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Color vision: Parsing spectral information for opponent color vision in the fish retina

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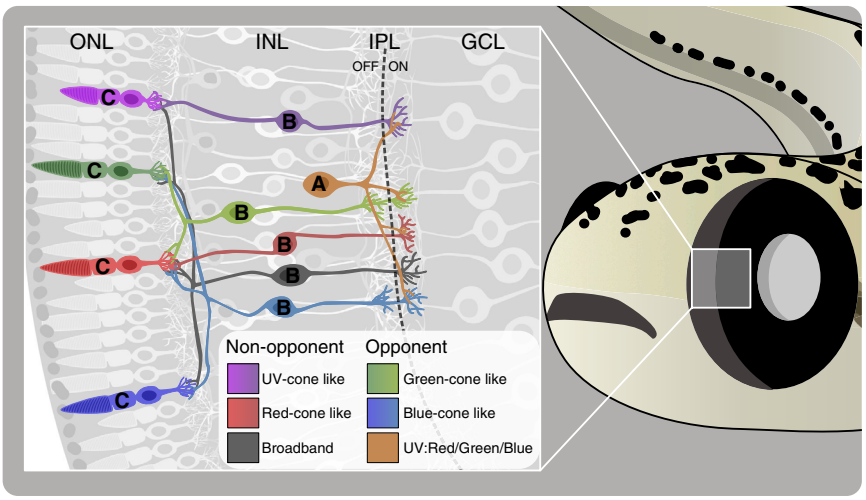
Environmental light carries spectral information, perceived as color. A new study in zebrafish shows how spectral information decoded by the cones' photoreceptors is transformed by retinal bipolar cells, adding a temporal component to the signal and establishing a third opponent axis for color vision.

Natural environments provide a plethora of visual information that is exploited by animals navigating through them. Evolution has led to ingenious ways of harnessing this information to enable the efficient detection of food sources and design strategies to evade predators by extracting information on luminance, contrast and spectral content, the last being what we perceive as 'color'. In a paper in this issue of *Current Biology*, Bartel *et al.*[1] reveal exciting new insights into how color stimuli are decoded in the eyes of zebrafish larvae.

Vision starts in the retina, a multi-layered neural structure in the back of the eye. Here, in the vertebrate eye, light is captured by the outermost retinal layer, composed of light-sensitive photoreceptor cells. These highly specialized cells come in two flavors: rod photoreceptors are highly light sensitive and provide achromatic vision at low light intensities; cone photoreceptors on the other hand need brighter light and paint our world in color, providing color perception at high temporal resolution. In order to provide information on the spectral content of light, cones come in different subtypes with differing spectral tunings. The ancestral composition of the vertebrate retina includes a complement of one rod and four cone subtypes, as still found in most non-mammalian vertebrates, including fishes. The evolutionary lineage leading to humans involved a fascinating history of photoreceptor loss and the regaining of cone subtypes, with spectral shifts along the way, leading to trichromatic vision in old world monkeys including ourselves[2,3].

How then does the retina manage to extract spectral (color) information from light? The first step of color vision is the wavelength–specific activation of cone photoreceptors, which have distributed activation maxima across the visible light spectrum, ranging from ultraviolet (UV), via blue and green to red light. How the spectral specific cone photoreceptor signals are subsequently processed in the inner retina by secondary neurons is still poorly understood.

Color vision works by comparing spectral information from different cone subtypes. Two main axes of such an 'opponency' have been described in primates: 'blue versus yellow' (where yellow is green + red); and 'green versus red'[2]. While in the first case this processing happens directly in the retina,



Current Biology

Figure 1. Bipolar cell spectral motifs in the zebrafish larval retina.
Zebrafish larval bipolar cells respond to chromatic stimuli mainly by recapitulating the behavior from the cone photoreceptors or by presenting an ON-broadband response. Notably, a third and new opponent axis originates in the inner retina where, probably via amacrine cell contribution, red, green and blue responses are opposed to UV. ONL, outer nuclear layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer; C, cone photoreceptor; B, bipolar cell; A, amacrine cell.

the second opponency probably arises later, in the brain proper[4,5].

Non-mammalian vertebrates have mostly maintained the ancestral set of cones, displaying four cone populations with absorption peaking in the UV, blue, green and red ranges, respectively[2]. Unlike mammals, which lost two of the original cone populations — perhaps due to nocturnal lifestyle in their evolutionary past — this full complement of wavelength-specific cones has the potential to support tetrachromatic vision by circuits formed directly in the retina, without the need to generate new color-opponent axes at higher brain levels.

In the past few years, larvae of zebrafish have been science's little helpers in tackling many basic questions concerning color vision. The Baden lab showed in an earlier paper[6] that, in the larval zebrafish eye, visual axes of color vision arise already at the first retina synapse, where the spectral tunings of cones are modulated by the crosstalk between horizontal cells and photoreceptors. However, the mechanisms of chromatic signal processing in the deeper layers of the retina have been elusive.

The four cone types in the zebrafish retina are connected to three functional groups of horizontal cells[6]. These cells form synapses with at least 21 anatomically different bipolar cells[7]. Subsequently, a minimum of 28 groups of amacrine cells[8] and at least 11 morphological types of ganglion cells[9] further modulate the signal before delivering it to the optic tectum and other brain regions. In order to understand the rules of visual processing in the retina, a deeper understanding of each step of this signaling process is required.

Following the previously used strategy to analyze cone tunings[6], in their new study Bartel *et al.*[1] took full advantage of optically cleared zebrafish larvae to analyze bipolar cell responses to color stimulation, employing a large battery of spectrally narrow light-emitting diodes (LEDs). Their state-of-the-art imaging strategy makes use of a calcium reporter expressed in the bipolar cells' terminals, enabling imaging of their responses to specific spectral stimulation in real time. The authors were able to separate individual bipolar cells and to cluster their responses by assigning bipolar cell regions of interest. This analysis led to the identification of 29 functional bipolar cell clusters that are highly diverse and mostly display regional bias throughout retinal regions.

Interestingly, Bartel *et al.*[1] found that a simple linear model that mainly draws from cone inputs and the sign-conserving or inverting properties of the bipolar cell itself is sufficient to account for most of the bipolar cell responses that they observed. The red-cone signal dominance that is already exhibited by cone tuning[6] is thus also reflected at the bipolar cell level, where six main spectral motifs contribute to bipolar cell behavior. These signals can be distinguished in three non-opponent and three opponent groups (Figure 1). Non-opponent motifs featured spectrally broad responses, representing the majority of the non-opponent clusters, UV-cone-like motifs and red-cone-like motifs. Opponent motifs featured green-cone-like clusters, blue-cone-like clusters and UV-cone versus red-, green- and blue-cone opponent clusters. This last opponent group appears to originate directly in the inner retina, as the reconstruction of bipolar cell responses through the linear model required opposite sign inputs from red, green and blue against UV signals.

In textbooks, we can read that the vertebrate retina displays a distinct division between sign-inverting and sign-conserving bipolar cell layers in the inner retina layer[10]. The inner plexiform layer presents sign-conserving (or OFF) circuits in its upper part, while sign-inverting (or ON) circuits are located in the lower regions. Most interestingly, however, in their new work Bartel *et al.*[1] documented a number of bipolar cell clusters where this apparent rule is violated by OFF-response dendrites populating the lower part of the alleged 'ON layer'. This violation is explained by the presence of most of the UV versus red, green and blue opponent clusters in that region of the inner plexiform layer, where sign-reversed red, green and blue signals input on UV-ON bipolar cells.

It is noteworthy that several clusters of these bipolar cells delivered a mixture of both temporal (transient and sustained) and spectral information, with a higher concentration of these clusters in the retinal inner plexiform layer, where also mammals present transient and sustained processing[11]. A similar behavior was previously modelled in zebrafish retinal ganglion cells[12], raising the question of whether the reported ganglion cell behavior is a simple reflection of bipolar cell computation. Future studies will be needed to determine how downstream circuits read out this color-temporal information.

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The exciting new results of Bartel *et al.*[1] paint a picture where bipolar cells mostly either sum stimuli received from all the four cones or oppose red, green, and blue, signals to UV ones. These results, however, appear to be at odds with the existence of 29 functionally distinct bipolar cell types and their possible interplay with amacrine cells. More insights regarding bipolar cells spectral tuning will probably arise from specific cone and amacrine cell silencing experiments.

Of all the opponency axes found in zebrafish, the one where UV signals are opposed to red, green and blue may be analogous to the short versus long-wavelength opponent circuits of mammals[12]. While some of the bipolar cell clusters that mediate these circuits in zebrafish appear in the same locations as in mammals and possess similar stratification patterns, it is still unclear whether there is a direct correspondence between these circuits in mammals and fish.

Overall, with their new work, Bartel *et al.*[1] have added another important piece to the puzzle of visual processing, providing us with a comprehensive description of the functional dynamics of most of the zebrafish retinal bipolar cells in response to a large range of narrow wavelength LEDs. Bipolar cells mainly inherit the signals from the four cones or represent a non-opponent broadband response. With the addition of spectral and temporal diversification of the cone signals, bipolar cells generate six spectral motifs including three opponent axes, of which one (UV versus red, green and blue) arises from the inner retina. Future cone ablation and/or amacrine cell inhibition experiments will likely reveal additional novel insights into cone signal modulation and may uncover additional spectral properties of zebrafish retinal bipolar cells.

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Sleep: The great adaptive diversity

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A new study shows that bird pupillary responses during sleep are opposite to those seen in mammals, findings that expand our understanding of the great adaptive diversity of sleep and the expression of its components across species.

Historically, two distinct states of sleep have been defined according to observed features in mammals. Non-rapid eye movement (NREM) sleep is characterized by decreased frequency and increased amplitude of cortical electroencephalographic (EEG) activity, slightly decreased body and brain temperature (with preserved thermoregulatory defenses to thermal challenges), reduced blood pressure, slow and regular breathing and heart rate, and raised arousal threshold. Rapid eye movement (REM) sleep, by comparison, is classically defined by cortical EEG activation (desynchronization), diminished or suspended thermoregulatory defenses to thermal stimuli, increased brain temperature, phasic bursts of muscle activity (rapid-eye movements and brief skeletal muscle twitches), skeletal muscle atonia, irregular cardiovascular and respiratory regulation, penile and clitoral