Dispatches

Visual Transduction: Microvilli Orchestrate Photoreceptor Responses to Light

How do the microscopic properties of a photoreceptor shape the transformation of photon inputs into electrical outputs? Adaptive feedback, combined with stochastic sampling of light by transduction units, efficiently captures visual information.

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All sensory systems capture information from the environment and represent it in electrical signals. As information that is lost at the first step in sensory transduction cannot be recovered, the fidelity of this process sets the performance limit for what downstream neural circuits can deduce about the world. These environmental cues can be presented across an incredible range of intensities. Photoreceptors, for example, must reliably transduce information both under very dim illumination, where only a few single photons are available, through broad daylight, when fluxes of millions of photons per second are routine (Figure 1A). Moreover, in fast flying insects like Diptera, visually guided course control requires photoreceptors to detect rapid changes in light intensity, approaching the millisecond time scale. Thus, understanding how sensory cells like photoreceptors are constructed to rapidly and reliably encode information across a wide range of input regimes represents an important challenge. In a study reported in this issue of *Current Biology*, Song *et al.* [1] derive a quantitative model that explains how the cellular and biophysical properties of photoreceptors and the transduction machinery shape response dynamics and information coding properties at both low and high light intensities.

The insect compound eye collects light through an array of small lenses that together sample visual information across space [2]. In Diptera, each of these unit eyes, the ommatidia, contains eight photoreceptors that detect light along distinct visual axes [3]. Each photoreceptor has a prominent apical specialization, the rhabdomere, a cylindrical body that functions as a light-guide, maximizing photon absorption. Each rhabdomere comprises thousands of oriented, finger-like protrusions known as microvilli. These microvilli contain the visual pigment rhodopsin, as well as the set of molecules that comprise the phototransduction cascade, linking photon absorption to the production of the light-induced current (Figure 1B; reviewed in [4,5]). Genetic, molecular and electrophysiological approaches have defined many of the molecular and biophysical properties of phototransduction [4,5]. Absorption of a single photon, followed by amplification of this signal via a sequence of biochemical reactions, gives rise to a typical current transient called a 'quantum bump'. In *Drosophila*, a quantum bump arises via the sequential activation of rhodopsin, a heterotrimeric G-protein, phospholipase C, and two TRP channels, opening of which causes membrane depolarization (Figure 1B; [4,6]).

This signaling pathway is the fastest known G-protein-coupled signaling pathway [5]. As each microvillus contains all of the components necessary to generate a bump, each acts as an individual photodetector with single photon sensitivity. After absorbing a photon and producing a bump, a microvillus enters a brief refractory state that must end before a new photon can be productively absorbed. A given photoreceptor's response to a light input then reflects the integrated output of all active microvilli at each time point. However, how the response dynamics of individual microvilli might be affected by global adaptation signals and integrated across the population to give rise to efficient information transfer was previously unknown.

Using a detailed model incorporating much of these data, Song *et al.* [1] quantitatively simulate a photoreceptor, and examine the individual components that give rise to its dynamic responses. This model explains how orchestrated properties of the population of microvilli, combined with global feedback mechanisms, gives rise to an adaptive and stochastic sampling scheme that yields efficient information encoding (Figure 1C). While stochastic sampling of microvilli contributes to the prevention of saturation and equalizes the use of available cellular resources, adaptation adjusts performance to input light conditions. Put together, these mechanisms achieve output contrast constancy, novel event enhancement, and reliable signal to noise reporting within a range of frequencies appropriate for different Diptera, across a wide range of illumination levels (Figure 1D).

Song *et al.* [1] begin by putting the phototransduction cascade into a broader context, emphasizing that each quantum bump can be considered a sample of the light level. The shape of the sample, or, equivalently, the bump waveform and its latency distribution, is established via Ca^{2+}-dependent global feedback mechanisms, as well as membrane voltage effects, that together make bumps smaller and briefer during light adaptation [6,7]. This increase in the 'temporal resolution' of the bump enables photoreceptors to encode higher frequency information under brighter illumination. At the same time, the sample rate, or equivalently, the bump production rate, is established via the availability of microvilli to actively absorb photons. This, in turn, depends on the dynamically changing refractory period of each microvillus (Figure 1C). Thus, under low light conditions, most microvilli are available to be activated, maximizing the quantum efficiency of the

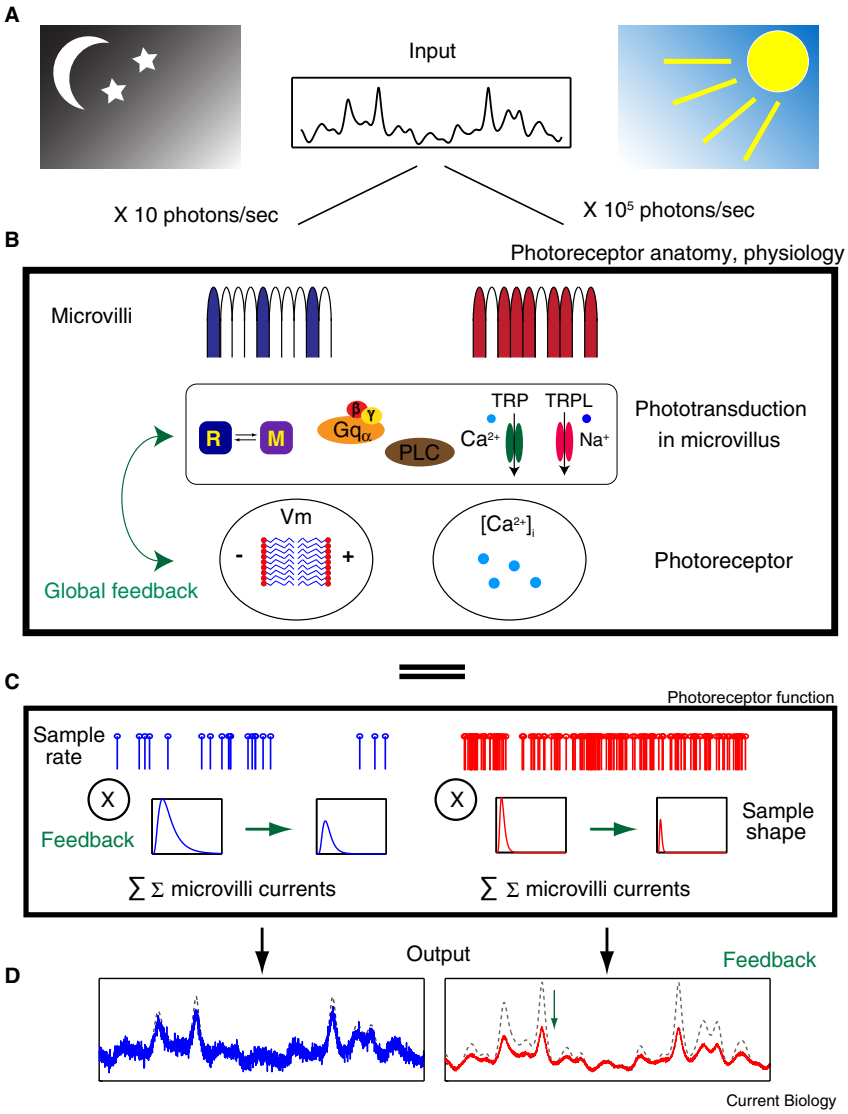

Figure 1. Adaptive feedback and stochastic sampling capture photoreceptor responses.

(A) Light inputs are dynamic, and can comprise small (at night) or large photon fluxes (during the day). (B) Microvillar activity is sparse when the photon flux is weak (blue) and dense when the photon flux is strong (red). Microvilli that are unavailable, either because they are active or because they are within the refractory period, are filled; available microvilli are empty. Each photon is amplified by a set of biochemical reactions (middle). This process is modulated by two feedback mechanisms: photoreceptor membrane voltage (Vm) and intracellular Ca^{2+} concentration ($[Ca^{2+}]$). (C) Phototransduction as an adaptive and stochastic sampling procedure. Bump production rates (top) are convolved with dynamically changing bump shapes. Feedback reduces the amplitude of bumps and makes them more transient (middle). The output currents of all microvilli are summed (bottom). Blue: dim light levels. Red: bright light levels. (D) The photoreceptor output–membrane voltage feedback acts to compress the output waveform (dashed gray curve, before compression; blue and red curves, after compression). The dynamics of the voltage output closely follow that of the light input at both dim (blue) and bright (red) light levels with only a modest reduction in signal to noise ratio at low light levels.

photoreceptor, while under high light conditions, many microvilli have already been activated, and are now in the refractory state, reducing the quantum efficiency of the photoreceptor.

Previous modeling efforts had already accounted for the generation of quantum bumps in response to single photon arrival, the shaping of bumps via feedback mechanisms, the associated distribution of latencies, and the control of the membrane voltage in photoreceptors [8–10]. But by putting all of these components together, Song *et al* [1] have been able to determine which processes govern performance under different conditions. For example, at high light levels, there is a rapid initial adaption process that reflects microvillar availability: when the first photons arrive, most microvilli are available, get activated and enter the refractory state simultaneously; photons that arrive later thereby encounter fewer microvilli that can be activated, and hence are less likely to be captured. In addition, there also exists a slower adaptation process that occurs at all light levels in which bump sizes decline continuously over time, an inhibitory effect attributable to calcium accumulation, and membrane depolarization.

Interestingly, as not all microvilli can be simultaneously active, and availability is governed by both the stochasticity of successful activation of the transduction cascade by an absorbed photon as well as by the distribution of refractory periods, saturation is prevented. Thus, while the quantum efficiency of photon absorption drops at high levels, the information rate does not. Finally, Song *et al*. [1] demonstrate that their adaptive and stochastic sampling scheme can reliably describe information rates and signal to noise ratios as a function of frequency for photoreceptors in multiple fly species by appropriate adjustment of model parameters. Thus, the model also reveals exactly how a few critical properties of the photoreceptor and the phototransduction process can be adjusted to match very different expected distributions of input frequencies associated with the different lifestyles of different kinds of flies.

At a high level, photoreceptors transform a set of discrete events, photon absorptions, into analog signals, membrane voltages, that are relayed via synaptic vesicle release to downstream circuitry. This type of transition between discrete and analog signaling is widespread in the nervous system. For example, analogous transitions occur when discrete opening and closing events of ion channels are converted into current flows and membrane voltages. It will be interesting to examine whether

the principles of adaptive and stochastic sampling that have been shown by Song *et al*. [1] to shape the discrete to analog conversion performed by photoreceptors are also applicable to other digital to analogue transitions in the brain. Future studies will reveal whether a general scheme for optimal information representation across these transitions exists.

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Endocytic Traffic: Vesicle Fusion Cascade in the Early Endosomes

New research shows that vesicles in the early endosomal network coalesce according to a classical theoretical description of aggregation put forward by Smoluchowski more than 100 years ago. This gives a new tool for unraveling complexities of the endocytic pathways.

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Endocytic pathways are dizzyingly complex [1,2]. Signals and cargo from outside of the plasma membrane are packaged into vesicles that are directed *en masse* to different parts of the cell. Over the years, much has been discovered about the molecular origin of signals and processes that govern these pathways [3–5]. However, it has not yet been possible to directly observe the detailed fate of the multiplicity of vesicles as they progress from the plasma membrane to their ultimate destination.

The flux of information and materials from the plasma membrane to the interior of the cell is made up of many microscopic events involving such vesicles, and aspects of the endocytic pathways will remain elusive until the nature of these individual events can be resolved. What is the rate of vesicle fusion? What is the rate of vesicle fission? Do these rates depend on the cargo? How do fission and fusion depend on the protein composition of the vesicle membrane? Quantitative answers to questions such as these would shed light on the mechanisms underlying endocytic pathways.

A new study in this issue of *Current Biology* by Foret *et al.* [6] provides further support to the idea that the early endosomal network is a vesicle fusion cascade, in which the dominant effect is the continuous merger of small vesicles into larger ones, which carry more and more cargo. Strikingly, the quantitative laws governing this cascade are essentially identical to those that were predicted nearly 100 years ago by Smoluchowski [7], and followed up years later by Chandrasekhar [8], in imagining the aggregation of small (e.g. colloidal) particles into large clusters [9].

To establish this conclusion, Foret *et al.* [6] directly imaged endosomal populations in HeLa cells, which were transfected with a transgene expressing a GFP-tagged version of Rab5c, a marker of the early endocytic pathway [10]. Cells in the early endosome therefore could be visually identified in a confocal microscope by GFP–Rab5 fluorescence. To study flux through the pathway itself, these authors then allowed the cells to take up low-density lipoprotein (LDL), which had been labelled with a different fluorophore, for a fixed period of time and imaged the endosomal co-localization of Rab-5 and LDL. They then quantified the number of endosomes — n(s) — with an LDL fluorescence intensity, s. By measuring this distribution for cells that had been allowed to take up the LDL for different time periods, they directly measured the time course of movement of fluorescent LDL through the early endosomal pathway. With increasing time exposure, the average amount of LDL in each endosome grows; over the course of an hour, the maximum fluorescence in a single endosome increases more than 10-fold.

To quantitatively interpret their results, Foret *et al.* [6] use a classical analysis of aggregation kinetics introduced by Smoluchowski [7], and expanded upon by Chandresekhar [8] (also see review by Leyvraz [11]). In its original form, this was imagined as a way to quantify the coagulation of small sticky particles undergoing Brownian motion in a liquid. When two particles collide they stick to each other, forming a cluster. When two clusters collide, they create a yet larger cluster. To predict the rate at which clusters grow, Smoluchowski wrote down a set of chemical rate equations for the number of clusters of a given size. For example, a cluster of five particles can be made by combining a four particle cluster with a single particle, or a two particle cluster with a three particle cluster. Note that