THE CYLINDRICAL CELL

WITH A TIME-VARIANT MEMBRANE RESISTANCE

MEASURING PASSIVE PARAMETERS

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ABSTRACT   The passive electrical properties of a cable can be measured by injecting
a step of current at a point and fitting the resulting potentials at several positions
along the cable with analytic solutions of the cable equation.   An error analysis is
presented for this method (which is based on constant membrane resistance) when the
membrane resistance is not constant, but increases linearly with time.   The increase of
r_m produces a "creep" in the membrane potential at long times, as observed in cardiac,
skeletal, and smooth muscle.   The partial differential equation describing the time-
varying cable was solved numerically for a step of current and these "data" were fit
by standard constant-resistance methods.   Comparing the resulting parameter values
with the known true values, we suggest that a correction of the standard methods is
not satisfactory for resistance changes of the kind observed; instead, the cable equation
must be solved again for the particular form of $r_m(t)$.   The practical implementa-
tion of a method by Adrian and Peachey for measuring the membrane capacitance and
an approximate method for estimating the rate-of-change of membrane resistance are
discussed in appendices.

INTRODUCTION

In a companion paper (1) we encountered the problem of determining the electrical
constants of a synthetic strand of cardiac muscle in which the membrane resistance
varied with time. In this circumstance, the solution of the partial differential equation
for a one-dimensional cable has no straightforward solution; indeed, no analytic solu-
tion could be found for the case of interest in which the membrane resistance varied
linearly with time. The only recourse was to fit the recorded waveforms with numerical
solutions of the equation and so obtain the cable parameters that gave the best fit in
each case.

The characteristic feature in the recordings from such preparations was that the
membrane potential displacement in response to a step of current did not approach a
steady value, but crept up slowly throughout the duration of the step. This kind of
response has apparently been observed, not only in other preparations of cardiac
muscle (2–6), but also in skeletal (7–9) and smooth (10–12) muscle. The solution to our
problem had, therefore, a broader application.   In a strict sense, the "standard"

methods of Hodgkin and Rushton (13) for obtaining the electrical properties of a cylindrical cell based on the analytic solution of the cable equation are invalidated in these circumstances. However, since the alternative of obtaining numerical solutions of the cable equations is, at best, inconvenient, and the computation facilities are not generally available, we inquired into the possibility that the standard methods might still be used to obtain at least an approximate value for some of the cable parameters. In particular, we have attempted to evaluate the error in the values of the cable parameters that would result from using the standard methods under such circumstances and have developed criteria to guide the investigator in their safe use.

DEFINITIONS

(See text for discussion of normalized units.)

b	Slope of early V vs. $T^{1/2}$ plot.
c_m	Membrane capacitance per unit length.
c_A	c_m from Adrian-Peachey (8) method.
c_G	c_m from Gage-Eisenberg (14) method.
c_H	c_m from half-maximum (13) method.
I_0	Amplitude of input current step.
r_i	Longitudinal resistance per unit length.
r_m	Membrane resistance per unit length.
$\bar{r}_m$	Initial value of membrane resistance.
R_o	Input resistance of cable at $X = 0$.
t	Time.
T	Time in normalized units.
T_{max}	Largest value of T used in finding c_A.
$T^0_{1/2}$	$X = 0$ intercept of half-maximum plot.
V	Transmembrane potential.
x	Distance along the cable.
X	Distance x in normalized units; current source at $X = 0$.
α	Time rate of increase of membrane resistance.
δ	Spacing of voltage and current electrodes.
λ	Length constant.
ν	Slope of line in half-maximum plot.
τ_m	Membrane time constant.

METHODS

The partial differential equation

$$\frac{1}{r_i} \frac{\partial^2 V}{\partial x^2} - c_m \frac{\partial V}{\partial t} - \frac{V}{r_m(t)} = 0 \tag{1}$$

with boundary conditions of an input current step at $x = 0$ and zero axial current at the other end was solved by the Crank-Nicolson implicit method (15). The membrane resistance r_m was assumed to increase linearly with time:

$$r_m(t) = \bar{r}_m(1 + \alpha t) \tag{2}$$

where $\bar{r}_m$ and α are constants.

A normalized system of units was used in all calculations, i.e. times are given in units of membrane time constants and lengths are given in units of length constants (both referred to $t = 0$ when the membrane resistance began to vary with time); to avoid confusion, the normalized variables will be represented throughout the remainder of this paper by the symbols T and X. At $T = 0$, resistances and capacitances have a value of 1.00. The amplitude of the input current step was set to make $V(0, \infty) = 1$ when the membrane resistance was constant. A cable length of 5 (length constants) was simulated in 100 segments with "electrodes" located at 0.05, 0.5, 1.0, and 1.5. The time step of integration was 0.00125 (time constants), a value chosen to make the mesh ratio (see, for example, 16) equal to 0.5.

All straight lines were fitted numerically by the least-squares technique. Arrival times for the half-maximum point at the electrode locations were computed by treating the potential at $T = 5$ as the "maximum" value and interpolating between potentials recorded at time intervals of 0.1 (time constants).

RESULTS

Our purpose was to evaluate the applicability of methods for obtaining the passive electrical properties of a one-dimensional cable in a situation in which they are (sensu stricto) inapplicable, in particular, where the membrane resistance is a linear function of time. It is natural to present this evaluation in the style of a classical cable analysis in which the experimental data—the potential displacement at various sites in response to a step of current—are obtained from numerical solutions of Eqs. 1 and 2. From this data, the input resistance, the length constant, and the time constant are determined and from these (by the appropriate formulae) the electrical cable parameters were derived. Comparisons between these "experimentally" determined values and the known true values from which the numerical solutions were obtained will be described in the relevant section of the results.

Resistance

Fig. 1 shows two examples of computed potential distributions $V(X, T)$ for two rates-of-change of membrane resistance, $\alpha = 0$ and $\alpha = 0.2$ (the latter is comparable to the value observed in a synthetic strand of cardiac muscle, 1). In the following, this data will be analyzed by standard cable methods, with the distribution in Fig. 1 A ($\alpha = 0$) serving as a control and error check. In Fig. 2, the potentials at $T = 5$ are plotted against distance on a semi-logarithmic scale. Straight lines fitted through these points yield the input resistance R_0 (the intercept at $X = 0$) and the length constant λ (the negative of the reciprocal of the slope). With these two "measurements," r_i and r_m were calculated from the following equations and the values listed in Table I.

$$r_i = \frac{R_0}{\lambda} \tag{3}$$

$$r_m = R_0 \lambda \tag{4}$$

Capacitance

Three approximate methods have been suggested for extracting the additional information required to calculate the membrane capacitance, c_m. Hodgkin and Rushton (13)
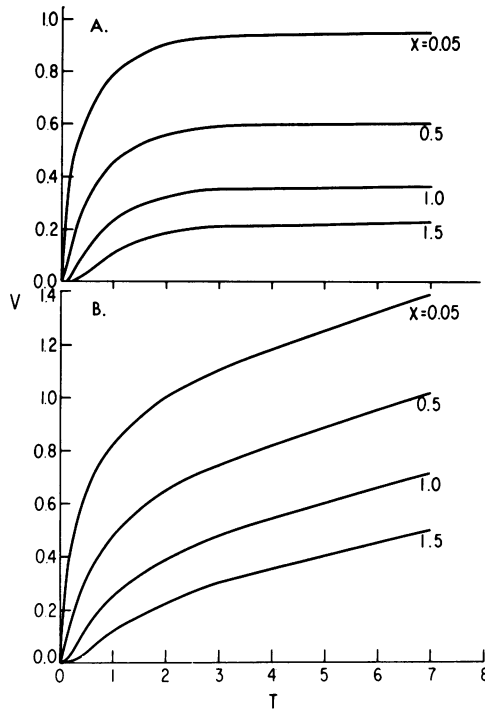
FIGURE 1   Transmembrane potential $V(x, t)$ for a step input of current at the end of a cable of length 5.   A: constant membrane resistance ($\alpha = 0$).   B: $\alpha = 0.2$.   See text for discussion of units.

refer to a method that uses the velocity of propagation of the half-maximum potential. The time of occurrence of the half-maximum potential at each electrode is plotted against distance from the current injection point and a straight line fitted through these points has a slope ν of approximately $\tau_m/2\lambda$, i.e. the half-maximum point propagates at a velocity of about $2\lambda/\tau_m$ (see 17).   Fig. 3 shows this plot for the distributions of
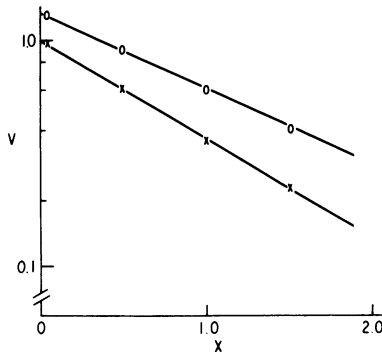

FIGURE 2   Transmembrane potentials from Fig. 1 at $T = 5$ plotted as a function of distance. Crosses: $\alpha = 0$ (Fig. 1 A).   Circles: $\alpha = 0.2$ (Fig. 1 B).   Straight lines fitted by least-squares method.

TABLE I
NORMALIZED CABLE PARAMETERS DERIVED FROM DATA IN FIG. 1
BY "STANDARD" METHODS

Data	r_i	r_m	c_A	c_G	c_H
Fig. 1 A($\alpha = 0$)	1.00	1.00	1.32	1.04	1.00
Fig. 1 B($\alpha = 0.2$)	1.05	1.67	1.37	1.30	1.21

r_i and c's should be compared with true values of 1.00 and r_m with $1 + 5\alpha$ (see text).

Fig. 1. Gage and Eisenberg (14) showed that the $X = 0$ intercept $T^0_{1/2}$ of the same plot is equal to $0.2274\tau_m$ (for time-invariant membrane) and we have calculated membrane parameters by this method also. Finally, Adrian and Peachey (8) described a method that derives c_m from the slope b of the early potential record near $x = 0$ (see Appendix A). In Fig. 4, the potentials at the electrode closest to the current injection point have been plotted versus time with $T_{max} = 0.25$. The straight line was fitted to the points without the requirement of passing through the origin. Only a single line and set of points are shown, since the points for $\alpha = 0$ and $\alpha = 0.2$ are indistinguishable on this graph.

The membrane capacitance was thus calculated by each of the following equations and the values were listed in Table I:

$$c_A = \frac{(2I_0)^2 R_0}{\pi\lambda b^2} \tag{5}$$

$$c_G = \frac{T^0_{1/2}}{0.2274\, R_0\lambda} \tag{6}$$
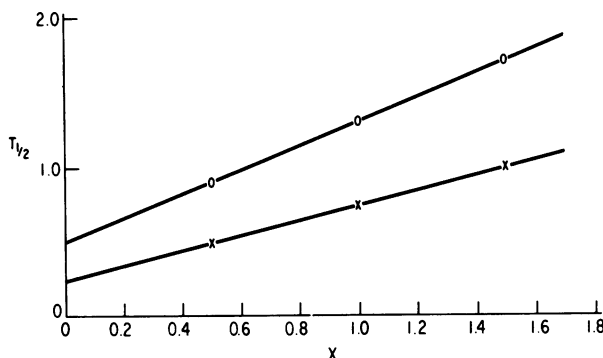
$$c_H = \frac{2\nu}{R_0} \tag{7}$$

FIGURE 3 Time of occurrence of half-maximum potentials at the three distant electrode sites plotted from the distributions of Fig. 1 as a function of distance. Crosses: $\alpha = 0$ (Fig. 1 A). Circles: $\alpha = 0.2$ (Fig. 1 B). Straight lines fitted by least squares method with a free intercept.
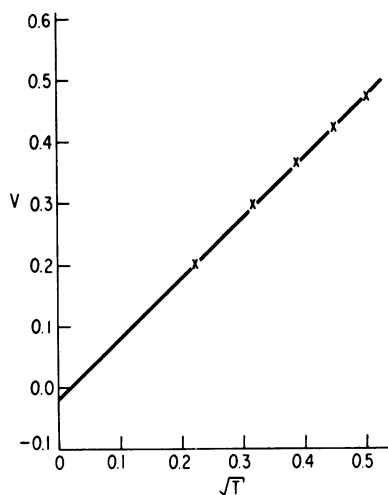
FIGURE 4 Early transmembrane potential at $X = 0.05$ for $\alpha = 0$ (Fig. 1 A) plotted versus $t^{1/2}$ for Adrian and Peachey (8) method. Straight line fitted by least squares method.

(I_0 is multiplied by a factor of 2 in Eq. 5 because the numerical solutions were for a semi-infinite cable.) When r_m is constant ($\alpha = 0$), the standard methods give accurate values for the cable parameters (except for the practical application of the method of Adrian and Peachey: see Appendix A).

When $\alpha = 0.2$, the resistance values deviate considerably from unity, primarily because there is no way of getting a good estimate of the input resistance when it is continually changing. Capacitance values based on the propagation of a "half-maximum" are also in error because there is no steady maximum. The error in c_A is not much greater at $\alpha = 0.2$ than at $\alpha = 0$, because the method is based on measurements during a short time interval during which r_m changes by only a small percentage.

Error Dependence on Alpha

The calculations illustrated above for two values of α were repeated for additional values up to $\alpha = 0.8$ and the results are shown in Fig. 5 A. For r_i and c_m, the deviations from the known value of 1.00 are plotted as functions of α, the rate of increase of r_m. The measurement of r_m itself is compared with the known value at the end of the measurement period, i.e. at $T = 5$.

While there is considerable error in most of the parameters for $\alpha > 0$, the increase with α is not uniform or even monotonic. The error in r_i does increase uniformly, however, and the estimate is remarkably good, considering the substantial change in shape of the potential distributions. The reason for this is evident in Eq. 3; as r_m increases, both R_0 and λ increase and their ratio stays approximately constant. The cancellation is not exact, however, because the effects are not in phase. The measured value of r_m lies, as might be expected, between the value 1.00 at the start of the current pulse and the instantaneous value at $T = 5$ when λ and R_0 are measured. The lags in
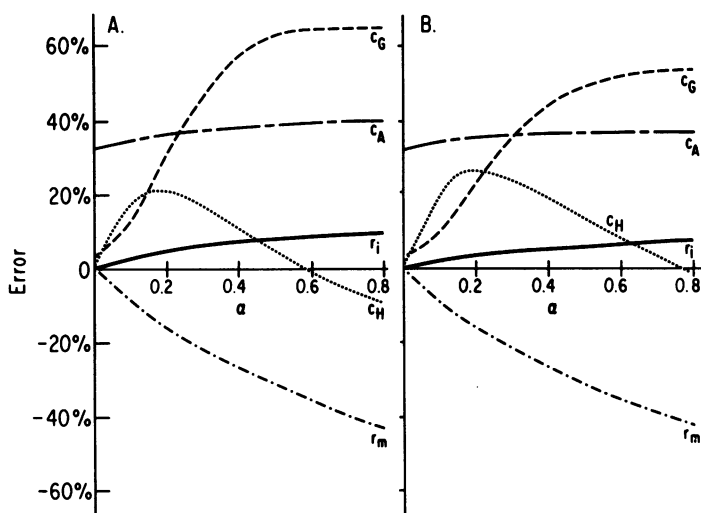
FIGURE 5 Error resulting from calculating (by standard methods) the passive electrical parameters of a cable in which the membrane resistance, r_m, increases linearly with time, $\dot{r}_m = r_m(1 + \alpha t)$, plotted as a function of α. A: electrodes at $X = 0.05, 0.5, 1.0,$ and 1.5 (same locations as in Figure 1). B: electrodes at $X = 0.05, 0.4, 0.8,$ and 1.2.

effect on R_0 and λ which nearly cancelled out for r_i now combine (Eq. 4) to produce a larger error in r_m.

The errors in parameter values also vary with the spacing of the measuring electrodes. In Fig. 5 B (where the electrode spacing has been reduced to 0.4) the error curves for c_G and c_H are changed substantially while the others are only slightly affected, compared with Fig. 5 A.

DISCUSSION

It was our original hope in undertaking these calculations that by tabulating a series of correction factors from numerical calculations as described above, we could derive reasonably accurate values for passive membrane parameters by correcting values obtained from "standard" methods when the membrane resistance increases with time. The results of the calculations show that the standard methods (based on constant parameters) do indeed produce errors in computing the membrane resistance or capacitance when the resistance is changing with time. However, the magnitude of these errors, and hence the correction factor, depends strongly on unknown quantities—the membrane time constant and length constant (the scales in Fig. 5 are functions of these quantities). This means that at best an iterative process would have to be used to correct values obtained by standard methods and a large number of error curves would be necessary to represent the error surfaces adequately. Moreover, even if it were practical to correct derived passive parameters by using such error curves, a different set of curves would be necessary each time a new functional dependence of r_m on t was assumed. Therefore, the only way to derive accurate passive membrane

parameters from a cable when r_m varies with time is to solve the appropriate partial differential equation numerically and fit parameters by nonlinear curve-fitting techniques, as we chose to do originally (1).

The curves in Fig. 5 do have some general utility; they can be used to judge when a full numerical fit is necessary. The linear form for $r_m(t)$ should be a good approximation for other functional forms when the total variation of r_m is small. To use Fig. 5, it is necessary to know the value of α for the experimental data: a means of estimating α is described in Appendix B based on the time and length constants from standard methods.

It might be argued that the case we have chosen (r_m changing uniformly along a cable) is likely to represent the true events in only a limited number of cases and a more likely general circumstance is that r_m varies with distance as well as time. It is unlikely, however, that this or any other choice of assumptions would alter our basic conclusion, namely that the standard methods cannot be used when there is substantial creep for whatever cause. Should one pursue the alternative of numerical computation, as we did previously (1), than the choice of a cause for the creep is decisive and must be based on other knowledge of the preparation.

ACKNOWLEDGMENT

APPENDIX A

In a paper on the membrane capacitance of frog skeletal muscle fibers, Adrian and Peachey (8) described an approximate method for extracting the membrane capacitance from square-pulse measurements on a cable-like preparation when the membrane resistance r_m is not known. If $(t/\tau_m)^{1/2}$ is small, the error function in the Hodgkin and Rushton (13) solution for $V(0, t)$ is replaced by a square root:

$$V(0, t) \simeq I_0 \left[\frac{tr_i}{\pi c_A} \right]^{1/2} \tag{A1}$$

Measured values of $V(0, t)$ at early times are plotted against the square root of t and then

$$c_A = \frac{r_i}{\pi b^2} \tag{A2}$$

where b is the slope of a straight line fitted through the experimental points.

The accuracy of the capacitance value, c_A, obtained from this approximation depends on the details of how the approximation is applied to the data, e.g. what range of time is used in fitting the line, whether or not the line is fitted through the origin, etc. To evaluate the effects of these details, approximate membrane capacitances have been calculated by the method of Adrian and Peachey from solutions for $V(x, t)$ in a one-dimensional cable in response to a step of input current at $x = 0$. A normalized system was used so that all times are in units of membrane time constants and the approximate capacitances can be compared to a correct value of 1.00; again, the symbols T and X will be used for the normalized variables. For
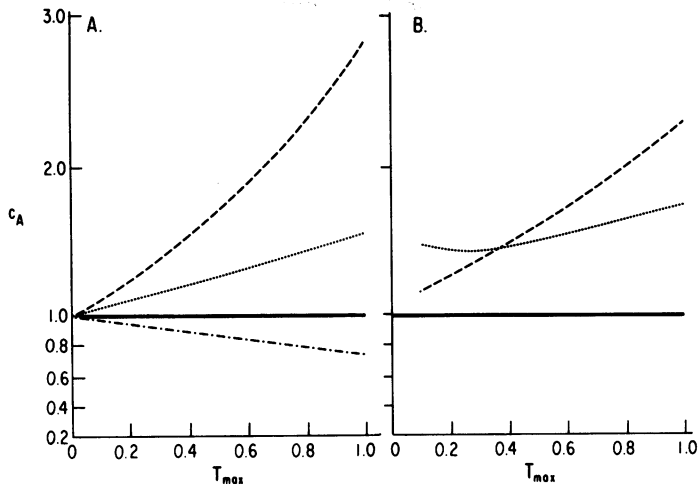
FIGURE 6 Membrane capacitance c_A calculated by the Adrian-Peachey (8) method for various values of T_{max} and methods of fitting. Solid line: correct value. Dashed line: line fit with adjustable intercept. Dotted line: line fit through origin. Dot-dash line: relative accuracy of square-root approximation for error function. A: values based on potentials measured at $X = 0$. B: values based on potentials measured at $X = 0.05$.

$X = 0$, Hodgkin and Rushton's solution was evaluated by summing an asymptotic series for the error function. For $X > 0$, solutions for $V(X, T)$ were obtained numerically by the implicit Crank-Nicolson method (15). A few of these solutions were checked for accuracy with the analytic solutions of Hodgkin and Rushton.

First, what is a reasonable value for T_{max}, the time limit for plotting V, so that T for any point is "small compared with the membrane time constant"? In Fig. 6 A, the lowest curve shows how the error of the square root approximation for the error function increases as T_{max} increases. The error in the derived c_A is larger, however, since c_A is proportional to the reciprocal of the square of the slope. The upper two curves in Fig. 6 A show the values of c_A derived from straight lines fitted through the experimental points either with a free intercept at $T = 0$ or passing through the origin. Clearly, a much more accurate value of c_A is obtained by fitting the line through the origin.

This conclusion must be qualified, however, because the experimental voltages usually plotted are not $V(0, T)$, but rather $V(\delta, T)$ where δ is the (small) spacing between the current and voltage electrodes. To illustrate the effect of nonzero δ, Fig. 6 B shows the results for c_A when $\delta = 0.05$ (length constants), a reasonable electrode spacing. Now the error in c_A does not approach zero as T_{max} is made smaller, but actually goes through a minimum at $T_{max} = 0.25$. This is a result of the propagation of V from $X = 0$ to $X = \delta$; there is a delay in V at $X = \delta$ and the slope of V is no longer given accurately by the chord. In fact for $T_{max} < 0.37$, c_A derived from a line fitted with a free intercept is more accurate. The error in the approximate membrane capacitance from the method of Adrian and Peachey thus increases sharply as δ is made larger than zero and accuracy requires the use of potentials recorded as close as possible to the current injection point (but this is forbidden by three-dimensional considerations, 18).

APPENDIX B

No exact formula for computing α from voltage records has been found when the membrane resistance varies with time, but the following approximate method is sufficiently accurate for

estimating the error in fitting passive parameters. According to the solution of Hodgkin and Rushton (13) for the case of constant membrane resistance, the potential $V(x, t)$ is proportional to the length constant λ. Taking the ratio of potentials at two times, $t_2 > t_1 \gg t$ and the same position x,

$$\frac{V(x, t_2)}{V(x, t_1)} \sim \frac{\lambda_2}{\lambda_1} = \left[\frac{r_m(t_2)}{r_m(t_1)}\right]^{1/2} = \left[\frac{1 + \alpha t_2}{1 + \alpha t_1}\right]^{1/2} \tag{B1}$$

Let the ratio of voltages in Eq. B 1 be equal to a and solve for α:

$$\alpha = \frac{a^2 - 1}{t_2 - t_1 a^2} \tag{B2}$$

For example, when $t_1 = 4$ and $t_2 = 5$ (time constants), taking a from the numerical calculation for $\alpha = 0.1$ gives an approximate value of α from Eq. B2 of 0.118. Eq. B2 gives values of α that are not in error by more than 25% for $\alpha < =0.8$ with these values for t_1 and t_2.

REFERENCES

1. LIEBERMAN, M., T. SAWANOBORI, J. M. KOOTSEY, and E. A. JOHNSON. 1975. A synthetic strand of cardiac muscle. Its passive properties. *J. Gen. Physiol.* **65**:527.
2. WEIDMANN, S. 1952. The electrical constants of Purkinje fibers. *J. Physiol. (Lond.).* **118**:348.
3. CORABOEUF, E., and S. WEIDMANN. 1954. Temperature effects on the electrical activity of Purkinje fibers. *Helv. Physiol. Pharmacol. Acta.* **12**:32.
4. SAKAMOTO, Y., and M. GOTO. 1970. A study of the membrane constants in the dog myocardium. *Jpn. J. Physiol.* **20**:30.
5. BONKE, F. I. M. 1973. Passive electrical properties of atrial fibers of the rabbit heart. *Pflügers Arch. Eur. J. Physiol.* **339**:1.
6. BONKE, F. I. M. 1973. Electrotonic spread in the sinoatrial node of the rabbit heart. *Pflügers Arch. Eur. J. Physiol.* **339**:17.
7. FALK, G., and P. FATT. 1964. Linear electrical properties of striated muscle fibers observed with intracellular electrodes. *Proc. R. Soc. (Lond.). B. Biol. Sci.* **160**:69.
8. ADRIAN, R. H., and L. D. PEACHEY. 1965. The membrane capacity of frog twitch and slow muscle fibers. *J. Physiol. (Lond.).* **181**:324.
9. SEVCIK, C., and T. NARAHASHI. 1972. Electrical properties and excitation-contraction coupling in skeletal muscle treated with ethylene glycol. *J. Gen. Physiol.* **60**:221.
10. TOMITA, T. 1966. Electrical responses of smooth muscle to external stimulation in hypertonic solution. *J. Physiol. (Lond.).* **183**:450.
11. ABE, Y., and T. TOMITA. 1968. Cable properties of smooth muscle. *J. Physiol. (Lond.).* **196**:87.
12. MEKATA, F. 1974. Current spread in the smooth muscle of the rabbit aorta. *J. Physiol. (Lond.).* **242**:143.
13. HODGKIN, A. L., and W. A. H. RUSHTON. 1946. The electrical constants of a crustacean nerve fiber. *Proc. R. Soc. (Lond.). B Biol. Sci.* **133**:444.
14. GAGE, P. W., and R. S. EISENBERG. 1969. Capacitance of the surface and transverse tubular membrane of frog sartorius muscle fibers. *J. Gen. Physiol.* **53**:265.
15. CRANK, J., and P. NICOLSON. 1947. A practical method for numerical evaluation of solutions of partial differential equations of the heat-conduction type. *Proc. Camb. Philos. Soc.* **43**:50.
16. GERALD, C. F. 1970. Applied Numerical Analysis. Addison-Wesley Publishing Co., Inc., Reading, Mass.
17. JACK, J. J. B., D. NOBLE, and R. W. TSIEN. 1975. Electric Current Flow in Excitable Cells. Clarenden Press, Oxford University Press, London.
18. EISENBERG, R. S., and E. A. JOHNSON. 1970. Three-dimensional electric field problems in physiology. *Prog. Biophys. Mol. Biol.* **20**:1.