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Shining new light into the workings of photoreceptors and visual interneurons

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Vision starts at the retina. Photoreceptors sample and process visual information and redistribute that synaptically over a rich array of retinal channels, enabling animals to see the world consistently over vastly varying light conditions. Owing to the recent advances in molecular biology, genetics, powerful recording methods and computers, much has been learned about how the phototransduction and visual interneurons work, shining new light into the design principles, mechanisms and computations that underlie early vision. To encourage systems perspective discussions between neurobiologists and engineers about this topic, covering multiple scales (from molecules to circuits) and various animal models (from insects to vertebrates), we organised the "1st interdisciplinary UK phototransduction and synaptic transmission workshop" at the University of Sheffield in September 2016. This special issue is a collection of review papers by the workshop speakers, highlighting the systems perspective in studying early vision.

Multi-scale modelling approaches to combine experiments with theory

In vitro and *in vivo* electrophysiological recordings have shown that phototransduction adapts continuously to changes in light input statistics, and these dynamics are species specific and nonlinear. Molecular biological and transgenetic approaches have identified a large body of molecules participants for these reactions, whilst theoreticians have proposed multiple perspectives how adaptation may optimise early visual information. However, the field has lacked a unified framework, which would explain mechanistically how photoreceptors work at different light conditions, linking molecular reactions to theoretical principles.

Two of the papers describe how to obtain new mechanistic understanding about phototransduction and adaptation dynamics at multiple scales by carefully combining biomimetic computational modelling approaches with intracellular recordings (Juusola & Song, 2017; Song & Juusola, 2017).

First, Song and Juusola (Song & Juusola, 2017) explain why and how a biophysically realistic fly photoreceptor model can both integrate the molecular dynamics and simulate realistic macroscopic responses to contrast stimuli over vastly varying light intensities, achieving a large dynamic range. The fly photoreceptor's remarkable capacity to light-adapt emerges naturally from its four structural and functional constraints: (1) its total number microvilli, sampling photon absorptions; (2) the stochastic nature of photon absorptions; (3) the refractory period in transducing photons to quantum bumps; and (4) the stochastic variations in the quantum bump latencies and waveforms.

Juusola and Song (Juusola & Song, 2017) then show how this stochastic adaptive sampling framework governs a fly photoreceptor's information capture. Interestingly, the same modelling framework can accurately predict the photoreceptor response dynamics in different fly species, from slow-flying *Drosophila* to fast-flying *Coenosia*. These findings suggest that evolution may use conserved computational adaptation mechanisms to match early visual information processing with animals' life-styles.

Evolutionary adaptations in different species

Because of their well-established genetic tool-kits, *Drosophila* and Mouse have played dominant roles in the recent experimental vision research. However, information from other species is becoming more frequent as the use of molecular genetics, advanced microscopy and functional recoding techniques is taking hold more preparations. Three reviews in this issue highlight some exciting discoveries obtained with these methods in the compound eyes of different invertebrate species (Arikawa, 2017; Immonen *et al.*, 2017; Stavenga *et al.*, 2017).

Immonen et al. (Immonen *et al.*, 2017) address how evolutionary selection may have affected ion channel expression in nocturnal and diurnal insect photoreceptors. By comparing electrophysiological EAG and Shab K^+-channel recordings in *Drosophila* and cockroach photoreceptors, respectively, they conclude that EAG might have been replaced by other delayed rectifiers in diurnal insects. In day-active *Drosophila*, bright light depolarises photoreceptors, activating their outward-rectifying Shab-channels to restrict depolarisation and extend membrane bandwidth. Conversely, in night-active cockroach, bright light strongly suppresses EAG conductance, causing a Ca^{2+}-mediated light-dependent inhibition (LDI). LDI increases membrane resistance and gain but reduces signalling bandwidth, which makes EAG unsuitable for light response conditioning during the day.

Stavenga et al. (Stavenga *et al.*, 2017) discuss the functional implications of dipteran flies' red eye colour, caused by the screening pigment inefficiency absorbing long wavelength light. Thus, the screening pigments could fail in preventing red light straying in the photoreceptors, potentially degrading spatial resolution. So what could be the functional role of the red screening pigments? The authors address this question by examining the complicated interplay between specific visual, sensitising and screening pigments. Red-stray light can maintain the R1-6 photoreceptor cells' light sensitivity by photo-converting meta-rhodopsin back to its native rhodopsin state, whereas its potential deleterious effects can be minimised by matching/separating the various visual and screening pigments' absorption spectrums, or by compensating through high rhodopsin turnover.

Photoreceptor arrangements for colour processing can vary dramatically across the species, and even between the sexes in the same species. This is summarised by Arikawa (Arikawa, 2017), through insightful spectral opponency comparisons between butterflies and other species, including humans. New evidence implies that rich synaptic connections between neighbouring photoreceptors contribute to spectral opponency; in contrast to such processing only happening later in the network, as was believed before. Interestingly, the random arrangement of spectrally heterogeneous ommatidia is highly conserved across insect species. The author's group investigates the underlying developmental mechanisms behind this phenomenon, giving unique evolutionary insight in these structure-function relationships.

Reconsidering the signal flow within retinal circuits

To understand early visual processing, phototransduction cannot be studied in isolation from synaptic transmission. Photoreceptors form sophisticated connections with downstream retinal circuitry, with these structures ranging from nano- to micrometers. Classical electron microscopy and immunolabeling studies have been limited by trade-offs in sample size and spatial resolution, constraining precise quantifications of robust synaptic connections between few individual cell types. Recent technological advances in serial scanning electron microscopy, super-resolution microscopy, and modern biosensor labelling enable visualisation of large-scale retinal circuits at extremely fine spatial resolution. Three papers unravel new retinal synaptic connections, found with these novel techniques, and discuss their role in early visual information processing (Chapot *et al.*, 2017; Franke & Baden, 2017; Rogerson *et al.*, 2017).

Rogerson et al. (Rogerson *et al.*, 2017) address the current deficit in a complete connectivity map of the outer retina. The authors analysed photoreceptor synapses in great detail from a large EM data set, and they discovered surprising new connections, including an unexpectedly high degree of interactions between rod and cone synapses, sparse photoreceptor sampling by several ON-cone-bipolar cell types, and atypical rod to cone-bipolar cell contacts. The timely review of these new connections suggests that the outer retina circuitry is much more complicated than previously thought, calling for new studies about their functional implications.

In line with the functional studies, Chapot et al. (Chapot *et al.*, 2017), from the same research group, reviewed the diverse and complex horizontal cell (HC) to cone feedback connections, which recent studies suggest to act at different spatial scales. In contrast to the traditional view of HCs simply averaging signals from many cones, providing only a global subtractive signal for ambient light adaptation, the authors provide an interesting perspective that HCs might modulate the cone output in concert both globally and locally. They argue that local modulation could minimise potential loss of local features, including chromatic signals from individual cones and high frequency spatial information.

In contrast to the new perspective on 'local processing' of HCs, Frank and Baden (Franke & Baden, 2017) cover an emerging concept by which retinal amacrine cells (ACs) might have multiple, more 'global' actions in modulating bipolar cell outputs, in addition to their specific roles at individual synapses. With the aid of new biosensors to image inhibition in large-scale networks, the authors provide a new view of how AC inhibition impact global retinal activity, extending the functional studies from individual circuits to interconnected AC populations. Intriguingly, this review presents the idea that interconnecting functional pathways involve many different types of ACs. The authors argue that the across-type AC interconnections are critical for establishing universal principles of retinal computation like parallel processing or motion anticipation.

All these new works call the eye researchers to rethink about the classical views of signal flow and processing in the retina.

The meeting highlighted the importance of systems perspective in retinal research, and was organised to stimulate communication in (1) multi-disciplinary integrative biophysical modelling approaches; (2) a multi-scale approaches covering topics from molecules to circuits; and (3) cross-species comparative approaches. The participants told us that they had much appreciated its unique and informative knowledge exchange experience, and voiced their support for similar future meetings.

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