A Population Density Model of Domain Calcium-Mediated Inactivation of L-Type Ca Channels

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Honors Thesis

Department of Mathematics

A Population Density Model of Domain Calcium-Mediated Inactivation of L-Type Ca Channels

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May 9, 2013
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Abstract

We present a minimal whole cell model of stochastic domain Ca\textsuperscript{2+}-mediated inactivation of low-density L-type Ca\textsuperscript{2+} channels. Our approach avoids the computationally demanding task of resolving spatial aspects of global Ca\textsuperscript{2+} signaling by using probability densities and associated moment equations to represent heterogeneous local Ca\textsuperscript{2+} signals [17, 18]. Using a minimal Markov chain model of an L-type Ca\textsuperscript{2+} channel, simulated whole cell responses to a two-pulse voltage clamp protocol yield an inactivation function for the whole cell Ca\textsuperscript{2+} current that deviates from that obtained by assuming instantaneous formation and collapse of Ca\textsuperscript{2+} domains, as in the domain-mediated Ca\textsuperscript{2+} inactivation model introduced by Sherman, Keizer, and Rinzel (1990). Parameter studies reveal that when domain Ca\textsuperscript{2+} formation and collapse are slow compared to channel kinetics (e.g., fast voltage-dependent gating), and the maximum domain concentration is held constant, inactivation in the high-voltage regime is attenuated. When the domain dynamics are slow compared to channel kinetics, and the channel permeability is held constant, inactivation is augmented for all voltages. We also derive an open system of moment equations as well as present a suggestion for moment closure that may facilitate analysis and simulation of domain Ca\textsuperscript{2+}-mediated inactivation of low-density L-type Ca\textsuperscript{2+} channels.
1 Introduction

Plasma membrane ion channels are essential to cell physiology. There are many kinds of ion channels (for review see Hille, 2001), but the focus of this project is on the L-type Ca$^{2+}$ channel (Figure 1), one of the ion channels responsible for the excitable properties of cardiac myocytes and neurons.

L-type Ca$^{2+}$ channels are voltage-gated, that is, the channel has a high probability of being closed, or deactivated, at low voltages (i.e. transmembrane potentials less than -80 mV), and a high probability of being open, or activated, at more depolarized voltages. As suggested by the name, L-type Ca$^{2+}$ channels are selectively permeable to Ca$^{2+}$ ions. The “L” refers to the large single channel conductance and the long-lasting current produced by these channels [6]. Generally, the intracellular Ca$^{2+}$ concentration is much lower than the extracellular Ca$^{2+}$ concentration; consequently, Ca$^{2+}$ flows into the cell when the channel opens as long as the cell is not overly depolarized. There are two important factors that control the magnitude of Ca$^{2+}$ influx: the voltage-gated activation of the channel and the driving force.

Figure 1: Schematic of Ca$^{2+}$ influx via an L-type Ca$^{2+}$ channel. The downward arrow represents Ca$^{2+}$ ions entering the cell. The curved arrow represents the Ca$^{2+}$-mediated inactivation of the Ca$^{2+}$ channel. Adapted from http://centriontherapeutics.com.
A minimal representation of the relationship between the cell membrane potential and the ionic current through L-type Ca\(^{2+}\) channels is given by the following ohmic current-voltage equation:

\[
I_{Ca}(V) = g_{Ca} m_{\infty}(V)(V - E_{Ca})
\]  

(1)

where the maximum conductance of the Ca\(^{2+}\) channel is \(g_{Ca}\), and \(m_{\infty}\) represents the voltage-dependent fraction of open channels. In the case of L-type Ca\(^{2+}\) channels, \(m_{\infty}(V)\) is monotonically increasing and sigmoid (Figure 2A). The \((V - E_{Ca})\) term in Eq. 1 represents the driving force (Figure 2B), i.e. the difference between the membrane potential and \(E_{Ca}\) (~120 mV), the Nernst equilibrium potential for Ca\(^{2+}\). When the voltage is less than \(E_{Ca}\), the current is inward (negative), and if the voltage is greater than \(E_{Ca}\), the current is outward (positive). The product of the activation function, \(m_{\infty}\), and the driving force, \((V - E_{Ca})\), is the current voltage relationship for the L-type Ca\(^{2+}\) current \(I_{Ca}(V)\), Figure 2C).

\[\text{Figure 2: Representation of current-voltage relationship. A: Voltage-activated gating properties of the channel, where } m_{\infty} = 1/(1 + e^{(V_{m}-V)/S_{m}}), \text{ and } P_{O} \text{ gives the probability of an open channel. B: Driving force given by } (V - E_{Ca}), \text{ where } E_{Ca} \text{ is the reversal potential. C: Current-voltage relationship given by Eq. 1. Note the largest inward current occurs when the voltage is } \sim 0 \text{ mV.}\]

L-type Ca\(^{2+}\) channels exhibit a phenomenon known as Ca\(^{2+}\)-dependent inactivation (see Figure 1). Channel inactivation occurs through binding of the Ca\(^{2+}\) ion on the cytosolic face of the ion channel and is characterized by a decreased Ca\(^{2+}\) current following a rapid increase in Ca\(^{2+}\) current.
Figure 3 shows simulated inactivation of an L-type Ca$^{2+}$ channel (see Model Formulation section for model used). As the voltage steps from -100 to 0 mV at $t = 25$ ms, the Ca$^{2+}$ channel activates and allows Ca$^{2+}$ ions to enter the cell. These Ca$^{2+}$ ions then bind to and inactivate the channel, decreasing the amount of inward current from $t = 25$ ms to $t = 200$ ms.

Figure 3: Voltage-dependent activation and Ca$^{2+}$-mediated inactivation. Channel activation occurs with the voltage increase at $t = 25$ ms. The decrease in the peak current (~12$\mu$A/$\mu$F when $t = 25$ ms) to the steady-state current (~5$\mu$A/$\mu$F when $t = 200$ ms) is the signature channel inactivation.

Ca$^{2+}$ inactivation of L-type Ca$^{2+}$ channels can be quantified experimentally through a two-pulse voltage clamp protocol (Figure 4) [11]. The command voltage is given initially by the holding potential, $V_h = 100$ mV. The simulated cell is held at $V_h$ for 300 ms to ensure that a steady-state is achieved. Voltage is then stepped up to a prepulse potential, $V_p$, and held at that voltage for a prescribed length of time ($t_p = 200$ ms). The prepulse potential $V_p$ takes a range of values and is the independent variable in the two-pulse protocol. The voltage is then stepped back down to the holding potential, $V_h = 100$ mV, for $t_h = 10$ ms, and then up to a test potential given by $V_t = 0$ mV. Channel inactivation is denoted by the inactivation function, $h_\infty(V_p)$, which is the normalized peak current during the test voltage pulse as a function of the prepulse potential:

$$h_\infty(V_p) = \frac{\text{peak}[I(V_p)]}{\text{peak}[I(V_p = V_h)]}.$$  \hspace{1cm} (2)
The peak current will be the largest in magnitude when \( V_p = V_h \), as activation does not occur during the prepulse potential phase, and thus inactivation does not occur during the test potential phase (see Figure 4). Consequently, the function gives the fraction of channels that are not inactivated and takes a range of \([0, 1]\). When \( h_\infty = 1 \), none of the channels are inactivated and when \( h_\infty = 0 \), all of the channels are inactivated. The current is measured during the test potential phase \( (V_t) \) as opposed to the prepulse potential phase \( (V_h) \) to ensure that the driving force is constant across trials during this phase of the experiment; thus, differences in current arise only from differences in channel inactivation.

![Figure 4: Simulated two-pulse protocol. The top panel shows several command voltages \( (V_{com}) \) over the course of the simulation. The bottom panel shows the evoked Ca\(^{2+}\) current for each voltage. The peak current in the last phase of the simulation (when \( V_{com} = V_t \)) is used to calculate the inactivation function \( h_\infty(V) \).](image)

Conventionally, models of Ca\(^{2+}\)-inactivation assume the formation of a Ca\(^{2+}\) domain or Ca\(^{2+}\) shell, depending the density of the Ca\(^{2+}\) channels in the plasma membrane (Figure 5), [11]. The shell model assumes a high (~100 \( \mu m^{-2} \)) density of Ca\(^{2+}\) channels in the membrane [11]. Upon depolarization, these channels activate and allow Ca\(^{2+}\) ions to flow into the cell. The buffered diffusion of Ca\(^{2+}\) leads to a shell of elevated intracellular Ca\(^{2+}\) near the inner surface of the plasma
membrane. In a shell model, the elevation of Ca\(^{2+}\) concentration near the plasma membrane is expected to be slow and all channels are exposed to the same Ca\(^{2+}\) concentration.

In contradistinction to the shell model, the domain model assumes a low density of Ca\(^{2+}\) channels, where regions of high Ca\(^{2+}\) concentration (Ca\(^{2+}\) “domains”) form around each channel when that particular channel is open. These domains are spatially localized and independent except through possible interactions with the bulk Ca\(^{2+}\) concentration. The domain model proposed by Sherman et al. in 1990 assumes that Ca\(^{2+}\) domains form instantly when the channel activates, and collapse instantly when the channel deactivates or inactivates. This formulation of domain Ca\(^{2+}\)-mediated inactivation of L-type Ca\(^{2+}\) domains is conventional, but might be inadequate when the dynamics of Ca\(^{2+}\) channel activation and inactivation are in fact not slow compared to domain formation and collapse.

In this thesis, I extend the framework for domain Ca\(^{2+}\)-mediated inactivation of L-type Ca\(^{2+}\) channels to include the time-dependent dynamics of domain formation and collapse. This formulation is subsequently used to investigate the dependence of the inactivation function on the exponential time constant for domain collapse. The following section details the compartments and fluxes in the model and develops a “population density approach” that uses univariate continuous
probability density functions for domain Ca$^{2+}$ concentration conditioned on the state of the L-type Ca$^{2+}$ channel to represent domain dynamics. Representative numerical simulations of simulated two-pulse voltage clamp protocols are presented. In Section 3, I present two related parameter studies of the effect of the exponential time constant for domain collapse on Ca$^{2+}$ channel inactivation. The thesis concludes with the derivation of the associated moment equations along with a suggestion for moment closure approach (Section 4), a discussion (Section 5), and suggestions for further work (Section 6).

2 Model Formulation

2.1 Compartments and Fluxes

Our approach to modeling an individual Ca$^{2+}$ domain involves three compartments: the extracellular compartment with concentration $c_{ext}$, the domain with concentration $c$, and the cytosol with concentration $c_{cyt}$ (Figure 6). We consider two fluxes between these three compartments: one from the extracellular space into the domain ($j_{\text{influx}}$), and one from the domain into the cytoplasm ($j_{\text{efflux}}$).

Figure 6: Compartments and fluxes in the population density formulation of domain Ca$^{2+}$-mediated inactivation. The right panel depicts a cell with multiple domains. The left panel shows the fluxes associated with a single domain. The influx to the domain is given by $j_{\text{influx}}$, which is nonzero when the Ca$^{2+}$ channel is open. The diffusion-mediated efflux of domain Ca$^{2+}$ to the cytosol is given by $j_{\text{efflux}}$. 

8
Consistent with Figure 6, the time-dependent dynamics of the \( \text{Ca}^{2+} \) domain concentration are governed by the following ODE:

\[
\frac{dc}{dt} = \frac{1}{\lambda_d} (j_{\text{influx}} - j_{\text{efflux}}).
\]

where \( \lambda_d = \hat{V}_d/V_{\text{cyt}} \) is the effective volume ratio between the domain and cytoplasm. This effective volume ratio accounts for both physical volume and buffering capacity, that is, \( \hat{V}_d = V_d/\beta_d \) and \( V_{\text{cyt}} = V_{\text{cyt}}/\beta_{\text{cyt}} \), where the \( \beta \) terms correspond to buffering factors (the proportion of total \( \text{Ca}^{2+} \) that is free, i.e. not bound) of the domain and cytoplasm. Writing \( \lambda_d^T = N\lambda_d, J_{\text{influx}}^T = Nj_{\text{influx}}, \) and \( J_{\text{efflux}}^T = Nj_{\text{efflux}}, \) where \( N \) is the number of release sites, the previous equation implies the following expression for the domain \( \text{Ca}^{2+} \) concentration in terms of total fluxes:

\[
\frac{dc}{dt} = \frac{1}{\lambda_d^T} (J_{\text{influx}}^T - J_{\text{efflux}}^T).
\]  

(3)

It remains to specify the two fluxes that appear in Eq. 3. \( J_{\text{efflux}}^T \) is given by:

\[
J_{\text{efflux}}^T = \frac{c - c_{\text{cyt}}}{\tau}
\]

where \( \tau \) is the exponential time constant for domain collapse, and \( c_{\text{cyt}} \) is the bulk \( \text{Ca}^{2+} \) concentration, assumed to be constant. The voltage and \( \text{Ca}^{2+} \)-dependent influx, \( J_{\text{influx}}^T \), is chosen to be consistent with the Goldmann-Hodgkin-Katz current equation [6]. That is, if all the \( \text{Ca}^{2+} \) channels were open,

\[
J_{\text{influx}}^T = -\frac{A_m}{zF} I_{\text{influx}}^T
\]  

(4)

where \( A_m = \frac{C_m\beta_{\text{cyt}}}{V_{\text{cyt}}} \) is a whole-cell capacitance scaling factor, and \( C_m \) is the capacitative membrane area, and the total \( \text{Ca}^{2+} \) current, \( I_{\text{influx}}^T \) is given by:

\[
I_{\text{influx}}^T = zF P V \left( \frac{c_{\text{eV/V}_\theta} - c_{\text{ext}}}{e^{V/V_\theta} - 1} \right).
\]

(5)

Eq. 4 and 5 can be combined and rearranged to obtain,
\[ J_{\text{influx}}^T = j_0 - j_1 c \]  

(6)

where \( j_0 \) and \( j_1 \) are functions of voltage (see Appendix A).

### 2.2 L-type Ca\(^{2+}\) channel model

To illustrate the population density approach to modeling domain Ca\(^{2+}\)-mediated inactivation, we utilize a Markov chain model with four states (Figure 7). These states (C, closed; O, open; IC and IO, inactivated) account for two independent processes: voltage-dependent activation of the channel and Ca\(^{2+}\)-dependent inactivation.

\[
\begin{align*}
\text{closed} & \quad \text{open} \\
\begin{array}{c}
\text{C} \\
\text{Ca}^{2+} \\
k_+ \quad k_- \\
\text{IC} \\
\text{IO} \\
\end{array} & \quad \begin{array}{c}
\text{O} \\
\text{Ca}^{2+} \\
k_- \quad k_+ \\
\text{IC} \\
\text{IO} \\
\end{array} \\
\end{align*}
\]

Figure 7: The transition state diagram for the four-state Ca\(^{2+}\) channel model. The horizontal transitions on the diagram are voltage-dependent. Binding of one Ca\(^{2+}\) ion is required for vertical transitions into the inactivated states.

The values of the rate constants for Ca\(^{2+}\) binding \((k_+ \text{ and } k_-)\) follow Sherman et al., 1990. The rates \( \alpha \) and \( \beta \) are functions of voltage:

\[
\alpha = \frac{m_\infty}{\tau_m} \quad \beta = \frac{1 - m_\infty}{\tau_m}
\]

where \( m_\infty \) and \( \tau_m \) (Appendix B) also follow Sherman et al., 1990.
2.3 Population density formulation

Although tradition Monte Carlo simulations of this model are possible, we present an alternative and computationally more efficient approach that employs probability densities. Assuming a large number of domains, we can define a continuous univariate probability density function for the domain Ca\(^{2+}\) concentration. That is,

\[ \rho^i(c, t) dc = \Pr\{c < \tilde{c}(t) < c + dc \text{ and } \tilde{S}(t) = i\} \]

where the index \(i \in \{C, IC, IO, O\}\) runs over the four Ca\(^{2+}\) channel states, and the tildes on \(\tilde{c}(t)\) and \(\tilde{S}(t)\) indicate random quantities. A system of advection-reaction equations describes the time-evolution of these joint probability densities:

\[
\frac{\partial \rho^C}{\partial t} = -\frac{\partial}{\partial c} \left(f^C \rho^C\right) - (\alpha + ck_+) \rho^C + \beta \rho^O + k_- \rho^{TC} \tag{7}
\]

\[
\frac{\partial \rho^O}{\partial t} = -\frac{\partial}{\partial c} \left(f^O \rho^O\right) - (\beta + ck_+) \rho^O + \alpha \rho^C + k_- \rho^{TO} \tag{8}
\]

\[
\frac{\partial \rho^{TC}}{\partial t} = -\frac{\partial}{\partial c} \left(f^{TC} \rho^{TC}\right) - (\beta + k_-) \rho^{TC} + \alpha \rho^C + ck_+ \rho^O \tag{9}
\]

\[
\frac{\partial \rho^{TO}}{\partial t} = -\frac{\partial}{\partial c} \left(f^{TO} \rho^{TO}\right) - (\alpha + k_-) \rho^{TC} + \beta \rho^{TO} + ck_+ \rho^C \tag{10}
\]

The arguments of each probability distribution, \(c\) and \(t\), are suppressed for compactness. Figure 8 shows example probability distributions for each state; the arrows depict ways that probability can change over time.

The reaction terms in Eqs. 7-10 account for the probability flux associated with channel state changes (blue arrows, Figure 8). The terms of the form \(\frac{\partial}{\partial c} (f^i \rho^i)\) represent the divergence of the probability flux, given by \(\phi^i(c, t) = f^i(c) \rho^i(c, t)\), where \(f^i(c)\) is the advection rate. The advection rates account for the deterministic dynamics of domain Ca\(^{2+}\) that occur when a channel occupies one
of the four states (red arrows, Figure 8), and are consistent with the ordinary differential equation describing the domain Ca$^{2+}$ concentration in terms of the total fluxes:

$$f^i = \frac{1}{\lambda_d} \left( \xi^i J_{\text{influx}}^T - J_{\text{efflux}}^T \right).$$

where $\xi^i = 0$ for $i \in \{C, IC, IO\}$ and $\xi^i = 1$ for $i \in \{O\}$.

The two quantities of primary interest in our studies of the effect of time-dependent domain Ca$^{2+}$-mediated inactivation are the whole cell current, given by:

$$I_{\text{influx}}^* = \frac{zF}{A_m} \int (j_0 - j_1 c) \rho^O(c, t) dc$$

and the conditional expectation of the domain Ca$^{2+}$ concentration:
\[ E[c]S(t) = \tilde{i}(t) = \frac{\int c \rho^i(c,t) dc}{\int \rho^i(c,t) dc}. \]  

where \( i \in \{C, O, IC, IO\} \)

Eqs. 7-13 specify the probability density model. The results presented in the next section were obtained by numerically integrating these equations using a finite difference scheme (see Appendices A and B).

3 Results

3.1 Representative Simulation

Figure 9 shows two snapshots (a solution at one particular time) of the four probability densities, one for each channel state, as a function of the domain concentration (in \( \mu M \)). Densities are given for two separate parameter regimes that assume either a quickly evolving Ca\(^{2+}\) domain (A) or a slow Ca\(^{2+}\) domain (B).

Figure 10 shows summary simulation results for a two-pulse voltage clamp protocol, that is, the probability densities are integrated as described in Appendix A and B for a given prepulse voltage, and the resulting current during the test pulse is measured. For clarity, the dynamics of the joint probability densities \( \rho^i(c,t) \) are not shown. Instead, the command voltage for 9 simulations is shown (top panel), as well as resulting Ca\(^{2+}\) currents (middle panel) and the expected value of the domain Ca\(^{2+}\) concentration irrespective of channel state (bottom panel).

Note that the largest inward currents during the test phase occur when the prepulse voltage \( V_p \) is very high or very low (dark blue and forest green, respectively). Little current is expressed at extreme prepulse voltages, preventing an accumulation of domain Ca\(^{2+}\). Because Ca\(^{2+}\) ion binding is required to transition to the inactivated states, the level of inactivation is proportional to the expected value of the domain Ca\(^{2+}\) concentration. Extreme prepulse potentials decrease the amount Ca\(^{2+}\)-mediated channel inactivation and consequently promote increased Ca\(^{2+}\) current.
Figure 9: Representative numerical solutions to the advection reaction equations. Note different scales on the vertical axis (units of $\mu M^{-1}$). The values of the integrated densities are shown in the upper right of each panel. These are the probabilities that a randomly sampled Ca$^{2+}$ channel is in each of the four states. As required, they sum to 1. Solutions are qualitatively different when the domain dynamics are either fast (A) or slow (B) relative to the channel dynamics.

Figure 11 (bottom panel) shows the inactivation curve $h_\infty(V_p)$ calculated as described in the Introduction (Eq. 2). For comparison, the peak current for each value of the prepulse voltage is also shown (top panel). Both the peak current and the inactivation functions are biphasic. Again, simulated Ca$^{2+}$ inactivation is minimal when the prepulse potential is very low or very high; channel inactivation is greatest for intermediate prepulse potentials.

3.2 Parameter Studies: Fixed $c_{ss}$

Assuming fixed maximum domain concentration, we consider the inactivation curve $h_\infty$ under two different parameter regimes: one in which the dynamics of the domain are fast compared to the channel (Figure 9A), and one in which the dynamics of the domain are slow compared to the channel (Figure 9B). In the fast domain/slow channel case, probability accumulates at low domain Ca$^{2+}$ concentrations for closed/inactivated channels, and at high domain Ca$^{2+}$ concentrations for open
channels. In the slow domain/fast channel case, the joint probability densities are similar. These regimes can be quantified by considering the ratio of the domain time constant ($\tau_d$) and channel time constant ($\tau_c$).

The channel time constant, $\tau_c$, is related to the magnitude of the nonzero eigenvalues of the coefficients that appear in the reaction terms of Eqs. 7-10, namely,

$$Q = \begin{pmatrix}
-(\alpha + ck_+) & \beta & 0 & k_- \\
\alpha & -(\beta + ck_+) & k_- & 0 \\
0 & ck_+ & -(\beta + k_-) & \alpha \\
ck_+ & 0 & \beta & -(\alpha + k_-)
\end{pmatrix}$$

where $c$ is in the range $[c_\infty, c_{ss}]$. The eigenvalues of $Q$ are $\lambda_1 = 0$, $\lambda_2 = \alpha + \beta$, $\lambda_3 = k_+c + k_-$, and $\lambda_4 = \alpha + \beta + k_+c + k_-$. 
Figure 11: The peak current (top) and inactivation function (bottom). The largest magnitude, i.e. most negative, peak currents occur for extreme voltages.

The domain time constant can be read off from the linear ODE describing domain concentration:

\[
\frac{dc}{dt} = \frac{1}{\lambda_d} \left( j_0 - j_1 c - \frac{(c - c_{cyt})}{\tau} \right).
\]

The reciprocal of the exponent of \(e\) in the solution gives \(\tau_d = \lambda_d^T / (j_1 + \frac{1}{\tau})\), where \(\tau\) is the exponential time constant of domain collapse and is a free parameter. We can therefore investigate the dependence of the inactivation function \(h_{\infty}\) on the separation of time scales by varying the domain collapse time constant \(\tau\).

Figure 12 shows the inactivation function resulting from simulations with \(\tau = 10\) ms, \(\tau = 50\) ms, and \(\tau = 100\) ms. Note that Ca\(^{2+}\)-mediated inactivation during the test pulse increases for decreasing \(\tau\) in the high voltage (\(> -10\) mV) regime. Figure 13 confirms this larger probability of channel inactivation for smaller \(\tau\) given a prepulse potential of 20 mV.

This result - that more inactivation occurs for faster collapsing domains - might seem coun-
Figure 12: Assuming fixed steady-state domain concentration, the inactivation function $h_\infty$ depends on the value of $\tau$. In the high voltage regime, the level of inactivation increases as the value of $\tau$ decreases. The dashed line is the prepulse voltage used in Figures 13-15.

Terintuitive. If the domain was slow to collapse, Ca$^{2+}$ ions would remain in the domain longer, increasing channel-binding and thus increasing channel inactivation. But this is clearly not the case, and an alternative argument must be considered. The explanation lies in the assumption that the maximum concentration value is constant; a smaller value of $\tau$ implies a larger value of the permeability $P_T$, which in turn implies a larger current (see Eq 5).

Figure 14 confirms this explanation by showing that larger currents are evoked for smaller values of $\tau$ regardless of the command potential. This increased current leads to increased domain concentration (Figure 15). Note that the expected domain concentration for all states, and in particular the open state, is larger for larger $\tau$. Additionally, values of $\tau$ are always larger than that of $\tau_c$, meaning that the channel will always inactivate faster than the domain can collapse. Solutions diverge only in the high voltage regime because $\alpha$ monotonically increases with voltage. Consequently, probability moves from the closed to the open state (see Figure 7), and the higher
Figure 13: Zeroth moments (jointly distributed with channel state) as a function of time for various domain collapse time constants, $\tau = 10$ ms (blue), $\tau = 50$ ms (green), and $\tau = 100$ ms (red). The second panel shows a decrease in open probability ($\mu^O_0$) for decreasing values of $\tau$. The third and fourth panels show an increase in the probability of channel inactivation ($\mu^{IO}_0 + \mu^{IC}_0$) for decreasing values of $\tau$.

expected domain concentration given the open channel state gives rise to increased $\text{Ca}^{2+}$ channel inactivation.

3.3 Parameter Studies: Fixed $P^T$

We also considered the dependence of the inactivation function on the time to domain collapse assuming fixed $\text{Ca}^{2+}$ channel permeability $P^T$. Figure 16 shows the inactivation function under this condition using values of $\tau$ identical to the previous section ($\tau = 10$ ms, 50 ms, 100 ms). As the domain collapse time constant $\tau$ increases, the inactivation function shifts downwards, corresponding to increased $\text{Ca}^{2+}$ channel inactivation. This results from residual $\text{Ca}^{2+}$ lingering in the domain, increasing the expected concentration value (Figure 17) and the level of inactivation (Figure 18). Although the expected domain concentration increases with $\tau$, the $\text{Ca}^{2+}$-current also decreases with $\tau$ (Figure 19). This results from the decreased open probability, which consequently allows fewer
Figure 14: Whole-cell Ca$^{2+}$ current for varying $\tau$. Smaller values of $\tau$ give rise to more inward current, due to the higher permeability used when the steady state domain concentration is fixed. When $\tau = 10$ ms, inactivation of the Ca$^{2+}$ current is substantial during both the prepulse and the test pulse.

Ca$^{2+}$ ions to enter the cell.

In summary, assuming fixed steady state domain concentration, my simulations suggest that an L-type Ca$^{2+}$ channel model with a four-state kinetic scheme (Figure 7) will exhibit more inactivation in the high prepulse voltage regime when domain collapse is rapid. Conversely, assuming fixed Ca$^{2+}$ channel permeability, Ca$^{2+}$ channels with fast domain collapse exhibit less inactivation for all prepulse voltages.

4 Moment Equations and Moment Closure

In this section, we derive a system of ODEs describing the time evolution of the moments of the joint densities that solve the previously described system of coupled advection-reaction equations. Defining the $q^{th}$ moment the $i^{th}$ joint density as $\mu^i_q = \int c^q \rho^i dc$, differentiating with respect to time yields:
Figure 15: Expected domain concentration conditioned on each channel state. The increased expected domain concentration in the open state, $E^O[\bar{c}]$, is consistent with the observed increased inactivation for small $\tau$.

Figure 16: Inactivation function for fixed permeability, $P^T$. As the domain collapse time constant $\tau$ increases, the level of inactivation increases for all voltages.
Figure 17: Expected domain concentration conditioned on each channel state. Larger values of $\tau$ result in increased expected domain concentration for all states.

Figure 18: Zeroth moments (jointly distributed with channel state) for different domain collapse time constant $\tau$ and fixed permeability $P^T$. The second panel shows an increase in open probability for decreasing values of $\tau$, while the third and fourth traces show an increase in inactivation probability for larger values of $\tau$. 
Figure 19: Whole-cell Ca\textsuperscript{2+} current for varying domain collapse time constants $\tau$. Ca\textsuperscript{2+} currents are equivalent during the first phase of the protocol. Less inward current occurs for larger values of $\tau$ during both the prepulse and test phases of the protocol.

\[
\frac{d\mu^C}{dt} = \int c^q \frac{\partial \rho^i}{\partial t} dc.
\] (14)

The equations solved by the $q^{th}$ moment of each state in the four-state system described above follow by substitution for $\frac{\partial \rho^i}{\partial t}$ using Eqs. 7-10, integration, application of boundary conditions, and identification of moments. For example, the moment equations for the closed state is derived by substituting Eq. 7 into Eq. 14 to obtain:

\[
\frac{\partial \mu^C}{\partial t} = \int c^q \left( -\frac{\partial}{\partial c} \left( f^C \rho^C \right) - (\alpha + ck_+ \rho^C + \beta \rho^O + k_- \rho^IC \right) dc.
\]

Distributing the integration over the sum gives:

\[
\frac{d\mu^C}{dt} = -\int c^q \frac{\partial}{\partial c} \left( f^C \rho^C \right) dc - \alpha \int c^q \rho^C dc - k_+ \int c^{q+1} \rho^C dc + \beta \int c^q \rho^O dc + k_- \int c^q \rho^IC dc.
\] (15)
Integration by parts of the first integral yields:

\[
\int c^q \frac{\partial}{\partial c} (f^C \rho^C) \, dc = -q \int c^{q-1} f^C \rho^C \, dc \tag{16}
\]

where the boundary term is zero because the advection rate \(f^C\) is zero at \(c = c_\infty\) and \(\rho^C\) is zero at \(c = c_{ss}\).

Using the definition of the advection rate, \(f^C = -(c - c_\infty)/\tau \lambda_d^T\) (Eq. 11), Eq. 16 can be expanded as follows,

\[
q \int c^{q-1} \frac{(c - c_\infty)}{\tau \lambda_d^T} \rho^C \, dc = \frac{q}{\tau \lambda_d^T} \int c^q \rho^C \, dc - \frac{qc_\infty}{\tau \lambda_d^T} \int c^{q-1} \rho^C \, dc.
\]

Thus, by making use of the definition of a moment and simplifying wherever possible, Eq. 15 becomes

\[
\frac{d\mu_q^C}{dt} = \frac{q}{\tau \lambda_d^T} \mu_q^C + \frac{qc_\infty}{\tau \lambda_d^T} \mu_{q-1}^C - \alpha \mu_q^C - k_+ \mu_{q+1}^C + \beta \mu_{q+1}^O + k_- \mu_q^O
\tag{17}
\]

Using a similar process, we can find the ODEs for the \(q^{th}\) moment of the open state as well.

Defining \(m_1 = \frac{1}{\lambda_d^T} (c_\infty \tau + j_0)\), and \(m_2 = \frac{1}{\lambda_d^T} (j_1 + \frac{1}{\tau})\), we find that the \(q^{th}\) moment of the \(\rho^O\) solves:

\[
\frac{d\mu_q^O}{dt} = -qm_1 \mu_{q-1}^O +qm_2 \mu_q^O - \beta \mu_q^O - k_+ \mu_{q+1}^O + \alpha \mu_q^C + k_- \mu_q^C
\tag{18}
\]

Similarly,

\[
\frac{d\mu_q^{TC}}{dt} = \frac{q}{\tau \lambda_d^T} \mu_q^{TC} + \frac{qc_\infty}{\tau \lambda_d^T} \mu_{q-1}^{TC} - \alpha \mu_q^{TC} - k_- \mu_q^{TC} + \beta \mu_q^{TO} + k_+ \mu_{q+1}^{TC}
\tag{19}
\]

\[
\frac{d\mu_q^{TO}}{dt} = \frac{q}{\tau \lambda_d^T} \mu_q^{TO} + \frac{qc_\infty}{\tau \lambda_d^T} \mu_{q-1}^{TO} - \beta \mu_q^{TO} - k_- \mu_q^{TO} + k_+ \mu_q^{TC} + k_- \mu_q^C
\tag{20}
\]

Notice that Eqs. 17-20 are an open system of ODEs because the equation for the \(q^{th}\) moment
depends on the \( q^{th} \) moment, the \((q-1)^{th} \) moment, and the \((q+1)^{th} \) moment. One method of closing these equations is to assume that analytical expression that the variance, given by \( \frac{\mu_i^2}{\mu_0^2} - \left( \frac{\mu_i}{\mu_0} \right)^2 \), is 0 for each state \( i \). This gives the following expression for the second moments, \( \mu_2 = \frac{(\mu_1^2)^2}{\mu_0^2} \). This technique does not constrain the conditional expected \( q^{th} \) domain calcium concentration and will likely work well when formation and collapse of the calcium domain is rapid. Closing the moment equations in this manner results in two ODEs per channel state: one for the zeroth moment \( \mu_i^0 \), and one for the first moment \( \mu_i^1 \) (8 ODEs in total).

For example, after truncating and closing the moment equations associated with the closed state, we have:

\[
\frac{d\mu_C^0}{dt} = \frac{1}{\tau \lambda_d} \mu_C^1 + \frac{c_\infty}{\tau \lambda_d} \mu_0^C - \alpha \mu_0^C - k_+ \mu_C^1 + \beta \mu_0^O + k_- \mu_0^C
\]

\[
\frac{d\mu_C^1}{dt} = \frac{1}{\tau \lambda_d} \mu_C^1 + \frac{c_\infty}{\tau \lambda_d} \mu_0^C - \alpha \mu_1^C - k_+ \mu_C^1 \left( \frac{\mu_1^1}{\mu_0^1} \right)^2 + \beta \mu_0^O + k_- \mu_1^C.
\]

Similar ODEs can be obtained for the open and inactivated states. The resulting system of ODEs provides an alternative to solving the advection-reaction equations, as the quantities of primary interest can be expressed as functions of the moments. For example, whole-cell flux given by:

\[
J_{\text{influx}}^* = \int P_T Z F V \frac{c_{\text{ext}} V}{V_\theta} - \frac{c_{\text{ext}}}{V/e_{t_\theta}} - 1 \rho^O(c, t) dc
\]

can be re-written in terms of the moments as follows:

\[
J_{\text{influx}}^* = j_0 \mu_0^O - j_1 \mu_1^0
\]

where \( j_0 \) and \( j_1 \) are functions of voltage, \( j_0 = A_m P_T \frac{V_{\text{ext}} V/e_{t_\theta}}{V_\theta (e^{V/e_{t_\theta}} - 1)} \), \( j_1 = A_m P_T \frac{V/e_{t_\theta}}{V_\theta (e^{V/e_{t_\theta}} - 1)} \). In future work, one might attempt to demonstrate through numerical simulation that this moment closure method approximates the solutions of the population density calculations.
5 Discussion

This project employed a novel population density approach to simulation of Ca\(^{2+}\)-mediated inactivation of voltage-gated Ca\(^{2+}\)-channels. This approach assumes a large number of low-density Ca\(^{2+}\) channels, but avoids explicitly spatial aspects of Ca\(^{2+}\) signaling (e.g. propagating Ca\(^{2+}\) waves). It allows for heterogeneity among Ca\(^{2+}\) domains - a potentially important feature not captured in more traditional common pool models, and it avoids the computational demands of a Monte Carlo simulation of the time-dependent dynamics of many domains. Using the population density formalism, we were able to investigate the dependence of the inactivation curve of a minimal L-type Ca\(^{2+}\) channel model on the exponential time constant of domain collapse. Changing this parameter required either a reciprocal change in the permeability, or a change in the maximum steady state Ca\(^{2+}\) concentration (see Eqs. 21-23 in Appendix A). Simulations were performed under both conditions. When the permeability changes with \(\tau\), so that \(c_{ss}\) is fixed, channels with faster collapsing domains experience more inactivation than channels with slower collapsing domains in the high voltage regime. When the permeability is held constant, channels with faster collapsing domains experience less inactivation regardless of voltage. In both cases, a smaller value of \(\tau\) produces a larger inward Ca\(^{2+}\) current during depolarizing voltage pulses. Simulations were analyzed to clarify these observations. In the first case, the larger inward current for faster collapsing domains is due to the increased permeability and consequently, gives a higher expected domain concentration and more inactivation. In the second case, the larger inward current is a result of the lack of inactivation (compared to the channels with slower collapsing domains); in the absence inactivation, the qualitative current would be the same. Although these explanations are qualitative at this moment due a the lack of illuminating analytical expressions for the aforementioned phenomena, the figures shown in the previous sections strongly support my interpretation.

The choice to vary \(\tau\) in order to separate the time scales of the channel and the domain is not only a logical one that follows from the consideration of parameters that appear in both time scales, but it is also an experimentally relevant decision. Unlike the domain time constant, the channel time constant is a relatively well-determined value. The time to domain collapse depends
on the diffusion of Ca\(^{2+}\) ions in the domain, which depends on the conditions within the domain. Notably, the buffering capacity has a direct effect on the diffusion coefficient \([12, 15]\). Although experimental protocols involving Ca\(^{2+}\) imaging can reveal the diffusion coefficient, the relationship between the time to domain collapse and the inactivation properties of the channel is difficult to determine experimentally. However, this is a case where both experiment and theory can contribute to understanding. Our predictions for the inactivation curve with different assumptions regarding the intrinsic channel properties and time-dependent domain dynamics can be confirmed or rejected by experimental results that measure the inactivation function for different values of the diffusion coefficient for Ca\(^{2+}\) (which can be manipulated by the application of exogenous Ca\(^{2+}\) buffers like EGTA or BAPTA).

Several assumptions were made in the development of this model, but the most significant assumption is that the domains are uncoupled and well-mixed (see Future Directions). One of the more notable difficulties encountered in this project is the difficulty with the numerical simulation. As shown in Williams et al., 2005, the population density approach is computationally more efficient compared to the traditional Monte Carlo approach \([18]\). However, the parameter regime of the model considered in this project resulted in stiff ODEs, and I was forced to re-normalize the probability distributions throughout the simulations to ensure conservation of probability. This problem was especially evident for small values of \(\tau\), and prevented parameter studies involving extremely small time constants for domain collapse. Some results included in this thesis may involve artifacts associated with the numerical scheme chosen; however, all simulation results were carefully considered and rejected if numerical instability was evident. Because numerical schemes for stiff ODEs are commonplace, the problems I encountered with numerical integration of the advection-reaction equations might be solved through moment-based methods.
6 Future Directions

Several future directions for this project appear plausible. Perhaps the most obvious is evaluating
the proposed moment closure technique. The proposed moment closure method will likely work well
for fast domains, but may fail when domains are slow. If so, the search for a better moment closure
method might prove fruitful. Previous work has focused on an approach involving truncation of
moment equations at \( q = 3 \) and use of an algebraic relation for \( \mu_3 \) in terms of lower moments that
would be strictly correct if the joint probability densities were beta distributions [17].

The presented model framework could be employed with a more realistic model of the channel
and/or the Ca\(^{2+}\) dynamics within a cell. In development of this model, we assumed a fixed cytosolic
concentration. If we relaxed this assumption, \( c_{cyt} \) would no longer be a constant, but rather a time-
dependent bulk Ca\(^{2+}\) quantity given by the solution of an ODE of the form:

\[
\frac{dc_{cyt}}{dt} = -J_{out} + J_{efflux}^*
\]

where, for example, \( J_{out} = k_{out}c_{cyt} \) represents the action of ATP-dependent plasma membrane Ca\(^{2+}\)
transporters whose rate depends on the bulk cytosolic Ca\(^{2+}\) concentration. In this situation, the
efflux from domains to the cytosolic bulk would be:

\[
J_{efflux}^* = \int \frac{1}{\tau} (c - c_{cyt}(t)) \rho^T(c, t)dc.
\]

This flux depends on the joint probability densities through the term \( \rho^T(c, t) = \rho^C(c, t) + \rho^{TC}(c, t) + \rho^{TO}(c, t) + \rho^O(c, t) \), which is the probability density of the domain [Ca\(^{2+}\)] irrespective of
the state of a randomly sampled domain.

An important limitation of the population density formulation is that the concentration within
domains is not in fact constant. Indeed, the concentration profile solves to the reaction-diffusion
equations for the buffered diffusion of Ca\(^{2+}\) that are explicitly spatial, and it is unclear how to extend
the population density approach in a manner that accounts for the shape of the Ca\(^{2+}\) domains [12].
This limitation may be significant because the Ca\(^{2+}\) ions closest to the channel are the ones that will
inactivate the channel. In addition, the model of the Ca\textsuperscript{2+}-channel used in this project is highly simplified. Fortunately, the probability density approach is fully generalizable to Ca\textsuperscript{2+} channels with an arbitrary number of states [18]. The framework presented can easily accommodate more biophysically realistic models of L-type Ca\textsuperscript{2+}-channels (see Figure 21).

![Figure 20](image.png)

**Figure 20:** L-type Ca\textsuperscript{2+} channel model that is more realistic than the minimal model used in this thesis. The model exhibits both Ca\textsuperscript{2+}-dependent and voltage-dependent inactivation. Reproduced from Faber et al., 2007.

Previous work has employed the probability density approach in the context of Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+}-release (CICR) from the sarcoplasmic reticulum in cardiac myocytes [17, 18], but this framework has not yet been used to model CICR from the endoplasmic reticulum in neurons. This phenomenon, in conjunction with voltage-gated Ca\textsuperscript{2+} channel dynamics alone are known to play a role in neuronal Ca\textsuperscript{2+} signaling, dendritic excitability, signal integration, and synaptic plasticity [1, 4]. Because the biophysics of the intracellular channels that give rise to CICR are well-known [8], extensions in this direction would be straightforward. Additionally, Ca\textsuperscript{2+} can influence the gating of other ion channels, e.g. Ca\textsuperscript{2+}-activated potassium channels [2]. A natural extension of this project is to employ the population density approach to investigate the dynamics of the class of Ca\textsuperscript{2+}-
activated potassium channels, known as SK channels. These channels play important physiological roles in the heart, brain, liver, pancreas, and muscle [13, 16]. This population density approach is well-suited to investigate the whole-cell potassium current evoked by SK channels that are spatially co-localized with L-type Ca$^{2+}$ channels, where both channel types exhibit stochastic gating properties and are influenced by both voltage and domain Ca$^{2+}$ concentration. Previous work done by Stanley et al. has showed that the stochastic gating of Ca$^{2+}$ channels increases the activation of SK channels [13], but the effects of domain heterogeneity on the whole cell response have not been explored. The population density could also be used to simulate Ca$^{2+}$ binding of sensor proteins, e.g. calmodulin, that play an essential role in Ca$^{2+}$ signaling and sensitization of intracellular Ca$^{2+}$ channels [14], [10].

**Appendix**

**Appendix A: Boundary Conditions**

We numerically integrate the coupled advection-reaction equations (Eqs. 7-10) using a high-resolution finite difference scheme [3, 7, 18]. The boundaries of the independent variable $c$ are given by the maximum and minimum domain concentrations, $c_{ss}$ and $c_{cyt}$, respectively. Boundary conditions for $\rho^i(c, t)$ at $c = c_{cyt}$ and $c = c_{ss}$ can be determined by noting that conservation of probability implies zero probability flux at the boundaries, that is, $\left.\dot{\rho}^i\right|_{c_{ss}} = 0$ and $\left.\dot{\rho}^i\right|_{c_{cyt}} = 0$. Because $f^c(c_{ss}) = 0$ and $f^i(c_{cyt}) = 0$ for $i \in \{C, IC, IO\}$, the requirement of no probability flux at $c_{ss}$ and $c_{cyt}$ leads to four Dirichlet (absorbing) boundary conditions, one for each probability density, namely, $\rho^O(c_{cyt}, t) = 0$ and $\rho^i(c_{ss}, t) = 0$ for $i \in \{C, IC, IO\}$.

The numerical value of $c_{ss}$ is determined by the balance of Ca$^{2+}$ fluxes when the Ca$^{2+}$ channel is open, i.e.,

$$j_0 - j_1 c_{ss} - \frac{c_{ss} - c_{cyt}}{\tau} = 0.$$

Solving this expression for the steady state Ca$^{2+}$ concentration gives
\[ c_{ss} = \frac{j_0 + c_{cyt}/\tau}{j_1 + 1/\tau} \]  

where \( j_0 \) and \( j_1 \) are

\[ j_0 = A_m P^T \frac{V c_{ext} e^{V/V_\theta}}{V_\theta (e^{V/V_\theta} - 1)} \]  

\[ j_1 = A_m P^T \frac{V e^{V/V_\theta}}{V_\theta (e^{V/V_\theta} - 1)}. \]

Because \( c_{ss}(V) \) varies throughout the voltage clamp protocol, we use the largest value of \( c_{ss} \) for the prescribed range of voltages. Parameter studies that involve changing the domain time constant \( \tau \) are performed in one of two fashions: either \( P^T \) is fixed, i.e. \( c_{ss} \) increases as \( \tau \) increases, or alternatively, \( c_{ss} \) is fixed and \( P^T \) decreases as \( \tau \) increases.

**Appendix B: Numerical Scheme**

We employed a total variation diminishing algorithm following [3, 18]. We discretized \( c \) according to \( c_\ell = \ell \Delta c \), where \( \ell = 0, 1, \ldots, L \), and \( \Delta c = (c_{ss} - c_{cyt})/L \). The numerical scheme can be written as:

\[ \frac{d\rho_\ell}{dt} = -\frac{1}{\Delta c} [g_\ell - g_{\ell-1}] + \text{[reaction terms]} \]

The advective term is solved through a second-order upwind method with \( g_\ell \) and \( g_{\ell-1} \) given by:

\[ g_\ell = \phi^*_\ell + \frac{1}{2} \psi^+_{\ell+\frac{1}{2}} \left( \phi_{\ell+1} - \phi^*_{\ell+\frac{1}{2}} \right) + \psi^-_{\ell+\frac{1}{2}} \left( \phi_{\ell+1} - \phi^*_{\ell+\frac{3}{2}} \right) \]

where \( \phi_\ell \) is the probability flux, \( \phi^*_{\ell+\frac{1}{2}} \) is the first order Roe flux, and \( \psi^+_{\ell+\frac{1}{2}}, \psi^-_{\ell+\frac{3}{2}} \) are Roe’s Superbee type flux limiters.
Appendix C: Parameters

The standard parameters used in the model simulations are listed in the table below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>Faraday’s constant</td>
<td>96,480 coul mol⁻¹</td>
</tr>
<tr>
<td>R</td>
<td>Gas Constant</td>
<td>8314 mJ mol⁻¹ K⁻¹</td>
</tr>
<tr>
<td>T</td>
<td>Absolute Temperature</td>
<td>310 K</td>
</tr>
<tr>
<td>P</td>
<td>Total permeability / unit specific capacitance</td>
<td>$7 \times 10^{-4}$ cm s⁻¹ cm⁻² µF⁻¹</td>
</tr>
<tr>
<td>V₀</td>
<td>L-Type Ca²⁺ channel activation threshold</td>
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</tr>
<tr>
<td>Cₘ</td>
<td>Capacitive membrane area</td>
<td>$1.534 \times 10^{-4}$ µF</td>
</tr>
<tr>
<td>cₑₓᵗ</td>
<td>Extracellular Ca²⁺ concentration</td>
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</tr>
<tr>
<td>c∞</td>
<td>Bulk Ca²⁺ concentration</td>
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</tr>
<tr>
<td>cₛₛ</td>
<td>Maximum Ca²⁺ concentration</td>
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</tr>
<tr>
<td>Aₘ</td>
<td>Capacitance surface to volume ratio</td>
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</tr>
<tr>
<td>Vₘ</td>
<td>Ca²⁺ activation half-max</td>
<td>-30 mV</td>
</tr>
<tr>
<td>Sₘ</td>
<td>Ca²⁺ activation dynamic range</td>
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</tr>
<tr>
<td>Tₘ</td>
<td>Time constant for Open Channels</td>
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</tr>
<tr>
<td>βₙₙ</td>
<td>Cytoplasmic buffering factor</td>
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</tr>
<tr>
<td>Vₙₚₚ</td>
<td>Cytoplasmic volume</td>
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<tr>
<td>βₙₙ</td>
<td>Domain buffering factor</td>
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<tr>
<td>Vₙ₂</td>
<td>Domain volume</td>
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</tr>
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<td>k⁻</td>
<td>Ca²⁺ de-inactivation rate constant</td>
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</tr>
<tr>
<td>k⁺</td>
<td>Ca²⁺ inactivation rate constant</td>
<td>3.6e-3 µm⁻¹ ms⁻¹</td>
</tr>
</tbody>
</table>

Appendix D: Derivation of $m_\infty(V)$

If $m$ represents the fraction of channels open at any time, and we consider only the open and closed states of a channel (with rates $\alpha$ and $\beta$ that may depend on voltage), then $m$ will satisfy the following ODE:
\[
\frac{dm}{dt} = \alpha (1 - m) - \beta m
\]

with a steady state given by \( m_\infty = \frac{\alpha}{\alpha + \beta} \). Consistent with prior work [11], \( m_\infty \) is given by the Boltzmann function:

\[
m_\infty = \frac{1}{1 + e^{\frac{V_m - V}{s_m}}}
\]

We set \( \tau_m = \frac{1}{\alpha + \beta}, \alpha = \frac{m_\infty}{\tau_m}, \) and \( \beta = \frac{1 - m_\infty}{\tau_m} \). Although \( \alpha \) and \( \beta \) are functions of voltage, we use \( \tau_m = 1.25 \text{ ms} \) as in prior work, and unsurprisingly, \( \alpha + \beta = 1/\tau_m \) is constant.
References


