Synaptic plasticity: taming the beast

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Synaptic plasticity provides the basis for most models of learning, memory and development in neural circuits. To generate realistic results, synapse-specific Hebbian forms of plasticity, such as long-term potentiation and depression, must be augmented by global processes that regulate overall levels of neuronal and network activity. Regulatory processes are often as important as the more intensively studied Hebbian processes in determining the consequences of synaptic plasticity for network function. Recent experimental results suggest several novel mechanisms for regulating levels of activity in conjunction with Hebbian synaptic modification. We review three of them—synaptic scaling, spike-timing dependent plasticity and synaptic redistribution—and discuss their functional implications.

Activity-dependent modification of synapses is a powerful mechanism for shaping and modifying the response properties of neurons, but it is also dangerous. Unless changes in synaptic strength across multiple synapses are coordinated appropriately, the level of activity in a neural circuit can grow or shrink in an uncontrolled manner. Hebbian plasticity, in the form of long-term potentiation (LTP) and depression (LTD), provides the basis for most models of learning and memory, as well as the development of response selectivity and cortical maps. These models often invoke *ad hoc* mechanisms to stabilize levels of activity. Here we review a number of recent developments, both experimental and theoretical, that suggest how changes of synaptic efficacy can be distributed across synapses and over time so that neuronal circuits can be modified flexibly yet safely.

Hebb originally conjectured that synapses effective at evoking a response should grow stronger, but over time Hebbian plasticity has come to mean any long-lasting form of synaptic modification (strengthening or weakening) that is synapse specific and depends on correlations between pre- and postsynaptic firing. By acting independently at each synapse, Hebbian plasticity gains great power, but also acquires stability problems. To avoid excessively high or low firing rates, the total amount of excitatory drive to a neuron or within a network must be tightly regulated, which is difficult to do if synapses are modified independently. What is needed is a mechanism that maintains an appropriate level of total excitation, but allows this to be distributed in different ways across the synapses of a network by Hebbian processes.

Bienenstock, Cooper and Munro suggested one such mechanism[1]. In the BCM model, correlated pre- and postsynaptic activity evokes LTP when the postsynaptic firing rate is higher than a threshold value and LTD when it is lower. To stabilize the model, the threshold shifts or slides as a function of the average postsynaptic firing rate. For example, the threshold increases if the postsynaptic neuron is highly active, making LTP more difficult and LTD easier to induce. Although this idea is attractive as a computational model, experimental evidence for the sliding threshold is largely indirect[2].

Three other candidate mechanisms for regulating neuronal activity during synaptic modification—synaptic scaling, spike-timing dependent plasticity (STDP) and synaptic redistribution—have been characterized experimentally and theoretically. We review these recent developments, focusing primarily on the issue of stabilizing Hebbian plasticity, but touching briefly on other functional implications. Our primary aim is to show that it is now possible to build models of synaptic plasticity, based directly on experimental data, that provide both flexible and stable mechanisms for shaping neuronal responses.

Synaptic scaling

Hebbian plasticity is a positive-feedback process because effective synapses are strengthened, making them even more effective, and ineffective synapses are weakened, making them less so. This tends to destabilize postsynaptic firing rates, reducing them to zero or increasing them excessively. An effective way of controlling this instability is to augment Hebbian modification with additional processes that are sensitive to the postsynaptic firing rate or to the total level of synaptic efficacy. A frequent approach in neural network models is to globally adjust all the synapses onto each postsynaptic neuron based on its level of activity[3]. The adjustment can take two forms, depending on whether the synapses to a particular neuron are changed by the same amount (subtractive) or by an amount proportional to their strength (multiplicative).

Hebbian plasticity is often used to model the development and activity-dependent modification of neuronal selectivity to various aspects of a sensory input, for example the selectivity of visually responsive neurons to the orientation of a visual image. This typically requires competition between synapses, so that the neuron becomes unresponsive to some features while growing more responsive to others. Many of the mechanisms designed to stabilize Hebbian plasticity introduce such competition. Both subtractive and multiplicative global adjustments lead to competition because they weaken all the synapses to a given neuron if any subset of synapses evokes a high level of activity. In general, multiplicative global adjustment is less competitive than subtractive adjustment, and it may be insufficiently competitive for some applications[3]. Competition can be enhanced under a multiplicative scheme if synapses that are weakened below a threshold level are eliminated.

These global adjustment schemes were introduced into the models *ad hoc*, but future models can be constructed on the basis of recent data. A biological mechanism that globally modifies synaptic strengths, called synaptic scaling, occurs in cultured networks of neocortical[4], hippocampal[5] and spinal-cord[6] neurons. Pharmacologically blocking ongoing activity in these systems caus-

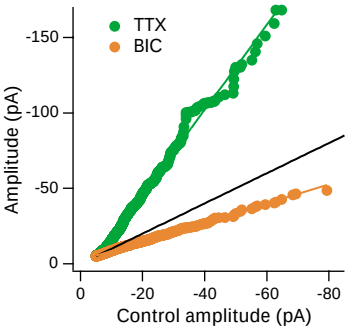

Fig. 1. Synaptic scaling is multiplicative. Quantal amplitudes of miniature EPSCs recorded from cortical pyramidal neurons in cultures that experience normal levels of spontaneous activity (control amplitude) are rank ordered and plotted against amplitudes recorded in sister cultures in which activity was either blocked with the sodium channel blocker tetrotodoxin (TTX) or enhanced by blocking inhibition with bicuculline (BIC) for two days. Activity blockade scales up mEPSC amplitude, whereas activity enhancement scales it down. The plots are well fit by straight lines, indicating that in both cases the scaling is multiplicative. Adapted from ref. 4.

es synaptic strengths, characterized by the amplitudes of miniature excitatory postsynaptic currents (mEPSCs), to increase in a multiplicative manner (Fig. 1). Conversely, enhancing activity by blocking inhibition scales down mEPSC amplitudes (Fig. 1).

Some biophysical mechanisms responsible for the bidirectional and multiplicative properties of synaptic scaling are understood. Direct application of glutamate[4] and fluorescent labeling of receptors[5,6] show that synaptic scaling is due to a postsynaptic change in the number of functional glutamate receptors. Furthermore, increasing synaptic strength during reduced activity is associated with a decrease in the turnover rate of synaptic AMPA-type glutamate receptors[6]. If receptor insertion and removal rates are differentially scaled by activity, this can produce multiplicative changes in synaptic strength[7].

Synaptic scaling in combination with LTP and LTD seems to generate something similar to a synaptic modification rule analyzed by Oja[8] that illustrates the power of stable, competitive Hebbian plasticity (see Math Box). The Oja rule combines Hebbian plasticity with a term that multiplicatively decreases the efficacy of all synapses at a rate proportional to the square of the postsynaptic firing rate. In simple neuron models, this generates an interesting form of input selectivity, related to a statistical method called principal component analysis, in which neurons become selective to the linear combination of their inputs with the maximum variance. This is, in some sense, the most interesting and informative combination of inputs to which the neuron can become responsive.

Activity manipulations scale both AMPA- and NMDA-receptor-mediated forms of glutamatergic synaptic transmission[9]. Scaling of the NMDA receptor component has implications for Hebbian plasticity, because LTP and LTD are produced by calcium entry through NMDA receptors. The standard view is that large amounts of calcium entry induce LTP, whereas smaller amounts cause LTD[10]. If neurons scale down NMDA receptor currents in response to enhanced activity, this may make it more difficult to evoke LTP and easier to induce LTD. Thus, in addition to multiplicatively adjusting synaptic strengths, synaptic scaling may modify Hebbian plasticity in a manner functionally similar to the BCM model's sliding threshold.

Spike-timing dependent synaptic plasticity

Synaptic scaling is a non-Hebbian form of plasticity because it acts across many synapses and seems to depend primarily on the postsynaptic firing rate rather than on correlations between pre- and postsynaptic activity. Purely Hebbian forms of plasticity can also be used to regulate total levels of synaptic drive, but this requires a delicate balance between LTP and LTD. The sensitivity of synaptic plasticity to the timing of postsynaptic action potentials (STDP) can provide a mechanism for establishing and maintaining this balance.

It has long been known that presynaptic activity that precedes postsynaptic firing or depolarization can induce LTP, whereas reversing this temporal order causes LTD[11–13]. Recent experimental results have expanded our knowledge of the effects of spike timing on LTP and LTD induction[14–21]. Although the mechanisms that make synaptic plasticity sensitive to spike timing are not fully understood, STDP seems to depend on an interplay between the dynamics of NMDA receptor activation and the timing of action potentials backpropagating through the dendrites of the postsynaptic neuron[15,22,23].

The type and amount of long-term synaptic modification induced by repeated pairing of pre- and postsynaptic action potentials as a function of their relative timing varies in different preparations (Fig. 2). In general, synaptic modification is maximal for

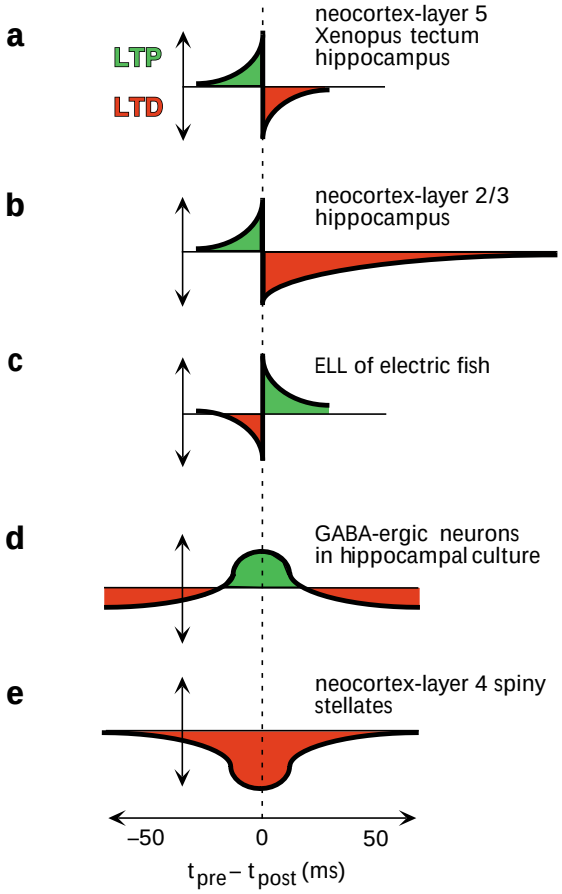

Fig. 2. The amount and type of synaptic modification (STDP) evoked by repeated pairing of pre- and postsynaptic action potentials in different preparations. The horizontal axis is the difference $t_{pre} - t_{post}$ between the times of these spikes. The numerical labels on this axis are approximate and are only intended to give an idea of the general scale. Results are shown for slice recordings of neocortex layer 5 and layer 2/3 pyramidal neurons[14,21] and layer 4 spiny stellate cells[20], *in vivo* recordings of retinotectal synapses in *Xenopus* tadpoles[19], *in vitro* recordings of excitatory and inhibitory synapses from hippocampal neurons[11–13,15,17,18] (Ganguly *et al.*, *Soc. Neurosci. Abstr.* **25**, 291.6, 1999) and recordings from the electrosensory lobe (ELL), a cerebellum-like structure in mormyrid electric fish[16].

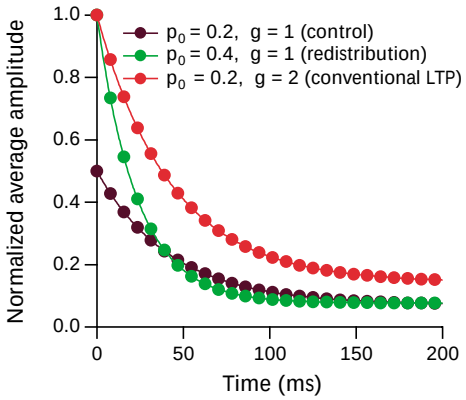

Fig. 3. Time dependence of the normalized average transmission amplitude for a model synapse showing short-term depression and synaptic redistribution, based on the model described in the Math Box. Following activation at a presynaptic rate of 100 Hz, the average transmission amplitude decreases rapidly. The control case (brown) shows a synapse with a maximum transmission probability of $p_0 = 0.2$. The parameter $g = 1$ is used to characterize the relative strength of the postsynaptic conductance induced by vesicle release. The other curves show two ways that this synapse might be strengthened. If LTP occurs through synaptic redistribution that changes p_0 to 0.4 but leaves g unchanged, the average initial amplitude is increased, but the ultimate average steady-state amplitude remains unchanged (green). If, instead, the synapse is strengthened by an increase in the postsynaptic conductance, which changes g to 2 but leaves p_0 at its initial value of 0.2, both the average initial and steady-state amplitudes increase (orange).

small differences between pre- and postsynaptic spike times, and no plasticity is induced if this difference grows too large. In some cases, the sign of the time difference (that is, whether the presynaptic spike precedes or follows the postsynaptic spike) determines whether the protocol induces LTP or LTD (Fig. 2a–c). In other cases, synaptic plasticity depends on the relative timing of the pre- and postsynaptic spikes, but not on their order (Fig. 2d and e). In the cerebellum-like structure of electric fish, LTP and LTD are reversed relative to other systems (Fig. 2c), perhaps because the postsynaptic neuron is inhibitory rather than excitatory. We do not consider these cases further, but concentrate instead on the form of plasticity observed in retinotectal connections and neocortical and hippocampal pyramidal cells (Fig. 2a and b).

This form of LTP timing dependence provides a mechanism for realizing Hebb's original hypothesis that synapses are strengthened only when presynaptic activity causes postsynaptic firing. Such a causal relationship clearly requires the pre-then-post temporal ordering that increases synaptic efficacy under STDP. The amount of LTP falls off roughly exponentially as a function of the difference between pre- and postsynaptic spike times with a time constant that is of the same order as a typical membrane time constant. This assures that only those presynaptic spikes that arrive within the temporal range over which a neuron integrates its inputs are potentiated, further enforcing the requirement of causality. STDP weakens inputs that fire shortly after a postsynaptic action potential and therefore do not contribute to evoking it. When presynaptic spikes occur randomly in time with respect to postsynaptic action potentials, both LTP and LTD can be induced, and it is interesting to ask which dominates. In the case of layer 2/3 pyramidal neurons (Fig. 2b), random pairings lead to an overall reduction in synaptic strength[21]; in other words, LTD dominates over LTP in this case. This makes functional sense, because it weakens inputs that 'accidentally' fire in approximate coincidence with postsynaptic action potentials, but that do not consistently contribute to evoking them.

STDP is a synapse-specific Hebbian form of plasticity, and although we might expect that the firing-rate instabilities that plague purely Hebbian models would also occur with STDP, this is not the case. STDP can regulate both the rate and variability of postsynaptic firing[24,25]. For this to occur, synaptic strengths must be bounded between zero and a maximum allowed value, but no further global non-Hebbian mechanisms or *ad hoc* constraints are required[25].

To see how STDP can stabilize postsynaptic firing rates, imagine a neuron that initially receives excessively strong uncorrelated excitatory drive from many synapses, making it fire at an unacceptably high rate. The strong multi-synaptic input to such a neuron is effectively summed into a relatively constant input current. In response to such input, a neuron will fire in much the same way as it would in response to the injection of the equivalent constant current through an electrode, by firing rapidly and regularly. In such a situation, the neuron acts as an integrator, and there is little correlation between the timing of its spikes and those of its inputs. If LTD dominates over LTP for random pre- and postsynaptic spike pairings[21], this leads to an overall weakening of synaptic efficacy. As STDP weakens the synaptic drive, the neuron eventually moves into a regime where the average synaptic current is either barely able or unable to make the postsynaptic neuron fire. In this case, action potentials are primarily generated by chance clusterings in the timing of presynaptic spikes[26]. The neuron acts somewhat like a coincidence detector and produces an irregular pattern of postsynaptic firing. Presynaptic spikes are more likely to occur slightly before than slightly after postsynaptic action potentials in this situation, because clusters of presynaptic spikes are required to evoke a postsynaptic response. The dominance of pre- followed by postsynaptic spiking causes synapses to be potentiated more often than they are depressed, which compensates for the dominance of LTD over LTP produced by random spike timing. This ultimately leads to a nonuniform distribution of synaptic strengths and a postsynaptic neuron that fires at a reasonable rate, but irregularly[25]. Thus, STDP not only stabilizes Hebbian modification, it drives neurons to a noisy but temporally sensitive state that resembles what has been suggested to exist *in vivo*[26].

STDP also introduces competition into Hebbian plasticity[19,24,25,27]. Groups of synapses that are effective at rapidly generating postsynaptic spikes are strengthened by STDP, making them even more effective at controlling the timing of postsynaptic spikes. Synapses from other inputs that fire at random times with respect to this dominant group will then be weakened if LTD dominates over LTP for random temporal pairings[21].

If two neurons are reciprocally connected and have correlated activities, Hebbian plasticity will typically strengthen the synapses between them in a bidirectional manner. This can produce strong excitatory loops that cause recurrently connected networks to suffer from self-excitatory instabilities. STDP is temporally asymmetric and, indeed, in the case of Fig. 2a, essentially antisymmetric. If neurons with correlated activities tend to fire in a specific temporal order, synapses from the leading neuron to the lagging neuron will be strengthened, whereas synapses in the opposite direction will be weakened. Thus, the temporal asymmetry of STDP suppresses strong recurrent excitatory loops. As a result, it is possible for stable recurrent networks to develop based on STDP without generating the runaway network activity typically resulting from Hebbian plasticity.

MATH BOX

Although space does not permit a full discussion of the techniques used to model the phenomena discussed in the text, we present some basic approaches.

1. Synaptic scaling can be implemented along with Hebbian synaptic modification by using something similar to the Oja rule of artificial neural network theory[8]. If the presynaptic neuron fires at a rate r_{pre} and the postsynaptic neuron at a rate r_{post}, the normal assumption of Hebbian plasticity is that the synaptic strength changes at a rate proportional to $r_{pre}r_{post}$. Synaptic scaling can be modeled by including an additional non-Hebbian term, so that the synapse modification rate is proportional to $r_{pre}r_{post} - f(r_{post})w$, where f is some function, and w is the synaptic weight parameter that characterizes the strength of the synapse. In the case of the Oja rule, $f(r_{post}) = (r_{post})^2$, but the experimental data support a function that is either positive or negative depending on the postsynaptic firing rate[4–6].

2. STDP can be modeled[25] most easily by making the approximation that each pre- and postsynaptic spike pair contributes to synaptic modification independently and in a similar manner, although the data show deviations from these simplifying assumptions[14,18]. We assume that the curves appearing in Fig. 2 (in particular, Fig. 2a and b) can be approximated by two exponential functions; $A_+ \exp(t/\tau_+)$ (with $A_+ > 0$) for $t < 0$ and $A_- \exp(-t/\tau_-)$ (with $A_- < 0$) for $t \geq 0$. A simple way to keep track of all the spike pairs contributing to STDP at a given synapse is to define functions $P_{pre}(t)$ and $P_{post}(t)$ that satisfy the equations $\tau_+ dP_{pre}/dt = -P_{pre}$ and $\tau_- dP_{post}/dt = -P_{post}$. $P_{pre}(t)$ is incremented by an amount A_+ every time the presynaptic terminal receives an action potential. Similarly, $P_{post}(t)$ is decremented by an amount A_- every time the postsynaptic neuron fires an action potential. $P_{pre}(t)$ then determines how much the synapse is strengthened if the postsynaptic neuron fires an action potential at time t, and $P_{post}(t)$ determines how much the synapse is weakened if the presynaptic terminal transmits an action potential at time t. Synaptic strengthening and weakening are subject to constraints so that the synaptic strength does not go below zero or above a certain maximum value.

3. Synaptic redistribution requires that we model the process of synaptic depression and how it is modified by LTP[37–39]. Suppose that a given synapse transmits a presynaptic action potential with probability p. If the synapse has been inactive for a sufficiently long period of time, p approaches its maximum value p_0. When the synapse is active, we assume that p decreases at a rate proportional to the transmission rate due, for example, to vesicle depletion. When transmission is not occurring, p recovers exponentially to p_0 with a recovery time constant τ_D. The assumption is then that, in the case of synaptic redistribution, LTP modifies the value of p_0. The curves in Fig. 3 were generated from this model with $\tau_D = 300$ ms.

In keeping with the emphasis of this review on stability, we have focused on this aspect of STDP, but incorporating sensitivity to timing into Hebbian plasticity has a host of other interesting implications. STDP can act as a learning mechanism for generating neuronal responses selective to input timing, order and sequence. For example, STDP-like rules have been applied to coincidence detection[27], sequence learning[28-30], path learning in navigation[31,32], and direction selectivity in visual responses[32,33]. In general, STDP greatly expands the capability of Hebbian learning to address temporally sensitive computational tasks.

Synaptic redistribution

A synapse can be strengthened postsynaptically by increasing the number or efficacy of receptor channels, or presynaptically by increasing the probability or amount of transmitter release. These mechanisms can have quite different functional consequences. A dramatic example of this involves the interplay of long- and short-term synaptic plasticity.

Synaptic depression is a form of short-term synaptic plasticity that seems to be a widespread feature of cortical synaptic transmission[34], which has significant functional implications for neural coding[35–39]. Short-term depression, which is thought to arise, at least in part, from depletion of the pool of readily releasable vesicles at a synaptic release site, is a use-dependent reduction in the probability that a presynaptic action potential will induce release of transmitter. This takes the form of a reduction in the probability of release with each transmission event, followed by an exponential recovery to a baseline release probability (see Math Box).

At some cortical synapses, LTP modifies the short-term plasticity of synapses[40,41], an effect called synaptic redistribution[40]. Although the precise mechanism of synaptic redistribution is not known, it is consistent with a form of LTP that acts presynaptically to increase the probability of transmitter release. This increases the likelihood of transmission occurring early in a sequence of presynaptic action potentials, but also decreases the availability of readily releasable vesicles for transmission later in the sequence. The overall effect is to enhance the average transmission amplitude for presynaptic action potentials that occur after a period of inactivity, but also to increase the onset rate of synaptic depression. Synaptic redistribution can significantly enhance the amplitude of synaptic transmission for the first spikes in a sequence, while having no effect on the ultimate steady-state amplitude (Fig. 3; although this figure was generated by a model, similar effects are seen experimentally[37,38]). There is no steady-state effect because the increased probability of release and the increased amount of short-term depression cancel each other. It is not yet clear if forms of LTD reverse the redistribution found in LTP, that is, decrease the probability of release and reduce the amount of short-term depression.

After redistribution, a synapse is much more effective at conveying transients, but there is no change in its efficacy for steady-state transmission. As a result, synaptic redistribution allows Hebbian modification to act without increasing either the steady-state firing rates of postsynaptic neurons or the steady-state excitability of recurrent networks. The presence of synaptic depression allows networks to support stronger recurrent excitation without becoming unstable. Such networks produce occasional spontaneous bursts of activity during otherwise quiet periods, but prolonged periods of high activity are suppressed[42,43].

The temporal aspects of plasticity induction due to STDP can interact with the dynamics of short-term depression in interesting ways if STDP acts presynaptically and evokes synaptic redistribution (as reported[40]). STDP strengthens synapses that are effective at making a neuron fire with short latency. By increasing the short-

term efficacy of a synapse while decreasing its ability to sustain multiple transmissions, synaptic redistribution constructs synapses with exactly the properties that lead to enhancement by STDP. The sequence-learning properties of STDP also couple in interesting ways to the temporal characteristics of synaptic depression. For example, synaptic depression has been suggested as a mechanism for generating direction selectivity in simple cells of the primary visual cortex[39]. STDP that induces synaptic redistribution can generate such responses (Buchs *et al.*, *Soc. Neurosci. Abstr.* 25, 2259, 1999), as well as providing a developmental mechanism for orientation selectivity[44].

Discussion

Modeling studies have clearly demonstrated the utility and power of synaptic scaling, STDP and synaptic redistribution as mechanisms of learning and development. Properties of these forms of plasticity have been shown in studies of cultured neurons and brain slices, and also to some extent *in vivo*. Preliminary data suggest that blocking visual input to cortical neurons *in vivo* during the critical period (through intraocular injection of tetrodotoxin) strengthens synapses (measured subsequently in slices) in a multiplicative manner (N.S. Desai, S.B.N. and G.G. Turrigiano, unpublished data). This effect is similar to the synaptic scaling induced by blocking activity in culture preparations. Recordings from hippocampal place cells of behaving rats suggest that STDP may occur during normal behavior[32,45]. Place cells fire when a rat passes through a particular location, known as the place field, in a familiar environment. Models that incorporate STDP predict that place fields located along a path that a rat traverses repeatedly in a fixed direction should shift backward along the path (that is, in the direction opposite to the rat's motion) as a result of this experience[29,31]. The predicted shifts have been observed experimentally[32,45]. Finally, evidence for the occurrence of synaptic redistribution *in vivo* is provided by slice recordings following sensory deprivation in rat somatosensory cortex[46].

All three mechanisms we have discussed can contribute to the stability of neuronal firing rates, and they might thus appear redundant. However, each has its own distinctive functional roles. Synaptic scaling, by realizing something equivalent to the Oja rule, can cause a neuron to become selective to the most variable aspects of its inputs. Furthermore, among the mechanisms we have discussed, synaptic scaling is the only one that does not require postsynaptic activity. It can thus rescue a neuron that has become inactive due to insufficient excitatory synaptic drive. Both STDP and synaptic redistribution can produce interesting temporal effects. STDP provides a mechanism for learning temporal sequences, but in some cases may require the addition of a synaptic scaling mechanism to generate sufficient competition between synapses[47,48]. Synaptic redistribution acts primarily to modify transient rather than steady-state responses. Thus, it seems likely that all three forms of plasticity, and other forms that we have not discussed, are needed to provide a full repertoire of developmental and learning mechanisms.

Most excitatory synapses onto excitatory neurons (but not onto inhibitory neurons) examined to date show some form of long-term plasticity. The forms of plasticity, at least as characterized by their temporal sensitivity, vary considerably across different brain regions and even across layers within one region (Fig. 2). Similarly, redistribution occurs at neocortical synapses[40,41], but seems not to be a feature of LTP in the CA1 region of the hippocampus[49,50]. Given the complexity of learning and memory, it is not surprising to see many forms of synaptic plasticity with different mechanisms of induction and expression. Determining how these fit together to account for the wide variety of learning and developmental phenomena is a challenge for theoretical work in the years ahead.

Acknowledgements

Research supported by NIH-MH58754, NIH-EY11116, the Sloan Center for Theoretical Neurobiology at Brandeis University and the W.M. Keck Foundation. We thank Gina Turrigiano, Eve Marder and Jesper Sjöström for comments.

Received 24 May; accepted 26 September 2000

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Viewpoint • In the brain, the model is the goal

Both computational and empirical studies use models of neural tissue to make inferences about the intact system. Their aims and scope are complementary, however, and their methods have different strengths and weaknesses. For example, much of our knowledge of synaptic integration comes from *in vitro* slices. These slices, which finish out their brief lives in man-made extracellular fluid, are crude models of the intact brain, with deeper resting potentials, lower background firing rates, higher input resistances, severed inputs, and so on. Test pulses delivered to a nerve or puffs of glutamate to a dendritic branch are crude models of synaptic stimulation *in vivo*. Recordings of one or two voltages within a spatially extended neuron provide a highly reduced model of the cell's electrical state. Similarly, long-term potentiation is a simplified model for learning, and high-contrast bars on a gray background are simplified models for visual stimulation. Yet many things have been learned from experiments on such simplified empirical models, the results of which—often called 'data'—underlie our current primitive understanding of brain function.

In contrast, computer studies use models whose elements and principles of operation are explicit, usually encoded in terms of differential equations or other kinds of laws. These models are extremely flexible, and subject only to the limitations of available computational power: any stimulus that can be conceptualized can be delivered, any measurement made, and any hypothesis tested. In a model of a single neuron, for example, it is simple to deliver separate impulse trains to 1,000 different synapses, controlling the rate, temporal pattern of spikes within each train (periodic, random, bursty), degree of correlation between trains, spatial distribution of activated synaptic contacts (clustered, distributed, apical or basal, branch tips, trunks), spatiotemporal mix of excitation and inhibition, and so on. Furthermore, every voltage, current, conductance, chemical concentration, phosphorylation state or other relevant variable can be recorded at every location within the cell simultaneously. And if necessary, the experiment can be *exactly* reproduced ten years later.

Nor are such experiments confined to reality: computers permit exploration of pure hypotheticals. Models can contrast a system's behavior in different states, some of which do not exist. For example, several spatial distributions of voltage-dependent channels could be compared within the same dendritic morphology to help an investigator dissect the dastardly complex interactions between channel properties and dendritic structure, and to tease apart their separate and combined contributions to synaptic integration. This sort of hands-on manipulation gives the computer experimentalist insight into general principles governing the surrounding *class* of neural systems, in addition to the particular system under study.

The need for modeling in neuroscience is particularly intense because what most neuroscientists ultimately want to know about the brain *is* the model—that is, the laws governing the brain's information processing functions. The brain as an electrical system, or a chemical system, is simply not the point. In general, the model as a research tool is more important when the system under study is more complex. In the extreme case of the brain, the most complicated machine known, the importance of gathering more facts *about* the brain through empirical studies must give way to efforts to relate brain facts to each other, which requires models matched to the complexity of the brain itself. There is no escaping this: imagine a neuroscientist assigned to fully describe the workings of a modern computer (which has only 10^{10} transistors to the brain's 10^{15} synapses). The investigator is allowed only to inject currents and measure voltages, even a million voltages at once, and then is told to simply *think* about what the data mean. The task is clearly impossible. Many levels of organization, from electron to web server, or from ion channel to consciousness—each governed by its own set of rules—lie between the end of the experimentalist's probe and a deep understanding of the abstract computing system at hand. A true understanding of the brain implies the capacity to build a working replica in any medium that can incorporate the same principles of operation—silicon wafers, strands of DNA, computer programs or even plumbing fixtures. This highly elevated 'practioner's' form of understanding must be our ultimate goal, since it will not only allow us to explain the brain's current form and function, but will help us to fix broken brains, or build better brains, or adapt the brain to altogether different uses.

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