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Features and functions of nonlinear spatial integration by retinal ganglion cells

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ABSTRACT

Ganglion cells in the vertebrate retina integrate visual information over their receptive fields. They do so by pooling presynaptic excitatory inputs from typically many bipolar cells, which themselves collect inputs from several photoreceptors. In addition, inhibitory interactions mediated by horizontal cells and amacrine cells modulate the structure of the receptive field. In many models, this spatial integration is assumed to occur in a linear fashion. Yet, it has long been known that spatial integration by retinal ganglion cells also incurs nonlinear phenomena. Moreover, several recent examples have shown that nonlinear spatial integration is tightly connected to specific visual functions performed by different types of retinal ganglion cells. This work discusses these advances in understanding the role of nonlinear spatial integration and reviews recent efforts to quantitatively study the nature and mechanisms underlying spatial nonlinearities. These new insights point towards a critical role of nonlinearities within ganglion cell receptive fields for capturing responses of the cells to natural and behaviorally relevant visual stimuli. In the long run, nonlinear phenomena of spatial integration may also prove important for implementing the actual neural code of retinal neurons when designing visual prostheses for the eye.

1. Introduction

The vertebrate retina represents the input stage of the visual system. Here, light is transformed by photoreceptors into electrical signals, which are then processed by a complex neural network of horizontal cells, bipolar cells, and amacrine cells (Wässle, 2004; Masland, 2012). Finally, retinal ganglion cells collect the outcomes of these network operations and encode them in patterns of spikes for transmission along the optic nerve to various downstream brain regions.

The signal processing by its neural network means that the retina is not the equivalent of a CCD camera for the rest of the brain. While much of the processing and signal transmission proceeds in a spatially ordered way, it does not occur in a simple pixel-by-pixel fashion. Instead, the retinal network provides convergent as well as divergent signaling pathways, a large diversity in the anatomy and physiology of the different neuron types, a high degree of adaptivity to prevailing lighting conditions, and different types of nonlinear operations at both cellular and synaptic levels. Together, these circuit properties endow the retina with complex signal processing capabilities, which have only partially been elucidated and whose characteristics remain a central topic of current research in neuroscience. The spike patterns of ganglion cells do not simply represent the level of incident light at a certain spot within the visual field, but rather can encode more complex features of the visual stimulus. Several recent examples have shown that the specific computations underlying the detection and representation of these features can be understood based on how the respective ganglion cells pool visual inputs over space and time.

These findings have called renewed attention to the critical role of nonlinearities in retinal signal integration (Gollisch and Meister, 2010; da Silveira and Roska, 2011; Schwartz and Rieke, 2011). Although it has long been known that nonlinear integration exists in the retina and that ganglion cells can distinctly differ in whether they act linearly or nonlinearly (Enroth-Cugell and Robson, 1966), there are only few examples of quantitative assessments of the relevant nonlinearities. This calls for new efforts and approaches to take nonlinear signal integration explicitly into account in both experimental and modeling studies. Here, we discuss some emergent ideas regarding the computational roles, the functional forms, and the experimental assessment of nonlinearities in the receptive fields of retinal ganglion cells.

2. Signal convergence and integration in the retina

Ganglion cells receive their excitatory input from bipolar cells, which in turn are driven by photoreceptors. This structure leads to a high degree of signal convergence onto single ganglion cells (Hartline, 1940b; Barlow, 1953), leading to the pooling of signals

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from more than a hundred bipolar cells by some ganglion cells (Freed and Sterling, 1988). Bipolar cells of the same type are organized in fairly regular spatial patterns (Lin and Masland, 2005; Wässle et al., 2009), and their dendritic trees – and correspondingly their receptive fields – are typically much smaller than that of the postsynaptic ganglion cell.

Bipolar cells, in turn, collect inputs in a similar fashion from typically several photoreceptors (Freed et al., 1987; Tsukamoto et al., 2001). This stage therefore provides another important site of stimulus integration. Both sites of spatial signal integration – from photoreceptors to bipolar cells and from bipolar cells to ganglion cells – are modulated by inhibitory interactions, mediated by horizontal cells and amacrine cells, respectively. These add lateral interactions over space and thereby directly influence spatial integration. But they also act locally by modulating or antagonizing the feed-forward excitation of individual bipolar cells and thereby influence which local signals are integrated by ganglion cells.

How ganglion cells integrate signals over their receptive fields is a question nearly as old as the history of recording electrical signals from the retina (Adrian and Matthews, 1927a; Hartline, 1940b). Early investigations of optic nerve responses in the eel (Adrian and Matthews, 1927b, a) and of signals from individual cells in frog retina (Hartline, 1940a; Barlow, 1953) already asked whether the retina could make use of pooling signals over space. Indeed, it was found that stimulating larger areas reduced the required stimulus intensity for producing a certain optic nerve response or for triggering spikes by an individual ganglion cell. In these early investigations, this spatial integration was assumed to occur in an approximately linear fashion, at least for small enough stimulation areas; yet high-precision measurements of stimulus integration were still lacking.

3. Linear X cells and nonlinear Y cells

That both linear and nonlinear spatial integration occur in the retina was later shown by the seminal work of Enroth-Cugell and Robson (1966) who categorized ganglion cells in the cat retina as either X cells or Y cells, depending on their response characteristics under stimulation with reversing gratings. While X cells and Y cells have first been characterized in the cat retina and their distinction appears particularly pronounced in this species, the classification has also been extended to various other species, such as guinea pig (Demb et al., 1999; Zaghloul et al., 2007), rabbit (Caldwell and Daw, 1978; Hamasaki et al., 1979; Famiglietti, 2004), and monkey (de Monasterio, 1978; Petrusca et al., 2007; Crook et al., 2008). Using examples recorded in mouse retina, Fig. 1 exemplifies the experimental distinction between linear and nonlinear ganglion cells based on stimulation with reversing gratings.

This classical approach for analyzing spatial integration works as follows. A spatial grating – sinusoidal or square-wave – is shown to the retina and periodically reversed in polarity (or alternatively turned on and off), for example once every half second. The spiking responses of a measured ganglion cell are then analyzed according to whether there is an increase in firing rate to either of the grating reversals or to both. This measurement is then repeated for different spatial phases of the grating, that is, for different locations of the bright and dark regions. For a linearly integrating X cell (Fig. 1A), one finds that, for each grating position, only one of the two reversal directions positively activates the cell, namely the reversal direction that increases the preferred contrast within the receptive field – positive contrast for On cells and negative contrast for Off cells. The other reversal direction rather suppresses the cell's firing below the baseline level. Furthermore, one can typically identify grating positions that balance both contrasts over the receptive field so that neither of the two reversals substantially excites the cell.

By contrast, the responses of nonlinearly integrating Y cells (Fig. 1B) are characterized by positive responses for both directions of the grating reversals for several grating positions, in particular when positive and negative contrast are balanced over the receptive field. These response characteristics cannot be explained by a model with linear integration of light signals over space. More formally, the distinction between linear X cells and nonlinear Y cells is often based on computing the amplitudes of the first and the second harmonic of the firing rate in response to the periodic grating reversals (Hochstein and Shapley, 1976). X cell responses are dominated by the first harmonic (Fig. 1C), whereas the fact that Y cells can respond to both grating reversals leads to frequency doubling and an often dominant second harmonic in the firing rate profile (Fig. 1D).

Note that the linear spatial integration in X cells does not imply that these cells respond to the two opposite grating reversals with firing rate profiles that are equal in magnitude with opposite signs, as would be expected for a completely linear system. In fact, retinal ganglion cells, like most other neurons in the nervous system, display a nonlinear dependence of the firing rate on stimulus strength simply because the spiking itself is subject to a threshold and potentially saturation. Thus, positive responses upon grating reversals are typically more pronounced than the amount of suppression observed for the opposing reversal. This can be viewed as a nonlinear transformation of the integrated activation signal. This nonlinearity, however, does not affect how signals are integrated over space prior to this output transformation. We will return to this distinction between different nonlinear stages in the stimulus–response relation of ganglion cells below.

The separation between X cells and Y cells does not always appear clear-cut and may in some systems rather represent the extremes of a continuum with different degrees of nonlinear integration, as reported, for example, for mouse retina (Carcieri et al., 2003). Moreover, the fact that anatomical investigations typically distinguish around ten to twenty different types of ganglion cells (Masland, 2001; Rockhill et al., 2002; Dacey, 2004; Kong et al., 2005; Coombs et al., 2006; Field and Chichilnisky, 2007; Masland, 2012) suggests that the classification of X and Y cells represents only a coarse categorization, which might allow further division into subtypes, for example, by refined measurements of the spatial integration characteristics.

The finding of nonlinearly integrating ganglion cells has led to the development of subfield models, which describe the receptive field structure of Y cells as composed of spatial subfields whose signals are nonlinearly combined (Fig. 2). These model efforts were initiated by measurements of Y cell responses to sinusoidal temporal modulations of different spatial patterns (Hochstein and Shapley, 1976). In particular, stimuli that superimposed several sinusoidal modulations were successfully applied to tease apart different filtering stages and to characterize the nonlinear transformations in Y cells (Victor et al., 1977; Victor and Shapley, 1980). This led to the description of Y cells by a so-called sandwich model, in which a nonlinear transformation occurs between two linear filtering stages (Victor and Shapley, 1979). A detailed analysis of the model components showed that the filters of the first stage had center–surround characteristics and that the subsequent nonlinear transformations occurred in a spatially local fashion. This suggested that bipolar cells form these filter elements and that their signals undergo a nonlinear transformation, which was found to have a rectifying nature (Victor and Shapley, 1979; Enroth-Cugell and Freeman, 1987). Until today, nonlinear pooling of subfield signals has remained the prime framework for modeling spatial nonlinearities in ganglion cells, and there is good evidence now that the subfields indeed correspond to the receptive fields of presynaptic bipolar cells (Demb et al., 1999).