A Continuum Model of Electrical Stimulation of Multi-Compartmental Retinal Ganglion Cells

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***Abstract*— A continuum multi-domain model of electrical stimulation of the retina is presented. Each point in the retinal ganglion cell layer could be thought of as representing a single cell, whose biophysics is described using a four-compartment formulation incorporating varying ion channel expressions in the soma, axon initial segment, dendrites and axon. Our continuum model was validated against a discrete morphologically-realistic OFF RGC model, using intra- and extra-cellular electrical stimulation scenarios. Simulations from the continuum model reproduced the same results as that of the discrete model. Our continuum model is the first multi-domain model to represent all main RGC compartments, not just the soma. Moreover, we demonstrated that this model allows the investigation of axonal activation which has been observed to influence the perception of phosphenes.**

I. INTRODUCTION

Several research groups have conducted extensive experimental and modeling work to enhance the efficacy of retinal prostheses. In particular, computational models have provided valuable information about the behavior of retinal tissue that may not be attained by experimental techniques, hence, supporting the improvement of retinal implants [1].

Discrete models represent the most accurate retinal electrical stimulation models, since they rely on the reconstruction of morphologically-realistic retinal ganglion cells (RGCs) from traced images as well as incorporating information on ion channel distribution from electrophysiological experiments. However, they suffer from high computational cost when simulations of large populations of cells are desired. An alternate approach is continuum models, which are ideal for examining the spatial activation of bulk retinal tissue, without explicit representation of individual cells. Such continuum models have been employed extensively in cardiac and recently in neural tissue simulations [1], [2]. These continuum bidomain models describe the electrical activity of bulk tissue by coupling the intra- and extra-cellular domains [2].

The present study aims to extend this bidomain approach into a multi-domain model of electrical stimulation of rabbit OFF RGCs. The model was validated over three stages against a recently published morphologically-realistic discrete model of an OFF RGC [3].

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II. METHODS

Validation of our continuum model of electrical stimulation of rabbit OFF RGCs was undertaken over three stages. The first stage was the implementation of extracellular electrical stimulation of a recently published discrete morphologically-realistic rabbit OFF RGC model [3]. The second stage was to reduce this RGC model to a four-compartment version by using a set of finite difference equations and computing the internal conductivities that connect OFF RGC compartments to each other. The final stage was the implementation of a continuum model of a rabbit OFF RGC based on compartmental equations and the calculated conductivities. We deemed that the model was valid if RGC activation sites of the first stage (discrete model) and the third stage (continuum model) were similar.

A. Extracellular Electrical Stimulation Model of Rabbit OFF RGCs (Stage 1)

The morphologically-realistic rabbit OFF RGC model of Guo et al. [3], originally simulated using NEURON software, was reconstructed successfully using COMSOL Multiphysics finite-element simulation software (COMSOL AB, Sweden). A modified cable equation was used to describe electric excitation and propagation within the RGC. Model implementation was validated when Figure 3 of [3] was reproduced by applying intracellular electrical stimulation to the soma of our COMSOL OFF RGC model.

Subsequently, we used this model to simulate extracellular electrical stimulation of the morphologically-realistic rabbit OFF RGC in COMSOL. The morphologically realistic cell, consisting of soma, dendrites, axon hillock, axon initial segment (AIS) and axon, was immersed inside a semi-ellipsoid domain representing the extracellular medium. A hexagonal arrangement of circular disc electrodes was implemented, each being 190 μm in radius with 730 μm center-center spacing (Fig. 1a). The central electrode was the active electrode, with the surrounding electrodes being the return electrodes set as ground. A cathodic monophasic current stimulus 160 μA in amplitude and 0.5 ms in duration was applied. To map spatial activation, the RGC was positioned 120 μm from the plane of the electrodes at each of the 25 sites of a 5 x 5 grid of points, spaced 500 μm x 500 μm apart (Fig. 3a). For each position, one set of simulations was

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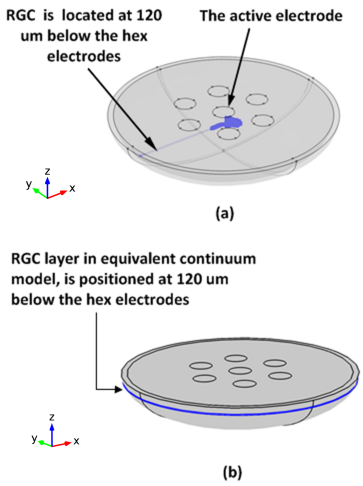

Fig. 1. (a) Configuration of the discrete RGC model, used for validation. (b) Layout of the equivalent continuum model.

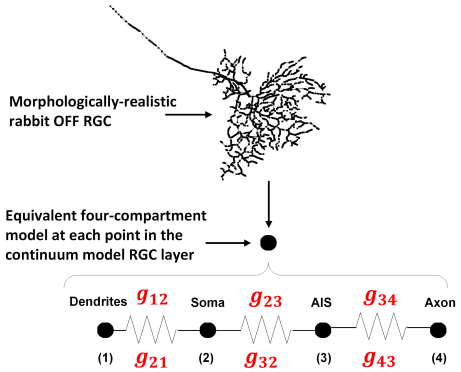

Fig. 2. Four-compartment representation of each point in the RGC layer of the continuum model after reducing the full morphologically-realistic RGC into a four-compartment point model.

obtained when the axon was oriented along the x-axis while another set was taken with axonal orientation along the y-axis.

B. Reducing the Morphologically-Realistic Rabbit OFF RGC Model to a Point Model (Stage 2)

The morphologically-realistic rabbit OFF RGC was composed of thousands of compartments, each classified as one of: dendrites, soma, axon hillock, axonal initial segment (AIS), and axon, based on ion channel expression. For further simplicity, we combined the soma and axon hillock into one compartment (called hereafter the soma) due to their identical maximum ion channel conductance values. We implemented a Matlab (Mathworks, USA) script to reduce the morphologically-realistic RGC to a four-compartment point model.

Between each two adjacent compartments, there are two internal conductivities to describe the influence of each compartment on its neighbor, as seen in Fig. 2. The biophysical properties of each compartment will play a crucial role in determining the magnitude of its electrotonic influence on its neighboring compartments. A total of six conductivities were used to connect between all RGC compartments.

C. Continuum Model of Extracellular Electrical Stimulation of Rabbit OFF RGC (Stage 3)

A 3D finite element model consisting of vitreous fluid and ganglion cell layer was implemented in COMSOL Multiphysics (Fig. 1b). The settings of this model were identical to the settings of the first stage (discrete model), with the exception of the following: instead of the presence of a discrete morphologically-realistic RGC, a continuum RGC layer was incorporated. The four compartmental equations and the six values of internal conductivities were used to represent a cell at each point of the layer and predict the extent of spatial activation, instead of using a cable representation of each cell. To allow comparison of the two approaches, the responses of rabbit OFF RGCs in the continuum model were sampled at the same 25 sites utilized in the first stage (discrete model) for both cases of axon orientation (along the x- or y-axis).

D. Mathematical Formulations

For both stage 1 (discrete) and stage 3 (continuum) models, Poisson's equation was used to govern the extracellular voltage distribution (V_e):

$$\nabla.(-\sigma_b \nabla V_e) = I \tag{1}$$

where σ_b is the electric conductivity of 1.28 (S/m) for the vitreous layer [2] and I is the volumetric current density source (A/m^3) due to cell membrane current flow.

In the discrete model, the RGC activation was determined using our modified cable equation, which considers the variation among the radius of RGC compartments, as follows:

$$\frac{\partial}{\partial x}[\frac{r^2}{2\rho_i}\frac{\partial V_m}{\partial x}] = r(C_m \frac{dV_m}{dt} + i_{ion}) \tag{2}$$

where V_m represents membrane potential, x is the axial cable distance, r the RGC compartment's radius (μm), ρ_i the intracellular resistivity $(\Omega \cdot cm)$, and (C_m) membrane capacitance per unit membrane area $(\mu F/cm^2)$. i_{ion} is the total membrane ionic current of each RGC compartment per unit membrane area.

For the continuum model, each point (X,Y, Z) inside the RGC layer represents a RGC composed of four compartments (dendrites, soma, AIS, and axon), as described in stage 2. The effective extracellular potential for these compartments should not be the same, particularly for the axonal and dendritic compartments. For the soma and AIS compartments, the V_e value at (X,Y, Z) was used. In the case of the dendrites, a circular dendritic field was accounted for by averaging V_e at four distal points to calculate the effective dendritic $V_{e(dend)}$.

$$\begin{aligned} V_{e1} &= V_e(X - x_1) \\ V_{e2} &= V_e(X + x_2) \\ V_{e3} &= V_e(Y - y_1) \\ V_{e4} &= V_e(Y + y_2) \\ V_{e(dend)} &= (V_{e1} + V_{e2} + V_{e3} + V_{e4})/4 \end{aligned} \tag{3}$$

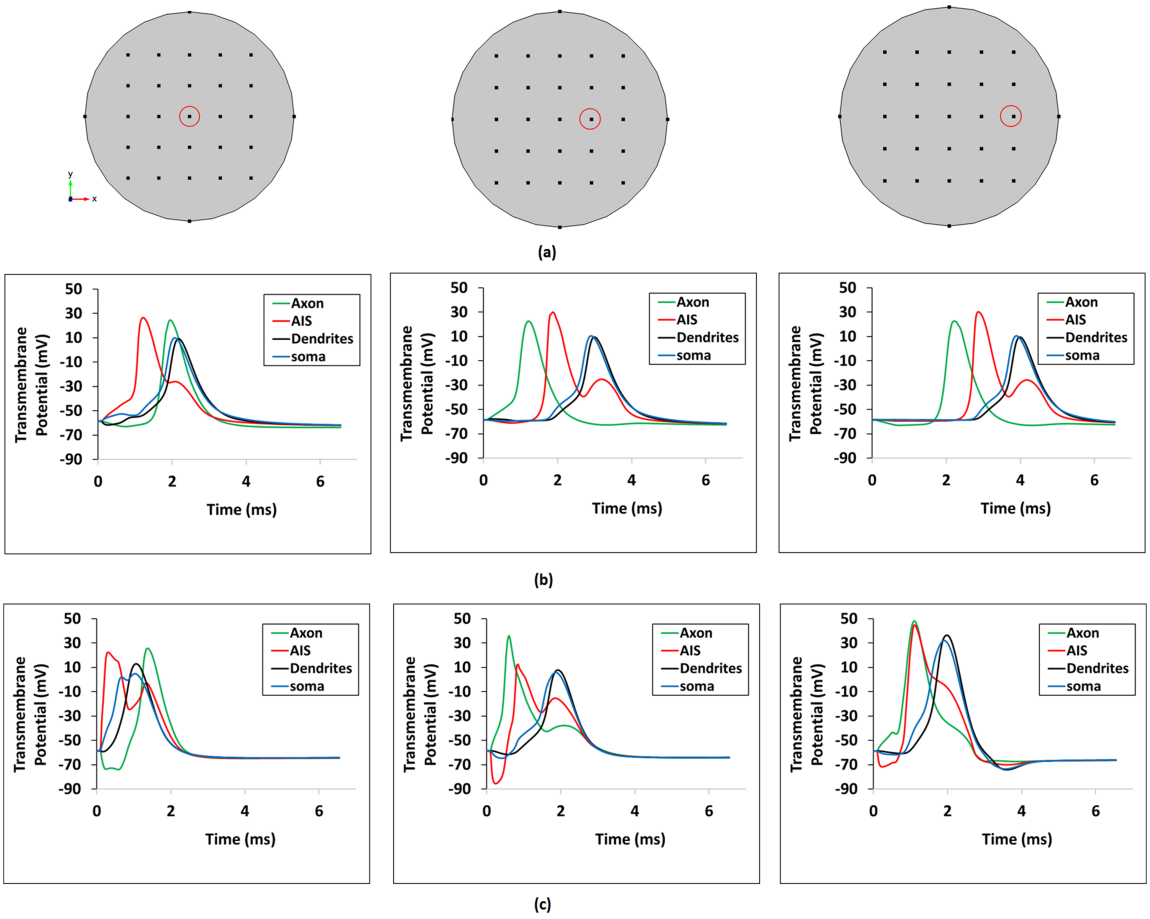

Fig. 3. Comparison of spatial activation using discrete and continuum computation approaches in response to extracellular electrical stimulation. In both cases of RGC representation, the axon was oriented along the x-axis. (a) The 25 point grid representing the locations where RGC spatial activation was measured. Red circles represent the sites of RGC activation. For each of these three sites, action potential traces from various compartments utilizing the (b) discrete and (c) continuum modelling approaches are presented.

where x_1 and x_2 are each set to 100 μm, and y_1 and y_2 are each set to 100 μm.

The value of extracellular potential at the axon was computed from a remote point according to

$$V_{e(axon)} = V_e(X - x)$$
$$V_{e(axon)} = V_e(Y - y) \quad (4)$$

where x and y are set to 650 μm when the axon was oriented along the x- and y-axis directions, respectively.

RGC activation within the continuum model was described by using a set of compartmental equations determined from stage 2 as follows:

$$V_{m(dend)} = \frac{-i_{ion}}{C_m} + \frac{g_{12}(V_{m2} - V_m)}{C_m} \quad (5)$$

$$V_{m_2(soma)} = \frac{-i_{ion2}}{C_m} + \frac{g_{21}(V_m - V_{m2})}{C_m} + \frac{g_{23}(V_{m3} - V_{m2})}{C_m} \quad (6)$$

$$V_{m_3(AIS)} = \frac{-i_{ion3}}{C_m} + \frac{g_{32}(V_{m2} - V_{m3})}{C_m} + \frac{g_{34}(V_{m4} - V_{m3})}{C_m} \quad (7)$$

$$V_{m_4(axon)} = \frac{-i_{ion4}}{C_m} + \frac{g_{43}(V_{m3} - V_{m4})}{C_m} \quad (8)$$

where i_{ion}, i_{ion2}, i_{ion3}, and i_{ion4} are the ionic currents for the dendrites, soma, AIS, and axon compartments, respectively.

III. RESULTS

A. Extracellular Electrical Stimulation of Morphologically-Realistic RGC

Fig. 3a displays the 25 placement sites of the rabbit OFF RGC under extracellular electrical stimulation when the axon was oriented parallel to the x-axis. The RGC was activated only at 3 out of 25 sites as seen in Fig. 3b.

B. Reducing the Full Morphologically-Realistic RGC to a Point Model: Intracellular Stimulation

Fig. 4 demonstrates the capability of our compartmental equations, implemented in Matlab, in reducing the morphologically-realistic RGC with thousands of compartments into a point model. The optimized six internal conductivities calculated from stage 2 are g_{12} = 3, g_{21} = 15, g_{23} = 3, g_{32} = 15, g_{34} = 15, and g_{43} = 3, with all conductivities in mS/cm^2.

C. Continuum Model of RGC Extracellular Electrical Stimulation

Spatial activation inside the RGC layer following extracellular electrical stimulation was probed at the same 25 locations used in stage 1 (discrete model). Fig. 3c shows that the continuum model reproduced the same results as the discrete model with RGC activation over the same three sites for the same stimulus current. Significantly, in terms of computational requirements, the continuum model which represents thousands of RGCs required 1.52 GB of RAM and less than 30 minutes to solve for a 7 ms simulation period, compared to a discrete model with only five RGCs which was needed about 70 minutes and 7.53 GB to be solved with identical simulation and solver settings.

IV. DISCUSSION

Continuum models of retinal electrical stimulation have increased our knowledge of the response of bulk retina to electrical stimulation. In a recent paper [4], current thresholds required to stimulate RGCs was investigated in the presence of retinal layers and with three different electrode locations (epiretinal, subretinal, and suprachoroidal). Other studies simulated and compared various current stimulation strategies, and investigated the retinal network effects on RGC activation [5], [6]. However, published continuum models of retinal electrical stimulation are associated with some limitations. These studies had each only considered one type of RGC and ignored other subtypes. Interestingly, several experimental studies have confirmed that each RGC subtype has unique responses when exposed to electrical or light stimulation [7], [8]. Moreover, existing continuum models only considered the RGC soma or axon initial segment, which were assumed to be the site of action potential (AP) initiation.

In the present study, we validated our continuum model against a recent discrete RGC model, which incorporates detailed ionic currents and realistic morphological architecture [3]. Moreover, all RGC compartments have been accounted for in this newer model. The effect of axon orientation on RGC activation is well-reproduced by our multi-compartment continuum model. This will be useful in future for studying axonal activation, which has been shown to cause distortions in the shape of evoked phosphenes [9]. Point models are a class of simplified models that reduce the full morphologically-realistic cell with thousands of compartments into a point with a limited number of compartments (four compartments in our model) connected to each other by a set of conductances. Hence, more detailed features, such as the variation between discrete and point models in terms of AP peak and onset in each compartment, as well as the number of spikes as seen in Fig. 3 and Fig. 4, are expected. This variation in timing also occurs between different compartments of discrete models, for example between proximal and distal dendrites. However, our continuum model was able to reproduce the general aspects of the discrete model results, especially in terms of activation threshold and spatial activation pattern. For example, OFF

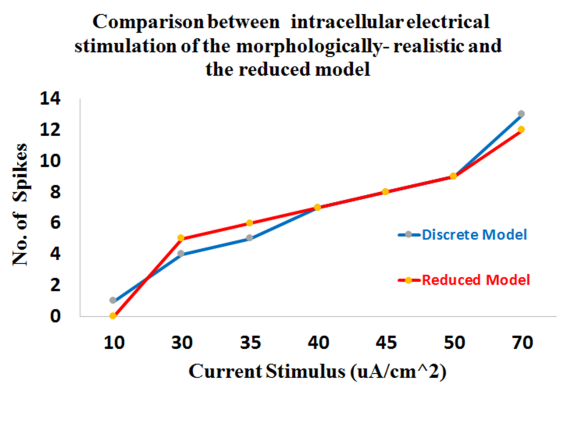

Fig. 4. Comparison of the responses of the morphologically-realistic OFF RGC and the reduced four-compartment model to intracellular stimulation. In both cases, cathodic constant-current injections was delivered into the AIS for 100 ms.

RGCs were activated only at 3 out of 25 sites (Fig. 3c) when the axon was oriented along the x-axis in the continuum model, similar to the discrete model (Fig. 3b). Activation of the RGC directly below the active electrode was caused by AIS activation first, with the AP then propagating to other compartments, while at the other two sites axonal activation occured first, followed by activation of other compartments retrogradely. The same results were obtained when the axon was oriented along the y-axis for both discrete and continuum models (results not shown).

In future studies, we will include additional retinal layers and RGC subtypes to investigate and optimize novel electrical stimulation strategies for vision prostheses.

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