Short-term synaptic plasticity as a temporal filter

Eric S. Fortune and Gary J. Rose

Synaptic efficacy can increase (synaptic facilitation) or decrease (synaptic depression) markedly within milliseconds after the onset of specific temporal patterns of activity. Recent evidence suggests that short-term synaptic depression contributes to low-pass temporal filtering, and can account for a well-known paradox – many low-pass neurons respond vigorously to transients and the onsets of high temporal-frequency stimuli. The use of depression for low-pass filtering, however, is itself a paradox; depression induced by ongoing high-temporal frequency stimuli could preclude desired responses to low-temporal frequency information. This problem can be circumvented, however, by activation of short-term synaptic facilitation that maintains responses to low-temporal frequency information. Such short-term plasticity might also contribute to spatio–temporal processing.

Short-term synaptic plasticity has been a subject of intense study for several decades[1,2]. There has been significant progress in understanding the mechanisms underlying synaptic plasticity (Box 1). The functional relevance of short-term synaptic plasticity in neural circuits, however, has remained relatively obscure.

Traditionally, short-term synaptic depression and facilitation have been functionally linked to behavioral habituation and sensitization, respectively[1,3,4]. The ubiquity of short-term plasticity in neural circuits, however, suggests that roles beyond simple forms of learning are probable. Recently there has been increasing interest in the computational roles of short-term synaptic plasticity[4–16]. A new hypothesis for short-term plasticity is emerging: short-term depression and facilitation generate filtering functions that are used in information processing[8–10,13,14]. Specifically, the differential activation and integration of short-term synaptic depression and facilitation might enhance and sustain low-pass temporal filtering[14] and generate shifts in the phase of peak responses[10,14,17].

Synaptic depression and temporal processing

Many sensory neurons in the cortices of mammalian species, sensory systems of invertebrate species, and electrosensory midbrains of some species of fish, respond strongly to low-temporal frequency stimuli, for example <10 Hz (see Fig. 1a,b), and weakly or not at all to ongoing high-temporal frequencies[6,10,17–19]. Many of these neurons, paradoxically, respond strongly to sensory transients and the onsets of high-temporal frequency stimuli, even though most of the power in these stimuli is at frequencies >10 Hz (Refs 20,21).

Recent models and intracellular data suggest that short-term synaptic depression accounts for a significant portion of this low-pass temporal filtering[10,14,17]. Because afferent activity is necessary for initiating short-term depression, responses to sensory transients are not filtered by this mechanism[20,21]. By contrast, low-pass filtering that results from the passive electrical properties of the membrane of a neuron does not pass sensory transients[22].

These temporal filtering characteristics – low-pass filtering with paradoxical responses to transients – are neural correlates of well-understood behaviors in a species of weakly electric fish (*Eigenmannia virescens*). Behavioral studies have established that these fish view their electrosensory environment through a temporal filter: patterns of activity resulting from slow changes (<10 Hz) in signal amplitude are passed, whereas fast (>10 Hz), repetitive patterns are rejected (reviewed in Ref. 23). *Eigenmannia* adjust their electric organ discharge frequencies so that the interference patterns caused by the interactions of the electric field of neighboring fish occur at rates of 10 Hz or more. Individuals are able to locate objects in their environment using their electric sense amidst this background of ongoing, high-frequency interference[24]. Paradoxically, intermittent high-frequency transients (>20 Hz) presented at low rates (~5 Hz) can elicit behaviors that are normally triggered by low-frequency stimuli[21]. This suggests that synaptic depression might be a mechanism for generating this behavioral low-pass filter.

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Intracellular recordings have shown that passive and active membrane properties of midbrain neurons in *Eigenmannia* make significant contributions to this low-pass temporal filter[22]. Activity-dependent declines in PSP amplitude, however, can increase low-pass temporal filtering by an additional 400% (~12 dB, Fig. 1d)[14,21]. These declines in PSP amplitude are neither caused by inhibitory postsynaptic input (because they remain intact when neurons are hyperpolarized) nor are they the result of changes in the input resistance of these cells[21]. Results from 'paired-pulse' experiments suggest that these activity-dependent declines in PSP amplitude

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Box 1. Short-term plasticity mechanisms

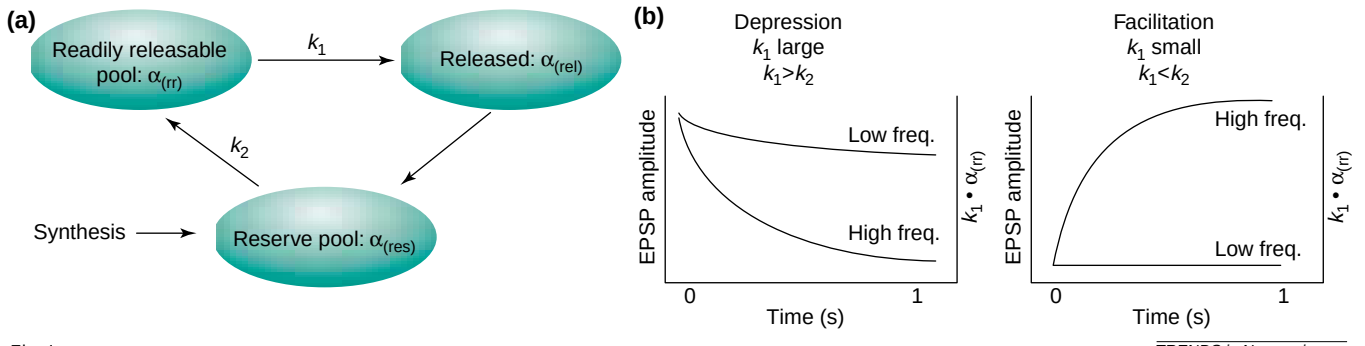

Fig. I

TRENDS in Neurosciences

Short-term synaptic plasticity is the activity-dependent decrease (depression) or increase (facilitation) in synaptic transmission that occurs within several hundred milliseconds of the onset of activity (reviewed in Refs a,b). These rapid changes in synaptic strength are mainly the result of presynaptic processes, although postsynaptic desensitization might contribute in some cases[c,d].

Ca^{2+}-dependent release of transmitter from a presynaptic terminal, following arrival of an action potential, is a function of the size of the readily releasable pool, $\alpha_{(rr)}$, and the rate constant of release, k_1; only a fraction of the total vesicle population is available for release. Restoration of the readily releasable pool then depends on the size of the reserve pool, $\alpha_{(res)}$, and the rate constant, k_2, of transfer to the readily releasable pool. The reserve pool is fed by recovery of released transmitter and new synthesis (Fig. Ia).

The probability that a quantum will be released (Pr) following a single presynaptic spike differs markedly across synapses. Facilitation generally occurs at 'low-Pr' synapses, whereas depression is prominent at 'high-Pr' synapses. The depression at 'high-Pr' synapses follows from the large reduction in $\alpha_{(rr)}$ resulting from previous spike activity, with an insufficient rate of replenishment; that is, $k_1 > k_2$. Higher frequency activity results in stronger depression, even though the rate of replenishment can actually be increased as a result of activity-dependent Ca^{2+} influx. This increase in k_2 thereby speeds up the rate of recovery following cessation of the stimulus train.

At facilitating synapses, $\alpha_{(rr)}$ is only minimally decreased by the first few spikes; k_1 is small initially. If the interval between successive spikes is sufficiently brief, residual Ca^{2+} could build up in the terminal, thereby increasing k_1, that is, transmitter release is facilitated (Fig. Ib) (reviewed in Ref. b). If k_2 is sufficiently large, $\alpha_{(rr)}$ will not decrement appreciably, and this enhanced transmission will be sustained for some time.

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are most probably caused by homosynaptic short-term depression[14], although plasticity of presynaptic inhibitory input[3,5,25,26] cannot be ruled out as a mechanism.

Short-term synaptic depression appears to be a widespread and predominant mechanism underlying the plasticity of sensory responses in mammalian cortices and in other circuits[6,14,17,27–32]. Why have these diverse, independently evolved sensory systems employed short-term synaptic depression as a mechanism for low-pass temporal filtering? A reasonable hypothesis is that this form of plasticity serves common functional roles in each of these circuits. Short-term synaptic depression has been implicated in gain control[7,29], including balancing excitation and inhibition[5,11], detection of synchronous changes in presynaptic activity, and rhythmic firing (reviewed in Ref. 7). Importantly, synaptic depression also generates advances in the phase of peak response amplitudes[10,14,17].

These phase shifts could be a mechanism for the implementation of 'delay lines' needed for computing the direction of motion of sensory images[10,17]. In neurons with significant synaptic depression, the peak response amplitude will be phase-advanced relative to that for neurons without synaptic depression. Indeed, the strength of synaptic depression is correlated with larger phase shifts, with maximum shifts of at least 20 degrees. For a low temporal-frequency stimulus, for example 2 Hz, such phase shifts might generate time disparities of greater than 25 ms (Ref. 32). Unlike 'hard-wired' delay lines[33], plasticity-based time disparities could vary with the velocity of stimulus motion.

The interplay between synaptic depression and synaptic facilitation

The use of synaptic depression for low-pass temporal filtering presents a paradox. If all the inputs to a neuron experience short-term depression, it might not respond to low-temporal frequency information in the presence of depressing high-temporal frequency stimulation. For many behaviors this would defeat

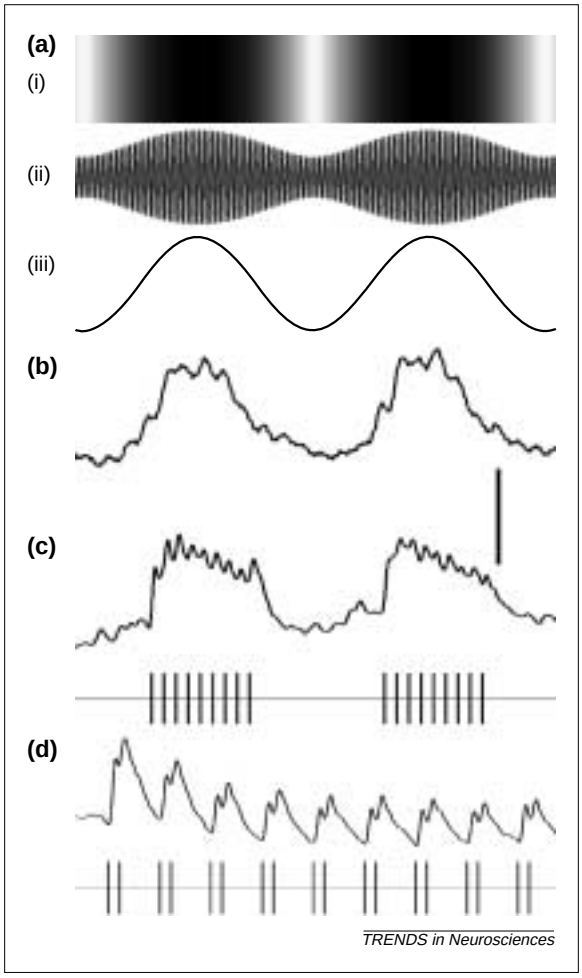

Fig. 1. (a) Time-varying sensory stimuli. (i) Either a moving sine wave grating or contrast modulation of a sine wave grating. (ii) Amplitude-modulated sinusoidal stimulus. (iii) Sine stimulus. This could represent a somatosensory or electrosensory (ampullary) stimulus. Signals shown are 400 msec in duration. (b) Current-clamp recording of an ampullary electrosensory neuron in the midbrain of *Eigenmannia* to the 5 Hz sinusoidal stimulus above it. The shapes of the EPSPs are nearly identical to those seen in cortical neurons responding to, for example, a sinusoidally modulated visual stimulus. Scale bar, 10 mV. (c) and (d) Responses of a midbrain neuron to direct stimulation of its afferents at temporal frequencies of 5 Hz (c) and 20 Hz (d). (c) Pulse trains are 100 ms in duration, pulses are presented at a rate of 100 Hz. This pattern of afferent stimulation elicits EPSPs similar to those elicited by 5 Hz sensory stimulation [compare with EPSPs in (b); data from the same neuron]. (d) Pairs of pulses presented at a 20 Hz periodicity. The same total number of stimulus pulses as in (c). There is a large response at the onset of the stimulus that is then depressed; depression continues as long as the stimulus pattern is maintained. This response profile is similar to 20 Hz sensory stimulation (not shown).

the function of the low-pass filter. For example, as stated above, ongoing high-temporal frequency electrosensory information does not impair behavioral responses to biologically relevant low-temporal frequency stimuli in *Eigenmannia*[24,34]. Recently we have shown that this problem is solved in *Eigenmannia* by the differential activation of short-term synaptic facilitation[14]. In certain midbrain neurons, a 100 ms train of pulses presented at 100 Hz can generate EPSPs that are quite similar to those elicited by sensory stimuli with temporal frequencies of about 4–5 Hz (Fig. 1c). Afferent stimulation with a periodicity of 20 Hz, triggers depression (Fig. 1d). Nonetheless, large EPSPs can be elicited by a 100 ms duration, 100 Hz afferent stimulus train, even when following prolonged, depressing afferent stimulation at 20 Hz periodicity (Fig. 2a). This facilitated response requires a longer-duration stimulus train for activation compared with depression: facilitation was evident after approximately the fourth pulse in a 100 Hz train (Fig. 2a). This differential frequency dependence of depression and facilitation, therefore, enhances neuronal responses to low-temporal frequency stimuli in the presence of ongoing high-temporal frequency interference[14,21].

Although not studied in relation to depression, similar patterns of facilitation have been observed in the mammalian CNS (Ref. 8). In addition, depressing high-frequency bursts of activity can induce transient increases in synaptic strength[35,36]. Longer lasting enhancement of synaptic strength, as seen in the descending electrosensory system, appears to mediate a 'searchlight' function in weakly electric fish[37].

A simple working model to account for the results obtained in *Eigenmannia* is shown in Fig. 2b. In this model, neurons receive input from two classes of synapses: those that show strong short-term depression and others that show strong short-term facilitation. Two classes of synapses are employed because it appears unlikely that a single 'high-Pr' (high probability of release) synapse can also exhibit facilitation (Box 1); facilitation generally occurs at low-Pr synapses, whereas short-term depression is more prevalent at high-Pr synapses. These input types might arise from the same or from different neurons.

Assume that plasticity at these two types of synapses is differentially frequency dependent; depression begins at spike frequencies of ~10 Hz, and increases at higher frequencies, whereas facilitation begins for spike rates of ~50 Hz, and peaks at ~100 Hz. For simplicity, also assume that the temporal pattern of spike activity at the presynaptic side of each class of synapses is identical. When spikes occur at a rate of about 5 spikes per s (sp/s), maximal release from the depressing synapses will occur, resulting in large postsynaptic EPSPs. Because there are nearly 200 ms between successive action potentials, little depression develops in response to subsequent spikes at this rate. Little release will occur from the facilitating synapse (low-Pr).

Now let the frequency of the presynaptic spike activity increase to ~20 sp/s. At this frequency, strong depression of transmission develops at the depressing synapse, and EPSP amplitude declines accordingly. Because facilitation only occurs for spike rates greater than ~50 Hz, transmission across the facilitating synapse continues to be low. The

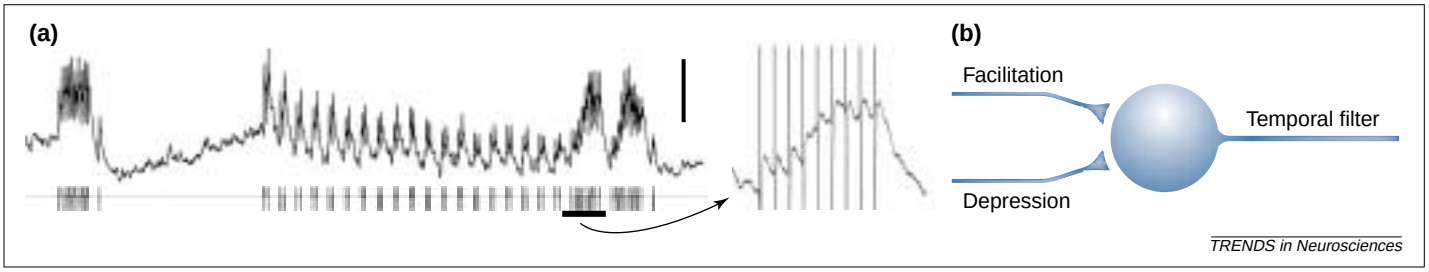

Fig. 2. (a) Interplay of short-term synaptic depression and facilitation in response to afferent stimulation. Intracellular recording (filtered to remove most of the stimulus artifact) from a midbrain electrosensory neuron *in vivo*; pattern of afferent stimulation is shown below. Control 100 ms/100 Hz burst (response similar to 5 Hz sensory stimulation) followed by a single test pulse and recovery period. The depressing stimulus is composed of pairs of pulses presented at 20 Hz periodicity for 1 s. Immediately following the depressing stimulus are two 100 ms/100 Hz bursts. This neuron responded strongly to the bursts in spite of the activation of synaptic depression. Expanded view of a section of the recording trace (marked by bar; right) shows facilitation in the response to the first trailing 100 ms/100 Hz burst (unfiltered, clipped trace). In some neurons depression induced by the 20 Hz-like stimulus also depressed the responses to the trailing bursts: no facilitation occurred in such neurons. (b) A model showing the convergence of depressing and facilitating afferent synapses for the generation of a temporal filtering function. These two types of synapses might originate from the same neuron or from different neurons.

postsynaptic neuron will respond to the onset of the 20 sp/s activity.

Now consider what will happen if, during the course of this 20 Hz spike train, a series of 'bursts', of 100 ms duration, occur. Within each burst the spike frequency is approximately 100 sp/s. Facilitation will be triggered and, after several spikes at this frequency, a large summating EPSP is generated by the facilitating synapse. This simple circuit 'rejects' the sustained input at intermediate frequencies, while remaining sensitive to intermittent bursts of much faster activity.

Conclusions

Independently evolved sensory systems, including the visual system of mammals and electrosensory systems of weakly electric fish, have convergently employed synaptic depression as a mechanism for low-pass temporal filtering. Because other mechanisms exist for achieving this filtering, it is probable that synaptic depression serves some common functional demands in these systems beyond low-pass filtering. Future studies should examine the hypothesis that the depression-induced phase advances in activity peaks plays an essential role in computing the direction of motion of sensory images. This hypothesis can be tested using *in vivo* intracellular recordings while alternately presenting spatio–temporally varying sensory stimuli or stimulating afferents directly. This level of analysis, although technically difficult, can be achieved (Figs 1 and 2a).

The plasticity-based model in Fig. 2b shows short-term depression and facilitation operating at discrete synapses. This is a working model; frequency-dependent facilitation following synaptic depression might occur at a single synapse. Such homosynaptic plasticity could result from a variety of processes, including activity-dependent changes in presynaptic Ca^{2+} conductances[38] and postsynaptic release from polyamine blockade[39]. In the electrosensory midbrain, neurons receive convergent input from the three somatotopic maps in electrosensory lateral line lobe[40]. One intriguing hypothesis is that synapses made by afferents from each of the three maps differ in the type of plasticity that they exhibit. Such convergence of synaptic types could occur in many CNS circuits.

The findings in the electrosensory system, shown in Figs 1 and 2a, underscore the importance of employing biologically relevant temporal patterns of afferent stimulation. Standard measures of synaptic plasticity, for example, responses to particular stimulation frequencies or pairs of pulses, are insufficient to elicit the emergent temporal processing seen in these and other neurons[7,9,14,31]. These complex temporal filters appear to be derived from the interplay of particular combinations of short-term synaptic depression and facilitation[8,13]. In our view, these emergent properties are the basis for the generation of a wide variety of transfer functions for temporal information in CNS circuits.

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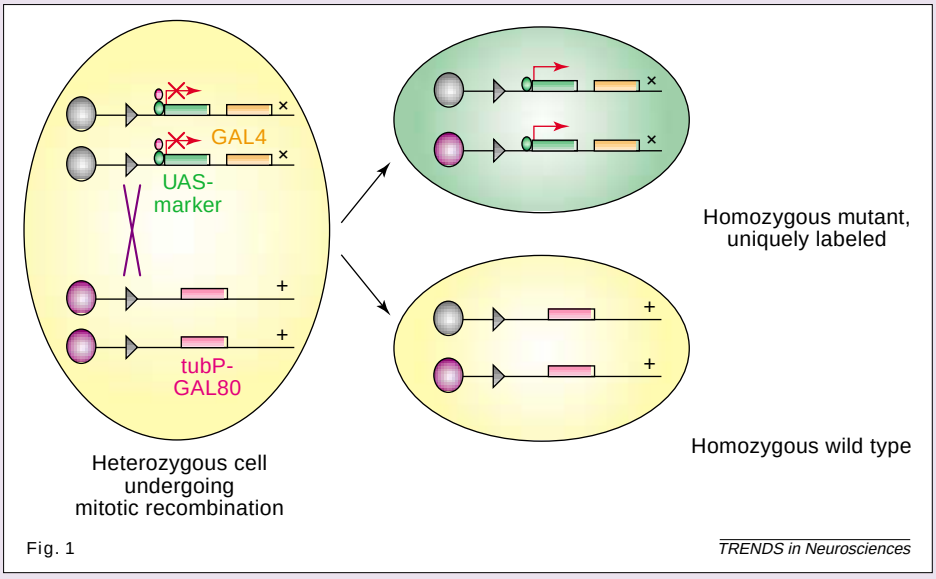
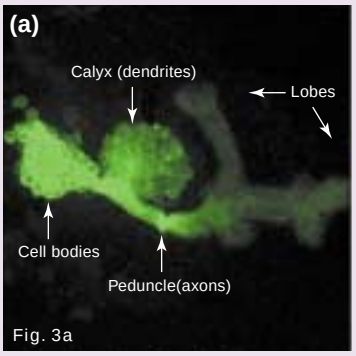


Fig. 1



Erratum

In the article entitled 'Mosaic analysis with a repressible cell marker (MARCM) for *Drosophila* neural development' by Tzumin Lee and Liqun Luo, which appeared in the May 2001 issue of *TINS*, there were errors in Figs 1 and 3a. For Fig. 1, the transcription inhibition (indicated by a red cross in the yellow heterozygous cell on the left) in the homozygous uniquely labelled mutant cell (green cell) should be absent, and hence the green marker can be specifically turned on by GAL4 (orange box) as indicated in the corrected figure. For Fig. 3a, the composite confocal image of a neuroblast clone of a mushroom body neuron with the correctly labelled calyx and lobes is shown above. We apologize to the authors and readers.