Nonlinear Cable Equations for Axons

I. Computations and Experiments with Internal Current Injection

N. J. ARISPE and J. W. MOORE

From the Department of Physiology and Pharmacology, Duke University Medical Center, Durham, North Carolina 27710 and the Marine Biological Laboratory, Woods Hole, Massachusetts 02543. Dr. Arispe's present address is Escuela de Biologia, Facultad de Ciencias, Universidad Central de Venezuela, Caracas, Venezuela.

ABSTRACT Steady-state potential and current distributions resulting from internal injection of current in the squid giant axon have been measured experimentally and also computed from nonlinear membrane cable equation models by numerical methods, using the Hodgkin-Huxley equations to give the membrane current density. The solutions obtained by this method satisfactorily reproduce experimental measurements of the steady-state distribution of membrane potential. Computations of the input current-voltage characteristic for a nonlinear cable were in excellent agreement with measurements on axons. Our results demonstrate the power of Cole's equation to extract the nonlinear membrane characteristics simply from measurement of the input resistance.

INTRODUCTION

For a long time axons have been considered analogous to a leaky electrical cable and the differential equations describing it derived in many papers (e.g., Cole and Curtis, 1941; Hodgkin and Rushton, 1946; Taylor, 1963). Extensive and excellent reviews of the analytic solutions of these equations for passive membranes have been provided by Cole (1968) and Jack et al. (1976).

However the marked nonlinearities of the squid axon membrane (Cole and Curtis, 1939, 1941; Cole, 1941, 1949; Hodgkin et al., 1952) limit analytic solutions for the potential and current distributions generally to small potential perturbations. For large potential changes in an axon having a nonlinear membrane, numerical integrations are necessary to obtain solutions of the cable equations.¹ We have obtained such solutions using the 1952 equations of Hodgkin and Huxley (HH).

Moore and Green (1965) gave a preliminary report on steady-state solutions of the nonlinear cable equations by both analog and digital methods. Two different commonly used experimental situations for axons were simulated:

¹ When this work was done in 1970, no analytic methods were available. In their book, Jack et al. (1976) showed that some qualitative solutions could be obtained by using a polynomial approximation for the membrane's nonlinear characteristics.
(a) injection of current at a point inside a nerve in a large volume of electrolyte solution containing the return current electrode;
(b) both current electrodes on the exterior of the nerve membrane bathed in a small volume of solution whose longitudinal resistance is comparable to that of the cell interior.

At that time experimental data was either not available or entirely satisfactory for comparison with the calculations. For case a, Doctors J. Brinley and L. Mullins, University of Maryland School of Medicine, Baltimore, supplied us with data relating the potential inside an axon as a function of the distance from a cut end. Although curves could be fitted to the data points, rather large (or small) values of axoplasm resistance had to be assumed. Cole and Curtis (1941) made measurements on squid axons under the conditions of case b. At first we thought that their data was adequate but we found that an essential point of information, the distance between the electrodes was not given. To our inquiry, Cole replied that he had no record of the value of this parameter and that the axon chamber was not available for measurement. Furthermore, Cole wrote (1968, p. 155) that the conductances which they measured were “far higher than found before and the action potential extremely low for what still appear to be quite unknown reasons . . . It may only be good luck that the results have been found at least qualitatively correct.” Therefore, it seemed necessary and reasonable to repeat their experiments and to compare them with computer simulations of the cable equations. In the process we planned to obtain and fit data for experimental changes, including natural deterioration of the axon’s excitability. The methods used in the experiments and computations are rather different for the two cases. Therefore, we have decided to treat the steady-state case of internal injection of current at a point inside an axon in a large bath in this paper. The following paper will deal with current flows from external current electrodes situated in a narrow channel holding the axon (Moore and Arispe, 1979).

**COMPUTATIONAL METHODS AND RESULTS**

**Cable Equations and Solution for a Linear Membrane**

When current is injected inside the axon at a point as in Fig. 1, it divides into two symmetrical, longitudinal flows which decrease rapidly with distance. For an axon in a large bath, the external longitudinal resistance is negligible and the external voltage gradient may be neglected. The transmembrane potential, Vm, will equal the internal potential.

The internal longitudinal potential gradient is given by the product of the longitudinal current, ia, and resistance per unit length of axoplasm, r_a

$$\frac{dV_m}{dx} = -r_a i_a. \quad (1)$$

The sign is negative because the flow of current away from the point of injection causes the displacement in membrane potential to decrease with an increasing x. For conservation of charge, the exit of current per unit length of membrane, i_m, must equal the longitudinal gradient of the axial current, i_a, or

$$\frac{d i_a}{dx} = -i_m. \quad (2)$$
Elimination of $i_a$ between Eqs. 1 and 2 leads to the usual form of the cable equation
\[
\frac{d^2V_m}{dx^2} = r_m \cdot \frac{V_m}{r_m},
\]
where $r_m$ is the membrane resistance per unit length. For a point source of current in an infinite cable with an ohmic membrane, the analytic solution is
\[
V_m = V_m e^{-x/\lambda},
\]
where \( \lambda = \sqrt{r_m/r_a} \) in centimeters and is called the length constant.

**Figure 1.** Schematic drawing of current injection into an axon and measurement of potential as a function of the distance $x$ from the point of injection. In this case the axon is in a large bath and the current returns to a large electrode at ground. The electrical equivalent circuit is shown below. The resistance external to the membrane is taken as zero.

**Computer Solutions for the Nonlinear Membrane**

For the cable with a nonlinear membrane such as the squid axon, where $r_m$ is a strong function of the membrane potential, the value of potential for a given input current (or vice versa) cannot be found analytically and must be solved by machine methods. The current crossing the membrane may be calculated from the HH equations (or other models) for any potential and inserted on the right side of Eqs. 2 and 3.

Our original attempts to integrate these equations iteratively on an analog or digital computer, assuming better values of the voltage at the origin for the given current injected proved to be impractical. The membrane potential was unstable with distance from the origin, flying off to ± infinity because of error in the value of the voltage assumed at the origin. The higher resolution in this value possible in the digital computer allowed the integration to proceed to a few length constants.
We found that it was much more satisfactory to start the integration far enough from the origin so that the membrane potential is small enough for the membrane current-voltage relation to be linear. For a given small voltage perturbation the axial current flowing at this point can be calculated. With these initial conditions, integration can proceed toward the origin without instability under any conditions. A single integration sufficed to provide solutions for any input current value up to the maximum. This method is also applicable to short cables. The terminating conditions are readily determined and entered as the initial conditions for the integration toward a current source. Furthermore, it is most convenient for generating other characteristic curves such as the cable input conductance-voltage relationships.

Digital Program
A digital program was written in the FOCAL language and computation carried out on either a LINC-8 or PDP-15 computer (Digital Equipment Corp., Marlboro, Mass.). For the longitudinal axoplasm resistivity, we used a value of 35 Ωcm (used by Hodgkin and Huxley, 1952; also see Cole and Moore, 1960). The axon diameter was taken as 500 μm for most computations. For the initial voltage deflection (0.1 mV or less), the initial axial current distal to the starting point was found for the initial value of $V_m$ from the characteristic resistance for a semi-infinite cable ($r_\infty = r_a$). Integration of Eqs. 1 and 2 (with signs reversed) proceeded toward the point of current injection until the desired current or voltage maximum was attained.

With this technique, the computation is almost trivial and the axial currents and membrane potentials may be immediately plotted or stored as a function of the distance for later plotting.

Computation Results

Integration Method Tests Solutions using a single-step Euler integration were found to converge to an invariant plot as the $x$ increment was reduced to 1 mm or less. This solution was indistinguishable from one using a Runge-Kutta method and all subsequent calculations were made using the Euler method with steps of 0.25 or 0.5 mm.

We also investigated the effect of the choice of the initial membrane voltage on the shape of the steady-state membrane voltage distribution. We found that the solutions for a 500 μm (diameter) axon for initial voltages of 0.01, 0.1, and 1 mV in the depolarizing direction overlaid each other to within the width of the plotted lines. Similar superpositions of solutions were also obtained with equivalent initial hyperpolarizing displacements. Thus, we were assured that no appreciable error was made by choosing an initial membrane potential displacement of 1 mV or less.

Nonlinearities Fig. 2 A gives a comparison of the relative steepness of the potential distribution in an ohmic and a HH membrane. Identical initial conditions were used and the computations were terminated when a depolarization of 100 mV had been achieved. For convenience in comparing distributions associated with different parameters, the x origins will be relocated at the point of current injection in subsequent figures. Fig. 2 B shows the membrane current per unit length, $i_m$, and the axial current, $i_a$, corresponding to the HH potential distribution shown in Fig. 2 A.

"Jack et al. (1976, p. 435) also suggest this procedure."
Rectification of the HH membrane is reflected in the very different potential distribution for injection of hyperpolarizing and depolarizing currents (Fig. 3 A). The higher membrane conductance associated with depolarization causes the decay of the membrane potential with the distance to be much steeper and required injection of much larger currents than for an equivalent hyperpolarization. The deviation of the axon from an ohmic cable is most readily seen in semi-log plots where a linear membrane produces a straight line relation between the log $V_m$ and $x$. Fig. 3 B shows such semilog relations for absolute values of potential displacement arising from depolarizing currents (right).

**Figure 2.** (A) A comparison of the potential distribution for a depolarization of 100 mV in an axon with an ohmic (linear) membrane and one with a HH membrane. (B) The distributions of HH membrane potential and current density along with the axial current. The units for full scale are: $V = 100$ mV, $I_m = 5$ mA/cm$^2$, $i_a = 50 \mu$A.
Figure 3. (A) The voltage distribution for a depolarizing current (above) and for a hyperpolarizing current (below) in an axon with an HH membrane. For purposes of comparison, the currents injected at the origin were adjusted to give equal and opposite maximum membrane potential displacements. (B) The logarithms of the absolute values of the same potential distributions plotted along with those for a linear membrane for purposes of comparison.
applied to HH and linear cables and from hyperpolarizing currents (left). For purposes of comparison, the currents injected at the origin were adjusted to give equal and opposite membrane potential displacements. It is clear that the HH cable is essentially ohmic only if the membrane voltage displacement is < 1 or 2 mV.

**Diameter Effects** In a cable with an ohmic membrane, the form of the voltage distribution (Eq. 4, an exponential decay with distance) is diameter independent. The diameter affects the length constant \( \lambda \) which varies with the square root of the diameter, \( D \), i.e.,

\[
\sqrt{\frac{r_m}{r_a}} = \sqrt{\frac{R_m}{\pi D}} \frac{4R_a}{\pi D^2} = K_1 \sqrt{D},
\]

where \( R_m \) and \( R_a \) are the specific membrane axoplasm resistivities. Therefore current and potential distributions for any diameter can be obtained from another by scaling the length axis by the square root of the diameter ratios.

Although the term “length constant” loses its meaning for a nonlinear cable, the computed potential distribution patterns for different axon diameters (\( D \), relative to a standard 500 \( \mu \)m) can be superimposed when potential displacements are plotted as a function of the normalized length, \( X = \sqrt{500/D} \). Alternatively, the potential or current distributions for any given axon can be obtained from that for a 500-\( \mu \)m axon simply by multiplying the \( x \) axis by \( \sqrt{500/D} \).

The characteristic cable input conductance varies as \( D \) raised to the three-halves power as can be seen making the same substitutions as above for \( r_m \) and \( r_a \) in the expression \( G_c = \frac{1}{r_m r_a} \). For a nonlinear membrane this conductance is not constant, but one can calculate an equivalent cable input conductance by finding the current-to-voltage ratio at each step as the integration progresses. The input conductance for a 500-\( \mu \)m axon with a HH membrane is shown as a function of input potential in Fig. 4. For depolarizations, the cable input conductance increases rapidly, saturating at about 0.5 mmho. For hyperpolarizations, it decreases slightly from about 0.1 mmho becoming nearly constant at about 0.06 mmho. In contrast, the characteristic conductance for a linear cable with a membrane of 1,000 \( \Omega \)cm\(^2\) would be represented by a horizontal straight line at the 0.1 mmho level.

Our simulations show that the characteristic input conductance of a nonlinear cable also varies directly with \( D^{3/2} \). The normalized characteristic shape of input conductance as a function of input voltage is obtained by multiplying the ordinate \( I_0/V_m \) by \( (500/D)^{3/2} \).

**Experimental Methods and Results**

An axial wire 100 \( \mu \)m in diameter and insulated except at the tip was inserted longitudinally into squid axons for injection of current at a point. A KCl-filled glass micropipette penetrating the axon membrane was used to measure the internal or membrane potential. The axon was bathed in a volume of seawater (at \( \sim 22^\circ \)C) large enough so that external potential gradients were negligible. The length of the axon was usually 6 cm, about 10 resting “length constants.”
Voltage Distributions

The steady voltage displacement of the interior of the axon was measured for a family of values of injected currents when the current and potential electrodes were at the same position. Then the more easily moved axial electrode was repositioned by a measured distance and the family of currents was repeated. Thus, families of longitudinal potential distribution associated with several levels of currents was measured conveniently and rapidly. As a control, the measurements were repeated as the axial wire was returned, stepwise, to the origin. The experimental observations were very similar to the distributions shown in Fig. 3.

\[ G_{cable} = \frac{r_{ax} d_{ax}}{4} \frac{dI}{dV_m} \]  

Figure 4. The input conductance-voltage relation for a 500 μm axon with a Hodgkin-Huxley membrane. An ohmic membrane of 1,000 Ω cm² resistivity would be represented by a horizontal line at the 0.1 mmho level.

Membrane Characteristics

The power of the Cole (1961) equation to extract membrane characteristics from input current-voltage relation may not be fully appreciated. One form for membrane current per unit length is

\[ i_m = \frac{r_{ax} d_{ax}}{4} \frac{dI}{dV_m} \]  

This convenience was at the expense of a probable error when the point of current injection approached the cut end of the axon. This could cause the injected current to divide unequally in the two directions. Somewhat more current would take the slightly lower resistance path out through the cut end. However, most of the measurements were made with the electrode no closer than one or two resting space constants away from the cut end. For depolarizing currents the "effective" space constant would become shorter and this should help restore equality. For hyperpolarizing currents, the "effective" space constant would be larger and enhance any possible current inequality. Therefore, we will restrict comparison of our data with simulations to current-voltage relations near the center of the axon.
where $I_0$ is the total current injected internally at the origin (see Fig. 1). For computation purposes we converted this to the membrane current density form and performed simple numerical differentiation (assuming straight lines between the points) to evaluate $I_m$ as a function of $V$. These data points are compared with the Hodgkin-Huxley membrane in Fig. 5 A using an axoplasm resistivity of 28 $\Omega$m. The axoplasmic resistivity is the only adjustable parameter; our choice for it is 1.4 times that of seawater, in agreement with recent measurements of Cole (1975) and Carpenter et al. (1975). Considering the coarseness of spacing of the raw data and the crudeness of the numerical differentiation, the fit of the HH model to the data is surprisingly good. In fact, it is so good that it did not seem worth using a parabolic or more sophisticated numerical differentiation method.

Instead of such manipulation of data, it is preferable to simulate membrane models in a form which can be compared directly with the data. This has been done in Fig. 5 B which gives the experimental input current-voltage observations as points and the input current-voltage relation computed for the same diameter axon with a HH membrane. The fit of the HH model to the data is seen to be excellent when the axoplasm resistivity is taken as 28 $\Omega$m.

**DISCUSSION**

This paper extends the previous steady-state treatment of the axon beyond the few millivolts of the linear range (e.g., Hodgkin and Rushton, 1949) into the very nonlinear region. Problems of instabilities of machine methods in obtaining the current and voltage distributions are discussed and a method is described to circumvent the difficulties.

The nonlinearities of a cable with HH membrane do not become apparent or significant until the membrane potential displacement exceeds 1–2 mV. This can be seen directly in the semilog presentation of Fig. 3 B in which the cable with a HH membrane is compared with a cable having a constant membrane resistance equal to that of the resting HH membrane. This observation is consistent with the result of testing the effect of the initial membrane displacement on the subsequent integration. The solutions superimposed for initial values of $V_m$ up to and including 1 mV; there was a just noticeable (line width) difference in the solution for an initial condition of 2 mV. With caution one can approximate a real axon by a linear cable model for displacements of up to $\pm$ 10 mV with peak errors of ~20%.

Nonlinearities in membrane characteristics do not invalidate the usual method of scaling distributions in axons with linear membranes of different diameters. If the distributions are known for one diameter, those for a second can be obtained simply by multiplying the increments of length along the second fiber by $\sqrt{D_1/D_2}$, (where $D_1$ and $D_2$ are the diameters of the two fibers, respectively).

The usefulness of the Cole equation to transform the axon input current-voltage data to the membrane form is demonstrated. At the same time, the fit of this cable data to the Hodgkin-Huxley model reemphasizes its applicability. Furthermore, this fit indicates that our axons were in good physiological condition with the resting membrane resistance of the HH membrane, 850 $\Omega$cm$^2$.

Cole and Curtis (1941) reported finding a 100/1 ratio of the limits of input conductance for their axons. Because the experimental results here fit the HH
Figure 5. (A) Points on the axon membrane current-voltage relation derived from the cable input relation by the Cole equation are compared with the solid line calculated from the Hodgkin-Huxley model. Axon 8-16-72; 408 μm. (B) Points on the input current-voltage curve for the same axon are compared with the solid line showing the cable input characteristics of an axon of the same diameter with a Hodgkin-Huxley membrane.
model so well, our observations of input conductance must follow that of Fig. 4, where the ratio of the limits is only 10/1. However, in the following paper (Moore and Arispe, 1979), the best fit was obtained by decreasing the leakage five-fold. There the ratio of the limits of input conductance becomes 50/1, much closer to the Cole and Curtis value. Perhaps the insertion of an axial wire (in the Hodgkin-Huxley experiments and in this paper) increased the leakage over that where external electrodes were used (Cole and Curtis [1941] and in the following paper, Moore and Arispe [1979]).

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REFERENCES

CARPENTER, D. O., M. M. HOVEY, and A. F. BAK. 1975. Resistivity of axoplasm. II. Internal resistivity of giant axons of squid and Myxicola. J. Gen. Physiol. 66:139-148.

COLE, K. S. 1941. Rectification and inductance in the squid giant axons. J. Gen. Physiol. 25:29-51.

COLE, K. S. 1949. Dynamic electrical characteristics of the squid axon membrane. Arch. Sci. Physiol. 3:233-258.

COLE, K. S. 1961. Non-linear current-potential relations in an axon membrane. J. Gen. Physiol. 44:1055-1057.

COLE, K. S. 1968. Membranes, Ions, and Impulses. University of California Press, Berkeley, Calif.

COLE, K. S. 1975. Resistivity of axoplasm. I. Resistivity of extruded squid axoplasm. J. Gen. Physiol. 66:133-138.

COLE, K. S., and H. J. CURTIS. 1939. Electric impedance of the squid giant axon during activity. J. Gen. Physiol. 22:649-670.

COLE, K. S., and H. J. CURTIS. 1941. Membrane potential of the squid giant axon during current flow. J. Gen. Physiol. 24:551-563.

COLE, K. S., and J. W. MOORE. 1960. Liquid junction and membrane potentials of the squid giant axon. J. Gen. Physiol. 43:971-980.

HODGKIN, A. L., and A. F. HUXLEY. 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. (Lond.). 117:500-544.

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

HODGKIN, A. L., and W. RUSHTON. 1946. The electrical constants of a crustacean nerve fibre. Proc. R. Soc. Lond. B Biol. Sci. 133:444-479.

JACK, J., D. NOBLE, and R. TSIEN. 1975. Electric Current Flow in Excitable Cells. Clarendon Press, Oxford.

MOORE, J. W., and N. J. ARISPE. 1979. Nonlinear cable equations for axons. II. Computations and experiments with external current electrodes. 73:737-745.

MOORE, J. W., and J. E. GREEN. 1965. Integration of the cable equation for membranes with variable conductances. Biophys. Soc. Annu. Meet. Abstr. 12.

TAYLOR, R. E. 1963. Cable theory. Phys. Tech. Biol. Res. 6:219-262.