly in Fig. 8*c*, where log n is plotted against V. The sloping long-dashed curve shows steady-state n (the HH function $n_\infty(V)$). This curve intersects the horizontal short-dashed line labeled RESTING n at the resting state point (upper right). A strong anodal instantaneous shock displaces the state point horizontally to the left from the resting state along the short-dashed line, for a distance proportional to the charge Q of the shock. Then it travels downward and to the right, crosses the steady-state curve, and appears to merge with the limiting trajectory.

The curve for the limiting trajectory was computed to a good approximation (as in Fig. 7) by imposing a strong ($-100\mu\text{A} \cdot \text{cm}^{-2}$) anodal current pulse of infinite duration. The initial part of this trajectory, which departs somewhat from the limiting trajectory, lies off the diagram to the left and is not seen.

Following infinite duration pulses of amplitude I, the trajectories start on the steady-state curve and again approach the limiting trajectory. Three such cases are shown, for $I = -40$, -20, and $-10\,\mu\text{A} \cdot \text{cm}^{-2}$ (there was not room to label the last one in the figure).

The trajectory curves appear different in Figs. 8*a* and 8*b* from those in Fig. 8*c*, because the relaxation times of m and h are smaller than those of n. The following asymptotic expressions can be derived from the HH functions and give good approximations for $V < -100$ mV:

$$\log \tau_m \sim 0.02413\ V - 0.6021$$
$$\log \tau_h \sim 0.02171\ V + 1.1549$$
$$\log \tau_n \sim 0.00543\ V + 0.9031$$

If log τ is plotted against V from these expressions, it is seen that the straight line for τ_m lies below the other two. The line for τ_h lies below that for τ_n to the left of their intersection point at $V = -15.46$ mV (the intersection point for the exact expressions is at -17.19 mV). Thus for very negative V, m is the fastest variable, n is the slowest, and h is in between.

In Fig. 8, it is seen that the curves for h return more abruptly to the limiting trajectory than those for n, while those for m are still more rapid. In Fig. 8*b* the limiting trajectory hides the steady-state curve on the left, but they diverge slightly at the right. In Fig. 8*a* these two curves appear to coincide. The only trajectory for an infinite duration pulse is an unlabeled one (hard to see) at the very right of Fig. 8*b* for $I = -10\,\mu\text{A}\cdot\text{cm}^{-2}$; none at all are visible in Fig. 8*a*.

Other forms of anodal stimuli were not tried, but it is reasonable to expect them to behave similarly to the two extreme cases considered above, and to have trajectories, following the stimulus, which approach the limiting trajectory.

For 17°C the limiting trajectory is suprathreshold. By increasing the anodal stimulus amplitude sufficiently, a trajectory is reached which is close enough to the limiting trajectory to be suprathreshold also. The limiting trajectory changes to subthreshold as the temperature passes 17.13°C. For higher temperatures, an anodal stimulus cannot excite, no matter how strong, since increasing the strength only brings the trajectory closer to the subthreshold limiting trajectory. 17.13°C is thus a universal critical temperature for anodal stimuli, of any shape or duration, which are followed by a return to zero current.

If one considers anodal stimuli which are followed by a return to some other current value than zero, each such value has a corresponding limiting trajectory. Figs. 3 and 6 show what to expect for their critical temperatures. If the final current value I_1 is positive (or negative), the anodal break threshold goes to infinity at a higher (or lower) temperature than 17.13°C.

DISCUSSION

The difference between cathodal and anodal excitation in a space-clamped membrane can be summarized as follows. For extreme values of the potential V, the steady-state values of the variables m, h, and n $(m_\infty, h_\infty, n_\infty)$ approach limits (1, 0, 1 for positive V; 0, 1, 0 for negative V). In other words, they saturate for large V of either sign. During a cathodal current pulse, as V changes positively from the resting potential, the decision whether excitation takes place or not depends on what happens in the potential range from 0 to 10 mV (FitzHugh, 1969, Fig. 4-6). The outcome depends on the relative strengths and speeds of the excitatory (V, m) process and the recovery or accommodative (h, n) process. In this V range, m, h, and n are far from saturation. Since m_∞, h_∞, and n_∞ are changing rapidly as functions of V, the variables m, h, and n can undergo wide changes, depending on the stimulus current I. Thus the inhibitory effect of increasing temperatures can always be overcome by increasing I sufficiently, and the curve of cathodal rheobase or threshold charge rises steadily with temperature (Figs. 2, 4). Note that this argument applies only to a space-clamped membrane. Block does occur above a certain temperature for cathodal stimulation of a propagated impulse (Huxley, 1959), but the cable properties of the axon play a role there.

An anodal current pulse makes V negative and "de-accommodates" the membrane, by resetting h and n to new values. Together with the new m, they determine whether excitation takes place or not after the end of the pulse (by postinhibitory rebound), as V returns toward zero. As the strength of the anodal pulse is increased, V enters the range where saturation occurs, and h and n are driven toward their anodal limits (1 and 0). Once nearly there, further current increases are less and less effective in overcoming the inhibitory effect of raising the temperature. A critical temperature is reached at which, no matter how big the current is, excitation fails.

This critical temperature is the same for both very long and very short current pulses. It appears that all anodal stimuli of sufficient strength push the state point close to a particular limiting trajectory in phase space, which is suprathreshold below the critical temperature, but subthreshold above it. Thus all strong anodal stimuli have the same critical temperature, regardless of their duration or wave form.

Although this paper deals only with the standard Hodgkin-Huxley model, its results can be expected to apply qualitatively to any model for which the conductance-determining variables of state approach finite limits (saturate) as V becomes very negative. Since changes of conductance seem to be determined by the motion in an electric field of charged constituents of the membrane, such saturation would be expected in any physically reasonable model.

The anodal break thresholds measured experimentally by Guttman and Hachmeister (1972) are hard to compare with the theoretical predictions of this paper, for two reasons. As they say, "it was difficult to study the effect of temperature upon the anode break strength-duration curve of real axons since the experimental procedure was so drastic that repeated runs at different temperatures could usually not be carried out on the same axon." Moreover, although their strength-duration curves were similar to the computed ones for durations up to about 10 ms, for longer pulses the current values dropped to far lower values, apparently as a result of slow processes which increase excitability during very long anodal pulses, but which are not described by the HH equations. They obtained anodal break excitation in some axons for 20 and 25°C, which are above the computed critical temperature. From their Fig. 3 it is clear that the rheobase number 1 (which corresponds to the computed HH rheobase) increased for these higher temperatures. In the only axon which they succeeded in testing at three different temperatures, the rheobase increased with temperatures up to 20°C (their Fig. 6), but unfortunately this was their rheobase number 3, which corresponds to pulses of much longer duration, roughly 1 s.

Introducing slower processes into the HH model might drastically change or even eliminate the critical temperaaure. Nevertheless, since the phenomenon of a critical temperature arises from the saturation of the steady-state values of the conductance-determining variables for strongly hyperpolarized membrane potentials, it is likely (see for example Chandler and Meves, 1970*a*, *b*) that such saturation would also occur for other, slower variables in the membrane. It is therefore still worth looking for experimentally, though the difficulty of getting reproducible results on squid axons under such conditions are formidable.

Whether or not the phenomenon of a critical temperature for anodal stimuli can be substantiated by experiment, it is still important to understand these mathematical properties of the HH model. It is interesting that this previously unsuspected phenomenon should turn up in such a well-known set of equations.

The critical temperature arises in the HH model as the result of the interaction of three conditions: (*1*) a response with a sharp threshold following the end of an inhibitory stimulus, (*2*) a net decrease of excitability as the temperature is increased, because of the speedup of the inhibitory process relative to the excitatory one, and (*3*) a limitation of the excitatory effect of increasing the stimulus amplitude, due to saturation.

The critical temperature is that at which the threshold stimulus goes to infinity. Another way to state this is in terms of response and the all-or-none law, instead of in terms of stimulus, and say that at the critical temperature the maximum obtainable response changes from a high (all) to a low value (none). If condition (*1*) is relaxed to permit a more graded response, the critical temperature would be replaced by a critical range of temperatures over which the maximum obtainable response changes from high to low. In the HH equations, as mentioned above, the threshold is, in a strict sense, graded at all temperatures, but still looks quite sharp at 17.13°C. Thus the "critical temperature" does not have an exact value, but corresponds to a very narrow critical range of temperatures. If the threshold phenomenon were much more graded, then the width of the critical temperature range might become large enough to be apparent in the computed results. It might also be measurable experimentally, if a graded anodal break response existed in a real nervous system.

Does anodal break excitation occur as a normal physiological phenomenon? Guttman and Hachmeister (1972) mention visual off-responses as a possibility. These result from inhibition either in a single photoreceptor or at a subsequent inhibitory synapse. The former case occurs in photoreceptors of the scallop *Pecten* (McReynolds and Gorman, 1970*a*, *b*) and in the hardshell clam *Mercenaria* (Wiederhold et al., 1973). Background firing of the receptor in the dark can be either absent or present. When absent, the burst of firing which follows the flash of light would have a sharp threshold (ignoring random fluctuations). However, if background firing is present, the burst would be a graded response with no sharp threshold.

An anodal break response might also occur at an inhibitory synapse. A recent example, studied by recording from single cells, is given by Alkon (1973, 1975) in the mollusc *Hermissenda*.

In any of the above cases, it would be worth trying to measure the effect of varying the temperature on the threshold of off-responses, to see if anything like a critical temperature or temperature range occurs.

It has also been suggested to me (by Dr. William A. Hagins) that a critical temperature might help explain the sharp temperature set point of thermoreceptors in the hypothalamus. It might be worth looking for a neural model based on this idea.

Mr. John Shaw helped in developing and running an earlier threshold search program on which the present one was based. Prof. C. W. Gear kindly provided a recent version of his program DIFSUB for solving differential equations numerically.

The figures for this paper were prepared using the modeling program MLAB on the DEC system-10 computer at National Institutes of Health.

Doctors Gerald Ehrenstein, Harold Lecar, and John Rinzel made useful suggestions for improving the manuscript.

Received for publication 6 June 1975.

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