

## Modeling the effect of an external electric field on the velocity of spike propagation in a nerve fiber

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The effect of an externally generated electric field on the propagation of action potentials is modeled, assuming the Hodgkin-Huxley equation for the voltage-dependent conductance of the membrane of a nerve fiber. With some simplifying assumptions, this conductance together with Maxwell's equations leads to the Hodgkin-Huxley differential equations for propagation, modified by a term proportional to the gradient of the externally generated electric field component along the nerve fiber. Computer solution of these equations shows the influence of an electric field gradient on propagation velocity. When the electric field oscillates, voltage spikes starting later along a given axon advance or lag relative to earlier spikes, so the time between spikes at the receiving end differs from the time between spike originations. The amount that a low-frequency electric field modulates pulse timing at the end of a fiber relative to that at the beginning is estimated under several conditions. [S1063-651X(99)04811-4]

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### I. INTRODUCTION

The interaction of electricity with the human body has been of interest for over a century; in recent decades, questions have been posed concerning possible health effects of extremely low-frequency (ELF) electric fields produced by power lines. This report generalizes a recent analysis of the current density induced in nerve fibers by ELF fields [1], to account for nonlinear membrane conductivity. It will be shown that because of the nonlinear relation between voltage and current density across the membrane, an externally generated electric field can slightly speed or retard the propagation of action potentials.

The propagation of an action potential requires a nonlinear relation between voltage and current density across a membrane, as was quantified by Hodgkin and Huxley in their investigations of spike propagation along the giant axon of the squid [2]. It is important to distinguish in their model between (1) the equations relating current density across the membrane to voltage drop and (2) the equations derived from these (by use of circuit theory) for the propagation of voltage spikes along the axon. Later Scott derived these propagation equations from the equations for current density across the membrane, Maxwell's equations for the electromagnetic field, and a few approximations, without assuming circuit theory [3].

Another example of an effect in animals which depends on the nonlinear membrane conductance is the naturally occurring conversion of a receptor potential into a train of voltage spikes in a nerve fiber [4,5]. In this example, the mean time interval between spikes codes the intensity of sensation. Coding information into intervals between voltage spikes on nerve fibers is ubiquitous across the animal kingdom.

This report concerns a nonlinear response of a nerve fiber to an ELF electric field. The gradient of the ELF field component along a nerve fiber will be shown to influence the velocity of propagation. If the ELF field oscillates, then so does the propagation velocity, with the result that spike-to-

spike time intervals can be different at the receiving end of a nerve fiber from the intervals at the transmitting end. In other words, an ELF field modifies the information coded into pulse intervals.

Hodgkin and Huxley obtained data by which to determine parameters for their model and against which to test the model by imposing an externally generated voltage as a step-function of time across the cell membrane and assuming that the current density transverse to the membrane would be the same as it would for the same voltage function naturally generated. Thus their model in its construction and specifically in its relation to measured data assumes that a membrane voltage as a function of time results in a certain current density as a function of time, regardless of the source of the voltage. The model proposed here uses the Hodgkin-Huxley equations for current density across the cell membrane in relation to membrane voltage, and follows Hodgkin and Huxley in assuming applicability of these equations even when an external source influences the membrane voltage. In Sec. II, Scott's derivation of the propagation equations from Maxwell's equations is generalized to allow for an externally generated ELF field. This results in the Hodgkin-Huxley differential equations for spike propagation, modified by a term for the externally generated ELF field. Computer solution of the differential equations then produces a relation between the gradient of the ELF field component along an axon and the propagation velocity, as described in Sec. III. Section IV extrapolates these results to estimate the effect of an external field gradient that oscillates in time.

### II. FORMULATION OF PROPAGATION EQUATIONS

Scott discussed the relation between Maxwell's equations for the electromagnetic field and the Hodgkin-Huxley equations for propagation of a voltage spike along a nerve for the case of zero incident field [3]. The formulation here accounts for an incident field and attends in more detail to certain approximations needed to arrive at the desired propagation equations.

In cylindrical coordinates  $(\rho, \phi, z)$ , the nerve fiber is a cylinder defined by  $\rho \leq a$ . An electromagnetic field is defined both inside and outside a boundary defined by  $\rho = a$ ; the membrane of the nerve fiber is modeled as a limiting case of zero thickness. Thus the membrane partitions space into an inner region  $\rho < a$  and an outer region  $\rho > a$ . The voltage-dependent conductance of the membrane is expressed by a nonlinear boundary condition joining the two regions at  $\rho = a$ .

Maxwell's equations relate the electric field  $\mathbf{E}$ , the electric displacement  $\mathbf{D}$ , the magnetic field  $\mathbf{H}$ , the magnetic induction  $\mathbf{B}$ , the charge density, written here as  $\eta$ , and the current density  $\mathbf{J}$ . Using SI units, let  $\mu_0$  be the magnetic permeability of free space. Letting the index  $j$  take the values "in" and "out," let  $\epsilon_j$  and  $\sigma_j$  be the dielectric permittivity and the electrical conductivity, respectively, in region  $j$ . Azimuthal symmetry is assumed ( $\partial/\partial\phi=0$ ), as is a transverse magnetic field:  $\mathbf{H} = \mathbf{e}_\phi H_\phi$  (so  $H_\rho = H_z = 0$ ). From this it follows that the electric field has only  $\rho$  and  $z$  components, and these are determined by  $H_\phi$  [3]:

$$\left( \epsilon_j \frac{\partial}{\partial t} + \sigma_j \right) E_\rho = \epsilon_j \frac{\partial}{\partial t} E_\rho + J_\rho = - \frac{\partial}{\partial z} H_\phi, \quad (1)$$

$$\left( \epsilon_j \frac{\partial}{\partial t} + \sigma_j \right) E_z = \epsilon_j \frac{\partial}{\partial t} E_z + J_z = \frac{1}{\rho} \frac{\partial}{\partial \rho} \rho H_\phi. \quad (2)$$

Maxwell's equations provide a scalar wave equation for the governing components  $H_\phi$ :

$$\left[ \frac{\partial^2}{\partial z^2} + \frac{\partial}{\partial \rho} \frac{1}{\rho} \frac{\partial}{\partial \rho} \rho - \mu_0 \left( \epsilon_j \frac{\partial}{\partial t} + \sigma_j \right) \frac{\partial}{\partial t} \right] H_\phi = 0. \quad (3)$$

The main focus of analysis is on the potential difference  $\Phi(z, t)$  across the membrane. This potential will be related to  $H_\phi$  in two ways: the first way uses Eq. (1) and the continuity of  $H_\phi$  at  $\rho = a$  together with the Hodgkin-Huxley equations relating membrane voltage to membrane current density; the second uses Eq. (2) along with a boundary condition as  $\rho \rightarrow \infty$ , which depends on the incident electric field from an external source and expresses the incident electric field in the model. Elimination of  $H_\phi$  between these two relations will provide the propagation equations for  $\Phi$ , modified to account for the incident electric field.

#### A. First relation: continuity of $H_\phi$

To establish the first relation, impose the continuity of  $H_\phi$  (but not its normal derivative) at  $\rho = a$ . From this follows the continuity of  $\partial H_\phi / \partial z$ , and in turn, by Eq. (1), the continuity of  $(\epsilon_j \partial E_\rho / \partial t + J_\rho)$ . One views the membrane as a limiting case in which a thickness  $\delta$  shrinks to zero, with  $E_\rho \delta \rightarrow -\Phi$  and  $\epsilon_{\text{mem}} / \delta \rightarrow C_M$ , where  $\Phi$  is the potential of the outside of the membrane relative to the inside and  $C_M$  is a capacitance per unit area of the membrane. This form is consistent with the following relation between the  $\rho$  component of current in the membrane  $J_{\text{mem}}$  and the components of  $E_\rho$  and  $J_\rho$  outside the membrane:

$$\begin{aligned} & \epsilon_{\text{in}} \frac{\partial}{\partial t} E_\rho(a^-, z, t) + J_\rho(a^-, z, t) \\ &= \epsilon_{\text{out}} \frac{\partial}{\partial t} E_\rho(a^+, z, t) + J_\rho(a^+, z, t) \\ &= -C_M \frac{\partial}{\partial t} \Phi(z, t) + J_{\text{mem}}(z, t). \end{aligned} \quad (4)$$

With Eq. (1), one obtains from this

$$\frac{\partial}{\partial z} H_\phi(a, z, t) = C_M \frac{\partial}{\partial t} \Phi(z, t) - J_{\text{mem}}(z, t). \quad (5)$$

[If the membrane were characterized by a voltage-independent conductivity  $\sigma_{\text{mem}}$ , one would have  $J_{\text{mem}} = -\sigma_{\text{mem}} \Phi / \delta$ . Then for the static situation (in which  $\partial/\partial t = 0$ ) in the case for which  $\sigma_{\text{in}} = \sigma_{\text{out}}$ , it is easy to check that Eq. (4) implies the condition (B12) in [1], in the limit as  $\delta \rightarrow 0$ ; however, for nonstatic situations, the capacitive term  $\partial\Phi/\partial t$  is important.]

#### B. Second relation: boundary condition as $\rho \rightarrow \infty$

To establish the second relation between  $\Phi$  and  $H_\phi$ , one notices that close to any point on the membrane, the electric field is well approximated by the gradient of a potential which satisfies the Laplace equation. As analyzed by Scott [3], this implies that a voltage drop across the membrane has a  $z$  derivative related to a jump in the tangential electric field component  $E_z$  from  $\rho = a^+$  to  $\rho = a^-$ :

$$\frac{\partial}{\partial z} \Phi(z, t) = E_z(a^-, z, t) - E_z(a^+, z, t). \quad (6)$$

Applying the operator

$$\left( \sigma_{\text{in}} + \epsilon_{\text{in}} \frac{\partial}{\partial t} \right) \left( \sigma_{\text{out}} + \epsilon_{\text{out}} \frac{\partial}{\partial t} \right)$$

to Eq. (6) and using Eq. (2), one obtains

$$\begin{aligned} & \left( \sigma_{\text{in}} + \epsilon_{\text{in}} \frac{\partial}{\partial t} \right) \left( \sigma_{\text{out}} + \epsilon_{\text{out}} \frac{\partial}{\partial t} \right) \frac{\partial}{\partial z} \Phi(z, t) \\ &= \left( \sigma_{\text{out}} + \epsilon_{\text{out}} \frac{\partial}{\partial t} \right) \frac{1}{\rho} \frac{\partial}{\partial \rho} \rho H_\phi(a^-, z, t) \\ &\quad - \left( \sigma_{\text{in}} + \epsilon_{\text{in}} \frac{\partial}{\partial t} \right) \frac{1}{\rho} \frac{\partial}{\partial \rho} \rho H_\phi(a^+, z, t). \end{aligned} \quad (7)$$

The next task is to determine the  $\rho$  derivative of  $H_\phi$  as  $\rho \rightarrow a^\pm$  in terms of  $H_\phi(a, z, t)$ . This determination involves a boundary condition on  $H_\phi$  as  $\rho \rightarrow \infty$ , which in turn depends on the incident field, conceived as the electromagnetic field that would be present due to an external source if the nerve fiber were removed. It is convenient to specify the incident field by  $E_z^{\text{inc}}(0, z, t)$ , the  $z$ -component of the incident electric field along the axis of the nerve fiber, and to work with Fourier transforms.

Denote the Fourier transform with respect to  $t$  and  $z$  by an overbar, so an arbitrary function  $g(z, t)$  has as its transform

$$\bar{g}(\beta, \omega) \stackrel{\text{def}}{=} \frac{1}{2\pi} \int \int dt dz e^{i(\omega t - \beta z)} g(z, t); \quad (8)$$

the inverse transform is

$$g(z, t) = \frac{1}{2\pi} \int \int d\omega d\beta e^{-i(\omega t - \beta z)} \bar{g}(\beta, \omega). \quad (9)$$

The nonlinear aspect of the problem is confined to the boundary at  $\rho = a$ , so Maxwell's equations are applicable; from Eqs. (2) and (3), it follows that

$$\bar{E}_z^{\text{inc}}(\rho, \beta, \omega) = \bar{f}(\beta, \omega) I_0(k_{\text{out}} \rho), \quad (10)$$

where  $f$ , supposed known, is defined by

$$f(z, t) \stackrel{\text{def}}{=} E_z^{\text{inc}}(0, z, t), \quad (11)$$

the propagation constant in region  $j$  is defined by

$$k_j^2 = \beta^2 - \mu_0(\epsilon_j \omega^2 + i\omega \sigma_j), \quad (12)$$

and  $I_0$  is a modified Bessel function [6]. It is routine [3,7] to show that (for coefficients  $C(\beta, \omega)$  and  $D(\beta, \omega)$  yet to be determined):

$$\bar{H}_\phi(\rho, \beta, \omega) = \begin{cases} \bar{H}_\phi(a, \beta, \omega) I_1(k_{\text{in}} \rho) / I_1(k_{\text{in}} a) & \text{if } \rho \leq a, \\ C(\beta, \omega) I_1(k_{\text{out}} \rho) + D(\beta, \omega) K_1(k_{\text{out}} \rho) & \text{otherwise,} \end{cases} \quad (13)$$

from which it follows that

$$\frac{1}{\rho} \frac{\partial}{\partial \rho} \rho \bar{H}_\phi(\rho, \beta, \omega) = \begin{cases} k_{\text{in}} \bar{H}_\phi(a, \beta, \omega) I_0(k_{\text{in}} a) / I_1(k_{\text{in}} a) & \text{as } \rho \rightarrow a^-, \\ k_{\text{out}} [C(\beta, \omega) I_0(k_{\text{out}} a) - D(\beta, \omega) K_0(k_{\text{out}} a)] & \text{as } \rho \rightarrow a^+. \end{cases} \quad (14)$$

The Fourier transform of Eq. (2) is used to specify a boundary condition of the total field approaching the incident field as  $\rho \rightarrow \infty$ :

$$\frac{1}{\rho} \frac{\partial}{\partial \rho} \rho \bar{H}_\phi(\rho, \beta, \omega) \rightarrow (\sigma_{\text{out}} - i\omega \epsilon_{\text{out}}) \bar{E}_z^{\text{inc}}(\rho, \beta, \omega); \quad (15)$$

this and Eq. (14) result in

$$k_{\text{out}} C(\beta, \omega) = (\sigma_{\text{out}} - i\omega \epsilon_{\text{out}}) \bar{f}(\beta, \omega). \quad (16)$$

Continuity of  $H_\phi$  at  $\rho = a$  and Eq. (13) imply

$$\bar{H}_\phi(a, \beta, \omega) = C(\beta, \omega) I_1(k_{\text{out}} a) + D(\beta, \omega) K_1(k_{\text{out}} a). \quad (17)$$

Solving Eqs. (16) and (17) for  $C$  and  $D$  and substituting these solutions into Eq. (14) produce

$$\frac{1}{\rho} \frac{\partial}{\partial \rho} \rho \bar{H}_\phi(\rho, \beta, \omega) = \begin{cases} k_{\text{in}} \bar{H}_\phi(a, \beta, \omega) I_0(k_{\text{in}} a) / I_1(k_{\text{in}} a) & \text{as } \rho \rightarrow a^-, \\ (\sigma_{\text{out}} - i\omega \epsilon_{\text{out}}) \bar{f}(\beta, \omega) / [k_{\text{out}} a K_1(k_{\text{out}} a)] & \\ -k_{\text{out}} \bar{H}_\phi(a, \beta, \omega) K_0(k_{\text{out}} a) / K_1(k_{\text{out}} a) & \text{as } \rho \rightarrow a^+. \end{cases} \quad (18)$$

The substitution of Eq. (18) into the Fourier transform of Eq. (7) yields

$$i\beta \bar{\Phi}(\beta, \omega) = \left( \frac{k_{\text{in}} I_0(k_{\text{in}} a)}{(\sigma_{\text{in}} - i\omega \epsilon_{\text{in}}) I_1(k_{\text{in}} a)} + \frac{k_{\text{out}} K_0(k_{\text{out}} a)}{(\sigma_{\text{out}} - i\omega \epsilon_{\text{out}}) K_1(k_{\text{out}} a)} \right) \bar{H}_\phi(a, \beta, \omega) - \frac{\bar{f}(\beta, \omega)}{k_{\text{out}} a K_1(k_{\text{out}} a)}. \quad (19)$$

### C. Combining the two relations

Eliminating  $\bar{H}_\phi$  between Eq. (19) and the Fourier transform of Eq. (5), one finds

$$(i\beta)^2 \bar{\Phi}(\beta, \omega) = \left( \frac{k_{\text{in}} I_0(k_{\text{in}} a)}{(\sigma_{\text{in}} - i\omega \epsilon_{\text{in}}) I_1(k_{\text{in}} a)} + \frac{k_{\text{out}} K_0(k_{\text{out}} a)}{(\sigma_{\text{out}} - i\omega \epsilon_{\text{out}}) K_1(k_{\text{out}} a)} \right) \times [-i\omega C_M \bar{\Phi}(\beta, \omega) - \bar{J}_{\text{mem}}(\beta, \omega)]$$

$$-\frac{i\beta\bar{f}(\beta, \omega)}{k_{\text{out}}aK_1(k_{\text{out}}a)}, \quad (20)$$

which implies the following equation, more convenient for inverting the transforms to the  $(z, t)$  domain:

$$\begin{aligned} \bar{\mathcal{G}}(\beta, \omega)(\sigma_{\text{in}} - i\omega\epsilon_{\text{in}}) & \left( -\beta^2\bar{\Phi} + \frac{i\beta\bar{E}_z^{\text{inc}}(0, \beta, \omega)}{k_{\text{out}}aK_1(k_{\text{out}}a)} \right) \\ & = -i\omega C_M\bar{\Phi}(\beta, \omega) - \bar{J}_{\text{mem}}(\beta, \omega), \end{aligned} \quad (21)$$

where  $\bar{\mathcal{G}}(z, t)$  is defined by its transform

$$\bar{\mathcal{G}}(\beta, \omega) = \left( \frac{k_{\text{in}}I_0(k_{\text{in}}a)}{I_1(k_{\text{in}}a)} + \frac{(\sigma_{\text{in}} - i\omega\epsilon_{\text{in}})k_{\text{out}}K_0(k_{\text{out}}a)}{(\sigma_{\text{out}} - i\omega\epsilon_{\text{out}})K_1(k_{\text{out}}a)} \right)^{-1}. \quad (22)$$

The function  $\mathcal{G}$  is sharply peaked relative to the time scale of change of  $\Phi$  with  $z$  and  $t$ . In the  $(\beta, \omega)$  domain, one has

$$\begin{aligned} \bar{\mathcal{G}}(\beta, \omega) & = \frac{a}{2} \left( 1 + \frac{(k_{\text{in}}a)^2}{8} \right. \\ & \quad \left. + (k_{\text{out}}a)^2 \ln(2/k_{\text{out}}a) \frac{(\sigma_{\text{in}} - i\omega\epsilon_{\text{in}})}{2(\sigma_{\text{out}} - i\omega\epsilon_{\text{out}})} \right)^{-1} \\ & \quad + O((k_{\text{out}}a)^4 \ln^2(k_{\text{out}}a)), \end{aligned} \quad (23)$$

so that  $\bar{\mathcal{G}}$  is flat over the region  $|k_{\text{out}}a| \ll 1$  in which  $\bar{\Phi}(\beta, \omega)$  is significant. To arrive at the propagation equation of Hodgkin and Huxley (with or without an external field), one makes two approximations, the first of which replaces  $\mathcal{G}$  by  $a/2$  times a  $\delta$  function. The denominator in Eq. (21) which divides the external field  $\bar{f}$  is

$$\begin{aligned} k_{\text{out}}aK_1(k_{\text{out}}a) & = 1 - \frac{1}{2}(k_{\text{out}}a)^2 [\ln(2/k_{\text{out}}a) + \frac{1}{2} - \gamma] \\ & \quad + O[(k_{\text{out}}a)^4 \ln(k_{\text{out}}a)], \end{aligned} \quad (24)$$

where  $\gamma = 0.5772 \dots$  is Euler's constant [6]. The Fourier transform of an ELF external field gradient  $\partial f / \partial z$  is negligible outside the region defined by  $|\beta| \ll 1/a$  and  $|\omega^2| \ll |a^2 / \mu_0 \epsilon_j|$ , so in this case the denominator (24) can be replaced by 1; this and the replacement of  $\bar{\mathcal{G}}$  by  $a/2$  yield

$$\begin{aligned} \frac{a}{2} \left( \sigma_{\text{in}} + \epsilon_{\text{in}} \frac{\partial}{\partial t} \right) & \left( \frac{\partial^2}{\partial z^2} \Phi(z, t) + \frac{\partial}{\partial z} E_z^{\text{inc}}(0, z, t) \right) \\ & = C_M \frac{\partial}{\partial t} \Phi(z, t) - J_{\text{mem}}(z, t). \end{aligned} \quad (25)$$

In deriving the Hodgkin-Huxley propagation equation, a second approximation is made: one neglects  $\omega\epsilon_{\text{in}}$  compared with  $\sigma_{\text{in}}$ , thereby simplifying Eq. (25) to

$$\begin{aligned} \frac{a\sigma_{\text{in}}}{2} & \left( \frac{\partial^2}{\partial z^2} \Phi(z, t) + \frac{\partial}{\partial z} E_z^{\text{inc}}(0, z, t) \right) \\ & = C_M \frac{\partial}{\partial t} \Phi(z, t) - J_{\text{mem}}(z, t). \end{aligned} \quad (26)$$

#### D. Propagation equation modified for an external field

As their model for  $J_{\text{mem}}$ , Hodgkin and Huxley take

$$J_{\text{mem}}(z, t) = J_{\text{HH}}[\Phi], \quad (27)$$

where they call  $-J_{\text{HH}}[\Phi]$  the ‘‘ionic current density’’ and define it by a system of equations that are ordinary differential equations in  $t$ , with coefficients that are functions of both  $t$  and  $z$ :

$$\begin{aligned} -J_{\text{HH}}[\Phi] & \stackrel{\text{def}}{=} g_K n^4 (\Phi - \Phi_K) + g_{Na} m^3 h (\Phi - \Phi_{Na}) \\ & \quad + g_L (\Phi - \Phi_L), \end{aligned} \quad (28)$$

where  $\Phi_K = 77$  mV and  $\Phi_{Na} = -50$  mV,  $\Phi_L = 54.401079$  mV; the first two play the role of Nernst potentials, while  $\Phi_L$  is chosen in a way discussed below. The  $g$ 's are constants with units of conductance per unit area:  $g_K = 360$  S/m<sup>2</sup>,  $g_{Na} = 1200$  S/m<sup>2</sup>, and  $g_L = 3$  S/m<sup>2</sup>.

The functions  $n = n(z, t)$ ,  $m = m(z, t)$ , and  $h = h(z, t)$  are all between 0 and 1 and correspond to the opening and shutting of gates that regulate conductance. At any point  $z$  along the fiber  $n$ ,  $m$ , and  $h$  depend on the history of voltage at that point, according to the ordinary differential equations

$$r^{-1} \frac{dn}{dt} = \alpha_n(1-n) - \beta_n n, \quad (29)$$

$$r^{-1} \frac{dm}{dt} = \alpha_m(1-m) - \beta_m m, \quad (30)$$

$$r^{-1} \frac{dh}{dt} = \alpha_h(1-h) - \beta_h h, \quad (31)$$

where  $r$  is a temperature-dependent rate constant defined by

$$r(T) = 3^{(T-6.3)/10} \text{ kHz}, \quad (32)$$

and  $T$  is the temperature in degrees centigrade. Hodgkin and Huxley state the  $\alpha$ 's and  $\beta$ 's as functions of an offset voltage  $v$  defined by

$$v \stackrel{\text{def}}{=} \Phi - \Phi_R. \quad (33)$$

For  $v$  in mV:

$$\alpha_n(v) = 0.1 \frac{(0.1v + 1.0)}{\exp(0.1v + 1.0) - 1}, \quad (34)$$

$$\beta_n(v) = 0.125 \exp(v/80.0), \quad (35)$$

$$\alpha_m(v) = \frac{(0.1v + 2.5)}{\exp(0.1v + 2.5) - 1}, \quad (36)$$

$$\beta_m(v) = 4.0 \exp(v/18.0), \quad (37)$$

$$\alpha_h(v) = 0.07 \exp(v/20.0), \quad (38)$$

$$\beta_h(v) = 1 / [\exp(0.1v + 3.0) + 1.0]. \quad (39)$$

The square brackets in  $J_{\text{HH}}[\Phi]$  indicate that the membrane current density at  $(z, t)$  is a function of the history of membrane voltage at  $z$  for times earlier than  $t$ , i.e.,  $\Phi(z, t')$  for  $t' \leq t$ .

In order to study the dependence of propagation velocity on parameters, it is convenient to reexpress these equations in dimensionless time and distance parameters:

$$\tau = r(T)t \quad (40)$$

and

$$\zeta = (2g_K/a\sigma_{\text{in}})^{1/2}z. \quad (41)$$

In these variables,  $r^{-1}\partial/\partial t$  in Eqs. (29)–(31) is replaced by  $\partial/\partial\tau$  while Eqs. (26)–(28) combine to produce

$$\begin{aligned} & \frac{\partial^2}{\partial\zeta^2}\Phi(\zeta, \tau) - (rC_M/g_K)\frac{\partial}{\partial\tau}\Phi(\zeta, \tau) \\ &= n^4(\Phi - \Phi_K) + \frac{g_{Na}}{g_K}m^3h(\Phi - \Phi_{Na}) \\ &+ \frac{g_L}{g_{Na}}(\Phi - \Phi_L) - F(\zeta, \tau), \end{aligned} \quad (42)$$

where  $F$  is  $(a\sigma_{\text{in}}/2g_K)\partial E_z^{\text{inc}}(0, z, t)/\partial z$  expressed in the  $(\zeta, \tau)$  coordinates:

$$F(\zeta, \tau) = (a\sigma_{\text{in}}/2g_K)^{1/2}\frac{\partial}{\partial\zeta}E_z^{\text{inc}}(0, (a\sigma_{\text{in}}/2g_K)^{1/2}\zeta, r^{-1}\tau). \quad (43)$$

Hence the approximations used to derive the propagation equations of Hodgkin and Huxley produce for the case of an external field the additional (driving) term  $-F$  proportional to  $-\partial E_z^{\text{inc}}/\partial z$  in Eq. (42).

### E. Static case and the resting potential

Consider the case in which  $\partial\Phi/\partial\tau=0$  and  $\partial F/\partial\tau=0$ . In this case, one has a membrane voltage  $\Phi(\zeta)$  with no dependence on  $\tau$ , and  $n(\zeta, \tau)$  has a static value  $n_s(\zeta)$ , found by setting  $d/dt=0$  in Eq. (29):

$$n_s(\zeta) = \{1 + \beta_n(\Phi(\zeta))/\alpha_n(\Phi(\zeta))\}^{-1}, \quad (44)$$

with similar equations for  $m_s$  and  $h_s$ . Thus the order of the system of differential equations drops from 5 to 2, and one has in place of Eq. (42) the second-order system:

$$\begin{aligned} & \frac{\partial^2}{\partial\zeta^2}\Phi(\zeta) = n_s(\Phi(\zeta))^4(\Phi - \Phi_K) \\ &+ \frac{g_{Na}}{g_K}m_s(\Phi(\zeta))^3h_s(\Phi(\zeta))(\Phi - \Phi_{Na}) \\ &+ \frac{g_L}{g_{Na}}(\Phi - \Phi_L) - F(\zeta). \end{aligned} \quad (45)$$

When the additional constraint is imposed that  $\Phi$  and  $F$  be invariant with  $\zeta$ , one has the quiescent case, which is just the algebraic (rather than differential) equation for a membrane voltage  $\Phi_0(F)$  independent of  $\zeta$  as well as independent of  $\tau$ :

$$\begin{aligned} 0 = & n_s(\Phi_0(F))^4[\Phi_0(F) - \Phi_K] \\ &+ \frac{g_{Na}}{g_K}m_s(\Phi_0(F))^3h_s(\Phi_0(F))[\Phi_0(F) - \Phi_{Na}] \\ &+ \frac{g_L}{g_{Na}}[\Phi_0(F) - \Phi_L] - F. \end{aligned} \quad (46)$$

The Hodgkin and Huxley model, partially specified, contains a parameter  $\Phi_L$  that must be assigned a numerical value to fully specify the model. Hodgkin and Huxley assumed implicitly that the value assigned to  $\Phi_L$  is independent of any external field, and hence independent of the external field gradient  $F$ , and that assumption is made here. Thus if  $\Phi_L$  is defined for one special case of  $F$ , it is defined for all cases. For the case  $F=0$ , the value of  $\Phi$  that makes the ionic current 0, satisfying Eq. (46), depends on  $\Phi_L$ . Conversely, if one knows the voltage  $\Phi_R$  (called the resting potential) at which the ionic current is 0 for the case  $F=0$ , one can assign to  $\Phi_L$  the value for which the solution to Eq. (46) is the resting potential. Hodgkin and Huxley chose the value for  $\Phi_L$  such that

$$\Phi_0(0) = \Phi_R = 65 \text{ mV}. \quad (47)$$

### III. TRANSLATIONAL INVARIANCE FOR CONSTANT $\partial F(z, t)/\partial z$

In case  $\partial E_z^{\text{inc}}(z, t)/\partial z$  is constant,  $F=F_0$  is constant and there exists an everywhere-finite solution to Eq. (42) of the form  $\Phi(\tau - \zeta/\gamma)$  for an as yet undetermined normalized velocity parameter  $\gamma$ . This corresponds in the variables  $(z, t)$  to a propagating action potential that is a function of  $(t - z/\theta)$  where the physical velocity is

$$\theta = (a\sigma_{\text{in}}/2g_K)^{1/2}r(T)\gamma. \quad (48)$$

One obtains in this way the following fifth-order system of ordinary differential equations, which contains a given constant gradient  $F_0$  and the as yet undetermined velocity  $\gamma$  as parameters:

$$\begin{aligned} & \frac{d^2}{d\tau^2}\Phi(\tau) = \gamma^2 \left[ \frac{rC_M}{g_K} \frac{d}{d\tau}\Phi(\tau) + n^4[\Phi(\tau) - \Phi_K] \right. \\ &+ \frac{g_{Na}}{g_K}m^3h[\Phi(\tau) - \Phi_{Na}] \\ &+ \left. \frac{g_L}{g_K}[\Phi(\tau) - \Phi_L] - F_0 \right], \end{aligned} \quad (49)$$

accompanied by the normalized form of Eqs. (29)–(31):

$$\frac{dn}{d\tau} = \alpha_n(1 - n) - \beta_n n, \quad (50)$$

$$\frac{dm}{d\tau} = \alpha_m(1-m) - \beta_m m, \quad (51)$$

$$\frac{dh}{d\tau} = \alpha_h(1-h) - \beta_h h. \quad (52)$$

These four equations (and the definitions of the  $\alpha$ 's and  $\beta$ 's) define a propagating action potential. The main focus of this report is on determining  $\gamma$  as a function of  $F_0$  (and of  $rC_M/g_K$ ). The procedure is the same as that used by Hodgkin and Huxley for the case  $F_0=0$ . As is well known for the case  $F_0=0$ , solutions that are everywhere finite exist only for special values of  $\gamma$ . For a single-spike solution,  $\gamma$  is unique and depends on  $F_0$ , as well as on the parameter ( $rC_M/g_K$ ).

To find  $\gamma(F_0, rC_M/g_K)$ , one proceeds by trial and error, guided by the fact that, just as for the case of  $F_0=0$ , a guessed value that exceeds  $\gamma$  leads—on integrating the system of equations—to a trajectory that dives toward negative infinity, while a guessed value that is too low leads to a trajectory that rises without bound.

#### A. Defining $\gamma$

For  $F$  constant, the system of ordinary differential equations is autonomous, and so is characterized by a vector field defined on a five-dimensional phase space with coordinates  $(\Phi, d\Phi/d\tau, n, m, h)$  [8]. This field and hence the integral curves corresponding to solutions of the system are parameterized by  $F_0$ ,  $rC_M/g_K$ , and the trial value for  $\gamma$ . For any values of  $F_0$ ,  $rC_M/g_K$ , and the trial value for  $\gamma$ , there is a trajectory that starts from the quiescent point having coordinates  $(\Phi_0, 0, n_0(\Phi_0), m_0(\Phi_0), h_0(\Phi_0))$ , where  $\Phi_0$  is short for  $\Phi_0(F_0)$ . This is a singular point, a saddle point. Only for the special value  $\gamma$  does this trajectory return to the quiescent point; for all other values it shoots off to plus or minus infinity in the  $\Phi$  coordinate. Searching over trial values of  $\gamma$  back and forth between the regions that generate positive and negative overshoot determines the special value.

#### B. Initial conditions

Trial values of  $\gamma$  are found to be too small or too big by integrating the system of equations. For any trial value, initial conditions for this integration follow from linearizing the system of ordinary differential equations around values  $\Phi$ ,  $n$ ,  $m$ , and  $h$  that define the singular point. For this linearized system, one finds a solution that begins with exponential growth by numerically finding the real roots of the characteristic polynomial. (The exponent is a function of  $F_0$  and a trial value of the velocity parameter  $\gamma$ , for which one can solve numerically.) This initial condition, more precise than the initial condition used by Hodgkin and Huxley, is motivated by the desire for as much precision as possible in determining how  $\gamma(F_0, rC_M/g_K)$  depends on  $F_0$ .

### IV. NUMERICAL ANALYSIS

The numerical solution of  $\gamma(F_0, r(T)C_M/g_K)$  was performed as follows, using a fourth-order Runge-Kutta routine [9] to forward integrate the equations in arithmetic carried

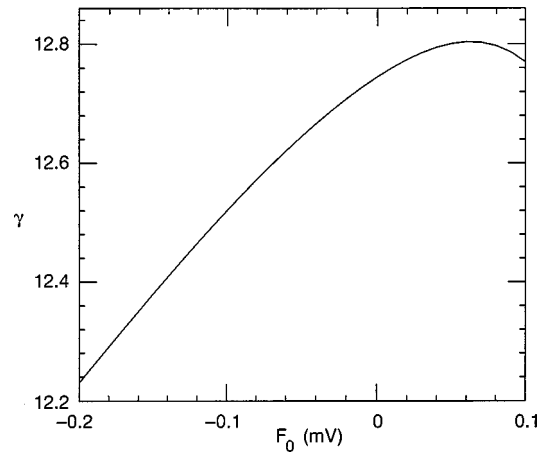


FIG. 1. Plot of  $\gamma$  versus  $F_0$  for  $rC_M/g_K=1/36$ .

out to 15 decimal places. The parameter  $r(T)C_M/g_K$  was set first at the value corresponding to the squid axon at  $6^\circ\text{C}$ , and then for several other values. For each such value,  $F_0$  was set at a succession of values. For each value of  $F_0$ , an initial guess was made for  $\gamma$ , and the system of ordinary differential equations was integrated, starting from values on the linearized trajectory close to the singular point, at which  $\Phi = \Phi_0(F_0) - 0.0001$  mV. Integration was continued until the trajectory exceeded either a positive bound of 135 mV or a negative bound of  $-135$  mV. Two values of  $\gamma$  were determined such that one resulted in a positive overshoot, the other negative; then a binary search produced a succession of values of  $\gamma$ , so as to close in on the value  $\gamma(F_0, r(T)C_M/g_K)$  which partitions the positive from the negative overshooting. Fifty iterations determined this value to better than ten significant digits.

For a temperature of  $6.3^\circ\text{C}$  and  $C_M=1$   $\mu\text{F}/\text{cm}^2$  ( $=0.01$   $\text{F}/\text{m}^2$ ), this procedure yields the results shown in Figs. 1 and 2 for  $\gamma(F_0, r(T)C_M/g_K)$  and  $\gamma^{-1}\partial\gamma/\partial F_0$ , respectively, the latter in units of  $\text{mV}^{-1}$ . For likely fields from external sources,  $|F_0| < 0.01$  mV, and in this regime Fig. 1 shows that  $\gamma(F_0, r(T)C_M/g_K)$  is well approximated by only the first

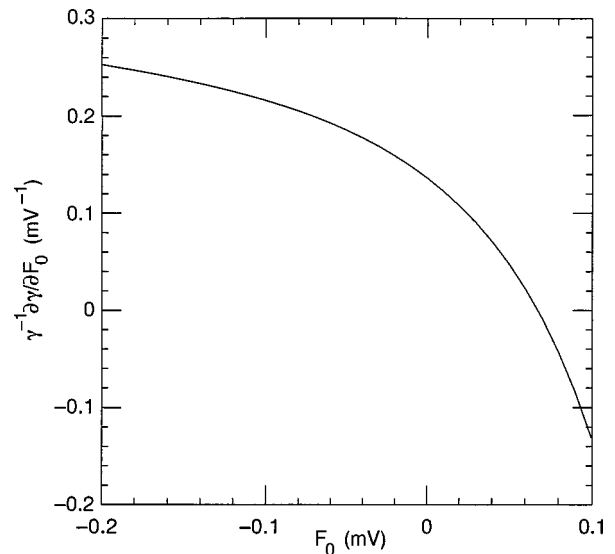


FIG. 2. Plot of  $\gamma^{-1}\partial\gamma/\partial F_0$  versus  $F_0$  for  $rC_M/g_K=1/36$ .

TABLE I. Dependence of  $\gamma$  and  $\dot{\gamma}$  on  $r(T)$  at  $F=0$ .

$r(T)C_M/g_K$	$\gamma(0)$	$\gamma(0)^{-1}\dot{\gamma}$ (mV <sup>-1</sup> )
1.00/36=0.027777777	12.743143653	0.129445819
1.50/36=0.041666666	9.760029779	0.107600697
2.00/36=0.055555555	8.029646202	0.102590168
2.50/36=0.069444444	6.877171563	0.104611181
3.00/36=0.083333333	6.044387337	0.110250898
3.50/36=0.097222222	5.409165600	0.118032410
4.00/36=0.111111111	4.905562618	0.127230295
4.50/36=0.125000000	4.494557981	0.137460700
5.00/36=0.138888888	4.151453199	0.148513560
5.50/36=0.152777777	3.859783923	0.160275428
6.00/36=0.166666666	3.608113894	0.172690892
6.50/36=0.180555555	3.388228726	0.185742098

two terms of a Taylor expansion:

$$\begin{aligned} \gamma(F_0, rC_M/g_K) &\approx \gamma(0, rC_M/g_K) \\ &+ F_0 \frac{\partial}{\partial F_0} \gamma(F_0, rC_M/g_K) \Big|_{F_0=0}. \end{aligned} \quad (53)$$

It is convenient to abbreviate the terms on the right-hand side of the approximation (53) by writing  $\gamma(0)$  for  $\gamma(0, rC_M/g_K)$  and  $\dot{\gamma}$  for  $(\partial/\partial F_0)\gamma(F_0, rC_M/g_K)|_{F_0=0}$ . Numerical computations of  $\gamma(0)$  and  $\gamma(0)^{-1}\dot{\gamma}$  in units of mV<sup>-1</sup> as functions of the temperature-dependent rate  $r(T)$  are shown in Table I.

## V. MODULATION OF PULSE TRAINS

### A. Slow variation in $F$

An estimate of the effect of a slowly oscillating incident electric field on the timing of successive pulses propagated along a nerve can now be made. The first step is to define ‘‘slowly.’’

An action potential propagating along a nerve defines time and distance scales in the normalized variables  $\tau$  and  $\zeta$ . Let  $\tau_{\text{pass}}$  be the normalized time duration for the passage of an action potential past a given position, and let  $\zeta_{\text{occ}}$  be the normalized distance along the axon occupied by an action potential at a given time. While  $\tau_{\text{pass}}$  is roughly constant from 6 to 20 °C,  $\gamma$  varies with the parameter  $rC_M/g_K$  as shown in Table I; for the axon studied by Hodgkin and Huxley  $\tau_{\text{pass}} \approx 5$ , and the corresponding  $t_{\text{pass}}$  is about 5 ms at 6.3 °C and 1.2 ms at 18.5 °C. The normalized distance along the axon occupied by an action potential at a given time is

$$\zeta_{\text{occ}} = \gamma \tau_{\text{pass}}, \quad (54)$$

which implies a physical distance  $z_{\text{occ}} \approx 6$  cm at 6 °C and 2.3 cm at 18.5 °C.

The purpose of this section is to study an axon subjected to an incident electric field gradient  $F$  along its axis that oscillates slowly with normalized position  $\zeta$  and time  $\tau$  (in contrast to the assumption of Sec. III). By *slowly* is meant

that  $F$  changes by no more than a few percent of its peak value as  $\tau$  changes by  $\tau_{\text{pass}}$  and as  $\zeta$  changes by  $\zeta_{\text{occ}}$ .

### B. Pulse trains subject to slowly varying gradients

The Hodgkin-Huxley equations have solutions not only for the isolated voltage spike studied above, but also for trains of such spikes, with nearly the same velocity as for a single spike. Consider a sequence of voltage spikes, each of which propagates along an axon along the  $z$  axis of a coordinate system, and suppose the axon is subjected to an incident electric field parallel to the axon having a gradient  $F$  defined in Eq. (43). If  $F$  varies slowly with  $\tau$  and  $\zeta$ , then each spike can be expected to vary in its speed of propagation as would a single spike propagating with a constant  $F_0$  equal to the value of  $F$  at the time and place of the spike. That is, the (normalized) time  $\tau(\zeta, \tau_A)$  at which a spike starting at  $\zeta=0$  at time  $\tau_A$  reaches position  $\zeta$  is determined by assuming that the (normalized) velocity of a spike along the way at  $(\zeta', \tau')$  is  $\gamma(F(\zeta', \tau'))$ . From this assumption of ‘‘locally flat’’ behavior follows a differential equation for the normalized time  $\tau(\zeta, \tau_A)$  at which a spike passing  $\zeta=0$  at time  $\tau_A$  reaches  $\zeta$ :

$$\frac{d}{d\zeta} \tau(\zeta, \tau_A) = 1/(\text{local velocity}) = 1/\gamma[F(\zeta, \tau(\zeta, \tau_A))]. \quad (55)$$

To solve this equation approximately, it is convenient to first transform it into an integral equation, assuming that at  $\tau = \tau_A$  the spike is at  $\zeta=0$ :

$$\tau(\zeta, \tau_A) = \tau_A + \int_0^\zeta d\zeta' \{ \gamma[F(\zeta', \tau(\zeta', \tau_A))] \}^{-1}. \quad (56)$$

Under the very reasonable assumption that a first-order Taylor expansion expresses  $\gamma(F_0)$  viewed as a function of  $F_0$  (omitting to write explicitly the dependence of  $\gamma$  on the parameter  $rC_M/g_K$ ), one has

$$\gamma[F(\zeta, \tau(\zeta, \tau_A))] = \gamma(0) + \dot{\gamma} F(\zeta, \tau(\zeta, \tau_A)), \quad (57)$$

where  $\gamma(0)$  and  $\dot{\gamma}$  are coefficients independent of  $\zeta$  and  $\tau$ :  $\gamma(0)$  is short for  $\gamma(0, rC_M/g_K)$  and

$$\dot{\gamma} \stackrel{\text{def}}{=} \frac{\partial}{\partial F_0} \gamma(F_0, rC_M/g_K) \Big|_{F_0=0}. \quad (58)$$

Substituting Eq. (57) into Eq. (56) yields

$$\begin{aligned} \tau(\zeta, \tau_A) &= \tau_A + \int_0^\zeta d\zeta' \{ \gamma(0) + \dot{\gamma} [F(\zeta', \tau(\zeta', \tau_A))] \}^{-1} \\ &\approx \tau_A + \int_0^\zeta d\zeta' \gamma(0)^{-1} \\ &\quad \times \left\{ 1 - \frac{\dot{\gamma}}{\gamma(0)} [F(\zeta', \tau(\zeta', \tau_A))] \right\} \\ &= \tau_A + \frac{\zeta}{\gamma(0)} - \frac{\dot{\gamma}}{\gamma(0)} \int_0^\zeta d\zeta' F(\zeta', \tau(\zeta', \tau_A)), \end{aligned} \quad (59)$$

which is suitable for solution by successive approximations. Let  $\tau^{(0)}(\zeta, \tau_A) = \tau_A + \zeta/\gamma(0)$  and define

$$\tau^{(n)}(\zeta, \tau_A) = \tau_A + \frac{\zeta}{\gamma(0)} - \frac{\dot{\gamma}}{\gamma(0)} \int_0^\zeta d\xi' F(\xi', \tau^{(n-1)}(\xi', \tau_A)). \quad (60)$$

When the sequence converges,  $\lim_{n \rightarrow \infty} \tau^{(n)}(\zeta, \tau_A) = \tau(\zeta, \tau_A)$ . Under the assumed conditions of ‘‘small  $F$ ,’’ the first approximation is already a good approximation:

$$\tau(\zeta, \tau_A) \approx \tau_A + \frac{\zeta}{\gamma(0)} - \frac{\dot{\gamma}}{\gamma(0)} \int_0^\zeta d\xi' F(\xi', \tau_A + \xi'/\gamma(0)). \quad (61)$$

### C. Example

As a straightforward example, let  $F(\zeta, \tau) = f_0 \cos \omega\tau$ , independent of  $\zeta$ . Then the integral in the approximation (61) is elementary and one obtains

$$\begin{aligned} \tau(\zeta, \tau_A) &= \tau_A + \frac{\dot{\gamma} f_0}{\omega \gamma(0)} \{ \sin \omega[\tau_A + \zeta/\gamma(0)] - \sin \omega \tau_A \} \\ &= \tau_A - \frac{2 \dot{\gamma} f_0}{\omega \gamma(0)} \sin[\zeta/2\gamma(0)] \cos[\tau_A + \zeta/2\gamma(0)]. \end{aligned} \quad (62)$$

Suppose a sequence of spikes is propagated starting at  $\tau_A = np$  for  $n=0, 1, 2, \dots$ . The corresponding arrival times at  $\zeta$  are  $\hat{\tau}_n$ ; then by Eq. (62) one readily computes

$$\begin{aligned} \hat{\tau}_n - \hat{\tau}_{n-1} &= p + \frac{4 \dot{\gamma} f_0}{\omega \gamma(0)} \sin \frac{\omega p}{2} \sin \frac{\omega \zeta}{2\gamma(0)} \\ &\quad \times \sin \omega \left[ \left( n - \frac{1}{2} \right) p + \frac{\zeta}{2\gamma(0)} \right]. \end{aligned} \quad (63)$$

The argument in the sine in the last factor advances by  $\omega p$  for each pulse, contributing to pulse-to-pulse variation in transmission delay. The time duration between the arrivals of spike  $n-1$  and spike  $n$  at  $\zeta$  differs from the time duration between them at transmission by the fraction

$$\begin{aligned} \frac{\Delta p}{p} &= \frac{4 \dot{\gamma} f_0}{\gamma(0) \omega p} \sin \frac{\omega p}{2} \sin \frac{\omega \zeta}{2\gamma(0)} \\ &\quad \times \sin \omega \left[ \left( n - \frac{1}{2} \right) p + \frac{\zeta}{2\gamma(0)} \right]. \end{aligned} \quad (64)$$

This modulation of the interval between spikes is bounded in magnitude by

$$\left| \frac{\Delta p}{p} \right| \leq \frac{2 \dot{\gamma} f_0}{\gamma(0)}, \quad (65)$$

which in physical units corresponds to

$$\left| \frac{\Delta p_{\text{phys}}}{p_{\text{phys}}} \right| \leq \frac{\dot{\gamma} a \sigma_{\text{in}}}{\gamma(0) g_K} \frac{\partial}{\partial z} E_z^{\text{inc}}(0, z, t). \quad (66)$$

Hence as the nerve diameter decreases, so does the modulation of pulse intervals caused by an incident electric field gradient.

An explicit example for the squid giant axon (of radius  $238 \mu\text{m}$ ) is the following. If  $\omega \approx \pi/p$  and  $\zeta \approx p\gamma(0)$ , then spikes transmitted at even intervals  $p$  arrive at  $\zeta$  with intervals that alternate between  $p[1 - 4\dot{\gamma}f_0/\pi\gamma(0)]$  and  $p[1 + 4\dot{\gamma}f_0/\pi\gamma(0)]$ . In other words, there is pulse-interval modulation, with the intervals alternately stretched and shrunk by a fraction  $4\dot{\gamma}f_0/\pi\gamma(0)$ . Shifting to physical coordinates, at a temperature of  $18.5^\circ\text{C}$ , one finds (interpolating in Table I) that  $rC_M/g_K = 3.82/36$ ,  $\gamma(0) \approx 5$ , and  $\dot{\gamma}/\gamma(0) = 0.124 \text{ mV}^{-1}$ . This implies that a gradient of  $1 \text{ mV/cm}^2$  ( $10 \text{ V/m}^2$ ) in the longitudinal component of an incident electric field at  $60 \text{ Hz}$  modulates pulse intervals transmitted every  $8.3 \text{ ms}$  along a squid giant axon of length  $16 \text{ cm}$ , producing a fractional modulation of the pulse intervals of  $1.47\%$ . It would be interesting to see if measurements confirm this.

### ACKNOWLEDGMENTS

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