Multicompartment retinal ganglion cells response to high frequency bi-phasic pulse train stimulation: simulation results

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Abstract—**Retinal ganglion cells (RGCs) are the sole output neurons of the retina that carry information about a visual scene to the brain. By stimulating RGCs with electrical stimulation, it is possible to elicit a sensation of light for people with macular degeneration or retinitis pigmentosa. To investigate the responses of RGCs to high frequency bi-phasic pulse train stimulation, we use previously constrained models of multi-compartment OFF RGCs. The morphologies of mouse RGCs are taken from the Chalupa set of the NeuroMorpho database. The cell models are divided into compartments representing the dendrites, soma and axon that vary between the cells. A total of 132 cells are simulated in the NEURON environment. Results show that the cell morphology plays an important role in the response characteristics of the cell to high frequency bi-phasic pulse train stimulation.**

I. INTRODUCTION

In visually impaired people who have lost their photoreceptors due to macular degeneration or retinitis pigmentosa, a sensation of light can be elicited by excitation of surviving retinal ganglion cells (RGCs) with electrical stimulation. RGCs are the sole output neurons of the retina that carry information about a visual scene to the brain. ON and OFF RGCs respond in opposite fashions to changes in light intensity. ON cells increase their spike rate in response to light increments, while OFF cells increase their spike rate to light decrements [7]. In this study, we focus on OFF RGCs.

To stimulate RGCs directly, a retinal implant is usually placed in close proximity to the ganglion cells, as shown in Fig. 1. This approach is a subject of clinical investigation in [11], [12] among others. The efficacy of various stimulation strategies of RGCs have been studied [5], [6], [14], [17]. While some studies show that RGCs can be activated with a high frequency bi-phasic train stimulation [5], [17], others show attenuation of the RGCs responses when stimulated with the high frequency bi-phasic pulses [6]. The effects of frequency of stimulation on a human psychophysics have been investigated in [20]. While bi-phasic pulse train stimulation is the most common strategy used in retinal implants, other types of stimulation of RGCs have been studied, including sinusoids and white noise [3], [4], [13]. In other types of neurons, the influence of the stimulus waveform and frequency on neuronal output have been investigated computationally in [10], [15].

To investigate responses of neurons to different stimulation strategies, computational models of RGCs are often used.

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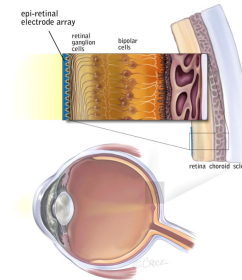
Fig. 1.   Possible placements of a high-acuity retinal prosthesis. Image courtesy Bionic Vision Australia.

The ability to control parameters of the experiment precisely and to analyze underlying mechanisms in separation are the main advantages of a computational simulation approach over experimental approaches.

The response of a RGC to electrical stimulation is determined by the neuron's morphology and its intrinsic electrophysiology. We hypothesize that the discrepancies between the results in [5], [17] and [6] are due to the different morphologies of the cells recorded in these experiments. This study is a first step to investigate the responses of different morphological RGC types to high-frequency electrical stimulation. To investigate the responses of RGCs to electrical stimulation, the multicompartment models of mouse RGCs cells were used. A total of 132 cells of different morphologies were simulated, and their responses to a high-frequency bi-phasic pulse stimulation were analyzed.

II. METHODS

To investigate the responses of RGCs to high-frequency bi-phasic stimulation, we use previously constrained models of multicompartment, biologically correct OFF RGCs [8]. These models were constrained and validated using published experimental data and were able to reproduce various phenomena observed experimentally, including rebound excitation, burst firing and subthreshold oscillation [9]. All modelled cells had spontaneous activity. The RGCs' morphologies were taken from the Chalupa set (mice RGCs) from the NeuroMorpho database [1]. The cell models were divided into compartments representing the dendrites, soma, and axon that varied between the cells.

The equation governing the membrane potential of RGCs was obtained by summing all membrane currents using
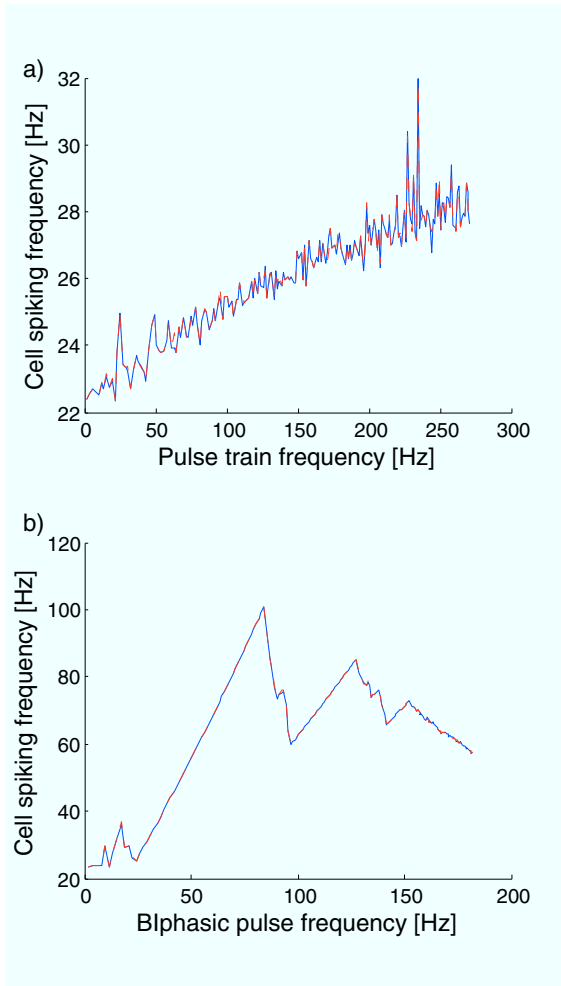
Fig. 2. Spiking frequency in the soma (blue) and in the axon (black) in response to bi-phasic train stimulation. Phase duration of 0.095 ms was used in this simulation. a) Pulse amplitude $\pm$ 0.2 nA. b) Pulse amplitude $\pm$ 0.5 nA.

Fig. 3. Stimulation with bi-phasic pulses of varying frequencies. Phase duration is 0.095 ms and phase amplitude is ± 0.5 nA for all simulations. a) Spiking frequency for 1 out of 128 cells that were minimally activated. b) Spiking frequency for 1 out of 4 cells that were highly activated by the bi-phasic pulse stimulation.

Kirchoff's law:

$$C_{\mathrm{m}}\frac{dV}{dt} + I_{\mathrm{Na}} + I_{\mathrm{Ca}} + I_{\mathrm{K}} + I_{\mathrm{K,A}} + I_{\mathrm{K(Ca)}}$$

$$+I_{\mathrm{T}} + I_{\mathrm{Nap}} + I_{\mathrm{h}} + I_{\mathrm{L}} = I_{\mathrm{stim}}. \tag{1}$$

The dynamics of each voltage-gated ionic current are governed by Hodgkin-Huxley-type gating variables, which was described by first-order kinetic equations as given in [2]. Sodium, I_{Na}, L-type calcium, I_{Ca}, potassium, $I_{\mathrm{K,A}}, I_{\mathrm{K(Ca)}}, I_{\mathrm{K}}$, low-voltage activated T-type calcium, I_{T}, hyperpolarization-activated, I_{h}, sodium-persistent, I_{NaP}, and leak, I_{L}, currents were constrained as discussed in [2], [8], [18], [19], and [16]. C_{m} is a specific membrane capacitance, I_{Stim} is an intracellular stimulation current. The standard Euler numerical integration method with time step 0.025ms was used in the simulation. All voltage-dependent parameters were initialized using a membrane potential of -70 mV. All simulated cells had different morphology but the same concentration of ionic channels.
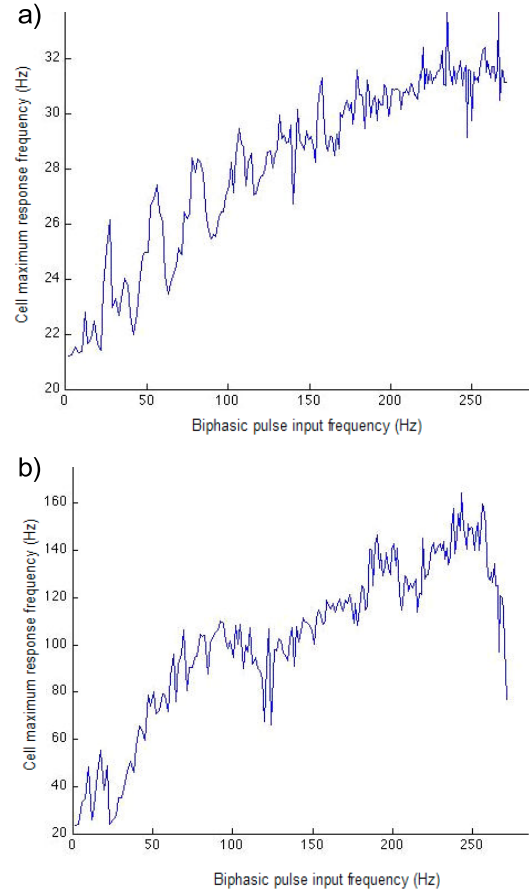
A total of 132 cells were simulated in response to bi-phasic pulse train stimulation of varying frequencies. The duration of the cathodic and anodic phases was set to 0.095 ms initially, and then increased to 1 ms. The amplitudes of the cathodic and anodic phases were set to ± 0.2 nA initially, and then increased to ± 0.5 nA. In all simulations, the interphase gap was fixed to 1 ms. The frequency of the pulse train stimulation was systematically varied from 1 to 280 Hz with a step size of 10 Hz. The models of RGCs were used to explore the following:

- The spiking frequency in the soma and in the axon, when stimulated at a high frequency in the soma.
- The effect of the pulse phase duration upon the cell's response to a high frequency bi-phasic stimulation.
- The effect of the cell total surface area upon the cell's response to a high frequency bi-phasic stimulation.

III. RESULTS

Spiking frequency in the soma and in the axon when stimulated at a high frequency in the soma.

We found that for all cells the number of spikes in the soma and in the axon was equal, even when stimulated with

short duration (0.095 ms) pulses, refer to Fig. 2. The black (spiking frequency in the soma) and blue (spiking frequency in the distant axon) traces are almost indistinguishable for an exemplary cell shown.

The effect of the pulse phase duration upon the cell's response to high frequency stimulation.

Out of 132 RGCs models stimulated with 0.095 ms phase duration bi-phasic pulses, 128 cell models were minimally activated, refer to Fig. 3a. Note that all cells had spontaneous activity. The RGCs responded to few pulses only (note 30 Hz spiking when stimulated at 200 Hz). Four cells increased their spiking frequency dramatically when stimulated with high frequency pulse train, refer to Fig. 3b. It is unclear what particular morphological features are different between these four cells and the rest.

Out of 132 cells simulated with 1 ms phase duration pulses, 106 cells reached a saturation level, or reached saturation and then decreased the spiking frequency even when the stimulation frequency was increased, see Fig. 4a. 26 cells were able to follow high frequency stimulation, see Fig. 4b. The relationship between the bi-phasic train frequency and the cells' maximum spiking frequency is given in Fig. 4c. It is unclear what morphology the outliers, circled in green, had. This investigation is left for future research.

The effect of a cell's total surface area upon the cell's response to high frequency stimulation.

The effect of a cell's total surface area on its output maximum spiking frequency in response to high frequency stimulation is given in Fig. 5. Fig. 5a shows the results for 0.095 ms pulse phase duration, Fig. 5b shows the results for 1 ms pulse phase duration; the figure shows that the larger cells tended to respond with lower frequency. Red circles in Fig. 5 show the cells that were able to follow high frequency stimulation.

IV. CONCLUSIONS

In this study, we investigated the responses of modeled RGCs to electrical stimulation. The models represented realistic morphologies of mouse RGCs and were constrained based on the published experimental data. A total of 132 cells with different morphologies were simulated in NEURON, and their responses to high-frequency bi-phasic pulse stimulation were analyzed in Matlab. We found that only a small percentage of modeled RGCs were able to follow high-frequency electrical stimulation. The investigation of the morphological RGCs types that were able to respond to high-frequency stimulation is left for future research. The effects of the cells' electrophysiology on their responses to bi-phasic stimulation was not discussed here and is left for future research.

V. ACKNOWLEDGMENTS

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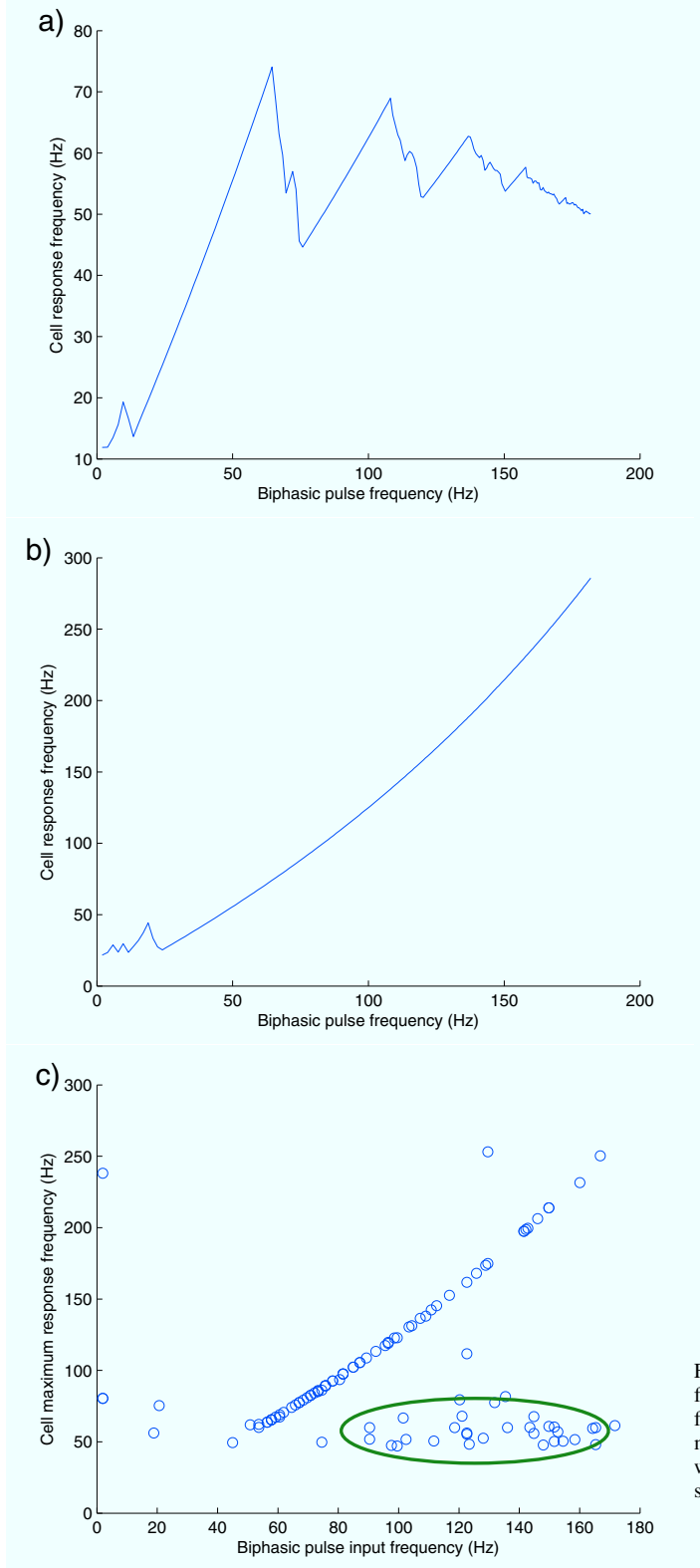
Fig. 4. Stimulation with bi-phasic pulses of varying frequencies. Phase duration is 1 ms, phase amplitude is ±0.5 nA for all simulations. a) Spiking frequency for 1 out of 106 cells that reached a plateau when stimulated with the high frequency bi-phasic pulses. b) Spiking frequency for 1 out of 26 cells that were able to follow high frequency bi-phasic pulse stimulation. c) The relationship between the bi-phasic pulse train stimulation frequency and the cells' maximum frequency of spiking. Cells with large surphase area that were unable to follow high frequency stimulation are circled in green.
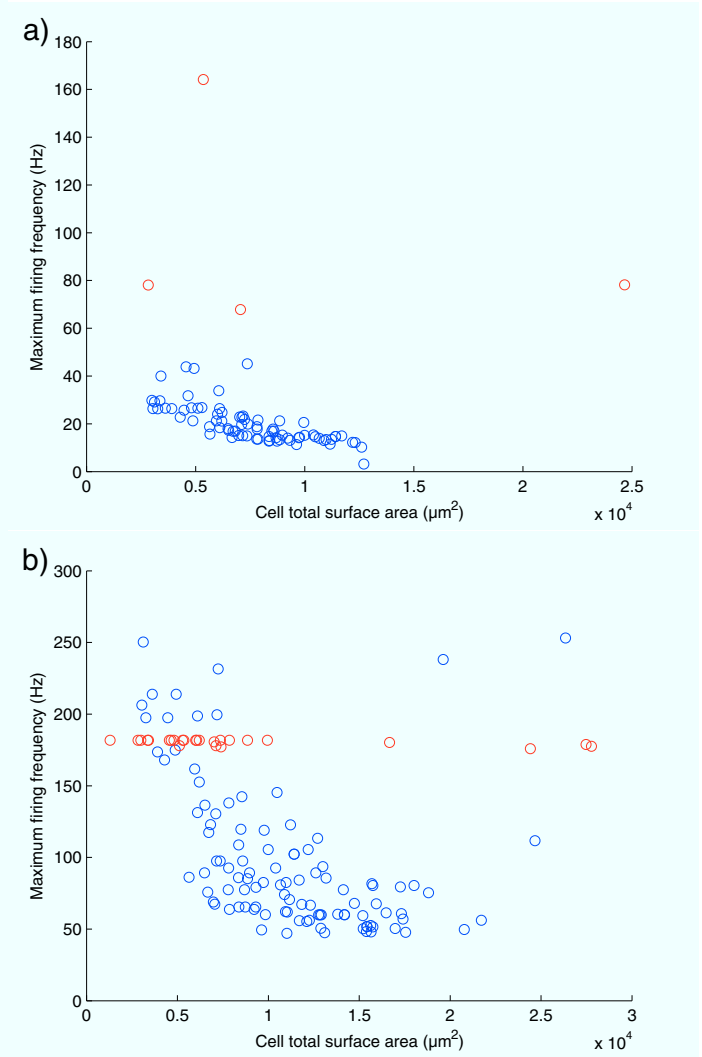

Fig. 5. The effect of a cell's total surface area on its maximum firing frequency in response to bi-phasic pulse train stimulation of varying frequency. a) Pulse phase duration 0.095 ms. b) Pulse phase duration 1 ms. Blue circles: cells with response as in Figs. 3a, 4a. Red circles: cells with response as in Figs. 3b, 4b (that were able to follow high-frequency stimulation).