

in vivo. While this is difficult to prove, it is interesting to note that in HD, the specific pattern of cell death is lost in the juvenile forms of the disease, with the cerebellum being affected. These forms correspond to an extremely long polyQ tract. It is then possible that, in vivo, huntingtin that contains a very long polyQ would bind to PQBP-1 and induce the degeneration of the cerebellum as it is observed in the juvenile forms. Also, one might take into account the subcellular localization of the disease proteins. While ataxin-1 is mostly nuclear in neurons, huntingtin is initially localized in the cytoplasm. However, to be toxic, huntingtin need to translocate in the nucleus. Thus, during the development of the disease, the kinetics of PQBP-1 interaction with ataxin-1 and huntingtin might be different.

Finally, future studies will certainly reveal that cell specificity is regulated at multiple levels. At the transcriptional level, CRX in SCA7 and PQBP-1 in SCA1 are important components in mediating cell death specificity. DNA arrays experiments have already shown that within the set of transcripts that have an altered profile, some of them are common to the different disorders. However, some are specific to a cell type and could then participate in the selectivity of degeneration. One example is the selective dysregulation of BDNF transcription in HD. Indeed, Zuccato et al. (2001) suggested that a lack of BDNF support in the striatum could explain the preferential vulnerability of striatal neurons in HD.

Cell specificity might also be achieved during other biological processes involved in the pathogenesis of polyQ disorders. In HD, the selective death of medium spiny neurons of the striatum might also be governed by the selective subunit composition of the NMDA glutamate receptor (Zeron et al., 2002). A variety of intracellular pathways or proteins have been shown to regulate death induced by the polyQ proteins. This includes, for example, the ubiquitin-proteasome pathway, the apoptotic machinery, and the chaperone proteins. Little is known about their contribution in vivo to the disease process. In the case of the ubiquitin machinery, all the specific enzymes involved in the degradation process of a particular polyQ protein are not yet identified. Furthermore, it will be important to determine the spatial and temporal pattern of these regulators. In conclusion, by combining all these partners, one given neuron could have a unique repertoire of proteins that could make it particularly vulnerable to one polyQ protein.

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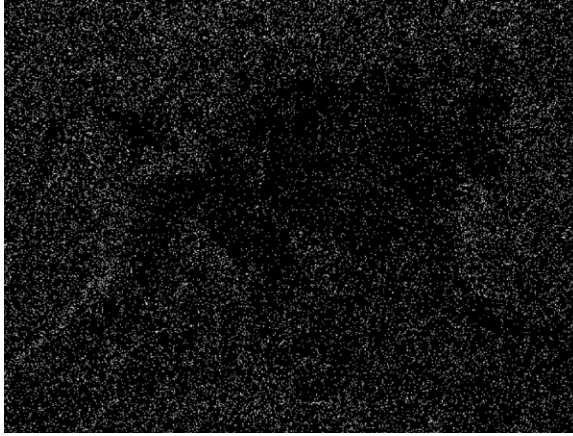
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Needle from a Haystack: Optimal Signaling by a Nonlinear Synapse

Commonly, a neuron must separate a small, rare event carried by one of its inputs from the noise carried by many others. In this issue of *Neuron*, Field and Rieke (2002) demonstrate that to solve this problem, the rod bipolar neuron in mouse retina selectively amplifies a rod's single-photon signal only when it is larger than average. This nonlinearity rejects nearly three-fourths of the single-photon signals. Yet, by also rejecting noise, it provides nearly optimal filtering near absolute visual threshold.

The report by Field and Rieke in this issue of *Neuron* addresses two fundamental questions. First, how can a neuron separate a small, rare event carried by one of its inputs from the noise carried by many others? If it sums n inputs linearly, the noise will rise as \sqrt{n} , and a small, rare signal will be swamped. Second, in separating the event from noise, where should a neuron draw the line? A relaxed criterion will generate false positives, but a strict one will inevitably discard some of the precious events.

Both problems arise for mammalian vision in starlight, where photons are so sparse that over a 0.2 s integration time, only one photon is captured by 10,000 rods. This photon flux is just adequate to paint a faint, "pointillist" image on the photoreceptor sheet (see First Figure). To convey this image to the brain, a circuit should collect from a large patch of rods and amplify the single photon event to cause spikes at the retinal output. Indeed, one photon does evoke a small burst of spikes in each of several ganglion cells (Barlow et al., 1971; Mastronarde, 1983). But how does the neural circuit separate this rare, small event from so much noise? And regarding the

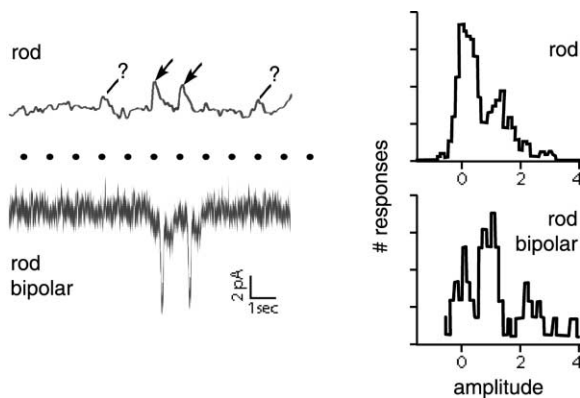


Baboon in Simulated Starlight

Each pixel received zero or one photon (bright dot) with a probability governed by a Poisson distribution whose mean corresponded roughly to the intensity under starlight. Field and Rieke show that a neural circuit does best by removing dots that are probably noise despite the loss of many dots that are true photons. Image reprinted courtesy of A. Hsu and R. Smith.

pointillist image, is it better to be strict and lose some dots or to relax and allow additional dots to scatter randomly over the image?

Investigating this problem in mouse retina, Field and Rieke find that the average single-photon current in a rod only slightly exceeds the continuous noise (by 3-fold). Single-photon responses much larger than average are easily recognized, but the smaller responses merge with the continuous noise and cannot be reliably identified (see Second Figure, upper left). Matters could get even worse at the first synaptic stage because the 20 rods



Rod Bipolar Cell Separates Single-Photon Events from Continuous Noise

(Left) In a rod, single-photon events (arrows) rise clearly above the continuous noise only when they are considerably larger than average. Same events in the rod bipolar are faster with much improved signal-to-noise.

(Right) Rod responses to repeated flash show peaks at amplitude 0 (no photon) and slightly greater than 1 pA, but the two distributions overlap extensively. Rod bipolar responses show three peaks (zero, one, and two photons), but these distributions are cleanly separated by nonlinear amplification at the rod → rod bipolar synapse (responses replotted from Field and Rieke).

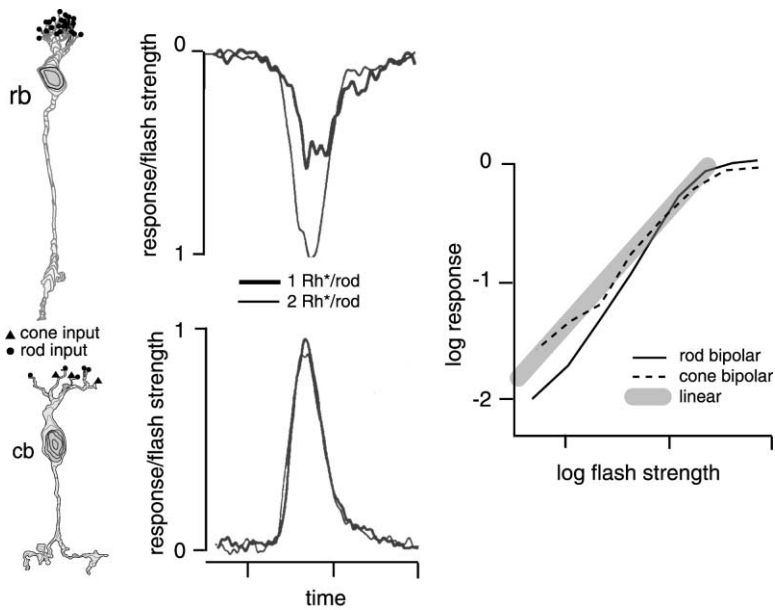
converging on the rod bipolar cell could contribute the continuous noise from transduction plus the vesicle noise from Poisson release. This would increase post-synaptic noise by more than 4.5-fold and, thus, obscure even the largest single-photon signals. A solution was proposed by Baylor et al. (1984) and explored computationally by van Rossum and Smith (1998): amplify nonlinearly to pass the larger signals (mostly photons) and remove the smaller ones (mostly noise).

To test this idea, Field and Rieke first presented weak flashes to the isolated mouse rod and confirmed that it responds linearly: double the photons, double the current (Baylor et al., 1984). Next, they recorded from the rod bipolar cell in situ and found, as predicted, that it responds supralinearly: double the photons, more than double the current (see Third Figure). This nonlinearity was observed under voltage clamp and in the presence of GABA and glycine antagonists, so it was neither caused by voltage-activated conductances, nor by inhibitory feedback onto the bipolar axon terminal. Furthermore, the shape of the nonlinearity reflected greater responsiveness to larger presynaptic voltages (Third Figure)—opposite to the nonlinearity for transmitter release at the amphibian rod, which favors smaller voltages. This narrows attention to a postsynaptic mechanism (van Rossum and Smith, 1998).

The rod's steady release of glutamate in darkness might saturate glutamate receptors at the rod bipolar dendritic tip or activate enough of them to close all the local cation channels. Small decrements in glutamate, due to hyperpolarizations from continuous noise and randomness in release, would insufficiently reduce its concentration in the synaptic cleft to relieve the saturation. But a larger-than-average hyperpolarization (photon-induced) would suppress glutamate release strongly enough to desaturate and open cation channels. Whether the saturation occurs in the cleft or intracellularly remains to be determined, but, the first question posed above is answered: postsynaptic "thresholding" at the rod bipolar dendritic tips clearly separates the rare photon events from the noise (Second Figure).

The second question is also answered. The threshold removes not only noise, but also most of the photon events, leaving only the largest 25%! This is certainly counterintuitive, but Field and Rieke show that it actually makes sense. When photons are as sparse as they are at visual threshold, a less-stringent cutoff would pass more small "events," but most of them would be noise. At this intensity, an event is probably a photon only if it is at least 1.2 times the average single-photon response. Field and Rieke calculate that the nonlinearity for this intensity could potentially improve signal-to-noise by 420-fold, and they estimate from the bipolar responses that it actually improves by >350-fold. Thus, near absolute visual threshold, the nonlinear synapse sets the threshold nearly optimally.

But, as photon density rises, the odds shift. Now a small hyperpolarization is less likely to be noise and more likely to be a photon. By intensities 100-fold brighter than absolute threshold (1 photon/100 rods), the nonlinear synapse can potentially improve signal-to-noise only by ~8-fold, and the actual improvement is only ~4-fold. For this modest benefit, losing 75% of photons would be a poor trade. Fortunately, there is



Rod Bipolar (Nonlinear Synapse) Is Best for Starlight, but Cone Bipolar (Linear Synapse) Is Best at 100-Fold-Higher Intensities

(Left) The rod bipolar cell collects collects chemical synapses from 20 rods, while the cone bipolar cell collects from only a few rods. However, each rod probably pools signals from neighboring rods via gap junctions. (Middle) Response amplitudes are normalized for flash intensity. Cone bipolar response doubles for twice the intensity, but rod bipolar response more than doubles.

(Right) Input/output curve for cone bipolar is essentially linear, but for rod bipolar, it is clearly nonlinear. (Neurons reprinted from Tsukamoto et al, 2001; responses replotted from Field and Rieke).

another circuit whose transfer characteristics are better matched to the new odds.

Rods contact a second type of bipolar cell, one that gets most of its input from cones (Third Figure). This circuit was discovered only recently, and its role in vision has been puzzling (Soucy et al. 1998; Hack et al., 1999; Tsukamoto et al. 2001). Field and Rieke show that this cone bipolar circuit is sensitive, like the rod bipolar circuit, but transfers signals linearly (Third Figure). As rising photon flux renders the nonlinear synapse less efficient, the linear synapse becomes more efficient. This comparison between cone and rod bipolar cells serves as a nice “control” (showing the difference between linear versus nonlinear behavior) but, more importantly, it suggests the first clear rationale for the alternative rod pathway.

Combining this result with the anatomical structure of this rod-to-cone bipolar circuit implies an answer to another general problem: how common need a signal event be in order to be pooled prior to synaptic transfer (Smith et al., 1986)? In this system, only a few rods synapse directly onto the cone bipolar; the rest contact each other in clusters via gap junctions, presumably forming electrical syncytia that pool signals from ~10 rods preceding the chemical synapse (Tsukamoto et al., 2001). If these junctions were coupled at visual threshold, noise would be pooled before the nonlinearity and thresholding would come too late. Consequently, rod-rod junctions should uncouple in the dimmest light and couple only when photon flux rises to levels served best by the OFF bipolar cell.

In elucidating these computational issues for early visual processing, Field and Rieke provide some general insights. For example, the convergence of 20 rods upon the rod bipolar cell is only the first of four stages that ultimately converge several thousand rods to a ganglion cell. To accomplish this huge convergence in a single step would require a much more stringent threshold, which would remove a much higher fraction of the true photon events. Thus, a repeating cycle: threshold →

sum → threshold → etc., may be a broadly useful computational strategy for the brain’s hybrid analog-digital design (Sarpeshkar, 1998).

Other brain regions also display massive convergence. About 1000 olfactory axons whose peripheral receptors detect the same odorant converge on a single glomerulus. And 100,000 parallel fibers converge on a single Purkinje neuron. In these examples, both pre- and postsynaptic neurons spike and, thus, employ their own nonlinearities. These and other central structures may solve the problem of convergent noise differently, but this paper will be broadly helpful, particularly, in emphasizing that the filtering strategy should be adjusted to the signal statistics.

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