

# The Impact of Potassium Concentration on Refractory Period in the Hodgkin Huxley Model

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December 7, 2001

## **Abstract**

We investigated the role of external potassium concentration in determining the absolute refractory period of a simulated axon described by the Hodgkin-Huxley model. In addition to verifying that increasing the external potassium concentration increases the absolute refractory period, we explored the underlying mechanisms by which potassium concentration affects the refractory period and discovered novel oscillatory behavior in the model. We show that potassium concentration changes affect the refractory period by changing the membrane potential. Increasing the external concentration of potassium increases the membrane potential, and the higher membrane potential reduces the sodium conductance inactivation factor  $h$ . The lowered value of  $h$  keeps down the value of the sodium conductance, preventing additional action potentials from propagating and thus causing a refractory effect. The observed oscillatory responses are related to increased membrane potentials and can be triggered independently of potassium concentration changes by changing the leakage Nernst potential.

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# 1 Introduction

An electrically excitable cell generates a potential difference across its membrane, called an action potential (AP), in response to external current stimuli above its threshold. The change in membrane potential is accompanied by longitudinal current flows through the intracellular and extracellular media as well as across the cell membrane [1]. The Hodgkin-Huxley model explains the observed electrical properties of an unmyelinated giant squid axon in terms of the relations of the membrane potential and the membrane currents.

Nerve cells are refractory, meaning that immediately after one AP there is a delay before a second AP can be generated. If the interval between pulses is less than the absolute refractory period, it is impossible to generate a second AP at all, regardless of how high the intensity of the stimulus is for the second pulse. For intervals slightly longer than the absolute refractory period, there is a relative refractory period. During that time, a second AP can be generated, but the threshold needed to do so is increased. The properties and causes of the refractory period can be predicted using the Hodgkin-Huxley model.

According to the Hodgkin-Huxley model, immediately after the peak of an AP the membrane potential is higher than the resting potential. The increase in membrane potential increases the final value of the activation factor  $n$ , which causes the potassium conductance to increase. The higher membrane potential also reduces the final value of the inactivation factor  $h$ , which prevents the sodium conductance from increasing. Consequently, we expected that for a brief period of time after an AP, the inhibited sodium conductance would prevent or impede the propagation of new APs.

During the refractory period, the increased potassium conductance and decreased sodium conductance force the membrane potential toward the potassium Nernst potential. That value can be changed by modifying the external concentration of potassium. Decreasing the external concentration of potassium would lower the membrane potential during the refractory period. A lower membrane potential would increase the value of the inactivation factor  $h$ , which would in turn increase the sodium conductance. An increased sodium conductance should enable the propagation of action potentials sooner than would otherwise be expected, in effect reducing the refractory period. We hypothesized that by decreasing the external potassium concentration in the Hodgkin-Huxley model for an axon, the absolute refractory period would be reduced.

## 2 Methods

We made three sets of measurements to test our hypothesis. The first set involved determining how the absolute refractory period changed as  $C_K^o$  was increased. The second set measured how the Hodgkin-Huxley model broke down due to changes in the membrane resting potential. Finally, the third set involved examining the role of the sodium conductance in changing the refractory period as well as how the sodium conductance responded to changes in  $C_K^o$ .

### 2.1 Refractory Period Measurements

We began by measuring the absolute refractory period for simulations with different values for the external concentration of potassium. We used the Propagating Action Potential model

from the 6.021J Matlab software. The stimuli used consisted of two pulses, each with an amplitude of 0.5 mA and a duration of 0.5 ms. All simulation parameters except the external potassium concentration were unchanged from their default values.

In estimating the absolute refractory period, first a large value for the delay was chosen and the value for the delay was incrementally decreased until there was no longer a visible second AP response. For each value for the delay tested, we looked at the fixed space  $V_m$  versus time graph to see the cell's response to the stimuli. When there was a doubt as to whether an AP was actually generated, the time-space graph was used to make certain the wave for the second AP traveled down the 3 cm length of the axon decrement-free. The value for the external concentration of potassium was varied in order to assess the effects of  $C_K^o$  on the length of the refractory period. The  $C_K^o$  values used were 0.2011, 2.011, 5.000, 10.000, 15.000, 20.110 (the default value), 25.000, 30.000, and 35.000 mmol/L.

## 2.2 Oscillation Control Measurements

In order to determine if the appearance of oscillatory responses was associated with membrane resting potential independent of the value of  $C_K^o$ , we took several measurements of propagating APs using different values for  $V_L$ , the leakage Nernst potential. For several different values of  $V_L$ , we measured the membrane potential  $V_m$  as a function of time. These measurements were taken by examining the fixed space comparison plot at a distance of 3 cm. Except for the values of  $V_L$ , these tests used the default Hodgkin-Huxley model parameters.

## 2.3 Sodium Conductance Control Measurements

We conducted additional measurements to explore how changes in  $C_K^o$  affect the refractory period. The absolute refractory period was measured for several different values of  $G_{Na}$ . In addition, measurements of the sodium conductance and inactivation factor  $h$  were also taken for different values of  $C_K^o$ .

Measurements of the absolute refractory period for different values of  $G_{Na}$  were conducted in a similar manner to the refractory period measurements described in Section 2.1. The only difference was that instead of varying the external potassium concentration while keeping all other simulation parameters at their default values, we varied the baseline sodium conductance while keeping the external potassium concentration fixed at its default value of 20.11 mmol/L.

We measured sodium conductance and inactivation factor  $h$  values as a function of time for stimuli consisting of single pulses. Like those used in the refractory period measurements, these pulses had an amplitude of 0.5 mA and a duration of 0.5 ms. We collected these data by examining the fixed space comparison plots for both  $G_{Na}$  and  $h$  at a distance of 3 cm for several different values of the external potassium concentration. The potassium concentrations used were the same as those used for the refractory period measurements described in Section 2.1.

### 3 Results

#### 3.1 Refractory Period Analysis

For external concentrations of potassium from 0.2011 mmol/L to 36 mmol/L, the trend in absolute refractory periods was as predicted. As the external potassium concentration decreased, the length of the absolute refractory period decreased linearly. That relationship is shown clearly in Figure 1.

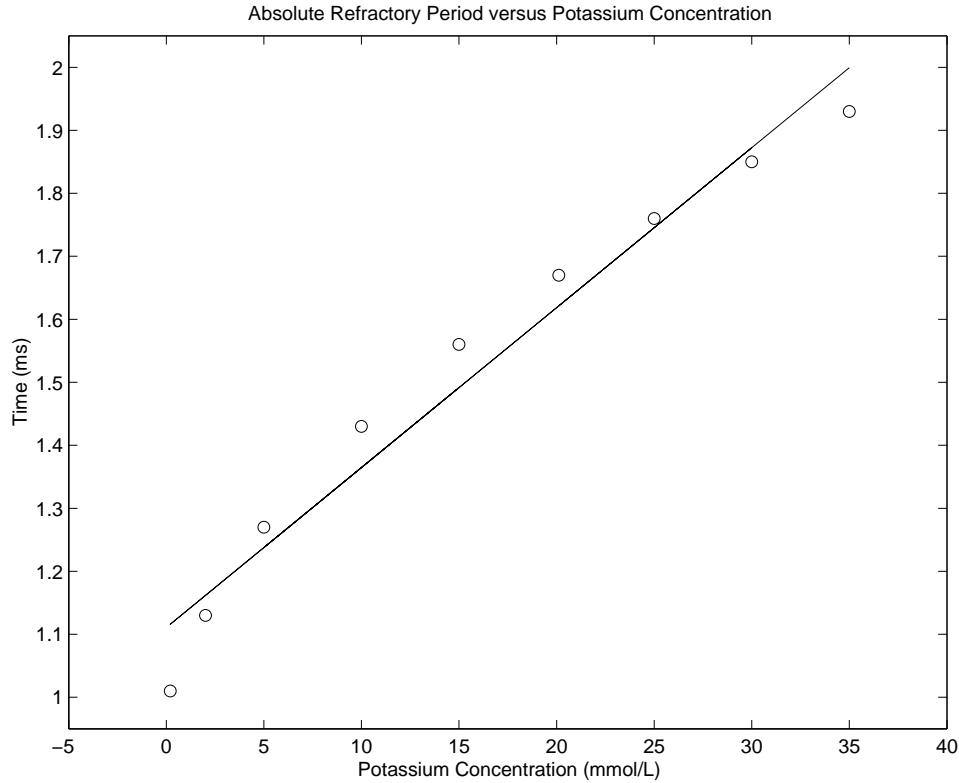


Figure 1: As the external potassium concentration increases, the absolute refractory period increases. The straight line that best fit this data was generated using the least squares method. The equation for that line is  $T = 0.0254 + 1.1107C_K^o$  where  $T$  and  $C_K^o$  have the units of ms and mmol/L, respectively. The quality of the fit can be measured by examining the norm of the residuals,  $r$ . For this fit,  $r = 0.1735$ .

However, this relationship broke down for external potassium concentrations above 37 mmol/L. A single pulse elicits an unexpected response; rather than falling back to rest after a single pulse, another action potential is generated with a lower amplitude, which in turn elicits another action potential with an even lower amplitude, and so on until the membrane potential finally reaches rest. The train of response APs generated by the first stimulus pulse interfere with the onset of the second pulse, making it difficult to find a meaningful measure of the absolute refractory period.

### 3.2 Oscillatory Response Analysis

Measurements of both the membrane potential and the sodium conductance inactivation factor  $h$  for several different values of the leakage Nernst potential are shown in Figures 2. Figure 2 shows that as the leakage potential increases, the membrane potential at rest and immediately following an AP increases monotonically. Furthermore, these results suggest that as the leakage potential (and correspondingly, the membrane potential) rise, oscillatory effects begin to appear.

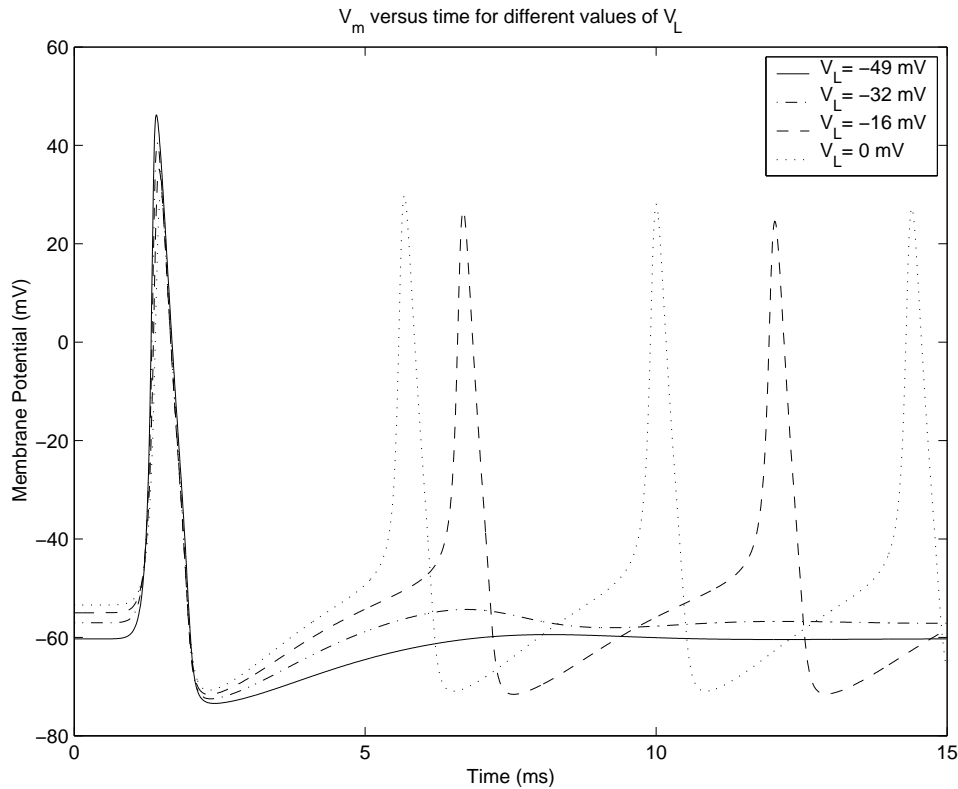


Figure 2: As the leakage potential increases, the membrane potential increases and the oscillatory effects appear.

### 3.3 Sodium Conductance Analysis

We expected that potassium concentration changes the refractory period by affecting the sodium conductance. The results of a series of tests to measure refractory period for different values of sodium conductance are shown in Figure 3. These results indicate that increases in the sodium conductance correspond directly to reductions in the refractory period.

To verify that changes in potassium concentration really do change sodium conductance, we examined how the sodium conductance changes over time as a function of the external potassium concentration. These results are shown in Figure 4. They demonstrate that as the potassium concentration increases the sodium conductance decreases overall. To more clearly illustrate this trend, we determined the peak conductance values for each curve in Figure 4 and plotted these values as a function of potassium concentration. These results are shown

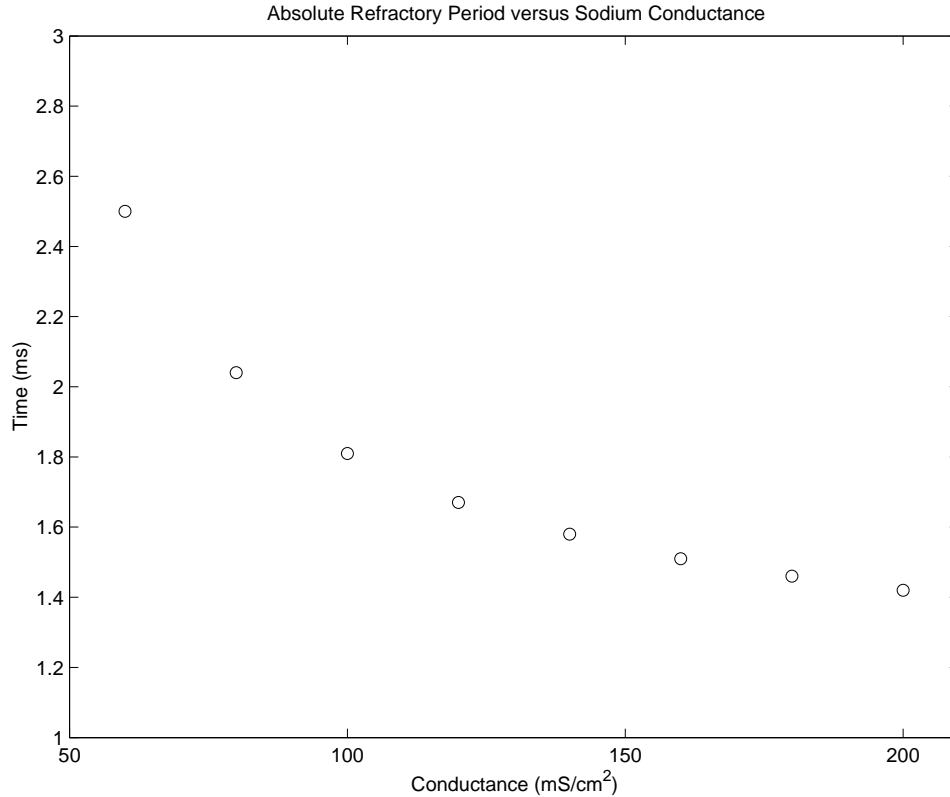


Figure 3: Increasing sodium conductance corresponds with a shorter absolute refractory period.

in Figure 5. This plot indicates that the sodium conductance decreases monotonically as the potassium concentration increases.

Finally, to elucidate the role of the potassium concentration in changing the sodium conductance inactivation factor  $h$ , we plotted  $h$  as a function of time for several different values of the potassium concentration in Figure 6. These results indicate that as the potassium concentration increases, the value of  $h$  decreases.

## 4 Discussion

Simulation results have verified our hypothesis that increasing the external potassium concentration in the Hodgkin-Huxley model for an axon will increase the refractory period. In addition, the simulations have demonstrated an interesting failure mode for the model. We knew that higher potassium concentrations result in a higher Nernst potential for potassium ( $V_K$ ) which increases the membrane's resting potential. Furthermore, we suspected that  $V_m$  might be raised high enough so that the falling edge of the first AP would end at a voltage above the membrane's threshold voltage. That would cause each AP to trigger the production of another AP. Under conditions that raise the resting membrane potential sufficiently, a single stimulus pulse will result in a train of diminishing APs. This response from the Hodgkin-Huxley model suggests an interesting avenue for laboratory research; experiments that attempt to reproduce the same behavior in real axons.

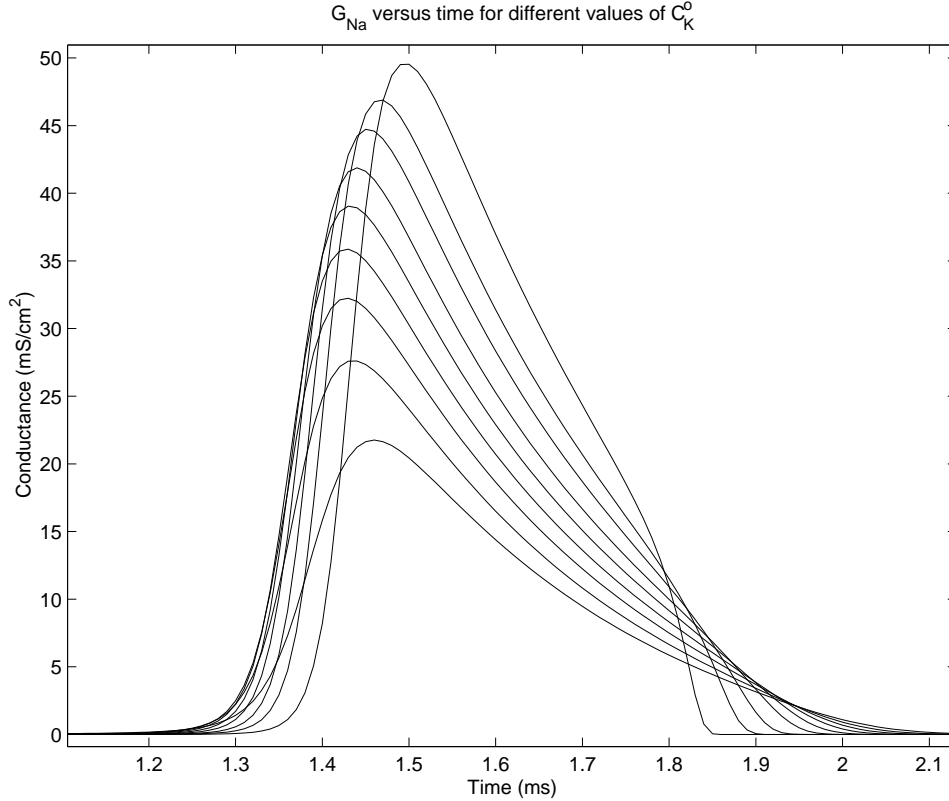


Figure 4: From the top down, curves correspond to increasing values of potassium concentration. As the potassium concentration increases, the sodium conductance decreases.

Analysis of our results suggests that potassium concentration changes bring about changes in the resting membrane potential. Membrane potential dependence on external potassium concentration is effected by corresponding changes in the Nernst equilibrium potential for potassium.

By raising the membrane potential overall, increases in the external potassium concentration result in a lowering of the inactivation factor  $h$ . The lowered value of  $h$  prevents the sodium conductance from rising. Since a rapid increase in the sodium conductance is needed for APs to propagate, clamping the sodium conductance prevents or impedes the propagation of additional APs. We have shown that this clamping of the sodium conductance is the basis of the refractory effects observed in the Hodgkin-Huxley model.

## Works Cited

- [1] Weiss, T. F., *Cellular Biophysics: Teaching and Learning with Computer Simulations*. Cambridge MA: Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, 2000.

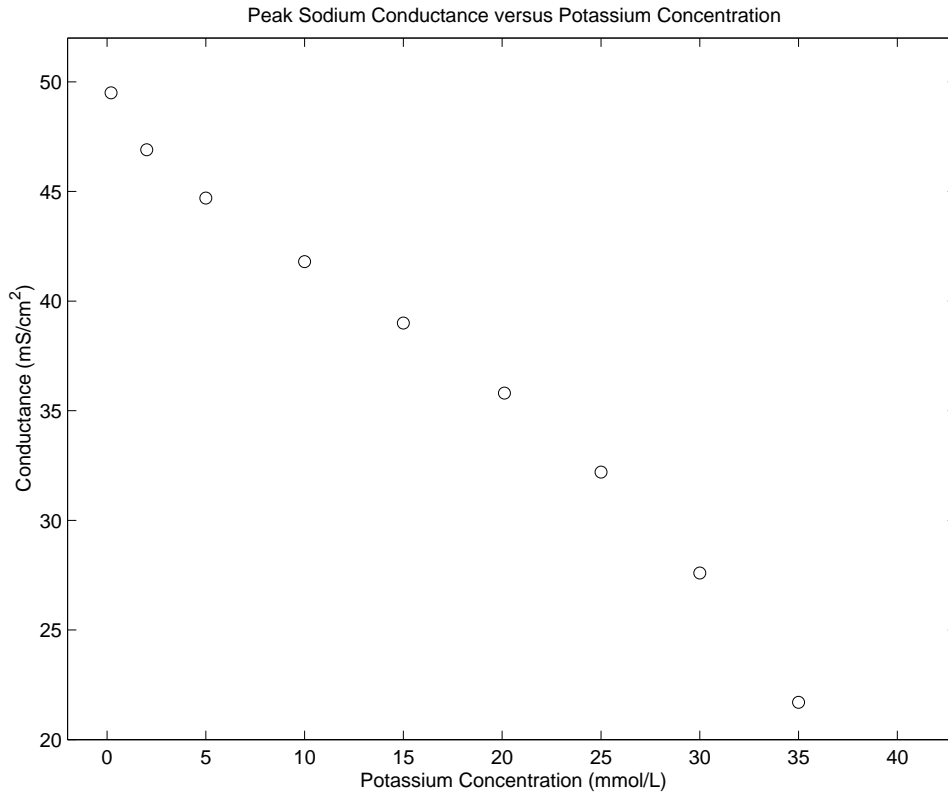


Figure 5: Like Figure 4, shows that as the potassium concentration increases, the sodium conductance decreases.

## A Project Proposal

### A.1 Potassium's impact on the refractory period

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#### A.1.1 Hypothesis

Decreasing the external potassium concentration in the Hodgkin-Huxley model for an axon will reduce the refractory period.

#### A.1.2 Background

Immediately after the peak of an action potential, the HH model suggests that the membrane potential will be higher than the resting potential. Raising the membrane potential increases the final value of the exponential function  $n$ , which causes the potassium conductance to increase. The higher membrane potential also reduces the final value of the exponential function  $h$ , which prevents the sodium conductance from increasing. Consequently, we anticipate that for a brief period of time after an action potential, the inhibited sodium conductance will prevent or impede the propagation of new action potentials. We believe that this inhibition is the underlying mechanism for the refractory effect observed in the HH model.

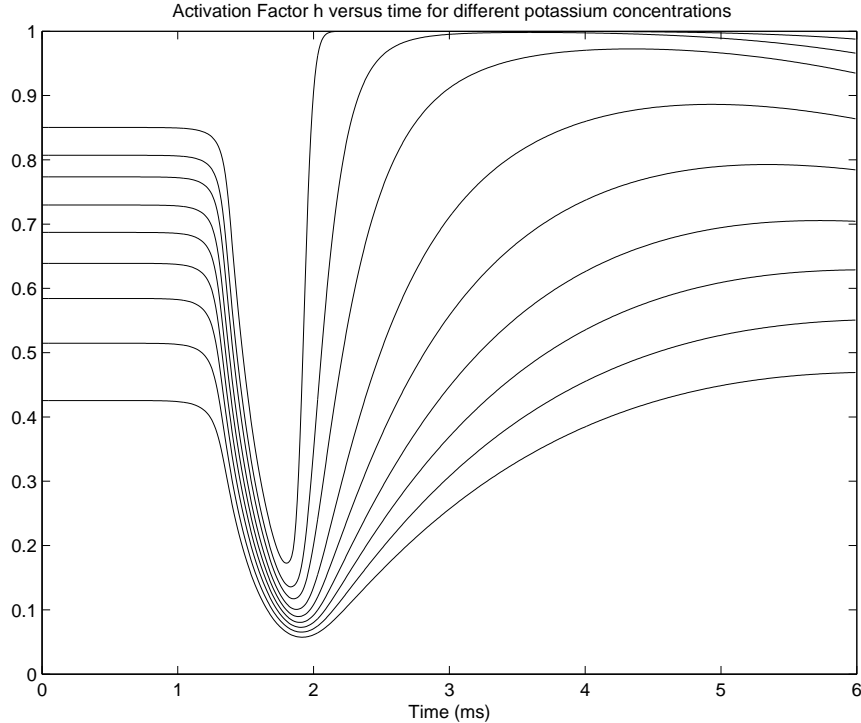


Figure 6: From the top down, curves correspond to simulations with increasing potassium concentration. As potassium concentration increases, the value of  $h$  decreases.

However, during the refractory period, the increased potassium conductance and decreased sodium conductance forces the membrane potential near the value of the potassium Nernst potential. That value can be changed by modifying the external concentration of potassium. We believe that by decreasing the external concentration of potassium, we can lower the Nernst potential for potassium which should force the membrane potential lower during the refractory period. A lower membrane potential would increase the final value of the exponential function  $h$ , which would in turn increase the sodium conductance. An increased sodium conductance should enable the propagation of action potentials sooner than would otherwise be expected, in effect reducing the refractory period.

### A.1.3 Procedure

We plan on measuring the absolute refractory period of an axon using the standard Hodgkin Huxley model for five different values of the external potassium concentration. Those five values correspond to one hundred times, ten times, one, one tenth, and one hundredth the standard model's prescribed potassium concentration.

In order to measure the absolute refractory period, we will use a computer simulation of the HH model to stimulate the simulated nerve with pairs of short current pulses. The pulses will be 0.5 ms in duration and have amplitudes of 0.05 and 0.5 milliamps. We will conduct a series of trials to determine the minimum delay needed for the second pulse to produce any action potential response at all. In order to determine if an action potential has been generated, we will check to see if the response passes decrement free down the first 3 centimeters of the axon.