release. Second, a predictive and detailed model is required for understanding the functional circuit level consequences of transmission dynamics. Before such a comprehensive model is possible, some additional details need to be resolved. For example, in the current model, synchronized and delayed release are assumed to share the same calcium dependence, but this assumption appears not to hold at some other synapses (Atluri and Regehr, 1999). Additional factors will also be required to explain differences in the kinetics of facilitation of synchronous and delayed release, and perhaps to explain multiple kinetic components of depression.

Lu and Trussell's results argue compellingly that inhibition is functioning in a sustained and global fashion to modify the bushy cell's response to its excitatory input. In this system, it may be important for inhibition not to be precisely timed, since the firing of the inhibitory neurons are already not tightly phase locked to auditory input. Instead, inhibition in this circuit may provide gain control that is updated on a much slower time scale than excitation. Is this more tonic mode of inhibitory transmission unique to brainstem auditory nuclei? Recent work on the functional role of inhibition in cortical and hippocampal circuits has tended to emphasize the importance of precisely timed inhibition for pacing oscillatory firing in pyramidal neurons (Cobb et al., 1995; Thomson et al., 1996). However, trains of stimuli at these synapses also produce inhibitory plateaus, and these can decay more slowly than individual responses (Thomson et al., 1996; Varela et al., 1999), although other potential mechanisms for this have not yet been ruled out. PTP and enhanced asynchronous release following trains are prominent at GABAergic synapses in hippocampal cultures (Jensen et al., 1999). Asynchronous release may also play a larger role than previously appreciated at excitatory synapses driving inhibitory neurons in some systems. For example, Atluri and Regehr (1999) estimated that at synapses made by cerebellar granule cells onto inhibitory stellate neurons, a train of only three action potentials can evoke delayed release that exceeds that released synchronously. In each of these examples, high levels of activity within the circuit tend to recruit high levels of desynchronized inhibition. Lu and Trussell suggest that asynchrony may be important for "smoothing" the inhibitory current by spreading quanta more evenly in time. The recent finding that classes of functionally related interneurons in the neocortex are coupled into networks via gap junctions also suggests that inhibition can function in a more global and coordinated fashion (Galarreta and Hestrin, 1999; Gibson et al., 1999). Such connections could serve to distribute inhibition spatially, much as asynchronous release appears to distribute it temporally. In each of these circuits, inhibition is almost certainly serving multiple roles. While some of these roles require focal and precisely timed release, others may be best served by releasing quanta in a more graded and distributed fashion. Testing this hypothesis will be difficult, since it may require independently manipulating synchronous and asynchronous release in a preparation intact enough to perform at least part of its normal function. Lu and Trussell have taken a major step in that direction. Their results suggest a novel view of central inhibitory circuits in which asynchronous release is not merely an oddity or afterthought of transmission, but a crucial means by which inhibitory signals are evenly distributed in time.

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Selected Reading

Atluri, P.P., and Regehr, W.G. (1998). J. Neurosci. *18*, 8214–8227.

Cobb, S.R., Buhl, E.H., Halasy, K., Paulsen, O., and Somogyi, P. (1995). Nature *378*, 75–78.

Del Castillo, J., and Katz, B. (1954). J. Physiol. *124*, 574–585.

Dittman, J.S., Kreitzer, A.C., and Regehr, W.G. (2000). J. Neurosci. *20*, 1374–1385.

Galarreta, M., and Hestrin, S. (1999). Nature *402*, 72–75.

Gibson, J.R., Beierlein, M., and Connors, B.W. (1999). Nature *402*, 75–79.

Goda, Y., and Stevens, C.F. (1994). Proc. Natl. Acad. Sci. USA *91*, 12942–12946.

Lu, T., and Trussell, L.O. (2000). Neuron *26*, this issue, 683–694.

Oertel, D. (1999). Annu. Rev. Physiol. *61*, 497–519.

Thomson, A.M., West, D.C., Hahn, J., and Deuchars, J. (1996). J. Physiol. *486*, 81–102.

Trussell, L.O. (1999). Annu. Rev. Physiol. *61*, 477–496.

Varela, J.A., Song, S., Turrigiano, G.G., and Nelson, S.B. (1999). J. Neurosci. *19*, 4293–4304.

An Optimal Preparation for Studying Optimization

Imagine a fly navigating through a forest at 2 m/s. In order to correct for the effects of the wind and other flight instabilities, the fly must continually estimate its heading direction if only to avoid running into a tree or inadvertently flying in circles. Given the striking prominence of eyes on a fly's body, it is not surprising that vision plays a key role in many of its behaviors, including flight (Egelhaaf and Borst, 1993). In fact, when a fly is suspended from a wire inside a rotating drum so that the visual scene in front of the fly moves to the right, the fly uses its wings to turn its body to the right, presumably to try to maintain what it perceives as its current heading direction (Reichardt and Poggio, 1976). However, flies do not exhibit this behavior following lesions to subsets of the 50 or so identified neurons in the lobular plate that respond to wide-field visual motion (Hausen and Wehrhahn, 1983). The fact that these neurons are involved in stabilizing heading direction, which is critical for chasing potential mating partners and avoiding obstacles, suggests that there has probably been strong evolutionary pressure on their performance. One of these neurons, H1, is particularly accessible experimentally, allowing stable extracellular recordings for hours and even days.

In a series of papers over the past decade, de Ruyter van Steveninck, Bialek, and colleagues have exploited the accessibility of H1 and the constraints from fly behavior to address a number of general questions in neural coding and computation. This work combines experiment, theory, and new methods of data analysis to quantify the performance of the fly's visual system. Rather than addressing the cellular mechanisms that underlie the neuron's behavior, their approach has been to address questions with a teleological flavor. What problem is the fly trying to solve? How good is the system at solving this problem? What aspects of the system's response are essential for this performance?

Central to this work is the design of stimuli that capture the important features of the natural situation confronting the fly during flight. This is crucial for three basic reasons. First, neurons adapt to their inputs. For example, it is well known that visual neurons adapt to the mean luminance, to the luminance contrast, and to the mean velocity of visual motion. Second, neural responses often are nonlinear. Therefore, one cannot completely characterize a neuron by cataloging its responses to a limited set of stimuli, such as moving gratings of different spatial and temporal frequencies, even if the experimenter can convincingly rule out adaptation effects. Third, there is evidence from H1 (de Ruyter van Steveninck et al., 1997), as well as from other systems (Mainen and Sejnowski, 1995; Berry et al., 1997), that the reliability of the neural response is different for static and for dynamic or naturalistic stimuli: neurons that seem very noisy when stimulated with the traditional neurophysiologist's toolbox may be much more reliable in their responses to more complex stimuli. Thus, if we want to understand how the brain deals with more natural stimuli, we cannot expect to generalize from experiments with much simpler inputs.

The response of H1 to complex, dynamic inputs exhibits some remarkable features. The spike train of H1 actually can be decoded to reconstruct an estimate of a time varying velocity signal (Reike et al., 1997). Further, this estimate is so precise that it is almost as accurate as possible, given that the fly looks out at the world through optics with finite resolution and that the signals in the photoreceptor cells of the retina are noisy. This photoreceptor noise in turn comes largely from the random arrival of photons, even at relatively high light levels. On time scales of relevance to fly behavior, the precision of the reconstructions corresponds to motions that are a small fraction of the spacing between receptors on the retina. This "hyperacuity" is confirmed in more direct experiments using the pattern of action potentials from H1 to discriminate between motion steps of different sizes. This is a clear example where the performance of the neuron closely approaches the limits imposed by the physics of the visual inputs.

We can also ask how efficiently the outputs of neural computation are represented in the spike trains. To answer this, it is useful to examine the amount of "information" in the spike train. Information, in this context, is a statistical measure of stimulus-evoked responses that quantifies both the reliability of responses to specific stimuli as well as the richness of the space of stimuli encoded by the neuron (Rieke et al., 1999). Strong et al. (1998) developed a practical method for directly measuring information transmission in spiking neurons that does not require assumptions about which aspects of the stimulus are important to the neuron or which aspects of the neural response are most informative. In this way, direct methods for measuring information can help remove experimenter bias. Using this technique, de Ruyter van Steveninck et al. (1997) found that H1 transmits information at surprisingly high rates, within a factor of two of the limit set by the variability (or "entropy") of the neuron's responses.

How is the near optimal performance of H1 achieved? There are a number of reasons to think that adaptation is a crucial part of the answer. As the fly moves through the world, wind-induced fluctuations in its heading direction result in random wide-field horizontal motion of the visual world, which is the motion signal of relevance for H1. This motion signal can be obscured by several sources of "noise" that are present even when the fly follows a perfectly straight trajectory. For example, the apparent size, velocity, and angle of view of each nearby object changes as the fly moves relative to it. In addition, some objects may themselves be moving. All of this spurious local motion in the visual scene can be confounded with the wide-field rigid motion the fly is trying to detect. The signal is further degraded by noise at the photoreceptors, particularly when the visual stimulus has low luminance contrast. Potters and Bialek (1994) took great pains to design stimuli that were analytically tractable yet complex enough to model these sources of real-world noise. This points out another benefit of this preparation: because it is clear from the outset what aspect of the visual stimulus is the relevant signal for H1, several sources of noise relevant to this signal can be manipulated by the experimenter at the level of the stimulus, which is very useful for studying optimality.

In a theoretical tour de force, Potters and Bialek (1994) calculated the optimal strategy for estimating the rigid motion signal in this model environment. Their analysis was quite involved, but it was justified because it produced a qualitatively new understanding of a well-studied biological system. For many years prior to this work, there were two schools of thought that debated whether visual systems—from insects to humans—computed visual motion by correlating responses from pairs of neighboring photoreceptors (the Reichardt model) or by a more elaborate method that integrates the responses from many photoreceptors for extended periods of time (for example, see Hildreth and Koch, 1987). There were data to support each group's claims, yet these algorithms were perceived as being fundamentally different. Potters and Bialek showed that despite the apparent differences, each scheme was actually a limiting case of the globally optimal estimation method—Reichardt's corresponds to the optimal strategy when the wide-field motion signal is small compared to the various sources of noise, which can happen when the fly enters a shady part of the forest, while the second method is optimal when the motion signal is strong. A crucial point is that the "signal-to-noise" ratio is a statistical concept, and hence the optimal motion estimator would adapt its strategy to the statistical structure of its visual environment. Some aspects of this predicted "statistical adaptation" have been demonstrated in H1 (de Ruyter van

Steveninck et al., 1994), but many open questions remain.

In this issue of *Neuron*, Brenner et al. (Brenner et al., 2000) go a step further and demonstrate that H1 is optimal in a concrete way. They start by deriving a new analytical tool which builds on the more common approach of computing the average stimulus preceding a spike. Under some circumstances, this spike-triggered average stimulus can be thought of as the feature in the stimulus that drives the neuron to fire and can be a meaningful way to characterize a neuron's responses. However, by studying the full distribution of stimuli preceding a spike rather than just the average of this distribution, the authors show that quickly varying dynamic stimuli have a more subtle effect on H1, so that there are essentially two relevant functions of the stimulus (roughly, the velocity and acceleration of the motion signal) that affect the firing of the neuron. In this approach, the number of parameters, as well as their relation to the stimulus, are determined by the structure of the data. Having found this simplified parameterization, it is possible to fully characterize the nonlinear input/output relation of the neuron.

Next, Brenner et al. show that H1 adapts to the variance of the velocity distribution of the motion signal, as it must do when the fly switches from straight flight to chasing behavior, for example. It is important to remember that this is an adaptation to the statistics of an ensemble of stimuli rather than to a particular stimulus or stimulus feature. They emphasize that all measurable higher order statistics of the spike train adapt, not just the firing rate. Yet, they find that the adaptation can be fully described in terms of a single parameter, the "stretch factor," which determines how the neuron matches its limited dynamic range of spike rates to the dynamic range or variance of its inputs. By computing the information rate in a model neuron set to different values of the stretch factor for the same stimulus ensemble, they prove their main result: H1 adapts to changes in the dynamic range or variance of the motion signal so as to maximize the rate of information of its output. Once again, constructing the appropriate stimuli and introducing new methods of analysis reveal optimal design principles necessitated by evolutionary pressure.

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Selected Reading

Berry, M., and Meister, M. (1997). Proc. Natl. Acad. Sci. USA *94*, 5411–5416.

Brenner, N., Bialek, W., and de Ruyter van Steveninck, R.R. (2000). Neuron *26*, this issue, 695–702.

de Ruyter van Steveninck, R.R., Bialek, W., Potters, M., and Carlson, R.H. (1994). In The IEEE International Conference on Systems, Man, and Cybernetics, 302–307.

de Ruyter van Steveninck, R.R., Lewen, G.D., Strong, S.P., Koberle, R., and Bialek, W. (1997). Science *275*, 1805–1808.

Egelhaaf, M., and Borst, A. (1993). J. Neurosci. *13*, 4563–4574.

Hausen, K., and Wehrhahn, C. (1983). Proc. R. Soc. Lond. B Biol. Sci. *21*, 211–216.

Hildreth, E.C., and Koch, C. (1987). Annu. Rev. Neurosci. *10*, 477–533.

Mainen, Z.F., Sejnowski, T.J. (1995). Science *268*, 1503–1506.

Potters, M., and Bialek, W. (1994). J. Phys. I France *4*, 1755–1775.

Reichardt, W., and Poggio, T. (1976). Quart. Rev. Biophys. *9*, 311–375.

Rieke, F., Warland, D., de Ruyter van Steveninck, R.R., and Bialek, W. (1997). Spikes (Cambridge, MA: MIT Press).

Strong, S.P., Koberle, R., de Ruyter Van Steveninck, R.R., and Bialek, W. (1998). Phys. Rev. Lett. *80*, 197–200.

Attending to Contrast

Studies of the neural mechanisms underlying attention build on the foundation of classical studies of the primate visual system that have focused on understanding how visual images are transduced, encoded, and analyzed by the brain. In most of these classical studies, anesthetized animals were presented with visual stimuli while physiologists recorded the activity of neurons carrying information from the retina to the lateral geniculate nucleus of the thalamus and then on to the hierarchically organized visual cortices. As Hubel and Wiesel (1959) were among the first to demonstrate, the sensitivity of each neuron in the visual cortex to patterns of light and dark can be described by a *receptive field*, which is the pattern of light and dark that maximally excites the cell. In a typical cell in cortical area V1, for example, the receptive field might be described as two vertically oriented dark regions flanking a vertically oriented light region: a vertical band of light flanked by darkness falls on a particular retinal location and maximally activates the cell. Perhaps the most interesting property of such a cell is that uniform illumination of the receptive field gives rise to no neuronal activity; it is the strength of the contrast between the light and dark regions that the cell encodes. For this reason a horizontally, as opposed to vertically, aligned bar of light fails to activate this cell because it does not present a light/dark contrast along the vertical axis. Of course, the receptive fields of cells in visual cortical areas vary in their responsiveness to the orientation, width (the spatial frequency of the light and dark bands), wavelength, and even the speed and direction of stimuli, but nearly all cells share this fundamental sensitivity to contrast.

Psychological studies have demonstrated that attending to a location improves our ability to detect or discriminate visual stimuli at that location (Sperling and Dosher, 1986; Kinchla, 1992; Lu and Dosher, 1998; Carrasco et al., 2000), and it seems only natural to ask how the neural architecture described by classic studies might accomplish this improvement. This question became experimentally tractable in the 1970s when it became possible to study the activity of neurons in the visual cortices of awake animals trained to attend to particular locations. Over the past 15 years this area of research has made significant progress, and two competing hypotheses have evolved to explain the neural