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

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A fifteen state kinetic model for Na\textsuperscript{+} 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 six 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.
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].

For Na+ channels with slow inactivation, the Na+ current $I_{Na}$ may be described by the expression $I_{Na} = m^3 h s (V_{Na} - V)$ [2] where $V_{Na}$ is the equilibrium potential, and 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 $\alpha_g$ and $\beta_g$ 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 voltage sensors to open the channel, a two stage fast inactivation process [6] and subsequent slow inactivation [7]. This model is consistent with a recent study, based on the effect of molecular inhibitors on Na+ channel gating, that has proposed that fast and slow Na+ channel inactivation are sequential processes [8] and that the activation of the DIV sensor has an essential role in each type of inactivation [9].

Single channel recording techniques have demonstrated that ion channels are thermally activated between closed and open states [10], 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 [11]. 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 [12]. As the relaxation within each 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 [13]. 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 [14, 15], and is similar to that obtained from a numerical solution [16].

For a system of differential equations that has a separation of time scales, a reduced system may be derived explicitly by expressing the solution as an asymptotic expansion that is dependent on the fast and slow time scales [17]. A variable that attains a quasi-steady 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 [17, 18].

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 inac-
tivation rate function is dependent on the fast inactivation variable \( h_f(t) \). The kinetic model describing Na+ channel gating may be further 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.

**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 [19]. However, subsequent experimental studies have shown that the probability of Na+ channel 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 provide a good description of the ionic and gating currents during a voltage clamp [6].

If the Na+ channel conductance is dependent on the activation of three voltage sensors coupled to a two-stage inactivation process [6], the kinetics may be described by a twelve state kinetic 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

\[
\frac{dC_1}{dt} = -(\alpha_{i1} + \alpha_{C1})C_1(t) + \beta_{C1}C_2(t) + \beta_{i3}A_1(t) \tag{4}
\]

\[
\frac{dC_2}{dt} = -(\alpha_{i2} + \alpha_{C2} + \beta_{C1})C_2(t) + \alpha_{C1}C_1(t) + \beta_{C2}C_3(t) + \beta_{i2}A_2(t) \tag{5}
\]

\[
\frac{dC_3}{dt} = -(\alpha_{i3} + \alpha_{O} + \beta_{C2})C_3(t) + \alpha_{C2}C_2(t) + \beta_{O}O(t) + \beta_{A3}A_3(t) \tag{6}
\]

\[
\frac{dO}{dt} = -(\beta_{O} + \alpha_{A4})O(t) + \alpha_{O}C_3(t) + \beta_{i4}A_4(t) \tag{7}
\]

\[
\frac{dA_1}{dt} = -(\alpha_{A1} + \beta_{i1} + \gamma_{i1})A_1(t) + \alpha_{i1}C_1(t) + \delta_{i1}I_1(t) + \beta_{A1}A_2(t) \tag{8}
\]
The membrane current equation is for a two stage voltage sensor activation process \[ \text{[22, 23]} \]. Therefore, the \[ \gamma_j \text{ (Na+, K+ and leakage)} \] and \[ \alpha \text{ dependence of} \] be derived from a kinetic model for K+ channel gating where the voltage and \[ \beta \text{ values in a time that is smaller than the relaxation of the membrane potential} \[ \text{[1]} \].

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 quasi-stationary values in a time that is smaller than the relaxation of the membrane potential.

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

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

\[
\frac{dA_4}{dt} = -(\beta_{A3} + \beta_{i4} + \gamma_{i4})A_4(t) + \alpha_{i4}O(t) + \delta_{i4}I_4(t) + \alpha_{A3}A_3(t) \tag{11}
\]

\[
\frac{dI_1}{dt} = -(\alpha_{I1} + \delta_{i1})I_1(t) + \gamma_{i1}A_1(t) + \beta_{I1}I_2(t) \tag{12}
\]

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

\[
\frac{dI_3}{dt} = -(\alpha_{I3} + \beta_{I2} + \delta_{i3})I_3(t) + \gamma_{i3}A_3(t) + \alpha_{I2}I_2(t) + \beta_{I3}I_4(t). \tag{14}
\]

\[
\frac{dI_4}{dt} = -(\beta_{I3} + \delta_{i4})I_4(t) + \gamma_{i4}A_4(t) + \alpha_{I3}I_3(t). \tag{15}
\]

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 \[ \text{[1]} \]

\[
\frac{dn}{dt} = \alpha_n - n(t)(\alpha_n + \beta_n), \tag{16}
\]

and \( \alpha_n \) and \( \beta_n \) are voltage dependent rate functions. This equation may be derived from a kinetic model for K+ channel gating where the voltage dependence of \( \alpha_n \) and \( \beta_n \) may be expressed in terms of the transition rates for a two stage voltage sensor activation process \[ \text{[22, 23]} \]. Therefore, the membrane current equation is

\[
C \frac{dV}{dt} = i_e - \bar{g}_NaO(t)(V - V_{Na}) - \bar{g}_K^n(t)^4(V - V_K) - \bar{g}_L(V - V_L), \tag{17}
\]

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 quasi-stationary 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) to (15) may be reduced to an eight state system by expressing the solution as a two-scale asymptotic expansion and eliminating secular terms [17] (see Fig. 2).

\[
\frac{dC_1}{dt} = -(\rho_1 + \alpha C_1)C_1(t) + \beta C_1 C_2(t) + \sigma_1 I_1(t) \quad (18)
\]

\[
\frac{dC_2}{dt} = -(\alpha C_2 + \beta C_1 + \rho_2)C_2(t) + \alpha C_1 C_1(t) + \beta C_2 C_3(t) + \sigma_2 I_2(t) \quad (19)
\]

\[
\frac{dC_3}{dt} = -(\alpha O + \beta C_2 + \rho_3)C_3(t) + \alpha C_2 C_2(t) + \beta O O(t) + \sigma_3 I_3(t) \quad (20)
\]

\[
\frac{dO}{dt} = -(\beta O + \rho_4)O(t) + \alpha O C_3(t) + \sigma_4 I_4(t) \quad (21)
\]

\[
\frac{dI_1}{dt} = -(\alpha I_1 + \sigma_1)I_1(t) + \rho_1 C_1(t) + \beta I_1 I_2(t) \quad (22)
\]

\[
\frac{dI_2}{dt} = -(\alpha I_2 + \beta I_1 + \sigma_2)I_2(t) + \alpha I_1 I_1(t) + \beta I_2 I_3(t) + \rho_2 C_2(t) \quad (23)
\]

\[
\frac{dI_3}{dt} = -(\alpha I_3 + \beta I_2 + \sigma_3)I_3(t) + \alpha I_2 I_2(t) + \beta I_3 I_4(t) + \rho_3 C_3(t), \quad (24)
\]

\[
\frac{dI_4}{dt} = -(\beta I_3 + \sigma_4)I_4(t) + \alpha I_3 I_3(t) + \rho_4 O(t), \quad (25)
\]

where the derived rate functions for Na+ channel inactivation and recovery are, for each \(k\),

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

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

The Na+ and K+ channel activation rate functions between closed and open states may also be expressed in terms of the transition rates of a two or three stage process [22], that 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, the HH rate equations for Na+ channel activation and inactivation are exact solutions of an eight state kinetic model for channel gating [19, 26]. However, activation and inactivation are coupled processes, and if \(\alpha_{11} \gg \rho_1\) and \(\sigma_1 \gg \beta_{11}\), based on empirical rate functions for a Na+ channel [6], by expressing the solution as an asymptotic expansion that is dependent on fast and slow time scales and solving the equations to lowest
order [17], Eqs. (18) and (23) may be approximated by (see Fig. 3)

\[
\begin{align*}
\frac{dC_1}{dt} &= -(\alpha C_1 + \hat{\rho}_1)C_1(t) + \beta C_1 C_2(t) + \hat{s}_1 I_2(t) \\
\frac{dI_2}{dt} &= -(\alpha I_2 + \hat{s}_1 + \sigma_2)I_2(t) + \beta I_2 I_3(t) + \hat{\rho}_1 C_1(t) + \rho_2 C_2(t)
\end{align*}
\] (28) (29)

where

\[
\begin{align*}
\hat{\rho}_1 &= \frac{\rho_1 \alpha I_1}{\alpha I_1 + \sigma_1}, \\
\hat{s}_1 &= \frac{\sigma_1 \beta I_1}{\alpha I_1 + \sigma_1},
\end{align*}
\]

(30) (31)

\[
I_1(t) \approx \frac{\rho_1 C_1(t) + \beta I_1 I_2(t)}{\alpha I_1 + \sigma_1}
\] (32)

and \( n \) and \( V \) are determined by Eqs. (16) and (17) (see Fig. 4).

In Eqs. (24), (25) and (29), it is assumed that 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 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 [17], it may be shown that Eqs. (18) to (25) may be reduced to a five state kinetic model (see Fig. 5)

\[
\begin{align*}
\frac{dC_1}{dt} &= -(\rho_1 + \alpha C_1)C_1(t) + \beta C_1 C_2(t) + \hat{s}_{1r} I(t) \\
\frac{dC_2}{dt} &= -(\alpha C_2 + \beta C_1 + \rho_2)C_2(t) + \alpha C_1 C_1(t) + \beta C_2 C_3(t) + \sigma_{2r} I(t) \\
\frac{dC_3}{dt} &= -(\alpha O + \beta C_2 + \rho_3)C_3(t) + \alpha C_2 C_2(t) + \beta O O(t) + \sigma_{3r} I(t) \\
\frac{dO}{dt} &= -(\beta O + \rho_4)O(t) + \alpha O C_3(t) + \sigma_{4r} I(t) \\
\frac{dI}{dt} &= -(\hat{s}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r})I(t) + \\
&\quad \hat{\rho}_1 C_1(t) + \rho_2 C_2(t) + \rho_3 C_3(t) + \rho_4 O(t)
\end{align*}
\]

(33) (34) (35) (36) (37)

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

\[
\hat{s}_{1r} = \frac{\hat{s}_1 \beta I_2 \beta I_3}{\alpha I_2 \alpha I_3 + \alpha I_2 \beta I_3 + \beta I_2 \beta I_3}
\]

\[
\sigma_{2r} = \frac{\sigma_{2r} \beta I_2 \beta I_3}{\alpha I_2 \alpha I_3 + \alpha I_2 \beta I_3 + \beta I_2 \beta I_3}
\]

(38) (39)
\[
\sigma_{3r} = \frac{\sigma_3 \alpha_2 \beta_{I3}}{\alpha_2 \alpha_{I3} + \alpha_2 \beta_{I3} + \beta_{I2} \beta_{I3}} \quad (40)
\]
\[
\sigma_{4r} = \frac{\sigma_4 \alpha_2 \beta_{I3}}{\alpha_2 \alpha_{I3} + \alpha_2 \beta_{I3} + \beta_{I2} \beta_{I3}} \quad (41)
\]

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

\[
I_2(t) \approx \frac{\beta_{I2} \beta_{I3} I(t)}{\alpha_2 \alpha_{I3} + \alpha_2 \beta_{I3} + \beta_{I2} \beta_{I3}} \quad (42)
\]
\[
I_3(t) \approx \frac{\alpha_2 \beta_{I3} I(t)}{\alpha_2 \alpha_{I3} + \alpha_2 \beta_{I3} + \beta_{I2} \beta_{I3}} \quad (43)
\]
\[
I_4(t) \approx \frac{\alpha_2 \alpha_{I3} I(t)}{\alpha_2 \alpha_{I3} + \alpha_2 \beta_{I3} + \beta_{I2} \beta_{I3}} \quad (44)
\]

Where \(I(t) = I_2(t) + I_3(t) + I_4(t)\). Eqs. (42) to (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) to (25) may be approximated by the solution of Eqs. (33) to (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) to (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 and \(h(t)\) is an inactivation variable, Eqs. (33) to (37) may be expressed as

\[
\frac{dm_1}{dt} = -(\rho_1 + \alpha C_1 + \sigma(t) - \rho(t)) m_1(t) + \beta_{C1} m_2(t) + \sigma_{1r} (1/h(t) - 1) \quad (45)
\]
\[
\frac{dm_2}{dt} = -(\alpha C_2 + \beta C_1 + \rho_2 + \sigma(t) - \rho(t)) m_2(t) + \alpha C_1 m_1(t) + \beta_{C2} m_3(t) + \sigma_{2r} (1/h(t) - 1) \quad (46)
\]
\[
\frac{dm_3}{dt} = -(\alpha O + \beta C_2 + \rho_3 + \sigma(t) - \rho(t)) m_3(t) + \alpha C_2 m_2(t) + \beta_{O} m_O(t) + \sigma_{3r} (1/h(t) - 1) \quad (47)
\]
\[
\frac{dm_O}{dt} = -(\beta_O + \rho_4 + \sigma(t) - \rho(t)) m_O(t) + \alpha O m_3(t) + \sigma_{4r} (1/h(t) - 1) \quad (48)
\]
\[
\frac{dh}{dt} = \hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r} - h(t)(\hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r} + \rho(t)) \quad (49)
\]
where

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

\[
\sigma(t) = (\hat{\sigma}_1 + \sigma_2 + \sigma_3 + \sigma_4)(1/h(t) - 1). \quad (51)
\]

The inactivation rates \(\rho_k\) and recovery rates \(\sigma_k\), 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) to (48) for the activation variables may be approximated by (see Fig. 7)

\[
\frac{dm_1}{dt} = -\alpha_C m_1(t) + \beta_C m_2(t) \quad (52)
\]

\[
\frac{dm_2}{dt} = -(\alpha_C + \beta_C) m_2(t) + \alpha_C m_1(t) + \beta_C m_3(t) \quad (53)
\]

\[
\frac{dm_3}{dt} = -(\alpha_O + \beta_C) m_3(t) + \alpha_C m_2(t) + \beta_O m_O(t) \quad (54)
\]

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

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 \((\alpha_C = 3\alpha_m, \alpha_C = 2\alpha_m, \alpha_O = \alpha_m, \beta_C = \beta_m, \beta_C = 2\beta_m, \beta_O = 3\beta_m)\), Eqs. (52) to (55) have the solution

\[
m_1(t) = (1 - m(t))^3, \quad m_2(t) = 3m(t)(1 - m(t))^2, \quad m_3(t) = 3m(t)^2(1 - m(t)), \quad m_O(t) = m(t)^3, \quad \text{where } m(t) \text{ satisfies}
\]

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

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 generally has a faster time constant than \(h(t)\), \(\rho(t)\) may be approximated by

\[
\beta_h = \hat{\beta}_1 (1 - m_\infty)^3 + 3\rho_2 m_\infty(1 - m_\infty)^2 + 3\rho_3 m_\infty^2(1 - m_\infty) + \rho_4 m_\infty^3 \quad (58)
\]

where \(m_\infty = \alpha_m / (\alpha_m + \beta_m)\) for each membrane potential, and \(\beta_h\) is a voltage dependent function, as assumed by HH [1]. The activation function \(m_\infty\) and each inactivation rate \(\rho_k\) has an exponential voltage dependence for
a small depolarization but for larger potentials, the variation has a plateau, and therefore, accounts for the voltage dependence of $\beta_h$ (see Fig. 8).

Eq. (49) may be expressed as

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

(59)

where

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

(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 $\alpha_h$ is approximately exponential [1] (see Fig. 8), but may attain a plateau value for a large hyperpolarization [6, 21, 24].

If the previous conditions for each stage of reduction are satisfied, the solution of the twelve state kinetic model, Eqs. (4) to (15), during an action potential, may be approximated by the solution of Eqs. (56) and (59), 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 [6]. 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 $m^3h$ [19], strongly coupled activation and inactivation is also compatible with the open state probability $O(t) = m(t)^3h(t)$.

**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 [8], and therefore, the kinetics may be described by a fifteen state model (see Fig. 11)

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

(61)

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

(62)
\[
\begin{align*}
\frac{dC_3}{dt} &= -(\alpha_{i3} + \alpha_O + \beta_{c2})C_3(t) + \alpha_cC_2(t) + \\
&\quad \beta_O O(t) + \beta_{i3}A_3(t) \\
\frac{dO}{dt} &= -(\beta_O + \alpha_{i4})O(t) + \alpha_O C_3(t) + \beta_{i4}A_4(t) \\
\frac{dA_1}{dt} &= -(\alpha_{A1} + \beta_{i1} + \gamma_{i1})A_1(t) + \alpha_{i1}C_1(t) \\
&\quad + \delta_{i1}I_1(t) + \beta_{A1}A_2(t) \\
\frac{dA_2}{dt} &= -(\alpha_{A2} + \beta_{A1} + \beta_{i2} + \gamma_{i2})A_2(t) + \alpha_{i2}C_2(t) \\
&\quad + \delta_{i2}I_2(t) + \alpha_{A1}A_1(t) + \beta_{A2}A_3(t) \\
\frac{dA_3}{dt} &= -(\alpha_{A3} + \beta_{A2} + \beta_{i3} + \gamma_{i3})A_3(t) + \alpha_{i3}C_3(t) \\
&\quad + \delta_{i3}I_3(t) + \alpha_{A2}A_2(t) + \beta_{A3}A_4(t) \\
\frac{dA_4}{dt} &= -(\beta_{A3} + \beta_{i4} + \gamma_{i4})A_4(t) + \alpha_{i4}O(t) \\
&\quad + \delta_{i4}I_4(t) + \alpha_{A3}A_3(t) \\
\frac{dI_1}{dt} &= -(\alpha_{I1} + \delta_{i1})I_1(t) + \gamma_{i1}A_1(t) + \beta_{I1}I_2(t) \\
\frac{dI_2}{dt} &= -(\alpha_{I2} + \beta_{I1} + \delta_{i2} + \mu)I_2(t) \\
&\quad + \gamma_{i2}A_2(t) + \alpha_{I1}I_1(t) + \beta_{I2}I_3(t) + \nu S_2(t), \\
\frac{dI_3}{dt} &= -(\alpha_{I3} + \beta_{I2} + \delta_{i3} + \mu)I_3(t) \\
&\quad + \gamma_{i3}A_3(t) + \alpha_{I2}I_2(t) + \beta_{I3}I_4(t) + \nu S_3(t) \\
\frac{dI_4}{dt} &= -(\beta_{I3} + \delta_{i4} + \mu)I_4(t) \\
&\quad + \gamma_{i4}A_4(t) + \alpha_{I3}I_3(t) + \nu S_4(t) \\
\frac{dS_2}{dt} &= -(\alpha_{I2} + \nu)S_2(t) + \beta_{I2}S_3(t) + \mu I_2(t) \\
\frac{dS_3}{dt} &= -(\alpha_{I3} + \beta_{I2} + \nu)S_3(t) + \alpha_{I2}S_2(t) + \beta_{I3}S_4(t) \\
&\quad + \mu I_3(t) \\
\frac{dS_4}{dt} &= -(\beta_{I3} + \nu)S_4(t) + \alpha_{I3}S_3(t) + \mu I_4(t),
\end{align*}
\]

where $S_2(t), S_3(t)$ and $S_4(t)$ are the occupational probabilities for the slow inactivated states, and $\mu$ and $\nu$ are voltage dependent transition 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. By expressing the solution as a two-scale asymptotic expansion and eliminating secular terms \cite{17}, Eqs. (61) to (75) may be reduced to an eleven 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 $k \cite{24}$ (see Fig. 12).

\[
\begin{align*}
\frac{dC_1}{dt} &= -(\rho_1 + \alpha_{C1})C_1(t) + \beta_{C1}C_2(t) + \sigma_1I_1(t) \quad (76) \\
\frac{dC_2}{dt} &= -(\alpha_{C2} + \beta_{C1} + \rho_2)C_2(t) + \alpha_{C1}C_1(t) + \beta_{C2}C_3(t) + \sigma_2I_2(t) \quad (77) \\
\frac{dC_3}{dt} &= -(\alpha_O + \beta_{C2} + \rho_3)C_3(t) + \alpha_{C2}C_2(t) + \beta_OO(t) + \sigma_3I_3(t) \quad (78) \\
\frac{dO}{dt} &= -(\beta_O + \rho_4)O(t) + \alpha_OC_3(t) + \sigma_4I_4(t) \quad (79) \\
\frac{dI_1}{dt} &= -(\alpha_{I1} + \sigma_1)I_1(t) + \rho_1C_1(t) + \beta_{I1}I_2(t) \quad (80) \\
\frac{dI_2}{dt} &= -(\alpha_{I2} + \beta_{I1} + \sigma_2 + \mu)I_2(t) + \alpha_{I1}I_1(t) + \beta_{I2}I_3(t) + \rho_2C_2(t) + \nu S_2(t) \quad (81) \\
\frac{dI_3}{dt} &= -(\alpha_{I3} + \beta_{I2} + \sigma_3 + \mu)I_3(t) + \alpha_{I2}I_2(t) + \beta_{I3}I_4(t) + \rho_3C_3(t) + \nu S_3(t), \quad (82) \\
\frac{dI_4}{dt} &= -(\beta_{I3} + \sigma_4 + \mu)I_4(t) + \alpha_{I3}I_3(t) + \rho_4O(t) + \nu S_4(t), \quad (83) \\
\frac{dS_2}{dt} &= -(\alpha_{I2} + \nu)S_2(t) + \beta_{I2}S_3(t) + \mu I_2(t) \quad (84) \\
\frac{dS_3}{dt} &= -(\alpha_{I3} + \beta_{I2} + \nu)S_3(t) + \alpha_{I2}S_2(t) + \beta_{I3}S_4(t) + \mu I_3(t) \quad (85) \\
\frac{dS_4}{dt} &= -(\beta_{I3} + \nu)S_4(t) + \alpha_{I3}S_3(t) + \mu I_4(t). \quad (86)
\end{align*}
\]

Assuming that $\alpha_{I1} \gg \rho_1$ and $\sigma_1 \gg \beta_{I1} \cite{6}$, Eqs. (76) and (81) may be expressed as

\[
\begin{align*}
\frac{dC_1}{dt} &= -(\alpha_{C1} + \hat{\rho}_1)C_1(t) + \beta_{C1}C_2(t) + \hat{\sigma}_1I_2(t) \quad (87) \\
\frac{dI_2}{dt} &= -(\alpha_{I2} + \hat{\sigma}_1 + \sigma_2 + \mu)I_2(t) + \beta_{I2}I_3(t) + \nu S_2(t) + \hat{\rho}_1C_1(t) + \rho_2C_2(t), \quad (88)
\end{align*}
\]

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. (82) to (86) and (88), it is assumed that 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 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 [17], Eqs. (76) to (86) are reducible to a six state kinetic model (see Fig. 14).

\[
\begin{align*}
\frac{dC_1}{dt} &= -(\rho_1 + \alpha_{C1})C_1(t) + \beta_{C1}C_2(t) + \hat{\sigma}_{1r}I(t) \quad (89) \\
\frac{dC_2}{dt} &= -(\alpha_{C2} + \beta_{C1} + \rho_2)C_2(t) + \alpha_{C1}C_1(t) + \beta_{C2}C_3(t) + \sigma_{2r}I(t) \quad (90) \\
\frac{dC_3}{dt} &= -(\alpha_O + \beta_{C2} + \rho_3)C_3(t) + \alpha_{C2}C_2(t) + \beta_OO(t) + \sigma_{3r}I(t) \quad (91) \\
\frac{dO}{dt} &= -(\beta_O + \rho_4)O(t) + \alpha_{O}C_3(t) + \sigma_{4r}I(t) \quad (92) \\
\frac{dI}{dt} &= -(\hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r} + \mu)I(t) \\
&\quad + \hat{\rho}_1C_1(t) + \rho_2C_2(t) + \rho_3C_3(t) + \rho_4O(t) + \nu S(t) \quad (93) \\
\frac{dS}{dt} &= \mu I(t) - \nu S(t) \quad (94)
\end{align*}
\]

where \(\hat{\sigma}_{1r}, \sigma_{2r}, \sigma_{3r}\) and \(\sigma_{4r}\) are defined in Eqs. (38) to (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) to (44), and the slow inactivation probabilities \(S_2(t), S_3(t)\) and \(S_4(t)\) may be expressed as

\[
\begin{align*}
S_2(t) &\approx \frac{\beta_{I2}\beta_{I3}S(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}} \quad (95) \\
S_3(t) &\approx \frac{\beta_{I2}\beta_{I3}S(t)}{\alpha_{I3}\alpha_{I3} + \alpha_{I2}\beta_{I3} + \beta_{I2}\beta_{I3}} \quad (96) \\
S_4(t) &\approx \frac{\beta_{I2}\beta_{I3}S(t)}{\alpha_{I2}\alpha_{I3} + \alpha_{I3}\beta_{I3} + \beta_{I2}\beta_{I3}} \quad (97)
\end{align*}
\]

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

Expressing \(C_1(t) = m_1(t)h(t), \ C_2(t) = m_2(t)h(t), C_3(t) = m_3(t)h(t), O(t) = m_O(t)h(t)\) 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. (89) to (92), it may be shown that
\[ m_1(t) = (1 - m(t))^3, \quad m_2(t) = 3m(t)(1 - m(t))^2, \quad m_3(t) = 3m(t)^2(1 - m(t)), \quad m_O(t) = m(t)^3, \]
where \( m(t) \) satisfies Eq. (56), \( h(t) \) and \( S(t) \) satisfy
\[ \frac{dh}{dt} = \alpha_h (1 - S(t)) - h(t)(\alpha_h + \beta_h) \]
\[ \frac{dS}{dt} = \mu (1 - h(t)) - S(t)(\mu + \nu), \]
and \( \beta_h \) and \( \alpha_h \) are defined in Eqs. (58) and (60).

Defining total inactivation \( T(t) = I(t) + S(t) = 1 - h(t) \), Eqs. (98) and (99) may be expressed as
\[ \frac{dT}{dt} = \beta_h + \alpha_h S(t) - T(t)(\alpha_h + \beta_h) \]
\[ \frac{dS}{dt} = \mu T(t) - S(t)(\mu + \nu). \]

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 \( 1 \leq j \leq 4 \), and the activation variable \( n(t) \) satisfies Eq. (16), the membrane current equation is
\[ C \frac{dV}{dt} = \bar{g}_N O(t)(V - V_{Na}) - \bar{g}_K n(t)^j (V - V_K) - \bar{g}_L (V - V_L), \]
where \( O(t) = m(t)^3(1 - T(t)) \).

The variable \( S(t) \) has a slow variation relative to fast inactivation, and therefore, writing \( h(t) = h_f(t)(1 - S(t)) \), Eqs. (98) and (99) may be expressed as
\[ \frac{dh_f}{dt} \approx \alpha_h - h_f(t)(\alpha_h + \beta_h) \]
\[ \frac{dS}{dt} = \mu (1 - h_f(t)) - S(t)[\mu (1 - h_f(t)) + \nu], \]
and the forward rate for slow inactivation is dependent on the fast inactivation variable \( h_f(t) \), similar to the dependence of the fast inactivation rate \( \rho(t) \approx \beta_h \) on the activation variable \( m(t) \) in Eq. (57). Defining \( s(t) = 1 - S(t) \), Eq. (103) is equivalent to
\[ \frac{ds}{dt} = \nu - s(t)[\nu + \mu (1 - h_f(t))]. \]
During a voltage clamp of the Na+ channel membrane, $h_f(t)$ may be approximated by $h_f(\infty)(V) = \alpha_h/(\alpha_h + \beta_h)$ following the relaxation of the fast inactivation process, and from Eq. (105), we may write

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

(106)

where $\alpha_s = \nu$ and $\beta_s \approx \mu(1 - h_f(\infty))$. If $\mu$ has a weak voltage dependence, there is a plateau in the voltage dependence of $\beta_s$ for a large depolarization potential, consistent with the slow inactivation voltage clamp data for a Na+ channel [2]. Therefore, Eq. (102) may be expressed as

$$C \frac{dV}{dt} = i_e - \bar{g}_{Na}m^3h_fs(V - V_{Na}) - \bar{g}_K^n(V - V_K) - \bar{g}_L(V - V_L),$$

(107)

and Eqs. (16), (56), (103), (106), and (107) are the empirical equations that describe spike frequency adaptation [2].

The variation in the probability $S$ that the inactivation sensor occupies a slow inactivation state is an order 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 $(m, n, T, V)$ subsystem. 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), (100) and (101) where $n$ and $V$ are determined by Eqs. (16) and Eq. (107) (see Fig. 15).

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 $\nu$ for slow inactivation is sufficiently large, and the bursting oscillation resumes [4] (see Fig. 16). More generally, bursting activity serves an important role in the nervous system and in addition to the slow inactivation of Na+ channels, may also be generated by inactivating K+ channels and the activation of slow M-type K+ channels [28]. Although the cardiac ventricular action potential is dependent on Na+, K+ and Ca++ currents as well as intracellular ion concentration changes [7], 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, the stationary state of the subsystem is stable for small values of $S$, but may lose its stability as $S$ increases and therefore, the plateau may develop an oscillation (see Figs. 17 and 18).
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 \( m^3 h s (V_{Na} - V) \) 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 [8].

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 twelve state kinetic model may be reduced to a seven state system when the first forward and backward inactivation transitions are rate limiting, and the recovery rate for fast inactivation \( \sigma_1 \) from the first inactivated state \( I_1 \) is an order of magnitude larger than the deactivation rate \( \beta_{I1} \). If the transition rates between the fast inactivated states \( I_2 \) and \( I_4 \) are larger then 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, 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 \( h \). Assuming that the activation sensors are mutually independent, the twelve state kinetic model may be reduced to equations for \( m \) and \( h \), and therefore, decreases the computation time for the simulation of action potentials.

The rate of recovery from inactivation \( \alpha_h \) is dependent on the rate functions \( \alpha_{I1} \) and \( \beta_{I1} \), and the recovery rate \( \sigma_1 \), as \( \sigma_2, \sigma_3, \sigma_4 \ll \sigma_1 \), but for a moderate hyperpolarization, the voltage dependence of \( \alpha_h \) may be approximated by the exponential function \( \beta_{I1} \), in agreement with experimental studies on Na+ channel gating [1, 6, 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 \( \rho_k \) 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 \( \beta_h \), as assumed by HH [1]. Therefore, the parameters for inactivation may be calculated from the transition rates of the kinetic model based on the structure of the wild-type or mutant Na+.
ion channel. However, the inactivation rates $\rho_k$ and recovery rates $\sigma_k$ are an order of magnitude smaller than activation and deactivation rates, and it may be shown that $\rho_k$, $\sigma_k$ 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, the kinetic model for channel gating may be reduced to a six state system of equations when, in addition to the conditions satisfied by the fast inactivation rates, the transition rates between the slow inactivated states are an order of magnitude larger than the slow inactivation and recovery rates. Assuming that the activation sensors are mutually independent, a fifteen state kinetic model of Na+ channel gating may be reduced to equations for activation, and fast and slow inactivation that approximate the empirical 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.
References

[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. 493.1, 83 (1996).

[3] D.L. Capes, M. Arcisio-Miranda, B.W. Jarecki, R.J. French and B. Chanda, P.N.A.S. 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 Biology 3, e175 (2005).

[6] D.L. Capes, M.P. Goldschen-Ohm, M. Arcisio-Miranda, F. Bezanilla and B. Chanda, J. Gen. Physiol. 142, 101 (2013).

[7] C.E. Clancy and Y. Rudy, Nature 400, 566 (1999).

[8] J.D. Osteen, K. Sampson, V. Iyer, D. Julius and F. Bosmans, P.N.A.S. 114, 6836 (2017).

[9] N. Mitrovic, A.L. George and R. Horn, J. Gen. Physiol. 115, 707 (2000).

[10] E. Neher and B. Sackmann, Nature 260, 779 (1976).

[11] R. F. Fox and Y. Lu, Phys. Rev. 49, 3421 (1994).

[12] N. G. van Kampen, Stochastic Processes in Physics and Chemistry, (North Holland, Amsterdam, 2007)

[13] C. W. Gardiner, Handbook of Stochastic Methods, 2nd ed. (Springer, New York, 1985).

[14] S.R. Vaccaro, J. Chem. Phys. 132, 145101 (2010).

[15] S.R. Vaccaro, J. Chem. Phys. 135, 095102 (2011).

[16] D. Sigg, H. Qian and F. Bezanilla, Biophys. J. 76, 782 (1999).

[17] J. Kevorkian and J.D. Cole, Multiple Scale and Singular Perturbation Methods, (Springer, New York, 1996).

[18] J. Keener and J. Sneyd, Mathematical Physiology, 2nd ed. (Springer, New York, 2009).
[19] B. Hille, Ion Channels of Excitable Membranes, 3rd ed. (Sinauer, Sunderland, M.A. 2001).

[20] C. M. Armstrong, 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 2007).
Figure 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.
Figure 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 $\rho_k$ and $\sigma_k$ are defined in Eqs. (26) and (27).
Figure 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).
Figure 4: For the solution of Eqs. (18) to (25) during an action potential (solid line), Eqs. (18), (22) and (23) 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:

$\alpha_m = 0.1(V+35)/(1-\exp[-(V+35)/10]), \quad \beta_m = 4 \exp[-(V+60)/18], \quad \alpha_{C1} = 3 \alpha_m, \quad \beta_{C1} = \beta_m, \quad \alpha_{C2} = 2 \alpha_m, \quad \beta_{C2} = 2 \beta_m, \quad \alpha_O = \alpha_m, \quad \beta_O = 3 \beta_m, \quad \alpha_{I1} = \alpha_{C1}, \quad \beta_{I1} = 0.016 \beta_{C1}, \quad \alpha_{I2} = \alpha_{C2}, \quad \beta_{I2} = \beta_{C2}, \quad \alpha_{I3} = \alpha_O, \quad \beta_{I3} = \beta_O, \quad \alpha_{ik} = 1, \quad \gamma_{ik} = 22.2, \quad \beta_{ik} = \exp[-V/10], \quad \delta_{i1} = 2.5, \quad \delta_{i2} = \delta_{i3} = \delta_{i4} = 0.04, \quad \rho_k = \alpha_{ik}/(1 + \beta_{ik}/\gamma_{ik})$

for $k = 1, 4, \quad \sigma_1 = \delta_{i1}/(1 + \gamma_{i1}/\beta_{i1}), \quad \sigma_2 = \sigma_3 = \sigma_4 = 0.016 \sigma_1$ (ms$^{-1}$) $\alpha_n = 0.01(V + 50)/(1-\exp[-(V + 50)/10]), \quad \beta_n = 0.125 \exp[-(V + 60)/80], \quad$ and $\bar{g}_{Na} = 120$ mS/cm$^2, \quad \bar{g}_K = 36$ mS/cm$^2, \quad \bar{g}_L = 0.3$ mS/cm$^2, \quad V_{Na} = 55$ mV, $V_K = -75$ mV, $V_L = -60$ mV, $C = 1 \mu$F/cm$^2, \quad i_e = 1 \mu$A/cm$^2.$
Figure 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.
Figure 6: The solution of a Na+ channel eight state kinetic model, Eqs. (18) to (25) (solid line) may be approximated by the solution of Eqs. (33) to (37) (dotted line), where \( n \) and \( V \) are determined by Eqs. (16) and (17), and \( I_1 \) to \( I_4 \) are calculated from Eqs. (32) and (42) to (44). The rate functions are:

\[
\begin{align*}
\alpha_m &= 0.1(V + 35)/(1 - \exp[-(V + 35)/10]), \\
\beta_m &= 4 \exp[-(V + 60)/18], \\
\alpha_{C1} &= 3\alpha_m, \\
\beta_{C1} &= \beta_m, \\
\alpha_{C2} &= 2\alpha_m, \\
\beta_{C2} &= 2\beta_m, \\
\alpha_O &= \alpha_m, \\
\beta_O &= 3\beta_m, \\
\alpha_{I1} &= \alpha_{C1}, \\
\beta_{I1} &= 0.016\beta_{C1}, \\
\alpha_{I2} &= 2\alpha_{C2}, \\
\beta_{I2} &= 2\beta_{C2}, \\
\alpha_{I3} &= 2\alpha_O, \\
\beta_{I3} &= 2\beta_O, \\
\alpha_{ik} &= 1, \\
\gamma_{ik} &= 22.2, \\
\beta_{ik} &= \exp[-V/10], \\
\delta_{i1} &= 2.5, \\
\delta_{i2} &= \delta_{i3} = \delta_{i4} = 0.04, \\
\rho_k &= \alpha_{ik}/(1 + \beta_{ik}/\gamma_{ik}) \\
\text{for } k = 1, 4, \\
\sigma_1 &= \delta_{i1} 25(1 + \gamma_{i1}/\beta_{i1}), \\
\sigma_2 &= \sigma_3 = \sigma_4 = 0.016\sigma_1, \\
\alpha_n &= 0.01(V + 50)/(1 - \exp[-(V + 50)/10]), \\
\beta_n &= 0.125 \exp[-(V + 60)/80] \\
\text{(ms}^{-1})\text{, and} \\
\bar{g}_{Na} &= 120 \text{ mS/cm}^2, \\
\bar{g}_K &= 36 \text{ mS/cm}^2, \\
\bar{g}_L &= 0.3 \text{ mS/cm}^2, \\
V_{Na} &= 55 \text{ mV}, \\
V_K &= -75 \text{ mV}, \\
V_L &= -60 \text{ mV}, \\
C &= 1 \mu\text{F/cm}^2, \\
\iota_e &= 1 \mu\text{A/cm}^2. 
\end{align*}
\]
During an action potential, the solution of the Na+ channel activation equations, Eqs. (45) to (48) (solid line) may be approximated by the solution of Eqs. (52) to (55) (dotted line), when the inactivation and recovery rates are an order of magnitude smaller than the activation and deactivation rates, and n, V and h are determined by Eqs. (16), (17) and (49). The rate functions are

\[ \alpha_m = 0.1(V + 35)/(1 - \exp[-(V + 35)/10]), \]
\[ \beta_m = 4 \exp[-(V + 60)/18], \alpha_C = 3\alpha_m, \beta_C = \beta_m, \alpha_C2 = 2\alpha_m, \beta_C2 = 2\beta_m, \]
\[ \alpha_O = \alpha_m, \beta_O = 3\beta_m, \alpha_I1 = \alpha_C1, \beta_I1 = 0.016\beta_C1, \alpha_I2 = 2\alpha_C2, \beta_I2 = 2\beta_C2, \alpha_I3 = 2\alpha_O, \beta_I3 = 2\beta_O, \alpha_{ik} = 26, 1, \gamma_{ik} = 22.2, \beta_{ik} = \exp[-V/10], \]
\[ \rho_k = \alpha_{ik}\gamma_{ik}/(\beta_{ik} + \gamma_{ik}) \] for \( k = 1, 4 \), \( \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, \( C = 1 \) µF/cm\(^2\), \( i_e = 1 \) µA/cm\(^2\).
Figure 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 \( \alpha_m = 0.1(V + 35)/(1 - \exp[-(V + 35)/10]) \), \( \beta_m = 4 \exp[-(V + 60)/18] \), \( \alpha_{C1} = 3 \alpha_m \), \( \beta_{C1} = \beta_m \), \( \alpha_{C2} = 2 \alpha_m \), \( \beta_{C2} = 2 \beta_m \), \( \alpha_O = \alpha_m \), \( \beta_O = 3 \beta_m \), \( \alpha_{I1} = \alpha_{C1} \), \( \beta_{I1} = 0.016 \beta_{C1} \), \( \alpha_{I2} = 2 \alpha_{C2} \), \( \beta_{I2} = 2 \beta_{C2} \), \( \alpha_{I3} = 2 \alpha_O \), \( \beta_{I3} = 2 \beta_O \), \( \alpha_{I4} = 1 \), \( \gamma_{ik} = 22.2 \), \( \beta_{ik} = \exp[-V/10] \), \( \sigma_{i1} = 2.5 \), \( \delta_{i2} = \delta_{i3} = \delta_{i4} = 0.04 \), \( \rho_k = \alpha_{ik}/(1 + \beta_{ik}/\gamma_{ik}) \) for \( k = 1, 4 \), \( \sigma_1 = \delta_{i1}/(1 + \gamma_{i1}/\beta_{i1}) \), \( \sigma_2 = \sigma_3 = \sigma_4 = 0.016 \sigma_1 \) (ms\(^{-1}\)).
Figure 9: During an action potential, the solution of a Na+ channel twelve state kinetic model, Eqs. 11 to 15 (solid line) may be approximated by $C_1 = (1-m)^3 h$, $C_2 = 3m(1-m)^2 h$, $C_3 = 3m^2(1-m) h$, $O = m^3 h$, $I = 1 - h$ (dotted line), where $m$ and $h$ satisfy Eqs. 15 and 59, and $n$ and $V$ are determined by Eq. 16 and Eq. 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 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 $k = 1, 4$, $\sigma_1 = \delta_{i1}/(1+\gamma_{i1}/\beta_{i1})$, $\sigma_2 = \sigma_3 = \sigma_4 = 0.016\sigma_1$, $\alpha_n = 0.01(V+50)/(1 - \exp[-(V+548)/10])$, $\beta_n = 0.125 \exp[-(V+60)/80] \text{ (ms}^{-1}\text{)},$ and $g_{Na} = 120 \text{ mS/cm}^2$, $g_K = 36 \text{ mS/cm}^2$, $g_L = 0.3 \text{ mS/cm}^2$, $V_{Na} = 55 \text{ mV}$, $V_K = -75 \text{ mV}$, $V_L = -60 \text{ mV}$, $C = 1 \mu\text{F/cm}^2$, $i_e = 1 \mu\text{A/cm}^2$. 
Figure 10: The solution of a Na+ channel twelve state kinetic model, Eqs. (14) to (15) (solid line) may be approximated by
\[ C_1 = (1 - m)^3 h, \]
\[ C_2 = 3m(1 - m)^2 h, \]
\[ C_3 = 3m^2(1 - m) h, \]
\[ O = m^3 h, \]
\[ I = 1 - h \] (dotted line), where \( m \) and \( h \) satisfy Eqs. (56) and (59), and \( n \) and \( V \) are determined by Eq. (16) and Eq. (17). The rate functions are
\[ \alpha_m = 7.45 \exp[0.5V/25], \]
\[ \beta_m = 0.8 \exp[-0.9V/25], \]
\[ \alpha_{C1} = 3\alpha_m, \]
\[ \beta_{C1} = \beta_m, \]
\[ \alpha_{C2} = 2\alpha_m, \]
\[ \beta_{C2} = 2\beta_m, \]
\[ \alpha_O = \alpha_m, \]
\[ \beta_O = 3\beta_m, \]
\[ \alpha_{I1} = \alpha_{C1}, \]
\[ \beta_{I1} = 0.01\beta_{C1}, \]
\[ \alpha_{I2} = 2\alpha_{C2}, \]
\[ \beta_{I2} = 0.2\beta_{C2}, \]
\[ \alpha_{I3} = 2\alpha_O, \]
\[ \beta_{I3} = 0.2\beta_O, \]
\[ \alpha_{I4} = 2000 \exp[-2.4V/25], \]
\[ \beta_{I4} = 200 \exp[-2.4V/25], \]
\[ \delta_{i1} = 1, \]
\[ \delta_{i2} = \delta_{i3} = \delta_{i4} = 0.1, \]
\[ \alpha_{ik} = 2.1, \]
\[ \gamma_{ik} = 25, \]
\[ \rho_k = \alpha_{ik}/(1 + \beta_{ik}/\gamma_{ik}), \]
\[ \sigma_k = \delta_{ik}/(1 + \gamma_{ik}/\beta_{ik}), \] for
\[ k = 1, 4, \]
\[ \alpha_n = 0.01(V + 50)/(1 - \exp[-(V + 50)/10]), \]
\[ \beta_n = 0.125 \exp[-(V + 60)/80], \] (ms\(^{-1}\)), and \( g_{Na} = 20 \text{ mS/cm}\(^2\), \( g_K = 10 \text{ mS/cm}\(^2\), \( g_L = 1 \text{ mS/cm}\(^2\), \( V_{Na} = 40 \text{ mV}, V_K = -90 \text{ mV}, V_L = -80 \text{ mV}, C = 1 \mu F/cm\(^2\), \( i_e = 1 \mu A/cm\(^2\).
Figure 11: 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 to states $I_1(t)$ to $I_4(t)$, and slow inactivation to states $S_2(t)$ to $S_4(t)$. 
Figure 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 $\rho_k$ and $\sigma_k$ defined in Eqs. (26) and (27).
Figure 13: The eleven state system for Na+ channel gating in Fig. 12 may be reduced to a ten 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).
Figure 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.
\( V = 0.1(V + 43.9)/(1 - \exp[-(V + 43.9)/10]) \), \( \beta_m = 0.108 \exp[-V/19.1] \), \( \alpha_{C1} = 3\alpha_m \), \( \beta_{C1} = \beta_m \), \( \alpha_{C2} = 2\alpha_m \), \( \beta_{C2} = 2\beta_m \), \( \alpha_O = \alpha_m \), \( \beta_O = 3\beta_m \), \( \alpha_{I1} = \alpha_{C1} \), \( \beta_{I1} = 0.0135\beta_{C1} \), \( \alpha_{I2} = \alpha_{C2} \), \( \beta_{I2} = \beta_{C2} \), \( \alpha_{I3} = \alpha_O \), \( \beta_{I3} = \beta_O \), \( \alpha_{ik} = 0.9 \), \( \gamma_{ik} = 25 \), \( \beta_{ik} = 2\exp[-V/10] \), \( \delta_{i1} = 2.5 \), \( \delta_{i2} = \delta_{i3} = \delta_{i4} = 0.0135\delta_{i1} \), \( \rho_k = \alpha_{ik}(1 + \beta_{ik}/\gamma_{ik}) \), \( \sigma_k = \delta_{ik}(1 + \gamma_{ik}/\beta_{ik}) \), for \( k = 1, 4, \mu = 0.047(1 + \exp[-(V + 17)/10]) \), \( \nu = 0.00001\exp[-V/25] \), \( \alpha_n = 0.007(V + 58.9)/(1 - \exp[-(V + 58.9)/10]) \), \( \beta_n = 0.038 \exp[-V/80] \) (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, \( j = 4 \), \( C = 1 \) \( \mu F/cm^2 \), and \( i_e = 1 \) \( \mu A/cm^2 \).
\( \beta = 4, \)

and the bursting oscillation resumes. The rate functions are

\[ \nu = \text{the subthreshold oscillation, the stationary state of the subsystem loses its} \]

\[ S \text{ terminates the burst of spikes, and as the slow variable relaxes during} \]

\[ T \text{ and } S \text{ satisfy Eqs. (56), (100) and (101), and } n \text{ and } V \text{ are determined} \]

\[ \text{by Eqs. (16) and (102). The increase in the slow inactivation probability} \]

\[ S \text{ terminates the burst of spikes, and as the slow variable relaxes during} \]

\[ \text{the subthreshold oscillation, the stationary state of the subsystem loses its} \]

\[ \text{stability when the recovery rate } \nu \text{ for slow inactivation is sufficiently large,} \]

\[ \text{and the bursting oscillation resumes. The rate functions are } \alpha_m = 0.1(V +} \]

\[ 43.9)/(1 - \exp[-(V + 43.9)/10]), \quad \beta_m = 0.108\exp[-V/19.1], \quad \alpha_{C1} = 3\alpha_m, \quad \beta_{C1} = \beta_m, \quad \alpha_{C2} = 2\alpha_m, \quad \beta_{C2} = 2\beta_m, \quad \alpha_O = \alpha_m, \quad \beta_O = 3\beta_m, \quad \alpha_I = \alpha_{C1}, \quad \beta_I = 0.0135\beta_{C1}, \quad \alpha_{I2} = \alpha_{C2}, \quad \beta_{I2} = \beta_{C2}, \quad \alpha_{I3} = \alpha_O, \quad \beta_{I3} = \beta_O, \quad \alpha_{ik} = 0.9, \quad \gamma_{ik} = 25, \quad \beta_{ik} = 2\exp[-V/10], \quad \delta_{i1} = 5.75, \quad \delta_{i2} = \delta_{i3} = \delta_{i4} = 0.0135\delta_{i1}, \quad \rho_k = \alpha_{ik}/(1 + \beta_{ik}/\gamma_{ik}), \quad \sigma_k = \delta_{ik}/(1 + \gamma_{ik}/\beta_{ik}), \quad \text{for } g^{k} = 1.4, \quad \mu = 0.14/(1 + \exp[-(V + 17)/10]), \quad \nu = 0.0001\exp[-V/25], \quad \alpha_n = 0.007(V + 58.9)/(1 - \exp[-(V + 58.9)/10]), \quad \beta_n = 0.038\exp[-V/80], \quad \text{(ms}^{-1}), \quad \text{and } g_{Na} = 12 \text{ mS/cm}^2, \quad g_K = 3 \text{ mS/cm}^2, \quad g_L = 0.03 \text{ mS/cm}^2, \quad V_{Na} = 50 \text{ mV, } V_K = -77 \text{ mV, } V_L = -54.4 \text{ mV,} \]

\[ j = 4, \quad C = 1 \text{ F/cm}^2, \quad \text{and } i_e = 1 \text{ mA/cm}^2. \]
Figure 17: The solution of a Na+ channel fifteen state kinetic model, Eqs. (61) to (75) (solid line) may be approximated by $C_1 = (1 - m)^3 (1 - T)$, $C_2 = 3m(1-m)^2 (1-T)$, $C_3 = 3m^2 (1-m)(1-T)$, $O = m^3 (1-T)$, $T = I + S$, $I = I_2 + I_3 + I_4$ and $S = S_2 + S_3 + S_4$ (dotted line), where $m$, $T$ and $S$ satisfy Eqs. (56), (100) and (101), $n$ and $V$ are determined by Eqs. (16) and (102), and the rate of recovery from inactivation is sufficiently small to generate a cardiac plateau. The rate functions are $\alpha_m = 0.1(V + 34.3)/(1 - \exp[-(V + 34.3)/15])$, $\beta_m = 4 \exp[-(V + 59.3)/25]$, $\alpha_{C1} = 3 \alpha_m$, $\beta_{C1} = \beta_m$, $\alpha_{C2} = 2 \alpha_m$, $\beta_{C2} = 2 \beta_m$, $\alpha_O = \alpha_m$, $\beta_O = 3 \beta_m$, $\alpha_{I1} = \alpha_{C1}$, $\beta_{I1} = 0.0135 \beta_{C1}$, $\alpha_{I2} = 10 \alpha_{C2}$, $\beta_{I2} = \beta_{C2}$, $\alpha_{I3} = \alpha_O$, $\beta_{I3} = \beta_O$, $\alpha_{ik} = 0.012$, $\gamma_{ik} = 25$, $\beta_{ik} = 4.2 \exp[-2.3(V - 31.9)/25]$, $\delta_{11} = 0.1$, $\delta_{12} = 0.0135 \delta_{11}$, $\delta_{i3} = \delta_{i4} = 0.00135 \delta_{11}$, $\rho_k = \alpha_{ik}/(1 + \beta_{ik}/\gamma_{ik})$, $\sigma_k = \delta_{ik}/(1 + \gamma_{ik}/\beta_{ik})$, for $k = 1, 4$ (ms$^{-1}$), $\mu = 0.06 \exp[0.1(V + 11)/25]$ (s$^{-1}$), $\nu = 0.108 \exp[-1.95(V + 11)/25]$ (s$^{-1}$), $\alpha_n = 0.015(V + 25)/(1 - \exp[-(V + 25)/10])$, $\beta_n = 0.5 \exp[-(V + 65)/80]$ (s$^{-1}$), and $\tilde{g}_{Na} = 36$ mS/cm$^2$, $\tilde{g}_K = 3$ mS/cm$^2$, $\tilde{g}_L = 2$ 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 $i_e = 27 \mu A/cm^2$. 


The rate functions are increased to generate a cardiac action potential with a plateau oscillation.

The rate functions are determined by Eqs. (16) and (102), and the rate of recovery from inactivation $\sigma_1$ is increased to generate a cardiac action potential with a plateau oscillation.

The rate functions are $\alpha_m = 0.1(V + 34.3)/(1 - \exp[-(V + 34.3)/15])$, $\beta_m = 4\exp[-(V + 59.3)/25]$, $\alpha_C = 3\alpha_m$, $\beta_C = \beta_m$, $\alpha_O = 2\alpha_m$, $\beta_O = \beta_m$, $\alpha_I = \alpha_C$, $\beta_I = 0.0135\beta_C$, $\alpha_{I2} = 10\alpha_C$, $\beta_{I2} = \beta_C$, $\alpha_{I3} = \alpha_O$, $\beta_{I3} = \beta_O$, $\alpha_{ik} = 0.012$, $\gamma_{ik} = 25$, $\beta_{ik} = 4.2\exp[-2.3(V - 31.9)/25]$, $\delta_{i1} = 0.12$, $\delta_{i2} = 0.0135\delta_{i1}$, $\delta_{i3} = \delta_{i2}/\mu$. $\beta_k = \alpha_{ik}/(1 + \beta_{ik}/\gamma_{ik})$, $\sigma_k = \delta_{ik}/(1 + \gamma_{ik}/\beta_{ik})$, for $k = 1, 4$ (ms$^{-1}$), $\mu = 0.06\exp[0.1(V + 11)/25]$ (s$^{-1}$), $\nu = 0.108\exp[-1.95(V + 11)/25]$ (s$^{-1}$), $\alpha_n = 0.015(V + 25)/(1 - \exp[-(V + 25)/10])$, $\beta_n = 0.5\exp[-(V + 65)/80]$ (s$^{-1}$), and 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 $i_c = 27$ $\mu$A/cm$^2$. 

Figure 18: The solution of a Na$^+$ channel fifteen state kinetic model, Eqs. (61) to (75) (solid line) may be approximated by $C_1 = (1 - m)^3(1 - T)$, $C_2 = 3m(1 - m)^2(1 - T)$, $C_3 = 3m^2(1 - m)(1 - T)$, $O = m^3(1 - T)$, $T = I + S$, $I = I_2 + I_3 + I_4$ and $S = S_2 + S_3 + S_4$ (dotted line), where $m$, $T$ and $S$ satisfy Eqs. (56), (100) and (101), $n$ and $V$ are determined by Eqs. (16) and (102), and the rate of recovery from inactivation $\sigma_1$ is increased to generate a cardiac action potential with a plateau oscillation.