Activation and inhibition of retinal ganglion cells in response to epiretinal electrical stimulation: a computational modelling study
Activation and inhibition of retinal ganglion cells in response to epiretinal electrical stimulation: a computational modelling study

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Abstract
Objective. Retinal prosthetic devices aim to restore sight in visually impaired people by means of electrical stimulation of surviving retinal ganglion cells (RGCs). This modelling study aims to demonstrate that RGC inhibition caused by high-intensity cathodic pulses greatly influences their responses to epiretinal electrical stimulation and to investigate the impact of this inhibition on spatial activation profiles as well as their implications for retinal prosthetic device design.

Another aim is to take advantage of this inhibition to reduce axonal activation in the nerve fibre layer. Approach. A three-dimensional finite-element model of epiretinal electrical stimulation was utilized to obtain RGC activation and inhibition threshold profiles for a range of parameters.

Main results. RGC activation and inhibition thresholds were highly dependent on cell and stimulus parameters. Activation thresholds were 1.5, 3.4 and 11.3 μA for monopolar electrodes with 5, 20 and 50 μm radii, respectively. Inhibition to activation threshold ratios were mostly within the range 2–10. Inhibition significantly altered spatial patterns of RGC activation. With concentric electrodes and appropriately high levels of stimulus amplitudes, activation of passing axons was greatly reduced. Significance. RGC inhibition significantly impacts their spatial activation profiles, and therefore it most likely influences patterns of perceived phosphenes induced by retinal prosthetic devices. Thus, this inhibition should be taken into account in future studies concerning retinal prosthesis development. It might be possible to utilize this inhibitory effect to bypass activation of passing axons and selectively stimulate RGCs near their somas and dendrites to achieve more localized phosphenes.

Keywords: epiretinal electrical stimulation, computational modelling, retinal ganglion cells, retinal prosthesis

(Some figures may appear in colour only in the online journal)

1. Introduction

Retinal prosthetic devices aim to restore vision in patients suffering from outer retinal degeneration by means of electrical stimulation of the surviving neurons, such as retinal ganglion cells (RGCs), which are known to remain largely viable and functional [1, 2]. Although several clinical trials have reported that phosphenes can be evoked in blind subjects via electrical stimulation of the retina [3–6], the induced images have sub-optimal quality and resolution. Most of these
studies report perception of only a limited number of phosphenes, which often lack predictable shapes and locations within the visual field [7]. The complexity of the induced phosphenes is more prominent when multiple electrodes are used for stimulation [7–9]. On the other hand, to allow simple task performance such as face recognition and navigation, the implanted array may need to consist of several hundred electrodes [10–12] and be capable of inducing a large number of localized phosphenes with desired spatial patterns.

To better understand how RGCs respond to electrical stimuli and to determine appropriate stimulus parameters to improve the performance of retinal implant devices, extensive experimental and modelling studies have been carried out over the past decade [13–21]. In many of these studies, to quantify RGC behaviour in response to electrical stimulation, activation thresholds were measured. However, the impact of a second threshold, termed inhibition threshold, on shaping these responses has been almost completely overlooked. This inhibition is a result of hyperpolarization of the neural membrane following electrical stimulation (see a review by Ranck [22]), as described below. To the best of our knowledge, the implications of this inhibitory effect for retinal implant design have not been explored previously.

When an extracellular electrode delivers cathodic pulses to a neuron, a decrease in extracellular potential locally depolarizes the cell membrane. According to the principle of current conservation, current cannot be generated or destroyed. Thus for a focal depolarizing current at the stimulation site, there is a hyperpolarizing current of equal magnitude elsewhere in the neuron, which spreads over a larger membrane region and is therefore relatively weak. Hence, if an action potential (AP) is initiated at the depolarized region, it can often propagate through these weakly hyperpolarized areas of the neuronal membrane. However, when cathodic stimulus pulses are well above activation threshold, intense depolarization of the cell membrane occurs at the stimulation site, which consequently results in excessive hyperpolarization of the nearby regions. This strong hyperpolarization can inhibit AP initiation and/or propagation. Therefore, paradoxically, an electrode which is delivering high amplitude cathodic pulses might be incapable of activating a nerve fibre [22]. This effect has been shown in experimental studies, where cathodic currents 2–3 times activation threshold inhibited APs in motor nerves [23], and those 8–10 times threshold produced AP inhibition in spinal cord neurons [24, 25]. A computational modelling study has quantified this effect, estimating the lower and upper threshold limits for nerve fibres [26].

A result of this membrane hyperpolarization is that neurons which have low thresholds and/or are located too close to the stimulating electrodes may well be inhibited, while those which have higher thresholds and/or are located further away from the electrode might be activated due to more moderate levels of depolarization and hyperpolarization of their neuronal membrane [22]. An experimental study has taken advantage of this hyperpolarization effect to selectively activate high-threshold small motor axons in cats, while inhibiting those with larger diameters and lower activation thresholds [27].

With stimulus amplitudes several times above activation threshold, as are commonly used in clinical trials, excessive RGC hyperpolarization is likely to be a significant contributor in forming retinal activation patterns. Such high stimulus intensities will lead to high levels of RGC inhibition near the electrodes, while resulting in activation of RGCs and axons further away. Such an effect would result in a shift of activation regions, causing percepts in unwanted sites within the visual field. This could at least in part be the reason for unpredictable phosphenes and shapes reported in clinical studies.

The aim of the present study was to investigate RGC inhibition thresholds and their spatial activation patterns as a function of cell and stimulus parameters following epiretinal electrical stimulation. Another aim was to explore the possibility of utilizing this inhibitory effect to bypass activation of passing axons in the retinal nerve fibre layer, which have lower thresholds and are located closer to epiretinal stimulating electrodes, while selectively activating RGC somas and dendrites.

2. Methods

A 3D computational model of epiretinal electrical stimulation of RGCs was implemented in COMSOL Multiphysics 4.3a software (COMSOL AB, Sweden). The RGC model was based on the ionic formulation of Fohrmeister et al [28], as described below.

2.1. Retinal and RGC geometry

The model geometry consisted of a 1 mm × 1.4 mm × 140 μm domain, which comprised of several conductive volumes representing the retinal layers (figure 1(a)). RGCs were embedded within the retina and the cell geometry was reconstructed from morphological data of small-area rat RGCs reported by Fohrmeister et al [28]. The RGC was implemented as an equivalent-cylinder cable model, consisting of one-dimensional infinitesimally-thin edge segments representing the soma, dendrites, axonal initial segment (AIS) and high sodium channel density (HSCD) band, as well as the distal axon (figure 2), with radii (r in equation (6)) of 10, 0.4, 0.5, 0.3 and 0.5 μm, respectively. The dendritic tree was approximately 100 μm in diameter, roughly three times smaller than that reported by Fohrmeister et al [28]. This smaller dendritic tree was chosen so that the RGC in the present study would be more comparable in size with midget cells in human retina [29]. For simplicity, all dendrites were positioned in the same lateral plane. The length of the geometric edges representing the soma and the HSCD region were 10 and 90 μm, respectively [28]. The distal axon was >600 μm in length and extended from the distal end of the HSCD band to the geometric boundary of the model domain.

To provide direct comparison between relative excitability of the various neuronal elements, in an initial set of
Figure 1. Model geometry consisted of retinal layers, RGCs and epiretinal stimulating electrodes placed on the retinal surface. To represent the retinal nerve fibre layer, two arrays of RGCs were positioned 5 and 20 μm below the retinal surface, with 10 μm lateral spacing. The somas of these cells were at least 0.5 mm from the stimulation site. To avoid complexity of the model geometry, the dendritic trees of these RGCs were removed. Near the stimulating electrodes, RGCs were either centred under the electrode (as shown here) or were positioned 50 or 100 μm laterally. At each lateral position, there were two RGCs with dendritic trees located at 30 and 40 μm depths, while their HSCD bands and axons were positioned 5 μm below the retinal surface. The entire model geometry (a) as well as the zoomed-in side view (b) and top view (c) of the epiretinal electrodes, RGCs and passing axons are shown.

Figure 2. Cell geometry was reconstructed from the morphological data of a small-area rat RGC reported by Fohmistein et al [28]. The RGC consisted of edge segments representing the soma, dendrites, AIS and HSCD band, as well as the distal axon. All dendrites were placed within the same lateral plane. The dendritic tree of the RGC shown here is positioned 40 μm below the retinal surface. Other cases where the dendritic tree was 5 or 30 μm below the retinal surface were also tested. In all cases, the axon was located 5 μm below the retinal surface.

Simulations all of these elements were positioned at the same depth, 5 μm below the retinal surface. In the subsequent simulations, the soma and the dendritic tree were moved deeper into the retina, 30 or 40 μm below the retinal surface, to better represent the RGC architecture. Figure 2 illustrates the case where the RGC dendritic tree is located 40 μm below the retinal surface. In all cases, the AIS connected the soma to the HSCD band such that the proximal end of the HSCD band was always positioned at a 45 μm lateral distance from the soma. For the RGC located at 5 μm depth, the AIS consisted of a 45 μm straight line segment; while for deeper RGCs, the AIS was a cubic Bezier curve, as shown in figure 2. Activation of the AIS, including the effect of its geometry, was not systematically investigated.

In some simulations, the spatial extent of retinal activation was investigated. To represent passing axons, two arrays of RGCs were positioned 5 and 20 μm below the retinal surface, with 10 μm lateral spacing (figure 1). The somas of these cells were at least 0.5 mm from the stimulation site. There were 20 cells in each row. This number was chosen so that the full lateral extent of activation could be studied (i.e. the furthest axons were never activated). To avoid complexity of the model geometry, the dendritic trees of these RGCs were removed. Owing to the large distance from the stimulating electrodes, removal of the dendritic trees had no appreciable effect on activation of the distal axons (data not shown). Because of the geometrical symmetry, these passing axons were placed on one side of the electrodes only. Near the stimulation site, RGCs were either centred under the stimulating electrode (as is the case for RGCs in figure 1) or were positioned 50 or 100 μm laterally. At each position, there were two RGCs with dendritic trees located at 30 and 40 μm depths, while their HSCD band and axons were positioned 5 μm below the retinal surface. Performing one set of simulations that included all of these cells would be computationally demanding, due to the large number of elements that would be required to mesh all the neurons present. Instead, the model geometry was subdivided such that one set of simulations were performed for all of the passing axons, and one set was conducted for each of the lateral cell positions. There were seven lateral positions in total. Hence, a total of eight sets of simulations were conducted for each electrode configuration. All model parameters were kept fixed throughout these simulations. It was found that the presence of neighbouring cells had no impact on RGC activation. Hence, performing separate simulations did not influence the outcome.

2.2. Model formulation

The extracellular voltage ($V_e$) distribution was given by:

\[ \nabla \cdot (-\sigma_e \nabla V_e) = I_n + I_{lim}. \]  

(1)

where $\sigma_e$ is the local conductivity of each retinal layer. These
Figure 3. Conductivities of the retinal layers. Filled circles are the experimental values reported by Kasi et al. [30]. For simplicity in the present model, neighboring conductivity values from the experimental data were averaged, yielding seven conductivity values (columns) for the retinal tissue. The total retinal thickness was 140 μm.

Conductivities were chosen based on data reported by Kasi et al. [30], who carried out in vitro measurements of electrical conductivity of the rat retina (figure 3). For simplicity in the present model, neighboring conductivity values from the data of Kasi et al. were averaged, yielding seven conductivity values for the retinal tissue. Thus in the model, the retinal geometry was divided into seven layers of equal sizes and each layer assigned its corresponding conductivity value (table 1). The stimulus current ($I_{stim}$) was delivered into the extracellular space. $I_{m}$ is the RGC transmembrane current per unit volume, derived from an equivalent-cylinder cable formulation [31]. Consider a cylindrical neuron of radius $r$, discretized into several compartments each of length $\Delta s$. Between each segment, we define an intracellular node, such that there is current flow into and out of the node from the two adjacent compartments as well as through the local membrane, as shown in figure 4.

Denoting the intracellular conductivity by $\sigma_i$, then the intracellular resistance between two nodes is given by

$$ R_i = \frac{\Delta s}{\sigma_i A} = \frac{\Delta s}{\sigma_i \pi r^2}, $$

where $A$ is the cross-sectional area. If we define the ionic current per unit membrane area by $J_{ion}$, then the total ionic current through the membrane is equal to $J_{ion}$ multiplied by the cylindrical surface area $2\pi r \Delta s$. Furthermore, if we define the membrane capacitance per unit area as $C_m$, then the total membrane capacitance of the cylindrical segment is $C_m 2\pi r \Delta s$. From figure 4, the total membrane current per unit cylindrical volume, $I_m$, is given by

$$ I_m = C_m 2\pi r \Delta s \frac{\partial}{\partial t} \left( V_{l,k} - V_{e,k} \right) + J_{ion} 2\pi r \Delta s $$

$$ = \frac{2}{r} \left( C_m \frac{\partial}{\partial t} \left( V_{l,k} - V_{e,k} \right) + J_{ion} \right) $$

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Figure 4. Discretized electrical-equivalent circuit of equivalent cylinder neuron centered at node $k$. $V_{l,k}$ represents the extracellular potential at node $k$, whilst $V_{r,k-1}$, $V_{r,k}$ and $V_{r,k+1}$ are the intracellular potentials at nodes $k - 1$, $k$, and $k + 1$, respectively. $J_{ion}$ and $C_m$ are the ionic current and membrane capacitance per unit area respectively, $\sigma_i$ is the intracellular conductivity, $r$ is the cylindrical radius, and $\Delta s$ is the inter-nodal spacing.

Also, the total current exiting node $k$ must equal zero from Kirchhoff’s current law, and is given by

$$ \frac{\partial V_{r,k}}{\partial t} - \frac{\partial V_{r,k-1}}{\partial t} + \frac{2}{\Delta s} \frac{\partial}{\partial t} \left( V_{l,k} - V_{e,k} \right) + J_{ion} 2\pi r \Delta s = 0. $$

(4)

On re-arranging, equation (3) combined with equation (4) leads to

$$ \frac{2}{r} \left( C_m \frac{\partial}{\partial t} \left( V_{l,k} - V_{e,k} \right) + J_{ion} \right) $$

$$ = \sigma_i \left( V_{r,k-1} - 2V_{r,k} + V_{r,k+1} \right) $$

$$ = \sigma_i \left( V_{r,k-1} - 2V_{r,k} + V_{r,k+1} \right) $$

(5)

Note that the middle term in parentheses in equation (5) is equivalent to the finite-difference approximation of the second-derivative of the intracellular potential. Taking the limit as $\Delta s \to 0$, and defining the transmembrane potential as $V_m = V_r - V_l$, where $V_r$ and $V_l$ are the intra- and extracellular potentials respectively, we obtain the continuum equivalent-cylinder cable representation:

$$ I_m = \frac{2}{r} \left( C_m \frac{\partial V_m}{\partial t} + J_{ion} \right) $$

$$ = \sigma_i \frac{d^2 V}{d s^2}, $$

(6)

where $s$ is the arc-length along the 1D neural element.

As noted, $J_{ion}$ represents the total ionic current per unit membrane area, according to RGC formulation of Fohlmeister et al. [28]. In their model, ionic channel distribution and kinetics in rat RGCs were determined based on experimental data. They estimated a unique set of ionic conductances ($g_i$ terms in equation (7)) for each of the five morphological elements, namely the soma, dendrites, AIS, HSCD region and distal axon, as given in table 2. In the present model, the membrane conductance for the leakage current ($g_l$) was adjusted to maintain a stable resting potential in the absence
Table 1. Model parameters.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_m$</td>
<td>Membrane capacitance</td>
<td>1</td>
<td>$\mu F \ cm^{-2}$</td>
</tr>
<tr>
<td>$\sigma_{\alpha,L1}$</td>
<td>Extracellular conductivity of retinal layer 1 (innermost layer)</td>
<td>0.88</td>
<td>$S \ m^{-1}$</td>
</tr>
<tr>
<td>$\sigma_{\alpha,L2}$</td>
<td>Extracellular conductivity of retinal layer 2</td>
<td>0.55</td>
<td>$S \ m^{-1}$</td>
</tr>
<tr>
<td>$\sigma_{\alpha,L3}$</td>
<td>Extracellular conductivity of retinal layer 3</td>
<td>0.4</td>
<td>$S \ m^{-1}$</td>
</tr>
<tr>
<td>$\sigma_{\alpha,L4}$</td>
<td>Extracellular conductivity of retinal layer 4</td>
<td>0.34</td>
<td>$S \ m^{-1}$</td>
</tr>
<tr>
<td>$\sigma_{\alpha,L5}$</td>
<td>Extracellular conductivity of retinal layer 5</td>
<td>0.25</td>
<td>$S \ m^{-1}$</td>
</tr>
<tr>
<td>$\sigma_{\alpha,L6}$</td>
<td>Extracellular conductivity of retinal layer 6</td>
<td>0.28</td>
<td>$S \ m^{-1}$</td>
</tr>
<tr>
<td>$\sigma_{\alpha,L7}$</td>
<td>Extracellular conductivity of retinal layer 7 (outermost layer)</td>
<td>0.34</td>
<td>$S \ m^{-1}$</td>
</tr>
<tr>
<td>$\sigma_{i}$</td>
<td>Intracellular conductivity</td>
<td>0.7</td>
<td>$S \ m^{-1}$</td>
</tr>
<tr>
<td>$V_{Na}$</td>
<td>Sodium reversal potential</td>
<td>60.60</td>
<td>mV</td>
</tr>
<tr>
<td>$V_K$</td>
<td>Potassium reversal potential</td>
<td>-101.34</td>
<td>mV</td>
</tr>
<tr>
<td>$V_L$</td>
<td>Leakage reversal potential</td>
<td>-64.58</td>
<td>mV</td>
</tr>
</tbody>
</table>

of external stimulation

$$
J_{ion} = \sigma_{Na} m^2 h (V_m - V_{Na}) + \sigma_{K} h (V_m - V_k)
+ \sigma_{Ca} \alpha (V_m - V_{Ca}) + \sigma_{Ca_L} \beta (V_m - V_L)
+ \sigma_{Ca_2} (V_m - V_{L}) + \sigma_{L} (V_m - V_L)
$$

where $\sigma_{Na}$, $\sigma_{K}$, $\sigma_{Ca}$, $\sigma_{Ca_L}$, $\sigma_{Ca_2}$, $\sigma_{L}$ are the conductivities of the layers in question, and $z$ is the vertical coordinate normal to each internal boundary.

Electrical stimulation was simulated using epiretinal electrodes (figure 1). On electrode boundaries, an inward current density boundary condition was imposed. Two electrode configurations were tested: monopolar and concentric bipolar. For the monopolar configuration, the stimulus current was returned to a distant ground, which was the outermost geometric boundary beneath the retina. For the concentric electrode configuration, the ring surrounding the stimulating electrode returned the stimulus current. Except for the electrode and the ground boundaries, all other external boundaries were assigned a zero-flux boundary condition:

$$
\frac{\partial V_e}{\partial n} = 0, \quad \frac{\partial V_i}{\partial n} = 0,
$$

where $n$ represents the normal coordinate to that boundary.

2.3. Electrodes and stimulus parameters

Stimulating disc electrodes were 5, 20 and 50 $\mu$m in radius. For the case of the 5 $\mu$m stimulating electrode, the inner and outer radii of the return electrode ring were 12.5 and 17.5 $\mu$m, respectively. These values corresponded to 50 and 70 $\mu$m in the case of the 20$\mu$m stimulating electrode, and 125 and 175 $\mu$m for the 50 $\mu$m stimulating electrode. Spatial activation profiles were investigated using 20$\mu$m monopolar and concentric electrodes. To study the effect of neighbouring electrodes, two 20 $\mu$m concentric electrodes were used with 200 $\mu$m centre-to-centre spacing.

Additional stimulations were performed to provide direct comparison of model results with published experimental data. Since in the present model RGC parameters and retinal conductivity values used were those reported for rat retina, the activation threshold data predicted by the model was compared with experimental data obtained from rat RGCs reported by Sekirnjak et al [14]. Similar to the experimental method used by Sekirnjak et al., epiretinal electrodes in the model were monopolar discs of 2.5, 5 and 12.5 $\mu$m radii. In all simulations, electrical stimulus signals were 100 $\mu$s square cathodic monophasic current pulses.

2.4. Activation and inhibition thresholds

Each neuron was considered activated if depolarization caused by the stimulus pulse resulted in AP generation and propagation along its axon. In some cases, excessive hyperpolarization of the surrounding membrane inhibited AP generation and/or propagation. To measure thresholds, simulations were performed for a range of stimulus

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