Computational Modeling of Thermal Effects in Optogenetic Neurostimulation

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ABSTRACT— Optogenetics is an advanced optical tool in neuroscience research. However, light stimulation in optogenetic experiments may also affect neural function by generating heat. In this paper, the effect of increasing the temperature of the brain tissue was studied during light stimulation. The Hodgkin-Huxley model and the hippocampal pyramidal cell model have been used to investigate the effect of temperature on spike neurons. The modeling results show that irradiation of brain tissue by pulsed laser with a frequency of 40 Hz, the duty cycle of 90% and wavelength of 593 nm at a distance of 10 µm from the tip of the fiber, for 60 seconds with a power of 1 and 40 mW leads to the temperature change from 37 °C to 39 °C. The obtained results show that the laser intensity decreases to zero at a distance of 1 mm from the tip of a fiber, which is absorbed by the tissue and causes a temperature rise of 2 °C that can increase the spike rate of neurons by 16.6%.

KEYWORDS: Hodgkin and Huxley model, Optogenetic, Photocycle model, Spike, Temperature.

I. INTRODUCTION

Optogenetics is a combination of optical systems and genetic engineering technologies. In optogenetic studies, light-sensitive proteins called opsin are produced on neural cells by gene manipulation. These light-sensitive ion channels are open and close in a specific light wavelength. In neural networks, each neuron has a spike when its membrane potential exceeds a threshold. In optogenetics, the most popular opsin is ChR2, activated by blue light and allows sodium ions to pass through the nerve channels. High-intensity light used to stimulate opsin, may raise the temperature and cause problems. The temperature of the tissue increases, which may damage the brain tissue or the increase in temperature affects the performance of neuronal activity. Therefore, temperature can be a suitable candidate for neuronal stimulation. Also, an increase in temperature can increase the spike rate of a group of neurons, while the same increase in temperature can decrease the spike rate of another group of neurons. Therefore, predicting the spatial intensity and extent of any temperature increase during optogenetic stimulation is particularly important. This paper investigates the effects of heat transfer due to light stimulation on brain tissue. Then, the activity of neural cells was modeled using the thermal effects of light diffusion in the brain tissue.

II. PHYSICS OF LASER INTERACTION WITH BRAIN TISSUE

In optogenetics, optical fiber is used to deliver light to the desired area in the tissue, which is placed in the target area inside the brain tissue through surgery [1]. In this paper, MATLAB software has been used to model light absorption in the tissue's depth. The value of transmittance, T, is obtained through Eq. (1) by considering the effects of light absorption and scattering [1]:

$$T = \frac{b}{a\ \sinh(bd\mu s)\ +\ b\ \cosh(bd\mu s)} \tag{1}$$

Constant values a, and b can be obtained as:

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$$a = 1 + \frac{\mu a}{\mu s} \tag{2}$$

$$b = \sqrt{a^2 - 1} \tag{3}$$

where μ_a and μ_s are the absorption coefficient, and Mie scattering coefficient, respectively. The geometric loss, g_{loss}, which indicates the scattering of light in the tissue at a distance d from the tip of the fiber, is obtained as [1]:

$$g_{loss} = \frac{\rho^2}{(d + \rho)^2} \tag{4}$$

where r represents the fiber optic radius, and ρ is defined as:

$$\rho = r\sqrt{\left(\frac{n_t}{NA_{fib}}\right)^2 - 1} \tag{5}$$

where n_t is the refractive index of Texture and NA_{fib} is the Numerical aperture of fiber optic, which in modeling are equal to 0.2 mm, 1.36, and 0.48, respectively. Studies show that in mammalian brain tissue, the effects of scattering are much greater than those of absorption [2], so normal light intensity, I_N, is obtained as:

$$I_N = \frac{I(d)}{I(d=0)} = g_{loss}.T \tag{6}$$

The light intensity at the tip of the fiber $I(d=0)$ is calculated as:

$$I(d=0) = \frac{P}{A\eta} \tag{7}$$

power of the light source is denoted by P, and η is the coupling efficiency between light and optical fiber. Therefore, the desired intensity at a certain depth in the tissue is obtained as:

$$I(d) = I(d = 0)\ \mathrm{I}_N \tag{8}$$

Also, the bio-heat equation can be used to measure the amount of heat in brain tissue resulting from photon absorption and the phenomenon of metabolism :

$$\rho C_\rho \frac{\partial T}{\partial t} - \nabla(k\nabla T) + \rho_b \omega_b C_b (T - T_b) = Q \tag{9}$$

where ρ indicates density, C_p specific heat, and k represents the thermal conductivity of brain tissue. Blood density is denoted by ρ_b, C_b is the specific heat of blood, ω_b is the blood perfusion, T is brain temperature, and T_b is blood temperature. The parameters related to the above relations are considered according to [2].

III. Physics the Effect of Temperature on the Spike Rate of Neurons

The Hodgkin-Huxley model investigates how action potentials initiate and propagate in neurons. In this model, the lipid bilayer is represented as a capacitance. Voltage-gated ion channels are represented by electrical conductances that depend on voltage and time. Neural ion channels can control the membrane current, including sodium, potassium, and leaky ion channels.

The probability of opening and closing ion channels is given by the values of m, n, and h [3]:

$$i_m = C_m \frac{\partial V_m}{\partial t} + g_{Na+} m^3 h (V_m - E_{Na+}) + g_{K+} n^4 (V_m - E_{K+}) + g_l (V_m - E_l) = C_m \frac{\partial V_m}{\partial t} + i_{Na^+} + i_{K^+} + i_l \tag{10}$$

Time-dependent and voltage-dependent ion channels are denoted by g_n, and leaky channels are denoted by linear conduction of g_L, membrane potential by V_m, and capacitor membranes by C_m. where i_m is the total membrane current per unit area and i_l denotes the leakage current. i_{Na+} and i_{K+} are fast transient sodium and persistent potassium current, respectively.

Temperature affects the maximum conductivity and the rate of opening and closing of ion channels. Usually, a mathematical content called the Q_{10} factor is used to consider the

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effects of temperature on neural activity, which is defined as [4]:

$$Q_{10}(T,a) = a^{\frac{T-T_0}{10}} \tag{11}$$

where T_0 indicates the reference temperature, which is considered 37 °C. The effect of temperature on the gating kinetics is more significant than on maximum channel conductivity. Therefore, to investigate temperature in the Hodgkin- Huxley model, in Eq. (10), the gate kinetics are multiplied at Q_{10} by a factor of a=3, while the maximum channel conductivity, g_s, is multiplied at Q_{10} by a factor of a=1.5 [5]. If opsin is expressed in the neuron, the light-sensitive channel is added, as shown in Fig. 1.

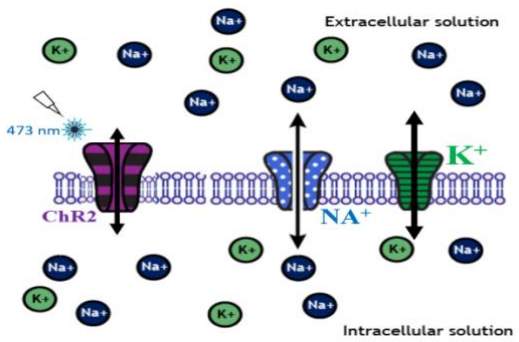

Fig. 1: Schematic of ion channels.

The light-induced changes in the electrical properties of the channels upon opening can be modeled as a four-state photocycle consisting of two closed states (C_1 and C_2) and two light-induced open states (O_1 and O_2) as shown in Fig. 2. Light-sensitive ion channel current, I_{chR2}, is obtained through the four-state model of the photon cycle which is also added to Eq. (10). The action potential at different temperatures can be investigated as:

$$C_m \frac{dV}{dt} = -(Ii + I_{ChR2}) \tag{12}$$

where I_i is the total membrane current of the cell, V is membrane potential, and C_m is the membrane capacitance.

ChR2 molecules are initially in the closed C_1 state, then go to the open state, O_1, upon light irradiation. As the radiation continues, they go to the open state O_2, which has lower conductivity than O_1, or switch to C_1 [6].

After that, they either go to O_1 or C_2 again, and when the light turns off, they slowly return to C_1. This process can be described through the following set of rate equations[7]:

$$\begin{aligned}
\frac{dC_1}{dt} &= G_r C_2 + G_{d1} O_1 - K_1 C_1 \\
\frac{dO_1}{dt} &= K_1 C_1 - (G_{d1} + e_{12}) O_1 + e_{21} O_2 \\
\frac{dO_2}{dt} &= K_2 C_2 - (G_{d2} + e_{21}) O_2 + e_{12} O_1 \\
\frac{dC_2}{dt} &= G_{d2} O_2 - (K_2 + G_r) C_2
\end{aligned} \tag{13}$$

where $C_{(1,2)}$ and $O_{(1,2)}$ are the closed and open state probabilities, such that $C_1+C_2+O_1+O_2=1$. G_r, $Gd_{(1,2)}$, $K_{(1,2)}$, e_{12} and e_{21} correspond to the transition rates between open and closed states.

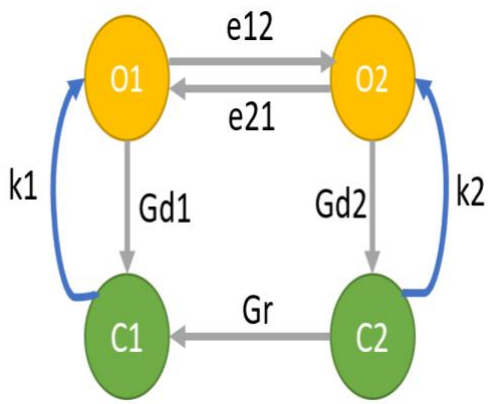

Fig. 2. The ChR2 is modeled as a four-state photocycle.

The light-assisted transitions $K_{(1,2)}$ represents activation of $C_{(1,2)}$ and are described by [8]:

$$K_{(1,2)} = \varepsilon_{(1,2)} FU \tag{14}$$

where F is the photon flux, and ε is the quantum efficiency of retinal photon absorption in C_1 or C_2. U is the state-dependent activation function related to the non-instantaneous response of retinal to light described as:

$$\frac{dA}{dt} = \frac{\left(S_0(\theta) - U\right)}{T_{ChR2}} \tag{15}$$

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where T_{ChR2} is the time constant for activation and $S_0(\theta)$ is the sigmoidal function that calculated as:

$$S_0(\theta(t)) = 0.5\{1+\tanh[120(\theta(t)-0.1)]\} \quad (16)$$

and the laser radiation pattern, $\theta(t)$, is defined by the Heaviside function:

$$\theta(t) = \sum_i \Theta(t-t_{on}) - \Theta(t-t_{off}) \quad (17)$$

The experimentally measured photocurrent entering the neuron membrane from this light-activated ion channel is given as [8]:

$$I_{ChR2} = g_{ChR2}(O_1 + \Upsilon O_2)(V - E_{ChR2}) \quad (18)$$

where g_{ChR2} is the maximal conductance of ChR2, V is the neuron membrane potential, E_{ChR2} is the reversal potential, and γ measures the relative contribution of the two open states to the total conductance of the channel. To investigate the temperature, similar to ion channels, Q_{10} is multiplied at gate kinetics and maximum channel conductivity of the light-sensitive channel. The action potential of neurons has been simulated using the Hodgkin-Huxley model and the four-state model of the photon cycle in Comsol software. The parameters related to the above relationships are considered according to [8].

IV. Results and Discussion

Figure 3 shows the obtained results for the light intensity at a certain depth in the tissue according to Eq. (8). Considering the intensity of 10 mw/mm^2, which is a suitable intensity for stimulating cells and is shown as a dashed line in Fig. 3, it can be seen that the desired distance from the fiber tip is 0.39 mm for ChR2 activation. These results show that only neurons in the vicinity of the fiber are affected by light stimulation, and the light intensity at a distance of 1 mm from the fiber tip tends to be zero.

Figure 4 shows the rise in temperature through Comsol software for a distance of 10 μm from the fiber tip using Eq. (8) and Eq. (9), and it shows that using a 593 nm laser with a power of 40 mW for 60 seconds, can increase the tissue temperature by 2 °C.

Figure 5 shows a typical response of a neuron with optogenetic cell stimulation. As can be seen, changing the laser frequency from 10Hz to 40Hz, with an intensity of 40 mW/mm^2 can increase the spike rate by 33.3%.

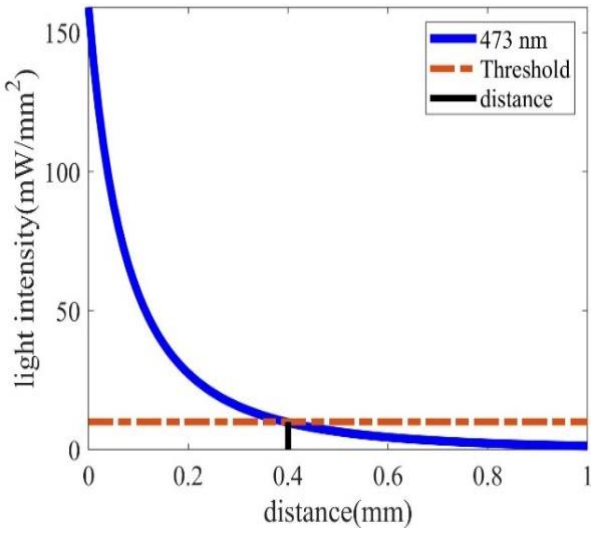

Fig. 3. The light intensity in the depth of the texture for blue light.

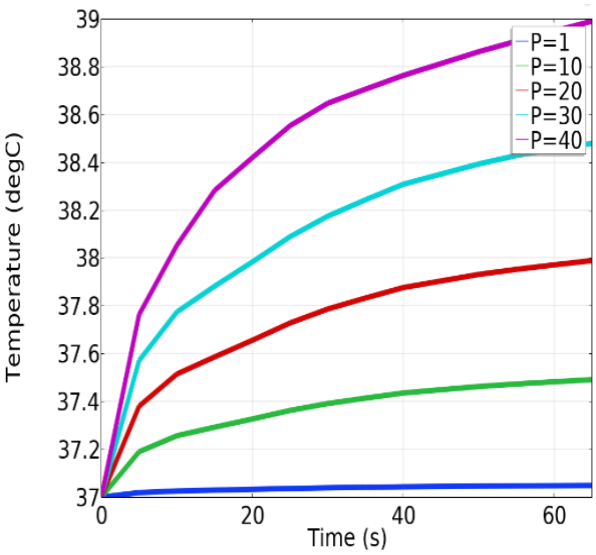

Fig. 4. Temperature variations for the 593 nm wavelength.

But changing the temperature, without considering the optogenetic effect, can also change the spike rate of neurons. As a result, to model the spike of neuron, the light-sensitive ion channel current in Eq. (18) must be added to other currents in Eq. (10), Then, by obtaining the value of the action potential using Hodgkin-Huxley's equations, the spike rate of neurons

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can be checked. Membrance potential (V_m) and neural spike rates are investigated at 37 °C and 39 °C in Fig. 6.

Figure 6 shows that by increasing the temperature of 2 °C in the brain tissue using 40 mW laser illumination at 593 nm, a pulsed laser at 40 Hz and 90% duty cycle, and at 10 µm distance from the center of the fiber tip, the spike rate increased by 16.6% compared to the brain temperature at 37 °C.

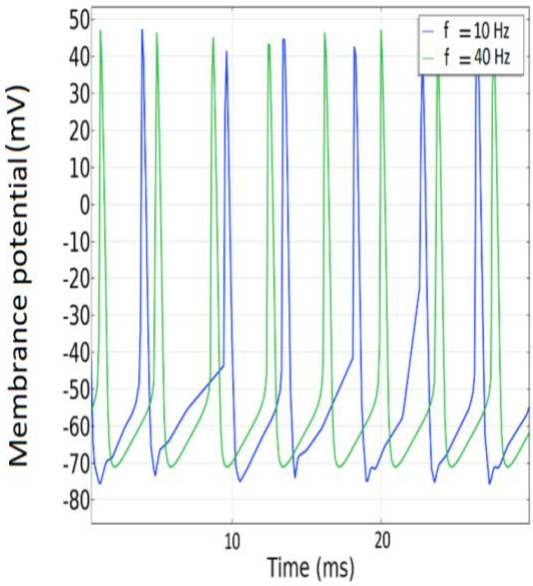

Fig. 5. The response of the neuron with light-sensetive channel, ChR2, in optogenetic studies to laser light irradiation with frequency of 10Hz and 40Hz.

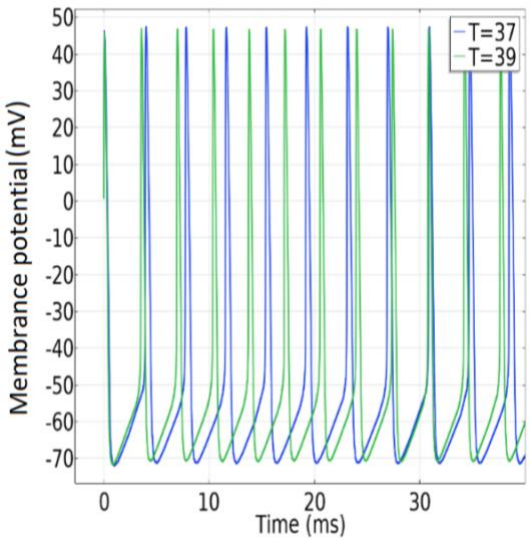

Fig. 6. Action potential at 37 °C and 39 °C.

Temperature changes the action potential of neurons by affecting the maximum conductivity and the rate of opening and closing ion channels [5].

Therefore, due to the diversity of ion channels in different neurons, the effect of temperature on neurons is different. An increase in the temperature in some neurons increases the spike of that neuron, while the same increase in temperature in other neurons can prevent the spike from firing.

For example, the temperature has a different effect on cortical neurons and Hippocampus CA1 neurons shown in Fig. 7.

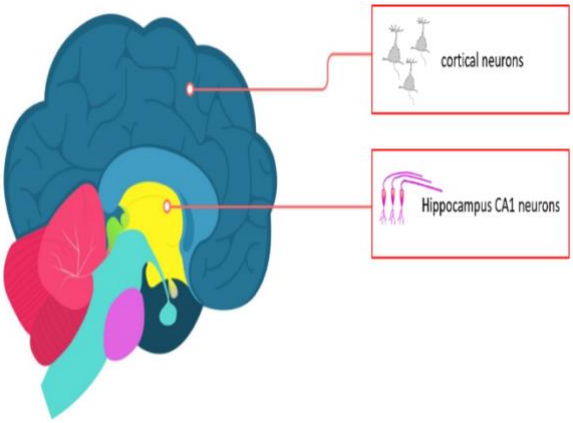

Fig. 7. Schematic of cortical neurons and Hippocampus CA1 neurons.

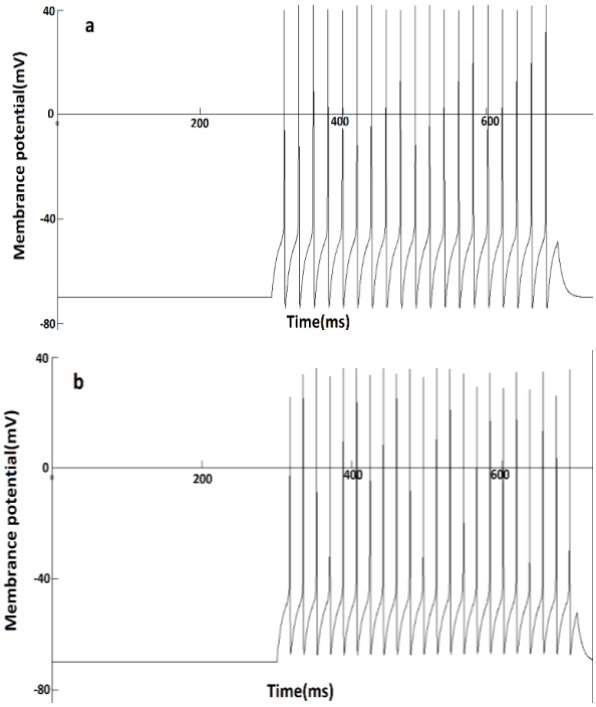

Fig. 8. Action potential of cortical neurons (a) at 37 °C and (b) at 39 °C.

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As shown in Fig. 8(a) and 8(b), increasing the temperature from 37 °C to 39 °C can increase the spike rate of the cortical neurons by 15.7% obtained through NEURON simulation.

While an increase in the temperature suppresses the spikes of some Hippocampus CA1 neurons, as shown in Fig. 9(a) and 9(b). Therefore, increasing the temperature by 2 °C will decrease their spike rate by 20%.

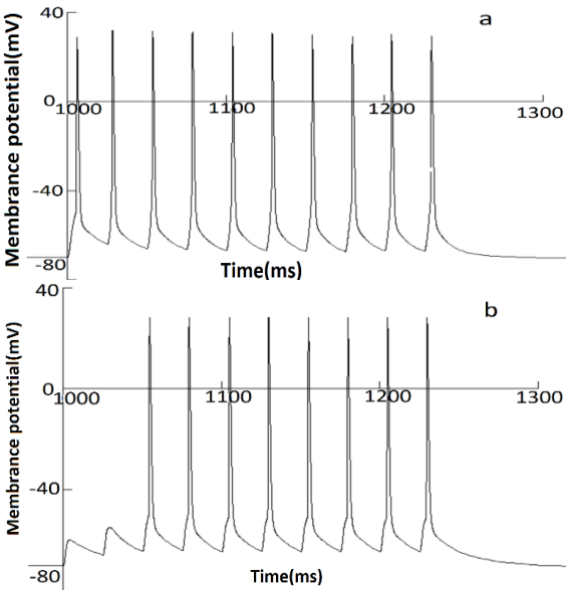

Fig. 9. Action potential of Hippocampus CA1 neurons (a) at 37 °C and (b) at 39 °C.

Therefore, in future studies, the effect of temperature on different neurons should be studied according to the diversity of ion channels.

V. Conclusion

Using high-intensity light for optogenetic stimulation can raise the temperature. In this article, it was observed that increasing the temperature by 2 °C by a pulsed laser with a frequency of 40 Hz and a duty cycle of 90%, at a distance of 10 μm, changes the spike rate from 250 Hz to 300 Hz. In this paper, homogeneous absorption coefficients are used for a given wavelength, but light is unevenly absorbed in the brain. As a result, the effect of temperature on different areas of the brain should be investigated according to the anisotropic absorption coefficients and the spatial distribution of blood vessels in the brain. Also, in optogenetic studies, it is necessary to choose the radiation pattern in a way that does not lead to temperature changes in brain tissue so as not to disrupt the neural signal process caused by light stimulation.

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