Adaptive Synaptogenesis Can Complement Associative Potentiation/Depression

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ABSTRACT

Adaptive modifiability is a hallmark of the nervous system and many neural like networks. Consistent with this presumption, there are many network simulations where connection weight modifications store information. However, almost all of these simulations are built with an immutable set of prespecified connections even though natural networks probably can make or break a synapse based on a modest set of rules and on the activity history of each neuron.

In an attempt to relate the experimental literature on synapse formation to such activity dependent rules, we have identified some particularly relevant anatomical studies. These studies imply two simple rules that, together with associative modification of existing synapses, might make up a complete set of rules controlling connectivity of excitatory synapses. In particular, we are inspired by various experimental studies to hypothesize a presynaptic mechanism and a postsynaptic mechanism that together control new synapse formation. We have previously pointed out that such anatomical observations, and the implied growth rules, are consistent with and complement the experimentally observed associative synaptic modification rule of the hippocampal dentate gyrus.

The purpose of this communication is to show, via computer simulations, that these simple microscopic rules can reproduce some of the normal and experimentally induced electrophysiological observations of the developing visual cortex.

As pointed out by Hebb (1949) there is little reason to consider the issues of perceptual development and the issues of learning to be fundamentally different—whether studying them as abstract cognitive processes or studying them at the microscopic, biological level. That is, regardless of how old an animal is, there

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is the problem of how the brain uses experience to determine its own connectivity. With this perspective and with supporting evidence that implies synaptic modification throughout the lifetime of an animal, we are comfortable interrelating observations from various times in the organism’s life to understand adaptive modifications of brain circuitry based on synaptic modification. Within this philosophy one question to consider is—What are the local modification rules used by neurons to control their own connections?

Modification of connectivity falls into two broad classes: modification of existing synapses and synaptogenesis. We have explained previously the evidence for one particular class of associative weight modification rules (Levy, 1982; Levy & Desmond, 1985a, and b; Levy & Steward, 1979). A rule of this class seems also to control the functional characteristics of developing neurons in the kitten visual cortex (Rauschecker & Singer, 1979, 1981). On the other hand, synaptogenesis and the conditions that favor synaptogenesis appear distinct from this associative modification rule based on observations in a number of systems outside of the hippocampus and visual cortex (Lomo & Rosenthal, 1972; Sabel & Schneider, 1988; Wolff, Joo, Dames, & Feher, 1979).

The purpose of this chapter is to describe a pair of synaptogenesis rules consistent with the studies above that: (a) is complementary to the associative weight modification rule; (b) allows a network to usefully self-organize from zero connections; and (c) explains, i.e. reproduces, a set of experimental observations concerning cortical development.

The observations of cortical development of interest here are the ocular dominance characteristics of neurons in visual cortex. Ocular dominance, or just ocularity, refers to the relative ability of a stimulus presented to one eye to fire a neuron compared to the ability of the same stimulus to fire a neuron when presented to the other eye. This chapter presents simulations of the normal development of ocularity of cells in the kitten visual cortex. Additional simulations investigate the effect of monocular deprivation when such deprivation occurs either alone or combined with pharmacological agents that augment or inhibit the processes underlying associative modification and synaptogenesis.

**Background**

The need for a complementary relationship among the adaptive rules governing synaptic modification, including new synapse formation, has not yet become widely appreciated. In particular, most people seem happy with Hebb’s idea that one associative rule should govern both new synapse formation and modification of existing synapses. Hebb’s suggestion, however, leads to poorly used neurons. We, on the other hand, take it as axiomatic that the nervous system adaptively wires itself so that with high probability a neuron is not poorly used but is well used. (A poorly used cortical neuron is one that is not firing very much or is firing only in response to one or very few afferents.)
In his 1949 book, Hebb posits his now famous idea that coactivity of pre- and postsynaptic elements forming a synapse leads to a strengthening of this synapse via an associative weight modification rule. However, before such a modification occurs, Hebb posits a synaptogenesis mediated by an associative, electrotaxis property that brings neural processes together. That is, coactivity of an axon and a dendrite that are nearby but not in contact leads to a contact (synapse) being formed. However, it is now known that neurons often have many axon collaterals and that sprouting can occur so that single axons seem to easily collateralize. If we consider Hebb’s developmental picture plus the capability for such sprouting, there is the immediate inference that a positive feedback situation results. The initial innervation increases the degree of coactivity between the afferent(s) forming the earliest synapse(s) and its postsynaptic targets. With sprouting, more synapses form and correlated coactivity increases even more. Thus, following Hebb’s logic of associative electrotaxis, a postsynaptic cell will become dominated by one or a small set of inputs that made the earliest synapses.

Likewise, there is the problem of the poorly used cell due to inactivity. Without a certain minimal level of excitatory input, such a cell does not fire, and thus it transmits no information due to its input. This cell is essentially wasted without additional innervation. Fortunately, new innervation requires coactivity, which is precisely what this uninnervated cell does not have. Thus we see that without other special postulates Hebb’s new synapse rule leaves much to be desired in the sense that it cannot guarantee cells are well used. Other authors have considered (Grossberg, 1982) and modeled (Hirai, 1980) similar consequences of specific rules governing new synapse formation.

As we became disenchanted with this one of Hebb’s ideas, we began to study the biological literature on new synapse formation. Most importantly, we looked for experimental studies where manipulations of variables local to a presynaptic or postsynaptic cell resulted in changes clearly related to synaptogenesis. In our reading, not all studies were of equal value. Clear and unambiguous manipulation of a functionally related variable was very important. Regarding the measured variables of synaptogenesis experiments, neurophysiologically studied modifications are ambiguous as to whether the observed changes are caused by the modification of existing synapses or by the formation of new synapses. Carefully controlled anatomical work, however, can unambiguously identify the formation of new synapses or even precursor events to new synapse formation.

We now briefly review the features of these studies (see also Levy & Desmond, 1985a) pertinent to the description of the rules governing synaptogenesis. Insight into the postsynaptic rule comes from studies of the peripheral nervous system by two research groups. Lomo and colleagues (see, e.g., Lomo & Rosenthal, 1972; Lomo & Slater, 1978) use the adult neuromuscular system to show that lowered postsynaptic activity leads to increased innervation. Wolff and colleagues (see, e.g., Wolff, Joo, Dames, & Feher, 1979, 1981) use the superior cervical ganglion to show that inhibitory substances, such as y-aminobutyric acid.
(GABA), produce a proliferation of postsynaptic sites, and that these sites are permissive for innervation when a suitable presynaptic nerve is nearby. The most relevant experiments were performed in the superior cervical ganglion, but we first review work in the neuromuscular junction that preceded the ganglion work and foreshadowed the later results.

Normally an adult muscle is innervated by a single nerve. However, if the activity of the muscle is depressed by any one of a variety of manipulations including application of tetrodotoxin or curare, then multiple innervation ensues. When excitatory stimulation is applied, the extra connections are lost via a competitive process that seems no different, in the abstract, from associative potentiation/depression in the dentate gyrus.

The experiments performed in the superior cervical ganglion are more relevant to formulating a rule for the brain for at least two reasons. First, ganglion synapses are more similar than neuromuscular junctions to brain synapses. Second, a normally present inhibitory substance is used in the experiments. In these experiments, bathing the ganglion with the inhibitory substance produces a proliferation of the postsynaptic portion of a synapse; that is, there are more postsynaptic densities without associated presynaptic structures following the treatment. This proliferation of free postsynaptic sites is due to an increase in the number of such sites, not a disengagement of existing presynaptic structures. Two other results from this laboratory extend these observations. First, similar manipulations have similar effects in cerebral cortex, which normally has very few, <1%, free postsynaptic density sites (Balcar, Erdo, Joo, Kasa, & Wolff, 1987). Second, if a cut axon bundle is placed near these free postsynaptic sites in the superior cervical ganglion, then innervation of the free site occurs. However, if the free sites are not induced, then no innervation occurs (Joo, Dames, & Wolff, 1983). Our conclusions from this body of work are that the postsynaptic, target structure limits new synapse formation and that postsynaptic inhibition, or perhaps just lack of postsynaptic excitation, is the trigger for providing sites for additional innervation.

The presynaptic rule comes from work by Schneider and colleagues (see e.g., Sabel & Schneider, 1988) and is based on an observation they call the pruning effect. In gardening, one can prune some portion of a shrub or a tree in order to stimulate growth elsewhere. This is just what they observed in mammalian brain during development. Retinal ganglion cells innervate both the lateral geniculate nucleus and the superior colliculus. If the innervation to the superior colliculus is destroyed, presynaptic terminals in the lateral geniculate proliferate. Sabel and Schneider (1988) describe recent evidence implying that the effect is one of pruning and not of reactive synaptogenesis (i.e., the lesion induced sprouting extensively documented in the hippocampus, see e.g., Steward, 1986).

From studies like these and our own work on associative potentiation/depression (see appendix, and e.g. Levy & Steward, 1979) we devised three adaptive
rules (Levy & Desmond, 1985a): An associative modification rule for existing synapses (including both potentiation and depression, or in other words a competition); a presynaptic synaptogenesis rule (avidity); and a postsynaptic synaptogenesis rule controlling the number of suitable sites (receptivity).

We now detail these three rules. Consider a postsynaptic cell $j$, presynaptic cell $i$, and the possibility of one or more synapses $\{k\}$ between $i$ and $j$ with individual weights $w_{i,j}$ Then the version of three adaptive rules from Levy and Desmond (1985b) that are used here are:

I. Weight modification ($\Delta w_{i,j}$) of existing synapses: Long term associative potentiation/depression controls excitatory synapse modification as

$$\Delta w_{i,j} = \varepsilon f(y_j)(cx_i - w_{i,j}),$$

where $\Delta w_{i,j}$ is the change in the weight $w_{i,j}$; $x_i$ is the activity of the $i^{th}$ presynaptic cell, $y_j$ is the postsynaptic activity ($= \sum \sum_{k} w_{i,j} x_i$) of the $j^{th}$ cortical cell; $f(y_j)$ is a monotonically increasing function of postsynaptic activity (for simplicity in the simulations a linear function is used though experimental evidence favors a highly nonlinear relationship); $\varepsilon$ is a small positive constant that controls the rate of convergence of $w_{i,j}$ to a steady-state value; and $c$ is a positive constant to match units of $x_i$ and $w_{i,j}$. The basis of this rule is found in Levy and Steward (1979) and Levy and Desmond (1985b).

II. New synapse formation—Postsynaptic receptivity ($R_j$) for new innervation: This variable increases as postsynaptic activity decreases as

$$R_j = \frac{1}{1 + c_s(y_j)^q},$$

where $\bar{y}_j$ is the average activity of $j$ (in the simulations here $\bar{y}_j$ is averaged over an interval 500 times longer than the interval governing $\varepsilon$); $c_s$ is a constant that determines the value of postsynaptic activity resulting in half-maximal receptivity; and $q$ is a positive constant that determines the steepness of the receptivity curve. This receptivity rule is our quantification of Wolff’s and Lomo’s research described earlier.

III. New synapse formation—Presynaptic avidity ($A_i$) for growing into a postsynaptic site. This variable increases as the total weight of a presynaptic cell (i) decreases as

$$A_i = \frac{1}{1 + c_d(\sum \sum_{j,k} w_{i,j})^p}.$$
where $\sum_{j} \sum_{k} w_{ik}$ is the total synaptic weight of presynaptic cell $i$; $c_a$ is a constant that determines the total presynaptic weight that results in half-maximal avidity; and $p$ is a constant that determines the steepness of the avidity curve. This avidity rule is one of our quantifications of Schneider's theory of pruning induced terminal proliferation. A more complex rule is the dynamic version found in Levy and Desmond (1985a).

In order to confirm the viability and the compatibility of these three rules, we modeled four sets of observations generated by research on the developing kitten visual cortex. The variable of interest in all these experiments is ocularity (the ability of a stimulus presented to the left eye to fire a cell compared to the ability of the same stimulus presented to the right eye to fire the same cell). The modal result of kitten development in a normal environment is the existence of cells that are roughly equivalent in their responsiveness to the left or right eye although many cells show varying degrees of biased responsiveness to left versus right eye stimuli. One control and three experimental conditions are simulated:

1. Normal environment: This environment leads to normal, binocularly responsive postsynaptic cells (Hubel & Wiesel, 1962). The other three conditions are manipulations that follow rearing in the normal environment and the ensuing normal innervation. These additional manipulations are made within the critical period during which environmental conditions can alter neuronal eye preference.

2. Monocular deprivation by closing one eye: This condition leads to postsynaptic cells whose activity is dominated by the open eye (Hubel & Wiesel, 1970).

3. Monocular deprivation while the drug 2-amino-5-phosphonovaleric acid (APV) is infused into a region of visual cortex: APV blocks associative modification without blocking either pre- or postsynaptic activity (Kleinschmidt, Bear, & Singer, 1987). With this drug present, monocular deprivation no longer produces ocularity shifts.

4. Monocular deprivation while the GABA agonist muscimol is present in one region of visual cortex. Muscimol inhibits postsynaptic activity and thus blocks associative modification. For the cells outside the region of drug action, however, the environment is the same as in Condition 2 and the result is the same. For cells within the drugged region, the opposite result occurs, namely a shift in ocularity toward the closed eye (Reiter & Stryker, 1988).

The difficulty encountered in explaining all four of these results via the associative synaptic modification rule described earlier is that, under both drug conditions, the associative synaptic modification rule is inoperative. That is, because associative modification depends on excitation, the drug manipulation in Condition 4, which enhances inhibition, does not allow associative modification
3. SYNAPTOGENESIS COMPLEMENTS POTENTIATION/DEPRESSION

...yet an ocularity shift occurs under Condition 4 but not Condition 3. Additionally, because the ocularity shift is opposite of the one normally produced, something more than associative modification seems to be involved.

**Modeling Development of Ocular Dominance**

The network model is a highly simplified version of visual cortex, consisting of two postsynaptic cortical cells that are candidates to receive inputs from 16 lateral geniculate (LGN) cells. Eight of the LGN cells are driven by the right eye, and the other eight are driven by the left eye. Normal activity patterns are stochastically generated with a fair amount of correlated activity between the LGN axons of the two eyes. (The level of correlation was varied in different runs of the simulations.) Monocular deprivation is modeled by reducing the correlation and/or the average level of activity of the LGN cells associated with the deprived eye. Drug effects are modeled by appropriate adjustment of equation parameters. In all cases synaptic weights are regularly updated in parallel. Postsynaptic activity is calculated in parallel and is based on input activity, drug effects, and the relevant synaptic weights.

In order to use rules II and III, new synapse formation is modeled as a stochastic process. Postsynaptic receptivity is equivalent to the number of available, unoccupied postsynaptic sites. Presynaptic avidity quantifies the probing, searching, ameboid-like movements of a cell's axonal branches. This probing growth increases as the presynaptic cell's total synaptic weight \( \sum \sum w_{ij} \) decreases. Increases of receptivity or avidity then contribute to increases in the probability of an encounter between an axonal branch of \( i \) and a vacant postsynaptic site of \( j \) to form a new synapse \( i,j \).

In order to perform the simulations, there are variables to set that do not appear in the modification rules. One of these is the weight value of a new synapse. In practice it was rather easy to specify a value that was small, that allowed the simulations to duplicate the biological experiments, and that seemed sensible relative to synaptic strengths of potentiated synapses.

Another variable not appearing in the rules, and one that was modeled in two ways, is the minimum strength of a synapse. [Note that Rule I guarantees non-negativity and only zero asymptotically (Levy & Geman, 1982)] The simulations produced the same results when the minimum was zero or a slightly larger number. However, if the minimum weight was set as non-zero so that the synapse vanishes when its strength falls below this minimum, then it was necessary to specify the initial value of a new synapse to be slightly larger than this minimum.

The receptivity curve \( R \) was chosen so that (a) synapse formation is low in the steady-state following normal development and so that (b) in the presence of muscimol, receptivity increases as implied by Balcar et al. (1987). Likewise, the avidity curve \( A \), was chosen so that avidity is low in the steady-state normal
environment and increases when synaptic weight is lost due to Rule 1 induced depression.

Results

Setting the free variables to fit all the experimental observations was readily accomplished. Further work showed that the simulations were relatively insensitive to the exact values of any particular variable.

The network automatically wires the postsynaptic cells to produce binocularity, thus satisfying Condition 1. Figure 3.1 shows an example of how cell activity and the adaptively modifiable variables develop over time in a simulation of normal environmental conditions. The initial innervation is extremely rapid because at the earliest time points both receptivity and avidity are at a maximum for all cells. Note that even in a normal environment there is enough fluctuation in the amount and correlation of input activity to cause ongoing associative synaptic modification as well as occasional increases in avidity. Finally, based on relative weights, each postsynaptic cell is nearly, but not perfectly binocular. Extensive simulations indicate that the mirror symmetry of ocularity between these two cells is not accidental but arises from the modification rules and the statistics of the input environment.

Condition 2, visual deprivation of one eye, was simulated either as a decrease in average activity or as a decrease in the correlation between the afferents of the deprived eye. In either case Rule 1 causes the synaptic weight(s) of afferents associated with the closed (left) eye to decrease and those associated with the open eye to increase. As a result of these synaptic weight changes, there is a net shift in ocularity toward the open (right) eye for both cortical cells. Figure 3.2 shows the effect of normal development followed, at cycle 10, by the monocular deprivation condition. In this example, monocular deprivation is modeled by greatly decreasing the correlated cell firing of the afferents driven by the deprived eye. Note that the competition effect, i.e. the shift in ocularity towards the open eye, occurs rapidly with the open (right) eye afferents dominating the activity of both postsynaptic cells.

For the two drug manipulations, Conditions 3 and 4, we simulate the experiments as if the drug reaches one cell but the other cell is too distant and remains drug free.

If a drug like APV is used to block Rule 1 without blocking postsynaptic activity (as in Condition 3), then the ocularity shift favoring the open (right) eye is blocked. Figure 3.3 shows the effect of monocular deprivation with APV blocking Rule 1 for one of the cortical cells beginning at cycle 10. Where APV blocks Rule 1, there is no shift in ocular dominance even though Rules II and III are operating. On the other hand, the untreated cells simultaneously show the normal ocularity shift with monocular deprivation. Because drugs like APV block associative potentiation in the hippocampus (Herron, Lester, Coan, &
FIG. 3.1. Development under normal conditions. This figure, and all succeeding figures, illustrate the simulation of a single experiment. Figure 3.1 shows the results of 25 cycles of a normal input environment. The top graph (postsynaptic activity) shows the activity of the two postsynaptic cortical cells, designated A and B, in response to the afferent activity sequence. The next graph (ocularity) shows ocular preference for each of the two cells A and B. Positive numbers indicate left preferring and negative numbers indicate right preferring. The values plotted are the differences between the percentages of total synaptic weight of afferents associated with each eye. Zero is perfectly binocular; plus and minus 100% are perfectly monocular. The middle graph shows the receptivity of cells A and B. The lower two graphs (avidity) shows the avidity of afferents associated with each eye. Each eye commands eight LGN afferents. The values used in this simulation and the other illustrated simulations are:

\[ c_s = 200; \sigma_s = 10^6; p = 4; \sigma = 5. \]

A generated stream of 0's and 1's is corrupted by noise (15% of the bits are complemented at random) and converted to frequency by a coarse running-averager. In Condition 1 the average activity of the afferents (i.e., the probability of a particular afferent firing at any given time step in the simulation) is 0.155. The input correlations between left and right eye afferents, before noise corruption are:

\[ (0.85;\{0,0\}),(0.05;\{1,0\}),(0.05;\{0,1\}),(0.05;\{1,1\}) \]

The decimal fraction is the probability of the bivariate binary event in the brackets.

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Normal Environment

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<th>Ocularity Dominance</th>
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<th>Avidity $A_i$</th>
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<th>Avidity $A_i$ (Left Eye)</th>
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<th>Avidity $A_i$ (Right Eye)</th>
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Cycle
Collingridge, 1986), Condition 3 demonstrates the operation of a similar process in developing visual cortex (Artola & Singer, 1987).

Condition 4 produces a different result than Condition 3 because both postsynaptic activity and associative modification are blocked by muscimol application. Figure 3.4 shows the simulation of Condition 4. At cycle 10, monocular deprivation occurs and muscimol blocks Rule 1 at one of the two cortical cells. Even so, there is an ocularity shift at both cells. In the cortex outside of the drugged region, the situation is identical to Condition 2. That is, presynaptic afferents associated
Monocular Deprivation with APV

Fig. 3.3: The effect of APV on monocular deprivation. After ten cycles of normal activity, the activity pattern is altered to approximate monocular deprivation of the left eye as in Figure 3.2. In this simulation, cortical Cell A is in a region affected by the drug APV. APV blocks associative modification but not the activity of Cell A. Cell B is outside the region affected by APV. The effect of APV is simulated by reducing \( f(\gamma) \) 100-fold. Note that, for Cell A, a shift in ocularity does not occur. Conversely, the undrugged Cell B shows an ocularity shift as in Figure 3.2. See Figure 3.1 for more details of the simulation.

with the closed, left eye lose synaptic weight via Rule I while afferents associated with the open eye inputs gain weight.

Now consider the drugged cell. For this cell, Rule I is blocked, and, at the same time, postsynaptic activity is greatly reduced. It is this reduction of postsynaptic activity that causes the receptivity of this cell to rise. If there are presynaptic afferents of high avidity, new synapses will form. Since afferents driven by the deprived eye are losing the competition for synaptic weight on the undrugged postsynaptic
cell, their avidity is higher. As a result, muscimol plus deprivation induces many new synapses between high avidity afferents of the deprived (left) eye and the drug-inhibited, high receptivity cortical cell. Thus, the net effect for the drugged cortical cell is a shift in ocularity toward the closed eye.

**Discussion**

This research demonstrates how a set of three microscopic, locally sensing and locally operating modification rules can be implemented to produce a rather simple, but biologically relevant, self-assembling neural network. What is inter-
Estimating about these simulations compared to some others in the literature is that the simulation concerns neocortical development although the three rules are based on experimental results generated outside of neocortex and in adult systems. In terms of the attractiveness of these rules it is important to note that each of these rules depends only on parameters readily available to each neuron.

Even though this model successfully simulates cortical development across the four conditions set forth here, the problem of modeling this development process is not uniquely solved by our system of equations. We note that Bear and Cooper (1990) have been able to fit these same developmental observations using a rather different rule. In fact, it was their work that pointed out to us the interesting set of developmental observations modeled here, and we are grateful for their communicating their own results to us prior to publication.

It is also interesting that the rules presented here share some of the characteristics, though not the form, of the rule advocated by Cooper's lab, see e.g., Bienenstock, Cooper, and Munro (1982). In particular, both their and our approaches depend on average postsynaptic activity where the time constant for these averaging processes must be much slower than the time constant controlling weight modification. A second similarity is the appearance of nonlinearities in the slow modification process(es). There are, however, significant differences, particularly in the associative modification rule itself (see Munro, 1983). Most notably, Cooper's synaptic weight modification rule requires presynaptic activity, whereas the weight modification rule presented here requires postsynaptic activity for modification to occur. Second, Cooper's rule requires an adaptively modified threshold. Our rules will work with or without a modifiable threshold.

In contrast to Hebb's (1949) original suggestion, the three rules used here are complementary because they help guarantee that neurons will be well-used. This well-used characteristic can be interpreted more generally than its relation to visual cortex. The postsynaptic receptivity rule prevents individual neurons from being underutilized, in that the activity levels of all neurons will converge toward the same average value and thus the same probability of firing and the same Shannon entropy. This, in turn, would guarantee that each neuron carries its share of the representational information of the network (see Levy, 1989). In a similar vein, the avidity rule prevents all postsynaptic cells from being dominated by the same set of well-correlated inputs by biasing against synapse formation with presynaptic cells that have made numerous synapses. More specifically, because of the avidity rule, there should be less statistical dependence between postsynaptic cells which, in effect, helps maximize the actual representational entropy of a set of such cells.

Though modeled as developmental processes, we believe these same rules govern connectivity in adult animals. In new environments, or more specifically in environments where the network perceives as new, postsynaptic activity will tend to decrease because the old correlations, which set up the network originally, will no longer be present. The set of rules used here allows for the establishment of new connections that can then encode new correlations. However, implementation of
such modification processes is likely a delicate affair in terms of losing previously learned environments. It may be necessary to consider the existence of permissive hormonal events or mismatch detectors to fully account for control of synaptic modification in the adult animal.

ACKNOWLEDGMENTS

Supported by NIH RO1 NS15488 and NIMH RSDA MH00622 to WBL and by the Department of Neurological Surgery, Dr. John A. Jane, Chairman. CMC was supported MSTP Training Grant NIH 5T32 GM0726713.

APPENDIX

The associative modification equation used in our models is the one implied by experiments in the hippocampal dentate gyrus. In these experiments there are two inputs: a powerfully depolarizing ipsilateral input that controls the postsynaptic term \( f(y) \) and a very weakly excitatory contralateral input whose activity corresponds to the presynaptic term \( x \).

Although these experiments are crude field potential studies, only qualitative questions need to be answered in order to eliminate many of the proposed synaptic modification equations found in the literature. The underlying assumption is that increases of intensity or frequency at a stimulating electrode do not decrease, and sometimes increase, the immediately evoked monosynaptic response.

The initially important observation is that both potentiation and depression can occur simultaneously on the same cells. (This observation is based on an anatomically based argument.) These increases and decreases of synaptic strength are a function of (a) the strength of ipsilaterally evoked postsynaptic excitation; (b) the presynaptic frequency or number of pulses; and (c) the previous history of modification.

Observation (1) includes experiments that varied the ipsilateral frequency of activation or varied its intensity (= the number of active inputs). From these manipulations two conclusions are clear: The postsynaptic requirement is highly nonlinear, probably threshold-like; and the same postsynaptic decision process is permissive for both potentiation or depression.

If a properly timed postsynaptic permissive event is provided in an experiment, then potentiation, depression or no change is a function of both the activity of the test input, \( x \), and a function of how much potentiation or depression has been induced previously. Higher frequencies of \( x \) cause potentiation, and lower frequencies cause depression. The more a synapse has been potentiated without depression, the less it can be potentiated in the future. The equivalent result holds for depression. The simplest way to express this behavior is the equation given
in Rule I where the parenthetical term takes on value zero when \(c_\lambda = w_\mu\) and is either positive or negative otherwise. The functions \(f(y_j)\) and \(\varepsilon\) are, by definition, always non-negative.

Our final comment concerns the temporal dependence of associativeness. In order to get potentiation the permissive input must follow the weak input (i.e., the one being potentiated) although too large a time window leads to depression of the weak input.

REFERENCES


