Intersegmental Coordination of Rhythmic Motor Patterns

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Submitted 7 April 2003; accepted in final form 22 April 2003

INTRODUCTION

The study of the neural basis of motor patterns that underlie wavelike behaviors such as undulatory swimming has contributed to our general understanding of coordination in the nervous system. Numerous studies have shown that the isolated nervous system is capable of producing rhythmic motor output in the absence of sensory feedback (Marder and Calabrese 1996). In addition, in many cases these rhythmic motor patterns are similar to those required for specific behaviors in the intact animal. For example, in the lamprey forward swimming is accomplished by means of side-to-side undulations that travel from anterior to posterior along the length of the body (Wallén and Williams 1984). In the lamprey, as in many other animals, wavelike motor patterns arise from a network of neurons that is distributed longitudinally along the neural axis. This type of neural network consists of a chain of coupled segmental oscillators, local neural networks that are capable of independently generating rhythmic output (Skinner and Mulloney 1998a). The appropriate phase relationships between these segmental oscillators arise as an emergent property of the segmental oscillators and the coupling between them. Although this distributed organization is found in many different animals, there are large differences in terms of the properties of the segmental oscillators, the strength and symmetry of coupling, and the importance of sensory feedback. In this review, we will discuss some of the variations in design found in three animals: the lamprey, leech, and crayfish.

PHASE CONSTANCY IS NECESSARY FOR UNDULATORY SWIMMING

The leech and the lamprey both swim in an undulatory fashion with the body forming approximately one full wave at any given time during swimming. To maintain this mode of swimming as an animal changes its swim cycle period, the phase between the body contractions in different segments must remain constant. In the leech, there are 18 body segments that are actively used for swimming. Thus the phase lag between consecutive body segments is about 20° in the swimming animal (Kristan et al. 1974). Intersegmental phase lags that are nearly independent of cycle period are also observed in isolated chains of the leech nerve cord consisting of as few as two ganglia (Pearce and Friesen 1985). However, in contrast to the intact animal, the phase lag per segment within a long chain of ganglia in vitro is only about 8°.

In the leech swim network, the segmental oscillators are not uniform in their ability to generate rhythmic output. Isolated ganglia from the anterior end to the midpoint of the ventral nerve cord are capable of generating swim-like oscillations, but not individual posterior ganglia (Hocker et al. 2000; cf. Tunstall et al. 2002). In addition, there is a U-shaped gradient of cycle period. Isolated mid-cord ganglia produce oscillations with a shorter cycle period than either individual anterior ganglia or short chains of posterior ganglia.

A segmental oscillator of the leech swim network consists of motor neurons and oscillator interneurons within a single ganglion that are organized into two bilaterally symmetric segmental circuits. Oscillations originate within a single ganglion from the local circuit formed by these oscillator interneurons, which are connected almost exclusively by inhibitory synapses (Friesen and Pearce 1993). The hemisegments within a single ganglion oscillate synchronously based on strong electrical and chemical coupling across the midline (Friesen and Hocker 2001). This activity pattern is appropriate since the leech swims by dorsoventral undulations, which require synchronous activation of muscles on the left and right sides of the body. Because the two hemisegments are equivalent, in studying intersegmental coordination it is justified to consider only the circuitry on one side of the animal. The segmental oscillators are coupled by ascending and descending projections of the oscillator interneurons, which synapse directly with oscillator interneurons in other ganglia (Fig. 1).

In principle, the generation of phase lags appropriate for forward swimming can be explained by a system consisting of a chain of coupled oscillators in which the anterior oscillators have shorter inherent periods than the posterior oscillators (Ikeda and Wiersma 1966; Matsushima and Grillner 1992). When a system such as this is coupled, all segmental oscillators of the network share the same period, but the faster oscillators will lead in phase. In the case of the leech swimming, this explanation is not sufficient to explain forward swimming because the segmental oscillators with the shortest cycle period lie at the midpoint of the ventral nerve cord. Experimental and modeling work has provided evidence that forward swimming most likely arises from asymmetries in the coupling between the segmental oscillators (Cang and Friesen 2002).

Intersegmental coupling, which spans six segments in both the ascending and the descending directions, is approximately equal in functional strength in either direction (Friesen and Hocker 2001; Pierce and Friesen 1985). However, at the level of specific interconnections there are many asymmetries. The oscillator interneurons are active at three different phases sep-
segmental coordination in the leech than in the lamprey, which coupling and sensory feedback are more important for inter-

Experimental in which the nervous system was transected

mechanical coupling are indeed important for appropriate coordi-

nation (Cang and Friesen 2002; Friesen and Cang 2001).

The resulting computer model produced a phase lag observed in the intact animal, these mechanisms

were added to the computer model (Cang and Friesen 2000; Yu et al. 1999). A computer model that incorporates these asymmetries but not the inherent period differences produced a 8–10° phase lag similar to that seen in long chains of isolated nerve cords as well as phase constancy with changing cycle period (Cang and Friesen 2002).

Although the model replicated the behavior of the isolated nerve cord, the 8° phase lag between segments is clearly too small to produce a traveling wave of one wavelength along the body. To test the idea that sensory feedback from stretch receptors embedded in the body wall and mechanical coupling between muscles in neighboring segments may contribute to the phase lag observed in the intact animal, these mechanisms were added to the computer model (Cang and Friesen 2000; Yu et al. 1999). The resulting computer model produced a phase lag of 17° per segment, which is similar to the value in the intact animal (20°), suggesting that sensory feedback and mechanical coupling are indeed important for appropriate coordination (Cang and Friesen 2002; Friesen and Cang 2001).

Experiments in which the nervous system was transected (Wallén 1982; Yu et al. 1999) have shown that mechanical coupling and sensory feedback are more important for intersegmental coordination in the leech than in the lamprey, which is discussed in the following text. Perhaps a high degree of peripheral feedback is necessary in an animal such as the leech, which has a hydrostatic skeleton.

In the lamprey as in the leech, forward swimming results from a traveling wave of one body length that begins at the anterior end of the animal. The lamprey has about 100 body segments; therefore, the phase difference between body segments is about 1% in the intact animal. An identical phase difference occurs in the isolated spinal cord when rhythmic activity is induced with the NMDA receptor agonist, d-gluta-
mate (Wallén and Williams 1984).

Although it is not possible to identify individual interneurons as in the leech swim network, two classes of interneurons, excitatory (E) and inhibitory (C), appear to be essential for burst generation (Grillner et al. 1995). The E interneurons synapse ipsilaterally with other E interneurons and with C interneurons (Fig. 2). The mutual excitation between E interneurons appears to support the generation of bursts in hemiseg-

ments (Hellgren-Kotaleski et al. 1999b). The C interneurons project contralaterally and inhibit other C interneurons as well as E interneurons (Buchanan 1982). These interneurons are responsible for producing alternating activity between the right and left sides of the spinal cord, which is necessary for side-
to-side undulatory swimming (Hellgren-Kotaleski et al. 1999a).

In the first model of a segmental oscillator in this system, burst termination was governed by reciprocal inhibition and the hemisegments were incapable of independent bursting. This network generated oscillations with a duty cycle (burst dura-
tion divided by cycle period) of 50%, a characteristic property of a half-center oscillator (Skinner et al. 1994; Wallén et al. 1992). In contrast, in the biological system, the duty cycle is 30–40% and when inhibitory synapses are pharmacologically blocked, the hemisegments burst endogenously (Hagevik and McClellan 1994; Wallén and Williams 1984).

Recent work has confirmed that reciprocal inhibition is not

![FIG. 1. Intersegmental coupling between two hemisegmental oscillators of the leech swim network. Intersegmental synaptic connections between oscillator interneurons are shown (intrasegmental connections have been omitted for simplicity). The interneurons in each ganglion are arranged in rows according to the phase of their activity. Each of the interneurons shown occurs as a bilateral pair except for the unpaired interneuron 208. The filled circles represent inhibitory synapses. The T symbols represent excitatory synapses. Question marks indicate that certain targets are unknown. Figure adapted from Cang and Friesen (2002).](http://jn.physiology.org/)

![FIG. 2. A segmental oscillator of the lamprey swim network. The segmental oscillator consists of 2 bilaterally symmetric hemisegmental circuits. The interneurons (E, C, and L) generate oscillations. E interneurons excite all neurons within a hemisegmental oscillator. C interneurons inhibit all neurons of the contralateral hemisegmental oscillator. L interneurons inhibit ipsilateral C interneurons but are not critical for ipsilateral burst termination (Hellgren et al. 1992). The motor neurons (M) receive synaptic input from the E and C interneurons. The stretch receptors (triangles) excite ipsilateral and inhibit contralateral neurons. E and L interneurons project ipsilaterally in both directions. C interneurons project in the descending direction and cross the midline. Open circles indicate excitatory synapses, and black circles indicate inhibitory synapses. Synapse symbols impinging on the circle around a hemisegmental oscillator indicate that synapses are made with all of the neurons within the circle. Figure adapted from Bern et al. (2003).](http://jn.physiology.org/)
the primary factor that terminates bursts, but rather the activation of two types of Ca\(^{2+}\)-dependent K\(^+\) channels (K\(_{Ca}\)). One type, activated by Ca\(^{2+}\) that enters during action potentials, causes postspike afterhyperpolarizations that lead to spike frequency adaptation (Tegnér et al. 1998). The other type, activated by Ca\(^{2+}\) that enters through open NMDA channels during each burst, produces a more gradual hyperpolarization (Brodin et al. 1991). The incorporation of these mechanisms into a model of a segmental oscillator results in hemisegments that can oscillate independently and a duty cycle similar to that of the biological system (Hellgren-Kotaleski et al. 1999b). The addition of a mechanism in which the amount of adaptation (based loosely on K\(_{Ca}\) activation) increases as the cycle frequency increases resulted in a model that was capable of oscillating with a constant duty cycle over roughly a 10-fold frequency range, which would be necessary for the animal to swim at different speeds (Ullström et al. 1998).

Important early theoretical work (Kopell and Ermentrout 1988) indicated that appropriate phase lags for lamprey swimming may be generated by two mechanisms: asymmetries in the coupling between segmental oscillators and differences in inherent segmental periods. Evidence for coupling asymmetries comes from a variety of experiments. Movements imposed on the isolated spinal cord can entrain the activity of the entire swim network by activating intra-spinal stretch receptors, which provide sensory feedback to the interneurons (Fig. 2) (Grillner et al. 1981). Interestingly, movement applied to the caudal end of the spinal cord can entrain the system to a greater range of frequencies than movements applied to the rostral end (Williams et al. 1990). Additionally, split-bath experiments in which the rostral and caudal halves of the spinal cord were bathed in pools with different concentrations of n-glutamate demonstrated that the rostral spinal cord dominates the frequency of the coupled network (Sigvardt and Williams 1996). In another study, physiological and computer modeling results suggested that longitudinal coupling is due primarily to ipsilateral excitatory coupling that is stronger in the descending direction than in the ascending direction (Hagevik and McClellan 1994). There is also evidence of anatomical coupling asymmetries. For example, whereas the E interneurons project symmetrically over a few segments both rostrally and caudally, the C interneurons project 14–20 segments caudally but have only short rostral projections (Buchanan 1982; Dale 1986).

Evidence for, or against, the existence of a gradient of segmental oscillator frequency is more limited than for asymmetric coupling. Pharmacologically induced frequency gradients can alter and even reverse the normal rostrocaudal phase lags in the isolated spinal cord (Matsushima and Grillner 1992; Tegnér et al. 1993). Although such experiments cannot demonstrate that such a gradient exists naturally, they show that at least in principle a gradient could produce the appropriate phase lags. Presumably in the intact system a gradient of oscillator frequencies could be produced by a corresponding gradient of descending synaptic drive as has been found in the swim network of Xenopus embryos (Tunstall and Roberts 1994). In contrast to these results, surgically isolated sections of the spinal cord do not vary in frequency in a systematic way (Cohen 1987). One problem with this study, however, is that the rhythm was induced pharmacologically rather than by normal descending spinal pathways. To address this problem, a study was conducted in which fictive swimming was induced by pharmacological microstimulation of the brain. By blocking local rhythmic activity in either the rostral or the caudal half of the spinal cord with a low Ca\(^{2+}\) saline, it was possible to measure the activity of independent sections of the spinal cord (Hagevik and McClellan 1999). This study revealed faster oscillations in the rostral spinal cord than in the caudal spinal cord.

The extent of longitudinal coupling between segmental oscillators in the lamprey is doubtless another important factor for determining phase lags. Functional coupling that determines phase appears to extend over a much more limited range than the full projection range of 30–50 segmental reported for some interneurons (Rovainen 1974). In one study, the lamprey spinal cord was placed in a chamber with partitions allowing the rostral, middle, and caudal sections to be bathed in different solutions (Miller and Sigvardt 2000). Local synaptic activity was blocked in the middle section with a solution containing low-Ca\(^{2+}\) and high-Mg\(^{2+}\) without affecting spike conduction in axons spanning the middle compartment. The results indicated that although the maximal functional length of propriospinal coupling is 16–20 segments, phase was controlled by short-range coupling that spans only 4–6 segments (see also McClellan and Hagevik 1999). It has been proposed that the interneurons which comprise a segmental oscillator act not only to generate the local rhythm but also project to, and influence, rhythm generation in other segments. The feasibility of this idea, which has been termed “synaptic spread,” has been demonstrated in modeling studies in which the synaptic contacts made locally by an interneuron are also made with similar targets in neighboring segments but with lower synaptic strengths (Buchanan 1992; Ekeberg 1993; Wadden et al. 1997; Williams 1992). Recent models incorporating cellular and synaptic properties of the swim network can replicate many of the observed properties of the swimming animal such as a reversal of phase lag necessary for backward swimming (Ullström et al. 1998).

At first glance, sensory feedback appears to be less important for swimming in the lamprey than in the leech since the motor output of the isolated spinal cord closely resembles the pattern of the intact animal (Wallén and Williams 1984). To assess the contribution of sensory feedback, a model was created that included the swim network, muscle activation, body mechanics, counteracting water forces, and sensory feedback (Ekeberg 1993; Ekeberg et al. 1999). In this model, stretch receptors had very little effect on swimming movements in still water. However, when the virtual lamprey swam in a cross current, a model incorporating stretch receptors performed much better than a model lacking them. In the latter, transversely flowing water forced the head to one side, eventually resulting in a complete change of direction. In the model with stretch receptors, the sensory feedback counteracted the perturbing effects of the current and allowed the simulated lamprey to swim straight. Therefore although sensory feedback does not contribute strongly to phase lag as in the leech, it is necessary to counteract environmental perturbations.

**PHASE FLEXIBILITY IN THE LEECH HEARTBEAT NETWORK**

The timing network that paces the leech heartbeat differs in many ways from the two systems discussed so far. In this
system, the interaction between segmental oscillators is characterized by phase flexibility rather than phase constancy. The heartbeat network contains two segmental oscillators located in the 3rd and 4th ganglia of the ventral nerve cord (Fig. 3A) (Peterson 1983a,b). The output of these two segmental oscillators paces and coordinates the activity of a network of interneurons and motor neurons that control the peristaltic contractions of two lateral heart tubes that run the length of the body (Calabrese et al. 1995).

The phase between these oscillators in isolated nerve cords is stable for the duration of an experiment but varies between preparations from about −12 to +20% (the median phase difference is 6%; a positive phase lag indicates that the G4 segmental oscillator leads in phase) (Masino and Calabrese 2002a). A combination of physiological and modeling work has demonstrated that this wide phase range can be accounted for by the specific network configuration combined with intrinsic period differences between the segmental oscillators.

At the core of each segmental oscillator is a pair of heart interneurons (HN cells) that form reciprocally inhibitory synapses across the ganglion midline and constitute a half-center oscillator (Fig. 3A). For example, the heart interneuron on the left side of the 3rd ganglion [HN(L,3)] is reciprocally inhibitory with its contralateral homologue. Similar to the hemisegments in the lamprey spinal cord, these interneurons are capable of endogenous oscillations when inhibitory synapses are blocked (Cymbalyuk et al. 2002). However, physiological and modeling data show that although the individual oscillator interneurons are capable of endogenous bursting, the half-center configuration makes the oscillations more robust, ensures bilateral alternation of bursting, alters period substantially from the inherent period, and fixes duty cycle near 50% (Cymbalyuk et al. 2002). The two segmental oscillators are coupled by coordinating interneurons that have cell bodies in the first and second ganglia but have spike initiation sites and form reciprocally inhibitory synapses with ipsilateral oscillator interneurons in the 3rd and 4th ganglia (Fig. 3A) (Masino and Calabrese 2002a; Peterson 1983b).

To understand how phase and cycle period are controlled in this system, alternative models that incorporated different assumptions about the system were created (Hill et al. 2002). Based on anatomical and physiological data, one possible configuration of the network is a “symmetric” model in which the oscillator neurons of both segmental oscillators equally inhibit the ipsilateral coordinating interneurons (Fig. 3B). This model assumes that the G3 spike initiation sites of the coordinating interneurons are silent and that all spikes originate at the G4 sites (Fig. 3A). In this model, the activity of a coordinating interneuron is completely inhibited when either the G3 or the G4 oscillator interneuron on the same side of the body is...

**FIG. 3.** The timing network of the leech heartbeat neural network. A: the timing network contains 4 pairs of bilaterally symmetric interneurons that have cell bodies in the first 4 midbody ganglia. There are 2 segmental oscillators located in the 3rd and 4th ganglia. The coordinating interneurons of the first 2 ganglia are functionally equivalent and are therefore combined in representation. Open circles represent cell bodies; open squares represent sites of spike initiation; small filled circles represent inhibitory synapses. B: the symmetric model. Circles represent oscillator interneurons of the 3rd and 4th ganglia. Squares represent the active neurites of the coordinating interneurons, which initiate spikes and make reciprocally inhibitory synapses with the oscillator interneurons. C: simulated activity of heart interneurons in the symmetric model. The model interneurons are labeled HN and are indexed by body side and midbody ganglion number. The model neurons contain Hodgkin–Huxley–style voltage-dependent conductances. The maximal conductance of the hyperpolarization-activated current ($g_h$) was set to different values within the 2 pairs of oscillator interneurons ($g_h$ equals 4.0 nS in the G3 oscillator interneurons and 5.4 nS in G4 oscillator interneurons). An increase in $g_h$ leads to faster oscillations (Hill et al. 2001). Symbols above each voltage trace indicate the occurrence of the median spike within each burst. The yellow rectangles show the windows of time in which the coordinating interneurons were active. Figure adapted from Hill et al. (2002).
active. Therefore a coordinating interneuron only fires in the window of time when neither the ipsilateral G3 nor the G4 interneuron is active (yellow rectangles in Fig. 3C).

In a model in which the two segmental oscillators had the same intrinsic period, the phase difference was zero and the duty cycle of the coordinating interneurons was large (40%, not shown). Under conditions where the intrinsic period of one segmental oscillator was shorter than the other, the faster segmental oscillator led in phase and the duty cycle of the coordinating interneurons was reduced (30%, Fig. 3C). In the symmetric model, either segmental oscillator can lead in phase and the period of the system is equal to the period of the faster segmental oscillator (Hill et al. 2002). The range of phase values (−20 to +20%) is greater in the negative direction than in the biological system (−12 to +20%), perhaps reflecting a tendency of the real G4 oscillator to be inherently faster than the G3 oscillator (Masino and Calabrese 2002b).

How are stable phase lags created in this system and why is the range of stable phase lags so great? On a cycle-by-cycle basis the faster segmental oscillator will lead in phase due to its shorter intrinsic period. As a result, the oscillator interneurons of the faster segmental oscillator will terminate the bursts of the ipsilateral coordinating interneurons. Thus during each cycle there is a brief interval in which an interneuron of the slower segmental oscillator only receives inhibition from its contralateral partner. The faster oscillator interneuron “removes” inhibition that would normally fall late during the inhibited phase of the slower oscillator interneuron’s cycle. In this way, the faster segmental oscillator speeds the slower segmental oscillator to its own period. The greater the phase difference, the greater the removal of inhibition and the stronger the speeding effect on the slower segmental oscillator. At the limit the faster segmental oscillator can accelerate the coupled system to the slower oscillator’s half-center oscillator period—the period that it expresses in the absence of inhibition from the coordinating interneurons. Beyond this point, the two oscillators do not share the same period (Hill et al. 2002).

The properties of this symmetric network depend not only on the details of the network configuration, but also on the intrinsic properties of the interneurons themselves. For this reason many voltage-dependent currents have been incorporated in the model oscillator interneurons (Hill et al. 2001). For example, the bursts are supported by several currents including a low-threshold, slowly inactivating Ca²⁺-current \( I_{CaS} \). \( I_{CaS} \) is important because it inactivates during a burst, causing a slow decline in the membrane potential. This decline leads to a reduction in spike frequency, which helps to release the contralateral interneuron from synaptic inhibition. Simultaneously, \( I_h \) becomes activated in the contralateral interneuron, helping it to escape from inhibition and begin to burst. Late in the inhibited phase, small changes in the amount of inhibition can have large effects on the timing of the next burst (Hill et al. 2002). Therefore the removal of inhibition can effectively speed an oscillator interneuron that lags in phase. Similar results, showing that inhibitory input can cause either phase advances or delays depending on its timing, have been found in a modeling study of intersegmental coordination in the tadpole swim network (Tunstall et al. 2002).

The predictions of this simple symmetric model are largely in agreement with physiological data (Masino and Calabrese 2002a,b). In mutual entrainment experiments in which the two segmental oscillators were reversibly uncoupled by blocking spike conduction in the connective between the 3rd and 4th ganglia, the period of the coupled system was equal to that of the faster oscillator regardless of which oscillator was faster (G3 or G4). In addition, in split-bath experiments the application of pharmacological agents that accelerated or slowed the period of a segmental oscillator allowed for a reversal in the phase relationships between the oscillators (Masino and Calabrese 2002b). For example, in a preparation in which the G4 oscillator originally led in phase, a decrease in the intrinsic period of the G3 segmental oscillator allowed the latter to lead in phase.

The agreement between the model and the biological data breaks down, however, in experiments in which repetitive pulses of current were used to drive one of the segmental oscillators to periods faster or slower than that of the mutually entrained system (analogous to the forcing experiments described in the lamprey) (Masino and Calabrese 2002c). This symmetric model predicts that the driven oscillator cannot slow the follower segmental oscillator by lagging in phase because there is no mechanism to add inhibition to the follower oscillator. In contrast, in the biological system the driven segmental oscillator may lag in phase and consequently slow the system. A new generation of the model, which incorporates details such as spike frequency adaptation of the coordinating interneurons, has been able to account for this property (Jezzini et al. 2000).

In addition, contrary to the assumptions of the symmetric model, the driving experiments have revealed that the system can behave asymmetrically. The driven G3 oscillator can entrain the network over a broader range of cycle periods than the G4 oscillator (Masino and Calabrese 2002c). This result shows that the leech heartbeat network changes dynamically depending on the experimental conditions. The network behaves symmetrically under conditions of mutual entrainment but asymmetrically when driven by external input. The ability of the system to switch between these two modes has been explored in a new model in which coordinating interneurons have two spike initiation zones (Jezzini et al. 2000).

The functional role of the large variations in phase observed in the mutually entrained system is not known. The experiments and modeling to date have been concerned with short isolated chains of ganglia. In experiments in which phase was measured between segmental motor neurons in long, de-afferented chains, intersegmental phase differences were consistent between preparations and were independent of cycle period (Wenning et al. 2000). The study of semi-intact preparations in which afferent input is preserved may yield further information about the normal phase relations in this system.

A LARGE AND CONSTANT PHASE LAG IS NECESSARY FOR THE BEATING OF CRAYFISH SWIMMERETS

Intersegmental coordination has also been studied in the crayfish swimmeret system (Mulloney et al. 1993, 1998). The crayfish swims forward by beating four pairs of swimmerets located ventrally on the abdomen. Normally the two swimmerets located on a single abdominal segment beat synchronously in a cycle consisting of a power-stroke followed by a return-stroke (Hughes and Wiersma 1960). Together the swim-
merets beat in a wavelike pattern that begins with the posterior-most pair and then spreads anteriorly with a phase lag of 25% between neighboring abdominal segments. As in the leech and lamprey swim networks, the phase lag between segments is independent of cycle frequency (Braun and Mulloney 1993).

The isolated abdominal nerve cord of the crayfish can produce a rhythm that is nearly identical to that in the intact animal (Braun and Mulloney 1993, 1995; Ikeda and Wiersma 1964). In addition, a single isolated ganglion can produce a normal and robust motor pattern (Murchison et al. 1993). Similar to the lamprey swim network, a segmental oscillator consists of two hemisegmental pattern-generating circuits that are capable of independent oscillation, although in the crayfish the hemisegments are active in phase as would be necessary for synchronous beating of swimmeret pairs (Murchison et al. 1993).

Each hemisegment contains all the circuitry necessary to control a single swimmeret (Murchison et al. 1993). In addition to two groups of antagonistic motor neurons and a set of primary afferent neurons, each hemisegment contains four local, nonspiking interneurons. Two of these interneurons (1A and 1B) depolarize during the return-stroke portion of each cycle while the other two interneurons (2), which are identical, depolarize during the power-stroke phase (Fig. 4) (Paul and Mulloney 1985a,b). Alternating oscillations between these two groups of interneurons may be based on reciprocal inhibition (Fig. 4) (Skinner and Mulloney 1998b).

It was originally proposed that the wavelike activation of the swimmerets arises from a gradient of intrinsic segmental oscillator periods (Ikeda and Wiersma 1964). However, no systematic difference in segmental oscillator periods was subsequently found between isolated ganglia (Mulloney 1997). In contrast, the pattern of intersegmental connectivity is asymmetric. Three types of coordinating interneurons have been identified that are necessary and sufficient for intersegmental coordination (Namba and Mulloney 1999). In each hemisegment, there are two interneurons that project in the ascending direction (ASC_L and ASC_E), and one interneuron that projects in the descending direction (DSC) (Fig. 4). The ASC_L and ASC_E interneurons fire bursts in phase with the power-stroke in their home ganglion, whereas the DSC interneuron fires bursts in phase with return-stroke. These coordinating interneurons have little direct effect on activity in their home ganglion but affect the timing of motor output in their target ganglia where they make spike-mediated synapses with local, nonspiking commissural interneurons, which in turn entrain hemisegmental activity (Mulloney and Hall 2002; Namba and Mulloney 1999).

Chains of only two ganglia exhibited normal phase relationships, leading to the original assumption that intersegmental coordinating interneurons project only to neighboring ganglia (Skinner and Mulloney 1998b). However, when the rhythmic activity of an individual ganglion of a chain was blocked with a low-Ca^2+, high-Mg^2+ saline, the segmental oscillators on either side maintained their normal phase difference, demonstrating that coordinating interneurons project to targets at least two ganglia away (Tschuluun et al. 2001). In agreement with the synaptic spread model proposed for lamprey swimming these distant connections are weaker than those between neighboring ganglia. In contrast, the appropriate phase lag of about 50% is maintained between the two ganglia on either side of the inactive ganglion, suggesting that the connections in distant ganglia are not identical to those made in neighboring ganglia.

A variety of models have been used to help understand how intersegmental coordination is accomplished in the crayfish swimmeret system. In one model, the swimmeret network was represented as a system of phase-coupled oscillators (Skinner et al. 1997). Fitting this model to the experimental data resulted in a number of predictions: coupling is asymmetric; ascending and descending coupling are about equal in strength, and either ascending or descending coupling alone can generate a phase difference of 25%. To understand what these asymmetries mean in synaptic terms, a cellular model was created in which the segmental oscillators were modeled using Morris–Lecar-type equations to represent the nonspiking interneurons (Skinner and Mulloney 1998b). A number of alternative circuits, constrained by experimental results and the predictions of the phase-coupled model, were tested. One circuit exhibited at constant phase of 25% over a range of oscillation frequencies. As predicted by the phase-coupled oscillator model, either the ascending or the descending coordinating interneurons alone could produce a 25% phase lag. However, only the full circuit model showed phase constancy. This cellular-based model shows that the asymmetric coupling may be embodied in differences in phases of coordinating interneuron activity, choices of intersegmental targets, and signs of intersegmental connections.

The cellular model predicts that certain network configurations produce appropriate phase lags but cannot explain why

![Fig. 4. Pattern of intersegmental coupling between hemisegmental oscillators of the crayfish swimmeret system predicted by a model. A circuit of nonspiking interneurons that are mutually inhibitory generates the oscillatory rhythm. Interneurons 1A and 1B are active in phase with the return-stroke. A pair of identical interneurons (2) is active in phase with the power-stroke. There are 3 coordinating interneurons in each hemisegment. ASC_L and ASC_E project in the ascending direction, whereas DSC projects in the descending direction. The coordinating interneurons were not explicitly modeled but were simply represented as connections directly between oscillator interneurons. The output of the descending interneuron (DSC) can presumably be split among more than 1 target and can have different signs, since the coordinating interneurons act through intermediary nonspiking commissural interneurons (Mulloney and Hall 2002). The solid circles represent inhibitory synapses; open triangles represent excitatory synapses. Figure adapted from Jones et al. (2003).](http://jn.physiology.org/doi/abs/10.1152/jn.001001.2003)
these phase lags are stable. In a study based on the assumptions of weakly coupled oscillator theory, coupling functions were calculated for individual intersegmental connections in the cellular model (Jones et al. 2003). These coupling functions are curves that predict stable phase lags for individual connections and when added together can predict stable phase lags within a full network. For example, in the cellular model a stable phase lag of 25% was found with a specific pair of ascending excitatory and inhibitory connections. By examining the coupling functions of these two connections, it was possible to see that although neither connection on its own produces an appropriate phase, together they yield a stable phase lag of 25%. Furthermore, this analysis explained why bidirectional connections are required for phase constancy. With only either ascending or descending connections, the predicted phase lags shifted systematically with oscillation frequency. In a model with bidirectional coupling, however, these phase shifts cancelled out, resulting in a constant phase lag over a range of frequencies.

CONCLUSIONS

This review has focused on intersegmental coordination in a few well-studied preparations. Discovering how motor patterns are coordinated in these model systems may help us to understand how coordination is accomplished in more complicated networks such as those responsible for terrestrial limbed locomotion (Bem et al. 2003; Butt et al. 2002). At the most fundamental level of rhythm generation there are clear similarities between the model systems we have discussed. For example, in the lamprey swim network and in the leech heartbeat system, hemisegments are capable of endogenous bursting even though they are embedded in a half-center oscillator circuit. However, at the network level, the differences are perhaps more striking than the similarities. For example, the swimming behaviors of leech and lamprey are very similar yet the two underlying neural circuits are very different in terms of their architecture and the role of sensory feedback.

A further complexity is that a given network may operate differently depending on experimental conditions. For example, the leech heartbeat system behaves nearly symmetrically under conditions of mutual entrainment but asymmetrically during driving experiments, demonstrating an ability to change dynamically that is similar to network reconfiguration in the crustacean stomatogastric nervous system (Marder and Calabrese 1996; Masino and Calabrese 2002b,c).

The future of this field will clearly continue to involve modeling work because the dynamic nature of these oscillatory networks makes comprehension based on static circuit diagrams impossible. The use of models with different levels of detail, as in the study of the crayfish swimmeret system, may be the best approach. Abstract models provide a general indication of the important features of a system, while more detailed models allow for a direct comparison with the biological system.

REFERENCES


Mulloney B and Hall WM. Local commissural interneurons are targets of swimmeret coordinating axons. Abst Soc Neurosci 270.5, 2002.


