Hodgkin and Huxley Cell Membrane Model Simulation

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***Abstract*—The electrical behaviours of specific kind of organs and structures in human body provide crucial information about the workings of physiological level structures and mechanisms of certain diseases. For diagnosis regarding such structures, many imaging methods have been developed exploiting these behaviors. To do so, a good understanding of the electrical cell behavior is required. This report provides a theoretical background for the action potential behavior, using Hodgkin-Huxley's explanation and explains the methodology to create a simulation software that illustrates the generation and propagation of the action potentials.**

I. Intro

Hodgkin and Huxley [1] published a series of five paper in 1952 to explain the generation mechanism of the action potential by introducing their experimental setup and the method. The first paper focused on explaining how the nueron cells work. The second paper investigated the relationship between sodium ion concentration and the membrane voltage, also mentioning the action potential behavior. The third paper examined the effect of sudden conductance changes in the generation of the action potential. It was the fourth paper where Hodgkin and Huxley first explained the sodium inactivation phenomenon. In the last paper, the authors compiled their experimental results and came up with a formulation that explains the action potential generation process.

A. Voltage Clamp Experiment

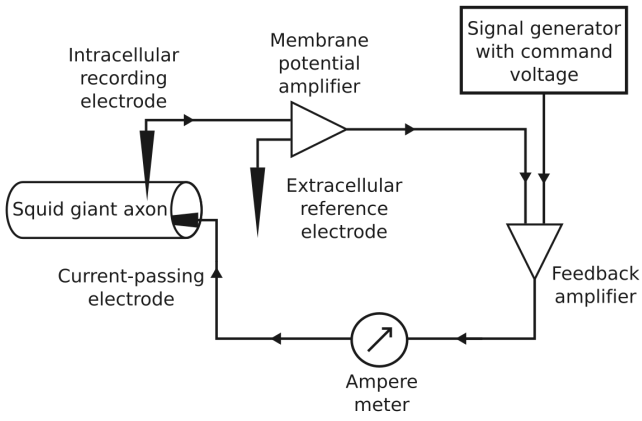

Fig. 1: Voltage Clamp Experiment Setup

Voltage clamp is an experimental setup to measure the ionic currents that produce the electrical behavior of the excitable cells. It utilizes an iterative feedback mechanism, and the corresponding circuit, to achieve the desired or set voltage level of the membrane potential. Keeping the equivalent circuit model Figure 2 and the equations governing the node voltage relations in this circuit, the researchers clamped the voltage at the Nernst potential and observed the transient and steady-state behavior of the resultant ionic currents. The measurement provided by these experiments paved the way to discovering the analytical relationship between cell membrane voltage and ionic conductances via curve fitting.

II. Theory

A. Mathematical Model

Conductance: The instantaneous conductances of different ion channels are calculated using the following relations:

$$g_{Na} = m^3 h \overline{g_{Na}} \tag{1}$$
$$g_K = n^4 \overline{g_K} \tag{2}$$
$$g_L = \overline{g_L} \tag{3}$$

The parameters that control the change of conductances in terms of deviation from membrane voltage, *i.e.* negative depolarization $V_{rest} - V_m$, are also expressed in first order linear differential equations of time as follows:

$$\frac{\partial n}{\partial t} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n \tag{4}$$
$$\frac{\partial m}{\partial t} = \alpha_m(V_m)(1-n) - \beta_m(V_m)n \tag{5}$$
$$\frac{\partial h}{\partial t} = \alpha_h(V_m)(1-n) - \beta_h(V_m)n \tag{6}$$

where V_m is the deviation.

Activation and Inactivation Parameters: The activation and inactivation parameters given in Equations (4) to (6) are formulated via curve fitting in Hodgkin and Huxley experiments. The resultans formulation are provided in Equations (7) to (12).

$$\alpha_n(V_m) = \frac{0.01(10 - V_m)}{e^{(1-0.1V)} - 1} \tag{7}$$

$$\alpha_m(V_m) = \frac{0.01(25 - V_m)}{e^{(2.5-0.1V)} - 1} \tag{8}$$

$$\alpha_h(V_m) = 0.07e^{(\frac{-V}{20})} \tag{9}$$

$$\beta_n(V_m) = 0.125e^{(\frac{-V}{80})} \tag{10}$$

$$\beta_m(V_m) = 4e^{(\frac{-V}{18})} \tag{11}$$

$$\beta_h(V_m) = \frac{1}{e^{(3-0.1V)} - 1} \tag{12}$$

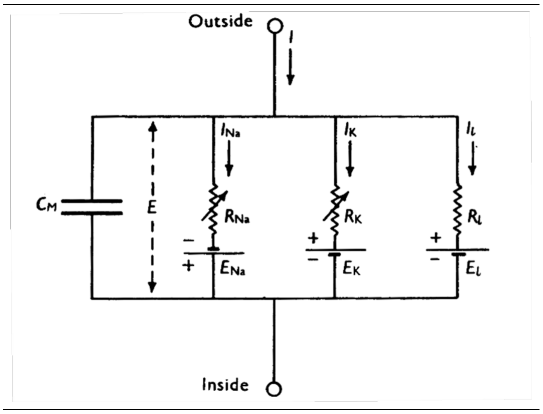

Fig. 2: Equivalent Circuit of Hodgkin and Huxley membrane model

Equivalent Circuit Model: Employing the node relations on the equivalent circuit, one can derive the relations given in Equations (13) to (17) for any time, hence any value of negative depolarization.

$$I_{Na} = g_{Na}(V_{membrane} - \mathcal{E}_{Na}) \tag{13}$$

$$I_K = g_K(V_{membrane} - \mathcal{E}_K) \tag{14}$$

$$I_{Cl} = g_L(V_{membrane} - \mathcal{E}_{Cl}) \tag{15}$$

$$I_{ionic} = I_{Na} + I_K + I_{Cl} \tag{16}$$

$$I_{Capacitive} = I_{total} - I_{ionic} \tag{17}$$

$$\Delta V_m = I_{Capacitive}(i)dt/C_m; \tag{18}$$

where I_{total} is the stimulation current applied to the cell.

1) Action Potential Propagation: In addition to the time behavior of an action potential on a single point, the behavior of the action potential progating on an axon is also important to have a complete understanding of space-time behavior of the action potentials. To derive the formulation that explains such a concept, one needs to model the patch of a membrane.

By using the model illustrated in Figure 3, Equation (19) can be derived.

$$\frac{\partial^2 V_m}{\partial x^2} = (r_i + r_e)i_m + r_i i_s \tag{19}$$

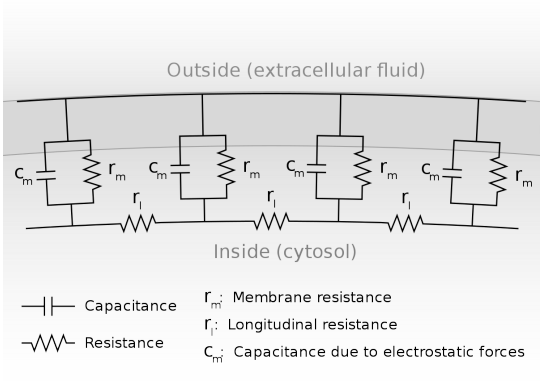

Fig. 3: Cable Model [2]

where i_m is the axial current defined from extracellular region to intracellular region and i_s in the input stimulation current.

Using the general cable equation defined in Equation (19), Equation (20) can be utilized to calculate the current along the entire axon given the stimulation current:

$$I_{total} = I_{stim} + \frac{\frac{\partial^2 V_m}{\partial x^2} + r_e I_{stim}}{2\pi a(r_i + r_e)} \tag{20}$$

In the numerical implementation, however, the second degree partial derivative term should be replaced with its numerical approximation:

$$\frac{\partial^2 V_m}{\partial x^2} = \frac{(V(x-1) - V(x)) - (V(x) - V(x+1))}{\Delta x^2} \tag{21}$$

B. Method

1) Implementation Environment: The software is developed in MATLAB R2022(The MathWorks, Inc., Natick, Massachusetts, United States) along with the graphical user interface. The user interface provides visualizations for selected state vectors along time and space depending on the simulation type. The pseudocode for the software developed is presented in Algorithms 1 and 2. The screenshots of the graphical user interfaces along with the default inputs that result in outputs that illustrate the main features are presented in Figures 4 and 5.

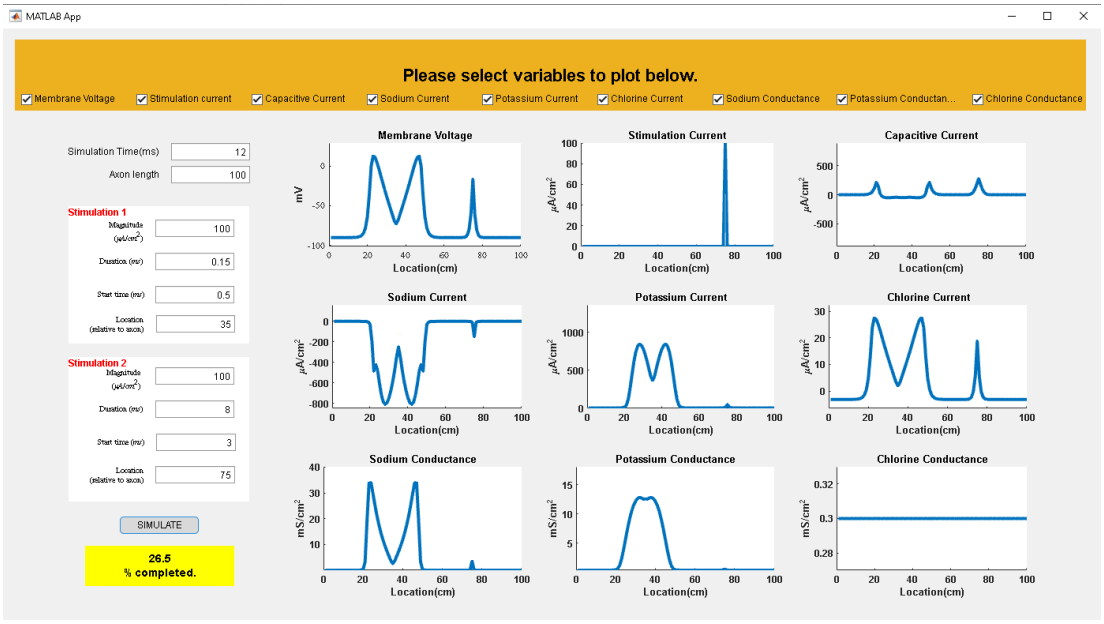

Fig. 4: Action potential propagation software GUI

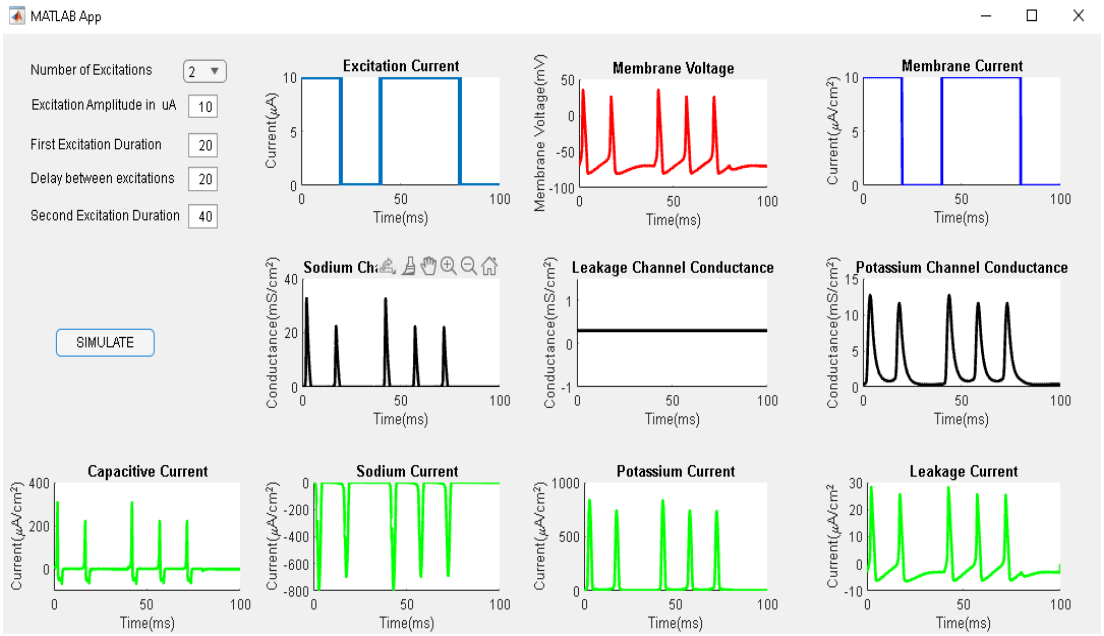

Fig. 5: Action potential generation software GUI

2) Generation: For the generation part of the algorithm, the time steps are discretized and the update equations are constructed utilizing the differential Equations (4) to (6) and (18).

Algorithm 1 Action Potential Generation

Input:#Stim,Duration,Amplitude
Output:Voltage, Current, Conductance

procedure HHITERATE($V_m{}^i$)
  Calculate membrane voltage ▷ $V_m = v_m + \Delta v_m$.
  Calculate $g(V_m)$ ▷ eqs. (1) to (3)
  Calculate ionic currents. ▷ eqs. (13) to (15)
  Calculate capacitive current. ▷ eqs. (16) and (17)
  Update ΔV_m ▷ eq. (18).
  Update m,n & h. ▷ eqs. (4) to (6)
  return $V_m{}^{i+1}$
end procedure

Ensure: $t_{stimulation} \leq t_{simulation}$
Assign cell parameters. ▷ $C_m, \overline{g}_{Na,K,Cl}, \mathcal{E}_{Na,K,Cl}$
Initialize state vectors. ▷ G, m, n, h
Assign initial values using $\alpha(0), \beta(0)$
Design stimulation vector. ▷ Use Δt
for $i = 1, i <= IterationSteps$ **do**
  $V_m{}^{i+1}$ = HHITERATE($V_m{}^i$)
end for
return V_m, g, I

3) Propagation: The stimulus, conductance and current vectors are now initialized in two dimensions, representing the time and 1 dimensional space that represents the axon axis. Using Equation (21), the current along the axis is calculated for every time step of the simulation and for each location, the `HHiterate` procedure defined in Algorithm 1 is called for the voltage update.

Algorithm 2 Action Potential Propagation

Input:#Stim,Duration,Amplitude, Axon Length
Output:Voltage, Current, Conductance

Ensure: $t_{stimulation} \leq t_{simulation}$
Assign cell parameters. ▷ $C_m, \overline{g}_{Na,K,Cl}, \mathcal{E}_{Na,K,Cl}$
Initialize state vectors. ▷ G, m, n, h
Assign initial values using $\alpha(0), \beta(0)$
Design stimulation vector. ▷ Use Δt
for t: simulation time step **do**
  for x: discretized locations along the axon **do**
    Calculate current using Equation (21)
    Employ `HHiterate` in Algorithm 1
  end for
end for
return V_m, g, I

To guarantee convergence, the mesh ratio defined in Equation (22) should be as small as possible:

$$meshratio = \frac{\Delta t}{r_i c_m \Delta x^2} \tag{22}$$

C. Results

In this section, some characteristic behaviors of the action potentials during their generation and propagations are replicated through the developed software and the corresponding visualizations are going to be presented to illustrate and explain the associated mechanisms.

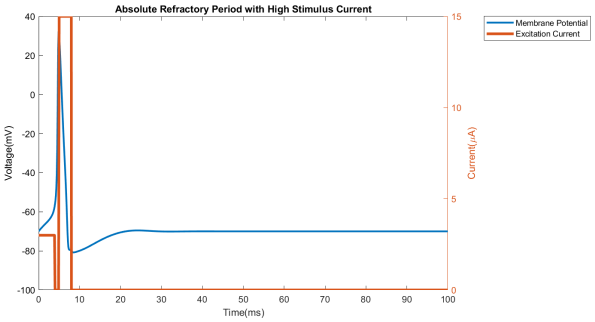

Fig. 6: Absolute refractory period

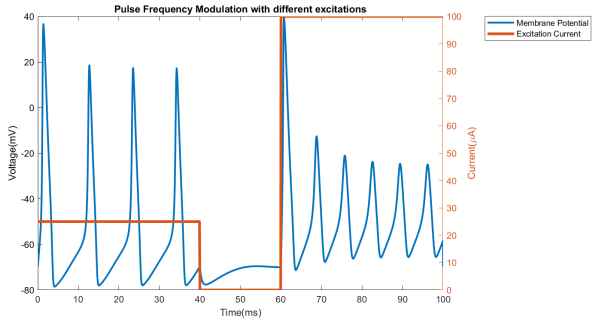

Fig. 7: Frequency modulation

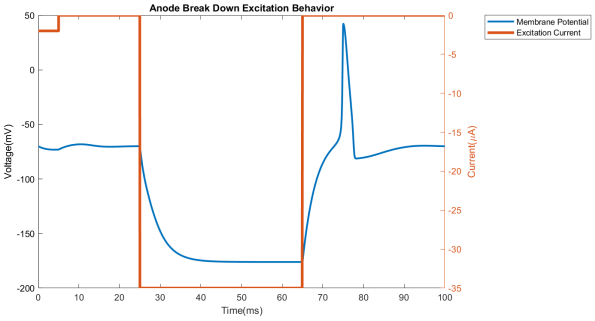

Fig. 8: Anode breakdown excitation

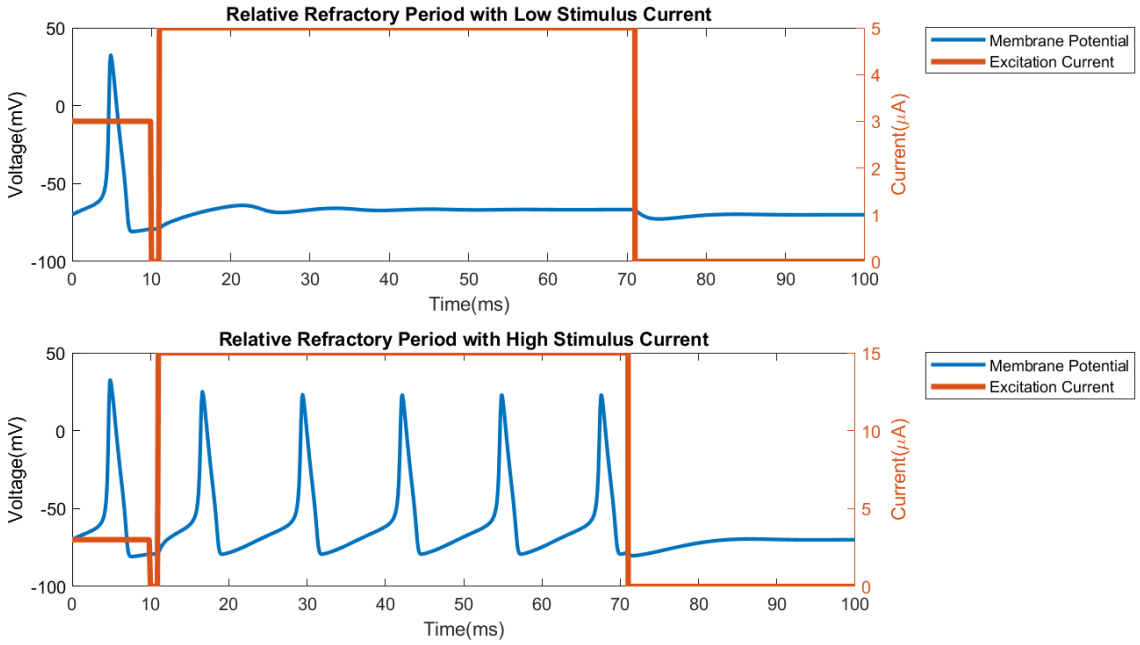

Fig. 9: Relative refractory period

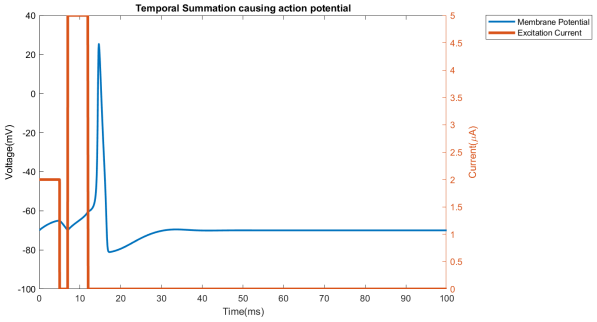

Fig. 10: Temporal summation

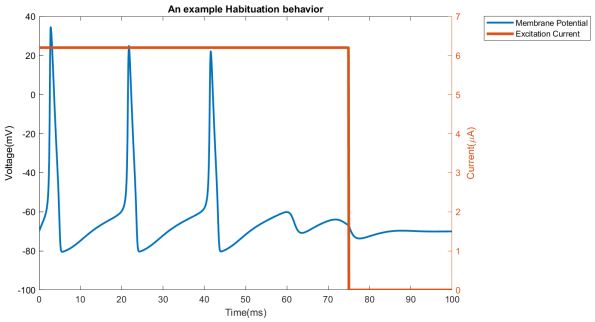

Fig. 12: Habituation

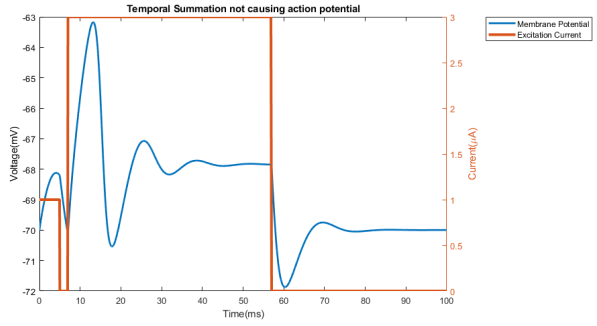

Fig. 11: Temporal summation under subthreshold condition

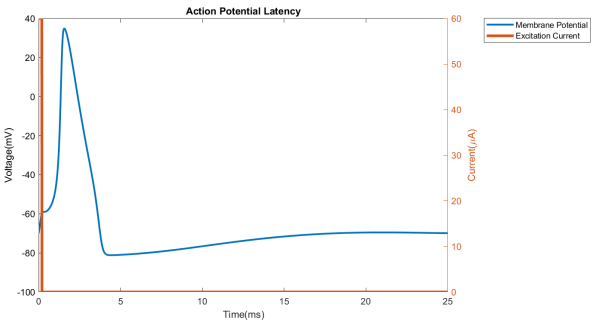

Fig. 13: Action potential latency

D. Discussion

1) Action potential threshold: According to Hodgkin Huxley model, the electrically active cells start to fire an action potential after the membrane voltage reaches to a specific value called **Threshold voltage**. To investigate the value of the threshold voltage that is indirectly defined by the ionic concentrations of the cell, a series of software experiments are done. In Figure 14, one can observe that the cell did not fire an action potential for a membrane voltage of -66mV. In the subfigure at the bottom, however, we observe that there is a sharp increase in the membrane potential starting from arond -65mV. Hence, it can be deduced that the threshold voltage is around -65 mV. It is important to note that the action potential generation does not stop even if the stimulus source is cut.

2) Absolute refractory period: The absolute refractory period is defined as the time period after the repolarization when the cell cannot be excited again even with an abnormally high stimulus current. In Figure 6, we apply a $3\frac{\mu A}{cm^2}$ stimulus for 5 milliseconds and observe that the action potential was fired. Shortly after that, in the repolarization phase of the cell, we again apply a stimulus, this time 5 times the magnitude of the first tone that started the action potential. However, at this time we observe that the cell did not fire an action potential. Hence, this region is in the absolute refractory period.

3) Frequency Modulation: Frequency modulation behavior is defined as higher number of action potentials with response to a higher stimulus at the same time period. In Figure 7, we see that two stimuli with amplitudes 25 and $100\frac{\mu A}{cm^2}$ are applied to the cell for 40 ms. The higher stimulus resulted in 6 action potentials whereas the lower stimulus caused cell to fire only 4 action potentials. With 4 times higher stimulus, the frequency of action potential generation increased by 50%.

4) Anode Breakdown Excitation: Anode breakdown excitation describes the action potential generation behavior when the cell returns back to its resting state after excited with a negative stimulation for a time period. In Figure 8, it can be observed that the cell is excited with -$2\frac{\mu A}{cm^2}$ stimulus for 3 milliseconds and the membrane voltage went a little lower than the resting potential. when -$35\frac{\mu A}{cm^2}$ was applied to the cell for 40 milliseconds, the membrane behaved like an RC circuit under subthreshold conditions and the membrane voltage asymptotically approached to approximately -180mV. When the stimulus is cut, the membrane voltage quickly returns to its resting value, however, it overshoots the threshold voltage while doing so. Hence, we observe an action potential generation after the membrane voltage reaches threshold voltage.

5) Relative refractory period:

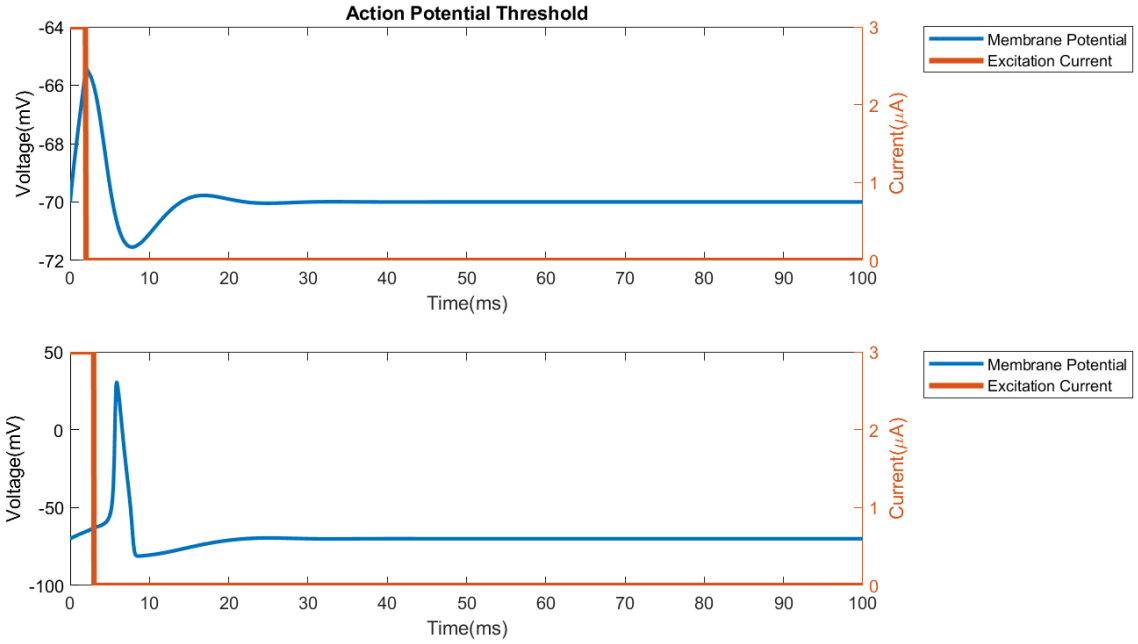

Fig. 14: Action potential threshold

References

[1] A. L. Hodgkin and A. F. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve," *The Journal of physiology*, vol. 117, no. 4, p. 500, 1952.

[2] [Online]. Available: https://en.wikipedia.org/wiki/Cable_theory.