Integrating Finite Element Method for Multiscale Modeling and Simulation of Retinal Ganglion Cell Stimulation Strategies

Sharique Ali Asghar[1] and Manjunatha Mahadevappa[2]

***Abstract*—The finite element method (FEM) has become an increasingly popular tool for the computational modeling of multiscale biological systems, including the electrode-tissue interface and the behavior of individual neural cells. However, a significant challenge in these studies is integrating multiple levels of complexity, each with its biophysical properties. This paper presents a single platform solution for modeling these multiscale systems using the finite element method. The proposed method combines different finite element formulations tailored to the specific biophysical properties of each scale into a single unified simulation platform. The results of this method are compared to experimental data to demonstrate the accuracy and efficacy of the proposed approach. With the goal of eliciting the most significant possible response from the retinal ganglion cell's (RGC) multiple components, we devised an electrical stimulation strategy and electrode placement setup that took into account both the RGC's horizontal and vertical location. We found that the activity in a single RGC model could be elicited by a cathodic pulse of amplitude 34 µA. We observed that the optimum electrode placement for a neural response is around the initial axon segment, 30 µm from the soma, and 10 µm above the RGC. Our results show that the proposed method can accurately capture the complex behavior of these multiscale systems and provide a valuable tool for further research in retinal prostheses.**

***Clinical Relevance*— To develop efficient electrical stimulation schemes for retinal prosthesis applications, this research can shed light on the behavior of the electrode-tissue interface and individual neural cells. Electrical stimulation of RGCs has shown promise in the application of retinal prostheses. Still, a thorough understanding of the electrode-induced electric field is essential for the design of effective and safe stimulation protocols. Electrical stimulation's side effects may require knowledge of multiple physics disciplines (such as thermal or structural deformation owing to implant placement inside the eye). Finding a solution to diseases that cause vision impairment could be aided by a finite element method (FEM) framework that simulates the neuronal response to extracellular electrical stimulation for realistic 3D cell and electrode geometries.**

I. Introduction

Electrical stimulation of the retinal tissue has shown promise as a potential treatment for preserving or restoring vision in a patient suffering from retinal degenerative diseases such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP) [1], [2] and computational models can be a valuable supplement to experimental data in this regard. In particular, sophisticated mathematical modeling is required to overcome practical restrictions, such as high invasiveness and in-vivo experimentation on animals, and gain deeper insights into the biophysical mechanisms driving retinal ganglion cell (RGC) activation [3]. Successful implant prediction also requires comprehensive models, which can be easily adjusted within a customized medicine framework. A computational approach is a potent way to comprehend electrical stimulation strategies used to foretell the response of tissues to the implanted electrode and examine the characteristics of the current stimuli. The neural responses to electrical stimulation have been studied both in vitro and in vivo, with simulations providing further evidence in most cases [4]. Computational simulations play a crucial role in translating experimental data into potential technical solutions for treatments or the design of neural implants, as well as in interpreting experimental results and predicting the outcome of tailored studies. The demands placed on computer simulations grow in tandem with the complexity of the experiments. Combining a multi-compartment model with a model that computes the electric field created by a stimulating electrode—analytically or numerically, using methodologies like the finite element method (FEM)—is the most popular way of simulating the neuron response to electrical stimulation [5].

There are several challenges to achieving selective electrical stimulation of RGCs. Limitations in resolution, timing accuracy, and nonselective activation of visual pathways are three of the main obstacles to the retinal prosthesis's ability to perform its visual functions. The distribution of current across the retina, as well as the size and spacing of the stimulating electrodes, all contribute to the low spatial resolution. For comparison, variables like the RGCs' response time and the constraints of the stimulation circuitry contribute to the low temporal resolution. Some of the significant difficulties include electrode placement and individual cell stimulation, which requires the development of electrodes with fine-scale spatial resolution. However, the majority of today's stimulation tactics stimulate both ON and OFF circuits at the same time, leading to an undesired mix of responses. The problem arising from stimulating both ON and OFF-visual pathways are that it can lead to blurred or indistinct vision, as the two types of neuron cells have different functions in processing visual information. This can reduce the effectiveness of the stimulation and limit the overall visual outcomes. One possible solution to this problem is to use more selective stimulation techniques, such as those based on microelectrode arrays and individual cell stimulation. Here we can use FEM modeling and simulation to optimize the electrode design, stimulation protocol, and individual neuron

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cell response to achieve selective stimulation of RGCs. This can help to minimize the stimulation of the undesired RGCs and improve visual outcomes. In order to simulate the effect of electrical stimulation on inferred RGC models, we set up a two-stage computational framework. At first, we estimated the threshold electric field as a function of space and time across the retinal tissue for a specific input current value. Secondly, the rheobase current, a threshold current-related variable in the RGC model, was estimated using the strength duration curve. To simulate the neuronal response, we applied it to the appropriate model nodes.

II. Multiscale Modeling and Simulation

A. Modeling of microelectrode-retinal tissue

The complete model is constructed in 3D rectangular geometry for retinal tissue with a work plane on top of the box to serve the proposed microelectrode array arranged in four different topologies, as shown in Fig. 1. The microelectrodes of size 10 µm each, the distance between neighboring electrodes (pitch), and their symmetry nature for a different configuration have been mentioned in Table I is spread over 280*250 µm^2 area with a thickness of 100 µm of retinal tissue. Stimulating RGCs in retinal prostheses often employs a hexagonal electrode configuration due to its many advantages, including its ability to provide complete coverage of the retinal surface, its resemblance to the natural RGC organization, its reduction of cross-talk, and its facilitation of the use of high-density electrode arrays. The alternatives to the hexagonal arrangement of electrodes, namely pentagons, and octagons, are also considered regular polygons and have been used for comparative evaluation with the hexagonal arrangement.

To calculate the scalar electric potential, and electric field distribution, we use the electric currents physics interface to solve the current conservation equation using Ohm's law. The current conservation equation solves the electric potential distribution in all domains. In order to stimulate the retinal tissue with a microelectrode, an input current must be applied at the setup's epicenter as a boundary condition. Grounding the remaining peripheral electrodes in each microelectrode topology is the other boundary condition.

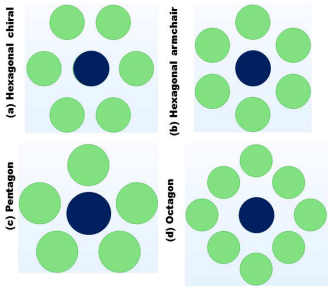

Fig. 1. The blue circle represents the stimulating electrode in each topology, while the peripheral electrodes serve as the ground. These schematics describe various microelectrode array design arrangements of varying sizes and shapes.

B. Microelectrode placement for efficient stimulation schemes leading to action potential generation in RGC

To replicate the functions and mechanisms of neurons, we need to construct the biophysical model. To do this, we employed a biophysical model [6] of the action potential that included both N_{av} channels that are inactivated and K_v channels that are not. The simulation is done in Comsol Multiphysics 6.0, and the corresponding biophysical model's architecture is quite simple: it consists of a spherical soma (30 mm in diameter), a long dendrite (6 mm in diameter and 1,000 mm in length), and a thin, unmyelinated axon (diameter:1 mm, length; 500 mm). Given that the soma is voltage-clamped, electrically isolating the dendrites from the axon, most simulations can safely ignore the dendrite. The stimulating electrode is positioned with a minimum separation of 30 µm distance of grounding along the axon, with the soma-dendritic compartment as a reference point. We have selected four electrode sites along the X and Y axes, as illustrated in Fig.2, to improve the microelectrode array design and stimulation strategies for RGC.

The RGC's response is simulated by incorporating the most up-to-date parameters for the RGC's soma and axon into the simulation framework [7], [8]. Table II lists the values of the biophysical model's parameters, and we employed standard activation dynamics involving a single gate, with a constant time constant being used.

$$I_{Na} = G_m(E_{Na} - V) \quad (1)$$

$$\tau_m . \frac{dm}{dt} = m_\infty(V) - m \quad (2)$$

$$m_\infty(V) = \frac{1}{1+exp((V_{0.5}-V)/k)} \quad (3)$$

TABLE I. Quantitative Values for the Biophysical Model's Parameters

Characteristics	Electrode Configuration			
	Hexagonal chiral	***Hexagonal armchair***	***6 Ring***	***9 Ring***
Pitch (Distance between successive neighboring electrodes in the ring)	200 µm	200 µm	100 µm	200 µm
Pitch (Distance from the center electrode to all other electrodes)	200 µm	200 µm	100 µm	400 µm (4 electrodes far away from the center) 200 µm (4 electrodes closer to the center)
Symmetry nature	Yes	Yes	Structurally symmetric in one plane	Structurally symmetric. Non-equidistant topology from the center electrode

III. Results and Discussion

The microelectrode's stimulating current induces a local electric field within the tissue, serving as the retinal tissue's activation threshold criterion. The scheme's threshold criterion for activating retinal tissue is an electric field of 3000 V/m [9]. The electric current value is 34 µA for threshold attainment for retinal tissue activation. As a result of our observations, as shown in Fig. 3, we found that electric field patterns in pentagons and octagons are neither uniform nor converging as

intended. This is due to their non-equidistant topology from the central electrode and their geometric non-symmetry in both the horizontal and vertical planes. In octagonal arrangements, four electrodes in the outer ring widen the electric field even further. However, the electrical field shapes in a hexagon chiral or armchair structure are concentrated and uniform. Therefore, the hexagonal microelectrode design allows for targeted, specific, and selective electrical stimulation.

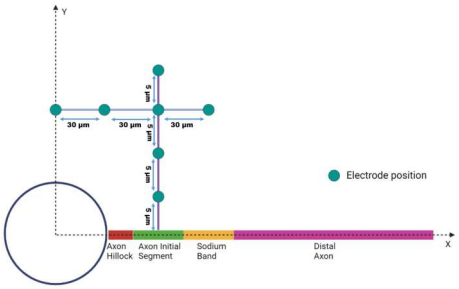

Fig. 2. This study looked at the planar RGC model with the electrode in four distinct locations. Horizontally, the position of the electrode ranges from X = 30 µm (closer to AIS) to 90 µm (towards the distal axon). The vertical position of the electrode is altered between Y = 5 µm (more relative to the soma) and 20 µm (a point where stimulation becomes insufficient to elicit a response).

TABLE II. QUANTITATIVE VALUES FOR THE BIOPHYSICAL MODEL'S PARAMETERS

Entity	**Parameters**		
	Physical description	***Symbol***	***Values***
Voltage-gated sodium (N_{av}) Channels	Soma conductance	g_{Na} , soma	250 S/m^2
	Axon initial segment (AIS) conductance	g_{Na} , AIS	3,500–7,400 S/m^2
	Resting potential	E_{Na}	70 mV
	Half-activation voltage of m-gating in soma	$V_m^{0.5}$, soma	-30 mV
	Half-activation voltage of h-gate in soma	$V_h^{0.5}$, soma	-60 mV
	Half-activation voltage of m-gate in AIS	$V_m^{0.5}$, AIS	-35 mV
	Half-activation voltage of h-gate in AIS	$V_h^{0.5}$, AIS	-65 mV
	The rate constant of m-gate	k_m	5 mV
	The rate constant of h-gate	k_h	5 mV
	The time constant of m-gate	τ_m	150 µs
	The time constant of h-gate	τ_h	5 µs
Voltage-gated potassium (K_v) Channels	Soma conductance	g_K , soma	100 S/m^2
	Axon initial segment (AIS) conductance	g_K , AIS	1500 S/m^2
	Resting potential	E_K	-90 mV
	The rate constant of n-gate	$V_n^{0.5}$	-70 mV
	The rate constant of n-gate	k_n	20 mV
	The time constant of n-gate	τ_n	1 ms

The extent of stimulation depends on the electric field's size, shape, and strength; larger fields induce larger depolarizations and more action potentials. The stimulation can also be altered by altering the electrode configuration, which limits the electric field's spatial distribution and hence the retina's stimulation pattern. A key component of many vision-related scientific and restorative applications is the capacity to selectively excite RGCs by applying an electrical field.

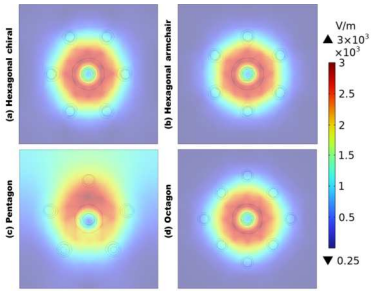

Fig. 3. This contour plot displays the electric field produced by all microelectrodes setup designed to stimulate retinal tissue.

With electrodes placed 30 µm along the horizontal axis and 10 µm along the vertical axis near the AIS compartment of RGC, a cathodic pulse with a width of 1 ms and the electric field generated by the microelectrodes are sufficient to stimulate the RGCs by depolarizing their membranes and triggering the generation of action potentials from RGC, as shown in Fig. 4.

A cathodic pulse with a width of 1 ms and the electric field generated by the microelectrodes is sufficient to stimulate the RGCs by depolarizing their membranes and triggering the generation of action potentials from RGC, and this is considerably enhanced by an electrode positioning of 30 µm along the horizontal axis and 10 µm along the vertical axis near the AIS compartment of RGC and this can be depicted in Fig. 4.

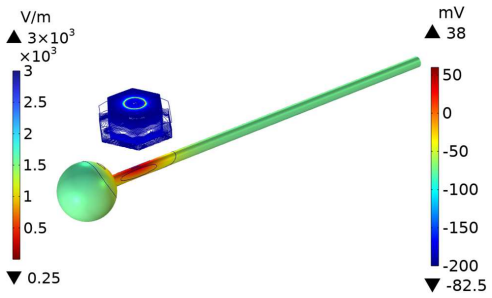

Fig. 4. The contour represents the threshold electric field of 3000 V/m created by hexagonally packed electrodes with a localized field pattern and the optimal electrode proximity for stimulating RGC to elicit an action potential of 38 mV.

As can be seen in Fig. 5 (a), the action potential occurs swiftly at 1.2 ms following the application of a stimulus pulse of 1 ms, with smooth repolarization. However, hyperpolarization is seen, and the neuron fires more slowly when the stimulus pulse has a long pulse duration of 5 ms or 10 ms. With changes in stimulus pulse amplitude and pulse width, the action potential is evoked and travels down the axon. The response to a cathodic 34 µA pulse with a duration of 1 ms demonstrates a distinct peak during the rising phase of the action potential, as shown in Fig. 5 (b). In contrast, the response achieved with a longer pulse duration has a broader peak width and decays exponentially with time at a slower rate. Responses to longer pulses are sluggish or less excitable due to the fact that the time constant is much shorter than the time period required for the membrane capacitor to discharge. Therefore, applying a stimulation of 1 ms pulse width is

deemed highly productive in the context of retinal prosthesis design, as it aligns with the temporal response characteristics of retinal neurons. This is consistent with published experimental studies and ensures that neurons are appropriately depolarized to evoke an action potential without becoming desensitized or adapted [10].

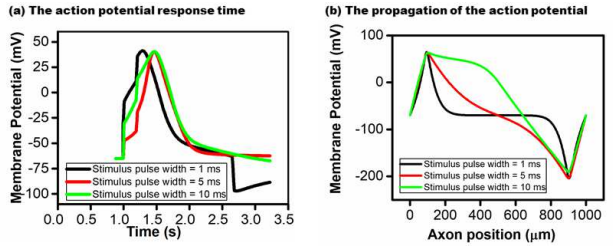

Fig. 5. Visualization of (a) retinal ganglion cell action potential generation and (b) propagation along axon with different stimulus pulse widths.

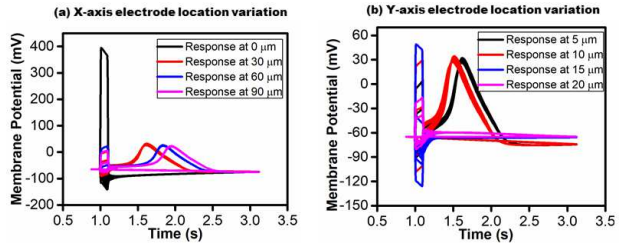

Fig. 6. The membrane potential is shown here as a function of the stimulus electrode's orientation in the horizontal and vertical planes.

The black curve in Fig. 6 (a) shows that the action potential is not initiated when the electrode is above soma and the cell remains depolarized. Action potential propagates smoothly at 30-90 μm as the electrode position is adjusted along the X-direction. When the electrode is put at the height of 15-20 μm, there is not enough electric field intensity to elicit a neural response, as demonstrated by the pink and blue curve in Fig. 6 (b). The action potential propagates consistently throughout the axon when the electrode is positioned at the RGC AIS component at roughly 10 μm above.

IV. Conclusion

This research presents a single-platform solution using the finite element method to model multiple-scale biological systems. The findings of this study show that the proposed method works and is accurate, and they shed light on the dynamics of the electrode-tissue interface and individual neural cells. This work may also be helpful for future studies on electrical stimulation's side effects that require knowledge of multiple physics disciplines (such as thermal or structural deformation owing to implant placement inside the eye). FEM simulations with in vitro and in vivo experiments, as well as advanced imaging and recording techniques, can help to validate the accuracy of FEM models and provide a complete understanding of the neural mechanisms of the retina and the response of RGCs to electrical stimulation.

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References

[1] A. Santos *et al.*, "Preservation of the Inner Retina in Retinitis Pigmentosa: A Morphometric Analysis," *Arch. Ophthalmol.*, vol. 115, no. 4, pp. 511–515, Apr. 1997, doi: 10.1001/ARCHOPHT.1997.01100150513011.

[2] J. L. Stone, W. E. Barlow, A. H. Milam, E. Juan, and A. H. Milam, "Morphometric Analysis of Macular Photoreceptors and Ganglion Cells in Retinas With Retinitis Pigmentosa," *Arch. Ophthalmol.*, vol. 110, no. 11, pp. 1634–1639, Nov. 1992, doi: 10.1001/ARCHOPHT.1992.01080230134038.

[3] J. T. Thorn, E. Migliorini, E. Borda, and D. Ghezzi, "Progress in Biomedical Engineering Advances in visual prostheses : engineering and biological challenges Progress in Biomedical Engineering OPEN ACCESS Advances in visual prostheses : engineering and biological challenges," 2022.

[4] M. Stefano, F. Cordella, A. Loppini, S. Filippi, and L. Zollo, "A Multiscale Approach to Axon and Nerve Stimulation Modeling: A Review," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 29, pp. 397–407, 2021, doi: 10.1109/TNSRE.2021.3054551.

[5] A. Fellner, A. Heshmat, P. Werginz, and F. Rattay, "A finite element method framework to model extracellular neural stimulation," *J. Neural Eng.*, vol. 19, no. 2, 2022, doi: 10.1088/1741-2552/ac6060.

[6] S. Goethals and R. Brette, "Theoretical relation between axon initial segment geometry and excitability," *Elife*, vol. 9, pp. 1–34, 2020, doi: 10.7554/eLife.53432.

[7] Y. C. Chang, D. H. Ghaffari, R. H. Chow, and J. D. Weiland, "Stimulation strategies for selective activation of retinal ganglion cell soma and threshold reduction," *J. Neural Eng.*, vol. 16, no. 2, 2019, doi: 10.1088/1741-2552/aaf92b.

[8] J. Jeng, S. Tang, A. Molnar, N. J. Desai, and S. I. Fried, "The sodium channel band shapes the response to electric stimulation in retinal ganglion cells," *J. Neural Eng.*, vol. 8, no. 3, 2011, doi: 10.1088/1741-2560/8/3/036022.

[9] S. A. Asghar, P. Pal, K. Nazeer, and M. Mahadevappa, "A Computational Study of Graphene as a Prospective Material for Microelectrodes in Retinal Prosthesis and Electric Crosstalk Analysis," *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS*, vol. 2020-July, pp. 2291–2294, 2020, doi: 10.1109/EMBC44109.2020.9176388.

[10] W. Li, D. Haji Ghaffari, R. Misra, and J. D. Weiland, "Retinal ganglion cell desensitization is mitigated by varying parameter constant excitation pulse trains," *Front. Cell. Neurosci.*, vol. 16, no. August, pp. 1–12, 2022, doi: 10.3389/fncel.2022.897146.