Stimulant, or Depressant? How Alcohol Affects Neuron Firing

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Abstract

Alcohol use has numerous effects on the brain and body, which some users consider to be positive (e.g. having a drink to loosen up or feel more confident). However, there can be serious repercussions after repeated and frequent use, particularly on the brain and its' neurons. Neurons are the electrically excitable cells that process and transmit information through electrical and chemical signals. In 1952, the Hodgkin-Huxley mathematical model was developed to describe the firings of the brains neurons; we will use a modified version of this model which will incorporate the effects of alcohol. Because alcohol is known to act as both a stimulant and a depressant, we want to analyze these modified equations (referred to as the Fitzhugh-Nagumo equations) and study the behaviors at hand. We will introduce a fixed time delay and use bifurcation analysis to gather data including equilibria and stability, and use Matlab software to compare the unaffected neuron behaviors to the delayed neuron behaviors.

Major Objectives

As stated above, we know that alcohol is a peculiar drug in that it can act as either a stimulant or depressant; the deciding factor on which behavior will prevail is the amount consumed [9]. So while it is technically classified as a depressant, if an individual consumes more than the body (e.g. liver, kidneys, brain) can handle, they will feel the depressant effect. The major objective of this research will be to determine what concentration, and at what times, the different effects of alcohol will be present. In order to do so, we will have lesser objectives to tackle first-- most
importantly, the introduction of a time delay into the established Fitzhugh-Nagumo model for neuron firing. We will also have to use literature from the biological sciences to determine which ionic concentrations in the brain would suggest a significant region of excitability, and thus imply that a unique behavior is occurring.

**Background**

For the background of this project, we will discuss the three main components of our focus. Firstly, the science behind the brain and how neurons function. Secondly, the reasons as to why alcohol is our substance of choice. Lastly, the different mathematical models we will work with, and what they embody.

Brain functions involve communication among the brain’s nerve cells, or neurons. Each neuron connects with hundreds, sometimes thousands, of other neurons and messages travel as electrical impulses across these web-like structures. These neurons are capable of sending electrical impulses because they are considered “excitable” cells; an excitable cell can “generate an action potential at its membrane in response to depolarization and may transmit an impulse along the membrane.” In other words, these specialized cells have the ability to communicate using tiny volts of electricity (measured in millivolts) because of ionic charges. [1] Not all cells in the body are capable of this type of communication- blood cells or skin cells do not have this capacity. But neurons (as well as muscle fibers) do in fact share this important trait of excitability.

To give a clearer picture of what excitability involves, we must discuss the importance of ionic charges. The ions that are within the scope of this project include sodium and potassium, although calcium and chlorine are also present in the brain. Excitable cells have special ion-
channels that are controlled by voltage gates that allow the influx and efflux of sodium and potassium. Furthermore, the membrane of each neuron has an unequal distribution of these ions, and it is this inequality that essentially creates electrical charges. The outside of the membrane has a positive charge, while the inside has a negative charge; this charge difference is called the membrane potential. When the membrane potential is held relatively stable, it is called the resting potential. However, membrane potential is not always stable of course. There is another phase called the action potential, which is when the charge inside the membrane spikes (relatively) high due to an influx of sodium ions.

Between the resting and action potentials, we have a phase of excitability known as depolarization. Depolarization (shown in the figure below) must be sparked by a stimulus. The stimulus will cause diffusion of sodium ions into the cell membrane, and if the threshold is reached, typically around -55 to -50 mV, then the action potential is generated in the cell. [1]

As seen in Figure 1, hyperpolarization is the final stage of excitability, and is an area of focus for us. Hyperpolarization begins when an efflux of potassium rushes out of the neuron membrane, and the charge drops down to around -70 to -80 mV. After hyperpolarization occurs, the charge
of the membrane potential becomes less negative in an attempt to reach its resting potential charge.

From here, it is important to note that hyperpolarization is the phase most affected by the introduction of alcohol. In addition to it being a peculiar drug (able to act as either depressant or stimulant), a study in 1996 showed that alcohol accelerates the release of potassium ions. [3] This study, conducted by Richard Gross and Rose Gubitosi-Klug, gives us some insight as to the effects that alcohol may play on firing behaviors. Since potassium concentration plays a vital role in hyperpolarization, we can make a presumption that hyperpolarization will be impacted. The accelerated release of potassium seems to imply that hyperpolarization would happen more quickly, since the ions are flushing out more quickly. If hyperpolarization happens faster, then it would follow that depolarization would happen more quickly on the following “cycle” of excitability. However, as we know, alcohol can have a tendency to act as a depressant, and this is why we have chosen alcohol to study. The logical hypothesis that stems from existing literature seems to be contradictory to the nature of the drug.

In order to study the behaviors of neurons, we must use mathematical models to give us insight. Let’s begin by discussing the Hodgkin and Huxley Model. This model was crucial in research conducted in 1952 by Alan Hodgkin and Andrew Huxley; their research was initially conducted on a squid axon, which was studied under the stimuli of voltages. The model they created (Figure 2) was a system of four ordinary differential equations, with three variables that represented the voltage-gated ion channels, symbolized as \( n \), \( m \), and \( h \) as well as the membrane potential, \( v \).
The $m$ and $h$ gates are responsible for sodium flow, $n$ is responsible for potassium flow, and $v$ is the “unequal distribution of ions,” or membrane potential, that we discussed earlier. This model, though created by studying a squid brain, is an appropriate behavioral model for both invertebrate and vertebrate neurons. [3]

The next model that is within the scope of our project is referred to as the Fitzhugh-Nagumo equations, and is essentially a manipulation of the Hodgkin Huxley Model:

$$ \frac{dv}{dt} = f(v) - \omega + I_i $$
$$ \frac{d\omega}{dt} = b v - \gamma \omega $$
$$ f(v) = v(a - v)(v - 1) $$

Figure 3

The logic that led to this “simplified” system of equations was that certain elements of Hodgkin Huxley could be neglected. Firstly, $m$ denotes the opening of the sodium gates in the neuron membrane, and is relatively instantaneous when compared to the other gates. Thus, the time derivative of $m$ would be zero, so the $\frac{dm}{dt}$ term from the initial model comes to equal zero. Next, the Fitzhugh Nagumo equations took notice that the original system stayed constant when the $h$ gate was set as the constant $h_0$ and thus, the $\frac{dh}{dt}$ term could too be neglected.
From there, the four equations became two, with the variable $\omega$ becoming what is known as the “recovery variable” for the voltage-gated ion channels, and $v$ still representing the membrane potential. The recovery variable specifically refers to the recovery of hyperpolarization, and it encapsulates potassium gating. [5] As stated above, we assume alcohol will affect this specific element in the model, particularly in the timing of recovery. This will be important to note later in our results. Furthermore, the parameters of $a$, $b$, and $\gamma$ are all positive values which are not time dependent, while the $I_a$ term is the magnitude of the stimulus current.

Using these key pieces of information, we are able to move forward to study the behaviors of neurons in the absence of alcohol, but more importantly, under the influence.

**Methods**

This project took many different shapes as progress was made; initially, we worked with the Hodgkin Huxley model to determine what approach we could take. Working by hand, the system of ODEs was difficult to work with and pressed us to do more research on available literature to see if other information on neuron modeling was available.

Fortunately, the search led to the discovery that the Fitzhugh Nagumo equations would work appropriately for the scope of our project. With a system of just two equations, a bifurcation approach was considered, chiefly because it could be done by hand and then studied using software that was available at no cost for students. This software, known as P-Plane, gave us the flow fields and null clines for our system of equations at both depolarization and hyperpolarization (pictures provided in the Results section of this paper).
We next wanted to find the flow fields and null clines for the system with a fixed time delay. This presented a problem, as P-Plane could not handle the scope of the equations with a time delay introduced. Thus, we turned to different software, Matlab. Matlab had many different ODE solvers, as well as packages to plot time-dependent equations. Using this software, we were able to use information from previous literature to determine the parameters, and find different portraits of the behaviors of our system.

**Results**

When it came to our results, we had two distinct stages, the first involving the model without any external influence, and the second involving the altered model to account for time delay (which embodied the introduction of the stimulus of alcohol).

The first stage involved finding the equilibrium points for the original Fitzhugh Nagumo, then constructing and computing the Jacobian. As a clarifying note, the Jacobian in our case is a 2x2 matrix that uses the partial derivative of each equation, with respect to the two different time-dependent variables. Jacobian matrices allow the local linearization of non-linear systems around a given equilibrium point and so allows the use of linear systems techniques, such as the calculation of eigenvalues. [6] Our Jacobian is shown below:

\[
J = \begin{bmatrix}
\frac{\partial f_1}{\partial v} & \frac{\partial f_1}{\partial \omega} \\
\frac{\partial f_2}{\partial v} & \frac{\partial f_2}{\partial \omega}
\end{bmatrix} = \begin{bmatrix}
2av - a - 3v^2 + 2v - 1 & -1 \\
2 & b - 1
\end{bmatrix}
\]

We noticed here that our \(\omega\) term has disappeared when we computed our partial derivatives, thus we will only have to consider two of our equilibrium points, which are as follows:
\[ \nu = \frac{2\sqrt[3]{y^2 + 2\sqrt[3]{3}}}{2}, \frac{2\sqrt[3]{y^2 - 2\sqrt[3]{3}}}{2} \]

At this point, we plug in our two \( \nu \) values to classify our equilibrium, and we get that both points result in a stable spiral with the \( \nu \) and \( \omega \) nullclines shown in red and yellow, respectively:

Figure 4
Nullclines and flow field at Depolarization

Figure 5
Nullclines and flow fields at Hyperpolarization

Even though both points give us spiral-like shapes with all flow fields points inwards, towards the critical point, they do exhibit slightly different behaviors. At depolarization, the spiral is more severe, with a tight curve centering on the critical point. If we recall what depolarization entails, it is before the action potential occurs, so it seemed that the system wanted to remain at that equilibrium. Hence, the tight spiral seemed to imply that the flow fields all congregated towards the central critical point. However looking at the hyperpolarization behavior, it looked like the two nullclines intersected twice, once tangentially and once again at a distinct point. This seemed to imply that the system did not favor a single critical point as strongly as it did Fig. 4. This made sense as well, as hyperpolarization is not the “end” of the excitability stage; it is the undershoot phase before the membrane attempts to regain resting potential.
Next, we moved on to introducing time delay, as the previous work had only focused on the unaltered Fitzhugh Nagumo equations. Introducing the time delay was simple for our \( v \) equation; we know that our \( \omega \) will be affected, as it is both time-dependent and our recovery variable. [4]

By introducing \( T \) as our fixed delay variable, we have:

\[
\frac{dv}{dt} = v(v - 1)(a - v) - \omega(t - T) + I
\]

However, the \( \omega \) is a bit more involved; the differential equation for \( \frac{d\omega}{dt} \) means that both terms in our linear equation will be dependent on time and \( \omega \). Therefore, we must apply \( T \) to both terms:

\[
\frac{d\omega}{dt} = \frac{1}{T} (bv - \gamma \omega)
\]

By keeping \( T \) as a fraction, we hope to see different areas (in relation to time) where the variable creates a delay versus an acceleration. Now that we have our equations with delay, we attempt to study the behaviors as we did via the P-Plane software. However this software has limitations and adding the extra parameter of \( T \) does not allow us to use P-Plane to study the critical points. Thus, we move on to Matlab for our plotting.

There are certain packages on Matlab that are useful for solving a system of ordinary differential equations, the two most common ones being “ode23” and “ode45.” In order to use these packages, which we refer to as “ODE solvers,” [7] we must determine the values for the parameters that are not dependent on time, namely \( a, b, I_a, \) and \( \gamma \). From a 2001 study, we are able to determine some appropriate base points, and continue the simulations from there. Below is a table of the values used. [3] Furthermore, the initial values remain constant, with the membrane potential remaining at -.055, in units of millivolts, and time beginning at 0.
<table>
<thead>
<tr>
<th>$a$</th>
<th>$b$</th>
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Table 1  
Parameters at Depolarization

<table>
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Table 2  
Parameters at Hyperpolarization

From these tables, we can see that three parameters must be kept constant while changing the fourth variable gives us our results. The images below are figures created by the plotting tools option of Matlab, after using primarily the ode45 ODE solver. We are comparing the unaltered Fitzhugh Nagumo equations on the left, with our delayed equations on the right.

![Time graphs of depolarization](image1)

Time graphs of depolarization: original equations on the left, time delayed on the right.  
Time versus membrane potential (seconds vs millivolts)

Something interesting that we could see was that the differing concentrations of our $b$ parameter truly did not skew the plots in any significant way. After obtaining our first sets of graphs with
our highest values of \( b \) (and this signifying the highest concentration of \( b \)) the graphs stay so close to the same that it was negligible. However, as can be seen above, the difference between the original system and the time-delayed system is dramatic. As reference, we offer below a graph generated by the lowest concentration value of \( b \) for our time-delayed system:

![Graph](image)

If we compare this to our initial time-delayed plot, we can see a tiny difference along the time axis. This tiny difference is consistent for the graph of depolarization and hyperpolarization. Because of the lack of findings, we can conclude that time matters more than concentration.

![Graph](image)

Time graphs of hyperpolarization: original on the left, time-delayed on the right
Time versus membrane potential (seconds vs millivolts)
Here we see the graphs for hyperpolarization concentrations. On the left, we see the voltage for the membrane potential plateau rather quickly, which is exactly what we hope for during hyperpolarization. On the right, after the delay is introduced we see an unusual spike in the membrane potential; normally (as seen back in Figure 1) the voltage should become very negative, then creep back up to slightly less negative. In our plot on the right hand side however, this spike is not consistent with the behavior we expect to see. Therefore, it seems that this time delay is in fact causing behavior that would imply the depressant effects of alcohol have taken over. Again, differing the concentrations of $b$ does not produce any significantly different plot, and the only thing that is dissimilar is a tiny shift on the time axis.

**Discussion**

After using Matlab to study the behaviors of the system of ODEs, it seems that our hypothesis drawn after reading the 1996 study was not correct. We assumed that the acceleration of potassium ions would cause hyperpolarization to occur more quickly, which would in turn, cause depolarization to happen more quickly. Again, because alcohol is said to act as either a depressant or stimulant, we were hoping to see evidence that concentration levels would bring out the stimulant effects of alcohol. It is, of course, possible that these stimulant effects could be seen using more direct studies—such as a study from a biological standpoint. However, in the scope of our project, we are only able to see the delayed behaviors.

Furthermore, it is possible that our behavioral models do not take into account many different variables that would play important factors in the human body. Details such as weight, height, drinking frequency (or tolerance) and even what an individual might have eaten before
consumption of alcohol would all play an important part in how the substance is metabolized. Because these pieces of information are not taken into account in either the Hodgkin Huxley or the Fitzhugh Nagumo equations, we merely have a framework of how our bodies are affected by alcohol. It would be interesting to further investigate this same question with a greater number of these types of resources at hand.

References

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