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A Multi-Scale Computational Model for the Study of Retinal Prosthetic Stimulation

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Abstract

An implantable retinal prosthesis has been developed to restore vision to patients who have been blinded by degenerative diseases that destroy photoreceptors. By electrically stimulating the surviving retinal cells, the damaged photoreceptors may be bypassed and limited vision can be restored. While this has been shown to restore partial vision, the understanding of how cells react to this systematic electrical stimulation is largely unknown. Better predictive models and a deeper understanding of neural responses to electrical stimulation is necessary for designing a successful prosthesis. In this work, a computational model of an epi-retinal implant was built and simulated, spanning multiple spatial scales, including a large-scale model of the retina and implant electronics, as well as underlying neuronal networks.

I. Introduction

Many people lose their sight due to degenerative diseases, such as macular degeneration or retinitis pigmentosa, which destroy photoreceptors over time. However, the retinal cells further downstream in their vision system remain viable. Artificial stimulation of these cells via systematic electrical stimulation through an epi-retinal implanted electrode array has been shown to create some vision in blind patients [1]. Clinical trials have been conducted to study the optimal stimulus parameters for such a system. The responses are based on the percept of the patient and have provided thresholds for the magnitude of current required to elicit a visual response, as well as described shapes and colors the subject sees [2]. These

results are undeniably interesting and patients are given the ability to see some objects again. However, the system is lacking a correlation between the stimulus and the affected neural networks. The stimulation does not restore the lower-level processing that occurs in the retinal layers, which accounts for some contrast-detection, color, brightness, etc. [3] If the stimulus could be tailored to selectively stimulate specific types of cells, then natural vision restoration may be possible.

Simulations of the system that incorporate the complexity of the neural networks and the stimulation electronics could be used for estimating the response and optimizing the stimulus towards this goal. Numerical simulation methods, such as finite difference methods, have proven useful in studying the path of current due to a given stimulus by discretizing a retinal tissue model based on the tissue conductivity and solving for the voltage throughout the model [15]. However, these simulations lack the complexity and nonlinearity of the underlying neural networks. Variations of cable equations have been used for studying the complex nonlinear behaviors of single cells and networks of cells, predicting how they will respond to stimulation [5]. However, they usually consider the cell to be in a homogeneous medium and do not consider an accurate representation of the extracellular fields.

Combining these two techniques, we create a multi-scale approach to modeling the affect of electrical stimulation on retinal tissue, taking advantage of the benefits of both systems. By including the complexity at the spatio-temporal scales of cellular networks, as well as the field calculations throughout the tissue and implant electronics, we essentially link the system level with the cellular level of the vision process in a single model. We apply a novel Admittance Method for the extracellular voltage calculations [4], and NEURON software [5] for calculating the effect at the cellular level, using cellular models based on Transmission Electron Microscopy (TEM) images of rabbit retina [6]. Software was written to link these simulation platforms, providing the Admittance Method voltage results as boundary conditions for the extracellular space in NEURON simulations. NEURON is then used to model the cellular activity. This model may serve as a platform for studying retinal prosthesis design at a high level of detail, with the overall goal of advancing epi-retinal prosthetic design to produce pseudo-natural vision to those who have lost their sight. In the following sections, the specifics of this model and how it may be used to simulate and study specific stimulation parameters are described.

II. Model

The multi-scale model consists of two main components, one describing the retina at a system level, and the other describing the cellular network level. Fig. 1 provides plots of both models in a diagram describing how they are correlated.

A. Large-Scale System Level

First, a large-scale model was constructed, containing the layers of the retina, the vitreous humor, and an implanted electrode array. The model was discretized into a 3-dimensional matrix of cubic voxels, each noted by a tag that is unique to a specific material type. The curvature of the retina and the depth of the layers were based on literature [7],[8]. The

resolution of the model is 5 μm per voxel and the size is 400×400×300 voxels. Each retinal layer was rippled to represent a more accurate representation of the boundary between layers. This was accomplished by varying the height of the layer due to a given 2D Gaussian plane. The height and width of the peaks in the plane were chosen based on approximate density and size of the cells inside each individual layer. After building the tissue model, a 2×3 electrode array was added on top of the optic nerve layer in the retina, as shown in Fig. 1. The electrodes were based on the Argus-II design by Second Sight [9]. They are cylindrical with a diameter of 200 μm and a depth of 10 μm. Each voxel in the model is described by its resistivity. Values for the resistivity of the retinal layers are as found in literature for low frequency (below 100 Hz), and the electrodes were approximated with the properties of platinum. The resistivity values for all tissues are shown in Table 1 [8].

B. Small-Scale Cellular Network

A computational model of a cellular network in the inner plexiform layer of the retina was built using highly anatomically and physiologically-accurate connectome data. This data is based on nanoscale Transmission Electron Microscopy (TEM) images of rabbit retina, augmented by picoscale ultrastructural reimaging [11],[14]. Thousands of observed connections between cells in a 250 μm diameter sub volume of the inner plexiform layer were quantified, providing accurate data for use in a computational model. For the purposes of this paper, sixty cone bipolar cells that communicate with two ON ganglion cells were selected to be modeled and are shown in Fig. 1. This 250 μm diameter model was considered to be placed in the proper layers of the large-scale tissue model, residing in the cell-body layers in the bipolar and ganglion cell layers, as well as the inner plexiform layer between them, in which most of the communication between the two layers occurs. By duplicating the cellular model, the entire ganglion, bipolar, and inner plexiform layers in this model were populated with cone bipolar and ganglion cells. The morphology of the cells was then compartmentalized for use with NEURON software, as discussed in the next section.

III. Simulation Methods

A. Admittance Method

To simulate the electric field magnitude throughout the tissue-level model, a time-stepping multi-resolution variant of the admittance method (AM) was used [8]. In this method, a matrix describing the admittance (G), or resistance, throughout the model is defined. The diagonal of the matrix defines the resistance at each node, while the surrounding values define the resistances between nodes, producing a sparse, diagonal matrix. The admittance is described as in Equation 1, in terms of the conductivity and the distance in the x, y, and z directions.

$$g_x^{i,j,k} = \sigma_x^{i,j,k} \frac{\Delta y \Delta z}{\Delta x} \quad (1)$$

A current vector (I) is then defined, with current values applied to whichever nodes contain a source. A voltage vector (V) can then be solved for using G and I in Equation 2. The linear system of equations is solved using a biconjugate gradient algorithm.

$$GV=I \quad (2)$$

Prior to building and solving this system, a 3D multiresolution meshing algorithm is applied to the model. It maintains minimal resolution surrounding boundaries, and increases the voxel size further away where the fine resolution is unnecessary. For example, near the boundaries between retinal layers, the resolution would remain 5 μm per voxel, whereas towards the center of the layers, the resolution may be as low as 20 μm per voxel. To help illustrate this process, an example of a 2D slice of a model meshed with this algorithm is shown in Fig. 2. By decreasing the number of nodes and edges, the computational complexity of the system is decreased.

B. Connecting to NEURON

The response to the electrical stimulation at the neural network level is solved for using NEURON software. NEURON uses a compartmentalization system for solving for membrane and axial parameters. The model is split into compartments based on the type of neuronal branch and the change in radii. Each compartment is modeled as a tapered cylinder with a cable circuit model, describing the intracellular and membrane properties as circuital elements. The user can define the conductance, resistance, etc. for each compartment, as well as synaptic properties between cells. The connectome data used for this model was automatically converted to a NEURON-compatible format for describing the synaptic connections. Each synapse was then tested by applying a current clamp to the cell that is the source for each synapse and recording at the synaptic location on the target cell, ensuring there was a response. Also, a modified version of the built-in Hodgkin-Huxley mechanism was used to model the active mechanisms in the cells, in which the conductance of potassium, sodium, and calcium channels were specified. [5]

The results from the AM simulation were applied to this model as boundary conditions. NEURON has a built-in mechanism called “extracellular,” which allows for two extra layers of potentials and resistances to be added in series with each compartment [5]. One of these layers was utilized. 3D linear interpolation was used to estimate the voltage at the center of each compartment based on the surrounding eight nodes in the AM model. This voltage was set to the extracellular potential value in this model for each time step. A diagram describing the link between these tools is shown in Fig. 3. NEURON can then simulate the effect those voltages at each compartment have on the membrane and axial voltage, showing whether or not specific cells spike.

IV. Results

An example simulation was conducted to test the model. A single cycle of a sinusoidal current pulse with a magnitude of 10 μA and a frequency of 10 Hz was applied to one of the electrodes in the large-scale model shown in Fig. 1 over 20 time steps. The voltages

throughout the model were solved for using the admittance method. These voltages were then used to calculate the electric field in the x, y, and z directions by taking the ratio of the change in voltage and the change in distance in each respective direction. The magnitude of the electric field in the model for each step can then be solved for using Equation 3. A 2D slice of the electric field magnitude at the location of the stimulation at one time step is shown in Fig. 4.

$$E = \sqrt{E_x^2 + E_y^2 + E_z^2} \quad (3)$$

The voltage results were interpolated to produce an extracellular voltage value for each compartment in the NEURON model for the ON ganglion and bipolar network. A NEURON simulation was run, producing a membrane voltage value for every compartment at every millisecond. A plot showing the resulting membrane voltage for 1, 3, and 5 milliseconds after the sinusoidal pulse stimulation on a ganglion cell and a bipolar cell are shown in Fig. 4. The compartments are plotted as cylinders, which are color-coded based on the membrane voltage. Blue is the resting voltage defined as –60 mV and red is a voltage above +20 mV.

V. Discussion

This multi-scale computational model for a retinal prosthetic is just one step towards advancing the prosthesis design. It can serve as a testbench for testing many different parameters, such as the effect of the location of the ground or firing electrodes, stimulus magnitude or shape, etc. One specific application that is currently being pursued is optimizing the stimulus to stimulate certain types of cells. This directly applies to the goal of mimicking natural vision. Driving color percepts will require differentially stimulating surviving midget pathways previously linked to a CNS color network. Modeling such networks will, in turn, require access to primate or human connectomes. If a person is in bright light during the day, mostly circuits involving cones would need to be stimulated, and mostly those with rods in the case of less lighting [3]. This will require applying more complex channel mechanisms to describe the frequency dependence of specific cell types [10], and further research for deciding on the choice of stimuli that may elicit a response in a desired cell type, but not others.

The model can also be expanded to include more interesting neural circuits that have been observed during the connectome research used to build the neural network models. There are far more circuits than ON-ganglion cell networks that can be incorporated [11]. There is feedforward and feedback inhibition, electrical coupling between bipolar cells, sheets of amacrine cells, etc. In addition, the cells shown and discussed that are part of this connectome model do not include axons. These may be added to the computational model since they are likely the location of extracellular electrical stimulation. More spatial scales can be integrated as well, including smaller scales down to the molecular level for describing the synapses and channel mechanisms with even higher complexity. It has been shown that small changes at the molecular level can have an impact on the neural-level reaction to electrical activity [12]. Through these modifications, a highly accurate model for

studying many different research topics involving circuitry in the retina may be studied. For example, variations in system performance induced by pathologic network remodeling [13] can be assessed by comparison to this normal retinal framework. This approach can be extended to neuropathologies in general.

The model described in this paper combines two spatio-temporal scales of retina that are prevalent in literature. Linking them creates a simulation tool that will hopefully prove useful across multiple disciplines, in understanding the interaction between electric fields and tissue reaction, as well as the underlying electrophysiological phenomena.

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References

1. Humayun MS, Weiland JD, Fujii GY, Greenberg R, Williamson R, Little J, Mech B, Cimmarusti V, Boemel GV, Dagnelie G, de Juan E Jr. Visual perception in a blind subject with a chronic microelectronic retinal prosthesis. Vision Research. 2003; 43:2573–2581. [PubMed: 13129543]
2. Mahadevappa M, Weiland JD, Yanai D, Fine I, Greenberg RJ, Humayun MS. Perceptual thresholds and electrode impedance in three retinal prosthesis subjects. IEEE Trans Neural Syst Rehabil Eng. Jun.2005 13(2)
3. Kandel, ER.; Schwartz, JH.; Jessell, TM. Principles of Neural Science. New York: The McGraw-Hill; 2013.
4. Cela CJ, Lee RC, Lazzi G. Modeling cellular lysis in skeletal muscle due to electric shock. IEEE Trans Biomed Eng. May.2011 58(5)
5. Carnevale, NT.; Hines, ML. The NEURON Book. Cambridge, UK: Cambridge University Press; 2006.
6. Anderson JR, Mohammed S, Grimm B, Jones BW, Koshevoy P, Tasdizen T, Whitaker R, Marc R. The Viking viewer for connectomics: scalable multi-user annotation and summarization of large volume data sets. J Microscopy. 2011; 241:13–28.
7. Spitzer V, Ackerman MJ, Scherzinger AL, Whitlock D. The visible human male: A technical report. J Amer Med Inform Assoc. Apr; 1996 3(2):118–130. [PubMed: 8653448]
8. Cela, CJ. PhD dissertation. Dept. Elect. Eng., N. Carolina Univ; Raleigh, NC: 2010. A multiresolution admittance method for large-scale bioelectromagnetic interactions.
9. Ahuja AK, Behrend MR. The Argus II retinal prosthesis: Factors affecting patient selection for implantation. Prog Retin Eye Res. 2013; 36:1–23. [PubMed: 23500412]
10. Freeman D, Jeng JS, Kelly SK, Hartveit E, Fried SI. Calcium channel dynamics limit synaptic release in response to prosthetic stimulation with sinusoidal waveforms. J Neural Eng. 2011; 8:1–19.
11. Marc RE, Jones BW, Watt CB, Anderson JR, Sigulinsky C, Lauritzen S. Retinal connectomics: towards complete, accurate networks. Prog Retin Eye Res. Nov.2013 37:141–162. [PubMed: 24016532]
12. Bouteiller JMC, Allam SL, Hu EY, Greget R, Ambert N, Keller AF, Bischoff S, Baudry M, Berger TW. Integrated multiscale modeling of the nervous system: predicting changes in hippocampal network activity by a positive AMPA receptor module. IEEE Trans Biomed Eng. Oct; 2011 58(10):3008–3011. [PubMed: 21642035]
13. Marc RE, Jones BW, Watt CB, Strettoi E. Neural Remodeling in Retinal Degeneration. Prog Retin Eye Res. 2003; 22:607–655. [PubMed: 12892644]

14. Anderson JR, Jones BW, Watt CB, Shaw MV, Yang JH, DeMill D, Lauritzen JS, Lin Y, Rapp KD, Mastronarde D, Koshevoy P, Grimm B, Tasdizen T, Whitaker R, Marc RE. Exploring the retinal connectome. Molecular Vision. 2011; 17:355–379. [PubMed: 21311605]

15. Xie J, Wang GJ, Yow L, Cela CJ, Humayun MS, Weiland JD, Lazzi G, Jadvar H. Modeling and percept of transcorneal electrical stimulation in humans. IEEE Trans Biomed Eng. Jul.2011 58(7)

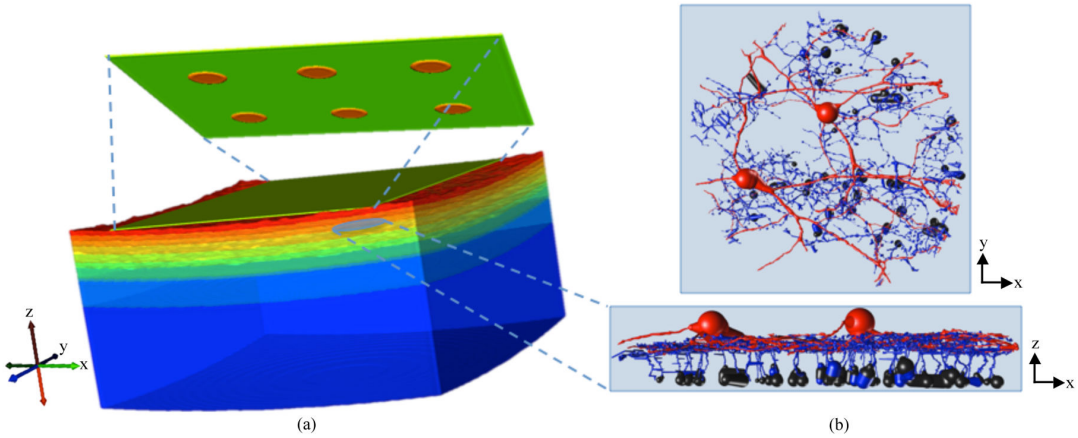

Figure 1.

Diagram of multi-scale model, including (a) 3D plot of the discretized model of the retina with an electrode array and (b) top and side-view plots of the morphology of a neural network considered for simulation, including two ON ganglion cells and 60 cone bipolar cells.

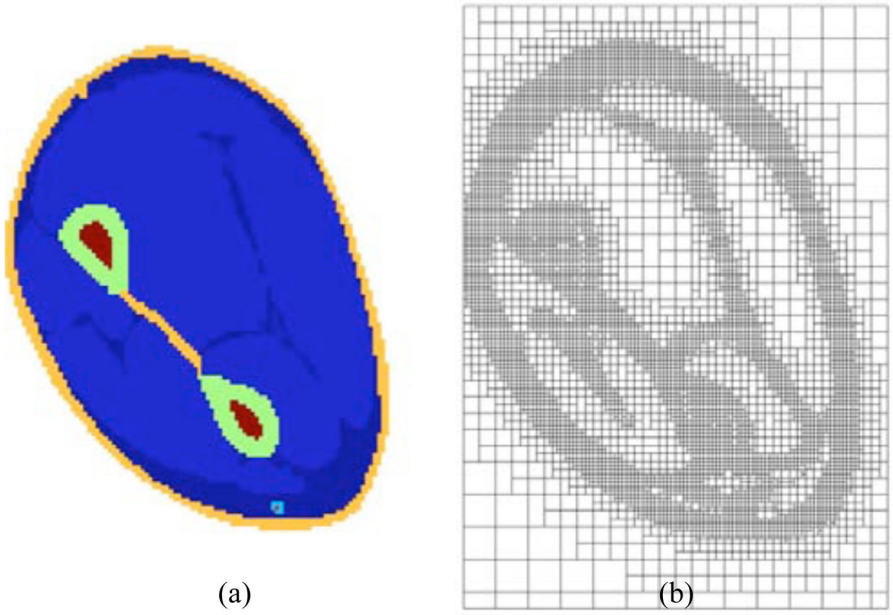

Figure 2.
Example 2D slice of a meshed model [4], including (a) an unmeshed slice of a model, using uniform cubic voxels, and (b) the same model after applying the multiresolution meshing algorithm with maximum size of 8 voxels per cell.

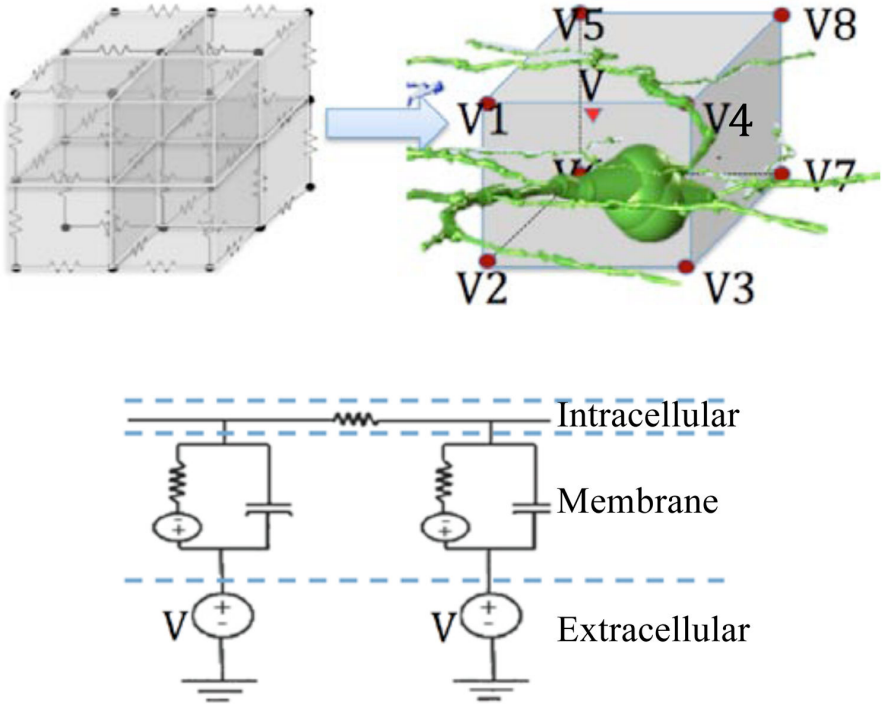

Figure 3.

Diagram of the link between the admittance method results and NEURON. An extracellular voltage for each compartment (V) is estimated by 3D linear interpolation of the voltages at the nearest surrounding nodes from the admittance method simulation results.

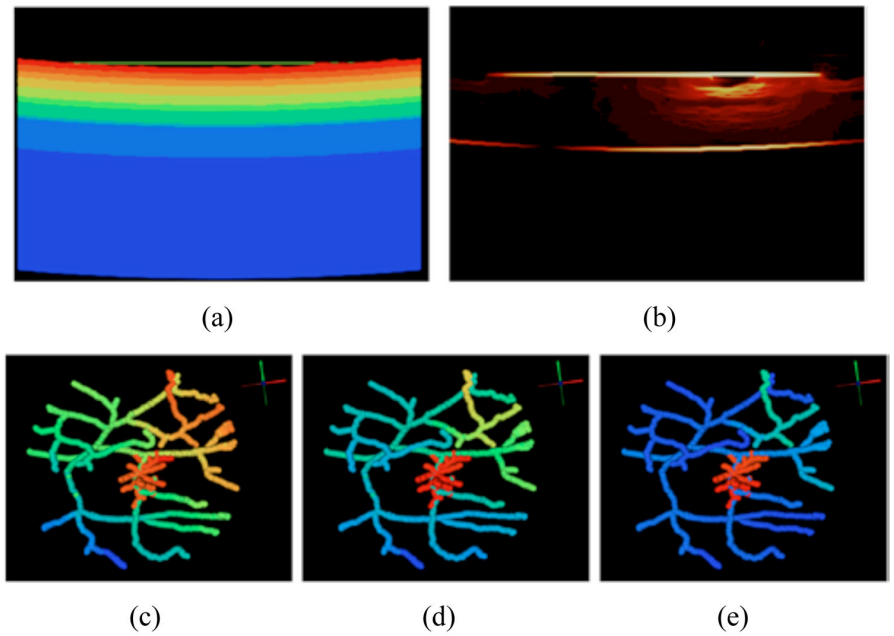

Figure 4.
Simulation results. (a) Reference 2D slice, (b) Electric field magnitude at one time step during an admittance method simulation, (c–e) Color-coded membrane potential on a single ganglion and bipolar cell at 1, 3, and 5 milliseconds, respectively.

Table I

Tissue Resistivites

Tissue	Resistivity (Ω-m)
Photoreceptors	50.50
Outer Nuclear Layer	60.00
Outer Plexiform Layer	70.00
Inner Nuclear Layer	65.00
Inner Plexiform Layer	18.00
Ganglion Cell Layer	70.00
Bipolar Cell Layer	70.00