The role of short-term synaptic dynamics in motor control
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During the past few years, much attention has been given to the role of short-term synaptic plasticity, in particular depression and facilitation, in sculpting network activity. A recent study shows that synaptic depression in rhythmic motor networks could switch the control of network frequency from intrinsic neuronal properties to the synaptic dynamics. Short-term synaptic plasticity is also involved in the stabilization and reconfiguration of motor circuits and in the initiation, maintenance and modulation of motor programs.

Introduction
Motor networks are constantly reorganized and reconfigured according to both the task at hand and the context within which that task is performed. Numerous studies have demonstrated that neuromodulation plays a pivotal role in sculpting functional motor networks from a ‘hard-wired’ anatomical circuit (for reviews, see [1,2]). It has also been shown that presynaptic inhibition of sensory and modulatory inputs is an important mechanism for the functional shaping and implementation of motor systems (for a review, see [3]). Although more controversial, long-term forms of synaptic plasticity such as facilitation and short-term depression. The mechanisms underlying these forms of synaptic plasticity, and the important question of whether the site of plasticity is presynaptic or postsynaptic, have been (and still are) studied extensively. However, for many years, the issue of assigning any functional role to these interesting synaptic properties had remained untouched.

Pattern generation and the selection of motor programs depend on the plasticity of their regulatory mechanisms. It has been proposed that intrinsic characteristics of neurons, emerging from the interplay of nonlinear ionic currents, provide the basis for flexible regulatory mechanisms (for a review, see [6]). Recent work shows that short-term synaptic dynamics are just as important as the intrinsic cellular dynamics in producing flexible motor outputs. Most studies on the functional roles of synaptic plasticity have been carried out on cortical synapses. We start with a brief review of the different types of short-term synaptic plasticity. We proceed with a brief description of the important findings in this area from studies of the cortex, the hippocampus and some sensory systems. We then turn our discussion to motor systems, and describe how these and other mechanisms of plasticity are, or could be, used in motor control.

Different types of short-term synaptic plasticity
First, it is important that we define what ‘short-term’ means in the context of synaptic plasticity. Synaptic changes that are of the order of tens of seconds or less are generally considered short-term [7,8]. Processes that persist for 30 min or longer, such as LTP or LTD, are usually defined as ‘long-term’ [9]. Long-term forms of synaptic plasticity often involve structural or genetic modifications, whereas short-term forms of synaptic plasticity rely on biochemical changes in neuronal properties, such as modification of transmitter release resulting from changes in intracellular Ca^2+ levels.

In synapses with a low probability of release, postsynaptic potentials often increase in magnitude during repetitive activation. This physiological phenomenon, first described at the neuromuscular junction in the 1940s, was named short-term enhancement (STE) [10]. Since those pioneering times, it has been discovered that STE consists of different components, such as fast-decaying facilitation, slow-decaying facilitation, augmentation and post-tetanic potentiation. In synapses with a high probability of release, the opposite effect is often found: the postsynaptic amplitude declines during repetitive stimulation of the presynaptic neuron. This effect is collectively termed ‘short-term depression’ (STD). STD also has many variations, including lateral inhibition [11], release inactivation.
systems. We now turn our attention to motor systems.


The role of short-term synaptic plasticity in central and sensory systems

Over the past three to four years, researchers have realized that short-term synaptic plasticity may have significant implications for neuronal processing. At the dawn of this new era, two independent groups proposed a functional role for synaptic depression in the neocortex [13,15]. Both groups demonstrated that ‘depressing’ synapses are sensitive to changes in firing rate, irrespective of the absolute firing frequency. The steady-state amplitude of a depressing synapse is inversely proportional to the firing frequency. Therefore, the amplitude of the depressing synapse changes in proportion to the fractional (rather than absolute) change in the firing frequency. Thus, depressing synapses enable cortical circuits to amplify slow or rapid transient signals, while restricting steady-state activity. This mechanism may provide a dynamic, built-in gain-control system for these cortical circuits.

The demonstration of possible functional roles for STD in the cortex has renewed interest in this form of neuronal plasticity. Subsequently, additional functional roles have been suggested. These include network stability [16,17], selection of pathways [18], directional selectivity [19], low-pass filtering [20], synchronization in recurrent networks [21], interval and sequence determination [22], and burst detection [23]. These examples clearly indicate the numerous ways through which short-term synaptic plasticity may be exploited by sensory, motor and processing systems. We now turn our attention to motor systems.

Functions of short-term synaptic plasticity in motor circuits

Very little is known about the functional significance of short-term synaptic dynamics in the motor system, but many possibilities have been indicated. In this section, we will describe some of the recent studies that illustrate such functional implications. We will break up the descriptions of these studies according to the function of short-term modulation that they propose.

Rhythlogenesis

Many motor tasks are rhythmic activities originating from specialized neuronal networks known as central pattern generators (CPGs). These rhythms may be generated by pacemaker neurons or may emerge from synaptic interactions among the CPG neurons. In the latter case, synaptic properties in general and, more specifically, synaptic dynamics, are essential for the generation of the rhythm. For example, circuits of neurons interconnected by reciprocal inhibition are important modules in motor circuits [24]. Oscillation in such circuits is usually generated by alternation of activity — known as half-center oscillation — between two neurons, or two groups of neurons. The transition of activity from one half (i.e. one neuron or group) to the other is promoted by some adaptation process that may be mediated by synaptic fatigue, a variant of synaptic depression [25]. In the leech swim CPG, for example, multiple reciprocally inhibitory pairs of neurons have been implicated as the elemental oscillators. It has been found that synapses in this circuit exhibit fatigue, but the functional consequences of this property have not been directly demonstrated [25].

In networks that involve recurrent excitation, STD may also be functionally important for rhythmogenesis, although through a completely different mechanism. The isolated spinal cord of the chick embryo, for instance, generates spontaneous episodes of rhythmic activity. These episodes are separated by quiescent intervals lasting several minutes. A simplified mathematical model of this network demonstrates that this rhythmic activity may arise from the interplay between recurrent excitation and fast synaptic depression [26].

Network stabilization

Fast synaptic transmission plays a major role in shaping the cycle-to-cycle activity of CPGs [27]. Because CPGs operate under a wide range of frequencies and phasing patterns, they use a variety of mechanisms for maintaining reliable synaptic transmission while allowing for adaptability of the network. It has been suggested that in the lamprey spinal cord, depletion of transmitter vesicles causes an initial synaptic depression. This effect is, however, opposed by an activity-dependent mechanism, perhaps mobilization of vesicles from a reserve pool [28]. By monitoring cellular or synaptic activity, the neurons involved adjust their transmitter release as required for different network outputs. This mechanism ensures stability of synaptic transmission over a wide range of rhythmic activities.

Synaptic depression was also found in the stomatogastric nervous system (STNS) of crustacea [29]. Manor and colleagues investigated the properties of the sole inhibitory feedback synapse onto the pacemaker neurons of the lobster STNS pyloric network. They found that this strategically placed synapse shows depression and that the depression is dependent on network activity. Both the amplitude and the peak time of the postsynaptic current change with the frequency and duty cycle of the presynaptic signal (Figure 1). The kinetics of depression and recovery of this synapse are tuned so that synaptic transmission is sensitive to changes in the temporal pattern (frequency and duty-cycle) of the presynaptic neuron. The results of Manor and colleagues imply that this synapse quickly adapts to any rapid changes in the pyloric frequency or to a strong sensory input. It was suggested that the dynamics of this synapse have a buffering effect on fluctuations of rhythm and phase, thereby serving as a
mechanism to stabilize network oscillations. A recent simplified model of the pyloric circuit shows that these dynamics may play a central role in the phase-maintenance of the pyloric neurons in response to changes in frequency (Manor Y, Nadim F, unpublished data; Figure 2).

Network reconfiguration

It is now widely accepted that neuromodulation can modify the output of a motor network by changing the relative strengths of synaptic connections, thereby sculpting new functional circuits. Such a modulated circuit is believed to continue producing its characteristic output as long as the neuromodulator is present in the appropriate concentration and locality. A simplified model, motivated by the synaptic dynamics within the lobster STNS, sheds new light on this classical view of neuromodulation [30**]. Depressing synapses are commonly viewed as weak synapses that become transiently strong if allowed to recover. The model of Nadim and colleagues [30**] shows that depressing synapses, when embedded in recurrent networks, can have much more interesting effects. This model demonstrates that in a reciprocally inhibitory network that includes an intrinsic oscillator, a regenerative mechanism can be engaged. This regenerative mechanism creates a dramatic amplification in the strength of the synapse and can lead to a large change in network behavior. By exploiting the dynamics of a network arising from short-term synaptic plasticity, transient neuromodulation can produce long-lasting effects on the network function. According to this novel view, neuromodulation may act by merely triggering the self-reorganization of a neuronal network.

Short-term synaptic plasticity can also be used to dynamically select between different motor patterns. Combes and colleagues [31**] show that, in the gastric mill CPG of the lobster STNS, two distinct motor patterns are selected between by changing the balance between two interneurons, one excitatory and one inhibitory, that provide input to the CPG. A common sensory neuron differentially excites both interneurons: the synapse to the excitatory interneuron is weakly facilitating whereas the synapse to the inhibitory interneuron is strongly facilitating. When
the sensory stimulus is weak, the excitatory pathway is dominant and this dominance results in the selection of a specific gastric mill motor pattern. When the sensory stimulus is increased, strong facilitation enhances the inhibitory pathway. As a result, a different gastric mill motor pattern is selected. Another example comes from the locomotion CPG of *Tritonia*. In this case, heterosynaptic facilitation (i.e. indirect facilitation of a pathway other than the one activated) is used to select not between different motor patterns, but between distinct motor programs — namely, rhythmic swimming and single-shot reflexive withdrawal [32,33].

**Initiation and modulation of motor programs**

In *Aplysia*, a command-like neuron initiates ingestion motor programs produced in the buccal ganglia. Recently, it was found that synapses between this command-like neuron and the premotor and motor neurons in these ganglia exhibit homosynaptic STE [34**]. In an experimental protocol that resembled the physiological conditions, the authors demonstrated that augmentation and post-tetanic potentiation could be used to initiate the ingestion buccal motor program (iBMP) at a lower firing frequency. Moreover, the authors showed that STE might increase the cycle frequency, thereby modulating the motor program. This mechanism could contribute to the increased bite frequency observed during feeding arousal [35].

**Dynamic gain control**

As in the case of cortical circuits, an important aspect of plasticity in motor circuits is the ability to adapt rapidly to a changing environment. Often, such adaptation involves altering the balance between excitation and inhibition. In *Aplysia*, dynamic interactions between excitatory and inhibitory interneurons contribute to the function and plasticity of the siphon withdrawal reflex (SWR). For example, decreasing activity in the inhibitory pathways in this circuit may lead to sensitization of the reflex [36]. In contrast, following weak tactile stimulation, there is an increased inhibition within the SWR circuit [37]. The net effect of this enhanced inhibition is an increase in the effective threshold for the motor response triggered by the stimulus, thereby decreasing or preventing sensitization. Thus, STE in this inhibitory synapse is shown to produce an intrinsic mechanism for the dynamic regulation of the SWR [37]. This finding provides a direct link between short-term
Synaptic plasticity is itself activity-dependent, being regulated by neuromodulation [40,41], sensory experience [42] or a combination of the two [7]. The adaptability of synaptic dynamics themselves, originally discovered in long-term forms of synaptic plasticity, has been termed ‘metaplasticity’ [40]. Recently, it has been shown that metaplasticity is also found for short-term forms of synaptic plasticity.

An example that illustrates the way in which metaplasticity of short-term synaptic dynamics could be used to regulate motor behavior comes from work on the goldfish Mauthner cell (M) axon, which excites relay interneurons that initiate an escape response. Activity-dependent depression of M-axon output synapses may help to prevent the initiation of two overlapping escape sequences, a response that could be counterproductive. A recent work [43•] finds that depression at the M-axon output synapses is differentially modified by presynaptic injection of Ca\(^{2+}\) or guanosine triphosphate-5’ γS (GTPγS). These authors propose that the modulation of synaptic depression may regulate the interval at which double responses could be produced.

In Aplysia, a tail shock (or exposure to serotonin) induces differential metaplasticity at a synapse that inhibits the SWR [7]. By suppressing the plasticity of this synapse, a tail shock stimulus disinhibits the reflex system. This mechanism could prime the system to facilitate subsequent induction of classical conditioning, dishabituation or sensitization.

In the lamprey swim circuit, in vitro experiments reveal depression in synapses among excitatory and inhibitory interneurons of the locomotor network [44**]. In the absence of neuromodulation, inhibitory synapses exhibit strong depression, while excitatory synapses show weak depression. This balance changes in the presence of neuromodulators such as serotonin and substance P. This metaplasticity at the synaptic level correlates well with the effect of neuromodulation on the network output, and could potentially be a mechanism that contributes to modulation and coordination of rhythmic activity.

Facilitation at the neuromuscular junction of crustacea is also subject to neuromodulation. It was found [45] that facilitation of the junctional potential is modified not by affecting the temporal dynamics, but by changing release probability and affecting the initial amplitude of the excitatory junctional potential. Because of the fact that release probability is inversely related to facilitation [45,46], this finding has interesting functional consequences. When neuromodulation increases the amplitude of the junctional synaptic potential, facilitation becomes less significant but the effect of temporal summation starts to be considerable. In this case, the muscle fiber membrane potential will depend primarily on the firing frequency of the motor neuron and less on its burst duration [47]. In contrast, neuromodulation that decreases the amplitude of the junctional synaptic potential will increase the effect of facilitation and firing frequency, but the effect of temporal summation will decrease. Thus, the membrane potential in the muscle fiber will depend both on burst duration and firing frequency of the motor neuron.

Interactions between short-term plasticity and long-term plasticity

It is reasonable to expect that short-term forms of synaptic plasticity affect longer-lasting forms such as LTP or LTD. For instance, induction of LTP is related to the increase of postsynaptic intracellular Ca\(^{2+}\) above a certain concentration. During the induction phase, strong synapses are more likely than weaker synapses to achieve this concentration threshold. In fact, pairing between neocortical pyramidal neurons induces an increase in the initial postsynaptic response, whereas it has no effect on the steady-state response [48]. The most likely mechanism for explaining this result is an increase in the probability of transmitter release. Indeed, during normal activity, synaptic strength is strongly modulated by facilitation and depression [49•]. Hence, the mechanism of LTP expression may be closely related to short-term synaptic plasticity [9].

A study of STE and LTP in different areas of the neocortex reveals that STE is prominent in somatosensory areas, but not in motor areas [50]. Interestingly, the magnitude of STE is strongly correlated with the magnitude of the subsequently induced LTP. This work [50] shows that short-term plasticity may be critical for the expression of long-term forms of synaptic plasticity, and it provides a possible explanation for why motor cortex is less capable than somatosensory cortex of generating LTP.

In the cerebellar cortex, the climbing fiber (CF) input to Purkinje cells (PCs) shows paired-pulse depression (PPD) that is long-lasting (3–4 s) relative to the mean interspike interval of CF inputs (~1 s). It is, therefore, probable that this short-term synaptic plasticity has some functional significance. Experiments in cerebellar slices show that PPD at the CF to PC synapse modulates the Purkinje cell excitability, in particular the response of the Purkinje cell to subsequent CF inputs [51]. Since the CF input is known to trigger LTD at the parallel fiber (PF) pathway [52], it is suggested that STD determines the efficacy of LTD. Because LTD at the PF pathway is involved in motor learning [5], this study implicates STD in learning aspects of motor processing. Short-term synaptic plasticity and motor processing are further linked by the results of an intriguing mouse knockout study [53]. Mice deficient in paired-pulse facilitation and post-tetanic potentiation (but not in LTD or LTP) at the PF pathway had impaired ability to learn complex motor tasks. Pekhletska and
colleagues [53] engineered a mutant mouse lacking a glutamate receptor subtype that is highly localized to cerebellar synapses, specifically between PFs and PCs. The knockout mouse was impaired in its ability to learn complex motor tasks. Surprisingly, electrophysiological recordings revealed that the PF to PC synapses showed normal LTD, but paired-pulse facilitation and post-tetanic potentiation were both significantly reduced. Although this result does not prove that the motor deficit is caused by the impairment in short-term facilitation and potentiation, it is provoking enough to stir interest in possible roles of short-term plasticity in motor learning.

Conclusions
It is ironic that, although short-term synaptic plasticity was discovered in motor circuits, so little is known about its functional role in motor systems in comparison to other systems. The extensive work on cortical synapses has taught us that short-term synaptic plasticity is not simply an empirical curiosity, but that it has important implications for network function. It seems that short-term synaptic dynamics not only affect network function directly, but also affect neuromodulation and the expression of long-term synaptic plasticity, both of which are implicated in motor processing. Ideas from studies of cortical synapses should be applicable to any system in which short-term synaptic plasticity exists, and we would like to highlight some examples of this. For instance, short-term synaptic plasticity has been suggested as a general mechanism for interval and sequence determination [22•]. It is clear how this neuronal capability can be exploited in sensory tasks, including speech perception in humans, call detection in frogs or song discrimination in birds. However, interval and sequence determination is also relevant for a range of motor tasks, such as the recognition of rhythmic motor patterns [54,55•]. In another example, synaptic depression has been shown to act as a mechanism of low-pass filtering, as demonstrated for electrococulation in electric fish [20•]. It has been speculated that synaptic depression at the olivo-cerebellar synapse, an important pathway involved in motor coordination, plays a similar role in the motor system [56]. In a third example, synaptic depression can be used for network stability, as demonstrated in cortical circuits [17]. In the leech crawling circuit, it has been proposed that wave propagation is mediated by a positive feedback mechanism, which could result from reciprocally excitatory connections between motor neurons [57]. The issue of network stability was not assessed in this case, but it is tempting to suggest that synaptic depression may be involved. Fourth, in a recent study of cerebellar synapses, Kreitzer and Regehr [58] propose that enhanced facilitation may increase the signal-to-noise ratio of cerebellar synapses. If signals converging on the cerebellar cortex are encoded in bursts, as Lisman proposes for hippocampal circuits [23], the increased signal-to-noise ratio would be advantageous for decoding tasks in this important intersection path of motor processing. In a fifth example, higher levels of motor processing, planning and execution of movement have been associated with precise synchronization of individual spike discharges among selected clusters of neurons in the motor cortex [59]. To date, it is not known how this behaviorally relevant synchronization is achieved. A recent model proposes that synchronization may be obtained in a recurrent network of inhibitory and excitatory neurons, randomly interconnected via depressing synapses [21•]. It will be interesting to discover whether such a mechanism, which can explain population bursts throughout the neocortex, plays a role in cognitive motor processes in the brain.

We believe that functional roles for short-term synaptic plasticity will be found in motor circuits if only they are searched for in these systems. Short-term forms of synaptic plasticity are difficult to study experimentally because of the fact that manipulating synapses in a controlled manner is technically difficult. The use of sophisticated electrophysiology tools, such as the dynamic clamp technique [60], should facilitate this mission.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
**of outstanding interest

14. Lev-Tov A, Pinter M, Burke R: Posttetanic potentiation of group I EPSPs: possible mechanisms for differential distribution among


In the electro-sensory system of the electric fish Eigenmannia, frequency-dependent synaptic depression acts as a low-pass temporal filter. Together with the active and passive properties of tactual neurons in the electric organ, this mechanism enables the electric organ to reject jamming signals. Jamming occurs when two fish with similar electric organ discharge profiles approach each other. The combination of these discharges can produce signal modulation that interferes with the ability of each fish to electrolocate. In this work, synaptic depression is viewed from a network-learning perspective. The system samples several beat cycles, evaluates the stimulus frequency and attenuates or enhances its response according to an internal target frequency. This enables the fish to habituate to fast changes in signal amplitude (for example, as a result of a jamming response) while preserving its capacity to respond to slow modulations (during electrolocation).


This work describes a model of a recurrent network in which inhibitory and excitatory neurons are randomly interconnected via depression synapses. The network spontaneously self-organizes to produce synchronous bursts in which almost all the neurons participate. These population bursts were elicited by external stimuli in an all-or-none manner according to the intensity of the stimulus. This type of population burst could be the basis of synchronous activity found throughout the neocortex. This would provide the cortex with the ability to respond rapidly and faithfully to sensory stimuli. The particular intensities of the external stimuli to specific neurons determine whether the population can be triggered to burst or not. This topographic sensitivity depends on the spectrum of basal discharge rate across the population. This work suggests that networks in which neurons are connected via depression synapses could exhibit a response that is sensitive to the nature of the activity found throughout the neocortex. This would provide the cortex with the ability to encode sensory information.


This study proposes that dynamic changes in the balance of excitatory-inhibitory interactions, mediated by short-term plasticity, underlie the generation of temporally selective responses. The authors show that a large network model of excitatory and inhibitory units, interconnected via slow-inhibitory and frequency-dependent synapses, can perform temporal and sequence discrimination. Interval timing can arise from changes in synaptic strength alone. The results indicate that neural circuits are able to process temporal information through intrinsic mechanisms without the use of delay lines. (Delay lines are dynamics due to the propagation time of action potentials along elongated axons.)


The isolated spinal cord of the chick embryo generates spontaneous episodes of rhythmic activity, separated by quiescent intervals of several minutes. The rhythmic activity emerges from a recurrent network of excitatory neurons connected by depression synapses. Based on these experimental data, the authors have built a simplified model. The model demonstrates that cycling may arise from the interplay between fast synaptic depression and recurrent excitation in the following manner. Recurrent excitation generates spontaneous activity. During this period of activity, synaptic depression develops, until network activity ceases. During the quiescent period, synapses are depressed by afferent input, until a new cycle of activity is initiated.


The authors describe a modeling study inspired by the pyloric rhythm generated by the lobster STNS. The pyloric rhythm is generated by a pacemaker group of neurons that receive feedback from a depressing inhibitory synapse. Experimental work shows that often, but not always, elimination of the feedback from a synapse speeds up the rhythm. To understand this discrepancy in ability, the authors constructed a simple model consisting of a recurrent network connected via reciprocal inhibition to a follower neuron, with a feedback depressing synapse from the follower neuron to the rhythm neuron. They found that the depressing synapse gives rise to two distinct modes of network operation: in the pacemaker-dominated mode, the synaptic transmission is weak and the rhythm is controlled by the intrinsic properties of the pacemakers. In the synapse-dominated mode, synaptic transmission is strong and controls the rhythm frequency. The transition between the two modes is abrupt. The authors show that the synapse-dominated regime arises from a regenerative mechanism that greatly amplifies the strength of the synapse. Within a particular parameter range, the two oscillation regimes co-exist, creating bistability.


The lobster STNS generates the gastric mill rhythm, which controls the muscles that move the two lateral and one medial tooth used in chewing. Two variants of gastric mill activity are discussed: in the first variant, all the motor neurons controlling the muscles of the three teeth are active in synchrony (type I); in the second variant, the medial- and lateral-teeth power-stroke motor neurons are active in anti-phase (type II). These two rhythms are activated by two parallel pathways, both of which are activated by one mecanoreceptor neuron, the anterior gastric receptor (AGR). When activity in AGR is weak, the excitationary pathway is prevalent and the gastric mill operates in the type-I mode. When AGR is strongly active, facilitation enhances the inhibitory pathway. As a result, the CPG is reconfigured to operate in the type-II pattern. Because both pathways operate independently, the gastric mill activity is activity-dependent, it can be used to convert firing rate of a sensory nerve into a selection between two distinct motor patterns.


To show that ST could contribute to initiation of the iBMP, the firing frequency of the command neuron was adjusted to a level below that required to elicit the iBMP (5 Hz). Following a recovery period of 10 minutes (during which the ST was disinhibited), the command neuron was stimulated at high frequency (10 Hz), which elicited a rhythmic iBMP. Following this, the firing frequency in the command neuron was restored to a lower level (5 Hz). Nevertheless, the command neuron now elicited iBMP with high reliability. The authors show that the synapse-dominated regime arises from a regenerative mechanism that greatly amplifies the strength of the synapse. Within a particular parameter range, the two oscillation regimes co-exist, creating bistability.


