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# A mathematical model to study the relative contributions and plasticity of the rod and cone pathways to the mouse retinal output

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## Background

In the mouse retina, rod and cone photoreceptors capture light and convert it into electrical signals. These signals can reach the retinal ganglion cells (RGCs) through different pathways with distinct sensitivities: three rod pathways and the cone pathway (figure 1). These pathways combine together to ensure continuous signaling throughout the entire operating range of the retina. Recent findings have provided insights into the relative contributions of these different pathways to the light responses of a particular type of RGC: the **transient OFF alpha RGC (tOFF αRGC)** [1]. However, the precise way these pathways merge to control the retinal output under varying lighting conditions, as well as the influence of the circadian adaptive mechanisms remains largely unknown.

## Purpose

This study aims to build a comprehensive mathematical model of the retinal circuitry integrating realistic representations of the three rod pathways. This model serves as a powerful tool for studying the relative weighting of rod- and cone-derived signals and their routing within retinal circuits under varying lighting conditions.

## Methodology

Each retinal cell class is modeled using conductance-based models (CBMs) following Hodgkin-Huxley formalism [2], whose parameters are based on morphologic and biophysical data mined in the literature [3,4,5]. In CBMs, the dynamics of the membrane potential  $V$  is described by a general equation in the form:

$$C \frac{dV}{dt} = - \sum_{ion} I_{ion} + I_{inputs}$$

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

**Photocurrent** [6] (photoreceptors only):

$$I_{photo} = A \cdot \left( 1 - \exp^{-t/\tau_{b1}} - \frac{1}{1 + \exp^{-(t+b)/\tau_{b2}}} \right) + y$$

$$\frac{dy}{dt} = -\frac{y}{\tau} + \sqrt{\frac{2 \cdot \sigma^2}{\tau}} \cdot \xi(t)$$

stochastic term (includes both intrinsic and recording noise)

**Interactions** [7, 8]

• **Chemical synapse model**

$$I_{chem} = g_{chem} \cdot s_{chem} \cdot (V - E_{chem})$$

$$s_{chem} = 0.5 \cdot \left( \tanh\left(\frac{V_{pre} - V_{1/2}}{k}\right) + 1 \right)$$

• **Gap junction model**

$$I_{gap} = g_{gap} \cdot (V_{pre} - V_{post})$$

The model includes 38,416 rods, 1,225 cones, 1,600 RBCs, 650 OFF-CBCs and 256 AIIIs, distributed in a circular-grid with a diameter of 300 μm, mirroring the dendritic field diameter of a single tOFF αRGC [5]. The number of cells in each class is determined based on cell densities and synaptic convergence and divergence ratio. The connections between these different retinal cell classes are established according to biological data on retinal circuitry [3,4].

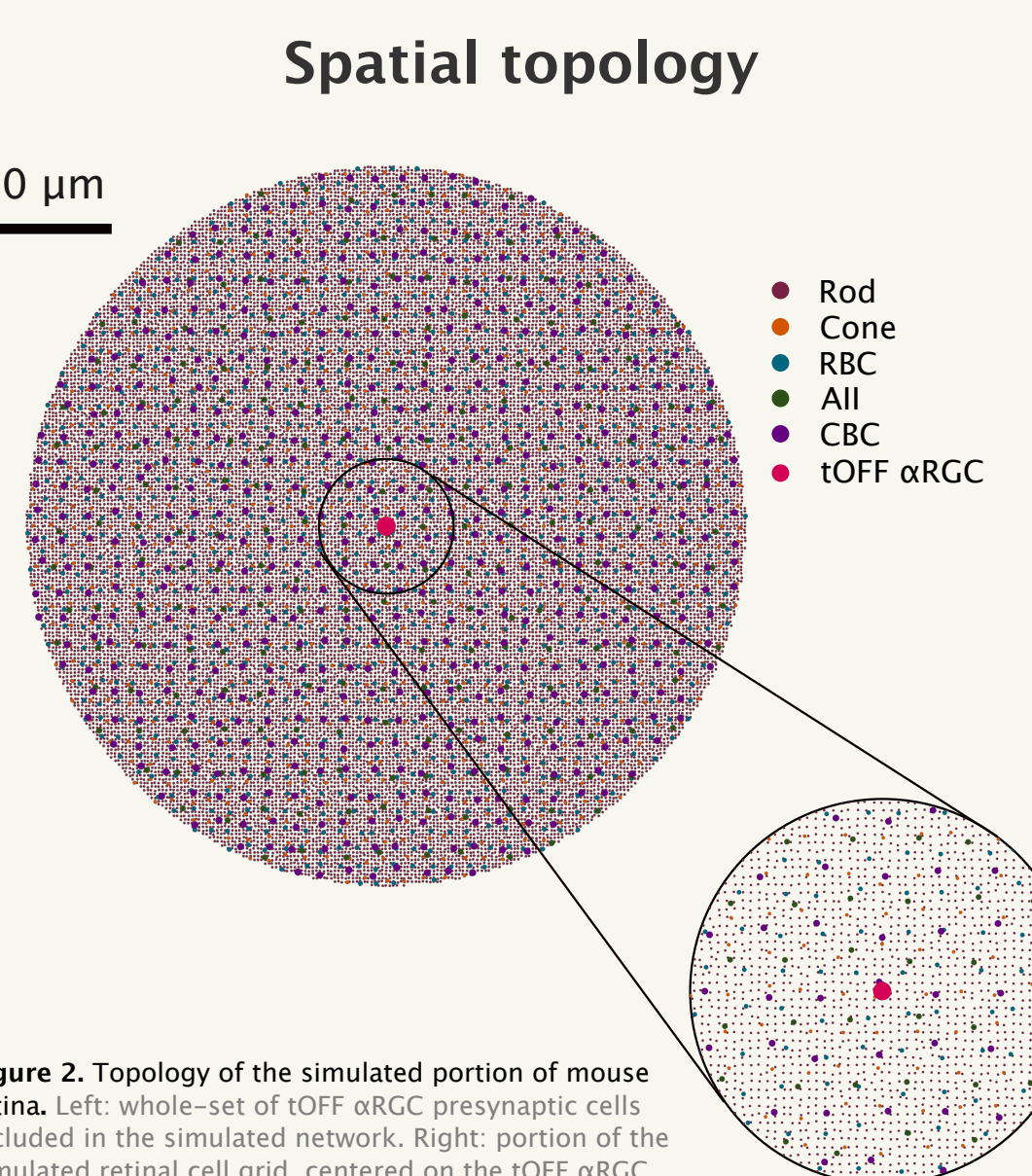


Figure 2. Topology of the simulated portion of mouse retina. Left: whole-set of tOFF αRGC presynaptic cells included in the simulated network. Right: portion of the simulated retinal cell grid, centered on the tOFF αRGC.

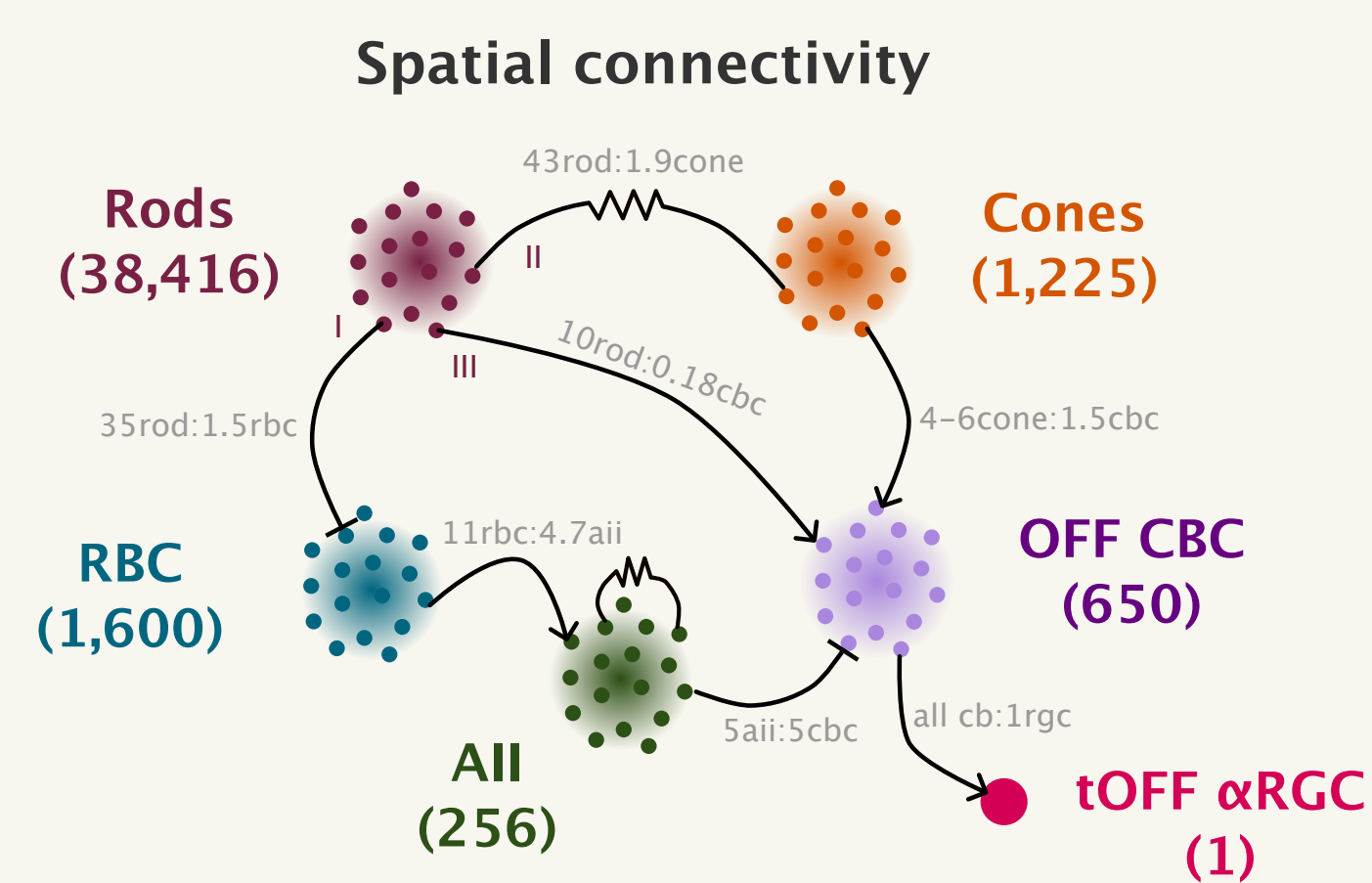


Figure 3. Diagram of the simulated primary, secondary and tertiary rod pathways to a single tOFF αRGC. The number below each cell name denotes the number of cells in the class. X Npre : X Npost denotes the convergence:divergence ratio between the pre- and post-synaptic groups.

## Results

### Light responses of the retinal rods

Exposure to a background of light triggers an inward current within isolated rod photoreceptors. The magnitude and kinetics of this current depend on both the duration and the intensity of the light stimulus. Rod photoreceptors are able to signal a wide spectrum of light intensities, ranging from single-photon absorption events to the absorption of hundreds of photons.

**Rod photocurrent.** We reproduce the experimental settings described in [1]. In particular, a 500-ms background of light stimulus was presented at different intensities. The experimental recordings exhibit noise — replicated in simulations — originating from various sources [9].

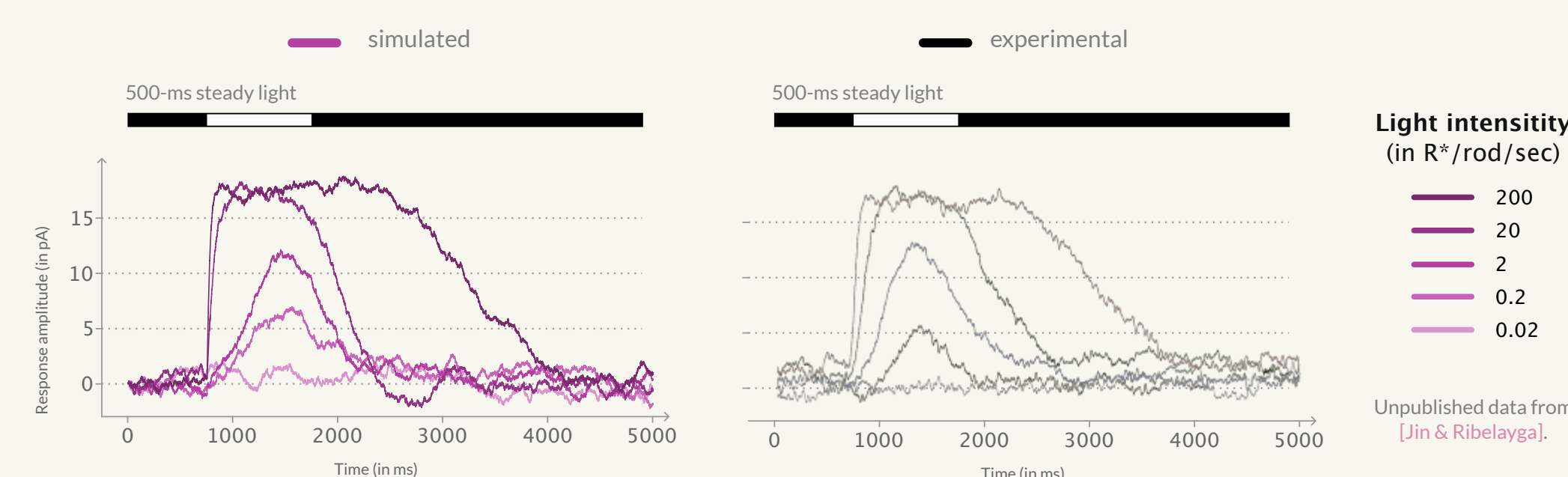


Figure 4. Rod simulated (left) and experimental (right) photocurrent triggered by isolated rods (no rod/cone coupling) by a 500-ms background light stimulus exposure, at 0.02, 0.2, 2, 20 and 200 effective isomerizations per rod per second (R\*/rod/sec).

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

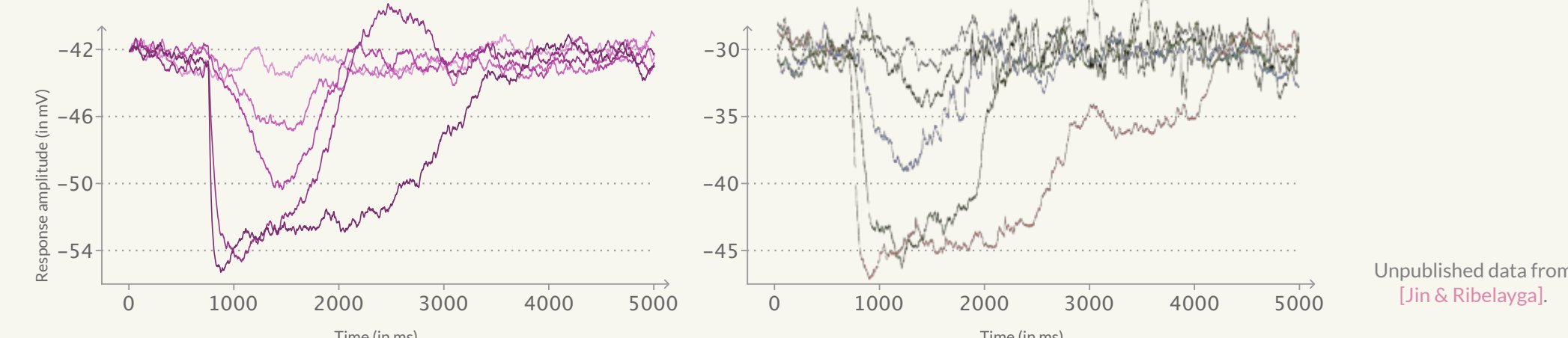


Figure 5. Rod simulated (left) and experimental (right) photovoltage without rod/cone coupling.

### Simulations

Simulations are performed using Brian2 python package neuron simulator [10], with exponential Euler integration method (timestep of 0.1 ms). Running simulations of 35,000+ neurons and their connections (~30 equations per neuron) for a duration of 4s requires approximately 8m50s.

## Discussion

- Our mathematical model accurately depicts the spatial topology and connectivity of rod pathways within the mouse retina, providing a realistic framework for understanding retinal circuitry.
- Our model closely replicates the essential quantitative and qualitative features of the tOFF αRGC dynamics observed in the experimental settings [1].

These results validate our model and its suitability for further in silico hypothesis testing.

### Perspectives

Currently, our focus lies on investigating the impact of light and circadian adaptive mechanisms on signal processing within retinal circuits, particularly their influence on tOFF αRGC light responses [6,11]. Our model holds promise for advancing our comprehension of visual processing (patho)physiology. Its potential extends to biomedical applications, such as quantifying the effects of blinding diseases on retinal function and evaluating the efficacy of novel treatments.

### Thresholds of the rod-driven pathways

Rod signaling at the retinal output extends beyond the operating range of single rods to cover more than 6 log units in intensity, due to the high convergence of rod to intermediate retinal cells. Rod-driven signals contribute to the retinal output via three different rod pathways, including different intermediate retinal cell populations:

- The primary rod pathway: rods > RBCs > AIIIs > (ON or OFF) CBCs > (ON or OFF) RGCs
- The secondary rod pathway: rods > cones > (ON or OFF) CBCs > (ON or OFF) RGCs
- The tertiary rod pathway: rods > OFF CBCs > OFF RGCs

**tOFF αRGC light-responses.** Here, we present examples of tOFF αRGC light responses at three distinct intensities: 0.06, 2, and 20 R\*/rod/second. By eliminating one pathway at a time, we delineate the relative contributions of the three rod pathways to the tOFF αRGC light responses. Comparing our simulations with experimental recordings [1], we demonstrate the model's ability to accurately predict, at the retinal output level, the sensitivity and operational range of each rod pathway — their activation and saturation thresholds (defined as 5% and 95% of maximal response, respectively).

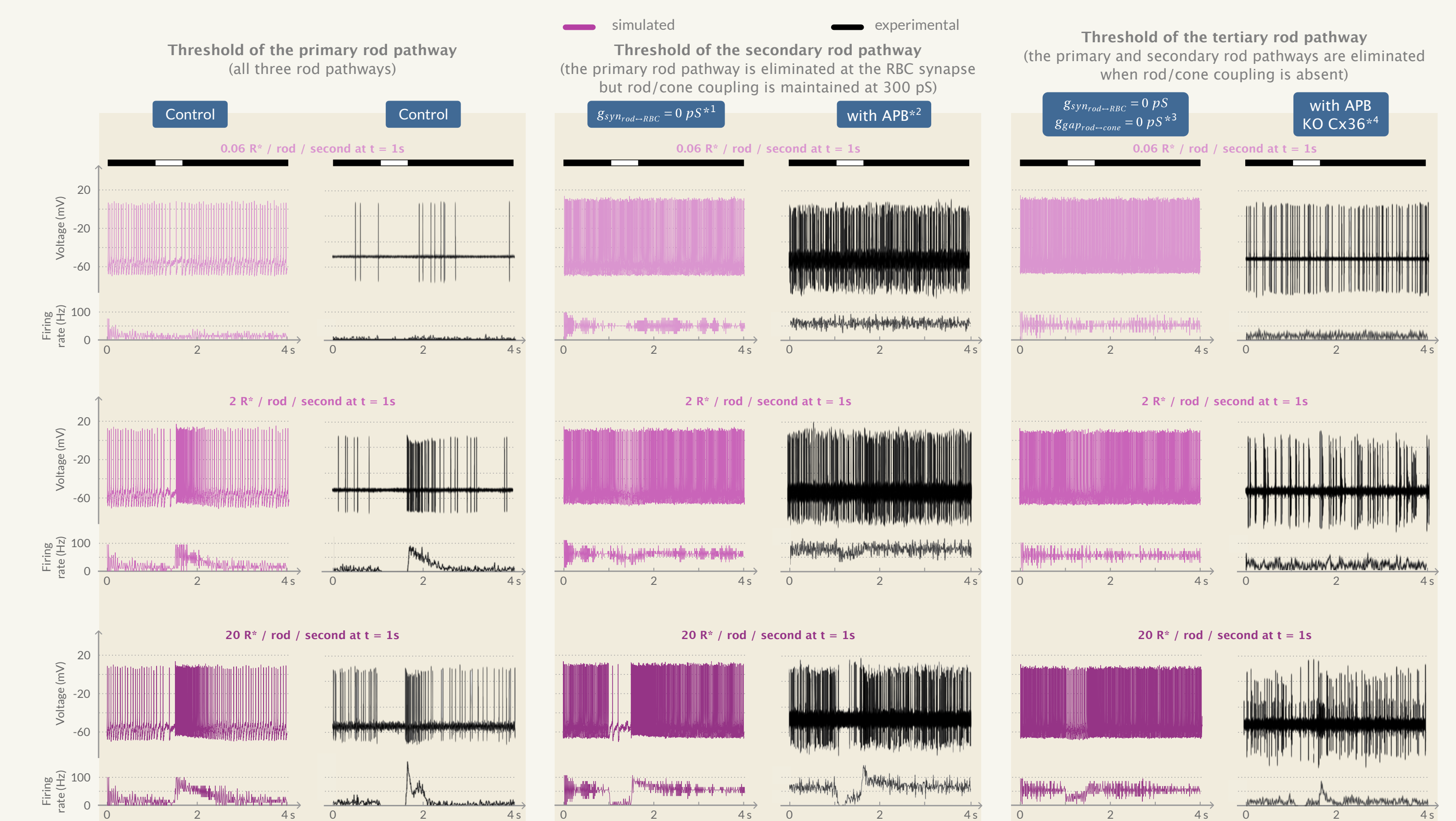


Figure 6. Contribution of the rod pathways to the retinal output. Top: Simulated (left) and experimental (right) tOFF αRGC responses to three different 500-ms background light intensities (0.06, 2, and 20 R\*/rod/sec) under three conditions (all three rod pathways, primary rod pathway eliminated, primary and secondary rod pathways eliminated). Bottom: Mean firing rates calculated from 10 different simulations (left) and 25 consecutive recordings (right) under the three conditions. \*1 rod to RBC synaptic conductance; \*2 L(+)-2-amino-4-phosphonobutyric acid; \*3 rod/cone transjunctional conductance; \*4 rod- or cone- Connexin36 knockout. Experimental data adapted from [1].

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