Fly Motion Vision

Alexander Borst, Juergen Haag, and Dierk F. Reiff

Department of Systems and Computational Neurobiology, Max-Planck-Institute of Neurobiology, Martinsried, Germany; email: borst@neuro.mpg.de

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Key Words

optic flow, ego-motion, motion detection, receptive field, lobula plate, tangential cell

Abstract

Fly motion vision and resultant compensatory optomotor responses are a classic example for neural computation. Here we review our current understanding of processing of optic flow as generated by an animal's self-motion. Optic flow processing is accomplished in a series of steps: First, the time-varying photoreceptor signals are fed into a two-dimensional array of Reichardt-type elementary motion detectors (EMDs). EMDs compute, in parallel, local motion vectors at each sampling point in space. Second, the output signals of many EMDs are spatially integrated on the dendrites of large-field tangential cells in the lobula plate. In the third step, tangential cells form extensive interactions with each other, giving rise to their large and complex receptive fields. Thus, tangential cells can act as matched filters tuned to optic flow during particular flight maneuvers. They finally distribute their information onto postsynaptic descending neurons, which either instruct the motor centers of the thoracic ganglion for flight and locomotion control or act themselves as motor neurons that control neck muscles for head movements.

Contents

INTRODUCTION

In an animal's daily life, visual motion is abundant. Motion occurs, for example, when another animal, be it predator or prey, is moving in the observer's environment. Its motion usually increases the saliency of the moving animal, attracting the attention of the observer to the patch of the image where motion occurred. Therefore, many species developed a particular pattern of locomotion during which the episodes of self motion are as short as possible, with the animal being frozen in between, as if the animal knows how its motion takes off the magic hood provided otherwise by its camouflaging body pattern. Besides attracting visual attention, motion cues can segregate objects from background and indicate what is moving: The man in the dark with light bulbs on the joints of his arms and legs is a noninterpretable collection of points as long as he is at rest, but he becomes a man as soon as he starts walking (Johansson 1973). Although these two examples include a passive observer, motion cues also occur when the observer itself is actively moving. Then, the behavior of the observer largely determines the sensory input and causes the whole image to move across the observer's retinae. The resulting distribution of motion vectors is called optic flow (Gibson 1950). Optic flow depends on two things: first, on the observer's type of movement in three-dimensional (3D) space, and second, on the 3D structure of the environment in which the observer is moving (Koenderink & van Dorn 1987). However, the simultaneous extraction of exact information about the ego-motion and the structure of the environment from the optic flow represents an ill-posed problem because both parameters mutually depend on each other. Nevertheless, organisms seem to make meaningful assumptions on both aspects. They interpret a particular optic flow in terms of ego-motion as well as in terms of the environment's 3D structure. An expanding flow field with the pole of expansion in front can signal forward motion of the animal with an impending collision (Braitenberg & Taddei Ferretti 1966; Borst & Bahde 1988a,b; Rind & Simmons 1992; Hatsopoulos et al. 1995). Similarly, a high-velocity patch embedded in a low-velocity surround may indicate a nearby object in front of a more distant background (Reichardt & Poggio 1979).

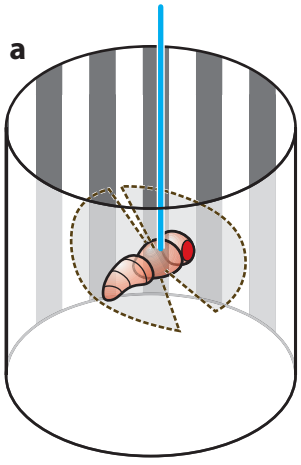
Neural mechanisms underlying the analysis of optic flow may have evolved particularly well in animals that move fast and have poor spatial vision, leaving them with motion vision as their primary source of visual information. These considerations make flies favorable subjects in which to study optic flow processing. Moreover, the fly's nervous system contains only a few hundred thousand neurons as opposed to billions and more found in the vertebrate central nervous system. This simplicity makes circuit analysis in the fly's nervous system, compared with a vertebrate system, a more manageable task, at least to some extent. Finally, the combination of physiological recording and genetic manipulation of neuronal function has now been established in the fruit fly *Drosophila melanogaster*. Thus, activity recording as well as behavioral studies can be combined with interfering with the fly's nervous system using sophisticated genetic tools.

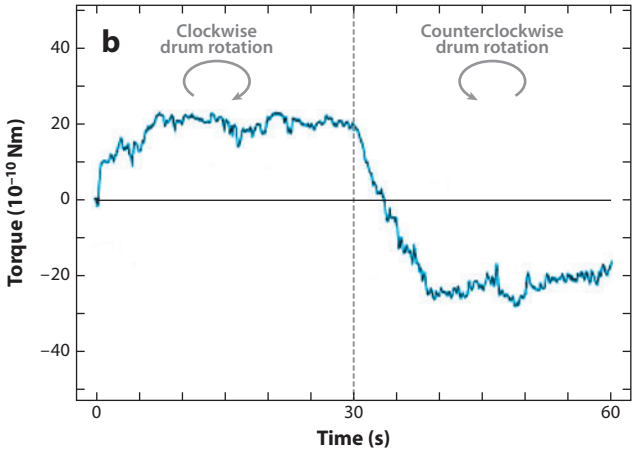
OPTOMOTOR RESPONSE AND THE ELEMENTARY MOTION DETECTOR

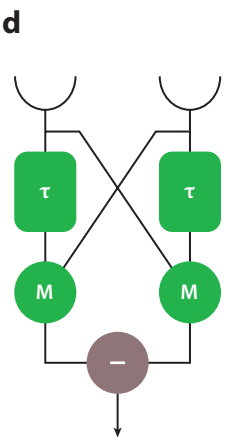
The optomotor response represents the behavioral paradigm that has most influenced the study of insect motion vision. When a fly is tethered in the center of a striped drum (**Figure 1*a***) and the drum is rotating clockwise, the insect tries to turn clockwise, too. When the drum is moving in the opposite direction, the insect turns counterclockwise (**Figure 1*b***). Thus, the optomotor response consists of a following reaction, syndirectional with the motion of the surround, that builds up slowly over several seconds. Measuring it in a tethered animal that cannot move its head offers two advantages: First, it isolates the visual response component from the proprioceptive, vestibular one; second, it allows investigators to allocate the visual motion stimulus on the animal's retina with ultimate precision. This approach was pioneered by Hassenstein & Reichardt (1956), who analyzed the turning tendency of the beetle *Chlorophanus viridis* walking on a spherical Y-maze built from straws (**Figure 1*c***). Their experiments finally led them to propose a specific model of elementary motion detection that accounts for all their observations in a quantitative way. This algorithmic model for elementary motion detection consists of two subunits, which are mirror-symmetrical to each other (**Figure 1*d***) (Reichardt 1961, 1987; Borst & Egelhaaf 1989; Borst 2007). Each subunit reads the luminance values measured in two adjacent ommatidia and multiplies them after one has been processed (i.e., delayed) by a low-pass filter. The output values of both subunits finally become subtracted. In contrast with a simple speedometer, whose output linearly increases with image speed, the model predicts a speed optimum at which the response is maximal. This optimum speed is set by the time constant of the low-pass filter. Beyond the optimum speed, the response decreases again. Furthermore, the optimum speed is a linear function of the pattern wavelength. Thus, optimum speed divided by pattern wavelength remains constant. The dimension of this ratio is a temporal frequency.

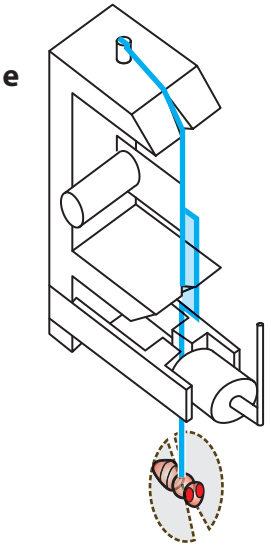
Thus, the Reichardt detector responds maximally to a certain number of spatial periods passing by a single photoreceptor, not to a certain image speed. In more general terms, the model predicts a highly counterintuitive dependence of the motion-detection process on pattern properties, such as its spatial wavelength as well as its contrast. Following these seminal studies of Hassenstein and Reichardt, sophisticated devices, such as the torque meter (**Figure 1*e***)(Goetz 1964), the wing beat analyzer (Goetz 1987), or a patterned Styrofoam ball, the movement of which was automatically detected (Buchner 1976), were introduced to measure the insect's turning tendency in flight or during walking. Using these kinds of setups, a number of experiments were performed showing the Reichardt detector to underlie motion vision in houseflies (*Musca domestica*; Fermi & Reichardt 1963, Eckert 1973) and fruit flies (*Drosophila melanogaster*; Goetz 1964, 1965). The optimum temporal frequency of both species was determined at ~1 Hz, which allows investigators to infer the time constant of the filters involved. To assess the sampling base of the elementary motion detector, sine-gratings of different wavelengths were used: For pattern wavelengths smaller than twice the sampling base, an inversion of the response (spatial aliasing) is expected (Goetz 1964). Determining the wavelength at which the response becomes negative revealed a sampling base of ~2 degrees in *Musca* (Eckert 1973) and 4.6 degrees for *Drosophila* (Goetz 1964, 1965; Buchner 1976). This conclusion fits exactly the interommatidial angle of each of the two species. Thus, nearest-neighbor interactions within the retina form the input to the Reichardt detector in the fly.

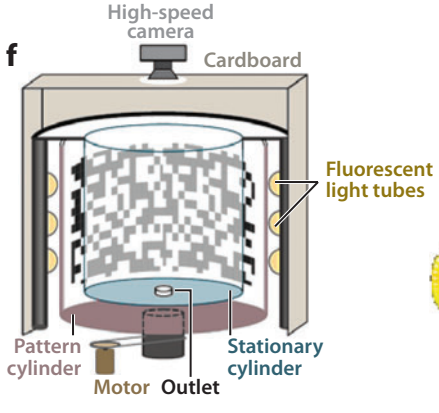
Although the optomotor response of tethered insects proved to be seminal for the discovery of the elementary motion-detection process, its role in free flight is more complex and more difficult to address. Under free-flight conditions, experimental parameters are less well defined, and multiple sensory inputs are integrated. In addition to the visual input, the

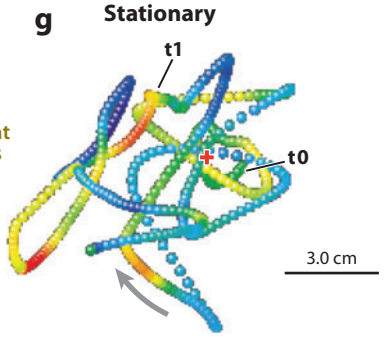


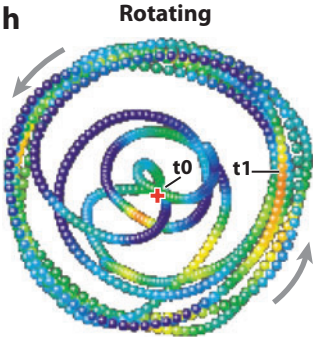












animal is informed about its ego-motion by numerous proprioreceptors, first of all its halteres (Mayer et al. 1988, Nalbach & Hengstenberg 1994, Chan et al. 1998, Sherman & Dickinson 2002). Nevertheless, high-speed video analysis of fruit flies flying inside a transparent cylinder (**Figure 1*f***) showed that free-flight behavior is dramatically influenced by rotation of a surrounding textured drum (Mronz & Lehmann 2008). When the drum is stationary, flies display their typical saccade-like flight structure with rather straight episodes interspersed by rapid changes in their flight direction (**Figure 1*g***). In contrast, when the drum is rotating, the flight path becomes much more curved, syndirectional to the drum's rotation, with straight flight episodes and saccades almost absent (**Figure 1*b***).

NEURAL ARCHITECTURE OF THE OPTIC LOBES

The fly's nervous system consists of two ganglia: the head and the thoracic ganglion (for an overview, see Strausfeld 1976). Because the head is covered with various sensory organs, most conspicuously the eyes, large parts of the head ganglion are devoted to the processing of information coming from these sensory organs. In the present context, the visual ganglia (**Figure 2**) are of specific interest. They consist of four different layers called the lamina, the medulla, the lobula, and the lobula plate. All these layers exhibit the same columnar structure as the retina. The principle underlying this building plan is retinotopy, i.e. neighboring image points are processed by neighboring facets in the eye and by neurons within neighboring columns in each of the layers of the visual ganglia. There exist two large chiasms between the optic ganglia, reversing the image along the antero-posterior axis twice: The first, known as the outer chiasm, occurs between the lamina and the medulla, and the second one, the inner chiasm, occurs between the medulla and the lobula complex. At the lobula plate level, a set of large motion-sensitive neurons can be found, known as lobula plate tangential cells. These tangential cells are key players with respect to optic flow processing and visual course control.

The neural processing of motion vision starts in the eye. Each eye is composed of facets or ommatidia, which are each equipped with a set of eight photoreceptors, with six outer photoreceptors, R1-6, surrounding the two central ones, R7 and R8. The photoreceptors carry their densely packed photopigment in rhabdomeres. Hardie (1986) described five populations of photopigments with different spectral properties in the fly retina. Their expression is strictly regulated during development (Wernet et al. 2006). Pigment Rh1 found in all R1-6 cells throughout the retina has two absorption peaks, one in the ultraviolet and the other one in the green. Four other pigments with single absorption peaks are expressed in R7 or R8, forming a stochastic matrix for color vision. When activated by light, all fly photoreceptors become depolarized through the opening of trp and trp-like channels (for review, see Hardie & Raghu 2001, Wang & Montell 2007). This depolarization is a fast process; thus, fly photoreceptors can follow sinusoidal luminance modulations up to 200–300 Hz depending on the fly species. The different photoreceptors in one ommatidium have different optical axes, but certain groups of photoreceptors within neighboring ommatidia have parallel optical axes. By connecting these groups of photoreceptors to

Figure 1

Optomotor behavior and elementary motion detection. (*a*) A fly tethered to a torque meter is surrounded by a striped drum. (*b*) When the drum is rotating clockwise, the fly exerts a clockwise turn; when the drum is rotating counterclockwise, the fly tries to turn counterclockwise, too (from Heisenberg & Wolf 1984). This reaction is called an optomotor response. (*c*) A beetle walking on a spherical Y-maze (from Hassenstein 1991). (*d*) The Reichardt detector model for elementary motion detection. (*e*) A torque meter as devised by Goetz (1964). (*f–h*) Flight arena with tracks from individual flies, with a stationary panorama (*g*) and while the panorama is rotating at a constant speed (*h*) (from Mronz & Lehmann 2008).

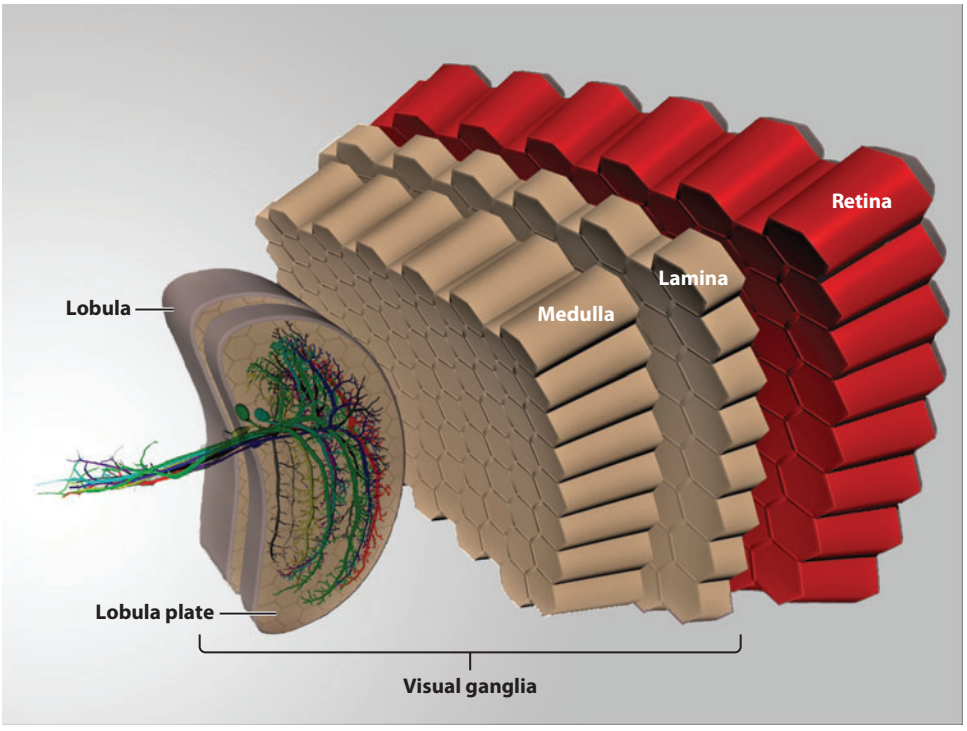


Figure 2

Schematic of the fly optic lobe. In the lobula plate, the group of vertical system (VS) cells is shown as three-dimensional reconstructions from 2-photon image stacks of single dye-filled cells (from Cuntz et al. 2007).

the same postsynaptic target, a so-called optic cartridge (Vigier 1908, Trujillo-Cenoz & Melamed 1966, Braitenberg 1967), the sensitivity of the system is increased without sacrificing acuity (Kirschfeld 1967). This principle is called neural superposition. Whereas the axons of photoreceptors R1–6 stop in the lamina, where they connect to large monopolar cells and amacrine cells, the axons of photoreceptors R7,8 run through the lamina without forming synapses and terminate in specific layers of the medulla.

The lamina contains, in addition to wide-field amacrine cells, eight different cell types per column, which connect it to the medulla: five lamina monopolar cells, L1–5, two centrifugal cells called C2 and C3, and the T1 cell. Ultrastructural studies on the connectivity within the lamina by serial sectioning transmission electron microscopy and subsequent 3D reconstruction (Meinertzhagen & O'Neill 1991) revealed that only L1-3 and the amacrine cell receive direct input from photoreceptor R1–6 terminals via tetradic synapses. At these tetrads photoreceptor synaptic transmission involves the release of histamine by R1-6 (Hardie 1989). Histamine gated chloride channels defective in the *ort* mutation (O'Tousa et al. 1989) and encoded by the gene *hclA* (Gengs et al. 2002) are expressed on the postsynaptic target cells of R1–6 and mediate signal-inverting synaptic communication: a strong, transient hyperpolarization upon illumination onset of the eye, which is followed by a sustained component that disappears with increasing light intensity (Jaervilehto & Zettler 1971, Straka & Ammermueller 1991, Zheng et al. 2009). When the light is switched off, a rebound depolarization is observed. The response of large monopolar cells L1 and L2 readily adapts to the

mean luminance over several orders of magnitude while leaving its contrast sensitivity almost unchanged (Laughlin & Hardie 1978, Laughlin et al. 1987). Within each cartridge, L4 receives its exclusive input from L2 (Braitenberg 1970, Strausfeld 1970) and connects to two neighboring posterior cartridges by synapsing again onto L2 (Braitenberg 1970).

Starting with the work of Cajal & Sanchez (1915), the columnar cell types of the medulla, lobula, and lobula plate have all been identified and described on the basis of Golgi impregnations in the housefly (Strausfeld 1976) as well as in *Drosophila* (Fischbach & Dittrich 1989). In addition to the terminals of R7/8 and the terminals of all the lamina neurons (except the lamina intrinsic amacrine cells), each medulla column houses more than 60 different cells per column. All incoming terminals ramify in different layers of the medulla (Takemura et al. 2008). This layout suggests a splitting of photoreceptor signals into several parallel pathways that might supply different functions such as the detection of form, polarization patterns, ultraviolet, color, and motion processing. However, because of the small diameter of columnar neurons' processes, until now, only a few electrophysiological recordings from identified neurons have described the visual response properties of some of them (DeVoe 1980; Gilbert et al. 1991; Douglass & Strausfeld 1995, 1996).

In the lobula plate, large neurons run perpendicular to the columns covering many hundreds or thousands of them with their dendrites. These are the lobula plate tangential cells, investigated in great detail first by Hausen and Hengstenberg (Hausen 1984, Hengstenberg et al. 1982). A total of 60 different cells are found in the blow fly *Calliphora vicina* all of which are motion sensitive. Some of these cells have also been described for *Drosophila* (Fischbach & Dittrich 1989, Scott et al. 2002, Raghu et al. 2007, Joesch et al. 2008, Maimon et al. 2010, Schnell et al. 2010). Interestingly, the same cells in different individuals turn out to be highly stereotyped with respect to the area covered by their dendrites within the lobula plate, but not with respect to the branching pattern (Cuntz et al. 2008). Using ablation experiments (Heisenberg et al. 1978, Geiger & Nässel 1981, Hausen & Wehrhahn 1983), investigators concluded that lobula plate tangential cells are involved in the fly's optomotor response.

REICHARDT-TYPE MOTION COMPUTATION IN THE OPTIC LOBES

The most significant response characteristic of the lobula plate tangential cells is their directional selectivity (**Figure 3** and see sidebar, Simulation Details): If a grating moves in one direction (the cell's preferred direction), the cell depolarizes or fires a train of action potentials. When the grating moves in the opposite direction (the cell's null direction), the cell hyperpolarizes or ceases to fire. In contrast, the photoreceptor signal is nondirectional, i.e. a single photoreceptor displays the same response regardless of whether the grating moves in one or the opposite direction. Thus somehow a nondirectional response at the photoreceptor level is transformed into a directional signal at the lobula plate tangential cell level. The Reichardt detector describes this transformation in amazing detail.

As mentioned above, one of the hallmarks of the Reichardt detector is its temporal frequency optimum: the larger the pattern wavelength, the higher the optimum speed (**Figure 3*b***, left panel). As already verified in the optomotor response, this property is also found in the visual responses of lobula plate tangential cells of the blow flies (**Figure 3*b***, middle panel) (Haag et al. 2004) and of fruit flies (**Figure 3*b***, right panel) (Joesch et al. 2008). For both species, this optimum is found at ~1 Hz. In contrast with the optomotor response, which is inherently slow, recordings in blow fly tangential cells also allowed for a comparison between the response transients of cellular responses and the ones of the Reichardt detector. When the velocity of a grating is stepped from zero to a constant value, the Reichardt detector exhibits a transient ringing at the temporal frequency of the pattern

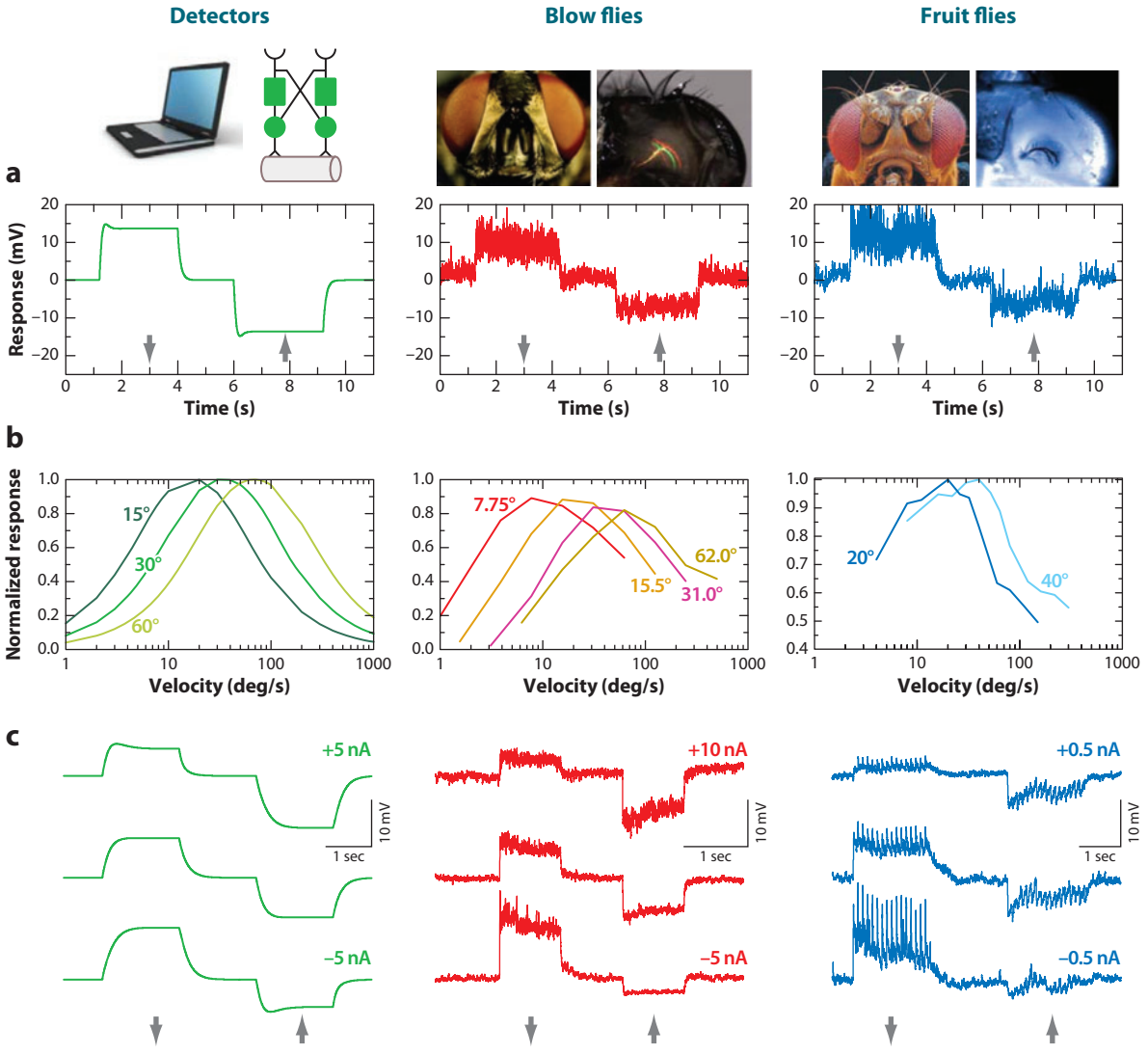


Figure 3

Comparison of the responses of an array of Reichardt detectors (*left column*) and of lobula plate tangential cells in blow flies (*middle column*) as well as in fruit flies (*right column*). (*a*) Visual response to preferred direction (downward, *indicated by the arrow*) and null direction (upward) motion. (*b*) Steady-state responses to sine-gratings with different spatial wavelengths drifting at constant velocities. The optimum is shifted toward larger velocities with increasing wavelength of the pattern in such a way that the optimum is always at the same temporal frequency (ratio of velocity and pattern wavelength). This optimum temporal frequency is roughly 1 Hz in both blow flies and *Drosophila*. (*c*) Evidence for a push-pull configuration of local motion input to lobula plate tangential cells. Visual motion along the preferred and null directions was presented during injection of depolarizing and hyperpolarizing current in the recorded cell. When the cell is artificially depolarized, the preferred-direction (PD) response becomes smaller; when the cell is hyperpolarized, the null-direction response becomes smaller. Experimental data are from Haag et al. (2004), Joesch et al. (2008), and J. Haag & A. Borst, unpublished observations.

motion before settling at the steady state (Borst & Bahde 1986). Such a transient ringing could indeed be observed in lobula plate tangential cells of the blow fly (Egelhaaf & Borst 1989). Furthermore, the amplitude of the ringing showed a characteristic time constant by which it decays to the steady state, which depended on the contrast of the moving pattern as well as on the pattern contrast before the onset of motion (Reisenman et al. 2003, Joesch et al. 2008). These findings led to an elaborated Reichardt detector with high-pass filters inserted in the cross-arms, the time constant of which rapidly adapts (Borst et al. 2003). Given these modifications, the Reichardt model can account for both the steady state and all transient response features of the lobula plate tangential cells in a detailed way. This statement applies not only to stimulus situations using velocity steps, but also to Gaussian white-noise velocity profiles. When using such stimuli with different standard deviations, the response exhibited a velocity gain control; i.e., the response-velocity function was found to be steeper the smaller the velocity fluctuations (Brenner et al. 2000). Astonishingly and completely counterintuitively, the Reichardt detector replicates this velocity-gain control even when all its filter time constants are fixed (Borst et al. 2005, Safran et al. 2007). Last, even though tangential cells spatially integrate the output signals of local motion detectors and, thus, should represent their summated output, the signals of individual motion detectors can also be observed experimentally, either when spatial integration is prevented by presentation of grating motion through a slit or by local calcium measurements in fine dendritic branches. Both these techniques revealed local signals that have all the characteristics of local motion detectors of the Reichardt type (Egelhaaf et al. 1989, Single & Borst 1998, Haag et al. 2004).

Given the evidence that has been accumulated for Reichardt-like motion computation in the optic lobes of different fly species, the question naturally arises about its neural implementation: Which neurons form the input to the Reichardt detector? Which neurons constitute the Reichardt detector? What are the biophysical mechanisms underlying mathematical operations such as low-pass and high-pass filtering and multiplication? As for the question about the input, it is fairly undisputed that motion vision is fed primarily by signals from photoreceptors R1–6, but not from R7 and 8. This statement is supported by the observation that the optomotor response in *Drosophila* is abolished by genetic elimination of R1–6, but unaffected when R7 is missing (Heisenberg & Buchner 1977). Furthermore, the optomotor response turned out to be color-blind under certain experimental conditions: When presenting a grating of alternating color, there is a brightness ratio, the so-called point of equiluminance, at which the optomotor response is

SIMULATION DETAILS

The visual pattern consisted of a sine grating with 100% contrast covering a visual angle of 60 degrees. It was moved at a precision of 0.001 degrees/ms. The detector array comprised 32 detectors with a sampling base of 1.875 deg. Signals from each photoreceptor were low-pass filtered (1st order filter, time constant = 100 ms) and multiplied with the high-pass filtered (1st order filter, time constant = 200 ms) signal from the adjacent receptor. A DC value of 100 nS was added to the summed output of these multiplications, and the resulting signal was clipped when negative. This signal provided the excitatory conductance to a passive one-compartment model neuron. A mirror-symmetrical operation was used to provide the inhibitory conductance to the model neuron. The membrane potential V_m was calculated as

$$V_m = \frac{E_{exc} \cdot g_{exc} + E_{inh} \cdot g_{inh} + I_{inj}}{g_{exc} + g_{inh} + g_{leak}},$$

with $E_{exc} = 40$ mV, $E_{inh} = -40$ mV, and $g_{leak} = 100$ nS. In panels *a* and *c*, the pattern had a spatial wavelength of 60 degrees and was moved at 15 degrees/s. In panel *b*, the patterns had a wavelength of 15, 30, and 60 degrees, respectively, moving at velocities between 1 and 1000 degrees/s. In panel *c*, a current of +5 nA and −5 nA was injected permanently, resulting in an offset of the membrane potential of + and – 16.6 mV, respectively, corresponding to an input resistance of 3.33 MΩ while the pattern was at rest. During motion, this input resistance dropped by ∼5%–10%, depending on the specifics of the stimulus conditions.

zero (Yamaguchi et al. 2008). With respect to the other questions raised above, experimental evidence is rare, leaving room for many speculations. At present, it is not clear which columnar neurons provide synaptic input to the lobula plate tangential cells. Most evidence speaks in favor of the bushy T cells, T4 and T5, as potential input candidates, one of which (T5) has been reported to respond to moving gratings in a directionally selective way, the other one (T4) to be only weakly directionally selective (Douglass & Strausfeld 1995, 1996). So far, a single study has shown unequivocally a chemical synapse between a horizontal system (HS)-cell dendrite and a columnar T4 cell (Strausfeld & Lee 1991). Additional circumstantial evidence in favor of T4 and T5 cells includes the observation that these cell types exist in four different subtypes per column, each of which ramifies in a different stratum of the lobula plate. Anatomical investigations have revealed that horizontally and vertically sensitive lobula plate tangential cells extend their dendrites to four different strata of the lobula plate, according to their preferred direction. These four strata have also been labeled in the *Drosophila* brain by using the 2-deoxyglucose (2-DG) method (Buchner et al. 1984, Bausenwein & Fischbach 1992) simultaneously with the most proximal layer of the medulla, exactly where T4 cells ramify, and the posterior layer of the lobula, where T5 cells extend their branches. The direction of motion that activates a specific stratum, as labeled using the 2-DG method, matches the preferred direction of those lobula plate tangential cells that extend their dendrite in this stratum.

Although it is still unclear which neurons constitute the Reichardt detector, good evidence indicates that motion-sensitive neurons with opposite preferred directions provide excitatory and inhibitory input to the dendrites of lobula plate tangential cells. In terms of the Reichardt model, these inputs correspond to the mirror-symmetrical detector subunits. A conductance-based model of an isopotential compartment that receives input from two arrays of such subunits predicts the following (**Figure 3*c***, left panel): Depolarizing the postsynaptic compartment by a tonic injection of positive current decreases the preferred-direction response amplitude while increasing the null-direction response amplitude. Hyperpolarizing the postsynaptic compartment by a tonic injection of negative current increases the preferred-direction response amplitude while decreasing the null-direction response amplitude. The reason for this effect is simply the reduction of the respective driving force by manipulating the postsynaptic membrane potential. This exact effect can be observed in tangential cells of blow flies (**Figure 3c**, middle panel) (J. Haag and A. Borst, unpublished observations) and fruit flies (**Figure 3c**, right panel) (Joesch et al. 2008). These results support the subtraction stage in the Reichardt detector to be realized on the tangential cells' dendrites (see also Borst & Egelhaaf 1990). Given this push-pull input organization, a moving pattern of increasing size is expected to stimulate increasingly more local motion detectors and, thus, to decrease the input resistance of the integrating cell. Thus the response as a function of pattern size will saturate while still being sensitive to image velocity. This so-called gain control is indeed observed in blow fly tangential cells under various conditions (Haag et al. 1992, 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 and revealed excitatory nicotinic acetylcholine receptors (nAChRs) as well as inhibitory γ-aminobutyric acid receptors (GABARs) on these cells (Brotz & Borst 1996). Blocking the inhibitory input in vivo by injecting the GABAR-antagonist Picrotoxinin leads to an enhanced preferred-direction response, whereas the null-direction response is reversed (Egelhaaf et al. 1990, Single et al. 1997). Because blocking the inhibitory input should isolate the excitatory input, investigators thought it indicated a weak direction selectivity of each of the two subunits: The enhanced preferred-direction response revealed an inhibitory

activity during preferred-direction motion, and the positive null-direction response uncovered an excitatory activity during null-direction response. Accordingly, the full direction selectivity as observed under control conditions in the tangential cells is the result of subtracting two inputs with opposite preferred directions realized by the push-pull input organization.

Drosophila offers the possibility to visualize the intracellular distribution of certain transmitter receptors with high resolution. This visualization was done first by proving the expression of a particular receptor on a given cell by antibody staining. Then, a labeled version of the same receptor subtype could be expressed in the same cell in an otherwise unlabeled brain (**Figure 4**). Using a Gal4-driver line that led to expression in lobula plate tangential cells and two types of labeled reporter genes, excitatory and inhibitory transmitter receptors were found to be located on the fine dendritic branches of HS and VS cells (Raghu et al. 2007, 2009). One such reporter gene encodes the GABA receptor subunit Rdl (resistance against Dieldrin, Dieldrin being a potent insecticide; Ffrench-Constant et al. 1990) fused to a small hemagglutinin (HA) tag (Sanchez-Soriano et al. 2005). This way the receptor subunit can be visualized by antibody staining against the HA tag. The other transgene encodes the alpha

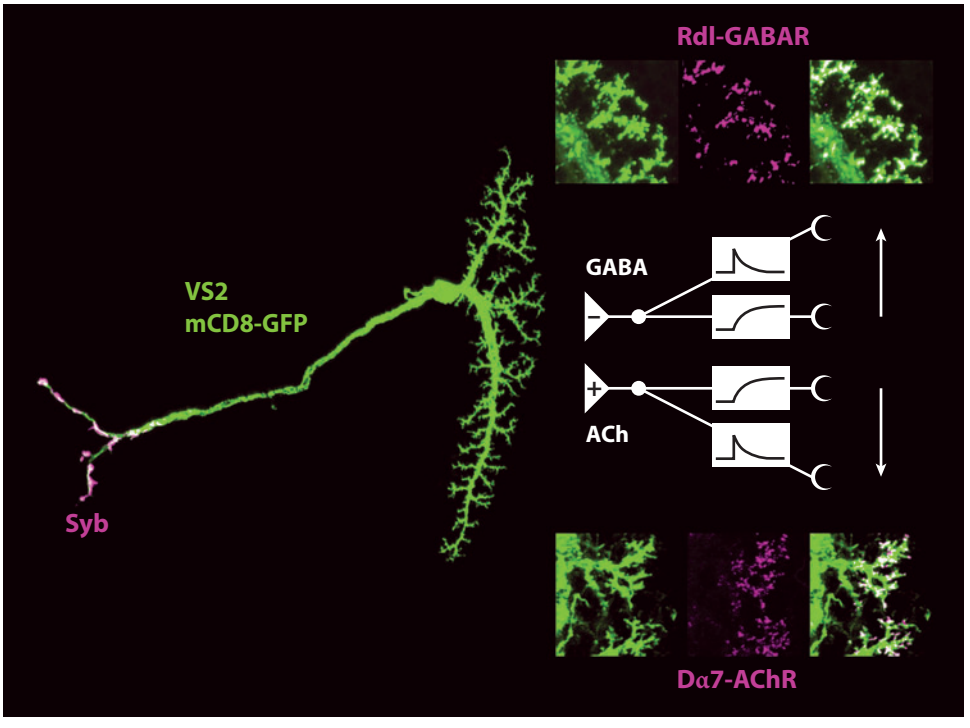


Figure 4

Immunohistochemistry reveals synaptic polarity in *Drosophila* VS cells. Staining of an individual VS2 cell was obtained by a mosaic analysis with repressible cell marker (MARCM) technique (Lee & Luo 1999). The anatomy of the cell is visualized using an mCD8-GFP transgene (*green*). Presynaptic terminals are labeled by a DsRed fluorophore tagged to synaptobrevin (magenta). Driving expression of receptor subunits of the acetylcholine receptor Dα7 [*bottom three insets*: anatomy (*left*), Dα7 fluorescence (*center*), overlay (*right*)], or the GABA receptor Rdl [*top three insets*: anatomy (*left*), Rdl fluorescence (*center*), overlay (*right*)] visualizes the location of excitatory and inhibitorys input onto the VS2 cell on the small higher-order branchlets of its dendrite (compiled from Raghu et al. 2007, 2009). These inputs may correspond to directionally selective subunits of the Reichardt type, schematically represented to the right.

subunit 7 (Dα7) of the *Drosophila* nicotinic acetylcholine receptor tagged with green fluorescent protein (GFP). Taken together with the available pharmacology of lobula plate tangential cells (Brotz & Borst 1996) and immunohistochemical data in blow flies (Brotz et al. 2001), these data strongly suggest that retinotopically organized local motion detectors with opposite-direction selectivity provide excitatory and inhibitory input onto the dendrites of tangential cells, endowing them with direction selectivity (**Figure 4**).

GLOBAL OPTIC-FLOW ANALYSIS IN THE LOBULA PLATE AND BEYOND

Local motion detection constitutes the first step in optic flow analysis by providing the nervous system with a vector field as represented by the output signals from the retinotopic array of Reichardt-type motion detectors. This optic flow information is now processed within the lobula plate by the so-called tangential cells. All these cells have large dendrites by which they spatially integrate over various subpopulations of local motion detectors. According to their overall preferred direction, they are grouped into horizontal (H) and vertical (V) cells, respectively (for details, see Hausen 1984, Borst & Haag 2002). Cells of the horizontal system have their dendrites located in the anterior layer of the lobula plate. Well-studied representatives of this group are the three HS cells (Hausen 1982a,b), the two CH cells (Eckert & Dvorak 1983, Egelhaaf et al. 1993, Gauck et al. 1997), H1, and and H2 (Hausen 1984). The vertical system is composed of 10 VS cells (Hengstenberg 1982, Hengstenberg et al. 1982) in large fly species and presumably only 6 VS cells in *Drosophila* (Scott et al. 2002). VS cells orient their dendrites along the dorso-ventral axis in the posterior layer of the lobula plate (**Figure 2**). VS cells are numbered sequentially according to the location of their dendrite from most lateral (VS1) to proximal (VS10).

Most tangential cells (HS and VS cells) respond to visual motion in a graded way: In response to motion along their preferred direction, they depolarize, and this depolarization is superimposed by action potentials of irregular amplitude (Hengstenberg 1977, Haag & Borst 1996). In response to null-direction motion, they hyperpolarize. However, some tangential cells such as H1, H2, H3, H4, or V1 produce regular action potentials. These spiking neurons extend their axon across the midline of the brain to contact neurons of the contralateral lobula plate. Passive and active membrane properties of HS, CH, and VS cells were investigated by current- and voltage-clamp experiments and optical recording of calcium concentration, accompanied by detailed biophysical modeling (Egelhaaf & Borst 1995; Borst & Haag 1996; Haag et al. 1997, 1999; Borst & Single 2000; Haag & Borst 2000; Oertner et al. 2001; Single & Borst 2002). In addition, the contribution of these active membrane properties to the encoding of motion information as well as the impact of photon noise on the response reliability could also be clarified (Haag & Borst 1997, 1998; Borst & Haag 2001; Borst 2003; Shi & Borst 2006).

According to the retinotopic layout of the lobula plate, the location of a cell's dendrite within the lobula plate is a good predictor of its receptive field center. Thus, the three HS cells, which cover the lobula plate in the northern (HSN), equatorial (HSE), and southern (HSS) parts, have their receptive field centers in the dorsal, middle, and ventral parts of the fly's visual field. Even within the dendrite of a single cell, the retinotopic arrangement of the lobula plate becomes evident when local motion stimuli are presented at different positions within the receptive field while visualizing dendritic activity via calcium imaging (Borst & Egelhaaf 1992, Borst & Single 2000).

However, when investigating the receptive fields of lobula plate tangential cells in detail, Krapp and Hengstenberg (Krapp & Hengstenberg 1996, Krapp et al. 1998) discovered that the receptive fields extend over a much larger area along the azimuth than expected from their dendritic field within the lobula plate. Furthermore, they found that the receptive

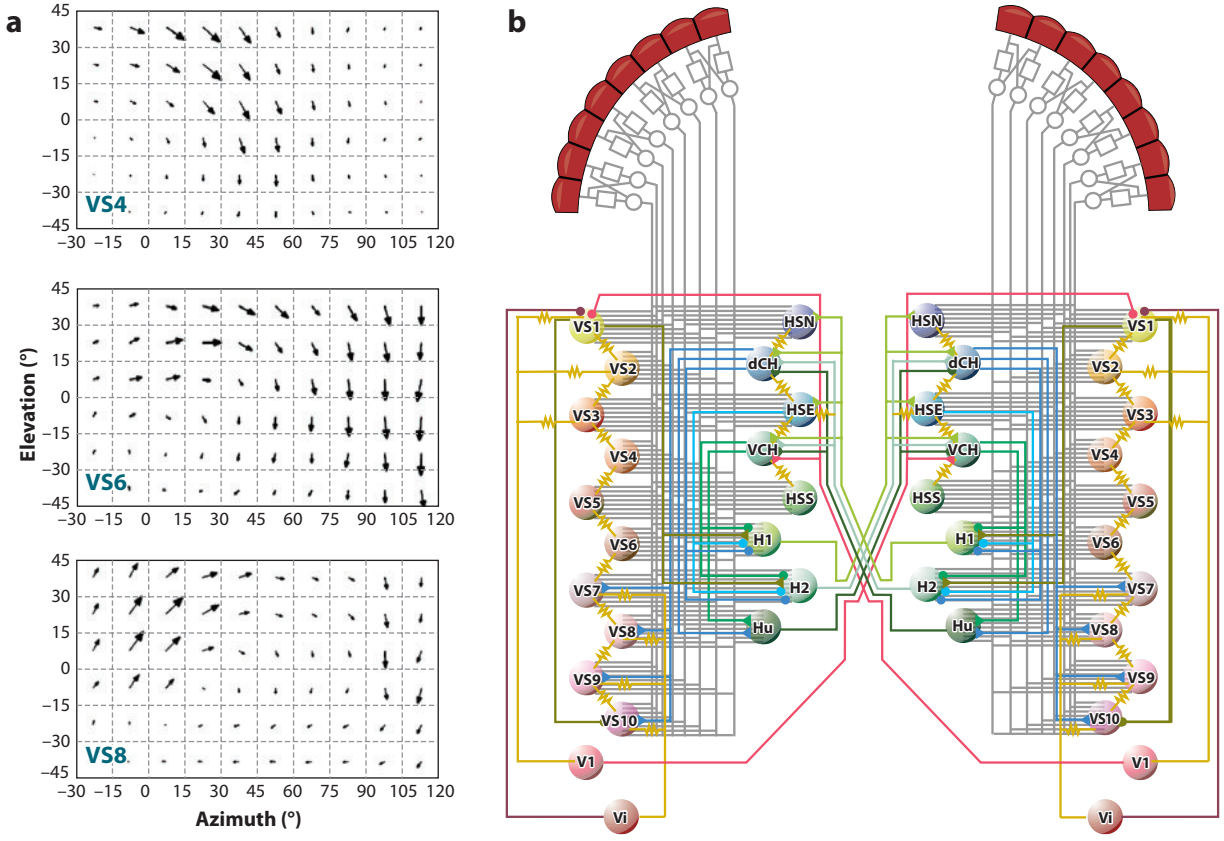


Figure 5

(*a*) Receptive fields of three VS cells (from Wertz et al. 2009). (*b*) Network circuitry of the different tangential cells of the blow fly lobula plate. In addition to receiving retinotopic input from arrays of local motion detectors, cells are strongly interconnected either within one hemisphere or between the two hemispheres. Excitatory and inhibitory chemical synapses are symbolized by triangles and circles, respectively. Resistor symbols represent electrical synapses.

fields are composed of areas with different preferred directions. This property is shown in **Figure 5*a*** for three different VS cells. The receptive fields of VS cells exhibit maximum sensitivity to downward motion that corresponds with their location within the lobula plate. In addition, they are sensitive to horizontal motion in the dorsal part of the visual field as well as to upward motion at a position that is ~180 degrees displaced along the azimuth. In sum, the receptive fields have the appearance of curled vector fields, such as an optic flow occurring when the animal rotates around a particular body axis. Because each cell had a different receptive field, this finding gave rise to the notion that the tangential cells could act as matched filters, responding maximally during certain flight maneuvers (Franz & Krapp 2000). This hypothesis was indeed confirmed experimentally (Karmeier et al. 2005).

Although this observation puts the lobula plate tangential cells on center stage for visual course control, the question remains of how these receptive fields come about. If acting in isolation and strictly in parallel, the receptive fields of all these cells should be much narrower. In addition, their elementary motion detector input is expected to have a mostly uniform

preferred direction, given that most of the cells ramify within only one layer of the lobula plate. A solution to this problem was provided by a series of experiments during which the signals of two tangential cells were recorded simultaneously. In these experiments, current was injected in one of the cells while the response to the current injection was recorded in the respective other cell (Haag & Borst 2004). These and other experiments revealed an intriguing network within the lobula plate (**Figure 5*b***); most of the tangential cells were connected to each other, within each hemisphere as well as between the two hemispheres (Hausen 1984; Horstmann et al. 2000; Haag & Borst 2001, 2002, 2003, 2004, 2005, 2007, 2008; Kurtz et al. 2001; Farrow et al. 2006; Kalb et al. 2006). Many of these connections are based on electrical instead of chemical synapses. This connectivity was hypothesized to account for the large and complex receptive fields: While one part of the receptive field would be brought into the cell via its dendrite, additional information should arrive at the cell indirectly via its neighbors. Therefore, ablating certain cells within the lobula plate should affect the receptive fields of the remaining cells. Performing such experiments via single-cell photoablation in blow flies indeed revealed defective receptive fields in the remaining cells (Farrow et al. 2003, 2005), as correctly predicted by detailed computer simulations of the lobula plate network (Cuntz et al. 2003, 2007). Furthermore, these computer simulations predicted that, based on the electrical compartmentalization of VS cells and the specific contact site between neighboring VS cells at the axon terminal, different receptive fields should be observable in the dendrite and in the axon terminal (Cuntz et al. 2007): Using calcium imaging to visualize such signals even in the thinnest branches, Elyada et al. (2009) confirmed this prediction experimentally. Thus much experimental evidence indicates that the receptive fields of the lobula plate tangential cells come about by dendritic integration of local, motion-sensitive input elements in addition to the interconnectivity among the tangential cells themselves.

Much optic flow analysis is already performed at the lobula plate level. In the next step toward flight control, lobula plate tangential cells synapse onto descending neurons that either connect to the motor centers in the thoracic ganglion or directly innervate the neck muscles for head motion control (Strausfeld & Bassemir 1985, Strausfeld & Seyan 1985, Milde et al. 1987, Strausfeld et al. 1987, Gronenberg et al. 1995, Huston & Krapp 2008). As two representatives of such neurons, DNOVS1 and DNOVS2 (descending neurons of the ocellar and vertical system) have been recently examined in great detail (Haag et al. 2007; Wertz et al. 2008, 2009). Using current injection during dual intracellular recording from DNOVS cells and various VS cells, their connectivity to VS cells was established. It appeared that the two DNOVS cells are tuned to two different axes of rotation similar to the tuning of their input VS cells (Wertz et al. 2009). Also, the tuning width of DNOVS cells turned out to be similar to those of their input VS cells. However, during rotation of naturalistic images, the responses of DNOVS cells are rather smooth, whereas the signals of VS cells strongly fluctuate over time (Wertz et al. 2009). This effect can be attributed to the axo-axonal gap junctions between the VS cell terminals, which perform a linear interpolation of the output signals (Cuntz et al. 2007, Weber et al. 2008, Elyada et al. 2009) and which become fully visible in the membrane potential of the postsynaptic cells. Therefore, it is not the selectivity for particular optic flows that increases when going from the lobula plate to descending neurons, but rather the robustness of the responses against the particular layout of the visual environment. Of course, the small number of descending neurons that have been studied in such detail does not allow for any generalization at the moment, and indeed, extracellular recordings from the fly cervical connective, which contains, depending on the species, between 3600 and 8000 axons of ascending and descending neurons (Coggshall et al. 1973), revealed a large number of rather diverse and often highly nonlinear response types (Borst 1991).

FUTURE ISSUES

Approximately a half-century after the Reichardt detector correctly described the process of elementary motion vision in insects, it is still unclear which cells are responsible for the computations as defined in this model. However, this situation may change in the future. Promise comes from recently developed genetic techniques in *Drosophila* (for an introduction, see Borst 2009). Here, combining cell-specific expression lines (enhancer trap or Gal4-lines; Brand & Perrimon 1993) with genetically encoded indicators of neural activity (Miyawaki et al. 1997) or blockers of synaptic transmission (van der Bliek & Meyerowitz 1991) provides the tools to identify those columnar elements involved in motion processing. In a series of experiments, our lab has tested a large set of genetically encoded calcium indicators under identical conditions at the neuromuscular junction of *Drosophila* larvae (Guerrero et al. 2005, Reiff et al. 2005, Mank et al. 2006, Hendel et al. 2008). One of the indicators, TN-XXL (Mank et al. 2008), proved to be best suited for in vivo imaging in the visual system of adult flies with respect to signal-to-noise ratio, calcium sensitivity range, and kinetics. Using this indicator, we started to record the activity of columnar neurons in the optic lobes of *Drosophila* in response to visual motion stimuli. In a different approach, selected sets of columnar neurons can be removed from the circuit while recording from the lobula plate tangential cells during motion stimulation: Any alteration of the wild-type motion response (Joesch et al. 2008) will indicate the participation of the respective neurons in the motion-detection circuitry. As appealing as this approach may look initially, its biggest caveat concerns the often-variable expression level and lack of selectivity of the different driver lines available. A negative result (wild-type-like motion response) during blockade of cell X can mean that cell X does not participate in the circuit or that the expression level of the toxin was not high enough to suppress synaptic transmission. A positive result can mean that cell X does indeed participate in the circuit or that another cell Y, which somehow went unnoticed, is part of the expression pattern and is the real player. Such effects may explain why three different studies, performed to determine which lamina cells represent the input channels to motion vision, came to rather divergent conclusions (Rister et al. 2007, Katsov & Clandinin 2008, Zhu et al. 2009). Controlled and standardized expression levels in well-defined and small sets of neurons are highly desirable, such as those resulting from enhancer fragment lines currently being produced (Pfeiffer et al. 2008). Given these new developments, we are confident that both techniques outlined above represent the way to answer the long-standing question about the cellular nature of elementary motion detection.

Another important question concerns the performance of the system under natural conditions. How does fly motion vision cope with natural images? How is it adapted to the animal's specific flight style, with its rapid saccadic turns interleaved by fairly straight flight episodes, and what are the specific roles of the different tangential cells under these conditions? Investigating the performance of Reichardt detectors when confronted with natural image sequences, O'Carroll and colleagues found the ambiguity of the Reichardt detector with respect to velocity estimation to vanish under these conditions owing to the predictable spatial frequency content of natural scenes (Dror et al. 2001). When recording the responses of HS cells in hoverflies, they indeed found these neurons to encode the velocity of natural images independently of the particular image used, despite large differences in contrast between the images (Straw et al. 2008). To assess the information encoded in the tangential cell's signals, Egelhaaf, van Hateren, and colleagues used flight trajectories of blow flies recorded by a coil system (Schilstra & van Hateren 1999) and reconstructed the exact retinal motion sequences experienced by the fly during flight. Playing back these stimuli to a tethered fly while recording intracellularly from tangential cells, HS cells encoded

information about the spatial structure of the environment during straight flight segments between saccadic turns (Karmeier et al. 2006). As a complementary approach, *Drosophila* offers the possibility to ablate individual neurons or subpopulations of the set of tangential cells genetically using targeted expression of, e.g., translational blockers such as Ricin A (Moffat et al. 1992). By testing these flies in free flight or walking paradigms, differences in behavior should be attributable to the specific loss of genetically determined functional classes of neurons. Thus, a combined genetic, physiological, and behavioral approach should shed further light on the cellular processing of optic flow and the role of different neurons in behavior.

DISCLOSURE STATEMENT

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