# An Introduction to Neural and Electronic Networks

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# Covariance Storage in the Hippocampus

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## INTRODUCTION

This chapter is primarily concerned with the use of modeling techniques to uncover principles of brain function. This is a different but related enterprise from the practical problems of building machines that solve engineering problems. These two goals, however, are not incompatible. An advance in our understanding of how the brain works is likely to provide new designs for massively parallel computers; the technology being developed could, in turn, be used to help model the brain. However, even within the domain of computational neuroscience there are a number of modeling approaches that should be distinguished (Sejnowski, Koch, & Churchland, 1988).

### Realistic Brain Models

One modeling strategy consists of using very large scale simulations that attempt to incorporate as much of the cellular detail as is available (Koch & Segev, 1989). We call these realistic brain models. While this approach to simulation can be very useful, the realism of the model is both a strength and a weakness. As the model is made increasingly realistic by adding more variables and parameters, the danger is that the simulation ends up as poorly understood as the nervous system itself. Equally worrisome, since we do not yet know all the cellular details, important features may be inadvertently left out, thus invalidating the results. Finally, realistic simulations are highly computation intensive. Present constraints limit simulations to tiny nervous systems or small components of more complex systems. Only recently has sufficient computer power been available to go beyond the simplest models. Realistic models require a substantial empirical database; it is all too easy to make a complex model fit a limited subset of the data.

### Simplifying Brain Models

Because even the most successful realistic brain models may fail to reveal the function of the tissue, computational neuroscience needs to develop simplifying models that capture important principles. Textbook examples in physics that admit exact solutions are typ-

ically unrealistic, but they are valuable because they illustrate physical principles. Minimal models that reproduce the essential properties of physical systems, such as phase transitions, are even more valuable. The study of simplifying models of the brain can provide a conceptual framework for isolating the basic computational problems and understanding the computational constraints that govern the design of the nervous system. Simplifying models are essential but are also dangerously seductive; a model can become an end in itself and lose touch with nature.

In this chapter we present a set of theoretical ideas and experimental results about plasticity in the nervous system. We will show that a combination of modeling and experimentation can help overcome some of the limitations inherent in the complexity of the brain. In the next few sections we present several simplifying neural network models that were developed for modeling associative memory. Later in this chapter we describe a novel form of Hebbian synaptic plasticity in the mammalian hippocampus that confirms predictions made from covariance models of associative memory. There is already some evidence to indicate that similar forms of plasticity are also found in the cerebral cortex.

## ASSOCIATIVE MEMORY

In 1949 Donald Hebb published *The Organization of Behavior* in which he introduced several hypotheses about the neural substrates of learning and memory, including the Hebb learning rule or Hebb synapse. The Hebb rule and variations on it have also served as the starting point for the study of information storage in simplifying models (Sejnowski, 1981; Kohonen, 1984; McClelland & Rumelhart, 1986; Rumelhart & McClelland, 1986; Sejnowski & Tesauro, 1989). Many types of networks have been studied—networks with random connectivity, networks with layers, networks with feedback between layers, and a wide variety of local patterns of connectivity. Even the simplest network model has complexities that are difficult to analyze.

The Hebb synapse, or Hebb rule, has been used to signify a wide variety of ideas and mechanisms, so it would be worthwhile to start by examining what Hebb (1949) actually proposed. "When an axon of cell A is near enough to excite cell B or repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."

This verbal description is a general statement about the factors and conditions that could be important for changing synaptic strengths. There are two ways to sharpen the statement. First, we can formalize the verbal description as a quantitative equation, and second, we can specify in greater physiological detail what is meant by having one cell "excite" another.

Consider first a neuron $A$, with average firing rate $V_A(t)$, that projects to neuron $B$, with average firing rate $V_B(t)$. The synaptic connection from $A$ to $B$ has a strength value $W_{BA}$, which determines the degree to which activity in $A$ is capable of exciting $B$. In linear models, the average postsynaptic depolarization of $B$ due to $A$ is taken to be the product of the firing rate $V_A$ times the synaptic strength value $W_{BA}$. In other models the relationship between the inputs and outputs could be nonlinear. The statement of Hebb above states that the strength of the synapse $W_{BA}$ should be modified in some way which is dependent on both activity in $A$ and activity in $B$. The most general expression which captures this notion is

$$\Delta W_{BA}(t) = F\,(V_A(t), V_B(t)) \tag{1}$$

which states that the change in the synaptic strength $W_{BA}$ at any given time is some as yet unspecified function $F$ of both the presynaptic and the postsynaptic firing rates. Given this general form of the assumed learning rule, it is then necessary to choose a particular form for the function $F(V_A, V_B)$. The most straightforward interpretation of what Hebb said is a simple product

$$\Delta W_{BA}(t) = \varepsilon\, V_A(t)\, V_B(t) \tag{2}$$

where $\varepsilon$ is a numerical constant usually taken to be small. However, there are many other choices possible

for the function $F(V_A, V_B)$. The choice depends on the particular architecture and the problem at hand. Equation 2 might be appropriate for a simple associative memory task, but for other tasks one would need different forms of the function $F(V_A, V_B)$. For example, in classical conditioning, the precise timing relationships of the presynaptic and postsynaptic signals are important, and plasticity must then depend on the rate of change of firing, or on the "trace" of the firing rate, that is, weighted average over previous times, rather than simply depending on the current instantaneous firing rate (Tesauro, 1986; Klopf, 1988).

Probably the most important and most thoroughly explored use of the Hebb rule is in the formation of associations between one stimulus or pattern of activity and another. The Hebb rule is appealing for this use because it provides a way of forming global associations between macroscopic patterns of activity in assemblies of neurons using only the local information available at individual synapses. It is important to keep in mind that much more complex rules are possible, such as a function $F(V_A, V_B, V_C)$, which depends additionally on a third neuron $C$ in a heterosynaptic fashion.

The earliest models of associative memory were based on network models in which the output of a model neuron was assumed to be proportional to a linear sum of its inputs, each weighted by a synaptic strength. Thus,

$$V_B(t) = \sum_{A=1}^{N} W_{BA} V_A(t) \qquad (3)$$

where $V_B$ are the firing rates of a group of $M$ output cells, and $V_A$ are the firing rates of a group of $N$ input cells, and $W_{BA}$ is the synaptic strength between input cell $A$ and output cell $B$. Note that $A$ and $B$ are being used here as indices to represent one output of a group of cells.

The transformation between patterns of activity on the input vectors to patterns of activity on the output vectors is determined by the synaptic weight matrix, $W_{BA}$. How should this matrix be chosen if the goal of the network is to associate a particular output vector with a particular input vector? The earliest suggestions were all based on the Hebb rule (Steinbuch, 1961; Longuet-Higgins, 1968; Anderson, 1970; Kohonen, 1970). It is easy to verify by direct substitution of Equation 2 into Equation 3 that the increment in the output is proportional to the desired vector and the strength of the learning rate, $\varepsilon$, can be adjusted to scale the outputs to the desired values.

More than one association can be stored in the same matrix, as long as the input vectors are not too similar to each other. This is accomplished by using Equation 2 for each input–output pair. This model of associative storage is simple and has several attractive features. First, the learning occurs in only one trial; second, the information is distributed over many synapses, so that recall is relatively immune to noise or damage; and third, input patterns similar to stored inputs will give output similar to the stored outputs, a form of generalization. This model also has some strong limitations, such as interference between information associated with similar input vectors. Nonlinear models can overcome some of these limitations (Kohonen, 1984; Hopfield & Tank, 1986); however, the learning algorithms used in these models are similar to those presented here for simpler linear models.

## THE COVARIANCE RULE

One problem with any synaptic modification rule that can only increase the strength of a synapse is that the synaptic strength will eventually saturate at its maximum value. The weights can be reduced by nonspecific decay, but the stored information will also decay and be lost at the same rate. Another approach is to renormalize the total synaptic weight of the entire terminal field from a single neuron to a constant value (von der Malsburg, 1973). This could be accomplished, for example, by a mechanism for heterosynaptic depression, in which the persistent firing of neuron $A$, which increased the strength of the synapse to neuron $B$, would depress the strengths of all other synapses on neuron $B$.

Alternatively, a more flexible learning rule could be used that decreased the strength of a plastic synapse as

specifically as the Hebb rule increased it. The covariance rule is an example of a variation on the Hebb rule that solves the problem of dynamical range and saturation at a plastic synapse, while permitting differential modifications contingent upon the statistics of the presynaptic and postsynaptic activities (Sejnowski, 1977a,b). According to this rule, the change in strength of a plastic synapse should be proportional to the covariance between the presynaptic firing and postsynaptic firing

$$\Delta W_{BA}(t) = \varepsilon\,(V_B(t) - \langle V_B \rangle)\,(V_A(t) - \langle V_A \rangle) \qquad (4)$$

where $\langle V_B \rangle$ are the average firing rates of the output neurons, averaged over a longer time interval than $V_B$, and $\langle V_A \rangle$ are the average firing rates of the input neurons (Chauvet, 1986). Thus, the strength of the synapse should increase if the firing of the presynaptic and postsynaptic elements are positively correlated, decrease if they are negatively correlated, and remain unchanged if they are uncorrelated.

The covariance rule is a special case of the form of the Hebb rule in Equation 1. It differs from the simple Hebb rule in Equation 2 by the addition of an extra term. If we take the time average of Equation 4 we can rewrite it in the form

$$\langle \Delta W_{BA}(t) \rangle = \varepsilon\,(\langle V_B(t)\, V_A(t) \rangle - \langle V_B \rangle \langle V_A \rangle) \qquad (5)$$

Both terms on the right hand side have the same form as the simple Hebb synapse in Equation 2. Thus, the covariance learning algorithm can be realized by applying the Hebb rule relative to a "threshold" that varies with the product of the time-averaged presynaptic and postsynaptic activity levels. The time scale for taking the average activity levels must be longer than that for the synaptic plasticity. The effect of the threshold is to ensure that no change in synaptic strength should occur if the average correlation between the presynaptic and postsynaptic activities is at chance level.

The covariance form of the Hebb rule in Equation 5 has the important advantage that the strength of the synapse can be used throughout its dynamical range. Thus, the strength of a synapse that was near its maximum value could be selectively decreased if the activity of the presynaptic terminal and the postsynaptic neuron were negatively correlated. This would occur if the postsynaptic neuron was active while the presynaptic terminal was inactive, or *vice versa*.

## SYNAPTIC PLASTICITY IN THE HIPPOCAMPUS

Until recently, preparations for studying long term plasticity at synapses were not available, so it was difficult to test Hebb's hypothesis. Phenomena such as posttetanic potentiation last only a few minutes. Seventeen years ago Bliss and Lømo (1973) identified a long lasting enhancement of synaptic strength in the mammalian hippocampus, now called long term potentiation (LTP). When input fibers to pyramidal cells were stimulated at a high frequency, in the 30–100 Hz range, synaptic strengths remained elevated for many hours. This effect was homosynaptic, since the potentiated synapses were the same ones that were stimulated.

Experiments designed to test the involvement of the postsynaptic cell in the generation of LTP were reported by Kelso, Ganong, and Brown (1986), Malinow and Miller (1986), and Gustafsson et al. (1987). They stimulated the presynaptic terminals with a high frequency tetanus while simultaneously injecting current into a postsynaptic cell with an intracellular microelectrode. They reported that pairing the stimulus with a depolarization produced LTP, but pairing with hyperpolarization blocked the induction of LTP. This is consistent with a Hebbian mechanism.

In his description of the conditions for plasticity, Hebb specified the excitation of the postsynaptic cell leading to its firing an action potential. In the hippocampus, LTP can be induced even when action potentials in the postsynaptic cell are blocked (Kelso, et al., 1986). Evidently, it is enough for the postysnaptic cell to be strongly depolarized at the same time that the presynaptic terminal is stimulated. Although this does not change the spirit of the Hebb rule, the details make a difference with regard to dendritic processing. Neighboring synapses on a dendrite could communi-

**TABLE 1 Summary of the Combinations of Presynaptic Activity and Levels of Postsynaptic Potentials that Lead to Different Forms of Synaptic Plasticity in the Hippocampus**

| | Postsynaptic activity | |
|---|---|---|
| Presynaptic activity | Hyperpolarization | Depolarization |
| Low | — | Heterosynaptic depression |
| High | Homosynaptic depression (LTD) | Hebbian potentiation (LTP) |

cate through depolarization without involving more distant synapses. An influence that spread through somatic action potentials would involve many more synapses, but a mechanism that was based on subthreshold depolarization would allow each branch of dendrite to act semi-independently in locally regulating synaptic plasticity (Finkel & Edelman, 1985). Thus, the focus that Hebb placed on the cell as the processing unit may have to shift to a finer level, perhaps to the level of individual dendritic branches (Shepherd et al., 1985). Of course, the ionic currents generated in the dendrites sum in the cell body to produce an output which is typically encoded as trains of action potentials.

If depolarization of the postsynaptic cell together with presynaptic activity is sufficient to produce LTP, then a weak presynaptic stimulus, which by itself is not strong enough to produce LTP, should be potentiated when paired with the strong stimulation of another separate pathway. This, in fact, happens and has been called associative LTP because of the cooperativity between inputs (McNaughton, Douglas, & Goddard, 1978; Levy & Steward, 1979, 1983; Barrionuevo & Brown, 1983). Thus, correlations *between* neighboring synapses could be detected with this mechanism and information in the correlations could be stored through associative LTP of the relevant synapses.

Table 1 is a summary of the possible conditions for plasticity based on coincidence or noncoincidence of presynaptic and postsynaptic activity. The Hebbian condition occurs when they are both active. There is some evidence for synaptic depression of the sort that would be needed for the covariance rule in Equation 5. When one set of inputs to an area is inactive (Dunwiddie & Lynch, 1977; Lynch, Dunwiddie, & Gribkoff, 1977, Levy & Steward, 1979) or weakly active (Levy & Steward, 1983) during the stimulation of a strong input, the strengths of the inactive synapses are depressed. This is a heterosynaptic form of depression and does not depend on the pattern of weak input activity. Also, the duration of the depression is typically not as long lasting as LTP. A candidate mechanism for long term depression (LTD) should have roughly the same strength and duration as LTP itself.

We recently searched for conditions under which the stimulation of a hippocampal pathway, rather than its inactivity, could produce either long term depression or potentiation of synaptic strengths, depending on the pattern of stimulation (Stanton & Sejnowski, 1989). The stimulus paradigm that we used (Figure 1) is based on the finding that high frequency bursts of stimuli at 5 Hz are optimal in eliciting LTP (Larson & Lynch, 1986). This is close to the 5–6 Hz theta rhythm normally recorded in the hippocampus during some behaviors associated with learning. A strong bursting stimulus was applied to the Schaffer collaterals and a weak low frequency stimulus was applied to a separate subicular input on the opposite side of the recording site; each shock of the weak input was either superimposed on the middle of each burst of the strong input (IN PHASE) or occurred symmetrically between the bursts (OUT OF PHASE).

Extracellular evoked field potentials were recorded from the apical dendritic and somatic layers of CA1 pyramidal cells. The weak stimulus train was first applied alone and did not itself induce long lasting

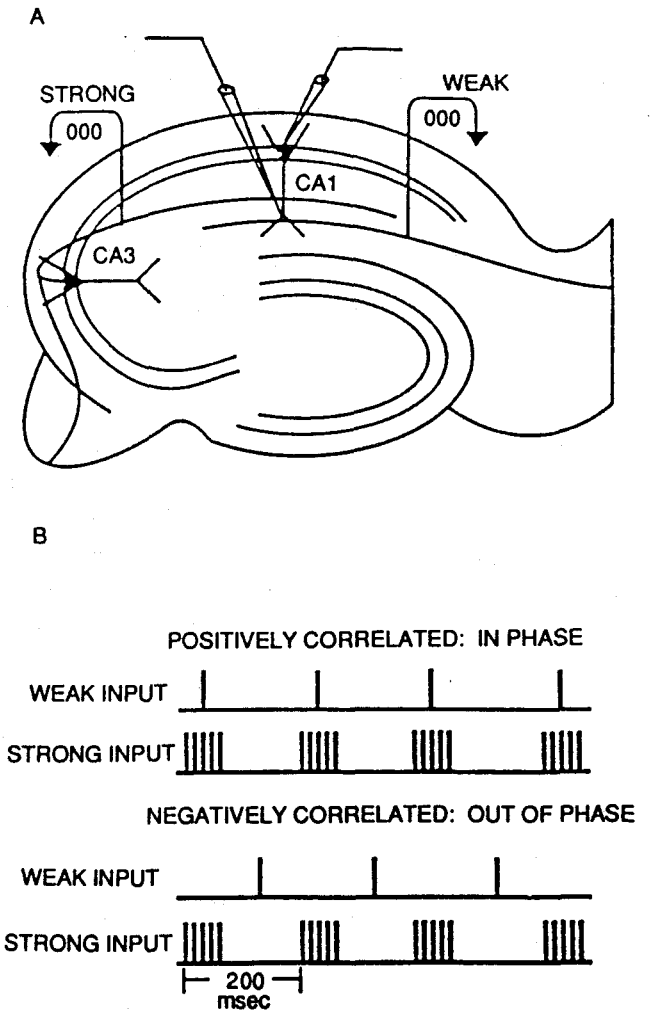


**FIGURE 1** Hippocampal slice preparation and associative stimulus paradigms. A. Schematic diagram of the *in vitro* hippocampal slice showing recording sites in the CA1 pyramidal cell somatic (stratum pyramidale) and dendritic (stratum radiatum) layers, and stimulus sites activating Schaffer collateral (STRONG) and commissural (WEAK) afferents. B. Schematic diagram of stimulus paradigms used. Strong input stimuli (STRONG INPUT) were four trains of 100 Hz bursts. Each burst had five stimuli and the interburst interval was 200 msec. Each train lasted 2 sec and had a total of 50 stimuli. Weak input stimuli (WEAK INPUT) were four trains of shocks at 5 Hz frequency, each train lasting for 2 sec. When these inputs were IN PHASE, the weak single shocks were superimposed on the middle of each burst of the strong input, as shown. When the weak input was OUT OF PHASE, the single shocks were placed symmetrically between the bursts.

changes in synaptic strength. The strong site was then stimulated alone, which elicited homosynaptic LTP of the strong pathway while not significantly altering the amplitude of responses to the weak input. When weak and strong inputs were activated in phase, there was an associative LTP of the weak synapses (Figure 2A). Both the synaptic excitatory postsynaptic potential and population action potential were significantly enhanced for at least 60–180 min following stimulation.

In contrast, when weak and strong inputs were applied out of phase, we observed an associative long term depression of the weak input synapses (Figure 2B). There was a marked reduction in the population spike with smaller decreases in the EPSP. Note that the stimulus patterns applied to each input were identical in these two experiments, and only the relative phase of the weak and strong stimuli was altered. With these stimulus patterns, synaptic strength could be repeatedly enhanced and depressed in a single slice (Figure 2C).

The simultaneous depolarization of the postsynaptic membrane and activation of glutamate receptors of the *N*-methyl-*D*-aspartate (NMDA) subtype appears to be necessary for LTP induction (Collingridge, Kehl, & McLennan, 1983; Harris, Ganong, & Cotman, 1984; Wigstrom & Gustafsson, 1984). The spread of current from strong to weak synapses in the dendritic tree paired with glutamate release from the weak input could account for the ability of a strong pathway to associatively potentiate a weak one (Barrionuevo & Brown, 1983). Consistent with this hypothesis, we find that the NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (AP5, 10 $\mu M$) blocks the induction of associative LTP in CA1 pyramidal neurons. In contrast, the application of AP5 to the bathing solution at this same concentration had no significant effect on associative LTD. Thus, the induction of depression seems to involve mechanisms different from potentiation.

In further experiments, intracellular recordings from CA1 pyramidal neurons were made using standard techniques. Induction of associative LTP (Figure 3, WEAK S+W IN PHASE) produced an increase in

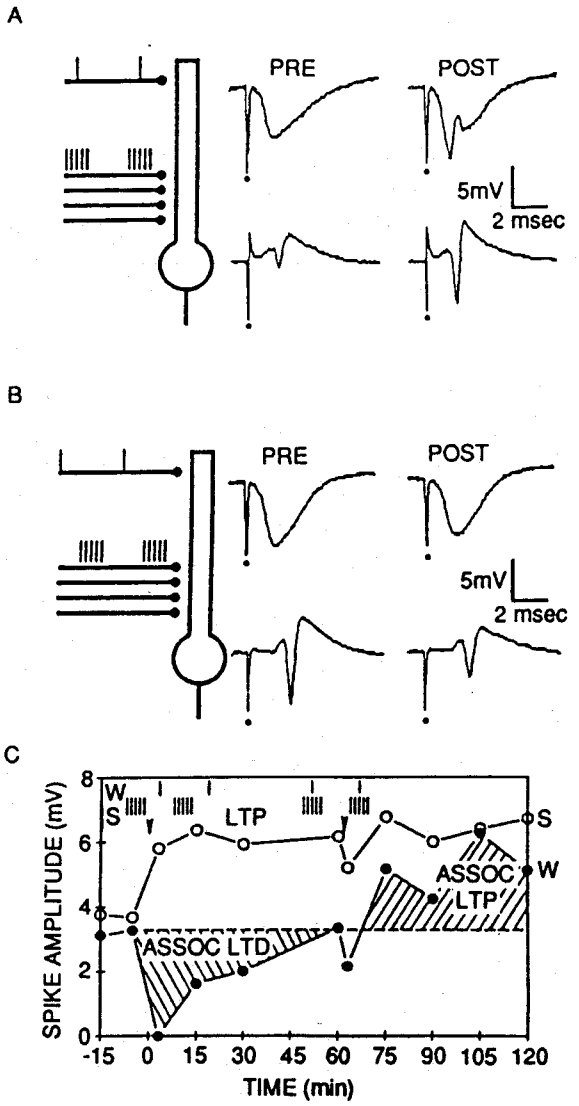


**FIGURE 2** Illustration of associative long-term potentiation (LTP;A) and associative long-term depression (LTD;B) using extracellular recordings. A. Associative LTP of evoked excitatory postsynaptic potentials (EPSPs) and population action potential responses in the weak input. Test responses are shown before (Pre) and 30 min after (Post) application of weak stimuli in phase with the coactive strong input. B. Associative LTD of evoked EPSPs and population spike responses in the weak input. Test responses are shown before (Pre) and 30 min after (Post) application of weak stimuli out of phase with the coactive strong input. C. Time course of the changes in population spike amplitude observed at each input for a typical experiment. Test responses from the strong input (S, open circles) show that the high-frequency bursts (5 pulses/100 Hz, 200 msec interburst interval as in Figure 1) elicited synapse-specific LTP independent of other input activity. Test responses from the weak input (W, filled circles) show that stimulation of the weak pathway out of phase with the strong one produced associative LTD (Assoc LTD) of this input. Associative LTP (Assoc LTP) of the same pathway was then elicited following in-phase stimulation. Amplitude and duration of associative LTD or LTP could be increased by stimulating input pathways with more trains of shocks.

amplitude of the excitatory postsynaptic potential (EPSP) and a lowered action potential threshold in the weak pathway, as reported previously (Barrionuevo & Brown, 1983). Conversely, the induction of associative LTD (Figure 3, WEAK S+W OUT OF PHASE) was accompanied by a long lasting reduction of EPSP elicited by weak input stimulation.

A weak stimulus that is out of phase with a strong stimulus arrives when the postsynaptic neuron is hyperpolarized as a consequence of inhibitory postsynaptic potentials and afterhyperpolarization from mechanisms intrinsic to pyramidal neurons. This suggests that postysnaptic hyperpolarization coupled with presynaptic activation may trigger LTD. To test this hypothesis, we injected current with intracelluar microelectrodes to hyperpolarize or depolarize the cell while stimulating a synaptic input at low frequency. Pairing the injection of depolarizing current with weak input stimulation led to LTP of those synapses (Figure 4A, STIM), while a control input inactive during the stimulation did not change (CONTROL), as reported previously (Kelso, et al., 1986; Malinow & Miller, 1986; Gustafsson et al., 1987). Conversely, prolonged hyperpolarizing current injection paired with the same weak stimuli led to induction of LTD in the stimulated pathway (Figure 4B, STIM), but not in the unstimulated pathway (CONTROL). The application of either depolarizing current, hyperpolarizing current, or the weak 5 Hz synaptic stimulation alone did not induce long term alterations in synaptic strengths. Thus, hyperpolarization and simultaneous presynaptic activity is sufficient for the induction of LTD in CA1 pyramidal neurons.

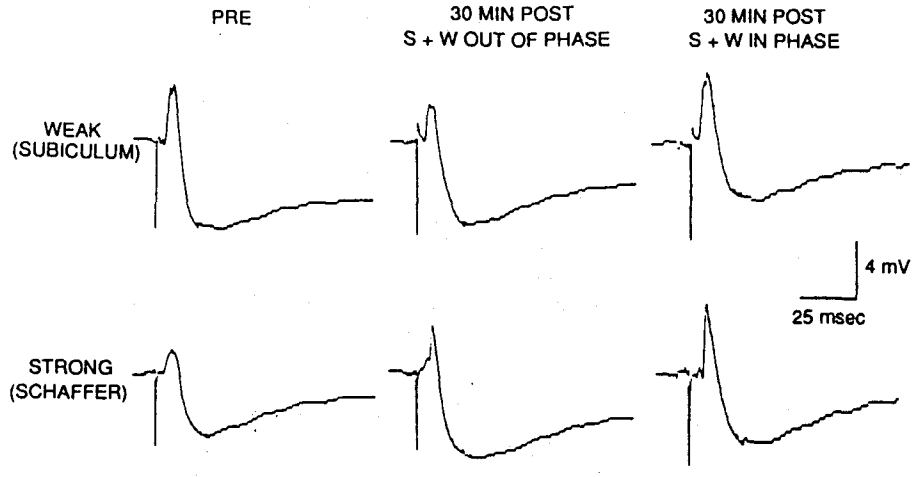


**FIGURE 3** Demonstration of associative LTP and LTD using intracellular recordings from a CA1 pyramidal neuron. Intracellular EPSPs prior to repetitive stimulation (Pre), 30 min after out of phase stimulation (S+W OUT OF PHASE), and 30 min after subsequent in phase stimuli (S+W IN PHASE). The strong input (Schaffer collateral side, lower traces) exhibited LTP of the evoked EPSP independent of weak input activity. Out of phase stimulation of the weak (subicular side, upper traces) pathway produced a marked persistent reduction in EPSP amplitude. In the same cell, subsequent in phase stimuli resulted in associative LTP of the weak input that reversed the LTD and enhanced amplitude of the EPSP past the original baseline.

The properties of associative LTD described here make it a good candidate for the covariance learning rule outlined in the last section. Since there is a large variation in the strength and duration of both LTP and LTD in different slices, we designed a stimulus pattern to compare them in the same slice at the same time. The stimulus combined both the weak input shocks superimposed with the bursts and between the bursts, so that on average there was no net covariance between weak and strong inputs. This stimulus produced no net change in synaptic strength using extracellular recording techniques, as predicted by the covariance rule in Equation 4. Thus, the associative LTP and LTD mechanisms appear to be balanced.

## SYNAPTIC PLASTICITY IN THE VISUAL CORTEX

Neurons in the visual cortex of cats and monkeys respond preferentially to oriented bars and edges. A network model for the development of neuronal selectivity incorporating the Hebbian form of plasticity was proposed by Bienenstock, Cooper, and Munro (1982). The BCM model requires patterned visual inputs and in this respect is similar to an earlier proposal by von der Malsburg (1973). The BCM algorithm for synaptic modification is a special case of the general Hebb rule in Equation 1,

$$\Delta W_{BA} = \phi(V_B, \langle V_B \rangle) V_A \tag{6}$$

where the function $\phi(V_B, \langle V_B \rangle)$ is shown in Figure 5. The synapse is strengthened when the average postsynaptic activity exceeds a threshold, and is weakened when the activity falls below the threshold level. Furthermore, the threshold varies according to the average postsynaptic activity

$$\theta = \langle V_B \rangle^2 \tag{7}$$

Bienenstock et al. (1982) show that this choice has desirable stability properties and allows neurons to become selectively sensitive to common features in input patterns.

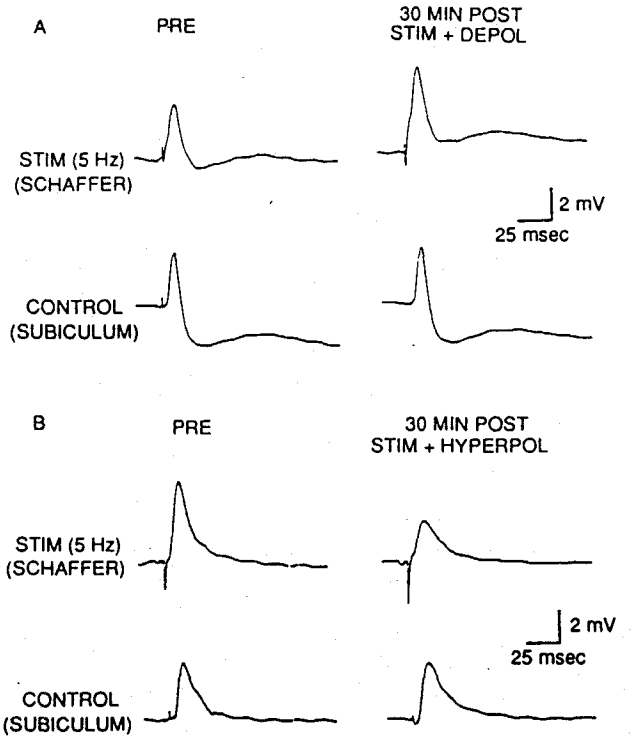


**FIGURE 4** Pairing of postsynaptic hyperpolarization with stimulation of synapses of CA1 hippocampal pyramidal neurons produces LTD specific to the activated pathway, while pairing of postsynaptic depolarization with synaptic stimulation produces synapse-specific LTP. A. Intracellular invoked EPSPs are shown at stimulated (STIM) and unstimulated (CONTROL) pathway synapses before (Pre) and 30 min after (Post) pairing a 20 mV depolarization (constant current, +2.0 nA) with 5 Hz synaptic stimulation. The stimulated pathway exhibited associative LTP of the EPSP while the control, unstimulated input showed no change in synaptic strength. (RPM = -65 mV; $R_N$ = 35 MΩ) B. Intracellular EPSPs are shown evoked at stimulated and control pathway synapses before (Pre) and 30 min after (Post) pairing a 20 mV hyperpolarization (constant current, -1.0 nA) with 5 Hz synaptic stimulation. The input (STIM) activated during the hyperpolarization showed associative LTD of synaptic evoked EPSPs while synaptic strength of the silent input (CONTROL) was unaltered.

The covariance form of the Hebb synapse has been used by Linsker (1986) to model the formation of receptive fields in the early stages of visual processing. The model is a layered network having limited connectivity between layers and uses the learning rule in Equation 5. As the learning proceeds, the units in the lower layers of the network develop on-center and off-center receptive fields that resemble the receptive fields of ganglion cells in the retina, and elongated receptive fields develop in the upper layers of the network that resemble simple receptive fields found in visual cortex. This model demonstrates that some of the properties of sensory neurons could arise spontaneously during development by specifying the general pattern of connectivity and a few parameters to control the synaptic plasticity. One surprising aspect of the model is that regular receptive fields develop even though only spontaneous activity is present at the sensory receptors.

The visual response properties of neurons in the visual cortex of cats and monkeys are plastic during the first few months of postnatal life, and can be permanently modified by visual experience (Wiesel & Hubel, 1965; Sherman & Spear, 1982). Normally, most cortical neurons respond to visual stimuli from either eye. Following visual deprivation of one eye by eyelid suture during the critical period, the ocular preference of neurons in primary visual cortex shifts toward the nondeprived eye. In another type of experiment, a misalignment of the two eyes during the critical period produces neurons that respond to only one eye and, as a consequence, binocular depth perception is impaired. These and many other experiments have led to testable hypotheses for the mechanisms underlying synaptic plasticity during the critical period (Bear, Cooper, & Ebner, 1987).

Singer (1987) has suggested that the voltage-dependent entry of calcium into spines and the dendrites of postsynaptic cells may trigger the molecular changes required for synaptic modification in visual cortex. This hypothesis is being tested at a molecular level using a combined pharmacological and physiological technique. NMDA receptor antagonists infused into visual cortex block the shift in ocular dominance normally associated with monocular deprivation (Kleinschmidt, Bear, & Singer, 1986). The NMDA receptor is a candidate mechanism for triggering synaptic modification because it allows calcium to enter a cell only if the neurotransmitter binds to the receptor while the

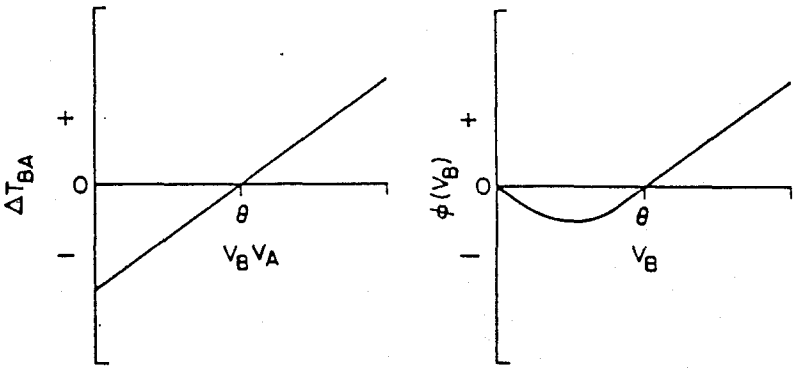


**FIGURE 5** *Left*, change in synaptic strength $\Delta T_{BA}$ as a function of the average correlation $\langle V_A V_B \rangle$ between the presynaptic and postsynaptic activity levels, as indicated in Equation 5. The threshold $\theta$ is given by $\langle V_B \rangle \langle V_A \rangle$. *Right*, the postsynaptic factor $\phi(V_B, \langle V_B \rangle)$ in the BCM learning algorithm in Equation 6, where the threshold $\theta = \langle V_B \rangle^2$ (Bienenstock, Cooper, & Munro, 1982).

postsynaptic membrane is strongly depolarized. In a sense, the NMDA receptor is a "Hebb molecule" since it is only activated when there is a conjunction of presynaptic and postsynaptic activity. The NMDA receptor also is critically involved in the induction of LTP in the hippocampus (Collingridge et al., 1983; Harris et al., 1984; Wigstrom & Gustafsson, 1984).

Stent (1973) has suggested that the effects of monocular deprivation could be explained if the synaptic weight were to decrease when the synapse is inactive and the postsynaptic cell is active. This is similar to the condition that leads to heterosynaptic depression in the hippocampus (Lynch et al., 1977; Levy & Steward, 1979, 1983). The evidence for synaptic depression found in visual cortex during the critical period would correspond to the upper right corner of Table 1, in which presynaptic activity is absent but postsynaptic activity is normal.

The conditions that correspond to the lower left corner of Table 1 have only recently been tested in the visual cortex. Chronic hyperpolarization of neurons was produced by infusion of muscimol, a GABA agonist, while one of the eyes was sutured shut during the critical period. When the eye was opened, neurons in visual cortex near the site of infusion could be driven only by the closed eye, in contrast to neurons more distant from the infusion site, which could only be driven from the open eye (Reiter & Stryker, 1987). One interpretation of these results is that presynaptic transmitter release onto hyperpolarized cells leads to a long term depression of the input synapses arising from the lateral geniculate nucleus, but that inactive terminals are not affected. These conditions are similar to those reported here that lead to associative LTD in the hippocampus (Stanton & Sejnowski, 1989). Thus, the Hebbian mechanisms found in the hippocampus are likely to be found elsewhere in the central nervous system.

The mechanisms for plasticity in the cerebral cortex during development may be related to mechanisms responsible for synaptic plasticity in the adult. The evidence so far favors the general form of Hebbian plasticity in Equation 1. However, the details of how this plasticity is regulated on short and long time scales may be quite different during development and in the adult. Recently, it has been shown that the receptive field properties of cells in cat visual cortex can be altered even in the adult by visual experience paired with ionophoretic excitation or depression of cellular activity (Fregnac, Schulz, Thorpe, & Bienenstock, 1988; Greuel, Luhmann, & Singer, 1988). These results are consistent with the presence

of Hebbian covariance mechanisms, though the complexity of visual cortex prevents a direct interpretation of these results at the level of identified synapses.

## CONCLUSIONS

The experiments on associative synaptic depression in the hippocampus summarized in this chapter were based on ideas that first arose in the context of modeling some aspects of memory. These simplifying models leave out most of the biological details of real neurons and do not even refer to specific brain areas. What such models provide is a general framework for thinking about the complex relationships that could exist between signals in neural circuits like those found in the hippocampus. Simplifying models suggest possible experiments and help with interpreting their outcomes. In our experiments, the choice of the stimulus parameters was inspired by the prediction made by the covariance model of memory that anticorrelation was the critical condition for synaptic depression (Sejnowski, 1977b).

However, the covariance model did not provide the details of the stimulus paradigm, but only the general conditions. The choice of 100 Hz for the burst rate and 5 Hz for the burst repetition rate was determined by properties of the hippocampus. What the model did provide was the idea that synaptic depression comparable in magnitude and duration to LTP is likely to be found in the hippocampus, and the general properties that would characterize its occurrence. The covariance model pointed to anticorrelation as the key variable. The model only narrowed the range of possibilities. Two forms of synaptic depression have in fact been found in the hippocampus in different areas under different conditions. These are likely to have different functions. The homosynaptic form of LTD that we described in this chapter has many of the characteristics needed to balance LTP.

LTP and LTD are candidate mechanisms for long term information storage in neuronal networks. If the strength of synapses in the hippocampus can be enhanced or depressed repeatedly, then these coupled mechanisms could also provide a means for implementing a "working memory." This type of memory could be used to temporarily store the information needed to accomplish a task. For example, the strengths of some synapses could be incremented by LTP and these strengths maintained for an indefinite interval. When this information was no longer needed, the synaptic strengths could be selectively decreased with LTD. It is known that the long term memories of facts and events are stored not in the hippocampus, but in the cerebral cortex, so it will be of particular interest to determine whether mechanisms similar to LTP and LTD are found there as well.

More needs to be known about the timing relationships for LTP and LTD, and also about the spatial integration of information within dendritic trees. Realistic models can help with sorting out these relationships, but only if enough data can be obtained to fully constrain the models. Here is an example of how two different types of models, both simplifying and realistic, can each contribute, on different levels, to the solution of difficult problems in storing and retrieving information in neural populations.

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