Letter

Anticipation and negative group delay in a retina

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The mechanism of negative group delay (NGD) is used to understand the anticipatory capability of a retina. Experiments with retinas from bullfrogs are performed to compare with the predictions of the NGD model. In particular, whole field stochastic stimulations with various autocorrelation times are used to probe anticipatory responses from the retina. We find that the NGD model can reproduce essential features of experimental observations characterized by the cross correlations between the stimulation and the retinal responses. Experiments with dark light pulse stimulations further support the NGD mechanism, with the retina producing time-advanced pulse responses. However, no time-advanced pulse responses are produced by bright pulses. Counterintuitively, the NGD model shows that it is the delay in the system which gives rise to anticipation because of the negative feedback adaptation mechanism.

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Anticipation [1] is a process in which a system generates responses ahead of the actual occurrence of events in the incoming stimulation. For physical systems, a device can produce anticipatory responses when there is negative group delay (NGD) [2]. At first sight, anticipation might seem to violate causality but there is a requirement that the signal should be correlated, meaning that the signal can be predicted from its past [3]. NGD devices have been fabricated for fast communication applications in which the NGD of transmitted signals can improve the performance of the system [4]. There is plenty of evidence that biological systems possess anticipatory capabilities [1]. It is believed that biological systems make use of anticipation to compensate for the delay in signal processing and propagation in neural systems [5]. Even baseball games [6] can be shown to be related to anticipation. However, it is not clear whether the observed anticipations in biological systems are the result of complex information operations of neural circuits in the brain or just simply an NGD effect.

It has been known for a long time that visual systems can produce anticipatory illusion [7]. Only recently, Berry *et al.* [8] and Shwartz *et al.* [9] demonstrated that anticipation can start as early as in the sensor, namely the retina. In the phenomenon of omitted stimulation response (OSR) [9], a retina was shown to anticipate a missing incoming pulse by endogenously generating a response with appropriate timing after a periodic pulse stimulation is abruptly stopped. Chen *et al.* [10] showed in an extension to OSR that a retina can also distinguish between stochastic pulses generated by a hidden Markov model (HMM) and an Ornstein-Uhlenbeck (OU) process by producing anticipatory responses only for the HMM signal. Since an HMM signal should have also elicited anticipatory responses from a NGD filter, it is possible that the retina is behaving as a NGD device. One important ingredient for a system to possess anticipatory capability is delayed negative feedback (DNF). Voss [2] has shown that DNF can directly lead to NGD. Contrast and gain controls are common for retinas and presumably they are accomplished by the mechanism of DNF similar to other control systems [11].

Here, we propose that the NGD mechanism can be used to understand the anticipatory properties of retinas and test this idea by both constructing an NGD model and performing experiments with bullfrog retinas in a multielectrode array (MEA) system. We are interested in comparing the responses from the retina with those from the NGD model when driven by the same stimulation. A comparison of the prediction of the NGD model with retina experiments shows that anticipatory dynamics of a retina can indeed be described well by the NGD model with physiologically plausible parameters. Counterintuitively, the NGD model shows that it is the delay in the system which gives rise to anticipation.

In the original NGD model of Voss [2], the response $y(t)$ of a system driven by input $x(t)$ through a delayed feedback is given by $\dot{y}(t) = -\alpha y(t) + k[x(t) - y(t-\zeta)]$, where α and k are the relaxation rate and the gain of the system while $y(t-\zeta)$ is the delayed feedback of y from an earlier time ζ. This form of NGD model needs storage of $y(t)$ which might not be physiologically feasible. Here, we consider the delayed feedback as coming from another variable $z(t)$ which is a low-pass version of $y(t)$ as

$$\dot{y}(t) = -\alpha y(t) + k[x(t) - z(t)], \tag{1}$$

$$\dot{z}(t) = -\beta z(t) + g y(t), \tag{2}$$

where β and g are defined similarly to α and k. With this form, there is no need for the storage. Similar to Ref. [2],

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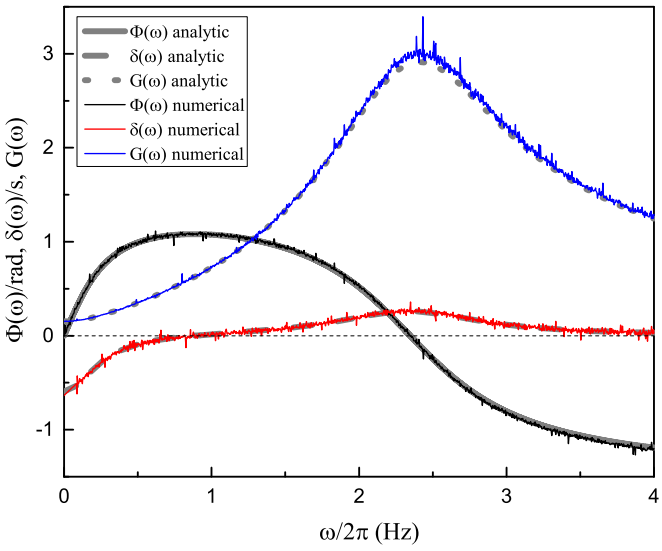

FIG. 1. Frequency dependence of gain $[G(\omega)]$, phase $[\Phi(\omega)]$, and group delay $[\delta(\omega)]$ of the response function from the NDG model with $\alpha = 6\ \mathrm{s}^{-1}$, $\beta = 1.6\ \mathrm{s}^{-1}$, $k = 22$, and $g = 10$. Both analytic and numerical results are shown. Numerical data points are obtained from the simulation described in the text.

with $X(\omega)$ and $Y(\omega)$ being the Fourier transforms of $x(t)$ and $y(t)$, respectively, the group delay of the system can be obtained as $\delta(\omega) \equiv -d\Phi(\omega)/d\omega$, with $\Phi(\omega)$ being the phase of the response function defined as $H(\omega) = Y(\omega)/X(\omega) \equiv G(\omega)e^{i\Phi(\omega)}$ at frequency ω. From Eqs. (1) and (2), Φ can be computed as

$$\Phi(\omega) = -\arctan\left[\frac{w(\beta^2 - gk + w^2)}{\beta gk + \alpha(\beta^2 + w^2)}\right]. \tag{3}$$

Figure 1 shows the ω dependence of $\delta(\omega)$, $G(\omega)$, and $\Phi(\omega)$ with $x(t)$ generated from a time series of random numbers with low-pass filtering similar to Ref. [2]. The values of the parameters used to produce Fig. 1 are chosen to match observations from the experiments as explained below. From Fig. 1, a negative $\delta(\omega)$ can be obtained only when ω is small enough. This is consistent with the idea that only signals with long enough autocorrelation times can be predictable. An interesting feature in the figure is that there is a maximum in $G(\omega)$ at about 2.5 Hz. This will show up as oscillations in responses of the system. Note that Eq. (2) can be solved as $z(t) = \int_{-\infty}^{t} K(t - t')y(t')dt'$ with the kernel $K(t - t') = ge^{-\beta(t-t')}$. The case of the Voss model can be recovered by setting $K(t) = \delta(t - \xi)$. Equation (1) and the kernel form of $z(t)$ can be then considered as a generic form for anticipatory dynamics, with $z(t)$ being the convolution of the output $y(t)$ with some kernel $K(t)$ to provide delay. If there is no delay in the system, there will be no NGD effect. We will refer to this model as the NGD model.

Next, we set up experiments to test if this generic form of anticipation dynamics can also be found in a retina. The experiment setup and procedures were similar to Ref. [10]. Retinas used in the experiments were obtained from bullfrogs which were dark adapted for 1 h before dissection. A small patch of retina tissue was then cut and fixed on a 60-channel multielectrode array (Qwane Bioscience) with electrodes 10 μm in diameter spaced at 200 μm. The retina was perfused with oxygenated Ringer's solution [12] at a rate of 1 ml/min. Each retina was experimented at room temperature within 6 h after dissection. We used a smoothed Ornstein-Uhlenbeck (OU) time series to generate stimulation. The OU time series $\{s_i\}$ was first generated with $s_{i+1} = (1 - \frac{\Delta t}{\tau})s_i + \xi_i\sqrt{D\Delta t}$, where the time step Δt was 10 ms, ξ a white noise with unit amplitude, $D = 4\ \mathrm{s}^{-1}$ the amplitude of the noise, and τ the relaxation time of the system. Next, stimulations $\{x_i\}$ with various autocorrelation times were generated from $\{s_i\}$ by using low-pass filters with different cutoff frequencies (f_c). The time series $\{x_i\}$ were then used to control the light intensity $I(t)$ of a light-emitting diode (LED) (peak of wavelength = 560 nm) to stimulate the whole retina. The maximum and minimum light intensities used were 18 and 2 mW/m^2, respectively, with an average intensity of 10 mW/m^2. Responses from the retina ($\{r_i\}$) were recorded by the MEA as a function of different f_c and τ.

In a typical successful experimental recording, about 70% of the MEA electrodes are generating responses. For the responding electrodes, they usually give different responses. Presumably, this diversity is due to the existence of different pathways in a retina [13]. The spikes obtained are spikes sorted to remove redundant detection. In Ref. [2], cross-correlation functions (XCFs) between stimulation and response $\langle y(t)x(t + \delta t)\rangle_t$ at different time delays δt are used to characterize the anticipatory property of the system. If there is a peak in $\langle y(t)x(t + \delta t)\rangle_t$ at location $\delta t = \delta t_p$, a positive δt_p signifies that $y(t)$ is anticipatory of $x(t)$ and δt_p can be considered as the prediction horizon. These XCFs are similar to the spike triggered average (STA) [14] which characterizes the averaged wave form before the generation of a spike at $\delta t = 0$. In the experiments, the forms of the STA obtained from different channels can roughly be divided into two groups, namely predictive (P channel) and nonpredictive (NP channel) as explained below. Since the behaviors of every retina can be quite different in details and cannot be averaged, we are reporting the behaviors of a single retina below. But the reported behaviors are representative of more than ten retinas from ten different animals.

Figure 2(a) shows the inverted STA (iSTA = −STA) obtained from a typical P channel for two different τ with various f_c. We need to use iSTA here because the NGD model will produce results similar only for iSTA of a P channel as shown below. A remarkable feature of Fig. 2(a) is that there are two sets of peaks in the iSTA, marked as set A and set B in the figure. Note that the peak positions (δt_p) of the iSTA in set B are shifted towards more positive δt when the f_c are reduced while those of set A are shifted in the opposite direction. Anticipatory behaviors can be inferred from some of the peaks in the set B peaks which are located at $\delta t_p > 0$ when their corresponding f_c are small enough. This is the reason for labeling these kinds of responses as predictive. No such predictive behavior can be found from the NP channel see Fig. S1 in the Supplemental Material (SM) [15]. The effect of autocorrelation of an incoming signal on anticipation found here is similar to those of Ref. [10] by the method of time lag mutual information (TLMI), namely prediction is possible

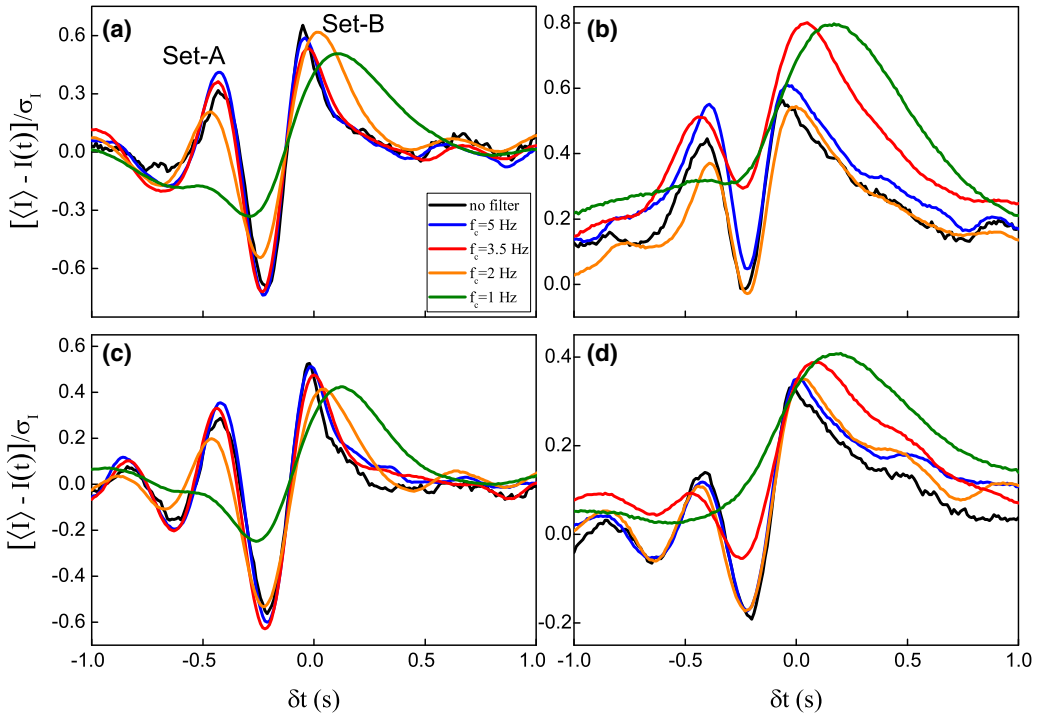

FIG. 2. Comparison of spike triggered average (STA) obtained from experiments and simulation with various f_c and τ: (a) and (b) are the inverted STAs from experiment with $\tau = 0.1$ and 0.6 s, respectively. Note that the oscillatory nature of the iSTA gives rise to two sets of peaks in the iSTA which are marked as Set A and set B. (c) and (d) are the corresponding STAs generated from the NDG model with the same parameters of Fig. 1 and with the same stimulation used in (a) and (b). The data are obtained from experiments in which the stimulation lasted for 300 s.

only for stimulation with a long enough autocorrelation time. In fact, a similar conclusion can also be reached with the method of TLMI (Fig. S2 in SM).

To test if the NGD model can capture the essential features of the experiments, we have performed a simulation of the NGD model with the same stimulation from the experiment by adjusting the parameters (α, β, k, g) to best match with the shapes of experimental iSTA. Figures 2(c) and 2(d) show the corresponding STA from the NGD model. These STA are generated by first passing $y(t)$ generated from the NGD model through an activation function and then using the activated output $[\lambda(t)]$ to generate a Poisson spike train with a firing rate proportional to the $\lambda(t)$. These model-generated STAs are very similar to those of the iSTA from experiments. A retina can generate responses through its ON and OFF pathways [13] when there is an increase (ON) or decrease (OFF) in the input light intensity. With this convention, the NGD model is an ON pathway. Since spikes recorded from the P channel give an overall characteristic of an OFF pathway, we need to use the iSTA of a P channel when compared with the STA from the NGD model.

Note that set A and set B peaks are also reproduced by the simulation. Similar to the experiments, δt_p of peaks in set B from simulation are also shifted towards more positive δt when f_c are lowered. The f_c and τ dependences of t_p of set B peaks for both experiments and simulations are shown in Fig. 3. In the figure, δt_p from both experiments and simulation shows a similar dependence on f_c but not for the τ dependence. Presumably, the retina might have dynamics which are not captured by the NGD model. Furthermore, both STAs from experiments and simulation show oscillations with a characteristic frequency consistent with the peak position of $G(\omega)$ in Fig. 1. All the simulation results reported here are

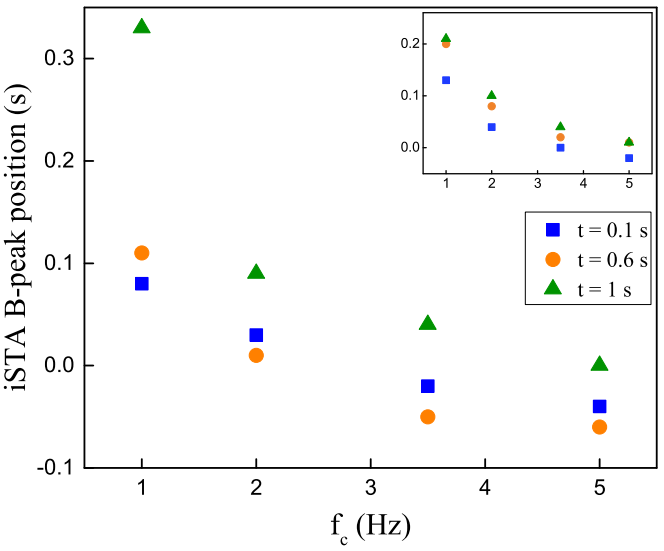

FIG. 3. Peak positions (δt_p) of peaks in set B of the iSTA or STA as a function of cutoff frequencies for three different values of τ from both experiments and simulations (inset). Note that a positive value of δt_p indicates an anticipatory response from the retina or the NGD model.

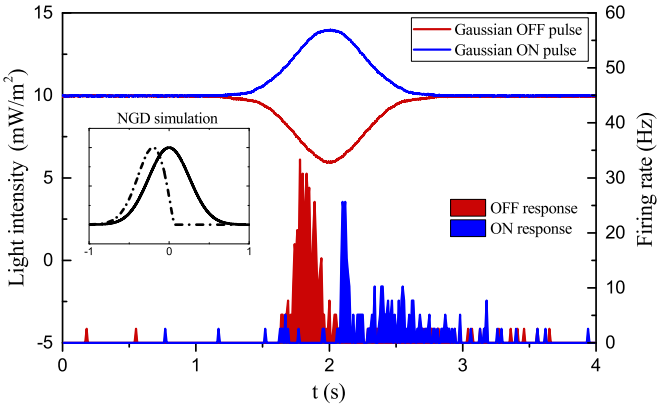

FIG. 4. Responses of a retina and the NDG model to Gaussian pulses from a P channel. The red and blue traces are for the bright (ON) and dark (OFF) pulse stimulations, respectively, in the experiments. The corresponding responses from the retina measured as the firing rate are also shown with respective colors. The data are obtained by averaging the responses from the same retina over 40 runs. The inset shows the anticipatory response (dashed line) of the NGD model with the same parameters used to generate Figs. 2(c) and 2(d) for an incoming Gaussian pulse (black line).

generated with only one single set of parameters, indicating that the simulation can mimic the experiment at least for the f_c dependence.

One of the hallmarks of a NGD system is the generation of a time-advanced pulse [16]. To further test the NGD properties of the retina, Gaussian pulses are used to test if the pulses can be advanced by the retina. Figure 4 shows the responses of the retina for both ON and OFF pulses in the form $S(t) = I_0 \pm I_p e^{-\frac{1}{2}(t/2\sqrt{2\ln(2)}\tau_w)^2}$, with τ_w being the half maximum width of the pulse. The reason for using both ON and OFF pulses is that the retina can respond to both increasing and decreasing light stimulation in its ON and OFF pathway [13]. Figure 4 shows that the ON pulse is delayed in the response of the retina while that from the OFF pulse is advanced. It seems that the retina is an NGD device only for the OFF pulses. The pulse response from an NP channel is very different (see Fig. S3 in SM for details). The simulation of a pulse input has also been performed with the NGD model as shown in the inset with the same set of parameters in Fig. 1, showing agreement with experiments. Figure 4 shows that the P channels are capable of producing both ON and OFF spikes. The same is also true for the NP channel (Fig. S3 of SM). From both of these P-channel and NP-channel recordings, it can be seen that it is the OFF responses which are predictive of the incoming pulses. However, for faster stimulation, as in Figs. 2(a) and 2(b) for a P channel, it is not clear why most of the spikes are coming from the OFF pathway and therefore rendering the P channel predictive.

In the experiments, the ratio of P and NP channels can vary from close to 0% to close to 100%, depending on the location of the retina being attached to the MEA. It is clear that the extended Voss NDG model can capture the essential features of the anticipatory behaviors of a retina but only for the P channel. Presumably, a model more sophisticated than the NDG model is needed to understand the coding of the NP channel. The essence of the NDG mechanism is a delayed negative feedback and it is well known that there is delayed feedback from the horizontal cell to the photodetector cells (cone cells) in a retina. In fact, the rate constants α and β in the model can be related to the relaxation time constants of the cone (τ_y) and horizontal (τ_h) cells, respectively. Drinneberg *et al.* [17] studied the effect of this feedback with retinas from rats also under a whole field stimulation. The rate constants $\tau_y^{-1} = 19.8\ \mathrm{s}^{-1}$ and $\tau_h^{-1} = 2.7\ \mathrm{s}^{-1}$ used in Ref. [17] are of the same order of magnitude of $\alpha = 6\ \mathrm{s}^{-1}$ and $\beta = 1.6\ \mathrm{s}^{-1}$ used here in the NGD model for a frog, indicating that the NGD model is physiologically feasible. In fact, the $z(t)$ in the NGD model is similar to the convoluted output of the cone cell produced by the horizontal cell in Ref. [17].

The anticipatory model described by Eqs. (1) and (2) should not be limited to the description of senors such as the retina. It can also be considered as a generic adaptive sensing model. The term $[x(t) - z(t)]$ can be understood as the "error" between the environmental signal $x(t)$ and an internal adaptive reference $z(t)$. The action of the model is simply to update the internal reference and adjust its output $y(t)$ by minimizing this error so as to adapt to the environment. Counterintuitively, it is precisely the delay of the system in updating the internal reference $z(t)$ which gives rise to the anticipatory response in $y(t)$. Consequently, the prediction horizon of $y(t)$ will be lengthened when there is a longer delay and there is no limit on the prediction horizon as long as there is a long enough autocorrelation time in $x(t)$. However, for a retina from a bullfrog, the longest anticipatory time was found to be of the order of 1 s [10], similar to our observations here. Since biological sensing systems should have the ability to adapt to changes in their environment through negative feedback, presumably anticipatory capabilities can be found in a wide variety of biological systems as in the cases of auditory [18] and sensorimotor systems [19]. In the concept of perceptual control [20], the observed anticipatory response of such a system is simply the result of the control of perception $[y(t)]$ of the external world $[x(t)]$ through a delayed negative feedback mechanism.

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