A Deeper Analysis of the FitzHugh-Nagumo Neuron Model

Bifurcations and Synchronization

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Abstract

In this paper, we explore the Fitzhugh-Nagumo model's derivation as well as its phase portrait and the Hopf bifurcation that is exhibited. We discuss the biological relevancy of Hopf bifurcations and begin to examine the activity of coupled neurons using a modified FitzHugh-Nagumo model.

1 Introduction and Motivation

1.1 Background

The firing action of neurons has been well-studied. One of the earliest known models of a neuron was derived by Lapicque in 1907 (Abbott, 1999). In this "integrate-and-fire" model, Lapicque treats the neuron as a simple electrical circuit comprised of a capacitor and resistor in parallel; these represent the capacitance (C) and resistance (R) of the neuronal membrane, respectively. These variables can be combined with the membrane potential (V), the resting membrane potential (V_{rest}), and an injected current (I), to give the final equation $I(t) = C_m \frac{dV_m(t)}{dt}$. Although Lapicque's model was an excellent initial foray into neuronal modeling, it does not take into account the refractory period of a neuron as well as the "all-or-none" response found in actual neurons (p. 303).

Following Lapicque, others have advanced more detailed neuronal models. In 1952, Hodgkin and Huxley studied the giant squid axon and developed a four-dimensional system based off of their findings; this model remains as one of the most widely-accepted and frequently discussed models to this day. Similar to Lapicque's, the Hodgkin-Huxley model also compares a neuron to an electrical circuit, but with three resistors in parallel with a capacitor instead of just one. Each of the three resistances correspond to sodium channels (g_{Na}) through which sodium current flows, potassium channels through which potassium current flows (g_K), and a leakage channel (g_L). In series with these resistors are the respective reversal potentials for each current: E_{Na}, E_K, and E_L. After using Ohm's Law to manipulate these variables and adding gating variables m, h, and n, the Hodgkin-Huxley model is elucidated:

$$\begin{cases} C_m \frac{dV}{dt} = -g_{Na}(V - E_{Na}) - g_K(V - E_K) - g_L(V - E_L) + I_{ext}(t) \\ \frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)} \\ \frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)} \\ \frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)} \end{cases} \tag{1}$$

While the Hodgkin-Huxley model is a very thorough one that allows one to manipulate different currents with precision, it becomes extremely complicated to analyze for multiple-neuron systems, as each neuron requires its own set of equations. FitzHugh (1961) sought to simplify the Hodgkin-Huxley equations into a two-dimensional system from a four-dimensional one so that it could be modeled in a phase plane.

One model that FitzHugh drew from for inspiration when simplifying the Hodgkin-Huxley equations was the van der Pol Oscillator, derived by Balthasar van der Pol in 1928. These equations modeled what van der Pol called "relaxation oscillators," which are now known as limit cycles. FitzHugh realized that a "physiological state diagram" could be derived from the van der Pol Oscillator; he also noted that this diagram could similarly be developed from the Hodgkin-Huxley equations (mathematically) and that these diagrams had "different regions...that correspond to different physiological states of a nerve

membrane" (p. 446). FitzHugh then sought to extract the similarities from the two models in order to formalize a new set of equations that could be visualized in a phase plane, and used the van der Pol Oscillator as his starting point.

Fitzhugh added a linear term W to the second equation of the van der Pol model in order to change its originally-unstable fixed point to that of a stable one in order to simulate the threshold properties of a neuron. He also restricted parameter values so that there would always be only intersection between the nullclines, and thus only one fixed point. After adding a term I to represent an injected current (later represented as z), his work culminated in a two-dimensional system:

$$\begin{cases} \dot{V} = V - \frac{V^3}{3} - W + I \\ \dot{W} = 0.08(V + 0.7 - 0.8W) \end{cases} \tag{2}$$

1.2 Motivation / Context

In this paper, we will attempt to study the FitzHugh-Nagumo equations to gain a deeper understanding of the Hopf bifurcations that arise when modeling this system. Using the FitzHugh-Nagumo model as a starting point instead of the Hodgkin-Huxley model will allow us to successfully analyze and plot the phase portrait of a two-dimensional system, which would not be possible with the H-H equations. From there, we can investigate how Hopf bifurcations arise as parameters are changed.

One way Hopf bifurcations can be explored is by placing them in the context of diseases in which neurons misfire, such as Alzheimer's disease, Parkinson's disease, and epilepsy. Xie, Chen, Kang, and Aihara (2008) hypothesize that in such diseases, controlling when and where Hopf bifurcations occur, and how strongly they oscillate, may be the key to effective therapeutic solutions. Similarly, Titcombe, Glass, Guehl, and Beuter (2001) postulate that electrical deep brain stimulation, which suppressors resting tremor in Parkinson's patients, works by inducing a Hopf bifurcation to destabilize the oscillations causing the tremors. Further research on Hopf bifurcations may eventually lead to significant therapeutic treatments for these debilitating diseases.

2 Methods

Our goal was to gain a better understanding FitzHugh's model of neurons by first going through its derivation from the van der Pol Oscillator. We then explored the bifurcations that the model exhibits; there has not been much in-depth study of the specific bifurcations (especially the subcritical Hopf) that occur in the model, and we thought it would be best to clearly define and deeply study these bifurcations. We were also interested in seeing how these bifurcations are relevant to neuronal pathology.

2.1 FitzHugh's Model

FitzHugh (1961) developed his model from the van der Pol equations, given by:

$$\ddot{x} + c(x^2 - 1)\dot{x} + x = 0 \tag{3}$$

Using the definition of a Lienard system:

$$\frac{d^2x}{dt^2} + f(x)\frac{dx}{dt} + g(x) = 0$$

FitzHugh found a function $g(x)$ defined as

$$g(x) = \frac{\dot{x}}{c} + \frac{x^3}{c} - x$$

and rewrote equation (3) as a two-dimensional system of two first-order differential equations:

$$\begin{cases} \dot{x} = c(y + x - x^3/3) \\ \dot{y} = -x/c \end{cases} \tag{4}$$

Finally, FitzHugh added a few terms (z, a, b) to the equations in order to better model a neuron's function:

$$\begin{cases} \dot{x} = c(y + x - x^3/3 + z) \\ \dot{y} = -(x - a + by)/c \end{cases} \tag{5}$$

2.2 Variables, Parameters, and Assumptions

As an analog of I, the input variable in the HH equations, z indicates voltage coming from other neurons. a and b are constants given by:

$$1 - 2b/3 < a < 1, \qquad 0 < b < 1, \qquad b < c^2$$

3 Results & Analysis

We used FitzHugh's model to analytically find bifurcation points in the system.

3.1 Diagramming the Bifurcations

In this section we studied the bifurcation of the system as the input variable z was varied. This corresponds biologically to the voltage that a neuron's dendrites receive from other neurons, which after a certain voltage can trigger an action potential. Since FitzHugh used a different method than is conventional, instead of a threshold of $I = -50\text{mV}$, our model has one of $z = -0.34$. FitzHugh's model is also 'flipped' in comparison to conventional models, since he used the equation $V = V_{in} - V_{out}$. Figure(3.1) illustrates the bifurcation diagram for the bifurcation parameter z.

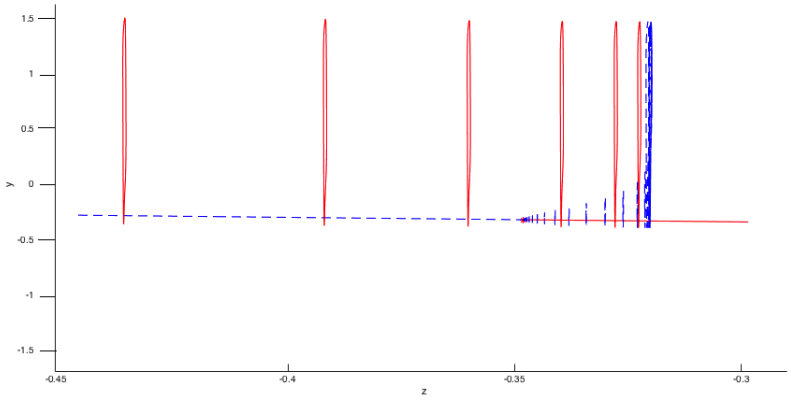


Figure 1: There is a subcritical Hopf bifurcation at $z_H = -0.3465$ and a saddle-node bifurcation of limit cycles at $z_c = -0.332$

3.2 Solving for Bifurcation Points

First, let's recall the system:

$$\begin{cases} \dot{x} = c(y + x - x^3/3 + z) \\ \dot{y} = -(x - a + by)/c \end{cases} \tag{5}$$

with null clines

$$y = x^3/3 - x - zy = (a - x)/b$$

To find the Hopf bifurcation, first we find the Jacobian:

$$\begin{pmatrix} (c - cx^2) & c \\ -\frac{1}{c} & -\frac{b}{c} \end{pmatrix}$$

and solve for the characteristic equation:

$$\lambda^2 - ((c - cx^2) - \frac{b}{c})\lambda - (b - bx^2) + 1 = 0. \tag{6}$$

For a Hopf bifurcation to be possible, $\lambda = \mu \pm i\omega$ must have a zero real portion. Therefore, we can assume a solution of the form $\lambda = \pm i\omega$ (ω nonzero) and plug it back into the characteristic equation (6). In doing so, we are presented with:

$$-\omega^2 - ((c - cx^2) - \frac{b}{c})i\omega - (b - bx^2) + 1 = 0$$

Since the real and imaginary parts must both be equal to zero in order to satisfy the equation, we then have:

$$\begin{cases} -\omega^2 - (b - bx^2) + 1 = 0 \\ (c - cx^2 - \frac{b}{c})\omega = 0 \end{cases} \tag{7}$$

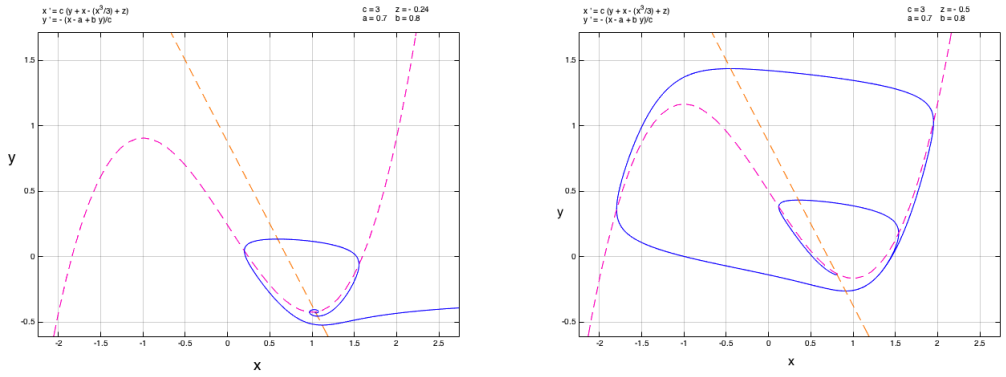
We then solved the first for $\omega = \pm\sqrt{1 - b(1 - x^2)}$ and the second for $\omega = 0$ and $1 - x^2 = b/c^2$. Since our conditions at the beginning were that ω is nonzero, we are left with just two equations, substituting the second into the first where applicable:

$$\omega = \pm\sqrt{1 - b^2/c^2}$$

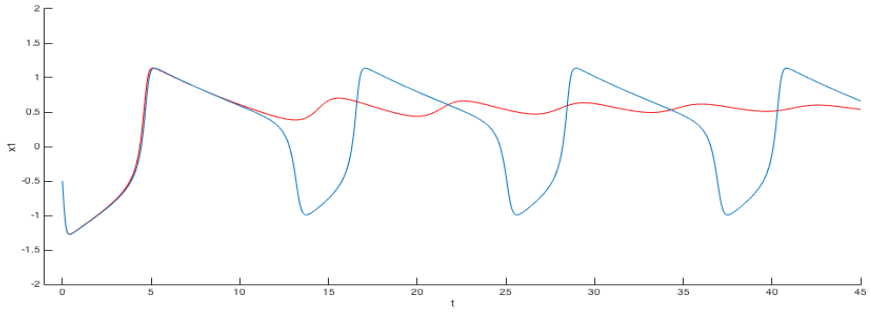
$$1 - x^2 = b/c^2$$

Finally, we can solve for $x = \sqrt{1 - b/c^2}$, set the null clines equal to each other to find the intersection point, and plug in x to solve for the z-value where the Hopf bifurcation rests ($z_H = (a - x)/b + x - x^3/3$). For our values of a, b, and c, we find $z_H = -0.3465$, which corresponds to FitzHugh's value.

Finding the saddle-node bifurcation was much more difficult analytically, but from our numerical results we can see that it rests at $z_c = -0.332$ and is the creation of two limit cycles, one stable and one unstable. As z decreases, the unstable limit cycle moves away from the stable cycle and inward, towards the stable fixed point nested within. When z reaches z_H, the unstable limit cycle collides with the stable fixed point in a subcritical Hopf bifurcation, knocking the remaining fixed point into unstability.



a) b)



c)

Figure 2: Figures 2a and 2b indicate the phase plane before and after the saddle-node and Hopf bifurcations. Figure 2c overlays the two time series; the pre-bifurcation time series (in red) shows a single pulse which is not quite enough to set off an action potential, then the system returning to equilibrium, while the post-bifurcation (in blue) is a train of impulses set off by an action potential; the neuron is firing.

Before the bifurcations begin (remember, we are *decreasing* z in this case) there is only one qualitative feature to the system: the stable fixed point. Afterwards, quite suddenly, there appears a limit cycle; this corresponds to an action potential and its respective impulse train. This continues until z decreases back past z_c (**not** z_H!), when the neuron returns to its resting state.

4 Discussion

Here we discuss our results. We used FitzHugh's model but our own analysis techniques to explore the bifurcations.

4.1 Bifurcations in Biology

The bifurcating behavior exhibited in the model occurs almost instantaneously– from the saddle-node creation of two limit cycles to the subcritical Hopf bifurcation results from only a little more than 0.05mV. So, while the creation and destruction of the unstable cycle is mathematically interesting, in reality, the change is almost simultaneous. Biologically, this explains how an action potential can spike so suddenly after the system reaches a certain voltage (in the HH model, -50mV).

Although subcritical Hopf bifurcations can be disastrous, as the unstable limit cycle created means that solutions oscillate towards infinity, the Hopf bifurcation in normal neuronal function is not dangerous because of the previously created stable limit cycle that puts a sort of "cap" on the system, which does not allow trajectories to escape. Dangerous subcritical Hopf bifurcations without this "cap" are prevalent in such neurodegenerative diseases as Alzheimer's and Parkinson's diseases; understanding Hopf bifurcations in the brain, therefore, is imperative if we wish to understand the mechanisms of these diseases and, someday, find a cure.

4.2 Future Directions

One way our model could be furthered is by modifying the FitzHugh-Nagumo model to represent the firing of coupled neurons to observe their behavior. In reality, one neuron in the brain is connected to hundreds of other neurons, and so the more neurons that are included in the model, the more biologically accurate our model would become. We have began to look into coupling neurons on a basic level:

For a synchronization model, we wanted to see what would happen if we linked two neurons together, with the first neuron firing and signaling to the second. The system is partially decoupled, since only one affects the other. Notice that the first system of equations $(\dot{x_1}, \dot{y_1})$ does not contain any terms from the second, but the second $(\dot{x_2}, \dot{y_2})$ has replaced z with $(z + y_1)$. This is because FitzHugh's equation for the membrane potential was $V = V_{in} - V_{out}$. Since $z = V_{in}$ and $V(t) = x(t)$, the voltage output of neuron 1 is given by $z - x(t)$:

$$\begin{cases} \dot{x_1} = c(y_1 + x_1 - x_1^3/3 + z) \\ \dot{y_1} = -(x_1 - a + by_1)/c \end{cases} \quad \begin{cases} \dot{x_2} = c(y_2 + x_2 - x_2^3/3 + z - x_1) \\ \dot{y_2} = -(x_2 - a + by_2)/c \end{cases} \tag{8}$$

One assumption that we are making when creating this two-neuron system is that we are coupling them in a biologically accurate manner and not just an arbitrary one. Another assumption we make is that the parameters that we set for each equation are biologically relevant; we assume that these parameters are similar to what actual parameters would be in a two-neuron system.

If we continued our research, we would explore more deeply the dynamics of this simply connected system of equations. One issue that we would come across is that as more neurons are added, it becomes exponentially more difficult to model the system. Advanced computing techniques would be required in order to process the extremely large amounts of data that result from modeling an entire neuronal network.

A way in which this multi-neuron model could be applied is to help further understanding of diseases in which neurons misfire, such as Alzheimer's disease, Parkinson's disease, and epilepsy. Although there is some evidence of Hopf bi-

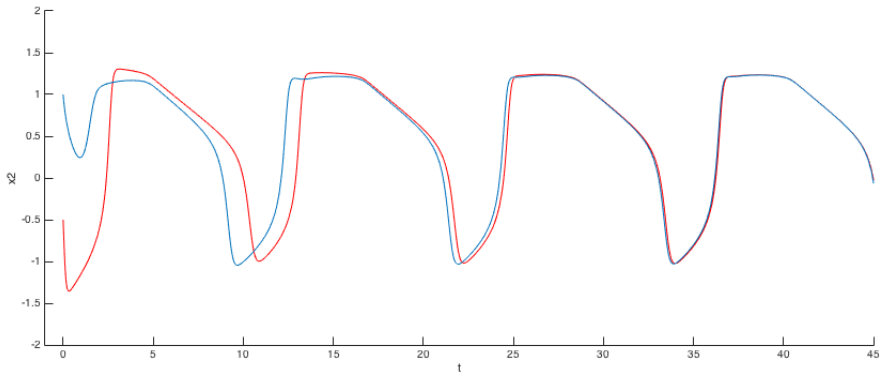


Figure 3: Two neurons (neuron 1 in red, 2 in blue) are initially out of sync. Through a partially coupled system of differential equations, neuron 2 is gently nudged into synchronous firing with neuron 1.

furcations playing a role in how this diseases work, many other factors must be taken into account if this model were to be applied. For example, the specific brain region(s) and exact neurons that are malfunctioning must be known. Currently, this is something that is very difficult to achieve. In addition, if specific neuronal networks were identified, this model would have to be expanded in a unique manner to be able to accurately represent the neuronal network in question. Again, the issue of massive data processing arises when attempting to model biologically-accurate neuron networks; until the proper technology is developed to handle this information, true neuronal network modeling can only be performed via approximation.

5 References

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