are not related at the sequence level to TA systems [14,15]. However, both systems are regulated by a bistable switch involving the Spo0A transcriptional regulator [14,15]. A bistable switch, cued initially by stochastic variations in gene expression at the single-cell level, divides a population of genetically identical cells into two stable but alternative cell states [16]. Two regulatory mechanisms have been proposed to bring about bistability — either a positive-feedback loop or a pair of reciprocally repressing repressors [16]. It is not readily apparent how the regulatory circuit that governs MrpC and MazF-mx activity could give rise to bistability (Figure 1). In particular, even though MrpC2 positively regulates the expression of *mrpC* in a positive-feedback loop, it also activates transcription of *mazF*-mx. This predicts that MrpC and MrpC2 would accumulate in parallel with MazF-mx. Therefore, it is not evident that the positive-feedback loop involved in *mrpC* expression would give rise to bistability, although *M. xanthus* cells do sort into survivors (spores) and non-survivors (dead cells) under starvation conditions. Is there a hidden bistable switch to be discovered or is there a different logic for the design of the programmed cell death circuit involved in *M. xanthus* development?

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DOI: 10.1016/j.cub.2008.02.060

Fly Vision: Neural Mechanisms of Motion Computation

A wide range of novel approaches are being used to dissect the visual system of the fly, both the neural networks of motion detection and the performance of these networks under complex natural stimulus conditions.

Martin Egelhaaf

Anyone who observes two flies chasing each other will be fascinated by their breathtaking aerial acrobatics: the human eye is hardly able even to follow their flight paths, but the pursuing fly is quite capable of catching its speeding target. During their virtuoso flight manoeuvres, flies can make up to ten sudden, so-called saccadic turns per second, during which they reach angular velocities of up to 4,000 degrees per second [1,2]. The flies rely to a great extent on information extracted by the neural circuits in their brain from the rapid displacements of the retinal images across the eyes. This visual motion information is then transformed in a series of processing steps into motor control signals that are used to steer the flight course. A lot of progress has been made in the last few years in determining what information is encoded by networks of output neurons of the fly visual system under natural stimulus conditions [3,4], but the cellular mechanisms underlying local motion detection — the first step of visual motion computation — are still largely unknown. But progress is being made towards elucidating these mechanisms, as illustrated by recent studies combining genetic tools with behavioural [5] or, even more specifically, electrophysiological analyses [6].

The fly visual system is optimised for reliable performance in flight behaviour and is amenable to analysis by a broad spectrum of neuronal and behavioural methods; it has consequently proved to be an outstanding model system for tracing the computations which serve to process image motion proceeding from the eyes [2,7–9]. Retinal image motion is not perceived directly by the eye; rather, the photoreceptors in the retina register just a continuously changing spatial array of brightness values. From this, the nervous system has to go through a series of steps to evaluate information on the image movements. Local motion detectors in the medulla compare the brightness data of adjacent light-sensitive cells (Figure 1, upper right). Movement is signaled when two of these detectors report the same brightness value in immediate succession, for example, bright–bright. During this process, each motion detector reacts with a large excitatory signal to movement in a given direction and with a negative

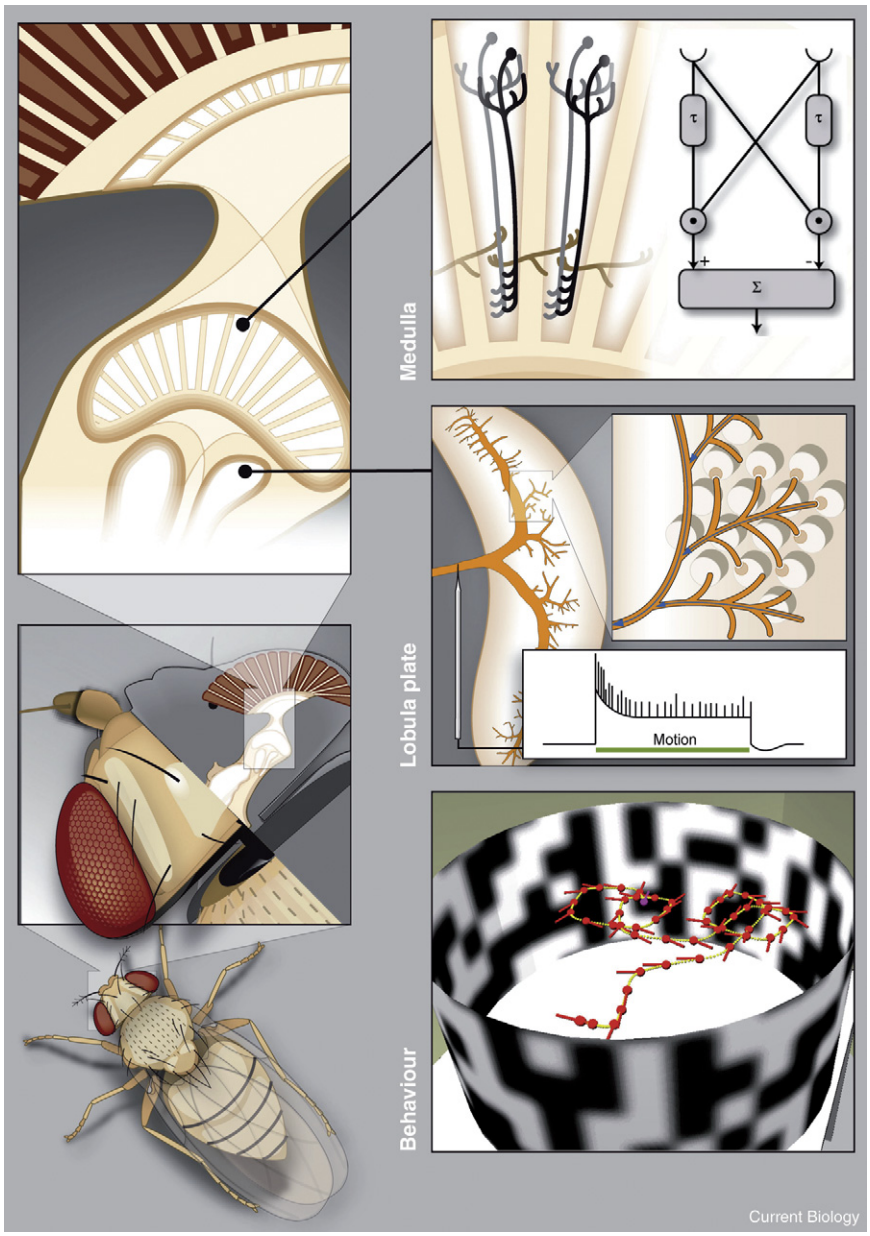

Figure 1. Levels of analysing the mechanisms underlying visual motion computation in the fly.

Visual motion pathway of flies at different magnifications (left): the intact fly (bottom left), its head with a schematic of the visual system drawn into the right half of the head (middle diagram) and an enlarged part of the visual system (upper left). The fly visual system consists of the large compound eye and three visual neuropiles. Motion detection is accomplished locally by the neural circuits within and between retinotopically organised columns of the second visual neuropile, the medulla; local motion detection can be described formally by the correlation-type movement detector (upper right). The outputs of many local motion detectors are spatially pooled on the dendrites of the tangential cells, such as the so-called VS-cells (middle right); as a consequence of its local motion detector input, the tangential cells respond directionally selective to motion; VS-cells respond to downward motion with graded depolarisation superimposed by small-amplitude spikes (inset, middle right). Visually guided behaviour of flies relies to a large extent on the processing of visual motion information. The underlying mechanisms can be constrained by various behavioural paradigms, such as by monitoring free-flight behaviour with high-speed cameras; the position of the fly's head and its orientation are represented at subsequent instants of time for a flight sequence in textured flight arena (bottom right). (Figure courtesy of Christian Spalthoff.)

(inhibitory) signal to motion in the opposite direction. The information from numerous retinotopically organised local motion detectors is summated in a subsequent brain area, the lobula plate, by integrating neurons, the tangential cells which, as a consequence, respond directionally selective to motion within their large receptive fields (Figure 1, middle right).

This detailed knowledge of visual motion processing has been accumulated by anatomical, electrophysiological, pharmacological and single-cell imaging techniques, mainly in the relatively large blowflies. We now understand in great detail the intricate synaptic interactions within the network of tangential cells (for example [7,10–13]). As a consequence of these interactions, the tangential cells are able to detect specific global visual motion patterns that are characteristic of distinct behavioural situations, for instance, when the flying fly changes its direction [7,9,14,15]. Thanks to recent advances in reconstructing the complex retinal motion sequences seen by flies during aerobatic manoeuvres and the development of novel visual stimulation techniques, it has even been possible to assess the coding properties of populations of tangential cells under the complex stimulus conditions flies experience during their virtuosic flight manoeuvres. In particular, tangential cells have been shown to provide information about the spatial structure of the environment during the straight flight segments between saccadic turns [3,4].

But there are still large gaps in our knowledge, mainly because not all regions of the visual system are accessible equally well to techniques that allow us to probe into neuronal function. Most of our knowledge about the mechanisms of motion detection has been obtained by relatively indirect means. Many features of visual motion computation, including the complex responses of tangential cells to natural optic flow, can be accounted for using a computational model, known as the correlation-type movement detector [16–18] (Figure 1, upper right). Although this is one of the most successful models that have been developed in computational neuroscience, the cellular processes underlying its mathematically formulated operations have so far resisted systematic disclosure. Despite detailed knowledge about the anatomical fine structure of the

relevant brain area and heroic attempts to physiologically characterise the tiny input neurons of tangential cells [19], the functional role these neurons play in motion detection is still tentative.

In recent years, an alternative approach to unravelling the cellular mechanisms of motion detection has been introduced, exploiting the extensive toolkit that is available for molecular and genetic analysis in the fruitfly *Drosophila* [5]. The idea is to use these tools to manipulate neuronal information processing in a targeted way, for instance, by blocking synaptic transmission between identified neurons or by functionally eliminating neurons from a neural circuit. But manipulating neural circuits on its own is not sufficient: the functional consequences of the manipulations need to be assessed. Until now, this has mainly been done using a variety of behavioural paradigms to monitor motion-induced responses of individuals or of whole populations of flies (for example [5,20]; Figure 1, bottom right). Although behaviour reflects the ultimate outcome of all neural processing, it is difficult to deduce the cellular mechanisms underlying local motion detection from behavioural analysis alone: there are many intermediate processing steps between the motion detection circuits and multiple parallel pathways are likely to play a role in behavioural control. More direct indicators of motion performance would thus facilitate a complete mechanistic understanding of how visual information is processed at the level of identified cells and circuits.

In this light, the paper by Joesch *et al.* [6], published recently in *Current Biology*, represents a breakthrough in the field. These authors have managed, for the first time, to record in *Drosophila* the activity of tangential cells during visual motion stimulation, and thereby to monitor the activity of neurons directly postsynaptic to the neural circuits accomplishing local motion detection. To be able to record from *Drosophila* tangential cells, the authors employed a trick: they were able to express a fluorescence marker in a subset of tangential cells. This greatly facilitated the targeted positioning of the recording electrode, so that motion-induced electrical responses could be recorded from a stained and anatomically identified cell. The analysed *Drosophila* tangential cells showed basically the same dependence on visual motion parameters as their homologues in larger fly species. This finding is highly relevant for further research strategies into motion computation.

Most important, it is now possible to employ the full repertoire of genetic and molecular tools available in *Drosophila* for the dissection and manipulation of identified neurons in neural microcircuits and to test the effects on visual motion detection by recording the responses of tangential cells. As these are directly fed by the neural motion detection circuits, much more specific information can be extracted for unravelling the cellular basis of motion computation than from the rather indirect behavioural paradigms. Moreover, the new results [6] form a basis to switch between tiny *Drosophila* and big blowflies when analysing the cellular basis underlying motion computation, depending on which techniques can be applied best in the different fly species. It will thus be possible to put experimental results from both animal models into a common conceptual framework of visual motion processing. The new study of Joesch *et al.* [6] is another important step towards elucidating in unprecedented detail the neuronal computations at the relevant processing stages from photoreceptor input to the final behavioural output and, thus, towards understanding neural information processing underlying the visual control of the breathtaking aerobatic manoeuvres of flies.

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DOI: 10.1016/j.cub.2008.02.046