Analyzing Cardiac Action Potentials with the Fitzhugh-Nagumo Model

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Abstract

We examine the Fitzhugh-Nagumo model for cardiac action potentials. In a cardiac action potential, ions move through the cell membrane, altering the membrane potential. The Fitzhugh-Nagumo model is a simple model for cardiac cell dynamics. In the Fitzhugh-Nagumo model, we see threshold behavior, continuous action potentials, and the spread of the action potential with diffusion.

1 Introduction

The human body is a complex system made up of many intricate processes. For example, the heart has four different compartments that each have different purposes. It pumps blood throughout the body so that we can obtain the oxygen we need to survive. This process occurs through the contractions of the heart. Each cell contributes to the heart's contractions by sending out small electrical impulses called action potentials. Mathematical models can be used to better understand the dynamics of these action potentials in a surprisingly accurate way. In this paper, we look at the Fitzhugh-Nagumo model as a means of analyzing action potentials in cardiac cells.

1.1 Cardiac Action Potentials

All of our cells have a cell membrane with a series of protein channels. These protein channels control the movement of ions to and from the cell. They open and close based on different conditions, and, when these conditions are satisfied, the specified ion is allowed to pass through. The sodium-potassium pump uses energy in the form of ATP to push 3 sodium ions out of the cell for every 2 potassium ions pushed into the cell (figure 1). As a result,

more positively charged ions lie outside of the cell compared to the inside, establishing a negative membrane potential of approximately $-80\ mV$.

Figure 1 also shows the cell's protein channels which transport ions across the membrane. In cardiac cells, certain protein channels open with depolarization due to a small electrical stimulus. However, if the stimulus does not surpass a certain threshold, little change in membrane potential will occur. When a sufficient stimulus is introduced, however, the sodium channel opens up, causing a sudden influx of positively charged sodium ions to enter the cell. Figure 2 illustrates these two situations. This results in a net positive charge inside of the cell (i.e. a positive membrane potential). At one point, potassium channels have completely opened, and potassium rapidly exits the cell. This causes the cell to become more negative, allowing the membrane potential to land back at its resting state. These changes in membrane potential constitute action potentials.

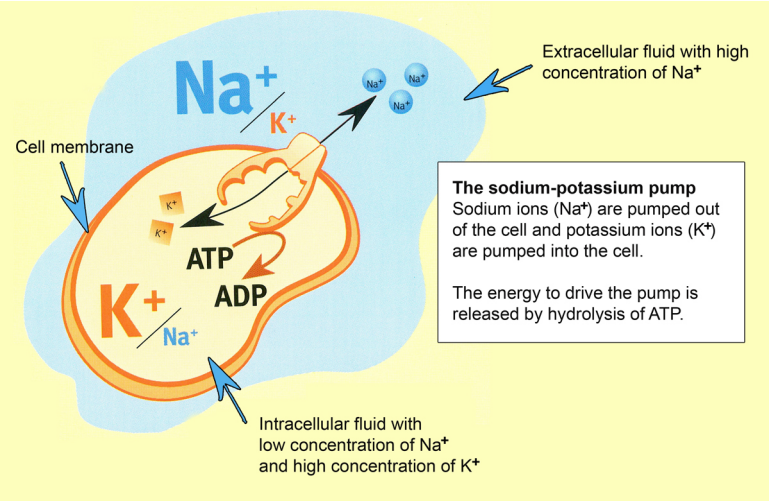


Figure 1: Cardiac Cell Illustrating Sodium-Potassium Pumps
Source: http://www.au.dk/fileadmin/www.au.dk/forskning/nobelprisen_i_kemi_1997/natrium-kalium-pumpen/cellenuk.jpg

2 Modeling the Dynamics

Cardiac action potentials can be modeled with many different models, but they are all based on the Hodgkin-Huxley model. Although difficult to analyze, the Hodgkin-Huxley model provides a clear, biological, and mechanistic model for cardiac action potentials.

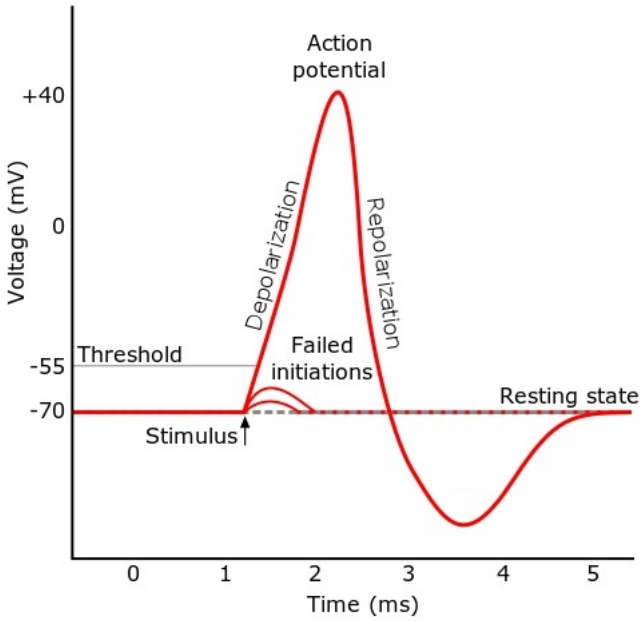


Figure 2: Action Potential Demonstrating Threshold Behavior
Source: http://upload.wikimedia.org/wikipedia/commons/4/4a/Action_potential.svg

2.1 The Hodgkin-Huxley Model

The Hodgkin-Huxley model is represented by the following set of differential equations:

$$C_m \frac{dv}{dt} = -g_L(v - v_L) - g_{Na} m^3 h(v - v_{Na}) - g_K n^4 (v - v_K)$$

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

$$\frac{dh}{dt} = \alpha_h(v)(1 - h) - \beta_h(v)h$$

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

In this model, the cardiac action potential is explained through the opening and closing of protein channels. The first differential equation is a current balance law, where v represents the voltage of the membrane potential. The variables m, n and h each represent a fraction of open protein channels. More specifically, m and h represent the fraction of sodium channels that are open, while n controls the fraction of potassium channels that are open.

The next three differential equations model the mechanics behind the opening of each channel. The parameters α and β are rate constants which

help determine how fast each channel opens. For example, the sodium channels open much faster than the potassium channels. Therefore, m and h should approach 1 much more quickly than n. As such, the parameters α and β should be adjusted accordingly.

2.1.1 Relating the Model to Cardiac Action Potential Phases

The Hodgkin-Huxley model provides insight into the phases of cardiac action potentials. Figure 3 shows a diagram of a cardiac action potential. Before any action potentials occur, the cardiac cell's membrane potential is at a resting state, phase 4. With a small electrical stimulus (increase in v), the sodium channels rapidly open. That is, m and h quickly approach 1. As the influx of sodium quickly increases, the cell depolarizes and v rises above 0. This is known as phase 0. During phase 0, the potassium channels *slowly* begin to open and release potassium. Mathematically, this means n will slowly approach 1. When all potassium channels are open (i.e. $n = 1$), the outflux of potassium will overcome the influx of sodium, and the voltage will level off. This is known as phase 1. During phase 2, the voltage remains relatively constant as calcium enters the cell while potassium exits. During phase 3, only potassium levels change, and the voltage decreases back to the resting state, phase 4. This is the repolarization of the cardiac cell. During phase 4, the channels are closed (i.e. m, n, and h are all very close to 0), and voltage remains constant (i.e. $\frac{dv}{dt} = 0$).

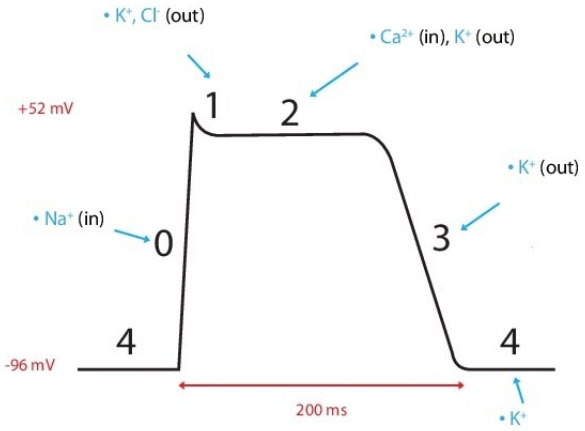


Figure 3: Cardiac Action Potential and Ion Channel Currents
Source: http://upload.wikimedia.org/wikipedia/commons/c/cb/Action_potential_ventr_myocyte.gif

2.2 The Fitzhugh-Nagumo Model

As seen in the previous section, the Hodgkin-Huxley model is fairly complex and would be difficult to analyze in any satisfactory manner. The Fitzhugh-Nagumo model simplifies some aspects by reducing the number of differential equations to two. One models the change in voltage (i.e. the fast variable), while the other models the recovery of the action potential (i.e. the slow variable). This reduction makes analysis much simpler.

The Fitzhugh-Nagumo model is represented by the following set of differential equations:

$$\frac{dv}{dt} = -v(v-\alpha)(v-1) - w$$

$$\frac{dw}{dt} = \epsilon(\beta v - w)$$

Here, v is the membrane potential of the cardiac cell, w is the recovery variable, while α, β, and ϵ are parameters which control some specific behaviors of the model. The first term of $\frac{dv}{dt}$ captures the basic dynamics of sodium and leakage currents in a cell. The second term, $-w$, is a simple model of the potassium current exiting the cell.

3 Model Behavior

3.1 Steady States

In order to find the steady states of the Fitzhugh-Nagumo model, we must find where the model's two differential equations are both equal to 0. First, we define where $\frac{dv}{dt} = 0$ and $\frac{dw}{dt} = 0$:

$$w = -v(v-\alpha)(v-1)$$

$$w = \beta v$$

These are known as the nullclines of the model. To see where the nullclines intersect, we set their corresponding equations equal to each other:

$$\beta v = -v(v-\alpha)(v-1)$$

This gives us our first steady state, $v = 0$. If we assume $v \neq 0$, we can divide by v and get:

$$-(v-\alpha)(v-1) = \beta$$

With a little algebraic manipulation, we find:

$$v^2 - v(\alpha + 1) + (\alpha + \beta) = 0$$

We can now generically solve for v using the quadratic formula:

$$v = \frac{-(\alpha + 1) \pm \sqrt{(\alpha + 1)^2 - 4(\alpha + \beta)}}{2}$$

This gives us our last two steady states. Depending on the parameters of our model (α and β), it is possible that they will be complex. To guarantee only real solutions, we set the discriminant to be greater than 0:

$$(\alpha + 1)^2 - 4\alpha - 4\beta \geq 0$$

Again, with a little algebraic manipulation, we get:

$$\frac{(\alpha - 1)^2}{4} \geq \beta$$

Therefore, if β is less than or equal to $\frac{(\alpha-1)^2}{4}$, we will have 3 real steady states.

3.2 Stability of the Steady States

In order to find the stability of our steady states, we must find the Jacobian matrix for our model and solve for the Jacobian determinant. Next, we will solve for the eigenvalues at each steady state, which will allow us to determine the steady state's stability.

First, we will use the following definitions:

$$F_1 = \frac{dv}{dt}$$

$$F_2 = \frac{dw}{dt}$$

For this situation, the Jacobian matrix is defined as follows:

$$\mathbf{J} = \begin{bmatrix} \frac{\partial F_1}{\partial v} & \frac{\partial F_1}{\partial w} \\ \frac{\partial F_2}{\partial v} & \frac{\partial F_2}{\partial w} \end{bmatrix}$$

Therefore, the following is our Jacobian matrix:

$$\mathbf{J} = \begin{bmatrix} -3v^2 + (2\alpha + 2)v - \alpha & -1 \\ \epsilon\beta & -\epsilon \end{bmatrix}_{(v^*, w^*)}$$

Here, (v^*, w^*) is the steady state being evaluated.

Using the following definition relating eigenvalues and eigenvectors, we will be able to solve for the stability of the steady states:

$$A\vec{v} = \lambda\vec{v}$$

Manipulating this equation, we get:

$$\vec{v}(A - \lambda I) = 0$$

Here, A is the Jacobian matrix, I is the identity matrix, $\vec{v}$ is the eigenvector, and λ is the eigenvalue. If we substitute our Jacobian matrix for A and simplify, we get:

$$\vec{v}\begin{bmatrix} -3v^2 + (2\alpha + 2)v - \alpha - \lambda & -1 \\ \epsilon\beta & -\epsilon - \lambda \end{bmatrix} = 0$$

By taking the determinant of the matrix in the equation above and setting it to 0, we can solve for the eigenvalues of the model. After evaluating the determinant and simplifying, we get:

$$\lambda^2 + \lambda(\alpha + 3v^2 - 2(\alpha + 1)v + \epsilon) + \epsilon(3v^2 - 2(\alpha + 1)v + \alpha + \beta) = 0$$

To solve for λ, we use the quadratic formula:

$$\lambda = \frac{-(\alpha + 3v^2 - 2(\alpha + 1)v + \epsilon) \pm \sqrt{(\alpha + 3v^2 - 2(\alpha + 1)v + \epsilon)^2 - 4\epsilon(3v^2 - 2(\alpha + 1)v + \alpha + \beta)}}{2}$$

This gives us our two eigenvalues, λ_1 and λ_2. Note that they may be real or complex depending on the sign of the discriminant.

With these eigenvalues, we are able determine the stability of any steady state. If we let Δ be the discriminant of the λ equation, we can use the following conditions [5]:

1. If $\Delta \geq 0$ (real eigenvalues)
   (a) λ_1, λ_2 are *both* > 0: Unstable Node
   (b) λ_1, λ_2 *both* < 0: Stable Node
   (c) λ_1 and λ_2 are opposite signs: Unstable Saddle Node
2. If $\Delta < 0$ (complex eigenvalues)
   (a) Real parts of λ_1 and λ_2 are *both* > 0: Unstable Spiral
   (b) Real parts of λ_1 and λ_2 *both* < 0: Stable Spiral

3.3 Stability of the Zero State

We have already discovered that $v = 0$ is a steady state of the model, regardless of the parameter values. Now, we can find out more about its stability. To do this, we will substitute $v = 0$ into the generic equations for the eigenvalues. If both eigenvalues are negative, then $v^* = 0$ is stable.

After substituting $v = 0$, we get the following:

$$\lambda_1 = \frac{-\alpha - \epsilon + \sqrt{(\alpha + \epsilon)^2 - 4\epsilon\alpha - 4\epsilon\beta}}{2}$$

$$\lambda_2 = \frac{-\alpha - \epsilon - \sqrt{(\alpha + \epsilon)^2 - 4\epsilon\alpha - 4\epsilon\beta}}{2}$$

After simplifying the two equations, we get:

$$\lambda_1 = \frac{-\alpha - \epsilon + \sqrt{(\alpha - \epsilon)^2 - 4\epsilon\beta}}{2}$$

$$\lambda_2 = \frac{-\alpha - \epsilon - \sqrt{(\alpha - \epsilon)^2 - 4\epsilon\beta}}{2}$$

Because our parameters must be greater than 0, both λ_1 and λ_2 are negative. Therefore, $v^* = 0$ is a stable steady state.

However, depending on the value of β, it is possible that the eigenvalues will also be complex. To get complex eigenvalues, the discriminant must be less than 0:

$$(\alpha - \epsilon)^2 - 4\epsilon\beta < 0$$

With some algebraic manipulation, we get:

$$\beta > \frac{(\alpha - \epsilon)^2}{4\epsilon}$$

Therefore, if β satisfies this inequality, our eigenvalues will be negative (stable steady state) and complex (spiral behavior).

3.4 Phase Plane Analysis of the Fitzhugh-Nagumo Model

Before analyzing the Fitzhugh-Nagumo model, we must first understand the concept of phase plane analysis. If we set the two differential equations to 0, we get:

$$w = -v(v - \alpha)(v - 1)$$

$$w = \beta v$$

When these equations are satisfied, $\frac{dv}{dt} = 0$ or $\frac{dw}{dt} = 0$ (i.e. v or w is not changing). Therefore, these are called the nullclines of the model. The nullclines are shown in figure 4 below. When the two nullclines intersect, we have what is called a steady state, where v and w are not changing. If v or w is moved slightly away from this steady state, the point may return back (stable steady state) or move away (unstable steady state). With phase plane analysis, we can visually see the behavior of the system. In the next few sections, we explore what occurs when we keep two parameters constant and change the third.

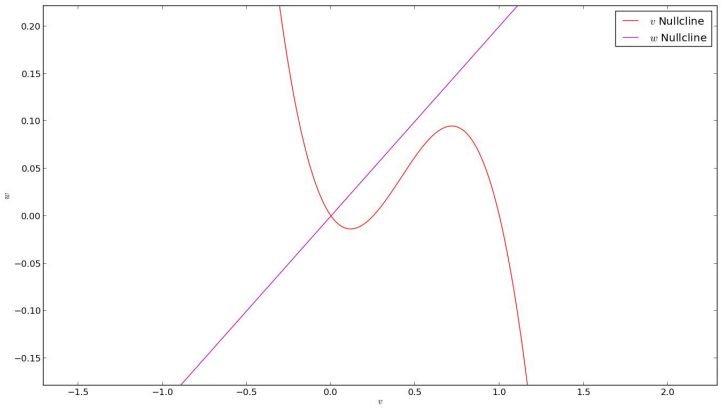


Figure 4: The nullclines of the Fitzhugh-Nagumo Model with $\alpha = 0.25$ and $\beta = 0.2$

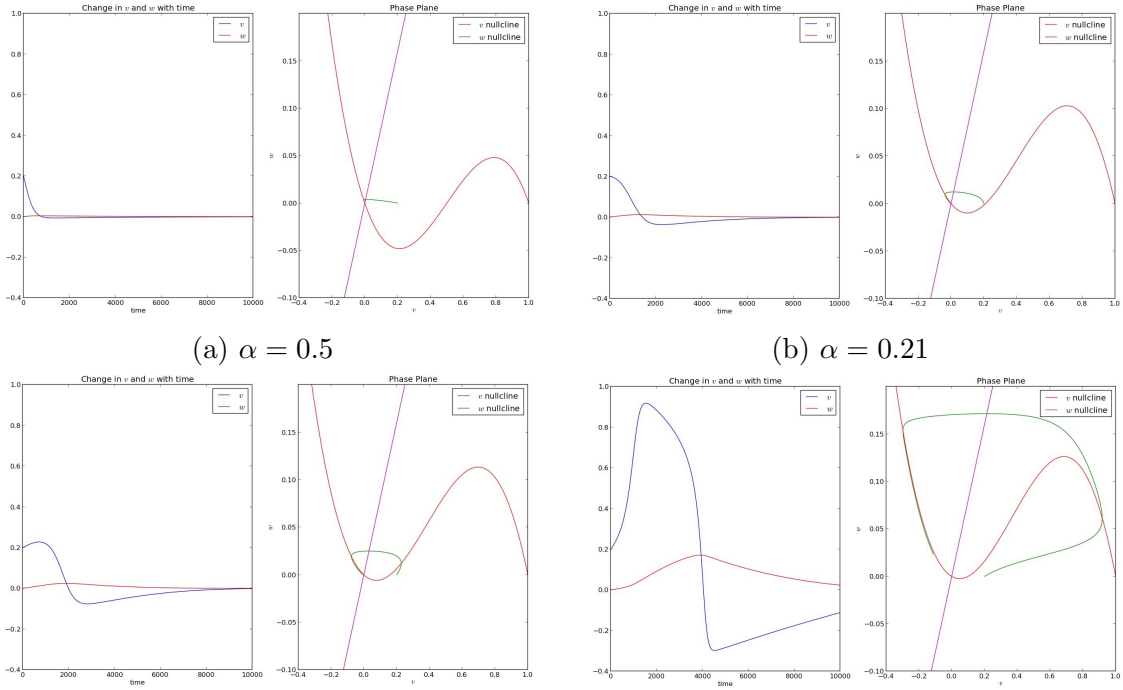
First, we define the following:

- v_0 is the initial voltage added to the system. We let $v_0 = 0.2$.
- w_0 is the initial recovery of the system. We let $w_0 = 0$.

3.4.1 Altering the Value of α

Figure 5 shows what happens when β and ϵ are kept constant, and α changes. Here, we let $\beta = 0.8$ and $\epsilon = 0.01$. In figure 5, we see how the threshold value, α, affects the behavior of the system.

If α is increased above the initial voltage, v_0, an action potential is not generated, as shown in figure 5a. If α is set just above v_0, an action potential is still not generated, but the action potential moves back to rest with a more gradual slope as illustrated by figure 5b. Furthermore, if α is slightly below v_0, a full action potential is still not generated, but a delay occurs before the action potential returns to rest, as shown in figure 5c. Lastly, if the value of α is substantially below v_0, an action potential is generated, as illustrated by figure 5d.



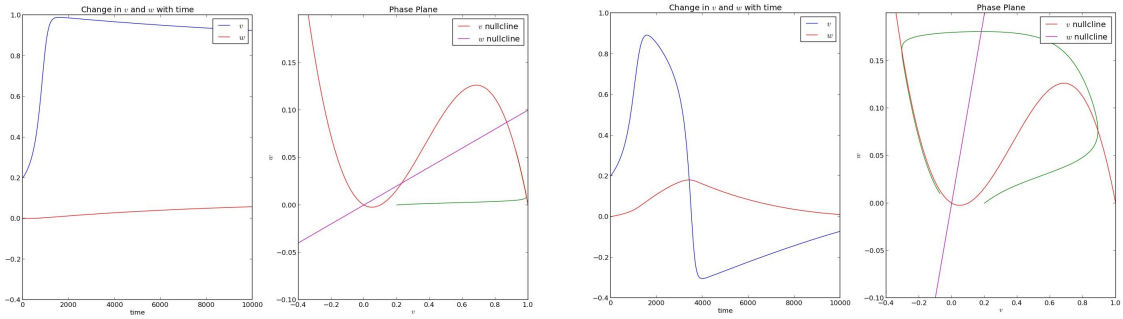
(a) $\alpha = 0.5$ (b) $\alpha = 0.21$

(c) $\alpha = 0.16$ (d) $\alpha = 0.1$

Figure 5: Simulations with Different Values of α

3.4.2 Altering the Value of β

Figure 6 shows what happens when α and ϵ are kept constant, and β changes. Here, we let $\alpha = 0.1$ and $\epsilon = 0.01$. From the equation of the w nullcline, it is clear that β is the nullcline's slope. Therefore, if β is small enough, it will intersect the v nullcline at two more places, resulting in three steady states. The two outer steady states will be stable which is known as bistability. Instead of approaching 0, v will approach the other stable steady state at some higher v. Biologically, this is called depolarization block. The cell is dead and is unable to depolarize.



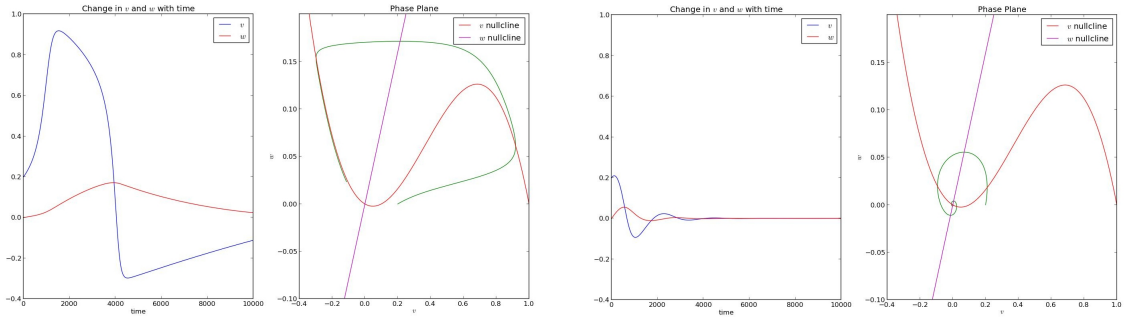
(a) $\beta = 0.1$ (b) $\beta = 1$

Figure 6: Simulations with Different Values of β

3.4.3 Altering the Value of ϵ

Figure 7 shows what happens when α, and β are kept constant, and ϵ changes. Here, we let $\alpha = 0.1$ and $\beta = 0.8$. ϵ scales the recovery variable (w). If ϵ is large (with these parameter values, we consider $\epsilon \geq 0.03$ large), v will not increase nearly as much in comparison to what would occur with a small value of ϵ. The action potential will also complete more quickly with a large value of ϵ. In figure 7a, we see that $v_{max} \approx 0.9$, where v_{max} is the maximum value of v. Also, v reaches the steady state $v^* = 0$ when $t > 10000$. On the other hand, figure 7b shows $v_{max} \approx 0.21$ and v reaches the steady state $v^* = 0$ at $t \approx 5000$. This shows how a larger ϵ affects the dynamics of the model.

Also notice the spiraling behavior near the steady state $v^* = 0$ in figure 7b. Biologically, this is known as afterdepolarization, where the cell's membrane potential increases at the end of an action potential.



(a) $\epsilon = 0.01$ (b) $\epsilon = 0.1$

Figure 7: Simulations with Different Values of ϵ

4 Fitzhugh-Nagumo Model with Excitation Block

Above, we described the Fitzhugh-Nagumo model as a model with a single action potential. An initial voltage v was added, and it may or may not have generated an action potential before returning to rest. In reality, however, cardiac cells continuously experience electrical stimuli which instantiate action potentials. As a result, we see vastly different behavior since the action potentials form a steady rhythm. In this new model, this extra voltage kick is called the excitation block because it excites the system and spurs the generation of multiple action potentials.

The following equations represent Fitzhugh-Nagumo model with the addition of the excitation block:

$$\frac{dv}{dt} = -v(v-\alpha)(v-1) - w + I$$

$$\frac{dw}{dt} = \epsilon(\beta v - w)$$

Here, I represents the excitation block. Notice that this is the only addition needed for the excitation block.

4.1 Analyzing the Excitation Block

Under different parameters, the addition of the excitation block produces different results. In the figures, we let $v_0 = 0.2$ and $I = 0.2$. The values of α, β and ϵ will depend on the scenario at hand.

4.1.1 Typical Action Potentials

In order to produce a typical action potential as seen in figure 8, we let $\alpha = 0.1$, $\beta = 0.8$, and $\epsilon = 0.01$. In the figure, we see the periodic generation of action potentials. In the phase plane, the green line follows the v nullcline indefinitely. This occurs because the addition of the excitation block constantly pushes v past the threshold mark (α).

4.1.2 Oscillating Action Potentials

In order to produce a spiraling oscillation, we need only choose parameters such that the eigenvalues of the function are complex. We must satisfy the expression $\beta > \frac{(\alpha-\epsilon)^2}{4\epsilon}$ as noted in section 3.2. To do this, we let $\alpha = 0.1$, $\beta = 0.8$, and $\epsilon = 0.1$. In figure 9, we observe two things. First, there are more

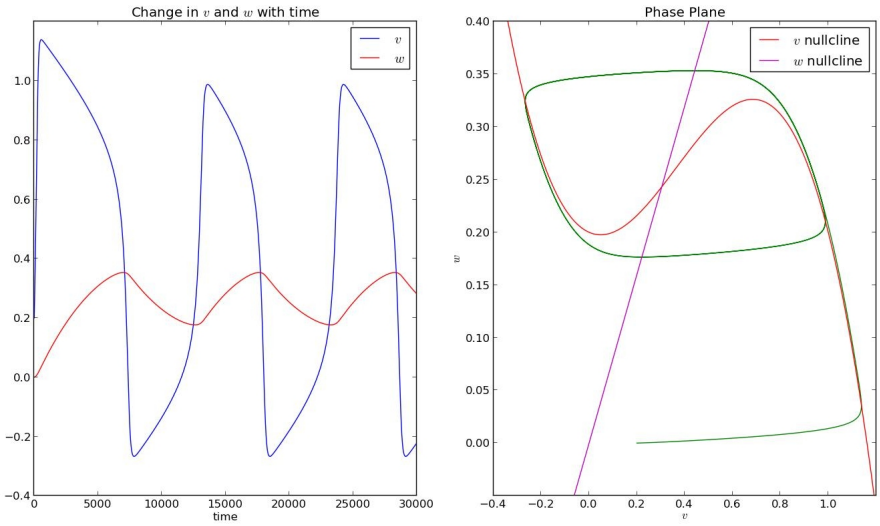


Figure 8: A Typical Action Potential with the Excitation Block

action potentials than in 8. This is, however, only caused by the increase in ϵ. Second, the phase plane line is tilted. Instead of moving around the nullclines, it is slanted around them.

4.1.3 Action Potentials with Bistability

In order to observe the behavior of the excitation block with bistability, we must choose parameters which give the model three real steady states. To do this, we need to satisfy the expression $\beta \leq \frac{(\alpha-1)^2}{4}$ as noted in section 3.1. Therefore, we let $\alpha = 0.1$, $\beta = 0.1$, and $\epsilon = 0.01$. With the excitation block, the behavior does not change drastically as seen in figure 10. The only difference is that v stabilizes at a higher stable steady state. Notice that with the addition of the excitation block, the bistability disappears. Instead, the stable steady state of the model is now on the right of the v nullcline instead of the left.

5 Adding Diffusion to the Fitzhugh-Nagumo Model

So far, our models have only dealt with the generation of action potentials in a single cardiac cell. We have analyzed the effects of different parameters on the generation of each action potential, as well as described the effects of the addition of a constant applied current. Now, we need only describe how this

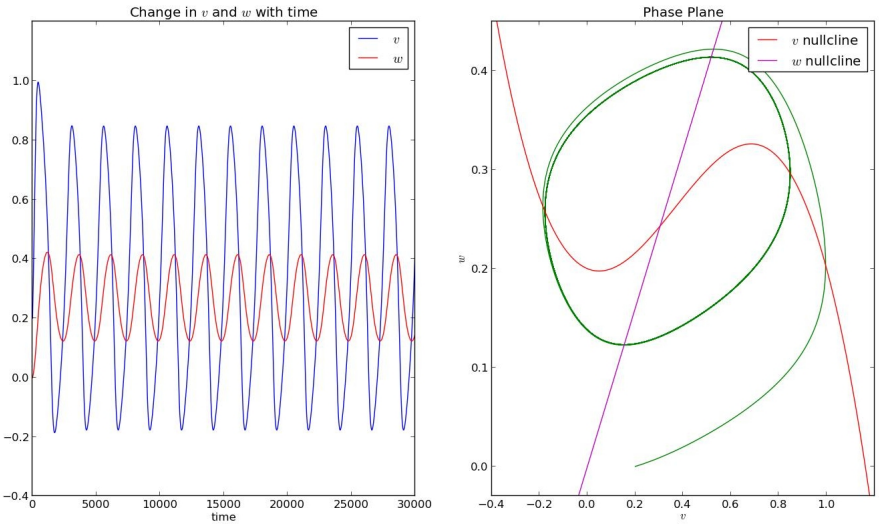
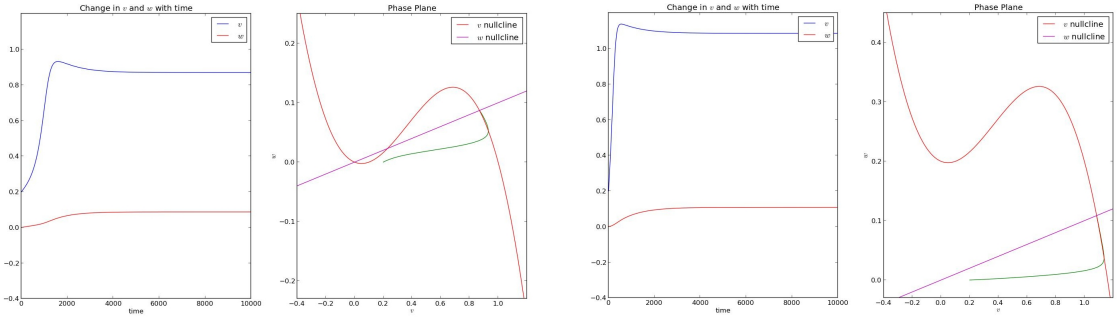


Figure 9: An Oscillating Action Potential with the Excitation Block



(a) Without Excitation Block

(b) With Excitation Block

Figure 10: Action Potentials with Attempted Bistability

idea of an action potential applies to not one cardiac cell, but to a piece of cardiac tissue containing hundreds of cells. The current flows from one cell to another through the channels that connect them. This makes the mathematical model of diffusion a good choice. Diffusion shows how something spreads across space. The reaction term defines *what* is spread across space. In the Fitzhugh-Nagumo model, the reaction term is our original equation. In order to accounts for spatial diffusion, we must alter the Fitzhugh-Nagumo Model in the following way:

$$\frac{dv}{dt} = -v(v-\alpha)(v-1) - w + D\frac{\partial^2 y}{\partial x^2}$$

$$\frac{dw}{dt} = \epsilon(\beta v - w)$$

The new term, $D\frac{\partial^2 y}{\partial x^2}$, explains how an action potential moves through space, represented by x. This diffusion term shows how the action potential travels through all cardiac cells.

5.1 Diffusion in a Single Dimension

In figure 11, the action potential begins in a single cell. Once it begins to depolarize, the action potential starts traveling across the medium, triggering the depolarization of other cells. As the action potentials begin traveling outwards, the recovery variable slowly begins to repolarize the action potentials.

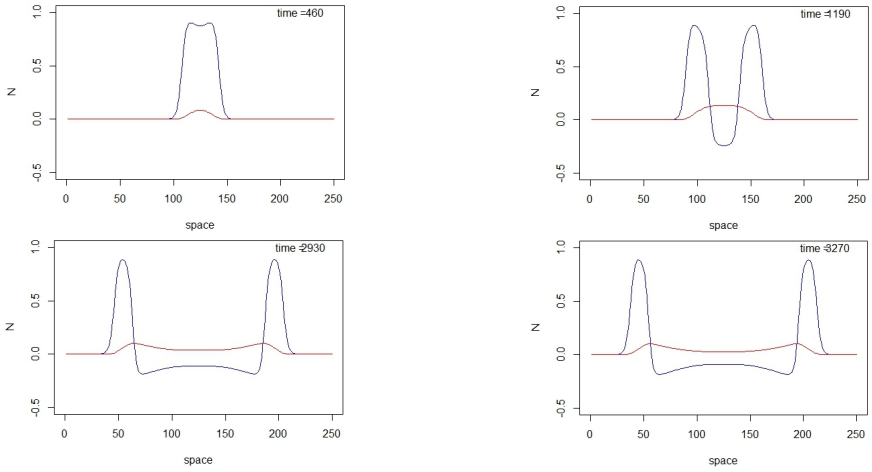


Figure 11: Diffusion of an Action Potential in One Dimension

5.2 Diffusion in Two Dimensions

We are also able to model how action potentials travel across two-dimensional space. In figure 12, the yellow pulse represents the action potential traveling across cells in two dimensional space. This is the most accurate representation of the movement of action potentials through cardiac cells. It demonstrates how the action potential starts with the depolarization of a single cell and then triggers a chain reaction leading to the depolarization of all its surrounding cells. The action potential continues to travel until every cell in the heart cross-section has been activated.

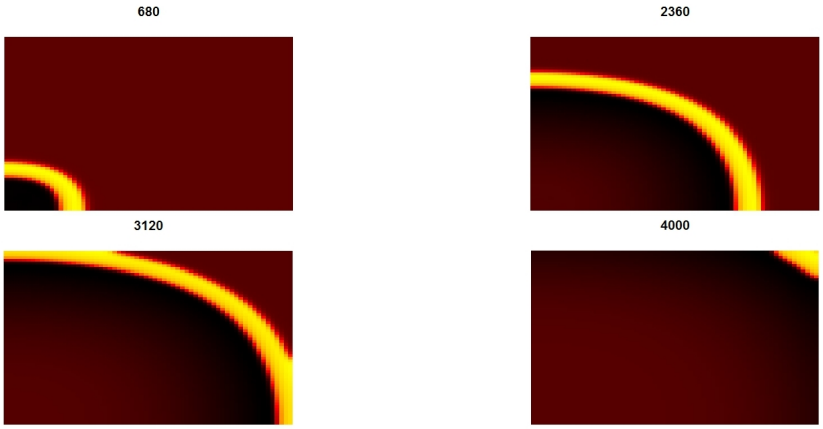


Figure 12: Diffusion of an Action Potential in Two Dimensions

6 Summary

Our analysis of the Fitzhugh-Nagumo model consisted of altering different parameters and observing their effects. As we changed the value of α, we realized that this paramter was the primary determinant for the threshold for action potentials. If our initial membrane potential, v_0, was less than the threshold, an action potential would fail to generate. However, when $v_0 > \alpha$, we saw different behavior. When v_0 was increased slightly above α, a small increase in v would occur. On the other hand, when v_0 was increased enough above α, an obvious action potential would occur. This proved to us that this model *did not* show all-or-none action potentials.

The effect of our second parameter, β, was slightly different. With a small enough value of β, we saw a phenomenon known as bistability, where the model has two stable states rather than one. As a result of this, v stabilized at a higher membrane potential rather than returning to $v = 0$ after the generation of an action potential. Biologically, this is called depolarization block. The cell is dying and is unable to repolarize.

When altering the final parameter, ϵ, we saw that it was a scalar value, describing the rate of recovery. With a small ϵ, the maximum value of the membrane potential, v_{max}, was much higher compared to v_{max} with a large value for ϵ. In the voltage curves, we saw a much higher spike with smaller values of ϵ. We also found that the action potential would complete much faster with a smaller ϵ as the recovery variable would be having less of an effect.

After basic analysis, we included a continuous applied current (excitation block) and also diffusion. Our main observation with the excitation block was continuous action potentials. With diffusion, we were able to see how

the action potential spread from cell to cell. By analyzing the action potentials in this simple model, we can better understand the phenomenon that cause normal behavior of the heart as well as certain heart disorders like arrhythmias and electrical alternans, which can lead to heart failure if not taken care of.

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