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...
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 spike 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.