Seeing Things in Motion: Models, Circuits, and Mechanisms

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Motion vision provides essential cues for navigation and course control as well as for mate, prey, or predator detection. Consequently, neurons responding to visual motion in a direction-selective way are found in almost all species that see. However, directional information is not explicitly encoded at the level of a single photoreceptor. Rather, it has to be computed from the spatio-temporal excitation level of at least two photoreceptors. How this computation is done and how this computation is implemented in terms of neural circuitry and membrane biophysics have remained the focus of intense research over many decades. Here, we review recent progress made in this area with an emphasis on insects and the vertebrate retina.

Introduction

Motion vision serves many different tasks; when moving through the environment, the images of the environment as projected onto the photoreceptor layer are constantly in motion. Since the particular distribution of motion vectors on the retina, called optic flow, depends on the specific movement of the animal, whether it is moving forward or making a turn, the optic flow represents a rich source of information that is widely used for navigation and visual course control. Motion cues also occur when the observing animal is standing still but another animal is moving. Obviously, detecting such a potential mate, prey, or predator and knowing which direction it is moving can be of utmost importance for the survival of the observer. Thus, it is not surprising that neurons responding to visual motion cues in a direction-selective (DS) way are found in different parts of the nervous system across the animal kingdom. However, despite the high behavioral relevance of motion vision, the direction of motion is not encoded explicitly by the signals of individual photoreceptors: When moving a bar from left to right and back again, the output signal of a photoreceptor will be the same both times, no matter in which direction the bar has been moving. However, a few synapses downstream into the nervous system, cells are found that respond differently to the two directions. In between, some computation is happening, turning the direction unselective response of the photoreceptor into a DS response of the interneuron. This problem has become a classic example for neural computation that has attracted researchers from different fields over many decades (see also review by Clifford and Ibbotson, 2002). Focusing on the insect optic lobe and the vertebrate retina, we will provide an overview of what has been learnt about the circuits and biophysical mechanisms underlying the extraction of motion information from image sequences in different animal species. As will become evident, much progress has been made recently so that a solution seems to be within reach.

Models of Direction Selectivity

Before discussing the neurons that respond specifically to the direction of a moving stimulus, we will first take a look at the problem from a computational point of view and discuss models that have been proposed to account for this computation.

Defining the Computations

In physics, the velocity of a moving object is defined as the object's spatial displacement over time. For the visual detection of displacement, physical motion has to go along with changes in the spatial brightness distribution on the retina. What characterizes visual motion? Consider a smooth edge in an image moving from left to right, passing in front of a single photoreceptor (Figure 1A). If the edge is moving slowly, the output signal will ramp up slowly, too. If the same edge is moving at a high velocity, the photoreceptor output signal will climb up steeply. Obviously, the faster the object moves, the steeper the output signal. Now consider two edges of different steepness passing by the same photoreceptor at the exact same velocity (Figure 1B): If the steep edge is moving, the output signal will again rise steeply, if the shallow edge is moving, the output signal will rise slowly. Obviously, the steeper the gradient, the steeper the output signal. Therefore, neither the speed nor the direction of the moving object can be deciphered from this output signal alone. However, both of the above dependences are captured by the following formula, relating the temporal signal change dR/dt to the product of the spatial brightness gradient dI/dx and the velocity dx/dt (Limb and Murphy, 1975; Fennema and Thompson, 1979):

$$\frac{dR}{dt} = \frac{dI}{dx} * \frac{dx}{dt}$$

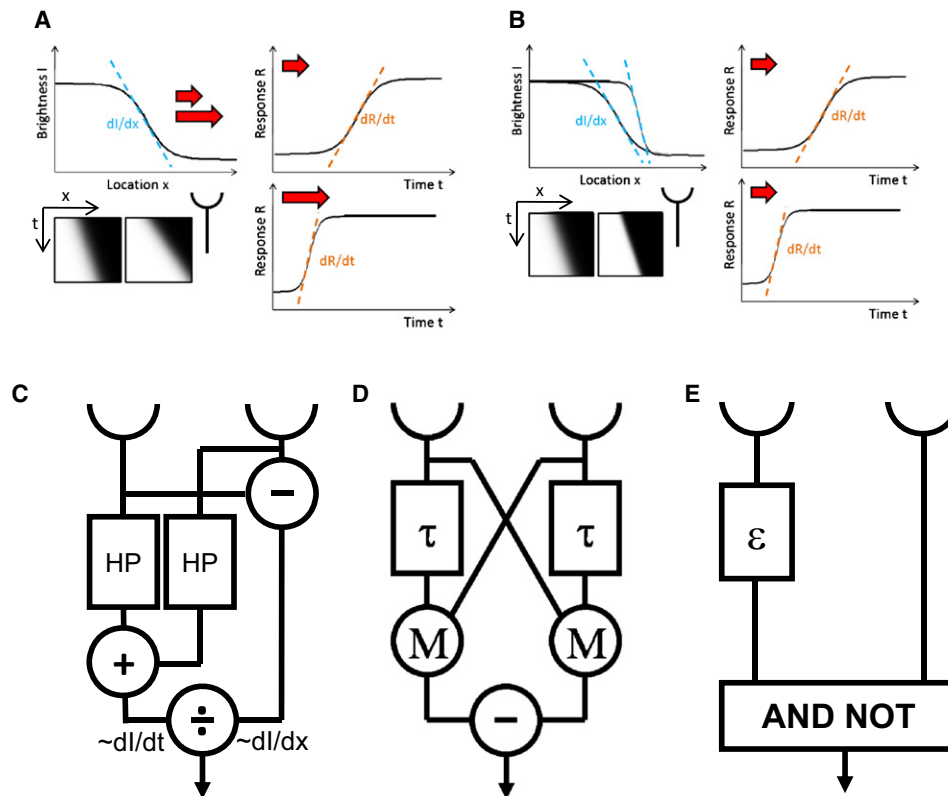The velocity dx/dt can, thus, be recovered by dividing the temporal change dR/dt by the spatial gradient dI/dx.

Figure 1. Models of Motion Detection

(A) A flat gradient is moving at two different velocities (spatial profile, top left; corresponding xt plots bottom left). The slow velocity results in a shallow temporal gradient (top right), the fast velocity in a steep temporal gradient (bottom right).

(B) Two different spatial gradients are moving at the same velocity (spatial profile, top left, corresponding xt plots bottom left). The shallow gradient results in a shallow temporal gradient (top right); the steep gradient results in a steep temporal gradient (bottom right).

(C) The gradient detector calculates the direction and magnitude of image velocity by dividing the temporal brightness gradient dI/dt by the spatial gradient dI/dx. The spatial gradient is approximated by the difference between the brightness values at two adjacent image points (high-pass filter [HP]).

(D) The Reichardt detector calculates the direction of image motion by multiplying (M) the brightness values at two adjacent image points after one of them has passed a low-pass filter with a time constant τ. This is done in two mirror-symmetrical subunits, the outputs of which are subtracted from one another ($-$).

(E) The Barlow-Levick detector calculates the direction of image velocity by processing the brightness values at two adjacent image points through a logical AND-NOT gate after one of them is delayed by ε ms.

Motion-Detector Models

Several models have been proposed in the past that calculate the direction of motion from the brightness changes as captured by the photoreceptors.

The gradient model (Figure 1C) describes the most straightforward way to implement a motion detector with the above mentioned mathematical relationship. Here, the spatial gradient dI/dx is approximated by the brightness difference dI, of the pattern, I, sampled at two neighboring image points separated by a distance, dx. Both input signals become high-pass filtered, approximating the temporal derivative, and then added together. These two quantities are then divided by each other yielding an estimate of the local image velocity (Srinivasan, 1990). This estimate will only depend on the image velocity and not on the spatial structure of the moving pattern because the local image contrast is expressed in a steeper spatial, as well as in a steeper temporal gradient: Dividing them leads to a cancellation of image contrast.

However, as attractive as the gradient model of motion detection might appear, most models that were proposed to account for biological motion detectors actually do not calculate the spatial and the temporal gradient of the moving image. They rather correlate the brightness values measured at two adjacent image points with each other after one of them has been filtered in time (correlation model, Figure 1D). Consequently, their output is not proportional to image motion but rather deviates from it in a characteristic way. In fact, this deviation has been the crucial hint for researchers in motion vision to propose exactly this type of model. The first correlation detector was proposed on the basis of experimental studies on the optomotor behavior of insects (Hassenstein and Reichardt, 1956; Reichardt, 1961; 1987). This correlation detector is commonly referred to as the Reichardt detector (van Santen and Sperling, 1985), and has also been applied to explain motion detection in different vertebrate species including man (for review, see Borst and Egelhaaf, 1989). Such a detector consists of two mirror-symmetrical subunits. In each subunit, the signals derived from two neighboring inputs are multiplied with each other after one of them has been shifted in time by a temporal low-pass filter. The final

detector response is given by the difference of the output signals. Various elaborations of the basic Reichardt model have been proposed to accommodate this motion detection scheme to perform in a species-specific way.

Perhaps the simplest correlation-type movement detector has been proposed by Barlow and Levick to explain their experimental findings on DS ganglion cells in the rabbit retina (Barlow and Levick, 1965). The Barlow-Levick model (Figure 1E) is almost identical with respect to its layout but with only one subunit of the basic Reichardt model. It consists of two input lines carrying the brightness signals which are compared after one of the signals has been delayed. In contrast to the Reichardt model, this comparison is accomplished by a specific logical operation, an AND-NOT or veto gate, suppressing the detector's activity when the delay line is activated first and, consequently, both signals arrive simultaneously at the AND-NOT gate. The corresponding direction of motion, i.e., from left to right, is, therefore, the detector's null direction. For motion in the detector's preferred direction the veto signal arrives too late to have an effect.

Another model which is often applied to human psychophysics and motion-sensitive neurons in the mammalian cortex is the so-called motion energy model (Adelson and Bergen, 1985). Interestingly, if the Reichardt model is equipped with the same spatial and temporal filters in its input channels, it assumes the same specific functional characteristics as the energy model and even is mathematically equivalent (van Santen and Sperling, 1985; Adelson and Bergen, 1985). This identity, however, only holds for the final, fully opponent output signal of both detectors and does not pertain to its internal structure.

Despite many differences in detail, all models of motion detection share the following commonalities: (1) they all have at least two spatially separated input lines that read the brightness levels of adjacent pixels in the image, (2) they all have some sort of asymmetry with respect to the temporal filtering of the input (a temporal derivative in case of the gradient detector, a low-pass filter in one of the input channels of the Reichardt detector, a delay line in the Barlow-Levick model), and (3) they all possess an essential nonlinearity (division in the gradient detector, a multiplication in the Reichardt detector, and an AND-NOT gate in the Barlow-Levick model).

They differ, however, in many other aspects that can be used to discriminate between them experimentally. (1) As a characteristic hallmark, the gradient detector delivers a signal that is proportional to image velocity independent of the local image contrast. (2) The output of the Reichardt detector grows quadratically with image contrast. Furthermore, it displays a maximum at a certain image velocity. The optimum velocity is proportional to the spatial pattern wavelength such that the maximum response is always at the same temporal frequency (image velocity divided by pattern wavelength). (3) The Barlow-Levick model is characterized by a null-direction inhibition.

For an experimental analysis, it is also important to make the distinction between the response properties of the individual local motion detector, and those of a spatially integrated detector array. When stimulated by a periodic grating moving at a constant velocity, the local gradient detector will signal a constant value as well. In contrast, the output signal of a local Reich-

ardt detector will consist of two parts: a constant DC shift that is DS and, superimposed, a periodic modulation with the local brightness of the pattern. Only when the summed output of an array of Reichardt detectors is considered, these local modulations will disappear since they are phase-shifted with respect to each other. This also holds true for the Barlow-Levick model.

DS Cells

Neurons responding differently to visual stimuli moving in opposite directions are called DS. Such neurons have long been known to exist in the visual system and other parts of the vertebrate and invertebrate nervous system.

Insects

In invertebrates, the first DS neurons were found in flies, located in a brain structure called the lobula plate. The lobula plate is the third of a stack of neuropiles of the fly's optic lobe, each forming a retinotopic representation of the image as initially formed by the compound eye. Starting from the periphery, these are called lamina, medulla, and lobula complex, the latter being divided into an anterior lobula and a posterior lobula plate (Figure 2A). As a consequence of the retinotopic structure, each neuropile is built from repetitive columns containing an identical set of neurons first described anatomically by Ramón y Cajal on the basis of Golgi staining (Cajal and Sanchez, 1915). For the fruit fly *Drosophila melanogaster*, a large set of columnar neurons has been cataloged (Fischbach and Dittrich, 1989). More recently, this set has been complemented by assigning transmitter systems to various columnar neurons (e.g., Morante and Desplan, 2008; Raghu and Borst, 2011; Raghu et al., 2011). Each columnar neuron, whether located in the lamina, medulla, or lobula complex, has distinct arborizations in particular layers of its neuropile and some neurons connecting the lamina with the medulla or the medulla to the lobula plate. Furthermore, all these cells restrict their arborizations to a small part of their respective neuropile, mostly respecting the columnar borders. This is different for the lobula plate, where dendrites of the so-called lobula plate tangential cells span large parts of the neuropile, apparently collecting signals from local neurons within hundreds of columns. These tangential cells have been thoroughly analyzed, first in the blow fly *Calliphora* (Hausen, 1982a; 1982b; Hengstenberg, 1982; Hengstenberg et al., 1982; Borst and Haag, 1996; Haag et al., 1997; 1999) and, more recently, also in the fruit fly *Drosophila* (Joesch et al., 2008; Schnell et al., 2010).

Although the exact number depends on the species, the tangential cells comprise roughly 50 neurons, each of which can be uniquely identified on the basis of its anatomy, receptive field, and electrical response properties. All tangential cells respond to visual motion in a DS way. Among them, the three cells of the horizontal system, called HS cells, respond most strongly to horizontal image motion: When the pattern moves from the front to the back, the cells depolarize (Figure 2B). This direction of image motion is their preferred direction. When the pattern moves from the back to the front, they hyperpolarize. This direction of image motion is their null direction. When stimulated by a moving bar instead of a grating, their preferred and null direction remains the same, no matter whether a white bar is moving a black background or a black bar on a white
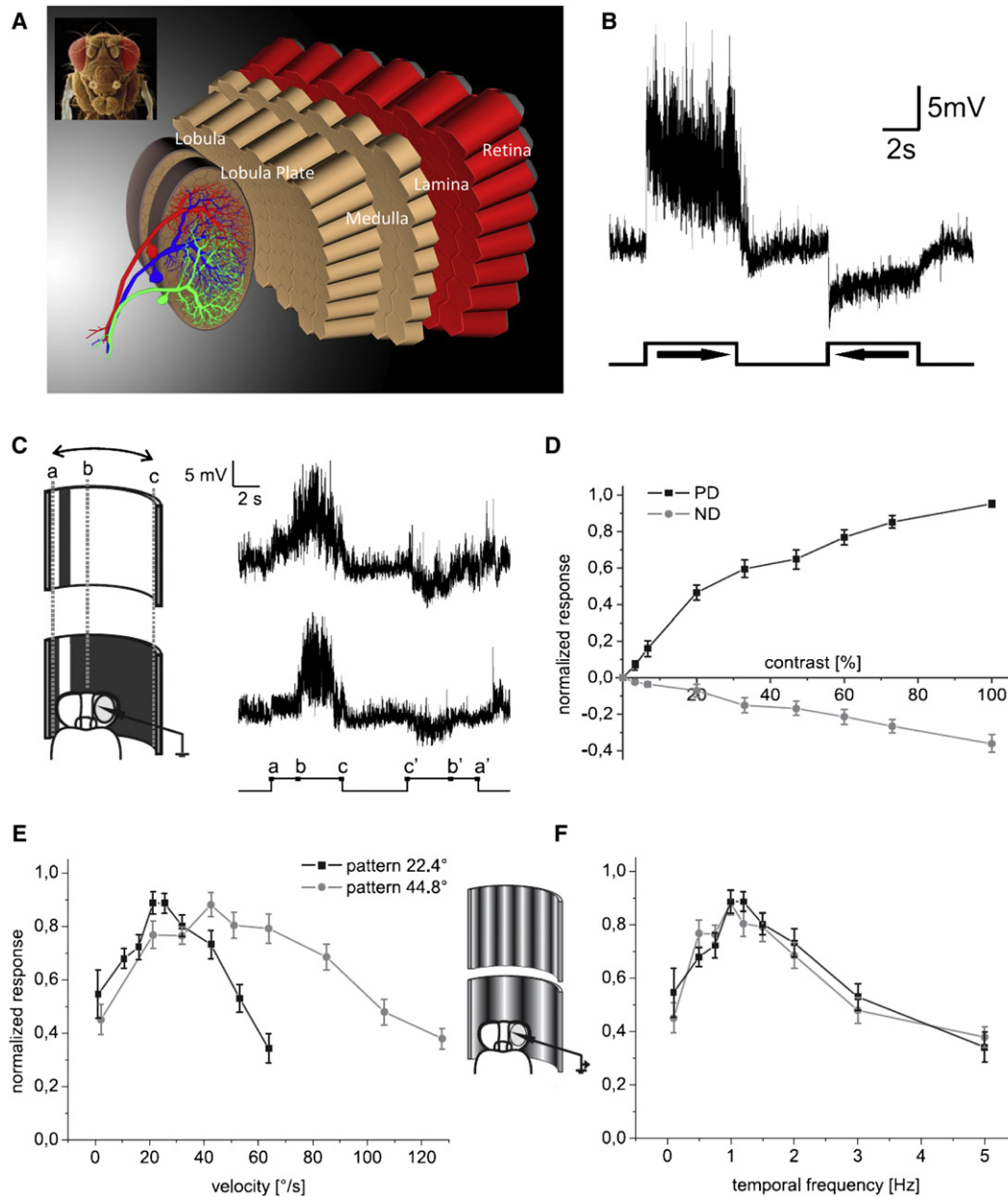
Figure 2. Motion-Sensitive Neurons in the Fly Visual System

(A) Schematic of the *Drosophila* optic lobe showing the three horizontal cells (horizontal system northern in red, horizontal system equatorial in blue, horizontal system southern in green) in the lobula plate.

(B) DS response of HS cells to a moving grating. When the grating is moving in the preferred direction (rightward), the cell depolarizes; when the grating is moving in the null direction (leftward), the cell hyperpolarizes.

(C) DS response of HS cells to a moving bar. Again, as in B, the cell depolarizes during preferred direction motion of the bar and hyperpolarizes during null direction motion. Note that the response is the same; no matter whether a black bar is moving on a white background (upper panel) or a white bar is moving on a black background (lower panel).

(D) Responses of HS cells to a moving grating as a function of grating contrast.

(E) Response of HS cells to moving gratings with two different spatial wavelengths as a function of grating velocity. The larger wavelength results in a higher velocity optimum.

(F) Same data as presented in (E), but plotted as a function of temporal frequency. The temporal frequency is defined as the grating velocity divided by the spatial wavelength. Both gratings produce the maximum response at the same temporal frequency.

All data are from Schnell et al. (2010).

background (Figure 2C). Another prominent group, the cells of the vertical system, called VS cells, in general respond most strongly to vertical image motion; downward is their preferred direction and upward is their null direction. However, precise mapping of the cells' local preferred directions revealed a spatially nonuniform receptive field; the different preferred directions in different parts of the fly's visual field resemble an optic flow pattern as might be elicited by the fly during certain flight maneuvers (Krapp and Hengstenberg, 1996; Krapp et al., 1998). These large and elaborate receptive fields could be shown to result from a combination of direct feed-forward input the tangential cells receive from columnar motion-sensitive elements and lateral synaptic interactions between the various tangential cells within the lobula plate (Borst and Weber, 2011; for review, see Borst et al., 2010).

As for the nature of their retinotopic input elements, the lobula plate tangential cells have been subjected to numerous tests investigating whether they conform to the Reichardt model in blow flies, hover flies, and fruit flies. In these experiments, tangential cells were stimulated by periodic gratings moving at a constant velocity (Haag et al., 2004; Joesch et al., 2008; Schnell et al., 2010) or with a dynamic velocity profile (Egelhaaf and Reichardt, 1987; Egelhaaf and Borst, 1989; Borst et al., 2003; Reisenman et al., 2003; Borst et al., 2005; Spavieri et al., 2010). Some studies investigated the local motion response by restricting the field of view to a small window through which the pattern was shown to the fly (Egelhaaf et al., 1989) or by using intracellular calcium concentration changes as a readout for local activity in the dendrite (Single and Borst, 1998; Haag et al., 2004). Tangential cells were also stimulated by natural images (Dror et al., 2001) or by apparent motion stimuli consisting of spatially displaced sequences of discrete brightness steps (Egelhaaf and Borst, 1992). All these studies concluded that the Reichardt detector accurately describes the behavior of these input elements. As an example, the responses of *Drosophila* HS cells have been measured as a function of pattern contrast (Figure 2D): Although the response does not rise quadratically as predicted by a perfect multiplication, it clearly increases with increasing pattern contrast, thus ruling out a division of temporal by spatial gradient as specified in the gradient detector. When stimulated by a periodic grating drifting at different velocities, the response of HS cells displays a velocity optimum, as predicted by the Reichardt detector (Figure 2E, black trace). Furthermore, when the test is repeated with a grating of twice the spatial wavelength, the optimum velocity is doubled (Figure 2E, gray trace). When the pattern velocity is divided by the spatial wavelength of the pattern, both curves coincide, revealing a peak at the same temporal frequency of 1 Hz (Figure 2F), exactly as predicted by the Reichardt detector.

Vertebrate Retina
The first reports of DS neurons in the vertebrate retina appeared in the 1960s (for references see Wyatt and Daw, 1975). In particular, an elegant series of papers by Barlow, Levick, and coworkers (e.g., Barlow and Hill, 1963; Barlow et al., 1964; Barlow and Levick, 1965) on DS ganglion cells in the rabbit retina initiated more than 40 years of research that established the retinal

DS circuitry as one of the most investigated and best understood neuronal circuitries in the vertebrate brain.

Types of DS Ganglion Cells
The first type of retinal DS ganglion cells fires both at the leading and the trailing edge of a stimulus moving along the preferred direction through the receptive field (Barlow and Levick, 1965). In other words, a bright spot on a dark background evoked very similar DS responses as a dark spot on a bright background. Due to this contrast independence, this cell type is referred to as ON/OFF DS ganglion cell (for review, see Masland, 2004; Vaney et al., 2001). They have a distinct morphology with loopy dendrites (Figure 3A; Amthor et al., 1984; 1989) ramifying in both the ON and the OFF sublamina of the inner plexiform layer (IPL) (Figure 3D, red cell). The two arborizations can differ in size and shape (Oyster et al., 1993; Vaney, 1994), suggesting that the ON and the OFF DS circuits work independently. ON/OFF DS ganglion cells are inhibited by synchronous motion outside their receptive field center and are, thus, sensitive to motion contrast (Chiao and Masland, 2003). As a result of their response properties, ON/OFF ganglion cells are considered to be local motion detectors. They display a rather broad tuning in both the temporal and spatial frequency domain (see e.g., Figure 2 in Grzywacz and Amthor, 2007). Nevertheless, they seem to be tuned to the temporal frequency of the stimulus rather than to its velocity, speaking in favor of the Reichardt detector as an appropriate description of the underlying mechanism. ON/OFF DS cells can be clustered into four functional subtypes (Oyster and Barlow, 1967), each of which preferring a different motion direction roughly parallel to the dorsal-ventral (superior, inferior) or nasal-temporal (anterior, posterior) axis (Figure 3D, bottom).

A second type of DS cell responds to only the leading edge of a bright stimuli moving on a dark background and is, therefore, referred to as an ON DS ganglion cell. They are monostratified (Figure 3B), and their dendritic arborization ramifies in the inner (ON) sublamina of the IPL (Figure 3D, blue cell) (Amthor et al., 1989; Buhl and Peichl, 1986; He and Masland, 1998). In contrast to ON/OFF DS cells, ON DS cells respond best to global motion (Wyatt and Daw, 1975) and are tuned to lower temporal frequencies (Grzywacz and Amthor, 2007). With respect to their preferred direction, ON DS ganglion cells can be clustered into three subtypes (Figure 3D, bottom). There is also recent evidence for further functional subdivision into transient and sustained types, each of which has distinct anatomical features (Kanjhan and Sivyer, 2010).

Recently, a third type of DS cell was discovered in transgenic mice expressing green fluorescent protein under the control of the junctional adhesion molecule B (JAM-B) promoter exclusively in a subset of ganglion cells (Kim et al., 2008). JAM-B positive cells have a peculiar morphology: Their asymmetrical wedge-shaped dendritic arbors are aligned with the dorsal-ventral axis of the retina and point ventrally (Figure 3C). They respond best to centripetal motion, i.e., from the soma to the dendritic tips, and thus, are directionally tuned to upward motion (Figure 3C, bottom)—taking into account that the lens inverts the retinal image. With the exception of very large diameter spots, they fire only at the offset of a light spot and have their dendrites at the distal border of the IPL (Figure 3D, green cell). Nevertheless, they respond to preferred direction motion for both
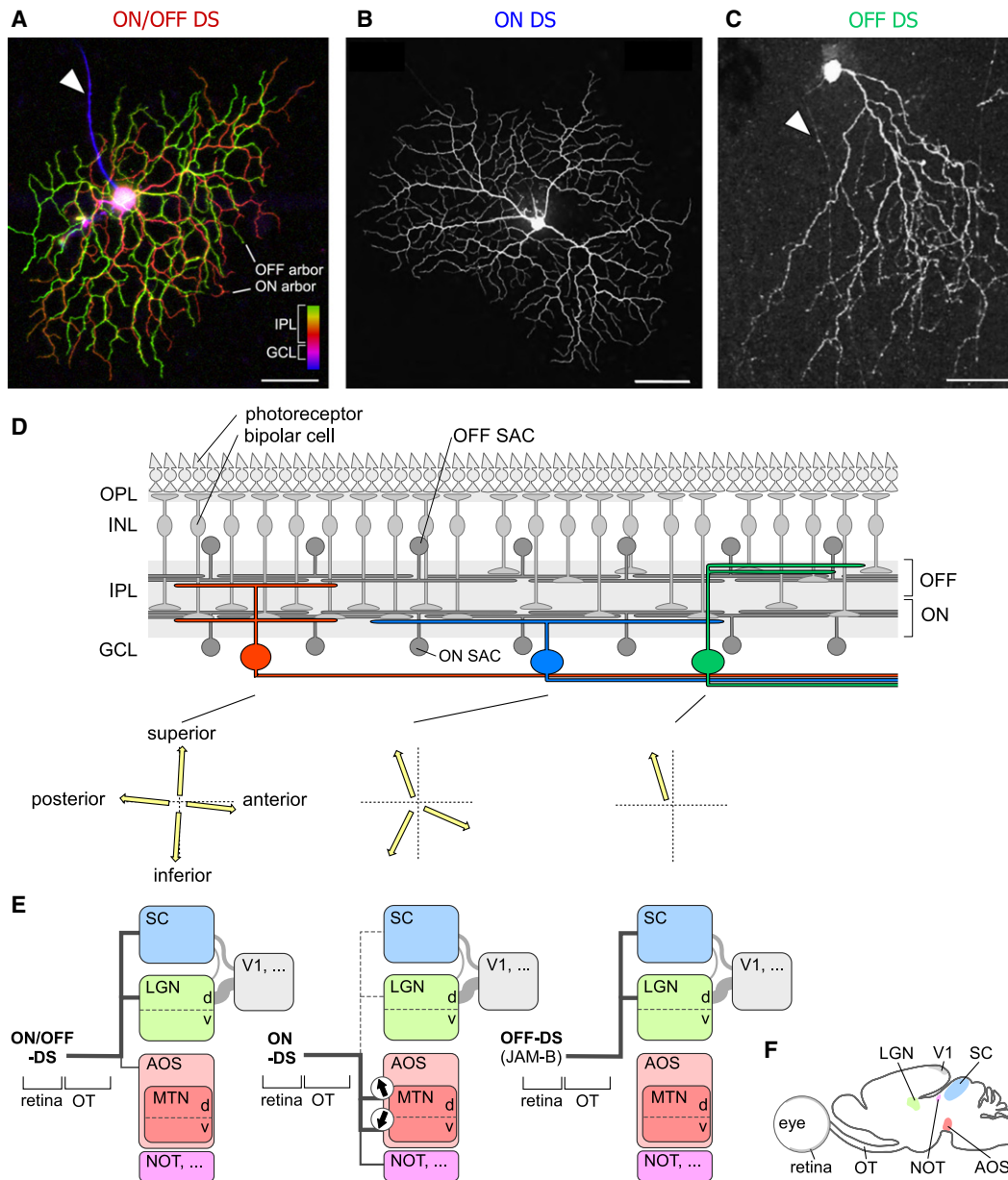
Figure 3. DS Cells in the Mammalian Retina

(A–C) ON/OFF DS ganglion cell (A) and ON DS ganglion cell (B, from Kanjhan and Sivyer, 2010) in the rabbit retina; JAM-B positive OFF DS ganglion cell in mouse retina (C, from Kim et al., 2008). The scale bars represent 50 μm; arrowheads in A and C indicate axons (which are out of focus in B).

(D) Schematic vertical section of the retina with the dendritic stratification of the three type of DS cells from (A–C). Below the cells, the preferred directions of motion with respect to the visual field for each (sub)type are indicated. The following abbreviations are used: SAC, starburst amacrine cell; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer.

(E) Flow charts illustrating the current knowledge on the main signal pathway from the different types of retinal DS ganglion cells to their target areas/nuclei in the brain. The following abbreviations are used: d, dorsal; v, ventral; MTN, medial terminal nucleus; OT, optic tract; LGN, lateral geniculate nucleus; V1, primary visual cortex; SC, superior colliculus; AOS, accessory optic system; NOT, nucleus of the optic tract. For clarity, most interconnections between areas and nuclei are omitted. Colors indicate different target regions in the brain (see also F), thickness of lines connecting the areas represent relative contributions.

(F) Schematic overview of the important projection targets of retinal DS cells (sagittal cross section of a mammalian brain; for abbreviations see [E]).

contrasts (Kim et al., 2008). Interestingly, ganglion cells with asymmetrical dendrites but orientation-selective responses, reminiscent of mouse JAM-B cells, have been reported in the rabbit (Amthor et al., 1989). Thus, OFF DS ganglion cells might also exist in other species.

Projections of Retinal DS Ganglion Cells

Starburst cells represent a type of amacrine cell (Famiglietti, 1983; Masland and Mills, 1979) that had been suggested to be critical for direction selectivity. When selectively ablated through a nifty genetic manipulation, ON and ON/OFF DS ganglion cell
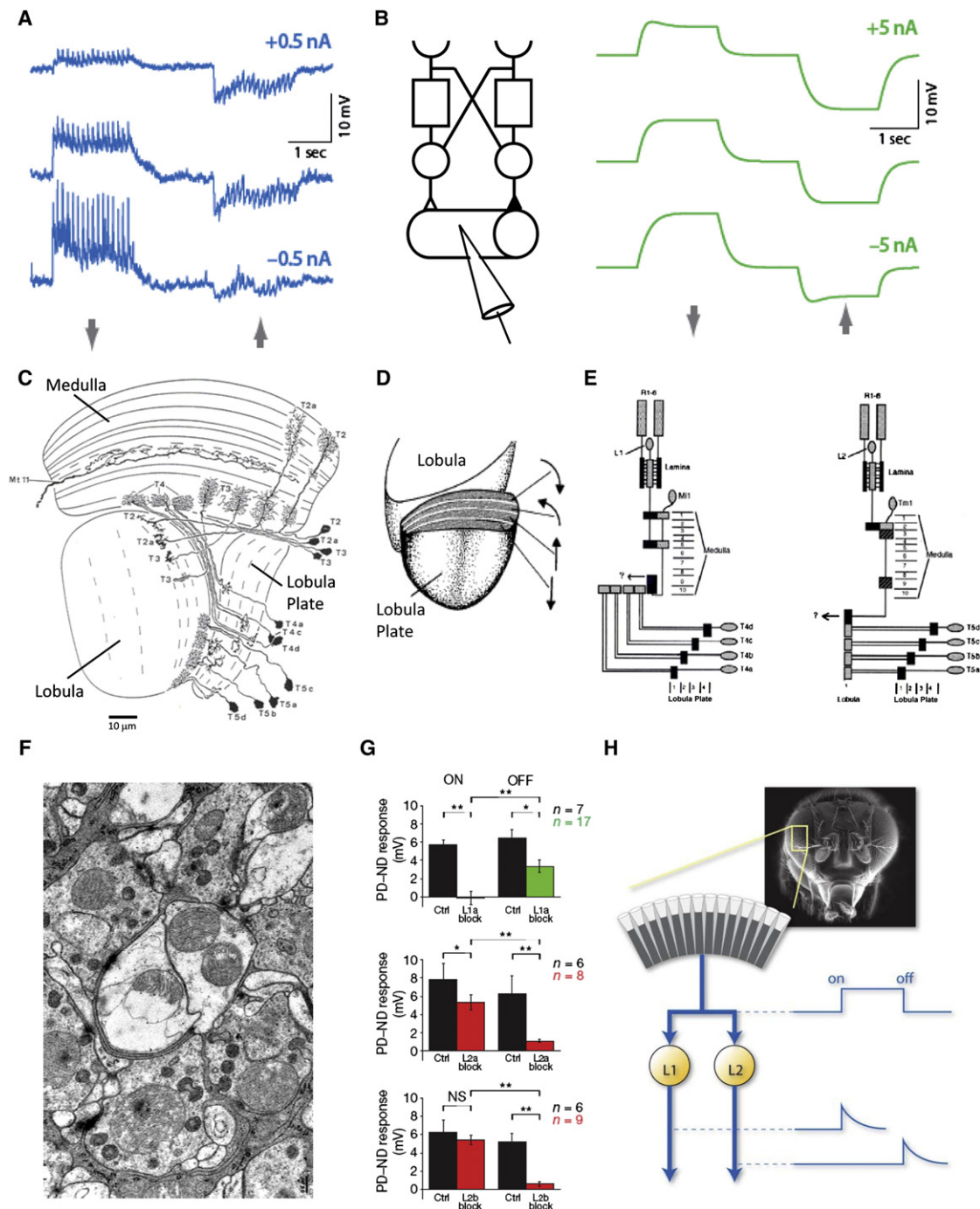
Figure 4. Mechanisms of Direction Selectivity in the Fly Visual System

(A) Preferred and null direction response of a *Drosophila* VS cell during de- and hyperpolarizing current injection (from Joesch et al., 2008).

(B) Simulation of a Reichardt detector (left) with the two subunits controlling excitatory and inhibitory conductances on a single-compartment model neuron (from Borst et al., 2010).

(C) Horizontal view of the optic lobe, including columnar T4 and T5 cells that represent potential presynaptic neurons of the lobula plate tangential cells (from Fischbach and Dittrich, 1989).

(D) Schematic 3D view of the fly lobula plate indicating 2-deoxy-glucose uptake in four different layers depending on the direction of the moving grating (from Buchner et al., 1984).

(E) Parallel L1- and L2-pathways as proposed by Fischbach et al. (1992) based on costratification of columnar neurons and motion-dependent activity labeling.

(F) EM-micrograph of a single lamina cartridge of *Drosophila*. The two central profiles represent lamina monopolar cells L1 and L2 that are surrounded by the terminals of the six photoreceptors R1–R6.

responses became indiscriminate to directional motion (Yoshida et al., 2001). Moreover, this manipulation also resulted in a complete loss of the optokinetic nystagmus (OKN) (Amthor et al., 2002; Yoshida et al., 2001). This indicates that one or both of these DS cell types provide signals essential for the control of eye movement and gaze stabilization (reviewed in Berson, 2008; Vaney et al., 2001). It is likely that ON DS cells are the main source of visual input for these tasks (Oyster et al., 1972), because they prefer global motion, as caused by image slippage. Furthermore, their preferred directions correspond to the three axes of the semicircular canals in the inner ear (Figure 3D, bottom; see also Simpson et al., 1988b). Instead of projecting to the superior colliculus (SC) and the lateral geniculate nucleus (LGN), like the majority of other ganglion cell types, ON DS ganglion cells indeed project to the accessory optic system (AOS), a collection of nuclei that controls eye movement (Figures 3E and 3F, for review, see Berson, 2008). Using transgenic mice, researchers confirmed that the axonal projections of ON DS cells with different preferred direction form discrete clusters in the medial terminal nucleus, the primary nucleus of the AOS (Yonehara et al., 2009), as proposed earlier (Simpson et al., 1988a). The ON/OFF DS ganglion cells also provide some input to the AOS and, therefore, contribute to the control of eye movement, possibly for higher velocities. Consistent with this is also the fact that their preferred directions are roughly aligned with the four directions of apparent movement caused by eye muscles contractions (Oyster and Barlow, 1967). ON/OFF DS ganglion cells send collaterals to the SC and the LGN and, therefore, may serve other visual functions as well, such as directing attention to moving objects (reviewed in Berson, 2008). No projections to the AOS were found for the JAM-B positive OFF DS ganglion cells; they project to the SC and the dorsal LGN (Kim et al., 2008), but the functional role of these inputs is not yet understood. Altogether, with the exception of the contribution to the optokinetic system, little is currently known about the functional role of retinal direction selectivity for higher visual processing.

Retinal Direction Selectivity across Vertebrate Species

Only recently, with the tremendous increase in transgenic mouse diversity, research on DS mechanisms started to shift from rabbits, on which most studies had focused, toward mice. Despite a few minor differences, ON and ON/OFF DS ganglions cells are functionally and morphologically very similar in mice (Sun et al., 2006; Weng et al., 2005) and rabbits. There is evidence for retinal direction selectivity in other mammals (for review see Vaney et al., 2001), and therefore, it is conceivable that this function is largely conserved among mammals. Interestingly, in primates the existence of retinal direction selectivity has not yet been convincingly shown. It is possible that this absence reflects a sampling bias specific to primates: Compared to the overwhelming number of, for example, midget ganglion cells, which underlie high acuity vision, DS cells may be too infrequent. Supporting the notion that these cells might have been missed in

physiological recordings, primate ganglion cells that are morphologically equivalent to rabbit DS cells have been documented (Dacey, 2004; Yamada et al., 2005). Also starburst amacrine cells, which are crucial to the DS circuitry, have been found (Rodieck, 1989). Furthermore, retrograde tracing data on the retinal projections to the AOS are consistent with the presence of ON DS ganglion cells in primates (Telkes et al., 2000).

Direction selectivity has also been studied in several nonmammalian vertebrates (Vaney et al., 2001; Wyatt and Daw, 1975). For instance, DS ganglion cells in turtle (Marchiafava, 1979) have functional properties very similar to those of mammals (Borg-Graham, 2001). Birds also possess retinal DS cells (for research on pigeons see Pearlman and Hughes, 1976), but little is known about the underlying circuitry (e.g., Uchiyama et al., 2000). Results from fish suggest how the refinement of retinal DS circuitry might have progressed during evolution: In ancient fish, such as dogfish, DS ganglion cells were found by recording retinal input from pretectal neurons, but no clustering of preferred directions is evident (Masseck and Hoffmann, 2008). By contrast, recordings from the optic tectum of modern fish, like carp, provide evidence for retinal ON and OFF DS cells, each with three clusters of preferred directions (Damjanović et al., 2009).

Network, Cellular, Subcellular, and Biophysical Mechanisms

Having introduced the neurons found in various animal species that respond to image motion in a DS way, we will now discuss what cellular, subcellular, and biophysical mechanisms give rise to this particular response property.

Insects

As outlined above, there is overwhelming evidence that the lobula plate tangential cells of flies receive input from arrays of local motion detectors of the Reichardt type. However, the small size of the columnar elements in the optic lobe has made it difficult to determine which of the many cells take part in the neural circuitry implementing this algorithm. However, this situation has changed recently, largely due to the application of electrophysiological recording techniques to *Drosophila* (Wilson et al., 2004; Joesch et al., 2008; Maimon et al., 2010), in combination with the wide armory of genetic tools already available for this organism (for review, see Borst, 2009).

First of all, it was demonstrated that *Drosophila* tangential cells receive excitatory and inhibitory input from local motion sensitive elements with opposite preferred direction (Joesch et al., 2008). This was done by injecting depolarizing and hyperpolarizing current into the tangential cell during motion stimulation in the preferred and null direction (Figure 4A): Without current injection, visual stimulation leads to depolarization of the cell during preferred direction motion and hyperpolarization during null direction motion (Figure 4A, middle trace). When depolarizing current is injected, the preferred direction response becomes

(G) Blocking the synaptic output from either L1 or L2 results in selective loss of tangential cell responses to either moving ON-edges (L1-block, in green) or moving OFF edges (L2-block, two different driver lines, in red). Asterisks indicate the significance level of the difference between the mean values: *p < 0.05, **p < 0.001. NS is an abbreviation for not significant. (from Joesch et al., 2010).
(H) Splitting of brightness information into ON and OFF pathways, corresponding to L1 and L2, respectively.

smaller and the null direction response larger (top trace). The opposite is observed during injection of hyperpolarizing current (bottom trace). This can be reproduced by simulation of a single electrical compartment model that receives two synaptic inputs with reversal potentials above and below the resting potential of the cell: The depolarizing current injection reduces the driving force for the excitatory input while increasing it for the inhibitory input, and hyperpolarizing current injection does the opposite (Figure 4B). These results suggest that the subtraction stage in the Reichardt detector is localized within the tangential cells' dendrites. Earlier experiments on blow fly tangential cells arrived at similar conclusions (Borst and Egelhaaf, 1990; Borst et al., 1995; Single et al., 1997). The chemical identity of the transmitter systems involved in this push-pull input organization was clarified by in vitro studies of blow fly lobula plate tangential cells. These studies indicated that excitation is mediated by excitatory nicotinic acetylcholine receptors (nAChRs) and inhibition by γ-aminobutyric acid (GABA) receptors (Egelhaaf et al., 1990; Brotz and Borst, 1996; Brotz et al., 2001; Single et al., 1997). Through the use of a Gal4-driver line that leads to expression in lobula plate tangential cells of two types of labeled reporter genes, excitatory and inhibitory transmitter receptors were found to be colocalized on the fine dendritic branches of HS and VS cells of Drosophila (Raghu et al., 2007; 2009). Thus, direction selectivity in the tangential cells results from summation of two inputs with opposite preferred directions.

But what neurons represent these excitatory and inhibitory input elements to the lobula plate tangential cells? For a number of reasons, bushy T cells are the prime candidates for providing input to the lobula plate tangential cells. T4 cells exist in four different subtypes per column, with dendrites ramifying in the most proximal layer of the medulla. Each of the four T4-cell subtypes projects into one out of four different strata of the lobula plate (Figure 4C). In a similar way, four subtypes per column are found for T5 cells as well, and they connect the posteriormost layer of the lobula to one of the four strata of the lobula plate. Following extended stimulation by moving gratings, Buchner et al. (1984) found strong 2-deoxy-glucose labeling in one of the four layers in the lobula plate depending on the particular direction of the motion stimulus (Figure 4D). The direction of motion which activates a specific stratum, as labeled using the 2-deoxy-glucose method, matches the preferred direction of those tangential cells extending their dendrite in that stratum. In addition to the lobula plate, 2-deoxy-glucose labeling was highest in the most proximal layer of the medulla, where T4 cells ramify, and in the posterior most layer of the lobula, where T5 cells extend their branches (Buchner et al., 1984). Finally, an electron microscopy study in the blow fly has shown unequivocally a chemical synapse between an HS-cell dendrite and a columnar T4 cell (Strausfeld and Lee, 1991). Because of their small size, however, the visual response properties of T4 and T5 cells have proven very difficult to study. The few successful recordings showed that T5 cells reveal a fully DS response, whereas T4 cells are direction unselective (Douglass and Strausfeld, 1995; 1996). As to the type of transmitter these cells use, recent studies identified T4 cells as among the group of neurons activating the ChAT-promoter, which controls the expression of the enzyme choline-acetyl-transferase (ChAT) involved in the

synthesis of acetylcholine (ACh) (Raghu and Borst, 2011), while T5 cells activate the promoter upstream of the gene encoding the vesicular glutamate transporter (VGluT) (Raghu and Borst, 2011). However, a conclusive physiological proof that indeed T4 cells are cholinergic and T5 cells are glutamatergic, and whether they exert excitatory or inhibitory action on the lobula plate tangential cells, is still missing. Furthermore, it is not known which cells provide the above mentioned GABAergic input to the tangential cells.

Based on the costratification of columnar cells in individual layers of the medulla, lobula, and lobula plate as well as 2-deoxy-glucose labeling, T4 and T5 cells were proposed to be the target cells of two separate pathways starting from the photoreceptor terminals R1-6 in the lamina (Figure 4C; Fischbach et al., 1992). Here, the photoreceptor terminals surround the dendrites of two large lamina neurons, called L1 and L2, which contact separate strata in the medulla (Figure 4E). There, the signals are supposed to be picked up by specific intrinsic and transmedullary neurons that terminate in the dendritic areas of T4 and T5 cells, respectively. Keeping in mind the limited evidence for the existence of these pathways to begin with, one could only speculate how the signals in these two pathways differ and how they might correspond to the Reichardt model.

This situation has changed due to a study where tangential cell responses were recorded in Drosophila while the chemical transmitter release from L1 or L2 cells (Figure 4F) was genetically blocked in a cell-specific way (Joesch et al., 2010). While blocking the output from either L1 or L2 led to reduced but still significant responses to drifting gratings, blocking L1 completely and selectively abolished the response to drifting ON-edges, and blocking L2 erased the response to drifting OFF edges (Figure 4G). Using a behavioral readout instead of tangential cell responses, another study obtained similar results (Clark et al., 2011). These findings demonstrate that in fruit flies, the photoreceptor signal from R1-6 is split in the lamina into separate ON and OFF pathways, represented by L1 and L2 cells, respectively. This is analogous to the vertebrate retina where cone photoreceptors contact ON and OFF bipolar cells in parallel (reviewed in Wässle, 2004). However, in the vertebrate retina the split is implemented by different types of glutamate receptors in ON and OFF bipolar cells (Nomura et al., 1994) so that light depolarizes ON bipolar cells and hyperpolarizes OFF bipolar cells. In fruit flies, however, the dendritic membrane response to light is identical in L1 and L2 and consists of a transient hyperpolarization at the beginning and a rebound excitation at the end of a light pulse. In L2 cells, the selectivity for light decrements seems to originate in the axon terminal, as suggested by Ca^{2+} imaging (Reiff et al., 2010): Whereas the intracellular calcium concentration is only slightly reduced at the onset of light, a large and long lasting calcium increase is elicited by light offset. Thus, L2-terminals amplify predominantly the off-signal to postsynaptic neurons. L1-terminals reveal calcium signals similar to the ones of L2-terminals but with a stronger decrease of calcium concentration at light onset (Clark et al., 2011). The easiest way to explain the selectivity for light increments in the L1-pathway would be to assume a signal inversion by inhibition with subsequent rectification in the neurons postsynaptic to L1. This, however, remains a pure speculation at present.

An interesting question following from the finding about the splitting of the input into ON and OFF pathways concerns the number of motion detector subtypes being at work in the fly brain: Do four different detectors exist, one for each stimulus combination (ON-ON, OFF-OFF, ON-OFF, OFF-ON), or are there only two detectors (ON-ON, OFF-OFF)? The most intuitive experiment to investigate this question is the use of apparent motion stimuli in which the brightness in two adjacent bars is stepped sequentially from an intermediate level, that is also present in the surround, to either a high (ON-Step) or to a low (OFF-Step) level. By applying such stimuli to blow flies and fruit flies, various studies consistently found positive responses to ON-ON and OFF-OFF sequences and negative responses to ON-OFF and OFF-ON sequences, either at the level of lobula plate tangential cells or in a behavioral assay (Egelhaaf and Borst, 1992; Eichner et al., 2011; Tuthill et al., 2011; Clark et al., 2011). While these findings seem to clearly indicate the existence of four detector subtypes, careful quantitative modeling, including the peripheral filter stages, suggests that responses to mixed-brightness steps can also be obtained from only two detectors (ON-ON and OFF-OFF) if some residual information about the average brightness level is preserved at the motion-detector input. Using a more selective stimulus sequence consisting of brief brightness pulses instead of steps led to responses to pulse sequences of the same sign only, ruling out the existence of mixed-sign motion detectors in blow flies and fruit flies (Eichner et al., 2011). This conclusion is supported by an earlier study on house flies, *Musca domestica*, that used sophisticated optics to sequentially stimulate individual photoreceptors within one ommatidium projecting to neighboring cartridges in the lamina (Franceschini et al., 1989). While ON-ON and OFF-OFF sequences along the preferred direction of the cell led to strong responses in the H1 tangential cell, no responses were detected for mixed-sign sequences, i.e., ON-OFF and OFF-ON.

In contrast to the two-detector model, Clark et al. (2011) advocate for a model consisting of six detectors, with an asymmetric distribution of the mixed detectors across the two pathways (L1: ON-ON, OFF-OFF, OFF-ON; L2: ON-ON, OFF-OFF, ON-OFF), which are nevertheless selective for ON and OFF edges, respectively. However, to achieve this selectivity, the model requires highly specific stimulus conditions as well as model parameters that are hard to reconcile with previous work. The delay-filter time constant of 10 s, necessary to reproduce edge selectivity in Clark's model, is two to three orders of magnitude larger than the value derived from all previous studies (e.g., Guo and Reichardt, 1987; Egelhaaf and Reichardt, 1987; Dror et al., 2001; Safran et al., 2007). This large time constant introduces a long-lasting ringing in response to the onset of motion (A.B., unpublished data), incompatible with the observed cellular responses (Egelhaaf and Borst, 1989; Reisenman et al., 2003). A further conflict arises in this model's prediction of negative responses to ON-OFF and OFF-ON pulses, which are clearly absent in the experimental data (Eichner et al., 2011). Nevertheless, while we feel that there is evidence arguing against the six-detector model with mixed channels, definitive clarification of the discrepancies will require further direct investigation.

Taken together with the evidence of the pathways leading from L1 to T4 and from L2 to T5 cells, respectively, our current view is that in the fruit fly, two separate motion detection systems operate in parallel, one analyzing the movement of light increments and the other one the movement of light decrements (Figure 4H). While the exact nature and role of the participating neurons is still unclear, the splitting of the positive- and negative-going brightness signal into two channels, one for signals of the positive, the other for signals of the negative sign, has interesting consequences for the multiplication as postulated in the Reichardt detector. Without splitting, the output of such a putative multiplication neuron would need to increase in a supralinear way when both input signals go positive as well as when they go negative. Such a mechanism is difficult to realize. However, splitting the input into separate channels leads to positive signals only, and while a number of biophysically plausible mechanisms have been proposed to do that (Torre and Poggio, 1978; Srinivasan and Bernard, 1976; Gabbiani et al., 2002; Haeusselt et al., 2007; Enciso et al., 2010), the exact mechanism active within these neurons presynaptic to the fly LPTCs remains to be determined. In a similar way, the biophysics underlying the temporal filtering as postulated by the Reichardt detector represents another challenge for future research.

Vertebrate Retina

Since the majority of studies focused on ON/OFF DS cells and their circuitry, we will concentrate on those, while only briefly touching upon other types (see Mechanisms in Other Types of Retinal DS Ganglion Cells). The original Barlow-Levick model (Barlow et al., 1964; reviewed in Masland, 2004) proposed that DS ganglion cells receive delayed and/or long lasting inhibition preferentially from interneurons displaced to the null side of their dendritic field. Note that the term "null/preferred side" refer to the positions from which the null/preferred direction stimulus enters the ganglion cell's dendritic field. This inhibition would be triggered by a stimulus moving in the null direction toward the cell's receptive field center and would cancel out any excitation caused by the stimulus when it eventually enters the center. Understandably, the original model does not fully capture the multitiered organization of the retinal DS circuitry as it is known today. The original model did, however, identify the key properties of any DS circuit (see above). A hallmark of retinal ON/OFF DS cells is their surprising robustness: The retinal cells easily outperform their counterparts in primary visual cortex (V1) in many respects—except maybe for directional tuning width ($\pm 45°$ in retinal ON/OFF cells versus $\geq \pm 15°$ in V1, reviewed in Grzywacz and Amthor, 2007). The direction of motion within the ON/OFF DS cell's receptive field center is reliably detected largely independent of contrast (Merwine et al., 1998) and velocity (Grzywacz and Amthor, 2007; Oyster et al., 1972; Wyatt and Daw, 1975), even for small movements of a few micrometers (Grzywacz et al., 1994). Although their spiking frequency peaks at velocities of $\sim 30°/s$, direction discrimination is constant over a velocity range of more than two orders of magnitude (reviewed in Grzywacz and Amthor, 2007). In the light of this robustness, it is very likely that the underlying circuitry relies on multiple pathways and computational mechanisms to generate and enhance DS signals, as we discuss in the following.
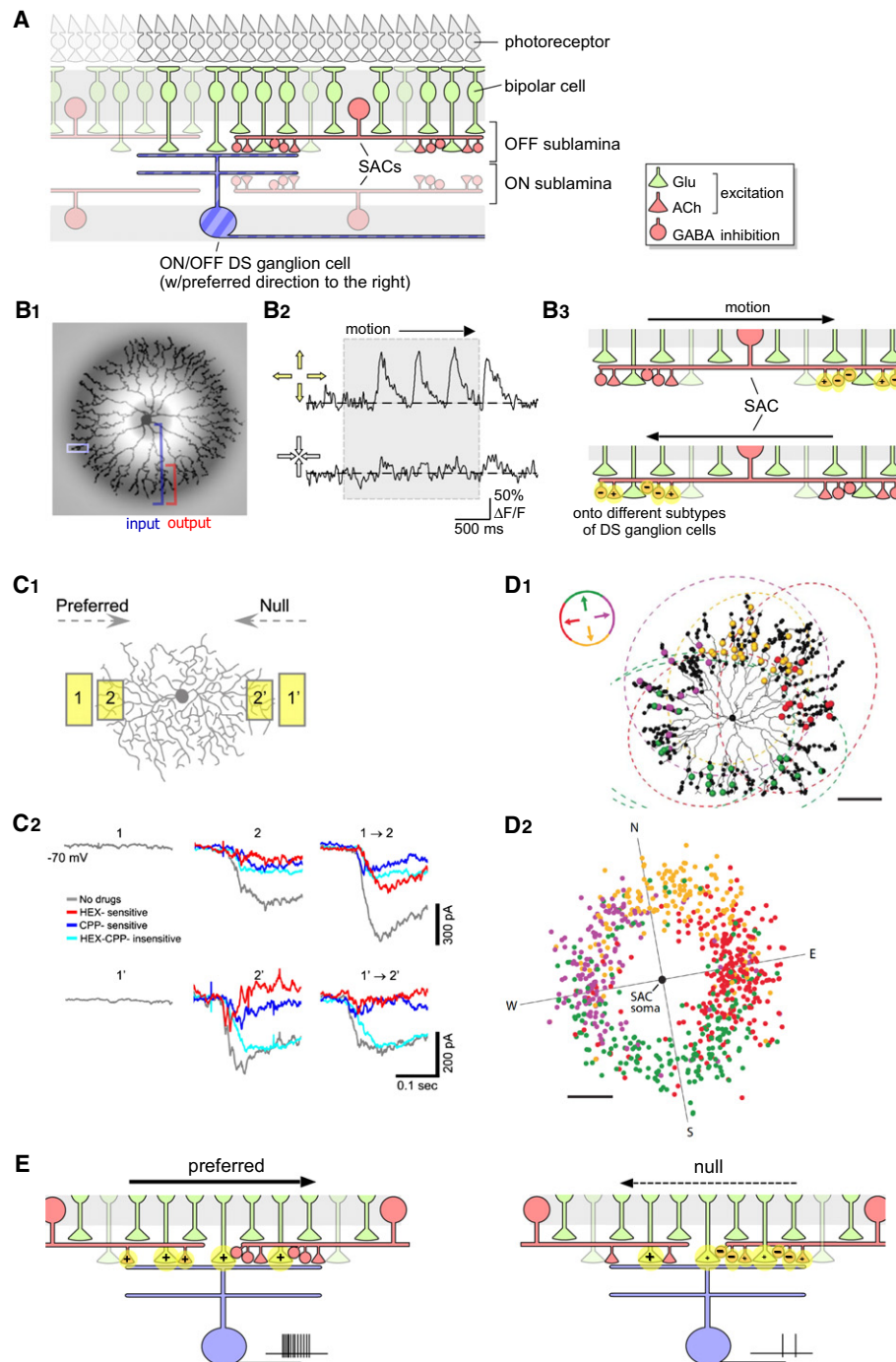
Figure 5. Different Levels of DS Mechanisms in the Retinal ON/OFF DS Circuitry

(A) Schematic retinal cross-section showing the key elements of the circuitry of ON/OFF DS ganglion cells (blue, with motion to the right as its preferred direction) in the mammalian retina, including bipolar cells (green) and starburst amacrine cells (SACs, red). While for simplicity, the illustration is focused on the OFF sublamina of the inner plexiform layer (IPL), the circuit is assumed to be largely the same in both the ON and the OFF sublamina. Also not explicitly shown are: (1) GABAergic interactions between neighboring SACs, and (2) other GABA- and glycinergic amacrine cells participating in the DS circuitry (see The Circuitry of ON/OFF DS Ganglion Cells).

(B) Ca^{2+} signals in the distal dendrites of SACs are intrinsically DS. SAC with dendritic input and output zones indicated; circular wave stimulus overlaid (B1). Centrifugal motion evokes larger Ca^{2+} signals in the distal dendrites than centripetal motion (B2). Since dendritic sectors of SACs are largely isolated from each other, different motion directions activate different sectors, resulting in direction-dependent release of neurotransmitter (B3).

(C) Preferred direction responses in DS ganglion cells are facilitated by DS cholinergic input from SACs (adapted from Lee et al., 2010). Apparent motion stimulation scheme with the position of the stimuli along the preferred null axis of an ON/OFF DS ganglion cell (C1). Responses to single flashes (C2, left two columns) and flash sequences (right column) in preferred (top) and null direction (bottom) without and in the presence of acetylcholine (ACh) receptor blockers (HEX and CPP).

The Circuitry of ON/OFF DS Ganglion Cells

DS ON/OFF ganglion cells receive excitatory input from bipolar cells but also from the previously mentioned starburst cells (Figure 5A), which are also known as cholinergic amacrine cells (Famiglietti, 1983; Masland and Mills, 1979). Besides ACh, starburst amacrine cells (SACs) also release GABA (Brecha et al., 1988; Masland et al., 1984b; Vaney and Young, 1988) and provide DS ganglion cells with inhibition as well (Figure 5A). In addition, the DS ganglion cells receive both GABA and glycinergic inhibition from other amacrine cell types (reviewed in Dacheux et al., 2003). The role of this additional inhibition in the DS circuitry, however, is not yet well understood (see e.g., Neal and Cunningham, 1995).

Starburst amacrine cells (Figure 5B1) feature a characteristic morphology (Famiglietti, 1983; Tauchi and Masland, 1984; Vaney, 1984) that is well conserved across vertebrate species: Their dendritic arbor is composed of 4–6 sectors, each arising from a primary dendrite that radiates from the soma before dividing into smaller branches. SACs come in an ON and an OFF variety, which appear to be functionally equivalent. They costratify with the respective dendritic subtrees of ON/OFF DS cells; ON SACs also costratify with the ON DS type (Figure 5A) (Famiglietti, 1992). Each SAC dendrite is anatomically and physiologically strongly polarized: Synaptic inputs from both bipolar and amacrine cells cover the whole dendritic length, but outputs are restricted to the distal part (Figure 5B1) (Famiglietti, 1983). In addition, some channels and transporters are differentially distributed along SAC dendrites, which, in combination with the morphology, leads to electrical isolation of the sectors from each other (Miller and Bloomfield, 1983; Velte and Miller, 1997). As a result, the individual dendritic sectors can be considered as largely independent processing units (Borg-Graham and Grzywacz, 1992; Euler et al., 2002; Miller and Bloomfield, 1983; Vaney, 1990). In contrast to most retinal neurons, SACs display an extensive dendritic overlap (Tauchi and Masland, 1984), which enables them to provide independent neuronal hardware for the different functional subtypes of DS cells.

It has been proposed earlier that SACs are importantly involved in the DS computation (Borg-Graham and Grzywacz, 1992; Masland et al., 1984a; Vaney et al., 1989), but experimental proof for this notion came less than 10 years ago, when it was shown that massive ablation of SACs results in a selective loss of retinal direction selectivity (Amthor et al., 2002; Yoshida et al., 2001; but see He and Masland, 1997). Optical measurements of light-stimulus-evoked Ca^{2+} concentration changes (Denk and Detwiler, 1999) in the dendrites of SACs demonstrated that stimuli moving from the soma to the dendritic tips, i.e., centrifugal motion, evoked larger Ca^{2+} responses in the distal dendrites than motion in the opposite direction, i.e., centripetal motion (Figure 5B2) (Euler et al., 2002). Because SAC output synapses are located in the distal dendrites (Fami-

glietti, 1991) and transmitter release from SACs is Ca^{2+}-dependent (O'Malley et al., 1992; Zheng et al., 2004), this indicated that SACs are able to provide DS ganglion cells with directionally tuned input. In fact, since the dendritic sectors are electrically isolated from each other, each sector can be thought of as an independent detector for centrifugal motion (Figure 5B3). Around the same time, the related long-standing question as to whether retinal direction selectivity is computed in the ganglion cells themselves or presynaptically by interneurons (reviewed in Masland, 2004) was successfully addressed. Patch-clamp studies revealed that the synaptic input to ON/OFF DS cells is already DS (Borg-Graham, 2001; Fried et al., 2002; Taylor and Vaney, 2002): Preferred direction motion elicits more excitation and less inhibition in the ganglion cells, whereas null direction motion elicits more inhibition and less excitation. This suggested (1) that both inhibitory and excitatory inputs are DS, (2) that the Barlow-Levick model does not fully capture retinal DS computations, and (3) that the latter are indeed already performed presynaptically by interneurons. Note that the latter point does not exclude that postsynaptic, i.e., ganglion cell-intrinsic mechanisms contribute to the overall direction selectivity observed in ganglion cells (see Mechanisms at the Ganglion Cell Level).

The Role of Inhibition

It was already known for long that blocking GABA$_A$ receptors abolishes DS responses in the ganglion cells but leaves their responsiveness intact (Caldwell et al., 1978; Massey et al., 1997). This indicated that GABAergic inhibition plays a crucial role not only in directly cancelling of null direction motion responses in the ganglion cells (Barlow and Levick, 1965), but also in rendering the excitatory input to the ganglion cells DS (see The Role of Excitation). Furthermore, in combination with the SAC ablation experiments (Amthor et al., 2002; Yoshida et al., 2001), it suggested that SACs are a major source for this GABAergic inhibition. While a contribution from other GABAergic amacrine cells cannot be excluded, it seems unlikely that they fit the role of SACs because they typically are not numerous enough to provide the different functional subtypes of DS ganglion cells with adequate input (reviewed in Vaney et al., 2001). This lack of cells may, however, be compensated for by highly localized dendritic processing.

To distinguish between different mechanistic hypotheses of direction selectivity, it is important to differentiate between directionally tuned (Figure 5B) and spatially offset inhibition (Figure 5D). While both originate, at least in part, in SACs, they represent different aspects of the DS computation. Spatially offset inhibition as such can be sufficient to render ganglion cell responses DS (Figures 5D and 5E; Borg-Graham and Grzywacz, 1992; Koch et al., 1983; Barlow and Levick, 1965). Spatially offset inhibition is a recurrent theme in the retinal DS circuit (Fried et al., 2005). It acts not only at the level of the ganglion cell, but possibly also at the bipolar cell terminals presynaptic to the DS ganglion cells

(D) Asymmetric synaptic wiring between SACs and DS ganglion cells, determined from large-scale ultrastructural reconstruction of retina that was functionally characterized with optical recordings (see Briggman et al., 2011, for details). Specific connectivity of synaptic SAC outputs (black skeleton), with varicosities indicated by black dots (D1). Synapses are color-coded by the preferred direction of the postsynaptic DS ganglion cells (color-coded dashed ellipses indicate their dendritic trees; the inset shows their preferred motion directions). Locations relative to the SAC somas of output synapses (n = 831) from all 24 reconstructed SACs (D2). The scale bars represent 50 μm.
(E) Direction selectivity in ganglion cells (blue) result from multiple presynaptic mechanisms: (1) DS in SAC dendrites (see B), resulting in (2) null direction inhibition via asymmetrical GABAergic input (see D) and (3) preferred direction excitation via symmetrical cholinergic input (see C and The Role of Excitation).

(Figure 5E) and possibly between SACs. The first evidence for DS ganglion cells receiving spatially offset inhibition from SACs as a consequence of asymmetrical wiring came from paired recordings. These revealed that SACs located on the null side of a ganglion cell provide significantly stronger inhibition than SACs located on its preferred side (Fried et al., 2002; Lee et al., 2010; Wei et al., 2011). The anatomical correlate for such asymmetrical wiring has been elusive, since neither the DS cell's morphology (Amthor et al., 1984) nor the distribution of synaptic inputs (Jeon et al., 2002) allowed researchers to predict its preferred direction. While complex synaptic arrangements between SACs and DS ganglion cells have been described at the ultrastructural level (Dacheux et al., 2003), very recently, a new EM technique for recording tissue volumes of sufficient size and resolution (Briggman and Denk, 2006) allowed researchers to statistically analyze the SAC-DS ganglion cell connectivity for the first time (Figure 5D). In their elegant study, Briggman et al. (2011) revealed two important circuit properties: (1) The great majority of SAC synapses a DS ganglion cell receives come from SAC dendrites that roughly point in the ganglion cell's null direction, meaning that the respective SAC somata are located preferentially on the ganglion cell's null side. (2) SACs provide input to all DS ganglion cells within their dendritic field but only via dendrites pointing in the null direction of the respective ganglion cell. Moreover, Briggman et al. (2011) found that the probability for a synaptic contact is substantially higher when the local angle of the SAC dendrite closely matches the ganglion cell's null direction, suggesting that the synapse forming mechanism makes use the local dendritic geometry and/or activity.

The retinal DS circuitry does not solely rely on spatially offset inhibition from SACs but ensures that this inhibition itself is DS (Figure 5B). A number of models have been put forward to explain the generation of dendritic direction selectivity in SACs (reviewed in Euler and Haeusselt, 2008). While these models differ in the neuron types recruited or in the biophysical mechanisms employed, they are not necessarily mutually exclusive. One class of models focuses on intrinsic properties of SACs and makes use of the fact that their dendrites are polarized computational subunits (see The Circuitry of ON/OFF DS Ganglion Cells). Passive models predict that SAC dendrites generate weak DS signals simply by input summation along the dendrite (Tukker et al., 2004). As a result, centrifugal motion (which extends from the soma to the dendritic tips) evokes a larger signal in the dendritic tips, whereas centripetal motion evokes a larger signal in the soma (see also Borg-Graham and Grzywacz, 1992; Branco et al., 2010). As the SACs' output synapses are located in the dendritic tips, centrifugal motion would lead to a larger output signal. In this scenario, the location of the output synapses serves as spatial asymmetry and the threshold for transmitter release as the essential nonlinearity. The direction selectivity found in passive models seems, however, small and too sensitive to stimulus parameters to explain the robust direction discrimination observed at the ganglion cell level. Also, passive models predict a larger electrical signal at the soma for centripetal motion which contradicts experimental observations (Euler et al., 2002; Peters and Masland, 1996).

To circumvent the deficits of passive models, voltage-gated channels have been incorporated as nonlinearities. Voltage-gated channels are suited to boost the SAC's DS response if differentially activated in a way that depends on the motion direction (e.g., Borg-Graham and Grzywacz, 1992; Haeusselt et al., 2007; Tukker et al., 2004). SACs possess a variety of suitable voltage-gated Ca^{2+} (Cohen, 2001) as well as tetrodotoxin-resistant Na^+ channels (O'Brien et al., 2008). Recently, the latter shifted into the focus of interest since blocking these Na^+ channels led to a reduction in dendritic direction selectivity in SACs (Oesch and Taylor, 2010). Aside from the radially asymmetric distribution of SAC output synapses, two kinds of gradients along SAC dendrites have been proposed to serve as functional asymmetry for DS detection: a voltage and a Cl^- concentration gradient. Optical Ca^{2+} measurements in SACs suggest that the distal dendrite is tonically depolarized relative to the soma (Haeusselt et al., 2007), possibly due to tonic glutamatergic input (Taylor and Wässle, 1995; but see Oesch and Taylor, 2010). Modeling suggests that even a small dendritic voltage gradient in combination with voltage-gated channels could generate a robust DS signal in SAC dendrites (Haeusselt et al., 2007). In another model it was proposed, that SACs generate a Cl^- concentration gradient along their dendrites due to a differential distribution of Cl^- intruders and extruders, and that this results in GABAergic input causing depolarization at the proximal and hyperpolarization at the distal dendrite, respectively (for details see Enciso et al., 2010; Gavrikov et al., 2003; Gavrikov et al., 2006). According to this model, the asymmetry in the effect of GABAergic inputs leads to dendritic direction selectivity. Other than the voltage gradient model, the Cl^- gradient model requires GABAergic input and therefore does not account for the finding that SAC responses remain DS in the presence of GABA receptor blockers (see below).

Ultrastructural (Millar and Morgan, 1987) and functional data (Zheng et al., 2004) indicate that mature SACs form reciprocal GABAergic synapses, which have been implicated in the computation of DS signals (e.g., Münch and Werblin, 2006). If a SAC is excited, it inhibits its neighbor—this in turn reduces the neighbor's GABA release and in effect enhances the first SAC's response. Such interaction may sharpen the DS contrast in neighboring SAC dendrites pointing in opposite directions (Lee et al., 2010; Lee and Zhou, 2006). However, since GABA receptor antagonists do not abolish dendritic direction selectivity in SACs (Euler et al., 2002; Haeusselt et al., 2007; Oesch and Taylor, 2010), it is unlikely that these interactions are essential for the SAC's intrinsic DS mechanism.

The Role of Excitation

In addition to inhibition, DS ganglion cells receive DS excitatory input from bipolar cells (Fried et al., 2005). This tuning could arise from DS suppression of bipolar cell output by GABAergic amacrine cells (Figure 5E), which would explain why this excitatory DS pathway is eliminated by GABA receptor blockers (see The Role of Inhibition). Because ablating SACs abolishes ganglion cell DS responses (Amthor et al., 2002; Yoshida et al., 2001), it is likely that SACs are involved in tuning bipolar cell output—if other amacrine cells were crucial, some residual direction selectivity after ablation would be expected.

Besides glutamatergic excitation, DS ganglion cells also receive excitatory cholinergic input from SACs (reviewed in Vaney et al., 2001). Blocking cholinergic receptors in the presence
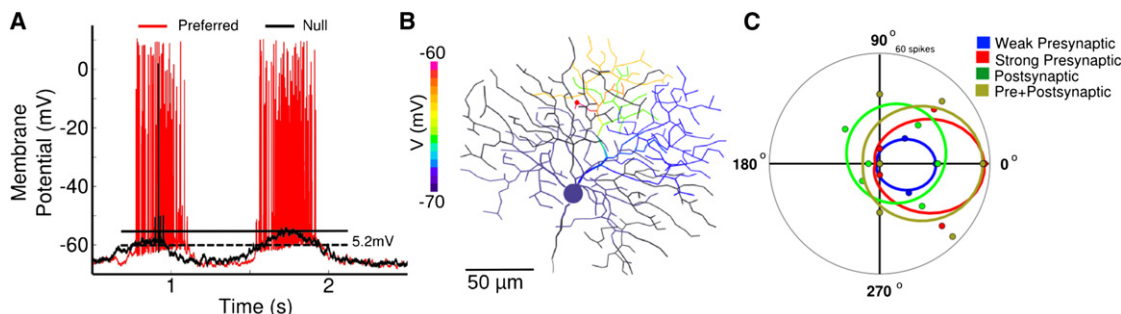
Figure 6. Postsynaptic Amplification in Retinal ON/OFF DS Ganglion Cells
(A) Voltage response recorded from an ON/OFF DS ganglion cell soma to preferred (red) and null (black) direction motion. Peak depolarization is significantly larger for null compared to preferred motion, yet spikes are generated much more reliably for preferred direction.
(B) Results from a biophysical model of an ON/OFF DS ganglion cell. For a passive model, that is without voltage-gated channels, and for weak synaptic input (at the location marked by a red dot), dendrites are electrotonically well isolated (color-coded voltage distribution shown 50 ms after the onset of the stimulus).
(C) Directional tuning of a modeled DS ganglion cell (from C) for different conditions: only presynaptic DS mechanisms with weak (blue) or strong (red) input to the ganglion cell included, only postsynaptic mechanisms included (green), both pre- and postsynaptic mechanisms together (yellow).
All panels from Schachter et al. (2010), for details see there.

of GABA receptor antagonists reduces the responses of DS ganglion cells independent of motion direction (Chiao and Masland, 2002), suggesting that cholinergic excitation provides motion-sensitive but not DS excitation (He and Masland, 1997). On the other hand, there is also evidence that this cholinergic input is DS (Figure 5C, Fried et al., 2005; Lee et al., 2010). In fact, paired recordings confirmed that SACs provide DS ganglion cells with cholinergic input from all sides but also showed that this input is modulated by GABA (Lee et al., 2010). SACs on the preferred side of a DS cell release ACh unhindered and thereby facilitate the motion response of the ganglion cell, whereas the ACh release from SACs on the ganglion cell's null side is suppressed by inhibitory inputs (Figure 5E, Lee et al., 2010). In other words, in the cholinergic pathway direction selectivity results from DS modulation of otherwise symmetrical input to the ganglion cells. This is in stark contrast to the GABAergic pathway where the asymmetry is implemented as spatially-biased synaptic connectivity. Three findings highlight that the interactions between the cholinergic and the GABAergic pathways are still not fully understood: (1) The cholinergic pathway appears to be more relevant for grating stimuli (Grzywacz et al., 1998). (2) EM data suggest that SACs located on the preferred side of a DS ganglion cell make only few synapses with this cell (Briggman et al., 2011), which leaves one wondering how the cholinergic signals are relayed. Paracrine ACh release is a possibility, which is supported by the fact that while SACs are the sole source of retinal ACh, even ganglion cells that do not costratify with SACs possess ACh receptors. (3) In SACs, GABA and ACh are differentially released in a Ca^{2+} level-dependent way, likely from separate vesicle populations (Lee et al., 2010), adding another level of complexity to the circuitry.

Recent modeling data (Poleg-Polsky and Diamond, 2011; Schachter et al., 2010) suggest that the observed direction-dependent difference in excitatory input can be alternatively explained by interactions between excitatory and inhibitory conductances in the ganglion cells, without requiring DS excitation. Such electrotonic interactions are to be expected if a cell's membrane potential cannot be spatially well controlled, which

is likely considering the highly branched morphology of DS ganglion cells.

Mechanisms at the Ganglion Cell Level
By using dendritic Ca^{2+} imaging, it was shown that light stimuli can locally initiate spikes in DS ganglion cell dendrites and that these dendritic spikes are independent of the somatic spike generator (Oesch et al., 2005). The role of these dendritic spikes in ON/OFF DS cells was recently studied in a detailed biophysical compartment model (Figure 6, Schachter et al., 2010). The simulation results suggest that the dendritic arbor of DS ganglion cells is partitioned into separate electrotonic regions (Figure 6B), each of which sums locally inhibitory and excitatory inputs to decide whether or not a dendritic spike is fired. The dendritic spikes not only sharpen the directional tuning of the synaptic input, but are also needed to relay the decision of the dendritic region—independently of the activity in other regions—to the soma, where a somatic spike can then be triggered. The model also suggests that synaptic inhibition can prevent local spike initiation but is not strong enough to suppress spike propagation. Schachter and colleagues (2010) provide a sensible explanation for the so-called nondiscriminating zone, an area without DS responses located at the preferred side of the ganglion cell's dendritic arbor (Barlow and Levick, 1965): They suggest that the distal dendrites of DS ganglion cells are intrinsically DS with their preferred directions oriented radially from the cell's center. Such intrinsic direction selectivity would interact with the DS synaptic input, enhancing it at the null side while antagonizing it at the preferred side. Taken together, dendritic spike initiation and electrotonic isolation of dendritic regions allow the ganglion cells to respond reliably to different scales of motion within their receptive field center and to sharpen the rather broad directional tuning of the synaptic inputs (Figure 6C).

Mechanisms in Other Types of Retinal DS Ganglion Cells
Although much less is known about the DS mechanisms in the other types of DS ganglion cells, it is likely that the circuitry of the ON DS cells resembles that of ON/OFF DS cells in many respects. For instance, conductance measurements revealed that ON DS cells receive directionally tuned inhibitory and

excitatory input (Sivyer et al., 2010)—similar to the ON/OFF cells. There are some circuit differences to be expected because unlike their ON/OFF counterparts, ON DS cells respond to global motion. The recent finding that wide-field amacrine cells affect ON DS cell responses via gap junctions (Ackert et al., 2009) may be relevant in this context.

While JAM-B positive OFF DS cells (Kim et al., 2008) have not yet been studied in detail, there are a number of findings indicating that they employ rather different mechanisms than the ON and ON/OFF types: (1) Because the dendrites of OFF DS ganglion cells stratify in a different IPL level than the SACs (Figures 4C and 4D, Kim et al., 2008), a substantial involvement of SACs is unlikely. (2) The DS tuning strength of OFF DS cells is positively correlated with the degree of dendritic asymmetry, suggesting that the cells' curious morphology plays a crucial role for DS (Kim et al., 2008). This is in contrast to ON/OFF DS ganglion cells, where the cell's morphology does not predict its preferred direction. (3) In the OFF DS cells, the responses to dark moving spots are tuned to higher velocities than those to bright moving spots, suggesting different ON and OFF DS mechanisms—again in contrast to ON/OFF DS ganglion cells.

Establishment of DS during Development

Another intriguing question is what mechanisms lead to the selective asymmetrical wiring in neuronal circuits that compute the direction of motion during development.

Insects

The stereotyped anatomy of the insect optic lobe, which has a high degree of invariance of identified neurons between different individuals, seems to indicate, right from the beginning, that visual experience does not play a major role in shaping the circuits in the visual system, including the ones responsible for direction selectivity. However, in contrast to these expectations, early visual experience was demonstrated to have a rather strong effect on the size of the optic lobes in *Drosophila* (Barth et al., 1997). Monocular deprivation (done by painting over one eye) decreased the total volume of the lamina, medulla, and lobula plate by up to 6%, and the lamina showed a volume difference of up to 30%. The changes in the lamina were largely attributable to changes in the terminals of the photoreceptor cell axons. Another study in house flies similarly concluded that flies reared in constant darkness have about 20% fewer synapses than the control group (Rybak and Meinertzhagen, 1997).

However, the question is still whether the motion detection circuit function is impaired by the changes reported above. This question has been addressed by investigating the anatomy and physiology of the lobula plate tangential cells. Studying their anatomy in blow flies, Cuntz and colleagues (2008) quantified the dendrites of the same identified neurons from different individuals. They measured the branching topology in terms of numbers and distribution of branch points and branch angles, as well as the area covered by the dendrite, their so-called spanning field, within the lobula plate. The astonishing outcome was that branching topology varies widely from individual to individual while the dendritic spanning field is highly invariant and can be used as a single parameter to distinguish between different lob-

ula plate cells. Thus, the dendritic spanning field seems developmentally tightly controlled, while the branching topology is not. Assuming that synapses are located mostly toward the endings of the dendritic branch, this would suggest that branch topology has no influence on the wiring of the particular cell as long as the branches reach their presynaptic input at the proper location. Another study directly investigated the effect of sensory experience on the anatomy of the lobula plate tangential cell VS1 in *Drosophila* (Scott et al., 2003). The authors compared this cell from individuals that were raised in a 12 hr/12 hr light-dark cycle to the same cell in flies that were dark-reared. When the morphology of the dendrite as well as the axon terminals was examined, no conspicuous differences could be observed between the two groups. Thus, visual experience has no influence on the anatomy of the tangential cells. A third study investigated the influence of visual experience on the receptive field properties of tangential cells in blow flies (Karmeier et al., 2001). Again, the authors compared neurons from two groups, one raised at a 12 hr/12 hr light-dark cycle and the other reared in the dark. The receptive field of the neurons from both groups turned out to be indistinguishable. This clearly indicates that, despite the quite dramatic changes seen in the peripheral parts of the visual system, the circuits responsible for direction selectivity in the fly do not require visual experience to properly develop.

Vertebrate Retina

How the retinal DS circuitry arises during development has not yet been solved (Elstrott and Feller, 2009). This process very likely does not require visual input: DS responses in ganglion cells can be recorded already at eye opening (Masland, 1977) and attempts at modifying retinal direction selectivity by various manipulations, such as dark-rearing (Chan and Chiao, 2008; Chen et al., 2009; Elstrott et al., 2008; Yonehara et al., 2009), blocking of GABAergic inhibition (Wei et al., 2011), or raising animals in environments with biased motion direction statistics (Daw and Wyatt, 1974), were unsuccessful. SACs appear very early during development (Feller et al., 1996) and form a network that is dominated by excitatory cholinergic interactions and involved in generating activity waves (reviewed in Masland, 2005), which have been proposed to participate in the DS circuitry generation. Recent work, however, suggests that these activity waves are not crucial for setting up the asymmetrical wiring of the DS circuitry because ganglion cell DS responses were not altered in knock-out mice lacking cholinergic waves (Elstrott et al., 2008). Also recent recordings of DS ganglion cells in the developing retina showed that while the cells responded to passing waves, the direction of wave propagation did not modulate the cells' responses (Elstrott and Feller, 2010).

The dendritic architecture of DS ganglion cells and SACs is established before the retina becomes light responsive (Wong and Collin, 1989; Wong, 1990; Stacy and Wong, 2003). Two recent studies investigated the development of the synaptic connectivity between SACs and DS ganglion cells by using two different but equally elegant experimental approaches. Yonehara et al. (2009) used optogenetics to examine the development of the connectivity between SACs and ON DS ganglion cells in transgenic mice, in which (1) upward motion preferring ON DS ganglion cells were fluorescently labeled, and (2) SACs

expressed Cre-recombinase. Via viral transfection, the latter allowed for targeted expression of channelrhodopsin (Ch2R), a light-sensitive cation channel (Nagel et al., 2003). In this way, SACs could be directly light-activated before the retina becomes light sensitive, which in mice is around postnatal day (P) 10. By activating SACs at different positions around an ON DS cell, they probed the synaptic connections between the two cell types. They revealed that within a 2 day time window (P6–P8) inhibitory connections change from symmetrical to asymmetrical, and there is an increase in inhibition from SACs on the null side and a decrease in inhibition from SACs on the preferred side. In the second study, Wei et al. (2011) performed paired recordings from SACs and one subtype of ON/OFF DS ganglion cells. For mice at P3–P4, they found that the inhibitory SAC input to the ganglion cells was spatially symmetrical. At P14 or later, however, the inhibitory input the ganglion cell received from SACs on the null side was strongly increased, whereas the preferred side inhibition had remained constant. Despite minor deviations, the results from the two studies are largely consistent: Retinal DS circuitry maturation takes place rather quickly before bipolar cells connect and the retina becomes light sensitive. That the inhibitory events measured in ganglion cells do not change in amplitude but become more frequent (Wei et al., 2011) suggests a change in synapse number rather than strength, pointing at selective synapse formation and/or elimination that facilitates the development of asymmetric processing along the dendrite. It is likely that molecular cues or marker gradients along the different retinal axes are involved in this process (Elstrott and Feller, 2009); however, the identity of these markers and the underlying guidance mechanisms are unknown.

Species Commonalities and Differences
Given the still unclear situation about the cellular and subcellular mechanisms of direction selectivity, both in the insect optic lobe and in the vertebrate retina, a comparison is rather challenging. Further complications arise from the fact that it is not obvious which DS cell types and circuitries are functionally equivalent between insects and vertebrates. Nevertheless, as premature the situation might be, we will draw some conclusions in the following based on the data available at present.

ON-OFF Input Rectification
Independent of DS, the most conspicuous commonality between the visual processing in insects and vertebrates relates to the splitting of the photoreceptor input into ON and OFF channels (Werblin and Dowling, 1969; Franceschini et al., 1989; Joesch et al., 2010). One obvious function of such a split is to increase the dynamic range for coding light increments and decrements. Also, it is an economic way of handling metabolic costs: If mainly the changes of brightness levels are to be transmitted to downstream circuits, then without such a split, a second order neuron would have to maintain a high constant level of activity in order to signal both light increments and decrements. In addition, splitting the visual input signal is beneficial for subsequent motion detection circuits: Given the requirement for nonlinear processing from at least two displaced input, dealing exclusively with positive signals alleviates the biophysical implementation significantly.

Optic Flow Processing Neurons
Neurons responding to optic flow stimuli are found in the insect lobula plate (Krapp and Hengstenberg, 1996) as well as in area medial superior temporal visual area (MST) of primates (Duffy and Wurtz, 1997). In both cases, these neurons have extremely large receptive fields and possess different preferred directions in different locations of the receptive field. Furthermore, both classes of neurons receive DS input from upstream cells that have small receptive fields. Whether this input to MST cells also has a push-pull organization with neurons of opposite preferred directions making excitatory and inhibitory contacts onto the dendrite of MST cells such as is realized in fly lobula plate tangential cells is not known at present. Interestingly, the receptive fields match an optic flow occurring during certain types of ego-motion such as translation for various heading directions in case of MST cells and rotation around various body axes in case of fly lobula plate tangential cells (Krapp et al., 1998). For lobula plate tangential cells, it is known that the network connectivity between the various tangential cells is responsible for the exact spatial lay-out of the receptive field (Borst and Weber, 2011; for review see Borst et al., 2010). For MST neurons, it is unclear whether the layout of their receptive field is due to dendritic sampling of appropriately oriented local motion-sensitive input elements or to a connectivity between the MST neurons themselves.

Multistep and Multilevel Computation of DS
A push-pull type of input organization, however, has indeed been found for ON/OFF DS ganglion cells of the retina. As outlined above, the excitatory as well as inhibitory inputs to these ganglion cells are already, to some extent, DS as a result of complex presynaptic interactions. Other circuit features such as the spatially offset inhibition, together with particular dendritic processing, seem to significantly enhance direction selectivity at the level of the ganglion cell output, as compared to the input signals driving them. In a similar way, direction selectivity is produced in the insect optic lobe as a multistep process (Borst and Egelhaaf, 1990; Single et al., 1997; Joesch et al., 2008). In fly lobula plate tangential cells, the spatial layout of the input does not contribute to the direction selectivity: Each part of the receptive field can be stimulated separately with moving gratings, and the cell will respond the same way provided it has the same sensitivity in both locations. Interestingly, DS ganglion cells behave in a similar way: With the exception of the nondiscriminating zone (see Mechanisms at the Ganglion Cell Level), motion restricted to different subsections of the receptive field elicits similar DS responses. As to direction selectivity of fly neurons further upstream in the processing chain, mechanisms similar to the ones in ganglion cells and starburst amacrine cells might account for direction selectivity, for example in the dendrites of T4 or T5 cells.

Development of DS Circuitries
In higher visual centers, such as the amphibian tectum (Engert et al., 2002) or ferret area V1 (Li et al., 2008), visual experience is not only necessary but also instructive for the development of DS (reviewed in Elstrott and Feller, 2009). In contrast, at early sensory stages like in the vertebrate retina or the insect's lobula

plate, the development of DS circuitries appears to be independent of visual experience and even activity independent to some extent. This suggests that the development of DS circuitries is largely genetically guided by processes that are still hardly understood—an interesting and exciting commonality between vertebrate retina and insect DS pathways and a common challenge for future comparative research.

CONCLUSION

The last decade has witnessed much progress in our understanding of the cellular and subcellular mechanisms underlying direction selectivity. To a large extent, this is due to the application of advanced optical as well as genetic methods to this problem. Optical methods are indispensible whenever different anatomical compartments of a neuron turn out to be electrically separated, operating almost in isolation from the rest of the cell, such as the different dendritic branches of a SAC in the vertebrate retina (Euler et al., 2002) and the output terminals versus the dendrite of lamina cells (Reiff et al., 2010) or the dendrite of lobula plate tangential cells in the fly (Elyada et al., 2009). Looking at the corresponding circuits at the ultrastructural level reveals an intriguing complexity, both within the IPL of the retina (Briggman et al., 2011) as well as in the columns of the insect optic lobe (Takemura et al., 2008). The above examples demonstrate that this complexity has to be taken into account when modeling the corresponding circuits (e.g., Poleg-Polsky and Diamond, 2011; Schachter et al., 2010; Hausselt et al., 2007). Another amazing fact is how much effort over so many years had to be invested in this one single problem of direction selectivity in order to achieve the current level of understanding, a problem that, in terms of computation and information processing, seems quite modest (telling leftward from rightward), compared to the complex intellectual capabilities of humans. Our hope is that understanding this simple neural computation of direction selectivity in full detail will provide an important stepping stone toward our understanding of more complex functions of the nervous system.

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