Effects of Ion Channel Currents on Induced Action Potentials*

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Abstract—With development of electric devices, continuous exposure of electromagnetic (EM) fields to human bodies has become great concerns. Despite our interest, their effects on human bodies have not been well-determined. We have an interest in the non-thermal effects of the EM fields on neurons and attempt to establish a scientific explanation. Elucidation of the EM effects on neurons could allow us to make use of the induced current for spike initiation.

As the first step toward understanding the connection between the applied current and the triggering action potentials, we simulated how the generated action potential would change depending on the applied current using a fundamental mathematical model on a simple geometry. Five periodic waves having different shapes were used as the applied current. Analysis showed that not only how the current increased the value but also how it decreased the value was important. We also concluded that the sine wave would be the best as the applied current among the five to generate action potentials.

I. INTRODUCTION

We are continuously exposed to electromagnetic (EM) fields generated by electronic devices; therefore the effects of EM waves on human bodies are of great interest. Although no definitive evidence has been found, it is generally considered that exposure to low energy EM waves could be a risk to human health [1]. In spite of the concern, some beneficial effects were also reported [2], which inspired us to understand the biological process of the EM effects on the brain. The non-thermal effects caused by extremely low-frequency EM fields are of our interest.

Our goal is to establish a scientific explanation for how and why neurons and networks can function as EM receivers and demodulators for given EM transmitter characteristics. The EM waves generated near the head penetrate the skull and reach neurons in the brain. It is considered that the current induced by the EM fields could stimulate neurons and generate the action potentials. Thus if the mechanism of the EM effects on the neuronal network is elucidated, we could make use of the induced current to fire action potentials, and this could enable scientists to invent treatments of new types in the future.

As the first step, we implemented simulation to discover the relationship between the applied current and the triggered action potentials using a fundamental mathematical model on a simple geometry. We explored what type of current would be the best to apply to generate action potentials. The membrane potential was computed with five different types of alternating current as the applied current, and the results were compared and analyzed to determine which type of current could be used in practice. Analysis indicated that not only the increase but also the decrease of the applied current plays an important role and that the sine wave would be the best to use as the applied current on the simulation.

II. METHOD

In order to determine which type of wave would be the best to apply to generate action potentials, we explored the relationship between the applied current and the resulting action potentials by simulation. There are quite a few different mathematical descriptions for neural behavior; for example, models based on the integrate-and-fire model and the Hodgkin-Huxley (HH) type models. Which model to use depends on what we need to do [3]. Since we like to know the fundamental mechanism of the biological behavior of neurons, we chose the HH model [4] because it describes the physiological process. The equations of the model are presented in Appendix A. The simulation was done using this mathematical model on a simple geometry, just a single soma, and simulator called NEURON (www.neuron.yale.edu).

For applied current $I_{\text{app}}$, five periodic alternating currents having the same cycle were used. We call the number of cycles per second fundamental frequency here; that is, the cycle and fundamental frequency are reciprocal.

In order to observe what the sufficient value to trigger spikes, we first considered as the applied current a step

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Fig. 1. Example of five waves used for the applied current; sine (red), sawtooth (blue), reverse sawtooth (magenta), triangle (green), and square (cyan) waves. The amplitude and fundamental frequency are 6.5 $\mu$A/cm$^2$ and 20 Hz, respectively.
function increasing the value from \( I_1 \) to \( I_2 \) at time \( t_0 \geq 0 \), that is,

\[
I_{\text{app}} = \begin{cases} 
I_1 & (t < t_0) \\
I_2 & (t \geq t_0) 
\end{cases} .
\tag{1}
\]

In [5], it is shown that whether firing occurs or not depends on not only \( I_2 \) but also the step size \( \Delta I = I_2 - I_1 \); even though \( I_2 \) is large enough to trigger a spike, if \( \Delta I \) is small, then the action potential occurs only once. To have repetitive firing, it is concluded that \( I_2 > 6 \) (\( \mu A/cm^2 \)), and the graph presented in [5] shows that \( \Delta I = 2 \) (\( \mu A/cm^2 \)) is sufficient enough for continual action potential.

We simulated the membrane potential changing \( I_1 \) and \( I_2 \). We first increased \( I_2 \) starting from 0.5 at the rate of 0.5; on the other hand, \( I_1 \) was fixed to 0. Then we increased \( I_1 \) at the rate of 0.5 with fixed \( I_2 \).

Next, we explored how different the simulated membrane potentials were if the applied current had different types of waveform. Five commonly used alternating currents were selected for this purpose; sine, sawtooth, reverse sawtooth, triangle, and square waves. We compared the resulting membrane potentials, which were computed with those five waves having the same amplitude and fundamental frequency, i.e., the same cycle of a period. Each current was applied for 150 milliseconds (msec), between 100 and 250 msec; as an example, the five waves with amplitude 6.5 \( \mu A/cm^2 \) and fundamental frequency 20 Hz (50 msec per cycle) are presented in Fig. 1.

III. RESULTS AND DISCUSSION

Simulation results using the step function defined by equation (1) showed that the repetitive action potentials did not occurred until \( I_2 = 6.5 \) with \( I_1 = 0 \), and this result can be considered to be consistent with what is determined in [5], i.e., \( I_2 > 6 \). With fixed \( I_2 = 6.5 \), \( \Delta I = I_2 - I_1 \) needed to be 2 or larger for repetitive firing, which also agreed with the results presented in [5]. The simulation results indicated that two things were required for the applied current in order to have a periodic spike train; adequate strength and sufficiently large increase. From these results, two different amplitudes were selected for the next simulation using periodic waves. One was 6.5 \( \mu A/cm^2 \), which was the minimum value of \( I_2 \) to generate repetitive firing. The other was the half of this amplitude, 3.25 \( \mu A/cm^2 \), which is large enough for \( I_2 \) with \( I_1 = 0 \) to have a single spike.

Fig. 2 shows how the number of the spikes changed as the fundamental frequency of the waves increased. As expected, the higher amplitude triggered more spikes; however, it should be noted that the double amplitude did not yield the double number of the action potentials. As we can guess from the relationship between the number of spikes and the fundamental frequency, only one spike was generated at a cycle for all the waves except the square wave with amplitude 6.5 \( \mu A/cm^2 \) and fundamental frequency 10 and 20 Hz.

For amplitude 3.25 \( \mu A/cm^2 \) and fundamental frequency 10 Hz, only the reverse sawtooth and square waves generated action potential (Fig. 2a). These two waves are the only ones among the five that have upward steps; in other words, each cycle had the time point where they instantly changed the value from the minimum to the maximum. It can be inferred that these steps worked as the initiator of an action potential; we can therefore consider that the speed of increasing the value played an important role.

Despite this observation, Fig. 2 shows that the reverse sawtooth wave did not perform as well as the sine or triangle waves when the fundamental frequency became larger. We assumed that this occurred owing to either the frequency components of these waves or the way of decrease of the value. To consider the possibility of the former case, the circuit of the linearized HH equations (Appendix B) was considered. The impedance \( Z_{Na} \) and \( Z_K \) corresponding to the \( Na^+ \)- and \( K^+ \)-channels respectively are written with resistance \( R_K, R_{KNa}, R_{Na}, R_{NaNa}, R_{NaL} \) and conductance \( L_{Kn}, L_{NaNa}, L_{NaL} \) as follows:

\[
\frac{1}{Z_{Na}} = \frac{1}{R_{Na}} + \frac{1}{R_{NaNa} + \frac{L_{NaNa}}{dt}} + \frac{1}{R_{NaL} + \frac{L_{NaL}}{dt}} .
\]

\[
\frac{1}{Z_K} = \frac{1}{R_K} + \frac{1}{R_{KNa} + \frac{L_{KNa}}{dt}} ,
\]

The linearized HH model is therefore expressed as the
The equivalent circuit and its amplitude response function are shown in Fig. 3. The amplitude response function for the reverse sawtooth wave is shown in Fig. 4. As the fundamental frequency became larger, the time of the peak of the action potential exponentially got smaller for the sine and triangle waves. On the other hand, linear increase was observed for the reverse sawtooth wave, although the slope was very gentle. These results show that for the sine and triangle waves, the higher the fundamental frequency, the shorter the period between the time when a cycle of the wave started and a spike was triggered. In other words, if multiple cycles of the waves were applied, the sine and triangle waves had the longer time period from the peak of the action potential to the beginning of the next cycle of the wave than the reverse sawtooth wave did. Considering that the membrane needs to have enough time to recover for the next spike, it was natural that the sine and triangle waves should show better performance than the reverse sawtooth wave. We showed only the case for amplitude $A = 3.25 \, \mu A/cm^2$ here, but the similar trends were observed for the amplitude of $6.5 \, \mu A/cm^2$.

At the end, we briefly mention the relationship between the amplitude and frequency of the sine wave. Fig. 6 shows the number of the spikes against the amplitude for the sine waves with frequencies between 40 and 120 Hz. These graphs illustrate that the number of the spikes did not change much or at all after a certain value of the amplitude. As we mentioned before, generally only one or no spike occurred at each cycle of the waves; thus thinking of the recovery time discussed above, this is natural.

**IV. CONCLUSIONS**

We should note that linearization presented in the previous section has a drawback; if the terms higher than the first-order, which were not taken into consideration due to linearization, have big contribution to the biological process, then the results following from the circuit are not appropriate for the analysis. Actually, simulations with the linearized
model did not produce action potentials. The shape of the resulting potential was similar to that of applied current; for example, if the applied current was the sine wave shown in Fig. 1, then the simulated potential became periodic with three cycles. Therefore, it remains uncertain how much the frequency components contribute to generation of spikes; however, it is clear that the slopes of the applied current have a great impact.

We saw that the square wave triggered the most number of spikes among the five waves, and the second best was the sine wave when the amplitude and the fundamental frequency were the same. A square wave is theoretically expressed as the infinite sum of sine waves having different frequencies, which means in practice, more work is required to generate than a sine wave. On the other hand, the difference of the number of triggered spikes was generally not very large as shown in Fig. 2. We can therefore consider that sine wave is the best to use as the applied current with the original HH model on the simple geometry.

The HH model we used here had been developed based on experimental results at temperature 6.3°C; however, the actual temperature of the human body is much higher. Also only one potassium and sodium channels are taken into consideration in the model. Therefore, we should consider using a physiologically more realistic model next.

Another issue is the geometry; the results shown here are only from a single soma, so the outcomes may not be directly applicable to simulations with multiple neurons or a network of neurons. Thus it is required to expand to a larger scale of environment before we move on to the experimental work.

The optimized induced current could be used to fire action potentials. Thus if we clarify the biological process of the EM effects on neurons, that could potentially help development of new types of treatment in the future; for example, invention of a nanomachine which stimulates the region of the brain malfunctioning owing to a neurodegenerative disease from the outside of or inside the body and reconstruct the network [6]. Elucidation of the mechanism of the neuronal network could enable scientists to develop such methods for treatment.

APPENDIX

A. Hodgkin-Huxley Model

The HH model is defined as the following system of ordinary differential equations:

\[
\begin{align*}
C_m \frac{dV}{dt} &= -I_{Na} - I_K - I_L + I_{app}, \\
\frac{dx}{dt} &= \alpha_x(1 - x) - \beta_x x \quad (x: m, h, n),
\end{align*}
\]

where

\[
\begin{align*}
I_{Na} &= g_{Na} m^3 h (v - v_{Na}), \\
I_K &= g_K h^4 (v - v_K), \\
I_L &= g_L (v - v_L),
\end{align*}
\]

and \(I_{app}\) is the applied current. Functions for \(\alpha\)'s and \(\beta\)'s are:

\[
\begin{align*}
\alpha_m &= \frac{2.5 - 0.1v}{e^{2.5-0.1v} - 1}, \\
\alpha_h &= 0.07e^{-0.05(v-54)}, \\
\alpha_n &= 0.1 - 0.11v, \\
\beta_m &= 4e^{-v/18}, \\
\beta_h &= \frac{1}{e^{3-0.1v} + 1}, \\
\beta_n &= 0.125e^{-v/80},
\end{align*}
\]

and \(g_{Na} = 120, g_K = 80, g_L = 4.3, C_m = 1\). Potential \(v\) is shifted from the membrane potential by the equilibrium potential -65 mV so that the resting potential will be at \(v = 0\). The equilibrium potentials for the leakage, \(Na^+\), and \(K^+\) channels are also shifted, i.e., \(v_{Na} = 115, v_K = -12,\) and \(v_L = -10.6\).

B. Linearization of \(Na^+\) and \(K^+\) Ionic Currents

We consider small variations of \(\delta I_{Na}\) and \(\delta I_K\) around the resting potential \(v_r = 0\) for \(I_{Na}\) and \(I_K\), respectively. If we linearize equations (2) and (3) around \(v_r\), so ignoring the terms higher than the first-order, we obtain the following equations [7][8]:

\[
\begin{align*}
\delta I_{Na} &= \left( \frac{1}{\bar{g}_{Na}} m^3(v_r) \cdot h(v_r) \right) \cdot \delta v, \\
\delta I_K &= \left( \frac{1}{\bar{g}_K} n^4(v_r) \right) \cdot \delta v, \\
\end{align*}
\]

where

\[
\begin{align*}
G_{Na1} &= 3\bar{g}_{Na} \cdot m^2(v_r) \cdot h(v_r) \cdot (v_r - v_{Na}), \\
G_{Na2} &= \bar{g}_{Na} \cdot m^3(v_r) \cdot (v_r - v_{Na}) \cdot \gamma_m(v_r), \\
G_K &= 4\bar{g}_K \cdot n^3(v_r) \cdot (v_r - v_K) \cdot \gamma_n(v_r), \\
\end{align*}
\]

with \(\gamma_x(v_r) = \alpha_x(v_r) - \chi_x(v_r) \cdot (\alpha_x(v_r) + \beta_x(v_r)) \quad (x: m, h, n).

REFERENCES