cone opsin, Kefalov and colleagues expressed human rhodopsin and red cone opsin separately in rods and cones of transgenic *Xenopus* (Kefalov et al., 2003). In this elegant study, they demonstrated that photoreceptor desensitization and speeding of the photoresponse were properties conferred intrinsically by a cone pigment unrelated to its cellular environment. They estimated that thermal isomerization of cone visual pigments in a *Xenopus* photoreceptor was equivalent to the capture of 200 photons per second. Together, dissociation and thermal activation of the chromophore in cone pigments accounts for most if not all of the reduced sensitivity observed in cones.

What about the faster photoresponse in cones? The target molecule of the visual transduction cascade is a cyclic GMP (cGMP)-gated cation channel that is permeable to calcium ions (Figure 1). Constitutive activation of the cascade in cones due to dissociation and thermal isomerization of opsin results in depressed intracellular levels of calcium. Calcium acts through two myristoylated proteins to regulate steps in the visual transduction cascade. The first is recoverin, which inhibits rhodopsin kinase in its calcium bound state (Chen, 2002). Rhodopsin kinase phosphorylates MII, which then binds arrestin to inactivate it. Thus, when calcium is low, the activity of rhodopsin kinase is high, and the life span of MII is short. Guanylate cyclase-activating protein in its calcium bound state inhibits guanylate cyclase and therefore lowers cGMP (Palczewski et al., 2004). When calcium is low, guanylate cyclase activity is high, and the photoreceptor recovers rapidly from light stimulation. These two effects contribute significantly to the faster photoresponse observed in cones.

The work of Kefalov et al. has also raised some interesting questions. For example, the high dissociation rate of cone opsins combined with the irreversibility of rhodopsin formation underscores the tendency of rods to steal chromophore from cones. This is a potentially serious problem for cones in bright light, since rods are much more abundant than cones in most retinas, and the rates of photon capture by rods and cones are similar. Thus, saturated rods consume great quantities of chromophore under daylight conditions while contributing nothing to useful vision. Evidence for an alternate visual cycle, affording cones a private supply of chromophore precursor and thus freeing them from competition with rods, was recently published (Mata et al., 2002). However, the catalytic activities of this pathway were only observed in cone-dominant chicken and ground squirrel retinas. Given the new results from Kefalov and colleagues, it will be interesting to see if these activities can be detected in retinas that contain a preponderance of rods.

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Building Better Models of Visual Cortical Receptive Fields

Scientists usually study the receptive fields of visual cortical neurons by measuring responses to "optimal stimuli." In this issue of *Neuron*, Rust and colleagues have taken a promising alternative approach: build a receptive field model based on the cell responses to a stimulus subset and then use the model to predict responses to other stimuli.

The response properties of visual cortical neurons use to be studied with slide projectors and a creative collection of light shapes. In those "good old days," each cortical neuron was often studied for hours until the optimal stimulus was found. This was an extremely successful approach that led to the discovery of orientation selectivity—cortical cells respond to bars presented at certain orientations (Hubel and Wiesel, 2005). But unlike retinal and thalamic neurons, cortical cells were found to be very diverse in their response properties, and the combination of properties represented by each cell was too large to be searched completely.

When overwhelmed by diversity, scientists usually group things into categories. Hubel and Wiesel took this approach by coining the terms "simple cell" and "complex cell" early in the 60s. Simple cells were a small population of cortical neurons with receptive fields that resembled, in many ways, the receptive fields of thalamic inputs. Complex cells were a much larger population that included cells with very diverse nonsimple receptive fields; out of 272 cells studied in rhesus monkey, only 25 were classified as simple by Hubel and Wiesel (Hubel and Wiesel, 2005). Simple and complex cells were just two cell categories, a very small number when compared with the multiple morphological types described in primary visual cortex (Cajal, 1899). The disparity between physiology and morphology motivated an intensive search for new physiological cell types and cell classifications in the 70s and 80s, sometimes aiming to replace the original simple/complex cell terminology. The alternative cell

categories confronted a great deal of skepticism: did each category represent a cell type that correlates with morphology, layer, and input/output, or was it a mere arbitrary distinction? (See Mechler and Ringach, 2002; Priebe et al., 2004 for a recent replay of this theme.)

Most research groups kept the classification scheme of Hubel and Wiesel, but instead of using their four criteria, which was time consuming and subjective, they used a fast quantitative test based on response linearity. When cortical cells are stimulated with a sinusoidal drifting grating, the responses of most simple cells resemble a linear replica of the sinusoidal stimulus, while the responses of complex cells do not. Measurements of response linearity were fast, were bimodally distributed, and seemed to correlate well with the Hubel and Wiesel classification (Movshon et al., 1978). But the fast test was far from being perfect. Movshon et al. (1978) found that one-third of simple cells were not linear, and for some unknown reason, simple cells, as defined by this test, suddenly became easier to record from; for instance, compare the ratio of simple/complex cells in recent papers with the 25/272 ratio reported by Hubel and Wiesel (2005). Accurate or not, the test of response linearity provided an important quantitative measurement of receptive field type that could be reproduced in computational models. But there was a caveat: receptive field diversity was largely ignored.

In this issue of *Neuron*, Rust and colleagues (Rust et al., 2005) revived some of the ideas from the 70s and 80s by bringing together diversity and model. They did that by creating an individualized linear-nonlinear-Poisson (LNP) model for each cortical cell that they recorded from primate V1. Their LNP model used spatiotemporal linear filters obtained from responses to randomized flashed bars with spike-triggered average and spike-triggered covariance (de Ruyter van Steveninck and Bialek, 1988; Touryan et al., 2002). By collecting a large number of spikes, Rust et al. obtained a surprisingly diverse set of excitatory and suppressive spatiotemporal filters for each cortical neuron studied. The authors did the proper controls to demonstrate that these filters were significant and not artifacts generated by eye movements and/or the binary stimuli. The LNP model is reminiscent of the energy model (Adelson and Bergen, 1985), but it is very different in that it incorporates a much more diverse number of filters, which can be either excitatory or suppressive and are weighted independently.

Modelers love a "theory of everything" and dream of a single algorithm that can explain what appears dissimilar at first sight. Rust et al. are not different in that respect and claim that the "same" LNP model can be used to fit any type of cortical receptive field, simple or complex. This claim is certainly provocative but could be wrongly interpreted. By incorporating more spatiotemporal filters, the LNP model does a better job than previous models at predicting the responses of a cortical cell to a diverse set of stimuli (Figure 1). However, sharing a common LNP model does not mean sharing similar inputs or similar mechanisms. As the authors show in their Figure 8, their method does not allow them to draw any strong conclusion about the inputs that feed the cortical cells studied.

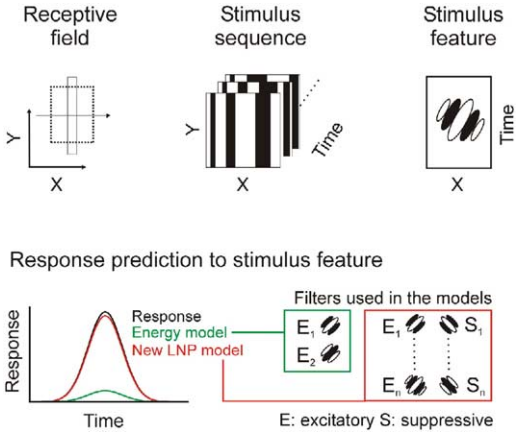

Figure 1. Stimulus and Model of a Cortical Receptive Field

(Top left and middle) Receptive field and stimulus sequence used in Rust et al.'s experiment. (Top right) Spatiotemporal stimulus presented to a V1 neuron after analyzing the neuronal responses to the flashed bars. (Bottom) Response of the V1 neuron to the spatiotemporal stimulus shown at the top right and predictions from the energy model and the new LNP model.

The results from Rust et al. are important because they demonstrate a great diversity of computations in cortical neurons and show us how much we miss when we try to fit different cortical receptive fields within the same box. The results are also important because they show that cortical receptive fields are better modeled when using both excitatory and suppressive filters, a finding that resonates well with the anatomy—a cortical cell that receives only excitatory input has yet to be discovered. Unfortunately, the approach developed by Rust et al. cannot be used to pull apart different cell types and still leave us with important unanswered questions. For example, what distinguishes the computations of cells from the different cortical layers? What is different among the computations of complex cells that receive direct geniculate input, those that receive simple cell input, and those that receive complex cell input only (Alonso and Martinez, 1998)? While studies in the retina have revealed 20 different cell types as defined by anatomy and physiology (Dacey et al., 2003), studies in the visual cortex have not been able to achieve this level of segregation yet. Perhaps the future will give us the opportunity to identify different cortical cell types by combining improved methods of receptive field analysis (Rust et al., 2005) with a new generation of tools to measure functional anatomy (e.g., Ohki et al., 2005).

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