Mathematical Modeling Action Potential in Cell Processes

Kenneth Leander Anderson Jr.[1], Jackie Chism[2], Quarail Hale[3], Paul Klockenkemper[2], Chelsi Pinkett[4], Christopher Smith[2], and Dr. Dorjsuren Badamdorj[2]

[1]Benedict College.
[2]Tennessee State University,
[3]Norfolk State University,
[4]Claflin University,
June 21, 2013

Abstract

The purpose of this paper is to analyze and understand three different models for action potential cell processes in computational cell biology. The three models were: Hodgkin-Huxley, FitzHugh-Nagumo, and Morris-Lecar. Using differential equations, linear algebra, and computer assisted simulations in the computer program MatLab, we were able to approximate numerical solutions and do phase portrait analysis and bifurcation analysis for each of the three models. We also came up with a modified form of the FitzHugh-Nagumo model using a Sine Function.

1 Introduction

A considerable question to answer is how does the body process information. For example, if a person touches a hot stove with his or her hand, the hand must send information to brain, which registers the data and sends a message back to the hand to pull away. In order to understand the dynamics of the process, it is important to understand the composition of neuron cells and nerve impulse transmission. In this paper, we will analyze a few proposed models that describe how information is transmitted through a neuron.

To begin with, it is important to note the physical make up of a cell. The cell membrane is a bi-layer that is permeable to certain materials. In other words, it allows some materials to pass through it while blocking the passage of others. During naturally occurring processes, some ionic compounds such as potassium chloride (KCl) will disassociate and try to diffuse through the cell membrane. Since the cell membrane is selectively permeable to K^+, the K^+ will diffuse through the cell membrane leaving the Cl^- behind. The process will create a positive net flow of charge into or out of the cell depending on the concentration difference. Consequently, there will be a electrical potential difference with one side of the cell membrane more positive than the other. Hence, the cell membrane can be viewed as a capacitor with the bi-layer being two charged plates. Thus, the cell membrane has a capacitance, an assumption needed to derive the subsequent nerve impulse transmission models.

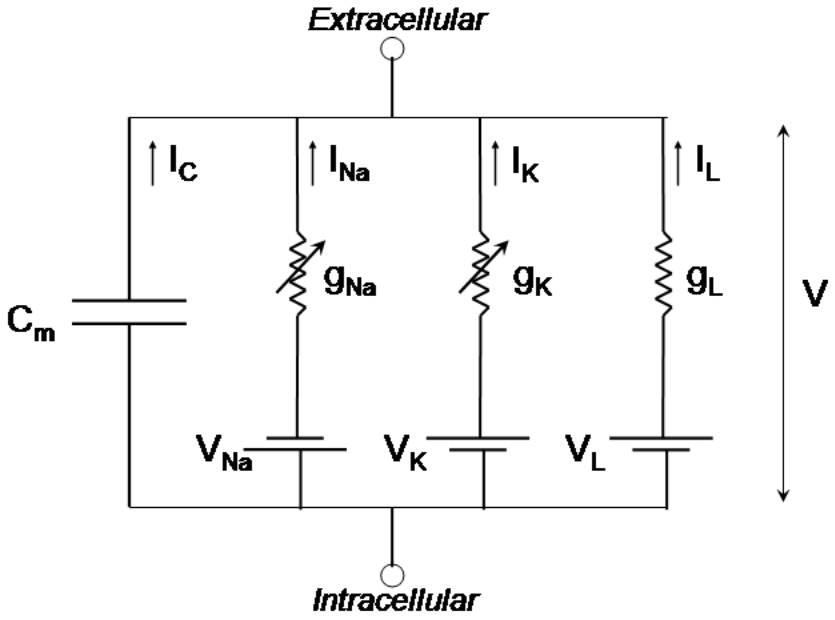
Accordingly, let there be a stimulus, such as the heat from the stove, the brain must send a signal to the hand to pull away. The brain sends messages through the body via electrical currents, also known as action potentials. When a stimulus is applied, a sodium ion channel opens up and allows an influx of sodium ions to come into the cell. The cell is generally polarized, however when the sodium rushes into the cell, the cell becomes depolarized at that point. Once the cell reaches a threshold potential more sodium ion channels open up and the depolarization moves down the cell. This process is called the action potential. Once the action potential has passed, the sodium ion channels close, and the sodium-potassium pump works to get the cell back to its normal resting potential, which is around $-70\ mV$.

The modeling of the forementioned process through mathematics is difficult, but there are several approaches. A well accepted approach is the Hodgkin-Huxley model proposed in 1952 by Alan Lloyd Hodgkin and Andrew Huxley. The Hodgkin-Huxley model consists of four differential equations, which is hard to analyze. Therefore, there are simpler models that exhibit the behavior of the Hodgkin-Huxley model qualitatively. Two such models we will examine are the FitzHugh-Nagumo model and Morris-Lecar, both of which are only a set of two differential equations; thus, they will be simpler to analyze and solve.

2 Hodgkin-Huxley Model

2.1 Derivation of Hodgkin-Huxley Model

The Hodgkin-Huxley model is based on the idea that the electrical properties of a segment of a cell membrane can be modeled by an equivalent circuit. In the picture below, one can see the flow of current (denoted by I) through the circuit.



Above: The equivalent circuit to a segment of the cell membrane.
Picture from http://thephysicsdomain.com/2013/03/28/047-hodgkin-huxley-hysteria/

Because a cell membrane behaves very much like a capacitor, the derivation of the Hodgkin-Huxley model for ion transport across a cell membrane begins with the general physical definition of capacitance:

$$C = \frac{Q(\mathbf{r}, t)}{V(\mathbf{r}, t)} \tag{1}$$

with

$$\mathbf{r} = \mathbf{r}(x, y, z), \tag{2}$$

where C is capacitance, $\mathbf{r}$ is the spatial coordinates vector, $Q(\mathbf{r}, t)$ is electrical charge as a function of space and time and $V(\mathbf{r}, t)$ is electric potential (or voltage) as a function of space and time. For a cell membrane, provided that the membrane capacitance (now denoted by C_m) remains constant and electric current is the rate of change of electric charge with respect to time ($\frac{\partial Q}{\partial t}$), conservation laws dictate that the capacitive current, denoted by $I(V, \mathbf{r}, t)$, would be

$$\frac{\partial Q}{\partial t} = C_m \frac{\partial V}{\partial t} = I(V, \mathbf{r}, t) = -\nabla \cdot \mathbf{J}(\mathbf{r}) + I_{ion}(V, t) \tag{3}$$

where, $I_{ion}(V, t)$ is the cell membrane current and $\mathbf{J}(\mathbf{r})$ is the space dependent current vector. So, more specifically, Equation (3) becomes

$$C_m \frac{\partial V}{\partial t} = -\nabla \cdot \mathbf{J}(\mathbf{r}) + I_{ion}(V, t), \tag{4}$$

However, using space clamps positioned at specific points along the membrane will make the voltage uniform across the system, meaning that the space dependence can be ignored, i.e.

$$\nabla \cdot \mathbf{J}(\mathbf{r}) \quad = \quad 0 \tag{5}$$

reducing Equation (3) further down to

$$C_m \frac{dV(t)}{dt} = I_{ion}(V, t). \tag{6}$$

Now consider the movement of an ion A across the membrane, moving transverse to I_{ion}. The transverse potential drop across the membrane due to the concentration differences caused by this movement is given by the Nernst Potential:

$$V_A = \frac{RT}{zF} \ln \frac{[A]_e}{[A]_i}, \tag{7}$$

where $[A]_i$ and $[A]_e$ denote respective internal and external concentrations of the ion A, R is the universal gas constant, T is absolute temperature, F is Faraday's constant, and z is the charge of ion A. The potential drop across the membrane due to a transverse electrical current is denoted by $\frac{1}{g}(I_\tau)$, where g is the membrane conductance. Summing these two potential drops (yielding the total potential V) and than solving for the transverse current yields

$$I_\tau = g(V - V_A). \tag{8}$$

For multiple types of ions moving across the membrane the transverse current becomes

$$I_\tau = \sum_j g_j(V - V_j). \tag{9}$$

where j is the number of ion types (including leakage).

Using the principle in Kirchoff's current law that the sum of all currents in a closed system equals zero, or

$$\sum_k I_k = 0, \tag{10}$$

we can deduce that

$$I_{ion} + I_\tau = 0 \Rightarrow I_{ion} = -I_\tau. \tag{11}$$

When a disturbance occurs (such as external stimuli acting on the cell), then the sum of the two former currents will equal the external or applied current (denoted by I_{app}), giving us

$$I_{ion} = -I_\tau + I_{app}, \tag{12}$$

which yields our first differential equation:

$$C_m \frac{dV(t)}{dt} = -\sum_j g_j(V - V_j) + I_{app}. \tag{13}$$

Note: I_{app} here is in units of μA/cm^2 and could either be constant or a function of time (e.g. sinusiodal current).

When a stimulus occurs, the sodium ion channels open and there is an influx of sodium ions rushing into the cell. Once the action potential has moved further along the cell axon the sodium ion channels close and the potassium ion channels open. For this system with sodium (Na) and potassium (K) ions passing across the cell membrane (with some ion leakage L), Equation (13) becomes

$$C_m \frac{dV(t)}{dt} = -g_{\bar{N}a}(V - V_{Na}) - g_{\bar{K}}(V - V_K) - g_L(V - V_L) + I_{app}, \tag{14}$$

with g_L being an experimentally determined constant. If the values of $g_{\bar{K}}$ and $g_{\bar{N}a}$ are also held constant, the model breaks down. Therefore, the membrane conductances of Sodium and Potassium must be treated as functions of voltage as well as time, i.e

$$g_{\bar{N}a}(V,t) = F_{Na}(V,t) \tag{15}$$

$$g_{\bar{K}}(V,t) = F_K(V,t) \tag{16}$$

making the Sodium conductance

$$\frac{\partial g_{\bar{N}a}}{\partial t} = f_{Na}(V,t) = g_{Na} m^3 h, \tag{17}$$

now with g_{Na} being an experimentally determined constant, m being the sodium ion activation gates (there are three between the space clamps, hence m^3 which is consistent with experimental data), and h being the sodium ion deactivation gate. Both m and h are functions of time and satisfy the following two differential equations:

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

$$\frac{dh(t)}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h, \tag{19}$$

where the coefficients $\alpha_m(V)$, $\beta_m(V)$, $\alpha_h(V)$, and $\beta_h(V)$ are all experimentally determined functions of voltage. Similarly for Potassium, the conductance is

$$\frac{\partial \bar{g_K}}{\partial t} = f_K(V,t) = g_K n^4, \tag{20}$$

with g_K now also being an experimentally determined constant and n being the potassium ion influx gates (there are four between the space clamps, hence the n^4 which also is consistent with experimental data), which is a function of time and satisfies the last of four differential equations:

$$\frac{dn(t)}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n, \tag{21}$$

where the coefficients $\alpha_n(V)$ and $\beta_n(V)$ are also functions of voltage determined by experimental results.

Using experimental data, Hodgkin and Huxley chose the following values for these six coefficient functions of voltage:

$$\alpha_m(V) = \frac{(0.1)(25-V)}{e^{(\frac{25-V}{10})}-1} \tag{22}$$

$$\beta_m(V) = 4e^{\frac{-V}{18}} \tag{23}$$

$$\alpha_h(V) = (0.07)e^{\frac{-V}{20}} \tag{24}$$

$$\beta_h(V) = \frac{1}{e^{(\frac{30-V}{10})}+1} \tag{25}$$

$$\alpha_n(V) = \frac{(0.01)(10-V)}{e^{(\frac{10-V}{10})}-1} \tag{26}$$

$$\beta_n(V) = (0.125)e^{\frac{-V}{80}}. \tag{27}$$

Thus, our system of four differential equations modeling the behavior of a stimulated cell membrane is:

$$C_m\frac{dV(t)}{dt} = -g_K n^4(V-V_K) - g_{Na}m^3h(V-V_{Na}) - g_L(V-V_L) + I_{app} \tag{28}$$

$$\frac{dm(t)}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m \tag{29}$$

$$\frac{dh(t)}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h \tag{30}$$

$$\frac{dn(t)}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n \tag{31}$$

with conductance constants:

$$\begin{aligned} g_K &= 36\mu\text{S/cm}^2 \\ g_{Na} &= 120\mu\text{S/cm}^2 \\ g_L &= 0.3\mu\text{S/cm}^2 \end{aligned} \tag{32}$$

ion voltage constants:

$$\begin{aligned} V_{Na} &= 115\text{mV} \\ V_K &= -12\text{mV} \\ V_L &= 10.6\text{mV} \end{aligned} \tag{33}$$

membrance capacitance constant:

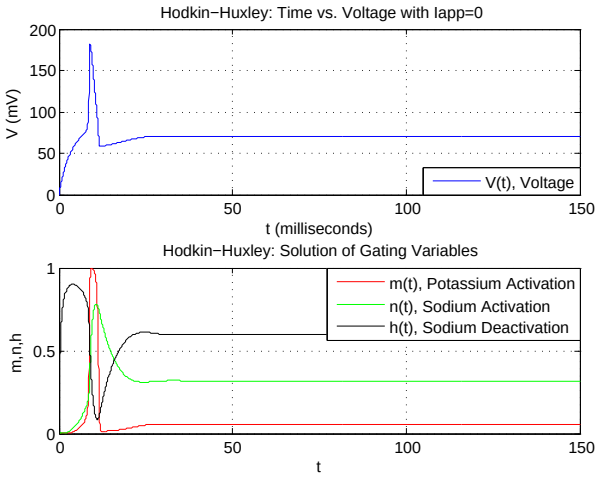
$$C_m = 1.0\mu\text{F/cm}^2 \tag{34}$$

and initial conditions for membrane potential and the dimensionless gating variables:

$$\begin{aligned} V(0) &= -70\text{mV} \\ m(0) &= 0 \\ h(0) &= 0 \\ n(0) &= 0 \end{aligned} \tag{35}$$

2.2 Analysis of the Hodgkin-Huxley Model

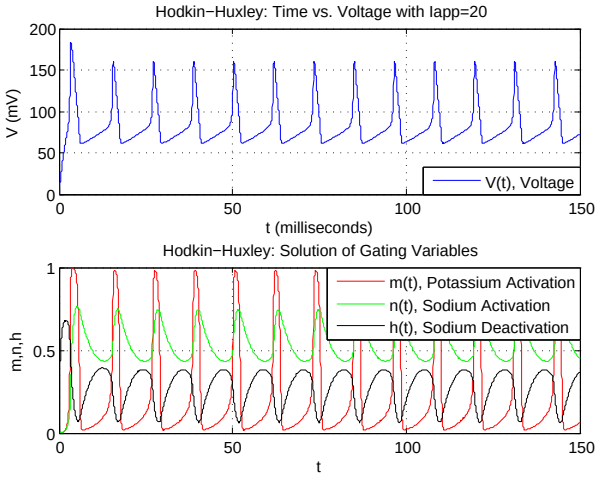
Because it is impossible to find an explicit solution for the Hodgkin-Huxley model, computer simulations are required to approximate the graphs of the system of equations. To analyze what the model means, we first simulate the membrane potential as a function of time with no applied current ($I_{app} = 0\mu\text{A/cm}^2$) and the dimensionless gating variables, each as a function of time, with a time period of 150 milliseconds.



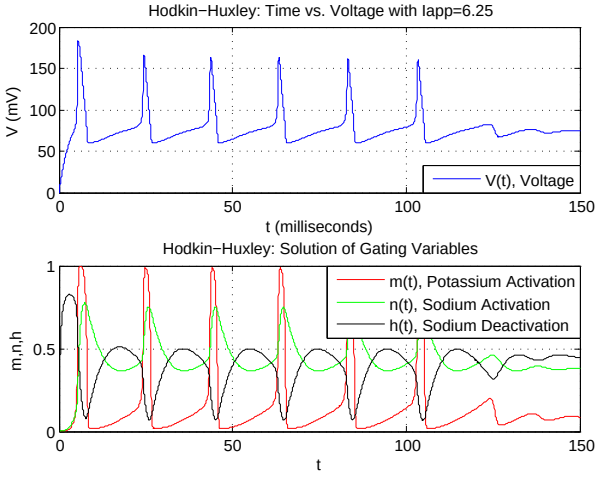
From these graphs, we can see that without an external stimulus, there will be one oscillation and then the membrane returns to equilibrium. Because of the complexity of this system, there will always be at least one spike no matter what the initial conditions are.

Hodgkin-Huxley: Constant Current

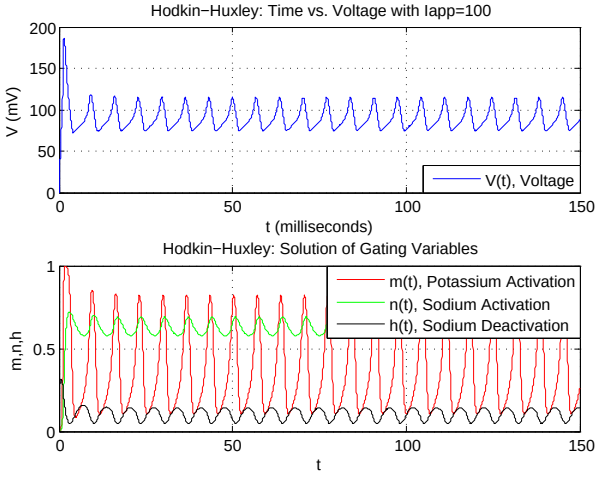
When a constant external current is applied (e.g. $I_{app} = 20\mu\text{A/cm}^2$), there will be continuous oscillations, as shown in the following graphs:



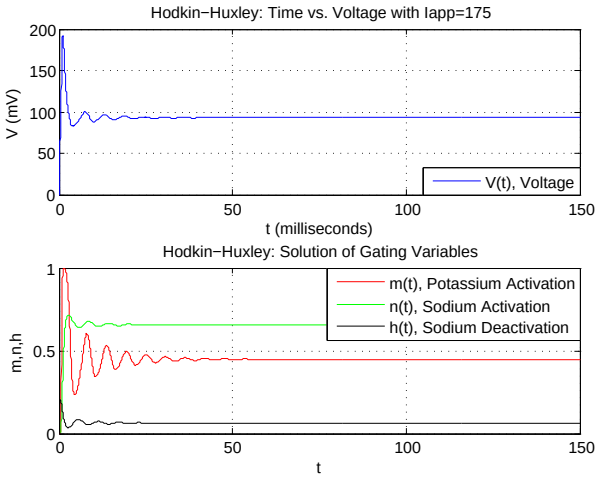
Because the applied current is constant, the oscillations are smooth and steady. If the applied current is below 6.26 μA/cm^2 (say $I_{app} = 6.25\mu$A/cm^2) the oscillations will fall off within the 150 millisecond time period.



At 100 μA/cm^2, the oscillations are a lot smaller after the initial spike but don't die off yet within the 150 millisecond time period.

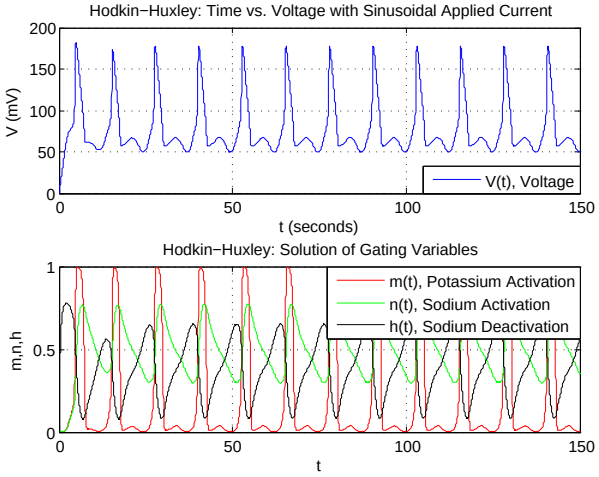


By 175 μA/cm^2, the oscillations are dying off quickly and returning to equilibrium within the 150 millisecond time period once again.



Hodgkin-Huxley: Sinusiodal Current

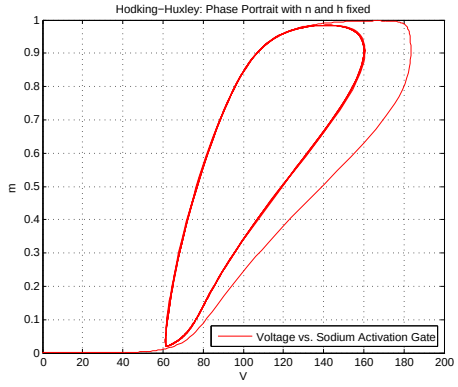
If instead of a constant external current, we apply an in-phase sinusiodal current with an angular frequency of 1 rad/s and an amplitude of 20 μA/cm^2 (e.g. $I_{app} = 20 \sin t$) our graphs are:



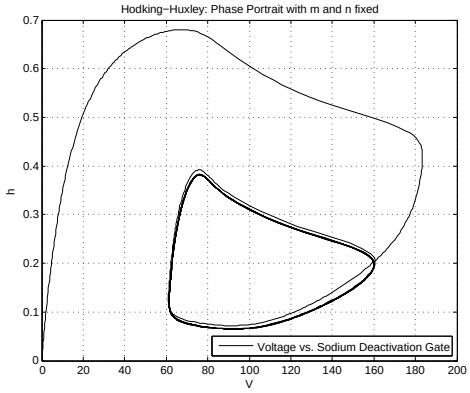
giving us bumpier yet continuous oscillations.

Phase Portrait Analysis

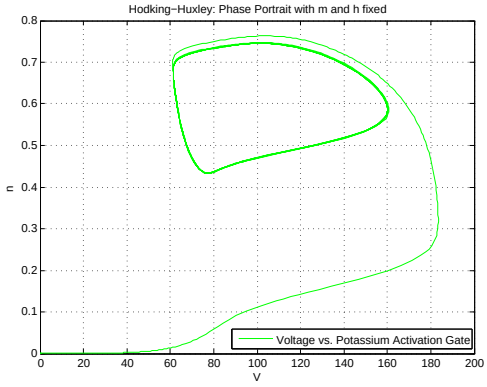
In order to get a nullcline plot, we must fix two of the three gating variables. We will also fix I_{app} back to 20 μA/cm^2. If we fix n and h, that leaves us with m as a function of V in the following graph:



Likewise, if we fix m and n, we get a graph with h as a function of V:



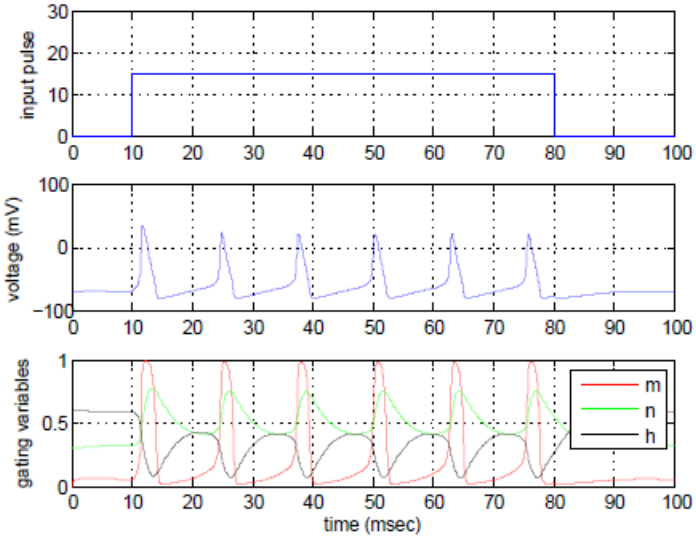
And n as a function of V with m and h fixed yields:



From these graphs, it's clear that as the sodium channels close, the potassium channels open. Hence the phase portraits for h and n being mirror images of each other.

2.3 Solving Hodgkin-Huxley Numerically

Due to the difficulty in explicitly solving this four dimensional system (as noted above), another method must be used to approximate the solutions of the system. One of various numerical methods to solve such a system is the Runge-Kutta method of order. Using this method yields the following graphs:



The top graph here shows the duration of an applied stimulus. The middle graph shows oscillations, which is the depiction for the action potential moving along the cell membrane for the duration of the applied stimulus. The bottom graph shows the activation and deactivation of the gating variables.

3 FitzHugh-Nagumo Model

3.1 From Hodgkin-Huxley to FitzHugh-Nagumo

From the Hodgkin-Huxley model, we know that the cell-membrane carries potential across the inner and outer surface of the cell. However, with the use of the voltage ion channels and currents that flow through it, shows the electrical behavior of the cell by using a system of four differential equations. The Hodgkin-Huxley is considered to be difficult to non- dimensionalize because of the difficulty to do the partial derivative for four equations. So, its very simple to half the Hodgkin- Huxley into two equations. Overtime, the system of equations being use in the Hodgkin-Huxley model can be modified into a simplified form of two differential equations. This type of system, that involve a linear nullcline for the slow variable and an N shaped Nullcline for the fast variable that forms oscillation. This became the motivation of the FitzHugh-Nagumo model. The FitzHugh-Nagumo consist of variable, one fast(v) and one slow(w).The fast variable has a cubic nullcline and its called the dependent variable, and the slow variable is the recovery variable that is consistently increasing. A parameter that plays a major role in the FitzHugh-Nagumo model is Epsilon .This parameter has been added to more easily control the speed of one variable that is connected to the other. The FitzHugh-Nagumo doesnt need to be biologically based to solve the model like the Hodgkin-Huxley, but simply mathematically based. Since the FitzHugh-Nagumo model is simplified version of the Hodgkin-Huxley which models the activation and deactivation dynamics of the cell membrane, gave way of the idea that the cell-membrane relates more to a non-linear current-voltage device or electrical circuit with three components; a resistor, inductor, and a battery. This system was suggested by Fitzhugh and the equivalent circuit by Nagumo himself. By using the Kirchhoffs Law, Nagumo gave us differential equations for the behavior of the cell-membrane circuit which will be mention in this report.

3.2 Fitz-Hugh Nagumo

The Hodgkin-Huxley model can be represented in terms of two variables, one fast and one slow. The FitzHugh-Nagumo model presents this as a simplified form with (v) being the fast variable and (w) being the slow one. The general set of equations for the FitzHugh-Nagumo model are:

$$\epsilon \frac{dv}{dt} = f(v,w) + I \tag{36}$$

and

$$\frac{dw}{dt} = g(v,w) \tag{37}$$

The nullcline $f(v,w) = 0$ of the fast variable (v) is has a cubic shape, while the nullcline $g(v,w) = 0$ of the slow variable (w) is monotonically increasing. The nullclines of both the fast and slow variables have a single intersection point denoting the critical point. Thus, the graph of the phase plane of these nullclines is

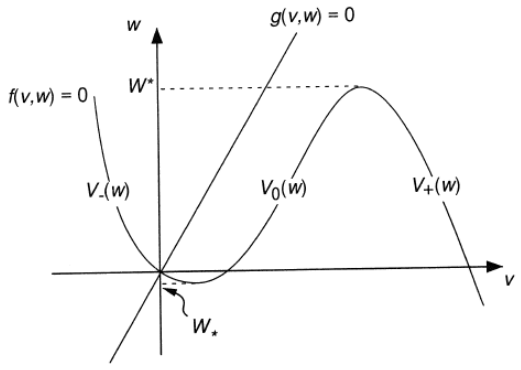


Figure 1: This image was taken from Sneyd and Keener's "Mathematical Physiology"

We start by understanding cell membrane capacitance. It is a nonlinear current-voltage device. A Japanese electrical engineer, Nagumo, built this nonlinear circuit in the 1960s using a tunnel diode.

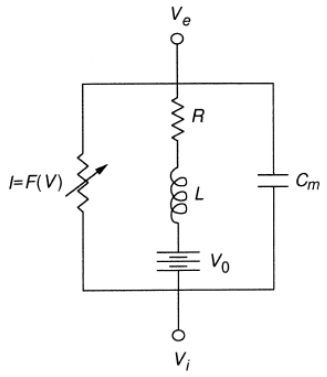


Figure 2: This image was taken from Sneyd and Keener's "Mathematical Physiology

Using the Kirchoff's laws, the equations for the circuit diagram are:

$$C_m \frac{dV}{d\tau} + F(V) + i = -I_0. \tag{38}$$

and

$$L\frac{di}{d\tau} + Ri = V - V_0 \tag{39}$$

where I_0 is the applied external current, i is the current that is traveling through the resistor-inductor into battery V_0 that give us the potential gain across the battery. The membrane potential is differentiated to the dimensional time (τ). The reason is that time (t) is introduced as a dimensionless time variable. The function F(V) is assumed to be the "cubic" shape, but that is more into the electrical physics side of the model. After Electrical physicist introduce the dimensionless variables, $\frac{V}{V_1}$, $w = \frac{R_1 i}{V_1}$, $f(v) = \frac{-R_1 F(V_1 v)}{V_1}$, and $t = \frac{L\tau}{R_1}$, the differential equation becomes the function of both state variables (v, w)

$$\epsilon \frac{d(v)}{d(t)} = f(v) - w - w_0 \tag{40}$$

$$\frac{d(w)}{d(t)} = v - \gamma w - v_0 \tag{41}$$

where, $\epsilon = \frac{R_1^2 C_m}{L}$, $w_0 = \frac{R_1 I_0}{V_1}$, $v_0 = \frac{V_0}{V_1}$, and $\gamma = \frac{R}{R_1}$. Epsilon (ϵ) controls the speed of the parameter of the equation and Gamma (γ) is the slope of the equation.

The two sets of equations that we used to give the Fitzhugh-Naguno models are

$$A = \begin{cases} 0.01\dfrac{dv}{dt} = v(v-0.1)(1-v) - w + I \\ \dfrac{dw}{dt} = v - 0.5w \end{cases} \tag{42}$$

$$B = \begin{cases} 0.01\dfrac{dv}{dt} = v(v+0.1)(1-v) - w + I \\ \dfrac{dw}{dt} = v - 0.5w \end{cases} \tag{43}$$

Solving these sets of equations will yield the following graphs:

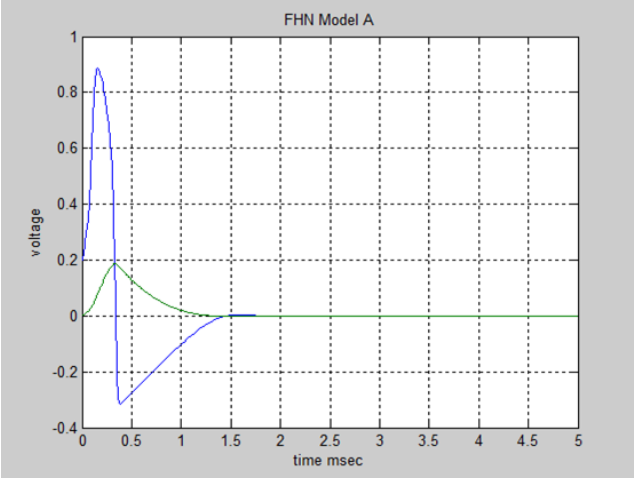


Figure 3: Graph of $\boldsymbol{A}$

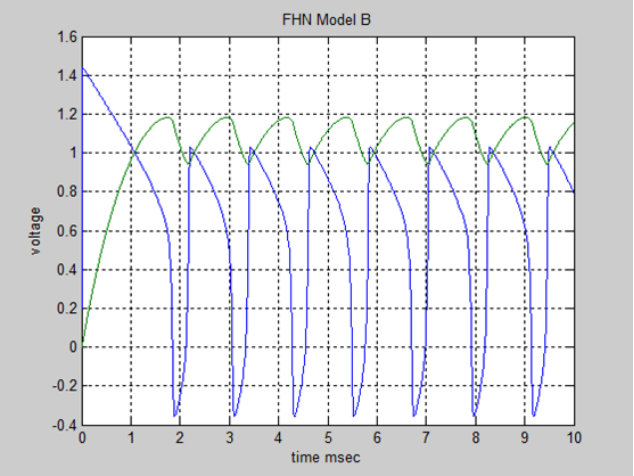


Figure 4: Graph of $\boldsymbol{B}$

The fast variable, $\boldsymbol{v}$, is shown in blue and the slow variable, $\boldsymbol{w}$, is shown in green. Notice that the graph of $\boldsymbol{A}$ only has one spike while the graph of $\boldsymbol{B}$ spontaneous oscillates. The only difference between the sets of equations (7) and (8) is the sign on $(v \pm 0.1)$. There was no external current applied to either equation $(I = 0)$. In order for $\boldsymbol{A}$ to oscillate like $\boldsymbol{B}$, a contant external current needs to be applied. This will be shown later. This is very important. With no external current applied, the graph should spike and then die out. This tells us that the $(+)$ instead of the $(-)$ sign is critical. The set of equations in $\boldsymbol{B}$ would not be ideal to use because it does not model natural behavior. With no applied stimulus, there should not be spontaneous oscillations.

Below are the phase planes for each of the two graphs:

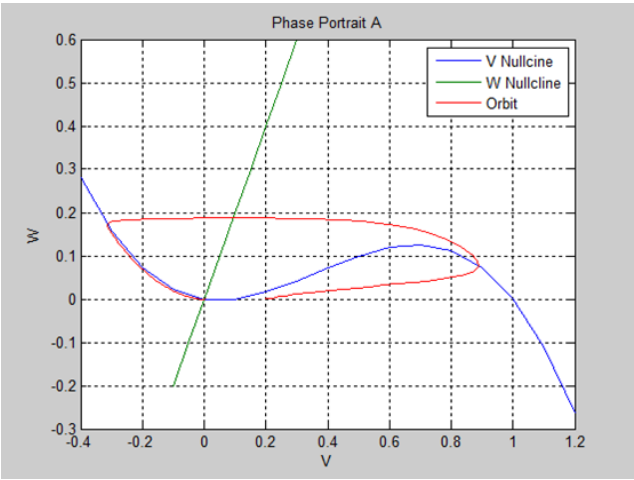


Figure 5: Phase portrait of $\boldsymbol{A}$

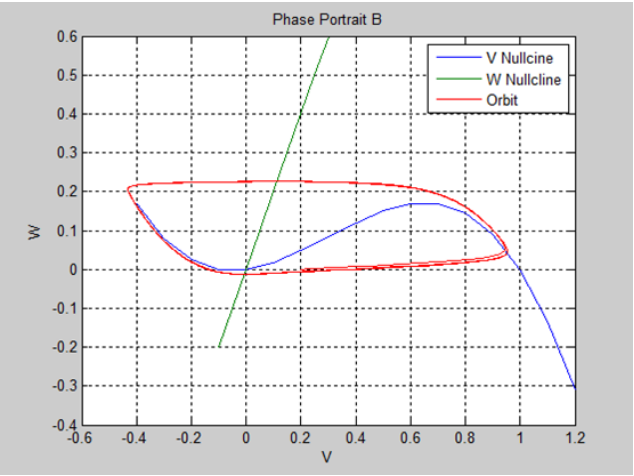


Figure 6: Phase portrait of $\boldsymbol{B}$

For $\boldsymbol{A}$, the nullcline for $\boldsymbol{v}$ is $w = -v^3 + 1 + 1.1V^2 - 0.1v$ which is shown in blue and the nullcline for $\boldsymbol{w}$ is $g(v) = 2v$ and is shown in green. For $|boldcymbolB$, the nullcline for $\boldsymbol{v}$ is $w = -v^3 + 1 + 0.9V^2 - 0.1v$ which is shown in blue and the nullcline for $\boldsymbol{w}$ is $g(v) = 2v$ and is shown in green.Notice that each of the graphs are identical with Sneyd and Keener's illustration of the phase plane (Figure 1). Just as the graph of $\boldsymbol{A}$ only had one peak before it died out, the phase plane of $\boldsymbol{A}$ starts at the initial condition and only does one orbit. The graph of $\boldsymbol{B}$ oscillates and likewise, the phase plane has continuous orbit.

The nullclines intersect at (0,0), which is the only critical point. In order to see the stability of the critical point, we computed the Jacobian at (0,0).

$$\mathbf{J}(\mathbf{0},\mathbf{0}) = \begin{pmatrix} \dfrac{\partial(f)}{\partial(v)}(0,0) & \dfrac{\partial(f)}{\partial(w)}(0,0) \\ \dfrac{\partial(g)}{\partial(v)}(0,0) & \dfrac{\partial(g)}{\partial(w)}(0,0) \end{pmatrix} = \begin{pmatrix} -3(0)^2 + 2.2(0) - 0.1 & -1 \\ 1 & -0.5 \end{pmatrix} = \begin{pmatrix} -0.1 & -1 \\ 1 & -0.5 \end{pmatrix}$$

The eigenvalues for this matrix are $\lambda = 0.3 + 0.9798i$ and $\lambda = 0.3 - 0.9798i$. This means that the critical point is stable and spiral.

Next we want to see the changes of behavior in our functions when one parameter changes. Thus, we do a bifurcation analysis testing different values of I, $\boldsymbol{\gamma}$, and $\boldsymbol{\epsilon}$. The general form of the studied FHN model is

$$A = \begin{cases} f(v,w) = \dfrac{1}{\boldsymbol{\epsilon}} v(v-\alpha)(1-v) - w + I \\ g(v,w) = v - \boldsymbol{\gamma} w \end{cases} \tag{44}$$

The original values of I, $\boldsymbol{\gamma}$, and $\boldsymbol{\epsilon}$ were $I = 0$, $\boldsymbol{\gamma} = 0.5$, and $\boldsymbol{\epsilon} = 0.01$. The following graphs show the variations in the oscillations for different parameter values.

Adding constant current gives the following changes to the graph of $\boldsymbol{A}$:

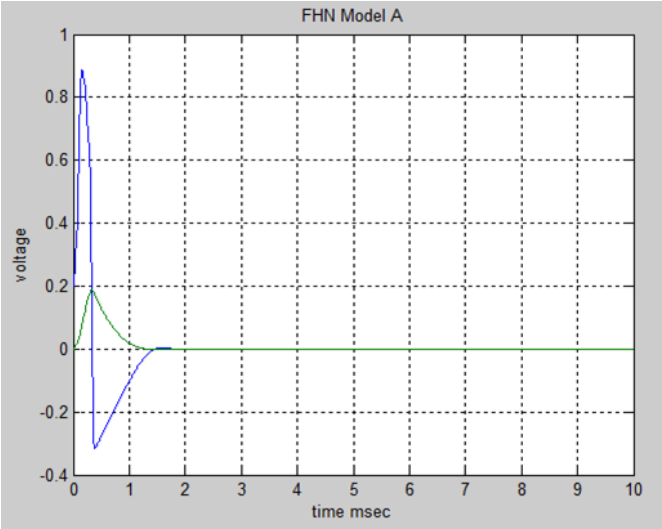


Figure 7: $I = 0 \longrightarrow$ One spike, no oscillations

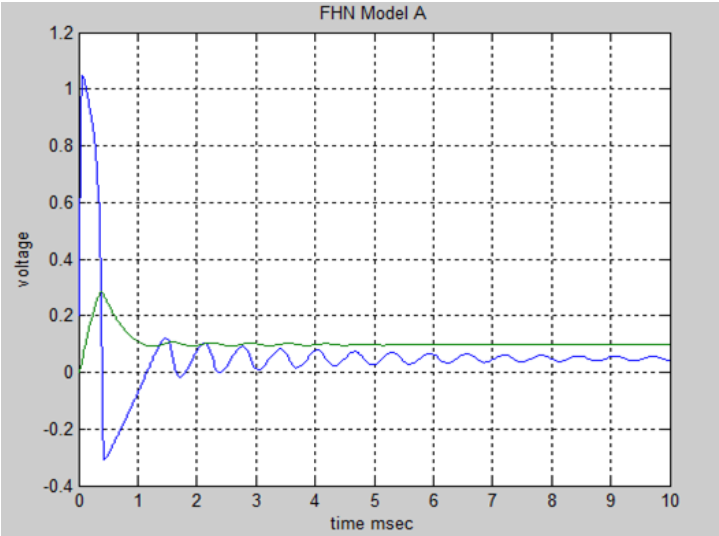


Figure 8: $I = 0.1 \longrightarrow$ Oscillations die out, not enough stimuli

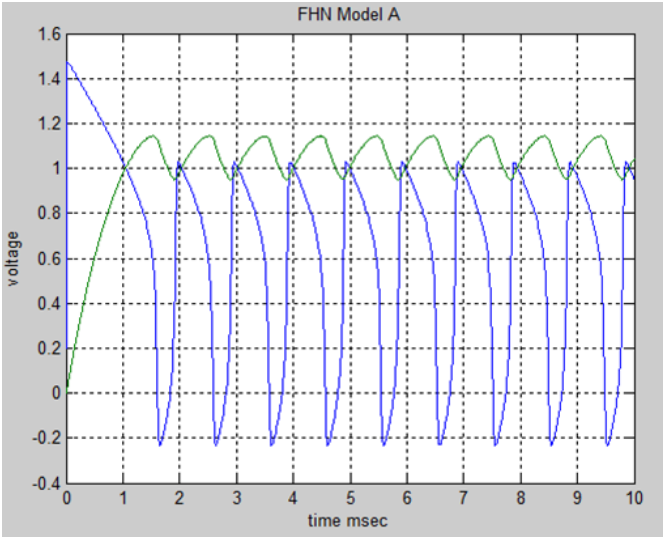


Figure 9: $I = 1 \longrightarrow$ Constant oscillations

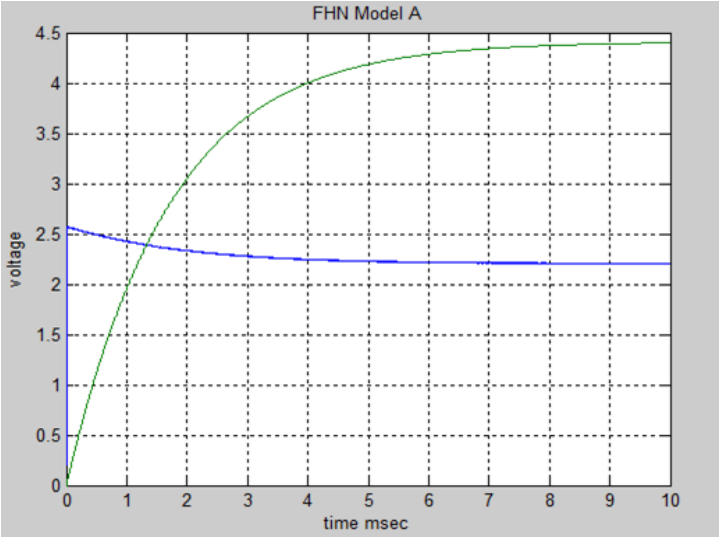


Figure 10: $I = 10, \longrightarrow$ Too much applied current

Studying these parameter values tells us that the constant applied current, I, is $0.11 < I < 1.2$.

With a constant applied current of $I = 1$, changing values of γ gives the following changes to the graph of $\boldsymbol{A}$:

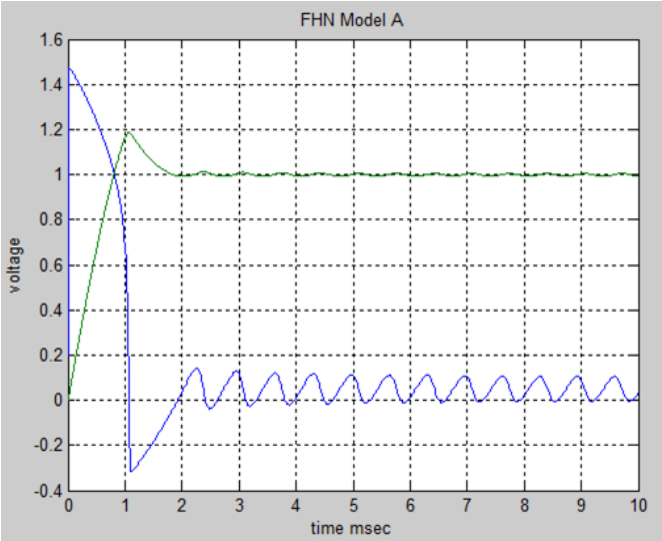


Figure 11: $\boldsymbol{\gamma} = 0.05 \longrightarrow$ Oscillations die out

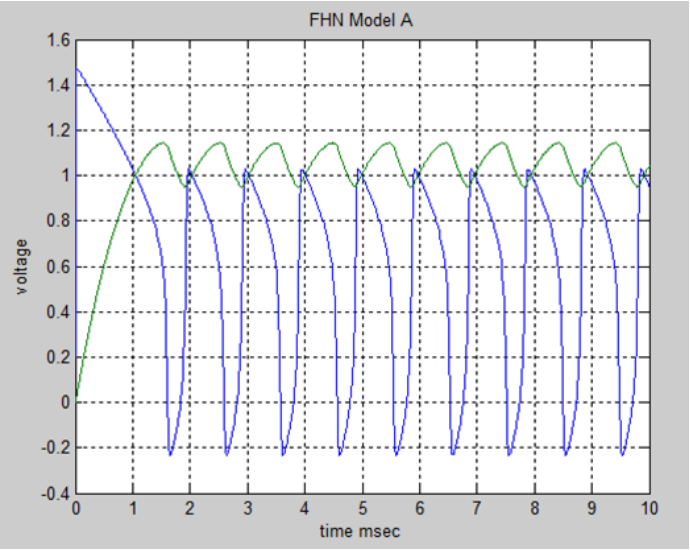


Figure 12: $\boldsymbol{\gamma} = 0.5 \longrightarrow$ Constant oscillations

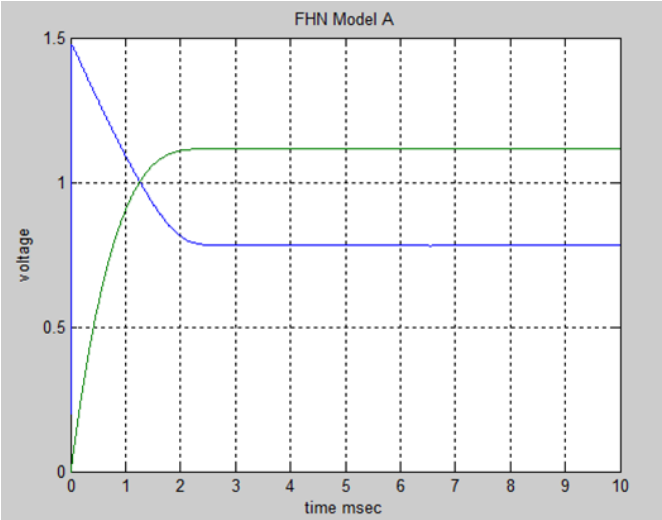


Figure 13: $\boldsymbol{\gamma} = 0.7 \longrightarrow$ Model does not work

Studying these parameter values tells us that the values of $\boldsymbol{\gamma}$ need to be $0.05 < \boldsymbol{\gamma} < 0.6$.

With a constant applied current of $I = 1$ and $\gamma = 0.5$, changing values of ϵ gives the following changes to the graph of $\boldsymbol{A}$:

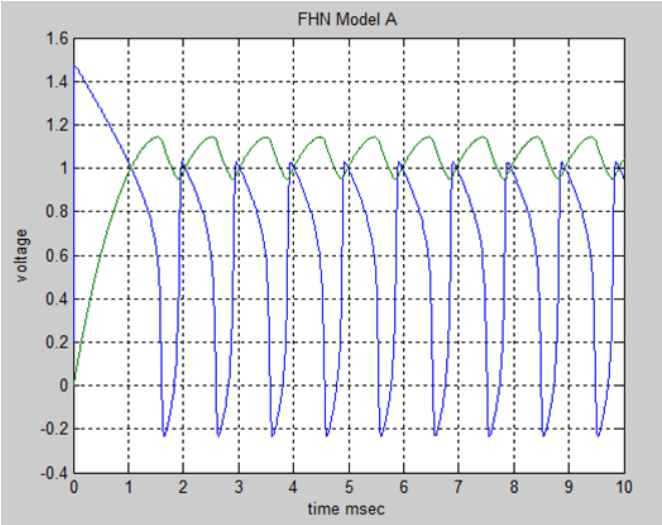


Figure 14: $\epsilon = 0.01 \longrightarrow$ Continuous oscillations

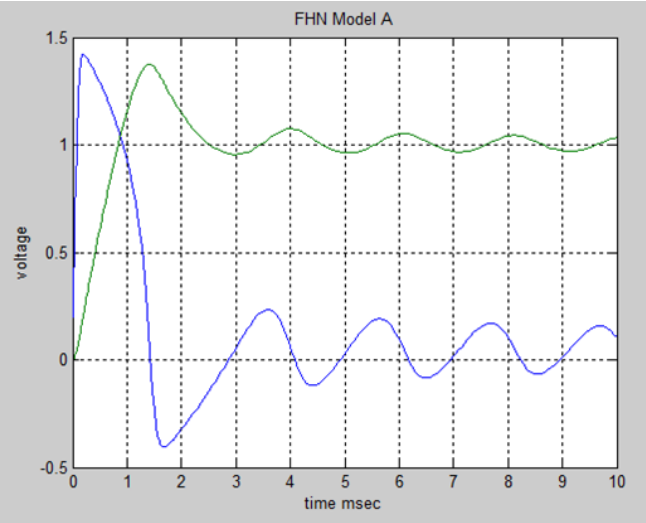


Figure 15: $\epsilon = 0.1 \longrightarrow$ Oscillations die out

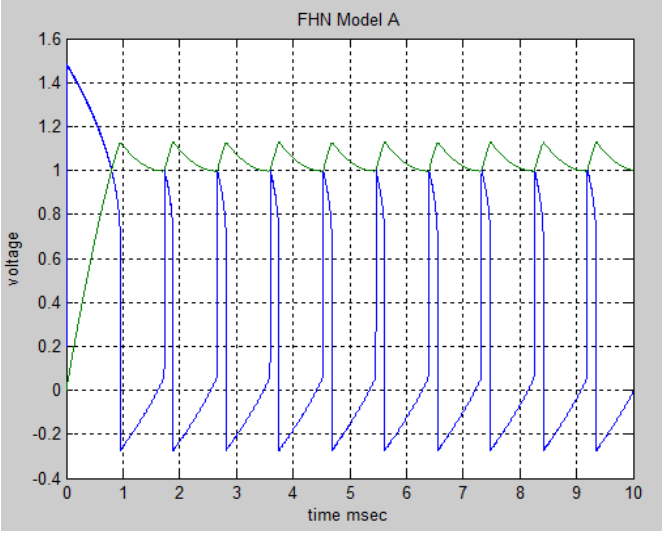


Figure 16: $\epsilon = 0.0001 \longrightarrow$ Continuous oscillations

Studying these parameter values tells us that the values of ϵ need to be $\epsilon < 0.1$.

3.3 Modified FitzHugh-Nagumo Model

The FitzHugh-Nagumo general model has two equations whose nullclines display a cubic shape function and a monotonically increasing function. The new cubic shape function, $f(v, w)$, that we derived with the previous increasing function, $g(v, w)$, is:

$$A = \begin{cases} f(v,w) = \frac{1}{\epsilon} sin(v) - w + I \\ g(v,w) = v - \gamma w \end{cases} \tag{45}$$

The model behaves the same way as the original FHN model and exhibits the same phase plane.

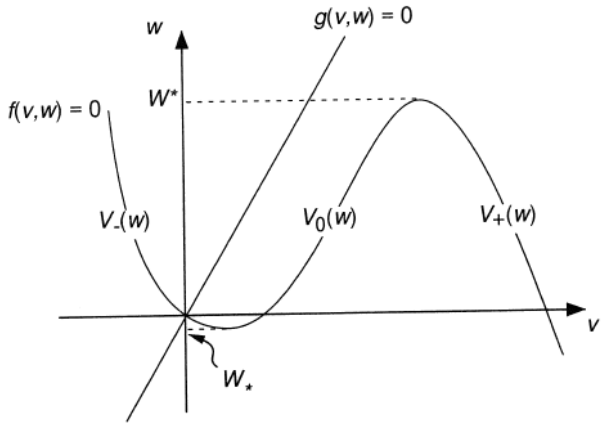


Figure 17: Original FHN Phase Plane

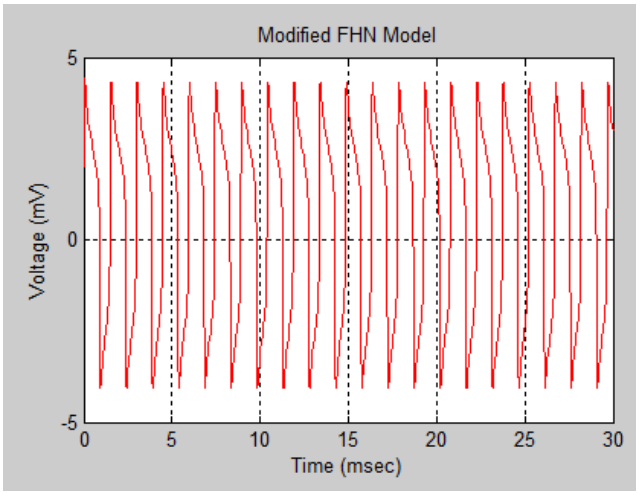


Figure 18: Modified FHN Model Graph

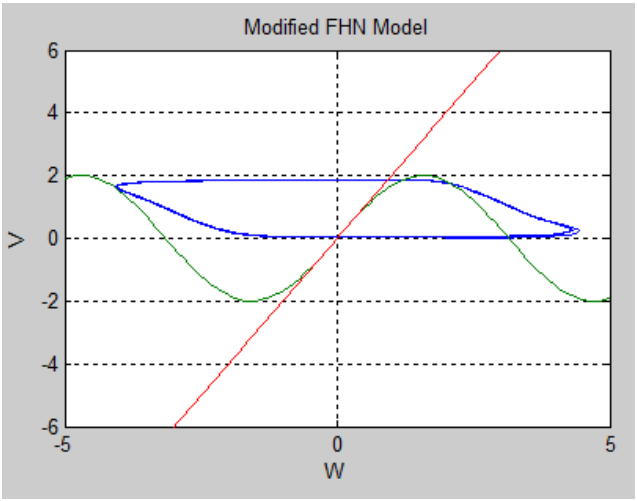


Figure 19: Modified FHN Model Phase Plane

The function, $f(v, w)$, has parameter values of $\epsilon = 0.01$, an applied stimulus of $I = 1$, and $\gamma = 0.5$. Though the function does not fit a biological model because it oscillates even without applied stimulus, it still has the same behavior as the original FHN model.

The nullclines intersect at (0,0), which is the only critical point. In order to see the stability of the critical point, we computed the Jacobian at (0,0).

$$\mathbf{J}(\mathbf{0},\mathbf{0}) = \begin{pmatrix} \dfrac{\partial(f)}{\partial(v)}(0,0) & \dfrac{\partial(f)}{\partial(w)}(0,0) \\ \dfrac{\partial(g)}{\partial(v)}(0,0) & \dfrac{\partial(g)}{\partial(w)}(0,0) \end{pmatrix} = \begin{pmatrix} 0.8cos(0) & -1 \\ 1 & -0.5 \end{pmatrix} = \begin{pmatrix} 0.8 & -1 \\ 1 & -0.5 \end{pmatrix}$$

The eigenvalues for this matrix are $\lambda = 0.15 + 0.759934i$ and $\lambda = 0.15 - 0.759934i$. This means that the critical point is stable and spiral. The behavior of the critical point is identical with the behavior of the critical point in the original FHN model.

4 Morris-Lecar Model

4.1 History of the Morris-Lecar Model

In 1981, Charles Morris and Harold Lecar proposed their eponymous equation as an reduced excitation model in the vein of the Hogdkin-Huxley equations, which constitutes an exact description of the conductance-based model for the giant squid neuron. In particular, they begin with an "already reduced" system of equations taken from the voltage clamp studies of Keynes, which proposes that the relevant state variables for the barnacle muscle are, along with the membrane potential, the proportion of voltage dependent Ca^+ and K^+ ion channels open at a given time(in which, the Na+ conduction plays no significant role in dynamics). The Morris-Lecar Model is a two-dimensional "reduced" excitation model applicable to systems having two non-inactivating voltage-sensitive conductance. The original form of the model employed an instantaneously responding voltage-sensitive Ca^+ conductance for excitation and a delay voltage-dependent K^+ conductance for recovery. The biological system studied was the Purkinje fibers through its membrane potential and the concentrations which had an effect on it. This model used a simplified version of the Hodgkin-Huxley model. A reduced system of equations was created that produce the same results for most cases. In order to approximate the muscle reactions appropriately, the models are based off of one you would use to follow an equivalent circuit design.

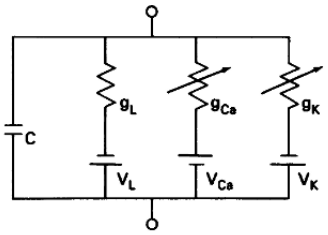


FIGURE 1 Equivalent circuit for a patch of space-clamped barnacle sarcolemma.

4.2 Morris-Lecar

Using the Morris-Lecar Model, techniques employed are known as current and space clamping, which essentially eliminated spatial variations the traveling action potential and fixed the current across the membrane to set parameter which the experimenter could control. Then in order to reduce the model, they submerged the barnacle muscle in various solutions in order to eliminate either Ca^+ and Na^+ conductance, or in the case of the Morris-Lecar equation, simultaneously optimize them. By doing this, they reduced the dynamics of the system to two state variables (depending on which solution the barnacle is submersed in), which considerably simplifies possible behavior the system can exhibit due to special topological properties of the phase plane that is not enjoy by higher dimensional Euclidean space (namely that a simple closed curve divides the plane into two distinct connected components.

4.2.1 Principle Assumptions

Generally, excitable systems have more than two relevant excitation variables, because there are often more than two species of gated channels and also because some channels have autonomous inactivation processes. Thus the primary assumption in using a two-dimensional model is that the true higher-order system can in fact be projected onto a two-dimensional phase space without altering the topological properties of the phase profile. This is true for the four-dimensional Hodgkin-Huxley system, which has a single singular point and exhibits excitation phenomena that can all be duplicated in two dimensions. There are other neural excitation phenomena such as bursting oscillations or chaotic firing which are intrinsically higher-dimensional, and cannot be duplicated in the phase plane. The principal assumptions underlying the Morris-Lecar model include:

- Equations apply to a spatially iso-potential patch of membrane.
- There are two persistent (non-inactivating) voltage-gated currents with oppositively biased reversal potentials. The depolarizing current is carried by Na^+ or Ca^{2+} ions (or both), depending on the system to be modeled, and the hyperpolarizing current is carried by K+.
- Activation gates follow changes in membrane potential sufficiently rapidly that the activating conductance can instantaneously relax to its steady-state value at any voltage.

- The dynamics of the recovery variable can be approximated by a first-order linear differential equation for the probability of channel opening. This assumption is never exactly true, since channel proteins are composed of subunits, which must act in concert, to reach the open state. Despite missing delays in the onset of recovery, the model appears to be adequate for phase-plane considerations for many excitable systems.

4.2.2 Variables and Parameter of Morris-Lecar Model

Listed below are the dimensional parameters and variables for the Morris-Lecar Model:

- V - Membrane Potential (mV)
- W - Recovery Variable (mV)
- I_{app} - Applied Current Stimulus($\frac{\mu A}{cm^2}$)
- T - Time (ms)
- C_m - Membrane Capacitance($\frac{\mu F}{cm^2}$)
- g - Instantaneous(or maximum) Membrane Conductance($\frac{mmho}{cm^2}$)
- V_{Ca}, V_K, V_L - equilibrium potential corresponding to leak, Ca++, and K+ conductances, respectively (mV)
- v_1 - potential (mV)
- v_2 - reciprocal of slope of voltage dependence (mV)
- v_3 - potential (mV)
- v_4 - reciprocal of slope of voltage dependence (mV)
- K - Potassium
- Ca - Calcium
- L - Leakage

4.2.3 Morris-Lecar Model

Using the variables from the previous section, Morris and Lecar was able to derive the equations of the model:

$$C_m \frac{dV}{dt} = -g_{Ca} M_\infty(V)(V - V_{Ca}) - g_K W(V - V_k) - g_L(V - V_L) + I_{app} \tag{46}$$

$$\frac{dW}{dt} = \frac{W_\infty(V) - W}{T_W(V)} \tag{47}$$

4.3 Solving the Morris-Lecar Model

To solve the Morris-Lecar Model, we wrote our own code in MatLab. We started by inputting the given dimensional values, listed before. Next, we assigned those given dimensional values to the non-dimensional parameters.

4.3.1 Non-dimensional Variables and Parameters

In this project, the first task was to find a non-dimensional representation of the Morris-Lecar equations in terms of variables:

- $v = \frac{V}{V_{Ca}}$
- $t = \frac{g_K T}{2C_m}$
- $w = W$

To go along with these given variables, we realized that we assign the following parameters to find the non-dimensional representation:

$V_1 = \frac{V_{Ca}}{v_2} V_2 = \frac{v_1}{v_2} V_3 = \frac{v_{Ca}}{v_4} V_4 = \frac{v_3}{v_4} V_5 = \frac{v_K}{v_{Ca}} V_6 = \frac{v_L}{v_(Ca)}$
$a = \frac{g_{Ca}}{g_K} b = \frac{2*g_L}{gK} c = \frac{2}{g_K * v_{Ca}} d = \frac{\theta * g_K}{2 * C_m}$

Also, we needed to substitute in non-dimensional functions a list of the non-dimensional functions used in the non-dimensional equations:

- $M_\infty = \frac{1}{2} 1 + tanh(V_1 V - V_2)$
- $W_\infty = 1 + tanh(\frac{V_3 V - V_4}{2})$
- $l = cosh(\frac{V_3 V - V_4}{2})$

After we reassigned the values of the original model, so that we could work with the non-dimensional equations, those equations are as such:

$$\frac{dv}{dt} = -aM_\infty(V)(V-1) - 2w(V - V_5) - b(V - V_6) + cIapp \tag{48}$$

$$\frac{dw}{dt} = W_\infty \tag{49}$$

4.3.2 Non-dimensional Form of ML Model

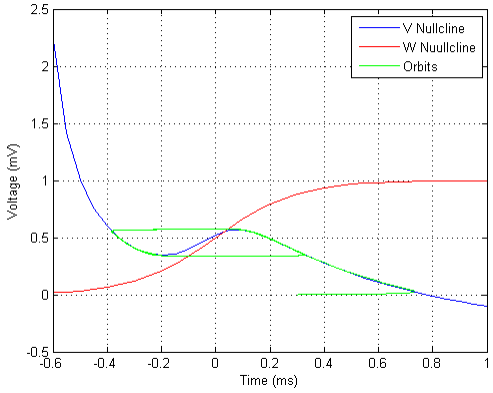
After we reassigned the values of the original model, so that we could work with the non-dimensional equations, those equations are as such:

$$\frac{dv}{dt} = -aM_\infty(V)(V-1) - 2w(V - V_5) - b(V - V_6) + cIapp \tag{50}$$

$$\frac{dw}{dt} = W_\infty \tag{51}$$

4.4 Phase Portrait

Shown in the graph below, the resulting V-nullcline, W-nullcline, and the trajectory.



4.4.1 Jacobian and Eigenvalues

The character of each singular point is determined by the roots of the characteristic equation for the eigenvalues of the equations linearized in the neighborhood of the singular point. These roots in turn are determined by a discriminant involving the elements of the Jacobian matrix evaluated at that point. These roots are determined by the slopes and angles of intersection of the two nullclines at the singular point. Because of the non-linear characteristics of both nullclines, there are a number of different geometric possibilities for the intersections, and hence a surprising number of singular-point patterns. Thus the singular points can be stable or unstable, nodes or foci as determined by changes in the roots of the

characteristic equation that are sensitive to modest changes in the conductance parameters. For this research project, equations (5) and (6) were used to calculate Jacobian matrix that is stated below:

$$\begin{bmatrix} -a\frac{1}{M^2}(V_1) + 2w + \beta & -2v \\ a\sinh(0.5(V_3v - V_4))(0.5V_3)[W - w] + \cosh(0.5(V_3v - V_4))[\frac{V_3}{W}] & -a\cosh(0.5(V_3v - V_4)) \end{bmatrix}$$

Once we derived this Jacobian matrix, the use of the critical points, $(0.0333, 0.553)$ found using the function psolve in MatLab, gives a the following Jacobian matrix:

$$\begin{bmatrix} \text{-4.987} & -0.0666 \\ 2.6871 & -0.5508 \end{bmatrix}$$

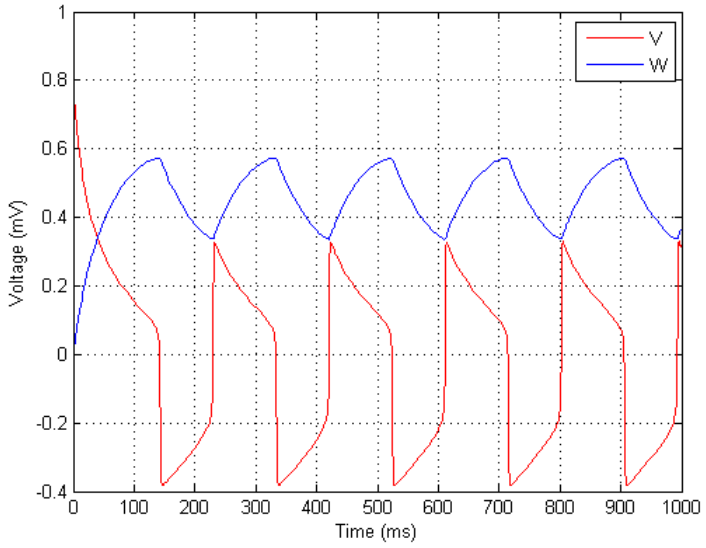
The resulting eigenvalues of the Jacobian matrix are -4.9463 and -0.5915. There is a theorem that states:

An equilibrium point x of the differential equation 1 is stable if all the eigenvalues of J, the Jacobian evaluated at x, have negative real parts. The equilibrium point is unstable if at least one of the eigenvalues has a positive real part.

Because the eigenvalues of the Jacobian are both negative and real numbers, one can conclude that the Jacobian is stable.

4.5 Solutions

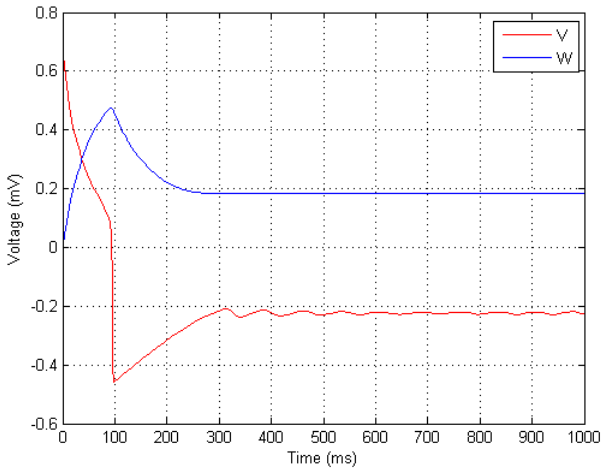
Using the new non-dimenstional equations, MATLAB can then be used to analyze the new model numerically and provide the following graph:

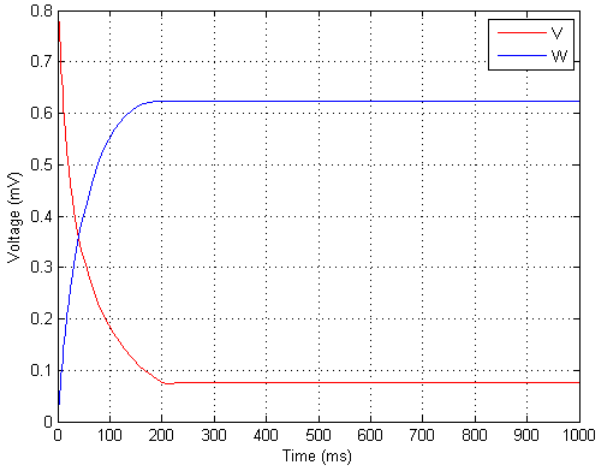


- This graph is important because it portrays the oscillatory behavior that model represents.

4.5.1 Bifurcation Analysis

Bifurcation theory is concerned with how solutions change as parameters in a model are varied. After a bifurcation analysis, I_{app} is discovered to be an important variable in the equation because of the outcome of the graphs that it produces. Numerically solving for the boundaries of I_{app}, it was discovered that the lower boundary of I_{app} was 95.75 mA/cm^2 because this was the lowest amount of current that could be applied that would cause oscillatory behavior. The upper boundary was calculated to be 192.5 mA/cm^2 because this was the highest amount of current that could be applied that would overload the model, thus getting rid of the oscillatory behavior.


V
W
Voltage (mV)
Time (ms)
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
0
100
200
300
400
500
600
700
800
900
1000


V
W
Voltage (mV)
Time (ms)
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
100
200
300
400
500
600
700
800
900
1000

5 Conclusion

The Hodgkin-Huxley model is entirely biologically driven and therefor the most detailed of the the three models. However, because of its complexity (being a system of four differential equations) it is very difficult to solve. The FitzHugh-Nagumo model greatly simplifies the procedure to find a solution. It being completely mathematically driven however, means that not all of its parameters can be explained biologically. The Morris-Lecar model combines the relative simplicity of the FitzHugh-Nagumo Model with the biological detail of the Hodgkin-Huxley model.

6 References

- Rinzel Rinzel, J. *Chapter 4 Hodgkin-Huxley Model*, publisher, 2012.
- Strassberg Strassberg, Adam F., and Louis J. DeFelice. *Limitations of the Hodgkin-Huxley Formalism: Effects of Single Channel Kinetics on Transmembrane Voltage Dynamics*, Neural Computation, 5.6, (1993), pages 843-55.
- http://hbcudigest.com/tennessee-state-takes-right-path-on-homecoming-parade-route-issue/
- http://www.webbiology.com/the-nervous-system
- https://www.boundless.com/#microbiology/bacteria-archaea-and-eukaryote-cell-structure/transport-across-the-cell-membrane/active-transport/
- http://cheezburger.com/2748402944
- http://en.wikipedia.org/wiki/Hodgkin%E2%80%93Huxley_model
- https://en.wikipedia.org/wiki/FitzHugh%E2%80%93Nagumo_model
- http://www.scholarpedia.org/article/Morris-Lecar_model
- Fall, Christopher P., Eric S. Maryland, John M. Wagner, and John J. Tyson. *Computational Cell Biology.* Vol. 20. New York: Springer, 2002. Print.
- Kenner, James, James Sneyd. *Mathematical Physiology I: Cellular Physiology (Interdisciplinary Applied Mathematics).* New York: Spinger, 2008. Print.
- http://thephysicsdomain.com/2013/03/28/047-hodgkin-huxley-hysteria/
- Lecar, H, and C Morris. "Voltage oscillations in the barnacle giant muscle fiber." Biophys. J. 35: 193 - 213.. 35. (1981): 193-213. Print.
- Lecar, Harold. N.p.. Web. 19 Jun 2013. http://www.scholarpedia.org/article/Morris-Lecarmodel.