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Dynamics of Central Pattern Generating Networks: Locus of Control

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Oscillatory activity, paramount throughout the central nervous system, is of special significance in the production of rhythmic motor movement, such as locomotion, breathing, and chewing. Such movements are typically generated by networks of synaptically coupled neurons, known as *central pattern generators* (CPGs), which can produce rhythmic output even without patterned sensory or other extrinsic inputs. In an oscillatory network, participating neurons are commonly active at a specific phase of the network cycle, a phenomenon known as *phase locking*. The activity phase of neurons within a CPG corresponds to the order in which the involved muscles become active and is thus decisive in the production of meaningful motor behavior. Additionally, most motor rhythms operate across a range of frequencies—e.g., walking vs. running—and the operation of a CPG thus depends on factors that maintain or change the activity phase of CPG components as a function of network frequency.

Factors that determine phase in an oscillatory network have attracted considerable attention from theorists [4]. In particular, methods of dynamical systems, such as geometric singular perturbation theory and averaging, have been successfully applied to understand how coupled oscillatory components interact to produce phase-locked network oscillations. Extensive theory has been developed for weakly coupled networks, such as coupled oscillators with similar frequencies, but theoretical analysis of networks involving moderate to strong coupling of disparate components has lagged behind. This is so in part because the outputs of such networks are much more dependent on the coupling architecture, which cannot be averaged or universally approximated.

It is commonly found that the generation of network oscillations results from dynamic interaction between properties of synapses and voltage-gated ionic currents. However, network oscillations may be more dependent on a subset of network parameters as opposed to others. Recent mathematical and computational studies have shown that networks in different states of activity—in different frequency ranges, for example—can be sensitive to synaptic parameters or to parameters affecting intrinsic properties of involved neurons, but not both. It is well known that most synapses can change in efficacy in a use-dependent manner, a phenomenon known as *short-term synaptic plasticity* (STSP), which can take the form of facilitation or depression, depending on whether the synaptic strength is increased or decreased. STSP is important in determining network dynamics because the time scales at which it operates are the same as the gating time scales of nonlinear ionic currents underlying intrinsic neuronal properties. The architecture of the network, moreover, determines how STSP is utilized. In the remainder of this article, we describe mathematical studies that highlight the importance of STSP in determining the locus of control in oscillatory networks.

In feed-forward networks, the frequency of pacemaker neurons will affect the level of synaptic influence on downstream neurons because of STSP. Consider the example of a simplified oscillator–follower (O–F) network. If the synapse from O to F exhibits short-term depression, the activity phase of the postsynaptic neuron F can be controlled by distinct mechanisms that depend on the frequency of O. When O has high frequency, the O to F synapse becomes depressed and weak, and the intrinsic properties of F have a stronger influence in determining the activity phase of F. Alternatively, when O has low frequency, the synapse is strong; parameters associated with this feed-forward synapse then play the main role in setting phase. At intermediate frequencies both intrinsic and synaptic parameters participate.

In this example, the extent of synaptic depression is a continuous function of the frequency of O. This function can be used to derive a "feed-forward map" that describes the activity phase of F as a function of the frequency of O. The map depends both on the frequency-dependent synapse from O to F and on the intrinsic parameters of F. The sensitivity of this map to different parameters then determines the locus of control of the activity phase of F as a function of network frequency [5].

STSP can play a more subtle role in a feed-forward network by unmasking the full influence of certain voltage-gated ionic currents. In the feed-forward O–F network, short-term synaptic depression can allow a low-threshold-activated transient outward current (A-current) to participate in setting the phase of F firing at very low frequencies [1]. In this case, the feed-forward map is composed of two distinct maps—one describing the inactive duration of F as a function of the frequency of O, and the other relating the inactive duration of F to the effect of the A-current in setting the F activity phase. STSP allows these two maps to act synergistically to expand the locus of control to parameters associated with the A-current. In the absence of STSP, the influence of the A-current would become frequency-independent, and the current would not participate in changing the activity phase of F as frequency is modified.

Oscillatory networks, including CPGs, involve both feed-forward mechanisms that coordinate the activities of different components and feedback mechanisms that affect the locus of control. Compared with feed-forward networks, feedback networks can utilize STSP in a more discrete manner. Feedback to the pacemaker typically forces the network to lock into a stable periodic solution of fixed frequency, which consequently sets the level of STSP. In such networks, multiple stable dynamic states can co-exist, with the frequency of each state determined by a distinct mechanism [2,6,7] (see Figure 1 on next page). The dynamics of this network are described as a composition of two maps: a feed-forward map, which sets synaptic strength as a function of network frequency, and a feedback map, which determines frequency as a function of synaptic strength. Mathematical analysis of such feedback networks reveals that the presence of bistability in certain parameter regimes is a generic mechanism for switching the locus of control [2].

In the cases described so far, STSP determines which set of parameters is most critical at which frequencies in setting network behavior. STSP also plays a surprising and perhaps more profound role in redefining the network actions of neuromodulators. For example, when a network is in an intrinsically controlled state, the values of its synaptic parameters are largely irrelevant. Neuromodulators that target synaptic properties can thus do so without affecting network activity, but they might serve to prime the network for a situation in which synaptic control could be more effective. Such a mechanism could underlie the priming effect of one neuromodulator by another, seemingly ineffective neuromodulator [3].

The enigma in the operation of oscillatory neural networks, in particular CPGs that produce rhythmic motor activity, is not the mechanism underlying the generation of oscillations. Rather, it is the surprising balance of network stability and plasticity in response to external inputs that change the frequency of the network yet allow it to retain its coordinated output. Mathematicians have addressed this problem by finding mechanisms that produce the largest range of frequencies for which coordinated oscillations exist. The analysis of such networks via dynamical systems techniques has been critical in revealing how STSP, by providing multiple loci of control for network output, can be an important factor in producing network flexibility.

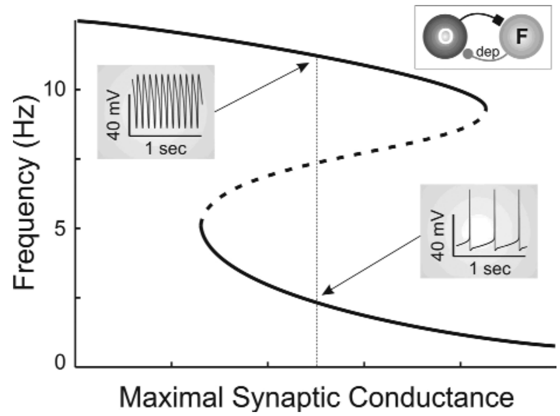

Figure 1. *Bistability in an oscillator–follower (O–F) network with a feedback-depressing synapse (schematic in top right inset). Two stable oscillatory states can exist at the same value of the maximal synaptic conductance parameter: an intrinsic-parameter control of a high-frequency, weak-synapse state (inset, top left) and a synaptic-parameter control of a low-frequency, strong-synapse state (inset, bottom right). Adapted from [2].*

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