Alcohol's Effect on Neuron Firing

California State Polytechnic University, Pomona

and

Loyola Marymount University

Department of Mathematics Technical Report

Jeannine T. Abiva[*], Edna S. Joseph[†], Arpy K. Mikaelian[‡], Charles R. Rogers[§]

Applied Mathematical Sciences Summer Institute
Department of Mathematics & Statistics,
California State Polytechnic University Pomona
3801 W. Temple Ave.
Pomona, CA 91768

Faculty Mentors: Erika T. Camacho[¶] and Stephen A. Wirkus[‖]

August 2005

[*]Loyola Marymount University
[†]University of the Virgin Islands
[‡]University of California Santa Barbara
[§]North Carolina State University
[¶]Loyola Marymount University
[‖]California State Polytechnic University, Pomona

Abstract

Neurons are responsible for transmitting messages throughout the body via long distance electrical signals known as action potentials. These depend on the active transport of sodium and potassium ions across the cell membrane. The effect of various drugs on the process of neuron firing is a current research interest. The Hodgkin-Huxley equations, a system of four nonlinear ordinary differential equations, mathematically model the influx and efflux of these ions across the cell membrane. In the presence of alcohol, the release of potassium ions is accelerated. We propose a modified version of these equations, which incorporates the effect of alcohol, and examine its implications through mathematical analysis in dynamical systems. We investigate the qualitative behavior and interpret the results of the steady-state solutions in the fast and fast-slow phase planes.

1 Introduction

The effects of alcohol on the human body continue to be of interest to current researchers. The consumption of alcohol is known to negatively affect the processes in the brain, impair judgment, decrease balance, and generally slow cognitive behavior. Alcohol affects people in two main different ways. For some, alcohol works as a sedative: slurring speech, making one drowsy, and reducing alertness. For others alcohol works as a stimulant: causing violent, abusive, and irrational behavior [8]. These negative biological effects of alcohol suggest that alcohol interferes with the transmission of messages throughout the body. By affecting potassium levels in the cell membrane, alcohol interferes with a neuron firing. This process which occurs throughout the brain is often referred to as an action potential. In 1952, Alan Lloyd Hodgkin and Andrew Fielding Huxley, along with Bernard Katz, unraveled the dynamic ionic conductances that generate the nerve action potential [14]. In response to a constant applied current of ample magnitude, action potentials occur periodically.

The main focus of our research is to investigate in detail the biological background involved in an action potential in order to mathematically model the effects of alcohol on a single neuron firing using the Hodgkin-Huxley model as a framework. Bifurcation theory will be used to examine this model and determine how we should modify it based on the known biological effects of alcohol. We hope our results will serve as a guide for other researchers to better understand alcohol's effects on the human body and thereby find possible ways of reducing these effects.

2 The Biological Neuron

The human brain is made up of roughly 10 billion interconnected neurons, or nerve cells. Neurons [Figure 1] make up the Central Nervous System (CNS). Each neuron specializes in the transmission of information by receiving and processing rapid biochemical and electrical signals. A neuron is connected to 1,000 neighboring neurons by dendrites which are responsible for receiving messages from other neurons. During a neuron firing, dendrites carry signals (messages) toward the soma. The soma, or cell body, houses the nucleus, but does not play an important role in the processing incoming or outgoing data. Similar to the dendrites, the primary function of the nucleus involves receiving and integrating incoming signals [12].

The part of the cell body that processes incoming or outgoing data is the axon hillock. The axon hillock is also referred to as the *triggering zone*, because it is the site where signals from the neuron firing are triggered, or initiated. These signals are then sent away from the cell body along the axon, or nerve fiber, towards the highly branched axon terminals. These terminals release neurotransmitters that simultaneously influence many other neurons they come into close association with [12]. Each axon terminal is connected to other neurons across small gaps called synapses. The neurochemical and physical characteristics of each synapse determines the polarity and strength of the next neuron firing [7]. Functionally, the

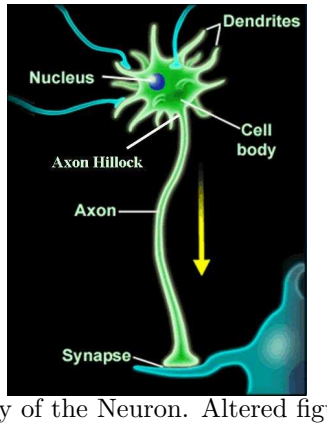


Figure 1: Anatomy of the Neuron. Altered figure courtesy of [1].

axon is usually referred to as the *conducting zone* of the neuron, while the axon terminals comprise its *output zone* [12].

Neurons are responsible for transmitting messages throughout the body. A membrane potential is formed due to charged ions present in the extracellular (ECF) and intracellular (ICF) fluid. Membrane potential is the difference of charges across a cell membrane, that is, the potential of the ICF minus the potential of the ECF. This difference is caused by changes in cell membrane permeability. This separation of charges across a membrane is also known as polarization.

The cell membrane potential is mainly caused by the unbalanced concentration of positive sodium ions and positive potassium ions. There is a greater concentration of potassium ions in the ICF and a greater concentration of sodium ions in the ECF. Consequently, potassium ions have a tendency to move out of the cell while sodium ions have a tendency to move into the cell. When the cell is not transmitting messages, the membrane potential is constant. This is known as resting potential. Potassium influences the resting potential more than sodium since the cell membrane is much more permeable to potassium ions. When potassium is isolated, its equilibrium potential is -90mV; similarly when sodium is isolated, its equilibrium potential is +60mV. Therefore resting potential occurs at -70mV. While at resting potential, the positively charged sodium and potassium ions are moving along their concentration gradients. In order to keep the membrane potential constant, the sodium-potassium ATPase pump is continuously transporting potassium ions into the cell and sodium ions out of the cell to counteract the leakage. [12].

In order for messages to be transmitted throughout the body, a neuron must go through an action potential. An action potential is a long distance electrical signal that involves numerous voltage-specific sodium and potassium channels scattered throughout the cell membrane. These channels have gates that control the flow of positive sodium and potassium ions across the cell membrane. The sodium and potassium gates open and close in response to voltage changes during an action potential. The following diagrams will give a brief overview of the types of gate dynamics that are involved during an action potential.

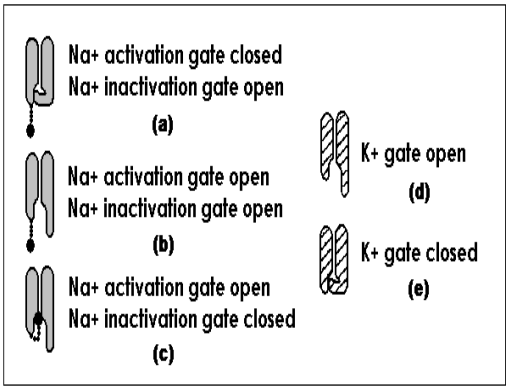


Figure 2: Sodium and Potassium Channels. At the closed but capable of opening state, the inactivation gate is open and the activation gate is closed (a). At the activated state, both the activation and the inactivation gates are open allowing the sodium ions to flow into the cell (b). At the inactivated state, the inactivation gate is closed and the activation gate is open(c). The potassium channel is activated if the gate is open(d) and inactivated if the gate is closed (e).

Voltage-gated channels that control the flow of positive sodium ions in a neuron have two gates, an activation and an inactivation gate. [See Figure 2 (a-c)]. Each type of gate operates differently. The activation gate operates by opening and closing like to a hinged door. However, the inactivation gate of the sodium channel consists of a sequence of amino acids that are built like a ball and chain. When the ball hangs straight from the chain of amino acids, the channel is open; and when the ball binds to the receptor located at the opening of the channel, the channel is closed. Both the activation and inactivation gates must be open for the channel to be open and allow sodium ions into the cell. There are three different states that the voltage-gated sodium channel can exist: closed but capable of opening, opened (activated), and closed and not capable of opening (inactivated). The voltage-gated channel that controls the flow of positive potassium ions on the other hand is a simpler model than that of sodium. The potassium channel consists of only an activation gate. [See Figure 2 (d,e)]

The permeability of sodium and potassium ions across the cell membrane is dependent on the state of their respective channels[Figure 3]. At resting potential (-70mV), the sodium and potassium activation gates are closed, thus keeping the potential constant. Although the sodium channel is closed, it is still capable of opening since its inactivation gate is open. Once a triggering event that stimulates the neuron occurs, the cell begins to depolarize towards threshold potential at approximately -50mV. Depolarization occurs when the membrane potential is less negative than at resting potential. This change in potential, causes the sodium activation gates to open, allowing an influx of sodium ions into the cell. Once the cell has reached threshold potential, the remaining sodium activation gates swing open, causing the cell membrane to become more permeable to sodium ions. Sodium rushes into the cell, making the membrane potential less polarized. Consequently, the membrane potential increases towards +30mV and thus favoring the sodium equilibrium potential of +60mV. A little before reaching membrane potential peak reversal point of +30mV, the sodium inactivation gates begin to close while the potassium activation gates begin to open. The sodium inac-

tivation gates taking longer to close than the potassium gates take to open, thus resulting in approximately a 0.5 ms delay in depolarization, or before the falling phase begins. As a result, both sodium and potassium channels are open for this short time. The inactivation gates of the sodium close at +30mV, the permeability to sodium rapidly decreases. As more potassium gates open, the efflux of potassium increases. This efflux causes the membrane potential to become more negative and moves towards resting potential of -70 mV. This portion of an action potential is referred to repolarization. The efflux of potassium causes the membrane potential to overshoot the resting potential, hyperpolarizing to approximately -85 mV. At the lowest point of the action potential curve, the inactivation sodium gates opens while the sodium activation gates close and the potassium activation gates close. Now, the sodium channel is in a closed but capable of opening state making the membrane potential receptive to another stimulus capable of causing an action potential. With the channels for both sodium and potassium closed, the cell has returns to the configuration before the action potential. Now the neuron is ready for another action potential to occur. Although the concentration gradients have been disrupted by the action potential, the ATPase pump gradually restores the gradients to their original condition at resting potential [12].

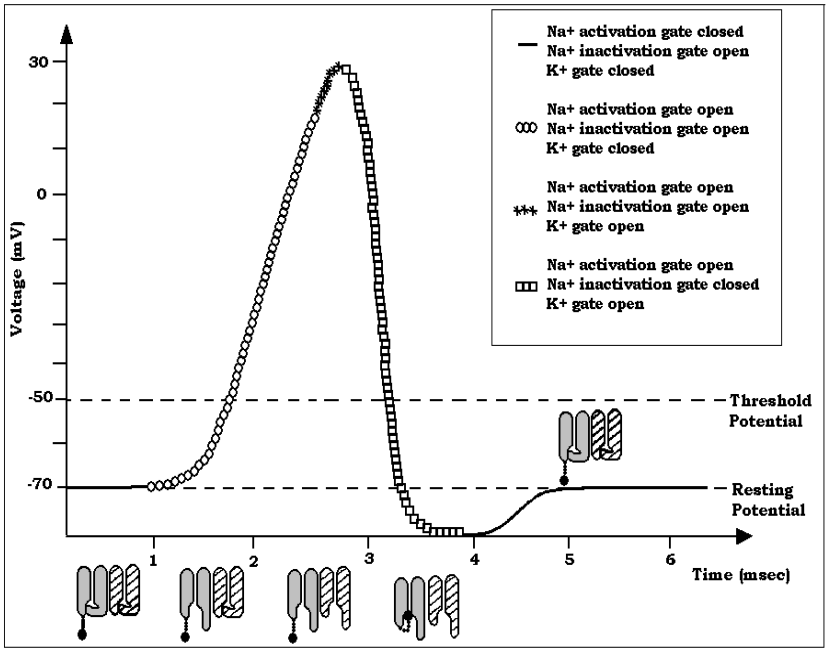


Figure 3: Complete Action Potential Diagram

3 Hodgkin-Huxley Mathematical Model

In 1952, Alan Hodgkin and Andrew Huxley developed the first quantitative model of the neuron firing along a squid giant axon. By numerically solving a system of four first order

ordinary differential equations, the model exhibits the ionic dynamics of a single neuron action potential. The four equations model the changing voltage and the proportion of open sodium activation, sodium inactivation, and potassium gates during an action potential. The Hodgkin-Huxley (HH) model is arguably one of the most important landmark in physiological literature today. The terms and underlying biophysical meanings of the HH model are explained in the following section.

3.1 Hodgkin-Huxley Equations

After numerous trial-and-error models, which were solved laboriously on mechanical calculators, Hodgkin and Huxley found it necessary to focus on the currents involved in an action potential. These currents are formed by sodium ions(Na^+), potassium ions(K^+), and other ions lumped together in the leakage current (L). They also attached variables to the gates involved in an action potential, where m, n, h represent the proportion of open sodium activation gates , potassium gates, and sodium inactivation gates open at a given time, respectively. [22].

The voltage-gated channels control the flow of positive sodium and potassium ions across a cell membrane. The rate at which these channels go from a closed state to an open state is represented by α and the rate at which the channels go from an open state to a closed state is represented by β. These α and β rates are dependent on voltage. For simplicity, we will omit the explicit dependence of α on v and let $\alpha = \alpha(v)$ and $\beta = \beta(v)$. Since m denotes the proportion of sodium activation gates in the open state, $1 - m$ denotes the proportion of closed sodium activation gates [14]. Equations (1) shows the Hodgkin-Huxley equation modelling the sodium activation gates where $\alpha_m(1-m)$ denotes the proportion of gates that are closed but moving to an open state at rate α_m and $\beta_m m$ denotes the proportion of open gates moving to a closed state at rate β_m. Hodgkin and Huxley formulated similar transition equations to model the potassium gates n and sodium inactivation gates h. (See Equations 2 3 below).

$$\frac{dm}{dt} = \alpha_m \cdot (1 - m) - \beta_m m. \tag{1}$$

$$\frac{dn}{dt} = \alpha_n \cdot (1 - n) - \beta_n n, \tag{2}$$

$$\frac{dh}{dt} = \alpha_h \cdot (1 - h) - \beta_h h. \tag{3}$$

The fourth variable involved in the Hodgkin-Huxley model is voltage. An action potential is measured in voltage v which is time-dependent. Note that v is the membrane potential V minus the resting potential V_{eq}, ($v = V - V_{eq}$); which shifts the action potential graph up by -70mV. To fit their collected data, Hodgkin and Huxley assumed that the Na^+ channel consists of three sodium activation, m, gates and one sodium inactivation, h, gate, each of which can be either at an open or closed state. As the gates operate independently, the proportion of open Na^+ channels is m^3h. Similarly, they assumed that the K^+ channel has four potassium activation, n, gates where all of them must be at an open state for potassium

to flow out of the cell. [14] As a result, the proportion of open K^+ channels is n^4. Recall from physics that the change in voltage multiplied by a capacitance will equal the sum of the contributing currents. Hodgkin and Huxley considered the total current of the ionic flow which is $I = I_{Na} + I_K + I_L$. As a result, Hodgkin and Huxley derived equation (4).

$$C_m \frac{dv}{dt} = -\overline{g}_K n^4 (v - v_K) - \overline{g}_{Na} m^3 h (v - v_{Na}) - \overline{g}_L (v - v_L) - I_{app}. \tag{4}$$

The respective functions α and β in equations (5) - (10) proposed by Hodgkin and Huxley, correspond to experimental parameters defined by current values of voltage in their system. In units of $(\text{ms})^{-1}$ the voltage-dependent quantities α_n, α_m, α_h, β_n, β_m, and β_h are represented in equation (5) - (10).

$$\alpha_n = 0.01 \cdot \left(\frac{10 - v}{\exp\left(\frac{10-v}{10}\right) - 1} \right), \tag{5}$$

$$\beta_n = 0.125 \cdot \exp\left(\frac{-v}{80}\right), \tag{6}$$

$$\alpha_m = 0.1 \cdot \frac{25 - v}{\exp\left(\frac{25-v}{10}\right) - 1}, \tag{7}$$

$$\beta_m = 4 \cdot \exp\left(\frac{-v}{18}\right), \tag{8}$$

$$\alpha_h = 0.07 \cdot \exp\left(\frac{-v}{20}\right), \tag{9}$$

$$\beta_h = \frac{1}{\exp\left(\frac{30-v}{10}\right) - 1}. \tag{10}$$

The remaining constants that appear in the Hodgkin-Huxley equations are: $\overline{g}_{Na} = 120$, $\overline{g}_K = 36$, and $\overline{g}_L = 0.3$ with adjusted equilibrium potentials of $v_{Na} = 115$, $v_K = -12$, and $v_L = 10.6$ [14].

In summary, the Hodgkin-Huxley equations consist of four differential equations $(1 - 4)$ with nonlinear terms. The exponential functions in the rates make the analysis very difficult.

To gain more insight into the process of the action potential, we considered the approach given by Richard FitzHugh in 1960, 1961, and 1969, which is based on the behavior of ionic movements during the initial stages of an action potential. In both of his reduced models, FitzHugh used the fact that certain variables of the original model have fast kinetic properties while other variables have slow kinetic properties. Observing the initial stages of the

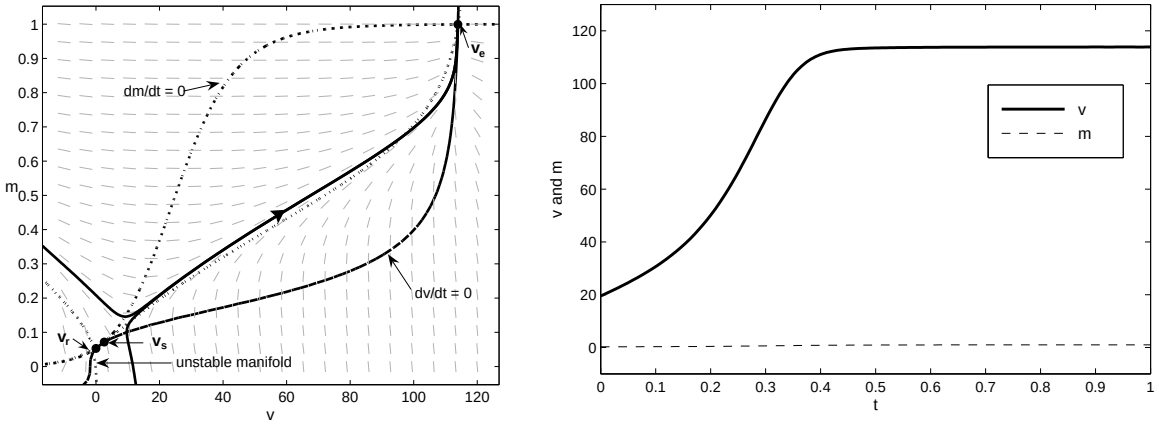
action potential, FitzHugh classified the m and v variables as fast and the n and h variables were classified as slow [**?**]

3.2 The Fast Phase-Plane

By considering the system that gives rise to the fast-phase plane, here FitzHugh held two slow variables constant and focused on the two fast variables, m and v. He fixed the slow variables n and h to their respective resting states $n_0 = 0.3176$ and $h_0 = 0.596$. The following differential equations constitute FitzHugh's fast phase-plane model:

$$C_m \frac{dv}{dt} = -\overline{g}_k n_0 (v - v_k) - \overline{g}_{Na} m^3 h_0 (v - v_{Na}) - \overline{g}_L (v - v_L) \tag{11}$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \tag{12}$$



(a) **(b)**

Figure 4: (a) The Hodgkin-Huxley Fast Phase-Plane. Borrowed figure courtesy of [14].
(b) The corresponding graph for the trajectory in terms of v and t.

To understand the underlying implications of this reduced model, we study the fast phase-plane [Figure 4a]. The nullclines of the fast phase-plane (defined as $\frac{dm}{dt} = 0$ and $\frac{dv}{dt} = 0$) intersect at three different points. The three intersection points correspond to three equilibrium points in the fast phase-plane, v_r, v_s, and v_e. These three steady state solutions are respectively labelled according to their states: resting, saddle, and excited. v_r and v_e are stable steady states of the fast phase-plane while v_s is a saddle point, thus semi-stable. This saddle point creates a one-dimensional unstable manifold which divides the graph into two regions. Following its semi-stable property, trajectories starting from the left of unstable manifold of the saddle point v_s are unable to reach the excited state v_e and must return to the resting state v_r. Also, any trajectory starting from the right of the unstable manifold of the saddle point v_s is prevented from returning back to v_r and is directed to the excited state

v_e where it will remain. Since this unstable manifold determines whether the trajectory will reach the excited state or not, it acts as the threshold level previously described. Although the fast phase-plane provides a useful way to study the excitation of a neuron firing, it does not model a completed action potential. In [Figure 4b], the trajectory to the right of the unstable manifold is graphed with respect to voltage and time. Notice that the curve never returns to a resting state. Only the rising phase of a neuron firing is accurately illustrated. This is due to the fact that only the fast, or excitation variables were considered. Ignoring the slow, or recovery variables omits the falling phase of an action potential. Since it does not represent a complete action potential, we will not be concentrating on this reduced model in our research [14].

3.3 The Fast-Slow Phase-Plane

In order to obtain a more accurate reduced model of the Hodgkin-Huxley equations, a fast variable and a slow variable need to be considered. Because the fast-slow phase-plane captures the entire action potential using a fast and slow variable and explicitly incorporates the dynamics of potassium, we will be examining it in detail. To produce this reduced model of the Hodgkin-Huxley equations, FitzHugh chose the fast variable (v) and recognized that m can be considered an instantaneous function of v. So $m = m_\infty(v)$ at all times, where $m_\infty(v)$ is the steady state of m. The next step that FitzHugh took to complete the reduced model was setting $h \approx 0.8 - n$. This approximation was based on the symmetry between the $h(t)$ and $n(t)$ functions as seen in [Figure 5]. Here FitzHugh noticed that $h + n \approx 0.8$ [14]. With these modifications, the Hodgkin-Huxley equations can be written as:

$$C_m \frac{dv}{dt} = -\overline{g}_K n^4 (v - v_K) - \overline{g}_{Na} m_\infty^3 (0.8 - n)(v - v_{Na}) - \overline{g}_L (v - v_L) \tag{13}$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n \tag{14}$$

The nullclines of the fast-slow phase-plane are shown in [Figure 6a]. The v nullcline has a cubic shape and it is defined as $\frac{dv}{dt} = 0$. The n nullcline is monotonically increasing and is defined by $\frac{dn}{dt} = 0$. Notice in [Figure 6a] that there is only one intersection point and therefore only one steady state. The curve $\frac{dv}{dt} = 0$ is known as the slow manifold [14]. These are named according to the behavior of the trajectory. When the trajectory is along the slow manifold, it is changing with respect to the slow variable n. The middle branch of the slow manifold is unstable. This causes a trajectory curve to fire only to the right of the middle branch of $\frac{dv}{dt} = 0$. This middle branch acts as the threshold level. When a trajectory to the right of this middle branch is graphed with respect to voltage and time, as seen in [Figure 6b], an action potential is achieved. We will be focusing on the fast-slow phase-plane in our research, since this reduced model accurately depicts a completed action potential.[14]

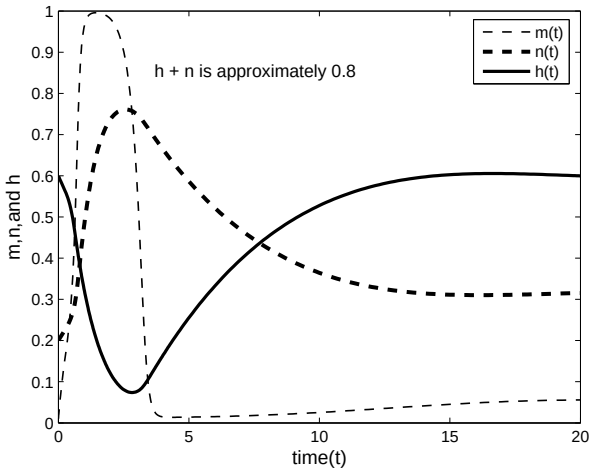


Figure 5: The proportion of open n, m, and h at a given time. Altered figure courtesy of [1].

3.4 Effects of Alcohol in Detail

After gaining a deep understanding of both the biology and the mathematics of the Hodgkin-Huxley equations and the FitzHugh reduced system, the next step is to understand how and where alcohol affects these systems. When referring to alcohol, its metabolites, oleic acid and ethanol, are considered. Experimental data showed that alone, ethanol did not have an effect on the kinetics of ionic current. However, when both oleic acid and ethanol were applied kinetic variations in a neuron firing occurred [16]. Alcohol, as previously mentioned, is a stimulant: causing violent, abusive and irrational behavior. The negative biological effects of alcohol suggest that alcohol interferes with the transfer of messages during the firing of neurons within the brain. [8] Researching the biological details of message transfer by neuron activity found that alcohol, specifically the metabolites of alcohol, ethanol and oleic acid, accelerate the release of potassium ions [16].

Thorough research into biological and neurological processes shed light onto alcohol's interference with the transfer of messages through neuron firings. It was found from an experimental study that voltage-dependent potassium channels are predominant in axons, presynaptic terminals, and parts of the neuron that actively synthesize metabolites of alcohol. [16]. Since these sites are targets for alcohol toxicity, potassium is the most affected by alcohol. From the experimental study just mentioned, the time necessary for depolarization decreased due to an increase in the activation rate constants of potassium. From this, it was concluded that alcohol dramatically accelerates the kinetics of the voltage dependent potassium channel. Thus, the release of potassium accelerates in the presence of alcohol [16].

The effects of alcohol in this study also include a substantially steeper slope of repolarization due to a greater efflux of potassium ions. The greater efflux of potassium ions lowers the maximum voltage achieved during an action potential. This promotes a depression of the action potential through an enhanceAlso, the decreased time required to return to resting

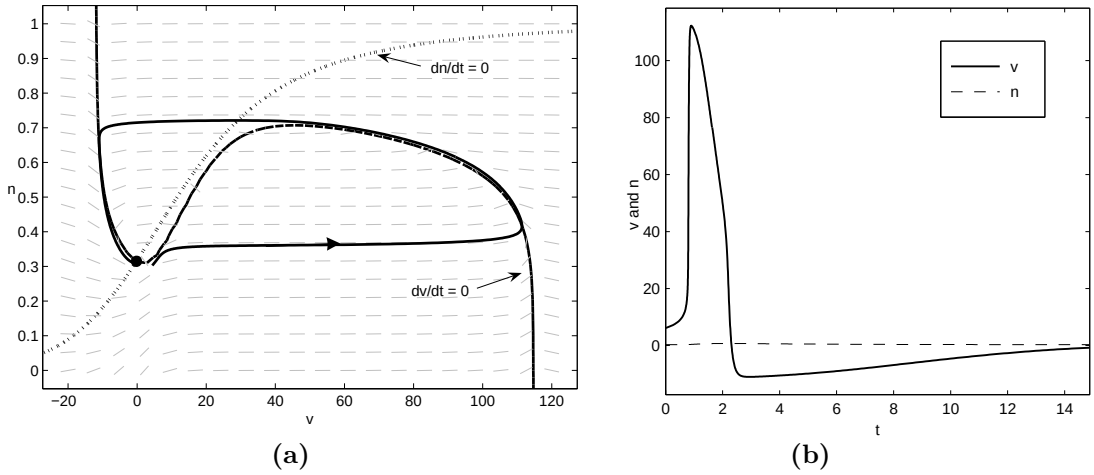


Figure 6: (a) The Hodgkin-Huxley Fast-Slow Phase-Plane. Borrowed figure courtesy of [14]. (b) The corresponding graph for the trajectory in the fast-slow phase-plane in terms of v and t.

potential repolarization [16]. [**?**]. During repolarization, the neuron is receptive to another action potential. An enhancement of repolarization increases the allotted time for a second action potential, making the neuron more receptive to multiple firings [4]. The depression in action potential induced by alcohol can be interpreted by a lower peak reversal point and an earlier hyperpolarization time. Alcohol has a stimulating effect because the time available for another neuron firing during the recovery phase to occur is increased. Now, it is less likely for the neuron to achieve a threshold membrane potential since it takes longer for the neuron to recover and return to resting potential [16]. Thus, alcohol has a quieting effect.

We hypothesize that alcohol causes an action potential to have lower amplitude, overshoot sooner and the time it takes to return to resting potential decreases. Therefore we also hypothesize that the potassium equilibrium may occur sooner or may decrease. In addition, we hypothesize that the slope of the efflux for potassium would become steeper. We justify this hypothesis by the effects of alcohol found in experimental data [16]. Specifically, since alcohol causes an accelerated efflux of potassium, the cell becomes more rapidly negative inside. Greater internal negativity correlates to the slope of the action potential after the peak reversal point bringing the membrane potential back to rest. Lastly, we hypothesize that the deepest point of hyperpolarization would occur sooner. Experimental studies confirm that alcohol causes a neuron to be less excitable. Thus, it is less likely to reach a threshold potential for a stimulus that under normal conditions would had initiated an action potential. These hypotheses can be mathematically modelled by changing the rate at which the potassium gates open, α_n. Changing α_n indirectly changes the flow of potassium out of the cell.

4 Mathematically Modeling the Effects of Alcohol

To mathematically model the effects of alcohol we modify α_n for the reasons given below. We analyze the resulting modified model by again considering the fast-slow phase plane. We do these modifications for two main reasons. The first, as mentioned previously, is due to the fact that the fast-slow phase plane system is capable of illustrating an entire action potential whereas the fast phase-plane is not. Second, the reduced model consists of dv/dt and dn/dt whereas the fast phase-plane model consists of dv/dt and dm/dt. Thus, the latter does not consider the slow variable n, which is central to the modifications we made when considering alcohol. As in the FitzHugh model, having only two equations allows us to do a planar analysis and allows for a more thorough understanding of the mathematical results. The reduced models allowed us to find equilibrium points using the nullcline curves, analyze the flow or trajectory of the neuron firing, and gain insight into how we can use our results from the modified FitzHugh equations as a guide to the behavior of the complete set of Hodgkin-Huxley equations.

4.1 Conductance

The conductance of a certain ion relates to the permeability of the cell membrane to that specific ion. If the conductance of a certain ion is low, the cell membrane is not very permeable to that ion, thus these ions flow in or out of the cell slowly. Conversely, if the conductance of a certain ion is high, these ions move in and out of the cell membrane at a high rate. As mentioned before, alcohol increases the release of potassium ions causing the cell membrane potential to be more negative. This accelerated release of potassium due to alcohol implies a change in the conductance of the potassium ions. Experimental data that measured the current through potassium channels before and after alcohol was introduced [16]. This experimental data showed that the potassium current increased dramatically after the input of alcohol. Given the relationship of conductance and ionic current,

$$g_K = \frac{I_K}{V - V_K} \tag{15}$$

an increase in potassium current corresponds to an increase in potassium conductance. Knowing that α is the rate of conversion for a gate to go from a closed to open state, and that alcohol increases the rate at which potassium is released, we will compare the conductance of potassium with α and α_{nmod}. The α_{nmod} should produce a moderate increase in potassium conductance when compared to conductance using the original α_n[16]. We also notice that the conductances increase with greater a of α_{nmod}.

4.2 Hypothesis and Criteria for Choosing α_{nmod}

As mentioned earlier, the biological literature suggests that alcohol dramatically accelerates the release of potassium from within the axon. Because α is the rate of conversion from

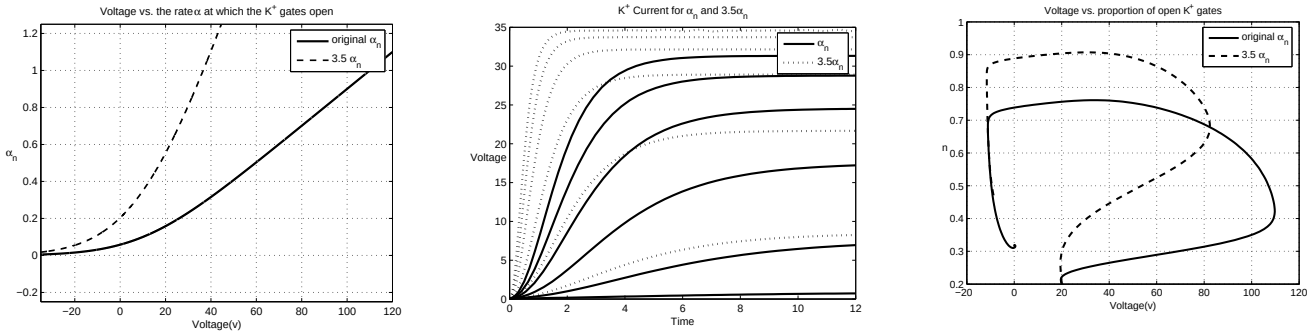
closed to open, and alcohol increases the rate at which potassium is released, we model the effect of alcohol by modifying α_n. This assumption was further supported by an article which compared the current due to the flow of potassium of a normal neuron and one affected by alcohol. The results supported that the rate of potassium activation affected by alcohol will increase [21].

The modified rates of conversion from closed to open for potassium are denoted α_{nmod}s. Since research suggests that the presence of alcohol increases the efflux of potassium ions, it was understood that the modified α_{nmod} graph should be higher than the original α_n for $v > v_c$, for some v_c. Another requirement for α_{nmod} is to approach zero as its limit goes to negative infinity and to approach positive infinity as its limit approaches positive infinity. A third requirement is to obtain a function that agrees, at least qualitatively, with the graphs of conductance given in [16]. A fourth requirement is to obtain a function $\alpha_n mod$ that predicts a greater proportion of open potassium gates than for α_n when using the Hodgkin-Huxley equations. These criteria will be used to pick biologically meaningful α_{nmod} functions.

4.3 First Modification

We first tried a modified α_n that was always greater than the original α_n. This was done by simply multiplying the original α_n by a particular constant a.

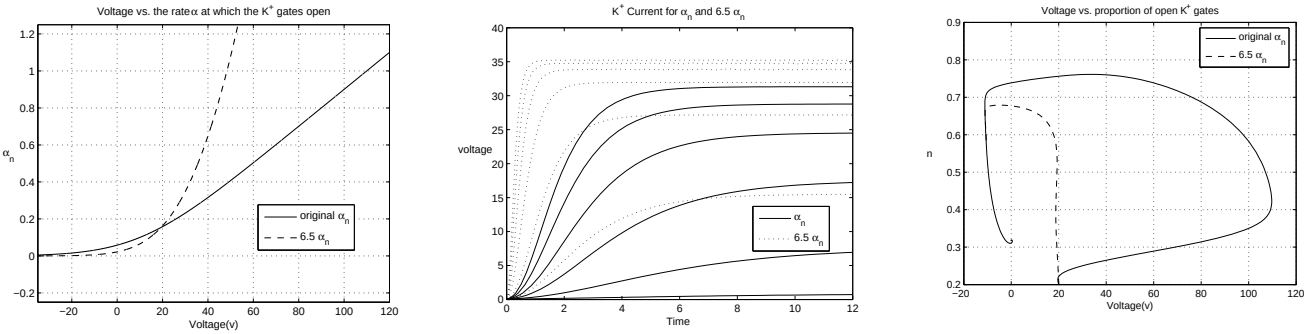
$$a \cdot (\alpha_n) = a \cdot \left(0.01 \left(\frac{v + 10}{\exp(1 + 0.1v) - 1} \right) \right), \tag{16}$$



(a) **(b)** **(c)**

Figure 7: (a) Original α_n vs $3.5\alpha_n$ (b)Potassium Current of α_n vs $3.5\alpha_n$ (c) Voltage vs Proportion of Open Potassium Channels for α_n vs $3.5\alpha_n$

While this modified α_n satisfied the 1st and 2nd requirements, it did not satisfy the 3rd of 4th ones. The difference between the modified α_n and the original α_n did not correlate with the biological research conducted because a dramatic increase in the proportion of open potassium gates was not observed in the original α_n from the Hodgkin-Huxley equations.



(a) **(b)** **(c)**

Figure 8: (a) Original α_n vs $6.5\alpha_n$ (b)Potassium Current of α_n vs $6.5\alpha_n$ (c) Voltage vs Proportion of Open Potassium Channels for α_n vs $6.5\alpha_n$

Also, the conductance curves did not qualitatively agree with experimental data from [16]. The dramatic increase in conductance occurs before threshold potential of 15 mV and thus does not agree biologically. Also, using this modification of α_n, there is a rapid increase of potassium gates n at low voltages. This increase is too dramatic and thus does not reflect the effects of alcohol accurately in the voltage versus n plane. [[Figures 7, Figure 8]

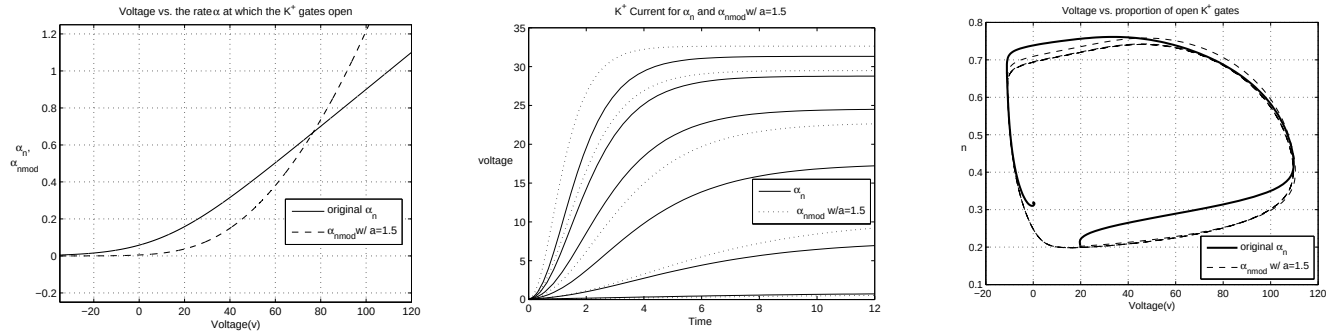
4.4 Second Modification

Consequently, we considered a quadratic change in α_n. A quadratic change would correlate to a faster increase in the release of potassium ions due to alcohol. This was done by squaring the original α_n and, analogous to the original modification, we multiplied α_{n^2} by a constant a. For future reference this modified α_n will be referred to as α_{nmod}.

$$\alpha_{nmod} = a \cdot (\alpha_n)^2 = a \cdot \left(0.01 \cdot \left(\frac{10 - v}{\exp\left(\frac{10-v}{10}\right) - 1} \right) \right)^2, \tag{17}$$

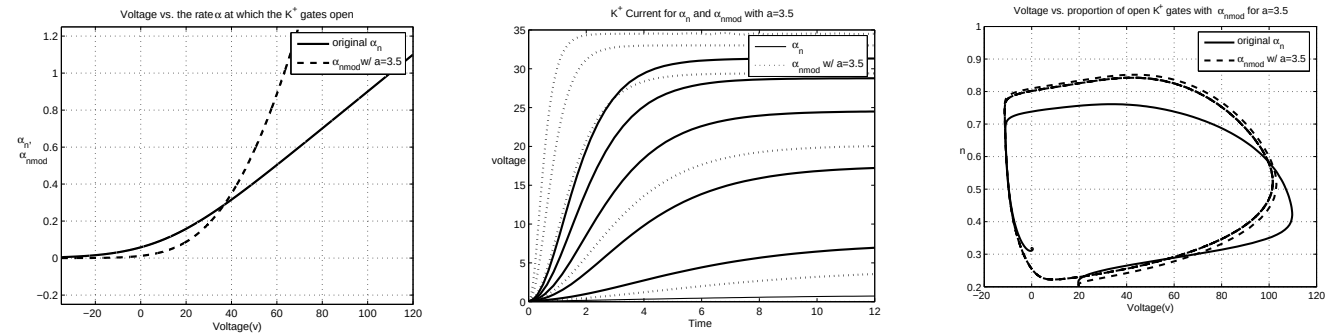
The unique feature of this $\alpha_n mod$ is its intersection with the graph of α_n. This can be interpreted as the efflux of potassium will be greater past a voltage v_c but will be less before v_c. By changing the constant a, we explored various other intersection points. Since we hypothesized that the threshold potential, 15mV, might be affected by the change in potassium efflux, we varied the coefficient a in α_{nmod} so that it intersected the original α_n at 15mV. Also, since the potassium gates are open at the peak of the action potential, we considered an intersection at 100mV. To determine the appropriate α_{nmod}, we used Matlab[10] to ensure that the proposed modifications to the potassium activation parameter qualitatively matched numerical data of [16].

These positive changes in conductance are demonstrated in [Figure 9, Figure 10, Figure 11, Figure 12]. When the coefficient a of α_{nmod} is decreased, this corresponds to a lower rate



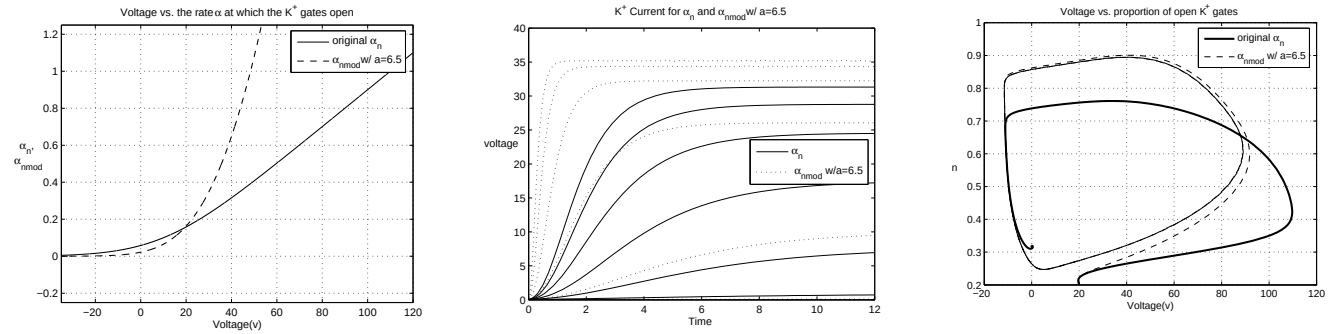
(a) **(b)** **(c)**

Figure 9: (a) Original α_n vs α_{nmod} with $a = 1.5$ (b)Potassium Current of α_n vs α_{nmod} with $a = 1.5$ (c) Voltage vs Proportion of Open Potassium Channels for α_n vs α_{nmod} with $a = 1.5$



(a) **(b)** **(c)**

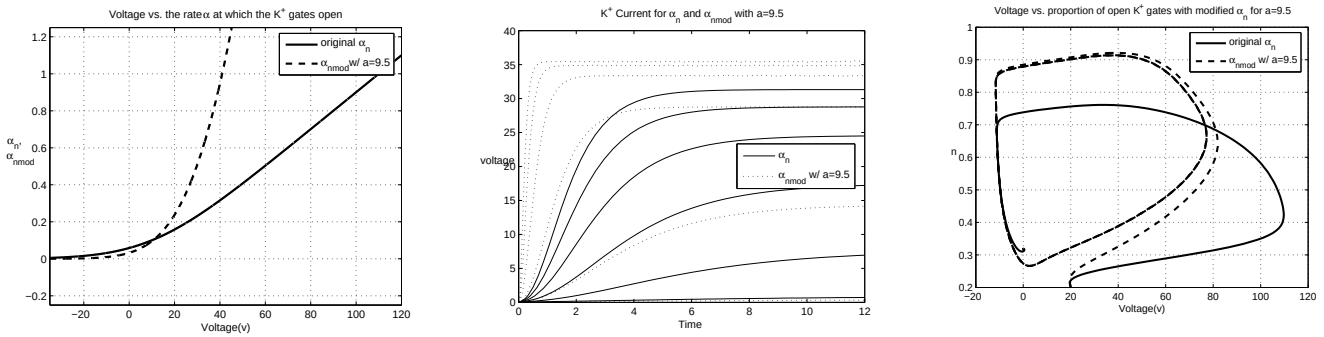
Figure 10: (a) Original α_n vs α_{nmod} with $a = 3.5$ (b)Potassium Current of α_n vs α_{nmod} with $a = 3.5$ (c) Voltage vs Proportion of Open Potassium Channels for α_n vs α_{nmod} with $a = 3.5$



(a) **(b)** **(c)**

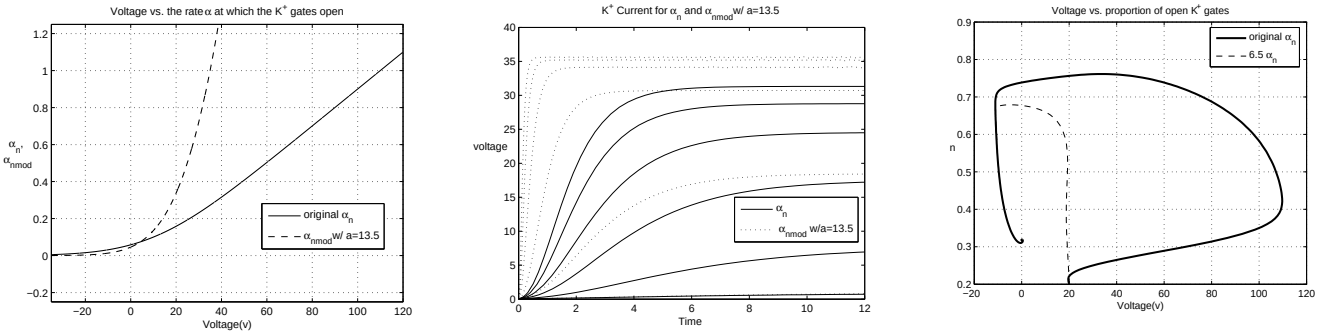
Figure 11: (a) Original α_n vs α_{nmod} with $a = 6.5$ (b)Potassium Current of α_n vs α_{nmod} with $a = 6.5$ (c) Voltage vs Proportion of Open Potassium Channels for α_n vs α_{nmod} with $a = 6.5$

of activation for the potassium gate. Consequently, the voltage dependent potassium gates causes the pinnacle of an action potential to rise as time passes. Recall that the sodium inactivation gate typically closes at a slower rate than the opening of the potassium activation gate. However, we find that when a is small, the sodium inactivation gate closes at a rate faster than the time required for the potassium activation gate to open. As a result, the peak of the action potential is higher than a typical action potential for smaller a values.



(a) **(b)** **(c)**

Figure 12: (a) Original α_n vs α_{nmod} with $a = 9.5$ (b)Potassium Current of α_n vs α_{nmod} with $a = 9.5$ (c) Voltage vs Proportion of Open Potassium Channels for α_n vs α_{nmod} with $a = 9.5$



(a) **(b)** **(c)**

Figure 13: (a) Original α_n vs α_{nmod} with $a = 13.5$ (b)Potassium Current of α_n vs α_{nmod} with $a = 13.5$ (c) Voltage vs Proportion of Open Potassium Channels for α_n vs α_{nmod} with $a = 13.5$

4.5 The Modified Equations

Let us reconsider the original Hodgkin-Huxley equations with this modified α_{nmod}.

$$\frac{dm}{dt} = \alpha_m \cdot (1 - m) - \beta_m m, \tag{18}$$

$$\frac{dn}{dt} = \alpha_{nmod} \cdot (1 - n) - \beta_n n, \tag{19}$$

$$\frac{dh}{dt} = \alpha_h \cdot (1 - h) - \beta_h h. \tag{20}$$

$$C_m \frac{dv}{dt} = -\overline{g}_K n^4 (v - v_K) - \overline{g}_{Na} m^3 h (v - v_{Na}) - \overline{g}_L (v - v_L) - I_{app}. \tag{21}$$

In units of $(ms)^{-1}$ the voltage-dependent quantities α_{nmod}, α_m, α_h, β_n, β_m, and β_h are

$$\alpha_{nmod} = \mathbf{a} \left(0.01 \cdot \left(\frac{10 - v}{\exp\left(\frac{10-v}{10}\right) - 1} \right) \right)^2, \tag{22}$$

$$\beta_n = 0.125 \cdot \exp\left(\frac{-v}{80}\right), \tag{23}$$

$$\alpha_m = 0.1 \cdot \frac{25 - v}{\exp\left(\frac{25-v}{10}\right) - 1}, \tag{24}$$

$$\beta_m = 4 \cdot \exp\left(\frac{-v}{18}\right), \tag{25}$$

$$\alpha_h = 0.07 \cdot \exp\left(\frac{-v}{20}\right), \tag{26}$$

$$\beta_h = \frac{1}{\exp\left(\frac{30-v}{10}\right) - 1}. \tag{27}$$

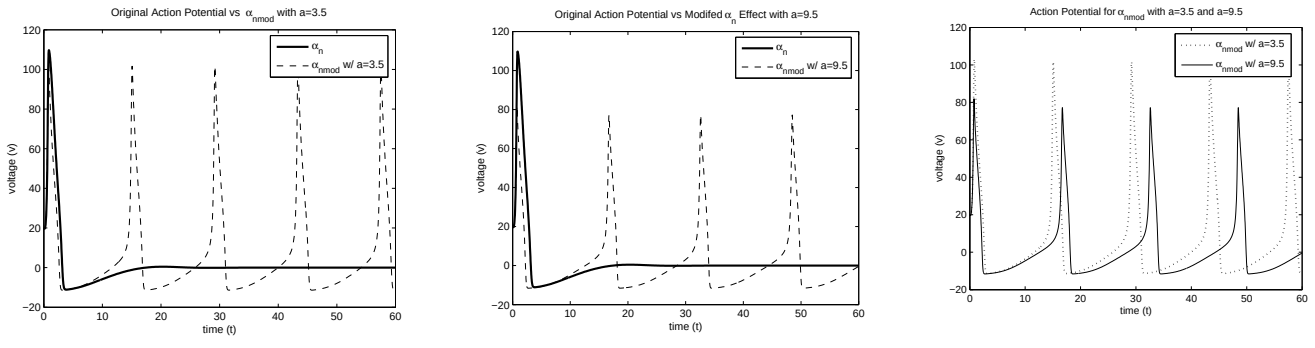
Thus, our modification due to alcohol (specifically the ethanol and oleic acid [16]), only affects the equations (19) and (22), those involved in the opening of the potassium gates.

5 Analysis/Results

The parameter we focus on is the constant a of α_{nmod}. We utilize Matlab to examine the action potential in the modified Hodgkin-Huxley equations. Each of the α_{nmod} functions used here was also graphed in [Figures 9 through 13]. Since the rate of potassium efflux is responsible for the repolarization increase or decrease, it is also responsible for bringing the action potential back to resting potential. With different α_{nmod}, we notice the peak and repolarization behavior of the action potentials vary.

When a is greater than 2.5, the peak of the action potential decreases while the time it takes for hyperpolarization to occur decreases [Figure 14]. Under the influence of alcohol, the potassium gates open at a much higher rate causing large efflux of potassium. This causes the peak reversal point of the action potential to occur at a lower voltage, corresponding to repolarization occurring sooner than normal. However, α_{nmod} becomes less than α_n when $v < v_c$ and thus the efflux is actually less than it was with α_n. This causes the voltage to rise slightly and another action potential to occur. The stable limit cycle involved with this action potential causes continuous oscillation. This is seen as a stable limit cycle in the phase plane.

Noting the various behavior corresponding to different coefficients a of α_{nmod}, see [Figure 15], recall that a relates to the efflux of potassium and the amount of alcohol in the cell. Consequently, we realize that positive changes in a increases the permeability of potassium in the cell under the influence of alcohol. As the coefficient a of α_{nmod} increases, corresponding to a greater efflux of potassium, the maximum voltage attained in an action potential decreases. A greater efflux of potassium also causes the peak of the action potential to decrease and the downward slope of the falling phase to become steeper. In addition, since this information correlates with experimental data found [16] and the qualitative changes agree biologically, our rationale supports our α_n modifications.



(a) **(b)** **(c)**

Figure 14: (a) Original Action Potential vs. α_{nmod} with $a = 3.5$(b)Original Action Potential vs. α_{nmod} with $a = 9.5$ (c) α_{nmod} with $a = 3.5$ vs. α_{nmod} with $a = 9.5$

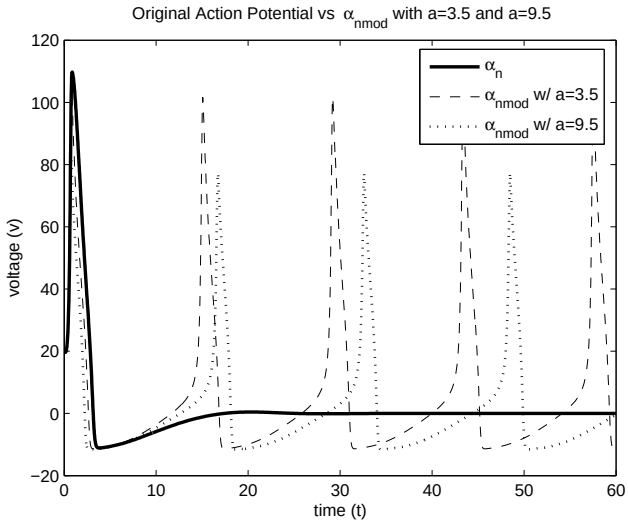
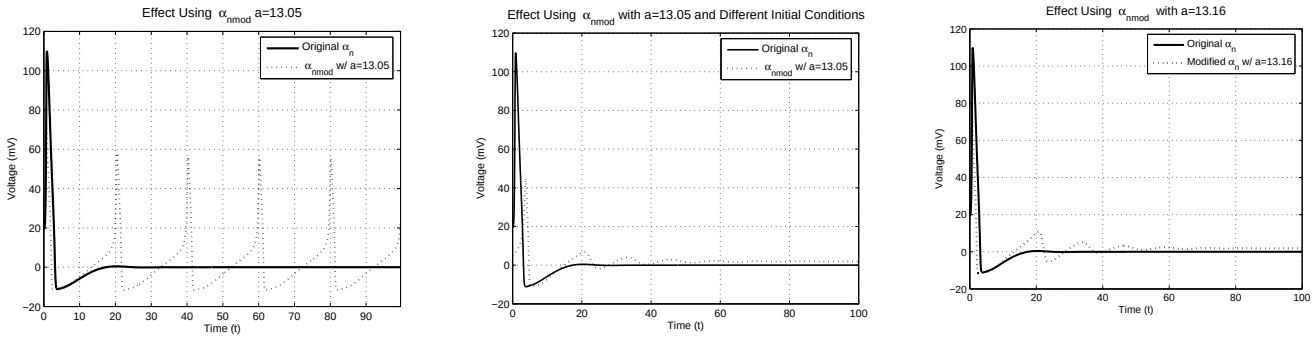


Figure 15: Action Potentials for α_n, α_{nmod} with $a = 3.5$ and $a = 9.5$

5.1 Qualitatively Different Behaviors and Bifurcations

When analyzing various action potentials using α_{nmod} we noticed some interesting mathematical phenomena. A qualitative difference was observed between two different action potentials when different initial conditions were applied. For $a = 13.05$, we noticed a periodic action potential, which implies a stable limit cycle. However, when we changed the initial conditions for voltage and kept a at 13.05, a significant qualitative difference was observed. The action potential for the different initial condition no longer oscillated. In fact, any solution trajectory would approach a stable equilibrium point [Figure 16 a,b]. The fact that a different initial condition caused a change from periodic action potentials to a stable action potential leads us to infer that an unstable limit cycle must encircle the stable equilibrium point.



(a) **(b)** **(c)**

Figure 16: (a) Notice that the Action Potential for α_{nmod} with $a = 13.05$ oscillates (b)Notice that the Action Potential for α_{nmod} with $a = 13.05$ reaches a steady state with slightly different initial conditions (c) The action potential using α_{nmod} with $a = 13.16$ will always reach a steady state regardless of the initial conditions

We also noticed an interesting bifurcation occurrence. With $a = 13.05$, as previously mentioned, the action potentials were periodic. However, at a=13.16 the action potential approaches a stable equilibrium point and there is no longer a possibility of a periodic action potential [Figure 16 c] The fact that from a=13.05 to a=13.16 the action potential went from being periodic to approaching a steady state implies that a saddle-node bifurcation of cycles has occurred. This bifurcation has occurred because the stable limit cycle and unstable limit cycle has coalesced. These qualitatively different behaviors and saddle node bifurcation of cycles reveal an interesting mathematical event. As interesting as the mathematics may be, it is not biologically relevant to our research.

6 Conclusion

Intensive study of the mathematical Hodgkin-Huxley model together with thorough biological research motivated us to consider $alpha_n$ as the leading factor that incorporates the effects of alcohol on a single neuron firing. Since the change of potassium conductance using α_{nmod} match experimental data of potassium current under the influence of alcohol [16], our modification of α_n supports our hypothesis. Through researching biological literature we have found that the criteria used for choosing α_{nmod} is sound. We have accurately modelled how α_{nmod} changes the rate at which potassium gates open, the increase in potassium current, (decrease on time constant approach to steady state), and the change in voltage with respect to the proportion of open potassium gates n. Our hypothesis that the initial proportion of open potassium gates can not be less than that for the original Hodgkin-Huxley equations is supported since our numerical analysis showed that α_{nmod} increased the proportion of open potassium gates. After numerically studying these various modifications, we found that α_{nmod} was indeed the function that best illustrates the biological effects of alcohol on an action potential. In other words, α_{nmod} made the neuron less excitable by depressing depolarization and enhancing the recovery period. The enhanced recovery period implies that a stronger stimulus is required during the recovery period for a second action potential to be achieved. Thus, under the influence of alcohol a neuron is less receptive to any stimulus. Foremost, the hypotheses that we test and confirm with thorough analysis explains how alcohol effects a single neuron firing.

7 Future Work

There are some interesting mathematical and biological matters that we would like to explore in the near future. We plan to focus on the dynamics of α_{nmod} in the fast-slow phase-plane and examine how α_{nmod} can be incorporated into the simpler FitzHugh-Nagumo equations. The FitzHugh-Nagumo equations are of interest to us because they display similar mathematical characteristics of the Hodgkin-Huxley model. We are interested in finding different α_{nmod} functions that could also mathematically describe the effects of alcohol on a neuron firing. Another siginificant area to investigate are other bifurcations of the Hodgkin-Huxley equations using α_{nmod}. Lastly, we would also like to determine the significance of sodium under the influence of alcohol on an action potential. Finding answers to these various areas

of interest will help us further understand and model the entire effects of alcohol on the Hodgkin-Huxley equations.

8 Acknowledgements

This research was conducted at the Applied Mathematical Sciences Summer Institute (AMSSI) and has been partially supported by grants given by the National Science Foundation (DMS-0453602) and National Security Agency (MSPF-04IC-227). Substantial financial and moral support was also provided by Don Straney, Dean of the College of Science at California State Polytechnic University, Pomona. Additional financial and moral support was provided by the Department of Mathematics at Loyola Marymount University and the Department of Mathematics Statistics at California State Polytechnic University, Pomona. We would like to thank our advisors Steve Wirkus and Erika Camacho for pushing us towards reaching our "potential". This project would not have been possible without their guidance and encouragement. We would also like to thank John Shelton and Alaina Jones for taking the opportunity to mentor and assist us academically. We really appreciate them making sure that we were able to enjoy an enlightening and truly memorable summer. The authors are solely responsible for the views and opinions expressed in this research; it does not necessarily reflect the ideas and/or opinions of the funding agencies and/or Loyola Marymount University or California State Polytechnic University, Pomona.

References

[1] Neuron Parts http://www.morphonix.com/software/education/science/brain/game /specimens/neuron_parts.html July 6, 2005

[2] Neuroscience for Kids - Action Potential http://faculty.washington.edu/chudler/ap.html July 6, 2005

[3] Gary G. Matthews Neuron Action Potential http://www.blackwellpublishing.com/matthews/ channel.html July 11, 2005

[4] Close to Home Animation: Alcohol http://www.pbs.org/wnet/closetohome/animation/gaba-anim2-main.html July 11, 2005

[5] A. Davies Neural Effects of Alcohol http://employees.csbsju.edu/hjakubowski/classes/Chem %20and%20Society/Alcohol_Drugs/olEtOHneural.htm July 11, 2005

[6] Hodgkin-Huxley and Fitzhugh-Nagumo Models PHASER: MAA Short Course http://www.phaser.com/modules/maa05/h-h_model.pdf July 12, 2005

[7] Neil Fraser Neural Effects of Alcohol http://vv.carleton.ca/ neil/neural/neuron-a.html July 13, 2005

[8] Narconon of Southern California. Effects of Alcohol on the Brain. http://www.addictionca.com/user-news.htm?id=39. July 13, 2005.

[9] John C. Polking. ODE Software for Matlab. http://math.rice.edu/ dfield/. June 28, 2005.

[10] The MathWorks http://www.mathworks.com/. June 28, 2005.

[11] Maplesoft http://www.maplesoft.com/ June 28, 2005.

[12] Lauralee Sherwood *Human Physiology: From Cells to Systems, 4th edition.* Brooks and Cole Publishers, 2001. (pg 89-103)

[13] *Mathematical Physiology* World Scientific, New Jersey, 1998.

[14] James Keener and James Sneyd. *Mathematical Physiology* Springer-Verlag, New York, NY, 1998. (pg 104, 119, 127-8)

[15] Steven H. Strogatz. *Nonlinear Dynamics and Chaos* Perseus Books Group, Cambridge, MA, 1994. (pg. 44)

[16] RoseA. Gubitosi-Klug and Richard W. Gross. *Fatty Acid Ethyl Esters, Nonoxidative Metabolities of Ethanol,Accelerate the Kinetics of Activation of the Human Brain Delayed Rectifier K Channel, Kv1.1* Journal of Biological Chemistry Vol. 271, No. 51, December 20 Issue, pp. 32519-32522, 1996.

[17] D.A. Haydon and B.W. Urban. *The Action of Alcohols and other Non-Ionic Surface Active Substances on the Sodium Current of the Squid Giant Axon.* The Journal Of Physiology Vol. 341 , August 1983, pgs. 411-427

[18] S. Doi, S. Nabetani, and S. Kumagai. *Complex Nonlinear Dynamics of the Hodgkin-Huxley Equations Induced by Time Scale Changes* Biological Cybernetics Vol. 85, Issue 1 , July 2001, pgs. 51-64

[19] P J Hahn and DM Durand *Bistability dynamics in simulations of neural activity in high-extracellular-potassium conditions* Journal Of Computational Neuroscience Volume 11, Issue 1 , July - August 2001, Pages 5-18

[20] Wang Jiang, Che Yanqiu, Fei Xiangyang and Li Li. *Multi-parameter Hopf-bifurcation in Hodgkin-Huxley model exposed to ELF external electric field* Chaos, Solitons Fractals Volume 26, Issue 4, November 2005, Pages 1221-1229

[21] John R Clay *Axonal excitability revisited* Progress In Biophysics And Molecular Biology Volume 88, Issue 1 , May 2005, Pages 59-90

[22] Rebecca Suckley and Vadim N. Biktashev *The Asymptotic Structyre of the Hodgkin-Huxley Equations*

9 Glossary

Action Potential: brief, rapid, large (100 mV) changes in membrane potential during which the potential actually reverses so that the inside of the excitable cell transiently becomes more positive than the outside; electrical signal over long distances.

Activation Gate: guards the channel by opening and closing like a hinge door.

Anion: negatively charged ion.

ATPase Pump: keeps the neuron at resting potential (-70mV for a giant squid axon) by balancing the ions across the cell membrane.

Cation: positively/negatively charged ion.

Concentration Gradient: The graduated difference in concentration of a solute per unit distance through a solution.

Depolarization: the membrane is less polarized (less negative) that at resting potential; fewer charges are separated that at resting potential .

Electrical Gradient: the rate at which the current is flowing up or down the action potential.

Gated Channels: channels that can be opened or closed in response to specific triggering events.

Hyperpolarization: point where membrane becomes more polarized (more negative) than at resting potential (i.e. ¡ -70 mV).

Inactivation Gate: consists of a ball-and-chain-like sequence of amino acids; open when ball dangles free on chain, closed when ball binds to it receptor at the channel's opening.

Leak Channels: channels that are open all the time.

Membrane Potential: The potential inside a cell membrane measured relative to the fluid just outside; it is negative under resting conditions and becomes positive during an action potential.

Permeability: rate of flow of a liquid or gas through a porous material.

Polarization: when charges are separated across plasma membrane of a cell; when membrane has potential.

Repolarization: membrane returns to resting potential after having been depolarized.

Resting Potential: constant membrane potential that exists when a nerve/muscle cell is not displaying rapid changes in potential (-70mV).

Threshold Potential: point where an explosive depolarization takes place typically between -50 and -55 mV.