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Targeted Stimulation of Retinal Ganglion Cells in Epiretinal Prostheses: A Multiscale Computational Study

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Abstract

Retinal prostheses aim at restoring partial sight to patients that are blind due to retinal degenerative diseases by electrically stimulating the surviving healthy retinal neurons. Ideally, the electrical stimulation of the retina is intended to induce localized, focused, percepts only; however, some epiretinal implant subjects have reported seeing elongated phosphenes in a single electrode stimulation due to the axonal activation of retinal ganglion cells (RGCs). This issue can be addressed by properly devising stimulation waveforms so that the possibility of inducing axonal activation of RGCs is minimized. While strategies to devise electrical stimulation waveforms to achieve a focal RGCs response have been reported in literature, the underlying mechanisms are not well understood. This paper intends to address this gap; we developed morphologically and biophysically realistic computational models of two classified RGCs: D1-bistratified and A2-monostratified. Computational results suggest that the sodium channel band (SOCB) is less sensitive to modulations in stimulation parameters than the distal axon (DA), and DA stimulus threshold is less sensitive to physiological differences among RGCs. Therefore, over a range of RGCs distal axon diameters, short-pulse symmetric biphasic waveforms can enhance the stimulation threshold difference between the SOCB and the DA. Appropriately designed waveforms can avoid axonal activation of RGCs, implying a consequential reduction of undesired strikes in the visual field.

Keywords

Retinal prostheses; Multi-scale computational modeling; Admittance Method; NEURON; Electrical stimulation

I. INTRODUCTION

RETINITIS pigmentosa and age-related macular degeneration are retinal degenerative diseases, which start with the degeneration of photoreceptors. In early stages of degeneration, while photoreceptors are largely damaged, inter retinal neurons and ganglion cells remain mostly intact. To restore partial vision for patients suffering from blindness by degenerative diseases, retinal prosthetic devices have been developed. These devices electrically stimulate surviving neurons in the degenerated retina to evoke visual percepts. The efficacy of this approach has been proven by several research groups and led to the development of various retinal prosthetic systems [1]–[5]. While clinical trials have shown the effectiveness of these devices, further understanding of neuronal response to electrical stimulation is vital to improve the performance of such devices for patients to better recognize patterns, such as objects and letters [4], [5].

In epiretinal prosthetic devices, retinal ganglion cells (RGCs) are the main target of electrical stimulation. There are many challenges with this stimulation strategy. For example, a wide activation range of retinal neurons due to the close proximity of two neighboring electrodes in a high-density multielectrode array has been shown to limit the spatial resolution of these devices [6]. To focus the stimulation site, hexapolar electrode configurations [7], [8] and virtual electrode designs [9] have been utilized. Recently, a ‘shaping’ algorithm has been proposed to predict the pattern of retinal activity from simultaneous stimulation of the multielectrode and optimize the electrical stimulation pattern of the multielectrode array to match with a target activation pattern [10].

Evidence suggests that axonal activation of RGCs is also one of the main critical challenges with current epiretinal implants. Clinical studies on Argus II patients have revealed that a single electrode stimulation resulted in activation of RGCs axonal pathways and therefore the elongated phosphenes perceived by subjects [11], [12]. Several attempts have been made towards developing stimulation waveforms utilizing direct and indirect stimulation of RGCs to improve the efficacy of current devices [13]–[25]. In [24], sinusoidal electrical stimulation at 25 Hz resulted in selective activation of bipolar cells (BCs); in fact, it has been further shown that electrical stimulation with a longer pulse duration (~ 25 ms) can reduce the spatial pattern of activated RGCs and avoid the activation of passing axonal fibers [25]. However, clinical and animal studies have also reported the percept fading due to repetitive indirect stimulation of RGCs which has led to desensitization [26]–[28]; therefore, direct electrical stimulation of RGCs with short pulse durations has been utilized to obtain focal activation of RGCs [29]–[32] and overcome desensitization and phosphene fading challenges [26]–[28].

Experiments have been performed to identify optimal stimulation waveforms to avoid axonal activation and selectively target RGC somas [31], [32]. Biphasic charge-balanced stimulus

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waveforms with a relatively short pulse width ($\sim 120 \mu\text{s}$) are shown to result in more focal responses from RGCs and only activation of RGC somas using a calcium imaging technique [31]. However, there are a wide range of different RGCs subtypes sending unique visual information to the brain [33]–[36]. Previous calcium imaging approaches indiscriminately visualize responses of a large number of RGCs to epiretinal electrical stimulation and provide no information regarding the differential stimulus threshold of the axon initial segment (AIS) and passing axons [31]. Therefore, it would be essential to capture the response of various RGCs subtypes to electrical stimulation and further characterize factors affecting the axonal activation of morphologically and biophysically different types with different sensitivity to electrical stimulation.

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While these studies are promising towards improving the effectiveness of epiretinal implants, limited progress has been made towards the development of a computational platform to predict the response of a large population of different RGCs subjected to external stimulation. Predictive computational tools would help gain additional insights into underlying mechanisms and physiological changes due to direct electrical stimulation of RGCs. Using our group's Admittance Method (AM)/NEURON computational platform [37]–[45], we focused on exploring the sensitivity of passing axons and the SOCB of RGCs to both cathodic and anodic-first symmetric biphasic stimulus pulses with various durations.

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Biophysical properties of different RGC subtypes estimated from experimental data in vitro have been used to implement a single-compartment model [46]. For this paper, morphologically and biophysically realistic models of two subtypes of RGCs, A2-monostratified and D1-bistratified, have been developed and their accuracy has been tested by comparing computational results with neural recordings from experiments reported in [46]. The modeled RGCs have realistic representation of axons, including the initial segment which plays a significant role in the response of RGCs to epiretinal electrical stimulation. This multiscale platform, in conjunction with the developed RGC models, allow us to determine the field distribution inside the retina tissue and predict the response of a large population of realistic RGCs to electrical stimulation. We centered our focus on neuronal responses of A2 and D1 RGCs to epiretinal stimulation of different pulse widths considering first a single cell, and later a large population of cells.

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Our results show that the AIS, and particularly the SOCB, is less sensitive to modulations in pulse durations compared to the DA. We further demonstrate that morphological (soma and dendritic field size) and biophysical differences between the two RGCs do not significantly contribute to the stimulus threshold of RGCs distal axon. This indicates that the DA properties are largely responsible for the sensitivity of passing axons to electrical stimulation. Considering the passing axon diameter variations between the cells, our computational findings suggest that modulations in pulse durations can influence the differential stimulus threshold between the SOCB and DA. This can potentially improve the chance for select activation of the SOCBs and avoid axonal excitation of RGCs. More focalized response of RGCs to direct electrical stimulation can enhance the spatial resolution of current epiretinal prosthetic systems.

II. METHODS

A. Admittance Method (AM): Modeling the Electronics and the Retina Tissue

To calculate the extracellular voltage generated due to electrical stimulation, we constructed a model of bulk retina tissue and an electrode. Material properties are assigned for each voxel in the model [37]–[42]. Current is injected to the electrode and the resulting voltage is computed at each node in the voxel. Then, to obtain the extracellular voltage input to each neuronal compartment, a linear interpolation function is used to calculate the voltage at each compartment in multicompartment model of RGCs.

The anatomy of healthy mammalian retina has been modified to represent the degenerated retina tissue, shrinking the thickness of the outer part of the retina including the outer plexiform and outer nuclear layers. The retina tissue laminar properties are identical to those provided in [37]. An electrode with diameter of 200 μm is placed on the center of the bulk retina tissue with 18 million computational cells. A 3D computational model of retinal electrical stimulation and the resulting voltage are shown in Fig. 1a, and 1b. The biphasic charge-balanced electrical stimulation waveform and parameters utilized in this study are provided in Fig. 1c. Further details about the AM modeling platform can be found in [37]–[42].

B. NEURON Model

The A2 and D1 RGCs morphology was extracted from the NeuroMorpho dataset [49], [50] and imported to NEURON software [51]. Morphological parameters of the extracted cells can be found in [52]. Fig. 2a shows the morphology of the cell, including the levels of stratification in the inner plexiform layer (IPL) of the retina. As can be seen, D1-bistratified cells consist of two levels of dendritification, in which one layer of dendritic tree is ramified inside the inner part, and another is placed in the outer section of the IPL. Whereas, the dendritic structure of the A2-monostratified cell types is only distributed in the inner part of the IPL. The axon of the cells was patched to the cell body and includes four different regions. The axon hillock (AH) is the closest portion that connects to the soma. The nearest segment of the AH to the soma is extended 20 μm down and 20 μm to the left. The second band next to the AH is the SOCB that has the highest density of sodium channel. The narrow segment (NS) of the axon is connected to the distal end of the SOCB. The remaining portion of the axon adjacent to the distal end of the NS is called distal axon (DA). The morphological parameters of axonal sections are adapted from *Jeng et al.* [47] as shown in Fig. 2b.

This morphologically realistic cell is finely compartmentalized and its response to electrical stimulation is solved using a multi-compartmental Hodgkin–Huxley model. Each compartment includes several ionic channels modeled as a voltage-dependent conductance in parallel with the membrane capacitance. In addition to the five ionic channel models from *Fohlmeister and Miller* [53], [54] for the ganglion cells, two more ionic currents have been considered to more accurately represent the intrinsic electrophysiological properties of different RGCs. This includes the difference between ON and OFF cell types [55] and the phenomenon of rebound excitation, which plays a fundamental role in encoding the visual

percept [56], [57]. The hyperpolarization-activated and LVA calcium ionic channels were modelled as in [58], and [59] respectively. The expression of rate constants for different ionic channels is listed in Table I.

Recently, single-compartment models of ganglion cells were used to find the constraints for the maximum ionic conductance values, in which the model output can replicate the electrophysiological properties of different RGC types [46]. First, the results of this paper were reproduced; second, the models of RGCs were further developed to a multi-compartmental model of both morphologically and biophysically realistic RGCs by tuning the density of ion channels accordingly in the soma, dendrites, and axon. The axon conductances only consist of sodium, potassium, and leakage channels. The biophysical properties of the axon were adapted from the work of [47]. The experimentally recorded signals of the A2 and D1 cells were used for the model tuning [46]. The range of variation in the density of ion channels of the dendrites and axon is based on the constraints demonstrated by *Fohlmeister et al.* in [53]. The tuned biophysical properties of the cell for the soma, dendrites, and axonal segments are represented in Table II and Table III.

This leads to the most realistic model representing the experimental data for A2 and D1 cells as shown in Fig. 3. Intracellular hyperpolarizing step currents of 200 pA with 400 ms duration were injected into the cell, and the response was recorded from the cell body. As illustrated, the RGC model can closely reproduce the experimental data. This includes the rebound excitation phenomenon, which is described as action potentials initiation after termination of a hyperpolarizing current.

C. Extracellular Stimulation: Admittance Method Linked With NEURON

Resulting extracellular voltages induced in the tissue from the AM model were applied to multi-compartment models of neurons using NEURON software, and then neuronal responses of individual RGCs were recorded. The AM and NEURON are sharing the same coordinates. Thus, a script was written to superimpose the voltage calculated in the tissue volume onto the NEURON model and apply it as an extracellular voltage to each compartment using the “extracellular” mechanism built into NEURON. Further details can be found in [37]–[45].

D. Stimulation Threshold

In this paper, we centered our focus on two cases: i) single cell analysis of RGCs, ii) a large population of RGCs, considering their response to epiretinal electrical stimulation.

1) A Single Sell Study: The stimulation threshold of the two cells was measured as alterations in the position of the electrode along a straight line with a 20 μm spacing from, and in parallel to, the axon. This study first helped validate our multiscale computational modeling results with physiological experiments and previously published modeling with the NEURON simulation [47]. Further, we were able to compare the stimulus threshold sensitivity of the two RGCs passing axons (distal axon) to electrical stimulation. It is vital to explore whether cells with high AIS sensitivity to electrical stimulation indeed experience a greater sensitivity of passing axons to electrical stimulation.

2) A large population of RGCs: We constructed a large population of RGCs and measured the stimulation threshold of each cell. The developed RGCs were tiled to populate the inner layers of retina (inner plexiform and ganglion cell layers) using the AM as described in the previous section. The population of RGCs includes 30×40 individual RGCs populated over a $3 \text{ mm} \times 3 \text{ mm}$ area of the inner retina. The center to center distance between cells is set to $50 \mu\text{m}$. This resulted in 1200 cells and each is simulated independently. A synthetic network of RGCs including the position of the stimulating electrode and the axonal direction is shown in Fig. 4.

For a given input current, we estimated the spatial pattern of elicited RGCs using the 2D stimulus threshold map. This would help us determine the AIS and DA activation areas depending on the relative position of the cells and their DAs with respect to the stimulating electrode. A range of stimulation waveforms was applied to find stimulus pulse widths that allow for a more focal response of RGCs for a given current magnitude. We were also interested to find the difference in the axonal activation area of the two cells. Therefore, we simulated and analyzed the cells separately in a similar fashion.

To find the stimulation threshold, a script was written giving an initial guess and changing the input current accordingly. If there is no action potential, the input current is incremented by a factor up to the point that the action potential is observed, and vice versa. To obtain the minimum current with a higher precision ($\pm 0.1\%$), this process is further repeated by reducing this factor by half until an action potential (or no action potential) is observed. This estimated stimulus threshold is then set as an initial guess for the next electrode position (for a single cell study) or the next cell (for a large population of RGCs study).

E. Electrical Stimulation

1) Single Cell Study: Here, we focused on a charge-balanced biphasic stimulus waveform due to the tissue safety concern of using monophasic pulses. We applied a cathodic-first symmetric stimulus pulse with a constant pulse width of 0.5 ms to a point source and a disk electrode with a diameter of $200 \mu\text{m}$ and analyzed the response of both A2 and D1 RGCs to electrical stimulation as the stimulating location changed along and in parallel to the axonal pathway.

2) Large Population of RGCs: Distorted phosphenes observed by users of the epiretinal implant (Argus II by Second Sight: 0.45 ms pulse duration, no interphase gap) [12] is theorized to be due to the axonal activation of RGCs. A computational model of the topographic structure of optic nerve fibers showed that the orientation of the perceived phosphenes by the Argus II subjects are well aligned with the tangent line of the axonal pathway of RGCs [12]. Using our computational platform, we applied a similar biphasic symmetric charge-balanced waveform with a pulse duration of 0.5 ms. We plotted the 2D stimulus threshold map of the two RGCs to predict the elongated percepts related to the axonal activation of RGCs to epiretinal electrical stimulation.

3) Stimulus Waveform to Eliminate the Axonal Activation of RGCs: Most recent experiments on the responses of a population of RGCs to electrical stimulation have shown the possibility of avoiding the axonal activation of RGCs [31]. It is shown that a symmetric

biphasic waveform with a short pulse duration has the ability to selectively target the RGC somas and achieve a more focal shape of percept. Here, we developed the realistic models of two different subtypes of RGCs with the use of our multi-scale computational platform. We applied charge-balanced, biphasic waveforms: symmetric cathodic-first, symmetric anodic-first, with a range of pulse durations from 0.1 ms to 10 ms (Fig. 1c). This would help us deepen our understanding of underlying mechanisms affecting the selective activation of RGCs somas.

III. RESULTS

A. Single Cell Study of RGCs

Stimulation thresholds of the two RGCs as the position of the stimulating source (point source and disk electrode with diameter of 200 μm) changes along the axon is shown in Fig. 5. In agreement with physiological experiments and NEURON modeling of an individual RGC [47], [48], the minimum stimulus threshold of both cells was observed when the electrode is placed above the SOCB for the point source simulations. However, the disk electrode has a higher stimulus threshold and the site of the lowest threshold is shifted to the right and further from the soma at the narrow segment as shown in Fig. 5. This is mainly due to the higher electric field gradient (the activation function) at the disk electrode periphery. We assumed identical axonal properties for both RGCs to identify the impacts of morphological and biophysical differences between the cells on the stimulus threshold of passing axons separately from the potential difference in the length and ionic channel density of the RGCs axon initial segment. This assumption arises from the fact that the previous study has shown that the SOCB band length, location, and the sodium channel density do not influence the DA threshold [47]. Fig. 5 further indicates that the stimulus threshold of DA was not significantly altered by the physiological differences between the two RGCs, suggesting that passing axons threshold can be exclusively determined by properties of the DA.

B. Larger Population of RGCs

The spatial activation patterns of the two RGCs due to a symmetric biphasic cathodic-first electrical stimulation with pulse widths of 0.1 ms and 0.5 ms are shown in Fig. 6. Each dot in the figure represents the location of a RGC cell body and the color bar indicates the stimulus threshold of the corresponding cells. As shown in Fig. 6a and b, the relative longer pulse width of 0.5 ms resulted in the distal axons activation of RGCs (axonal activation). While the spatial activation threshold and area of those A2 and D1 RGCs whose cell bodies are either overlaid by the stimulating disk electrode or are close to the electrode have shown dissimilarity, the axonal excitation area and threshold difference between the two cells are negligible. The elongated area of activation computed using this multiscale modeling platform supports the fact that the orientation of the distorted phosphenes is aligned with the RGCs axonal pathway [12]. Fig. 6c and d represent the spatial threshold patterns of RGCs for a shorter pulse width of 0.1 ms. As shown, a more focal response of RGCs can be achieved using a shorter pulse duration. The stimulation threshold of the D1 cell was previously shown to be lower (see Fig. 5) and therefore the activation region of this cell is larger compared to the A2 cell.

To better understand the mechanisms leading to a more focal response of RGCs using short pulse durations, the lowest stimulation threshold originated in the SOCB was compared with the excitation threshold of the DA for pulse durations ranging from 0.1 ms to 10 ms for both A2 and D1 RGCs, as depicted in Fig. 7. Results demonstrate that as we shorten the pulse duration, the greatest difference between the SOCB and axonal thresholds can be achieved. This indicates the possibility of selective activation of the AIS with the highest safety margin of avoiding RGCs axonal activation using short pulse durations.

Computational modeling reveals less sensitivity of the SOCB to modulations in stimulus pulse durations relative to the DA. While there is a difference in the stimulation threshold of the two cells over a range of pulse widths at the SOCB, this difference cannot be seen at the DA (Fig. 7). This demonstrates a strong contribution of DA difference among RGCs to activation threshold of passing axons. Therefore, we modulated the DA diameter of the two cells over their maximum range of changes (1.2 μm and 0.8 μm) [34], [35] and monitored its impact on the DA threshold. The gray and black curves in Fig. 7 represent the stimulation threshold of the DA with 1.2 μm and 0.8 μm diameters, respectively. As shown, there is still a wide window for the preferential excitation of the SOCB over the DA using a short pulse duration.

The resulting stimulus threshold from the symmetric biphasic cathodic-first waveform is compared with an anodic-first waveform in Fig. 8. As expected, similar to the symmetric cathodic-first pulses, the greater difference between the SOCB and DA threshold of RGCs has been observed with a shorter pulse duration. However, stimulation threshold of anodic-first stimulation waveforms is higher compared to cathodic-first waveforms [13], [61], [62]. As a result, we observed the greater differential stimulus threshold between the SOCB and DA using an anodic-first pulse compared to a cathodic-first pulse, indicating a higher chance for selective activation of the AIS. This is due to the lower sensitivity of the SOCB to changes in polarity of stimulus waveforms relative to the DA as represented in Fig. 8.

Our computational findings are in good agreement with recent experiments on the spatial response of RGCs to electrical stimulation showing that focal activation can be obtained using a symmetric biphasic stimulation with a shorter pulse width [31]. This modeling framework further enabled us to identify factors leading to a more focalized response of RGCs by investigating realistic models of two different classified RGCs: D1-bistratified and A2-monostratified.

IV. DISCUSSION

We applied a multiscale AM/NEURON computational platform to better understand the spatial activation pattern of a large population of RGCs to different electrical stimulation parameters. We have considered studies of a single cell and a large population of cells, analyzing the stimulation threshold and the activated area of a synthetic network of RGCs through different symmetric biphasic waveforms with various pulse durations.

A. Selective Stimulation of RGC SOCBs

Our computational modeling framework correctly predicts phosphene shape and elongated axonal activation of RGCs reported in both clinical research studies [12] and electrophysiological experiments [25], [31]. Results show that RGCs somas with the periphery of stimulating electrode (the greatest electric field gradient) placed above the SOCB can be selectively targeted using short pulse durations. This results in more focal shape of activated region and therefore the spatial resolution improvement of epiretinal implants.

Prior physiological experiments and multi-compartmental modeling of a single RGC found that the SOCB has the lowest stimulation threshold with the highest density of voltage-gated sodium channels [47], [48]. Here, we modeled two different subtypes of RGCs, A2 and D1 cells, with the aim of exploring the impact of morphological and biophysical differences between the two cells on activation threshold of passing axons as well as validating the modeling framework. It was thought that different sensitivity of AIS among RGCs to electrical stimulation could lead to activation threshold difference of RGCs passing axons and therefore a major challenge for avoiding RGCs axonal activation [65]. However, our both single cell and a large population of RGCs studies demonstrated that while the stimulus threshold of the two cells are different at the SOCB, this differential threshold is negligible at the DA assuming identical axonal properties for the cells (Figs. 5 and 6).

B. Impact of AIS Properties

The AIS properties can vary among different types of RGCs and as a result can modulate the AIS stimulation threshold of cells [47], [48]. We assumed identical AIS properties for the cells because the stimulation threshold difference between the cells at the AIS was not the focus of this study. Moreover, a prior work showed that the density, length, and location of the SOCB did not alter the threshold of DA [47]. The computational findings of this study explored that passing axons threshold is most likely determined by the properties of distal axon. Over a range of DA diameter alterations between the two cells, the differential threshold of the SOCB and DA remains high enough for select excitation of the SOCB with short stimulus pulses (Fig. 7). We observed that the SOCB is less sensitive to both pulse duration and polarity changes relative to the distal axon (Figs. 7 and 8), offering a chance to avoid activating RGCs axon bundles with pulse duration modulations. The previous calcium imaging approach may not be sensitive enough to detect the threshold of AIS regions such as the SOCB [31].

C. Clinical Implications

In this work, we used the same system and electrode size implemented in current epiretinal implants to predict the elongated phosphene reported by Argus II patients [12]. While very short pulse durations can avoid axonal activation, the required threshold for neural activation and power consumption are high. Fig. 9 compares charge threshold of the SOCB and DA as a function of pulse duration for the A2 and D1 cells. As shown, charge threshold remains almost constant using pulse widths less than 0.5 ms. However, charge threshold increases using longer pulse durations. This indicates the possibility of safe delivery of electrical

stimulation using very short pulse durations, although high power consumption leads to generation of more heat.

There are other approaches aiming at improving the spatial resolution of retinal implants by localizing the electric field near the stimulation electrodes and manipulating the spread of current. Studies have investigated the use of small electrodes [66], [67] as well as local return electrodes of different configurations to control the spread of RGCs activations [68], [69]. However, these studies may not necessarily guarantee to avoid axon bundle activation. For example, the use of 10 μm stimulating electrode diameter has been shown to result in RGCs axonal activations [67]. Therefore, future work will incorporate stimulation strategies to avoid activation of axon bundles and at the same time limit the current distribution near each stimulating electrode to achieve focalized response from RGCs in high-density electrode arrays.

D. Limitations of Neural Network Modeling

While our AM-NEURON computational platform correctly predicts the activation of axon bundles, the spread of RGCs activation near the stimulating electrode may not be precisely modeled. For instance, it has been reported the presence of electrical couplings between neighboring RGCs [70], [71] and in fact research has shown that the application of gap junction blocker can limit the RGCs activated region [72]. Further, the network-mediated response can also influence the spatial activation of RGCs in response to epiretinal stimulation [73]. There are synaptic connections between ganglion cells and intermediate neurons such as horizontal, amacrine, and bipolar cells, which may have contributions on the extracellular response of cells. This was limited in this study to only consider the neural activity of individual ganglion cells in direct response to electrical stimulation. This assumption is due to the fact in the late-stage of degeneration, synapses likely lose their functionally and connectivity [63], [64]. Moreover, it is well demonstrated in the literature that while indirect stimulation of RGCs can be achieved using long pulse widths [18]–[25], direct activation of ganglion cells can be obtained using short phase durations [30]–[32]. Since the main stimulation waveform carried out in this study is a symmetric biphasic waveform with a short pulse width, it is admissible to only assess directly activated RGCs. In the future, we will incorporate other subtypes of RGCs as well as outer retinal neurons and their chemical and electrical synaptic and gap junctional connectivity.

V. CONCLUSION

A multi-scale computational study using a combined AM/NEURON model was applied to better understand RGCs response to electrical stimulation. We developed morphologically and biophysically realistic models of two classified RGCs, D1 and A2 cells. Our model shows that the difference in stimulus threshold of AIS across RGCs does not necessarily lead to the difference in the stimulation threshold of RGCs passing axons. We found the SOCB threshold to be less sensitive to pulse duration modulations relative to the DA threshold. Further, the DA threshold increases more with reversing the polarity of stimulation (anodic-first) compare to the SOCB threshold. Therefore, very short pulse widths significantly augment stimulus threshold difference between the SOCB and DA,

offering less chance for activation of axon bundles. Correlation of our computational findings with recent experiments allowed us to better capture RGCs axonal activation and closely replicate the elongated phosphene drawn by patients. We further utilized this tool to design electrical stimulation parameters and gain additional insights leading to more focal activation of RGCs. This computational platform can lead into a generalized modeling framework capable of evaluating responses of a large population of RGCs to different electrical stimulation waveforms and designing new electrode geometry to improve the spatial resolution of epiretinal prostheses in high density electrode arrays.

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Fig. 1.

Multiscale model of electrical stimulation of the retina tissue. (a) A 3D voxelized model, consisting of bulk retina tissue with a single stimulating electrode. (b) The distributed voltage inside the retina tissue using Admittance Method (AM). This voltage is applied as an extracellular voltage in the NEURON model. (c) Electrical stimulation waveform applying symmetric charge-balanced biphasic with alterations in cathodic and anodic pulse durations.

Fig. 2.

A2-type and D1-type RGCs morphology as implemented and coded in our multiscale Admittance Method/NEURON computational platform. (a): The dendrites of the A2-RGC are ramified in the inner part of inner plexiform layer (IPL), while the dendrites of the D1-RGC are placed in both inner and outer part of the IPL. The morphology was extracted as a SWC file from the NeuroMorpho dataset [49], [50], [52]. (b): Different axonal segments representation of both cells. AH: axon hillock; SOCB: sodium channel band; NS: narrow segment; DA: distal axon; L: length of each band; D: diameter of each band.

Fig. 3.

Comparison between experimental (top) and computational (bottom) membrane voltages in the cell body (soma) in response to intracellular stimulation. The hyperpolarizing step current stimulation was applied between 100 ms and 500 ms. (a): A2 cell; (b): D1 cell. Experimental data obtained from [46].

Fig. 4.

A large population of RGCs. A single cell was tiled to populate the entire ganglion cell and IPL ($3 \text{ mm} \times 3 \text{ mm}$). The center to center distance between the nearby cells is set to $50 \mu\text{m}$ and the stimulating electrode is placed at the center of the model. The axon is oriented in x-direction, this would allow us to better determine the impact of axonal pathway on distorted phosphenes. A2 and D1 cells were simulated separately to better investigate the axonal activation threshold difference between the two cells.

Fig. 5.

Stimulation threshold of A2 and D1 RGCs as alterations in position of stimulating electrode. Dash lines: point source, solid lines: disk electrode (200 μm diameter). We used a symmetric charge-balanced cathodic-first waveform with a pulse duration of 0.5 ms. Results show that while the stimulus threshold of the AIS varies between the RGCs, the difference in the activation threshold of DA is almost negligible.

Fig. 6.

2D stimulus threshold map for A2 and D1 RGCs. Each dot represents the center of the corresponding cell body. The stimulating electrode is positioned at the center of the model. Left: A2 RGCs; right: D1 RGCs. Symmetric biphasic cathodic-first waveforms with pulse widths of (a) and (b) 0.5 ms; (c) and (d) 0.1 ms, are applied to the electrode.

Fig. 7.

Activation threshold difference between the SOCB and DA of A2 and D1 cells as a function of change in pulse duration. Symmetric cathodic-first biphasic pulses are applied. Dash lines: the SOCB stimulus threshold, solid lines: the DA stimulus threshold (axonal activation). The gray and black lines show the passing axons diameters of $1.2\ \mu\text{m}$ and $0.8\ \mu\text{m}$, respectively. Shorter pulse width of 0.1 ms resulted in the highest excitation threshold difference between the SOCB and DA over a range of variations in passing axon diameters.

Fig. 8.

Anodic-first (AF). vs cathodic-first (CF) symmetric biphasic pulses: the SOCB and DA stimulus threshold difference for A2 and D1 cells. Results indicate that the sensitivity of the SOCB threshold is low not only to pulse duration changes, but also to modulations in polarity. Whereas, the DA threshold significantly changes with alterations in both pulse widths and stimulus polarity. Therefore, the excitation threshold difference between the SOCB and DA is greater using a short anodic-first biphasic waveform, offering a higher chance for more focalized response of RGCs.

Fig. 9.

Charge threshold as alterations in pulse durations for both A2 and D1 RGCs using cathodic-first biphasic pulses. The solid and dash lines represent the charge threshold of the DA and the SOCB, respectively. Data show that although current threshold increases as we shorten pulse widths, charge threshold remains low using short pulse durations.

TABLE I

RATE CONSTANTS OF IONIC CURRENTS

Na Channel	$\alpha_m = \frac{-0.6(E + 30)}{e^{-0.1(E + 30)} - 1}$ $\alpha_h = 0.4 e^{-(E + 50)/20}$	$\beta_m = 20 e^{-(E + 55)/18}$ $\beta_h = \frac{6}{e^{-0.1(E + 20)} + 1}$
Ca Channel	$\alpha_c = \frac{-0.3(E + 13)}{e^{-0.1(E + 13)} - 1}$	$\beta_c = 10 e^{-(E + 38)/18}$
K Channel	$\alpha_n = \frac{-0.02(E + 40)}{e^{-0.1(E + 40)} - 1}$	$\beta_n = 0.4 e^{-(E + 50)/80}$
A Channel	$\alpha_A = \frac{-0.006(E + 90)}{e^{-0.1(E + 90)} - 1}$ $\alpha_{h_A} = 0.04 e^{-(E + 70)/20}$	$\beta_A = 0.1 e^{-(E + 30)/10}$ $\beta_{h_A} = \frac{0.6}{e^{-0.1(E + 40)} + 1}$
h Channel	$\alpha_l = e^{0.08316(E + 75)}$	$\beta_l = e^{0.033264(E + 75)}$
T Channel	$\alpha_{m_T} = \left(1.7 + e^{-(E + 28.8)/13.5}\right)^{-1}$ $\alpha_{h_T} = e^{-(E + 160.3)/17.8}$ $\alpha_d = \frac{1 + e^{(E + 37.4)/30}}{240 \left(0.5 + \left(0.25 + e^{(E + 83.5)/6.3}\right)^{0.5}\right)}$	$\beta_{m_T} = \frac{e^{-(E + 63)/7.8}}{1.7 + e^{-(E + 28.8)/13.5}}$ $\beta_{h_T} = \alpha_{h_T} \left((0.25 + e^{(E + 83.5)/6.3})^{0.5} - 0.5 \alpha_{h_T} \right)$ $\beta_d = \alpha_d \left(0.25 + e^{(E + 83.5)/6.3} \right)^{0.5}$

TABLE II

MAXIMUM IONIC CONDUCTANCE VALUES FOR A2 AND D1 CELLS [S/cm²]

	RGC types			
	A2		D1	
	Soma	Dendrite	Soma	Dendrite
g_{Na}	0.3	0.1	0.2	0.08
g_K	0.12	0.05	0.211	0.08
$g_{K,A}$	$3 * g_K$	$3 * g_K$	$3 * g_K$	$3 * g_K$
$g_{K,Ca}$	$0.004 * g_K$	$0.004 * g_K$	$0.004 * g_K$	$0.004 * g_K$
g_{Ca}	0.137	0.05	0.013	0.01
g_h	0	0	0.0001	$3e-5$
g_T	0.004	0	0.0024	0.001

TABLE IIIMAXIMUM IONIC CONDUCTANCE VALUES OF THE AXON FOR A2 AND D1 CELLS [S/cm²]

	AH	SOCB	NS	DA
g_{Na}	0.2	2.4	0.4	0.2
g_K	0.1	0.8	0.2	0.1
$g_{K,A}$	$3 * g_K$	$3 * g_K$	$3 * g_K$	$3 * g_K$