Rate equations for a Na+ channel gating master equation during the action potential within a neural membrane

S. R. Vaccaro

Department of Physics, University of Adelaide, Adelaide, South Australia, 5005, Australia

svaccaro@physics.adelaide.edu.au

The action potential in a neural membrane is generated by Na+ and K+ channel ionic currents that may be calculated from a current equation and the rate equations for activation variables $m$ and $n$, and the Na+ inactivation variable $h$. Assuming that a Na+ channel has three activation sensors, and activation and inactivation are cooperative processes, a twelve state master equation that describes channel gating may be reduced to kinetic equations for a five state system when the occupational probability of the first inactivated state is small, and the remaining inactivated states contribute to a total inactivated state. In the case of independent activation sensors, the inactivation rate is, in general, dependent on the activation variable $m(t)$ as well as the forward inactivation transition rates. However, when $m(t)$ has a faster time constant than $h(t)$, the inactivation rate may be approximated by a voltage-dependent function, and therefore, the solution of the master equation during an action potential may be approximated by the solution of Hodgkin-Huxley rate equations for $m$ and $h$. 
INTRODUCTION

By assuming that Na+ channel activation is independent of inactivation, 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 [1], and the approach has been applied to a wide range of voltage-dependent ion channels in nerve, muscle and cardiac membranes. The HH rate equations for the Na+ channel are exact solutions of an eight state master equation for channel gating where the inactivation sensor and three activation sensors are independent [2, 3]. However, subsequent experimental studies have shown that the probability of Na+ inactivation increases with the degree of activation of the channel [4], the recovery from inactivation is more probable following deactivation [5], and the kinetic equations for coupled Na+ activation and inactivation processes represent ion channel states and their transitions, and provide a good description of the ionic and gating currents during a voltage clamp [6]. From the solution of a nine state master equation that describes Na+ channel gating with two independent activation sensors and a coupled inactivation process, the open state probability during a depolarizing clamp may be expressed as \( m^2 h \) where \( m(t) \) and \( h(t) \) satisfy rate equations, and therefore, the HH description of the Na+ current during a voltage clamp is consistent with a coupled Na+ channel gating model [7].

In this paper, it is shown that during an action potential, the solution of a six state master equation that describes coupling between a single Na+ channel activation sensor and a two-stage inactivation process may be approximated by interacting rate equations for activation and inactivation, when the first forward and backward inactivation transitions are rate limiting. When the Na+ channel has three activation sensors, by application of a reduction method, a twelve state master equation may be expressed as kinetic equations for a five state system, and if the activation sensors are independent, the inactivation rate is dependent on the activation variable \( m(t) \) but may be approximated by a voltage-dependent function when \( m(t) \) has a faster time constant than \( h(t) \). Therefore, the solution of the Na+ channel master equation during an action potential may be approximated by the solution of HH rate equations for \( m \) and \( h \).

Na+ CHANNEL MASTER EQUATION WITH A SINGLE ACTIVATION SENSOR

In this section, it is assumed that the activation of a single voltage sensor regulating the Na channel conductance is coupled to a two-stage inactivation process (see Fig. 1), and therefore, the kinetics may be described by a six-state master equation, that may be reduced to a four state system when the
first forward and backward transitions are rate limiting [7] (see Fig. 2)

\[
\frac{dC_1}{dt} = -(\rho_1 + \alpha_m)C_1(t) + \beta_mO(t) + \sigma_1 B_1(t) \\
\frac{dO}{dt} = \alpha_mC_1(t) - (\beta_m + \rho_2)O(t) + \sigma_2 B_2(t) \\
\frac{dB_1}{dt} = \rho_1 C_1(t) - (\alpha_B + \sigma_1)B_1(t) + \beta_B B_2(t) \\
\frac{dB_2}{dt} = \rho_2 O(t) + \alpha_B B_1(t) - (\beta_B + \sigma_2)B_2(t)
\]

(1) (2) (3) (4)

where \(C_1(t), O(t), B_1(t), B_2(t)\) are the occupational probabilities for the closed, open and inactivated states.

The Na current during deactivation of an inactivated ion channel is small [4], and therefore, the recovery rate \(\sigma_1 \gg \sigma_2 \approx 0\). It may be assumed that \(\rho_1 \ll \alpha_B\) because inactivation is a slower process than activation, and during the action potential, \(\sigma_1 \gg \beta_B\), and therefore, from Eq. (3)

\[
B_1(t) \approx \frac{\rho_1 C_1(t) + \beta_B B_2(t)}{\alpha_B + \sigma_1}.
\]

(5)

That is, Eqs. (1) and (4) may be reduced to (see Fig. 3)

\[
\frac{dC_1}{dt} = -(\hat{\rho}_1 + \alpha_m)C_1(t) + \beta_mO(t) + \hat{\sigma}_1 B_1(t) \\
\frac{dO}{dt} = \alpha_mC_1(t) - (\beta_m + \rho_2)O(t) + \sigma_2 B_2(t) \\
\frac{dB_2}{dt} = \rho_2 O(t) + \hat{\rho}_1 C_1(t) - (\hat{\sigma}_1 + \sigma_2)B_2(t)
\]

(6) (7) (8)

where

\[
\hat{\rho}_1 \approx \frac{\rho_1 \alpha_B}{\alpha_B + \sigma_1}, \\
\hat{\sigma}_1 \approx \frac{\sigma_1 \beta_B}{\alpha_B + \sigma_1}.
\]

(9) (10)

and \(C_1(t) + O(t) + B_2(t) = 1\). From Eq. (10), for moderate depolarizations \(\hat{\sigma}_1 \approx \beta_B\), but for large hyperpolarizing potentials, \(\hat{\sigma}_1 = \sigma_1 \beta_B / (\alpha_B + \beta_B + \sigma_1)\) and hence \(\hat{\sigma}_1\) attains a plateau value of \(\sigma_1\) when \(\beta_B \gg \sigma_1\) [7].

Assuming that \(C_1(t) = (1 - m(t))h(t)\), \(O(t) = m(t)h(t)\), \(B_2(t) = 1 - h(t)\) in Eqs. (6) to (8), the variables \(m(t)\) and \(h(t)\) satisfy

\[
\frac{dm}{dt} = \alpha_m - m(t)[\alpha_m + \beta_m + (\rho_2 - \hat{\rho}_1)(1 - m(t))] +
\]
In Eq. (11), \( \sigma_2 \approx 0 \) and the terms \((\rho_2 - \hat{\rho}_1)\left(1 - m(t)\right)\) and \(\hat{\sigma}_1(1/h(t) - 1) \ll \alpha_m + \beta_m\) whereas in Eq. (12), it may be assumed that \(m(t) \approx m_s = \alpha_m/ (\alpha_m + \beta_m)\) as \(m(t)\) has a faster time constant than \(h(t)\). Therefore, defining

\[
\alpha_h = \hat{\sigma}_1 + \sigma_2 \approx \hat{\sigma}_1
\]

\[
\beta_h = \hat{\rho}_1 + (\rho_2 - \hat{\rho}_1)m_s,
\]

Eqs. (11) and (12) may be approximated by

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

\[
\frac{dh}{dt} = \alpha_h - (\alpha_h + \beta_h)h,
\]

and therefore, during a depolarizing voltage clamp of the Na\(^+\) channel membrane, the expression for the open state probability \(O(t) = m(t)h(t)\), where \(m(t)\) and \(h(t)\) satisfy Eqs. (15) to (16), is in agreement with the voltage clamp solution of Eqs. (1) to (4) \([7]\).

Although the K\(^+\) and Na\(^+\) ion channel currents generate the action potential in the squid axon, it will be assumed that the action potential is determined by the Na\(^+\) and leakage currents, as in myelinated nerve membrane \([8, 9]\), and therefore, the membrane current equation is

\[
C \frac{dV}{dt} = I_e - \bar{g}_{Na}O(t)(V - V_{Na}) - \bar{g}_L(V - V_L),
\]

where the Na\(^+\) current is dependent on the open state probability \(O(t) = m(t)h(t)\), \(\bar{g}_{Na}\) and \(\bar{g}_L\) are the Na\(^+\) and leakage conductances, and \(V_{Na}\) and \(V_L\) are the equilibrium potentials, \(C\) is the membrane capacitance, and \(I_e\) is the electrode current. The solution of the master equation for coupled activation and inactivation, Eqs. (11) to (14), and Eq. (17) may be approximated by the solution of Eqs. (15), (16) and (17) (see Fig. 4).

**Na\(^+\) CHANNEL MASTER EQUATION WITH TWO OR THREE ACTIVATION SENSORS**

The time dependence of the Na\(^+\) current during a voltage clamp of myelinated nerve membrane may be described in terms of the expression...
$m^2h$ [8], and therefore, assuming that the activation of two voltage sensors regulating the Na$^+$ channel conductance is coupled to a two-stage inactivation process, the kinetics is determined by a nine state master equation that may be reduced to a six state system when the first forward and backward inactivation transitions are rate limiting ($\beta_{ik} \gg \delta_{ik}$ and $\gamma_{ik} \gg \alpha_{ik}$, for $k = 1$ to 3) [7]

\[
\frac{dC_1}{dt} = -(\rho_1 + \alpha_C)C_1(t) + \beta_C C_2(t) + \sigma_1 B_1(t) \tag{18}
\]

\[
\frac{dC_2}{dt} = \alpha_C C_1(t) - (\alpha_O + \beta_C + \rho_2)C_2(t) + \beta_O O(t) + \sigma_2 B_2(t) \tag{19}
\]

\[
\frac{dO}{dt} = \alpha_O C_2(t) - (\beta_O + \sigma_3)O(t) + \sigma_3 B_3(t) \tag{20}
\]

\[
\frac{dB_1}{dt} = \rho_1 C_1(t) - (\alpha_{B1} + \sigma_1)B_1(t) + \beta_{B1} B_2(t) \tag{21}
\]

\[
\frac{dB_2}{dt} = \rho_2 C_2(t) + \alpha_{B1} B_1(t) - (\alpha_{B2} + \beta_{B1} + \sigma_2)B_2(t) + \beta_{B2} B_3(t) \tag{22}
\]

\[
\frac{dB_3}{dt} = \rho_3 O(t) + \alpha_{B2} B_2(t) - (\beta_{B2} + \sigma_3)B_3(t), \tag{23}
\]

From Eq. (21), if $\alpha_{B1} \gg \rho_1$ and $\sigma_1 \gg \beta_{B1}$, the occupation probability $B_1(t)$ is dependant on the variation of $C_1(t)$ and $B_2(t)$, and therefore, Eqs. (18) and (21) may be reduced to (see Fig. 5)

\[
\frac{dC_1}{dt} = -(\alpha_C) + \hat{\rho}_1 C_1(t) + \beta_C C_2(t) + \hat{\sigma}_1 B_2(t) \tag{24}
\]

\[
\frac{dB_2}{dt} = \hat{\rho}_1 C_1(t) + \rho_2 C_2(t) - (\alpha_{B2} + \hat{\sigma}_1 + \sigma_2)B_2(t) + \beta_{B2} B_3(t) \tag{25}
\]

where

$$\hat{\rho}_1 \approx \frac{\rho_1 \alpha_{B1}}{\alpha_{B1} + \sigma_1}, \tag{26}$$

$$\hat{\sigma}_1 \approx \frac{\sigma_1 \beta_{B1}}{\alpha_{B1} + \sigma_1}. \tag{27}$$

In Eqs. (24) and (25), the $B_2(t)$ and $B_3(t)$ terms are an order of magnitude larger than the closed and open state terms, and therefore, defining $B(t) = B_2(t) + B_3(t)$, the inactivation probabilities $B_2(t)$ and $B_3(t)$ may be expressed as

$$B_2(t) \approx \frac{\beta_{B2} B(t)}{\alpha_{B2} + \beta_{B2}}, \tag{28}$$

$$B_3(t) \approx \frac{\alpha_{B2} B(t)}{\alpha_{B2} + \beta_{B2}}. \tag{29}$$
and, therefore, Eqs. (18) to (23) may be reduced to the four-state master equation (see Fig. 6)

\[
\begin{align*}
\frac{dC_1}{dt} &= - (\hat{\rho}_1 + \alpha C)C_1(t) + \beta C_2(t) + \hat{\sigma}_{1r}B(t) \\
\frac{dC_2}{dt} &= \alpha C_1(t) - (\alpha O + \beta C + \rho_2)C_2(t) + \beta O(t) + \sigma_{2r}B(t) \\
\frac{dO}{dt} &= \alpha O_2(t) - (\beta O + \rho_3)O(t) + \sigma_{3r}B(t) \\
\frac{dB}{dt} &= \hat{\rho}_1C_1(t) + \rho_2C_2(t) + \rho_3O(t) - (\hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r})B(t)
\end{align*}
\]

where

\[
\begin{align*}
\hat{\sigma}_{1r} &= \frac{\hat{\sigma}_1B_2}{\alpha B_2 + \beta B_2} \\
\sigma_{2r} &= \frac{\sigma_2B_2}{\alpha B_2 + \beta B_2} \\
\sigma_{3r} &= \frac{\sigma_3B_2}{\alpha B_2 + \beta B_2},
\end{align*}
\]

and \(C_1(t) + C_2(t) + O(t) + B_2(t) = 1\).

Assuming that \(C_1(t) = m_1(t)h(t), C_2(t) = m_2(t)h(t), O(t) = m_O(t)h(t), B(t) = 1 - h(t)\), where \(m_1(t), m_2(t)\) and \(m_3(t)\) are activation variables and \(h(t)\) is an inactivation variable, Eqs. (30) to (33), may be expressed as

\[
\begin{align*}
\frac{dm_1}{dt} &= - (\hat{\rho}_1 + \alpha C + \sigma(t) - \rho(t))m_1(t) + \beta Cm_2(t) + \hat{\sigma}_{1r}(1/h(t) - 1) \\
\frac{dm_2}{dt} &= \alpha Cm_1(t) - (\alpha O + \beta C + \rho_2 + \sigma(t) - \rho(t))m_2(t) + \beta Om_O(t) + \sigma_{2r}(1/h(t) - 1) \\
\frac{dm_O}{dt} &= \alpha Om_2(t) - (\beta O + \rho_3 + \sigma(t) - \rho(t))m_O(t) + \sigma_{3r}(1/h(t) - 1) \\
\frac{dh}{dt} &= (\hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r})(1 - h(t)) - h(t)\rho(t)
\end{align*}
\]

where

\[
\begin{align*}
\rho(t) &= \hat{\rho}_1m_1(t) + \rho_2m_2(t) + \rho_3m_O(t) \\
\sigma(t) &= (\hat{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r})(1/h(t) - 1).
\end{align*}
\]
As the inactivation terms are an order of magnitude smaller than the activation terms, Eqs. (37) to (39) may be approximated by

\[
\frac{dm_1}{dt} = -\alpha C m_1(t) + \beta C m_2(t) \\
\frac{dm_2}{dt} = \alpha C m_1(t) - (\alpha + \beta) m_2(t) + \beta O m_O(t) \\
\frac{dm_O}{dt} = \alpha O m_2(t) - \beta O m_O(t).
\]

The membrane current equation for a Na+ channel with two activation sensors and a leakage channel is

\[
C \frac{dV}{dt} = I - \varrho_Na O(t)(V - V_{Na}) - \varrho_L(V - V_L),
\]

where \( O(t) = m_O(t) h(t) \) and the solution of Eqs. (18) to (23) and Eq. (46) may be approximated by the solution of Eq. (40) and Eqs. (43) to (46) (see Fig. 7).

If the activation sensors are independent \((\alpha_C = 2\alpha_m = 2\alpha_O, \beta_O = 2\beta_C = 2\beta_m)\), from Eqs. (43) to (45), \( m_1(t) = (1 - m(t))^2 \), \( m_2(t) = 2m(t)(1 - m(t)) \), \( m_O(t) = m(t)^2 \), where \( m(t) \) satisfies

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

As the activation variables have a faster time constant than \( h(t) \), \( \rho(t) \) may be approximated by \( \beta_h = \dot{\rho}_1 m_{1s} + \rho_2 m_{2s} + \rho_3 m_{Os} \) where \( m_{1s}, m_{2s} \) and \( m_{Os} \) are the stationary values of \( m_1(t) \), \( m_2(t) \) and \( m_O(t) \). Therefore, defining \( \alpha_h = \dot{\sigma}_1 + \sigma_2 + \dot{\sigma}_3 \), Eq. (40) may be expressed as

\[
\frac{dh}{dt} = \alpha_h - h(t)(\alpha_h + \beta_h),
\]

and the solution of Eqs. (18) to (23) and Eq. (46) may be approximated by the solution of Eqs. (46) to (48) (see Fig. 8). Assuming that 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 master equation that may be reduced to an eight state system when the first forward and backward inactivation transitions are rate limiting (\( \beta_{ik} \gg \delta_{ik} \) and \( \gamma_{ik} \gg \alpha_{ik} \), for \( k = 1 \) to 4)

\[
\frac{dC_1}{dt} = -(\rho_1 + \alpha C_1)C_1(t) + \beta C_1 C_2(t) + \sigma_1 B_1(t)
\]

7
\[
\frac{dC_2}{dt} = \alpha C_1 C_1(t) - (\alpha C_2 + \beta C_1 + \rho_2)C_2(t) + \beta C_2 C_3(t) + \sigma_2 B_2(t) \tag{50}
\]
\[
\frac{dC_3}{dt} = \alpha C_2 C_2(t) - (\alpha O + \beta C_2 + \rho_3)C_3(t) + \beta O(t) + \sigma_3 B_3(t) \tag{51}
\]
\[
\frac{dO}{dt} = \alpha O C_3(t) - (\beta O + \rho_4)O(t) + \sigma_4 B_4(t) \tag{52}
\]
\[
\frac{dB_1}{dt} = \rho_1 C_1(t) - (\alpha B_1 + \sigma_1)B_1(t) + \beta B_1 B_2(t) \tag{53}
\]
\[
\frac{dB_2}{dt} = \alpha B_1 B_1(t) - (\alpha B_2 + \beta B_1 + \sigma_2)B_2(t) + \beta B_2 B_3(t) + \rho_2 C_2(t) \tag{54}
\]
\[
\frac{dB_3}{dt} = \alpha B_2 B_2(t) - (\alpha B_3 + \beta B_2 + \sigma_3)B_3(t) + \beta B_3 B_4(t) + \rho_3 C_3(t), \tag{55}
\]
\[
\frac{dB_4}{dt} = \alpha B_3 B_3(t) - (\beta B_3 + \sigma_4)B_4(t) + \rho_4 O(t), \tag{56}
\]

From Eq. \(53\), if \(\alpha B_1 \gg \rho_1\) and \(\sigma_1 \gg \beta B_1\), substituting from

\[
B_1(t) \approx \frac{\rho_1 C_1(t) + \beta B_1 B_2(t)}{\alpha_B + \sigma_1}, \tag{57}
\]

Eqs. \(50\) and \(53\) may be reduced to

\[
\frac{dC_1}{dt} = -\left(\alpha_C + \hat{\rho}_1\right)C_1(t) + \beta C_1 C_2(t) + \hat{\sigma}_1 B_2(t) \tag{58}
\]
\[
\frac{dB_2}{dt} = \hat{\rho}_1 C_1(t) + \rho_2 C_2(t) - \left(\alpha_B + \hat{\sigma}_1 + \sigma_2\right)B_2(t) + \beta B_2 B_3(t) \tag{59}
\]

where \(\hat{\rho}_1\) and \(\hat{\sigma}_1\) are defined in Eqs. \(26\) and \(27\). In Eqs. \(51\) to \(56\), the \(B_2(t), B_3(t)\) and \(B_4(t)\) terms are an order of magnitude larger than the closed and open state terms, and therefore, defining \(B(t) = B_2(t) + B_3(t) + B_4(t)\), the inactivation probabilities \(B_2(t), B_3(t)\) and \(B_4(t)\) may be expressed as

\[
B_2(t) \approx \frac{\beta B_3 B_3 B(t)}{\alpha B_2 \alpha B_3 + \alpha B_2 \beta B_3 + \beta B_2 \beta B_3} \tag{60}
\]
\[
B_3(t) \approx \frac{\beta B_2 B_2 B(t)}{\alpha B_2 \alpha B_3 + \alpha B_2 \beta B_3 + \beta B_2 \beta B_3} \tag{61}
\]
\[
B_4(t) \approx \frac{\beta B_3 B_3 B(t)}{\alpha B_2 \alpha B_3 + \alpha B_2 \beta B_3 + \beta B_2 \beta B_3} \tag{62}
\]

and Eqs. \(49\) to \(55\) may be reduced to the five-state master equation (see Fig. 9)

\[
\frac{dC_1}{dt} = -(\rho_1 + \alpha C_1)C_1(t) + \beta C_2 C_2(t) + \hat{\sigma}_1 r B(t) \tag{63}
\]
\[
\begin{align*}
\frac{dC_2}{dt} &= \alpha C_1 C_1(t) - (\alpha C_2 + \beta C_1 + \rho_2)C_2(t) + \beta C_2 C_3(t) + \sigma_{2r} B(t) \quad (64) \\
\frac{dC_3}{dt} &= \alpha C_2 C_2(t) - (\alpha O + \beta C_2 + \rho_3)C_3(t) + \beta O O(t) + \sigma_{3r} B(t) \quad (65) \\
\frac{dO}{dt} &= \alpha O C_3(t) - (\beta_O + \rho_4)O(t) + \sigma_{4r} B(t) \quad (66) \\
\frac{dB}{dt} &= \dot{\rho}_1 C_1(t) + \rho_2 C_2(t) + \rho_3 C_3(t) + \rho_4 O(t) - \\
&\quad (\dot{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r}) B(t) \quad (67)
\end{align*}
\]

where

\[
\begin{align*}
\dot{\sigma}_{1r} &= \frac{\dot{\sigma}_1 \beta_{B2} \beta_{B3}}{\alpha_{B2} \alpha_{B3} + \alpha_{B2} \beta_{B3} + \beta_{B2} \beta_{B3}} \quad (68) \\
\sigma_{2r} &= \frac{\sigma_2 \beta_{B2} \beta_{B3}}{\alpha_{B2} \alpha_{B3} + \alpha_{B2} \beta_{B3} + \beta_{B2} \beta_{B3}} \quad (69) \\
\sigma_{3r} &= \frac{\sigma_3 \alpha_{B2} \beta_{B3}}{\alpha_{B2} \alpha_{B3} + \alpha_{B2} \beta_{B3} + \beta_{B2} \beta_{B3}} \quad (70) \\
\sigma_{4r} &= \frac{\sigma_4 \alpha_{B2} \beta_{B3}}{\alpha_{B2} \alpha_{B3} + \alpha_{B2} \beta_{B3} + \beta_{B2} \beta_{B3}} \quad (71)
\end{align*}
\]

and \( C_1(t) + C_2(t) + C_3(t) + O(t) + B(t) = 1 \).

Assuming that \( C_1(t) = m_1(t)h(t), C_2(t) = m_2(t)h(t), C_3(t) = m_3(t)h(t), \)
\( O(t) = m_O(t)h(t), B(t) = 1 - h(t) \), 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. \( (63) \) to \( (67) \),
may be expressed as

\[
\begin{align*}
\frac{dm_1}{dt} &= -(\rho_1 + \alpha C_1 + \sigma(t) - \rho(t))m_1(t) + \beta C_1 m_2(t) + \\
&\quad \dot{\sigma}_{1r}(1/h(t) - 1) \quad (72) \\
\frac{dm_2}{dt} &= \alpha C_1 m_1(t) - (\alpha C_2 + \beta C_1 + \rho_2 + \sigma(t) - \rho(t))m_2(t) + \beta C_2 m_3(t) + \\
&\quad \sigma_{2r}(1/h(t) - 1) \quad (73) \\
\frac{dm_3}{dt} &= \alpha C_2 m_2(t) - (\alpha O + \beta C_2 + \rho_3 + \sigma(t) - \rho(t))m_3(t) + \beta_O m_O(t) + \\
&\quad \sigma_{3r}(1/h(t) - 1) \quad (74) \\
\frac{dm_O}{dt} &= \alpha_O m_3(t) - (\beta_O + \rho_4 + \sigma(t) - \rho(t))m_O(t) + \\
&\quad \sigma_{4r}(1/h(t) - 1) \quad (75) \\
\frac{dh}{dt} &= (\dot{\sigma}_{1r} + \sigma_{2r} + \sigma_{3r} + \sigma_{4r})(1 - h(t)) - h(t)\rho(t) \quad (76)
\end{align*}
\]
where
\[ \rho(t) = \dot{\rho}_1 m_1(t) + \rho_2 m_2(t) + \rho_3 m_3(t) + \rho_4 m_O(t) \]  
(77)
\[ \sigma(t) = (\dot{\sigma}_1 + \sigma_2 + \sigma_3 + \sigma_4)(1/h(t) - 1) \].  
(78)

The inactivation terms are an order of magnitude smaller than the activation terms, and therefore, Eqs. (72) to (75) may be approximated by
\[ \frac{dm_1}{dt} = -\alpha C_1 m_1(t) + \beta C_1 m_2(t) \]  
(79)
\[ \frac{dm_2}{dt} = \alpha C_1 m_1(t) - (\alpha C_2 + \beta C_1)m_2(t) + \beta C_2 m_3(t) \]  
(80)
\[ \frac{dm_3}{dt} = \alpha C_2 m_2(t) - (\alpha O + \beta C_2)m_3(t) + \beta O m_O(t) \]  
(81)
\[ \frac{dm_O}{dt} = \alpha O m_3(t) - \beta O m_O(t) \].  
(82)

If the activation sensors are independent \((\alpha C_1 = 3\alpha_m, \alpha C_2 = 2\alpha_m, \alpha O = \alpha_m, \beta C_1 = \beta_m, \beta C_2 = 2\beta_m, \beta O = 3\beta_m)\), Eqs. (79) to (82) have the solution
\[ m_1(t) = (1 - m(t))^3, \quad m_2(t) = 3m(t)(1 - m(t))^2, \quad m_3(t) = 3m(t)^2(1 - m(t)), m_O(t) = m(t)^3 \], where \(m(t)\) satisfies
\[ \frac{dm}{dt} = \alpha_m - m(t)[\alpha_m + \beta_m]. \]  
(83)

From Eq. (77), the inactivation rate \(\rho(t)\) in Eq. (76) is dependent on the activation variable \(m(t)\) as well as the forward inactivation rates. However, as the activation variable \(m(t)\) generally has a faster time constant than \(h(t)\), \(\rho(t)\) may be approximated by
\[ \beta_h = \dot{\rho}_1 m_{1s} + \rho_2 m_{2s} + \rho_3 m_{3s} + \rho_4 m_O \]  
(84)
where \(m_{1s}, m_{2s}, m_{3s}\) and \(m_{O}\) are the stationary values for each membrane potential, and Eq. (76) may be expressed as
\[ \frac{dh}{dt} = \alpha_h - h(t)(\alpha_h + \beta_h) \]  
(85)
where
\[ \alpha_h = \dot{\sigma}_1 + \sigma_2 + \sigma_3 + \sigma_4. \]  
(86)

Assuming that the 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
\[ \frac{dn}{dt} = \alpha_n - n(t)[\alpha_n + \beta_n], \]  
(87)
and $\alpha_n$ and $\beta_n$ are rate functions, the membrane current equation is

$$C\frac{dV}{dt} = I - \bar{g}_{Na}O(t)(V - V_{Na}) - \bar{g}_{K}n(t)^4(V - V_{K}) - \bar{g}_{L}(V - V_{L}), \quad (88)$$

where $O(t) = m_{O}(t)h(t)$, $\bar{g}_{K}$ is the K$^+$ conductance, and $V_{K}$ is the K$^+$ equilibrium potential. The solution of Eqs. (49) to (56), and Eqs. (87) and Eq. (88) may be approximated by the solution of Eqs. (83), (85), (87) and (88) - see Figs. 10 and 11 for a Na$^+$ channel with an inactivation rate independent of the closed or open state [1], and Fig. 12 for a channel where the probability of Na$^+$ inactivation increases with the degree of activation of the channel [6].

**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 the shape of the action potential waveform, the speed of propagation, the threshold potential, and the refractory period of the squid axon membrane [1]. The model assumes that the activation and opening of Na$^+$ channels is independent of the inactivation process that blocks Na$^+$ conductance, and is mathematically equivalent to a Markovian master equation with three activation sensors and one inactivation sensor where the inactivation and recovery rate functions are independent of the closed or open state, and the activation and deactivation rate functions between closed states are equal to those between inactivated states. However, experimentally, the inactivation rate is dependant on the degree of activation [4], and the recovery from inactivation is more probable following deactivation [5], and thus activation and inactivation are coupled processes.

A master equation for coupled activation and two-stage inactivation accounts for the kinetics and voltage dependence of Na$^+$ inactivation and the recovery from inactivation when the backward inactivation rate is small for the open state but increases as the activation sensors deactivate [6]. From the solution of a nine state master equation with two activation sensors during a voltage clamp, the open state probability may be expressed as $m(t)^2 h(t)$ where $m(t)$ and $h(t)$ satisfy rate equations [7], and therefore, the HH description of the Na$^+$ current during a voltage clamp is consistent with a coupled Na$^+$ channel gating model.

In this paper, it has been shown that a master equation that describes the gating of a Na$^+$ channel with a single activation sensor coupled to inactivation, may be approximated by interacting rate equations for inactivation and activation when the first forward and backward transitions are rate lim-
iting. A nine state master equation describing Na+ channel gating with two activation sensors and two-stage inactivation may be reduced to a five state system when $\alpha_B \gg \rho_1$ and $\sigma_1 \gg \beta_B$ and the first inactivated state $B_1(t)$ makes a small contribution to the dynamics. For the remaining inactivated state equations, the $B_2(t)$ and $B_3(t)$ terms are an order of magnitude larger than the closed and open state terms, and defining $B(t) = B_2(t) + B_3(t)$, the system may be reduced to kinetic equations in the activation variables $m_1, m_2$ and $m_O$ and the inactivation variable $h$.

If a Na+ channel has three activation sensors and a two-stage inactivation process, a twelve state master equation may be reduced to a system of equations in the variables $m_1, m_2, m_3, m_O$ and $h$, where the expression for the inactivation rate is dependent on the forward transition rates of the DIV sensor as well as the degree of activation of the other sensors, and the rate of recovery from inactivation is dependent on the rate functions of the DIII sensor between inactivated states, in agreement with experimental studies and the known structure of the Na+ channel. By assuming that the activation sensors are independent, the inactivation rate is, in general, dependent on the activation variable $m(t)$ but, when $m(t)$ has a faster time constant than $h(t)$, it reduces to a voltage-dependent function, and therefore, the solution of the master equation during an action potential may be approximated by the solution of HH rate equations for $m$ and $h$. 
References

[1] A.L. Hodgkin and A.F. Huxley, J. Physiol. 117, 500 (1952).
[2] B. Hille, Ion Channels of Excitable Membranes, 3rd ed. (Sinauer, Sunderland, M.A. 2001).
[3] J. Keener, J. Math. Biol. 58, 447 (2009).
[4] C. M. Armstrong, F. Bezanilla, J. Gen. Physiol. 70, 567 (1977).
[5] C-C. Kuo and B.P. Bean, Neuron 12, 819 (1994).
[6] D.L. Capes, M.P. Goldschen-Ohm, M. Arcisio-Miranda, F. Bezanilla and B. Chanda, J. Gen. Physiol. 142, 101 (2013).
[7] S.R. Vaccaro, Phys. Rev. E 90, 052713 (2016).
[8] S.Y. Chiu, J.M. Ritchie, R.B. Robart and D. Stagg, J. Physiol. 292, 149 (1979).
[9] T. Brismar, J. Physiol. 298, 171 (1980).
Figure 1: State diagram for Na+ channel gating where horizontal transitions represent the activation of a single voltage sensor that opens the pore, and vertical transitions represent a two-stage inactivation process.
Figure 2: The six state system for Na+ channel gating in Fig. 1 may be reduced to a four state system when $\beta_{ik} \gg \delta_{ik}$ and $\gamma_{ik} \gg \alpha_{ik}$, for $k = 1$ to $2$, where $\rho_k$ and $\sigma_k$ are derived rate functions for a two-stage Na+ inactivation process.
Figure 3: The four state system for Na+ channel gating in Fig. 2 may be reduced to a three state system when $\alpha_B \gg \rho_1$ and $\sigma_1 \gg \beta_B$, and $B_1(t) \approx (\rho_1 C_1(t) + \beta_B B_2(t))/(\alpha_B + \sigma_1)$.
Figure 4: The action potential solution for a master equation describing single sensor activation of a Na+ channel, Eqs. (11) to (14), and the current equation, Eq. (17) (solid line) is approximated by the solution of rate equations for Na+ activation and inactivation, Eqs. (15) and (16), and Eq. (17) (dotted line), where the rate functions are $\alpha_m = 0.1(V + 25)/(1 - \exp[-(V + 25)/10])$, $\beta_m = 4\exp[-(V + 50)/18]$, $\alpha_B = \alpha_m$, $\beta_B = 0.0135\beta_m$, $\rho_1 = \rho_2 = 1/(1 + 0.17\exp[-2.3V/25])$, $\sigma_1 = 2.5/(1 + 5.9\exp[2.3V/25])$, $\sigma_1 = 0.0135\sigma_2$ (ms$^{-1}$), $\bar{g}_{Na} = 8$ mS/cm$^2$, $\bar{g}_L = 0.9$ mS/cm$^2$, $V_{Na} = 55$ mV, $V_L = -80$ mV, $I = 1\mu$A/cm$^2$.17
Figure 5: A six-state system for Na\textsuperscript{+} channel gating may be reduced to a five-state system when $\alpha_{B1} \gg \rho_1$ and $\sigma_1 \gg \beta_{B1}$. 
Figure 6: The five state system for Na+ channel gating in Fig. 5 may be reduced to a four state system when the $B_2(t)$ and $B_3(t)$ terms in Eqs. (23) and (25) are an order of magnitude larger than the closed and open state terms.
Figure 7: The action potential solution for a Na+ channel six state master equation, Eqs. (18) to (23) and the current equation, Eq. (46) (solid line) is approximated by the solution of Eqs. (46) to (48) (dotted line), where the rate functions are

\[ \alpha_m = 0.1(V + 25)/(1 - \exp[-(V + 25)/10]), \]
\[ \beta_m = 4\exp[-(V + 50)/18], \]
\[ \alpha_C = 2\alpha_m, \beta_C = \beta_m, \]
\[ \alpha_O = \alpha_m, \beta_O = 2\beta_m, \]
\[ \alpha_{B1} = \alpha_C, \beta_{B1} = 0.0135\beta_C, \alpha_{B2} = \alpha_O, \beta_{B2} = \beta_O, \]
\[ \rho_1 = \rho_2 = \rho_3 = 1/(1 + 0.17\exp[-2.3V/25]), \]
\[ \sigma_1 = 2.5/(1 + 5.9\exp[2.3V/25]), \sigma_2 = 0.0135\sigma_1, \]
\[ \sigma_3 = \sigma_2, \]
\[ g_{Na} = 8 \text{ mS/cm}^2, g_L = 0.9 \text{ mS/cm}^2, V_{Na} = 55 \text{ mV}, V_L = -80 \text{ mV}, \]
\[ I = 22\mu A/cm^2. \]
Figure 8: The action potential solution for a Na+ channel six state master equation with two independent activation sensors, Eqs. (18) to (23) and the current equation, Eq. (46) (solid line) is approximated by the solution of rate equations for Na+ activation and inactivation and Eq. (46) (dotted line), where the rate functions are

\[
\alpha_m = 0.1(V + 25)/(1 - \exp[-(V + 25)/10]), \\
\beta_m = 4\exp[-(V + 50)/18], \\
\alpha_C = 2\alpha_m, \beta_C = \beta_m, \alpha_O = \alpha_m, \beta_O = 2\beta_m, \\
\alpha_{B1} = \alpha_C, \beta_{B1} = 0.0135\beta_C, \alpha_{B2} = \alpha_O, \beta_{B2} = \beta_O, \rho_1 = \rho_2 = \rho_3 = 1/(1 + 0.17\exp[-2.3V/25]), \sigma_1 = 2.5/(1 + 5.9\exp[2.3V/25]), \sigma_2 = 0.0135\sigma_1, \sigma_3 = \sigma_2 \text{ (ms}^{-1}), \ g_{Na} = 8 \text{ mS/cm}^2, g_L = 0.9 \text{ mS/cm}^2, \ V_{Na} = 55 \text{ mV}, \ V_L = -80 \text{ mV}, \ I = 22\mu A/cm^2.
\]
Figure 9: The 8 state system for Na+ channel gating with 3 sensors may be reduced to a 5 state system when $\alpha_B^1 \gg \rho_1$, $\sigma_1 \gg \beta_B^1$ and the transition rates between inactivated states are larger than inactivation and recovery rates.
Figure 10: The voltage dependence of the Na+ channel HH inactivation rate function $\alpha_h + \beta_h$, 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. (84) and (86) where the rate functions are defined as $\alpha_m = 0.1(V + 25)/(1 - \exp[-(V + 25)/10])$, $\beta_m = 4\exp[-(V + 50)/18]$, $\alpha_{C1} = 3\alpha_m$, $\beta_{C1} = \beta_m$, $\alpha_{C2} = 2\alpha_m$, $\beta_{C2} = 2\beta_m$, $\alpha_O = \alpha_m$, $\beta_O = 3\beta_m$, $\alpha_{B1} = 3\alpha_{C1}$, $\beta_{B1} = 0.0165\beta_{C1}$, $\alpha_{B2} = 2\alpha_{C2}$, $\beta_{B2} = 2\beta_{C2}$, $\alpha_{B3} = \alpha_O$, $\beta_{B3} = 3\beta_O$, $\rho_1 = \rho_2 = \rho_3 = \rho_4 = 1/(1 + 0.03\exp[-2.5V/25])$, $\sigma_1 = 2.5/(1 + 6\exp[2.5V/25])$, $\sigma_2 = 0.0165\sigma_1$, $\sigma_3 = \sigma_4 = \sigma_2(\text{ms}^{-1})$, $g_{Na} = 120\text{ mS/cm}^2$, $g_K = 36\text{ mS/cm}^2$, $g_L = 0.3\text{ mS/cm}^2$, $V_{Na} = 55\text{ mV}$, $V_L = -50\text{ mV}$, $I_e = 9\text{ }\mu A/cm^2$. 
Figure 11: The solution of a Na+ channel eight state master equation, Eqs. (49) to (56), Eq. (87) and Eq. (88) (solid line) may be approximated by the solution of Eqs. (83) to Eq. (88) (dotted line), where the rate functions are

\[
\begin{align*}
\alpha_m &= 0.1(V + 25)/(1 - \exp[-(V + 25)/10]), \\
\beta_m &= 4 \exp[-(V + 50)/18], \\
\alpha_{C1} &= 3\alpha_m, \\
\beta_{C1} &= \beta_m, \\
\alpha_{C2} &= 2\alpha_m, \\
\beta_{C2} &= 2\beta_m, \\
\alpha_O &= \alpha_m, \\
\beta_O &= 3\beta_m, \\
\alpha_{B1} &= 3\alpha_{C1}, \\
\beta_{B1} &= 0.0165\beta_{C1}, \\
\alpha_{B2} &= 2\alpha_{C2}, \\
\beta_{B2} &= 2\beta_{C2}, \\
\alpha_{B3} &= \alpha_O, \\
\beta_{B3} &= 3\beta_O, \\
\rho_1 &= \rho_2 = \rho_3 = \rho_4 = 1/(1 + 0.03 \exp[-2.5V/25]), \\
\sigma_1 &= 2.5/(1 + 6\exp[2.5V/25]), \\
\sigma_2 &= 0.0165\sigma_1, \\
\sigma_3 &= \sigma_4 = \sigma_2(\text{ms}^{-1}), \\
\sigma_{Na} &= 120 \text{ mS/cm}^2, \\
g_K &= 36 \text{ mS/cm}^2, \\
g_L &= 0.3 \text{ mS/cm}^2, \\
V_{Na} &= 55 \text{ mV}, \\
V_L &= -50 \text{ mV}, \\
I_e &= 9 \mu\text{A/cm}^2.
\end{align*}
\]
Figure 12: The solution of a Na+ channel eight state master equation, Eqs. (49) to (56), Eq. (87) and Eq. (88) (solid line) may be approximated by the solution of Eqs. (83) to Eq. (88) (dotted line), where the rate functions are 

\[ \begin{align*}
\alpha_m &= 7.45 \exp[0.5V/25], \quad \beta_m = 0.8 \exp[-0.9V/25], \\
\alpha_{C1} &= 3\alpha_m, \quad \beta_{C1} = \beta_m, \quad \alpha_{C2} = 2\alpha_m, \quad \beta_{C2} = 2\beta_m, \quad \alpha_O = \alpha_m, \quad \beta_O = 3\beta_m, \\
\alpha_{B1} &= 3\alpha_{C1}, \quad \beta_{B1} = 0.01\beta_{C1}, \quad \alpha_{B2} = 2\alpha_{C2}, \quad \beta_{B2} = 0.2\beta_{C2}, \quad \alpha_{B3} = \alpha_O, \quad \beta_{B3} = 0.3\beta_O, \\
\rho_1 &= 2.1/(1 + 80 \exp[-2.4V/25]), \quad \rho_2 = 2.1/(1 + 8 \exp[-2.4V/25]), \\
\rho_3 &= 2.1/(1 + 0.8 \exp[-2.4V/25]), \quad \rho_4 = 2.1/(1 + 0.08 \exp[-2.4V/25]), \\
\sigma_1 &= 80/(80 + \exp[2.4V/25]), \quad \sigma_2 = 0.8/(8 + \exp[2.4V/25]), \quad \sigma_3 = 0.08/(0.8 + \exp[2.4V/25]), \quad \sigma_4 = 0.008/(0.08 + \exp[2.4V/25]) \text{ (ms}^{-1}), \\
g_{Na} &= 20 \text{ mS/cm}^2, \quad g_K = 6 \text{ mS/cm}^2, \quad g_L = 2.3 \text{ mS/cm}^2, \quad V_{Na} = 55 \text{ mV}, \quad V_L = -80 \text{ mV}, \quad V_K = -90 \text{ mV}, \quad I_e = 20 \mu\text{A/cm}^2.
\end{align*} \]