# The electrophysics of a nerve fiber*

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**The "action potential" is a pulselike voltage wave which carries information along a nerve fiber. Starting with fundamental concepts of biochemistry and electromagnetic theory, the derivation of the nonlinear diffusion equation which governs propagation of the action potential is reviewed. Our current understanding of this equation is discussed, paying particular attention to questions of interest in physics and applied mathematics.**

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## I. INTRODUCTION

In the twenty fourth question added to the second edition of his *Optiks*, Newton (1718) asked

> *Qu.* 24. Is not Animal Motion perform'd by the Vibrations of this Medium, excited in the Brain by the power of the Will, and propagated from thence through the solid, pellucid and uniform Capillamenta of the Nerves into the Muscles, for contracting and dilating them?

He was fairly close to the mark for, as we shall see, a proper theory for the electrodynamics of the nerve fiber begins with the field equations of Maxwell just as does the science of optics. First, of course, it was necessary to develop the science of electricity, and this was, in turn, profoundly influenced by Galvani's research on animal electricity and Volta's subsequent development of the battery later in the 18th century.

I do not propose to review this early history; the delightful survey by Brazier (1959 [see also Harmon and Lewis (1966)] could not be equaled without an enormous expense of time and effort which would necessarily be subtracted from my main task. I will, however, attempt to place in context those contributions which have directly led to an understanding of the nonlinear wave dynamics associated with propagation of a voltage pulse, or "action potential," along a nerve fiber.

In 1850 Helmholtz used a cleverly designed apparatus (see Fig. 1) to show that the signal velocity on a frog's sciatic nerve is not immeasurably large as was assumed (perhaps due to the continuing influence of Newton's twenty fourth question) but some 27 mps. Details of this work can be found in Helmholtz (1850), but the basic idea is both simple and elegant. Closure of switch ($V$) simultaneously breaks the primary ($P$) initiating a nerve pulse ($N$), and starts a time measurement on the ballistic galvanometer ($G$). When the muscle ($M$) twitches, a mercury contact at $k$ is broken and the measurement terminates. The difference of times measured for inputs at terminals (3–4) and (5–6) divided into the corresponding distance along

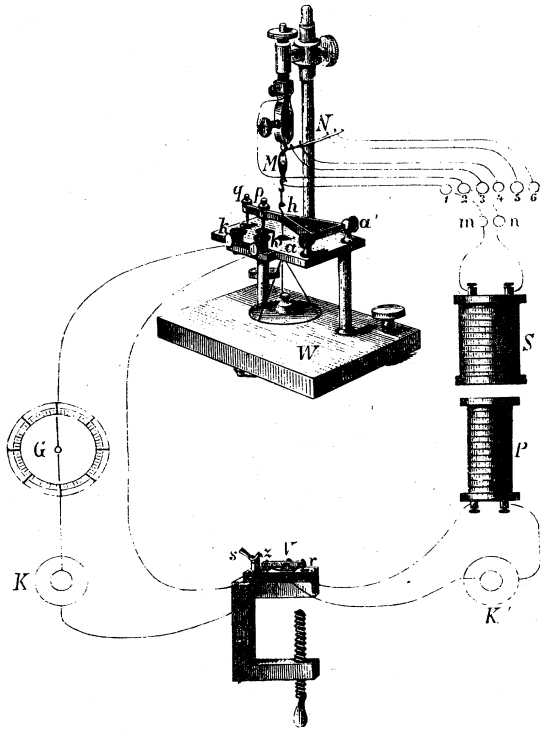


FIG. 1. Apparatus used by Helmholtz to measure the signal velocity on a nerve fiber [Hermann (1879I)].

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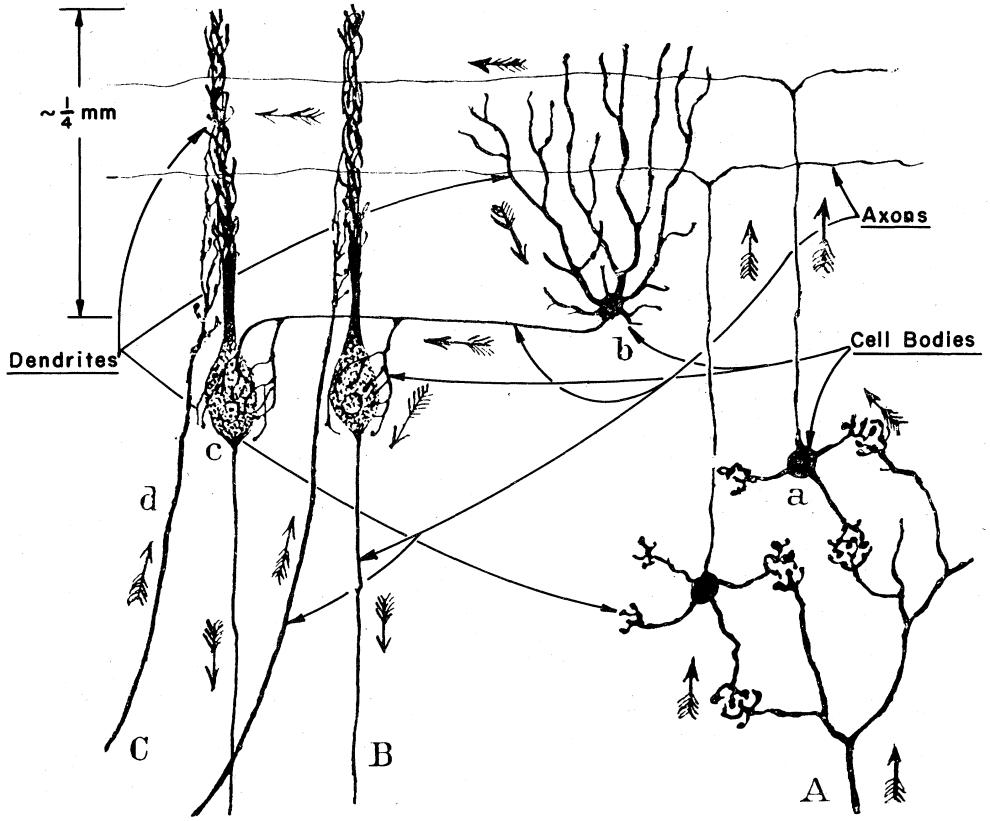


FIG. 2. A semischematic diagram of neuron structure in the cerebellum by Ramón y Cajal (1908). (A) mossy fiber input, (a) Granule cell (B) Purkinje axon output, (b) basket cell, (c) Purkinje cell body, (C–d) climbing fiber input.

the nerve yields a velocity. Bernstein (1868) described the details of an even more impressive experimental *tour de force*; he measured the *shape* (potential vs time) of the action potential on a frog's nerve and showed that the velocity was equal to the signal velocity measured by Helmholtz. It is a fascinating experience to read over these early papers and appreciate the experimental results which were obtained a full half century before Gasser and Erlanger (1922) introduced the cathode ray oscilloscope into electrophysiological research.

The problem was to understand the physical process involved in the propagation of the action potential. Weber (1873) took an important step with his fundamental study of the flow of electricity in cylinders; indeed, we shall begin our analytic consideration with this calculation in the following section. Hermann (1879 II) seems to have the correct physical ideas in mind. He notes the similarity of nerve propagation to a line of burning powder but rejects a purely chemical explanation since this would seem to require activity throughout the entire cell. He describes circulating currents which excite the neighborhood of a pulse and indicates that these equations would lead to a form of the "heat equation." This line of thought, he wrote in 1879, "*genügt uberhaupt . . . der gestellten Aufgabe nicht.*" Hermann did not appreciate the descriptive power of a *nonlinear* diffusion equation until later and even then he felt such problems would lead to "enormous mathematical difficulties" [Hermann (1905)]. By this time Bernstein (1902), building on studies of charge transport in ionic solutions by Nernst (1888, 1889), and Planck (1890a,b) had carefully stated in his "membrane hypothesis" that the action potential was the discharge of a (Nernst) diffusion potential caused by an increase in ionic permeability of the membrane.

The concept of a nerve cell or "neuron" as an independently functioning unit was firmly established through the extensive anatomical studies of Ramón y Cajal (1908), and a survey of this work written at the end of his life in 1934 has recently become available in English [Ramón y Cajal (1954)]. Most neurons display an input branching structure of "dendrites" called the dendritic trees, an enlarged cell body, and an output fiber or "axon" which eventually branches into an axonal tree. If appropriate firing conditions are established at the dendritic inputs, the cell body will send a pulse outward on the axon. An idea of the variety of neurons which fall within this basic pattern may be obtained through reference to Fig. 2 which is from the 1906 Nobel lecture of Ramón y Cajal and indicates some of the cerebellar (or motor control) circuitry in the central nervous system of vertebrates. A variety of tree shapes are observed each, presumably, adapted for the function of a particular cell. The size of nerve cells also varies widely. For example the sciatic nerve of a giraffe contains axons which are several meters in length, and the giant axon of the squid can be almost a millimeter in diameter. In this review the term nerve fiber implies both axons and dendrites although most of the available experimental data are for large axons.

The following decades saw: the demonstration of the

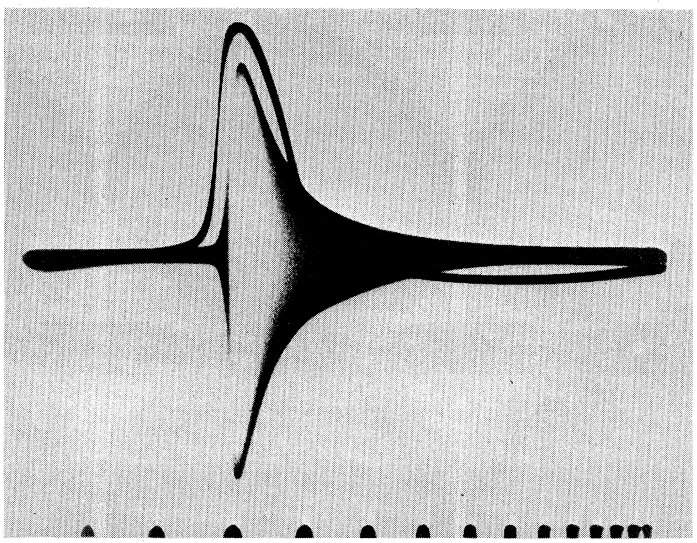

FIG. 3. Direct measurement of the increase in membrane conductance (band) during the action potential (line) on the squid giant axon [Cole and Curtis (1938)]. Time marks are 1 msec.

"all or nothing" nature of nerve fiber response to stimulation [Lucas (1909), Adrian (1914)], confirmation of the existence of the cell membrane, and measurement of its electrical capacitance [Fricke (1923)], discovery of the squid giant axon [Young (1936)], demonstration that the membrane conductance of a squid giant axon increases during the action potential [Cole and Curtis (1938, 1939)] (see Fig. 3), and the observation by Cole (1949) that membrane voltage (rather than current) is the more useful dependent variable for a phenomenological description. The activities of these years are described in detail in the recent book by Cole (1968). Part history, part careful scientific discussion, this book should be studied by everyone who wishes to understand twentieth century electrophysiology. Finally, the pieces of the problem were put together in the brilliant work of Hodgkin and Huxley (1952). They showed how measurements of the conductive parameters of a nerve fiber can be used to directly calculate both the shape and the velocity of an action potential on the squid giant axon.

In retrospect it seems that applied mathematicians forewent an unusual opportunity to make important scientific contributions by ignoring the study of the nonlinear diffusion equation. One exception to this generalization was the work by Kolmogoroff, Petrovsky and Piscounoff (1937) on the equation[1]

$$\phi_{xx} - \phi_t = F(\phi) \tag{1.1}$$

which was related to the biological problem of genetic diffusion. They showed how steplike initial conditions would evolve into a unique solitary wave solution of the form

$$\phi(x, t) = \phi_T(x - ut) \qquad u \text{ const.}, \tag{1.2}$$

developed phase plane techniques for determining $\phi_T$, and derived explicit formulas for the traveling wave velocity $u$. This uniquely important contribution was completely overlooked by electrophysiologists in the U.S.A.; indeed it is not even noted in the otherwise exhaustive bibliography of the book by Cole (1968). The failure of applied mathematicians to undertake a timely study of (1.1) cannot be ascribed to technical inefficiency in the face of the "enormous mathematical difficulties" envisaged by Hermann (1905). The studies by Boussinesq (1872) and by Korteweg and deVries (1895) of the hydrodynamic solitary waves described by Scott Russell (1844) indicate an ample understanding even before the turn of the century. As Cohen (1971) has suggested, the difficulty may have been the assumption by most mathematicians that the diffusive and nonpropagating behavior of linear diffusion equations would carry over to the nonlinear case.

But one need not turn to Hermann's line of burning powder or the Japanese incense investigated by Kato (1924) for a clear physical representation of nonlinear diffusion; the ordinary candle had been lighting scientific study tables for centuries. Diffusion of heat down the candle releases wax to the flame where it burns to supply the heat. If $P$ is the power (joules/second) necessary to support the flame, and $E$ is the chemical energy stored per unit length of the candle (joules/meter), then the flame (nonlinear wave) will travel at the velocity $u$ for which

$$P = uE. \tag{1.3}$$

The rate at which energy is eaten ($uE$) must equal the rate at which it is digested by the flame ($P$). Equation (1.3) is of more than pedagogical interest; when we turn to the development of formulas for the calculation of nerve pulse propagation velocity we shall use (1.3) to find solutions of (1.1) with the traveling wave character indicated in (1.2).

I take the point of view that nonlinear wave problems can be divided into two main classes: (i) those for which solitary traveling waves imply a balance between rate of energy release by the nonlinearity and its consumption and is indicated by (1.3), and (ii) those for which energy is conserved and therefore obey a conservation law

$$\mathcal{E}_t + \mathcal{P}_x = 0, \tag{1.4}$$

where $\mathcal{E}$ is energy density, and $\mathcal{P}$ is the power flow. Wave problems of class (ii) include the hydrodynamic waves which were studied by Boussinesq (1972) and by Korteweg and deVries (1895). In this case solitary waves involve a balance between the effects of nonlinearity and dispersion, and the propagation velocity is an adjustable parameter in a family of solutions. Such energy conserving solitary waves sometimes exhibit an infinite number of conservation laws and the nondestructive collisions characteristics of "solitons." Nothing further will be said here about class (ii); the interested reader is referred to Scott, Chu, and McLaughlin (1973) for a review of the current status of this research. Although the present discussion will concentrate upon nonlinear wave problems of class (i), it should not be assumed that conservation laws are unimportant. Indeed we shall find that an approximate conservation law for electric charge can be useful in determining the conditions necessary to stimulate a nerve fiber to the threshold of excitation, and also that a conservation law for pulses

[1] Equation (1.1) should perhaps be called the KPP equation.

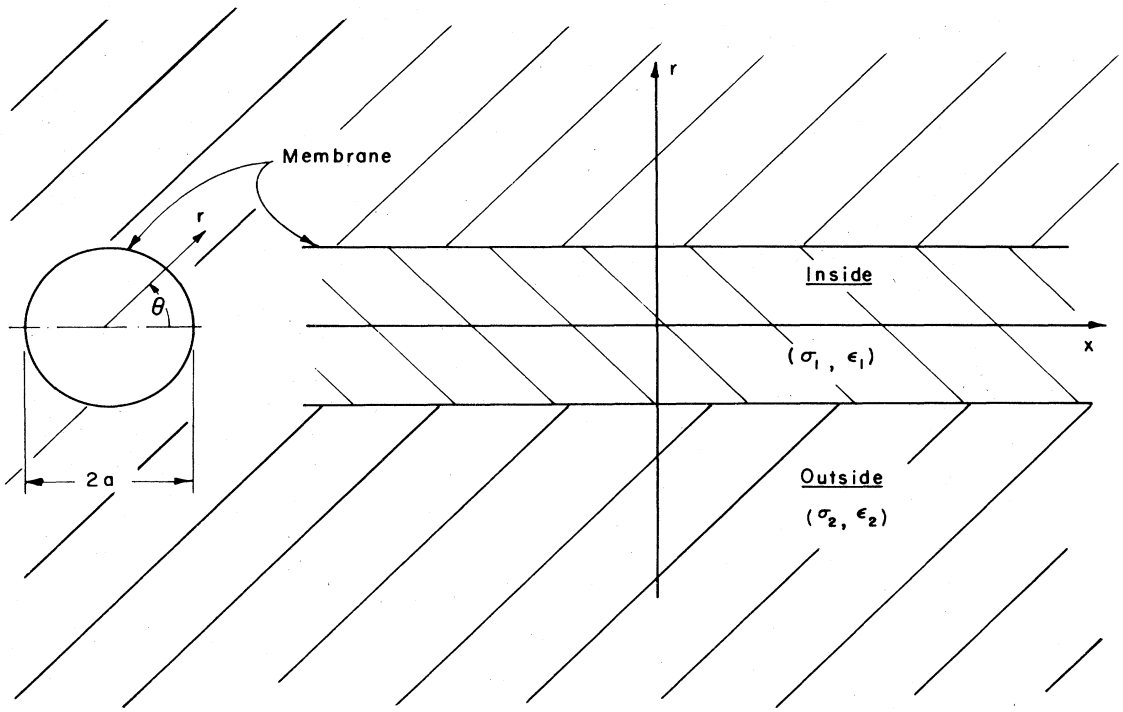


FIG. 4. Cylindrical geometry for electromagnetic analysis of a nerve fiber.

helps to analyze the evolution of a pulse burst along a fiber.

The Hodgkin and Huxley (1952d) calculation of the action potential shape and velocity from measured parameters of the nerve cell was a scientific achievement of extraordinary significance. They demonstrated that a physical theory for the electrophysiology of a nerve cell could be based on a phenomenological description of the membrane and mooted thereby much of the previous tendency of biomathematicians toward "modeling." The main objective of this review is to present as clearly and simply as possible the elements of such a theory paying particular attention to the contributions of physicists, applied mathematicians, and bioengineers. Thus I begin with an electromagnetic analysis leading to appropriate nonlinear partial differential equations and using ideas familiar to the microwave engineer; and then proceed to a study of ion current flow through a nerve membrane which should be of interest to the solid state physicist. For those who are anxious to get on to an analysis of nonlinear pulse propagation on a nerve fiber, these sections may seem unnecessarily extensive; but the problem of deciding *which* equations to analyze is not at all trivial especially in situations where the traditional geometry of an infinitely long circular cylinder is altered. The phenomenological description of nerve membrane electrodynamics developed by Hodgkin and Huxley is then presented and used as a basis for subsequent mathematical analysis. Emphasis is placed upon those aspects of the mathematical picture where future developments seem likely such as the theory of motor nerves which are "myelinated" to increase pulse velocity and the threshold theory for active fibers. A final section introduces several problems of current research interest involving the interaction of nonlinear pulses on nerve fibers.

## II. NONLINEAR PARTIAL DIFFERENTIAL EQUATIONS

Stimulated by attempts of Hermann and Matteucci to understand the manner in which electricity flows through a nerve fiber, Weber (1873a,b) carried out a fundamental study of time independent current density in and near a partially conducting cylinder. The basic coordinate system for this problem is shown in Fig. 4; a cylindrical *membrane* separates an *inside* region with conductivity $\sigma_1$ and dielectric constant $\epsilon_1$ from an *outside* region with conductivity $\sigma_2$ and dielectric constant $\epsilon_2$. Weber assumed that the electrical potential both inside and outside the membrane satisfies Laplace's equation and applied suitable boundary conditions at the membrane. This approach has been followed by several other investigators up to recent times [Clark and Plonsey (1966, 1968), Geselowitz (1966, 1967), Hellerstein (1968). Lorente de Nó (1947), Plonsey (1964, 1965), Rall (1969), Weinberg (1941, 1942)] and, indeed, is a very good approximation for potentials which vary as slowly as is indicated in Fig. 2. On the other hand it is not more difficult to proceed with the complete Maxwell equations [Pickard (1968, 1969), Rosenfalk (1969), Scott (1972) and this approach allows us to comprehend more precisely the implications of a quasistatic approximation. Thus we write[2]

$$\text{curl } \bar{E}_i = -\mu_0(\partial \bar{H}_i/\partial t) \tag{2.1a}$$

$$\text{curl } \bar{H}_i = \sigma_i \bar{E}_i + \epsilon_i(\partial \bar{E}_i/\partial t) \qquad i = 1, 2. \tag{2.1b}$$

[2] The mks system of electromagnetic units will be used throughout this paper. In this section, subscripts denote vector components so partial derivatives will be explicitly indicated.

where $i = 1$ inside the membrane and $i = 2$ outside. These equations are entirely *linear*. The nonlinearity in the problem appears at the membrane boundary where the normal current density, $J_{12}$, is some nonlinear function of the transverse voltage, $v$, across the membrane. Thus we can write symbolically

$$J_{12} = N(v), \tag{2.2}$$

but we must be careful to remember that $N(v)$ can be a rather complex function of $v$ and its time derivatives. In order to appreciate this complexity, the reader might look ahead to the discussion of the Hodgkin–Huxley equations in Sec. IV.

The fact that nonlinear effects occur only on the cylindrical membrane boundary greatly simplifies the study of the electromagnetic problem. For an infinitely long fiber, the regions both inside and outside the membrane are invariant to:

(i) translation in the $x$ direction
(ii) rotation in the $\theta$ direction, and
(iii) translation with time ($t$).

Thus we can compose the fields of elementary functions which vary as $\exp[i(\beta x - \omega t + n\theta)]$ both inside the membrane and outside.

Furthermore we shall begin our analysis by assuming rotational symmetry of the fields as implied by

$$\partial/\partial\theta = 0 \quad \text{or} \quad n = 0. \tag{2.3}$$

The implications of this assumption will be considered below but for the present it allows us to concentrate our attention upon those TM (transverse magnetic) solutions of (2.1) for which

$$(\bar{H})_r = (\bar{H})_x = 0 \qquad \text{and} \qquad (\bar{E})_\theta = 0. \tag{2.4}$$

The TE (transverse electric) modes for which $(\bar{E})_r = (E)_x = 0$ and $(\bar{H})_\theta = 0$ are of little interest since the condition $(\bar{E})_r = 0$ implies zero normal current at the membrane surface. From (2.2) such TE modes would not interact with the nonlinearity of the membrane.

Then we write the $\theta$ component of the magnetic intensity vector

$$(\bar{H})_\theta = H_\theta(r) \exp[i(\beta x - \omega t)] \tag{2.5}$$

and similarly for $(\bar{E})_r$ and $(\bar{E})_x$ (where it should be understood that subscripts 1 or 2 are added for fields inside or outside the membrane) whereupon Maxwell's equations (2.1) reduce to

$$\partial^2 H_\theta/\partial r^2 + r^{-1}(\partial H_\theta/\partial r) - (1/r^2 + k^2)H_\theta = 0, \tag{2.6a}$$

$$E_r = -(i\beta/\sigma^*)H_\theta, \tag{2.6b}$$

$$E_x = (1/\sigma^* r)[\partial(rH_\theta)/\partial r]. \tag{2.6c}$$

In these equations $\sigma^*$ is the complex conductivity

$$\sigma^* = \sigma + i\omega\epsilon, \tag{2.6d}$$

and

$$k^2 = i\omega\mu_0\sigma^* + \beta^2. \tag{2.6e}$$

Equations (2.6) indicate that $H_\theta$ is a rather convenient variable for which to solve. Knowing $H_\theta$, one can determine $E_r$ and $E_x$ through (2.6b) and (2.6c). Equation (2.6a) is Bessel's as defined by Watson (1962). Since $K_1$ goes to infinity at the origin, $I_1$ is the appropriate solution inside the membrane; and, since $I_1$ goes to infinity for large values of $r$, $K_1$ is the appropriate solution outside. The magnitude of $H_\theta$ at $r = a$ can be easily determined from Ampere's circuital law (which is (2.1b) in integral form) from the total current flowing in the $x$ direction inside the membrane as

$$2\pi a H_\theta = I. \tag{2.7}$$

Thus a complete solution for $H$ which (i) satisfies Maxwell's equations both inside and outside the membrane, (ii) has no $\theta$ variation as required by assumption (2.3), (iii) corresponds to a TM mode with a current component perpendicular to the membrane boundary, (iv) satisfies the appropriate electromagnetic boundary condition at the origin, and (v) goes to zero at large radius, is:

*inside*

$$H_\theta = \frac{I}{2\pi a}\frac{I_1(k_1 r)}{I_1(k_1 a)}, \tag{2.8a}$$

*outside*

$$H_\theta = \frac{I}{2\pi a}\frac{K_1(k_2 r)}{K_1(k_2 a)}, \tag{2.8b}$$

where $k_1^2 = i\omega\mu_0\sigma_1^* + \beta^2$ inside the membrane and $k_2^2 = i\omega\mu_0\sigma_2^* + \beta^2$ outside the membrane.

At this point in the analysis it is important to recognize that Eqs. (2.8) have been derived without considering the nonlinear aspects of the problem symbolically expressed in (2.2). The appropriate values for $\omega$ and $\beta$ out of which the action potential is to be determined are, as yet, entirely undetermined. We shall now use (2.8) to develop the nonlinear partial differential equations which relate the total longitudinal current flowing inside the membrane, $i(x, t)$, and the ($\theta$ independent) voltage across the membrane, $v(x, t)$, as is indicated in Fig. 5a.

To obtain a pde involving the $x$ derivative of $v$, consider the diagram of the electric field components near the membrane in Fig. 5b where the positive reference directions for the $x$ component of the inside field, $(\bar{E}_1)_x$, and the outside field, $(\bar{E}_2)_x$, are indicated. With these references, the sum of potentials around the path $A\ B\ C\ D$ becomes

$$v(x + dx) + (\bar{E}_1(a, x, t))_x\, dx - v(x) + (\bar{E}_2(a, x, t))_x\, dx = 0$$

for any time. Thus

$$\partial v/\partial x = -(\bar{E}_1(a, x, t))_x - (\bar{E}_2(a, x, t))_x. \tag{2.9}$$

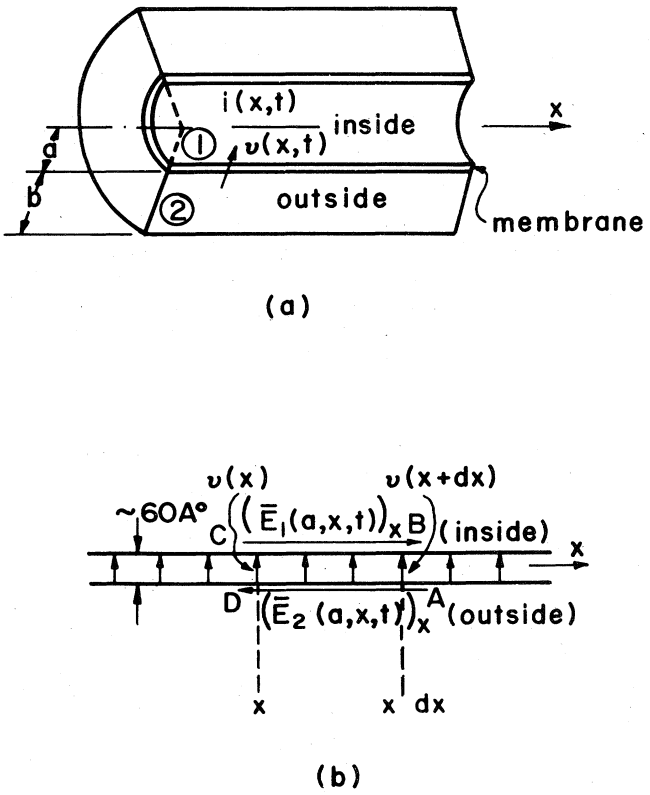


FIG. 5. (a) Geometry for an idealized nerve fiber, and (b) electric field components near the membrane.

Equation (2.9) is the source of the pde we are after. It can be related to the longitudinal current, $i(x, t)$, in the following way. First consider the expansion of $(\bar{E}_1)_x$ into its spatial and temporal components as

$$(E_1(a, x, t))_x = \int\int E_{1x}(a) \exp[i(\beta x - \omega t)]\, d\beta\, d\omega \quad (2.10)$$

and similarly for $(E_2)_x$. Then using Eqs. (2.6c) and (2.7) we can write

$$E_{1x}(a) = z_1 I \quad \text{and} \quad E_{2x}(a) = z_2 I \quad (2.11a, b)$$

where $z_1$ and $z_2$ are impedances. Assuming $H_\theta \to 0$ as $r \to \infty$ gives

$$z_1 = \left(\frac{1}{\pi\sigma_1^* a^2}\right)\left[\frac{k_1 a I_0(k_1 a)}{2I_1(k_1 a)}\right], \quad (2.12a)$$

$$z_2 = \left(\frac{1}{\pi\sigma_2^* a^2}\right)\left[\frac{k_2 a K_0(k_2 a)}{2K_1(k_2 a)}\right]. \quad (2.12b)$$

Thus (2.9) becomes

$$\partial v/\partial x = -\int\int (z_1 + z_2) I(\beta, \omega) \exp[i(\beta x - \omega t)]\, d\beta\, d\omega, \quad (2.13)$$

where $I(\beta, \omega)$ is the spatial and temporal Fourier transform of $i(x, t)$.

Equation (2.13) is not nearly as intractable in practice as it might appear at first glance. First it is important to remember that it is entirely linear; the only nonlinearities appear in connection with current flow through the membrane (2.2) and this effect has not yet been considered. Secondly the temporal frequency components, $\omega$, in a typical action potential are of the order of $10^3$ rad/sec (see Fig. 3) and the conductivity, $\sigma$, both inside and outside the fiber is approximately that of sea water (4 mho/m). Thus it is a very good approximation to write

$$\sigma^* \approx \sigma \text{ (a real constant)}$$

both inside and outside the fiber. Thirdly the radial parameter $k$ which appears in (2.12) is given by (2.6e)

$$k^2 = 4i/\delta^2 + \beta^2 \quad (2.14)$$

where

$$\delta = (2/\sigma\mu_0\omega)^{1/2} \quad (2.15)$$

is the electromagnetic penetration depth in the conductive medium at frequency $\omega$. For $\sigma \sim 4$ mho/m, $\omega \sim 10^3$ rad/sec and $\mu_0 = 4\pi \times 10^{-7}$ H/m, $\delta \sim 20$/m, which is much greater than the spatial extent of typical action potentials. Thus it is a very good approximation to write (2.14) as

$$k \approx \beta. \quad (2.16)$$

Finally the spatial extent of a typical action potential is typically an order of magnitude or more larger than the fiber radius, $a$. Small argument approximations are then appropriate for the evaluation of the Bessel functions which appear in (2.12). For example (2.12a) becomes

$$z_1 = (1/\pi a^2\sigma_1)\{1 + 0[(k_1 a)^2]\}, \quad (2.17)$$

and the most important effect of the $0[(k_1 a)^2]$ terms is to introduce an inductive component into $z_1$. In a later section the effect of this inductive component will be studied in detail and it will be shown to be entirely negligible. Thus we can write

$$z_1 \approx r_1, \quad (2.18)$$

where

$$r_1 = 1/\pi a^2\sigma_1 \quad (2.19)$$

is the resistance inside the fiber to longitudinal ($x$ directed) current flow. The ratio of outside to inside longitudinal impedance from (2.12)

$$\frac{z_2}{z_1} = \left(\frac{\sigma_1}{\sigma_2}\right)\left[\frac{K_0(\beta a) I_1(\beta a)}{K_1(\beta a) I_0(\beta a)}\right] \quad (2.20)$$

the square bracket of which is plotted in Fig. 6. Neglecting $z_2$ with respect to $z_1$ is seen to introduce an error of no more than a percent.

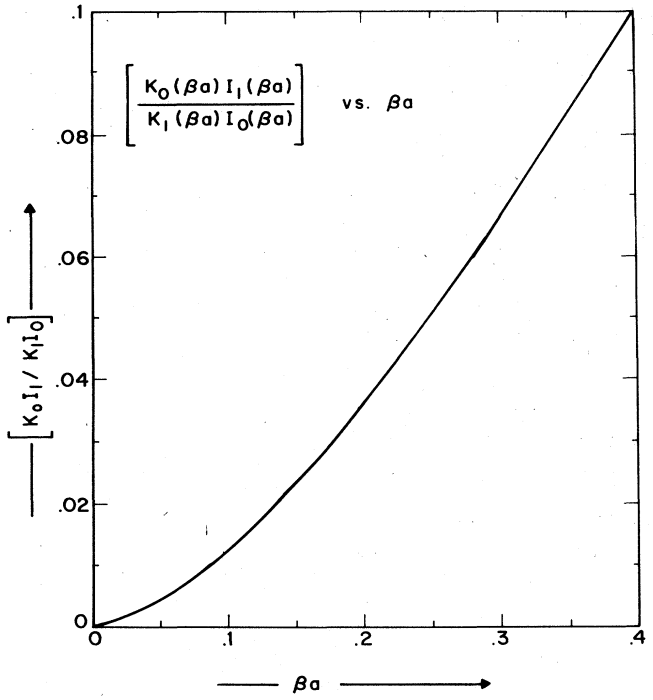


FIG. 6. Plot of the factor $[K_0I_1/K_1I_0]$ as a function of $\beta a$. This is approximately equal to the ratio of external to internal series resistance for $\beta b \gg 1$ [Scott (1973)].

Equation (2.13) reduces to

$$\partial v/\partial x = -r_s i, \tag{2.21a}$$

where $r_s = r_1 + r_2 \approx r_1$ as indicated in (2.19). This is one of the two partial differential equations we seek. The other is nonlinear and relates the spatial derivative of $i$ to the membrane voltage $v$. It is obtained from (2.6b) by noting, first, that $(\bar{H})_\theta$ is proportional to $i$ as indicated in (2.7) and, second, that $(\bar{E})_r$ evaluated at $r = a$ gives the current density normal to the membrane which appears in (2.4). Thus

$$\partial i/\partial x = -2\pi a N(v). \tag{2.21b}$$

It is often useful to combine Eqs. (2.21) to obtain a second-order equation which involves only the membrane voltage

$$\partial^2 v/\partial x^2 = 2\pi a r_s N(v). \tag{2.22}$$

Equation (2.22) is not quite as simple as it looks since $N(v)$ is a rather complex nonlinear function of $v$. But it is perhaps more simple than one expects for the geometry indicated in Fig. 5(a). Thus it may be useful at this point to recapitulate the assumptions which were involved in the derivation of (2.22).

## A. Rotation symmetry of fields

A basic assumption connected with (2.22) is that the membrane voltage is a function only of $x$ and $t$ and is not a function of the angle of rotation around the cylinder axis, $\theta$. In the course of the analysis, this restriction allowed us to exclude non-TM modes from consideration. Rall (1969) has studied the question of angle dependence in detail for a cylinder of fixed length. He has shown that the time constant, $\tau_n$, for angle variation [as $\exp(in\theta)$] to disappear is related to the basic time constant of the membrane, $\tau$, by

$$\frac{\tau_n}{\tau} \approx \frac{a}{n}\left(\frac{1}{\sigma_1} + \frac{1}{\sigma_2}\right) G, \tag{2.23}$$

where $G \equiv \partial N/\partial v$ is a conductance per unit area of the membrane. For typical values of the parameters, the right-hand side of (2.23) is something like $10^{-4}/n$. Thus, for uniform cylindrical geometry, we can expect angularly dependent fields to relax to the angularly independent case in a time which is very short compared with the time scale for solutions of (2.22).

## B. Uniform fiber cross section

A real nerve fiber is often not shaped as the uniform circular cylinder indicated in Fig. 5(a); angular bends, local distention, tapering, and collapse into a ribbon shaped cross section are some of the deviations easily observed. Judgment is required to determine the degree of confidence which one can place in (2.22) in such cases. First, of course, the $\pi a^2$ which appears in (2.12) and (2.19) should be replaced by the cross sectional area of the fiber, and the $2\pi a$ in (2.21b) and (2.22) should be replaced by the fiber circumference. [Some calculations for flat cells are presented by Minor and Maksimov (1969)]. A more serious difficulty arises from the scattering of TM fields [described by (2.22)] into non-TM modes; this effect is not represented at all. Furthermore if the nonuniformities vary with $x$ on a scale short with respect to $\beta^{-1}$ (the length of the action potential), the easy transition from (2.13) to (2.21a) will no longer be valid. On the other hand, some progress has been made with the solution of the nonlinear problem with a gradual exponential taper [Lindgren and Buratti (1969)]. Another important case is the so called "myelinated axon" for which $N(v)$ is approximately zero except at periodically spaced active nodes. This situation is also considered in detail in Sec. VIII.

## C. Infinite external medium

In the development of the expression for outside impedance (2.12b) we assumed that the dimension "$b$" in Fig. 5(a) is large enough to insure that $K_1(k_2 b)$ is zero in (2.8b). From (2.16) a more precise statement of this requirement is

$$b \gg \beta^{-1}, \tag{2.24}$$

where, as was noted before, $\beta^{-1}$ is of the order of the length of the action potential. Although this condition is easily satisfied in experiments on isolated fibers, it also easily violated. Furthermore cells and fibers are often closely packed in functioning neural systems; thus the situation when (2.24) is not satisfied deserves careful attention.

If the external current is constrained to flow in a region $b \ll \beta^{-1}$ (i.e., very close to the membrane surface), the outside resistance will increase from approximately zero to

$$r_2 \approx 1/A_0\sigma_2, \tag{2.25}$$

where $A_0$ is the cross-sectional area outside the membrane. However if $A_0$ does not exhibit rotational symmetry, the TM fields will again be scattered into non-TM modes in a manner which is not described by (2.22). Furthermore if the changes in $A_0$ take place on a distance scale short compared with $\beta^{-1}$ the easy transition from (2.13) to (2.21a) will again no longer be valid. Qualitative effects of various experimental restrictions in the external geometry have been reviewed by Taylor (1963). Often nerve fibers are not isolated but arranged in bundles surrounded by a sheath of connective tissue. The sciatic nerve of vertebrates (see Fig. 35) is constructed this way to permit the transmission of a multicomponent message from the spinal cord to the muscle. This situation has been carefully investigated by Clark and Plonsey (1968) who present several numerical calculations which help to determine the effect of fiber geometry upon $r_2$.

## D. Resistive approximation for the longitudinal impedances

Equation (2.22) specifically assumes that the sum of the inside and outside longitudinal impedances can be approximated by a single real number

$$r_s \equiv r_1 + r_2 \approx z_1 + z_2. \tag{2.26}$$

This approximation ignores terms of order $(ka)^2$ in evaluating the small argument expressions for $z_1$ and $z_2$ in (2.12). Physically this implies neglect of the effect of time dependent magnetic field on the electric field, or inductive effects. In a later section, after the nature of the nonlinear propagation process has been clarified, we shall see that the only sensible effect of this inductive correction is to preclude a pulse velocity greater than the velocity of light.

A transmission line equivalent circuit can easily be constructed which corresponds to Eqs. (2.13) and (2.21b). For example in the differential ladder network of Fig. 7(a), the change in series current over a differential distance, $dx$, is found from Kirchoff's current law (or conservation of electric charge) to be

$$i(x) - i(x + dx) = 2\pi a N(v)\,dx \tag{2.27}$$

which implies (2.21b). In a similar way the change in shunt voltage over a differential distance, $dx$, is obtained from Kirchoff's voltage law (or conservation of energy) to be

$$v(x) - v(x + dx) = dx\mathfrak{I}^{-1}\{(z_1 + z_2)\mathfrak{I}[i]\} \tag{2.28}$$

where $\mathfrak{I}$ and $\mathfrak{I}^{-1}$ respectively represent the Fourier transform on both $x$ and $t$ and its inverse. Equation (2.28) implies (2.13).

Transmission line equivalent circuits (TLEC) of this sort have found wide application in electronics since the development of the electric telegraph [Kelvin (1855)] and in electrophysiology since the turn of the century [Hoorweg (1898), Hermann (1905)]. For rather complete reviews see Taylor (1963) and Cole (1968). Various attitudes may be taken toward the TLEC, two of which are as follows:

(1) The TLEC can be considered simply a mnemonic device through which the partial differential equations under consideration, (2.13) and (2.21b), are represented pictorially. It is often useful to suggest reasonable higher approximations for further study [Scott (1970)].

(2) The TLEC can be taken as the starting point for analysis. Equations (2.27) and (2.28) are then considered fundamental equations from which (2.21b) and (2.13) are derived. This attitude has characterized much of past research in electrophysiology [Cole (1968)].

It is my opinion that the problems which arise in studying the electrophysics of the nerve cell are sufficiently difficult that neither attitude should dominate. For a nerve fiber which approximates the idealized geometry of Fig. 5(a), it is clearly more satisfying (for the physicist, at least) to begin the analysis with Maxwell's equations. Various approximations can be itemized and explicit analytic expressions can be obtained for $z_1$ and $z_2$. This analysis, on the other hand, can eventually lead to the nonlinear pde (2.22) which is also obtained directly from (2.27) and (2.28). In situations with more complex geometry, where the electromagnetic analysis may not be tractable, one can begin with a TLEC and appeal to the results for simpler geometry as a justification. Rall (1962, 1964) has demonstrated the power of this approach through his application of "compartmental analysis" to study the rather complex geometrical effects which arise in dendritic fibers.

The general TLEC to be considered in this review is shown in Fig. 7(b) for which suitable expressions to determine $r_1$ and $r_2$ are given in (2.19) and (2.25). With the series inductances, $l_1$ and $l_2$, equal to zero, this TLEC was studied by Offner as early as 1937 and serves as the basis for the calculation of conduction velocity for an action potential by Offner, Weinberg, and Young (1940). We will continue to assume these inductances equal to zero for the initial development of the nonlinear analysis. In a later section explicit expressions and values will be calculated, and a nonlinear propagation problem will be solved in order to demonstrate that it is a valid assumption to take these inductances equal to zero. Notice that the shunt element in Fig. 7(b) is represented differently than that in Fig. 7(a). The reason for this change is that in Fig. 7(b) it is explicitly recognized that membrane current consists of two distinct components: displacement current and ion current. Equating the shunt currents in the two figures yields

$$2\pi a N = c(\partial v/\partial t) + j_i, \tag{2.29}$$

where $j_i$ is the ion current, and $c(\partial v/\partial t)$ the displacement current passing through the membrane both per unit length in the $x$ direction. The decomposition indicated in (2.29) is especially interesting because there is substantial experimental evidence [Cole (1968)] to show that $c$ is a constant throughout the course of the action potential [see, however, FitzHugh and Cole (1973)]. Substituting (2.29) into (2.22) yields a new form for the basic equation of nerve propagation

$$\partial^2 v/\partial x^2 - r_s c(\partial v/\partial t) = r_s j_i\,. \tag{2.30}$$

Notice that (2.30) has the form of the nonlinear diffusion equation discussed briefly in the introduction. In the following sections we will consider the chemical physics of the nerve membrane and the development of phenomenological theories to describe the nonlinear dependence of $j_i$ upon $v$.

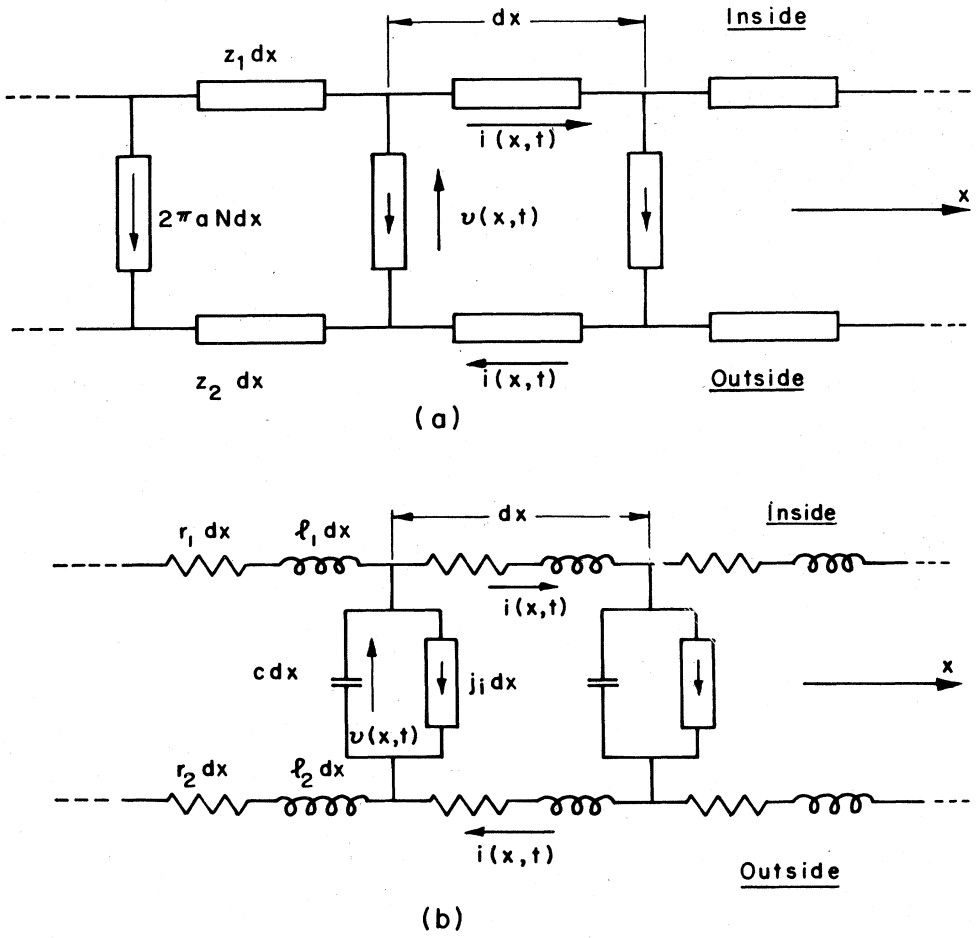


FIG. 7. (a) Transmission line equivalent representation of (2.13) and (2.21b), and (b) equivalent circuit for a nerve fiber to be considered in this review.

## III. PHYSICS OF A CELL MEMBRANE

Our next task is to become acquainted with the physical character of the cell membrane which is indicated merely as a surface in Fig. 4, and as a homogeneous region in Fig. 5. The existence of a membrane for red blood cells was confirmed by the measurements of Fricke (1923, 1925a,b) on the conductivity vs frequency of cell suspensions. He measured a membrane capacitance of 0.81 $\mu$F/cm$^2$ which, for an assumed relative dielectric constant of 3, implied a membrane thickness of 33Å. At about the same time Gorter and Grendel (1925) demonstrated that these cells "are covered by a layer of fatty substances that is two molecules thick." It is well to devote a moment to the measurement technique of Gorter and Grendel because it exemplifies nicely the energetics of membrane structures. The general structure of a lipid (fatty) molecule is "cigar shaped" with a charged head group localized at one end of a hydrocarbon tail. [See Chap. 10 of Lehninger (1970) for many chemical details.] Building upon a previous demonstrated by Lord Rayleigh (1899) that oil films on a water surface become monomolecular, Langmuir (1917) [see also Adam (1921, 1922)] showed that the structure of the monolayer is with the charged head groups oriented toward the water surface where the electric field energy can be reduced by the high dielectric constant of water (ca. 80 $\epsilon_0$), and the hydrocarbon tails maintained in a closely packed, vertical structure by transverse van der Waals attraction. Gorter and Grendel distilled the lipid material from a known quantity of blood cells and found that the area of the monolayer which could be obtained with this lipid at an air–water interface was about twice the area of the cell surfaces. Thus the red blood cell membrane appeared to be largely the lipid bilayer shown in Fig. 8. This same structure was proposed [Danielli and Davson (1935), Danielli (1936)] from an energetic comparison of various lipid organizations, as the basic structure of biological cell membranes. Membrane distillates always contain a substantial fraction (>50%) of protein [Bretscher (1973), Kilkson (1969)]; and if these are located within the lipid phase they are called *intrinsic* [Green (1971)] or *integral* [Singer and Nicolson (1972)]. Proteins attached weakly to the surface of the lipid bilayer, called *extrinsic* or *peripheral* are considered to be of less importance for membrane function. Green, Ji, and Brucker (1972) have emphasized the importance of protein domains through which long-range ordering of (perhaps octal) protein subunits is established [Vanderkooi and Green (1970)] as indicated in

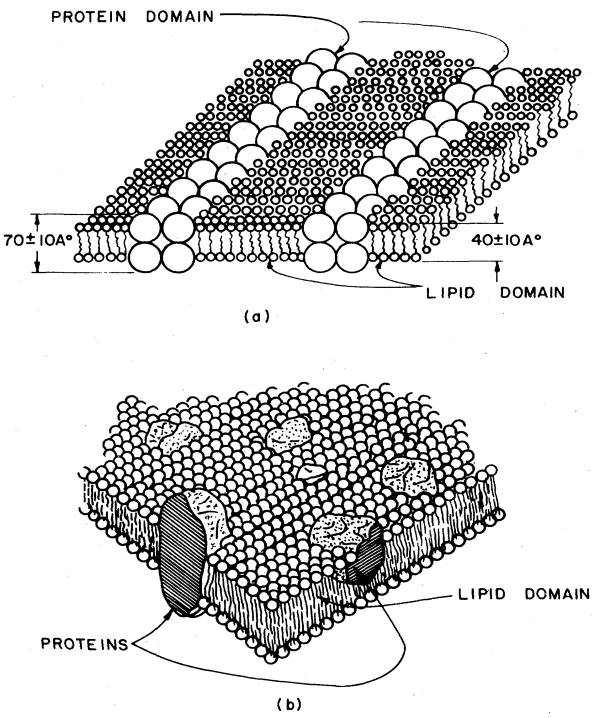


FIG. 8. Membrane models. (a) The "structure-function unitization model" redrawn from Green, Ji, and Brucker (1972). Domain geometry is assumed to be highly variable from membrane to membrane. (b) The "fluid mosaic model" redrawn from Singer and Nicolson (1972).

Fig. 8(a). Singer and Nicolson, on the other hand, have suggested that the proteins may be considered to float in the two-dimensional lipid liquid [Fig. 8(b)]. Good general surveys of biological membranes are given in the recent books by Cereijido and Rotunno (1970), Jain (1972), and Nystrom (1973), and many of the historically important papers have been collected by Branton and Park (1968). The direct synthesis of a biological membrane was attempted by Bungenberg de Jong and Bonner (1935), Devaux (1936), Dannielli (1936), Teorell (1936), Langmuir and Waugh (1938), and Dean (1939) who produced bulayer films with a capacitance of about 1 $\mu$F/cm$^2$ [Dean, Curtis and Cole (1940)]. This work lay dormant for more than two decades until the ease with which lipid bilayers can be formed was demonstrated by Mueller, Rudin, Tien, and Wescott (1962). The key idea was an observation in Newton's *Optiks* on the color patterns of soap bubbles. He had observed that: "after all the Colours were emerged at the top, there grew in the center of the Rings a small round black Spot . . . which continually dilated itself till it became sometimes more than 1/2 or 3/4 of an inch in breadth." Newton was observing that it is energetically favorable for a soap film to thin into a lipid bilayer. In this case, the charged head groups are oriented inward toward a remnant layer of water. Such a soap film appears "black" (i.e., almost reflectionless) because its thickness ($\sim$100Å) is very much less than the wave length of light. [I can only avoid the temptation to say more about this subject by directing the reader to the delightful descriptions prepared by Lawrence (1929) and by Mysels, Shinoda and Frankel (1959).] Mueller, Rudin *et al.* (1962) showed that the same result could be obtained for lipid films between aqueous phases.

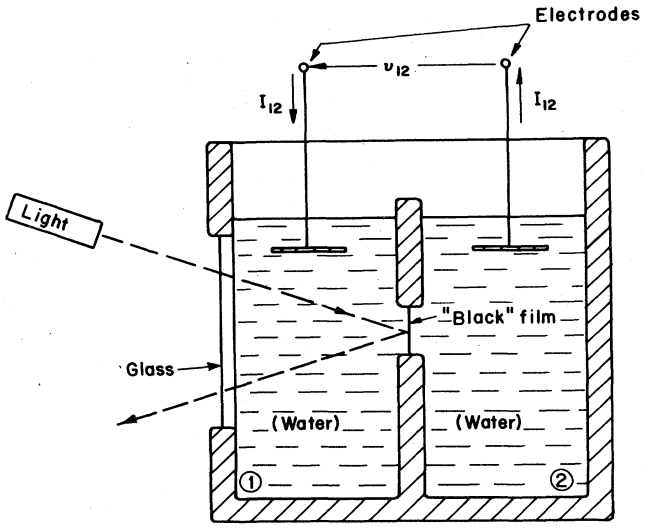


FIG. 9. A basic experimental arrangement for physical measurements on artificial lipid bilayers.

A diagram of the basic arrangement for measurements on artificial lipid bilayers is given in Fig. 9. A camel's hair brush is dipped in the lipid solution and then stroked across a small ($\sim$1 mm) hole in a two chamber vessel. The resulting thick lipid film thins in about 10 minutes, as Newton described, to a lipid bilayer of black film. Optical measurements of film thickness and electrical measurements of capacity and conductivity can then proceed. The experimentalist who wishes to begin such an investigation is referred to the review by Goldup, Ohki, and Danielli (1970), the careful discussion of experimental details by Howard and Burton (1968), and the recent book by Jain (1972).

The processes by which ions flow across the membranes of living cells are often divided into *passive* and *active* mechanisms. Passive transport is considered to be in response to a gradient of the electrochemical potential. Active transport involves the flow of ions against the electrochemical potential; a good discussion of such processes can be found in Chapter 27 of Lehninger (1970). During the propagation of an action potential along a nerve fiber (Fig. 3) only passive transport is involved; active processes merely recharge the energy sources. My objective here is to present a simple phenomenological description of passive transport from which the ionic current components in (2.2) can be constructed.

It should be understood from the start that intrinsic membrane proteins completely dominate ion flow in a living membrane. To appreciate the truth of this assertion, it is instructive to begin with an investigation of passive transport of only sodium ions across an ideal lipid bilayer as is indicated in Fig. 10. The steady state current density from chamber ① to ②, $J_{12}$, will be proportional to the ion density [Na$^+$] and to the gradient of the electrochemical potential, $\psi$. Thus we can write the Nernst–Planck equation [Nernst (1888, 1889), Planck (1890a, b), Smith (1961)]

$$J_{12} = \mu q[\mathrm{Na}^+](d\psi/dr), \tag{3.1}$$

where $q$ is the electronic charge and $\mu$ is the ionic mobility.

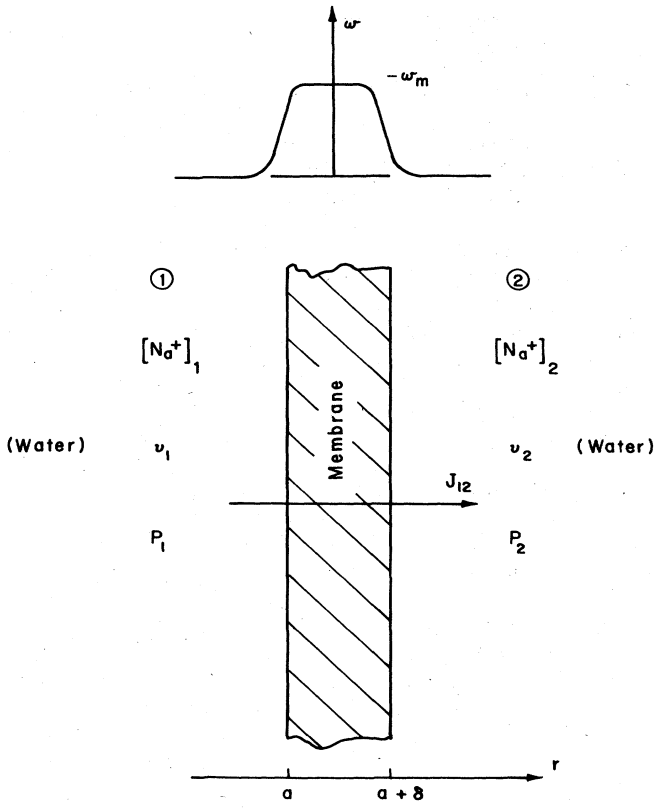


FIG. 10. Simple geometry for passive transport of a single ion through a uniform membrane.

Assuming that the pressure gradient can be neglected, the electrochemical potential is

$$\psi = (kT/q)\log[\mathrm{Na}^+] + v + w, \tag{3.2}$$

where $v$ is the externally applied electrical potential, and $w$ is the contribution to the electrochemical potential arising from the presence of the membrane. Since the dielectric constant of water ($\sim 80\,\epsilon_0$) is much greater than that of the lipid, a major contribution to $w$ will be the image force at the water-membrane boundary. [In direct physical terms, the electrostatic field energy associated with the ion is much lower in the water phase where the ionic charge can be neutralized by rotating water molecules.] The factor $(kT/q)$ in (3.2) [where $k$ is the Boltzmann constant and $T$ is absolute temperature] appears from the Einstein (1905) relation between diffusion constant, and mobility.

Substituting (3.2) into (3.1) gives

$$J_{12} = -\mu kT\left\{\frac{d[\mathrm{Na}^+]}{dr} + \frac{[\mathrm{Na}^+]q}{kT}\frac{d}{dr}(v+w)\right\}, \tag{3.3}$$

which, in steady state, must be independent of $r$. The boundary conditions to be satisfied at the edges of the membrane are

$$r = a: \quad [\mathrm{Na}^+] = [\mathrm{Na}^+]_1, \quad v = v_1, \quad w = 0 \tag{3.4a}$$

$$r = a + \delta: \quad [\mathrm{Na}^+] = [\mathrm{Na}^+]_2, \quad v = v_2, \quad w = 0. \tag{3.4b}$$

The expression for sodium ion concentration which satisfies these boundary conditions and maintains $J_{12}$ constant has been determined by Neumke and Läuger (1969) as [see also Boltaks, Vodyanoi and Fedorovich (1971) and Markin, Grigor'ev and Yermishkin (1971)]

$$[\mathrm{Na}^+] = \exp[-(v+w)q/kT]\Big[[\mathrm{Na}^+]_1\exp(v_1q/kT) + \{[\mathrm{Na}^+]_2\exp(v_2q/kT) - [\mathrm{Na}^+]_1\exp(v_1q/kT)\} \times \Big(\int_a^{a+r}\exp[(v+w)q/kT]\,dr\Big)\Big/\Big(\int_a^{a+\delta}\exp[(v+w)q/kT]\,dr\Big)\Big] \tag{3.5}$$

which upon substitution into (3.4) yields

$$J_{12} = \Big(\mu kT\Big/\int_a^{a+\delta}\exp[(v+w)q/kT]\,dr\Big) \times \{[\mathrm{Na}^+]_1\exp(v_1q/kT) - [\mathrm{Na}^+]_2\exp(v_2q/kT)\}. \tag{3.6}$$

For a detailed discussion of the effect of barrier shape, $w(r)$, on volt-ampere characteristics see Hall, Mead and Szabo (1973). Under experimental conditions for which the membrane structure remains independent of the applied voltage, they have demonstrated that $w(r)$ can be computed from volt-ampere measurements. The measured barrier height is close to the difference in electrostatic energy of the ion in lipid and in water; the shape is trapezoidal as indicated in Fig. 10.

Introducing the notational definitions

$$v_{12} \equiv v_1 - v_2, \tag{3.7}$$

and

$$V = (kT/q)\log([\mathrm{Na}^+]_2/[\mathrm{Na}^+]_1), \tag{3.8}$$

we obtain from (3.6)

$$J_{12} = (kT/q)G[\exp[(v_{12} - V)q/kT] - 1] \tag{3.9}$$

$$\approx G(v_{12} - V) \quad \text{for} \quad |v_{12} - V| < kT/q, \tag{3.10}$$

where

$$G \equiv \mu q[\mathrm{Na}^+]_2\exp(v_2q/kT)\Big/\int_a^{a+\delta}\exp[(v+w)q/kT]\,dr. \tag{3.11}$$

From (3.2) it is clear that $(v_{12} - V)$ is the change in electrochemical potential from chamber ② to chamber ①. For a small enough difference in electrochemical potential, (3.10) indicates that the relation between voltage and ion current density should be linear. If the concentration gradient is zero, $[\mathrm{Na}^+]_1 = [\mathrm{Na}^+]_2$, this linear relation

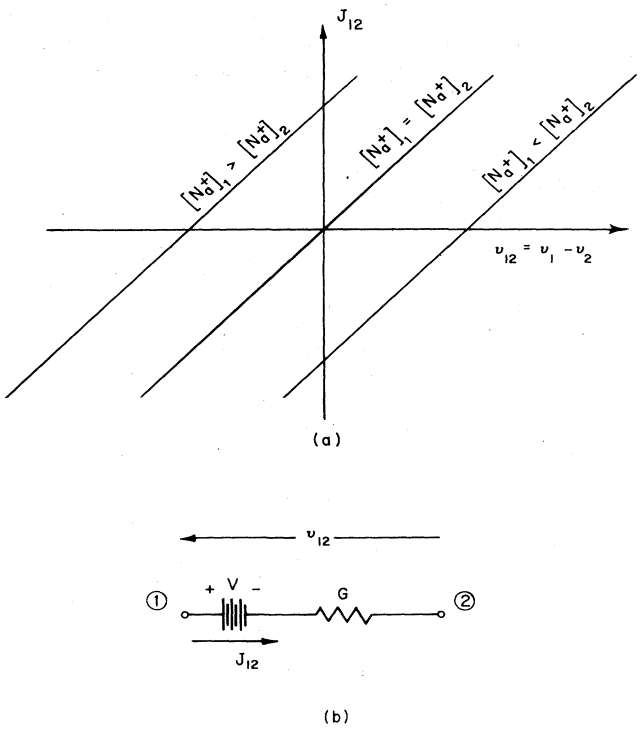


FIG. 11. (a) Sodium ion current density at a small difference of electrochemical potential. (b) An equivalent circuit for the current density carried by sodium ions.

should go through the origin as indicated in Fig. 11(a). For positive ions if $[Na^+]_1 < [Na^+]_2$ and the current density is zero, chamber ① will have a positive potential with respect to ②. If $[Na^+]_1 > [Na^+]_2$, the polarity of the zero current voltage difference will be reversed. Thus each ionic species appears in the membrane as [see Fig. 11(b)] a *battery* of voltage given by (3.8) with its positive terminal directed toward decreasing (increasing) ion concentration for positive (negative) ions. In general there will be several species of ions present which makes the analysis considerably more difficult. In 1943 Goldman derived a generalization of (3.6) under the assumption of a constant electric field (electroneutrality), and Offner (1971) has recently discussed numerical techniques which do not require this assumption. See Rosenberg (1969) for a comparison of resting potential formulas.

Let us now consider an experiment in which a pure lipid bilayer is carefully prepared in the apparatus of Fig. 9 [Howard and Burton (1968)] with equal concentrations for all ions so the ionic batteries are zero. The initial slope of the current density–voltage curve can be as low as [Goldup, Ohki and Danielli (1970)]

$$G \sim 10^{-9} \text{ mho/cm}^2$$

which, for a membrane thickness of about 100Å ($\sim 10^{-6}$ cm), implies a membrane resistivity

$$\rho \sim 10^{15} \text{ ohm-cm.}$$

Thus a clean lipid bilayer should be classified as a *very* good insulator, and the importance of the protein complex in facilitating ionic conduction through biological membranes cannot be overemphasized.

Mueller, Rudin, Tien and Wescott (1962) showed that the addition of small amounts of properly chosen and refined proteinaceous material (called EIM for "excitability inducing material") will increase the membrane conductivity by many orders of magnitude, and can introduce the nonlinearity essential for generation of an action potential. At low protein concentrations the conductance has been observed to increase in quantum units of about $4 \times 10^{-10}$ mhos [Goldup *et al.* (1970)]. When alamethicin (a circular polypeptide with molecular weight ~1800) is added to the aqueous phase of a clean experiment, the membrane conductance is found to increase with the sixth power of concentration [Mueller and Rudin (1968b)]. These observations suggest that the alamethicin molecules may be coördinated in groups of six to permit ionic conduction through the membrane. Hille (1970) has surveyed a wide variety of kinetic, electrochemical, and pharmacological data for biological nerve membranes and concluded that the conductance changes observed during the action potential (see Fig. 3) are caused by the opening and closing of localized conductance channels. The term "pore" is often used in a generic sense to indicate a localized region of high conductivity on the membrane. For such a porous membrane (3.6) is no longer useful. The barrier potential, $w(r)$, and the ionic mobility, $\mu$, depend strongly upon the position on the membrane surface and also upon the membrane voltage.

In this situation it is helpful to return to (3.1) and write it in the form

$$J_{12} = G(v_{12} - V) \tag{3.12}$$

where, as was previously noted, $(v_{12} - V)$ is the negative of the change in electrochemical potential from chamber ① to ②. The conductivity is not a constant but a nonlinear function of the experimental variables. The form of (3.12) merely makes explicitly evident the zero in ion current which appears when the electrochemical difference for that ion is zero. Often, the conductance per unit area, $G$, appears as a function only of the transmembrane volrage, $v_{12}$. An exceptionally clear example of this has recently been published by Eisenberg, Hall, and Mead (1973) in connection with their careful study of the effect of alamethicin on artificial lipid bilayer membranes. The volt–ampere curve in Fig. 12(a) exhibits a distinct region of negative differential conductance; but the conductance [see in Fig. 12(b)] shows a simple exponential rise throughout this region. The experimental rise is the same as that observed without an ion imbalance. Thus it is clear that in this case we can write (3.12) in the form

$$J_{12} = G(v_{12})(v_{12} - V). \tag{3.13}$$

As has been pointed out by Cole (1968, p. 289) and by Mueller and Rudin (1968a, b), the condition for negative differential conductance can then be expressed by differentiating (3.13) with respect to $v_{12}$

$$dJ_{12}/dv_{12} = G'(v_{12} - V) + G$$

so

$$dJ_{12}/dv_{12} < 0 \Rightarrow G'(V - v_{12}) > G. \tag{3.14}$$

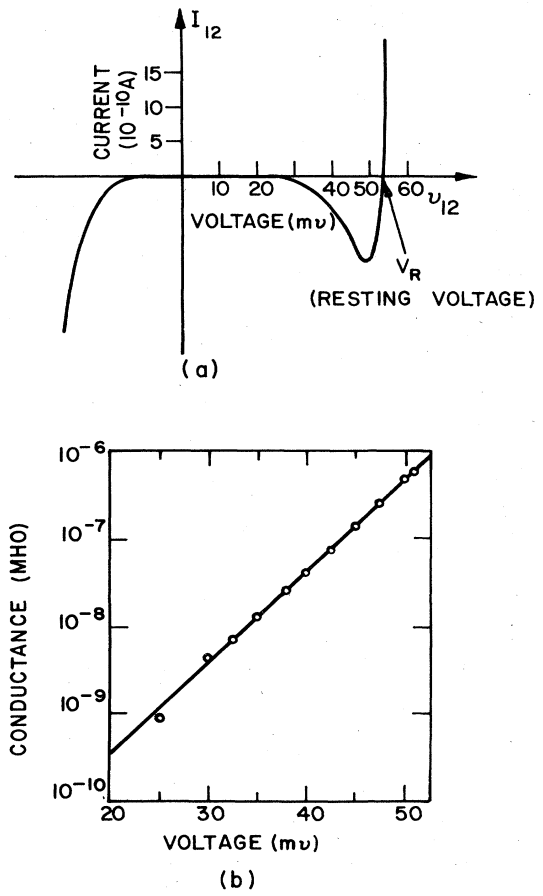


FIG. 12. Measurements on an artificial lipid bilayer membrane in a 100:1 KCl gradient. Chamber ①: 0.5 m KCl and $6 \times 10^{-7}$ g/ml alamethicin. Chamber ②: 0.005 m KCl and $9 \times 10^{-6}$ g/ml alamethicin. From Eisenberg, Hall and Mead (1973). (a) Current vs voltage. (b) Conductance vs voltage.

This condition for negative differential conductance was first demonstrated for an alamethicin-doped artificial lipid bilayer membrane by Mueller and Rudin (1968b). Whenever membrane current ($J_{12}$) is related to membrane voltage ($v_{12}$) as in (3.13), the condition can be expressed in the following simple physical terms: *negative differential conductance will appear when* G *is rising rapidly enough below the resting voltage.* Since the resting voltage depends upon ion concentrations, negative differential conductance of a membrane can be made to appear or disappear simply by changing the composition of the external solutions! Thus, as Agin (1969) has emphasized, the mere appearance of a negative conductance need not depend upon exotic effects such as interaction of divalent ions, conformational changes of macromolecules, micelle transformations of lipid systems, enzyme reactions, ion specific carriers, redistributions of pores, chemical gates, etc.

Cole (1968, pp. 287–290) points out that the functional form in (3.12) is especially useful for description of a squid axon membrane since $G$ remains constant for times up to the order of 100 $\mu$sec. The current flow in response to more rapid changes in voltage is simply ohmic.

It should be noted that the current indicated in Fig. 12(a) is due to *both* potassium and chlorine ions. In general a membrane which separates $n$ ionic species can be represented as in Fig. 13 whereupon current is related to transmembrane potential by [Cole (1968, pp. 193–7)]

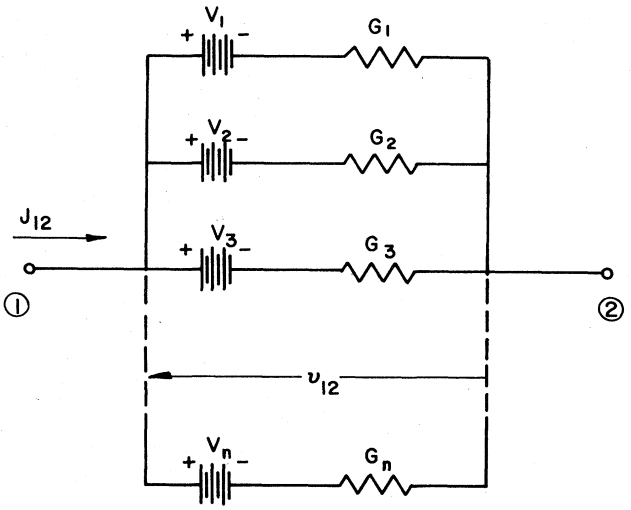


FIG. 13. Membrane equivalent circuit for $n$ ionic species.

$$J_{12} = [\sum_{i=1}^{n} G_i] v_{12} - \sum_{i=1}^{n} (G_i V_i) \tag{3.15}$$

which has the same form as (3.12). From the discussion related to Fig. 11 it should be clear that for positive ions of concentrations $[C^+]_1$ and $[C^+]_2$

$$V_i = (kT/q) \log([C^+]_2/[C^+]_1). \tag{3.16a}$$

as in (3.8). For negative ions of concentrations $[C^-]_1$ and $[C^-]_2$

$$V_i = (kT/q) \log[C^-]_1/[C^-]_2). \tag{3.16b}$$

The resting potential (i.e., the value of $v_{12}$ for $J_{12} = 0$) is

$$V_R = \sum (G_i V_i)/\sum G_i; \tag{3.17}$$

thus if the conductance, $G$, for a particular ion becomes large, the resting potential will approach the battery voltage for that ion. To see how these equations can be used, consider the data of Fig. 12(a). The resing potential, $V_R = 53$ mV and, from the ion concentration ratios and (3.16), $V_K = +115$ mV and $V_{Cl} = -115$ mV. Thus from (3.17) we find at the resting potential that $G_K/G_{Cl} = 2.7$ so about 73% of the ion current flowing in the vicinity of the resting potential should be carried by potassium ions.

Depending upon one's point of view, (3.15) can be considered as (i) a flexible and useful description of multicomponent ion flow, or (ii) a phenomenological representation without physical meaning. The second attitude has been presented in detail by Tasaki (1968). He points out that if no restrictions are placed upon the functional dependence of the $G$'s, then (3.15) says nothing more than (3.12). Furthermore (3.17) is of no value for calculation of a resting potential unless other information about the

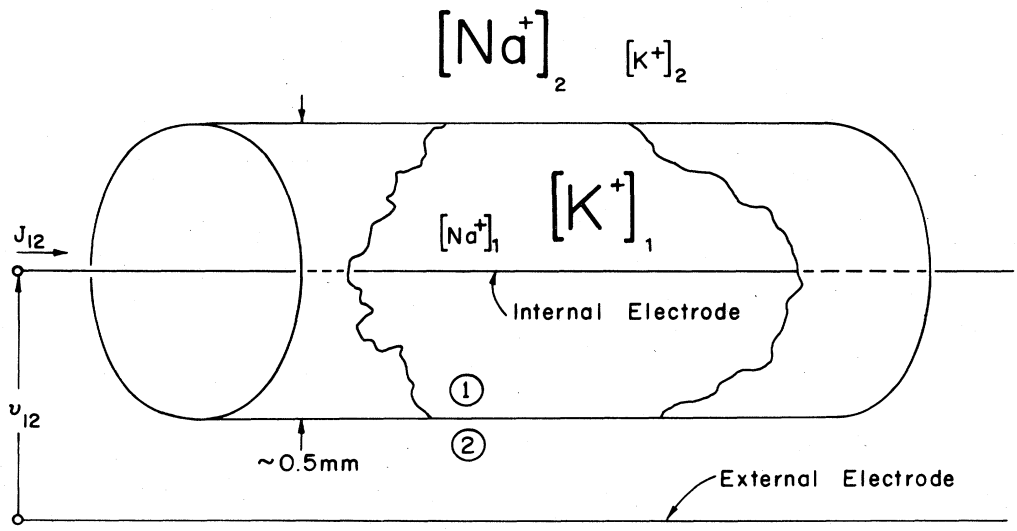


FIG. 14. Geometry for a space clamped measurement on a squid nerve membrane.

membrane permeability to various ions is available. Tasaki (1968) carefully considers the calculation of resting potentials from physical considerations under a variety of simplifying assumptions. A complementary discussion is presented in the recent book by Khodorov (1974).

As an example of the kind of equation which can be derived for the resting voltage, Hodgkin and Katz (1949) assumed that each ion obeys the Nernst–Planck equation (3.3) and that the ion concentration just inside the membrane is a partition coefficient, $\gamma$, times the corresponding concentration outside the membrane. Then for univalent ions

$$V_R = (kT/q) \log \frac{\sum^+ \mu_i\gamma_i[C^+]_2 + \sum^- \mu_i\gamma_i[C^-]_1}{\sum^+ \mu_i\gamma_i[C^+]_1 + \sum^- \mu_i\gamma_i[C^-]_2}. \quad (3.18)$$

where $\sum^+$ ($\sum^-$) indicates summation over the positive (negative) ions.

So far we have been considering only passive (i.e., nonmetabolic) mechanisms for ion transport across a cell membrane. Active ion transport is extremely important in the operation of a living cell; and, although the details of such processes are not yet well understood, the broad outlines are emerging [(Lehninger (1970)]. The inside of a nerve cell, for example, is usually some 60–70 mV negative with respect to the outside. Using the convention of Figs. 5 and 10

$$J_{12} = 0 \quad \text{for} \quad v_{12} = V_R \approx -65 \text{ mV}.$$

For the squid giant axon [Hodgkin and Huxley (1952)]

$$[Na^+]_2/[Na^+]_1 \approx 7.5 \Rightarrow V_{Na} = +50 \text{ mV}$$

and

$$[K^+]_1/[K^+]_2 \approx 30 \Rightarrow V_K = -77 \text{ mV}.$$

Thus metabolic energy must be expended to pump sodium ions outward and potassium ions inward against the resting potential. We shall see that the electric field energy associated with the resting potential is expended in the propagation of an action potential [Hodgkin (1964)]. Current knowledge of the processes for outward pumping of $Na^+$ and inward pumping of $K^+$ has recently been reviewed by Thomas (1972). There are indications that three sodium ions are removed for each two potassium ions which enter. The energy for this process is supplied by the conversion of ATP (adenosine*tri*phosphate) to ADP (adenosine*di*-phosphate). The ATP, in turn, is reconstituted in the membranes of subcellular units known as mitochrondria.

## IV. ELECTRODYNAMICS OF AN ACTIVE NERVE MEMBRANE

The most extensive nerve membrane measurements have been made on the giant axon of the squid [see Cole (1968) for a thorough discussion of the literature and a beautiful color photograph of the animal]. This fiber is between 0.5 and 1 mm in diameter, and several centimeters in length. It is easily removed from the squid and continues to function for at least several hours and often as long as a day.[3]

A typical experimental arrangement for measuring the electrodynamic properties of a membrane is indicated in Fig. 14 [Hodgkin, Huxley, and Katz (1952)]. This is called a "space-clamped" measurement because the electrode arrangement eliminates the possibility of longitudinal variation of voltage and the associated wave propagation effects; it is also called a "voltage clamped" measurement if a negative feedback amplifier is introduced to reduce the source impedance and permit $v_{12}$ to be independently specified. We are interested in interpreting the relationship between $J_{12}$ and $v_{12}$ to extract the nonlinear character of the membrane indicated simply by $J_{12} = N(v_{12})$ in (2.2). As was previously mentioned in connection with (2.29), $J_{12}$ is composed of a displacement current component through

[3] An introduction to the surgical procedures for removal of a nerve fiber is provided by the two part film loop *Nerve Impulse* available from Ealing Corp., 2225 Massachusetts Ave., Cambridge, Mass. 02140.

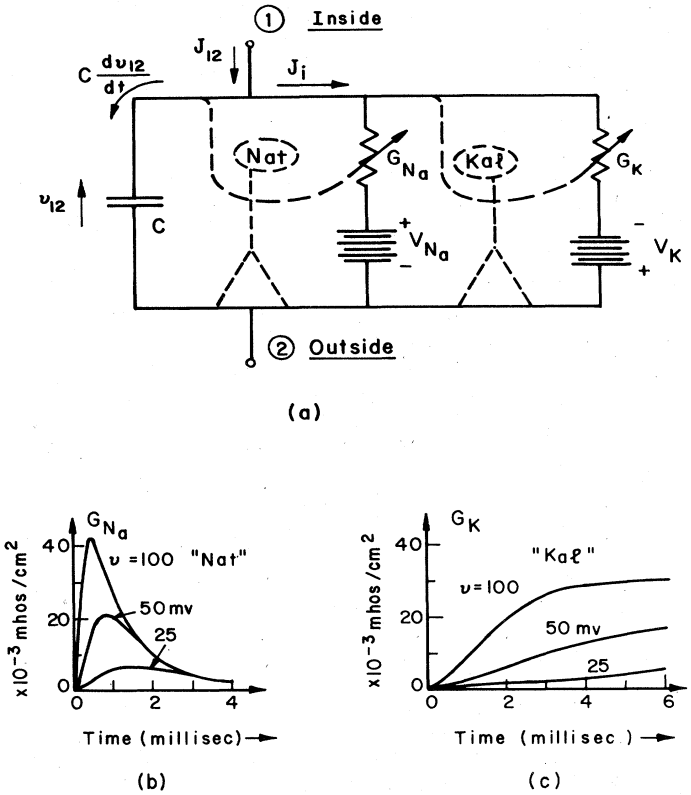


FIG. 15. (a) A simplified equivalent circuit for a unit area of squid membrane. (b) The reaction of Nat to displacement of membrane voltage from the resting value. (c) Ditto for Kal [Cole (1968), p. 272].

the membrane capacity, and an ion current through the membrane. Thus

$$J_{12} = C(dv_{12}/dt) + J_i, \tag{4.1}$$

where $C$ is the capacitance per unit area of the membrane (about 1 $\mu$F/cm$^2$), and $J_i$ is the sum of all the individual ionic currents through the membrane. If $v_{12}$ is independent of time, the displacement current is zero, and the ion current should be a sum of terms as in (3.15). In measuring the ionic currents, it is therefore convenient to hold the membrane voltage fixed. It was this voltage-clamp measurement [Cole (1949), Marmot (1949)] which led Hodgkin and Huxley (1952) to a representation of $J_i$ which could be used to solve (2.30) for a propagating action potential.

The sodium and potassium ion currents are most interesting because they respond nonlinearly to changes of voltage across the membrane. The behavior of these nonlinear currents has been described in a simple and appealing way by Katz (1966) and by Cole (1968) using the equivalent circuit shown in Fig. 15(a). This representation includes a sodium battery of about 50 mV directed inward and a potassium battery of about 77 mV directed outward. As was noted in the previous section, the ion batteries account for the tendency of sodium ions to diffuse inward and for potassium ions to diffuse outward. These batteries are in series with a sodium conductance per unit area, $G_{Na}$, and a potassium conductance per unit area, $G_K$, respectively as is indicated in Fig. 13. A small boy (named "Nat") senses the voltage across the membrane and adjusts $G_{Na}$ according to some rules of his own, and another small boy (named "Kal") does the same for $G_K$. What Nat and Kal do is conveniently described in terms of the change of potential inside the membrane with respect to its resting value. Thus we define

$$v \equiv v_{12} - V_R. \tag{4.2}$$

If the voltage inside the membrane is made more negative (*hyperpolarized*), the membrane conductances remain small with little change in value. If the voltage inside the membrane is made less negative (*depolarized*), the reactions of Nat and Kal are indicated in Fig. 15(b) and (c). The individual ion current components can be measured by assuming the validity of (3.15) and adjusting the external salt solution to make $V_{Na}$ or $V_K$ equal to zero.

The curves in Fig. 15 indicate the way $G_{Na}$ and $G_K$ change with time for a *fixed* change in voltage. If the circuit is not voltage clamped, however, it will "switch." The reason for this is that a small depolarizing voltage ($v > 25$ mV) increases the conductance of the membrane to sodium ions. Thus sodium ions flow *into* the membrane which *increases* the depolarizing voltage causing the sodium ion conductance to increase even more. It is a positive feedback effect; once initiated the membrane will rapidly approach the sodium ion battery voltage $v_{12} = V_{Na}$ or $v = V_{Na} - V_R \simeq$ 115 mV due to the inrush of sodium ions. Then $G_{Na}$ will fall back toward zero [Fig. 15(b)] and $G_K$ will rise [Fig. 15(c)] allowing an outflow of potassium ions. This outward potassium ion current will bring the membrane potential back to its resting value. Increasing the potential inside the membrane by 25 mV or more is something like pulling the chain on the hopper; once the process starts it goes through the complete cycle. In large fibers the total ionic flow during one switching cycle is a very small fraction of the total ion concentration; many hundreds of thousands of firings can occur in a squid giant axon before the ionic batteries become discharged. In smaller fibers, such as those shown in Fig. 2, the ionic flow per impulse can be a substantial fraction of the total ion concentration.

This is a description of *what* happens. *Why* it happens is not yet understood, but some interesting clues can be gleaned from an investigation of the total ion current which flows in response to a fixed voltage (so $J_{12} = J_i$). From Fig. 16 it can be seen that if the voltage $v_{12}$ is held at a value less than $V_{Na}$, the current $J_{12}$ is first negative (inward), then positive (outward). From these curves it is possible to define an initial peak, $J_p$, and a final steady state value, $J_{ss}$ as is indicated for the curve at $v_{12} = -20$ mV in Fig. 16. Both $J_p$ and $J_{ss}$ can then be plotted against the corresponding value of the voltage step as is indicated in Fig. 17(a). The early, $J_p$, branch of the curve is primarily sodium ion current; while the steady state, $J_{ss}$, branch is primarily potassium ion current. The membrane appears to be in a high conductance state for $v_{12} > -40$ mV and a low conductance state for $v_{12} < -50$ mV. Returning to the inequality condition for differential negative conductance expressed in (3.14), we see that in the range $-50$ mV $< v_{12} < -40$ mV the conductance is rising "rapidly enough."

Similar data for other electrically active biological membranes are plotted in Figs. 17(b)–(f). In each case there is an early current density ($J_p$) or current ($I_p$) which exhibits negative differential conductivity and eventually relaxes

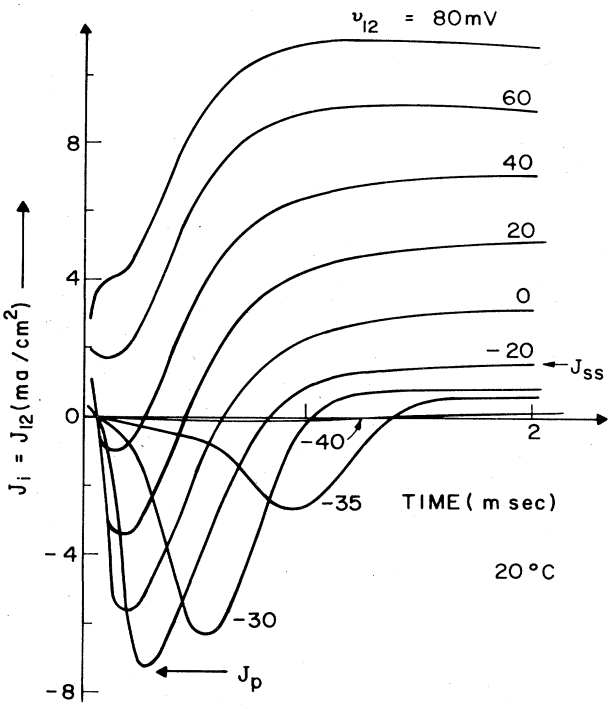


FIG. 16. Typical response of squid membrane current density to fixed steps of voltage [Cole (1968), p. 326].

into a steady state current density ($J_{ss}$) or current ($I_{ss}$) with only positive differential conductivity. In Figs. 17(a)–(d) the early current is carried primarily by sodium ions and the later current is carried primarily by potassium ions. In the measurement on *Aplysia californica* shown in Fig. 17(e), Geduldig and Gruener (1970) find clear evidence for a calcium ion contribution to the early current [see also Kryshtal', Magura and Parkhomenko (1969) and Chap. 5 of Khodorov (1974)]. The data in Fig. 17(f) are from a plant cell, the fresh water alga *Nitella*. This plant, which produces giant internodal cells with about the same dimension as the squid giant axon, has been described in detail by Scott (1962). For *Nitella* it appears that the early current is carried by an outward flux of chloride ions, while the later current is primarily outward potassium. The time required to relax from the $J_p$ branch to the $J_{ss}$ branch is the order of seconds for *Nitella* in contrast with a time of the order of milliseconds for the animal fibers in Figs. 17(a)–(c).

No universally acceptable theory has yet been proposed to explain the relation between membrane electrodynamics (Fig. 17) and membrane biochemistry (Fig. 8). An important recent contribution to this quest, however, is the review of various proposed mechanisms in Chapter 9 of the book by Khodorov (1974). These mechanisms include (i) mobile carriers with affinities for particular ions, (ii) special pores with ionic selectivity and the ability to open and close, (iii) conformational changes in membrane micromolecules, and (iv) special mechanisms for artificial membranes. Khodorov's discussion is particularly valuable because it brings the work of Russian scientists into focus.

As Tasaki (1968, 1974b) and Changeux (1969) have demonstrated, there is a considerably body of experimental evidence to suggest that the basic process of excitation in natural membranes involves a transition between two conformational states of the membrane. Figure 17 certainly suggests the ubiquitous nature of two conductivity states, and more detailed data includes: (i) direct observation of two conductivity states when $Ca^{++}$ is used as the external cation [Inoue, *et al.* (1973)], (ii) observation of switching between these states by variation of the temperature, (iii) changes in extrinsic fluorescence during the time course of an action potential [Tasaki 1974a], (iv) electron micrographs of configurational transitions involving collapse and extension of "headpiece stalks" in mitochondrial membranes [Hatase *et al.* (1972)], and of lattice structure on electrically excitable membranes of insect photoreceptors [Gemmel (1969)], (v) nonaxoplasmic birefringence changes during the action potential [Cohen *et al.* (1970), Watanabe *et al.* (1973), Sato *et al.* (1973)], (vi) protein binding of a nontoxic dye during the action potential [Levin *et al.* (1968)], and (vii) direct observation of spatial nonuniformity during switching of a squid axon [Inoue *et al.* (1974)]. The absence of birefringence change in pure lipid bilayers reported by Berestovskii *et al.* (1970) reinforces the attitude of Green *et al.* (1972) that protein complexes play the key role in membrane function. The physical ideas recently suggested by Frölich (1970) may clarify the understanding of protein conformational states.

It should be emphasized that the concept of a conformational change during activity of a natural membrane does not conflict with the idea that ions flow through channels or "pores" in the membrane which was discussed in detail by Hille (1970). The two points of view can be considered as complementary aspects of a more complex reality. On the other hand, one should not conclude that the switching observed on the leading edge in Fig. 3 is direct evidence of membrane macromolecular dynamics [Changeux *et al.* (1967); Lehninger (1968); Nachmansohn and Neuman (1974)]. The basic positive feedback mechanism which drives an action potential is that discussed above and diagrammed in Fig. 18 [Hodgkin (1951, 1964)]. Several scientists have indicated how one might proceed from an essentially conformational membrane model to the ionic current data of Fig. 16 which, in turn, implies the feedback mechanism of Fig. 18 [Goldman (1964), Jain *et al.* (1970), Chizmadzhev *et al.* (1972, 1973)].

In 1952 Hodgkin and Huxley introduced a phenomenological expression for the ion current density through a squid membrane with the form

$$J_i = \bar{G}_K n^4 (v_{12} - V_K) + \bar{G}_{Na} m^3 h (v_{12} - V_{Na}) + G_L (v_{12} - V_L), \tag{4.3}$$

where $\bar{G}_K$ and $\bar{G}_{Na}$ are, respectively, the maximum potassium and sodium conductances per unit area, and $G_L$ is a constant leakage conductance. The phenomenological variables $n$, $m$, and $h$ lie between zero and unity; the potassium conductance is "turned on" by $n$, and the sodium conductance is "turned on" and "turned off" by $m$ and $h$, respectively. It is assumed that $n$, $m$, and $h$ are independently relaxing toward equilibrium values $n_0$, $m_0$, and $h_0$, with characteristic times $\tau_n$, $\tau_m$, and $\tau_h$. Thus

$$dn/dt = -(n - n_0)/\tau_n; \quad dm/dt = -(m - m_0)/\tau_m; \quad dh/dt = -(h - h_0)/\tau_h. \tag{4.4a,b,c}$$

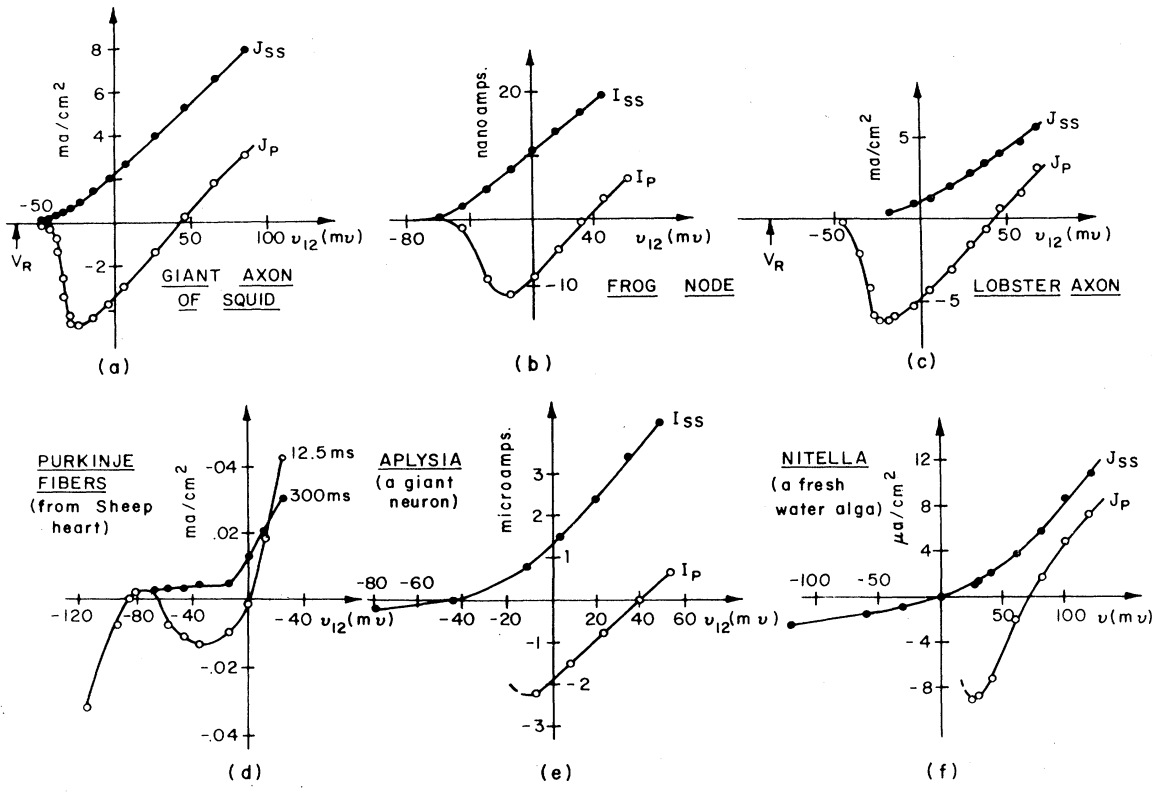


FIG. 17. Voltage clamp data from various active biological membranes. (a), (b), and (c) redrawn from Cole (1968), (d) redrawn from Deck and Trautwein (1964), (e) redrawn from Geduldig and Gruener (1970), and (f) redrawn from Kishimoto (1965). $J_p$ and $J_{ss}$ are defined in Fig. 16.

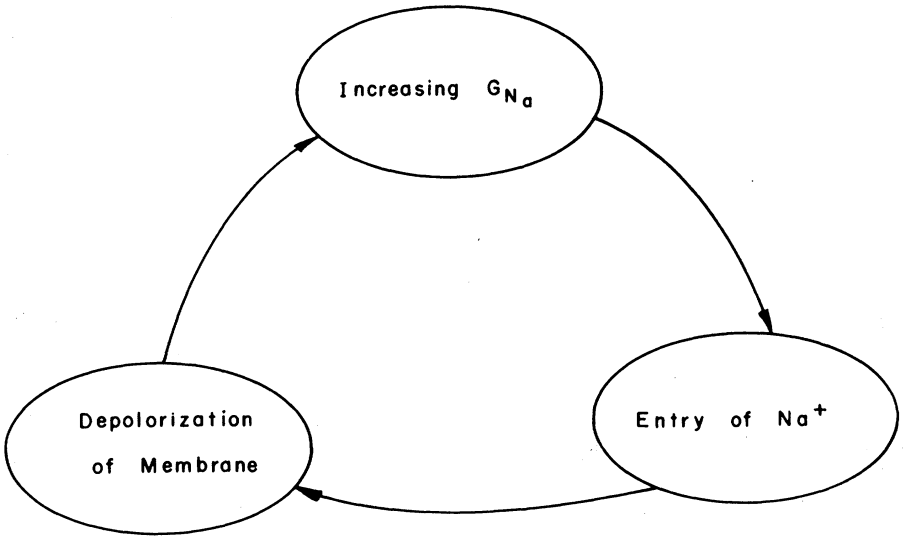


FIG. 18. The basic positive feedback mechanism for switching of a squid nerve membrane [Hodgkin (1964)].

The relaxation parameters ($n_0$, $m_0$, $h_0$, $\tau_n$, $\tau_m$, and $\tau_h$) can be determined as functions of voltage such that (4.3) will reproduce voltage clamp data as in Fig. 16. The nature of this functional dependence is shown in Fig. 19(a) where the constant values given by Cole (1968) are also indicated.

When the corresponding variables are determined for the active node of a frog myelinated axon (area $\sim 20\ \mu^2$), the results are strikingly similar as shown in Fig. 19(b). This result might be anticipated from a comparison of Figs. 17(a) and 17(b).

Hodgkin and Huxley obtained analytic expressions for the parameters in (4.4) of the form

$$dn/dt = \alpha_n(1 - n) - \beta_n n, \tag{4.4'a}$$

$$dm/dt = \alpha_m(1 - m) - \beta_m m, \tag{4.4'b}$$

$$dh/dt = \alpha_h(1 - h) - \beta_h h. \tag{4.4'c}$$

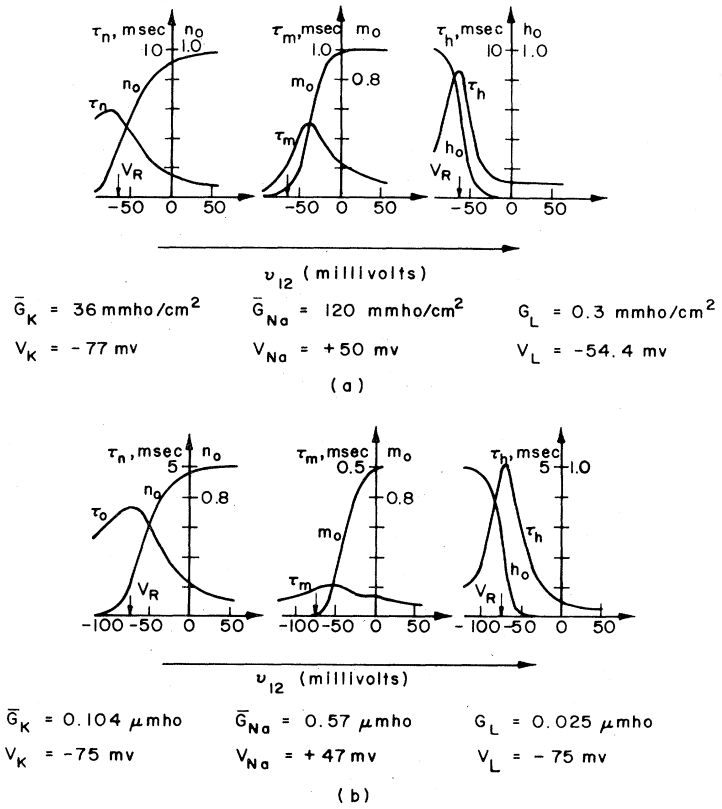


FIG. 19. The functional dependence of Hodgkin–Huxley phenomenological parameters on membrane voltage. (a) For a typical squid axon and (b) for a frog mode of area $\approx 20\ \mu^2$. Redrawn from Cole (1968) p. 283, 479.

Then, as functions of the voltage $v = v_{12} - V_R$ defined in (4.2) and measured in millivolts,

$$\alpha_n = \frac{0.01(10 - v)}{[\exp(10 - v)/10 - 1]}, \tag{4.5a}$$

$$\beta_n = 0.125 \exp(-v/80), \tag{4.5b}$$

$$\alpha_m = \frac{0.1(25 - v)}{[\exp(25 - v)/10 - 1]}, \tag{4.5c}$$

$$\beta_m = 4 \exp(-v/18), \tag{4.5d}$$

$$\alpha_h = 0.07 \exp(-v/20), \tag{4.5e}$$

$$\beta_h = \frac{1}{[\exp(30 - v)/10 + 1]}, \tag{4.5f}$$

where the units are msec$^{-1}$. Equations (4.5) give the rate constants measured at a temperature of 6.3°C. For other temperatures they should be multiplied by the factor $\kappa$ where

$$\kappa = \exp[(T - 6.3)/10]. \tag{4.6}$$

Clearly (4.3) and (4.4) provide wide flexibility for fitting voltage clamp data similar to that displayed in Figs. 15 and 16. Although the ion battery potentials ($V_K$, $V_{Na}$ and $V_L$) are fixed by the respective concentration ratios, the maximum conductivities ($\bar{G}_K$, $\bar{G}_{Na}$ and $G_L$) can be adjusted in addition to the six functions of $v$ required to specify (4.4). Furthermore the choice of powers appearing in (4.3) is somewhat arbitrary. The fourth power of $n$ was chosen to yield the "sigmoidicity" in the initial rise of potassium conductance evident from Fig. 15(c); and, as Hodgkin and Huxley note, "better agreement might have been obtained with a fifth or sixth power, but the improvement was not considered to be worth the additional complication." A later study by Cole and Moore (1960) suggested that the twenty-fifth power of $n$ is more appropriate in order to reproduce the time delay which appears when the membrane is switched on from the hyperpolarized state.[4] Similar considerations apply to the $m^3h$ factor in (4.3). The task is to represent a sodium conductance which first rises then falls as is indicated in Fig. 15(b). Such an experimental result can be described by dependence upon a single variable which obeys a second-order differential equation or upon two variables each of which obeys a first-order differential equation. Hodgkin and Huxley note, "the second alternative was chosen since it was simpler to apply the experimental results."

The Hodgkin–Huxley expression for ion current density (4.3) is well defined, and useful for a variety of numerical and intuitive checks on experimental results. It has stimulated an everwidening analytical study which extends far beyond the professional boundaries of neurophysiology. Thus there is an inevitable (and regrettable) tendency to consider (4.3–5) as "graven on a stone tablet." The applied mathematician should be more concerned with the qualitative features of (4.3) than the algebraic details. The biochemist, on the other hand, should concentrate upon the development of a fundamental theory of membrane dynamics which can reproduce the voltage clamped data as displayed in Fig. 16. Useful reviews of the Hodgkin–Huxley equations include Noble (1966) and Moore (1968) in addition to the books by Cole (1968) and Khodorov (1974).

Various other suggestions for analytical representations

[4] A suggestion which "wasn't recognized for tongue-in-cheek" (Cole, 1975).

of the potassium conductance include the work of:

(i) Tille (1965) who takes

$$I_K = \bar{G}_K N \tag{4.7}$$

where

$$dN/dt = a_1 N + a_2 N^2 + a_3 N^3 + a_4 N^4 + a_5 N^5 \tag{4.8}$$

and the $a_i$ are appropriately chosen functions of membrane voltage,

(ii) FitzHugh (1965) who obtains (4.7) with $N = \exp(-\mu)$ and

$$d\mu/dt = \alpha - \beta\mu \tag{4.9}$$

where $\alpha$ and $\beta$ are functions of the membrane voltage, and

(iii) Hoyt (1963) who uses (4.4a) from Hodgkin and Huxley (1952) then empirically determines the functional form for $G_K(n)$. She finds deviation from a power law at larger values of $n$.

In a discussion following the presentation of FitzHugh (1965), Cole points out the wide range of functional expressions which can represent the sigmoid nature of the potassium conductance rise with roughly equal accuracy. During this discussion Cole, Hoyt and FitzHugh are in agreement that there is no uniquely superior analytical form. For the Purkinje fibers in the mammalian heart, however, Noble (1962) has described a modified representation for the potassium which accounts for the slow recovery indicated in Fig. 17(d). This slow recovery is necessary for the generation of heartbeats.

Analytical study of the rise and fall of sodium conductance [Fig. 15(b)] has been of more fundamental importance. Frankenhaeuser and Huxley (1964) have shown for myelinated axons of the toad (*Xenopus laevis*) that an $m^2h$ dependence is more appropriate. Hoyt (1963, 1968) and Hoyt and Adelman (1970) have demonstrated that for a squid giant axon the sodium conductance is somewhat better represented by dependence upon a single variable which satisfies a second-order differential equation or, equivalently, two variables which satisfy coupled first order equations. Hoyt and Adelman state: "These conclusions imply that the mechanism responsible for the increase in sodium conductance is more likely to be dependent upon the production of an intermediate state than on the competition of two antagonistic but independent processes . . ."; but see also Jakobsson (1963). Molecular theories leading to coupled equations include the work of Mullins (1959), Goldman (1964), Fishman *et al.* (1972), and Chizmadzhev *et al.* (1972, 1973). Other models for membrane dynamics with varying degrees of phenomenology and membrane biochemistry include the work of Jain, Marks, and Cordes (1970), Offner (1970, 1972, 1974), Moore and Jakobsson (1971), and Jakobsson and Scudiero (1975). Hoyt and Strieb (1971) and Landdowne (1972) have independently suggested that the time course of the sodium conductance [Fig. 15(b)] may be explained by assuming the current to be carried primarily by ions stored *within* the membrane. This implies a temperature dependence of ion flux which is much weaker than is indicated by (4.6), and initial experiments seem to confirm this prediction [Landowne (1973), Cohen and Landowne (1974)].

## V. THE HODGKIN–HUXLEY AXON

We are now in a position to discuss the nonlinear dynamics of the nerve fiber shown in Fig. 5(a). The first order partial differential equations are (2.21) together with (4.4). Combining (2.21b) with (2.29) we can write these as

$$\partial v/\partial x = -r_s i, \tag{5.1a}$$

$$\partial i/\partial x + c(\partial v/\partial t) = -j_i(v, n, m, h), \tag{5.1b}$$

$$\partial n/\partial t = -[n - n_0(v)]/\tau_n(v), \tag{5.1c}$$

$$\partial m/\partial t = -[m - m_0(v)]/\tau_m(v), \tag{5.1d}$$

$$\partial h/\partial t = -[h - h_0(v)/\tau_h(v)], \tag{5.1e}$$

where $j_i$ in (5.1b) is the membrane ion current per unit length. From here on it is typographically convenient to use the voltage variable $v = v_{12} - V_R$ defined in (4.2); evidently this makes no difference on the left-hand sides of (5.1a) and (5.1b). From (4.3)

$$j_i = \bar{g}_K n^4 (v - V_R - V_K) + \bar{g}_{Na} m^3 h (v - V_R - V_{Na}) + g_L (v - V_R - V_L), \tag{5.2}$$

where $\bar{g}_K = 2\pi a \bar{G}_K$, $\bar{g}_{Na} = 2\pi a \bar{G}_{Na}$ and $g_L = 2\pi a G_L$.

The "average axon" chosen for numerical study by Hodgkin and Huxley (1952) had the following parameters in addition to those specified in the previous section.

| | |
|---|---|
| Resting potential: | $V_R = -65$ mV. |
| Axoplasm conductivity: | $\sigma = 2.9$ mho/m. |
| Axon radius: | $a = .238$ mm. |
| Membrane capacitance: | $C = 1\ \mu$F/cm$^2$. |

One approach to the analysis of these equations is to seek traveling wave solutions where all dependent variables $(v, i, h, m, h)$ are functions only of a moving spatial variable

$$\xi = x - ut. \tag{5.3}$$

This can be considered as a special case of the more general independent variable transformation

$$x \to \xi = x - ut \qquad \partial/\partial x \to \partial/\partial\xi,$$

so

$$t \to \tau = t \qquad \partial/\partial t \to \partial/\partial\tau - u(\partial/\partial\xi). \tag{5.4}$$

*Assuming* independence with respect to $\tau$ in the $(\xi$–$\tau)$ system, we can replace $\partial/\partial x$ by $d/d\xi$, and $\partial/\partial t$ by $-ud/d\xi$, whereupon Eqs. (5.1) become the ordinary differential

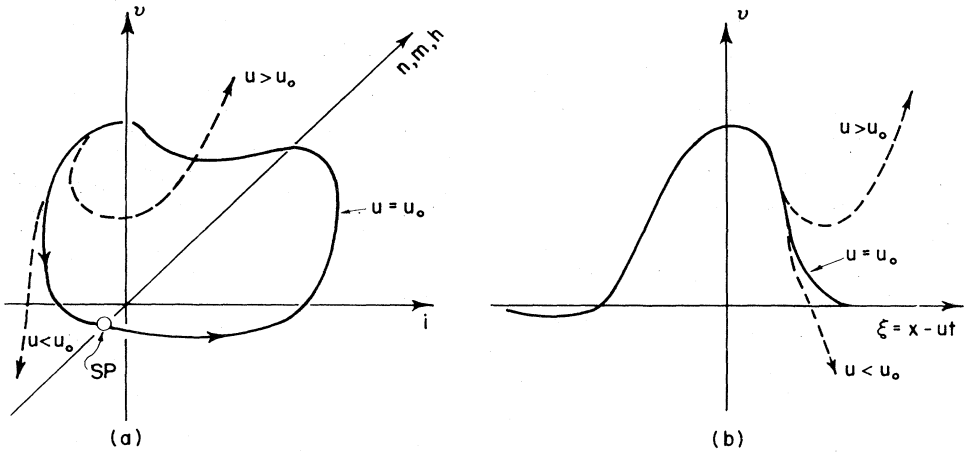


FIG. 20. (a) Phase space trajectory corresponding to (b) an action potential. The phase space actually has five dimensions, but $n$, $m$, and $h$ are indicated along a single axis.

equations

$$dv/d\xi = -r_s i,$$
$$di/d\xi = -r_s cui - j_i,$$
$$dn/d\xi = (n - n_0)/u\tau_n,$$
$$dm/d\xi = (m - m_0)/u\tau_m,$$
$$dh/d\xi = (h - h_0)/u\tau_h. \qquad (5.5)$$

This is an *autonomous* set of equations [Hurewicz (1958), Lefschetz (1962)] since the derivatives are uniquely defined as functions of the dependent variables. Thus phase space techniques can be helpful in understanding the structure of solutions [Kolmogoroff *et al.* (1937)]. It is important to note, however, that $u$ (the velocity of the moving spatial coordinate in (5.4)) appears as an adjustable parameter in (5.5). In general one can expect the topological character of the phase space trajectories to depend upon the value chosen for the velocity $u$. Only those trajectories for which the dependent variables are bounded will be of physical interest. In particular a trajectory corresponding to the action potential shown in Fig. 3 should have the qualitative character indicated in Fig. 20(a). The values $v = 0$, $i = 0$, and $(n, m, h) = (0.35, 0.06, 0.6)$ are a solution of (5.1) so the corresponding point in the phase space of (5.5) is a *singular point* (SP) at which all the $\xi$ derivatives are equal to zero. The task of finding a pulselike traveling wave solution for (5.1) involves determining the proper value of the velocity $u$ at which a trajectory which emanates from this singular point (at $\xi = -\infty$) eventually returns to it (as $\xi \to +\infty$). Such a trajectory is sometimes called *homoclinic*, while a *heteroclinic* trajectory would pass between two different singular points.

A homoclinic trajectory was determined by Hodgkin and Huxley (using a hand calculator) in 1952. Voltage and membrane conductance are plotted as a function of time from this calculation in Fig. 21 for the proper value of 18.8 mps. This value is in satisfactory agreement with the measured value of 21.2 mps; and, as a comparison of Figs. 3 and 21 will show, so also are the waveforms $v(t)$ and $G(t)$.

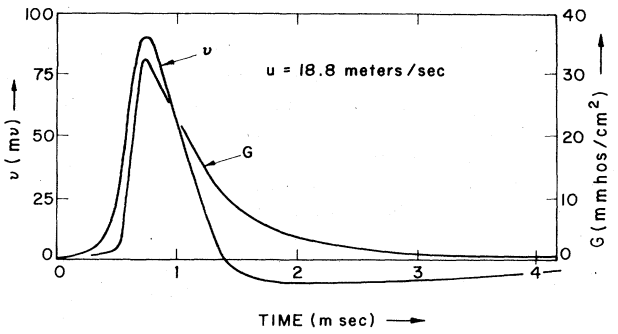


FIG. 21. Waveforms of the action potential and membrane conductance calculated from (5.5) at 18.5°C. Redrawn from Hodgkin and Huxley (1952d).

From a theoretical point of view, the discovery of a pulselike traveling wave solution for (5.1) from an investigation of the phase space topology associated with (5.5) does not mean that the pulse is stable to perturbations of its shape. Such *waveform instability* involves dependence upon $\tau$, and (5.5) was derived with the specific assumption of independence with respect to $\tau$. We will study this question in detail below. Another form of instability which appears in these calculations is *numerical instability* during the integration of (5.5). This arises because the assumed pulse velocity, $u$, is an adjustable parameter in the analysis. Choosing $u$ slightly too small or too large may cause the computed waveform to diverge as is indicated in Fig. 20. Such numerical instability of a solution to (5.5) seems to be a necessary condition to avoid a waveform instability in the corresponding solution of (5.1) [Scott (1970)].

Machine computations for the space clamped membrane were first reported by Cole, Antosiewicz, and Rabinowitz in 1955, and for the propagating axon by FitzHugh and Antosiewicz and by Huxley in 1959. Huxley demonstrated the existence of a second pulse solution (shown in Fig. 22) which propagates with only 30% of the velocity of the full action potential. This pulse has an unstable waveform; it will either decay to zero or rise to the full action potential

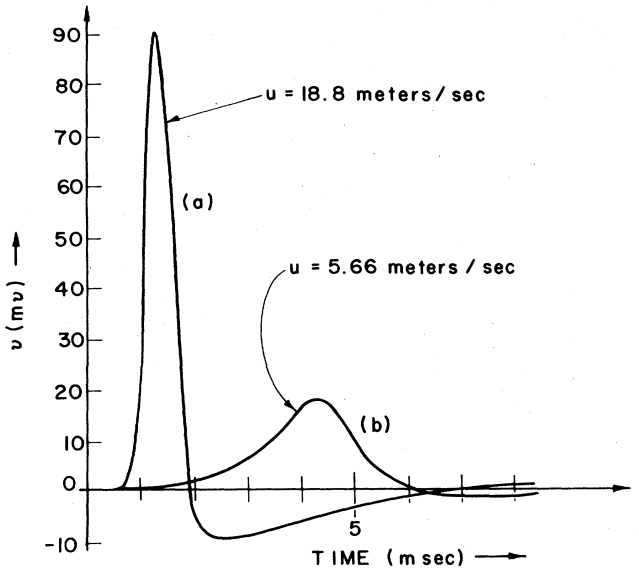


FIG. 22. (a) A full sized action potential and (b) an unstable threshold pulse for the Hodgkin–Huxley axon at 18.5°C. Redrawn from Huxley (1959).

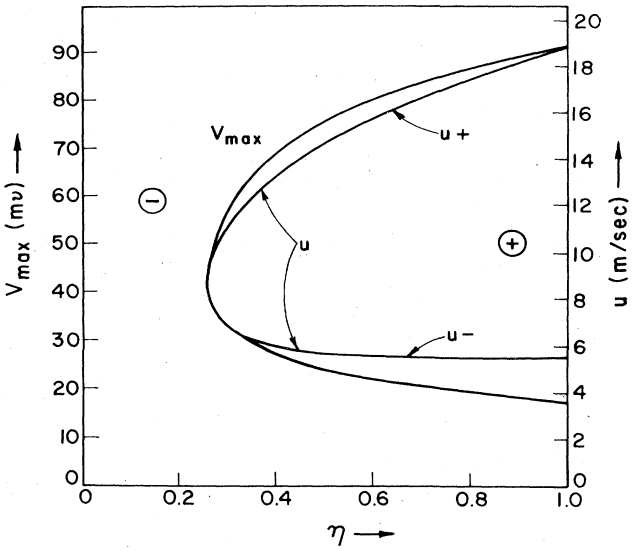


FIG. 23. Amplitude and velocity for a traveling wave pulse on a Hodgkin–Huxley axon vs a "narcotization factor," $\eta$, which reduces the sodium and potassium conductances. Redrawn from Cooley and Dodge (1966).

and thus represents a boundary or threshold state of the fiber. Huxley (1959) also indicated the possibility of a subthreshold wave train which would correspond to a closed cycle in the phase space sketched in Fig. 20. The observation of a threshold pulse was confirmed by Cooley and Dodge (1966) through direct integration of (5.1). They extended the result by assuming that the effect of a narcotic agent would be to lower $\bar{g}_{Na}$ and $\bar{g}_K$ by a factor $\eta$. The results are plotted in Fig. 23 where it can be seen that *no* attenuationless propagation or threshold effect obtains for $\eta < \eta_0 = .261$. At smaller values of this "narcotization factor" a "decremental" pulse [Lorente de Nó and Condouris (1959)] propagates with slowly deminishing amplitude as shown in Fig. 24. Since this pulse is not a function only of the argument $x - ut$, it is not represented by solutions of (5.5) and requires the complete set (5.1) for its description. Such decremental or "graded" pulses have also been extensively discussed by Leibovic (1972). Decremental pulses have been of great interest to physiologists in decades past and some of the flavor of these discussions is captured in the accounts by Kato (1924, 1970). Numerical analysis of the Hodgkin–Huxley axon not only indicates the possibility of decremental conduction, but the experimental conditions under which it should be observed. Recently Kashev and Bellman (1974) have introduced a new method of "differential quadrature" for more rapid integration of (9.1).

It is interesting to relate the results of these numerical studies to the notion of power balance which was introduced in (1.3). The $u - \eta$ locus in Fig. 23 indicates where pulse solutions can be found which satisfy (1.3). Since the lower branch is unstable, the inside $\oplus$ region is where pulse solutions for (5.1) can be found with $uE > P$. In the outside $\in$ region, $uE < P$ for all pulse solutions of (5.1). For $\eta$ slightly less than $\eta_0$, we expect that $uE$ for a pulse with appropriate shape and velocity will be almost equal to $P$. In this case an approximate calculation using only data from the traveling wave analysis may be useful. To see this, note that the data in Fig. 23 are fairly well represented by

$$[u - u_0(\eta)]^2 = k(\eta - \eta_0), \tag{5.6}$$

where $u_0 \equiv \frac{1}{2}(u_+ + u_-)$ and $k = 74$ m$^2$/sec$^2$. When $\eta = \eta_0$, there will be a traveling wave pulse with the Fourier transform, $F_0(\beta)$.

$$v_0[x - u_0(\eta_0)t] = \int_{-\infty}^{\infty} F_0(\beta) \exp[i\beta(x - u_0 t)]\, d\beta. \tag{5.7}$$

When $\eta < \eta_0$, (5.6) indicates a *complex* value for the traveling wave velocity

$$u = u_0 \pm iu_i \tag{5.8}$$

where $u_i \equiv [k_0(\eta_0 - \eta)]^{1/2}$. The primary effect of the imaginary component of velocity is to modify the magnitude of the Fourier transform. Thus an approximate expression for the evolution of a decremental pulse is

$$v(x, t) \approx \int_{-\infty}^{\infty} F_0(\beta) \exp(-|\beta| u_i t) \exp[i\beta(x - u_0 t)]\, d\beta. \tag{5.9}$$

The reason for taking the absolute value of $\beta$ is to keep the Fourier transform symmetric so $v(x, t)$ remains real; the justification is that the roots in (5.8) may be interchanged without introducing a physical discontinuity when $\beta = 0$. Equation (5.9) may of course be written as the convolution of $v_0(x - u_0 t)$ with the Lorentzian pulse

$$\left\{(\pi u_i t)\left[1 + \left(\frac{x - u_0 t}{u_i t}\right)^2\right]\right\}^{-1}$$

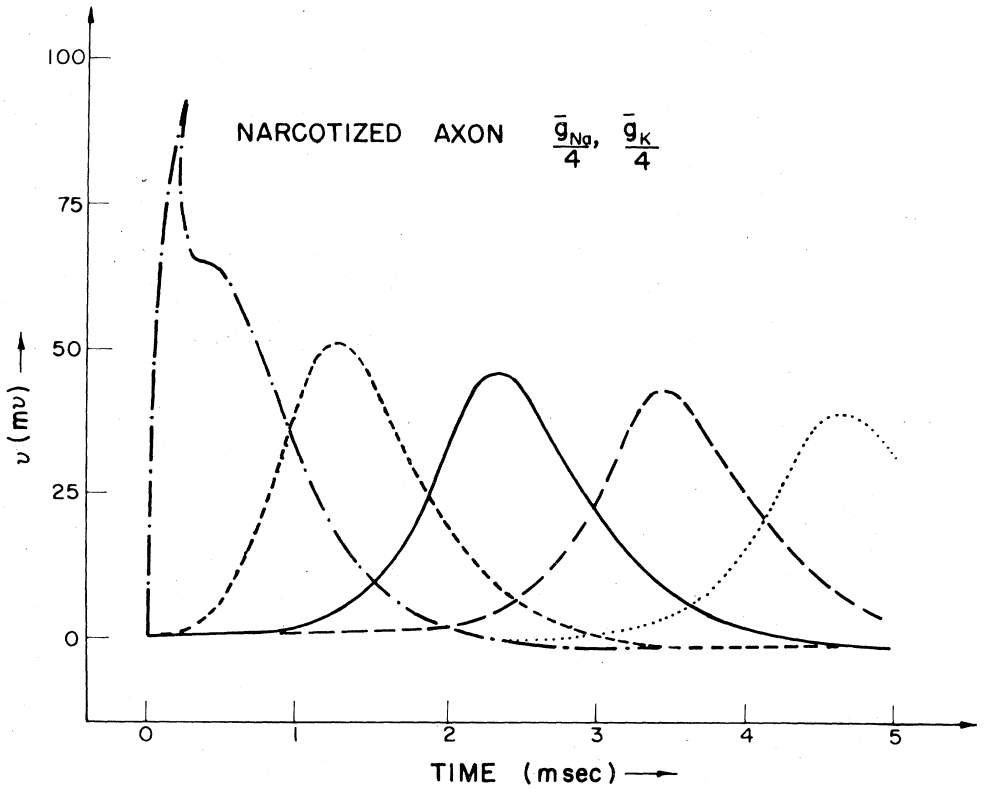


FIG. 24. Propagation of a decremental pulse on a Hodgkin–Huxley axon narcotized by a factor of 0.25. Curves are voltage waveforms at 1 cm intervals. Redrawn from Cooley and Dodge (1966).

which has unit area and a half-width of $2u_i t$. For large $t$, (5.9) implies decay as $t^{-1}$ rather than exponentially which is clearly incorrect. A numerical evaluation of (5.9) is currently being made for intermediate values of time.

Impedance bridge measurements by Cole and Baker (1941) indicated that the membrane appears to have an inductive current component at small ac amplitudes between 30 cps and 200 kc. For the membrane equivalent circuit representing 1 cm$^2$ of membrane shown in Fig. 25(a), they found $C = 1$ $\mu$F, $R = 400$ $\Omega$ and $L = 0.2$ H. Hodgkin and Huxley (1952) investigated the dynamical relation between small changes in voltage and current in (4.3) and directly calculated in values $R = 820$ ohms and $L = 0.39$ H with a threefold increase in $L$ for a 10° fall in temperature. Such an inductance is much too large to have any connection with magnetic fields; thus a physical interpretation is illustrated in Fig. 25(b) which depends upon the experimental fact that membrane conductance [$G$ in Eq. (3.12)] remains constant for times of the order of 100 $\mu$sec or less [Mauro (1961)]. If the current is concave in the direction of depolarization, a sudden change of current from $J_1$ to $J_2$ must be associated with a change of voltage from $v_1$ to $v_2'$. The voltage will then slowly relax toward a smaller difference $v_2$. These conditions are met by the $n$ and $h$ dependencies in (4.3) both of which contribute to the inductance indicated in Fig. 25(a). Extensive studies of this effect include those by Chandler *et al.* (1962) and Mauro *et al.* (1970). Offner (1969) has related membrane reactance to the dynamics of internal ions.

The phenomenological inductance also influences the propagation of alternating subthreshold waves on the axon; this is evident from the "overshoot" in the return to rest of the action potential in Fig. 21. Subthreshold oscillatory propagation has been studied in detail by Sabah and Leibovic (1960) [Leibovic (1972)] using Laplace transform techniques and by Mauro, Freeman, Cooley and Cass (1972). Mauro *et al.* use both numerical analysis of (5.1) and experimental observations on squid axons to show that phase velocity of an oscillatory subthreshold wave is rather closely related to the pulse velocity of an action potential as indicated in Table I. [See also Optowski (1950) in connection with this relation.] In electronic jargon the squid axon looks like a low $Q$, bandpass filter tuned to about 100 cps when it is stimulated by a subthreshold, oscillatory current.

Cooley and Dodge (1966) also computed the response of a Hodgkin–Huxley axon to a steady stimulation by longitudinal current [$i(0, t) = \text{const}$ in Fig. 5(a)]. For a steady current around 3.4 $\mu$A a periodic train of spikes was generated with a frequency rather insensitive to the stimulation. This result is in contrast to the real axon which generates a burst of only a few spikes. FitzHugh (1969) has suggested that the real axon exhibits an "adaptation" effect which tends to decrease excitability with a time constant of the order of a second. Such an effect, which is not represented by the Hodgkin–Huxley equations, may be connected with slow changes in ion concentration or in temperature.

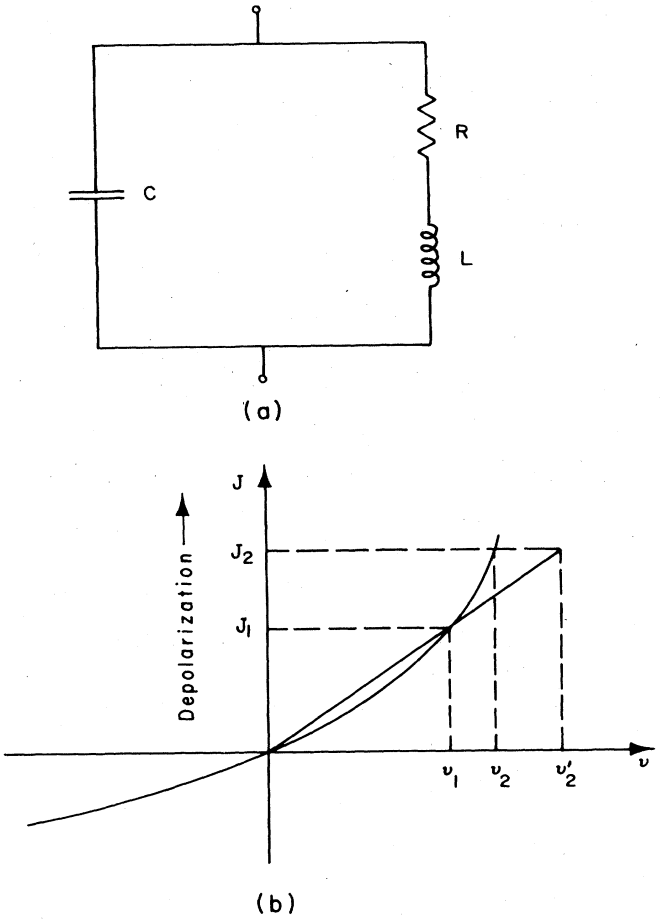


FIG. 25. (a) Membrane small signal equivalent circuit measured by Cole and Baker (1941). (b) Physical explanation of the phenomenological inductance.

## VI. PROPAGATION OF THE LEADING EDGE

Comparison of numerical results reported in the previous section with corresponding experimental data indicates that the Hodgkin–Huxley equations (5.1) are of considerable value in describing the facts of electrophysiology, but it is also of interest to consider approximate forms of (5.1) which can be analytically investigated. Physical motivation for one such approximation stems from the observations (see Fig. 21) that (i) the most rapid dynamical change occurs on the leading edge of an action potential, (ii) this leading edge transition carries the membrane potential from its resting potential to approximately the sodium diffusion potential, $V_{\mathrm{Na}}$, and (iii) the velocity of the leading edge determines the velocity of the entire action potential. For the squid giant axon the functions $n_0$, $m_0$, $h_0$, $\tau_n$, $\tau_m$, and $\tau_h$ are sketched in Fig. 19(a) from which it is evident that the relaxation time, $\tau_m$, for sodium turn on is about an order of magnitude less than $\tau_n$ and $\tau_h$ for potassium turn on and sodium turn off respectively. Thus it is interesting to consider the approximation [FitzHugh (1969)]

$$\tau_m = 0, \qquad \tau_n = \tau_h = \infty,$$

whereupon the ion current through the membrane (5.2) becomes simply a function of voltage $j_i \approx j(v)$, where

$$j(v) = \bar{g}_{\mathrm{K}} n_0^4(V_R)(v - V_R - V_{\mathrm{K}}) + \bar{g}_{\mathrm{Na}} m_0^3(v) h_0(V_R)(v - V_R - V_{\mathrm{Na}}) + g_L(v - V_R - V_L). \tag{6.1}$$

This approximation is valid only for dynamical processes which occur in times long compared with $\tau_m$ and short compared with $\tau_n$ and $\tau_h$, but, as reference to Fig. 21 indicates, the leading edge transition comes close to fulfilling these requirements. Equation (2.30) then takes the form[5]

$$v_{xx} - r_s c v_t = r_s j(v) \tag{6.2}$$

which is the equation for nonlinear diffusion discussed in the Introduction. Together with (6.2) it is convenient to write (2.21) in the form

$$v_x = -r_s i \tag{6.3a}$$

$$i_x + c v_t = -j(v) \tag{6.3b}$$

as an equivalent set of first order pde's.

Equation (6.1) does not have a particularly convenient analytic form, but we expect it to go through zero at the origin (the resting potential), at a higher voltage $V_2 = V_{\mathrm{Na}} - V_R$, and at a voltage, $V_1$, somewhere between. With this in mind, let us apply the transformation (5.4) discussed in the previous section to (6.3) with the assumption that $\partial/\partial\tau = 0$. Then the set of ordinary equations which are equivalent to (5.5) becomes

$$dv/d\xi = -r_s i \tag{6.4a}$$

$$di/d\xi = -r_s c u i - j(v). \tag{6.4b}$$

Singular points for this set occur where $i = 0$ and $j(v) = 0$, i.e., at $v = 0$, $V_1$ and $V_2$. If we define

$$g(v) \equiv dj/dv, \tag{6.5}$$

then $g(0)$ and $g(V_2)$ will be positive, and $g(V_1)$ will be negative as is indicated in Fig. 26(a). From this one can show [Scott (1970), McKean (1970)] that the singular points at $(i, v) = (0, 0)$ and $(0, V_2)$ are saddle points, while the intermediate singular point at $(0, V_1)$ is an inward (outward) node or focus for $u > 0$ ($<0$). Kunov (1967) used "Bendixon's negative criterion" [Andronov *et al.* (1966)] to show that (6.4) has a homoclinic trajectory, corresponding to a "pulselike" solution of (6.3), only for zero velocity. Thus the basic solutions with nonzero velocity

TABLE I. Velocities of the action potential and a subthreshold oscillation vs temperature for the H–H axon. [Mauro *et al.* (1972)].

| Temperature (°C) | Pulse velocity of action potential (mps) | Phase velocity of subthreshold oscillation (mps) |
|---|---|---|
| 18.5 | 18.8 | 16.1 |
| 12.5 | 16.1 | 14.6 |
| 6.3 | 12.7 | 13.3 |

[5] From here on the conventional subscript notation for partial differentiation will be used wherever it is typographically convenient.

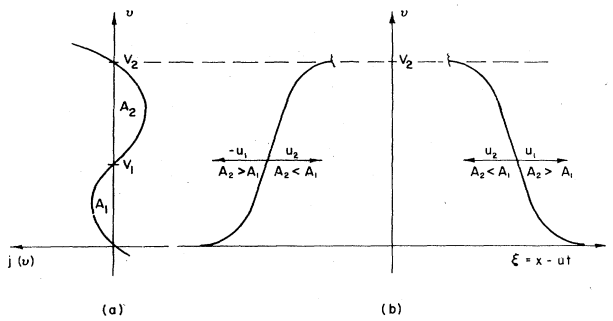


FIG. 26. (a) A representation of $j(v)$ as in (6.1). (b) Propagating waves which change the voltage level.

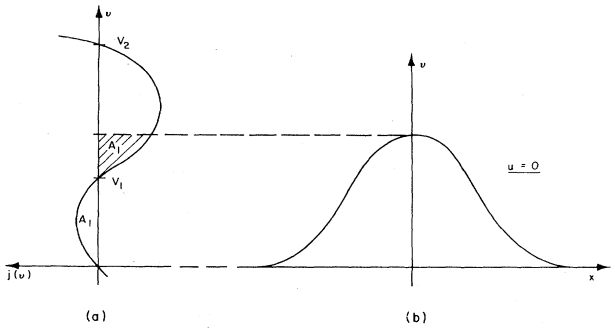


FIG. 27. (a) $j(v)$ with $A_2 > A_1$. (b) A stationary pulse solution.

are the "level change" waves shown in Fig. 26(b). From the phase space point of view, the velocity of such a transition is fixed by the condition that an isolated trajectory leaving one saddle point (at $\xi = -\infty$) must become an isolated trajectory approaching the other saddle point (as $\xi \to \infty$). Yoshizawa (1971) has demonstrated that these waves can either charge the membrane capacitance when area $A_2$ is greater than area $A_1$, or discharge the capacitance for $A_1 > A_2$. In either case, the power balance condition (1.3) must be satisfied.

If $A_1 = A_2$ these velocities are equal to zero which is a special case of the zero velocity pulse indicated in Fig. 27 for the case $A_2 > A_1$. From (6.4) with $u = 0$, it is easily seen that a pulse like solution is obtained by substituting into (6.4a) the homoclinic trajectory

$$i = \pm\left[\frac{2}{r_s}\int_0^v j(v')\,dv'\right]^{1/2}. \tag{6.6}$$

Although, as we shall see below, this solution is unstable, it is of interest because it specifies the condition for threshold stimulation of a fiber. Lindgren and Buratti (1969) have shown the pulse velocity to be nonzero for a tapered fiber.

A family of analytic solutions for the wave forms and velocities indicated in Fig. 26 can be obtained by writing [Scott (1974)]

$$dv/d\xi = T(v), \tag{6.7}$$

whereupon (6.4) requires that $T$ must satisfy

$$T' = j(v)/T - r_s c u. \tag{6.8}$$

For $u = 0$, the pulselike trajectory of (6.6) is recovered. Now suppose $u \neq 0$ and $j(v)$ is a polynomial of order $n$, and $T(v)$ is a polynomial of order $m$, then $T'$ is of order $(m-1)$, and from (6.8)

$$n = 2m - 1. \tag{6.9}$$

The case $m = 2$ implies $n = 3$ so $j(v)$ must be approximated by a cubic polynomial [Nagumo, Arimoto and Yoshizawa (1965), FitzHugh (1969)]

$$j(v) = Bv(v - V_1)(v - V_2), \tag{6.10}$$

where $B$ is a constant (with units of mho/V$^2$) chosen to make $j(v)$ approximate $2\pi a J_p$ from Fig. 17(a) as closely as possible. Since $m = 2$, a suitable quadratic trajectory is

$$i = Kv(v - V_2)$$

which, upon differentiation, gives

$$di/dv = 2Kv - KV_2.$$

But $di/dv$ can also be evaluated by dividing left- and right-hand sides of (6.4) to obtain

$$di/dv = cu + (B/r_s K)(v - V_1).$$

Thus $K = -(B/2r_s)^{1/2}$ so

$$u = (B/2r_s c^2)^{1/2}(V_2 - 2V_1) \tag{6.11}$$

and (6.4a) can be integrated to

$$v = \tfrac{1}{2}V_2\{1 + \tanh[\tfrac{1}{2}V_2(\tfrac{1}{2}Br_s)^{1/2}(x - ut)]\}. \tag{6.12}$$

Note that the velocity given by (6.11) changes sign as $V_1$ becomes greater than $V_2/2$. This corresponds to the area condition indicated on Fig. 26(b). Similar results have been obtained for other nonlinear wave systems simulating the nerve axon by Il'inova and Khokhlov (1963) and by Parmentier (1969).

Another approximation for $j(v)$ which permits an analytic solution for (6.4) corresponds to the case $m = 1$; so from (6.9) $n = 1$ and we have a piecewise linear curve indicated in Fig. 28. Below a voltage $V_1$ the membrane is assumed to remain in a *resting* state with low conductance; above $V_1$ it is assumed to switch into an *active* state of much higher conductance. Such an approximation is certainly suggested by several of the curves for $J_p$ vs $v_{12}$ in Fig. 17. Using the notation of Tasaki (1968), we write [Scott (1962), McKean (1970)]

$$\begin{aligned} j(v) &= g_r v && \text{for } v < V_1 \\ &= g_a(v - V_2) && \text{for } v > V_1. \end{aligned} \tag{6.13}$$

The discontinuity at $V_1$ is acceptable because Eqs. (6.2) and (6.3) do not involve derivatives of $j(v)$. With $j(v)$ approximated as in (6.13), Eq. (6.2) is *linear* both above and below $V_1$. Thus the nonlinearity in the problem mani-

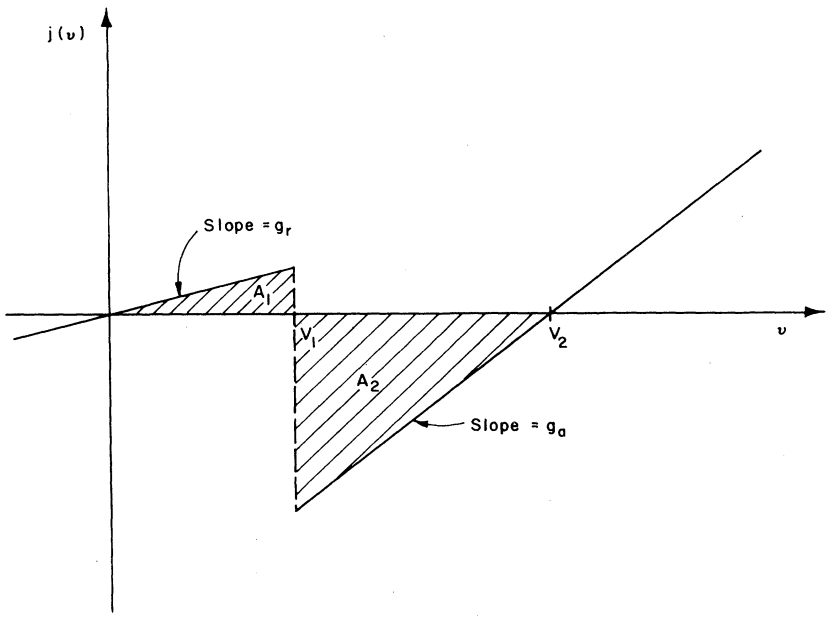


FIG. 28. Piecewise linear approximation for $j(v)$ [Tasaki (1968)].

fests itself only where $v = V_1$. To simplify the discussion we will begin by assuming that $g_r = 0$. Equation (10.4) can be written

$$d^2v/d\xi^2 + r_s cu(dv/d\xi) - r_s j(v) = 0$$

which becomes

$$d^2v/d\xi^2 + r_s cu(dv/d\xi) = 0 \qquad \text{for } v < V_1, \tag{6.14a}$$

and

$$d^2v/d\xi^2 + r_s cu(dv/d\xi) - r_s g_a(v - V_2) = 0 \qquad \text{for } v > V_1. \tag{6.14b}$$

If, for convenience, we choose $\xi = 0$ to be where $v = V_1$, a leading edge which makes a transition between zero and $V_2$ [see Fig. 26(b)] and satisfies (6.14) is easily constructed. Thus

$$v = V_1 \exp(-\gamma_1 \xi) \qquad \text{for } v < V_1, \tag{6.15a}$$

and

$$v = V_2 - (V_2 - V_1)\exp(\gamma_2 \xi) \qquad \text{for } v > V_1, \tag{6.15b}$$

where $\gamma_1 = r_s cu$ and $\gamma_2 = (r_s cu/2)[-1 + (1 + 4g_a/r_s c^2 u^2)^{1/2}]$. The velocity of propagation is not yet determined in (6.15) but it may be computed in either of two ways [Scott (1962)]:

(i) Equate the total power being produced by $j(v)$ and absorbed by $r_s$ over the waveform to $\frac{1}{2}cV_2^2 u$, the power being absorbed by the membrane capacitance at velocity $u$; or

(ii) Demand continuity in the longitudinal current, $i$, at $\xi = 0$.

Approach (i) is employment of the power balance idea behind (1.3) which was discussed in the Introduction. The leading edge must absorb energy (electrical energy in the membrane capacitance) at the same rate it is being produced for a steady traveling wave to exist. Approach (ii) is equivalent to (i) and somewhat more convenient. From (6.15) and (6.4a), $i(\xi)$ is easily calculated for the ranges $\xi > 0$ and $\xi < 0$, and current continuity at $\xi = 0$ implies $\gamma_2(V_2 - V_1) = \gamma_1 V_1$ which is readily solved for the velocity as

$$u = [g_a/r_s c^2]^{1/2}[(V_2 - V_1)/(V_2 V_1)^{1/2}]. \tag{6.16}$$

The case $g_r \neq 0$ has been studied in detail by Kunov (1966) and by Vorontsov, Kozhevnikova and Polyakov (1967) who use a similar technique to find

$$u = \frac{\{[(V_2 - V_1)/V_1]^2 g_a - g_r\}}{(r_s c^2[V_2(V_2 - V_1)/V_1^2]\{[(V_2 - V_1)/V_1]g_a + g_r\})^{1/2}} \tag{6.17}$$

[see also Kompaneyets (1971)]. It can be seen that a necessary condition for a steady wave of transition from $v = 0$ to $V_2$ is $(V_2 - V_1)^2 g_a > V_1^2 g_r$. This again implies again that the areas $A_2$ and $A_1$ in Fig. 28 must satisfy the inequality

$$A_2 > A_1. \tag{6.18}$$

The effect of "narcotization," discussed in the previous section in connection with Figs. 23 and 24, is to reduce $g_a$. Eventually the inequality (6.18) is violated and only decremental conductance can take place.

The value of (6.16) can be assessed by using it to calculate the velocity of the action potential for the Hodgkin–Huxley axon shown in Fig. 21. From the Hodgkin–Huxley axon parameters given in the previous section, the factor $(g_a/r_s c^2)^{1/2}$ is equal to 33.2 m/sec. Taking $V_2 = V_{Na} - V_R = 115$ mV and (from Fig. 17) $V_1 = 40$ mV gives $u = 36.6$ m/sec which is almost a factor of 2 higher than

that calculated by Hodgkin and Huxley. The source of this error seems to be the assumption that $\tau_m = 0$ which was made at the beginning of this section. This assumption implies that sodium current will begin to flow fully as soon as the membrane voltage changes by 40 mV. But inspection of Fig. 19 or Fig. 21 indicates that this is not so. The time delay associated with sodium turn on requires the membrane voltage to change by about 60 mV before the membrane conductance rises to half of its full active value. Taking $V_1 = 60$ mV gives $u = 22$ m/sec which is quite satisfactory considering the nature of the approximations which have been made.

The importance of time delay in the conductance rise was emphasized by Offner, Weinberg, and Young (1940) who developed a velocity formula similar to (6.16) shortly after Cole and Curtis (1939) recorded the waveforms displayed in Fig. 3. This delay is also of theoretical importance since (6.16) and (6.17) imply

$$u \to [(g_a/r_s c^2)(V_2/V_1)]^{1/2} \to \infty \qquad \text{as } V_1 \to 0; \tag{6.19}$$

but, with $\tau_m \neq 0$, the effective value of $V_1$ cannot reach zero. Thus an infinite propagation velocity is prevented by the nonzero value of $\tau_m$.

Early attempts to calculate the propagation velocity of an action potential have been reviewed by Offner, Weinberg, and Young (1940). Since that time, additional approaches have been developed by Rosenblueth, Wiener, Pitts, and Garcia Ramos (1948), Huxley (1959) Kompaneyets and Gurovich (1965), Balakhovskii (1968), Namerow and Kappl (1969), Smolyaninov (1969), Pickard (1966), and Markin and Chizmadzhev (1967), of which the last two references relate propagation velocity to the rate of rise on the leading edge of the action potential. Such a relation is easily obtained from (6.15a) since

$$\partial v/\partial t\,|_{\max} = -u\, dv/d\xi\,|_{\xi=0} = \gamma_1 u V_1.$$

Thus

$$u = [v_{t,\max}/r_s c V_1]^{1/2}, \tag{6.20}$$

as is readily verified for the waveform in Fig. 21. This is the formula used by Zeeman (1972).

We now turn out attention briefly to the effect of magnetic fields, which are associated with the longitudinal currents and represented as the inductors $l_i + l_0 = l_s$ in Fig. 7(b), upon the propagation velocity. This question arises because it has been suggested [Lieberstein (1967a, b, 1973), Brady (1970), Isaacs (1970), Lieberstein and Mahrous (1970)] that (2.30) should be augmented to the form

$$\partial^2 v/\partial x^2 - l_s c(\partial^2 v/\partial t^2) = r_s(c(\partial v/\partial t) + j_i) + l_s(\partial j_i/\partial t). \tag{6.21}$$

The numerical instability discussed in connection with Fig. 20 can then be avoided if *both* sides are individually set to zero at a velocity

$$u = [l_s c]^{-1/2}. \tag{6.22}$$

Van Der Pol (1957) has proposed a similar model for propagation on a nerve fiber. To examine this question [Scott (1971)] we will again ignore turn on delay and assume $\tau_m = 0$, $\tau_n = \tau_n = \infty$. The first order partial differential equations corresponding to Fig. 7(b) and (6.21) become

$$v_x = -l_s i - r_s i,$$

$$i_x = -c v_t - j(v). \tag{6.23}$$

Taking $j(v)$ as in Fig. 28 with $g_r = 0$ and assuming a steady wave of propagation, $v(x - ut) = v(\xi)$, then yields [Scott (1963, 1970)]

$$u = \left\{\left(\frac{g_a}{r_s c^2}\right)\frac{(V_2 - V_1)^2}{V_2 V_1}\left[1 - \frac{g_a l_s}{r_s c}\frac{(V_2 - V_1)}{V_2}\right]\right\}^{1/2}. \tag{6.24}$$

This implies that series inductance will have a negligible effect upon velocity if it satisfies the inequality

$$l_s \ll \left(\frac{r_s c}{g_a}\right)\left(\frac{V_2}{V_2 - V_1}\right). \tag{6.25}$$

The left-hand side of (6.25) can be evaluated from (2.12) and (2.14) using small argument approximations for the Bessel functions as

$$z_i + z_0 \approx (1/\pi\sigma_1{}^* a^2) + i\omega(\mu_0/4\pi)[1 - 2\log(\beta a)], \tag{6.26}$$

the second term of which gives the series reactance from magnetic fields both inside and outside the fiber. Thus

$$l_s = (\mu_0/4\pi)[1 - 2\log(\beta a)] \tag{6.27}$$

where $\mu_0 = 4\pi \times 10^{-7}$ H/m is the mks magnetic permeability of nonmagnetic materials. Taking $\beta a \sim 10^{-2}$ implies $l_s \sim 10^{-6}$ H/m. The right-hand side of (6.25) is greater than 100 H/m, thus the inequality is satisfied by eight orders of magnitude, and magnetic energy storage will have no measurable effect upon the normal propagation of an action potential. This conclusion is further supported by the numerical studies of Kaplan and Trujillo (1970). Solutions of (6.21) at the velocity given in (6.22) for which both sides of the equation go to zero would correspond to a decoupling of high frequency electromagnetic waves from the membrane. While this may have been what Newton (1718) had in mind when he posed his "twenty-fourth question," it does not correspond to normal nerve activity.

## VII. THE FITZHUGH–NAGUMO EQUATION

The previous two sections have bracketed (in the sense of an artilleryman) the representation of a propagating nerve fiber. The Hodgkin–Huxley equations, (5.1) and (5.2), give a fairly accurate description of spike propagation but are somewhat difficult to analyze without the aid of an automatic computer. The nonlinear diffusion equation (6.2) is simple enough for analytical investigation and yields some useful results [e.g., Eq. (6.16) for the conduction velocity], but it fails to reproduce the qualitatively important feature of pulse recovery which is necessary for repeated firing of the fiber. In this situation FitzHugh

(1961) and Nagumo, Arimoto and Yoshizawa (1962) proposed a modification of the nonlinear diffusion equation which would retain its simplicity but allow the action potential to return to a resting level. In properly chosen units of space, time and voltage, (6.2) can be written $V_{xx} - V_t = F(V)$, where $F(V)$ is a function with the character indicated in Figs. 26(a) or 28. Augmenting this equation with a new "recovery" variable $R$ to [FitzHugh (1969)]

$$V_{xx} - V_t = F(V) + R,$$

where

$$R_t = \epsilon(V + a - bR) \tag{7.1a, b}$$

yields the desired recovery. To see this note that $R$ in (7.1a) acts as an outward ion current which tends to decrease the area $A_2$ in Figs. 26(a) or 28. With reference to the Hodgkin–Huxley equations (5.1) and (4.4a), there is a correspondence between

$$R \sim n,$$
$$\epsilon b \sim \kappa \tau_n^{-1},$$
$$\epsilon V \sim \kappa n_0 \tau_n^{-1},$$

where $\kappa$ is the "temperature factor" indicated in (4.6). The constant $a$ in (7.1b) can be absorbed into the definition of $R$ and $F$ so there is no loss of generality in setting it to zero. The constant $b$ is often arbitrarily assumed equal to zero. Since $\epsilon$ is proportional to $\kappa$, it can be considered as a parameter which increases with temperature.

Equation (7.1) is beginning to assume the role with respect to nerve fiber propagation that the equation of Van Der Pol (1926, 1934) has played with respect to oscillator theory. "Van Der Pol's equation" displays the qualitative features of many oscillators (spontaneous excitation, limit cycle, continuous transition between sinusoidal and blocking behavior, etc.) without necessarily being an exact representation of any particular dynamical system. As recent studies [Cohen (1971), Hastings (1972), Greenberg (1973)] indicate, such a model is very stimulating and useful for the applied mathematician. Equation (7.1) is often called "Nagumo's equation" [McKean (1970), Greenberg (1973)] although FitzHugh (1968, 1969) refers to it as the "BVP equation" in recognition of the introduction by Bonhoeffer (1948) of phase plane analysis into the study of the passive iron nerve model, and of Van Der Pol. The reference to Van Der Pol, however, is somewhat unfortunate for in 1957 he introduced his own modification for application to nerve problems which failed to consider the diffusive character of the nerve fiber. Thus the name "FitzHugh-Nagumo equation" used by Cohen (1971), Rinzel and Keller (1973), and Hastings (1975a) seems most appropriate.

The general utility of (7.1) can be appreciated by considering the design of a neuristor or electronic analog of the active nerve fiber proposed by Crane (1962). Equations (7.1) describe the most natural technique for achieving pulse return in an electronic neuristor [Nagumo *et al.* (1962), Crane (1962), Scott (1962, 1964), Berestovskiy (1963), Noguchi, Kumagai and Oizumi (1963), Yoshizawa and Nagumo (1964), Sato and Miyamoto (1967)] and are closely related to the dynamical equations for active superconducting transmission lines which employ tunneling of either normal electrons (Giaever-type) or superconducting electrons (Josephson-type) [Scott (1964, 1970), Parmentier (1969, 1970), Johnson (1968), Nakajima, Yamashita and Onodera (1974), Nakajima, Onodera, Nakamura and Sato (1974)]. Considered as a model for the nerve axon, (11.1) neglects (i) turn-on delay for the sodium current, (ii) the fourth power dependence of potassium current upon $n$, and (iii) the dependence of $\tau_n$ upon $v$. More exact second-order systems have recently been considered by Krinskii and Kokoz (1973). A good general survey of these problems is given in the thesis by Kunov (1966).

The analysis of (11.1) was begun by Nagumo, Arimoto and Yoshizawa (1962) who considered the ordinary differential equations for traveling wave solutions of the form $V = V(x - ut) = V(\xi)$ and $R = R(x - ut) = R(\xi)$ as indicated in (5.3). Then $V$ and $R$ must satisfy

$$dV/d\xi = W, \tag{7.2a}$$

$$dW/d\xi = F(V) + R - uW, \tag{7.2b}$$

$$dR/d\xi = \frac{\epsilon}{u}(bR - V - a). \tag{7.2c}$$

They assumed $F(V)$ to be cubic, took $b = 0$, and obtained numerical evidence for the existence of two homoclinic trajectories for sufficiently small values of $\epsilon$. At a critical value, $\epsilon_c$, these solutions merged and for $\epsilon > \epsilon_c$ no homoclinic orbits were found, just as in Fig. 23. Such results suggest the existence of two pulse like traveling wave solutions to (7.1), as in Fig. 22, and experiments on an electronic analog indicated that only the pulse with higher velocity is stable. These results were confirmed by FitzHugh (1968, 1969) through numerical studies of (7.1) and (7.2) with $b \neq 0$ and

$$F(V) = \tfrac{1}{3}V^3 - V. \tag{7.3}$$

Velocities of the two branches vs. the "temperature parameter" $\epsilon$ are shown in Fig. 29. FitzHugh (1968) also made a motion picture entitled "Impulse propagation in a nerve fiber"[6] which is based upon numerical integration of (7.1). Some selected frames from this film are reproduced in Fig. 30 which show the propagation of two pulses away from a point of stimulation. In the fully developed pulses [Figs. 30(f), (g) and (h)], the recovery variable, $R$, follows behind the voltage, $V$. These pulses correspond to the upper velocity ($A'$) at $\epsilon = 0.08$ in Fig. 29. The lower velocity pulse ($B'$) is unstable. Again the locus of allowed traveling wave velocities in the $u - \epsilon$ plane indicates where the power balance condition (1.3) is satisfied. For $\epsilon > \epsilon_c$, only decremental conduction is possible.

Arima and Hasegawa (1963) have considered a generalized form of (7.1) with $R_t = G(V)$. With suitable restrictions on $F$, $G$, and the smoothness of the initial data, they show that a unique solution exists in the half-space $|x| > \infty$

[6] Available on loan from the National Medical Audiovisual Center (Annex) Station K, Atlanta, Georgia 30333.

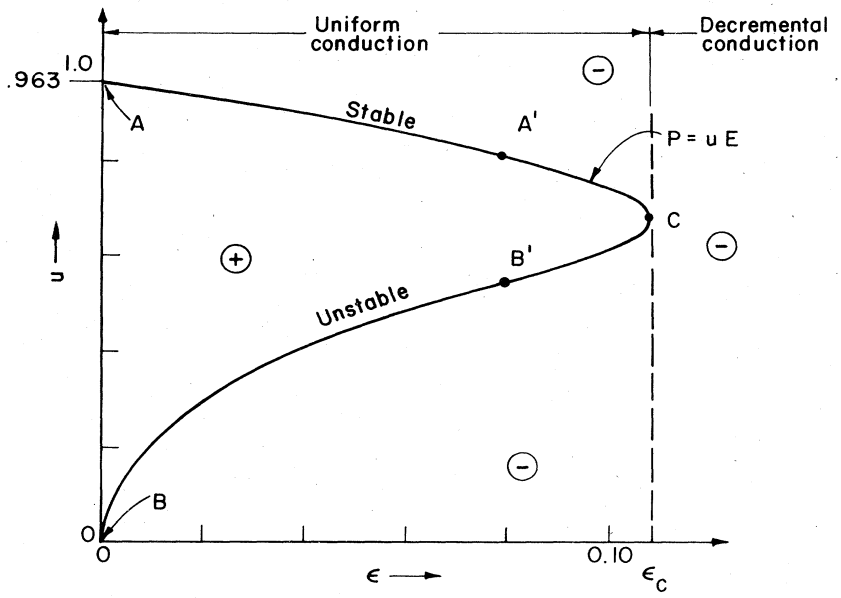


FIG. 29. Propagation velocity for traveling wave pulse solutions of the FitzHugh-Nagumo equations (7.1) vs the temperature parameter $\epsilon$ for $a = 0.7$ and $b = 0.8$. Redrawn from FitzHugh (1969).

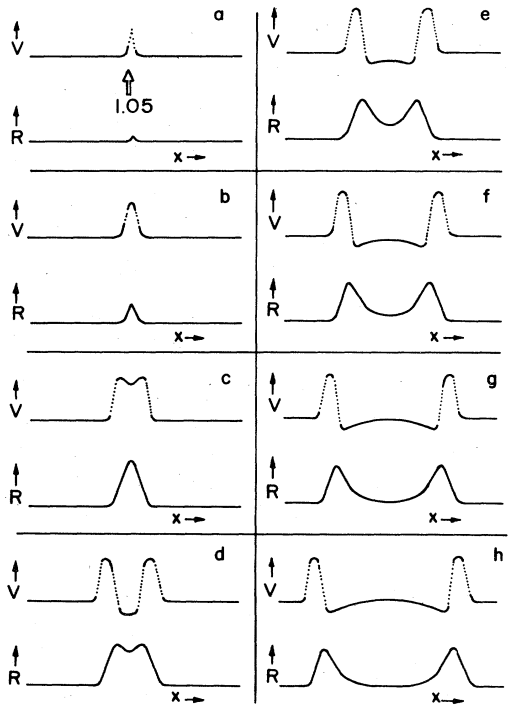


FIG. 30. Frames from computer movie of FitzHugh (1968) showing results of a local stimulation of (7.1) 5% above threshold with $\epsilon = 0.08$, $a = 0.7$, and $b = 0.8$.

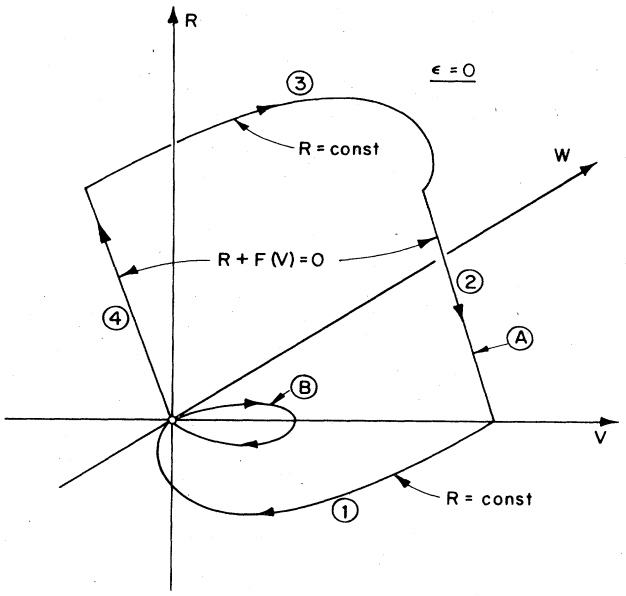


FIG. 31. Phase space sketch of homoclinic trajectories for (7.2) with $\epsilon = 0$.

and $t > 0$. Building on this result Yamaguti (1963) showed that solutions of (7.1) with $a = 0$, $b = 0$ and $VF \geq CV^2$ tend uniformly to zero. A related result was obtained by Yoshizawa and Kitada (1969) who considered (7.1) with $b = 0$ but $F(V)$ a cubic polynomial. They confirm the existence of a threshold by showing that every solution in some neighborhood of zero converges to zero with increasing time. Green and Sleeman (1974) have established upper and lower bounds for the velocity of a traveling wave.

The existence of homoclinic trajectories for Eqs. (7.2) has been studied in detail by Carpenter (1974) and Hastings (1975b); and important analytical results have been obtained by Casten, Cohen and Lagerstrom (1975) using singular perturbation methods. To see this consider Fig. 31 which shows two homoclinic orbits in the limit $\epsilon = 0$ which implies (7.2c) $R = \text{const}$. Orbit B corresponds to point $B$ in Fig. 29 and is just the trajectory given in (6.6) for the zero velocity "threshold pulse" shown in Fig. 27. Orbit $A$ which corresponds to point $A$ in Fig. 29 is somewhat more complex. It is the singular orbit approached as $\epsilon \to 0$ of a family of homoclinic orbits which correspond to the pulse shown in Fig. 32. Going backward in $\xi$ or forward in time, this pulse can be described as follows: ① The "leading edge"

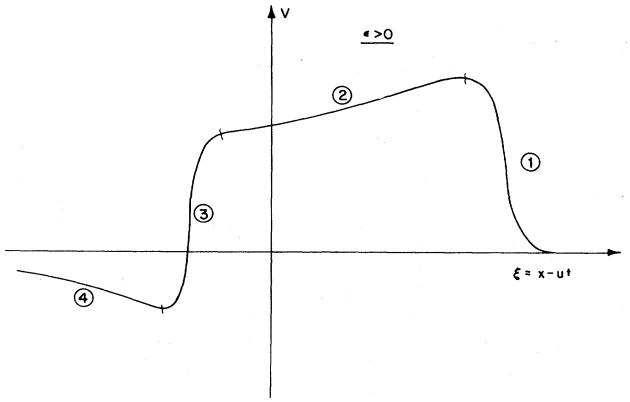


FIG. 32. Voltage pulse corresponding to orbit A in Fig. 31 with $\epsilon > 0$.

involves a rapid transition between the outer zeros of $F(V)$ as was discussed in detail in the previous section. ② A "slow relaxation" from $R = 0$ to a new value $R_1$ determined by (7.2c) with the condition $F(V) + R \approx 0$. ③ A rapid downward voltage transition between the two outer zeros of $F(V) + R_1$. The value of $R_1$ must be such that this trailing edge will have the same velocity as the leading edge (see Fig. 26). ④ Finally there is a slow relaxation from $R = R_1$ back to zero.

The velocity, $u_0$, of the singular orbit A is just that velocity discussed in the previous section. Assuming $a = 0$, $b = 0$, and $\epsilon > 0$, we can write

$$u = u_0 + \epsilon u_1^{\mathrm{A}} + \epsilon^2 u_2^{\mathrm{A}} + \cdots, \tag{7.4a}$$

$$V = V_0 + \epsilon V_1 + \epsilon^2 V_2 + \cdots, \tag{7.4b}$$

$$R = R_0 + \epsilon R_1 + \epsilon^2 R_2 + \cdots. \tag{7.4c}$$

We can then substitute into (7.2), and equate powers of $\epsilon$ to obtain

$$d^2V_0/d\xi^2 + u_0(dV_0/d\xi) - [F(V_0) + R_0] = 0, \tag{7.5}$$

$$R_0 = \text{const}, \tag{7.6}$$

$$d^2V_1/d\xi^2 + u_0(dV_1/d\xi) - V_1F'(V_0) = R_1 - u_1^{\mathrm{A}}(dV_0/d\xi), \tag{7.7}$$

$$dR_1/d\xi = -V_0/u_0. \tag{7.8}$$

Using (7.5) and some integration by parts, it is not difficult to show that the left-hand side of (7.7) is orthogonal to

$$(dV_0/d\xi)\exp(u_0\xi).$$

Thus, from (7.7) and (7.8), $u_1^{\mathrm{A}}$ is determined as

$$u_1^{\mathrm{A}} = -\frac{1}{u_0}\int_{-\infty}^{\infty}\left(\int_{-\infty}^{\xi} V_0(\xi')\,d\xi'\right)\frac{dV_0}{d\xi}\exp(u_0\xi)\,d\xi \Big/ \int_{-\infty}^{\infty}\left(\frac{dV_0}{d\xi}\right)^2\exp(u_0\xi)\,d\xi. \tag{7.9}$$

From Fig. 29 it is clear that the approximation

$$u \approx u_0 + u_1^{\mathrm{A}}\epsilon \tag{7.10}$$

is useful over a substantial portion of the upper (stable) branch; and, it is important to notice, the determination of $u_1^{\mathrm{A}}$ in (7.9) requires only knowledge of the singular pulse $V_0(\xi)$.

For the orbit $B$ in Fig. 31, $u_0 = 0$ and (7.9) cannot be used. In this case Casten *et al.* write

$$V = V_0 + \epsilon^{1/2}V_1 + \cdots, \tag{7.11a}$$

$$R = \epsilon^{1/2}R_1 + \cdots, \tag{7.11b}$$

$$u = \epsilon^{1/2}u_1^{\mathrm{B}} + \cdots, \tag{7.11c}$$

to obtain

$$d^2V_0/d\xi^2 - F(V_0) = 0, \tag{7.12}$$

$$d^2V_1/d\xi^2 - F'(V_0) = R_1 - u_1^{\mathrm{B}}(dV_0/d\xi), \tag{7.13}$$

$$dR_1/d\xi = -V_0/u_1^{\mathrm{B}}. \tag{7.14}$$

The orthogonality condition still holds for the left-hand side of (7.13) so

$$u_1^{\mathrm{B}} = +\left(\int_{-\infty}^{\infty} V_0^2\,d\xi \Big/ \int_{-\infty}^{\infty}\left(\frac{dV_0}{d\xi}\right)^2 d\xi\right)^{1/2}. \tag{7.15}$$

Again we see that the approximation

$$u \approx \epsilon^{1/2}u_1^{\mathrm{B}} \tag{7.16}$$

is useful over much of the lower branch in Fig. 29.

Closed trajectories satisfying (7.2) correspond to the periodic wave solutions which were originally suggested by Huxley (1959) for the Hodgkin–Huxley equations. The existence of such closed orbits has been studied by Hastings (1974a) and by Carpenter (1974) using the concept of "isolating blocks" [Conley (1973)] around a singular orbit. Rinzel and Keller (1973) have studied solutions of (7.2) with $a = 0$, $b = 0$, and

$$F(V) = V \text{ for } V < V_1$$
$$= V - 1 \text{ for } V > V_1. \tag{7.17}$$

This is the function of Fig. 28 with $g_a = g_r$ so the phase space equations are linear except along the plane $V = V_1$. For a periodicity defined by

$$V(\xi) = V(\xi + \lambda) \tag{7.18}$$

some numerical values for velocity, $u$, and amplitude, $A$, are shown as functions of $\lambda$ in Fig. 33. Again there are two waves for each period, the slower wave being unstable.

Currently it is of great interest to extend such exact results to the full Hodgkin–Huxley equations (5.1) or to the corresponding ordinary differential equations for traveling wave solutions (5.5). Evans and Shenk (1970) have

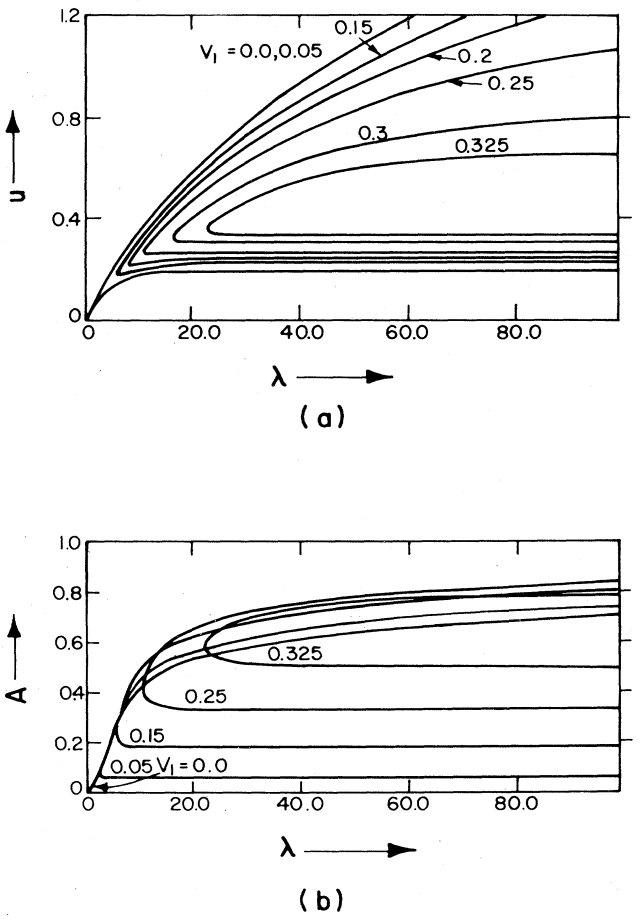


FIG. 33. (a) Velocity, and (b) amplitude vs pulse spacing, λ, for periodic solutions for the FitzHugh–Nagumo equation with $\epsilon = 0.05$, $a = 0$, $b = 0$, and $F(V)$ as in (7.17). Redrawn from Rinzel and Keller (1974).

shown that (5.1) has a unique solution for arbitrary bounded initial conditions with continuous dependence on the initial conditions. Quite recently Carpenter (1974) has extended the concept of isolating blocks to the higher dimensional phase space associated with (5.5) and indicated in Fig. 20. To do this she takes $m$ to be a fast variable so $v$, $i$, and $m$ vary along branches ① and ③, and only $n$ and $h$ vary along branches ② and ④. The small parameters are then $\tau_m$, $\tau_n^{-1}$, and $\tau_h^{-1}$, and both homoclinic and periodic orbits are established. The analysis by Hastings (1974b) which does not assume $\tau_m$ small is probably closer to physiological reality as we saw in the previous section; however periodic orbits were not obtained.

## VIII. THE MYELINATED AXON

Examination of (6.16) reveals a major design difficulty of the smooth nerve fiber. Since $g_a = 2\pi a G_a$, $c = 2\pi a C$ and $r_s = (\pi a^2 \sigma_1)^{-1}$, where $a$ is the radius of the fiber, the conduction velocity is proportional to

$$u \propto a^{1/2} \tag{8.1}$$

or to the fourth root of the cross-sectional area. [See FitzHugh (1973) for a careful application of dimensional analysis to nerve problems.] In order to double the velocity, the area (and therefore the volume) of the fiber must increase by a factor of sixteen; to triple the velocity requires a factor of eighty-one. Since the giant axons of the squid transmit "escape signals" (generated in forward nerve cell complexes) to the appropriate muscles (located aft) there is evolutionary pressure to increase the speed, and this probably explains the unusually large size of the fiber. But clearly the fibers can't get much faster without using an unacceptable fraction of the squid's cross section, and only a single bit of information ("leave" or "stay") is being transmitted at any instant of time. Equation (6.16) also indicates a way out of this dilemma. If the fiber is partially covered by an insulating material so only a fraction $f$ of the active membrane remains exposed, $g_a/c$ and $r_s$ would remain the same. But $c$ would be proportional to $f$, so the conduction velocity should depend upon the exposed fraction roughly as

$$u \propto f^{-1/2}. \tag{8.2}$$

Thus velocity can be increased without changing the cross-sectional area by making $f$ small.

Something like this takes place in the design of the motor axons of vertebrates. The structure of the fiber appears as in Fig. 34 where the fiber is almost everywhere covered by a relatively thick insulating coat of *myelin* consisting of a couple of hundred layers of cell membrane [Hodgkin (1951, 1964)]. Only at small active nodes (nodes of Ranvier) can the membrane function in the normal way and these are spaced apart by a distance $D \sim 1$ mm. In this manner the diameter of the fiber can remain as small as 10 $\mu$, while the conduction velocity is as large as that on the squid fiber. The frog nerve studied by Helmholtz (1850) and shown in Fig. 1 is actually a bundle of many axons myelinated as in Fig. 34. Young (1951) has prepared a graphic comparison of the squid giant axon and the sciatic nerve of a rabbit which is reproduced in Fig. 35. The conduction velocity is about the same in both cases, so the myelinated nerve bundle can carry at least two orders of magnitude more bits of information per unit time. This high information rate permits the fine muscular control which is one of the striking features of higher animals.

The role of isolated active nodes in increasing conduction speed was first recognized by Lillie (1925, 1936) in connection with his experiments on the passive iron wire analog for the nerve fiber. He showed that the conduction velocity on this model was greatly increased when the wire was enclosed in a glass tube broken into segments; and he noted that the excitation seemed to "jump" quickly from one opening in the glass tubing to the next, an effect called "saltatory" conduction by physiologists.[7] Shortly thereafter Osterhout and Hill (1930) demonstrated that conduction in *Nitella* which had been blocked in fresh water by chloroform could be restored by introducing a salt bridge around the block, and Kato (1934) isolated in the conductable state a single fiber from the sciatic nerve of the Japanese toad. Building on these classic results, Tasaki (1939) demonstrated that conduction jumped from node to node in a single Japanese toad fiber. For general surveys of experi-

[7] *Saltare* is the Latin and modern Italian verb "to jump."

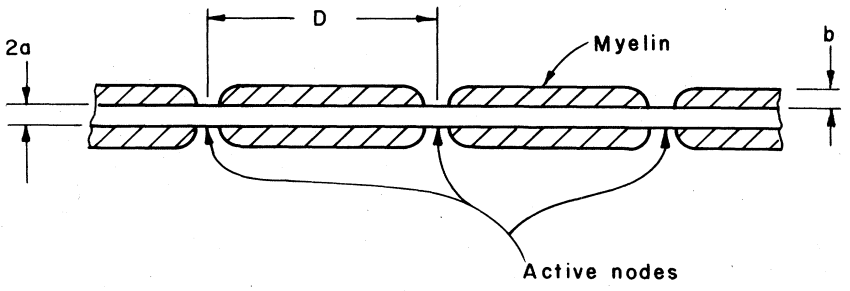


FIG. 34. Structure of a myelinated nerve fiber (not to scale).

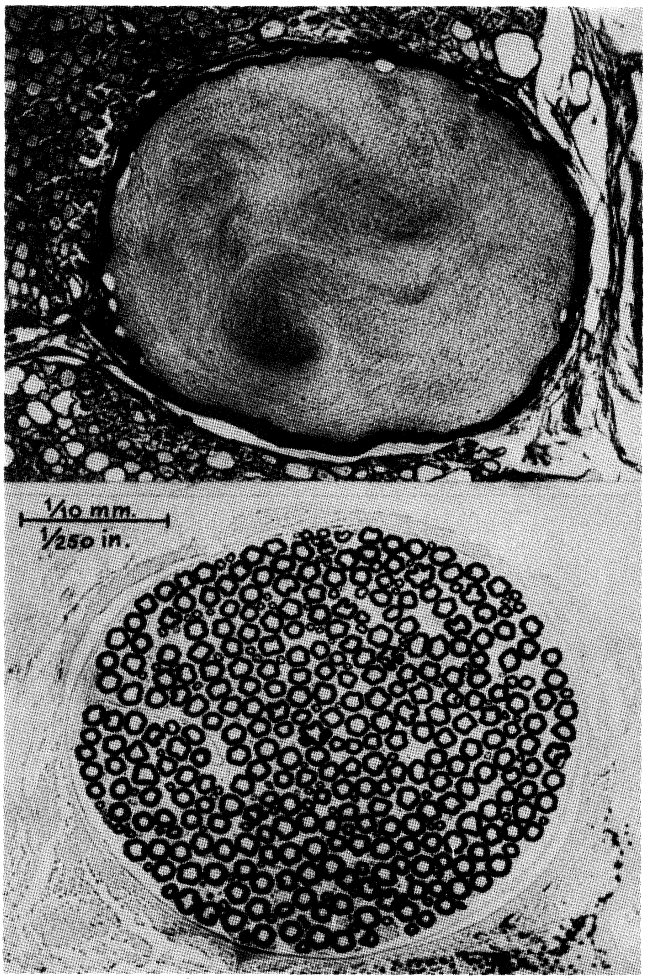


FIG. 35. Comparison of cross sections for the squid giant axon (above) and the sciatic nerve bundle controlling the calf muscle of a rabbit (below). There are about 400 myelinated fibers in the rabbit nerve each conducting pulses at about 80 meters per second [Young (1951)].

ments on myelinated fibers the reviews by Tasaki (1959) and Hodgkin (1951, 1964) are suggested in addition to the discussion by Cole (1968); here we list some representative data on the frog myelinated fiber collected by Hodgkin (1964).

It is interesting to note how close this average conduction velocity is to the value of 27 m/sec measured by Helmholtz in 1850.

TABLE II. Data on frog myelinated fiber.

| | |
|---|---|
| Fiber radius (a) | 7 $\mu$ |
| Myelin thickness (b) | 2 $\mu$ |
| Distance between active nodes (D) | 2 mm |
| Area of active node | $2.2 \times 10^{-7}$ cm$^2$ |
| Internal resistance per unit length | 140 MΩ/cm |
| Capacity of myelin per unit length | 10–16 pF/cm |
| Conductance of myelin per unit length | $2.5\text{–}4 \times 10^{-8}$ mho/cm |
| Capacity of active node | 0.6–1.5 pF |
| Resting resistance of node | 40–80 MΩ |
| Conduction velocity | 23 m/sec |

The square root of the ratio of squid fiber radius (238 $\mu$) to that in Table II is 5.83. The inverse square root of the fraction of exposed area multiplied by the ratio of total capacitance to node capacitance is 10.6. Thus (8.1) and (8.2) imply that the squid axon velocity should be 0.55 times that of the frog, axon whereas in fact they are about equal. This simple estimate ignores: (i) the effect of concentrating the active membrane at isolated points, (ii) the differences between frog and squid membrane dynamics indicated in Fig. 19, and (iii) differences in conductivity of the axoplasm. The first of these corrections can be brought into focus by noting, from the considerations of Sec. II, that the myelinated fiber is closely approximated by a linear diffusion equation which is periodically loaded by the active nodes [Pickard (1966), Markin and Chizmadzhev (1967)]. This picture can be further simplified by lumping the internode capacitance of the myelin together with the nodal capacitance. This leads to the equivalent circuit indicated in Fig. 36, where

$$R = 28\ M\Omega,$$

$$C = 2.6 - 4.7\ \text{pF},$$

and $I(i)$ is the ion current calculated at the $i$th node from Eqs. (4.3) and (4.4) using the data in Fig. 19(b). Equations (5.1a, b) are then replaced by the *difference differential equations*

$$v_i - v_{i-1} = -i_i R, \tag{8.3a}$$

$$i_{i+1} - i_i + C(dv_i/dt) = -I(i). \tag{8.3b}$$

To determine a conduction velocity the traveling wave assumption, displayed in (5.3) and (5.4), must be replaced by a search for solutions which satisfy the condition

$$v_{i-1}(t) = v_i(t - T), \tag{8.4a}$$

$$i_{i-1}(t) = i_i(t - T), \tag{8.4b}$$

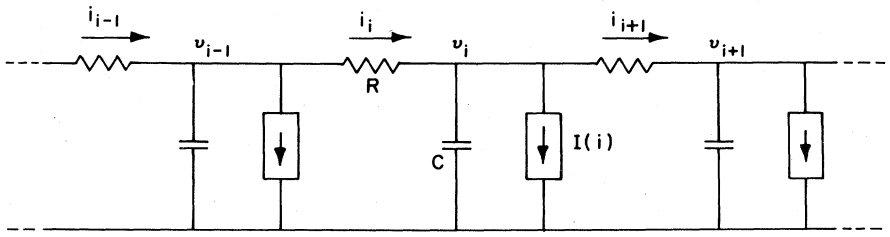


FIG. 36. A difference differential representation of the myelinated nerve fiber.

where $T$ is a *section delay*. If $T$ can be found, the conduction velocity for the myelinated fiber is evidently

$$u_m = D/T. \tag{8.5}$$

In solving for the section delay, it is interesting to begin by assuming $I(i) = I(v_i)$, where

$$\begin{aligned} I(v_i) &= 0 \qquad \text{for } v_i < V_1, \\ &= G(v_i - V_2) \qquad \text{for } v_i > V_1, \end{aligned} \tag{8.6}$$

as we did in (6.3) for the smooth axon. Then, for $R$ and $G$ sufficiently small, the differences in (8.3) can be approximated as $x$ derivatives and (6.16) gives

$$T \approx [RC^2/G]^{1/2}[(V_2V_1)^{1/2}/(V_2 - V_1)]. \tag{8.7}$$

The problem is to determine $T$ as a function of $R$, $C$, $G$, $V_1$, and $V_2$ when the approximation of (8.7) is *not* valid. This problem was carefully studied by Kunov and Richer at the Electronics Laboratory of the Technical University of Denmark during 1964–65. A detailed description of this work is included in the thesis by Kunov (1966) from which some of the salient points have been published [Kunov (1965), Richer (1965, 1966)]. Kunov's thesis describes a variety of analytical studied including: (i) numerical integration of (8.3) for a finite number of sections, (ii) an iterative computation to find solutions with the form (8.4), (iii) a Laplace transform solution, and (iv) measurements on an electronic analog [Kunov (1965)]. These studies indicate that the ratio of conduction velocity on the myelinated axon, $u_m$, to that calculated from (6.16) for the smooth axon, $u_0$, is a function of the parameters $RG$, and $(V_2 - V_1)/V_2$. Thus

$$u_m/u_0 = \gamma[RG, (V_2 - V_1)/V_2], \tag{8.8}$$

and curve specifying $\gamma$ are reproduced in Fig. 37. For the frog axon, the data in Fig. 19(b) give $G = 0.57$ $\mu$mho so

$$RG = 16,$$

and in Sec. VI the value of $V_1$ which seemed to account for delay in sodium turn on was about 60 mV. Thus

$$(V_2 - V_1)/V_2 = 0.5.$$

From Fig. 37 these two values indicate a reduction in velocity of the myelinated fiber over that of a smooth axon by the factor

$$\gamma = 0.4,$$

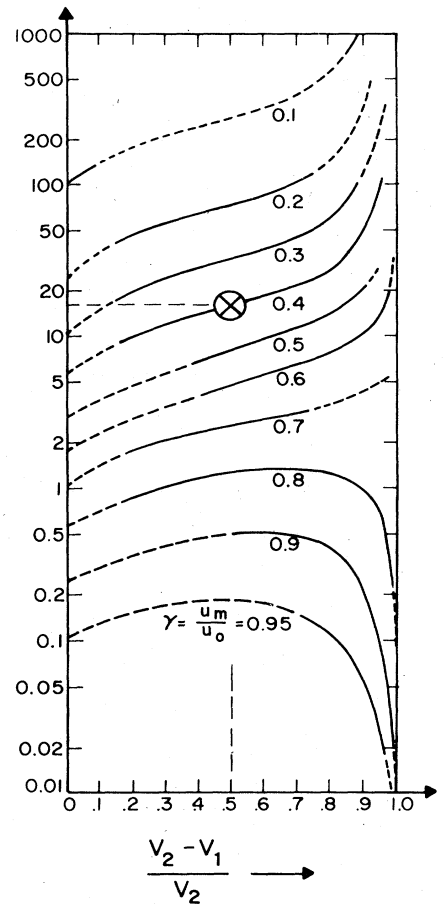


FIG. 37. Ratio of myelinated conduction velocity ($u_m$) to that of the corresponding smooth fiber ($u_0$) given by (6.16). Dashed lines indicate extrapolated or interpolated values.

whereas our rough estimate obtained above by comparison of squid and frog fibers was

$$\gamma = 0.55.$$

This is rather close agreement considering the uncertainty in the capacitance $C$ and the indication in Fig. 19(b) that the frog membrane responds somewhat more quickly than that of the squid. Furthermore the appropriate value for $G$ may not be as large as 0.57 $\mu$mho since potassium and leakage currents flow in the opposite direction and, in addition, leakage current through the myelin and the resting conductance may have a noticeable effect as indicated in (6.17) [Kompaneyets (1971)].

Richer (1966) has made an important contribution to

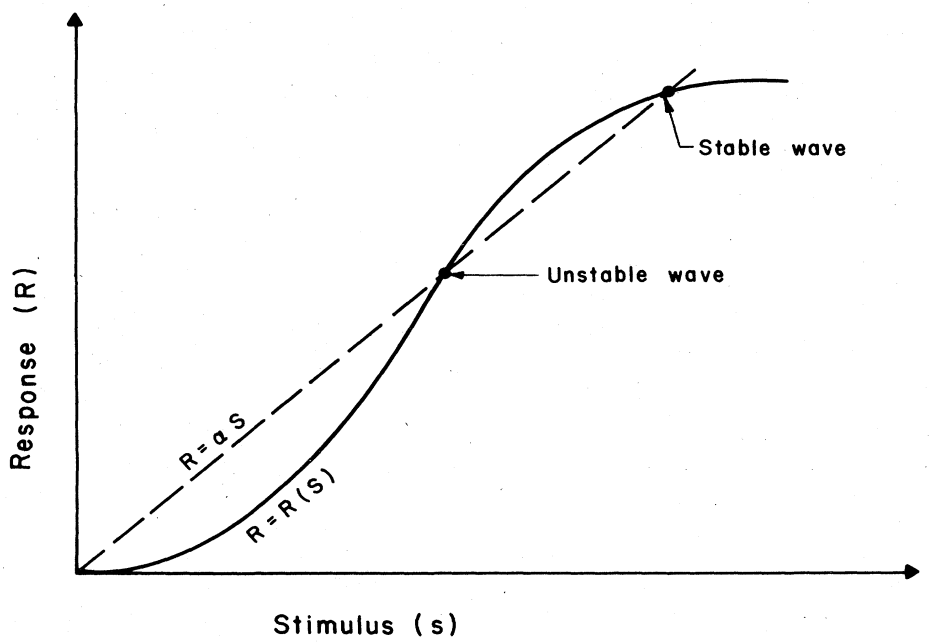


FIG. 38. Nasonov diagram for a myelinated nerve fiber.

this problem by finding an *exact* solution for the case $G = \infty$ which he calls "switch-line." This solution gives an implicit relation between normalized section delay, $T/RC$, and $(V_2 - V_1)/V_2$ as

$$(V_2 - V_1)/V_2 = \exp\left(-\int_0^{\pi/2} F(\alpha, T/RC)\, ctn\alpha\, d\alpha\right), \tag{8.9}$$

where

$$F(\alpha, T/RC) \equiv (2/\pi)\tan^{-1}[(ctn\alpha)\tanh(2T/RC\sin^{-2}\alpha]. \tag{8.10}$$

Equation (8.9) appears a bit unwieldy, but fortunately it can be closely approximated by the much simpler expression

$$(V_2 - V_1)/V_2 \approx (1 + T/RC)^{-1} \tag{8.11}$$

which is found to be asymptotically correct for both large and small values of $T$, and overestimates $T$ by about 10% at $T/RC$ equal to unity. A simple algebraic relation which interpolates between (8.11) and (8.7) is

$$\frac{T}{RC} = \left(\frac{V_2}{V_2 - V_1}\right)\left[\left(\frac{V_1}{V_2}\right)\left(\frac{1}{RG} + \frac{V_1}{V_2}\right)\right]^{1/2}. \tag{8.12}$$

This equation agrees well with digital computer solutions for a long but finite system and also with the results of analog simulation [Kunov (1966)]. Richer (1965) has also considered the addition of resting conductance as in Fig. 28 and has shown that only a positive or negative level change can propagate (not a pulse) just as in the smooth axon. It is interesting to note that he finds an intermediate range for which neither wave can propagate.

Kunov (1966) considers recovery models or discrete FitzHugh–Nagumo systems, and Markin and Chizmadzhev (1967) discuss propagation when the internodes are described by the linear diffusion equation. FitzHugh (1962) computed the initiation and conduction of pulses on a linear diffusion equation periodically loaded with Hodgkin–Huxley nodes, and improved computations have recently been reported by Goldman and Albus (1968). The high velocity (stable) and low velocity (unstable) pulses which appear in Figs. 23 and 29 for the Hodgkin–Huxley and FitzHugh–Nagumo equations can be appreciated on the myelinated fiber by considering the "Nasonov diagram" [Averbach and Nasonov (1950), FitzHugh (1969)] in Fig. 38. If it is assumed that: (i) each node has a "sigmoid" stimulus-response curve, and (ii) a fraction, $1/\alpha$, of the response for each node is presented as a stimulus to the next, then *stationary* levels of activity occur where the sigmoid curve intersects the line $R = \alpha S$. The lower amplitude intersection is unstable since a small increase in $S$ will lead to a larger increase in $R$, etc. The upper intersection, on the other hand, appears to be stable. As the parameter $\alpha$ is increased, these two intersections eventually merge; and above this critical value of $\alpha$ only decremental conduction obtains.

## IX. WAVEFORM STABILITY

In Sec. V–VIII we have considered the problem of finding traveling wave solutions for the partial or difference differential equations describing nerve fibers. For pde's the analytic technique was to *assume* that dependent variables are functions of $x$ and $t$ only through the argument $\xi = x - ut$ as indicated in (5.3). This is equivalent to introducing the independent variable transformation (5.4) and then assuming no dependence upon $\tau$ ($\partial/\partial\tau = 0$). Having found such traveling wave solutions, it is interesting to know whether or not they are *stable* with respect to perturbations

which might reasonably be expected to arise in an experimental situation. To study the time evolution of such perturbations, it is necessary to consider the $\tau$ dependence.

To introduce the basic ideas of waveform stability analysis we will investigate the KPP form of the nonlinear diffusion equation (1.1),

$$V_{xx} - V_t = F(V), \tag{9.1}$$

traveling wave solutions for which were considered in detail in Sec. VI assuming a cubic form for the function F(V). Equation (9.1) is simple enough for exposition and the results to be obtained serve as a basis for stability investigation of the FitzHugh–Nagumo and Hodgkin–Huxley traveling waves.

Under the transformation (5.4), (9.1) becomes

$$V_{\xi\xi} + uV_\xi - V_\tau = F(V), \tag{9.2}$$

where $V$ is now considered a function of $\xi$ (space in a coordinate system moving with velocity $u$) and $\tau$ (the same time scale as $t$). The traveling wave solution $V_T(\xi)$ must satisfy

$$V_{T,\xi\xi} + uV_{T,\xi} = F(V_T) \tag{9.3}$$

and a general solution of (9.2) can be considered as the sum of a traveling wave solution and a perturbation $V_P(\xi, \tau)$. Thus

$$V(\xi, \tau) = V_T(\xi) + V_P(\xi, \tau). \tag{9.4}$$

Substituting (9.4) into (9.2) gives

$$V_{P,\xi\xi} + uV_{P,\xi} - V_{P,\tau} = F(V_P + V_T) - F(V_T) \tag{9.5}$$

as a nonlinear and $\xi$-dependent pde for the evolution of the perturbation. It is important to recognize that *no* approximations have been made in going from (9.1) to (9.5).

Investigation of (9.5) for the evolution of $V_P(\xi, \tau)$ subject to prescribed initial and boundary conditions constitutes the "waveform stability problem" for a traveling wave solution to (9.1) with velocity $u$. This equation has been studied in connection with the propagation of: (i) flames [Zeldovich and Barenblatt (1959), Kanel' (1962)], (ii) "Gunn effect" domains in bulk semiconductors, [Knight and Peterson (1967), Eleonskii (1968)], and (iii) traveling waves on "neuristors" and electronic analogs for the nerve fiber [Parmentier (1967, 1968, 1969, 1970), Buratti and Lindgren (1968), Lindgren and Buratti (1969), Maginu (1971)].

One approach to the study of (9.5) is to assume the perturbation small enough so the right-hand side can be approximated by

$$\begin{aligned} F(V_P + V_T) - F(V_T) &\approx dF/dV\,|_{V=V_T} \times V_P \\ &\equiv G(V_T)\,V_P, \end{aligned} \tag{9.6}$$

whereupon (9.5) is "linearized" to

$$V_{P,\xi\xi} + uV_{P,\xi} - V_{P,\tau} = G[V_T(\xi)]V_P. \tag{9.7}$$

Elementary solutions to (9.7) will either decay exponentially with time, grow exponentially with time, or remain constant. Thus, *with respect to the linearized equation*, we can say the system is: (i) *asymptotically stable* if *all* elementary solutions decay, (ii) *unstable* if *any* elementary solution grows, and (iii) *stable* if (i) and (ii) are not satisfied.

This is a neat scheme but we must be wary of drawing conclusions from (9.7) which are not relevant to the application of (9.5) in a real situation. While we might conclude asymptotic stability with respect to (9.7), for example, it may not be reasonable to assume perturbations small enough for (9.7) to apply. As Eckhaus (1965) puts it "infinitesimal disturbances are certainly unavoidable, but not all unavoidable disturbances may be considered infinitesimal."[8] On the other hand if (9.7) indicates elementary solutions which grow, these will eventually be bounded by the nonlinear character of (9.5). Such a bound may be so close to the original solution that the system is, in effect, stable. With these caveats in mind, let us proceed to the analysis of (9.7).

If $V_P$ is constructed from elementary product solutions of the form

$$V_P \sim \phi(\xi)\,\exp(-\lambda\tau), \tag{9.8}$$

then $\phi$ must satisfy the eigenvalue equation

$$\phi_{\xi\xi} + u\phi_\xi + \{\lambda - G[V_T(\xi)]\}\phi = 0. \tag{9.9}$$

The condition for asymptotic stability is that all the eigenvalues, $\lambda$, which are allowed for solutions of (9.9) must have positive real parts. This would require that the magnitude of the corresponding elementary solution (9.8) will decay exponentially with time. In a certain sense asymptotic stability is never possible. To see this, differentiate (9.3) for the traveling wave solution with respect to $\xi$ to obtain

$$(V_{T,\xi})_{\xi\xi} + u(V_{T,\xi})_\xi - G(V_T)\,V_{T,\xi} = 0, \tag{9.10}$$

and note that this is the same equation obeyed by $\phi$ when $\lambda = 0$. Thus the eigenfunction of (9.9) with zero eigenvalue is

$$\phi = V_{T,\xi} \qquad \text{for } \lambda = 0. \tag{9.11}$$

The physical meaning of this result is seen by considering an infinitesimal translation, $\alpha$, of $V_T$ along the $\xi$ axis. Since

$$V_T(\xi + \alpha) = V_T(\xi) + \alpha V_{T,\xi}, \tag{9.12}$$

this is equivalent to adding an infinitesimal amount of the $\lambda = 0$ eigenfunction. But we expect a translational perturbation neither to grow nor decay. The observation that *the perturbation eigenfunction corresponding to zero eigenvalue is the derivative of the traveling wave* is quite general and not at all restricted to solutions of (9.1). Many investigators avoid this situation by defining stability with respect to a metric which permits arbitrary translations with $\xi$ [Zeldovich and Barenblatt (1959), Kanel' (1962), Maginu (1971), Evans (1972), Brooke Benjamin (1972), Sattinger (1975)].

[8] Those who experiment with real nerve fibers will probably agree.

Next it is of interest to determine whether or not $\lambda = 0$ is the lowest eigenvalue; if it is not, (9.8) indicates instability. We shall make this determination with respect to the boundary conditions

$$\phi \to 0 \qquad \text{as } |\xi| \to \infty, \tag{9.13}$$

which imply perturbations of finite energy. If the change of dependent variable

$$\phi = \exp[-(u/2)\xi]\psi \tag{9.14}$$

is introduced into (9.9) [Parmentier (1967)], $\psi$ must satisfy the Schrödinger equation

$$\psi_{\xi\xi} + \{\lambda - \tfrac{1}{4}u^2 - G[V_T(\xi)]\}\psi = 0 \tag{9.15}$$

for which the eigenvalues are real and bounded from below [Morse and Feshbach (1953) pp. 766–8]. If $\lambda = 0$ and $G \to G_1 > 0$ as $\xi \to +\infty$, $\psi$ must also satisfy the boundary condition (9.13). Then $\lambda = 0$ is the lowest eigenvalue if the corresponding eigenfunction $dV_T/d\xi$ has no zero crossings. This condition is satisfied for the "level change" waves in Fig. 26 but not for the pulse wave in Fig. 27. Thus the smooth level change waves are *stable* with respect to the linearized equation, but any solution for which $V_T$ is not monotone increasing with $\xi$ will have eigenvalues $\lambda < 0$ and, from (9.8) will be *unstable*. This conclusion is independent of the form of the function $F(V)$ in (9.1).

This result can be extended to perturbations which are not infinitesimal by expressing the right-hand side of (9.5) by the Taylor series

$$F(V_T + V_P) - F(V_T) = F'(V_T)V_P + \tfrac{1}{2}F''(V_T)V_P^2 + \cdots \tag{9.16}$$

for $V_P$ within the appropriate range of convergence. Lindgren and Buratti (1969) have constructed a Lyapunov functional which implies nonlinear stability from linear stability if $V_P$ is small enough compared with the first positive eigenvalue in (9.15). Maginu (1971) has obtained a stronger result. He writes

$$V_P = V_P^{(1)} + V_P^{(2)} + \cdots, \tag{9.17}$$

where $V_P^{(1)} + V_P^{(2)} + \cdots + V_P^{(n)}$ satisfies (9.5) to $n$th order with the right-hand side approximated up to the $n$th derivative in the Taylor series (13.16). Then he shows that as $\tau \to \infty$, $V_P^{(1)} \to \alpha V_{T,\xi}$, $V_P^{(2)} \to \frac{1}{2}\alpha^2 V_{T,\xi\xi}$, $\ldots$, $V_P^{(n)} \to (\alpha^n/n!)V_{T,\xi}n$. Thus

$$V_P \to V_T(\xi + \alpha) - V_T(\xi) \qquad \text{as } \tau \to \infty. \tag{9.18}$$

This is nonlinear stability with respect to a metric which permits translations in the $\xi$ direction. The only restriction on $V_P$ is that it must lie within the range of convergence in (9.16).

To see how this proof goes, note first that we have already demonstrated, through analysis of (9.7), that $V_P^{(1)} \to \alpha V_{T,\xi}$ as $\tau \to \infty$. To second order $V_P^{(2)}$ must satisfy

$$V_{P,\xi\xi}^{(2)} + uV_{P,\xi}^{(2)} - V_{P,\tau}^{(2)} = F'(V_T)V_P^{(2)} + \tfrac{1}{2}F''(V_T)(V_P^{(1)})^2. \tag{9.19}$$

Differentiating (9.3) twice with respect to $\xi$ gives

$$V_{T,\xi\xi\xi\xi} + uV_{T,\xi\xi\xi} = F'(V_T)V_{T,\xi\xi} + F''(V_T)V_{T,\xi}^2. \tag{9.20}$$

The variable

$$w \equiv V_P^{(2)} - \tfrac{1}{2}\alpha^2 V_{T,\xi\xi} \tag{9.21}$$

obeys the equation $[(9.19) - \frac{1}{2}\alpha^2\ (9.20)]$ or

$$w_{\xi\xi} + uw_\xi - w_\tau = F'(V_T)w + \tfrac{1}{2}F''(V_T)[(V_P^{(1)})^2 - \alpha^2 V_{T,\xi}^2]. \tag{9.22}$$

But, as $\tau \to \infty$, this approaches

$$w_{\xi\xi} + uw_\xi - w_\tau = F'(V_T)w \tag{9.23}$$

which is identical to (9.7), so $w \to \alpha_1 V_{T,\xi}$. Then from (9.21)

$$V_P^{(1)} + V_P^{(2)} \to (\alpha + \alpha_1)V_{T,\xi} + \tfrac{1}{2}\alpha^2 V_{T,\xi\xi} \tag{9.24}$$

as $\tau \to \infty$. The addition of $\alpha_1$ to $\alpha$ in the first term constitutes a second-order correction to the translation caused by the initial perturbation; it can be absorbed simply by redefining $\alpha$ in (9.21) and (9.22). Higher order estimates are treated in a similar manner.

Consider finally the nonlinear bounds on those traveling waves, $V_T(\xi)$, which are not monotone increasing and therefore unstable with respect to the linearized equation (9.7). These will grow no further than the stable, monotone increasing transition wave and they will decay no further than zero. It seems reasonable to speculate that these are the bounds of interest.

It should be emphasized that these conclusions do not apply to transition waves between 0 and $V_1$ in Fig. 26. Since the singular point at $V_1$ corresponds to negative differential conductance of the membrane, it is unstable even under space clamped conditions. The stability of such waves is studied in connection with a problem of genetic diffusion where the dependent variable must be less than or equal to its value at the singular point [Fisher (1936), Kolmogoroff *et al.* (1937), Canosa (1973), Rosen (1974)]. Aronson and Weinberger (1975) have carefully compared the asymptotic behavior of (9.1) for $F(V)$ equal to $V(1 - V)$ with $V(1 - V)(V - V_1)$.

A corresponding stability investigation for a traveling wave solution of the FitzHugh–Nagumo equation (7.1) is considerably more difficult because the linearized problem is third order. Thus the eigenvalue problem, corresponding to (9.9), cannot be made self-adjoint and the eigenvalues are in general complex. The eigenfunction for $\lambda = 0$ is still $V_{T,\xi}$, but there is no simple relation between the number of zero crossings of the eigenfunctions and the order of the real parts of the corresponding eigenvalues. However we have already shown branches ① and ③ of the singular orbit Ⓐ in Fig. 31 to be stable, which is consistent with the numerical results of FitzHugh (1969) and Rinzel and

Keller (1973) indicating stability along the high velocity branch for particular functions $F(V)$.

In a series of papers, Evans (1972) has investigated a generalization, of the Hodgkin–Huxley equations with the form suggested by FitzHugh (1969)

$$V_{xx} - V_t = F_0(V, w_1, \ldots w_n),$$
$$w_{i,t} = F_i(V, w_1, \ldots w_n) \qquad i = 1, \ldots n, \qquad (9.25)$$

where the $F$'s are twice continuously differentiable. This set reduces to (i) the KPP equation for $n = 0$, (ii) the FitzHugh–Nagumo equations with $n = 1$, and (iii) the Hodgkin–Huxley equations with $n = 3$. Writing $W \equiv col(V, w_1, \ldots w_n)$ and assuming a traveling wave solution of the form $W(x, t) = W_T(x - ut) = W_T(\xi)$, a general solution can be written $W(\xi, \tau) = W_T(\xi) + W_P(\xi, \tau)$. The linearized equation for $W_P$ is then [as in (9.7)]

$$\begin{bmatrix} V_{P,\xi\xi} \\ 0 \\ 0 \\ \cdot \\ \cdot \\ \cdot \\ 0 \end{bmatrix} + uW_{P,\xi} - W_{P,\tau} = AW_P, \qquad (9.26)$$

where $A$ is an $(n + 1) \times (n + 1)$ matrix with elements obtained by differentiating the $F$'s with their arguments and evaluating at $W_T$. Evans shows:

(i) The solution for (9.25) decays exponentially to $W_T(\xi + \alpha)$ (from a suitably small initial perturbation) if and only if the solution for (9.26) decays exponentially to $W_{T,\xi}$.

(ii) The solution for (9.26) decays exponentially to $W_{T,\xi}$ if and only if the associated eigenvalue equation

$$\begin{bmatrix} \phi_{0,\xi\xi} \\ 0 \\ 0 \\ \cdot \\ \cdot \\ \cdot \\ 0 \end{bmatrix} + u\Phi_\xi + (\lambda - A)\Phi = 0, \qquad (9.27)$$

where

$$\Phi \equiv col(\phi_0, \phi_1, \ldots, \phi_n)$$

has no eigenvalues with negative real parts, and $\Phi = W_{T,\xi}$ is the *only* eigenfunction for $\lambda = 0$.

A similar result has quite recently been obtained by Sattinger (1975) for a more general system which allows the $F$'s in (9.25) to depend upon the $w_{i,x}$. The zero eigenvalue of the linear operator must be isolated at the origin of the complex plane, and the remaining eigenvalues must lie within a certain parabola in the right half-plane. Evans (1974) has extended his work to show that there must be an unstable pulse as well as a stable pulse.

The stability investigation of waveforms on myelinated fibers is yet to begin. Beyond the speculations associated with Nasonov diagrams (see Fig. 38), there is only the work of Predonzani and Roveri (1968) which treats equilibrium stability of a lossless transmission line that is periodically loaded with active bipoles. Thus much remains to be done before the study of waveform stability is complete. This work should not be dismissed by the experimentalist as merely of mathematical interest. The point of Sec. IV is that a fundamentally correct theory of ion currents has not yet been established. Stability theory is necessary to decide what a given description of the membrane will predict to occur in the laboratory.

## X. THRESHOLD FOR AN ACTIVE FIBER

The classic experimental procedure for determining threshold conditions of a piece of nerve membrane is the "strength-duration" measurement. A current of strength ($I$) is applied for a time duration ($\tau$) which just causes the membrane to fire [see Fig. 39(a)]. Then both $I$ and $\tau$ are adjusted to find their functional relation under this condition. For the space clamped membrane shown in Fig. 14 the relation between $I$ and $\tau$ is easily understood. When $\tau \ll \tau_n$ and $\tau_h$, the current pulse must supply the charge, $Q_\theta$, necessary to change the potential across the membrane to a value at which the ion current flows inward. From the curves of Fig. 17, this is about 20 mV. Thus

$$I\tau = Q_\theta. \qquad (10.1)$$

As $I$ is reduced, the duration necessary for threshold excitation increases; and, eventually, $I$ reaches a level below which steady application will never cause inward ion current. This level is traditionally called the "rheobase." If the stimulating current is turned on slowly (with respect to $\tau_n$ and $\tau_h$), the outward potassium current begins to flow which offsets the inward sodium current and increases the rheobase. These effects have been phenomenologically described by the "two factor" theory of Rashevsky (1960) and Hill (1936). See Katz (1939) for an excellent survey of the early studies; recent work has recently been carefully reviewed by FitzHugh (1969).

Here our attention will be focused on similar calculations for the nerve fiber. The experimental situation is as indicated in Fig. 39(b) where the longitudinal stimulating current, $i(t)$, is conveniently chosen to have the character indicated in Fig. 39(a). In this case also the strength-duration curve is given by (10.1) for small values of $\tau$, and reaches a rheobase for large $\tau$. Computations by Cooley and Dodge (1966) for the Hodgkin–Huxley axon are presented in Fig. 40 which agrees well with experimental results [Noble and Stein (1966), Cole (1968)]. As Noble (1966) has emphasized, the threshold condition for a fiber cannot be calculated from the condition that the voltage at the end of the fiber change by a fixed amount. Indeed, attempts to derive a strength-duration curve from this condition invariably lead to a relation $I(t)^{1/2} = \text{constant}$ for small $\tau$ which is manifestly incorrect [Kunov (1966), Scott (1973)].

One simple and fundamental way to evaluate $Q_\theta$ for a propagating axon is to notice that for small $\tau$ and large $I$, $| c\, \partial v/\partial t | \gg | j_i |$ in (5.1b). Thus (5.1b) can be written as

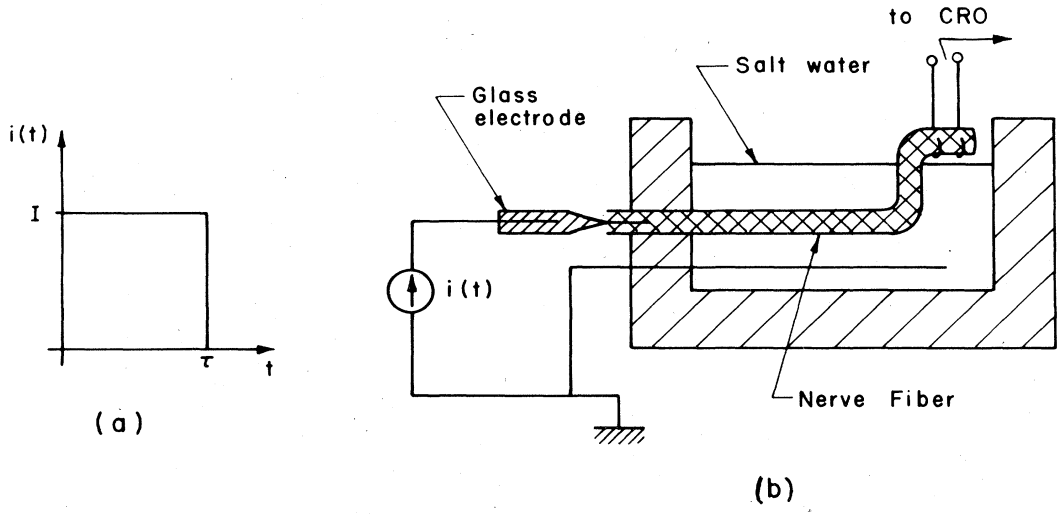


FIG. 39. (a) Strength (I) and duration ($\tau$) for a threshold measurement. (b) An experiment to measure strength duration curves for a nerve fiber.

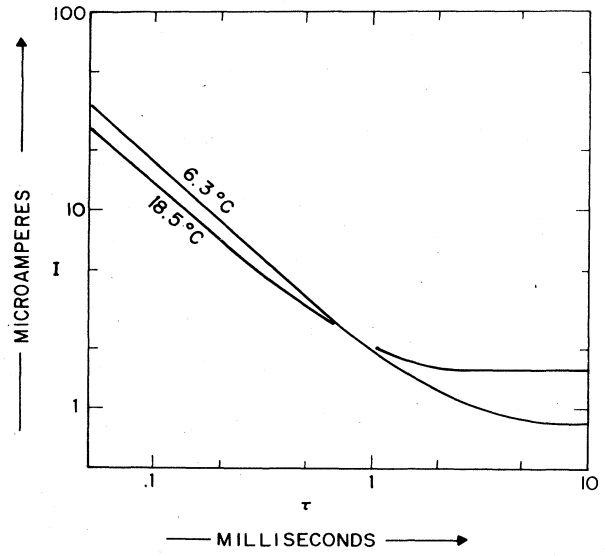


FIG. 40. Calculated strength duration curves for the Hodgkin–Huxley axon. Redrawn from Cooley and Dodge (1966).

the *approximate conservation law* [Scott (1973a)]

$$\partial i/\partial x + \partial(cv)/\partial t \approx 0. \tag{10.2}$$

Longitudinal current, $i$, is the *flow*, and $(cv)$ is the *density* of the approximately conserved quantity which is, therefore, a quantity of charge. Equation (10.2) is approximately satisfied on the leading edge of an action potential since the displacement current is greatest (i.e., $\partial v/\partial t$ is maximum) and the turn on of sodium current is delayed by $\tau_m$ [Hodgkin–Huxley (1952)]. Thus the amount of approximately conserved charge carried by the leading edge of a pulse can be evaluated as

$$Q_0 = \int_{\text{[leading edge]}} i\,dt. \tag{10.3}$$

From (5.1a), $i = -v_x/r_s$; and, from (5.3), $v_x = -v_t/u$ so (10.3) is readily evaluated as

$$Q_0 = V_{\max}/ur_s, \tag{10.4}$$

where $V_{\max}$ is the height of the action potential. Estimates of $Q_0$ for the fully developed action potential on the Hodgkin–Huxley axon are compared with the corresponding values of threshold charge, $Q_\theta$, (from Fig. 40) in Table III.

TABLE III. Comparison of $Q_0$ for fully developed action potention until $Q_0$ threshold charge.

| Temperature (°C) | $Q_0$ (C) | $Q_\theta$ (C) | $Q_\theta/Q_0$ |
|---|---|---|---|
| 18.5 | $2.52 \times 10^{-9}$ | $1.33 \times 10^{-9}$ | 0.53 |
| 6.3 | $4.23 \times 10^{-9}$ | $1.71 \times 10^{-9}$ | 0.41 |

The fact that conserved charge carried in the leading edge is about twice as large as the threshold charge should not be surprising. This "safety factor" is necessary in order to insure reliable propagation of the pulse in the presence of inhomogeneities of the fiber [Smolyaninov (1968), Markin and Patushenko (1969), Patushenko and Markin (1969), Khodorov, *et al.* (1969–1971), Berkinblit, *et al.* (1970), Aronov and Kheifets (1971), Polyakov (1973)]. Table III implies the relation

$$Q_\theta = \alpha Q_0, \tag{10.5}$$

where $\alpha$ is a constant approximately equal to 1/2. In general it can be estimated as the ratio of leading edge charge for a threshold pulse to that of a stable action potential. On this basis the curves in Fig. 22 indicate $\alpha = 0.63$. The discrepancy is probably connected with the fact that the approximate conservation law (10.2) is not so well satisfied for the leading edge of the threshold pulse. More precise measures of threshold pulses using an appropriately defined Lyapunov functional [Parmentier (1970), Elias and Ghausi (1972)] may be useful in improving these estimates. In myelinated fibers the threshold conditions are somewhat more complex [Tasaki (1959), BeMent and Ranck (1969)] but a recent study by Bean (1974) indicates that a threshold condition

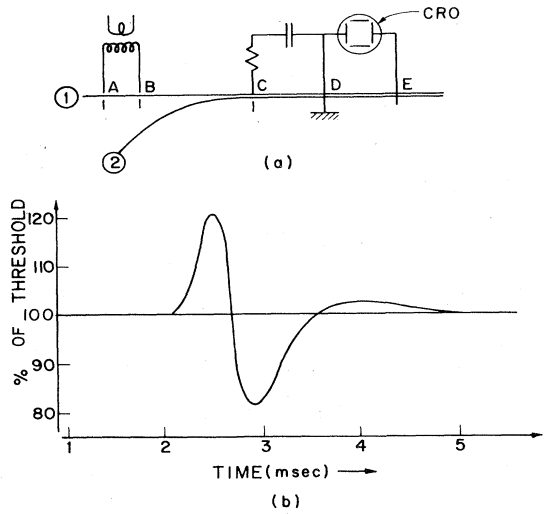


FIG. 41. (a) Experiment of Katz and Schmitt (1939) to measure interaction in parallel fibers. (b) Change in threshold on ② caused by presence of a pulse on ①.

of fixed voltage change, corresponding to a nodal charge, is appropriate.

## XI. PULSE INTERACTIONS

### A. Single fiber interactions

The well established experimental fact that two oppositely directed nerve pulses will annihilate each other upon collision is readily understood from our previous development of leading edge dynamics. Consider the interaction of two oppositely directed leading edge transitions shown in Fig. 26. If the approximate conservation law (10.2) is assumed, then together with (5.1a) the leading edge interaction is governed by the linear diffusion equation which can be written

$$\partial^2/\partial x^2(v - V_2) \approx r_s c(\partial/\partial t)(v - V_2). \tag{11.1}$$

Thus we expect a relaxation toward $v = V_2$ for $j(v)$ as indicated in Fig. 26(a) if (11.1) remains valid until the voltage rises above $V_1$. As soon as $(v - V_2)$ lies within the range of convergence for the Taylor series expansion for $j(v)$ about $V_2$, $v$ must decay to $V_2$. In terms of (10.4), we can say that the *net* approximately conserved charge for the leading edges is zero. Referring back to Fig. 32 for the action potential of the FitzHugh–Nagumo equation, we expect next a slow relaxation with a time constant $\tau_n$. The third stage is the interaction of the trailing edges which, according to the same argument employed for the leading edges, should bring the voltage to a negative value followed by a slow relaxation toward zero.

### B. Parallel fiber interactions

No more than a glance at the lower photograph in Fig. 35 should be necessary to justify an interest in the interaction of pulses which are traveling on parallel fibers. The study of this effect was initiated in an elegant series of experiments by Katz and Schmitt (1939, 1940, 1942). Working on a pair of naturally adjacent fibers from the limb nerve of a crab, their basic apparatus was as shown in Fig. 41. A reference pulse was initiated at AB on fiber ① at a fixed time; and at an adjusted later time the threshold for pulse excitation on fiber ② at CD was measured. The result is recorded in Fig. 41(b) and is interpreted as a stimulation of fiber ② which is roughly proportional to the derivative of the voltage (or from (5.1a) the membrane current) in fiber ①. They also observed the effects of mutual pulse interaction between impulses simultaneously initiated on the two fibers which produced various combinations of speeding or slowing depending upon the phase relation. In particular, *synchronization* of the pulses could be observed if their independent velocities did not differ by more than about 10%. All interaction effects could be increased by reducing the conductivity of the interstitial fluid. Similar effects have been observed by Crane (1964) on neuristors and by Kunov (1966) on electronic analogs for nerve fibers.

Recently Markin (1970a, b) has developed a nonlinear theory for parallel fiber interactions. Starting from a TLEC representing two fibers which share the external medium, he derived a pair of coupled nonlinear diffusion equations with the form

$$(1/\gamma)[(r_2 + r_3)v_{1,xx} - r_3 v_{2,xx}] - c_1 v_{1,t} = j_1, \tag{11.2a}$$

$$(1/\gamma)[(r_1 + r_3)v_{2,xx} - r_3 v_{1,xx}] - c_2 v_{2,t} = j_2, \tag{11.2b}$$

where $r_1$, $c_1$, $j_1$, and $v_1$ are the series resistance/length, shunt capacitance/length, membrane ion current/length, and transmembrane voltage for fiber ① and similarly for fiber ②. The interstitial resistance/length is $r_3$ and $\gamma \equiv r_1 r_2 + r_1 r_3 + r_2 r_3$; so as $r_3 \to 0$, (11.2a, b) become two uncoupled equations with the form (2.30). Nonlinear pulse interaction was studied by representing $j_1(t)$ as

$$\begin{aligned} j_1(t) &= 0 && \text{for } t < 0, \\ &= -J_1 && \text{for } 0 < t < \tau_1, \\ &= +J_2 && \text{for } \tau_1 < t < \tau_1 + \tau_2, \\ &= 0 && \text{for } \tau_1 + \tau_2 < t, \end{aligned} \tag{11.3}$$

where the condition $J_1\tau_1 = J_2\tau_2$ is imposed for zero net charge transfer and pulse return. A similar form was assumed for $j_2(t)$ but with an adjustable time delay. This simple description of the nerve pulse was previously shown [Markin and Chizmadzhev (1967), Undrovinas *et al.* (1972)] to give both the stable (upper) and unstable (lower) velocities which arise in the FitzHugh–Nagumo description. They found that two pulses on adjacent fibers can have three stable bound (collective) states if the uncoupled velocities are sufficiently close together. More recently Markin (1973a, b) has extended this approach to the study of interactions in fiber bundles. The derivation and solution of coupled nonlinear diffusion equations should be of considerable interest to physicists and mathematicians during the next few years.

### C. Interactions at branching points of axons and dendrites

As we saw in Fig. 2, the action potential propagates away from the cell body along an axon or outgoing fiber which may or may not be myelinated. This outgoing pulse travels up to the axonal tree and eventually delivers inputs to many other cells through chemical contacts called *synapses*. On the input end, the dendrites and cell body receive many

synaptic inputs which somewhow contribute to a firing decision by the cell body or the main axon. Extensive branching occurs both in the axonal (output) tree and dendritic (input) trees. The behavior of pulses near these branching points does not yet appear to be well understood.

On the axonal side it is often assumed that the "parent" fiber excites all "daughters" at each branching point so the signal travels without interruption to every distal (distant) twig, but experiments by Barron and Matthews (1935), Krnjevic and Miledi (1959), Chung, Raymond, and Lettvin (1970), Parnas (1972), and Grossman, Spira and Parnas (1973) cast doubt on this simple picture. In these studies, the branch points of some axons emerge as regions of low safety factor where high frequency blockage and alternate firing can take place. Some understanding of this situation may be obtained considering the concept of "threshold charge" expressed in (10.5). From (10.4) it can be seen that $Q_0$ is proportional to $d^{3/2}$ (where $d$ is the fiber diameter) so we can write [Scott (1973b)]

$$Q_0 = kd^{3/2}. \tag{11.4}$$

For conduction from a parent of diameter $d_2$ to two daughters each of diameter $d_1$, the leading edge charge carried by the parent must equal the sum of the threshold charges required by the daughters. This requirement implies

$$d_2/d_1 \geq (2\alpha)^{2/3}, \tag{11.5}$$

where the equality indicates marginal transmission. From our approximate estimate $\alpha \approx 1/2$ (see Table III), marginal conduction should occur when the parent and daughters are of roughly equal size. Conduction through the branch point under marginal conditions might be influenced by small changes in local geometry and electric coupling from pulses on neighboring fibers as well as fatigue from repetition. Thus axonal branch points might provide a location for modification of neural transmission or learning.

On the dendritic side of the nerve cell, the situation is even less clear. Much of the confusion is connected with the implications of the "all or nothing law" of propagation [Lucas (1909), Adrian (1914)] on an active fiber which has dominated the thinking of electrophysiologists for over half a century [Lorente de Nó and Condouris (1959)]. If this "law" is interpreted as implying that an action potential will fire all active fibers to which it is connected, then the integrative function of the dendritic trees cannot be understood unless they are assumed to be passive or at least decremental. But the situation is not so simple. In the first place, as FitzHugh (1955, 1969) has pointed out, the continuity properties for the Hodgkin–Huxley equations [Lefschetz (1962)] do not permit a discontinuous jump from "off" to "on" as the initial conditions are changed. Either the latent period before firing goes to infinity or the latent period is bounded and the derivative of response with respect to stimulus is also bounded. Of course discontinuous response could be invoked by assuming fast regeneration in the phase change of the membrane which was discussed in Sec. IV; and, on the other hand, a continuous rise of response can be so steep that it is indistinguishable from a discontinuous jump in the presence of unavoidable laboratory noise. In sum, therefore, it seems that threshold problems should be approached through careful study rather than imprecise generalities.

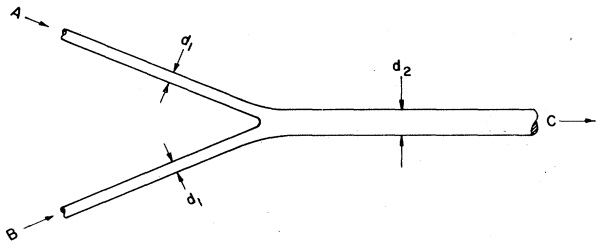


FIG. 42. A simple dendritic bifurcation.

There are experimental results which indicate that information proceeds through the dendritic trees of some neurons by purely passive means [Purpura and Grundfest (1956), von Euler, Green and Ricci (1956), Grundfest (1958)], and a corresponding mathematical theory of passive dendrites has been developed [Rall (1959, 1962a, b, 1964, 1967), Pokrovskii (1970), Pickard (1947)] which essentially involves solving a linearized version of (2.30) with the coefficients taken as functions of $x$. Rall (1959, 1962a) paid particular attention to impedance matching conditions and pointed out that the characteristic admittance $Y_0$ (defined as the square root of the ratio of shunt admittance/length to $r_s$) is proportional to the 3/2 power of the fiber diameter. Thus

$$Y_0 \propto d^{3/2} \tag{11.6}$$

which was used to define an "equivalent dendritic cylinder [Rall (1962b)], satisfying the condition $\Sigma d_i^{3/2} = \text{const}$ at each successive branching, in order to simplify dendritic computations.

But experiments indicating passive dendritic conduction are open to various interpretations [Bishop (1958), Eccles (1960), Rall and Shepherd, (1968), Rall (1970), Bogdanov and Golovchinskii (1970)], and there have been several studies which imply that action potentials can propagate at least on the larger branches of some dendritic trees [Lorente de Nó (1947), Cragg and Hamlyn (1955), Eyzaquirre and Kuffler (1955), Fatt (1957), Hild and Tasaki (1962), Anderson, Holmquist and Voorhoeve (1966), Llinás, Nicholson, Freeman and Hillman (1968), Luk'yanov (1970), Nicholson and Llinás (1971), Llinás and Nicholson (1971)]. Lorente de Nó (1960), Arshavskii *et al.* (1965), Gutman (1971), Waxman (1972), Scott (1973b), Llinás *et al.* (1969) and Gutman and Shimolinuas (1973) have pointed out that the dendrites should be able to perform elementary logical operations at branching points if they can propagate action potentials or even decremental pulses. However the elementary application of the "all or nothing law" must be replaced by a consideration of threshold conditions at each branching point.

A simple argument to indicate the nature of active dendritic logic can be presented in connection with the bifurcation shown in Fig. 42 [Scott (1973b)]. The "OR" condition obtains if an incoming pulse on either branch A or branch B can provide the charge necessary to stimulate an active pulse on branch C. From (11.4) the leading edge charge coming in on a daugher branch is $kd_1^{3/2}$. This charge will divide between the parent and the other daughter in a ratio which is fixed by their respective characteristic ad-

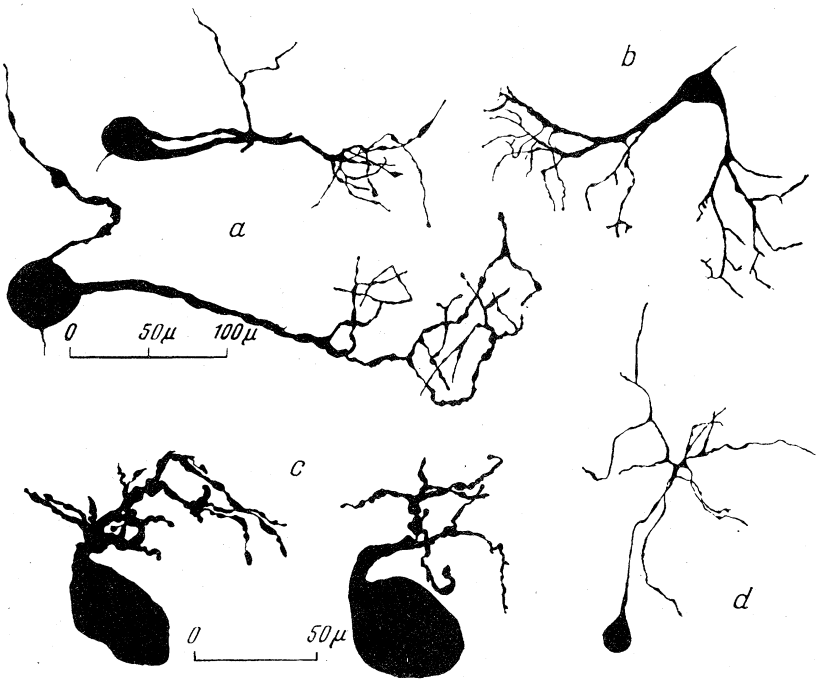


FIG. 43. Cochlear neurons of (a) monkey, (b) hedgehog, (c) owl and (d) bat from Bogoslovskaya *et al.* (1973).

mittances below threshold as given in (11.6). Then a fraction $d_2^{3/2}/(d_1^{3/2} + d_2^{3/2})$ of the incoming charge will reach the parent and this must exceed $\alpha k d_2^{3/2}$ in order to fire the parent. This condition is equivalent to

$$d_1/d_2 > [\alpha/(1-\alpha)]^{2/3} \tag{11.7}$$

as the requirement on the diameter ratios for "OR" logic at the branch point. If the inequality in (11.7) is not satisfied, input pulses on both daughters A "AND" B are necessary in order to fire the parent. Corresponding expressions are easily obtained when the daughter fibers are unequal, or for the threshold number of daughter fibers which must be excited on the "tufted" branching points which Ramón–Molinar (1962) describes as being typical for dendrites of sensory neurons. Pastushenko, Markin, and Chizmadzhev (1969a, b) have conducted a much more detailed analysis of this problem using (2.30) to describe the nerve, but with $j_i$ as in (11.3). Their basic boundary condition was Kirchhoff's current law and their threshold requirement was that the voltage rise should reach a preassigned level at $t = 0$ in (11.3). They derive relations corresponding to (11.7), and they account for nonsynchronous effects in "AND" junctions. Berkinblit *et al.* (1971) have studied the problem numerically using the Hodgkin–Huxley equations (5.1) to represent the three fibers. In addition to confirming previous results, they were able to demonstrate *inhibition* by a subthreshold pulse on one daughter of a properly delayed pulse on the other daughter. Some time ago, Tauc and Hughes (1963) demonstrated similar effects during experiments with axons of nerve cells in a mollusk.

The possibility of dendritic logic opens intriguing lines for speculation and future research. As an example, consider the dendrites of the cerebellar Purkinje cell shown in Fig. 2. These trees lie in a plane about $\frac{1}{4} \times \frac{1}{4}$ mm$^2$ and about 6 $\mu$ thick for man and receive some 80 000 synaptic inputs from perpendicular parallel fiber axons [Eccles (1973), Szentágothai (1968)]. The output axon provides inhibitory signals for muscle control; and, as has been suggested by Marr (1969) and Albus (1971), the cell may function as a "Perceptron" [Block (1962), Block, Knight and Rosenblatt (1962)] which merely calculates a weighted sum of the inputs and decides whether or not it is above a threshold for firing the cell body and/or the axon. But if each of the branching points can function as a logic gate, the computing power would be much greater than that of a Perceptron. Rall (1962) has suggested that careful dendritic studies may also be relevant to the problem of learning and memory. Rose *et al.* (1960), for example, have suggested that the regrowth of cortical dendrites observed after radiation damage may be due to a "normal, continuous growth of central neurons." Thus the logical character of an existing branch point might be modified by changes in its geometry or in the geometry of neighboring cells. It might be possible to observe such effects in tissue culture experiments similar to those conducted by Hild and Tasaki (1962).

Efforts to understand the nature of propagation on nonuniform fibers [Smolyaninov (1968), Khodorov *et al.* (1969), Pastushenko and Markin (1969), Khodorov *et al.* (1970), Khodorov and Timin (1970, 1971), Pastushenko and Markin (1973), Parnas *et al.* (1973), Goldstein and Rall (1974), Khodorov (1974)] should be viewed in relation to the question of axonal and dendritic logic. A widening of the fiber leads to a propagation delay [Markin and Pastushenko (1969), Berkinblit *et al.* (1970), Khodorov *et al.* (1971), Goldstein and Rall (1974)] which appears to be caused by charging of the extra membrane capacitance to a threshold level. Bogoslovskaya *et al.* (1973) suggest that varicose regions in the dendrites of cochlear neurons (see Fig. 43) may be related to information processing functions.

### D. Pulse burst dynamics

Whitham (1974) has developed a technique for finding solutions to nonlinear wave problems that are locally periodic, but for which the frequency, wave length and amplitude are *slowly varying* functions of space and time. Such periodic solutions are not sinudoidal (often they are elliptic functions) and the corresponding dispersion equation is of the form $\omega = \Omega(\beta, A)$, where

$$\omega = 2\pi/T \quad \text{and} \quad \beta = 2\pi/\lambda \tag{11.8a, b}$$

and $T$, $\lambda$, $A$ are, respectively, the wave time and space periods, and the amplitude. Two quasilinear equations for the slow evolution of $\omega$, $\beta$, and $A$ are obtained from variation of a Lagrangian density which has been averaged over a cycle of the periodic wave. Such a Lagrangian density can be obtained from an energy conservation law (1.4). A third quasilinear equation is *conservation of wave crests*

$$\partial\beta/\partial t + \partial\omega/\partial x = 0. \tag{11.9}$$

For nerve fiber problems, we do not have conservation of energy; propagation is governed instead by the power balance condition (1.3). Furthermore, as Fig. 33 indicates, the frequency, propagation constant and amplitude for a stable periodic wave are fixed by the local propagation velocity

$$u = \omega/\beta. \tag{11.10}$$

Thus $\omega = \omega(u)$, $\beta = \beta(u)$, and $A = A(u)$, so only (11.9) is needed to describe the slow evolution of $\omega$, $\beta$, and $A$. Conservation of wave crests becomes

$$\partial u/\partial t + U(u)\,(\partial u/\partial x) = 0, \tag{11.11}$$

where

$$U(u) \equiv d\omega/d\beta \tag{11.12}$$

is a *nonlinear group velocity*. For the periodic wave described in Fig. 33(a), a typical $\omega - \beta$ diagram is sketched in Fig. 44(a). Along the stable (high velocity) branch it is clear that

$$U(u) < u \tag{11.13}$$

as was noted by Rinzel and Keller (1973). Thus, as is indicated in Fig. 44(b), the compressed region of a pulse burst should drift to the rear. The question of "rear end collisions" [Crane (1964)] may be important for a nerve fiber just as it is in a corresponding study of automobile traffic dynamics [Whitham (1974)].

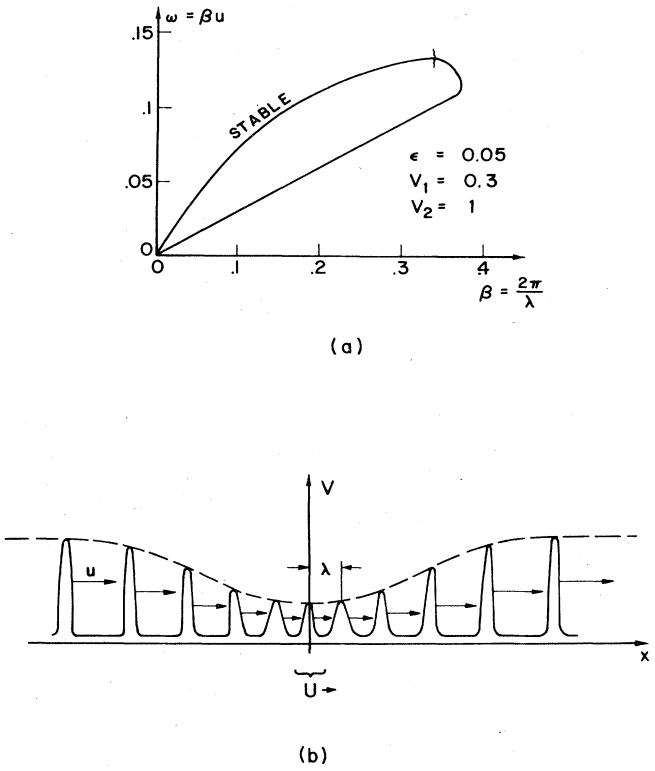


FIG. 44. (a) $\omega$–$\beta$ diagram for a curve from Fig. 33(a). (b) A slowly varying train of pulses.

## XII. CONCLUSION

It may be appropriate to end this review by presenting some reasons for which I believe a physicist should be interested in studying the nerve fiber. First, as we saw in Secs. III and IV, a fundamental connection has not yet been established between a dynamical description of the nerve membrane and the underlying biochemistry. The special knowledge of solid state physics may be helpful to biochemists who are attempting to solve this intriguing riddle. Second, nerve fiber studies present a number of well defined problems (e.g., pulse properties, pulse interactions, threshold effects, decremental conduction, stability, electromagnetic consideration of nonuniform fibers, etc.) which should be challenging for many physicists and applied mathematicians to consider. Finally there is the program, outlined by Caianiello (1961), which begins with an appropriate description of neural elements and proceeds toward an understanding of brains. In addition to providing a sound "atomic theory" for this program, study of the nerve fiber provides an excellent example of the "hierarchy of boundary conditions" which Polanyi (1962, 1965, 1968) finds characteristic of life. The organization of protein bearing lipid membranes into branching tubes with different internal and external salt solutions clearly introduces "higher principles" associated with special forms of the nonlinear diffusion equation. These principles must necessarily be understood in order to describe the dynamics of nerve pulses and they exist not in conflict with the principles of physics and chemistry but in addition to them. Problems of perceiving and understanding such higher principles become acute as one considers more complex dynamic systems, but the danger for those who miss the point has been emphasized by Goethe[9]

Wer will was Lebendig's erkennen und beschreiben,
Sucht erst den Geist heraus zu treiben,
Dan hat er die Teile in seiner Hand,
Fehlt leider nur das geistige Band.

[9] Quoted by Franz Boas in his introduction to Ruth Benedict's *Patterns of Culture*.

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## REFERENCES

Abbott, B. C., A. V. Hill and J. V. Howarth, 1958, "The positive and negative heat production associated with a nerve impulse," Proc. Roy. Soc. (London) B **148,** 149.

Adam, N. K., 1921, 1922, "The properties and molecular structure of thin films," Proc. Roy. Soc. (London) Ser. A. **99,** 336; **101,** 452; and 516.

Agin, D., 1969, "An approach to the physical basis of negative conductance in the squid axon," Biophys. J., **9,** 209.

Albus, J. S., 1971, "A theory of cerebellar function," Math. Biosci **10,** 25.

Anderson, P., B. Holmquist and P. E. Voorhoeve, 1966, "Entorhinal activation of dentate granule cells," Acta. Physiol. Scand. **66,** 448.

Andronov, A. A., A. A. Vitt and S. E. Khaikin, 1966, *Theory of Oscillators*, (Addison Wesley, Reading, Mass.)

Arima, R., and Y. Hasegawa, 1963, "On global solutions for mixed problem of a semi-linear differential equation," Proc. Japan Acad., **39,** 721.

Aronov, I. Z. and L. M. Kheifets, 1971, "Spread of an impulse in a model of the nerve fibre," Biophysics, **16,** 766.

Aronson, D. G., and H. F. Weinberger, 1975, "Nonlinear diffusion in population genetics, combustion, and nerve propagation," Proc. Tulane Program in PDE.

Arshavskii, Yu. I., M. B. Berkinblit, S. A. Kovalev, V. V. Smolyaninov, and L. M. Chailakhyan, 1965, "The role of dendrites in the functioning of nerve cells," Doklady Akademii Nauk SSSR **163,** 994.

Averbach, M. S., and D. N. Nasonov, 1950, "The law of self regulation of spreading stimulation ("all or nothing")" Fiziologicheskii Zhurnal SSSR **36,** 46 (in Russian).

Balakhovskii, I. S., 1968, "Constant rate of spread of excitation in an ideal excitable tissue," Biophysics **13,** 864.

Bean, C. P., 1974, "A theory of micro-stimulation of myelinated fibers," (to be published).

BeMent, S. L., and J. B. Ranck, Jr., 1969, "A model for electrical stimulation of central myelinated fibers with monopolar electrodes," Exp. Neurol. **24,** 171.

Berestovskiy, G. N., 1963, "Study of single electric model of neuristor," Rad. Eng. & Elec. Phys. **18,** 1744.

Berestovskii, Liberman, Lunevskii, and Frank, 1970, "Optical investigations of change in the structure of the neural membrane on passage of a nerve impulse," Biophysics **15,** 60.

Berkinblit, M. B., I. Dudzyavichus and L. M. Chailakhyan, 1971, "Dependence of the rate of spread of an impulse in a nerve fiber on the capacitance of its membrane," Biophysics **16,** 594.

Berkinblit, M. B., N. D. Vvedenskaya, L. S. Gnedenko, S. A. Kovalev, A. V. Kholopov, S. V. Fornin and L. M. Chailakhyan, 1970, "Computer investigation of the features of conduction of a nerve impulse along fibres with different degrees of widening," Biophysics, **15,** 1121.

Berkinblit, M. B., N. D. Vvedenskaya, L. S. Gnedenko, S. A. Kovalev, A. V. Kholopov,S. V. Formin, and L. M. Chailakhyan, 1971, "Interaction of the nerve impulses in a node of branching (investigation on the Hodgkin-Huxley model)" Biophysics, **16,** 105.

Bernstein, J., 1868, "Ueber den zeitlichen Verlauf der negativen Schwankung des Nervenstroms," Arch. ges. Physiol., **1,** 173.

Bernstein, J., 1902, "Untersuchungen zur Thermodynamik der bioelektrischen Ströme," Arch. ges. Physiol. **92,** 521.

Bishop, G. H., 1958, "The dendrite: receptive pole of the neurone," Electroenceph. Clin. Neurophysiol. Suppl. **10,** 12.

Block, H. D., 1962, "The Perceptron: A model for brain functioning," Rev. Mod. Phys. **34,** 123.

Block, H. D., B. W. Knight, Jr., and F. Rosenblatt, 1962, "Analysis of a four-layer series-coupled Perceptron," Rev. Mod. Phys. **34,** 135.

Bogdanov, K. Yu., and V. B. Golovchinskii, 1970, "Extracellularly recorded action potential and the possibility of spread of excitation over the dendrites," Biophysics **15,** 672.

Bogoslovskaya, L. S., I. A. Lyubinskii, N. V. Pozin, Ye. V. Putsillo, L. A. Shmelev and T. M. Shura-Bura, 1973, "Spread of excitation along a fiber with local inhomogeneities (results of modelling)" Biophysics **18,** 944.

Bonhoeffer, K. F., 1948, "Activation of passive iron as a model for the excitation of nerve," J. Gen. Physiol., **32,** 69.

Boltaks, B. I., V. Ya. Vodyanoi, and N. A. Fedorovich, 1971, "Mechanisms of conductivity of phospholipid membranes," Biophysics **16,** 856.

Boussinesq, M. J., 1872, "Théorie des oudes et des remous qui se propagent le long d'un canal rectangulaire horizontal, en communiquant au liquide contenu dans ce canal des vitesses sensiblement pareilles de la surface au fond," J. Math. Pures Appl. **17,** 55.

Brady, S. W., 1970, "Boundedness theorems and other mathematical studies of differential equations," Math. Biosci. **6,** 209.

Branton, D., and R. B. Park, 1968, *Papers on Biological Membrane Structure*, (Little Brown Co., Boston).

Brazier, M. A. B. 1959 , "The historical development of neurophysiology," in *Handbook of Physiology*, Am. Physiol. Soc., Sec. 1, Vol. I, p. 1.

Bretscher, M. S., 1973, "Membrane structure: some general principles," Science **176,** 622.

Brooke Benjamin, T., 1972, "The stability of solitary waves," Proc. R. Soc. Lond. A. **328,** 153.

Bungenberg de Jong, H. G. and J. Bonner, 1935, "Phosphatide autocomplex coacervates as ionic systems and their relation to the protoplasmic membrane," Protoplasma **15,** 198.

Buratti, R. J., and A. G. Lindgren, 1968, "Neuristor wave forms and stability by the linear approximation," Proc. IEEE **56,** 1392.

Caianiello, E. R., 1961, "Outline of a theory of thought-processes and thinking machines," J. Theor. Biol. **2,** 204.

Canosa, J., 1973, "On a nonlinear diffusion equation describing population growth," IBM J. Res. Dev. **17,** 307.

Carpenter, G., 1974, "Traveling wave solutions of nerve impulse equations," Ph.D. Thesis, U. of Wisconsin.

Casten, R. G., H. Cohen and P. A. Lagerstrom, 1975 "Perturbation analysis of an approximation to the Hodgkin-Huxley theory," Quart. Appl. Math **32,** 365.

Cereijido, M., and C. A. Rotunno, 1970, *Introduction to the Study of Biological Membranes*, (Gordon and Breach, New York).

Chandler, W. K., R. Fitzhugh and K. S. Cole, 1962, "Theoretical stability properties of a space clamped axon," Biophys. J. **2,** 105.

Changeux, J. P., Thiéry, J., Tung, Y, and Kittel, C., 1967, "On the cooperativity of biological membrances," Proc. Natl. Acad. Sci. **57,** 335.

Chizmadzhev, Yu. A., Markin, V. S., and Muler, A. L., 1973, "Conformational model of excitable cell membrances—II. Basic equations," Biophysics **18,** 70.

Chizmadzhev, Yu. A., Muler, A. L., and Markin, D. S., 1972, "Conformational model of excitable cell membranes—I. Ionic permeability," Biophysics **17,** 1061.

Chung, S. H., S. A. Raymond and J. Y. Lettvin, 1970, "Multiple meaning in single visual units," Brain Behav. Evol. **3,** 72.

Clark, J., and R. Plonsey, 1966, "A mathematical evaluation of the core conductor model," Biophs. J. **6,** 95.

Clark, J., and R. Plonsey, 1968, "The extracellular potential field of the single active nerve fiber in a volume conductor," Biophs. J. **8,** 842.

Cohen, H., 1971, "Nonlinear diffusion problems," in *Studies in Applied Mathematics* (A. H. Taub, ed.) Math. Assoc. Am., Prentice-Hall, 27.

Cohen, L. B., R. D. Keynes, and B. Hille, 1968, "Light scattering and birefringence changes during nerve activity," Nature, 218, 438.

Cohen, L. B., B. Hille, and R. D. Keynes, 1970, "Changes in axon birefringence during the action potential," J. Physiol. **211,** 495.

Cohen, L. B. and D. Landowne, 1974, "The temperature dependence of the movement of sodium ions associated with nerve impulses," J. Physiol. **236,** 95.

Cole, K. S., 1949, "Dynamic electrical characteristics of the squid axon membrane," Arch. Sci. Physiol. **3,** 253.

Cole, K. S., 1968, *Membranes, ions and impulses*, (University of California Press, Berkeley and L. A.).

Cole, K. S., 1975, "Neuromembranes: paths of ions," *Neurosciences: Paths of Discovery*, edited by G. Adelman (Rockefeller U. P., New York).

Cole, K. S., H. A. Antosiewicz and P. Rabinowitz, 1955, "Automatic computation of nerve excitation," SIAM Jour. **3,** 153.

Cole, K. S., and R. F. Baker, 1941, "Longitudinal impedance of the squid giant axon," J. Gen. Physiol. **24,** 771.

Cole, K. S. and H. J. Curtis, 1938, "Electrical impedance of nerve during activity," Nature **142,** 209.
Cole, K. S. and Curtis, H. J., 1939, "Electric impedance of the squid giant axon during activity," J. Gen. Physiol. **22,** 649.
Cole, K. S., and Moore, J. W., 1960, "Potassium ion current in the squid giant axon: Dynamic characteristic," Biophys. J. **1,** 1.
Conley, C., 1973, "On the existence of bounded progressive wave solutions of the Nagumo equation," (unpublished notes).
Cooley, J., F. Dodge, and H. Cohen, 1965, "Digital computer solutions for excitable membrane models," J. Cell. Comp. Physiol. **66** (Supp.), 99.
Cooley, J. W. and F. A. Dodge, Jr., 1966, "Digital computer solutions for excitable and propagation at the nerve impulse," Biophys. J. **6,** 583.
Cragg, B. G., and L. H. Hamlyn, 1955, "Action potential of the pyramidal neurons in the hippocampus of the rabbit," J. Physiol. London, 129, 608.
Crane, H. D., 1962, "Neuristor—a novel device and system concept," Proc. IRE, **50,** 2048.
Crane, H. D., 1964, "Possibilities for signal processing in axon system," in *Neural Theory and Modeling*, edited by R. F. Reiss, (Stanford U. P., Stanford).
Danielli, J. F., 1936, "Some properties of lipoid films in relation to the structure of the plasma membrane," J. Cellular Comp. Physiol. **7,** 393.
Danielli, J. F. and H. Davson, 1935, "A contribution to the theory of permeability of thin films," J. Cellular Comp. Physiol. **5,** 495.
Dean, R. B., 1939, "Potentials at oil water interfaces," Nature **144,** 32.
Dean, R. B., H. J. Curtis and K. S. Cole, 1940, "Impedance of bimolecular films," Science **91,** 50.
Deck, K. A., and W. Trautwein, 1964, "Ionic currents in cardiac excitation," Arch. ges. Physiol. **280,** 63.
Devaux, H., 1936, "Determination de l'épaisseur de la membrane d'albumine formée entre l'eau et la benzine et propriétés de cette membrane," C. R. Acad. Sci., **202,** 1957.
Eccles, J. C., 1960, "The properties of the dendrites," in *Structure and Function of the Cerebral Cortex*, (American Elsevier, New York).
Eccles, J. C., 1973, *The Understanding of the Brain*, (McGraw-Hill, New York).
Eckhaus, W., 1965, *Studies in Non-Linear Stability Theory*, (Springer-Verlag, New York).
Einstein, A., 1905, "Über die von der molekular-kinetischen Theorie der Wärme geforderte Bewegung von in ruhenden Flüssigkeiten suspendierten Teilchen," Ann. der Physik **17,** 549.
Eisenberg, M., Hall, J. E., and C. A. Mead, 1973, "The nature of the voltage-dependent conductance induced by alamethicin in black lipid membranes," J. Membrane Biol. **11,** 1–34.
Eleonskii, V. M., 1968, "Stability of simple stationary waves related to the nonlinear diffusion equation," Sov. Phys. JETP **26,** 382.
Elias, N. J., and M. S. Ghausi, 1972, "An analysis of excitation thresholds in nonlinear distributed neuristor circuits," J. Franklin Inst. **293,** 421.
von Euler, C., J. D. Green, and G. Ricci, 1956, "The role of hippocampal dendrites in evoked responses and after discharges," Acta. Physiol. Scand. **42,** 87.
Evans, J., and N. Shenk, 1970, "Solutions to axon equations," Biophys. J. **10,** 1090.
Evans, J. W., 1972, "Nerve axon equations: I. Linear approximations, II. Stability at rest, III. Stability of the nerve impulse, Ind. U. Math. J., **21,** 877; **22,** 75 and 577.
Evans, J. W., 1974, "Nerve axon equations: IV. The stable and the unstable impulse," Ind. U. Math. J. (to be published).
Eyzaguirre, C., and S. W. Kuffler, 1955, "Further study of some, dendrite and axon excitation in single neurons," J. Gen. Physiol. **39,** 121.
Falk, G. and P. Fatt, 1964, "Linear electrical properties of striated muscle fibres observed with intracellular electrodes," Proc. Roy. Soc. (London) Ser. B., **160,** 69.
Fatt, P., 1957, "Electrical potentials occurring around a neurone during its antidromic activation," J. Neurophysiol. **20,** 27.
Fisher, R. A., 1937, "The wave of advance of advantageous genes," Ann. Eugenics (now Ann. Human Genetics) **7,** 355.
Fishman, S. N., B. I. Khodorov and M. V. Volkenshtein, 1972, "Molecular mechanisms of change in the ionic permeability of an electro-excitable membrane—II. Model of the process of activation," Biophysics **17,** 637.
FitzHugh, R., 1955, "Mathematical models of threshold phenomena in the nerve membrane," Bull. Math. Biophys. **17,** 257.
FitzHugh, R., 1961, "Impulses and physiological states in theoretical models of nerve membrane," Biophys. J., **1,** 445.
FitzHugh, R., 1962, "Computation of impulse initiation and saltatory conduction in a myelinated nerve fiber," Biophys. J., **2,** 11.
FitzHugh, R., 1965, "A kinetic model of the conductance changes in nerve membrane," J. Cell. and Comp. Physiol. **66,** 111.
FitzHugh, R., 1969, "Mathematical models of excitation and propagation in nerve," in *Biological Engineering*, edited by H. P. Schwan (McGraw Hill, New York), 1–85.
FitzHugh, R., 1973, "Dimensional analysis of nerve models," J. Theor. Biol. **40,** 517.
FitzHugh, R. and H. A. Antosiewicz, 1959, "Automatic computation of nerve excitation—detailed corrections and additions," SIAM Jour. **7,** 447.
FitzHugh, R. and K. S. Cole, 1973, "Voltage and current clamp transients with membrane dielectric loss," Biophys. J. **13,** 1125.
Frankenhaeuser and A. F. Huxley, 1964, "The action potential in the myelinated nerve fibre of *Xenopus Laevis* as computed on the basis of voltage clamp data," J. Physiol. **171,** 302.
Fricke, H., 1923, "The electric capacity of cell suspensions," Phys. Rev. **21,** 708.
Fricke, H., 1925a, 1926, "A mathematical treatment of the electric conductivity and capacity of disperse systems," Phys. Rev. **24,** 575; **26,** 678.
Fricke, H., 1925b, "The electric capacity of suspensions with special reference to blood," J. Gen. Physiol. **9,** 137.
Frölich, H., 1970, "Long range coherence and the action of enzymes," Nature **228,** 1093.
Gasser, H. S. and J. Erlanger, 1922, "A study of the action currents of nerve with a cathode ray oscillograph," Am. J. Physiol. **62,** 496.
Geduldig, D. and R. Gruener, 1970, "Voltage clamp of the *Aplysia* giant neurone: early sodium and calcium currents," J. Physiol. **211,** 217.
Geselowitz, D. B., 1966, "Comment on the core conductor model," Biophys. **6,** 691.
Geselowitz, D. B., 1967, "On bioelectric potentials in an inhomogeneous volume conductor," Biophys. J. **7,** 1.
Goldman, D. E., 1943, "Potential, impedance and rectification in membranes," J. Gen. Physiol. **27,** 37.
Goldman, D. E., 1964, "A molecular structural basis for the excitation properties of axons," Biophys. J. **4,** 167.
Goldman, L. and J. S. Albus, 1968, "Computation of impulse conduction in myelinated fibers; theoretical basis of the velocity diameter relation," Biophys. J., **8,** 596.
Goldstein, S. S. and W. Rall, 1974, "Changes of action potential shape and velocity for changing core conductor geometry," Biophys. J. **14,** 731.
Goldup, A., S. Ohki and J. F. Danielli, 1970, "Black lipid films," in *Recent Progress in Surface Science*, edited by J. F. Danielli, A. C. Riddiford and M. D. Rosenberg, New York, p. 193.
Gorter, E. and F. Grendel, 1925, "On biomolecular layers of lipoids on the chromocytes of the blood," J. Exptl. Med. **41,** 439.
Green, D. E., 1971, "Membrane structure," Science **174,** 863.
Green, D. E., S. Ji and R. F. Brucker, 1972, "Structure-function unitization model of biological membranes," Bioenergetics **4,** 527.
Greenberg, J. M., 1973, "A note on the Nagumo equation," Quart. J. Math. **24,** 307.
Grossman, Y., M. E. Spira and I. Parnas, 1973, "Differential flow of information into branches of a single axon," Brain Research **64,** 379.
Grundfest, H., 1958, "Electrophysiology and pharmacology of dendrites," Electroenceph. Clin. Neurophysiol. Suppl., **10,** 22.
Gutman, A. M., 1971, "Further remarks on the effectiveness of the dendrite synapses," Biophysics **16,** 131.
Gutman, A., and A. Shimoliunas, 1973, "Finite dendrite with an *N*-shaped current-voltage characteristic for the membrane," Biophysics **18,** 1013.
Hall, J. E., C. A. Mead, and G. Szabo, 1973, "A barrier model for current flow in lipid bilayer membranes," J. Membrane Biol. 11, 75.
Harmon, L. D. and E. R. Lewis, 1966, "Neural modeling," Physiol. Rev. **46,** p. 513.
Hastings, S. P., 1972, "On a third order differential equation from biology," Quart. J. Math. **23,** 435.
Hastings, S. P., 1974a, "The existence of periodic solutions to Nagumo's equation," Quart J. Math. (to be published).
Hastings, S. P., 1974b, "On travelling wave solutions of the Hodgkin-Huxley equations," Arch. Rat. Mech. Anal. (to be published).

Hastings, S. P., 1975a, "Some mathematical problems from neurobiology," Am. Math. Month. (to be published).
Hastings, S. P., 1975b, "The existence of homoclinic orbits for Nagumo's equations" (to be published).
Hatase, O., T. Wakabayashi, H. Hayashi and D. E. Green, 1972, "Collapse and extension of the headpiece-stalk projections in mitochondrial electron transport partiles," Bioenergetics, **3,** 509.
Hearon, J. Z., 1964, "Application of results from linear kinetics to the Hodgkin-Huxley equations," Biophys. J., **4,** 69.
Hellerstein, D., 1968, "A generalization of the theory of electrotonus," Biophys. J. **8,** 358.
Helmholtz, H., 1850, "Messungen über den zeitlichen Verlauf der Zuchung animalischer Muskeln und die Fortpflanzungsgeschwindigkeit der Reizung in den Nerven," Arch. Anta. Physiol. 276.
Hermann, L., 1879, *Handbuch der Physiologie* I. Bewegungsapparate, II. Nervensystems. (Leipzig).
Hermann, L., 1905, "Beiträge zur Physiologie und Physik des Nerven," Arch. ges. Physiol. **109,** 95.
Hild, W., and I. Tasaki, 1962, "Morphological and physiological properties of neurons and glial cells in tissue culture," J. Neurophysiol. **25,** 277.
Hill, A. V., 1936, "Excitation and accommodation in nerve," Proc. Roy. Soc. (London), B **119,** 305.
Hille, B., 1970, "Ionic channels in nerve membranes," Prog. Biophys. Mol. Biol. **21,** 3.
Hodgkin, A. L., 1951, "The ionic basis of electrical activity in nerve and muscle," Biol. Rev. **26,** 339.
Hodgkin, A. L., 1964, *The Conduction of the Nervous Impulse*, (Liverpool U. Press. Liverpool).
Hodgkin, A. L. and A. F. Huxley, 1952a, "Currents carried by sodium and potassium ions through the membrane of the giant axon of *Loligo*," J. Physiol., 116, 449.
Hodgkin, A. L. and A. F. Huxley, 1952b, "The components of membrane conductance in the giant axon of *Loligo*," J. Physiol., **116,** 473.
Hodgkin, A. L. and A. F. Huxley, 1952c, "The dual effect of membrane potential on sodium conductance in the giant axon of *Loligo*," J. Physiol. **116,** 497.
Hodgkin, A. L. and A. F. Huxley, 1952d, "A quantitative description of membrane current and its application to conduction and excitation in nerve," J. Physiol., **117,** 500.
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., **116,** 424.
Hodgkin, A. L., and B. Katz, 1949, "The effect of sodium ions on the electrical activity of the giant axon of the squid," J. Physiol. **108,** 37.
Hoorweg, J. L., 1898, "Ueber die elektrischen Eigenschaften der Nerven," Arch. ges. Physiol. **71,** 128.
Howard, R. E. and R. M. Burton, 1968, "Thin lipid membranes with aqueous interfaces: apparatus design and methods of study," J. Am. Oil Chem. Soc. **45,** 202.
Hoyt, R. C., 1963, "The squid giant axon; mathematical models," Biophys. J. **3,** 399.
Hoyt, R. C. 1968, "Sodium inactivation in nerve fibers," Biophys. J. **8,** 1074.
Hoyt, R. C., and W. J. Adelman, Jr., 1970, "Sodium inactivation; experimental test of two models," Biophys. J. **10,** 610.
Hoyt, R. C. and J. D. Strieb, 1971, "A stored charge model for the sodium channel," Biophys. J. **11,** 868.
Hurewicz, W., 1958, *Lectures on Ordinary Differential Equations*, (Wiley, New York).
Huxley, A. F., 1959a, "Ion movements during nerve activity," Ann. N.Y. Acad. Sci., **81,** 221.
Huxley, A. F., 1959b, "Can a nerve propagate a subthreshold disturbance?" J. Physiol. **148,** 80P.
Il'inova, T. M. and R. V. Khokhlov, 1963, "Wave processes in lines with nonlinear shunt resistance," Rad. Eng. Elec. Phys., **8,** 1864.
Inoue, I., Y. Kobatake and I. Tasaki, 1973, "Excitability, instability and phase transitions in squid axon membrane under internal perfusion with dilute salt solutions," Biochemica et Biophysica Acta **307,** 471.
Inoue, I., I. Tasaki and Y. Kobatake, 1974, "A study of the effects of externally applied sodium-ions and detection of spatial nonuniformity of the squid axon membrane under internal perfusion," Biophysical Chemistry **2,** 116.
Isaacs, C. D., 1970, "Analog-digital-hybrid studies of the reformulated equations of Hodgkin-Huxley," Math. Biosci. **7,** 305.
Jain, M. K., 1972, *The Bimolecular Lipid Membrane*, (Van Nostrand Reinhold, New York).
Jain, M. K., R. H. L. Marks and E. H. Cordes, 1970, "Kinetic model of conductance changes across excitable membrances," Proc. Nat. Acad. Sci. **67,** 799.
Jakobsson, E., 1973, "The physical interpretation of mathematical models for sodium permeability changes in excitable membranes," Biophys. J. **13,** 1200.
Jakobsson, E. and C. Scudiero, 1975, "A transient excited state model for sodium permeability changes in excitable membranes," (to be published).
Johnson, W. J., 1968, "Nonlinear wave propagation on superconducting tunneling junctions," Ph.D. Thesis, U. of Wisconsin.
Kanel' Ya. I., 1962, "On the stability of the Cauchy problem for equations occurring in the theory of flames," Matematicheskii Sbornik **59 (101),** 246.
Kaplan, S. and D. Trujillo, 1970, "Numerical studies of the partial differential equations governing nerve impulse conduction: The effect of Lieberstein's inductance term," Math. Biosci. **7,** 379.
Kashef, B. and R. Bellman, 1974, "Solution of the partial differential equation of the Hodgkin-Huxley model using differential quadrature," Math. Biosci. **19,** 1–8.
Kato, G., 1924, *The Theory of Decrementless Conduction in Narcotized Region of Nerve*, (Nankōdō, Tokyo, Japan).
Kato, G., 1934, *Microphysiology of Nerve*, (Maruzen, Tokyo, Japan).
Kato, G., 1970, "The road a scientist followed," Ann. Rev. Physiol. **32,** 1.
Katz, B., 1939, *Electric Excitation of Nerve*, (Oxford Univ. Press, London).
Katz, B., 1966, *Nerve, Muscle and Synapse*, (McGraw-Hill, New York).
Katz, B. and O. H. Schmitt, 1939, "Excitability changes in a nerve fibre during the passage of an impulse in an adjacent fiber," **96,** 9p.
Katz, B., and O. H. Schmitt, 1940, "Electric interaction between two adjacent nerve fibers," J. Physiol. **97,** 471.
Katz, B. and O. H. Schmitt, 1942, "A note on the interaction between nerve fibers," J. Physiol., **100,** 369.
Kelvin, Lord (William Thompson), 1855, "On the theory of the electric telegraph," Proc. Roy. Soc. (London) **7,** 382.
Khodorov, B. I., 1974, *The Probability of Excitability*, (Plenum Press, New York).
Khodorov, B. I., Ye. N. Timin, S. Ya. Vilenkin, and F. B. Gul'ko, 1969, "Theoretical analysis of the mechanisms of conduction of a nerve pulse over an inhomogeneous axon. I. Conduction through a portion with increased diameter," Biophysics, **14,** 323.
Khodorov, B. I., Ye. N. Timin, S. Ya. Vilenkin and F. B. Gul'ko, 1970, "II. Conduction of a single impulse across a region of the fiber with modified functional properties," Biophysics **15,** 145.
Khodorov, B. I. and Ye. N. Timin, 1970, "III. Transformation of rhythms in the cooled part of the fibre," Biophysics, **15,** 526.
Khodorov, B. I., Ye. N. Timin, N. V. Pozin, and L. A. Shmelev, 1971, "IV. Conduction of a series of impulses through a portion of the fibre with increased diameter," Biophysics, **16,** 96.
Khodorov, B. I. and Ye. N. Timin, 1971, "V. Phenomena of Vvedenskii in portions of the fiber with reduced sodium and potassium conductivity of the membrane," Biophysics, **16,** 513.
Kilkson, 1969, R., "Symmetry and function of biological systems at the macromolecular level," in *Nobel Symposium* **11,** edited by A. Engström and B. Strandberg (Wiley-Interscience, New York), 257.
Kishimoto, U., 1965, "Voltage clamp and internal perfusion studies on *Nitella* internodes," J. Cell. Comp. Physiol. **66** *Supp.* 2, 43.
Knight, B. W. and G. A. Peterson, 1967, "Theory of the Gunn effect," Phys. Rev. **155,** 393.
Kokoz, Yu. M. and V. I. Krinskii, 1973, "Analysis of equations of excitable membranes—II. Methods of analysing the electrophysiological characteristics of the Hodgkin-Huxley membrane," Biophys. **18,** 937.
Kolmogoroff, A., I. Petrovsky, and N. Piscounoff, 1937, "Étude de l'équation de la diffusion avec croissance de la quantité de matière et son application á un problème biologique," Bull. Univ. Moscou, Série Int., A **1,** 1.
Kompaneyets, A. S., 1971, "Influence of ohmic resistance of the nerve fiber membrane on certain effects of nervous excitation," Biophysics **16,** 926.
Kompaneyets, A. S. and V. Ts. Gurovich, 1965, "Propagation of an impulse in a nerve fiber," Biophysics **11,** 1049.
Korteweg, D. J. and G. de Vries, 1895, "On the change of form of long waves advancing in a rectangular canal, and on a new type of long stationary wave," Phil. Mag. **39,** 422.
Krinskii, V. I., and Yu. M. Kokoz, 1973, "Analysis of equations of

excitable membranes—I. Reduction of the Hodgkin-Huxley equations to a second order system," Biophysics, **18,** 533.
Kryshtal', O. A., I. S. Magura and N. T. Parkhomenko, 1969, "Ionic currents across the membrane of the soma of giant neurones of the edible snail with clamped shifts of the membrane potential," Biophysics, **14,** 987.
Kunov, H., 1965, "Controllable piecewise-linear lumped neuristor realization," Electronics Lett. **1,** 134.
Kunov, H., 1966, "Nonlinear transmission lines simulating nerve axon," Thesis, Electronics Laboratory, Technical University of Denmark.
Kunov, H., 1967, "On recovery in a certain class of neuristors," Proc. IEEE, **55,** 428.
Landowne, D., 1972, "A new explanation of the ionic currents which flow during the nerve impulse," J. Physiol. **222,** 46P.
Landowne, D., 1973, "Movement of sodium ions associated with the nerve impulse," Nature **242,** 457.
Langmuir, I., 1917, "The constitution and fundamental properties of solids and liquids," **39,** 1848.
Langmuir, I., and D. F. Waugh, 1938, "The adsorption of proteins at oil-water interfaces and artificial protein-lipoid membranes," J. Gen. Physiol. **21,** 745.
Lawrence, A. S. C., 1929, *Soap Films,* (Bell, London).
Lefschetz, S., 1962, *Differential Equations: Geometric Theory,* (Wiley-Interscience, New York).
Leibovic, K. N., 1972, *Nervous System Theory,* (Academic Press, New York).
Leibovic, K. N., and N. H. Sabah, 1969, "On synaptic transmission, neural signals and psychophysiological phenomena," in *Information Processing in the Nervous System,* edited by K. N. Leibovic, (Springer-Verlag, New York).
Lehninger, A. L., 1968, "The neuronal membrance," Proc. Nat. Acad. Sci. **60,** 1069.
Lehninger, A. L., 1970, *Biochemistry,* (Worth Pub. Co., New York).
Levin, S. V., D. L. Rozenfal' and Ya. Yu. Komissarchik, 1968, "Structural changes in the axon membrane on excitation," Biophysics **13,** 214.
Lieberstein, H. M. 1967a, "On the Hodgkin-Huxley partial differential equation," Math. Biosci. **1,** 45.
Lieberstein, H. M., 1967b, "Numerical studies of the steady-state equations for a Hodgkins-Huxley model," Math. Biosci. **1,** 181.
Lieberstein, H. M., 1973, *Mathematical Physiology: Blood Flow and Electrically Active Cells,* (Am. Elsevier, New York).
Lieberstein, H. M. and M. A. Mahrous, 1970, "A source of large inductance and concentrated moving magnetic fields on axons," Math. Biosci. **7,** 41.
Lillie, R. S., 1925, "Factors affecting transmission and recovery in the passive iron nerve model," J. Gen. Physiol. **7,** 473.
Lillie, R. S., 1936, "The passive iron wire model of protoplasmic and nervous transmission and its physiological analogues," Biol. Rev. **11,** 181.
Lindgren, A. G. and R. J. Buratti, 1969, "Stability of wave forms on active nonlinear transmission lines," Trans IEEE on Circuit Theory, CT-**16,** 274.
Llinás, R., C. Nicholson, J. A. Freeman, and D. E. Hillman, 1968, "Dendritic spikes and their inhibition in alligator Purkinje cells," Science **160,** 1132.
Llinás, R., C. Nicholson and W. Precht, 1969, "Preferred centrepital conduction of dendritic spikes in alligator Purkinje cells," Science **163,** 184.
Llinás, R., and C. Nicholson, 1971, "Electrophysiological properties of dendrites and somata in alligator Purkinje cells," J. Neurophysiol. **34,** 532.
Lorente de Nó, 1947a, "A study of nerve physiology," Studies from the Rockefeller Institute, **132,** 384.
Lorente de Nó, R., 1947b, "Action potential of the motoneurons of the hypoglossus nucleus," J. Cell. Comp. Physiol. **29,** 207.
Lorente de Nó, R., 1960, "Decremental conduction and summation of stimuli delivered to neurons at distant synapses," in *Structure and Function of the Cerebral Cortex,* (American Elsevier, New York).
Lorente de Nó, R., and G. A. Condouris, 1959, "Decremental conduction in peripheral nerve. Integration of stimuli in the neuron," Proc. N.A.S. **45,** 592.
Lucas, K., 1909, "The 'all-or-none' confraction of amphibian skeletal muscle," J. Physiol. **38,** 113.
Luk'yanov, A. S., 1970, "Generation of action potentials by dendrites in the frog optic tectum," Fiziologicheskii Zhurnal SSSR **56,** 1130–1135; translated in Neurosciences Translations, **16,** 74 (1970–71).
Maginu, K., 1971, "On asymptotic stability of wave forms on a bistable transmission line," Professional Group on Nonlinear Problems NLP **70-24** (in Japanese).
Markin, V. S. and Yu. A. Chizmadzhev, 1967, "On the propagation of an excitation for one model of a nerve fiber," Biophysics **12,** 1032.
Markin, V. S., P. A. Grigor'ev, and L. N. Yermishkin, 1971, "Forward passage of ions across lipid membranes. I. Mathematical model," Biophysics **16,** 1050.
Markin, V. S. and V. F. Pastushenko, 1969, "Spread of excitation in a model of an inhomogeneous nerve fibre. I. Slight change in dimensions of fibre," Biophysics **14,** 335.
Markin, V. S., 1970a, "Electrical interaction of parallel nonmyelinated nerve fibres. I. Change in excitability of the adjacent fibre," Biophysics, **15,** 122.
Markin, V. S., 1970b, "II. Collective conduction of impulses," Biophysics, **15,** 713.
Markin, V. S., 1973a, "III. Interaction in bundles," Biophysics, **18,** 324.
Markin, V. S., 1973b, "IV. Role of anatomical inhomogeneities of nerve trunks," Biophysics **18,** 539.
Marmont, G., 1949, "Studies on the axon membrane. I. A new method," J. Cellular Comp. Physiol. **34,** 351.
Marr, D., 1969, "A theory of cerebellar cortex," J. Physiol. **202,** 437.
Mauro, A., 1961, "Anomalous impedance, a phenomenological property of time-variant resistance," Biophys. J., **1,** 353.
Mauro, A., F. Conti, F. Dodge, and R. Schor, 1970, "Subthreshold behavior and phenomenological impedance of the squid giant axon," J. Gen. Physiol., **55,** 497.
Mauro, A., A. R. Freeman, J. W. Cooley and A. Cass, 1972, "Propagated subthreshold oscillatory response and classical electrotonic response of squid giant axon," Biophysik, **8,** 118.
McKean, H. P., Jr., 1970, "Nagumo's equation," Adv. Math., **4,** 209.
Minor, A. V. and V. V. Maksimov, 1969, "Passive electrical properties of the model of a flat cell," Biophysics, **14,** 349.
Moore, J. W., 1968, "Specifications for nerve membrane models," Proc. IEEE **56,** 895.
Moore, L. E. and E. Jakobsson, 1971, "Interpretation of the sodium permeability changes of myelineated nerve in terms of linear relaxation theory," J. Theoret. Biol., 33, 77.
Morse, P. M. and H. Feshbach, 1953, *Methods of Theoretical Physics,* (McGraw-Hill, New York).
Mueller, P. and D. O. Rudin, 1968a, "Resting and action potentials in experimental bimolecular lipid membranes," J. Theoret. Biol. **18,** 222.
Mueller, P. and D. O. Rudin, 1968b, "Action potentials induced in bimolecular lipid membranes," Nature, **217,** 713.
Mueller, P., D. O. Rudin, H. T. Tien and W. C. Wescott, 1962, "Reconstitution of cell membrane structure *in vitro* and its transformation into an excitable system," Nature, **194,** 979.
Mullins, L. J., 1959, "An analysis of conductance changes in squid axon," J. Gen. Physiol. **42,** 1013.
Mysels, K. J., K. Shinoda and S. Frankel, 1959, *Soap Films, Studies of Their Thinning and a Bibliography,* (Pergamon Press, New York).
Nachmansohn, D. and E. Neuman, 1974, "Properties and function of proteins in excitable membranes: An integral model of nerve excitability," Ann. N.Y. Acad. Sci., **227,** 275.
Nagumo, J., S. Arimoto and S. Yoshizawa, 1962, "An active pulse transmission line simulating nerve axon," Proc. IRE, **50,** 2061.
Nagumo, J., S. Yoshizawa and S. Arimoto, 1965, "Bistable transmission lines," Trans. IEEE on Circuit Theory, *CT*-**12,** 400.
Nakajima, K., Y. Onodera, T. Nakamura and R. Sato, 1974, "Numerical analysis of vortex motions on Josephson structures," J. Appl. Phys. **45,** 4095.
Nakajima, K., T. Yamashita and Y. Onodera, 1974, "Mechanical analogue of active Josephson transmission line," J. Appl. Phys. **45,** 3141.
Namerow, N. S., and J. J. Kappl, 1969, "Conduction in demyelinated axons—a simplified model," Bull. Math. Bioph. **31,** 9.
Nernst, W., 1888, "Zur Kinetik der in Lösung befindlichen Köper: Theorie der Diffusion," Zeit. Physik Chem. **2,** 613.
Nernst, W., 1889, "Die electromotorische Wirksamkeit der Ionen," Zeit physik chem., **4,** 129.
Neumke, B., and P. Läuger, 1969, "Nonlinear electrical effects in lipid bilayer membranes, II. Integration of the generalized Nernst-Planck equations," Biophys. J. **9,** 1160.
Newton, I., 1718, Optiks: or, a treatise of the reflections, refractions, inflections and colours of light, 2nd ed. with additions, p. 328.
Newton, I., 1952, *Optiks* (based on the fourth edition, London, 1730) (Dover Publications, Inc., New York).

Nicholson, C., and R. Llinás, 1971, "Field potentials in the alligator cerebellum and theory of their relationship to Purkinje cell dendritic spikes," J. Neurophysiol. **34,** 509.
Noble, D., 1962, "A modification of the Hodgkin-Huxley equations applicable to Purkinje fibre action and pacemaker potentials," J. Physiol. **160,** 317.
Noble, D., 1966, "Applications of Hodgkin-Huxley equations to excitable tissues," Physiol. Rev. **40,** 1.
Noble, D. and R. B. Stein, 1966, "The threshold conditions for initiation of action potentials by excitable cells," J. Physiol. **187,** 129.
Noguchi, S., Y. Kumagai and J. Oizumi, 1963, "General considerations on the neuristor circuits," Sci. Rept. Res. Inst. Tohoku U. **14,** 155.
Nystrom, R. A., 1973, *Membrane Physiology*, (Prentice-Hall, New Jersey).
Offner, F. F., 1969, "Ionic forces and membrane phenomena," Bull. Math. Biophys. **31,** 359.
Offner, F. F., 1970, "Kinetics of excitable membranes. Voltage amplification in a diffusion regime," J. Gen. Physiol. **56,** 272.
Offner, F. F., 1971, "Nernst-Planck-Poisson diffusion equation: numerical solution of the boundary value problem," J. Theor. Biol. **31,** 215.
Offner, F. F., 1972, "The excitable membrane. A physiochemical model," Biophys. J. **12,** 1583, 1629.
Offner, F. F., 1974, "Solution of the time-dependent ionic diffusion equation," J. Theoret. Biol. **45,** 81.
Offner, F., A. Weinberg, and G. Young, 1940, "Nerve conduction theory: some mathematical consequences of Bernstein's model," Bull. Math. Biophys. **2,** 89.
Opatowski, I., 1950, "The velocity of conduction in nerve fiber and its electric characteristics," Bull. Math. Biophys. **12,** 277.
Osterhout, W. J. V., and S. E. Hill, 1930, "Salt bridges and negative variations", J. Gen. Physiol. **13,** 547.
Parmentier, R. D., 1967, "Stability analysis of neuristor waveforms," Proc. IEEE **55,** 1498.
Parmentier, R. D., 1968, "Neuristor waveform stability analysis by Lyapunov's second method," Proc. IEEE **56,** 1607.
Parmentier, R. D., 1969, "Recoverable neuristor propagation on superconductive tunnel junction strip lines," Solid-State Electron., **12,** 287.
Parmentier, R. D., 1970a, "Neuristor analysis techniques for nonlinear distributed electronic systems", Proc. IEEE **58,** 1829.
Parmentier, R. D., 1970b, "Estimating neuristor excitation thresholds," Proc. IEEE **58,** 605.
Parnas, I., 1972, "Differential block at high frequency of branches of a single axon innervating two muscles," J. Neurophysiol. **35,** 903.
Pastushenko, V. F. and V. S. Markin, 1973, "Spread of excitation in a nerve fiber with septa—II. Blocking of the impulse by the septum," Biophysics **18,** 740.
Pastushenko, V. F. and V. S. Markin, 1969, "Propagation of excitation in a model of an inhomogeneous nerve fibre. II. Attenuation of pulse in the inhomogeneity," Biophysics **14,** 548.
Pastushenko, V. F., V. S. Markin and Yu. A. Chizmadzhev, 1969[a], "Propagation of excitation in a model of the inhomogeneous nerve fibre. III. Interaction of pulses in the region of the branching mode of a nerve fibre," Biophysics **14,** 929.
Patushenko, V. F., V. S. Marking and Yu. A. Chizmadzhev, 1969[b], "IV. Branching as a summator of nerve pulses," Biophysics **14,** 1130.
Pickard, W. F., 1966, "On the propagation of the nervous impulse down medullated and unmedullated fibers," J. Theoret. Biol. **11,** 30.
Pickard, W. F., 1968, "A contribution to the electromagnetic theory of the unmyelinated axon," Math. Biosci. **2,** 111.
Pickard, W. F., 1969[a], "The electromagnetic theory of electrotonus along an unmyelinated axon," Math. Biosci. **5,** 471.
Pickard, W. F., 1969[b], "Estimating the velocity of propagation along myelinated and unmyelinated fibers," Math. Biosci. **5,** 305.
Pickard, W. F., 1974, "Electrotonus on a nonlinear dendrite," Math Biosci. **20,** 75.
Planck, M., 1890[a], "Ueber die erregung von Elektricität und Wärme in Elektrolyten," Ann. Physik. Chem. **39,** 161.
Planck, M., 1890[b], Ueber die Potential differenz zwischen zwei verdünnuten Lösungen binärer Elektrolyte," Ann. Physik. Chem. **40,** 561.
Plonsey, R., 1964, "Volume conductor fields of action currents," Biophys. J., **4,** 317.
Plonsey, R., 1965, "An extension of the solid angle potential formulation for an active cell," Biophys. J., 5, 663.
Pokrovskii, A. N., 1970, "Mechanism of origin of electric potentials in nerve tissue," Biophysics **15,** 914.
Van Der Pol, B., 1926, "On relaxation oscillations," Phil. Mag. Ser 7, **2,** 978.
Van Der Pol, B., 1934, "The nonlinear theory of electric oscillations," Proc. IRE **22,** 1051.
Van Der Pol B., 1957, "On a generalisation of the non-linear differential equation $U_{tt} - \epsilon(1 - u^2) U_t + u = 0$," Proc. Acad. Sci. Amsterdam, **A60,** 477.
Polanyi, M., 1961, "Knowing and being," Mind **70,** 458.
Polanyi, M., 1962, "Tacit knowing: its bearing on some problems of philosophy," Rev. Mod. Phys. **34,** 601.
Polanyi, M., 1965, "The structure of consciousness," Brain **88,** 799.
Polyakov, I. V., 1973, "Rising, quasi-stationary voltage waves in nonhomogeneous lines with nonlinear resistance," Rad. Eng. Elec. Phys. **18,** 722.
Predonzani, G., and Roveri, A., 1968, "Criteri di stabilita per una linea contenente bipoli attive concentrati non-lineari," Note, Receusioni e Notizie, **17,** 1433.
Purpura, D. P. and H. Grundfest, 1956, "Nature of dendritic potentials and synaptic mechanisms in cerebral cortex of cat," J. Neurophysiol. **19,** 573.
Rall, W., 1959, "Branching dendritic trees and montoneuron membrane resistivity," Exp. Neurol. **1,** 491.
Rall, W., 1962[a], "Theory of physiological properties of dendrites," Ann. N.Y. Acad. Sci., **96,** 1071.
Rall, W., 1962b, "Electrophysiology of a dendritic neuron model," Biophys. J., **2,** 145.
Rall, W., 1964, "Theoretical significance of dendritic trees for neuronal input-output relations," *Neural Theory and Modeling*, edited by R. F. Reiss, (Stanford U. Stanford) p. 73.
Rall, W., 1967, "Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of synaptic input," J. Neurophysiol. **30,** 1138.
Rall, W., 1969, "Distributions of potential in cylindrical coordinates and time constants for a membrane cylinder," Bioph. J. **9,** 1509.
Rall, W., 1970, "Dendritic neuron theory and dendrodendritic synapses in a simple cortical system," *The Neurosciences: Second Study Program*, edited by F. O. Schmitt, (The Rockefeller U. P., New York).
Rall, W. and G. M. Shepherd, 1968, "Theoretical reconstruction of field potentials and dendrodendritic synaptic interactions in olfactory bulb," J. Neurophysiol. **31,** 884.
Ramón y Cajal, S., 1908, "Structure et connexious des neurons," Anchivio di Fisiologia **5,** 1.
Ramón y Cajal, S., 1954, *Neuron Theory or Reticular Theory?* Cous. Sup. de Invest. Cientificas, Madrid.
Ramon-Moliner, E., 1962, "An attempt at classifying nerve cells on the basis of their dendritic patterns," J. Comp. Neurol. **119,** 211.
Rashevsky, N., 1960, *Mathematics Biophysics* (Dover, New York).
Richer, I., 1965, "Pulse transmission along certain lumped nonlinear transmission lines," Electron. Lett. **1,** 135.
Richer, I., 1966, "The switch-line: a simple lumped transmission line that can support unattenuated propagation," Trans. IEEE on Circuit Theory, *CT*-**13,** 388.
Rinzel, J. and J. B. Keller, 1973, "Traveling wave solutions of a nerve conduction equation," Biophys. J. **13,** 1313.
Rinzel, J. and W. Rall, 1974, "Transient response in a dendritic neuron model for current injected at one branch," Biophys. J. **14,** 759.
Rose, J. E., L. I. Malis, L. Kruger and C. P. Baker, 1960, "Effects of heavy, ionizing, monoenergetic particles on the cerebral cortex. II. Histological appearance of laminar lesions and growth of nerve fibers after laminar destructions," J. Comp. Neurol. **115,** 243.
Rosen, G., 1974, "Approximate solution to the generic initial value problem for nonlinear reaction-diffusion equations," SIAM J. Appl. Math. **26,** 221.
Rosenberg, S. A., 1969, "A computer evaluation of equations for predicting the potentials across biological membranes," Biophys. J. **9,** 500.
Rosenblueth, A., N. Wiener, W. Pitts and J. Garcia Ramos, 1948, "An account of the spike potential of axons," J. Cell. Comp. Physiol. **32,** 275.
Rosenfalk, P., 1969, *Intra- and extracellular potential fields of active nerve and muscle fibres*, (Akademisk Forlag, Copenhagen).
Sabah, N. H. and K. N. Leibovic, 1969, "Subthreshold oscillatory responses of the Hodgkin-Huxley cable model for the squid giant axon," Biophys. J., **9,** 1206.
Sato, R. and H. Miyamoto, 1967, "Active transmission lines," Elec. and Comm. in Japan, **50,** 131.
Sato, H., I. Tasaki, E. Carbone and M. Hallett, 1973, "Changes in

axon birefringence associated with excitation: implications for the structure of the axon membrane," J. Mechanochem. Cell Motility **2,** 209.
Sattinger, D. H., 1975, "On the stability of waves of nonlinear parabolic systems," (to be published).
Scott, A. C., 1962, "Analysis of nonlinear distributed systems," Trans. IRE, *CT*-**9,** 192.
Scott, A. C., 1963, "Neuristor propagation on a tunnel diode loaded transmission line," Proc. IEEE **51,** 240.
Scott, A. C., 1964[a], "Steady propagation on nonlinear transmission lines," Trans. IEEE on Circuit Theory, *CT*-**11,** 146.
Scott, A. C., 1964[b], "Distributed device applications of the superconducting tunnel junction," Solid State Elec. **7,** 137.
Scott, A. C., 1970, *Active and Nonlinear Wave Propagation,* (Wiley, New York).
Scott, A. C., 1971, "Effect of the series inductance of a nerve axon upon its conduction velocity," Math. Biosci. **11,** 277.
Scott, A. C., 1972, "Transmission line equivalent for an unmyelinated nerve axon," Math. Biosci. **13,** 47.
Scott, A. C., 1973a, "Strength duration curves for threshold excitation of nerves," Math. Biosci. **18,** 137.
Scott, A. C., 1973b, "Information processing in dendritic trees," Math. Biosci. **18,** 153.
Scott, A. C., 1974, "The application of Bäcklund transforms to physical problems," Proc. of NSF Workshop on Contact Transformations, Vanderbilt U., Sept. 1974 (to be published).
Scott, A. C., F. Y. T. Chu, D. W. McLaughlin, 1973, "The soliton: a new concept in applied science," Proc. IEEE **61,** 1443.
Scott, B. I. H., 1962, "Electricity in plants," Sci. Am. **207,** No. 4, 107.
Scott Russell, J., 1844, "Report on waves," Proc. Roy. Soc., Edinburgh, 319.
Singer, S. J. and G. L. Nicolson, 1972, "The fluid mosaic model of the structure of cell membranes," Science **175,** 720.
Smith, R. A., 1961, *Semiconductors,* (Cambridge Univ. Press, Cambridge, England) p. 234.
Smolyaninov, V. V., 1968, "Omission of pulses in an elementary fiber model," Biophysics, **13,** 587.
Smolyaninov, V. V., 1969, "Speed of conduction of excitation along a fibre and a syncytium," Biophysics **14,** 357.
Szentágothai, J., 1968, "Structuro-functional considerations of the cerebellar neuron network," Proc. IEEE **56,** 960.
Tasaki, I., 1939, "The electro-saltatory transmission of the nerve impulse and the effect of narcosis upon the nerve fiber," Am. J. Physiol. **127,** 211.
Tasaki, I., 1959, "Conduction of the nerve impulse," Handbook of Physiology, Section 1, 75.
Tasaki, I., 1968, *Nerve Excitation, A Macro-molecular Approach,* (C. C. Thomas, Springfield, Illinois).
Tasaki, I., 1974a, "Energy transduction in the nerve membrane and studies of excitation processes with extrinsic fluorescence probes," Ann. N.Y. Acad. Sci., **227,** 247.
Tasaki, I., 1974b, "Nerve excitation. New experimental evidence for the macromolecular hypothesis," in *Actualités Neurophysiologiques,* (Masson et Cie, Paris), 79.
Tauc, L. and G. M. Hughes, 1963, "Modes of initiation and propagation of spikes in the branching axons of molluscan central neurons," J. Gen. Physiol. **46,** 533.
Taylor, R. E., 1963, "Cable theory," in *Physical Techniques in Biological Research,* edited by W. L. Nastuk, Vol. **6,** ch. 4, (Academic Press, New York), 219.
Teorell, T., 1936, "Electrical changes in interfacial films," Nature **137,** 994–995.
Thomas, R. C., 1972, "Electrogenic sodium pump in nerve and muscle cells," Physiol. Rev. **52,** 563.
Tille, J., 1965, "A new interpretation of the dynamic changes of the potassium conductance in the squid giant axon," Biophys. J. **5,** 163.
Undrovinas, A. I., V. F. Pastushenko and V. S. Markin, 1972, "Calculation of the shape and speed of nerve impulses," Doklady Biophysics **204,** 47.
Vanderkooi, G. and D. E. Green, 1970, "Biological membrane structure, I. The protein crystal model for membrances," Proc. Nat. Acad. Sci. **66,** 615.
Vorontsov, Yu. I., M. I. Kozhevnickova, and I. V. Polyakov, 1967, "Wave processes in active RC-lines," Rad. Eng. Elec. Phys., **11,** 1449.
Watanabe, A., S. Terakawa and M. Nagano, 1973, "Axoplasmic origin of the birefringence change associated with excitation of a crab nerve," Proc. Japan Acad. **49,** 470.
Watson, G. N., 1962, *Theory of Bessel fnctions,* (Cambridge U. Press, Cambridge, England) 2nd ed.
Waxman, S. G., 1972, "Regional differentiation of the axon: a review with special reference to the concept of the multiplex neuron," Brain Research **47,** 269.
Weber, H., 1873a, "Ueber die Besselschen Functionen und ihre Anwendung auf die theorie der elektrischen Strome," J. Reine Angew. Math. **75,** 75.
Weber, H., 1873b, "Ueber die stationären Strömungen der Elektricität in Cylindern," J.F.D. reine und angew. Mathematik, **76,** 1.
Weinberg, A. M., 1941, "Weber's theory of the kernleiter," Bull. Math. Bioph. **3,** 39.
Weinberg, A. M., 1942, "Green's functions in biological potential problems," Bull. Math. Biophy. **4,** 107.
Whitham, G. B., 1974, *Linear and Nonlinear Waves,* (Wiley-Interscience, New York).
Yamaguti, M., 1963, "The asymptotic behavior of the solution of a semi-linear partial differential equation related to an active pulse transmission line," Proc. Japan Acad. **39,** 726.
Yoshizawa, S., 1971, "Asymptotic behavior of a bistable transmission line," IECE Professional Group on Nonlinear Problems, NLP 71-1 (in Japanese).
Yoshizawa, S. and Y. Kitada, 1969, "Some properties of a simplified nerve equation," Math. Biosci. **5,** 385.
Yoshizawa, S. and J. Nagumo, 1964, "A bistable distributed line," Proc. IEEE, **52.**
Young, J. Z., 1936, "Structure of nerve fibers and synapses in some invertebrates," Cold Spring Harbor Symp. Quart. Biol. **4,** 1.
Young, J. Z., 1951, *Doubt and Certainty in Science,* (Oxford Clarendon Press).
Zeeman, E. C., 1972, "Differential equations for the heartbeat and the nervous impulse," *Toward a Theoretical Biology,* edited by C. H. Waddington, (Aldine Publ. Co., Chicago, Ill.)
Zeldovich, Y. B. and G. I. Barenblatt, 1959, "Theory of flame propagation," Combust. Flame, **3,** 61.

## ADDITIONAL REFERENCES

Barron, D. H. and B. H. C. Matthews, 1935, "Intermittent conduction in the spinal cord," J. Physiol. **85,** 73.
Changeux, J. P., 1969, "Remarks on the symmetry and cooperative properties of biological membranes," in *Nobel Symposium* **11,** edited by A. Engström and B. Strandberg (Wiley-Interscience, New York), 235.
Gemme, G., 1969, "Axon membrane crystallites in insect photoreceptors," in *Nobel Symposium* **11,** edited by A. Engström and B. Strandberg (Wiley-Interscience, New York), 305.
Green, M. W. and B. D. Sleeman, 1974, "On FitzHugh's nerve axon equations," J. Math. Biol. **1,** 153.
Krnjevič, K. and R. Miledi, 1959, "Presynaptic failure of neuromuscular propagation in rats," J. Physiol. **149,** 1.
Parnas, I., S. Hochstein, H. Parnas and M. Spira, 1973, "Numerical solution to the Hodgkin–Huxley equations applied to spike train transmission across an axon inhomogeneity," Israel J. Med. Sci. **9,** 681.

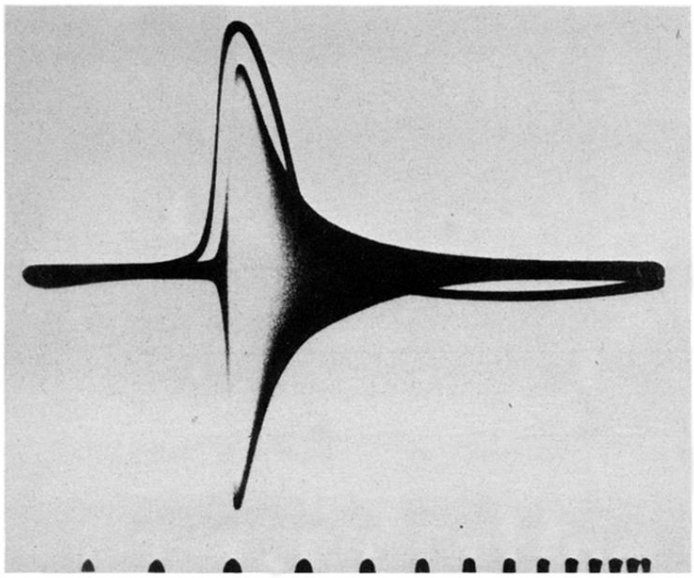

FIG. 3. Direct measurement of the increase in membrane conductance (band) during the action potential (line) on the squid giant axon [Cole and Curtis (1938)]. Time marks are 1 msec.

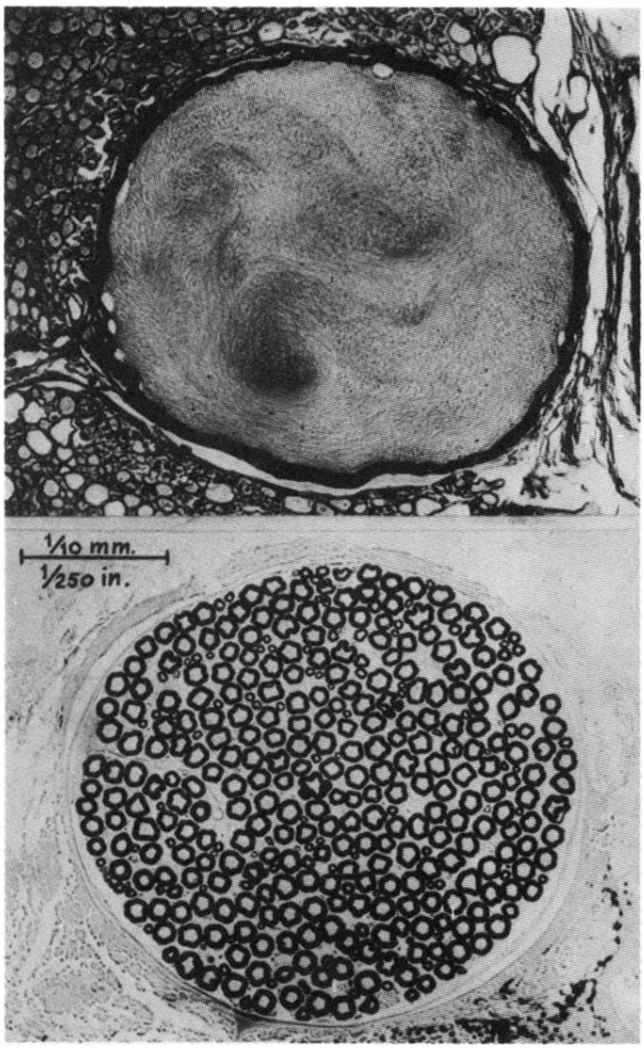


FIG. 35. Comparison of cross sections for the squid giant axon (above) and the sciatic nerve bundle controlling the calf muscle of a rabbit (below). There are about 400 myelinated fibers in the rabbit nerve each conducting pulses at about 80 meters per second [Young (1951)].