Stochastic Versions of the Hodgkin-Huxley Equations

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ABSTRACT A Hodgkin-Huxley model algorithm for the numerical simulation of noise in neurons is contracted from a master equation description (cellular automoton) into a Langevin description. This reduction reduces the time required for a simulation by about two orders of magnitude. Earlier work is summarized, condensed, and made explicit to make the algorithm transparent and facilitate applications. Two approximate treatments are reported. An extension of this approach is presented that includes spatial dependence and the propagation of a noisy action potential along an axon.

INTRODUCTION

The theoretical foundation for our present understanding of nerve membrane ion currents was laid by Hodgkin and Huxley (1952). Their ideas determined experimental approaches until the development of the patch-clamp technique of Neher and Sakmann (1976), which permitted the possibility of measuring ion currents through individual ion channels. This advance has revolutionized both experimental and theoretical approaches. It has made accurate determination of channel model parameters possible. A crucial realization has been that individual ion channels are essentially stochastic entities that open and close in a random way (Lecar and Nossal, 1971a,b; Skaugen and Walløe, 1979; Hille, 1992; Nossal and Lecar, 1991). Experimental and theoretical work by DeFelice and co-workers (DeFelice and Isaac, 1992; Strassberg and DeFelice, 1993) produced a computer model, of cellular automaton type, that described the noise properties of clusters of ion channels in a small area of membrane. It was this work that prompted our entry into this area of research (Fox and Lu, 1994).

We were able to show that if the ion channel density was sufficiently large, then the cellular automaton model could be contracted into a Langevin description. This fact is a result of capacitative coupling among nearby channels, each depending on the same local value of the membrane potential. In the cellular automaton model, every ion channel subunit is independently modeled, and it is this feature that makes this treatment of the simulation so time intensive, even on the most powerful computers. The Langevin description involves channel density variables instead, thereby reducing the number of variables needed for the simulation by orders of magnitude. This reduction is achieved by noting that a cellular automaton model is equivalent to a master equation model, which in turn is reducible (through an intermediate Fokker-Planck equation) to a Langevin model (Fox and Lu, 1994). We have recently performed numerical experiments on several approximations to the Langevin description. When these approximations are legitimate, further savings in time are achieved. The purpose of this paper is to make these methods accessible to a wider group of researchers and to extend the results to include spatial dependence.

The paper is organized as follows. In the Materials and Methods section, a summary of our earlier work is presented in which explicit expressions appear that had been left implicit in the earlier paper (Fox and Lu, 1994). Only if the reader has worked through the derivations in this earlier paper will some, but not all, of these equations already have been met. This includes the basic theory as well as the noise simulation methods. In the Results section, the numerical experiments done recently on approximations to the complete Langevin equation are described. A number of applications by other researchers are cited. In addition, algorithms for an extension to spatial dependence are presented for the first time. In the Discussion section, we end the paper with a number of proposals for further work.

MATERIALS AND METHODS

Summary of Hodgkin-Huxley stochastics

This section expands the results obtained in our earlier paper (Fox and Lu, 1994). These explicit algorithms greatly simplify one's ability to implement applications of the earlier, implicit results.

The results take on three distinct forms. There is a fundamental matrix Langevin description, made explicit here in all details for the first time. There is an approximation to this description that is much more readily implemented numerically and has been found to be very accurate for certain parameter regimes. There is also a further approximation to the noise terms that again simplifies implementation without loss of accuracy in approprate parameter regimes. Tests of these two approximations are described in the Results section.

Noiseless Hodgkin-Huxley description

The membrane voltage evolution equation is (Nossal and Lecar, 1991; Katz, 1966)

$$\frac{d}{dt}V_m = -\frac{1}{C}[G_L(V_m - E_L) + G_K(V_m - E_K) + G_{Na}(V_m - E_{Na})], \quad (1)$$

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where V_m is the membrane potential in (mV); C is the specific membrane capacitance (μF/cm^2); E_L is the leakage reversal potential (mV); E_K is the potassium reversal potential (mV); E_{Na} is the sodium reversal potential (mV); G_L is the leakage conductance density in millisiemens per square centimeter (mS/cm^2); G_K is the potassium conductance density (mS/cm^2); and G_{Na} is the sodium conductance density (mS/cm^2).

The potassium and sodium conductance densities are given by

$$G_K = \Gamma_K N_K n^4 \quad \text{and} \quad G_{Na} = \Gamma_{Na} N_{Na} h m^3, \tag{2}$$

where Γ_K is the potassium conductance per channel in picosiemens (pS); Γ_{Na} is the sodium conductance per channel (pS); N_K is the potassium channel density (cm^{-2}); and N_{Na} is the sodium channel density (cm^{-2}).

In Fox and Lu (1994), the symbols N_K and N_{Na} denote channel numbers rather than densities, and are equal to $N_K A$ and $N_{Na} A$ in the present notation, where A is the area of a membrane patch.

The gate parameters, n, h, and m, satisfy relaxation equations

$$\frac{d}{dt} n = \alpha_n(1 - n) - \beta_n n \tag{3}$$

$$\frac{d}{dt} h = \alpha_h(1 - h) - \beta_h h \tag{4}$$

$$\frac{d}{dt} m = \alpha_m(1 - m) - \beta_m m. \tag{5}$$

The α's and β's are gate opening and closing rates (ms^{-1}) and depend on the membrane potential, V_m, according to empirically determined formulas (Strassberg and DeFelice, 1993; Rubinstein, 1995), such as

$$\alpha_n = \frac{0.01(V_m + 55)}{1 - \exp[-(V_m + 55)/10]}$$

and

$$\beta_n = 0.125\exp[-(V_m + 65)/80] \tag{6}$$

$$\alpha_h = 0.07\exp[-(V_m + 65)/20]$$

and

$$\beta_h = \frac{1}{1 + \exp[-(V_m + 35)/10]} \tag{7}$$

$$\alpha_m = \frac{0.1(V_m + 40)}{1 - \exp[-(V_m + 40)/10]}$$

and

$$\beta_m = 4\exp[-(V_m + 65)/18]. \tag{8}$$

A noiseless numerical simulation involves simultaneous solution of Eqs. 1–8. A typical simulation might pertain to a membrane area of, say, 1 μm^2, which is 10^{-8} cm^2. In such an area, there are perhaps a few tens of channels, e.g., $N_K \approx 18/\mu\text{m}^2 = 18 \times 10^8/\text{cm}^2$. Therefore, G_K has units of order pS $\times$ 18 $\times$ 10^8/cm^2 = 1.8 mS/cm^2. If the individual channel conductance is, say, 20 pS, then $G_K \approx 36$ mS/cm^2. Typically, $C = 1$ μF/cm^2. Thus, in Eq. 1, the potassium term on the right-hand side gives a rate of order

$$\frac{G_K}{C} \sim 36\,\frac{\text{mS}}{\mu\text{F}} = 36\,\frac{10^{-3}A/V}{10^{-6}C/V} = 36\,\frac{1}{10^{-3}\text{s}} = \frac{36}{\text{ms}}, \tag{9}$$

which suggests that the natural unit for time is milliseconds. We find we get very good accuracy in numerical simulations using step sizes on the order of 0.005–0.01 ms.

Complete Langevin description

The n^4 term in the potassium conductance density in Eq. 2 represents the idea that a potassium channel has four subunits and is conducting only if all four subunits are in the open state. The total number of potassium channels in area A is $N_K A$. Let x_i be the fraction of $N_K A$ channels with i subunits in the open state, for $i = 0, 1, 2, 3$, or 4. Clearly,

$$x_0 = 1 - x_1 - x_2 - x_3 - x_4. \tag{10}$$

In Fox and Lu (1994) it is shown that

$$\frac{d}{dt} x_p = R_p(\vec{x}) + S_{pq}\tilde{g}_q(t), \tag{11}$$

where $p, q = 1, 2, 3$, or 4; q is summed; $\vec{x}$ is shorthand for x_1, x_2, x_3, and x_4; and the stochastic terms are Gaussian with moments

$$\langle \tilde{g}_q(t) \rangle = 0 \quad \text{and} \quad \langle \tilde{g}_q(t)\tilde{g}_{q'}(t') \rangle = 2\delta_{qq'}\delta(t - t'). \tag{12}$$

The matrix S_{pq} satisfies

$$(S^2)_{pq} = D_{pq}, \tag{13}$$

and R_p is defined by

$$R_p = K_p - \left(\frac{\partial}{\partial x_j} S_{pq}\right) S_{jq}, \tag{14}$$

where j and q are summed. $K_p(\vec{x})$ is defined for $p = 1, 2, 3$, and 4 by

$$K_p(\vec{x}) = -(p\beta_n + (4 - p)\alpha_n)x_p + (p + 1)\beta_n x_{p+1}(1 - \delta_{p4}) + (4 - (p - 1))\alpha_n x_{p-1}, \tag{15}$$

and is defined by

$$\begin{aligned} D_{pq}(\vec{x}) = \frac{1}{2N_K A}\,[&\delta_{pq}\{(p\beta_n + (4 - p)\alpha_n)x_p + (p + 1)\beta_n x_{p+1} \\ &\cdot (1 - \delta_{p4}) + (4 - (p - 1))\alpha_n x_{p-1}\} \\ &- p\beta_n x_p \delta_{q\,p-1}(1 - \delta_{q4}) - (4 - p)\alpha_n x_p \delta_{q\,p+1} \\ &- q\beta_n x_q \delta_{p\,q-1}(1 - \delta_{p4}) - (4 - q)\alpha_n x_q \delta_{p\,q+1}]. \end{aligned} \tag{16}$$

Equation 11 replaces Eq. 3, and the potassium conductance density in Eq. 2 must be changed to

$$G_K = \Gamma_K N_K x_4 \tag{17}$$

before it is used in Eq. 1. Using Eqs. 13 and 16, it is clear from Eq. 14 that R_p and K_p differ by a term of order $1/N_K A$, which is usually small enough to be ignorable without significant loss of accuracy. The fact that R_p and K_p are not identical has to do with technicalities involving the Ito and Stratonovich versions of stochastic calculus (Arnold, 1974). We use the Stratonovich interpretation throughout this paper.

These results for $K_p(\vec{x})$ and $D_{pq}(\vec{x})$ are the first and second moments of an underlying transition probability. Let C_p denote the number of channels with p subunits in the open state. For a short time interval, Δt, the

expression for the transition probability, $W(\vec{C}',\vec{C})$, is found to be given by

$$W_n(\vec{C}', \vec{C}) = \sum C_p([1 - p\beta_n\Delta t - (4-p)\alpha_n\Delta t]\delta_{p',p}\Delta_0 + [p\beta_n\Delta t\delta_{p',p-1} + (4-p)\alpha_n\Delta t\delta_{p',p+1} \cdot (1-\delta_{p4})]\delta_{C_{p'},C_p-1}\delta_{C_{p'},C_{p'}+1}\Delta_2), \quad (18)$$

in which the summation is over both p and p' from 0 to 4, and in which Δ_0 and Δ_2 denote Kronecker delta products for the $\vec{C}'$ and $\vec{C}$ components. Δ_0 means that all components with the same index are equal, and Δ_2 means that all but those components with indices p and p' are equal. This expression is used to calculate $K_q(\vec{C})$ and $D_{rs}(\vec{C})$ according to the formulae

$$K_q(\vec{C}) = \int d^4C'(C'_q - C_q)W_n(\vec{C}', \vec{C})/\Delta t \quad (19)$$

$$2D_{rs}(\vec{C}) = \frac{1}{N_K A}\int d^4C'(C'_r - C_r)(C'_s - C_s)W_n(\vec{C}', \vec{C})/\Delta t. \quad (20)$$

Taking the limit $\Delta t \to 0$ and setting $\vec{x} = \vec{C}/N_K$ yields Eqs. 15 and 16. Notice that the Δ_0 term in Eq. 18 makes no contribution to either Eq. 15 or Eq. 16.

The hm^3 term in the sodium conductance density in Eq. 2 represents the idea that a sodium channel has four subunits, one of type h and three of type m, and is conducting only if all four subunits are in the open state. The total number of sodium channels is $N_{Na}A$. Let y_{jk} be the fraction of the $N_{Na}A$ channels with j m-subunits in the open state and k h-subunits in the open state, for $j = 0$, 1, 2, or 3 and $k = 0$ or 1. Clearly,

$$y_{00} = 1 - y_{10} - y_{20} - y_{30} - y_{01} - y_{11} - y_{21} - y_{31}. \quad (21)$$

In Fox and Lu (1994) it was shown that

$$\frac{d}{dt}y_{pr} = R_{pr}(\vec{y}) + S_{pr\,qs}\tilde{g}_{qs}(t), \quad (22)$$

in which p, $q = 0$, 1, 2, or 3; r, $s = 0$ or 1 (excluding $p = 0$ and $r = 0$ simultaneously, and $q = 0$ and $s = 0$ simultaneously); q and s are summed; $\vec{y}$ is shorthand for $y_{10}, y_{20}, y_{30}, y_{01}, y_{11}, y_{21}$, and y_{31}; and the stochastic terms are Gaussian with moments

$$\langle\tilde{g}_{qs}(t)\rangle = 0 \quad \text{and} \quad \langle\tilde{g}_{qs}(t)\tilde{g}_{q's'}(t')\rangle = 2\delta_{qq'}\delta_{ss'}\delta(t-t'). \quad (23)$$

The matrix $S_{pr\,qs}$ satisfies

$$(S^2)_{pr\,qs} = D_{pr\,qs}, \quad (24)$$

and R_{pr} is defined by

$$R_{pr} = K_{pr} - \left(\frac{\partial}{\partial y_{ab}}S_{pr\,qs}\right)S_{ab\,qs}, \quad (25)$$

in which a, b, q, and s are summed. $K_{pr}(\vec{y})$ is defined for $p = 0$, 1, 2, and 3 and $r = 0$ or 1, but not both $p = 0$ and $r = 0$ simultaneously, by

$$K_{pr}(\vec{y}) = -(p\beta_m + (3-p)\alpha_m + r\beta_h + (1-r)\alpha_h)y_{pr} + (p+1)\beta_m y_{p+1\,r}(1-\delta_{p3}) + (3-(p-1))\alpha_m y_{p-1\,r}(1-\delta_{p0}) + (r+1)\beta_h y_{p\,r+1}(1-\delta_{r1}) + (1-(r-1))\alpha_h y_{p\,r-1}(1-\delta_{r0}), \quad (26)$$

and $D_{pr\,qs}(\vec{y})$ is defined by

$$D_{pr\,qs}(\vec{y}) = \frac{1}{2N_{Na}A}[\delta_{pq}\delta_{rs}\{(p\beta_m + (3-p)\alpha_m)y_{pr} + (p+1)\beta_m y_{p+1\,r}(1-\delta_{p3}) + (3-(p-1))\alpha_m y_{p-1\,r}(1-\delta_{p0}) + (r\beta_h + (1-r)\alpha_h)y_{pr} + (r+1)\beta_h y_{p\,r+1}(1-\delta_{r1}) + (1-(r-1))\alpha_h y_{p\,r-1}(1-\delta_{r0})\} - \delta_{rs}\{p\beta_m\delta_{q\,p-1}(1-\delta_{q3})y_{pr} + (3-p)\alpha_m\delta_{q\,p+1}(1-\delta_{q0})y_{pr} + q\beta_m\delta_{p\,q-1}(1-\delta_{p3})y_{qs} + (3-q)\alpha_m\delta_{p\,q+1}(1-\delta_{p0})y_{qs}\} - \delta_{pq}\{r\beta_h\delta_{s\,r-1}(1-\delta_{s1})y_{pr} + (1-r)\alpha_h\delta_{s\,r+1}(1-\delta_{s0})y_{pr} + s\beta_h\delta_{r\,s-1}(1-\delta_{r1})y_{qs} + (1-s)\alpha_h\delta_{r\,s+1}(1-\delta_{r0})y_{qs}\}]. \quad (27)$$

Equation 22 replaces Eqs. 4 and 5, and the sodium conductance density in Eq. 2 must be changed to

$$G_{Na} = \Gamma_{Na}N_{Na}y_{31} \quad (28)$$

before it is used in Eq. 1. Using Eqs. 24 and 27, it is clear from Eq. 25 that R_{pr} and K_{pr} differ by a term of order $1/N_{Na}A$, which is usually ignorable without significant loss of accuracy.

These results are obtained in a manner similar to the way in which the corresponding formulae for potassium channels were obtained. First, we need transition probabilities like those in Eq. 18, but with two differences. For the m-subunits, the upper value for the index is 3 rather than 4, and for the the h-subunit, the upper index is 1 rather than 4. In addition, the α and β subscripts are, respectively, m and h rather than n. Second, the transition probability for a sodium channel is the product of the m and h transition probabilities, but only including those terms to first order in Δt.

Numerical implementation of noise terms

Suppose we contemplate a numerical simulation of the simultaneous system of equations made up of Eqs. 1, 3–8, and 10–28 (recall that Eq. 2 is replaced by Eqs. 17 and 28). Let the step size be denoted by Δt. One may use an Euler integration for the nonstochastic terms, although it is more accurate to use at least Runge-Kutta 2, if not Runge-Kutta 4. To this, at each time step, must be added the noise terms. These are generated by the Box-Muller algorithm (Knuth, 1969), which in principle exactly generates Gaussian noise from uniformly distributed random numbers. The individual stochastic terms in Eq. 12 or Eq. 23 are created as follows. Let a and b be two uniformly distributed random numbers from the unit interval. Let Δg denote either $\tilde{g}_q(t)$ or a $\tilde{g}_{qs}(t)$, depending upon which term is being considered. The simulated noise term is given by

$$\Delta g = \sqrt{4\Delta t\log(a)}\cos(2\pi b). \quad (29)$$

Notice the factor of 4, which is twice the factor of 2 in the second moments of Eqs. 12 and 23. The symbol "log" denotes the Naperian logarithm. A term such as this is needed for each noise term, and each must utilize independently generated random numbers a and b (in fact, replacing $\cos(2\pi b)$ with $\sin(2\pi b)$ in Eq. 29 creates an independent Gaussian random number, so that a and b may be used to create two independent Gaussian

random numbers at the same time). Because Gaussian random numbers can have arbitrarily large positive or negative values, it is possible that in the course of the simulation an x_p value or a y_{pr} value will fall outside the range of [0,1], which is required of these simple fractions. Thus a simulation code must be written such that this restriction is satisfied at each time step; this is easily achieved by simply including a do-loop that is exited if the desired restriction is realized for the generated a's and b's. We have found that this precaution avoids unwanted numerical overflows and that the do-loops are rarely repeated for step sizes on the order of 0.005 ms.

Higher order noise algorithms

In a number of recent papers (e.g., Collins et al., 1995a,b) that utilize a reduced description of the neuronal firing dynamics, higher order noise simulations have been used. In this work, the Fitzhugh-Nagumo equation (FHN) is used and is integrated by a second-order Runge-Kutta scheme that also includes noise terms of higher order than the Box-Muller algorithm. These higher order noise terms are based on an algorithm for colored noise (Mannella and Palleschi, 1989). The spirit of this approach is to use noise (called "colored noise") that has an exponential correlation instead of the Dirac delta correlation of Eqs. 12 and 23. The relaxation time constant in the exponential correlation can be made sufficiently small in the simulation so that one is effectively simulating white noise. Using this procedure is much easier than attempting to directly implement a higher order white noise algorithm. By doing this with the noise, the entire simulation is made second order in both the secular terms and the noise terms.

As can be seen from Eq. 29, the white noise algorithm depends on the square root of the step size. A second-order Runge-Kutta integration of the secular terms would include the first and second powers of the step size. To get noise terms to the same order, it is necessary to include terms depending on step size to orders 1/2, 2/2, 3/2, and 4/2. In fact, the Mannella-Palleschi algorithm includes terms only to order 3/2. Fox (Fox, 1992; Honeycutt, 1990) has extended this algorithm to order 4/2 in the noise. Should it prove to be desirable to use higher order noise terms in the Hodgkin-Huxley simulations described above, this is the algorithm to use.

RESULTS

An accurate approximation

The complete Langevin treatment given above requires that at each time step the square root matrices, S, must be computed for both the potassium and the sodium terms. Although very efficient routines are available for the implementation of these steps, they nevertheless slow down the computation. Recently we have shown that a faster approximate implementation is possible in which one numerically solves the simultaneous system of equations, Eqs. 1–8, but in which Eqs. 3–5 are made stochastic directly. They take the form

$$\frac{d}{dt}n = \alpha_n(1 - n) - \beta_n n + \tilde{g}_n(t) \tag{30}$$

$$\frac{d}{dt}h = \alpha_h(1 - h) - \beta_h h + \tilde{g}_h(t) \tag{31}$$

$$\frac{d}{dt}m = \alpha_m(1 - m) - \beta_m m + \tilde{g}_m(t), \tag{32}$$

in which the stochastic terms are Gaussian with moments (only the m case is given, because the others are then obvious)

$$\langle \tilde{g}_m(t) \rangle = 0$$

and

$$\langle \tilde{g}_m(t)\tilde{g}_m(t') \rangle = \frac{2}{N_{Na}A}\frac{\alpha_m(1 - m) + \beta_m m}{2}\delta(t - t'). \tag{33}$$

In this correlation formula, α_m, β_m, and m have the instantaneous values for the time step involved. The Box-Muller algorithm in this case requires that we add, in analogy to Eq. 29,

$$\Delta g_m = \sqrt{2\Delta t \frac{\alpha_m(1 - m) + \beta_m m}{N_{Na}A}} \log(a) \cos(2\pi b). \tag{34}$$

It is now necessary, as before, to include do-loops to guarantee that m, n, and h do not leave the unit interval [0, 1].

Another approximation

In Eq. 34, the instantaneous value of m occurs. If the relaxations of n, h, and m are sufficiently faster than the dynamics for V_m, then it is possible, and accurate, to replace m (and n and h in the corresponding formulas) by its instantaneous steady-state value, m_s, according to Eq. 5. This is given by

$$m_s = \frac{\alpha_m}{\alpha_m + \beta_m} \tag{35}$$

and this implies that

$$\frac{\alpha_m(1 - m_s) + \beta_m m_s}{2} = \frac{\alpha_m \beta_m}{\alpha_m + \beta_m}, \tag{36}$$

in which the right-hand side depends on the instantaneous value of V_m. The Box-Muller expression is accordingly modified.

Interpretation of the approximations

The subunit interpretation of the nonlinear terms, n^4 and m^3h, in the Hodgkin-Huxley equations preceded the structural determination of these ion channels. It represents a simplified picture of their true structure and of their cooperative protein interactions. Thus these terms in the dynamics should not be taken too literally. It is gratifying, therefore, to find that various simplifying approximations in the treatment of noise properties of these terms, such as those described above, lead to results very close (within 1% error) to those obtained from the complete Langevin description. Thus far, rigorous mathematical criteria for the applicability of the approximations have not been deduced, and the quality of approximate results must be assertained empirically.

Applications of the noise algorithm

Threshold fluctuations in a sodium channel model of the node of Ranvier have been studied with a Hodgkin-Huxley automaton model of the DeFelice type (Rubinstein, 1995). Up to 32,000 channels of the m^3h subunit variety were simulated. Rubinstein (personal communication) has reported implementation of the algorithm presented here. He found a speedup of two orders of magnitude over the automaton algorithm. For 800 or more channels, the two algorithms were statistically indistinguishable with regard to poststimulus time histograms and input output functions.

Facilitation of synaptic transmission involving calcium channels is another current area of study (Bertram et al., 1996; Bertram and Sherman, 1996). The stochastic character of calcium channel opening and closing is considered important for these studies, and the algorithm for sodium and potassium presented here, modified for calcium, is being considered for these investigations (Sherman, personal communication).

We are currently engaged in benchmarking the Langevin method against the earlier cellular automaton results of scheme 2a of Skaugen and Walløe (1979).

Spatial dependence in the Hodgkin-Huxley equations

In addition to the list of variables given earlier, the inclusion of spatial dependence requires two more quantities, a and r_i: a is the axon radius (cm); r_i is the specific electrical resistivity of the cytoplasmic core (ohm-cm).

These will suffice for consideration of a long axon with a cross-sectional circumference sufficiently small that circumferencial spatial dependence is ignorable. Thus the present treatment covers a one-dimensional axon, with the spatial variable x chosen to represent the position along the axon.

Propagation of an action potential along the axon is described by the cable equation (Nossal and Lecar, 1991; Katz, 1966)

$$\frac{a}{2r_i}\frac{\partial^2 V_m}{\partial x^2} = C\frac{\partial V_m}{\partial t} + I_{ionic}(V_m, t), \tag{37}$$

where

$$I_{ionic}(V_m, t) \tag{38}$$
$$= G_L(V_m - E_L) + G_K(V_m - E_K) + G_{Na}(V_m - E_{Na}),$$

and the conductance densities are given by Eq. 2. Here we must consider the membrane potential, V_m, to be a function of both x and t. In the simplest cases, C, N_K, N_{Na}, Γ_K, and Γ_{Na} are constants with respect to x. However, they can be given x dependence in Eqs. 37 and 38 if desired, as long as they remain independent of t. The gate parameters n, m, and h, on the other hand, will be functions of both x and t through their dependence on $V_m(x, t)$.

Complete Langevin description

In the complete Langevin description, Eqs. 37 and 38 are solved together with Eqs. 17 and 28 in place of Eq. 2. In Eqs. 11 and 22, the noise terms are multiplied by S matrices that depend on both x and t because the associated D matrices in Eqs. 16 and 27 depend on the α's and β's, which in turn depend on $V_m(x, t)$. Moreover, the membrane patch area A in the prefactor denominators of Eqs. 16 and 27 must be replaced by $2\pi a\Delta x$, the area of a segment of axon with circumference $2\pi a$ and length Δx. This complete Langevin treatment is very intensive numerically, because the D matrix square roots, the S matrices, must be evaluated at each value of x for each increment of time Δt. A considerable savings of time accrues if either of the approximations discussed above is valid.

Approximate treatment

In the approximate treatment we solve simultaneously the system of equations made up of Eqs. 37, 38, 2, and 30–34. However, it must be understood that n, m, and h are functions of x, so that once the x axis has been discretized for the purpose of a numerical integration, there are n, m, and h variables for each discrete value of x. Moreover, the α's and β's in these equations depend on the local x values of $V_m(x, t)$. In addition, in the denominators of Eqs. 33 and 34 we must replace A by $2\pi a\Delta x$, as was discussed above. It is even faster to make use of the additional approximation of the noise correlations given by Eq. 36, modified for each position x.

Numerical integration with spatial dependence

If the nth discrete position along the axon is denoted by x_n, then the numerical integration of Eq. 37 may take the form (this is called the forward time centered space (FTCS) method; Press et al., 1988)

$$V_m(x_n, t + \Delta t) = V_m(x_n, t) - \Delta t\frac{1}{C}I_{ionic}(V_m(x_n, t))$$
$$+ \Delta t\frac{a}{2r_iC\Delta x^2}(V_m(x_{n+1}, t) + V_m(x_{n-1}, t)$$
$$- 2V_m(x_n, t)). \tag{39}$$

Typical values for the parameters are $a \approx 10^{-4}$-10^{-3} cm, $r_i \approx 30$–100 ohm-cm, and $\Delta x \approx 10^{-4}$ cm. If we still use Δt on the order of 10^{-5} s, then the magnitude of the coefficient in the second term of the right-hand side of Eq. 39 can be as large as 10^5. The condition for stability of integration using this FTCS method (Press et al., 1988) is that this coefficient should be less than 1. Thus we are far from a stable algorithm if we use Eq. 39 unless we reduce Δt considerably, which would make the algorithm take an inordinately long time, or increase Δx to at least a millimeter, which is spatially too coarse. Instead, we should use an implicit

method (Press et al., 1988) or perhaps a modified Crank-Nicholson method.

A straightforward application of standard implicit methods for partial differential equations is complicated by the presence of the ionic current density term in Eq. 37. Nevertheless, this term, which is evaluated from the conductance densities according to Eq. 38, is easily accommodated as follows. To get the conductance densities, the values of the membrane potential at each discrete value of x from the most recent time step are used. Either the discrete analogs of Eqs. 17 and 28 are used, or the discrete analogs of the approximation equations, Eqs. 30–34, are used. Either way, an updated set of discrete ionic current values at each discrete value of x is obtained. These are subsequently used in the algorithm's next stage, which is implicit for the diffusive part alone. This takes the form

$$\begin{aligned} V_m(x_n, t + \Delta t) = V_m(x_n, t) - \Delta t \frac{1}{C} I_{ionic}(V_m(x_n, t)) \\ + \Delta t \frac{a}{2r_i C \Delta x^2}(V_m(x_{n+1}, t + \Delta t) \\ + V_m(x_{n-1}, t + \Delta t) - 2V_m(x_n, t + \Delta t)), \end{aligned} \tag{40}$$

wherein the third term on the right-hand side is evaluated at $t + \Delta t$ rather than at t, and the ionic current density is the updated version just discussed. Let D be defined by

$$D = \frac{\Delta t a}{2r_i C \Delta x^2}. \tag{41}$$

Equation 40 may be transformed into the equivalent equation

$$\begin{aligned} -D(V_m(x_{n+1}, t + \Delta t) + V_m(x_{n-1}, t + \Delta t)) \\ + (1 + 2D)V_m(x_n, t + \Delta t) \\ = V_m(x_n, t) - \Delta t \frac{1}{C} I_{ionic}(V_m(x_n, t)). \end{aligned} \tag{42}$$

This is a tridiagonal system for each time step, and it can be easily solved by standard methods (Press et al., 1988). This produces an updated set of discrete values for the membrane potential, and this two-stage process may be iterated for as long as one desires. Preliminary work on this problem with these methods has produced promising results. We have obtained good agreement with spatially dependent automaton simulations performed independently by Bill Goolsby.

DISCUSSION

In this presentation, earlier work on the numerical simulation of noisy ion channel behavior in neurons has been expanded and made explicit for applications. The results are for the Hodgkin-Huxley model and are applicable to any related model involving multisubunit channels. We have shown how the number of subunits and the number of types of subunits in a channel are incorporated into the results in general. For example (Nossal and Lecar, 1991), the node of Ranvier of myelinated frog sciatic nerve, a motoneuron, is modeled by a Hodgkin-Huxley model with n^2 and m^2h structure. The present results are easily altered to apply to this case (see the treatment of sodium above). Other species of ion channel, such as for Ca (Bertram et al., 1996; Bertram and Sherman, 1996), could also be easily modeled by using the present results.

The extension of these results to include spatial dependence has also been presented here for the first time. Whereas this extension primarily requires a discretization of the spatial variable and implementation of the spatially independent algorithm, appropriately modified, to every discrete spatial location, it also requires some mixing of the membrane potential at different spatial locations because of the diffusive coupling in the cable equation. Some care must be exercised to achieve a stable algorithm. In particular, it is necessary to use an implicit method for the diffusive coupling. Because we have described this procedure for the situation that includes noise, it will now be possible to numerically study a number of problems associated with the influence of noise on spike propagation and on interspike statistics.

The two simplifying approximations of the noise algorithm discussed above save time. They amount to two different ways of introducing stochasticity directly into the gate parameter equations. Their domain of applicability is currently determined empirically. A problem for future research is to find analytic criteria for their applicability.

We are also in a position to explore other possible approximations or reductions of the description. For example, the Fitzhugh-Nagumo model has recently been used extensively to investigate the importance of stochastic resonance in neuron function (Longtin, 1993; Collins et al., 1995a,b). This greatly reduced model is rapidly simulated. How well it represents the firing dynamics of the full Hodgkin-Huxley model is not yet known, especially when noise is included. A number of reduced models other than the FHN model are known, and their noise properties also must be studied. Generally, a reduction of a noiseless dynamics does not automatically imply a corresponding reduction for the noisy dynamics. For example, the noiseless part of the sodium dynamics described above at the Langevin level can be factored into a part for the m subunits and a part for the h subunit (Chow and White, 1996). However, the noisy part of this dynamics does not factor.

Clearly, many questions can be approached by using the stochastic methods presented here. Because the noise parameters are determined intrinsically and are not put in in an ad hoc manner, fundamental understanding of the influence of noise in neuronal dynamics is possible.

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