Simulation of voltage-gated ion channels behavior during infrared neural inhibition (INI)

Hassan Tajarehnejad Abdollahi and Mohamamd Ali Ansari*

Laser and Plasma Research Institute, Shahid Beheshti University, Tehran, Iran
***Corresponding author email: m_ansari@sbu.ac.ir**

Received:Jan. 16, 2023, Revised: Mar. 2, 2023, Accepted: Mar. 4, 2023, Available Online: Mar. 13, 2023
DOI: 10.30495/ijbbe.2023.1977865.1020

ABSTRACT— Infrared (IR) radiation is a non-invasive method to reduce neural responses, while its mechanism is still unclear. Here, using the modified Hodgkin-Huxley model, the effects of IR light on the parameters participating in the action potential (AP) blocking are investigated to study the mechanism of infrared neural inhibition (INI). Considering the temperature dependence neural model, the voltage membrane changing, ion currents variation and ion channels activation/inactivation gates behavior under IR pulses are studied. The results show that IR pulses can successfully block APs and confirm that potassium ion currents have an influential role in suppressing APs. Moreover, it is shown that infrared light during the suppression of AP has little effect on increasing the sodium ion currents. However, it seems that sodium ion channel gates play an effective role during INI. It is observed that infrared light increases the rate of opening and closing of activation/inactivation gates of ion channels. This study also presents why the suppression of action potentials continues after the end of the IR pulse. It seems this is related to the incomplete refractory period of AP, which is probably due to the disturbance in the reopening of the sodium channel inactivation gate (h-gate). The current report helps to improve the IR laser medical applications for reducing nerve pain.

KEYWORDS: Action potential, Infrared, Neural block, Ion channel.

I. INTRODUCTION

Chronic pain is one of the most common diseases affecting millions of people every year[1]. Due to the side effects of using pain drugs, there is a need to develop non-invasive treatment methods, that neuromodulation can be considered a significant way for chronic pain management[2]. Infrared (IR) light can affect living organisms' nervous systems, providing a safe and effective method for neural inhibition [3–7]. However, based on recent related studies, there is still much ambiguity in the accurate explanation of the laser-tissue interaction during IR nerve inhibition. Photothermal mechanisms and temperature changes can be proposed as an important reason for manipulating neural responses under IR laser radiation [8–10]. IR light can rapidly increase tissue temperature due to the high absorption of the biological tissues [11,12]. The increase in temperature can suppress neural responses and block action potentials (APs) even after ending the IR pulse [13]. The purpose of this study is to investigate the effect of IR light in suppressing the APs and underlying biophysics of this phenomenon during and after IR radiation. For the first time, the changes of ion currents in different phases of production of a single AP under IR pulse are studied. Also, by studying the activation/inactivation gates of the ion channels, the effect of the action potential refractory period on the block of neural activity in post-irradiation is investigated.

Here, using the modified Hodgkin-Huxley model [14], the blocking APs in unmyelinated axons are simulated and, the temperature increase effect on this process is studied. In the modified Hodgkin-Huxley model, all model

parameters are assumed to depend on temperature based on described relations in previous articles [15,16]. First, we study the effect of IR short and long pulses in small diameter unmyelinated axons and show IR pulses successfully reduce the amplitude of APs. Then according to the AP includes four phases: depolarization (DP), repolarization (RP), hyperpolarization (HP), and afterhyperpolarization (AHP), the efficiency of the blocking of AP during these four phases and the efficient time interval to suppress the AP are investigated. Given that ionic currents play a significant role in the generation of APs, the effect of these ion channels on AP suppression is also investigated. Measuring the changes in ion currents at each phase of AP generation shows potassium channels' role in the AP block. Moreover, the results show that the rate of sodium channel activation gates (m-gates), potassium channel activation gates (n-gates), and sodium channel inactivation gate (h-gate) are effective in reducing APs amplitude. Also, comparing ion channel activation/inactivation gates situation before and after IR pulse demonstrates that APs suppression after IR pulse stops probably related to the incomplete or long refractory period of AP. Finding the mechanism of infrared nerve block will help optimize the use of this method for medical purposes. Especially considering the advances in compact and implantable device design based on INI [17].

will be selected automatically. If any style is changed, you can use markup styles from the pull-down style menu at the left of the Formatting Toolbar at the top of your Word window.

II. METOD

In this study, NEURON software [18] is applied to model a 30 μm diameter unmyelinated axon that the parameters of the axon are depicted in Table. A.1 (shown in APPENDIX section). In the original Hodgkin-Huxley model, the membrane capacity is assumed to be constant. However, the original model is modified to describe the neural behavior under infrared radiation, and all parameters of the model are assumed to be dependent on axon temperature. As a result, according to the presented results [14,19], the relationship between membrane capacity and temperature can be indicated as follows:

$$C_m = c_o + \frac{k}{\delta T}, \quad (1)$$

where δT is defined in this as follows:

$$\delta T = T_c - T, \quad (2)$$

where $k = 2.2\frac{\mu F}{cm^2}$, $c_o = 0.9\frac{\mu F}{cm^2}$. Given that previous experimental results have shown that the electrical characteristics, including the size of the resting potential and the maximum action potential of the giant squid axon, remain approximately constant at temperatures up to 35 ° C, we also assumed T_c=35° C [20]. It has been experimentally shown that heat generated by the laser light in short pulses increases the temperature in the irradiated area and the temperature rises linearly. After the laser stops, the temperature decreases exponentially. Temperature relationships during short pulse radiation can be defined as follows [21]:

$$T = \Delta T \gamma t \quad t < t_{pulse} \quad (3.a)$$

$$T = \Delta T \beta \{\varphi e^{-n_1 t} + (1 - \varphi) e^{-n_2 t}\} \quad t > t_{pulse} \quad (3.b)$$

ΔT denotes the magnitude of the temperature changes and constant parameters $n_1 = 0.015$, $n_2 = 0.03$, and $\varphi = 0.454$. γ and β are also numbers between 0 and 1 that change with temperature changes. However, for longer pulses, can be defined the laser-induced temperature rise behavior logarithmically [22,23]:

$$T = \Delta T \gamma L \quad t < t_{pulse} \quad (4.a)$$

$$T = \Delta T \beta \{\varphi e^{-n_1 t} + (1 - \varphi) e^{-n_2 t}\} \quad t > t_{pulse} \quad (4.b)$$

The relationship between temperature changes of the temperature-dependent membrane can be written as follows:

$$\frac{dC_m}{dt} = \frac{k}{\delta T^2}\frac{dT}{dt} \quad (5)$$

That temperature change over time is obtained using Eqs.3-4. The total flow through the membrane is defined as follows with respect to the variable membrane capacity relationship:

$$I = C_m\left(\frac{dV}{dt}\right) + (V)\left(\frac{dC_m}{dt}\right). \quad (6)$$

Membrane total current in temperature-dependent Hodgkin-Huxley model considered as:

$$I = C_m\left(\frac{dV}{dt}\right) + I_k + I_{Na} + I_l + I_{IR}. \quad (7)$$

The values of ion currents depend on the condition of the activation or inactivation gates (m, n, and h) and the maximum conductance coefficients of each channel as following.

$$I_k = g_k(V - V_K),$$

$$I_{Na} = g_{Na}(V - V_{Na}),$$

$$I_l = g_l(V - V_l),$$

g_k , g_{Na} ,g_l respectively, are the conductivity of the potassium, sodium, and leakage currents, and V_K, V_{Na}, and V_l are the reversal potentials of the potassium, sodium, and leakage channels. The conductivity of ionic currents are defined as follows:

$$g_K = x_1 n^4$$

$$g_{Na} = x_2 m^3 h$$

$$g_L = x_3$$

Where $x_1, x_2,$ and x_3 respectively are the maximum conductance values of potassium, sodium, and leakage ion currents. The temporal variation of m, n, and h parameters depends on membrane voltage and varies from 0 (closed gate) to 1 (opened gate). A probability variable should be applied because it is impossible to say with certainty which particular gate is open or closed. The physical interpretation of the activation/inactivation values of m, n, and h is that sodium channels have activation gates, m, that have a high response rate to voltage changing and have an inactivation gate, h, which has a lower response rate. Potassium channels also have activation gates, n, activated by voltage variation more slowly than sodium channel activation gates [24,25]. The temperature coefficient determined temperature dependency of activation/inactivation parameters of ion channels that define as:

$$Q_{10} = 3^{\frac{(T-T_0)}{10}} \quad (8)$$

These activation/inactivation variables determine the speed of opening or closing ion channels and describing the various AP generation phases. To simulate AP generation, we used a constant electric current in the ranges of 16 to 22 nA (the current of 16 nA was the axon excitation threshold).

III.RESULTS AND DISCUSSION

To study the biophysical mechanism behind the blocking APs, the results shown in Refs. [26,27] are employed. So, the effects of applying IR pulses with a pulse duration of 20 and 500 ms on an unmyelinated axon are estimated. The estimated temperature changes are close to the presented results shown in Ref. [26], between 2 and 11 ° C. Then, the axon is stimulated by applying a 22 nA electric current step with a duration of 1200 ms. By applying a pulse of 20 ms, causing an 8.7 ° C temperature increase at the excitation location, the amplitude of the action potential was reduced by 14 mV (Fig. 1. a). In the next experiment, to investigate the effect of longer pulses (the axon excited by an electric current of 20 nA) a 500 ms pulse, causing a temperature increase of 11°C applied on the axon. It is observed that during irradiation, the amplitude of the APs decreases about 19 mV with a gentle slope (see Fig. 1. b). Although in the experimental results shown in Ref. [26], reduction of the amplitude of APs for 20 and 500 ms pulses was 3.4 and 10 mV, but the shape of voltage changes and reduction of the amplitude of the AP in our simulations corresponded very well with those results.

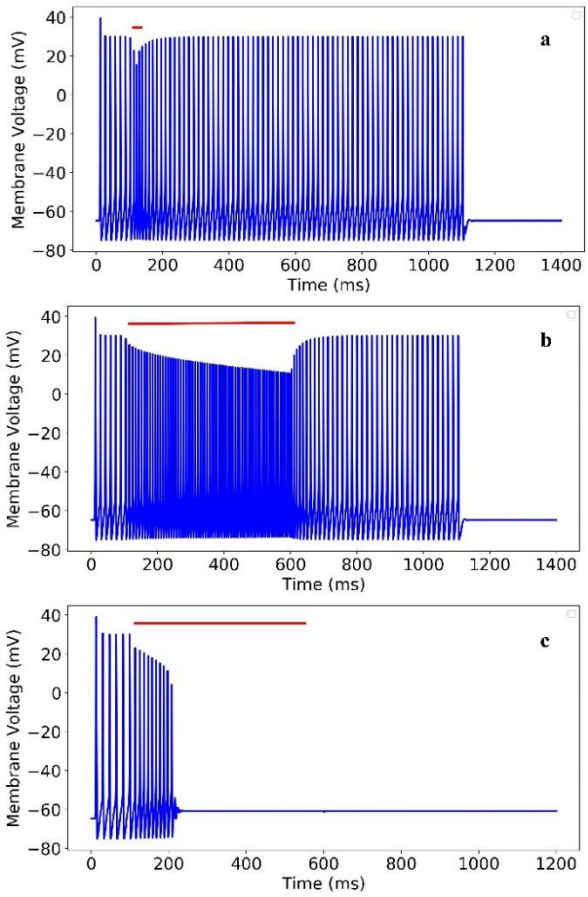

Fig. 1 The effect of short and long IR pulses on an electrically stimulated unmyelinated axon. Reduction of APs amplitude due to applying a 20 ms of IR pulse (a). Reduction of APs amplitude by application of 500 ms of IR pulse (b). Axon excitation with 16 nA threshold current and application of 500 ms IR pulse causing an 11 ° C temperature increase and successful suppression (c). (Red bar shows IR pulse position.)

Moreover, by reducing the magnitude of the electric current to 16 nA, similar to those experimental results in Ref. [26], a 500 ms laser pulse suppresses the APs completely. (See Fig. 1. c). Then, the effect of the temperature change on suppressing the APs during four constituent phases of AP is studied. The AP includes four phases: depolarization (DP), repolarization (RP), hyperpolarization (HP), and afterhyperpolarization (AHP). The duration of a single AP is less than 10 ms, and each of the four phases of an AP takes about 2 ms. To better see the influence of IR pulse on voltage changes, ion currents, and activation/inactivation gates, one must use pulses with duration of 1 ms or less (see Fig. 2. a). The axon was stimulated by a 16 nA electric current step with a duration of 1200 ms. As seen in Fig. 2. b, the threshold temperature for successful suppression of the AP in different phases were obtained 9.2 ° C for DP, 9.1 ° C for RP, 8.1 ° C for HP, and 2.3 ° C for AHP. The required temperature change to suppress the AP in the AHP phase is about 75% lower than the required temperature in other phases. In the DP phase, it was observed that temperature changes due to IR pulse reduce sodium ion current and increase potassium ion current (see Fig. 2. c). In the RP phase, the sodium and potassium currents still behave similarly to the pulse application during the DP phase, but the variation of ion currents was less than before. In the AHP phase, in which the ion currents are almost zero due to the closure of the sodium and potassium channels, the sodium ion current fluctuated very little, while the potassium current increased significantly (Fig. 2. c). Examining the 1 ms pulse application at different phases of a single AP (Fig. 2), it is observed that the threshold temperature required for nerve suppression in the AHP is about one-fourth of the temperature threshold required during pulse application in other phases. It is also observed that the heat generation by the IR pulses during INI is highly effective in increasing the potassium ion currents, which indicates the critical role of potassium ion currents in the AP suppression [28–30]. IR pulses have a tiny effect on increasing sodium ion currents while effectively reducing the sodium ion currents. It shows that sodium ion currents are not influential on AP blocking [28].

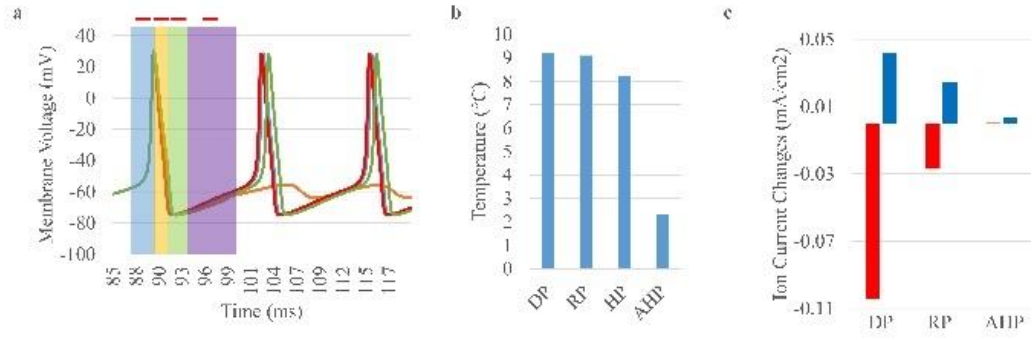

Fig. 2 Applying short IR pulses (1 ms) at each phase of the AP to investigate the effects on ionic currents and the threshold temperature required for the AP suppression. The red bars indicate the location of the IR pulse at each phase (DP (blue area), RP (yellow area), HP (green area), and AHP (purple area)). (a) Applying laser pulses causing a 2.5 ° C temperature increase in the AHP phase can successfully suppress the AP (orange line). In the rest of the phases, it did not significantly affect the APs amplitude after the pulse. (b) The required minimum temperature for successfully blocking the AP when IR pulse is applied at each phase. (c) The variation of ion currents in different phases. When IR pulse is applied during the DP phase, the sodium ion current decreases by about $100\frac{\mu A}{cm^2}$, while this reduction is about 30 $\frac{\mu A}{cm^2}$ in the DP phase. During IR irradiation in the AHP phase, IR radiation has very little effect on sodium currents and increased by about $0.4\frac{\mu A}{cm^2}$. However, in the case of potassium ion currents in the DP, RP, and AHP phases, they increase by 42, 29, and $4\frac{\mu A}{cm^2}$ respectively; the red (blue) bar indicates the sodium (potassium) ion current.

In the last experiment, the effect of IR pulse on parameters of m, n, and h to block APs is studied. The intention behind this experiment is to compare two different modes of neural inhibition. In the first case, the IR pulse only reduces the amplitude of APs, and in the second case, the IR pulse completely blocks the APs, and this suppression continues even for some time after the pulse stops. It can explain the behavior of activation/inactivation parameters in reducing neural activity and the reason for tens of milliseconds APs blocking after IR illumination stops. For this purpose, temporal variations of these parameters before, during, and after IR illumination in DP and AHP phases are studied. To do this, first, the axon is stimulated by a 16 nA electrical current with a duration of 110 ms, and then a 1 ms IR pulse is applied to the axon. Fig. 3 shows the temporal variation of the amplitude of AP after the application of IR pulse in the DP phase. After applying the IR pulse, the parameter of m and n gates does not change significantly. For h-gate, one can see an increase in the amplitude of its changes, so IR pulse increases the probability of opening this gate. At the same time, the opening and closing rate of all of the gates increases. As a result, one can see a reduction in the amplitude of the APs. After 40 ms, the rate of opening and closing of these gates and the AP amplitude return to the pre-inhibition state. These results show that the change in the opening and closing rate of the gates and the noticeable effect of IR heat on the inactivation of sodium ion channels are essential factors in reducing the amplitude of action potential (Fig. 3).

Conversely, when one applies the same short pulse in the AHP phase, different results can be observed, and it can completely block the APs. The results show that IR laser illumination can change the value of m, n and h, as presented in Fig. 4. One can see that before axon excitation, when the axon is in the excitable phase, the probability of opening the potassium activation gates, n, is about 30%. However, when IR light is applied, this probability increases to 38%. In sodium activation gates, before stimulation, only 5% of these gates are open, which means they are almost closed. After applying IR light, they have little change, and the probability of opening these gates increases to 9%. But in the case of sodium channel inactivation gate, h, the amount of change is more significant, while before electrical stimulation, the probability of opening the h-gate is about 60%. However, after the application of IR pulse, when the APs

are blocked, this amount has been reduced to be 44%. So IR pulse causes the activation gates of sodium and potassium ion channels to be more open than before. More importantly, the sodium ion channel inactivation gate is less open than before. The application of IR laser pulses at this phase affects the h-gates, which slowly open to reach the pre-AP phase or the resting potential state and prevent them from opening.

Because in the excitable membrane, the h-gate is open, so the membrane is kept in an unexcitable state. Comparing the state of m, n, and h gates at rest and blocked state shows that the effect of IR on the inactivation of sodium ion channels is more significant than that in the activation of sodium and potassium ion channels. So, the disturbance in the h-gate is the most important factor in blocking the APs after pulse stopping. Because, in the refractory period of the AP (a period after the DP during which the membrane is unable to be exited), the h-gates are reopening; if another stimulus wants to depolarize the membrane, the h-gate remains closed in response. Hence, the refractory period remains incomplete, or it takes longer than usual. It seems similar to the electrical neural blocking mechanism, disturbance in the refractory period during infrared neural inhibition also plays a significant role [31]. Also, it is the reason that the temperature threshold to suppress the AP in the AHP phase is lower than the required temperature in other phases (Fig. 2. b).

The model used in this paper was designed based on the original Hodgkin-Huxley model, which describes the giant squid axon using activation/inactivation of voltage-dependent ionic currents. In this model, two significant ion currents, sodium and potassium, were used for describing, while it is evident that in different animal species and humans, axons have more participating ionic currents in the generation of APs. In this article, the thermal effect due to IR radiation was studied, while maybe the wavelength and shape of the pulse are also effective in neural responses [32]. Compared to the experimental results, the presented model can successfully simulate AP blocking in unmyelinated axons with a small diameter (30 μm). However, large-diameter or myelinated axons require more physiological parameters. Hodgkin-Huxley's model can describe fundamental biological interactions in neural activity. So the presented model can develop and redesign for a further specific study about pain relief purposes, such as studying AP suppression in C-fibers that are important in pain transmission.

IV. CONCLUSION

In this paper, using the temperature-dependent Hodgkin-Huxley model, neural suppression by short and long IR pulses was investigated. The changes of APs amplitude of unmyelinated axon, ion currents and activation/inactivation gates of ion channels by considering temperature changes under IR pulses illumination were studied. It was shown that while IR pulses increase potassium ion currents significantly during nerve block, they have minimal effect on increasing sodium ion currents. In contrast, IR pulses are effective in reducing sodium ion currents during INI. This study confirms previous results about the essential role of potassium ion currents and the ineffective role of sodium ion currents during INI. However, our results showed that sodium ion channel gates play an effective role during INI. The results show inactivation gate of the sodium ion channel is effective in reducing APs amplitude. Also, our results showed incomplete refractory period of AP due to disturbance in the reopening of sodium inactivation gate is the reason for APs block in post-irradiation. In addition, the reason for decreasing in AP block temperature threshold in the AHP phase is probably related to the incomplete refractory period of AP.

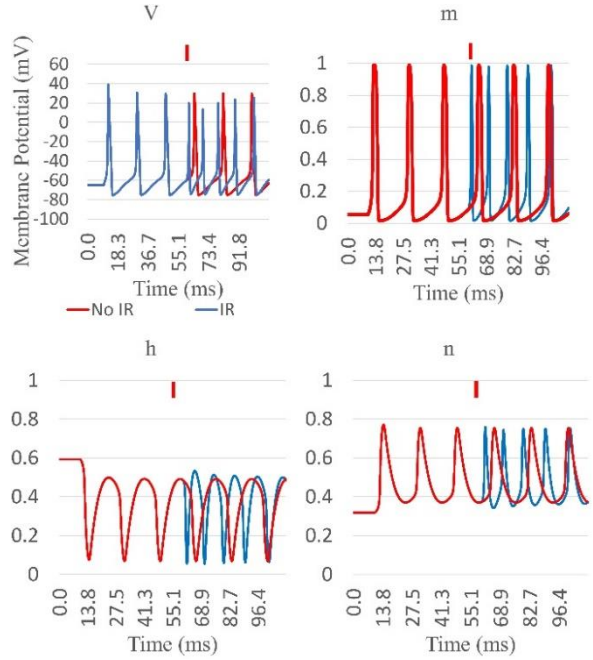

Fig.3 Variation of parameters of m, n, h gates during INI. A 16 nA current step for 110 ms is applied to stimulate the axon. Then a 1 ms IR pulse causing a temperature change of 7.7 °C is applied. (V) Shows the reduction of the amplitude of the APs when IR pulse applies. (In all graphs, the red lines indicate the values without applying IR pulse and the blue lines indicate the changes under the IR pulse). (m) Shows the temporal variation of probability of the m-gates opening. (h) Shows the temporal variation probability of the h-gate opening. (n) Shows the temporal variation of probability of n-gates opening. (Red bar shows IR pulse position)

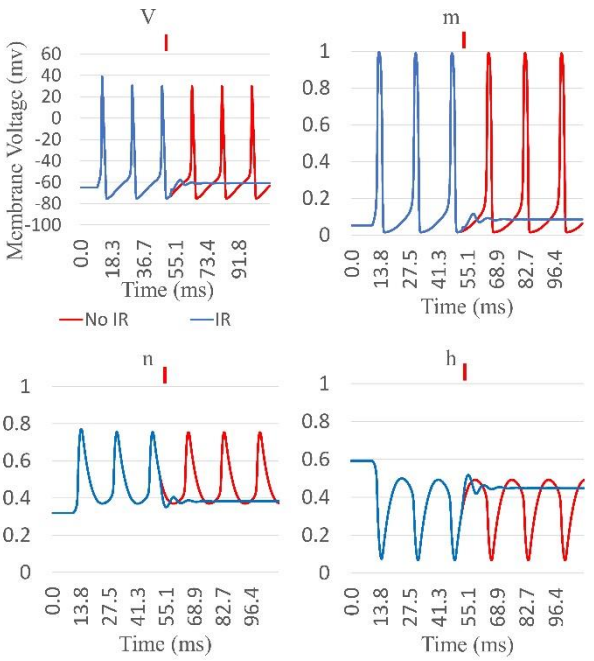

Fig.4 Dynamic of IR suppression when IR pulse is applied in AHP phase. A 110 ms excitation of an axon with 16 nA electric current and applying a 1 ms IR pulse with 7.7 ° C increase in temperature in the AHP phase. (In all graphs, the blue lines indicate the value of parameters without applying IR pulse and the red lines indicate the changes under the IR pulse). (V) Denotes IR suppression on the amplitude of AP. (m) denotes the temporal variation of probability of the m-gates opening. (h) Denotes the temporal variation of probability of h-gate opening. (n) Denotes the temporal variation of probability of n-gate opening. (Red bar shows IR pulse position)

ACKNOWLEDGMENT

This work is based upon research funded by Iranian National Science Foundation (INSF) under project No. 98029460.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

[1] M. H. Pitcher, M. Von Korff, M. C. Bushnell, and L. Porter, "Prevalence and Profile of High-Impact Chronic Pain in the United States," J. Pain, vol. 20, no. 2, pp. 146–160, 2019.

[2] K. Yu, X. Niu, and B. He, "Neuromodulation Management of Chronic Neuropathic Pain in the Central Nervous System," Adv. Funct. Mater, vol. 30, no. 37, pp. 1908999 (1-36), 2020.

[3] S. R. Tsai and M. R. Hamblin, "Biological effects and medical applications of infrared radiation," Journal of Photochemistry and Photobiology B: Biology, vol. 170. Elsevier B.V, pp. 197–207, 2017.

[4] E.H. Lothet, K.M. Shaw, H. Lu, J. Zhuo, Y.T. Wang, and S. Gu "Selective inhibition of small-diameter axons using infrared light," Sci. Rep. vol. 7, no. 1, pp. 1–8, 2017.

[5] Q. Xia and T. Nyberg, "Inhibition of cortical neural networks using infrared laser," J. Biophotonics, vol. 12, no. 7, pp. e201800403, 2019.

[6] A. J. Walsh, G. P. Tolstykh, S. Martens, B. L. Ibey, and H. T. Beier, "Action potential block in neurons by infrared light," Neurophotonics, vol. 3, no. 4, pp. 040501 (1-5), 2016.

[7] J. M. Cayce, R. M. Friedman, E. D. Jansen, A. Mahavaden-Jansen, and A. W. Roe, "Pulsed

infrared light alters neural activity in rat somatosensory cortex in vivo," Neuroimage, vol. 57, no. 1, pp. 155–166, 2011.

[8] M. G. Shapiro, K. Homma, S. Villarreal, C. P. Richter, and F. Bezanilla, "Infrared light excites cells by changing their electrical capacitance," Nat. Commun. vol. 3, no. 1, pp. 1–11, 2012.

[9] A. R. Duke, M. W. Jenkins, H. Lu, J. M. McManus, H. J. Chiel, and E. D. Jansen, "Transient and selective suppression of neural activity with infrared light," Sci. Rep. vol. 3, no. 1, pp. 1–8, 2013.

[10] Z. Mou, I. F. Triantis, V. M. Woods, C. Toumazou, and K. Nikolic, "A simulation study of the combined thermoelectric extracellular stimulation of the sciatic nerve of the xenopus laevis: The localized transient heat block," IEEE Trans. Biomed. Eng. vol. 59, pp. 1758–1769, 2012.

[11] M. H. Niemz, *Light Acting on Matter*, in Laser-Tissue Interactions, Springer International Publishing, 2019.

[12] A. J. Saubermann and V. L. Scheid, "Elemental Composition and Water Content of Neuron and Glial Cells in the Central Nervous System of the North American Medicinal Leech (Macrobdella decora)," J. Neurochem. vol. 44, no. 3, pp. 825–834, 1985.

[13] Q. Xia and T. Nyberg, "Photothermal inhibition of cortex neurons activity by infrared lasXia Q, Nyberg T (2019) Photothermal inhibition of cortex neurons activity by infrared laser. In: IFMBE Proceedings. Springer Verlag, pp 99–104er," in IFMBE Proceedings, vol. 68, no. 3, pp. 99–104, 2019.

[14] A. L. Hodgkin and A. F. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve," J. Physiol. vol. 117, no. 4, pp. 500–544, 1952.

[15] S. Fribance, J. Wang, J. R. Roppolo, W. C. de Groat, and C. Tai, "Axonal model for temperature stimulation," J. Comput. Neurosci. vol. 41, no. 2, pp. 185–192, 2016.

[16] M. A. Ansari and V. V. Tuchin, "Infrared neurostimulation of earthworm: from modeling to experiment," Opt. Eng. vol. 59, no. 06, pp.1-11, 2020.

[17] Á. Csaba Horváth, S. Borbély, Ö. Csanád Boros, L. Komáromi, P. Koppa, P. Barthó, and Z. Fekete "Infrared neural stimulation and inhibition using an implantable silicon photonic microdevice," Microsystems Nanoeng. vol. 6, pp. 1–12, 2020.

[18] M. L. Hines and N. T. Carnevale, "The NEURON Simulation Environment," Neural Computation, vol. 9, pp. 1179–1209, 1997.

[19] H. Richard Leuchtag, "Fit of the dielectric anomaly of squid axon membrane near heat-block temperature to the ferroelectric Curie-Weiss law," Biophys. Chem. vol. 53, no. 3, pp. 197–205, 1995.

[20] A. L. Hodgkin and B. Katz, "The effect of temperature on the electrical activity of the giant axon of the squid," J. Physiol. vol. 109, no. 1–2, pp. 240–249, 1949.

[21] Q. Liu, M. J. Frerck, H. A. Holman, E. M. Jorgensen, and R. D. Rabbitt, "Exciting cell membranes with a blustering heat shock," Biophys. J. vol. 106, no. 8, pp. 1570–1577, 2014.

[22] Y. Xu, R. Wang, S. Ma, L. Zhou, Y. R. Shen, and C. Tian, "Theoretical analysis and simulation of pulsed laser heating at interface," J. Appl. Phys. vol. 123, no. 2, pp. 025301, 2018.

[23] G. Arias-Gil, F. W. Ohl, K. Takagaki, and M. T. Lippert, "Measurement, modeling, and prediction of temperature rise due to optogenetic brain stimulation," Neurophotonics, vol. 3, no. 4, pp. 045007 (1-12), 2016.

[24] D. Shepardson, "Algorithms for inverting Hodgkin-Huxley type neuron models," Georgia Institute of Technology, 2009. Accessed: May 01, 2021. [Online]. Available: http://hdl.handle.net/1853/31686

[25] W. Heitler, "The Hodgkin-Huxley Model for the Generation of Action Potentials," Feb. 2020. https://www.st-andrews.ac.uk/~wjh/hh_model_intro/ (accessed May 01, 2021).

[26] X. Zhu, J.-W. Lin, and M. Y. Sander, "Infrared inhibition and waveform modulation of action potentials in the crayfish motor axon," Biomed. Opt. Express, vol. 10, vol. 6580–6594, 2019.

[27] M. Y. Sander, J.-W. Lin, and X. Zhu, "Infrared block of Na+ and Ca2+ spikes in in crayfish neuromuscular junction," in Optogenetics and Optical Manipulation , vol. 10866, pp. 108660E (1-8), 2019.

[28] M. Ganguly, J. B. Ford, J. Zhuo, M. T. McPheeters, M. W. Jenkins, H. J. Chiel, E. D. Jansen, "Voltage-gated potassium channels are critical for infrared inhibition of action potentials: an experimental study," Neurophotonics, vol. 6, no. 04, p. 1, Oct. 2019.

[29] X. Liu, Z. Qiao, Y. Chai, Z. Zhu, K. Wu, W. Ji, D. Li, Y. Xiao, L. Mao, Ch. Chang, Q. Wen, B. Song, and Y. Shui, "Nonthermal and reversible control of neuronal signaling and behavior by midinfrared stimulation," Proc. Natl. Acad. Sci. U. S. A. vol. 118, no. 10, pp. e2015685118 (1-9), 2021.

[30] M. Ganguly, M. W. Jenkins, E. D. Jansen, and H. J. Chiel, "Thermal block of action potentials is primarily due to voltage-dependent potassium currents: A modeling study," J. Neural Eng. vol. 16, no. 3, pp. 036020, 2019.

[31] Z. Feng, Y. Yu, Z. Guo, J. Cao, and D. M. Durand, "High frequency stimulation extends the refractory period and generates axonal block in the rat hippocampus," Brain Stimul. vol. 7, no. 5, pp. 680–689, 2014.

[32] Y. Xu, M. Magnuson, A. Agarwal, X. Tan, and C. P. Richter, "Infrared neural stimulation at different wavelengths and pulse shapes," Prog. Biophys. Mol. Biol. 2021.

APPENDIX

To calculate the voltage changes of the neuronal membrane, NEURON uses the following equations for each segment:

$$\frac{dm}{dt} = Q_{10}(\alpha_m(1-m) + \beta_m m)$$

$$\frac{dh}{dt} = Q_{10}(\alpha_h(1-h) + \beta_h h)$$

$$\frac{dn}{dt} = Q_{10}(\alpha_n(1-n) + \beta_n n)$$

$$\alpha_m = \frac{0.1(V+40)}{e^{\frac{-(V+40)}{10}} - 1}$$

$$\beta_m = 4e^{\frac{-(V+65)}{18}}$$

$$\alpha_n = \frac{-0.01(V+55)}{e^{\frac{-(V+55)}{10}} - 1}$$

$$\beta_n = 0.125e^{\frac{-(V+65)}{80}}$$

$$\alpha_h = 0.07e^{\frac{-(V+65)}{20}}$$

$$\beta_h = \frac{1}{e^{\frac{-(V+35)}{10}} + 1}$$

$$Q_{10} = 3^{\frac{(T-T_0)}{10}}$$

Table.A.1- Parameters used to model the axon.

Value	Parameter
30 μm	Axon diameter
-65 (mV)	Resting potential
-54 (mV)	Leak Reversal Potential
50 (mV)	Na Reversal Potential
-77(mV)	K Reversal Potential
0.12 (s/cm^2)	Na conductance x_2
0.036 (s/cm^2)	K conductance x_1
0.003 (s/cm^2)	Leak conductance x_3
21 (°C)	Axon Initial Temperature
1 μF	Initial membrane capacitance

THIS PAGE IS INTENTIONALLY LEFT BLANK.