coupling between synapses and the spike-initiating zone in the region near the cell body (*7*). Hebb, who postulated such a coincidence-based learning mechanism to explain associative learning, would have been pleased by these discoveries, although perhaps not surprised (*8*).

In the second report, a technical tour de force, Markram *et al.* (*4*) recorded from neighboring pyramidal neurons in layer 5 of neocortical slices and varied the timing of the spikes in the presynaptic and postsynaptic cells. When the presynaptic action potential preceded the postsynaptic action potential, the synaptic response increased, but if the order was reversed, the synaptic response decreased. The window for synaptic plasticity was around 100 ms wide, and a difference in spike timing of 10 ms near coincidence switched the plasticity from LTP to LTD. The discovery that dendrites can transmit information about spike timing and that differences in spike timing of a few milliseconds are crucial for synaptic plasticity raises the stakes in the debate as to whether the precise timing of action potentials is important in cortical processing (*9*).

These remarkable results must now be put into the context of normal information processing in the cortex, which is characterized by a constant chatter of ongoing spike activity. Every spike in a pyramidal cell could potentially affect every excitatory synapse of that cell that was active within 100 ms. Even if the mean synaptic strength were not changed by a particular spike, the random walk would wash away any information stored at the synapse. There are, however, reasons to believe that synaptic plasticity is strictly regulated in vivo. First, backpropagation of an action potential in the dendrite can be throttled by input from inhibitory neurons (*10*, *11*), suggesting that there may be local control of the invasion of backpropagating action potentials into dendritic branches. Second, the delivery of neuromodulators such as acetylcholine and dopamine, which depends on the behavioral and cognitive state of an animal, could affect the induction of synaptic plasticity (*12*, *13*).

The most direct evidence for the regulation of backpropagating dendritic action potentials comes from a new technique that promises to revolutionize cortical physiology. Svoboda *et al.* (*14*) have recently shown that cortical neurons can be visualized in vivo by means of two-photon laser-scanning microscopy, which allows the full three-dimensional dendritic tree of a neuron to be scanned and reconstructed. Spines on the dendrites of cortical pyramidal neurons can be visualized (see figure). After injection of a calcium indicator dye, these authors observed dendritic calcium entry during sodium spikes recorded from the cell body. Under the conditions that they studied, however, these responses declined steeply and disappeared in the distal apical dendrite, suggesting failure of the back-propagating spikes. In addition, widespread calcium influx expected for dendritic calcium action potentials was not observed in response to sensory stimulation. This result suggests that calcium influx triggering synaptic plasticity may only occur in vivo under special conditions that have yet to be determined.

Dendrites have additional levels of complexity that we are just beginning to understand (*1*, *15*). Many types of voltage-dependent ion channels are distributed nonuniformly throughout neurons, with a wide range of time courses for activation and inactivation (*2*, *16*). A cortical neuron is, therefore, like a city with diverse neighborhoods, each with a different character, with constant traffic between them. Compartmental models of reconstructed neurons that incorporate detailed biophysical properties of ion channels provide a way to explore the dynamic properties that emerge from the nonlinear interactions between different parts of the neuron (*17*).

More has been learned about the secret lives of dendrites in the last year than in all previous years. At the recent Annual Meeting of the Society for Neuroscience, there was a collective sense that new techniques for studying cortical neurons are ushering in an exciting era that will lead to many more surprises.

An enhanced version of this Perspective, with live links, can be seen in *Science* Online on the Web at http://www.sciencemag.org/

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NEUROSCIENCE

More Than Just Frequency Detectors?

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Synapses, the junctions through which neurons communicate with each other, can display frequency and pattern-dependent behavior—no surprise to those familiar with the work of Katz *et al.* (*1*) in the 1950s and 1960s on the neuromuscular junction. Now two recent studies (*2*, *3*), one on page 221 of this issue, present a simplified mathematical model of the frequency-dependent behavior of one class of synapse to predict the outcome of changes in the activity of many similar inputs impinging on a single target neuron. This is a welcome refinement of more traditional models, in which inputs were simply assigned a static efficacy, regardless of their pattern of activity.

The experimental observation underlying these studies is that the connection from one cortical pyramidal cell to another exhibits frequency-dependent depression (*4*); that is, a second action potential elicits a smaller response than the first, the third a smaller response than the second, and so on until a plateau or steady-state output is reached (*5*) (see figure, P3→P2 and P1→P2). The faster the rate at which the presynaptic neuron fires, the more rapidly and powerfully does the connection depress, so that over a large range of rates, the summed potential elicited at steady state is the same (P3→P2). These properties determine that the connections transfer little information about steady-state frequency. Whether a hundred inputs fire steadily at a low or high average rate makes little difference to the response. Connections like these would be sensitive, however, to significant proportional changes in frequency of individual inputs (as in P1→P2) or to simultaneous changes in many inputs. Such depressing synapses, therefore, en-

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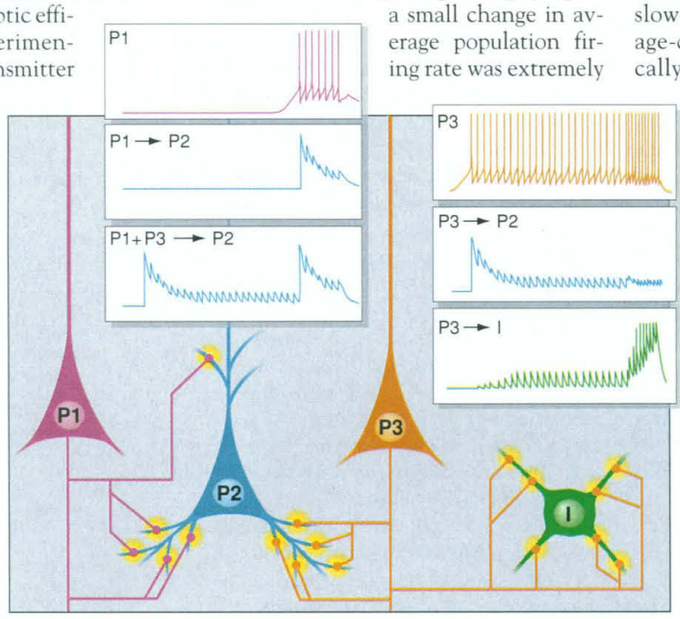
code dynamic, rather than static, information and could act as coincidence detectors (6).

With the more detailed electrophysiological data available to them (5), Markram and Tsodyks discuss this dynamic behavior in relation to changes in synaptic efficacy. By manipulating experimentally the probability that transmitter will be released by a single action potential, they test the hypothesis that each connection has a given maximum output, determined by the number of release sites at that connection, and that after release there is inactivation of release sites. It follows that during recovery from inactivation, only the proportion of the maximum that either has not yet been used or that has already recovered from inactivation will be available for the next response. The higher the probability that the first action potential will release transmitter, the larger the proportion of the maximum output that will have been used, and the more powerfully the connection will depress. The more rapidly the presynaptic neuron fires in relation to the time constant for recovery from inactivation, the more powerfully and rapidly the connection depresses. Using a novel protocol for inducing lasting synaptic enhancement (akin to long-term potentiation), Markram and Tsodyks show that an increase in the probability of transmitter release increases the low-frequency response, but because the rate of depression also increases, the steady-state response to higher frequencies is unchanged (similar to P3→P2). Potentiating the synapses does not alter the model neuron's response even to many inputs at steady state, but it does change the temporal coding of inputs. This does not even require a change in mean input frequency, provided only that some of the previously low-frequency inputs increase their rate [see also (2, 3)].

The model proposed by Abbott *et al.* (2) predicts a similar outcome by comparing inputs that display strong frequency-dependent depression with those that display none. A single model cell's responses to oscillatory changes in firing frequency of two groups of 100 synapses—one firing at a high and the other at a low mean rate—were computed. At nondepressing synapses, the postsynaptic response was modulated only by large absolute changes in input firing rates. Modulating the low-frequency input had little effect. However, at depressing synapses a small change in average population firing rate was extremely effective provided it occurred at previously low-frequency inputs. The same absolute modulation of rate at the high-frequency inputs was not detected.



Model predictions. Artist's impression of the average postsynaptic responses resulting from trains of action potentials in pyramidal cell 1 (P1) and pyramidal cell 3 (P3) in two target cells, pyramidal cell 2 (P2) and I, given the predictions from (*2, 3*). P2 receives two strongly depressing inputs, from P1 and P3. Once P3 has been firing repetitively for some time, an increase in its firing rate alone produces little additional input to P2. P1 has been silent for some time, has recovered from inactivation, and generates a significant response in P2 when it starts to fire. If both of these spike discharges occurred together, P2 would respond phasically when P3 starts to fire and again when P1 begins. The predicted response at a pyramid-to-interneuron connection (P3→I) is also shown, at which an increase in frequency increases input. Regular spike trains are shown for simplicity, but are not typical of many pyramidal cells (*2, 3, 5*).

The extent to which these simple mathematical models of synaptic depression predict the real cell's responses to many inputs remains to be determined experimentally. Synaptic depression can be modeled as a single mechanism with an exponential decay [τ_{Decay} = 0.3 s (*2*) or 1 s (*3*)], but it should be remembered that the refractoriness of synapses proposed to dominate the first phase of depression (*4, 7*) may decay much more rapidly (τ < 50 ms), and that other contributory factors with slower kinetics (such as postsynaptic receptor desensitization and exhaustion of readily releasable transmitter pools) dominate at lower frequencies. If these mechanisms can also be modulated independently, future models (*2*) will need additional components.

In addition, both of the new studies use a simple, single-compartment postsynaptic cell model. Real pyramidal cells have complex dendritic trees, with some inputs arising close to the cell body and generating relatively large and fast events there. Others arising more distally are degraded and slowed in their transfer. Moreover, voltage-dependent events that can dramatically alter the shape and amplitude of synaptic potentials can be elicited in the dendrites. It is therefore impressive how closely the model proposed by Tsodyks reproduces the effects of single inputs in Markram's data, although these effects largely involved relatively proximal inputs distributed among separate dendritic branches (*8*), limiting nonlinear interactions between sites. A more complex picture may emerge when many inputs are activated throughout the dendritic tree. It is even possible that the complexities of pyramidal cells will be found to enhance their dynamic sensitivity to particular spatiotemporal patterns of inputs.

Is information about firing rate completely lost within the circuit? Perhaps not; some pyramid-to-interneuron connections (*9*) exhibit very low probabilities of release and code instantaneous frequency effectively because they display dramatic frequency-dependent facilitation (P3→I) (*10, 11*).

Several technical advances have been responsible for this new and exciting phase in our understanding of circuitry: paired intracellular recordings in vitro, multi-unit recordings in vivo, and models of circuits containing thousands of neurons that generate specific questions that can then be tackled experimentally.

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