Possible Mechanism of Dual-peak Response in Retinal Ganglion Cells: a Computational Study

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***Abstract*—It has been observed that a subpopulation of ganglion cells in the chicken retinas responds to repetitive light flashes with a particular dual-peak response. The dual-peak response includes two successive phases: a peak in firing rate occurring shortly after the onset and/or offset of the light flash and another peak in firing rate occurring following the first one with a short interval where the firing rate is quite low. A computational retina model is developed to investigate the origination of the dual-peak response. For simplicity, only a single representative of each neuron type is modeled because of the spatially homogeneous light stimulation we used. Computation results indicate that the fast transient amacrine cell and the slow transient amacrine cell are key neurons for the reproduction of the dual-peak response. The dual-peak response may results from a delayed inhibitory input to a sustained ganglion cell that splits its response into two distinct parts. Besides the dual-peak response, other normal response types of ganglion cell also can be reproduced by the retina model.**

Keywords-computational retina model; dual-peak response; ganglion cell; amacrine cell

I. INTRODUCTION

It was previously observed that a subpopulation of ganglion cells in the chicken retinas responds to repetitive light flashes with a dual-peak response [1], which clearly differs from the classical sustained or transient response types. The dual-peak response consists of two separated peaks in firing rate: one occurs shortly after the onset and/or offset of the light stimulation, the other occurs following the first one with a short interval where the firing rate is quite low.

Similar dual-peak responses were also observed by Nirenberg and Meister in the mouse retinas [2]. However, the intrinsic mechanism for the origination of the dual-peak response still remains unclear. It is well accepted that amacrine cells shape the temporal structure of ganglion cell's firing activity, which implies that they may play a key role in the generation of the dual-peak response. However, amacrine cells are comprised of numerous subtypes and each subtype is provided with different morphological or biochemical properties [3-5]. Furthermore, most amacrine cells use the common neurotransmitters and receptors to transmit information [6-8]. So it is difficult to study the origination of the dual-peak response just using pharmacological tools.

A way that helps to resolve this question is to develop a computational retina model. Several retina models have been developed to explain the generation of synchronous oscillations in ganglion cell response [9], various stages of light adaptation [10], and nonlinear response characteristics of Y cells [11,12]. However, none of these retina models has been applied to investigate the physiological foundations of complex temporal structure in ganglion cell response. Thiel et al. reported that some transient ON/OFF ganglion cells in the turtle retinas transmits changes in light intensity as a series of distinct spike events and the temporal structure of these spike events series depends on the stimulus intensity [13]. To investigate the mechanism of the temporal structure of the spike events series, they developed a computational retina model that well reproduces such temporal structure under various experimental conditions. The dual-peak response of ganglion cells in the chicken retinas demonstrates a similar temporal structure to the firing activities of ganglion cells observed by Thiel et al in the turtle retinas. Therefore, the computational retina model developed by Thiel et al. is modified to investigate the possible mechanism for the origination of the dual-peak response.

II. MATERIALS AND METHODS

A. Experiment procedure

The detailed experiment procedure was fully described previously [14]. In brief, extracellular recordings were made in isolated chicken retinas using a multi-electrode array (MEA, Multi Channel Systems MCS GmbH, Germany), which consists of 60 electrodes (10 μm in diameter) arranged in an 8 × 8 matrix with 100 μm tip-to-tip distance. A small piece of retina quickly isolated from young born chicken (about 1-3 weeks) was attached with the ganglion cell side onto the surface of MEA. Spatially uniform white light was generated from a video monitor (796 FD II, MAG) and was focused to form a 0.75 × 0.75 mm2 image on the isolated retina via a lens system. Stimulus consisting of full-field white light (12.18 nW/cm2) with duration of 1 s and dark interval of 9 s was given repeatedly for 50 times. The firing activities of retinal ganglion cells during response to the stimuli were simultaneously recorded by MEA using the commercial software MC_Rack (Multi Channel Systems MCS GmbH, Germany) with a sampling rate of 20 kHz and stored for off-line analyses. Spikes from individual neurons were sorted

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based on the principal component analysis as well as the spike-sorting unit in MC_Rack [15,16].

B. Retina model description

Due to the spatially homogeneous light stimuli we used, it is assumed that each type of neurons in the retina receives identical inputs and thus behaves the same. Therefore, only a single representative of each neuron type is modeled in the computational retina model, as illustrated in Figure 1. Using a temporal integration step size of 1 ms, each model neuron's membrane potential $v(t)$ is described by the following equation [11]:

$$\frac{dv(t)}{dt} = -A_v v(t) + d_v(t)\left[D_v - v(t)\right] - h_v(t)\left[H_v + v(t)\right]. \quad (1)$$

Here A_v represents the passive decay rate toward the resting membrane potential in the dark; D_v and H_v represent the saturation levels for depolarization and hyperpolarization, respectively; $d_v(t)$ represents the total depolarization inputs and h_v(t) the total hyperpolarization inputs to the neuron. The absolute value of the membrane potential in the dark is set to 0. Therefore, positive excursions are interpreted as depolarization and negative excursions as hyperpolarization.

The depolarized and hyperpolarized portions of the membrane potential $v(t)$ are indicated by

$$\begin{cases} v^+ = vH(v) \\ v^- = v(1 - H(v)), \end{cases} \quad (2)$$

where H indicates the Heaviside step function. For simplicity, the complete differential equations describing the potential dynamics of each neuron type are omitted. Instead, only the depolarization inputs d_v(t) and hyperpolarization $h_v(t)$ to the model neurons are given. The detailed descriptions of the computational model are listed below [13].

$$\textbf{\textit{Photoreceptor}} \begin{cases} d_p(t) = -W_p^h h^-(t - \Delta t_h) \\ h_p(t) = s(t - \Delta t_s) \end{cases}$$

$$\textbf{\textit{Horizontal cell}} \begin{cases} d_h(t) = W_h^p p^+(t) \\ h_h(t) = -W_h^p p^-(t) \end{cases}$$

$$\textbf{\textit{ON bipolar cell}} \begin{cases} d_{bON}(t) = -W_b^p p^-(t - \Delta t_{ON}) - W_{bON}^{aSON} a_{SON}^-(t) \\ h_{bON}(t) = W_b^p p^+(t - \Delta t_{ON}) + W_{bON}^{aSON} a_{SON}^+(t) \end{cases}$$

$$\textbf{\textit{OFF bipolar cell}} \begin{cases} d_{bOFF}(t) = W_b^p p^+(t - \Delta t_{OFF}) - W_{bOFF}^{aSOFF} a_{SOFF}^-(t) \\ h_{bOFF}(t) = -W_b^p p^-(t - \Delta t_{OFF}) + W_{bOFF}^{aSOFF} a_{SOFF}^+(t) \end{cases} \quad (3)$$

$$\textbf{\textit{Sustained ON amacrine cell}} \begin{cases} d_{aSON}(t) = W_{aS}^b b_{ON}^+(t) \\ h_{aSON}(t) = -W_{aS}^b b_{ON}^-(t) \end{cases}$$

$$\textbf{\textit{Sustained OFF amacrine cell}} \begin{cases} d_{aSOFF}(t) = W_{aS}^b b_{OFF}^+(t) \\ h_{aSOFF}(t) = -W_{aS}^b b_{OFF}^-(t) \end{cases}$$

$$\textbf{\textit{Slow transient ON/OFF amacrine cell}} \begin{cases} d_{aST}(t) = W_{aST}^{bON} b_{ON}^+(t) + W_{aST}^{bOFF} b_{OFF}^+(t) \\ h_{aST}(t) = 0 \end{cases}$$

$$\textbf{\textit{Fast transient ON/OFF amacrine cell}} \begin{cases} d_{aFT}(t) = W_{aFT}^{bON} b_{ON}^+(t) + W_{aFT}^{bOFF} b_{OFF}^+(t) \\ h_{aST}(t) = W_{aFT}^{aST} a_{ST}^+(t) \end{cases}$$

$$\textbf{\textit{Ganglion cell}} \begin{cases} d_g(t) = W_g^{bON} b_{ON}^+(t) + W_g^{bOFF} b_{OFF}^+(t) \\ h_g(t) = W_g^{aFT} a_{FT}^+(t) \\ f(t) = G(g(t) - \Theta)^+ + R \end{cases}$$

The stimuli signal $s(t - \Delta t_s)$ is fed to the photoreceptor as a hyperpolarization input. Besides, the photoreceptor also receives delayed depolarization input $h^-(t - \Delta t_h)$ from the model horizontal cell. This input is weighted by the synaptic strength W_p^h, with the subscript p indicating the photoreceptor as the target cell of the connection, and the superscript h denoting horizontal cell as the signal source. The description of the other simulated neurons can be understood similarly.

The Inhomogeneous Poisson process model is employed to generate action potentials at the form of 1-0 trains according to the membrane potential of the simulated ganglion cell, 1 and 0 correspond to the ganglion cell firing or not.

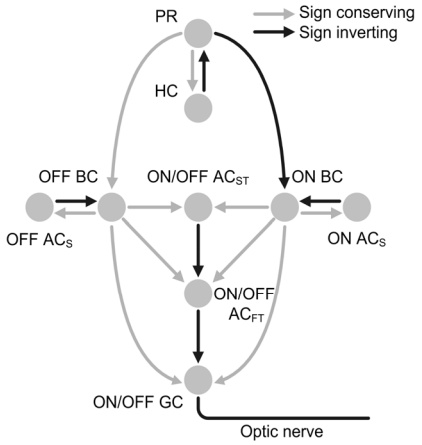


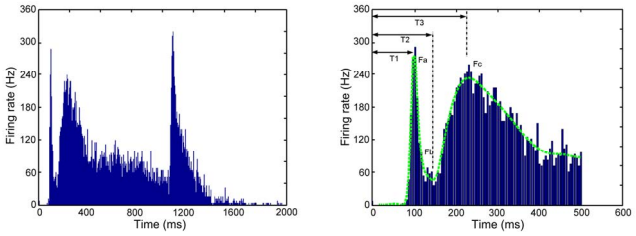
Figure 1. Schematic illustration of the computational retina model. All major retinal neuron types are taken into account: photoreceptor(PR), horizontal cell(HC), bipolar cell(BC), sustained amacrine cell(AC$_S$), slow transient amacrine cell(AC$_{ST}$), fast transient amacrine cell(AC$_{FT}$) and ganglion cell(GC). Black arrows indicate sign inverting connections, while gray arrows indicate sign conserving connections.

III. RESULTS

It was observed that some chicken retinal ganglion cells show a particular dual-peak response property. Figure 2(a) gives an example of the ganglion cell's dual-peak response. 6 parameters are defined to identify the dual-peak response from the traditional transient or sustained ones, as illustrated in Figure 2(b). F_a indicates the value of the first peak in firing rate. The latency of the first peak T1 is usually shorter than 125 ms (T1 < 125 ms). The first peak is transient with the firing rate descending quickly and reaching a minimal value F_b at T2 (F_b <50% F_a). If there is a second peak that arises following the first one with a value F_c 50% higher than the valley value (F_c >150% F_b) and a peak latency not longer than 500 ms after the onset and/or offset (T3 ≤ 500 ms) of light stimulation, a dual-peak response can be identified.

The computational retina model is developed to study the intrinsic mechanism for the origination of the dual-peak response. Since most retinal ganglion cells recorded in our study show ON/OFF response property, both ON and OFF pathways are included into the computational retina model and signals from the two pathways finally converge onto the same ganglion cell. A "1-0" time series (length=2200) that denotes the light stimulation is fed to the photoreceptor as an original

signal to the computational retina model. "1" and "0" represent the light-on and light-off duration, respectively. Thus, the membrane potential of each model cell can be computed sequentially.



(a) (b)

Figure 2. (a) An example of the retinal ganglion cell's dual-peak response (50 repeats, bin=5 ms). The light stimulation starts at 0 ms and ends at 1000 ms. (b) An expansion of panel (a) at the onset part (0–500 ms). Dashed line indicates the smoothed curve of the firing rate. F_a, F_b and F_c are the firing rates measured at the first peak, the valley and the second peak, respectively. T1, T2 and T3 are the response latencies of the first peak, the valley and the second peak, respectively [1].

Figure 3 demonstrates the responses of the different simulated neuron types in the retina model. Both the ON bipolar cell and the OFF bipolar cell show a sustained response property. Our simulation results show that when the synaptic strength between the fast ON/OFF amacrine cell and the ganglion cell is weak, the normal sustained ON/OFF response of the retina ganglion cell can be easily reproduced. Figure 4(a) shows the normal sustained response of the ganglion cell generated by the model. When the synaptic strength between the fast ON/OFF amacrine cell and the ganglion cell is strong, the dual-peak response of the ganglion cell can be reproduced. The second peak results from the inhibitory input from the fast transient amacrine cell and its response latency rests on the time when the inhibitory output reaches its peak level. Figure 4(b) shows the dual-peak response of the ganglion cell generated by the model.

IV. Discussion

A subpopulation of ganglion cells in the chicken retina shows a particular dual-peak response to the repetitive light flashes, which has been elaborated above. One possible mechanism that can result in the dual-peak response supposes that a delayed inhibitory input to a sustained ganglion cell splits its response into two distinct parts. Applying the computational retina model described above, we succeed in reproducing the dual-peak response.

The fast transient ON/OFF amacrine cell and the slow transient ON/OFF amacrine cell are necessary for the reproduction of the dual-peak response. The existence of such ON/OFF amacrine cells has been confirmed by experiment [17]. The latter peak of the ganglion cell's dual-peak response results from a delayed inhibitory input from the fast transient ON/OFF amacrine cell.

Although the simulation results indicate a possible mechanism for the reproduction of the dual-peak response, however, the specific details about the dual-peak response remain unclear, which need more experiments and theoretical analysis in the future.

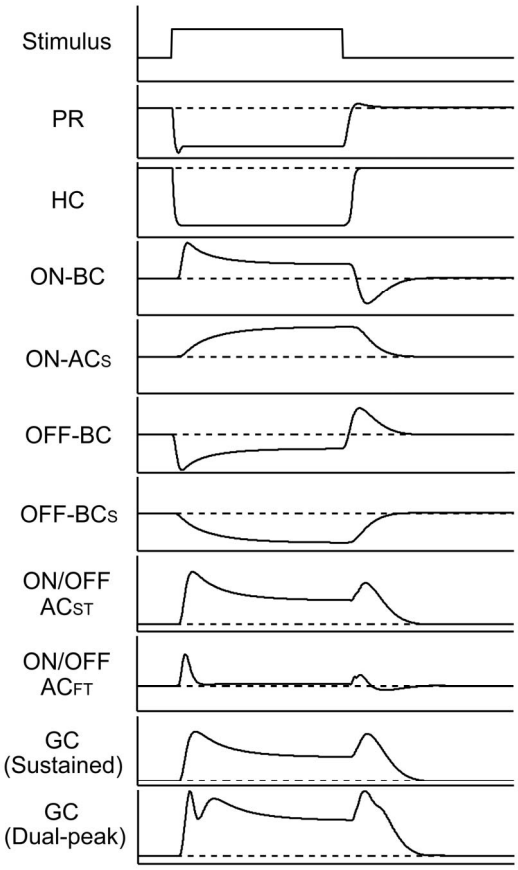
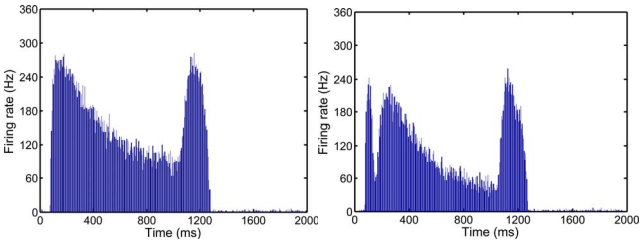


Figure 3. Responses of the different simulated neuron types in the retina model. Dotted horizontal lines indicate each model neuron's dark resting membrane potential. A '1-0' time series (top panel) is constructed to denote the light intensity of the stimulation used in the simulation study. "1" and "0" represent the light-on and light-off duration, respectively.



(a) (b)

Figure 4. Responses types reproduced by the computational retina model. (a) Sustained response. (b) Dual-peak response.

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