Synapses get smarter
Terrence J. Sejnowski

The cerebral cortex has long been known to be important for learning and memory, but because of its daunting anatomical complexity it has not been studied as well as the hippocampus, an older and simpler structure. Techniques have improved and it is now possible to pick a pair of cells in a neocortical slice, record from them with whole-cell patch recording, and induce long-term potentiation (LTP) at the synaptic contacts between those cells with Hebbian pairing of presynaptic and postsynaptic action potentials. On page 807 of this issue, Markram and Tsodyks report that LTP strengthens the response to the first stimulus in a train of stimuli, as expected from hippocampal studies, but can also reduce synaptic responses to subsequent stimuli. This shows that synaptic activity at a cortical excitatory synapse cannot be adequately described by a single number like the strength or 'weight' that is often used in models of neural networks, nor can the effect of LTP be simply described as a strengthening of the synaptic weight. This observation has important consequences for the computational power of synapses in neural networks and the biophysical basis of synaptic plasticity. Synapses may be smarter than we had imagined.

Synaptic strengths are constantly being adjusted from moment to moment. In response to a pair of closely spaced stimuli, the response to the second could get larger or smaller than the first depending on the synapse and its previous history. Short-term facilitation and short-term depression to a train of stimuli occur on time scales ranging from tens of milliseconds to many seconds. A decade ago, Karl Magleby concluded a review on synaptic plasticity with the prediction that "In addition to long-term changes in synaptic efficacy, which can be assessed with single test pulses, there may be other, more dynamic, long-term changes that can only be detected with patterned stimulation". Markram and Tsodyks have now examined long-term changes in short-term synaptic dynamics in neocortical slices and report that the rapidity of short-term depression is substantially and persistently enhanced following LTP.

Although it is possible to develop a phenomenological description of the rates at which short-term synaptic facilitation and depression occur, we ultimately need to understand the subcellular mechanisms that are involved in synaptic plasticity. A cascade of intracellular events is triggered when calcium enters the presynaptic terminal following an action potential (see figure). There is a readily available pool of vesicles that can be mobilized within milliseconds. Short-term depression at peripheral synapses can result from a reduced number of vesicles in the readily releasable pool. The events leading to transmitter release and vesicle recycling can be modelled by kinetic equations, and the rate constants in these equations may be subject to long-term modification. The apparent change in the rate of the short-term depression could result from an increase in the probability of release and subsequent decrease in the population of readily releasable vesicles. These mechanisms make synapses dynamical systems in their own right.

The effects of short-term synaptic dynamics can be counterintuitive. For instance, the steady-state response of a postsynaptic cell to a train of stimuli is independent of firing rate above around 20 Hz (refs 2, 4). This occurs because short-term depression is inversely related to the firing rate, which cancels the term that is proportional to the firing rate. One consequence is that the postsynaptic neuron becomes more sensitive to changes in the firing rate especially when the baseline firing rate is high (L. F. Abbott, personal communication). The changes in short-term dynamics reported by Markram and Tsodyks following LTP would tend to make the cortical network even more sensitive to changes in inputs, because potentiating the response to the first stimulus and more rapidly depressing responses to subsequent stimuli would tend to shift the impact of a train towards the onset of the response (H. Markram, personal communication). The actual impact of LTP in vivo, though, could be more complex because the inputs to cortical neurons are highly irregular; when the same irregular train of stimuli is delivered before and after LTP, the responses to some spikes are potentiated, but others can be depressed.

During visual recognition of complex objects, changes in the event-related potential correlated with the category of the object can be registered at 150 ms after presentation of a stimulus. This is within the range of short-term dynamical changes in strengths of cortical synapses, so synaptic dynamics could be an essential compo-
Has the fat lady sung?

David Bishop

This year is the tenth anniversary of the discovery of high-temperature superconductors. To those of us who have worked on the problem for the past decade, it has been an object lesson in humility. I am reminded of the old joke that you should be careful about what you wish for, as it might come true. If asked ten years ago, most solid-state physicists, including me, might have wished for a liquid-nitrogen-temperature superconductor, believing that it would revolutionize modern electronic technology and society along with it. Just such a class of materials was indeed discovered ten years ago by Bednorz and Müller', with superconducting transition temperatures now twice the boiling point of liquid nitrogen. But to the best of my knowledge, a revolution has not yet occurred. Where did we go wrong?

The answer lies partially in the pathological behaviour of the magnetic vortices that penetrate these compounds. How these vortices can misbehave is clearly demonstrated in an experiment described on page 791 of this issue² by Schilling and colleagues. They have confirmed that the magnetic vortex lattice is able to melt into a new state of matter called a vortex liquid. The presence of this liquid means that even modest magnetic fields can cause these materials to be more resistive to the flow of electrical currents than an ordinary piece of copper wire. Therefore, no revolution, or at least one that is going to take a little longer to roll out.

To understand why this happens, one needs to think about how superconductors respond to an applied magnetic field, and about the two classes of superconductor. In general, the superconducting state is inimical to magnetic fields and develops a number of responses to minimize the amount of magnetic flux in its interior. At low fields, below a critical field called $H_c1$, all the flux can be excluded from the interior of a sample — this is the Meissner state. Above a second critical field, $H_c2$, the superconducting state is destroyed and the normal metal is regained.

The first class of superconducting materials, called type I, has $H_c1=H_c2$. In equilibrium, the field is either totally expelled or superconductivity is completely destroyed. In general, type-I materials are low-field superconductors and are not useful.

All of the technologically important superconductors, including the high-$T_c$ materials, belong to the second class, type II. In these materials $H_c1<H_c2$ and at intermediate values of the applied field, between $H_c1$ and $H_c2$, the field can penetrate but not completely or uniformly ($a$ in the figure). Instead it enters the sample in the form of quantized bundles of magnetic flux called flux lines. The amount of field in each flux line is exactly the same, so the density of lines changes with the applied field. These lines of magnetic flux arrange themselves into a triangular lattice. In the absence of defects this lattice will be a perfectly arranged solid — a solid in the same sense that the chair you are sitting on is a solid; it has a finite shear modulus, whereas liquids and gases have zero shear modulus.

Soon after the high-$T_c$