Analysis of Spreading Depolarization as a Traveling Wave in a Neuron-Astrocyte Network

Thesis

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Abstract

We analyze an existing neuron-astrocyte network model of spreading depolarization propagated by extracellular $K^+$. We reduce the model to the form of a bistable diffusion equation in extracellular $K^+$ to understand how key parameters influence the underlying traveling wave solution. Our analysis suggests that, when coupled with the maintenance of astrocytic isopotentiality, increased astrocyte $K^+$ permeability and “instantaneously”-increased sodium-potassium pump strength effectively augment the resistance of the network to spreading depolarization.
Dedicated to my parents.
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Vita

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Fields of Study

Major Field: Mathematical Sciences
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Chapter 1: Introduction

Information is received and transmitted in the brain in the form of electrochemical signals propagated through networks of neurons. Neurons are primed to participate in these signaling processes through the maintenance of ionic gradients across the intracellular and extracellular spaces of the cell [5]. These gradients are mediated by the selective permeability of the neural membrane, and maintained by the ATP-fueled exchange of intracellular $Na^+$ and extracellular $K^+$ carried out by trans-membrane protein pumps [5]. These ionic gradients establish competing electrical and diffusive forces that balance to produce a resting electrical potential difference of approximately -70 mV across the cell membrane [5].

Neural signaling occurs when this stored energy is released in a brief depolarizing burst, or action potential [5]. The departure from the equilibrium potential is brief, lasting only 1 millisecond, and the magnitude of the ionic fluxes producing this depolarizing event is so small that the resting ionic gradients are largely maintained [3].

1.1 Spreading Depolarization

As explained in the reviews by Dreier [3] and Kramer [11], pathological insults to the brain may upset or strain normal homeostatic mechanisms and trigger prolonged loss of the resting potential in an area of the brain. Unlike in an action potential, such
damaging stimuli may trigger significant shifts in ionic balances, and recovery from depolarization is not necessarily immediate. An affected neuron may induce similar reactions in surrounding cells, initiating a spreading breakdown of ionic gradients and a cascading loss of neuronal membrane potentials in a phenomenon called spreading depolarization. During a spreading depolarization wave, the influx of ions into affected neurons leads to cell swelling, and extended depolarization prevents the firing of action potentials [3] [11].

Spreading depolarization has been observed to accompany a number of brain pathologies [11]. In traumatic brain injury, spreading depolarization occurs in an estimated 50-70% of patients, and is statistically associated with worse patient outcomes [11]. In a study of patients with aneurysmal subarachnoid hemorrhage (SAH), spreading depolarization was observed in roughly 70% of subjects, and is thought to be a possible causative agent in the onset of delayed cerebral ischemia [11], a commonly-associated and potentially fatal complication of SAH [11] [14]. In stroke, spreading depolarization can arise recurrently in the ischemic penumbra, and is associated with expansion of the ischemic core [11] [3].

The precise cause and mechanism of spreading depolarization is not fully understood. A hypothesis advanced by Grafstein implicates extracellular $K^+$ in the propagation of spreading depolarization waves [6] [13]. Spreading depolarization is associated with increased extracellular potassium [3] [13] [11]. In Grafstein’s theory, extrusion of $K^+$ into the extracellular space leads to neuronal depolarization, triggering further $K^+$ release. Diffusion of $K^+$ depolarizes neighboring cells, again triggering $K^+$ extrusion. This positive feedback loop produces a wave of $K^+$-induced spreading depolarization[6] [13].
If spreading depolarization emerges from extrusion of $K^+$, astrocytes may play a crucial role in influencing the onset and character of the resulting wave, since buffering of extracellular potassium is one of several functions [1] that astrocytes carry out to facilitate proper neural activity. Two major mechanisms for astrocytic $K^+$ buffering include net $K^+$ uptake and spatial buffering [10]. Active net $K^+$ uptake occurs via trans-membrane transporters, such as the sodium-potassium pump [1]. Spatial $K^+$ buffering describes a proposed clearance process in which locally elevated extracellular $K^+$ is passively taken up and shuttled through a network of astrocytes to be released at regions of lower $K^+$ [1] [10]. The effectiveness of this mechanism hinges on high astrocyte membrane permeability to potassium, and electrical coupling of neighboring astrocytes, which allows for the maintenance of approximate membrane isopotentiality to drive $K^+$ uptake and for the transfer of $K^+$ between cells[10] [1] [12].

In “Neuroprotective Role of Gap Junctions in a Neuron Astrocyte Network Model” (2016) [8], Huguet et al. use a biophysical model to examine the role of gap junctions in preventing spreading depolarization propagated by extracellular $K^+$. They showed that approximate isopotentiality conferred by gap junction coupling could facilitate astrocytic $K^+$ uptake and prevent spreading depolarization initiation in the presence of injected extracellular $K^+$. The model examined the influence of gap junction coupling strength and sodium-potassium pump strength (in both neuron and astrocyte) on spreading depolarization events.

In this study, we interrogate the model of Huguet et al. to understand additional factors that influence the initiation and propagation of $K^+$-induced spreading depolarization. In particular, we investigate the role that astrocyte potassium buffering plays in preventing wave propagation. We find that increased astrocytic membrane
potassium permeability is not sufficient for preventing spreading depolarization in the face of an initial potassium insult. However, when coupled with the maintenance of astrocytic isopotentiality, increased potassium permeability can successfully deter the initiation of spreading depolarization. We also investigate how changes to neuronal sodium-potassium pump activity influence the resistance of the system to spreading depolarization, and find that instantaneous reduction of the sodium-potassium pump strength decreases the threshold for wave initiation.
Chapter 2: The Model

We model a linear network of neuron-astrocyte cells, each with shared extracellular volume. The model follows that of Huguet (2016) [8], with some parameters changed (in bold) and gap junction currents removed. Differential equations describe the membrane potentials of the neuron $V_N$ and astrocyte $V_A$, as well as neuron, astrocyte, and extracellular $[Na^+]$ and $[K^+]$.

For each cell, the Hodgkin-Huxley equations [5] are used to model the neuron, which incorporates transient sodium ($I_{Na}$), persistent sodium ($I_{NaP}$), delayed rectifier potassium ($I_K$), sodium-potassium pump ($I_{NaK}$), and leak ($I_L$) currents ($\mu A/cm^2$). The membrane potential $V_N$ (mV) satisfies the differential equation:

$$c_M \frac{dV_N}{dt} = -(I_{Na} + I_{NaP} + I_K + I_L + I_{NaK}).$$

Neuron sodium and potassium concentrations (mM) satisfy the following equations:

$$\frac{d[K^+]}{dt} = - \frac{10S}{F_{Vol_N}}(I_K - 2I_{NaK})$$
$$\frac{d[Na^+]}{dt} = - \frac{10S}{F_{Vol_N}}(I_{Na} + I_{NaP} + 3I_{NaK})$$

Passive model currents in the Hodgkin-Huxley formulation are modeled following Ohm’s law, as the product of the membrane conductance and the electrical driving
force:

\[ I_{Na}(t) = g_{Na}(t)(V_N(t) - V_{Na}(t)) \]
\[ I_{NaP} = g_{NaP}(t)((V_N(t) - V_{Na}(t)) \]
\[ I_K = g_K(t)(V_N(t) - V_K(t)) \]
\[ I_L(t) = g_L(V_N(t) - V_L) \]

There is a fixed leak conductance \( g_L \). The ionic current conductances are given by the product of some maximal conductance \( \hat{g} \) and the fraction of open ion channels permitting the flow of each current:

\[ g_{Na}(t) = \hat{g}_{Na}m_{\infty}^3(1 - n) \]
\[ g_{NaP}(t) = \hat{g}_{NaP}m_{p\infty}h_p \]
\[ g_K(t) = \hat{g}_K n^4. \]

The channel gating terms \( m_{\infty}, n, m_{p\infty}, \) and \( h_p \) together determine the fraction of activated channels for each current.

The fast sodium and potassium currents are modeled after the Hodgkin-Huxley equations. In the fast \( Na^+ \) current, the \( m \)-gate is assumed to approach \( m_{\infty} \) instantaneously, and the inactivation gate \( h \) from the Hodgkin-Huxley formulation is approximated by \( (1 - n) \), as in Butera et al. [2].

The persistent \( Na^+ \) current is modeled following that of Model 1 in Butera et al. [2]. The \( m_p \) gating variable is assumed to instantaneously converge to its steady state \( m_{p\infty} \).
As in the Hodgkin-Huxley formulation, the gating variable $X$ satisfies a differential equation of the form

$$\frac{dX}{dt} = \frac{X_\infty(V_N) - X}{\tau_X(V_N)}.$$ 

Thus, for fixed $V_N$, $\tau_X(V_N)$ determines the rate at which $X$ approaches the steady state value $X_\infty(V_N)$.

The steady state values are dependent on the membrane potential, and are given by

$$m_\infty(V_N) = \frac{1}{1 + e^{-(V_N-\theta_m)/\sigma_m}},$$
$$n_\infty(V_N) = \frac{1}{1 + e^{-(V_N-\theta_n)/\sigma_n}},$$
$$m_{p_\infty}(V_N) = \frac{1}{1 + e^{-(V_N-\theta_{mp})/\sigma_{mp}}},$$
$$h_{p_\infty}(V_N) = \frac{1}{1 + e^{-(V_N-\theta_{hp})/\sigma_{hp}}},$$

where $\theta_m = -34$, $\sigma_m = 5$, $\theta_n = -55$, $\sigma_n = 14$, $\theta_{mp} = -40$, $\sigma_{mp} = 6$, $\theta_{hp} = -48$, and $\sigma_{hp} = -6$.

The time constants are given by

$$\phi_n\tau_n(V_N) = \tau_{n_0} + \frac{\tau_{n_1}}{1 + e^{-(V_N-\theta_{n_\tau})/\sigma_{n_\tau}}},$$
$$\phi_{h}\tau_{h_\tau}(V_N) = \frac{\tau}{\cosh((V_N - V_{h_\tau})/(2\sigma_{h_\tau}))},$$

where $\tau_{n_0} = 0.05$, $\tau_{n_1} = 0.27$, $\theta_{n_\tau} = -40$, $\sigma_{n_\tau} = -12$, $\tau = 10000$, $V_{h_\tau} = -48$, and $\sigma_{h_\tau} = 6$.

The electrical driving force for each ionic current is given by the difference between the membrane potential and the Nernst potential $V_X$ of the ion $X$. The Nernst potential (mV) describes the membrane potential for which the intracellular and
extracellular concentrations of a given ion are at equilibrium, assuming the membrane is not permeable to other ions [5]. It is given by

\[ V_X = \frac{RT}{F} \log \left( \frac{[X_e]}{[X_i]} \right), \]

where \( R = 8.310 \text{ J/(mol K)} \) is the ideal gas constant, \( T = 310 \text{ K} \) is the temperature in Kelvins, and \( F = 96485 \text{ C/mol} \) is Faraday’s constant. Note, here \( V_X \) must be multiplied by 1000 to convert from V to mV.

The sodium-potassium pump current is given by

\[ I_{NaK} = \frac{\rho_N}{(1 + \frac{2}{K^+_e})(1 + \frac{T}{Na^+_i})^3}, \]

where \( \rho_N \) (\( \mu \text{A/cm}^2 \)) is the maximal current through the pump. The form of the current is based on the pump current used in Kager et al. [9].

The astrocyte membrane potential \( V_A \) (mV) is dependent on a sodium current, potassium current, and sodium-potassium pump:

\[ c_M \frac{dV_A}{dt} = -(I_{Na}^A + I_K^A + I_{NaK}^A) \]

Astrocyte sodium and potassium concentrations (mM) satisfy the following equations:

\[ \frac{d[K^+]_i^A}{dt} = -\frac{10S_A}{F \text{vol}_A} (I_K^A - 2I_{NaK}^A) \]

\[ \frac{d[Na^+]_i^A}{dt} = -\frac{10S_A}{F \text{vol}_A} (I_{Na}^A + 3I_{NaK}^A) \]

The sodium and potassium currents (\( \mu \text{A/cm}^2 \)) are modeled using the Goldman-Hodgkin-Katz equations [5]

\[ I_K^A = p_K F \phi_A \left( \frac{[K_e]^+ e^{-\phi_A} - [K_i^A]^+}{e^{-\phi_A} - 1} \right) \]

\[ I_{Na}^A = p_{Na} F \phi_A \left( \frac{[Na_e]^+ e^{-\phi_A} - [Na_i^A]^+}{e^{-\phi_A} - 1} \right), \]
where $\phi_A = V_A \frac{F}{RT}$.

The astrocyte sodium-potassium exchanger ($\mu\text{A}/\text{cm}^2$) has the same form as that of the neuron pump:

$$I_{NaK}^A = \frac{\rho_A}{(1 + \frac{2}{K_c})(1 + \frac{10}{Na_i})^3},$$

where $\rho_A$ ($\mu\text{A}/\text{cm}^2$) is the maximal current flux through the pump.

Ionic currents and diffusion determine the changes in extracellular sodium and potassium concentrations:

$$\frac{\partial [K^+]_e}{\partial t} = D_K \frac{\partial^2 [K^+]_e}{\partial x^2} + \frac{10S}{F_{vol_e}} (I_K - 2I_{NaK})$$
$$\frac{\partial [Na^+]_e}{\partial t} = D_{Na} \frac{\partial^2 [Na^+]_e}{\partial x^2} + \frac{10S}{F_{vol_e}} (I_{Na} + I_{Na,p} + 3I_{NaK}),$$

where the $K^+$ diffusion constant $D_K = 1.96 \times 10^{-5}$ cm$^2$/s [7], and we take the simplification $D_{Na} = 0$. Note we have assumed that the extracellular space is continuous. For simulations of the discrete network, we approximate diffusion using the second-order central finite difference, with a discrete constant of diffusion $\hat{D}_K = 0.001$ ms$^{-1}$ and $h \approx 0.044$ mm the distance between cells.

The extracellular volume is given by $vol_e = \delta vol_N$ (note, the original model used $vol_e = \delta (vol_N + vol_A)$).
<table>
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<th>Notation</th>
<th>Value</th>
<th>Unit</th>
<th>Description</th>
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<tr>
<td>$R$</td>
<td>8.31</td>
<td>J/mol K</td>
<td>Ideal gas constant</td>
</tr>
<tr>
<td>$T$</td>
<td>310</td>
<td>K</td>
<td>Temperature</td>
</tr>
<tr>
<td>$F$</td>
<td>96485</td>
<td>C/mol</td>
<td>Faraday’s constant</td>
</tr>
<tr>
<td>$S$</td>
<td>922</td>
<td>$\mu$m$^2$</td>
<td>Neuron surface area</td>
</tr>
<tr>
<td>$S_A$</td>
<td>1600</td>
<td>$\mu$m$^2$</td>
<td>Astrocyte surface area</td>
</tr>
<tr>
<td>$vol_N$</td>
<td>2160</td>
<td>$\mu$m$^3$</td>
<td>Neuron volume</td>
</tr>
<tr>
<td>$vol_A$</td>
<td>2000</td>
<td>$\mu$m$^3$</td>
<td>Astrocyte volume</td>
</tr>
<tr>
<td>$\delta$</td>
<td>0.1</td>
<td></td>
<td>Extrac. volume fraction of neuron vol.</td>
</tr>
<tr>
<td>$\hat{g}_{Na}$</td>
<td>50.0</td>
<td>mS/cm$^2$</td>
<td>Maximal fast $Na^+$ conductance</td>
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<tr>
<td>$\hat{g}_{NaP}$</td>
<td>0.8</td>
<td>mS/cm$^2$</td>
<td>Maximal persistent $Na^+$ conductance</td>
</tr>
<tr>
<td>$\hat{g}_{K}$</td>
<td>15</td>
<td>mS/cm$^2$</td>
<td>Maximal $K^+$ conductance</td>
</tr>
<tr>
<td>$g_L$</td>
<td>0.5</td>
<td>mS/cm$^2$</td>
<td>Leak conductance</td>
</tr>
<tr>
<td>$c_M$</td>
<td>1</td>
<td>$\mu$F/cm$^2$</td>
<td>Specific membrane capacitance</td>
</tr>
<tr>
<td>$\phi_n$</td>
<td>0.8</td>
<td>ms$^{-1}$</td>
<td>$n$-gate rate constant</td>
</tr>
<tr>
<td>$\phi_h$</td>
<td>0.05</td>
<td>ms$^{-1}$</td>
<td>$h_p$-gate rate constant</td>
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<tr>
<td>$\rho_N$</td>
<td></td>
<td>$\mu$A/cm$^2$</td>
<td>Maximal neuron $Na^+$-$K^+$ pump current</td>
</tr>
<tr>
<td>$p_{Na}$</td>
<td>$1.5 \times 10^{-8}$</td>
<td>cm/s</td>
<td>Astrocyte $Na^+$ permeability coefficient</td>
</tr>
<tr>
<td>$p_K$</td>
<td></td>
<td>cm/s</td>
<td>Astrocyte $K^+$ permeability coefficient</td>
</tr>
<tr>
<td>$\rho_A$</td>
<td>5</td>
<td>$\mu$A/cm$^2$</td>
<td>Maximal astrocyte $Na^+$-$K^+$ pump current</td>
</tr>
</tbody>
</table>

Table 2.1: Model Parameters
Chapter 3: Analysis

3.1 Mathematical Traveling Waves

Spreading depolarization recalls wave propagation, and we apply the mathematical concept of traveling waves to better understand our model. One-dimensional mathematical traveling waves arise as solutions to partial differential equations of the form

\[
\frac{\partial u}{\partial t} = f(u) + \frac{\partial^2 u}{\partial x^2},
\]

(3.1)

where \( f(u) \) has a cubic shape intersecting the \( u \)-axis at three points [5]. An equation of this form is referred to as a scalar bistable diffusion equation, bistable because in the absence of the diffusive term, the particular cubic shape of \( f \) implies that the system exhibits two stable fixed points. Traveling wave solutions are characterized by a fixed spatial profile that is translated in time, connecting the lower and upper fixed points of \( f(u) \) as \( x \to \pm \infty \) [5].

For example, let \( f(u) = u(1-u)(u-a) \), where \( 0 < a < \frac{1}{2} \). One can show that there exists a traveling wave solution with a fixed wave profile \( U \), where

\[
\lim_{z \to -\infty} U(z) = 0,
\]

\[
\lim_{z \to \infty} U(z) = 1.
\]
Put $\xi = x + ct$. Then taking $u(x,t) = U(\xi)$ and substituting into (3.1) yields the ordinary differential equation

$$c \frac{dU}{d\xi} = f(U) + \frac{d^2U}{d\xi^2}. \quad (3.2)$$

Letting $\frac{dU}{d\xi} = W$, we can reduce (3.2) to the first order system

$$\frac{dU}{d\xi} = W \quad (3.3)$$
$$\frac{dW}{d\xi} = cW - f(U). \quad (3.4)$$

The fixed points $(U^*, W^*)$ are $(0,0)$, $(a,0)$, and $(1,0)$, given by the zeroes of $f$. A traveling wave solution of the original PDE is a heteroclinic orbit connecting the two fixed points $(0,0)$ and $(1,0)$ of the nonlinear system (3.3-4). One can prove that such an orbit exists for a unique wave speed $c$ [5].

Multiplying 3.2 by $\frac{dU}{d\xi}$ and integrating, we arrive at an expression for $c$ [5]:

$$c \int_{-\infty}^{\infty} (\frac{dU}{d\xi})^2 d\xi = \int_{-\infty}^{\infty} \frac{dU}{d\xi} (f(U) + \frac{d^2U}{d\xi^2}) d\xi$$
$$= \int_0^1 f(u) du + \int_{-\infty}^{\infty} \frac{1}{2} \left( \frac{dU}{d\xi} \right)^2 d\xi$$
$$= \int_0^1 f(u) du + \frac{1}{2} \left( \frac{dU}{d\xi} \right)^2 \bigg|_{-\infty}^{\infty}$$
$$= \int_0^1 f(u) du$$
$$\Rightarrow c = \int_0^1 f(u) du / \int_{-\infty}^{\infty} (\frac{dU}{d\xi})^2 d\xi.$$

Solving the expression on the right gives the unique wave speed for which a traveling wave solution exists for 3.1. Since the denominator is always positive, the integral $F = \int_0^1 f(u) du$ in the numerator determines the direction of the wave. We observe that the wave travels left ($c > 0$) for $\int_0^1 f(u) du > 0$, the wave travels right for $\int_0^1 f(u) du < 0$ ($c < 0$), and the wave is stationary for $\int_0^1 f(u) du = 0$ [5].
3.2 Model Reduction

The discrete network is computationally slow and not particularly amenable to analysis. In order to understand the influence of various parameters on the model, we reduce the full model to a single reaction-diffusion equation in $[K^+]_e$. The reduced equation admits traveling wave solutions, and the effect of various parameters on the character of the wave provides insight into the behavior of the full system.

We assume a continuous, unbounded network of neuron-astrocyte cells, yielding the following system of partial differential equations:

$$
\frac{\partial V_N}{\partial t} = \Phi_{V_N} \\
\frac{\partial V_A}{\partial t} = \Phi_{V_A} \\
\frac{\partial [K^+]_i}{\partial t} = \Phi_{[K^+]_i} \\
\frac{\partial [Na^+]_i}{\partial t} = \Phi_{[Na^+]_i} \\
\frac{\partial [K^+]_A}{\partial t} = \Phi_{[K^+]_A} \\
\frac{\partial [Na^+]_A}{\partial t} = \Phi_{[Na^+]_A} \\
\frac{\partial [K^+]_e}{\partial t} = \Phi_{[K^+]_e} + D_K \frac{\partial^2 [K^+]_e}{\partial x^2} \\
\frac{\partial [Na^+]_e}{\partial t} = \Phi_{[Na^+]_e} + D_{Na} \frac{\partial^2 [Na^+]_e}{\partial x^2} \\
\frac{\partial n}{\partial t} = \phi_n n_{\infty}(V) - n \\
\frac{\partial h_p}{\partial t} = \phi_h h_{p\infty}(V) - h_p,
$$

where $\Phi_X$ represents the reaction (non-diffusion) terms for the differential equations of each species $X$, as defined in Chapter 2.

To reduce our model to the form of the bistable diffusion equation, we note that the spreading depolarization wave is propagated through diffusion of extracellular
Since $Na^+$ is not essential to the propagation of the wave, we take $[Na^+]_e$, and $[Na^+]_A^A$ to be constant. Additionally, $vol_e$ small compared to $vol_A$ implies that large changes to $[K^+]_e$ are accompanied by relatively small changes to $[K^+]_A^A$, so we also take $[K^+]_A^A$ to be constant. Assuming conservation of ions at each point in $(x,t)$, we arrive at an expression for $[K^+]_i$ in terms of $[K^+]_e$:

$$[K^+]_i = \frac{1}{vol_N} (K^+_i - vol_e[K^+]_e - vol_A[K^+]_A^A),$$

where $K^+_i$ is determined by initial potassium concentrations in the neuron $[K^+]_i^0$, astrocyte $[K^+]_A^A$, and extracellular space $[K^+]_e^0$:

$$K^+_i = vol_N[K^+]_i^0 + vol_A[K^+]_A^A + vol_e[K^+]_e^0.$$

For our results, we use $[K^+]_i^0 = [K^+]_A^A = 135$, and $[K^+]_e^0 = 3.5$.

Similarly, for $[Na^+]_i$, we have

$$[Na^+]_i = \frac{1}{vol_N} (Na^+_i - vol_e[Na^+]_e - vol_A[Na^+]_A^A),$$

where

$$Na^+_i = vol_N[Na^+]_i^0 + vol_A[Na^+]_A^A + vol_e[Na^+]_e^0,$$

and $[Na^+]_i^0 = [Na^+]_A^A = 3.5$, and $[Na^+]_e^0 = 135$.

We eliminate the differential equations for the gating variables by letting $n = n_\infty$, and taking $h_p$ a fixed constant (the convergence of $h_p$ to $h_{p,\infty}$ is slow).

This leaves the 3-equation reduced system

$$\frac{\partial V_N}{\partial t} = \Phi_{V_N},$$

$$\frac{\partial V_A}{\partial t} = \Phi_{V_A},$$

$$\frac{\partial [K^+]_e}{\partial t} = D_K \frac{\partial^2 [K^+]_e}{\partial x^2} + \Phi_{[K^+]_e}.$$
Since $V_N$ and $V_A$ are fast relative to $[K^+]_e$, we take $V_N$ and $V_A$ satisfying $\Phi_{V_N} = 0 = \Phi_{V_A}$, and we are left with a single PDE:

$$\frac{\partial [K^+]_e}{\partial t} = D_K \frac{\partial^2 [K^+]_e}{\partial x^2} + \Phi_{[K^+]_e}.$$

This is a reaction-diffusion equation, and a traveling wave solution $[K^+]_e(x, t) = [K^+]_e(x + ct)$ for some $c$ is admitted for $\Phi_{[K^+]_e}$ of the appropriate cubic form.
Chapter 4: Analysis of the Cubic $\Phi_{[K^+]_e}$

Traveling wave solutions in $[K^+]_e$ for the reduced, continuous model are determined in large part by the form of $\Phi_{[K^+]_e}$. In particular, the integral of the cubic determines the direction of wave translation, and the fixed points of the cubic determine the limits in $[K^+]_e$ of the wave profile. The speed of the wave is also influenced by $\Phi_{[K^+]_e}$. In addition to the relationship between the cubic and the traveling wave solution, $\Phi_{[K^+]_e}$ determines the diffusion-independent flow of $[K^+]_e$ for each cell of the discrete network. For these reasons, we are interested in how the shape of the cubic is altered by changes to key parameters in the model.

4.1 Numerical Computation of $\Phi_{[K^+]_e}$

We compute $\Phi_{[K^+]_e}$ using the 4th-order Runge-Kutta method in XPPAUT [4]. We let $V_N$ and $V_A$ satisfy the differential equations as in the 3-dimensional reduced system. Since $\Phi_{V_N}$ and $\Phi_{V_A}$ are large, we let

$$\frac{d[K^+]_e}{dt} = \epsilon$$

$$[K^+]_e(0) = 1,$$
where $\epsilon = 0.001$. Since $[K^+]_e$ increases slowly, $V_A$ and $V_N$ approach their steady state values for each value of $[K^+]_e$. To compute $\Phi_{[K^+]_e}$, we let

$$\frac{dy}{dt} = \Phi_{[K^+]_e} - y$$

$$y(0) = 0.$$

Since $[K^+]_e$ increases slowly, $y$ stays near $\Phi_{[K^+]_e}$ for each value of $[K^+]_e$.

### 4.2 Dependence on Astrocyte Potassium Buffering ($p_K$)

As noted previously, astrocytes play a critical role in extracellular $K^+$ homeostasis [1] [10]. In our reduced model, $p_K$ scales the magnitude of potassium flux through astrocyte potassium channels, and changes to $p_K$ can dramatically alter the form of $\Phi_{[K^+]_e}$.

In Fig. 4.1, we plot the integral of $\Phi_{[K^+]_e}$ (with upper $a$ and lower $b$ limits equal to the upper and lower fixed points of $\Phi_{[K^+]_e}$) for 13 values of $p_K$, with each value increasing by a factor of 2 between $p_K = 1 \times 10^{-8}$ and $p_K = 4.096 \times 10^{-5}$. For each value of $p_K$, the cubic is computed with $h$, $[Na^+]_e$, $[Na^+]_i$, and $[K^+]_i$ fixed at the steady state values for the network system with a single cell. We use $\rho_N = 5$.

In red, we plot $\int_a^b \Phi_{[K^+]_e}$. We observe that $\int_a^b \Phi_{[K^+]_e} \approx 9.1$ for $p_K = 1 \times 10^{-8}$, and levels off for increasing values of $p_K$ to $\int_a^b \Phi_{[K^+]_e} \approx 8.7$. This corresponds to wave solutions in which the upper fixed point of the cubic dominates ($[K^+]_e \rightarrow a$ for all $x$). This suggests that for each value of $p_K$, the astrocyte fails to serve as an adequate sink for extracellular potassium. The inability of the astrocyte to buffer $[K^+]_e$ in the model is rooted in the relationship between the astrocytic potassium current and $V_A$. 

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We recall that

\[ I_K^A = p_K F \phi_A \left( \frac{[K_e]^+ e^{-\phi_A} - [K_A]^+}{e^{-\phi_A} - 1} \right) \]

where \( \phi_A = V_A \frac{F}{RT} \). Buffering of \([K^+]_e\) is achieved through an inward current, which requires \( I_K^A < 0 \). The more negative the current, the greater rate of \([K^+]_e\) uptake into the astrocyte. A strongly inward current is achieved by the combination of elevated \([K^+]_e\) and strongly negative \( V_A \). However, increasing \([K^+]_e\) also serves to increase \( V_A \). As \( V_A \) becomes less negative, the threshold of elevated \([K^+]_e\) at which \( I_K^A \) turns inward increases. Increasing \( V_A \) also decreases the magnitude of any inward current, so in the event \( I_K^A \) does become negative, astrocytic potassium uptake may occur at a rate too slow to prevent the propagation of an elevated \([K^+]_e\) wave.

Gap junction coupling between astrocytes allows for the maintenance of roughly isopotential \( V_A \) throughout a network of astrocytes, despite dramatic changes to local \( K^+ \) equilibrium potential [12]. To simulate the isopotentiality of an astrocyte syncytium, we plot \( \Phi_{[K^+]_e} \) for fixed \( V_A \), where \( V_A \) is taken near its one-cell steady state value (Fig. 4.1, blue). In this case, changing \( p_K \) causes \( \int_a^b \Phi_{[K^+]_e} \) to decrease in a fashion similar to exponential decay. For \( p_K \) sufficiently large, the integral becomes negative, and the direction of the traveling wave solution is flipped. Here, the low \([K^+]_e\) fixed point becomes the dominant stable state in the system, corresponding to no propagation of an elevated \([K^+]_e\) wave. The maintenance of a polarized \( V_A \) ensures that \( I_K^A \) becomes negative more quickly in response to increasing \([K^+]_e\). For increasing \( p_K \), the magnitude of this inward current increases, which leads to a decrease in the upper fixed point of the cubic and a corresponding decrease in the value of the integral.
Figure 4.1: Value of $\int_a^b \Phi_{[K^+]_e}$ for varying $p_K$ and fixed (blue) or varying (red) $V_A$.

Taken together, the changes to the shape of $\Phi_{[K^+]_e}$ suggests that increasing $p_k$ alone has little influence on wave initiation and propagation. However, if isopotentiality is maintained in the astrocyte network, increasing $p_k$ makes the system steadily more resistant to the propagation of an elevated $[K^+]_e$ wave, and associated spreading depolarization.

4.3 Dependence on Sodium-Potassium Pump Strength ($\rho_N$)

Since the energy-dependent activity of the sodium-potassium pump is necessary for the maintenance of neuronal homeostasis [5], we seek to examine the effect of the maximal sodium-potassium exchange rate, $\rho_n$, on the resulting traveling wave
solution. For $\rho_N = 5, 10, 15, \ldots, 50$, we take $p_K = 1 \times 10^{-6}$ and fix $h_p, [Na^+]_e, [Na^+]_i^A, [K^+]_i^A$, and $V_A$ at the steady state values of the associated one-cell system. In Figure 4.2 (A), we observe that $\int_a^b \Phi_{[K^+]_e}$ increases as $\rho_N$ is increased. Moreover, in (B) we see that the lower and middle zeroes of $\Phi_{[K^+]_e}$ decrease very slightly for increasing $\rho_N$, but the upper zeroes increase sizably. Thus, the system admits traveling wave solutions with increasingly elevated maximal $[K^+]_e$, while the threshold beyond which $[K^+]_e$ increases to its elevated fixed point decreases slightly. This suggests that, as $\rho_N$ increases, the corresponding steady state of the system becomes more amenable to the spreading propagation of elevated $[K^+]_e$.

Since sudden energy deficit represents a pathological disruption from a normal resting state, we may ask how changes to $\rho_N$ affect $\Phi_{[K^+]_e}$ for a shared set of fixed parameters, instead of at each $\rho_N$-specific steady state. Letting $p_K = 1 \times 10^{-6}$ and $\rho_N = 5$, we fix $h_p, [Na^+]_e, [Na^+]_i^A, [K^+]_i^A$, and $V_A$ at the steady state values of the one-cell system. Now varying $\rho_N$ between 5 and 50, we observe that “instantaneous” increase of $\rho_N$—simulating sudden recovery or increased energy supply—decreases $\int_a^b \Phi_{[K^+]_e}$, gradually for $\rho_N \in [5, 25]$ and more rapidly as $\rho_N$ is increased further (Fig. 4.3 A). For $\rho_N = 5$ we have $\int_a^b \Phi_{[K^+]_e} \approx 5.7$. For $\rho_N = 50$, however, we have $\int_a^b \Phi_{[K^+]_e} \approx 0.33$.

Additionally, the middle fixed point of $\Phi_{[K^+]_e}$ increases roughly exponentially for increasing $\rho_N$ (Fig. 4.3 B). In Figure 4.4, we plot $\Phi_{[K^+]_e}$ for $\rho_N = 5, 40, 50$, and observe that $\Phi_{[K^+]_e}$ appears to follow two distinct curves, with a “jump-up” transition between them that occurs for successively larger values of $[K^+]_e$ as $\rho_N$ increases. Since the upper fixed points change only slightly (from $[K^+]_e \approx 129$ for $\rho_N = 5$ to $[K^+]_e \approx 122$ for $\rho_N = 50$), instantaneously increasing $\rho_N$ from 5 to 50 does little to change the
upper \([K^+]_e\) state of the traveling wave solution. However, the dramatic increase in the middle fixed point of \(\Phi_{[K^+]_e}\) implies that increasing \(\rho_N\) effectively increases the \([K^+]_e\) threshold for wave initiation.
Figure 4.2: $\Phi_{[K^+]}$ is computed with $p_K = 1 \times 10^{-6}$ and $h_p$, $[Na^+]_e$, $[Na^+]_i$, $[K^+]_i$, and $V_A$ fixed at the steady state values of the corresponding single-cell system. (A) $\int_a^b \Phi_{[K^+]}$ increases for increasing $\rho_N$. (B) Lower (blue), middle (red), and upper (green) zeroes of $\Phi_{[K^+]}$ are plotted for increasing $\rho_N$. Lower and middle zeroes decrease slightly as $\rho_N$ increases, while the high fixed points increase significantly.
Figure 4.3: $\Phi_{[K^+]_e}$ is computed for each $\rho_N$ with $h_p$, $[Na^+]_e$, $[Na^+]_i^A$, $[K^+]_i^A$, and $V_A$ fixed at the steady state values of the single-cell system obtained with $p_K = 1 \times 10^{-6}$ and $\rho_N = 5$. (A) $\int_a^b \Phi_{[K^+]_e}$ decreases for increasing $\rho_N$. (B) Lower (blue), middle (red), and upper (green) zeroes of $\Phi_{[K^+]_e}$ for increasing $\rho_N$. Lower and upper zeroes decrease as $\rho_N$ increases, while the middle fixed points increase in an exponential shape.
Figure 4.4: $\Phi_{[K^+]_e}$ for $\rho_n = 5, 40, 50$. $\Phi_{[K^+]_e}$ is computed for each $\rho_N$ with $h_p$, $[Na^+]_e$, $[Na^+]_i^A$, $[K^+]_i^A$, and $V_A$ fixed at the steady state values of the single-cell system obtained with $p_K = 1 \times 10^{-6}$ and $\rho_N = 5$. $\Phi_{[K^+]_e}$ roughly follows the shape of two curves, with $\rho_N$ modulating the point at which $\Phi_{[K^+]_e}$ records a steep “jump-up” to transition from one curve to the other. Increased $\rho_N$ increases the value of $[K^+]_e$ at which this jump-up occurs.
Chapter 5: The Cubic Approximates the Behavior of the Discrete Network

There are substantial differences between the reduced, continuous model and the discrete network. The reduced model admits a traveling wave connecting low $[K^+]_e$ and elevated $[K^+]_e$ steady states, while the discrete network admits traveling "pulses", where neuronal depolarization is followed by a return to the resting state. We think of the continuous model as an approximation to the wave “front” of a given traveling pulse solution to the discrete network, and despite the significant approximations used to obtain $\Phi_{[K^+]_e}$, we find that the cubic allows us to make predictions regarding the behavior of the discrete network.

All simulations are executed in XPPAUT [4], using the 4th order Runge-Kutta method.

For the following results, we simulate the linear network using 30 cells and Neumann boundaries.

A representative solution for the discrete network, using $\rho_N = 5$, $p_K = 1 \times 10^{-6}$, and remaining parameters as in Table 2.1 is shown in Figure 5.1. With the exception of compartments 1-4, all dynamic quantities in each compartment are initialized at their one-cell steady state values. In cells 1-4, we simulate an initial potassium insult with elevated $[K^+]_e = 19$, $V_N = -49$, and $V_A = -51.18$. We also let $[K^+]_i = 135.2903$ in
cells 1-4 to maintain equal initial total $K^+$ in each cell of the network. We observe that elevated $[K^+]_e$ in the first four cells initiates a wave of elevated $[K^+]_e$ that propagates through the network, along with an associated wave of spreading depolarization.

Figure 5.1: Solution arrays for 30-compartment network with parameters as in Table 2.1, $\rho_N = 5$, $p_K = 1 \times 10^{-6}$.

In Figure 5.2, we isolate the behavior of cell 15 of the array and plot selected dynamic quantities over the first 20 seconds of the simulation. We observe that the cell remains at steady state until the arrival of the spreading potassium wave triggers a sharp increase in $[K^+]_e$ (b). This is accompanied by a rapid and prolonged neuronal depolarization (a), a sharp drop in $[Na^+]_e$ (c), and prolonged astrocyte depolarization (e).
Figure 5.2: 20-second solution for selected elements of compartment 15 of the discrete network, with the same parameters and initial conditions used to generate Fig. 5.1.

5.1 Dependence on Astrocyte Potassium Buffering ($p_K$)

The scalar equation provides cues for understanding the behavior of the discrete system. In the scalar equation, we recall that changes to $p_K$ alone have little effect
on the integral of the cubic or the stable states of the traveling wave solution. For the discrete model, we expect that the speed with which spreading depolarization propagates through the system will similarly be largely unaffected by changes in $p_K$. In Figure 5.3, we plot in blue the wave speed as a function of $p_K$ for the network model. For each trial, an initial $K^+$ insult is simulated with initial elevated $[K^+]_e = 20$ in cells 1-4 ($[K^+]_i$ is adjusted accordingly, as before). All other variables are initialized at the respective steady state values for the one-cell system, taking $\rho_N = 5$. Just as varying $p_K$ was largely inconsequential for the traveling wave solution admitted by the bistable diffusion equation, wave speed in the discrete model is virtually unchanged for $p_K$ between $1 \times 10^{-8}$ and $4.096 \times 10^{-5}$. The minimum and maximum recorded speeds span a range of roughly 0.25 mm/min. (We note that all recorded speeds lie within the typical range of 2-6 mm/min [3]).

By contrast, when $V_A$ was fixed in the scalar case to simulate astrocyte isopotentiality, changes to $p_K$ did have a large impact on the resulting traveling wave solution. We recall that increasing $p_K$ decreased $\int_a^b \Phi_{[K^+]_e}$ roughly exponentially. We repeat the previous simulations for the discrete network, this time maintaining $V_A$ at its single-cell steady state for each value of $p_K$. Increasing $p_K$ in conjunction with the maintenance of astrocyte isopotentiality produces a gradual decline in the speed of the resulting wave, until for trials with $p_K \geq 2.56 \times 10^{-6}$, a wave fails to initiate altogether (Fig 5.3, green curve). Thus, it holds also in the full network model that neither increased $p_K$ nor astrocyte isopotentiality alone are necessarily sufficient, but both must exist in conjunction to deter the propagation of a wave of spreading depolarization.
5.2 Dependence on Sodium-Potassium Pump Strength ($\rho_N$)

Next, we recall that changes to $\rho_N$ had varying effects on the traveling wave in the scalar bistable case, depending on the choice of parameters. With $V_A$, $h_p$, $[Na^+]_e$, $[Na^+]_i^A$, and $[K^+]_i^A$ taken at their $\rho_N$-specific, single-cell steady state values, increasing $\rho_N$ produced increasing values of $\int_a^b \Phi_{[K^+]_e}$, reduced $[K^+]_e$ thresholds for wave initiation, and increased upper $[K^+]_e$ fixed points. However, when the cubic was computed for varying $\rho_N$ while $V_A$, $h_p$, $[Na^+]_e$, $[Na^+]_i^A$, and $[K^+]_i^A$ were fixed at the $\rho_N = 5$ steady state values, increasing $\rho_N$ sharply decreased the value of $\int_a^b \Phi_{[K^+]_e}$ while increasing the middle fixed point of $\Phi_{[K^+]_e}$.
We observe a corresponding phenomenon for the wave speeds of the discrete network. As in the previous section, for each value of $\rho_N$ we initialize the network with elevated $[K^+]_e = 20$ in the first four cells (again adjusting $[K^+]_i$ accordingly), and all other dynamic variables at the single-cell steady state values, with $p_k = 1 \times 10^{-6}$. We plot the resulting wave speeds for each $\rho_N = 5, 10, \ldots, 50$ in Figure 5.4 (blue curve), and observe that wave speed increases for increasing $\rho_N$. For $\rho_N = 50$, a wave is propagated through the network at a rate of approximately 6.19 mm/min.

However, the opposite effect on wave speed is observed when $\rho_N$ is varied while the initial conditions are unchanged. We initialize the network with elevated $[K^+]_e = 20$ in the first four cells, $p_k = 1 \times 10^{-6}$, and the remaining initial conditions according to the single-cell steady states for $\rho_N = 5$. As $\rho_N$ is increased “instantaneously”, simulating sudden recovery, wave speed decreases. For $\rho_N = 20, 25, \ldots, 50$, wave initiation does not occur (Figure 5.4, green curve). Thus, as in the case of the scalar equation, instantaneous increase in $\rho_N$ of sufficient magnitude can prevent the initiation of a wave of elevated $[K^+]_e$ and associated spreading depolarization. We recall that, in the scalar case, instantaneous increase in $\rho_N$ increased the middle fixed point of the cubic. Our results suggest that the threshold for wave initiation in the network model similarly increased gradually with instantaneously increasing $\rho_N$. When the threshold exceeded the initial $[K^+]_e$ insult, wave initiation was suppressed.
Figure 5.4: Wave speeds of the discrete network for changing $\rho_N$, computed with fixed $V_A$. Speeds for instantaneous changes to $\rho_N$ (all simulations share a common set of initial condition, obtained for $\rho_N = 5$ in the single-cell system) are given in green, while speeds for $\rho_N$-specific initial conditions are given in blue. Wave speeds of 0 indicate failure to initiate a spreading depolarization wave.
Chapter 6: Discussion

We have investigated the simple biophysical model of Huguet et al. [8] for $[K^+]_e$-induced spreading depolarization, and presented a reduced approximation of the model using the concept of mathematical traveling waves. Examination of $\Phi_{[K^+]_e}$ in the scalar bistable equation produced qualitative predictions for the behavior of the full discrete network. Our studies suggest that astrocytic potassium channels may play an important role in the suppression of spreading depolarization waves, and underscored the functional importance of the maintenance of isopotentiality amongst networks of astrocytes. We also observed that instantaneous increase in sodium-potassium pump strength effectively increases the threshold for wave propagation in both the discrete and continuous models.

In Huguet et al. [8], numerical simulation of a neuron-astrocyte network was carried out in order to understand the role of gap junctions in the initiation and propagation of spreading depolarization. The authors showed that isopotentiality achieved by astrocytic gap junctions can increase the resistance of a linear network of neuron-astrocyte cells to wave propagation. However, once a wave is initiated, gap junction connectivity may increase the speed of the wave. We depart from this study by introducing the mathematical traveling wave as a tool for analysis. This provides a conceptual framework for analyzing how changing astrocyte potassium permeability
influences wave propagation, which is not carried out in [8]. Focusing on the relationship between the reduced scalar model and the discrete network, we remove gap junction currents, which are not represented in the scalar case. Thus, astrocytic isopotentiality is assumed, rather than achieved mechanistically.

Importantly, we have only considered the behavior of the “wave front” in our analysis. $Na^+$ concentrations are assumed constant in the reduced $K^+$ reaction-diffusion model, but in the full model, the sharp increase in $[K^+]_e$ is accompanied by an increase in $[Na^+]_i$ and a steep decline in $[Na^+]_e$. Further analysis may focus on the impact of changing $[Na^+]_e$ and $[Na^+]_i$ on the shape of the cubic in the reduced model, and relate this influence to the behavior of the full model. Decreased $[Na^+]_e$ (and associated increased $[Na^+]_i$) appears to increase the integral of the cubic. This may explain the effect of increasing $\rho_N$, since increased $\rho_N$ produces an increased one-cell $[Na^+]_e$ steady state.

Spreading depolarization is an extremely complex phenomenon, and the model we have implemented does not capture a number of biological details associated with this process. As stated, we do not include gap junctions in the maintenance of astrocytic isopotentiality. Other considerations for future study include cell volume change and glutamate-activated NMDA currents, which contribute to neuronal depolarization and $K^+$ efflux during spreading depolarization [11].

Nevertheless, we hope that this analysis may provide an instructive framework for understanding the potential role of extracellular $K^+$ in the initiation and propagation of spreading depolarization. In particular, the concept of mathematical traveling waves as applied to $K^+$ diffusion provides a simple means for understanding how
various parameters may influence the spread of $K^+$ in a discrete neuron-astrocyte network.
Bibliography


