Time-Course of Potential Spread along a Skeletal Muscle Fiber under Voltage Clamp

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ABSTRACT The equations describing the time-course of potential spread into a terminated segment of muscle fiber are given for the condition that a step of voltage is applied at $x = 2\ell$. Measurements of $V(2\ell) - V(\ell)$ were made at 16.7-19.5°C, using a three-microelectrode voltage clamp, to compare with the theory. Best least squares fits of calculated curves to data obtained in Ringer's solution (5 mM K) gave $G_L = 10 \mu$mho/cm and $C_m' = 1.6 \mu$F/cm$^2$. Similar measurements in 100 mM K solution, with the inward rectifier shut off by a positive prepulse, gave $G_L = 20 \mu$mho/cm and $C_m' = 2.0 \mu$F/cm$^2$. The time-course of $V(2\ell) - V(\ell)$, measured when the inward rectifier was fully activated by a negative prepulse, was in good agreement with the curve calculated assuming no change in $G_L$ and $C_m'$ and that the only effect of the negative prepulse was to increase the conductance of surface and tubular membranes.

INTRODUCTION

The preceding paper (Schneider and Chandler, 1976) described a method for measuring electrical capacitance in skeletal muscle fibers using a small voltage step applied with a three-microelectrode voltage clamp. With this technique it was relatively easy to investigate the effect of membrane potential on capacitance by superimposing the small test step on a conditioning prepulse. The changes in capacitance which were found appeared to be due to two different mechanisms, an inherent voltage dependence of the capacitative properties of muscle membrane and a voltage dependence of the apparent or effective capacitance due to changes in the T-system space constant $\lambda_T$.

One of the advantages of the method is its relative simplicity. The charge necessary to change the potential across the fiber capacitance is simply obtained by integrating the transient component of $\Delta V(=V_2 - V_1)$, the voltage difference which can be considered to be proportional to membrane current. Unfortunately, however, the method does not give information concerning the individual contributions of surface and of tubular membranes. Furthermore, if a change in $\lambda_T (= \sqrt{G_L/G_w})$ occurs the method does not indicate whether it is due to a change in $G_w$, the conductance of tubular membranes per unit volume, or to a change in $G_L$, the radial conductance of the lumen of the T system.

One way to obtain information on these points is to analyze in detail the time-
course of the signal corresponding to membrane current. The general aim of this paper is to show how this can be done if the electrical properties of the T system can be described by a model which has an equivalent circuit representation given by Fig. 1. Such a description is possible for the distributed model, both with (Peachey and Adrian, 1973) or without (Adrian et al. 1969; Schneider, 1970) an access resistance $r_{ac}$, although there is no simple relationship between each RC element and a particular part of the T system.

**METHODS**

The voltage clamp technique and data-sampling procedures were similar to those described in the preceding paper (Schneider and Chandler, 1976). The only change was that a Fabritek Signal Averager (Nicolet Instrument Corp., Madison, Wis., model 1072) was added to the equipment for the purpose of sampling data pointwise in time.

When a voltage step is imposed at $x = 2\ell$, there is a delay associated with the voltage at $x = \ell$ reaching a steady level. The magnitude of this delay depends, in part, on both the electrode spacing $\ell$ and the delays introduced by the T system. Since the point of the experiments was to separate surface and tubular contributions to capacitance, using tubular delay to distinguish the two components, it was important to have the T system contribute as large a fraction as possible of the total delay. This was accomplished by using a short electrode spacing, $172 \mu m \leq \ell \leq 190 \mu m$. $\ell$ varied from 19 to 38 $\mu m$.

The test pulses used for the capacitance measurements were approximately $\pm 10$ mV, duration 14 ms, exponentially rounded with time constant $\tau_i$ (12–30 $\mu s$). The "on" transients were monitored in the usual way using the integral method with sampling intervals of 2 ms. In addition, pointwise samples were taken by the Fabritek during the 1-ms period just preceding the test pulse and for the first 10 ms after the step. The Fabritek sampling rate was 10 KHz and there was a 20-$\mu s$ ($= \tau_d$) filter in the input circuit. At the end of each experiment the digital numbers stored in the Fabritek were written down by hand. During the initial part of the transient, when $AV$ was changing rapidly, every point was recorded. Later in the step, every second or fifth point was recorded (see Fig. 2, traces d, and Fig. 3).

Two solutions were used, a Ringer's solution with 5 mM-K (similar to solution A in Table I of the preceding paper but containing K instead of Rb) and a 100 mM-K SO$_4$.
solution (solution D, preceding paper). Measurements of specific conductivity gave values of 12.7 mmho/cm for the Ringer's solution and 17.1 mmho/cm for the 100 mM-K solution, both at 22.4°C. Temperature in the muscle experiments ranged from 16.7 to 19.5°C. The sartorius muscles were stretched to 1.3 times slack length.

**THEORY**

The purpose of this section is to develop the equations which describe the spread of voltage along a terminated fiber when a step change is imposed at \( x = 2\ell \). The equivalent circuit for the surface membrane plus the T system is considered to be represented by the circuit in Fig. 1.

**Cable Equation with Initial and Boundary Conditions**

The cable equation for voltage along the fiber is given by

\[
\frac{\partial^2 V}{\partial x^2} = \frac{V}{\lambda^2} + r_i c_m \frac{\partial V}{\partial t} + \sum_{n=1}^{N} r_n c_n \frac{\partial V_n}{\partial t}.
\]  

(1)

\( V \) is the voltage across \( c_m \) and \( V_n \) is the voltage across \( c_n \); \( r_i \) is the internal longitudinal resistance per unit length and \( \lambda \) is the DC space constant of the fiber (= \( \sqrt{r_i c_m} \)). For each series \( r_n c_n \) element there is a separate equation

\[
c_n \frac{\partial V_n}{\partial t} = \frac{V - V_n}{r_n}, \quad n = 1, 2, \ldots, N.
\]  

(2)

The mathematical approach for solving Eqs. 1 and 2 is similar to the one used in the Appendix of Chandler et al. (1976) for the Falk and Fatt (1964) circuit \( (N = 1 \) in Fig. 1). The solution will be derived for the "off" response, i.e. when the voltage at \( x = 2\ell \) is stepped from the pulse voltage \( V_p \) to 0 at time \( t = 0 \). Once this is known superposition can be used to obtain the on response.

The initial conditions for the off response are given by

\[
V(x,0) = V_p \frac{\cosh (x/\lambda)}{\cosh (2\ell/\lambda)}, \quad 0 \leq x < 2\ell
\]  

(3)

and

\[
V_n(x,0) = V_p \frac{\cosh (x/\lambda)}{\cosh (2\ell/\lambda)}, \quad 0 \leq x \leq 2\ell, \quad n = 1, 2, \ldots, N.
\]  

(4)

The boundary conditions are

\[
V(2\ell t) = 0,
\]  

(5)

\[
(\partial V/\partial x)_{x=0} = 0.
\]  

(6)

Eqs. 3 and 4 arise from the steady-state voltage along the cable which is established during the pulse. Eq. 5 gives the condition of pulse off at \( x = 2\ell \) and Eq. 6 follows from the requirement that the longitudinal current is zero at \( x = 0 \), the end of the fiber.

**General Solution**

The general solution for Eqs. 1 and 2 with conditions in Eqs. 3–6, found by separation of variables, is given by
\[ V = \sum_{k=0}^{\infty} A_k \cos (\mu_k x) \phi_k(t), \]  
\[ V_n = \sum_{k=0}^{\infty} A_k \cos (\mu_k x) \psi_{kn}(t), \quad n = 1, 2, \ldots, N. \]

where

\[ \mu_k = \frac{(2k + 1)\pi}{4\ell}, \quad k = 0, 1, 2, \ldots \]

\[ \phi_k(0) = 1, \]
\[ \psi_{kn}(0) = 1, \]
\[ \phi_k(\ell) = 0, \]
\[ \psi_{kn}(\ell) = 0. \]

To give the initial voltage distribution, conditions in Eqs. 3 and 4, the coefficients \( A_k \) must satisfy

\[ \sum_{k=0}^{\infty} A_k \cos (\mu_k x) = V_p \frac{\cosh(x/\lambda)}{\cosh(2\ell/\lambda)}, \quad 0 \leq x < 2\ell. \]  

The coefficients can be evaluated by multiplying both sides of Eq. 14 by one of the cosine terms, then integrating from \( x = 0 \) to \( x = 2\ell \). Only one term on the left is different from zero so that by rearrangement one obtains

\[ A_k = (-1)^k \frac{V_p}{\ell} \frac{\mu_k}{1/\lambda^2 + \mu_k^2}. \]  

The initial conditions for \( V \) and \( V_n \) are the same so that the solutions for \( V \) and \( V_n \) (Eqs. 7 and 8) differ only in the functions \( \phi_k(t) \) and \( \psi_{kn}(t) \).

**Evaluation of the Functions \( \phi \) and \( \psi \)**

When Eqs. 7 and 8 are inserted into Eqs. 1 and 2, the following set of equations are obtained for each value of \( k \):

\[ -\mu_k^2 \phi_k = \frac{1}{\lambda^2} \phi_k + r \epsilon_m \frac{d\phi_k}{dt} + \sum_{n=1}^{N} r \epsilon_n \frac{d\psi_{kn}}{dt}, \]  
\[ \tau_n \frac{d\psi_{kn}}{dt} = \phi_k - \psi_{kn}, \quad n = 1, 2, \ldots, N \]

where \( \tau_n = r \epsilon_n \). Eqs. 17 can be combined with Eq. 16 to give

\[ -\mu_k^2 \phi_k = \frac{1}{\lambda^2} \phi_k + r \epsilon_m \frac{d\phi_k}{dt} + \sum_{n=1}^{N} \frac{r_n}{r_m} (\phi_k - \psi_{kn}), \]  
which can be rearranged

\[ \frac{d\phi_k}{dt} = -f_k \phi_k + \frac{\xi_k}{r_m \epsilon_m} \psi_{kn}, \]
where

\[ f_k = \frac{1}{r_{km}}\left(\mu_k^2 + \frac{1}{\lambda^2} + \sum_{n=1}^{N} r_n\right). \tag{20} \]

The solution of Eqs. 17 and 19 for \( \phi_k(t) \), derived in the Appendix, is

\[ \phi_k(t) = -\sum_{i=1}^{N+1} \frac{\mu_i^2/r_i + g_m}{p_{ki} \left(\frac{dy_m}{dp}\right)_{p=p_m}} \exp(p_{ki}t), \tag{21} \]

where

\[ y_m(p) = g_m + PC_m + \sum_{n=1}^{N} \frac{PC_n}{1 + p r_n} \tag{22} \]

and \( p_{ki} \) is the \( l \)th root of

\[ y_m(p) = -\mu_k^2/r_k. \tag{23} \]

The function \( y_m(p) \) is the admittance of the circuit in Fig. 1, which is an equivalent circuit for the surface membrane and the T system (Adrian et al., 1969).

**Complete Solution**

The complete solution for voltage \( V \) for the off response may be written as

\[ V(x,t) = -\sum_{k=0}^{N} A_k \cos(\mu_kx) \sum_{i=1}^{N+1} \frac{\mu_i^2/r_i + g_m}{p_{ki} \left(\frac{dy_m}{dp}\right)_{p=p_m}} T_k(t), \tag{24} \]

where

\[ T_k(t) = \exp(p_{ki}t). \tag{25} \]

The solution for the on, when the voltage at \( x = 2\ell \) is stepped from 0 to \( V_p \) at \( t = 0 \), is given by

\[ V(x,t) = V_p \cosh \left(\frac{x}{\lambda}\right) = \sum_{k=0}^{N} A_k \cos(\mu_kx) \sum_{i=1}^{N+1} \frac{\mu_i^2/r_i + g_m}{p_{ki} \left(\frac{dy_m}{dp}\right)_{p=p_m}} T_k(t), \tag{26} \]

which holds for \( 0 \leq x \leq 2\ell \) or by

\[ V(x,t) = -\sum_{k=0}^{N} A_k \cos(\mu_kx) \sum_{i=1}^{N+1} \frac{\mu_i^2/r_i + g_m}{p_{ki} \left(\frac{dy_m}{dp}\right)_{p=p_m}} [1 - T_k(t)], \tag{27} \]

which holds for \( x < 2\ell \) but not at \( x = 2\ell \).

The solutions for \( V_s(x, t) \), the voltages across the individual capacitances \( C \) in Fig. 1, can be evaluated in a similar way.

**Equations for \( y_m(p) \)**

For most of the calculations in this paper the distributed model of the T system (Adrian et
al., 1969; Schneider, 1970) was used. The admittance of the T system per unit fiber length, \( y_T(p) \), is given by

\[
y_T(p) = 2\pi a \sqrt{\frac{G_L}{G_k}} \left( \left[ \frac{\frac{1}{aL}}{C_w + pC_w} \right] \right)
\]

where \( a \) is the fiber radius, \( G_L \) is the conductance of the lumen of the T system in the radial direction, \( G_k \) is the conductance of the tubular membranes per unit volume, and \( C_w \) is the capacitance of the tubular membranes per unit volume. Since the equivalent circuit for \( y_T(p) \) requires an infinite number of elements, the question arises whether the analysis for finite values of \( N \) applies as \( N \) becomes indefinitely large. The properties of distributed RC networks indicate that it does (Ghausi and Kelly, 1968) and additional support for this view is provided by the fact that the same equations can be obtained using the method of Laplace transform. In any event for numerical computations only the first 20 elements of the tubular circuit (containing 98% of total capacitance) were used, i.e. \( N = 20 \).

The admittance \( y_m(p) \) of surface membrane and T system is given by

\[
y_m(p) = g_m' + pC_m' + y_T(p)
\]

with \( g_m' \) and \( C_m' \) being the conductance and capacitance of the surface membrane. If \( g_T [/= y_T(0)] \) is used to denote the conductance of the T system per unit fiber length, Eqs. 29 and 22 are identical if

\[
g_m = g_m' + g_T
\]

and

\[
y_T(p)/[1 + p\tau_s] = g_T/[1 + p\tau_T].
\]

In one set of calculations (see Table III) an access resistance \( r_{ac} \) was added in series with \( y_T(p) \) (Peachey and Adrian, 1973). In this case Eq. 29 was replaced by

\[
y_m(p) = g_m' + pC_m' + [y_T(p)/[1 + r_{ac}y_T(p)]]
\]

with \( y_T(p) \) given, as before, by Eq. 28. Eqs. 30 and 22 are identical if

\[
g_m = g_m' + \frac{g_T}{(1 + r_{ac}g_T)}
\]

and

\[
y_T(p)/[1 + r_{ac}y_T(p)] = \frac{g_T}{[1 + r_{ac}g_T]} = \sum_{n=1}^{N} \frac{pC_n}{(1 + p\tau_n)}.
\]

**Effect of Delays**

In practice the voltage measured at \( x = 2\ell \) was not stepped instantaneously but followed an exponential time-course with time constant \( \tau_s \). For the on

\[
V(2\ell,t) = V_p [1 - \exp(-t/\tau_s)]
\]

and for the off

\[
V(2\ell,t) = V_p \exp(-t/\tau_s).
\]
The effect of the rounding on the time-course Eqs. 24 and 27 is to add an exponential delay $\tau_r$ to the function $V(x, t)$. This can be done term by term, with the result that $T_{kl}(t)$ given by Eq. 25 is replaced by

$$T_{kl}(t) = \exp\left(\frac{\rho_{kl} \tau_1}{1 + \rho_{kl} \tau_1}\right) \exp\left(-\frac{t}{\tau_1}\right) \exp\left(-\frac{t}{\tau_2}\right). \tag{33}$$

Eqs. 24 and 27, using Eq. 33, are valid for $x < 2\ell$.

Three processes in series enter into this delay. The first is the time constant associated with the exponential rounding of the command pulse. The second is the delay with which the actual potential at $x = 2\ell$ follows the command, and the third is the delay associated with measuring that potential using a microelectrode. Experimentally it was found that for the command pulse time constants which were usually used, 20–30 $\mu$s, the measured $V(2\ell, t)$ followed an exponential time-course with about the same time constant, different by only 1–2 $\mu$s. Therefore, the three processes in series introduce a delay which can be represented by a single time constant $\tau_r$. Furthermore, since the $V_1$ and $V_2$ microelectrodes were selected to have the same resistance and since the input amplifiers had the same characteristics, the same $\tau_r$ applies to measurements of both $V(\ell, t)$ and $V(2\ell, t)$.

A delay was also introduced by the Fabritek signal averager which had a 20-$\mu$s filter in the input circuit. The digitized output used for the time-course analysis, therefore, was lagged by two exponential delays, so that for the on

$$V(2\ell, t) = V_p \left[1 - \frac{\exp\left(-\frac{t}{\tau_1}\right)}{1 - \frac{\tau_1}{\tau_2}} - \frac{\exp\left(-\frac{t}{\tau_2}\right)}{1 - \frac{\tau_1}{\tau_2}}\right], \tag{34}$$

and for the off

$$V(2\ell, t) = V_p \left[\frac{\exp\left(-\frac{t}{\tau_1}\right)}{1 - \frac{\tau_1}{\tau_2}} + \frac{\exp\left(-\frac{t}{\tau_2}\right)}{1 - \frac{\tau_1}{\tau_2}}\right]. \tag{35}$$

An analysis similar to that used in deriving Eq. 33 gives the result that Eqs. 24 and 27 apply to $V(x, t)$ for $x < 2\ell$ using

$$T_{kl}(t) = \frac{\exp\left(\frac{\rho_{kl} \tau_1}{1 + \rho_{kl} \tau_1}\right) \exp\left(-\frac{t}{\tau_1}\right)}{1 + \rho_{kl} \tau_1} \left(1 + \frac{\rho_{kl} \tau_1}{1 + \rho_{kl} \tau_1}\right)$$

$$+ \frac{\rho_{kl} \tau_1 \exp\left(-\frac{t}{\tau_2}\right)}{1 + \rho_{kl} \tau_1} \left(1 - \frac{\tau_1}{\tau_2}\right) + \frac{\rho_{kl} \tau_2 \exp\left(-\frac{t}{\tau_2}\right)}{1 + \rho_{kl} \tau_2} \left(1 - \frac{\tau_2}{\tau_1}\right). \tag{36}$$

**Computational Procedure**

For a given fiber, the parameters $\lambda$ and $r_{c,m}$ were determined from the steady levels of $\Delta V$ and $V_2$ and their time integrals (Schneider and Chandler, 1976). For the circuit in Fig. 1

$$c_m = c_m' + \sum_{n=1}^{k} c_n. \tag{37}$$

$V_3(t)$ was then evaluated from Eqs. 27 and 36 using these two parameters as constraints; $V_2(t)$ was calculated from Eq. 34. Four other parameters are required to specify the solution: $(a/\lambda_T)$, $(r_m/\tau_1)$, $(c_m'/c_m)$, and $(r_i \tilde{G}_i)$ where small $r$'s and $c$'s denote values per unit length. The first two parameters were arbitrarily assigned, usually as zero, and the last two were adjusted to give a best least squares fit to the $\Delta V$ data. The final adjustment of $(c_m'/c_m)$ and $(r_i \tilde{G}_i)$ was done using 0.001- and 0.1-cm$^{-2}$ increments, respectively. The computations were carried out using standard numerical procedures on a PDP-8/e.
computer (Digital Equipment Corporation, Maynard, Mass.), Fortran IV double precision (17 digit) accuracy.

**Limitations of the Theory and its Application**

The assumptions used to develop the equations are of the simplest kind and do not take into account many factors which might influence the experimental results. For example, the surface membrane is assumed to be a circular cylinder which is insulated at one end, although fibers are known to taper and to be noncircular in cross section. At the end, there are extensive interdigitations of the muscle fiber with tendon connective tissue, and these would be expected to increase the apparent surface capacitance $C_m'$ (L. D. Peachey, personal communication). The geometrical models of the T system used for curve fitting (Eqs. 28–29 or 29–30) are highly idealized and consequently are inexact representations of the actual morphology. The capacitative properties of the membranes are assumed to be voltage and frequency independent; the first assumption is now known to be incorrect (Schneider and Chandler, 1973; Adrian and Almers, 1976; Schneider and Chandler, 1976) and the second has never been directly tested (see, for example, Cole, 1968). Other defects of the theory are that possible electrical leaks around the $V_1$ electrode are ignored as are effects which arise from three-dimensional considerations (Eisenberg and Johnson, 1970). Because of these and other uncertainties the values of certain circuit parameters such as $G_L$ and $C_m'$ obtained by us and by previous investigators may require modification in the future.

**RESULTS**

**Analysis of Time-Course in 5 mM-K Ringer's**

The first experiments were done on muscles in Ringer's solution (5 mM-K) to find out whether the values of parameters measured with the three-microelectrode method agree with values obtained using other techniques. Fig. 2 illustrates the results from one such experiment, using a -10-mV test pulse (part A) and a +10-mV pulse (part B). The traces labeled a–c show photographs of single oscilloscope sweeps; a shows $V_2$, b shows $V_1$, and c shows the difference $AV$ ($= V_2 - V_1$). The digitized results from the Fabritek, signal averaged 10 times, are plotted as points in part d.

The theoretical curves in part d of Fig. 2 are best fits of the equations for cable spread along the fiber using a distributed model for the T system (Eqs. 27, 28, 29, 34, and 36) and assuming that $(a/\lambda_T) = 0$. The values of $\lambda$ and $r_1c_m$ were obtained from the integral method (Schneider and Chandler, 1976) and were used as constraints in fitting the curves. These values are given in columns 2 and 3 of Table I, fiber 82.2. The best fit values for the adjusted parameters $c_m'/c_m$ and $r_1G_L$ are given in columns 4 and 5. Column 7 gives $G_L$ obtained by dividing $r_1G_L$ (column 4) by $r_1$ (column 6). Values of 12.5 and 10.3 $\mu$mho/cm were obtained using the -10- and +10-mV test pulses.

Fiber radius $a$ was calculated assuming that the fiber was a perfect cylinder,

$$a = \sqrt{R_i/\pi r_i},$$

and that $R_i$, the internal resistivity, equals 169 $\Omega$cm at 20°C with $Q_{10} = 0.73$
The radius of fiber 82.2 was estimated to be 38.7 μm, Table II column 2.

From the values of $r, C_m, r, \tau, a$ it is possible to determine fiber capacitance $C_m$ expressed in terms of surface area, $C_m = \frac{c_m \tau a}{r}$. The two values from fiber 82.2 were 8.61 and 9.84 μF/cm² (Table II, column 3) which, when multiplied by $c_m'/c_m$, give 2.18 and 2.18 μF/cm² for $C_m'$ (Table II, column 4), the surface capacitance. (The values of $G_L$ and $C_m'$ which were calculated for fiber 80.1 are well outside the range obtained for the other fibers and have therefore been excluded in calculating the averages in Tables I and II.)

The average value of $G_L$, 10.4 μmho (Table I, column 7), is within the range of values obtained by other methods: 4 μmho/cm at sarcomere spacings 2.5–2.8 μm (Schneider, 1970), 9 μmho/cm (Hodgkin and Nakajima, 1972 b), 7.7 μmho/cm at a sarcomere spacing of 2.5 μm (Valdiosera et al., 1974), and 10.0 μmho/cm at a spacing of 2.0 μm (Valdiosera et al., 1974). The average value of $C_m'$, 1.57
PARAMETERS USED FOR FITTING TIME-COURSE OF AV IN RINGER'S SOLUTION

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<td>0.144</td>
<td>47.7</td>
<td>10.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean±SEM 10.4±0.7

* Fiber 80.1 excluded from mean and SEM.

The values in columns 2, 3, and 6 were obtained using integrals of ΔV, Vs, and I as described in the preceding paper. For the circuit in Fig. 1, c_m is given by Eq. 37. Columns 4 and 5 were derived as best fit values for the time-course of the ΔV transient (Eqs. 27, 28, 29, 34, and 36). a/λ_p and r_m were taken as zero. τ_s = 24.5 or 30.3 µs; τ_s = 20 µs; ℓ = 177-186 µm; temperature = 18.4-19.5°C. The records from fibers 80.1, 80.2, and 80.3 were signal averaged twice, the others 10 times. The first row for each fiber was obtained with a −10-mV test pulse, the second row with a +10-mV pulse.

μF/cm² (Table II, column 4), is somewhat higher than the values of about 1 μF/cm² reported in the same papers. The larger value in the present experiments is probably due to the fact that our experiments were carried out at the end of the fibers, where an increase in C_m is expected because of short sarcomere spacing (Valdiosera et al., 1974) and interdigitations of muscle fiber with tendon (see page 172).

Effect of λ_p, R_ac, and Clamp Delay on Estimates of Gc and C_m'

The effect of changing λ_p, R_ac (tubular access resistance), or clamp delay τ_s was investigated on the fitted parameters in Tables I and II, excluding fiber 80.1. The results are tabulated in Table III. The first row gives average values of Gc and C_m' from Table I column 7 and Table II column 4. The second row gives
#### TABLE II
VALUES OF RADIUS AND SURFACE CAPACITANCE IN RINGER'S SOLUTION

<table>
<thead>
<tr>
<th>Fiber</th>
<th>a (μm)</th>
<th>(C_m) (μF/μm²)</th>
<th>(C_m') (μF/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80.1</td>
<td>65.8</td>
<td>21.34</td>
<td>4.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24.01</td>
<td>4.51</td>
</tr>
<tr>
<td>80.2</td>
<td>40.9</td>
<td>7.99</td>
<td>2.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.00</td>
<td>1.86</td>
</tr>
<tr>
<td>80.3</td>
<td>39.8</td>
<td>4.84</td>
<td>1.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.93</td>
<td>1.59</td>
</tr>
<tr>
<td>81.1</td>
<td>43.4</td>
<td>7.03</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.71</td>
<td>0.74</td>
</tr>
<tr>
<td>82.1</td>
<td>36.9</td>
<td>6.83</td>
<td>2.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.67</td>
<td>1.96</td>
</tr>
<tr>
<td>82.2</td>
<td>38.7</td>
<td>8.61</td>
<td>2.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.84</td>
<td>2.18</td>
</tr>
<tr>
<td>82.3</td>
<td>34.6</td>
<td>8.27</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.88</td>
<td>1.28</td>
</tr>
</tbody>
</table>

Mean ± SEM

1.57 ± 0.18

* Fiber 80.1 excluded from mean and SEM.
Column 2 gives values of radius calculated from Eq. 38. \(C_m\) in column 3 was obtained by dividing column 3 in Table I by column 6, then dividing by \(2πa\) using the value of \(a\) in column 2 of this table.

#### TABLE III
EFFECT OF \(\lambda_T\), \(R_{ac}\), AND CLAMP DELAY ON THE DETERMINATION OF \(G_L\) AND \(C_m'\)

<table>
<thead>
<tr>
<th>Conditions for curve fit</th>
<th>(G_L) (μS/cm)</th>
<th>(C_m') (μF/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard ((\lambda_T = \infty), (R_{ac} = 0))</td>
<td>10.4 ± 0.7</td>
<td>1.57 ± 0.18</td>
</tr>
<tr>
<td>(\lambda_T = 50) μm</td>
<td>10.5 ± 0.7</td>
<td>1.45 ± 0.19</td>
</tr>
<tr>
<td>(R_{ac} = 25) Ω/cm²</td>
<td>11.3 ± 0.8</td>
<td>2.16 ± 0.16</td>
</tr>
<tr>
<td>10 μs subtracted from (\tau_1)</td>
<td>11.8 ± 0.8</td>
<td>1.44 ± 0.18</td>
</tr>
<tr>
<td>10 μs added to (\tau_1)</td>
<td>8.5 ± 0.5</td>
<td>1.98 ± 0.17</td>
</tr>
</tbody>
</table>

Average ± SEM values from Table I column 7 and Table II column 4 and similar calculations carried out using the conditions listed in the first column. In applying the condition \(\lambda_T = 50\) μm and \(R_{ac} = 25\) Ω/cm² it was necessary to assume a value for fiber radius; the values given in column 2 Table II were used. The results from fiber 80.1 were excluded from the averages.
values obtained from similar curve fit calculations using $\lambda_T = 50 \mu m$. The third row shows the effect of introducing an access resistance of 25 $\Omega cm^2$ in series with the T system (Peachey and Adrian, 1973; Valdiosera et al., 1974). The fourth and fifth rows show the effects of changing the value of $\tau_1$ by 10 $\mu s$. The last set of calculations was carried out to evaluate the magnitude of error which would arise if $\tau_1$ were estimated incorrectly.

The general conclusion from these calculations is (a) that the estimate of $G_L$ is relatively insensitive to whether $\alpha/\lambda_T$ is different from zero or to whether a small access resistance is present; (b) that the estimate of $C_m'$ is sensitive to $R_{ac}$; and (c) that an error of 5–10 $\mu s$ in the estimate of $\tau_1$ would have a small effect on the determinations of $G_L$ and $C_m'$.

**Time-Course in 100 mM-K Using a Positive Conditioning Prepulse**

A series of experiments similar to those in Ringer’s solution were carried out in
fibers immersed in 100 mM-K solution. Test pulses of ±10 mV were superimposed on conditioning prepulses which took V2 approximately ±60 mV from the holding potential. The idea behind the experiments was to determine $G_L$ and $C_m$ from the positive prepulse measurements in which the ingoing rectifier was turned off and therefore $(\alpha/\lambda_T)$ could be assumed to equal zero. These values were then used to analyze the changes in conductance and capacitance which were observed with negative prepulses which turned on the ingoing rectifier.

Fig. 3 Aa and Ba show data and theoretical curves from one of the experiments. Fig. 3 Aa was obtained with a −10-mV test pulse and Fig. 3 Ba with a +10-mV test pulse; in both cases a positive prepulse was used. Data from this fiber and six others are summarized in Tables IV and V. The calculations were carried out in the same manner as those in Tables I and II. The average value for $G_L$ was 20.4 μmho/cm which is about twice the value found in Ringer's. For comparison, the conductivity of the 100 mM-K solution is 1.35 times that of

### Table IV

<table>
<thead>
<tr>
<th>Fiber</th>
<th>$\lambda$</th>
<th>$\tau_{G_m}$</th>
<th>$\tau_{C_m}$</th>
<th>$\tau_{G_L}$</th>
<th>$\tau_{C_L}$</th>
<th>$G_L$</th>
<th>$C_L$</th>
</tr>
</thead>
<tbody>
<tr>
<td>90.1</td>
<td>0.109</td>
<td>746</td>
<td>0.180</td>
<td>79.6</td>
<td>2.006</td>
<td>39.7</td>
<td>37.0</td>
</tr>
<tr>
<td>91.1</td>
<td>0.141</td>
<td>678</td>
<td>0.431</td>
<td>47.8</td>
<td>2.011</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td>92.1</td>
<td>0.150</td>
<td>696</td>
<td>0.462</td>
<td>57.3</td>
<td>18.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>92.2</td>
<td>0.116</td>
<td>641</td>
<td>0.154</td>
<td>94.2</td>
<td>22.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>93.1</td>
<td>0.148</td>
<td>718</td>
<td>0.190</td>
<td>58.4</td>
<td>22.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>93.2</td>
<td>0.160</td>
<td>614</td>
<td>0.335</td>
<td>35.4</td>
<td>10.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>94.2</td>
<td>0.264</td>
<td>689</td>
<td>0.234</td>
<td>48.1</td>
<td>2.602</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>0.264</td>
<td>708</td>
<td>0.208</td>
<td>49.1</td>
<td>18.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean ±SEM 20.4 ±2.4
Table V

VALUES OF RADIUS AND SURFACE CAPACITANCE IN 100 mM-K SOLUTION

<table>
<thead>
<tr>
<th>Fiber</th>
<th>Fiber</th>
<th>$a$</th>
<th>$C_m$</th>
<th>$C_m'$</th>
</tr>
</thead>
<tbody>
<tr>
<td>90.1</td>
<td>54.9</td>
<td>10.78</td>
<td>1.94</td>
<td></td>
</tr>
<tr>
<td>91.1</td>
<td>54.4</td>
<td>9.87</td>
<td>4.25</td>
<td></td>
</tr>
<tr>
<td>92.1</td>
<td>37.2</td>
<td>6.35</td>
<td>1.78</td>
<td></td>
</tr>
<tr>
<td>92.2</td>
<td>47.1</td>
<td>8.96</td>
<td>1.53</td>
<td></td>
</tr>
<tr>
<td>93.1</td>
<td>40.9</td>
<td>6.66</td>
<td>2.33</td>
<td></td>
</tr>
<tr>
<td>93.2</td>
<td>33.8</td>
<td>5.93</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>94.2</td>
<td>47.6</td>
<td>8.86</td>
<td>2.07</td>
<td></td>
</tr>
</tbody>
</table>

Mean $\pm$ SEM 2.02 $\pm$ 0.32

Curve-fitting procedures and layout of columns and rows same as Table II; same fibers as Table IV.

Ringer's. The value of $C_m'$ was somewhat higher in 100 mM-K (2.02 $\mu$F/cm²) than in Ringer's (1.57 $\mu$F/cm²) but the difference is not statistically significant.

Time-Course in 100 mM-K Using a Negative Conditioning Prepulse

The analysis of curve a in Fig. 3 A, using $(a/\lambda_7) = 0$, gave a value of 586 ms/cm² for $r_iC_m$. The surface contribution $r_iC_m'$ was estimated to be 205 ms/cm² and the tubular contribution $r_iC_m (1-C_m'/C_m)$ to be 381 ms/cm² (columns 5 and 4, Table IV). When the -10-mV test pulse was superimposed on a negative prepulse, the ingoing rectifier was turned on and the $\Delta V$ points in curve b (Fig. 3 A) were obtained. The integral analysis of this record gave $r_iC_m = 442$ ms/cm². If the surface component remained unchanged at 205 ms/cm², the tubular contribution, $r_iC_m (1-C_m'/C_m)$, decreased from 381 ms/cm² with the positive prepulse to 237 ms/cm² with the negative one.

There is now enough information to compute a theoretical curve, shown in Fig. 3 Ab, based on the assumption that the only effect of the negative prepulse was to increase the conductance of surface and tubular membranes. The parame-
ters used to calculate the curve were $\lambda = 0.0528$ cm and $r_i c_m = 442$ ms/cm$^2$, obtained from analysis of integrals; $c_m'/c_m = 0.464$, from the ratio of 205 ms/cm$^2$ to 442 ms/cm$^2$; $r_i \tilde{G}_L = 41.2$ cm$^{-2}$, from curve fitting the positive prepulse record Fig. 3 Aa (Table IV, column 5); $a/\lambda_T = 1.58$, from the ratio 257/381 of values of $r_i c_m(1 - c_m'/c_m)$ at the two voltages and Eq. 14 of Schneider and Chandler (1976); $r_{ac} = 0$, as assumed. The points and curve in Fig. 3 Bb were obtained in the same way, using a +10-mV test pulse; $\lambda = 0.0543$ cm, $r_i c_m = 476$ ms/cm$^2$, $c_m'/c_m = 0.432$, $r_i \tilde{G}_L = 35.4$ $\mu$mho/cm, $a/\lambda_T = 1.44$, and $r_{ac} = 0$. The two theoretical curves in Fig. 3 Ab and Bb are clearly in good agreement with the data.

**DISCUSSION**

The main conclusion of this paper is that the time-course of the $\Delta V$ transient, obtained with the three-microelectrode voltage clamp, can be analyzed using certain simplifying assumptions to provide information about the passive electrical properties of the surface membrane and T system. Specifically, the time-course analysis can give estimates (a) of the proportion of total capacitance which is associated with the surface $(c_m'/c_m)$ and (b) of the magnitude of $\tilde{G}_L$. Values obtained in Ringer's solution with this method are in agreement with values obtained using other techniques (Schneider, 1970; Hodgkin and Nakajima, 1972b; Valdiosera et al., 1974). In addition, results of experiments on fibers in 100 mM-K solution are consistent with the notion that turning on inward rectification changes only membrane conductance and does not affect $r_i$, $c_m'$, or $\tilde{G}_L$.

Although the values of $c_m'/c_m$ and of $\tilde{G}_L$ may be subject to change in the future, as the theory is refined (see page 172), it is encouraging that the analysis of a brief voltage clamp experiment gives information similar to that obtained using more precise AC methods.

**APPENDIX**

The purpose of this section is to obtain the functional form of $\phi_d(t)$ by solving Eqs. 17 and 19. The mathematics are simplified if at this stage the function $Y_{kn}$ is introduced,

$$Y_{kn} = \sqrt{\frac{c_m}{C_m}} \psi_{kn}. \quad (1a)$$

Eqs. 19 and 17 become

$$\frac{d\phi_k}{dt} = -f_k \phi_k + \sum_{n=1}^{N} \frac{1}{r_n \sqrt{c_m c_m'}} Y_{kn}, \quad (2a)$$

$$\frac{dY_{kn}}{dt} = \frac{1}{r_n \sqrt{c_m c_m'}} \phi_k - \frac{1}{r_n} Y_{kn}, \quad n = 1, 2, \ldots, N \quad (3a)$$
Eqs. 2a and 3a can be written in matrix notation
\[ \frac{d}{dt} (F_k) = M_k F_k. \] (4a)

\( F \) is a column vector
\[ F_k = \begin{pmatrix}
\phi_k \\
Y_{k1} \\
Y_{k2} \\
\vdots \\
Y_{kN}
\end{pmatrix} \] (5a)
and \( M_k \) is a square matrix, dimension \( N+1 \),
\[ M_k = \begin{pmatrix}
-f_k & 1/\sqrt{c_1 c_m} & 1/\sqrt{c_2 c_m} & \cdots & 1/\sqrt{c_N c_m} \\
1/\sqrt{c_1 c_m} & -1/\tau_1 & 0 & \cdots & 0 \\
1/\sqrt{c_2 c_m} & 0 & -1/\tau_2 & \cdots & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
1/\sqrt{c_N c_m} & 0 & 0 & \cdots & -1/\tau_N
\end{pmatrix}. \] (6a)

Eq. 4a has the solution
\[ F_k = \exp (M_k t) F_k(0), \] (7a)
in which \( F_k(0) \) is the value of the vector at \( t = 0 \).

Eq. 7a can be converted into a more convenient form for calculations by diagonalizing the matrix \( M_k \). This is a fairly straightforward procedure since \( M_k \) is symmetric by virtue of the scaling provided by Eqs. 1a. The first step is to find the eigenvalues \( p_k \) and eigenvectors \( X_k \) of the matrix \( M_k \), a procedure which requires solving
\[ M_k X_k = p_k X_k. \] (8a)
This has nontrivial solutions \( (X_k \neq 0) \) only if the determinant
\[ \left| M_k - p_k I \right| = 0. \] (9a)
\( \mathbf{I} \) is the identity matrix of order \( N + 1 \).

The matrix \( \mathbf{M}_k \) has nonzero elements only along the diagonal and in the first row and first column, so that the determinant has only \( N + 1 \) terms. Eq. 9 a becomes

\[
(-f_k - p_k) \prod_{j=1}^{N} \left( -\frac{1}{\tau_j} - p_k \right) - \sum_{n=1}^{N} \frac{1}{r_n c_n \epsilon_m} \prod_{j=1, j \neq n}^{N} \left( -\frac{1}{\tau_j} - p_k \right) = 0. \tag{10 a}
\]

Since, in the models of the T system which will be considered, all the time constants \( \tau_n \) \((=r_n c_n)\) are different from each other and in general different from \( f_k \), none of the roots of Eq. 10 a can equal one of the \(-\tau_n^{-1}\). Therefore, the product terms in Eq. 10 a are nonzero and both sides may be divided by

\[
\prod_{j=1}^{N} \left( -\frac{1}{\tau_j} - p_k \right)
\]

to give

\[
-f_k - p_k - \sum_{n=1}^{N} \frac{1}{r_n c_n \epsilon_m \left( -\frac{1}{\tau_n} - p_k \right)} = 0. \tag{11 a}
\]

Eqs. 11 a and 20 can be rearranged to give

\[
g_m + p_k \left[ c_m' + \sum_{n=1}^{N} \frac{c_n}{1 + p_k \tau_n} \right] = -\frac{\mu_k^2}{r_1}, \tag{12 a}
\]

where \( g_m = 1 h_m \). This is the characteristic equation of \( \mathbf{M}_k \) and there are \( N + 1 \) distinct roots \( p_k \) for the cases which are of interest here.

Once \( p_k \) are determined the eigenvectors \( \mathbf{X}_{kl} \) can be obtained from Eq. 8 a. If the elements of \( \mathbf{X}_{kl} \) are denoted by \( x_i(kl) \), where the subscript refers to the row, rows 2 to \( N + 1 \) of the relation \( \mathbf{M}_k \mathbf{X}_{kl} = p_k \mathbf{X}_{kl} \) provide the recurrence relations

\[
\frac{1}{r_n \sqrt{c_n \epsilon_m}} x_i(kl) - \frac{1}{\tau_n} x_{i+1}(kl) = p_k x_{i+1}(kl), \tag{13 a}
\]

which may be written

\[
x_{i+1}(kl) = \sqrt{\frac{c_n}{c_m}} \frac{1}{1 + p_k \tau_n} x_i(kl), \quad n = 1, 2, \ldots, N. \tag{14 a}
\]

The first element is \( x_i(kl) \) is chosen to normalize the vector \( \mathbf{X}_{kl} \)

\[
x_i^2(kl) \left[ 1 + \frac{1}{c_m} \sum_{n=1}^{N} \frac{c_n}{1 + p_k \tau_n} \right] = 1, \tag{15 a}
\]

or

\[
x_i(kl) = \left[ 1 + \frac{1}{c_m} \sum_{n=1}^{N} \frac{c_n}{1 + p_k \tau_n} \right]^{-1/2}. \tag{16 a}
\]

Eqs. 16 a and 14 a determine the elements of the normalized eigenvectors \( \mathbf{X}_{kl} \). Since \( \mathbf{M}_k \) is a symmetric matrix, these eigenvectors are orthogonal to each other. The next step is to construct a square \( N + 1 \) matrix \( \mathbf{U}_k \) such that the columns are the orthonormal vectors \( \mathbf{X}_{kl} \). The transpose of \( \mathbf{U}_k \), denoted by \( \mathbf{U}_k^T \), satisfies the relation
so that \( \mathbf{U}_k = \mathbf{U}_k \mathbf{U}_k^{-1} = \mathbf{I} \),

\[
\begin{align*}
\mathbf{U}_k \mathbf{U}_k = \mathbf{I},
\end{align*}
\]

(17 a)

so that \( \mathbf{U}_k = \mathbf{U}_k^{-1} \). Moreover, \( \mathbf{M}_k \) is diagonalized by the orthogonal transformation

\[
\mathbf{P}_k \mathbf{M}_k \mathbf{P}_k^{-1} = \mathbf{U}_k^{-1} \mathbf{M}_k \mathbf{U}_k,
\]

(18 a)

where the elements of \( \mathbf{P}_k \) are the eigenvalues \( p_{kl} \), arranged along the diagonal

\[
\mathbf{P}_k = \begin{pmatrix}
    p_{k1} & 0 & 0 & \cdots & 0 \\
    0 & p_{k2} & 0 & \cdots & 0 \\
    0 & 0 & p_{k3} & \cdots & 0 \\
    \vdots & \ddots & \ddots & \ddots & \ddots \\
    0 & 0 & 0 & \cdots & p_{k(N+1)}
\end{pmatrix}.
\]

(19 a)

We may now write

\[
\mathbf{M}_k = \mathbf{U}_k \mathbf{U}_k^{-1} \mathbf{M}_k \mathbf{U}_k \mathbf{U}_k^{-1}
\]

(20 a)

so that Eq. 7 a becomes

\[
\mathbf{F}_k = \exp \left( \mathbf{U}_k \mathbf{P}_k \mathbf{U}_k^{-1} \right) \mathbf{F}_k(0)
\]

(22 a)

\[
\mathbf{F}_k = \mathbf{U}_k \exp \left( \mathbf{P}_k \right) \mathbf{U}_k^{-1} \mathbf{F}_k(0),
\]

(23 a)

with \( \exp(\mathbf{P}_k t) \) being given by

\[
\exp (\mathbf{P}_k t) = \begin{pmatrix}
    \exp (p_{k1} t) & 0 & 0 & \cdots & 0 \\
    0 & \exp (p_{k2} t) & 0 & \cdots & 0 \\
    0 & 0 & \exp (p_{k3} t) & \cdots & 0 \\
    \vdots & \ddots & \ddots & \ddots & \ddots \\
    0 & 0 & 0 & \cdots & \exp (p_{k(N+1)} t)
\end{pmatrix}.
\]

(24 a)

The initial conditions for all \( \phi \) and \( \psi \) are unity (see Eqs. 10 and 11) so that

\[
\mathbf{F}_k(0) = \begin{pmatrix}
    1 \\
    \sqrt{c_1} \\
    \sqrt{c_2} \\
    \vdots \\
    \sqrt{c_N}
\end{pmatrix}
\]

(25 a)

The element of the \( l \)th row of \( \mathbf{U}_k^{-1} \mathbf{F}_k(0) \) is given by
so that the element of the $l$th row of $\exp(P_k t) U_k^{-1} F_k(0)$ is

$$1 + \frac{1}{C_m} \sum_{n=1}^{N} \frac{c_n}{1 + p_k \tau_n} \exp(p_k t).$$

The function $\phi_k(t)$ is given by the first element of the vector $F_k$,

$$\phi_k(t) = \sum_{l=1}^{N+1} \frac{1}{C_m} \sum_{n=1}^{N} \frac{c_n}{1 + p_k \tau_n} \exp(p_k t).$$

If $y_m(p)$ is defined by

$$y_m(p) = g_m + p\left(c_m' + \sum_{n=1}^{N} \frac{c_n}{1 + p \tau_n}\right),$$

Eq. 12.1 becomes

$$y_m(p_k) = -\frac{\mu_s^2}{r_t}.$$
We thank Mr. Harry Fein and staff of the electronic and machine shop for help with the design and construction of equipment. The computer of average transients and Fabritek signal averager were lent by Dr. J. M. Ritchie and Dr. G. Aghajanian, respectively. We are grateful to Dr. R. W. Tsien for helpful discussion and for reading the manuscript, and to Mrs. Patty Redenti for expert typing of several versions of the manuscript.

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BIBLIOGRAPHY


