

Synaptic computation

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Neurons are often considered to be the computational engines of the brain, with synapses acting solely as conveyers of information. But the diverse types of synaptic plasticity and the range of timescales over which they operate suggest that synapses have a more active role in information processing. Long-term changes in the transmission properties of synapses provide a physiological substrate for learning and memory, whereas short-term changes support a variety of computations. By expressing several forms of synaptic plasticity, a single neuron can convey an array of different signals to the neural circuit in which it operates.

Synapses conduct signals between neurons in an ever-changing manner. The effect of a signal transmitted synaptically from one neuron to another can vary enormously, depending on the recent history of activity at either or both sides of the synapse, and such variations can last from milliseconds to months. Activity-dependent changes in synaptic transmission arise from a large number of mechanisms known collectively as synaptic plasticity. Synaptic plasticity can be divided into three broad categories: (1) long-term plasticity, involving changes that last for hours or longer, is thought to underpin learning and memory^{1–3}; (2) homeostatic plasticity of both synapses and neurons allows neural circuits to maintain appropriate levels of excitability and connectivity despite changes brought about by protein turnover and experience-dependent plasticity^{4–6}; (3) short-term plasticity, which is the main focus of this review, occurs over milliseconds to minutes⁷ and allows synapses to perform critical computational functions in neural circuits. It is clear that we cannot understand neural coding or information processing without taking synaptic dynamics into account. Here, we review some of the forms of synaptic plasticity and discuss their implications for neuronal coding and signalling.

Expression and induction of plasticity

Synapses transmit information when presynaptic action potentials cause the membrane fusion of neurotransmitter-containing vesicles. This is followed by binding of the released transmitter to receptors that modify postsynaptic activity^{8–10}. On rapid timescales (milliseconds to minutes) the release of neurotransmitter depends on the pattern of presynaptic activity, and synapses can be thought of as filters with distinctive properties. This provides synapses with computational potential and has important implications for the diversity of signalling within neural circuits. Neural responses are typically described by specifying the sequences of action potentials that neurons fire. Such sequences are used to characterize the selectivities and information content of neuronal responses, and they form the basis of virtually all studies of neural coding. Implicit in this approach is the assumption that individual neurons ‘speak with a single voice’. This ‘voice’ consists of the action potential sequences that would, for example, be recorded from the neurons in standard electrophysiology experiments. The remarkable range and variety of synaptic plasticity mechanisms make this single voice, ‘spikes equal signal’ assumption untenable.

Synapses from the same neuron can express widely different forms of plasticity^{11–13}. Moreover, connections between neurons can sometimes consist of a single release site^{12,14} where the release of neurotransmitter is probabilistic

and the likelihood of release is modified by activity through short-term plasticity. Such synapses selectively, although unreliably, filter the flow of information between neurons. Given the stochastic nature of transmission, a neuron firing a sequence of action potentials is likely to generate a different pattern of vesicle releases at each of its thousands of synaptic terminals. So, each neuron transmits not just one, but a large number of different signals to the neural circuit in which it operates. Individually, these synapse-specific signals are selectively filtered versions of the action potential sequence that the neuron generates, modified by the context of previous presynaptic and postsynaptic activity. Collectively, knowing which synapses transmit a given action potential — the signal by which neurons interact — provides more information than simply knowing that a neuron has fired. Communication from a single neuron is thus a chorus not a single voice.

Just as the expression of synaptic plasticity involves a huge range of timescales, its induction can be rapid or can involve integration of activity over long periods of time. Induction requirements for synaptic plasticity can impose complex contingencies on the temporal patterns of activity that maximize effective circuit connectivity. The potential computational power of synapses is large because their basic signal transmission properties can be affected by the history of presynaptic and postsynaptic firing in so many different ways^{7,15}. Three classes of induction requirements can be identified depending on the direction of information flow across the synapse. The basic process of synaptic transmission is feedforward, with the presynaptic neuron sending a signal to its postsynaptic target (downward in Fig. 1a, b). Several forms of plasticity are feedforward in character, meaning that their induction depends solely on presynaptic activity (right-pointing arrows in Fig. 1b). Such forms of plasticity are the main focus of this review. However, the flow of information across a synapse can also be bidirectional, which greatly enhances computational potential. Synaptic plasticity can depend on feedback from the postsynaptic neuron (upward in Fig. 1b) through the release of retrograde messengers^{16,17} (left-pointing arrows in Fig. 1b). This ‘feedback plasticity’ may operate in isolation or in conjunction with presynaptic activity (associative plasticity). Feedforward, feedback and associated forms of synaptic plasticity have quite different functional and computational implications.

Forms of synaptic plasticity

Many factors affect how a postsynaptic neuron responds to the arrival of a presynaptic action potential at a particular synapse. On the postsynaptic side, receptor desensitization, in which prolonged exposure to the neurotransmitter inactivates

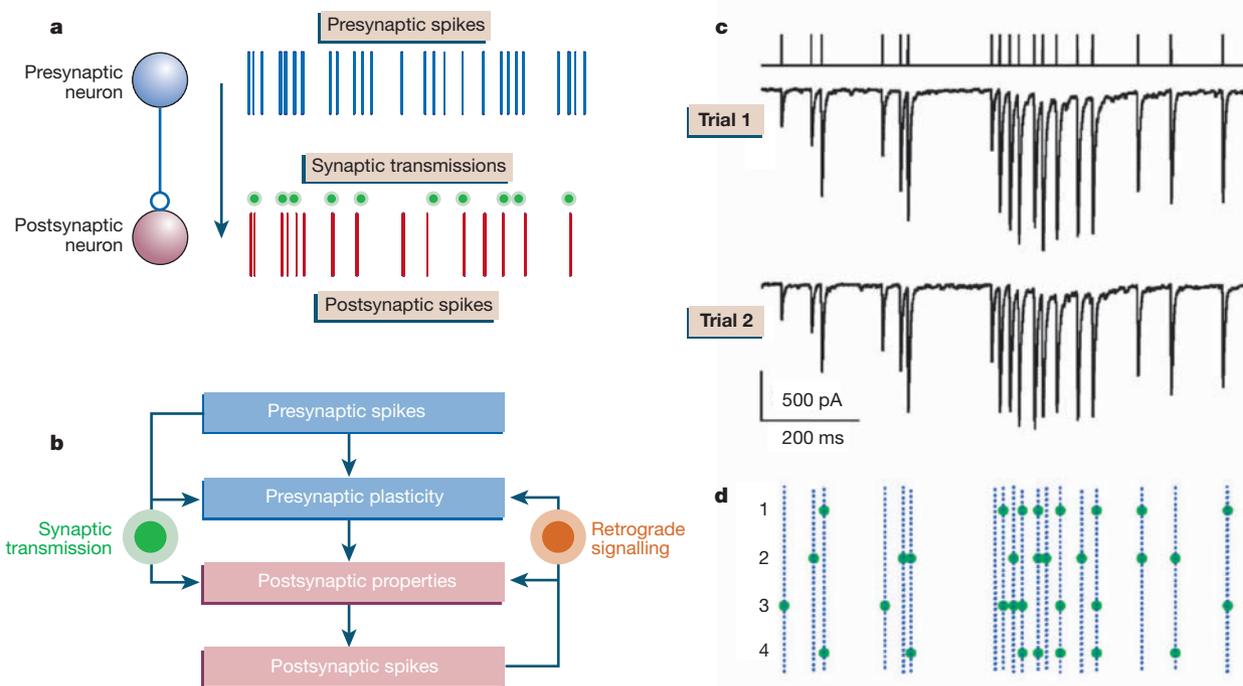


Figure 1 Several processes determine how a presynaptic neuron influences the firing pattern of its postsynaptic targets. **a**, Representative firing patterns of presynaptic and postsynaptic neurons. Blue lines denote presynaptic spikes; green dots denote synaptic vesicle releases (that is, transmissions); and red lines denote postsynaptic spikes. **b**, Pathways through which the firing patterns of presynaptic and postsynaptic neurons influence each other and synaptic transmission, including feedforward (pre-to-post) and feedback (post-to-pre) effects. **c**, **d**, Influence of short-term synaptic plasticity on synaptic transmission evoked by irregular stimulus

trains. **c**, Stimulation from the same stimulus train over two trials results in similar synaptic currents (top). These synaptic currents are measured in cerebellar Purkinje cells in response to parallel fibre activation. **d**, Simulated vesicle releases at an individual bouton over four trials with the same stimulus train as in **c**. Stimulus timing is indicated by the vertical blue lines and vesicle release is indicated by a green dot. Time bar is the same as in **c**. The occurrences of vesicle fusions were not measured in these experiments but are included to illustrate what probably occurs at individual release sites. Fig. 1c adapted from ref. 48.

receptors, decreases the ability of the postsynaptic cell to respond to the neurotransmitter^{18–22}. The type of receptor activated at the synapse also affects the postsynaptic response. Glutamate, for example, can activate AMPA receptors, NMDA receptors, and metabotropic glutamate receptors (mGluRs)¹⁰. AMPA receptors show a range of properties but usually have rapid kinetics. NMDA receptors have much slower kinetics and are voltage dependent. mGluRs are coupled to second messenger systems that can lead to modulation and activation of channels and to the release of calcium from internal stores²³. Finally, the location of a synapse on the dendritic arbor in relation to the general morphology of the neuron and its distribution of active conductances, as well as the presence of other active synapses, all have important roles in determining the postsynaptic response^{24,25}.

We cannot cover all the factors that contribute to the transformation from a presynaptic action potential to a postsynaptic response in this review. Because we are interested in the computational potential of dynamic synapses, we will focus on plasticity at the synapse: activity-dependent changes in the probability of vesicle release and in the response of postsynaptic receptors. Numerous mechanisms of plasticity acting over a wide range of timescales influence the release of neurotransmitter-containing vesicles. The initial probability of release and use-dependent plasticity of synapses are determined by the identities of the presynaptic and postsynaptic neurons, as well as by the history of action potential activity and by the local environment^{26,27}. There are numerous examples of boutons from the same axon giving rise to facilitating synapses (that enhance synaptic strength) for some types of target neurons and to depressing synapses (that reduce synaptic strength) at others^{13,27}. The target can also induce the expression of distinctive modulatory receptors in presynaptic boutons²⁶. These findings indicate that the postsynaptic cell

influences the presynaptic properties of the synapse, either through direct contact or by liberating a retrograde messenger. There is, however, considerable diversity in the properties of synaptic connections between two cell types, indicating that additional refinement of synaptic properties can occur. The dynamic properties of synapses are also refined in a use-dependent manner by long-term mechanisms of synaptic plasticity.

Feedforward plasticity

Periods of elevated presynaptic activity can cause either an increase or a decrease in neurotransmitter release⁷. Facilitation reflects an increase in the probability of neurotransmitter release (p) that lasts for up to hundreds of milliseconds. Depression reflects a decrease in the probability of neurotransmitter release that persists for hundreds of milliseconds to seconds. Facilitation and depression seem to coexist at synapses, with their relative weight depending largely on the initial p : high p favours depression, low p favours facilitation. On longer timescales (tens of seconds to minutes), longer-lasting forms of depression reduce synaptic strength and augmentation and post-tetanic potentiation (PTP) enhance it. Repeated presynaptic activation is typically required to produce appreciable synaptic plasticity. Several forms of these longer-lasting types of enhancement and depression coexist at most synapses.

To understand how short-term plasticity affects how a presynaptic neuron influences the firing of its postsynaptic targets (Fig. 1a), it is useful to activate synaptic inputs and record the responses in whole-cell voltage clamp. In Fig. 1c, synaptic inputs are activated with an irregular stimulus train of the sort that might occur at many types of synapse *in vivo*. Synaptic currents start out small, increase in amplitude during high-frequency bursts and then decrease following

quiescent periods. In the two trials shown in Fig. 1c, the responses are remarkably stereotyped and there is relatively little variability. This is because the response is mediated by many tens of synaptic contacts. If, on the other hand, the response of individual synaptic contacts is considered, stochastic variability becomes important (Fig. 1d). Release patterns from individual boutons in response to the same pattern of stimulation vary considerably, as is illustrated by the four simulated traces in Fig. 1d. Similarly, on single trials the same stimulus can evoke different patterns of transmitter release at different synaptic contacts. But despite large trial-to-trial variations, the facilitation present at this synapse can be seen in Fig. 1d. Greater enhancement of release can be seen during high-frequency bursts than following periods of inactivity.

Feedback plasticity

Recent studies have also identified plasticity operating on rapid timescales that depends on postsynaptic activity^{28–31}. Several retrograde messengers have been identified that once released from dendrites act on presynaptic terminals to regulate the release of neurotransmitter^{16,31–34}. The endocannabinoid system is the most widespread signalling system that mediates retrograde signalling¹⁶. Endocannabinoids are released from the postsynaptic cell following the cleavage of lipid precursors. This release of endocannabinoids leads to an inhibition of neurotransmitter release that lasts for tens of seconds^{35–37}. Endocannabinoid release can be triggered by increased concentrations of calcium in postsynaptic cells and by activation of second messenger systems. This suggests that the state of the postsynaptic cell exerts control on neurotransmitter release from the presynaptic terminals by regulating the release of endocannabinoids.

The roles of retrograde inhibition by endocannabinoids are not yet well understood. One possibility is that this inhibition provides a general means for postsynaptic neurons to control the inputs they receive, providing homeostatic regulation of synaptic strength based

on postsynaptic activity levels. Although an intriguing possibility with parallels on longer timescales, the exceptionally high calcium concentrations required for calcium-dependent endocannabinoid release³⁸ make it unlikely that endocannabinoids normally operate in this manner. Instead it seems that endocannabinoids can lead to synapse-specific modulation³⁹. For example, burst firing in presynaptic cells can evoke local endocannabinoid release and selective synaptic regulation. One interesting, yet to be tested, possibility is that endocannabinoids provide a mechanism of short-term associative plasticity (as is the case for long-term plasticity^{40–42}), in which endocannabinoid release and synaptic modulation are controlled by postsynaptic and presynaptic activity.

Associative plasticity

Short-term forms of associative plasticity would be useful for several reasons⁴³. Network models based on short-term plasticity can lead to persistent activity in a subset of neurons that represent a particular memory. Models based on fast associative plasticity are more robust than models relying solely on finely tuned synaptic weights within the network⁴⁴. Rapid associative plasticity could also be useful for improving performance on a task where predictions are made and then error signals are used to correct deviations from those predictions⁴⁵. This is because associative plasticity allows the error signal to make appropriate corrections by modifying synapses that lead to incorrect performance. Despite these potential uses of short-term associative plasticity, in contrast to the many associative forms of long-term depression and potentiation (LTD and LTP) that have been identified, far less is known about synaptic mechanisms that could implement associative plasticity on the seconds to tens of seconds timescale.

Functional roles of short-term plasticity

A number of functional roles have been proposed for synaptic dynamics^{46–61}. Short-term synaptic plasticity can drastically alter how a neuron activates its postsynaptic targets^{48,62}. Figure 2 compares the variety of ways that different synapses respond to patterns of spiking. In these examples, the synaptic responses are measured in voltage-clamp mode and the postsynaptic cell is not allowed to fire an action potential, although it is clear that synapses with such different dynamics would lead to very different postsynaptic firing. The climbing fibre synapse has a high initial *p* and therefore depression dominates the short-term plasticity during bursts, with gaps in the presynaptic activity allowing recovery. Parallel fibre synapses are low *p* synapses and facilitation dominates their short-term plasticity, with relaxation occurring during pauses in presynaptic activity. Hippocampal Schaffer collateral synapses have an intermediate *p* and show a large transient enhancement of synaptic strength but a less pronounced steady-state level of enhancement.

Patterns of activation and details of spike timing have a profound influence on synaptic strength. For these synapses, the interplay between multiple forms of plasticity determines the response properties of the synapses. This interplay exists when either depression or facilitation is dominant, but it is most apparent when the initial probability of release is intermediate (when both depression and facilitation are prominent). In all cases, the timing of synaptic activation matters and the use dependence is important in conveying information about the timing and structure of the presynaptic train to the postsynaptic cell.

Synaptic filtering

An important consequence of synaptic dynamics is that synapses can act as filters with a wide range of properties^{48,50,51,57}. This is readily appreciated by plotting steady-state responses as a function of stimulus frequency (Fig. 2b). Synapses with a low initial probability of neurotransmitter release, such as parallel fibre synapses, function as high-pass filters, whereas synapses with a high initial probability of release, such as climbing fibre synapses, act as low-pass filters that are

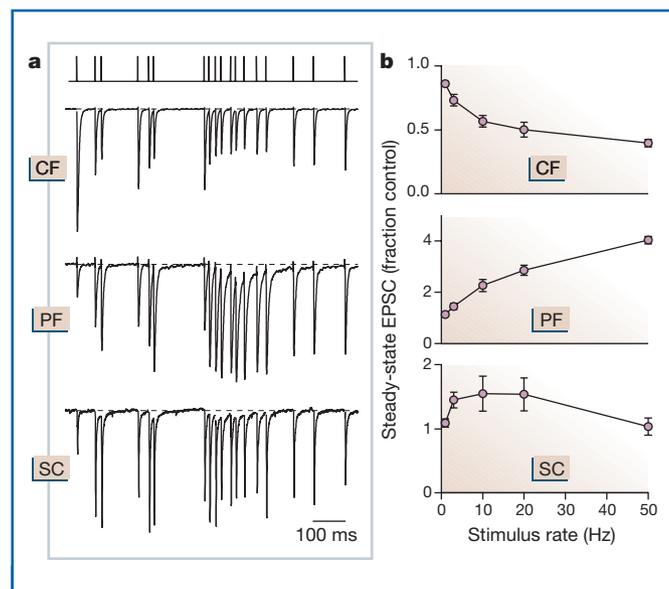


Figure 2 Examples of excitatory postsynaptic currents (EPSCs) recorded in response to an irregular stimulus train with an average rate of 20 Hz at the climbing fibre, parallel fibre and Schaffer collateral synapses. These results illustrate low-pass (climbing fibre), high-pass (parallel fibre) and band-pass (Schaffer collateral) filtering characteristics. **a**, Diversity of short-term plasticity. Top, climbing fibre to Purkinje cell EPSCs; middle, parallel fibre to Purkinje cell EPSCs; bottom, CA3 to CA1 Schaffer collateral EPSCs. Traces are averages of four to six trials. **b**, Average magnitude of the eighth to tenth EPSC from a regular train, normalized by the first EPSC and plotted as a function of stimulus frequency for climbing fibre (top), parallel fibre (middle) and Schaffer collateral (bottom) synapses. Adapted from ref. 48.

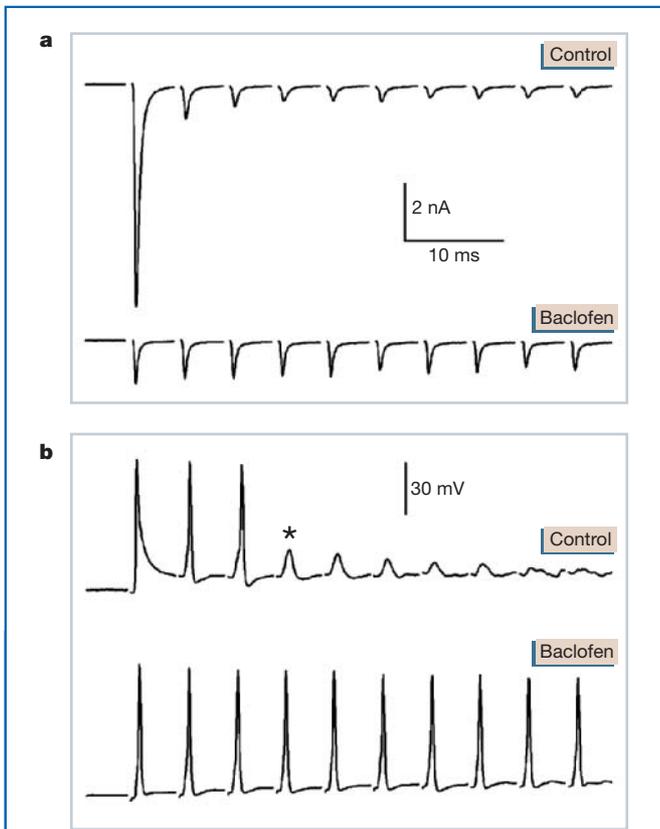


Figure 3 Synaptic modulation regulates synaptic dynamics and influences the transmission function of synapses. Presynaptic modulation with the GABA (γ -aminobutyric acid) receptor agonist baclofen affects the response of the end-bulb synapse formed by auditory nerve terminals onto the soma of neurons in the avian nucleus magnocellularis. Responses to high-frequency stimulus trains were measured by voltage clamp (**a**) and by current clamp (**b**). In **a**, although the synaptic current evoked by the initial stimulus is greatly inhibited by baclofen, responses late in the train are larger in baclofen-treated synapses than in control synapses. **b**, In current clamp stimulation during high-frequency trains, transmission is more reliable in baclofen-treated synapses than in control synapses. In control conditions, only the first two stimulus pulses trigger spikes and subsequent spikes fail, whereas in baclofen-treated synapses there are only three spike failures in the entire train. (Asterisk indicates examples of failures to produce spikes.) Adapted from refs 63, 65.

most effective at the onset of presynaptic activity. Synapses with an intermediate probability of release, such as Schaffer collateral synapses, act as band-pass filters that are most effective at transmitting impulses when there is an intermediate range of presynaptic activity.

The filtering characteristics of a given synapse are not fixed; they can be adjusted through modulation of the initial release probability or other aspects of synaptic transmission⁴⁸. Many neuromodulators activate presynaptic receptors, and the result is often a reduction in the probability of release. As a result of this decrease in the amount of neurotransmitter released, the filtering characteristics of the modulated synapse are altered so that depression makes a smaller contribution to synaptic dynamics and facilitation becomes more prominent. In this way, presynaptic inhibition can convert a synapse from a low-pass filter to a band-pass filter, or from a band-pass filter to a high-pass filter.

In some circumstances, the interaction of different forms of synaptic plasticity can cause modulation to have counterintuitive effects. For example, at the end-bulb synapse formed by auditory nerve terminals onto the soma of neurons in the avian nucleus magnocellularis, presynaptic inhibition greatly reduces the initial synaptic current evoked during a train, but for high-frequency activation there is less steady-state reduction of release than would be expected

(Fig. 3a). In this case, presynaptic inhibition paradoxically results in a synapse that is more effective at inducing the postsynaptic cell to fire spikes during a high-frequency train⁶³ (Fig. 3b). This behaviour arises because this synapse is particularly prone to receptor desensitization when the probability of release is high^{64,65}. By reducing the probability of release, presynaptic inhibition causes less desensitization and therefore the ‘inhibition’ actually increases the effective strength of the synapse during ongoing high-frequency activation.

Adaptation and enhancement of transients

Neurons typically respond most vigorously to new rather than to static stimuli. Synaptic depression provides a possible explanation for this virtually universal feature of sensory processing. Consider the case of sensory input to a neuron A that in turn excites neuron B through a depressing synapse. Even if a prolonged sensory stimulus activates neuron A in a sustained manner, the response of neuron B may only be prominent at the onset of stimulation because synaptic depression produces a synapse-specific decrease in the drive to neuron B. This results in a neuron that only responds to new stimuli. Synaptic depression acting in this manner may contribute to contrast adaptation⁶⁶ and to suppression by masking stimuli^{67,68} in primary visual cortex.

Decorrelation and burst detection

Figure 4 shows a sample presynaptic spike train along with the pattern of transmission it evokes from two types of model synapse. Both model synapses have time-dependent transmission probabilities, but one shows depression and the other facilitation (see Fig. 4 legend for details). Both transmit about 25% of the presynaptic action potentials at the average presynaptic firing rate shown (35 Hz), but their pattern of transmission differs. The depressing synapse produces transmission sequences that are more regular than those generated by the facilitating synapse. The coefficient of variation for the inter-transmission intervals of the facilitating synapse is more than double that for the depressing synapse (1.5 for facilitating synapse; 0.7 for depressing synapse). The transmissions produced by

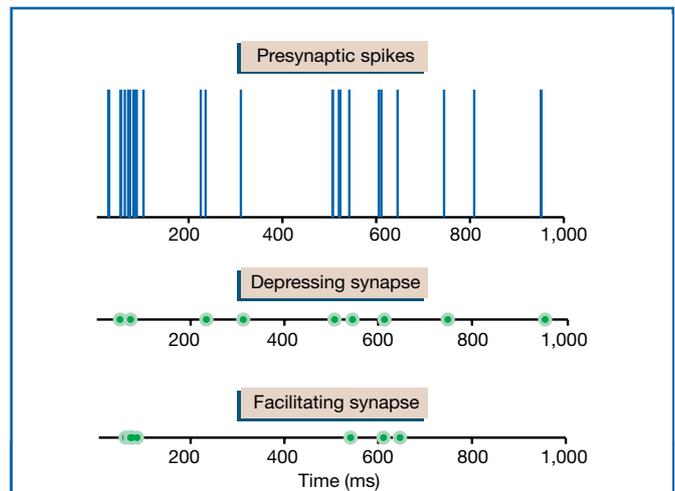


Figure 4 Stochastic transmission from two model synapses. A presynaptic spike train (blue lines) induces the sequences of transmissions in these two synapses (green dots). One model synapse shows depression and the other facilitation. Immediately after a successful transmission, the transmission probability for the depressing synapses is set to zero. The probability then recovers exponentially back towards one with a time constant of 200 ms. The facilitating synapse has a resting transmission probability of zero in the absence of presynaptic activity. Each presynaptic action potential reduces the distance between the value of the transmission probability and its maximum allowed value of one by 10%. Between presynaptic spikes, the transmission probability for the facilitating synapse decays exponentially back towards zero with a time constant of 50 ms.

depressing synapses tend to be more regular and less positively correlated than the presynaptic spike sequences that evoke them. Because of this, synaptic depression has been proposed as a mechanism that removes redundant correlations so that transmission sequences convey information in a more efficient manner⁵⁹. Facilitating synapses tend to produce transmission sequences that are more irregular and more positively correlated than the presynaptic spike trains that evoked them because facilitation favours burst-like clusters of transmissions. This suggests that facilitation could enhance information coding that is mediated by bursts of action potentials⁶⁰.

Information flow

Transmission across a synapse is obviously the conveyance of information carried in a presynaptic action potential to the postsynaptic neuron. However, for dynamic synapses each synaptic transmission also contains information about the previous history of spiking. This contextual information can be quantified^{49,69,70}. Synaptic plasticity assures that current activity reflects both the current state of a stimulus and the previous history of activity within the neural circuit. Neuronal adaptation can also contribute to this effect, but synaptic plasticity has the advantage of carrying information which is specific to the activity of an individual presynaptic neuron.

Sound localization

Synaptic depression may also have an important role in sound localization^{71,72}. In the avian brain, neurons in nucleus laminaris (NL) represent the spatial location of a sound. Firing of NL neurons requires precisely coincidental arrival of binaural input, and results in high sensitivity to differences in sound conduction delays between the

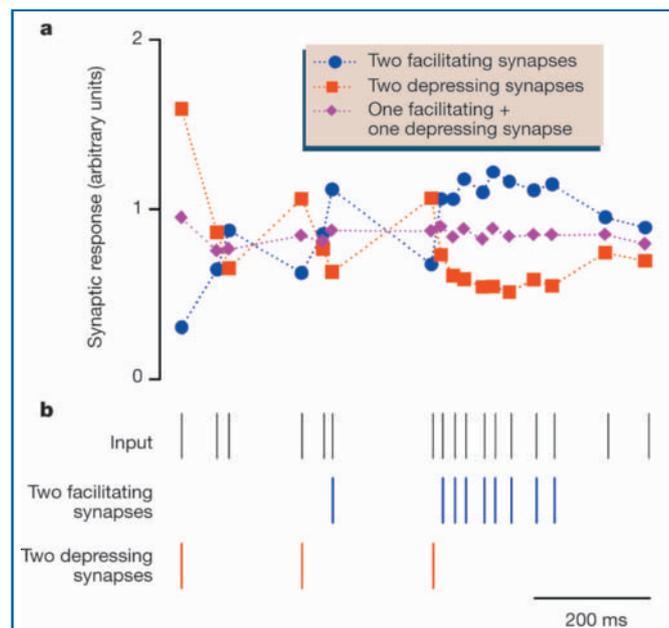


Figure 5 The ability of coactivated synapses to activate their targets depends on whether the synaptic inputs have the same use-dependent plasticity. **a**, The amplitudes of synaptic currents resulting from the simultaneous stimulation of two inputs: both facilitating, both depressing or one of each type. If the synapses share the same type of plasticity they reinforce each other's variations in synaptic strength. In contrast, if a facilitating and a depressing synapse are activated, their variations in synaptic strength tend to cancel each other out. This affects the ability of the synapses to fire their targets. **b**, The amplitudes of the responses cross a threshold and fire the postsynaptic cell during high-frequency bursts of two facilitating synapses (blue) and following pauses in presynaptic activity for two depressing synapses (red). The combination of a facilitating and a depressing synapse gives a relatively uniform input that is unable to evoke any postsynaptic spikes (not shown).

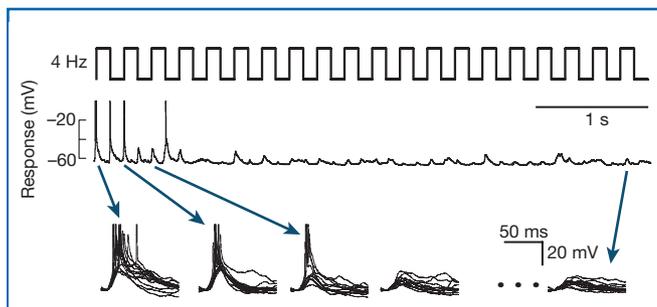


Figure 6 Synaptic depression of thalamocortical synapses underlies sensory adaptation in the cortex. The primary whisker of a rat is stimulated at 4 Hz (top) and the response of a cortical neuron in the corresponding region of barrel cortex is measured with an intracellular recording electrode (middle). Even though whisker stimulation is maintained, action potentials are only evoked in the cortical cell during the first second of stimulation. This stimulation is repeated 12 times. An expanded view of the responses observed in the cortical cell during different periods of stimulation (bottom) shows that as the train progresses, EPSPs became progressively smaller and eventually are no longer able to evoke action potentials. Extensive experiments suggest that synaptic depression at the thalamocortical synapse underlies the sensory adaptation observed during whisker stimulation. Adapted from ref. 75.

two ears, and so to sound location⁷³. These neurons localize sounds over a broad range of intensities. Increases in sound level elevate the firing rates of the inputs to NL neurons, suggesting that intensity could be a complicating factor in spatial discrimination. Synaptic depression of the inputs onto NL neurons provides a possible explanation for how sound localization operates over a broad range of intensities^{71,72}. Although a louder sound provides higher frequency inputs to NL neurons, this effect is offset by synaptic depression. As a result, the total synaptic input delivered is independent of stimulus frequency and therefore independent of sound intensity.

Dynamic input compression

Neurons integrate thousands of inputs, each firing over a range of about 1–100 Hz. But they keep their output firing rates within this same range. Doing this requires precise mechanisms of gain control and input compression. Sensory systems face similar compression problems owing to the enormous range of intensities found in nature for most stimuli. Many sensory responses obey a Weber–Fechner law, meaning that changes in stimulus intensity are interpreted in relative or percentage terms rather than on an absolute scale. This results in a logarithmic compression of the intensity scale. Synaptic depression seems to allow a similar form of compression to occur at the neuronal level^{52,74}. This is because, when depression is occurring, the level of synaptic transmission at high rates is proportional to the inverse of the presynaptic firing rate. A rapid change in the presynaptic firing rate thus results in a transient synaptic current that is proportional to the size of that change scaled by the baseline firing rate.

Interactions of synaptic inputs

Neural responses typically arise from the summation and interaction of several synaptic inputs. Figure 5 shows the response of a neuron to two synaptic inputs with various forms of short-term plasticity. Two depressing synapses produce the largest synaptic responses after long periods of presynaptic inactivity (Fig. 5a; red squares), whereas two facilitating synapses are most effective at transmitting at the end of a burst of activity (Fig. 5a; blue circles). In contrast, the plasticity of a depressing synapse counteracts the plasticity of a facilitating synapse, so the summed output of a facilitating and a depressing synapse shows fewer pronounced use-dependent alterations in amplitude (Fig. 5a; purple diamonds).

The degree to which coactivated synapses share properties of short-term plasticity influences their ability to stimulate postsynaptic

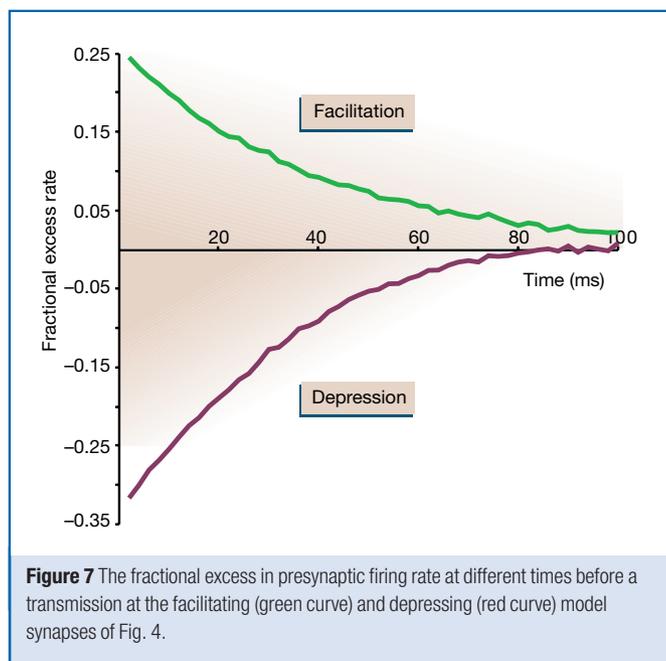


Figure 7 The fractional excess in presynaptic firing rate at different times before a transmission at the facilitating (green curve) and depressing (red curve) model synapses of Fig. 4.

targets (Fig. 5b). In Fig. 5, if the two inputs both facilitate, they trigger the postsynaptic cell to fire late in a burst (Fig. 5b; blue bars); if the two inputs both depress, they trigger spikes following periods of inactivity in the presynaptic cells (Fig. 5b; red bars). Finally, if one facilitates and the other depresses, no spikes at all are triggered in the postsynaptic cell (not shown). These results indicate that two or more cells that fire with a given pattern of activity are more effective at influencing their postsynaptic targets if they exhibit the same type of synaptic plasticity, owing to mutual reinforcement.

Synaptic depression *in vivo*

Experimental studies of synaptic properties in brain slices and theoretical considerations have established numerous potential roles for synaptic plasticity. Establishing the function of such short-term plasticity *in vivo* has been more difficult, but a recent study showed that this is possible⁷⁵. Neurons in somatosensory cortex respond to initial whisker stimulation but they stop responding to repeated stimulation (Fig. 6). Such sensory adaptation is useful in that only novel stimuli are able to evoke robust responses and repeated stimuli can be ignored. *In vivo* whole-cell recordings established that depression at thalamocortical synapses was responsible for this sensory adaptation⁷⁵. Repeated whisker stimulation led to repeated synaptic activation, and depressed synaptic responses to such an extent that they were no longer able to activate cortical neurons.

Characterizing synaptic filtering

The stochastic filtering of the presynaptic spike train that dynamic synapses perform can be characterized by computing the average pattern of presynaptic spiking that precedes a synaptic transmission. In other words, we can count the number of presynaptic action potentials that occur within specified time intervals (bins) centred at various times before each synaptic transmission over a long period of spiking, and divide this by the number of transmissions and the width of the time bins being used. The result gives the average temporal evolution of the firing rate of the presynaptic neuron before a synaptic transmission. Next, we subtract the time-averaged firing rate of the presynaptic neuron from this time-dependent firing rate, and again divide the result by the number of transmissions and the width of time bins used. This produces the plots of average fractional excess presynaptic firing rate before a synaptic transmission shown in Fig. 7. The bin at zero is omitted from this plot because it is very large and positive. This reflects the fact that there is always a presynaptic action

potential at the time of a synaptic transmission; it is the action potential that evokes the transmission. If the synapse had no intrinsic dynamics, the excess presynaptic firing rate would be zero for all the other bins plotted.

Not surprisingly, facilitating synapses typically transmit after periods of excessive presynaptic spiking (Fig. 7, green line), and depressing synapses transmit preferentially after periods of less-than-average spiking (Fig. 7, red line). Interestingly, the curve for the facilitating synapse decays to zero more slowly than the curve for the depressing synapse even though the recovery time for depression is considerably greater than that for facilitation in these models (200 ms versus 50 ms). This is because facilitation builds up on each pre-synaptic spike, whereas depression occurs only when there is a successful transmission.

If we keep in mind that there is a sharp upward spike in the curves of Fig. 7 at the zero time point (which has been omitted for clarity), it is apparent that the depressing synapse performs an approximation of differentiation, and that the facilitating synapse performs a short-term integration. A linear filter that approximates differentiation would have a sharp positive spike at time zero and a matching sharp negative spike after a short time. The negative portion of the red curve in Fig. 7 is not a sharp spike, which means that differentiation by the depressing synapse is a low-pass filtered approximation. The integration being performed by the facilitating synapse is of a similarly leaky form.

The transmission-triggered average

The curves in Fig. 7 characterize the selectivity of depressing and facilitating synapses in terms of presynaptic spike sequences. Neuronal selectivity, however, is typically characterized in terms of the stimulus used to evoke a response. One of the most powerful and widely used methods for characterizing such neural selectivity is the ‘spike-

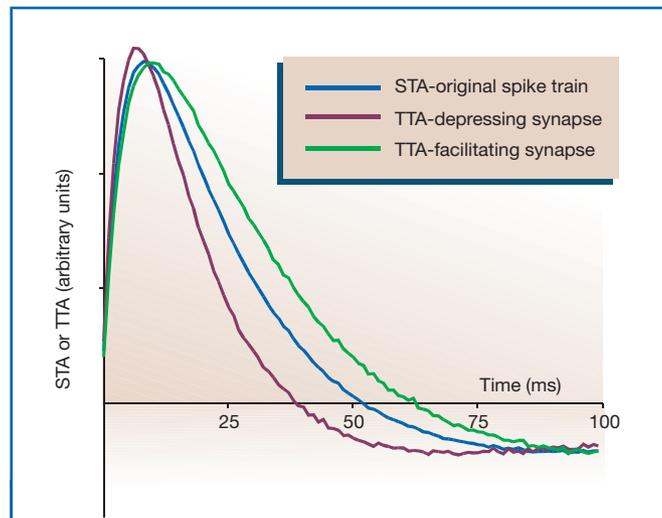


Figure 8 STAs and TTAs for a model neuron. The blue curve is an STA of a white-noise stimulus plotted against time before the triggering action potential. The red and green curves are TTAs obtained in the same way as the STA, but with the stimulus averaging triggered on each transmission from either a depressing (red curve) or a facilitating (green curve) synapse. For all three traces, a model neuron is driven by a white-noise stimulus to produce a sequence of action potentials. The model neuron consists of a linear filter, chosen to match typical temporal response properties of sensory neurons, providing input to a Poisson spike generator. To obtain the STA, the white-noise stimulus is sampled before each action potential is generated by the model neuron, and these samples are averaged over a long period of spiking. To compute TTAs, the spike sequence generated by this model neuron is fed into the model synapses shown in Fig. 4. Each time a presynaptic spike results in a transmission, the preceding stimulus is sampled, and an average taken over all transmissions.

triggered average' (STA). In this procedure, a stimulus is used (usually of the white-noise variety) to activate a neuron and the evoked action potentials are recorded. The STA stimulus is then computed by sampling the stimulus for a period of time before each action potential and then by averaging the samples obtained in this manner over all the recorded action potentials. The STA thus characterizes what 'typically' happens before a spike, and it is a standard measure of neuronal selectivity.

An extension of the concept of the STA that is useful for our discussion of synaptic dynamics is the 'transmission-triggered average' (TTA). To compute a TTA we compute the average stimulus that occurs before each transmission at a given synapse. By doing this for individual synapses showing different forms of plasticity, such as depression or facilitation, we can explore forms of selectivity that are relevant to neural circuits but that cannot be detected directly by conventional methods of experimental electrophysiology.

Figure 8 provides a comparison of a conventional STA with TTAs for two types of model synapses. The STA (Fig. 8, blue curve) shows that the model neuron is particularly responsive to positive values of the stimulus that occur about 5–30 ms before an action potential. For even earlier times relative to the action potential (50–100 ms before the action potential), the neuron responds preferentially to negative stimuli. Such reversals of selectivity over time are often seen in the temporal receptive fields of sensory neurons. For more than 150 ms before an action potential the STA goes to zero (not shown). The TTAs for the depressing and facilitating synapses are indicated by the red and green curves in Fig. 8. The red curve, corresponding to the depressing synapse, shows sensitivity to the stimulus over a shorter time period than the STA would imply, whereas the green curve, corresponding to the facilitating synapse, reveals a longer lasting sensitivity to the stimulus. Note that the temporal selectivity that we would normally infer for this neuron, given by the STA (blue curve), does not correctly characterize the selectivity seen by postsynaptic targets connected by synapses displaying these types of plasticity. Postsynaptic targets connected through depressing synapses receive a signal corresponding to a short temporal integration of the stimulus, whereas other targets connected by facilitating synapses receive a signal corresponding to a longer temporal integration period.

The key point is that the temporal selectivity for a neuron that transmits through synapses showing different forms of plasticity cannot be characterized by a single temporal receptive field function. Normally the STA (Fig. 8, blue curve) would be used for this purpose but, depending on the particular target being considered, either the red or the green TTA provides a more accurate measure of the temporal selectivity of this neuron. Characterizing the total signal that this neuron delivers to its postsynaptic targets would require an entire family of TTAs with a variety of forms.

Conclusion

The firing pattern of a group of neurons is often used to describe the 'state' of a neural circuit, but this description is clearly incomplete. To predict how a circuit will respond to a stimulus and to interpret that response, we also need to know the dynamic state of its synapses. Given that there are many more synapses than neurons in a typical circuit, the state of a neural network might better be described by specifying the state of its synapses than the firing pattern of its neurons. We might even extend this viewpoint by stating that the role of synapses is to control neuronal firing within a neural circuit, but the role of neural firing is to set the states of the synapses. Experimental and theoretical approaches to the problem of synaptic computation are beginning to put neurons and synapses on a more equal footing with regard to their roles in neural computation. □

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