34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Activation using infrared light in a mammalian axon model *

Erik J. Peterson, *Student Member, IEEE*, Dustin J. Tyler, Ph.D., *Member, IEEE*

Abstract— **Infrared neural stimulation (INS) offers the potential to selectively activate very small populations of neurons. Before it will be possible to design efficient and effective INS interfaces, the mechanisms of INS need to be better understood. The presented study builds on work indicating that INS generates a significant capacitive current by the application of infrared light to cell membranes. A computational model is presented to investigate realistic spatial delivery of INS and to investigate whether axonal structure and ion channel composition are likely to facilitate INS activation through capacitive changes alone. Findings indicate that capacitance changes are unlikely to be the sole mechanism, because the determined thresholds to activation were higher than the capacitance changes observed in previously reported work [1].**

I. Introduction

A growing number of therapies and prosthetics are being developed that interface with the nervous system to treat disease and restore function after injury [2–4]. One of the primary challenges of these approaches is fine control of the neurons activated by an interface. Optical neural interfaces are another approach to selective interfaces because light can be shaped and delivered in ways electrical stimulus cannot [5–7]. Focused infrared light has been used to stimulate neural tissue without electrical stimulus artifact or electrochemical charge transfer at the metal-solution interface in the body [8], [9]. The mechanism by which infrared neural stimulation (INS) activates neural tissue has not been fully described [6]. Until recently, the leading theory on infrared neural interface design has been that a spatial and temporal thermal gradient in the nerve leads to activation [10]. Recently, Shapiro *et al.* have shown that application of infrared light to a membrane causes depolarizing current due to changes in capacitance of the electrolyte-membrane interface [1]. The data presented by Shapiro *et al.* indicate that the capacitive current originates from a change of approximately 8% of the baseline capacitance, and is proportional to the level of radiant energy at the cell membrane [1]. This result seems to contradict earlier work indicating that INS works best with a sharp thermal gradient [10], because it would indicate that increased irradiation of the cell membrane area would increase the effect of INS.

Shapiro *et al*. were not able to elicit purely optically evoked action potentials in the cells used for their study, but suggested that the structure of neurons may lend to action potential generation [1]. The current computational study examines axon structure and ion channel composition roles in activation through changing membrane capacitance and temperature. This study is based on a double-cable model of a myelinated mammalian axon [11] that has been modified to include currents and temperature-related rate changes as a result of applying infrared light in a realistic spatial distribution. Because it is unclear what role myelin could play in the capacitive current, two models are investigated. In the first model, the entire membrane is capable of generating capacitive current. In the second, only membrane at the nodes of Ranvier is affected by infrared light. We hypothesize that axon structure will not lower the requirements for capacitive and thermal changes below the range reported by [1].

II. Methods

A. Physical INS Delivery Parameters

To simulate the physical parameters of infrared delivery through a bare optical fiber, the capacitance and temperature changes in each axon segment were scaled spatially along the length of the axon. Maximal change occurred at the center of the beam, or where incident energy is highest. The magnitude of both variables was then decreased with increased distance from the beam center, following a Gaussian distribution with the peak aligned to the center-most node of Raniver. This Gaussian beam profile is observed when using bare optical fibers (measurements not shown), and result in a similar thermal profile in tissue as reported by [10]. Gaussian distributions similar to measured infrared spot data from 200, 400, and 600 μm optical fibers were used. Temperature changes were applied only to nodes of Ranvier, as the passive internodal segments had no temperature-sensitive elements. Temporally, capacitance and temperature increases were modeled with a linear increase during the infrared pulse, then exponential decay to baseline after infrared deposition [1].

B. Axon Model

All simulations were performed using NEURON 7.1 [13]. The axons with fiber diameters ranging 5 to 20 um were modeled using a 21-node of Ranvier mammalian

*Funding provided by DARPA/MTO CIPhER Award and Lockheed Martin Aculight Corporation.

E. J. Peterson is a Ph.D. Graduate Student with the Biomedical Engineering Department, Case Western Reserve University, Cleveland, OH 44106 USA, (e-mail: erik.j.peterson@case.edu).

D. J. Tyler is an Assoc. Prof. at Case Western Reserve University, Cleveland, OH 44106, USA and biomedical engineering with the Louis-Stokes, Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH 44106, USA. (corresponding author, phone: 216- 368- 0319; fax: 216- 368- 4969; e-mail: dustin.tyler@case.edu).

myelinated axon described by [11]. The McIntyre, Richardson & Grill voltage gated ion channel model was modified such that the temperature was variable in each axon segment to model spatial and temporal changes in temperature. Axon simulations were performed to test temporal and spatial temperature variations, and verified that all channel rate variables were correctly updated.

Traditionally, membrane capacitance is assumed constant in computational models of the axon (Fig. 1a), but Shapiro *et al*. show this is not correct under infrared radiation [1] (Fig. 1b). The presented axon simulations were modified to accommodate a changing membrane capacitance (Fig. 1c) by adding a current source in parallel to the membrane capacitor. The magnitude of this current source was proportional to the membrane voltage and the time derivative of the membrane capacitance, and accounted for a +140 mV reversal potential reported by [1].

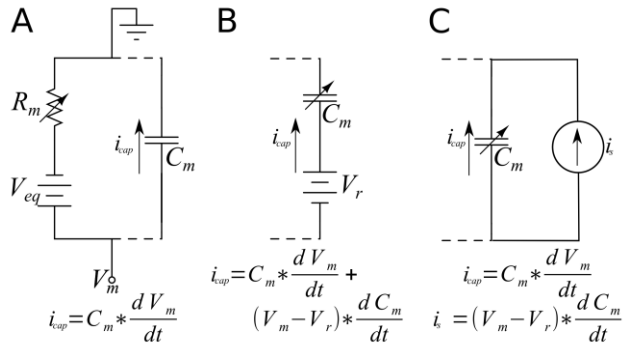

Figure 1 – Electrical models of the cell membrane where V_m is the membrane potential, V_{eq} represents the equivalent lumped reversal potential of the ion channels, R_m is the net resistance of the voltage-gated and leak channels, C_m is the membrane capacitance, and V_r is the reversal potential of the infrared-evoked capacitance changes. A) Traditional model where C_m is assumed constant. B) Variable capacitance model based on [1]. C) Model implementation of B.

C. Axon Simulations

Two models were used in this investigation. Axons were either simulated with capacitive current sources inserted in the nodes of Ranvier and internodal segments of the axon, or only inserted in the nodes of Ranvier. Simulated optical pulse durations included 0.100, 0.200, 0.500, 1.00, and 2.00 ms pulses to reflect the typical range of reported infrared pulse durations used in INS [10], [14]. Axon fiber diameters between 5 and 20 µm were simulated using each pulse duration. The maximum membrane capacitance change was adjusted in a binary search algorithm to determine the minimum change in capacitance needed to generate a propagated action potential.

III. RESULTS

The threshold capacitance change, as a percentage of nominal capacitance increases with axon diameter (Fig. 2). Membrane capacitance change thresholds are much lower when the capacitance change occurs over the entire membrane (Fig. 2a) than when the capacitance change occurs only at the nodes of Ranvier (Fig. 2b). Across simulations, the threshold range is 15-45% when capacitive current originates from all membrane segments and 897-3159% when it originates from the node of Ranvier only.

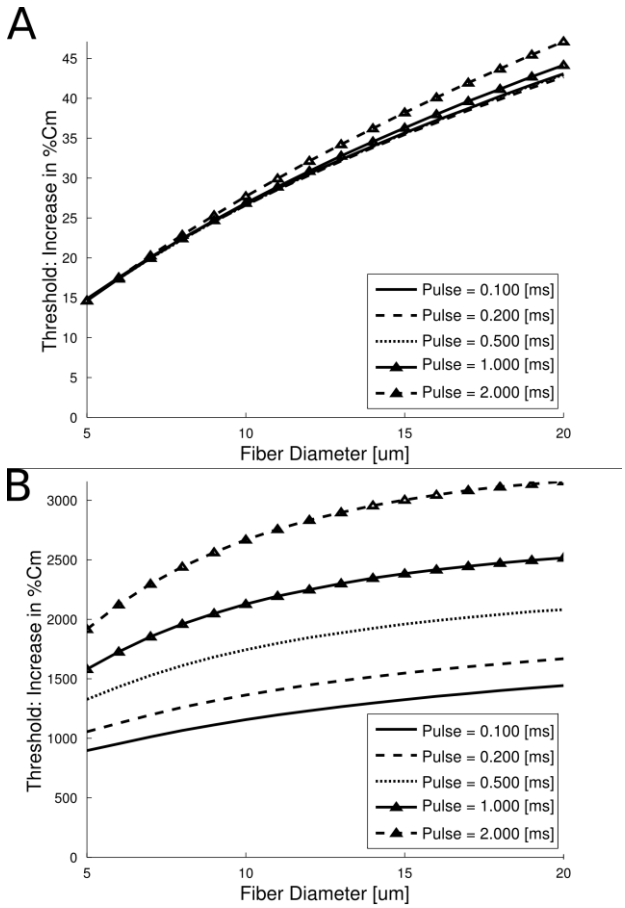

Figure 2 – Minimum membrane capacitance change (% of baseline) required to elicit a propagated action potential in the mammalian myelinated axon model. Thresholds decrease for shorter pulse durations and smaller fiber diameters. Threshold levels are much lower when A) the entire cell membrane capacitance is affected, than when B) when capacitance changes only the nodes of Ranvier.

Increasing the duration over which the capacitive change is applied increases threshold for both cases, since the derivative of the capacitance change is smaller for longer pulse widths. This effect is more pronounced when capacitance changes only in the nodes of Ranvier. Changing the axon diameter has a greater effect on changing the relative magnitude of threshold in the full membrane model than in the node only model.

Increasing the incident beam width resulted in a decrease in threshold (Fig. 3). This effect was only observed when capacitance change occurred in the nodes and internodes. Thresholds were identical across beam diameters for the node-only case (results not shown). Even the 600 µm diameter optical beam was not wide enough to affect capacitive changes at more than one node of Ranvier at a

time, so the simulations for all beam diameters were effectively the same for this simulation set.

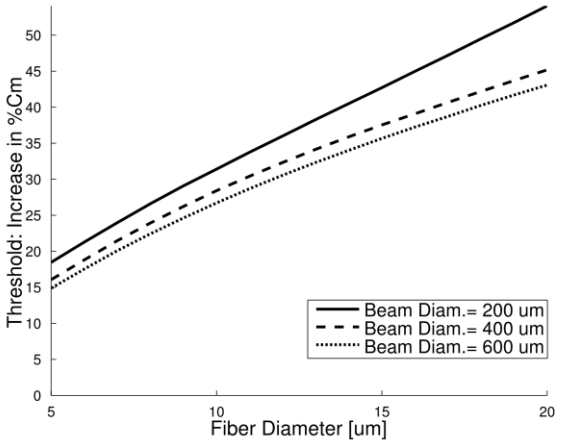

Figure 3 – Threshold for capacitive change necessary to trigger an action potential in axons when optical fiber size is varied. Results are shown for the model with capacitive changes in both node and interernodal segments. Thresholds did not change between beam diameters only the nodes were sensitive (results not shown).

IV. Discussion

Our goal with developing this model was to investigate the feasibility of capacitance and temperature changes as the only mechanisms of INS activation. Development of a mechanistic model of INS activation would give us the ability optimize optical stimulation parameters and design interfaces. The primary assumptions of the presented model are: 1) membrane temperature and capacitance changes constitute the mechanism of INS activation, and 2) these changes, or their primary effects, are either localized to the nodes of Ranvier or occur throughout the cell membrane.

This model tested cases where the effects were localized to the nodes of Ranvier or affected the length of the axon uniformly, i.e. including myelinated segments. It is possible that the insulating myelin sheath reduces membrane capacitance changes in the internodal region, but not completely. The result would be a capacitive current in the internodal regions that is greater than zero but reduced from the full, unimpeded value. The models used in this study were chosen to provide upper and lower bounds on capacitive changes necessary to initiate action potentials. Results where internodal currents were half maximum (results not shown) fell within the above reported range. Ongoing *in vivo* work in rat peripheral nerves seeks to validate assumptions of the models used in this work, primarily whether INS sensitivity is localized to regular structures along the axon.

The differences in results from the two models are worth examining as well. The threshold range for the node-only model was orders of magnitude larger than the membrane capacitance change expected under typical INS parameters [1]. This indicates that proximity to the high density of voltage-gated ion channels of a small capacitive change is not sufficient to trigger action potentials. Instead, a much larger current is necessary, achieved by increasing the magnitude of the capacitance change or increasing the membrane area affected. Pulse duration also has a larger effect on the node-only model than the uniformly sensitive membrane model. This is likely due to current diffusion away from the node during longer pulses than when current is generated in the membrane around the node as well.

The lowest capacitive change required to elicit activation predicted by these models is still twice the magnitude of reported values. The capacitance changes that Shapiro *et al.* measured in vitro were on the order of 2-8%, with an evoked capacitive current of 86 nA when stimulating a cell membrane much larger than the infrared beam size [1]. Shapiro *et al.* found that using similar temperature and capacitive changes could trigger action potentials in a generalized computational membrane model with voltage-gated ion channels [1]. However, when optically stimulating a non-neural cell expressing $Na_V1.4\alpha,\beta$ sodium and Shaker potassium voltage-gated ion channels, an action potential could not be triggered without first electrically stimulating to just sub-threshold [1]. Shapiro *et al*. reasoned that the structure and ion channel distribution in axons may facilitate activation. Physical delivery parameters of INS to a peripheral axon mean that with optimal alignment through a beam, only about 4% of the total beam would be incident on a 20 µm diameter fiber. This limits the amount of cell membrane exposed to the incident beam, and reduces the total current generated in the cell. The results of this study indicate that the structure of a myelinated axon does not facilitate activation enough to make up for this decreased exposure; otherwise, capacitive change thresholds would be lower or similar to the reported 2-8%. When these simulation results are considered along with the reported experimental data in the transfected cell, it seems likely that changes in membrane capacitance are only part of the mechanism driving INS.

The types of ion channels present in the membrane could also affect activation using INS in ways not yet considered, meaning the capacitive change mechanism cannot be ruled out. $Na_V1.4$ channels are commonly found in muscle fibers [15], but $Na_V1.6$ channels are common to nodes of Ranvier [16]. The specifics of how sodium channel activation and inactivation is impacted by temperature are non-linear, with the overlap of sodium and potassium channel activations impacting neural excitability [17]. Limitations in the expressed ion channels [1] and the fact that the McIntyre, Richardson, and Grill axon model [11]was optimized for physiologic body temperatures, mean that both approaches have potential limitations in replicating behavior observed stimulating peripheral nerve tissue [10]. Additional experimental validation is necessary to determine whether these limitations are significant.

The results presented by Shapiro *et al.* do indicate that membrane capacitance changes are a factor in INS activation. Taking the membrane capacitance change to at least be involved in the mechanism of INS, this model still potentially provides guidance on interface design if the assumption about nodal versus internodal sensitivity can be verified experimentally. The results of changing fiber diameter indicate that maximizing delivery area will increase

the capacitive current generated, and make axon activation more likely. This would seem to contradict the interface design guidance from Wells *et al.* stating that establishing a spatial and temporal gradient is the driving force behind INS [10]. These explanations can be reconciled somewhat, though, because the work by Wells *et al.* did not separate out the spatial and temporal aspects of the gradient and identify the contributions of each [10]. The results of this study indicate that an increased temporal gradient and wider beam area decrease the activation thresholds. If the temporal gradient is the more important gradient, then these two mechanisms are not incompatible. If, on the other hand, infrared sensitivity is limited to the nodes of Ranvier, the increased spatial gradient will help to focus and more effectively deliver infrared energy to an axon. In this case, both the spatial and temporal gradients would help drive INS activation. Increased beam diameter would only spread out energy deposition and decrease the effect on an axon until it was wide enough to influence more than one node. A wider beam may, however, increase the probability of reaching more nodes of different fibers, and increase the overall observed response.

Another notable result is that this model predicts that smaller fiber diameters will have lower activation thresholds than larger diameters. This is expected based on the capacitive model equivalent circuit, since the additional capacitive current acts like an intracellular current injection. The potential consequence is that optical stimulation may exhibit physiologic recruitment order, as opposed to the size-recruitment reversal observed when using electrical stimulation [18].

V. Conclusion

The results of this simulation study predict that membrane capacitance changes necessary to activate an axon with physically-relevant deposition parameters exceed the changes expected to occur with typical INS delivery parameters. The presented analysis does not support an evoked membrane capacitance change as the mechanism driving INS activation, though it is a factor that should be considered in future INS investigations.

References

[1] M. G. Shapiro, K. Homma, S. Villarreal, C.-P. Richter, and F. Bezanilla, "Infrared light excites cells by changing their electrical capacitance," *Nature Communications*, vol. 3, p. 736, Mar. 2012.

[2] C. R. Butson and C. C. McIntyre, "Role of electrode design on the volume of tissue activated during deep brain stimulation," *J. Neural Eng.*, vol. 3, no. 1, pp. 1–8, Mar. 2006.

[3] N. B. Dommel, Y. T. Wong, T. Lehmann, C. W. Dodds, N. H. Lovell, and G. J. Suaning, "A CMOS retinal neurostimulator capable of focussed, simultaneous stimulation," *Journal of Neural Engineering*, vol. 6, no. 3, pp. 035006–035006, 2009.

[4] D. Lulic, A. Ahmadian, A. A. Baaj, S. R. Benbadis, and F. L. Vale, "Vagus nerve stimulation," *Neurosurgical FOCUS*, vol. 27, no. 3, p. E5, Sep. 2009.

[5] S. Matar, L. Golan, N. Farah, I. Reutsky, and S. Shoham, "Holographic photo-stimulation for dynamic control of neuronal population activity," in *Neural Engineering, 2009. NER '09. 4th International IEEE/EMBS Conference on*, 2009, pp. 84–87.

[6] C.-P. Richter, A. I. Matic, J. D. Wells, E. D. Jansen, and J. T. Walsh, "Neural stimulation with optical radiation," *Laser & Photon. Rev.*, vol. 5, no. 1, pp. 68–80, Jan. 2011.

[7] N. I. Smith, Y. Kumamoto, S. Iwanaga, J. Ando, K. Fujita, and S. Kawata, "A femtosecond laser pacemaker for heart muscle cells," *Opt. Express*, vol. 16, no. 12, pp. 8604–8616, Jun. 2008.

[8] A. D. Izzo, C.-P. Richter, E. D. Jansen, and J. T. Walsh, "Laser stimulation of the auditory nerve," *Lasers in Surgery and Medicine*, vol. 38, no. 8, pp. 745 – 753, 2006.

[9] J. Wells, C. Kao, E. D. Jansen, P. Konrad, and A. Mahadevan-Jansen, "Application of infrared light for in vivo neural stimulation," *Journal of Biomedical Optics*, vol. 10, p. 064003, 2005.

[10] J. Wells, C. Kao, P. Konrad, T. Milner, J. Kim, A. Mahadevan-Jansen, and E. D. Jansen, "Biophysical Mechanisms of Transient Optical Stimulation of Peripheral Nerve," *Biophysical Journal*, vol. 93, no. 7, pp. 2567–2580, 2007.

[11] C. C. McIntyre, A. Richardson, and W. M. Grill, "Modeling the Excitability of Mammalian Nerve Fibers: Influence of Afterpotentials on the Recovery Cycle," *The Journal of Neurophysiology*, vol. 87, no. 2, pp. 995–1006, Feb. 2002.

[12] M. L. Hines and N. T. Carnevale, "The NEURON simulation environment.," *Neural Comput*, vol. 9, no. 6, pp. 1179–1209, 1997.

[13] A. R. Duke, J. M. Cayce, J. D. Malphrus, P. Konrad, A. Mahadevan-Jansen, and E. D. Jansen, "Combined optical and electrical stimulation of neural tissue in vivo," *J. Biomed. Opt.*, vol. 14, no. 6, Nov. 2009.

[14] E. Matthews and M. G. Hanna, "Muscle channelopathies: does the predicted channel gating pore offer new treatment insights for hypokalaemic periodic paralysis?," *The Journal of Physiology*, vol. 588, no. 11, pp. 1879–1886, 2010.

[15] J. H. Caldwell, K. L. Schaller, R. S. Lasher, E. Peles, and S. R. Levinson, "Sodium Channel Nav1.6 Is Localized at Nodes of Ranvier, Dendrites, and Synapses," *PNAS*, vol. 97, no. 10, pp. 5616–5620, May 2000.

[16] Y. Yu, A. P. Hill, and D. A. McCormick, "Warm Body Temperature Facilitates Energy Efficient Cortical Action Potentials," *PLoS Comput Biol*, vol. 8, no. 4, p. e1002456, Apr. 2012.

[17] W. M. Grill and J. T. Mortimer, "Stimulus waveforms for selective neural stimulation," *Engineering in Medicine and Biology Magazine, IEEE*, vol. 14, no. 4, pp. 375–385, 1995.