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Numerical simulation of neuronal spike patterns in a retinal network model*★

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Abstract

This study utilized a neuronal compartment model and NEURON software to study the effects of external light stimulation on retinal photoreceptors and spike patterns of neurons in a retinal network. Following light stimulation of different shapes and sizes, changes in the spike features of ganglion cells indicated that different shapes of light stimulation elicited different retinal responses. By manipulating the shape of light stimulation, we investigated the effects of the large number of electrical synapses existing between retinal neurons. Model simulation and analysis suggested that interplexiform cells play an important role in visual signal information processing in the retina, and the findings indicated that our constructed retinal network model was reliable and feasible. In addition, the simulation results demonstrated that ganglion cells exhibited a variety of spike patterns under different light stimulation sizes and different stimulation shapes, which reflect the functions of the retina in signal transmission and processing.

Key Words: computational network model; retina; light stimulation; ganglion cell; spike pattern

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INTRODUCTION

The visual system is the most important signal-receiving pathway in many animals, and the retina constitutes its first functional structure. The retina is composed of three layers of cells (photoreceptors, bipolar cells and ganglion cells), which form vertical pathways, while another two layers of cells (horizontal cells and amacrine cells) form horizontal pathways. Therefore, the retina can be represented as a three-dimensional model with multiple layers, which is responsible for initial processing of visual information and transmitting signals to the second visual processing center (the lateral geniculate nucleus) in the form of action potential sequences[1].

Neural circuits in the retina are relatively complex, and their synaptic connections are mainly distributed in two layers: the inner plexiform layer and the outer plexiform layer. Receptors in the outer plexiform layer, including rods and cones, can connect to several types of bipolar cells through chemical synapses. In addition, these receptors can form chemical synapses with horizontal cells, and gap junctions exist between rods and cones[2]. In the inner plexiform layer, bipolar cells can form chemical synapses with ganglion cells and amacrine cells, and amacrine cells can connect with bipolar cells through negative feedback chemical synapses. Moreover, bipolar cells can also connect with ganglion cells via chemical synapses. The bipolar cells act as a bridge between the outer and the inner plexiform layers in the retinal network, while ganglion cells are the final level cells that process light information[1, 3]. Apart from amacrine cells, ganglion cells are the only neurons in the retinal network that can generate action potentials. That is, only ganglion cells can transmit light signals to visual center in the form of action potential sequences[4].

Relatively few studies have examined interplexiform cells, and their function is currently unclear[5-10]. The perikarya of the interplexiform cells are located in the inner nuclear layer, along with the amacrine cell somata, but unlike the amacrine cells their processes extend to both plexiform layers. Dowling and Ehinger[11] have described the synaptic connections of these cells in goldfish and the *Cebus* monkey retina. Electron microscopy studies have revealed that the processes of the inner plexiform layer cells are both pre- and post-synaptic to amacrine cells[1, 4]. In contrast, the outer plexiform layer processes are presynaptic only, making contact with both horizontal and bipolar cells. These results suggest that interplexiform cells could provide a centrifugal pathway within the retina, and could exert control over the centripetal flow of information.

A large number of theoretical studies have been conducted to investigate the visual system at the cellular level, examining the structure and function of the retina and its neurons, including. Various studies have investigated receptors[12-13], bipolar cells[14-18], and amacrine cells[19-21]. In addition, some studies have established a role for ganglion cells in the conduction of light information through the ON/OFF pathway[22-28], and its effects through mathematical models of the structure and function of the entire retinal network[3, 29-30]. The present study used a compartment model to characterize individual neurons, and included synaptic connections between neurons to construct a three-dimensional network model of the retina and investigate the network response under different light stimulation patterns, focusing on the pattern of neuronal spiking. In addition, we analyzed the role of interplexiform cells in visual signal processing in our retinal network model.

RESULTS

Photoreceptor and light stimulation

The current network model involved two types of photoreceptors: rod cells and cone cells. Rod cells were used as examples to analyze variations in photoreceptor membrane potential when exposed to light of different intensities, and demonstrate the changing characteristics of photoreceptors. We expressed light current as previously described[26]:

$$I = I_{dark} + A[(1-e^{-t/\tau_1}) - (\frac{1}{1+e^{-(t-b)/\tau_2}}) + (1-e^{-t/\tau_3})$$

I_{dark} denotes dark current (−2.0 nA). τ_1 = 30 ms, τ_2 = 40 ms, τ_3 = 10 ms, b = 500 ms are constants, A denotes the amplitude of light current. Figure 1 shows the variation of rod cells' membrane potential against different values of *A*, and the sensitivity of photoreceptors under various conditions of light stimulation.

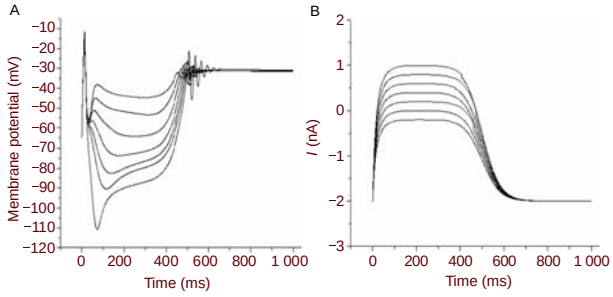

Figure 1 Light stimulation and response. *I*: Llight current stimulation; time: time of stimulation.
(A) Diagram of membrane potential of rod cells for light stimulation of different amplitudes; from top to bottom, the values of the light stimulation amplitude are 0.9, 1.0, 1.1, 1.2, 1.3, 1.4 and 1.5 nA.
(B) The variation of light current for different stimulation amplitudes; from bottom to top, the values of light stimulation amplitude are 0.9, 1.0, 1.1, 1.2, 1.3, 1.4 and 1.5 nA.

Three different pathways for light signal transmission

As shown in Figure 2, the final light information processing results were different among the three different pathways for light signal transmission, indicating variation in ganglion cell membrane potential spikes. These differences are consistent with the complexity of retinal information processing. For this reason, we constructed a comprehensive retinal network model by incorporating these three different pathways to investigate light information processing in the retina.

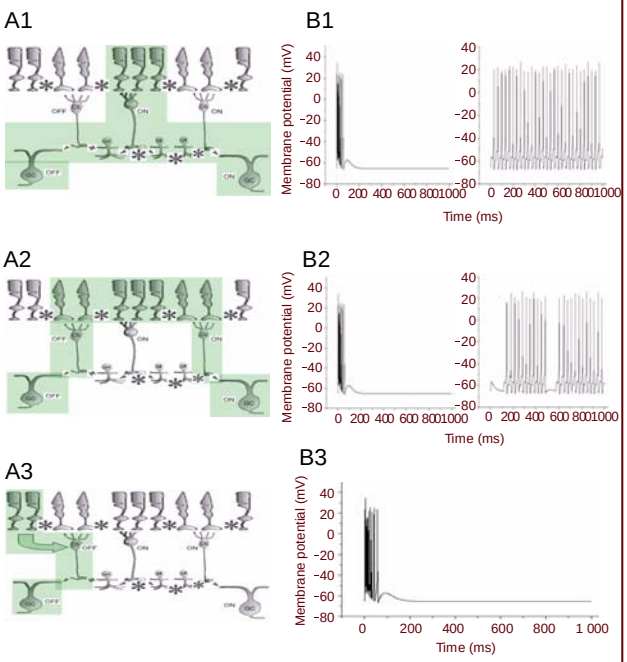

Figure 2 Multiple rod pathways in the retina (modified from [25]). (A1)In the primary rod pathway, the rod-mediated signals are transmitted to rod bipolar cells and subsequently to A II amacrine cells. A II amacrine cells make sign-conserving electrical synapses with ON cone bipolar cell axon terminals, as well as sign-inverting chemical synapses with OFF cone bipolar cell axon terminals in the inner plexiform layer. In turn, the ON and OFF cone bipolar cells transmit the rod signals to ON and OFF ganglion cells, respectively. In all panels, the asterisks indicate electrical synapses, arrowheads indicate chemical synapses, and shaded areas mark the elements of the particular rod pathway. CB: Cone bipolar cell; RB: rod bipolar cell; A II: A II amacrine cells; GC: ganglion cell. (A2) In the secondary rod pathway, the rod-mediated signals move directly from rod to cone photoreceptors *via* interconnecting gap junctions. The rod signals are then relayed to ON and OFF cone bipolar cells, which carry the signals to ganglion cells in the inner retina. (A3) A tertiary rod pathway provides an additional route for rod-mediated signals to reach OFF ganglion cells. In this pathway, the rod photoreceptors make direct, sign-conserving chemical synapses with a type of OFF cone bipolar cell, which, in turn, transmits rod signals to OFF ganglion cells. The large arrow indicates the direct chemical contact between rod cells and OFF bipolar cells. B1, B2 and B3 are the quantitative results corresponding to A1, A2 and A3. Membrane potential maps of OFF ganglion cells are shown on the left, while those of ON ganglion cells are shown on the right. Light stimulus intensity (amplitude of light current) = 1.5 nA.

Membrane potential maps of retinal cells

There were six kinds of cells in the network model, including rod cells, cone cells, rod bipolar cells, cone bipolar cells, amacrine cells and ganglion cells. Both rod and cone cells received light stimulation, and the membrane potential maps of these cells were obtained using NEURON software (Figure 3). The results revealed substantial diversity in the spike patterns of different retinal cells, such that different kinds of cells produced different firing patterns for a given stimulus. All of these patterns reflected the sensitivity of the retinal network under external light stimulation.

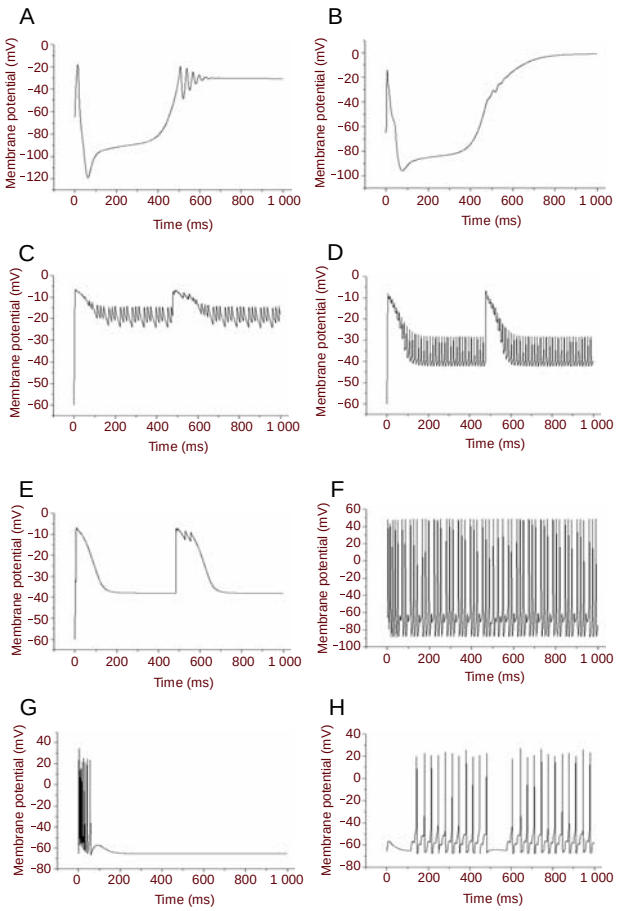

Figure 3 Membrane potential maps of different cells. (A) Rod cell; (B) cone cell; (C) OFF cone bipolar cell; (D) ON cone bipolar cell; (E) rod bipolar cell; (F) A II amacrine cells; (G) OFF ganglion cell; (H) ON ganglion cell. Stimulus intensity (amplitude of light current) = 1.5 nA.

Retinal network activities under different light stimulation ranges

As the first information processing station of the visual system, the retina plays a vital role in visual information transmission and processing. To analyze variation among retinal cells, we constructed a model network involving 100 photoreceptors, composed of 60 rod cells and 40 cone cells (Figure 4). We examined the importance of the retinal ganglion cells, focusing on the activities of the ganglion cells that represent the output of the whole retinal network.

The diagrams shown in B1–3 and C1–3 in Figure 4 clearly show that light stimuli of different ranges were able to elicit a variety of firing patterns in ganglion cells, which can also be demonstrated from changes in the membrane potential sequences in different colors. These results demonstrated substantial diversity in the activity of ganglion cells when they were presented with light stimuli of different ranges.

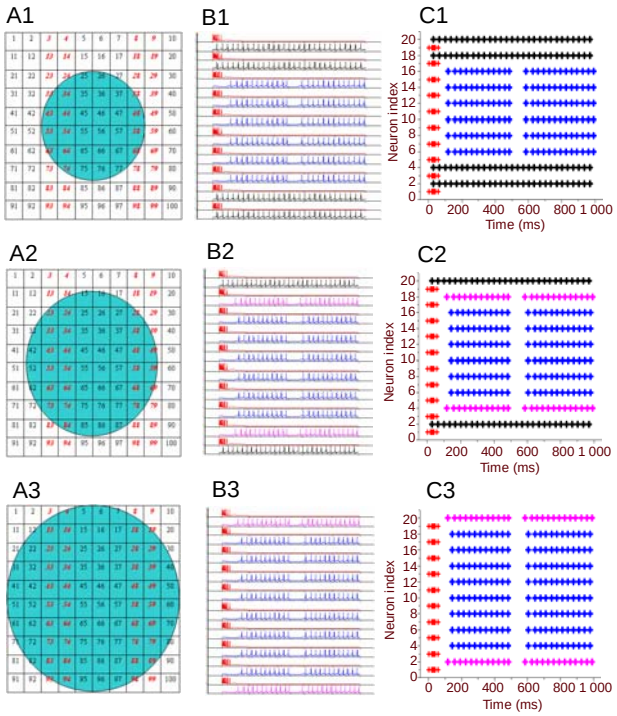

Figure 4 Spike patterns of ganglion cells under different sizes of light stimulation. A1–3: Light stimulus from different ranges (100 numbers represent 100 photoreceptors, including 60 rod cells and 40 cone cells, in which black numbers denote rod cells, red numbers denote cone cells, and the shaded part of the circle denotes the stimulation range. Cells located in the shaded part of the circle would receive light stimulation, while other cells would not receive any stimulation). B1–3: Membrane potential maps of the 20 ganglion cells corresponding to A1–3 (purple, blue and black curves represent three firing patterns). C1–3: Diagrams of ganglion cells' activities corresponding to A1–3. X-axis: time scale; Y-axis: Number of ganglion cells (each point indicates that one of 20 ganglion cells is at a firing state at that time point; colors represent different firing patterns of corresponding neurons). The neuron index indicates a corresponding number of 20 ganglion cells in the network. Stimulus intensity (amplitude of light current) = 1.5 nA.

Retinal network activity in response to different shapes of light stimulation

Diagrams B1–3 and C1–3 in Figure 5 show that different shapes of light stimuli elicited various firing patterns of retinal ganglion cells, which can be observed from changes in membrane potential sequences in different colors. These results are likely to reflect the dynamic sensitivity of retinal cells to light stimuli of different sizes or different shapes.

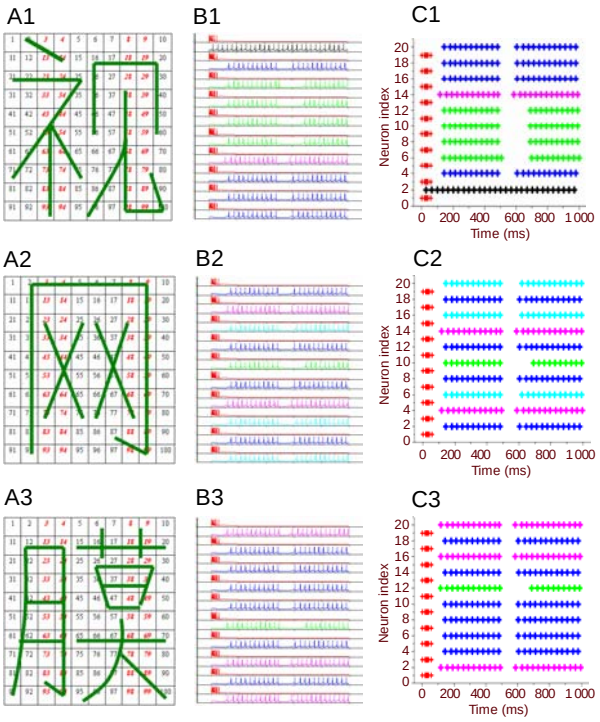

Figure 5 Spike patterns of ganglion cells under different light stimulation types. A1–3: Light stimulus from character “视”, “网” and “膜” (the 100 numbers represent 100 photoreceptors, including 60 rod cells and 40 cone cells, in which black numbers denote rod cells, red numbers denote cone cells, and the region covered by the large character denotes the type of stimulation. Cells located in the character region received light stimulation, while other cells did not receive any stimulation). B1–3: Membrane potential maps of the 20 ganglion cells corresponding to A1–3 (purple, blue and green curves represent three firing patterns). C1–3: ganglion cells’ activities corresponding to A1–3. X-axis: time scale; Y-axis: Number of ganglion cells. Representation of different colors is the same as in Figure 4. Stimulus intensity (amplitude of light current) = 1.5 nA.

Influence of gap junctions on retinal information processing

The light stimulation in the area covered by character “视” in Figure 6 revealed that altering the electrical synaptic strength between cells caused variation in retinal ganglion cells’ membrane potential, which was analyzed in further detail. In addition, the effects of light stimulation in the area covered by the character “视” revealed that information processing by the retina changed with variations in synaptic strength, reflecting the activity of ganglion cells. The results of our simulation provide insight into the role of gap junctions, which are widely distributed in the retina, in visual information processing.

Role of interplexiform cells in retinal information processing

A total of 20 interplexiform cells were added to the original retina network model of Figure 7.

The synaptic connections can be described in detail as follows: interplexiform cells receive excitatory input from amacrine cells, then exert inhibitory synaptic effects on bipolar cells (rod bipolar cells and cone bipolar cells). Feedback circuits from amacrine cells-interplexiform cells-bipolar cells-amacrine cells are thus formed. To investigate the influence of this feedback circuit on visual signal transmission and processing in the retinal network model, we used light stimulation in the shape of character “视”. First, the membrane potential maps of interplexiform cells were obtained (Figure 8A) using NEURON software, in addition to the action potential maps of ON and OFF ganglion cells (Figure 8B). Maps (1)–(4) in Figure 8B show differences in membrane potential maps of interplexiform cells. Clear differences were evident, particularly in the same kind of cells under different conditions. A comparison of C and D in Figure 8 reveals the impact of feedback inhibition from interplexiform cells in the model, indicating an important role of interplexiform cells in visual signal processing in the retina.

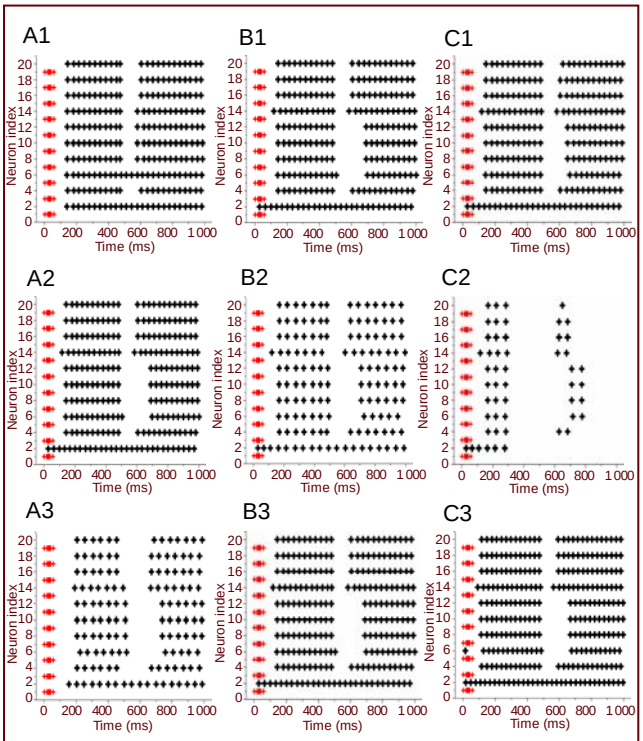

Figure 6 Diagrams of ganglion cells at different synaptic strengths between cells exposed to light stimulation from character “视”. A1, B1 and C1: Gap junctions between rod cells and cone cells; the values were 0, 30 and 50, respectively. A2, B2 and C2: Gap junctions between amacrine cells; the values were 0.5, 20 and 22, respectively. A3, B3 and C3: Gap junctions between amacrine cells and ON cone bipolar cells; the values were 1.5, 4.0 and 6.5, respectively. X-axis: time scale; Y-axis: No. of ganglion cells. Each point indicates that one of 20 ganglion cells is at the firing state at that time point. The colors represent different firing patterns of corresponding neurons. The neuron index indicates the corresponding number of 20 ganglion cells in the network. Stimulus intensity (amplitude of light current) = 1.5 nA.

DISCUSSION

Volgyi *et al* [2] investigated and demonstrated three different pathways that are responsible for the

transmission of rod signals across the mouse retina using a multidisciplinary approach. Each pathway serves a primarily non-overlapping range of stimulus intensities, with ganglion cells receiving either segregated or convergent inputs. In the present study, these three pathways were tested in a retinal network model, and quantitative results were consistent with previous findings[25]. Importantly, the findings also demonstrated the feasibility of the network model constructed in this study.

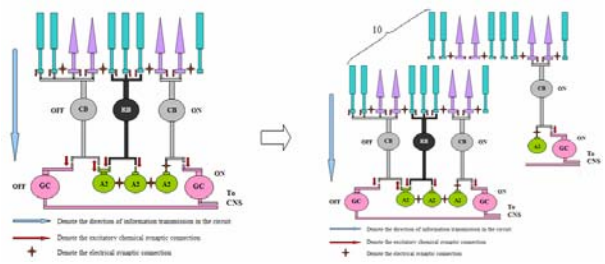

Figure 7 An illustration of the constructed retinal network model. Upper rod: rod cells; upper cone: cone cells; CB: cone bipolar cell; RB: rod bipolar cell; A2: amacrine cell; GC: ganglion cell.

In the currently proposed retinal network model, a large number of electrical synapses or gap junctions are widely distributed among different cell types. One previous study reported the role of gap junctions in a retina network model[26]. To examine the importance of gap junctions in retinal information processing, we analyzed retinal cell activity due to variations of electrical synaptic strength.

In the present study, a retinal network model was established based on the actual retina structure. We used a neuron compartment model and NEURON software to analyze the membrane potential spike patterns of several important cell types in the retina, and investigated the role of interplexiform cells in visual signal processing. The analysis revealed the following theoretical results regarding the neuronal spike pattern in the retinal system:

(1) A high level of neuronal spike activity occurred in our retinal network model. Varying external light stimulation caused clear changes in the response of photoreceptors in the retina. Importantly, the results revealed that this was the case for all three pathways of light signal transmission included in our network model.

(2) By representing photoreceptors in a two-dimensional matrix, we investigated the output activity of retinal ganglion cells exposed to different ranges and different patterns of light stimulation. The results revealed substantial differences in activity. These findings can inform future research.

(3) The influences of the widely distributed gap junctions in the retina were analyzed, and the quantitative results extend current understanding of the important role of synapses in retinal information processing.

(4) Finally, the observable role of interplexiform cells in visual signal processing in the retina was explored.

The findings extend current understanding of the retinal system, especially the various cell types in retina, the density of ion channels, the geometric morphology of dendrites and axons, and the specific locations of synaptic connections. Importantly, the results confirmed that the currently proposed model is reliable. Some typical properties that can be inferred from the numerical results in this study can be investigated in future using this retinal network.

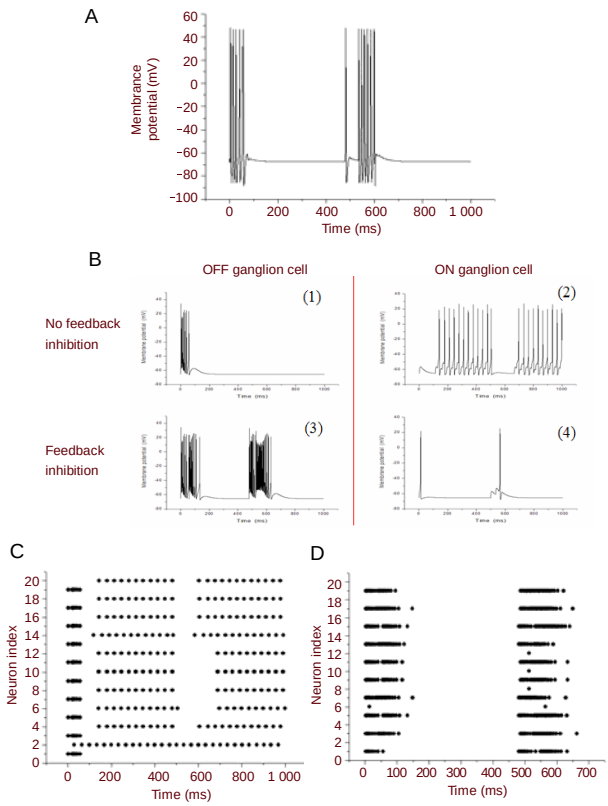

Figure 8 Membrane potential and spike patterns of ganglion cells. X-axis: Time scale; Y-axis: number of neurons. Stimulus intensity (amplitude of light current) = 1.5 nA.
(A) Membrane potential map of interplexiform cells.
(B) Membrane potential maps of ganglion cells in the absence and presence of feedback inhibition.
(C) Diagram of ganglion cells exposed to light stimulation under the region covered by character in the absence of feedback inhibition from interplexiform cells.
(D) Diagram of ganglion cells exposed to light stimulation under the region covered by character in the presence of feedback inhibition from interplexiform cells.

MATERIALS AND METHODS

The retinal network model contained 180 cells, including 40 cone cells, 60 rod cells, 20 cone bipolar cells, 10 rod bipolar cells, 30 amacrine cells and 20 ganglion cells. The model used previously described synaptic connection parameters between cells[2]. Apart from

amacrine cells, the electrophysiological parameters of other cells were used as previously described[31-32]. The hierarchy of neuronal structure in the retinal network was simple, clear, and orderly. The retinal network model was constructed based on the anatomy of the retina[3-4, 29], including specific ion channels in several cell types[31-32], and detailed synaptic connections between retinal cells[2]. This model was very similar to the natural structure of the retina. The circuit of retina could be modulated and the excitatory afferent into cells could be controlled (Figure 7). In the theoretical analysis of the network model, a single cell can be described by conductance-based models, and the morphology of each cell can be characterized by a compartment model. Chemical synapses and electrical synapses were used to describe the connections between cone, rod, cone bipolar, rod bipolar, amacrine and ganglion cells. If cell B was excited by cell A, the N-methyl-D-aspartate (NMDA)-and alpha-amino-3-hydroxy-5-methyl-4-isoxa-zolep-propionate (AMPA)-type excitatory chemical synaptic currents were added on the receiving end of cell B. For electrical synapses, cells on both sides of electrical synapses were able to receive afferent inputs from each other. The three types of synaptic connections used in this model are listed, and the details of the synaptic strength between cells are shown in Table 1.

Table 1 Synaptic connection strength between cells (mS/cm^2)

	Rod	Cond	Rod-Bipolar	Cone-Bipolar	A II amacrine	Ganglion
Rod	–	30	NMDA: 0.7 AMPA: 0.2	NMDA: 0.7 AMPA: 0.2	–	–
Cond	30	–	–	NMDA: 0.7 AMPA: 0.2	–	–
Rod-Bipolar	–	–	–	–	NMDA: 0.105 AMPA: 0.03	–
Cone-Bipolar	–	–	–	–	NMDA: 0.035 AMPA: 0.01	NMDA: 0.175 (off)/ 0.00525 (on) AMPA: 0.05 (off)/ 0.0015 (on)
A II amacrine	–	–	–	NMDA: 0.175 AMPA: 0.05	0.5	4.0 (on)
Ganglion	–	–	–	–	4.0 (on)	–

NMDA: N-methyl-D-aspartate; AMPA: alpha-amino-3- hydroxy-5-methyl-4-isoxa-zolep-propionate.

(1) AMPA synaptic currents:

$$I_{AMPA} = g_{AMPA}\exp(-t/\tau)(V-E_{AMPA})$$

τ represents the delay time constant of synapse; E_{AMPA} is the reversal potential; g_{AMPA} is the maximal excitatory synaptic strength.

(2) NMDA synaptic currents:

$$I_{NMDA} = g_{NMDA}[mg^{2+}](Ron + Roff)(V-E_{NMDA})$$

E_{NMDA} is the reversal potential; g_{NMDA} is the maximal excitatory synaptic strength.
$[mg^{2+}] = 1/[1 + \exp(-0.062V)/3.57]$ representing Mg^{2+} concentration.
Ron′ = $-$*Ron*/2.6, *Roff′* = $-$*0.035*/*Roff*, representing the state variables of channels. E_{AMPA} = 0 mV, E_{NMDA} = 0 mV.
(3) Electrical synaptic currents: $i_{ij} = g_{ij}(V_i - V_j)$. i_{ij} is the synaptic current between cell i and cell j; g_{ij} is synaptic strength.

The retinal network model was constructed using NEURON software (Neuron Software Ltd.)[33], and data processing was conducted using ORIGIN (OriginLab, Northampton, MA, USA) and MATLAB (MathWorks, Natick, MA, USA) software. The light simulation results were repeatedly verified.

Author contributions: Lei Wang conducted the experiment, participated in confirming data integrity, conducting data analysis, and writing the manuscript. Shenquan Liu participated in study design, supervision, and manuscript revision. Shanxing Ou participated in study design, data analysis and manuscript revision.

Conflicts of interest: None declared.

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