Direction selectivity in ganglion cells: pre or post?

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Contrary to a recent finding in rabbit retina, Borg-Graham reports that inputs to retinal ganglion neurons in turtles are already directionally selective.

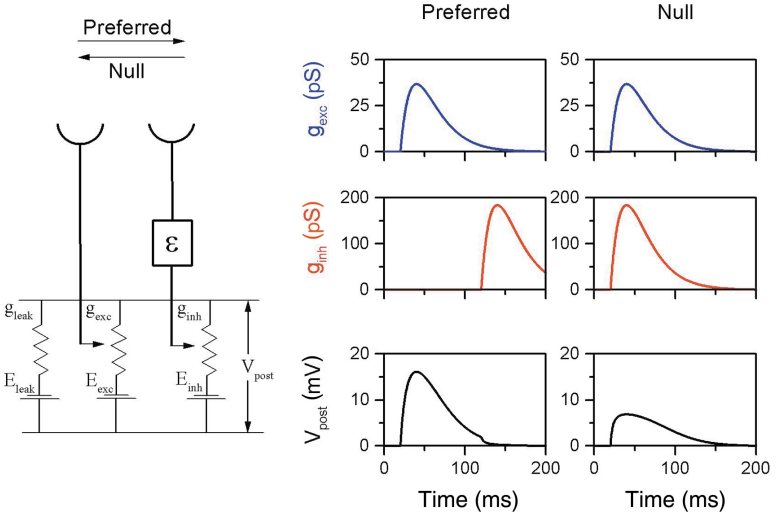
Everyone who has visited an IMAX theater will readily agree that visual motion, even if presented without any vestibular cues, elicits very strong illusions of self-motion. Therefore, it does not come as a surprise that many neurons within the visual system respond to visual motion. Often, they do so in a directionally selective way: motion in one direction excites the neurons (their preferred direction, PD), whereas motion in the opposite direction suppresses the neuron's response (their anti-preferred or null direction, ND). Depending on the species, the earliest stage at which one finds directionally selective neurons in mammals is either the retina or the primary visual cortex.

Interestingly, the direction of motion is the result of neural computation; it is not encoded explicitly in the output signal of a single photoreceptor. The way that this computation is implemented in the biophysics of membranes, receptors and channels is under scrutiny in an article on page 176 of this issue[1]. Specifically, Borg-Graham tested a model that arose from the work of Barlow and Levick[2]. According to this model, each ganglion cell receives signals derived from two neighboring image locations, one excitatory and one inhibitory (Fig. 1). With respect to the excitatory input, the inhibitory input is displaced toward the preferred direction of the ganglion cell. When the inhibitory signal is additionally delayed, the circuit is able to discriminate between different directions of motion: for movement along the preferred direction of the cell, the inhibitory action is ineffective because it always arrives too late. However, for motion along the null direction, both signals ideally coincide, with the effect that the inhibitory signal shunts most of the depolarizing action of the excitatory input (Fig. 1). Implementing such a postsynaptic shunting inhibition mechanism in the dendrite of computer models of retinal ganglion cells[3] indeed leads to direction-selective responses such as those recorded by experimentalists.

In his study[1], Borg-Graham tested whether real ganglion cells indeed acquire their most significant response property in the way outlined above, or alternatively, whether their input signals are already directionally selective. Thus, as so often in neuroscience, the problem boils down to the question, "pre or post?" To decide between these alternatives, the author used an isolated preparation of turtle retina, which allows for long and stable recordings, and voltage-clamped ganglion cells during visual motion stimulation. To keep the membrane voltage constant under these conditions, the amplifier needs to counteract the excitatory and inhibitory currents caused by the input synapses to the ganglion cell. The current needed is the negative sum of both synaptic currents, each being the product of the conductance (g) and the driving force, which is the difference between the holding potential (V_h) and the reversal potential (E) for the respective ion.

Assuming for a moment that we know the excitatory and inhibitory reversal potentials E_{exc} and E_{inh}, this leaves one equation with two unknowns (one unknown too many). The solution of the problem is to repeat such a measurement using a different holding potential V_h. This eventually leads to two linear independent equations with two unknowns g_{exc} and g_{inh}, which can be solved easily. Stimulating along the neuron's preferred and null direction allowed the author to determine whether the input conductances were directionally selective, which would speak in favor of 'pre', or whether the input conductances were directionally non-selective, speaking in favor of

Fig. 1. Shunting inhibition model of direction selectivity in the retina (modified from ref. 9). Inputs from two retinal locations converge on one postsynaptic neuron, one controlling an excitatory conductance, the other controlling an inhibitory conductance after being delayed by ε. In the preferred direction, the inputs are activated left first, then right. Because the inhibitory signal is additionally delayed, it does not overlap much with the excitatory conductance change. Therefore, the membrane voltage rises up to almost 20 mV above resting. Conversely, during null-direction motion, both conductance changes are induced simultaneously. Now, the inhibitory conductance shunts the excitatory conductance, allowing the postysnaptic membrane potential to depolarize only about 8 mV. The difference between preferred- and null-direction response might be further enhanced by the nonlinearity ('threshold') for spike generation in the postsynaptic cell.



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'post'. In brief, the major finding was that whereas the inhibitory input conductance was similar for the two directions of motion, the excitatory input conductance differed significantly for preferred and null direction motion: the excitatory input to the turtle ganglion cell is already directionally selective! The author even goes one step further: by constructing a biophysically realistic model of the ganglion cell, he implemented a postsynaptic mechanism[3], and then simulated the experiments he was going to do on the real ganglion cells. He thus obtained an expectation of what he should see if the postsynaptic 'shunting inhibition' model were true. The prediction that came out of this modeling was that the overall conductance change observed during null direction motion should, first, outlast the one observed during preferred direction motion, and, second, be almost twice as large as the resting conductance of the neuron. Otherwise, the inhibitory input would not effectively shunt the excitatory input. Both of these predictions failed. The postsynaptic shunting inhibition model thus was killed twice: not only was the inhibitory conductance insufficient to produce any sort of direction selectivity in the ganglion cell, but also the excitatory input was already directionally selective. So, the answer we are given by Borg-Graham is clear-cut: it's pre.

This would be the end of a long-standing debate, if not for a paper published a few months ago stating just the opposite conclusion[4]. Applying an experimental protocol similar to Borg-Graham (whole-cell patch recording under voltage-clamp conditions), Taylor *et al.* investigated the same phenomenon in retinal ganglion cells of the rabbit. By increasing the internal chloride concentration, and thus shifting the equilibrium (reversal) potential for chloride toward 0 mV (making inhibitory and excitatory inputs both produce inward currents), the authors were able to completely eliminate direction- selective responses. Because this should not have any effect on an input that is already directionally selective, this finding was hard to reconcile with a presynaptic mechanism. Based on this and other experiments, the conclusion drawn by the authors was that it's post.

What are we left with? There are several possibilities to consider. Because both studies were carried out on different species, no factual discrepancy exists so far. It might well be that rabbits and turtles indeed have found different solutions to the same problem in evolution, so that the final answer will be turtles pre, rabbits post. This should be relatively easy to test by the different research teams. The other possibility is that the process creating direction selectivity is a local one, and some aspects of its operation simply escape the reach of the electrode in whole-cell protocols. Such phenomena exist[5,6], and looking at the intricate mesh of synapses formed in the inner plexiform layer by glutamatergic terminals of bipolar cells, amacrine cells synapses co-releasing acetylcholine and GABA[7], and ganglion cell dendrites, we realize that the substrate for local circuits exists there in plenty. Finally, the search for 'the' mechanism underlying direction selectivity, even in the retina of one species, could be hampered by the existence of a multi-step process[8], with the spike threshold of the ganglion cell being the final step in enhancing direction selectivity. In conclusion, while the present study marks an important step forward, there still remains a big nut to be cracked—so stay tuned!

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Going with the (virtual) flow

In theory, navigation toward a goal could be guided by several visual cues. The direction of a goal could be calculated with respect to the body (the 'egocentric direction hypothesis'). Alternatively, people might move in the direction that minimizes the error between cues from the expanding radial pattern on the retina ('optic flow' is produced by self-movement) and the goal. In practice, these two strategies for visual control are difficult to distinguish because they predict the same behavior. However, Warren and colleagues from Brown University (page 213) created a virtual reality environment that allows their subjects to walk through a world where the laws of optics are under experimental control. The authors can create conditions that never occur in the natural world, such as displacing the optic flow field from the actual direction of walking. In such a virtual world, the egocentric direction and optic flow hypotheses make different predictions about the shape of a subject's path toward a goal. The authors found that when little optic flow information was available, subjects' behavior was consistent with the egocentric direction hypothesis. However, when the environment was made more complex, for example by adding textured floors and ceilings, optic flow information increasingly dominated behavior. These results demonstrate that the visual system can control locomotion robustly under a variety of environmental conditions, and that optic flow cues are used to control human walking when they are available.

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