

6 The Rules of Elemental Synaptic Plasticity

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The hypothesis that learning and memory involve neuronal modifications antedates the advent of the synaptic doctrine. In 1862, Herbert Spencer postulated that memory storage occurred via altering one cell's ability to excite another cell as a function of prior activity. According to Ramon y Cajal (1911), Tanzi proposed that neural networks develop their functional capacities by altering synaptic interactions. Some time later, and benefiting from few, if any, relevant experimental facts, Hebb (1949) correctly predicted the apparent essence of the elemental, synaptic learning rule that forms the cellular basis of perceptual development and associative learning and memory.

In formulating elemental learning rules, Hebb and succeeding theoreticians posit rules that, when incorporated into a suitable neuroanatomical model, yield systems with capabilities analogous to some mammalian cognitive functions (e.g. associative memory, concept formation, and pattern recognition). This performance and any inherent mathematical elegance of the system are the primary arguments for the biological reality of the proposed synaptic process. Because many of these theories are largely unfettered by biological fact (in the Hebbian tradition), a rich array of synaptic learning rules are proposed, of which only a small number are likely to resemble actual synaptic physiology.

This chapter proposes rules similar to some postulated from purely theoretical considerations. However, the rules are presented here in a context strongly limited by recent experiments on adult neural plasticity. Influencing these hypotheses are the rationale used by Hebb and other theoreticians and two additional, interacting reasons:

1. The elemental rules are useful building blocks for cognitive function.
2. The rules are mutually complementary.
3. The cellular changes are not unreasonable given our current knowledge of cell biology.

Rather than focusing exclusively upon the first rationale with a detailed mathematical exposition of its implications, this chapter emphasizes the second and third rationales, which ensure that the elemental rules are coherent and biologically feasible.

In subsequent sections, the regulatory principles are listed for excitatory synapses followed by a teleological discussion of the utility and parsimony of these rules, their mathematical expression, and some biological data justifying the results. Following the discussion of excitatory synaptic modification rules are similar sections concerning inhibitory synapses.

EXCITATORY SYNAPSES

The Postulated Rules

Four rules are postulated to govern changes in connectivity and synaptic efficacy at excitatory synapses within the mature brain.

1a. Convergent coactivity increases synaptic efficacy at active synapses (the Hebb rule).

1b. Presynaptic inactivity during postsynaptic activity decreases synaptic efficacy at the inactive synapse (anti-Hebb rule).

2. The receptivity of (or possibly the request by) a postsynaptic target for new innervation varies as an inverse function of its activity (postsynaptic growth rule).

3. An afferent's propensity for axonal growth and competitiveness for claiming an available postsynaptic site is dynamically regulated, increasing with heightened levels of activity and decreasing with lowered levels of activity (axonal growth rule).

Partial Explication and Teleology

The overriding theoretical position directing the selection of "useful" rules is that individual synapses would be extremely useful memory units. Such a unit would store information that can help predict the activity of converging afferents and the postsynaptic cell. This synaptic function is not original. Many theoreticians (e.g. Amari, 1977; Anderson, 1968; Kohonen, 1970; Marr, 1971; Uttley, 1976a, 1976b, 1976c) propose this idea because it ex-

plains various aspects of associative memory and also forms the basis of higher functions such as concept formation. Thus, the elemental rules that help synapses store the appropriate correlations and that contribute to the ability of cells to form concepts and perform pattern recognition are generally consistent with current directions in neurodynamics.

Excitatory Rule 1a: Hebb Rule. Thirty years ago, Hebb (1949) proposed that associative learning and memory emerge from microscopic associations occurring at the level of cell-to-cell synaptic interactions. As a general scheme, the operative principles governing these microscopic associations are well known and almost universally accepted by neural modelers. The Hebb rule states that when a presynaptic afferent is coactive with a postsynaptic cell, the synaptic efficacy between the two elements increases. With recurring associated activity, the efficacy of each synapse resembles the correlation between the activity of the presynaptic afferent and the postsynaptic cell. This rule is useful in various neuropsychological processes, including concept formation (Anderson, 1979), associative recall (Kohonen, 1977), and visual development (Cooper, Liberman, & Oja, 1979).

The three remaining excitatory rules are formalized to optimize synaptic participation in concept formation and prediction and to fit the experimental data.

Excitatory Rule 1b: Anti-Hebb Rule—Depression¹. Ranck (1964), Rosenblatt (1967), and most exactly Stent (1973) propose a complementary microscopic law of dissociation. Specifically, decreases in synaptic efficacy occur when the postsynaptic cell is active concurrently with presynaptic inactivity. Kohonen, Lehtio, and Rovano (1974) and Cooper et al. (1979) incorporate a similar assumption in their elemental learning rules. This anti-Hebb rule allows for a self-organizing system by permitting the removal of inappropriate correlations. In the same vein, this rule allows for unlearning when an individual feature of a temporally discrete concept is no longer associated with the original concept because of the dissociation of two events

A second anti-Hebb rule, which our experimental impressions do not support, should be distinguished. This other anti-Hebb rule produces depression when the presynaptic element is active and the postsynaptic cell is inactive. Cooper et al. (1979) incorporate this rule in their elemental learning rules. Although we agree that the nervous system ought to appreciate this type of noncorrelation, we prefer to include this learning rule at inhibitory synapses (*vide infra*).

Together, rules 1a and 1b provide a self-organizational capability whereby a system with initially random connections forms "specific" (i.e., properly

¹The term *depression* is equivalent to *depotentiation* as discussed by Levy (Chapter 1, this volume).

specified) connections based on correlated activity. As a result, the postsynaptic cell comes to identify concepts (specific groupings of afferent activity) via potentiation. Simultaneously, the activity of synapses is depressed if their existence indicates inappropriate correlations relative to the history of afferent activity. Finally, these two rules also provide a developmental mechanism for the formation of topographic mappings in sensory systems where correlated activity of nearby receptors ensures mapping specificity (cf. Singer, chapter 2, this volume).

Excitatory Rule 2: Postsynaptic Growth. Rule 2 states that postsynaptic inactivity produces a postsynaptic condition compatible with new excitatory innervation (and vice versa for postsynaptic hyperactivity). This dynamic rule controls the maximum number of synapses a cell can receive, with the maximum a function of the time-averaged activity of the postsynaptic cell. Thus, the maximum number of synapses permitted increases as the overall postsynaptic excitation decreases.

Three hypoactive conditions lead to receptivity (or even request by) a postsynaptic neuron for innervation: (1) gross inactivity of its afferents; (2) uncorrelated (i.e., asynchronous) afferent activity, with depression consistently removing potentiation; and (3) correlated afferent activity whose postsynaptic expression (cell firing or large amounts of localized dendritic excitation) is blocked by simultaneous, convergent inhibition.

Excitatory Rule 3: Axonal Growth. Rule 3 is the presynaptic complement of Rule 2 and defines afferents with the potential for synaptogenesis. Synaptogenesis is theorized to be limited by the dynamically regulated amount of functional presynaptic surface area. This presynaptic area is integrated across all collateral synapses of a single afferent. Functional surface area may reflect the amount of "release sites," for example, or the readily releasable store of neurotransmitter.

Presynaptic activity controls the dynamic aspect of Rule 3. Thus, the greater an afferent's average activity, the greater is its optimum amount of functional presynaptic surface area. For one afferent maintaining a constant, average level of activity, the total amount of functional surface area summed across all its synapses is limited to a single maximum value. If the afferent's activity increases, this value increases; if activity decreases, the value also decreases. Those afferents lacking their full complement of presynaptic territory are the ones most likely to participate in synaptogenesis.

Although afferents whose average activity has recently increased are obvious candidates for synaptogenesis, this need not be the case. Afferents with increased average activity may undergo sufficient proliferation of functional presynaptic surface area at existing synapses to maintain their optimum territory. Similarly, some afferents with an unchanged average level of activity

may also participate in synaptogenesis (e.g., those afferents losing synaptic territory at other collateral synapses due to depression [excitatory rule 1b]).

In sum, excitatory rule 3 provides the basis for axonal growth regulated by excitatory rules 1a and 1b and by endogenous afferent activity. Excitatory rule 3 facilitates the formation of synaptic correlations, or associations, between afferents. However, afferents with many established synaptic correlations tend to not grow new synapses. Afferents of equivalent average activity with fewer or less potent synapses, on the other hand, do participate in axonal growth.

Further teleological motivation for this form of excitatory rule 3 arises from consideration of synaptogenesis without this rule. Without rule 3, presynaptic growth is random or based merely on spatial proximity between an afferent and a receptive postsynaptic cell. Nonspecific formulations of rule 3 might posit random growth by all afferents or the simplest form of trophic factor theory where the trophic factor induces afferent growth without regard to an afferent's activity or number of release sites.

A nonspecific rule 3 lacking activity-based specificity results in two unfavorable situations. First, synaptogenesis would not yield as much new information to correlate between afferents. Those afferents already innervating an inactive dendrite are not very useful, yet they have the most advantageous access, via random growth, to newly available postsynaptic sites. These same afferents would also receive the largest concentration of trophic factor. In neither case would synapse formation provide new correlations. Second, the redundant innervation resulting from random growth wastes free postsynaptic sites. Not only is it unlikely that the activity of these nearby afferents correlates with postsynaptic activity, but rule 1b does not remove this redundant innervation because insufficient postsynaptic activity exists to invoke the rule. A more useful afferent from which to obtain new information, and one that does not result in groups of identical clusters throughout the nervous system, is an afferent obeying rule 3.

Rule 2, in concert with rule 3, facilitates the formation of the maximum number of extant, but differing correlations, saving those unused (condition 1 of rule 2), confused (condition 2), and indecisive (condition 3) cells from a wasted existence. Rule 2 helps unused and indecisive neurons to form associations. Rule 3 provides the opportunity for afferents that are incompletely correlated relative to their activity levels to develop new correlations. Whether or not a postsynaptic structure, operating under the aforementioned conditions, can, by itself, stimulate synaptic proliferation via secretion of a trophic factor is important biologically, but not critical to the argument here. However, if trophic factors are secreted, an interactive decision process between pre- and postsynaptic structures seems advantageous for synapse formation.

Mathematical Embodiment of the Proposed Excitatory Rules

Excitatory Rules 1a and 1b: Hebb/anti-Hebb Rule. For a particular moment of time,

$$\frac{dm_{ij}}{dt} = \epsilon \cdot f(y) \cdot (c_1 x_i - m_{ij})$$

where m_{ij} is the strength of the synapse formed by the i th afferent with the j th cell;

ϵ is a small number;

c_1 is a positive constant;

x_i is the firing frequency of the i th afferent; and

$f(y)$ is the net excitation of the postsynaptic structure.

The values of $f(y)$ are nonnegative (Levy & Steward, unpublished observations), increasing with increasing excitatory synaptic activation and decreasing with increasing inhibitory synaptic activation. Although the postsynaptic structure j is often spoken of as a cell, it is probably some portion of a cell (e.g., a dendritic segment). The linear assumption $f(y) = \Sigma m_{ij} x_i$ is often used and has simplicity in its favor. Of course, a binary function and more complicated continuous functions, such as those used by Cooper, Munro, and Scofield (chapter 9, this volume) are possible.

Changes in synaptic efficacy are related to the afferent firing frequency and synaptic strength. When $x_i > m_{ij}$, dm_{ij}/dt is positive, and the amount of potentiation increases in proportion to the amount of postsynaptic excitation [$f(\Sigma m_{ij} x_i)$]. When the i th afferent fires at low frequency (i.e., when $x_i < m_{ij}$), the amount of depression at the synapse is also an increasing function of the amount of postsynaptic excitation [$f(\Sigma m_{ij} x_i)$].

Excitatory Rule 2: Postsynaptic Growth. We propose two alternate forms of this rule. The first alternative is expressed in terms of the number of vacant postsynaptic sites; the more vacant sites a postsynaptic structure has, the more likely the postsynaptic structure will receive new innervation. This alternative could be equivalently formulated in terms of the amount of trophic factor secreted. Again, the idea is that the more trophic factor is secreted, the better the chances of the postsynaptic structure receiving new innervation. The first alternative takes the form of

$$\text{number of vacant sites on cell } j = \frac{c_2}{E[(y_j^P)] + c_3}$$

where c_2 , c_3 , and P are positive constants;

$E(\cdot)$ is an expected value; and

y_j is the net postsynaptic effect.

In the term y_j , active excitatory synapses are added linearly through their synaptic strengths while active inhibitory synapses are divisors scaled by frequency and synaptic strength. This formulation may be modified to accommodate subtractive inhibition.

Notice that in this equation, the number of vacant sites increases as postsynaptic activity decreases. In this scheme, the probability of new innervation increases in proportion to the number of vacant postsynaptic sites. As a convenience, excitatory rule 2 is expressed as a function of cell activity. Some smaller unit of integration (e.g., a dendritic segment) seems the more likely postsynaptic integrating unit.

The second alternative expression of excitatory rule 2 is formulated in terms of the total excitatory synaptic strength of the postsynaptic integrating unit. This equation is a dynamic formulation of von der Malsburg's (1973) suggestion that the sum of the synaptic strengths is a constant. This alternative form is

$$\sum_i m_{ij} = \frac{c_2}{E[(y_j^p)] + c_3}$$

All terms in this equation are as defined previously for excitatory rules 1 and 2. Note, however, that this alternative postsynaptic rule is summed over the i th afferents for one postsynaptic structure j .

Excitatory Rule 3: Axonal Growth. There are two candidate forms of this excitatory rule. Both express a tendency for axonal growth with increased activity as tempered by the number (or amount) of extant synapses. The first alternative describes a boundary condition that constrains the system, whereas the second merely treats the system probabilistically. The boundary condition can be expressed as

$$\sum_j m_{ij} = c_4 E(x_i)$$

whereas the probabilistic expression is

$$\frac{c_4 E(x_i)}{\sum_j m_{ij}} = r_i$$

where c_4 is a positive constant;

$E(\cdot)$ is an expected value; and

i and j are as described previously.

In contrast to excitatory rule 2, which is summed over the i th afferents for one particular postsynaptic unit j , excitatory rule 3 is summed over the j th postsynaptic units for one particular afferent i .

The term r_i is a competitive factor for afferent i that expresses the relative probability of axonal growth. The larger the value of r_i , the better the particu-

lar afferent i will do in competition with homologous afferents for vacant postsynaptic sites.

Supporting Biological Data

Ample evidence (see Globus, 1975, for a general review) exists to support our basic premise that synaptic plasticity occurs in the mature nervous system, ranging from long-term potentiation within the hippocampal formation (Bliss & Lømo, 1973) to increases in cortical dendritic length and number following experience with an enriched environment (Juraska, Greenough, Elliott, Mack, & Berkowitz, 1980; Uylings, Kuypers, Diamond, & Veltman, 1978; Uylings, Kuypers, & Veltman, 1978) and perhaps with age in humans (Buell & Coleman, 1979, 1981).

Excitatory Rules 1a and 1b: Hebb/anti-Hebb Rule. To explain learned perception, Hebb (1949) originally suggested that the synaptic efficacies of individual excitatory synapses might be adjusted as a function of the correlated activity between each synapse and the integrated activity of its target postsynaptic cell. Most critical to the performance of model neural systems and most critical for their correctness and relevance to brain function is the exact form of the Hebb rule. Our experimental work has concentrated on defining and demonstrating the elemental synaptic learning rule as it actually exists in the mammalian brain (see Levy, Chapter 1, this volume).

Synapses consistent with the Hebb/anti-Hebb rule have been characterized in the rat hippocampal formation (Levy & Steward, 1979) and proposed in kitten visual cortex (Rauschecker & Singer, 1979, 1981). A striking similarity exists between Rauschecker and Singer's explanation of the cellular mechanism subserving binocular competition and the associative potentiation/depression data of Levy and Steward (1979). In the entorhinal cortex-dentate gyrus system, convergent activity of the ipsilateral and crossed entorhinal inputs leads to enhanced synaptic efficacy in the dentate gyrus, whereas presynaptic inactivity during postsynaptic activity decreases synaptic efficacy (Levy & Steward, 1979). A change in ocular dominance in kitten visual cortex following monocular suture results from one input being inactive (sutured) while the other input is active (nonsutured) (Rauschecker & Singer, 1979, 1981). In other words, the competitive interaction between an afferent and its convergent, nearby neighbors depends on the form of the integrated postsynaptic excitation and is a function of the coactivity of each converging afferent. Two biological exemplars of the Hebb/anti-Hebb rule are thus well documented in the central nervous system.

Associative potentiation/depression receives substantial attention and some good experimental support in developing systems under rubrics such as competitive interactions, binocular competition, and selective stabilization (Changeux, chapter 5, this volume; Changeux & Danchin, 1976; Con-

stantine-Paton & Law, 1978; Hebb, 1949; Law & Constantine-Paton, 1980, 1981; LeVay, Wiesel, & Hubel, 1980; Pittman & Oppenheim, 1979; Sargent & Dennis, 1981).

We have been purposely vague about the nature of the postsynaptic element involved in the synaptic learning rule. The postsynaptic unit could be localized regions of dendritic excitation or postsynaptic cell firing. Unambiguous definition of the form of $f(y)$ is difficult, especially as the postsynaptic event permitting potentiation/depression may be localized to particular dendritic zones (Levy & Steward, in preparation). Therefore, the efferent activity of the postsynaptic cell does not necessarily reflect the relevant variable for plasticity. During conditioning stimulation, for example, localized forms of inhibition might inhibit postsynaptic cell firing but would be substantially irrelevant to the primary regions of synaptic activation.

Excitatory Rule 2: Postsynaptic Growth. Excitatory rule 2 permits new synapses to grow only when the activity of the postsynaptic integrating unit is low. On the other hand, when postsynaptic activity is high, the number of vacant synaptic sites is practically zero, and little postsynaptic growth occurs. Whether or not trophic factors are released by the postsynaptic cell is not critical to this theory. However, increased release of trophic factors with inactivity is consistent with the overall concept of excitatory rule 2.

Even though the intuitive perspectives of Ariens Kappers (1921) and Hebb (1949) yield the notion that postsynaptic activity is a stimulus for the formation of new synapses, inactivity is a more useful trigger for synaptic proliferation. Inactivity as the stimulus ensures maximum utilization of all cells while avoiding the formation of cells that are active in the extreme. This perspective does not, however, eliminate the importance of postsynaptic activity. As soon as innervation occurs, the competitive synaptic principles of associative potentiation/depression, in part ruled by some form of postsynaptic excitation, assume control of synapse survival.

Although counterintuitive from Hebb's (1949) viewpoint, data from peripheral synapses support the notion of a dynamic constant. At the neuromuscular junction, denervation-induced supersensitivity has been known for years. Preeminent is the work of Lømo and colleagues (Lømo, 1980, Lømo & Slater, 1978) who demonstrated experimentally that additional and new innervation of adult muscle depends on and requires postsynaptic inactivity. Junctional inactivity leads to a surface membrane receptive to new innervation (Fex, Sonesson, Thesleff, & Zelena, 1966; Lømo & Rosenthal, 1972; Miledi, 1963). Moreover, successful hyperinnervation of the rat soleus muscle depends on muscle inactivity (Jansen, Lømo, Nicolaysen, & Westgaard, 1973).

In nervous tissue, an experiment by Wolff, Joo, Dames, and Feher (1979) provides the strongest evidence for the inverse relationship between receptivity for new innervation and postsynaptic activity. Treating the adult superior

cervical ganglion with an inhibitory neurotransmitter, γ -aminobutyric acid (GABA), leads to the appearance of postsynaptic junctional densities at extrasynaptic dendritic loci, as well as increased extrasynaptic surface of the ganglion cells. Because GABA application to the superior cervical ganglion suppresses presynaptic action potentials, GABA (though probably not usually present) inhibits dendritic activity of the ganglion cells. The formation of extrasynaptic postsynaptic densities supports the notion that inactive dendrites are receptive to new innervation.

The work of Wolff et al. (1979) suggests a mechanism that might be operative in the dentate gyrus. Namely, large amounts of GABA-mediated inhibition may yield postsynaptic cells receptive to new innervation.

The second alternative form of excitatory rule 2, that the total excitatory strength of the postsynaptic integrating unit is a constant, has an experimental prediction about synaptic shedding not explicit in the rule's first form. It may seem that excitatory rule 1b can account for the shedding of synapses. Actually, this rule only predicts that a synapse asymptotically approaches the value of zero without ever reaching zero as long as the afferent making the synaptic contact maintains a minimum noise level of activity. In the second formulation of excitatory rule 2, the competitive idea of excitatory rule 1b is extended to its ultimate manifestation.

Data supporting the second form of excitatory rule 2 comes from a study of associative potentiation/depression in the dentate gyrus (Desmond & Levy, 1983, Levy & Desmond, in preparation). Following conditioning stimulation of the entorhinal afferents to the dentate gyrus, synaptic density increases not within the region of the dentate molecular layer receiving the greatest synaptic excitation, but within the regions bordering the zone of maximal synaptic activation. This localized increase in synaptic density is interpreted as synaptic proliferation triggered by postsynaptic inactivity surrounding a central band of excitation. Given the well-known distribution of GABAergic synapses in the dentate molecular layer (Nadler, White, Vaca, & Cotman, 1977; Palacios, Wamsley, & Kuhar, 1981; Ribak, Vaughn, & Saito, 1978), disynaptic inhibition may result from entorhinal activation such that outside the central lamina of active synapses, there is net inhibition. These dendritic regions consistently receiving net inhibition prepare sites for synaptic attachment at which "prototype" synapses are induced.

Excitatory Rule 3: Axonal Growth. The activity dependence of excitatory rule 3 stands in distinct contrast to excitatory rule 2. Although both rules exert control over new synapse formation, they govern opposite sides of the synapse and do so in quite opposite ways. That is, their dynamic dependencies are reversed, with axonal growth of an input becoming more energetic as that afferent's average activity increases. In contrast, postsynaptic targets, according to excitatory rule 2, become more receptive to new innervation as their activity decreases.

The evidence that axons can find new synaptic connections is quite abundant for the mature nervous system. When one input to a structure is lesioned, a second input normally innervating that structure extends its axons to occupy dendrites previously contacted by the lesioned axons. This sprouting phenomenon has been demonstrated in a variety of CNS regions, including spinal cord (Bernstein & Bernstein, 1967, 1969), red nucleus (Tsukahara, 1978), septum (Raisman, 1969), and hippocampus (Cotman & Nadler, 1978). Results of complex environment experiments (Greenough, 1976) also support the contention that axons extend to form novel synaptic contacts.

Bernstein and Bernstein (1967) are among the first to suggest that the amount or number of synapses an axon possesses limits its tendency to grow and develop further synapses. Experiments in the peripheral and central nervous systems support this idea, suggesting that an afferent can only maintain a limited number of synapses (however, cf. Jansen et al., 1973). In the Bixby and Van Essen (1979) study of peripheral nervous system, transplanting a nerve to a normally innervated skeletal muscle results in the proliferation of new synapses and the loss of old synapses. In later developmental stages of the central visual system, lesions that remove one target tissue of an afferent result in the proliferation of that same afferent in other regions (Schneider, 1973). These studies show that limits are placed on the extent of an afferent field. Whether or not this value is dynamically regulated is an experimental question. If afferents are generally near their maximum allowable size, then synaptic proliferation experiments require dynamic regulation, e.g., studies producing synaptogenesis with electrical stimulation (Rutledge, 1978; Levy & Desmond, in preparation).

The influence of the activity level of these axons remains unexplored. Excitatory rule 3 posits that highly active axons may search for novel synaptic connections or become particularly sensitive to trophic factors released by target neurons. A study using electrical stimulation to increase presynaptic activity and thereby improve reinnervation of a lesioned structure would provide good experimental support for excitatory rule 3. However, care would be required to ensure that postsynaptic activity is not altered when performing the study so that the results can be interpreted strictly relative to this rule.

Certainly, however, rules 2 and 3 are very specific in their predictions for regrowth in the mature sprouting system where sprouting is often incomplete. These rules suggest that a greater amount of synaptogenesis can be obtained with concurrent pharmacological inhibition of the target cells and stimulation of the sprouting axons.

The great similarity between the rules presented here and the rules postulated to account for neural development is not likely to be by chance. For instance, axonal extension and dendritic shedding are issues in developmental neurobiology (see, e.g., the selective stabilization hypothesis of Changeux &

Danchin, 1976, the dynamic equilibrium hypothesis of Young, 1951, and Vaughn & Sims', 1978 study of synapse development).

The fact that these rules are not limited to any particular stage of an animal's life is intentional. The well-known differences in synaptic plasticity with age need not be attributed to aging of the enzymatic machinery or cellular DNA. Rather, the reduced plasticity of older animals may simply reflect the fact that the overall environment is highly regular and that most cells and synapses are near their prescribed equilibrium values.

INHIBITORY SYNAPSES

This section on inhibitory synapses is necessarily brief because, compared with excitatory synapses, there are little data from which to conceptualize the modification rules for inhibitory synapses. This is not to say that inhibitory synapses lack plasticity with time and/or use. Not only does intuition argue that Nature would not waste 15% of the cerebral cortical synapses, but experiments certainly exist showing inhibitory synaptic plasticity. The problem with these experiments is that it is unclear just what the correlated and noncorrelated activity of the pre- and postsynaptic cells are. Experiments demonstrating inhibitory modifications include Rutledge (1978), Liebowitz, Pedley, and Cutler (1978), McNamara, Peper, & Patrone (1980), Nadler (1981), and Valdes, Dasheiff, Birmingham, Crutcher, & McNamara (1982). These studies involve very gross manipulations such as lesions or daily electrical stimulations with unknown, diffuse, and complex responses of the inhibitory cells. These inhibitory neurons are presumably interneurons and therefore are not monosynaptically activated by the conditioning stimulations.

The Postulated Rules

Because we cannot rely on physiology to direct us as we did for the excitatory synaptic modification rules, there is only intuition as a guide. In this case intuition is shaped by two elements: (1) the framework already provided by the rules for excitatory synaptic modification; and (2) our attempts (Levy, in preparation) to construct neural models that perform realistically within various aspects of the classical conditioning paradigm as well as models that give responses based on conditional probabilities.

For these two modeling problems, the noncorrelation of input active-output silent must be encoded. Excitatory rule 1b encodes the other noncorrelation event (i.e., input silent-output active [*vide supra*]). Although Cooper et al. (1979) prefer to incorporate the input active-output inactive noncorrelation in their model at excitatory synapses, our solution is to encode this required noncorrelation at inhibitory synapses.

The inhibitory rules that follow refer to the conditions leading to synaptic alterations for inhibitory synapses:

1a. Presynaptic activity paired with postsynaptic inactivity leads to potentiation at the active inhibitory synapse.

1b. Postsynaptic activity should be required for a loss of strength of the inhibitory synapse. Three forms of this rule have been found satisfactory: (1) postsynaptic activity without presynaptic inactivity; (2) postsynaptic activity with presynaptic activity; and (3) both (1) and (2).

2. Postsynaptic activity increases the receptivity of the postsynaptic cell for new inhibitory innervation.

3. The limits of presynaptic growth increase with increasing presynaptic activity and decrease with decreasing presynaptic activity.

Mathematical Embodiment of the Proposed Inhibitory Rules

Inhibitory Rules 1a and 1b. Depending on the anatomical interrelationships assumed and the system performance desired, one of the following three alternative forms of inhibitory rule 1 are suitable for constructing systems that produce conditional probabilities, conditional odds, and likelihood ratios. The respective equations, for a particular moment of time, are:

$$\frac{dl_{ij}}{dt} = \epsilon_2 \cdot (c_5 x_i - y_j l_{ij}),$$

$$\frac{dl_{ij}}{dt} = \epsilon_2 c_6 x_i - \epsilon_2 y_j (c_5 x_i + l_{ij}),$$

and

$$\frac{dl_{ij}}{dt} = \epsilon_2 y_j (E(x_i) - x_i - c_5 l_{ij})$$

where l_{ij} is the strength of the inhibitory synapse formed by the i th afferent with the j th cell;

ϵ_2 is a small number;

c_5 and c_6 are positive constants;

x_i is the firing frequency of the i th afferent;

y_j is the net excitation of the postsynaptic unit; and

$E(x_i)$ is the expected value of x_i .

We have assumed a linear relationship between y_j and $\sum_i l_{ij} x_i$; however, this need not be the case.

A third equation is suitable for combination with excitatory rule 1 to build a system that mimics the classical conditioning paradigm, including extinction and blocking:

$$\frac{dl_i}{dt} = \epsilon_2 c_5 x_i (l - c_6 y_j)$$

Inhibitory Rules 2 and 3. Two alternative forms of each of these inhibitory rules exist. In the interest of brevity, each rule is presented in only one form. However, the alternative forms that parallel the alternatives of excitatory rules 2 and 3 should be given equal consideration.

For inhibitory rule 2,

$$\frac{\text{number of vacant inhibitory postsynaptic sites on cell } j}{\text{postsynaptic sites on cell } j} = \frac{c_7 E(y_j^p)}{\sum_i l_{ij} + c_8}$$

whereas inhibitory rule 3 is summed over the j th postsynaptic units for one particular afferent i .

Teleology

Inhibitory Rules 1a and 1b. The importance of inhibitory rules 1a and 1b has already been indicated for learning responses based on conditional probabilities and for the extinction portion of the classical conditioning paradigm. In addition, encoding this form of noncorrelation (input active-output silent) is required to explain those aspects of visual development modeled by Cooper et al. (this volume).

Inhibitory Rules 2 and 3. Inhibitory rules 2 and 3 provide for the formation of new inhibitory synapses and are formulated in the same vein as excitatory rules 2 and 3. However, in contrast to excitatory rule 2, highly active cells are more likely to receive new inhibitory information than are less active cells. Just like excitatory rule 3, the more active inhibitory presynaptic afferents are those with the most available information and are more likely to establish new synapses.

Finally, we should point out an essential difference between some excitatory and inhibitory connections. The existence of multiple synaptic contacts on one cell seems rare for many types of excitatory afferents, but often seems the rule for inhibitory afferents. In addition, in many systems inhibitory neurons are greatly outnumbered by excitatory cells and the number of excitatory afferents. It may be that inhibitory systems are much more coarsely modulated than are excitatory systems. Thus, rather than three separate inhibitory modification rules, there might be only one rule that has the same net effect as the three rules, but merely modulates synapse number rather than the strength of individual inhibitory synapses. The properties of this one inhibitory rule should, however, resemble the properties of the three individual rules proposed here.

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