Original Article :

Investigating Different Paradigms of Electrical Stimulation for Retinal Prosthesis.

Abdulrahman Alqahtani

Department of Medical Equipment Technology, College of Applied MedicalScience, Majmaah University, AL-Majmaah 11952, Saudi Arabia

Received on Jan 21, 2024, accepted for publication on March 01, 2024, dx.doi.org/10.5455/mjhs.2024.02.011

Corresponding author:
Abdulrahman Alqahtani
Department of Medical Equipment Technology, College of Applied MedicalScience, Majmaah University, AL-Majmaah 11952, Saudi Arabia
a.alqahtani@mu.edu.sa , +966551537752

OPEN ACCESS Distributed under Creative Commons CC BY-NC-ND 4.0

Abstract

Background and Aims:
Retinal prostheses have been suggested to restore vision for those with retinal diseases. This study aimed to identify the most effective stimulation approaches for retinal prostheses.

Methods:
This study examined various return electrode configurations on a realistic retinal ganglion cell model. Two return electrode configurations, monopolar and hexapolar, were implanted on epiretinal side. There were four waveforms used to send electrical current through the active electrode. The study also compared two stimulation methods: single stimulation and concurrent (parallel) stimulation.

Results:
Directly placing the retinal ganglion cell beneath the active electrode resulted in no significant difference in the required current for stimulating retinal ganglion cells between monopolar and hexapolar return electrodes, regardless of the stimulation waveform. For retinal ganglion cells located away from the active electrode, differences in the required current were noted between the two return electrode configurations. The study discovered that parallel stimulation with two or three active electrodes lowered current requirements by up to 70% compared to single stimulation. Monophasic anodic stimulation yielded the most effective pulse waveform, regardless of the configuration (monopolar or hexapolar) or stimulation mode (single or parallel). Moreover, monophasic cathodic stimulation usually targets retinal ganglion cells around the active electrode.

Conclusions:
These results illuminate the best stimulation strategies for enhancing the efficacy of retinal prosthesis. The study highlights the importance of electrode arrangement, waveform selection, and single or concurrent stimulation for improving retinal ganglion cell activation.

Keywords:
RGC, Monopolar, Hexapolar, Single Stimulation, Concurrent Stimulation, Pulse waveform.

Introduction

Vision impairment was projected to have a worldwide prevalence of 596 million individuals in 2020, with 43 million of them being classified as blind. It is projected that the prevalence of blindness will reach 61 million by 2050, as life expectancy continues to advance. Prolonged productivity losses in the United States alone are estimated to amount to 16.5 billion USD, which carries substantial economic ramifications on a global scale [1]. Permanent vision loss is commonly attributed to retinal degeneration, which is distinguished by the progressive degradation and impairment of photoreceptor function. The two most prevalent forms of retinal degenerative diseases are age-related macular degeneration (AMD) and retinitis pigmentosa (RP). Around 30 to 50 million individuals are afflicted with AMD on a global scale, whereas in the United States, the number exceeds 2 million. An estimated 1.5 million individuals globally are affected by RP [2]. As advancements in bioelectronics systems and biomaterials technology continue to progress, researchers are exploring the potential of bionic methods to restore functional vision for individuals with RP [3]. Different therapeutic approaches, such as laser treatments, gene therapies, and pharmacological interventions, are being investigated for the treatment of various degenerative vision disorders [4].

Retinal prostheses devices offer a promising approach for restoring vision in people with visual problems. These devices work by electrically activating the remaining retinal neurons. Different approaches for stimulation have been investigated in the study of visual prosthesis, such as epiretinal, subretinal, suprachoroidal, thalamic, extraocular, cortical, and optic nerve methods [5]. The three primary categories of retinal prostheses that have been suggested are epiretinal, subretinal, and suprachoroidal. The primary objective, irrespective of the particular variant employed, is to electrically stimulate the undamaged retinal ganglion cells in order to produce perceptual sensations that communicate visual data. Blind patients, following the implantation of retinal prostheses and participation in rehabilitation training, have demonstrated the ability to see and recognize basic shapes, as evidenced by clinical studies [6]. Nevertheless, the present resolution of these devices is still restricted and necessitates future enhancement.

Various operational and safety issues have an impact on the performance of retinal implants. An essential factor to consider is the level of charge injected, which must be kept under a safe threshold for the electrodes [6]. In order to avoid neurological

harm and electrode erosion, ensuring that the charge density on platinum electrodes does not exceed the established safe threshold of 300 μC cm−2 7. Furthermore, various research studies have found that the duration of the pulse, as well as its length, kind, and symmetry, have a notable influence on neuronal electrical stimulation [8, 9, 10]. Retinal implants have effectively used shorter pulses (0.1 ms) or bigger pulses (25 ms) to prevent the activation of passing axons, which can impact the resolution of the perceived picture [9]. Moreover, research has demonstrated that pulse asymmetry can lower the threshold required to activate retinal neurons. Hence, the examination of efficacious stimulation paradigms can aid in improving the efficacy of retinal prostheses.

The selection of return electrodes employed during electrical stimulation significantly affects the activation threshold and spatial activation, as evidenced by research conducted on cochlear and visual implants [6, 11]. Different configurations of return electrodes, including monopolar, bipolar, tripolar, and hexapolar, have been suggested for cochlear and visual prostheses. In general, these investigations have demonstrated that the monopolar arrangement stimulates neurons with a lower charge injection, whereas other configurations result in more localized activation [6, 11].

The effects of return electrode configurations on retinal electrical stimulation were investigated in this research. With epiretinal stimulation, this investigation employs a model of retinal ganglion cells (RGCs) that are morphologically realistic. This study also investigates, besides the two distinct return electrode configurations, the influence of either single or concurrent stimulation and the influence of pulse waveforms.

Methods

The finite-element simulation software (COMSOL AB, Sweden) was utilized to accurately reproduce the morphologically realistic model of a rabbit OFF retinal ganglion cell (RGC) as described by 12, with the necessary modifications. A semi-ellipsoid shape was positioned around the OFF RGC cell in order to represent the extracellular environment. This cellular structure was composed of the following components: an axon, a soma, dendrites, an axon hillock, and an axon initial segment (AIS) (Fig. 1a). The electrodes were arranged in a hexagonal configuration in the shape of circular discs, each measuring 200 μm in diameter, with a distance of 400 μm between their centers (see Figure 1c). The active electrode in the hexagonal configuration was the central electrode, while the return electrodes, denoted as six adjacent

local electrodes connected to the ground, functioned as return electrodes (see Figure 1c). In the monopolar configuration, the return electrode was positioned at a considerable distance, specifically at the lower boundary of the ellipsoid (Fig. 1b).

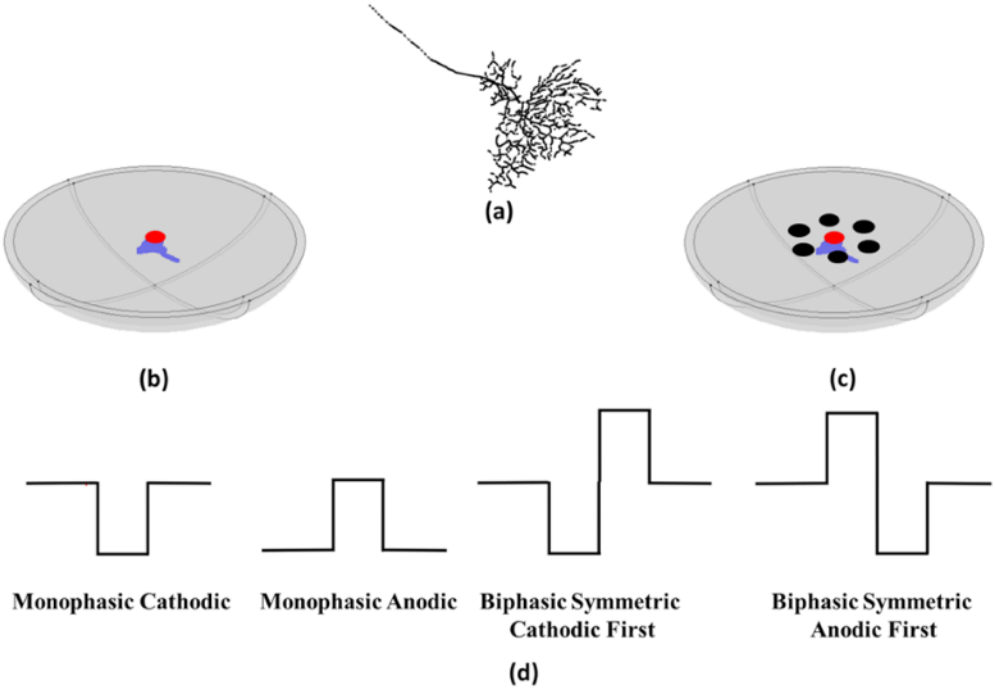


Fig. 1 The setup of the models used for epiretinal stimulation—(a) the realistic OFF RGC (b) the monopolar return electrodes (c) the hexapolar return electrodes and (d) the four stimulus waveforms employed in this study. The red circles indicate the active electrodes, while the black circles denote the return electrodes.

The four waveforms utilized were monophasic cathodic, biphasic anodic, and biphasic cathodic first pulses; all four were symmetric charge-balanced and had a duration of 0.5 ms without an interphase delay (Fig. 1d). In order to determine the thresholds required to activate the RGCs, the RGC was placed 120 µm below the active electrode. Also, measurements were taken at three (single active electrode) or five (two and three active electrodes) different spots, both 120 µm vertically, 400 µm, and 800 µm to the left and right of the active electrode's plane.

It is necessary to clarify a few abbreviations that will be used more frequently in subsequent sections of this document. Four pulse waveforms were employed in this study: monophasic anodic (MA), monophasic cathodic (MC), biphasic anodic (BA), and biphasic cathodic (BC). Additionally, there are five designated measurement locations: center (C), right (R), left (L), far right (FR), and far left (FL).

Mathematical Formulations

In our discrete model of the OFF retinal ganglion cell (RGC), the distribution of extracellular voltage (V_e) was deter-

mined by Poisson's equation:

$$\nabla.(-\sigma_b \nabla V_e) = I \quad (1)$$

where in the equation, the electric conductivity of the vitreous layer, denoted as σ_b and measured at 1.28 (S/m) [13], and the volumetric current density I resulting from the flow of cell membrane current, are considered.

Based on the varying-radius cable equation, the RGC activation was calculated using the following formula [14]:

$$\frac{\partial}{\partial_x}\left[\frac{r^2}{2p_i}\frac{\partial V_m}{\partial x}\right] = r\,(C_m \frac{dV_m}{dt} + i_{ion}) \quad (2)$$

where in the equation, the membrane potential is denoted as V_m, x represents the axial cable distance, r describes the radius of the retinal ganglion cell (RGC) compartment (μm), ρ_i represents the intracellular resistivity, which was set to 110 Ω • cm, and the membrane capacitance (C_m) is expressed as a function of membrane area (μF /cm2). The total ionic current flowing through the RGC membrane, also expressed as a function of membrane area, is indicated by the symbol i_ion.

For a more comprehensive understanding of the model, including the gating variables, detailed ionic current formulations, conductance, and kinetic parameter values for each rate and RGC compartment, please refer to [12].

Results

Single Monopolar vs Single Hexapolar Electrodes Configuration

To evaluate the required current for activating retinal ganglion cells (RGCs) through epiretinal electrical stimulation, we conducted assessments using both monopolar and hexapolar return electrode designs. Our simulations, depicted in Fig.2, revealed that there was no statistically significant distinction in current thresholds between monopolar and hexapolar configurations when the RGC was positioned directly beneath the stimulating electrode, regardless of the four different stimulus waveforms employed. The threshold of RGC activation was the lowest with MA pulse in monopolar settings at all three locations and in hexapolar settings only in the center compared to other pulse waveforms. Measurements taken on the right side were lower compared to measurements on the left side when using either monopolar or hexapolar configurations with MA or BA pulses. In contrast, when MC or BC pulses were employed, no significant difference was observed between right and left measurements for either monopolar or hexapolar electrode configurations. This variation in the threshold between right and left measurements, even with the same distance of 400 μm could come

from the morphology of RGC dendrites or from the influence of the pulse waveform itself. In hexapolar settings when the RGC was moved to the left, the threshold was increased by more than 1255% (MA pulse), 800% (MC pulse), 800% (BA pulse), and 580% (BC pulse) compared to the center measurements. In hexapolar settings when the RGC was moved to the right, the threshold was increased by more than 1000% (MA), 770% (MC), 640% (BA), and 660% (BC) compared to the center measurements. In monopolar settings when the RGC was moved to the left, the threshold was increased by more than 660% (MA), 700% (MC), 550% (BA), and 475% (BC) compared to the center measurements. In monopolar settings when the RGC was moved to the right, the threshold was increased by more than 450% (MA), 730% (MC), 400% (BA), and 515% (BC) compared to the center measurements.

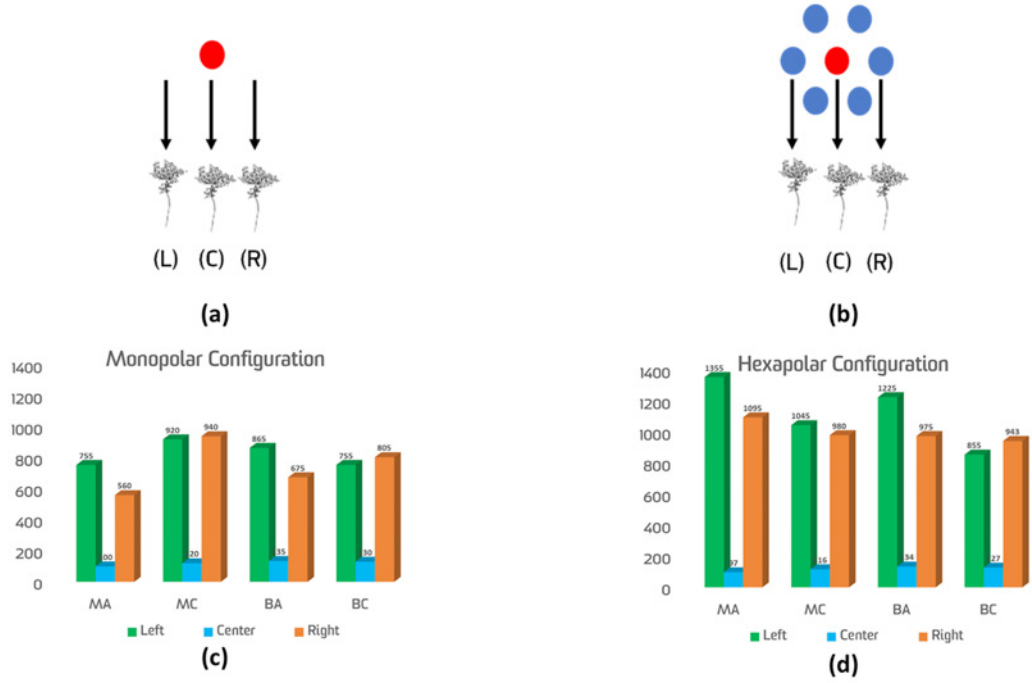


Fig. 2 The three RGC measurement sites for the configurations of the single monopolar and hexapolar electrodes (a, b) and the current thresholds in (μA) for the single monopolar and hexapolar electrodes (c, d) with using the four pulse durations: monophasic anodic (MA), monophasic cathodic (MC), biphasic anodic (BA) and biphasic cathodic (BC). R is pointing to the right, C is pointing to the center, and L is pointing to the left. The red circles indicate the active electrodes, while the blue circles denote the return electrodes.

Two Active Monopolar vs Two Active Hexapolar Electrodes Configuration

In the two active monopolar and two active hexapolar electrodes configuration, the right and left locations are like the center location in the single monopolar configuration, whereas the far left and far right locations are like the left and right locations, respectively (Fig.3). The left and right measurements in the two monopolar

and two hexapolar configurations are almost similar to the center measurements in the single electrode configurations. MA waveform had the lowest threshold for both monopolar and hexapolar at all five locations compared to other pulse waveforms, except for the far left location of monopolar electrodes settings. When the active electrode was directly above the RGC (left & right locations), the required activation current was similar for both monopolar and hexapolar with using BA or BC waveforms. In the center measurements in two hexapolar settings, the threshold was reduced by around 50 % for all used pulse waveforms (MA, MC, BA, BC) compared to either far right or far left measurements. In the center measurements in two monopolar settings, the threshold was reduced by around 50 % for pulse waveforms (MA & BA) compared to either far right or far left measurements whereas there is no significant variation when using MC or BC. In the two hexapolar electrodes configuration at the center location, the threshold was reduced by more 70% (MA), 50% (MC), 65% (BA), and around 50% (BC) compared to the left measurements of single hexapolar measurements. In the two hexapolar electrodes configuration at the center location, the threshold was reduced by more than 65% (MA), around 50% (MC), around 60% (BA), and 50% (BC) compared to the right measurements of single hexapolar measurements. In the two monopolar electrodes configuration at the center location, the threshold was reduced around 60% (MA), 10% (MC), 60% (BA), and 14% (BC) compared to the left measurements of single monopolar measurements. In the two monopolar electrodes configuration at the center location, the threshold was reduced 45% (MA), 13% (MC), 45% (BA), and 20% (BC) compared to the right measurements of single monopolar measurements. At the center location of two active electrodes settings, monopolar configuration exhibited an increase in current threshold of 60% and around 50% when using monophasic cathodic and biphasic cathodic first, respectively, compared to the two active hexapolar electrodes configuration whereas there is no significant difference between these two electrodes configuration when using either monophasic anodic or biphasic anodic first. In the two hexapolar electrodes configuration at the far left (FL) location, the threshold was reduced by around 55% (MA), no difference (MC), 35% (BA), and increased by around 10% (BC) compared to the left measurements of single hexapolar measurements. In the two monopolar electrodes configuration at the far left (FL) location, the threshold was almost similar for all pulses compared to the left measurements

of single monopolar measurements. In the two hexapolar electrodes configuration at the far right (FR) location, the threshold was reduced by around 42% (MA), 15% (MC), 33% (BA), and 20% (BC) compared to the right measurements of single hexapolar measurements. In the two monopolar electrodes configuration at the far right (FR) location, the threshold was almost similar for all pulses compared to the right measurements of single monopolar measurements.

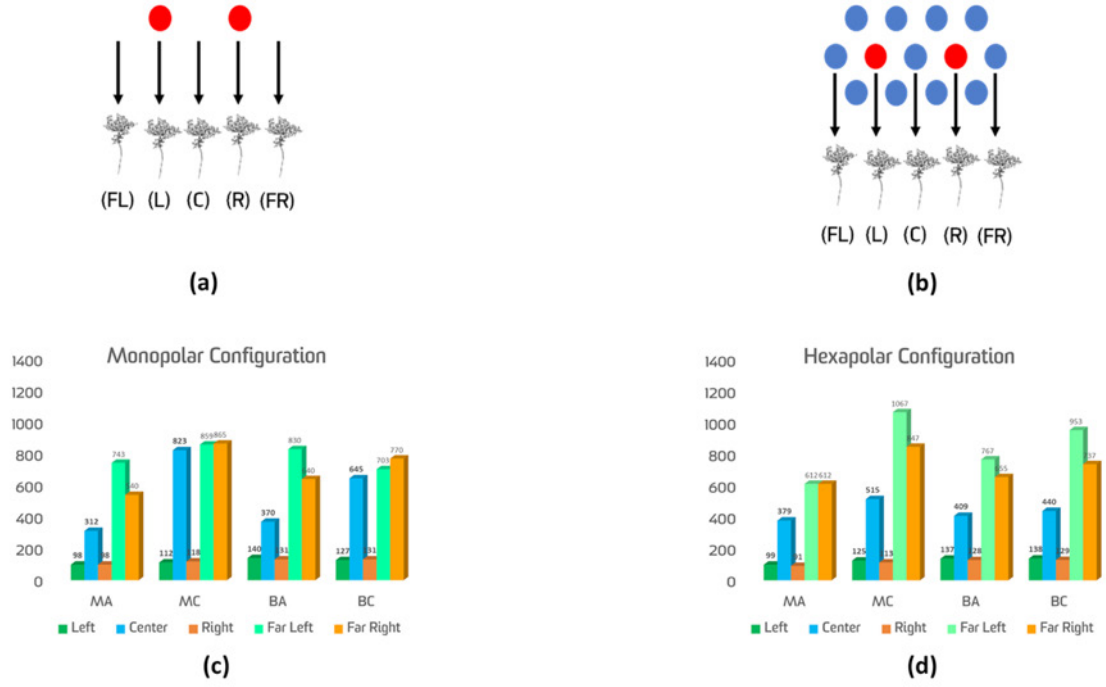


Fig. 3 The five RGC measurement sites for the configurations of the two active monopolar and two active hexapolar electrodes (a, b) and the current thresholds in (μA) for the two active monopolar and two active hexapolar electrodes (c, d) with using the four pulse durations. FR is pointing to the far right and FL is pointing to the far left. The red circles indicate the active electrodes, while the blue circles denote the return electrodes.

Three Active Monopolar vs Three Active Hexapolar Electrodes Configuration

In the three active monopolar and three active hexapolar electrodes configuration, the center, right and left locations are like the center location in the single monopolar configuration, whereas the far left and far right locations are like the left and right locations, respectively (Fig.4). The (MA) pulse almost had the lowest threshold (68 μA) among all pulses and all five locations when using either three active monopolar or three active hexapolar electrodes configuration. This value (68 μA) was the lowest measurement among all measurements in this study and there was a reduction in the current threshold by 30 % and 20% for hexapolar and monopolar configuration compared to either a single hexapolar or monopolar electrodes config-

uration. Moreover, there is a reduction in current thresholds extending from 10% to 30% at the center location among all pulse waveforms when using either monopolar or hexapolar electrodes configuration compared to the center measurements for either single monopolar or single hexapolar electrodes configuration. Compared to the left measurement of the single hexapolar electrodes configuration, three active hexapolar electrodes configuration at the far left measurements exhibited a reduction in current thresholds ranging from 11% to 33% among all pulse waveforms. Compared to the right measurement of the single hexapolar electrodes configuration, three active hexapolar electrodes configuration at the

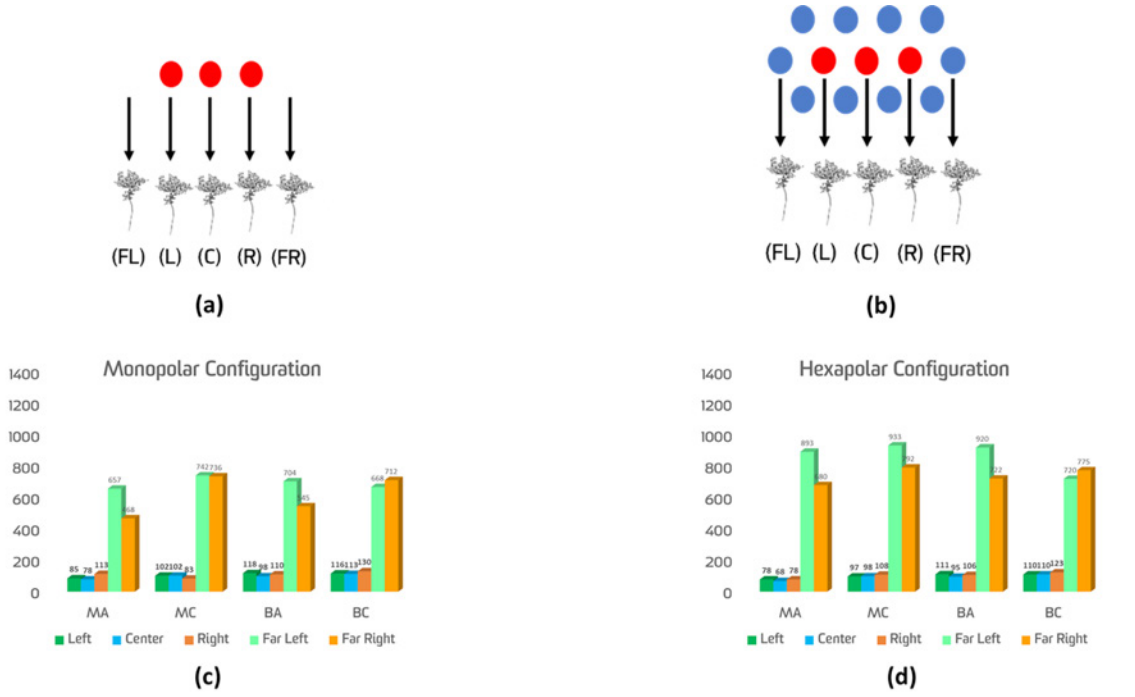


Fig. 4 The five RGC measurement sites for the configurations of the Three active monopolar and three active hexapolar electrodes (a, b) and the current thresholds in (μA) for the three active monopolar and three active hexapolar electrodes (c, d) with using the four pulse durations. The red circles indicate the active electrodes, while the blue circles denote the return electrodes.

far right measurements exhibited a reduction in current thresholds ranging from 18% to 36% among all pulse waveforms. Compared to the left measurement of the single monopolar electrodes configuration, three active monopolar electrodes configuration at the far left measurements exhibited a reduction in current thresholds ranging from 10% to 20% among all pulse waveforms. Compared to the right measurement of the single monopolar electrodes configuration, three active monopolar electrodes configuration at the far right measurements exhibited a reduction in current thresholds ranging from 13% to 21% among all pulse waveforms. When the active electrodes are

positioned directly above the retinal ganglion cell (RGC) (center location), there is no notable distinction found between monopolar and hexapolar electrode configurations among all pulse waveforms. In the three active electrodes settings at the far left location measurements, the monopolar electrodes configuration showed a decrease in current thresholds compared to the hexapolar electrodes configuration ranging from 7% to 27% among all pulse waveforms.

Discussion

Regardless of the four different stimulus waveforms and the use of single or concurrent stimulation paradigms (with two or three active electrodes), our simulations did not reveal a statistically significant difference between the monopolar and hexapolar current thresholds when the retinal ganglion cell (RGC) was positioned directly beneath the stimulating electrode, as seen in (Figures 2,3 and 4). These findings appear to contradict the general agreement among in vitro and in vivo investigations [6, 11, 15]. Prior studies have demonstrated that the required current for activating RGCs using the hexapolar configuration is generally greater than twice as high as that for the monopolar configuration. However, the results of a previous study that used computer modeling and in vitro testing showed that the current thresholds needed to stimulate RGCs during suprachoroidal electrical stimulation are not significantly different between monopolar and multipolar configurations and are closely aligned with our simulations [16]. In addition, our simulations align with recent modeling studies that show the difference between monopolar and hexapolar approaches is minimal when the distance between the electrodes and the targeted tissue is greater than the diameter of the electrodes [7, 17, 18].

The disparity in current thresholds between monopolar and hexapolar return electrode configurations becomes apparent when the retinal ganglion cell (RGC) is situated at a significant distance from the stimulating electrode, as illustrated in (Figures 2, 3, and 4). When the RGC is positioned 400 μm to the left, the hexapolar arrangement shows current thresholds that are 1.1 to 1.8 times greater than those of the monopolar design for all pulse durations. Similarly, when the RGC is placed at the same distance on the right side, the hexapolar configuration shows a range of current thresholds that is 1.05 to 2 times higher than the monopolar configuration. This indicates a more significant difference in current thresholds between the two setups of return electrodes (Fig. 2). In the two active electrodes settings measurements, monopolar and hexapolar configurations

showed almost similar current thresholds in the far right location. In contrast, the monopolar configuration exhibited higher current thresholds than hexapolar with anodic pulses by 1.2 times with MA and 1.08 times with BA, whereas the hexapolar configuration showed higher thresholds than monopolar with cathodic pulses by 1.24 times with MC and 1.35 times with BC in the far left location (Fig. 3). In the three active electrodes settings measurements, hexapolar electrode settings displayed an increase in current threshold compared to monopolar electrode settings in all pulses, ranging from 1.06 to 1.44 times in either the far right or far left locations, with the obvious variation coming with the anodic pulses (Fig. 4). This finding suggests that a significant distinction exists between the two types of return electrodes, but only for those RGCs positioned at a considerable distance from the active electrode, even when the distance between the active electrode and the RGC is smaller than the diameter of the electrode. These significant findings integrate and provide an explanation for several in vivo and in vitro experiments [6, 11, 15]. These experiments generally found that the monopolar configuration necessitated lower current thresholds than the hexapolar configuration. In contrast, a few in vitro and modeling studies [7, 17, 18] concluded that there is no significant distinction between monopolar and hexapolar configurations.

The retinal electrical stimulation might be substantially altered by concurrent (parallel) stimulation. During concurrent stimulation, the interaction in the electric field between two monopolar or two hexapolar active electrodes is evident for all pulses employed. As shown in Figure 3, this interaction has the potential to substantially decrease the current needed to activate RGCs by as much as 70% and 60% for hexapolar and monopolar configurations, respectively,

in comparison to measurements taken with a single monopolar or hexapolar electrode configuration. Furthermore, it is observed that the center measurements for stimulation of three active electrodes with a monopolar or hexapolar electrode configuration result in 30% lower current thresholds across all pulse waveforms, in comparison to the center measurements obtained with a single monopolar or single hexapolar electrode configuration (see Figures 2 & 4). These findings are consistent with the results of an in vitro experiment conducted on feline retinae [15] which demonstrated that concurrent monopolar stimulation decreased the thresholds by 20%, and with a modeling study [7] which found that parallel stimulation reduced the required current by as much as 53%. Par-

allel stimulation appears to induce significant interference between adjacent electric fields, according to these findings. It is noteworthy that a clinical trial involving blind participants and epiretinal implants documented this effect [19].

The predominant type of pulses used in retinal prostheses is biphasic charge-balanced pulses, which typically begin with a cathodic initial pulse [20, 21, 22]. The anodic phase of the pulse hyperpolarizes nearby neurons 20, while the cathodic phase depolarizes neurons in close proximity to the stimulating electrode, leading to the generation of action potentials. When the electrode is in close proximity to neural cells, a cathodic pulse requires a lower charge to elicit an action potential [21]. However, some in vitro studies using subretinal prostheses have shown that

anodal stimulation requires a lower charge to elicit an action potential compared to cathodal stimulation [20, 22]. The proximity and positioning of the stimulating electrode with respect to retinal neurons play crucial roles in neuronal responses [7, 22]. Our simulations extensively elucidated the effects of pulse duration on epiretinal electrical stimulation of retinal ganglion cells (RGCs). We found that, in general, the current threshold was lowest for monophasic anodic pulse duration, regardless of the location and whether single or parallel stimulation (involving two or three active electrodes) was used. This observation is consistent with recent research findings [8, 10, 20, 22] (Figures 2, 3 & 4). Furthermore, in hexapolar configurations, the biphasic cathodic pulse was found to be more efficient in initial charge injection, except when the RGCs were directly beneath the stimulating electrode. This aligns with the findings of an experimental study conducted by [23] on optimization, as illustrated in Figure 2b. Furthermore, it was observed that the monophasic cathodic pulse duration, as opposed to all other pulse durations that target the RGC axon, successfully stimulated the RGCs situated beneath the stimulating electrode (results not shown). This pulse specifically targets the soma or axon initial segment (AIS) of the RGC rather than its distal axon, which is consistent with the findings of [10]. The activation of the axon occurred prior to the soma or AIS, irrespective of the duration of the applied pulse, when the RGC was positioned away from the stimulating electrode (results not shown). One of the challenges associated with retinal implants is preferable retinal activation; this discovery will be beneficial in addressing this issue.

Conclusion

The effect of return electrode configuration on retinal electrical stimulation was

examined under two forms of stimulation (single and parallel) and four distinct current pulse types. When the distance between the stimulating electrode and the RGC is less than the diameter of the electrode (RGC is positioned directly below the stimulating electrode), current thresholds for both hexapolar and monopolar return electrode configurations are comparable. When RGC is positioned remotely from the stimulating electrode on the left or right, monopolar return configuration requires less current for activating RGCs compared to hexapolar configuration. For nearly all locations and for both single and parallel stimulation (two to three active electrodes), the monophasic anodic current waveform was more effective in both hexapolar and monopolar configurations. Concurrent or parallel stimulation, using two or three active electrodes, can decrease the necessary current for activating retinal ganglion cells (RGCs) by up to 70% compared to single stimulation.

Conflict of Interest

No conflicts of interest, financial or otherwise, are declared by the authors.

References

1. Borda E, Ghezzi D. Advances in visual prostheses: engineering and biological challenges. Progress in Biomedical Engineering. 2022 Aug 5;4(3):032003.
2. Yue L, Weiland JD, Roska B, Humayun MS. Retinal stimulation strategies to restore vision: Fundamentals and systems. Progress in retinal and eye research. 2016 Jul 1;53:21-47.
3. Zrenner E. Will retinal implants restore vision?. Science. 2002 Feb 8;295(5557):1022-5.
4. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. New England Journal of Medicine. 2008 Jun 12;358(24):2606-17.
5. Li M, Yan Y, Wang Q, Zhao H, Chai X, Sui X, Ren Q, Li L. A simulation of current focusing and steering with penetrating optic nerve electrodes. Journal of neural engineering. 2013 Oct 18;10(6):066007.
6. Shivdasani MN, Luu CD, Cicione R, Fallon JB, Allen PJ, Leuenberger J, Suaning GJ, Lovell NH, Shepherd RK, Williams CE. Evaluation of stimulus parameters and electrode geometry for an effective suprachoroidal retinal prosthesis. Journal of neural engineering. 2010 May 18;7(3):036008.
7. Abramian M, Lovell NH, Habib A, Morley JW, Suaning GJ, Dokos S. Quasi-monopolar electrical stimulation of the retina: a computational modelling study. Journal of neural engineer-

ing. 2014 Feb 21;11(2):025002.

8. Tong W, Meffin H, Garrett DJ, Ibbotson MR. Stimulation strategies for improving the resolution of retinal prostheses. Frontiers in neuroscience. 2020 Mar 26;14:262.
9. Weitz AC, Nanduri D, Behrend MR, Gonzalez-Calle A, Greenberg RJ, Humayun MS, Chow RH, Weiland JD. Improving the spatial resolution of epiretinal implants by increasing stimulus pulse duration. Science translational medicine. 2015 Dec 16;7(318):318ra203-.
10. Chang YC, Ghaffari DH, Chow RH, Weiland JD. Stimulation strategies for selective activation of retinal ganglion cell soma and threshold reduction. Journal of neural engineering. 2019 Feb 4;16(2):026017.
11. Matteucci PB, Chen SC, Tsai D, Dodds CW, Dokos S, Morley JW, Lovell NH, Suaning GJ. Current steering in retinal stimulation via a quasimonopolar stimulation paradigm. Investigative ophthalmology & visual science. 2013 Jun 1;54(6):4307-20.
12. Guo T, Tsai D, Morley JW, Suaning GJ, Kameneva T, Lovell NH, Dokos S. Electrical activity of ON and OFF retinal ganglion cells: a modelling study. Journal of Neural Engineering. 2016 Feb 23;13(2):025005.
13. Alqahtani A, Al Abed A, Guo T, Lovell NH, Dokos S. A continuum model of electrical stimulation of multi-compartmental retinal ganglion cells. In2017 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) 2017 Jul 11 (pp. 2716-2719). IEEE.
14. Alqahtani A, Alabed A, Alharbi Y, Bakouri M, Lovell NH, Dokos S. A varying-radius cable equation for the modelling of impulse propagation in excitable fibres. International Journal for Numerical Methods in Biomedical Engineering. 2022 Aug;38(8):e3616.
15. Matteucci PB, Barriga-Rivera A, Eiber CD, Lovell NH, Morley JW, Suaning GJ. The effect of electric cross-talk in retinal neurostimulation. Investigative ophthalmology & visual science. 2016 Mar 1;57(3):1031-7.
16. Eiber CD, Dokos S, Lovell NH, Suaning GJ. Multipolar field shaping in a suprachoroidal visual prosthesis. IEEE Transactions on Neural Systems and Rehabilitation Engineering. 2017 Jul 24;25(12):2480-7.
17. Moghaddam GK, Lovell NH, Wilke RG, Suaning GJ, Dokos S. Perfor-

mance optimization of current focusing and virtual electrode strategies in retinal implants. Computer methods and programs in biomedicine. 2014 Nov 1;117(2):334-42.

18. Alqahtani A, Al Abed A, Lovell NH, Dokos S. Optimizing stimulation strategies for retinal electrical stimulation: A modelling study. In2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) 2019 Jul 23 (pp. 2872-2875). IEEE.

19. Horsager A, Greenberg RJ, Fine I. Spatiotemporal interactions in retinal prosthesis subjects. Investigative ophthalmology & visual science. 2010 Feb 1;51(2):1223-33.

20. John SE, Shivdasani MN, Williams CE, Morley JW, Shepherd RK, Rathbone GD, Fallon JB. Suprachoroidal electrical stimulation: effects of stimulus pulse parameters on visual cortical responses. Journal of Neural Engineering. 2013 Aug 8;10(5):056011.

21. Liang T, Zhao L, Sui X, Zhou C, Ren Q, Qi Y. Threshold suprachoroidal-transretinal stimulation current required by different-size electrodes in rabbit eyes. Ophthalmic Research. 2011 Sep 17;45(3):113-21.

22. Jensen RJ, Rizzo III JF. Thresholds for activation of rabbit retinal ganglion cells with a subretinal electrode. Experimental eye research. 2006 Aug 1;83(2):367-73.

23. Hadjinicolaou AE, Savage CO, Apollo NV, Garrett DJ, Cloherty SL, Ibbotson MR, O'Brien BJ. Optimizing the electrical stimulation of retinal ganglion cells. IEEE Transactions on neural systems and rehabilitation engineering. 2014 Oct 17;23(2):169-78.