The strength of a synapse does not remain constant over time but instead depends partly on the elapsed time between individual input events. The biophysical mechanisms underlying this short-term synaptic plasticity are numerous and complex (29). As a result of such variety, different synapses supplied with the same temporal pattern of inputs may respond very differently. Thus a synapse does not simply transmit impulses from the presynaptic to the postsynaptic neuron; it applies a transfer function by which interevent interval is transformed into voltage amplitude.

Over the past few years, researchers have identified many neural circuits in which successful performance depends on the specific transfer function found at a component synapse (for reviews, see Refs. 1, 13, 21, 22, 33, and 36). Two forms of short-term plasticity—facilitation and depression—have distinct influences on the synaptic transfer function (30, 31). Facilitation is an increase in synaptic strength with each successive input event, whereas depression is a decrease. Theoretical analysis has demonstrated their respective contributions toward temporal integration and differentiation of synaptic inputs, resulting in enhanced sensitivity toward input intensity and timing, respectively (31).

Here we review recently discovered uses for temporal discrimination by depressing synapses. Computational tasks performed by depressing synapses in simple feedforward circuits include signaling of average input rate (2, 4, 8, 30, 34), gain control (2, 10, 30), coincidence detection (10, 14), and input rate filtering (3, 5, 6, 9, 11, 24), and in oscillatory networks the setting of phase offset (8, 16) and cycle period (20, 28) and the regulation of spontaneous oscillatory activity (27, 32). Organism behaviors dependent on these computations include sensory tasks such as habituation (4), sound localization (10, 14), and sensory input selection (5–9, 24, 33), as well as rhythmic motor tasks such as mammalian intestinal peristalsis (28) and the crustacean pyloric rhythm (20).

The effect of depression on the neuronal input-output transformation cannot be predicted by any general rules, because it depends on both the kinetics of depression and the context. The context includes activity patterns of individual inputs and the input population as well as intrinsic properties of the postsynaptic membrane. The versatility of synaptic depression as a timing device helps explain its ubiquity in the nervous system.

The Depression Transfer Function

In short-term depression, synaptic efficacy decreases immediately following an input event and then recovers over time toward its original value. In most cases this process can be described by a mathematical model defined by two parameters (assuming no summation between successive events): the strength of depression ($D$, a positive value $\leq 1$ representing the proportion by which synaptic efficacy decreases following an input event) and the rate of recovery from depression, $\tau_D$ (30, 34). The magnitude of synaptic efficacy can be described in terms of the size of a pool of synaptic resources, $R$, of which a fraction ($D$) is used at the time of a synaptic event. For simplicity we ignore the time course of a synaptic event by having the resources used on each event inactivate instantaneously and then return to the pool of resources with a time constant of $\tau_D$. Synaptic efficacy at time $t$ is defined as $G = R/D$, where $R_t$ is the magnitude of $R$ just before a synaptic event at time $t$. The magnitude of $R_t$ is determined by the following formula:

$$R_t = R_{t-\tau} + (1 - R_{t-\tau})(1 - e^{-t/\tau_D})$$

where the first term, $R_{t-\tau}$, equal to $R_{t-\tau}(1 - D)$, is the magnitude of $R$ just after the previous synaptic event (i.e., the event at time $t - \Delta$) and the second term is the fraction of all inactivated resources just after the previous synaptic event that has recovered during the interim. In this formulation, the maximum synaptic efficacy is normalized to 1. This model is independent of the biophysical mechanisms by which depression is implemented at a synapse.

The synapse’s transfer function is affected by the depression parameters and input rate as shown in...
Information about its synaptic input, representing input features by means of its PSP amplitude (2, 30, 34). PSP amplitude averaged over time represents average input rate. Signaling of average input rate underlies the earliest identified behavioral role for depressing synapses: sensory adaptation. In *Aplysia*, for example, depression of synapses from sensory to motor neurons is responsible for habituation of the gill-withdrawal response (4). A resting *Aplysia* sensory neuron is exposed to a novel stimulus, it fires rapidly, the synapse onto the motor neuron begins to depress, average PSP amplitude decreases, and the motor neuron eventually becomes less likely to fire. A similar process has been shown to underlie rapid sensory adaptation in mammalian neocortex (9). Due to depression at the thalamocortical synapse, rat barrel cortex neurons become less responsive over time to repetitive whisker deflection. This mechanism may complement feedback inhibition, which has also been proposed to cause adaptation of thalamic input to cortex (19).

There are at least two nonlinear processes that enrich the depressing synapse’s representation of temporal input features (FIGURE 2) (2, 30). First, steady-state PSP amplitude is a nonlinear decreasing function of input rate. At high input rates it becomes approximately the inverse of input rate (FIGURE 2A, blue curve). Consequently, above a limiting frequency, average depolarization (which is approximately proportional to the product of PSP amplitude and input rate) becomes nearly independent of input rate (FIGURE 2A, red curve). Thus the synapse can filter out input rate from the signal it transmits.

In the second nonlinear process, PSP amplitude during a transition between input rates is approximately the derivative of input rate (i.e., the fractional rate of change of input rate; FIGURE 2B). As discussed, depression causes a higher input rate to have a smaller steady-state PSP amplitude. However, depression takes time. At the onset of a transition to a higher rate, the decrease in PSP amplitude lags behind the increase in frequency. Therefore, a temporary increase in membrane depolarization occurs during the transition until the new, lower steady-state amplitude is reached.
Relative PSP amplitude

1.5

1000

10 Hz

2.0

y

40 Hz

A

on rate at all (the steady-state depolarization dotted line). At high rates, \( A(r) \) is proportional to \( 1/r \), and 10 Hz and 40 Hz is approximately the same (horizontal absolute rate increase). The steady-state depolarization at with a 10-fold rate increase, is greater than amplitude \( y \), rate increases, and the amplitude of the transient PSPs undergoing transitions from 1 to 10

Nonlinear processes endowed by depressing synapses

A: average depolarization becomes nearly independent of input rate (adapted from Ref. 2, Fig. 1). PSP amplitude at steady state, \( A(r)_s \), at input rates from 1 to 100 Hz and average depolarization, \( rA(r)_s \), the product of steady-state PSP amplitude and input rate, are shown. At high input rates, the red curve becomes asymptotic to a horizontal line (2, 30). Assuming that synaptic events add linearly, a synapse's contribution to average somatic depolarization is proportional to the product of input rate and PSP amplitude. In the absence of depression, PSP amplitude remains constant, so average depolarization is proportional to input rate. In contrast, in the presence of depression, above a limiting frequency steady-state PSP amplitude becomes inversely proportional to input rate. Therefore, above the limiting frequency, average depolarization approaches independence from input rate. The limiting frequency increases as \( D \) increases and \( \tau_0 \) decreases. B: transition PSP amplitude represents the fractional change in input rate (adapted from Ref. 30, Fig. 4). Average membrane voltage response (\( V_m \)) recorded from a postsynaptic cortical neuron after stimulating a pyramidal neuron with the sequence of 200 different Poisson spike trains undergoing transitions from 1 to 10 to 40 Hz. PSP amplitude increases transiently when input rate increases, and the amplitude of the transient increase is a function of the fractional rather than the absolute change in rate. Note that amplitude \( x \), occurring with a 10-fold rate increase, is greater than amplitude \( y \), occurring with a 4-fold rate increase (but a larger absolute rate increase). The steady-state depolarization at 10 Hz and 40 Hz is approximately the same (horizontal dotted line). At high rates, \( A(r) \) is proportional to \( 1/r \), and the steady-state depolarization \( [-rA(r)] \) does not depend on rate at all (A). When a high rate increases further to \( r_i = r + \Delta r \), synapse strength eventually decreases from \( A(r) \) to \( A(r_i) \), with the new steady-state depolarization \( \approx r_iA(r_i) \), but only after several transition PSPs at the previous amplitude \( A(r) \), giving a temporarily higher depolarization \( \approx r_iA(r_i) \). Since \( A(r) \approx 1/r \), the depolarization during this transient period \( \approx r/r_i \), the fractional (rather than the absolute) change in rate.

This briefly higher depolarization signals the rate transition with a magnitude approximating the derivative of the rate change. Similarly, a briefly lower depolarization occurs with a rate decrease (see FIGURE 2B legend for further explanation).

Gain Control

Abbott et al. (2) demonstrated a form of gain control that capitalizes on these two nonlinear processes. They built a computer model of a neocortical neuron receiving input from two groups of randomly firing afferent neurons distinguished by their average firing rates (FIGURE 3A). In the absence of depression, a sinusoidal rate change in the slowly firing group was difficult to detect because the response was dominated by the rapidly firing group. PSP amplitude was equal in the two groups, but average depolarization, which depends also on input rate, was greater in the rapidly firing group. That group consequently had more influence on output rate (FIGURE 3B).

In the presence of depression, the influences of the two groups were more balanced. The neuron monitored slowly firing afferents at high gain and rapidly firing afferents at low gain. Average depolarization from each group was nearly independent of input rate, a consequence of the first nonlinear process described above. Transition PSP amplitude was similar in the two groups in response to a given percentage change in rate, due to the second nonlinear process. As a result, the neuron's output rate had nearly equal sensitivity to the two input groups, both in sustained activity level and in synchronized rate changes (FIGURE 3C).

There is a different form of gain control that depends on steady state but not transition PSP amplitude. Cook et al. (10) demonstrated this device in a computer model of chick auditory brain stem sound localization neurons and explained how it enhances their performance (FIGURE 4).

The neurons of nucleus laminaris (NL) are nearly ideal coincidence detectors that use their firing rate to signal the degree of synchrony between two groups of synaptic inputs. The phase delay between sound waves arriving at the two ears, which represents sound source location along the azimuth, is transmitted to NL cells as the phase delay between two sets of cyclically firing afferents (FIGURE 4A). Perfect phase alignment between the two sets of input (0° phase delay, i.e., input synchrony) generates the highest peak amplitude of summed PSPs and thus the highest likelihood of exceeding threshold on each sound wave cycle. There is a smooth reduction of NL firing rate as phase delay is increased from 0° to 180° (FIGURE 4B, LEFT, blue).

In slices of auditory brain stem, Cook et al. (10)
These results indicate that a different PSP amplitude is required to provide coincidence detection at high and low sound pressure levels. Synaptic depression provided an automatic mechanism for adjusting PSP amplitude. In the presence of depression, a high sustained input rate was compensated by a low steady-state PSP amplitude. For input rates near the limiting frequency (above which steady state PSP amplitude becomes inversely related to input rate), the rate of PSP summation to threshold was nearly independent of input rate. The resulting output rate represented the degree of input synchrony (sound location) but not input rate (sound intensity) (FIGURE 4B, RIGHT).

Of note, in addition to the decrement in PSP summation, there is an additional mechanism in NL neurons responsible for the reduction in their firing rate as phase delay is increased. Perfect phase alignment generates the greatest fluctuation, i.e., variance, in membrane potential. Specialized intrinsic membrane properties of these neurons observed depression of the synapses onto NL neurons. They described how it solved a dynamic range problem. Due to circuit constraints, the firing rate of NL afferents increases with sound intensity, such that synaptic events occur more frequently during louder sounds (i.e., on more cycles of the sound wave). In the absence of depression, PSPs are equal in amplitude regardless of sound intensity. Consequently, PSPs sum to threshold on more cycles during louder sounds, even to the saturation limit of the NL spike-generating mechanism.

As shown in the computer model, firing rate saturation in response to intense input distorted the smooth gradation of output rate as a function of input phase delay (FIGURE 4B, LEFT; compare red with blue). This distortion at high input intensities was avoided by using a smaller simulated synaptic conductance, which resulted in lower PSP amplitude and lower NL firing rate (FIGURE 4B, CENTER, red). However, with the smaller conductance, the NL cell failed to fire at any phase delay in response to low-intensity input (FIGURE 4B, CENTER, blue).

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FIGURE 4. Synaptic depression in sound localization
A, left: NL cell circuit diagram (Adapted from Ref. 10, Figs. 1 and 2). Each NL cell receives synaptic inputs from ipsilateral (red) and contralateral (blue) NM cells. A, right: a pure tone (upper "sound wave") arriving at the ipsilateral ear elicits phase-locked NM-NL excitatory postsynaptic potentials (EPSPs; red trace) that converge on one set of an NL neuron's dendrites. The same tone arriving with some phase delay (lower "sound wave") at the contralateral ear triggers phase-delayed trains of EPSPs (1 train shown in blue) that converge on a second set of the NL neuron's dendrites. The number of EPSPs arriving at the NL cell varies from cycle to cycle because each NM cell fires once on only a fraction of the sound cycles. Note that the EPSPs shown in this diagram do not depress.

B: gain control in chick auditory NL cells (adapted from Ref. 10, Fig. 4).
B, left: output firing rate of model NL neuron as a function of phase delay in a model neuron with high synaptic conductance. With a smoothly graded curve (low input intensity, average firing rate of inputs to NL neuron = 150 Hz) input phase delay can be ascertained from the NL neuron output firing rate. With high input intensity (average firing rate of inputs = 400 Hz), the NL action potential-generating mechanism is saturated, and the maximum firing rate occurs at all phase delays <90°, distorting the smoothly graded curve.
B, center: output firing rate vs. phase delay in the same model neuron with low synaptic conductance. Here the smoothly graded curve occurs with high input intensity (400 Hz), but firing fails to occur with low input intensity (150 Hz). B, right: output firing rate vs. phase delay in the same model neuron, this time with depressing synapses in which the maximum synaptic conductance is high. A smoothly graded curve is produced when input intensity is either high (400 Hz) or low (150 Hz). C: a short $\tau_f$ allows PSP amplitude to reach its new steady state rapidly when input rate changes. Firing rate of a model NL neuron at 0° phase delay is shown as a function of sound cycle number for a 600-Hz sound frequency. With initiation of sound at low intensity (average firing rate of inputs to NL neuron = 150 Hz) input phase delay can be ascertained from the NL neuron output firing rate. With high input intensity (average firing rate of inputs = 400 Hz), the NL action potential-generating mechanism is saturated, and the maximum firing rate occurs at all phase delays <90°, distorting the smoothly graded curve. B, center: output firing rate vs. phase delay in the same model neuron with low synaptic conductance. Here the smoothly graded curve occurs with high input intensity (400 Hz), but firing fails to occur with low input intensity (150 Hz). B, right: output firing rate vs. phase delay in the same model neuron, this time with depressing synapses in which the maximum synaptic conductance is high. A smoothly graded curve is produced when input intensity is either high (400 Hz) or low (150 Hz). C: a short $\tau_f$ allows PSP amplitude to reach its new steady state rapidly when input rate changes. Firing rate of a model NL neuron at 0° phase delay is shown as a function of sound cycle number for a 600-Hz sound frequency. With initiation of sound at low intensity (average firing rate of inputs to NL neuron = 150 Hz) input phase delay can be ascertained from the NL neuron output firing rate. With high input intensity (average firing rate of inputs = 400 Hz), the NL action potential-generating mechanism is saturated, and the maximum firing rate occurs at all phase delays <90°, distorting the smoothly graded curve. B, center: output firing rate vs. phase delay in the same model neuron with low synaptic conductance.
produce high-pass filtering behavior; that is, the neuronal responses are selective for large rapid fluctuations in membrane potential (23). They therefore fire fastest at the lowest phase delays.

In a surprising gain-control mechanism observed in this model, synaptic depression at times increased output rate above that found in its absence. This effect was due to the high-pass filtering property of NL neurons, which prevents repetitive firing during sustained depolarization (23).

Without depression, the model neuron nearly ceased to fire in response to high-intensity input at the greatest input phase delays (FIGURE 4B, LEFT, red). When the two 400-Hz sound waves were exactly out of phase (180° phase delay), PSPs arrived at nearly 800 Hz, due to synaptic events occurring on most cycles of both sound waves. Temporal summation of these closely spaced PSPs caused sustained depolarization above the level at which repetitive firing was disabled.

In the presence of depression, the sustained depolarization was lower in amplitude; valleys between PSP peaks reached more negative membrane potentials that caused more removal of sodium channel inactivation so that more action potentials could be generated. The increased firing at large phase delays contributed to a smoothly graded phase-delay curve (FIGURE 4B, RIGHT, red).

Rapid fluctuation of sound frequency in the natural world imposes stringent requirements on depression parameters. Gain control is most effective when PSP amplitude has reached steady state. It is therefore optimized by minimization of the period of PSP amplitude adjustment during frequency transitions. An undesirably large number of PSPs would occur before steady state is achieved at the high input rates of 100–600 Hz seen at these synapses, unless the high rates were compensated by a large D or short τp (see DEPRESSION TRANSFER FUNCTION, above, and FIGURE 1B). In fact the fast component of τp measured by Cook et al. was extremely short (15 ms), such that the transition period was limited to the first few cycles of a new sound stimulus (FIGURE 4C, interval x). An even shorter transition period occurred at a change from low to high sound intensity (FIGURE 4C; compare y to x), since PSP amplitude was already depressed close to its target steady state. In NL afferents, an unusually high spontaneous firing rate of 94 Hz (35) maintains synapses in a continually depressed state. This extraordinary energy expenditure further shortens the transition period in response to a new sound stimulus (FIGURE 4C; compare z to x), ensuring rapid sound localization at all times.

Appropriate depression parameters can also optimize the value of the limiting frequency (30). Limiting frequencies of ~200 Hz in avian auditory brain stem (10) and ~20 Hz in mammalian cerebral cortex (30) appear well matched to the respective input rates observed in those systems.

Interestingly, Kuba et al. (14) proposed another way in which depression improved coincidence detection in NL neurons. In slice recordings, the successive reduction in PSP amplitude during a train of stimuli successively narrowed the time window for spatial summation of PSPs, requiring successively greater input synchrony to exceed threshold. They stimulated a neuron simultaneously with two trains of 100-Hz inputs, systematically increasing synchrony by decreasing the phase offset between the trains. In trains with low input synchrony, firing probability dropped off steeply and was low late in the train. In contrast, with more synchronized input, firing probability remained high throughout the train. The distinction between low and high input synchrony was most evident late in the train, when PSP amplitude had reached steady state. These results predict that sound localization becomes accurate only after the first few cycles of a sound stimulus, in agreement with previous findings (10), although by a different mechanism.

Selective Rate Filtering

Although depressing synapses can filter out input rate as in some gain-control tasks, they selectively filter input rate in other tasks. For example, Rose and Fortune (24) described the use of synaptic depression for low-pass filtering of input rate. In low-pass filtering, output firing occurs selectively in response to low input rates. This contrasts with gain control, in which the dependence of output rate on input rate is minimized.

The weakly electric fish _Eigenmannia_ performs a behavior known as the jamming avoidance response (JAR), in which it adjusts the frequency of its electric organ discharges (EODs) to avoid interference from EODs of a neighboring fish. The difference between the EOD frequencies of the two fish (the beat frequency) is detected by electroreceptors on the surface of the fish and is transmitted to a midbrain nucleus, the torus, via a secondary projection. A low beat frequency (3–8 Hz) represents the most detrimental interference and results in rapid firing of toral neurons to signal the need for a JAR. Toral neurons respond poorly to beat frequencies >30 Hz.

Rose and Fortune (24) proposed that depression of synapses onto the toral neuron contributes to this preferential response to low-frequency input. In an in vivo preparation, as they decreased the beat frequency of electrical field oscillations from 30 Hz to 2 Hz, compound PSPs from afferent neurons occurred with lower frequency. As a result,
synaptic efficacy had more time to recover between compound PSPs, so the amplitude of these compound PSPs increased and the torus action potential rate consequently increased.

Active membrane properties of toral neurons (12) were found to contribute to this low-pass filtering. For example, burst firing in response to slow oscillations of membrane potential, prevented in NL neurons by their membrane properties (23), was amplified by toral membrane properties. This amplification resulted in high output rates, thereby more intensively driving the JAR when input rate was low.

The behavioral benefit of low-pass filtering can depend either on selective firing when input rate is low, as in Eigenmannia, or, equivalently, on suppression of firing when input rate is high, as in mammalian thalamus (Ref. 6; see also Ref. 7). In quiescent rats, thalamocortical transmission of high-frequency sensory stimulation is suppressed; only stimulation below 2 Hz is relayed to neocortex. In active rats, however, sensory stimulation up to 40 Hz is relayed. This thalamic circuit studied in vivo by Castro-Alamancos (6) depends not only on synaptic depression but also on network properties.

Strong depression was seen at the excitatory synapse onto the ventroposterior medial thalamus from trigeminal nucleus neurons (6). During the quiescent behavioral state, thalamocortical neurons were found to be relatively hyperpolarized by separate tonic inhibitory inputs. Repetitive whisker stimulation in resting rats, relayed through trigeminal neurons, elicited thalamic responses only at low stimulation frequencies (up to 2 Hz) at which PSP amplitudes were large. Higher-frequency sensory information was not relayed to neocortex due to low PSP amplitude, which failed to overcome the hyperpolarization from inhibitory inputs.

Castro-Alamancos induced an activated behavioral state either by direct stimulation of the brain stem reticular formation or by application of acetylcholine in the thalamus. In the activated state, thalamic neurons were found to be relatively depolarized, due both to a reduction in tonic inhibitory conductance and to an increase in excitatory conductance. Under these permissive conditions, thalamic neurons responded to whisker stimulation at up to 40 Hz, because even the depressed PSPs were able to reach firing threshold. In this circuit, synaptic depression provided thalamic neurons with a low-pass filter for sensory input frequency. However, the frequency level at which the gate was set (2 Hz or 40 Hz) depended on the relative activity levels of inhibitory and excitatory inputs, which in turn were dictated by behavioral state (quiescent vs. activated).

Selective Filtering Based on Instantaneous Rate

Incorporation of both depression and facilitation in the synaptic transfer function allows for more complex processing than depression alone. For example, individual presynaptic action potentials can be filtered selectively based on their relative timing, that is, on the instantaneous rate during the preceding interevent interval. Such filtering has been proposed to regulate transmission of bursts of presynaptic action potentials in hippocampus at the synapse from the Schaffer collateral onto the CA1 neuron (15).

Due to a presynaptic form of facilitation at this synapse, failed vesicle release in response to a presynaptic action potential increases the probability of vesicle release to >0.9 at the next action potential occurring within a short interval (5–100 ms) (26). However, due to depression at the same synapse, successful vesicle release reduces the probability of subsequent vesicle release to <0.1 at ~6 ms (26). The facilitation nearly ensures that at least one vesicle is released in response to a burst of several closely spaced presynaptic action potentials. The depression discourages release of more than one vesicle. A very rapid recovery from depression was measured (τ_r = 15 ms), consistent with the high frequency of bursts at this synapse (~200 Hz); recovery occurs during the long interevent intervals between bursts but not during the brief ones within a burst. This complex synaptic transfer function may thus be promoting a single vesicle release for a burst of presynaptic action potentials while filtering out spurious individual presynaptic action potentials (15).

Oscillatory Circuits

The function of an oscillatory neural circuit depends on appropriate relative timing of events among multiple neurons. The relevant feature of each neuron's output spike train is the latency of the action potential (i.e., the output phase) relative to periodic network activity. Synaptic depression can alter action potential latency in a variety of ways. A depressing synapse can shift the output phase by altering the latency of the peak amplitude of an oscillating membrane potential. Chance et al. (8) demonstrated this phenomenon in a simulated primary visual cortex (V1) cell. In the absence of depression at afferent synapses, the V1 cell's membrane potential varied sinusoidally in response to a sinusoidally varying input rate (FIGURE 5B, TOP, green traces). In the presence of depression, peak membrane potential occurred at an earlier phase of the cycle (FIGURE 5B, TOP, red traces). The phase
FIGURE 5. Model of a directionally selective simple cell in the primary visual cortex (V1) A: two sets of lateral geniculate nucleus afferents to the V1 cell. One set has depressing synapses and one set has nondepressing synapses (black and gray circles, respectively). Each circle corresponds to a subset of afferents that share a center-surround receptive field. Those marked “C” represent a subset of afferents that most effectively stimulate the V1 cell when the central portion of the receptive field is exposed to luminance and the surrounding portion is not. Those marked “S” represent a subset of afferents with the opposite firing behavior. A luminance contrast grating is swept across the visual field at a rate such that the central portion of a receptive field is exposed to two cycles of sinusoidal variation in luminance each second. The diagram schematically demonstrates that the receptive fields of afferents with depressing synapses overlap those of afferents with nondepressing synapses by half the width of the central portion of the receptive field.

adapted from Ref. 8, with permission. B: membrane potential of a model directionally selective V1 cell in response to a moving luminance grating. The moving grating sequentially excites the two sets of neurons that converge onto the V1 cell. The top shows the timing of relative Vm changes in the V1 cell in response to only the afferents with depressing (red) or nondepressing (green) synapses. Bottom shows the Vm response to both sets of afferents together. Top left: grating moving in the preferred direction. Because the time to peak Vm is shorter with depressing synapses, the interval between Vm peaks is wide (interval y). Top right: grating moving in the nonpreferred direction. Visual input is aligned with the receptive fields of afferents with depressing synapses first. The interval between Vm peaks is wide (interval y). Bottom right: in response to the combined input, the model neuron fails to fire action potentials.

Advance occurred because PSP amplitude increased as a function of the derivative of input rate (FIGURE 2B). Maximum depolarization occurred when the derivative of input rate reached its peak, before input rate reached its peak. The degree of phase advance increased with the strength of depression, D.

Chance et al. (8) demonstrated how a shift in output phase might allow a V1 neuron to respond selectively to a specific direction and rate of movement of a luminous grating. The cell had two sets of simulated lateral geniculate nucleus (LGN) afferents with distinct receptive fields (FIGURE 5A). One afferent set had depressing synapses (FIGURE 5A, black circles). When a grating moved in the preferred direction, it aligned with the receptive fields of the afferents with nondepressing synapses (FIGURE 5A, gray circles) before it aligned with those that depressed. At the preferred rate, the temporal delay of receptive field alignment matched the phase advance imparted by the depressing synapses, such that peak membrane depolarization from the two sets of input occurred nearly in synchrony. The resulting PSP was suprathreshold (FIGURE 5B, BOTTOM LEFT). An array of such V1 cells with distinct values of D at their afferent synapses could uniquely identify any direction and rate of movement.

The parameters of synaptic depression can determine cycle period, as demonstrated in a computer simulation of intestinal peristalsis (28). The migrating motor complex (MMC) of the guinea pig small intestine is a cyclic pattern that lasts ~100 min. In this system, neural activity drives muscular contractions in broad bands that are slowly propagated down the intestine. The intestine’s excitatory neural network has both circumferentially and longitudinally oriented connections. Longitudinal connections project farther in the distal direction, resulting in the directional bias of propagation.

In the model, a small constant external stimulus, representing activation of mechanosensitive receptors in the intestinal wall, was applied to a quiescent section of the network. Positive feedback at recurrent connections drove a circumferential section of the network into a high firing-rate state. Stimulation from this section drove adjacent sections into the same state, propagating the activity longitudinally. In the absence of synaptic depression, all neurons in the network eventually fired at the same high rate. Such a result would be physiologically undesirable, since simultaneous muscular contraction would prevent orderly directional flow of intestinal contents. In the presence of synaptic
depression, the high firing rate reduced PSP amplitude, which reduced positive feedback and allowed an eventual return of each circumferential section to the quiescent state. Each region was then receptive to the next wave of stimulation from its more proximal neighboring region.

The parameter $\tau_e$ had a significant influence over cycle period. Increasing the time for recovery of PSP amplitude lengthened the delay before return to the excitatory state at which activity could be reinitiated. $\tau_e$ of 30 min supported a 100-min cycle period. The behavior of this oscillatory circuit was influenced additionally by postsynaptic factors such as duration of the slow EPSP and by network features such as density of connections and external stimulus frequency.

Networks of independently firing neurons with depressing synapses can spontaneously generate synchronized oscillations (Ref. 32; see also Ref. 27). In a computer simulation, Tsodyks et al. (32) found that synchronized bursts of activity were led by the presynaptic neurons with the lowest firing rates. The slowest-firing neurons were the most effective recruiters, because the synapses onto their target neurons had the most time to recover from depression and therefore had the greatest PSP amplitudes. These same slowly firing neurons were also easily recruited, because they were often close to threshold. As a group, they initiated a nearly synchronized stimulus pulse that activated other neurons. In this study, cycle period was governed by a dynamic network property, the distribution of firing rates among neurons. The cycle period was therefore capable of changing over time.

Complex Networks
Complex temporal processing has lately been demonstrated in computer models composed of recurrent networks with multiple depressing and/or facilitating synapses (3, 17, 20, 25). Nadim et al. (20) studied the crustacean pyloric network, a pattern-generating circuit that produces rhythmic movements. Their model demonstrates that synaptic depression can give rise to two distinct modes of network operation. The cycle period is governed in one mode by the oscillation period of a postsynaptic membrane conductance and in the other mode by the strength and kinetics of the depressing synapse. The network is switched between these two modes by a small change in the maximal conductance of the depressing synapse.

Conclusion
We have discussed only a few of the many timing functions that synaptic depression can perform in neural circuits. New roles for depression are continually being discovered as interest in this topic has grown dramatically over the past several years. An important challenge is the in vivo demonstration of roles for depression. Of the studies we have discussed, only two (Refs. 6 and 24; see also Refs. 7 and 9) showed depression at work in the intact organism; the others relied on convincing demonstrations of concepts using in vitro preparations and/or computer simulations. Of particular interest would be studies in which the effect on a specific behavior is observed after depression is selectively and locally blocked.

Dynamic factors such as network activity level can determine the relative influences of input rate, change in input rate, and input synchrony on the neuron's computed result (2, 30, 34). The depression parameters themselves are also dynamic, because they are subject to activity-dependent adjustment (18) and neuromodulation (30). Synaptic depression is a flexible device that endows the postsynaptic neuron, the network, and, by extension, the organism with the ability to adapt to a changing environment.

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