MANIPULATION OF THE DEPOLARIZING CURRENT IN THE HODGKIN-HUXLEY MODEL

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Abstract. With the goal of creating a faster and more efficient way by which brain mapping can be studied and the intricacies of the neural network understood, I study the membrane potential sent between neurons via the Hodgkin-Huxley Axon model. In this setting, I simulate a single axon, manipulating the initial conditions of the sodium activation and inactivation channels, the potassium activation channel and the applied current as both a constant and a function of time. Through the manipulation of the applied current, custom and more complex blocks of information can be sent through these axons.

Mathematical Statement of the Problem.

$$I_{tot} = I_{cap} + I_{ionic} \tag{Equation 1}$$

$$I_{cap} = C\frac{dV_m}{dt} \tag{Equation 2}$$

$$I_{ionic} = I_L + I_K + I_{Na} \tag{Equation 3}$$

$$I_{tot} = 0 \tag{Equation 4}$$

$$C\frac{dV_m}{dt} = -I_L - I_K - I_{Na} \tag{Equation 5}$$

$$I_{ion} = g_{ion}(V_m - E_{ion}) \tag{Equation 6}$$

$$C\frac{dV_m}{dt} = -g_L(V_m - E_L) - g_{K^+}n^4(V_m - E_{K^+}) - g_{Na^+}m^3h(V_m - E_{Na^+}) \tag{Equation 7}$$

$$\alpha_n(V_m) = \frac{-(V_m - V_2)}{V_1(e^{\frac{-(V_m - V_2)}{V_3}} - 1)} \tag{Equation 8}$$

$$\beta_n(V_m) = V_4 e^{\frac{-(V_m - V_5)}{V_6}} \tag{Equation 9}$$

$$\alpha_m(V_m) = \frac{-(V_m - V_8)}{V_7(e^{\frac{-(V_m - V_8)}{V_9}} - 1)} \tag{Equation 10}$$

$$\beta_m(V_m) = V_{10}e^{\frac{-(V_m-V_{11})}{V_{12}}} \tag{Equation 11}$$

$$\alpha_h(V_m) = V_{13}e^{\frac{-(V_m-V_{14})}{V_{15}}} \tag{Equation 12}$$

$$\beta_h(V_m) = \frac{1}{V_{16}(e^{\frac{-(V_m-V_{17})}{V_{18}}}+1)} \tag{Equation 13}$$

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n \tag{Equation 14}$$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m \tag{Equation 15}$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h \tag{Equation 16}$$

Parameters for (Equation 7).

$C = 1 \frac{\mu F}{cm^2}$

$g_L = 0.3 \frac{mS}{cm^2}$

$E_L = -54.387 \, mV$

$g_{K^+} = 36 \frac{mS}{cm^2}$

$E_{K^+} = -77 \, mV$

$g_{Na^+} = 120 \frac{mS}{cm^2}$

$E_{Na^+} = 50 \, mV$

Parameters for α_n (Equation 8).

$V_1 = 100 \, mV \cdot ms$

$V_2 = -55 \, mV$

$V_3 = 10 \, mV$

Parameters for β_n (Equation 9).

$V_4 = 0.125 \, ms^{-1}$

$V_5 = -65 \, mV$

$V_6 = 80 \, mV$

Parameters for α_m (Equation 10).

$V_7 = 10 \, mV \cdot ms$

$V_8 = -40 \, mV$

$$V_9 = 10 \ mV$$

Parameters for β_m (Equation 11).

$$V_{10.} = 4 \ ms^{-1}$$
$$V_{11} = -65 \ mV$$
$$V_{12} = 18 \ mV$$

Parameters for α_h (Equation 12).

$$V_{13} = 0.07 \ ms^{-1}$$
$$V_{14} = -65 \ mV$$
$$V_{15} = 20 \ mV$$

Parameters for β_h (Equation 13).

$$V_{16} = 1 \ ms$$
$$V_{17} = -35 \ mV$$
$$V_{18} = 10 \ mV$$

These parameters set the resting potential to $\approx \ -65 \ $ mV

There are no applicable discretizations of these equations when using the runge kutta method

Description of the numerical method.
With the provided parameters, and some initial membrane potential(V), α_n, β_n, α_m, β_m, α_h and β_h can be solved for the first iteration, using equations 14-16. These values will be updated at the beginning of each iteration, using the instantaneous membrane potential(V) from the previous iteration and equations 14-16.

The Runge-Kutta fourth order approximation is used to iteratively solve for n, m, h and V.

$$n^* = n_i + \tfrac{dt}{2}(\alpha_{n_i}(1 - n_i) - \beta_{n_i} n_i)$$

$$m^* = m_i + \tfrac{dt}{2}(\alpha_{m_i}(1-m_i) - \beta_{m_i}m_i)$$

$$h^* = h_i + \tfrac{dt}{2}(\alpha_{h_i}(1-h_i) - \beta_{h_i}h_i)$$

$$V^* = V_i + \tfrac{dt}{2}((\tfrac{1}{C})(-g_L(V_i-E_L) - g_{K^+}n_i^4(V_i-E_{K^+}) - g_{Na^+}m_i^3h_i(V_i-E_{Na^+})))$$

$$n^{**} = n_i + \tfrac{dt}{2}(\alpha_{n_i}(1-n^*) - \beta_{n_i}n^*)$$

$$m^{**} = m_i + \tfrac{dt}{2}(\alpha_{m_i}(1-m^*) - \beta_{m_i}m^*)$$

$$h^{**} = h_i + \tfrac{dt}{2}(\alpha_{h_i}(1-h^*) - \beta_{h_i}h^*)$$

$$V^{**} = V_i + \tfrac{dt}{2}((\tfrac{1}{C})(-g_L(V^*-E_L) - g_{K^+}(n^*)^4(V^*-E_{K^+}) - g_{Na^+}(m^*)^3h^*(V^*-E_{Na^+})))$$

$$n^{***} = n_i + dt(\alpha_{n_i}(1-n^{**}) - \beta_{n_i}n^{**})$$

$$m^{***} = m_i + dt(\alpha_{m_i}(1-m^{**}) - \beta_{m_i}m^{**})$$

$$h^{***} = h_i + dt(\alpha_{h_i}(1-h^{**}) - \beta_{h_i}h^{**})$$

$$V^{***} = V_i + \tfrac{dt}{2}((\tfrac{1}{C})(-g_L(V^{**}-E_L) - g_{K^+}(n^{**})^4(V^{**}-E_{K^+}) - g_{Na^+}(m^{**})^3h^{**}(V^{**}-E_{Na^+})))$$

The following equations are updated every iteration.

$$n_{i+1} = n_i + \tfrac{dt}{6}((\alpha_{n_i}(1-n_i) - \beta_{n_i}n_i) + 2(\alpha_{n_i}(1-n^*) - \beta_{n_i}n^*) + 2((\alpha_{n_i}(1-n^{**}) - \beta_{n_i}n^{**}) +$$
$$(\alpha_{n_i}(1-n^{***}) - \beta_{n_i}n^{***})$$

$$m_{i+1} = m_i + \tfrac{dt}{6}((\alpha_{m_i}(1-m_i) - \beta_{m_i}m_i) + 2(\alpha_{m_i}(1-m^*) - \beta_{m_i}m^*) + 2((\alpha_{m_i}(1-m^{**}) - \beta_{m_i}m^{**}) +$$
$$(\alpha_{m_i}(1-m^{***}) - \beta_{m_i}m^{***})$$

$$h_{i+1} = h_i + \tfrac{dt}{6}((\alpha_{h_i}(1-h_i) - \beta_{h_i}h_i) + 2(\alpha_{h_i}(1-h^*) - \beta_{h_i}h^*) + 2((\alpha_{h_i}(1-h^{**}) - \beta_{h_i}h^{**}) +$$
$$(\alpha_{h_i}(1-h^{***}) - \beta_{h_i}h^{***})$$

$$V_{i+1} = V_i + \tfrac{dt}{6}((\tfrac{1}{C})(-g_L(V_i-E_L) - g_{K^+}n_i^4(V_i-E_{K^+}) - g_{Na^+}m_i^3h_i(V_i-E_{Na^+})) +$$
$$2(\tfrac{1}{C})(-g_L(V^*-E_L) - g_{K^+}(n^*)^4(V^*-E_{K^+}) - g_{Na^+}(m^*)^3h^*(V^*-E_{Na^+})) +$$
$$2(\tfrac{1}{C})(-g_L(V^{**}-E_L) - g_{K^+}(n^{**})^4(V^{**}-E_{K^+}) - g_{Na^+}(m^{**})^3h^{**}(V^{**}-E_{Na^+})) +$$
$$(\tfrac{1}{C})(-g_L(V^{***}-E_L) - g_{K^+}(n^{***})^4(V^{***}-E_{K^+}) - g_{Na^+}(m^{***})^3h^{***}(V^{***}-E_{Na^+}))$$

This process begins again with the new values for n_{i+1}, m_{i+1}, h_{i+1} and V_{i+1}, and continues until a desired maximum time is reached .

Pseudo code.

```
tMAX=100; dt=0.05;
for(i=0;i<tMAX-dt;i+=dt)
{
alphan=-(V-V2)/(V1*(exp(-(V-V2)/V3)-1));
betan=V4*exp(-(V-V5)/V6);

alpham=-(V-V8)/(V7*(exp(-(V-V8)/V9)-1));
betam=V10*exp(-(V-V11)/V12);

alphah=V13*exp(-(V-V14)/V15);
betah=1/(V16*(exp(-(V-V17)/V18)+1));

nstar=n+0.5*dt*(alphan*(1-n)-betan*n);
mstar=m+0.5*dt*(alpham*(1-m)-betam*m);
hstar=h+0.5*dt*(alphah*(1-h)-betah*h);
Vstar=V+0.5*dt*(1/C)*(-g_l*(V-V_l)-g_K*pow(n,4)*(V-V_K)-
        g_Na*pow(m,3)*h*(V-V_Na))+Iapp);

nstar2=n+0.5*dt*(alphan*(1-nstar)-betan*nstar);
mstar2=m+0.5*dt*(alpham*(1-mstar)-betam*mstar);
hstar2=h+0.5*dt*(alphah*(1-hstar)-betah*hstar);
Vstar2=V+0.5*dt*(1/C)*(-g_l*(Vstar-V_l)-g_K*pow(nstar,4)*(Vstar-V_K)-
        g_Na*pow(mstar,3)*hstar*(Vstar-V_Na))+Iapp);

nstar3=n+dt*(alphan*(1-nstar2)-betan*nstar2);
mstar3=m+dt*(alpham*(1-mstar2)-betam*mstar2);
hstar3=h+dt*(alphah*(1-hstar2)-betah*hstar2);
Vstar3=V+dt*(1/C)*(-g_l*(Vstar2-V_l)-g_K*pow(nstar2,4)*(Vstar2-V_K)-
        g_Na*pow(mstar2,3)*hstar2*(Vstar2-V_Na))+Iapp);

nn=n+(dt/6)*((alphan*(1-n)-betan*n)+2*(alphan*(1-nstar)-betan*nstar)+
        2*(alphan*(1-nstar2)-betan*nstar2)+(alphan*(1-nstar3)-betan*nstar3));
```

```c
nm=m+(dt/6)*((alpham*(1-m)-betam*m)+2*(alpham*(1-mstar)-betam*mstar)+
    2*(alpham*(1-mstar2)-betam*mstar2)+(alpham*(1-mstar3)-
    betam*mstar3));
nh=h+(dt/6)*((alphah*(1-h)-betah*h)+2*(alphah*(1-hstar)-betah*hstar)+
    2*(alphah*(1-hstar2)-betah*hstar2)+(alphah*(1-hstar3)-betah*hstar3));
nV=V+(dt/6)*((1/C)*(-g_l*(V-V_l)-g_K*pow(n,4)*(V-V_K)-
        g_Na*pow(m,3)*h*(V-V_Na))+Iapp)+
    2*(1/C)*(-g_l*(Vstar-V_l)-g_K*pow(nstar,4)*(Vstar-V_K)-
    g_Na*pow(mstar,3)*hstar*(Vstar-V_Na))+Iapp)+
    2*(1/C)*(-g_l*(Vstar2-V_l)-g_K*pow(nstar2,4)*(Vstar2-V_K)-
        g_Na*pow(mstar2,3)*hstar2*(Vstar2-V_Na))+Iapp)+
    (1/C)*(-g_l*(Vstar2-V_l)-g_K*pow(nstar2,4)*(Vstar2-V_K)-
    g_Na*pow(mstar2,3)*hstar2*(Vstar2-V_Na))+Iapp));


I_l=-g_l*(V-V_l);
I_K=-g_K*pow(n,4)*(V-V_K);
I_Na=-g_Na*pow(m,3)*h*(V-V_Na);
I=I_l+I_K+I_Na+Iapp;



fprintf(fp,"%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\n",n,m,h,I,V,i,I_l,I_K,I_Na,Iapp);

    n=nn;
    m=nm;
    h=nh;
    V=nV;
    }
```

Technical Specifications.
CPU - Intel Core i7-6700HQ Processor 2.6 GHz (Up to 3.5 GHz)
RAM - 16 GB DDR4 2400 MHz
Hard Drive - 1 TB SSD (Read 545 MB/s Write 520 MB/s)

Graphics Card - GeForce GTX 980M 8GB DDR5

Results.

Fixed Parameters.

$$C = 1 \frac{\mu F}{cm^2}$$

$$g_L = 0.3 \frac{mS}{cm^2}$$

$$E_L = -54.387 \ mV$$

$$g_{K^+} = 36 \frac{mS}{cm^2}$$

$$E_{K^+} = -77 \ mV$$

$$g_{Na^+} = 120 \frac{mS}{cm^2}$$

$$E_{Na^+} = 50 \ mV$$

$$V_1 = 100 \ mV \cdot ms$$

$$V_2 = -55 \ mV$$

$$V_3 = 10 \ mV$$

$$V_4 = 0.125 \ ms^{-1}$$

$$V_5 = -65 \ mV$$

$$V_6 = 80 \ mV$$

$$V_7 = 10 \ mV \cdot ms$$

$$V_8 = -40 \ mV$$

$$V_9 = 10 \ mV$$

$$V_{10.} = 4 \ ms^{-1}$$

$$V_{11} = -65 \ mV$$

$$V_{12} = 18 \ mV$$

$$V_{13} = 0.07 \ ms^{-1}$$

$$V_{14} = -65 \ mV$$

$$V_{15} = 20 \ mV$$

$$V_{16} = 1 \ ms$$

$$V_{17} = -35 \ mV$$

$$V_{18} = 10 \ mV$$

The parameters subject to change are the following: n_i, m_i, h_i, V_i and $I_{applied}$
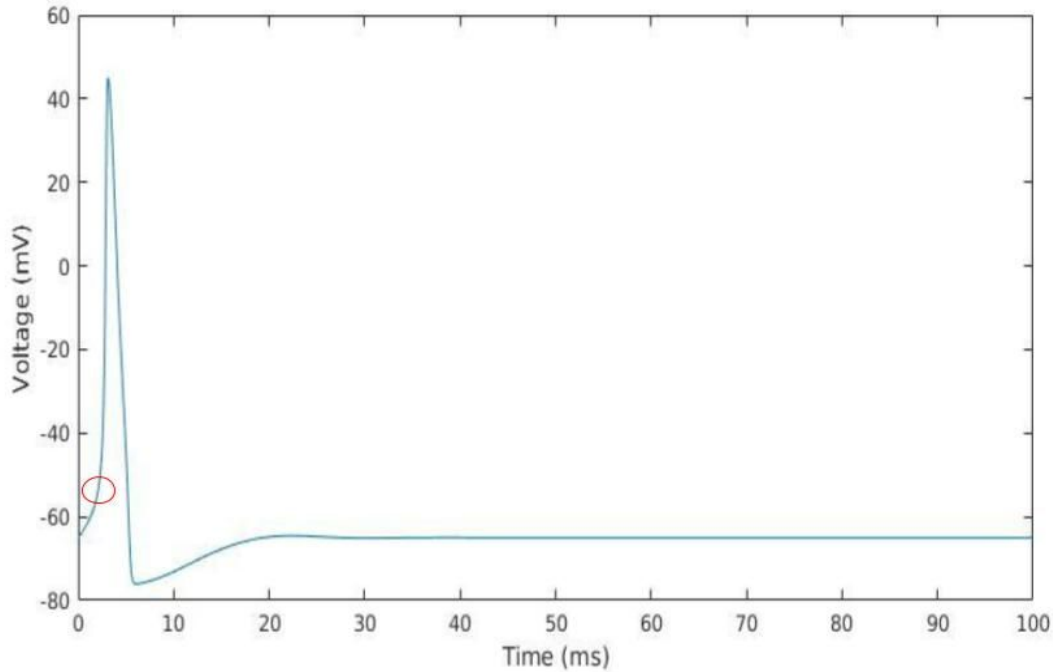
Figure 1 - A graph of membrane potential versus time. The red circle represents the approximate

location of the membrane potential threshold.
$n_i = 0$, $m_i = 0$, $h_i = 0.5$, $V_i = -65\ mV$ and $I_{applied} = 0\ mA$
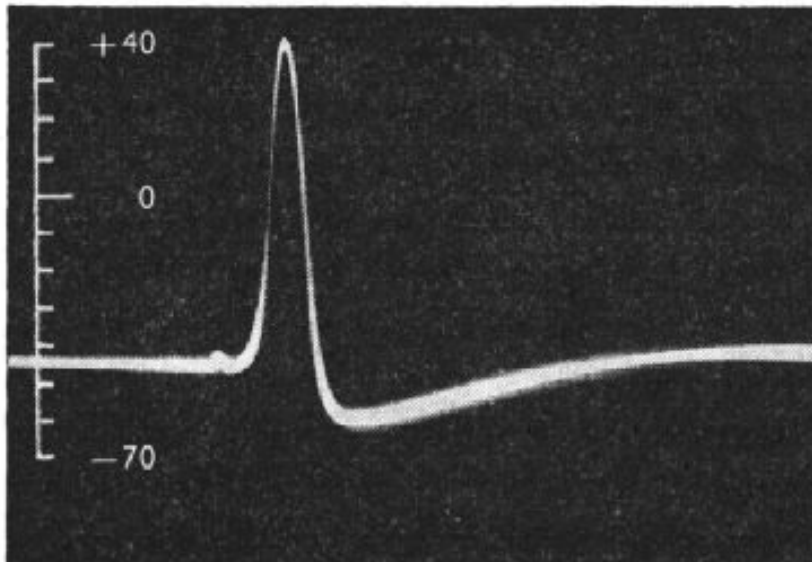

Figure 2 - A graph of membrane potential versus time. The first recorded action potential via oscilloscope, by Hodgkin and Huxley in 1939.

Using a combination of the Hodgkin-Huxley system of equations and the Runge-Kutta fourth order approximation I replicated the results of Hodgkin's and Huxley's early experiments on the axon of the Atlantic squid. The approximated data is displayed in figure 1 and the experimental data is displayed in figure 2.
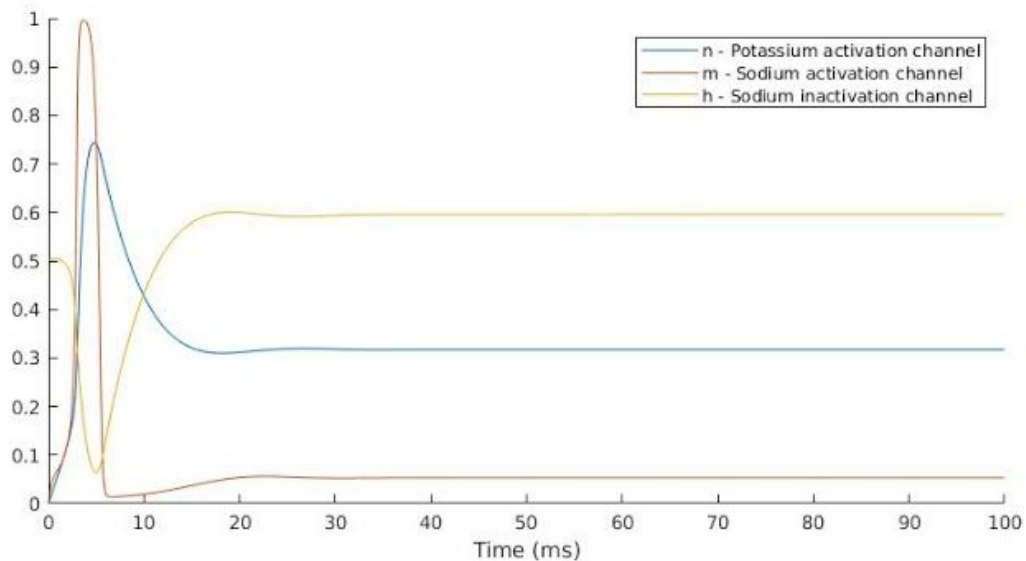
Figure 3 - a graph of the state of the Potassium activation channel and of the Sodium activation and inactivation channels versus time.

$n_i = 0$, $m_i = 0$, $h_i = 0.5$, $V_i = -65\ mV$ and $I_{applied} = 0\ mA$

Additionally, I plotted the states of the following voltage-gated ion channels: the Potassium activation channel and the Sodium activation and inactivation channels. The data exhibited in figure 3, accurately represents the natural phenomenon as it would occur in the real world.

A stimulus received by the brain creates a depolarizing current that is sent down the axon and causes the sodium activation channels to open. Now that the sodium activation channel is open, Na^+ ions rush into the axon and their presence in the axon increase the membrane potential, depolarizing the axon. The Na^+ ions continue to rush into the axon uninhibited, causing an action potential or spike in the potential, provided that the membrane potential crosses the membrane potential threshold necessary to produce an action potential. If the membrane potential does not cross this threshold it can not produce an action potential and this is known as the all-or-none phenomenon. Once the potassium activation channel opens the K^+ ions inside of the axon rush outside via the potassium activation channel, ending the depolarization phase. At roughly the time the potassium activation channels open, the sodium activation channels close and initiate the process of repolarization, where the membrane potential moves back down to its resting potential. However, the membrane potential will move below its resting potential, also known as hyperpolarization, because the potassium activation channels stay open for too long. With K^+ ions on the outside of the axon and Na^+ ions on the inside, the sodium potassium pump begins to pull the K^+ ions back inside the axon and push the Na^+ ions to the outside, bringing the membrane potential back up to its resting state.

According to figure 3, at t t=0 ms the sodium and potassium activation channels are closed but the sodium inactivation channel is open. At this time, according to figure 1, the membrane potential is sitting at roughly its resting state of -65 mV. When the sodium inactivation channel is open and the other two channels are closed the axon is prepared to participate in an action potential. As soon as the axon receives a depolarizing current, the membrane potential will begin to climb towards 0 mV. The membrane potential will become more positive until about t=5ms, when the sodium inactivation channel closes and the potassium activation channel opens. At nearly the same time that the potassium activation channel opens, the sodium activation channel close, causing the membrane potential to move back again towards its resting state of about -65 mV, where it will remain for the remainder of the simulation.
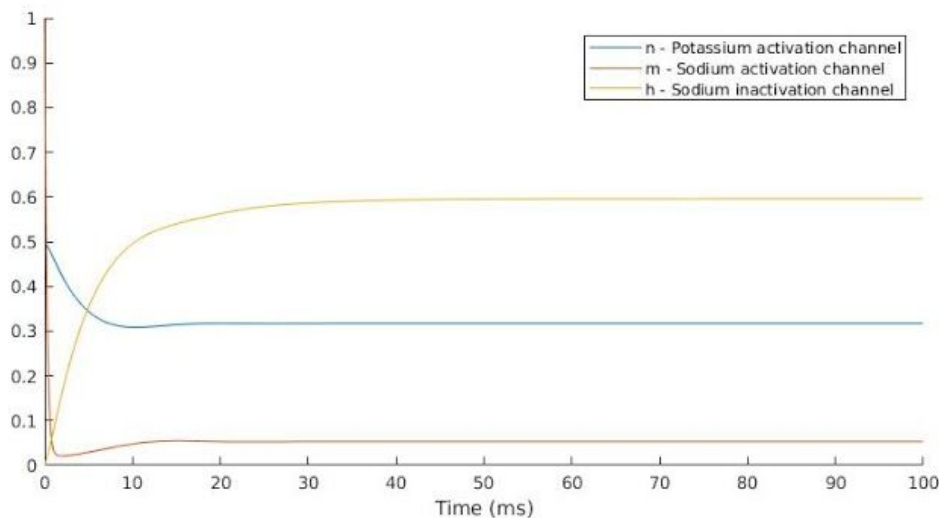

Figure 4 - a graph of the state of the Potassium activation channel and of the Sodium activation and inactivation channels versus time, where the membrane potential does not produce an action potential.
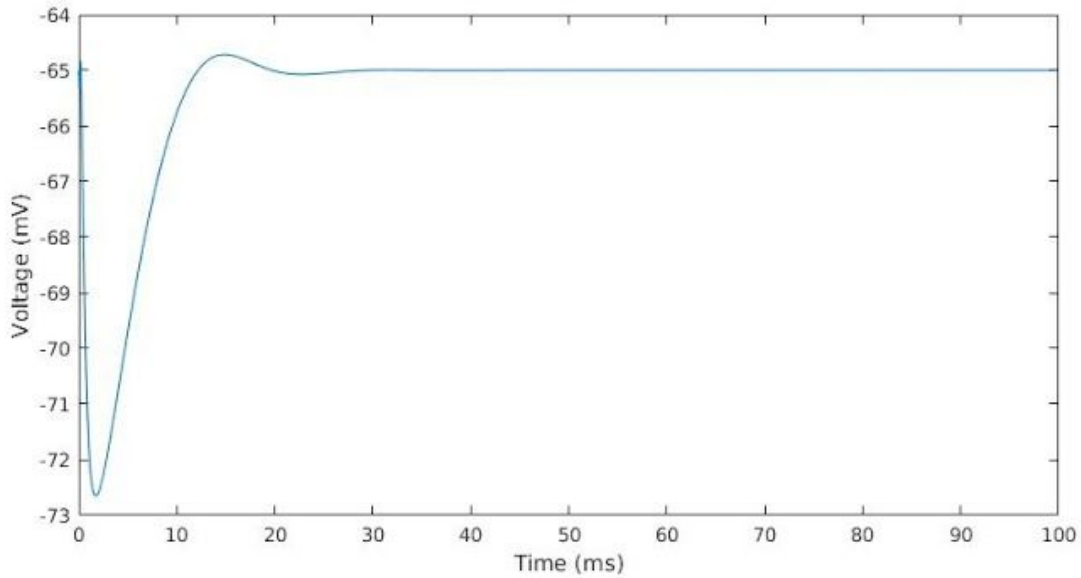$n_i = 0.5$, $m_i = 1$, $h_i = 0$, $V_i = -65\ mV$ and $I_{applied} = 0\ mA$

Figure 5 - A graph of membrane potential versus time, where the membrane potential does not produce an action potential.
$n_i = 0.5$, $m_i = 1$, $h_i = 0$, $V_i = -65\ mV$ and $I_{applied} = 0\ mA$

According to figure 4, at t=0 ms, both the potassium and the sodium activation channels are open and the sodium inactivation channel is closed. The sodium activation channel then rapidly closes while the potassium activation channel slow closes, allowing the membrane potential to become more negative, as seen in figure 5. In this scenario, K^+ ions are moving to the outside of the axon while Na^+ ions are moving inside the axon, preventing any significant depolarization from occurring. As a result, the membrane potential can not reach much higher than the resting state membrane potential, producing a graded potential. A graded potential is a membrane potential that fails to reach a given threshold necessary for an action potential. Eventually, the sodium inactivation gate opens completely and the other two gates come to a close, bringing the membrane potential back to its resting state.
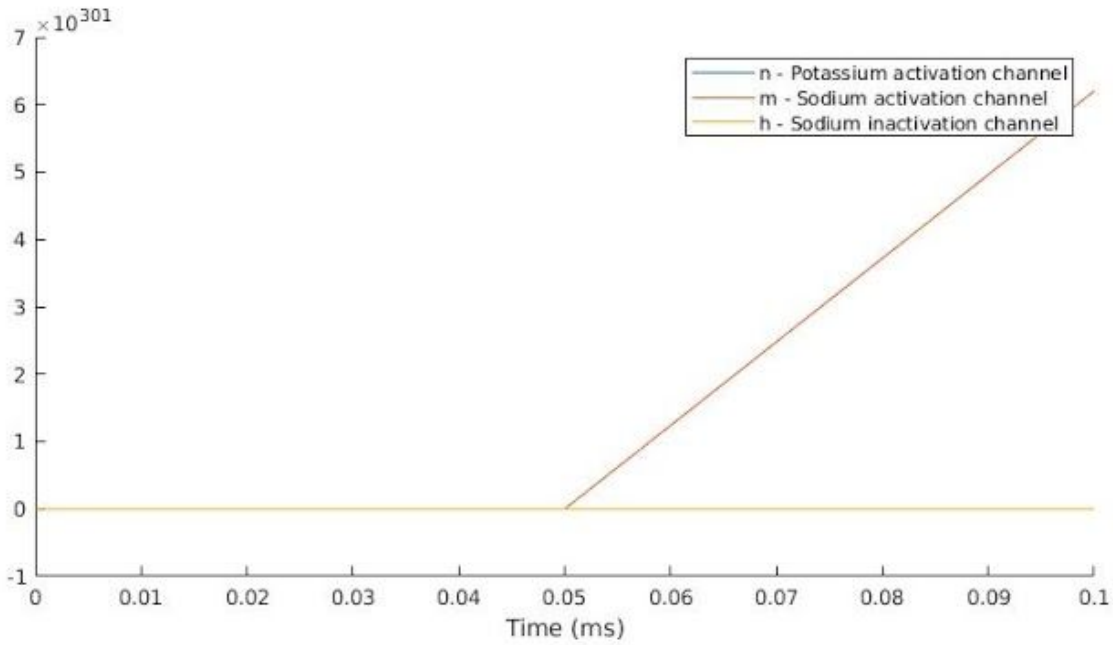
Figure 6 - a graph of the state of the Potassium activation channel and of the Sodium activation and inactivation channels versus time.

$n_i = 1$, $m_i = 1$, $h_i = 1$, $V_i = -65\ mV$ and $I_{applied} = 100\ mA$
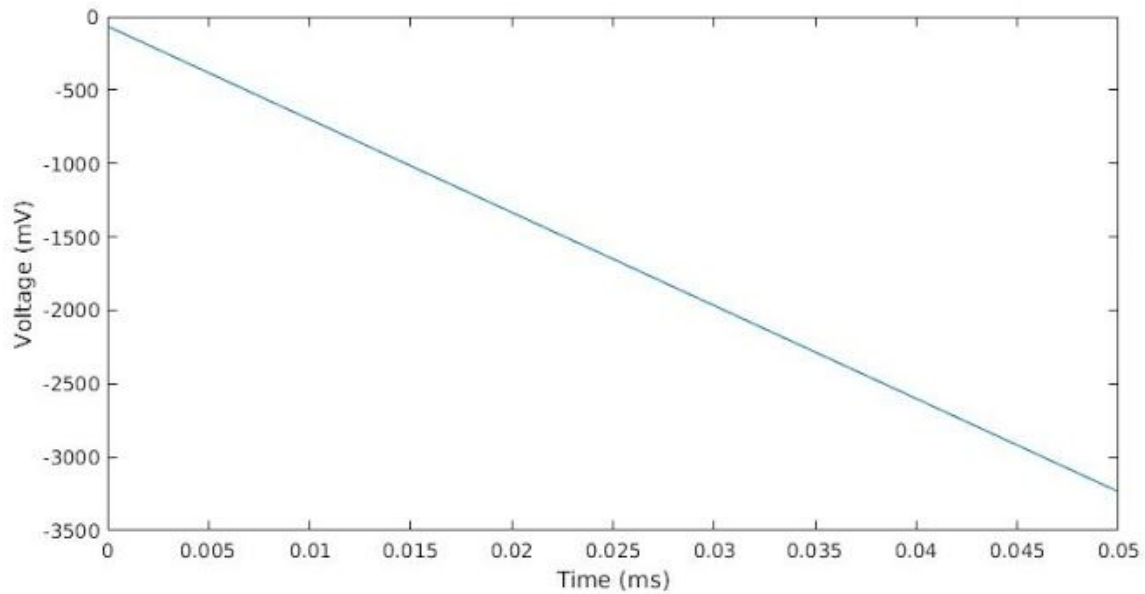

Figure 7 - A graph of membrane potential versus time.

$n_i = 1$, $m_i = 1$, $h_i = 1$, $V_i = -65\ mV$ and $I_{applied} = 100\ mA$

When analyzing figures 6 and 7, the immediate impression is that there must be some error within the simulation code, causing such large values for an otherwise

minuscule system. However, the code is operating as intended. The issue lies in the given parameters. According to figure 6, at t=0 ms all the ion channels are open and in addition there is an applied depolarizing current of 100 mA. The depolarizing current over stimulates the sodium activation channel and prevents it from closing, allowing the membrane potential to become more and more negative without limitation from the other channels. The other channels can not compensate for this accumulation of negative membrane potential because they do not react as quickly as the sodium activation channel. As a result, the over stimulating applied current and the late reaction of the other channels, produce the massive membrane potential displayed in figure 7, and reveal sensitivity in the Hodgkin-Huxley system of equations. This sensitivity means that some thought needs to go into the selection of the parameters when building this simulation.
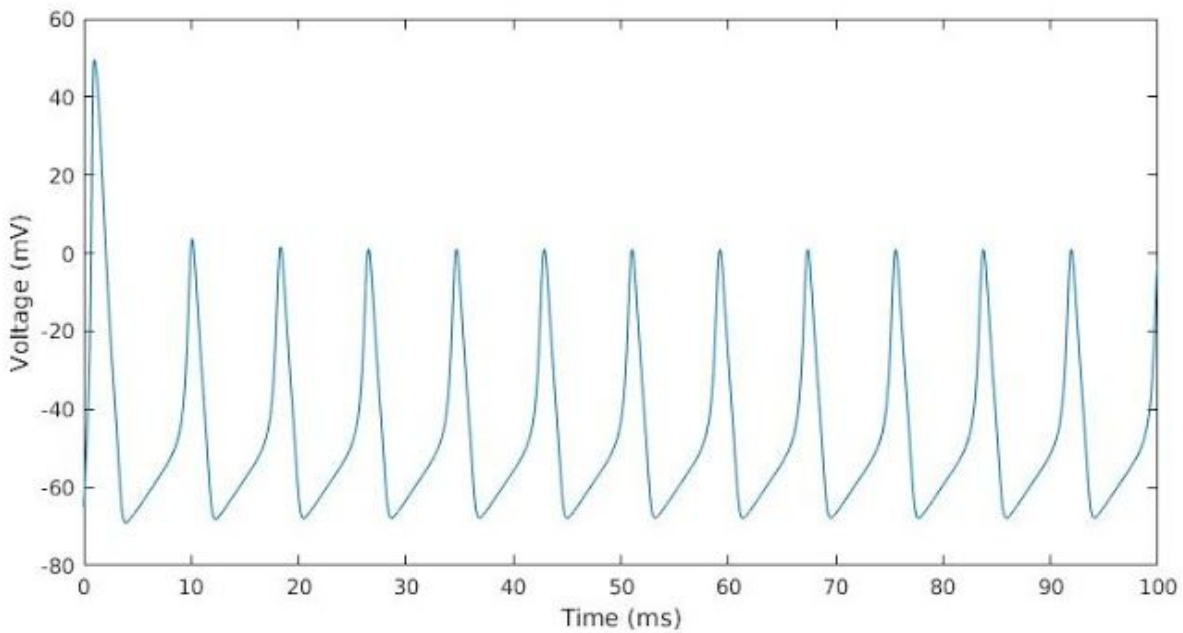

Figure 8 - A graph of membrane potential versus time,with a constant applied current
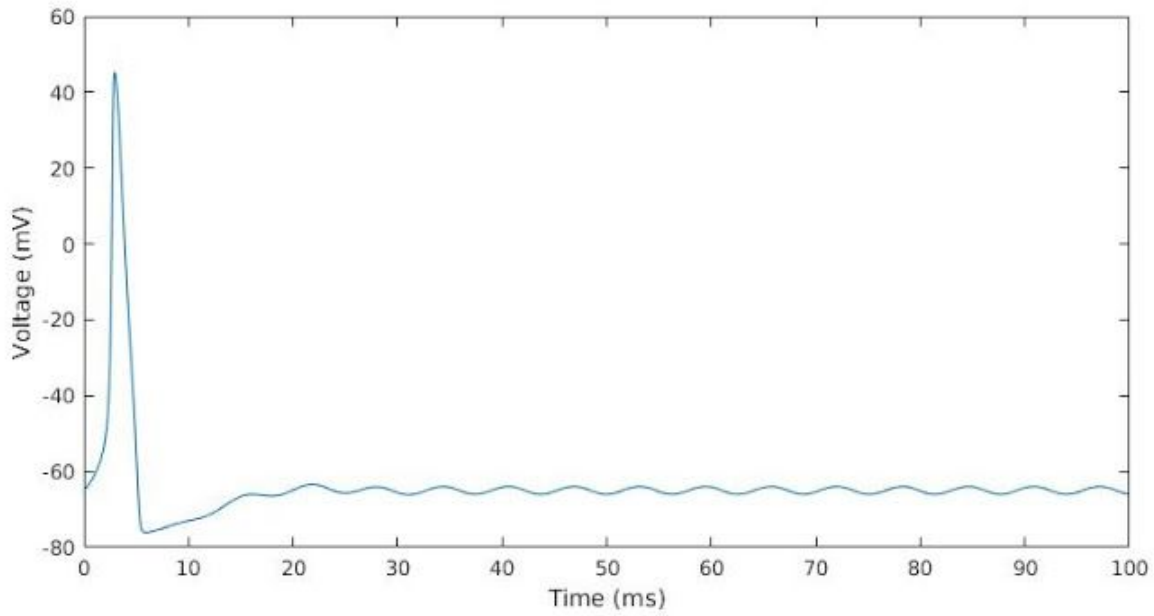$n_i = 0$, $m_i = 0.5$, $h_i = 0$, $V_i = -65 \ mV$ and $I_{applied} = 60 \ mA$

Figure 9 - A graph of membrane potential versus time, where the applied current changes as a function of time $n_i = 0$, $m_i = 0.5$, $h_i = 0$, $V_i = -65 \ mV$ and $I_{applied} = sin(t) \ mA$
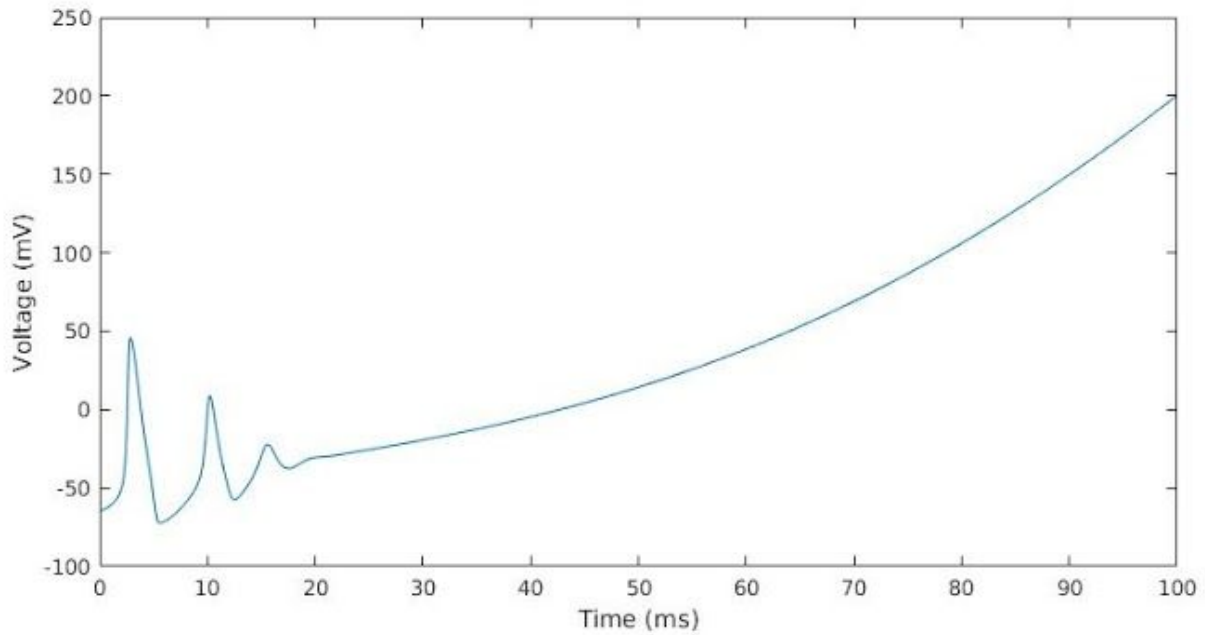

Figure 10 - A graph of membrane potential versus time, where the applied current changes as a function of time $n_i = 0$, $m_i = 0.5$, $h_i = 0$, $V_i = -65 \ mV$ and $I_{applied} = t^2 \ mA$

In figure 8, the applied current is set to a constant 60 mA and a pattern of action potentials arises. This pattern has a frequency and reflects very similarly the way

in which neurons send and receive information. However if we were to take the complexity of the information we were sending a step further we can change the applied current as a function of time. In figures 9 and 10, the applied current changes as a function of time and while the graph of the membrane potential retains similar characteristics to prior iterations, they have the capacity to reflect far more than just a single action potential or a single frequency. With the increased complexity of the messages sent between neurons, scientists could generate a custom impulse to be sent to a neuron, tracing its path and its multitude of connections, aiding in the science of brain mapping. Consequently, this potential of an enhanced understanding of neural networks could rapidly speed up the implementation of more advanced prosthetics limbs and organs.

Works Cited

Hodgkin, A. L.; Huxley, A. F. (1952). "A quantitative description of membrane current and its application to conduction and excitation in nerve". *The Journal of Physiology*. **117** (4): 500–544.

http://brainbeans.net/history/2