

Numerical Solution of the Hodgkin–Huxley Equations in a Moving Coordinate System. Simulation of Nerve Impulse Transmission over Long Distances

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The theory required for the solution of the Hodgkin–Huxley equations for the transmission of the nerve impulse in a moving coordinate system are presented. Using this theory, simulations of the transmission of the nerve impulse over large distances (e.g., 1 m) may be carried out rapidly and accurately. The above theory may be applied to other diffusion problems by appropriate modification to the problem concerned.

1. INTRODUCTION

Considerable interest has been focused in recent years on diffusion problems in both the physical and biological sciences of which the Hodgkin–Huxley (HH) equations [1] for the transmission of a nerve impulse down a nerve axon are a prime example. In the HH equations the transmembrane potential is described by a non-linear diffusion equation coupled to three partial differential equations which, in turn, describe the dynamics of the ionic conductances. The HH equations were initially solved under the assumption of a constant propagation velocity for the nerve impulse

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which converts the four partial differential equations into three ordinary ones [1]. With the advent of large scale digital computers, a numerical solution of the complete HH equations became possible by means of numerical integration with respect to both distance and time [2, 3]. However, these solutions were limited to small lengths of axon (less than 10 cm) as the distance over which simulations could be carried out was determined by the spatial integration interval h (e.g., for a total length of 10 cm and a value of h of 0.1 cm a total of 400 ordinary differential equations is required). Despite improvements in the speed of modern computers, the problem of the number of differential equations in relation to computer time remains.

In the present paper we present a method for simulating large lengths of axon by means of a moving coordinate system such that the total number of ordinary differential equations remains relatively small (e.g., 400), the computer time to simulate lengths as long as 1 m is reasonable and a high degree of accuracy is maintained. This method may be applied to other diffusion problems by appropriate modification to the problem concerned.

2. THEORY

2.1. The HH Equations

In a static coordinate system, the non-linear diffusion equation describing the change of membrane potential as a function of time and position during the course of the propagation of a nerve impulse along an axon is given by [1]:

$$\frac{\partial V}{\partial t} = -\sum_m \frac{G_m}{C} (V - V_m) + \frac{1}{RC} \frac{\partial^2 V}{\partial x^2}. \quad (1)$$

The symbols and definitions of the variables and constants are given in Tables I and II, respectively. From Hodgkin and Huxley [1], G_m takes the forms

$$G_K = \bar{G}_K N^4, \quad G_{Na} = \bar{G}_{Na} M^3 H, \quad G_L = \bar{G}_L. \quad (2)$$

M , N and H are voltage and time dependent variables varying between 0 and 1, and are the solutions of partial differential equations of the type

$$\begin{aligned} \frac{\partial P}{\partial t} &= f(V, P) \\ &= [A_p - P(A_p + B_p)]/0.001, \end{aligned} \quad (3)$$

where P is used to represent M , N and H . The terms A_p and B_p are given by

$$\begin{aligned} A_M &= 0.1(V + 25)/\{\exp[(V + 25)/10] - 1\}, & B_M &= 4 \exp(V/18), \\ A_N &= 0.1(V + 10)/\{\exp[(V + 10)/10] - 1\}, & B_N &= 0.125 \exp(V/80), \\ A_H &= 0.07 \exp(V/20), & B_H &= 1/\{\exp[(V + 30)/10] + 1\}. \end{aligned} \quad (4)$$

TABLE I
Symbols and Definitions of the Variables in the HH Equations

Variable	Definition
t	Time (msec) in the fixed coordinate system.
T	Time (msec) in the moving coordinate system.
x	Distance (cm) along axon from stimulating electrode (fixed coordinate system).
X_i	Distance (cm) from moving origin. ($X_i = ih$, where h is the spatial integration interval.)
$V_i(t)$	Membrane potential (mV) at the i th segment measured in the sense of internal minus external potential. The resting potential V_{rest} has a value of 0.
$I_{i,m}(t)$	Ionic current per unit length of axon ($\mu A/cm$) at the i th segment of the m th species, where m is the sodium (Na), potassium (K) and non-specific leakage (L) components.
M_i, N_i, H_i	Hodgkin-Huxley conductance variables (dimensionless) at the i th segment (M_{rest}, N_{rest} and H_{rest} are the resting values of M, N and H , respectively).

TABLE II
Symbols and Definitions of the Constants in the HH Equations^a

Constant	Definition (value)
h	Spatial integration interval (0.1 cm). [Also known as the spatial increment or the spatial mesh.]
a	Radius of axon (0.05 cm).
C	Capacitance per unit length of axon ($\pi \times 10^{-7} \mu F/cm$).
ρ	Specific resistance of axoplasm (30 ohm · cm).
R	Resistance per unit length of axon (3820 ohm/cm). [$R = \rho/(\pi a^2)$.]
\bar{G}_{Na}	Maximum sodium conductance per unit length of axon (37.7 mmho/cm).
\bar{G}_K	Maximum potassium conductance per unit length of axon (11.3 mmho/cm).
\bar{G}_L	Non-specific leakage conductance per unit length of axon (0.094 mmho/cm).
V_m	Equilibrium potential of the m th species ($V_{Na} = +115$ mV, $V_K = -12$ mV and $V_L = +10.6$ mV).
V_{stim}	Membrane potential during stimulation (+30 mV).
u	Velocity of moving axes (18.80 m · sec ⁻¹).

^a The values of the constants used in the numerical solution presented in this paper are shown in parentheses.

The partial differential equations (1) and (3) cannot be solved analytically so that one is limited to a numerical solution. The numerical solution of Eqs. (1) and (3) requires the conversion of the partial differential equations into a set of ordinary differential equations by means of an appropriate finite difference approximation involving spatial discretization. For reasonable accuracy in the spatial discretization it is necessary to take a value for the spatial increment $h \lesssim 0.1$ cm [2, 3], and for reasonable economy of the numerical solution one cannot afford much more than 100

segments (400 dependent variables). Thus, in a static coordinate system the length L of axon simulated is restricted to about 10 cm, which can comfortably accommodate the pulse without serious end effects. To extend the length of axon simulated therefore requires the use of a moving coordinate system.

2.2. *Solution of the HH Equations in a Moving Coordinate System*

To change from a static coordinate system t, x to a moving coordinate system T, X , we make the transformation

$$\begin{aligned} T &= t, \\ X &= x - ut - c, \end{aligned} \tag{5}$$

where u is the velocity of the moving origin X , and c is a constant. Then

$$\begin{aligned} \frac{\partial}{\partial t} &= \frac{\partial T}{\partial t} \frac{\partial}{\partial T} + \frac{\partial X}{\partial t} \frac{\partial}{\partial X} \\ &= \frac{\partial}{\partial T} - u \frac{\partial}{\partial X} \end{aligned} \tag{6}$$

and

$$\begin{aligned} \frac{\partial}{\partial x} &= \frac{\partial T}{\partial x} \frac{\partial}{\partial T} + \frac{\partial X}{\partial x} \frac{\partial}{\partial X} \\ &= \frac{\partial}{\partial X}. \end{aligned} \tag{7}$$

Therefore, combining Eqs. (1), (3), (6) and (7) we obtain the partial differential equations describing the behaviour of the membrane potential V and the normalized ionic conductance variables P as a function of time and position in a moving coordinate system:

$$\frac{\partial V}{\partial T} - u \frac{\partial V}{\partial X} = -\sum_m \frac{G_m}{C} (V - V_m) + \frac{1}{RC} \frac{\partial^2 V}{\partial X^2}, \tag{8}$$

$$\frac{\partial P}{\partial t} - u \frac{\partial P}{\partial X} = f(V, P). \tag{9}$$

Ahead of the pulse, V and P have their resting values V_{rest} and P_{rest} so that appropriate boundary conditions at $X = L$ are

$$V = V_{\text{rest}}, \quad P = P_{\text{rest}} = A_p / (A_p + B_p) \tag{10}$$

evaluated at V_{rest} . These are also the initial values at $t = 0$. Behind the pulse, however, V and P have values close to V_{rest} and P_{rest} , respectively, but not exactly equal to them since there is a relatively slow final relaxation of no significance. What

matters in choosing the boundary conditions at $X = 0$ is to avoid unreal reflections at the $X = 0$ boundary caused by the finite number of grid points in the finite difference approximation; since in fact $\partial V/\partial X$ and $\partial P/\partial X$ are very small behind the pulse, it is appropriate to choose boundary conditions which avoid any upstream propagation. This is achieved by imposing the boundary conditions

$$\partial V/\partial X = 0, \quad \partial P/\partial X = 0 \quad (11)$$

at $X = 0$, which are consistent as can be seen by differentiating Eq. (3) with respect to x and using Eq. (7). The use of a moving coordinate system, and therefore the need for boundary conditions on P , does not start until the stimulation pulse has ended; the first equation of (11) is modified during the pulse (see Eq. (14)).

To extend the effective length of axon simulated, we switched from the static coordinate system to the moving coordinate system as soon as the pulse was well in the middle of the first 10 cm of axon, experimenting with the velocity u of the moving origin until the pulse moved only slowly relative to it, and so stayed nearly centred in the now (moving) 10-cm length. It was easy to choose this velocity so that we could simulate the transmission of the nerve impulse along approximately 1 m of axon, without having the pulse shape affected by the boundaries; this was helped by imposing the boundary conditions (10) and (11) to Eqs. (8) and (9).

Equations (8) and (9) are discretized as

$$\begin{aligned} \frac{dV_i}{dT} = & -\sum_m \frac{G_m}{C} (V_i - V_m) + \left(\frac{1}{RCh^2} + \frac{u}{2h} \right) (V_{i+1} - V_i) \\ & + \left(\frac{1}{RCh^2} - \frac{u}{2h} \right) (V_{i-1} - V_i) \end{aligned} \quad (12)$$

and

$$\frac{dP_i}{dT} = f(V_i, P_i) + \frac{u}{2h} (P_{i+1} - P_i) - \frac{u}{2h} (P_{i-1} - P_i), \quad (13)$$

respectively. Equations (12) and (13) apply for $0 < i < n$. Taking the boundary conditions (11) into account, and noting that $u = 0$ during the stimulus, we have at $X = 0$

$$\frac{dV_0}{dT} = -\sum_m \frac{G_m}{C} (V_0 - V_m) + \left(\frac{1}{RCh^2} + \frac{u}{2h} \right) (V_1 - V_0) + \frac{S_1}{RCh^2} (V_{\text{stim}} - V_0), \quad (14)$$

where $S_1 = 1$ during the stimulus and 0 otherwise (thus applying a constant stimulus voltage $V_{-1} = V_{\text{stim}}$ for a fixed time, after which we take $V_{-1} = V_0$), and similarly

$$\frac{dP_0}{dT} = f(V_0, P_0) + \frac{u}{2h} (P_1 - P_0). \quad (15)$$

At $i = n$, we use Eqs. (12) and (13) with the boundary conditions (10) applied at $i = (n + 1)$, obtaining

$$\begin{aligned} \frac{dV_n}{dT} = & -\sum_m \frac{G_m}{C} (V_n - V_m) + \left(\frac{1}{RC h^2} + \frac{u}{2h} \right) (V_{\text{rest}} - V_n) \\ & + \left(\frac{1}{RC h^2} - \frac{u}{2h} \right) (V_{n-1} - V_n), \end{aligned} \quad (16)$$

$$\frac{dP_n}{dT} = f(V_n, P_n) - \frac{u}{2h} (P_{n-1} - P_n) + \frac{u}{2h} (P_{\text{rest}} - P_n). \quad (17)$$

In practice, we introduced an additional switch variable S_2 , replacing u by $S_2 u$ everywhere in Eqs. (12) to (17), so that we could switch to the moving coordinate system by changing S_2 from 0 to 1 (and restarting the numerical integration to allow for the discontinuity).

Since Eqs. (14) and (15) effectively apply the boundary conditions (11) at $X = -\frac{1}{2}h$, while Eqs. (16) and (17) apply the boundary conditions (10) at $i = (n + 1)$, the length simulated while using moving coordinates, is given accurately by $L = (n + \frac{3}{2})h$. However, this is an unimportant quantity; the constancy of pulse shape and the propagation velocity are more interesting.

3. COMPUTATION

Numerical integration was performed by means of the program FACSIMILE which employs a modified version of Gear's backward differentiation method [4] together with sparse matrix handling subroutines, automatic sparsity pattern determination, automatic initial step size selection and a problem oriented high level language [5-7]. All computations were performed on an IBM-370/168 computer (AERE, Harwell) and the storage requirement was 540 kbytes.

The HH equations ((1) to (5)) are stiff because of the interactions between the membrane potential V and the three dimensionless conductance variables M , N and H . The FACSIMILE program offers much more (namely, a problem oriented high level language) than available solvers using band matrix techniques, which require Fortran coding for derivative evaluation and, in highly non-linear cases such as this one, Jacobian matrix evaluation. The FACSIMILE program was therefore chosen to minimize problem solving time rather than computer time; nevertheless, the FACSIMILE numerical integrator is competitive in terms of computer time with solvers using band matrix techniques [7, 8].

The length of the spatial mesh h was chosen by first solving the problem on a coarser mesh and then estimating how fine a mesh was needed for accurate representation of the pulse shape and spatial derivatives. The value of h used in the simulations presented in this paper was 0.1 cm.

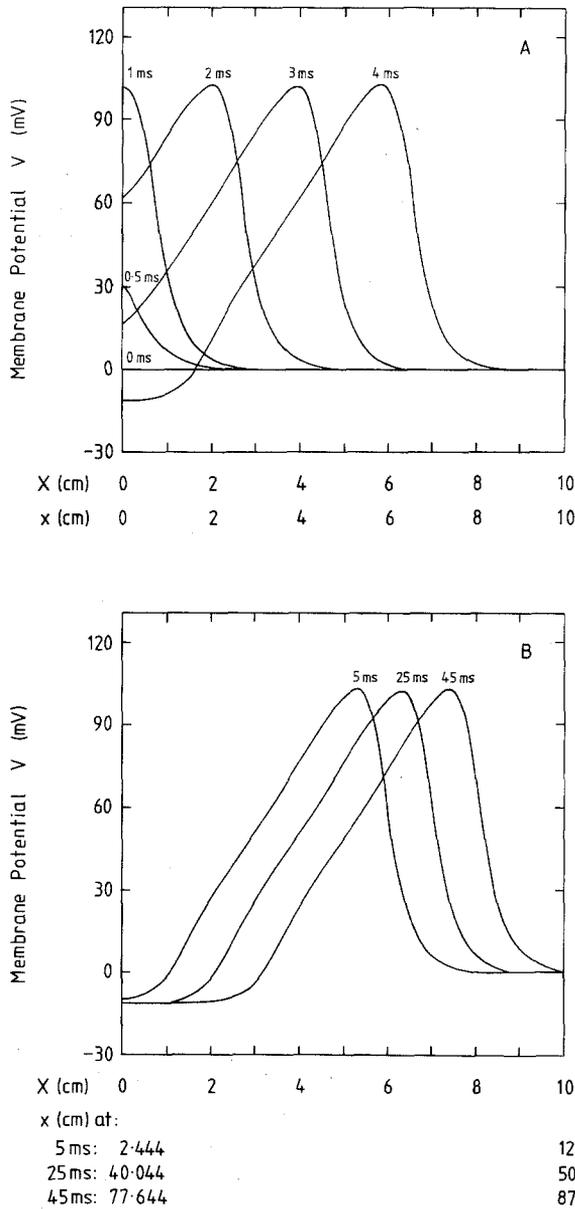


FIG. 1. Simulation of the transmission of a nerve impulse down an axon in static (A) and moving (B) coordinate systems. The first element of the axon is stimulated at $t = 0$ sec by making the membrane potential 30 mV more positive for 0.5 msec; from 0.5 to 3.7 msec the coordinate system remains static (A). From 3.7 to 50 msec the coordinate system is made to move at a velocity of $18.80 \text{ m} \cdot \text{sec}^{-1}$ (B).

Error control on T integration was based on a tolerance of 10^{-3} on a relative truncation error estimate per step, which has been thoroughly validated on many test problems [7, 8].

The complete solution of the HH equations presented in this paper involves starting the integration procedure three times owing to discontinuities: at $t = 0$ sec when the the axon is stimulated, at $t = 0.5$ msec when the stimulus is switched off, and at 3.7 msec when the coordinate system is made to move. The respective starting integration step sizes chosen by FACSIMILE were 7.7690×10^{-16} , 1.0709×10^{-6} and 3.8484×10^{-7} sec.

4. RESULTS

The results of the simulation of the transmission of a nerve impulse along approximately 1 m of axon are shown in Fig. 1. At $t = 0$ sec the first element of the axon is stimulated by making the membrane potential 30 mV more positive for a period of 0.5 msec. From 0.5 to 3.7 msec the coordinate system remains static. From 3.7 to 50 msec the coordinate system is made to move at a velocity u of $18.80 \text{ m} \cdot \text{sec}^{-1}$ so that from Eq. (5) the distance x (in metres) along the axon from the point of stimulation is given by

$$x = X + 18.80(t - 3.7 \times 10^{-3}).$$

The value of u was chosen so as to make the pulse move slowly relative to the moving coordinate so that the transmission of the pulse along approximately 1 m of axon could be simulated without having the pulse shape affected by the boundaries (see Section 2.2).

By graphical measurements on Fig. 1 (measuring the position along the axon of the peak of the pulse at different times), we find that the steady state velocity is $19.30 \text{ m} \cdot \text{sec}^{-1}$ and is reached very rapidly (by $t = 2$ msec). (It should be noted that the value we obtain for the steady state velocity is different from that obtained by Cooley and Dodge [2] and Moore *et al.* [3] because the values chosen for the resistivity and axon radius are slightly different, see Table II.) From 4 msec onwards the waveform of the pulse remains unaltered.

The total computer time required for the simulation in Fig. 1 was approximately 3 min on an IBM-370/168 computer. By choosing the velocity of the moving axes u to be $19.30 \text{ m} \cdot \text{sec}^{-1}$, equal to the velocity of the nerve impulse, an even greater length of axon could be simulated.

5. DISCUSSION

The numerical solution of the HH equations presented here makes no assumption as to a constant propagation velocity and uniform waveform which were assumptions

in the original solution of Hodgkin and Huxley [1]. Although the numerical solution of the complete HH equations does not offer rigorous proof of the above assumption, we have shown that the steady state velocity of the nerve impulse remains unaltered over long distances (approx. 1 m), and that the solution of the ordinary differential equations derived on the assumption of a constant propagation velocity agrees with the solution of the partial differential equations once the steady state velocity and waveform have been established. Thus, we have shown that the solution of the complete set of HH equations is stable over long distances (i.e., no oscillations are observed, and no progressive damping and decay of the impulse is seen).

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