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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).

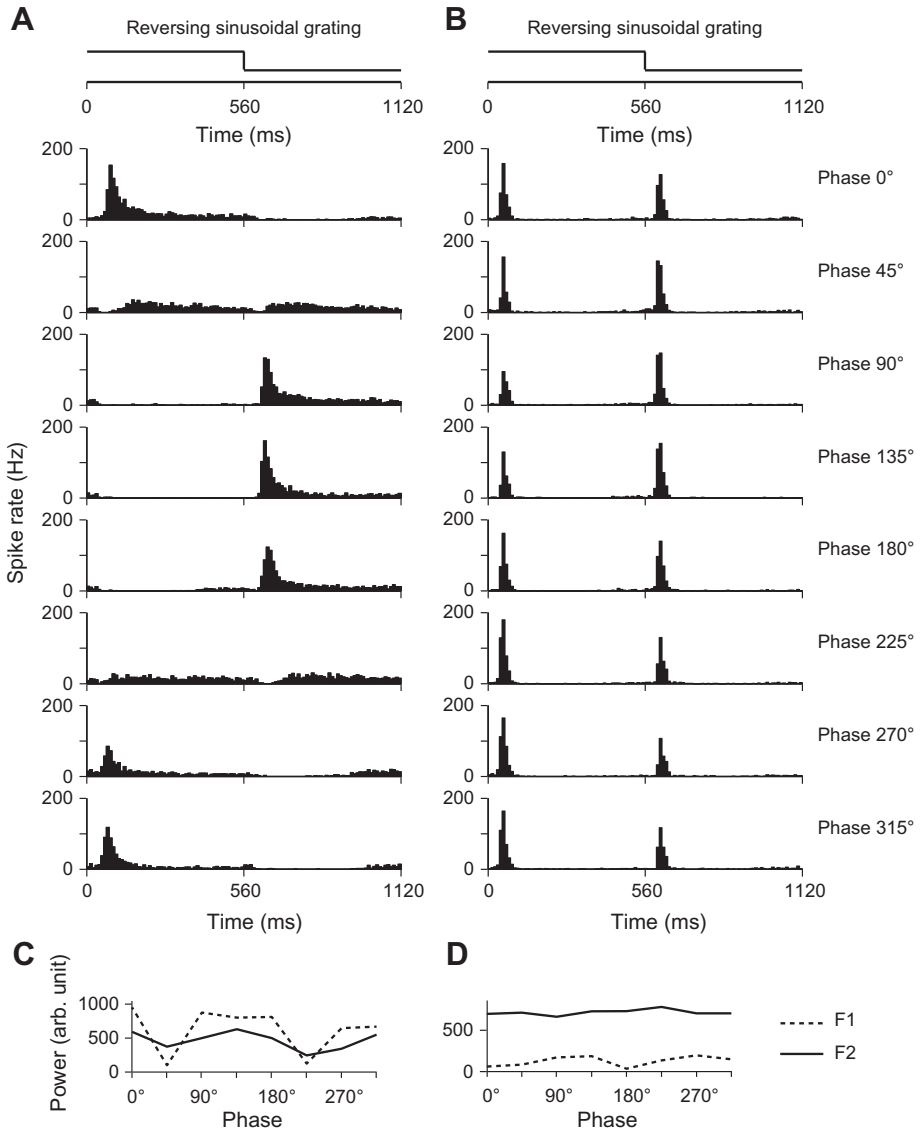

Fig. 1. Responses of an X cell and a Y cell in mouse retina to reversing gratings. (A) Firing rate profiles of an X cell recorded extracellularly with a multi-electrode array from isolated mouse retina under stimulation with reversing gratings at different spatial phases. The cell never responds to both reversal directions and shows grating phases without any substantial response. This indicates linear spatial integration. (B) Same as (A), but for a Y cell. The fact that the cell always responds well to both grating reversals indicates nonlinear spatial integration. (C) First and second Fourier components of the response profiles of the X cell. Except for the spatial phases where the cell does not respond to the grating reversals, the responses are dominated by the fundamental frequency F_1, again confirming that this cell is a linearly integrating X cell. (D) First and second Fourier component of the response profile of the Y cell. The responses are dominated by the second Fourier component F_2, confirming that this cell is a nonlinearly integrating Y cell.

4. Spatial integration in linear–nonlinear cascade models

As an alternative to these characterizations of ganglion cell responses with grating stimuli and sinusoidal temporal modulations, investigations based on white-noise stimulation and analyses with linear–nonlinear (LN) cascade models (Hunter and Korenberg, 1986; Sakai, 1992; Meister and Berry, 1999; Chichilnisky, 2001; Paninski, 2003) have garnered much popularity and advanced the understanding of retinal signal processing. In this approach, the stimulus–response relation of retinal ganglion cells is phenomenologically described by a sequence of a linear stimulus filter and a subsequent nonlinear transformation of the filter output. The result of this LN model is interpreted as the firing rate or as the probability of spike generation. The input to the LN model can be a purely temporal sequence of light intensities, a spatio-temporal stimulus with spatial structure as well as temporal dynamics, or also include other stimulus dimensions, such as chromatic components. In each case, the linear filter provides information about which subset of stimulus components is relevant for activating the cell. The filter is thus related to the cell's temporal, spatial, or spatio-temporal receptive field. The nonlinear transformation describes how the activation of the receptive field is translated into neuronal activity and thus measures the neuron's overall sensitivity and captures its response threshold, gain, and potential saturation.

The particular appeal of this model stems from the relative ease with which the model components can be obtained in physiological experiments. The linear filter, for example, is readily obtained as the spike-triggered average in response to white-noise stimulation (Chichilnisky, 2001; Paninski, 2003; Schwartz et al., 2006), and the nonlinear transformation can subsequently be found by determining how the linear filter predictions relate to the actual observed firing rate (Chichilnisky, 2001; Schwartz et al., 2006). In this way, the LN model has found a large number of applications,

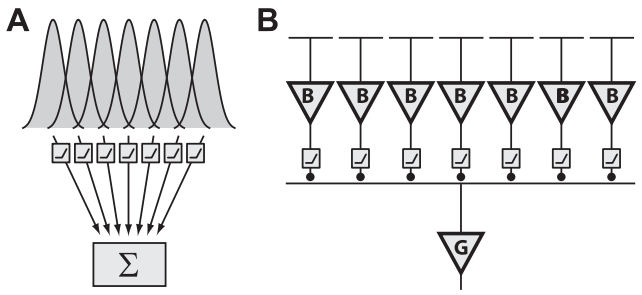

Fig. 2. Schematic depictions of subfield models to account for nonlinear spatial integration by ganglion cells. (A) Simplified version of a classical phenomenological subfield model (Victor and Shapley, 1979). Subfields are represented by overlapping Gaussian curves, which represent a weighted linear summation of light signals within each subfield. The subfield signals then undergo a nonlinear transformation, here half-wave rectification, before summation. Note that the original subfield model also contains a linear component of the receptive field, modeled by an additional, wider Gaussian curve, as well as a component to account for surround suppression. (B) Subfield model depiction based on simplified retinal circuitry. The subfields correspond to the receptive fields of bipolar cells B, which tile the receptive field of the ganglion cell G. The bipolar cells are thought to integrate light patterns linearly, but their signals undergo a nonlinear transformation, here again half-wave rectification, before pooling by the ganglion cell. Note that other retinal cell types, in particular amacrine cells, are not considered for simplicity.

including assessments of spatial and temporal receptive field properties (Field and Chichilnisky, 2007), classification of different ganglion cell types (Segev et al., 2006; Field and Chichilnisky, 2007; Farrow and Masland, 2011; Marre et al., 2012), and characterization of contrast adaptation (Kim and Rieke, 2001; Baccus and Meister, 2002; Zaghloul et al., 2005). For more complex stimuli, including natural images and movies, more elaborate techniques exist for matching LN models to data, based on information theory or maximum-likelihood methods (Paninski, 2003, 2004; Sharpee et al., 2004; Pillow and Simoncelli, 2006). Furthermore, the basic form of the LN model has further been extended by including explicit spike generation dynamics together with feedback effects of the cell's own spiking activity (Keat et al., 2001; Pillow et al., 2005) as well as interactions between nearby ganglion cells (Pillow et al., 2008). These models have been shown to often provide reasonable predictions of a ganglion cell's spiking responses, at least under the particular type of white-noise stimulation used for obtaining the model parameters. The spatio-temporal version of the LN model has even been shown to be a promising starting point for improving the activity patterns of ganglion cells in prosthetic approaches (Nirenberg and Pandarinath, 2012). Yet, in all these versions of the LN model, it is the linear filter stage that accounts for stimulus integration. Thus, stimulus integration is implicitly assumed to be linear under these approaches.

This leads one to ask how well the LN model actually works as a framework for capturing the spatio-temporal response properties of ganglion cells, in particular for cells that show nonlinear spatial integration. First, it is important to note that the linear spatio-temporal filter obtained by a spike-triggered-average analysis typically provides accurate information about the receptive field shape even though nonlinearities within the receptive field are not accounted for by the LN model. Beyond characterizing the receptive field, however, the question arises how well the obtained LN model can be used for predicting the spiking response of a ganglion cell. The general lore appears to be that LN models can yield reasonable predictions when probed with the same type of spatially coarse, temporally broad-band noise stimuli as used for fitting the model, whereas accurate predictions of responses to natural stimuli have remained elusive (Schwartz and Rieke, 2011).

One reason for this may lie in the fact that natural stimuli contain spatial correlations in the stimulus (Ruderman and Bialek, 1994) as well as abrupt transitions, owing to the presence of objects and their boundaries. Across an object boundary, for example, one half of a receptive field may receive strong positive activation while the other experiences strong negative activation. In this case, a putative nonlinear thresholding of input signals would lead to a strong spiking response, following the positively activated inputs, whereas linear integration might result in complete cancelation of positive and negative activation and thus no spikes. Such stimulus patterns therefore emphasize the difference between linear and nonlinear spatial integration.

For Gaussian white-noise stimulation, on the other hand, these types of patterns are rare. Rather, individual spatial stimulus components are activated independently of each other, and at any point in time, most components will be only weakly activated. Thus, differences between models of linear and nonlinear stimulus integration tend to be smaller and less systematic than under the strong spatial structure of natural scenes, and spatio-temporal LN models may provide reasonable predictions of ganglion cell responses under white-noise stimulation, even without nonlinear substructure of the receptive fields, at least when the spatial stimulus structure is coarse enough so that individual stimulus components can provide sufficient drive to trigger the ganglion cells. Future investigations should make these considerations more quantitative. In fact, a better understanding of spatial processing by retinal ganglion cells should emerge from systematically studying under what stimulus conditions spatio-temporal LN models work or fail in predicting responses, which stimulus patterns lead to systematic failures, and which types of nonlinear extensions can overcome such shortcomings.

Nonetheless, even pure Gaussian white-noise stimulation can be used to probe the linearity of stimulus integration by a simple extension of the spike-triggered-average analysis. While the spike-triggered average is restricted to providing a single linear filter, an analysis of the spike-triggered covariance (STC) matrix can result in several filters (Brenner et al., 2000; Paninski, 2003; Bialek and de Ruyter van Steveninck, 2005; Rust et al., 2005; Schwartz et al., 2006; Samengo and Gollisch, 2012). These form the basis of a multi-filter LN model, in which several parallel filters perform stimulus integration and feed their results into a multi-dimensional nonlinearity (Fig. 3A). If STC analysis results in a single filter only, stimulus integration under the applied stimulus conditions is mostly linear; if multiple filters are obtained, this indicates nonlinear effects of stimulus integration.

If stimuli are not Gaussian (or more specifically not spherically symmetric (Samengo and Gollisch, 2012)), for example if natural stimuli are applied, alternatives to STC analysis can be used for determining whether a single filter is sufficient or whether and which multiple filters are required for describing stimulus integration. These alternatives rely on information theory, maximum likelihood, or Bayesian inference (Paninski, 2003; Sharpee et al., 2004; Pillow and Simoncelli, 2006; Park and Pillow, 2011; Rajan et al., 2012). Note, though, that obtaining multiple filters in the STC analysis does not mean that a multi-filter LN model is the only or simplest way of extending the LN model to fit the data; a single-pathway multi-stage cascade model, such as the sandwich model discussed above or a nested LN model, corresponding to an LNLN cascade, could provide simple alternatives, underscoring the need to consider different model structures and analytical approaches.

A typical example of STC analysis for a salamander retinal ganglion cell under stimulation with spatio-temporal white noise is shown in Fig. 3B–D, here using only one spatial dimension so that the stimulus consists of flickering stripes. The spike-triggered average (Fig. 3B) identifies the cell as an Off-type neuron. Spike-triggered covariance analysis, however, provides a more refined picture, yielding three spatio-temporal filters (Fig. 3C). These filters differ mostly in their pronounced spatial structure, revealing spatially antagonistic components even within the receptive field

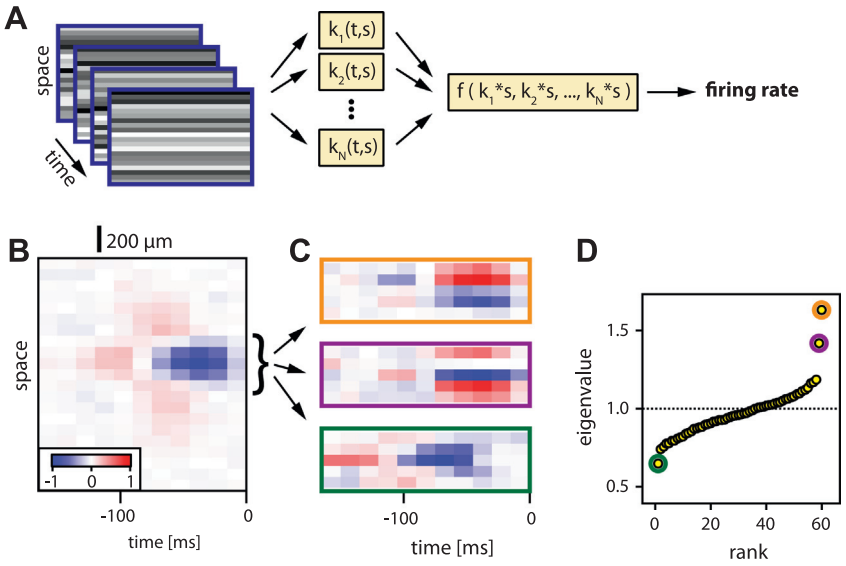

Fig. 3. Spike-triggered average and spike-triggered covariance analysis for a salamander retinal ganglion cell under spatio-temporal stimulation. (A) Structure of the LN model. The stimulus (left) is spatio-temporal flicker of stripe patterns, where the light intensity of each stripe for each frame is drawn independently from a Gaussian distribution. The model assumes that the stimulus is filtered by a set of N parallel spatio-temporal filters k_i. In the case of spike-triggered-average analysis, only a single filter is considered. The outputs of all filters, indicated by the convolutions $k_i * s$ of the filters with the stimulus s, are fed into a multi-dimensional nonlinearity f, whose output yields the time-dependent firing rate of the model. (B) Spatio-temporal spike-triggered average of an Off-type salamander retinal ganglion cell measured with flickering stripes. (C) Three filters extracted from a spike-triggered covariance analysis for the same cell. To reduce the dimensionality of stimulus space for this analysis, only the central five stripes that span the receptive field center of the cell were analyzed. The filters show distinct spatial structure, containing regions with opposite signs. By contrast, along the temporal dimension, the filters largely retain the homogeneous structure of the spike-triggered average. This indicates that the receptive field of this cell is strongly affected by nonlinear operations. (D) Eigenvalue spectrum of the spike-triggered covariance analysis of this cell. The three filters of (C) are obtained by an eigenvalue analysis of the spike-triggered covariance matrix as those eigenvectors that correspond to eigenvalues that deviate from the continuous spectrum of the remaining eigenvalues. The three relevant eigenvalues are marked by colored circles, matching the colors of the frames of the corresponding filters in (C).

center. This analysis thus indicates that nonlinear spatial integration plays a major role for determining the spike response in this type of ganglion cell.

However, determining the nature of these nonlinearities is typically difficult, at least when more than two filters are found to be relevant, because large amounts of data are required and because nonlinearities of stimulus integration have to be separated from the output nonlinearity of spike generation. Yet, STC analysis can provide a useful starting point for further investigations of nonlinear stimulus integration. An interesting case where STC analysis has provided the basis for detailed investigations of input integration by retinal ganglion cells concerns On–Off ganglion cells, which are characterized by their responses to both increases and decreases in light intensity. For these cells, it has been shown that the stimulus sequences that triggered spikes can form two clusters in stimulus space, according to whether On-type or Off-type stimulation was primarily responsible for eliciting a given spike (Fairhall et al., 2006; Geffen et al., 2007; Gollisch and Meister, 2008a). Analogously, interesting future extensions of STC analysis might aim at identifying actual physiological pathways underlying nonlinear spatial integration, for example corresponding to individual bipolar cells.

The LN model provides a particularly compact description of ganglion cell responses, with easy-to-obtain parameters, capturing many features of retinal processing. Yet, when a closer correspondence with the elements of retinal anatomy is desired, other modeling frameworks are likely more appropriate. Given that bipolar cell input into Y cells already corresponds to an LN model (Victor and Shapley, 1979), a sandwich model, corresponding to an LNL cascade, may be a suitable alternative, which can be further expanded to an LNLN cascade in order to capture effects of the ganglion cell's own output nonlinearity. More generally, including further details of the retinal circuitry may be desirable, depending on the demands of the research question (Herz et al., 2006), such as synaptic dynamics (Jarsky et al., 2011; Ozuysal and Baccus, 2012), gain control (Shapley and Victor, 1981; Berry et al., 1999; Wohrer and Kornprobst, 2009), neuronal morphology (Brown et al., 2000; Schwartz et al., 2012), or explicit inhibitory interactions (Thiel et al., 2006; Baccus et al., 2008). In fact, it has recently been shown that by combining nonlinear signal transmission with anatomical information about the locations of presynaptic inputs from bipolar cells onto the dendritic tree of mouse On alpha cells, responses of these cells to a diverse set of visual stimuli can be successfully predicted (Schwartz et al., 2012).

5. Circuit mechanisms for spatial signal integration

The primary site within the retinal circuitry for nonlinear spatial integration appears to be in the retina's inner plexiform layer where bipolar cells transmit their signals to their postsynaptic partners, ganglion cells and amacrine cells. The nonlinear effects are likely to arise in the synaptic transmission at the bipolar terminals (Baccus et al., 2008; Molnar et al., 2009; Werblin, 2010), which more easily increase their release of neurotransmitter than decrease it from baseline. In addition, recent findings have indicated that bipolar cell terminals may even produce spiking activity (Baden et al., 2011; Dreosti et al., 2011) and thereby further enhance the nonlinearity of signal transmission. Furthermore, voltage signals within the bipolar cells already display nonlinear effects in the form of saturation at high enough contrast levels (Burkhardt et al., 1998).

Prior to bipolar cell signaling, however, the retina appears to process light stimuli largely in a linear fashion, at least over some relevant contrast range. Photoreceptors respond to light largely in a linear fashion (Baylor et al., 1974), and the ribbon synapses between photoreceptors and bipolar cells are particularly suited for linear signal transmission, as they can sustain high baseline

release rates and respond to gradual changes in membrane potential via a linear relationship between internal calcium concentration and transmitter release (Witkovsky et al., 1997; Thoreson et al., 2003). Correspondingly, several measurements in horizontal cells (Tranchina et al., 1981) and bipolar cells have found support for a linear representation of light signals at this level. Light responses in bipolar cells, for example, can be well captured by linear filter models in the catfish retina (Sakai and Naka, 1987) as well as in the salamander retina (Rieke, 2001; Baccus and Meister, 2002), consistent with the approximately linear current–voltage relation in isolated bipolar cells in the salamander (Mao et al., 1998).

One exception to this rule of linear signal transmission to bipolar cells, however, has been found in the processing at low light levels, with important functional consequences. In the mouse retina, the synapses between rods and rod bipolar cells threshold the signal, with the effect that much of the noise is cut off so that despite a certain accompanying loss in the signal, detection of single photon events occurs with nearly optimal signal-to-noise ratio (Field and Rieke, 2002; Berntson et al., 2004; Sampath and Rieke, 2004). As in the examples of nonlinear integration by ganglion cells, nonlinear integration of photoreceptor signals by rod bipolar cells is essential for this function; the nonlinearity discards unreliable information and selects signals that provide the best evidence for the relevant signal to be detected, here simply the occurrence of a photon.

6. Functional roles of nonlinear spatial integration

Several recent findings of particular ganglion cell types whose activity patterns encode specific relevant visual features have demonstrated the connection of nonlinear spatial integration to neural computation. It is the nonlinear nature of signal processing that endows the investigated cell types with their computational characteristics, making them selective to certain stimulus features while discarding information about others (Gollisch and Meister, 2010; da Silveira and Roska, 2011).

One of the best studied examples are object-motion-sensitive ganglion cells, first observed in salamander and rabbit retina (Ölveczky et al., 2003). These cells respond strongly to local motion signals over their receptive fields, such as a jittering texture patch, but are strongly suppressed when the motion signal is global, that is when the receptive field periphery experiences the same motion trajectory as the center. Further studies of the adaptation characteristics of these cells (Ölveczky et al., 2007) and of the responses of other cell types in the relevant neural circuit (Baccus et al., 2008) have provided a thorough understanding about the neural circuit that underlies this complex feature extraction. First, in response to motion over their receptive field centers, these cells receive sparse, temporally precise excitatory events, owing to the fact that the presynaptic bipolar cells strongly threshold the transmitted signals. These events are locked to the trajectory of the motion signal in the receptive field center. Second, wide-field amacrine cells in the receptive field periphery detect motion through a presynaptic circuit equivalent to the one in the receptive field center of the ganglion cell. Thereby, these amacrine cells provide precisely timed inhibitory signals to the ganglion cell, which are locked to the motion trajectory in the periphery and which therefore cancel the excitatory signals if the trajectories in the center and in the periphery coincide. The nonlinear thresholding inherent to the bipolar cell signals is essential for this function. First, it makes the ganglion cell sensitive to motion signals while providing invariance to the detailed spatial pattern that moves. Second, the high threshold selects strong signals to provide a sparse representation of the motion trajectory, allowing a robust distinction between whether these signals coincide in the center and in the periphery or not.

A type of ganglion cell with similar function and circuitry has recently been discovered in mouse retina. These so-called W3 ganglion cells are sensitive to small moving objects in front of a still background (Zhang et al., 2012). Excitatory input is provided by both On-type and Off-type bipolar cells in the receptive field, each after undergoing a half-wave rectifying nonlinear transformation. This convergence of On-type and Off-type signals makes the cells sensitive to any change in the receptive field. Similar to the object-motion-sensitive cells discussed above, this excitation is opposed by an inhibitory circuit that detects signals in the periphery in a way analogous to the operation of the center circuit. Thus, any peripheral or global signals will suppress the ganglion cell; only a small, locally restricted visual input leads to activation – and may trigger an escape reaction to a potential approaching threat (Zhang et al., 2012). Again, the nonlinearities associated with the pooling of signals over space represent a critical feature; they let the cells become sensitive to small stimuli of the size of bipolar cell receptive fields while avoiding cancelation by negative activation at other locations.

On-type and Off-type bipolar cell signals also converge in the receptive field center of another type of ganglion cell, found in the salamander retina (Gollisch and Meister, 2008b). Again, these excitatory signals undergo half-wave rectification so that any local change of the visual signal within the receptive field center can contribute to driving the ganglion cell. A crucial feature of these cells, however, is a relative delay of the On-type inputs by about 30–40 ms compared to the Off-type signals. This provides the cells' spiking responses with a characteristic temporal structure; the latency of the first spike after the occurrence of a new visual scene encodes the relative contributions of darkening and brightening within the receptive field and thus provides a rapid information channel about spatial structure in the scene.

Functionally similar to the W3 cell discussed above, but based on a different circuit, an Off-type ganglion cell found in mouse retina has been associated with the detection of approaching objects, representing potential threats. These cells respond strongly to an increase in size of a dark object, even when combined with an overall brightening of the scene, whereas laterally moving or receding objects do not activate these cells (Münch et al., 2009). Again, a nonlinear circuit has been proposed to underlie this specific motion detection. Both local excitation and local inhibition are transmitted nonlinearly to these Off-type ganglion cells. According to this model, activation by slow changes in light level is suppressed by the nonlinear transmission and thereby hardly influences the cell's activity. Advancing Off-type edges, as occur for an expanding dark object, on the other hand, provide strong excitation. This excitation drives the cell's spiking activity, unless opposed by inhibition that is triggered by advancing On-type edges, which occur behind a dark object during translational movement, but which are absent during mere expansion of the object.

The examples discussed so far all use some version of half-wave rectification at the synapse between bipolar cells and their postsynaptic partners to explain their functional characteristics. Recently, however, it has been shown that different types of nonlinear spatial integration can be observed in different ganglion cells in the salamander retina and can be associated with different functional roles (Bölinger and Gollisch, 2012). The majority of measured ganglion cells in this study indicated that inputs from bipolar cells were transformed by a threshold-quadratic nonlinearity. For the remaining third of cells, inhibitory signals from amacrine cells added further nonlinear integration characteristics, which occurred in a dynamic way during the response to a new stimulus. These inhibitory signals act as a local gain control, leading to a

particular sensitivity of these cells to spatially homogeneous stimuli. Functionally, the former type of spatial integration leads to good detection of small, high-contrast objects, whereas the latter type favors detection of larger objects, even at low contrast (Bölinger and Gollisch, 2012). The distinction of these different types of spatial stimulus integration was possible by a new experimental approach, based on identifying iso-response stimuli in closed-loop experiments. This technique can provide new insights into stimulus integration by aiming at a quantitative assessment of the nonlinearities involved and will thus be further discussed in the following.

7. Iso-response measurements: A new tool for studying stimulus integration

Computational models that are based on nonlinear stimulus integration have been successfully used to account for the response characteristics of the various functional ganglion cell types discussed above. However, the particular form of the nonlinearity often remained an assumption of the model, typically in the form of half-wave rectification, which sets negative signals to zero and transmits positive signals in a linear fashion. Yet, the importance of these nonlinear structures for retinal function raises the question how to test their characteristics more directly.

In some cases, it has been possible to parameterize the nonlinearity of the bipolar cell signals and optimize the shape so that ganglion cell responses best be captured (Victor and Shapley, 1979; Victor, 1988; Baccus et al., 2008; Gollisch and Meister, 2008a). This has corroborated the thresholding effect of the nonlinearity and, at least for some cells, suggested that, beyond the threshold, the nonlinearity may rather be expansive, such as quadratic or exponential (Gollisch and Meister, 2008a).

Recently, a different approach has been used to more directly measure the nonlinearities associated with spatial integration in the retina (Bölinger and Gollisch, 2012). The challenge for these measurements lies in disentangling the different stages of nonlinearities, namely those that are involved with spatial integration from those that subsequently transform the ganglion cell response, for example, by enforcing a spiking threshold. A solution to this problem has been suggested in the form of iso-response measurements, which aim at identifying different stimulus combinations that lead to the same, predefined neural response (Gollisch et al., 2002; Gollisch and Herz, 2005). The idea behind this approach is that these stimulus combinations are all affected in the same way by the ganglion cell's intrinsic nonlinearity. Thus, nonlinearities involved in integrating these stimulus components are revealed by analyzing which combinations of stimulus components reach the predefined response. To search for such stimulus combinations in electrophysiological experiments, closed-loop experiments provide the necessary efficiency by using measured responses to determine future stimulus patterns (Benda et al., 2007).

How this approach works is best illustrated best by model examples. Fig. 4 shows two models with two inputs each. The inputs are either linearly integrated (Fig. 4A) or summed after transformation by a threshold-quadratic function (Fig. 4B). In a final step, a sigmoidal output nonlinearity is applied, which mimics thresholding and saturation in spike generation. While the overall response surfaces are dominated by the sigmoidal shape of the output nonlinearity, it is the contour lines, displayed underneath the surface plots, that distinguish the models and give a clear signature of the linear and of the threshold-quadratic integration, respectively (Bölinger and Gollisch, 2012).

This can be applied to the question of spatial integration in retinal ganglion cells by finding a cell's receptive field, subdividing it into distinct stimulus components, and searching for such combinations that give the same response, for example a certain spike count or first-spike latency when the stimulus combination is briefly flashed. Fig. 4 shows such iso-response measurements for two sample ganglion cells from salamander retina. The first (Fig. 4C) is representative of the majority of cells recorded in this species; for both spike count and first-spike latency, the iso-response stimuli lie on curves that resemble those of the threshold-quadratic integration model of Fig. 4B, indicating the presence of such a nonlinearity in the receptive fields of these cells.

However, for the second example (Fig. 4D), representative of about a third of the recorded ganglion cells, the iso-response curves for spike count and first-spike latency differed, and the former displayed a characteristic notch along the direction where both stimulus components experienced the same negative contrast. This means that these cells feature a particular sensitivity for homogeneous stimulation of their receptive fields, but only when considering the spike count. Apparently, this characteristic sensitivity is not yet present when the very first spike is generated and rather develops over the course of the response in a dynamic fashion. Further experiments showed that it relies on inhibitory signaling in the retinal circuit (Bölinger and Gollisch, 2012). This also explains why the first-spike latency is not affected, as the inhibition needs an additional synaptic stage via an amacrine cell and is thus delayed compared to direct excitation (Werblin and Dowling, 1969; Roska et al., 2006; Cafaro and Rieke, 2010). Spatial stimulus integration in these ganglion cells is thus a dynamic process, which endows these cells with particular sensitivity to detect large objects, even at low contrast, as already discussed above.

The finding of two different types of nonlinear spatial integration underscores the importance of quantitatively investigating stimulus integration rather than only assessing whether or not integration occurs in a linear fashion. The results also exemplify the power of the iso-response method for this task, as it allows separating spatial integration from subsequent cell-intrinsic nonlinearities. In the same way, the iso-response method had previously been used to elucidate spectral and temporal integration in insect auditory receptor cells (Gollisch et al., 2002; Gollisch and Herz, 2005) and has recently also been applied to understanding how neurons in primate visual cortex represent color information (Horwitz and Hass, 2012). Application of the iso-response method is most useful for directly testing the integration of few stimulus components. In the above example, the stimulus consisted of the contrast values in just two spatial regions; other examples have applied iso-response measurements with three stimulus components (Gollisch et al., 2002; Horwitz and Hass, 2012). Beyond three stimulus components, both the high-dimensional search and the visual display of the results will become increasingly tricky. The strength of the iso-response method clearly rather lies in the fact that it can be applied with a limited, selected set of stimulus components to obtain details of their integration.

In the example of Fig. 4, the selected stimulus components were relatively large parts of the receptive field center, thereby each combining the contributions of several presynaptic bipolar cells. The generality of the results can then be tested by measuring iso-response curves with different layouts of the two spatial stimulus components, for example, by using smaller parts of the receptive field, down to the size of individual bipolar cell receptive fields, or by spatially interleaving the components (Bölinger and Gollisch, 2012). Together, these investigations can aid the development of a full spatial integration model of how a retinal ganglion cell pools over tens or hundreds of parallel input channels. For example, the spatial scale at which nonlinear phenomena occur – given, for example, by the spatial separation of two small stimulus components or by the size of spatially interleaved components –

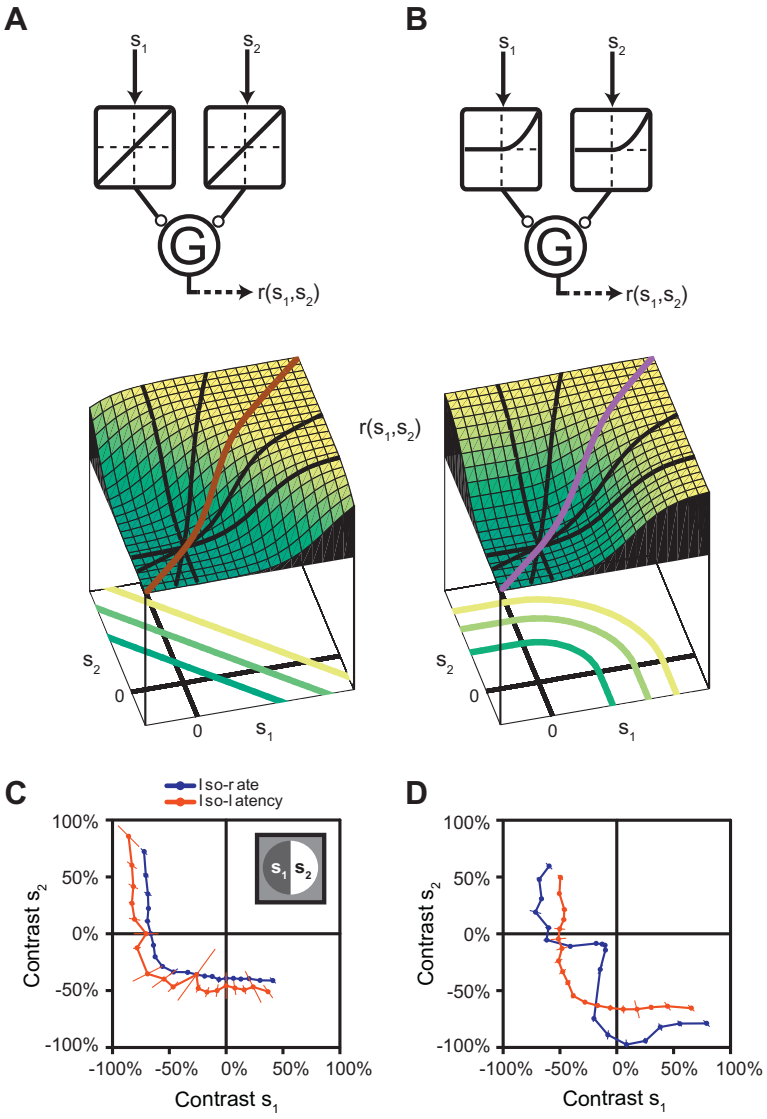

Fig. 4. Illustration of the iso-response method for assessing spatial nonlinearities in retinal ganglion cells. (A) Responses of a simple model that takes two inputs s_1 and s_2, combines them linearly by a ganglion cell G, and finally applies a sigmoidal output nonlinearity. The response surface, which displays the model response for different combinations of inputs s_1 and s_2, is dominated by the sigmoidal structure of the output nonlinearity. The iso-response curves shown underneath, however, are straight lines, thus providing a signature of the linear stimulus integration in this model. (B) Same as (A), but for a model with a threshold-quadratic nonlinear transformation of the inputs before pooling by the ganglion cell G. Again, the response surface is dominated by the sigmoidal output nonlinearity, but the iso-response curves shown underneath provide a signature of the threshold-quadratic nonlinearity that affects stimulus integration. (C) Sample iso-response curves for a salamander retinal ganglion cell, measured for both spike count (blue) and first-spike latency (red). The inset shows the stimulus layout; the approximately circular receptive field center was divided into two halves, which were stimulated with contrast values s_1 and s_2, respectively. These stimuli were flashed for 500 ms with different combinations of s_1 and s_2. Both curves are similar to the iso-response curves shown in (B) and thus indicate a threshold-quadratic signal transformation. (D) Same as (C), but for a different salamander retinal ganglion cell with a distinct shape of the iso-rate curve. This curve shows a characteristic notch along the lower-left diagonal, indicating that spatial integration is modified in such a way that the receptive field becomes particularly sensitive to homogeneous stimulation. Reprinted from (Bölinger and Gollisch, 2012), Copyright (2012), with permission from Elsevier.

can be used to distinguish between contributions from photoreceptors and bipolar cells (Bölinger and Gollisch, 2012). Yet, identifying actual individual channels, such as the locations and receptive fields of individual presynaptic bipolar cells, will have to rely on other methods, such as anatomical assessments (Schwartz et al., 2012) or spike-triggered-covariance (STC) analysis as discussed above.

STC analysis is designed for identifying stimulus components that undergo nonlinear integration. To further analyze how the identified stimulus features are integrated, one can calculate iso-response curves within subspaces spanned by two or three relevant stimulus features (Rust et al., 2005). Again, the iso-response approach here allows separating nonlinearities of stimulus integration from the output nonlinearity. Note, though, that this *a posteriori* calculation of iso-response curves may be less efficient than in the closed-loop approach. Furthermore, STC analysis may yield a large number of relevant stimulus features, and all features that are not directly considered in a particular subspace analysis effectively act as noise sources. In such cases, it may help to make use of the complementary nature of these two approaches by first identifying relevant stimulus components through STC analysis and subsequently studying their integration characteristics through designated iso-response measurements.

8. Discussion and future challenges

The anatomical diversity of retinal ganglion cells presents an important challenge for understanding visual processing and the function of the retinal network. This has been particularly puzzling

in light of the uniform description of ganglion cells in terms of their center-surround receptive field structure. As seen above, several recent studies have now provided new insight into this conundrum by showing that different types of ganglion cells obtain different functional attributes by how they integrate visual information over their receptive fields, both center and surround. At the heart of these processing schemes lie nonlinear signal transformations that shape incoming signals before pooling by the ganglion cell. Distinguishing between linear and nonlinear spatial integration has long been recognized as an important feature for characterizing cell types, but only recently has nonlinear spatial integration emerged as a critical factor for providing different ganglion cell types with their functional characteristics. This suggests that in the quest for a functional separation of different ganglion cells that matches the anatomical diversity, the quantitative features of the nonlinearities involved in spatial integration might be an important factor.

Thus, new methods are needed to assess what kinds of nonlinear operations are at work. One approach has been to use parameterized models of ganglion cell stimulus–response functions and find the nonlinear transformation from the set of parameters that maximizes how the model output fits to measured responses (Victor and Shapley, 1979; Victor, 1988; Baccus et al., 2008; Gollisch and Meister, 2008a). This approach works well when a good understanding of the basic model structure already exists and when sufficient data can be obtained to extract the potentially large number of parameters in the model. Yet, this approach can naturally only capture such nonlinear operations within the scope of the parameterization, and complex models with many parameters may be difficult to handle computationally and prohibit reliable extraction of the optimal parameter sets. Thus, limitations in data availability and computational tools may restrict the nonlinear transformations to those that can be described with only one or few parameters, such as a threshold and an exponent.

As discussed above, iso-response measurements represent an alternative, as they provide a way to assess nonlinear stimulus integration without the need of an *a priori* parameterization of the nonlinearities (Bölinger and Gollisch, 2012). The strength of the method lies in the fact that the measured iso-response curves provide a characteristic signature of the type of stimulus integration and that this signature is independent of nonlinear transformations at the output stage of the system. Note, though, that the functional forms of the nonlinear transformations are not provided directly, but are inferred from analyzing the shape of the iso-response curves, for example by comparing or fitting to computational model predictions. Furthermore, in order to apply the technique efficiently, automated online analysis and closed-loop experimental designs have to be set up, which may make the method more demanding than, for example, reverse correlation analyses with white-noise stimulation.

Based on the iso-response method, it has been possible to distinguish between two fundamentally different types of nonlinear spatial integration (Bölinger and Gollisch, 2012), thus showing that the complexity of nonlinear transformations within the receptive field goes beyond the often assumed threshold-linear half-wave rectification. These findings furthermore suggest that not all nonlinearly integrating ganglion cells should be classified under the single label of Y cells; instead, there may be important functional divisions between nonlinear ganglion cells, potentially corresponding to different types of ganglion cells as determined by anatomy or molecular markers. A quantitative assessment of spatial nonlinearities could thus help provide a better physiological signature of different ganglion cell types and thereby facilitate classification schemes (Carcieri et al., 2003; Segev et al., 2006; Zeck and Masland, 2007; Farrow and Masland, 2011; Marre et al., 2012), in particular for extracellular recordings where the morphologies of the recorded neurons are not available.

Similarly relevant as the question how ganglion cells integrate visual signals over their receptive field centers is the question how they pool signals in their receptive field surrounds and how center signals and surround signals are combined. Evidence for nonlinear interactions between center and surround comes from the finding that the surround appears to act in a divisive fashion rather than in a linear, subtractive way (Merwine et al., 1995). Furthermore, it was observed that the effect of surround inhibition strongly differs for On-type and Off-type responses of On–Off ganglion cells in the frog retina, pointing towards further intricate receptive field structure (Barlow, 1953). As discussed above, stimulus integration in the surround is an important component for specific ganglion cell types, in particular object-motion-sensitive cells and W3 cells. More generally, it may be interesting to see whether stimulus integration in the surround allows similar classifications as for the linear or nonlinear integration over the receptive field center.

The models that have been used to describe nonlinear spatial integration in center and surround have been inspired by retinal anatomy, typically using bipolar cells as subunits, assumed to cover the receptive field of the ganglion cell in some regular fashion. Two recent methodological advances ought to provide opportunities to bring this substrate for nonlinear integration in closer alignment with the actual circuitry. First, large-scale reconstructions at the electron-microscope-level can provide circuit diagrams for individual cells after they have been physiologically characterized (Helmstaedter et al., 2008; Briggman et al., 2011; Denk et al., 2012). This may help relate the spatial sub-structure of receptive fields to actual circuit elements on a single-cell basis. Second, physiological mappings of receptive fields at very high spatial resolution have shown that it is possible to identify the locations and identities of individual cone photoreceptors that provided signals for a measured ganglion cell (Field et al., 2010). It is conceivable that this can lay the foundation for detailed assessments of nonlinear transformations in the transmission from cones to ganglion cells, for example, by measuring iso-response stimuli when activating pairs of individual cones.

The focus of this review has been on spatial integration. Yet, different nonlinear effects also occur in temporal integration by retinal ganglion cells. This has been demonstrated, for example, by the fact that STC analysis of retinal ganglion cell responses to temporal flicker of light intensity with spatially homogeneous stimuli generally yields more than a single relevant stimulus feature (Fairhall et al., 2006). As the relevant stimulus features are of a purely temporal nature and are combined in a nonlinear fashion (otherwise they would form a single feature), this indicates the presence of temporal nonlinearities. For On–Off ganglion cells, one contribution to these temporal nonlinearities comes from the nonlinear combination of On-type and Off-type inputs, which correspond to different temporal filters (Fairhall et al., 2006; Geffen et al., 2007; Gollisch and Meister, 2008a). More generally, temporal nonlinearities may likely arise from negative or positive feedback processes, capturing refractoriness, gain control, and intrinsic spike burst generation (Berry and Meister, 1998; Berry et al., 1999; Keat et al., 2001; Pillow et al., 2005; Fairhall et al., 2006). An interesting direction for future research will thus be to study how spatial and temporal nonlinearities have to be combined to arrive at an accurate model of spatio-temporal signal processing in retinal circuits.

Finally, a better understanding of spatial integration by retinal ganglion cells appears to be a prerequisite for capturing their responses to natural stimuli. While there have been successful attempts to model how ganglion cells respond to natural temporal sequences of light intensity (van Hateren et al., 2002), natural spatio-temporal stimuli appear to present a more fundamental challenge, most likely because the processing by spatial subfields, regarding both nonlinear transformations and adaptive processes,

is more relevant under natural stimulation than for white-noise stimuli. Including such subfield structure and appropriate nonlinear spatial stimulus integration should thus improve our understanding of how the retina operates in the real world. In the long-run, these improved models of how ganglion cells integrate visual stimuli over space and time should also help in the endeavor to restore vision through prosthetic devices (Zrenner, 2002; Busskamp et al., 2012) by incorporating the retinal operations into the electrical or optical activation scheme of ganglion cells (Nirenberg and Pandarinath, 2012).

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