2.4 Membrane Potential Transients and Membrane Time Constant of Motoneurons (1960), *Exptl. Neurol.* 2:503–532

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This paper is concerned with the interpretation of passive membrane potential transients produced in a neuron when intracellular microelectrodes are used to apply current across the soma membrane. It is also concerned with the specific problem of estimating the nerve membrane time constant from experimental transients in neurons having extensive dendritic trees. When this theory is applied to the most recent results published for cat motoneurons, the resulting membrane time constant estimates are significantly larger than the values estimated by Eccles and collaborators. The time course of soma membrane potential is solved for a variety of applied currents: current step, brief pulse of current, sinusoidal current, voltage clamping current, and a current of arbitrary time course. The sinusoidal case provides a theoretical basis for a purely electrophysiological method of estimating the fundamental ratio between combined dendritic input conductance and soma membrane conductance. Also included is the time course of passive decay to be expected to follow various soma-dendritic distributions of membrane depolarization or hyperpolarization. The discussion includes an assessment of the observations, hypotheses, and interpretations that have recently complicated our understanding of synaptic potentials in cat motoneurons. It appears that electrotonic spread between the dendrites and soma can account for the observations which led Eccles and collaborators to postulate a prolonged residual phase of synaptic current in cat motoneurons.

Introduction

The experimental recording of motoneuron membrane potential transients resulting from the application of an electric current step across the soma membrane is one of the remarkable recent achievements made possible by intracellular microelectrodes (1, 6, 7, 19). A correct inter-

It is a pleasure to acknowledge the stimulation provided by discussion with many colleagues. Suggestions made by Dr. J. Z. Hearon led to some of the more generalized mathematical results. Preliminary results (25) were obtained while the author was in the Biophysics Division, Naval Medical Research Institute, Bethesda, Maryland.

pretation of these experimental results is important because it provides an estimate of the membrane time constant; this, in turn, has implications for the interpretation of synaptic potentials and for theoretical concepts of synaptic excitation and inhibition.

The fact that a large portion of the applied electric current must spread (electrotonically) from the neuron soma into its several dendritic trees was neglected in the first interpretations of such experimental transients. It is now becoming clear that this dendritic current is of primary importance in the estimation of motoneuron membrane properties (25, 28).

Synaptic Potential Decay and Membrane Time Constant. During the 10 years from 1946 to 1956, a rather simple and useful concept of the "synaptic potential" was developed by Eccles and his collaborators (2, 9, 12, 13). It was held that synaptic activation causes the motoneuron membrane to undergo a brief "active" phase of depolarization; when below the threshold for reflex discharge, this depolarization was assumed to undergo a passive decay having an exponential time constant of about 4 msec. The brief "active" phase was found to persist for not more than 0.5 msec (2, 13), an interval later revised to 1.2 msec (9); it was believed to result from a large nonselective increase in the ionic permeability of the motoneuron membrane (9). Because the subsequent synaptic potential decay was assumed to be passive,[2] and because the depolarization was implicitly assumed to be effectively uniform over the neuron surface,[3] this decay was expected to have an exponential time constant equal to the membrane time constant, $\tau = R_m C_m$, of the resting membrane. The average value of this τ was thus found to be about 4 msec, with a range from about 3 to 5 msec for cat motoneurons (13, pp. 116 and 142).

Rapid Transients Misinterpreted. In 1956, unexpectedly rapid membrane potential transients were recorded by Frank and Fuortes (19), and confirmed by Eccles and collaborators (6, 14). These transients were produced experimentally by the application of a current step across the soma membrane; their rapid time course was misinterpreted as evidence

[2] The word "passive" is used to imply that the membrane resistance, capacity, and electromotive forces all remain constant at their physiological resting values.

[3] This assumption of uniform distribution deserves explicit mention. A simple exponential decay is not to be expected when the dendritic depolarization is significantly different from that of the soma. The effect of nonuniform depolarization is represented mathematically in Eq. [23] and is illustrated graphically in Fig. 4.

for a membrane time constant that was significantly smaller than the time constant of synaptic potential decay; the values reported for τ were 1 to 1.4 msec (19) and 2.5 msec (6, 14).

If these values had correctly represented the true membrane time constant, they would have made the earlier simple concept of the synaptic potential untenable. Thus, Frank and Fuortes concluded that the long duration of the synaptic potential "is not a consequence of the time constant of the membrane itself, but rather of a similarly long-lasting change occurring elsewhere" (19, p. 468). Coombs, Curtis, and Eccles (6) developed a more detailed explanation; they calculated a hypothetical time course of synaptic current that was assumed to be necessary to account for the synaptic potential. Using their 2.5-msec time constant, they obtained a hypothetical time course that was characterized by a prolonged residual phase of current following the brief early phase of current; this hypothetical time course has been widely illustrated (6; 14, Figs. 11 and 23; 15, Fig. 2; 16, Fig. 5). Fatt (17), on the other hand, preferred to preserve the hypothesis that the "active" phase of depolarization is brief; he assumed that synaptic potential decay would be dominated by the dendritic membrane time constant which he assumed to be longer than that of the soma. Assuming that a large amount of the synaptic potential is generated in the dendrites, he suggested that electrotonic spread from dendrites to soma would cause the dendritic membrane time constant to dominate the decaying phase observed at the soma.

Dendritic Electrotonus Accounts for Rapid Transient. The apparent need for these various hypotheses was then shown to have resulted from a misinterpretation of the experimental results. It was pointed out in a preliminary communication (25), that when the transient characteristics of the motoneuron dendrites are taken into account, the recently obtained experimental transients agree quite well with theoretical predictions based upon the older membrane time constant value of around 4 msec. Briefly, this follows from the fact that the electrodes do not apply the current directly across the extensive dendritic surfaces; the current is applied across the soma membrane and must spread electrotonically into the dendrites. When these dendrites are approximated as cylinders of infinite length, it follows that the dendritic contribution to the motoneuron potential transient should be expected to resemble the uppermost curve in Fig. 1; this transient is already well established in the theory of axonal electrotonus (11, 21); it can be expressed $erf\ \sqrt{t/\tau}$. This transient is significantly faster than the simple exponential transient, $1 - e^{-t/\tau}$ (see

lowermost curve in Fig. 1), that would be expected in the case of uniformly applied current.

The resultant whole neuron transient recorded across the soma membrane can be expected to represent a combination of these dendritic and somatic components. This transient function depends upon the relative weights given to the dendritic and somatic contributions. These weights depend upon the steady state ratio between the current flowing into all

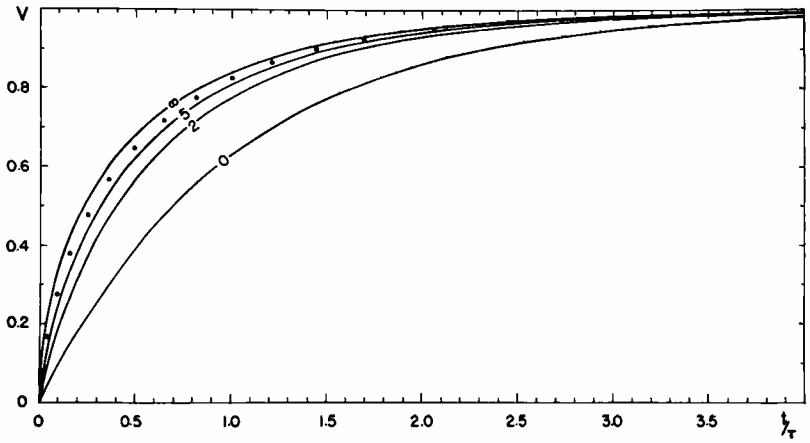

FIG. 1. Transients of passive soma membrane potential when a constant current step is applied across the soma membrane at zero time. The electrotonic potential, V, is expressed relative to its final steady value during constant applied current. Time is expressed relative to the membrane time constant. Curves are drawn for $\varrho = 0$, 2, 5, and ∞; the dots correspond to $\varrho = 10$. The uppermost curve, $\varrho = \infty$, represents the limiting case in which the dendrites are completely dominant. The lowermost curve, $\varrho = 0$, represents the limiting case of a soma without dendrites.

dendrites and the current flowing across the soma membrane (27, 28). The dependence of the resultant transient upon this ratio, ϱ, is illustrated in Fig. 1; it is expressed mathematically in Eq. [9] of the Appendix.

Although estimates of this dendritic-to-soma ratio vary (7, 25, 28), they all imply some degree of dendritic dominance, for motoneurons in cat and in man. The "standard motoneurone" of Eccles and his collaborators implies a ratio of 2.3 (7); however, the sample of motoneurons analyzed by Rall (28) suggests that values of this ratio are more likely to lie in the range from 21 to 35; known uncertainties permit an even wider range of values extending from about 10 to 47 (28, pp. 519-520).

The method of membrane time constant estimation used below has the advantage of being applicable over this entire range of dendritic dominance (i.e., for ratios from 2 to 50). Results obtained by this method support the conclusions of the preliminary note (25): the rapid experimental transients (6, 14, 19) do not conflict significantly with the old estimate of about 4 msec for the cat motoneuron membrane time constant; these transients do not force abandonment of the concept of passive synaptic potential decay.

Reinterpretations. The need to take the dendritic contribution into account has recently been accepted by Coombs, Curtis, and Eccles (7). Consequently, their membrane time constant estimate has been revised upwards (7), and the magnitude of their hypothetical residual synaptic current has been revised downwards (10). Nevertheless, these authors still find their membrane time constant estimates too small to be consistent with a passive synaptic potential decay (7, 10); also, they appear to regard their interpretations of several related experiments as evidence in support of their hypothetical residual synaptic current (10). Alternative interpretations of their experiments are considered below in the Discussion.

Assumptions and Method

It is assumed that a majority of readers will be more interested in a descriptive presentation of the theoretical results than in the details of the mathematical derivations. Consequently, the mathematical treatment has been condensed and placed in an Appendix. It should be emphasized that the method of this research actually depends upon the following logical sequence: Select simplifying assumptions which facilitate mathematical treatment without losing too much that is physiologically essential. Deduce the theoretical properties of this model in general, and also for special cases of current physiological interest. Demonstrate the implications of these theoretical results for the interpretation of recent experimental data.

The theoretical analysis is applied to an idealized model of a neuron possessing several branching dendritic trees. It is assumed that the membrane potential is effectively uniform over the soma surface, and that the extracellular gradients of electric potential can be neglected in the treatment of dendritic membrane electrotonous. These two assumptions, together with other assumptions used to idealize the geometric and passive electric membrane properties of neurons, have been given de-

tailed presentation and assessment elsewhere (27, 28); previous Figs. 1, 2 and 5 (28) can be used to help visualize the spread of electric current in terms of the formal model.

Results

Membrane Time Constant Estimation

Analysis of Transient Obtained with Current Step Applied to Soma. The estimation procedure presented here is a rather simple and practical procedure that has the following advantages: it utilizes a linear plot of the experimental results; it thus permits full use of all reliable portions of the experimentally recorded transient; however, any obviously unreliable portion of the experimental transient need not be used; also, this method does not depend upon the prior assumption of any particular ratio between the dendritic and somatic contributions to the transients.

This method does require that the experimental records exhibit a noise level sufficiently low to permit reasonably reliable measurements of the slope, dV/dt, at various times after the onset of the current step. Given these measurements, the procedure is the following:

$$\text{plot log } \{\sqrt{t}\ (dV/dt)\}, \text{ versus } t.$$

Subject to qualifications (expressed below), these points should fit a straight line; when calculated with natural logarithms, the negative slope of this line gives the reciprocal of the membrane time constant, τ.

The theoretical basis for this procedure (and its qualifications) is provided by Eqs. [12, 13, 15] of the Appendix. For the limiting case of complete dendritic dominance, Eq. [13] shows that the above procedure applies without any qualifications. For lesser dendritic dominance (i.e., values of ϱ greater than 2 but less than infinity) the error resulting from use of the same plotting procedure can be calculated from Eq. [15]; this error can be shown to be small at times for which the quantity, $\varrho \sqrt{t/\tau}$, is not too small. Graphical illustration of this is provided by the (dashed) curves in the lower left part of Fig. 2, for $\varrho = 5$ and 2; a value of 7 msec was used for τ to simplify comparison with the plotted data in Fig. 2. It can be seen that there is little error at times greater than $\tau/2$, when $\varrho = 5$; the error is less for larger values of ϱ. Even for the low value, $\varrho = 2$, the curve between $t = \tau$ and 2τ is almost straight and has a slope which is about 5 per cent less steep than that for $\varrho = \infty$. Consequently, the same simple plotting procedure is useful when the value of ϱ is unknown but can reasonably be assumed to be greater than 2;

whenever ρ is known, the correction can be calculated. For the limiting case of a soma without dendrites ($\rho = 0$), Eq. [12] reduces to Eq. [14], and a linear relation exists between $\log(dV/dt)$ and t.

Illustrative Application to Cat Motoneurons. This linear plotting procedure was applied to some of the experimental transients published recently by Coombs, Curtis, and Eccles (7). The left half of Fig. 2 summarizes the applied current step analysis of one of their motoneurons (7, Figs 3 and 5); the right half of Fig. 2 summarizes both a current step and a current pulse analysis of a different motoneuron (7, Fig. 6). Photographic enlargements of the published figures were used; the slope, dV/dt, was measured at intervals of 1 msec. In the case of applied current steps, the natural logarithm of $\sqrt{t}(dV/dt)$ was plotted as ordinate against time as abscissa; these points are shown as open circles in Fig. 2.

The three sets of open circles (in the left half of Fig. 2) correspond to three different amplitudes of current, 6, 8, and 10 x 10^{-9} amperes, applied as steps to a single motoneuron (7, Fig. 5). The three corresponding sets of crosses represent the same data after correction for an estimated 500-msec time constant in the experimental recording system; see figure legend for details. The straight lines drawn through the circles and crosses were fitted by the method of least squares.[4] The three sets of crosses fit slopes corresponding to τ values of 7.1, 8.1, and 7.3 msec, respectively; the weighted mean of these values yields a best estimate of 7.5 msec for the membrane time constant of this motoneuron.[5]

From their analysis of the same transients, Coombs *et al.* estimated a τ value of 5.1 msec for this motoneuron (7, Table 3 with Figs. 3 and 5); their estimate is about 30 per cent below that obtained here. Even if this motoneuron were to have the small dendritic-to-soma ratio, $\rho = 2$,

[4] Equal weighting was assumed for the ordinates (expressed as logarithms). This is equivalent to the not unreasonable assumption that the errors in slope measurement tend to be proportional to the magnitude of the slope (i.e., a constant coefficient of variation).

[5] This weighted mean has a standard error of about 0.2 msec. Such a mean is justified because the differences between the three component τ values are not statistically significant; the three standard errors are 0.28, 0.33, and 0.22, respectively; the largest difference between the three τ estimates yields a t value of 2.3, which is less than that required for significance at the 2 per cent level. The corresponding difference for the uncorrected slopes (open circles) gives a t value of 3.6, which exceeds that required for significance at the 1 per cent level, and nearly reaches the 0.1 per cent level.

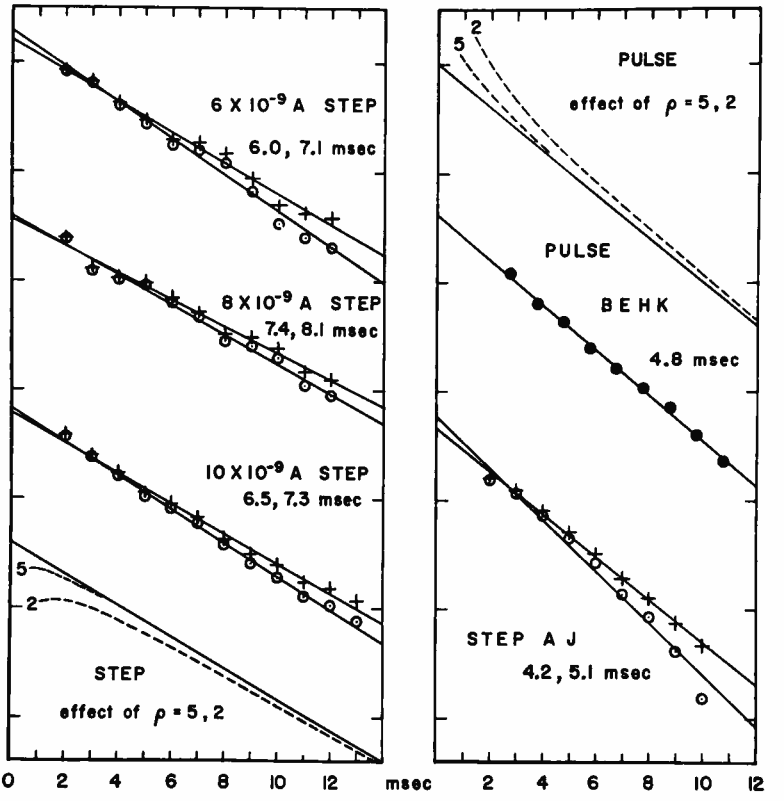

FIG. 2. Linear plots of experimental transient data. The left side is based upon transients obtained with applied current steps of three different amplitudes in a single neuron (7, Fig. 5); the right side is based upon experiments with a different motoneuron, that was subjected to both pulses and steps of applied current (7, Fig. 6). The open circles (both left and right) represent current step experiments; their ordinates represent the natural logarithm of the product $\sqrt{t}(dV/dt)$; their abscissae represent time from onset of the applied step. The crosses include a correction for the time constant of the recording system; see below in this figure legend. The straight lines represent least square fits;[4] the value of τ corresponding to each slope is stated in the figure. The filled circles represent current pulse experiments (7, Fig. 6, curves B, E, H, K); their ordinates represent the natural logarithm of the product, $\sqrt{t}(-dV/dt) / (1 + \tau/2t)$; correction for the recording system time constant is negligible in this case; the abscissae represent time from the mid-point of the pulse. The (dashed) curves at lower left illustrate the effect of $\varrho = 5$, and 2 to be expected with the step transient plotting procedure (see text); the (dashed) curves in the upper right illustrate the corresponding effect to be expected with the pulse

the corresponding 5 per cent slope correction (lower left of Fig. 2), would reduce the 7.5-msec estimate by less than 0.4 msec; however, the value of ρ is likely to be greater than 10 (28), and the corresponding correction would be negligible.

In the right half of Fig. 2, the open circles and crosses summarize a similar analysis for a different motoneuron (7, Fig. 6, records A and J). Although the circles exhibit a systematic deviation from a straight line relation, this is not true of the crosses, which include a correction for an estimated 200-msec time constant in the experimental recording system; see figure legend for details. The least square fit through the crosses yields a membrane time constant estimate of 5.08 msec, with a standard error of about 0.13 msec.[6] This estimate is not significantly different from that obtained with a pulse analysis on the same motoneuron (filled circles of Fig. 2, explained below).

Transient Following Application of a Brief Current Pulse. When a brief pulse of current is applied across the soma membrane, the decay of the disturbance can be approximated quite well by that which would be theoretically expected to follow an instantaneous current pulse; the

[6] Combs, Curtis, and Eccles (7, Table 3) did not publish their estimate for this motoneuron. However, application of their estimation procedure to the step transients (7, Fig. 6, records A and J), seems to yield a value between 3.4 and 3.6 msec; this is about 30 per cent below the estimate obtained here.

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transient plotting procedure (see text). The unit of the ordinate scale is one (i.e., the natural logarithm of e).

Correction for instrumental time constant: Coombs, Curtis, and Eccles state that a time constant of at least 200 msec was always present in their recording system (7, p. 507). The correction formula to use is $dV/dt = dU/dt + U/\tau_r$, where V represents the true transient voltage, U represents the distorted recording, and τ_r represents the time constant of the recording system. When U reaches its extremum, $dU/dt = 0$, and $\tau_r = U/(dV/dt)$. Neglecting other possible complications, such as electrode polarization and local response, it follows from this, and from Eq. [13], that τ_r can be estimated as $\sqrt{\pi\tau_m t^*}\, e^{t^*/\tau_m}$, where t^* represents the time at which $dU/dt = 0$, and τ_m is the membrane time constant. A 200-msec time constant was estimated for (7, Fig. 6), because records A to J appear to reach their extrema at times between 10 and 15 msec (corresponding to τ_r between 90 and 310 msec), and because the control records (C to L) exhibit a slope corresponding approximately to $\tau_r = 200$ msec. The value of τ_r appropriate to (7, Fig. 5) is considerably less certain because these are tracings that already include some correction; in view of this, and because the extrema of records J and K (7, Fig. 3) correspond to τ_r in the approximate range from 150 to 700 msec, it was decided that a correction for $\tau_r = 500$ msec would represent a reasonable compromise.

approximation is quite good except at very short times after the pulse. This is illustrated by the theoretical curves in Fig. 3, where the calculations were simplified by assuming complete dendritic dominance. The passive responses have been calculated for square current pulses of several durations (by means of Eq. [10]), and for an instantaneous pulse (by

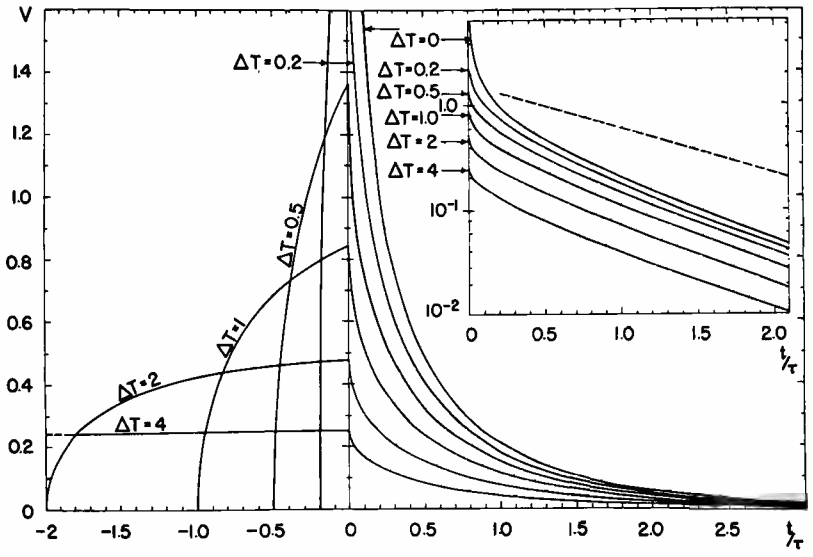

FIG. 3. Transients of passive soma membrane potential when a square pulse of current is applied across the soma membrane. Zero time corresponds to the instant when current is turned off. Pulse durations compared are $\Delta(t/\tau) = 4, 2, 1, 0.5, 0.2$, and instantaneous ($\Delta T = 0$). The amplitude of each current has been adjusted to make each pulse deliver the same amount of charge. The ordinate value, 1.0, represents the steady state value of V during a constant current having the same amplitude as that of the $\Delta T = 1.0$ pulse. Dendritic dominance has been assumed here. The inset presents the same curves with logarithmic scaling of the ordinates; the dashed line displays the corresponding slope for simple exponential decay, $e^{-t/\tau}$.

means of Eq. [17]). All amplitudes have been scaled to provide the same amount of charge displacement in every case. The logarithmically plotted inset (in Fig. 3) shows that the decay rates of neighboring curves differ rather little at times greater than $\tau/2$. Furthermore, the agreement between the instantaneous pulse curve and the shorter square pulse curves becomes excellent (for times greater than $\tau/2$) when the origin of the instantaneous pulse curve is shifted to the mid-point of each pulse dura-

tion; this is important for location of $t = 0$ when fitting experimental results.

Procedure for Brief Pulse Analysis. When a pulse is very brief and dendritic dominance can be assumed, a linear plotting procedure can be based upon Eq. [18] of the Appendix. The procedure is the following:

$$\text{plot log } [\sqrt{t}(-dV/dt)/(1 + \tau/2t)], \text{ versus } t.$$

When the correct value of τ is used in the factor, $(1 + \tau/2t)$, the plotted points can be expected to fit a straight line; the negative slope (calculated with natural logarithms) gives the reciprocal of τ. This procedure thus requires that a tentative value of τ be used in the factor, $(1 + \tau/2t)$, to obtain a preliminary plot of the data. With the resulting estimate for τ, the factor $(1 + \tau/2t)$ can be recalculated and the plotting procedure can be repeated. In practice, few repetitions of the procedure will be found sufficient.

Errors resulting from lesser dendritic dominance can be calculated from Eqs. [18] and [19]; graphical illustrations of such errors are provided by the (dashed) curves in the upper right part of Fig. 2, for $\rho = 5$ and 2; a value of 5 msec was used for τ. There is little error at times greater than $\tau/2$, when $\rho = 5$ or greater. For the low value, $\rho = 2$, the curve between $t = \tau$ and $t = 2\tau$ is almost straight and has a slope which is about 5 per cent steeper than that for the $\rho = \infty$. Errors associated with finite pulse duration were considered above, with Fig. 3.

Illustration of Brief Pulse Analysis. This procedure was applied to a set of experimental transients published by Coombs, Curtis, and Eccles (7, Fig. 6, records, B, E, H, K). At intervals of 1 msec, these slopes were measured in photographic enlargement, and averaged over the four curves. Then, using the procedure described above, the points shown as filled circles were plotted in Fig. 2; correction for the estimated 200-msec time constant in the experimental recording system is negligible in this case. The least square fit through these points yields a membrane time constant estimate of 4.84 msec, with a standard error of about 0.14 msec. This does not differ significantly from the estimate obtained with the step analysis on the same motoneuron (STEP AJ, crosses in Fig. 2). If these two estimates are given equal weight, a best estimate of about 5.0 msec is obtained for the membrane time constant of this motoneuron.[6]

Assessment of Motoneuron Membrane Time Constant Estimates. The experimental results of Coombs, Curtis, and Eccles (7) provide a valuable sample of eighteen carefully studied motoneurons. Although it would

obviously be desirable to perform similar linear plots for all eighteen of their motoneurons, the two cases analysed here (Fig. 2) suggest that there is a significant difference between the method of membrane time constant estimation used by them, and the method presented here. In these two cases, their method yields estimates that are about 30 per cent below those obtained here. If these should prove to be representative of the entire sample, it would follow that the average membrane time constant estimate of this sample should be increased from 3.1 msec to about 4.4 msec. This would suggest that the present method of estimation yields membrane time constant values about 75 per cent greater than the earlier method of Coombs, Curtis, and Eccles (6, 14), which took no account of dendritic transient characteristics. This should not, however, be used as the basis for a computational short cut, such as, for example, an increase of the correction factor, 1.2, used by Coombs, Curtis, and Eccles (7, pp. 518-519) to a larger value of 1.75; some hazards of such short cuts are noted in the fine print below.

The apparent simplicity of the estimation procedure used by Coombs, Curtis, and Eccles (7) should be weighed against the following disadvantages. Their procedure depends upon their assumption of one particular degree of dendritic dominance, $\varrho = 2.3$, based upon their "standard motoneurone." The measurement of half decay times is complicated by uncertainties in the asymptotic baseline and by the fact that this transient does not possess a characteristic time for half decay. Because of the second difficulty, these authors (7, p. 519) recommend the measurement of two successive half decay times commencing at $t = 0.6\tau$; however, τ is not known in advance, and in their Fig. 5 their arrows reveal that their measurements commenced at about 2 msec, in spite of a τ value of 5.1 msec (their estimate) or 7.5 msec (estimate of this paper); such an error would be expected to result in a low estimate. Also, the device of averaging two successive "half times" is equivalent to halving a single "quarter time"; the accuracy of this "quarter time" depends upon the accuracy of two points together with the accuracy of the baseline used; all information contained in the experimental transient, but not fully contained in this "quarter time," is effectively disregarded by their procedure.

With regard to questions of statistical significance, the eighteen estimates of Coombs, Curtis, and Eccles (7, Table 3, column 5) have a mean of 3.14 msec, and a standard deviation of 1.01, implying a value of 0.24 for the standard error of the mean. Relative to these statistics, an application of the "t" test for the significance of a difference between this mean and a larger true mean gives the following result: if this mean is 25 per cent below the true mean, the difference corresponds to significance at the 0.001 level. Such significance levels are subject to the usual qualifications, and they should be considered together with the sources of error described above.

Application of Voltage Clamp. If it is assumed possible to apply a perfect voltage step across the entire soma membrane, then the time course

of the current that must be supplied by the electronic clamping circuit would provide a valuable means of estimating the membrane time constant. Because the soma membrane capacity would have to be charged instantaneously, the transient time course of the applied current would be determined by the dendrites. Thus, the membrane time constant of the dendrites could be determined separately from the soma, and independently of ϱ.

The linear plotting procedure in this case would be the following:

$$\text{plot log } [t^{3/2}(-dI_A/dt)] \text{ versus } t,$$

where I_A represents the applied current. This procedure follows from Eq. [25] of the Appendix. It should be added that a mathematically more complicated result must be used if there is a significant amount of series resistance between the neuron membrane and the regions where the constant voltage difference is maintained.

Passive Decay of Soma-Dendritic Polarization

The time course of passive decay from an initial soma-dendritic membrane depolarization (or hyperpolarization) depends upon the initial distribution of the disturbance over the soma-dendritic surface. Graphical illustration of this is provided by Fig. 4, which is based upon Eqs. [22] and [23]. The upper curve ($a = 0$) represents a simple exponential decay following a uniformly distributed initial depolarization. The two lower curves show the more rapid decay, to be expected at the soma, when the initial depolarization of the dendrites is reduced (as an exponential function of distance from the soma); see figure legend. The effect illustrated in Fig. 4 is relevant to synaptic potential decay if this is assumed to be a passive electrotonic process following a brief depolarization. For example, the relative rates of EPSP decay and IPSP decay reported by Curtis and Eccles (10), would fit the hypothesis that IPSP initiation is confined more closely to the soma than is EPSP initiation; see Discussion.

In contrast to these cases, a slower passive decay would be expected at the soma following an initial depolarization that is greater in the dendrites than in the soma.

Sinusoidal Applied Current and Dendritic Dominance

Here is described the manner in which the application of sinusoidal current[7] across the soma membrane may provide a means of estimating

[7] It was suggested to me by Dr. L. Stark, that the soma-dendritic analysis be extended to include the sinusoidal case.

dendritic dominance quite independently of anatomical information. The fundamental parameter of dendritic dominance is the ratio, ϱ, of combined dendritic input conductance to soma membrane conductance (28); see also (7, 8, 25, 26). Previous estimates of this ratio have had to depend upon calculations which combine anatomical information obtained

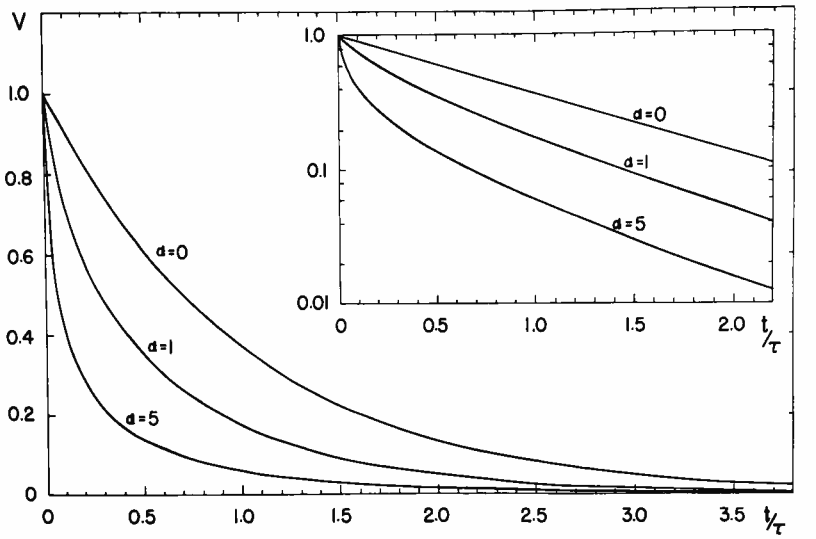

FIG. 4. Effect of initial distribution of soma-dendritic depolarization upon the time course of passive decay to be expected at the soma. The initial distribution is assumed to be $V(X,0) = e^{-ax/\lambda}$, for the three cases, $a = 0$, 1, and 5; the case, $a = 0$, represents a uniform distribution; when $a = 1$, 63 per cent of the dendritic depolarization is distributed proximally to $x = \lambda$; when $a = 5$, the total amount of dendritic depolarization is further reduced by a factor of 5, and 63 per cent of this is distributed proximally to $x = 0.2\lambda$. The logarithmically plotted inset permits an easier comparison of the three rates of decay. In contrast to this figure, when depolarization is least near the soma, Eqs. [22] and [23] imply that the rate of decay at the soma is slower than for the uniform case.

from one sample of neurons with electrophysiological information from another sample of neurons (28, pp. 508, 517-520).

Essentially, the experiment would consist of applying a sinusoidal current across the soma membrane, at several different frequencies, and recording the oscillatory electrotonic potential that is developed across the soma membrane. It would be anticipated, intuitively, that at low frequencies there must be significant current spread into the dendrites,

while at high frequencies most of the current would flow across the soma membrane capacity. For very high frequencies, the current would be almost entirely capacitative; in other words, the phase angle between current and voltage would be very close to 90°. For very low frequencies, the current would be almost entirely resistive, implying a phase angle close to zero.

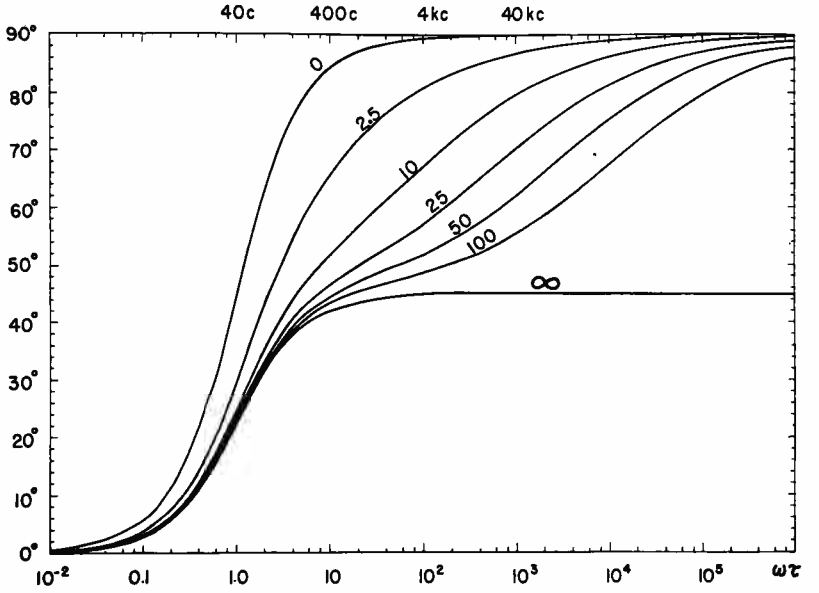

FIG. 5. Theoretical relation between phase shift and frequency when a sinusoidal current is applied across the soma membrane, for $\varrho = 0$, 2.5, 10, 25, 50, 100, and ∞. Zero phase angle implies a whole neuron impedance that is effectively a pure resistance; the 90° value corresponds to effectively pure capacitance. The $\omega\tau$ scale can be used for any τ value, the frequencies at the top of the figure apply when τ is 4 msec. This is based upon Eq. [29].

The transition from zero phase angle to 90° phase angle is displayed graphically in Fig. 5; phase angles are plotted against a logarithmic scale of frequency, for several dendritic to soma conductance ratio values, $\varrho = 0$, 2.5, 10, 25, 50, 100, and infinity. It can be seen that these curves offer a basis for distinguishing electrophysiologically between different values of ϱ.

These curves were calculated from Eq. [29] of the Appendix. A simple method of calculating ϱ from such experimental data is provided by the

formula, Eq. [30], obtained by a rearrangement of the first equation. These equations were derived from the assumption of a passive membrane impedance composed of a pure resistance and pure capacitance in parallel; possible complications from additional reactive components have been considered and judged likely to require only a small correction to the mid-range illustrated in Fig. 5; see Appendix. Complications resulting from physical instrumentation also may have to be taken into account.

Discussion

Electrophysiological Estimation of Neuron Parameters

Estimation of ϱ and τ Independently of Anatomy. The theoretical formulations presented in this paper provide the basis for electrophysiological estimation of the membrane time constant, $\tau = R_m C_m$, and of the dendritic to soma conductance ratio, ϱ, both independently of anatomical data. In principle, simultaneous best estimates of both ϱ and τ could be obtained from good experimental data of the kind corresponding to Figs. 1 and 5. In practice, when there is good reason to believe that ϱ is greater than 2, it is simplest to make a first estimate of τ by the method of Fig. 2; then, using this value of τ, estimate ϱ by the method of Fig. 5. After ϱ has been estimated, the estimate of τ can be re-examined to see if successive approximations are required.

Validation of Sinusoidal Method. The sinusoidal method for estimating ϱ has not yet been tested, and the possibility of unanticipated difficulties must not be overlooked. However, the theoretical results of the preceding paper (28; cf. also 7), provide the means for an independent estimate of ϱ; this is based upon anatomical data in combination with a measurement of R_N. Comparisons would ideally be carried out under conditions where the electrode placement can be confirmed visually, and the soma dendritic dimensions of the same cell can be obtained under essentially the same conditions; obvious candidates are cells in tissue culture, possibly cells in tissue slices, and also cells such as the crustacean stretch receptors.

Estimation of R_m and C_m Depends on Anatomy. Although it now appears to be possible to estimate ϱ and τ independently of anatomical data, the same cannot be said for the membrane constants R_m and C_m, which apply to unit area. In order to estimate R_m from the whole neuron resistance, R_N, it is not sufficient to have the value of ϱ; it is also necessary to know either the soma surface area, or a combined dendritic

size parameter (28).[8] The corresponding analysis of axons by Hodgkin and Rushton (21) demonstrated how four electrical constants can be determined from four electrical measurements. However, in that case it was also necessary to supplement the electrical measurements with an anatomical measurement (axon diameter) before the fundamental parameters, R_m, C_m and R_i could be estimated. In the soma-dendritic problem, the value of R_i is not regarded as a serious source of uncertainty and a reasonable value is assumed (28). Thus, the most essential motoneuron parameters may be given as R_m, C_m (or τ) and ϱ, plus a suitable measure of neuron size.

Hypothesis Advanced by Fatt

When the apparent discrepancy between synaptic potential decay and the erroneously low membrane time constant was first being discussed, Fatt (17, pp. 74 and 79) suggested that soma-dendritic electrotonic coupling might account for this discrepancy. This suggestion is in agreement with the present work. More particularly, Fatt's hypothesis was that the dendritic membrane has a larger R_m value than the soma. Assuming a uniform membrane capacity everywhere, this would result in a larger membrane time constant in the dendrites than in the soma. This hypothesis is not in conflict with the present results and interpretations. In view of the large dendritic to soma conductance ratio found, it can be said that the experimental results are determined mainly by the dendritic membrane and that a smaller value for the somatic τ and R_m would have little effect. Fatt gave two reasons for postulating smaller somatic values. Such somatic R_m values would correlate with a membrane threshold difference postulated to exist between soma and dendrites; this remains a possibility. Also, a smaller somatic τ value was intended to account for the rapid soma membrane potential transients observed with an applied current step; Fig. 1 shows that this assumption is not necessary when ϱ is large.

Hypotheses Advanced by Eccles and Collaborators

Because of their 2.5-msec time constant estimate, Coombs, Curtis, and Eccles were led to postulate a prolonged residual phase of synaptic cur-

[8] For neurons whose dendrites dominate the whole neuron conductance, it would be wiser to use a combined dendritic size parameter, especially if ϱ has been estimated by the sinusoidal method. This is because we do not yet know how much of the soma surface behaves as though it lies at $X = 0$ in the electrophysiological determination of ϱ. Once this question has been answered experimentally, it may be possible to simplify the procedure by using an appropriate estimate of the soma surface area.

rent (6, 14, 15, 16). It was subsequently postulated that this residual current is due to continued action of a negatively charged transmitter substance, and that the action of an applied hyperpolarizing current is to accelerate the removal of this transmitter substance from the synaptic cleft (14, pp. 63-64; 10, p. 543).

Although these authors have now accepted the necessity of considering dendritic electrotonous in the estimation of the motoneuron membrane time constant, they have explicitly objected to the suggested consequences (25), namely a membrane time constant of about 4 msec, and the removal of the need for a hypothetical prolongation of synaptic current time course. Their revised estimate of the average membrane time constant is 3.1 msec, with a range from 1.8 to 5.1 msec (7); this value allows them to interpret experiments which they find difficult to interpret with a 4-msec value (7, p. 526). However, there is now good reason to believe that even their revised membrane time constant estimates (7) are too low by a significant amount; see pp. 513 and 514.

The hypothetical time course of synaptic current, which originally showed a significant residual phase (6, 14, 15, 16), has now been revised by Curtis and Eccles (10) to a time course showing a much smaller residual phase than before. As explained in the fine print below, this calculated residuum does not establish the existence of actual residual synaptic currents; a very similar calculated residuum could be obtained in the complete absence of actual residual synaptic current.

Other evidence offered by Curtis and Eccles (10) in support of their hypothetical residual synaptic current is also considered in the fine print below. It appears that the various observations upon which Curtis and Eccles have based their arguments can be explained, at least approximately, by giving adequate consideration to electrotonic spread between dendrites and soma. Thus it would seem that the evidence presented by these authors (10) does not establish the existence of significant residual synaptic currents in these motoneurons.

Hypothetical Synaptic Current Time Course. The formula used by Curtis and Eccles (10) to calculate this current time course is equivalent to the well-known differential equation for current flow through a parallel resistance and capacity; this equation can be expressed $I = V/R + C(dV/dt)$. The validity of its application to the present problem depends fundamentally upon two requirements: The synaptic current must be uniformly distributed over the soma and dendrites; and the correct value for the membrane time constant must be used. Although Curtis and Eccles (10, p. 531) mention these requirements, it seems unlikely that either requirement has been adequately satisfied in their applications of this formula.

Even if the assumption of uniformly distributed synaptic current were valid, computation with a membrane time constant estimate, τ_e, that is significantly different from the true value, τ, would be expected to result in a computational artifact. Thus, in the complete absence of residual synaptic current, a uniform passive decay would imply that the formula, $V/\tau_e + dV/dt$, has a time course proportional to the expression, $(\tau - \tau_e)e^{-t/\tau}$. This equals zero only when τ_e equals τ. When τ_e is significantly smaller than τ, this artifact has a positive time course somewhat similar to that originally presented (6, 14, 15, 16) as evidence for residual synaptic currents.

With regard to the assumption of a uniform synaptic current distribution, these authors themselves (10, pp. 533-534, 541-542) suggest that the synaptic current is "largely generated by synapses in proximity to the soma." If this is true, their simple formula cannot be expected to yield synaptic current; it yields something best regarded as an analytical artifact. During a completely passive decay following brief synaptic current, the time courses of V and dV/dt to be expected at the soma must resemble Eqs. [23, 24]. As illustrated in Fig. 4, such passive decay is more rapid than for the uniformly distributed case. It can be shown that the formula, $V/\tau_e + dV/dt$, yields only negative values when τ_e equals τ; however, when τ_e is smaller than τ, this analytical artifact can have negative values during the first few milliseconds (after the brief large current) and then have positive values for the remainder of the decay. This artifact can account, at least approximately, for the "trough," the "reversal of current," and the "low residuum" obtained by Curtis and Eccles (10). Consequently, none of these features should be assumed to represent synaptic current; the "trough" and the "reversal" can be attributed to electrotonic spread from soma to dendrites, as was noted also by Curtis and Eccles (10, p. 541); the positive "residuum" can be attributed to calculation with a low estimate of the membrane time constant.

Comparison of EPSP and IPSP. Curtis and Eccles (10, p. 542) base one of their arguments upon the observation that IPSP decay is faster than EPSP decay. Such observations can be explained simply if one assumes that IPSP initiation is confined more closely to regions near the soma than is EPSP initiation. An illustration of such a difference is provided by Fig. 4; for example, the middle curve could represent an EPSP decay, and the lowest curve could represent an IPSP decay; the uppermost curve represents the simple exponential decay of a uniform disturbance. The logarithmically plotted inset shows that such IPSP decay would be faster than both of the other decays at all times; also, the decay following a brief pulse applied to the soma (see Fig. 3), is very similar to the lowest curve in Fig. 4. Curtis and Eccles (10, p. 542) reject an explanation of this kind on inadequate grounds. Although their τ_{IPSP} and τ_{EPSP}, as well as their τ_m, must be viewed with reservations (because they all appear to be based upon half decay times of curves that must not be assumed to be exponential), the following tentative interpretations would seem reasonable: the fact that their τ_{IPSP} is considerably smaller than the true τ_m, and that it is slightly larger than their estimate of τ_m, is what would be expected if the IPSP is initiated mainly near the soma; also, their larger τ_{EPSP} values may be fairly close to the true τ_m, suggesting that a significant amount of EPSP initiation probably takes place in the dendrites as well as the soma. It may be concluded that the more rapid rate of IPSP decay does not establish a need for prolonged residual synaptic current to explain EPSP decay.

Antidromic Interactions with Synaptic Potentials. Curtis and Eccles (10) base another argument for prolonged residual synaptic current upon their observation of a rebuilding of EPSP following its destruction by an antidromic impulse. Prior to 1956 the same type of experiment was used as evidence for the brevity of synaptic current (2, 9, 13); however, after the 2.5-msec membrane time constant was announced, Eccles (14, pp. 35-36) reinterpreted "small effects" that had been dismissed previously. These small residual depolarizations "are now regularly observed in all experiments in which the conditions are rendered specially favorable by the large size of the EPSP and the low noise level of the intracellular recording (10, pp. 535-536).

There is an alternative explanation for such observations. It is necessary only to assume that at least part of the dendritic surface does not have its synaptic potential destroyed by antidromic invasion; this surviving depolarization would then spread electrotonically to the soma. This suggestion has features in common with the ideas of Fatt (17, p. 74); it is mentioned and rejected by Curtis and Eccles (10, p. 542) on what appear to be inadequate grounds. Although Fatt did place emphasis upon dendritic synapses, this electrotonic explanation would be applicable even if dendritic synaptic activity were not predominant. In view of this alternative explanation, this complicated observation does not establish the existence of a prolonged residual synaptic current.

Effect of Hyperpolarizing Current upon EPSP Decay. The shortening of the time course of an EPSP, generated during the flow of hyperpolarizing current, was first reported and discussed by Coombs, Eccles, and Fatt (9). After the 2.5-msec time constant was announced, Eccles (14, pp. 62-64) postulated that the action of the hyperpolarizing current is to remove or loosen a negatively charged transmitter substance from the sub-synaptic membrane; this action would reduce the postulated residual synaptic currents. These hypotheses are restated by Curtis and Eccles (10, pp. 543-544), who also remark that "no explanation seems to be available for these results if, as suggested by Rall (1957), τ is as long as τ_{EPSP} and there is no residual transmitter action" (10, p. 542). Such an explanation is given below.

It is simplest, but not necessary, to consider an excitatory conductance increase (14, Figs. 22 and 56) to be distributed uniformly over the soma and dendritic membrane; then a purely passive decay would be a simple exponential with the time constant of the membrane. Even in this case, the synaptic current density would not be uniformly distributed when this conductance increase occurs during application of steady hyperpolarizing current. Because such hyperpolarizing current is applied across the soma membrane, the steady state hyperpolarization of the membrane must be greatest at the soma and must decrease electrotonically with distance along the dendrites. Under such conditions, both the density of synaptic current and the amount of depolarization caused by the brief excitatory conductance increase must be greatest at the soma. This nonuniformity will cause a more rapid EPSP decay of the kind illustrated in Fig. 4. Mathematical justification for the applicability of Eq. [23] and of Fig. 4 to the present problem is given in the Theoretical Appendix, following Eq. [23]. A similar argument applies also when the membrane conductance increase is itself not uniformly distributed; the apparent EPSP decay would be expected to be more rapid in the presence of hyperpolarizing current than

in its absence. Similar arguments apply to the case of after-hyperpolarization following a spike (10, pp. 541-543); however this case is complicated by increased membrane conductance and by uncertainties about the amount of dendritic invasion by the spike.

The effects described above must contribute to the acceleration of EPSP decay observed during such hyperpolarization. Whether this effect can account completely for the observed phenomenon must be answered by future research. It is possible that additional complications will have to be taken into consideration. At present, the evidence does not appear to require postulation of significant residual synaptic current, or postulation of a negatively charged transmitter substance that is loosened or removed by the hyperpolarizing current (10, 14).

Generality of the Theory

The theoretical results in the Appendix are more general than most of the applications presented as results in the body of this paper. The theory can be applied to passive membrane responses in other neurons. Applied disturbances need not be limited to steps, pulses, and sinusoidal variation; they can also be applied currents or voltages of arbitrary time course. The transient response is obtained not only for the soma, but also for various distances along a dendritic tree. The theory can also be generalized to include the passive membrane response to various soma-dendritic distributions of synaptic current (27, pp. 520-523).

Theoretical Appendix

The necessary assumptions, definitions, and symbols have been listed and discussed elsewhere (27, 28). A derivation of the fundamental equations can be found in (27, pp. 484-488, 517-523) and in the classical papers on axonal electrotonus (11, 21). Here we begin with the partial differential equation

$$\partial^2 V/\partial X^2 = V + \partial V/\partial T \qquad [1]$$

where $X = x/\lambda$, $T = t/\tau$, and $V \equiv V_m - E$ is the electrotonic potential. The point, $X = 0$, represents the soma-dendritic junction; all dendritic trunks have a common origin there; the soma is treated as a lumped membrane impedance at $X = 0$.[9] The variable, X, represents "electro-

[9] The lumped soma membrane corresponds to the simplifying assumption of soma isopotentiality. During steady state soma-dendritic electrotonus, the error in this assumption may be as large as 2 per cent (8, p. 523). A larger error can occur during the early part of a transient; however, such transient nonuniformity over the soma surface tends to decay with a microsecond time constant (23, 24); see also *Abstracts of National Biophysics Conference,* 1957; full details have not yet been published. The transient error was also found to be small in tests made with a resistance-capacitance network analog, by McAlister (22).

tonic distance" along a dendritic cylinder. When changes in λ are taken into account at points of dendritic branching, Eq. [1] is applicable to an entire dendritic tree, provided that all branch points satisfy the criteria for $B_j = 1$; see (28, pp. 499-501).

When current is applied across the membrane at $X = 0$, the amount of this current must equal the sum of the somatic current and the combined dendritic current. This continuity condition implies

$$I_A = (1/R_s)(V + \partial V/dT) + (\varrho/R_s)(-\partial V/\partial X), \text{ at } X = 0,$$

where I_A is the applied current, R_s is the soma membrane resistance, and ϱ represents the ratio between the combined dendritic input conductance and the soma membrane conductance.[10] Rearrangement results in the soma-dendritic boundary condition

$$\partial V/\partial X = (1/\varrho)[V + \partial V/\partial T - I_A R_s], \text{ at } X = 0. \qquad [2]$$

The other boundary condition is that V remains bounded as X approaches infinity.

This boundary value problem can be solved by methods making use of the Laplace Transformation (3, 4). Using the notation of Churchill (4), Eqs. [1] and [2] became transformed to

$$d^2v/dX^2 = (s + 1)\, v - V(X,0) \qquad [3]$$

and

$$dv/dX = (1/\varrho)[(s + 1)v - V(X,0) - i_A R_s], \text{ at } X = 0, \qquad [4]$$

where v and i_A represent Laplace transforms of $V(X,T)$ and $I_A(T)$, and $V(X,0)$ represents the initial condition of $V(X,T)$.

When the initial condition is zero, this boundary value problem is satisfied by

$$v(X,s) = \frac{C_o(\varrho + 1)\, f(s) e^{-X\sqrt{s+1}}}{s + 1 + \varrho\sqrt{s+1}}, \qquad [5]$$

[10] The combination of all dendritic transient current into a single expression is strictly valid only when all of the dendrites (whether extended cylinders or branching trees) have the same separate transient response characteristic at $X = 0$. This does not require the several dendrites to be of the same diameter. It does require them to be electrotonically equivalent to cylinders of the same electrotonic ($X = x/\lambda$) length. For the solutions given in this Appendix, this electrotonic length is assumed to be effectively infinite. If, instead, finite electrotonic length is explicitly assumed, the boundary value problem is changed and a different class of solutions must be used. Some solutions of this class have been illustrated (26); details will be presented elsewhere.

where $f(s)$ is the Laplace transform of the time course, $F(T)$, of the applied current, and C_0 is a constant defined by

$$C_0F(T) = I_AR_N = I_AR_s/(\varrho + 1). \quad [6]$$

This definition has the merit that C_0 equals the steady electrotonic potential at $X = 0$ during a constant applied current; this is because the steady resistance, R_N, of the whole neuron is smaller than that of the soma, by the factor, $(\varrho + 1)$; see (28).

The general solution above, Eq. [5], is still in terms of Laplace transforms; after inverse Laplace transformation, we can express this general result in the following form

$$V(X,T) = C_0F(T) * K(X,T) \quad [7]$$

where the right hand side represents a concise notation for the convolution operation (4, pp. 35-41), and

$$K(X,T) = (\varrho + 1)e^{\rho X + (\rho^2-1)} \, erfc\left[\frac{X}{2\sqrt{T}} + \varrho\sqrt{T}\right]; \quad [8]$$

see Churchill's Transform No. 87 and his Operation No. 11 (4); the complementary error function, abbreviated *erfc*, is defined, expanded, and tabulated by Carslaw and Jaeger (3, Appendix II).

There are two simple physical interpretations that can be given for the function, $K(X,T)$. It expresses the transient (passive electrotonic) response when $F(T)$ is a very brief pulse, i.e., "unit impulse" (4, 20) applied at $T = 0$. Also, when $F(T)$ is a unit step applied at $T = 0$, $K(X,T)$ defines the time derivative, dV/dT, of the response, as a function of X and T.

Equations [7] and [8] express a general result of considerable power. On the one hand, it can be reduced to numerous simpler special cases; on the other hand, it can serve as the basis for numerical calculation of $V(X,T)$ from any given $F(T)$, and conversely.

The simplest special cases can be obtained by various combinations of setting $X = 0$, $\varrho = 0$ or $\varrho = \infty$, and making $F(T)$ a unit step function or a unit impulse function. When $F(T)$ is a unit step applied at $T = 0$, $f(s) = 1/s$; also, with certain qualifications (4, 20), when $F(T)$ approximates a unit impulse (instantaneous monophasic pulse) applied at $T = 0$, we can treat $f(s)$ as equal to unity.

Soma Response to Applied Current Step. We set $X = 0$ and $f(s) = 1/s$ to obtain

$$V(0,T) = \frac{C_0}{\varrho - 1}\left[\varrho \, erf\sqrt{T} - 1 + e^{(\rho^2-1)T} \, erfc(\varrho\sqrt{T})\right] \quad [9]$$

This is illustrated in Fig. 1 for several values of ϱ. When $\varrho = \infty$, this simplifies to

$$V(0,T) = C_0 \; erf \sqrt{T} \; ; \qquad [10]$$

this limiting case can be interpreted as "dendrites without soma" (25), or in other words, complete dendritic dominance; this equation agrees with results previously obtained for axons (11, 21), for a constant current step applied at $X = 0$. The other limiting case, $\varrho = 0$, can be interpreted as a "soma without dendrites" (25); in this case

$$V(0,T) = C_0(1 - e^{-T}); \qquad [11]$$

this is the well-known result for the application of a constant current step to a lumped resistance in parallel with a lumped capacity, where $T = t/\tau$ and $\tau = RC$.

Soma dV/dt for Applied Current Step. As a basis for linear plotting of data, we make use of the corresponding time derivatives. From Eq. [9] we obtain

$$dV/dt = C_0\left[\frac{\varrho + 1}{\tau}\right] e^{(\varrho^2-1)t/\tau} \; erfc \; (\varrho \sqrt{t/\tau}). \qquad [12]$$

When $\varrho = \infty$, this simplifies to

$$dV/dt = \frac{C_0 e^{-t/\tau}}{\sqrt{\pi\tau t}}, \qquad [13]$$

and when $\varrho = 0$,

$$dV/dt = (C_0/\tau)e^{-t/\tau}. \qquad [14]$$

The deviation of Eq. [12] from Eq. [13] can be assessed. Rearrangement of Eq. [12] gives

$$\sqrt{\pi t} \; (dV/dt)e^{+t/\tau} \propto \varrho \sqrt{\pi t/\tau} \; e^{\varrho^2 t/\tau} \; erfc \; (\varrho \sqrt{t/\tau}). \qquad [15]$$

It can be shown (3, Appendix II) that the expression on the right differs from unity by less than 0.02 when $\varrho \sqrt{t/\tau}$ is greater than 5, and by about 0.1 when $\varrho \sqrt{t/\tau} = 2$; see illustration in Fig. 2, lower left.

Brief Current Pulse Applied to Soma. Assume $F(T)$ to be sufficiently brief that $f(s) = 1$. Then $V(X,T)$ is proportional to $K(X,T)$ of Eq. [8]. When $\varrho = \infty$, this simplifies to

$$V(X,T) = \frac{C_0}{\sqrt{\pi T}} e^{-\frac{X^2}{4T} - T}, \qquad [16]$$

which agrees with an earlier result for cylinders provided by Hodgkin (18, p. 363). When also $X = 0$,

$$V(0,T) = \frac{C_0 e^{-T}}{\sqrt{\pi T}} \qquad [17]$$

and

$$dV/dt = \frac{-C_0 e^{-t/\tau}}{\sqrt{\pi \tau t}} \left(1 + \frac{\tau}{2t}\right). \qquad [18]$$

Eq. [17] has been used for the $\Delta T = 0$ curve in Fig. 3, and Eq. [18] has been used as the basis for linear plotting of experimental pulse data in Fig. 2. When ϱ is not effectively infinite, the time derivative at $X = 0$ is more general than Eq. [18]; then

$$dV/dT = C_0(\varrho + 1)e^{-T}\left[(\varrho^2 - 1)e^{\varrho^2 T} erfc\ (\varrho\sqrt{T}) - \frac{\varrho}{\sqrt{\pi T}}\right]. \qquad [19]$$

When $\varrho\sqrt{t/\tau}$ is not too small, we can use the asymptotic expansion (3, Appendix II) to obtain

$$dV/dT = \frac{-C_0(\varrho + 1)e^{-T}}{\varrho\sqrt{\pi T}}\left[1 + \frac{(\varrho^2 - 1)}{2\varrho^2 T} - \frac{3(\varrho^2 - 1)}{4\varrho^4 T^2} \cdots\right]$$

The limit of this expression, as $\varrho \to \infty$, is Eq. [18]. Such deviations are illustrated in Fig. 2, upper right.

Soma-Dendritic Response to Current Step. For a current step applied at the soma, $f(s) = 1/s$ in Eq. [5]. If we do not set $X = 0$, the inverse Laplace transformation is more complicated than those considered previously. The problem can be solved by noting that

$$\frac{\varrho^2 - 1}{\sqrt{s}\,(s-1)(\sqrt{s} + \varrho)} = \frac{\varrho}{\sqrt{s}\,(s-1)} + \frac{1}{\sqrt{s}\,(\sqrt{s} + \varrho)} - \frac{1}{s-1}$$

and then using Carslaw and Jaeger's transforms, Nos. 13, 19, and 30 (3). The final result can be expressed

$$V(X,T) = \frac{C_0}{2}\left[e^{-X} erfc\left(\frac{X}{2\sqrt{T}} - \sqrt{T}\right) - \left(\frac{\varrho + 1}{\varrho - 1}\right)e^{X} erfc\left(\frac{X}{2\sqrt{T}} + \sqrt{T}\right)\right] + \left(\frac{C_0}{\varrho - 1}\right)e^{\varrho X + (\varrho^2 - 1)T} erfc\left(\frac{X}{2\sqrt{T}} + \varrho\sqrt{T}\right) \qquad [20]$$

For the limiting special case, $\varrho = \infty$, Eq. [20] simplifies to the result previously obtained for axons (21, Eq. 4.1) and (11, p. 452, Eq. 36b).

Nonzero Initial Condition. When $V(X,0)$ is not zero in Eqs. [3, 4], the solution, Eq. [5], must be modified. In particular, if

$$V(X,0) = Ae^{-aX}$$

we obtain

$$v(X,s) = (\varrho+1)C_o\left[\frac{f(s)e^{-X\sqrt{s+1}}}{s+1+\varrho\sqrt{s+1}}\right]+\left[\frac{A}{s+1-a^2}\right]\left[e^{-aX} - \frac{a(\varrho+a)e^{-X\sqrt{s+1}}}{s+1+\varrho\sqrt{s+1}}\right].$$

The inverse Laplace transformation can be obtained by noting that

$$\frac{\varrho^2-a^2}{\sqrt{s}\,(s-a^2)(\sqrt{s}+\varrho)} = \frac{\varrho}{\sqrt{s}\,(s-a^2)} + \frac{1}{\sqrt{s}\,(\sqrt{s}+\varrho)} - \frac{1}{s-a^2}$$

and then using Carslaw and Jaeger's transforms, Nos. 13, 19, and 30 (3). The final result can be expressed

$$\begin{aligned} V(X,T) &= C_oF(T) * K(X,T) \\ &+ (A/2)e^{-aX+(a^2-1)T}\left[1 + erf\left(\frac{X}{2\sqrt{T}} - a\sqrt{T}\right)\right] \\ &+ (A/2)\left(\frac{\varrho+a}{\varrho-a}\right)e^{aX+(a^2-1)T}\,erfc\left(\frac{X}{2\sqrt{T}} + a\sqrt{T}\right) \\ &- \left(\frac{Aa}{\varrho-a}\right)e^{\varrho X+(\varrho^2-1)T}\,erfc\left(\frac{X}{2\sqrt{T}} + \varrho\sqrt{T}\right) \end{aligned} \qquad [21]$$

where $K(X,T)$ is given by Eq. [8].

The same method can be used to generate results for more complicated initial conditions provided these can be expressed as a linear combination of exponential terms like the one considered above.

Passive Decay from Brief Depolarization. Consider passive decay from a soma-dendritic depolarization (or hyperpolarization). If this depolarization can be represented as the initial condition

$$V(X,0) = Ae^{-aX} + B \qquad [22]$$

and there is no current being applied at $X = 0$, then Eq. [21] implies a passive decay with a time course at $X = 0$ that can be expressed

$$V(0,T) = \frac{A}{\varrho-a}\left[\varrho e^{(a^2-1)T}\,erfc\ (a\sqrt{T}) - ae^{(\varrho^2-1)T}\,erfc\ (\varrho\sqrt{T})\right] + Be^{-T}. \qquad [23]$$

This time course is illustrated graphically in Fig. 4, for three values of a, with $B = 0$; of course, the exponential rate of decay that would be associated with B is the same as that associated with A when $a = 0$.

Equation [23] also expresses the time course following a very brief synaptic current pulse whose soma-dendritic density is proportional to Eq. [22]. Although this can be appreciated intuitively, it is demonstrated mathematically by the agreement between Eq. [23] and a similar result obtained by another approach (27, pp. 520-523). If such a soma-dendritic distribution of depolarizing current were instantaneously applied (at $T = 0$) during a maintained steady application of hyperpolarizing current at $X = 0$, this would be equivalent to setting $F(T) = 1$, in Eq. [21], and adding $C_0 e^{-X}$ to the initial condition of Eq. [22]. It follows from Eqs. [21, 7, 8, 9], that the time course, $V(0,T) - V(0,\infty)$, of return to steady state hyperpolarization, is identical with the right side of Eq. [23]. This result is relevant to the interpretation of certain experiments (10); see Discussion, where it is important to note that the distribution of synaptically induced depolarization is different in the presence and absence of applied hyperpolarization.

The time derivative of Eq. [23] is needed in another part of the Discussion; it can be expressed

$$dV/dt = \frac{A}{\tau(\varrho - a)} \left[\varrho(a^2 - 1)e^{(a^2-1)T} \, erfc\,(a\sqrt{T}) - a(\varrho^2 - 1)e^{(\varrho^2-1)T} \, erfc\,(\varrho\sqrt{T}) \right] - (B/\tau)e^{-T} \qquad [24]$$

Voltage Step Applied to Soma. We assume that a voltage step, V_A, is applied across the membrane at $X = 0$ and $T = 0$. This implies the Laplace transformed boundary condition

$$v(0,s) = (V_A - E)/s,$$

where E is the resting potential, and $V(X,0)$ is assumed zero before the step. It follows, therefore, from Eq. [5], that

$$f(s) \propto 1 + \frac{1}{s} + \frac{\varrho\sqrt{s+1}}{s}.$$

The first two terms correspond to the instantaneous current and the steady current that must be supplied to the soma; the last term corresponds to the current being supplied to the dendrites. This implies that after the initial instant,

$$I_A \propto erf\sqrt{T} + \frac{e^{-T}}{\sqrt{\pi T}} + \text{constant};$$

see Churchill's Transform No. 38 and Operation No. 11 (4).

Thus, the time derivative of applied current after the initial instant has a time course given by

$$dI_A/dt \propto -(e^{-t/\tau})/(t^{3/2}) \qquad [25]$$

Sinusoidal Current Applied Across Soma Membrane. Here we make use of the relation between Laplace transform admittance functions and the complex admittance of a-c steady state analysis (20, p. 176; 29, pp. 24-31). Assuming a passive membrane consisting of pure resistance in parallel with pure capacitance, the complex a-c admittance, Y_m, per unit area of membrane, is related to the membrane conductance, G_m, per unit area as follows

$$Y_m/G_m = 1 + j\omega\tau \qquad [26]$$

where $\tau = R_m C_m$ is the membrane time constant, $j = \sqrt{-1}$, and $\omega/2\pi$ is the frequency in cycles per second. If we set $X = 0$ in Eq. [5], the resulting expression implies an admittance function proportional to the expression $s + 1 + \varrho\sqrt{s+1}$. This implies a complex a-c admittance

$$Y_N = [G_N/(\varrho + 1)]\,[Y_m/G_m + \varrho\sqrt{Y_m/G_m}] \qquad [27]$$

for the whole neuron during steady state a-c current application across the membrane at X = 0.

By using the identity

$$\sqrt{1 + j\omega\tau} = \sqrt{r}\, e^{j\theta/2} = \sqrt{(r+1)/2} + j\sqrt{(r-1)/2}$$

it follows from Eqs. [26] and [27], that

$$Y_N = [G_N/(\varrho + 1)]\,[1 + \varrho\sqrt{(r+1)/2} + j(\omega\tau + \varrho\sqrt{(r-1)/2})] \qquad [28]$$

where

$$r = \sqrt{1 + \omega^2\tau^2}\,.$$

This complex admittance implies a phase angle

$$\psi = \arctan\left[\frac{\omega\tau + \varrho\sqrt{(r-1)/2}}{1 + \varrho\sqrt{(r+1)/2}}\right] \qquad [29]$$

for the whole neuron. This is the relation illustrated in Fig. 5, for several values of ϱ. An explicit expression for ϱ in terms of $\omega\tau$ and $\tan\psi$ can be obtained by a rearrangement of Eq. [29]; this gives

$$\varrho = \sqrt{2(r-1)}\left[\frac{\omega\tau - \tan\psi}{\omega\tau\tan\psi - (r-1)}\right]. \qquad [30]$$

The sensitivity of the dependence of ϱ upon values of $\omega\tau$ and ψ can be characterized as follows: when $\omega\tau$ and $\varrho\sqrt{\omega\tau}$ are both large compared

with unity, and ψ has moderate values (from about 60° to about 75°), an error of 20 per cent in the value of $\omega\tau$ would cause 10 per cent error in the value calculated for ρ; also, an error of 1 degree in the value of the phase angle, ψ, would cause 10 per cent error in the value calculated for ρ.

Two possible complications should be mentioned. Application to experimental results may require that phase shift resulting from the physical instrumentation be included in the theoretical formulation. Also, Drs. K. S. Cole and R. FitzHugh have called my attention to the possibility that the soma-dendritic membrane impedance may contain additional reactive components like those of squid membrane. In the case of squid giant axons, three such reactances have been characterized. Of these, the one corresponding to the "sodium-on" process of the Hodgkin and Huxley model, is the most important for the present problem. This reactance can be treated as either a capacitance with series resistance, or a negative inductance with negative series resistance; at 6.3° C, it has a time constant of about 0.24 msec, associated with a resistance of about 2.3×10^3 Ωcm^2 (Cole and FitzHugh, personal communication; also see 5). When Eqs. [26] to [30] are modified to include this reactance, calculations with squid membrane parameters indicate a difference of about 1 degree in the phase angle for a frequency of 1 kilocycle per second and $\rho = 10$; higher frequencies result in smaller differences. Furthermore, it is possible that the motoneuron membrane exhibits less of this reactance than does squid membrane; experimental evidence from cat motoneurons provides some support for this possibility (personal communication with K. Frank).

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