J. Physiol. (1972), **226**, *pp.* 573–591
With 8 *text-figures*
Printed in Great Britain

THE RELATION OF RUSHTON'S 'LIMINAL LENGTH' FOR EXCITATION TO THE RESTING AND ACTIVE CONDUCTANCES OF EXCITABLE CELLS

BY D. NOBLE

From the University Laboratory of Physiology, Parks Road,
Oxford OX1 3PT

(*Received 2 June 1972*)

SUMMARY

1. The minimum (or liminal) length of an excitable cable that must lie above the inward current threshold in order to initiate propagation is derived using a simple polynomial representation of the ionic current–voltage relation.

2. This model is then used to obtain an approximate equation for the liminal length that may easily be applied to excitable cells using experimental measurements of the ionic current.

3. The equations are used to show that the liminal length in cardiac Purkinje fibres is expected to be much smaller than in squid nerve. The values calculated are similar to those obtained by Fozzard & Schoenberg (1972) from strength–duration curves.

4. It is shown that the strength–duration curve for non-uniform excitation is virtually independent of the resting membrane resistance. The strength–duration time constant may not, therefore, be related to the membrane time constant.

INTRODUCTION

Fozzard & Schoenberg (1972) have described experiments on the strength–duration curves in cardiac Purkinje fibres and have analysed their results using Rushton's (1937) concept of 'liminal length'. The purpose of this paper is to analyse this parameter in terms of the current theory of excitation.

Definitions

(units are expressed with respect to a unit length of fibre where appropriate)

V membrane potential expressed as a deviation from the resting potential V_A (mV).

V_B threshold for uniform excitation (= voltage at which ionic current reverses direction from outward to inward) (mV).

V_C threshold for point excitation of cable (mV).

V_{D}	peak active voltage (mV).
i_{i}	ionic current flowing through membrane (μA/cm).
c	membrane capacitance (μF/cm).
x	distance along fibre (cm).
x_{LL}	liminal length (cm).
r_{a}	axial resistance (Ω/cm).
r_{m}	resting membrane resistance (Ω cm).
g_{r}	resting membrane conductance ($= 1/r_{\mathrm{m}}$) (mho/cm).
λ	resting space constant $= \sqrt{(1/g_{\mathrm{r}} r_{\mathrm{a}})}$ (cm).
λ_{B}	'active' space constant at threshold (defined in text) (cm).
X	$= x/\lambda$.
X_{LL}	$= x_{\mathrm{LL}}/\lambda$.
g_1	slope conductance near threshold (defined in text) (mho/cm).
Q	charge on membrane.
Q_∞	steady-state charge on membrane.

THEORY

To excite a nerve or muscle cell by applying current uniformly to its membrane it is sufficient to depolarize the membrane to the potential at which the net ionic current changes sign from positive (outward) to negative (inward).

Since

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\frac{i_{\mathrm{i}}}{c} \tag{1}$$

the potential will then change spontaneously in a positive (depolarizing) direction.

The situation in a cable structure excited at one point is more complex than this since the membrane potential, and hence also the ionic current, will vary with distance along the fibre. Flow of outward current at less depolarized areas of membrane at a distance from the electrode may prevent the inward current near the electrode from initiating a propagated action potential. The condition for excitation is then that the sum of ionic current flow over the cable as a whole should become inward, i.e. that

$$\int_0^\infty i_{\mathrm{i}}\,\mathrm{d}x < 0. \tag{2}$$

In order for this to occur, the area of membrane supplying inward current must be large enough to allow

$$\int_{x_1}^{0} i_{\mathrm{i}}\,\mathrm{d}x > \int_{x_1}^{\infty} i_{\mathrm{i}}\,\mathrm{d}x, \tag{3}$$

where x_1 is the distance at which the ionic current changes from inward to outward (see Fig. 1). For a given cable, there will be a minimum length for which this condition holds. When the length of cable supplying inward current is equal to this length, the cable is at threshold. This is the length that Rushton defined as the 'liminal length', x_{LL}. We then have

$$\int_{x_{\mathrm{LL}}}^{0} i_{\mathrm{i}}\,\mathrm{d}x = \int_{x_{\mathrm{LL}}}^{\infty} i_{\mathrm{i}}\,\mathrm{d}x. \tag{4}$$

The purpose of this paper is to relate x_{LL} to the ionic current–voltage relation of the excitable cell membrane and, hence, to parameters that may be measured using voltage clamp techniques.

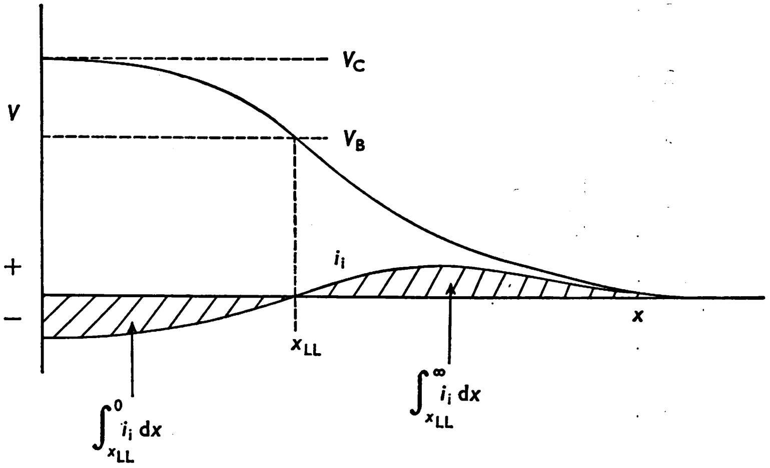

Fig. 1. Diagram illustrating variations in voltage and current with distance in a cable at the steady-state threshold. V_{C} is the threshold voltage at $x = 0$. V_{B} is the voltage at which the ionic current reverses direction. x_{LL} is the length of cable for which the voltage exceeds V_{B}. At threshold, the hatched areas are equal.

We will first consider a fibre whose membrane obeys a simple ionic current–voltage relation given by the polynomial

$$i_{\mathrm{i}} = \frac{1}{K}\left\{V - V^2 + \left(\frac{V}{2}\right)^3\right\}. \tag{5}$$

This relation resembles that observed experimentally in excitable cells and is plotted in Fig. 2. To relate the potential axis to the mV scale usually used in work on excitable cells we may arbitrarily set each unit on the voltage axis equal to 20 mV. The threshold for uniform excitation then lies at 23 mV ($V_{\mathrm{B}} = 1{\cdot}171$). The threshold for cable excitation V_{C} may be shown to be at about 36 mV by using the equation

$$\int_{V_{\mathrm{B}}}^{V_{\mathrm{C}}} i_{\mathrm{i}}\,\mathrm{d}V = \int_{V_{\mathrm{B}}}^{V_{\mathrm{A}}} i_{\mathrm{i}}\,\mathrm{d}V \tag{6}$$

(cf. Noble & Hall, 1963, Fig. 6 and equations 7–9). This equation defines $V_{\rm C}$ in terms of $i_{\rm i}(V)$ only. Although $V_{\rm C}$ is the cable threshold, no other information on the cable properties is required.

Equation (5) may be used together with the cable equation

$$\frac{1}{r_{\rm a}}\frac{{\rm d}^2V}{{\rm d}x_2} = i_{\rm i} = \frac{1}{K}\left\{V - V^2 + \left(\frac{V}{2}\right)^3\right\} \qquad (7)$$

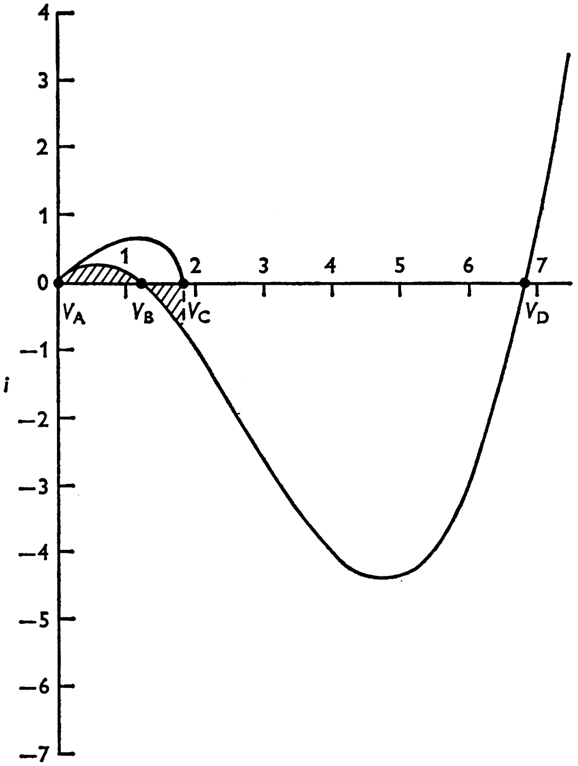

Fig. 2. Current–voltage relation given by eqn. (5). $V_{\rm A}$ is the resting potential, $V_{\rm B}$ is the uniform voltage threshold, $V_{\rm C}$ is the cable voltage threshold (see Fig. 1) and $V_{\rm D}$ is the height of the 'action potential' generated by the system. The relation intersecting the voltage axis at $V_{\rm C}$ is the cable input current–voltage relation obtained from eqn. (5) by plotting values proportional to $\sqrt{\left(\int_{V_A}^{V} i_{\rm i}\,{\rm d}V\right)}$. The hatched areas shown on the uniform current–voltage relation are equal. Each unit on V axis is 20 mV.

to give analytical solutions for the spatial spread of voltage and current (see Jack, Noble & Tsien, 1973, chap. 12). Eqn. (7) may also be readily solved using numerical integration techniques. Fig. 3 shows solutions obtained for various values of voltages applied at the point $x = 0$. The threshold is reached when $V_{x=0} = 36$ mV (1·8 units of V). The length of cable whose potential lies above V_{B} and therefore supplies inward current is 1·5 space constants. The space constant is readily obtained by considering the linear form of (7) when V is small. We then obtain

$$\frac{K}{r_{\mathrm{a}}}\frac{\mathrm{d}^2V}{\mathrm{d}x^2} = V \tag{8}$$

and $\lambda = \surd(K/r_{\mathrm{a}})$. K is therefore the resting resistance. In the remainder of this treatment, the liminal length will be expressed in dimensionless co-ordinates and, following Fozzard & Schoenberg, we will use the symbol X_{LL} ($= x_{\mathrm{LL}}/\lambda$). In the present case we may write $X_{\mathrm{LL}} = 1{\cdot}5$.

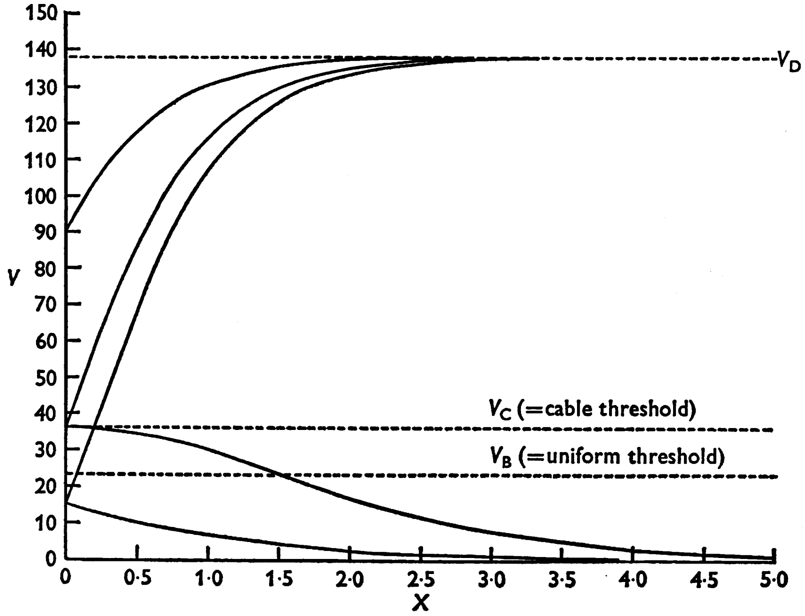

Fig. 3. Variation in voltage with distance computed from eqn. (7) for various values of V at $x = 0$ and $x = \infty$. Below $V_{x=0} = V_{\mathrm{C}}$ there are two solutions for each value of $V_{x=0}$. Above V_{C} there is only one solution for each value of $V_{x=0}$. The curve starting at V_{C} and decaying towards V_{A} is similar to that plotted in Fig. 1. The point at which V_{B} occurs is the liminal length X_{LL}.

To show more clearly what determines X_{LL} we consider a simplication of eqn. (5) shown in Fig. 4. The i_{i} (V) relations near the resting potential and near the uniform voltage threshold, V_{B}, are represented by linear segments. Let $g_{\mathrm{r}} = 1/K$ and $g_1 = (\mathrm{d}i_{\mathrm{i}}/\mathrm{d}V_{\mathrm{B}})$ then

$$g_1 = \frac{1}{K}(1 - 2V_{\mathrm{B}} + \tfrac{3}{8}V_{\mathrm{B}}^2).$$

Since $V_B = 1{\cdot}171$

$$g_1 = -\frac{0{\cdot}828}{K} = -0{\cdot}828 g_r.$$

Now consider solutions for the cable equation

$$\frac{1}{r_a}\frac{d^2V}{dx^2} = g_1(V - V_B) = g_1 \Delta V, \tag{9}$$

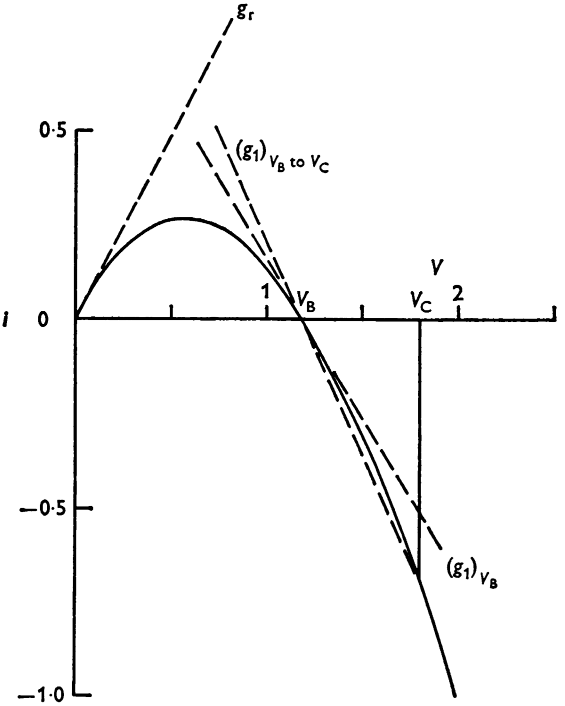

Fig. 4. Linear approximations for eqn. (5) in the region of V_A to V_C. The line given by slope g_r is used to represent resting membrane to calculate resting space constant $\lambda = \sqrt{(1/g_r r_a)}$. The lines given by $(g_1)_{V_B}$ and $(g_1)_{V_B \text{ to } V_C}$ are used to calculate active 'space constants' $\lambda_B = \sqrt{(-1/g_1 r_a)}$.

where ΔV is the voltage expressed as a deflexion from V_B. Since g_1 is negative, the general solution is best written in the form

$$\Delta V = A \sin(x\sqrt{(-g_1 r_a)}) + B\cos(x\sqrt{(-g_1 r_a)}) \tag{10}$$

or

$$\Delta V = A\sin(X\lambda/\lambda_B) + B\cos(X\lambda/\lambda_B), \tag{10a}$$

where $\lambda_B = 1/\sqrt{(-g_1 r_a)}$. Since, at threshold, $(dV/dX)_0 = 0$, $A = 0$ so that

$$\Delta V = (V_C - V_B)\cos(X\lambda/\lambda_B) \tag{11}$$

Thus we obtain oscillatory solutions for ΔV, the cycle period being equal to $2\pi\lambda_B/\lambda$. In the present case $\lambda_B/\lambda = 1/\sqrt{(0{\cdot}828)}$ so that the period is $2\pi/\sqrt{(0{\cdot}828)} = 6{\cdot}886$.

Now provided that the linear segment with slope g_1 is a good approximation to the current–voltage relation for voltages just above the uniform threshold, V_B, the first quarter cycle of a solution starting from the voltage V_C will be the same as the corresponding solution of eqn. (7). This is illustrated in Fig. 5. Since the length of the cable between V_C and V_B is X_{LL} we may write

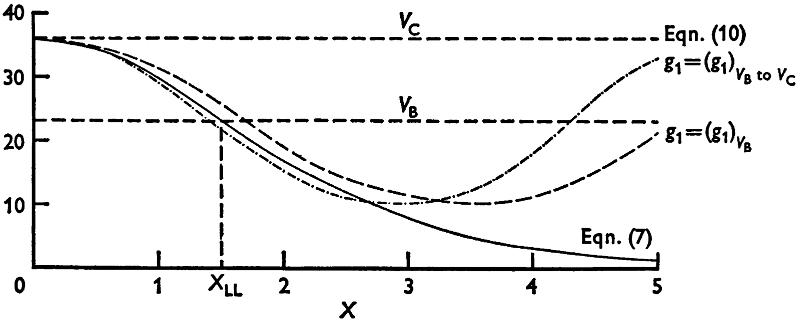

Fig. 5. Comparisons between solutions given by the linear eqn. (10) and that given by the non-linear eqn. (7). The best approximation to the non-linear solution in the region $0 < X < X_{LL}$ is given by using $(g_1)_{V_B \text{ to } V_C}$ to calculate λ_B.

$$X_{LL} = \frac{6{\cdot}886}{4} = 1{\cdot}721$$

which is only a little longer than the value of X_{LL} obtained by solving the non-linear eqn. (7). The deviation is in the right direction since the current–voltage relation becomes steeper than the slope g_1 when V_C is approached. A better linear approximation of the relation between V_B and V_C would therefore require a slope larger than g_1. In fact, as shown in Fig. 4, the best slope is about 1·2 rather than 0·828. We then obtain

$$X_{LL} = \pi/2\sqrt{(1{\cdot}2)} = 1{\cdot}43$$

which is closer to the result obtained using eqn. (7).

Thus, in general, we may write

$$X_{LL} \simeq \frac{\pi}{2}\lambda_B/\lambda = \frac{\pi}{2}\sqrt{\left(-\frac{g_r}{g_1}\right)} \qquad (12)$$

and to obtain a good approximate estimate of X_{LL} we simply require the resting conductance and the slope of the best-fitting linear segment for voltages between V_B and V_C.

In the case of squid nerve, the appropriate information for calculating X_{LL} may be obtained from the current–voltage relation measured by Hodgkin, Huxley & Katz (1952, Fig. 10). This is reproduced in Fig. 6. To a first approximation $g_1 = -4g_r$. Hence we obtain

$$(X_{\mathrm{LL}})_{\mathrm{squid}} = \frac{\pi}{2\sqrt{4}} = 0{\cdot}77$$

which may be compared with the value of 0·55 obtained by Fozzard & Schoenberg using linear cable equations to compute the strength–duration curve.

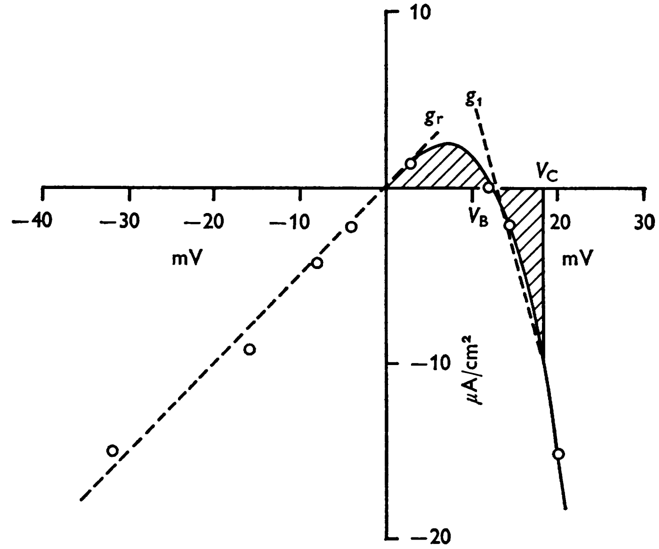

Fig. 6. Ionic current voltage relation of squid nerve obtained by Hodgkin, Huxley & Katz (1952). The points are replotted from Fig. 10 of Hodgkin *et al.* V_C was calculated as the voltage at which the hatched areas are equal. The value of g_1 in this case is about 4 times larger than g_r.

It is more difficult to obtain a reliable estimate of X_{LL} for the Purkinje fibre. Mobley & Page (1972) have obtained microscopic estimates of the membrane surface area in Purkinje fibres and by combining these with Weidmann's (1952) measurements of the cable constants, they obtained 1 μF/cm^2 for the specific membrane capacitance and 20,000 Ω/cm^2 for the specific membrane resistance, i.e. 0·05 mmho/cm^2 for the specific membrane conductance. These values compare with 1 μF/cm^2 and 700 Ω/cm^2 for squid nerve. The value of g_1 for Purkinje fibres cannot yet be obtained directly since voltage-clamp measurements of the sodium current in cardiac muscle are unreliable (see Beeler & Reuter, 1970). However, it is known that the maximum rate of depolarization during the action potential is similar to that in squid nerve, i.e. of the order of 500 V/sec (see Hodgkin & Huxley, 1952; Weidmann, 1955). Since the specific capacitances are similar (when the cable C_m of 12 μF/cm^2 is corrected for membrane surface area as done by Mobley & Page), eqn. (1) requires that the peak values of i_{Na} should be similar. The best assumption we can make at present, therefore, is that g_1 is also similar to that in the squid. The major difference between the two membranes would then lie in the values of g_r, which for the Purkinje fibre is only 0·035 of that in squid nerve. Hence

$$(X_{LL})_{\text{Purkinje fibre}} = \frac{\pi}{2}\Big/\sqrt{\left(\frac{0\cdot035}{4}\right)} = 0\cdot15$$

which is within the range of values 0·1–0·2 obtained by Fozzard & Schoenberg (1972).

These calculations show that Fozzard & Schoenberg's estimates for X_{LL} are similar to those that may be obtained from the information available on the values of g_r and g_1 for squid nerve and Purkinje fibre membranes.

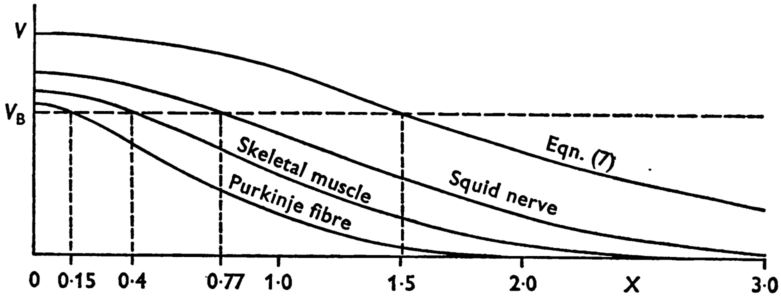

Fig. 7. Diagram illustrating threshold $V(X)$ relations for cardiac Purkinje fibre, frog skeletal muscle and squid nerve. The relations were drawn using the liminal length values derived in the text and representing the curves above V_B as sinusoidal. The curves were then continued below V_B to join the linear cable solution $V \propto \exp(-X)$. The threshold $V(X)$ relation given by eqn. (7) is also shown. For the sake of easing comparison, the uniform threshold voltage (V_B) is assumed to be the same in each case. The liminal lengths used were 1·5 (eqn. (7)), 0·77 (squid nerve), 0·4 (skeletal muscle) and 0·15 (Purkinje fibre).

Exact agreement between the values of X_{LL} derived here and those obtained by Fozzard & Schoenberg would not be expected since they obtain X_{LL} from measurements of the strength–duration curve by assuming that the fibre behaves as a *linear* cable until excitation occurs, whereas the analysis given in the present paper derives X_{LL} from the relevant *non-linear* properties of the cell membrane or from a linear segment approximation of these non-linearities. It is therefore an important question to ask why Fozzard & Schoenberg's linear equations work as well as they appear to do.

First of all, as Fozzard & Schoenberg have pointed out, there is a very general reason for expecting a strong relationship between the shape and time constant of the strength–duration curve and the liminal length for excitation. This reason is based on the speed at which charge is applied to different parts of a cable. Thus, charge is applied very rapidly to the membrane close to the stimulating electrode but spreads more slowly to more distant parts of the cable (Hodgkin & Rushton, 1946). If a large length of cable must be brought to threshold we therefore expect a relatively long time constant for excitation, whereas when the liminal length is short, a much shorter length of cable must be brought to threshold and the time constant for excitation will be must briefer.

This point is illustrated in Fig. 7 which compares the threshold steady-state charge distribution for squid nerve and Purkinje fibres (using the liminal length values calculated previously) and a cable obeying eqn. (7). Using these diagrams we may define an adequate stimulus as one that applies an amount of charge Q_∞ where Q_∞ is given by

$$Q_\infty = C\int_0^\infty V_\infty \mathrm{d}x \tag{13}$$

and V_∞ is the steady-state value of V at each x at threshold as plotted in Fig. 7. Clearly the shorter the liminal length, the smaller the value of Q_∞ and, since the charge is then more concentrated near the electrode, the faster will be the time constant of excitation.

Although such a stimulus will be adequate, it will generally be larger than threshold. The reason for this is that the activation of sufficient inward current for propagation may occur *before* the applied charge has had time to redistribute on the cable towards the steady-state distribution. Since, at all times before the steady-state the charge will be even more concentrated on areas of the cable near the electrode than in Fig. 7, an amount of charge smaller than Q_∞ may be sufficient to cause excitation.

An alternative approach is to calculate the amount of charge necessary at each stimulus strength to raise the liminal length of cable above the inward current threshold. This approach may also tend to overestimate the threshold charge (although to a smaller extent than does Q_∞) since, in order to raise the voltage at the point X_{LL} to V_{B}, the voltage at $X = 0$ must be raised beyond V_{C} when the cable is linear. However, some of this excess charge (i.e. in excess of that required on the liminal length of cable at the non-linear steady-state threshold) will leak to more distant parts of the cable before the inward current is activated. Whether this redistribution effect will be sufficient to fully account for the excess charge applied on the cable between $X = 0$ and $X = X_{\mathrm{LL}}$ will depend on how quickly the sodium current is activated. For the present we will simply note that the assumption that an amount of charge similar to the excess charge will be redistributed during sodium activation is not implausible since the time constants of charge redistribution ($\doteqdot r_a c x_{LL}^2$) and sodium activation are similar in magnitude, i.e. $\leqslant$ 1 msec.

If this assumption is made then the strength–duration curve may be calculated as described by Fozzard & Schoenberg, i.e. by calculating the times taken for various currents to depolarize the point X_{LL} to the inward current threshold (see Fozzard & Schoenberg (1972), Fig. 8). Using the liminal lengths calculated above, it is also clear that, as Fozzard & Schoenberg suggest, the substantial differences between squid nerve and Purkinje fibre strength–duration curves may be accounted for largely by the fact that the liminal length is very much shorter in Purkinje fibres.

The comparison between the time constant of charge redistribution and that for sodium activation may require further explanation. We consider the charge on the liminal length region to decay from the capacitance of that region ($= cx_{LL}$) through the axial resistance for the region ($= r_a x_{LL}$) to flow to other less highly charged parts of the cable. The time constant for this process will therefore be of the order of $r_a c(x_{LL})^2$ which, in terms of absolute values for the intracellular resistivity, R_i, and membrane capacitance, C_m is equal to

$$\tau = \frac{2R_i C_m (x_{LL})^2}{a}, \qquad (14)$$

where a is the fibre radius. Assuming values for R_i and C_m of 100 Ω cm and 12 μF/cm² for Purkinje fibres (Weidmann, 1952), $x_{LL} = 0{\cdot}02$ cm and $a = 0{\cdot}005$ cm we obtain

$$\tau_{\mathrm{P.F.}} = 100 \times 12 \times 10^{-6} \times (0{\cdot}02)^2/0{\cdot}005 \text{ sec}$$
$$= 1{\cdot}2 \times 10^{-4} \text{ sec} = 120\ \mu\text{sec}.$$

Similarly for squid nerve we may use $C_m = 1\ \mu$F, $R_i = 35\ \Omega$ cm, and $a = 0{\cdot}024$ cm (cf. Hodgkin & Huxley, 1952) which together with $x_{LL} = 0{\cdot}3$ cm gives

$$\tau_{\text{squid}} = 35 \times 10^{-6} \times (0{\cdot}3)^2/0{\cdot}024 \text{ sec}$$
$$= 140 \times 10^{-6} \text{ sec} = 140\ \mu\text{sec}.$$

Thus, in both cases, the time constant for charge leakage from the liminal length region is similar to the time constant of sodium activation (about 200 μsec). It should be noted that this comparison can only be approximate. Most of the capacitance of the liminal length of cable discharges through a smaller resistance than $r_a x_{LL}$ before leaving the liminal length region. On the other hand, the charge must also flow through axial resistance beyond the point x_{LL}. The quantity $r_a c x_{LL}^2$ therefore gives only a fairly rough indication of the speed of charge decay from the liminal length region. This process is not an exponential one and can only be given an approximate time constant. Similarly, the sodium activation process is not exponential but sigmoid. The time constant of the m variable is therefore only an approximate indication of the rate of sodium activation. These considerations make it difficult to give a more exact analysis of charge redistribution and sodium activation without resorting to full integrations of the cable and Hodgkin–Huxley equations.

DISCUSSION

The major conclusions of this paper are (*a*) that Rushton's liminal length parameter may be fairly simply derived from voltage-clamp measurements of current–voltage relations in excitable cells and (*b*) that the values derived in this way for squid nerve and cardiac Purkinje fibres correspond fairly well with those derived from strength–duration curves by Fozzard & Schoenberg. In general, therefore, the results support Fozzard & Schoenberg's analysis and provide some justification for its use. However, there are two difficulties in the analysis that call for further discussion. These concern the effects of accommodation and the sodium activation time.

Effects of accommodation

Fozzard & Schoenberg found that the best fit to the strength–duration curve for long Purkinje fibres was obtained by allowing X_{LL} to vary by a factor of about 2·5 between short stimuli and long stimuli. As Fozzard & Schoenberg suggest, this effect is likely to result from accommodation since, as the stimulus duration is prolonged, g_1 will decrease due to partial inactivation of the sodium conductance. X_{LL} will therefore increase. The question, therefore, is whether this effect may be expected to be larger in the Purkinje fibre than in squid nerve and whether the magnitude of the effect assumed by Fozzard & Schoenberg is consistent with experimental data on the accommodation process.

The resting time constant, $r_m c$, in squid is about 0·7 msec compared to 20 msec for the Purkinje fibre. The voltage in response to a step depolarizing current will, therefore, increase much more slowly in the Purkinje fibre than in squid nerve. This fact is, of course, reflected in the very different time constants obtained for the uniform strength–duration curves in the two tissues (about 30 msec for Purkinje fibres, Fozzard & Schoenberg, Table 2; and 3 msec for squid nerve), although this correlation should be treated with caution since there is no very simple relation between the strength–duration time constant and the membrane time constant (see Noble & Stein, 1966). Nevertheless, we may expect that considerably more accommodation will occur during stimuli near rheobasic levels in the Purkinje fibre than occurs in squid nerve and that a substantial increase in X_{LL} may occur at long durations. Fozzard & Schoenberg's analysis suggests that X_{LL} increases by a factor of 2·5 which, according to eqn. (2), requires g_1 to decrease by a factor of 6.

Is a decrease in g_1 of this order of magnitude consistent with what is known about accommodation in Purkinje's fibres? As Fozzard & Schoenberg note, the potassium currents in Purkinje fibres activate far too slowly to be involved here. We are therefore concerned solely with sodium inactivation. A rheobasic current must depolarize the membrane from a resting potential of about -80 mV to the sodium threshold of about -60 mV. Weidmann's (1955) data on the sodium inactivation process (see his Fig. 3) show that in the steady state a fall in h of the order of 10 can occur between these potentials. Moreover, the time constant for h is of the order of a few msec (Weidmann, 1955) so that h could fall substantially towards its steady-state value during a pulse lasting about 8 msec, i.e. about 2*S–D* time constants, as required by Fozzard & Schoenberg's assumed relation between X_{LL} and duration of pulse (see their Fig. 12). The effect of accommodation therefore creates very little difficulty and Fozzard & Schoenberg's analysis is consistent with the experimental measurements of accommodation in Purkinje fibres.

Effect of sodium activation time

The second difficulty is more serious. The analysis does not take explicit account of the speed of inward current activation. Implicitly, it is assumed that this process occurs at a rate that is slow enough to allow charge on the liminal length region in excess of that required for excitation to redistribute itself to regions of the cable beyond X_{LL}. This assumption is clearly somewhat arbitrary although, as noted earlier in this paper, it is not implausible to assume that the sodium activation rate is of the right order of magnitude for the charge redistribution to occur before excitation occurs.

Unfortunately, there is no guarantee that the charge on the region between $X = 0$ and $X = X_{\mathrm{LL}}$ will in fact decay to the value of Q_∞ for this region. On the contrary, the fact that the strength–duration time constant is a function of the sodium activation rate indicates that it is the exception rather than the rule for this assumption to be observed at all accurately. Thus, the strength–duration time constant is a function of temperature (Cooley, Dodge & Cohen, 1965; Guttman, 1962, 1966), which changes the rate of sodium activation while having little effect on the absolute magnitude of the sodium conductance (Hodgkin & Huxley, 1952). The liminal length, as defined by eqn. 12, will therefore be relatively independent of temperature. As a result, as temperature is increased, g_{Na} will activate too rapidly to allow Q on the liminal length region to decay towards Q_∞ for this region. Hence a smaller amount of charge will be adequate for excitation. The only way in which this effect could be incorporated is to allow the liminal length parameter used in Fozzard & Schoenberg's equations to be a function of the sodium activation rate.

Fozzard & Schoenberg have in fact shown that the value for X_{LL} computed for squid nerve from charge and voltage thresholds decreases from 0·54 to 0·39 when the temperature is raised from 6·3 to 18·5°. Using a Q_{10} of 3, this temperature change corresponds to a fourfold increase in the rate of sodium activation so that excitation may then occur well before the charge on the liminal length region has decayed towards Q_∞ for that region. Unfortunately, it is not at all clear how this effect may be quantified to allow an explicit relation between the effective value of X_{LL} and sodium activation rate to be derived. Clearly, the steady-state approach described in the present paper does not readily allow time-dependent phenomena to be included. This difficulty is less severe in Fozzard & Schoenberg's analysis inasmuch as the effective value of X_{LL} in their theory can be obtained from measured charge and voltage thresholds, so that the relation between the effective X_{LL} and sodium activation rate might be determined empirically or numerically. The difficulty in this case lies in providing any further explanation for the relation since Fozzard & Schoenberg's theory does not explicitly include the non-linear properties of the membrane on which X_{LL} must depend.

This is a suitable point at which to emphasize a further difficulty in the interpretation of strength–duration curves. This is that the strength–duration time constant for *non-uniform* excitation bears virtually no relation to the resting membrane time constant. The major determinants are the values of g_{Na}, the membrane capacitance, the axial resistance and the rate of activation of g_{Na}. Although the resting membrane conductance appears in the equation for liminal length (see eqn. (12)), this is only because X_{LL} is expressed in dimensionless terms. If, instead, we write

$$x_{\mathrm{LL}} = \lambda X_{\mathrm{LL}} = \frac{\pi}{2}\lambda_{\mathrm{B}} = \frac{\pi}{2\sqrt{(-g_1 r_{\mathrm{a}})}} \tag{15}$$

it becomes clear that the *absolute* magnitude of the liminal length is independent of the value of g_{r}. Since strength–duration curves are normally obtained using external electrodes that excite a fibre at one point, it is clear that the results cannot be used to estimate the membrane time constant, even approximately. As Fozzard & Schoenberg (1972) have shown, the strength–duration time constant for *uniform* excitation is much closer to the membrane time constant. Of course, the conditions required to achieve uniform excitation are generally those required to estimate the membrane time constant by more direct means.

Application of analysis to skeletal muscle

The large effect that cable properties may have on the time constant of the strength–duration curve has been known for a long time. Davis (1923) and Grundfest (1932) showed that, in skeletal muscle, the strength–duration time constant is much shorter when the tissue is excited by a very small current source than when it is excited by a large current source. A much smaller difference was noted in the case of nerve. The analysis given in the present paper and that given by Fozzard & Schoenberg indicates that these results may be interpreted to mean that the liminal length for excitation is shorter in skeletal muscle than in nerve. An estimate for nerve has been given earlier in this paper. It is, therefore, of some interest to obtain an estimate for skeletal muscle.

Adrian, Chandler & Hodgkin (1970, Fig. 8) have measured the ionic current–voltage relation of frog skeletal muscle in the vicinity of the sodium current threshold. From their results, it is clear that the ratio $-g_1/g_r$ is high. The best fitting linear segment between the uniform and cable thresholds in this case is about 10–20 times steeper than the resting conductance. Using eqn. (12) this gives a value for X_{LL} which is between 0·35 and 0·5. These values are smaller than the estimate of 0·77 for squid nerve given earlier in this paper, as required if the cable effects on the strength–duration time constant are larger.

Comparison between liminal length theories

Finally, it is of some importance to compare the rather different approaches to the problem of liminal length described in this paper and in that of Fozzard & Schoenberg, and to show how they relate to each other.

One way of doing this is to regard the two approaches as being different simplications of the full cable equation

$$\frac{1}{r_a}\frac{\partial^2 V}{\partial x^2} = c\frac{\partial V}{\partial t} + i_i. \tag{16}$$

Fozzard & Schoenberg's analysis neglects the non-linear dependence of i_i on V and substitutes V/r_m for i_i to give the classical linear cable equation. Excitation is then assumed to occur when a liminal length of nerve is raised above a certain voltage. The linear cable equation is assumed to apply up to that time. By contrast, the analysis given in the present paper neglects the capacity current, $c\,(\partial V/\partial t)$. The cable is assumed to approach threshold slowly enough to allow steady-state solutions to the non-linear cable equation to apply. As noted earlier in the Discussion, this requires the assumption that the opposing effects of sodium activation time and charge redistribution time largely cancel each other.

These two simplications allow very different, although complementary, accounts to be given. By neglecting non-linearities, Fozzard & Schoenberg's analysis cannot obtain the liminal length as a function of the ionic current flow. On the other hand, given a value for the liminal length, the analysis allows the strength–duration curve to be predicted. Alternatively, the liminal length may be derived from the strength–duration curve or from the charge and voltage thresholds (see Appendices 1 and 2 of Fozzard & Schoenberg's paper).

By contrast, the analysis given in the present paper allows the liminal length to be derived from the non-linear properties of i_i (it should be noted that, although the linear approximate eqn. (12) is given for X_{LL}, the analysis is based on the solution to the non-linear eqn. (7) (see Fig. 3) which may be solved analytically for many i (V) relations, see Jack, Noble & Tsien, 1973), but does not give an account of time-dependent phenomena, unless the two approaches are 'married' by using liminal lengths derived from steady-state non-linear theory to compute strength–duration curves from transient linear theory.

At first sight, it may appear that Rushton's (1937) analysis avoids both simplications since his equations include non-linearity in i_i and time dependent parameters such as dQ/dt. However, it is important to note that the latter are assumed to play a negligible role in determining the net current flow across the fibre. Thus, on page 215 of Rushton's paper we find that the membrane resistance ρ lying in parallel with the membrane capacitance is assumed to be negligibly small compared to a sheath resistance R in series with it. In practice, therefore, the capacitance is shorted by a large conductance and the cable equations used by Rushton approximate to steady-state equations in which the membrane resistance r_m is replaced by the, mathematically speaking, identical parameter R. Rushton's approach is therefore similar to that adopted in the present paper. The major difference lies in the fact that he assumed a step change in membrane e.m.f. to underlie excitation so that the current–voltage relation assumed does not accurately simulate the voltage-clamp results obtained in excitable cells. The relation between Rushton's (1937) analysis and that described here is discussed further in the Appendix.

I should like to thank Dr J. J. B. Jack for valuable discussions on the theory presented in this paper, and Dr H. A. Fozzard and Dr M. Schoenberg for their comments on the manuscript.

APPENDIX

Relation of equations to Rushton's equation for liminal length

Rushton's (1937) derivation of an equation for the liminal length for excitation differs considerably from that given here. However, we may show that the equations give approximately the same results when the approach described in this paper is applied to Rushton's model.

Rushton assumed a current–voltage relation of the form shown in Fig. 8. At the uniform threshold voltage V_B, the membrane e.m.f. is assumed to change abruptly from V_A to V_D. The conductance was assumed to remain unchanged.

Now

$$\int_{V_A}^{V_B} i_i \mathrm{d}V = gV_B \frac{V_B}{2} = \frac{gV_B^2}{2}$$

and

$$\int_{V_C}^{V_B} i_i \mathrm{d}V = (V_C - V_B)\, g \left(\frac{2E - V_B - V_C}{2}\right).$$

Since V_C is the cable threshold, these integrals must be equal. Hence

$$V_B^2 = -V_C^2 + 2V_C E - 2V_B E + V_B^2.$$

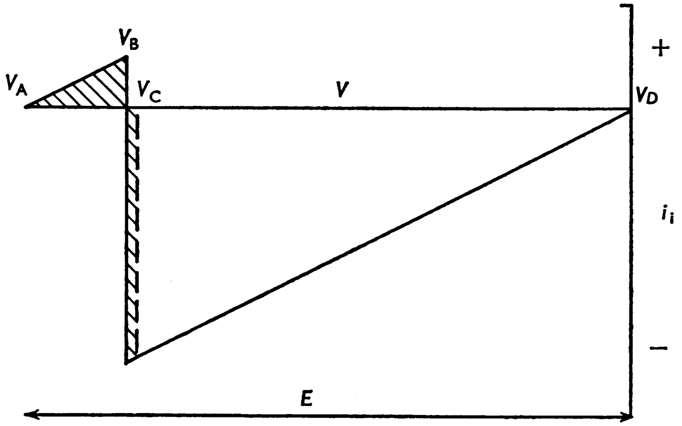

Fig. 8. Current–voltage diagram used in Rushton's (1937) model.

Solving for V_C we obtain

$$V_C = E - \sqrt{(E^2 - 2V_B E)}.$$

Now consider the cable equation

$$\frac{1}{r_a}\frac{\mathrm{d}^2 V}{\mathrm{d}x^2} = i_i$$

between the points V_C (at $x = 0$) and V_B (at $x = x_{LL}$).
Then

$$\frac{1}{r_a}\frac{\mathrm{d}^2 V}{\mathrm{d}x^2} = -g(E - V)$$

or

$$\lambda^2 \frac{\mathrm{d}^2 V}{\mathrm{d}x^2} = -g(E + V).$$

The solution is

$$\begin{aligned} V &= (V_C - E)\cosh(X) + E \\ &= E - \{\sqrt{(E^2 - 2V_B E)}\}\cosh(X), \end{aligned}$$

where $X = x/\lambda$.

When $V = V_B$, $X = X_{LL}$ so that

$$V_B = E - \{\surd(E^2 - 2V_B E)\}\cosh(X_{LL})$$

or

$$\cosh(X_{LL}) = \frac{E - V_B}{\surd(E^2 - 2V_B E)}$$

and we obtain

$$X_{LL} = \ln\left[\frac{E - V_B}{\surd(E^2 - 2V_B E)} + \surd\left(\frac{(E - V_B)^2}{E(E - 2V_B)} - 1\right)\right].$$

When V_B is small compared with E this simplifies to

$$X_{LL} \simeq \ln\left(1 + \frac{V_B}{E}\right) \simeq \frac{V_B}{E}.$$

Rushton's equation (see his eqn. (7)) is

$$x_{LL} = -\frac{\lambda}{2}\ln\left(1 - \frac{2RQ_B}{\tau E}\right),$$

where R is a sheath resistance, Q_B a threshold charge and τ the membrane time constant. In the steady state, Rushton's model allows RQ_B/τ to be equated to V_B in the present treatment. Hence

$$X_{LL} = x_{LL}/\lambda = -\tfrac{1}{2}\ln\left(1 - \frac{2V_B}{E}\right)$$

which also approximates to V_B/E when V_B is small.

REFERENCES

Adrian, R. H., Chandler, W. K. & Hodgkin, A. L. (1970). Voltage clamp experiments in striated muscle fibres. *J. Physiol.* **208**, 607–644.

Beeler, G. W. & Reuter, H. (1970). Voltage clamp experiments on ventricular myocardial fibres. *J. Physiol.* **207**, 165–190.

Cooley, J., Dodge, F. & Cohen, H. (1965). Digital computer solutions for excitable membrane models. *J. cell. comp. Physiol.* **66**, suppl. 2, 99–110.

Davis, H. (1923). The relationship of the 'chronaxie' of muscle to the size of the stimulating electrode. *J. Physiol.* **57**, 81–82*P*.

Fozzard, H. A. & Schoenberg, M. (1972). Strength–duration curves in cardiac Purkinje fibres: effects of liminal length and charge redistribution. *J. Physiol.* **226**, 593–618.

Guttman, R. (1962). Effect of temperature on the potential and current thresholds of axon membrane. *J. gen. Physiol.* **46**, 257–266.

Guttman, R. (1966). Temperature characteristics of excitation in space clamped squid axons. *J. gen. Physiol.* **49**, 1007–1018.

Grundfest, H. (1932). Excitability of the single fibre nerve-muscle complex. *J. Physiol.* **76**, 95–115.

Hodgkin, A. L. & Huxley, A. F. (1952). A quantitative description of the membrane current and its application to conduction and excitation in nerve. *J. Physiol.* **117**, 500–544.

HODGKIN, A. L., HUXLEY, A. F. & KATZ, B. (1952). Measurement of current–voltage relations in the membrane of the giant axon of *Loligo*. *J. Physiol.* **116**, 424–448.

HODGKIN, A. L. & RUSHTON, W. A. H. (1946). The electrical constants of a crustacean nerve fibre. *Proc. R. Soc.* B **133**, 444–479.

JACK, J. J. B., NOBLE, D. & TSIEN, R. W. (1973). *Electric Current Flow in Excitable Cells*. Oxford: Clarendon Press (in the press).

MOBLEY, B. A. & PAGE, E. (1972). The surface area of sheep cardiac Purkinje fibres. *J. Physiol.* **220**, 547–563.

NOBLE, D. & HALL, A. E. (1963). The conditions for initiating 'all-or-nothing' repolarization in cardiac muscle. *Biophys. J.* **3**, 261–274.

NOBLE, D. & STEIN, R. B. (1966). The threshold conditions for initiation of action potentials by excitable cells. *J. Physiol.* **187**, 129–162.

RUSHTON, W. A. H. (1937). Initiation of the propagated disturbance. *Proc. R. Soc.* B **124**, 210–243.

WEIDMANN, S. (1952). The electrical constants of Purkinje fibre. *J. Physiol.* **118**, 348–360.

WEIDMANN, S. (1955). The effect of the cardiac membrane potential on the rapid availability of the sodium-carrying system. *J. Physiol.* **127**, 213–227.