Multiple retinal mechanisms preserve visual sensitivity as the properties of the light inputs change. Rapid gain controls match the effective signaling range of retinal neurons to the local image statistics. Such gain controls trade an increased sensitivity for some aspects of the inputs for a decreased sensitivity to others. Rapid, local gain control comes at another cost: noise in the signal controlling gain (e.g. from the photoreceptors) will cause gain itself to vary even when the statistics of the light input are constant.

Here, we focus on three constraints on rapid gain control mechanisms in the retina and their relationships to recent insights into retinal circuitry and processing. First, the statistics of natural visual inputs, for example the temporal and spatial scale over which the mean light intensity changes, set the landscape in which gain controls operate (reviewed by [4,5]). Second, the signals controlling gain must be derived from the photoreceptor signals, which poses an inherent limit to the accuracy with which gain can be controlled. Third, gain controls do not operate in a vacuum, but instead interact with other computations carried out in the retinal circuitry; these interactions can make some gain control locations more sensible than others.

The challenges the dynamic range of vision poses for our understanding of neural function recur throughout the nervous system. In particular, nearly all sensory systems must accurately represent a wide range of input signals in their output spike trains. The auditory system, for example, can detect sounds producing movements of the hair cell stereocilia similar in magnitude to the diameter of a hydrogen atom (reviewed by [6]), and yet can also avoid saturation for sounds a trillion times louder [7]. Studies of retinal gain controls provide an excellent opportunity to understand these general issues because the circuitry is well defined and retinal signals can be compared directly to over a century of behavioral measures of visual fidelity.

Gain controls and efficient coding

Figure 1 illustrates some of the challenges of encoding realistic visual inputs. The statistics of the light inputs in different regions of a scene differ substantially [8] (reviewed by [4]). In Figure 1 and below, we emphasize changes in mean intensity and in contrast, that is, local variations in intensity about the mean. Efficient encoding of visual images requires matching the gain of visual neurons to the image statistics so as to make good use of the limited dynamic range of the responses of a cell.

Eye movements change the region of the scene sampled by the receptive field of a cell. This causes spatial differences in mean and contrast to produce corresponding temporal changes in the signals encountered by the cell [9,10]. Local eye movements (microsaccades) will cause the temporal contrast — the temporal variations about the mean — of the signal encountered to reflect the local spatial structure in the scene (e.g. upper left trace in Figure 1). Under free-viewing conditions, larger eye movements (saccades) change fixation on a time scale of ~200 msec [11]. Saccades will often change the mean (Figure 1 top) and contrast (Figure 1 bottom)
encountered within the receptive field. Efficient encoding under these conditions requires that gain is controlled more rapidly than fixation changes. Indeed, some retinal gain controls operate in less than 100 msec following a change in mean intensity [12,13] or contrast [14]; such gain controls are well suited for adjusting sensitivity to match the statistics of a local region of the visual scene during a single fixation.

Gain controls that are engaged following a change in mean or contrast have different effects on the relationship between light input and neural response. Increases in mean intensity shift and broaden the stimulus–response relationship (reviewed by [1,2]), centering it on the mean intensity (Figure 1, top right). Increases in temporal contrast broaden the stimulus–response relationship [15,16], matching the dynamic range of a cell to the range of input signals encountered (Figure 1, bottom right).

Constraints imposed by photoreceptor signals and image statistics

Like most things in life, adaptation does not come for free. Adaptation poses two potential problems for the visual system. First, it involves decreasing sensitivity to some aspects of the light inputs while increasing sensitivity to others. Simple examples are our poor ability to estimate mean light intensity (try setting your camera exposure manually) or visual illusions that exploit ambiguities created by adaptation of selected stimulus features. Second, gain controls necessarily operate on a finite spatial and temporal scale. As a consequence, gain is likely to vary even when the statistics of the input signals are constant.
An unavoidable source of noise in the signals controlling gain comes from variability in the photoreceptor signals themselves. This noise can be reduced by averaging over multiple photoreceptors and/or over time. The effectiveness of such averaging, however, is limited by the extent of spatial and temporal correlations in the visual inputs. Furthermore, in some cases it is advantageous to adapt before combining photoreceptor signals. As summarized below, these tradeoffs depend on light level and differ substantially for rod- and cone-mediated signals.

The good, bad and ugly of adapting in single photoreceptors

Figure 2c shows responses of a primate cone to an increase in light intensity from darkness to a level roughly equivalent to a typical interior setting. The responses to superimposed flashes monitor gain. This increase in background light intensity causes a noticeable change in the gain of cone signals [17] (25% in Figure 2c) and of downstream neurons in primate retina [18–20].

At typical interior light levels, both physiological and behavioral experiments indicate that gain controls operating in single cones contribute substantially to the overall control of the gain of cone-mediated signals. The intensity dependence of the response gain of single primate cones resembles that of horizontal cells [13,17,20]. Furthermore, behavioral experiments show a nonlinear mechanism indicative of adaptation that operates on a spatial scale consistent with that of a single cone [21]. Taken together, these observations suggest an important site of adaptation operating on the signals generated by a single cone, that is, in the cone phototransduction cascade or output synapse.

The gain of cone-mediated signals changes within 100 msec following a change in mean light level [12,13], well-matched to the time between saccades. With such rapid mechanisms in mind, Figure 2d shows a 400 msec section of the cone response centered on the time of the increase in mean intensity. Detecting the change in mean is possible but difficult on this time scale because of noise intrinsic to the cone signals. The intrinsic dark noise of primate cones is equivalent to ~4000 absorbed photons per second [17]; at mean light levels below this the cone signals are dominated by intrinsic noise.

The high level of noise in the cone responses suggests that gain fluctuates over time even when the mean light...
level is constant. Figure 3 illustrates this issue. The smooth curve summarizes measurements of the dependence of the gain of primate cone responses on mean light intensity [17]. Gain, however, is not directly controlled by mean light intensity but instead by a neural signal that depends on the mean intensity, for example, the mean cone voltage. Poisson fluctuations in photon absorption and noise intrinsic to the cone produce noise in the signal controlling gain. This noise will masquerade as a real change in mean intensity and hence produce changes in gain. Expressing the variations in the signal controlling gain as equivalent variations in input light level, we can use the relationship between gain and mean intensity to estimate the gain fluctuations (dashed lines in Figure 3). Because gain is controlled on a time scale similar to the integration time of the cone responses, fluctuations in gain will introduce noise comparable to that produced by quantal fluctuations in the incident light and the cone dark noise. This relatively large contribution of gain fluctuations to cone noise will hold true under all conditions in which gain controls are active. Noise introduced by gain fluctuations are a necessary evil of rapid gain control.

Adaptation at the level of single cones is not without benefits. For example, adaptation is naturally cone-type specific, that is, changes in the photon absorption rate and response gain of one cone type do not influence gain in other cone types. Both gain changes measured in the horizontal cells [22] and behavioral color matching experiments [23] show cone-type specific gain controls.

The possible locations for controlling the gain of signals from a single cone type are limited because signals from different cone types are mixed early in retinal processing. Gap junctions between cones [24] and non-selective feedback from horizontal cells to the cone synaptic terminal [25] mean that cone signals are already mixed in the cone synaptic output. Additional mixing of cone signals occurs in convergence of signals from different cone types within the retinal circuitry. In both primate and rodent, signals from short-wavelength sensitive (S) cones remain segregated from those of middle- (M) and long-wavelength (L) sensitive cones in the receptive field centers of specific bipolar and ganglion cells [26–28,29,30], whereas in primate retina the surrounds of these cells receive mixed M and L cone input. In primate, most evidence points to a mixing of M and L cone signals [31,32] (but see [33]), except in the receptive field centers of cells receiving single cone inputs, that is, midget bipolar cells and midget ganglion cells in the central retina. In addition to this mixing, gain controls

Figure 3

Rapid gain controls introduce noise. Controlling gain quickly necessarily introduces fluctuations in gain. The smooth curve approximates the dependence of cone gain (response amplitude normalized by response in darkness) on mean intensity (in photon absorptions per cone per second, P*/cone/sec, see [17]), plotted on linear axes rather than the more typical logarithmic axes. Dotted lines illustrate how variability in the number of photons translates into variability in gain values. Noise in the cone response and the finite temporal integration time of the mechanism controlling the gain of cone-mediated signals will cause gain itself to vary in time even when the mean intensity is constant.
located in cells receiving single cone input cannot benefit from convergence to decrease cone noise and the consequent gain fluctuations (see below). Thus, cone-type specific adaptation is best achieved in cone outer segments.

Another benefit of adaptation in cones is that computations within the circuitry can benefit from the normalization of signals provided by adaptation. For example, the inverse scaling of gain with mean intensity provided by Weber adaptation causes a cell to encode contrast rather than light intensity; such encoding simplifies the task of subsequent mechanisms responsible for contrast adaptation.

**Convergence and network adaptation**

Gain controls operating downstream of the photoreceptors can exploit convergence to obtain more reliable estimates of the relevant scene statistics than is possible based on responses of a single photoreceptor. This spatial averaging expands the conditions under which gain can be controlled effectively.

**Cone-mediated signals**

The retinal circuitry reading out the cone signals provides multiple opportunities for gain control. Indeed, the gain of cone-mediated responses measured in parasol (magnocellular projecting) ganglion cells, which can receive input from hundreds of cones, is altered by mean intensities that do not affect the gain of the cone responses themselves (Figure 4, middle) [18,19]. The situation is less clear for midget (parvocellular projecting) ganglion cells (Figure 4, left).

Figure 2a shows responses of a primate cone to a step increase in light intensity that produces a change in parasol but not cone gain; Figure 2b shows a 400 msec period centered on the step onset. The step produces a small (~0.2 mV) hyperpolarization that is nearly impossible to detect on a short time scale based on the response...
of a single cone. Thus, controlling the gain of cone-mediated signals at these light levels requires averaging over multiple cones. Although such averaging makes gain control possible, noise in the signal controlling gain is still likely to cause gain fluctuations such as those illustrated in Figure 3.

Contrast gain controls face similar issues. Figure 2e shows the response of a cone to a step from 0 to 25% contrast. Similar changes by contrast strongly influence the gain of ganglion cell responses [16,34] (reviewed by [3]), with some mechanisms operating in ~100 msec [14]. Figure 2f shows a 400 msec segment of the cone response centered on the time of the contrast change. Cone noise obscures the contrast change on this time scale, as it did the response to the light step in Figure 2a. Indeed, contrast affects the gain of the retinal readout of the rod and cone responses, but not the gain of the photoreceptor responses themselves [34,35]. Much of the rapid (~100 msec) contrast gain control appears to be intrinsic to the ganglion cells [36,37]. This location is beneficial for several reasons. First, it could enable a contrast gain control mechanism to exploit the rescaling of signals provided by prior mean gain controls (see above). Second, residual noise in the signal controlling gain should be reduced by the spatial averaging provided by the ganglion cell receptive field (see Box 1).

Rod-mediated signals

The intrinsic noise of rods is about a million times less than that of cones [38], enabling vision to operate when photons are scarce. Vision under these conditions relies on amplification of the single photon responses of rods and convergence of signals from thousands of rods onto downstream ganglion cells [39]. The combination of amplification and convergence poses a danger of saturating neural responses at light levels that still produce rare photon absorptions in individual rods. The scarcity of photons makes controlling gain rapidly on the basis of signals from a single rod impossible over much of the operational range of rod vision. Instead, saturation is avoided by gain controls operating in the retinal circuitry (Figure 4, right) [40–42]. Gain controls operating at these low light levels must contend with the irreducible statistical fluctuations in photon absorption (see Box 1).

Where might such gain controls be located? Rod signals are read out by three known pathways (reviewed by [43]). The rod bipolar pathway provides the dominant readout at low light levels [44,45]; in this pathway rod and cone signals are mixed late in retinal processing (Figure 4, right). At higher light levels two other pathways contribute: one based on rod–cone electrical coupling [46], and the other on synapses from rods to a class of OFF cone bipolar cells [47–50]. These pathways mix rod and cone signals immediately. Thus, the rod bipolar pathway provides a unique opportunity for specialized processing operating exclusively on rod signals (e.g. [51–53]), including gain controls.

Behavioral measurements show that at least one mechanism controlling the gain of rod-mediated signals extends spatially over a region encompassing ~50 rods [54,55]. This is consistent with the convergence of rod signals onto rod bipolar cells [39,48]. Our own physiological recordings identify the synapse between the rod bipolar cells and AII amacrine cells as a key gain-control site at low light levels [56]. Taken together, these studies suggest that the gain control mechanism enjoys only modest averaging over rods, and that gain is modulated by a handful of photons in the rod bipolar pathway. As for the cone signaling described above, this suggests that gain varies considerably even when the mean light level is constant.

Conclusions

Understanding retinal gain controls will require a synthesis of four issues, which to date have been largely studied in isolation. First, gain controls operate at multiple locations in the retina and have diverse temporal and spatial properties. Second, these mechanisms serve multiple functional roles: protecting neural responses from saturation, discarding unimportant or uninformative responses...
normalizing signals according to their fidelity, emphasizing novel stimuli [58*], and so on. Third, these mechanisms operate in the context of natural image statistics. Fourth, gain controls impact, both positively and negatively, other computations taking place in the retinal circuitry. We have emphasized how photoreceptor noise interacts with these other considerations to determine how reliably gain can be controlled and the tradeoffs associated with different gain control locations.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

● of special interest
●● of outstanding interest


The authors demonstrate that long- and middle-wavelength cones are electrically coupled, mixing the signals from these cone types early in retinal processing. Modeling suggests that such coupling decreases chromatic sensitivity while increasing luminance sensitivity. No evidence for short-wavelength cone coupling was found, although the sample size was small compared with that for the other cone types. Li and DeVries [82] provided stronger evidence for a lack of electrical coupling between short-wavelength and middle wavelength cones in squirrel retina.


This anatomical study reveals exclusive connectivity between short (S)-wavelength cones and S-cone bipolar cells identified in a transgenic mouse. Even cones containing dual opsins (short and middle wave-lengths) do not contact these specialized S-cone bipolar. Similarities with the primate S-cone circuitry could be evidence for a common primordial color system.


This study is the first functional demonstration of cone connectivity to cone bipolar in the mammalian retina. Paired recordings between short (S) and middle (M) wavelength cones and S-cone bipolar cells identified in a transgenic mouse. Even cones containing dual opsins (short and middle wavelength) do not contact these specialized S-cone bipolar. Similarities with the primate S-cone circuitry could be evidence for a common primordial color system.


The authors’ systematic examination of long (L) and middle (M) wave-length-sensitive cone inputs to horizontal cells, midget, and parasal ganglion cells tests predictions of cone-selective and random wiring. The first hypothesis states that L and M cone inputs are segregated in the center and surround regions of a receptive field. The results show equal mixing of...
L and M cone inputs to all three cell types, supporting the random wiring hypothesis in the peripheral primate retina (but see Solomon et al. [53]).


This work systematically examines the anatomical connections between OFF midget cone bipolars and midget ganglion cells in marmosets with two or three cone types. The authors reach three main conclusions: first, a midget bipolar cell can contact multiple midget ganglion cells; second, midget ganglion cells appear to contact all midget bipolar cells within the area spanned by their dendrites; and third, the wiring is similar with 2 or 3 cone types. Thus, the anatomy does not meet the expectations for selective wiring that exploits the extra cone type to increase chromatic sensitivity.


This work shows that contrast adaptation in mammalian ganglion cells involves roughly equal contributions from mechanisms operating on synaptic inputs and ganglion cell spike generation. This is consistent with previous work in salamander retina (Kim and Rieke, [63]).


This work shows that adaptation mechanisms in the retina are much more diverse than previously appreciated. In particular, these mechanisms increase sensitivity to changes from one distribution of stimuli to another for several classes of complex stimuli (horizontal versus vertical bars, temporally correlated or anticorrelated intensity waves, and so on).


