Sensory Biology: How to Structure a Tailor-Made Retina

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A new study of the zebrafish retina using sophisticated imaging has revealed how anisotropic properties of the retina are closely matched to the statistics of the natural visual world that the fish experiences.

Animals navigate in a complex natural world overflowing with information. Sensory systems have evolved to filter this abundance of information and provide the organism's brain with a condensed and altered version that is relevant for survival and reproduction. Neuronal computation comes at a high price, as attested to by our own large and (metabolically) hungry brain. Hence, there is high selective pressure on economizing information flow, which starts at the interface between the organism and its environment. In this issue of *Current Biology* Zimmermann *et al.* [1] report how their work on zebrafish vision has revealed an ingenious strategy that nature has evolved in which the structure of the retina is fine-tuned to economize on visual processing taking the specific light environment of the animal into account.

The need to economize on the processing of available sensory information is particularly pressing for the vertebrate retina, a thin neuronal structure lining the back of the eye. In this outpost of the brain, the physical stimulus of light is converted into a biological signal. All this happens in the outer retina, where light sensitive cells, aptly named photoreceptors, sit. Vertebrate photoreceptors are of two kinds. Rod photoreceptors are very sensitive to light and mediate vision at low-light conditions. Your own personal experience immediately tells you that rod photoreceptors support achromatic vision, hence at night all cats are grey. Color perception, on the other hand, is mediated by cone photoreceptors that come in different flavors, depending on their maximal absorption spectrum. Humans are trichromats, having three cone types with maximal sensitivities in the blue, green and red spectrum of light. The ancient condition of vertebrates, however, is to be tetrachromatic, sporting also a color channel in the ultraviolet range. Tetrachromacy has been retained in most vertebrate species, including in the majority of fishes.

One does not do justice to the retina by describing it as primarily a sensory structure for light detection. The retina is also a complex computational network that strongly shapes the initial visual input before sending this information via the optic nerve to higher brain centers. Many neuroscientists have been, and will be for the foreseeable future, busy trying to understanding the intricacies of this complex neural network. Most of this information processing takes place in the inner retina, where interneurons, most prominently bipolar cells, form networks that compute the visual information flow.

The visual input experienced by an animal is typically complex, as the visual environment is strongly non-uniform with different brightness levels and colors dominating different parts of most visual scenes. As staunch believers in evolution, we would except that retinas have adapted to their particular visual environment. Such an adaptation should be apparent in both morphology and function of the retina.

Investigating this hypothesis is difficult, as it requires the ability to perform *in vivo* measurements of light-driven neuronal activity. This is where the zebrafish (*Danio rerio*) swims into the picture. This highly visual tropical pet fish has become the darling of many experimental biologists, including geneticists, developmental biologists and neuroscientists. They sport transparent larvae and are amenable to the full range of genetic manipulations. Zebrafish larvae are nature's gift to vision scientists. Even just a few days after fertilization, these larvae use their visual system to hunt for food and to avoid predation [2]. These little creatures, about 8 mm in length, definitely take vision seriously, dedicating about half of all their brain's neurons to processing information in the retina.

An initial approach to understanding how the retina has adapted to a non-uniform visual scene is to directly measure the visual environment of zebrafish larvae. Zimmermann *et al.* [1] traveled to the natural habitat of zebrafish, surface freshwater of the Indian subcontinent, and used two complementary approaches to defining the fish's natural light environment. First, they took underwater high-resolution photographs using an action camera with optics mimicking the larvae's wide-angled eyes. This analysis showed that, indeed, the visual scene is very non-uniform with color (chromatic) information dominating the visual horizon and the lower visual field, while the upper visual field is effectively achromatic (Figure 1).

Such an analysis does not, however, take the peculiarities of zebrafish tetrachromatic vision fully into account, so Zimmermann *et al.* [1] took a second approach to gaining a fish's perspective and performed a hyperspectral scan of the visual surround taking the spectral sensitivities of the four cone types into account. This analysis showed that the available light under water is red-shifted, suggesting a prominent role for red-sensitive cones in mediating contrast-driven visual inputs such as movement. Taking the spectral sensitivity functions of the individual cones into consideration, the model predicted an interesting function for enigmatic ultraviolet vision. The little ultraviolet light that is additionally scattered by dissolved organic matter is

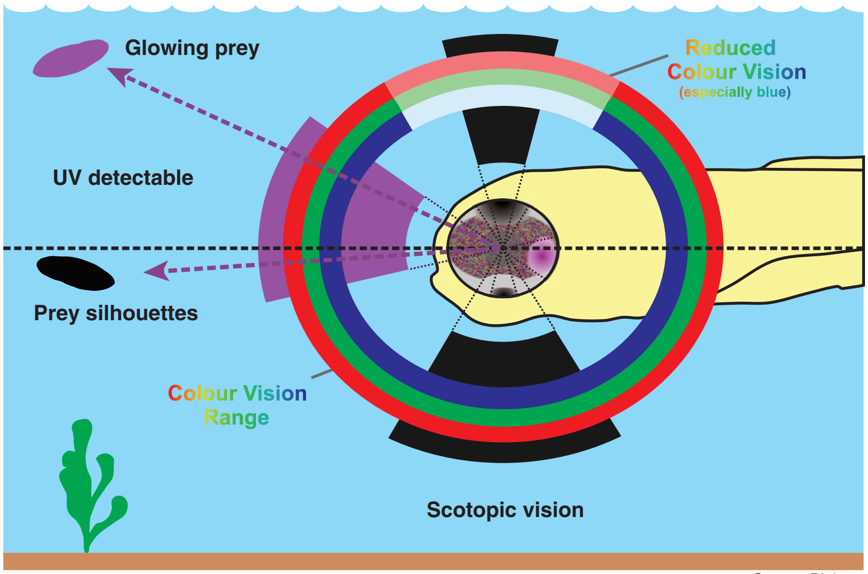

Figure 1. How a zebrafish larva sees its world.
The retina of zebrafish larvae is highly anisotropic, matching the visual environment. Color vision is concentrated over the visual horizon and the scene below, while ultraviolet light detection is concentrated in a striking zone specialized for prey detection. See details in the text. (Adapted from [1] by Matthias Gesemann.)

predicted to give a diffuse ultraviolet-background light, which may help the animal to spot ultraviolet-dark silhouettes against an ultraviolet-bright background. Optically translucent prey, such as Paramecia, a favorite food for zebrafish larvae, will advertise their position above the visual horizon, hence supporting prey capture from below.

These intriguing experiments make three readily testable predicted features of efficient-coding retinal circuits. First, that circuits sampling light from above should be achromatic or short-wavelength biased. Second, that there should be an ultraviolet-dominated strike zone where the image of prey will fall. And third, that there should be chromatic circuits along the visual horizon.

Zimmermann *et al.* [1] performed two sets of experiments, one morphological and the other functional, to test and indeed confirm these predictions. They first studied the distribution of photoreceptors in the retina. In line with their prediction, the number of cone photoreceptors — comprising 92% of all photoreceptors in the outer retina — is highest at the horizon. Most interestingly, ultraviolet cones are concentrated in the upper horizon, exactly where the strike zone for prey capture is expected. The lower visual space is also mainly served by cones with a somewhat larger red cone contribution. Rod photoreceptors mainly monitor the achromatic upper field and the lower visual field, maybe for mediating optic flow information (Figure 1). This unequal (anisotropic) distribution is matched by the inner retina, where for instance the visual horizon features a thicker synaptic layer.

All this is very suggestive, but what about functional read-outs? In experiments that would be very difficult to do in any other vertebrate retina, Zimmermann *et al.* [1] expressed an activity indicator gene — the calcium-sensor GCaMP6 for those that really want to know — in bipolar cells of the inner retina for optically measuring their responses following spectral light stimulation. These cells directly collect input from photoreceptors and contact all other classes of retinal neurons. Again, these results showed that the inner retina is also functionally anisotropic. This is particularly impressive in the strike zone, where indeed bipolar cell terminals exhibited near exclusively ultraviolet light responses. In a *tour de force*, the authors survey the response properties of more than 4000 synaptic terminals, identifying response clusters that are again anisotropically distributed over the retina in agreement with the color content of the natural world. This functional anisotropy is also apparent in the layering of the synaptic layers.

After carefully describing the morphological and functional anisotropy of the retina, one remaining open question concerns how such an adapted retina is built? The diversity could stem solely from the unequal distribution of transcriptionally and morphologically defined bipolar cell types, or (not necessarily mutually exclusive) the same bipolar cell types could be functionally divers due to their position in a local network. By sampling three transgenically labeled morphologically defined bipolar cell types, Zimmermann *et al.* [1] found convincing evidence for functional diversity among the same morphologically defined subtypes. This strongly argues that functional diversity depends to a large part on their surrounding neuronal network. However, since these identifiable cell types were not randomly distributed over the retina, the position of bipolar cell types is also functionally relevant.

The new work of Zimmermann *et al.* [1] opens a number of interesting avenues to pursue. Their study subject is the larval retina of the zebrafish: the situation must be very different in the adult zebrafish, where photoreceptors are arranged in a precise mosaic row pattern [3]. Therefore, the observed anisotropy of photoreceptors must be reconstructed at some time point between the early larval and the adult stages. Will such a change also result in different behaviors of the animals, for instance by changing the food preference from translucent single cellular organisms to opaque insect larvae?

The role of ultraviolet vision can be further illuminated by performing detailed prey capture experiments in mutant fish lines having reduced numbers of ultraviolet cones [4,5]. The larval zebrafish retina is generally considered to be functionally cone dominant [6]. Thus, the unequal distribution of rods is of interest, potentially hinting at mediating functions that have escaped detection by previously used functional assays.

The paper by Zimmermann *et al.* [1] beautifully demonstrates how a sense organ is shaped by the specific properties of its surveyed environment driven by the need to economize neuronal computation. This study is unusual in linking a detailed survey of the visual space as seen by the animal and a detailed description of the morphological and functional adaptations of the sense organ.

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Auditory Perception: *Laurel* and *Yanny* Together at Last

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An auditory illusion caught the world's attention recently. For the same noisy speech utterance, different people reported hearing either 'Laurel' or 'Yanny'. The dichotomy highlights how perceptions are inferences from inherently ambiguous sensory information, even though ambiguity is often unnoticed.

When Katy Hetzel, a high-school student, went to the website *Vocabulary.com* to look up the word 'Laurel', she could certainly not have imagined how events would unfold. The website had hired professional singers to record words with a clear pronunciation. But, as Katy saved her sound clip with presumably a low-quality recorder, she serendipitously realized that she did not hear 'Laurel' anymore: rather she heard, very clearly, 'Yanny'. Thanks to another high-school student, Fernando Castro, the sound clip was released on social media. A minor meltdown ensued. Opinions were split, sharply. Some heard 'Laurel', others heard 'Yanny'. Commentators expressed incredulousness, bewilderment, consternation, sometimes down to outright aggression toward each other from different sides of the perceptual divide. Yet others could not even understand how anyone could be fooled by such a poor trick, as for them the sound clip obviously could be heard as either. Celebrities took up the meme, politicians, the media: at long last, the world had the auditory equivalent of the visual sensation known as #TheDress [1].

What is the reason for this dichotomy in the way people interpret the same sound? Figure 1A shows a visual representation of the contentious sound clip (middle, Audio S1), displaying the simulated output of peripheral auditory processing. Also illustrated are processed versions of the clip, for which either the low-frequency content (left, Audio S2) or high-frequency content (right, Audio S3) is emphasized. We ran an online experiment asking participants (N = 289) to choose between 'Laurel' and 'Yanny' for these sounds. The original clip produced both 'Laurel' and 'Yanny' responses as expected. The lowpass versions were heard more as 'Laurel', whereas the highpass versions were heard more as 'Yanny'. Remarkably, for some people, the bias was very strong; they heard the same word for more than 90% of trials, irrespective of acoustic filtering (N = 93 'Laurel', N = 41 'Yanny'; Figure 1B).

These observations suggest a simple interpretation to the effect. The time-frequency content of the original sound clip contained enough acoustic cues to hear 'Laurel', whereas the high-frequency content was close enough to 'Yanny'. Interestingly, a cue in the middle of the range — the wavy line visible in all examples in Figure 1A — was compatible with either interpretation: it could be the second formant of 'Laurel', or the third formant of 'Yanny' (or 'Yari', 'Yelli', 'Yowee'; all forms having been reported but for simplicity we treat them as 'Yanny'). So, as is common with many illusions [1,2], the available evidence was ambiguous and compatible with more than one percept. We suggest that listeners perceptually emphasized different parts of the frequency range, leading to a greater weight of the 'Laurel' or 'Yanny' cues.

Frequency biases varied widely across listeners, as shown by the histogram of the acoustic point of subjective equivalence for the group of people who reported each