Cover

Information Processing: Amacrine Cells

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Keywords

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Glossary

buffer - a device that collects signals from a source and distributes them to targets without taxing the limited capacity of the source

dendrodendritic synapses - unique synaptic motifs where both pre- and postsynaptic assemblies coexist on the same neuronal dendrite rather than segregating them to dendrites and axons respectively; the fundamental mode for biological feedback in sensory pathways

directional selectivity - the ability of a neuron to preferentially spike in response to stimuli originating from a given visual quadrant, but not others

feedback - the use of a portion of an output signal as an additional unpstream input to modify amplification in a network. Negative feedback reduces the gain, reduces noise and improves the frequency response (spatial, temporal, or spectral). Positive feedback can be used to further tune the frequency response or generate resonance.

feedforward - the use of a portion of an output signal as an additional parallel input to a downstream target. Negative feedforward selectively improves the frequency response (spatial, temporal, or spectral) but has little benefit on system noise or stability. Positive feedforward can be used to further amplify the effect of a signal.

gain - the ratio of output and input amplitudes for a system, typically specified logarithmically as decibels of power [10 log (P_{out}/P_{in})] or squared voltage [20 log (V^2_{out}/V^2_{in})].

nested feedback - the use of a portion of the feedback signal on the feedback process itself, allowing the effect of feedback to be more precisely tuned.

sign-conserving synapses - post-synaptic events mediated by receptors whose activation generates the same polarity of signal as the pre-synaptic terminal; typically AMPA, NMDA and nicotinic acetylcholine receptors.

sign-inverting synapses - post-synaptic events mediated by receptors whose activation generates the opposite polarity of signal as the pre-synaptic terminal; typically GABA and glycine.

transfer function - the output of a given cell or device relative to its input, usually expressed as gain versus temporal or spatial frequency.

Synopsis

Amacrine cells (ACs) are multipolar retinal neurons branching within the inner plexiform layer of the retina to collect and decode bipolar cell (BC) signals, recoding them as synaptic release patterns of 4-aminobutyrate (GABA), glycine, and other neurotransmitters to modulate the activity of ganglion cells (GCs). There are numerous AC classes in the mammalian retina, reflecting the complex signal processing that shapes trigger features of different GCs: motion, direction, orientation, form, and color. Though much is known about the morphology and neurochemistry of ACs, the topologies of their micronetworks are but crudely characterized.

Body

Amacrine Cells

ACs and axonal cells (AxCs) are multipolar neurons that shape GC function. While two to four classes of horizontal cells (HCs) provide lateral signal processing in the outer plexiform layer, ACs and AxCs are the most diverse neuronal group of any brain region, with over 30 classes in mammals and even more in highly visual non-mammalians such as cyprinid fishes, where over 70 ACs classes have been documented.

AC Classification, Form and Patterns

The neural retina is composed of three superclasses of cells: (1) Sensory neuroepithelial cells (photoreceptors and BCs); (2) Multipolar Neurons (ACs, AxCs, GCs); and (3) Gliaform neurons (HCs). Retinal multipolar neurons are further divisible into projection neurons (GCs and AxCs) and *bona fide* local circuit neurons, the ACs. This is an important distinction. The definition of the term "amacrine" means lacking an axon and ACs are neurons that mix presynaptic and postsynaptic specializations on their dendrites. These dendrodendritic specializations make them homologous to the "anaxonic" granule cells (GrCs) of the olfactory bulb (Fig. 1). Both ACs and GrCs are inhibitory neurons that provide in-channel and cross-channel feedback. Conversely GCs are classical projection neurons with exclusively postsynaptic retinal dendrites and presynaptic axon

terminal ramifications in the CNS. The AxC group is a collection of diverse non-amacrine retinal neurons that are GC-like in having distinct dendritic arbors and one or more long intraretinal axons. The AxC group includes polyaxonal cells in mammals and avians, certain dopaminergic neurons, and interplexiform cells. Interestingly, topologically similar axonal cells in the olfactory bulb are the periglomerular cells and some of them are also dopaminergic.

Different kinds of ACs form two large superclasses with shared features. (1) Lateral ACs are precisely stratified in a single or a few layers of the inner plexiform layer, and spread their dendrites laterally either in a narrow to wide span as needed for their function. Most of these cells are GABAergic ACs γ ACs). (2) Vertical ACs distribute their dendrites across several levels of the inner plexiform layer, mostly in narrow and medium spans, and most all of these cells are glycinergic (gly ACs). Figure 2 illustrates 3 very different structural patterns of vertebrate ACs. Radiate γ ACs (Fig. 2A) are cone BC-driven pyriform cells with a single thick proximal dendrite that descends to a given level of the inner plexiform layer and then generates some 50 dendrites that each radiate unbranched through the retina at one level for up to 0.5 mm. It exists in both ON and OFF varieties, each branching extensively in a narrow band of the inner plexiform layer as a sparse field of processes. Similar cells are present in most vertebrates but are incompletely studied. Another lateral cell is the widely studied starburst γ AC (Fig. 2A,B). It exists

in both ON and OFF varieties, each branching extensively in a narrow band of the inner plexiform layer as a dense field of processes. In non-mammalians with thick inner plexiform layer layers, it is a pyriform cell, but in most mammals it is a multipolar cell. Mammalian rod gly ACs exemplify the vertical phenotype (Fig. 2A,B,C), with deeply branching arboreal dendrites that collect signals from rod BCs in the proximal inner plexiform layer, mid-inner plexiform layer gap junctions with ON cone BCs, and both inputs and outputs onto OFF BCs from lobular dendrites in the distal inner plexiform layer. As these cells illustrate, the inner plexiform layer is laminated according to cone BC type (Fig. 2C), with OFF cells terminating in the distal part and ON cells in the proximal part. Amacrine cell processes fill the inner plexiform layer from the AC layer to the GC layer. The ON and OFF starburst ACs indicate the positions of two fine ON and OFF sublayers and exemplify the lateral motif of a large cohort of γ ACs. The gly rod ACs exemplify the vertical motif, bridging both ON and OFF layers and transporting scotopic information in the ON → OFF direction.

AC branching is quantified many ways. The fractal box dimension (D) summarizes how effectively a dendritic pattern captures synaptic space in a plane. D = 1 for a line and 2 for a complete plane. For radiate cells D is ≈ 1.2 (low capture effciency), while it approaches 1.5 for starburst cells (very high capture efficiency). In biological terms, radiate cells rigidly cover space but not synapses and contact

inputs stochastically as they traverse wide swaths of the image. Conversely, starburst cells aggressively capture many synapses rather than space with curving dendrites. Thus these cells will have very different signal processing functions. Most ACs are distributed in coverings, which is one of the three types of 2D cell patterns. The other two are packings (photoreceptors) and tilings (GCs). Patterns are partly defined by how much overlap exists between members of a cell group (the coverage factor, CF) and how evenly the geometric centers of the cell fields are distributed over space (the conformity ratio, CR). Packings like blue cones have CF < 1 and CRs of ≈ 3 (weakly orderly) in mammals to >15 (crystalline) in fishes. GCs tile, with CFs ≈ 1 and CRs ≈ 3. Coverings shown by ACs have CF > 1 to 100, meaning that, for some ACs, dendritic fields of over 100 cells overlap a single point in the image plane, implying intense synaptic control of signaling in that zone. Most CRs for ACs range from 1-4 in mammals. Using our examples from above (Fig. 2D), radiate cells have CF ≈ 4-6 (center-to-center spacing) and form a sparse but orderly synaptic mesh over the retina. Starburst cells have CF ≈ 60 or more and densely pack synaptic space. Narrow field glycinergic ACs have CF ≈ 1 and act as non-spatial intercalary amplifiers or cross-channel controllers (discussed below).

AC Synapses and Neurochemistry

Almost all ACs are driven by BCs at ribbon synapses, decoding that glutamatergic input with AMPA receptors. ACs driven by rod BCs almost exclusively use AMPA receptor-mediated currents, while most of those driven by cone BCs amplify and

sustain the initial AMPA-driven currents with NMDA receptors. Most native AMPA receptors are heteromers (some homomers may exist) of two or more of four known subunits: GluR1, GluR2, GluR3 and GluR4. There is no required stoichiometry, but receptors with mixture of GluR2 and GluR3 subunits are common in brain and retina. There are post-translational modifications that change receptor conductances, kinetics and glutamate sensitivity. The most important of these is *gluR2* mRNA pre-editing of a codon that converts a pore-lining neutral Q residue to a cationic R residue. Almost all mature GluR2 subunits are edited. The expressing of a GluR2 subunit has four important actions regardless of its partners: (1) it nearly abolishes the AMPA receptor Ca^{2+} permeability; (2) it decreases the channel conductance 2-fold or more; (3) it linearizes the I-V relation; (4) it eliminates GluR1 subunit phosphorylation-dependent increases in receptor conductance. Thus ACs can express a range of sensitivities to glutamate. The most glutamate-sensitive neuron in the retina is the starburst AC populations. Similarly, ACs express different levels and kinds of NMDA receptors resulting in a broad spectrum of response attributes.

The outputs of ACs are conventional synapses targeting BCs, ACs and GCs. Thus ACs are positioned to powerfully shape all signal flow through the retina. However, there is a key difference in the high tonic vesicle fusion rate synapses of photoreceptor and BC ribbon synapses and the transient vesicle fusion of ACs. As a result, ACs act as temporal filters and signal through bursts of apparently precisely-

timed inhibitory transmitters. The presynaptic vesicle pools of ACs are generally very small, with tens to hundreds of vesicles, rather than the pools of thousands harbored by BCs. Thus the actions of ACs are both swift and subtle. This is unlike the strong tonic influence of HCs as we shall see below.

Of the roughly 30 classes of ACs described for mammals, half to 2/3 of the classes are GABAergic and release GABA via small to large patches of vesicles at conventional synapses. Most of the remaining cells are narrow field glycinergic cells. These two fast classical inhibitory transmitters act largely by opening anion permeant channels which, in most cases, generate hyperpolarizing inward chloride currents. The purpose of two kinds of anion channel transmitters is additivity: they do not occlude each other's receptors either by desensitization or sub-additivity as in the cases of side-by-side GABA receptor patches.

The targets of GABAergic ACs decode GABA signals with either ionotropic $GABA_A$ or $GABA_C$ receptors (which modulate anion conductances) or metabotropic $GABA_B$ receptors that modulate K^+ conductances or the operating range of voltage-gated Ca^{2+} channels. The difference between $GABA_A$ and $GABA_C$ receptors is similar to the difference between fast AMPA receptors and slower, more sustained NMDA receptors. $GABA_A$ receptors are heteromeric pentamers of GABA receptor subunits. Though they can have large anion conductances, they tend to desensitize quickly and act transiently. GCs and ACs predominantly express $GABA_A$ receptors. Ionotropic $GABA_C$ receptors are homomeric assemblies of ρ subunits and are,

arguably, a subset of the $GABA_A$ receptor group. When activated by GABA, $GABA_C$ receptor conductances are smaller but more sustained, and they are more GABA sensitive. These receptors are primarily expressed by BCs. Because both ionotropic GABA and glycine receptor types activate chloride conductances, their efficacies can vary with the membrane potential of the target cell and the chloride gradient. Another mechanism that mediates inhibition is shunting inhibition, where large conductance increases dminish the space and time constants of small dendrites. This inhibition is independent of the postsynaptic voltage and the chloride gradient and is most effective on small processes far from the major dendrites of a cell. $GABA_B$ receptors are also highly effective regardless of membrane potential. They are GPCRs that either increase the voltage threshold of synaptic Ca^{2+} channels or the conductance of K^+ channels, strongly hyperpolarizing cells (both slowing synaptic release). The former effect seems more prominent on BC axon terminals and the latter in GC dendrites or somas. Each mechanism can inhibit synaptic signaling in target processes with different timing and efficacy. However, the synaptic gain of such signaling is generally low and is often <1. Thus individual GABAergic or glycinergic synapses are rather weak and stimulus-dependent synchronicity is required for strong effects.

Several additional neuroactive signals associated with GABAergic ACs are co-transmitters: acetylcholine (ACh), certain catecholes, serotonin in non-mammalians, several peptides, and nitric oxide (NO). The differential regulation (if any) of GABA

and ACh, catecholamine, serotonin or peptide release is poorly understood. Glutamate may also be an excitatory AC co-transmitter for glycinergic ACs that express vGlut3, a vesicular glutamate transporter. Further, the roles of peptides and monoamines in information processing per se are also not completely clear, though some data suggest that peptides such as somatostatin may improve signal-to-noise ratios through an unknown mechanism.

ACs and Signal Processing Fundamentals

ACs are components of small network submotifs (stereotyped aggregates of cell processes and synapses) that carry out analog signal processing operations, including filtering (spatial, temporal and spectral), gain control, signal-noise separation, signal buffering and feature definition. Feedback is an essential control process in all amplification systems. Sign-inverting feedback (Fig. 3a) is the primary mechanism by which most of these operations are effected in biology and electronics, and its essential nature is the addition of a scaled, inverted copy of the output of an amplification stage back to that stage. Every system has an input-output response R that, for simple time-invariant linear systems, can be expressed as a transfer function of stimulus frequency G(s), where G is the system gain and s is frequency. This is often referred to as the open-loop gain and has a shape like that in Fig. 3. As inputs become faster (higher frequency), the gain begins to fall off. In a moving transient world we would prefer to have the best gain at a higher frequency and negative feedback is the mechanism. The electronic negative feedback

amplifier was invented by Harold Stephen Black of Bell Laboratories in 1927 … and the biological one by evolution some 3 billion years BP. By providing an inverted signal with transfer function H(s) to the input, R changes from G(s) to G(s)/[G(s)H(s)+1]. For H(s) ≥ 1, the shape of response function changes based on the shape of H(s). If H(s) is a slow, tonic response, by depressing slow frequencies more that fast ones, $R_{feedback}$ has an improved frequency response. Similarly, feedback can reduce noise. Negative feedforward is also common biologically and can be even more potent in shaping outputs specific kinds of inputs than feedback, although it is not as effective for frequency response or noise control.

We can think of the retina as having only two amplification stages: (1) photoreceptors → BCs and (2) BCs → GCs (Fig. 4). Every stage of feedforward gain also requires feedback or feedforward control, whether made of silicon or cells. In retina, an amplification stage is a small collection of properly connected excitatory and inhibitory synapses. Each synapse is itself a bicellular amplifier that encodes a presynaptic input voltage as a time varying neurochemical signal, and postsynaptically decodes it as a direct current via ionotropic receptors or an indirect current or response modulation (e.g. intracellular Ca^{2+} release) typically through G-protein coupled receptors (GPCRs). Excitatory synapses typically have amplifications or gains >>1, while inhibitory synapses typically have gains < 1. ACs

are the key feedback and feedforward devices of the inner plexiform layer and their spatial distributions shape nature of their interactions BCs and GCs.

In detail, there are three primary submotifs that can strongly shape how ACs are involved in signal processing (Fig. 4). The first is the classical reciprocal feedback synapse BC⇆AC wherein a signal from a BC ribbon onto an AC process is directly antagonized by an AC, typically a γ AC. This signaling pathway increases the frequency response and stabilizes the gain of the BC itself. The second is the parallel classical feedforward synapse chains $BC_1 \rightarrow G$ and $BC_1 \rightarrow AC \rightarrow G$ where the AC synapse antagonizes the BC excitation directly in the GC. However, as any BC noise has already been amplified by the $BC_1 \rightarrow G$ synapse, feedforward is ineffective in improving the signal-to-noise ratio. But it is very effective in generating stimulus specific lateral signals in GCs. The third submotif is the AC → AC synapse. While extremely common, the kind of signal processing associated with this submotif is poorly understood. In its most concrete form, homotypic or even autotypic AC synapses appear to be a fundamental attribute of the reciprocal feedback system by adding a loop known as nested feedback: BC⇆AC↻. This process is reminiscent of nested transconductance amplifiers where stages of looped self-inverting signals are used to “tune-up” the ampifier, endowing it with better high-frequency performance and giving it a wider bandwidth. Nested AC feedback may do the same.

Examples of AC Networks

There are almost no AC systems whose complete range of functions is completely understood, largely owing to their diversity and the difficulty of obtaining large physiological samples. Four generic mammalian AC networks and signal processing functions that are of particular interest are outlined here.

γ ACs of the rod pathway

γ ACs of the rod pathway mediate temporal processing, gain control and noise supression. Extensive anatomy, ultrastructure, physiology and pharmacology reveal the serotonin-accumultating (S1/S2) γ ACs of the mammlian retina to be archetypal in-channel feedback devices. The mammalian rod pathway is unique among vertebrates (as far as is known) in using two cycles through BC amplification (Fig. 5). All the outputs of the rod BC target ACs of two major classes: γ ACs that engage in feedback and gly ACs that engage in "re-entrant" feedforward to pass rods signals through the cone ON and OFF channels. Every BC displays γ feedback synapses, which suggests that the narrowly-stratified medium-to-wide field γAC is a standard motif component. Rod BCs display clear GABAC-mediated inhibition and the S1/S2 γ ACs that provide feedback are strongly AMPA driven, ON-center ACs. This simple feedback circuit will provide the BC with better temporal response as scotopic light gets brighter and improve signal-to-noise performance. Though the mammalian

retina contains no serotonin, it is likely that the indoleamine transporting S1/S2 cells are descendants of the non-mammalian serotoninergic/γ (S γ AC) system, which forms feedback synapses with both OFF and ON mixed rod-cone BCs. The disappearance of serotonin signaling is clearly a recent evolutionary event, but the association of this simple BC⇆AC network with rod BC pathways is clearly ancient.

Gly ACs of the rod pathway

Gly ACs of the rod pathway mediate cross-channel feedforward buffering. In electronics, a buffer is an element interposed between two device stages to provide improved transfer. Buffers are often used to "fanout" input signals to several different outputs while isolating the input stage from the output loads. The gly rod AC represents an evolutionary buffer to further amplify the rod signal and distribute it in a low noise-manner. All vertebrates send rod signals to the CNS via GCs that also carry cone signals. There is no private rod pathway to the brain, though almost all species have private pure cone photopic channels (e.g. the primate foveal midget pathway). Non-mammalians combine rod and cone pathways at the first synapse in the outer plexiform layer by converging on mixed rod-cone BCs. This chain involves two high-gain ribbon synapses: rod → mixed BC → GC. Mammalians combine rod and cone pathways by fanning out from a pure rod BC pathway back into cone pathways via two scotopic motifs in the inner plexiform layer :

(1) rod → rod BC → gly rod AC :: ON cone BC → GC

(2) rod → rod BC → gly rod AC → OFF cone BC → GC

This circuit is more complex as there are two photopic motifs:

(3) cone → OFF cone BC → gly rod AC

(4) cone → ON cone BC :: gly rod AC

There are also γ AC → gly AC inputs of unknown provenance. Physiologically, dark adapted rod ACs have strong transient AMPA-like depolarizations while light adapted cells have more more sustained, small depolarizations. How all of the inputs are regulated remains unknown.

Small γ ACs of the primate midget BC → GC pathway

These cells may mediate the red-green color opponent pathway. These ACs receive direct input from midget BCs of either the ON or OFF pathway and provide reciprocal feedback as well as feedforward to a small patch of midget GC dendrites. Midget GCs apparently connect almost exclusively to cones that express the long-wave system (LWS) pigment gene: either LWS VP 560 nm (red, R) or LWS VP 530 nm (green, G) cones. By extension, midget BCs exist as R and G forms. Ultrastructural data suggest that each AC collects signals from several midget BCs and is presynaptic to each. This suggests that there is no R-G chromatic selectivity in the AC surround … that a midget-pathway AC has no mechanism to sort BC chromatic type. This sets the stage for one of the longest running controversies in

primate vision. Are midget CG receptive fields are truly center/surround (C/S) pure opponent [+R/-G, -R/+G, +G/-R, -G/+R] or are they a collection of cells with a weighted distribution of surrounds that range from predominantly R or G or a mixture of R+G or yellow (Y) signals? A purely theoretical model has been proffered that involves glyc ACs as nulling tools to remove the inappropriate signal, making the surround appear pure. In any case, the appearance of small spectrally pure antagonistic surrounds is inconsistent with large yellow-dominated HC surrounds observed in blue ON center GCs. How that signal disappears from R and G cone BCs remains a mystery in the face of strong evidence of cone⇆HC feedback.

γ ACs of the directionally selective (DS) GC pathway

γ ACs mediate feature detection in the DS GC pathway. The best-known feature detection event the retina is the dependence of mammalian DS GC signaling on ionotropic GABA receptors. DS GCs exist in both ON and ON-OFF varieties but the qualitative feature of their signaling is similar. DS GCs have two response modes. (i) When a stimulus spot approaches the cell from the excitatory side the cell fires, excited by both cone BC glutamate release activating AMPA receptors and starburst AC acetylcholine (ACh) activating nicotinic ACh receptors. Similar to the rod gly AC, starburst ACs provide the afferent flow with another burst of gain: cone → cone BC → starburst AC → GC. As starburst ACs are one of the most glutamate-sensitive cells in the retina, this makes DS cells exceptionally responsive.

(ii) When a stimulus spot approaches the cell from the null side, firing is inhibited by a GABAergic mechanism, possibly a γ AC or AxC (see below) with an eccentric output field so that it receives excitation long before the DS GC does. Blockade of ionotropic $GABA_A$ receptors converts the DS GC into a highly excitable cell with no directional bias. It has been found that starburst ACs themselves have a directional bias in that stimuli starting at the tips of the dendrites tend to hyperpolarize and those starting "dead-center" and moving away tend to depolarize, and some authors argue this is sufficient to build a DS network. However, given the coverage factor of the starburst ACs (>100) compared to that of the DS GCs (≈1), the geometric requirements for this seem difficult to achieve. It is possible, even probable, that an additional γ AC or AxC is involved as shown in Figure 6.

Axonal Cells

A subset of retinal neurons are the axonal or polyaxonal cells, which includes one of the dopaminergic neurons of the mammalian retina. Many are clearly GABAergic, while others such as the dopaminergic neuron may be dual glutamate/dopamine neurons. The essential feature of AxCs is the axon: a long range output device that enables these neurons to send signals to regions substantially displaced from the soma and dendritic arbor. AxCs (including dopamine neurons) show either ON or ON-OFF responses. In non-mammalian retinas, object motion selective

(OMS) cells achieve their feature detection via polyaxonal γ AxCs. This raises the question of whether the mammalian DS GC uses the same strategy.

ACs and disease

Over the past five years it has become evident that, like the CNS, the retina undergoes extensive remodeling in response to sensory deafferentation effected by retinal degenerations, especially the retinitis pigmentosas. ACs are especially active components of remodeling, often sprouting new dendrites and participating in anomalous synaptic structures known as microneuromas. And like other retinal neurons, they can be induced to relocate to ectopic somatic clusters loci (either to the distal retinal margin or ganglion cell layer) via anomalous migration columns. The most cells of resilient of all, they are the last to die as the retina is slowly depleted of neurons. In fact, ACs may be a key component of neural survival in the remnant retina by providing a periodic source of neural activity in the absence of photoreceptors.

Reading

Baccus, S.A., Olveczky, B.P., Manu, M., and Meister, M. (2008) A retinal circuit that computes object motion. J Neurosci. **28**, 6807-6817.

Famiglietti, E.V. Jr. (1983) On and off pathways through amacrine cells in mammalian retina: the synaptic connections of "starburst" amacrine cells. Vision Res **23**, 1265-1279.

Kittila, C.A. and Massey, S.C. (1997) Pharmacology of directionally selective ganglion cells in the rabbit retina. J Neurophysiol **77**, 675-689.

MacNeil, M.A., Heussy J.K., Dacheux R.F., Raviola, E., and Masland, R. H. (1999) The shapes and numbers of amacrine cells: matching of photofilled with Golgi-stained cells in the rabbit retina and comparison with other mammalian species. J Comp Neurol **413**, 305–326.

Marc, R.E. (1999) Kainate activation of horizontal, bipolar, amacrine, and ganglion cells in the rabbit retina. J Comp Neurol **407**, 65-76.

Marc, R.E. (2004). Retinal neurotransmitters. In Chalupa, L. and Werner, J. (eds.) The Visual Neurosciences vol. 1, pp 315-330. Cambridge, Mass: MIT Press.

Marc, R.E. (2008) Functional neuroanatomy of the retina. In (Albert, D.M. and Miller, J.W (eds.) Albert & Jakobiec's Principles and Practice of Ophthalmology, 3rd edition, pp 1565-1592. Saunders Elsevier.

Slaughter, M.M. (2004) Inhibition in the retina. In Chalupa, L. and Werner, J. (eds.) The Visual Neurosciences vol. 1, pp 355-368. Cambridge, Mass: MIT Press.

Tauchi, M. and Masland, R.H. (1984) The shape and arrangement of the cholinergic neurons in the rabbit retina. Proc R Soc Lond [B] **223**, 101-119.

Vaney, D.I. (1990) The mosaic of amacrine cells in the mammalian retina. In Chader, J. and Osborne, N. (eds) Progress in Retinal Research, pp 49-100. New York: Pergamon.

Vaney, D.I. (2004) Retinal amacrine cells. In Chalupa, L. and Werner, J. (eds.) The Visual Neurosciences vol. 1, pp 395-409. Cambridge, Mass: MIT Press.

Völgyi, B., Xin, D., Amarillo, Y., and Bloomfield, S.A. (2001) Morphology and physiology of the polyaxonal amacrine cells in the rabbit retina. J Comp Neurol **440**, 109-125.

Wilson, M. and Vaney, D.I. (2008) Amacrine cells. In Masland, R.H. and Albright, T. (eds.) The Senses: A comprehensive reference, pp 361-367. Vision. Amsterdam: Elsevier.

Zhang, J., Jung C.S., and Slaughter M.M. (1997) Serial inhibitory synapses in retina. Vis Neurosci **14**, 553-563.

Zhang J., Li W., Trexler, E.B., and Massey, S.C. (2002) Confocal analysis of reciprocal feedback at rod bipolar terminals in the rabbit retina. J Neurosci **22**, 10871-10882.

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Figure Captions

Figure 1. Signal processing in the olfactory bulb (top) and retina (bottom). Glutamatergic sensory neurons such as olfactory receptors (OR) and photoreceptors (PR) directly drive glutamatergic target neurons in the afferent chain, olfactory mitral cells (MC) and retinal bipolar cells (BC) respectively. MCs and BCs then target the next glutamatergic elements as well as sets of inhibitory GABAergic local circuit neurons: olfactory granule cells (GrC) and retinal amacrine cells (AC). Both of these neurons provide local inhibitory feedback onto their source neurons. ACs also provide inhibitory feedforward onto ganglion cells (GC) in the chain. Blue elements are glutamatergic. Red elements are GABAergic.

Figure 2. Schematic shapes and patterns of three canonical varieties of retinal ACs. A. Top view of two lateral ACs and one vertical AC. Red: An OFF radiate γ AC from goldfish retina, with a wide-field, monostratified non-branching dendritic arbor over 0.5 mm in diameter. These cells appear to be present in all vertebrates. Yellow: a goldfish OFF starburst γAC a with medium, monostratified, bifurcating, wavy arbor about 0.2 mm in diameter. Starburst cells are found in all vertebrates. In species with thick inner plexiform layers, they are pyriform with a single proximal dendrite; in those with thin inner plexiform layers (mammals) they are multipolar Cyan: a mammalian vertical gly AC, with a small, multistratified arbor about 0.05 mm in diameter. B. Oblique view of the starburst γ AC and gly rod ACs showing that the starburst cell captures more synaptic space, but is laminated between the distal and proximal dendrites of the gly rod AC. C. Vertical and top view of the gly rod AC. Immediately beneath the soma are several large lobular dendrites that contact OFF BCs. Deep in the inner plexiform layer are arboreal dendrites that

capture rod BC inputs at their tips and as the ascend through the inner plexiform layer make gap junctions with cone BCs. The inner plexiform layer is divided into ON and OFF layers exemplified by the yellow starburst AC dendritic bands. D. Coverage patterns of ACs. The red radiate γ ACs are sparse and have coverage factors (CF) of about 4-6. The yellow starburst ACs are more frequent and have CF >100 and capture a great fraction of the synaptic space in a thin stratum of the inner plexiform layer. The cyan rod gly ACs are densely packed but have CF ≈ 1.

Figure 3. Basic principles of feedback. Top: An operational amplifier feedback circuit with an "open loop" sign-conserving transfer function G(s) and part of the output fed back to the sign-inverting input the transfer function H(s) and net output transfer of G(s)/[G(s)H(s)+1]. Bottom: The effect of feedback on a given amplifier's performance. With no feedback, the response R as a function of frequency slowly rolls off. With feedback, the normalized peak response is at a higher frequency.

Figure 4. The basic connectivity of ACs. Top: The stages of amplification in the retina flowing from cones (C) to BCs (B) to GCs (G). Cones provide lateral excitatory signals to coupled sheets of HCs (H::H) which in turn provide lateral feedback to cones and lateral feedforward to BCs. Cone signals birfurcate, generating sign-conserving responses in OFF BCs (B) and sign-inverting responses in ON BCs (B). Similarly, any feedforward HC signals must also bifurcate to generate sign-inverting signals in OFF BCs and anomalous sign-conserving signals in ON BCs. BC signals bifurcate and drive both ACs and GCs with sign conserving mechanisms. ACs have the most complex topology, with feedback signals to

BCs, feedforward signals to GCs, and nested feedforward / feedback by re-entrant loops. Every pairwise signal transfer has a transfer function, e.g. B → A has transfer a_{BA}. Bottom: The topology of AC signaling at the BC → GC synapse. BCs provide fast glutamatergic ribbon synapse input to ACs and GCs via AMPA receptors (blue dashes). ACs provide small conventional synapse GABA inhibition at predominantly ionotropic GABA receptors (red dashes) on ACs, BCs and GCs.

Figure 5. A comparison of rod and cone convergence onto GCs in mammalian and non-mammalian retinas. Non-mammalians use conventional mixed-rod-cone BCs with direct input onto GCs and classical GABAergic feedback. Mammals predominantly exploit a rod BC that drives an intermediate stage of gain via the gly rod AC, which re-enters the cone pathways at the inner plexiform layer. The gly rod AC drives the OFF BC pathway with sign-inverting glycine receptors and the ON BC pathway with gap junctions. Similar to non-mammalians, the γ rod AC provides BC feedback.

Figure 6. One topology for the generic ON directionally-selective (DS) pathway. The ON DS GC receives glutamatergic excitation directly from ON cone BCs (black arrows and dots) and cholinergic feedforward excitation (red arrows and dots) from local patches of starburst ACs. The starburst ACs also provide GABAergic feedback to BCs (open arrows and dots). While some argue that the starburst alone can generate directional surrounds for DS GCs, the symmetry of starburst AC fields makes this a challenging model. Similar to object motion sensitive (OMS) GCs, it is also possible that a γ polyaxonal AxC provides asymmetric inhibition for targets approaching from the null direction.

Figure 1

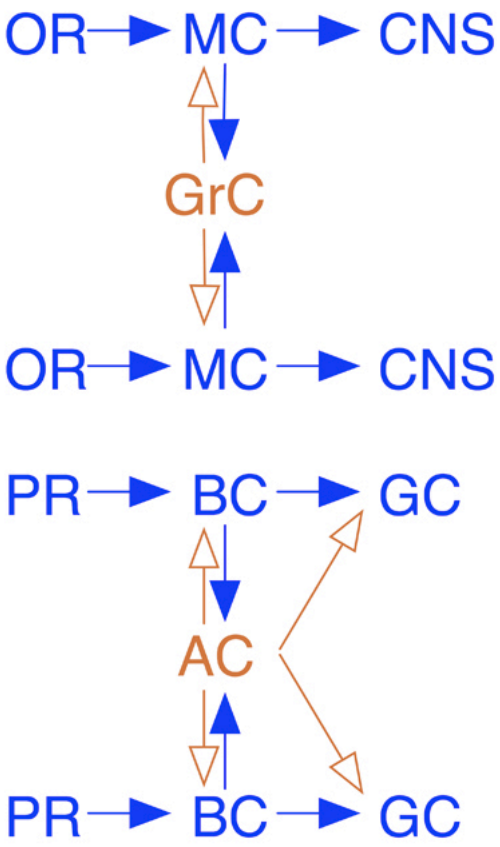


Figure 3

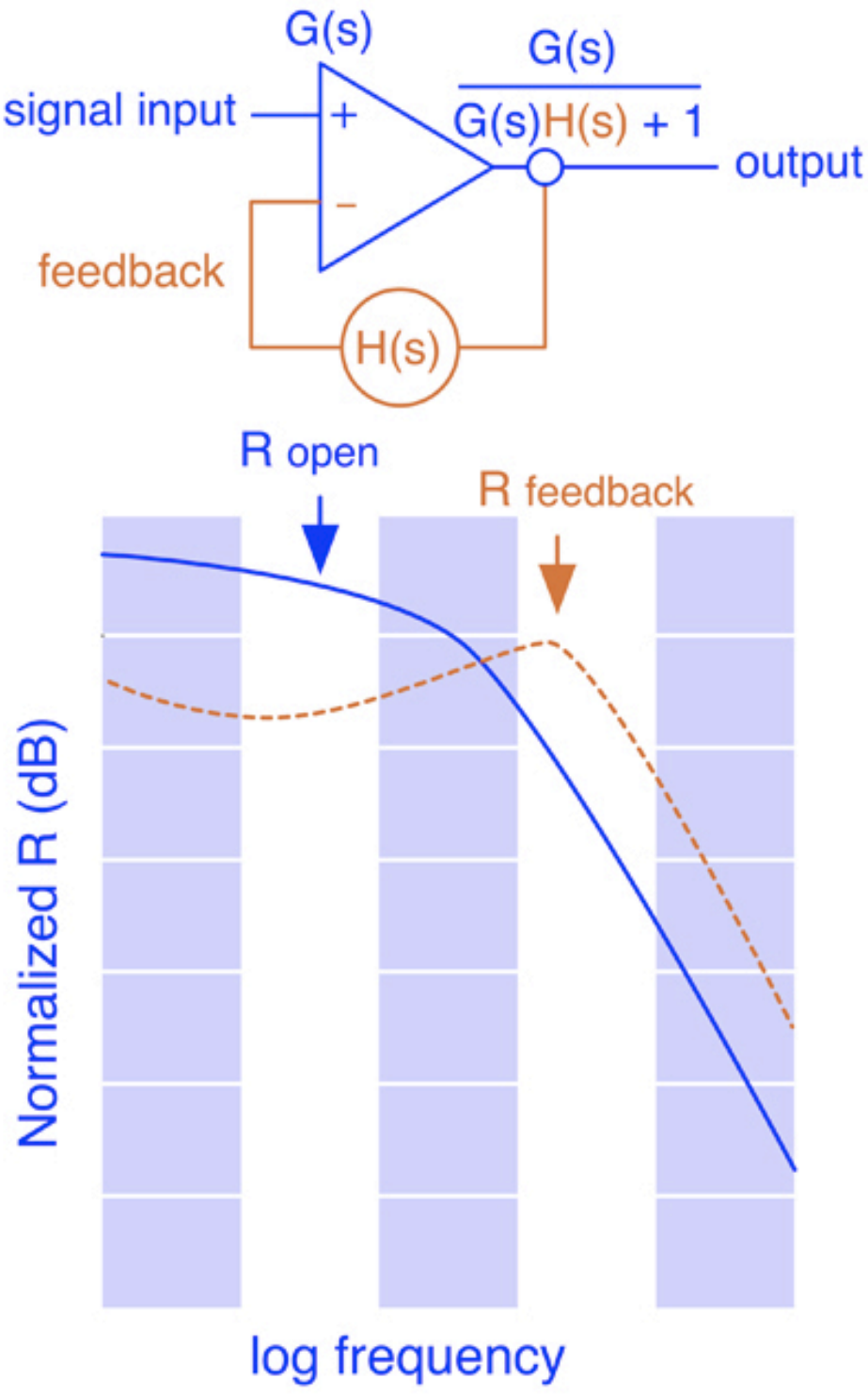
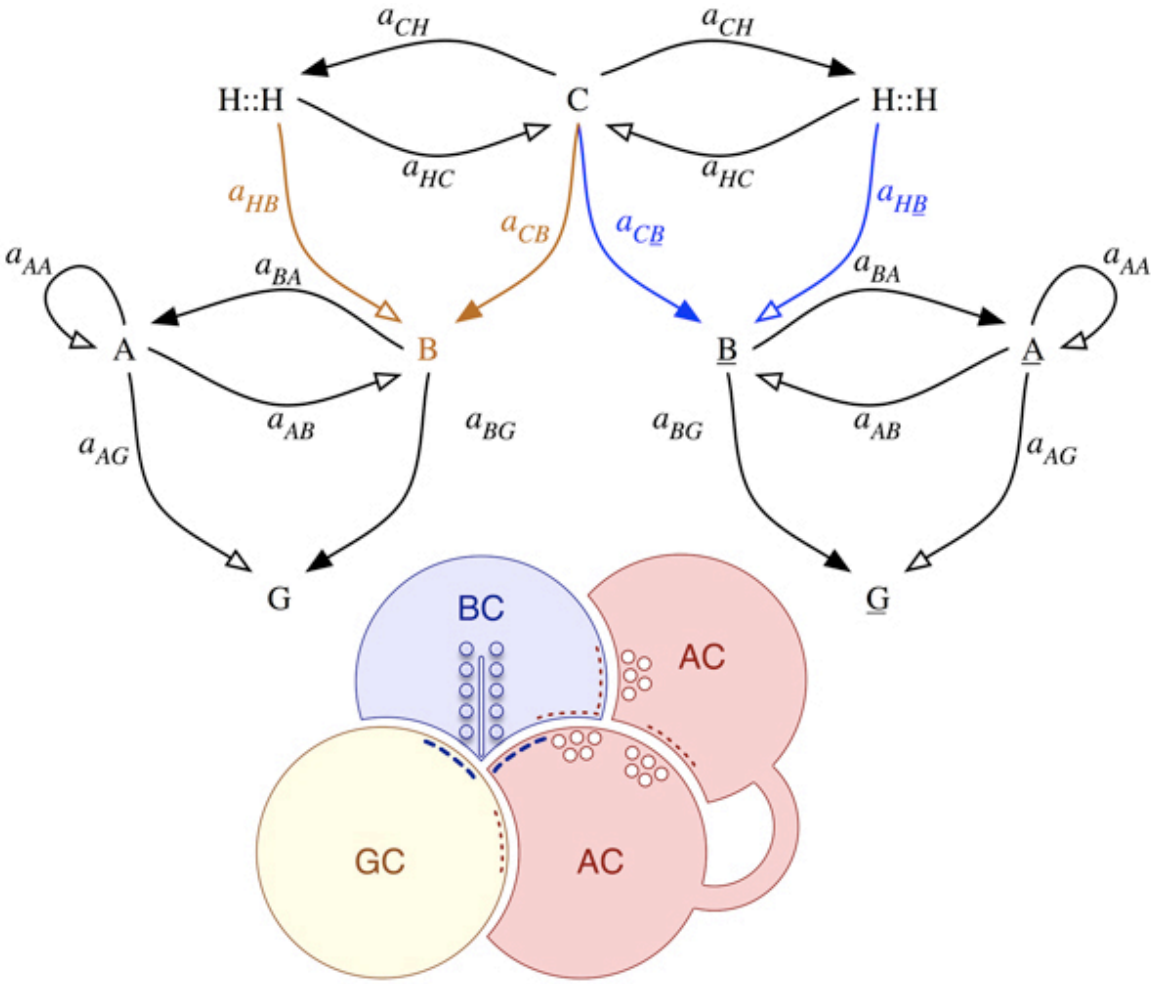

G(s)
G(s)
signal input
+
G(s)H(s) + 1
output
−
feedback
H(s)
R open
R feedback
Normalized R (dB)
log frequency

Figure 4


a_{CH}
a_{CH}
H::H
C
H::H
a_{HC}
a_{HC}
a_{HB}
a_{CB}
$a_{C\underline{B}}$
$a_{H\underline{B}}$
a_{AA}
a_{BA}
a_{BA}
a_{AA}
A
B
B
A
a_{AB}
a_{BG}
a_{BG}
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a_{AG}
G
G
BC
AC
GC
AC

Figure 5

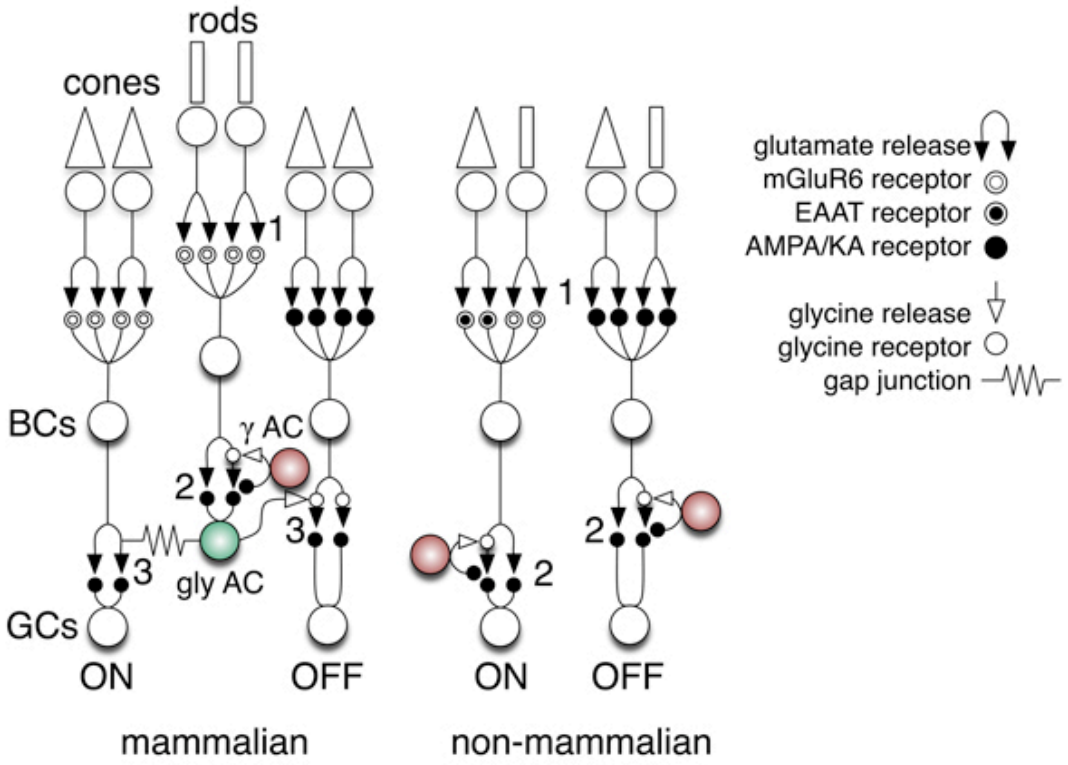
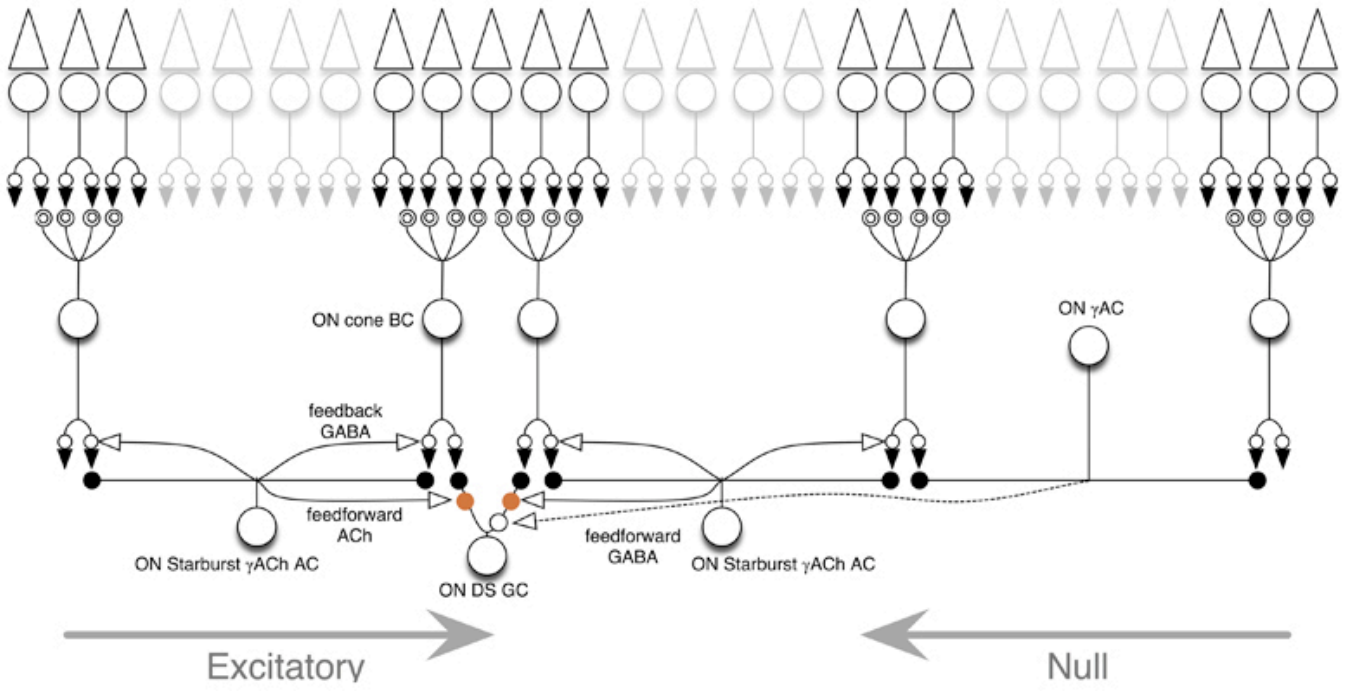

rods
cones
1
BCs
γ AC
2
3
3
gly AC
GCs
ON
OFF
mammalian
1
2
2
ON
OFF
non-mammalian
glutamate release
mGluR6 receptor
EAAT receptor
AMPA/KA receptor
glycine release
glycine receptor
gap junction

Figure 6


ON cone BC
ON γAC
feedback
GABA
feedforward
ACh
feedforward
GABA
ON Starburst γACh AC
ON DS GC
ON Starburst γACh AC
Excitatory
Null