The fundamental plan of the retina

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The retina, like many other central nervous system structures, contains a huge diversity of neuronal types. Mammalian retinas contain approximately 55 distinct cell types, each with a different function. The census of cell types is nearing completion, as the development of quantitative methods makes it possible to be reasonably confident that few additional types exist. Although much remains to be learned, the fundamental structural principles are now becoming clear. They give a bottom-up view of the strategies used in the retina's processing of visual information and suggest new questions for physiological experiments and modeling.

A simple concept of the retina's function—lateral inhibition by horizontal and amacrine cells, a direct pathway mediated by bipolar cells—is part of the everyday canon of neurobiology. In reality, the retina is a more complex and more subtle structure than the textbooks imply. This is of course true also for other structures of the central nervous system—such as the hippocampus or cortex—where a similar mismatch exists between a simple iconic physiology and the facts of the biological structure. Here I make an initial attempt to come to grips with the real retina, to encompass the system's actual cellular complexity.

Neuroanatomical studies have reached a milestone. The identification and classification of retinal neurons (**Fig. 1**), begun more than 100 years ago by Santiago Ramon y Cajal, is nearing completion—the first time that this has been accomplished for any significantly complex structure of the mammalian CNS. This statement is possible because much of the recent work on retinal cell populations has been quantitative. Staining cells as whole populations permits comparison of their numerical frequency. More importantly, when the number of cells of a general class (such as amacrine cells) is known, one can then determine when the identified types add up to the class total[1–4]. Much detail remains to be learned, and a few additional cell types are sure to be discovered. However, we now know at least that no large cell populations remain unidentified, that there are no major pieces 'missing' within the retina's machinery[5].

Unexpectedly, for most mammals, the numbers of bipolar and amacrine cells are distributed fairly evenly among the different types. This differs from initial impressions, which were much influenced by early studies in primates. The primate fovea is anomalous in being dominated numerically by a single type of retinal ganglion cell, with an associated, specialized type of bipolar cell (see below). In other mammalian retinas, and away from the fovea in primates, individual bipolar, amacrine and ganglion cell types are numerically distributed in a more level way. Although variations certainly exist (generally, there are fewer wide-field than narrow-field neurons), there are no dominant types. In other words, the retina is not composed of a few major players surrounded by a diverse cast of minor ones. Instead, it consists of many parallel, anatomically equipotent microcircuits.

How can this awesome list of cell types be sorted? What unifying principles might allow us to conceive of the retina more simply? From the work of many laboratories[6–11], the fundamental backbone of the retina's structural organization has come into view. It reinforces certain principles learned from physiological experiments, and suggests new questions for further ones. Here I review the retina's structure and point out some unresolved functional issues that it suggests.

Parallel pathways from cones to ganglion cells

A typical mammalian retina contains 9–11 different types of cone-driven bipolar cells. These represent an assortment of pathways from cones to the inner retina, each carrying a different type of information. This diversity was initially shown in the cells' structures and the distinct proteins that each expresses. Electrophysiological experiments are now beginning to reveal its functional consequences.

In most mammalian species, rods outnumber cones by approximately 20-fold, and rods were once considered the primordial photoreceptors. However, molecular cloning of the visual pigments (opsins) that render these cells light-sensitive led to the conclusion that cone pigments evolved long before rhodopsin, the rod pigment[12–14]. The early photoreceptor thus seems to have been some type of cone (**Fig. 2a**). In retrospect, this makes sense; in building a cell to detect light, one would surely design it for times when copious light is available. (In starlight, a human rod photoreceptor has been calculated to receive only one photon every 10 minutes[8,15].) Cones are associated with a complex network of postsynaptic cells, whereas the circuitry strictly associated with rods is minimal; even though rods outnumber cones, most mammalian retinas have 8 to 10 cone-driven neurons for every cell associated primarily with the rod pathway.

The existence of multiple subclasses of cone-driven bipolar cells ('cone bipolars') was initially predicted on structural and molecular grounds[11,16,17]. First, bipolar cells branch at different levels of the inner plexiform layer[18], which contain processes of different types of amacrine and ganglion cells. Some ganglion cell types have dendrites confined mainly to level 1 of the inner plexiform layer, others to level 2, and so on. The inner plexiform layer, named as though it formed a single, tangled 'plexus,' is in fact an ordered stack of synaptic planes, more like a club sandwich than a plate of spaghetti. Specific bipolar cells make their synapses within specific planes,

and this confines their possible synaptic partners to cells with processes that occupy those same levels. Second, different types of bipolar cells have different numbers and distributions of synapses, without a gradation of intermediate forms between the types. The conclusion reflects more than neuroanatomical anecdote; a formal cluster analysis showed that cone bipolars segregate into discrete groups based on synapse number and distribution[16,19]. Third, individual bipolar cell types have characteristic sets of neurotransmitter receptors and calcium-binding proteins[20–22]. These molecular distinctions reflect different modes of intracellular signaling and different types of excitatory and inhibitory inputs from other retinal neurons, either at their inputs from cones or from amacrine cells that synapse on their axon terminals. At the cone synapses, different glutamate receptors are present. At their axon terminals, different bipolar cells can receive inhibitory glycinergic or GABAergic input via one of two different kinds of GABA receptors. The different receptors and their channels have differing affinities and rates of activation and inactivation, which give the cells different postsynaptic responsiveness[22–25].

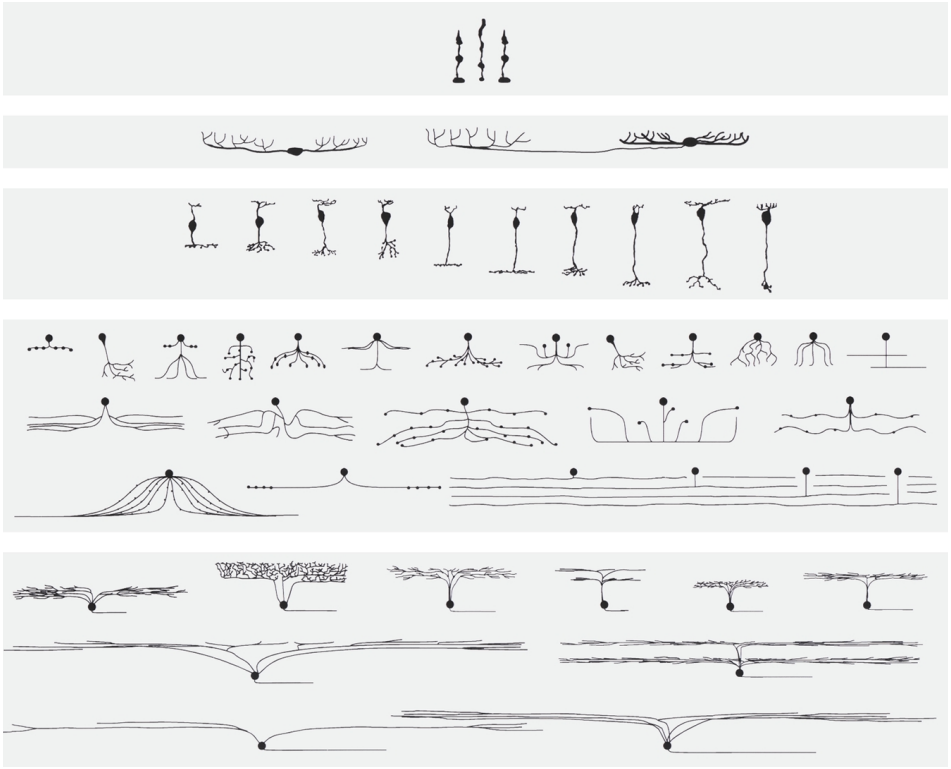

Fig. 1. The major cell types of a typical mammalian retina. From the top row to the bottom, photoreceptors, horizontal cells, bipolar cells, amacrine cells and ganglion cells. Amacrine cells, the most diverse class, have been studied most systematically in the rabbit[3,4], and the illustration is based primarily on work in the rabbit. Most of the cells are also seen in a variety of mammalian species. The bipolar cells are from work in the rat[39]; similar ones have been observed in the rabbit, cat[16] and monkey[17]. For steric reasons, only a subset of the wide-field amacrine cells is shown.

How are these differences manifested physiologically? First, the output of the cone photoreceptors is separated into ON and OFF signals (**Fig. 2b**). All cone synapses release glutamate, but bipolar cell types respond to glutamate differently. Some bipolar cells have ionotropic glutamate receptors: glutamate opens a cation channel, and the cell depolarizes. Other bipolar cells have a sign-inverting synapse mediated by metabotropic glutamate receptors, mainly mGluR6; these bipolar cells hyperpolarize in response to glutamate[26,27]. As it happens, photoreceptor cells work 'backward' (they hyperpolarize when excited by light, causing their synapses to release less glutamate), but the ensuing series of sign-reversals is not important for present purposes. When the retina is stimulated by light, one type of bipolar cell hyperpolarizes, and the other type depolarizes. OFF and ON bipolar cells occur in approximately equal numbers. The distinction, created at the first retinal synapse, is propagated throughout the visual system.

The classes of ON and OFF bipolars are each further subdivided; there are three to five distinct types of ON and three to five types of OFF bipolars (**Figs. 2c** and **3**). The purpose of the subdivision is, at least in part, to provide separate channels for high-frequency (transient) and low-frequency (sustained) information. Thus, there are separate ON-transient, ON-sustained, OFF-transient and OFF-sustained bipolar cells[28–30]. An elegant series of experiments shows that the distinction is caused by different glutamate receptors on the respective OFF bipolar cells; they recover from desensitization quickly in the transient cells and more slowly in the sustained cells[31].

An often-cited reason for splitting the output of the cones into separate temporal channels is to expand the overall bandwidth of the system. However, this would imply that the frequency bandwidth present at the output of a cone is too broad for transmission through the cone-to-bipolar synapse, which is uncertain given the many modes of synaptic transmission available. An alternative is that fractionating the temporal domain facilitates the creation of temporally distinct types of ganglion cells (**Fig. 4**).

An important point here is that there are no dedicated cones—cones that provide input, say, only to ON bipolars or only to OFF bipolars (as shown for simplicity in **Fig. 2**). Instead, the output of each cone is tapped by several bipolar cell types to provide many parallel channels, each communicating a different version of the cone's output to the inner retina (**Figs. 3**, **4** and **6**).

The foundations of color vision

The bipolar cells discussed so far are not chromatically selective, and this would prevent the retina from discriminating among wavelengths. A single type of cone, no matter how narrow its spectral tuning, cannot create color vision. A cone's synaptic output is a single signal, which can vary only in magnitude. For that reason, a cone's signal to the brain is inevitably ambiguous; there are many combinations of wavelength and intensity that will evoke the same output from the cone. To specify the wavelength of a stimulus, the outputs of at least two cones must be compared.

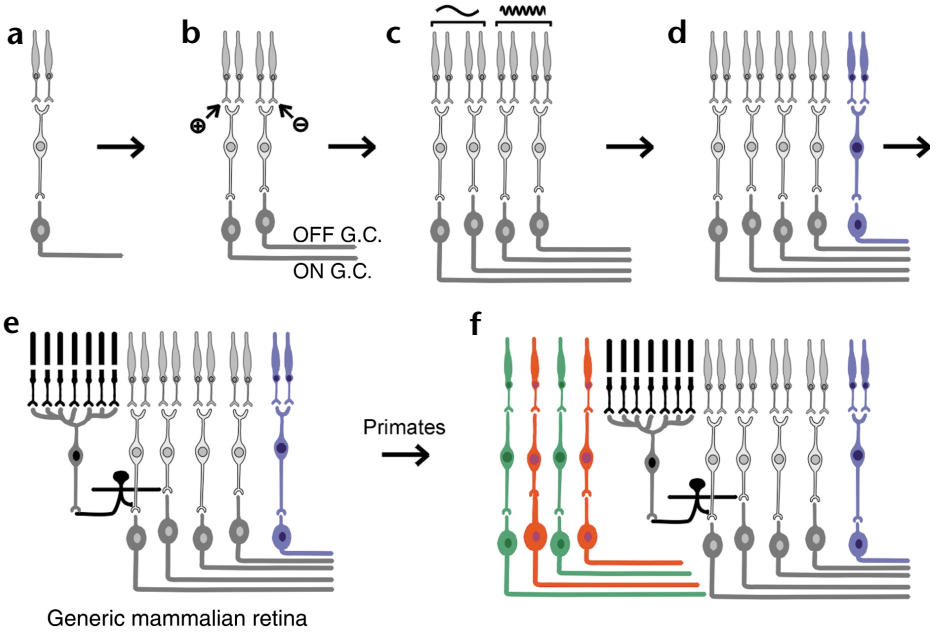

Fig. 2. The bipolar cell pathways of mammalian retinas, assembled from individual components. This diagram is intended to emphasize the overall organization of the parallel channels, and much detail is omitted. Many primate retinas have midget bipolar and ganglion cells, but only a few have a separate red and green channels. Rods are not as clumped as would be suggested here. For visual clarity, cones are shown contacting only a single bipolar cell each; in fact, all cones contact several bipolar cells, as shown in Figs. 3, 4 and 6. For the detailed synaptology of the rod pathway, see refs. 36, 37, 125.

Early in evolution, two cone opsins diverged, one with maximal absorption at long wavelengths and one with maximal absorption at short wavelengths[12–14]. Because an individual cone contains only a single spectral type of opsin, this creates two types of cones, one reporting on long wavelengths and one on short; by comparing their outputs, the retina can create a single signal that reflects the spectral composition of the stimulus.

The short-wavelength-sensitive cone, familiarly termed the 'blue cone,' occupies a distinct and simple position in the array of retinal circuitry: blue cones synapse on their own specialized type of bipolar cell, which in turn synapses on a dedicated class of retinal ganglion cells[32,33]. Blue cones generally make up less than 15% of all cones. The retina thus contains many long-wavelength cones, which communicate to ganglion cells via a variety of bipolar cells, a single type of blue cone, and a single type of blue cone-driven bipolar cell (**Figs. 2d** and **3**).

The synaptic connections of the inner retina are arranged so that the outputs of some ganglion cells compare the responses of the blue cones with those of the long-wavelength cones. For example, the ganglion cell may be excited by short-wavelength stimuli and inhibited by long wavelengths. This represents an economy; a single signal tells the brain where along the spectrum from blue to yellow the stimulus lies.

This combination of a short-wavelength cone and one or more long-wavelength cones is a virtually universal feature of mammalian retinas[14]. At one time, many mammals were thought to lack color vision, and indeed an animal with only these two visual pigments is a dichromat—in everyday language, red–green 'color blind.' But the phrase is misleading; the distance between the peak sensitivities of the short and long opsins spans the wavelengths reflected by important objects in the natural world, and an animal with only those opsins has a strong form of color vision. If any doubt exists on this point, one should remember that roughly 5% of humans inherit this form of dichromacy, but many learn of it only during adulthood, when first confronted by tests designed to reveal variations in color vision.

The pathway from rods to ganglion cells

Most amacrine cells and all ganglion cells receive their main bipolar cell synapses from cone bipolars, but retinas work in starlight as well as daylight, and this range is created by a division of labor between cones (for bright light) and rods (for dim light). Signals originating in rod photoreceptors reach the retinal ganglion cells via an indirect route using as its final path the axon terminals of the cone bipolar cells[34–37].

That a single set of ganglion cells is used for both starlight and sunlight represents an obvious efficiency, long known from electrophysiological findings. However, it was not obvious *a pri-*

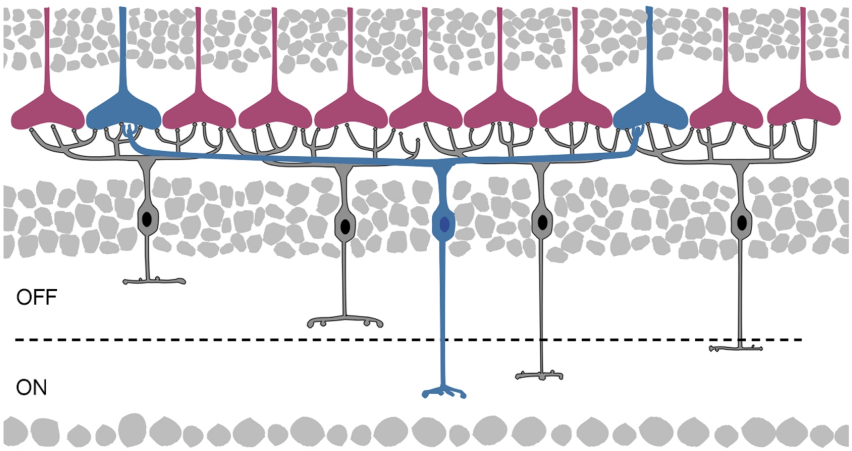

Fig. 3. The connections with cones and axonal stratification of different types of bipolar cells. Five different types of bipolar cells are illustrated. Two of them are diffuse (chromatically nonselective) ON bipolar cells terminating in the inner half of the inner plexiform layer. Two are diffuse OFF bipolar cells terminating in the outer half. Each samples indiscriminately from the spectral classes of cones. The blue cone bipolar, however, contacts only blue cones and thus is spectrally tuned to short wavelengths. Within the ON or OFF sublayer, axons of the bipolar cells terminate at different levels, indicating that they contact different sets of postsynaptic partners. After refs. 9 and 17.

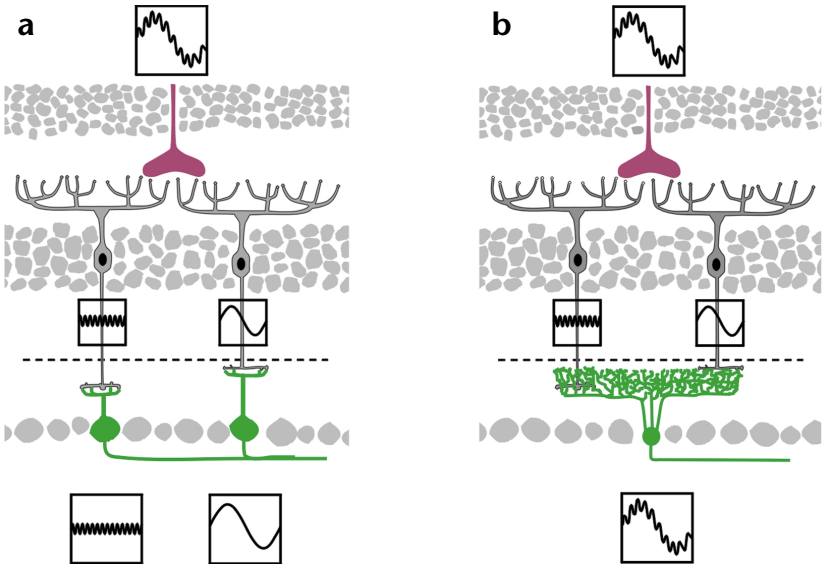

Fig. 4. How transient (high-pass) and sustained (low-pass) bipolar cells decompose the output of a cone. The resulting high- and low-frequency channels can contact narrowly stratified ganglion cells (**a**), in which case the two frequency bands are transmitted via separate, parallel channels to the brain. Bottom, a more broadly stratified ganglion cell (such as a beta cell) receives input from both types of bipolar cells[123]. Such a ganglion cell (**b**) has a broadband response. Many such combinations are possible, as are many permutations of input from amacrine cells.

ori that rod-driven information would reach the ganglion cells by an indirect path. Furthermore, rod photoreceptors far outnumber cones in most mammalian retinas; it was a surprise to learn, when quantitative methods became available, that cone bipolars outnumber rod bipolars in all but a few mammalian retinas[2,38]. The reason is that more rods converge onto a single rod bipolar than cones onto cone bipolars; the rod system trades acuity for sensitivity, and the circuitry associated with rods is simpler than that of cones (**Fig. 2e**).

Because rods evolved after cones, the likely scenario is that the rod circuitry was grafted onto the cone pathways. Only one kind of rod photoreceptor exists, and rods drive only a single type of bipolar cell. It synapses on a specialized amacrine cell, termed AII, which then transmits the output of rod bipolar cells to ganglion cells. This occurs largely via synapses (chemical or gap junctional) by AII onto axon terminals of cone bipolar cells, which then excite the ganglion cells.

It may seem strange that rod bipolar cells would not simply drive retinal ganglion cells directly, but seems less strange when one appreciates the complexity of the pre-existing inner retinal circuitry of the cone pathways. By synapsing on the axon of the cone bipolar cell, the rod pathway gains access to the elaborate circuitry of the cone pathway, including its associated amacrine circuitry. For example, the directionally selective type of ganglion cell retains its function in very dim light, even though it receives no direct synapses from the rod bipolar cells. The rod system piggybacks on the cone circuitry rather than re-inventing it.

Added complexities in the primate retina

At one time, primate retinas were thought to be somehow simpler than those of lower mammals, because recordings from the central retina of monkeys show mainly a simple type of center–surround ganglion cell physiology; complex properties like direction selectivity are statistically rare. However, the relative conservation of bipolar and amacrine cell types in monkeys and other mammals is now well documented[7,17,22,38–41]. Furthermore, such a conclusion would imply, remarkably, that retinal circuitry evolved over millennia was discarded. Instead, to the already existing retina were added three specializations: an additional chromatic class of cone, a rod-free fovea, and a huge number of small bipolar and ganglion cells, the so-called midget system (**Fig. 2f**).

The retina of a macaque monkey contains approximately 1,500,000 retinal ganglion cells; a cat, 160,000; a rabbit, 380,000 (refs. 1, 9, 42) . Around 70% of the ganglion cells of the monkey's retina are midget cells. They have a simple center–surround organization with linear spatial summation in the receptive field center. Associated with midget ganglion cells is a special midget bipolar cell. In the fovea, an individual ganglion cell receives direct input from only a single cone. The fundamental advantage offered by a midget system is a high sampling density, which enables great spatial resolution. In the central fovea, the spatial resolution of the entire system—photoreceptors, bipolars and ganglion cells—is limited only by the cone packing density[43].

In humans and some species of monkey, gene duplication followed by mutations affecting a few amino acids caused the long-wavelength opsin present in all mammals to evolve into two closely related opsins with slightly different absorption maxima[44,45]. Such retinas thus contain the widely conserved blue cone (with its specialized bipolar and ganglion cells), a long-wavelength 'green' cone and a slightly different long-wavelength 'red' cone. This does not change the fundamental organization of color vision; it simply creates better color discrimination between long wavelengths.

How the output of red and green cones is transmitted to the central visual system is a matter of controversy. The majority opinion is that it is transmitted via the midget system[10,11,46,47]. Midget bipolar and ganglion cells automatically have the spectral sensitivity of the single cone from which they receive input, so that the existence of the midget system perforce creates separate channels for the two longer wavelengths. A minority view holds that there is an as-yet-undiscovered ganglion cell, analogous in its circuitry to the blue/yellow ganglion cell, that compares red and green wavelengths[48].

Two types of horizontal cells

All rods and cones receive feedback from horizontal cells, but these cells are a numerically small proportion of the retina's interneurons, generally less than 5% of cells of the inner nuclear layer[2,38,40]. In most mammals, there are two morphologically distinct types of horizontal cells[49–52]. (Mice and rats have only one.) In monkeys, these have different numbers of synapses with different types of cones. The reason for this biasing is not yet certain; it may involve chromatic opponency in the red–green system. Traditionally, horizontal cells are said to enhance contrast between adjacent light and dark regions. Excitation of a central cone causes feedback inhibition of both the excited cone and a ring of neighboring ones. Because each cone—both the central one and its neighbors—transmits a sig-

nal to the inner retina, the upshot is that a small stimulus excites those ganglion cells that lie directly under the stimulus, but inhibits neighboring ganglion cells. This is the classical 'center–surround' organization, in which a ganglion cell is excited or inhibited by stimuli falling in its receptive field center, whereas stimulation of the surrounding region has an opposite effect.

An alternate formulation of the same facts is that horizontal cells adjust the system's response to the overall level of illumination—they measure illumination across a broad region and subtract it from the signal that is transmitted to the inner retina about a local image[8]. In effect, this reduces redundancy in the signal transmitted to the inner retina. The mean luminance across a large region of retina is shared by many cones and contains little information. When a local stimulus occurs, it exceeds or falls below the mean; the occurrence of that local event is the main signal transmitted to the inner retina.

Rods receive a separate type of horizontal cell feedback; this is accomplished by a specialization of one of the horizontal cells (the b/H2 type) that contacts cones. An axonal process of this horizontal cell contacts the rods, but does it far enough away from the horizontal cell's soma that the axonal arbor is electrotonically isolated[53]. The rod feedback system is thus isolated from the cone feedback system, sensibly because the ranges of brightness covered by rods and cones are so enormously different. This may be another consequence of the late evolution of rods. It allows the rods to have an independent horizontal cell feedback, driven by rods and feeding back to rods, without the creation of a third type of horizontal cell.

Twenty-nine types of amacrine cells

All retinal ganglion cells receive input from cone bipolar cells, but direct synapses from bipolar cells are a minority of all synapses on the ganglion cells; most are from amacrine cells[54–56]. The exact fraction varies among different functional types of ganglion cells, ranging from roughly 70% for alpha cells (large, movement-sensitive ganglion cells found in most mammals) to 50% for the midget ganglion cells located in the monkey central fovea. Amacrine cells also make inhibitory synapses on the axon terminals of bipolar cells, thus controlling their output to ganglion cells. In contrast to horizontal cells, which have a single broad role, amacrine cells have dedicated functions—they carry out narrow tasks concerned with shaping and control of ganglion cell responses.

Traditional presentations of the retina underweight the importance of amacrine cells, which are sometimes illustrated in a 1:1 ratio with horizontal cells[57,58]. They in fact outnumber horizontal cells by amounts that range from 4:1 to 10:1 (depending on the species) and can outnumber ganglion cells by 15 to 1 (refs. 2, 38, 40) . How can this complexity be understood? A first impulse is to deny that it exists—perhaps the taxonomy has been made artificially complex, or cells that look different actually have identical functions? It turns out that neither of these is tenable. The different amacrine cells have distinct pre- and postsynaptic partners, contain a variety of neurotransmitters, survey narrow areas of the visual scene or broad ones, branch within one level of the inner synaptic layer or communicate among many[3,4]. Both their molecules and their form point to diverse functions.

Amacrine cells seem to account for correlated firing among ganglion cells. Shared input from a common amacrine cell will tend to make ganglion cells fire together; the cross-correlation is broad if mediated by chemical synapses and narrower if mediated by gap junctions, known to couple amacrine and ganglion cells[59]. Correlated firing between ganglion cells has been proposed to represent a form of multiplexing, which could expand the information-carrying capacity of the optic nerve[60,61].

Those amacrine cells with functions that are more precisely understood do remarkably specific jobs. The dopaminergic amacrine cells globally adjust the retina's responsiveness under bright or dim light[62–64]. They are numerically sparse (9000 cells in a rabbit retina that has 4,500,000 amacrine and 380,000 ganglion cells)[65] and have wide-spreading arbors located in inner plexiform layer 1. Dopamine affects many elements of the retina's circuitry; it alters the gap-junctional conductance between horizontal cells and between amacrine cells[66,67], potentiates the responses of ionotropic glutamate receptors on bipolar cells, and ultimately affects the center–surround balance of ganglion cells[68,69]. Remarkably, retinal dopamine can even cause pigment migration in cells of the retinal pigment epithelium, a neighboring non-neural tissue[70]. In the latter case (and very likely some of the former as well), this is mediated non-synaptically, via a diffuse, paracrine release of the neurotransmitter. Elegant experiments using transgenically labeled amacrine cells in culture show that the extrasynaptic release is controlled by spontaneous action potentials in the absence of synaptic input and modulated by inputs, presumably also paracrine ones, from other retinal neurons[71,72].

In contrast, the starburst amacrine cells seem to be narrowly associated with a particular computational circuit. They arborize in thin (2–4 μm) strata within the inner plexiform layer, where they make excitatory cholinergic synapses on certain retinal ganglion cells, notably those particularly sensitive to moving stimuli. By feedforward excitation and/or inhibition (these neurons release both acetylcholine and GABA[73]), they are important for direction selectivity[74–76].

Ten to fifteen types of retinal ganglion cells

It became possible to record from retinal ganglion cells before modern anatomical techniques were invented, and early ideas of this population were much influenced by electrophysiological results, with their inherent sampling biases. These described two types of concentrically organized receptive fields, one with a small, linearly summing receptive field center (X cell) and another with a large, non-linear responsive area (Y cell). Systematic anatomical studies now make it apparent that many other types of ganglion cells exist. These are easily distinguished by their branching level, their dendritic arbor width (that is, the area of the visual field that they sample), and in many cases, their directly recorded physiology[77–80] (**Figs. 1** and **5**).

In all cases studied thus far, cells distinguished by structural criteria have turned out to have distinct physiologies. In the cat, the correspondence between X-cells and β, and Y-cells and α was established long ago, as was the analogous match between P and M, midget and parasol cells in the monkey[17]. Other cell types were studied early in the rabbit, using direct recording from the retina (where the problem of electrode selectivity is lessened)[81–85]. A bistratified neuron is the famous ON–OFF direction-selective cell. A similar but monostratified medium-field neuron is the ON-type direction-selective cell, which projects to the accessory optic system and provides an error signal for eye velocity in optokinetic nystagmus. An extremely small, monostratified neuron is the local edge detector described in classic electrophysiological studies.

In the monkey, a small bistratified neuron is the blue ON cell, and a larger, sparser neuron is a blue OFF cell. In both the

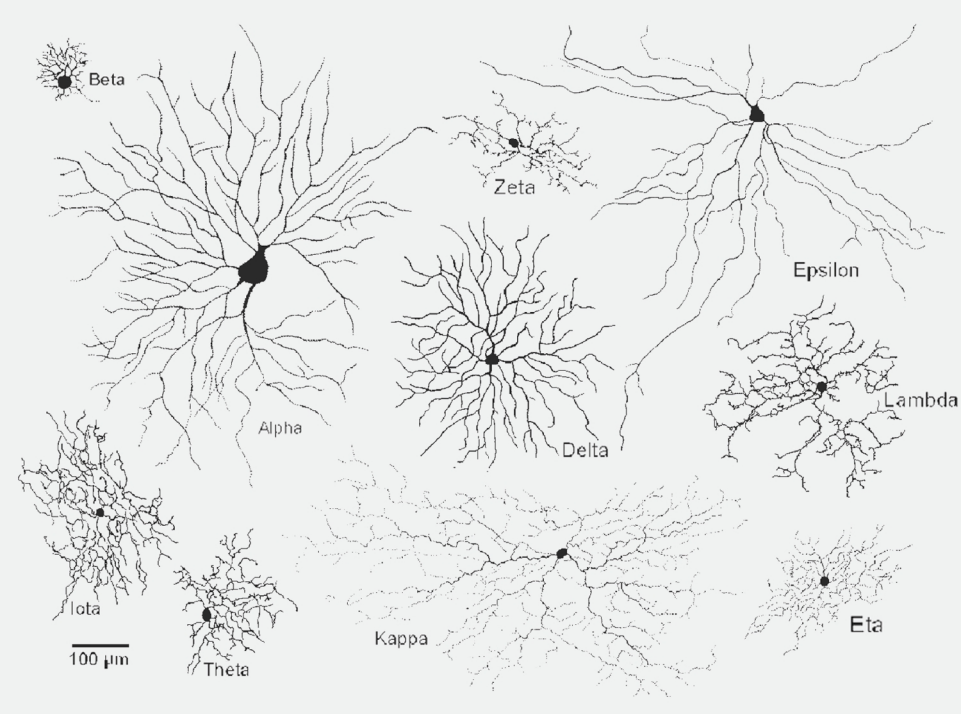

Fig. 5. The types of ganglion cells identified thus far in the retina of the cat. Ongoing work in the rabbit and monkey confirms this diversity, and many of the cells observed are probably homologs of those seen in the cat. Courtesy of D. Berson[77–80].

cat and monkey, a very large, very rare neuron has tonic responses to light and projects to a pretectal nucleus; it seems to control pupillary size. A similarly rare neuron projects to the cat suprachiasmatic nucleus, presumably to entrain circadian rhythms. Remarkably, this cell seems to be directly photosensitive (D.M. Berson, F.A. Dunn & M. Takao, *Invest. Ophthalmol. Vis. Sci.* **42**, S113, 2001)[86].

The primate fovea, with its huge number of midget cells, seems to have been superimposed upon existing ganglion cell populations that were little changed during the primate's evolution from earlier mammals. Some of these cells seem to correspond to neurons present in lower mammals and carry out 'vegetative' functions, such as the control of pupil size and optokinetic responses. Evidence for autonomous subcortical pathways that mediate these functions in the monkey is that both survive combined lesions of the visual cortex and superior colliculus[87]. It takes only a few neurons to measure the ambient level of illumination, which controls the pupillary aperture. There is no particular need for this number to increase as the total number of ganglion cells increases, and they end up as a small fraction of the total cells. A monkey retina that has 1,050,000 midget ganglion cells could comfortably 'contain' the ganglion cell population of an entire cat or rabbit retina within its remaining 450,000 cells[11].

For this purely statistical reason, non-midget, non-parasol cells in the monkey have largely been ignored. However, modern methods, notably, visually guided microinjection[88,89], are now providing an increasingly clear anatomical view of the other ganglion cells of the monkey[90–93]. There is some reason to suspect that the geniculostriate system receives non-midget, non-parasol types of information, and learning more about these cells' physiology seems important (see below).

Visual function: new certainties and new questions

A reward of structural studies is the level of certainty that their hard-won conclusions provide. The demonstration that X and Y cells are anatomically distinct entities helped still an acrimonious taxonomic controversy among electrophysiologists. Psychophysicists had long suspected that vision along the blue–yellow axis is different from vision along the red and green axis, which is given a concrete basis in the sparseness of blue cones and their bipolar cells. An exact synaptic wiring[33,47,91,94] now underpins the receptive field of the blue-ON ganglion cell, accurately predicted 35 years ago[95].

A different kind of contribution comes from the quantitative nature of such studies. Human visual acuity, for example, is now known to precisely match the packing density of the foveal cones[43,96]. This contribution is sometimes taken for granted, but should not be; our concept of central visual processing would be different if primate M cells were not 8% of all ganglion cells, as shown anatomically, but 30–50%, as would be concluded from their encounter frequency in electrophysiological experiments. As modeling of higher visual processes becomes more precise, knowledge of such physical parameters becomes increasingly useful.

Structural results also raise new questions; the cell populations of the retina hint at unsuspected subtleties in the retina's input–output relationships, some of which must have consequences for vision. For example, what are the remaining physiological types of retinal ganglion cells, and how do they contribute to behavior? The question here is the physiological response properties of the non-concentric (X and Y, M and P) types of cells and their function in the central structures to which they project. For subcortically projecting cells, those roles may be very sophisticated. The ON directionally selective cell of the rabbit, for example, projects to the accessory optic system and drives optokinetic responses[85,97]; the baroque morphologies of non-midget, non-parasol cells that project subcortically in the monkey suggest equally subtle physiologies. These questions should be answerable by *in vitro* recording followed by microinjection[89,92].

We need to complete our understanding of the synaptic basis of color vision. Here our colleagues who study higher visual centers are struggling; the cortical coding of color has been a tangled subject[98–100]. If the red–green axis is coded in the retina by a distinct, dedicated set of retinal ganglion cells, then one might expect a single cortical mechanism to code for color along both the red–green and blue–yellow axes. If red and green are transmitted separately, via the late-evolving midget system, higher centers may have anatomically and/or computationally independent ways of handling the two axes.

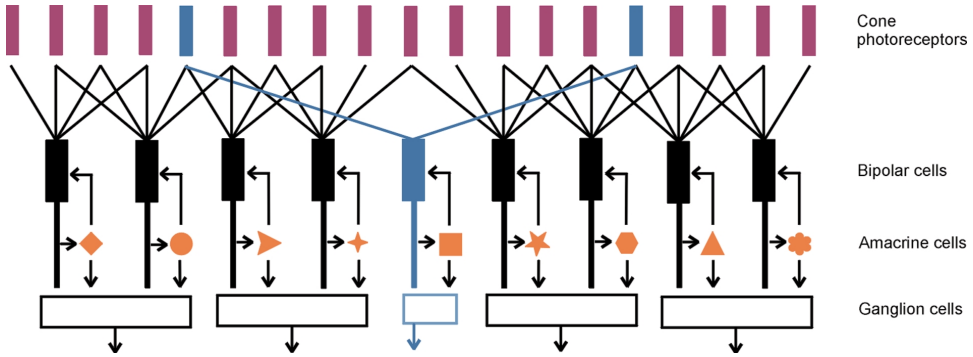

Fig. 6. The fundamental signal-carrying pathways of a generic mammalian retina, reduced to a conceptual minimum. Each type of bipolar cell (black) transmits a different type of information to the inner retina. The information that it transmits is determined by the bandwidth of the cones that it contacts, the number and type of those cones, the transfer function of the cone to bipolar synapse, and its interplay with amacrine cells. This is a minimal representation of the amacrine cells, which also include wide-field cells and which have synaptic contacts among each other. The different types of bipolar cells are contacted by distinct types of amacrine cells, in a variety of synaptic arrangements. These converge upon the retinal ganglion cells, in which specific combinations of bipolar and amacrine inputs create many functional types of ganglion cells.

In the lateral geniculate body of the monkey, several specialized types of cells project to the K (koniocellular) layers of the lateral geniculate body[101,102]. There are hints of other types of cells mixed among the cells of the magnocellular and parvocellular layers, and history teaches that it is possible to miss even a sizable class of cells when using metal microelectrodes[103]. Even though the remaining cells may be few in number, they are not necessarily unimportant for vision. The blue-ON ganglion cells make up less than 6% of all ganglion cells in the monkey but are a fundamental basis of primate color vision. Similarly, parasol cells make up 8% of all ganglion cells, yet are thought to be the source of a major stream of cortical information flow. Newly expanded techniques for recording from ganglion cells backfilled from specific central targets (D.M. Dacey *et al.*, *Invest. Ophthalmol. Vis. Sci.* **42**, 114, 2001) should soon provide a more complete description of the information that enters the geniculostriate system.

Microstructure within the receptive field center

A surprise when the complete array of amacrine cells was revealed was the plethora of narrow-field amacrines, which make up almost 50% of amacrine cells in the rabbit, rat and monkey and thus represent 20–30% of neurons in the inner nuclear layer[3,4,104,105]. How do they affect ganglion cell physiology?

In addition to amacrine AII (a link between the rod system and the ganglion cells), there are, in the mid-periphery of the rabbit retina, 11 types of amacrine cells with dendritic arbors less than 100 μm in diameter. In the same region, the diameters of retinal ganglion cell arbors range from 200 to 1000 μm. This means that many narrow-field amacrine cells exist within the dendritic field, and thus the receptive field center, of most ganglion cells.

If nothing else, the finding invalidates the textbook generalization that the function of amacrine cells is to carry information laterally across the retina; these cells are scarcely more laterally conducting than are the bipolar cells. It also suggests that more information processing occurs within the center of the ganglion cell's receptive field than is usually credited. Indeed, many narrow-field amacrine cells of each of several types tile the retina within each ganglion cell's receptive field. They must affect the transfer of information through the retina, with a spatial resolution similar to that of the bipolar cells, but the nature of the transformation remains to be learned.

A likely possibility is that some of the narrow-field amacrines are involved in contrast gain control[106], which may cause, among other things, a 'predictive' response of ganglion cells to moving stimuli[107]. However, it is not at all apparent why a conceptually simple function such as a negative, contrast-driven feedback would require 11 different kinds of amacrine cells. Other narrow-field amacrine cells carry out temporal sharpening; amacrine AII generates regenerative currents, which give the leading edge of its response to light a fast rise time[108,109]. Many narrow-field cells communicate among several layers of the inner plexiform layer and thus carry out 'vertical inhibition'[110], named by analogy to the familiar lateral inhibition mediated by horizontal cells.

Too many wide-field amacrines

Why there are so many wide-field amacrine cells? The rabbit has five kinds of medium-field amacrine cells (dendritic arbors ~175 μm) and at least ten wide-field types[3,4]. The latter can have dendrites that run for millimeters across the retinal surface[111,112], suggesting that long-range lateral integration, spreading far across the retina, may be more important than has been recognized[113]. Some of the cells have sparse, relatively simple arbors. Others have garden-variety dendritic arbors but also have axon-like processes that can span 5 to 10 mm across the retina's surface. Recording from two types in mammals reveals that they have receptive fields coterminous with their dendritic arbors and that they generate action potentials, which should conduct activity far from the main dendritic arbor[114,115].

Hints that activity spreads over long trans-retinal distances were evident long ago from the 'periphery effect,' a simple demonstration that stimulation outside the classical receptive field can change retinal sensitivity within the receptive field. There is also a recent report of oscillatory 40-Hz activity correlated for up to 10 mm across the cat's retina[116,117]. However, the exact function of these lateral effects is not known, nor is the need for multiple types of wide-field amacrine cells explained. Perhaps lateral conduction is required in viewing natural scenes, which contain wider ranges of contrast and more complex trans-retinal motion than the usual laboratory stimuli.

Contrast gain control is a critical 'normalization' function at the front end of the visual system, and there is direct evidence for both narrow and wide forms of it. Recently, two studies eval-

uated temporal contrast adaptation using reverse correlation and flickering checkerboards. They produced evidence for both a mechanism that works on a large spatial scale[118] and one that is extremely local—operating on a scale, in the rabbit, of approximately 100 μm, a fraction of the size of the receptive field center for many ganglion cells[119]. There is some evidence that the rate of adaptation is different for different-sized stimuli. This suggests the existence of multiple, independent forms of contrast adaptation. One form of temporal contrast adaptation seems to operate entirely within the bipolar cells themselves, because it persists in the presence of pharmacological agents that should block amacrine cell function. For larger stimuli, the array of amacrine cells may contain several mechanisms by which the responsiveness of the retina is tuned to the characteristics of the visual environment.

What are the fundamental channels of vision?

A final question concerns events at the heart of the retina's design. What are the separate filters represented by the different types of bipolar cells, and how are they reflected in the information transmitted centrally?

The diffuse bipolar cells represent as-yet-undeciphered parallel channels by which the retina parses the visual input (**Fig. 6**). In some cases, the operation performed by bipolar cells is obvious. The blue bipolar cell acts as a spectral filter tuned to wavelengths peaking at about 420 nm, and to moderate spatial frequencies. The red and green midget bipolars of primates are tuned to their particular wavelengths and to higher spatial frequencies. Roughly half the diffuse bipolar cells carry out a sign inversion creating the ON and OFF classes of response. Within each broad class (ON or OFF) of diffuse bipolars, though, there are at least four specific subtypes of bipolar cells of uncertain tuning. We learn their approximate spatial tuning from their dendritic spread, but we have only hints from their neurotransmitter receptors and channels about their dynamic properties.

From early studies in cold-blooded vertebrates[28,29,120], and more recent studies in mammals, bipolar cells were found to come in sustained (low-pass) and transient (high-pass) varieties. Results from salamander retina[30,121] point to even greater diversity, and this is also clear in the existing recordings from cone bipolar cells of mammals[25,31,122]. Although these experiments are technically difficult, a critically important challenge to physiologists is to precisely characterize the behavior of each channel.

Another challenge is to learn how the bipolar channels are recombined at the level of the ganglion cell (**Figs. 4** and **6**). Here, modeling techniques may be useful. The central problem is to understand, especially in the temporal domain, how the final response of a ganglion cells is created from one or several bipolar cell inputs[123]. It is unlikely that anyone will soon record simultaneously from one ganglion cell and two bipolar cells; models or simulations may clarify our thinking in this realm.

A higher-order question is how the parallel channels created by bipolar cells are reflected in the central visual system. The first limiting event for scotopic vision is the capture of photons by the cone mosaic. Even though cones' output is much transformed later—within the retina and higher in the visual system—vision's overall sensitivity, chromatic selectivity and resolution depend exactly on the number and spacing of the different types of cones[43,124]. The second limiting event in vision is the transmission of signals from the cones to the inner retina by the bipolar cells. Bipolar cells are the mandatory link between cones (or rods) and the rest of the visual system—all visual information must flow through them. Even though these signals, too, are later shaped and recombined, it is inescapable that the separate channels inherent in bipolar cell diversity represent fundamentals of vision, basic building blocks from which all further codings are constructed. In principle, we should eventually be able to deconvolve the outputs of individual bipolar channels from signals encountered even deep within the central visual system.

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Neuron
Review

Eye Smarter than Scientists Believed: Neural Computations in Circuits of the Retina

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We rely on our visual system to cope with the vast barrage of incoming light patterns and to extract features from the scene that are relevant to our well-being. The necessary reduction of visual information already begins in the eye. In this review, we summarize recent progress in understanding the computations performed in the vertebrate retina and how they are implemented by the neural circuitry. A new picture emerges from these findings that helps resolve a vexing paradox between the retina's structure and function. Whereas the conventional wisdom treats the eye as a simple prefilter for visual images, it now appears that the retina solves a diverse set of specific tasks and provides the results explicitly to downstream brain areas.

Introduction

The retina is a neural circuit of marvelous anatomical complexity that famously fascinated Cajal (Cajal, 1893) and has since drawn many researchers into its spell. Every technical advance in microscopy, imaging, or cell labeling has further reinforced the message of intricacy and precision in the retina's wiring. At last count, the network is composed of at least 50 clearly distinct cell types (Masland, 2001b) (Figure 1A). They differ widely in shape, from very local neurons tens of micrometers in size to some whose processes span clear across the eye. The neurons are arranged in three cellular layers and are interconnected in the intervening two synaptic layers (Figures 1B and 1C). On a finer scale, one finds finer structure: within the inner plexiform layer, one can distinguish at least ten thin sublayers, and the processes of a given cell type are often restricted to just one of these (Wu et al., 2000; Wässle, 2004). On the single-neuron scale, one finds even greater specificity; for example, the blue ON bipolar cell connects only to blue cones, even though these form a tiny minority among photoreceptors (Dacey and Packer, 2003; Haverkamp et al., 2005). The retina's output is conveyed to the brain by many different ganglion cell types, numbering about 15 in mammalian retinas. The population from each type covers the visual field and thus conveys a complete but processed visual image (Wässle, 2004). Much of this intricate and specific structural organization is conserved from mouse to man, indicating that it serves a continuing computational purpose common to many animals.

But what is that purpose? Most vision researchers will argue that the retina's principal function is to convey the visual image through the optic nerve to the brain, where the cortex can bring a great deal of clever circuitry to bear on it. They may acknowledge that light adaptation is an important retinal function, akin to an automatic gain control. On further thought, the retina also implements some lateral inhibition—embodied by the center-surround antagonism in the ganglion cell's receptive field—to sharpen the image in space and also in time. This picture of the retina as a simple spatiotemporal prefilter is espoused almost universally by textbooks and review articles (including one by a present author: Meister and Berry, 1999). And it is adopted, at least implicitly, by virtually all neuroscientists who work in visual areas beyond the retina, where the truly sophisticated, heavy-duty computations are thought to take place. Yet the paradox is clear: to implement simple functions, like light adaptation and image sharpening, there is no need for 50 neuron types with fantastically intricate network structure. In fact, the retina of the horseshoe crab accomplishes all this already within the layer of photoreceptors (Ratliff and Hartline, 1959; Fuortes and Hodgkin, 1964). What are the other 49 cell types doing in the vertebrate retina?

There is a distinct possibility that we haven't yet understood what the retina is for. What if it is not merely a sharpening filter for a cable to the visual cortex? Perhaps each of the many ganglion cell types already computes something rather specific about the visual scene. Each type would then need a dedicated neural circuit to extract the visual feature of interest. In this picture, the downstream areas in the brain receive not a generic pixel representation of the image, but a highly processed set of extracted features. Indeed, there is a well-known example of this kind of processing: the direction-selective ganglion cell. These neurons respond strongly to moving stimuli, such as traveling spots or bars, but they greatly prefer one direction of motion over the others (Barlow et al., 1964; Taylor and Vaney, 2003; Demb, 2007). The phenomenology is remarkable; for example, only a tiny movement of the spot through 1/10 of the cell's receptive field is needed to elicit the direction-selective response. Now there is something distinctly different about this direction-selective processing compared to a center-surround prefilter. First, it computes a specific feature of the visual input, namely the direction of movement within the receptive field. Second, as a result of this specificity, a good amount of stimulus information is discarded; for example, the cell does not fire at all for certain directions, regardless of the details of the moving

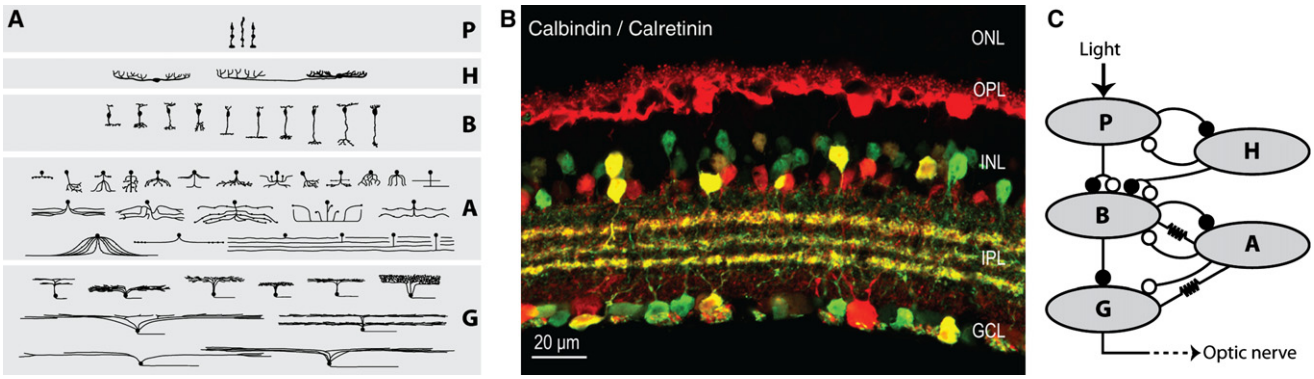

Figure 1. Retinal Circuitry

(A) Diversity of retinal cell types. For all five classes of retinal neurons—photoreceptors (P), horizontal cells (H), bipolar cells (B), amacrine cells (A), and ganglion cells (G)—a number of types can be identified according to morphological characteristics and dendritic stratification patterns. The image shows the major cell types of a typical mammalian retina. Reprinted with permission from Masland, 2001a.

(B) Specificity of retinal wiring. Double immunostaining for calbindin (red) and calretinin (green) in a vertical section of mouse retina (Haverkamp and Wässle, 2000) visualizes some of the structure and complexity of the retinal network. The staining labels horizontal cells, certain amacrine cells in the inner nuclear layer (INL), and some ganglion cells in the ganglion cell layer (GCL). The interposed outer and inner plexiform layers (OPL and IPL) are the sites of massive and often very specific synaptic contacts between the various cell types. For example, the labeled amacrine cells and ganglion cells extend their dendrites into three distinct thin strata of the IPL, which underscores the specificity of retinal microcircuits. Reprinted with permission from Haverkamp and Wässle, 2000; see also Wässle, 2004.

(C) Schematic drawing of connections between the basic cell classes. The neurons in the retina are connected through chemical synapses that are either sign preserving (excitatory, closed circles) or sign inverting (inhibitory, open circles). In addition, one finds a considerable amount of electrical coupling between cells via gap junctions within all cell classes (data not shown) and across some types of cells (marked by resistor symbols). The input into the network is incident light, which hyperpolarizes the photoreceptors. The connections from photoreceptors to bipolar cells are of either sign, producing both OFF-type and ON-type bipolars. Horizontal cells provide negative feedback and lateral inhibition to photoreceptors and bipolar cells. Bipolar cells are reciprocally connected to amacrine cells with chemical synapses and, for some types, through electrical gap junctions. Ganglion cells represent the output layer of the retina; their axons form the optic nerve. They collect excitation from bipolar cells and mostly inhibition from amacrine cells. In addition, ganglion cells and amacrine cells can be electrically coupled. This general connectivity sets the framework for any specific retinal microcircuit.

object. Third, the result of the computation is represented explicitly in the response of the cell. Firing versus not-firing indicates whether the spot moves one way or the other. Finally, no "higher processing" is needed to extract the information. For example, a downstream neuron could obtain the exact angle of the spot's trajectory simply by pooling the firing of various direction-selective ganglion cells in a weighted summation.

Here we explore the notion that this kind of processing, namely the selective computation of specific stimulus features, is not the exception but the rule in retinal function. In doing so, we will repeatedly encounter the above-mentioned characteristics of task specificity, selective encoding of information, and explicit straightforward representation. At the core of these abilities lie certain strongly nonlinear processing steps, and identifying these key nonlinearities gets to the heart of the retina's computations. The popular concept of linear spatiotemporal prefiltering may well apply to particular kinds of retinal ganglion cells under certain conditions; but in other cases, the classic center-surround receptive field reflects a crude average of the ganglion cell's behavior under stimuli that fail to probe its function properly. As we will see, it helps to work with visual stimuli that somehow reflect the actual challenges the visual system faces in its natural environment. In a search for general computational abilities of the vertebrate retina, we will focus on visual tasks relevant to all species: detecting light at low intensity; dealing with image motion caused by objects in the scene or the movement of the observer; and adapting to changing visual environments. Because of the generic nature of these tasks, we will freely discuss results obtained from different animal models.

Light Detection

The most straightforward task of the visual system is the detection of dim lights. Human observers can sense a flash of light even at very low intensities that lead to only a handful of successful photon absorptions in the retina (Hecht et al., 1941; Sakitt, 1972). Correspondingly, rod photoreceptors display small responses to single photon absorptions, ~1 mV in amplitude (Baylor et al., 1979; Schneeweis and Schnapf, 1995), and retinal ganglion cells can indeed signal these events to the brain (Barlow et al., 1971). A ganglion cell typically collects inputs from many hundreds of rods (Sterling et al., 1988). Thus, the computational challenge for the retina lies in separating the small single-photon signal in one or a few rods from the continuous electrical noise that is present in all photoreceptors. Indeed the problem arises already at the first stage of convergence, where the rod bipolar cell collects the outputs from tens of rods via graded synapses (Freed et al., 1987; Tsukamoto et al., 2001). How the retina sorts the sparse signal from the ubiquitous noise is beginning to be understood.

The light-independent fluctuations in the rod's membrane potential are of two kinds. One, called "discrete noise," results from spontaneous thermal isomerization of the photopigment (Baylor et al., 1980). These events are identical in all respects to authentic single-photon signals and thus cannot be separated out. In fact, human visual sensitivity at absolute threshold is likely limited by this noise source (Barlow, 1956; Baylor, 1987). The other kind, called "continuous noise," arises from spontaneous activations within the chemical transduction machinery downstream of photon absorption (Baylor et al., 1980). As a result, it

has a different frequency spectrum from the single-photon signal. This spectral difference could support a separation of signal from noise by the method of temporal filtering: enhancing the frequencies that primarily contain light signals and suppressing the others. One can predict the optimal filter function for this task (Bialek and Owen, 1990), and indeed a transformation of the predicted type is observed in the transmission from rods to bipolar and horizontal cells of the salamander retina (Armstrong-Gold and Rieke, 2003). The filter appears to be implemented presynaptically in the rod through a combination of electrical coupling between rods and calcium dynamics at the transmitter release sites.

The temporal filtering improves the signal-to-noise ratio for photon events coming from a single photoreceptor. But still this signal is threatened to be swamped by noise from other photoreceptors. If the rod bipolar cell combined activity linearly from all its presynaptic rods, a single photon event would easily be lost in the accumulated noise. Yet, the bipolar cell produces clear depolarizing potentials in response to single-photon stimulation (Ashmore and Falk, 1976; Field and Rieke, 2002). It had therefore been proposed that the bipolar cell sums rod signals in a very nonlinear fashion (Baylor et al., 1984; van Rossum and Smith, 1998).

This strategy has indeed been confirmed by studies on mouse retina (Field and Rieke, 2002): the output of each rod photoreceptor is first thresholded before summation by the rod bipolar cell. Rod signals below the threshold level are simply discarded, and this affects some of the bona fide light responses as well: around 50% (Berntson et al., 2004) to 75% (Field and Rieke, 2002) of single-photon events do not pass the synapse. But this loss in signal is more than compensated by the reduction in noise. In fact, the observed threshold is positioned nearly optimally to maximize the signal-to-noise ratio in the rod bipolar cells (Field and Rieke, 2002). As discussed above, it is essential that the thresholding take place before the summation, to avoid the summing of many noise signals. Indeed, the mechanism that generates the threshold is found to be local to individual synapses between rods and bipolar cells. In darkness, the synapse is in a state of saturation so that some minimal level of presynaptic activity is required before a postsynaptic depolarization occurs (Sampath and Rieke, 2004). This aspect appears to be unique to the rod-bipolar pathway, which is specialized for detection at very low light levels. OFF bipolar cells, which are distinct from rod bipolars but also receive input from rod photoreceptors, respond to light stimuli in an approximately linear fashion (Field and Rieke, 2002).

Schematically, the proposed neural circuit that achieves the separation of dim light stimuli from noise thus consists of the following elements (Figure 2A): signals from individual rods are first temporally filtered, then rectified by a threshold mechanism, and finally summed over many rods. This processing sequence appears to be a useful basic circuit design; we will encounter it repeatedly in the examples that follow. Here, it implements a computation that results in a selective neuronal response only if sufficient evidence is encountered that a photon event has occurred.

Motion Detection and Discrimination

Beyond mere light detection, the visual system must interpret the many spatiotemporal patterns in photoreceptor activation on the retina. Among the myriad possible input patterns, only a minuscule minority is ultimately of behavioral interest. A dominant feature in the retinal input is image motion, which has two kinds of sources. The first results because movement of body, head, or eye of the observer induces global optic flow on the retina. This image motion largely represents "noise" for the purpose of visually guided behavior, and though the brain has dedicated the entire vestibulo-optic reflex pathway to reducing it, a significant global image jitter remains at all times. The second kind results from the motion of objects within the scene: for most intents, this is the behaviorally relevant "signal." We will see that the retina contributes already to sorting this important signal from the morass of distracting noise, just as it did in the context of photon detection.

Texture Motion

When a textured image patch moves across the retina, it causes an increase of light intensity at some points and a decrease at others. To be sensitive to this motion signal, a circuit would want to detect and integrate many such local changes. The so-called "Y-type" ganglion cells seem to signal the result of such a computation. These neurons fire when the texture moves, and the activity is largely independent of the direction of motion or the spatial layout of the moving pattern. Such ganglion cells have been identified in many species (Enroth-Cugell and Robson, 1966; Hochstein and Shapley, 1976; Caldwell and Daw, 1978; Kaplan and Shapley, 1982; Demb et al., 1999; Petrusca et al., 2007).

A seemingly paradoxical feature of the Y cell is its sensitivity to high spatial frequencies, for example gratings that are much finer than the receptive field size. If the neuron simply pooled intensity signals from points throughout its receptive field, the positive and negative changes induced by grating motion should neatly cancel out and produce zero response. Instead, the Y cell pools inputs from smaller subregions in the receptive field whose signals are individually rectified, which endows the Y cell with its characteristic nonlinear response properties (Figure 2B). There is good evidence now that the subfields correspond to individual bipolar cells: these interneurons match the size of the subfields (Demb et al., 1999; Dacey et al., 2000), and their synaptic input to ganglion cells can indeed show strong rectification (Demb et al., 2001).

This circuit explains qualitatively how the Y cell responds to moving textures regardless of the direction or the spatial pattern. Small features of the texture activate different subfields as they move around. The subfields have strongly transient responses, embodied in the biphasic shape of their impulse response function (Figure 2B). This makes the subfields sensitive to local changes, but not to static patterns. The nonlinear rectification then allows accumulation of signals from many activated subfields while preventing cancellation from other subfields that experience nonpreferred stimulus changes. A time-varying velocity of the image pattern leads to a time-varying firing rate, and the simple Y cell circuit model (Figure 2B) can predict this output quantitatively (Victor and Shapley, 1979; Enroth-Cugell and Freeman, 1987; Ölveczky et al., 2003). The transformation is dominated by the spatiotemporal receptive fields of bipolar cells (Baccus et al., 2008). While this circuit encodes the velocity signal reliably, it discards information about the spatial layout of

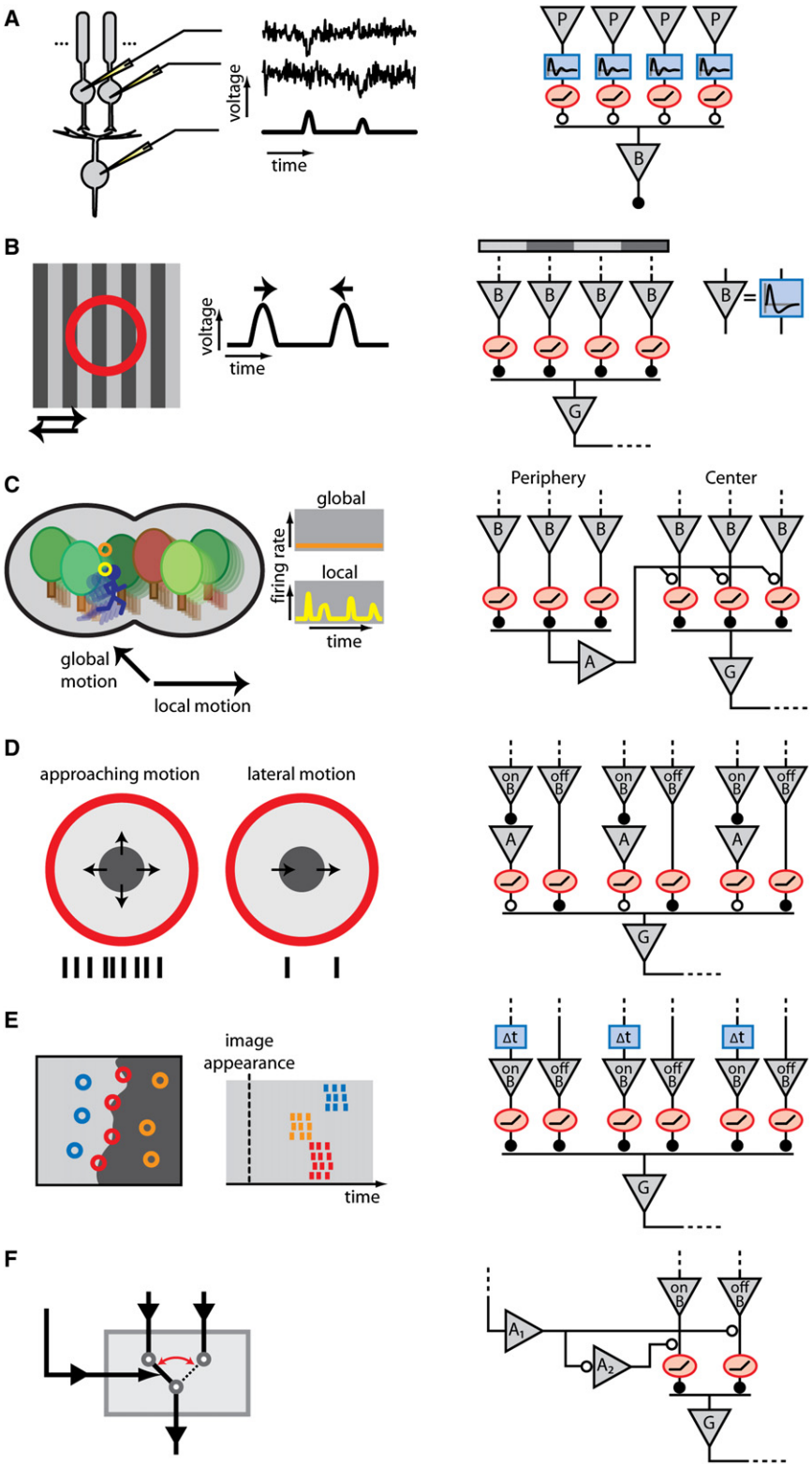

Figure 2. Computations Performed by the Retina and Their Underlying Microcircuits

(A) Detection of dim light flashes in the rod-to-rod bipolar pathway. (Left) Rod bipolar cells pool over many rod photoreceptors, which show distinct responses to single-photon activation embedded in noise. Bipolar cell potentials are not swamped by the accumulated noise in all rods, but instead show distinct activations from single photons, as shown by the voltage traces from a simple model simulation. (Right) The important elements of the corresponding retinal microcircuitry. Each photoreceptor output is sent through a band-pass temporal filter followed by a thresholding operation before summation by the rod bipolar cell (Field and Rieke, 2002). Notation for this and all circuit diagrams: triangle, neuron; rectangle, temporal filter function; oval, instantaneous rectifier; closed/open circle, sign-preserving/inverting synapse.

(B) Sensitivity to texture motion. (Left) Y-type ganglion cells show activation when a fine grating shifts in either direction over the receptive field (circle), even though the average illumination remains constant. (Right) The underlying microcircuit. Each shift of the grating excites some bipolar cells and inhibits others. The bipolar cells have biphasic dynamics (see impulse response in inset) and thus respond transiently. Only the depolarized bipolar cells communicate to the ganglion cell, because of rectification in synaptic transmission. Thus, the ganglion cell fires transiently on every shift (Hochstein and Shapley, 1976).

(C) Detection of differential motion. (Left) An object-motion-sensitive ganglion cell remains silent under global motion of the entire image but fires when the image patch in its receptive field moves differently from the background. (Right) The circuitry behind this computation is based on similar elements as for the Y cell (panel B). Rectification of bipolar cell signals in the receptive field center creates sensitivity to motion. Polyaxonal amacrine cells in the periphery are excited by the same motion-sensitive circuit and send inhibitory inputs to the center. If motion in the periphery is synchronous with that in the center, the excitatory transients will coincide with the inhibitory ones, and firing is suppressed (Ölveczky et al., 2003; Baccus et al., 2008).

(D) Detection of approaching motion. (Left) A certain type of retinal ganglion cell responds strongly to the visual pattern of an approaching dark object, as indicated by the schematic spike train below, but only weakly to lateral object motion. (Right) The circuit that generates this approach sensitivity is composed of excitation from OFF bipolar cells and inhibition from amacrine cells that are activated by ON bipolar cells, at least partly via gap junction coupling. Importantly, these inputs are nonlinearly rectified before integration by the ganglion cell (Münch et al., 2009).

(E) Rapid encoding of spatial structures with spike latencies. (Left) Specific retinal ganglion cells encode the structure of a new image by their spike latencies. Cells with receptive fields (circles) in a dark region fire early, those in a bright region fire late. Cells whose receptive fields contain both dark and bright produce intermediate latencies and thus encode the boundary in their synchronous firing. (Right) The responses result from a circuit that combines synaptic inputs from both ON and OFF bipolar cells whose signals are individually rectified. The timing differences in the responses follow from a delay (Δt) in the ON pathway (Gollisch and Meister, 2008a).

(F) Switching circuit. (Left) A control signal selectively gates one of two potential input signals. (Right) In the retina, such a control signal is driven by certain wide-field amacrine cells (A_1), which are activated during rapid image shifts in the periphery. Their activation leads to a suppression of OFF bipolar signals and, through a putative local amacrine cell (A_2), to disinhibition of ON bipolar signals (Geffen et al., 2007).

the moving pattern. As a consequence, when different Y cells experience the same motion trajectory, but with different spatial patterns at their receptive field locations, they can show the same activity profile and thereby signal a common origin of their activation. We will recognize this as an essential aspect in the retina's scheme for segregating moving objects.

Object Motion

To detect that an object moves within the observed scene, it is not sufficient, as one first might think, to measure the motion signal at the location of the object. The reason is that the visual system faces incessant motion signals that result from movements of the eye. Even when we try to fix our gaze on a static scene, minute drift and tremor in eye position provide a persistent source of image motion, whose trajectory is shared by all locations on the retina (Martinez-Conde et al., 2004). Object motion thus manifests itself on the retina in the difference between the motion trajectory of a local patch and that of the background. Neurons that detect this differential motion signal have been found in various parts of the visual system (Hammond and Smith, 1982; Frost and Nakayama, 1983; Born and Tootell, 1992), and they are particularly well studied in the retina. Here, object-motion-sensitive (OMS) ganglion cells were discovered that respond selectively to differential motion (Lettvin et al., 1959; Ölveczky et al., 2003). These neurons remain silent when the image moves across the retina rigidly, but fire vigorously when a local patch on the receptive field center moves with a trajectory different from the background (Figure 2C).

The circuits that implement the OMS computation have been probed in some detail (Ölveczky et al., 2003, 2007; Baccus et al., 2008). In the receptive field center, the OMS cell pools over rectified bipolar signals (Figure 2C), as discussed for Y cells. The resulting excitation is antagonized by inhibitory signals from similar Y-like motion detectors in a broad surrounding region. This inhibitory motion detector has been identified with a polyaxonal amacrine cell (Baccus et al., 2008), and it seems to act primarily via presynaptic inhibition of the bipolar cell terminals.

To detect differential motion, the circuit functions as follows. The motion in the center alone produces a sequence of excitatory inputs from bipolar cells to the ganglion cell. The time course of these inputs reflects the central motion trajectory. Analogously, the trajectory of the background motion results in a sequence of inhibitory signals in the polyaxonal amacrine cells. When the two trajectories are identical (global motion), the inhibition quenches the excitatory inputs at the bipolar cell terminals, and the ganglion cell remains silent. When the center motion differs from the background (differential motion), the excitatory signals do not coincide with inhibition and therefore reach the ganglion cell and cause it to spike, leading to an explicit representation of the local motion component.

It is interesting to note that the circuit distinguishes between global and differential motion by selectively suppressing a specific, yet very common visual signal: the coherent motion in the center and periphery of the receptive field. The only relevant stimulus feature for the comparison is the speed of image motion; by virtue of the Y-type circuitry (Figure 2B), both the direction of motion and the image pattern are ignored. This allows all parts of the background region to produce a coherent inhibitory signal regardless of their local pattern. Similarly, it allows the OMS cell to detect movement of an object regardless of its specific content (Ölveczky et al., 2003). In recent work, an OMS ganglion cell has been identified in the mouse retina that projects strongly to the superior colliculus, where it may direct orienting movements toward the site of object motion (Y. Zhang and M.M., unpublished data). Thus, these neurons likely serve an alarm role that triggers further inspection of the moving object with other visual mechanisms.

Approaching Motion

Objects moving vertically or horizontally in the visual field lead to translation on the retina. But what about motion in the third dimension of depth? An approaching object would produce an image patch that gradually expands on the retina, with no net displacement. Recently, a ganglion cell type was described that is indeed selective for this stimulus feature (Münch et al., 2009). Identification of this cell type in the mouse retina was facilitated by genetic labeling with a fluorescent marker. These ganglion cells showed OFF-type responses. They were driven strongly by an expanding dark spot, even if it was accompanied by a global brightening of the scene. Yet they remained silent during lateral motion of a dark spot.

The circuit that achieves the approach-specific responses is based on excitatory inputs into the ganglion cell through the OFF pathway and inhibitory inputs through the ON pathway (Figure 2D). When a dark object approaches, the ganglion cell receives strong excitation and no inhibition and therefore responds vigorously. If the object moves laterally, on the other hand, excitation from its leading edge is balanced by inhibition from the trailing edge, and the ganglion cell therefore remains silent. Inhibition thus serves to suppress responses to the non-preferred motion signal, similar to the strategy of the OMS cell circuit. In contrast to the OMS cells, however, it is essential that the inhibition act postsynaptically rather than presynaptically at bipolar terminals, since signals from different parts of the object must be combined.

Again, nonlinear processing constitutes an important step in the circuit model: excitation and inhibition are organized in small subfields whose signals must be rectified in order to account for the ganglion cell's approach sensitivity even during global brightening. Interestingly, the study conjectures that the direct inhibitory pathway to the ganglion cell passes from ON cone bipolar cells through electrical junctions to the inhibitory AII amacrine cells. Presumably the speed of the electrical synapse ensures that this pathway keeps up with the excitatory pathway that has one less interneuron. Note that the AII amacrine also serves an entirely different function during scotopic vision, namely to feed rod signals into the cone bipolar cells (Bloomfield and Dacheux, 2001). This is an interesting example of a single cell type that serves quite different roles (see also Manookin et al., 2008), even signaling in opposite directions, and it will be interesting to look for further examples of such functional promiscuity.

Detecting an approaching object is naturally of high behavioral relevance, and nervous systems have developed various mechanisms to deal with this challenge. Indeed, a different type of approach-sensitive response has been found in the frog retina. Here, retinal ganglion cells called dimming detectors engage in

highly synchronized oscillations during global dimming or for large expanding dark patches (Ishikane et al., 1999). The oscillations are generated in a retinal circuit presynaptic to the ganglion cells, presumably through negative feedback involving amacrine cells, because they can be abolished by pharmacological blockage of $GABA_A$ receptors (Arai et al., 2004). Little else is known about how the retina generates these responses, but it was possible to directly link them to a specific visually guided behavior: the frog's escape from an approaching dark object. Frogs whose retinal oscillations are suppressed pharmacologically no longer perform this escape response (Ishikane et al., 2005).

Anticipation

There is great survival value in being able to anticipate the future. Indeed, because of delays in our sensory pathways, the brain really experiences the past, and even knowing the present requires a measure of prediction. We will see how the retina can contribute to this process.

Motion Extrapolation

Detecting a moving object and its motion direction are generally not sufficient; to catch fleeing prey or to avoid an approaching predator an animal needs to track the object location precisely. This becomes a challenge because of the rather large response delays introduced by the process of phototransduction. Even in bright daylight conditions, the cone photoreceptor responds with a time to peak of several tens of milliseconds (Baylor et al., 1974; Schnapf et al., 1990). Thus, the neural signals in the photoreceptors already lag behind the actual object motion. During the phototransduction delay, a well-served tennis ball flies ~2 m, a distance many times larger than the receiving player's racket. Clearly, the visual system must somehow compensate for response delays introduced by the retina. It has been shown that the retina itself already contributes to this computation. It undoes the delay by relying on the fact that objects typically move in a smooth fashion, which allows an extrapolation of the motion trajectory.

When the image of an object moves on the retina, it creates a wave of neural activity among the ganglion cells. One should expect that this wave lags behind the object image because of the delay in phototransduction. Instead, experiments show that the activity in the ganglion cell layer moves at the true location of the object or even along its leading edge (Berry et al., 1999). Effectively, the retinal network computes the anticipated object location and thereby cancels the phototransduction delay. Surprisingly, this complex computation comes about through the interplay of rather generic features of retinal circuitry. The main contributors are the spatiotemporal receptive field of the ganglion cell and a dynamic gain-control mechanism. Because the receptive fields are extended in space, the object already activates ganglion cells that lie some distance ahead in its motion path. The spatial receptive field alone would predict an equally extended zone of activation behind the object. However, firing of those ganglion cells is suppressed first by the biphasic temporal receptive field, and second by a dynamic gain control mechanism, which itself gets activated by the response to the object (Shapley and Victor, 1978; Victor, 1987; Baccus and Meister, 2002). The gain control lets the ganglion cell be sensitive upon first entry of the object into the receptive field, but then shuts down the response. It is an essential component for the anticipatory response to motion stimuli (Berry et al., 1999) and gives this computation a highly nonlinear flavor.

By this algorithm, the retina performs a crude extrapolation of the object's trajectory, such that its current location is represented in the population activity of the ganglion cells. Clearly, the correction is only approximate: a perfect extrapolation would compensate for the photoreceptor delay irrespective of the speed of the object, whereas the retina's method has a characteristic spatial and temporal scale and thus functions only over some range of speeds. Similarly, the gain control depends on stimulus contrast, and thus extrapolation fails for low-contrast objects (Berry et al., 1999). Of course, most animals' visual performance, including that of expert tennis players, also degrades at high speeds and low contrasts.

In the salamander retina, the retina's algorithm works well for objects with the size and speed of small insects that form the animal's preferred prey. In this regime, the moving insect is represented at the retinal output by a blob of firing ganglion cells, whose center of mass is precisely aligned with the current location of the target (A. Leonardo and M.M., unpublished data). Thus, downstream circuits can read out the target position by a simple "population vector" average (Georgopoulos et al., 1986), in which each ganglion cell's firing rate is weighted by the vector representing its receptive field center (see also Figure 4). Of course this deceptively simple representation is the result of highly nonlinear operations that extrapolate the motion trajectory based on delayed data from the photoreceptors. The underlying computation reveals itself when the object makes a sharp turn: the neural image among the ganglion cells continues straight for a few tens of milliseconds, then turns and catches up with the new trajectory. When the object executes not a turn but a complete reversal of its trajectory, an additional response feature emerges: many ganglion cells near the reversal point fire a brief synchronized burst of spikes (Schwartz et al., 2007b). This signal may be read out by downstream processing stages to identify an error in the retina's prediction. What circuit mechanisms underlie this phenomenon is still unclear.

Omitted Stimulus Response

A somewhat different form of anticipation can be observed when the visual system is exposed to a periodic stimulus, such as a regular series of flashes. The activated visual neurons typically become entrained into a periodic response. If the stimulus sequence is interrupted, for example by omitting just one of the flashes, some neurons generate a pulse of activity at the time corresponding to the missing stimulus (Bullock et al., 1990, 1994). This phenomenon, termed the "omitted stimulus response," is quite widespread and has been noted in the brains of many species, including humans (McAnany and Alexander, 2009). Qualitatively it suggests the build-up of an anticipation for the next stimulus, and the large response reflects surprise at the missing element in the sequence. Unlike in the case of moving objects, where the anticipation involves lateral processing in space, here the information about the stimulus sequence must be propagated forward purely in time.

Recently, the omitted stimulus response has come under greater scrutiny in the retina, where superior experimental access allows a focused search for the underlying neural mechanisms (Schwartz et al., 2007a; Schwartz and Berry, 2008). The response requires the convergence of excitatory signals from the ON and OFF pathways to the ganglion cells. Remarkably it does not require any inhibition mediated by amacrine cells (Schwartz and Berry, 2008; Werner et al., 2008). In one model, the periodic stimulus is extrapolated in time by a tunable oscillator. The flash sequence sets up a resonance within the retina that locks onto the stimulus frequency. When the sequence ends, the internal oscillation continues and causes the large omitted stimulus response (Schwartz and Berry, 2008). A competing model suggests that the combination of excitatory inputs from ON and OFF bipolar cells by itself is sufficient to explain many aspects of the omitted stimulus response (Werner et al., 2008). At the cellular level, these two models make quite different predictions, so one expects this question to be resolved soon.

Saccadic Vision

In most animals, vision is an intermittent process: short periods of fixation where the eye is relatively still are interleaved with sudden and rapid reorienting movements, called ''saccades'' (Land, 1999). Recent work has illuminated the role of the retina in these two dramatically different phases.

Saccadic Suppression

During a saccade, the image sweeps across the retina violently for tens of milliseconds, precluding any useful visual processing. In humans, visual perception is largely suppressed during this period (Volkmann, 1986; Burr et al., 1994; Castet and Masson, 2000). The circuits of the retina are at least partly responsible for this suppression: many types of retinal ganglion cells are strongly inhibited during sweeps of the visual image (Roska and Werblin, 2003). This effect is mediated by spiking inhibitory amacrine cells, which are themselves excited by the global motion signal. Conceivably, the underlying circuitry resembles the one identified for OMS ganglion cells (Figure 2C). In fact, the OMS cells may be distinct simply by an enhanced sensitivity to the global inhibition, so they are suppressed even by the much smaller eye movements during a fixation.

Latency Coding

Once the retinal image comes to rest, the visual system must analyze the new scene within the short period of fixation, a few tenths of a second in humans. Indeed, visual perception can be surprisingly fast. Early psychophysical studies showed that a 100 ms presentation of an image is sufficient to generate an understanding of the image content (Potter, 1976), and more recent experiments revealed that distinct brain signals dependent on image content arise already within 100 ms (Thorpe et al., 1996; Liu et al., 2002). How does the retina provide the relevant information to allow such rapid processing? One possibility is that some of this information is already transmitted with the very first spikes of retinal ganglion cells after the appearance of a new image (Thorpe et al., 2001).

Such a neural code based on first-spike timing has been identified now for a type of ganglion cell in the salamander retina (Gollisch and Meister, 2008a). When a new image appears on the retina, every cell in the population fires a brief burst of spikes, nearly regardless of the image content. However, the responses differ systematically in the timing of the burst. The first spike occurs earlier if the receptive field turns dark and later if it turns bright (Figure 2E). A combination of dark and bright regions in the receptive field produces intermediate spike times. Therefore, the relative latencies among the very first spikes in this ganglion cell population already provide a neural representation of the image. This representation turns out to be contrast-invariant; changing the overall contrast of the image affects the number of spikes in the bursts and their absolute timing, but it preserves the relative latencies of burst onsets.

Pharmacology and modeling studies (Gollisch and Meister, 2008a, 2008b) have helped elucidate the circuitry that leads to this spike-timing code (Figure 2E). The key feature is that the ganglion cell receives excitation from multiple ON and OFF bipolar cells, which have small receptive fields. The signal from each of these subfields is rectified before integration by the ganglion cell. This explains why the ganglion cell fires whenever there is any image change within its receptive field. The latency code arises because the ON bipolar cells respond with slower kinetics than OFF bipolars. Thus, a burst caused by brightening is delayed in time relative to one caused by dimming. As in previous examples, the rectification of the signal from each small subunit of the receptive field is a crucial step in this computation. It allows every location within the ganglion cell's receptive field to contribute to the cell's activation and prevents cancellation of the contributions from ON and OFF pathways.

A related study focused on retinal processing in the archerfish, an intriguing animal subject that excels in precise, visually guided spitting behavior (Segev et al., 2007). Ganglion cell responses were measured under stimuli that simulated what the fish observed while aiming at targets, including both saccades and fixational eye movements. Again, much of the relevant image information was available already in the burst of spikes immediately following the saccade, and much of it could be extracted by measuring the burst latency. It is unclear, however, how the retina in the archerfish produces these responses; this will require relating the applied stimuli to the cells' receptive field characteristics.

Clearly it will be important to test whether these findings of latency coding in retinal ganglion cells generalize across species, and if so, whether it is accomplished by the same mechanism of ON/OFF convergence. Virtually all retinas contain ganglion cells with access to both ON and OFF bipolar signals in the inner plexiform layer: these include ganglion cell types with bistratified dendritic trees, those with broad arbors, and even some sharply monostratified cell types (Dacey et al., 2005; Dumitrescu et al., 2009). An interesting alternative circuit would combine excitation from one bipolar pathway with disinhibition via amacrine cells from the other pathway.

Switching Circuits

In the preceding examples, we encountered a retinal circuit that gates the transmission of local bipolar cell signals based on motion in the periphery (Figure 2C); another circuit uses the convergence of parallel ON and OFF bipolar pathways (Figure 2E). Combining these features, one can envision a switching circuit:

if the gating signal enhances one input pathway and suppresses the other, this would allow a single ganglion cell to switch between representing either of the two inputs (Figure 2F). Surprisingly, such a switching circuit has indeed been observed in the salamander retina.

In amphibian retinas, the OFF pathway tends to dominate. Even the ON-OFF ganglion cells that receive input from both ON and OFF bipolars are strongly biased toward OFF inputs. However, this imbalance can switch rather suddenly (Geffen et al., 2007). In particular, the switch can be triggered by a large peripheral image shift as would happen during a head saccade. For some hundred milliseconds after the shift, the ganglion cell transiently switches from transmitting OFF signals to transmitting ON signals. During this brief interval, excitation of the ganglion cell from the ON bipolar pathway is strengthened, whereas the OFF bipolar pathway is suppressed.

In searching for the underlying mechanisms, a wide-field ON amacrine cell emerged as an interesting suspect. These interneurons respond to the peripheral shift with a strong depolarization. Furthermore, electrical stimulation of such an amacrine cell caused a substantial shift in the ON-OFF balance of nearby ganglion cells. This suggests a circuit model for this switch where the wide-field amacrine cell gates transmission from OFF bipolar cells to the ganglion cell via presynaptic inhibition (Figure 2F). In addition, it inhibits a second type of amacrine cell that itself gates the ON bipolar input. The higher purpose of this switch for visual processing is still unclear. Perhaps the global image shift is not even the relevant trigger event; given that a single amacrine cell produces substantial gating (Geffen et al., 2007), the switching may be initiated by much more subtle image features.

From a broader perspective, such a gated switch is a powerful computational device, as it allows the dynamic routing of information through a circuit. It is impossible to imagine electronic computers without such switches, and they have been postulated to play equally essential roles for brain processing (Anderson and Van Essen, 1987; Olshausen et al., 1995). Thus, it is promising to find at least one neural implementation and similar mechanisms may act elsewhere in the nervous system.

Adaptive Computation

The visual computations in the retina are not bound to a static set of rules. Instead, their character changes dynamically along with the demands of the visual task. Since the retina receives little efferent input from the brain, these demands cannot be specified from the higher visual centers. Instead, the modulation of retinal function is largely determined by the recent history of the stimulus, which itself is a function of the visual environment as well as the animal's actions.

Light adaptation is a prominent form of such modulation. Because the ambient light level varies over ~9 orders of magnitude in the course of a day, while spiking neurons have a dynamic range of only ~2 log units, the early visual system must adjust its sensitivity to the prevailing intensities. This adaptation to light level is accomplished by the retina, beginning already in the photoreceptors, and the process is complete before spiking neurons get involved. Over a wide range of intensities, the sensitivity of the retina declines inversely with the average light level. As a result, the ganglion cell signals are more or less independent of the illuminating intensity, but encode the reflectances of objects within the scene, which are the ethologically important variables. The perceptual effects of light adaptation and its basis in the circuitry and cellular mechanisms of the retina have been studied extensively and covered in several excellent reviews (Shapley and Enroth-Cugell, 1984; Hood, 1998; Fain et al., 2001; Rieke and Rudd, 2009).

Contrast and Pattern Adaptation

In recent years, there has been considerable interest in other forms of adaptation. For example, the nature of retinal computations depends strongly on the contrast of the stimulus, namely the range between the low and high intensities in the scene. When the retina is brought from an environment of low contrast to high contrast, its sensitivity declines and its kinetics speed up (Shapley and Victor, 1978). One can roughly distinguish two components. In a rapid initial phase, lasting 0.1 s or less, the sensitivity decreases slightly, accompanied by a substantial change in kinetics; this has generally been called "contrast gain control" (Victor, 1987; Baccus and Meister, 2002). There follows a slow phase, lasting many seconds, during which the kinetics remain unaltered, but the sensitivity continues to decline; this has been called "contrast adaptation" (Smirnakis et al., 1997; Baccus and Meister, 2002; Manookin and Demb, 2006).

An even more intricate form of modulation is "pattern adaptation." This occurs upon a switch between two environments that may have the same mean intensity and contrast, but differ in the frequency of certain spatiotemporal patterns. For example, in an environment of horizontal bars, the retina's sensitivity to horizontal patterns declines, while the sensitivity to vertical patterns increases (Hosoya et al., 2005). Similarly, the response of an OMS ganglion cell (see above) undergoes a pronounced decline in sensitivity following the onset of differential motion (Ölveczky et al., 2007). These changes can be observed in individual retinal ganglion cells: the spatiotemporal receptive field becomes modified so as to suppress the dominant patterns in the environment. All these pattern adaptation effects have been of the slow kind, but the methods employed may have missed a substantial fast component.

Circuit Mechanisms Underlying the Gain Changes

To identify the neural mechanisms behind contrast adaptation, it helps to trace the emergence of gain changes in various neurons along the retinal pathways. Given the prominent feedback circuits within the retina, this is fraught with some risk, but it has yielded insights nonetheless. For example, following a switch from low to high contrast, the photoreceptor response undergoes no change in gain, quite unlike what happens in light adaptation. Neither is there any change in horizontal cells, suggesting that synaptic release from the photoreceptor is similarly unaffected (Rieke, 2001; Baccus and Meister, 2002; Beaudoin et al., 2007). In some bipolar cells, one begins to see a change in response properties, reflected by both accelerated kinetics and lower sensitivity (Rieke, 2001; Baccus and Meister, 2002). Similar effects are seen in some but not all amacrine cells (Baccus and Meister, 2002). However, the most pronounced effects of contrast gain control and adaptation are measured in the ganglion cells.

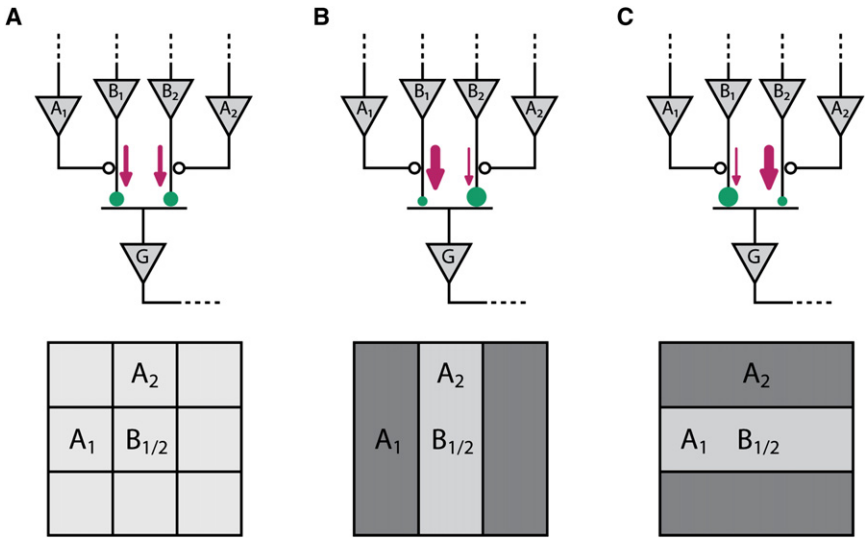

Figure 3. Pattern Adaptation Based on Synaptic Depression at Bipolar Cell Terminals

(A) Circuit model for pattern selectivity at bipolar terminals (top) with corresponding receptive field layout (bottom). A ganglion cell receives input from multiple bipolar cells. Here, bipolar cells B_1 and B_2 have the same receptive field, namely the center square of the lattice below. Their terminals, however, receive presynaptic inhibition from two amacrine cells A_1 and A_2 at different neighboring locations. This interaction leads to different transmitter release rates at the two terminals and makes the terminals preferentially respond to different visual patterns. The B_1 terminal, for example, receives co-occurring inhibition from A_1 for horizontal stripes and therefore responds more strongly to vertical stripes, while the B_2 terminal responds more strongly to horizontal stripes.

(B) During stimulation with flickering vertical stripes, bipolar cell B_1 and amacrine cell A_1 are activated out of phase, so there is no presynaptic suppression of release. The synaptic terminal of B_1 is therefore highly active (bold arrow), and over time, synaptic depression reduces the strength of this connection (small circle). Cells B_2 and A_2, on the other hand, are activated in phase. Thus, release at the terminal of B_2 is suppressed (thin arrow), vesicles can be replenished, and the connection recovers its strength (large circle). If one subsequently tests the ganglion cell's receptive field using a mixture of vertical and horizontal stripes (Hosoya et al., 2005), the sensitivity to horizontal stripes, mediated by the strong B_2 terminal, will exceed that to vertical stripes.

(C) During stimulation with horizontal stripes, the reverse changes take place. After synaptic depression has taken its course, the ganglion cell becomes more sensitive to vertical stripes.

To explain the substantial increase in adaptation from bipolar to ganglion cells, three mechanisms have been explored: intrinsic membrane conductances in the ganglion cell, interaction between bipolar and amacrine signals, and adaptation in synaptic transmission from bipolar cells. The ganglion cell itself does indeed display some adaptation to the range of its input (Zaghloul et al., 2005), as confirmed by direct current injection (Kim and Rieke, 2001), but this makes only a partial contribution (Manookin and Demb, 2006). Amacrine cell signals are not required for contrast adaptation, as shown convincingly in experiments with transmitter blockers (Rieke, 2001; Brown and Masland, 2001; Beaudoin et al., 2007). On the other hand, transmission from bipolar cells makes a large contribution to the adaptation. Although transmitter release has not been measured directly, strong evidence comes from recordings of synaptic currents in ganglion cells (Manookin and Demb, 2006) and from experiments that stimulate alternatingly different sets of bipolars connected to the same ganglion cell (Ölveczky et al., 2007). All these studies indicate a slow process of contrast adaptation in bipolar cell synaptic transmission.

We will briefly expand on the process of bipolar cell transmission, because it may well hold broader significance. In a simple view of the events, a high-contrast stimulus drives the bipolar cell more strongly, the synaptic terminal releases transmitter at a high rate, which over a few seconds leads to depletion of synaptic vesicles, and in turn decreases the gain of the synapse. Thus, the postsynaptic response gradually declines during the period at high contrast. Following a switch to low contrast, transmitter release drops immediately, the vesicles are gradually replenished, and the gain of the synapse recovers. Indeed, continued activation of a bipolar cell terminal does lead to presynaptic depression from vesicle use (Burrone and Lagnado, 2000), and the results can be seen in postsynaptic amacrine cells in the form of paired-pulse depression (Singer and Diamond, 2006; Li et al., 2007). Interestingly, this depression recovers with a time constant of 5–10 s, similar to the time course of various contrast adaptation phenomena.

If this picture is correct, then each bipolar cell synaptic terminal undergoes contrast adaptation independently. This would be a powerful design. A ganglion cell typically collects excitation from 10–100 bipolar cell terminals. Each of these terminals can have different response properties. This is clear if the terminals belong to different bipolar cells. But even for terminals from the same bipolar cell, spatial receptive fields and response kinetics may differ as a result of lateral inhibition from amacrine cells that synapse directly on the terminal (Dowling and Boycott, 1966). Because of this diversity, any given stimulus pattern drives some of these bipolar cell terminals strongly and others weakly (Figure 3). The active terminals will adapt and decline in strength, whereas the silent ones recover. Thus, the ganglion cell gradually becomes less sensitive to the prevailing stimulus pattern while it retains sensitivity to other patterns. In this way, the same cellular process of presynaptic depression may explain contrast adaptation as well as the various versions of pattern adaptation (Hosoya et al., 2005; Ölveczky et al., 2007). Note that this hypothesis for pattern adaptation really follows the traditional explanation invoked for such phenomena in the cortex: the fatigue of pattern-selective input units (Graham, 1989). Instead of neurons, here these input units are individual synaptic terminals.

Functional Purpose

What is the role of retinal contrast adaptation for vision? Prolonged viewing of high-contrast patterns leads to clear changes in perception: both a general decline in sensitivity and a specific decline for the adapting pattern (Blakemore and Campbell, 1969; Graham, 1989). The effects arise and decay on the timescale of

several to tens of seconds, as for the slow process in the retina. Similar adaptation phenomena have long been reported for neural responses in the visual cortex (Maffei et al., 1973; Movshon and Lennie, 1979). Initially they were attributed to processing within the cortex, but a substantial reappraisal of the evidence has taken place, and certain forms of contrast adaptation observed in cortex are now thought to be inherited from the retina (Baccus and Meister, 2004). One strong indicator was that most of cortical contrast adaptation arises in a purely monocular pathway (Truchard et al., 2000). Definitive evidence resulted from direct comparison of retinal and cortical signals in the same experiment (Solomon et al., 2004).

These developments suggest that contrast adaptation in the retina has a substantial effect on higher visual areas and even human perception. But what may be the ethological purpose of these adaptive dynamics? Here again it is important to distinguish the fast process (contrast gain control) from the slow one (contrast adaptation). As discussed above, human vision is characterized by brief fixations, when the gaze is held still, interrupted by eye saccades. The fast gain control adjusts within tens of milliseconds, considerably less than the length of a fixation (~0.3 s). Therefore, after every saccade of the eye, the retina will operate with somewhat different gain and kinetics depending on the local properties of the scene. Furthermore, this gain control is too fast to accumulate any kind of statistical measure of contrast in the scene, like the time-averaged standard deviation (Bonin et al., 2006). Slow contrast adaptation, on the other hand, occurs over many seconds, and thus may adjust retinal function more properly to the statistics of the environment, averaged over many successive fixations.

Discussion

As we have seen, the retina does not merely convey a prefiltered pixel image to the brain. Instead, it engages in substantial computations of specific image features, with different ganglion cell types taking on different tasks. Many of these computations can be understood as answers to particular challenges shared by many animals: the need to detect dim lights, the need to detect moving objects and locate them correctly, the struggles with a constantly moving image sensor, and the need to predict the future and adapt to changing conditions.

The Case for Retinal Computation

This view represents a significant departure from the conventional wisdom and will therefore meet with some skepticism. Here we discuss some of the concerns by answering questions from an imaginary critic, in order of increasing difficulty.

1. All these retinal nonlinearities seem to impose a serious complication for visual coding. How can the brain ever hope to decode the ganglion cell spikes and reconstruct the image on the retina? The animal as a whole is interested in survival and reproduction, not a veridical reconstruction of what was on the retina. For these goals, its visual system must distill the massive flood of raw visual information at the photoreceptors to just one bit (fight or flight) or maybe a few bits per second (air traffic controller). The retina simply begins this process of data reduction and sends on just those visual features that are useful for subsequent operations. This process is lossy, and we know well that the brain never recovers the original visual image. The discarding of image information in the retina fundamentally affects our spatial, temporal, and chromatic acuity and underlies many popular optical illusions. In this view, the power of retinal computation should be judged by how much raw information it filters out for discard, not by the amount it preserves.

2. Many of the examples quoted here are from "lower" vertebrates, meaning nonprimates. Isn't it well established that the smarter animals do much less processing with their retina? This is a persistent myth that deserves to be laid to rest. The anatomical structure of the primate retina is equally as intricate as that of other mammals. Several new ganglion cell types have been discovered recently, now bringing the total to about 17 (Dacey, 2004; Field and Chichilnisky, 2007). Their functions remain mysterious, because virtually all the physiological experiments concern just two classes of ganglion cells, the P and M cells. Although the P cells are by far the most numerous ganglion cell type, this is a simple consequence of their small receptive fields and the need to cover the retina. The newly discovered cell types collectively provide more capacity than the entire cat retina (Wässle, 2004), and thus can offer many additional channels of visual information that may not require a fine-grained representation. Indeed, several of the novel aspects of retinal function have been confirmed in the primate retina (Chander and Chichilnisky, 2001; Uzzell and Chichilnisky, 2004; Pillow et al., 2005; Petrusca et al., 2007) and thus are intimately relevant for an understanding of human vision. That said, the primate central fovea is a rather special case. In this small region of the retina, covering 1° of visual angle, there is little or no convergence from photoreceptors to bipolars or from bipolars to ganglion cells. Consequently, the circuits of Figures 2 and 3 cannot apply. For a specific understanding of high-acuity human vision, it will indeed be very helpful to learn more about foveal ganglion cells and interneurons.

3. The idea that the retina extracts specific visual features is a blast from the past, to be found in the first anecdotal reports of "bug detectors." Did we not banish this fuzzy thinking in the 1960s by performing careful parametric measurements of center-surround receptive fields? Indeed, some early studies of retinal function were guided by much more ethological sensitivity and tried to relate ganglion cell responses to specific tasks (Lettvin et al., 1959; Levick, 1967). The next generation overturned this anecdotal thinking and applied the rigorous new engineering tools from systems analysis (Rowe and Stone, 1980). Instead of showing the retina some arbitrary photographs of flies, these workers sampled the stimulus space systematically, feeding the retina with sine waves and white noise to measure its transfer function. Sadly, all the resulting ganglion cell receptive fields looked like Mexican hats with a biphasic time course, and the only possible conclusion was that the interesting visual computations are performed later in the brain (Stone, 1983). Now we understand that the problem was not with the ganglion cells, but with the stimuli. For example, the OMS ganglion cells discussed above have perfectly bland-looking center-surround receptive fields when studied with white-noise flicker. Of course the particular condition that reveals their function—differential motion of an image patch and its background—never occurs during white-noise flicker, whereas it represents a common occurrence on the retina in real life.

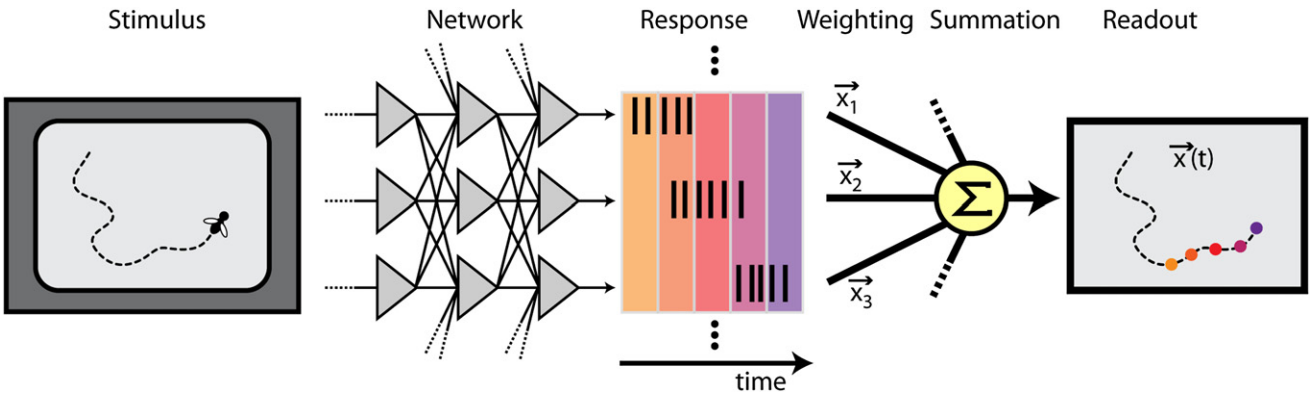

Figure 4. Linear Readout of a Neural Computation

A sensory neural network such as the retina responds to a stimulus, here the movement of an object in the visual field, by producing spike patterns in the output neurons. The network is postulated to solve a computational task, here compensating for the phototransduction delay and extrapolating a motion trajectory to the current object location. To claim that the network has solved this computation, we stipulate that the computational result should be obtainable as a linear combination of the output neurons' activities. In the present case, this readout is provided by binning the spike trains in short observation windows and weighting each neuron's spike count, $n_i(t)$, by the position vector of its receptive field center, $\vec{x}_i$. Summation of these weighted responses over all neurons yields successive representations of the current object position, $\vec{x}(t) = \sum_i \vec{x}_i \cdot n_i(t) / \sum_i n_i(t)$.

We think it is safe now to return to a more ethological consideration of the retina for several reasons. First, the impoverished traditional view of the retina's function clashes with its rich synaptic structure. By anatomical and molecular criteria, the mammalian retina has ~15 different ganglion cell types, whereas the parametric functional studies typically reveal around 5, and even those can have similar-looking receptive fields (Stone, 1983; Carcieri et al., 2003; Segev et al., 2006). The anatomical diversity suggests that there is much function left to be discovered and that we probably still have a good distance to go before understanding all the computations performed by the retina. Second, we have now far greater technical control over both the light input and the spike output from the retina, allowing a systematic exploration even of complex stimulus conditions like fixational image motion. Third, retinal processing is being studied in at least half a dozen different species, and a comparison among them can distinguish general processing principles from species-specific quirks. Finally, with improved technical access to the interneurons of the circuit, we can now build and test plausible circuit mechanisms to explain the new visual computations (Figure 2).

In many of the studies reviewed here, the ethological perspective served to single out specific tasks that were then studied with specifically designed, artificial stimuli that distilled the task-relevant features of the visual scene. This reductionist approach has proven quite successful for a systematic and quantitative investigation of computational principles. Yet, eventually we need to go a step further and understand retinal function within the rich complexity of natural stimuli. This endeavor will likely provide additional challenges because multiple processes occur simultaneously, for example, when the retina adapts to the large range of intensities and contrasts in a natural scene while at the same time facing different combinations of motion signals. Initial studies of responses to natural stimulus components have already demonstrated the rich dynamics that may arise (van Hateren et al., 2002).

4. What is special about the term "computation," and why doesn't it apply for the task of linear filtering that we used to assign to the retina? This is a more philosophical question, but we suggest that a "computation" should yield an *explicit* result to a *specific* question. For example, the question "is there a moving object near this location?" is answered in a simple yes/no manner by the firing of an OMS ganglion cell. No difficult high-order decoding is necessary to extract the desired result, which is an obvious benefit for speedy downstream reactions. The question "where exactly is the moving target right now?" is answered collectively by a population of motion-extrapolating ganglion cells (Figure 4). Now in this example, the coordinates of the target are not provided explicitly in the responses of single neurons but distributed across a population. This requires broadening the concept of "explicit," and we suggest a criterion that has been used effectively in the past (Marder and Abbott, 1995; Eliasmith and Anderson, 2002; Shamir and Sompolinsky, 2006): in a distributed representation, the answer of interest should be obtainable through linear decoding, namely by a simple weighted summation over the single-neuron activities (Figure 4). Such a decoding could be achieved in a single step by a downstream neuron that samples from the population. By this convention, a retina that merely filters the image on the photoreceptors performs no computation at all, since the desired result can be read via weighted summation directly from the photoreceptors themselves.

Circuit Models

As one investigates the computations of a new type of ganglion cell, how should the relationship between stimuli and responses be formulated? Given the vast range of possible stimulus movies one might show the retina, it is impossible to simply deduce the computation from an input-output table of stimuli and responses. One needs to develop some quantitative hypotheses for that relationship and test them in a directed manner. What is a useful format for these hypotheses?

One traditional approach has been to write the response as a Wiener expansion of the stimulus (Sakai and Naka, 1992). This is a highly principled method, with a solid mathematical basis which guarantees that every stimulus-response relationship can be expressed that way. It is particularly effective if the system responds approximately linearly. Unfortunately, the reality is that retinal responses are highly nonlinear under most conditions of practical interest. Estimating all the required Wiener kernels from experiments becomes unrealistic, and this approach has largely fallen out of fashion.

We have had good experiences with a very different formalism based on schematic circuit models (Figure 2). The stimulus is processed by a network of individually simple elements. These components and their interactions are fashioned after retinal neuron types, without simulating the actual biophysics in detail. Each element performs either linear filtering or an instantaneous nonlinear transformation. The list of elements includes: ON and OFF "bipolar cells," modeled as linear spatiotemporal filters; synaptic transmission, modeled as an instantaneous nonlinearity; pooling over many synaptic inputs, modeled as weighted summation; inhibition, modeled as instantaneous combination of two opposing signals. Others can be added as needed.

This style of modeling offers several benefits. First, it is intrinsically realistic. Any stimulus-response function written this way can be implemented by neural machinery, specifically the interneurons of the retina. Second, the formalism is nonetheless sufficiently broad. Theorems guarantee that one can write an arbitrary spatial transform of the input image this way (Funahashi, 1989; Hornik et al., 1989), though it would be interesting to extend this to spatiotemporal functions. Third, despite their simple graphical nature, these models are nonetheless rigorous. Any such circuit graphic can be translated into a mathematical relationship between input and output of the retina, with parameters that are embodied in the circuit elements. The circuit functions are easily simulated and make quantitative predictions that match actual ganglion cell firing remarkably well (Ölveczky et al., 2003; Baccus et al., 2008; Gollisch and Meister, 2008a). Finally, such a formula for the stimulus-response relationship is at the same time an explicit hypothesis for how the computation is done. It makes predictions about what happens at various stages inside the retina, and these can be tested independently. For example, the spatiotemporal receptive field of a bipolar cell can be measured directly, and that immediately reduces the free parameters of the model (Baccus et al., 2008). In this way, the circuit model for a ganglion cell response serves as the linking hypothesis between a systems level computation and the cellular level of components.

The Future: Labeled Neuron Types

Reverse-engineering the connectivity and function in a neural network made of 50 different component types is a daunting challenge. The task would be more plausible if each of the neuron types had a part number stamped on it, much as one finds for components in a radio. Actually, methods to tag specific cell types are now within reach. There has been great interest in the genetic mechanisms by which neuronal cell types are specified during development. As a benefit of this research, a number of cell-specific markers have been identified, and there already exist multiple lines of mice in which specific retinal cell types are labeled fluorescently (Trimarchi et al., 2007; Kim et al., 2008; Siegert et al., 2009; Wässle et al., 2009; Münch et al., 2009). Such type-specific labels are a great boon in studies of circuit function for several practical reasons.

First, a fluorescent marker allows one to focus physiological experiments on that specific type, since electrodes are easily aimed at the fluorescent cells. In this way, even a rare cell type can be studied in a dedicated fashion (Huberman et al., 2008; Kim et al., 2008), and one may hope to systematically address the question whether specific cell types participate in multiple computations. Second, the marking method can immediately reveal the shape of the cell, and thus its likely connectivity within the retina and to projection areas in the brain in the case of ganglion cells. Third, the genetic tag can also be recruited to modify the cell type, so it may be activated or inactivated at will (Lagali et al., 2008). Finally, a genetic marker enables more effective scientific communication. Different laboratories can work on the same cell type simply by using the same mouse line. Previously, the communication of cell types was often hampered by ambiguities in the morphological type definitions, or simply because detailed morphology was not available in physiological studies. One can envision a future in which every retinal cell type comes with a genetic handle, by which it can be visually marked or its function manipulated. Such a state of affairs would greatly enhance our ability to dissect neuronal circuitry, in the retina as elsewhere in the brain.

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