Biol. Cybern. 87, 392–403 (2002)
DOI 10.1007/s00422-002-0361-y

Biological Cybernetics

Spike timing dependent synaptic plasticity in biological systems

Patrick D. Roberts, Curtis C. Bell

Neurological Sciences Institute, Oregon Health & Science University, 505 N.W. 185th Avenue, Beaverton, OR 97006, USA

Received: 16 January 2002 / Accepted: 3 June 2002

Abstract. Association of a presynaptic spike with a postsynaptic spike can lead to changes in synaptic efficacy that are highly dependent on the relative timing of the pre- and postsynaptic spikes. Different synapses show varying forms of such spike-timing dependent learning rules. This review describes these different rules, the cellular mechanisms that may be responsible for them, and the computational consequences of these rules for information processing and storage in the nervous system.

Introduction

The idea that synaptic plasticity is responsible for learning and adaptation in neural systems is as old as the neuron doctrine itself (Cajal 1894). But Donald Hebb was the first to suggest a precise rule that might govern the synaptic changes underlying learning: "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" (Hebb 1949). Hebb's rule, and the "Hebb synapse" which the rule describes, have been central concepts in the fields of synaptic plasticity and the neural basis of learning.

Hebb's formulation of his rule has several important features. Causality is one such feature. According to Hebb, the firing of neuron A must be causally related to the firing of neuron B, which means in practice that spikes in neuron A must precede spikes in neuron B. A simple correlation in which the order of spike times is unimportant would not fit with Hebb's hypothesis. A second feature is the assignment of a critical role to spikes. This is explicit for the postsynaptic cell and is implicit for the presynaptic cell since Hebb's discussion always considers neuronal interaction as mediated by spikes. A final feature is one of omission. Hebb's rule describes the conditions under which synaptic efficacy increases but does not describe the conditions under which it decreases. Theoretical work shows that the reversibility of changes in synaptic efficacy is important not only for forgetting or avoiding saturation of synaptic efficacy (Sejnowski 1977; Bienenstock et al. 1982), but also for allowing maximum storage of information (Wilshaw and Dayan 1990).

The central roles of causality and spike-timing in Hebb's rule has not always been appreciated. This was partly due to widespread acceptance of the idea that information in the nervous system is coded by spike-rate rather than by the timing of individual spikes. Another reason for ignoring the possible importance of spike-timing was that use-dependent synaptic plasticity was first established by delivering high frequency trains of stimulation to presynaptic fibers (Lomo 1971; Bliss and Lomo 1973), and the same methodology has been extensively employed ever since. Such methodology ignores the timing of individual spikes.

The idea of spike rate as a means of coding information and the use of high frequency trains of stimuli to induce plasticity suggested correlational rules for synaptic change. In such rules, synaptic weight increases when the rates of pre- and postsynaptic spike trains are positively correlated, regardless of the relative timing of individual spikes. Weights may also decrease when the correlation is negative. Theoretical work has shown that neural networks in which synaptic efficacy obeys correlational rules can mediate many adaptive functions and can store a large number of different input patterns (Hopfield 1982; Kohonen 1989).

However, recent experimental studies show that correlational learning rules do not capture the full reality of synaptic plasticity in the nervous system. These studies show that Hebb was right, and that relative timing of pre- and postsynaptic spikes can be critical for the direction and magnitude of plastic change. Both potentiation and depression occur at synapses that obey such spike-timing dependent learning rules. Whether potentiation or depression is induced can depend on

Correspondence to: P. D. Roberts
(e-mail: robertpa@ohsu.edu)

variations of only a few milliseconds in the relative timing of pre- and post synaptic spikes during the period of association. The first section of this paper reviews the spike-timing dependent learning rules that have been experimentally established in various systems. This section also reviews the cellular mechanisms that have been demonstrated or suggested to be responsible for the temporal form of the different learning rules. The second section reviews theoretical work on the functional or computational consequences of embedding the different rules within neural networks. In this paper, the term "Hebbian" is used to describe synaptic plasticity in which potentiation of an excitatory postsynaptic potential (EPSP) occurs if a presynaptic spike is accompanied by an increase in the probability of a postsynaptic spike during the period of association, and the term "anti-Hebbian" is used to describe synaptic plasticity in which depression of the EPSP occurs under such conditions.

Spike-timing dependent synaptic plasticity

Hebbian plasticity at excitatory synapses

Most recent work in this area has induced changes in synaptic efficacy by pairing single postsynaptic spikes with single presynaptic spikes, but some earlier work, using trains of stimulation or spikes, also indicated the importance of relative timing for the induction of plasticity. Hippocampal studies in vivo (Levy and Steward 1983), in slices (Gustafsson 1987), and in slice culture (Debanne et al. 1994) all showed that synapses were potentiated only when trains of presynaptic stimuli preceded or were concurrent with strong postsynaptic activation, but that no change or depression occurred when the presynaptic train followed postsynaptic activation. Depression occurred at some of these synapses when presynaptic spikes occurred after the postsynaptic spikes (Debanne et al. 1994). This last finding suggests that Hebb's original rule governing potentiation must be supplemented with an opponent timing dependent process of depression. More recent studies also support such a supplement (Markram et al. 1997; Zhang et al. 1998).

Hebbian plasticity following pairing of individual spikes was first seen in recordings of cell pairs in layer V/VI of the mammalian neocortex (Markram et al. 1997). EPSP potentiation resulted from pairings in which the presynaptic spike preceded the postsynaptic spike by 10 ms, while EPSP depression resulted from pairings in which the presynaptic spike followed the postsynaptic spike by 10 ms. Pairings at 100 ms delays, in either temporal order, did not result in any change.

Similar bi-directional changes, with potentiation occurring after pairings with presynaptic spike first and depression after pairings with postsynaptic spike first, have also been found in the developing optic tectum of Xenopus (Zhang et al. 1998), in cultured hippocampal neurons (Bi and Poo 1998), and in vertical connections onto layer II/III pyramidal cells of the somatosensory cortex (Feldman 2000). These latter studies tested a large number of delays between pre- and postsynaptic spikes and thus provided a finer grained analysis of timing dependency than the first study by Markram et al. (1997). In the optic tectum and in cultured hippocampal cells, no potentiation was observed when the presynaptic spike preceded the postsynaptic spike by more than 20 ms and no depression was observed when the presynaptic spike followed the postsynaptic by more than 20 ms (Fig. 1A). Thus, the time intervals for depression and potentiation were similar at these two sites. These time intervals were not similar, however, in layer II/III pyramidal cells (Feldman 2000). Here, the interval for depression was considerably longer than the interval for potentiation (Fig. 1B). All of these learning rules are asymmetric, in that positive delays (where the postsynaptic spike follows the presynaptic spike) have different effects than negative delays (where the postsynaptic spike precedes the presynaptic spike). The presence of a second time interval for depression in hippocampal slices has been reported (Nishiyama et al. 2000). The second interval occurs when the postsynaptic spike follows the presynaptic spike by more than the interval of LTP (dashed line in Fig. 1A). However, some investigators

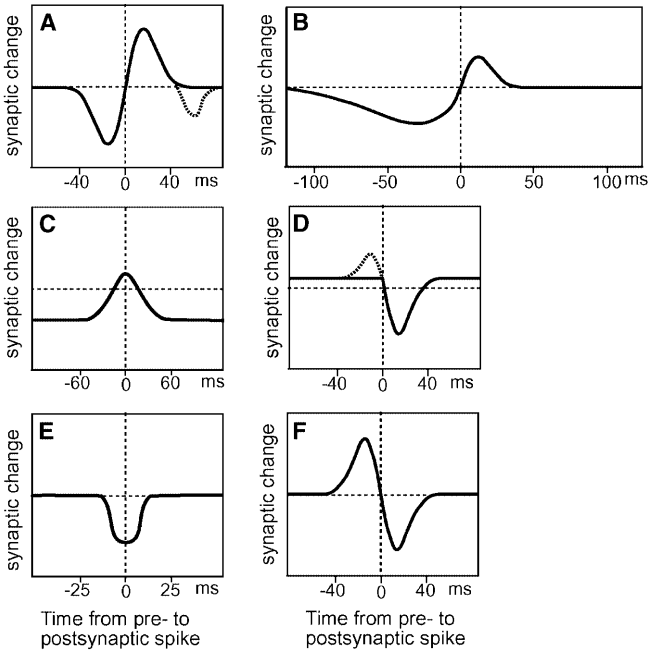

Fig. 1. Spike-timing dependent learning rules, where positive time indicates that the postsynaptic spike follows the presynaptic spike. (A) Antisymmetric Hebbian learning rule consistent with Markram et al. (1997), Zhang et al. (1998) and Bi and Poo (1998). A second and later LTD component (dashed line) has been reported in Nishiyama et al. (2000). (B) Antisymmetric Hebbian learning rule consistent with Feldman (2000). (C) Symmetric Hebbian learning rule at the neuromuscular junction (Dan and Poo 1998). (D) Anti-Hebbian learning rule that is consistent with data presented in Bell et al. (1997). The associative LTP component (dashed) is not statistically significant in vitro, but has been observed in vivo (Bell et al. 1993). (E) Symmetric anti-Hebbian learning rule (Egger et al. 1999). (F) Theoretical antisymmetric anti-Hebbian learning rule without non-associative potentiation

who have looked for plasticity dependence on the timing of single spikes have not observed it in hippocampal slice preparations (Pike et al. 1999).

In each of the above studies, the induction of potentiation depended on activation of n-methyl-d-aspartate (NMDA) receptors and a rise in postsynaptic calcium. The NMDA receptor dependence provides a ready explanation for the associativity and asymmetry of the learning rule. Full opening of the NMDA receptor channel and the consequent influx of calcium requires both the binding of glutamate to the receptor and postsynaptic depolarization (Mayer et al. 1984; Nowak et al. 1984). The binding of glutamate follows the release of a transmitter by the presynaptic spike, and the postsynaptic depolarization is provided by the postsynaptic spike. Thus, neither the release of glutamate alone nor the postsynaptic spike alone will result in opening of the receptor. Both must occur at the same time.

The mechanism for EPSP depression after pairings in which the presynaptic spike occurs just after the postsynaptic spike is less clear. Several groups have suggested that LTD is induced at a lower concentration of calcium (Lisman 1989; Artola et al. 1990) than required for induction of LTP. However, parameters of the timing window for depression are not fully predicted by the expected calcium concentration alone. In layer V/VI of the neocortex (Markram et al. 1997) of the developing frog optic tectum (Zhang et al. 1998) and cultured hippocampal cells (Bi and Poo 1998), the depression, like the potentiation, depended on activation of NMDA receptors, but the depression found in layer II/III cells did not (Feldman 2000). The NMDA dependent depression might be explained by a small influx of calcium through the NMDA channel even at the resting membrane potential (Oliet et al. 1997), and summation of this calcium level with residual calcium remaining in the cell after activation of voltage gated calcium channels by the postsynaptic spike, although this mechanism has not been demonstrated.

The final site for expression of the plasticity, that is, the step in the synaptic transmission process that changes as a result of pairing, is also not firmly established. However, experiments with paired pulses strongly suggest that presynaptic changes in transmitter release are responsible for both potentiation and depression in the cortical cells of layer V/VI (Markram et al. 1997). In these experiments, a pair of presynaptic stimulations generate two postsynaptic potentials that may be of different amplitudes due to presynaptic mechanisms. Thus, changes in this amplitude difference following the induction of synaptic plasticity is considered to be of a presynaptic origin.

A rather different symmetric learning rule was found at the developing neuromuscular junction when synaptic spikes were paired with pulses of acetylcholine (Dan and Poo 1998). If the spikes and the acetylcholine pulses were synchronous, there was either no change or a slight potentiation. All other delays resulted in a strong depression of synaptic efficacy (Fig. 1C). Although the depression does not require presynaptic spikes, the rescue from depression does require such spikes. This depression is probably due to a presynaptic decrease in transmitter release.

Anti-Hebbian plasticity at excitatory synapses

With anti-Hebbian plasticity, the effect of a presynaptic input is depressed when it is accompanied by an increase in the probability of a postsynaptic spike. Such plasticity tends to decouple neurons and has a variety of other functional consequences as described below in the section on implications of different learning rules.

Anti-Hebbian plasticity that obeys an asymmetric spike timing dependent learning rule has been observed in the electrosensory lobe of mormyrid electric fish. This lobe is a cerebellum-like structure where information from electroreceptors is first processed (Bell et al. 1997b). The plasticity occurs at the excitatory synapse of parallel fibers onto Purkinje-like cells and depends on the relative timing of presynaptic input and a postsynaptic dendritic spike. Pairings in which the postsynaptic spike is evoked within 50 ms of the parallel fiber stimulus result in depression of the parallel-fiber evoked EPSP (Fig. 1D). Pairings at all other timing delays, including those in which the presynaptic input follows the postsynaptic spike by a few milliseconds, result in a non-associative potentiation (Han et al. 2000). In this case, non-associative plasticity means that there is synaptic change due to presynaptic spikes only and independent of postsynaptic spikes.

Synaptic depression in the mormyrid electrosensory lobe depends on activation of NMDA receptors and an increase in postsynaptic calcium concentration (Han et al. 2000). This NMDA dependence explains the associativity and asymmetry of the learning rule, as in the cases of spike timing dependent Hebbian plasticity described in the previous section. The depression reversed the potentiation and vice versa. Changes in paired pulse facilitation indicated that both depression and potentiation are mediated by a presynaptic change in transmitter release.

Anti-Hebbian plasticity that obeys a symmetric learning rule is found at synapses between spiny stellate neurons in Layer IV of the neocortex (Egger et al. 1999). Depression occurs within a narrow window on either side of simultaneity, that is, for both positive and negative delays of up to 10 ms between pre- and postsynaptic spikes (Fig 1E). The depression requires activation of metabotropic glutamate receptors and voltage gated calcium channels, but does not require activation of NMDA receptors. In contrast to most of the other forms of spike timing dependent plasticity, only depression has been observed at this synapse, making one wonder why the neurons do not simply decouple as a result of chance occurrences of near simultaneity, unless there is an as yet unspecified form of LTP that reverses this type of LTD. Note that this rule is approximately the inverse of the rule described above for the neuromuscular junction (Fig. 1C; Dan and Poo 1998).

Long term depression (LTD) in the cerebellum

LTD at parallel fiber synapses in the cerebellum is a form of anti-Hebbian plasticity that has received much attention. In cerebellar LTD, parallel fiber-evoked EPSPs in Purkinje cells are depressed following pairing with climbing fiber activation (Ito et al. 1982; Ito 1989). The climbing fiber evokes a massive depolarization and calcium influx in Purkinje cell dendrites (Llinas l980), and pairing with strong postsynaptic depolarization elicits LTD in the same way as pairing with climbing fiber activation (Linden et al. 1991). Thus, the climbing fiber evokes a response that is very similar to a postsynaptic spike, and cerebellar LTD is therefore included in this review of spike timing dependent plasticity. Note, however, that climbing fiber activity is controlled by an external nucleus, the inferior olive, and not by the Purkinje cells themselves. Cerebellar LTD is therefore a form of supervised learning and distinct from the unsupervised learning present in the other forms of plasticity described in this review (Knudsen 1994; Doya 1999).

Cerebellar LTD is believed to be important for motor learning (Marr 1969; Albus 1971; Ito 1982). Theoretical work suggests that for LTD to have such a role, it must be temporally constrained and occur only when parallel fiber activity precedes climbing fiber activity by 100 to 150 ms (Lisberger 1994; Houk and Alford 1996). However, experimental studies of cerebellar LTD have not yet confirmed such timing constraints. Although some studies suggest a temporally constrained learning rule similar to that which seems to be necessary on theoretical grounds (Wang et al. 2000; Chen and Thompson 1995), other studies have concluded that LTD requires that the climbing fiber arrive between 0 and 10 ms after the parallel fiber input (Lev-Ram et al. 1995). Moreover, within the literature as a whole, the timing relations that have been found to elicit LTD range from climbing fiber first by 1.75 s to parallel fiber first by 250 ms (Ito et al. 1982; Karachot et al. 1994; Schreurs et al. 1996; Chen and Thompson 1995). Thus, the relative timing of parallel fiber and climbing fiber activity that is necessary for long term depression at the parallel fiber synapse is not yet established.

There is also no consensus concerning the cellular mechanisms for induction of cerebellar LTD, and various theories have been offered, each supported by experimental evidence. The theories all agree that the critical effect of climbing fiber input is to cause a large influx of calcium through voltage gated calcium channels, but the theories emphasize different effects of the parallel fiber input and have varied cellular explanations for the associativity between parallel and climbing fiber inputs. In one theory, activation of metabotropic glutamate receptors by parallel fiber input causes the formation of diacylglycerol which in turn activates protein kinase C, but only in the presence of the high levels of calcium caused by the climbing fiber input (Linden and Conner 1993; Ito 2001; Crepel and Jaillard 1991). Thus, for this theory, protein kinase C is the cellular locus of associativity. In a second theory, release of nitric oxide by the parallel fiber is considered critical. For this theory, the point of associativity is a guanyl cyclase in the Purkinje cell that requires both nitric oxide and high calcium levels (caused by the climbing fiber input) to make cGMP (cyclic guanosine monophosphate), or a cGMP kinase that is downstream of the nitric oxide activated cyclase which requires calcium as well as cGMP (Lev-Ram 1995). In a third theory, the point of associativity is the calcium sensitivity of inositol-3-phosphate (IP3) receptors in the endoplasmic reticulum (Miyata et al. 2000; Wang et al. 2000). Activation of metabotropic glutamate receptors by parallel fiber input causes the formation of IP3 which in turn causes a release of calcium from internal stores, but this release is strongly facilitated by high levels of calcium following climbing fiber activation. Description of the intracellular signaling pathways that are hypothesized to be downstream from these different sites of associativity is beyond the scope of this review (but see, Ito 2001; Xia et al. 2000).

Although there is no consensus regarding the mechanisms of induction of cerebellar LTD, there is a consensus regarding expression, namely that LTD expression reflects a change in the postsynaptic sensitivity of AMPA receptor mediated current to the glutamate released by parallel fibers.

One difficulty for LTD as an explanation for motor learning is that no physiological method has yet been found for reversing the pairing-induced depression. A non-associative potentiation of the parallel fiber evoked EPSP is elicited by high frequency stimulation of the fibers, but this potentiation is due to a presynaptic increase in transmitter release and thus can not reverse the postsynaptic depression caused by associative LTD (Salin et al. 1996). If these two forms of plasticity are the only ones operating, and if neither can be reversed, then a point would be reached, due to learning or to random associations, at which the presynaptic terminal is releasing a maximum amount of transmitter and the postsynaptic cell is responding minimally, with no further change possible.

Plasticity at inhibitory synapses

Inhibition is as important as excitation for brain function, and plasticity has been demonstrated at a number of different inhibitory synapses (Komatsu and Iwakiri 1993; Korn et al. 1992; Kano et al. 1992; Hirano 2000; Holmgren and Zilberter 2001). However, the learning rules governing plasticity at inhibitory synapses are not yet well established. In one case, for example, two different laboratories have obtained different results with regard to associativity at the same synapse, the synapse between inhibitory interneurons and Purkinje cells in the cerebellum. Kano et al. (1992) found that inhibition at the synapse between inhibitory interneurons and Purkinje cells was increased when depolarization of the Purkinje cell was paired with interneuron activity, whereas depolarization alone had no effect. In contrast, Hirano et al. (1991) found that depolarization

of the Purkinje cell alone did cause a potentiation of interneuron inhibition. Surprisingly, the latter authors even demonstrated a type of ''anti-associativity'' at this synapse. If activity of an interneuron was paired with postsynaptic depolarization, potentiation of the inhibition is suppressed.

The required timing relations have not been determined for inhibition in the cerebellum, but a type of spike timing dependent learning rules has been established for inhibitory synapses onto neocortical neurons (Holmgren and Zilberter 2001). Pairing presynaptic spikes with postsynaptic bursts in pyramidal cells produced depression of the inhibitory postsynaptic current when the presynaptic stimulus was coincident with the postsynaptic burst, or within 50 ms after the end of the burst, and potentiation if the presynaptic stimulus followed the burst with a delay of 400–800 ms.

Implications of spike-timing dependent learning rules

Relationships between spike timing dependent learning rules and other learning rules

Spike-timing dependent learning rules will sometimes have the same or equivalent computational consequences as learning rules that ignore the precise timing of spikes. Equivalence of the two types of rules will depend on how the spike trains encode information and can be identified by investigating the learning dynamics of each learning rule. By learning dynamics we mean how the learning rule changes synaptic weights and neuronal activity in a network. Equivalence is important because, once established, it allows one to determine the computational consequences of spike timing dependent rules from previous theoretical work on rules that do not depend on precise timing. We therefore examine the conditions under which the effects of spike timing dependent rules are similar to those of timing independent rules.

Associative learning rules based on spike rates in the pre- and postsynaptic cells are the most common types of rule in which the precise timing of spikes is ignored, with spike rate being modeled as a continuously varying parameter. An equivalent rate-based learning rule can be derived for any spike-timing dependent learning rule by calculating how synapses governed by the timing dependent learning rule respond to variations in the firing rates of pre- and postsynaptic neurons. The equivalent rate-based learning rule is obtained by determining how variations in the spike rates, as measured during a suitable time window (the time-average), affect synaptic efficacy (Kempter et al. 1999). Information about the timing of individual spikes is lost, of course, in computing the time average. Thus, a unique rate based rule can be derived from a spike timing dependent rule for a specified neuronal architecture and input pattern. However, the reverse is not true. One cannot derive a unique spike-timing dependent rule from a rate-based rule. Equivalence between spike timing dependent rules and rate-based rules is present when all of the information in the spike trains is conveyed by mean rate.

The effects of averaging can be seen by computing the ensemble average, which is the average over a large number of identically prepared experiments. The average in this case is calculated by integrating over a spike probability function. Suppose the change of a synaptic weight, w, at the time of a presynaptic spike can be expressed as,

$$\triangle w(t_{\mathrm{pre}}) = a + F(w)L(t_{\mathrm{post}} - t_{\mathrm{pre}}) \tag{1}$$

where a is a constant representing a non-associative component of the synaptic change, $L(t)$ is the spike-timing dependent learning function, and $F(w)$ is a function of the weight (Rubin et al. 2001). If we set the non-associative term to zero and assume that the changes in weights are small for each presynaptic spike so that we can approximate the synaptic change continuously,

$$\begin{aligned} \langle \triangle w(t_{\mathrm{pre}}) \rangle &= \langle F(w)L(t_{\mathrm{post}} - t_{\mathrm{pre}}) \rangle \\ &= \lambda \int L(t' - t_{\mathrm{pre}}) P_{\mathrm{post}}(t') \mathrm{d}t' \ , \end{aligned} \tag{2}$$

where $P_{\mathrm{post}}(t)$ is the probability of a postsynaptic spike at time t.

Hebbian spike timing dependent learning rules, in which synaptic efficacy increases when the presynaptic spike comes before the postsynaptic spike but decreases when it comes afterwards (Fig. 1A and B), can be shown mathematically to yield a differential Hebbian learning rule under conditions of time averaging, that is, when mean spike rate is considered to be the information bearing parameter (Roberts 1999; Rao and Sejnowski 2000). The first mode of the spike-timing learning function, $L(t)$, dominates if the LTP timing window is nearly antisymmetric as in the cases shown in Fig. 1A and 1B. This leads to a differential Hebbian learning rule (Roberts 1999), such that

$$\langle \triangle w(t_{\mathrm{pre}}) \rangle \propto \frac{\mathrm{d}}{\mathrm{d}t} P_{\mathrm{post}}(t)|_{t=t_{\mathrm{pre}}} \ . \tag{3}$$

A differential Hebbian learning rule is one in which synaptic efficacy increases when the correlation between the derivative of the presynaptic spike rate and the derivative of the postsynaptic spike rate is positive, but decreases when that correlation is negative.

The differential Hebbian learning rule (Kosko 1986) has a close connection to models of classical conditioning. Networks in which synaptic efficacy is governed by a differential Hebbian learning rule can implement a computational algorithm known as the 'temporal difference algorithm' (Klopf 1988) which has been shown to successfully model classical conditioning (Sutton and Barto 1981). A coarse-grained version of differential Hebbian learning is equivalent to the time difference learning rule:

$$\langle \triangle w(t) \rangle \propto \frac{1}{t - t'} \left(P_{\mathrm{post}}(t) - P_{\mathrm{post}}(t') \right) \ . \tag{4}$$

The temporal-difference algorithm measures the difference between the value of a functionally relevant quantity at different times. If the quantity represents an error, then an algorithm that minimizes that error will improve performance if the task is repeatedly performed. Together, these results imply that classical conditioning can be mediated by a network in which the synapses are governed by a Hebbian spike-timing dependent learning rule (Rao and Sejnowski 2001).

Spike timing dependent learning rules, like other learning rules, can lead to a strengthening of those inputs to a neuron that show correlated spike activity: ''Neurons that fire together wire together''(Aamodt and Constantine-Paton 1999; Willshaw 1976). However, there are some differences among the types of spike-timing dependent rules with regard to the effects of correlated inputs. A learning rule in which the LTD portion of the rule has a larger area than the LTP portion (Fig. 1B; Feldman 2000) results in a competitive process whereby correlated inputs are strengthened and uncorrelated inputs are weakened (Song et al. 2000). In contrast, a spike timing dependent learning rule in which the LTP and LTD portions are equal in area (Fig. 1A) will result in neither the strengthening of correlated inputs nor the weakening of uncorrelated inputs unless additional features are added. A rule with equal LTP and LTD areas will result in the strengthening of correlated inputs, however, if the amount of potentiation is inversely proportional to the original synaptic weight before pairing (van Rossum et al. 2000). Such an inverse relation, in which initially large EPSPs increase less than initially small EPSPs, has been observed experimentally in cultured hippocampal neurons (Bi and Poo 1998). Weakening of uncorrelated inputs, that is, competition, will occur with this latter learning rule if a global scaling of all synaptic inputs is present, based on the level of postsynaptic activity (van Rossum et al. 2000; Turrigano 1998).

An inverse relation between initial synaptic weight and potentiation as a result of learning has an important effect on the final distribution of synaptic weights after training with correlated inputs. Such an inverse relation is referred to as a 'multiplicative' rule of change and results in a unimodal distribution of synaptic weights after the training period, some being stronger and others weaker. In contrast, an 'additive' rule, in which efficacy increases by a fixed amount, or a fixed percentage, of the original weight, results in a bimodal distribution of weights in which the correlated inputs are saturated at their maximum values and the weights of all other inputs are minimized. The distribution of synaptic weights onto most real neurons appears to be unimodal, suggesting that multiplicative rules of change are more common than additive rules in nature. In the case of an additive learning rule, the function $F(w)$ in Eq. (1) is independent of the weight so that $F(w) = \lambda$ (Roberts and Bell 2000; Song et al. 2000). In a multiplicative learning rule, the function $F(w)$ is linearly dependent the weight so that $F(w) = \lambda w$ (Rubin et al. 2001).

Surprisingly, spike-timing dependent learning rules, like those shown in Fig. 1A, B and C in which LTP and LTD depend on the order of pre- and postsynaptic spikes, are not equivalent to covariant learning rules based on mean rate (Sejnowski 1977). In covariant rules, the synaptic weights are increased when the correlation between pre- and postsynaptic rates is positive, but decreased when the correlation is negative. Covariant learning rules have been widely used in studies of information storage in artificial neural networks. The lack of equivalence between the two types of rules is due to the asymmetric temporal properties of the spike timing dependent rules. More specifically, opposite changes occur on either side of zero delay between pre- and postsynaptic spikes and would require the additional non-associative terms to the learning rules for equivalency. The covariant rate-based learning rule compares the relative rates of pre- and postsynaptic activity during a time window centered on zero delay. In contrast, an anti-Hebbian spike timing dependent learning rule found in mormyrid electric fish (Fig. 1D) has been shown to be equivalent to an anti-covariant rule based on mean rate (Roberts and Bell 2000).

Thus, learning rules in which spike-rate is the controlling parameter will sometimes be equivalent to spike-timing dependent rules and sometimes not. It must be emphasized that spike-rate based rules often compute spike-rates by averaging over a hundred milliseconds or more (Bienenstock et al. 1982). In contrast, spike-timing based rules can be sensitive to variations in spike-timing of less than a millisecond (Gerstner et al. 1996). If the time window within which averages are computed is made smaller and approaches millisecond or sub-millisecond durations, then a spike-rate based rule becomes indistinguishable from a spike-timing based rule. At this point, however, a formulation of the rule in terms of spike-timing is both simpler and easier to understand physiologically than a formulation in terms of spike-rate.

Spike-timing dependent learning rules and the stability of neural networks

Networks with synapses governed by Hebb's original rule, which only allows for increases in strength, are dynamically unstable because synaptic strength can grow without bounds unless additional properties are included that limit synaptic strength. Since most of the spike-timing learning rules found in biological systems are bi-directional, having both an LTP and an LTD component, these learning rules can, in principle, limit the changes in synaptic strength. Not only can synaptic strength be limited with spike-timing dependent learning rules but such rules can also force the spike output rate of postsynaptic neurons to a fixed-point determined by the parameters of the learning rule.

Spike-timing dependent learning rules that have a larger LTD component than LTP component (Fig. 1B; Feldman 2000) have been shown to force the membrane potential of the postsynaptic neuron to a level near the spike threshold (Song and Abbott 2000). This has the advantage of tuning the postsynaptic neuron to a level of

excitation where it is most sensitive to variations in the input signals. Spike-timing dependent learning rules in which the LTP and LTD components are equal do not show this forcing of the membrane potential toward the spike threshold.

Synapses with anti-Hebbian learning rules typically do not have stability problems. Anti-Hebbian learning can lead to reductions in synaptic excitation to the point of silencing the postsynaptic cell unless there is an LTP component as well as an LTD component to the rule or some global renormalization mechanism. The anti-Hebbian spike-timing dependent learning rule found in mormyrid electric fish has such an LTP component, the LTP being non-associative (Fig. 1D). The combination of an associative LTD and a non-associative LTP forces the synaptic strengths to change in such a way that the final average spike frequency is at a level determined by the ratio of the learning rates for LTD and LTP (Roberts and Bell 2000). A similar fixed point is reached with another anti-Hebbian learning rule that has an associative potentiation component (Fig. 1F; Kashimori and Kambara 2000). In this latter case, however, stability of the fixed point requires a non-associative potentiation in the learning rule.

Recurrent excitatory connections in which the neurons excite other neurons in the network are common in many neural structures. Networks with such recurrent connections can act as neural integrators (Seung et al. 2000) although excitatory recurrent connections provide positive feedback that is inherently destabilizing. Such instability is minimized in a neural network if the excitatory synapses are governed by an anti-Hebbian spike-timing dependent learning rule in which depression occurs if the post synaptic spike follows the presynaptic spike and potentiation occurs if the postsynaptic spike comes first (Fig. 1F; Xie and Seung 2000). Such a learning rule reduces instability by reducing the strength of synapses carrying recurrent spikes.

New synaptic weights must remain stable after learning has occurred if information is to be reliably stored in a network . When synapses contribute significantly to the generation of postsynaptic spikes, spike-timing dependent learning rules have been shown to stabilize learning. After a learned distribution of synaptic weights has been established, the new spike-rates remain stable except for fluctuations due to noise (Kempter et al. 1999), even though the individual synaptic weights may fluctuate. Thus, spike-timing dependent learning rules allow for the stable storage of information in synaptic weights, even in the presence of the random variations in spike-timing that are present in all neural systems.

Processing and storage of temporal information

The question as to whether information in the brain is coded in terms of the precise timing of individual spikes or in terms of mean spike-rate is a central issue in neuroscience. The discovery of spike-timing dependent learning rules in the brain provides a strong argument for the importance of coding in terms of spike-timing. The fact that small, near millisecond, differences in the relative timing of two spikes can have radically different effects on synaptic efficacy strongly suggests that such small differences can also reflect significant changes in information content.

Neural networks in which synaptic efficacy is governed by spike-timing dependent synaptic learning rules inherit the exquisite timing sensitivity of the learning rule. Such networks can store precise temporal information in a static set of synaptic weights (Gerstner et al. 1993). It has been argued that rate based learning rules require integration over a longer time period and cannot therefore store temporal information with the same level of precision (Kempter et al. 1999).

An alternative to time averaging spikes from an individual neuron would be to average the spikes from a population of neurons (Shadlen and Newsome 1994). The disadvantage of this scheme is that spatial resolution would be lost because the neurons in the circuit would be contributing to the average rate and not carrying specific information individually. The temporal resolution of a network in which synaptic efficacy is controlled by a spike-timing based rule depends on the temporal resolution of the rule and on the temporal jitter or noise in the spike generation process. The actual temporal patterns that such networks can learn to discriminate or to generate depend on conduction and transmission delays within the network (Bi and Poo 1999).

Modeling studies have shown that networks which implement Hebbian spike-timing based rules (such as those shown in Fig. 1A and B) can learn to predict the next step in a sequence of inputs (Roberts 1999; Abbott and Blum 1996). Such a learning mechanism could be responsible for classical conditioning in which neuronal responses to conditioned stimuli predict the unconditioned stimuli after a learning period in which the two stimuli are presented repeatedly in the same sequence (Roberts 1999; Rao and Sejnowski 2001). Another example is provided by the hippocampus, where a modeling study showed that the asymmetric timing of a Hebbian spike based learning rule allows for the anticipation of spatial position during learning (Blum and Abbott 1996), and where an experimental study of place cells found such anticipatory neural activity during adaptation to a new environment (Mehta et al. 1997).

Anti-Hebbian spike-timing dependent synaptic plasticity has been shown to allow for the storage of temporally precise negative images of sensory input (Roberts and Bell 2000). A well characterized example of this is found in the electrosensory system of mormyrid electric fish (Bullock and Heiligenberg 1986). A subset of the fish's electrosensory afferents, the ampullary afferents, are tuned to be sensitive to externally generated electric signals such as those generated by other moving organisms. However, these fish generate their own electric signals that are used for navigation and communication. These electric discharges will interfere with the subtle external signals unless some mechanism exists to eliminate the reafferent signal.

Mormyrid electric fish increase the sensitivity of the ampullary afferent system by using the motor signal to their electric organ as a reference for canceling their response to their own electric discharge. A collateral from the motor pathway relays timing information to the electrosensory processing system. This information consists of a series of time delayed inputs that are presented to the plastic synapses of cells that also receive primary sensory input. By pairing the motor command signal with the reafferent electrosensory signal, the temporal pattern of the ampullary afferent response is stored in the electrosensory processing system. The system allows for the subtraction of predictable sensory features from the sensory inflow (Fig. 2; Bell et al. 1997a).

Modeling studies show that implementation of the spike-timing dependent learning rule measured in slice preparations (Fig. 1C) results in the storage of images that are stable and faithful negative copies of the original sensory response patterns. The spike probability after adaptation has taken place can be calculated as the fixed point of the learning equation (Eq. 2). If the postsynaptic spike probability is constant, $P_{\text{post}}(t) = \hat{P}$, and the average weight change vanishes, $\langle \triangle w(t_{\text{pre}}) \rangle = 0$, then the postsynaptic spike probability is equal to the ratio of the non-associative to the associative learning rates, $\hat{P} = a/\lambda$. Other spike-timing dependent learning rules lead to instabilities that distort the negative image (Fig. 3; Roberts and Bell 2000) and lead to poor cancellation of the reafferent signal.

The coding of information by means of the exact timing of spikes can be very sensitive to degradation if noise in the form of temporal variation is present in the system. It is often advantageous therefore to convert a timing code into a rate code that is less subject to degradation by noise (Carr and Friedman 1999). In the barn owl auditory system, for example, differences in spike timing as small as 10 ms carry information about the location of objects in the environment (Brainard 1993). The neural mechanism for measuring such small differences in the timing of spikes must be tuned and maintained with great precision. Theoretical studies have shown that such precise tuning can be created within a network by means of a spike-timing dependent learning rule (Gerstner et al. 1996; Kempter 2001). The temporal resolution of the learning rule must be as precise as the desired temporal resolution of auditory signals.

Relations between the cellular mechanisms of spike-timing dependent learning rules and their computational consequences

Knowledge of the cellular mechanisms of spike-timing dependent learning rules is of value in its own right and can provide pharmacological tools for experimentally investigating the roles of spike-timing dependent plasticity. Knowledge of mechanisms also bears on the computational consequences of spike-timing based rules and can suggest computational properties that would not be recognized otherwise.

Studies of plasticity distinguish between the mechanisms of induction and the mechanisms of expression.

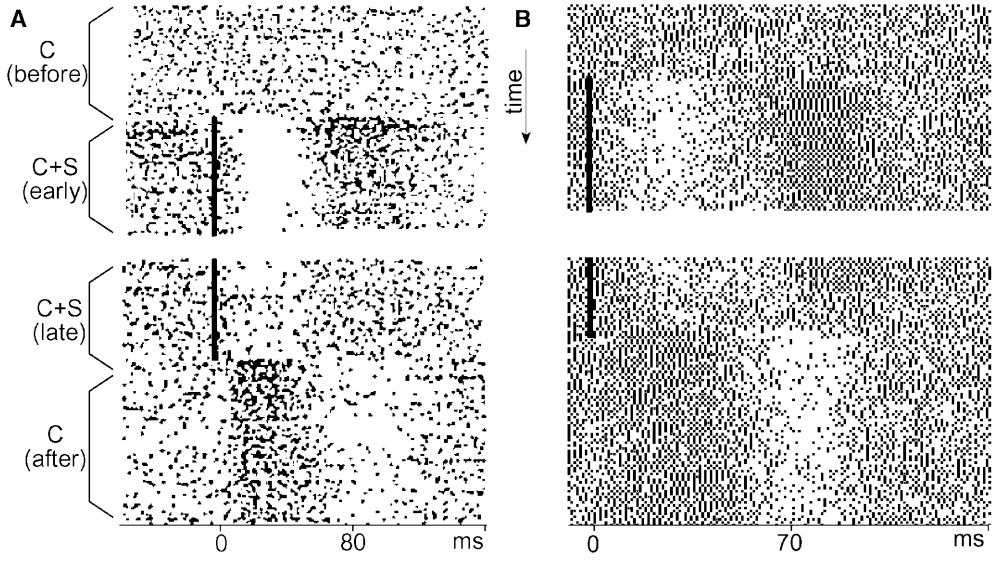

Fig. 2. Cancellation of Predicted Sensory Image. (A) A raster plot of neuron spike activity recorded in the electrosensory lateral line lobe of a mormyrid electric fish. Each horizontal trace is triggered by a motor command signal, C (at time zero on the plot). Each dot represents a spike and each row represents a cycle of the motor command. The cycles marked with a black line are paired with an artificial electrosensory stimulus that simulates an electric organ discharge, C + S. The neuron is responding with a pause followed by a burst of spikes to the electrosensory stimulus. However, after several minutes of pairing, the responses begin to fade as the neuron adapts to the sensory stimulus. After turning off the sensory stimulus, a response to the command alone appears that is opposite to the previously paired sensory stimulus (negative image) (B) Simulation of the predicted sensory image cancellation using the same pairing procedure except that a non-adaptive input representing the sensory stimulus is paired with a series of delayed inputs representing the motor command where the delays are correlated with the motor command signal and the synapses obey the learning rule of Fig. 1A (solid line). (Modified from Roberts and Bell 2000)

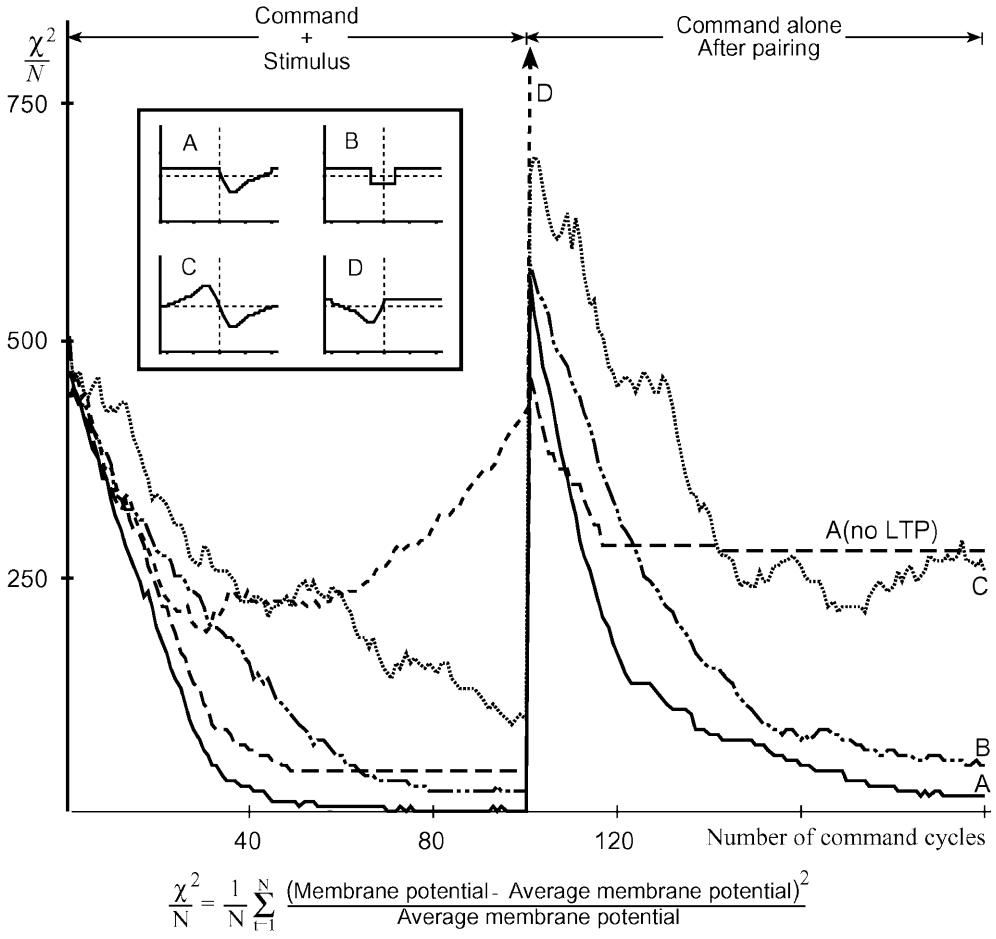

Fig. 3. Evolution in time of the negative image-simulation results. The difference from a perfect cancellation of the sensory response is measured by a chi-squared statistic. The formula is shown at the bottom where the sum is over the time steps in the command cycle up to the duration of the sensory response, N. Five learning rules are tested and shown in the inset. The fifth trace, A (no LTP) is the result that follows from learning rule like in A, but without any non-associative LTP. As the number of pairing cycles progresses (to the right), trace A decreases until the membrane potential is constant throughout the cycle and the sensory image is canceled. In this situation (lowest number), the fish would be most sensitive to any novel external stimuli because its own predictable field is filtered out. However, other learning rules (traces B, C, and D) are unstable and lead to oscillations that disrupt the image cancellation. The instabilities of the symmetric anti-Hebbian rule (B) are slow to develop, but eventually the value climbs as oscillations set in (not shown). The leading decent of these traces is a result of the associative depression along with non-associative enhancement. After pairing with the command alone, the negative image results in a large chi value that then decays for all rules except rule D with rule A showing the greatest decay (Modified from Roberts and Bell 2000)

Induction mechanisms include all of the cellular processes occurring during the learning period that establish the altered synaptic efficacy. Expression mechanisms include the final cellular sites where synaptic efficacy is altered after the induction process is complete. For example, induction of the synaptic changes responsible for the anti-Hebbian spike based learning rule in the mormyrid electrosensory system requires postsynaptic processes such as NMDA receptor activation and changes in intracellular calcium (Han et al. 2000). In contrast, expression of this form of plasticity appears to be a presynaptic change in the amount of transmitter released.

Spike-timing dependent rules require that a presynaptic spike and a postsynaptic spike occur in a particular temporal order. The process is therefore associative and studies of the mechanisms of induction have often focused on the cellular site of the associativity. The NMDA receptor is one such site of associativity, as previously described in this paper. Receptor properties such as the kinetics of glutamate binding and of calcium influx will determine the temporal features of the learning rule. The kinetics of cellular phenomena downstream from the influx of calcium will determine the learning rates, that is, the rates at which synaptic efficacy changes. Modulation of NMDA receptor properties, of back propagating dendritic spikes, and of downstream phenomena would in turn modulate the processes of synaptic change. Such modulation could result from changes in presynaptic activity levels, postsynaptic activity levels, neuromodulators, or activation of particular circuit elements such as inhibitory interneurons.

The effects of cellular processes are particularly important in order to generalize spike-timing dependent learning rules from single spike pairings to pairing trains

of presynaptic spikes with trains of postsynaptic spikes. In a combination of experimental data and modeling studies, it has been suggested that synaptic plasticity induced by spike pairings within the LTP time interval take precedence over pairings within the LTD time interval (Sjöström et al. 2001). In another example suggesting that spike pairings do not add equally, Froemke and Dan (2002) have observed that the early spikes in a burst have the strongest influence on the magnitude and direction of synaptic plasticity. A more complete understanding of induction mechanisms will help us to predict how computational studies should combine spike trains to generate changes in synaptic efficacy.

The cellular site of expression for synaptic plasticity also has important computational consequences. This is well illustrated by studies of a Hebbian spike-timing learning rule that is present at excitatory connections between neocortical pyramidal cells (Fig. 1A; Markram et al. 1997). The site of expression for this plasticity appears to be presynaptic, with potentiation being due to an increase in transmitter release and depression being due to a decrease. Potentiation and depression are accompanied by marked changes in the dynamics of the synapse. Postsynaptic responses to high frequency trains of presynaptic spikes are much more rapidly attenuated after potentiation than before. The increase in attenuation with potentiation means that there may not be a net increase in synaptic efficacy at higher frequencies of presynaptic input. Potentiation at this synapse may be better viewed as a conversion of the synapse from a low pass to a high pass filter, rather than as a generalized increase in efficacy. The findings illustrate that synaptic plasticity must always be viewed in the context of the activity patterns that the network normally processes.

Conclusions

The recent discovery that small variations in the relative timing of pre- and postsynaptic spikes can lead to marked changes in synaptic efficacy has profound implications for how information is coded, processed and stored within the nervous system. Our present understanding of this spike-timing dependent form of plasticity has been obtained through close collaboration with experimental and theoretical neuroscientists, and provides an excellent illustration of the fruitfulness of such collaboration.

Acknowledgements. This research is supported in part by a National Science Foundation grant IBN 98-08887 (awarded to PDR), and by National Institutes of Health grants R01-MH49792 (awarded to CCB), R01-MH60996 (awarded to CCB), and R01-MH60996 (awarded to PDR).

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