2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

A Computational Model Simulates Light-Evoked Responses in the Retinal Cone Pathway

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***Abstract*— Partial vision restoration on degenerated retina can be achieved by electrically stimulating the surviving retinal ganglion cells via implanted electrodes to elicit a signal corresponding to the natural response of the cells. Realistic computational models of electrical stimulation of the retina can prove useful to test different stimulation strategies and improve the performance of retinal implants. Simulation of healthy retinal networks and their dynamical response to natural light stimulation may also help us understand how retinal processing takes place via a series of electrical signals flowing through different stages of retinal processing, ultimately giving rise to visual percepts. Such models may provide further insights on retinal network processing and thus guide the design of retinal prostheses and their stimulation protocols to generate more natural percepts. This work aims to characterize the photocurrent generated by healthy cone photoreceptors in response to a light flash stimulation and the resulting membrane potential for the photoreceptors and its postsynaptic cone bipolar cells. A simple network of ten cone photoreceptors synapsing with a cone bipolar cell is simulated using the NEURON environment and validated against patch-clamp recordings of cone photoreceptors and ON-type bipolar cells (ON-BC). The results presented will be valuable in modeling light-evoked or electrically stimulated retinal networks that comprise cone pathways. The computational models and methods developed in this work will serve as an integral building block in the development of large and realistic retinal networks.**

***Clinical Relevance*— Accurate computational model of a retinal neural network can help in predicting cell responses to electrical stimulation in vision restoration therapies using prostheses. It can be leveraged to optimize the stimulation parameters to match the natural light response of the network as closely as possible.**

I. Introduction

The goals of computational modeling in neuroscience include simulating neural networks to understand their functional mechanisms better, predict how alterations in the network (due to disease or injury) can impact the signal flow, and design stimulation strategies for performance improvement of neuroprosthetic devices. The retina is a complex network of densely packed cells that converts photons entering the eye into electrical neural signals, which undergo layers of processing before reaching the visual cortex in the brain. Computational methods of retinal cells and networks are crucial in understanding how the retinal cells work together to create the visual signals that are transmitted to the optic nerve via ganglion cells. They are also useful in predicting how the signaling may change in a degenerating retina's network over time and how prosthetic systems can deliver efficient stimulation to restore some degree of vision to blind patients [1].

One way of improving the accuracy of retinal neural network models is to incorporate a stimulation protocol that can mimic the natural light response of photoreceptors. Models in the literature utilize current clamp, electrical stimulation or even rod photoreceptor light input paradigms to run single cell [2] or network level simulations [3, 4]. Once a reliable stimulation framework with validated cell responses can be established, we can use multi-scale methods with bulk tissue models [5] to assess the effects of electrical stimulation on retinal tissue [6]. It is important to differentiate and model both cone and rod signals, which control various aspects of vision such as color perception or visibility in low-light conditions, respectively. For example, computational results predictive of color encoding in ganglion cells [7], [8] can be expanded on with a realistic cone photocurrent model that can simulate L-, M- and S-type inputs to the network.

While the rod photocurrent has been studied and tested in multiple works [9, 10], the same has not been done for cones to best of our knowledge. It is critical to accurately model the cone pathway for building a complex and realistic retinal network because mesopic and photopic vision is largely dependent on cones. The differences between rod and cone responses to the same stimulus must be implemented correctly to accurately predict the signal flow in retina. To this end, we present a light stimulation protocol for cone photoreceptors specifically, which is verified using a simple network of cones and ON-type cone bipolar cells (ON-BC). Simulated response of cone photocurrent to a light flash input and the following changes in cone and ON-BC membrane potential are validated against various experimental recordings and compared with rod pathway simulations from previous work. Section II describes the specifics of the developed model and methods,

* This work was supported in part by the NEI (NIH Grant No. R21EY028744) and an unrestricted grant to the Department of Ophthalmology from Research to Prevent Blindness, New York, NY.

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section III presents the simulation results for validations and section IV discusses how this framework can be used in more complex networks and the next steps towards improving the computational methods for representing the natural phototransduction process.

II. METHODS

A. Photocurrent Input

The photocurrent input is applied as a current clamp on the cone photoreceptors, mimicking the current generated in its inner segment from incident light. The shape and amplitude of the current clamp is tuned according to the following conditions: the cones are saturated with respect to light intensity and the current waveform's duration and shape closely resembles the whole-cell recordings of cones resulting from light stimulation (Fig. 1). Recordings from cones of bass [11], salamander [12] and goldfish [13] show that a photocurrent generated after a flash of light (~10 ms duration at a wavelength of 500 nm) lasts about 500 ms and reaches a peak amplitude of 20 pA. The simulated photocurrent waveform (red) plotted in Fig. 1(a) can be obtained through the summation of four temporal functions as presented in the following equations:

$$\text{Part 1} = (1.05) * \left(1 - e^{-10*\frac{tr}{160}}\right)^{100}$$

$$\text{Part 2} = -\frac{0.015}{1+e^{-\frac{tr-555}{250}}}$$

$$\text{Part 3} = -\frac{0.81}{\left(1+e^{-\frac{3*tr-1500}{65}}\right)^{0.5}}$$

$$\text{Part 4} = -\frac{0.23}{1+e^{-\frac{3*tr-1200}{80}}}$$

$$I_{clamp} = \text{-(Part 1+Part 2+Part 3+Part 4)} \quad (1)$$

The current clamp is a mathematical function that is fixed for a given input. In other words, it is not influenced by any other variables in the simulation and must be adjusted before simulation. The time constant *tr* is the real-time value in milliseconds while the simulation runs. This model takes after the rod photocurrent waveform covered in the computational work of Barnes and Hille [14], Kourennyi and Liu [15] and Publio et al. [10]. However, due to the differences of phototransduction between rods and cones, the cone photocurrent has faster kinetics and has a smaller peak amplitude. We have addressed this need by adjusting the rod photocurrent model to match the natural response of cones, as defined in equation (1). This was done by algebraically scaling the rod photocurrent waveform to match a cone's photocurrent during light stimulation. The resulting waveform is plotted in Fig. 1(a) and Fig. 2(a).

The model reproduces the cone patch-clamp recordings from aquatic species such as bass, salamander and goldfish, which is a potential limitation. In fact, recordings from other species such as mouse [16, 17] and non-human primate [18, 19] suggest that the duration of current injection can be much shorter and peak amplitude at saturation can have large variability. The reason we chose to fit our model to recordings from the species shown in Fig. 1 is because the cell biophysical parameters are originally obtained using whole-cell recordings of tiger salamander cones [20] as well as bass and goldfish bipolar cells [21]. Further study will be necessary to tune the photocurrent model for mammalian retina, which is common in the eye research field.

B. Cell Biophysical Models

The physiological behavior of cone photoreceptors and ON-BCs are represented by modified Hodgkin-Huxley models of these cells. Each cell is made up of compartments and each compartment is defined by passive membrane and active ionic currents that are specific to the cell type. Model implementation and prediction of neural response are performed using NEURON simulation environment [Hines 1997]. Membrane potential and individual current channel responses are validated by replicating the patch clamp results with single compartment models. The photocurrents are first simulated in MATLAB to tune the waveform's shape and then translated into NEURON to be used as a current clamp input to photoreceptors. We adapted channel properties from previous experimental patch clamp data and models on cone photoreceptors and ON-BC. The biophysical model parameters will be summarized in this section.

i) Cone Photoreceptor

Cone photoreceptor biophysical model is adapted from the work of Koruennyi et al. [20]. However, the model had to be modified to obtain a response comparable to validation metrics for the considered photocurrent waveform (as described in Section II.A). The conductance and reversal potential values we have used for these channels are shown in Table 1. The compartment dimension has an important role in tuning the cell's membrane potential response. Because we treat the photoreceptors as point-sources (single compartment), there is flexibility in adjusting the compartment size to achieve a response close to experimental observation. After tuning, the cone compartment is set to be 4 μm in diameter and 2 μm in length for the optimal membrane potential response, similar to experimental recordings.

ii) Cone Bipolar Cell

Cone bipolar cells receive inputs from cone photoreceptors and form the principal visual pathway by making direct synaptic connections to the ganglion cells. There are two major types of cone bipolar cells, known as depolarizing (ON-type) or hyperpolarizing (OFF-type), as well as sub-types of which nine have been identified in rat [22]. We have adapted a generalized model for the non-spiking depolarizing ON-BC, which has the biophysical properties as outlined in work of Publio et al. [3]. Its biophysical parameters are summarized in Table 1. Tuning is done to obtain a membrane potential response close to experimental observations.

TABLE I. BIOPHYSICAL MODEL PARAMETERS

Cone Photoreceptor	ON Cone Bipolar Cell
I_{pas} [E= -40, g= 0.0005]	I_{pas} [E= -40, g= 0.02]
I_{Ca} [E= 40, g= 4.92]	I_{Ca} [E= -66, g = 0.0015]
I_{KCa} [E= -70, g= 0.1]	I_{KCa} [E=-66, g= 0.0014]
I_{Kv} [E= -60, g= 0.000318]	I_{Kv} [E = -58, g= 9]
I_h [E= -40, g= 60]	I_h [E= -17.7, g= 0.0311]
I_{Cl} [E= -45, g= 9.5]	
Compartment: diameter = 4 µm, length = 2 µm	**Compartment:** diameter = 8 µm, length = 8 µm

a. Reversal potential E is in mV and conductance g is in mho/cm^2.

C. Synaptic Model

Cone photoreceptor synapses are driven by their rate of glutamate release and modeled as a graded response, which is sensitive enough to detect a wide range of light intensity levels. We use the graded synapse model for rod – rod bipolar cells presented in [3] as a basis for defining the synapses between cone photoreceptors and ON-BCs. A major difference between the rod and cone pathways is that rod bipolar cells (RBC) can have synaptic connections with over 30 rod photoreceptors while the number of cones per ON-BC is much lower. According to the available literature on the convergence ratio of cones to ON-BCs, the average number of cones per bipolar cell is 10, albeit it can be as low as 7 depending on the species. Our previous computational work on the rod pathway [23] has an optimized synaptic model capturing the rod convergence pattern and here we apply a similar approach for cone convergence. The strength of cone-to-cone bipolar cell synapses is tuned to get a realistic membrane potential change on the bipolar cells that matched well with experimental recordings. The conductance of this synapse is set to be g = 0.756 mho/cm^2 for our model, which is about three times larger than the conductance used for rod synapses.

III. Simulation Results

A. Verification of the model with Experiments

We use the NEURON simulation environment [24] to apply a current clamp to the photoreceptors and compute the membrane potential of the cells at each time step. Fig. 1 shows the simulated photocurrent and resulting cell membrane potentials in cones and ON-BC. In each case, the simulation result (red) is plotted with corresponding experimental results (dashed) from different works. The curves representing the results from recordings are extracted using an online digitizer tool into .csv file format and then plotted together with the simulation curves for clear comparison. All three plots of Fig. 1 share the same time scale in milliseconds. Fig. 1(a) compares the simulated cone photocurrent model, Fig. 1(b) compares the simulated cone membrane potential and Fig. 1(c) compares the simulated ON-BC membrane potential with experimental whole-cell recordings. We only considered the experimental recordings which include stimulation protocol of a flash of light (< 50 ms) at saturation intensity and use whole-cell patch-clamp as method of recording. ERG recordings were not considered because they measure local field potentials across the eye and are not precise enough to use for validating a single cell model's accuracy. The cone membrane potential is validated using recordings from two separate turtle samples [19, 25, 26] and the ON-BC is validated using one sample from rabbit [27] and two separate samples from mouse [28, 29].

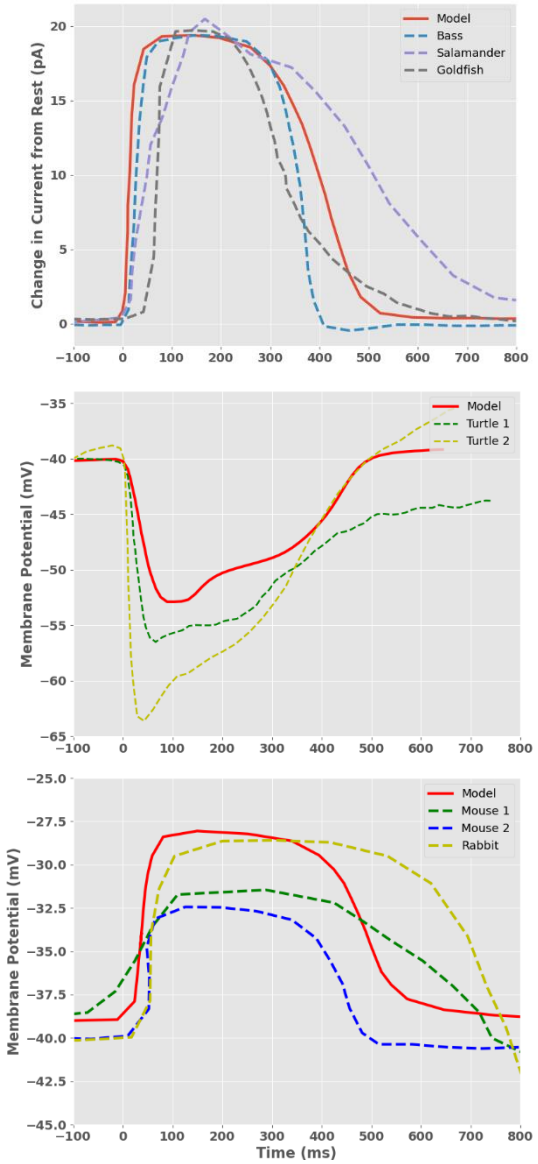

Figure 1. (a) The photocurrent generated by cones from a flash of light at saturation intensity, plotted with bass [11], salamander [12] and goldfish [13] recordings. (b) Cone hyperpolarization response following the light flash plotted with turtle 1 [19] and turtle 2 [24] recordings. (c) ON-BC depolarization following the light flash, plotted with rabbit [26], mouse 1 [27] and mouse 2 [28] recordings. The ON-BC response reflects a contribution of 12 cone inputs.

B. Comparison with the Rod Response

Previously, we developed a computational model of signal flow from rod photoreceptors to rod bipolar cells to compare the differences in rod bipolar cells of healthy and early-stage degenerated retinas [23]. We refer to this rod pathway model to examine the differences in cone and rod pathways. The simulated responses of cone and rod pathway models can be visualized in Fig. 2. The plots of photocurrents, photoreceptor membrane potentials, and post-synaptic bipolar cell membrane potentials are presented in Fig. 2(a), (b) and (c), respectively. The main difference between two photocurrents is the pulse duration, which is 0.5 seconds for cones and 7 seconds for rods. Even after a flash input, the rods stay active for longer and the repolarization to resting state takes several seconds. The saturation amplitude for cones is lower than rods, which is around 20 pA compared to 30 pA. The convergence patterns are different as well, where RBCs have 30 rod inputs ON-BCs have 10 cones inputs. How this difference influences the output from ganglion cells can be investigated in future studies with more complex networks. Becuase ON-BCs have direct synaptic connections with ganglion cells and RBC signals piggyback on the ON-BCs using AII amacrine cells [30], the contribution from both pathways to ganglion cell output will be a topic of interest in computational studies for understanding visual signaling.

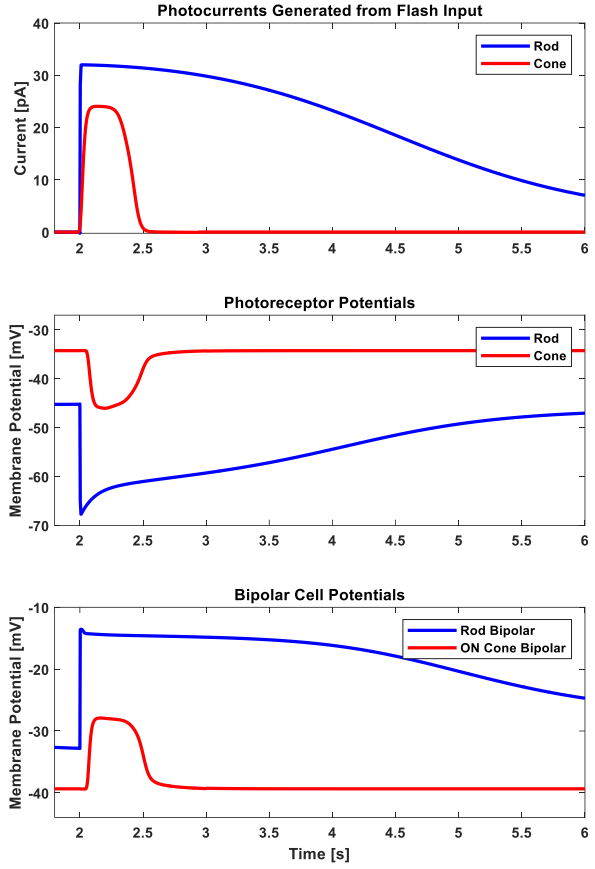

Figure 2. (a) The photocurrent from both rods and cone in response to a saturating light flash and the resulting change in their membrane potentials. (b) Change in membrane potential of rods and cones for a saturating light flash input. (c) Change in membrane potential of two bipolar cells for a saturating light flash input. Onset of stimulation is at the 2-second mark.

C. Challenges

While the recording protocols were selected to make validation comparisons as consistent as possible across experiments, the fact that different species from different studies were used adds a significant degree of variability to cell responses. It was observed that the pulse width of mouse, rabbit and non-human primate cone photocurrents was much narrower (~ 200 ms) [31] compared to the aquatic species that are presented here (Fig. 1(a)). The ideal case would be to have photocurrent, cone potential and ON-BC potential recorded simultaneously on the same slice or species. However, experiments focus either on cones or ON-BC when taking recordings and cross-validation has to be done. We note that while the peak cone photocurrent amplitude reaches saturation after a limit, the duration of activation is strongly dependent on light intensity and will continue to increase proportionally [27, 28]. Different classes of ON-BCs also have a range of responses, such as spiking vs. non-spiking [32] and monophasic vs. biphasic (hyperpolarizing tail at the end of repolarization) [27]. These factors should be accounted for when aiming to build a complex model of the retina with multiple cell-types.

IV. Discussion and Conclusion

In this work, we have used cone pathway recordings from the literature to tune existing light input protocols and present a realistic computational model to capture the natural photopic response of cones and ON-type cone bipolar cells. This was achieved by defining the photocurrent waveform as a time-varying mathematical function, which is independent from other biophysical parameters, and tuning it to match the actual cell responses recorded under a light stimulation protocol. The advantage of this approach is the flexibility in changing the waveform's properties as the situation dictates. For example, the equations can easily be tuned to match the photocurrent waveform generated by cones in human retina. This way, the photocurrent model can easily be translated to different species. However, the major limitation of this approach is the necessity to record the photoreceptors and post-synaptic bipolar cells under the same input protocol for validation. Because there is high variability between the cell responses of different species, translation of the model should be accompanied by whole-cell recordings of the target cells to create a realistic and reliable network model of that retina. Once the network response is validated for a given species, an adaptable light input-to-photocurrent conversion protocol could help improve the model efficiency by eliminating the need for manually changing equations for scotopic, mesopic or photopic vision simulation.

While there is still scope to improve the methods for phototransduction modeling, the present study offers a computational model that replicates the response of the retinal cone pathway under light-evoked stimulation. The strength of this approach lays in the multi-level validation of cell responses using the convergence pattern observed in a typical cone pathway. Using separate rod and cone pathway models of light-evoked responses as presented here can facilitate the

development of more complex and realistic retinal neural networks, which can have applications in visual signal processing, degeneration modeling and predictive simulations for electrical stimulation therapies.

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