Effects of External Sodium Concentration on Action Potential Produced by Hodgkin-Huxley Model

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***Abstract*—Action potentials are brief reversals of neuron membrane potentials which propagate from cell to cell based on various stimuli. The Hodgkin-Huxley Model describes how action potentials are created and propagated, using ion conductances and gating variables to explain the behavior. In this paper, we determine the effect of external sodium conductance on the action potential, specifically focusing on the refractory period.**

Keywords—action potential, Hodgkin-Huxley Model, sodium

I. INTRODUCTION

A. Action Potentials and the Hodgkin-Huxley Model

An action potential is defined as a brief reversal of membrane potential, consisting of stages of depolarization, repolarization, and hyperpolarization. Action potentials are triggered by the membrane potential reaching a threshold potential, upon when the membrane depolarizes rapidly.

During this initial depolarization, positively-charged sodium ions rush into the neuron through voltage-gated sodium channels. This usually brings the membrane potential from negatively to positively charged. Repolarization occurs as the sodium channels close and the potassium channels open, causing positively-charged potassium ions to rush out of the cell. This brings the membrane potential to be negatively charged once more. However, as the potassium channels are open and the positive ions are rushing out, the sodium channels reset, causing hyperpolarization as the membrane potential dips further. Eventually, as the channels and concentrations reset, the neuron reaches resting membrane potential once more.

The Hodgkin-Huxley Model describes how action potentials are created and propagated, as well as how the ion conductance and permeability plays in. The model specifically describes the behavior of the voltage-gated sodium and potassium channels that allow the action potential to be created as described above. It defines gating variables m, h, and n, which models the probability that a channel is open. The conductance of the sodium channels is proportional to $m^3 * h$, and the conductance of the potassium channels is proportional to n^4. The values for m, h, and n are determined by the membrane potential as well as the time. The specific equations are below:

$$G_{Na}(V_m, t) = \overline{G_{Na}} * m^3(V_m, t) * h(V_m, t)$$
$$G_K(V_m, t) = \overline{G_K} * n^4(V_m, t)$$

So, the Hodgkin-Huxley Model explains how the sodium and potassium channels opening and closing determines the ion conductance and permeability. The sodium conductance initially determines the beginning of the action potential (specifically the depolarization), but eventually drops off as the potassium conductance becomes the dominant one, determining depolarization and hyperpolarization. By identifying how these factors change, we can determine the behavior of the action potential.

B. The Nernst Potential and Refractory Periods

The Nernst potential of an ion is the resting potential of a cell if the cell's membrane were only permeable to that ion. The Nernst potential creates the driving force for each ion channel, so it contributes to determining the ion conductance at each time step. It is determined in part by the inside and outside concentrations of each ion. The Nernst equation is below:

$$V_i = \frac{R * T}{z * F} * \ln \frac{c_i^o}{c_i^i}$$

The refractory period is the period where a cell is incapable of producing an action potential, usually during and after a previous one. It is split into the absolute refractory period and the relative refractory period, where during the absolute refractory period the cell is completely incapable of producing an action potential regardless of stimulus strength and during the relative refractory period the cell can only produce and action potential if a strong enough stimulus is applied. During the relative refractory period, the sodium channels are being reset so this includes the period of hyperpolarization and gradual return to resting membrane potential. However, it is more difficult to produce an action potential as the potassium conductance is still active and the cell is still more permeable to potassium ions, whose movement opposes any depolarization should the sodium channels reopen. So, the relative refractory period length is determined both by the sodium channels resetting and potentially reactivating as well as the potassium channels closing and resetting.

C. Paper Overview and Hypothesis

In this paper, we will be investigating what effect the external sodium concentration has on action potential, and specifically on the refractory period. We hypothesize that changing the external concentration of sodium will not affect the refractory period. Increasing the external concentration of sodium will increase the Nernst potential, which determines sodium ion movement across the ion channels in the cell membrane. However, the sodium conductance is active at the beginning of the action potential, whereas the potassium conductance is dominant during the latter part of the action potential which plays a larger role in determining the refractory period and how much the cell must be stimulated before producing another action potential. So, we hypothesize that changes to the external sodium concentration will not change the refractory period.

We will next dive into our procedure for investigating the effect of external sodium concentration on action potentials and refractory periods. We use the Python neuron library as well as the 6.021 neuron-interface API to model membrane potential with different stimuli and varying external sodium concentration. Then, we will present the results of our experiments and provide an analysis into our findings. Finally, we will discuss the results.

II. Procedure

We will be using the Python neuron library in conjunction with the 6.021 neuron-interface API to model a neuron using the Hodgkin-Huxley model, specifically tracking the membrane potential's response to various stimuli and variables.

The default external sodium concentration is 140 mM. To measure the impact of increasing the external concentration of sodium, we will test the membrane potential's response to various sodium concentrations. Specifically, we will measure the refractory periods for c_{Na}^{o} = 140, 180, 220, 260, 340, where the concentrations are in mM. We define an action potential to be where the membrane potential crosses 0 mV.

To measure the refractory period, we will use a pulse train that repetitively stimulates the neuron and examine the resulting propagating action potential, with the pulse width at 1 ms and pulse magnitude at 1 uA. By varying the pulse period, we can find the lowest pulse period that stimulates the neuron into producing another action potential. We see in Fig. 1 examples of graphs produced by varying the pulse period from 16.7, 16.75, and 17 ms with the external sodium concentration at the default 140 mM. We see that the first pulse period that causes an action potential sooner and closer to the previous one is 16.75 ms, so that is the refractory period for a neuron whose external sodium concentration is 140 mM and all other variables at the default for the library and API. We will refer to the measuring of refractory period by external sodium concentration as experiment 1.

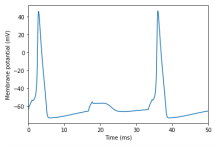

Fig. 1.a: 16.7ms@140mM

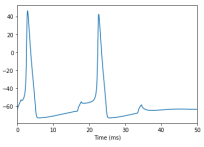

Fig. 1.b: 16.75ms@140mM

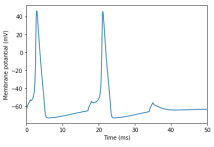

Fig. 1.c: 17ms@140mM

We then repeat the above steps, except we will keep the external sodium concentration at the default and instead vary the sodium channel conductance, $\overline{G_{Na}}$. We will measure the refractory period of the neuron similarly, at $\overline{G_{Na}}$ = .4 ,.12, .2, .28, where the default is .12 and the units is S/cm². We will refer to the measuring of refractory period by sodium channel conductance as experiment 2.

III. Results

For experiment 1, we measure the refractory periods resulting from various external sodium concentrations, where the refractory period is defined and measured as described in the Procedure section. The results from this experiment are outlined in Table 1.

c_{Na}^{o}[mM]	Refractory period total[ms]
140	16.75
180	16.25
220	16
260	15.75
340	15.25

Table 1: Results of experiment 1, Extracellular sodium concentration's effect on cellular refractory period

We then compare different concentration results, comparing the shape and size of the action potentials. Results are shown in Figure 2.

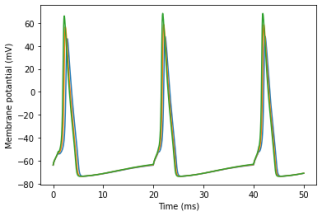

Fig. 2.a: c_{Na}^{o}[mM] = 140: Blue, 220: Orange, 340:Green

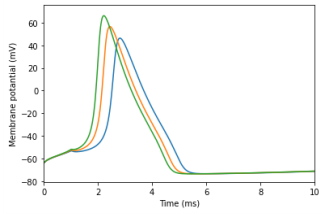

Fig. 2.b: Zoomed into Fig. 2.a.

In experiment 2, we measure the refractory periods resulting from different sodium channel conductances. The results from this experiment are shown in Table 2.

$\overline{G_{Na}}$ [S/cm²]	Refractory period total[ms]
0.12	16.75
0.15	15.5
0.18	14.25

Table 2: Results of experiment 2, Sodium channel conductance's effect on cellular refractory period at c_{Na}^{o} = 140mM

Finally, we compare the action potentials resulting from the different sodium channel conductances. The results are shown in Figure 3.

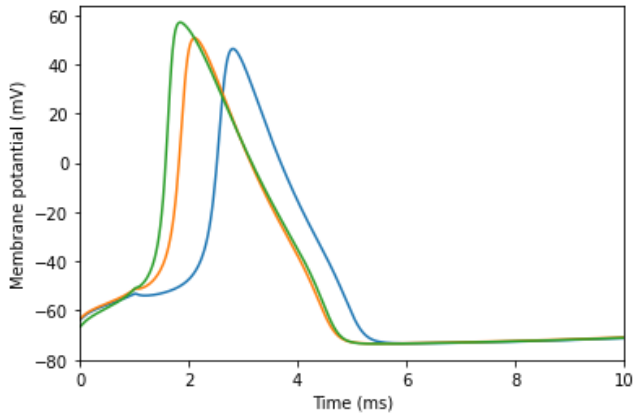

Fig. 3: c_{Na}^{o} = 140mM; $\overline{G_{Na}}$ = 0.12 S/cm²: Blue, 0.15 S/cm²:Orange, 0.18 S/cm²:Green

IV. Analysis

After running the first experiment by varying the sodium concentration with default parameters, we found that increasing extracellular concentration of sodium does indeed reduce the refractory period of a Hodgkin Huxley model of an action potential. The results of the experiment can be summarized in Table 1 where we can see that for every 40mM increase in concentration, we see about a 0.25 – 0.5 ms decrease in the refractory period, meaning that a new action potential can be excited sooner after an initial action potential.

This relationship occurs because the initial propagation of an action potential is reliant on sodium and sodium channels. As the cell starts to depolarize, a threshold voltage must be met in order for the cell to initiate an action potential. Therefore, by having a higher extracellular concentration of sodium, sodium contributes more towards reaching threshold even though it is potassium that

dominates the membrane voltage at this time. Once an action potential has occurred, the refractory period is the period of time immediately after in which another action potential cannot occur. In order to elicit another action potential during this period, a higher strength current is required, therefore raising the threshold for an action potential. It is this concept of a higher threshold that leads to the relationship found in experiment 1. By having a higher extracellular concentration of sodium, the cell is more easily able to meet the higher threshold needed as you increase this concentration from its contribution to the membrane voltage and availability of sodium when sodium channels open during depolarization, leading to a shorter refractory period.

Additionally, if we look at Figure 2, we notice a detail in the action potential plots when you plot different concentration results together. You will notice how with higher extracellular concentration of sodium, the peaks of the action potential increases. The reason for this is that the action potential peak is largely determined by the sodium Nernst potential of a membrane and this voltage has a positive relationship with extracellular concentration of sodium. The reason that the sodium potential dominates at the peak is because at the peak of an action potential, the current through sodium channels dominate, therefore the membrane potential is largely determined by the sodium Nernst Potential. In the zoomed in plot in Figure 2, you will also notice how higher concentration action potentials appear to propagate earlier. The reason for this is that due to greater extracellular sodium concentration, more sodium is readily available and the sodium potential is higher, making the overall membrane potential rise faster, speeding up the behavior of m factor dynamics in a sodium channel, hence a faster rise to the action potential peak.

Lastly, in the second experiment, we also varied the sodium channel conductance to see its effect in the Hodgkin Huxley Model after noticing how important the induced current is towards initiating an action potential. The results are summarized in Table 2 and it is immediately apparent how even a slight increase in the sodium channel conductance will lead to an about 1ms reduction in refractory period for every 0.03 S/cm^2 increase in channel conductance. As we've previously explained, the initial excitation of an action potential is a result of the opening of sodium channels, hence if the conductance of these channels increases, the action potential will reach its peak faster since sodium will be able to enter the cell at a faster rate, therefore showing a steeper slope reaching the peak. You will also notice how the peaks of the action potentials also increase (shown in Figure 3) with greater sodium channel conductance and this is a direct result of greater channel conductance making the sodium channel potential even more dominant and since the peak of an action potential to proportional to the sodium channel potential, greater conductance will increase the action potential peak.

V. Conclusion

As the findings of the experiments presented suggest, if we choose to focus in on the effects of the sodium channel on the Action Potential produced via the Hodgkin Huxley Model, we find the key importance of the parameters in a cell membrane regarding the sodium channels. If a cell membrane is put in a solution in which the extracellular concentration of sodium is progressively increased, you will see a reduction in the refractory period of the cell, thereby allowing the cell to propagate a signal at a much faster rate. Similarly, if one were to compare two cells with different sodium channel conductances, one would find that the cell with a higher conductance would also experience the same effect in a reduced refractory period. These results regarding the Hodgkin Huxley Model are fascinating and key to understanding the key role and dynamics of a sodium channel in the initiation of an action potential. Another key ion that influences the action potential in the Hodgkin Huxley Model is potassium, so a follow up to these experiments would be to explore the effects of varying potassium concentrations and potassium channel conductances.

Acknowledgment

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References

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