instance, the loss of dopamine also increases inhibitory synaptic drive from parvalbumin-positive interneurons onto iSPNs, but not dSPNs (Gittis et al., 2011). It will therefore be imperative to determine how the many modifications triggered by dopamine loss combine to influence the spiking properties of dSPNs and iSPNs. Clearly, there is much work to be done to understand the pathology of PD, and this Report by Parker et al. (2016) points to many new and exciting avenues for future investigations.

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Four to Foxtrot: How Visual Motion Is Computed in the Fly Brain

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In this issue of *Neuron*, Serbe et al. (2016) use cell-type-specific genetic tools to record and manipulate all major inputs to directionally selective neurons in *Drosophila*. Their results localize the site of motion computation and reveal unexpected complexity of temporal tuning in the underlying neural circuit.

An important task for the visual system of many animals, both vertebrate and invertebrate, is the detection of visual motion. Motion detection is essential for a range of visual functions, from maintaining gaze and guiding smooth pursuit eye movements in mammals, to detecting predators and stabilizing flight in flies. It was first hypothesized by Sigmund Exner in the late 1800s that visual motion detection is performed by specialized neural circuits—a prediction that turned out to be true. For more than a century, the challenge has been to delineate these circuits and to unravel their computational mechanisms.

The first algorithmic model for visual motion detection was devised in post-WWII Germany by Bernard Hassenstein and Werner Reichardt (Hassenstein and Reichardt, 1956). Founders of the field of biological cybernetics, Hassenstein and Reichardt applied their expertise in biology and physics to develop algorithmic descriptions of neural functions and behavior. Their studies of the turning behavior of a weevil (*Chlorophanus*), suspended from a post and walking on a Y-maze globe made of straw, led to an elegant and concise model for directional motion selectivity comprising three basic operations: temporal filtering, spatial offset, and multiplication (Figure 1A).

The Hassenstein-Reichardt model for elementary motion detection (HR-EMD) guided the development of systems neuroscience in invertebrates but was also rapidly adopted for studying the visual systems of vertebrates, following the discovery of directionally selective cells in the retina of the rabbit (Barlow and Levick, 1965). Its most significant contribution, however, is that it led to new theories of how neurons implement arithmetic operations like multiplication and subtraction and initiated the search to identify their specific neural substrates.

The search for the physical implementation of the HR-EMD model received a boost when a network of ~60 neurons in the optic lobe of the blowfly was found to respond selectively to distinct patterns of wide-field visual motion (Hausen, 1984). These neurons, the lobula plate

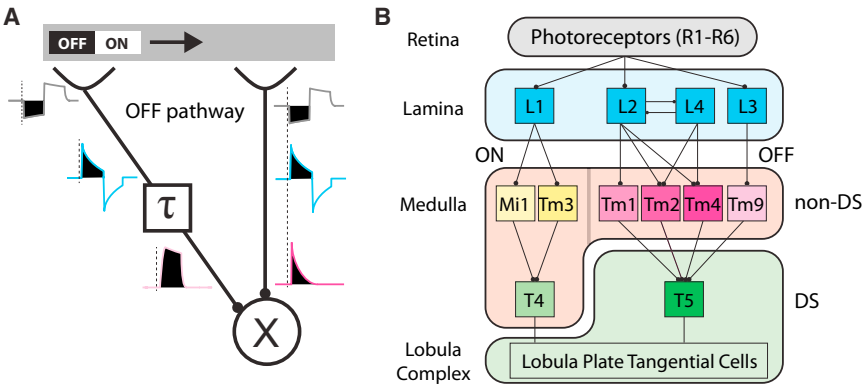

Figure 1. Schematic of a Hassenstein-Reichardt Correlator Subunit and Visual Motion Signaling Pathways in *Drosophila*

(A) Schematic of the Hassenstein-Reichardt model for visual motion detection. Luminance signals pass through a temporal filter (τ) before nonlinear integration (X) with signals from a neighboring optical unit. Waveforms represent responses of individual neurons to moving edges at successive layers within the fly motion circuit: photoreceptors (gray), lamina monopolar cells (cyan), and OFF-pathway transmedulla neurons (Tm; magenta).

(B) Neuronal connectivity of motion circuits in the fly optic lobes. The lamina monopolar cells (L1-L3) invert photoreceptor input; L4 makes reciprocal connections with L2. Lamina signals are transmitted into rectified ON and OFF pathways in the medulla. Medulla neurons exhibit diverse temporal tuning, indicated by color shading. Directional selectivity (DS) first emerges in the T4 and T5 dendrites. Directionally selective ON and OFF signals from T4 and T5 neurons are integrated within the lobula plate tangential cells (LPTCs), which are thought to control visual behavior.

tangential cells (LPTCs), seemed to integrate signals computed by local motion detectors and satisfied many predictions of the HR-EMD model. But details of the presynaptic motion detector circuits remained unclear for several more decades until the introduction of genetic tools to achieve cell-type-specific manipulations in the nervous system of the fruit fly, *Drosophila*, and the application of serial-section electron microscopy (EM) for connectomic reconstruction of visual circuits in the fly brain.

First, the second-order lamina monopolar cells (LMCs) L1 and L2 (Figure 1B) were identified as the primary inputs to the *Drosophila* motion system (Rister et al., 2007). Like the photoreceptors, LMCs respond to both bright and dark stimuli, though the sign of the response is inverted (Clark et al., 2011). L1 and L2 feed into rectified ON and OFF channels, giving rise to parallel light- and dark-selective motion pathways in the medulla (Joesch et al., 2010; Strother et al., 2014; Figure 1B). Simultaneous progress was made on the downstream circuits that provide motion input to the LPTCs. Calcium imaging showed that two neuron types, T4 and T5, exhibit directionally selective responses to moving bright and dark edges, respectively (Fisher et al., 2015a; Maisak et al., 2013), and blocking their output reduces LPTC motion-tuning and impairs optomotor behavior (Maisak et al., 2013). Finally, EM tracing revealed T4 and T5's presynaptic inputs and their spatial organization, establishing the putative circuits for motion computation in both the ON and OFF pathways (Takemura et al., 2013).

In this issue of *Neuron*, Serbe et al. (2016) explore the proposed circuit for the OFF motion pathway. According to previous work (Shinomiya et al., 2014; Takemura et al., 2013) the directionally selective T5 neurons receive the majority of their synaptic input from four excitatory transmedulla neuron types: Tm1, Tm2, Tm4, and Tm9 (Figure 1B). Combining genetic access with two-photon calcium imaging of visually evoked responses, Serbe et al. (2016) found that all four Tm types selectively respond to luminance decreases, confirming their OFF-pathway identity. They also found that the four types exhibit diverse temporal kinetics: Tm2 and Tm4 are transient (fast-adapting); Tm9 is sustained (non-adapting); and Tm1 is intermediate (slow-adapting). None of the four Tm neurons exhibited directional selectivity, and all had narrow-field center-surround receptive fields, although Tm9 showed additional sensitivity to wide-field stimuli. These results are largely consistent with prior physiological studies of Tm1, 2, and 9 (Behnia et al., 2014; Fisher et al., 2015b; Meier et al., 2014; Strother et al., 2014) and provide the first comprehensive physiological survey of the OFF motion pathway.

After characterizing the visual response properties of T5's predominant presynaptic inputs, Serbe et al. (2016) tested what each type contributes to motion detection by measuring the impact of their silencing on downstream motion-evoked responses. For each Tm neuron type, blocking the synaptic output by overexpressing a temperature-sensitive dynamin mutant (shibire^{ts}) decreased LPTC responses to moving OFF edges across a wide velocity range; the LPTC's ON input was unaffected, consistent with the circuit's parallel ON/OFF architecture. Eliminating sustained type Tm9 impacted downstream visual function most (~75% reduction). Subsequent silencing of Tm neuron types in pairwise combinations produced an additive effect, with the overall reduction greater than that of either type alone, supporting these conclusions. Thus, all four Tm neuron types contribute to the detection of moving OFF edges, but based on the dominant effect of silencing Tm9, not all Tm neurons contribute equally.

Next, Serbe et al. (2016) examined the optomotor behavior of walking flies while silencing each of the four Tm neuron types alone or in pairs. Taking advantage of the motion system's parallel ON/OFF architecture to measure OFF pathway function, they presented a visual motion stimulus that contained ON and OFF edges moving in opposite directions. With intact ON and OFF pathways, the opposite motion signals are balanced and fail to evoke turning behavior; loss of function in the OFF pathway would increase the influence of the ON signal, causing the fly to follow the ON edges (Clark et al., 2011). As expected, silencing Tm neurons in the OFF pathway evoked ON-direction turns. For Tm1, Tm4, and Tm9, the effect was restricted to low stimulus speeds, whereas for Tm2 the effect peaked at higher speeds, consistent with Tm2's fast visual response kinetics. Pairwise silencing produced stronger

behavioral phenotypes, consistent with the LPTC recordings.

The take-home message from these silencing experiments is that all four Tm neuron types presynaptic to T5 contribute incrementally to physiological and behavioral sensitivity to visual motion. No single Tm neuron type, or pair of Tm types, is strictly required for directional motion sensitivity in LPTC neurons or optomotor behavior—a valuable new insight. It is important to recognize, however, that the relationship between LPTCs and visual behavior is poorly understood. While silencing presynaptic T4 and T5 neurons impacts optomotor behavior (Maisak et al., 2013), it has yet to be shown that genetically silencing LPTC neurons reduces the optomotor response. More work is needed to uncover if, and how, motion tuning in LPTC neurons is translated into steering behavior during walking and flight.

A significant contribution of the work by Serbe et al. (2016) is how close it brings us to identifying the neurons and synapses in the fly visual system where directional motion is computed. Based on anatomical, behavioral, and physiological experiments from many labs, culminating in the present study, we now have a reasonable idea of where the three key features of the HR-EMD model are implemented in the *Drosophila* optic lobes.

The delay term in the model may be accounted for by the established differences in the temporal kinetics of Tm neurons (Behnia et al., 2014; Serbe et al., 2016). The origin of this temporal diversity, however, is not yet known. Sustained Tm9 may simply reflect the temporal properties of its input, L3 (Fisher et al., 2015b). But Tm1, Tm2, and Tm4 all sample from L2, indicating a key role for additional mechanisms including differences in cell-intrinsic filtering due to receptor or channel diversity, or inhibitory input from lateral, feedforward, or feedback projections.

The spatial offset in the model may be accounted for by the retinotopic organization of input from Tm2/Tm9 and Tm1/Tm2 pairs onto T5 as revealed by serial-section EM (Shinomiya et al., 2014). Still, a quantitative understanding of the relation between this anatomical asymmetry and directional selectivity is lacking. Serbe et al. (2016) showed that all four OFF Tm neurons have small receptive field centers—approximating the acceptance angle of one ommatidium. However, the observation that Tm9 neurons also encode wide-field stimuli (Fisher et al., 2015a) does not fit with the current model for local motion detection in T5. One way to test whether Tm receptive fields meet the requirements for spatial offset defined by the HR-EMD model would be to silence a single presynaptic Tm type while imaging downstream T5 neurons: if Tm neurons provide spatially offset input to T5 neurons, then this manipulation should impact T5 spatial receptive fields in a predictable manner.

The multiplication in the model appears to be implemented, at least in part, by synaptic integration within the T5 dendrites. By demonstrating that the inputs to directionally selective T5 are themselves not directionally selective, Serbe, Meier, and colleagues have localized OFF motion computation to the integration of synaptic input from Tm1/2/4/9 onto T5. Focused study of T5's dendritic response properties will be necessary to understand the details of this integration. Because the motion pathways (ON and OFF) are rectified, a strong nonlinear operation such as multiplication is no longer required. Furthermore, motion may be computed in an incremental, stepwise manner: weak directional selectivity originating at the level of the T5 dendrites may be sharpened through inhibitory interactions between T5 neurons with opposite preferred directions and wide-field pooling of motion signals in the downstream LPTCs.

The circuit that has emerged from studies in *Drosophila* shows a striking similarity with the original HR-EMD model. This is remarkable, considering that the model was based solely on behavioral observations. But our current understanding also refines it in two important ways. First, instead of two temporally distinct input lines, the OFF motion pathway in the fly uses at least four. The added diversity broadens the detector's performance range and may confer robustness across luminance conditions. Second, temporal diversity in the HR-EMD model is obtained by low-pass filtering of one of two otherwise identical inputs, which causes a relative delay by shifting the response time to peak and makes the response more sustained by selectively attenuating high temporal frequencies. Until recently, much emphasis has been placed on the relative delay (e.g., Behnia et al., 2014). The new data suggest an equally (if not more) important role for the temporal kinetics—transient versus sustained (Serbe et al., 2016).

In studies of directional selectivity in the vertebrate retina (rabbit, mouse), early evidence for non-HR-EMD-like mechanisms (Taylor and Smith, 2012) gave rise to working models that did not depend on presynaptic neurons with distinct temporal kinetics—a hallmark of the HR-EMD architecture. But a recent model of motion computation based on serial EM reconstruction challenges this view (Kim et al., 2014). Contact analysis suggests that the OFF-type directionally selective starburst amacrine cells, the apparent mammalian T5 analog, integrates synaptic input from two spatially offset interneuron populations, which are themselves not directionally selective, but whose distinct temporal kinetics (transient and sustained) give rise to directional selectivity. This model remains to be tested experimentally. If found to be true, this would be a remarkable example of parallel evolution of a neural circuit motif for computing directional motion.

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The Yin and Yang of Auditory Nerve Damage

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Chambers et al. investigate consequences in the central auditory system after profound cochlear denervation. They observed gains in firing rate in auditory cortex despite nearly absent auditorynerve and brainstem responses, suggesting an important role of central plasticity and its clinical implications.

In Chinese philosophy, the terms ''yin'' (dark) and ''yang'' (bright) are used to describe the opposite aspects of natural forces or phenomena that, while appearing contradictory on the surface, are intrinsically complementary and interconnected to each other. In many ways, this is how the properties of the nervous system are often presented to us. In this issue of *Neuron*, Chambers et al. (2016) describe a surprising finding on how auditory cortex recovers from devastating peripheral nerve damage. As we know, the auditory system has a long pathway leading from the cochlea to cortex, much longer than all other sensory systems. What we eventually hear depends on neural activities at the highest level (cortex), but all information has to go through the front door (cochlea). Damages to this front door often lead to permanent loss of hearing. The examples are plentiful, from genetically inherited abnormality of the inner ear to drug- or noise-induced hair cell losses. Sometimes even seemingly mild acoustic trauma to the peripheral organ can result in lasting damage in neural structures downstream. Such examples can be readily found in our daily hearing experience (for example, when attending a thundering rock concert or constantly listening to loud music from an earbud).

Acoustic trauma could cause long-lasting and irreversible damage to the hair cells connecting the auditory nerve. Several years ago, a landmark study showed that in noise-induced hearing loss, exposures causing only reversible behavioral threshold shifts (and no hair cell loss) nevertheless cause permanent loss of > 50% of auditory nerve/hair-cell synapses and delayed degeneration of the auditory nerve (Kujawa and Liberman, 2009). Our ears seem to be quite susceptible to noises in the hearing environment. However, how such perturbations to our peripheral auditory organ affect functions of the central auditory system remains largely unclear. Given what we have known of the mechanisms of the auditory periphery and brainstem, it has long been assumed that damage to the cochlear machinery would result in unrecoverable losses of function in neural structures beyond. On the other hand, in all sensory systems, damage to the peripheral organs often leads to compensatory reorganizations at cortical levels. For example, losing one's limb in an accident will eventually cause a shift in cortical representation of the limbs and surrounding body surfaces in the somatosensory cortex (Merzenich et al., 1984). Such reorganization can lead to sensation of the lost limb, the so-called ''phantom limb'' phenomenon (Flor et al., 1995). The underlying mechanism behind these changes is neural plasticity, in particular at the cortical level. However, besides topographic reorganizations in cortical maps, we know relatively little of what central plasticity could do in helping restore the information lost at the receptor level. In subjects with sensorineural hearing loss, commonly observed symptoms such as elevated hearing threshold, reduced frequency resolution, and increased difficulties in hearing in noisy backgrounds have traditionally been attributed to alterations in cochlear mechanics or the loss of particular cell types in the cochlea or auditory nerve (Moore, 2007). There has been a paucity of data on contributions from central auditory system to these behavioral symptoms.

Sensorineural hearing loss in human populations can be caused by environmental exposures or diseases and usually involves complicated changes that affect the cochlear transduction and amplification machinery. The mammalian cochlea is innervated by two types of afferent