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On the computation of a retina resistivity profile for applications in multi-scale modeling of electrical stimulation and absorption

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Abstract

This study proposes a methodology for computationally estimating resistive properties of tissue in multi-scale computational models, used for studying the interaction of electromagnetic fields with neural tissue, with applications to both dosimetry and neuroprosthetics. Traditionally, models at bulk tissue- and cellular-level scales are solved independently, linking resulting voltage from existing resistive tissue-scale models as extracellular sources to cellular models. This allows for solving the effects that external electric fields have on cellular activity. There are two major limitations to this approach: first, the resistive properties of the tissue need to be chosen, of which there are contradicting measurements in literature; second, the measurements of resistivity themselves may be inaccurate, leading to the mentioned contradicting results found across different studies. Our proposed methodology allows for constructing computed resistivity profiles using knowledge of only the neural morphology within the multi-scale model, resulting in a practical implementation of the effective medium theory; this bypasses concerns regarding the choice of resistive properties and accuracy of measurement setups. A multi-scale model of retina is constructed with an external electrode to serve as a test bench for analyzing existing and resulting resistivity profiles, and validation is presented through the reconstruction of a published resistivity profile of retina tissue. Results include a computed resistivity profile of retina tissue for use with a retina multi-scale model used to analyze effects of external electric fields on neural activity.

Keywords

effective medium theory; admittance method; multi-scale modeling; retina prosthesis; resistivity profile; connectome

1. Introduction

Computational modeling is commonly used for designing and analyzing the efficacy of neuroprosthetic electrodes as well as for safety implications of electromagnetic fields, and to understand physiology and anatomy of underlying neural cells. Model design varies, simplifying the domain in order to analyze the role of different parameters. The resolution ranges across a large spatial scale, from specific ionic current activity at the cellular membrane or a synapse (pm to μm), to large-scale models considering the current

distribution across prosthetic electrode arrays and bulk tissue (μm to cm). For example, in the retina, single cell models based on measured morphologies and membrane properties have been used to analyze the passive and active properties of cell membranes (Usui *et al* 1996, Greenberg *et al* 1999), the dynamics of voltage-gated ion channels (Freeman *et al* 2011, Kamenewa *et al* 2011), the stimulation region due to external electrodes (Schiefer and Grill 2006), and for modeling observed cell-type-specific phenomena (Fohlmeister *et al* 2010, Choi *et al* 2014). These models have quantified the cellular behavior, and have given insight as to what their roles may be in retinal circuitry. Consolidating findings from these single cell studies into cellular network models can then be used to analyze the role of connectivity (Publio *et al* 2009, 2012, Wang *et al* 2011). Other studies have focused instead on prosthetic designs rather than anatomy and physiology, considering geometry and placement of electrodes, differentiating existing devices and suggesting future design constraints (Rattay and Resatz 2004, Behrend *et al* 2011, Moghaddam *et al* 2014, Xie *et al* 2011). Work has also been done to more accurately represent the cellular composition of tightly packed cells and confined extracellular space, as shown in Meffin *et al* (2014) and Tahayori *et al* (2014). In this work, the authors propose a mean-field volume conductor model and a multidomain modeling framework that includes the effects of cellular composition on extracellular potential by modeling the neural tissue with an admittivity kernel, which can be incorporated into large-scale finite element simulation software.

As computational ability increases, and efforts in cellular physiology modeling and electrode design/electromagnetic (EM) modeling evolve, combining methodologies at both scales into multi-scale models has become more common. This consolidates the complexities of heterogeneous tissue in the extracellular space, and how the electromagnetic field patterns at this scale affect the response at the cellular level (Bouteiller *et al* 2011, Tsai *et al* 2012, Loizos *et al* 2014, Moghaddam *et al* 2014, Abramian *et al* 2015). However, existing models typically characterize the bulk extracellular resistive properties with resistivity values extracted from measurements of the involved tissue found in literature, which may not be accurate for the specific neural models considered due to measurements being taken from a different animal, the measurement setup conducted in different environments (controlled *in vitro*), or inaccuracies in the measurements themselves due, in part, to the small dimensions of the considered tissue. Also, the process of inserting a probe into neural tissue in attempt to measure at a fine spatial scale can damage the cells and possibly alter the morphology and resulting measurements.

The goal of such measurements is to provide data for EM models for analyzing implications of electrical stimulation. In this paper, we propose a method for reversing this process, using computational models to predict the resistivity of the tissue. This is essentially a practical realization of effective medium theory (Stroud 1998), using assumptions of resistive properties of microscale local elements to estimate effective bulk properties at a global scale. In order to link the EM model to a cellular model appropriately, we take exact morphological data from the cellular network model into consideration for reconstructing a resistivity profile of the bulk retina tissue. This process allows for ideal recording electrode placements, without the complications of measurement setups (electrode probe construction, segmenting neural tissue, modeling the electrical effects of the electrode interface, etc).

First, to provide motive for the resistivity calculations, stimulation thresholds were calculated using two measured resistivity profiles from literature, exposing an order of magnitude difference in required current magnitude for stimulating the retina cellular network and variation in the spike initiation location for the same pulse width. A multi-scale simulation process was used for simulating neural activity resulting from current source(s) applied to electrodes with realistic geometry and placement, following the process proposed in previous work, described in Loizos *et al* (2014). The Admittance Method is used to calculate voltage throughout a multi-resolution mesh, at a scale on the order of microns, representing bulk tissue that is discretized by resistivity. The resulting voltages are interpolated to obtain values at the center of each neural compartment within a retina neural network, and are applied as extracellular sources to observe resulting neural activity. A sensitivity analysis of the resistive properties of the model is conducted in this paper, using this multi-scale approach to simulate the neural response to epi-retinal electrical stimulation, comparing the responses when the tissue described using different resistivity profiles from literature. Differing from the work proposed in Loizos *et al* (2014), a more complete model of the neural network is utilized, incorporating amacrine cells (making a total of 163 cells) and observed synaptic connections, a higher resolution Admittance Method model with a resolution as fine as 1 μm , and different representations of the retina tissue, as described in further detail in the second section of this paper.

Further, and differing from Loizos *et al* (2014), the focus of the present manuscript is to propose a method for calculating the resistivity profile of the retina to address the discrepancies in neural activity between results of simulations determined using different empirical data, with the overall goal of increasing the accuracy of multi-scale simulation setups for analyzing electrical stimulation of retinal tissue. To do this, the cellular network was discretized and incorporated into a model that was used to calculate the resistance at various layers in the retina network using the Admittance Method. The methodology for the resistivity calculations was validated by simulating a resistivity profile of a currently used bipolar impedance probe in retinal tissue (Wang and Weiland 2015), matching the probe dimensions and experimental setup, resulting in a closely-matched profile. This validates the simulation methodology and shows application of this simulation setup as a predictive tool for resistivity measurements. By modifying the geometry and placement of the electrodes within the model, inaccuracies may be predicted and used as an aid in designing effective measurement probes and measurement setups. This is in addition to the overall goal of this work of leading to increased accuracy within multi-scale models, and therefore allowing for accurate estimation of current magnitude thresholds for electrical stimuli, aiding in decisions for current injection limits and innovative electrode design.

2. Simulation methods

First, simulations were run to provide a context for the need to calculate effective bulk resistivity of retina tissue. As mentioned in the introduction, a multi-scale modeling approach is taken for analyzing electrical stimulation of the retina. The retina model consists of two independent computational models. The first describes the retina at a μm -resolution, including an implant electrode and layered representation of retinal tissue. The retina layers are discretized by resistivity, and are defined here using two different empirical datasets

from literature to assess the sensitivity of the resistivity profile within this model when analyzing electric field throughout the tissue or neural activity. The transient voltage response to a time-stepping current source applied to the electrode was calculated throughout this model using the admittance method (Cela 2010). The second describes the underlying cells at a nm-resolution, incorporating morphological and synaptic data into a compartmentalized model, used for simulating induced neural activity using NEURON software (Carnevale and Hines 2006). The two are linked together by interpolating the voltage results to apply as extracellular sources to the neural segments, creating a complex multi-scale model. These methods are described in detail within this section. Section 3 then describes a proposed computational method for estimating effective resistivity directly applicable to this multi-scale model, addressing discrepancy in electric field and neural activity results due to resistivity variation in the model.

2.1. Bulk tissue level model

The large-scale model consists of a three-dimensional hexahedral multi-resolution mesh, with a resolution defined here to be as fine as 1 μm . It is discretized based on the dielectric properties of the tissue each voxel represents. These properties for the retina are described as layers of homogeneous resistivity, following measured values and layer depth found in literature. Two different resistivity profiles were considered to illustrate the variation that can occur in resulting electric field, and therefore variation in neural spiking activity, due to the choice of resistivity properties (Karwoski *et al* 1985, Kasi *et al* 2011). Two separate models were constructed for this comparative study. The first profile was the result of measurements taken with a bipolar electrode impedance probe, inserted into a rat retina sample at increments of 20 μm (Kasi *et al* 2011). The results produced a profile with a monotonically-increasing resistance with depth. This is unexpected, as the retina has a well-defined set of anatomical layers that would likely produce fluctuating resistance. The profile found is theorized to be due to the size of the electrode geometry, being orders of magnitude larger than the neuronal segments. The second profile is based on observed anatomical layers. Resistance measurements were averaged for each individual retina layer (Karwoski *et al* 1985), resulting in higher resistance in the nuclear layers than in the plexiform layers. A single planar disk electrode was placed epiretinally within both models, against the surface of the retina, in order to simulate electrical stimulation. It has a diameter of 200 μm and is flush with insulation, following dimensions of a currently-used retina prosthetic device (Zhou *et al* 2013). A rendering of the model, created in SCIRun (Parker and Johnson 1995), and plots of the two considered resistivity profiles are given in figure 1.

A multi-resolution variant of the admittance method was used to simulate electric potential fields within the model. The admittance method (AM) is a quasi-static electromagnetic field solver. It takes an admittance matrix (G) as input, which describes the admittance seen at, and in between, each node in the model. With a given set of current source(s) defined in a vector (I), a vector (V) containing the voltage at each node may be solved for using Kirchhoff's current law. A Krylov sub-space iterative solver is used for solving this linear system for node voltages. In-house code written in C++ was used for constructing the 3D models, the multi-resolution hexahedral meshing, solving the system for node voltages, and post-processing. Further details of the methodology are presented in Cela (2010) and Cela *et*

al (2011). This method has multiple benefits appropriate to this study: a multi-resolution mesh allows for decreased computational complexity while allowing for fine resolution in locations requiring it, and the setup as a circuit topology allows for the addition of individual circuit components in the model. Both of these features could be useful for modeling small-dimension neural segments and confined extracellular space (Meffin *et al* 2014). Also, as mentioned in the introduction, the ability to model electrodes of any geometry and placement for resistivity measurements allows for ideal systems that are impractical in experimental setups.

2.2. Cellular network model

While the AM solution can provide voltages throughout the tissue due to the induced field, it disregards any activity that is occurring in the neuronal networks, which is vital in understanding the retinal response to an electrical stimulus. Therefore, a neural network model was developed using a subset of a connectome dataset based on nanoscale transmission electron microscopy (TEM) images (Marc *et al* 2003, 2013). Extracted connectomics data provided the means for modeling neural networks within the retina, consisting of accurate morphologic and synaptic data. It was compartmentalized for use with NEURON software (Carnevale and Hines 2006), modeling individual segments as tapered cylinders with an electrical description defined with a modified cable model, of the following form.

For the purposes of this paper, an ON-ganglion cell network was considered, containing 163 cells, along with all observed gap junctions, and synapses. Complex ionic mechanisms were applied to each compartment, following published measurements and models. Varying parameters were applied depending on neuronal segment type (soma, axon, dendrite) and cell type, differentiating them as either ganglion, cone bipolar, rod bipolar, or amacrine (or horizontal) cells. Ganglion cell properties follow the conductance and rate equations given for a multi-compartmental cell by Fohlmeister *et al* (2010). Bipolar and amacrine cell properties are as listed in the network computational model given by Publio *et al* (2009). Ionic channel equations and gating rate constants are provided in the appendix, with further details on the current mechanisms provided in Usui *et al* (1996), Fohlmeister *et al* (2010) and Publio *et al* (2009). The functionality of the active and passive cellular properties was validated by applying voltage and current clamps to each, and comparing the resulting membrane voltage and current with those given in the papers the values were taken from.

2.3. Current threshold calculation

The effect that extracellular stimulation via epi-retinal electrodes has on the neural network was simulated. The AM simulations provide voltage potential fields throughout a model of retina and surrounding tissue for a time-stepping current input, which was applied as a 1 ms-wide cathodic pulse. By translating the NEURON model coordinates to a proper location within this retina model, about 50 μm into the retina beneath the surface of the electrode, the voltage values at the membrane of each compartment may be interpolated and extracted. This location of the cellular network model with respect to the retina bulk-tissue model is shown in the diagram in figure 2. The coordinates for the center of each neural segment were extracted from the NEURON model, and a script was written to interpolate voltages from

the nodes surrounding each of these coordinates within the Admittance Method results. These values are applied as a voltage source in series with the cell membrane, using the built-in 'extracellular' function in NEURON. This function allows for applying up to two layers of extracellular voltage in series with the membrane in the cable model. One node per neural segment was utilized for applying voltage that was interpolated to the location of the center of the neural segment. Resulting membrane voltage is then solved for in NEURON. The current magnitude threshold was found by scaling the input current to the nearest mA required for a ganglion cell in the network to activate.

The resulting current magnitude thresholds for activation of the ON ganglion cell network, as well as the voltage and electric field patterns throughout the bulk tissue resulting from Admittance Method simulations, were compared for these two setups to analyze differences found when applying different published retina resistivity representations.

3. Computing resistivity

3.1. Simulation strategy

After analyzing the variation in stimulation threshold that resulted from the choice of retina resistivity properties, a method was devised for constructing a resistivity profile of the tissue containing the cells in the connectome dataset used for creating the NEURON model. A 3D model was constructed with two planar electrodes on either side of the tissue, which was given a thickness of 50 μm , the height of the connectome retina sample. The x - and y -dimensions of the electrodes match the dimensions of the model, with a current source placed across the two, producing an ideal current source across the tissue. Thus, the resulting resistance of the tissue between the electrodes is found by solving for the voltage across the electrodes using the admittance method, and dividing it by the injected current, following Ohm's law, and the resistivity using Pouillet's Law. The meshing of this discretized 3D model and admittance method simulation was done using in-house admittance method code, as discussed in the simulation methods section. The methodology was tested by setting the inter-electrode tissue homogeneous properties with a known resistivity, and ensuring that the solution resistivity matched the defined value. A diagram of this method is shown in figure 3.

The morphological data for the connectome dataset was then voxelized and merged with this model, populating the inter-electrode space with the cellular network. The density of cells within the model was increased by duplicating the ON-ganglion cell network and populating the tissue space. This was done to more closely match the cellular density in the entire sample, rather than just including a single network. Assumptions regarding the resistivity of the cellular features at a micron-scale were based on the highly-resistive properties of inactive cellular membrane, set to 0.1 $\text{M}\Omega\text{m}$. The extracellular material was set a resistivity of saline, 0.78 Ωm . Rerunning the simulation with these new geometric features and resistive properties would produce the effective bulk resistivity of the tissue. This process was then repeated with segmented sections of the retina model. It was split into three sections: bipolar cell, inner plexiform, and ganglion cell layers, providing computed effective resistivity of the tissue using the exact neural network for the simulations described in the first section of this paper. This simulation setup was identical to the setup described above and shown in figure

3, except that the volume of tissue was cropped in the z -direction, leaving only the ganglion cell layer of retina tissue, and moving the electrodes to the z -boundaries of this layer. This was then repeated for the inner plexiform and bipolar cell layers. While a parallel plate electrode placement used here is impractical in an experimental setup, due to challenges associated with segmenting retina at this fine of a scale and unavoidable damage to each layer that would occur from segmentation, it is perfectly fine in simulation. The electrode placement was chosen to achieve as ideal as possible of a setup for calculating the resistivity. By placing electrodes above and below each volume of tissue of which the resistivity is to be calculated, current can only travel through this tissue, leading to an accurate description of the resistance of each simulated volume. This is illustrated in this study by segmenting individual layers of the retina that have observable anatomical differences.

3.2. Validation of methodology

The methodology used for computing effective resistivity for use with our simulations of electrical stimulation in retinal tissue was validated by recreating a resistivity measurement profile found experimentally (Wang and Weiland 2015), modifying the setup shown in figure 3 such that the electrode geometry and placement matched that of the experimental setup. A bipolar electrode probe was used, with a pencil-shaped tip. The 25 μm tip served as the anode, and a ring 25 μm up as the cathode. A model of this electrode probe was built, following the dimensions in Wang and Weiland (2015), and placed within the model of the cells described in the previous section, with the parallel plate electrodes removed. A rendering of this model is given in figure 4. Their process followed the peak resistance frequency (PRF) method, in which the resistance across the two leads is measured and scaled based on a k factor to calculate the resistivity. This k -value is found experimentally, measuring the resistance in a medium of known resistivity and calculating the scalar (units of cm^{-1}) that would result in the expected resistivity value. Simulations were run first without the cells included in order to compare the simulated k -value with the value found experimentally. The tissue was given a resistivity value of 0.637 Ωm , matching that of the solution used in the experimental study. Simulations were then repeated with the cellular network included, with the probe translated 10 μm further into the neural network with each successive run. The correlation between these results and the experimental data was analyzed, ensuring the ability of this method to predict measurements that would be seen experimentally.

4. Results

4.1. Current thresholds

The resulting current magnitude thresholds varied considerably between the two models with different resistivity profiles. For the first model, utilizing the profile with monotonically-increasing resistivity every 20 μm produced a current threshold of 78 μA in a ganglion cell. If the synapses and gap junctions were removed, the threshold was reduced to 71 μA . This is likely due to the exclusion of inhibitory input from the amacrine cells in the network. For the second model, with a resistivity profile varying based on measured resistivity of anatomical layers, the threshold was an order of magnitude lower, 2.7 μA and 2.87 μA for a ganglion cell with and without synaptic projections, respectively. This lower

threshold is likely due to the observed increase in curvature of voltage, as seen in figure 5(a), which follows the metric for analyzing activation of neural segments given by the activating function (Rattay 1986). In addition, the spike initiation occurs in different cells for both models. This is shown in figure 5(c), and is noted by higher membrane voltage at the soma of different cells.

The results from the first model are consistent with some clinical trials for patients newly implanted with an array of electrodes with the dimensions modeled here (Mahadevappa *et al* 2005). However, the array is known to lift-off of the retina surface and is likely not completely flush with the retina surface to begin with, as they are tacked to the retina without any means for disallowing conductive vitreous fluid to fill a space between the tissue and electrode (Mahadevappa *et al* 2005, de Balthasar *et al* 2008). This would lead to an increased threshold, as the vitreous humor has a high conductivity, serving as a likely path for the injected current to flow rather than traveling directly into the tissue. Thus, for an ideal case, as modeled in this work, where the electrode is completely flush with the tissue, a lower threshold would be expected. However, without linking the model appropriately, considering the underlying cellular morphology, an accurate estimated threshold cannot be realized.

4.2. Validation of methodology

The results for the model using a bipolar probe, used for validating the methodology for calculating resistivity proposed in section 3.2, closely match that of the measurements, staying within the standard deviation of the measured resistivity values. The simulated curve comprises a similar effect as the probe reaches the tissue, with an increasing resistance tens of μm before actually inserting into the cellular network, likely due to the geometry of the electrodes and the approaching boundary of the tissue. The resistivity increases monotonically as expected throughout the volume. However, the entire retina is not considered in this computational model. So, the resistivity drops off after the 50 μm slice, encompassing ganglion cells, bipolar cells, amacrine cells, and the inner plexiform layer. A plot of the simulated and measured curves are shown on the left in figure 6 for the region of retina containing the section of retina included in the computational model. A plot of the reported measured resistivity values across an entire retina slice are given on the right in figure 6. If an entire retina volume was used in the simulation, the resulting resistivity profile would be expected to match for the remaining sections of retina given in this plot as well.

In comparison with the two resistivity profiles shown in figure 1 that were used for exposing variability in neural activity results due to electrical stimulation with different resistivity, note that the shape and magnitude of the resistivity profile used in this validation study match the first resistivity profile closely. This is expected, since both studies utilized a bipolar electrode setup, with the two leads on a probe in a vertical placement with respect to the retina surface. Both studies resulted in a retina resistivity profile that increases monotonically with increased depth in the retina. As mentioned in section 2, this shape of resistivity profile is unexpected for the retina, since it contains distinct anatomical layers that would be expected to have layer-specific resistivity. This unexpected result is likely due to the geometry of the electrodes. In figure 4, a plot of the electrode geometry for this

validation study is shown for the initial placement of the probe above the neural network, drawn to scale. The electrode leads and inter-electrode distance are nearly as large as this retina sample. Therefore, the dimensions may not be small enough to realize resistivity changes at a scale as fine as retina anatomy. This leads to a useful application of our proposed resistivity calculation, allowing for the prediction of a resistivity profile using specific electrode geometry and experimental setup.

4.3. Computed resistivity

Differing from the electrode setup in the validation study above, the resistivity computations proposed in this work were in as ideal of a setup as possible. Parallel plate electrodes were placed on either side of the ganglion cell, the inner plexiform, and the bipolar cell layers in the retina volume used in this study. The computed resistivity of the the individual ganglion cell, inner plexiform, and bipolar cell layers are $0.9196 \Omega\text{m}$, $2.4255 \Omega\text{m}$, and $0.966 \Omega\text{m}$, respectively. Thus, the resistivity was found to be higher in the plexiform layer than in the nuclear layers. In addition, the ganglion cell layer and bipolar cell layer resistivity are within 10% of each other. The result was as hypothesized prior to conducting the computational study. As compared to the bipolar cell layer, the ganglion cell layer includes cells that are larger in diameter but with a smaller cellular density. By representing the cells as highly resistive elements, the resulting bulk resistivity is expected to match closely. Within the inner plexiform layer between the two, there is a high density of dendritic trees from both the bipolar and ganglion cell layers. Therefore, by the same highly resistive approximation, this layer was expected to have a higher resistivity.

5. Discussion

5.1. Scalability of methodology

While this study was conducted using the example of an implemented retinal electrode, the methodology is scalable to any neural tissue. The benefit of the organization of this process is that it requires no prior knowledge of the bulk resistivity of the tissue. The cells used in multi-scale models themselves may be used to construct resistivity profiles for use with EM modeling. For cases in which electrical stimulation is involved in tissue that is hard to measure *in vivo*, this process allows for an estimation of properties for calculation of stimuli parameters. For example, for the case with hippocampus electrical stimulation, large-scale neural models are available that may be used to calculate unknown resistive properties for application in multi-scale models for refining and evolving the stimulation tools and processes (Hendrickson *et al* 2015).

5.2. Factors of resistivity variation

The methodology included here may be expanded to include the cells themselves into the multi-scale modeling, rather than using bulk resistive properties. When observing the current density resulting from the simulation used for solving for resistivity, there is a clear peak in gaps between neuronal features, as seen in the normalized slice of current density shown in figure 7. The increased variation in current density may itself be responsible for spike initiation, following the mentioned activating function metric. One of the main reasons for utilizing bulk properties rather than merging the cells into the model is the additional

computational complexity introduced by the fine resolution required for incorporating cellular features. For a single network, it is feasible. However, as larger sections of retina, or other neural tissue, are considered, it becomes more difficult. Regardless, the effects of the varying current density magnitude should be considered.

5.3. Safety implications

This study was conducted in order to increase the accuracy of currently-used predictive multi-scale models for analyzing electrical neurostimulation. The current threshold study presented in this paper proves how vital accurate resistive properties become in such predictive studies. Without an accurately linked multi-scale model, there may be inaccuracies in the resulting implications of advantages of proposed electrode geometry, current stimuli, etc. Implementing arbitrary resistivity profiles from literature without incorporating a study to match the resistive properties of the cellular network to the bulk tissue can lead to inaccurate predictions of current magnitude thresholds. Such predictions are crucial in considering current injection limits for clinical applications.

6. Conclusion

Prior to this work, there has been minimal parameter-matching across spatial scales within multi-scale models for stimulation of the effects of specific neurostimulation processes (from bulk tissue-level to cellular level). Authors typically choose a homogeneous representation of the resistance of the tissue encompassing the cells whose activity they are modeling. Appropriately linking models on both scales is vital in producing accurate realizations of the underlying cellular activity to the resulting electric fields based on the defined current injection. In this paper, a sensitivity analysis of the resistivity profile choice for neural tissue in a multi-scale model, and its effects on resulting simulated neural activity, was conducted, emphasizing the importance of accurate resistivity. The proposed methodology for calculating resistivity based on knowledge of the morphology of the underlying cells can lead to a more accurate approach to investigating advantageous electrode geometry and current stimuli in neurostimulation systems. In addition, this methodology can be used as a predictive tool for designing resistivity measurement probes and validating experimental measurements.

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Appendix

The ganglion cell membrane model follows the five ionic-current model given by Fohlmeister *et al* (2010) The membrane current is found using Kirchhoff's current law, giving the equation below:

$$CdV/dt = -(g_{Na}m^3h(V-V_{Na}) + g_{Ca}c^3(V-V_{Ca}) + (g_Kn^4 + g_Aa^3h_A + g_{K,Ca})(V-V_K)),$$

where V = voltage, C = capacitance, $V_{Na} = 35$ mV, $V_K = -75$ mV,

Table A1

Rate constants for the ganglion cell ionic mechanisms.

Na	$\beta_m = 20e^{-(E+55)/18}$
$\alpha_m = \frac{-0.6(E+30)}{e^{-0.1(E+30)} - 1}$	
$\alpha_h = 0.4e^{-(E+50)/20}$	$\beta_h = \frac{6}{e^{-0.1(E+20)} + 1}$
Ca	$\beta_c = 10e^{-(E+38)/18}$
$\alpha_c = \frac{-0.3(E+13)}{e^{-0.1(E+13)} - 1}$	
K	$\beta_n = 0.4e^{-(E+50)/80}$
$\alpha_n = \frac{-0.02(E+40)}{e^{-0.1(E+40)} - 1}$	
A	$\beta_A = 0.1e^{-(E+30)/10}$
$\alpha_A = \frac{-0.006(E+90)}{e^{-0.1(E+90)} - 1}$	
$\alpha_{hA} = 0.04e^{-(E+70)/20}$	$\beta_{hA} = \frac{0.6}{e^{-0.1(E+40)} + 1}$

Table A2

Conductances for each ionic mechanism for all cells.

Conductance (mS cm ⁻²)	Ganglion	Cells		
	Soma	Dendrites	Bipolar cells	Amacrine cells
$\bar{g}_{passive}$	0.10	0.10	0.77	0.10
$\bar{g}_{Na}$	72.00	79.50	—	2.60
$\bar{g}_K$	50.40	23.40	0.318	0.26
$\bar{g}_A$	36.00	36.00	5.6	—
$\bar{g}_{Ca}$	1.20	1.20	2.00	—
$\bar{g}_{K,Ca}$	0.05	0.05	1.4	—
$\bar{g}_h$	—	—	31.1	—

$$I_{K,Ca} = g_{K,Ca} \left(\frac{[Ca^{2+}]_i/0.001}{1 + [Ca^{2+}]_i/0.001} \right) (V - V_K), \text{ and } [Ca^{2+}] = 0.0001 \text{ mM.}$$

The gating rate constants x (m , n , h , c , a , h_A) are found using the following equation:

$$dx/dt = -(\alpha_x + \beta_x)x + \alpha_x,$$

with α and β given in table A1 and conductances given in table A2. More information on the ganglion cell model is given in Fohlmeister *et al* (2010).

The bipolar cell model contains five ionic currents (I_h , I_{Ca} , I_K , $I_{K,A}$, $I_{K,Ca}$), with their active properties and conductances as described in further detail in Usui *et al* (1996). The conductances are given in table A2, with the rate equations α and β given in table A3, with the ionic current found using Kirchoff's current law, as with the ganglion cell model, with the sum of the membrane currents given by I below.

$$I = g_K m_K^3 h_K (V - V_K) + g_{Ca} m_{Ca}^4 h_{Ca} (V - V_{Ca}) + g_A m_A^3 h_A (V - V_K) + g_{K,Ca} m_{KCa}^2 m_{KCa1} (V - V_K) + g_h m_h (V - V_h)$$

Additional information on the ionic current mechanisms for the bipolar cell membrane model are given in Usui *et al* (1996). The amacrine cells were described to have only sodium and potassium channels, described using a basic Hodgkin–Huxley formulation, which allows the cells to spike, but without the repetitive firing ability of the ganglion cells. These amacrine and bipolar cell membrane models were taken from Publio *et al* (2009).

Table A3

Rate constants for the bipolar cell ionic mechanisms.

K	$\alpha_{mK} = \frac{400}{e^{-(E-15)/36} + 1}$ $\alpha_{hK} = 0.0003e^{-E/7}$	$\beta_{mK} = e^{-E/13}$ $\beta_{hK} = \frac{80}{e^{(E+115)/15} + 1} + 0.02$
Ca	$\alpha_{mCa} = \frac{12\,000(120 - E)}{e^{(E-120)/25} - 1}$	$\beta_{mCa} = \frac{40\,000}{e^{(E+68)/25} + 1}$
K, Ca	$\alpha_{mKCa} = \frac{100(230 - E)}{e^{(230-E)/52} - 1}$	$\beta_{mKCa} = 120e^{-E/95}$
A	$\alpha_{mA} = \frac{1200}{e^{(E-50)/28} + 1}$ $\alpha_{hA} = 0.045e^{-E/13}$	$\beta_{mA} = 6e^{-E/10}$ $\beta_{hA} = \frac{75}{e^{(E+50)/15} + 1}$
h	$\alpha_h = \frac{3}{e^{(E+110)/15} + 1}$	$\beta_h = \frac{1.5}{e^{-(E+115)/15} + 1}$

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Figure 1. (a) 3D Rendering of discretized model of retina tissue and electrode setup, and (b) resistivity profiles considered for discretizing tissue layers based on studies (Kasi *et al* 2011) (top) and (Karwoski *et al* 1985) (bottom).

Figure 2.

Slice of the retina admittance model with placement of the neural network extracted from the connectome dataset, and the cellular morphologies.

Figure 3.
Diagram of the admittance model used to estimate resistivity of tissue, with homogeneous (left) and inhomogeneous (right) properties.

Figure 4.
Rendering of admittance model including concentric bipolar electrode probe and cellular morphology.

Figure 5.

Simulation results after applied cathodic pulse at threshold current magnitude with pulse width of 1 ms for both resistivity profiles shown in figure 1, the top results considering resistivity based on Kasi *et al* (2011) and the bottom considering the resistivity based on Karwoski *et al* (1985). (a) Slices of voltage through the center of the firing electrode, (b) interpolated extracellular voltages at each compartment in cellular network, and (c) membrane voltage at every compartment resulting from the extracellular voltages during ganglion cell spike initiation.

Figure 6.

(Left) Resistivity computed using concentric bipolar electrode probe, compared with experimental measurements. The simulation included the 50 μm -thick cellular network extracted from a connectome dataset while the measurements were taken of a sectioned rat retina. (Right) Experimental measurements of the entire volume of a sectioned rat retina.

Normalized current density

Figure 7. Slice of normalized current density resulting from an admittance method simulation used for estimating bulk resistivity of the tissue sample.