A MATHEMATICAL MODEL OF THE MOUSE RETINA

Modeling the relative contribution of the rod and cone pathways to the retina output

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How the retina works?

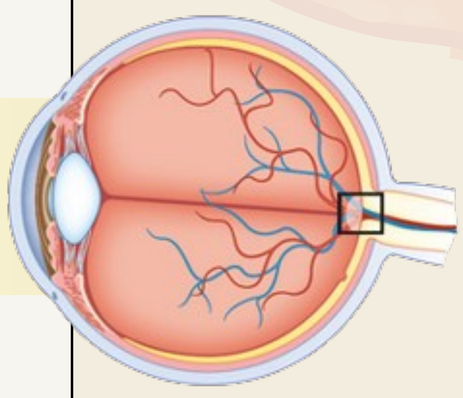
A window to the brain

The retina is a **sensory organ**, located at the rear of the eye, and **connected to the brain** through the optic nerve[1,2] .

Due to its location, the retina is **more accessible** than other brain regions. So, studying the retina not only improves our understanding of vision but also offers **insights into how other parts of the brain work**[1].

When light hits the retina, it activates photoreceptors (rods and cones), initiating an electrical signal that passes through other retinal cells before reaching the optic nerve and onward to the brain. Signals originating from photoreceptors can take **different pathways to reach the output of the retina**, the retinal ganglion cells (RGCs)[1,2].

Here, we present a mathematical model of the retinal network, designed to **better understand the relative weighting of rod- and cone-derived signals and their routing in retinal circuits** under different lightning conditions, that remain largely unknown[2].



Summary

Designing a portion of mouse retina

More than 35,000 neurons simulated with a realistic spatial topology and connectivity.

Comparing with experimental data

Our model closely replicates the essential quantitative and qualitative features of the retinal cell and network dynamics observed in experimental setting[2,9,10].

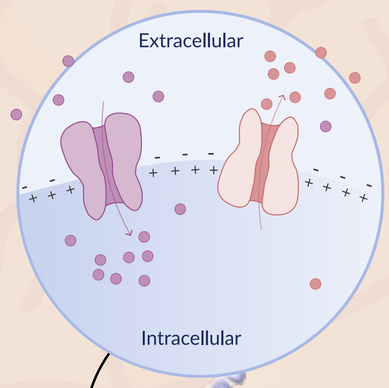
Further in silico hypothesis testing

The electrical activity of the retina is impaired in patients with either retinal pathology (e.g. retina pigmentosis or AMD) or neuropsychiatric disorders[11].

1. MODEL DESIGN

We develop a detailed mathematical model of the mouse retinal circuitry:
- based on morphological and biophysical data mined in the literature[1,2,3,4].
- including realistic representations of the different rod and cone pathways[2].

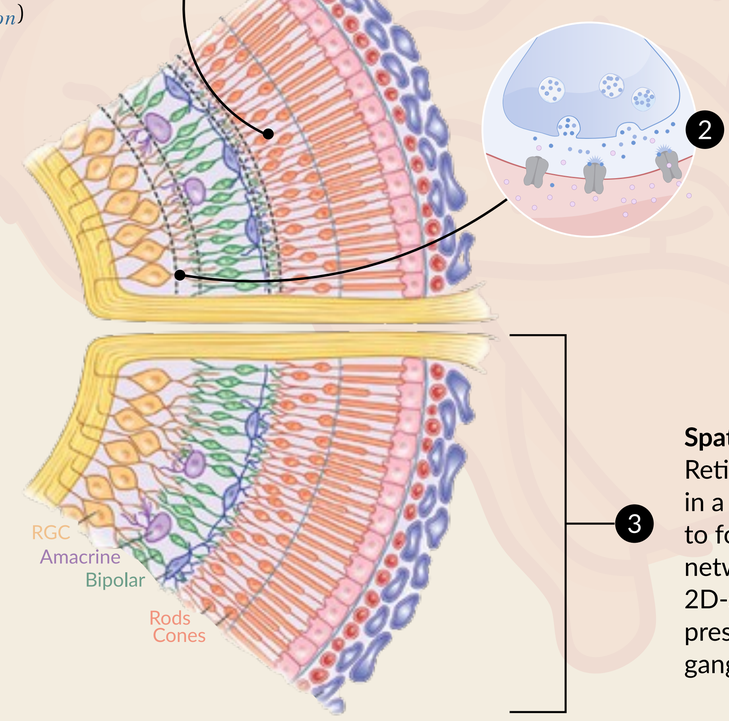
To build our model we adopt a **bottom-up approach**.



Ion channels

The electrical behavior of neurons depends on ion channels. There are approximately 5 to 6 different types of ion channels per retinal cell. The flow of ions through their channels is represented in our model by a general equation of the form:

$$I_{ion} = g_{ion} \cdot m_{ion} \cdot h_{ion} \cdot (V - E_{ion})$$



- constant parameter
- variable parameter

1 **Retinal cell models.**
There are 5 classes of retinal neurons: rod, cone, bipolar (BC), amacrine (AII), and retinal ganglion cells (RGCs). Each retinal cell class is implemented in our model using conductance-based models that follow the Hodgkin-Huxley formalism[5]. The dynamics of the membrane potential *V* is described by a general equation of the form[5,6]:

$$C\frac{\mathrm{d}V}{\mathrm{d}t} = -\sum_{ion} I_{ion} + I$$

2 **Synapse models.**
Many aspects of physiological neurotransmission are included into our model, such as synaptic convergence and divergence[3], synapse strength, etc.
The two main types of retinal synapses (chemical and electrical) are implemented in our model by the following equations[6,7]:

$$I_{chem} = g_{syn} \cdot s \cdot (V - E_{syn})$$
$$I_{gap} = g_{syn} \cdot (V_{post} - V_{pre})$$

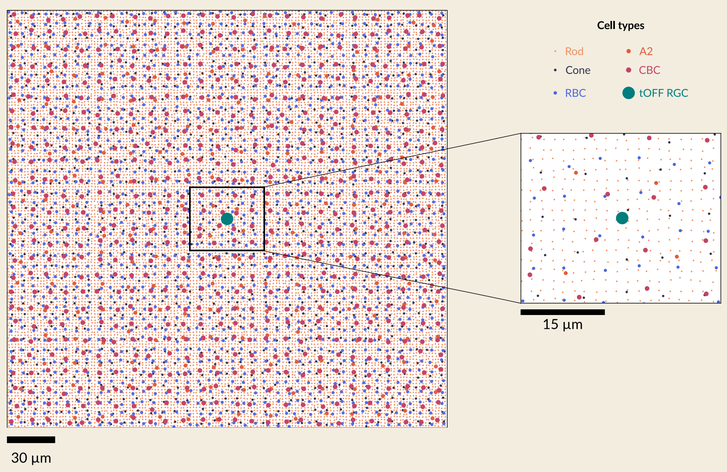
3 **Spatial topology and connectivity.**
Retina is composed of layers of neurons arranged in a specific spatial topology and interconnected to form a complex circuit[1,2,3]. In our retina network model, neurons are distributed within 2D-square grids. The network contains all presynaptic cells connected to a single retinal ganglion cell (RGC).

2. MODEL SIMULATION

Generation of the retinal network

The retina network model includes 38,416 rods, 1,225 cones, 1,600 RBCs, 650 OFF-CBCs, and 256 AII amacrine cells[3], distributed in a square-grid spanning 70,685 µm² (a small area of the retina), close to the dendritic field area of a single RGC[4].

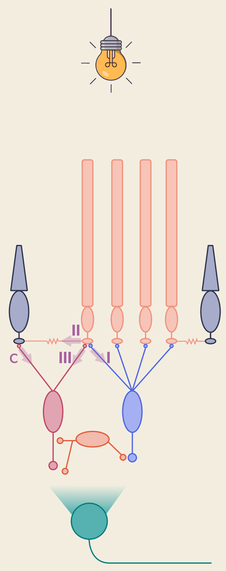
Cell mosaic distribution



The complexity of the model is tied to the intricate connectivity within the retina, where three distinct pathways emanate from the rods (I, II, and III), alongside another pathway stemming from the cones (C), collectively forming parallel signaling pathways each with unique sensitivity to light.

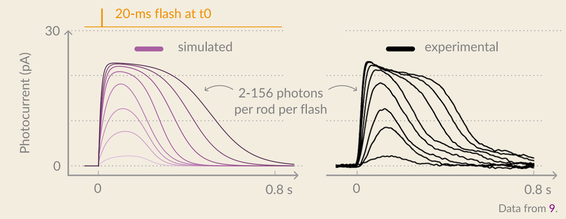
Light-responses of the retinal cells

Simulations are conducted using the simulation environment *Brian2*[8], using the exponential Euler integration method with a timestep of 0.1 ms. Running simulations of 35,000+ neurons (~30 equations per neuron model) and their connections for a duration of 4s requires approximately 3m 50s.

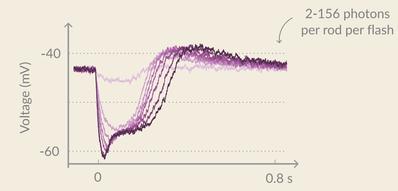


- I primary rod pathway
- II secondary rod pathway
- III tertiary rod pathway
- C cone pathway

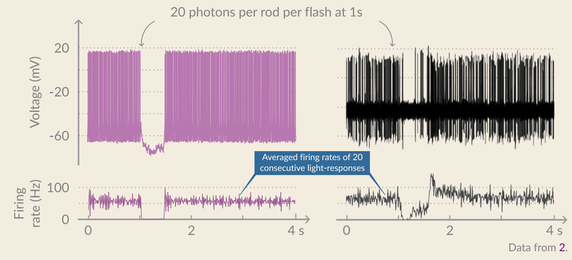
Rod photocurrent. A flash of light generates an inward current in rod photoreceptors, the amplitude and kinetics of which depend on the intensity of the light stimulus.



Rod photovoltage. The photocurrent entering the rod photoreceptor induces hyperpolarization of the cell membrane.



RGC light-response. Rod-driven signals then spread through synapses and ultimately contribute to the retinal output, characterized by its firing rate.



NEXT STEPS

Our findings affirm the validity of our model, and its suitability for further in silico hypothesis testing. We are currently examining the **effects of light and circadian adaptive mechanisms on signal processing** within retinal circuits and their implications for RGC light responses. This model holds promise for **deepening our understanding of visual (patho)physiology**.

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PUBLICATIONS

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