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Principles of Rhythmic Motor Pattern Generation

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Marder, Eve, and Ronald L. Calabrese. Principles of Rhythmic Motor Pattern Generation. *Physiol. Rev.* 76: 687–717, 1996.—Rhythmic movements are produced by central pattern-generating networks whose output is shaped by sensory and neuromodulatory inputs to allow the animal to adapt its movements to changing needs. This review discusses cellular, circuit, and computational analyses of the mechanisms underlying the generation of rhythmic movements in both invertebrate and vertebrate nervous systems. Attention is paid to exploring the mechanisms by which synaptic and cellular processes interact to play specific roles in shaping motor patterns and, consequently, movement.

I. INTRODUCTION

Although the role of single neuron oscillators and oscillatory circuits in the production of rhythmic movements has been appreciated for a long time (57, 99, 100, 123, 267), recent experimental and theoretical work has suggested that oscillatory processes are important in visual processing (107), olfaction (e.g., Refs. 172, 173), memory formation (177), and a wide variety of other sensory, motor, and cognitive tasks. The widespread significance of oscillatory processes in multiple brain computations makes it crucial to understand how single neuronal oscillators influence the dynamics of the circuits in which they operate, as well as to understand the mechanisms by which oscillatory circuits function.

The central pattern-generating circuits that generate rhythmic movements in many animals have been intensively studied for a long time, and there is a vast and often idiosyncratic literature in this field. Rather than attempt the impossible task of providing an exhaustive review of all preparations, here we have focused attention on several preparations that illustrate principles of organization in oscillatory networks. By so doing, we hope that the generalities among pattern-generating systems will be more apparent and that these may provide insight to those interested in oscillatory processes in nonmotor systems as well. Obviously, many preparations that we have neglected here have also provided fundamental insights into the mechanisms of rhythmic motor pattern generation in animals.

Rhythmic movements in animals are controlled by neural networks that provide the timing of motoneuron discharge. The central components of these networks are capable of producing rhythmic patterns of activity, although sensory information may be essential for the appropriate response of these networks to behavioral requisites (see Refs. 57, 113, 123, 242 for other recent reviews).

Historically, there was a long and protracted controversy between those who believed that rhythmic motor patterns result from chains of reflexes, in which each movement was "strung together" from successive activation of reflexes, versus those who believed that they were

generated by central neural oscillators. This debate was resolved for many with the demonstration that the salient features of the flight motor pattern in locust could be generated in the absence of patterned sensory input (324). Subsequently, numerous preparations were placed in vitro, with all sensory inputs removed or silenced, and investigators were able to obtain rhythmic motor patterns in preparations containing only the central nervous system (267). The strong correspondence between these fictive motor patterns and those seen in behaving animals caused many to neglect the importance of sensory shaping of motor patterns. Indeed, the importance of sensory control in producing an adaptive motor pattern has been elegantly demonstrated in the same animal, the locust, that was used to demonstrate the ability of the central nervous system to generate a fictive motor pattern (242, 325). The dynamic interplay between central and sensory mechanisms in the generation of adaptive movements is seen in all preparations. In some preparations, sensory information may be used primarily to initiate or terminate ongoing movements or to modulate cycle period and amplitude in a graded fashion. In others, sensory information provides critical timing cues.

II. WHAT KINDS OF BEHAVIORS ARE CONTROLLED BY PATTERN GENERATORS?

A wide variety of behaviors are generated by rhythmic pattern-generating circuits. These include ongoing and stereotyped movements such as breathing, chewing, walking, running, flying, and swimming. Some movements such as vertebrate respiration and the neurogenic leech heartbeat are ongoing; others are episodic. Some behaviors are only rarely and briefly seen, as in escape or scratch behaviors (25, 26, 292). Others, such as swimming in lampreys and fish, can occur for short or long periods of time. Some behaviors such as hatching (20, 21) or ecdysis (226) occur in development. Rhythmic behaviors also differ in the extent of their modulation by sensory input. Behaviors like respiration need only be modulated in frequency and amplitude to meet the animal's needs. Others such as locomotor rhythms require cycle-by-cycle corrective signals to match them to the environment. In limbed vertebrates, movements in which limbs can operate independently are selected from a repertoire of behaviors (25, 26, 292). In many movements, intersegmental coordination is required, and networks controlling different functions must often be coupled. For example, the rhythmic network controlling respiration must be coupled somehow to those controlling running. Most animals use the same muscles in different movements. Some of the central circuitry underlying these movements must involve the shared use of some of the elements that make up these rhythmic neural networks. Understanding which elements are shared and how these are grouped into functional circuits is one of the challenges of today's work.

III. CIRCUIT BUILDING BLOCKS

In response to the diversity found in the circuits that generate rhythmic behaviors, Getting (99, 100) introduced the term *building blocks* to describe circuit components that are commonly found in many circuits. Getting's aim was to describe the "alphabet" of neuronal properties that could be combined in central pattern-generating circuits to produce different functional ensembles of neurons. Getting's attempt to ascribe functional consequences to individual cellular properties and patterns of connectivity influenced greatly much of the work during the past 10 years and has aided many of us in organizing our ideas concerning circuit operation.

A. Identification of Neurons in Pattern-Generating Networks

One of the most daunting tasks facing motor systems physiologists is the identification of the neurons that form part of the central circuitry that generates rhythmic movements. Indeed, the extent to which progress has been made in understanding a given preparation can be largely attributed to the degree to which the component neurons or neuron classes have been successfully identified. Except in rare cases, almost all of the relevant neurons are found within complex central nervous systems, and they are usually embedded in ganglia, brains, and nuclei that also contain neurons with other functions. Before it is possible to establish the properties of the neurons and their interactions that give rise to rhythmic movements, it is necessary to locate at least a major number of the constituents and to have these in a preparation amenable to both intracellular and extracellular recording during ongoing fictive behaviors. A number of strategies are used to identify and locate the neurons of these central circuits.

In principle, the study of a motor system should start with a description of the behavior. Usually this is accomplished with video recordings of the animal during natural and unrestrained movement (e.g., Refs. 20, 30, 111, 112, 132, 168). This allows the investigator to determine the natural periods, durations, and variations in the behavior as it unfolds without experimental perturbation. The ultimate challenge of the motor system physiologist is to explain these unfettered movements.

Once a behavior is characterized, it is necessary to determine the sequence of muscles activated to produce it. Often implanted electromyogram (EMG) electrodes are used to characterize the sequences of muscles during behavior (e.g., Refs. 112, 256). This can be straightforward; in other cases, obtaining this information can be ex-

tremely difficult. This is especially true when numerous muscle groups are activated simultaneously in a complex movement or in the case of animals such as mollusks where body wall muscles are not organized into discrete bundles. However, in the absence of knowledge of the sequence of muscles activated, it can be difficult to determine the motor patterns required to make the movements and, therefore, to identify the motoneurons whose activity needs to be controlled.

The motoneurons that innervate a given muscle are usually not difficult to find. Most frequently, a combination of anatomic and physiological techniques allows the investigator to locate the neurons in the central nervous system that project directly to a muscle and innervate it. Although it is possible to make errors of identification if motoneurons innervating different muscles are electrically coupled, if the muscles are difficult to record from, or if the motoneurons cannot be stimulated individually, these errors result from technical limitations, not an inadequate conceptual framework.

Identification of the interneurons that participate in the generation of rhythmic movements depends on several criteria. Investigators look for *1*) interneurons that synapse directly on the relevant motoneurons, *2*) neurons that are active in time with the rhythmic motor pattern, and *3*) neurons that initiate, terminate, or change the expression of an ongoing rhythmic motor pattern. However, in practical terms, these approaches have intrinsic difficulties. For example, the interneurons that influence a behavior may not actually fire in time with that behavior. This is especially important as we come to appreciate the importance of neuromodulatory and neurosecretory influences that may modify the excitability of neurons over long time scales (123, 229, 230). Additionally, interneurons that are important in programming a behavior may be a part of a large set of interneurons, with overlapping connections and functions, so that perturbations of a single neuron may have little or no influence on the ongoing motor patterns. These two problems have, in practical terms, significantly hampered interneuronal identification in most vertebrate nervous systems and have complicated work even in invertebrate nervous systems.

Recent appreciation that pattern-generating neurons can change their activity patterns (75, 136, 137, 156, 201, 202, 311–313) seriously complicates the identification of interneurons that form pattern-generating circuits in both invertebrate and vertebrate nervous systems. Because neurons cannot be reliably identified on the basis of their activity patterns alone, cells with different patterns of activity cannot be assumed to be different classes of cells. Moreover, because the same neuron can display different patterns of activity, a single recording will also be inadequate for classification (209). The advent of slice preparations in the analysis of vertebrate motor systems has opened up the possibility of making simultaneous recordings from two or more neurons and offers the promise of further advances in this area.

B. Intrinsic Cellular Properties

When isolated from all synaptic inputs, some neurons are silent, some show tonic unpatterned activity, some fire bursts of action potentials, and some display plateau potentials.

1. Neuronal oscillators and plateau neurons

Neurons with slow oscillatory properties are found in all nervous systems (145, 178, 279, 293, 294). Neural oscillations are now thought to play significant roles in memory formation (143, 177), sensory processing (see Ref. 107 for a recent review), as well as in the generation of rhythmic movements.

Some neurons such as R15 in *Aplysia* and the anterior burster (AB) neuron in the crustacean stomatogastric ganglion (STG) are robust single-cell oscillators and generate periodic bursts of action potentials followed by silent interburst intervals. Such neurons maintain relatively fixed periods unless perturbed and can be entrained or reset in a 1:1 fashion within a limited frequency range, while other stimulus patterns result in other patterns of phase locking or loss of coordination (17, 51, 164, 200, 249, 250, 257, 261).

Single-cell oscillators have been extensively studied by theorists. A number of points relevant to the nervous system have emerged in modeling studies. First, by changing the balance of conductances in model oscillators, it is usually possible to obtain a range of behaviors from the "same" model, that is, silent, oscillatory, or excitable (174, 179, 257, 261). Second, using "realistic" conductance-based models, it is possible to produce membrane potential oscillations, or bursts, using a variety of different membrane conductances (19, 24, 27, 48–50, 52, 73, 88, 118, 133, 210, 258, 300). In real neuronal and muscle oscillators, many different combinations of ion channels are used to produce oscillatory activity (144, 300). Because the detailed waveform of the oscillator depends critically on the specific properties and types of the conductances found in the cell, each neuronal oscillator may have a unique frequency range and response to injected and synaptic current (286).

An intriguing result is seen in recent work of a model of R15 in *Aplysia* (48). This model can show different modes of activity, depending on initial conditions, without changing the parameters of any of the currents and can be persistently switched among these modes by a transient perturbation, such as that produced by a synaptic input. The interaction between the effects of modulators that change the balance of conductances and the mode

switches that can occur in the absence of changes in any of the parameters in the model was explored further (42, 49).

Modeling studies show that some properties of oscillators are generic, while other properties of oscillators, which may be critical to understanding their role in neural circuits, are not common to all oscillators (164, 291). All oscillators, by definition, can be reset or entrained. However, neural oscillators may respond differently to steady current injection or synaptic inputs. Skinner and co-workers (285, 286) varied the balance of the two conductances in the simple Morris-Lecar model (210). In some parameter ranges, the oscillator maintains a relatively constant burst duration, and as it is depolarized, it increases in frequency. In other parameter ranges, the burst duration is sensitive to the level of injected current, and the cycle frequency first increases and then decreases in response to depolarization (285, 286). Therefore, these two types of oscillators will respond to synaptic inputs in different ways. Moreover, modulatory substances that change the relative strengths or properties of one or more of the currents in a neuronal oscillator may alter qualitatively the oscillator's response to synaptic inputs (e.g., Ref. 159).

Neurons that display plateau properties make rapid transitions between two relatively stable membrane potentials (182). When such a neuron is at a hyperpolarized resting potential, a short pulse of depolarizing current will trigger a sustained depolarization (plateau) that will long outlast the stimulus. The time constants of inactivation of slow inward currents play an important role in determining the duration and stability of the plateau. When in the plateau, a short hyperpolarization will terminate the plateau.

The ability to produce plateaus may be strongly influenced by the pattern of activity in a neuron. In *Helix* (248), P cells fire single action potentials when stimulated at low frequencies, but high frequencies of stimulation induce sustained plateaus. In this case, the transition is explained by Ca^{2+}-dependent inactivation of the outward currents that are responsible for spike repolarization (63). Other neurons may require a prior period of inhibition to initiate a plateau. If the neuron's resting potential is relatively depolarized so that the inward current sustaining the plateau is substantially inactivated, then hyperpolarization will be required to deinactivate this current before a plateau can be produced (e.g., Ref. 8).

Plateau properties in follower neurons decrease the importance of synaptic strength in networks (182, 183) because even modest hyperpolarizations or depolarizations can trigger transitions between states. In the extreme case of perfect bistability, a neuron with plateau properties will only make the transition between its two stable membrane potentials when perturbed. However, many neurons spontaneously make the transition between a hyperpolarized resting potential and a depolarized plateau associated with rapid firing. Many neurons make the transition in the opposite direction spontaneously due to inactivation of the currents that support the depolarized plateau. Recent work in both vertebrate and invertebrate preparations is showing that plateau properties are a common feature in many neurons of motor circuits (18, 62, 138–141, 160, 254, 262).

In some oscillatory neural networks, it is clear that plateau properties are crucial to pattern generation (5, 8, 9, 234). They permit rapid transitions between inactive and active periods upon termination or escape from inhibition and provide sustained periods of depolarization during which they release transmitter (5, 46, 72). In other cases, plateaus may be crucial for determining the phase relationships among pattern-generating neurons (e.g., Ref. 222).

The ability to produce plateaus is highly modified by modulatory inputs. The activation of plateau properties may be the mechanism by which a rhythmic motor system is activated by neural inputs (18, 77, 221, 262, 312). Modulation of plateau properties may influence the specific phase relationships in a rhythmic motor pattern (87, 222) or may alter its frequency (262).

2. Intrinsic properties are voltage dependent

Injected current and synaptic potentials can appreciably change the firing patterns of many neurons. Trivially, silent neurons often fire tonically when depolarized. More interestingly, some neurons burst when depolarized, while others may only generate bursts or plateau properties when hyperpolarized (178). Some neurons, such as those found in thalamocortical networks, switch between different modes of activity, depending on their membrane potential (175, 198, 199, 294) which in turn is dependent on modulatable leak channels. The effects of membrane potential on the firing patterns of neurons result from the steady-state activation and inactivation properties of the specific mixes of membrane currents that are present at each membrane potential.

Many neurons have slow conductances that influence their behavior and those of networks over long time scales. One such conductance is I_h, an hyperpolarization activated inward current that plays an important role in many bursting and plateauing neurons (4, 73, 79, 104, 161, 162, 198, 290). This conductance can be "invisible" in some circumstances but can be significant under others. It is important to remember that the electrical properties of a neuron when isolated from all synaptic inputs may not easily predict its activity in a circuit, if the synaptic inputs it receives move its membrane potential to regions where different voltage-dependent conductances are active than those in which the isolated neuron fires.

3. Modulation of intrinsic membrane properties

Modulatory inputs can markedly change the intrinsic properties of neurons by modifying one or more of the

voltage-dependent conductances of a neuron or by evoking novel conductances (123, 152, 182, 183). Examples of neuromodulatory regulation of bursting and plateau properties abound in the literature (123). The effects of neuromodulatory agents are seen at every level in motor systems, from sensory neuron, to interneuron, to motoneuron to muscle, in invertebrate and vertebrate preparations.

Sensory neurons play crucial roles in initiating and modifying rhythmic movements. Therefore, modulatory control of the gain of sensory responses will strongly influence movement (54, 280). There are three general mechanisms by which sensory pathways can be modulated so that a given stimulus produces a different strength output: *1*) modulation of the transduction process itself, *2*) modulation of the excitability of the primary sensory neurons so that a given change in conductance produced by the stimulus is more or less effective in activating the primary sensory neuron, and *3*) modulation of the release of transmitter from the sensory neuron terminals so that the efficacy of sensory neuron action potentials is altered.

There are now examples of modulation of many different types of sensory neurons. Particularly relevant to movement control are proprioceptors, pain and touch receptors, and sensory receptors that respond to wind direction. Crustaceans have several different classes of muscle receptors that respond to stretch and/or muscle tension (236). These include the abdominal muscle receptor organs and the oval organs, which provide sensory feedback for the ventilatory system. The response of these sensory receptors to a defined stretch or perturbation is modified by amines and peptides (236). A similar story is found in locusts, where the forewing stretch receptors are modulated by octopamine (253).

The effect of modulatory substances on the release of transmitter from sensory neurons has been extensively studied in both vertebrate and invertebrate nervous systems. The release of substance P and other sensory transmitters from dorsal root ganglion neurons is modulated by enkephalin and a variety of peptides (90, 212, 327), and the biophysical mechanisms underlying the control of transmitter release from these neurons are extensively studied (83).

Modulation of the efficacy of synaptic strength has been extensively studied in the sensory to motoneuron reflex pathways in *Aplysia* (43, 127). In this preparation, modulation of the reflex pathway is behaviorally relevant, has been characterized in biophysical and biochemical detail, and is one of the premier illustrations of how modulatory transmitters can change the gain of synaptic connections in a behavioral context (127).

The functional significance of a sensory stimulus depends critically on the conductances found in the interneurons driven by those sensory neurons. This principle is well illustrated in recent work in the locust flight system (255), in which bursting properties in flight interneurons act to amplify the effect of proprioceptive inputs.

In almost all rhythmic motor systems, the pattern-generating circuitry is upstream from the motoneurons that actually drive the muscles. Until very recently, the motoneurons in almost all preparations were thought to fire in response to central drive, but not to have any long-lasting regenerative properties that could shape the duration of the muscle activation. However, numerous reports have recently appeared that show clearly that modulatory substances can elicit plateau properties in motoneurons, in both vertebrate and invertebrate preparations (138–141, 161, 162).

Most vertebrate skeletal muscles fire action potentials that serve to trigger muscle contraction, since the surface depolarization is carried into the t-tubule system. In contrast, many invertebrate muscles are multiply innervated, and contraction is a graded function of depolarization (142). In these muscles, the dynamic properties of the neuromuscular junctions significantly influence tension and movement. For example, a neuromuscular junction that displays considerable facilitation will evoke more tension development subsequent to high-frequency stimulation than it will if the motoneuron is fired more slowly. In preparations such as these, the detailed patterning of the motor pattern will strongly shape the movement.

Circulating hormones and neuromodulatory cotransmitters can strongly modulate the tension development at both vertebrate and invertebrate muscles (23, 32, 33, 44, 170, 200, 295). This can arise if modulatory substances influence the presynaptic release of transmitter, or by direct actions on the muscle fibers themselves. Peptides or amines released from motoneurons or circulating as hormones can act directly to modify the voltage-dependent membrane properties of the muscle fibers (32, 33). This can influence the amount of tension production as well as the contraction and relaxation rates (252, 314, 315) and can also induce intrinsic oscillatory action in the muscle fibers themselves (170, 176, 200, 295).

The presence of strong oscillatory and/or plateau properties in muscles acts to amplify the response of the muscle to a synaptic input that may be relatively small (200). Therefore, in neuromuscular systems that show considerable direct modulation of the active conductances of the muscles themselves, it is possible to use the same motoneurons and muscle fibers to produce a very large range of forces, with relatively few neurons and muscle fibers. A particularly intriguing illustration of the importance of modulation of the neuromuscular junction is seen in a recent study of the locust ovipositor opener muscle (23). In this preparation, the neurally released peptide proctolin upregulates the strength of the nerve-evoked muscle contractions driven by the central pattern generator for oviposition digging. However, during the

expression of the behavior, the release of proctolin decreases, and the movements abate, although the ongoing motor patterns continue (23).

C. Properties of Synaptic Connections

The critical role of the strength of synaptic interactions for the operation of neuronal networks is appreciated in both the biological community and among neural network theorists. Indeed, changes in the strength of synaptic connections are often considered adequate explanations for the changes that underlie plasticity. Not only does this position neglect the critical importance of modulation of membrane properties for plasticity in neural networks, but oftentimes, dynamic features of synaptic transmission that are crucial for network operation are neglected (100).

Some of the first synaptic connections to be studied were found at vertebrate and invertebrate neuromuscular junctions. These classic preparations have some common features: *1*) the synaptic current is rapid, *2*) there is a short latency between the presynaptic action potential and the postsynaptic response, *3*) there is an anatomically well-defined synaptic structure, and *4*) the threshold for transmitter release is at a level of presynaptic membrane potential sufficiently depolarized that presynaptic action potentials are required for transmitter release. Many of the synaptic connections in the networks that generate rhythmic behavior are likely to share these features, but other types of synaptic organization also play significant roles in pattern generation.

1. Time courses of synaptic currents

Typically at vertebrate skeletal muscle neuromuscular junctions, the synaptic currents rise and fall within several milliseconds. Such rapid time course events are also common in the brain. In many preparations, trains of presynaptic action potentials also evoke slow synaptic potentials that follow more rapid events. The best-known example of this is seen in the vertebrate sympathetic ganglion, where trains of preganglionic action potentials elicit rapid, nicotinic excitatory postsynaptic potentials (EPSPs) followed by a slow inhibitory postsynaptic potential (IPSP), a slow EPSP, and a late slow EPSP, which have time courses from many milliseconds for the slow IPSP and EPSP to minutes for the late slow EPSP (146).

2. Colocalized neurotransmitters

It is now clear that many, if not most, neurons contain multiple neurotransmitter substances. One of the interesting questions for circuit analysis is understanding how these multiple neurotransmitters function. It is important to determine how activity patterns may result in the differential release of these substances (170). In several cases, it is known that peptide cotransmitters appear to be released only after high-frequency trains of presynaptic activity (64, 243, 316, 317), while the small molecule transmitters are released by each action potential. Because in most cases the peptide and amines colocalized with small molecules are responsible for slower time course postsynaptic actions (2, 29, 170), this means that the integrative action of a given presynaptic element in a network may change as its pattern of activity changes.

3. Graded release of neurotransmitter

Influx of Ca^{2+} through voltage-sensitive Ca^{2+} channels is the primary signal for transmitter release. Many neurons only release neurotransmitter in response to a rapid and large depolarization, such as that produced by an action potential, presumably because the Ca^{2+} currents in the presynaptic terminal require significant depolarization for activation. Other neurons release transmitter at relatively hyperpolarized levels of membrane potential, presumably because their presynaptic terminals have Ca^{2+} currents that are activated at more hyperpolarized levels of membrane potential (5).

Many pattern-generating networks employ graded synaptic transmission (41, 74, 105, 106, 194, 241, 276). In some preparations, graded transmission controls transmitter release by local interneurons that may never spike. In other preparations, neurons may fire action potentials for distance communication while the integration important for pattern generation is primarily graded (106). It has been suggested that graded transmission may play a role in stabilizing pattern-generating networks (163). The strength of graded synaptic connections is subject to considerable modulation (147–150).

The cable properties of neurons can interact with the threshold for transmitter release to produce interesting "gating" phenomena. For example, in neurons of the stomatogastric nervous system, antidromic spikes may fail to release transmitter while orthodromic spikes do so (203, 215). This occurs because the action potentials generated within the neuropil of the STG ride on top of a slow-wave depolarization that brings the cell to threshold for transmitter release. In contrast, antidromic action potentials that propagate into the neuropil from distal spike initiation zones depolarize the presynaptic terminals considerably less, thus releasing little or no transmitter (190, 203).

4. Electrical coupling

Electrical coupling among pattern-generating elements is common. It has been long appreciated that electrical coupling tends to synchronize the activity of the coupled neurons. However, there are increasing numbers of examples in which electrically coupled neurons do not

fire synchronously and may even fire out of phase (271). A theoretical study (275) illustrates that out-of-phase activity can be produced at low coupling strengths. Moreover, electrically coupled neurons may have quite different intrinsic membrane properties that contribute to the emergent properties of the networks they form (1, 185, 207). One important lesson for circuit analysis is that neurons that are silent and may be below their transmitter release threshold and may nonetheless contribute to pattern formation when these neurons are electrically coupled to other neurons, as they provide current through the electrical junctions that will influence the activity of their coupled partners (135, 159, 271).

D. Network Modules: Small Networks

As the connectivity diagrams of neural circuits become characterized, it is clear that each of these has its particular features (100). However, it is also clear that certain two and three cell groupings are ubiquitous and may serve as computational elements within neural circuits. These elements include such relationships as *1*) reciprocal inhibition, *2*) delayed feed-forward inhibition with feedback excitation, and *3*) electrical coupling and one-way inhibition.

Many of our ideas about small-network modules come from invertebrate preparations, where these are easily found and studied. Although vertebrate systems contain many more neurons, it is common to find classes of neurons lumped together and connectivity diagrams drawn among small numbers of "cells" where the cells are now groups of neurons. This illustrates one of the paradoxes that is found throughout the vertebrate system literature. On the one hand, researchers studying complex brain regions often assert that many of the properties of their systems depend on the emergent dynamics of large networks. On the other hand, these workers often draw simplified connectivity diagrams that resemble those that actually describe smaller invertebrate circuits and attempt to explain complex dynamics of large brain regions with these simplified diagrams. For this reason, it is critical to actually determine how the dynamics of small networks depend on the network architecture and the dynamics of the network components.

IV. SPECIFIC CASES: PHYSIOLOGICAL AND COMPUTATIONAL APPROACHES

A. Elemental Pattern Generators: Intrinsic Membrane Properties and Reciprocal Inhibition

Rhythmic activity within pattern-generating networks results from the combination of intrinsic electrical properties of the component neurons and their synaptic interactions. The simplest elemental pattern generators employ a pacemaker neuron or neurons that can serve as a source of the rhythm. Synaptic interactions with other network elements can modify this rhythm, but the inherent activity of the pacemaker neuron is dominant. The best-characterized example of this mechanism is the pyloric rhythm generator of the crustacean stomatogastric nervous system.

Other elemental pattern generators use neurons that have pacemaking properties, which in some cases can be modulated on and off, but reciprocal inhibitory synaptic interactions play a more important role in determining the rhythm. The elemental generators underlying *Clione* and *Xenopus* swimming and the leech heartbeat system are thought to represent such cases. The gastric system in the stomatogastric nervous system is another example in which network dynamics are an emergent process from the interaction of intrinsic membrane properties and synaptic connections.

1. Pyloric system

The simplest mechanism with which to generate a rhythmic motor pattern is to employ a pacemaker neuron or neurons that can serve as a source of the rhythm. The pyloric rhythm of the crustacean STG is one of the best understood central pattern-generating circuits. In this preparation, the ability of a single oscillatory neuron to generate bursts plays a particularly important role in the generation of the rhythm, although the phase relationships and frequency of the rhythm depend critically on network interactions and sensory and central modulation.

The pyloric rhythm consists of alternating bursts of activity in the motoneurons that dilate and constrict the pyloric region of the stomach of lobsters and crabs. The purest form of the pyloric rhythm is a five-phase rhythm (Fig. 1*A*). The core of the rhythm is a repeating cycle of activity in which the lateral pyloric (LP), pyloric (PY), and pyloric dilator (PD) neurons fire sequentially. The inferior cardiac (IC) routinely fires in LP time, and the ventricular dilator (VD) often fires in PY time. Additionally, there is a single interneuron, the AB neuron, that fires in time with the PD neurons. The frequency of the pyloric rhythm can vary from ~0.2 Hz to ~3 Hz but is commonly in the 1-Hz range during ongoing behavior (131, 256) or in in vitro preparations (135, 229, 230).

An unusual feature of the STG is that the pattern-generating networks are formed by the motoneurons and a few interneurons. Therefore, recordings from the STG motoneurons provide direct information about the motor pattern, as well as information about the connectivity and membrane properties that contribute to rhythm and pattern generation. Moreover, the small number of neurons within the STG (25–32, depending on species) allows the

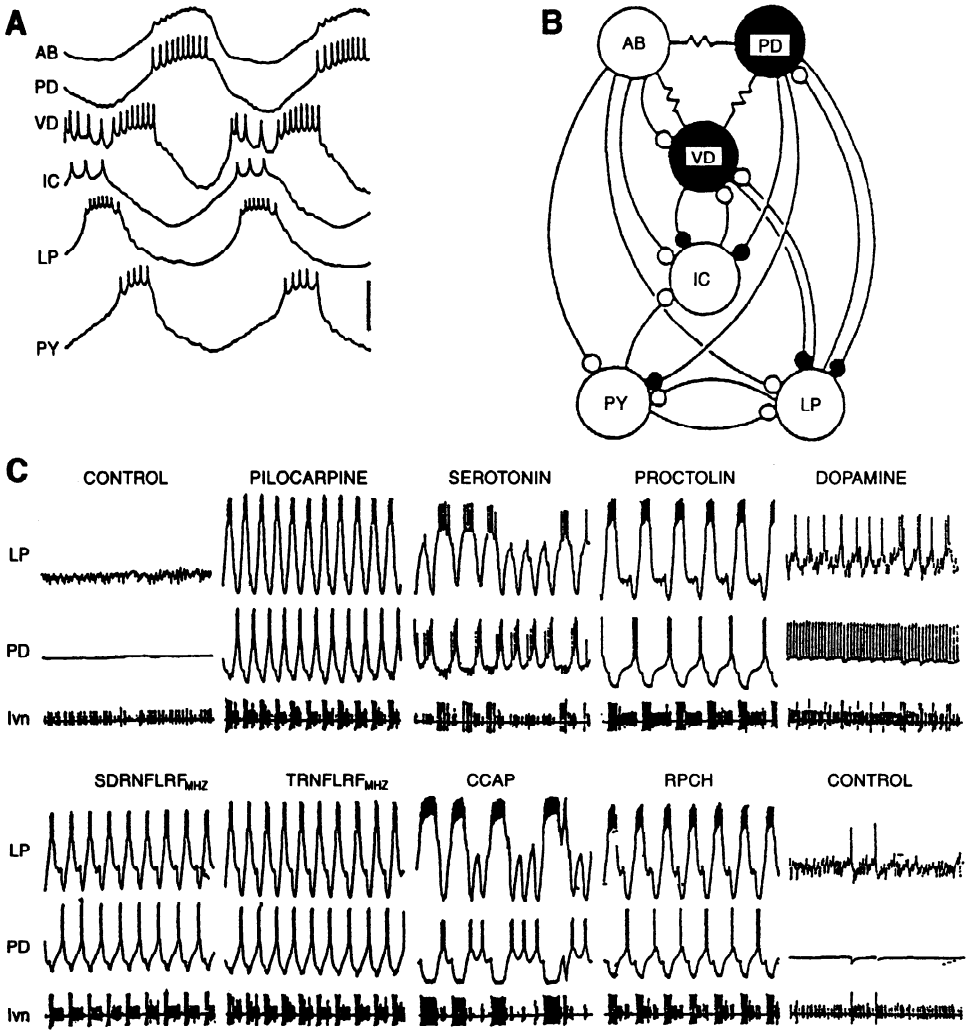

FIG. 1. Pyloric rhythm of crustacean stomatogastric ganglion. *A*: simultaneous intracellular recordings from 6 cell types that participate in pyloric rhythm. AB, anterior burster; PD, pyloric dilator; VD, ventricular dilator; IC, inferior cardiac; LP, lateral pyloric; PY, pyloric neurons. [Modified from Miller (205).] *B*: connectivity diagram of pyloric network of lobster *Panulirus interruptus*. Resistor symbols denote electrical connections, and circles represent inhibitory chemical synaptic connections. PD and VD neurons are cholinergic (solid), and other neurons are glutamatergic (open). [Modified from Hooper and Marder (135).] *C*: modulators produce characteristic and different forms of pyloric rhythm. Each panel shows simultaneous intracellular recordings from LP and PD neurons and an extracellular recording from lateral ventricular nerve (lvn). Stomatogastric ganglion was isolated by sucrose block, and preparation was washed between each application. RPCH, red pigment concentrating hormone; CCAP, crustacean cardioactive peptide. [Adapted from Marder and Weimann (189).]

simultaneous recording of a large enough number of elements of the network to make analysis feasible (e.g., Fig. 1*A*). Additionally, it is possible to delete single neurons from the network by photoinactivation subsequent to dye injection (206) and to block pharmacologically many of the chemical synaptic connections within the network (28, 85). With the use of a combination of these techniques, it has been possible to establish a connectivity diagram (Fig. 1*B*) for the pyloric rhythm and generate a qualitative description of how the pyloric rhythm is generated (186, 207, 208).

The AB neuron is the usual source of the pyloric rhythm, although when modulatory inputs are left attached to the STG, pyloric-type rhythms can persist after the AB neuron is killed (269). When isolated from the other pyloric network neurons, the AB neuron is able to generate bursts of action potentials (92, 122, 185, 207). The PD neurons depolarize and fire action potentials in time with the AB neuron because they are electrically coupled to the AB neuron. Thus the basic dilator phase of the pyloric rhythm is determined by the intrinsic oscillatory processes in the AB neuron, as shaped by the coupling to the PD neurons (1). The remaining neurons in the pyloric rhythm fire at various phase relationships that are determined by the synaptic connections among the remaining neurons and their intrinsic membrane properties. The LP and PY neurons are inhibited by the dilator group of the AB and PD neurons, but the LP neuron starts firing before the PY neurons. Factors that have been suggested to explain this difference in phase include the strength and time course of the synaptic potentials from the dilator group (86), the properties of transient outward current (I_A) in the follower neurons (120, 121, 124, 125, 296), and the I_h in the follower neurons (103, 125, 179).

Although the STG contains only 30 neurons, the nerve that connects the STG to the rest of the central nervous system (stn) has at least 60 fibers (61). Some of the stn fibers are axons from STG neurons; however, ~50 stn fibers are projections from somata in the brain and the commissural ganglia (61) that contain a large number of different modulatory substances (181, 188). Different modulatory substances evoke different forms of the pylo-

ric motor pattern, in which the component neurons fire bursts of varying intensities and varying phase relationships (Fig. 1*C*; Refs. 91, 119, 186, 189).

The AB and PD neurons differ in terms of their transmitter content (184), their responses to modulators (92, 135, 185, 187), and their intrinsic membrane properties (18, 185, 208). Each of these differences plays an interesting role in explaining how modulatory substances influence pyloric network dynamics.

A number of different substances activate the pyloric rhythm by directly activating the pacemaker AB neuron. These include amines (92, 185), peptides (135), and cholinergic agonists (187). However, it is important to remember that the frequency of the network depends not only on the frequency of the AB neuron, but also on the properties of the remaining neurons in the network, as has been shown physiologically (135) and theoretically (159, 271).

The differences in the intrinsic properties of the AB and PD neurons play a critical role in shaping the waveform of the oscillator ensemble. Although the AB neuron is the "pacemaker" for the pyloric rhythm, the properties of the AB neuron are critically shaped by virtue of its electrical coupling with the PD neurons. The isolated AB neuron is a constant burst duration oscillator (1), while the AB/PD electrically coupled ensemble maintains a constant duty cycle (1). The mechanism by which the oscillator waveform is transformed by the intrinsic properties of the electrically coupled PD neuron may be important for understanding numerous systems in which oscillatory elements are electrically coupled to elements with significantly different intrinsic membrane properties.

The AB neuron releases glutamate and the PD neurons release acetylcholine. The glutamatergic IPSPs are more rapid than the cholinergic IPSPs (85, 184). Therefore, the relative amounts of AB or PD released neurotransmitters control the relative duration of the inhibition the pacemaker group produces on the follower neurons (86) and can control the phase of follower neuron activity. Although the AB and PD neurons are electrically coupled, they are differentially modulated, and therefore, their contribution to transmitter output can vary as a function of synaptic and modulatory mixes. This provides an interesting mechanism by which phase relations of the follower neurons can be simply modulated (86). Other mechanisms for controlling and modulating the phase of the follower neurons depend on the properties of the voltage-dependent conductances in the follower neurons (77, 120, 121, 124, 179, 221, 296). In fact, the "take-home message" from this work on the pyloric rhythm is that the timing of the rhythm depends critically on the interplay between the strength and time course of the synaptic inhibition and the intrinsic membrane currents of the follower neurons. Indeed, modulation of any of these parameters will influence the phase of the follower neuron activity.

The pyloric network in its simplicity illustrates several very important lessons for the study of neural networks.

1) Even in a network that is "completely defined" in terms of the identity of the constituent neurons and their interactions, it is impossible to predict the dynamics of a network without fully understanding the dynamic properties of the individual neurons and their connections. Moreover, this process almost certainly requires some computational and or mathematical models.

2) Even very simple networks can produce multiple outputs, if any of the intrinsic or synaptic currents that participate in network function are subject to modulation.

3) The frequency of a pacemaker-driven network is not solely determined by the frequency of the isolated pacemaker, but network interactions influence it as well. Likewise, the phase of each of the components of the network is determined by both synaptic interactions and intrinsic membrane properties.

2. *Clione and Xenopus swimming*

The pelagic mollusk *Clione* swims continuously by flapping its winglike parapodia at ~1 Hz. Its isolated pedal ganglia produce alternating bursts in presumptive swim motoneurons, which elevate and depress the parapodia (11). In the pedal ganglia, two antagonistic populations of electrically coupled premotor interneurons form reciprocal inhibitory synapses (12–14, 263) (Fig. 2). These populations have different electrical and synaptic properties but produce similar alternating single plateaulike potentials of up to 150 ms in duration, that drive the elevator (dorsal phase) and depressor (ventral phase) motoneuron bursts (13, 14, 263) (Fig. 2*B*). All of the interneurons show strong postinhibitory rebound (13, 263), and at least some of them can produce regular trains of the plateaulike potentials when isolated from the ganglion (10). Removal of one of these populations from the circuit by strong hyperpolarization of a single neuron has been reported to halt oscillation in the network (263) (Fig. 2*B*), but other reports indicate that oscillation can persist with such hyperpolarization (11, 16).

In recent studies, Panchin et al. (235) were able to block inhibitory transmission from the ventral phase interneurons to the dorsal phase interneurons using atropine. Under these conditions, both populations continue to alternate, albeit at a somewhat lower frequency. These authors have interpreted this finding as a strong indication that endogenous pacemaking by the interneurons is the dominant mechanism for rhythm generation. Nevertheless, reciprocal inhibition and postinhibitory rebound shape the final alternating pattern, and cycle period is determined largely by the duration of the reciprocal inhibitory synaptic potentials (16). In *Clione*, these IPSPs are long (100 ms), at least in part due to the long duration of the "spikes" in the swim interneurons.

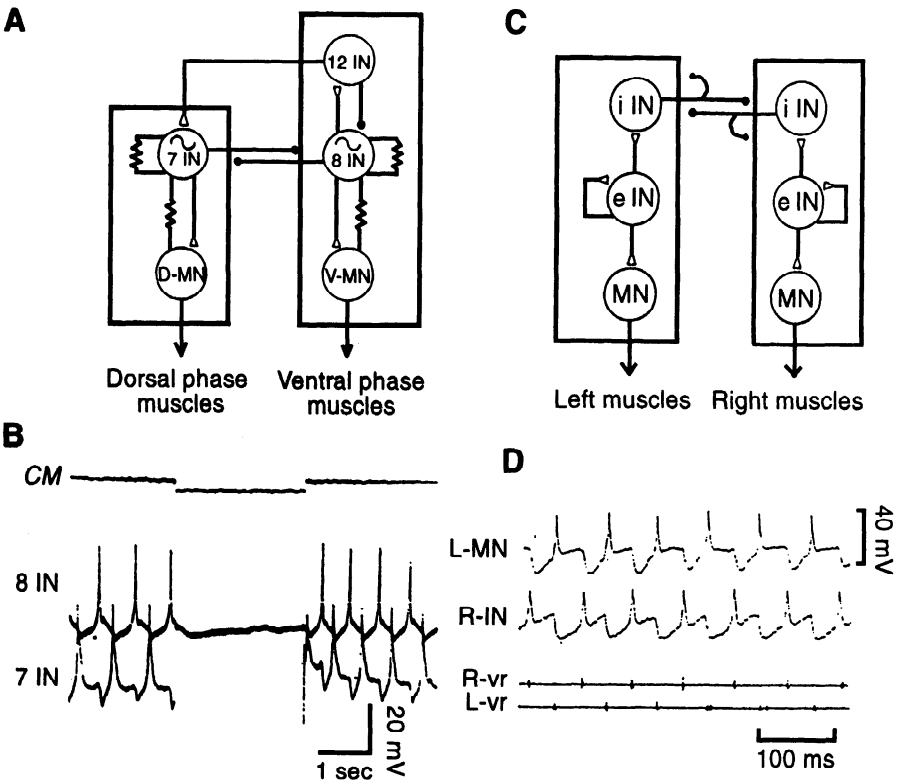

FIG. 2. *A*: synaptic connections in swimming pattern generator of *Clione*. IN, interneurons; D-MN, dorsal motoneurons; V-MN ventral motoneurons. Seven IN and eight IN interneurons form reciprocal inhibitory synapses that together with their intrinsic membrane properties lead to oscillation in swimming pattern generator. Connections from 12 IN interneurons to 7 IN/8 IN oscillator stabilize oscillation during intense swimming activity. [From Arshavsky et al. (16).] *B*: oscillations in reciprocally inhibitory 7 IN and 8 IN interneurons cease when one of the interneurons is hyperpolarized strongly with injected current (CM). [From Satterlie (263).] *C*: synaptic connections in swimming pattern generator of *Xenopus*. iIN, inhibitory interneurons; eIN, excitatory interneurons; MN, motoneurons. The iIN interneurons form reciprocal inhibitory synapses across midline that together with their intrinsic membrane properties lead to oscillation in swimming pattern generator. [From Arshavsky et al. (16).] *D*: oscillations in a left motoneuron (L-MN) and right interneuron (R-IN) and rhythmic firing in right (R-vr) and left (L-vr) ventral roots during swimming motor pattern. [From Arshavsky et al. (16).] In *A* and *C*, excitatory connections are indicated by open triangles, inhibitory connections are indicated by solid circles, and electrical junctions are indicated by resistor symbols.

The segmental motor pattern that underlies swimming in early stage tadpoles from *Xenopus* bears remarkable similarities to the *Clione* swim pattern, and the pattern-generating networks that give rise to these patterns are organized along parallel lines (16). In each spinal segment, motoneurons innervating axial muscles on each side alternate spikelike activity that produces the alternating lateral undulations of the body associated with swimming. In each spinal hemisegment, inhibitory premotor interneurons, which form reciprocal inhibitory connections across the midline (Fig. 2*C*), produce alternating spikelike potentials (Fig. 2*D*) that bear a remarkable similarity to those produced by the swim pattern-generating interneurons of *Clione*. Unfortunately, these interneurons have not been well characterized. It is assumed that, like the motoneurons, they fire only once during prolonged depolarization (65, 288), and they show strong postinhibitory rebound when they are depolarized (288). Rebound is thought to be important in pacing rhythmic activity, and simulated spinal networks of these interneurons generate a robust rhythm based on reciprocal inhibition and rebound. However, other mechanisms certainly contribute to rhythmicity in the network. In recent experiments, K^+ currents were blocked with tetraethylammonium or 3,4-diaminopyridine and caused stereotypical disruptions in the rhythm, indicating their importance in rhythm generation (302). Moreover, hemisected spinal cord preparations can generate a swimlike rhythm (287); this rhythm is thought to arise from recurrent inhibition of swim interneurons by ipsilateral glycinergic axons (67) and resultant postinhibitory rebound. In such hemisected preparations, some rhythmic neuronal discharge in motoneurons can be evoked by sensory stimulation even when glycinergic inhibition is blocked with strychnine (287), providing some evidence for inherent oscillatory neuronal properties.

Interesting contrasts and similarities between the *Xenopus* and *Clione* swim pattern generators highlight principles of organization. In both systems, at least under some conditions, inherent rhythmic activity by itself sustains rhythmicity. Postinhibitory rebound is pronounced in both systems, reciprocal inhibition produces alternation, and cycle period is determined largely by the duration of the reciprocal inhibitory synaptic potentials (16). In contrast to the *Clione* swim generator, which operates nearly continuously, that of *Xenopus* is geared to episodic activity. Excitation necessary to maintain the prolonged depolarization necessary for a swimming bout in *Xenopus* is provided by activation by sensory input of excitatory interneurons that use long dual-component [*N*-methyl-D-aspartate (NMDA) and non-NMDA] synaptic potentials; mutual excitation within the excitatory interneuron pool sustains activity and leads to a summed steady depolarization of the swim interneurons (66). Modeling studies indicate that non-NMDA-mediated mutual excitation can sustain oscillation but that NMDA-mediated mutual excitation, enhancing postinhibitory rebound, acts to stabilize swimming activity and extend its lower frequency range,

and it steepens the dependence of frequency on synaptic drive (259). Excitation within the *Clione* swim generator is sustained by electrical coupling within the reciprocally inhibitory interneuron pools (12, 13). Descending modulatory interneurons can also provide incremental excitation to initiate swimming activity should it stop or to accelerate ongoing activity, and during rapid swimming, a new class of depressor swim interneuron is recruited, which feeds back inhibition to the depressor interneurons and excitation to elevator interneurons (14, 15, 264, 265). Another fundamental difference between the two pattern generators relates to the distributed nature of the undulatory swimming in *Xenopus* tadpoles. Segmental axial muscles must be coordinated longitudinally to produce a swimming wave. On a neural level, each segment is thought to have its own pattern-generating network, and these segmental oscillators must be coordinated longitudinally. While this conception is useful, as we shall discuss below with reference to leech and lamprey swimming, systems controlling locomotion based on axial muscles can also be viewed as distributed, producing a spatially as well as a temporally varying pattern. This is contrasted to the concentrated *Clione* system where temporal aspects of the pattern predominate.

3. *Leech heartbeat*

The rhythmic constrictions (0.1 Hz) of the bilateral heart tubes of the leech, *Hirudo medicinalis*, are paced and coordinated by the rhythmically active segmental heart (HE) motoneurons (47) (Fig. 3*B*). A network of seven bilateral pairs of the heart (HN) interneurons, one pair of which is located in each of the first seven segmental ganglia of the nerve cord, produces rhythmic activity that paces the heart motoneurons (45, 47, 266) (Fig. 3*A1*). This network is continuously active in the isolated nervous system and produces a fictive motor program that can account for the constriction pattern of the hearts observed in situ. The synaptic connections among the interneurons (Fig. 3*A1*) and from the interneurons to the motoneurons are inhibitory.

The first four pairs of heart interneurons can reset and entrain the rhythm of the entire pattern-generating network of interneurons (Fig. 3*A2*). The other three pairs of HN neurons are followers of these anterior pairs (247). Two foci of oscillation in this network have been identified in the third and fourth ganglia, where the oscillation is dominated by the reciprocal interactions of the third and fourth pair of HN interneurons, respectively (245). Reciprocally inhibitory synapses between the bilateral pairs of HN neurons in these ganglia (Fig. 3, *A2* and *B*), combined with an ability of these interneurons to escape from inhibition and begin firing, pace the oscillation (245, 246). Thus each of these two reciprocally inhibitory heart interneuron pairs can be considered an elemental oscillator. The HN interneurons of the first and second ganglia act as coordinating fibers, serving to link these two elemental oscillators, thus forming the beat timing oscillator for the system (246) (Fig. 3*A2*). The beat timing oscillator network projects by inhibitory synapses to the more

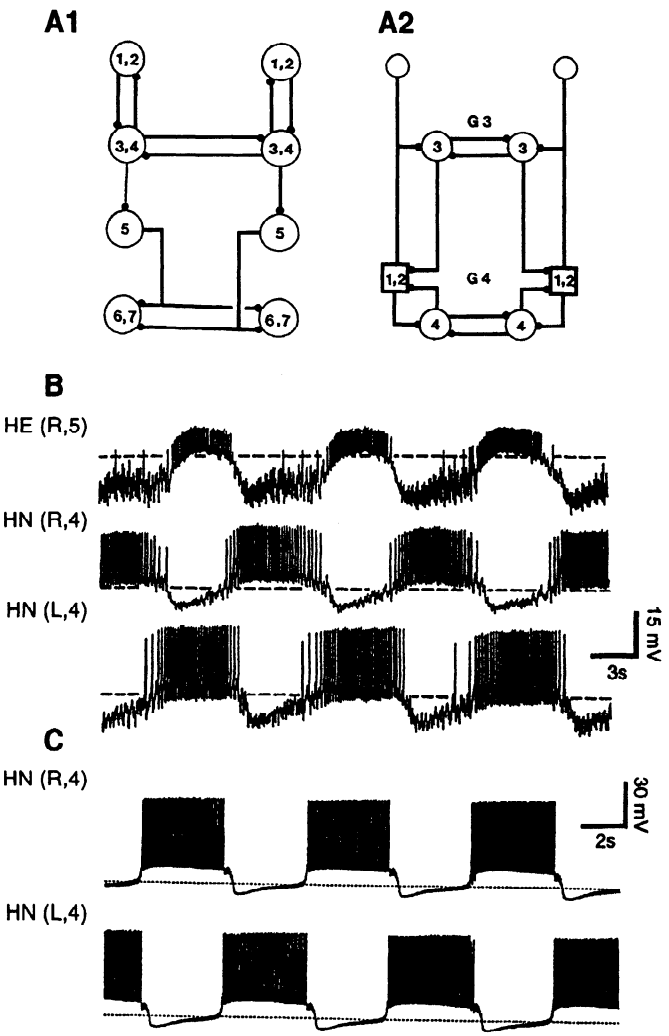

FIG. 3. Synaptic connections and oscillations in network of leech heart interneurons. *A1*: network of 7 identified pairs of heart interneurons (HN cells) responsible for generation and bilateral coordination of heartbeat. Cells that make similar connections and oscillate in phase are lumped together. All synaptic connections shown are inhibitory. *A2*: heartbeat timing oscillator includes 2 elemental oscillators in *ganglia 3* and *4*. These oscillators are connected via inhibitory connections with *cells HN(1)* and *HN(2)*. *B*: oscillations in an elemental heart interneuron oscillator. *Cells HN(R,4)* and *HN(L,4)* oscillate in antiphase. *Cell HE(R,5)* as well as all other ipsilateral heart motoneurons caudal to it receive inhibition from *cell HN(R,4)*. Oscillations in heart motoneurons are driven by input from HN cells. HE(R,5) trace shows large inhibitory postsynaptic potentials during inhibited phase, partially provided by *cell HN(R,4)*, and oscillates in antiphase with *cell HN(R,4)*. Dashed line marks a potential of −50 mV. *C*: oscillations in model elemental oscillator. Graded and spike-mediated inhibition from each cell to its contralateral homologue and intrinsic membrane properties enables cells to produce oscillations in antiphase with a period of ~8 s. Amplitude and frequency of action potentials are larger than in heart interneurons. Dashed line marks a potential of −50 mV. [From Nadim et al. (220).]

posterior heart interneurons, which are involved in intersegmental coordination of the motoneurons (Fig. 3*A1*).

Several ionic currents have been identified in single-electrode voltage-clamp studies that contribute to the activity of oscillator heart interneurons. These include, in addition to the fast Na^+ current that mediates spikes, two low-threshold Ca^{2+} currents (5) [one rapidly inactivating (I_{CaF}) and one slowly inactivating (I_{CaS})], three outward currents (282) [a fast transient K^+ current (I_A) and two delayed rectifier-like K^+ currents, one inactivating (I_{K1}) and one persistent (I_{K2})], a hyperpolarization-activated inward current (I_h) (79; mixed Na^+/K^+, reversal potential = −20 mV) (4), and a recently discovered low-threshold persistent Na^+ current (I_P) (234). The synaptic inhibition between oscillator interneurons consists of a graded component that is associated with the low-threshold Ca^{2+} currents (5) and a spike-mediated component that appears to be mediated by an undescribed high-threshold Ca^{2+} current (283). Spike-mediated transmission is sustained even at the high spike frequency observed during normal bursting (223, 224), while graded transmission wanes during a burst, owing to the inactivation of low-threshold Ca^{2+} currents (5). Blockade of synaptic transmission with bicuculline leads to tonic activity in oscillator heart interneurons and Cs^+, which specifically blocks I_h and disrupts normal bursting. In reduced Na^+ salines, spikes are blocked, and oscillations based solely on graded synaptic transmission occur (8, 9). Dynamic clamp studies, in which reciprocal inhibition was artificially restored in bicuculline-treated oscillator interneuron pairs, showed that even nonfatiguing inhibition sustains oscillation (284).

Much of this biophysical data was incorporated into a first generation conductance-based model of an elemental (2-cell) oscillator, using standard Hodgkin-Huxley (134) representations of each voltage-gated current. Synaptic connections were modeled with a synaptic transfer function that related transmitter release to presynaptic Ca^{2+} buildup and decline, via low-threshold Ca^{2+} currents and a Ca^{2+} removal mechanism, respectively (46, 72). The first generation model simulated the essence of the observed oscillation and showed the importance of I_h in regulating oscillation period through escape from inhibition. It had several flaws, however. Most importantly, there was no specific formulation for spike-mediated transmission, and discrete IPSPs were not observed in the model.

A second generation model has been recently formulated that adds spike-mediated synaptic transmission and addresses several other minor flaws of the older model with new experimental data (220, 233). Free parameters in the model were the maximal conductance (g_{ion}) for each current (voltage gated or synaptic). The g_{ion} values were adjusted to be close to the average observed experimentally. The reversal potential (E_{ion}) for each current, except leak current (I_l), was determined experimentally and was considered fixed. Final selection of parameters to form a canonical model was dictated by model behavior under control conditions, passive response of the model to hyperpolarizing current pulses, and reaction of the model to current perturbations. The model cells were required to fire tonically when all inhibition between them was blocked, because the real neurons fire tonically in bicuculline.

The canonical model generates activity that closely approximates that observed for an elemental oscillator (Fig. 3*C*). Analysis of current flows during this activity indicates that graded transmission occurs only at the beginning of the inhibitory period, acting to turn off the opposite neuron; sustained inhibition of the opposite neuron is all spike mediated. The inward currents in the model neurons act to overcome this inhibition and force a transition from off to on. The I_l always acts to drive the membrane toward its reversal potential (−52.5 mV), and I_h is slowly activated by the hyperpolarization-associated inhibition, adding a delayed inward current that drives the activation of I_P and eventually the low-threshold Ca^{2+} currents (I_{CaS} and I_{CaF}). These regenerative currents form a plateau that supports burst formation. Because it does not inactivate, I_P provides steady depolarization to sustain spiking, while the low-threshold Ca^{2+} currents help force the transition to the burst phase and provide graded inhibition to silence the opposite neuron, but inactivate as the burst proceeds. Outward currents also play important roles. The K^+ current I_{K2}, which activates and deactivates relatively slowly and does not inactivate, regulates the amplitude of the depolarized plateau that underlies the burst, whereas I_{K1}, which activates and deactivates relatively quickly and inactivates, controls spike frequency. Parameter searches in this model indicate that it is robust to large changes in g_{ion} and that the strength of spikes that mediate inhibition and magnitude of I_h conductance are particularly important in regulating period (233).

Detailed modeling studies of this types are necessary if we are to understand how reciprocal inhibition interacts with intrinsic membrane properties in other systems to produce oscillation.

4. General theoretical considerations on half-centers

Half-center oscillations have been studied by theorists for many years (e.g., Ref. 244). A very important conclusion from recent theoretical work is that reciprocal inhibition can produce synchrony (301) when the synaptic inhibition is slow relative to action potential or burst that elicits the synaptic inhibition. Indeed, a large number of behaviors can be obtained from reciprocally inhibitory neurons with noninstantaneous synaptic connections when the parameters controlling synaptic release are varied (274).

A general theoretical framework for understanding how reciprocally inhibitory neurons oscillate was developed by Wang and Rinzel (306). Their model neurons are minimal, consisting of a synaptic conductance that is a sigmoidal function of presynaptic membrane potential with a set threshold and instantaneous kinetics, a constant leak conductance, and a voltage-gated postinhibitory rebound conductance (g_{pir}). The g_{pir} is derived from a quantitative model of a T-type calcium current in thalamic neurons (306); it activates rapidly and inactivates slowly and is strongly inactivated at rest so that "hyperpolarization of sufficient duration and amplitude is required to deinactivate" g_{pir} to produce "rebound excitation after removal of hyperpolarization." The authors note that an I_h "would have a expression similar to" g_{pir}, and thus their model should be relevant to oscillators that employ I_h.

Two fundamentally different modes of oscillation appear in the model, "release" and "escape" (306). In the release mode, the inactivation of g_{pir} erodes the depolarized or active state of a neuron so that it falls below threshold for synaptic transmission. Consequently, its partner is released from inhibition and rebounds into the active depolarized state. By simply increasing g_{pir}, the escape mode can be realized. In the escape mode, once g_{pir} becomes deinactivated by the hyperpolarization associated with inhibition, it activates and overcomes the synaptic current so that the neuron escapes into the active phase. In the release mode, the transition from the inactive state to the active state is controlled by the active presynaptic neuron. In the escape mode, the transition from the inactive state to the active state is controlled by the inactive postsynaptic neuron.

Skinner et al. (285) expanded and clarified this model. Their neurons were correspondingly simple, employing the well-known Morris-Lecar equations (210), representing noninactivating Ca^{2+} and K^+ currents. Each contains a synaptic conductance that is fully activated when the presynaptic membrane potential crosses a set threshold and has instantaneous kinetics. They describe four modes of oscillation, two of which correspond to escape and two of which correspond to release. The submodes are differentiated by whether the releasing cell releases its partner by a transition from the active state to the off state (intrinsic release) or because its membrane potential crosses below threshold for synaptic inhibition (synaptic release), and by whether the escaping cell escapes because it crosses the threshold for transition from the off to the on state (intrinsic escape) or because it crosses the threshold for synaptic inhibition of its partner (synaptic escape). In this model, the period is relatively independent of synaptic threshold over a broad range when the intrinsic mechanisms operate, while the period is sensitive to changes in synaptic threshold for the synaptic mechanisms. For synaptic escape, period varies directly with threshold, while for synaptic release, period varies inversely with threshold. As threshold is increased, the system moves through synaptic escape (period increases with increasing threshold), intrinsic escape (period is insensitive to threshold), and synaptic release (period decreases with increasing threshold). Changes in the steepness of the synaptic transfer (sigmoidal function of presynaptic membrane potential) blurs the distinction between the modes and narrows the range of synaptic thresholds over which a constant period is maintained (i.e., the domain of intrinsic escape).

Using tonically firing gastric mill motoneurons from the crab STG, Sharp et al. (274) constructed reciprocally inhibitory two-cell networks using artificial synapses (half-sigmoidal presynaptic voltage-postsynaptic conductance relation) produced with the dynamic clamp (273, 274). These networks did not oscillate readily until artificial I_h were added to each with the dynamic clamp. These studies confirm the more theoretical studies of Skinner et al. (285); period is sensitive to changes in synaptic threshold for the synaptic mechanisms, and the domain of intrinsic escape is narrow due the half-sigmoidal synaptic threshold. Moreover, these studies demonstrate that modifications of the synaptic release threshold such as those seen with neuromodulators in the STG (150) are sufficient to move a network from the synaptic escape to the synaptic release mode of operation.

It appears that the heart interneuron oscillator operates in the escape mode. Whenever I_h is sufficiently activated to overcome the waning synaptic current, a transition from the inactive state to the active state occurs (220, 233). However, it is not clear whether this escape should be considered intrinsic or synaptic, because the gradual transition from the active to inactive states, and the gradual dependence of synaptic transfer on presynaptic potential, preclude any discrimination. In contrast, the *Clione* swim oscillator appears to operate in the intrinsic release mode. "Spike" (active state) termination shuts off inhibition and allows the opposite cell to rebound into the active state. Perhaps this mode is more suited to the operational frequency range of this oscillator, which is ~10 times faster that the leech heartbeat oscillator.

Considerable attention has been given to exploring the role of reciprocal inhibition and postinhibitory rebound in many other rhythmic networks, including several discussed below (3, 6, 7, 34, 93, 95, 112, 117, 261, 277–279, 303, 304).

5. *Gastric rhythm*

Inside the stomach of crustaceans, there are three teeth that grind and chew food. The lateral teeth and the medial tooth can display a variety of movements, including ones in which the lateral and medial teeth operate separately, and at least two modes in which the three

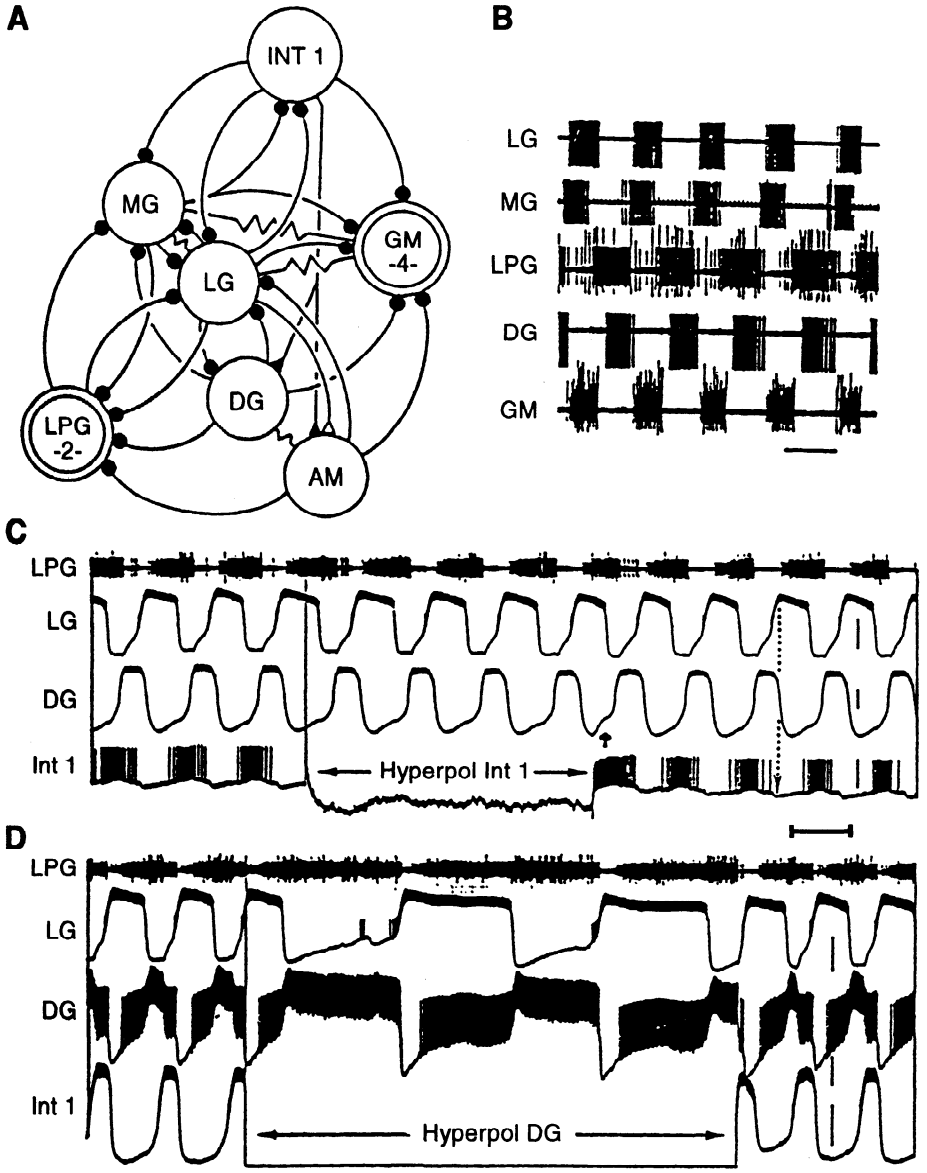

FIG. 4. Gastric mill rhythm of stomatogastric ganglion of lobster *Panulirus interruptus*. *A*: connectivity diagram for gastric network. INT 1, interneuron 1; GM, gastric mill neurons; MG, medial gastric neuron; LG, lateral gastric neuron; DG, dorsal gastric neuron; AM, anterior median neuron; LPG, lateral posterior gastric neuron. Resistor symbols designate electrical synapses, and solid circles represent chemical inhibitory synapses. *B*: extracellular recordings from motoneurons showing gastric mill motor pattern. *C*: simultaneous intracellular recordings from LG, DG, and INT 1 and extracellular recording from motor nerve carrying LPG units. Effects of hyperpolarization of INT 1 (*C*) and DG (*D*) during ongoing gastric rhythms elicited by pilocarpine application are shown. Calibrations: 10 mV, 10 s. [From Elson and Selverston (87).]

teeth are coordinately active. Heinzel (128, 129) used an endoscope to visualize the movements of the teeth in restrained animals. From these data, Heinzel (128, 129) characterized two main modes of chewing: the "squeeze" and the "cut and grind." In the squeeze mode, the cusps of the lateral teeth move toward the cusp of the medial tooth and the medial tooth moves forward, and the cusps meet. In the cut and grind mode, the medial tooth moves back while the lateral teeth move toward the midline. Then the medial tooth moves forward as the lateral teeth move backward and grind their cusps along the surface of the medial tooth.

The motoneurons that move lateral teeth and the medial tooth are found in the STG (Fig. 4). The first detailed attempt to understand the generation of the gastric mill rhythm (Fig. 4*B*) was that of Mulloney and Selverston (216, 217, 270). This work gave the first description of the connectivity (Fig. 4*A*) among the motoneurons and a single interneuron, INT 1, in the STG that were considered to constitute the central pattern generator for the gastric mill rhythm.

Unlike the case of the pyloric rhythm, there is no single pacemaker neuron for the gastric mill rhythm (217, 268), but the gastric rhythm appears to be a largely emergent network phenomenon. In particular, there are numerous sets of reciprocal inhibitory connections among the neurons that participate in the gastric rhythm (Fig. 4*A*), and the manner in which these are linked together to produce the gastric rhythm has been modeled (261).

As is the case of the pyloric rhythm, the gastric rhythm is richly modulated (87, 130, 312). However, recent work has shown that the generation of the gastric rhythm is quite complex. Elson and Selverston (87) studied the gastric network in *Panulirus interruptus* in the presence

of muscarinic cholinergic agonists and showed that the dorsal gastric (DG) neuron generates strong plateau potentials in the presence of pilocarpine (Fig. 4*C*). Similarly, Weimann et al. (312) found that the DG neuron in *C. borealis* generates strong plateau potentials in the presence of SDRNFLRF-NH_2. The importance of plateau potentials induced by activation of inputs from anterior ganglia is clear (222).

Recent work has further complicated and illuminated the circuitry underlying the generation of the gastric rhythm in the crab *C. borealis* (59, 60, 231). It is now clear that there are both electrical and chemical synaptic connections between the terminals of identified modulatory input fibers and the neurons of the gastric mill circuit. Indeed, at least in the crab, it now appears that these local circuit interactions are a necessary part of the connectivity that generates gastric rhythms (59). Thus the gastric rhythm can be best thought of to be an emergent product that depends on synaptic interactions among the STG neurons, between STG neurons and modulatory inputs, and the effects of modulators that evoke plateau capabilities in the STG neurons themselves.

B. Intersegmental Coordination

Swimming in lampreys and leeches poses a series of fascinating problems for the neural control of locomotion. Both animals move through the water by producing a traveling wave of body undulation that propels the animal. In both cases, a single wavelength is maintained in the body regardless of swimming frequency. To obtain the largest thrust at a given swim frequency, the animal should shape its body into a half-wave to produce the greatest possible wave amplitude (110), but this waveform is unstable and would lead to pitching of the head. A single wave in the body represents an ideal compromise between the conflicting strategies for thrust efficiency and stability (110) and has been adopted by both the leech (168) and the lamprey (108, 109, 305, 321). Therefore, the underlying motor program must provide for intersegmental phase differences that are invariant with swim period: phase constancy. Given that these animals can swim over a large frequency range (2-fold in leeches, >10-fold in lampreys), this creates a formidable problem in the coordination of segmental pattern-generating networks. In the lamprey, this problem is compounded by the ability of the animal to swim backward as well as forward, requiring reverse coordination of the segmental oscillators (114).

In both leeches and lampreys, the isolated nerve cord can generate fictive swimming motor patterns that resemble closely those seen in the animal (58, 167). To obtain fictive swimming in leeches, the cord is activated by stimulating a peripheral nerve (167) or by stimulating a gating or trigger neuron (34, 310). To obtain fictive swimming in lampreys, the cord is bathed in excitatory amino acids such as D-glutamate (0.25–1 mM) (35, 58), which substitutes for the normal pathways of swim activation. Isolated cord preparations that generate fictive swimming and semi-intact preparations in which a portion of the nerve cord is dissected but the ends of the animal still make swimming movements (168) have been invaluable for understanding the neural circuits that underlie the generation and intersegmental coordination of these motor patterns.

How are the fictive motor patterns of the isolated nerve cord preparations related to the patterns of muscular activity and movement seen in intact animals and semi-intact preparations? In freely swimming leeches, the traveling propulsive wave runs from the 1st through the 18th midbody segment, and intersegmental phase lags in the body wave are near 20° (~1 full wave in the body). When body wall movements and motor bursts in brainless suspended animals were compared directly with motor bursts in the subsequently isolated nerve cords, intersegmental phase lags were ~16, 12, and 8° per segment, respectively, for the body wave, for the motor bursts in the brainless suspended preparation, and for the motor bursts in the isolated nerve cord (168, 169, 237) (Fig. 5*D*). These studies suggest that sensory feedback from body wall movements helps to establish the intersegmental phase lags in motor bursts (95). They also indicate that the mechanical properties of the skeletal-motor system (hydroskeleton plus muscles) and the hydrodynamics of the body contribute to the larger phase lag observed in the animal's movement compared with its motor bursts (95).

In freely swimming lampreys, the traveling propulsive wave runs from near the head to the tail over ~100 segments, and intersegmental phase lags in the body wave are near 5° [0.72 ± 0.07 (SD) waves in the body], while the muscle activity (EMG) in the same animals showed an intersegmental phase lag of ~3.6° per segment [1.05 ± 0.10 (SD) waves of muscle activity in the body] (321). When muscle activity (EMG) in intact and spinal lampreys was compared with motor bursts in the subsequently isolated nerve cords, intersegmental phase lags were ~3.6° (or 1%) per segment for the muscle activity in both the intact and spinal lamprey and for the motor bursts in the isolated nerve cords (305) (Fig. 5*B*). The similarity in the intersegmental phase lags for muscle activity in intact lampreys and motor bursts in isolated nerve cords shows that sensory feedback from body wall movements is not necessary to establish the intersegmental phase lags in motor bursts. The discrepancy between the phase lags for swimming movements (5° per segment) and the phase lags in muscle activity in intact and spinal animals and motor bursts in isolated spinal cords (3.6° per segment) indicates that the mechanical properties of the skeletomotor system and the hydrodynamics of the body contribute to the larger phase lag observed in the animal's movement compared with its motor output (305, 321).

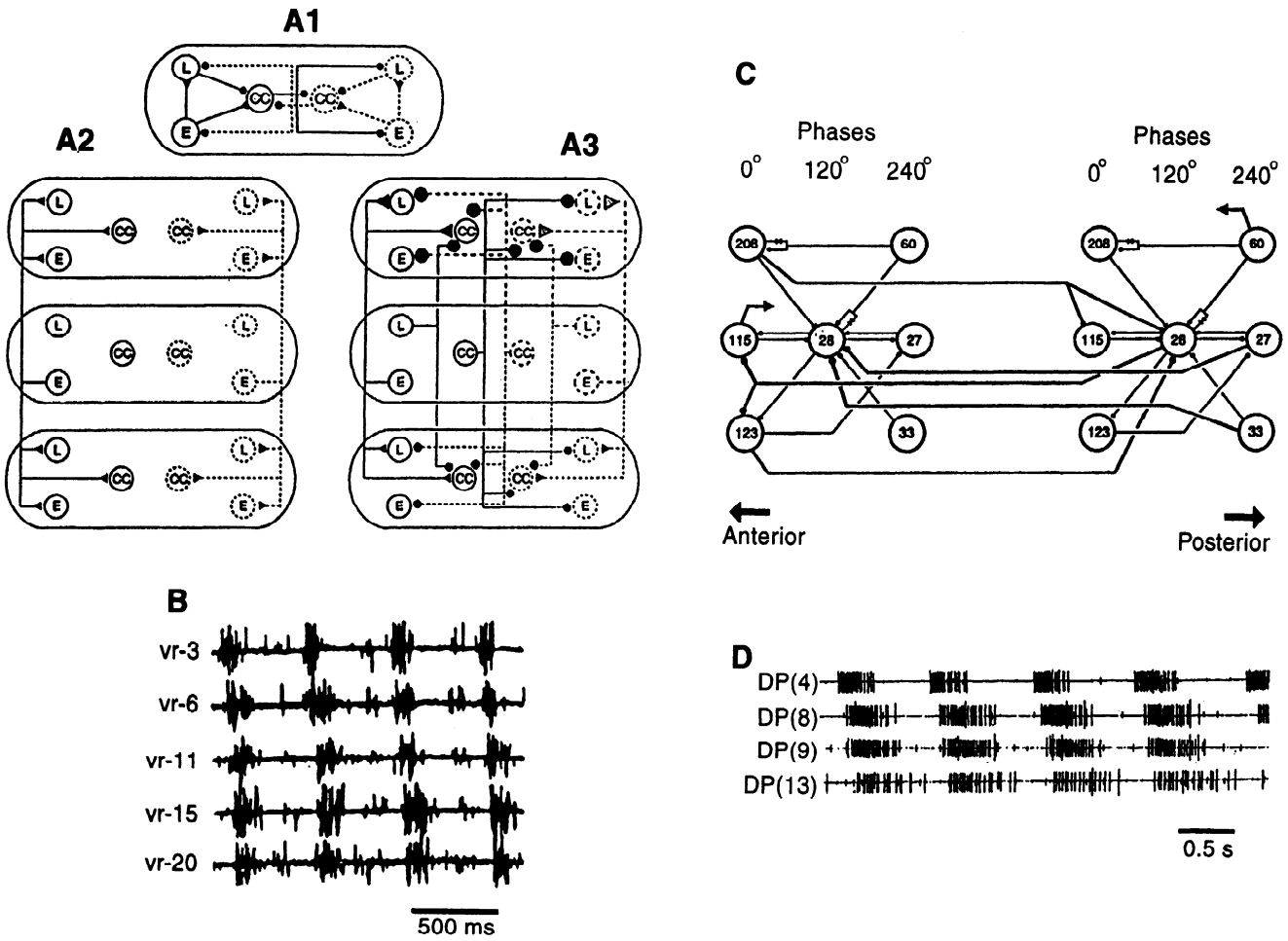

FIG. 5. *A*: lamprey spinal networks controlling swimming. *A1*: proposed network model for generation of rhythmic activity of a single segment in lamprey spinal cord (38). L, lateral interneuron; CC, inhibitory interneuron with contralateral caudally projecting axon; E, excitatory interneuron. Synaptic connections in model have been confirmed by pairwise intracellular recordings, except for inhibitory connection from CC to contralateral E. In this and subsequent panels of *A*, inhibitory connections are indicated with solid circles, and excitatory connections are indicated with solid triangles. *A2*: symmetrical intersegmental connections (191). *A3*: asymmetric intersegmental coupling (319). Larger symbols for ascending coupling represent stronger ascending connections. [From Sigvardt (278).] *B*: swimming motor pattern recorded from 5 different ventral roots (vr segments 3, 6, 11, 15, and 20) in an isolated lamprey spinal cord exposed to a uniform level of *N*-methyl-D-aspartate (150 μM) along its length. [From Matsushima and Grillner (191).] *C*: synaptic connections between oscillator interneurons that generate swimming motor pattern in medicinal leech. Both intrasegmental (light lines) and intersegmental (heavy lines) connections are shown. Solid circles indicate inhibitory synaptic connections, and diodes indicate rectifying electrical junctions. Oscillator interneurons are grouped into columns according to phase of their activity. Short arrows indicate intersegmental axonal projections for which no interneuronal targets have been found. Each of the neurons shown, except *cell 208*, occurs as a bilateral pair in midbody ganglia of nerve cord. [From Friesen and Pearce (95).] *D*: swimming motor pattern recorded from 4 different dorsal posterior nerves (DP segments 4, 8, 9, and 14) in an isolated leech nerve cord. Large unit recorded in each DP nerve is motoneuron innervating dorsal longitudinal muscle in that segment. [From Pearce and Friesen (238).]

To understand the production of swimming and its dynamic regulation in leeches and lampreys, several problems must be addressed. *1*) Are there unit oscillators, and if so, do they correspond to segmental boundaries? In other words, does the swimming result from coordination among a chain of unit oscillators, or is the pattern-generating network distributed over several segments? *2*) If there is a chain of unit oscillators, what kinds of coordinating fibers and intersegmental coupling produce coordinated activity along the cord? *3*) What is the role of sensory feedback in modifying the motor pattern? *4*) How is swimming activated and maintained?

1. *Lamprey*

In each segment of the lamprey spinal cord, a network of identified classes of inhibitory and excitatory interneurons interacts to produce the rhythmic activity that drives motoneurons during fictive swimming (38, 117) (Fig. 5, *A1* and *B*). Excitatory interneurons (EINs) provide

excitatory drive [mediated by excitatory amino acids (EAAs)] to motoneurons and feedback excitation to two classes of inhibitory interneurons, the lateral interneurons (LINs) and crossed interneurons (CCINs) (38, 39). The LINs (260) and CCINs (36) provide ipsilateral and contralateral inhibition, respectively, to interneurons and motoneurons.

Reciprocal inhibitory connections across the midline (commissural connections) between the CCINs are instrumental in generating oscillation in the segmental network (111, 112, 303). Recent experiments with partially split nerve cord preparations indicate that the commissural reciprocal interactions are essential for normal oscillation. Some rudimentary high-frequency rhythmicity persists after the commissural connections are severed, however. Descending reticulospinal neurons activate both NMDA and kainate/DL-α-amino-3-hydroxy-5-methylisoxazole-propionic acid receptors on all classes of the interneurons and on motoneurons (232) to elicit and sustain oscillation (196). The reticulospinal neurons in turn receive excitatory (as well as inhibitory) feedback from the spinal circuitry and thus participate in and sustain the rhythmic activity of the network (82).

Sensory input is provided to the segmental pattern-generating networks by intraspinal stretch receptors (edge cells) that sense the stretch associated with the bending movements during swimming (115). Two types of edge cells have been described: one with an ipsilateral axon provides excitation (EAA) to ipsilateral interneurons and motoneurons, and the other with a contralateral axon which is inhibitory (glycine) to contralateral CCINs (53, 80, 81). These stretch receptors are poised to provide the feedback necessary to coordinate the motor pattern to the ongoing movements by promoting formation of the motor burst ipsilaterally (excitation) when that side is stretched (axial muscle on the opposite side contracted) and terminating it contralaterally (inhibition). Rhythmic activation of the edge cells by bending the nerve cord at either end can entrain the fictive motor pattern over a broad frequency range ($\sim$10% below to 40% above the rest frequency) (116, 197).

Each of the three types of pattern-generating interneurons projects for several segments in the spinal cord (LINs, ipsilaterally and caudally up to 50 segments; CCINs, contralaterally and caudally up to 30 segments; EINs, ipsilaterally and either rostrally or caudally for at least 5 segments), and all synapse with neurons of other segments (36, 38, 39, 260). Although anatomically the distinction between segmental oscillatory networks is blurred, each segment acts as a functional oscillator because just a few segments of spinal cord can produce normal-looking fictive swimming motor bursts.

If one views the cord as organized into segmental oscillators, the intersegmental axons of the pattern-generating interneurons provide a substrate for intersegmental coordination of these oscillators. While excitatory coupling is provided by EIN axons that project both rostrally and caudally, inhibitory coupling is provided by LINs and CCINs that project only caudally. Other as yet undescribed pathways for coupling of segmental oscillators probably exist, but it is tempting to conclude from the available data that intersegmental coupling is asymmetric and that the inhibitory coupling is descending. Recent experiments (40) with partially split nerve cord preparations suggest that functional length of coupling between segmental oscillators has a length constant of about two segments. Given the paucity of hard data on intersegmental connectivity and synaptic strength in the network, it is perhaps not surprising that two opposing hypotheses to explain intersegmental coordination have been proposed.

The first hypothesis emphasizes the apparent symmetry of excitatory coupling. Intersegmental phase lags and phase constancy are envisioned to result from local excitability differences among segmental oscillators (trailing oscillator hypothesis) (114, 191, 192) (Fig. 5*A2*). In this model, when the nervous system is intact, descending reticulospinal inputs are thought to activate preferentially the rostral most segmental oscillators of the spinal cord. This leading oscillator then entrains, via symmetrical excitatory coupling, the more caudal trailing oscillators to the appropriate intersegmental phase lag. In this model, regardless of the period of the leading oscillator, the trailing oscillators will be entrained to the proper phase as long as they have a longer inherent period, yielding phase constancy. In sections of isolated nerve cord, removal of descending inhibition to the rostral-most segmental oscillator by section of LIN and CCIN descending axons is envisioned to enhance the excitability of the rostral most oscillator and make it lead. This assumption has been justifiably criticized for being simplistic (278). The hypothesis can also accommodate backward swimming; in that case, local sensory input which elicits the backward swim is hypothesized to excite preferentially the caudal-most segmental oscillators, causing them to lead, albeit transiently. Modeling studies using semi-realistic model neurons organized in a chain of oscillators based on the connectivity diagram of Buchanan and Grillner (38) and Grillner et al. (117) and using the simplified connectionist model of Buchanan and co-workers (37, 112) and symmetric excitatory coupling indicate that the trailing oscillator hypothesis can account for the observed coordination (114, 191, 192). However, this hypothesis is critically dependent on symmetry in the intersegmental coupling for the generation of the appropriate intersegmental phase lags and requires that the asymmetry in intrinsic frequency be maintained under all modulatory conditions to maintain constant rostral-caudal phase lags.

A second hypothesis (asymmetric coupling) deemphasizes segmental differences in excitability, because sections of nerve cord from different regions of the nerve

cord show no systematic differences in the intrinsic period of fictive swimming (55), although the extrapolation of this observation to the excitability state in intact cord or larger cord sections has been questioned (114). Extensive theoretical and mathematical analysis led to a plausible model wherein asymmetric coupling could generate the appropriate phase lags and phase constancy without any excitability differences (56, 165, 166, 278, 319, 320, 323). Experimental evidence pointed to the dominance of the ascending coupling (278). Williams (319) has suggested that this asymmetric coupling naturally follows from a simple connectivity rule called synaptic spread: whatever synaptic contacts each neuron makes within its own segment it also makes in neighboring segments (Fig. 5*A3*). This simple rule is consistent with the available connectivity data. Williams (319) simulated a chain of oscillators based on the connectivity diagram of Buchanan and Grillner (38) and Grillner et al. (117) using the simplified connectionist model of Buchanan (37) and this simple intersegmental connectivity rule. This model generates the appropriate front-to-rear phase lags and phase constancy as long as the coupling is asymmetric with the ascending coupling dominant (319). The predicted dominance of ascending coupling is in contrast to the known descending projections of the inhibitory interneurons (LINs and CCINs), although it is certainly possible that ascending fibers yet to be identified could subserve this function.

Considerable experimental evidence has been gathered in support of both hypotheses (asymmetric coupling, Refs. 278, 323; trailing oscillator, Refs. 191, 192). Much of this evidence comes from pharmacological experiments in which the excitability of one section of nerve cord relative to another is altered to determine the effect on intersegmental phase lags (191, 192, 278). Other evidence comes from attempts to determine whether the limits of entrainment of the motor pattern by edge cell activity evoked by rhythmic bending of the ends of the nerve cord, respectively, are asymmetric (323). More recently, a prediction of the asymmetric coupling model, that there should be a rostral boundary layer where intersegmental phase lags will be nonuniform, has been confirmed experimentally (322). To an impartial observer, resolution of the debate will not come from models, no matter how informative they may be, but from difficult to obtain experimental data. It will be critical to determine the length of the coordinating fibers and the strengths of their ascending and descending synaptic connections.

2. Leech

The leech central nervous system consists of a chain of segmental ganglia, each with ~400 (mostly bilaterally paired) neurons, linked by paired connectives. Each ganglion provides the sensory and motor innervation of the body wall in its segment. It is natural to ask whether each ganglion contains adequate circuitry to generate the alternating motor bursts required to control the body wall muscles to produce the alternating movements associated with swimming. Isolated single ganglia can produce crude alternating bursts in swim motoneurons only in the presence of exogenously applied neuromodulatory substances such as serotonin (126), or when linked to a chain of ganglia by a small group of fibers in the median connective that gate swimming (307). Thus they contain sufficient circuitry to sustain swim oscillations, and this circuitry can be thought of as composing a segmental swim oscillator. However, the oscillatory neural circuit can also be conceived as intersegmental and distributed (96, 97).

Each ganglion contains several interneurons that are considered part of the swim segmental oscillator because they are rhythmically active during fictive swimming, and because they are able to reset the ongoing fictive motor pattern (93–96, 309) (Fig. 5, *C* and *D*). The segmental oscillator produces a four-phase rhythm in segmental body wall motoneurons. Dorsal excitor motoneurons alternate with ventral excitor motoneurons, and dorsal inhibitor motoneurons alternate with ventral inhibitory motoneurons. Each class of motoneurons fires for ~25% of the cycle (169). The interneurons fire in a three-phase rhythm with activity centering around 0, 120, and 240° (95) and provide both excitatory and inhibitory drive to motoneurons both intra- and intersegmentally to sculpt their rhythmic bursts (251).

In both semi-intact animals and isolated nerve cords, swim activity can be triggered by mechanosensory input that activates identified descending trigger interneurons (34). These neurons in turn activate segmental swimming gating interneurons that provide tonic excitatory drive to the swim oscillator interneurons (227, 228, 308–310). The swim-gating interneurons receive excitatory and inhibitory feedback from the oscillator that sustains the excitatory state necessary for oscillation (227, 228, 308, 309). Sensory feedback from body wall stretch is thought to play a role in swim generation, (167) and as indicated above, there is evidence that such feedback is important in establishing intersegmental delays in motor activity (237), but the nature of the receptors involved and their connections with swim oscillator interneurons and motoneurons are unknown.

The oscillator interneurons are highly interconnected by both excitatory and inhibitory synapses (94–96, 309) (Fig. 5*C*). Sustained excitation from swim-gating interneurons and reciprocal inhibition between oscillator interneurons, together with postinhibitory rebound, are thought to be instrumental in rhythm generation within a segmental oscillator (93, 95). All of the oscillator interneurons project to other ganglia, some for at least five segments (96, 251, 309), providing the basis for intersegmental coordination of the unit oscillators. The known interganglionic

synaptic connections of the oscillator interneurons are largely repeats of the intraganglionic connections, conforming to the synaptic spread rule of Williams (319). They are, moreover, highly polarized and asymmetric; the 0° phase oscillator interneurons only descend, and the 120 and 240° phase oscillator interneurons only ascend, the nerve cord. The measured intersegmental synaptic connections are as strong as the local ones (94, 96, 309). Because of the extensive intersegmental connections among oscillator neurons and because many of these intersegmental connections join with intrasegmental connections to form closed inhibitory loops (96, 97), the oscillatory network appears intersegmental and distributed. Nevertheless, for the purpose of discussing intersegmental coordination and extracting principles of organization, it is useful to consider the system as a set of highly coupled segmental oscillators.

In the isolated nerve cord, the front-to-rear phase lag between homologous motor bursts in adjacent segments is ~8° or 2% (237) (Fig. 5*D*). When the periods of pairs of ganglia along the nerve cord were compared to determine whether there was a gradient in cycle period, it was found that posterior segments had shorter cycle periods than anterior segments (95, 238). According to the trailing oscillator hypothesis described above, this would lead to a rear-to-front phase progression in motor bursts along the cord. Manipulating this gradient by lowering temperature in a restricted portion of the nerve cord produced the expected phase delay in the slowed section (238, 239). Moreover, reducing the coupling between portions of nerve cord by severing one of the paired connectives that carry the intersegmental axons of the oscillator interneurons produced a reversal of phase relationships across the lesion (238, 239). This result suggests that the asymmetry of the strong coupling between segmental oscillators might be counteracting an opposing excitability gradient (95). When coupling was reduced by lesion, the effects of the excitability gradient were expressed; the phase progression of motor bursts along the nerve cord is determined by the relative influence of the "reversed" excitability gradient and the asymmetry of intersegmental coupling.

Experiments in which rhythmic activity in stretches of nerve cord was blocked (high divalent saline) but conduction in intersegmental axons was not blocked indicate that intersegmental coordinating information spans at least five segments (238, 239). Further experiments in which intersegmental phase lags were measured in progressively smaller stretches of nerve cord show that intersegmental phase lag is a function of chain length varying from 8° in the intact nerve cord to 40° in a two-ganglion chain. These results emphasize the importance of coupling from distant oscillators in establishing the proper phase progression along the nerve cord. Modeling studies of coordination of the segmental oscillators which incorporated the rear-to-front gradient in cycle period, the known bidirectional asymmetric intersegmental coupling, and long-range coupling with equivalent strength to homologous connections within the ganglion of origin, replicate all the salient features of the experimental data (240).

Studies of intersegmental coordination of swim activity in the leech nerve cord point to a hybrid explanation between "opposing" trailing oscillator and asymmetric coupling hypotheses posed for the lamprey. Not only do these studies illuminate the lamprey analyses, but they offer a satisfying, albeit teleological, explanation for the opposed arrangement apparent in this hybrid. With such an arrangement, the animal may be able to adjust intersegmental phase lags both up and down by adjusting a single variable, intersegmental coupling strength (95).

3. Other preparations

Considerable experimental effort has be expended to establish the mechanisms of intersegmental coordination in early *Xenopus* tadpole swimming (299) and crayfish swimmeret beating (214). In the swimmeret system, no gradient of excitability among segmental oscillators is thought to be present (214), and the origin of the intersegmental phase lags is unclear, although a diverse population of intersegmental neurons that convey coupling information has been identified (218, 219). Recent experiments in which gradients of excitability were created by application of cholinergic agonists are interpreted in favor of the asymmetric coupling organization (31).

The early *Xenopus* tadpole is particularly interesting because so much is known about the segmental oscillators (see sect. IV*A2*). Moreover, unlike any of the other intersegmental control systems reviewed, intersegmental time delays are constant between segmental motor bursts and independent of cycle period (297). A rostrocaudal gradient in tonic excitatory synaptic and phasic inhibitory synaptic drive during swim activity among segmental motoneurons has been observed (298, 299). If these gradients are also present in premotor spinal interneurons, they would be expected to have an important role in determining the rostrocaudal delays. It is interesting to note that the kinematics of early tadpole swimming show a longitudinally uniform intersegmental phase lag and phase constancy (68), suggesting that, as in the leech and lamprey, the mechanical properties of the skeletomotor system and hydrodynamics shape the neuromuscular output. As the tadpole develops, the swim segmental pattern generators change, the motor pattern becomes increasingly complex (and unfortunately less well understood), and the neural system achieves phase constancy (281).

C. Circuit Switching

All animals produce a wide range of behaviors, many of which require different patterns of activation of the

same motoneurons. Indeed, our leg muscles can be used in walking, running, swimming, bicycle riding, and standing, as well as in voluntary movements. Therefore, one important question is determining how much circuitry is unique in the specification of a given behavior, and how much of the interneuronal organization underlying these different motor functions is shared (289, 311, 326). On the one hand, one might imagine that there are entirely different groups of neurons that form relatively "hard-wired" circuits for each qualitatively different behavior. In this organizational model, an entirely distinct premotor circuit would exist for each behavior; that is, in animals that both swim and walk, different groups of neurons would form the premotor circuits for walking and for swimming. Alternatively, one might imagine that much of the same premotor circuitry is used to form both the swim and walking motor patterns, but that activation of several unique elements can change the network's output sufficiently to account for a significant number of qualitatively different motor patterns and, consequently, movements.

During the past 10 years, a significant amount of direct experimental evidence has come from invertebrate nervous systems that illustrates that many of the same neurons can be employed to form circuits capable of generating more than one behavior. At the same time, a body of circumstantial evidence in a variety of vertebrate preparations argues similarly that many circuit elements may be participating in the generation of more than one behavior.

1. Tritonia swim and reflex withdrawal

Tritonia is a mollusk that escapes from prey with a simple dorsal-ventral flexion. In the process of studying the organization of the central pattern generator for this episodic behavior, Getting and Dekin (100–102) first used the term *polymorphic circuit.* Getting's essential finding was that the same group of neurons could either generate a simple avoidance reflex or a full rhythmic escape behavior, depending on the strength of the sensory stimulus.

In the *Tritonia* system, a network of dorsal swim interneurons (DSIs) are all linked by excitatory connections to one another and to an interneuron I, which provides strong inhibitory feedback to the DSIs. In response to a weak sensory stimulus, a single DSI can be activated separately, because the DSIs functionally inhibit each other through I. Under these conditions, the animals make a simple defensive withdrawal. However, a strong aversive stimulus results in activation of another interneuron, C2, which inhibits I and drives the DSIs to produce synchronous bursts. Therefore, the DSIs alternate with the ventral swim interneurons (VSIs) to produce rhythmic dorsoventral flexions. Under these conditions, the DSIs strongly excite each other (102).

Getting and Dekin (101, 102) argued that it was important to distinguish between the anatomic network connecting neurons and the several different functional circuits that could be called into play under different physiological conditions. Getting (100) drew three different connectivity diagrams to illustrate *1*) the anatomic connectivity among the central pattern-generating networks, *2*) the functional circuitry he thought operational during the withdrawal behavior, and *3*) the functional circuitry during the *Tritonia* swim.

Recent work on the *Tritonia* swim circuit (153–155) illustrates that neurons that are part of pattern-generating networks may themselves also have modulatory roles and is adding new components to the swim circuit. In the present view (W. Frost and P. Katz, personal communication), sensory input excites the dorsal ramp interneuron (DRI), a newly identified command interneuron (98). The DRI then excites the DSIs. The DSIs then excite C2 as well as enhance its excitability and the strength of its synaptic connections. The excited C2 then polysynaptically excites DRI, creating a positive-feedback loop that sustains swimming. Alternation is produced by inhibition from the VSI neurons that are also excited by C2.

The DSI neurons have been recently shown to be serotonergic (195). The activation of the serotonergic DSI neurons increases the amplitude of synaptic connections in the swim system (153–155) by what appears to be heterosynaptic facilitation, modulation of transmitter release from the presynaptic terminals (153). Thus inputs to the swim system not only activate it, but in so doing upmodulate the essential circuitry for its operation. This has been termed "intrinsic modulation" (155) to distinguish it from modulatory control that is external to the circuit itself.

In another molluscan preparation, *Aplysia*, Wu et al. (326) used optical recording methods to record simultaneously from hundreds of neurons in the abdominal ganglion during spontaneous and evoked siphon withdrawals and argued that the same neurons were used in a variety of different movements.

2. Stomatogastric nervous system

Classically, the stomatogastric nervous system was thought to consist of four separate central pattern-generating networks: those controlling the production of the esophageal rhythm (10-s period), the cardiac sac rhythm (30- to 120-s period), the gastric mill rhythm (5- to 10-s period), and the pyloric rhythm (0.5- to 2-s period). Although it was always appreciated that there were synaptic connections among the neurons of these four functional networks (e.g., Refs. 69, 213), these were viewed as connections among elements of separate circuits. Studies carried out during the last 5 years have led to an entirely different conclusion.

Hooper and Moulins (136, 137) studied the firing patterns displayed by the VD neuron of the lobster, *Jasus lalandi.* The VD neuron was classically thought to be part

of the pyloric pattern generator (193) and often fires with the pyloric rhythm (Fig. 1*A*). Hooper and Moulins (136, 137) found that stimulation of a sensory neuron that activated strong cardiac sac activity caused the VD neuron to fire in time with the cardiac sac rhythm. Because the cardiac sac and pyloric rhythms have such different intrinsic periods, the VD neuron displays dramatically different patterns of firing in these two cases. Hooper and Moulins (136, 137) studied the cellular mechanism induced by the stimulation of the sensory nerve and showed that the ability of the VD neuron to generate plateau properties was decreased after sensory stimulation, allowing the timing of the VD to be governed by the excitatory drive from elements of the cardiac sac pattern generator.

Changes in the strength of synaptic interactions are thought to be responsible for another switch involving neurons of the gastric mill rhythm and the cardiac sac. Dickinson et al. (75) showed that bath application of the peptide red pigment concentrating hormone (RPCH) strongly potentiated the synaptic connections between the IV neurons (cardiac sac) and neurons of the gastric mill circuit. Consequently, in the presence of RPCH, a conjoint rhythm in which the gastric mill and cardiac sac neurons fire together is found (75).

Meyrand et al. (201, 202) have taken this theme considerably further. These authors found that activation of the pyloric supressor (PS) neurons of the lobster *Homarus gammarus* (probably homologous to the IV neurons previously described) produces a novel pattern that employs elements of all four pattern-generating networks previously described. The PS neurons synapse with most of the neurons of the STG. This drive strongly activates some of the neurons and strongly inhibits others, thus actively "dismantling" the integrity of the existing networks and creating a new one. The PS neuron activity controls the muscles of the valve between the esophagus and the cardiac sac and constructs a new motor pattern involving the whole foregut in coordinated activity (201, 202).

Many of the neurons of the crab *C. borealis* switch between pyloric-timed and gastric-timed activity patterns. Weimann et al. (313) found that when the pyloric rhythm was active but the gastric rhythm was not active, many of the neurons that innervate gastric mill muscles fire short pyloric-timed bursts of one or two spikes (Fig. 6*A*). However, when the gastric rhythm was either spontaneously active, or evoked by application of the peptide SDRNFLRF-NH_2, many of these neurons, as well as several neurons previously considered parts of the pyloric pattern generating circuit "switched" into gastric time (Fig. 6*B*) (312, 313). Similar switches can also be provoked by stimulation of the gastropyloric receptor neurons (156).

To study the possible behavioral consequences of the pyloric/gastric switches seen in crabs, Heinzel et al. (131) used an endoscope to monitor movements of the gastric mill during pyloric activity and during robust gastric mill movements, either spontaneously occurring or triggered by peptide and other modulator application (131). These experiments showed that the lateral teeth of the gastric mill produced small pyloric-timed movements when the lateral gastric (LG) and IC neurons were firing in pyloric time and demonstrated that even a few spikes/bursts produced significant movements. Moreover, activation of the muscles innervated by the IC produced movements of the lateral teeth, because of the complex mechanical coupling of the stomach muscles and ossicles (131). Thus these studies demonstrated that the pyloric/gastric switches seen in Weimann and co-workers (312, 313) are behaviorally meaningful.

The switches that describe the IV and PS neurons of the cardiac sac are interesting because they involve the activation of a set of neurons that makes a set of strong connections that tend to "drive" the STG neurons into a new firing pattern. In this case, although the local network interactions within the STG shape the influence those incoming synapses have on the final output of the STG, the major determinant of the new pattern is the set of synapses from the IV or PS neurons.

The crab pyloric/gastric switches are somewhat different from the switches that involve elements of the cardiac sac system discussed above. Weimann and Marder (311) studied the ability of the neurons that switch activity patterns to reset both ongoing pyloric and gastric rhythms. These experiments showed that when the LG and VD neurons fire in time with the pyloric network, they can reset (Fig. 6*C*) and entrain the pyloric network. Likewise, when they fire in time with the gastric rhythm, they can reset the gastric network. Thus it appears that changes in intrinsic properties and synaptic efficacy that allow the neurons to change their activity patterns "form" the functional networks and that the switching neurons are true members of different pattern-generating circuits at different times (311).

The crab system has also revealed other interesting features. Nusbaum et al. (231) found synaptic interactions between the terminals of the modulatory inputs and the intrinsic neurons of the STG. One such descending modulatory input, the modulatory commissural neuron 1 (MCN1) (60), receives inhibitory synaptic feedback at its STG terminals from the commisural gastric (CG) neuron (a major player in the gastric circuit) which can gate the output of MCN1. These local interactions in the STG effectively make the modulatory neuron an integral part of the gastric mill pattern generator. Descending activity originating in the CG activates the gastric rhythm, and local STG activity participates in generating the gastric rhythm (59). Thus the distinction between a modulatory input and a pattern-generating element is blurred by local interactions. Correspondingly, single elements serve multiple functions.

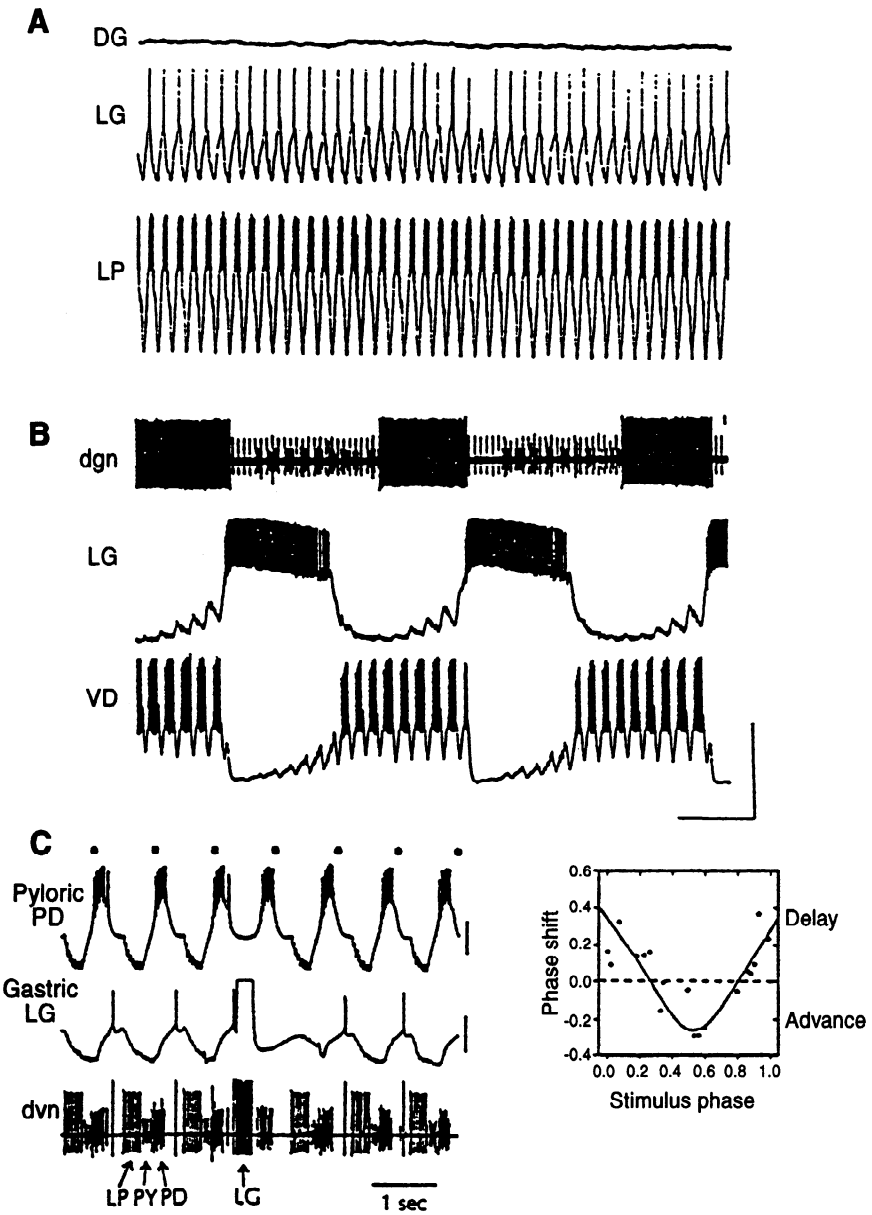

FIG. 6. Switching neurons of crab *Cancer borealis*. Abbreviations are as in Figures 1 and 4. *A*: control saline; simultaneous intracellular recordings from DG, LG, and LP neurons. Note that DG neuron is silent and LG neuron is firing in time with LP neuron (pyloric time). *B*: in presence of peptide SDRNFLRF-NH_2, LG neuron is now firing in gastric time, in alternation with DG neuron [seen as burst of action potentials on dorsal gastric nerve (dgn)]. *C*: depolarization of LG neuron resets pyloric rhythm, with phase response curve shown on *right*. [Modified from Marder and Weimann (189, 311).]

In summary, the conclusions of these studies on switching in the stomatogastric nervous system argue that the functional circuit that produces a series of motor patterns exists only in a defined modulatory and physiological state. Different modulatory and sensory inputs "construct" different motor functional circuits (76, 189, 201, 202) as needed for the appropriate behavior of the animal.

3. Other preparations

It is much more difficult to obtain direct experimental evidence that interneurons are part of several pattern-generating circuits in vertebrate systems. However, there is a growing body of circumstantial evidence supporting such an organization (22, 151, 204, 211, 289).

V. CONCLUSIONS

A. Reevaluating the Concept of Command Neurons

Descending inputs to pattern-generating networks, whether they be involved in leech or lamprey swimming (34, 117, 310), control of the crustacean foregut (59, 60, 69, 77, 78, 201, 221, 231), or any of a myriad of other rhythmic behaviors, often serve to gate specific motor patterns on or off. The observation that in invertebrate motor patterns this gating can be accomplished by stimulating single neurons led to the concept of motor "command neurons" (157, 318). The term was first applied to fibers dissected from the nerve cord of crayfish that when

stimulated extracellularly induced rhythmic movements of the swimmerets (318).

The concept of command neurons was influential in developing thinking about control of escape and many postural and rhythmic behaviors in vertebrates as well as invertebrates (70, 71, 84, 89, 157, 158, 180, 218, 219, 225).

The command neuron concept came under considerable scrutiny in the late 1970s, which led to the evolution of a set of rigid criteria for establishing a neuron as a command neuron (171). Kupfermann and Weiss (171) argued that a command neuron must be both necessary and sufficient for the activation of a motor pattern by sensory input. These criteria were so rigid that the concept has largely been abandoned, and the term *command neuron* has virtually disappeared from the literature on control of rhythmic motor systems. However, the recent discovery of the DRI neurons in *Tritonia* (98) provides a clear example of a neuron that meets all the established criteria for a command neuron. Additionally, the PS neurons in the stomatogastric nervous system (201, 202) also can be thought of as command neurons in the strict sense.

However, the notion that a neuron must be shown to be necessary as well as sufficient for the gating of a particular motor pattern before it can be usefully labeled as a command neuron flies in the face of our current experience. Parallel pathways participating in motor pattern gating, each pathway often with the ability to produce a particular pattern variant, appear to be the rule. Thus the failure of a specific neuron to be always active in association with a given motor pattern is to be expected and in no way negates the possible importance of such elements in the control of behavior. Moreover, local interaction of command elements with pattern-generating networks can sustain and even gate activity in the command elements themselves, thus making experimental efforts at determining sufficiency largely irrelevant.

Thus, in retrospect, this attempt at rigor seems to have destroyed the original utility of the concept loosely expressed in the term *command fiber*, and it may be time to retrieve it from disuse. Two examples will illustrate how this concept remains useful in discussing motor network organization. In the crustacean stomatogastric nervous system, descending activity in MCN1 initiates oscillatory activity in the gastric mill network of the STG, and inhibitory feedback to its terminals in the STG recruits this neuronal component as part of the oscillatory network (59). Other modulatory input neurons to the STG can also activate the gastric pattern generator, and presumably recruit the MCN1 STG terminals in the process. In the leech, a family of descending interneurons, called trigger neurons, in the subesophageal ganglion integrate mechanosensory input. Transient activity in these neurons excites a set of segmental swim-initiating interneurons in midbody ganglia. When excited, these interneurons, acting in parallel with segmental serotonergic interneurons, initiate the activity in swim oscillator networks in each midbody ganglion. These gating interneurons receive strong excitatory feedback from the oscillator networks that creates a reverberation that sustains the activity of the oscillator networks. Neither the MCN neurons of the stomatogastric nervous system nor the leech swim trigger or initiation neurons fulfill the "necessity" contingency discussed above, yet these neurons possess a motor command function and are the embodiment of the modern concept of command neurons. Single control neurons, acting alone or in concert with other neurons, that serve to activate whole networks that produce coordinated activity constitute a class of important cells that were first described as command neurons. These neurons in turn receive feedback from the network they activate and participate to a greater or lesser extent in network function. Thus a modern definition of a command neuron does not imply hierarchical position, nor does it imply necessity, but rather has functional implications.

B. Organizational Rules

All pattern-generating networks depend on intrinsic membrane properties and circuit building blocks to form patterned output. The output of all pattern-generating networks must be shaped to the needs of the organism. This is accomplished by a variety of control mechanisms that include sensory feedback, hormonal regulation, and modulatory inputs. As data are accumulated on a variety of preparations, it is becoming apparent that there are multiple sites of regulation and modulation within these networks and that each network is regulated by multiple routes.

Although we are starting to understand some of the basic cellular and biophysical mechanisms that are used to build unit oscillators, the organizational principles and the cellular mechanisms that underlie the interactions among networks to produce coordinated behaviors involving multiple limbs, posture, and respiration are still largely mysterious. At every level of analysis, the challenge is always to explain the behavior of a system in terms of the behavior of the component elements; that is, we must understand how the many currents in cells interact to produce the intrinsic properties of neurons, how neurons interact to produce a defined circuit, and how oscillatory circuits interact to produce coordinated behaviors. At each of these levels, this will require combined computational and experimental tools and the ability to take information gathered at one level and use it to understand the next.

Almost all textbooks in neuroscience introduce motor systems in vertebrates with excellent treatments of spinal reflexes, often leaving students with the idea that movement is still largely determined by reflex pathways.

In this review, we focused on the central control of movement. However, sensory feedback is certainly required in all rhythmic behaviors to allow the animal to move correctly. The importance of sensory feedback in the organization of the basic form of the motor pattern depends a great deal on the behavior, and this too is always context dependent.

In this review we neglected a discussion of the voluntary control of rhythmic movements, such as the internally generated decision to start walking in humans. Our eventual hope would be to understand the most challenging of human motor acts, speech, in which complex cognitive acts must be used to drive neurons and circuits that are also used in simpler behaviors such as breathing. Insights into these processes will require cooperation and coordination among groups of neuroscientists, in much the same way that any coordinated behavioral act requires coordination among multiple, complex neural circuits.

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REFERENCES

1. ABBOTT, L. F., S. L. HOOPER, AND E. MARDER. Oscillating networks: control of burst duration by electrically coupled neurons. *Neural Comput.* 3: 487–497, 1991.
2. ADAMS, M. E., AND M. O'SHEA. Peptide cotransmitter at a neuromuscular junction. *Science Wash. DC* 221: 286–288, 1983.
3. ALFORD, S., AND K. A. SIGVARDT. Excitatory neurotransmitters activate voltage-dependent properties in neurons in spinal motor system of lamprey. *J. Neurophysiol.* 62: 334–341, 1989.
4. ANGSTADT, J. D., AND R. L. CALABRESE. A hyperpolarization-activated inward current in heart interneurons of the medicinal leech. *J. Neurophysiol.* 9: 2846–2857, 1989.
5. ANGSTADT, J. D., AND R. L. CALABRESE. Calcium currents and graded synaptic transmission between heart interneurons of the leech. *J. Neurosci.* 11: 746–759, 1991.
6. ANGSTADT, J. D., AND W. O. FRIESEN. Modulation of swimming behavior in the medicinal leech. I. Effects of serotonin on the electrical properties of swim-gating cell 204. *J. Comp. Physiol A Sens. Neural Behav. Physiol.* 172: 223–234, 1993.
7. ANGSTADT, J. D., AND W. O. FRIESEN. Modulation of swimming behavior in the medicinal leech. II. Ionic conductances underlying serotonergic modulation of swim-gating cell 204. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 172: 235–248, 1993.
8. ARBAS, E. A., AND R. L. CALABRESE. Ionic conductances underlying the activity of interneurons that control heartbeat in the medicinal leech. *J. Neurosci.* 7: 3945–3952, 1987.
9. ARBAS, E. A., AND R. L. CALABRESE. Slow oscillations in membrane potential in interneurons that control heartbeat in the medicinal leech. *J. Neurosci.* 7: 3953–3960, 1987.
10. ARSHAVSKY, Y. I., T. G. BELIAGINA, G. N. ORLOVSKY, Y. PANCHIN, G. A. PAVLOVA, AND L. B. POPOVA. Control of locomotion in marine mollusc *Clione limacina*. VI. Activity of isolated neuron of pedal ganglia. *Exp. Brain Res.* 63: 106–112, 1986.
11. ARSHAVSKY, Y. I., I. N. BELOOZEROVA, G. N. ORLOVSKY, Y. PANCHIN, AND G. A. PAVLOVA. Control of locomotion in marine mollusc *Clione limacina*. I. Efferent activity during actual and fictitious swimming. *Exp. Brain Res.* 58: 255–262, 1985.
12. ARSHAVSKY, Y. I., I. N. BELOOZEROVA, G. N. ORLOVSKY, Y. PANCHIN, AND G. A. PAVLOVA. Control of locomotion in marine mollusc *Clione limacina*. I. Rhythmic neurons of pedal ganglia. *Exp. Brain Res.* 58: 263–272, 1985.
13. ARSHAVSKY, Y. I., I. N. BELOOZEROVA, G. N. ORLOVSKY, Y. PANCHIN, AND G. A. PAVLOVA. Control of locomotion in marine mollusc *Clione limacina*. III. On the origin of locomotory rhythm. *Exp. Brain Res.* 58: 273–284, 1985.
14. ARSHAVSKY, Y. I., I. N. BELOOZEROVA, G. N. ORLOVSKY, Y. PANCHIN, AND G. A. PAVLOVA. Control of locomotion in marine mollusc *Clione limacina*. IV. Role of type 12 interneurons. *Exp. Brain Res.* 58: 285–293, 1985.
15. ARSHAVSKY, Y. I., G. N. ORLOVSKY, Y. PANCHIN, AND G. A. PAVLOVA. Control of locomotion in marine mollusc *Clione limacina*. VII. Reexamination of type 12 interneurons. *Exp. Brain Res.* 78: 398–406, 1989.
16. ARSHAVSKY, Y. I., G. N. ORLOVSKY, Y. V. PANCHIN, A. ROBERTS, AND S. R. SOFFE. Neuronal control of swimming locomotion: analysis of the pteropod mollusc *Clione* and embryos of the amphibian *Xenopus*. *Trends Neurosci.* 16: 227–233, 1993.
17. AYERS, J., AND A. I. SELVERSTON. Monosynaptic entrainment of an endogenous pacemaker network: a cellular mechanism for von Holst's magnet effect. *J. Comp. Physiol.* 129: 5–17, 1979.
18. BAL, T., F. NAGY, AND M. MOULINS. The pyloric central pattern generator in crustacea: a set of conditional neuronal oscillators. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 163: 715–727, 1988.
19. BAXTER, D. A., AND J. H. BYRNE. Ionic conductance mechanisms contributing to the electrophysiological properties of neurons. *Curr. Opin. Neurobiol.* 1: 105–112, 1991.
20. BEKOFF, A., AND J. A. KAUER. Neural control of hatching: role of neck position in turning on hatching leg movements in post-hatching chicks. *J. Comp. Physiol.* 145: 495–504, 1982.
21. BEKOFF, A., AND J. A. KAUER. Neural control of hatching: fate of the pattern generator for the leg movements of hatching in post-hatching chicks. *J. Neurosci.* 4: 2659–2666, 1984.
22. BEKOFF, A., M. P. NUSBAUM, A. L. SABICHI, AND M. CLIFFORD. Neural control of hatching and walking motor output patterns in normal and deafferented chicks. *J. Neurosci.* 7: 2320–2330, 1987.
23. BELANGER, J. H., AND I. ORCHARD. The locust ovipositor opener muscle: proctolinergic central and peripheral neuromodulation in a centrally driven motor system. *J. Exp. Biol.* 174: 343–362, 1993.
24. BENSON, J. A., AND W. B. ADAMS. Ionic mechanisms of endogenous activity in molluscan burster neurons. In: *Neuronal and Cellular Oscillators*, edited by J. Jacklet. New York: Dekker, 1989, p. 87–120.
25. BERKOWITZ, A., AND P. S. G. STEIN. Activity of descending propriospinal axons in the turtle hindlimb enlargement during two forms of fictive scratching: broad tuning to regions of the body surface. *J. Neurosci.* 14: 5089–5104, 1994.
26. BERKOWITZ, A., AND P. S. G. STEIN. Activity of descending propriospinal axons in the turtle hindlimb enlargement during two forms of fictive scratching: phase analyses. *J. Neurosci.* 14: 5105–5119, 1994.
27. BERTRAM, R. A computational study of the effects of serotonin on a molluscan burster neuron. *Biol. Cybern.* 69: 257–267, 1993.
28. BIDAUT, M. Pharmacological dissection of pyloric network of the lobster stomatogastric ganglion using picrotoxin. *J. Neurophysiol.* 44: 1089–1101, 1980.
29. BISHOP, C. A., J. J. WINE, F. NAGY, AND M. R. O'SHEA. Physiological consequences of a peptide cotransmitter in a crayfish nerve-muscle preparation. *J. Neurosi.* 7: 1769–1779, 1987.
30. BOOTHBY, K. M., AND A. ROBERTS. The stopping response of *Xenopus laevis* embryos: behaviour, development and physiology. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 170: 171–180, 1992.
31. BRAUN, G., AND B. MULLONEY. Coordination in the crayfish swimmeret system: differential excitation causes changes in intersegmental phase. *J. Neurophysiol.* 73: 880–885, 1995.
32. BREZINA, V., C. G. EVANS, AND K. R. WEISS. Enhancement of Ca current in the accessory radula closer muscle of *Aplysia californica* by neuromodulators that potentiate its contractions. *J. Neurosci.* 14: 4393–4411, 1994.
33. BREZINA, V., C. G. EVANS, AND K. R. WEISS. Activation of K current in the acessory radula closer muscle of *Aplysia californica*

by neuromodulators that depress its contractions. *J. Neurosci.* 14: 4412–4432, 1994.
34. BRODFUEHRER, P. D., AND W. O. FRIESEN. From stimulation to undulation: an identified pathway for the control of swimming activity in the leech. *Science Wash. DC* 234: 1002–1004, 1986.
35. BRODIN, L. S., S. GRILLNER, AND C. ROVAINEN. NMDA, kainate and quisqualate receptors and the generation of fictive locomotion in the lamprey spinal cord. *Brain Res.* 325: 302–306, 1984.
36. BUCHANAN, J. T. Identification of interneurons with contralateral caudal axons in the lamprey spinal cord: synaptic interactions and morphology. *J. Neurophysiol.* 47: 961–975, 1982.
37. BUCHANAN, J. T. Neural network simulations of coupled locomotor oscillators in the lamprey spinal cord. *Biol. Cybern.* 66: 367–374, 1992.
38. BUCHANAN, J. T., AND S. GRILLNER. Newly identified "glutamate interneurons" and their role in locomotion in the lamprey spinal cord. *Science Wash. DC* 236: 312–314, 1987.
39. BUCHANAN, J. T., S. GRILLNER, S. CULHEIM, AND M. RISLING. Identification of excitatory interneurons contributing to generation of locomotion in lamprey: structure, pharmacology, and function. *J. Neurophysiol.* 62: 59–69, 1989.
40. BUCHANAN, J. T., S. KASICKI, AND D. KOMOROSKI. Swim oscillator coupling signals in lamprey spinal cord. *Soc. Neurosci. Abstr.* 21: 687, 1995.
41. BURROWS, M., AND M. V. SIEGLER. Graded synaptic transmission between local interneurons and motor neurons in the metathoracic ganglion of the locust. *J. Physiol. Lond.* 285: 231–255, 1978.
42. BUTERA, R. J., J. W. CLARK, C. C. CANAVIER, D. A. BAXTER, AND J. H. BYRNE. Analysis of the effects of modulatory agents on a modeled bursting neuron: dynamic interactions between voltage and calcium dependent systems. *J. Computat. Neurosci.* 2: 19–44, 1995.
43. BYRNE, J. H. Cellular analysis of associative learning. *Physiol. Rev.* 67: 329–439, 1987.
44. CALABRESE, R. L. Modulation of muscle and neuromuscular junctions in invertebrates. *Semin. Neurosci.* 1: 25–34, 1989.
45. CALABRESE, R. L., J. D. ANGSTADT, AND E. A. ARBAS. A neural oscillator based on reciprocal inhibition. In: *Perspectives in Neural Systems and Behavior*, edited by T. J. Carew and D. B. Kelley. New York: Liss, 1989, p. 33–50.
46. CALABRESE, R. L., AND E. DESHUTTER. Motor pattern generating networks in invertebrates: modeling our way toward understanding. *Trends Neurosci.* 15: 439–445, 1992.
47. CALABRESE, R. L., AND E. L. PETERSON. Neural control of heartbeat in the leech, *Hirudo medicinalis*. In: *Neural Origin of Rhythmic Movements*, edited by A. Roberts and B. Roberts. Cambridge, UK: Cambridge Univ. Press, 1983, p. 195–221.
48. CANAVIER, C. C., D. A. BAXTER, J. W. CLARK, AND J. H. BYRNE. Nonlinear dynamics in a model neuron provide a novel mechanism for transient synaptic inputs to produce long-term alterations of postsynaptic activity. *J. Neurophysiol.* 69: 2252–2257, 1993.
49. CANAVIER, C. C., D. A. BAXTER, J. W. CLARK, AND J. H. BYRNE. Multiple modes of activity in a model neuron suggest a novel mechanism for the effects of neuromodulators. *J. Neurophysiol.* 72: 872–882, 1994.
50. CANAVIER, C. C., J. W. CLARK, AND J. H. BYRNE. Simulation of the bursting activity of neuron R15 in *Aplysia*: role of ionic currents, calcium balance, and modulatory transmitters. *J. Neurophysiol.* 66: 2107–2124, 1991.
51. CARDI, P., F. NAGY, J. R. CAZALETS, AND M. MOULINS. Multimodal distribution and discontinuous variation in period of interacting oscillators in the crustacean stomatogastric nervous system. *J. Comp. Physiol.* 167: 23–41, 1990.
52. CHAY, T. R., AND J. KEISER. Minimal model for membrane oscillations in the pancreatic β-cell. *Biophys. J.* 42: 181–189, 1983.
53. CHRISTENSON, J., F. BONGIANNI, S. GRILLNER, AND T. HÖKFELT. Putative GABAergic input to axons of spinal interneurons and primary sensory neurons in the lamprey spinal cord as shown by intracellular Lucifer yellow and GABA immunohistochemistry. *Brain Res.* 538: 313–318, 1991.
54. CLARAC, F., A. EL MANIRA, AND D. CATTAERT. Presynaptic control as a mechanism of sensory-motor integration. *Curr. Opin. Neurol.* 2: 764–769, 1992.
55. COHEN, A. H. The structure and function of the intersegmental coordination system in the lamprey spinal cord. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 160: 181–193, 1987.
56. COHEN, A. H., P. J. HOLMES, AND R. H. RAND. The nature of the coupling between segmental oscillators of the lamprey spinal generator for locomotion: a mathematical model. *J. Math Biol.* 13: 345–369, 1982.
57. COHEN, A. H., S. ROSSIGNOL, AND S. GRILLNER. *Neural Control of Rhythmic Movements in Vertebrates*. New York: Wiley, 1988.
58. COHEN, A. H., AND P. WALLÉN. The neuronal correlate of locomotion in fish. "Fictive swimming" induced in an in vitro preparation of the lamprey spinal cord. *Exp. Brain Res.* 41: 11–18, 1980.
59. COLEMAN, M. J., P. MEYRAND, AND M. P. NUSBAUM. Presynaptic inhibition mediates a switch between two modes of synaptic transmission. *Nature Lond.* 378: 502–505, 1995.
60. COLEMAN, M. J., AND M. P. NUSBAUM. Functional consequences of compartmentalization of synaptic input. *J. Neurosci.* 14: 6544–6552, 1994.
61. COLEMAN, M. J., M. P. NUSBAUM, I. COURNIL, AND B. J. CLAIBORNE. Distribution of modulatory inputs to the stomatogastric ganglion of the crab, *Cancer borealis*. *J. Comp. Neurol.* 325: 581–594, 1992.
62. CONWAY, B. A., H. HULTBORN, O. KIEHN, AND I. MINTZ. Plateau properties in α-motoneurones induced by intravenous injection of L-dopa and clonidine in the spinal cat. *J. Physiol. Lond.* 405: 369–384, 1988.
63. CREST, M., E. EHILE, T. PIN, K. WATANABE, AND M. GOLA. Plateau-generating nerve cells in *Helix*: properties of the repolarizing voltage-gated and Ca^{2+}-activated potassium currents. *J. Exp. Biol.* 152: 211–241, 1990.
64. CROPPER, E. C., D. PRICE, R. TENENBAUM, I. KUPFERMANN, AND K. R. WEISS. Release of peptide transmitters from a cholinergic motor neuron under physiological conditions. *Proc. Natl. Acad. Sci. USA* 87: 933–937, 1990.
65. DALE, N. The isolation and identification of spinal neurons that control movement in the *Xenopus* embryo. *Eur. J. Neurosci* 3: 1025–1035, 1991.
66. DALE, N., AND A. ROBERTS. Dual-component amino-acid-mediated synaptic potentials: excitatory drive for swimming in *Xenopus* embryos. *J. Physiol. Lond.* 363: 35–59, 1985.
67. DALE, N., A. ROBERTS, AND S. R. SOFFE. The anatomy, development, physiology and role of glycinergic neurons in the *Xenopus* embryo spinal cord. In: *Glycine Neurotransmission*, edited by O. P. Ottersen and J. Storm-Mathisen. Chichester, UK: Wiley, 1990, p. 329–353.
68. DALE, N. C., AND S. R. SOFFE. Kinematic analysis of amphibian tadpole swimming (Abstract). *J. Mar. Biol. Assoc. UK* 71: 734, 1991.
69. DANDO, M. R., AND A. I. SELVERSTON. Command fibers from the supra-oesophageal ganglion to the stomatogastric ganglion in *Panulirus argus*. *J. Comp. Physiol.* 78: 138–175, 1972.
70. DAVIS, W. J., AND D. KENNEDY. Command interneurons controlling swimmeret movements in the lobster. I. Types of effects on motoneurons. *J. Neurophysiol.* 35: 1–12, 1972.
71. DAVIS, W. J., AND D. KENNEDY. Command interneurons controlling swimmeret movements in the lobster. II. Interaction of effects on motoneurons. *J. Neurophysiol.* 35: 13–19, 1972.
72. DE SHUTTER, E., J. D. ANGSTADT, AND R. L. CALABRESE. A model of graded synaptic transmission for use in dynamic network simulations. *J. Neurophysiol.* 4: 1225–1235, 1993.
73. DESTEXHE, A., A. BABLOYANTZ, AND T. J. SEJNOWSKI. Ionic mechanisms for intrinsic slow oscillations in thalamic relay neurons. *Biophys. J.* 65: 1538–1552, 1993.
74. DICAPRIO, R. A. Nonspiking interneurons in the ventilatory central pattern generator of the shore crab, *Carcinus maenas*. *J. Comp. Neurol.* 185: 83–106, 1989.
75. DICKINSON, P. S., C. MECSAS, AND E. MARDER. Neuropeptide fusion of two motor pattern generator circuits. *Nature Lond.* 344: 155–158, 1990.
76. DICKINSON, P. S., AND M. MOULINS. Interactions and combinations between different networks in the stomatogastric nervous system. In: *Dynamic Biological Networks: The Stomatogastric Nervous System*, edited by R. M. Harris-Warrick, E. Marder, A. I.

Selverston, and M. Moulins. Cambridge, MA: MIT Press, 1992, p. 139–160.
77. DICKINSON, P. S., AND F. NAGY. Control of a central pattern generator by an identified modulatory interneurone in crustacea. II. Induction and modification of plateau properties in pyloric neurones. *J. Exp. Biol.* 105: 59–82, 1983.
78. DICKINSON, P. S., F. NAGY, AND M. MOULINS. Control of central pattern generators by an identified neurone in crustacea: activation of the gastric mill motor pattern by a neurone known to modulate the pyloric network. *J. Exp. Biol.* 136: 53–87, 1988.
79. DIFRANCESCO, D., AND D. NOBLE. Current I_f and its contribution to cardiac pacemaking. In: *Neuronal and Cellular Oscillators*, edited by J. W. Jacklet. New York: Dekker, 1989, chapt. 2, p. 31–57.
80. DIPRISCO, G. V., R. DUBUC, P. WALLÉN, AND S. GRILLNER. 5-Hydroxytryptamine modulates spike frequency regulation in reticulospinal neurons involved in the control of locomotion in lamprey. *Neurosci. Lett.* 134: 279–283, 1992.
81. DIPRISCO, G. V., P. WALLÉN, AND S. GRILLNER. Synaptic effects of intraspinal stretch receptor neurons mediating movement-related feedback during locomotion. *Brain Res.* 530: 161–166, 1990.
82. DUBUC, R., AND S. GRILLNER. The role of spinal cord inputs in modulating the activity of reticulospinal neurons during fictive locomotion in the lamprey. *Brain Res.* 483: 196–200, 1989.
83. DUNLAP, K., AND G. D. FISCHBACH. Neurotransmitters decrease the calcium conductance activated by depolarization of embryonic chick sensory neurones. *J. Physiol. Lond.* 317: 519–535, 1981.
84. EATON, R. C., R. DIDOMENICO, AND J. NISSANOV. Role of the Mauthner cell in sensorimotor integration by the brain stem escape network. *Brain Behav. Evol.* 37: 272–285, 1991.
85. EISEN, J. S., AND E. MARDER. Mechanisms underlying pattern generation in lobster stomatogastric ganglion as determined by selective inactivation of identified neurons. III. Synaptic connections of electrically coupled pyloric neurons. *J. Neurophysiol.* 48: 1392–1415, 1982.
86. EISEN, J. S., AND E. MARDER. A mechanism for the production of phase shifts in a pattern generator. *J. Neurophysiol.* 51: 1375–1393, 1984.
87. ELSON, R. C., AND A. I. SELVERSTON. Mechanisms of gastric rhythm generation in the isolated stomatogastric ganglion of spiny lobsters: bursting pacemaker potentials, synaptic interactions and muscarinic modulation. *J. Neurophysiol.* 68: 890–907, 1992.
88. EPSTEIN, I. R., AND E. MARDER. Multiple modes of a conditional neural oscillator. *Biol. Cybern.* 63: 25–34, 1990.
89. EVOY, W. H., AND D. KENNEDY. The central nervous organization underlying control of antagonistic muscles in the crayfish. *Zoologist* 165: 223–238, 1967.
90. FIELDS, H. L., M. M. HEINRICHER, AND P. MASON. Neurotransmitters in nocioceptive modulatory circuits. *Annu. Rev. Neurosci.* 14: 219–245, 1991.
91. FLAMM, R. E., AND R. M. HARRIS-WARRICK. Aminergic modulation in the lobster stomatogastric ganglion. I. Effects on the motor pattern and activity of neurons within the pyloric circuit. *J. Neurophysiol.* 55: 847–865, 1986.
92. FLAMM, R. E., AND R. M. HARRIS-WARRICK. Aminergic modulation in the lobster stomatogastric ganglion. II. Target neurons of dopamine, octopamine, and serotonin within the pyloric circuit. *J. Neurophysiol.* 55: 866–881, 1986.
93. FRIESEN, W. O. Neuronal control of leech swimming movements. In: *Cellular and Neuronal Oscillators*, edited by J. W. Jacklet. New York: Dekker, 1989, p. 269–316.
94. FRIESEN, W. O. Neuronal control of leech swimming movements. II. Motor neuron feedback to oscillator cells 115 and 28. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 166: 205–215, 1989.
95. FRIESEN, W. O., AND R. A. PEARCE. Mechanisms of intersegmental coordination in leech locomotion. *Semin. Neurosci.* 5: 41–47, 1993.
96. FRIESEN, W. O., M. POON, AND G. S. STENT. Neuronal control of swimming in the medicinal leech. IV. Identification of a network of oscillatory interneurons. *J. Exp. Biol.* 75: 25–43, 1978.
97. FRIESEN, W. O., AND G. S. STENT. Generation of a locomotory rhythm by a neural network with recurrent cyclic inhibition. *Biol. Cybern.* 28: 27–40, 1977.
98. FROST, W. N., AND P. S. KATZ. Identification of *Tritonia* "ramp" interneuron: DRI neuron relays sensory input to the escape swim CPG and also participates in rhythm generation. *Soc. Neurosci. Abstr.* 20: 1201, 1994.
99. GETTING, P. A. Comparative analysis of invertebrate central pattern generators. In: *Neural Control of Rhythmic Movements in Vertebrates*, edited by A. H. Cohen, S. Rossignol, and S. Grillner. New York: Wiley, 1988, chapt. 4, p. 101–127.
100. GETTING, P. A. Emerging principles governing the operation of neural networks. *Annu. Rev. Neurosci.* 12: 185–204, 1989.
101. GETTING, P. A., AND M. S. DEKIN. *Tritonia* swimming: a model system for integration within rhythmic motor systems. In: *Model Neural Networks and Behavior*, edited by A. I. Selverston. New York: Plenum, 1985, chapt. 1, p. 3–20.
102. GETTING, P. A., AND M. S. DEKIN. Mechanisms of pattern generation underlying swimming in *Tritonia*. IV. Gating of central pattern generator. *J. Neurophysiol.* 53: 466–480, 1985.
103. GOLOWASCH, J., F. BUCHHOLTZ, I. R. EPSTEIN, AND E. MARDER. Contribution of individual ionic currents to activity of a model stomatogastric ganglion neuron. *J. Neurophysiol.* 67: 341–349, 1992.
104. GOLOWASCH, J., AND E. MARDER. Ionic currents of the lateral pyloric neuron of the stomatogastric ganglion of the crab. *J. Neurophysiol.* 67: 318–331, 1992.
105. GRAUBARD, K. Synaptic transmission without action potentials: input-output properties of a nonspiking presynaptic neuron. *J. Neurophysiol.* 41: 1014–1025, 1978.
106. GRAUBARD, K., J. A. RAPER, AND D. K. HARTLINE. Graded synaptic transmission between identified spiking neurons. *J. Neurophysiol.* 50: 508–521, 1983.
107. GRAY, C. M. Synchronous oscillations in neuronal systems: mechanisms and functions. *J. Computat. Neurosci.* 1: 11–38, 1994.
108. GRAY, J. Studies in animal locomotion. I. The movement of fish with special reference to the eel. *J. Exp. Biol.* 10: 88–103, 1933.
109. GRAY, J. Studies in animal locomotion. IV. The neuromuscular mechanism of swimming in the eel. *J. Exp. Biol.* 13: 170–180, 1936.
110. GRAY, J. *Animal Locomotion.* London: Weidenfeld & Nicolson, 1968.
111. GRILLNER, S., J. T. BUCHANAN, AND A. LANSNER. Simulation of the segmental burst generating network for locomotion in lamprey. *Neurosci. Lett.* 89: 31–35, 1988.
112. GRILLNER, S., J. T. BUCHANAN, P. WALLEN, AND L. BRODIN. Neural control of locomotion in lower vertebrates: from behavior to ionic mechanisms. In: *Neural Control of Rhythmic Movements in Vertebrates*, edited by A. H. Cohen, S. Rossignol, and S. Grillner. New York: Wiley, 1988, chapt. 1, p. 1–40.
113. GRILLNER, S., AND M. KONISHI, (Editors). Neural control. *Curr. Opin. Neurobiol.* 1: 553–555, 1991.
114. GRILLNER, S., T. MATSUSHINA, T. WADDEN, A. EL MANIRA, AND P. WALLÉN. The neurophysiological bases of undulatory locomotion in vertebrates. *Semin. Neurosci.* 5: 17–27, 1993.
115. GRILLNER, S., A. D. MCCLELLAN, AND C. PERRET. Entrainment of the spinal pattern generators for swimming by mechanosensitive elements in the lamprey spinal cord in vitro. *Brain Res.* 217: 380–386, 1981.
116. GRILLNER, S., A. D. MCCLELLAN, AND K. A. SIGVARDT. Mechanosensitive neurones in the spinal cord of the lamprey. *Brain Res.* 235: 169–173, 1982.
117. GRILLNER, S., P. WALLÉN, L. BRODIN, and A. LANSNER. Neuronal network generating locomotor behavior in lamprey: circuitry, transmitters, membrane properties, and simulation. *Annu. Rev. Neurosci.* 14: 169–169, 1991.
118. GUCKENHEIMER, J., S. GUERON, and R. M. HARRIS-WARRICK. Mapping the dynamics of a bursting neuron. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 341: 345–359, 1993.
119. HARRIS-WARRICK, R. M. Chemical modulation of central pattern generators. In: *Neural Control of Rhythmic Movements in Vertebrates*, edited by A. H. Cohen, S. Rossignol, and S. Grillner. New York: Wiley, 1988, p. 285–331.
120. HARRIS-WARRICK, R. M., L. M. CONIGLIO, N. BARAZANGI, J. GUCKENHEIMER, AND S. GUERON. Dopamine modulation of transient potassium current evokes phase shifts in a central pattern generator network. *J. Neurosci.* 15: 342–358, 1995.
121. HARRIS-WARRICK, R. M., L. M. CONIGLIO, R. M. LEVINI, S. GUERON, AND J. GUCKENHEIMER. Dopamine modulation of two

subthreshold currents produces phase shifts in activity of an identified motoneuron. *J. Neurophysiol.* 74: 1404–1420, 1995.
122. HARRIS-WARRICK, R. M., AND R. E. FLAMM. Multiple mechanisms of bursting in a conditional bursting neuron. *J. Neurosci.* 7: 2113–2128, 1987.
123. HARRIS-WARRICK, R. M., AND E. MARDER. Modulation of neural networks for behavior. *Annu. Rev. Neurosci.* 14: 39–57, 1991.
124. HARTLINE, D. K. Pattern generation in the lobster (*Panulirus*) stomatogastric ganglion. II. Pyloric network stimulation. *Biol. Cybern.* 33: 223–236, 1979.
125. HARTLINE, D. K., AND D. V. GASSIE. Pattern generation in the lobster (*Panulirus*) stomatogastric ganglion. I. Pyloric neuron kinetics and synaptic interactions. *Biol. Cybern.* 33: 209–222, 1979.
126. HASHENZADEH-GARGARI, H., AND W. O. FRIESEN. Modulation of swimming activity in the medicinal leech by serotonin and octopamine. *Comp. Biochem. Physiol. C Comp. Pharmacol.* 94: 295–302, 1989.
127. HAWKINS, R. D., E. R. KANDEL, AND S. A. SIEGELBAUM. Learning to modulate transmitter release: themes and variations in synaptic plasticity. *Annu. Rev. Neurosci.* 16: 625–665, 1993.
128. HEINZEL, H. G. Gastric mill activity in the lobster. I. Spontaneous modes of chewing. *J. Neurophysiol.* 59: 528–550, 1988.
129. HEINZEL, H. G. Gastric mill activity in the lobster. II. Proctolin and octopamine initiate and modulate chewing. *J. Neurophysiol.* 59: 551–565, 1988.
130. HEINZEL, H. G., AND A. I. SELVERSTON. Gastric mill activity in the lobster. III. The effects of proctolin on the isolated central pattern generator. *J. Neurophysiol.* 59: 566–585, 1988.
131. HEINZEL, H.-G., J. M. WEIMANN, AND E. MARDER. The behavioral repertoire of the gastric mill in the crab, *Cancer pagurus*: an in vivo endoscopic and electrophysiological examination. *J. Neurosci.* 13: 1793–1803, 1993.
132. HERMANS, C. O., AND R. A. SATTERLIE. Fast-strike feeding behavior in a pteropod mollusk, *Clione limacina Phipps. Biol. Bull.* 182: 1–7, 1992.
133. HINDMARSH, J. L., AND R. M. ROSE. A model of neural bursting with three coupled first order differential equations. *Proc. R. Soc. Lond. B Biol. Sci.* 221: 87–102, 1984.
134. HODGKIN, A. L., AND A. F. HUXLEY. A qualitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol. Lond.* 117: 500–544, 1952.
135. HOOPER, S. L., AND E. MARDER. Modulation of the lobster pyloric rhythm by the peptide proctolin. *J. Neurosci.* 7: 2097–2112, 1987.
136. HOOPER, S. L., AND M. MOULINS. Switching of a neuron from one network to another by sensory-induced changes in membrane properties. *Science Wash. DC* 244: 1587–1589, 1989.
137. HOOPER, S. L., AND M. MOULINS. Cellular and synaptic mechanisms responsible for a long-lasting restructuring of the lobster pyloric network. *J. Neurophysiol.* 64: 1574–1589, 1990.
138. HOUNSGAARD, J., H. HULTBORN, B. JESPERSEN, AND O. KIEHN. Bistability of α-motoneurones in the decerebrate cat and in the acute spinal cat after intravenous 5-hydroxytryptophan. *J. Physiol. Lond.* 405: 345–367, 1988.
139. HOUNSGAARD, J., AND O. KIEHN. Serotonin-induced bistability of turtle motoneurones caused by a nifedipine-sensitive calcium plateau potential. *J. Physiol. Lond.* 414: 265–282, 1989.
140. HOUNSGAARD, J., AND O. KIEHN. Calcium spikes and calcium plateaux evoked by differential polarization in dendrites of turtle motoneurones in vitro. *J. Physiol. Lond.* 468: 245–259, 1993.
141. HOUNSGAARD, J., AND O. KJAERULFF. Ca^{2+}-mediated plateau potentials in a subpopulation of interneurons in the ventral horn of the turtle spinal cord. *Eur. J. Neurol.* 4: 183–188, 1992.
142. HOYLE, G. *Muscles and Their Neural Control.* New York: Wiley, 1983.
143. HUERTA, P. T., AND J. E. LISMAN. Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. *Nature Lond.* 364: 723–725, 1993.
144. HUGUENARD, J. R., AND D. A. MCCORMICK. Simulation of the currents involved in rhythmic oscillations in thalamic relay neurons. *J. Neurophysiol.* 68: 1373–1383, 1992.
145. JACKLET, J. W. (Editor). *Neuronal and Cellular Oscillators.* New York: Dekker, 1989.
146. JAN, Y. N., L. Y. JAN, AND S. W. KUFFLER. A peptide as a possible transmitter in sympathetic ganglia of the frog. *Proc. Natl. Acad. Sci. USA* 76: 1501–1505, 1979.
147. JOHNSON, B. R., AND R. M. HARRIS-WARRICK. Aminergic modulation of graded synaptic transmission in the lobster stomatogastric ganglion. *J. Neurosci.* 10: 2066–2076, 1990.
148. JOHNSON, B. R., J. H. PECK, AND R. M. HARRIS-WARRICK. Temperature sensitivity of graded synaptic transmission in the lobster stomatogastric ganglion. *J. Exp. Biol.* 156: 267–285, 1991.
149. JOHNSON, B. R., J. H. PECK, AND R. M. HARRIS-WARRICK. Differential modulation of chemical and electrical components of mixed synapses in the lobster stomatogastric ganglion. *J. Comp. Physiol. A Sens. Neural. Behav. Physiol.* 175: 233–249, 1994.
150. JOHNSON, B. R., J. H. PECK, AND R. M. HARRIS-WARRICK. Distributed amine modulation of graded chemical transmission in the pyloric network of the lobster stomatogastric ganglion. *J. Neurophysiol.* 74: 437–452, 1995.
151. JOHNSTON, R. M., AND A. BEKOFF. Constrained and flexible features of rhythmical hindlimb movements in chicks: kinematic profiles of walking, swimming and airstepping. *J. Exp. Biol.* 171: 43–66, 1992.
152. KACZMAREK, L. K., AND I. B. LEVITAN (Editors). *Neuromodulation: the Biochemical Control of Neuronal Excitability.* New York: Oxford Univ. Press, 1987.
153. KATZ, P. S., AND W. N. FROST. Intrinsic neuromodulation in the *Tritonia* swim CPG: the serotonergic dorsal swim interneurons act presynaptically to enhance transmitter release from interneuron C2. *J. Neurosci.* 15: 6035–6045, 1995.
154. KATZ, P. S., AND W. N. FROST. Intrinsic neuromodulation in the *Tritonia* swim CPG: serotonin mediates both neuromodulation and neurotransmission by the dorsal swim interneurons. *J. Neurophysiol.* 74: 2281–2294, 1995.
155. KATZ, P. S., P. A. GETTING, AND W. N. FROST. Dynamic neuromodulation of synaptic strength intrinsic to a central pattern generator circuit. *Nature Lond.* 367: 729–731, 1994.
156. KATZ, P. S., AND R. M. HARRIS-WARRICK. Recruitment of crab gastric mill neurons into the pyloric motor pattern by mechanosensory afferent stimulation. *J. Neurophysiol.* 65: 1442–1451, 1991.
157. KENNEDY, D., AND W. J. DAVIS. The organization of invertebrate motor systems. In: *Handbook of Physiology. The Nervous System. Cellular Biology of Neurons.* Bethesda, MD: Am. Physiol. Soc., 1977, sect. 1, vol. I, chapt. 27, p. 1023–1087.
158. KENNEDY, D., W. H. EVOY, B. DANE, AND J. T. HANAWALT. The central nervous organization underlying control of antagonistic muscles in the crayfish. II. Coding of position by command fibres. *J. Exp. Zool.* 165: 239–248, 1967.
159. KEPLER, T. B., E. MARDER, AND L. F. ABBOTT. The effect of electrical coupling on the frequency of model neuronal oscillators. *Science Wash. DC* 248: 83–85, 1990.
160. KIEHN, O. Plateau potentials and active integration in the "final common pathway" for motor behaviour. *Trends Neurosci.* 14: 68–73, 1991.
161. KIEHN, O., AND R. M. HARRIS-WARRICK. Serotonergic stretch receptors induce plateau properties in a crustacean motor neuron by a dual-conductance mechanism. *J. Neurophysiol.* 68: 485–495, 1992.
162. KIEHN, O., AND R. M. HARRIS-WARRICK. Serotonergic modulation of hyperpolarization-activated inward current and a calcium-dependent outward current in a crustacean motor neuron. *J. Neurophysiol.* 68: 496–508, 1992.
163. KOCH, V. T., V. S. BÄSSLER, AND M. BRUNNER. Non-spiking neurons suppress fluctuations in small networks. *Biol. Cybern.* 62: 75–81, 1989.
164. KOPELL, N. Toward a theory of modeling central pattern generators. In: *Neural Control of Rhythmic Movements in Vertebrates*, edited by A. H. Cohen, S. Rossignol, and S. Grillner. New York: Wiley, 1988, chapt. 10, p. 369–413.
165. KOPELL, N., AND G. B. ERMENTROUT. Symmetry and phase coupling in chains of weakly coupled oscillators. *Commun. Pure Appl. Math.* 39: 623–660, 1986.
166. KOPELL, N., AND G. B. ERMENTROUT. Coupled oscillators and the design of central pattern generators. *Math. Biosci.* 90: 87–109, 1988.
167. KRISTAN, W. B., JR., AND R. L. CALABRESE. Rhythmic swimming

activity in neurons of the isolated nerve cord of the leech. *J. Exp. Biol.* 65: 643–668, 1976.
168. KRISTAN, W. B., JR., G. S. STENT, AND C. A. ORT. Neuronal control of swimming in the medicinal leech. I. Dynamics of the swimming rhythm. *J. Comp. Physiol.* 94: 97–119, 1974.
169. KRISTAN, W. B., JR., G. S. STENT, AND C. A. ORT. Neuronal control of swimming in the medicinal leech. III. Impulse patterns of the motor neurons. *J. Comp. Physiol.* 94: 155–176, 1974.
170. KUPFERMANN, I. Functional studies of cotransmission. *Physiol. Rev.* 71: 683–732, 1991.
171. KUPFERMANN, I., AND K. R. WEISS. The command neuron concept. *Behav. Brain Sci.* 1: 3–39, 1978.
172. LAURENT, G., AND H. DAVIDOWITZ. Encoding of olfactory information with oscillating neural assemblies. *Science Wash. DC* 265: 1872–1875, 1994.
173. LAURENT, G., AND M. NARAGHI. Odorant-induced oscillations in the mushroom bodies of the locust. *J. Neurosci.* 14: 2993–3004, 1994.
174. LEMASSON, G., E. MARDER, AND L. F. ABBOTT. Activity-dependent regulation of conductances in model neurons. *Science Wash. DC* 259: 1915–1917, 1993.
175. LERESCHE, N., S. LIGHTOWLER, I. SOLTESZ, D. JASSIK-GERSCHENFELD, AND V. CRUNELLI. Low frequency oscillatory activities intrinsic to rat and cat thalamocortical cells. *J. Physiol. Lond.* 441: 155–174, 1991.
176. LINGLE, C. The modulatory action of dopamine on crustacean foregut neuromuscular preparations. *J. Exp. Biol.* 94: 285–299, 1981.
177. LISMAN, J. E., AND M. A. P. IDIART. Storage of 7±2 short-term memories in oscillatory subcycles. *Science Wash. DC* 267: 1512–1515, 1995.
178. LLINAS, R. R. The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. *Science Wash. DC* 242: 1654–1664, 1988.
179. LOFARO, T., N. KOPELL, E. MARDER, AND S. L. HOOPER. Subharmonic coordination in networks of neurons with slow conductances. *Neural Comp.* 6: 69–84, 1994.
180. MA, P. M., B. S. BELTZ, AND E. A. KRAVITZ. Serotonin-containing neurons in lobsters: their role as gain-setters in postural control mechanisms. *J. Neurophysiol.* 68: 36–54, 1992.
181. MARDER, E. Neurotransmitters and neuromodulators. In: *The Crustacean Stomatogastric System*, edited by A. I. Selverston and M. Moulins. Berlin: Springer-Verlag, 1987, p. 263–300.
182. MARDER, E. Plateaus in time. *Curr. Biol.* 1: 326–327, 1991.
183. MARDER, E. Modulating membrane properties of neurons: role in information processing. In: *Exploring Brain Functions: Models in Neuroscience*, edited by T. A. Poggio and D. A. Glaser. Chichester, UK: Wiley, 1993, p. 27–42.
184. MARDER, E., AND J. S. EISEN. Transmitter identification of pyloric neurons: electrically coupled neurons use different neurotransmitters. *J. Neurophysiol.* 51: 1345–1361, 1984.
185. MARDER, E., AND J. S. EISEN. Electrically coupled pacemaker neurons respond differently to the same physiological inputs and neurotransmitters. *J. Neurophysiol.* 51: 1362–1374, 1984.
186. MARDER, E., AND S. L. HOOPER. Neurotransmitter modulation of the stomatogastric ganglion of decapod crustaceans. In: *Model Neural Networks and Behavior*, edited by A. I. Selverston. New York: Plenum, 1985, p. 319–337.
187. MARDER, E., AND P. MEYRAND. Chemical modulation of an oscillatory neural circuit. In: *Neuronal and Cellular Oscillators*, edited by J. Jacklet. New York: Dekker, 1989, p. 317–338.
188. MARDER, E., P. SKIEBE, AND A. E. CHRISTIE. Multiple modes of network modulation. *Dtsch. Zool. Ges.* 87: 177–184, 1994.
189. MARDER, E., AND J. M. WEIMANN. Modulatory control of multiple task processing in the stomatogastric nervous system. In: *Neurobiology of Motor Programme Selection: New Approaches to Mechanisms of Behavioral Choice*, edited by J. Kien, C. McCrohan, and W. Winlow. Oxford, UK: Pergamon, 1992, p. 3–19.
190. MARDER, E., J. M. WEIMANN, T. B. KEPLER, AND L. F. ABBOTT. Computational implications of a serotonin-sensitive region of axonal membrane on a dual function motor neuron. In: *Neural Systems: Analysis and Modeling*, edited by F. H. Eeckman. Boston: Kluwer, 1992, p. 377–390.
191. MATSUSHIMA, T., AND S. GRILLNER. Neural mechanisms of intersegmental coordination in lamprey: local excitability changes modify the phase coupling along the spinal cord. *J. Neurophysiol.* 67: 373–388, 1992.
192. MATSUSHIMA, T., AND S. GRILLNER. Local serotonergic modulation of calcium-dependent potassium channels controls intersegmental coordination in the lamprey spinal cord. *J. Neurophysiol.* 67: 1683–1690, 1992.
193. MAYNARD, D. M. Simpler networks. *Ann. NY Acad. Sci.* 193: 59–72, 1972.
194. MAYNARD, D. M., AND K. D. WALTON. Effects of maintained depolarization of presynaptic neurons on inhibitory transmission in lobster neuropil. *J. Comp. Physiol.* 97: 215–243, 1975.
195. MCCLELLAN, A. D., G. D. BROWN, AND P. A. GETTING. Modulation of swimming in *Tritonia*: excitatory and inhibitory effects of serotonin. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 174: 257–266, 1994.
196. MCCLELLAN, A., AND S. GRILLNER. Activation of "fictive swimming" by electrical microstimulation of brainstem locomotor regions in an in vitro preparation of the lamprey central nervous system. *Brain Res.* 300: 357–361, 1984.
197. MCCLELLAN, A. D., AND K. A. SIGVARDT. Features of entrainment of spinal pattern generators for locomotor activity in the lamprey spinal cord. *J. Neurosci.* 8: 133–145, 1988.
198. MCCORMICK, D. A., AND H.-C. PAPE. Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. *J. Physiol. Lond.* 431: 291–318, 1990.
199. MCCORMICK, D. A., AND H.-C. PAPE. Noradrenergic and serotonergic modulation of a hyperpolarization-activated cation current in thalamic relay neurones. *J. Physiol. Lond.* 431: 319–342, 1990.
200. MEYRAND, P., AND E. MARDER. Matching neural and muscle oscillators: control by FMRFamide-like peptides. *J. Neurosci.* 11: 1150–1161, 1991.
201. MEYRAND, P., J. SIMMERS, AND M. MOULINS. Construction of a pattern generating circuit with neurons of different networks. *Nature Lond.* 351: 60–63, 1991.
202. MEYRAND, P., J. SIMMERS, AND M. MOULINS. Dynamic construction of a neural network from multiple pattern generators in the lobster stomatogastric nervous system. *J. Neurosci.* 14: 630–644, 1994.
203. MEYRAND, P., J. M. WEIMANN, AND E. MARDER. Multiple axonal spike initiation zones in a motor neuron: serotonin activation. *J. Neurosci.* 12: 2803–2812, 1992.
204. MILLER A. D., S. NONANCKA, S. F. LAKOS, AND L. K. TAN. Diaphragmatic and external intercostal muscle control during vomiting: behavior of inspiratory bulbospinal neurons. *J. Neurophysiol.* 63: 31–36, 1990.
205. MILLER, J. P. Pyloric mechanisms. In: *The Crustacean Stomatogastric System*, edited by A. I. Selverston and M. Moulins. Berlin: Springer-Verlag, 1987, p. 109–137.
206. MILLER, J. P., AND A. I. SELVERSTON. Rapid killing of single neurons by an irradiation of intracellularly injected dye. *Science Wash. DC* 206: 702–704, 1979.
207. MILLER, J. P., AND A. I. SELVERSTON. Mechanisms underlying pattern generation in lobster stomatogastric ganglion as determined by selective inactivation of identified neurons. II. Oscillatory properties of pyloric neurons. *J. Neurophysiol.* 48: 1378–1391, 1982.
208. MILLER, J. P., AND A. I. SELVERSTON. Mechanisms underlying pattern generation in lobster stomatogastric ganglion as determined by selective inactivation of identified neurons. IV. Network properties of pyloric system. *J. Neurophysiol.* 48: 1416–1432, 1982.
209. MONTGOMERY, E. B., JR., M. H. CLARE, S. SAHRMANN, S. R. BUCHHOLZ, L. S. HIBBARD, AND W. M. LANDAU. Neuronal multipotentiality: evidence for network representations of physiological function. *Brain Res.* 580: 49–61, 1992.
210. MORRIS, C., AND H. LECAR. Voltage oscillations in the barnacle giant muscle fiber. *Biophys. J.* 35: 193–213, 1981.
211. MORTIN, L. I., AND P. S. G. STEIN. Spinal cord segments containing key elements of the central pattern generators for three forms of scratch reflex in the turtle. *J. Neurosci.* 9: 2285–2296, 1989.
212. MUDGE, A. W., S. E. LEEMAN, AND G. D. FISCHBACH. Enkephalin inhibits release of substance P from sensory neurons in culture

and decreases action potential duration. *Proc. Natl. Acad. Sci. USA* 76: 526–530, 1979.
213. MULLONEY, B. Organization of the stomatogastric ganglion of the spiny lobster. V. Coordination of the gastric and pyloric systems. *J. Comp. Physiol.* 122: 227–236, 1977.
214. MULLONEY, B., D. MURCHISON, AND A. CHRACHRI. Modular organization of pattern-generating circuits in a segmental motor system: the swimmerets of crayfish. *Semin. Neurosci.* 5: 49–57, 1993.
215. MULLONEY, B., AND A. I. SELVERSTON. Antidromic action potentials fail to demonstrate known interactions between neurons. *Science Wash. DC* 177: 69–72, 1972.
216. MULLONEY, B., AND A. I. SELVERSTON. Organization of the stomatogastric ganglion in the spiny lobster. I. Neurons driving the lateral teeth. *J. Comp. Physiol.* 91: 1–32, 1974.
217. MULLONEY, B., AND A. I. SELVERSTON. Organization of the stomatogastric ganglion in the spiny lobster. III. Coordination of the two subsets of the gastric system. *J. Comp. Physiol.* 91: 53–78, 1974.
218. MURCHISON, D., AND J. L. LARIMER. Dual motor output interneurons in the abdominal ganglia of the crayfish *Procambarus clarkii*: synaptic activation of motor outputs in both the swimmeret and abdominal positioning systems by single interneurons. *J. Exp. Biol.* 150: 269–293, 1990.
219. MURCHISON, D., AND J. L. LARIMER. Synaptic interactions among neurons that coordinate swimmeret and abdominal movements in the crayfish. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 170: 739–749, 1992.
220. NADIM, F., Ø. H. OLSEN, E. DE SCHUTTER, AND R. L. CALABRESE. Modeling the leech heartbeat elemental oscillator. I. Interactions of intrinsic and synaptic currents. *J. Computat. Neurosci.* 2: 215–235, 1995.
221. NAGY, F., AND P. S. DICKINSON. Control of a central pattern generator by an identified modulatory interneurone in crustacea. I. Modulation of the pyloric motor output. *J. Exp. Biol.* 105: 33–58, 1983.
222. NAGY, F., P. S. DICKINSON, AND M. MOULINS. Control by an identified modulatory neuron of the sequential expression of plateau properties of, and synaptic inputs to, a neuron in a central pattern generator. *J. Neurosci.* 8: 2875–2886, 1988.
223. NICHOLLS, J. G., AND B. G. WALLACE. Quantal analysis of transmitter release at an inhibitory synapse in the CNS of the leech. *J. Physiol. Lond.* 281: 171–185, 1978.
224. NICHOLLS, J. G., AND B. G. WALLACE. Modulation of transmission at an inhibitory synapse in the central nervous system of the leech. *J. Physiol. Lond.* 281: 157–170, 1978.
225. NISSANOV, J., R. C. EATON, AND R. DIDOMENICO. The motor output of the Mauthner cell, a reticulospinal command neuron. *Brain Res.* 517: 88–98, 1990.
226. NOVICKI, A., AND J. C. WEEKS. Organization of the larval preecdysis motor pattern in the tobacco hornworm, *Manduca sexta*. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 173: 151–162, 1993.
227. NUSBAUM, M. P. Synaptic basis of swim initiation in the leech. III. Synaptic effects of serotonin-containing interneurons (cell 21 and 61) on swim CPG neurons (cells 18 and 208). *J. Exp. Biol.* 122: 303–321, 1986.
228. NUSBAUM, M. P., W. O. FRIESEN, W. B. KRISTAN, JR., AND R. A. PEARCE. Neural mechanisms generating the leech swimming rhythm: swim-initiator neurons excite the network of swim oscillator neurons. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 161: 355–366, 1987.
229. NUSBAUM, M. P., AND E. MARDER. A modulatory proctolin-containing neuron (MPN). I. Identification and characterization. *J. Neurosci.* 9: 1591–1599, 1989.
230. NUSBAUM, M. P., AND E. MARDER. A modulatory proctolin-containing neuron (MPN). II. State-dependent modulation of rhythmic motor activity. *J. Neurosci.* 9: 1600–1607, 1989.
231. NUSBAUM, M. P., J. M. WEIMANN, J. GOLOWASCH, AND E. MARDER. Presynaptic control of modulatory fibers by their neural network targets. *J. Neurosci.* 12: 2706–2714, 1992.
232. OHTA, Y., AND S. GRILLNER. Monosynaptic excitatory amino acid transmission from the posterior rhombencephalic reticular nucleus to spinal neurones involved in the control of locomotion in lamprey. *J. Neurophysiol.* 62: 1079–1089, 1989.
233. OLSEN, Ø. H., F. NADIM, and R. L. CALABRESE. Modeling the leech heartbeat elemental oscillator. II. Exploring the parameter space. *J. Computat. Neurosci.* 2: 237–257, 1995.
234. OPDYKE, C. A., AND R. L. CALABRESE. A persistent sodium current contributes to oscillatory activity in heart interneurons of the medicinal leech. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 175: 781–789, 1994.
235. PANCHIN, Y. V., R. I. SADREEV, AND Y. I. ARSHAVSKY. Control of locomotion in marine mollusc *Clione limacina X*. Effects of acetylcholine antagonists. *Exp. Brain Res.* 106: 135–144, 1995.
236. PASZTOR, V. Modulation of sensitivity in invertebrate sensory receptors. *Semin. Neurosci.* 1: 5–14, 1989.
237. PEARCE, R. A., AND W. O. FRIESEN. Intersegmental coordination of leech swimming comparison of in situ and isolated nerve cord activity with body wall movement. *Brain Res.* 299: 363–366, 1984.
238. PEARCE, R. A., AND W. O. FRIESEN. Intersegmental coordination of the leech swimming rhythm. I. Intrinsic period gradient and coupling strength. *J. Neurophysiol.* 54: 1444–1459, 1985.
239. PEARCE, R. A., AND W. O. FRIESEN. Intersegmental coordination of the leech swimming rhythm. II. Comparison of long and short chains of ganglia. *J. Neurophysiol.* 54: 1460–1472, 1985.
240. PEARCE, R. A., AND W. O. FRIESEN. A model for intersegmental coordination in the leech nerve cord. *Biol. Cybern.* 58: 301–311, 1988.
241. PEARSON, K. G., AND C. R. FOURTNER. Nonspiking interneurons in walking system of the cockroach. *J. Neurophysiol.* 38: 33–52, 1975.
242. PEARSON, K. G., AND J. M. RAMIREZ. Parallels with other invertebrate and vertebrate motor systems. In: *Dynamic Biological Networks: The Stomatogastric Nervous System*, edited by R. M. Harris-Warrick, E. Marder, A. I. Selverston, and M. Moulins. Cambridge, MA: MIT Press, 1992, p. 263–281.
243. PENG, Y.-Y., AND J. P. HORN. Continuous repetitive stimuli are more effective than bursts for evoking LHRH release in bullfrog sympathetic ganglia. *J. Neurosci.* 11: 85–95, 1991.
244. PERKEL, D. H., AND B. MULLONEY. Motor pattern production in reciprocally inhibitory neurons exhibiting postinhibitory rebound. *Science Wash. DC* 185: 181–183, 1974.
245. PETERSON, E. L. Generation and coordination of heartbeat timing oscillation in the medicinal leech. I. Oscillation in isolated ganglia. *J. Neurophysiol.* 49: 611–626, 1983.
246. PETERSON, E. L. Generation and coordination of heartbeat timing oscillation in the medicinal leech. II. Intersegmental coordination. *J. Neurophysiol.* 49: 627–638, 1983.
247. PETERSON, E. L., AND R. L. CALABRESE. Dynamic analysis of rhythmic neural circuit in the leech, *Hirudo medicinalis*. *J. Neurophysiol.* 47: 256–271, 1982.
248. PIN, T., M. CREST, E. EHILE, G. JACQUET, AND M. GOLA. Plateau-generating nerve cells in *Helix*: morphological and electrophysiological characteristics. *J. Exp. Biol.* 152: 189–209, 1990.
249. PINSKER, H. M. *Aplysia* bursting neurons as endogenous oscillators. I. Phase-response curves for pulsed inhibitory synaptic input. *J. Neurophysiol.* 40: 527–543, 1977.
250. PINSKER, H. M. *Aplysia* bursting neurons as endogenous oscillators. II. Synchronization and entrainment by pulsed inhibitory synaptic input. *J. Neurophysiol.* 40: 544–556, 1977.
251. POON, M., W. O. FRIESEN, AND G. S. STENT. Neuronal control of swimming in the medicinal leech. V. Connections between oscillatory interneurons and the motor neurones. *J. Exp. Biol.* 75: 45–63, 1978.
252. PROBST, W. C., E. C. CROPPER, J. HEIERHORST, S. L. HOOPER, H. JAFFE, F. VILIM, S. BEUSHAUSEN, I. KUPFERMANN, AND K. R. WEISS. cAMP-dependent phosphorylation of *Aplysia* twitching may mediate modulation of muscle contractions by neuropeptide cotransmitters. *Proc. Natl. Acad. Sci. USA* 91: 8487–8491, 1994.
253. RAMIREZ, J. M., AND I. ORCHARD. Octopaminergic modulation of the forewing stretch receptor in the locust, *Locusta migratoria*. *J. Exp. Biol.* 149: 255–279, 1990.
254. RAMIREZ, J. M., AND K. G. PEARSON. Octopamine induces bursting and plateau potentials in insect neurones. *Brain Res.* 549: 332–337, 1991.
255. RAMIREZ, J. M., AND K. G. PEARSON. Alteration of bursting proper-

ties in interneurons during locust flight. *J. Neurophysiol.* 70: 2148–2160, 1993.
256. REZER, E., AND M. MOULINS. Expression of the crustacean pyloric pattern generator in the intact animal. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 153: 17–28, 1983.
257. RINZEL, J., AND G. B. ERMENTROUT. Analysis of neural excitability and oscillations. In: *Methods in Neuronal Modeling*, edited by C. Koch and I. Segev. Cambridge, MA: MIT Press, 1989, p. 135–169.
258. RINZEL, J., AND Y. S. LEE. Dissection of a model for neuronal parabolic bursting. *J. Math. Biol.* 25: 653–675, 1987.
259. ROBERTS, A., M. J. TUNSTALL, AND E. WOLF. Properties of networks controlling locomotion and significance of voltage dependency of NMDA channels: simulation study of rhythm generation sustained by positive feedback. *J. Neurophysiol.* 73: 485–495, 1995.
260. ROVAINEN, C. M. Synaptic interactions of identified nerve cells in the spinal cord of the sea lamprey. *J. Comp. Neurol.* 154: 189–206, 1974.
261. ROWAT, P. F., AND A. I. SELVERSTON. Modeling the gastric mill central pattern generator of the lobster with a relaxation-oscillator network. *J. Neurophysiol.* 70: 1030–1053, 1993.
262. RUSSELL, D. F., AND D. K. HARTLINE. Bursting neural networks: a reexamination. *Science Wash. DC* 200: 453–456, 1978.
263. SATTERLIE, R. A. Reciprocal inhibition and postinhibitory rebound produce reverberation in locomotor pattern generator. *Science Wash. DC* 229: 402–404, 1985.
264. SATTERLIE, R. A. Reciprocal inhibition and rhythmicity: swimming in a pteropod mollusc. In: *Neuronal and Cellular Oscillators*, edited by J. Jacklet. New York: Dekker, 1989, p. 151–171.
265. SATTERLIE, R. A. Neural control of speed changes in an opistobranch locomotory system. *Biol. Bull.* 180: 228–233, 1991.
266. SCHMIDT, J., AND R. L. CALABRESE. Evidence that acetylcholine is an inhibitory transmitter of heart interneurons in the leech. *J. Exp. Biol.* 171: 329–347, 1992.
267. SELVERSTON, A. I. (Editor). *Model Neural Networks and Behavior*. New York: Plenum, 1985.
268. SELVERSTON, A. I. Lobster gastric mill oscillator. In: *Neuronal and Cellular Oscillators*, edited by J. Jacklet. New York: Dekker, 1989, p. 339–370.
269. SELVERSTON, A. I., AND J. P. MILLER. Mechanism underlying pattern generation in lobster stomatogastric ganglion as determined by selective inactivation of identified neurons. I. Pyloric system. *J. Neurophysiol.* 44: 1102–1121, 1980.
270. SELVERSTON, A. I., AND B. MULLONEY. Organization of the stomatogastric ganglion of the spiny lobster. II. Neurons driving the medial tooth. *J. Comp. Physiol.* 91: 33–51, 1974.
271. SHARP, A. A., L. F. ABBOTT, AND E. MARDER. Artificial electrical synapses in oscillatory neurons. *J. Neurophysiol.* 67: 1691–1694, 1992.
272. SHARP, A. A., M. B. O'NEIL, L. F. ABBOTT, AND E. MARDER. Dynamic clamp: computer-generated conductances in real neurons. *J. Neurophysiol.* 69: 992–995, 1993.
273. SHARP, A. A., M. B. O'NEIL, L. F. ABBOTT, AND E. MARDER. The dynamic clamp: artificial conductances in biological neurons. *Trends Neurosci.* 16: 389–394, 1993.
274. SHARP, A. A., F. K. SKINNER, AND E. MARDER. Dynamic clamp constructed two-cell half-center circuits: mechanisms of oscillation and the interaction and modulation of synaptic and intrinsic conductances. *J. Neurophysiol.* In press.
275. SHERMAN, A., AND J. RINZEL. Rhythmogenic effects of weak electrotonic coupling in neuronal models. *Proc. Natl. Acad. Sci. USA* 89: 2471–2474, 1992.
276. SIEGLER, M. V. Nonspiking interneurons and motor control in insects. *Adv. Insect Physiol.* 18: 249–304, 1985.
277. SIGVARDT, K. A. Spinal mechanisms in the control of lamprey swimming. *Am. Zool.* 29: 19–35, 1989.
278. SIGVARDT, K. A. Intersegmental coordination in the lamprey central pattern generator for locomotion. *Semin. Neurosci.* 5: 3–15, 1993.
279. SIGVARDT, K. A., S. GRILLNER, P. WALLÉN, AND P. A. M. VAN DONGEN. Activation of NMDA receptors elicits fictive locomotion and bistable membrane properties in the lamprey spinal cord. *Brain Res.* 336: 390–395, 1985.
280. SILLAR, K. T. Synaptic modulation of cutaneous pathways in the vertebrate spinal cord. *Semin. Neurosci.* 1: 45–54, 1989.
281. SILLAR, K. T., J. F. S. WEDDERBURN, AND J. A. SIMMERS. The development of swimming rhythmicity in post-embryonic *Xenopus laevis*. *Proc. R. Soc. Lond. B Biol. Sci.* 246: 147–153, 1991.
282. SIMON, T. W., C. A. OPDYKE, AND R. L. CALABRESE. Modulatory effects of FMRF-NH2 on outward currents and oscillatory activity in heart interneurons of the medicinal leech. *J. Neurosci.* 12: 525–537, 1992.
283. SIMON, T. W., J. SCHMIDT, AND R. L. CALABRESE. Modulation of high-threshold transmission between heart interneurons of the medicinal leech by FMRF-NH2. *J. Neurophysiol.* 71: 454–466, 1994.
284. SKINNER, F. K., S. GRAMOLL, R. L. CALABRESE, N. KOPELL, AND E. MARDER. Frequency control in biological half-center oscillators. In: *Computation in Neurons and Neural Systems*, edited by F. H. Eeckman. Boston: Kluwer, 1994, p. 223–228.
285. SKINNER, F. K., N. KOPELL, AND E. MARDER. Mechanisms for oscillation and frequency control in reciprocal inhibitory model neural networks. *J. Computat. Neurosci.* 1: 69–87, 1994.
286. SKINNER, F. K., G. G. TURRIGIANO, AND E. MARDER. Frequency and burst duration in oscillating neurons and two-cell networks. *Biol. Cybern.* 69: 375–383, 1993.
287. SOFFE, S. R. Roles of glycinergic inhibition and *N*-methyl-D-aspartate receptor-mediated excitation in the locomotor rhythmicity of one half of the *Xenopus* embryos. *Eur. J. Neurosci.* 1: 561–571, 1989.
288. SOFFE, S. R. Active and passive membrane properties of spinal cord neurons which are rhythmically active during swimming in *Xenopus* embryos. *Eur. J. Neurosci.* 2: 1–10, 1990.
289. SOFFE, S. R. Two distinct rhythmic motor patterns are driven by common premotor and motor neurons in a simple vertebrate spinal cord. *J. Neurosci.* 13: 4456–4469, 1994.
290. SOLTESZ, I., S. LIGHTOWLER, N. LERESCHE, D. JASSIK-GERSCHENFELD, C. E. POLLARD, AND V. CRUNELLI. Two inward currents and the transformation of low frequency oscillations of rat and cat thalamocortical cells. *J. Physiol. Lond.* 441: 175–197, 1991.
291. SOMERS, D., AND N. KOPELL. Rapid synchronization through fast threshold modulation. *Biol. Cybern.* 68: 393–407, 1993.
292. STEIN, P. S. G. Spinal cord circuits for motor pattern selection in the turtle. *Ann. NY Acad. Sci.* 563: 1–10, 1989.
293. STERIADE, M., D. A. MCCORMICK, AND T. J. SEJNOWSKI. Thalamocortical oscillations in the sleeping and aroused brain. *Science Wash. DC* 262: 679–685, 1993.
294. STERIADE, M., A. NUÑEZ, AND F. AMZICA. Intracellular analysis of relations between the slow (<1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. *J. Neurosci.* 13: 3266–3283, 1993.
295. THOMPSON, K. J., AND R. L. CALABRESE. FMRFamide effects on membrane properties of heart cells isolated from the leech, *Hirudo medicinalis*. *J. Neurophysiol.* 67: 280–291, 1992.
296. TIERNEY, A. J., AND R. M. HARRIS-WARRICK. Physiological role of the transient potassium current in the pyloric circuit of the lobster stomatogastric ganglion. *J. Neurophysiol.* 67: 599–609, 1992.
297. TUNSTALL, M. J., AND A. ROBERTS. Longitudinal coordination of motor output during swimming in *Xenopus* embryos. *Proc. R. Soc. Lond. B Biol. Sci.* 244: 27–32, 1991.
298. TUNSTALL, M. J., AND A. A. ROBERTS. A longitudinal gradient of synaptic drive in the spinal cord of *Xenopus* embryos and its role in co-ordination of swimming. *J. Physiol. Lond.* 474: 393–405, 1994.
299. TUNSTALL, M. J., AND K. T. SILLAR. Physiological and developmental aspects of intersegmental coordination in *Xenopus* embryos and tadpoles. *Semin. Neurosci.* 5: 29–40, 1993.
300. TURRIGIANO, G. G., G. LEMASSON, AND E. MARDER. Selective regulation of current densities underlies spontaneous changes in the activity of cultured neurons. *J. Neurosci.* 15: 3640–3652, 1995.
301. VAN VREESWIJK, C., L. F. ABBOTT, AND G. B. ERMENTROUT. When inhibition not excitation synchronizes neural firing. *J. Computat. Neurosci.* 1: 313–321, 1994.
302. WALL, M. J., AND N. DALE. A role for potassium currents in the generation of the swimming motor pattern of *Xenopus* embryos. *J. Neurophysiol.* 72: 337–348, 1994.

303. WALLEN, P., O. EKEBERG, A. LANSNER, L. BRODIN, H. TRAVEN, AND S. GRILLNER. A computer-based model for realistic simulations of neuronal networks. II. The segmental network generating locomotor rhythmicity in the lamprey. *J. Neurophysiol.* 68: 1939–1950, 1992.
304. WALLÉN, P., AND S. GRILLNER. *N*-methyl-D-aspartate receptor-induced inherent activity in neurons active during fictive locomotion in the lamprey. *J. Neurosci.* 7: 2745–2755, 1987.
305. WALLÉN, P., AND T. L. WILLIAMS. Fictive locomotion in the lamprey spinal cord in vitro compared with swimming in the intact and spinal animal. *J. Physiol. Lond.* 347: 225–239, 1984.
306. WANG, X.-J., AND J. RINZEL. Alternating and synchronous rhythms in reciprocally inhibitory model neurons. *Neural Comp.* 4: 84–97, 1992.
307. WEEKS, J. C. Neuronal basis of leech swimming: separation of swim initiation, pattern generation and intersegmental coordination by selective lesions. *J. Neurophysiol.* 45: 698–723, 1981.
308. WEEKS, J. C. Synaptic basis of swim initiation in the leech. I. Connections of a swim-initiation neuron (cell 204) with motor neurons and pattern-generating "oscillator" neurons. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 148: 253–263, 1982.
309. WEEKS, J. C. Synaptic basis of swim initiation in the leech. II. A pattern-generating neuron (cell 208) which mediates motor effects of swim-initiating neurons. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 148: 265–279, 1982.
310. WEEKS, J. C., AND W. B. KRISTAN, JR. Initiation, maintenance and modulation of swimming in the medicinal leech by the activity of a single neuron. *J. Exp. Biol.* 77: 71–88, 1978.
311. WEIMANN, J. M., AND E. MARDER. Switching neurons are integral members of multiple oscillatory networks. *Curr. Biol.* 4: 896–902, 1994.
312. WEIMANN, J. M., E. MARDER, B. EVANS, AND R. L. CALABRESE. The effects of SDRNFLRFamide and TNRNFLRFamide on the motor patterns of the stomatogastric ganglion of the crab *Cancer borealis*. *J. Exp. Biol.* 181: 1–26, 1993.
313. WEIMANN, J. M., P. MEYRAND, AND E. MARDER. Neurons that form multiple pattern generators: identification and multiple activity patterns of gastric/pyloric neurons in the crab stomatogastric system. *J. Neurophysiol.* 65: 111–122, 1991.
314. WEISS, K. R., J. L. COHEN, AND I. KUPFERMANN. Modulatory control of buccal musculature by a serotonergic neuron (metacerebral cell) in *Aplysia*. *J. Neurophysiol.* 41: 181–203, 1978.
315. WEISS, K. R., D. E. MANDELBAUM, M. SCHONBERG, AND I. KUPFERMANN. Modulation of buccal muscle contractility by serotonergic metacerebral cells in *Aplysia*: evidence for a role of cyclic adenosine monophosphate. *J. Neurophysiol.* 42: 791–803, 1979.
316. WHIM, M. D., AND P. E. LLOYD. Frequency-dependent release of peptide cotransmitters from identified cholinergic motor neurons in *Aplysia*. *Proc. Natl. Acad. Sci. USA* 86: 9034–9038, 1989.
317. WHIM, M. D., AND P. E. LLOYD. Neuropeptide cotransmitters released from an identified cholinergic motor neuron modulate neuromuscular efficacy in *Aplysia*. *J. Neurosci.* 10: 3313–3322, 1990.
318. WIERSMA, C. A. G., AND K. IKEDA. Interneurons commanding swimmeret movements in the crayfish, *Procambarus clarkii* (Girard). *Comp. Biochem. Physiol.* 12: 509–525, 1964.
319. WILLIAMS, T. L. Phase coupling by synaptic spread in chains of coupled neuronal oscillators. *Science Wash. DC* 258: 662–665, 1992.
320. WILLIAMS, T. L. Phase coupling in simulated chains of coupled oscillators representing the lamprey spinal cord. *Neural Comp.* 4: 54–558, 1992.
321. WILLIAMS, T. L., S. GRILLNER, V. V. SMOLJANINOV, P. WALLÉN, S. KASHIN, AND S. ROSSIGNOL. Locomotion in lamprey and trout: the relative timing of activation and movement. *J. Exp. Biol.* 143: 559–566, 1989.
322. WILLIAMS, T. L., AND K. A. SIGVARDT. Intersegmental phase lags in the lamprey spinal cord: experimental confirmation of the existence of a boundary region. *J. Computat. Neurosci.* 1: 61–67, 1994.
323. WILLIAMS, T. L., K. A. SIGVARDT, N. KOPELL, G. B. ERMENTROUT, AND M. P. REMLER. Forcing of coupled nonlinear oscillators: studies of intersegmental coordination in the lamprey locomotor central pattern generator. *J. Neurophysiol.* 64: 862–871, 1990.
324. WILSON, D. The central nervous control of locust flight. *J. Exp. Biol.* 38: 471–490, 1961.
325. WOLF, H., AND K. G. PEARSON. Comparison of motor patterns in the intact and deafferented flight system of the locust. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* 160: 269–279, 1987.
326. WU, J., L. B. COHEN, AND C. X. FALK. Neuronal activity during different behaviors in *Aplysia*: a distributed organization. *Science Wash. DC* 263: 820–822, 1994.
327. ZIEGLGÄNSBERGER, W., AND T. R. TÖLLE. The pharmacology of pain signaling. *Curr. Biol.* 3: 611–618, 1993.