Emergent collective behavior in large numbers of globally coupled independently stochastic ion channels

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(Received 29 July 1993)

Individual ion channels that mediate sodium and potassium currents during action-potential generation in nerve membranes open and close stochastically with transition rates that are voltage dependent. The transmembrane voltage globally couples the otherwise stochastically independent ion channels through their voltage-dependent transition rates. As the membrane channel density increases, a transition to regular, collective behavior ensues. The mathematical basis for this transition is explained in terms of a hierarchy of description contractions. Stochastic and deterministic modifications of the Hodgkin-Huxley equations are obtained.

PACS number(s): 87.22.Bt, 05.40.+j

I. INTRODUCTION

Ion channels are found in all cell membranes. They are believed to be the molecular basis, at the cellular level, for excitability in many tissues, especially nerve and muscle. The central problem in the study of excitable membranes is the connection between the microscopic (molecular) properties of ion channels and the macroscopic properties of cells and tissues. The theoretical foundations for our present understanding of nerve membrane ion currents were laid down by Hodgkin and Huxley [1]. Their ideas determined experimental approaches up until the development of the patch-clamp technique of Neher and Sakmann [2], which permitted the possibility of measuring ion currents through individual ion channels. This advance has revolutionized both experimental and theoretical approaches. A crucial realization has been that individual ion channels are essentially stochastic elements which open and close in a random way. Nevertheless, recent studies by DeFelice and Isaac [3] have dramatically shown that global coupling across large domains of the cell membrane by the membrane's electrical capacitance enables clusters of stochastic ion channels to generate all of the known macroscopic electrical behaviors of tissues such as resting potentials, action potentials, spontaneous firing, and even chaos. Perhaps most notable, and unexpected, is the emergent, regular bursting characteristic of certain action potentials. That regular, nearly periodic, collective bursting can emerge from the global coupling of stochastic elements is fascinating theoretically and, until now, incompletely understood.

Individual ion channels that mediate sodium and potassium currents during action-potential generation in nerve membranes open and close stochasticity with transition rates that are voltage dependent. The transmembrane voltage (potential) is a global membrane property determined in part by the membrane capacitance. Through their transition rates, it globally couples the otherwise stochastically independent ion channels. When the membrane channel number is small, the individual channels open and close independently, producing a very noisy transmembrane potential. As the membrane channel number increases, a transition to regular, collective behavior occurs. This is manifested by small fluctuations superimposed on nearly periodic action potential spikes, the regularity of which becomes better with greater numbers. Typical results are exhibited in Figs. 1–3.

Regular bursting of globally coupled stochastic ele-

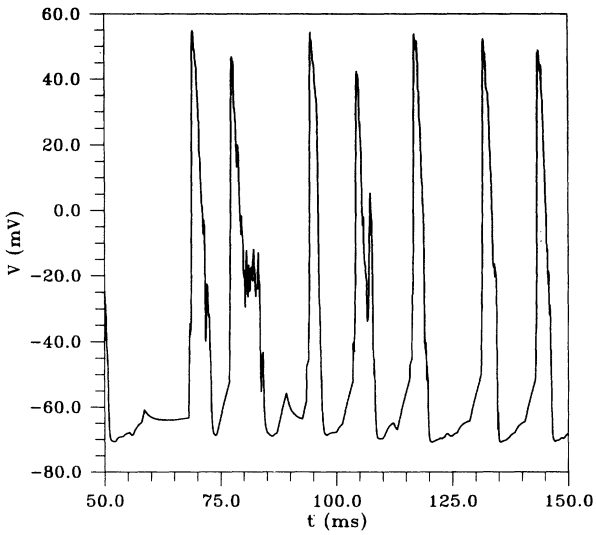

FIG. 1. Voltage profile generated by master equation (10) for potassium channels, master equation (21) for sodium channels, and Eq. (1) with an added leakage term. The leakage term used here and also in Figs. 2 and 3 is $-G_L(V-E_L)/(1\ \mu\text{F})$ where $G_L=1$ pS, $E_L=0.0$ mV. The channel-number ratio, Na:K, is 10:1. In this figure, there are 150 Na channels and 15 K channels and the membrane area A is 0.5 μm^2.

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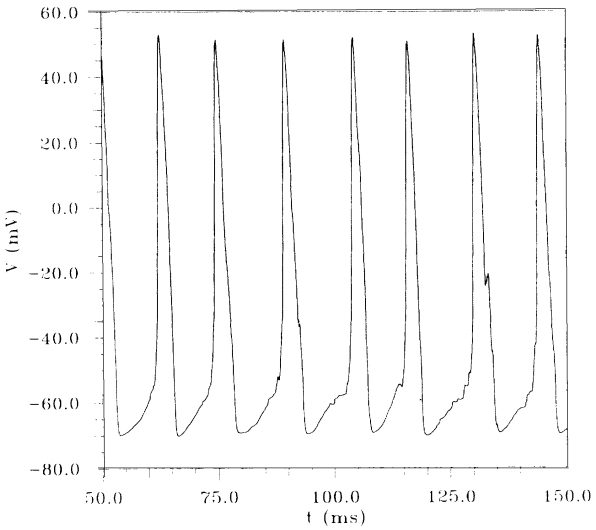

FIG. 2. This is the same as for Fig. 1, except that there are 1500 Na channels and 150 K channels and the membrane area A is 5 μm^2.

ments also has been experimentally observed in the behavior of the pancreatic β-cells and was analyzed by Sherman, Rinzel, and Keizer [4]. This bursting occurs in the islets of Langerhans in the pancreas and correlates with the secretion of insulin which is pulsatile. Theoretical modeling of this phenomenon with stochastically active pancreatic β cells shows that as the cluster size of the coupled cells (tightly coupled by gap junctions) increases, the electrical activity makes a transition from random spiking to regular bursting. While the case reported in the preceding paragraph involves the coupling of ion channels in a cell membrane, and the case here involves the coupling of cells in a tissue, the mathematical features are nearly the same. This suggests the possibility of a quite general phenomenon that may be exhibited in other

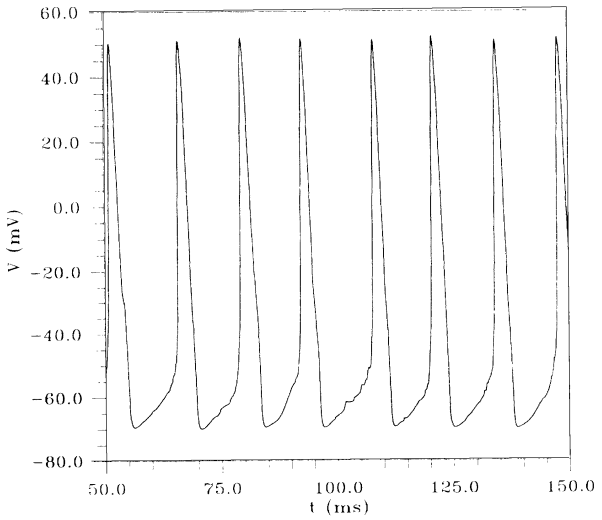

FIG. 3. This is the same as for Fig. 1, except that there are 3000 Na channels and 300 K channels and the membrane area A is 10 μm^2.

biological contexts as well. Moreover, for these two cases it eliminates the need to find macroscopic "pace-maker" centers since the regular bursting is an emergent property arising solely from the global coupling of stochastic elements. It is not inconceivable that such a mechanism would be responsible for the regular beating of the heart. Thus, deeper understanding of this mechanism may have importance in obtaining a more profound understanding of diseases such as diabetes (β cells) and cardiac arrhythmias (heart).

The mathematical basis for the transition from stochastic to regular collective behavior reported in this paper is presented in terms of a hierarchy of description contractions from computer model to master equation to Fokker-Planck equation to Langevin equations to deterministic equations. This explanation has significance for other nonbiological, globally coupled, multicomponent arrays, such as are encountered, for example, in the study of self-organized criticality [5]. These arrays include models closely related to the present study: the spring-block model [6] and the fiber-bundle model [7]; and the less closely related models: Josephson junction arrays [8], multimode laser propagation in optical fibers [9], and the Barkhausen effect [10].

This paper is organized as follows. A brief description of ion channel models is given in Sec. II. The deterministic Hodgkin-Huxley equations are presented in Sec. III. In Sec. IV, we review the stochastic computer (automaton) model pioneered by DeFelice and co-workers (see Ref. [3] and references therein). The equivalent master equation for potassium channels is the subject of Sec. V, and the corresponding Fokker-Planck equation is given in Sec. VI. In Sec. VII, we provide the analogous results for the more complicated sodium channels. In Sec. VIII, we discuss the deterministic limit and elucidate a new, modified Hodgkin-Huxley model. In Sec. IX, we present the Langevin equations used in numerical simulations. In Sec. X, we discuss these results, their implications for efficient numerical simulations, and deterministic and stochastic modifications of the Hodgkin-Huxley equations. We also review our explanation of the emergence of regular behavior in large numbers of globally coupled, independently stochastic channels.

II. ION CHANNEL MODELS

The Hodgkin-Huxley equations [1] are deterministic, coupled, nonlinear differential equations for the transmembrane voltage and for the conductances of potassium and sodium ions across the nerve membrane. Triggering of these ion currents is controlled by the transmembrane voltage, which is biased at the expense of metabolic energy, and which in turn is also strongly affected by the ion currents. The governing rate constants are voltage dependent. Each of the relevant variables is continuous. Under certain conditions, these equations produce solutions that exhibit spontaneous, periodic spiking that is very similar in appearance to measured electrical voltage spiking recorded by electrophysiologists in squid axon. While the spikes may cover a range in voltage of the order of 100 mV, measurements

also show incessant fluctuations of order a few mV. Since the Hodgkin-Huxley model is deterministic, it is incapable of showing these fluctuations.

The measurements made possible by the patch-clamp technique of Neher and Sakmann [2] show that individual ion channels produce these simple voltage fluctuations because the individual channels are simple stochastic elements that randomly open and close (this was already strongly suspected from earlier voltage noise measurements but was not so easily interpreted since they were not for individual channels). Almost certainly, this intrinsic stochasticity is of thermal origin, just as it is for simple chemical isomerizations.

The computer model used by DeFelice and Isaac [3] incorporates the stochasticity of the ion channels in its microscopic description of the channel dynamics. Thus, the model is intrinsically stochastic rather than deterministic. Without direct coupling, there is no reason for large numbers of channels to open or close in synchrony and macroscopic voltage spikes are not to be expected in such a model. However, the model does possess indirect coupling of the channels through their voltage-dependent transition probabilities and the very rapid capacitive equilibration of the transmembrane voltage over large regions of the membrane. Consequently, numerical simulations of the model show a transition, with increasing channel numbers, from independent random behavior of channels to large scale collective activity, i.e., regular bursting, as the voltage coupling involves larger and larger numbers of channels. One obvious prospect is to approach this stochastic computer model from the essentially equivalent viewpoint of a master equation and to subsequently contract this description to yield Langevin equations (or, equivalently, Fokker-Planck equations). The Langevin equations should amount to a stochastic version of the Hodgkin-Huxley equations. In the limit of vanishingly small fluctuations (i.e., large numbers of channels), the Langevin description should contract to the original deterministic Hodgkin-Huxley description. Since the collective voltage spiking is a property of these deterministic equations, we would see in this way how the emergent collective behavior arises from the global coupling of independently stochastic elements. In addition to obtaining this deeper understanding of the phenomenon, the advantage accrues that far less computer time is required for the simulation of the Langevin equations than for the original computer model, or for the simulation of the equivalent master equation, when the number of channels is large.

III. HODGKIN-HUXLEY EQUATIONS

The deterministic Hodgkin-Huxley equation for the voltage (omitting the so-called leakage terms) is [1,3]

$$\frac{d}{dt}V=-\frac{1}{AC}[G_{\mathrm{Na}}(V-E_{\mathrm{Na}})+G_{\mathrm{K}}(V-E_{\mathrm{K}})]\ , \qquad (1)$$

in which V is the transmembrane voltage (in mV) in squid axons, C is the membrane capacitance density (in $\mu\mathrm{F/cm}^2$), A is the area of the membrane region under study (typically 1 or 5 $\mu\mathrm{m}^2$), $E_{\mathrm{Na}}=55$ mV is the reversal voltage for sodium, $E_{\mathrm{K}}=-72$ mV is the reversal voltage for potassium, G_{Na} is the sodium conductance, and G_{K} is the potassium conductance. These conductances are products of three factors: an individual channel conductance, $\Gamma_{\mathrm{Na}}=6$ pS (picosiemens) or $\Gamma_{\mathrm{K}}=4$ pS, respectively, the number of channels in the area A, N_{Na} or N_{K} respectively, and a factor representing how many channels are in the open state at a given time t. For sodium this last factor is m^3h while for potassium it is n^4, and m, h, and n satisfy the equations

$$\frac{d}{dt}m=\alpha_m(1-m)-\beta_m m\ , \qquad (2)$$

$$\frac{d}{dt}h=\alpha_h(1-h)-\beta_h h\ , \qquad (3)$$

$$\frac{d}{dt}n=\alpha_n(1-n)-\beta_n n\ , \qquad (4)$$

in which each of the rate constants (in reciprocal msec) α_m, α_h, α_n, β_m, β_h, and β_n depends on the global voltage V. Explicit parametrization of the voltage dependence for these rate constants in the nerve membrane may be found in Ref. [3]. Taken together, these expressions and Eqs. (1)-(4) make up the Hodgkin-Huxley equations.

The powers used in the nonlinearities n^4 and m^3h are not absolute. For example, in kinetic models of the node of Ranvier in a myelinated frog sciatic nerve, a motoneuron, the description is given by n^2 and m^2h instead. Consequently, the analysis that follows in Secs. V and VII for the master equations will be given in a manner that is easily generalized to other powers. Ultimately, biochemically oriented electrophysiologists must address the question of the physico-chemical basis for these expressions. Tentatively, it is thought that the fourth power in the potassium case represents the cooperative action of four regulatory molecules (proteins) constituting a single channel.

IV. STOCHASTIC AUTOMATON MODEL

The published stochastic interpretation of this phenomenon is given in a different form [3]. It is expressed directly in terms of a computer algorithm. Every 5 μsec the state of the system is updated. For the potassium channels, $4N_{\mathrm{K}}$ two-state elements (proteins) are considered. Each element may be either open or closed. They are grouped in groups of 4 which represent a single channel. If an element is closed at time t, then the probability that it remains closed at time $t+\Delta t$ is $\exp[-\alpha_n(V)\Delta t]$, and if it is open at time t, then the probability that it remains open at time $t+\Delta t$ is $\exp[-\beta_n(V)\Delta t]$. These probabilities are realized in the computer algorithm by random number generation. If all four elements in a group of 4 are open at time t, then that particular channel is considered conducting at that time with conductance Γ_{K}; otherwise, it is nonconducting. At each time the total conductance is the sum over all of the conducting channels. An entirely analogous procedure is used to compute the sodium conductance. Each sodium channel is also considered a group of four elements, but this time there are three m elements and one h element.

The probabilities to remain closed or open are determined as above for potassium elements but with the appropriate α's and β's for m and h elements. This computer algorithm amounts to a particular type of automaton. For the particular parameter values indicated above, this automaton is very noisy when N_{Na} and N_{K} are of order 300 and 30, respectively. However, when they are of order 1500 and 150, respectively, the computed behavior is very similar to the output from the deterministic Hodgkin-Huxley equations. Small fluctuations superimposed on nearly periodic spiking emerge. This is the phenomenon we want to understand.

V. MASTER EQUATION FOR POTASSIUM CHANNELS

The first step toward explaining emergent, regular behavior is to render the automaton as a master equation. This is possible because the essential ingredient for a master equation is the transition probability [11,12]. This quantity is given by the exponential probabilities for remaining closed or open given above. Let us denote the configuration of a two-state element (of type, m, h, or n) by the symbols u, for open, and d, for closed:

$$u=\begin{bmatrix}1\\0\end{bmatrix}\quad d=\begin{bmatrix}0\\1\end{bmatrix}. \tag{5}$$

The state at time $t+\Delta t$ may be determined with the 2×2 transition-probability matrix $W(\Delta t)$ given by

$$W(\Delta t)=\begin{bmatrix}1-\beta(V)\Delta t & \alpha(V)\Delta t\\ \beta(V)\Delta t & 1-\alpha(V)\Delta t\end{bmatrix}, \tag{6}$$

if Δt is sufficiently small. For example, $u^{\dagger}W(\Delta t)d$ denotes the probability that an element makes a transition from closed to open in time Δt, i.e., $\alpha(V)\Delta t$. For a potassium channel, the channel state is the direct product of four element states, i.e., an eight-state quantity [3,13]. Only the channel configuration $u_n\otimes u_n\otimes u_n\otimes u_n$ is conducting. Let p denote the number of open elements in the channel. Let $W_n(p',p)$ denote the transition probability for a channel to go from p open elements to p' open elements in time Δt. We can construct $W_n(p',p)$ from a direct product of four matrices like the W in (6), except that for potassium channels the α's and β's must carry the subscript n. The result is (both p and p' go from 0 to 4),

$$W_n(p',p)=\sum_{q=0}^{4}\begin{bmatrix}p\\q\end{bmatrix}(\beta_n\Delta t)^q(1-\beta_n\Delta t)^{p-q}\times\begin{bmatrix}4-p\\p'-p+q\end{bmatrix}(\alpha_n\Delta t)^{p'-p+q}\times(1-\alpha_n\Delta t)^{4-p'-q}. \tag{7}$$

The global coupling, which makes each factor of α_n and each factor of β_n in this expression depend on the same value of the voltage, V, is the key to our ability to go further with the analysis. For sufficiently small Δt, this simplifies considerably to

$$W_n(p',p)=[1-p\beta_n\Delta t-(4-p)\alpha_n\Delta t]\delta_{p',p}+p\beta_n\Delta t\delta_{p',p-1}+(4-p)\alpha_n\Delta t\delta_{p',p+1}. \tag{8}$$

Thus, if there are N_{K} channels, the master-equation probability distribution must be a function of N_{K} channels. Let the number of channels with p open elements be denoted by C_p. The number of channels with all closed elements is not independent and is simply $C_0=N_{\mathrm{K}}-C_1-C_2-C_3-C_4$ (we use the shorthand notation C_0 in the equations below), and the number of conducting channels is simply C_4. It is now possible to write the probability distribution for N_{K} channels as a function of the C_p's. Let the vector $\mathbf{C}$ denote the configuration (C_1,C_2,C_3,C_4). The probability distribution may be written as $P(\mathbf{C},t)$ and the transition probabilities may be denoted by $W_n(\mathbf{C}',\mathbf{C})$. We obtain

$$W_n(\mathbf{C}',\mathbf{C})=C_pW_n(p',p) \tag{9}$$

if any only if $C_p'=C_p-1$, $C_{p'}'=C_{p'}+1$, $p'-p=\pm 1$, and all other C_p''s and C_p's are identical. The master equation takes the form

$$\frac{\partial}{\partial t}P(\mathbf{C},t)=\sum_{p=1}^{4}\{(C_p+1)w_n(p-1,p)P(C_{p-1}-1,C_p+1,t)+(C_{p-1}+1)w_n(p,p-1)P(C_{p-1}+1,C_p-1,t)-[C_pw_n(p-1,p)+C_{p-1}w_n(p,p-1)]P(\mathbf{C},t)\}, \tag{10}$$

where

$$w_n(p',p)=\lim_{\Delta t\to 0}\frac{W_n(p',p)}{\Delta t}=\delta_{p',p-1}p\beta_n+\delta_{p',p+1}(4-p)\alpha_n \tag{11}$$

for $p'\neq p$, which follows from Eqs. (8) and (9). In the first two terms on the right-hand side of (10) we have made explicit the two C_p's that change while leaving implicit the remaining two which do not change.

VI. FOKKER-PLANCK EQUATION FOR POTASSIUM CHANNELS

For sufficiently large N_{K}, we may use standard system-size procedures [11,12] to obtain a Fokker-Planck equation approximation to this master equation. Let $\mathbf{x}=\mathbf{C}/N_{\mathrm{K}}$ and denote by x_0 the quantity $1-x_1-x_2-x_3-x_4$. Also define

$$K_p(\mathbf{x})=w_n(p,p+1)x_{p+1}-w_n(p+1,p)x_p + w_n(p,p-1)x_{p-1}-w_n(p-1,p)x_p \quad \text{for } p=1,2,3 , \tag{12}$$

$$K_4(\mathbf{x})=w_n(4,3)x_3-w_n(3,4)x_4 , \tag{13}$$

$$D_{pq}(\mathbf{x})=-\frac{1}{2N_K}[w_n(p,q)x_q+w_n(q,p)x_p] \quad \text{for } p-q=\pm 1 , \tag{14}$$

$$D_{pp}(\mathbf{x})=\frac{1}{2N_K}[w_n(p,p+1)x_{p+1}+w_n(p+1,p)x_p + w_n(p,p-1)x_{p-1}+w_n(p-1,p)x_p] \quad \text{for } p\neq 4 , \tag{15}$$

$$D_{44}(\mathbf{x})=\frac{1}{2N_K}[w_n(3,4)x_4+w_n(4,3)x_3] . \tag{16}$$

The Fokker-Planck equation is

$$\frac{\partial}{\partial t}P(\mathbf{x},t)=-\sum_{p=1}^{4}\frac{\partial}{\partial x_p}K_p(\mathbf{x})P(\mathbf{x},t) + \sum_{p=1}^{4}\sum_{q=1}^{4}\frac{\partial^2}{\partial x_p \partial x_q}D_{pq}(\mathbf{x})P(\mathbf{x},t) . \tag{17}$$

The first term on the right-hand side determines the deterministic limit behavior through $K_p(\mathbf{x})$. The fluctuations are governed by the second term, the diffusion term $D_{pq}(\mathbf{x})$.

VII. SODIUM CHANNEL RESULTS

Sodium channels also have four elements, three of type m and one of type h. Let C_{pr} denote the number of channels with p m-type elements open and r h-type elements open. In the sodium case, $p=0$, 1, 2, or 3 and $r=0$ or 1. Only the channel configuration $u_m \otimes u_m \otimes u_m \otimes u_h$ is conducting [3,13]. C_{00} is not independent and will be used as shorthand for $C_{00}=N_{Na}-C_{10}-C_{20}-C_{30}-C_{01}-C_{11}-C_{21}-C_{31}$. The number of conducting channels is C_{31}. The probability distribution for N_{Na} channels may be written as a function of the C_{pr}'s. Let the seven-component vector $\mathbf{C}$ denote the configuration $(C_{10},C_{20},C_{30},C_{01},C_{11},C_{21},C_{31})$. The probability distribution may be written as $P(\mathbf{C},t)$ and the transition probabilities may be denoted by $W_{mh}(\mathbf{C}',\mathbf{C})$. We obtain

$$W_{mh}(\mathbf{C}',\mathbf{C})=C_{pr}W_m(p',p) \tag{18a}$$

if and only if $r'=r$, $C'_{pr}=C_{pr}-1$, $C'_{p'r}=C_{p'r}+1$, $p'-p=\pm 1$ or

$$W_{mh}(\mathbf{C}',\mathbf{C})=C_{pr}W_h(r',r) \tag{18b}$$

if and only if $r'\neq r$, $C'_{pr}=C_{pr}-1$, $C'_{pr'}=C_{pr'}+1$, $p'=p$ where $W_m(p',p)$ and $W_h(r',r)$ are defined as in (8) but with the appropriate changes in subscript and argument labels. In parallel with (11), we define

$$w_m(p',p)=\lim_{\Delta t\to 0}\frac{W_m(p',p)}{\Delta t} =\delta_{p',p-1}p\beta_m+\delta_{p',p+1}(3-p)\alpha_m , \tag{19}$$

$$w_h(r',r)=\lim_{\Delta t\to 0}\frac{W_h(r',r)}{\Delta t} =\delta_{r',r-1}r\beta_h+\delta_{r',r+1}(1-r)\alpha_h . \tag{20}$$

The master equation takes the form

$$\begin{aligned}\frac{\partial}{\partial t}P(\mathbf{C},t)=&\sum_{r=0}^{1}\sum_{p=1}^{3}[(C_{pr}+1)w_m(p-1,p)P(C_{p-1r}-1,C_{pr}+1,t)+(C_{p-1r}+1)w_m(p,p-1)P(C_{p-1r}+1,C_{pr}-1,t)]\\ &+\sum_{p=0}^{3}[(C_{p1}+1)w_h(0,1)P(C_{p0}-1,C_{p1}+1,t)+(C_{p0}+1)w_h(1,0)P(C_{p0}+1,C_{p1}-1,t)]\\ &-\sum_{r=0}^{1}\sum_{p=1}^{3}[C_{pr}+w_m(p-1,p)+C_{p-1r}w_m(p,p-1)P(\mathbf{C},t)]-\sum_{p=0}^{3}[C_{p1}w_h(0,1)+C_{p0}w_h(1,0)P(\mathbf{C},t)] .\end{aligned} \tag{21}$$

For sufficiently large N_{Na}, we may use standard system-size procedures [11,12] to obtain a Fokker-Planck equation approximation to this master equation. Let $\mathbf{y}=\mathbf{C}/N_{Na}$ and denote by y_{00} the quantity $1-y_{10}-y_{20}-y_{30}-y_{01}-y_{11}-y_{21}-y_{31}$. Also define

$$K_{pr}(\mathbf{y})=w_m(p,p+1)y_{p+1r}-w_m(p+1,p)y_{pr} + w_m(p,p-1)y_{p-1r}-w_m(p-1,p)y_{pr} + w_h(0,1)y_{p1}-w_h(1,0)y_{p0} \quad \text{for } p=1 \text{ and } 2, \text{ and } r=0 , \tag{22}$$

$$K_{pr}(\mathbf{y})=w_m(p,p+1)y_{p+1r}-w_m(p+1,p)y_{pr} + w_m(p,p-1)y_{p-1r}-w_m(p-1,p)y_{pr} - w_h(0,1)y_{p1}+w_h(1,0)y_{p0} \quad \text{for } p=1 \text{ and } 2, \text{ and } r=1 , \tag{23}$$

$$K_{30}(\mathbf{y})=w_m(3,2)y_{20}-w_m(2,3)y_{30} + w_h(0,1)y_{31}-w_h(1,0)y_{30} , \tag{24}$$

$$K_{31}(\mathbf{y})=w_m(3,2)y_{21}-w_m(2,3)y_{31} -w_h(0,1)y_{31}+w_h(1,0)y_{30} , \quad (25)$$

$$K_{01}(\mathbf{y})=w_m(0,1)y_{11}-w_m(1,0)y_{01} -w_h(0,1)y_{01}+w_h(1,0)y_{00} . \quad (26)$$

In addition, we define a much longer list of $D_{p'r',pr}(\mathbf{y})$ expressions in parallel with Eqs. (14)–(16). For the purposes of this paper, it is not necessary to explicitly exhibit these quantities. The crucial point is that they are proportional to $1/N_{\mathrm{Na}}$.

The Fokker-Planck equation is

$$\frac{\partial}{\partial t}P(\mathbf{y},t)=-\sum_{r=0}^{1}\sum_{p=1}^{3}\frac{\partial}{\partial y_{pr}}K_{pr}(\mathbf{y})P(\mathbf{y},t) -\frac{\partial}{\partial y_{01}}K_{01}(\mathbf{y})P(\mathbf{y},t) +\sum_{r=0}^{1}\sum_{s=0}^{1}\sum_{p=1}^{3}\sum_{q=0}^{3}\frac{\partial^2}{\partial y_{pr}\partial y_{qs}}D_{pr,qs}(\mathbf{y})P(\mathbf{y},t) . \quad (27)$$

The last term in this equation is expressed very compactly for brevity, and whenever $r=0$ and $p=0$ or $s=0$ and $q=0$ then the corresponding $D_{pr,qs}$ vanishes. Thus, there are no y_{00} derivatives, in keeping with the fact that y_{00} is not an independent variable.

Needless to say, the Fokker-Planck equation for sodium is rather more complicated than that for potassium. Explicit expressions for $D_{pr,qs}(\mathbf{y})$ take up more than twice the space used for equations (22)–(26) because there are 49 separate quantities.

VIII. DETERMINISTIC LIMIT

The deterministic limits of the Fokker-Planck equations for potassium and sodium are obtained for very large values of N_{K} and N_{Na} respectively. In this limit, the diffusion terms in Eqs. (17) and (27) may be dropped. What remains are partial differential equations with first-order derivatives on both the left and right-hand sides:

$$\frac{\partial}{\partial t}P(\mathbf{x},t)=-\sum_{p=1}^{4}\frac{\partial}{\partial x_p}K_p(\mathbf{x})P(\mathbf{x},t) , \quad (28)$$

$$\frac{\partial}{\partial t}P(\mathbf{y},t)=-\sum_{r=0}^{1}\sum_{p=1}^{3}\frac{\partial}{\partial y_{pr}}K_{pr}(\mathbf{y})P(\mathbf{y},t) -\frac{\partial}{\partial y_{01}}K_{01}(\mathbf{y})P(\mathbf{y},t) . \quad (29)$$

These equations have the solutions

$$P(\mathbf{x},t)=\delta(\mathbf{x}-\mathbf{x}(t)) \quad \text{and} \quad P(\mathbf{y},t)=\delta(\mathbf{y}-\mathbf{y}(t)) , \quad (30)$$

where $\mathbf{x}(t)$ and $\mathbf{y}(t)$ satisfy the deterministic equations

$$\frac{d}{dt}x_p(t)=K_p(\mathbf{x}), \quad \frac{d}{dt}y_{qr}(t)=K_{qr}(\mathbf{y}) \quad (31)$$

in which $p=1$, 2, 3, and 4; $q=1$, 2 , and 3, and $r=0$ and 1; or $q=0$ and $r=1$. The explicit forms of the right-hand sides of (31) are given by (11)–(13) and (19), (20), (22)–(26), respectively.

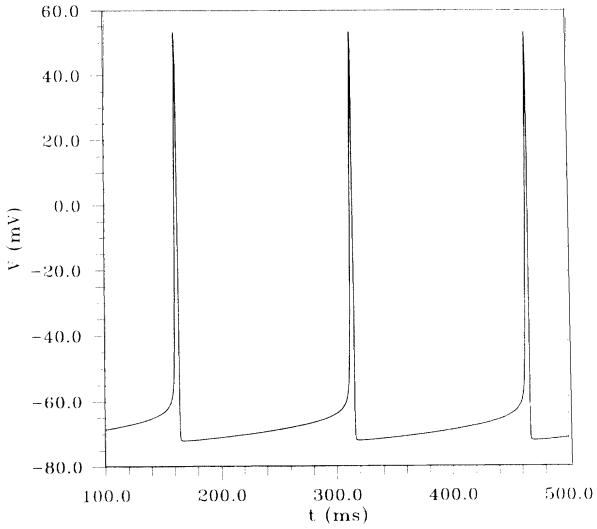

FIG. 4. Figures 4–11 are for $N_{\mathrm{Na}}=300$, $N_{\mathrm{K}}=30$, $C=1$ μF/cm^2, and $A=1$ μm^2 with a time step of 5 μsec. The initial conditions are the unstable steady-state values. This figure is the voltage for the Hodgkin-Huxley model.

This implies that the deterministic limit of the stochastic model is not precisely the Hodgkin-Huxley model given in (1)–(4), but is modified. Instead, we get (1) together with (31) with G_{K} and G_{Na} expressed by

$$G_{\mathrm{K}}=\Gamma_{\mathrm{K}}N_{\mathrm{K}}x_4 \quad \text{and} \quad G_{\mathrm{Na}}=\Gamma_{\mathrm{Na}}N_{\mathrm{Na}}y_{31} . \quad (32)$$

The quantities x_4 and y_{31} replace the quantities n^4 and m^3h found in the conductances in (1). Nevertheless, comparison of numerical simulations of the original Hodgkin-Huxley equations and these new, modified versions show remarkable quantitative agreement. This is shown in Figs. 4 through 11. In fact, the steady-state values of x_4 and n^4 and of y_{31} and m^3h are identical. Especially important for the understanding of the emer-

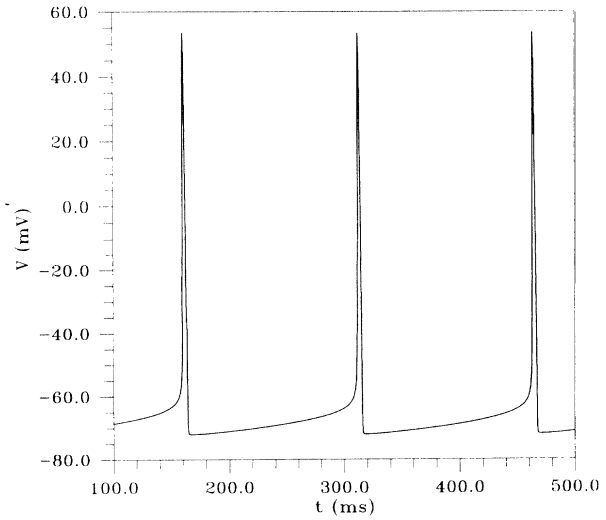

FIG. 5. This figure is the voltage for the modified Hodgkin-Huxley model.

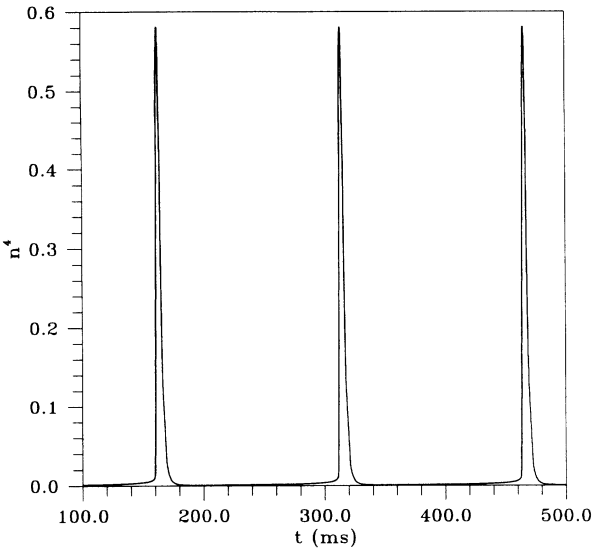

FIG. 6. This figure is n^4 for the Hodgkin-Huxley model.

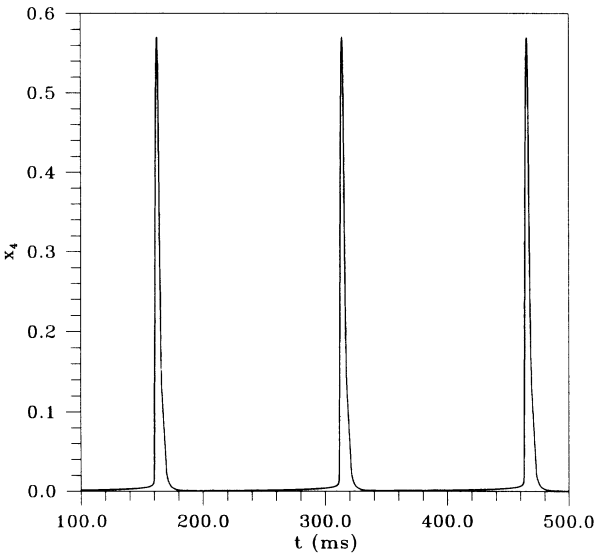

FIG. 7. This figure is x_4, the fraction of conducting potassium channels, for the modified Hodgkin-Huxley model.

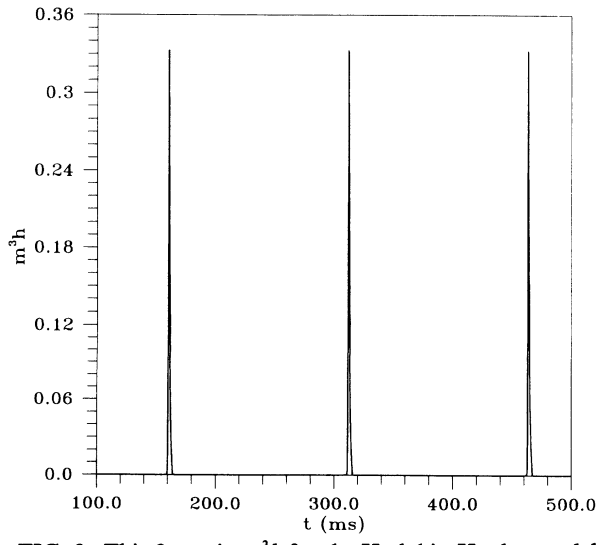

FIG. 8. This figure is m^3h for the Hodgkin-Huxley model.

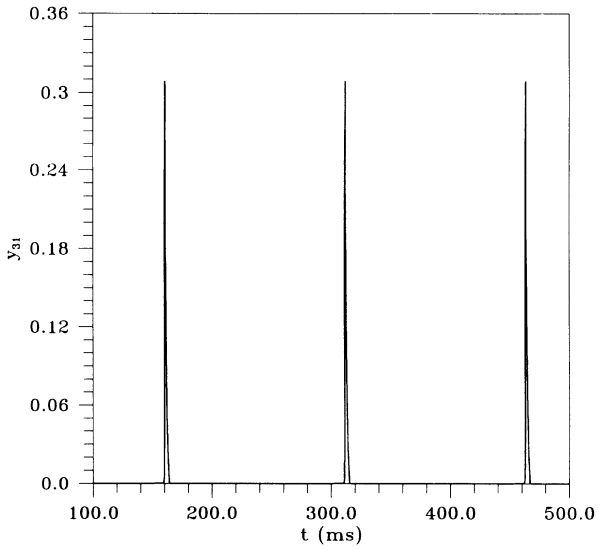

FIG. 9. This figure is y_{31}, the fraction of conducting sodium channels, for the modified Hodgkin-Huxley model.

gence of collective regular behavior in the stochastic model for large numbers of channels is the fact that Eqs. (1), (31), and (32) exhibit periodic spiking, just as do the original Hodgkin-Huxley equations (1)–(4).

IX. LANGEVIN DESCRIPTION

To every Fokker-Planck description there is associated a Langevin description. Since the Fokker-Planck description is in terms of partial differential equations, numerical simulations require a large lattice and become very time intensive. The Langevin description, on the other hand, involves stochastic, ordinary differential equations that are more easily realized by numerical

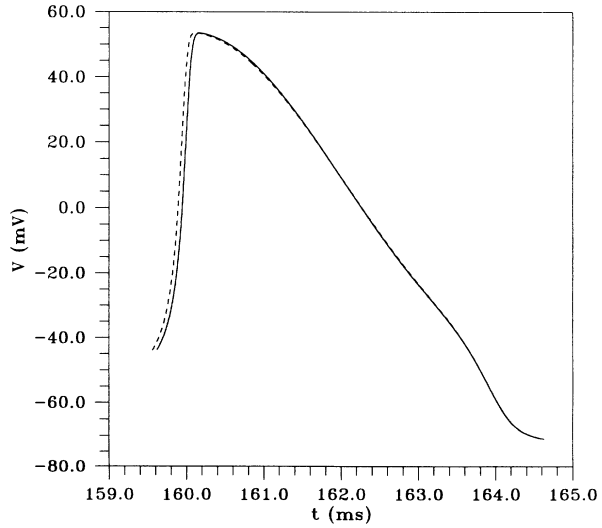

FIG. 10. This is a direct comparison of the voltage for the two models with the time axis expanded about 100-fold compared with Figs. 4 and 5. The dashed curve is for the Hodgkin-Huxley model and the solid curve is for the modified Hodgkin-Huxley model.

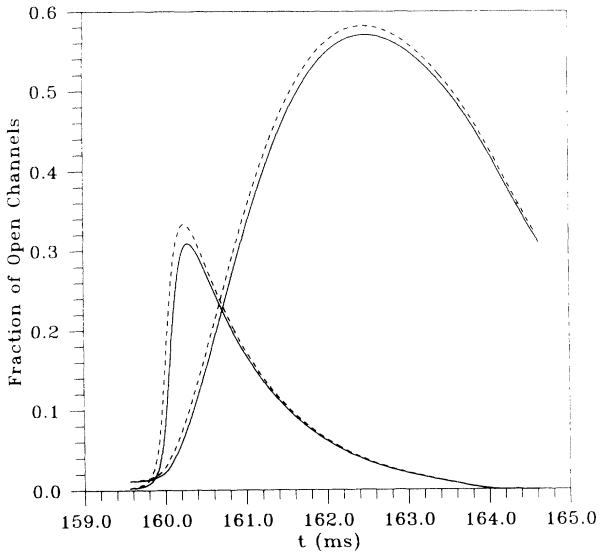

FIG. 11. This a direct comparison of n^4 with x_4, and of m^3h with y_{31}, with the time axis expanded about 100-fold compared with Figs. 6, 7, 8, and 9. The dashed curve is for the Hodgkin-Huxley model and the solid curve is for the modified Hodgkin-Huxley model. The higher pair of curves are for potassium.

simulations. Certain technical issues must be addressed in making this correspondence. Every stochastic thing we do here is done in the sense of Stratonovich [14].

Consider the Fokker-Planck equation (17) for the potassium-channel case. The associated Langevin equation may be written as [15]

$$\frac{d}{dt}x_p(t)=R_p(\mathbf{x}(t))+S_{pq}(\mathbf{x}(t))g_q(t) \tag{33}$$

in which the summation over the repeated index q is implicit, the g's are statistically independent Gaussian white

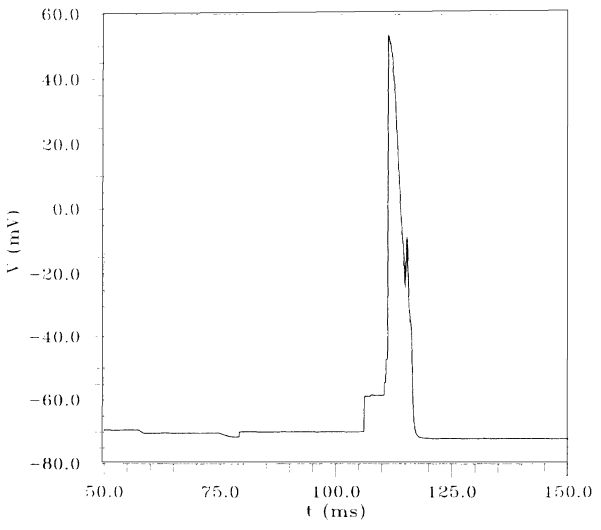

FIG. 12. Figures 12–19 are for $N_{Na}=300$, $N_K=30$, $C=1$ $\mu F/cm^2$, and $A=1$ μm^2 with a time step of 5 μsec. This figure is for the voltage calculated from the master equations (10) and (21) and the voltage equation (1).

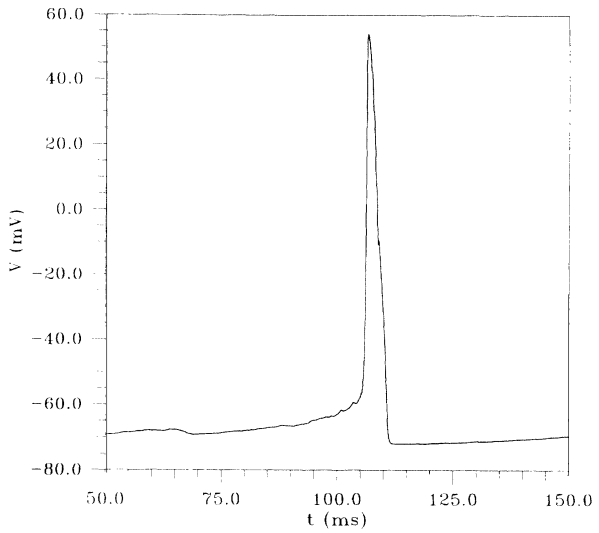

FIG. 13. This is the voltage calculated from the stochastic Hodgkin-Huxley model, Eqs. (41)–(44), and from the voltage equation (1).

noises with zero means and covariances of strength 2:

$$\langle g_q(t)\rangle=0 \quad \text{and} \quad \langle g_p(t)g_q(t')\rangle=2\delta_{pq}\delta(t-t') \tag{34}$$

and R_p and S_{pq} are defined by

$$S(\mathbf{x}(t))=[D(\mathbf{x}(t))]^{1/2}\,, \tag{35}$$

$$R_p(\mathbf{x}(t))=K_p(\mathbf{x}(t))-\left[\frac{\partial}{\partial x_j}S_{pq}(\mathbf{x}(t))\right]S_{jq}(\mathbf{x}(t))\,. \tag{36}$$

Since the matrix D_{pq} is symmetric, its square-root matrix S_{pq} is well defined. Moreover, since D_{pq} is of order $1/N_K$, the correction to K_p in the expression for R_p is also of order $1/N_K$. While technically necessary, this

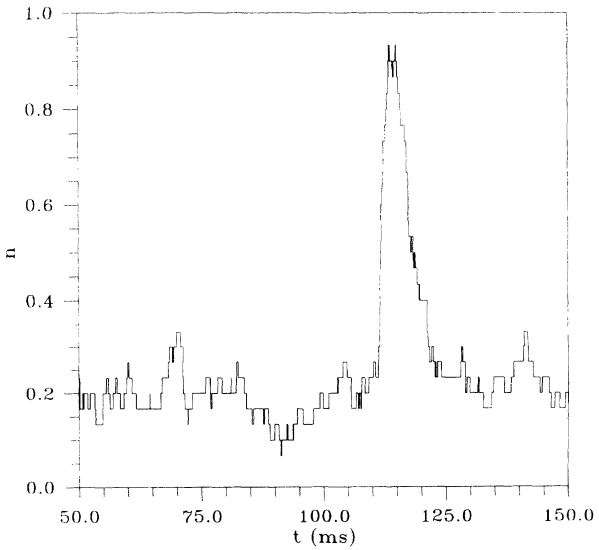

FIG. 14. This shows variable n determined from the master equations. To get n from the master-equation simulation, one counts the total number of first elements (out of four) in each channel that are open and divides by N_K.

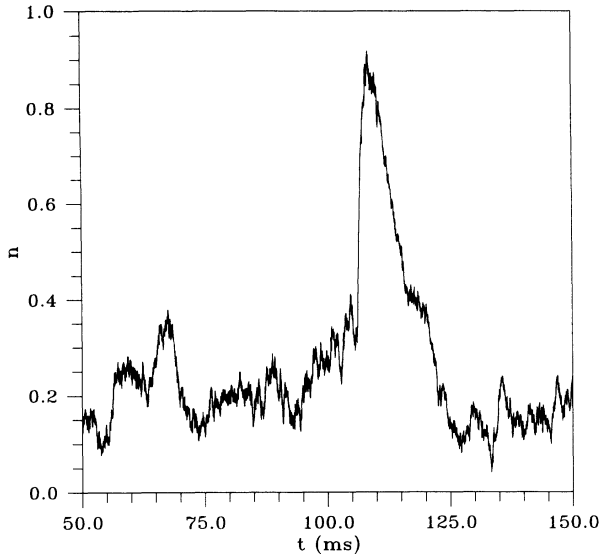

FIG. 15. This shows variable n determined from the stochastic Hodgkin-Huxley model.

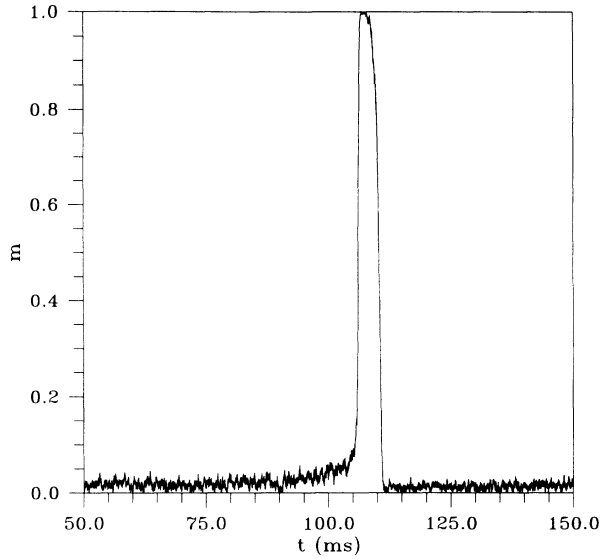

FIG. 17. This shows variable m determined from the stochastic Hodgkin-Huxley model.

correction term sometimes may be omitted since it is so small for large N_K.

Similar expressions are possible for the sodium-channel case. However, because the deterministic equations (1), (31), and (32) are so well approximated by the Hodgkin-Huxley equations (1)–(4), it turns out to be very accurate, and much simpler, to implement what amounts to a stochastic version of the Hodgkin-Huxley equations. That is, we simply introduce stochastic versions of Eqs. (2)–(4) and then raise n and m to the appropriate power for inclusion into the conductances for Eq. (1). This is vastly easier to implement than the procedure just outlined in the preceding paragraph. Nevertheless, if one works outside the parameter regime in which there is such good agreement between the modified Hodgkin-Huxley equations and the original Hodgkin-Huxley equations, then the more complicated scheme must be used instead.

The stochastic versions of (2)–(4) are special cases of the master equations (10) and (21). Instead of considering the potassium channels to be made up of four elements, we consider them to be made up of a single element of type n. Instead of considering the sodium channels to be made up of four elements, we also consider them to be made up of a single element, but this time there are two types, the m type and the h type. In all three cases, the master equation is simply of the form

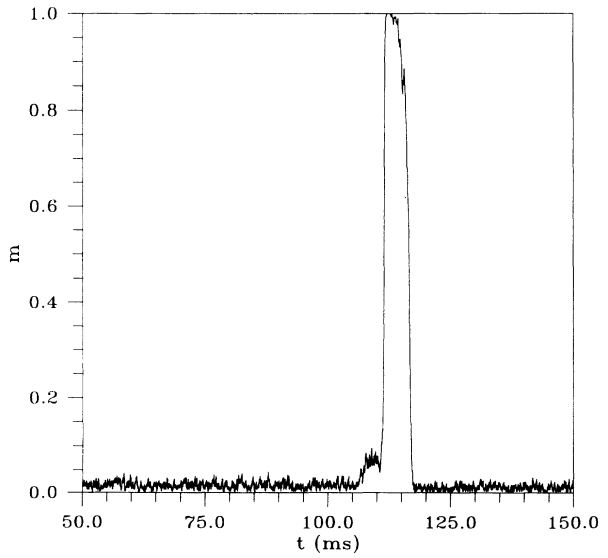

FIG. 16. This shows variable m determined from the master equations. To get m from the master-equation simulation, one counts the total number of first m elements (out of three) in each channel that are open and divides by N_{Na}.

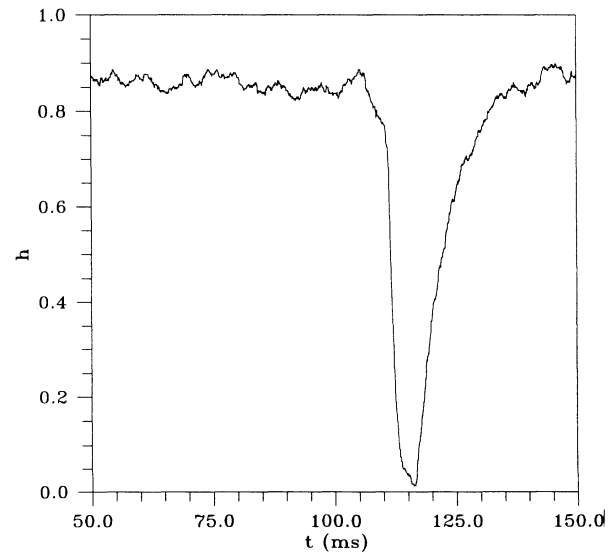

FIG. 18. This shows variable h determined from the master equations. To get h from the master-equation simulation, one counts the total number of h elements in each channel that are open and divides by N_{Na}.

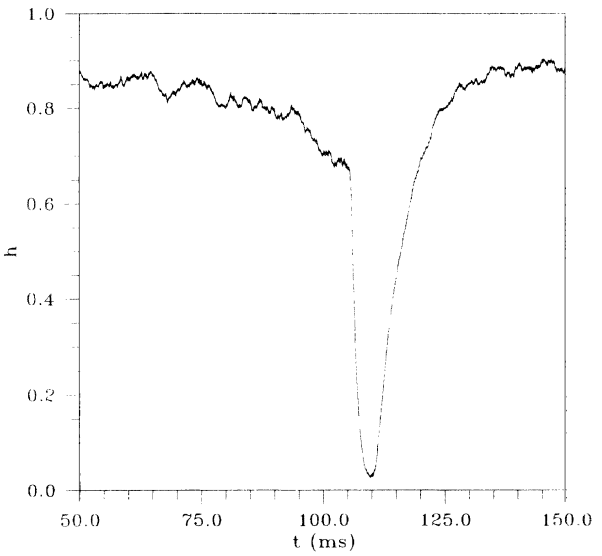

FIG. 19. This shows variable h determined from the stochastic Hodgkin-Huxley model.

$$\frac{\partial}{\partial t}P(c,t)=\{(c+1)\beta_n(t)P(c+1,t) +(N_K-c+1)\alpha_n(t)P(c-1,t) -[c\beta_n(t)+(N_K-c)\alpha_n(t)]P(c,t)\} , \quad (37)$$

which is explicitly for the n-type case and in which c denotes the number of one element channels that are open. For the m and h cases, only the subscripts n and K need to be changed. A master equation of this sort was studied by Fitzhugh [16] in 1965 but was not contracted down to a Langevin equation.

The corresponding Fokker-Planck equations are also special cases of the Fokker-Planck equations (17) and (27). Letting $n=c/N_K$ and $P(c,t)/N_K=P(n,t)$, we obtain

$$\frac{\partial}{\partial t}P(n,t)=-\frac{\partial}{\partial n}[\alpha_n(1-n)-\beta_n n]P(n,t) +\frac{\partial^2}{\partial n^2}\left[\frac{\alpha_n(1-n)+\beta_n n}{2N_K}\right]P(n,t) , \quad (38)$$

which is explicitly for the n-type case. For the m and h cases, again only the argument n and the subscripts n and K need to be changed.

Before we write down the corresponding Langevin equations, one more simplification is possible. In (38), the diffusion term may be replaced by its steady-state value for the instantaneous value of the voltage

$$\frac{\alpha_n(1-n)+\beta_n n}{2N_K}\rightarrow\frac{\alpha_n\beta_n}{N_K(\alpha_n+\beta_n)} , \quad (39)$$

because

$$n_s=\frac{\alpha_n}{\alpha_n+\beta_n} . \quad (40)$$

This approximation is independent of variable n and eliminates the analog of the second term on the right-hand side of (36).

The stochastic versions of (2)–(4), i.e., the Langevin equations, may be written as

$$\frac{d}{dt}n=\alpha_n(1-n)-\beta_n n+g_n(t) , \quad (41)$$

$$\frac{d}{dt}m=\alpha_m(1-m)-\beta_m m+g_m(t) , \quad (42)$$

$$\frac{d}{dt}h=\alpha_h(1-h)-\beta_h h+g_h(t) , \quad (43)$$

in which the g's are statistically independent Gaussian white noises with zero means and mean squares given, e.g., in the n-type case, by

$$\langle g_n(t)g_n(t')\rangle=2\frac{\alpha_n\beta_n}{N_K(\alpha_n+\beta_n)}\delta(t-t') \quad (44)$$

or with appropriate changes in the subscripts for the m and h cases. It is perhaps remarkable that after our long excursion from automaton through master equations, Fokker-Planck equations, and (finally arriving at) Langevin equations that a highly accurate approximation turns out to be simply a stochastic version of the original Hodgkin-Huxley equations with noise terms having the simple correlations given by (44). This is shown in Figs. 12 through 19.

In the general case, one must check by numerical simulation that this approximate treatment is an accurate substitute for the more intricate treatment we have developed in the preceding sections. So far, no purely analytic method has been developed for deciding this choice.

Two technical remarks are necessary in order to implement the stochastic equations (41)–(44). The noise terms are generated at each integration step by the Box-Muller [17] algorithm which starts with the generation of two uniformly distributed random numbers from the unit interval. Since n, m, and h are each bounded between 0 and 1, it is necessary to check, after each integration step, whether or not the noise term has taken the updated values of n, m, or h outside of [0,1]. If so, then one must redo the integration step, i.e., repeat the Box-Muller steps with new random numbers, until the updated values of n, m, and h each stay within [0,1]. This effective truncation of the Gaussian random numbers, the g's, is usually only required when the values of n, m, or h are near the extremes of the interval [0,1] and is in keeping with the constraints rigorously required by the underlying master equation. Since the Langevin description is an approximation to the master equation, it is consistent to approximate the Langevin implementation itself where necessary so that the master equation constraints are respected. In our programs, we achieve this truncation by internal do-loops. This is much less singular than, say, resetting n, m, or h to either 0 or 1 whenever its updated value leaves [0,1] at 0 or 1, respectively.

X. CONCLUDING REMARKS

In this paper, we have investigated the phenomenon of emergent, regular behavior in globally coupled, indepen-

dently stochastic ion channels as the number of coupled channels increases. While this kind of phenomenon occurs in a variety of contexts [4–10], our focus has been on the Hodgkin-Huxley model [1] for the generation of action potentials in squid axon. An important underpinning for our work was the realization that individual ion channels behave as stochastic elements. This insight was gleaned by Neher and Sakmann [2] in their revolutionary patch-clamp experiments, and was used in stochastic automaton modeling by DeFelice and co-workers [3] and by others [13].

The observation made in this earlier work [3] that caught our attention was the fact that global coupling of many otherwise stochastically independent ion channels leads to regular, or periodic, macroscopic behavior, i.e., the generation of bursting, spiking, or action potentials. It seemed obvious that the deterministic perspective of Hodgkin and Huxley and the stochastic perspective of DeFelice and others could be combined by standard procedures [11,12] that involve a succession of description contractions involving automatons, master equations, Fokker-Planck equations, Langevin equations, and finally the deterministic limit of these equations. That these contractions can occur is a consequence of the global coupling, which in this case is created by the membrane capacitance and the voltage-dependent rate constants. We foresaw that what would appear as purely stochastic behavior in small numbers of channels described by a stochastic automaton model would appear as periodic spiking in large numbers of channels described by the deterministic limit of the underlying automaton description. All that was needed to be done was to spell out the details of the successive contractions.

What we found to be the case, however, was more delicate than originally foreseen. In essence, the scenario just developed was realized, but with an important proviso. The automaton model does not literally contract into the Hodgkin-Huxley model. Instead, it leads to a modified Hodgkin-Huxley model given by Eqs. (1), (31), and (32). Nevertheless, in the parameter regime of interest in earlier studies, these two models yield quantitatively nearly identical results in numerical simulations of the voltage profile with time. Moreover, the Langevin stage of contraction for the automaton model is a stochastic extension of the modified Hodgkin-Huxley model. Its quantitative behavior is nearly indistinguishable from the behavior of a simpler, stochastic version of the Hodgkin-Huxley model, which is given by (1), (41), and (44). In the course of making these realizations, we have developed a master equation the equivalent of the automaton model and have done so in a way which is easily generalized to model variations. These variations include changes in the number and type of channel elements in multielement channels. We also showed how to contract out the corresponding Fokker-Planck equations and the equivalent Langevin equations. These developments make up the bulk of the content in Secs. V–IX. Thus, while achieving our goal with regard to explaining emergent collective behavior, we have also provided a general setting for a large class of master equations and their contractions for describing globally coupled ion channels and similar phenomena in other physical contexts [5–10].

An especially useful benefit of this extension is the observation that numerical implementation of Langevin descriptions is vastly more time efficient than numerical implementation of the corresponding master equation. In the case of the sodium and potassium action potentials, the savings were roughly 100-fold for $N_{Na}=1500$ and $N_K=150$.

ACKNOWLEDGMENTS

This work was supported by NSF Grant No. PHY-9203878, the State Education Commission of P.R. China, and the Emory–Georgia Tech Biomedical Technology Research Center. It benefited from extremely valuable consultations with L. DeFelice and B. Goolsby of Emory University.

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