Title: Multi-Scale Modeling of Electrical Stimulation of the Retina

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An implantable retinal prosthesis has been developed to restore vision to patients who have been blinded by degenerative diseases, such as Retinitis Pigmentosa or Age-Related Macular Degeneration, that destroy photoreceptors. By electrically stimulating the surviving ganglion and bipolar cells, the damaged photoreceptors may be bypassed and limited vision can be restored. While this has been shown to produce partial vision restoration, the understanding of how the retinal 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 the underlying neuronal networks.

First, the extracellular data was produced using the Admittance Method. We constructed and simulated a multi-scale model of a portion of the retina, including implant electronics, bulk tissue, and specific neurons. The model was discretized at a resolution of 5 μm, consisting of a separate spherical layer for each layer of retina. The boundaries between the specific layers were rippled to give a more accurate representation of retinal anatomy. An epi-retinal electrode array, with an electrode diameter of 200 μm, was placed against the optic nerve layer in the model. Each voxel was then described as a parallel admittance and capacitance in each direction, based on the dielectric properties of the materials. The fields traveling through this retinal model due to a biphasic pulse applied to one of the electrodes was then simulated using a time-stepping Admittance Method simulation. A multi-resolution meshing program was applied to the model prior to simulation in order to simplify the computation.

Second, an accurate model of neuronal networks inside this tissue was constructed. We are using nanoscale connectome data of large-scale retinal networks (augmented by picoscale ultrastructural reimaging) to develop the most biologically accurate, physiologically relevant retinal network models to date. Two major foci incorporate detailed morphometrics and synaptometrics into our models, thus optimizing model parameterization and constraining parameters to biologically-appropriate values. We have initially centered our efforts at quantifying the retinal bipolar cell-ganglion cell excitatory synaptic interface that drives retinal output signals to the brain, but will expand our models to include electrical coupling between bipolar cells as well as feedback and feedforward inhibition that shapes such excitatory signals. Our unique combination of neuroanatomical ground truth and network simulations will guide therapeutic strategies and retinal prosthetic development to cure blindness.

The morphology and biophysical data of the cells were imported into NEURON software. The extracellular voltages resulting from the large-scale simulation were linearly interpolated and applied as an extracellular source to the membrane voltage of each compartment in this neural network model. A simulation was then run in NEURON to model the change in membrane

voltage due to the biphasic pulse applied to one of the implant electrodes, showing whether the neurons fire. Once a network of neurons is constructed, it will be linked to the simulation that included the implant electronics and bulk tissue properties of retinal tissue.