SOLUTIONS TO AXON EQUATIONS

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ABSTRACT The solutions to a general class of axon partial differential equations proposed by FitzHugh which includes the Hodgkin-Huxley equations are studied. It is shown that solutions to the partial differential equations are exactly the solutions to a related set of integral equations. An iterative procedure for constructing the solutions based on standard methods for ordinary differential equations is given and each set of initial values is shown to lead to a unique solution. Continuous dependence of the solutions on the initial values is established and solutions with initial values in a restricted (physiological) range are shown to remain in that range for all time. The iterative procedure is not suggested as the basis for numerical integration.

I. INTRODUCTION

Hodgkin and Huxley in reference 1 postulated that transmembrane voltage $V(x, t)$ and other state variables $m(x, t)$, $h(x, t)$, and $n(x, t)$ governing specific ionic conductances in the giant axon of the squid should be solutions of the following system of partial differential equations

$$\frac{\partial V}{\partial t} - \frac{\partial^2 V}{\partial x^2} = g_{\mathrm{Na}} m^3 h(V_{\mathrm{Na}} - V) + g_{\mathrm{K}} n^4 (V_{\mathrm{K}} - V) + g_L (V_L - V),$$

$$\frac{\partial m}{\partial t} = \frac{m_\infty - m}{\tau_m},$$

$$\frac{\partial h}{\partial t} = \frac{h_\infty - h}{\tau_h},$$

$$\frac{\partial n}{\partial t} = \frac{n_\infty - n}{\tau_n}. \qquad (1)$$

Here the independent variables x (distance along the axon) and t (time) are given in units of the respective length and time constants for the axon in order to eliminate the constant coefficients multiplying the partial derivatives of V in reference 1. The other letters occurring in equations 1 designate empirically determined constants and infinitely differentiable functions of the voltage V as listed in the following.

Constants

g_{Na} = maximum sodium conductance.
g_K = maximum potassium conductance.
g_L = conductance of remaining (leakage) ions.
V_{Na} = sodium equilibrium potential.
V_K = potassium equilibrium potential.
V_L = equilibrium potential of remaining (leakage) ions.

Functions of V

m_∞ = steady-state value of m at voltage V.
h_∞ = steady-state value of h at voltage V.
n_∞ = steady-state value of n at voltage V.
τ_m = relaxation time of m at voltage V.
τ_h = relaxation time of h at voltage V.
τ_n = relaxation time of n at voltage V.

The constants g_{Na}, g_K, and g_L are positive while the given functions of V satisfy the restrictions

$$0 < m_\infty(V),\ h_\infty(V),\ n_\infty(V) < 1$$
$$0 < \tau_m(V),\ \tau_h(V),\ \tau_n(V) \qquad (2)$$

for all values of V.

Hodgkin and Huxley examined those solutions of equations 1 with each of the unknown functions in the form of an unmodulated wave traveling with constant velocity l down the axon so that $l^2(\partial^2V/\partial x^2) = \partial^2V/\partial t^2$. This yields a system of ordinary differential equations on substitution into equations 1. In references 2–4, the numerical integration of these ordinary differential equations by digital computer was given and in references 5 and 6 numerical integration by digital computer was reported for the system of partial differential equations 1 without restrictions on the wave form.

In this paper we study directly all solutions of a general class of systems of partial differential equations proposed by FitzHugh (7) which includes the Hodgkin-Huxley equations 1 as well as the systems of equations of FitzHugh (8) and Rall (9). We consider equations of the form

$$\frac{\partial V}{\partial t} - \frac{\partial^2 V}{\partial x^2} = f(V, W^1, \cdots, W^n),$$
$$\frac{\partial W^j}{\partial t} = g^j(V, W^1, \cdots, W^n) \text{ for } j = 1, 2, \cdots, n, \qquad (3)$$

with $V(t, x)$ the transmembrane voltage and $W^1(x, t), \cdots, W^n(x, t)$ auxillary state variables. Again x and t are given in units of the respective length and time constants for the axon.

The differential operator $(\partial/\partial t) - (\partial^2/\partial x^2)$ appearing on the left side of the first equation in equations 3 is that occurring in the diffusion or heat equation. This differential operator may be inverted by using the fundamental solution

$$F(x, y, t) = \frac{1}{2\sqrt{\pi t}} e^{-(x-y)^2/4t} \tag{4}$$

for the diffusion equation. The differential operator $\partial/\partial t$ in the remaining equations is inverted simply by integrating in time. This yields a system of integral equations equivalent to the initial value problem for equations 3 which may be solved by an iterative procedure modeled on Picard's method for solving the initial value problem for an ordinary differential equation.

We show that for arbitrary bounded initial values there exists a unique solution of equations 3 which may be constructed by iteration. This solution is defined for all $t > 0$ and is continuously dependent on the initial values. Under additional assumptions met by equations 1 it is shown that a solution with initial values in a restricted (physiological) range has values which remain in this range for all $t > 0$.

Section II deals with the fundamental solution to the diffusion equation. This fundamental solution is used in section III to derive a system of integral equations equivalent to equations 3 and in section IV an iteration procedure based on these integral equations is developed and proof of the convergence of this procedure to a solution to equations 3 is given. In section V a theorem on the continuous dependence of the solutions to equations 3 on the initial values is given and in section VI this result is used in showing that under added assumptions, satisfied by the Hodgkin-Huxley equation and others, solutions with initial values in a certain region have values in this region for all time. In the final section some concluding remarks are made.

II. THE FUNDAMENTAL SOLUTION TO THE DIFFUSION EQUATION

The function $F(x, y, t)$ given in equation 4 satisfies the diffusion equation with no source term

$$\left(\frac{\partial}{\partial t} - \frac{\partial^2}{\partial x^2}\right) F(x, y, t) = 0, \tag{5}$$

for each y and for $t > 0$ and has the property that

$$F(x, y, t) > 0 \quad \text{for all} \quad x, y \quad \text{and for all} \quad t > 0; \tag{6}$$

and that

$$\int_{-\infty}^{\infty} F(x, y, t)\, dy = 1 \quad \text{for all} \quad x \quad \text{and all} \quad t > 0. \tag{7}$$

More general solutions to the diffusion equation can be constructed using F. For $a(x)$, a bounded continuous function, the function

$$A(x, t) = \int_{-\infty}^{\infty} F(x, y, t)a(y)\, dy \tag{8}$$

is infinitely differentiable and satisfies

$$\left(\frac{\partial}{\partial t} - \frac{\partial^2}{\partial x^2}\right) A(x, t) = 0 \tag{9}$$

for $t > 0$ and all x with

$$\lim_{\substack{t \to 0 \\ t > 0}} A(x, t) = a(x) \tag{10}$$

for all x. For $b(x, t)$ bounded and continuous and for all x and $0 \leq t \leq T$ the function

$$B(x, t) = \int_0^t \int_{-\infty}^{\infty} F(x, y, t - s)b(y, s)dy\, ds \tag{11}$$

is continuous and $(\partial B/\partial x)(x, t)$ exists and is continuous for all x and $0 \leq t \leq T$. If $(\partial b/\partial x)(x, t)$ exists and is continuous for all x and $0 \leq t \leq T$, then $(\partial B/\partial t)(x, t)$ and $(\partial^2 B/\partial x^2)(x, t)$ exist, and $B(x, t)$ satisfies

$$\left(\frac{\partial}{\partial t} - \frac{\partial^2}{\partial x^2}\right) B(x, t) = b(x, t) \tag{12}$$

for all x and $0 < t \leq T$ with

$$\lim_{\substack{t \to 0 \\ t > 0}} B(x, t) = 0. \tag{13}$$

We now state proposition 1.

Proposition 1

Suppose that $a(x)$, $b(x, t)$, $(\partial b/\partial x)(x, t)$ are bounded and continuous for $0 \leq t \leq T$ and all x. Then the unique bounded solution to

$$\left(\frac{\partial}{\partial t} - \frac{\partial^2}{\partial x^2}\right) u(x, t) = b(x, t) \tag{14}$$

with

$$\lim_{\substack{t \to 0 \\ t > 0}} u(x, t) = a(x) \tag{15}$$

is given for $0 < t \leq T$ by the formula

$$u(x, t) = \int_{-\infty}^{\infty} F(x, y, t)a(y)\, dy + \int_0^t \int_{-\infty}^{\infty} F(x, y, t - s)b(y, s)dy\, ds. \quad (16)$$

The solution $u(x, t)$ is continuous for $0 \leq t \leq T$; $(\partial u/\partial t)(x, t)$ and $(\partial^2 u/\partial x^2)(x, t)$ are continuous for $0 < t \leq T$.

If the initial function $a(x)$ has a continuous bounded derivative then $(\partial u/\partial x)(x, t)$ exists and is continuous for $0 \leq t \leq T$.

This standard material is found in reference 1.

III. THE SYSTEM OF INTEGRAL EQUATIONS

To simplify the discussion we will assume throughout most of this paper that $n = 1$ in equations 3. The reader can easily modify the discussion to treat the case of arbitrary positive integers n. Also we will write W for W^1 and g for g^1 so that the initial value problem for equations 3 takes the form

$$\begin{aligned}
\left(\frac{\partial}{\partial t} - \frac{\partial^2}{\partial x^2}\right) V(x, t) &= f(V(x, t), W(x, t)), \quad \text{for} \quad 0 < t \leq T, \\
\frac{\partial}{\partial t} W(x, t) &= g(V(x, t), W(x, t)), \quad \text{for} \quad 0 < t \leq T, \\
V(x, 0) &= \varphi(x), \\
W(x, 0) &= \psi(x). \qquad (17)
\end{aligned}$$

We now show that the solutions to equations 17 are exactly' the solutions to a system of integral equations.

Theorem 1

Suppose that $f(V, W)$ and $g(V, W)$ have continuous bounded partial derivatives for all V and W and that the initial values $\varphi(x)$ and $\psi(x)$ and $(\partial\varphi/\partial x)(x)$ and $(\partial\psi/\partial x)(x)$ are continuous and bounded for all x. Then $V(x, t)$ and $W(x,' t)$ are solutions of equations 17 with V, W, $\partial V/\partial x$ and $\partial W/\partial x$ bounded for $0 \leq t \leq T$ and with $\partial V/\partial t$ and $\partial^2 V/\partial x^2$ continuous for $0 < t \leq T$ if and only if $V(x, t)$ and $W(x, t)$ are bounded and continuous for $0 \leq t \leq T$ and are solutions of the system of integral equations

$$V(x, t) = \int_{-\infty}^{\infty} F(x, y, t)\varphi(y)\, dy + \int_0^t \int_{-\infty}^{\infty} F(x, y, t - s)f(V(y, s), W(y, s))\, dy\, ds, \quad (18\,a)$$

$$W(x, t) = \psi(x) + \int_0^t g(V(x, s), W(x, s))\, ds. \quad (18\,b)$$

Proof. If V and W are solutions of equations 17 with the properties stated, then $f(V(x, t), W(x, t))$ and $g(V(x, t), W(x, t))$ and their x derivatives are continuous and bounded for $0 \leq t \leq T$ and all x so that an application of equation 16 to the first equation in equations 17 yields equation 18 a and integration of the second equation in equations 17 from 0 to t yields equation 18 b.

Now suppose that V and W are bounded continuous solutions of equations 18 a and b. The existence and continuity of $(\partial W/\partial t)(x, t)$ as well as the validity of the second of equations 17 follow from the fundamental theorem of calculus. The fourth equation in equations 17 is immediate.

The x derivative of the first integral in equation 18 a is given by

$$\int_{-\infty}^{\infty} F(x, y, t) \frac{d\varphi}{dy}(y)\, dy$$

and is therefore continuous and bounded for $0 \leq t \leq T$, and by the remark after equation 11, the x-derivative of the second integral in equation 18 a is continuous and bounded for $0 \leq t \leq T$.

We now consider equation 18 b as an ordinary differential equation in t for the function $W(x, t)$ with x as a parameter. Because the initial value $\psi(x)$ and the inhomogenous term $g(V(x, t), W)$ in this equation have continuous and bounded first partial derivatives with respect to the parameter x, the solution $W(x, t)$ also has a continuous and bounded x-derivative for $0 \leq t \leq T$. (See reference 11.)

Finally because we now have that $f(V(x, t), W(x, t))$ has a continuous and bounded x-derivative for $0 \leq t \leq T$, we can apply proposition 1 to conclude that $(\partial V/\partial t)(x, t)$ and $(\partial^2 V/\partial x^2)(x, t)$ are continuous for $0 < t \leq T$ and that the first and third of equations 17 are satisfied.

IV. THE ITERATION PROCEDURE

To obtain solutions to equations 18 a and b with initial values φ, ψ, we set

$$V_0(x, t) = \varphi(x) \quad \text{and} \quad W_0(x, t) = \psi(x) \quad \text{for} \quad 0 \leq t \leq T \quad \text{and all} \quad x.$$

Once $V_j(x, t)$ and $W_j(x, t)$ have been defined for $j \geq 0$ we set

$$V_{j+1}(x, 0) = \varphi(x), \quad W_{j+1}(x, 0) = \psi(x)$$

and

$$V_{j+1}(x, t) = \int_{-\infty}^{\infty} F(x, y, t)\varphi(y)\, dy + \int_0^t \int_{-\infty}^{\infty} F(x, y, t - s) f(V_j(y, s), W_j(y, s))\, dy\, ds, \quad (19\ a)$$

$$W_{j+1}(x, t) = \psi(x) + \int_0^t g(V_j(x, s), W_j(x, s))\, ds \quad (19\ b)$$

for $t > 0$. The resulting sequences of functions $\{V_j(x, t)\}$ and $\{W_j(x, t)\}$ are defined and continuous for $0 \leq t \leq T$ and all x. We will show that these sequences converge uniformly to a solution of equations 18 *a* and *b*.

Since φ and ψ are bounded by hypothesis and $F(x, y, t)$ has integral 1 over $-\infty < y < +\infty$ for each $t > 0$, it follows by induction that each of the functions V_j and W_j is bounded.

Let $\rho_j(t)$ be the least upper bound for all x of

$$| V_j(x, t) - V_{j-1}(x, t) | + | W_j(x, t) - W_{j-1}(x, t) |$$

for $0 \leq t \leq T$ and let L be an upper bound for

$$\left| \frac{\partial f}{\partial V}(V, W) \right|, \left| \frac{\partial f}{\partial W}(V, W) \right|, \left| \frac{\partial g}{\partial V}(V, W) \right|, \left| \frac{\partial g}{\partial W}(V, W) \right|$$

for all V and W. Then by the mean value theorem of calculus

$$|f(V_j(x, t), W_j(x, t)) - f(V_{j-1}(x, t), W_{j-1}(x, t))| \leq L\rho_j(t) \qquad (20)$$

and

$$| g(V_j(x, t), W_j(x, t)) - g(V_{j-1}(x, t), W_{j-1}(x, t)) | \leq L\rho_j(t). \qquad (21)$$

Therefore equations 19 *a* and *b* yield

$$| V_{j+1}(x, t) - V_j(x, t) | \leq \int_0^t \int_{-\infty}^{\infty} F(x, y, t - s)L\rho_j(s)\, dy\, ds$$

$$= L \int_0^t \rho_j(s)\, ds \quad \text{for all} \quad x \quad \text{and for} \quad 0 \leq t \leq T \qquad (22)$$

and

$$| W_{j+1}(x, t) - W_j(x, t) |$$

$$\leq L \int_0^t \rho(s)\, ds \quad \text{for all} \quad x \quad \text{and for} \quad 0 \leq t \leq T. \qquad (23)$$

On adding equations 22 and 23 we obtain

$$\rho_{j+1}(t) \leq 2L \int_0^t \rho_j(s)\, ds \quad \text{for} \quad 0 \leq t \leq T \quad \text{and} \quad j = 1, 2, \cdots. \qquad (24)$$

If K is then a bound on $\rho_1(t)$ for $0 \leq t \leq T$ we have

$$\rho_1(t) \leq K, \rho_2(t) \leq K\, 2Lt, \cdots, \rho_{j+1}^{(t)} \leq \frac{K(2Lt)^j}{j!}, \cdots. \qquad (25)$$

Thus

$$\sum_{j=1}^{\infty} \rho_j(t) \leq \sum_{j=1}^{\infty} K \frac{(2Lt)^{j-1}}{(j+1)!} = Ke^{2Lt}$$

and the sequences $\{V_j\}$ and $\{W_j\}$ converge uniformly to limit functions $V(x, t)$ and $W(x, t)$. Moreover by equations 20 and 21 the limit functions satisfy the integral equations 18 *a* and *b*.

The solution is unique, for suppose that $\tilde{V}(x, t)$, $\tilde{W}(x, t)$ is also a continuous bounded solution with initial values $\varphi(x)$ and $\psi(x)$, respectively. Then if $\rho(t)$ is the least upper bound for all x of $| V(x, t) - \tilde{V}(x, t) | + | W(x, t) - \tilde{W}(x, t) |$ calculations similar to those leading to equations 24 and 25 show that

$$\rho(t) \leq L2 \int_0^t \rho(s)\, ds$$

and thus $\rho(t) \leq (2LT)^j/j!$ for $0 \leq t \leq T$ and all $j \leq 1$. This shows that $\rho(t)$ is zero and hence that $V = \tilde{V}$ and $W = \tilde{W}$.

We state these results as the main theorem.

Theorem 2

The sequence $(V_m(x, t), W_m(x, t))$ converges uniformly to a solution $(V(x, t), W(x, t))$, of equation 17 and of equations 18 *a* and *b* for all x and for $0 \leq t \leq T$. The solution is the unique solution with $V(x, 0) = \varphi(x)$ and $W(x, 0) = \psi(x)$ for all x.

We remark here that this method would share all the disadvantages of Picard's method (for ordinary differential equations) if used as the basis for numerical integration.

V. CONTINUOUS DEPENDENCE ON INITIAL VALUES

The following theorem shows that two solutions of equations 3 remain close over a finite interval for bounded time provided the initial conditions are sufficiently close over a sufficiently large finite interval. We will apply this result in the next section of the paper.

Theorem 3

Let I be an arbitrary finite interval and M, ϵ, T arbitrary positive constants. There is a finite interval J and a $\delta > 0$ such that solutions $(V(x, t), W(x, t))$ and $(\tilde{V}(x, t), \tilde{W}(x, t))$ of equations 3 will satisfy

$$| V(x, t) - \tilde{V}(x, t) |, \quad | W(x, t) - \tilde{W}(x, t) | < \epsilon \quad \text{for} \quad x \quad \text{in} \quad I, \quad 0 \leq t \leq T \qquad (26)$$

provided

$$| V(x, 0) - \tilde{V}(x, 0) |, \quad | W(x, 0) - \tilde{W}(x, 0) | < \delta \quad \text{for} \quad x \quad \text{in} \quad J \tag{27}$$

and

$$| V(x, 0) |, \quad | W(x, 0) |, \quad | \tilde{V}(x, 0) |, \quad | \tilde{W}(x, 0) | \leq M \quad \text{for all} \quad x. \tag{28}$$

Proof. Since V, W, $\tilde{V}$, and $\tilde{W}$ are uniform limits of sequences $\{V_m\}$, $\{W_m\}$, $\{\tilde{V}_m\}$, and $\{\tilde{W}_m\}$ constructed by the iteration procedure defined by equations 19 *a* and *b* and since the rate of convergence depends only on L and M, there is an integer m such that $| V(x, t) - V_m(x, t) |$, $| W(x, t) - W_m(x, t) |$, $| \tilde{V}(x, t) - \tilde{V}_m(x, t) |$, and $| \tilde{W}(x, t) - \tilde{W}_m(x, t) |$ are less than $\epsilon/3$ for $0 \leq t \leq T$ and all x. Therefore it suffices to show that there exist $\delta > 0$ and J such that equation 27 implies $| V_m(x, t) - \tilde{V}_m(x, t) | < \epsilon/3$, $| W_m(x, t) - \tilde{W}_m(x, t) | < \epsilon/3$ for x in I and $0 \leq t \leq T$. Set $I_m = I$ and $\delta_m = \epsilon/3$. Define $\delta_j = \delta_{j+1}/(1 + 2M + 2LT + 2LPT)$ for $0 \leq j \leq m - 1$ where P is a bound on all iterates of equation 19 *a* and *b* for all x and $0 \leq t \leq T$ with initial conditions bounded by M.

Choose $\sigma_j (0 \leq j < m)$ such that

$$\frac{2}{\sqrt{\pi}} \int_{\sigma_j/\sqrt{4T}}^{\infty} e^{-t^2} \, dt < \delta_j$$

and define intervals $I_{m-1}, I_{m-2}, \cdots, I_0$ by requiring that I_j be the interval I_{j+1} expanded by σ_j in each direction. Set $\delta = \delta_0$ and $J = I_0$. Repeated application of the following lemma completes the proof of the theorem.

Lemma 2

If $| V_k(x, t) - \tilde{V}_k(x, t) |$, $| W_k(x, t) - \tilde{W}_j(x, t) | < \delta_k$ for x in I_k, then $| V_{k+1}(x, t) - \tilde{V}_{k+1}(x, t) |$, $| W_{k+1}(x, t) - \tilde{W}_{k+1}(x, t) | < \delta_{k+1}$ for x in I_{k+1}.

Proof. Let I_k^c consist of all x not in I_k; then we have

$$\begin{aligned} &| V_{k+1}(x, t) - \tilde{V}_{k+1}(x, t) | \\ &= \left| \int_{-\infty}^{\infty} (V_k(y, 0) - \tilde{V}_k(y, 0)) F(x, y, t) \, dy + \int_0^t \int_{-\infty}^{\infty} (f(V_k(y, s), W_k(y, s)) \right. \\ &\quad \left. - f(\tilde{V}_k(y, s), \tilde{W}_k(y, s))) F(x, y, t - s) \, dy \, ds \right| \leq \delta_k \int_{I_k} F(x, y, t) \, dy \\ &\quad + 2M \int_{I_k^c} F(x, y, t) \, dy + 2L\delta_k \int_0^t \int_{I_k} F(x, y, t - s) \, dy \, ds \\ &\quad + 2LP \int_0^t \int_{I_k^c} f(x, y, t - s) \, dy \, ds. \end{aligned}$$

Now

$$\int_{|x-y|\geq\sigma} F(x, y, t)\, dy = \frac{2}{\sqrt{\pi}} \int_{\sigma/\sqrt{4t}}^{\infty} e^{-z^2}\, dz \leq \frac{2}{\sqrt{\pi}} \int_{\sigma/\sqrt{4T}}^{\infty} e^{-z^2}\, dz$$

so that if x is in I_{k+1} we have

$$| V_{k+1}(x, t) - \tilde{V}_{k+1}(x, t) | \leq \delta_k + 2M\delta_k + 2L\delta_k T + 2LPT\delta_k \tag{30}$$

as desired. The corresponding statement for $| W_{k+1}(x, t) - \tilde{W}_{k+1}(x, t) |$ follows immediately from equation 19 *a*.

VI. SOLUTIONS IN A PHYSIOLOGICAL REGION

We say that a region D of n-dimensional space and constants $E_1 < E_2$ define a physiological region if for all $(W^1, \cdots, W^n)$ in D we have $f(E_1, W^1, \cdots, W^n) > 0$ and $f(E_2, W^1, \cdots, W^n) < 0$ and also that the vector $(g^1(V, W^1, \cdots, W^n), \cdots, g^n(V, W^1, \cdots, W^n))$ for $(W^1, \cdots, W^n)$ on the boundary of D is not zero and points into D for all $E_1 \leq V \leq E_2$. Under this assumption the solutions to $dW^i/dt = g^i(V, W^1, \cdots, W^n), i = 1, \cdots, n$ never leave the region D if $E_1 \leq V \leq E_2$.

In the Hodgkin-Huxley equations we take for D the region $0 < m, n, h < 1$ and for E_1 and E_2 the minimum and maximum of V_K, N_{Na}, V_L, respectively.

Theorem 4

Given the above conditions for a region D in n-dimensional space and constants $E_1 < E_2$, a solution to equations 3 with $E_1 < V(x, 0) < E_2$ and $(W^1(x, 0), \cdots, W^n(x, 0))$ in D for all x has $E_1 < V(x, t) < E_2$ and $(W^1(x, t), \cdots, W^n(x, t))$ in D for all $t \geq 0$ and all x.

Proof. We first assume that the initial conditions are periodic with period R so that $V(x, 0) = V(x + R, 0)$ and $W^i(x, 0) = W^i(x + R, 0), i = 1, \cdots, n$. Since the solution is unique we must have $V(x, t) = V(x + R, t)$ and $W^i(x, t) = W^i(x + R, t), i = 1, \cdots, n$ for all $t \geq 0$. Let t_0 be the greatest lower bound of those t such that $V(x, t) \leq E_1$ or $V(x, t) \geq E_2$ for some x. $V(x, t)$ is continuous. Therefore if t_0 is finite either the greatest lower bound of $V(x, t_0)$ for all x is equal to E_1 or the least upper bound of $V(x, t_0)$ for all x is equal to E_2 and since $V(x, t_0)$ is periodic in x there exists x_0 such that either $V(t_0, x_0) = E_1$ or $V(t_0, x_0) = E_2$. Because $E_1 \leq V(x, t) \leq E_2$ for $0 \leq t \leq t_0$ and by the condition on the region D we have that $(W^1(x, t), \cdots, W^n(x, t))$ is in D for all x and for $0 \leq t \leq t_0$. If $V(x_0, t_0) = E_2$, then x_0 is a maximum of $V(x, t_0)$, so that $\partial^2 V/\partial x^2 \leq$ and (by equations 3 and the assumption of f) $\partial V/\partial t < 0$, contradicting the inequality $E_1 \leq V(x, t) \leq E_2$ for $0 \leq t \leq t_0$. By a similar argument the equation $V(x_0, t_0) = E_1$ leads to a contradiction. Therefore t_0 is infinite.

Consider an arbitrary solution $V(x, t), W(x, t), \cdots, W^n(x, t)$ with initial values in the physiological range. There can be no (x_0, t_0) with $V(x_0, t_0) > E_2$ or $V(x_0, t_0) < E_1$ because by theorem 3, V can be approximated arbitrarily closely at (x_0, t_0) by a $\bar{V}$ arising from periodic initial conditions in the physiological range and we have seen that such a $\bar{V}$ must satisfy $E_1 < \bar{V}(x_0, t_0) < E_2$. Consequently $(W^1(x, t), \cdots, W^n(x, t))$ is in D for $t \geq 0$ and all x. A repetition of the previous argument shows that V can never equal E_1 or E_2 without violating equations 3.

VII. CONCLUDING REMARKS

The method of iterative construction given above can be applied to equations of the form

$$\frac{\partial V}{\partial t} - a(x, t)\frac{\partial^2 V}{\partial x^2} - b(x, t)\frac{\partial V}{\partial x} = f(x, t, V, W^1, \cdots, W^n)$$

$$\frac{\partial W^i}{\partial t} = g^i(x, t, V, W^1, \cdots, W^n), i = 1, \cdots, n \quad (31)$$

provided the fundamental solution to

$$\frac{\partial V}{\partial t} - a(x, t)\frac{\partial^2 V}{\partial x^2} - b(x, t)\frac{\partial V}{\partial x} = 0$$

has the relevant properties given in proposition 1 and provided there is a constant L such that

$$|f(x, t, V, W^1, \cdots, W^n) - f(x, t, \bar{V}, W^{\bar{1}}, \cdots, W^{\bar{n}})|$$
$$\leq L(|V - \bar{V}| + |W - W^{\bar{1}}| + \cdots + |W^n - W^{\bar{n}}|)$$

for all x and for $0 \leq t \leq T$ with a similar inequality holding for g^i, $1 \leq i \leq n$. Thus nonuniform dynamics and cable properties can be treated. Extension of this method to branching systems with boundary conditions is also possible.

The condition that the partial derivatives of f and g^i, $i = 1, \cdots, n$ in equations 3 be bounded for all $V, W^1, \cdots, W^n$ may not be satisfied. If a physiological range (as defined) can be found on which this condition is satisfied, then f, g^i, $1 \leq i \leq n$ can be modified outside the physiological range so that the condition is met for all $V, W^1, \cdots, W^n$. By theorem 4 it then follows that solutions of the modified system with initial values in the physiological range will satisfy the unmodified system of equations. Such a modification is needed for the Hodgkin-Huxley equations, for the equations of FitzHugh and for those of Rall.

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