Reduction of a kinetic model for Na^+ channel activation, and fast and slow inactivation within a neural or cardiac membrane

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A 15-state kinetic model for Na^+ channel gating that describes the coupling between three activation sensors, a two-stage fast inactivation process, and slow inactivated states may be reduced to equations for a 6-state system by application of the method of multiple scales. By expressing the occupation probabilities for closed states and the open state in terms of activation and fast inactivation variables, and assuming that activation has a faster relaxation than inactivation and that the activation sensors are mutually independent, the kinetic equations may be further reduced to rate equations for activation, and coupled fast and slow inactivation that describe spike frequency adaptation, a repetitive bursting oscillation in the neural membrane, and a cardiac action potential with a plateau oscillation. The fast inactivation rate function is, in general, dependent on the activation variable $m(t)$ but may be approximated by a voltage-dependent function, and the rate function for entry into the slow inactivated state is dependent on the fast inactivation variable.

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I. INTRODUCTION

During prolonged or repetitive depolarization, in addition to the fast inactivation of Na channels that contributes to repolarization of the membrane [1], a slow inactivation process reduces the number of Na^+ channels available for activation. The increase in slow inactivation of Na^+ channels during depolarization is associated with a delay to the next spike or a reduction in the firing frequency (spike frequency adaptation) [2] and is the result of a structural rearrangement in the selectivity filter region of the ion channel that generally occurs following the inactivation of the pore [3]. Slow inactivation of the transient and persistent components of the Na^+ current in a mesencephalic V neuron is associated with the termination of a bursting oscillation, and the increase in the amplitude of the subthreshold oscillation between bursts occurs during the recovery from slow inactivation [4]. In subicular neurons adjacent to the hippocampus, the transition from bursting to single spiking is influenced by the slow inactivation of Na^+ channels, and this may provide a mechanism for enhancing the effect of input signals [5].

The Na^+ channel protein is composed of four domains DI to DIV that surround the ion pore, and in response to membrane depolarization, the transverse motion of the charged S4 segments of DI to DIII is associated with activation, and the slower movement of DIV is correlated with fast inactivation [6]. A recent study of the effect of molecular inhibitors on Na^+ channel gating has proposed that fast and slow Na^+ channel inactivation are sequential processes [7], and that the activation of the DIV sensor has an essential role in each type of inactivation [8].

Based on the measurement of voltage clamp currents and the slow cumulative adaptation of spike firing for neocortical neurons, the Na^+ current I_{Na} may be described by the expression $m^3hs(V_{Na} - V)$ [2] where V_{Na} is the equilibrium potential, the activation variable m, the fast inactivation variable h, and the slow inactivation variable s satisfy the equations

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

$$\frac{dh}{dt} = \alpha_h - h(t)(\alpha_h + \beta_h), \quad (2)$$

$$\frac{ds}{dt} = \alpha_s - s(t)(\alpha_s + \beta_s), \quad (3)$$

and the rate functions α_g and β_g are dependent on the membrane potential V for $g = m, h,$ and s. The Na^+ current may also be expressed as $O(t)(V_{Na} - V)$ where $O(t)$ is the open state probability that is determined by a kinetic model where transitions between states represent the activation of three S4 voltage sensors to open the channel, a two-stage fast inactivation process [9] and subsequent slow inactivation [10].

Single-channel recording techniques have demonstrated that ion channels are thermally activated between closed and open states [11], and therefore, the Hodgkin Huxley (HH) equations describe the behavior of a large number of stochastic Na^+ and K^+ channels. The probability distribution for the number N of open Na^+ channels satisfies a master equation, and for sufficiently large N, by application of a system size expansion, the master equation may be approximated by a Fokker-Planck equation [12]. As the diffusion terms are small, it may be further reduced to deterministic equations that are equivalent to the rate equations for the activation variable m and the inactivation variable h.

Assuming that each voltage sensor is a Brownian particle in an energy landscape, the master equation for the random walk within the membrane may be reduced to a Smoluchowski equation that is dependent on a diffusion parameter and a potential of mean force [13]. As the relaxation within each

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deep well is rapid, the probability density may be expressed as the product of the stationary distribution and a survival probability that is the solution of a rate equation [14]. By approximating the potential function for the voltage sensor by a square well potential, the low-frequency component of the solution of the Smoluchowski equation may be expressed as differential equations for the survival probabilities of the closed and open states [15,16] and is similar to that obtained from a numerical solution [17].

For a system of differential equations that has a separation of timescales, a reduced system may be derived explicitly by expressing the solution as an asymptotic expansion that is dependent on the fast and slow times [18]. A variable that attains a quasisteady state after an initial fast transient, is the solution of an approximate algebraic equation that may be obtained as the lowest order term in an asymptotic expansion of the solution of the full system, and therefore, the long-time behavior is governed by the dynamics of the slow variables that form a subsystem of lower dimension. The method of multiple scales and other singular perturbation techniques have been applied to the equations in many areas of physics and biology, such as orbital mechanics, coupled nonlinear oscillators, and biochemical and enzyme reactions [18,19].

In this paper, it is shown that by taking account of the large relative magnitude of the transition rates between some states, a fifteen state kinetic model that describes Na^+ channel gating with three activation sensors, a two-stage fast inactivation process, and a slow transition to additional inactivated states, may be approximated by equations for a six state system. Assuming that the activation sensors are mutually independent and activation has a smaller relaxation time than fast inactivation, the inactivation rate function is, in general, dependent on the activation variable $m(t)$ but may be approximated by a voltage-dependent function, and the slow inactivation rate function is dependent on the fast inactivation variable $h_f(t)$. The kinetic model describing Na^+ channel gating may be reduced to rate equations for activation, and fast and slow inactivation with a solution that may exhibit spike frequency adaptation, a repetitive bursting oscillation and a cardiac action potential with a plateau oscillation.

II. REDUCTION OF A KINETIC MODEL FOR Na^+ CHANNEL ACTIVATION AND FAST INACTIVATION

By assuming that Na^+ channel activation and inactivation are independent, the Hodgkin-Huxley (HH) rate equations for Na^+ and K^+ channels and the membrane current equation provide a good account of the action potential waveform, the threshold potential, and subthreshold oscillations in the squid axon membrane [1], and the approach has been applied to a wide range of voltage-dependent ion channels in nerve, muscle and cardiac membranes [6]. However, subsequent experimental studies have shown that the probability of Na^+ channel fast inactivation increases with the degree of activation of the channel [20], the recovery from inactivation is more probable following deactivation [21], and the kinetic equations for coupled Na^+ activation and inactivation processes describe ion channel states and their transitions, and account for the ionic and gating currents during a voltage clamp [9].

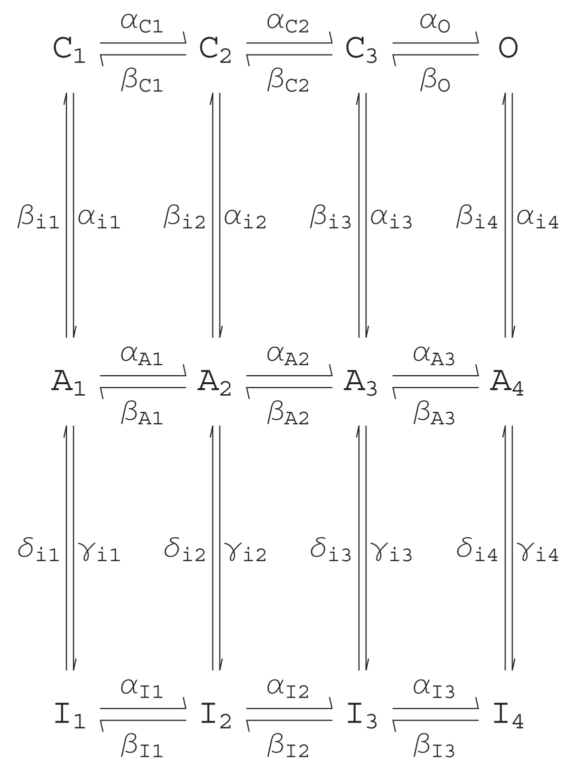

FIG. 1. State diagram for Na^+ channel gating where horizontal transitions represent the activation of three voltage sensors (DI, DII, and DIII) that open the pore, and vertical transitions represent the two-stage fast inactivation process of the DIV voltage sensor and the inactivation motif.

If the Na^+ channel conductance is dependent on the activation of three voltage sensors coupled to a two-stage inactivation process, then the kinetics may be described by a 12-state model (see Fig. 1) where the occupation probabilities of the closed states C_1, C_2, C_3, A_1, A_2, and A_3, the open states O and A_4 and the inactivated states I_1, I_2, I_3, and I_4 are determined by the equations

$$\frac{dC_1}{dt} = -(\alpha_{C1} + \alpha_{i1})C_1(t) + \beta_{C1}C_2(t) + \beta_{i1}A_1(t), \quad (4)$$

$$\frac{dC_2}{dt} = -(\alpha_{C2} + \beta_{C1} + \alpha_{i2})C_2(t) + \alpha_{C1}C_1(t) + \beta_{C2}C_3(t) + \beta_{i2}A_2(t), \quad (5)$$

$$\frac{dC_3}{dt} = -(\alpha_O + \beta_{C2} + \alpha_{i3})C_3(t) + \alpha_{C2}C_2(t) + \beta_O O(t) + \beta_{i3}A_3(t), \quad (6)$$

$$\frac{dO}{dt} = -(\beta_O + \alpha_{i4})O(t) + \alpha_O C_3(t) + \beta_{i4}A_4(t), \quad (7)$$

$$\frac{dA_1}{dt} = -(\alpha_{A1} + \beta_{i1} + \gamma_{i1})A_1(t) + \alpha_{i1}C_1(t) + \delta_{i1}I_1(t) + \beta_{A1}A_2(t), \quad (8)$$

$$\frac{dA_2}{dt} = -(\alpha_{A2} + \beta_{A1} + \beta_{i2} + \gamma_{i2})A_2(t) + \alpha_{i2}C_2(t) + \delta_{i2}I_2(t) + \alpha_{A1}A_1(t) + \beta_{A2}A_3(t) \quad (9)$$

$$\frac{dA_3}{dt} = -(\alpha_{A3} + \beta_{A2} + \beta_{i3} + \gamma_{i3})A_3(t) + \alpha_{i3}C_3(t) + \delta_{i3}I_3(t) + \alpha_{A2}A_2(t) + \beta_{A3}A_4(t), \quad (10)$$

$$\frac{dA_4}{dt} = -(\beta_{A3} + \beta_{i4} + \gamma_{i4})A_4(t) + \alpha_{i4}O(t) + \delta_{i4}I_4(t) + \alpha_{A3}A_3(t), \quad (11)$$

$$\frac{dI_1}{dt} = -(\alpha_{I1} + \delta_{i1})I_1(t) + \gamma_{i1}A_1(t) + \beta_{I1}I_2(t), \quad (12)$$

$$\frac{dI_2}{dt} = -(\alpha_{I2} + \beta_{I1} + \delta_{i2})I_2(t) + \gamma_{i2}A_2(t) + \alpha_{I1}I_1(t) + \beta_{I2}I_3(t), \quad (13)$$

$$\frac{dI_3}{dt} = -(\alpha_{I3} + \beta_{I2} + \delta_{i3})I_3(t) + \gamma_{i3}A_3(t) + \alpha_{I2}I_2(t) + \beta_{I3}I_4(t), \quad (14)$$

$$\frac{dI_4}{dt} = -(\beta_{I3} + \delta_{i4})I_4(t) + \gamma_{i4}A_4(t) + \alpha_{I3}I_3(t), \quad (15)$$

and the transition rates satisfy microscopic reversibility. The model is based on the measurement of currents for wild type and mutant Na$^+$ channels where the majority of the gating charge of the voltage sensors in domains DI to DIV is neutralized. Tke kinetic scheme describes the activation of the DI to DIII voltage sensors and pore opening, as well as the activation of the DIV sensor followed by occlusion of the ion pore by the inactivation motif [9].

It is assumed that Na$^+$ channels depolarize the membrane, K$^+$ and leakage channels repolarize the membrane, and the K$^+$ conductance is proportional to $n(t)^4$ where the activation variable $n(t)$ satisfies the equation [1]

$$\frac{dn}{dt} = \alpha_n - n(t)(\alpha_n + \beta_n), \quad (16)$$

and α_n and β_n are voltage-dependent rate functions. This equation may be derived from a kinetic model for K$^+$ channel gating where the voltage dependence of α_n and β_n may be expressed in terms of the transition rates for a two-stage voltage sensor activation process [22,23]. The membrane current equation is

$$C\frac{dV}{dt} = i_e - \bar{g}_{\rm Na}O(t)(V - V_{\rm Na}) - \bar{g}_{\rm K}n(t)^4(V - V_{\rm K}) - \bar{g}_L(V - V_L), \quad (17)$$

where $\bar{g}_j$ is the conductance, V_j is the equilibrium potential for each channel j (Na$^+$, K$^+$, and leakage), and i_e is the external current.

When the fast inactivation transition rates $\alpha_{ik} \ll \gamma_{ik}$, $\delta_{ik} \ll \beta_{ik}$, and $\gamma_{ik} + \beta_{ik}$ is greater than the activation and deactivation rate functions, for each k, the occupation probabilities of A_1 to A_4 attain quasistationary values in a time that is smaller than the relaxation of the membrane potential and the closed, open and inactivated states [24], and Eqs. (4)–(15) may be reduced to an eight-state system by expressing the solution as a two-scale asymptotic expansion and eliminating secular terms [18] (see Fig. 2 and Appendix A)

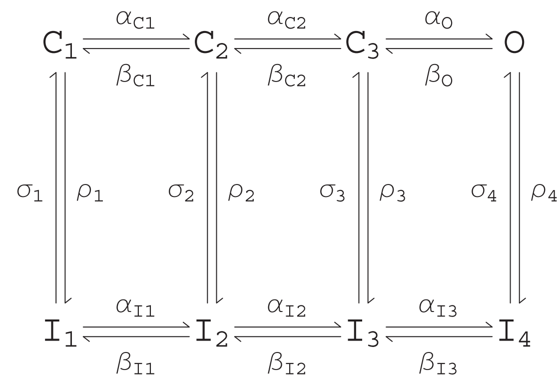

FIG. 2. The state diagram for Na$^+$ channel gating in Fig. 1 may be reduced to an eight-state model when $\beta_{ik} \gg \delta_{ik}$, $\gamma_{ik} \gg \alpha_{ik}$, and $\gamma_{ik} + \beta_{ik}$ is greater than the activation and deactivation rate functions, for each k, where the derived rate functions ρ_k and σ_k are defined in Eqs. (26) and (27).

$$\frac{dC_1}{dt} = -(\alpha_{C1} + \rho_1)C_1(t) + \beta_{C1}C_2(t) + \sigma_1 I_1(t), \quad (18)$$

$$\frac{dC_2}{dt} = -(\alpha_{C2} + \beta_{C1} + \rho_2)C_2(t) + \alpha_{C1}C_1(t) + \beta_{C2}C_3(t) + \sigma_2 I_2(t), \quad (19)$$

$$\frac{dC_3}{dt} = -(\alpha_O + \beta_{C2} + \rho_3)C_3(t) + \alpha_{C2}C_2(t) + \beta_O O(t) + \sigma_3 I_3(t), \quad (20)$$

$$\frac{dO}{dt} = -(\beta_O + \rho_4)O(t) + \alpha_O C_3(t) + \sigma_4 I_4(t), \quad (21)$$

$$\frac{dI_1}{dt} = -(\alpha_{I1} + \sigma_1)I_1(t) + \rho_1 C_1(t) + \beta_{I1}I_2(t), \quad (22)$$

$$\frac{dI_2}{dt} = -(\alpha_{I2} + \beta_{I1} + \sigma_2)I_2(t) + \alpha_{I1}I_1(t) + \beta_{I2}I_3(t) + \rho_2 C_2(t), \quad (23)$$

$$\frac{dI_3}{dt} = -(\alpha_{I3} + \beta_{I2} + \sigma_3)I_3(t) + \alpha_{I2}I_2(t) + \beta_{I3}I_4(t) + \rho_3 C_3(t), \quad (24)$$

$$\frac{dI_4}{dt} = -(\beta_{I3} + \sigma_4)I_4(t) + \alpha_{I3}I_3(t) + \rho_4 O(t), \quad (25)$$

where the derived rate functions for Na$^+$ channel inactivation and recovery are, for each k,

$$\rho_k = \frac{\alpha_{ik}\gamma_{ik}}{\beta_{ik} + \gamma_{ik}}, \quad (26)$$

$$\sigma_k = \frac{\delta_{ik}\beta_{ik}}{\beta_{ik} + \gamma_{ik}}. \quad (27)$$

If the fast inactivation rates γ_{ik} and β_{ik} are decreased by an order of magnitude, then the occupation probabilities A_1 to A_4 are not constant during the relaxation of the closed, open, and inactivated states, and the error of the approximation is increased. The Na$^+$ channel activation rate functions between closed and open states may also be expressed in terms of the

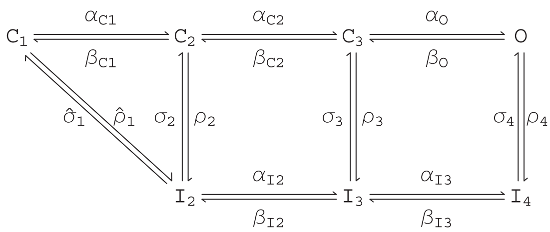

FIG. 3. The state diagram for Na^+ channel gating in Fig. 2 may be reduced to a seven-state model when $\alpha_{I1} \gg \rho_1$ and $\sigma_1 \gg \beta_{I1}$, where the derived rate functions $\hat{\rho}_1$ and $\hat{\sigma}_1$ are defined in Eqs. (30) and (31).

transition rates of a two or three-stage process [22], which are dependent on electrostatic and hydrophobic forces on the charged residues of the S4 voltage sensor [25].

If it is assumed that the inactivation sensor and the three activation sensors are independent, then the HH rate equations for Na^+ channel activation and inactivation are exact solutions of an eight-state kinetic model for channel gating [6,26]. However, activation and inactivation are coupled processes, and if $\alpha_{I1} \gg \rho_1$ and $\sigma_1 \gg \beta_{I1}$ for membrane potentials in the physiological range, based on empirical rate functions for a Na^+ channel [9], by expressing the solution as an asymptotic expansion that is dependent on fast and slow timescales and solving the equations to lowest order [18] (see Appendix B), then Eqs. (18) and (23) may be approximated by (see Fig. 3)

$$\frac{dC_1}{dt} = -(\alpha_{C1} + \hat{\rho}_1)C_1(t) + \beta_{C1}C_2(t) + \hat{\sigma}_1 I_2(t), \quad (28)$$

$$\frac{dI_2}{dt} = -(\alpha_{I2} + \hat{\sigma}_1 + \sigma_2)I_2(t) + \beta_{I2}I_3(t) + \hat{\rho}_1 C_1(t) + \rho_2 C_2(t), \quad (29)$$

where

$$\hat{\rho}_1 = \frac{\rho_1\alpha_{I1}}{\alpha_{I1} + \sigma_1}, \quad (30)$$

$$\hat{\sigma}_1 = \frac{\sigma_1\beta_{I1}}{\alpha_{I1} + \sigma_1}, \quad (31)$$

$$I_1(t) \approx \frac{\rho_1 C_1(t) + \beta_{I1}I_2(t)}{\alpha_{I1} + \sigma_1}, \quad (32)$$

and n and V are determined by Eqs. (16) and (17) (see Fig. 4). If $\alpha_{I1} + \sigma_1$ is reduced by a factor of three, then the relaxation of I_1 is slower and a deviation occurs between the solutions of the full system and the reduced equations.

In Eqs. (24), (25), and (29), it is assumed that for each membrane potential, the transition rates between fast inactivated states with occupation probabilities I_2, I_3, and I_4 are an order of magnitude larger than inactivation and recovery rates, and larger than activation and deactivation rates between closed and open states, and therefore, by expressing the solution as a two-scale asymptotic expansion and eliminating secular terms [18], it may be shown that Eqs. (18) to (25) may be reduced to a five state kinetic model (see Fig. 5 and Appendix C for an ion channel with fast and slow inactivated states)

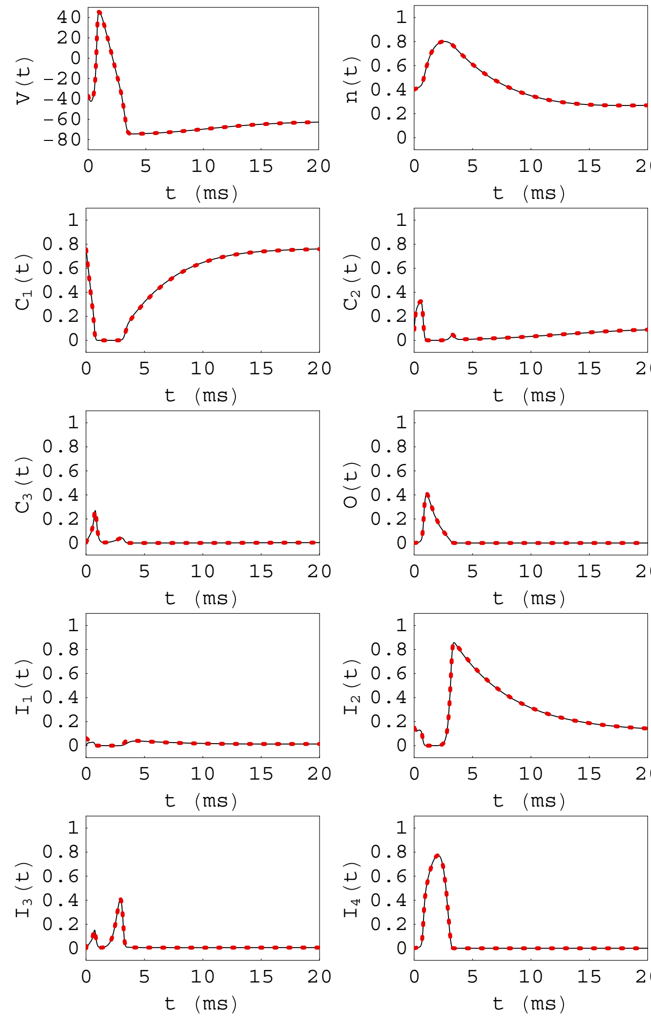

FIG. 4. During the action potential solution of Eqs. (18)–(25) for C_1, C_2, C_3, O, and I_1–I_4 (solid line), Eqs. (18), (22), and (23) for C_1, I_1, and I_2 may be approximated by Eqs. (28), (29), and (32) (dotted line), when $\alpha_{I1} \gg \rho_1$ and $\sigma_1 \gg \beta_{I1}$, and n and V are determined by Eqs. (16) and (17). The rate functions are $\alpha_m = 0.1(V+35)/\{1-\exp[-(V+35)/10]\}$, $\beta_m = 4\exp[-(V+60)/18]$, $\alpha_{C1} = 3\alpha_m$, $\beta_{C1} = \beta_m$, $\alpha_{C2} = 2\alpha_m$, $\beta_{C2} = 2\beta_m$, $\alpha_O = \alpha_m$, $\beta_O = 3\beta_m$, $\alpha_{I1} = \alpha_{C1}$, $\beta_{I1} = 0.016\beta_{C1}$, $\alpha_{I2} = 2\alpha_{C2}$, $\beta_{I2} = 2\beta_{C2}$, $\alpha_{I3} = 2\alpha_O$, $\beta_{I3} = 2\beta_O$, $\alpha_{ik} = 1$, $\gamma_{ik} = 22.2$, $\beta_{ik} = \exp[-V/10]$, $\delta_{i1} = 2.5$, $\delta_{i2} = \delta_{i3} = \delta_{i4} = 0.04$, $\rho_k = \alpha_{ik}/(1+\beta_{ik}/\gamma_{ik})$ for $k = 1$ to 4, $\sigma_1 = \delta_{i1}/(1+\gamma_{i1}/\beta_{i1})$, $\sigma_2 = \sigma_3 = \sigma_4 = 0.016\sigma_1$, $\alpha_n = 0.01(V+50)/(1-\exp[-(V+50)/10])$, $\beta_n = 0.125\exp[-(V+60)/80]$ (ms^{-1}), and $\bar{g}_{Na} = 120$ mS/cm^2, $\bar{g}_K = 36$ mS/cm^2, $\bar{g}_L = 0.3$ mS/cm^2, $V_{Na} = 55$ mV, $V_K = -75$ mV, $V_L = -60$ mV, $C = 1$ $\mu F/cm^2$, and $i_e = 1$ $\mu A/cm^2$.

$$\frac{dC_1}{dt} = -(\alpha_{C1} + \rho_1)C_1(t) + \beta_{C1}C_2(t) + \hat{\sigma}_{1r}I(t), \quad (33)$$

$$\frac{dC_2}{dt} = -(\alpha_{C2} + \beta_{C1} + \rho_2)C_2(t) + \alpha_{C1}C_1(t) + \beta_{C2}C_3(t) + \sigma_{2r}I(t), \quad (34)$$

$$\frac{dC_3}{dt} = -(\alpha_O + \beta_{C2} + \rho_3)C_3(t) + \alpha_{C2}C_2(t) + \beta_O O(t) + \sigma_{3r}I(t), \quad (35)$$

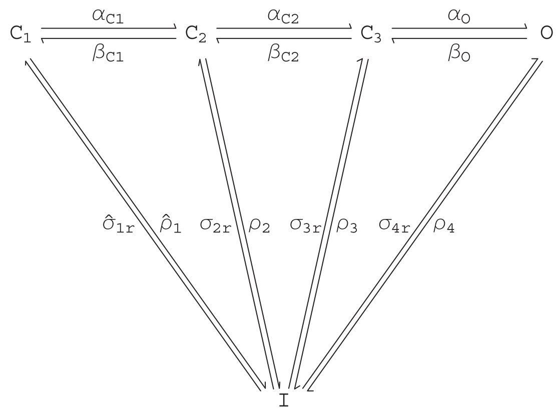

FIG. 5. State diagram for Na$^+$ channel gating in Fig. 3 may be reduced to a five state model when the transition rates between fast inactivated states are larger than inactivation and recovery rates.

$$\frac{dO}{dt} = -(\beta_O + \rho_4)O(t) + \alpha_O C_3(t) + \sigma_{4r} I(t), \qquad (36)$$

$$\frac{dI}{dt} = -(\hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r})I(t) + \hat{\rho}_1 C_1(t) + \rho_2 C_2(t) + \rho_3 C_3(t) + \rho_4 O(t), \qquad (37)$$

where $C_1(t) + C_2(t) + C_3(t) + O(t) + I(t) = 1$ and

$$\hat{\sigma}_{1r} = \frac{\hat{\sigma}_1 \beta_{I2}\beta_{I3}}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \qquad (38)$$

$$\sigma_{2r} = \frac{\sigma_2 \beta_{I2}\beta_{I3}}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \qquad (39)$$

$$\sigma_{3r} = \frac{\sigma_3 \alpha_{I2}\beta_{I3}}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \qquad (40)$$

$$\sigma_{4r} = \frac{\sigma_4 \alpha_{I2}\alpha_{I3}}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}. \qquad (41)$$

Following an initial transient, it may be shown that $I_2(t)$, $I_3(t)$, and $I_4(t)$ are approximated by

$$I_2(t) \approx \frac{\beta_{I2}\beta_{I3} I(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \qquad (42)$$

$$I_3(t) \approx \frac{\alpha_{I2}\beta_{I3} I(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \qquad (43)$$

$$I_4(t) \approx \frac{\alpha_{I2}\alpha_{I3} I(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \qquad (44)$$

where $I(t) = I_2(t) + I_3(t) + I_4(t)$ (see Appendix C). Equations (42)–(44) may also be obtained by application of singular perturbation analysis to a kinetic model for a cardiac Na$^+$ channel [27]. During an action potential, the solution of Eqs. (18)–(25) may be approximated by the solution of Eqs. (33)–(37), where n and V are determined by Eqs. (16) and (17), and I_1 to I_4 are calculated from Eqs. (32) and (42)–(44) (see Fig. 6).

Assuming that $C_1(t) = m_1(t)h(t)$, $C_2(t) = m_2(t)h(t)$, $C_3(t) = m_3(t)h(t)$, $O(t) = m_O(t)h(t)$ and $I(t) = 1 - h(t)$, where $m_1(t)$, $m_2(t)$, $m_3(t)$, and $m_O(t)$ are activation variables

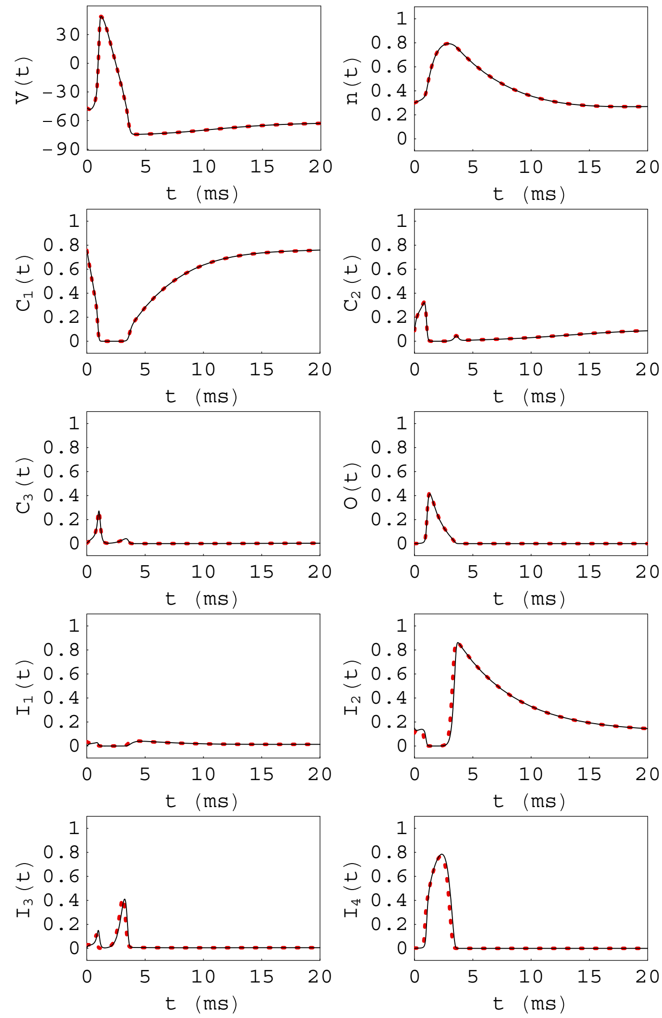

FIG. 6. The solution of a Na$^+$ channel eight-state kinetic model, Eqs. (18)–(25) for C_1, C_2, C_3, O, and I_1–I_4 (solid line) may be approximated by the solution of a five state model, Eqs. (33)–(37) (dotted line), where I_1–I_4 are calculated from Eqs. (32) and (42)–(44), and n and V are determined by Eqs. (16) and (17). The rate functions are $\alpha_m = 0.1(V+35)/\{1-\exp[-(V+35)/10]\}$, $\beta_m = 4\exp[-(V+60)/18]$, $\alpha_{C1} = 3\alpha_m$, $\beta_{C1} = \beta_m$, $\alpha_{C2} = 2\alpha_m$, $\beta_{C2} = 2\beta_m$, $\alpha_O = \alpha_m$, $\beta_O = 3\beta_m$, $\alpha_{I1} = \alpha_{C1}$, $\beta_{I1} = 0.016\beta_{C1}$, $\alpha_{I2} = 2\alpha_{C2}$, $\beta_{I2} = 2\beta_{C2}$, $\alpha_{I3} = 2\alpha_O$, $\beta_{I3} = 2\beta_O$, $\alpha_{ik} = 1$, $\gamma_{ik} = 22.2$, $\beta_{ik} = \exp[-V/10]$, $\delta_{i1} = 2.5$, $\delta_{i2} = \delta_{i3} = \delta_{i4} = 0.04$, $\rho_k = \alpha_{ik}/(1+\beta_{ik}/\gamma_{ik})$ for $k = 1$ to 4, $\sigma_1 = \delta_{i1}/(1+\gamma_{i1}/\beta_{i1})$, $\sigma_2 = \sigma_3 = \sigma_4 = 0.016\sigma_1$, $\alpha_n = 0.01(V+50)/\{1-\exp[-(V+50)/10]\}$, $\beta_n = 0.125\exp[-(V+60)/80]$ (ms^{-1}), and $\bar{g}_{Na} = 120$ mS/cm^2, $\bar{g}_K = 36$ mS/cm^2, $\bar{g}_L = 0.3$ mS/cm^2, $V_{Na} = 55$ mV, $V_K = -75$ mV, $V_L = -60$ mV, $C = 1$ μF/cm^2, and $i_e = 1$ μA/cm^2.

and $h(t)$ is an inactivation variable, Eqs. (33)–(37) may be expressed as

$$\frac{dm_1}{dt} = -[\alpha_{C1} + \rho_1 - \rho(t) + \sigma(t)]m_1(t) + \beta_{C1}m_2(t) + \hat{\sigma}_{1r}[1/h(t) - 1], \qquad (45)$$

$$\frac{dm_2}{dt} = -[\alpha_{C2} + \beta_{C1} + \rho_2 - \rho(t) + \sigma(t)]m_2(t) + \alpha_{C1}m_1(t) + \beta_{C2}m_3(t) + \sigma_{2r}[1/h(t) - 1], \qquad (46)$$

$$\frac{dm_3}{dt} = -[\alpha_O + \beta_{C2} + \rho_3 - \rho(t) + \sigma(t)]m_3(t) + \alpha_{C2}m_2(t) + \beta_O m_O(t) + \sigma_{3r}[1/h(t) - 1], \quad (47)$$

$$\frac{dm_O}{dt} = -[\beta_O + \rho_4 - \rho(t) + \sigma(t)]m_O(t) + \alpha_O m_3(t) + \sigma_{4r}[1/h(t) - 1], \quad (48)$$

$$\frac{dh}{dt} = \hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r} - h(t)[\hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r} + \rho(t)], \quad (49)$$

where

$$\rho(t) = \hat{\rho}_1 m_1(t) + \rho_2 m_2(t) + \rho_3 m_3(t) + \rho_4 m_O(t), \quad (50)$$

$$\sigma(t) = (\hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r})[1/h(t) - 1]. \quad (51)$$

The inactivation rates ρ_k and recovery rates σ_k, for each k, are an order of magnitude smaller than the activation and deactivation rates, and therefore, from an asymptotic expansion of the solution, it may be shown to lowest order that Eqs. (45)–(48) for the activation variables may be approximated by (see Fig. 7)

$$\frac{dm_1}{dt} = -\alpha_{C1}m_1(t) + \beta_{C1}m_2(t), \quad (52)$$

$$\frac{dm_2}{dt} = -(\alpha_{C2} + \beta_{C1})m_2(t) + \alpha_{C1}m_1(t) + \beta_{C2}m_3(t), \quad (53)$$

$$\frac{dm_3}{dt} = -(\alpha_O + \beta_{C2})m_3(t) + \alpha_{C2}m_2(t) + \beta_O m_O(t), \quad (54)$$

$$\frac{dm_O}{dt} = -\beta_O m_O(t) + \alpha_O m_3(t). \quad (55)$$

That is, the inactivation and recovery rates, and the variable $h(t)$, generally only have a small effect on the time-dependence of the activation variables.

If the activation sensors are mutually independent ($\alpha_{C1} = 3\alpha_m$, $\alpha_{C2} = 2\alpha_m$, $\alpha_O = \alpha_m$, $\beta_{C1} = \beta_m$, $\beta_{C2} = 2\beta_m$, $\beta_O = 3\beta_m$), then Eqs. (52)–(55) have the solution $m_1(t) = [1 - m(t)]^3$, $m_2(t) = 3m(t)[1 - m(t)]^2$, $m_3(t) = 3m(t)^2[1 - m(t)]$, $m_O(t) = m(t)^3$, where $m(t)$ satisfies

$$\frac{dm}{dt} = \alpha_m - m(t)(\alpha_m + \beta_m), \quad (56)$$

and therefore, from Eq. (50),

$$\rho(t) = \hat{\rho}_1[1 - m(t)]^3 + 3\rho_2 m(t)[1 - m(t)]^2 + 3\rho_3 m(t)^2[1 - m(t)] + \rho_4 m(t)^3. \quad (57)$$

However, as the activation variable $m(t)$ generally has a faster time constant than $h(t)$, $\rho(t)$ may be approximated by

$$\beta_h = \hat{\rho}_1(1 - m_\infty)^3 + 3\rho_2 m_\infty(1 - m_\infty)^2 + 3\rho_3 m_\infty^2(1 - m_\infty) + \rho_4 m_\infty^3, \quad (58)$$

where $m_\infty = \alpha_m/(\alpha_m + \beta_m)$ for each membrane potential, and β_h is a voltage-dependent function, as assumed by HH [1]. The activation function m_∞ and each inactivation rate ρ_k has an exponential voltage dependence for a small depolarization but for larger potentials, the variation has a plateau, and

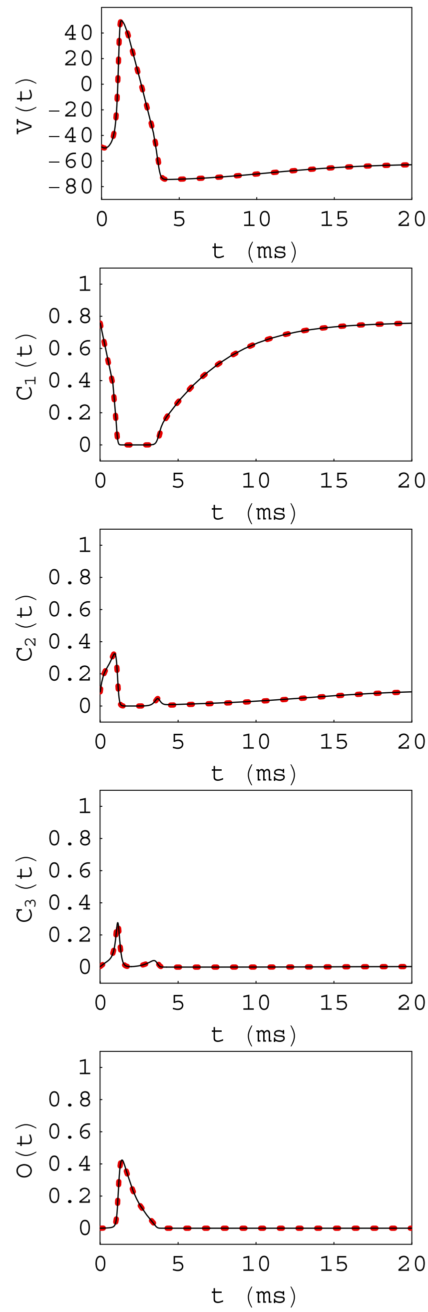

FIG. 7. If the Na^+ channel inactivation and recovery rates are an order of magnitude smaller than the activation and deactivation rates, then the occupation probabilities $C_1 = m_1 h$, $C_2 = m_2 h$, $C_3 = m_3 h$, and $O = m_O h$ calculated from the solution of Eqs. (45)–(49) for m_1, m_2, m_3, m_O, and h (solid line) may be approximated by the open and closed state probabilities obtained from the solution of Eqs. (49) and (52)–(55) (dotted line), where n and V are determined by Eqs. (16) and (17). The rate functions are $\alpha_m = 0.1(V+35)/\{1 - \exp[-(V+35)/10]\}$, $\beta_m = 4\exp[-(V+60)/18]$, $\alpha_{C1} = 3\alpha_m$, $\beta_{C1} = \beta_m$, $\alpha_{C2} = 2\alpha_m$, $\beta_{C2} = 2\beta_m$, $\alpha_O = \alpha_m$, $\beta_O = 3\beta_m$, $\alpha_{I1} = \alpha_{C1}$, $\beta_{I1} = 0.016\beta_{C1}$, $\alpha_{I2} = 2\alpha_{C2}$, $\beta_{I2} = 2\beta_{C2}$, $\alpha_{I3} = 2\alpha_O$, $\beta_{I3} = 2\beta_O$, $\alpha_{ik} = 1$, $\gamma_{ik} = 22.2$, $\beta_{ik} = \exp[-V/10]$, $\rho_k = \alpha_{ik}\gamma_{ik}/(\beta_{ik} + \gamma_{ik})$ for $k = 1$ to 4, $\delta_{i1} = 2.5$, $\delta_{i2} = \delta_{i3} = \delta_{i4} = 0.04$, $\sigma_1 = \delta_{i1}/(1 + \gamma_{i1}/\beta_{i1})$, $\sigma_2 = \sigma_3 = \sigma_4 = 0.016\sigma_1$, $\alpha_n = 0.01(V+50)/\{1 - \exp[-(V+50)/10]\}$, $\beta_n = 0.125\exp[-(V+60)/80]$ (ms^{-1}), and $\bar{g}_{Na} = 120$ mS/cm^2, $\bar{g}_K = 36$ mS/cm^2, $\bar{g}_L = 0.3$ mS/cm^2, $V_{Na} = 55$ mV, $V_K = -75$ mV, $V_L = -60$ mV, $C = 1$ $\mu F/cm^2$, and $i_e = 1$ $\mu A/cm^2$.

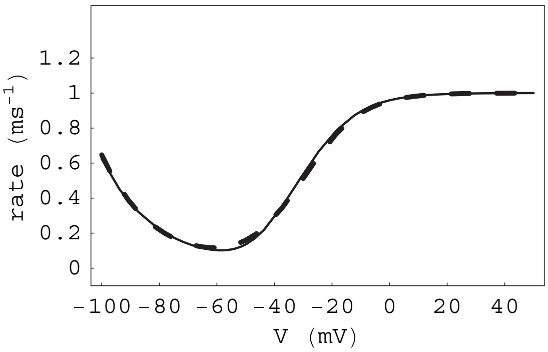

FIG. 8. The voltage dependence of the Na^+ channel HH inactivation rate function $\alpha_h + \beta_h$ (dotted line), where $\alpha_h = 0.07\exp[-(V+60)/20]$ and $\beta_h = 1/\{1+\exp[-(V+30)/10]\}$ may be approximated by the expressions in Eqs. (58) and (60) where the rate functions are defined as $\alpha_m = 0.1(V+35)/(1-\exp[-(V+35)/10])$, $\beta_m = 4\exp[-(V+60)/18]$, $\alpha_{C1} = 3\alpha_m$, $\beta_{C1} = \beta_m$, $\alpha_{C2} = 2\alpha_m$, $\beta_{C2} = 2\beta_m$, $\alpha_O = \alpha_m$, $\beta_O = 3\beta_m$, $\alpha_{I1} = \alpha_{C1}$, $\beta_{I1} = 0.016\beta_{C1}$, $\alpha_{I2} = 2\alpha_{C2}$, $\beta_{I2} = 2\beta_{C2}$, $\alpha_{I3} = 2\alpha_O$, $\beta_{I3} = 2\beta_O$, $\alpha_{ik} = 1$, $\gamma_{ik} = 22.2$, $\beta_{ik} = \exp[-V/10]$, $\delta_{i1} = 2.5$, $\delta_{i2} = \delta_{i3} = \delta_{i4} = 0.04$, $\rho_k = \alpha_{ik}/(1+\beta_{ik}/\gamma_{ik})$ for $k = 1$ to 4, $\sigma_1 = \delta_{i1}/(1+\gamma_{i1}/\beta_{i1})$, $\sigma_2 = \sigma_3 = \sigma_4 = 0.016\sigma_1$ (ms^{-1}).

therefore, accounts for the voltage dependence of β_h (see Fig. 8).

Equation (49) may be expressed as

$$\frac{dh}{dt} = \alpha_h - h(t)(\alpha_h + \beta_h), \tag{59}$$

where

$$\alpha_h = \hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r}, \tag{60}$$

and as $\sigma_{2r}, \sigma_{3r}, \sigma_{4r} \ll \hat{\sigma}_{1r}$, $\alpha_h \approx \hat{\sigma}_{1r}$. For a moderate hyperpolarization ($\sigma_1 \gg \alpha_{I1}, \beta_{I1}$), $\hat{\sigma}_{1r} \approx \hat{\sigma}_1 \approx \beta_{I1}$, and therefore, the voltage dependence of α_h is approximately exponential [1] (see Fig. 8), but it may attain a plateau value for a large hyperpolarization [9,21,24].

If the previous conditions for each stage of reduction are satisfied, then the solution of the twelve state kinetic model, Eqs. (4)–(15), may be approximated by closed, open, and inactivated state probabilities that are dependent on the solution of Eqs. (56) and (59) for m and h, where n and V are determined by Eqs. (16) and (17)—see Fig. 9 for a Na^+ channel with an inactivation rate independent of the closed or open state [1], and Fig. 10 for a channel where the Na^+ inactivation rate increases with the degree of activation of the channel [9] (the ion channel rate functions and parameters are summarized in Table I). Therefore, a HH model of a Na^+ channel may be expressed as a kinetic scheme that is consistent with the ion channel structure and the energy landscape of each S4 sensor during activation and inactivation processes. Although it is often assumed that the independence of Na^+ channel inactivation and activation is required for the Na^+ channel conductance expression m^3h [6], strongly coupled activation and inactivation is also compatible with the open state probability $O(t) = m(t)^3h(t)$.

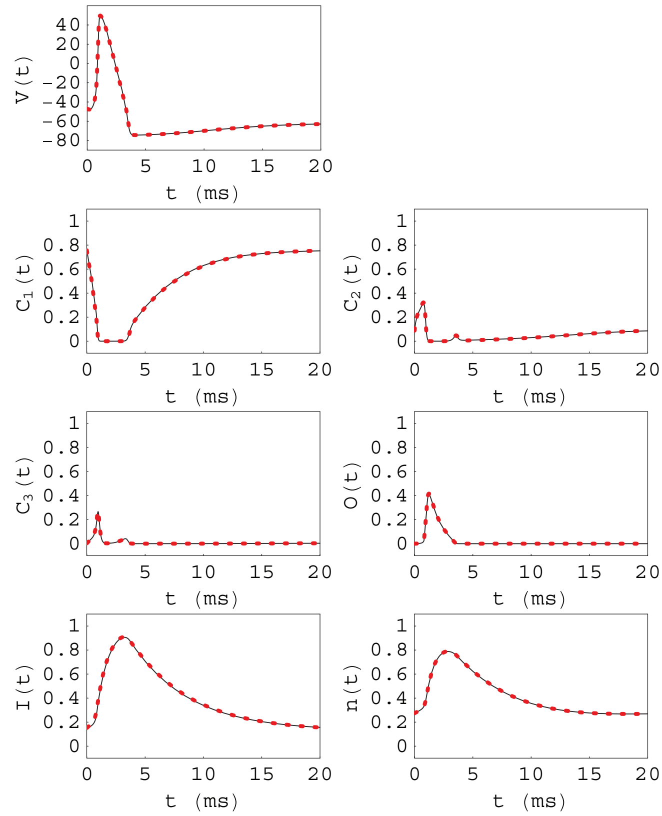

FIG. 9. The solution of a Na^+ channel 12-state kinetic model, Eqs. (4)–(15) (solid line) may be approximated by $C_1 = (1-m)^3h$, $C_2 = 3m(1-m)^2h$, $C_3 = 3m^2(1-m)h$, $O = m^3h$, $I = I_2 + I_3 + I_4 = 1-h$ (dotted line), where m and h satisfy Eqs. (56) and (59), and n and V are determined by Eqs. (16) and (17). The conditions for the reduction are that (1) the two-stage inactivation process satisfies $\beta_{ik} \gg \delta_{ik}$ and $\gamma_{ik} \gg \alpha_{ik}$, for each k (see Fig. 1), (2) $\alpha_{I1} \gg \rho_1$ and $\sigma_1 \gg \beta_{I1}$ (see Fig. 2), and (3) the transition rates between fast inactivated states are an order of magnitude larger than inactivation and recovery rates (see Fig. 3). The rate functions are $\alpha_m = 0.1(V+35)/\{1-\exp[-(V+35)/10]\}$, $\beta_m = 4\exp[-(V+60)/18]$, $\alpha_{C1} = 3\alpha_m$, $\beta_{C1} = \beta_m$, $\alpha_{C2} = 2\alpha_m$, $\beta_{C2} = 2\beta_m$, $\alpha_O = \alpha_m$, $\beta_O = 3\beta_m$, $\alpha_{I1} = \alpha_{C1}$, $\beta_{I1} = 0.016\beta_{C1}$, $\alpha_{I2} = 2\alpha_{C2}$, $\beta_{I2} = 2\beta_{C2}$, $\alpha_{I3} = 2\alpha_O$, $\beta_{I3} = 2\beta_O$, $\alpha_{ik} = 1$, $\gamma_{ik} = 22.2$, $\beta_{ik} = \exp[-V/10]$, $\delta_{i1} = 2.5$, $\delta_{i2} = \delta_{i3} = \delta_{i4} = 0.04$, $\rho_k = \alpha_{ik}/(1+\beta_{ik}/\gamma_{ik})$ for $k = 1$ to 4, $\sigma_1 = \delta_{i1}/(1+\gamma_{i1}/\beta_{i1})$, $\sigma_2 = \sigma_3 = \sigma_4 = 0.016\sigma_1$, $\alpha_n = 0.01(V+50)/\{1-\exp[-(V+50)/10]\}$, $\beta_n = 0.125\exp[-(V+60)/80]$ (ms^{-1}), and $\bar{g}_{Na} = 120$ mS/cm^2, $\bar{g}_K = 36$ mS/cm^2, $\bar{g}_L = 0.3$ mS/cm^2, $V_{Na} = 55$ mV, $V_K = -75$ mV, $V_L = -60$ mV, $C = 1$ $\mu F/cm^2$, and $i_e = 1$ $\mu A/cm^2$.

III. REDUCTION OF A KINETIC MODEL FOR Na^+ CHANNEL ACTIVATION, AND FAST AND SLOW INACTIVATION

In this section, it is assumed that the activation of three voltage sensors regulating the Na channel conductance is coupled to a two-stage inactivation process, and that slow inactivation is accessible from fast inactivated states [7], and therefore, the kinetics may be described by a 15-state model (see Fig. 11):

$$\frac{dC_1}{dt} = -(\alpha_{C1} + \alpha_{i1})C_1(t) + \beta_{C1}C_2(t) + \beta_{i1}A_1(t), \tag{61}$$

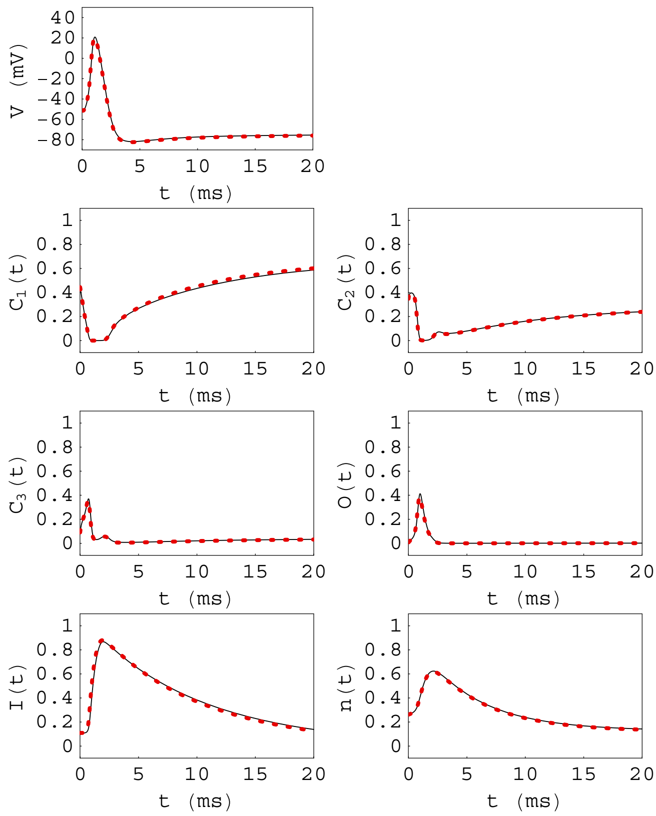

FIG. 10. The solution of a Na^+ channel 12-state kinetic model, Eqs. (4)–(15) (solid line) may be approximated by $C_1 = (1-m)^3 h$, $C_2 = 3m(1-m)^2 h$, $C_3 = 3m^2(1-m)h$, $O = m^3 h$, $I = I_2 + I_3 + I_4 = 1 - h$ (dotted line), where m and h satisfy Eqs. (56) and (59), and n and V are determined by Eqs. (16) and (17). The rate functions are $\alpha_m = 7.45\exp[0.5V/25]$, $\beta_m = 0.8\exp[-0.9V/25]$, $\alpha_{C1} = 3\alpha_m$, $\beta_{C1} = \beta_m$, $\alpha_{C2} = 2\alpha_m$, $\beta_{C2} = 2\beta_m$, $\alpha_O = \alpha_m$, $\beta_O = 3\beta_m$, $\alpha_{I1} = \alpha_{C1}$, $\beta_{I1} = 0.01\beta_{C1}$, $\alpha_{I2} = 2\alpha_{C2}$, $\beta_{I2} = 0.2\beta_{C2}$, $\alpha_{I3} = 2\alpha_O$, $\beta_{I3} = 0.2\beta_O$, $\beta_{i1} = 2000\exp[-2.4V/25]$, $\beta_{i2} = 200\exp[-2.4V/25]$, $\beta_{i3} = 20\exp[-2.4V/25]$, $\beta_{i4} = 2\exp[-2.4V/25]$, $\delta_{i1} = 1$, $\delta_{i2} = \delta_{i3} = \delta_{i4} = 0.1$, $\alpha_{ik} = 2.1$, $\gamma_{ik} = 25$, $\rho_k = \alpha_{ik}/(1 + \beta_{ik}/\gamma_{ik})$, $\sigma_k = \delta_{ik}/(1 + \gamma_{ik}/\beta_{ik})$, for $k = 1$ to 4, $\alpha_n = 0.01(V+50)/\{1-\exp[-(V+50)/10]\}$, $\beta_n = 0.125\exp[-(V+60)/80]$ (ms^{-1}), and $\bar{g}_{Na} = 20$ mS/cm^2, $\bar{g}_K = 10$ mS/cm^2, $\bar{g}_L = 1$ mS/cm^2, $V_{Na} = 40$ mV, $V_K = -90$ mV, $V_L = -80$ mV, $C = 1\ \mu$F/cm^2, and $i_e = 1\ \mu$A/cm^2.

$$\frac{dC_2}{dt} = -(\alpha_{C2} + \beta_{C1} + \alpha_{i2})C_2(t) + \alpha_{C1}C_1(t) + \beta_{C2}C_3(t) + \beta_{i2}A_2(t), \tag{62}$$

$$\frac{dC_3}{dt} = -(\alpha_O + \beta_{C2} + \alpha_{i3})C_3(t) + \alpha_{C2}C_2(t) + \beta_O O(t) + \beta_{i3}A_3(t), \tag{63}$$

$$\frac{dO}{dt} = -(\beta_O + \alpha_{i4})O(t) + \alpha_O C_3(t) + \beta_{i4}A_4(t), \tag{64}$$

$$\frac{dA_1}{dt} = -(\alpha_{A1} + \beta_{i1} + \gamma_{i1})A_1(t) + \alpha_{i1}C_1(t) + \delta_{i1}I_1(t) + \beta_{A1}A_2(t), \tag{65}$$

$$\frac{dA_2}{dt} = -(\alpha_{A2} + \beta_{A1} + \beta_{i2} + \gamma_{i2})A_2(t) + \alpha_{i2}C_2(t) + \delta_{i2}I_2(t) + \alpha_{A1}A_1(t) + \beta_{A2}A_3(t), \tag{66}$$

TABLE I. Rate functions, channel conductance, and equilibrium potentials for kinetic models with fast inactivation of the Na^+ channel.

	Figs. 4, 6–9	Fig. 10
Rate (ms^{-1})		
α_n	$\frac{0.01(V+50)}{1-\exp[-(V+50)/10]}$	$\frac{0.01(V+50)}{1-\exp[-(V+50)/10]}$
β_n	$0.125\exp[-(V+60)/80]$	$0.125\exp[-(V+60)/80]$
α_m	$\frac{0.1(V+35)}{1-\exp[-(V+35)/10]}$	$7.45\exp[0.5V/25]$
β_m	$4\exp[-(V+60)/18]$	$0.8\exp[-0.9V/25]$
α_{C1}	$3\alpha_m$	$3\alpha_m$
β_{C1}	β_m	β_m
α_{C2}	$2\alpha_m$	$2\alpha_m$
β_{C2}	$2\beta_m$	$2\beta_m$
α_O	α_m	α_m
β_O	$3\beta_m$	$3\beta_m$
α_{I1}	α_{C1}	α_{C1}
β_{I1}	$0.016\beta_{C1}$	$0.01\beta_{C1}$
α_{I2}	$2\alpha_{C2}$	$2\alpha_{C2}$
β_{I2}	$2\beta_{C2}$	$0.2\beta_{C2}$
α_{I3}	$2\alpha_O$	$2\alpha_O$
β_{I3}	$2\beta_O$	$0.2\beta_O$
α_{ik}	1	2.1
γ_{ik}	22.2	25
β_{i1}	$\exp(-V/10)$	$2000\exp(-2.4V/25)$
β_{i2}	$\exp(-V/10)$	$200\exp(-2.4V/25)$
β_{i3}	$\exp(-V/10)$	$20\exp(-2.4V/25)$
β_{i4}	$\exp(-V/10)$	$2\exp(-2.4V/25)$
δ_{i1}	2.5	1
δ_{i2}	$0.016\delta_{i1}$	$0.1\delta_{i1}$
δ_{i3}	$0.016\delta_{i1}$	$0.1\delta_{i1}$
δ_{i4}	$0.016\delta_{i1}$	$0.1\delta_{i1}$
Conductance (mS/cm^2)		
$\bar{g}_{Na}$	120	20
$\bar{g}_K$	36	10
$\bar{g}_L$	0.3	1
Equilibrium potential (mV)		
V_{Na}	55	40
V_K	−75	−90
V_L	−60	−80
$i_e(\mu$A/cm$^2)$	1	1
$C(\mu$F/cm$^2)$	1	1

$$\frac{dA_3}{dt} = -(\alpha_{A3} + \beta_{A2} + \beta_{i3} + \gamma_{i3})A_3(t) + \alpha_{i3}C_3(t) + \delta_{i3}I_3(t) + \alpha_{A2}A_2(t) + \beta_{A3}A_4(t), \tag{67}$$

$$\frac{dA_4}{dt} = -(\beta_{A3} + \beta_{i4} + \gamma_{i4})A_4(t) + \alpha_{i4}O(t) + \delta_{i4}I_4(t) + \alpha_{A3}A_3(t), \tag{68}$$

$$\frac{dI_1}{dt} = -(\alpha_{I1} + \delta_{i1})I_1(t) + \gamma_{i1}A_1(t) + \beta_{I1}I_2(t), \tag{69}$$

$$\frac{dI_2}{dt} = -(\alpha_{I2} + \beta_{I1} + \delta_{i2} + \mu)I_2(t) + \gamma_{i2}A_2(t) + \alpha_{I1}I_1(t) + \beta_{I2}I_3(t) + \nu S_2(t), \tag{70}$$

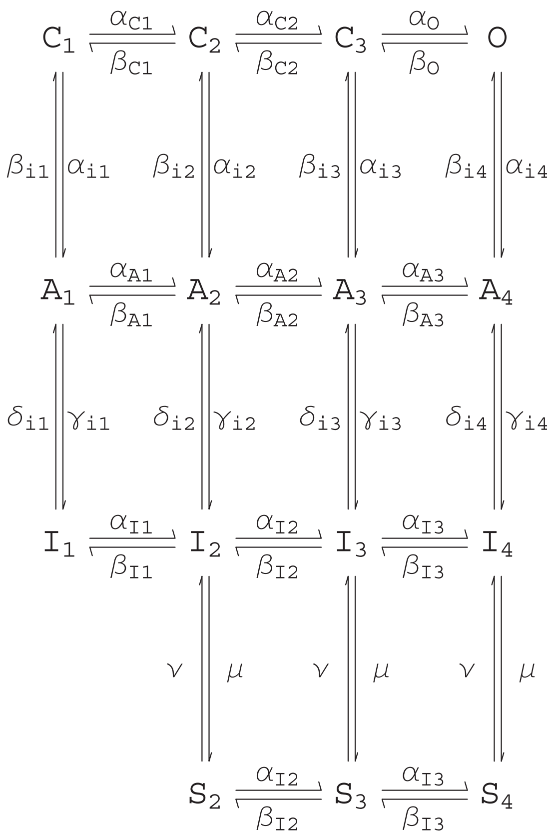

FIG. 11. State diagram for Na^{+} channel gating where horizontal transitions represent the activation of three voltage sensors (in the domains DI, DII, and DIII) that open the pore, and vertical transitions represent the two-stage fast inactivation process to states $I_1(t)$ to $I_4(t)$, and slow inactivation to states $S_2(t)$ to $S_4(t)$ (in domain DIV).

$$\frac{dI_3}{dt} = -(\alpha_{I3} + \beta_{I2} + \delta_{i3} + \mu)I_3(t) + \gamma_{i3}A_3(t) + \alpha_{I2}I_2(t) + \beta_{I3}I_4(t) + \nu S_3(t), \quad (71)$$

$$\frac{dI_4}{dt} = -(\beta_{I3} + \delta_{i4} + \mu)I_4(t) + \gamma_{i4}A_4(t) + \alpha_{I3}I_3(t) + \nu S_4(t), \quad (72)$$

$$\frac{dS_2}{dt} = -(\alpha_{I2} + \nu)S_2(t) + \beta_{I2}S_3(t) + \mu I_2(t), \quad (73)$$

$$\frac{dS_3}{dt} = -(\alpha_{I3}+\beta_{I2}+\nu)S_3(t) + \alpha_{I2}S_2(t) + \beta_{I3}S_4(t) + \mu I_3(t), \quad (74)$$

$$\frac{dS_4}{dt} = -(\beta_{I3} + \nu)S_4(t) + \alpha_{I3}S_3(t) + \mu I_4(t), \quad (75)$$

where $S_2(t)$, $S_3(t)$, and $S_4(t)$ are the occupational probabilities for the slow inactivated states, and μ and ν are voltage-dependent transition rates that are at least an order of magnitude smaller than the corresponding fast inactivation rates. As $I_1(t) \approx 0$ following a transient, it may be assumed that entry into the slow inactivated state corresponding to I_1 is also small, and has no effect on the dynamics.

It is assumed that the K^{+} and leakage channels repolarize the membrane, and if the K^{+} conductance is proportional to $n(t)^j$ where j is the number of voltage sensors such that $1 \leqslant j \leqslant 4$, and the activation variable $n(t)$ satisfies Eq. (16), the membrane current equation is

$$C\frac{dV}{dt} = i_e - \bar{g}_{\mathrm{Na}}O(t)(V - V_{Na}) - \bar{g}_K n(t)^j (V - V_K) - \bar{g}_L(V - V_L). \quad (76)$$

By expressing the solution as a two-scale asymptotic expansion and eliminating secular terms [18], Eqs. (61)–(75) may be reduced to an 11-state system when the two-stage inactivation transitions satisfy $\alpha_{ik} \ll \gamma_{ik}$, $\delta_{ik} \ll \beta_{ik}$, and $\gamma_{ik} + \beta_{ik}$ is greater than the activation and deactivation rate functions, for each k [24] (see Fig. 12 and Appendix A)

$$\frac{dC_1}{dt} = -(\alpha_{C1} + \rho_1)C_1(t) + \beta_{C1}C_2(t) + \sigma_1 I_1(t), \quad (77)$$

$$\frac{dC_2}{dt} = -(\alpha_{C2} + \beta_{C1} + \rho_2)C_2(t) + \alpha_{C1}C_1(t) + \beta_{C2}C_3(t) + \sigma_2 I_2(t), \quad (78)$$

$$\frac{dC_3}{dt} = -(\alpha_O + \beta_{C2} + \rho_3)C_3(t) + \alpha_{C2}C_2(t) + \beta_O O(t) + \sigma_3 I_3(t), \quad (79)$$

$$\frac{dO}{dt} = -(\beta_O + \rho_4)O(t) + \alpha_O C_3(t) + \sigma_4 I_4(t), \quad (80)$$

$$\frac{dI_1}{dt} = -(\alpha_{I1} + \sigma_1)I_1(t) + \rho_1 C_1(t) + \beta_{I1}I_2(t), \quad (81)$$

$$\frac{dI_2}{dt} = -(\alpha_{I2} + \beta_{I1} + \sigma_2 + \mu)I_2(t) + \alpha_{I1}I_1(t) + \beta_{I2}I_3(t) + \rho_2 C_2(t) + \nu S_2(t), \quad (82)$$

$$\frac{dI_3}{dt} = -(\alpha_{I3} + \beta_{I2} + \sigma_3 + \mu)I_3(t) + \alpha_{I2}I_2(t) + \beta_{I3}I_4(t) + \rho_3 C_3(t) + \nu S_3(t), \quad (83)$$

$$\frac{dI_4}{dt} = -(\beta_{I3} + \sigma_4 + \mu)I_4(t) + \alpha_{I3}I_3(t) + \rho_4 O(t) + \nu S_4(t), \quad (84)$$

$$\frac{dS_2}{dt} = -(\alpha_{I2} + \nu)S_2(t) + \beta_{I2}S_3(t) + \mu I_2(t), \quad (85)$$

$$\frac{dS_3}{dt} = -(\alpha_{I3} + \beta_{I2} + \nu)S_3(t) + \alpha_{I2}S_2(t) + \beta_{I3}S_4(t) + \mu I_3(t), \quad (86)$$

$$\frac{dS_4}{dt} = -(\beta_{I3} + \nu)S_4(t) + \alpha_{I3}S_3(t) + \mu I_4(t). \quad (87)$$

Assuming that $\alpha_{I1} \gg \rho_1$ and $\sigma_1 \gg \beta_{I1}$ [9], Eqs. (77) and (82) may be approximated by (see Appendix B)

$$\frac{dC_1}{dt} = -(\alpha_{C1} + \hat{\rho}_1)C_1(t) + \beta_{C1}C_2(t) + \hat{\sigma}_1 I_2(t), \quad (88)$$

$$\frac{dI_2}{dt} = -(\alpha_{I2} + \hat{\sigma}_1 + \sigma_2 + \mu)I_2(t) + \beta_{I2}I_3(t) + \nu S_2(t) + \hat{\rho}_1 C_1(t) + \rho_2 C_2(t), \quad (89)$$

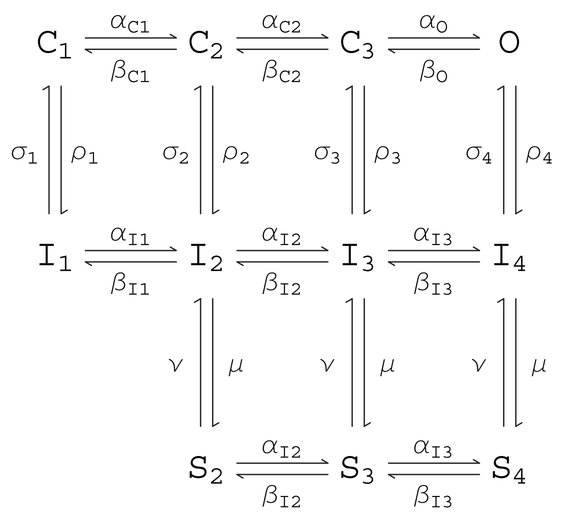

FIG. 12. State diagram for Na^+ channel gating in Fig. 11 may be reduced to an eleven state model when $\beta_{ik} \gg \delta_{ik}$, $\gamma_{ik} \gg \alpha_{ik}$, and $\gamma_{ik} + \beta_{ik}$ is greater than the activation and deactivation rate functions, for each k, where the derived rate functions are ρ_k and σ_k defined in Eqs. (26) and (27).

where $\hat{\rho}_1$ and $\hat{\sigma}_1$ are defined in Eqs. (30) and (31), and the kinetics may be represented by the ten state model in Fig. 13.

In Eqs. (83)–(87) and (89), it is assumed that for each membrane potential, the transition rates between fast inactivated states I_2, I_3, and I_4, and between slow inactivated states S_2, S_3, and S_4, are an order of magnitude larger than the corresponding inactivation and recovery rates, and larger than the activation and deactivation rates between closed and open states, and therefore, by expressing the solution as a three-scale asymptotic expansion and eliminating secular terms, Eqs. (77)–(87) are reducible to a six-state kinetic model (see Fig. 14 and Appendix C):

$$\frac{dC_1}{dt} = -(\alpha_{C1} + \rho_1)C_1(t) + \beta_{C1}C_2(t) + \hat{\sigma}_{1r}I(t), \quad (90)$$

$$\frac{dC_2}{dt} = -(\alpha_{C2} + \beta_{C1} + \rho_2)C_2(t) + \alpha_{C1}C_1(t) + \beta_{C2}C_3(t) + \sigma_{2r}I(t), \quad (91)$$

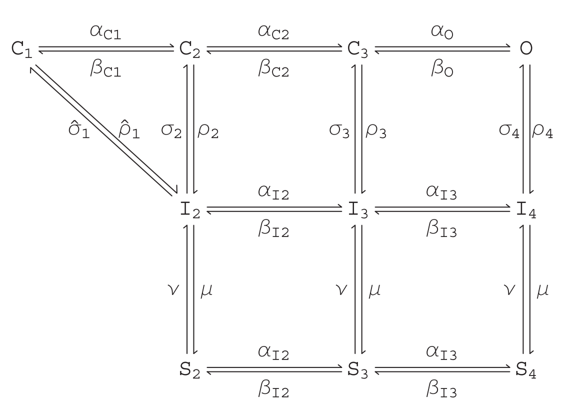

FIG. 13. The 11-state system for Na^+ channel gating in Fig. 12 may be reduced to a 10-state system when $\alpha_{I1} \gg \rho_1$ and $\sigma_1 \gg \beta_{I1}$, where the derived rate functions $\hat{\rho}_1$ and $\hat{\sigma}_1$ are defined in Eqs. (30) and (31).

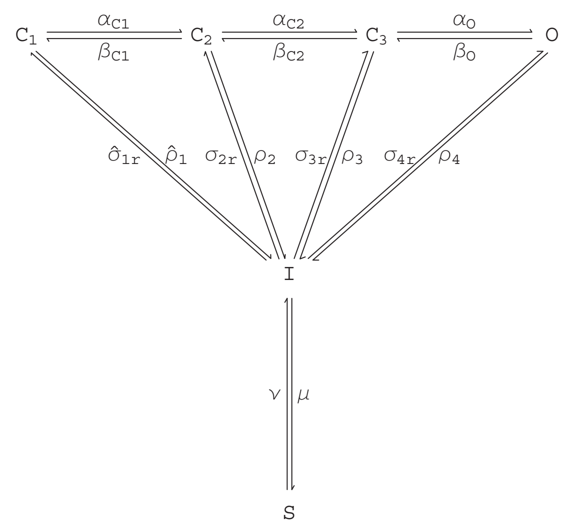

FIG. 14. The ten state system for Na^+ channel gating in Fig. 13 may be reduced to a six-state system when the transition rates between fast inactivated states $I_2(t)$ to $I_4(t)$, and between slow inactivated states $S_2(t)$ to $S_4(t)$ are larger than inactivation and recovery rates.

$$\frac{dC_3}{dt} = -(\alpha_O + \beta_{C2} + \rho_3)C_3(t) + \alpha_{C2}C_2(t) + \beta_O O(t) + \sigma_{3r}I(t), \quad (92)$$

$$\frac{dO}{dt} = -(\beta_O + \rho_4)O(t) + \alpha_O C_3(t) + \sigma_{4r}I(t), \quad (93)$$

$$\frac{dI}{dt} = -(\hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r} + \mu)I(t) + \hat{\rho}_1 C_1(t) + \rho_2 C_2(t) + \rho_3 C_3(t) + \rho_4 O(t) + \nu S(t), \quad (94)$$

$$\frac{dS}{dt} = \mu I(t) - \nu S(t), \quad (95)$$

where $\hat{\sigma}_{1r}$, σ_{2r}, σ_{3r}, and σ_{4r} are defined in Eqs. (38)–(41), $C_1(t) + C_2(t) + C_3(t) + O(t) + I(t) + S(t) = 1$, and following a transient, the inactivation probabilities $I_2(t)$, $I_3(t)$, and $I_4(t)$ may be approximated by Eqs. (42)–(44), and the slow inactivation probabilities $S_2(t)$, $S_3(t)$, and $S_4(t)$ may be expressed as

$$S_2(t) \approx \frac{\beta_{I2}\beta_{I3}S(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \quad (96)$$

$$S_3(t) \approx \frac{\alpha_{I2}\beta_{I3}S(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \quad (97)$$

$$S_4(t) \approx \frac{\alpha_{I2}\alpha_{I3}S(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \quad (98)$$

where $S(t) = S_2(t) + S_3(t) + S_4(t)$.

Writing $C_1(t) = m_1(t)h(t)$, $C_2(t) = m_2(t)h(t)$, $C_3(t) = m_3(t)h(t)$, $O(t) = m_O(t)h(t)$, and $h(t) = 1 - I(t) - S(t)$, where $m_1(t)$, $m_2(t)$, $m_3(t)$, and $m_O(t)$ are activation variables and $h(t)$ is an inactivation variable, and assuming that the activation sensors are independent ($\alpha_{C1} = 3\alpha_m, \alpha_{C2} = 2\alpha_m, \alpha_O = \alpha_m, \beta_{C1} = \beta_m, \beta_{C2} = 2\beta_m, \beta_O = 3\beta_m$), and that the inactivation rates are an order of magnitude smaller than the activation rates in Eqs. (90)–(93), it may be shown that $m_1(t) = [1 - m(t)]^3$, $m_2(t) = 3m(t)[1 - m(t)]^2$, $m_3(t) = 3m(t)^2[1 - m(t)]$, $m_O(t) = m(t)^3$, where $m(t)$ satisfies Eq. (56), $h(t)$ and $S(t)$ satisfy

$$\frac{dh}{dt} = \alpha_h[1 - S(t)] - h(t)(\alpha_h + \beta_h), \quad (99)$$

$$\frac{dS}{dt} = \mu[1 - h(t)] - S(t)(\mu + \nu), \quad (100)$$

and β_h and α_h are defined in Eqs. (58) and (60).

Defining total inactivation $T(t) = I(t) + S(t) = 1 - h(t)$, Eqs. (99) and (100) may be written as

$$\frac{dT}{dt} = \beta_h + \alpha_h S(t) - T(t)(\alpha_h + \beta_h), \quad (101)$$

$$\frac{dS}{dt} = \mu T(t) - S(t)(\mu + \nu). \quad (102)$$

Assuming that $h(t) = h_f(t)[1 - S(t)]$, where $h_f(t)$ is a fast inactivation variable, Eqs. (99) and (100) may be expressed as

$$\frac{dh_f}{dt} = \alpha_h - h_f(t)\left\{\alpha_h + \beta_h - \mu[1 - h_f(t)] + \frac{\nu S(t)}{1 - S(t)}\right\} \quad (103)$$

$$\frac{dS}{dt} = \mu[1 - h_f(t)] - S(t)\{\mu[1 - h_f(t)] + \nu\}, \quad (104)$$

and the forward rate for slow inactivation is dependent on $h_f(t)$, similar to the dependence of the fast inactivation rate $\rho(t) \approx \beta_h$ on the activation variable $m(t)$ in Eq. (57). Defining $s(t) = 1 - S(t)$, Eqs. (103) and (104) are equivalent to

$$\frac{dh_f}{dt} = \alpha_h - h_f(t)\left\{\alpha_h + \beta_h - \mu[1 - h_f(t)] + \nu\left(\frac{1}{s(t)} - 1\right)\right\}, \quad (105)$$

$$\frac{ds}{dt} = \nu - s(t)\{\nu + \mu[1 - h_f(t)]\}. \quad (106)$$

During a voltage clamp potential V_c of the Na^+ channel membrane, $h_f(t)$ approaches $h_{f\infty}(V_c) = \alpha_h/(\alpha_h + \beta_h)$, and from Eq. (106), we may write

$$\frac{ds}{dt} = \alpha_s - s(t)(\alpha_s + \beta_s), \quad (107)$$

where $\alpha_s = \nu$ and $\beta_s \approx \mu(1 - h_{f\infty})$. If μ has a weak voltage dependence, then there is a plateau in the voltage dependence of β_s for a large depolarization potential, consistent with the slow inactivation voltage clamp data for a Na^+ channel [2].

Equation (105) may be approximated by

$$\frac{dh_f}{dt} = \alpha_{hf} - h_f(t)(\alpha_{hf} + \beta_{hf}), \quad (108)$$

where

$$\beta_{hf} = \beta_h - \mu(1 - h_{f\infty}) + \nu\left(\frac{1}{s_\infty} - 1\right), \quad (109)$$

$\alpha_{hf} = \alpha_h$, and $s_\infty(V_c) = \alpha_s/(\alpha_s + \beta_s)$. As $O = m^3 h_f s$, Eq. (76) may be expressed as

$$C\frac{dV}{dt} = i_e - \bar{g}_{\rm Na} m^3 h_f s(V - V_{\rm Na}) - \bar{g}_{\rm K} n^j (V - V_{\rm K}) - \bar{g}_L(V - V_L), \quad (110)$$

where Eqs. (16), (56), (107), (108), and (110) are the empirical equations that describe spike frequency adaptation [2]. Although the voltage clamp data for an excitable membrane may be described by linear rate equations [1,2,4,6], more generally, during the action potential, the fast inactivation rate function is dependent on the activation variable $m(t)$, and the rate function for entry into the slow inactivated state is dependent on the fast inactivation variable $h_f(t)$, and therefore, the equations for h_f and s, Eqs. (105) and (106), are nonlinear in the rate variables.

The variation in the probability S that the inactivation sensor occupies a slow inactivation state is several orders of magnitude slower than for the fast inactivation probability I, and S may be treated as a parameter that modifies the stability of the stationary state of the (n, m, T, V) subsystem (see Appendix D). During a spike train, the increase in the value of the slow inactivation variable S is associated with a delay to the next spike, and when the stationary state of the subsystem becomes stable, the system returns to the resting potential. The solution of Eqs. (61) to (75) may be approximated by the solution of Eqs. (56), (105), and (106) where n and V are determined by Eqs. (16) and (110) (see Fig. 15, and Table II).

A similar process occurs during a repetitive bursting oscillation where slow inactivation increases until the stationary state of the subsystem becomes stable; however, in this case, as the slow variable relaxes during the subthreshold oscillation, the stationary state of the subsystem loses its stability when the recovery rate ν for slow inactivation is sufficiently large, and the bursting oscillation resumes (see Fig. 16). In a mesencephalic trigeminal neuron, a HH model that includes fast and slow components of the Na^+ current simulates a bursting oscillation that is frequently observed during stereotypic pattern generated behaviors such as locomotion and respiration [4]. Although the 15 differential equations in the full kinetic model have been reduced to 3 equations, the number of arithmetic operations per time step in the Euler numerical method of solution for each system is similar because the decrease in the number of variables is partially offset by an increase in the number of operations to compute the derived rate functions ρ_k and σ_{kr}. However, the computation time for the reduced system is approximately one third that of the full system because the number of required time steps is decreased when the fast processes are eliminated. An additional advantage of the reduced system is that it is defined by a smaller number of parameters with values that may be estimated from the voltage clamp data.

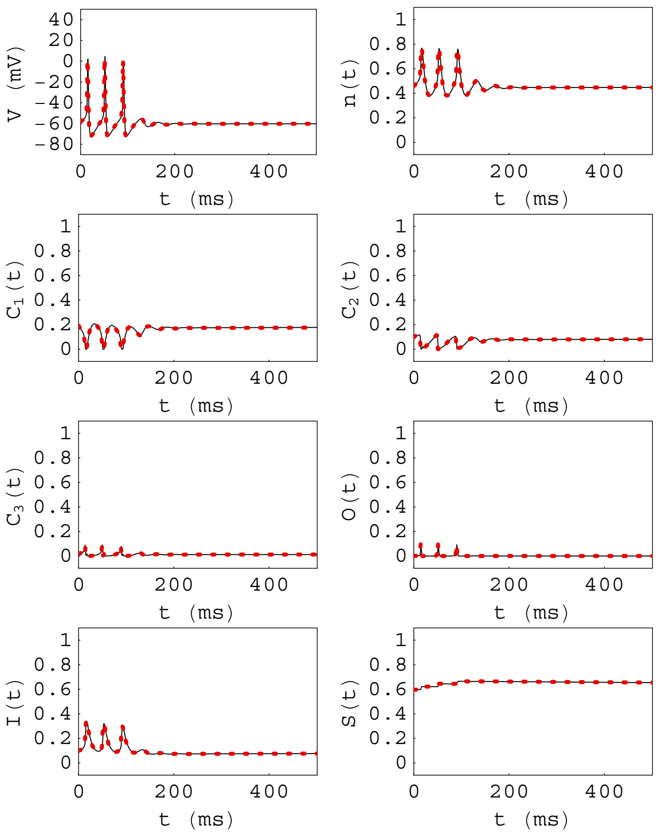

FIG. 15. The solution of a Na^+ channel 15-state kinetic model, Eqs. (61)–(75) (solid line) may be approximated by $C_1 = (1 - m)^3 h_f s$, $C_2 = 3m(1-m)^2 h_f s$, $C_3 = 3m^2(1-m)h_f s$, $O = m^3 h_f s$, $I = I_2 + I_3 + I_4 = (1-h_f)s$, and $S = S_2 + S_3 + S_4 = 1 - s$ (dotted line), where m, h_f, and s satisfy Eqs. (56), (105), and (106), and n and V are determined by Eqs. (16) and (76). The conditions for the reduction are that (1) the two-stage inactivation process satisfies $\beta_{ik} \gg \delta_{ik}$ and $\gamma_{ik} \gg \alpha_{ik}$, for each k (see Fig. 11), (2) $\alpha_{I1} \gg \rho_1$ and $\sigma_1 \gg \beta_{I1}$ (see Fig. 12), and (3) the transition rates between fast inactivated states I_2–I_4, and between slow inactivated states S_2–S_4 are at least an order of magnitude larger than inactivation and recovery rates (see Fig. 13). The decrease in the slow inactivation probability s limits the number of spikes (spike frequency adaptation), and the stationary state of the system is stable when the recovery rate ν for slow inactivation is sufficiently small. The rate functions are $\alpha_m = 0.1(V+43.9)/(1-\exp[-(V+43.9)/10])$, $\beta_m = 0.11\exp[-V/19.1]$, $\alpha_{C1} = 3\alpha_m$, $\beta_{C1} = \beta_m$, $\alpha_{C2} = 2\alpha_m$, $\beta_{C2} = 2\beta_m$, $\alpha_O = \alpha_m$, $\beta_O = 3\beta_m$, $\alpha_{I1} = \alpha_{C1}$, $\beta_{I1} = 0.0135\beta_{C1}$, $\alpha_{I2} = \alpha_{C2}$, $\beta_{I2} = \beta_{C2}$, $\alpha_{I3} = \alpha_O$, $\beta_{I3} = \beta_O$, $\alpha_{ik} = 0.9$, $\gamma_{ik} = 25$, $\beta_{ik} = 2\exp[-V/10]$, $\delta_{i1} = 2.5$, $\delta_{i2} = \delta_{i3} = \delta_{i4} = 0.0135\delta_{i1}$, $\rho_k = \alpha_{ik}/(1+\beta_{ik}/\gamma_{ik})$, $\sigma_k = \delta_{ik}/(1+\gamma_{ik}/\beta_{ik})$, for $k = 1$ to 4, $\mu = 0.047/\{1+\exp[-(V+17)/10]\}$, $\nu = 0.00001\exp(-V/25)$ $\alpha_n = 0.007(V+58.9)/\{1-\exp[-(V+58.9)/10]\}$, $\beta_n = 0.038\exp(-V/80)$ (ms^{-1}), and $\bar{g}_{Na} = 12$ mS/cm^2, $\bar{g}_K = 3$ mS/cm^2, $\bar{g}_L = 0.03$ mS/cm^2, $V_{Na} = 50$ mV, $V_K = -77$ mV, $V_L = -54.4$ mV, $j = 4$, $C = 1$ μF/cm^2, and $i_e = 1$ μA/cm^2.

The experimental data for wild type and ΔKPQ Na^+ channels may be simulated by a Markovian system with transitions between activated, and fast and slow inactivated states [10]. By incorporating K^+ and Ca^{++} currents as well as intracellular ion concentration changes, the model can account for the effect of the fast inactivation recovery rate of the ΔKPQ mutant on the plateau of the cardiac ventricular action potential. For a simplified model of the action potential that is dependent only on Na^+, K^+, and leakage currents, if the rate of recovery from Na^+ channel fast inactivation is increased, then the stationary state of the subsystem is stable for small values of $S = 1 - s$, but it may lose its stability as S increases and, therefore, the plateau may develop an oscillation (see Figs. 17 and 18, and Table II).

TABLE II. Rate functions, channel conductance and equilibrium potentials for kinetic models with fast and slow inactivation of the Na^+ channel. The parameters for Fig. 16 are the same as Fig. 15 but $\mu = 0.141/(1+\exp[-(V+17)/10])$, $\nu = 0.0001\exp(-V/25)$ and $\delta_{i1} = 5.5$, and the parameters for Fig. 18 are the same as Fig. 17 but $\delta_{i1} = 0.12$.

	Fig. 15	Fig. 17
Rate (ms^{-1})		
α_n	$\frac{0.007(V+58.9)}{1-\exp[-(V+58.9)/10]}$	$\frac{0.000015(V+25)}{1-\exp[-(V+25)/10]}$
β_n	$0.038\exp[-V/80]$	$0.0005\exp[-(V+65)/80]$
α_m	$\frac{0.1(V+43.9)}{1-\exp[-(V+43.9)/10]}$	$\frac{0.1(V+34.3)}{1-\exp[-(V+34.3)/15]}$
β_m	$0.11\exp[-V/19.1]$	$4\exp[-(V+59.3)/25]$
α_{C1}	$3\alpha_m$	$3\alpha_m$
β_{C1}	β_m	β_m
α_{C2}	$2\alpha_m$	$2\alpha_m$
β_{C2}	$2\beta_m$	$2\beta_m$
α_O	α_m	α_m
β_O	$3\beta_m$	$3\beta_m$
α_{I1}	α_{C1}	α_{C1}
β_{I1}	$0.0135\beta_{C1}$	$0.0135\beta_{C1}$
α_{I2}	α_{C2}	$10\alpha_{C2}$
β_{I2}	β_{C2}	β_{C2}
α_{I3}	α_O	α_O
β_{I3}	β_O	β_O
α_{ik}	0.9	0.012
γ_{ik}	25	25
β_{i1}	$2\exp(-V/10)$	$79\exp(-2.3V/25)$
β_{i2}	$2\exp(-V/10)$	$79\exp(-2.3V/25)$
β_{i3}	$2\exp(-V/10)$	$79\exp(-2.3V/25)$
β_{i4}	$2\exp(-V/10)$	$79\exp(-2.3V/25)$
δ_{i1}	2.5	0.1
δ_{i2}	$0.0135\delta_{i1}$	$0.0135\delta_{i1}$
δ_{i3}	$0.0135\delta_{i1}$	$0.00135\delta_{i1}$
δ_{i4}	$0.0135\delta_{i1}$	$0.00135\delta_{i1}$
μ	$\frac{0.047}{1+\exp[-(V+17)/10]}$	$0.00011\exp(0.1V/25)$
ν	$0.00001\exp(-V/25)$	$0.000025\exp(-1.95V/25)$
Conductance (mS/cm^2)		
$\bar{g}_{Na}$	12	36
$\bar{g}_K$	3	3
$\bar{g}_L$	0.03	2
Equilibrium potential (mV)		
V_{Na}	50	55
V_K	−77	−80
V_L	−54.4	−58.5
i_e(μA/cm^2)	1	27
C(μF/cm^2)	1	12

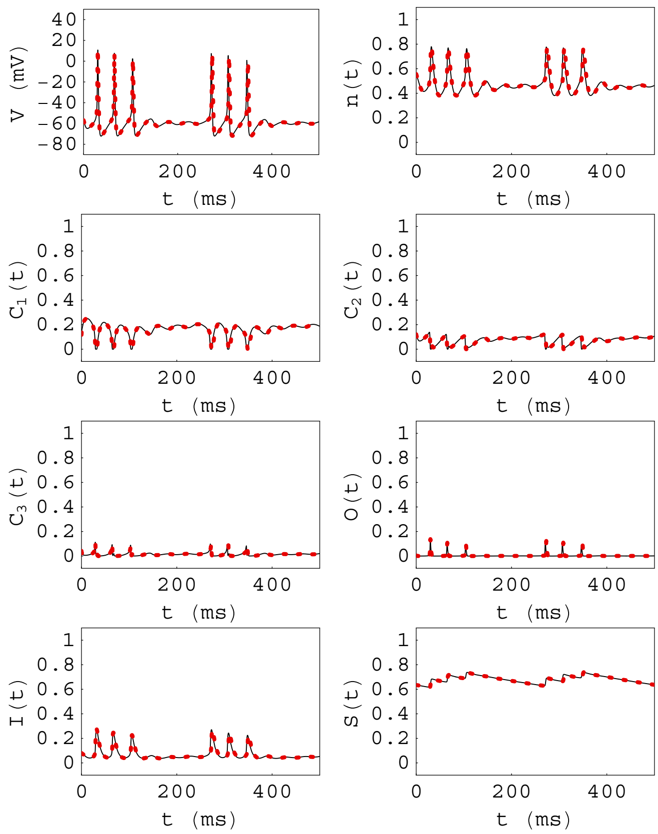

FIG. 16. The solution of a Na$^+$ channel 15-state kinetic model, Eqs. (61)–(75) (solid line) may be approximated by $C_1 = (1-m)^3 h_f s$, $C_2 = 3m(1-m)^2 h_f s$, $C_3 = 3m^2(1-m)h_f s$, $O = m^3 h_f s$, $I = I_2 + I_3 + I_4 = (1-h_f)s$ and $S = S_2 + S_3 + S_4 = 1 - s$ (dotted line), where m, h_f, and s satisfy Eqs. (56), (105), and (106), and n and V are determined by Eqs. (16) and (76). The decrease in the slow inactivation probability s terminates the burst of spikes, and as the slow variable relaxes during the subthreshold oscillation, the stationary state of the subsystem loses its stability when the recovery rate ν for slow inactivation is sufficiently large, and the bursting oscillation resumes. The rate functions are $\alpha_m = 0.1(V + 43.9)/\{1 - \exp[-(V + 43.9)/10]\}$, $\beta_m = 0.11\exp[-V/19.1]$, $\alpha_{C1} = 3\alpha_m$, $\beta_{C1} = \beta_m$, $\alpha_{C2} = 2\alpha_m$, $\beta_{C2} = 2\beta_m$, $\alpha_O = \alpha_m$, $\beta_O = 3\beta_m$, $\alpha_{I1} = \alpha_{C1}$, $\beta_{I1} = 0.0135\beta_{C1}$, $\alpha_{I2} = \alpha_{C2}$, $\beta_{I2} = \beta_{C2}$, $\alpha_{I3} = \alpha_O$, $\beta_{I3} = \beta_O$, $\alpha_{ik} = 0.9$, $\gamma_{ik} = 25$, $\beta_{ik} = 2\exp[-V/10]$, $\delta_{i1} = 5.5$, $\delta_{i2} = \delta_{i3} = \delta_{i4} = 0.0135\delta_{i1}$, $\rho_k = \alpha_{ik}/(1 + \beta_{ik}/\gamma_{ik})$, $\sigma_k = \delta_{ik}/(1 + \gamma_{ik}/\beta_{ik})$, for $k = 1$ to 4, $\mu = 0.141/\{1 + \exp[-(V + 17)/10]\}$, $\nu = 0.0001\exp(-V/25)$, $\alpha_n = 0.007(V + 58.9)/\{1 - \exp[-(V + 58.9)/10]\}$, $\beta_n = 0.038 \exp[-V/80]$, (ms^{-1}), and $\bar{g}_{\mathrm{Na}} = 12$ mS/cm^2, $\bar{g}_{\mathrm{K}} = 3$ mS/cm^2, $\bar{g}_L = 0.03$ mS/cm^2, $V_{\mathrm{Na}} = 50$ mV, $V_{\mathrm{K}} = -77$ mV, $V_L = -54.4$ mV, $j = 4$, $C = 1$ μF/cm^2, and $i_e = 1$ μA/cm^2.

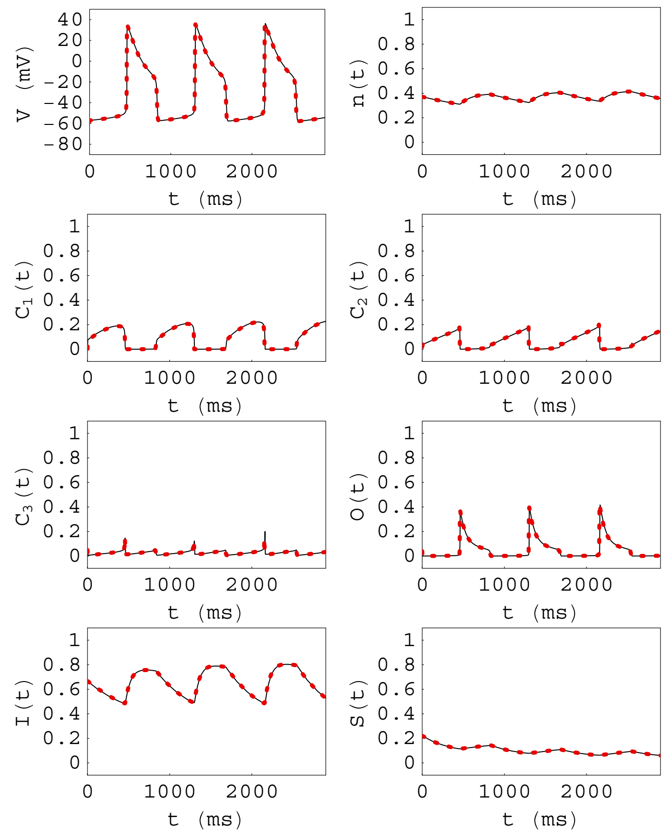

FIG. 17. The solution of a Na$^+$ channel 15-state kinetic model, Eqs. (61)–(75) (solid line) may be approximated by $C_1 = (1 - m)^3 h_f s$, $C_2 = 3m(1-m)^2 h_f s$, $C_3 = 3m^2(1-m)h_f s$, $O = m^3 h_f s$, $I = I_2 + I_3 + I_4 = (1-h_f)s$, and $S = S_2 + S_3 + S_4 = 1 - s$ (dotted line), where m, h_f, and s satisfy Eqs. (56), (105), and (106), n and V are determined by Eqs. (16) and (76), and the rate of recovery from inactivation σ_1 is sufficiently small to generate a cardiac plateau. The rate functions are $\alpha_m = 0.1(V + 34.3)/\{1 - \exp[-(V + 34.3)/15]\}$, $\beta_m = 4\exp[-(V + 59.3)/25]$, $\alpha_{C1} = 3\alpha_m$, $\beta_{C1} = \beta_m$, $\alpha_{C2} = 2\alpha_m$, $\beta_{C2} = 2\beta_m$, $\alpha_O = \alpha_m$, $\beta_O = 3\beta_m$, $\alpha_{I1} = \alpha_{C1}$, $\beta_{I1} = 0.0135\beta_{C1}$, $\alpha_{I2} = 10\alpha_{C2}$, $\beta_{I2} = \beta_{C2}$, $\alpha_{I3} = \alpha_O$, $\beta_{I3} = \beta_O$, $\alpha_{ik} = 0.012$, $\gamma_{ik} = 25$, $\beta_{ik} = 79\exp(-2.3V/25)$, $\delta_{i1} = 0.1$, $\delta_{i2} = 0.0135\delta_{i1}$, $\delta_{i3} = \delta_{i4} = 0.00135\delta_{i1}$ $\rho_k = \alpha_{ik}/(1 + \beta_{ik}/\gamma_{ik})$, $\sigma_k = \delta_{ik}/(1 + \gamma_{ik}/\beta_{ik})$, for $k = 1$ to 4 (ms^{-1}), $\mu = 0.11\exp(0.1V/25)$ (s^{-1}), $\nu = 0.025\exp(-1.95V/25)$ (s^{-1}), $\alpha_n = 0.015(V + 25)/\{1 - \exp[-(V + 25)/10]\}$, $\beta_n = 0.5\exp[-(V + 65)/80]$ (s^{-1}), and $\bar{g}_{\mathrm{Na}} = 36$ mS/cm^2, $\bar{g}_{\mathrm{K}} = 3$ mS/cm^2, $\bar{g}_L = 2$ mS/cm^2, $V_{\mathrm{Na}} = 55$ mV, $V_{\mathrm{K}} = -80$ mV, $V_L = -58.5$ mV, $j = 1$, $C = 12$ μF/cm^2, and $i_e = 27$ μA/cm^2.

IV. CONCLUSION

Based on an empirical description of the voltage clamp K$^+$ and Na$^+$ channel currents and the calculation of the membrane potential from the ion current equation, the HH model accounts for subthreshold oscillations and the action potential in the squid axon membrane [1]. The slow cumulative adaptation of spike firing during prolonged depolarization is associated with a reduction in the number of Na$^+$ channels available for activation, and the Na$^+$ current may be described by the expression $m^3 hs(V_{\mathrm{Na}} - V)$, where the HH equations for Na$^+$ activation m and fast inactivation h are supplemented by an independent rate equation for the slow inactivation variable s [2]. However, recently it has been proposed that fast and slow Na$^+$ channel inactivation are sequential processes, and therefore, fast and slow inactivation are mutually dependent [7].

In this paper, it has been shown that during an action potential, for a Na$^+$ channel with three activation sensors coupled to a two-stage inactivation process, by expressing the solution as a two-scale asymptotic expansion and eliminating secular terms, a 12-state kinetic model may be reduced to a

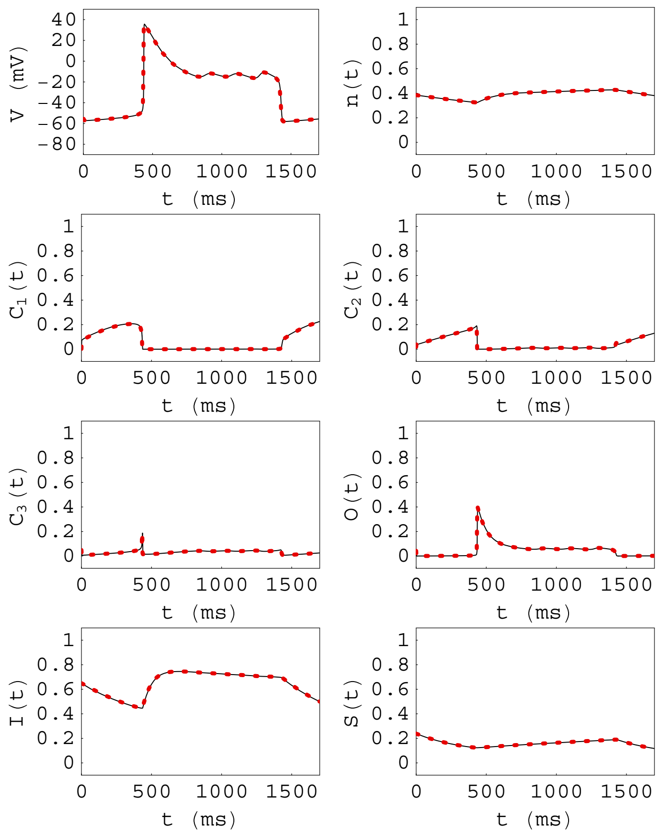

FIG. 18. The solution of a Na^+ channel 15-state kinetic model, Eqs. (61)–(75) (solid line) may be approximated by $C_1 = (1-m)^3 h_f s$, $C_2 = 3m(1-m)^2 h_f s$, $C_3 = 3m^2(1-m)h_f s$, $O = m^3 h_f s$, $I = I_2 + I_3 + I_4 = (1-h_f)s$, and $S = S_2 + S_3 + S_4 = 1 - s$ (dotted line), where m, h_f, and s satisfy Eqs. (56), (105), and (106), n and V are determined by Eqs. (16) and (76), and the rate of recovery from inactivation σ_1 is increased to generate a cardiac action potential with a plateau oscillation. The rate functions are $\alpha_m = 0.1(V+34.3)/(1-\exp[-(V+34.3)/15])$, $\beta_m = 4\exp[-(V+59.3)/25]$, $\alpha_{C1} = 3\alpha_m$, $\beta_{C1} = \beta_m$, $\alpha_{C2} = 2\alpha_m$, $\beta_{C2} = 2\beta_m$, $\alpha_O = \alpha_m$, $\beta_O = 3\beta_m$, $\alpha_{I1} = \alpha_{C1}$, $\beta_{I1} = 0.0135\beta_{C1}$, $\alpha_{I2} = 10\alpha_{C2}$, $\beta_{I2} = \beta_{C2}$, $\alpha_{I3} = \alpha_O$, $\beta_{I3} = \beta_O$, $\alpha_{ik} = 0.012$, $\gamma_{ik} = 25$, $\beta_{ik} = 79\exp(-2.3V/25)$, $\delta_{i1} = 0.12$, $\delta_{i2} = 0.0135\delta_{i1}$, $\delta_{i3} = \delta_{i4} = 0.00135\delta_{i1}$ $\rho_k = \alpha_{ik}/(1+\beta_{ik}/\gamma_{ik})$, $\sigma_k = \delta_{ik}/(1+\gamma_{ik}/\beta_{ik})$, for $k = 1$ to 4 (ms^{-1}), $\mu = 0.11\exp[0.1V/25]$ (s^{-1}), $\nu = 0.025\exp[-1.95V/25]$ (s^{-1}), $\alpha_n = 0.015(V+25)/\{1-\exp[-(V+25)/10]\}$, $\beta_n = 0.5\exp[-(V+65)/80]$ (s^{-1}), and $\bar{g}_{Na} = 36\,mS/cm^2$, $\bar{g}_K = 3\,mS/cm^2$, $\bar{g}_L = 2\,mS/cm^2$, $V_{Na} = 55\,mV$, $V_K = -80\,mV$, $V_L = -58.5\,mV$, $j = 1, C = 12$ $\mu F/cm^2$, and $i_e = 27\,\mu A/cm^2$.

7-state system when the first forward and backward inactivation transitions are rate limiting, and the recovery rate from the first inactivated state, $\sigma_1 \gg \beta_{I1}$. If the transition rates between the fast inactivated states I_2 and I_4 are larger than the corresponding inactivation and recovery rates, and the occupation probabilities for closed states and the open state are expressed in terms of activation and fast inactivation variables, then the model may be further reduced to a system of equations in the activation variables m_1, m_2, m_3, m_O and the inactivation variable h.

The rate of recovery from inactivation α_h is dependent on the rate functions α_{I1} and β_{I1}, and the recovery rate σ_1, as $\sigma_2, \sigma_3, \sigma_4 \ll \sigma_1$, but for a moderate hyperpolarization, the voltage dependence of α_h may be approximated by the exponential function β_{I1}, in agreement with experimental studies on Na^+ channel gating [1,9,21]. Assuming that the activation sensors are mutually independent, the expression for the inactivation rate $\rho(t)$ is dependent on $m(t)$, and the forward transition rates ρ_k of the DIV sensor, and if $m(t)$ has a faster relaxation than $h(t)$, $\rho(t)$ may be approximated by a voltage dependent function β_h, as assumed by HH [1]. However, it may be shown that the inactivation rates ρ_k, the recovery rates σ_k and the inactivation variable $h(t)$ generally only have a small effect on the time-dependence of the activation variable $m(t)$.

If the Na channel permits a slow transition to additional inactivated states, by expressing the solution as a three-scale asymptotic expansion and eliminating secular terms, then the kinetic model for Na^+ channel gating may be reduced to a six-state system of equations when the slow inactivation and recovery rates are at least an order of magnitude smaller than the corresponding fast inactivation rates. The reduced system requires a smaller number of parameters with values that may be estimated by comparison with experimental data, and for a repetitive action potential, the computation time for the solution of the full system is decreased when the fast processes are eliminated. Assuming that the activation sensors are mutually independent, a 15-state kinetic model of Na^+ channel gating may be reduced to equations for activation, and fast and slow inactivation that approximate the empirical linear rate equations that describe spike frequency adaptation in a neural membrane, a repetitive bursting oscillation that is modulated by the slow inactivation of Na^+ channels, and a plateau oscillation during a cardiac action potential.

APPENDIX A

For a Na^+ channel described by the twelve state kinetic model of Eqs. (4)–(15) (see Fig. 1), it is assumed that $\alpha_{ik} \ll \gamma_{ik}$, $\delta_{ik} \ll \beta_{ik}$, and $\gamma_{ik} + \beta_{ik}$ is greater than the activation and deactivation rate functions. The six-state equations for a single activation sensor and an inactivation sensor may be reduced to a four state system when the occupation probabilities for A_3 and A_4 rapidly decay to quasistationary values before the relaxation of the other states, and a similar analysis may be applied to the full system of equations. Eqs. (6), (7), (10), (11), (14), (15), and (17) may be expressed as

$$\omega_1 \frac{dC_3}{dT} = -\eta(\alpha_O + \alpha_{i3})C_3(t) + \eta\beta_O O(t) + \frac{\omega_1 \beta_{i3} A_3(t)}{\beta_i + \gamma_i}, \tag{A1}$$

$$\omega_1 \frac{dO}{dT} = -\eta(\beta_O + \alpha_{i4})O(t) + \eta\alpha_O C_3(t) + \frac{\omega_1 \beta_{i4} A_4(t)}{\beta_i + \gamma_i}, \tag{A2}$$

$$\omega_1 \frac{dA_3}{dT} = -\eta\alpha_{A3}A_3(t) - \frac{\omega_1(\beta_{i3}+\gamma_{i3})A_3(t)}{\beta_i+\gamma_i} + \eta\alpha_{i3}C_3(t) + \eta\delta_{i3}I_3(t) + \eta\beta_{A3}A_4(t), \tag{A3}$$

$$\omega_1 \frac{dA_4}{dT} = -\eta\beta_{A3}A_4(t) - \frac{\omega_1(\beta_{i4}+\gamma_{i4})A_4(t)}{\beta_i+\gamma_i} + \eta\alpha_{i4}O(t) + \eta\delta_{i4}I_4(t) + \eta\alpha_{A3}A_3(t), \tag{A4}$$

$$\omega_1 \frac{dI_3}{dT} = -\eta(\alpha_{I3}+\delta_{i3})I_3(t) + \eta\beta_{I3}I_4(t) + \frac{\omega_1\gamma_{i3}A_3(t)}{\beta_i+\gamma_i}, \tag{A5}$$

$$\omega_1 \frac{dI_4}{dT} = -\eta(\beta_{I3}+\delta_{i4})I_4(t) + \eta\alpha_{I3}I_3(t) + \frac{\omega_1\gamma_{i4}A_4(t)}{\beta_i+\gamma_i}, \tag{A6}$$

$$\omega_1 C\frac{dV}{dT} = \eta[i_e - \bar{g}_{\mathrm{Na}}O(t)(V-V_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}}n(t)^4(V-V_{\mathrm{K}}) - \bar{g}_L(V-V_L)], \tag{A7}$$

where $T = (\beta_i+\gamma_i)t$, $\beta_i = \beta_{i4}(V_c)$, $\gamma_i = \gamma_{i4}(V_c)$, $\tau = \omega_1(V_c)t$, ω_1 is the fast inactivation rate constant, V_c is a constant potential (for example, the resting or subthreshold potential), and $\eta = \omega_1(V_c)/(\beta_i+\gamma_i) \ll 1$. For the three-state system (O, A_4, I_4) that describes the transitions of the DIV sensor between open and fast inactivated states, it may be shown that

$$\omega_1 = \frac{\alpha_{i4}\gamma_{i4} + \delta_{i4}(\alpha_{i4}+\beta_{i4})}{\beta_{i4}+\gamma_{i4}} < \alpha_{i4} + \delta_{i4} \ll \beta_{i4} + \gamma_{i4}. \tag{A8}$$

The solution of Eqs. (A1)–(A7) for $C_3(t)$, $O(t)$, $A_k(t)$, $I_k(t)$ $k = 3, 4$, and $V(t)$ may be expressed as an asymptotic series where the terms are assumed to be functions of two timescales, the slow time τ and the fast time T,

$$C_3(t) = C_{30}(\tau, T) + \eta C_{31}(\tau, T) + \cdots, \tag{A9}$$

$$O(t) = O_0(\tau, T) + \eta O_1(\tau, T) + \cdots, \tag{A10}$$

$$A_k(t) = A_{k0}(\tau, T) + \eta A_{k1}(\tau, T) + \cdots, \tag{A11}$$

$$I_k(t) = I_{k0}(\tau, T) + \eta I_{k1}(\tau, T) + \cdots, \tag{A12}$$

$$V(t) = V_0(\tau, T) + \eta V_1(\tau, T) + \cdots, \tag{A13}$$

and, using the chain rule, to first order

$$\frac{dC_3}{dT} = \frac{\partial C_{30}}{\partial T} + \eta\frac{\partial C_{31}}{\partial T} + \eta\frac{\partial C_{30}}{\partial \tau}, \tag{A14}$$

$$\frac{dO}{dT} = \frac{\partial O_0}{\partial T} + \eta\frac{\partial O_1}{\partial T} + \eta\frac{\partial O_0}{\partial \tau}, \tag{A15}$$

$$\frac{dA_k}{dT} = \frac{\partial A_{k0}}{\partial T} + \eta\frac{\partial A_{k1}}{\partial T} + \eta\frac{\partial A_{k0}}{\partial \tau}, \tag{A16}$$

$$\frac{dI_k}{dT} = \frac{\partial I_{k0}}{\partial T} + \eta\frac{\partial I_{k1}}{\partial T} + \eta\frac{\partial I_{k0}}{\partial \tau}, \tag{A17}$$

$$\frac{dV}{dT} = \frac{\partial V_0}{\partial T} + \eta\frac{\partial V_1}{\partial T} + \eta\frac{\partial V_0}{\partial \tau}. \tag{A18}$$

Equating coefficients of powers of η in Eqs. (A1)–(A7), and Eqs. (A14)–(A18), we may write

$$\frac{\partial C_{30}}{\partial T} = \frac{\beta_{i3}A_{30}}{\beta_i+\gamma_i}, \tag{A19}$$

$$\frac{\partial O_0}{\partial T} = \frac{\beta_{i4}A_{40}}{\beta_i+\gamma_i}, \tag{A20}$$

$$\frac{\partial A_{k0}}{\partial T} = -\frac{(\beta_{ik}+\gamma_{ik})A_{k0}}{\beta_i+\gamma_i}, \tag{A21}$$

$$\frac{\partial I_{k0}}{\partial T} = \frac{\gamma_{ik}A_{k0}}{\beta_i+\gamma_i}, \tag{A22}$$

$$\frac{\partial V_0}{\partial T} = 0, \tag{A23}$$

and

$$\omega_1\left(\frac{\partial C_{31}}{\partial T}+\frac{\partial C_{30}}{\partial \tau}\right)=-(\alpha_O+\alpha_{i3})C_{30}+\beta_O O_O+\frac{\omega_1\beta_{i3}A_{31}}{\beta_i+\gamma_i}+\frac{\omega_1\beta_{i3}'V_1A_{30}}{\beta_i+\gamma_i}, \tag{A24}$$

$$\omega_1\left(\frac{\partial O_{1}}{\partial T}+\frac{\partial O_{0}}{\partial \tau}\right)=-(\beta_O+\alpha_{i4})O_0+\alpha_O C_{30}+\frac{\omega_1\beta_{i4}A_{41}}{\beta_i+\gamma_i}+\frac{\omega_1\beta_{i4}'V_1A_{40}}{\beta_i+\gamma_i}, \tag{A25}$$

$$\omega_1\left(\frac{\partial A_{31}}{\partial T}+\frac{\partial A_{30}}{\partial \tau}\right)=-\alpha_{A3}A_{30}+\alpha_{i3}C_{30}+\delta_{i3}I_{30}+\beta_{A3}A_{40}-\frac{\omega_1(\beta_{i3}+\gamma_{i3})A_{31}}{\beta_i+\gamma_i}-\frac{\omega_1(\beta_{i3}'+\gamma_{i3}')V_1A_{30}}{\beta_i+\gamma_i}, \tag{A26}$$

$$\omega_1\left(\frac{\partial A_{41}}{\partial T}+\frac{\partial A_{40}}{\partial \tau}\right)=-\beta_{A3}A_{40}+\alpha_{i4}O_0+\delta_{i4}I_{40}+\alpha_{A3}A_{30}-\frac{\omega_1(\beta_{i4}+\gamma_{i4})A_{41}}{\beta_i+\gamma_i}-\frac{\omega_1(\beta_{i4}'+\gamma_{i4}')V_1A_{40}}{\beta_i+\gamma_i}, \tag{A27}$$

$$\omega_1\left(\frac{\partial I_{31}}{\partial T}+\frac{\partial I_{30}}{\partial \tau}\right)=-(\alpha_{I3}+\delta_{i3})I_{30}+\beta_{I3}I_{40}+\frac{\omega_1\gamma_{i3}A_{31}}{\beta_i+\gamma_i}+\frac{\omega_1\gamma_{i3}'V_1A_{30}}{\beta_i+\gamma_i}, \tag{A28}$$

$$\omega_1\left(\frac{\partial I_{41}}{\partial T}+\frac{\partial I_{40}}{\partial \tau}\right)=-(\beta_{I3}+\delta_{i4})I_{40}+\alpha_{I3}I_{30}+\frac{\omega_1\gamma_{i4}A_{41}}{\beta_i+\gamma_i}+\frac{\omega_1\gamma_{i4}'V_1A_{40}}{\beta_i+\gamma_i}, \tag{A29}$$

$$\omega_1 C\left(\frac{\partial V_{1}}{\partial T}+\frac{\partial V_{0}}{\partial \tau}\right)=i_e-\bar{g}_{\rm Na}O_0(V_0-V_{\rm Na})-\bar{g}_{\rm K}n(t)^4(V_0-V_{\rm K})-\bar{g}_L(V_0-V_L), \tag{A30}$$

where $\beta_{ik}'=d\beta_{ik}/dV(V_0)$ and $\gamma_{ik}'=d\gamma_{ik}/dV(V_0)$ for $k=3,4$.

Eliminating A_{31} from Eqs. (A24), (A26), and (A28), and A_{41} from Eqs. (A25), (A27), and (A29), we may write

$$\omega_1\left(\frac{\partial C_{31}}{\partial T}+\frac{\beta_{i3}}{\beta_{i3}+\gamma_{i3}}\frac{\partial A_{31}}{\partial T}\right)=-\omega_1\left(\frac{\partial C_{30}}{\partial \tau}+\frac{\beta_{i3}}{\beta_{i3}+\gamma_{i3}}\frac{\partial A_{30}}{\partial \tau}\right)-(\alpha_O+\rho_3)C_{30}+\beta_O O_0$$
$$+\frac{\beta_{i3}}{\beta_{i3}+\gamma_{i3}}(\delta_{i3}I_{30}+\beta_{A3}A_{40}-\alpha_{A3}A_{30})+\frac{\omega_1V_1A_{30}}{\beta_i+\gamma_i}\left(\frac{\beta_{i3}'\gamma_{i3}-\beta_{i3}\gamma_{i3}'}{\beta_{i3}+\gamma_{i3}}\right), \tag{A31}$$

$$\omega_1\left(\frac{\partial O_{1}}{\partial T}+\frac{\beta_{i4}}{\beta_{i4}+\gamma_{i4}}\frac{\partial A_{41}}{\partial T}\right)=-\omega_1\left(\frac{\partial O_{0}}{\partial \tau}+\frac{\beta_{i4}}{\beta_{i4}+\gamma_{i4}}\frac{\partial A_{40}}{\partial \tau}\right)-(\beta_O+\rho_4)O_0+\alpha_O C_{30}$$
$$+\frac{\beta_{i4}}{\beta_{i4}+\gamma_{i4}}(\delta_{i4}I_{40}+\alpha_{A3}A_{30}-\beta_{A3}A_{40})+\frac{\omega_1V_1A_{40}}{\beta_i+\gamma_i}\left(\frac{\beta_{i4}'\gamma_{i4}-\beta_{i4}\gamma_{i4}'}{\beta_{i4}+\gamma_{i4}}\right), \tag{A32}$$

$$\omega_1\left(\frac{\partial I_{31}}{\partial T}+\frac{\gamma_{i3}}{\beta_{i3}+\gamma_{i3}}\frac{\partial A_{31}}{\partial T}\right)=-\omega_1\left(\frac{\partial I_{30}}{\partial \tau}+\frac{\gamma_{i3}}{\beta_{i3}+\gamma_{i3}}\frac{\partial A_{30}}{\partial \tau}\right)-(\alpha_{I3}+\sigma_3)I_{30}+\beta_{I3}I_{40}$$
$$+\frac{\gamma_{i3}}{\beta_{i3}+\gamma_{i3}}(\alpha_{i3}C_{30}+\beta_{A3}A_{40}-\alpha_{A3}A_{30})+\frac{\omega_1V_1A_{30}}{\beta_i+\gamma_i}\left(\frac{\gamma_{i3}'\beta_{i3}-\gamma_{i3}\beta_{i3}'}{\beta_{i3}+\gamma_{i3}}\right), \tag{A33}$$

$$\omega_1\left(\frac{\partial I_{41}}{\partial T}+\frac{\gamma_{i4}}{\beta_{i4}+\gamma_{i4}}\frac{\partial A_{41}}{\partial T}\right)=-\omega_1\left(\frac{\partial I_{40}}{\partial \tau}+\frac{\gamma_{i4}}{\beta_{i4}+\gamma_{i4}}\frac{\partial A_{40}}{\partial \tau}\right)-(\beta_{I3}+\sigma_4)I_{40}+\alpha_{I3}I_{30}$$
$$+\frac{\gamma_{i4}}{\beta_{i4}+\gamma_{i4}}(\alpha_{i4}O_0+\alpha_{A3}A_{30}-\beta_{A3}A_{40})+\frac{\omega_1V_1A_{40}}{\beta_i+\gamma_i}\left(\frac{\gamma_{i4}'\beta_{i4}-\gamma_{i4}\beta_{i4}'}{\beta_{i4}+\gamma_{i4}}\right), \tag{A34}$$

where

$$\rho_k=\frac{\alpha_{ik}\gamma_{ik}}{\beta_{ik}+\gamma_{ik}}, \tag{A35}$$

$$\sigma_k=\frac{\delta_{ik}\beta_{ik}}{\beta_{ik}+\gamma_{ik}}. \tag{A36}$$

The solution of Eqs. (A19)–(A23) for $k=3,4$ is

$$C_{30}(\tau,T)=C_{30}^{(1)}(\tau)+C_{30}^{(2)}(\tau)\exp(\lambda_3 T), \tag{A37}$$

$$O_{0}(\tau,T)=O_{0}^{(1)}(\tau)+O_{0}^{(2)}(\tau)\exp(\lambda_4 T), \tag{A38}$$

$$A_{k0}(\tau, T) = A^{(2)}_{k0}(\tau)\exp(\lambda_k T), \tag{A39}$$

$$I_{k0}(\tau, T) = I^{(1)}_{k0}(\tau) + I^{(2)}_{k0}(\tau)\exp(\lambda_k T), \tag{A40}$$

$$V_0(\tau, T) = V^{(1)}_0(\tau), \tag{A41}$$

where $\lambda_k = -(\beta_{ik} + \gamma_{ik})/(\beta_i + \gamma_i)$ and is dependent on the membrane potential V. Substituting from Eqs. (A37)–(A41), the sum of the terms that are independent of T must vanish to eliminate the secular terms on integration of Eqs. (A31)–(A34) and therefore, as $C_3(t) \approx C^{(1)}_{30}(\tau)$, $I_k(t) \approx I^{(1)}_{10}(\tau)$, for each k, $O(t) \approx O^{(1)}_0(\tau)$ and $V(t) \approx V^{(1)}_0(\tau)$ for longer times

$$\frac{dC_3}{dt} = -(\alpha_O + \rho_3)C_3(t) + \beta_O O(t) + \sigma_3 I_3(t), \tag{A42}$$

$$\frac{dO}{dt} = -(\beta_O + \rho_4)O(t) + \alpha_O C_3(t) + \sigma_4 I_4(t), \tag{A43}$$

$$\frac{dI_3}{dt} = -(\alpha_{I3} + \sigma_3)I_3(t) + \rho_3 C_3(t) + \beta_{I3} I_4(t), \tag{A44}$$

$$\frac{dI_4}{dt} = -(\beta_{I3} + \sigma_4)I_4(t) + \rho_4 O(t) + \alpha_{I3} I_3(t), \tag{A45}$$

$$\frac{\partial V}{\partial t} = i_e - \bar{g}_{\mathrm{Na}} O(t)[V(t) - V_{\mathrm{Na}}] - \bar{g}_{\mathrm{K}} n(t)^4 [V(t) - V_{\mathrm{K}}] - \bar{g}_L [V(t) - V_L]. \tag{A46}$$

In Eqs. (A26) and (A27), the sum of the terms that are independent of T also vanish, and therefore, following a transient, $A_k(t) \approx \eta A_{k1}$ and

$$A_3(t) \approx \frac{\alpha_{i3} C_3(t) + \delta_{i3} I_3(t)}{\beta_{i3} + \gamma_{i3}}, \tag{A47}$$

$$A_4(t) \approx \frac{\alpha_{i4} O(t) + \delta_{i4} I_4(t)}{\beta_{i4} + \gamma_{i4}}. \tag{A48}$$

APPENDIX B

For the eight-state kinetic model of Eqs. (18)–(25), it is assumed that the rate functions satisfy $\alpha_{I1} \gg \rho_1$ and $\sigma_1 \gg \beta_{I1}$ [9], and therefore, the occupation probability of the inactivated state I_1 rapidly decays to a quasistationary value before the relaxation of the other states. Equations (18), (22), and (23), and the current equation, Eq. (17), may be expressed as

$$\omega_1 \frac{dC_1}{dT} = -\eta(\alpha_{C1} + \rho_1)C_1(t) + \eta\beta_{C1} C_2(t) + \frac{\omega_1 \sigma_1 I_1(t)}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)}, \tag{B1}$$

$$\omega_1 \frac{dI_1}{dT} = \eta[\rho_1 C_1(t) + \beta_{I1} I_2(t)] - \frac{\omega_1(\alpha_{I1} + \sigma_1)I_1(t)}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)}, \tag{B2}$$

$$\omega_1 \frac{dI_2}{dT} = -\eta(\alpha_{I2} + \beta_{I1} + \sigma_2)I_2(t) + \eta\beta_{I2} I_3(t) + \eta\rho_2 C_2(t) + \frac{\omega_1 \alpha_{I1} I_1(t)}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)}, \tag{B3}$$

$$\omega_1 C \frac{dV}{dT} = \eta[i_e - \bar{g}_{\mathrm{Na}} O(t)(V - V_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}} n(t)^4 (V - V_{\mathrm{K}}) - \bar{g}_L (V - V_L)], \tag{B4}$$

where $T = [\alpha_{I1}(V_c) + \delta_{i1}(V_c)]t$, $\tau = \omega_1(V_c)t$, ω_1 is the rate constant for inactivation from the first closed state, V_c is a constant potential, $\eta = \omega_1(V_c)/(\alpha_{I1}(V_c) + \delta_{i1}(V_c)) \ll 1$, and $\delta_{i1} \approx \sigma_1$ when the membrane potential V is hyperpolarized. For the three-state system (C_1, I_1, I_2) that describes inactivation from the first closed state, it may be shown that

$$\omega_1 = \frac{\alpha_{I1}\rho_1 + \beta_{I1}(\sigma_1 + \rho_1)}{\sigma_1 + \alpha_{I1}} < \rho_1 + \beta_{I1} \ll \sigma_1 + \alpha_{I1}. \tag{B5}$$

The solution for $C_1(t)$, $I_1(t)$, $I_2(t)$, and $V(t)$ may be expressed as an asymptotic series where the terms are assumed to be functions of the slow time τ and the fast time T,

$$C_1(t) = C_{10}(\tau, T) + \eta C_{11}(\tau, T) + \cdots, \tag{B6}$$

$$I_1(t) = I_{10}(\tau, T) + \eta I_{11}(\tau, T) + \cdots, \tag{B7}$$

$$I_2(t) = I_{20}(\tau, T) + \eta I_{21}(\tau, T) + \cdots, \tag{B8}$$

$$V(t) = V_0(\tau, T) + \eta V_1(\tau, T) + \cdots, \tag{B9}$$

and using the chain rule, to first order,

$$\frac{dC_1}{dT} = \frac{\partial C_{10}}{\partial T} + \eta\frac{\partial C_{11}}{\partial T} + \eta\frac{\partial C_{10}}{\partial \tau}, \tag{B10}$$

$$\frac{dI_1}{dT} = \frac{\partial I_{10}}{\partial T} + \eta\frac{\partial I_{11}}{\partial T} + \eta\frac{\partial I_{10}}{\partial \tau}, \tag{B11}$$

$$\frac{dI_2}{dT} = \frac{\partial I_{20}}{\partial T} + \eta\frac{\partial I_{21}}{\partial T} + \eta\frac{\partial I_{20}}{\partial \tau}, \tag{B12}$$

$$\frac{dV}{dT} = \frac{\partial V_0}{\partial T} + \eta\frac{\partial V_1}{\partial T} + \eta\frac{\partial V_0}{\partial \tau}. \tag{B13}$$

Equating coefficients of powers of η, we may write

$$\frac{\partial C_{10}}{\partial T} = \frac{\sigma_1 I_{10}}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)}, \tag{B14}$$

$$\frac{\partial I_{10}}{\partial T} = -\frac{(\alpha_{I1} + \sigma_1)I_{10}}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)}, \tag{B15}$$

$$\frac{\partial I_{20}}{\partial T} = \frac{\alpha_{I1} I_{10}}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)}, \tag{B16}$$

$$\frac{\partial V_0}{\partial T} = 0, \tag{B17}$$

and

$$\omega_1\left(\frac{\partial C_{11}}{\partial T} + \frac{\partial C_{10}}{\partial \tau}\right) = -(\alpha_{C1} + \rho_1)C_{10} + \beta_{C1}C_2 + \frac{\omega_1\sigma_1 I_{11}}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)} + \frac{\omega_1\sigma_1' V_1 I_{10}}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)}, \tag{B18}$$

$$\omega_1\left(\frac{\partial I_{11}}{\partial T} + \frac{\partial I_{10}}{\partial \tau}\right) = \rho_1 C_{10} + \beta_{I1}I_{20} - \frac{\omega_1(\alpha_{I1} + \sigma_1)I_{11}}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)} - \frac{\omega_1(\alpha_{I1}' + \sigma_1')V_1 I_{10}}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)}, \tag{B19}$$

$$\omega_1\left(\frac{\partial I_{21}}{\partial T} + \frac{\partial I_{20}}{\partial \tau}\right) = -(\alpha_{I2} + \beta_{I1} + \sigma_2)I_{20} + \beta_{I2}I_3 + \rho_2 C_2 + \frac{\omega_1\alpha_{I1} I_{11}}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)} + \frac{\omega_1\alpha_{I1}' V_1 I_{10}}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)}, \tag{B20}$$

$$\omega_1 C\left(\frac{\partial V_1}{\partial T} + \frac{\partial V_0}{\partial \tau}\right) = i_e - \bar{g}_{\mathrm{Na}}O(t)(V_0 - V_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}}n(t)^4(V_0 - V_{\mathrm{K}}) - \bar{g}_L(V_0 - V_L), \tag{B21}$$

where $\sigma_1' = d\sigma_1/dV(V_0)$ and $\alpha_{I1}' = d\alpha_{I1}/dV(V_0)$.

Eliminating I_{11} from Eqs. (B18) and (B20),

$$\omega_1\left(\frac{\partial C_{11}}{\partial T} + \frac{\sigma_1}{\alpha_{I1} + \sigma_1}\frac{\partial I_{11}}{\partial T}\right) = -\omega_1\left(\frac{\partial C_{10}}{\partial \tau} + \frac{\sigma_1}{\alpha_{I1} + \sigma_1}\frac{\partial I_{10}}{\partial \tau}\right) - (\alpha_{C1} + \rho_1)C_{10} + \beta_{C1}C_2$$
$$+ \frac{\sigma_1}{\alpha_{I1} + \sigma_1}(\rho_1 C_{10} + \beta_{I1}I_{20}) + \frac{\omega_1 V_1 I_{10}}{\alpha_{I1}(V_c) + \delta_{i1}(V_c)}\left(\frac{\sigma_1'\alpha_{I1} - \sigma_1\alpha_{I1}'}{\alpha_{I1} + \sigma_1}\right), \tag{B22}$$

$$\omega_1\left(\frac{\partial I_{21}}{\partial T}+\frac{\alpha_{I1}}{\alpha_{I1}+\sigma_1}\frac{\partial I_{11}}{\partial T}\right)=-\omega_1\left(\frac{\partial I_{20}}{\partial \tau}+\frac{\alpha_{I1}}{\alpha_{I1}+\sigma_1}\frac{\partial I_{10}}{\partial \tau}\right)-(\alpha_{I2}+\beta_{I1}+\sigma_2)I_{20}+\beta_{I2}I_3+\rho_2C_2 +\frac{\alpha_{I1}}{\alpha_{I1}+\sigma_1}(\rho_1C_{10}+\beta_{I1}I_{20})+\frac{\omega_1V_1I_{10}}{\alpha_{I1}(V_c)+\delta_{i1}(V_c)}\left(\frac{\alpha'_{I1}\sigma_1-\alpha_{I1}\sigma'_1}{\alpha_{I1}+\sigma_1}\right). \tag{B23}$$

The solution of Eqs. (B14)–(B17) is

$$C_{10}(\tau,T)=C_{10}^{(1)}(\tau)+C_{10}^{(2)}(\tau)\exp(\lambda_1T), \tag{B24}$$

$$I_{10}(\tau,T)=I_{10}^{(2)}(\tau)\exp(\lambda_1T), \tag{B25}$$

$$I_{20}(\tau,T)=I_{20}^{(1)}(\tau)+I_{20}^{(2)}(\tau)\exp(\lambda_1T), \tag{B26}$$

$$V_0(\tau,T)=V_0^{(1)}(\tau), \tag{B27}$$

where $\lambda_1=-(\alpha_{I1}+\sigma_1)/[\alpha_{I1}(V_c)+\delta_{i1}(V_c)]$ and is sufficiently large at each membrane potential that I_1 attains the quasi-stationary value before the relaxation of C_1 and I_2. Substituting from Eqs. (B24)–(B27), the sum of the terms that are independent of T vanish to eliminate the secular terms on integration of Eqs. (B21)–(B23), and therefore, as $C_1(t)\approx C_{10}^{(1)}(\tau)$, $I_2(t)\approx I_{20}^{(1)}(\tau)$, and $V(t)\approx V_0^{(1)}(\tau)$, the reduced equations may be expressed as

$$\frac{dC_1}{dt}=-(\alpha_{C1}+\hat{\rho}_1)C_1(t)+\beta_{C1}C_2(t)+\hat{\sigma}_1I_2(t), \tag{B28}$$

$$\frac{dI_2}{dt}=-(\alpha_{I2}+\hat{\sigma}_1+\sigma_2)I_2(t)+\hat{\rho}_1C_1(t)+\rho_2C_2(t)+\beta_{I2}I_3(t), \tag{B29}$$

$$C\frac{\partial V}{\partial t}=i_e-\bar{g}_{\rm Na}O(t)[V(t)-V_{\rm Na}]-\bar{g}_{\rm K}n(t)^4[V(t)-V_{\rm K}]-\bar{g}_L[V(t)-V_L], \tag{B30}$$

where

$$\hat{\rho}_1=\frac{\rho_1\alpha_{I1}}{\alpha_{I1}+\sigma_1}, \tag{B31}$$

$$\hat{\sigma}_1=\frac{\sigma_1\beta_{I1}}{\alpha_{I1}+\sigma_1}. \tag{B32}$$

In Eq. (B19) the sum of the terms that are independent of T vanish, and therefore, following a transient,

$$I_1(t)\approx\frac{\rho_1C_1(t)+\beta_{I1}I_2(t)}{\alpha_{I1}+\sigma_1}. \tag{B33}$$

APPENDIX C

If the transition rates between fast inactivated states, and between slow inactivated states are at least an order of magnitude larger than the corresponding inactivation and recovery rates, and also larger than the activation and deactivation rates, then Eqs. (77)–(87) and the current equation, Eq. (76), may be expressed as

$$\omega_1\frac{dC_1}{dT}=\eta[-(\alpha_{C1}+\hat{\rho}_1)C_1(t)+\beta_{C1}C_2(t)+\hat{\sigma}_1I_2(t)], \tag{C1}$$

$$\omega_1\frac{dC_2}{dT}=\eta[-(\alpha_{C2}+\beta_{C1}+\rho_2)C_2(t)+\alpha_{C1}C_1(t)+\beta_{C2}C_3(t)+\sigma_2I_2(t)], \tag{C2}$$

$$\omega_1\frac{dC_3}{dT}=\eta[-(\alpha_O+\beta_{C2}+\rho_3)C_3(t)+\alpha_{C2}C_2(t)+\beta_OO(t)+\sigma_3I_3(t)], \tag{C3}$$

$$\omega_1\frac{dO}{dT}=\eta[-(\beta_O+\rho_4)O(t)+\alpha_OC_3(t)+\sigma_4I_4(t)] \tag{C4}$$

$$\omega_1 \frac{dI_2}{dT} = \frac{\omega_1[-\alpha_{I2} I_2(t) + \beta_{I2} I_3(t)]}{\alpha_I + \beta_I} + \eta[-(\hat{\sigma}_1 + \sigma_2 + \mu) I_2(t) + \nu S_2(t) + \hat{\rho}_1 C_1(t) + \rho_2 C_2(t)], \tag{C5}$$

$$\omega_1 \frac{dI_3}{dT} = \frac{\omega_1[-(\alpha_{I3} + \beta_{I2}) I_3(t) + \alpha_{I2} I_2(t) + \beta_{I3} I_4(t)]}{\alpha_I + \beta_I} + \eta[-(\sigma_3 + \mu) I_3(t) + \rho_3 C_3(t) + \nu S_3(t)], \tag{C6}$$

$$\omega_1 \frac{dI_4}{dT} = \frac{\omega_1[-\beta_{I3} I_4(t) + \alpha_{I3} I_3(t)]}{\alpha_I + \beta_I} + \eta[-(\sigma_4 + \mu) I_4(t) + \rho_4 O(t) + \nu S_4(t)], \tag{C7}$$

$$\omega_1 \frac{dS_2}{dT} = \frac{\omega_1[-\alpha_{I2} S_2(t) + \beta_{I2} S_3(t)]}{\alpha_I + \beta_I} + \eta[-\nu S_2(t) + \mu I_2(t)], \tag{C8}$$

$$\omega_1 \frac{dS_3}{dT} = \frac{\omega_1[-(\alpha_{I3} + \beta_{I2}) S_3(t) + \alpha_{I2} S_2(t) + \beta_{I3} S_4(t)]}{\alpha_I + \beta_I} + \eta[-\nu S_3(t) + \mu I_3(t)], \tag{C9}$$

$$\omega_1 \frac{dS_4}{dT} = \frac{\omega_1[-\beta_{I3} S_4(t) + \alpha_{I3} S_3(t)]}{\alpha_I + \beta_I} + \eta[-\nu S_4(t) + \mu I_4(t)], \tag{C10}$$

$$\omega_1 C \frac{dV}{dT} = \eta[i_e - \bar{g}_{\mathrm{Na}} O(t)(V - V_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}} n^j (V - V_{\mathrm{K}}) - \bar{g}_L (V - V_L)], \tag{C11}$$

where $T = (\alpha_I + \beta_I)t$, $\alpha_I = \alpha_{I2}(V_c)$, $\beta_I = \beta_{I2}(V_c)$, V_c is a constant potential, $\tau_1 = \omega_1(V_c)t$, ω_1 is the rate constant of fast inactivation, $\tau_2 = \omega_2(V_c)t$, ω_2 is the rate constant of slow inactivation, $\eta = \tau_1/T = \omega_1(V_c)/(\alpha_I + \beta_I) \ll 1$, and ϵ is defined by $\epsilon\eta^2 = \tau_2/T = \omega_2(V_c)/(\alpha_I + \beta_I) \ll 1$.

The solution of Eqs. (C1)–(C11) may be expressed as, for each k,

$$C_k(t) = C_{k0}(\tau_1, \tau_2, T) + \eta C_{k1}(\tau_1, \tau_2, T) + \eta^2 C_{k2}(\tau_1, \tau_2, T) + \cdots, \tag{C12}$$

$$O(t) = O_0(\tau_1, \tau_2, T) + \eta O_1(\tau_1, \tau_2, T) + \eta^2 O_2(\tau_1, \tau_2, T) + \cdots, \tag{C13}$$

$$I_k(t) = I_{k0}(\tau_1, \tau_2, T) + \eta I_{k1}(\tau_1, \tau_2, T) + \eta^2 I_{k2}(\tau_1, \tau_2, T) + \cdots, \tag{C14}$$

$$S_k(t) = S_{k0}(\tau_1, \tau_2, T) + \eta S_{k1}(\tau_1, \tau_2, T) + \eta^2 S_{k2}(\tau_1, \tau_2, T) + \cdots, \tag{C15}$$

$$V(t) = V_0(\tau_1, \tau_2, T) + \eta V_1(\tau_1, \tau_2, T) + \eta^2 V_2(\tau_1, \tau_2, T) + \cdots, \tag{C16}$$

where the terms are assumed to be functions of the fast time T, the fast inactivation time τ_1, and the slow inactivation time τ_2. Applying the chain rule, to second order,

$$\frac{dC_k}{dT} = \frac{\partial C_{k0}}{\partial T} + \eta\left(\frac{\partial C_{k1}}{\partial T} + \frac{\partial C_{k0}}{\partial \tau_1}\right) + \eta^2\left(\frac{\partial C_{k2}}{\partial T} + \frac{\partial C_{k1}}{\partial \tau_1} + \epsilon\frac{\partial C_{k0}}{\partial \tau_2}\right), \tag{C17}$$

$$\frac{dO}{dT} = \frac{\partial O_0}{\partial T} + \eta\left(\frac{\partial O_1}{\partial T} + \frac{\partial O_0}{\partial \tau_1}\right) + \eta^2\left(\frac{\partial O_2}{\partial T} + \frac{\partial O_1}{\partial \tau_1} + \epsilon\frac{\partial O_0}{\partial \tau_2}\right), \tag{C18}$$

$$\frac{dI_k}{dT} = \frac{\partial I_{k0}}{\partial T} + \eta\left(\frac{\partial I_{k1}}{\partial T} + \frac{\partial I_{k0}}{\partial \tau_1}\right) + \eta^2\left(\frac{\partial I_{k2}}{\partial T} + \frac{\partial I_{k1}}{\partial \tau_1} + \epsilon\frac{\partial I_{k0}}{\partial \tau_2}\right), \tag{C19}$$

$$\frac{dS_k}{dT} = \frac{\partial S_{k0}}{\partial T} + \eta\left(\frac{\partial S_{k1}}{\partial T} + \frac{\partial S_{k0}}{\partial \tau_1}\right) + \eta^2\left(\frac{\partial S_{k2}}{\partial T} + \frac{\partial S_{k1}}{\partial \tau_1} + \epsilon\frac{\partial S_{k0}}{\partial \tau_2}\right), \tag{C20}$$

$$\frac{dV}{dT} = \frac{\partial V_0}{\partial T} + \eta\left(\frac{\partial V_1}{\partial T} + \frac{\partial V_0}{\partial \tau_1}\right) + \eta^2\left(\frac{\partial V_2}{\partial T} + \frac{\partial V_1}{\partial \tau_1} + \epsilon\frac{\partial V_0}{\partial \tau_2}\right). \tag{C21}$$

Equating coefficients of powers of η, we may write,

$$\frac{\partial C_{k0}}{\partial T} = 0, \tag{C22}$$

$$\frac{\partial O_0}{\partial T} = 0, \tag{C23}$$

$$\frac{\partial I_{20}}{\partial T} = \frac{-\alpha_{I2}I_{20} + \beta_{I2}I_{30}}{\alpha_I + \beta_I}, \tag{C24}$$

$$\frac{\partial I_{30}}{\partial T} = \frac{\alpha_{I2}I_{20} - (\alpha_{I3} + \beta_{I2})I_{30} + \beta_{I3}I_{40}}{\alpha_I + \beta_I}, \tag{C25}$$

$$\frac{\partial I_{40}}{\partial T} = \frac{\alpha_{I3}I_{30} - \beta_{I3}I_{40}}{\alpha_I + \beta_I}, \tag{C26}$$

$$\frac{\partial S_{20}}{\partial T} = \frac{-\alpha_{I2}S_{20} + \beta_{I2}S_{30}}{\alpha_I + \beta_I}, \tag{C27}$$

$$\frac{\partial S_{30}}{\partial T} = \frac{\alpha_{I2}S_{20} - (\alpha_{I3} + \beta_{I2})S_{30} + \beta_{I3}S_{40}}{\alpha_I + \beta_I}, \tag{C28}$$

$$\frac{\partial S_{40}}{\partial T} = \frac{\alpha_{I3}S_{30} - \beta_{I3}S_{40}}{\alpha_I + \beta_I}, \tag{C29}$$

$$\frac{\partial V_0}{\partial T} = 0, \tag{C30}$$

and to first order,

$$\omega_1\left(\frac{\partial C_{11}}{\partial T} + \frac{\partial C_{10}}{\partial \tau_1}\right) = -(\alpha_{C1} + \hat{\rho}_1)C_{10} + \beta_{C1}C_{20} + \hat{\sigma}_1 I_{20}, \tag{C31}$$

$$\omega_1\left(\frac{\partial C_{21}}{\partial T} + \frac{\partial C_{20}}{\partial \tau_1}\right) = -(\alpha_{C2} + \beta_{C1} + \rho_2)C_{20} + \alpha_{C1}C_{10} + \beta_{C2}C_{30} + \sigma_2 I_{20}, \tag{C32}$$

$$\omega_1\left(\frac{\partial C_{31}}{\partial T} + \frac{\partial C_{30}}{\partial \tau_1}\right) = -(\alpha_O + \beta_{C2} + \rho_3)C_{30} + \alpha_{C2}C_{20} + \beta_O O_0 + \sigma_3 I_{30}, \tag{C33}$$

$$\omega_1\left(\frac{\partial O_1}{\partial T} + \frac{\partial O_0}{\partial \tau_1}\right) = -(\beta_O + \rho_4)O_0 + \alpha_O C_{30} + \sigma_4 I_{40}, \tag{C34}$$

$$\omega_1\left(\frac{\partial I_{21}}{\partial T} + \frac{\partial I_{20}}{\partial \tau_1}\right) = -(\hat{\sigma}_1 + \sigma_2)I_{20} + \hat{\rho}_1 C_{10} + \rho_2 C_{20} + \frac{\omega_1(-\alpha_{I2}I_{21} + \beta_{I2}I_{31})}{\alpha_I + \beta_I} + \frac{\omega_1 V_1(-\alpha'_{I2}I_{20} + \beta'_{I2}I_{30})}{\alpha_I + \beta_I}, \tag{C35}$$

$$\omega_1\left(\frac{\partial I_{31}}{\partial T} + \frac{\partial I_{30}}{\partial \tau_1}\right) = -\sigma_3 I_{30} + \rho_3 C_{30} + \frac{\omega_1(-(\alpha_{I3} + \beta_{I2})I_{31} + \alpha_{I2}I_{21} + \beta_{I3}I_{41})}{\alpha_I + \beta_I} + \frac{\omega_1 V_1(-(\alpha'_{I3} + \beta'_{I2})I_{30} + \alpha'_{I2}I_{20} + \beta'_{I3}I_{40})}{\alpha_I + \beta_I}, \tag{C36}$$

$$\omega_1\left(\frac{\partial I_{41}}{\partial T} + \frac{\partial I_{40}}{\partial \tau_1}\right) = -\sigma_4 I_{40} + \rho_4 O_0 + \frac{\omega_1(\alpha_{I3}I_{31} - \beta_{I3}I_{41})}{\alpha_I + \beta_I} + \frac{\omega_1 V_1(\alpha'_{I3}I_{30} - \beta'_{I3}I_{40})}{\alpha_I + \beta_I}, \tag{C37}$$

$$\omega_1\left(\frac{\partial S_{21}}{\partial T} + \frac{\partial S_{20}}{\partial \tau_1}\right) = \frac{\omega_1(-\alpha_{I2}S_{21} + \beta_{I2}S_{31})}{\alpha_I + \beta_I} + \frac{\omega_1 V_1(-\alpha'_{I2}S_{20} + \beta'_{I2}S_{30})}{\alpha_I + \beta_I}, \tag{C38}$$

$$\omega_1\left(\frac{\partial S_{31}}{\partial T} + \frac{\partial S_{30}}{\partial \tau_1}\right) = \frac{\omega_1(-(\alpha_{I3} + \beta_{I2})S_{31} + \alpha_{I2}S_{21} + \beta_{I3}S_{41})}{\alpha_I + \beta_I} + \frac{\omega_1 V_1(-(\alpha'_{I3} + \beta'_{I2})S_{30} + \alpha'_{I2}S_{20} + \beta'_{I3}S_{40})}{\alpha_I + \beta_I}, \tag{C39}$$

$$\omega_1\left(\frac{\partial S_{41}}{\partial T} + \frac{\partial S_{40}}{\partial \tau_1}\right) = \frac{\omega_1(\alpha_{I3}S_{31} - \beta_{I3}S_{41})}{\alpha_I + \beta_I} + \frac{\omega_1 V_1(\alpha'_{I3}S_{30} - \beta'_{I3}S_{40})}{\alpha_I + \beta_I}, \tag{C40}$$

$$\omega_1 C\left(\frac{\partial V_1}{\partial T} + \frac{\partial V_0}{\partial \tau_1}\right) = i_e - \bar{g}_{\mathrm{Na}}O_0(V_0 - V_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}}n(t)^4(V_0 - V_{\mathrm{K}}) - \bar{g}_L(V_0 - V_L), \tag{C41}$$

where $\alpha'_{Ik} = d\alpha_{Ik}/dV(V_0)$ and $\beta'_{Ik} = d\beta_{Ik}/dV(V_0)$ for $k = 2$ to 3, and to second order,

$$\frac{\partial C_{k2}}{\partial T} + \frac{\partial C_{k1}}{\partial \tau_1} + \epsilon\frac{\partial C_{k0}}{\partial \tau_2} = 0, \tag{C42}$$

$$\frac{\partial O_2}{\partial T} + \frac{\partial O_1}{\partial \tau_1} + \epsilon\frac{\partial O_0}{\partial \tau_2} = 0, \tag{C43}$$

$$\overline{\omega}_2\left(\frac{\partial I_{22}}{\partial T} + \frac{\partial I_{21}}{\partial \tau_1} + \epsilon\frac{\partial I_{20}}{\partial \tau_2}\right) = -\mu I_{20} + \nu S_{20}, \tag{C44}$$

$$\overline{\omega}_2\left(\frac{\partial I_{32}}{\partial T} + \frac{\partial I_{31}}{\partial \tau_1} + \epsilon\frac{\partial I_{30}}{\partial \tau_2}\right) = -\mu I_{30} + \nu S_{30}, \tag{C45}$$

$$\overline{\omega}_2\left(\frac{\partial I_{42}}{\partial T} + \frac{\partial I_{41}}{\partial \tau_1} + \epsilon\frac{\partial I_{40}}{\partial \tau_2}\right) = -\mu I_{40} + \nu S_{40}, \tag{C46}$$

$$\overline{\omega}_2\left(\frac{\partial S_{22}}{\partial T} + \frac{\partial S_{21}}{\partial \tau_1} + \epsilon\frac{\partial S_{20}}{\partial \tau_2}\right) = -\nu S_{20} + \mu I_{20}, \tag{C47}$$

$$\overline{\omega}_2\left(\frac{\partial S_{32}}{\partial T} + \frac{\partial S_{31}}{\partial \tau_1} + \epsilon\frac{\partial S_{30}}{\partial \tau_2}\right) = -\nu S_{30} + \mu I_{30}, \tag{C48}$$

$$\overline{\omega}_2\left(\frac{\partial S_{42}}{\partial T} + \frac{\partial S_{41}}{\partial \tau_1} + \epsilon\frac{\partial S_{40}}{\partial \tau_2}\right) = -\nu S_{40} + \mu I_{40}, \tag{C49}$$

$$\frac{\partial V_2}{\partial T} + \frac{\partial V_1}{\partial \tau_1} + \epsilon\frac{\partial V_0}{\partial \tau_2} = 0, \tag{C50}$$

where $\overline{\omega}_2 = \omega_2/\epsilon = \omega_1\eta$, and only variables of lowest order are retained on the right side of Eqs. (C42)–(C50).

The sum of Eqs. (C35)–(C37) and Eqs. (C38)–(C40) is

$$\omega_1\left(\frac{\partial I_{21}}{\partial T} + \frac{\partial I_{31}}{\partial T} + \frac{\partial I_{41}}{\partial T}\right) = -\omega_1\left(\frac{\partial I_{20}}{\partial \tau_1} + \frac{\partial I_{30}}{\partial \tau_1} + \frac{\partial I_{40}}{\partial \tau_1}\right) - (\hat{\sigma}_1 + \sigma_2)I_{20} - \sigma_3 I_{30} - \sigma_4 I_{40} + \hat{\rho}_1 C_{10} + \rho_2 C_{20} + \rho_3 C_{30} + \rho_4 O_0,$$

$$\omega_1\left(\frac{\partial S_{21}}{\partial T} + \frac{\partial S_{31}}{\partial T} + \frac{\partial S_{41}}{\partial T}\right) = -\omega_1(\frac{\partial S_{20}}{\partial \tau_1} + \frac{\partial S_{30}}{\partial \tau_1} + \frac{\partial S_{40}}{\partial \tau_1}). \tag{C51}$$

The sum of Eqs. (C44)–(C46) and Eqs. (C47)–(C49) is

$$\overline{\omega}_2\left(\frac{\partial I_{22}}{\partial T} + \frac{\partial I_{32}}{\partial T} + \frac{\partial I_{42}}{\partial T}\right) + \overline{\omega}_2\left(\frac{\partial I_{21}}{\partial \tau_1} + \frac{\partial I_{31}}{\partial \tau_1} + \frac{\partial I_{41}}{\partial \tau_1}\right)$$
$$= -\omega_2\left(\frac{\partial I_{20}}{\partial \tau_2} + \frac{\partial I_{30}}{\partial \tau_2} + \frac{\partial I_{40}}{\partial \tau_2}\right) - \mu(I_{20} + I_{30} + I_{40}) + \nu(S_{20} + S_{30} + S_{40}),$$
$$\overline{\omega}_2\left(\frac{\partial S_{22}}{\partial T} + \frac{\partial S_{32}}{\partial T} + \frac{\partial S_{42}}{\partial T}\right) + \overline{\omega}_2\left(\frac{\partial S_{21}}{\partial \tau_1} + \frac{\partial S_{31}}{\partial \tau_1} + \frac{\partial S_{41}}{\partial \tau_1}\right)$$
$$= -\omega_2\left(\frac{\partial S_{20}}{\partial \tau_2} + \frac{\partial S_{30}}{\partial \tau_2} + \frac{\partial S_{40}}{\partial \tau_2}\right) - \nu(S_{20} + S_{30} + S_{40}) + \mu(I_{20} + I_{30} + I_{40}). \tag{C52}$$

The solution of Eqs. (C22)–(C30), for each k, may be expressed as

$$C_{k0}(\tau_1, \tau_2, T) = C_{k0}^{(1)}(\tau_1, \tau_2), \tag{C53}$$

$$O_0(\tau_1, \tau_2, T) = O_0^{(1)}(\tau_1, \tau_2), \tag{C54}$$

$$I_{k0}(\tau_1, \tau_2, T) = I_{k0}^{(1)}(\tau_1, \tau_2) + I_{k0}^{(2)}(\tau_1, \tau_2)\exp(\lambda_1 T) + I_{k0}^{(3)}(\tau_1, \tau_2)\exp(\lambda_2 T), \tag{C55}$$

$$S_{k0}(\tau, T) = S_{k0}^{(1)}(\tau_1, \tau_2) + S_{k0}^{(2)}(\tau_1, \tau_2)\exp\lambda_1 T) + S_{k0}^{(3)}(\tau_1, \tau_2)\exp(\lambda_2 T), \tag{C56}$$

$$V_0(\tau_1, \tau_2, T) = V_0^{(1)}(\tau_1, \tau_2), \tag{C57}$$

where

$$
\begin{aligned}
&I_{20}^{(1)}(\tau_1,\tau_2) = k\beta_{I2}\beta_{I3}I_0^{(1)}, \quad I_{30}^{(1)}(\tau_1,\tau_2) = k\alpha_{I2}\beta_{I3}I_0^{(1)},\\
&I_{40}^{(1)}(\tau_1,\tau_2) = k\alpha_{I2}\alpha_{I3}I_0^{(1)}, \quad S_{20}^{(1)}(\tau_1,\tau_2) = k\beta_{I2}\beta_{I3}S_0^{(1)},\\
&S_{30}^{(1)}(\tau_1,\tau_2) = k\alpha_{I2}\beta_{I3}S_0^{(1)}, \quad S_{40}^{(1)}(\tau_1,\tau_2) = k\alpha_{I2}\alpha_{I3}S_0^{(1)},\\
&I_0^{(1)}(\tau_1,\tau_2) = I_{20}^{(1)}(\tau_1,\tau_2) + I_{30}^{(1)}(\tau_1,\tau_2) + I_{40}^{(1)}(\tau_1,\tau_2),
\end{aligned} \tag{C58}
$$

$$
S_0^{(1)}(\tau_1,\tau_2) = S_{20}^{(1)}(\tau_1,\tau_2) + S_{30}^{(1)}(\tau_1,\tau_2) + S_{40}^{(1)}(\tau_1,\tau_2), \tag{C59}
$$

$$
k = \frac{1}{\beta_{I2}\beta_{I3} + \alpha_{I2}\beta_{I3} + \alpha_{I2}\alpha_{I3}}, \tag{C60}
$$

and λ_1, λ_2 are solutions of

$$
\lambda^2 + \left(\frac{\alpha_{I2} + \alpha_{I3} + \beta_{I2} + \beta_{I3}}{\alpha_I + \beta_I}\right)\lambda + \frac{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}{(\alpha_I + \beta_I)^2} = 0. \tag{C61}
$$

If $\alpha_{I2} = 2\alpha_{I3}$ and $\beta_{I3} = 2\beta_{I2}$, then $\lambda_1 = -(\alpha_{I3} + \beta_{I2})/(\alpha_I + \beta_I)$ and $\lambda_2 = -2(\alpha_{I3} + \beta_{I2})/(\alpha_I + \beta_I)$.

Therefore, as $I_k(t) \approx I_{k0}^{(1)}(\tau_1,\tau_2)$ and $S_k(t) \approx S_{k0}^{(1)}(\tau_1,\tau_2)$, for each k, defining $I(t) = I_2(t) + I_3(t) + I_4(t)$ and $S(t) = S_2(t) + S_3(t) + S_4(t)$,

$$
I_2(t) \approx \frac{\beta_{I2}\beta_{I3}I(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \tag{C62}
$$

$$
I_3(t) \approx \frac{\alpha_{I2}\beta_{I3}I(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \tag{C63}
$$

$$
I_4(t) \approx \frac{\alpha_{I2}\alpha_{I3}I(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \tag{C64}
$$

$$
S_2(t) \approx \frac{\beta_{I2}\beta_{I3}S(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \tag{C65}
$$

$$
S_3(t) \approx \frac{\alpha_{I2}\beta_{I3}S(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \tag{C66}
$$

$$
S_4(t) \approx \frac{\alpha_{I2}\alpha_{I3}S(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}. \tag{C67}
$$

For each membrane potential, the rates λ_1 and λ_2 are sufficiently large that, following a brief transient, the expressions for $I_2(t)$ to $I_4(t)$ and $S_2(t)$ to $S_4(t)$ are in agreement with the solution of the full system.

Substituting from Eqs. (C53)–(C57), the sum of the terms in Eqs. (C31)–(C41) that are independent of T vanish, and the sum of the terms in Eqs. (C42)–(C50) that are independent of T and τ_1 also vanish to eliminate the secular terms. Therefore, as

$$
\frac{d}{dt} = \omega_1\frac{\partial}{\partial\tau_1} + \omega_2\frac{\partial}{\partial\tau_2}, \tag{C68}
$$

the reduced equations are

$$
\frac{dC_1}{dt} = -(\alpha_{C1} + \rho_1)C_1(t) + \beta_{C1}C_2(t) + \hat{\sigma}_{1r}I(t), \tag{C69}
$$

$$
\frac{dC_2}{dt} = -(\alpha_{C2} + \beta_{C1} + \rho_2)C_2(t) + \alpha_{C1}C_1(t) + \beta_{C2}C_3(t) + \sigma_{2r}I(t), \tag{C70}
$$

$$
\frac{dC_3}{dt} = -(\alpha_O + \beta_{C2} + \rho_3)C_3(t) + \alpha_{C2}C_2(t) + \beta_O O(t) + \sigma_{3r}I(t), \tag{C71}
$$

$$
\frac{dO}{dt} = -(\beta_O + \rho_4)O(t) + \alpha_O C_3(t) + \sigma_{4r}I(t), \tag{C72}
$$

$$
\frac{dI}{dt} = -(\hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r} + \mu)I(t) + \hat{\rho}_1C_1(t) + \rho_2C_2(t) + \rho_3C_3(t) + \rho_4O(t) + \nu S(t), \tag{C73}
$$

$$
\frac{dS}{dt} = \mu I(t) - \nu S(t), \tag{C74}
$$

where

$$\hat{\sigma}_{1r} = \frac{\hat{\sigma}_1 \beta_{I2}\beta_{I3}}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \tag{C75}$$

$$\sigma_{2r} = \frac{\sigma_2 \beta_{I2}\beta_{I3}}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \tag{C76}$$

$$\sigma_{3r} = \frac{\sigma_3 \alpha_{I2}\beta_{I3}}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}, \tag{C77}$$

$$\sigma_{4r} = \frac{\sigma_4 \alpha_{I2}\alpha_{I3}}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}}. \tag{C78}$$

APPENDIX D

The stationary solution $(n_s, m_s, T_s, S_s, V_s)$ of Eqs. (16), (56), (101), (102), and (110) is determined by the intersection of the nullclines, and hence

$$1 - \frac{\bar{g}_L(V_s - V_L) + \bar{g}_{\rm K} n_\infty(V_s)^j (V_s - V_{\rm K}) - i_e}{\bar{g}_{\rm Na} m_\infty(V_s)^3 (V_{\rm Na} - V_s)} = \frac{\beta_h(\mu + \nu)}{\beta_h(\mu+\nu) + \alpha_h \nu}, \tag{D1}$$

where $m_\infty(V) = \alpha_m/(\alpha_m + \beta_m)$ and $n_\infty(V) = \alpha_n/(\alpha_n + \beta_n)$. The stability of the stationary point may be computed by assuming that $n = n_s + \tilde{n}$, $m = m_s + \tilde{m}$, $T = T_s + \tilde{T}$, $S = S_s + \tilde{S}$, $V = V_s + \tilde{V}$ and the eigenvalues may be obtained from the Jacobian matrix of coefficients of the linearized equations in $\tilde{n}$, $\tilde{m}$, $\tilde{T}$, $\tilde{S}$, and $\tilde{V}$. For a solution with a single burst of spikes, each eigenvalue has a negative real part, but for a repetitive bursting oscillation, if two of the eigenvalues are complex conjugate, then the real part is small and positive.

If the rate functions $\mu \ll \beta_h$ and $\nu \ll \alpha_h$, then the variable S may be treated as a parameter, and the stationary point of the (n, m, T, V) subsystem, Eqs. (16), (56), (101), and (110), is determined by the intersection of

$$f_T(V) = \frac{\beta_h + \alpha_h S}{\beta_h + \alpha_h} \tag{D2}$$

and

$$f_V(V) = 1 - \frac{\bar{g}_L(V - V_L) + \bar{g}_{\rm K} n_\infty(V)^j (V - V_{\rm K}) - i_e}{\bar{g}_{\rm Na} m_\infty(V)^3 (V_{\rm Na} - V)}. \tag{D3}$$

For each value of S, the stability of the stationary point of the subsystem may be determined by assuming that $n = n_s + \tilde{n}$, $m = m_s + \tilde{m}$, $T = T_s + \tilde{T}$, $V = V_s + \tilde{V}$, where (n_s, m_s, T_s, V_s) is the stationary solution and we may write, to first order,

$$\frac{d\tilde{n}}{dt} = (\alpha_{ns} + \beta_{ns})[-\tilde{n} + n'_\infty(V_s)\tilde{V}], \tag{D4}$$

$$\frac{d\tilde{m}}{dt} = (\alpha_{ms} + \beta_{ms})[-\tilde{m} + m'_\infty(V_s)\tilde{V}], \tag{D5}$$

$$\frac{d\tilde{T}}{dt} = (\alpha_{hs} + \beta_{hs})[-\tilde{T} + f'_T(V_s)\tilde{V}], \tag{D6}$$

$$C\frac{d\tilde{V}}{dt} = 3\bar{g}_{\rm Na} m_s^2 (1 - T_s)(V_{\rm Na} - V_s)\tilde{m} - \bar{g}_{\rm Na}(V_{\rm Na} - V_s) m_s^3 \tilde{T} - \bar{g}_{\rm Na} m_s^3 (1 - T_s)\tilde{V} - j\bar{g}_{\rm K} n_s^{j-1}(V_s - V_{\rm K})\tilde{n} - \bar{g}_{\rm K} n_s^j \tilde{V} - \bar{g}_L \tilde{V}, \tag{D7}$$

where $\alpha_{gs} + \beta_{gs} = \alpha_g(V_s) + \beta_g(V_s)$ for $g = m, n$, and h. The eigenvalues λ of the Jacobian matrix M of coefficients of Eqs. (D4)–(D7) may be determined from the characteristic equation $\det(M - I\lambda) = 0$, and a Hopf bifurcation occurs at $S = S_1$ when there exists an eigenvalue $\lambda = \lambda_r + i\lambda_o$, $\lambda_r = 0$ such that $d\lambda_r/dS \neq 0$ [28].

By assuming that Na^+ channel activation is instantaneous, the characteristic equation may be expressed as

$$-\det(M - I\lambda) = \lambda^3 + D_1\lambda^2 + D_2\lambda + D_3 = 0, \tag{D8}$$

where

$$D_1 = r_n + r_T + r_V,$$
$$D_2 = r_n[r_T + r_V + n'_\infty(V_s)F_{\rm K}] + r_T[r_V + F(V_s)f'_T(V_s)],$$
$$D_3 = r_n r_T[r_V + F(V_s)f'_T(V_s) + n'_\infty(V_s)F_{\rm K}],$$
$$r_V = \frac{\bar{g}_{\rm K}}{C} n_s^j + \frac{\bar{g}_L}{C} - F'(V_s)(1 - T_s),$$

$$
\begin{aligned}
F(V) &= \frac{\bar{g}_{\mathrm{Na}}}{C} m_\infty(V)^3 (V_{\mathrm{Na}} - V),\\
F_{\mathrm{K}} &= j \frac{\bar{g}_{\mathrm{K}}}{C} n_s^{j-1} (V_s - V_{\mathrm{K}}),\\
r_m &= \alpha_{ms} + \beta_{ms},\\
r_n &= \alpha_{ns} + \beta_{ns},\\
r_T &= \alpha_{hs} + \beta_{hs}.
\end{aligned}
$$

If $D_1 D_2 = D_3$ and $D_2 > 0$, then $\det(M - I\lambda) = -(\lambda + D_1)(\lambda^2 + D_2)$, and therefore, two of the solutions of the characteristic equation are pure imaginary and a Hopf bifurcation occurs at $S = S_2 \approx S_1$, when activation is an order of magnitude faster than inactivation, and S_1 is determined from Eqs. (D4)—(D7).

If $\bar{g}_{\mathrm{K}} = 0$ and the K$^+$ activation variable n does not contribute to the membrane potential variation, then the characteristic equation reduces to

$$
\lambda^2 + \lambda\left[\alpha_{hs} + \beta_{hs} + \frac{\bar{g}_L}{C} - F'(V_s)(1 - T_s)\right] + (\alpha_{hs} + \beta_{hs})\left[\frac{\bar{g}_L}{C} - F'(V_s)(1 - T_s) + F(V_s) f_T'(V_s)\right] = 0, \tag{D9}
$$

and $\lambda_r = 0$ when V_s satisfies the equation

$$
\alpha_h(V_s) + \beta_h(V_s) + \frac{\bar{g}_L}{C} - \frac{F'(V_s)(\bar{g}_L(V_s - V_L) - i_e)}{F(V_s)} = 0 \tag{D10}
$$

and

$$
T_s = 1 - \frac{\bar{g}_L(V_s - V_L) - i_e}{F(V_s)}. \tag{D11}
$$

[1] A. L. Hodgkin and A. F. Huxley, J. Physiol. **117**, 500 (1952).
[2] I. A. Fleidervish, A. Friedman, and M. J. Gutnick, J. Physiol. **493**, 83 (1996).
[3] D. L. Capes, M. Arcisio-Miranda, B. W. Jarecki, R. J. French, and B. Chanda, Proc. Natl. Acad. Sci. USA **109**, 2648 (2012).
[4] N. Wu, A. Enomoto, S. Tanaka, C. Hsiao, D. Q. Nykamp, E. Izhikevich, and S. H. Chandler, J. Neurophysiol. **93**, 2710 (2005).
[5] D. C. Cooper, S. Chung, and N. Spruston, Plos Biol. **3**, e175 (2005).
[6] B. Hille, *Ion Channels of Excitable Membranes*, 3rd ed. (Sinauer, Sunderland, MA, 2001).
[7] J. D. Osteen, K. Sampson, V. Iyer, D. Julius, and F. Bosmans, Proc. Natl. Acad. Sci. USA **114**, 6836 (2017).
[8] N. Mitrovic, A. L. George, and R. Horn, J. Gen. Physiol. **115**, 707 (2000).
[9] D. L. Capes, M. P. Goldschen-Ohm, M. Arcisio-Miranda, F. Bezanilla, and B. Chanda, J. Gen. Physiol. **142**, 101 (2013).
[10] C. E. Clancy and Y. Rudy, Nature **400**, 566 (1999).
[11] E. Neher and B. Sackmann, Nature **260**, 799 (1976).
[12] R. F. Fox and Y. Lu, Phys. Rev. E **49**, 3421 (1994).
[13] N. G. van Kampen, *Stochastic Processes in Physics and Chemistry* (North Holland, Amsterdam, 2007).
[14] C. W. Gardiner, *Handbook of Stochastic Methods*, 2nd ed. (Springer, New York, 1985).
[15] S. R. Vaccaro, J. Chem. Phys. **132**, 145101 (2010).
[16] S. R. Vaccaro, J. Chem. Phys. **135**, 095102 (2011).
[17] D. Sigg, H. Qian, and F. Bezanilla, Biophys. J. **76**, 782 (1999).
[18] J. Kevorkian and J. D. Cole, *Multiple Scale and Singular Peturbation Methods* (Springer, New York, 1996).
[19] J. Keener and J. Sneyd, *Mathematical Physiology*, 2nd ed. (Springer, New York, 2009).
[20] C. M. Armstrong and F. Bezanilla, J. Gen. Physiol. **70**, 567 (1977).
[21] C-C. Kuo and B. P. Bean, Neuron **12**, 819 (1994).
[22] S. R. Vaccaro, Phys. Rev. E **90**, 052713 (2014).
[23] W. N. Zagotta, T. Hoshi, and R. W. Aldrich, J. Gen. Physiol. **103**, 321 (1994).
[24] S. R. Vaccaro, Phys. Rev. E **94**, 052407 (2016).
[25] H. Lecar, H. P. Larsson, and M. Grabe, Biophys. J. **85**, 2854 (2003).
[26] J. Keener, J. Math. Biol. **58**, 447 (2009).
[27] T. Stary and V. N. Biktashev, Chaos **27**, 093937 (2017).
[28] E. M. Izhikevich, *Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting* (MIT Press, Cambridge, MA, 2007).