USC Institute for Technology and Medical Systems Innovation

Non-invasive Electrical Stimulation Strategies for Selective Activation of Retinal Neurons: A Computational Study

USC Ginsburg Institute for Biomedical Therapeutics

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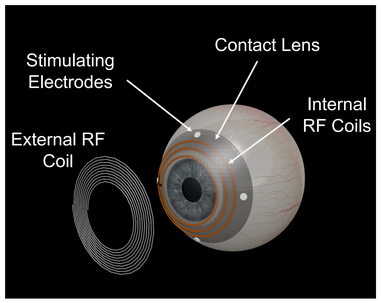
I. Purpose

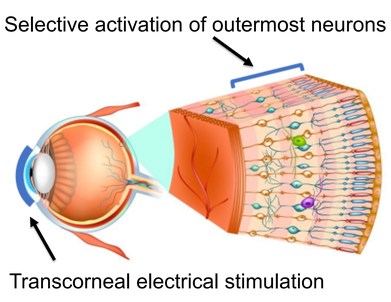
To slow down the progressive degeneration of the retina in eye diseases using non-invasive electrical stimulation.

❖ Retinitis Pigmentosa (RP) ❖ Age-Related Macular Degeneration (AMD) ❖ Glaucoma

Gene and stem cell therapies have been developed to cure AMD and RP. However, the clinical outcome of these approaches has been limited to specific population of patients, with the potential tissue and retina damage.

We have recently demonstrated that controlled microscale electromagnetic (EM) stimulation can lead to neuroprotective and epigenetic changes in the retina.





Goal: Design electrical stimulation strategies to better target outer retinal neurons affected at the early stages of degeneration.

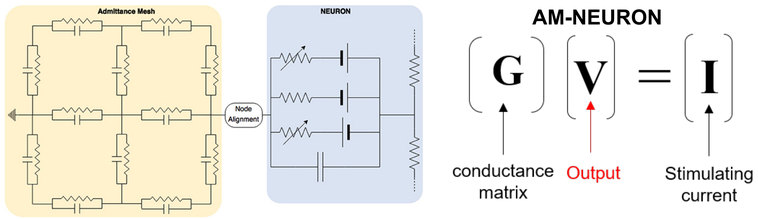
II. Methods

We have utilized our three-dimensional Admittance Method (AM)/NEURON multi-scale computational modeling platform to:

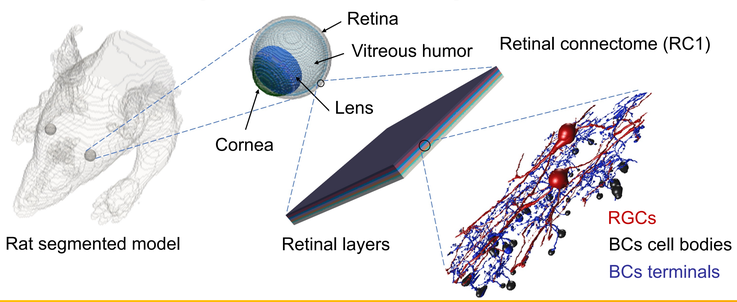
I) Predict the electric fields generated inside the retina tissue.

II) Couple the extracellular voltages to biophysically and morphologically realistic models of retinal ganglion cells (RGCs) and bipolar cells (BCs).

III) Determine the activation threshold of cells to electrical stimulation parameters.



- Constructing a large-scale rat voxel model, details of the eye, retinal layers, and cellular-level modeling of retinal network including RGCs and BCs.



III. Results

a) RGCs and BCs models:

- The verification of implemented computational models with the experimental data from the literature.

Fig 1. (a) the morphology of the DB4 BC; (b) experimental data showing the response of the cell to a sinusoidal current of 10 pA in amplitude at the frequency of 20 Hz; (c) the multi-compartment model of the DB4 cell and its response to the sinusoidal input current. The model can closely replicate the experimentally recorded signal and the characteristics of sodium and calcium spikes have been further shown in the figure.

Fig 2. (a) the morphology of the A2 RGC type; (b) comparison between experimental (top) and computational (left) membrane voltages in the cell body (soma) in response to intracellular stimulation The hyperpolarizing step current stimulation was applied between 100 ms and 500 ms.

Fig 1

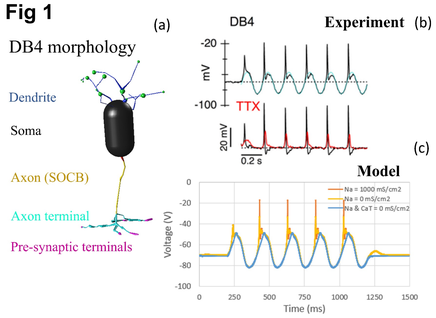
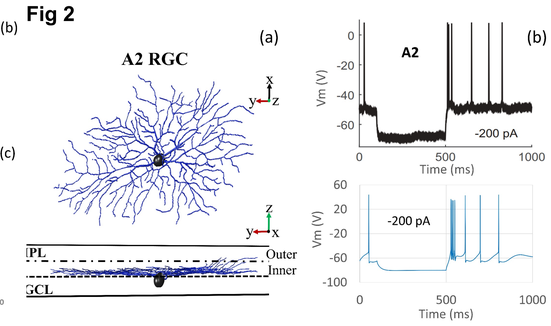


Fig 2



b) Transcorneal electrical stimulation

- The design of the ground electrode configuration and placement to maximize the induced electric field in the retina.
- Figures 3 and 4 show the voltage and current density distributions to 200 μA current amplitude transcorneal electrical stimulation, respectively.
- The ground electrode on the temporal region can focalize the voltage distribution on the eyes with the greatest electric field gradient (activation function) along the thickness of the retina.

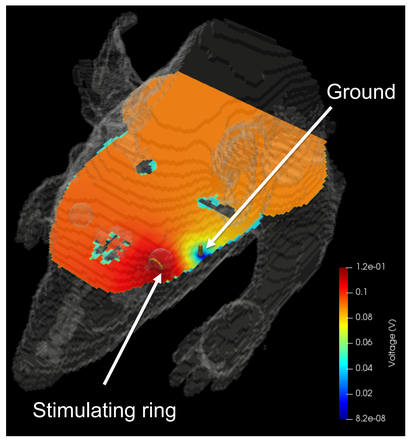


Fig 3. Electric potential (V)

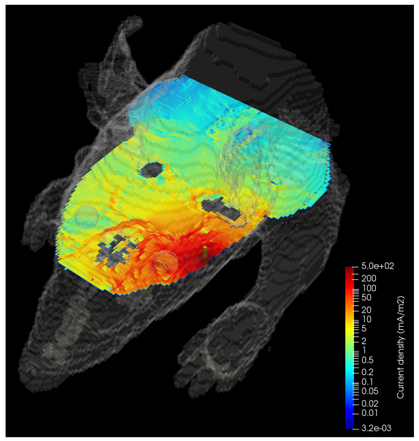
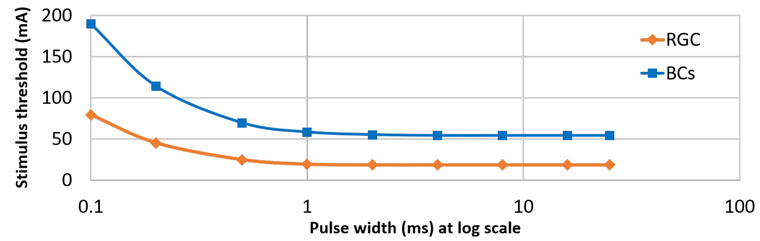


Fig 4. Current density (mA/m2)

c) Electrical stimulation waveforms

❑ A) Monophasic pulses



❑ B) Biphasic pulses

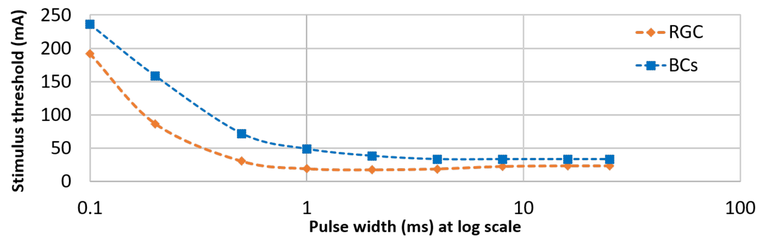


Fig 5. The strength-duration curves plotted for a range of pulse durations from 0.1 ms to 25 ms; (A) monophasic stimulus pulses; (B) biphasic stimulus pulses.

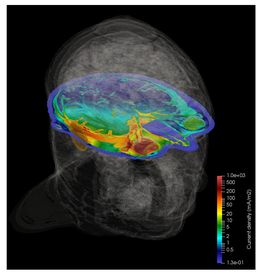
Computational results show that long biphasic pulse pulses augment the chance for the excitation of BCs and further reduce the differential stimulation threshold of RGCs and BCs.

IV. Discussion and Conclusion

- We demonstrated the greater sensitivity of spiking BCs to transcorneal electrical stimulation of long biphasic stimulus pulses using the proposed ground electrode placement.
- The greater potential for selective activation of BCs, which have been affected earlier in the progression of degeneration, using the designed non-invasive electrical stimulation strategy allows us to more effectively induce epigenetic changes in the retina and ultimately halt or slow down the progression of prevalent retinal diseases.

The future steps will be focused on:

- Stimulus waveforms to maximize the response ratio of outermost neurons over inner RGCs and more selectively target BCs.
- Incorporating the high-resolution human head model and designing electrical stimulus strategies to more effectively induce controlled electric fields in the retina.



V. Acknowledge and Support

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