Model for Intersegmental Coordination of Leech Swimming: Central and Sensory Mechanisms

JIANHUA CANG AND W. OTTO FRIESEN
Department of Biology, National Science Foundation Center for Biological Timing, University of Virginia, Charlottesville, Virginia 22904-4328

Received 31 August 2001; accepted in final form 4 February 2002

Cang, Jianhua, and W. Otto Friesen. Model for intersegmental coordination of leech swimming: central and sensory mechanisms. J Neurophysiol 87: 2760–2769, 2002; 10.1152/jn.00740.2001. Sensory feedback as well as the coupling signals within the CNS are essential for leeches to produce intersegmental phase relationships in body movements appropriate for swimming behavior. To study the interactions between the central pattern generator (CPG) and peripheral feedback in controlling intersegmental coordination, we have constructed a computational model for the leech swimming system with physiologically realistic parameters. First, the leech swimming CPG is simulated by a chain of phase oscillators coupled by three channels of coordinating signals. The activity phase, the projection direction, and the phase response curve (PRC) of each channel are based on the identified intersegmental interneuron network. Output of this largely constrained model produces stable coordination in the simulated CPG with average phase lags of 8–10°/segment in the period range from 0.5 to 1.5 s, similar to those observed in isolated nerve cords. The model also replicates the experimental finding that shorter chains of leech nerve cords have larger phase lags per segment. Sensory inputs, represented by stretch receptors, were subsequently incorporated into the CPG model. Each stretch receptor with its associated PRC, which was defined to mimic the experimental results of phase-dependent phase shifts of the central oscillator by the ventral stretch receptor, can alter the phase of the local central oscillator. Finally, mechanical interactions between the muscles from neighboring segments were simulated by PRCs linking adjacent stretch receptors. This model shows that interactions between neighboring muscles could globally increase the phase lags to the larger value required for the one-wavelength body form in freely swimming leeches. The full model also replicates the experimental observation that leeches with severed nerve cords have larger intersegmental phase lags than intact animals. The similarities between physiological and simulation results demonstrate that we have established a realistic model for the central and peripheral control of intersegmental coordination of leech swimming.

INTRODUCTION

Leeches and other elongated animals, such as lampreys and tadpoles, when swimming maintain a single-wavelength body form to achieve optimal efficiency and stability (Marder and Calabrese 1996). To express the single wave requires appropriately phase-delayed muscle contractions in successive body segments. These contractions arise sequentially due to phase lags in the activities of the segmental oscillators. Although the neuronal network producing the basic rhythmic pattern, the central pattern generator (CPG), is located within the CNS (Delcomyn 1980), proprioceptive feedback is essential for animals to produce efficient normal movements (Pearce and Friesen 1984; Pearson and Ramirez 1997).

Recent work combining experimental and computational analyses has advanced our understandings about the central mechanisms of intersegmental coordination (Skinner and Mulloney 1998b). Several types of models have proved useful. First, a mathematical model of phase-coupled oscillators (PCO) has been applied to the lamprey swimming (reviewed in Cohen et al. 1992) and crayfish swimmeret system (Skinner et al. 1997). Second, detailed cellular models have been constructed for these systems, and these have replicated some experimental findings (lamprey: Wadden et al. 1997; crayfish: Skinner and Mulloney 1998a). Third, Buchanan (1992) has employed a “connectionist” neural network of intermediate complexity by incorporating identical model neurons interconnected in accord with experimental data. Finally, Pearce and Friesen (1988) and Hagevik and McClelland (1994) employed phase models, which unlike a simple PCO model, cannot be solved in closed mathematical form. On the one hand, the PCO model is too abstract to include much cellular detail of the CPG, on the other hand, a detailed cellular model that does incorporate full biophysical details may be too complex to reveal underlying mechanisms. To steer a middle course, we now simulate the CPG of leech swimming by a chain of coupled phase oscillators but with many physiological details included.

Leech swimming behavior is an excellent system for studying the neuronal mechanisms of intersegmental coordination in both central and peripheral aspects. On the one hand, most neuronal components of the CPG and their intra- and intersegmental connections have been identified (Brodifuhrer et al. 1995; Friesen 1989). On the other hand, the fictive motor patterns generated by the nerve cords display smaller intersegmental phase lags than those in intact animals (Pearce and Friesen 1984). Alternatively, in leeches with severed nerve cords, where sensory feedback alone generates intersegmental coordination between rostral and caudal sectors, the phase lags are larger than those of intact animals (Yu et al. 1999), in contrast to results on the dogfish (Wallén 1982) and lamprey (McClelland 1990) where similar cuts of the spinal cord had little effect on intersegmental phase relationship. We recently demonstrated the relevance of sensory input by showing that...
the rhythmic activity of the stretch receptors associated with ventral longitudinal muscles alters the local intersegmental phase lag by delaying or advancing the phase of the segmental oscillator in a phase dependent manner (Cang and Friesen 2000). Some of the synaptic interactions between these stretch receptors and the CNS oscillator circuit are now identified (Cang et al. 2001). Such sensory input is important in setting intersegmental phase lags in the leech but appears not necessary in the crayfish swimmeret system or for swimming in adult lamprey (Friesen and Cang 2001).

Based on their experimental manipulations of chain length and coupling strength in the leech CNS (Pearce and Friesen 1985a,b), Pearce and Friesen (1988) constructed a model for intersegmental coordination of leech swimming in which the nerve cord was simulated by a chain of oscillators coupled by multiple channels. The coupling interactions were not based on specific projections but simply simulated the finding that multisegmental projections occur in both directions. To further study the interactions between the CPG and peripheral feedback in controlling intersegmental coordination, we have now revisited their model and refined it with physiologically realistic parameters. We have also incorporated the activities and functions of ventral stretch receptors into the model to examine whether these can increase the intersegmental phase lags generated by the isolated nerve cord to those of the intact animal, which expresses the one-wavelength body shape. Throughout our simulations from the CPG to intact animal, our approach was to constrain the model by experimental results and then to test it by comparison with an unrelated experiment.

METHODS

Simulation of the nerve cord

The CNS of leeches consists of the ventral nerve cord, which includes supraesophageal and subesophageal ganglia (the head ganglia), a chain of 21 metameric midbody ganglia, and a large posterior tail ganglion. For the purpose of our study, only the midbody ganglia, M1 to M18, are considered; ganglia posterior to ganglion 18 do not exhibit the rhythmic activity patterns (Kristan et al. 1974a,b). Although M1 and M18–M21 may have neuronal circuitry similar to that found in other midbody segments, there is no published data to support such a conjecture. Furthermore, the simulation result of a chain of 21 ganglia is very similar to that of 18 ganglia (not shown). The basic structure of the model follows that of the original one (Pearce and Friesen 1988); that is, the nerve cord is simulated by a chain of coupled phase oscillators, labeled n (1–18) to indicate their position along the chain (Fig. 1). The state of each oscillator is represented solely by its phase, \( \theta_n \), where \( \theta_n = 0 \) corresponds to the timing when motoneuron (MN) dorsal excitatory neuron 3 is most depolarized (median spike of dorsal posterior (DP) nerve bursts).

Segmentally repeated homologs of at least 13 intersegmental interneurons (INs), each active at a certain phase of the swimming cycle (Fig. 1A), provide the neuronal mechanism of intersegmental coordination (Friesen 1989; Friesen and Pearce 1993). Compared to the phase of DP nerve bursts, the activity phase of these INs falls into three phase groups. The INs in the 0° phase group project their axons caudally, and the INs in the 120° and 240° phase groups only project rostrally. In the model, these coordinating INs are simulated by three channels of coupling signals, directed either anteriorly or posteriorly, and active only during a specified sector of the cycle (Fig. 1B and Table 1). These channels send out impulses when active, and the impulses arrive at their target oscillators with a time delay (15 ms/segment, to mimic the finite conduction velocity of nerve impulses). The maximum distance traveled by impulses is specified by the parameter “span” (6 in our model) (see Friesen and Hacker 2001).

When a coupling impulse arrives at an oscillator, it instantaneously retards or advances the phase of the target oscillator (Fig. 1). The amount of this phase shift of the nth oscillator, \( \Delta \theta_n \), is determined by a phase response curve (PRC). In our model, the interactions mediated by individual INs are characterized by sinusoidal PRCs (Fig. 2) (see Cohen et al. 1992; Pearce and Friesen 1988; Skinner et al. 1997) and have the generic form: \( \Delta \theta_n = A \times \sin(\theta_n - x) \), when the coupling is active, i.e., when \( \theta_n \) is within an appropriate range of values; otherwise \( \Delta \theta_n = 0 \), where \( \theta_n \) is the phase of the oscillator that sends out the coupling signal and \( \theta_T \) is the phase of the target oscillator (we use the term \( \theta_n \) when describing a specific segmental oscillator, n); A is the maximum amplitude; and x is a phase parameter that is determined by the phase of target IN (see RESULTS) and is different for each channel (Table 1). Therefore, the phase of any oscillator n at time \( t + \Delta t \) is given by

\[
\theta_n(t + \Delta t) = \theta_n(t) + \Delta t \times 360°/P_n + \sum \Delta \theta_n
\]

where \( P_n \) is the intrinsic period of the nth oscillator, \( \sum \Delta \theta_n \) is the total phase shift summed over all channels from all connected oscillators that are active (up to 6 oscillators away in either direction). Our selection of PRCs of a sine-wave shape derives in part from prior usage (Pearce and Friesen 1988) and partly from the finding that PRCs...
of independently tested model neuronal circuits (see following text, Fig. 2) can be approximated by sine waves.

**Simulation of the periphery**

After verifying that the model replicates many features of the isolated nerve cord observed in experimental manipulations (see RESULTS), we incorporated sensory input from the leech body wall into the model. Detailed descriptions of model specifications are presented in RESULTS. Briefly, the muscles of individual segments are simulated by phase oscillators (peripheral oscillators) under the control of central oscillators in the nerve cord. Although not independent oscillators, muscle membrane potential and tension do oscillate because of MN input. Consequently, muscles oscillations act as peripheral oscillators that feed back to and phase shift the local central oscillators of their own segments. In addition, these peripheral oscillators interact with their nearest neighbors to mimic mechanical intersegmental muscle interactions in intact animals. The PRCs of these interactions have the generic form

$$\Delta \theta_{x} = A \times \sin (\theta_{x} - x) \times \cos (\theta_{y} - y)$$

where $\theta_{x}$ is the phase of target oscillator, either central or peripheral for different interactions, and $\theta_{y}$ is the phase of the oscillator sending the coupling signal (Table 1).

**Implementation of the model**

The model was programmed in the C++ language with Matlab (MathWorks, Natick, MA) as the interface and run on a Pentium PC. The following parameters are supplied to each simulation: number of oscillators in the chain (2–18); the intrinsic cycle period of each oscillator (unless otherwise stated, we use 750 ms and hence without a gradient along the chain); the parameters $A$, $x$, and $y$ of each PRC (Table 1); the span of coordinating signals (6 for the results presented here); the firing range of coupling INs (120°); and the intersegmental conduction delay for impulses (15 ms/segment). Although experiments on isolated pairs of nerve-cord ganglia or even individual ganglia revealed a U-shaped gradient in nerve cord cycle period (Hocker et al. 2000; Pearce and Friesen 1985a), this gradient was only documented for ganglia M2 through M12. Individual, or even short chains of ganglia, posterior to ganglion M12 do not exhibit rhythmicity. For model of the leech swim circuits, we chose not to incorporate these complexities.

Because the state of each oscillator is described completely by its phase, the progression of activity along the model chain is expressed by the phase lags of neighboring oscillators. For the initial state, the phase of the first oscillator is set to 180°, the phase of each successive oscillator is incremented or decremented by a random number between −10 and 10°. Time is then incremented by 5 ms steps (i.e., $\Delta t = 5$ ms) for 20–50 simulated seconds. This step size mimics an impulse rate of 200 Hz, about twice the maximum observed in leech oscillatory INs. After the simulation, the phase lags of neighboring oscillators are examined to check whether the simulation achieved stable phases, that is, that phase relationships along the modeled chain of ganglia have converged to constant values. All phase lags (or phase differences) plotted are the average of instantaneous phase lags over the last four simulated seconds.

**RESULTS**

Pearce and Friesen (1988) first simulated the leech nerve cord by a chain of phase oscillators coupled by multiple channels that shift the phases of target oscillators. Using mostly physiological parameters, they successfully reproduced many experimental findings of intersegmental coordination, including the effects of the ganglia number in the chain, manipulating the coupling strength by severing one of the paired lateral nerves, and blocking synaptic transmission in midbody ganglia. The coupling signal between oscillators, one of the most important properties in the model, however, was not based on physiological data. The projection direction of the coupling signals was set to be symmetrical, and the activity phases of the signals and the phase response curve (PRC) associated with them were defined somewhat arbitrarily (Pearce and Friesen 1988).

It is known that the oscillatory INs express their activities at different phases of the cycle, and can be assigned to three phase groups separated by 120° (Brodfuehrer et al. 1995; Friesen 1989). The INs in the 0° phase group (cells 115, 123, and 208) all project their axons caudally, and the INs in the 120° (cell 28) and 240° (cells 27, 33, and 60) phase groups only project rostrally (Fig. 1). These realistic parameters, i.e., the activity phase of the coupling INs and the direction of their projections, are implemented in the current model.

**Determination of the PRCs**

For impulse-mediated phase shifts, the PRC provides the phase shift (in degrees) for a single impulse at any phase of the cycle and is determined solely by the state (phase) of the target oscillator. Because of their simplicity, we employed sinusoidal PRCs similar to those used in previous modeling studies on the leech locomotion system (Pearce and Friesen 1988) and lamprey (Hagevik and McClelland 1994). In our model, the PRC of intersegmental coupling signals is given by: $\Delta \theta_{n} = A \times \sin(\theta_{n} - x)$ when the coupling is active, where $A$ is the maximum amplitude and $x$ is the phase parameter. The parameter $x$ is determined by the phase of the target oscillatory IN for each channel. Consider the diagram in Fig. 2A. Suppose a coupling signal phase-shifts the target oscillator by inhibiting an IN that is most depolarized at phase $\theta_{0}$ (0, 120, or 240° in our simulations). The membrane potential of this IN, assuming no other inputs, then is driven to oscillate with the form of $V_{m} = V \times$...
To test whether the sinusoidal PRC mimics synaptic inputs, we constructed a three-neuron circuit with recurrent cyclic inhibition (Fig. 2B1) using NeuroDynamix (Friesen and Friesen 1994). Parameters were chosen so that this circuit generates stable oscillations with a period of about 1 s. An oscillatory neuron in this circuit was subjected to inhibitory inputs, simulated by 10-ms, 2-nA hyperpolarizing current pulses at different phases of the cycle, and the phase shift was measured. The result is shown in Fig. 2B2. Although the predicted PRC does not perfectly represent the result, it sufficiently captures the most important features, namely, the bidirectional and sinusoidal-like phase shift effect at the predicted phase. Similarly, the PRC constructed from the same circuit to excitatory pulses can also be described by the sinusoidal function discussed above, with a negative amplitude parameter “-A” (Fig. 2B3). Note that the impulse amplitude (2 nA) is much larger than the current caused by a single spike, so the amplitude parameter for individual channels in our model for leech nerve cord should be much smaller than the value in Fig. 2B.

To further understand the meaning of the PRC, we studied a simple system in which two oscillators are coupled by only one channel, inhibition from oscillator 1 to 2 without any delay. We varied the center activity phase of the coupling signal (parameter \(\gamma\), 0, 120, or 240) and the parameter \(x\) in the PRC (i.e., the activity phase of its target neuron), and computed the final phase lag between the two oscillators \((\theta_1 - \theta_2)\). For example, if \(\gamma = 0\) (the coupling signal is active when \(\theta_1\) is in the range of \(-60\) to \(60\)) with the firing range \(120\)—this range approximates the duration of impulse activity in the oscillatory INs and \(x = 0\), meaning that the 0° phase neuron in the first oscillator inhibits the 0° phase neuron in the second oscillator, the final phase is about 180°, i.e., antiphase, as we expected (Fig. 3A). The results can be also plotted against the difference of \(x\) and \(\gamma\) (i.e., \(x - \gamma\), Fig. 3B) because, for instance, a 0° neuron of the first oscillator inhibiting a 0° neuron in the second oscillator causes the same phase relationship as a 120° neuron inhibiting a 120° neuron. Similarly, a 120° neuron of the first oscillator inhibiting a 0° neuron in the second oscillator causes the same phase relationship as a 240° neuron inhibiting a 240° neuron (final phase lag: 300°, i.e., \(\theta_1\) leading \(\theta_2\) 60°).

For stretch receptors and muscle interactions incorporated in later modeling, the phase shift is nonimpulse-mediated. The PRC of these interactions is given by: \(\Delta\theta_s = A \times \sin(\theta - \theta_s)\), where \(\theta_s\) is the phase of the target oscillator and \(\theta\) the phase of the oscillator sending the coupling channel. The term \(A \times \sin(\theta - \theta_s)\) is the same as that in impulse-mediated phase shift, whereas the term \(\cos(\theta_s - y)\) includes the consideration that the phase shift will be modified by the membrane potential (\(y\) is the center activity phase of this channel) rather than impulses of the coupling neuron. Figure 3B compares this type of PRC with that of impulse-mediated in the simple system. It is clear that the nonspike-mediated type of PRC produced results almost identical to that of spike-mediated phase shift.

### Simulated nerve cord

With these considerations, we were able to assign the PRC parameters \(\gamma\) (the center of its activity phase) and \(x\) (the activity phase of its target IN) for each channel (Table 1) based on the identified intersegmental connections between oscillatory INs.
effect of this channel is the excitatory input of cell 208 onto posterior cell 115 (Fig. 1A). Therefore the parameter \( x \) for the PRC of this descending signal is \( 0^\circ \) and the PRC is given by

\[
\Delta \theta_n = -0.2 \times \sin (\theta_n - 0^\circ), \ y = 0^\circ
\]

(1)

The two rostrally directed channels, inhibition of the \( 0^\circ \) INs by a \( 120^\circ \) IN and inhibition of the \( 120^\circ \) IN by \( 240^\circ \) INs, have the same effects (\( x - y = -120^\circ \), see Fig. 3B). Because the strengths of ascending and descending signals within the leech nerve cord are approximately equal (Friesen and Hocker 2001) and because there are twice as many ascending as descending interactions, we set the amplitude parameter for the two individual ascending signals to half of that of descending signals

\[
\Delta \theta_n = 0.1 \times \sin (\theta_n - 0^\circ), for \ y = 120^\circ \text{ and }
\]

\[
\Delta \theta_n = 0.1 \times \sin (\theta_n - 120^\circ), for \ y = 240^\circ
\]

(2)

(3)

Given these realistic coupling signals, this largely constrained model produces stable intersegmental coordination. The outputs of individual oscillators, \( \cos (\theta_n) \), are phase-locked with a rostro-caudal delay (Fig. 4A). The coordination becomes clearer when the intersegmental phase lags along the chain are plotted (Fig. 4B). For most of the chain, the phase lag is about \( 9^\circ/\text{segment} \), similar to that observed in nerve cords. A decrease occurs for the phase lag between oscillators 12 and 13; there are compensating phase increases further along the chain. [The reduction in phase lag is an edge effect because of the limited coupling span (6) and the finite chain length (18).] The only free parameter \( A \), the maximum amplitude of the phase shift caused by one spike, was not critical.

(Fig. IA). We also implemented other realistic parameters, including firing range (\( 120^\circ \) centered at the activity phase of each channel), projection direction, coupling span (6) (Friesen and Hocker 2001), and intersegmental delay (15 ms/segment) (Friesen et al. 1978). Because earlier model studies indicated that a gradient is not necessary to realize most of the observed features of the simulated nerve cord (Pearce and Friesen 1988) and because the data describing the intrinsic period of individual ganglion were obtained when swim oscillations were unrealistically weak), we set intrinsic periods of individual oscillators along the chain to be identical.

Because cells 208 and 123 are active in the same phase range, \([-60^\circ \ 60^\circ]\), and project caudally, they can be combined into a single channel. In the absence of information about the strengths of their individual synaptic interactions, the excitatory connection of cell 208 and inhibitory connection of cell 123 with posterior cell 28 were set to be equal and to sum linearly, thus the overall

\[
\theta_2 = \theta_1 + \Delta \theta_1 (\cos (\theta_1 - y) \times \sin (\theta_1 - x)) \quad \text{(nonspike-mediated)}
\]

\[
\theta_2 = \theta_1 + \Delta \theta_1 (\cos (\theta_1 - y) \times \sin (\theta_1 - x)) \quad \text{(spike-mediated)}
\]

(Fig. 3A-B). The coupling is spike-mediated with the PRC:

\[
A: \text{the coupling is spike-mediated with the PRC:} \quad \Delta \theta_2 = \sin (\theta_2 - x) \quad \text{when} \ \theta_1 \text{ between} \ y = 60^\circ \ \text{and otherwise} \ \Delta \theta_2 = 0, \text{where} \ x \text{and} \ y \text{are phase parameters. The average final phase lag between the } 2 \text{ oscillator} \ (\theta_1 - \theta_2) \text{ is plotted against } x \text{. B: for the same configuration, the results from A are plotted against } x - y \text{.}
\]

\[
B: \text{and} \ cos (\theta_1 - 0^\circ) = \frac{1}{2} \sin (\theta_1 - x) \cos (\theta_1 - y)
\]

\[
\theta_3 = \theta_2 + \Delta \theta_2 (\cos (\theta_2 - y) \times \sin (\theta_2 - x)) \quad \text{(nonspike-mediated)}
\]

\[
\theta_3 = \theta_2 + \Delta \theta_2 (\cos (\theta_2 - y) \times \sin (\theta_2 - x)) \quad \text{(spike-mediated)}
\]

(Fig. 4A). We implemented other realistic parameters, including firing range (\( 120^\circ \) centered at the activity phase of each channel), projection direction, coupling span (6) (Friesen and Hocker 2001), and intersegmental delay (15 ms/segment) (Friesen et al. 1978). Because earlier model studies indicated that a gradient is not necessary to realize most of the observed features of the simulated nerve cord (Pearce and Friesen 1988) and because the data describing the intrinsic period of individual ganglion were obtained when swim oscillations were unrealistically weak), we set intrinsic periods of individual oscillators along the chain to be identical.

Because cells 208 and 123 are active in the same phase range, \([-60^\circ \ 60^\circ]\), and project caudally, they can be combined into a single channel. In the absence of information about the strengths of their individual synaptic interactions, the excitatory connection of cell 208 and inhibitory connection of cell 123 with posterior cell 28 were set to be equal and to sum linearly, thus the overall

\[
\theta_2 = \theta_1 + \Delta \theta_1 (\cos (\theta_1 - y) \times \sin (\theta_1 - x)) \quad \text{(nonspike-mediated)}
\]

\[
\theta_2 = \theta_1 + \Delta \theta_1 (\cos (\theta_1 - y) \times \sin (\theta_1 - x)) \quad \text{(spike-mediated)}
\]
for the performance of the model over a large range (from 0.1 to 0.8) and was set to the same fixed values ($Eqs. 1–3$) in all simulations. [It should be noted that the amplitude parameter sets (–0.2, 0.1, 0.1) and (–0.2, 0.2, 0.2), denoting the relative PRC amplitudes of interactions from cells 208/123, cell 28, and cells 27/33, respectively, gave similar results.]

It is certainly of great interest to examine whether other configurations of coupling signals are able to generate appropriate intersegmental phase lags. We kept parameter $x$ unchanged for any two of the three channels and altered $x$ for the other channel ($0^\circ$, $120^\circ$, or $240^\circ$). The results (data not shown) show that the coupling configuration based on known connections is the only one that generates stable oscillations with appropriate anterior-to-posterior phase lags, suggesting the known interactions provide the neuronal basis for intersegmental coordination in the animals.

We subsequently tested whether the model could reproduce other experimental findings of intersegmental coordination. First, we varied the intrinsic period from 0.5 to 1.5 s and calculated the average phase lag generated by the simulated nerve cord. We found that over this range of periods, intersegmental phase lags are restricted in a small range (8.8–9.7°) and express a slight positive period dependence (Fig. 5A), as originally demonstrated in experiments on leech nerve cords (Kristan and Calabrese 1976; Pearce and Friesen 1984). Second, the simulation (Fig. 5B) also replicated the experimental finding that long chains have smaller phase lags per segment than short ones (Pearce and Friesen 1985b).

Incorporation of stretch receptors

With a suitable model of the leech swimming CPG in hand, we incorporated the activity of stretch receptors. Because the rhythmic activity of ventral stretch receptors (VSRs) alters the phase of segmental oscillators in a phase-dependent manner (Cang and Friesen 2000), we simulated the interaction from the VSR to the central oscillator by a PRC

$$\Delta \theta_v = A \times \sin (\theta_v - 0^\circ) \times \cos (\theta_{vsr})$$

where $\theta_v$ is the phase of the central segmental oscillator, and $\theta_{vsr}$ is the phase of the VSR of ganglion $n$. Because the phase shift is nonimpulse-mediated, the term $\cos(\theta_{vsr})$ is used to provide the membrane potential dependence of the VSR for the phase shift in the target oscillator. To determine the parameter $x$, we replicated our previous phase-shift experiment in which we manipulated the membrane potential of the VSRs with injected sinusoidal currents and found that phase lags between adjacent segments were delayed or advanced depending on the phase of the injected currents (Cang and Friesen 2000). In the simulation, the phase of the VSR of ganglion 10, $\theta_{vsr,10}$, was set to follow the oscillation of the central oscillator, $\theta_{cp}$, with a variable delay (from 0 to 360°), and the VSR, in turn, shifted the phase of the central oscillator. We found that the model reproduced the phase-dependent modulation observed in experiments when $x$ was set to about $0^\circ$, with the parameter $A$ set to a negative value (Fig. 6). In this simulation, phase lags between nonadjacent oscillators, 8 and 9 and 11 and 12, were not altered (Fig. 6), hence the phase shift effect was “local.”

Simulation of the intact animal

The primary motivation for conducting these simulations was to study whether sensory feedback could increase the

![Diagram](image_url)
In the example shown in Fig. 7, the parameter $x$ of Eq. 5 was set to 270° so that the phase of the VSR compared with the oscillator ($\theta_{r} - \theta_{vsr,n}$) was about 70° (when $A$ is 0.4), similar to that observed in experiments on the leech (100 to 150°) (Cang and Friesen 2000).

Next we consider whether mechanical interactions between the muscles in neighboring segments could ensure that the animal expresses one wavelength body form. In the simulation, the interactions between neighboring muscles are simulated by PRCs

$$\Delta \theta_{vsr,n} = A \times \sin (\theta_{vsr,n} - x) \times \cos (\theta_{r}) \quad (5)$$

where $\theta_{vsr,n}$ represents the state of the muscles, which is controlled by the local central oscillator, $\theta_r$.

These two central-peripheral interactions (Eqs. 4 and 5), however, did not increase the phase lags globally ($A$ is either 0.4 or 0.8). In the example shown in Fig. 7, the parameter $x$ of Eq. 5 was set to 270° so that the phase of the VSR compared with the oscillator ($\theta_{r} - \theta_{vsr,n}$) was about 70° (when $A$ is 0.4), similar to that observed in experiments on the leech (100 to 150°) (Cang and Friesen 2000).

Next we consider whether mechanical interactions between the muscles in neighboring segments could ensure that the animal expresses one wavelength body form. In the simulation, the interactions between neighboring muscles are simulated by PRCs

$$\Delta \theta_{vsr,n} = A \times \sin (\theta_{r} - x) \times \cos (\theta_{vsr,n-1} - y) \quad (6)$$

$$\Delta \theta_{vsr,n} = A \times \sin (\theta_{r} - x) \times \cos (\theta_{vsr,n+1} - y) \quad (7)$$

where Eq. 6 describes the anterior to posterior interaction and Eq. 7 the posterior to anterior interaction. The phase parameters should be identical for the two equations because the two interactions are at the same intersegmental boundary. Given this restriction, we found that the generation of stable output requires that the amplitude parameters $A_{x}$ and $A_{y}$ have different values. These interactions (see Table I for parameters) globally increase the phase lags generated by the simulated nerve cord to about 17°/segment (Fig. 8). It is interesting to notice that for most of the full simulations, the phase lags between muscles are larger than those of the nerve cord, as observed in leeches (Pearce and Friesen 1984) and that the intersegmental phase lag between muscle activity is larger at the posterior of the animal. Furthermore, the phase of VSRs compared with the oscillator ($\theta_{r} - \theta_{vsr,n}$) is no longer independent of position (Fig. 8B). When no muscle interactions were included, the phases of VSRs compared with the oscillator were about 70° for all segments (that generated Fig. 7B), whereas VSR phases assumed values of between −20° and 30° when these mechanical phases assumed values of between −20° and 30° when these mechanical phases assumed values of between −20° and 30° when these mechanical phases assumed values of between −20° and 30° when these mechanical phases assumed values of between −20° and 30° when these mechanical phases assumed values of between −20° and 30° when these mechanical...
segmental phase lag between oscillators 7 and 14 expressed by the simulated nerve cord was increased by 54° after the cut (from 119 to 173°), a value similar to that observed in the physiological experiments (45°, from 97 to 142°) (Yu et al. 1999). Also, the phase lag expressed by the muscles increased by 32° in simulation (from 138 to 170°) and 23° in experiments (from 147 to 170°) (Yu et al. 1999). The similarities between simulation and experimental results indicate our model has captured some very important mechanisms underlying intersegmental coordination in leech swimming.

DISCUSSION

The isolated nerve cord of leeches expresses oscillatory neuronal activity that underlies the undulatory movements of swimming; however, intersegmental phase lags generated by the nerve cord are too small to produce the one-wavelength body form (Pearce and Friesen 1984). The primary motivation for conducting these simulations was to study whether sensory feedback could increase the phase lags generated by the CPG. We simulated the leech swimming system by a chain of coupled oscillators with inputs from stretch receptors based on physiologically realistic parameters. First, the coupling signals in the model CPG were defined to simulate the identified oscillatory IN circuits (Figs. 1 and 2). Second, incorporation of the stretch receptors was constrained by the phase-shift effect.

FIG. 8. Simulation of intact swimming leeches. In addition to the configuration in Fig. 7, $\Delta \theta_{\text{var},n} = -0.8 \times \sin(\theta_{\text{var},n - 270°}) \times \cos(\theta_{\text{var},n})$ and $\Delta \theta_{\text{var}} = -0.8 \times \sin(\theta_{\text{var}}) \times \cos(\theta_{\text{var},n - 1} - 45°)$; mechanical interactions between neighboring muscles are simulated by PRCs: $\Delta \theta_{\text{mus},n} = -1.6 \times \sin(\theta_{\text{mus}}) \times \cos(\theta_{\text{mus},n - 1} - 45°)$ (diagram at the top). A: phase lags along the chain. The intersegmental phase lags expressed by the simulated nerve cord (○) and by the muscles (⋆) are increased from those of the isolated nerve cord (Fig. 4). Note that for most of the chain, the phase lags of the muscles are larger than those of the nerve cord as observed in swimming leeches (Pearce and Friesen 1984). Also, simulated phase lags of muscles are larger at the posterior, as in the animal. B: the phase of the VSR compared with the oscillator, $\theta_{\text{var}} - \theta_{\text{var},n}$. The phase differences are position dependent and between −20 and 30°.

FIG. 9. Simulation of intersegmental coordination with a severed nerve cord. With the same configuration as in Fig. 8, the intersegmental coupling signals within the simulated nerve cord were disconnected between oscillators 10 and 11 (diagram at the top). A: the phase lag between central oscillators 10 and 11 (○) increased dramatically after the cut. B: comparison of phase lag between segments 7 and 14 in simulation and behavioral experiments. The phase lag between segments 7 and 14 expressed by the simulated nerve cord (left ⊙) is increased by 54° after the cut, a similar number as in behavioral experiments (45°; left □) (Yu et al. 1999). The phase lag expressed by the muscles is increased by 32° in the simulation (right ⊙), compared with 23° in behavioral experiments (right □).
of the VSR (Fig. 6) (see also Cang and Friesen 2000). Our simulations have reproduced many features, both central and peripheral, of intersegmental coordination of leech swimming, including stable coordination in the simulated CPG with intersegmental phase lags of 8–10°/segment (Fig. 4); a slight positive period dependence of the intersegmental phase lags generated by the CPG (Fig. 5A) (compare with the results of Kristan and Calabrese 1976; Pearce and Friesen 1984); the effect of chain length on the average phase lag (Fig. 5B) (Pearce and Friesen 1985b); and mechanical interactions between segments that replicate the severed nerve cord experiment (Fig. 9) (Yu et al. 1999) and increase the phase lags generated by the CPG (Fig. 8).

Simulation of the leech swimming CPG with realistic parameters

Recent modeling studies indicate that the identified neuronal circuits within individual ganglia can generate the period and phase of oscillations observed in leech nerve cords (Taylor et al. 2000; Wolpert et al. 2000). Indeed, even individual ganglia of the anterior two-thirds of the nerve cord can generate the rudiments of the swim rhythm (Hocker et al. 2000). Furthermore, the neuronal circuits within individual ganglia function as unitary oscillators rather than pairs (Friesen and Hocker 2001). We therefore simulated the leech swimming CPG as a chain of concatenated oscillators but simplified the analyses by employing phase oscillators rather than attempting a more detailed biophysical model.

A period gradient of the central oscillators that decreases rostrocaudally along the chain was used in the original model based on the data available (Pearce and Friesen 1988). Recent experiments demonstrated, however, that the intrinsic period exhibits a U-shaped function: those in the most anterior ganglia and short chains of posterior ganglion are larger than those mid-cord ganglia (Hocker et al. 2000). However, the previous modeling studies indicated that the gradient is not necessary to replicate most features of the simulated nerve cord (Pearce and Friesen 1988), and current data for the swim periods of individual ganglia are not sufficient to provide details of intrinsic cycle period during normal swimming. Therefore to keep the modeling simple and interpretable, we set individual oscillators to a uniform intrinsic period along the chain.

The fact that the known intersegmental connections between oscillatory INs (Fig. 1A) are sufficient to produce appropriate coordination (Figs. 4 and 5) is encouraging but does not imply that all members and connections of the circuit have been identified. The caudally projecting neurons, cells 208 and 123, were combined into one channel with \( A = -0.2 \) (Eq. 1), meaning that in our model the connections onto posterior cell 28 from cells 208 (excitatory) and 123 (inhibitory) cancel each other. It is certainly possible that these connections have different strengths and that the amplitude parameters for rostrally projected channels (Eqs. 2 and 3) may not be identical either. Such differences could cause subtle differences between model and physiologically determined intersegmental phase lags, such as the edge effect (between ganglia 12 and 13 in Fig. 4). Although it is known that ascending and descending coupling strengths are nearly equal (Friesen and Hocker 2001), the actual strengths of individual intersegmental connections are currently unknown. Furthermore, the intersegmental targets of cells 115 and 60 are not known.

Modeling studies of intersegmental coordination in CPGs

In segmented animals, central oscillators controlling locomotion are found in most or all body segments (leech: Hocker et al. 2000; Weeks 1981; lamprey: Cohen and Wallén 1980; crayfish: Murchison et al. 1993). Recent modeling studies have helped clarify the central mechanisms of intersegmental coordination (reviewed in Skinner and Mulloney 1998b). A mathematical model of phase-coupled oscillators (PCOs) has been applied to the lamprey swimming (reviewed in Cohen et al. 1992) and crayfish swimmeret system (Skinner et al. 1997). The prediction of the PCO models that intersegmental coordination is produced by asymmetric couplings has been confirmed in the crayfish swimmeret system. Like in the leech, two ascending and one descending intersegmental signals that are active at different phases coordinate the series of four central oscillators underlying crayfish swimmeret movement (Namba and Mulloney 1999). On the other hand, detailed cellular models have been constructed for these systems, and replicated some experimental findings (lamprey: Wadden et al. 1997; crayfish: Skinner and Mulloney 1998a).

Because the PCO model is too abstract for describing cellular organization of the CPG and cellular model are too detailed for clarifying underlying mechanisms, it is useful to construct models with intermediate complexity. Our modeling is a step in this direction. First, the most important feature of our simulation is the use of physiological parameters, especially those of the coupling signals, including the activity phase and projection direction of the oscillatory IN, coupling span, and intersegmental conduction delay. Second, the PRCs in our model are superficially similar to the “H function” in the PCO model that represents the effect on the frequency of the subject oscillator and only depends on the phase difference between the two oscillators (Cohen et al. 1992; Skinner et al. 1997). In our model, the effect of phase shift (determined by PRCs) is also to accelerate or retard the oscillator, and the PRC depends on the phase difference between the coupling signal and the target IN (\( x - y \) in Fig. 3B). Furthermore, we have shown that the sinusoidal PRC for intersegmental interactions is valid (Fig. 2). Therefore a similar type of modeling can be used in lamprey and crayfish systems to link the PCO and cellular models.

Simulation of periphery and testable predictions

We implemented the periphery as oscillators coupled with central oscillators. The state of the muscles, represented by the phase of stretch receptors, is controlled by the central oscillator (Eq. 5), and feedback to the central oscillator through stretch receptors (Eq. 4). Our implementation of peripheral oscillators does not mean, however, the periphery can oscillate by itself. Instead, it should be viewed as a central-peripheral oscillator. Although the modeling results do not depend on the existence of central-peripheral oscillators, many experiments indicate that such oscillators indeed exist. Before the isolated nerve cord of leech was found to generate the basic pattern of swimming, Kristan and Stent (1975) showed that stretching muscles could change the MN activity and proposed that the
peripheral reflex loop is responsible for producing the rhythmic and coordinated pattern. More recently, it was observed that caudal half-leeches swim well even though isolated chains of caudal ganglia cannot generate the rhythm (Hocker et al. 2000). Furthermore, the swimming period of intact animals is shorter than that generated by the CPG alone (Yu et al. 1999). If the central-peripheral oscillators indeed exist, their period can be determined and incorporated into our model.

These simulations predict that the phase of VSRs in intact animals is dependent on position along the animal and between –20 and 30° (Fig. 8B), considerably different from the value when there is no intersegmental muscle interaction. Experimental tests of this prediction could refute or help establish the validity of our model. In addition, the PRCs for muscle interactions can be obtained from experiments that determine the phase parameters x and y in Eqs. 6 and 7. Furthermore, the model has only included the VSR. For the dorsal stretch receptors (DSRs) to have parallel effects with the VSRs to ensure the one-wavelength body shape, the PRC of the central oscillator to the DSR should be anti-phasic to that of VSR (Eq. 4) because dorsal muscles are anti-phasic to the ventral muscles. We believe that our model of the central and peripheral mechanisms that underlie leech swim movements is particularly valuable because it not only incorporates many physiological properties of this system but also serves to direct further research.

We gratefully acknowledge financial support by the National Science Foundation Grant 97-23320 to W. O. Friesen.

Present address of J. Cang: Rm 3065, BSB, Dept. Neuroscience, MC 0608, University of California San Diego, La Jolla, CA 92039-0608

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