When studying the human body, we often come across various processes and organs that are impossible to categorize and explain using the biological representations that we rely on so heavily in the medical field. For functions that have extremely complex mechanisms such as the brain, a different approach has to be used. The field of computational neurobiology was created for this very purpose: to use math to map the brain. Using mathematical models to characterize the various actions of the brain gives us the opportunity to correlate the molecular processes to their physical representations in the rest of the body.

Finding the connection between math and biology is fascinating to me. Often, within science, chemistry and physics are attributed to have a math basis. Biology is overlooked. However, math, being the study of patterns, is perfect for explaining living organisms and the many patterns that are linked to creating life. This study, often known as computational biology, seeks to find the relationship between the seemingly chaotic nature of the functions of organisms and the exact conditions that they need to survive. The brain fits particularly well into this category, seeming random in the way it works to control the rest of the body. By using calculus to map the functions of the brain, we will be able to specifically identify how each bodily function is controlled, and how we ourselves can control the brain.

I decided to explore the area of computational neuroscience and specifically describe the models that are used to map neurological signals and create a graph of the neuron’s activity in terms of voltage and time.

To begin, I first had to establish a basic understanding of how the brain actually works. In order to control the body, the brain uses a series of electrical impulses. These can be measured and observed using an EEG (electroencephalogram), which requires putting sensitive probes across the head to measure the electricity that is created. A graph is then created with each probe and the change in electric charge over time (See diagram 1). Each line correlates to a probe that was on the patient's scalp. This change in voltage can be isolated for a single neuron. This can be graphed as well, as seen by diagram 2 (Chen).

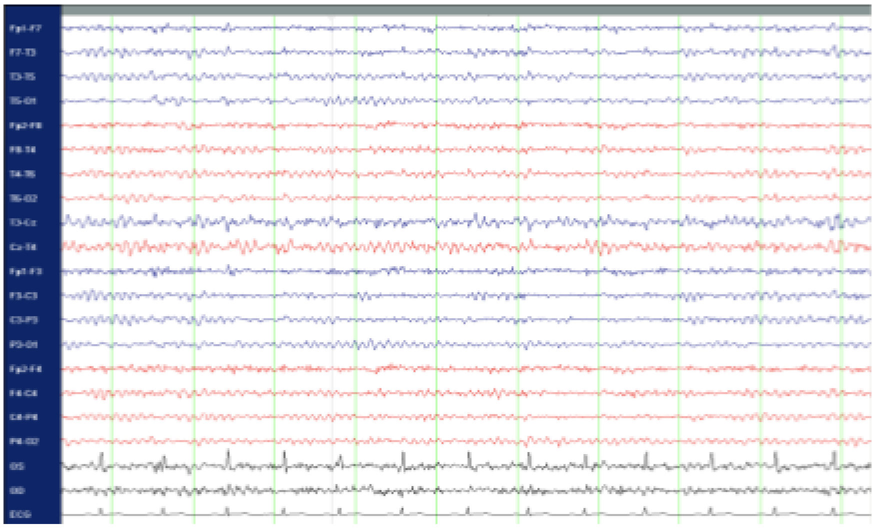

Diagram 1: EEG example
https://neurology.med.wayne.edu/pdfs/how_to_interpret_and_eeg_and_its_report.pdf

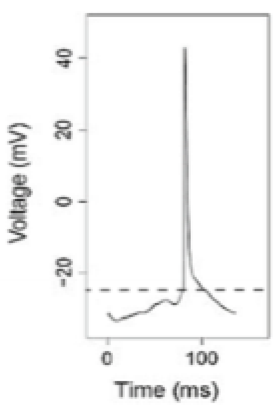

Diagram 2: Single neuron firing
https://www.stat.cmu.edu/~kass/papers/AnnRev2017final.pdf

My first big struggle with these graphs was figuring out how to read one. Specifically looking at diagram 2, I realized that the mathematical models used to create graphs of electrical impulses had their basis in these simple neuron observations. In order to truly understand each component of this graph (especially the dotted line), I had to learn more about the way that these axons fire. I found that neurons have different concentrations of potassium and sodium ions inside and outside of their membranes. They move into and out of the cell attempting to maintain a resting potential of around -70mv. When the neuron is stimulated, the sodium ions begin to move into the cell, changing the charge. The neuron has a certain threshold for this (the dotted line on the graph, around -50mv). When it exceeds this, an action potential is created. This causes a spark in voltage (known as depolarization) and the current is sent across the axon and transferred to other neurons. After the spike, the cell begins a process known as repolarization in which the potassium ions move out of the cell in an attempt to rebalance the charges (Chen). This creates a charge lower than the resting potential (hyper-polarization) that takes time and more diffusion of molecules to balance out in a period known as the refractory period that stops another action potential from being created.

One of the most difficult parts of this research was the medical vocabulary that are obviously very important to the description of the way that axons work in the brain. It took a lot of research and understanding to figure out how these neurons work and how I can use that to further explain the Hodgkin-Huxley Model that I intend to explore. A strong background had to be established in order for me to understand all of the components of the equation used for the model.

Beyond the simple graphing of the change in voltage in a neuron over time, the team of Alan Hodgkin and Andrew Huxley wanted to find a way to model the firing of a neuron with an equation that accounted for other variables and how their changes impacted the voltage spike. What they found became the basis for modern computational biology. By turning the axon into an electric circuit (see diagram 4), they could use basic electricity principles in physics such as Ohm's Law, the law of conservation of electric charge, and the definition of capacity to create a series of equations.

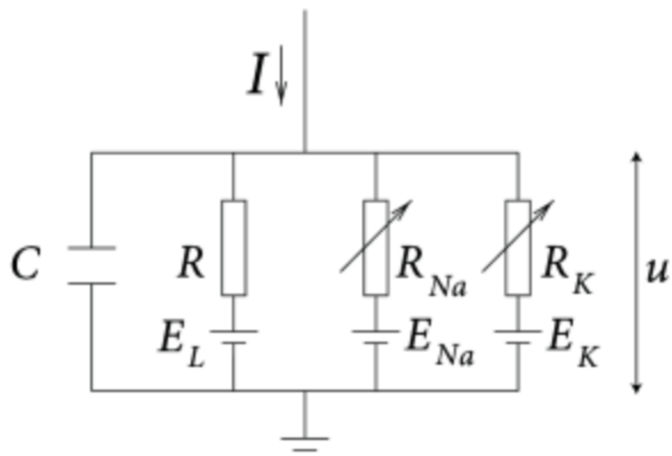

Diagram 4: Neuron as a circuit https://neuronaldynamics.epfl.ch/online/Ch2.S2.html

Hodgkin-Huxley Model Equations:

$$\sum_k I_k = g_{\mathrm{Na}}\, m^3 h\, (u - E_{\mathrm{Na}}) + g_{\mathrm{K}}\, n^4\, (u - E_{\mathrm{K}}) + g_L\, (u - E_L)$$

This is the first of the equations that Hodgkin and Huxley concluded could model the firing of a neuron. There are many variables that they accounted for with this equation that they developed using the brain of a giant squid. First, the equation is solving for the total current entering an axon as a result of the stimulus (I_{K}). Next, u is the total voltage across the membrane.

E_{Na} is the voltage of the "battery" created by the sodium ion pump, similar to E_{K} representing the potassium pump and E_{L} representing the other leakage pump. *m* represents the probability that the sodium pump is open and *h* shows when the pump is closed. *n* represents the opening of the potassium pump. The *g* is the value of the maximum conductance of the indicated pump. Using all of these variables, the equation is able to solve for the capacitance of the neuron and its change in voltage over time (du/dt) (Gerstner).

Solving this equation for u gives us the opportunity to see how the voltage changes with respect to the other variables.

$$\sum_k I_k = g_{\mathrm{Na}}\, m^3 h\, (u - E_{\mathrm{Na}}) + g_{\mathrm{K}}\, n^4\, (u - E_{\mathrm{K}}) + g_L\, (u - E_L)$$

$$\sum_k I_k + g_{Na} m^3 h E_{Na} + g_K n^4 E_K + g_L E_L = g_{Na} m^3 hu + g_K n^4 u + g_L u$$

$$u = \frac{I_k + g_{Na} m^3 h E_{Na} + g_K n^4 E_K + g_L E_L}{g_{Na} m^3 h + g_K n^4 + g_L}$$

This is useful in creating the graph of the neuron firing. However, it does not show the change in the voltage with respect to time. By deriving the equation, I can create a function that includes this time component. The second part of the Hodgkin-Huxley model provides ways to plug in for derivatives in the differential equation. The equations are as follows for all three probabilities (with V being the voltage):

$$\frac{dn}{dt} = -\frac{n - n_\infty(V)}{\tau_n(V)}$$

$$\frac{dm}{dt} = -\frac{m - m_\infty(V)}{\tau_m(V)}$$

$$\frac{dh}{dt} = -\frac{h - h_\infty(V)}{\tau_h(V)}$$

From here, I decided to integrate the Hodgkin-Huxley function.

$$\sum_k I_k = g_{\mathrm{Na}}\, m^3 h\, (u - E_{\mathrm{Na}}) + g_{\mathrm{K}}\, n^4\, (u - E_{\mathrm{K}}) + g_L\, (u - E_L)$$

$$\frac{dI_k}{dt} = g_{Na}((3m^2h\frac{dm}{dt} + m^3\frac{dh}{dt})(u - E_{Na}) + m^3h\frac{du}{dt}) + g_K((4n^3\frac{dn}{dt})(u - E_K) + n^4\frac{du}{dt}) + g_L\frac{du}{dt}$$

Plugging in the differential equations for dm/dt, dn/dt, and dh/dt and the fact that the current isn't changing (dI/dt=0), the equation is:

$$0 = g_{Na}((-\frac{3m^2h(m-m_\infty(u))}{\tau_m(u)} - \frac{m^3(h-h_\infty(u))}{\tau_h(u)})(u - E_{Na}) + m^3h\frac{du}{dt}) + g_K((-\frac{4n^3(n-n_\infty(u))}{\tau_n(u)})(u - E_K) + n^4\frac{du}{dt}$$

$$0 = -g_{Na}\frac{3m^2h(m-m_\infty(u))}{\tau_m(u)}u - g_{Na}\frac{m^3(h-h_\infty(u))}{\tau_h(u)}u + g_{Na}\frac{3m^2h(m-m_\infty(u))}{\tau_m(u)}E_{Na} + g_{Na}\frac{m^3(h-h_\infty(u))}{\tau_h(u)}E_{Na} + g_{Na}m^3h\frac{du}{dt}$$

$$-g_K\frac{4n^3(n-n_\infty(u))}{\tau_n(u)}u + g_K\frac{4n^3(n-n_\infty(u))}{\tau_n(u)}E_K + g_Kn^4\frac{du}{dt} + g_L\frac{du}{dt}$$

$$g_{Na}\frac{3m^2h(m-m_\infty(u))}{\tau_m(u)}u + g_{Na}\frac{m^3(h-h_\infty(u))}{\tau_h(u)}u - g_{Na}\frac{3m^2h(m-m_\infty(u))}{\tau_m(u)}E_{Na} - g_{Na}\frac{m^3(h-h_\infty(u))}{\tau_h(u)}E_{Na} + g_K\frac{4n^3(n-n_\infty(u))}{\tau_n(u)}u$$

$$-g_K\frac{4n^3(n-n_\infty(u))}{\tau_n(u)}E_K = g_{Na}m^3h\frac{du}{dt} + g_Kn^4\frac{du}{dt} + g_L\frac{du}{dt}$$

$$\frac{du}{dt} = (g_{Na}\frac{3m^{2}h(m-m_{\infty}(u))}{\tau_{m}(u)}u + g_{Na}\frac{m^{3}(h-h_{\infty}(u))}{\tau_{h}(u)}u - g_{Na}\frac{3m^{2}h(m-m_{\infty}(u))}{\tau_{m}(u)}E_{Na} - g_{Na}\frac{m^{3}(h-h_{\infty}(u))}{\tau_{h}(u)}E_{Na} + g_{K}\frac{4n^{3}(n-n}{\tau_{n}(u}$$

$$- g_{K}\frac{4n^{3}(n-n_{\infty}(u))}{\tau_{n}(u)}E_{K})/(g_{Na}m^{3}h + g_{K}n^{4} + g_{L})$$

This equation is extremely applicable. By looking at various voltages, we can create a graph of the change in voltage over time. First, the constants must be accounted for. For the purposes of this exploration, the following table will be used:

x	E_x [mV]	g_x $[\mathrm{mS/cm^2}]$
Na	55	40
K	-77	35
L	-65	0.3

In addition, I need to plug in n, h, and m as well as their respective constants. As an example, I will use the voltage of -65 mV, an estimation of the resting potential of a neuron. This is a good starting point because it is the point when the voltage starts increasing after the axon is fired or the signal is received from another neuron nearby.

The $n_\infty(V)$, $m_\infty(V)$, and the $h_\infty(V)$ can all be determined using the voltage, since the voltage causes the change in probability that the pump is open for the ions to travel through the membrane (See diagram 5). In addition, the $\tau_n(V)$ along with the other time constants are determined by the voltage and can be found by looking at a time constant graph (See diagram 6).

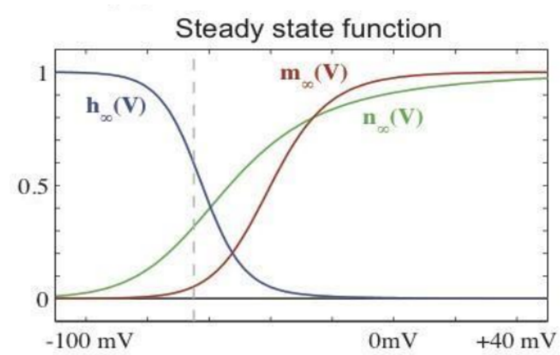

Diagram 5: Steady state https://www.stat.cmu.edu/~kass/papers/AnnRev2017final.pdf

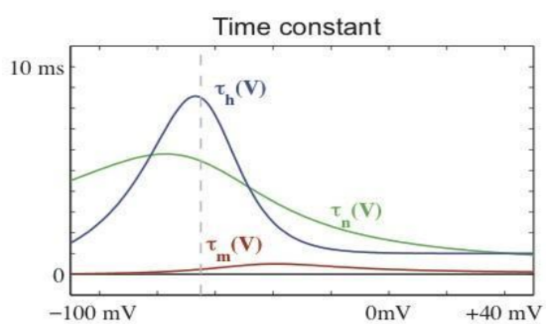

Diagram 6: Time constant https://www.stat.cmu.edu/~kass/papers/AnnRev2017final.pdf

In addition, the n, m, and h values for this voltage must also be found. These correspond to the amount of time that the pumps are expected to be open at a voltage. These values can also be found from a graph (Diagram 5). The value of the gating variable is what gets plugged into the equation. I struggled to read this graph due to three different variables being depicted on it. There is not much information about reading these graphs, especially since it is usually generated and read by a computer. However, by assuming that the time that I use for the x-axis to be 0 ms and the voltage to be the voltage that I chose (-65mV), I used the graph to find these values.

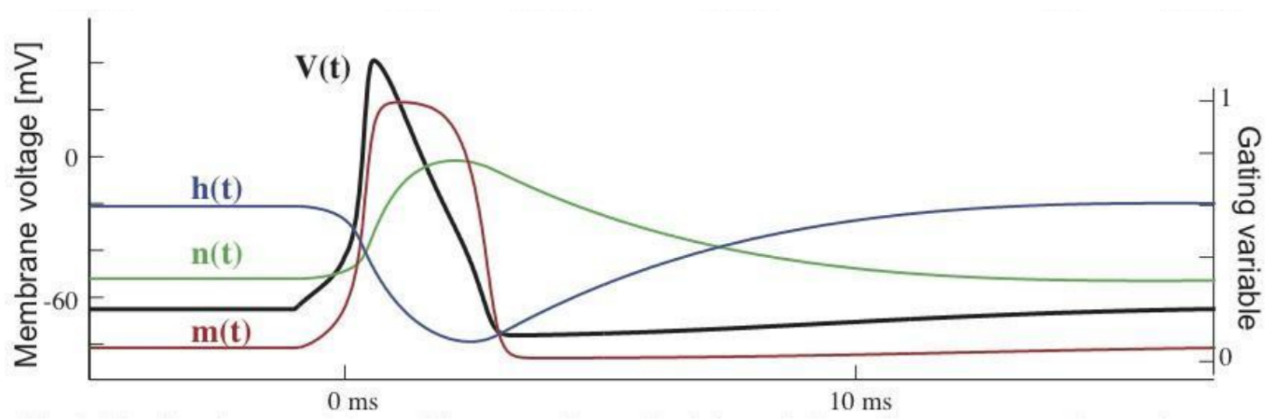

Diagram 7: n, m, and h values https://www.stat.cmu.edu/~kass/papers/AnnRev2017final.pdf

$$\frac{du}{dt} = (40(-\ 65(\frac{3(0.15)^2 0.1(0.15-0.1)}{0.5} + \frac{0.15^3(0.1-0.6)}{8}) - 55(\frac{3(0.15)^2 0.1(0.15-0.1)}{0.5} + \frac{(0.15)^3(0.1-0.6)}{8})) + 35((\frac{4(0.4}{}$$

$$-(\frac{4(0.4)^3(0.4-0.3)}{5} \times -\ 77\ ))/(40(0.15)^3(0.1)\ +\ 35(0.4)^4\ +\ 0.3)=2.467149442$$

If this is repeated with a wide variety of values across a range of voltages, a graph can be created for the change in voltage over time.

In the end, I found that the change in voltage is a measurable value that can be tracked as the neuron fires. To find this value, there are a lot of other variables that need to be known, such as the gating variable of the sodium and potassium pumps, the time that they open for, and the conductivity of the pumps themselves. This fact made the equation harder to find the derivative of. It required many of the rules that we have learned in class such as implicit differentiation and the product rule. Keeping track of all of the variables was difficult, especially since each one also had a rate of change. In the end, one equation was obtained and values could be plugged in to find the change in voltage over time.

This exploration was a lot harder than I expected. One struggle that I did not anticipate was the amount of vocabulary that I had to learn. This topic involved a very specific and professional area within medicine. This meant that I had to develop my background knowledge so that I was able to understand the sources that I was reading. The calculus portion of what I did was particularly different because it took the topics that we learned in class and greatly expanded on it. In general, we only have to deal with one or two variables in an equation. By deriving an equation with respect to 5 different variables, I applied the derivative methods that we have learned in a much more realistic way.

Overall, I was able to use the math skills that I've gained combined with what I have learned in my IB biology and physics to find an equation for a graph that is created from sensors and physically measured changes. By using an equation and relating the graph to more variables, a much more accurate depiction of the changes taking place in the neuron as the action potential travels through it. Although I didn't have the resources to fully model this process and show each variable as a function of time, I was able to create an accurate equation for the changing voltage in terms of all of the other variables.

Works Cited

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Gerstner, Wulfram. "2.2 Hodgkin-Huxley Model." *Neuronal Dynamics*, 8 Sept. 2014, neuronaldynamics.epfl.ch/online/Ch2.S2.html#Ch2.E6.