input from light signals, some third-order interneurons (e.g., DN, see Figure) also receive input from wind-sensitive hairs, and this information, like that obtained from visual cues, is transmitted to motor neurons in the head, wing, and rudder-like hind legs. The reciprocal L1-3 inhibitory input is well tuned for transmitting rapid changes in signaling, such as perhaps a transient change in light level or contrast in the visual scene. The excitatory input, which has, on the other hand, been shown to transmit continuously a tonic signal (Simmons, 2002b), would perhaps be more responsive to the ambient light level. Therefore, the ocellus visual system seems poised to become an excellent model system in which to study the processing of visual information, the integration of signals from different sensory modalities, and how this ultimately determines or fine tunes motor neuron output in a well defined behavior: flight.

Mary J. Palmer and Henrique von Gersdorff
The Vollum Institute
Oregon Health and Science University
3181 SW Sam Jackson Park Road
Portland, Oregon 97201

Selected Reading

Eliasof, S., and Jahr, C.E. (1997). Vis. Neurosci. *14*, 13–18.

Ferragamo, M.J., and Oertel, D. (2002). J. Neurophysiol. *87*, 2262–2270.

Leitinger, G., and Simmons, P.J. (2000). J. Comp. Neurol. *416*, 345–355.

Leitinger, G., and Simmons, P.J. (2002). J. Neurobiol. *50*, 93–105.

Lin, J.-W., and Faber, D.S. (2002). Trends Neurosci. *25*, in press.

Ohnuma, K., Whim, M.D., Fetter, R.D., Kaczmarek, L.K., and Zucker, R.S. (2001). J. Physiol. *535*, 647–662.

Simmons, P.J. (2002a). Neuron *35*, this issue, 749–758.

Simmons, P.J. (2002b). Microsc. Res. Tech. *56*, 270–280.

A New Mechanism for Neuronal Gain Control (or How the Gain in Brains Has Mainly Been Explained)

One of the more prosaic but necessary features of almost any information processing system is gain control. All such systems must have some way to adjust the relationship between input, which can vary dramatically depending on changes in the environment, and output, which is almost always required to remain within a limited range of amplitudes. While the volume control on a radio or the brightness control on a computer monitor are not the most exciting or highly touted features, imagine such devices without these forms of gain control. Many an engineer can attest to the large effort required to design automatic gain controls in telephones, cameras, and radio transmitters.

The brain is no different in its need for gain control. In the visual system, for example, it seems to occur at every stage. When adjusting between a sunny day and a moonless night, the retina changes the relationship between light level and neuronal output by a factor of more than 10^6, so that the signals sent to later stages of the visual system always remain within a much narrower range of amplitudes. In the visual cortex, which responds not to luminance but to local luminance contrast, neurons constantly adjust their contrast sensitivity according to the mean level of contrast present in the visual environment. Prolonged viewing of an Ansel Adams photograph, for example, often leads to changes in perception as the visual system gradually adapts to low or high contrast portions of the image, allowing subtle shadings to emerge.

The trigger for changes in gain need not always be external. Internally generated changes in attention seem to act through a gain control mechanism as well. For example, neurons in areas V4 and MT are tuned for the orientation or direction of visual stimuli, but the amplitude of their response depends on whether or not the animal is attending to the stimulus (McAdams and Maunsell, 1999; Treue and Martínez-Trujillo, 1999). Similar changes in neural response that can be well described by scaling have been observed throughout sensory and motor cortex (for review, see Salinas and Thier, 2000), so gain control seems to be as important for the brain as it is for man-made machines.

Unlike machines, however, the mechanisms underlying neuronal gain control have not been as readily apparent. One popular mechanistic explanation for gain control has been shunting inhibition. Shunting inhibition refers to a synaptically activated conductance with a reversal potential at or near the resting potential of a neuron. On its own, this conductance does not cause a significant change in membrane potential. But if the conductance of the synaptically activated channels is large enough, activating the shunting synapse will cause a significant decrease in the overall input resistance of the cell, which will in turn lead to an attenuation of the potential changes evoked by excitatory inputs. The attractive feature of shunting in the present context is that all EPSPs are scaled by the same amount (in proportion to the decrease in the input resistance of the cell), exactly what is required for a multiplicative gain control. Unfortunately, the effects of shunting are not quite so simple. Holt and Koch (1997) have pointed out in a theoretical study that accompanying the reduction, in input resistance is a reduction in time constant. The consequent reduction in the integration time of the neuron will have an independent effect on the relationship between membrane potential and firing rate. And as a result, the effect of shunting on the relationship between input (depolarization) and output (spike rate) is no longer (or more correctly, never was) a pure scaling.

In the present issue of *Neuron*, Chance, Abbott, and Reyes make a convincing experimental demonstration of the failure of shunting inhibition to account for gain control. But they then go on to describe and test a novel neural mechanism to account for this important function. They propose that a combined, noisy barrage of balanced inhibition and excitation, rather than simply a steady shunting input, can lead to a pure change in neuronal gain.

The input-output curves of the Figure illustrate the

A Shunt Only   **B** Noise Only   **C** Shunt and Noise

Firing Rate (spks/s)

Current   Current   Current
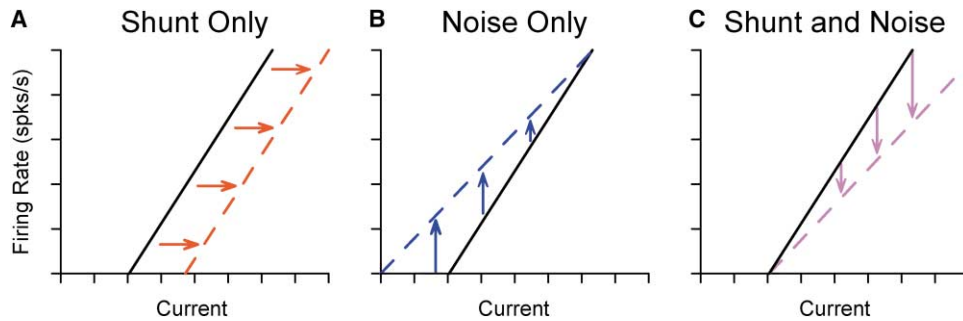
The Effects of Background Noise on the Input/Output Transformation of Cortical Neurons

essence of the authors' results. The input in this case was a steady injected current of different amplitudes, applied to layer 5 pyramidal neurons from slices of rat somatosensory cortex. The output was the mean firing rate of the neuron recorded during the current injection. The solid curve in the Figure (panel A) shows the typical threshold-linear input-output curve of a cortical cell. To test the effects of shunting inhibition, the authors then needed to simulate experimentally the conductance change underlying a shunting inhibitory input. This they did with a 2-electrode dynamic current clamp, in which a computer and analog multiplier circuit are used together to calculate in real time what current would flow through the currently active simulated synapses. The current depends not only on the specified conductance and reversal potential of each synapse, but on the instantaneous value of the membrane potential, which is recorded from one of the two electrodes. The calculated synaptic current is then injected into the cell through the second electrode. By using 2 electrodes rather than the now more commonly used single electrode voltage clamp, the authors avoid potentially serious errors in recorded potential that can arise from current being injected through the uncompensated electrode series resistance.

The effects of a pure shunting inhibition are shown in the dashed curve of the Figure, panel A. As predicted by Holt and Koch, the shunt does not simply scale the input-output curve, but instead shifts it to the right because of the effects of simultaneous decreases in input resistance and time constant. Chance et al. then studied the effect of a noisy background synaptic current on the spiking of neurons induced by the steady injected test current. The background synaptic current was composed of both excitatory and inhibitory inputs, placed in a balanced state in order not to cause a change in the average membrane potential of the neuron. At the same time, the noise input was adjusted to change one or both of two important parameters: the variance of the membrane potential around the average level and the overall conductance of the neuron. The authors found that when both of these parameters (noise and conductance) were increased, the response of the neuron to the injection of the steady test current decreased by a constant scaling factor, consistent with a gain change, not a subtractive change (Figure, panel C).

What is responsible for the observed change in gain? Using the dynamic clamp system to mimic synaptic in-

puts, Chance et al. were able to dissect the role of conductance changes from the role of noise (Sharp et al., 1993). Increasing the net conductance of the neuron alone caused a subtractive shift in the firing rate of the cell (Figure, panel A). Conversely, when noise was injected without the corresponding change in conductance, the response amplitude increased, but the increase in firing varied with the level of "signal" input, yielding larger increases at lower levels of signal input (Figure, panel B). When the two effects—increased conductance and increased noise—are introduced together, however, the shift in the response curve caused by the conductance and the differential gain change caused by the noise together yield a relatively pure decrease in the overall gain of the neuron across all signal amplitudes (Figure, panel C). And the larger the noise, the larger the decrease in gain. Given that both stimulus-evoked increases in synaptic noise and shunting inhibition (Anderson et al., 2001; Borg-Graham et al., 1998) are commonly observed phenomena in the brain, Chance et al.'s proposal represents an eminently plausible mechanism for generating changes in gain.

The authors' model (Chance et al., 2002) is not the first to turn attention toward the benefits of background synaptic noise for neuronal function. Shadlen and Newsome have suggested that a balance of noisy excitation and inhibition is required to keep the level of noise constant as signals progress from one area of the brain to the next (Shadlen and Newsome, 1998). It has been suggested that stochastic resonance can increase the sensitivity of sensory receptors (Bulsara et al., 1991; Wiesenfeld and Moss, 1995). And in our lab, we have shown that synaptic noise when uncorrelated with the stimulus can help to maintain the precise orientation tuning of visual neurons in the face of varying levels of visual contrast (a form of smoothing by noise, or dithering) (Anderson et al., 2000). Thus, the silver lining of noisy background synaptic input appears to be that it helps to maintain and scale the tuning of neurons under a range of environmental conditions.

The authors lay out an elegant theoretical background for the problems associated with changing the gain of neuronal responses, providing a textbook example of how theoretical and experimental neuroscience can work hand in hand. And as is often the case in groundbreaking research, the number of questions that arise is greater than the number answered. In the physiological and modeling data presented in Chance et al., the

balance between excitation and inhibition was precisely controlled. Is it the case that such control exists in cortical neurons? It appears to be very important to the model that the relationship between the shunting conductance and the input variability is precisely tuned to elicit true gain changes across varying input strengths. It remains to be shown that such a precise relationship exists in vivo. In addition, fast ionotropic receptors are used as the gain control input, a role traditionally set aside for the slower neuromodulators. Although neuromodulators might profoundly affect the conductance of the neurons, they would probably not elicit the required voltage variance necessary for gain change. Finally, is the distinction between modulatory background noise input and signal input appropriate? As the authors admit, this distinction probably does not really exist. If not, what is the relationship between those inputs that set the gain and those that signal for a given stimulus configuration? So there is much to explore, and it seems likely that Chance et al.'s work will trigger significant new interest in this old problem.

Nicholas J. Priebe and David Ferster
Department of Neurobiology and Physiology
Northwestern University
Evanston, Illinois 60202

Selected Reading

Anderson, J.S., Lampl, I., Gillespie, D.C., and Ferster, D. (2000). Science *290*, 1968–1972.

Anderson, J.S., Lampl, I., Gillespie, D.C., and Ferster, D. (2001). J. Neurosci. *21*, 2104–2112.

Borg-Graham, L.J., Monier, C., and Fregnac, Y. (1998). Nature *393*, 369–373.

Bulsara, A., Jacobs, E.W., Zhou, T., Moss, F., and Kiss, L. (1991). J. Theor. Biol. *152*, 531–555.

Chance, F.S., Abbott, L.F., and Reyes, A.D. (2002). Neuron *35*, 773–782.

Holt, G.R., and Koch, C. (1997). Neural Comput. *9*, 1001–1013.

McAdams, C.J., and Maunsell, J.H.R. (1999). J. Neurosci. *19*, 431–441.

Salinas, E., and Thier, P. (2000). Neuron *27*, 15–21.

Shadlen, M.N., and Newsome, W.T. (1998). J. Neurosci. *18*, 3870–3896.

Sharp, A.A., O'Neil, M.B., Abbott, L.F., and Marder, E. (1993). Trends Neurosci. *16*, 389–394.

Treue, S., and Martínez-Trujillo, J.C. (1999). Nature *399*, 575–579.

Wiesenfeld, K., and Moss, F. (1995). Nature *373*, 33–36.