4 Learning Rules from Neurobiology

Douglas A. Baxter and John H. Byrne

Among the more interesting properties of biological neural networks is their ability to be modified by experience. Many artificial neural networks seek to emulate this ability by including mathematical expressions that allow for experience-dependent modifications of some aspect of the network. Thus, in order both to understand biological neural networks and to simulate their properties, it is necessary to understand the conditions under which changes in the cellular parameters underlying learning are induced, maintained, and expressed. It has long been postulated that learning involves modifications of the efficacy or weights of the existing synaptic connections. Such experience-dependent modifications of synaptic efficacy would be expressed as an alteration in the relationship between activity in presynaptic and postsynaptic neurons and thus in the response of the network. Alternatively, the response properties of a network may be changed by experience-dependent modifications of the parameters that determine the threshold, pattern, or frequency of action potentials generated in the postsynaptic neuron in response to a given presynaptic input (i.e., the transfer or activation function of the postsynaptic cell). A third possibility is that learning involves the growth of entirely new synaptic connections and thus modifies the architecture of the network. Finally, learning may involve the nonlinear dynamic properties of individual neurons or networks such that learning is associated with shifting from one stable attractor to another. It is likely that learning involves aspects of all of these forms of plasticity.

Of the various mechanisms that have been proposed, the most extensive analyses have been done on learning rules that involve changes of synaptic weights. This chapter reviews these analyses of activity-dependent modifications of synaptic efficacy of the type believed to be involved in learning and describes several mathematical expressions that reflect some of the features of these forms of synaptic plasticity. Although many diverse rules govern the induction of synaptic plasticity, it is useful to distinguish two basic categories, nonassociative and associative. Nonassociative rules depend on one or more state variables, such as the state of activity in either the presynaptic *or* postsynaptic

neuron, whereas associative rules depend on the interaction of two or more state variables, such as the state of activity in the presynaptic *and* postsynaptic neurons. Moreover, associative rules generally require a specific temporal relationship between the two state variables.

NONASSOCIATIVE SYNAPTIC MODIFICATIONS

Nonassociative rules that govern the induction of synaptic plasticity are summarized in figure 4.1. There are two types: homosynaptic and heterosynaptic. Homosynaptic rules (figure 4.1A) are defined as rules in which changes to the weight of a given synapse are determined by the levels of activity in either the presynaptic or postsynaptic neurons of the given synapse (figure 4.1A, rules 1 and 2, respectively). The changes can be expressed as increases (figure 4.1A, upward arrows) or decreases (figure 4.1A, downward arrows) in synaptic strength. For heterosynaptic rules, changes in the weight of a given synapse are induced by either the levels of activity in nearby synapses (figure 4.1B, rule 3), or by the activity of modulatory systems (figure 4.1B, rule 4). Thus, homosynaptic rules depend strictly on local information or state variables (i.e., presynaptic or postsynaptic activity), whereas heterosynaptic rules depend on quasi-local (i.e., activity in nearby synapses) or global (i.e., activity in modulatory systems) state variables.

Homosynaptic Modifications

Consider first a simple synaptic arrangement in which a postsynaptic neuron, B, receives an excitatory input from a single presynaptic neuron, A (figure 4.1A). The synaptic input to cell B from cell A has a strength or weight of $w_{B,A}$. As discussed in chapter 3, the postsynaptic activity y_B is taken to be some nonlinear function f of presynaptic activity y_A and the synaptic weight. Thus, for the single synapse in figure 4.1A, the postsynaptic activity at a given time t is expressed as:

$$y_B(t) = f(w_{B,A}(t), y_A(t)). \tag{4.1}$$

During learning, the synaptic weight changes as a result of previous activity, thus:

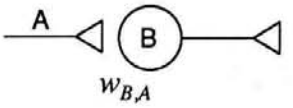
$$w_{B,A}(t+1) = w_{B,A}(t) + \Delta w_{B,A}(t) \tag{4.2}$$

where $t = 0, 1, 2, \ldots$ measures discrete time and $\Delta w_{B,A}$ is the activity-dependent change in synaptic weight. A nonassociative learning rule, which is attributed to Eccles (1953), states that changes in synaptic weight depend on activity in the presynaptic cell. The most general mathematical expression that captures this notion is:

$$\Delta w_{B,A}(t) = F(y_A(t)) \tag{4.3}$$

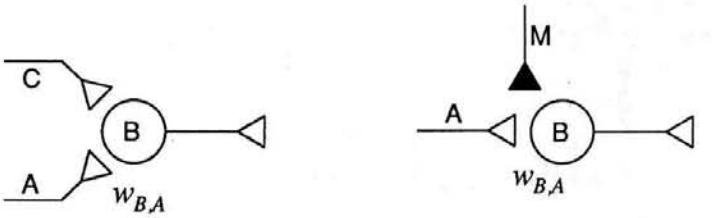
which relates the change in synaptic weight to a function F of activity in the presynaptic neuron. Many particular learning rules fall under this

A. Nonassociative Rules for Homosynaptic Modifications of Synaptic Weights



A	B	Rule 1a	Rule 1b	Rule 2a	Rule 2b
+		↑	↓		
	+			↑	↓

B. Nonassociative Rules for Heterosynaptic Modifications of Synaptic Weights



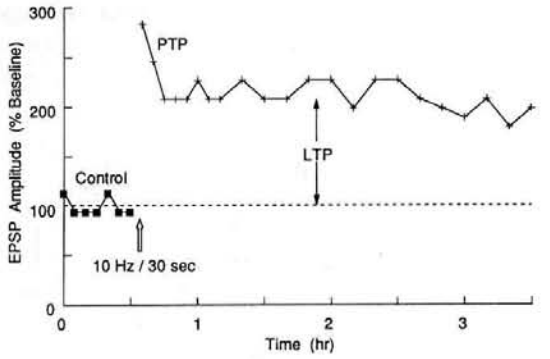
C	M	Rule 3a	Rule 3b	Rule 4a	Rule 4b
+		↑	↓		
	+			↑	↓

A, C	presynaptic neurons	↑	synaptic potentiation
B	postsynaptic neuron	↓	synaptic depression
M	modulatory neuron	+	active cell
w	synaptic weight		

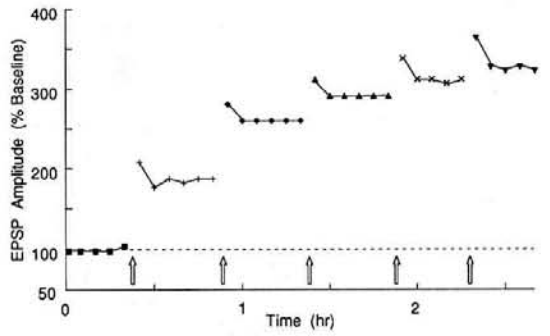
Rules for Nonassociative Synaptic Modifications

Figure 4.1 Nonassociative rules depend on one or more state variables, such as the state of activity in either the presynaptic or postsynaptic neuron. There are two classes of nonassociative rules: homosynaptic and heterosynaptic. (A) Homosynaptic rules are defined as rules in which changes to the weight of a given synapse are determined by the levels of activity in either the presynaptic (rule 1) or postsynaptic (rule 2) neuron of the synapse. The changes may be expressed as synaptic potentiation (upward arrows) or as synaptic depression (downward arrows). (B) Heterosynaptic rules are defined as rules in which changes to the weight of a given synapse are determined by either the levels of activity in nearby synapses (rule 3), or by the activity in a modulatory neuron (rule 4).

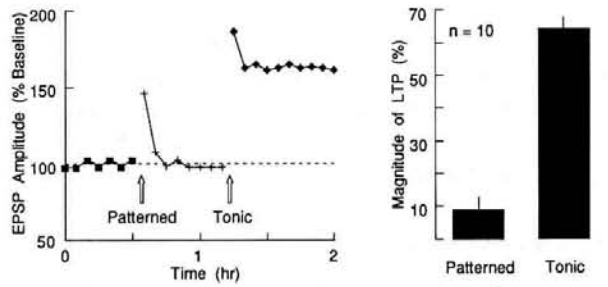
A. Long-Term Potentiation (LTP)



B. Saturation of the Induction of LTP



C. Optimal Pattern of Stimulation for Induction of LTP



Long-Term Potentiation in Opener-Neuromuscular Synapses of Crayfish

Figure 4.2 LTP, an enduring enhancement of synaptic efficacy, can be induced by a brief conditioning stimulus. (A) LTP of excitatory postsynaptic potentials (EPSPs) in opener-neuromuscular synapses of the crayfish. During the control period, EPSPs were elicited at a low frequency (0.3 Hz) that did not induce changes in the synapse. LTP was induced by stimulating the presynaptic neuron at 10 Hz for 30 s (arrow). The conditioning stimulus induced a enduring enhancement of synaptic efficacy that persisted for the duration of the experiment. (B) The LTP of EPSPs reaches an asymptote with repeated conditioning stimuli. Synaptic efficacy was monitored by eliciting EPSPs at a low frequency (0.3 Hz). Synaptic potentiation was induced by repeated conditioning stimuli of 10 Hz for 30 s (arrows). The induction of LTP appears to saturate with repeated conditioning stimuli. (C) A tonic stimulus induces LTP whereas a patterned stimulus does not. Both condition-

general form, depending on the properties of F. For example, F may be a positive function (rule 1a), in which case presynaptic activity would induce a potentiation of synaptic efficacy, or F may be a negative function (rule 1b), in which case presynaptic activity would induce a depression of synaptic efficacy.

Some forms of long-term potentiation (LTP) are examples of biological synaptic plasticity that comply with rule 1 and that provide some insights to the general features of $F(y_A)$. LTP is an enduring enhancement of synaptic efficacy, often persisting for many hours, that can be induced by a brief (several seconds) conditioning stimulus. This great asymmetry between the duration of the conditioning stimulus and the duration of the subsequent synaptic change provides an operational definition of LTP. LTP occurs in numerous synapses of the central and peripheral nervous systems of vertebrates and invertebrates, and there are likely to be many different forms of LTP. This conclusion is based, in part, on the observation that different rules have been found to govern the induction of LTP at various synapses (see below).

One example of LTP, which can be described by rule 1a, is the LTP of excitatory postsynaptic potentials (EPSPs) that has been observed in opener-neuromuscular synapses of the crayfish (Baxter et al. 1985; Bittner 1989; Keenan et al. 1987). The opener-neuromuscular synapse closely approximates the two key features of the simple, linear synaptic arrangement described in figure 4.1A and equation 4.1. First, the postsynaptic cells receive synaptic input from a single excitatory neuron. Second, the postsynaptic cells lack any voltage-gated ionic conductances that would introduce nonlinearities. Thus, the presynaptic release of the excitatory transmitter glutamate linearly depolarizes the postsynaptic cells over a wide range of membrane potentials, and the amplitudes of the EPSPs reflect the level of presynaptic activity and the efficacy of the synapse (equation 4.1). Figure 4.2A illustrates some experimental results. The efficacy of the synapse was tested by stimulating the presynaptic neuron at a low frequency (0.3 Hz) that did not induce changes in the synapse during the 30-min control period. In this experiment, potentiation was induced by eliciting action potentials in the presynaptic neuron at 10 Hz for 30 s. The potentiation had two kinetically distinct components. The first component decays rapidly with a time course corresponding to that of posttetanic potentiation (PTP; for a review of PTP see Zucker 1989). PTP is followed by a much longer enhancement of synaptic efficacy that persists for the duration of the experiment, in

ing stimuli delivered 300 presynaptic action potentials over 30 s. In the tonic stimulus, the 300 presynaptic spikes are elicited at a constant frequency of 10 Hz, whereas in the patterned stimulus, the 300 presynaptic spikes are arranged as brief (2 to 5 spikes), high-frequency (100 Hz) bursts that were evenly distributed throughout the 30 s. The results of ten experiments are summarized. The magnitude of LTP (the percent increase above the control value) was measured 30 min after the conditioning stimulus. (Modified from Keenan et al. 1987.)

some cases up to 8 hr. This latter component satisfies the operational definition of LTP.

Several lines of evidence suggest that the induction of LTP in the opener-neuromuscular synapse is nonassociative. First, there are no other excitatory synaptic inputs to the postsynaptic cells, and there is no modulatory system in the isolated claw preparation. Second, it is unlikely that postsynaptic depolarizations are necessary for LTP in this synapse since the postsynaptic cells do not fire action potentials and neither the test stimuli nor the conditioning stimulus significantly depolarize the postsynaptic cell. Third, a quantal analysis indicated that LTP could be accounted for by an increase in the presynaptic release of transmitter (Baxter et al. 1985). Thus, LTP in the opener-neuromuscular synapse is believed to be an example of a nonassociative, homosynaptic form of LTP that is induced by presynaptic activity (rule 1a). A similar rule appears to govern, or at least contribute to, the induction of LTP in several other excitatory synapses, including sensorimotor synapses of *Aplysia* (Walters and Byrne 1985), mammalian sympathetic ganglia (Alonso-deFlorida et al. 1991; Bachoo and Polosa 1991; Briggs and McAfee 1988), bullfrog sympathetic ganglia (Koyano et al. 1985), and the mossy fiber inputs to pyramidal neurons in the CA3 region of the hippocampus (Zalutsky and Nicholl 1990; see however, Jaffe and Johnston 1990).

Perhaps the simplest form of F (rule 1a) is a simple product:

$$\Delta w_{B,A}(t) = \varepsilon y_A(t) \tag{4.4}$$

where ε is a positive constant that determines the rate of increase in synaptic strength (often referred to as the learning rate) and y_A is some measure of presynaptic activity. The most common interpretation of y_A is that this state variable represents the frequency of presynaptic spike activity, which is averaged over several seconds prior to time t. The two key assumptions in equation 4.4 are that $\Delta w_{B,A}$ is a monotonically increasing function of presynaptic activity and that the proper measure for governing the induction of LTP is the average frequency of presynaptic activity. However, our current understanding of nonassociative LTP does not reflect these assumptions.

The first problem with equation 4.4 is that repeated conditioning stimuli do not induce ever-increasing synaptic potentiation. Rather, as illustrated in figure 4.2B, potentiation asymptotically approaches a maximum. The five upward arrows in figure 4.2B indicate the occurrences of conditioning stimuli (presynaptic stimulation at 10 Hz for 30 s). The accumulation of LTP with repeated conditioning stimuli resembles the negatively accelerating acquisition curves of the sort found in the Rescorla and Wagner (1972; see also Donegan et al. 1989) learning equations. Combining equations 4.2 and 4.4, and incorporating an expression that places asymptotic limits on synaptic strength yields:

$$w_{B,A}(t+1) = w_{B,A}(t) + [\varepsilon\, y_A(t)\, (\lambda_{\max} - w_{B,A}(t))] \quad (4.5)$$

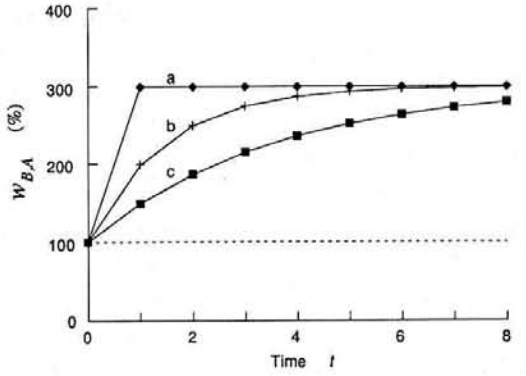
where $\lambda_{\max}$ is the maximum possible synaptic strength. Including $\lambda_{\max}$ as a limit for $\Delta w_{B,A}$ introduces an additional problem in that synaptic strength will inevitably saturate. Thus, some mechanism must be included to allow for the decrement of synaptic plasticity (see below).

It is possible to estimate values for $\lambda_{\max}$ and ε from current experimental data. The maximum magnitude of LTP has been found in a number of different vertebrate and invertebrate preparations to range between a 50% to 600% increase above the control value of $w_{B,A}$ (i.e., the value of $w_{B,A}$ at time $t = 0$). Thus, the value of $\lambda_{\max}$ should be no more than about six to ten times the value of $w_{B,A}$ ($t = 0$). It should be noted that $\lambda_{\max}$ may not represent the full dynamic range of the synapse. For example, in opener-muscular synapses, short-term facilitation can enhance synaptic transmission by several orders of magnitude (Bittner 1968, 1989; Zucker 1989), whereas the maximum magnitude of LTP is only about a three or four fold increase (figure 4.2B). LTP appears to approach its asymptotic value following only a few conditioning stimuli. Thus, the value of ε should be between about 0.01% to 0.5% of y_A. Figure 4.3A illustrates three numerical examples of the growth of $w_{B,A}$ that is predicted by equation 4.5 at three different stimulus strengths.

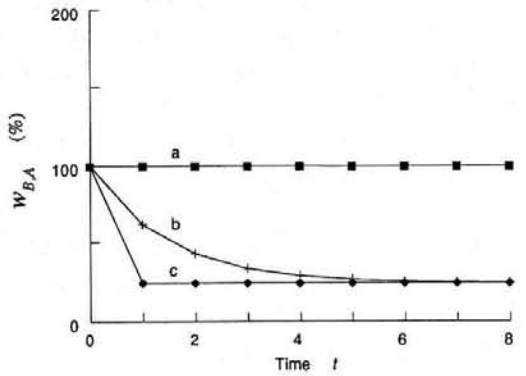
A second problem with equation 4.4 is that $\Delta w_{B,A}$ will always tend to increase because ongoing presynaptic activity will contribute to the time-averaged value of y_A. One solution to this problem is to compute $\bar{y}$, a measure of the sustained or background level of activity in the presynaptic neuron averaged over a much longer time span than y_A, and to use a function of $(y_A - \bar{y}_A)$ as the presynaptic expression in equation 4.5. Thus, potentiation would occur only when $y_A > \bar{y}_A$, and no change will occur when $y_A \leq \bar{y}_A$.

A third problem with equation 4.4 is that the average of presynaptic spike activity may not be the proper measure with which to control the induction of synaptic potentiation. For example, figure 4.2C illustrates an experiment that examines the ability of two conditioning stimuli to potentiate opener-neuromuscular synapses. The two conditioning stimuli are termed "tonic" and "patterned." Both conditioning stimuli have a duration of 30 s and elicit 300 presynaptic action potentials, i.e., an average presynaptic spike activity of 10 Hz for 30 s. In the tonic stimulus, the 300 spikes are elicited at a constant frequency of 10 Hz, whereas in the patterned stimulus, the 300 spikes are arranged as brief (2 to 5 spikes), high-frequency (100 Hz) bursts that were evenly distributed throughout the 30-s period. The patterned conditioning stimulus failed to induce potentiation, whereas the tonic conditioning stimulus induced potentiation. These results suggest that the induction of potentiation is governed by specific features of the conditioning stimulus. In addition, other experimental data suggest that various aspects of synaptic potentiation, such as the magnitude and duration, can be differentially con-

A. Equation 4.5



B. Equation 4.7



Effects of Different Stimulus Strengths on the Solutions of Equations 4.5 and 4.7

Figure 4.3 Equations 4.5 and 4.7 predict synaptic potentiation and depression, respectively, and place asymptotic limits on changes that can occur in synaptic efficacy. (A) As the presynaptic stimulus strength in equation 4.5 is increased from $y_A = 25$ (trace c) to $y_A = 50$ (trace b) to $y_A = 100$ (trace a), potentiation of $w_{B,A}$ reaches its asymptotic level with a smaller number of trials ($\varepsilon = 0.01$, $\lambda_{max} = 3$, and $w_{B,A}(t = 0) = 1$ in all three traces). For simplicity, each of these terms is dimensionless. Note that the strength of the conditioning stimulus y_A affects only the rate of growth, not the maximum level of synaptic potentiation. (B) Because of the inverse relationship between synaptic depression and the frequency of presynaptic activity in equation 4.7, a very low stimulus strength ($y_A = 0.01$, trace c) rapidly induces maximal depression of $w_{B,A}$ ($\varepsilon = 0.01$, $\lambda_{min} = 0.25$, and $w_{B,A}$ ($t = 0$) = 1 in all three traces). The rate of depression is slower as the stimulus strength is increased slightly to $y_A = 0.02$ (trace b). In contrast, more intense stimuli ($y_A = 3$, trace a) induce no observable depression.

trolled by parameters of the conditioning stimulus (Alonso-deFlorida et al. 1991; see also Grover and Teyler 1990). Thus, it appears that while equation 4.5 reflects some of the simpler features of synaptic potentiation, such as asymptotic limits to synaptic potentiation, it does not accurately reflect some of the more subtle properties of potentiation, such as the stimulus-specificity that governs induction. An alternative approach is to develop dynamic models of synaptic transmission that incorporate mathematical formalisms of the underlying cellular mechanisms. Such biologically realistic models are likely to express more precisely the features of synaptic transmission and plasticity. One such model, activity-dependent neuromodulation of synaptic efficacy, is described later in this chapter.

The stimulus specificity that is depicted in figure 4.2C illustrates a potentially intriguing aspect of information processing and storage in a single synapse. Namely, information processing and information storage can be controlled independently in a single synapse by different patterns of presynaptic activity. For example, in the opener-neuromuscular synapse, brief bursts of high-frequency presynaptic activity are the optimum stimulus for eliciting a behavioral postsynaptic response, consisting of significant postsynaptic depolarization and muscle contraction (Bittner 1968; Smith 1975). This type of stimulus, however, does not appear to induce LTP. In contrast, brief trains of low-frequency presynaptic activity do not elicit a muscle contraction, but do induce LTP. Thus, long-term changes in synaptic efficacy may be induced without significant activity in the postsynaptic cell, and conversely the postsynaptic cell can be activated without inducing long-term changes in the synapse. Moreover, once induced in opener-neuromuscular synapses, LTP was found to have a multiplicative (not additive) effect on the short-term synaptic plasticity (Keenan et al. 1987). Thus, LTP functions to increase the "gain" of information processing throughout the entire dynamic range of the synapse.

The inverse of LTP is long-term depression (LTD), a type of synaptic plasticity in which the efficacy of a synapse is persistently reduced. A form of nonassociative, homosynaptic depression that is induced by presynaptic activity (rule 1b) has been observed at several excitatory synapses, including the neuromuscular synapses in crayfish (Pahapill et al. 1987; Zucker and Bruner 1977), sensorimotor synapses in *Aplysia* (Byrne 1982; Castellucci et al. 1970), and inputs to the CA1 pyramidal cells of the rat hippocampus (Dudek and Bear 1992; Dunwiddie and Lynch 1978; Mulkey and Malenka 1992). Recent results indicate that the postsynaptic cell may play a role in the induction of synaptic depression in CA1 neurons (Dudek and Bear 1992; Mulkey and Malenka 1992). Thus, synaptic depression in CA1 neurons may turn out to be associative rather than nonassociative.

At many synapses, the magnitude of depression has been found to be inversely related, within a range of activity, to the frequency of presyn-

aptic activity. Thus, low frequencies of presynaptic stimulation (e.g., 0.01 Hz) induce more depression than higher frequencies of stimulation (e.g., > 1 Hz). Two expressions, which are fashioned after equations 4.4 and 4.5, can be used to describe synaptic depression. The first is a simple product in which the learning rate ε is now negative:

$$\Delta w_{B,A}(t) = \varepsilon\,(y_A(t))^{-1}. \tag{4.6}$$

In this equation and the next, y_A is restricted to a specific range of values that produces depression. This excludes, for example, $y_A = 0$; in the absence of presynaptic activity there should be no change in $w_{B,A}$. In addition, although this equation produces decreases in $w_{B,A}$, it is again not a biologically plausible expression in that it can lead to negative values for synaptic weights. In an alternate formulation, the learning rate ε can remain a positive value, but the asymptote λ for changes in synaptic strength is made to be less than the initial value of $w_{B,A}$ ($w_{B,A}$ at $t = 0$):

$$w_{B,A}(t+1) = w_{B,A}(t) + [\varepsilon\,(y_A(t))^{-1}\,(\lambda_{\min} - w_{B,A}(t))] \tag{4.7}$$

where $\lambda_{\min}$ is the minimum possible synaptic strength and values for $\lambda_{\min}$ are restricted to the range of $0 < \lambda_{\min} < w_{B,A}$ ($t = 0$). Figure 4.3B illustrates three numerical examples of the depression of $w_{B,A}$ that is predicted by equation 4.7.

Although the values of $\lambda_{\max}$ and $\lambda_{\min}$ in equations 4.5 and 4.7 are generally assumed to be constants, recent experimental evidence suggests that their values may depend on the state of the synapse. For example, a low-frequency conditioning stimulus (e.g., 100 pulses at 1 Hz) applied to Schaeffer collateral/commissural (Sch/comm) projections to CA1 pyramidal cells in the hippocampus selectively depressed potentiated synapses but had no effect on control synapses (Barrionuevo et al. 1980; Staubli and Lynch 1990). This result implies that the type of response (potentiation vs. no change vs. depression) induced by a given conditioning stimulus may depend on the strength of the synapse prior to the conditioning stimulus. Thus, a critical experimental issue is the determination of the intrinsic and/or extrinsic factors that control the state-dependent responses of synapses. An intriguing possibility is that the state-dependent responses of synapses may be influenced by modulatory transmitters. Thus, the plasticity at a given synapse could, in principle, be linked to more global factors that are associated with motivational or developmental states.

Shimbel (1950) proposed a learning rule in which changes in synaptic weight depend on postsynaptic activity (figure 4.1A, Rule 2). A general expression of this learning rule is:

$$\Delta w_{B,A}(t) = F(y_B(t)) \tag{4.8}$$

which relates the change in synaptic weight to a function F of postsynaptic activity y_B. Several examples of biological synaptic plasticity (see

below) comply with rule 2, and indicate postsynaptic activity can induce either synaptic potentiation (rule 2a) or depression (rule 2b).

A form of nonassociative, homosynaptic potentiation that is induced by postsynaptic activity (rule 2a) has been observed at two excitatory synapses: bullfrog sympathetic ganglion (Kumamoto and Kuba 1983) and stellate cells in layer II of the entorhinal cortex of the guinea pig (Alonso et al. 1990). In the bullfrog sympathetic ganglion, potentiation was induced by antidromic stimulation (20 Hz for 5 s) of the postganglionic nerve trunk. This postsynaptic electrical activity, which was not paired with presynaptic activity, led to a doubling of the amplitudes of the EPSPs. In the entorhinal cortex, potentiation of the projection from the piriform cortex to stellate cells in layer II was induced by depolarizing the postsynaptic cell. This unpaired postsynaptic conditioning stimulus led to an approximate doubling of synaptic efficacy.

A mathematical expression for postsynaptically induced potentiation, can be fashioned after equation 4.5 by replacing the presynaptic factor y_A with a term y_B that represents some measure of postsynaptic activity, such as the frequency of spike activity averaged over several seconds prior to time t. Experimental data suggest that the value of $\lambda_{\max}$ should be no more than about three times the control value of $w_{B,A}$. As discussed above, such a simple mathematical expression may not reflect some of the more subtle properties of postsynaptically induced synaptic plasticity. For example, the average of postsynaptic spike activity may not be the pertinent state variable. In the entorhinal cortex, potentiation was induced by subthreshold membrane depolarizations; i.e., there were no postsynaptic spikes. Moreover, only rhythmic postsynaptic depolarizations that resembled the intrinsic membrane potential oscillations that are present in the postsynaptic cells were effective in inducing potentiation. Thus, the postsynaptic induction of synaptic potentiation appears to be governed by specific features of the conditioning stimulus.

A form of nonassociative, homosynaptic depression that is induced by postsynaptic activity (rule 2b) has been observed in Sch/comm projections to CA1 pyramidal neurons in the hippocampus (Pockett et al. 1990; see also Dunwiddie and Lynch 1978). Depression of excitatory synaptic transmission was induced by antidromic stimulation (e.g., six bursts of 50 stimuli at 100 Hz, delivered at 10-s intervals) of the axons of CA1 pyramidal neurons. This postsynaptic electrical activity, which was not paired with presynaptic activity, decreased the amplitudes of EPSPs to as little as 14% of their control values. A function, which approximately describes postsynaptic induced depression, can be fashioned after equation 4.5 first by substituting y_B (postsynaptic activity) for the presynaptic term and by restricting the values of $\lambda_{\min}$ to a range of $0 < \lambda_{\min} < w_{B,A}(t = 0)$ (i.e., $\lambda_{\min}$ must be less than the control value for synaptic strength). Experimental data suggest that the lower limit of $\lambda_{\min}$ should be about 0.14.

Heterosynaptic Modification

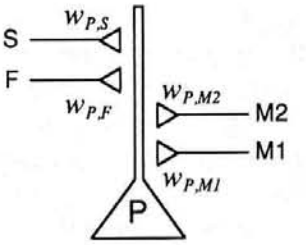
Consider a common synaptic arrangement in which a postsynaptic neuron, B, receives converging excitatory inputs from several presynaptic neurons, such as presynaptic neurons A and C in figure 4.1B. Experimental data suggest a learning rule in which changes in the synaptic weight of cell A can be a function of the activity in the neighboring presynaptic neuron C:

$$\Delta w_{B,A}(t) = F(y_C(t)) \tag{4.9}$$

where y_C is some measure of activity in neuron C. Activity in neuron C can either potentiate (rule 3a) or depress (rule 3b) the synaptic strength of the nonactive cell, neuron A. A mathematical expression for this form of heterosynaptic plasticity (rule 3) can be fashioned from equation 4.5 by replacing y_A with y_C. As before, this expression will represent synaptic potentiation if the value of $\lambda_{\max}$ is greater than $w_{B,A}\,(t = 0)$ (the control value of synaptic strength) and depression if the value of $\lambda_{\min}$ is less than $w_{B,A}\,(t = 0)$.

A form of nonassociative, heterosynaptic potentiation that can be induced in a set of nonactive synapses by activity in neighboring synapses (rule 3a) has been observed at several excitatory synapses, including inputs to the stellate ganglion of the cat (Bachoo and Polosa 1991) and certain classes of inputs to pyramidal cells in the CA3 region of the hippocampus (Bradler and Barrionuevo 1989, 1990). In the stellate ganglion, synaptic potentiation was examined by stimulating two distinct groups of preganglionic axons, the third and fourth thoracic white rami (T3WR and T4WR, respectively). A conditioning stimulus (e.g., 40 Hz for 5 s) applied to T4WR, while T3WR was unstimulated, induced heterosynaptic potentiation in the T3WR pathway and increased the T3WR response by an average of 600% above the control values. If the conditioning stimulus was applied to the test pathway, T3WR, homosynaptic potentiation was induced in T3WR. If the conditioning stimulus was applied to the postganglionic axons, no changes in synaptic efficacy were induced. Thus, the heterosynaptic potentiation in this preparation was not a consequence of postsynaptic electrical activity and these synapses can express both homosynaptic and heterosynaptic potentiation. Currently, little is known about the ways in which these two forms of synaptic plasticity interact within a single synapse.

A form of nonassociative, heterosynaptic depression that can be induced in a set of nonactive synapses by activity in neighboring synapses (rule 3b) has been observed in several excitatory synapses in the hippocampus, including inputs to: pyramidal cells in the CA1 (Dunwiddie and Lynch 1978; Lynch et al. 1977), pyramidal cells in the CA3 (Bradler and Barrionuevo 1989, 1990), and granule cells in the dentate gyrus (Abraham and Goddard 1983; Abraham et al. 1985; Levy 1985; Levy and Steward 1979, 1983; White et al. 1988, 1990). For example, in the CA3



M1	S	F	$w_{P,M1}$	$w_{P,M2}$	$w_{P,S}$	$w_{P,F}$
+			Homosynaptic Potentiation	Heterosynaptic Depression	Heterosynaptic Potentiation	Heterosynaptic Potentiation
	+		Heterosynaptic Depression		Homosynaptic Potentiation	
		+	Heterosynaptic Depression		Heterosynaptic Depression	Homosynaptic Potentiation

M1, M2	mossy fiber pathways	F	fimbrial pathway
S	Schaffer collateral / commissual pathways	w	synaptic weight
P	CA3 pyramidal neuron	+	tetanized pathway

Synaptic Plasticity Observed at Inputs to Hippocampal CA3 Pyramidal Neurons

Figure 4.4 Heterosynaptic plasticity at inputs to a hippocampal CA3 pyramidal neuron (P) was examined by stimulating four separate groups of presynaptic fibers: Schaeffer collateral/commissural (S), fimbrial (F), and two distinct groups of mossy fibers (M1, M2). Stimulation (+) of a subset of the mossy fiber input, M1, induced heterosynaptic depression in the nonstimulated mossy fiber input, M2, and heterosynaptic potentiation in the fimbrial and Schaeffer pathways. Stimulation of either the Schaeffer collateral/commissural or fimbrial inputs also induced heterosynaptic depression in the nonstimulated mossy fiber pathway. (Data summarized from Bradler and Barrionuevo 1990.)

region of the hippocampus, heterosynaptic depression was examined by stimulating up to four separate groups of presynaptic fibers: Schaeffer collateral/commissural (S), fimbrial (F), and two distinct groups of mossy fibers (M1, M2) (figure 4.4). A conditioning stimulus (five 6-pulse 100 Hz trains delivered at 0.02 Hz) applied to a subset of the mossy fiber inputs (M1) induced heterosynaptic depression in a nontetanized subset of mossy fibers, M2, whereas heterosynaptic potentiation was induced in the fimbrial and Schaeffer pathways. Heterosynaptic depression of the mossy fiber pathways also could be induced by conditioning stimuli applied to either the Schaeffer or fimbral pathways. Only the mossy fiber pathway was capable of inducing heterosynaptic potentiation and this heterosynaptic potentiation was restricted to non–mossy fiber pathways.

A feature of heterosynaptic plasticity not captured by rules similar to equation 4.5 is the spatial limitation that may apply to interactions among synapses. For example, White et al. (1988, 1990) found in the dentate gyrus that heterosynaptic depression could be induced only between

populations of synapses that converged onto overlapping dendritic regions. Indeed, the degree of heterosynaptic interactions, as measured by the magnitude of depression, was correlated with the extent of spatial overlap (i.e., the strength of heterosynaptic interactions between pathways was directly related to the proximity of the interacting synapses). Thus, mathematical expressions of heterosynaptic interactions should incorporate some description of the anatomical features of the dendritic tree and of the spatial arrangements of different populations of synapses on the dendrites. The spatial limitations of heterosynaptic interactions also suggest a intriguing aspect to single-cell information processing and storage—namely, different regions of a cell can process and store information independently. To capture this feature, single lumped parameter models of the postsynaptic cell are not appropriate.

As illustrated in figure 4.1B, the heterosynaptic interactions between neurons can be mediated by modulatory transmitters; that is, changes in synaptic weight are a function of the activity in a modulatory neuron or system, y_M:

$$\Delta w_{B,A}(t) = F(y_M(t)). \tag{4.10}$$

These modulatory neurons can either potentiate (rule 4a) or depress (rule 4b) the synaptic efficacy of neuron A. A particularly well-characterized example of such heterosynaptic interactions is the modulation of the sensory neurons that mediate defensive withdrawal reflexes in *Aplysia* (for reviews, see Byrne 1987; Byrne and Crow 1991; Byrne et al. 1991a, c; 1993; Kandel and Schwartz 1982). The properties of these sensory neurons can be affected by several modulatory transmitters, some of which induce heterosynaptic potentiation while others induce heterosynaptic depression. For example, serotonin (5-HT) can induce nonassociative heterosynaptic potentiation in sensory neuron synapses. Binding of serotonin to its receptors activates several second messenger/kinase systems in the sensory neurons, two of which are the cAMP-dependent protein kinase A system and the Ca^{2+}/phospholipid–dependent protein kinase C system (Bernier et al. 1982; Ocorr and Byrne 1985; Sacktor and Schwartz 1990). These second messenger/kinase systems, in turn, modulate the properties of ion channels, which results in increased neuronal excitability, increased spike duration, increased Ca^{2+} influx, and hence increased transmitter release from sensory neurons (Baxter and Byrne 1990; Klein and Kandel 1980; Sugita et al. 1992). In addition, these second messenger/kinase systems seem to directly modulate aspects of the secretory machinery, which in turn enhances transmitter release (Braha et al. 1990; Gingrich and Byrne 1984, 1985, 1987; Gingrich et al. 1988; Hochner et al. 1986; Pieroni and Byrne 1992).

In contrast, the neuropeptide FMRFamide can induce nonassociative heterosynaptic depression in sensory neuron synapses. FMRFamide activates the arachidonic acid second messenger pathway (Piomelli et al. 1987), and in general, the effects of FMRFamide are the opposite of

those induced by serotonin. FMRFamide modulates ion channels in such a way that neuronal excitability, spike duration, Ca^{2+} influx, and hence transmitter release, are all reduced (Belardetti and Siegelbaum 1988; Critz et al. 1991; Edmonds et al. 1990). In addition, FMRFamide seems to directly inhibit aspects of the secretory machinery, which in turn reduces transmitter release (Pieroni and Byrne 1992; see also Man-Son-Hing et al. 1989) and may have postsynaptic actions as well (Peter et al. 1992).

Thus, the actions of the modulatory transmitters that induce heterosynaptic modification are mediated via a complex assembly of interacting second messenger systems and enzymatic reactions that affect multiple subcellular processes. This complexity in the mechanisms that underlie heterosynaptic modulation can not be easily manifested by relatively simple mathematical expressions such as equations 4.5 or 4.10. More biologically realistic and dynamic models of the types of subcellular and molecular mechanisms that can underlie heterosynaptic modulation have been developed (Aszódi and Friedrich 1987; Aszódi et al. 1991; Buxbaum and Dudai 1989; Friedrich 1990; Gingrich and Byrne 1985, 1987; Gingrich et al. 1988; Greenberg et al. 1987; see below). These models illustrate that the molecular processes underlying neuronal functions, including the kinetics of enzyme reactions, interactions among second messenger systems, and regulation of transmitter release, play critical roles in determining the features of neuronal plasticity.

ASSOCIATIVE SYNAPTIC MODIFICATIONS

Associative modifications of synaptic efficacy depend on the temporal correlation between the activities in two neurons. Although several associative learning rules have been proposed on the basis of theoretical work, only recently have examples of associative synaptic modifications been demonstrated experimentally. Below are reviewed several examples of biological synaptic plasticity that are governed by the temporal interactions between two neuronal stimuli and that provide some insight to the formulation of biologically plausible associative learning rules.

Hebbian Rule for Synaptic Modification

Possibly the best known associative learning rule was proposed by Hebb (1949). His postulate for learning states:

> When an axon of cell A is near enough to excite a cell B and 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.

The key feature of the Hebbian rule is that increases in synaptic weight are dependent on concurrent activity in the presynaptic and postsyn-

aptic cells. This simple conjunctive mechanism for synaptic potentiation can be represented by the general expression:

$$\Delta w_{B,A}(t) = F(y_A(t), y_B(t)), \tag{4.11}$$

which relates the change in synaptic weight to a function F of both presynaptic and postsynaptic activity.

At least one form of synaptic potentiation, which has been examined extensively in the Sch/comm projections to CA1 pyramidal cells in the hippocampus, appears to conform to the Hebbian rule. A weak presynaptic stimulus, which by itself fails to induce any change in synaptic efficacy, can induce LTP when paired with intracellular depolarizations of the postsynaptic cell (Gustafsson et al. 1987; Kelso et al. 1986; Wigström et al. 1986). This form of LTP can be induced even when Na^+-mediated postsynaptic action potentials are blocked (Kelso et al. 1986). Evidently, it is sufficient that the postsynaptic cell to be strongly depolarized at the same time that the presynaptic cells are stimulated. The temporal specificity of this form of synaptic potentiation has been examined by varying the intervals between postsynaptic depolarization and presynaptic stimulation (Gustafsson et al. 1987; Kelso et al. 1986; see also Brown et al. 1989; Gustafsson and Wigström 1986; Hashemzadeh et al. 1991; Levy and Steward 1983). Simultaneous occurrences of presynaptic stimulation and postsynaptic depolarization are the most effective at inducing potentiation. In addition, potentiation can be induced with postsynaptic depolarizations that start several tens of milliseconds after the presynaptic activity, but not with postsynaptic depolarizations that terminate before the presynaptic activity. These results suggest that following presynaptic stimulation there remains a "trace" of previous activity during which time the synapses continue to be eligible for modification. (For other consequences of this trace, see chapter 2.)

Although neither firing postsynaptic action potentials per se nor strictly conjunctive activity may be required, potentiation of Sch/comm projections to CA1 cells is generally consistent with the Hebbian rule in that synaptic potentiation takes place only when the synapse is active in close temporal contiguity with strong postsynaptic depolarizations. A similar rule appears to govern the potentiation in excitatory projections from the entorhinal cortex to the dentate gyrus of the hippocampus (for review see Levy 1985), as well as excitatory synapses in a wide variety of brain areas (for reviews, see Teyler and DiScenna 1987; Teyler et al. 1990; Tsumoto 1990) and possibly some excitatory synapses of invertebrates (Miller et al. 1987).

There have been many mathematical formalisms suggested for the Hebbian rule (for reviews see Brown et al. 1990; Sejnowski and Tesauro 1989, 1990). The simplest implementation of the Hebbian rule is a product of the average frequencies of spike activity in the presynaptic and postsynaptic cells:

$$\Delta w_{B,A}(t) = \varepsilon\, y_A(t)\, y_B(t) \tag{4.12}$$

where ε is a small, positive constant. As discussed above (see discussion of equation 4.4), there are problems with a simple product equation. For example, the product equation predicts that $\Delta w_{B,A}$ is a monotonically increasing function of conjunctive activity. This prediction is in contrast, however, to experimental observations in which potentiation of Sch/comm projections to CA1 cells saturates with repeated conditioning stimuli (Gustafsson and Wigström 1986; Larson and Lynch 1986; see also Abraham et al. 1985; Levy and Steward 1979). Although this problem can be overcome by including an upper limit for $\Delta w_{B,A}$ such as $\lambda_{\max}$ in equation 4.5, limiting $\Delta w_{B,A}$ introduces the additional problem that chance coincidences of presynaptic and postsynaptic activity will inevitably lead to saturation of the synapse.

Brown et al. (1990; see also Kairiss et al. 1988; Kohonen 1984, 1990) suggested a more flexible expression: a bilinear equation that combines the product equation for Hebbian potentiation and mechanisms for decreases in synaptic strength:

$$w_{B,A}(t+1) = w_{B,A}(t) + (\varepsilon\, y_A(t)\, y_B(t)) - (\beta\, y_B(t)) - (\gamma y_A(t)) - \delta \qquad (4.13)$$

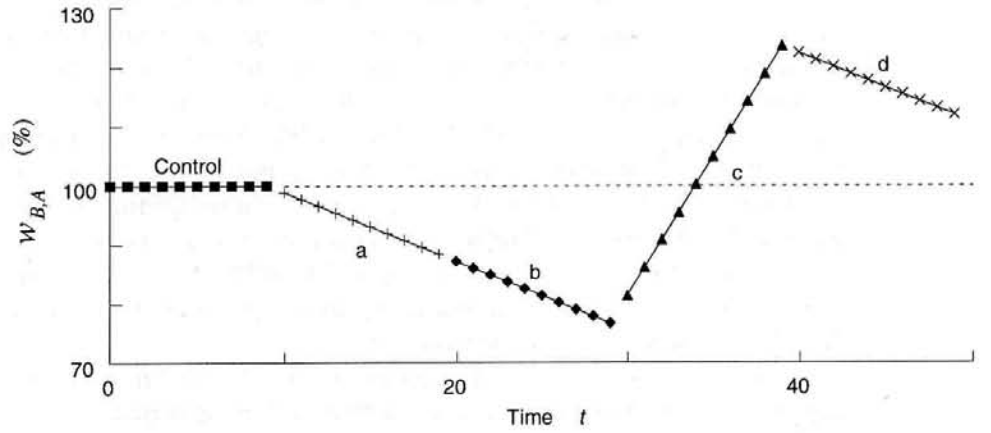
where β, γ and δ are constants in the simplest case, or functions in a more generalized form. Thus, the term $(-(\beta\, y_B))$ represents a form of nonassociative synaptic depression that is induced by postsynaptic activity (Pockett et al. 1990), the term $(-(\gamma y_A))$ represents a form of nonassociative synaptic depression that is induced by presynaptic activity (Dunwiddie and Lynch 1978), and the term $(-\delta)$ represents the passive decay of plasticity. Figure 4.5A illustrates the response of this bilinear equation (equation 4.13) to four phases of stimulation. During the first phase (phase a in figure 4.5A), only the presynaptic cell is active and $w_{B,A}$ undergoes homosynaptic depression. During the second phase (phase b), only the postsynaptic cell is active and $w_{B,A}$ again is depressed. During conjunction activity (phase c), $w_{B,A}$ potentiates as predicted by the product equation for the Hebbian rule. Finally, noncoincident activity (phase d) again results in synaptic depression.

Levy and co-workers (Levy 1985, 1989; Levy and Colbert 1991; Levy and Desmond 1985; Levy et al. 1983; Lopez et al. 1990) also have suggested a mathematical expression for the Hebbian rule that allows for reversible synaptic modifications and that incorporates asymptotic limits on both potentiation and depression of synaptic weight:

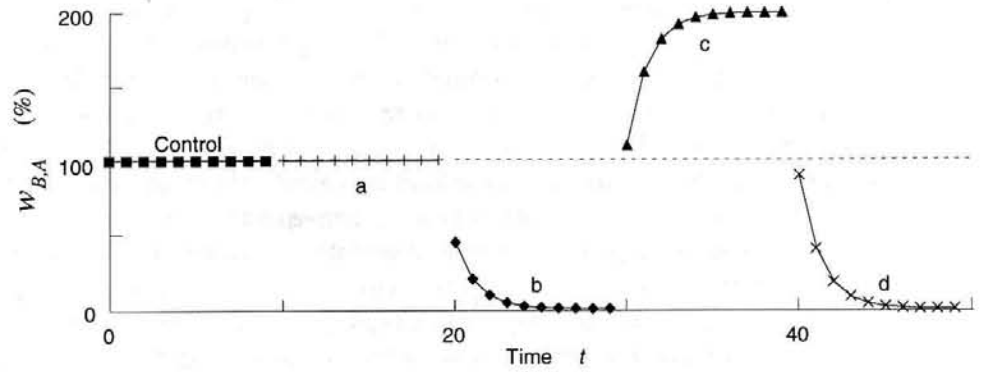
$$w_{B,A}(t+1) = w_{B,A}(t) + [\varepsilon\, G(y_B(t))\, (c\, y_A(t) - w_{B,A}(t))] \qquad (4.14)$$

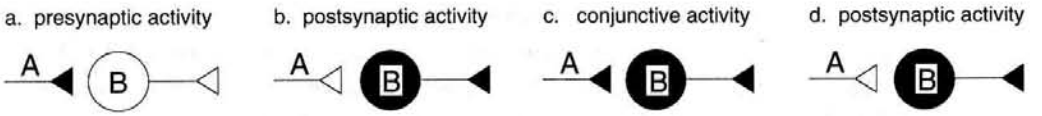
where G is some measure of the net postsynaptic depolarization or activity and c is a positive constant. (In the simplest case $G = y_B(t)$.) Figure 4.5B illustrates the response of equation 4.14 to four phases of stimulation. If the postsynaptic term, G, is equal to zero (phase a in figure 4.5B), then no change in synaptic weight occurs. Thus, the postsynaptic term is permissive of change. If $G > 0$, then the difference $c\, y_A - w_{B,A}$ determines whether potentiation or depression of synaptic

A. Equation 4.13



B. Equation 4.14





Changes in Synaptic Weight Predicted by Two Forms of the Hebbian Learning Rule

Figure 4.5. (A) Bilinear Hebbian rule (eq. 4.13) suggested by Brown et al. (1990). The changes in synaptic weight $w_{B,A}$ that are predicted by equation 4.13 are illustrated during four phases of stimulation ($\varepsilon = 0.00385$, $\beta = 0.005$, $\gamma = 0.005$, and $\delta = 1$, in all four phases and control value of $w_{B,A} = 1$). During phase a, only the presynaptic cell is active ($y_A = 40$ and $y_B = 0$) and $w_{B,A}$ undergoes homosynaptic depression. During phase b, only the postsynaptic cell is active ($y_A = 0$ and $y_B = 40$) and $w_{B,A}$ again is depressed. During phase c, conjunction activity ($y_A = 40$ and $y_B = 40$) induces potentiation of $w_{B,A}$. During phase d, noncoincident activity ($y_A = 0$ and $y_B = 40$) again induces depression. (B) Hebbian rule incorporating reversible synaptic modifications and asymptotic limits on both potentiation and depression of synaptic weight (eq. 4.14), suggested by Levy (1985). The changes

weight occurs. When $c\,y_A < w_{B,A}$, depression occurs (phase b). When $c\,y_A > w_{B,A}$, potentiation occurs (phase c). Finally, the potentiation can be reversed when $c\,y_A < w_{B,A}$ and $G > 0$ (phase d). This reversal of potentiation is termed depotentiation (Levy 1985; see also Fujii et al. 1991). Learning rules that allow both increases and decreases in synaptic strength avoid eventual saturation and allow synapses to function throughout a broader dynamic range.

An additional feature that can be incorporated into these mathematical expressions of the Hebbian rule is a term describing the temporal specificity. As discussed above, presynaptic activity appears to produce a "trace" that allows the synapses to remain eligible for potentiation for several tens of milliseconds following cessation of presynaptic stimulation. A common method for incorporating a "trace" is by offsetting the presynaptic term by a time τ (for examples and additional discussion see Brown et al. 1990; Klopf 1988, 1989; Sejnowski and Tesauro 1989; Sutton and Barto 1981; Tesauro 1986). A general equation for the Hebbian rule that incorporates the differential effects of several values of τ can be written as follows:

$$\Delta w_{B,A}(t) = \varepsilon \sum_{\tau=0}^{k} F(y_A(t-\tau))\, G(y_B(t)) \tag{4.15}$$

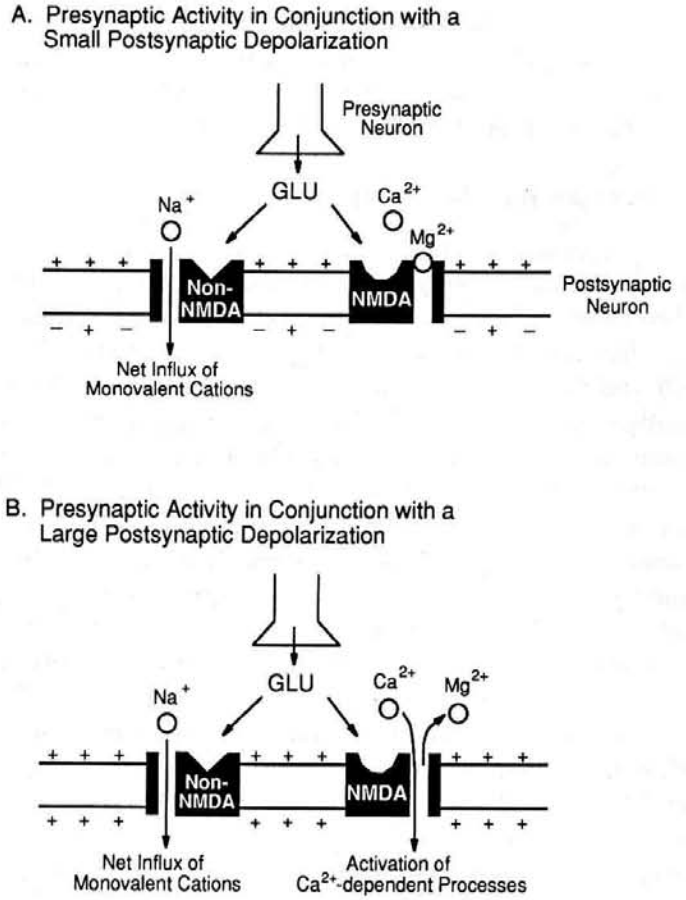
where $F(y_A(t-\tau))$ represents a function of the presynaptic stimulus "trace" and $G(y_B(t))$ represents a function of the postsynaptic activity. Several forms of the function F have been proposed. For example, F can equal the previous level of presynaptic activity, $c_\tau\, y_A(t-\tau)$ where c_τ is a positive coefficient that determines the contribution of each offset, or F can equal the change in the level of presynaptic activity, $c_\tau\,(y_A(t) - y_A(t-\tau))$. Similarly, there are a number of possible forms for G, such as the level of postsynaptic activity, $y_B(t)$, or the change in the level of postsynaptic activity. The use of changes in the level of activity is a way of reversing the sign of the synaptic modification (e.g., potentiation vs. depression) and thus avoids the problem of saturation (Klopf 1988, 1989).

In addition to the mathematical equations for the Hebbian rule discussed above (equations 4.12 through 4.15), a number of more biologically realistic and dynamic models of Hebbian synaptic plasticity have been developed (Gally et al. 1990; Gamble and Koch 1987; Holmes and Levy 1990; Kitajima and Hara 1990, 1991; Lisman 1989; Wickens 1988;

in $w_{B,A}$ that are predicted by equation 4.14 are illustrated during four phases of stimulation ($\varepsilon = 0.011$, and $c = 0.04$ in all four phases; initial value of $w_{B,A} = 1$). During phase a, only the presynaptic cell is active ($y_A = 50$ and $y_B = 0$) and $w_{B,A}$ remains unchanged. During phase b, only the postsynaptic cell is active ($y_A = 0$ and $y_B = 50$) and $w_{B,A}$ is depressed. During phase c, conjunctive activity ($y_A = 50$ and $y_B = 50$) induces potentiation of $w_{B,A}$. During phase d, noncoincident activity ($y_A = 0$ and $y_B = 50$) "depotentiates" $w_{B,A}$.

Zador et al. 1990). These models include formal descriptions of the many complex biophysical and/or biochemical processes that may underlie the induction and maintenance of associative LTP. For example, the central tenet of the Hebbian rule is the requirement for conjunctive presynaptic activity and postsynaptic depolarization in order for synaptic modifications to occur. It is generally agreed that this feature of Hebbian potentiation in CA1 area of the hippocampus is derived from an unusual property of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor: its dual regulation by transmitter and membrane voltage (for reviews see Brown et al. 1988, 1990, 1991; Bliss and Collingridge 1993; Collingridge and Bliss 1987; Collingridge and Singer 1990; Gustafsson and Wigström 1988; Madison et al. 1991; Nicoll et al. 1988; Siegelbaum and Kandel 1991; Teyler and DiScenna 1987; see also Cline 1991). As illustrated in figure 4.6, two events must occur before the ionophore of the NMDA receptor will open: The presynaptic transmitter, glutamate, must bind to the receptor and the Mg^{2+} block of the channel must be removed by a strong postsynaptic depolarization. The subsequent influx of Ca^{2+} through the open NMDA ionophore is critical for the induction of synaptic modifications (Collingridge et al. 1983; Lynch et al. 1983; Malenka et al. 1988). The elevation of postsynaptic Ca^{2+} is believed to trigger a complex sequence of enzymatic reactions that alter the properties of the postsynaptic and/or presynaptic cells (for reviews see Madison et al. 1991; Siegelbaum and Kandel 1991; Tsumoto 1990). (Chapter 2 discusses the consequences of this functioning for neuronal modeling, and chapter 3 points out similarities between the subsequent alteration of presynaptic transmitter release and connectionist models.)

Models that include quantitative descriptions of the NMDA receptor, of voltage-gated ionic channels, of the geometric and electrotonic structure of dendritic spines and process, and of the dynamics of the regulation of intracellular Ca^{2+} predict that short, high-frequency stimuli are more effective in elevating the concentration of Ca^{2+} than longer, low-frequency stimuli (Gamble and Koch 1987; Holmes and Levy 1990; Zador et al. 1990). Moreover, a model of Ca^{2+}-dependent enzymes in the postsynaptic spines predicts that the elevation of Ca^{2+} can trigger either potentiation or depression of synaptic efficacy (Lisman 1989). The "sign" of the modification is determined by the levels of Ca^{2+}: Lower levels of Ca^{2+} are predicted to induce synaptic depression and higher levels are predicted to induce potentiation. Taken together, these models appear to accurately predict the experimental observations that tonic, low-frequency stimulation tends to induce depression or depotentiation, whereas patterned, high-frequency stimulation tends to induce potentiation (Dudek and Bear 1992; Dunwiddie and Lynch 1978; Grover and Teyler 1990; Larson and Lynch 1986; Mulkey and Malenka 1992; Pavlides et al. 1988; Staubli and Lynch 1987, 1990). Moreover, these models provide insights into the spatial and temporal interactions among synapses in the complex dendritic structure of the postsynaptic cell. For



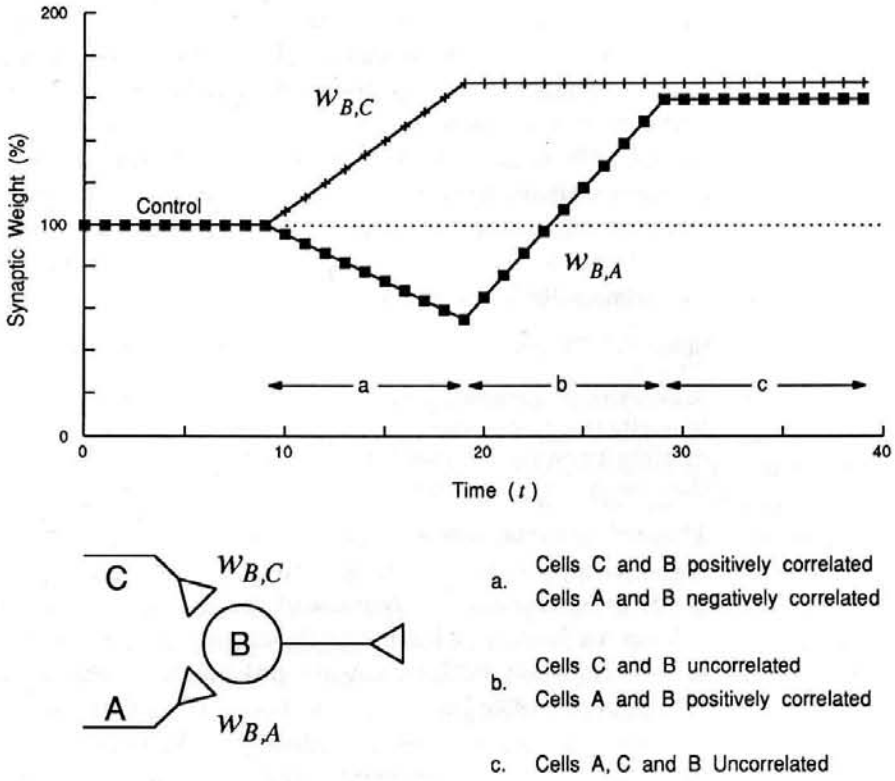
The NMDA Receptor: A Molecular Basis for the Hebbian Learning Rule

Figure 4.6 The dual regulation of the NMDA receptor by the binding of glutamate and by membrane voltage allows for the detection of conjunctive presynaptic and postsynaptic activity. (A) Presynaptic activity alone releases the excitatory transmitter glutamate (GLU), which binds to both NMDA and non-NMDA receptors. A net influx of monovalent cations through ionophores associated with the non-NMDA receptors produces postsynaptic depolarization. A voltage-dependent block by Mg^{2+} of the ionophore associated with the NMDA receptor prevents the postsynaptic influx of Ca^{2+} that is necessary for the induction of synaptic potentiation. (B) Presynaptic release of glutamate in conjunction with a large postsynaptic depolarization removes the Mg^{2+} block of the NMDA channel and allows Ca^{2+} influx into the postsynaptic neuron, activating Ca^{2+}-dependent processes that induce synaptic potentiation.

example, recent models indicate that postsynaptic spines play an important role in amplifying and compartmentalizing the Ca^{2+} signals that are crucial for synaptic modification (Gamble and Koch 1987; Holmes and Levy 1990; Koch et al. 1992; Zador et al. 1990).

Anti-Hebbian Rule for Synaptic Modification

An anti-Hebbian rule is one in which synaptic weights are decreased as a result of concurrent presynaptic and postsynaptic activity. As noted by Brown et al. (1990), the term anti-Hebbian is not used consistently in the literature. In addition, the terms "inverse-Hebbian" (Artola et al. 1990) and "reverse-Hebbian" (Donegan et al. 1989) have been used recently to describe synaptic depression resulting from concurrent presynaptic and postsynaptic activity. One form of synaptic plasticity that is generally consistent with the anti-Hebbian rule is LTD at the synapses from parallel fibers to Purkinje cells in the cerebellar cortex (for recent reviews of cerebellar LTD, see Ito 1989a, b, 1991, 1992; Siegelbaum and Kandel 1991). A similar form of anti-Hebbian synaptic depression recently has been observed in regions of the neocortex (Bindman et al. 1988; Hirsch and Crepel 1990). Stimulation of parallel fibers in conjunction with strong postsynaptic depolarizations, which elicit dendritic Ca^{2+} spikes, induces LTD at the stimulated synapses (Crepel and Jaillard 1991; Hirano 1990b; see also Crepel and Krupa 1988; Linden and Connor 1991; Linden et al. 1991). The induction of LTD is believed to require the concurrent increase in postsynaptic levels of Ca^{2+} (Sakurai 1990; see also Hirsh and Crepel 1992) and the activation of glutamate receptors (Kano and Kato 1987; Linden et al. 1991), which mediate parallel fiber to Purkinje cell transmission (Hirano 1990c; Hirano and Hagiwara 1988; Konnerth et al. 1990). These two events initiate a sequence of enzymatic reactions (for reviews see Siegelbaum and Kandel 1991; Ito 1991, 1992), the end result of which is to desensitize those glutamate receptors activated by the parallel fiber stimulation, which in turn depresses the efficacy of parallel fiber transmission. In addition to LTD, LTP of parallel fibers can be induced by either stimulating the parallel fibers alone, or stimulating them in conjunction with postsynaptic hyperpolarizations or with weak depolarizations, which elicit Na^{+} but not Ca^{2+} spikes (Crepel and Jaillard 1991; Hirano 1990a, b; Sakurai 1987). Thus, parallel fiber synapses can undergo either potentiation or depression and the determining factor is believed to be the level of Ca^{2+} in the postsynaptic cells: High levels of Ca^{2+} induce LTD, whereas low levels of Ca^{2+} allow for LTP. Interestingly, this is in contrast to plasticity in the CA1 region of the hippocampus, where high levels of postsynaptic Ca^{2+} are necessary for LTP and low levels are believed to induce LTD. There have been various attempts to model aspects of the cerebellar circuitry and to include mathematical expressions for plasticity at parallel fiber to Purkinje cell synapses (Chapeau-Blondeau and Chauvet 1991; Chauvet 1986;



a. Cells C and B positively correlated
Cells A and B negatively correlated

b. Cells C and B uncorrelated
Cells A and B positively correlated

c. Cells A, C and B Uncorrelated

Changes in Synaptic Weight Predicted by the Covariance Learning Rule

Figure 4.7 In the circuit shown, postsynaptic neuron B is innervated by two presynaptic neurons, A and C. The changes in synaptic weights predicted by the covariance rule, equation 4.16 (Sejnowski 1977), are illustrated during three phases of stimulation. During phase a, activity in cell A is negatively correlated with postsynaptic activity and its synaptic weight $w_{B,A}$ decreases ($y_A = 17$ and $y_B = 25$), whereas activity in cell C is positively correlated with the postsynaptic cell ($y_C = 25$ and $y_B = 25$), and its synaptic weight $w_{B,C}$ potentiates. During phase b, the activity in cell A is positively correlated with the postsynaptic cell, and its synaptic weight potentiates ($y_A = 27$ and $y_B = 25$), whereas activity of cell C is uncorrelated with the postsynaptic cell, and there is no change in its synaptic weight ($y_C = 20$ and $y_B = 25$). During phase c, the activities in both presynaptic cells are uncorrelated with activity in the postsynaptic cell, and there is no change in either of their synaptic weights ($y_A = 20$, $y_C = 20$, and $y_B = 20$). In all three phases, $\varepsilon = 0.003$, $\overline{y}_A = 20$, $\overline{y}_B = 20$, and $\overline{y}_C = 20$; initial values of both $w_{B,A}$ and $w_{B,C} = 1$).

Desmond and Moore 1988; Houk et al. 1990; Moore and Blazis 1989; Moore et al. 1989). Although the role that the cerebellum might play in motor learning is unclear (Bloedel et al. 1991; Donegan et al. 1989; Greenough and Anderson 1991; Thompson 1986, 1989; Wagner and Donegan 1989; Yeo 1991), these theoretical studies predict that the cerebellar circuitry and its related synaptic plasticity, in principle, can perform complex information processing and contribute to motor learning.

Covariance Rule for Synaptic Modification

Stent (1973) offered an extension to the Hebbian rule:

When the presynaptic axon of cell A repeatedly and persistently fails to excite the postsynaptic cell B while cell B is firing under the influence of other presynaptic axons, metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is decreased.

This rule further specifies that synaptic depression results from "an asynchronous activity pattern of the two cells"; not simply the disuse of the presynaptic axon. Aspects of this generalization of the Hebbian rule can be found in a learning rule that is referred to as the "covariance rule" (Sejnowski 1977; Sejnowski and Stanton 1990; see also Chauvet 1986; Cooper 1986; Dayan and Willshaw 1991; Reilly and Cooper 1990; Rubner and Schulten 1990). According to the covariance rule, changes in synaptic weight are proportional to the covariance between the firing rates of the presynaptic and postsynaptic cells:

$$w_{B,A}(t+1) = w_{B,A}(t) + [\varepsilon (y_A(t) - \overline{y}_A)(y_B(t) - \overline{y}_B)] \tag{4.16}$$

where $\overline{y}_A$ and $\overline{y}_B$ as before measure the sustained levels of activity in the presynaptic and postsynaptic cells, respectively. Thus, synaptic weight should increase if the pre- and postsynaptic activities are positively correlated, decrease if they are negatively correlated, and remain unchanged if they are uncorrelated. Figure 4.7 illustrates a numerical example showing how the synaptic weights of two presynaptic cells, A and C, can be governed by the covariance rule during three phases of stimulation. During the first phase (phase a in figure 4.7), activity in cell A is negatively correlated with postsynaptic activity and its synaptic weight ($w_{B,A}$) decreases. In contrast, the activity in cell C is positively correlated with the postsynaptic cell, and its synaptic weight ($w_{B,C}$) potentiates. During the second phase (phase b), the activity in cell A is positively correlated with the postsynaptic cell, and its synaptic weight potentiates. During this phase, activity of cell C is uncorrelated with the postsynaptic cell, and there is no change in its synaptic weight. Finally, in phase c, the activities in both presynaptic cells are uncorrelated with activity in the postsynaptic cell, and there is no change in either of their synaptic weights. Thus, the covariance rule overcomes a limitation inherent with nondecremental learning rules such as equation 4.12 and allows the weight of a synapse to be used throughout its dynamic range. In

addition, the covariance rule solves the problem of automatic growth in synaptic weight resulting from random coincidence of presynaptic and postsynaptic activity.

Recently, there have been reports of a form of synaptic depression in the hippocampus that appears to be a good candidate for the covariance rule (Sejnowski and Stanton 1990; Stanton and Sejnowski 1989; Stanton et al. 1989, 1991; see, however, Goldman et al. 1990). For example, a neural analog of the covariance rule was examined by stimulating two distinct inputs to CA1 pyramidal neurons, a strong input and a weak input. Stimulation of the strong input induced potentiation in the stimulated synapses without significantly affecting the unstimulated weak input. Stimulation of the weak input alone did not induce any changes in the synaptic efficacy of either input. If the weak input was stimulated out of phase with the strong input, however, depression was induced in the synapses stimulated by the weak input. This phenomenon was referred to as associative LTD (Stanton and Sejnowski 1989). Recently, a similar form of synaptic depression induced by asynchronous presynaptic and postsynaptic activity has been reported at vertebrate neuromuscular synapses in culture (Dan and Poo 1992). If the weak and strong inputs were stimulated in phase (simultaneously), potentiation was induced in the synapses of the weak input. The voltage of the postsynaptic cell may be an important determinant of this form of synaptic depression (Sejnowski and Stanton 1990). If stimulation of weak input was paired with intracellular depolarization of the postsynaptic cell, potentiation was induced in the synapses of the weak input. This is the Hebbian rule for synaptic potentiation. If stimulation of weak input was paired with hyperpolarization of the postsynaptic cell, however, depression was induced. A similar form of synaptic depression that results from pairing presynaptic activity with postsynaptic hyperpolarization recently has been observed in the dentate gyrus area of the hippocampus (Xie et al. 1992) and the visual cortex (Friedlander et al. 1993). Thus, there is evidence of a form of synaptic plasticity that is governed by the covariance rule, in that identical presynaptic stimulations of the weak input can produce either potentiation or depression depending on the phase relationship between presynaptic and postsynaptic activity.

Bidirectional/Variable Threshold Rule for Synaptic Modification

Bienenstock et al. (1982; see also Bear et al. 1987; Clothiaux et al. 1991; Cooper 1986; Cooper et al. 1979, 1985, 1990; Intrator and Cooper 1992) proposed a rule for synaptic modification that, in theory, might underlie the self-organization and learning in neural networks. This modification rule, sometimes referred to as the Bienenstock, Cooper, and Munro (BCM) rule, is predicated on the notion that individual synapses are capable of bidirectional modifications (both depression and potentiation) and whether the synaptic strength increases or decreases depends

upon the magnitude of the postsynaptic response as compared to a variable threshold θ. A general mathematical expression for this rule is:

$$\Delta w_{B,A}(t) = \phi(y_B(t), \theta(t))\, y_A(t)\,, \tag{4.17}$$

where ϕ is a scalar function of the postsynaptic activity that changes sign at a threshold θ and where y_B and y_A again represent activity in the postsynaptic and presynaptic cells, respectively. The precise form of ϕ is not critical as long as it has certain general characteristics:

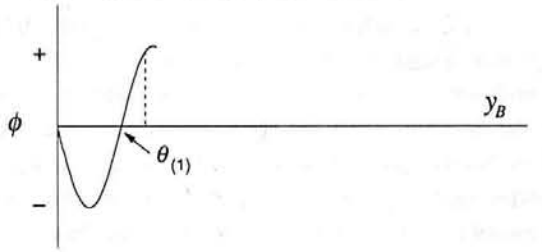
$$\phi = 0 \text{ for } y_B = 0; \quad \phi < 0 \text{ for } y_B < \theta; \tag{4.18a}$$

$$\phi = 0 \text{ for } y_B = \theta; \quad \phi > 0 \text{ for } y_B > \theta. \tag{4.18b}$$

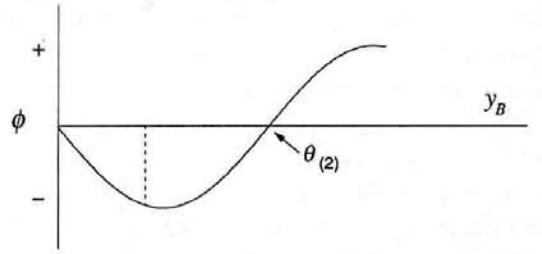
An arbitrary function that satisfies these general features is illustrated in figure 4.8 for two different values of the modification threshold θ. The two essential features of this rule are: first, ϕ changes sign at θ and second, the value of θ is not fixed. Thus, this rule predicts that a given presynaptic conditioning stimulus can produce such categorically different responses as potentiation, no change or depression depending on the magnitude of the postsynaptic response that the input elicits and on the current value of θ. For example, if the current threshold for synaptic modification is low (figure 4.8A, $\theta_{(1)}$), then a given presynaptic input that elicits the postsynaptic response indicated by the dotted line in figure 4.8A would induce synaptic potentiation; ϕ is positive. If the current threshold for synaptic modification is high (figure 4.8B, $\theta_{(2)}$), however, then the same presynaptic input and the same postsynaptic response (dotted line in figure 4.8B) would induce synaptic depression; ϕ is negative.

Recent experiments that examined synaptic plasticity in slices of visual cortex have provided support for some of the essential features of this rule. Artola et al. (1990; see also Reiter and Stryker 1988; Singer et al. 1990) found that identical presynaptic conditioning stimuli can lead to either no change, depression or potentiation of the activated synapses and that the critical determinant of the nature of synaptic modification appeared to be the level of postsynaptic depolarization or activity. Thus, presynaptic activity that was paired with postsynaptic hyperpolarization led to no change of synaptic efficacy, whereas presynaptic activity that was paired with moderate postsynaptic depolarizations led to synaptic depression, and presynaptic activity that was paired with stronger postsynaptic depolarizations led to synaptic potentiation. The molecular mechanism for the modification threshold θ is believed to involve the level of Ca^{2+} in the postsynaptic cell (Cooper et al. 1990; Kimura et al. 1990; Singer 1983, 1987, 1990). Moderate postsynaptic depolarizations are believed to activate voltage-dependent Ca^{2+} channels resulting in moderate increases in postsynaptic Ca^{2+} levels, which in turn lead to synaptic depression (see Bröcher et al. 1992). Stronger postsynaptic depolarizations are believed to activate Ca^{2+} influx through both voltage-dependent Ca^{2+} channels and NMDA receptors, which results in

A. Low Threshold for Synaptic Modification



B. High Threshold for Synaptic Modification



The Modification Function $\phi(y_B, \theta)$ Shown for Two Values of θ

Figure 4.8 ϕ is a theoretical function relating synaptic weight change to postsynaptic activity y_B. The sign of ϕ changes at θ, such that ϕ is negative (synaptic depression) for $y_B < \theta$, and ϕ is positive (synaptic potentiation) for $y_B > \theta$. The value of θ is variable. (A) Plot of ϕ for a low modification threshold, $\theta_{(1)}$. (B) Plot of ϕ for a high modification threshold, $\theta_{(2)}$. Thus, a presynaptic conditioning stimulus that produces the same level of postsynaptic activity (dotted lines) would produce synaptic potentiation if θ has a low value ($\theta_{(1)}$), but would produce synaptic depression if θ has a high value, ($\theta_{(2)}$). (Modified from Bienenstock et al. 1982, and from Yang and Faber 1991.)

greater levels of postsynaptic Ca^{2+} and synaptic potentiation (see Artola and Singer 1990; Artola et al. 1990; Bear et al. 1990; Singer et al. 1990).

In the original formulation of this learning rule (equation 4.17), it was proposed that θ vary as a nonlinear function of the average output ($\overline{y}_B$) of the postsynaptic cell (Bienenstock et al. 1982; see also Clothiaux et al. 1991):

$$\theta = F(\overline{y}_B) = (\overline{y}_B)^2 \,. \tag{4.19}$$

It should be noted that Bienenstock et al. (1982; see also Singer 1983, 1987) proposed that θ may also be influenced by global signals, such as modulatory systems; i.e., $\theta = F(\overline{y}_B, y_M)$. Recent experiments have illustrated that modulatory transmitters can have a permissive role for the induction of synaptic plasticity in the visual cortex (Greuel et al. 1988; Singer 1990). Recently Yang and Faber (1991) suggested as an alternative to equation 4.19 that the modification threshold θ might vary as a function of the initial level of synaptic efficacy: $\theta = F(w_{B,A})$. For example, potentiation of the synaptic inputs to the Mauthner cell of the goldfish can be induced by conjunctive presynaptic and postsynaptic activity

(Yang et al. 1990). If the synaptic efficacy is first elevated, however, the conditioning stimulus, which usually induces potentiation, produces synaptic depression instead (Yang and Faber 1991). Thus, the sign of the synaptic modification was changed by varying the level of synaptic efficacy. These results suggest the hypothesis that the modification threshold θ is increased for synapses with an initial efficacy that is elevated. Additional support for the hypothesis that θ may vary as a function of prior synaptic activity recently has been observed in the hippocampus (Huang et al. 1992).

The nature of the function that controls the modification threshold can have important implications for information processing and storage within single cells. Since $\overline{y}_B$ reflects postsynaptic activity, the value of θ would be the same for all presynaptic neurons that converge onto the cell. In contrast, if θ were a function of presynaptic efficacy, then each synapse could have a different value of θ. For example, consider a postsynaptic neuron, B, with one strong synaptic input, $w_{B,C}$, and one weak synaptic input, $w_{B,A}$. If θ were a function of $\overline{y}_B$, then the stronger synapse could maintain $\overline{y}_B$, hence θ, at a high level for both synapses, and thus could prevent the weaker synapse from potentiating. In contrast, if θ were a function of synaptic efficacy, then the value of θ should be less for the weaker synapse and greater for the stronger synapse.

Activity-Dependent Neuromodulation of Synaptic Efficacy

Activity-dependent neuromodulation is a form of associative synaptic plasticity in which presynaptic activity in conjunction with the presence of a modulatory transmitter produces a pairing-specific potentiation (or depression) of synaptic efficacy. This represents an extension of rule 4 (see figure 4.1) by requiring conjunctive activity in the two pathways. Thus, activity-dependent neuromodulation can be represented by the general expression:

$$\Delta w_{B,A}(t) = F(y_A, y_M)\,, \tag{4.20}$$

which relates changes in the efficacy of the synapse from neuron A to neuron B to activity in the presynaptic neuron y_A and in a modulatory neuron y_M. The key feature of this synaptic modification rule is that the conjunction of presynaptic activity and the presence of the modulatory transmitter produces a significantly greater change in synaptic efficacy than a simple summation of the effects that presynaptic activity alone (rule 1) and the modulatory transmitter alone (rule 4) have on synaptic efficacy. Activity-dependent neuromodulation has been observed in a number of excitatory synapses, including projections from the entorhinal cortex (perforant path) to granule cells in the dentate gyrus of the hippocampus (Williams et al. 1989), the mossy fiber synapses that arise from the dentate gyrus and terminate on the CA3 pyramidal neurons in the hippocampus (Hopkins and Johnston 1984, 1988; Johnston et al.

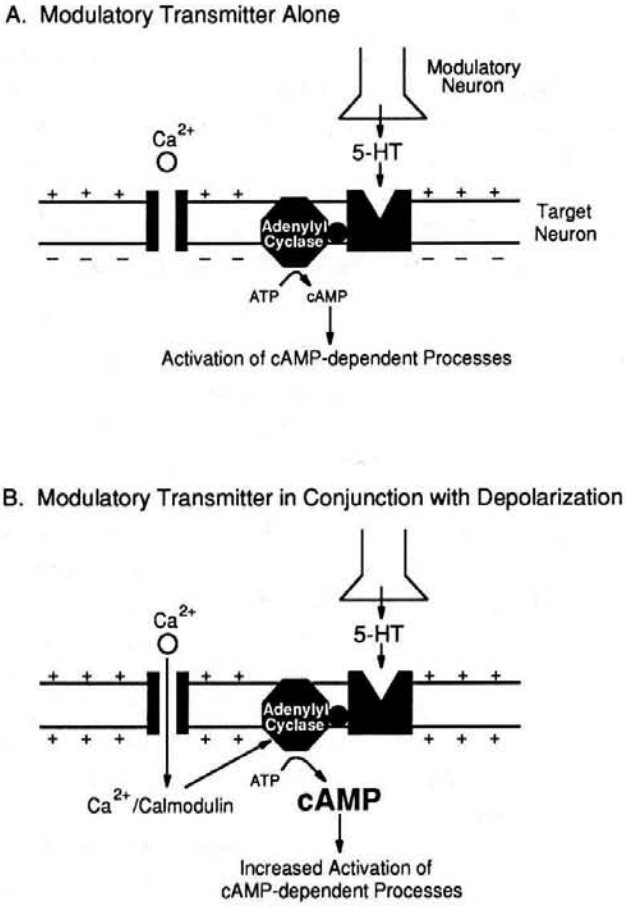
1989), Sch/comm projections to CA1 pyramidal neurons in the hippocampus (O'Dell et al. 1991; Small et al. 1992), crayfish neuromuscular synapses (Breen and Atwood 1983), and sensorimotor synapses of *Aplysia* (Buonomano and Byrne 1990; Hawkins et al. 1983; Small et al. 1989; Walters and Byrne 1983).

Gluck and Thompson (1987; see also Donegan et al. 1989) suggested a mathematical formalism to describe the activity-dependent neuromodulation of sensorimotor synapses in *Aplysia*:

$$\Delta w_{B,A}(t) = \varepsilon\, y_M(t)\, F(y_A(t-\tau))\, (\lambda_{\max} - w_{B,A}(t)) - (\gamma\, y_A(t)) \tag{4.21}$$

where y_M is a measure of activity in a modulatory neuron, $F(y_A(t-\tau))$ is a function describing a stimulus "trace" that is produced by presynaptic activity, and $(-(\gamma y_A(t)))$ represents a form of nonassociative homosynaptic depression that is induced by presynaptic activity. The temporal specificity of the associative interaction between the activities in the presynaptic neuron, y_A, and the modulatory neuron, y_M, is governed by the function $F(y_A(t-\tau))$. The suggested form of F was the product of exponentially decaying and rising functions. Thus, immediately after activation of the presynaptic neuron, the trace function F is 0, but then rises quickly to a peak and then slowly decreases. Equation 4.21 predicts that presynaptic activity ($y_A > 0$) in the absence of the modulator ($y_M = 0$) would result in nonassociative homosynaptic depression, and that activity in the modulatory neuron ($y_M > 0$) in the absence of presynaptic activity ($y_A = 0$) would not alter synaptic weight. Moreover, the temporal specificity function F predicts that simultaneous activity in the modulatory and presynaptic neurons would not induce synaptic potentiation. Rather, activity in the modulatory neuron would be most effective at inducing potentiation a short time after activity in the presynaptic neuron, when F reaches its peak.

Although equation 4.21 captures some features of activity-dependent neuromodulation, this formalism is an oversimplification of the cellular mechanisms contributing to this form of associative plasticity at sensorimotor synapses in *Aplysia*. Many of the biophysical and biochemical processes that contribute to activity-dependent neuromodulation in *Aplysia* have been determined (for reviews, see Abrams and Kandel 1988; Byrne 1987; Byrne and Crow 1991; Byrne et al. 1991a). For example, a key feature of this associative rule for synaptic plasticity is that the conjunction of presynaptic activity and the presence of the modulatory transmitter produces a significantly greater potentiation of synaptic efficacy than either treatment alone. It is generally believed that this feature of activity-dependent neuromodulation is derived from the dual regulation of the enzyme adenylyl cyclase in the sensory neurons by the modulatory transmitter serotonin and by intracellular Ca^{2+}/calmodulin (Abrams and Kandel, 1988; Abrams et al. 1991; Eliot et al. 1989; Ocorr et al. 1985; Yovell and Abrams 1992; see also Dudai 1987). As illustrated in figure 4.9, binding of serotonin to its receptor stimulates adenylyl



Adenylyl Cyclase: A Molecular Basis for the Activity-Dependent Neuromodulation Learning Rule

Figure 4.9 The enzyme adenylyl cyclase detects the conjunctive activity in a neuron and the modulatory effects produced in that neuron by a modulatory pathway. (A) Activity in the modulatory neuron releases the transmitter serotonin (5-HT). Binding of serotonin to its receptor stimulates adenylyl cyclase and elevates levels of cAMP in the target neuron. The increased levels of cAMP, in turn, activate cAMP-dependent processes that result in nonassociative heterosynaptic potentiation. (B) An influx of Ca^{2+} during action potentials in the target neuron interacts with a Ca^{2+}/calmodulin–sensitive component of adenylyl cyclase and significantly amplifies the production of cAMP elicited by the modulatory transmitter, and hence the activation of cAMP-dependent processes.

cyclase and elevates levels of cAMP in the sensory neurons (figure 4.9A). The increased levels of cAMP, in turn, activate cAMP-dependent processes, such as cAMP-dependent protein kinase A, that modulate a number of properties of the sensory neurons, including ion channels and secretory machinery, that contribute to synaptic potentiation. Thus, the release of the modulatory transmitter alone induces nonassociative heterosynaptic potentiation (for reviews, see Byrne et al. 1991c; Kandel and Schwartz 1982). The influx of Ca^{2+} during presynaptic activity (figure 4.9B) interacts with a Ca^{2+}/calmodulin–sensitive component of adenylyl cyclase and amplifies the production of cAMP elicited by the modulatory transmitter. This dual activation of adenylyl cyclase requires that the Ca^{2+} and modulatory transmitter temporally overlap. Thus, enhanced synthesis of cAMP by conjunctive presynaptic activity and the modulatory transmitter induces a pairing-specific potentiation of synaptic efficacy.

Two additional biologically realistic and dynamic models of activity-dependent neuromodulation have been developed that reflect aspects of the cellular mechanisms underlying this form of associative synaptic plasticity in sensory neurons of *Aplysia*.

Hawkins (1989a, b) developed a relatively simple model of seven differential equations that describe three phenomena: (1) nonassociative homosynaptic depression solely as a function of Ca^{2+} channel inactivation; (2) nonassociative heterosynaptic potentiation as a function of cAMP-dependent increases in spike duration, and therefore Ca^{2+} current; and (3) activity-dependent neuromodulation as a function of Ca^{2+}-dependent enhancement of cAMP synthesis.

Gingrich and Byrne (1984, 1985, 1987) developed a somewhat more detailed model. Some of the general features of the Gingrich and Byrne model are illustrated in figure 4.10. The details of this model have been described previously (Buonomano et al. 1990; Byrne and Gingrich 1989; Byrne et al. 1989; Gingrich and Byrne 1985, 1987; Gingrich et al. 1988; Raymond et al. 1992). The model contains differential equations describing two pools of transmitter, a releasable pool and a storage pool. During a presynaptic action potential, an influx of Ca^{2+} through voltage-dependent Ca^{2+} channels causes the release of transmitter. Thus, the amount of transmitter that is released is a function of both the dynamics of Ca^{2+} influx and the number of vesicles in the releasable pool. As a consequence of release, the releasable pool is depleted. In order to offset depletion, transmitter is delivered (mobilized) from the storage pool to the releasable pool. The mobilization process is regulated, in part, by the intracellular concentrations of cAMP and Ca^{2+}. The influx of Ca^{2+} during simulated action potentials leads to the release of transmitter and accumulation of intracellular Ca^{2+}. The pool of intracellular Ca^{2+} is divided into a submembrane compartment and an interior compartment. The Ga^{2+} within the submembrane compartment regulates the release of transmitter, whereas the Ca^{2+} within the interior compartment contrib-

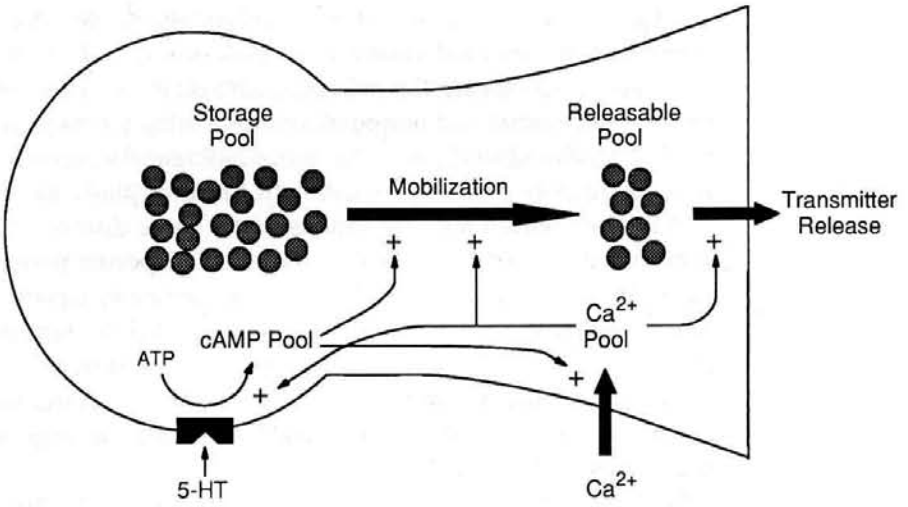
utes to the regulation of mobilization and to the regulation of cAMP synthesis (see below). Two fluxes remove Ca^{2+} from the interior compartment: one that represents active buffering of Ca^{2+} by organelles and one that represents diffusion of Ca^{2+} into an innermost compartment that serves as a Ca^{2+} sink.

The Gingrich and Byrne model also includes differential equations describing the concentration of cAMP and its effects on the release of transmitter. The modulatory transmitter, 5-HT, activates adenylyl cyclase, which leads to synthesis of cAMP. Increased levels of cAMP contribute to an increase in the duration of the action potential, which results in an increased influx of Ca^{2+} during a subsequent action potential in the sensory neuron, and hence, an increase in the release of transmitter from the sensory neuron. Empirical results indicate that the activity of adenylyl cyclase is also regulated by intracellular levels of Ca^{2+} (see above). In the model, an influx of Ca^{2+} during presynaptic spikes that precede the modulatory transmitter, primes the cyclase and amplifies the subsequent stimulation of cAMP synthesis, which in turn, leads to a pairing-specific enhancement of synaptic efficacy.

This dynamic model accurately simulates many aspects of empirically observed synaptic plasticity in sensory neurons of *Aplysia*. For example, this model simulates nonassociative homosynaptic depression and serotonin-induced heterosynaptic potentiation. In the model, this homosynaptic depression is due to the combined effects of Ca^{2+}-current inactivation and depletion of the releasable pool. Heterosynaptic potentiation is due to the combined effects of transmitter mobilization and cAMP-mediated broadening of the presynaptic action potential. In addition, this model simulates features of activity-dependent neuromodulation, including pairing-specific enhancement of synaptic potentiation and the requirement for a close temporal association between presynaptic activity and the presence of modulatory transmitter. In the model, neuromodulation is a function of the interstimulus interval (ISI) between presynaptic activity and application of the modulatory transmitter. Activity-dependent neuromodulation is optimal for an ISI of about 200 ms, in which presynaptic activity begins 200 ms before the application of the modulatory transmitter, whereas longer ISIs are less effective. This ISI-dependence of the model is a direct consequence of the kinetics of the buffering of intracellular Ca^{2+}. Thus, the elevation of intracellular Ca^{2+} produced by the presynaptic activity serves as a stimulus "trace" that becomes associated with the closely paired application of the modulatory transmitter.

CONCLUSIONS

Several general themes have been highlighted in this chapter. First, many diverse forms of activity-dependent synaptic plasticity exist. Indeed, individual neurons often express more than one form. Second, the in-



Gingrich and Byrne Model for Activity-Dependent Neuromodulation

Figure 4.10 The model contains equations describing two pools of transmitter, a releasable pool and a storage pool. During a simulated action potential, an influx of Ca^{2+} through voltage-dependent Ca^{2+} channels causes the release of transmitter. Transmitter is delivered (mobilized) from a storage pool to the releasable pool. The mobilization process is regulated, in part, by the intracellular concentrations of cAMP and Ca^{2+}. The modulatory transmitter 5-HT activates adenylyl cyclase, which leads to increased synthesis of cAMP. Increased levels of cAMP contribute to an increase in the duration of the action potential, and hence, an increased influx of Ca^{2+}. In the model, an influx of Ca^{2+} during presynaptic spike activity that precedes the modulatory transmitter, primes the cyclase and amplifies the subsequent stimulation of cAMP synthesis. Thus, convergence at adenylyl cyclase of the Ca^{2+} signal and the modulatory transmitter results in an associative amplification of the synthesis of cAMP, which in turn leads to a pairing-specific enhancement of synaptic potentiation. (Modified from Gingrich and Byrne 1987.)

duction of synaptic plasticity is governed by a complex set of spatial and temporal rules that can be imposed by the presynaptic neuron, postsynaptic neuron, neighboring synapses, or by modulatory neurons. Third, in neurons where multiple forms of synaptic plasticity are expressed, these rules can allow for the selective induction of a particular form of synaptic modification or for different regions of a single cell to act independently in the processing and storage of information. Moreover, these rules can allow for the dissociation of information storage from information processing within a single neuron.

Finally, two approaches have been used to describe and model synaptic plasticity quantitatively: biologically realistic, dynamic models and relatively simple, abstract mathematical equations. Each approach has its advantages and disadvantages. The relatively simple equations have the advantage of being computationally efficient; thus they can be readily incorporated into large-scale simulations of neural networks. In addition, they capture or provide a caricature of many of the more general features of the plasticity. These equations, however, do not

incorporate some features of synaptic plasticity that are likely to be important in neuronal information processing and storage, such the stimulus specificity for the induction and reversal of synaptic plasticity or complex spatial and temporal synaptic interactions (nor can they be readily modified to do so). The more biologically realistic models can more accurately predict how different forms of plasticity might emerge and interact within a single synapse, how these different forms of synaptic plasticity can be selectively induced by specific patterns of stimulation, the spatial and temporal interactions among synapses that converge onto overlapping dendritic regions, and the striking nonlinearities that characterize synaptic information processing and storage. Unfortunately, these biologically realistic models tend to be computationally intensive and thus are slow and cumbersome when used for large-scale simulations of neural networks.

Given the diversity of learning rules described in this chapter, an obvious question is, What types of learning do they mediate? Are some types of rules used selectively for some forms of learning (e.g., motor learning and skills) and other rules used for more cognitive other forms of learning (for discussion, see Mishkin et al. 1984; Squire 1987)? Answers to these questions are not yet available, but it seems likely that the consequences of a learning rule will depend very much on the circuit into which it is embedded. Indeed, any one learning rule may mediate different forms of learning. Several qualitative and quantitative modeling studies have demonstrated this principle (Baxter et al. 1991; Brindley 1967; Buonomano et al. 1990; Burke 1966; Byrne et al. 1991b; Gluck and Thompson 1987; Hawkins 1989a, b; Hawkins and Kandel 1984; Morris 1990; Raymond et al. 1992). For example, Gingrich and Byrne (1987; Byrne and Gingrich 1989; Byrne et al. 1989) illustrated how a single-cell model that incorporated the activity-dependent neuromodulation learning rule can simulate several simple featues of classical (Pavlovian) conditioning. Moreover, when incorporated into a simple three-cell network, the activity-dependent neuromodulation learning rule can simulate several higher-order features of classical conditioning, such blocking and second-order conditioning (Baxter et al. 1991; Buonomano et al. 1990; Byrne et al. 1991b; Gluck and Thompson 1987; Hawkins 1989a, b). Finally, when incorporated into a seven-cell network which spontaneously generates patterned activity, the activity-dependent neuromodulation learning rule can simulate many features of operant (instrumental) conditioning (Baxter et al. 1991; Byrne et al. 1991b; Raymond et al. 1992). Thus, it appears that a full understanding of the relationship between synaptic plasticity and learning requires an appreciation of different forms of learning and of the different neural architectures within which a given type of synaptic plasticity is embedded.

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