A Closer Look at Hodgkin–Huxley model: Six “Isotopes" of Neuron Action Potential

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1. Introduction

Action potential of a neuron is a rapid change in voltage across the cellular membrane of a neuron. The action potential of a neuron can produce a nerve impulse, which sends signals to subsequent neurons. Usually, the change in voltage involves a rapid rise following by a fall. The process is initiated only if there is sufficient current to depolarize the membrane to the threshold, or the neuron does not send electrical signal down the axon.[1]

In this project, I will adjust the values of vstart and vhold in the HH.m program to model the six “isotopes” of neuron action potential. Isotope stands for a family of one element with the same number of protons but different numbers of neutrons. These isotopes are categorized as one element, but possess different chemical properties. For the six isotopes of neuron action potential, they are all controlled by the potassium gates and the sodium gates, but the action potential patterns they display are different. I will show the patterns in the Result and Discussion section, and discuss why these patterns are displayed by analyzing the gating variables.

2. Equations[2]

In the in_mhnv.m program, the gating variables m, h, and n are set to be equal to their steady values under constant-v conditions:

$$m = \alpha_m(v)/(\alpha_m(v) + \beta_m(v)) \quad (2.1)$$

$$h = \alpha_h(v)/(\alpha_h(v) + \beta_h(v)) \quad (2.2)$$

$$n = \alpha_n(v)/(\alpha_n(v) + \beta_n(v)) \quad (2.3)$$

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[1] Britannica, Action Potential, https://www.britannica.com/science/action-potential

[2] Frank C. Hoppensteadt, Charles S. Peskin, 3.5 TheHodgkin-Huxley Equations for the Nerve Action Potential, in_mhnv.m, in_HH.m, Equation 3.5.19, 3.5.20, HH.m, Modeling and Simulation in Medicine and the Life Sciences (Second Edition)

In the in_HH.m program, the membrane parameters are initialized as the following:

Membrane capacitance per unit area: $C = 1.0\mu F/cm^2$ (2.4)

Max possible Na+ conductance per unit area: $\bar{g}_{Na} = 120\mu A/cm^2$ (2.5)

Max possible K+ conductance per unit area: $\bar{g}_K = 36(\mu A/mV)/cm^2$ (2.6)

Leakage conductance per unit area: $\bar{g}_L = 0.3(\mu A/mV)/cm^2$ (2.7)

Na+ equilibrium potential: $E_{Na} = 45mV$ (2.8)

K+ equilibrium potential: $E_K = -82mV$ (2.9)

Leakage channel reversal potential: $E_L = -59mV$ (2.10)

The time step and experiment duration are initialized as the following:

Duration of time step: $dt = 0.1ms$ (2.11)

Duration of experiment: $t_{max} = 50ms$ (2.12)

According to Equation (3.5.19) and (3.5.20), the Hodgkin-Huxley Equations for the Nerve Action Potential are given as the following:

Sodium conductance: $g_{Na} = \bar{g}_{Na}m^3h$ (2.13)

Potassium conductance: $g_K = \bar{g}_K n^4$ (2.14)

In the HH.m program:

Total conductance: $g = g_{Na} + g_K + \bar{g}_L$ (2.15)

g_E: $g_E = g_{Na} * E_{Na} + g_K * E_K + \bar{g}_L * E_L$ (2.16)

Voltage updating: $v = (v + (dt/C) * (g_E + izero(t)))/(1 + (dt/C) * g)$ (2.17)

3. Methods

The goal is to observe the change in the pattern of action potential. The original value of vhold is -70mV, while the original value of vstart is -55mV. The values are fixed. The following table, Table 3.1, shows the six situations in which I adjust the values of vstart and vhold. In the program izero.m, the current is set to be zero during the duration of experiment.

Table 3.1. The six isotopes in which vstart & vhold are adjusted

Name of the model	**vhold (starting with -70mV)**	**vstart (starting with -70mV)**
Isotope 1.1	Fix at -70	Increase by 1 for 30 times
Isotope 1.2	Fix at -70	Decrease by 1 for 30 times
Isotope 2.1	Increase by 1 for 30 times	Increase by 1 for 30 times
Isotope 2.2	Decrease by 1 for 30 times	Decrease by 1 for 30 times
Isotope 3.1	Increase by 1 for 30 times	Fix at -70
Isotope 3.2	Decrease by 1 for 30 times	Fix at -70

4. Results and Discussion

Subplot is used for all the figures in this section. The upper plot shows voltage change according to time, and the lower plot shows gating variables change according to time. In the lower plot of every figure, the blue curve, which resembles the voltage curve in the upper plot, stands for the m gate. The m gate, the activation gate, is usually closed at resting voltage, but reacts very fast when sensing a change in voltage. The n gate, shown by the yellow curve, is usually closed at the resting voltage, too. The n gate reacts slower to voltage change than m gate.

The h gate, which is the deactivation curve shown by the orange curve, is usually open at the resting voltage. But when depolarization happens, the neuron still intend to maintain a resting voltage. The h gate shuts when the neuron gets too positive, blocking Na+ from entering the neuron. This is why we observe a peak in the voltage plot. At the peak, the h gate opens to avoid getting the neuron too positive. The sodium channels close, and the potassium channels open. The downfall of voltage is called the repolarization stage. After the repolarization stage, the voltage can actually go below the resting voltage for a short period of time. This is called the refractory state, during which it is difficult for the neuron to fire.

For Isotope 1.1 (show in Figure 4.1), in which vhold is fixed at -70mV while vstart increases by 1 for 30 times with initial value -70mV, is the standard situation. Between the 6th and the 7th time step (-64mV < vstart < -63mV), the action potential suddenly appears. It means that when the neuron membrane is resting with voltage of -70mV, an increase of 6-7mV is enough to depolarize the neuron, and cause the membrane to reach to its threshold voltage.

When vstart increases from -63mV to -41mV, the peak of action potential becomes slightly higher and shifts to the left, and refractory period become longer. Therefore, bigger difference in voltage can depolarize the neuron faster, but also prolong the refractory period. There might be a tradeoff between speed of reaching action potential and time of refractory period. In a sense, if the neuron is stimulated by a strong voltage difference, it needs to rest longer before firing another time. Instead, the it takes the neuron stimulated by a relatively mild voltage difference less time to rest.

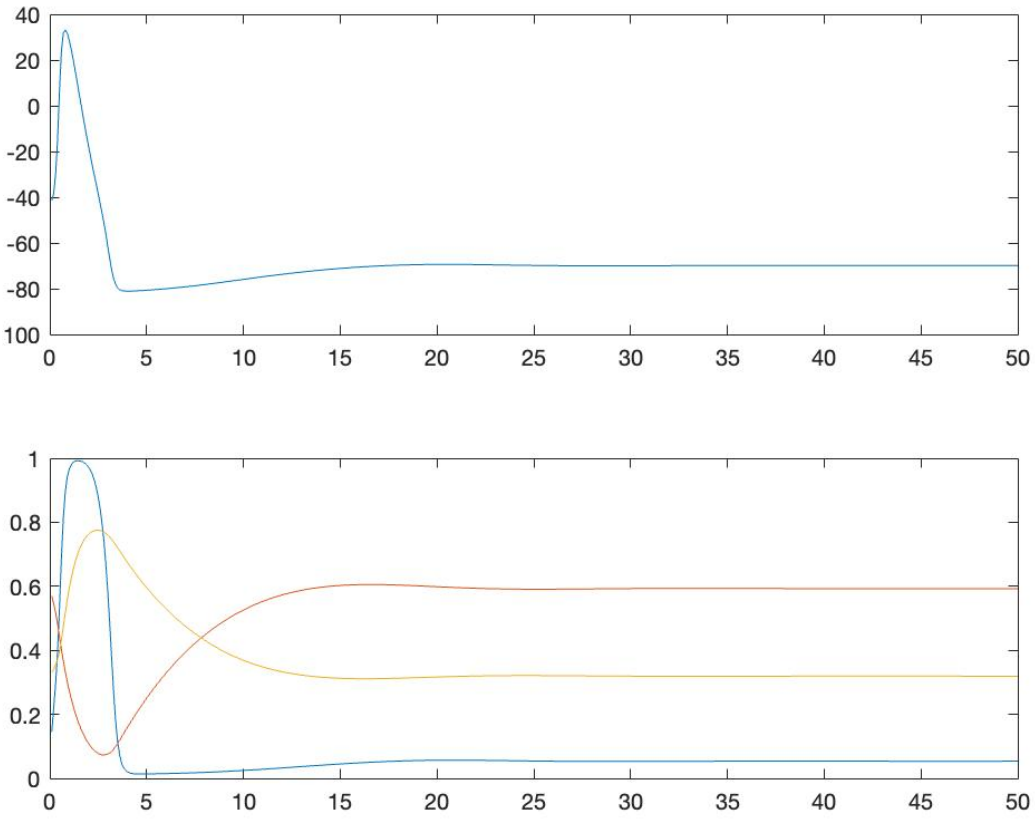

Figure 4.1. Isotope 1.1 when vhold = -70mV and vstart = -41mV

For Isotope 1.2 (shown in Figure 4.2), vstart has to drop 20 times (when vstart is about -90mV) for the activation potential to happen. After vstart reaches -90mV, the decrease of vstart causes the peak to shift to the left, and the refractory period is prolonged.

In Figure 4.2, the “bulk” of h gate curve is followed by a “canyon”. Before the action potential, the “bulk” keeps growing, while the “canyon” was not obvious. The neuron is absorbing more K+ to lower the membrane voltage. Observe that the “bulk” of h curve has a largest value around 0.7, and I predicted that is when the Na+ channels open up to help the neuron go back to the resting voltage, and no action potential should happen.

However, the Na+ channel don’t seem to close when the voltage is back to normal, but keeps opening until an action potential happens. The h gate then closes again to let more K+ into the neuron, and the neuron returns to resting voltage again after refractory period.

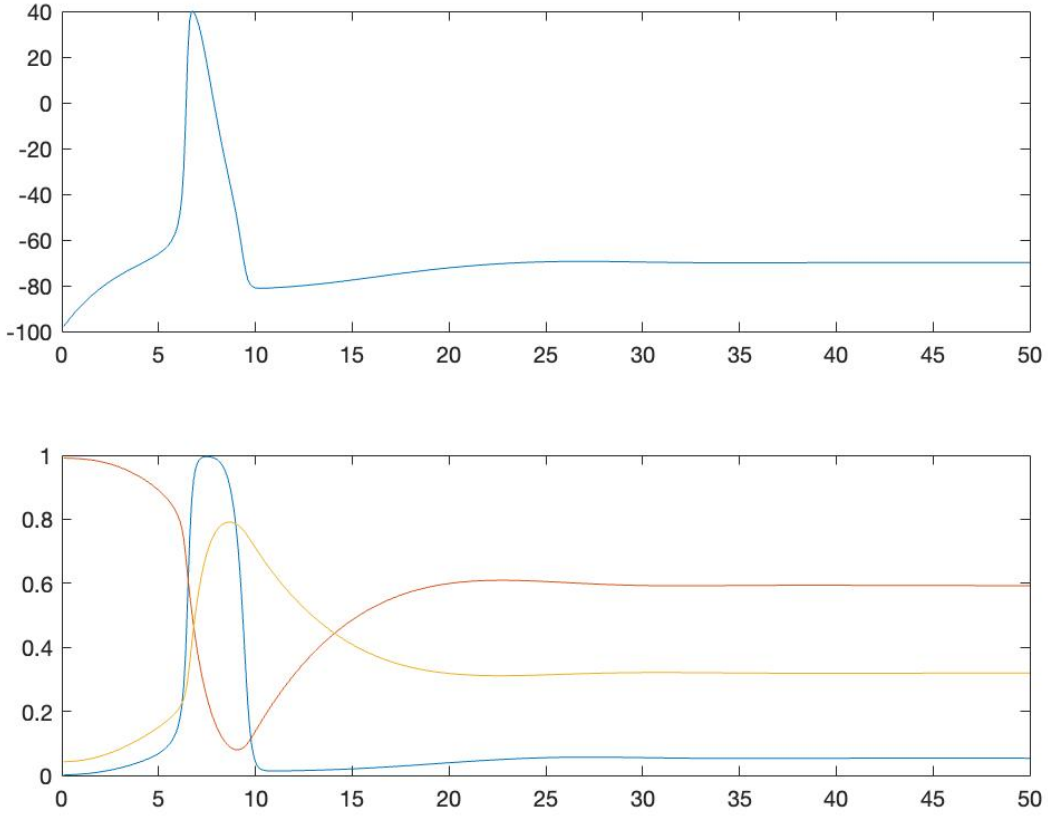

Figure 4.2. Isotope 1.2 when vhold = -70mV and vstart = -99mV

For Isotope 2.1 (shown in Figure 4.3), vhold and vstart are always held the same, both increasing from -70mV to -40mV. The more they increase, the longer it takes for the voltage to return to normal. No action potential is observed as the voltage never goes higher than 0mV. The left end of h curve falls, while the left ends of m and n curves rise.

Possible explanation is that since there is no difference in resting voltage and starting voltage, there should not be an action potential. However, this explanation is invalid according to the next model, Isotope 2.2.

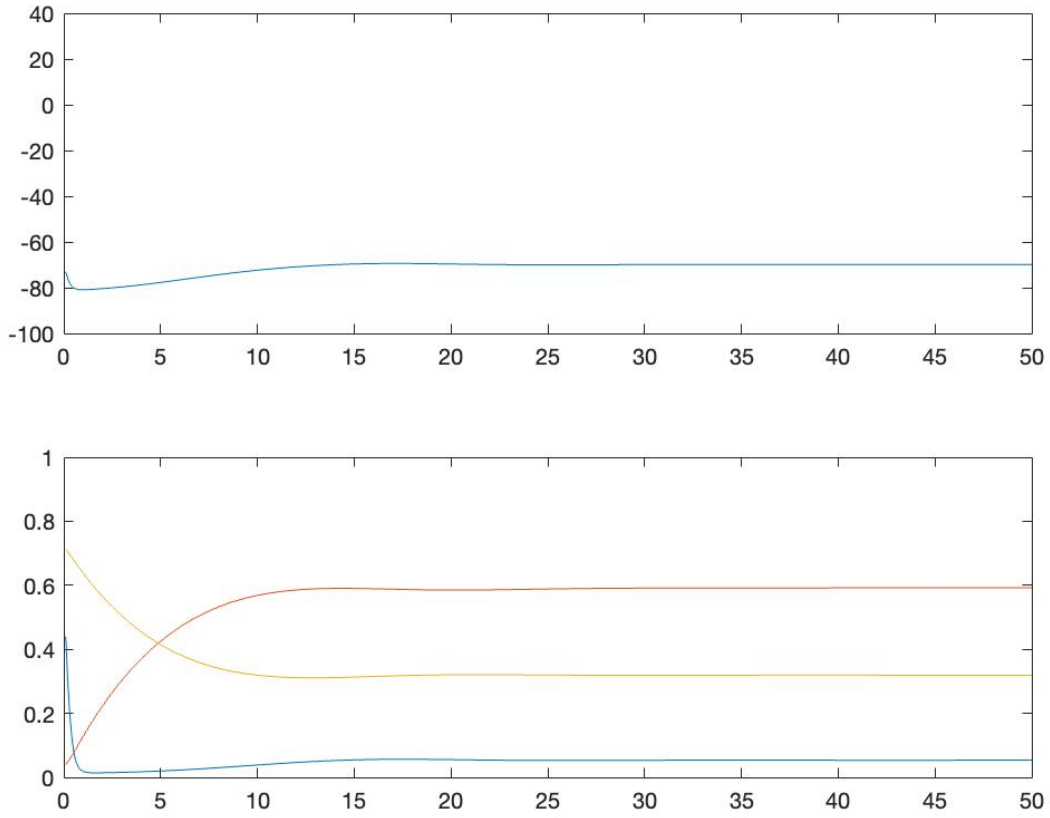

Figure 4.3. Isotope 2.1 when vhold = vstart = -41mV

For Isotope 2.2 (shown in Figure 4.4), vhold and vstart are always held the same, both decreasing from -70mV to -99mV. Approximately at the 3rd step, when vhold = vstart = -73mV, the action potential happens. The peak then starts to shift to the left and the refractory period is prolonged until the 10th step, when vhold=vstart=-80mV. After the 10th step, the peak starts to shift to the right and the refractory period starts to shorten until the last step.

It is unexpected that the action potential happens, as there is no voltage difference between starting voltage and resting voltage. The interesting thing about the gating variables is that in Isotope 2.1, when Na+ channels are open, the neuron does not fire. In Isotope 2.2, when K+ channels are open, the neuron fires. The action potential pattern of Isotope 2.2 is very similar to that of Isotope 1.2, but for some reason, the action potential of Isotope 2.2 begins to delay (the peak shifts to the right) when the voltages are lower then -80mV.

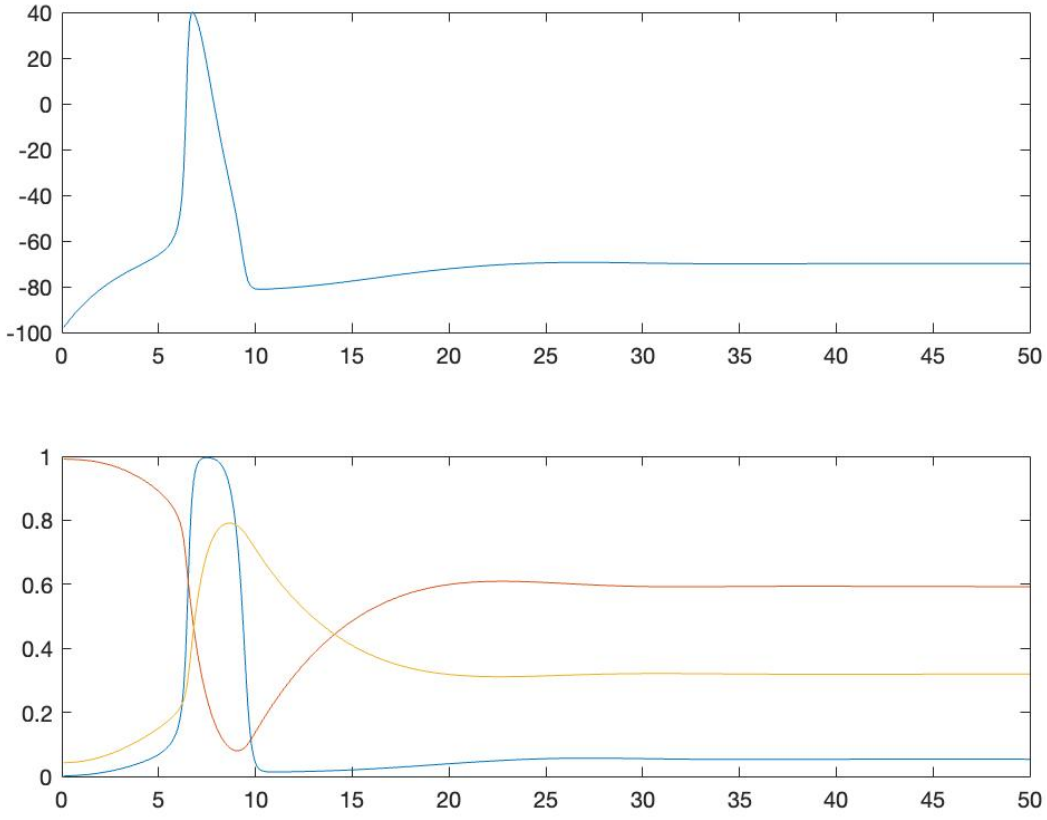

Figure 4.4. Isotope 2.2 when vhold = vstart = -99mV

For Isotope 3.1 (shown in Figure 4.5), vstart is fixed at -70mV, while vhold increases by 1 for 30 times with initial value -70mV. No action potential is observed. In this case, vhold, the resting voltage, is increased. It was predicted that Isotope 3.1 should display a similar pattern to that of Isotope 1.2, in which vhold is fixed, while vstart was decreased. However, no action potential is observed.

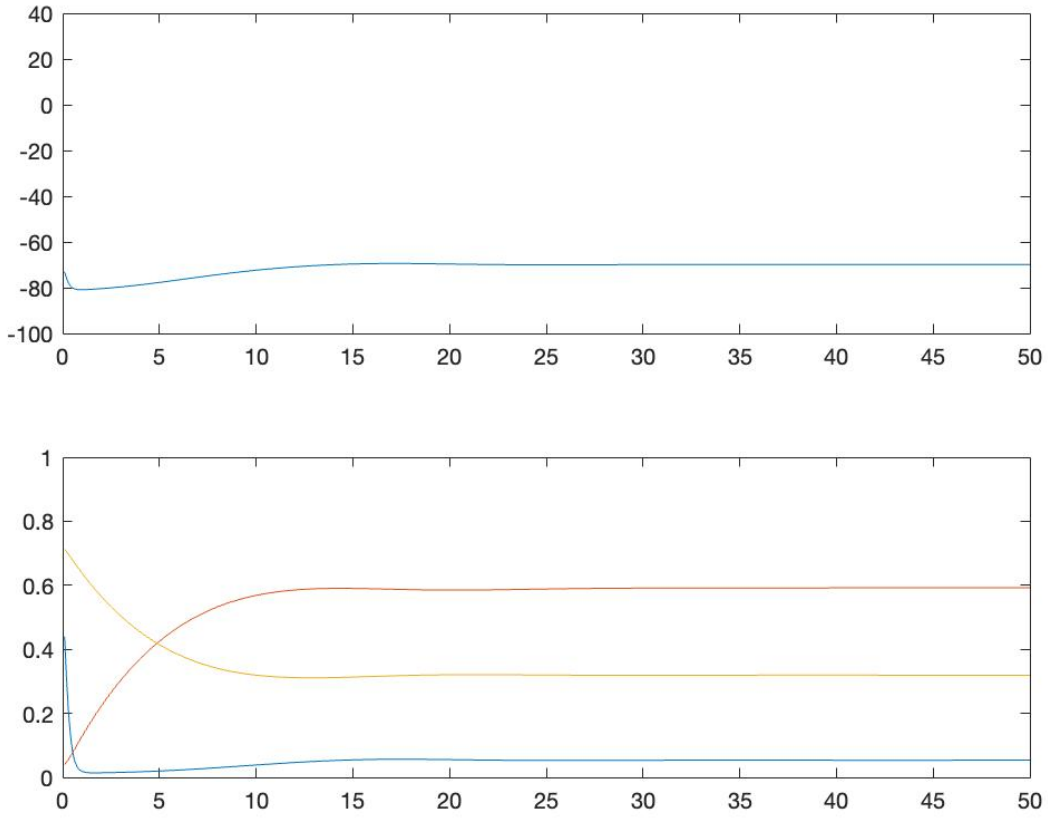

Figure 4.5. Isotope 3.1 when vstart = -70mV and vhold = -41mV

For Isotope 3.2 (shown in Figure 4.6), vstart is fixed at -70mV, while vhold decreases by 1 for 30 times with initial value -70mV. An action potential happens at around step 3, when vhold is approximately -73mV. The patter is predicted to be similar to that of the standard situation, Isotope 1.1, in which vhold is fixed, and vstart increases. The observation matches with the prediction. The depolarization stage display a slow increase in voltage at first. If we zoom in the voltage plot in Isotope 1.1, the depolarization stage should also display a slow increase in voltage. It was a positive feedback loop, during which Na+ channels are slowly increasing depending on a change in voltage, and as more Na+ channels open, the voltage change increases.

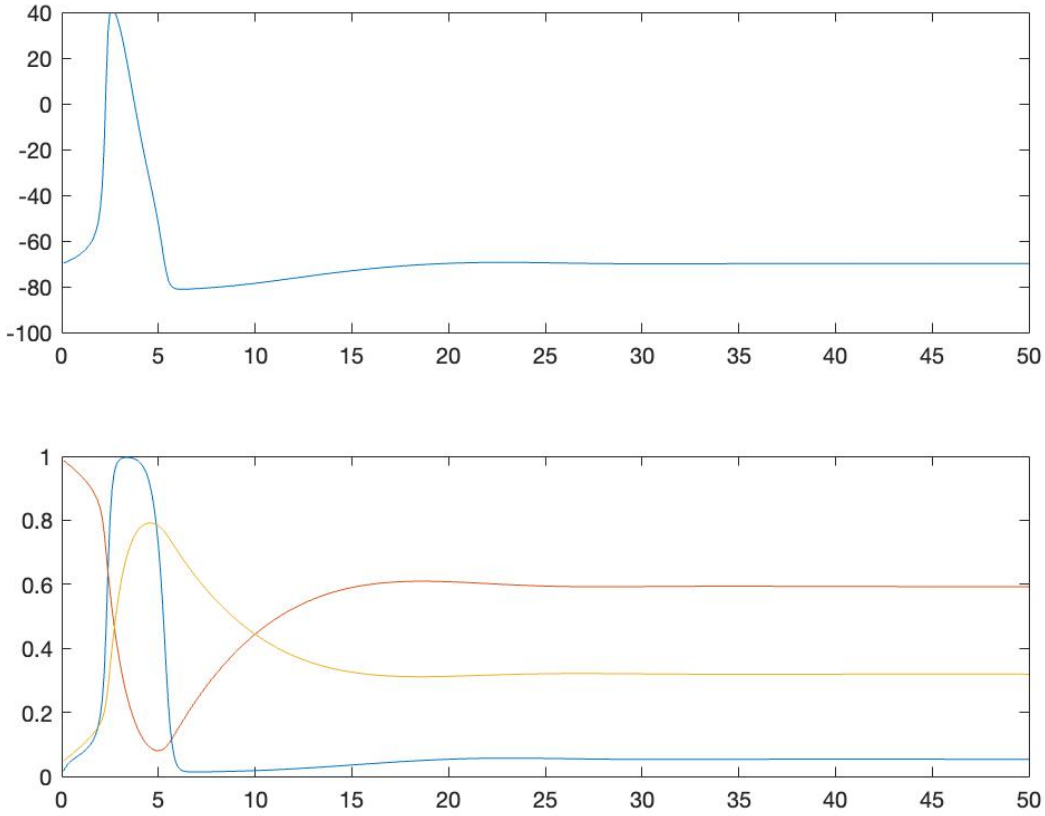

Figure 4.6. Isotope 3.2 when vstart = -70mV and vhold = -99mV

5. Conclusion

Table 5.1. Summary of observed attributes of the six Isotopes

Name of the model	Action potential happens at:	Similar to:
Isotope 1.1 (increase vstart)	-64mV < vstart < -63mV	Isotope 3.2
Isotope 1.2 (decrease vstart)	vhold=-70mV; vstart=-90mV	Isotope 2.2
Isotope 2.1 (both increase)	No action potential	Isotope 3.1
Isotope 2.2 (both decrease)	vhold = vstart = -73mV	Isotope 1.2
Isotope 3.1 (increase vhold)	No action potential	Isotope 2.1
Isotope 3.2 (decrease vhold)	vhold=-73mV; vstart=-70mV	Isotope 1.1

The relative change in vstart and vhold are similar for 1.1 and 3.2, 1.2 and 3.1, 2.1 and 2.2. Therefore I had the following predictions:
Prediction 1: Isotope 1.1 should be similar to Isotope 3.2 - True according to observation.
Prediction 2: Isotope 1.2 should be similar to Isotope 3.1 - False according to observation.
Prediction 3: Isotope 2.1 should be similar to Isotope 2.2 - False according to observation.

Isotope 1.2 has an action potential probably because too much K+ causes the Na+ channels to open. For some unknown reason, Na+ channels do not shut when the voltage is back to normal, but keeps opening until action potential is reached. And then the K+ channels open again to return the neuron to resting voltage.

Isotope 2.2 is similar to 1.2. The membrane is more permeable to K+ than to Na+. Therefore, the decrease in voltage first cause a lot of K+ to flow into the neuron, and then Na+ channels sense the change in voltage, and an action potential is reached, probably because of the same unknown reason as Isotope 1.2. As vstart and vhold continue to decrease, it takes longer for the neuron to reach the action potential. The reason might be that too muck K+ caused the increase in Na+ to have little effect on the voltage at first.

Isotope 2.1 and Isotope 3.1 are similarly probably because they both increase vhold. Increase in vhold means, at the resting stage, the neuron has more concentrated Na+ compared to normal neurons. Isotope 3.1 is able to keep the Na+ concentration high and the K+ concentration low at the beginning. The higher vhold is, the more concentrated Na+ is in the neuron, and the less concentrated K+ is in the neuron. However, the increase in vhold is not able to maintain the abnormal concentrations of ions. Overtime, K+ and Na+ concentration returns to normal.

Similar patter is observed in Isotope 2.1. In this case, Na+ concentration is already higher than normal as vhold increases, and the increase in vstart should make the Na+ concentration even higher. The abnormal concentrations of ions cannot hold either. They return to resting stage overtime.

In conclusion, the action potential display similar pattern in the following three situations:

(i) When vstart is increased, or vhold is decreased, a standard action potential is observed in each case. When vstart is increased, Na+ channels open in response to voltage. When vhold is decreased, it means in the resting stage there is less Na+ concentration than usual. Therefore, comparatively, a fixed vstart makes Na+ more concentrated as vhold decreases. Na+ channels opens to allow more Na+ enter the neuron, and an action potential forms

(ii) When vstart is decreased, or vstart and vhold are both decreased, the action potential happens. The pattern display an obvious slow starting, when Na+ channels are slowly opening in response to the increasing concentration of K+. The concentration of Na+ quickly increases to repress the concentration of K+, and it does not stop increasing when concentrations are back to normal, but keeps increasing and finally causes action potential.

(iii) When vhold alone is increased, or vhold and vstart are both increased, there is no action potential. A probable explanation is that the Na+ concentration is already set to be high as vhold increases. Therefore, if vstart does not increase, the action potential will not happen. When vstart does increase, it has to increase more than vhold does. When it increases along with vhold, there is not a enough difference in Na+ concentration to reach the threshold.

6. Additional Studies

Besides the six isotopes of neuron action potential, I also studied the standard case of neuron action potential, in which vhold = -70mV, and vstart = -55mV. I changed the value of dt, the time step duration of generating the plot, and the value of current i, and acquire the following results:

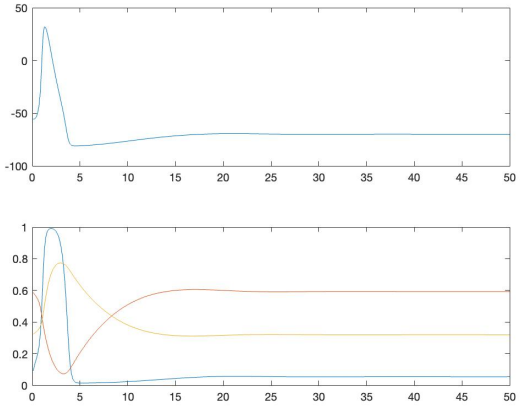

Figure 6.1. Original dt=0.1ms

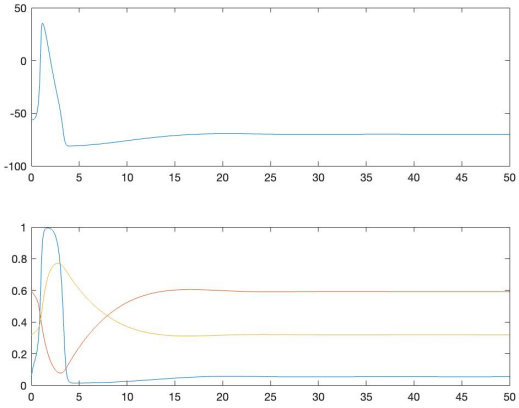

Figure 6.2. Refined dt=0.001ms

As shown in Figure 6.1 and 6.2, as dt becomes smaller, the time steps gets more delicate, and the plot we acquire is more accurate. When dt becomes 100 times smaller, the peak becomes slightly higher, and slightly shifts to the left. Therefore, when dt converges to zero, the actual action potential should happen slightly sooner than the simulated results.

Now I will use the refined plot with dt=0.001ms, and apply a current of $15\mu A$ between 10ms and 11ms. It is observed that there is a small peak during that time interval. However, the peak does not exceed zero, and therefore is not high enough to be an action potential (Figure 6.3). However, when a a current of $15\mu A$ is applied throughout the total time duration of the experiment, multiple action potentials are observed (Figure 6.4).

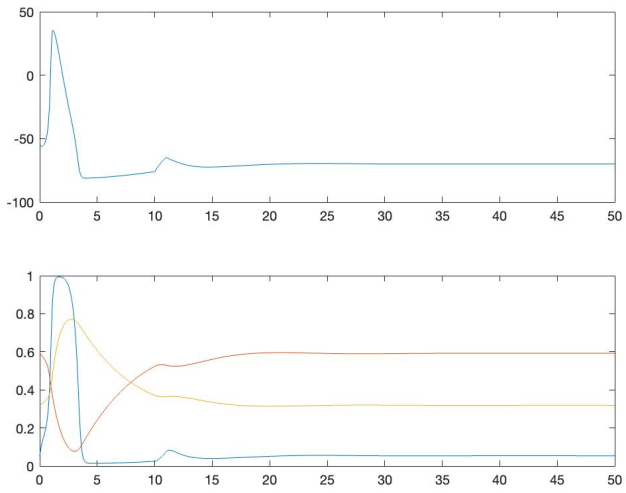

Figure 6.3. $15\mu A$ between 10ms and 11ms

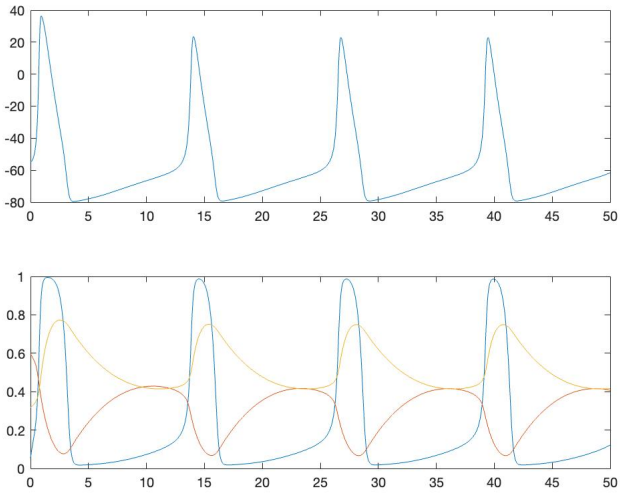

Figure 6.4. $15\mu A$ throughout the experiment

Therefore, a $15\mu A$ current is able to generate an action potential. So why the current at 10ms to 11ms time interval is not able to generate an action potential? It is observed that the neuron is at the refractory stage from 3.5ms to 14ms. The voltage is below resting voltage and slowly recovering. At refractory period it is difficult for a neuron to reach action potential again. In Figure 6.4, the multiple action potentials observed after the first peak do not happen during the refractory period. Observe that the second peak happens around 14ms, which is after the refractory period. Therefore, under the stimulus a constant current (the current must be high enough), a neuron is able to fire every time after the refractory period is over. The pattern, as observed in Figure 6.4, is periodic.

7. Appendix

The three MatLab programs, in_mhnv.m, in_HH.m, and HH.m are borrowed from https://www.math.nyu.edu/~peskin/ModSimPrograms/ch3/. The input files, in_mhnv.m and in_HH.m, are maintained the same. The change made in the plotting program, HH.m, are as the following:

In the original program, HH.m, Line 7 and Line 8 call for the two input files:

```
in_HH
in_mhnv
```

In my modified program, HH_new.m, I set up a counting variable nexp to adjust the values of vstart and vhold. Before the original Line 7, I insert :

```
for nexp = 1:30
```

I insert different codes for each isotope between the original Line 7 and Line 8:

Isotope 1.1: Fix vhold, increase vstart by 1 for 30 times

```
vhold = -70
vstart= -70+(1)*vStep*(nexp-1)
```

Isotope 1.2: Fix vhold, decrease vstart by 1 for 30 times

```
vhold = -70
vstart= -70+(-1)*vStep*(nexp-1)
```

Isotope 2.1: Increase vhold and vstart by 1 for 30 times

```
vhold = -70+(1)*vStep*(nexp-1)
vstart= -70+(1)*vStep*(nexp-1)
```

Isotope 2.2: decrease vhold and vstart by 1 for 30 times

```
vhold = -70+(-1)*vStep*(nexp-1)
vstart= -70+(-1)*vStep*(nexp-1)
```

Isotope 3.1: Fix vstart, increases vhold by 1 for 30 times

```
vhold = -70+(1)*vStep*(nexp-1)
vstart= -70
```

Isotope 3.2: Fix vstart, decreases vhold by 1 for 30 times

```
vhold = -70+(1)*vStep*(nexp-1)
vstart= -70
```

8. Reference (Alphabetic Order)

Britannica, Action Potential, https://www.britannica.com/science/action-potential

Charles S. Peskin, MatLab Programs (HH.m, in_HH.m, izero.m, in_mhnv.m), https://www.math.nyu.edu/~peskin/ModSimPrograms/ch3/

Frank C. Hoppensteadt, Charles S. Peskin, Chapter 3, Equation (3.5.19) (3.5.20), Modeling and Simulation in Medicine and the Life Sciences (Second Edition)