The Role of Time Delay in the Fitzhugh-Nagumo Equations: The Impact of Alcohol on Neuron Firing

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1 Abstract

Repeated and frequent alcohol use can have serious repercussions on the nervous system, particularly the brain. Here, we focus on the nerve cell (neuron), the fundamental component of the brain. In 1952, Hodgkin and Huxley received the Nobel Prize in Physiology and Medicine for their research on neuron dynamics (firing) with the help of a mathematical model. Our research begins with the assumption that alcohol impairs neuron dynamics. Hence, we begin with the Hodgkin and Huxley model but its complexity moved us to the Fitzhugh-Nagumo equations, a caricature of the Hodgkin and Huxley model. The Fitzhugh-Nagumo equations include only two variables, the membrane potential and the restoring force. In our research, we assumed that alcohol delays the effect of the restoring force and changes the normal state of the system. We analyzed the dynamics of the Fitzhugh-Nagumo equations with and without delay using computer simulations, the qualitative theory of dynamical systems, and bifurcation theory. Alternative hypotheses are discussed in the conclusions.

2 Introduction

Alcohol is a mood altering depressant drug that slows brain activity down and produces various effects on neural activity on brain function in different regions (see appendix). Alcohol induces many forms of typical behavioral changes such as impaired judgement, extreme emotion, and slowed behavior. Long-term effects include damage in cognitive behavior especially associated with the frontal lobes of the brain such as slowed processing of information, and difficulty in learning new material. The reason that alcohol can cause such extensive damage because there is no body cell resistant to alcohol. Alcohol is absorbed directly into the blood stream and moves quickly to the brain and passes the blood-brain barrier, which normally keeps harmful substances away from the brain.

In 1996, a study conducted by Richard Gross and Rose Gubitosi-Klug showed that alcohol accelerates the release of Potassium ions. This will result in a disruption that could inhibit the release of neurotransmitters [29]. Potassium ion play a major role in the hyper-polarization of the action potential. Since the ionic concentration of potassium determines how quickly hyper-polarization occurs, we can assume that hyper-polarization will take a longer time. The system takes a longer time to get to the resting state. Consequently, there is a delay in the firing of the neuron (depolarization).

Alcohol, ethyl alcohol, acts primarily on the nerve cells within the brain, interfering with communication between nerve cells and all other cells. Alcohol has the ability to enhance the effects of the neurotransmitter GABA, which is an inhibitory neurotransmitter. Enhancing an inhibitor would retard the process of message transfer between neurons. Glutamate is an example of an excitatory neurotransmitter weakened by alcohol. Thus, making transmitter less effective(Tsai [23]).

All brain functions involve communication among nerve cells, or neurons that connects with hundreds or thousands of adjacent neurons. Messages travel within the neuron as an electrical impulse. When a nerve signal is sent by the nervous system, the dendrites receive the signal. The axon then transmits the nerve signal to the axon terminals, which synapse with dendrites or other tissues such as a muscle. (Refer to the Figure1). Messages are then carried across synapses (gaps between neuron) by neurotransmitters. The neuron membrane has an unequal distribution of ions and electrical charge between the membrane. The outside of the membrane has a positive charge and inside has a negative charge. This charge difference is a resting potential and is measured in milli-volts. Nerve action potentials are the electrical signals sent out by the body to control bodily processes such as muscular movement, which are controlled by ions and their concentrations surrounding the nerve cell.

Sodium and Potassium ions are essential to the normal action potential. An external stimulus causes an influx of Sodium in the nerve cell. This depolarization (B) or action potential, see Figure 3, continues down the neural pathway until it reaches its destination. After the cell depolarizes, it must hyper-polarize to its resting potential before it can be stimulated again(depolarize). This hyper-polarization phase (C) is controlled by Potassium. Consequently, efflux of Potassium causes the potential to return to its resting state. hyper-polarization (C) occurs when the membrane potential is returning to the resting state and undershoot (D) occurs due the Potassium gate staying open longer.

There are three gates that are associated with the action potential: m, h, and n. Ion gates are protein channels that regulate ion flow into and out of the cell. The m and h

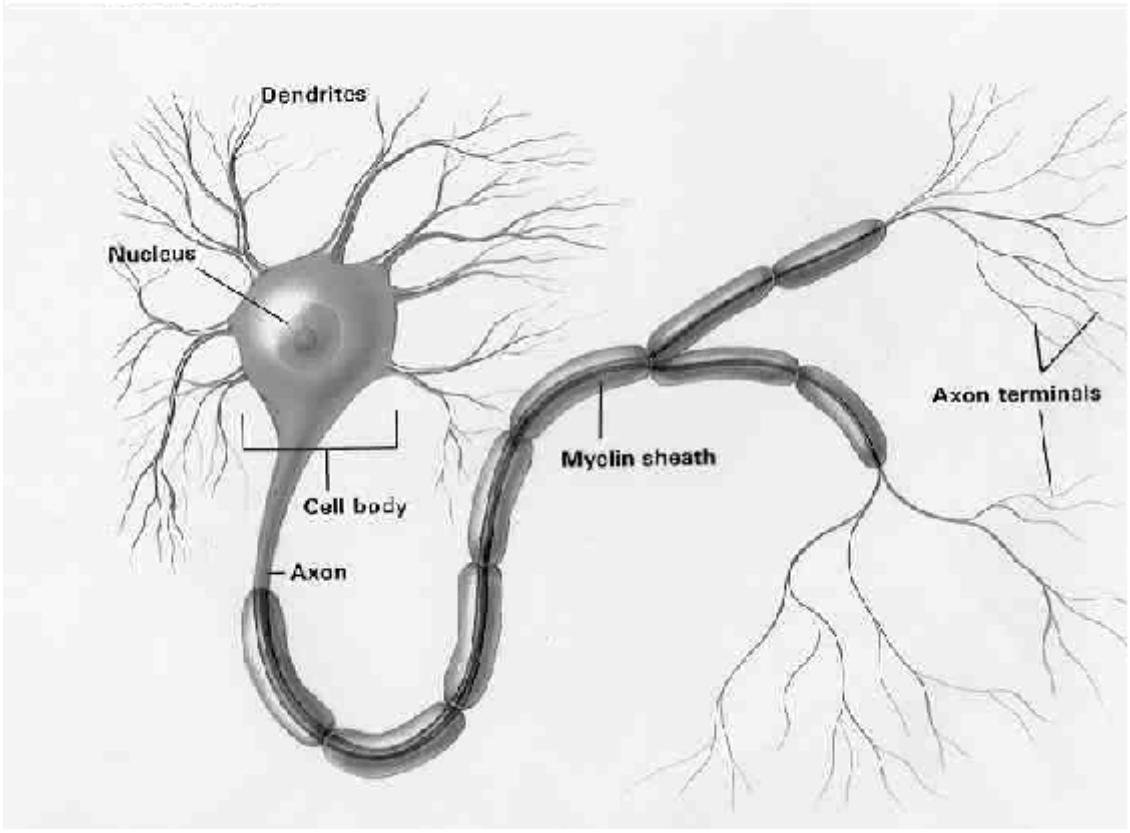

Figure 1: The Structure of the Neuron from Neurons, Hormones, and the Brain http://www.gpcpeachnet.edu/ reynold/backup/101-04.htm

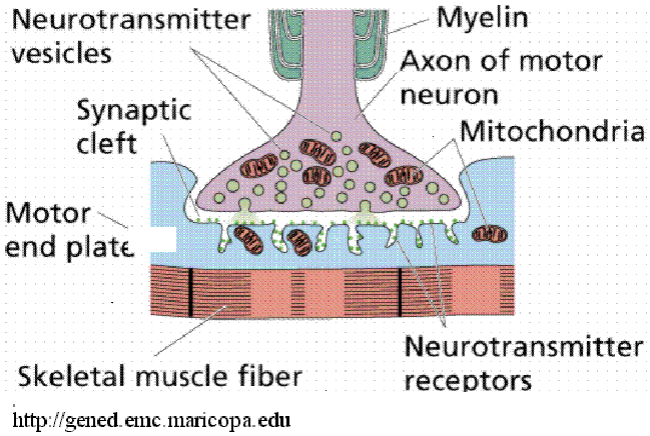

Figure 2: The nervous system:http://gened.emc.maricopa.edu/bio/bio181/BIOBK/BioBookNerv.htm

gates control sodium flow, while the n gate controls potassium flow. In reference to figure 3, the resting phase (A) of the action potential, the m gate is closed, while the h gate is open. Therefore, sodium is neither leaving nor entering the cell. The n gate is also closed, so potassium can neither leave nor enter the cell. During depolarization (B), the m gate opens, allowing sodium to diffuse its gradient, while the n gate is still closed. During hyperpolarization (C), the h gate closes, preventing sodium from coming into the cell. The n gate is open during this phase so potassium moves out. In the undershoot phase (D), the m gate closes, the h gate remains closed, and the n gate remains open. Finally, the h gate opens, the n gate closes, and resting state is once again achieved.

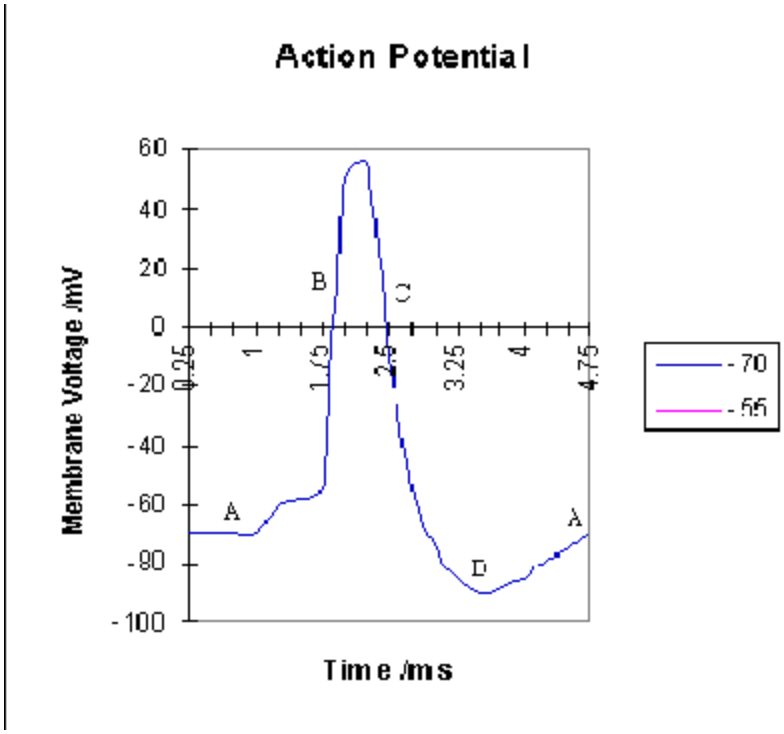

Figure 3: The Action Potential http://www.du.edu/ kinnamon/3640/actionpotential

Drinking alcohol affects many areas of the brain that control perception and reaction (see appendix for the order in which areas are affected). However, only indirect evidence of alcohol's actions are available. Therefore, we must be careful in our interpretations. From research articles we have found that alcohol interferes with messages transfer within the brain and between the brain and the body. Based on research previously conducted, we can say that alcohol disrupts the normal flow of electrical impulses and chemical systems, which will undoubtedly interfere with the communication between neurons. Thus, showing that alcohol delays the effect of the restoring force and changes the normal state of the system. In deriving a mathematical model to explain the change in the system, we will assume alcohol impairs neuron dynamics resulting in a time-delay in the firing of a neuron, which makes response slower.

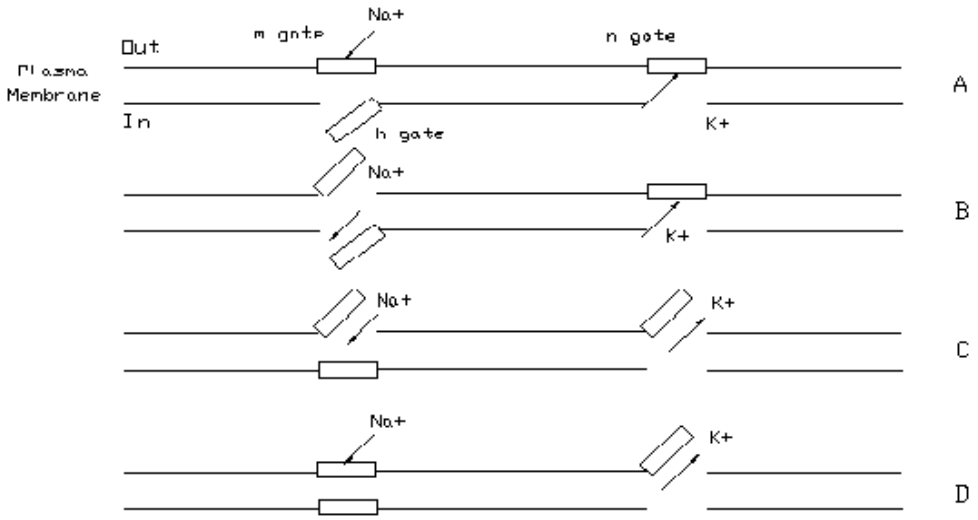

Figure 4: Ion gates during nerve action potential http://www.du.edu/ kinnamon/3640/actionpotential

3 Mathematical Model

3.1 Hodgkin and Huxley Model

Groups of neurons with similar functions extend from one brain region to another, forming neural circuits, which interact with one another to integrate the functions of the brain. Therefore, we decided to use the classical Hodgkin and Huxley mathematical model neuronal theory, which was derived from a series of experiments that Hodgkin and Huxley conducted on a squid axon in the 1950's.

The axon was placed in a bath of seawater, which was inserted with a microelectrode into the axon and stimulated by a voltage. To analyze the nerve action potential that occurred as the stimulus was applied, they measured the membrane potential during its propagation along the squid axon. The Hodgkin-Huxley model of the electrical and ionic behavior of the membrane of the squid axon describes the electrical behavior of both invertebrate and vertebrate neurons, and with slight modifications, of muscle cells and other cell types as well. This is discussed further in the appendix.

The Hudgkin and Huxley Equations:

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

$$\frac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v)m \tag{2}$$

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

$$\frac{dv}{dt} = -\frac{1}{C}[g_{Na}(v)(v-v_{Na}) + g_K(v)(v-v_K) + g_L(v-v_L)] \tag{4}$$

As stated earlier, the first set of equations that accurately gave insight to neural theory were the Hodgkin and Huxley equations, a system consisting of four coupled ordinary differential

equations with non-linear terms. Its complexity however, led us to look at a caricature of the Hodgkin-Huxley equations, the Fitzhugh-Nagumo equations.

3.2 Fitzhugh-Nagumo Model

The Fitzhugh-Nagumo model was independently derived by Fitzhugh, (Fitzhugh 1961) and Nagumo (Nagumo, Arimoto, and Yoshizawa 1962), from the Hodgkin-Huxley equations. Looking at equations (1) and (4), the argument was that since the time scales for $m,\ n$, and h were not all of the same order, certain assumptions could be made. For example, m can be neglected because this variable represents the opening of the sodium gates in the membrane. Relatively speaking this phenomena is instantaneous. Therefore, $\frac{dm}{dt} = 0$. Since the system still maintained most of the features observed experimentally when h is set equal to a constant h_0, h is also neglected. The Hodgkin and Huxley model was then reduced to a more traceable mathematical model. The result is a two variable (ω, v) model that can be approximated by the following dimensionless system,

$$\frac{dv}{dt} = f(v) - \omega + I_a, \qquad \frac{d\omega}{dt} = bv - \gamma\omega, \tag{5}$$

$$f(v) = v(a - v)(v - 1) \tag{6}$$

where $a,\ b$, and γ are all positive parameters, and $0 < a < 1$.

In this system of equations v plays the role of V in the Hodgkin-Huxley equations (1)-(4), the membrane potential, and ω the recovery variable, plays the role of all three variables $m,\ n$, and h in equations (1)-(4), it represents the recovery of hyper-polarization of neuronal action potential (Murray [17]).

Although the Fitzhugh-Nagumo equations are a very good mathematical portrayal of neural excitation, they are not meant to accurately convey the physiological mechanisms operating inside the axonal membrane. Instead, they are a behavioral paradigm, phrased in terms of equations that are mathematically easier to analyze as oppose to the Hodgkin-Huxley equations (Edelstein-Keshet [6]).

Mathematical investigations of the Fitzhugh-Nagumo model (5) and (6) have been performed in many works (see Murray [17] and Eldelstein-Keshet [6]). We used work by Fitzhugh 1961 [8] and also papers by Volokitin and Treskov, 1994 [26], and Armburster, Dieter 1997 [1]. It was proven in these investigations that the model Fitzhugh-Nagumo model demonstrates 21 topologically different phase portraits by varying parameters $a,\ b$, and γ, and gives a bifurcation of co-dimension 4, "three-multiple neutral equilibrium-focus with symmetry " (Khibnik et. al,1998 [14]). Corresponding bifurcation diagram is given in section 9.1. Due to the focus of our research, we are only interested in the portraits which correspond to the existence of a spike, like that of the dynamics similar to the ones seen in section 9.4b. In an attempt to simplify model (5) and (6) we normalized it in the form proposed by Bazykin and Berezovskaya 1995 [3].

Before our attempt to normalize we took $I = 0$, since it does not affect the possible number of phase portraits. We make $I = 0$ and normalize the system to simplify the process

of identifying which phase portraits correspond to normal neuron firing. We normalize the Fitzhugh-Nagumo equations in the following steps:

STEP 1: Let $\frac{d\omega}{dt} = z$, then take the time derivative of z and get $\frac{dz}{dt} = b\frac{dv}{dt} + \gamma\frac{d\omega}{dt}$.

STEP 2: Solve for v from $z = bv - \gamma\omega$ and substitute this new v into $\frac{dz}{dt}$.

STEP 3: Since we are dealing with small z we ignore terms that have z^3 *and* z^2.

STEP 4: We introduce a new parameter μ; $\omega = u + \mu$ and plug this new ω into $\frac{d\omega}{dt}$

After plugging this new ω into $\frac{dz}{dt}$ we manipulate it to make it look like the following equation.

$$\frac{d\omega}{dt} = F(u) + zG(u), \tag{7}$$

where $F(u)$ is a cubic polynomial and $G(u)$ is a quadratic polynomial.

Our final normalized equations are the following,

$$\frac{du}{dt} = z, \qquad \frac{dz}{dt} = \epsilon_1 + u\epsilon_2 - \frac{u^3\gamma^3}{b^2} + z\left(\epsilon_3 + Au - \frac{3u^2\gamma^2}{b^2}\right) \tag{8}$$

where $\epsilon_1, \epsilon_2, and\ \epsilon_3$ are new parameters that depend $a,\ b$, and γ.
(See appendix for full explanation of the normalization process and for ϵ_1, ϵ_2, and ϵ_3).

We now find the equilibria of (8), by setting $\frac{du}{dt} = 0$ and $\frac{dz}{dt} = 0$. we find:

$$z = 0, \tag{9}$$

$$\epsilon_1 + u\epsilon_2 - \frac{u^3\gamma^3}{b^2} = 0 \tag{10}$$

We solve found the roots of (10) using

$$x^3 + 3px + q = 0 \tag{11}$$

where the roots of (11) are given by the formula

$$x = 2\sqrt{-p}\cos\frac{\theta + (0, 2\pi, 4\pi)}{3} \quad where\ \ \theta = \cos^{-1}\left(\frac{-q}{2\sqrt{-p^3}}\right) \tag{12}$$

Note that if $q^2 + 4p^3 < 0$ we have 3 real roots, otherwise we have one real and two imaginary. This can be seen graphically in section 9.5a, where we know that we always have at least one root and at most three. Noting that whenever we have only two roots, a double root

and a single root, we have a saddle-node bifurcation occurring.

Manipulating (10) to look like (11) we get

$$F(u) = u^3 + 3u(\frac{-b^2}{3\gamma^3}\epsilon_2) + (-\epsilon_1\frac{b^2}{\gamma^3}) \tag{13}$$

by (12) our roots are

$$u_1 = \left(0, 2\sqrt{\epsilon_2\frac{b^2}{3\gamma^3}}\cos\frac{\theta}{3}\right) \tag{14}$$

$$u_2 = \left(0, 2\sqrt{\epsilon_2\frac{b^2}{3\gamma^3}}\left[-\frac{1}{2}\cos\frac{\theta}{3} - \frac{\sqrt{3}}{2}\sin\frac{\theta}{3}\right]\right) \tag{15}$$

$$u_3 = \left(0, 2\sqrt{\epsilon_2\frac{b^2}{3\gamma^3}}\left[-\frac{1}{2}\cos\frac{\theta}{3} + \frac{\sqrt{3}}{2}\sin\frac{\theta}{3}\right]\right) \tag{16}$$

where

$$\theta = \cos^{-1}\left(\frac{\epsilon_1\frac{b^2}{\gamma^3}}{2(\frac{\epsilon_2 b^2}{3\gamma^3})^{3/2}}\right) \tag{17}$$

Finding the Jacobian of the system and evaluating it at every fixed point would be the first step in determining the stability of each fixed point. By means of the determinant and the trace of the coefficient matrix we could determine its stability (Refer to section 9.5b for further aid in this process).

In our analysis, we found that by fixing one of the three parameters and varying the other two, the system displayed ten distinct phase portraits (see section 9.2 for the ten different domains). Being that our interest lied solely on the effects of alcohol on action potentials in neurons, we focused primarily on portraits that displayed stable limit cycles (Murray [17]), since these phase portraits correspond to the dynamics of periodic neuron firing (see section 9.4b). We first decided to analyze the system with the absence of alcohol via the normalized Fitzhugh-Nagumo (8), and identify parameter spaces that corresponded to continuous spiking. After identifying these parameter spaces we would then analyze how these parameter spaces would change due to a time delay. Based on research and on advice from both neurobiologist and applied mathematicians, we were able to assume that alcohol would cause a neuronal communication delay. Therefore, we placed the time delay on the recovery variable ω. This will be discussed in detail in a later section.

From the simulations we ran using TRAX, we found that the normalized equations (8), had ten different phase portraits, where each corresponded to a different parameter space. From the ten, we found stable spirals, stable and unstable nodes, stable and unstable limit cycles, and others that will not be discussed due to their irrelavance. As we said earlier we focused on portraits that had stable limit cycles. We discovered that when ever a stable

limit cycle does not exist we do not get a full complete spike, this can be compared to the original Fitzhugh model, where if the initial stimulus I is less than the threshold then we have no action potential but there is a short reponse (see section 9.3b). After analyzing these phase portraits we found that there are three possible outcomes, the rest are variation of these three. The absence of a stable limit cycle, is one of the three, where we know that we get dynamics like that of section 9.3b. Another possibility is when we do have limit cycles (see section 4a). In any of these cases we know that we will eventually end up with a u-t plane like section 9.4b, where we have continuous spiking occurring. The third, does not occur biologically but we will mention it only because we do have an action potential occurring. This case is a unique one because we only have one spike occurring (see section 9.3a). It is unique in the sense that this kind of dynamics is only seen for very specific parameter values. Referring to section 9.2, these particular parameter values correspond to a point that directly lies on the curve L, where L corresponds to the birth or destruction of a separatrix loop (see section 9.3a). That is why this is very unique because any perturbation of these values would give completely different outcomes. Now that we have found these parameter spaces we will see how a time delay, affects them.

4 Fitzhugh-Nagumo Delay Models

In the Fitzhugh-Nagumo system the ω term biologically means the recovery or hyperpolarization of neuronal action potential. This variable represents potassium gating, leakage currents, and ATP pump action. Since, we are assuming alcohol causes a neuronal communication delay, we will input the delay into the ω variable also referred to as the restoring force or recovery force. In reference to the spike (action potential), by the introduction of the delay into the ω variable we are assuming that the delay will be prevalent in the "slope" from sodium inactivation to resting potential. We will model the delay in two forms, a distributed delay and an explicit (fixed) delay.

4.1 Original Fitzhugh-Nagumo

$$\frac{dv}{dt} = v(a-v)(v-1) - \omega + I \tag{18}$$

$$\frac{d\omega}{dt} = bv - \omega\gamma = \epsilon(v - \gamma\omega)$$

mean of the ω variable: $\frac{1}{\epsilon\gamma}$
In the original Fitzhugh-Nagumo equation we observe that the recovery variable has an exponential distribution delay with mean $\frac{1}{\epsilon\gamma}$

4.2 Fitzhugh-Nagumo Distributed Delay in the Recovery Variable, ω

$$\frac{dv}{dt} = v(v-1)(a-v) - \omega + I \tag{19}$$

$$\frac{d\omega_1}{dt} = \epsilon(v - \delta\omega_1)$$

$$\frac{d\omega}{dt} = \epsilon(\delta\omega_1 - \delta\omega)$$

mean of the ω and ω_1 variable: $\frac{2}{\epsilon\delta}$
In the first approach we model the distributed delay. We reconstruct the ω variable into ω_1 and ω and we allow these two equation to have the characterisitic that it has a gamma-distribution(n=1). The ω_1 and ω variables now have mean time $\frac{2}{\epsilon\delta}$.

4.3 Fitzhugh-Nagumo Fixed Delay in ω

$$\frac{dv}{dt} = v(v-1)(a-v) - \omega(t-T) + I \tag{20}$$

$$\frac{d\omega}{dt} = \epsilon(v - \gamma\omega)$$

mean of the ω variable: T
In the second approach a fixed delay of length, T, is introduced into the recovery variable. The recovery variable now has mean time distribution of T.
To calibrate our model we first assume that the mean response time is the same for the three models, this allows a relationship between γ and δ to be constructed.
$T = \frac{1}{\gamma\epsilon}$ and $\frac{2}{\delta\epsilon} = \frac{1}{\gamma\epsilon}$. Further to depict a delay in the system the following mean time inequalities must be true and we will not be concerned with the variances.
$\frac{1}{\gamma\epsilon} < T$ and $\frac{1}{\gamma\epsilon} < \frac{2}{\delta\epsilon}$

5 Data Analysis of Fitzhugh-Nagumo Delay Equations

In this section we will consider two Fitzhugh-Nagumo delay equations with the bound on delta, $\delta < 2\gamma$, and the original Fitzhugh-Nagumo equation. The three equations that we will compare will use $\epsilon = 0.008$ and $a = 0.139$ as suggested by John Rinzel (2001). The following discussion will be of the data from the Matlab simulation of the original Fitzhugh-Nagumo and the two delay models.

Since we are investigating neuronal firing from the perspective of dynamical systems, we will make reference to certain bifurcation regions which have a biological interpretation. We want to investigate the delay in neuronal firing and as such we will be looking at periodic spiking. Periodic spiking in the neuro-computational sense depends on the bifurcation of large amplitude limit cycles [13]. The Fitzhugh-Nagumo equation has 15 qualitatively distinct regions in the bifurcation diagram (2). We will only investigate three regions with limit cycles and vary the impulse, I, and γ. The data for the three regions under investigation can be found in section 9.6 in the appendix. The graphs for all three regions can be found in the appendix sect 9.6 a, b, and c.

Note: In the discussion of the regions when referring to equation 18 we are discussing the original Fitzhguh-Nagumo, equation 19 the distributed delay, and equation 20 the fixed/explicit delay.

Region 1: γ=.04 and I=2.54

In this region, equation 18 has repetitive firing with spike period(SP) of 131.89 units of time(t), in comparison equation 19 has repetitive firing with SP of 216.795 t. This 60-percent increase in spike period directly depicts the delay in firing. We can also look at the spike width (SW) measured at one-half the amplitude height. SW for equation 18 is $43.047t$ and equation 19 is $81.129t$, thus, these values depict an 88-percent increase in width of the spike. Biologically this increase means that the communication between cells has decreased $i.e$ delay in neuron firing. Another significant aspect of the spike is the refractory period (RP) this is when the action potential reaches its peak at sodium inactivation and the cell begins hyper-polarization and approaches its resting potential. RP was found by measuring the time it takes for the spike to get from its maximum value to its minimum value. Normal RP, as depicted in equation 18, is $41.387t$ and in equation 19 is $86.095t$. A 108-percent increase in RP from normal firing to delay firing makes it obvious that the delay has affected the hyper-polarization. Biologically this means that the it will take a longer time for the neuron to respond to another stimulus, a delay in communication.

The behavior of the explicit time delay equation 20, as compared to the normal behavior of equation 18 depicts a significant delay. This difference is most likely due to the spike minimum value (S_{min}) reached by equation 20 at -.286 volt units(vu) versus the S_{min} of equation 18 which is -.246vu. This aspect is interesting because it shows an experimentally proven biological affect that alcohol has on neuron action potential, namely it causes GABA increase which in turn controls Chlorine (-) influx. Thus, the increase in influx of the negatively charged Chlorine ions serves to further hyperpolarize (lower the resting potential). This influx both explains the delay and why a lower spike minima is reached in the delay equation. Inspection of the SW shows a $43.047t$ and $87.91t$ measure from equation 18 to 20. This is a huge increase in the width of the spike, which correlates precisely with the expectation that a delay will occur. SP in equation 18 is $131.89t$ and in equation 20 is $195.89t$, a 48-percent increase compared to a 60-percent increase as seen between equation 18 and equation 19.

Note:There exists a slight difference between the distributed delay, equation 19, and the fixed delay, equation 20, this may be due to $T = \frac{2}{\delta\epsilon}$

Region 2:γ=0.027 and I=4.42

In this region, equation 18 and 19 show an overall delay; however, the delay is shorter than the behavior of the equations in region 1. SP for equation 18 in this region is $143.915t$ and for equation 19 is $183.775t$, this is only a 27-percent increase in spike period. Examining SW in this region give values $66.22t$ and $76.16t$, for equation 18 and 19 respectively. SW only increases by 15-percent. This decrease in delay from that of the region 1 comparison may be linked to some biological meaning such as, the BAC of the intoxicated person decreasing below a certain point or the bifurcation region under inspection may be one in which the action potential is highly altered. Inspecting the RP of the equations conveys the slight delay that the spike undergoes. RP is $67.88t$ and $72.847t$, for equation 18 and 19 respectively, accounting for only a 7-percent increase in the time it takes the spike to get from the peak, sodium inactivation, to the minimum value below resting potential. One factor that

may be affecting the decrease in delay percentage from region 18 to that of region 19 is the value of I, the impulse. Perhaps, the high impulse perturbs the delay in a similar fashion then would a high voltage stimulus on neuron. That is, if too high a stimulus is applied to the neuron it may actually cause some biological change in channels that then alters the normal behavior of the cell firing.
In this region, equation 20 maintains a delay; however, the delay seems to be shortened. S_{min} for equation 18 and 20 respectively is, -.1956(uv) and -.28565(uv), a 46.04-percent (equations 18 to 19 only showed a 30-percent increase) increase. Unfortunately, SP showed a close to zero (0.8-percent) increase which is alarming because this means that though the spike is reaching a lower resting potential it is going at frequency close to that of the non-delay spike. Equation 20, the explicit time delay, may be depicting this unexplainable behavior because this type of delay perturbs some of the dynamics represented by the Fitzhugh-Nagumo equation.

Region 3: γ=0.022 and I=4.65
In this region we expect to observe a delay, but not as high as that of region 1. Inspecting SW we only observe a 9.5-percent increase and an 11.2 percent increase in SP from equation 18 to equation 19. These small percent increases still account for a delay, but it is not that significant. Over time the periodic firing of the spike may return to that of the equation 18, implying that the greatest delay occurs for values in region 1 and other regions other then that may produce minimal delay. In this region the equation 19, shows a lower S_{min} value of -.256uv compared to equation 18 value of -.1956uv, a 30-percent increase. We know that S_{min} can not get too low because the minimum value or resting potential a neuron can attain is bounded below by potassium equilibrium. Thus, if we continue to observe a decline in S_{min} then we may be observing irrelevant mathematical data that has no biological interpretation when considering an action potential.

Considering the explicit delay equation and the original equation we observe unexpected results. For equation 18 and 20 the SW values are 69.53t and 70.43t, respectively, this only accounts for a 1.3-percent increase. Most perplexing is the SP, equation 18 depicts a 168.87t value and equation 20 depicts a 143.33t, a decrease of 15.2-percent, which biologically means that the spike is actually moving quicker in the delay equation. This behavior in spike frequency is indicative of the effect alcohol has been known to have on different areas of the brain, some areas are inhibited and some are excited.

6 Conclusion

The analysis of the data attained from the periodic spiking of the Fitzhugh-Nagumo dynamical system, considering two types of time delay and the original Fitzhugh-Nagumo form gives us an understanding of the different ways neuron firing frequency can change depending on what bifurcation region is considered. Further, it may lead us into the understanding that upon different bifurcation regions, i.e. (different electrophysiological environments for the neuron) behavioral changes in spiking can be delayed and can accelerated.

Although one region that we examined showed that neuron firing increases. This may mean that this model does not accurately represents our assumptions about the neuron. In the brain different neuron have different behavior and may respond differently when

alcohol is introduced into the system. Due to the fact that there are about 100 different neurotransmitters, which either stimulate or inhibit the flow of an impulse between neurons. Alcohol can behave differently based on the type of neurotransmitters and receptors in that particular region. Moreover, since alcohol can act as a depressant or stimulant, we can infer that in region 3 alcohol is acting as a stimulant. For the most part, we can conclude that the distributed and fixed time-delay models correctly support our assumptions. Therefore, we can say that alcohol causes a delay response in the firing of neuron.

7 Future Work

Tolerance refers to the decrease in sensitivity to a drug brought about by continued use of a substance. Alcohol elicits a wide variety of behaviors and tolerance of alcohol differs greatly from person to person. Continuous alcohol use will lead to a given dose having less of an effect and the need for increasing doses to obtain the same psychological or physiological effect which will have an impact on the delay of neuron firing. For our future work we could take the continuous use of alcohol into consideration.

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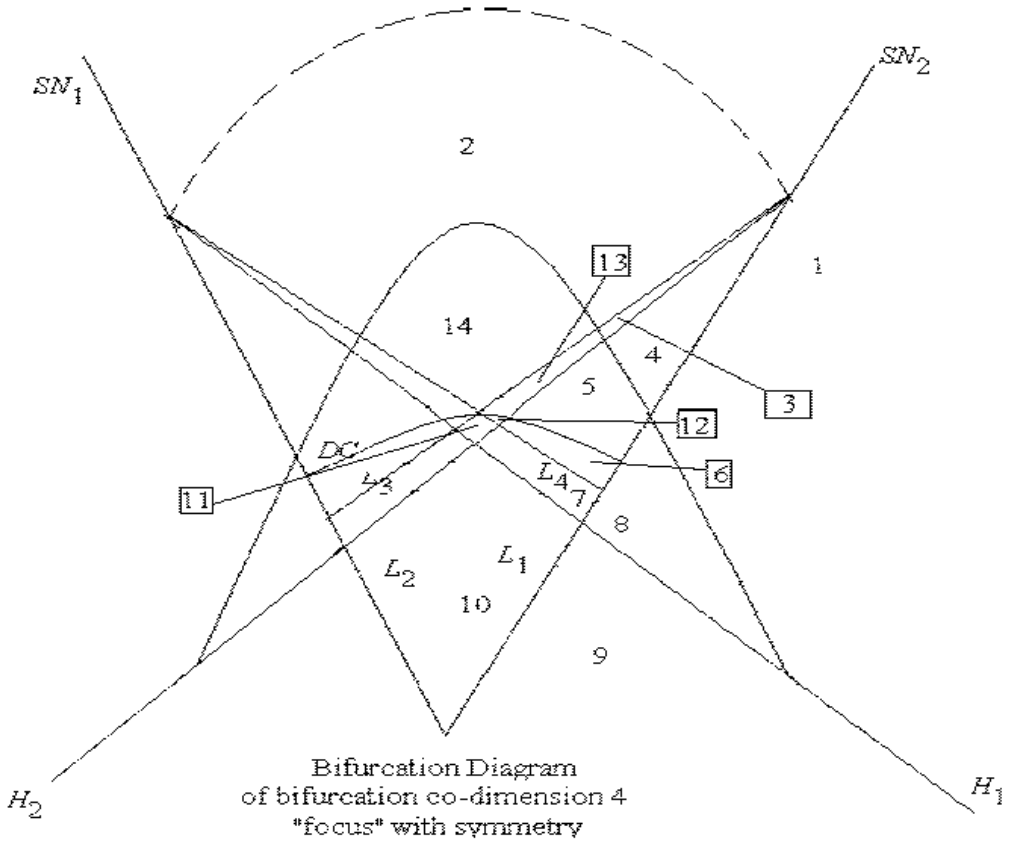
9 Bifurcation Diagrams and Phase Portraits

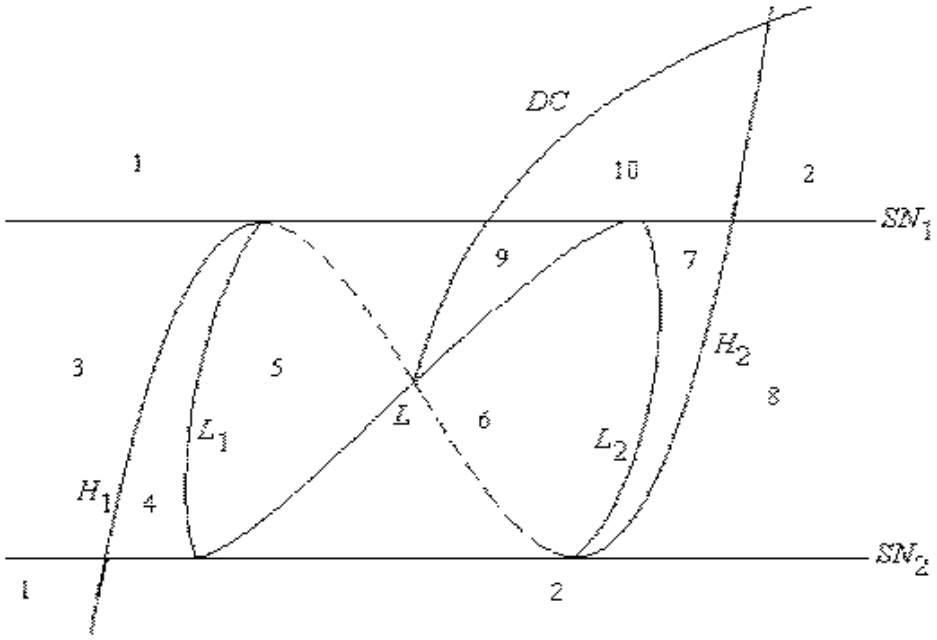
9.1 Bifurcation Diagram for the Fitzhugh-Nagumo Model



Bifurcation Diagram
of bifurcation co-dimension 4
"focus" with symmetry
See Ref # 13 and 23

Here, parameter curves correspond to the bifurcations in the mode SN, are the branches of the curve of equilibrium multiplicity. H are the branches of curve of the changes of stability of spirals. DC is the curve of multiple cycles. L curves correspond to Separatrix loops of saddle point.

9.2 Bifurcation Diagram for Normalized Fitzhugh-Nagumo Model

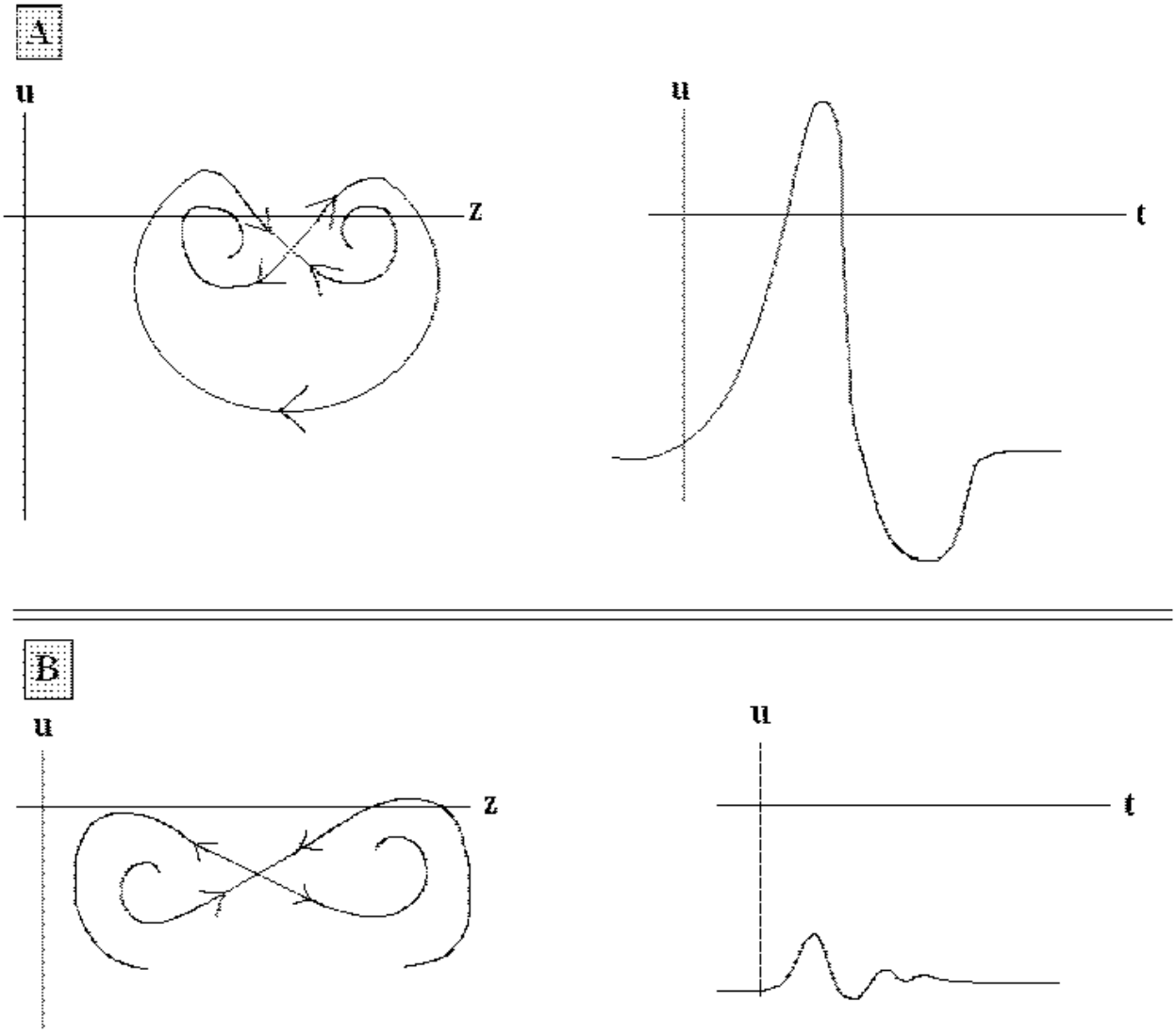


Normalized equations: $\frac{du}{dt} = z$

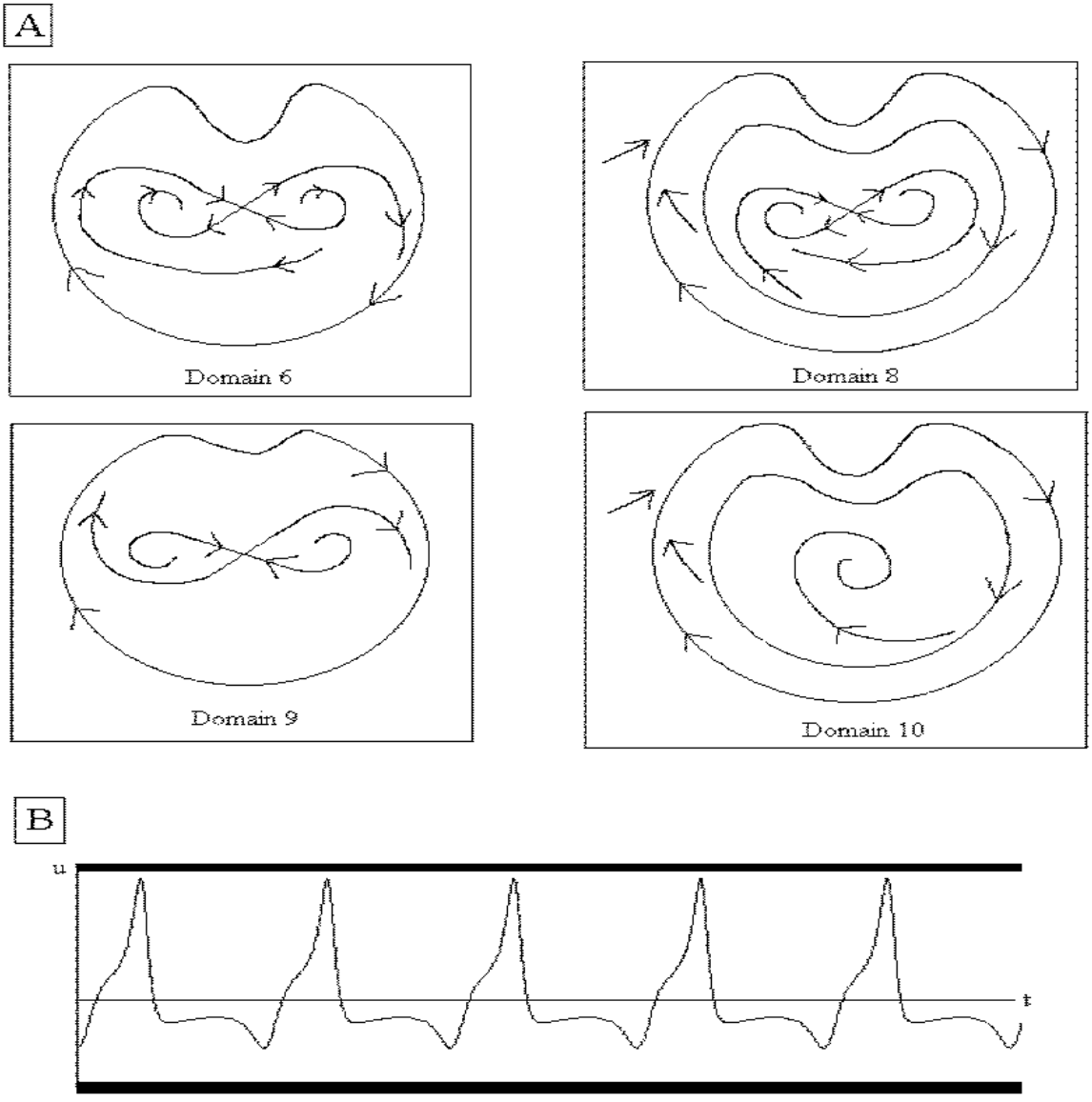
$$\frac{dz}{dt} = \varepsilon_1 + \varepsilon_2 u - \frac{\gamma^3 u^3}{b^2} + z\left(\varepsilon_3 + Au - \frac{3\gamma^2 u^2}{b^2}\right)$$

Here, parameter curves correspond to the bifurcations in the mode SN, are the branches of the curve of equilibrium multiplicity. H are the branches of curve of the changes of stability of spirals. DC is the curve of multiple cycles. L curves correspond to Separatrix loops of saddle point

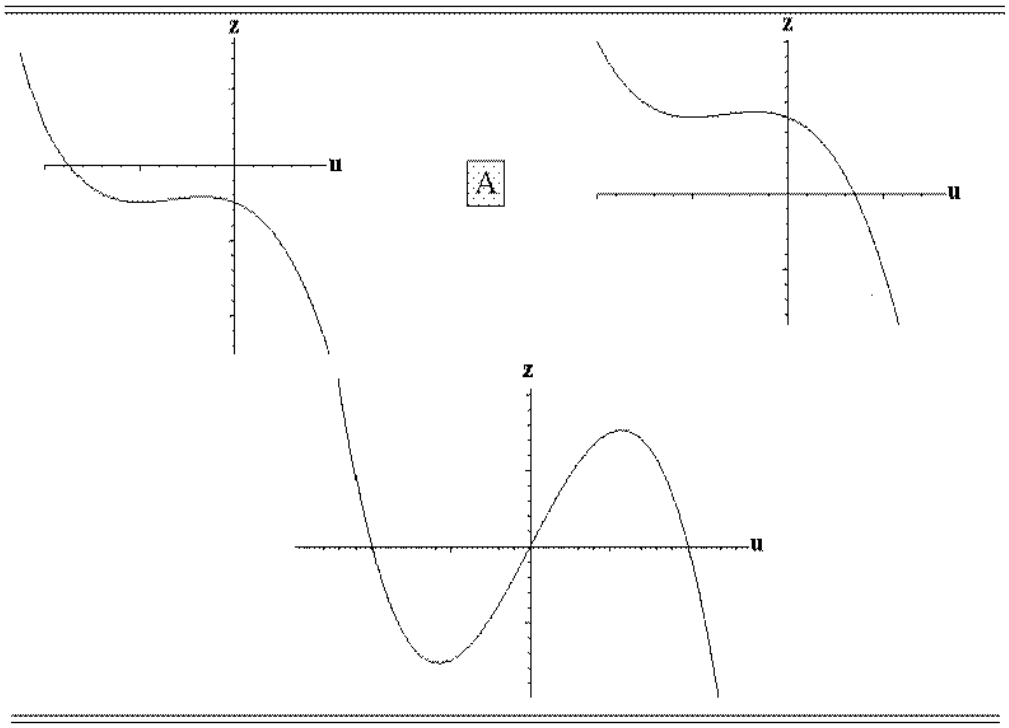
9.3 Phase Portraits and Corresponding u-t Plane

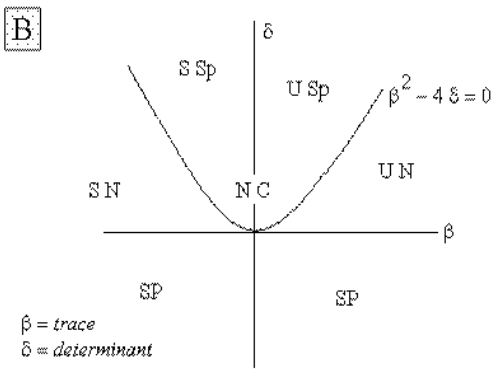


9.4 Stable Limit Cycles with Corresponding u-t Plane



9.5 Variability of Fixed Points and their Stability





The β δ parameter plane, figure 2 can be used to determine the stability of an equilibria

UN= Unstable Node: $\beta > 0$ and $\gamma > 0$

SP= Saddle Point: $\gamma < 0$

SN= Stable Node: $\beta < 0$ and $\gamma > 0$

US= Unstable Spiral: $\beta^2 < 4\gamma$ and $\beta > 0$

NC= Neutral Center: $\beta^2 < 4\gamma$ and $\beta = 0$

SP= Stable Spiral: $\beta^2 < 4\gamma$ and $\beta < 0$

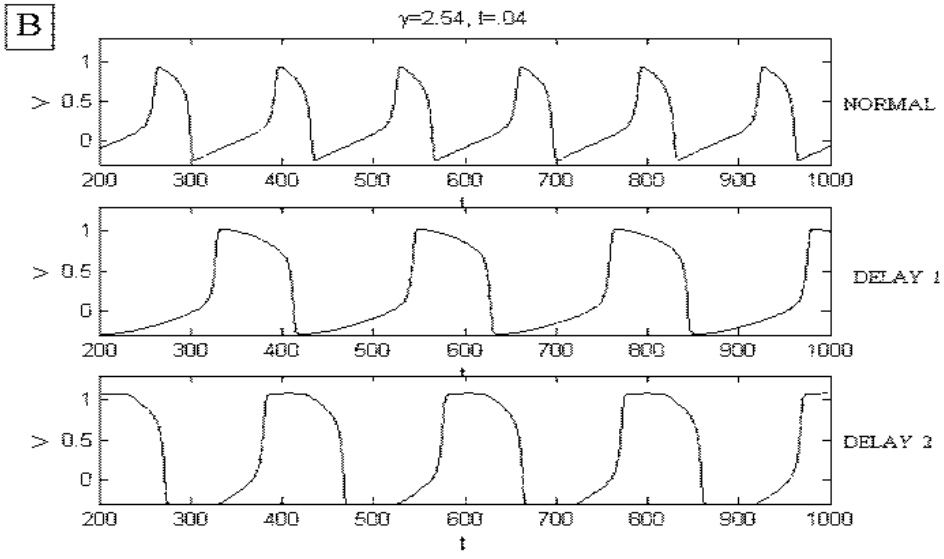
9.6 Data Analysis of Time Delay Equations (1)

A

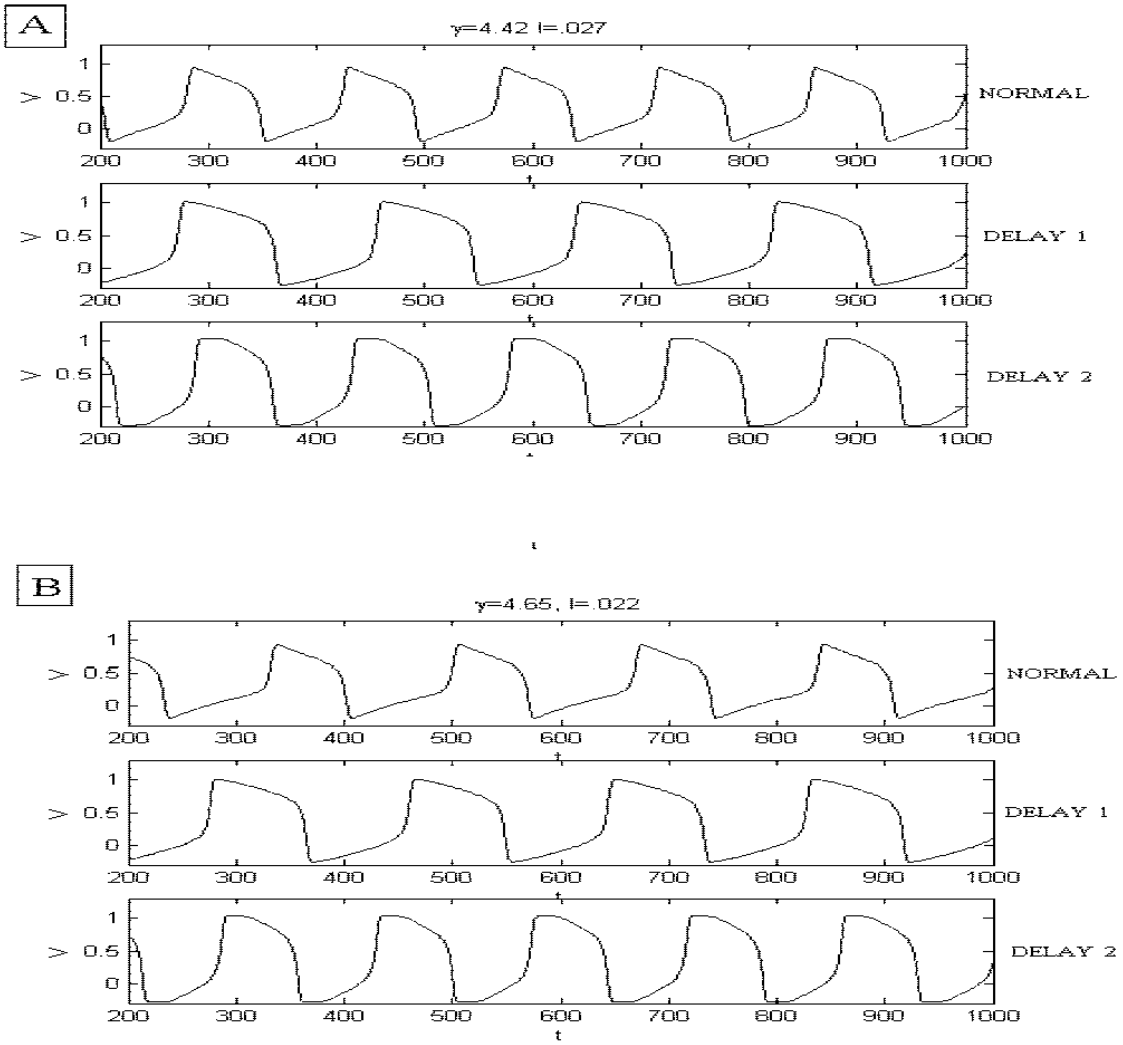
	Region1: gamma=.04, I=2.54			Region 2: gamma=.027, I=4.42			Region 3: gamma=.22, I =4.65		
	Normal	Delay 1	Delay 2	Normal	Delay 1	Delay 2	Normal	Delay 1	Delay 2
SH	0.937	1.019	1.0795	0.9427	1.0023	1.042	0.9255	1.0023	1.036
Smin	-0.246	-0.285	-0.3759	-0.1956	-0.256	-0.2857	-0.1897	-0.2098	-0.2814
SW	43.047	81.129	87.91	66.22	76.16	71.78	69.53	76.16	70.43
SP	131.89	216.795	195.89	143.915	183.775	145.19	168.87	187.81	143.33
RP	41.387	86.095		67.88	72.847		71.201	80.73	

SH = maximum spike height: measured in volt units
Smin = minimum spike value: measured in volt units
SW = spike with: measured in units of time
SP = spike period: measured in units of time
RF = refractory period: measured in units of time

B



9.7 Data Analysis of Time Delay Equations (2)



10 Appendix

10.1 How Areas in the Brain are Affected by Alcohol

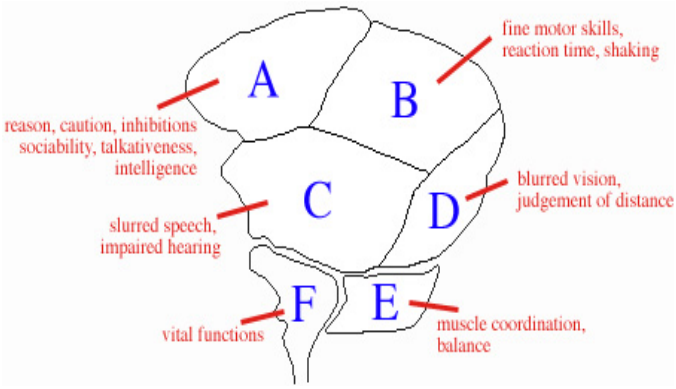


Figure 5: Function of the various regions of the brain

Brain Area	Order of Development	Function	Behavior Under the Influence of Alcohol
A	5th Developed	reason, logic, intellect, judgement	may be pleasant, sociable, relaxed or excited, decreased inhibitions, impulsive behavior, talkativeness, reason and caution impaired, driving ability impaired
B, C	4th Developed	Fine Motor Skills--more difficult to master...talking, writing, tying shoes, etc.	slight decrease in fine motor skills, poor judgement, slightly slurred speech, slow reaction time, impaired hearing
D	3rd Developed	Gross Motor Skills--basic movement	confusion, staggering, unable to stand upright, slurred speech, blurred vision, impaired judgement of distance
E	2nd Developed	Semi-Voluntary--muscle coordination and balance...reflexes, such as blinking eyes, which take place on their own but can be controlled at times	muscle coordination and balance impaired, severe confusion, semi-stuporous
F	1st Developed	Vital Functions--respiration, digestion...these functions occur automatically, they keep us alive	unconscious, coma, respiratory and cardiac distress, death

Figure 6: Area of the Brain Affected. McCarty [16]

10.2 Hodgkin and Huxley

Hodgkin and Huxley developed methods for observing the time and voltage dependence of sodium and potassium channels in the squid giant axon. Figure 4 shows their simulation of a propagated action potential. The time course of the membrane potential is a good, but not perfect, match to the time course of the action potential in a real squid measurements to simulate changes in conductance that take place during an action potential axon.

We can also examine the action potential by considering the electrical network considered in figure 4. The sequence of events during the propagated action potential is as follows: First, the membrane potential rises above threshold due to electronic current spread from nearby excited regions of the axon. Depolarization causes g_{Na} to increase, bringing about an increase in the inward flux of sodium and thereby a still greater depolarization (i.e. as g_{Na} increases, E_M moves towards E_{Na}) leading to further depolarization, which increases g_{Na} even more, and so on. The activation of g_{Na} is "regenerative", in that an increase in g_{Na} brings about a depolarization, which causes g_{Na} to increase still further. This regenerative cycle is known as the Hodgkin cycle. During the next phase of the action potential, the axon begins to hyper-polorize due to two occurrences: first, g_Na automatically inactivates, which allows the membrane potential to move away from E_{Na} and towards E_K and E_{Cl}. Second, depolarization causes activation of g_K, which occurs much more slowly than did activation of g_Na. Activation of g_K moves E_M toward E_K and, owing to the reduction of t_M due to increased g_K, the change in potential towards E_K occurs much more rapidly than without an increase in g_K. Finally, as the membrane potential approaches E_K, which is more hyperpolarized than resting potential, the voltage dependence of g_K brings about its return to the rest level, and the resting potential is again attained.

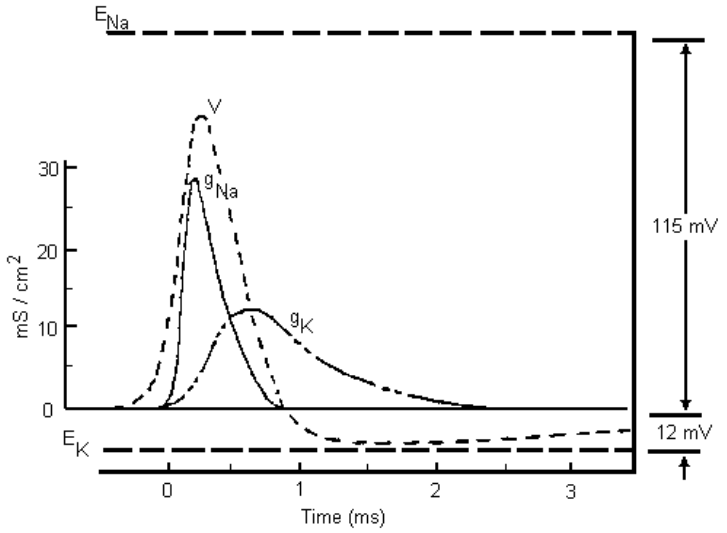


Figure 7: Simulation of a propagated action potential of a squid giant axon at 18.5 degrees Celcius. Redrawn from Huxley, based on data in Hodgkin and Huxley [7].

10.3 Normalizing the Fitzhugh-Nagumo equation

Normalizing the Fitzhugh-Nagumo equation

$$\frac{dv}{dt} = f(v) - \omega + I_a \tag{21}$$

$$\frac{d\omega}{dt} = bv - \omega\gamma \tag{22}$$

$$f(v) = v(a - v)(v - 1), \tag{23}$$

We let $z = \frac{d\omega}{dt}$ and $I_a = 0$ so then, $z = bv - \omega\gamma$. Taking the time derivative of z we get,

$$\frac{dz}{dt} = b\frac{dv}{dt} - \gamma\frac{d\omega}{dt} \qquad \text{(By Chain Rule)} \tag{24}$$

Pluging in $\frac{dv}{dt}$ *and* $\frac{d\omega}{dt}$ into (34) we get,

$$\frac{dz}{dt} = b\left[f(v) - \omega\right] - z\gamma \tag{25}$$

Since we know $z = bv - \omega\gamma$ we can solve for v and get $v = \frac{z+\omega\gamma}{b}$,
plugging v into (5)

$$\frac{dz}{dt} = b\left[f(\frac{z + \omega\gamma}{b}) - \omega\right] - z\gamma \tag{26}$$

$$\frac{dz}{dt} = b\left[\frac{(\gamma\omega + z)(a - \frac{\gamma\omega+z}{b})(\frac{\gamma\omega+z}{b} - 1)}{b} - \omega\right] - z\gamma \tag{27}$$

After distributing and factoring we get,

$$\frac{dz}{dt} = -\frac{z^3}{b^2} + z^2\left[-3\frac{\gamma\omega}{b^2} + \frac{a+1}{b}\right] + z\left[-3\frac{\gamma^2\omega^2}{b^2} + \frac{2\gamma\omega(a+1)}{b} - (a+\gamma)\right] \tag{28}$$

$$-\frac{\omega^3\gamma^3}{b^2} + \omega^2\left[\frac{\gamma^2(a+1)}{b}) - \omega(b + a\gamma\right] \tag{29}$$

Since we are examining very small z values, terms with z^3 and z^2 are ignored.
System now becomes:

$$\frac{dz}{dt} = -\frac{\omega^3\gamma^3}{b^2} + \omega^2\left[\frac{\gamma^2(a+1)}{b}\right] - \omega(b + a\gamma) + z\left[-3\frac{\gamma^2\omega^2}{b^2} + \frac{2\gamma\omega(a+1)}{b} - (a+\gamma)\right]$$

A new parameter μ expressed by parameters a b γ from (31) and (32), is introduced into ω where $\omega = \mu + u$. Substituting ω into $\frac{dz}{dt}$

$$\frac{dz}{dt} = -\frac{(\mu+u)^3\gamma^3}{b^2} + (\mu+u)^2\left[\frac{\gamma^2(a+1)}{b}\right] - (\mu+u)(b+a\gamma)$$

$$+z\left[-3\frac{\gamma^2(\mu+u)^2}{b^2} + \frac{2\gamma(\mu+u)(a+1)}{b} - (a+\gamma)\right].$$

Simplifying, we get

$$\frac{dz}{dt} = -u^3\frac{3\gamma^3}{b^2} - u^2\left[\frac{3\gamma^3\mu - b\gamma^2(a+1)}{b^2}\right] - u\left[\frac{3\gamma^3\mu^2 - 2b\mu\gamma^2(a+1) + b^2(a\gamma+b)}{b^2}\right]$$

$$-\frac{\gamma^3\mu^3 - b\gamma^2\mu^2(a+1) + b^2a\gamma\mu + b^3\mu}{b^2} \tag{30}$$

$$+z\left[-3\frac{u^2\gamma^2}{b^2} - u\left(\frac{6\mu\gamma^2 - 2b\gamma(a+1)}{b^2}\right) - \frac{3\gamma^2\mu^2 - 2b\gamma\mu(a+1) + b^2(\gamma+a)}{b^2}\right].$$

Observe that $\frac{dz}{dt}$ is now in the following form $\frac{dz}{dt} = F(u) + z\ G(u)$
where,

$$F(u) = -u^3\frac{3\gamma^3}{b^2} - u^2\left[\frac{3\gamma^3\mu - b\gamma^2(a+1)}{b^2}\right] - u\left[\frac{3\gamma^3\mu^2 - 2b\mu\gamma^2(a+1) + b^2(a\gamma+b)}{b^2}\right]$$

$$-\frac{\gamma^3\mu^3 - b\gamma^2\mu^2(a+1) + b^2a\gamma\mu + b^3\mu}{b^2},$$

And,

$$G(u) = -3\frac{u^2\gamma^2}{b^2} - u\left(\frac{6\mu\gamma^2 - 2b\gamma(a+1)}{b^2}\right) - \frac{3\gamma^2\mu^2 - 2b\gamma\mu(a+1) + b^2(\gamma+a)}{b^2}.$$

Looking at our normalized form

$$\frac{du}{dt} = z \quad \frac{dz}{dt} = \epsilon_1 + u\epsilon_2 - \frac{u^3\gamma^3}{b^2} + z\left[\epsilon_3 + Au - \frac{3u^2\gamma^2}{b^2}\right]$$

We see that

$$F(u) = \epsilon_1 + u\epsilon_2 - \frac{u^3\gamma^3}{b^2}\ and\ \ G(u) = \epsilon_3 + Au - \frac{3u^2\gamma^2}{b^2}$$

Noting that from $G(u)$ the coefficient of u^2 must equal to zero:

$$\frac{3\gamma^3\mu - b\gamma^2(a+1)}{b^2} = 0.$$

We solve for μ

$$\mu = \frac{b(a+1)}{3\gamma}.$$

Similarly we can solve for $\epsilon_1,\ \epsilon_2,\ \epsilon_3$, and A:

$$\epsilon_1 = -\frac{\gamma^3\mu^3 - b\gamma^2\mu^2(a+1) + b^2a\gamma\mu + b^3\mu}{b^2}, \quad \epsilon_2 = -\frac{3\gamma^3\mu^2 - 2b\mu\gamma^2(a+1) + b^2(a\gamma+b)}{b^2},$$

$$\epsilon_3 = -\frac{3\gamma^2\mu^2 - 2b\gamma\mu(a+1) + b^2(\gamma+a)}{b^2}, \quad A = -\frac{6\mu\gamma^2 - 2b\gamma(a+1)}{b^2}.$$

After substituting μ into $\epsilon_1,\ \epsilon_2,\ \epsilon_3$, and A we get the following

$$\epsilon_1 = \frac{b(a+1)(2\gamma - 5a\gamma + 2a^2\gamma - 9b)}{27\gamma}, \quad \epsilon_2 = \gamma\frac{a^2-a+1}{3} - b,$$

$$\epsilon_3 = \frac{a^2-a+1}{3} - \gamma, \qquad A = 0.$$

10.4 Change of Variables of the Fitzhugh-Nagumo Equations

We first consider

$$\frac{dv}{dt} = f(v) - \omega \qquad \frac{d\omega}{dt} = bv - \gamma\omega \qquad f(v) = v(a-v)(v-1) \tag{31}$$

We define v, ω, and t to be

$$v = Ax + B, \qquad \omega = Cy + D, \quad and \quad t = R\tau \tag{32}$$

Next we use a new system of equations, where it was first introduced in the original work of Fitzhugh (1961), see also Volokitin and Treskov (1994):

$$\frac{dx}{dt} = \frac{1}{\mu}(-x^3 + x - y) \qquad \frac{dy}{dt} = x - k_1 y - k_2 \tag{33}$$

We make

$$\frac{dx}{d\tau} = \frac{dx}{dv}\frac{dv}{dt}\frac{dt}{d\tau} \quad and \quad \frac{dy}{d\tau} = \frac{dy}{dv}\frac{d\omega}{dt}\frac{dt}{d\tau} \tag{34}$$

Finding $\frac{dx}{dt}$, $\frac{dy}{dt}$, and $\frac{d\omega}{dt}$ from (42)

$$\frac{dx}{dv} = \frac{1}{A} \qquad \frac{dy}{\omega} = \frac{1}{C} \qquad \frac{dt}{d\tau} = R \tag{35}$$

Making the necessary substitutions into (43) we get,

$$\frac{dx}{d\tau} = \frac{R}{A}\left[f(Ax + B) - (Cy + D)\right] \tag{36}$$

$$\frac{dy}{d\tau} = \frac{R}{C}[b(Ax + B) - \gamma(Cy + D)] \tag{37}$$

Simplifying,

$$\frac{dx}{d\tau} = \frac{R}{A}\left[-A^3x^3 + x^2(-3A^2B + A^2(a+1)) + x(-3AB^2 + 2AB(a+1) - aA\right) \tag{38}$$

$$-B^3 + B^2(a+1) - Ba - Cy - D)],$$

$$\frac{dy}{d\tau} = x\frac{RAb}{C} + y(R\gamma) + \frac{R}{C}(Bb - D\gamma) \tag{39}$$

Matching the coefficients of equations (47) and (48) to those of equations (42)
From $\frac{dx}{d\tau}$,

$$\frac{-A^3R}{A} = \frac{1}{\mu} \qquad -C = \frac{1}{\mu} \qquad R\left(\frac{-3A^2B + A^2(a+1)}{A}\right) = 0 \tag{40}$$

$$\left(\frac{-B^3+B^2(a+1)-Ba-D}{A}\right)=0 \quad \frac{R}{A}(-3AB^2+2AB(a+1)-Aa)=\frac{1}{\mu} \tag{41}$$

From $\frac{dy}{d\tau}$,

$$\frac{RAb}{C}=1 \quad K_1=B\gamma \quad K_2=\frac{R}{C}(Bb-D\gamma) \tag{42}$$

Using (47), (48), and (42) we can solve for $A,\ B,\ C,\ D,\ R,\ and\ \mu$

$$A=\frac{\sqrt{a^2-a+1}}{\sqrt{3}} \quad B=\frac{a+1}{3} \quad C=\frac{(a^2-a+1)^{\frac{3}{2}}}{3\sqrt{3}} \tag{43}$$

$$D=\frac{(a+1)(2a^2-5a+2)}{27} \quad \mu=\frac{9b}{(a^2-a+1)^2} \quad R=\frac{a^2-a+1}{3b} \tag{44}$$

After our transformation the initial system reduces to the form (42)
By change of variable (42):

$$z=x-K_1y-K_2 \quad and \quad u=y+\frac{K_2}{K_1}, \quad where\ K_1=0 \tag{45}$$

we obtain the following system

$$u=z \qquad z=\frac{1}{\mu}(-z^3+G(u)u^2+g(u)z+F(u)) \tag{46}$$

where

$$G(u)=-3uK_1 \tag{47}$$

$$g(u)=-(3K_1^2u^2+K_1\mu-1) \tag{48}$$

$$F(u)=-K_1^3u^3+u(K_1-1)+\frac{K_2}{K_1} \tag{49}$$

Comparing (55) to our original normalized equations,

$$\frac{du}{dt}=z, \quad \frac{dz}{dt}=\epsilon_1+u\epsilon_2-\frac{u^3\gamma^3}{b^2}+z\left(\epsilon_3+Au-\frac{3u^2\gamma^2}{b^2}\right), \tag{50}$$

it is reasonable to assume the following:

$$\epsilon_1=\frac{K_2}{K_1}, \quad \epsilon_2=K_1-1, \quad \epsilon_3=K_1\mu-1. \tag{51}$$

We now solve for $\epsilon_1,\ \epsilon_2\ and\ \epsilon_3$

$$\epsilon_1=\frac{b(a+1)(2\gamma-5a\gamma+2a^2\gamma-9b)}{27\gamma}, \quad \epsilon_2=\gamma\frac{a^2-a+1}{3}-b, \tag{52}$$

$$\epsilon_3=\frac{a^2-a+1}{3}-\gamma. \tag{53}$$