

Entrainment ranges of forced phase oscillators

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Abstract

In the vertebrate spinal cord, a neural circuit called the central pattern generator produces the basic locomotory rhythm. Short and long distance intersegmental connections serve to maintain coordination along the length of the body. As a way of examining the influence of such connections, we consider a model of a chain of coupled phase oscillators in which one oscillator receives a periodic forcing stimulus. For a certain range of forcing frequencies, the chain will match the stimulus frequency, a phenomenon called entrainment. Motivated by recent experiments in lampreys, we derive analytical expressions for the range of forcing frequencies that entrain the chain, and how that range depends on the forcing location. For short intersegmental connections, in which an oscillator is connected only to its nearest neighbors, we describe two ways in which entrainment is lost: internally, in which oscillators within the chain no longer oscillate at the same frequency; and externally, in which the chain no longer has the same frequency as the forcing. Long intersegmental connections do not necessarily change the entrainment ranges based on the nearest-neighbor model, provided that entrainment is lost externally, and that the connection strengths meet a certain ratio criterion. When the criterion holds, the range of entrained frequencies is a monotonic function of forcing location, unlike experimental results, in which entrainment ranges are larger near the middle of the chain than at the ends. Numerically, we show that similar non-monotonic entrainment ranges are possible if the ratio criterion does not hold, suggesting that in the lamprey central pattern generator, intersegmental connection strengths are not a simple function of the connection length.

Author Summary

In all vertebrates, the basic pattern of muscle activity for locomotion, such as swimming or walking, is produced by a neural network located in the spinal cord, called the central pattern generator (CPG). Some spinal neurons extend long distances along the spinal cord to coordinate different portions of the body: for instance, to keep the head and tail synchronized during swimming in fish. However, it is difficult to study these neurons experimentally. Instead, we analyzed a mathematical model of the CPG, using the way the model CPG responds to sensory input to examine the role of these coordinating neurons. For stimuli in a certain frequency range, the CPG can match the muscle activation pattern to the sensory input, a process called “entrainment”, thus tuning itself to the biomechanical demands of the behavior. We derived analytical expressions for the entrainment range and found that long connections make entrainment more robust. Also, by comparing those ranges to experimentally measured ranges, our results suggest that the connection strength of the coordinating neurons may not be a simple function of how long the connection is, but may depend on the connection’s length and whether it goes toward or away from the head.

Introduction

In all vertebrates, the muscle activation patterns for steady locomotory behaviors like swimming and walking are generated by a neural network called the central pattern generator (CPG). This network, located in the spinal cord, can produce the basic rhythm with no sensory input and no descending control from the brain [1]. Even though the CPG is capable of generating the locomotory rhythm without sensory feedback, it can be strongly modulated by proprioceptive input (i.e., the sense of the body’s own movement) [2–4]. In particular, if the CPG oscillates at a frequency ω_0 in the absence of sensory input, a rhythmic stimulus at a frequency ω_f , close to ω_0 , can cause the CPG frequency ω^* to match the stimulus frequency ω_f . We use ω^* to denote the average frequency of the chain during forcing, which may or may not be equal to the forcing frequency ω_f . When the CPG’s response is periodic with frequency $\omega^* = \omega_f$ the CPG is said to be *entrained*, and the range of forcing frequencies leading to entrainment is termed the *entrainment range*. Entrainment can be lost in two ways: *externally*, in which all oscillators in the chain have the same average frequency ω^* , but $\omega^* \neq \omega_f$; or *internally*, in which part of the chain has a frequency $\omega = \omega_f$, but the rest of the chain has a different average frequency.

Entrainment of CPGs has been examined experimentally, most notably in lampreys [5–7], but also in other animals (e.g., leech [8], locust [9], and cat [10]). The lamprey has also served as a basis for mathematical models [11–15]. One fruitful approach, first used by Cohen, Holmes, and Rand [11], has been to approximate the CPG as a chain of coupled oscillators, in which each oscillator is described by a single variable, its phase θ . Kopell and Ermentrout [16] extended the work in [11], deriving general conditions under which a chain of oscillators could maintain synchrony with biologically realistic inter-oscillator phase lags. Later work from Kopell, Ermentrout, and Williams [15] examined the effect of forcing the chain at one end, and compared their findings to experimental entrainment ranges [5]. They considered what they termed “internal entrainment” in which forcing is sufficiently strong that entrainment can only be lost due to changes in relative phases within the chain of oscillators.

In the current study, we extend previous analytical results by examining the effect of forcing a chain of phase oscillators not only at either end (like in [15]), but also at any location in the middle of the chain. We consider both internal and external loss of entrainment, and compare the influence of short- and long-distance intersegmental connections. For short connections, in which each oscillator is connected only to its nearest neighbors, we derive an analytical expression for how the entrainment range depends on forcing location and whether loss of entrainment is internal or external.

We also consider the effect of longer connections on external loss of entrainment. We derive a criterion for the ratio of connection strengths under which longer connections do not change the entrainment ranges produced by nearest-neighbor connections. In this case, the size of the entrainment range is a monotonic function of forcing location. Numerically, we show that non-monotonic entrainment ranges are possible if the ratio criterion does not hold.

Our modeling results help us to gain insight into recent experimental data from Tytell and Cohen [6], who found the entrainment ranges were approximately twice as large for bending stimuli applied near the middle of the preparation than for stimuli at the ends (Fig. 1, modified from [6]). Tytell and Cohen [6] suggested that larger entrainment ranges near the middle of the preparation were an intuitive result, because the bending stimulus had to propagate over a shorter distance to entrain the whole chain. In contrast, our results suggest that entrainment ranges that vary non-monotonically as a function of stimulus position are not a trivial result, and, in fact, provide important information about how intersegmental connection strengths vary as a function of length and direction.

Results

Below, we first describe the structure of the phase model used to consider entrainment of the lamprey CPG, then consider analytical results for the case when each oscillator is connected only to its nearest

neighbor. Next, we extend the nearest-neighbor results, showing that longer connections do not necessarily change the nearest-neighbor entrainment ranges, provided that the strengths of the long connections match a criterion we derive. Finally, we show numerical results for what happens when that criterion does not hold.

Model structure

To model forcing of the lamprey CPG, we consider a chain of n coupled phase oscillators with the m^{th} oscillator receiving input from a forcing phase oscillator:

$$\dot{\theta}_i = \omega + \sum_{j=1}^n \alpha_{i-j} \sin(\theta_j - \theta_i - \psi_{i-j}), \quad i \neq m \quad (1)$$

$$\dot{\theta}_m = \omega + \sum_{j=1}^n \alpha_{m-j} \sin(\theta_j - \theta_m - \psi_{m-j}) + \alpha_f \sin(\theta_f - \theta_m), \quad (2)$$

$$\dot{\theta}_f = \omega_f, \quad (3)$$

where θ_i for $i = 1, \dots, n$ are the absolute phases (mod 2π) of oscillators in the chain ($i = 1$ for the oscillator nearest the head) and θ_f is the absolute phase (mod 2π) of the forcing oscillator. The parameter ω is the uncoupled angular frequency of the oscillators in the chain, which we assume to be the same for all oscillators. The model assumes that coupling is *translation invariant*, meaning that the properties of the connection from oscillator j to oscillator i only depend on the relative position $k = i - j$: α_k is the strength of the connection and ψ_k is its preferred phase. Here, $k > 0$ for descending (toward the tail, or caudal) connections and $k < 0$ for ascending (toward the head, or rostral) connections. (Note the conflict between the anatomical terms “descending” and “ascending” and our indexing scheme in which i increases from head to tail.) There is no connection between an oscillator and itself, so $\alpha_0 = 0$. Forcing is described by its strength α_f and its angular frequency ω_f .

Unless otherwise stated, we will assume that coupling is *tuned*, meaning that $\psi_k = k\bar{\psi}$, so that the uncoupled chain has equilibrium relative phases $\theta_j - \theta_i = (i - j)\bar{\psi}$. To model the lamprey CPG, $\bar{\psi}$ should be approximately $2\pi(0.01)$. When coupling is tuned, without loss of generality we can assume that $\bar{\psi} = 0$ by the applying the change of coordinates $\theta_i^{(\text{new})} = \theta_i^{(\text{old})} + i\bar{\psi}$.

To study entrainment, we transform variables from absolute phases to relative phases. Specifically, we use the phase of each oscillator in the chain relative to the forcing oscillator: $\phi_i = \theta_i - \theta_f$, so that the equations of motion become

$$\dot{\phi}_i = \Delta + \sum_{j=1}^n \alpha_{i-j} \sin(\phi_j - \phi_i - \psi_{i-j}), \quad i \neq m \quad (4)$$

$$\dot{\phi}_m = \Delta + \sum_{j=1}^n \alpha_{m-j} \sin(\phi_j - \phi_m - \psi_{m-j}) - \alpha_f \sin \phi_m, \quad (5)$$

where $\Delta = \omega - \omega_f$.

Stable entrainment of the chain corresponds to a stable fixed point of equations (4)–(5) so that the relative phase between each oscillator in the chain and the forcing oscillator is constant in time. Ermentrout [17] provides sufficient conditions for stable phase-locking of coupled phase oscillators. Suppose that $(\theta_1, \dots, \theta_n, \theta_f)$ are absolute phases for model (1)–(3) such that the relative phases (ϕ_1, \dots, ϕ_n) are a fixed point of (4)–(5). Let A be the following $(n + 1) \times (n + 1)$ matrix whose entries are derivatives of

coupling functions:

$$A_{ij} = \begin{cases} \alpha_{i-j} \cos(\theta_j - \theta_i - \psi_{i-j}), & \text{if } i, j \leq n, \\ \alpha_f \cos(\theta_f - \theta_m), & \text{if } i = m \text{ and } j = n + 1, \\ 0 & \text{otherwise.} \end{cases} \quad (6)$$

Ermentrout showed that the relative-phase fixed point is asymptotically stable if $A_{ij} \geq 0$ for all i and j and if every oscillator j *indirectly influences* every other oscillator i , meaning that there are indices i_1, \dots, i_p such that $A_{i,i_1} A_{i_1,i_2} \cdots A_{i_{p-1},i_p} A_{i_p,j} > 0$. In our case, oscillators in the chain do not indirectly influence the forcing oscillator. However, a straightforward extension of the proof given by Ermentrout shows that stability holds under the weaker assumption that there is one oscillator (the forcing oscillator) that indirectly influences all other oscillators. Therefore, entrainment will be stable if α_f , α_1 and α_{-1} are all positive, $|\theta_f - \theta_m| < \pi/2$, and $|\theta_j - \theta_i - \psi_{i-j}| < \pi/2$ for all i, j such that $\alpha_{i-j} > 0$.

Nearest-Neighbor Coupling

Here we consider the case of tuned nearest-neighbor coupling. As noted above, we can assume that $\psi_k \equiv 0$ without loss of generality. Then, the equations of motion for the relative phases (4), (5) can be written as

$$\begin{aligned} \dot{\phi}_1 &= \Delta + \alpha_{-1} \sin(\phi_2 - \phi_1) - \alpha_{f,1} \sin \phi_1, \\ \dot{\phi}_i &= \Delta + \alpha_1 \sin(\phi_{i-1} - \phi_i) + \alpha_{-1} \sin(\phi_{i+1} - \phi_i) - \alpha_{f,i} \sin \phi_i, \\ &\quad \text{for } i = 2, \dots, n-1, \\ \dot{\phi}_n &= \Delta + \alpha_1 \sin(\phi_{n-1} - \phi_n) - \alpha_{f,n} \sin \phi_n, \end{aligned} \quad (7)$$

where $\alpha_{f,m} = \alpha_f$ and $\alpha_{f,i} = 0$ if $i \neq m$. For the case of nearest neighbor coupling, there are only three connection strength parameters α_{-1} , α_1 , and α_f , where α_{-1} is the connection strength from oscillator i to oscillator $i-1$, an ascending connection, and α_1 represents the strength of a connection from oscillator i to oscillator $i+1$, a descending connection.

For equilibria to exist, $\dot{\phi}_i = 0$ for all i . In the case $\alpha_1 \neq \alpha_{-1}$, we obtain

$$\begin{aligned} \sin(\phi_i - \phi_{i+1}) &= s_a(i) \stackrel{\text{def}}{=} \frac{(\alpha_1/\alpha_{-1})^i - 1}{\alpha_1 - \alpha_{-1}} \Delta, & \text{for } i < m, \\ \sin(\phi_i - \phi_{i-1}) &= s_d(i) \stackrel{\text{def}}{=} \frac{(\alpha_{-1}/\alpha_1)^{n+1-i} - 1}{\alpha_{-1} - \alpha_1} \Delta, & \text{for } i > m, \\ \sin(\phi_m) &= s_f(m) \stackrel{\text{def}}{=} \frac{\alpha_1(\alpha_1/\alpha_{-1})^{m-1} - \alpha_{-1}(\alpha_{-1}/\alpha_1)^{n-m}}{(\alpha_1 - \alpha_{-1})\alpha_f} \Delta, \end{aligned} \quad (8)$$

which can be verified by direct substitution into the equations of motion. Necessary and sufficient conditions for stable entrainment are that $|s_a(i)| < 1$ for $i < m$, $|s_d(i)| < 1$ for $i > m$, and $|s_f(m)| < 1$. Note that if $i < m-1$, then

$$\frac{|s_a(i+1)|}{|s_a(i)|} = \frac{|(\alpha_1/\alpha_{-1})^{i+1} - 1|}{|(\alpha_1/\alpha_{-1})^i - 1|} > 1.$$

Similarly, if $i > m+1$, then $|s_d(i-1)|/|s_d(i)| \geq 1$. Therefore, necessary and sufficient conditions for stable entrainment are that $|s_a(m-1)| < 1$, $|s_d(m+1)| < 1$, and $|s_f(m)| < 1$. These conditions can be

written as

$$|\Delta| < \frac{\alpha_1 - \alpha_{-1}}{(\alpha_1/\alpha_{-1})^{m-1} - 1}, \quad (9)$$

$$|\Delta| < \frac{\alpha_{-1} - \alpha_1}{(\alpha_{-1}/\alpha_1)^{n-m} - 1}, \quad (10)$$

$$|\Delta| < \frac{(\alpha_1 - \alpha_{-1})\alpha_f}{\alpha_1(\alpha_1/\alpha_{-1})^{m-1} - \alpha_{-1}(\alpha_{-1}/\alpha_1)^{n-m}}. \quad (11)$$

If $\alpha_{-1} = \alpha_1 = \alpha$, then the condition obtained by direct substitution into the equations of motion are

$$|\Delta| < \frac{\alpha}{m-1}, \quad |\Delta| < \frac{\alpha}{n-m}, \quad |\Delta| < \frac{\alpha_f}{n}.$$

As $|\Delta|$ increases, entrainment is lost when any of the three inequalities is violated. Simulations show that immediately after entrainment is lost, the absolute phases $\theta_1, \dots, \theta_n$ and θ_f break into two groups, in which all oscillators in a group have the same average frequency, but the groups have different average frequencies. The nature of the two groups depends on which inequality is violated first. Thus, we can categorize and describe the loss of entrainment as follows:

- **Rostral internal loss of entrainment.** If inequality (9) is violated first, then entrainment is lost when the relative phase between oscillator m and oscillator $m-1$ (the oscillator immediately rostral to the forcing location) approaches the stability limit $\pm\pi/2$. After entrainment is lost, part of the chain (oscillators m through n) has the same average frequency as the forcing oscillator and part of chain (oscillators 1 through $m-1$) has a different average frequency.
- **Caudal internal loss of entrainment.** If inequality (10) is violated first, then entrainment is lost when the relative phase between oscillator m and oscillator $m+1$ (the oscillator immediately caudal to the forcing location) approaches the stability limit $\pm\pi/2$. After entrainment is lost, part of the chain (oscillators 1 through m) has the same average frequency as the forcing oscillator and part of chain (oscillators $m+1$ through n) has a different average frequency.
- **External Loss of Entrainment.** If inequality (11) is violated first, then entrainment is lost when the relative phase between oscillator m and the forcing oscillator approaches the stability limit $\pm\pi/2$. After entrainment is lost, the chain of oscillators has a different average frequency than the forcing oscillator.

This last case corresponds to the way that entrainment of the lamprey CPG is thought to be lost as the bending frequency is varied. It is a straightforward exercise to show that the right-hand side of inequality (11) is a monotonic function of the forcing location m , unlike the experimental results in [6].

Figure 2 illustrates the three types of loss of entrainment for a chain of 50 oscillators with nearest-neighbor coupling. The connection strengths were chosen to be $\alpha_1 = 10$, $\alpha_{-1} = 10.1$, and $\alpha_f = 16$, so that ascending coupling is slightly stronger than descending coupling. The blue curves represent the theoretical limits of the entrainment range for external loss of entrainment; the red curves represent the theoretical limits of the entrainment range for rostral internal loss of entrainment; and the black curves represent the theoretical limits of the entrainment range for caudal internal loss of entrainment. For each forcing location $m = 1, \dots, 50$, the entrainment range is smallest of three possible entrainment ranges, as indicated by the dots in Fig. 2 with color indicating the type of loss of entrainment. For this example, forcing near the beginning of the chain produced caudal internal loss of entrainment, forcing the middle segments of the chain produced external loss of entrainment, and forcing near the end of the chain produced rostral internal loss of entrainment. The largest entrainment ranges are near the middle of the chain. However, this is only true because entrainment is lost internally near either end of the chain. If coupling within the chain were stronger, then entrainment would be lost externally for all locations along the chain, resulting in entrainment ranges whose size increases monotonically from head to tail (the blue curves in Fig. 2).

All-to-all Coupling

Here we consider examples in which all of the oscillators are coupled to all other oscillators, but where coupling strength is a function of connection length and direction. Our consideration of long-distance coupling is motivated by results showing that long connections in the lamprey CPG have substantial coupling strength [18–22]. The equations for an equilibrium of relative phases take the form (4)–(5). Similar to the nearest-neighbor results, we show how the entrainment ranges change as the location of the forcing is moved along the chain.

We first consider a condition under which longer connections do not change the entrainment ranges resulting from the nearest-neighbor connections:

Proposition 0.1 *If coupling is tuned, and entrainment is lost externally, and*

$$\alpha_k/\alpha_{-k} = (\alpha_1/\alpha_{-1})^k \quad (12)$$

for all lengths $k = 2, \dots, n$, then the entrainment range for forcing at oscillator m is given by equation (11) for nearest-neighbor coupling.

To prove this proposition, from (4) we have that

$$\sin(\phi_i - \phi_m) = \frac{1}{\alpha_{im}} \left(\Delta + \sum_{j \neq m} \alpha_{ij} \sin(\phi_j - \phi_i) \right), \quad \text{for } i \neq m,$$

where we are assuming that $\psi_k \equiv 0$. Substituting this expression into (5) yields

$$\begin{aligned} 0 &= \Delta + \sum_{i \neq m} \frac{\alpha_{m-i}}{\alpha_{i-m}} \left(\Delta + \sum_{j \neq m} \alpha_{i-j} \sin(\phi_j - \phi_i) \right) - \alpha_f \sin \phi_m \\ &= \Delta \left(1 + \sum_{i \neq m} \frac{\alpha_{m-i}}{\alpha_{i-m}} \right) + \sum_{i \neq m} \sum_{\substack{j \neq m \\ j < i}} \left(\frac{\alpha_{m-i}}{\alpha_{i-m}} \alpha_{i-j} - \frac{\alpha_{m-j}}{\alpha_{j-m}} \alpha_{j-i} \right) \sin(\phi_j - \phi_i) \\ &\quad - \alpha_f \sin \phi_m \\ &= \Delta \sum_{k=m-n}^{m-1} \left(\frac{\alpha_1}{\alpha_{-1}} \right)^k - \alpha_f \sin \phi_m, \end{aligned} \quad (13)$$

where we have used that

$$\begin{aligned} \left(\frac{\alpha_{m-i}}{\alpha_{i-m}} \alpha_{i-j} - \frac{\alpha_{m-j}}{\alpha_{j-m}} \alpha_{j-i} \right) &= \alpha_{i-j} \left(\frac{\alpha_{m-i}}{\alpha_{i-m}} - \frac{\alpha_{m-j}}{\alpha_{j-m}} \frac{\alpha_{j-i}}{\alpha_{i-j}} \right) \\ &= \alpha_{i-j} \left(\left(\frac{\alpha_1}{\alpha_{-1}} \right)^{m-i} - \left(\frac{\alpha_1}{\alpha_{-1}} \right)^{m-j} \left(\frac{\alpha_1}{\alpha_{-1}} \right)^{j-i} \right) \\ &= 0. \end{aligned}$$

It is now straightforward to show that solving (13) for $\sin \phi_m$ gives $\sin \phi_m = s_f(m)$ from (8) for nearest-neighbor coupling. Since we are assuming that entrainment is lost externally, equation (11) for the entrainment range follows directly from (8).

For example, a choice for the relationship between length and strength is to choose coupling strength to be exponentially decreasing with respect to length, which we term *exponential coupling* [23, 24] In

particular, for connections of length k

$$\alpha_k = A_d \exp(-k/\lambda_d), \quad (14)$$

$$\alpha_{-k} = A_a \exp(-k/\lambda_a), \quad (15)$$

where k and $-k$ denote descending and ascending connections, respectively, of length $k = |i - j|$. For exponential coupling,

$$\frac{\alpha_k}{\alpha_{-k}} = \left(\frac{A_a}{A_d}\right)^{k-1} \left(\frac{\alpha_1}{\alpha_{-1}}\right)^k,$$

which implies that the condition (12) in Proposition 0.1 holds independent of the length constants λ_a, λ_d , provided that $A_a = A_d$.

Figure 3 illustrates an example in which the assumptions of Prop. 0.1 hold and the entrainment ranges for nearest-neighbor coupling (filled blue squares) coincide with the entrainment ranges for exponential coupling (open red circles). In this example, the parameters for tuned nearest-neighbor coupling are $n = 50$, $\alpha_1 = 10$, $\alpha_{-1} = 10.1$, $\alpha_f = 8$, $\psi_1 = 2\pi(0.01)$, and $\psi_{-1} = -2\pi(0.01)$, and the parameters for tuned exponential coupling are $n = 50$, $A_d = A_a = 12$, $\lambda_d = 1/\log(A_d/10) \approx 5.485$, $\lambda_a = 1/\log(A_a/10.1) \approx 5.801$, $\alpha_f = 8$, and $\psi_k = 2\pi k(0.01)$. Figure 3 further illustrates the effects of detuned coupling on the entrainment ranges. If the coupling is detuned by decreasing ψ_k for each descending connection by $2\pi(0.01)$, entrainment ranges change dramatically for nearest-neighbor coupling (filled red triangles) but only slightly for exponential coupling (black dots). We therefore conclude that the long distance connections cause entrainment ranges to be more robust against model changes such as detuning.

When the conditions of Proposition 0.1 are met, the size of the entrainment range changes monotonically with forcing location m (closed blue squares and open red circles in Fig. 3). Note that the ratio condition (12) implies that either $\alpha_{-k} \geq \alpha_k$ for all k or $\alpha_{-k} \leq \alpha_k$ for all k , a property that we term *uniform coupling asymmetry*. Based on numerical results, we offer the following conjecture in which uniform coupling asymmetry is one of a set of sufficient conditions for monotonic entrainment ranges:

Conjecture 0.2 *Assume that coupling is tuned, entrainment is lost externally, and connection strengths decrease monotonically with length: $\alpha_1 \geq \alpha_2 \geq \dots \geq \alpha_{n-1}$ and $\alpha_{-1} \geq \alpha_{-2} \geq \dots \geq \alpha_{-(n-1)}$. If $\alpha_{-k} \geq \alpha_k$ (or $\alpha_{-k} \leq \alpha_k$) for all lengths $k = 1, \dots, n-1$, then the size of the entrainment range increases (or decreases) monotonically with forcing location m .*

Note that the conjecture's condition of uniform coupling asymmetry is more general than the the ratio condition (12) of Prop. 0.1, but that the conjecture's condition of monotonically decreasing connection strengths was not necessary in Prop. 0.1.

Figure 4A–B illustrates an example of exponential coupling that obeys all the conditions of the conjecture. The ascending connection strength is stronger than the descending connection strength for every length k (Fig. 4A), resulting in an entrainment range whose size increases monotonically with forcing location m (Fig. 4B). Figure 4C–D illustrates an example of exponential coupling that violates the conjecture's condition of uniform coupling asymmetry; descending connections are stronger for lengths $k \leq 13$ and ascending connections are stronger for lengths $k > 13$ (Fig. 4C). All other conditions of the conjecture hold. The size of the entrainment range is not a monotonic function of forcing position m , but instead shows a peak in the interior of of the chain (Fig. 4D), somewhat similar to experimental results of [6] (Fig. 1). There is also another peak at the head-end of the chain that is not clearly evident in the experimental results, although given the variation in the experimental data its presence cannot be ruled out.

Discussion

In this study we considered a chain of coupled phase oscillators with one oscillator being forced by an external oscillator. By making the specific choice of tuned sinusoidal coupling functions, we were able to

completely describe entrainment ranges for nearest-neighbor coupling for forcing at any location along the chain and for any strength of forcing. This description distinguished between internal (within the chain) and external (between the chain and the forcing oscillator) loss of entrainment.

In contrast, the study of Kopell, Ermentrout, and Williams [15] considered forcing only at either end and assumed that forcing was sufficiently strong so that entrainment could only be lost internally. On the other hand, they considered more general coupling functions than ours. In particular they did not assume that coupling was tuned. This difference is crucial if one considers whether the entrainment range shrinks to zero as the number n of oscillators increases. For tuned coupling, inequality (9) shows that the entrainment range for oscillator n will shrink to zero if $\alpha_1 \geq \alpha_{-1}$ and inequality (10) shows that the entrainment range for oscillator 1 will shrink to zero if $\alpha_{-1} \geq \alpha_1$. Thus, the entrainment range for at least one end of the chain will shrink to zero as n increases. However, [15] gives conditions for untuned coupling under which the entrainment range from neither end shrinks to zero.

The preceding indicates that tuned coupling as a simplifying assumption may be misleading if connection lengths are short compared to the length of the chain. This is further illustrated by our results showing that when entrainment is lost externally, the size of the entrainment range for nearest-neighbor coupling is a monotonic function of forcing location for tuned coupling, but not necessarily for untuned coupling (Eq. 11 and Fig. 3). However, our results suggest that the tuned-coupling assumption may be a reasonable approximation when coupling includes substantial long-distance coupling (Fig. 3), as is the case for the lamprey CPG [18–22, 25].

The results presented here provide an impetus to reexamine experimental data. Specifically, previous entrainment studies, including Tytell and Cohen’s study [6], which provided the motivation for this work, along with others [5, 7, 26], did not distinguish between internal and external loss of entrainment. In fact, even though previous theoretical work [15] only considered internal entrainment loss, the dominant experimental assumption was that entrainment is lost externally [5, 6]. Anecdotal observations indicate that internal entrainment loss, if it is present empirically, is not obvious, particularly when ω_f is not far outside of the entrainment range (E.D.T., T.K., personal observation).

It is possible that larger entrainment ranges observed near the middle of experimental preparations (Fig. 1 [6]) are due to external entrainment loss, while the smaller ranges near the ends are due to internal loss (as in Fig. 2). The distinction might have been overlooked in experiments due to the method of determining entrainment ranges. Empirically, entrainment is determined by 1:1 synchrony between a sinusoidal bending input and bursts of electrical activity in the motor nerves. If entrainment is lost internally, recordings from nerves close to the forcing would still show 1:1 synchrony, while nerves further away should have an increasing incidence of skipped or doubled bursts. Alternatively, if entrainment is lost externally, the frequency of skipped or doubled bursts will be consistent regardless of the location of the nerve. Looking at average CPG frequency ω^* , as Tytell and Cohen [6] did, would obscure these subtle differences.

Additionally, the current results indicate that internal loss of entrainment is more likely when the forcing strength α_f is strong relative to the internal coupling strengths α_k . In experiments, α_f is thought to correspond roughly to the amplitude of the bending stimulus. Increasing that amplitude would make internal loss of entrainment more likely, if it is present at all. Specifically, external entrainment loss (Eq. 11) depends on α_f , but internal loss (Eq. 9 and 10) do not. Increasing α_f thus increases the frequency range at which external entrainment loss occurs, potentially outside of the internal entrainment range (cf. Fig. 2). Similar experiments might also be useful to perform using leech preparations. In leech, entrainment ranges are very large (upper bounds close to twice the baseline frequency ω_0) for forcing near the middle of the chain [8]. As with lampreys, the leech study did not classify the type of entrainment loss, but the large entrainment range indicates relatively strong forcing compared to the internal coupling strength, and the possibility that entrainment might have been lost internally.

In conclusion, our results indicate that non-monotonic entrainment ranges as a function of forcing location, such as observed experimentally in the lamprey CPG, are not a generic property for a chain

of coupled oscillators but rather reflect properties of coupling within the chain. Our conjecture suggests that experimental entrainment ranges reflect a non-uniform coupling asymmetry in which ascending connections are stronger for some connection lengths and descending connections are stronger for other lengths. Empirical evidence is divided on the strength and direction of such connections in the lamprey. Kiemel et al. [21] found a bias toward stronger ascending connections. In contrast, McClellan and Hagevik [22], using inhibitory baths to examine very long distance connections, found that descending connections were stronger than ascending. Together, these two studies provide some support for our conjecture of non-uniform coupling asymmetry, but further experiments will need to be performed to establish it more thoroughly.

Methods

Numerical methods

For cases in which a closed-form expression for the entrainment range was not available (untuned cases in Fig. 3 and both examples in Fig. 4), the limits of the entrainment range were determined by using Newton's method to find a fixed point of the relative-phase system (4)–(5) with $\phi_m = \pm\pi/2$. These entrainment limits correspond to saddle-node bifurcations of the relative-phase system.

Lamprey experiments

The current study is based on data from Tytell and Cohen [6], who extended the experimental protocols developed by Williams et al. [5] and McClellan and Sigvardt [7]. Briefly, approximately 50 segments of the lamprey spinal cord were dissected out and pinned in a dish containing chilled lamprey saline and an excitatory amino acid, D-glutamate, that activated the CPG circuit. The CPG rhythm was monitored with extracellular records of activity in the ventral root nerves, which contain axons of motor neurons that would activate the muscles in the intact animal. A bending stimulus was applied at points along the spinal cord, and the bending frequency was slowly increased or decreased. The entrainment range was estimated by noting when the CPG maintained a 1:1 synchronization with the bending stimulus (Fig. 1, modified from [6]).

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Figure Legends

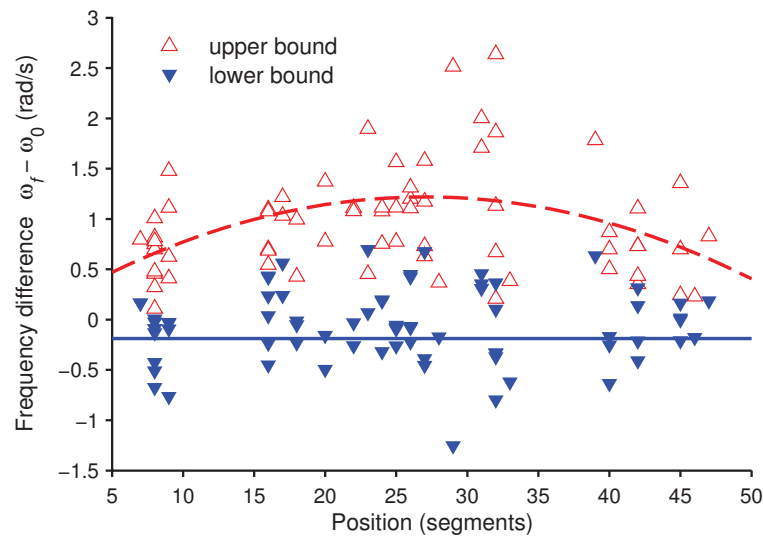


Figure 1. Entrainment ranges for lamprey spinal cords with sinusoidal bending stimuli at different locations. Open red upward-pointing triangles represent upper entrainment bounds; filled blue downward-pointing triangles represent lower bounds. The dashed red and solid blue lines are the significant terms ($p < 0.05$) from quadratic polynomial fits to the upper and lower bound data, respectively. The quadratic term was not significant for the lower bound regression. Replotted based on data from [6].

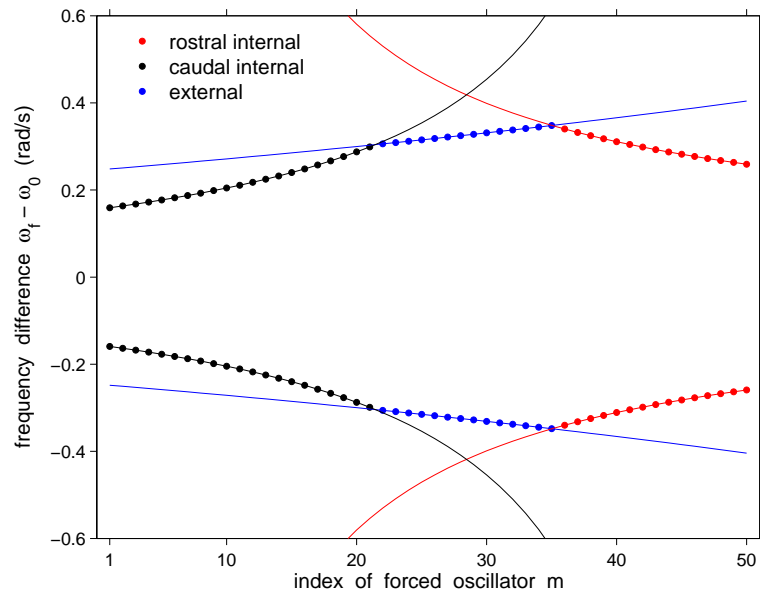


Figure 2. Entrainment range as a function of forcing location for nearest-neighbor coupling. Circles show limits of entrainment range: red circles if entrainment is lost internally rostral to the forcing location (Eq. 9); black circles if entrainment is lost internally caudal to the forcing location (Eq. 10); and blue circles if entrainment is lost externally (Eq. 11). Continuous curves are constraint equations for each type of loss of entrainment. The frequency ω_0 of the unforced chain equals the intrinsic frequency ω of each oscillator.

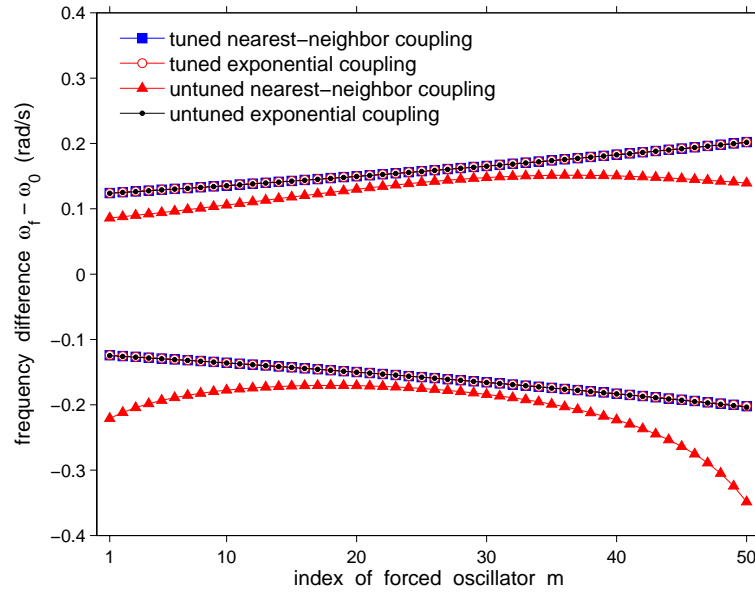


Figure 3. Nearest-neighbor and all-to-all coupling produce the same entrainment ranges when Proposition 0.1 holds, but all-to-all coupling is more robust to detuning. For this example, the exponential coupling meets the conditions of Proposition 0.1 so that tuned nearest-neighbor coupling (filled blue squares) and tuned exponential coupling (open red circles) have the same entrainment ranges. However, when coupling is detuned by decreasing ψ_k for each descending connection by $2\pi(0.01)$, entrainment ranges change dramatically for nearest-neighbor coupling (filled red triangles) but only slightly for exponential coupling (black dots). For tuned coupling, the frequency ω_0 of the unforced chain equals the intrinsic frequency ω of each oscillator. For untuned coupling, $\omega_0 \neq \omega$.

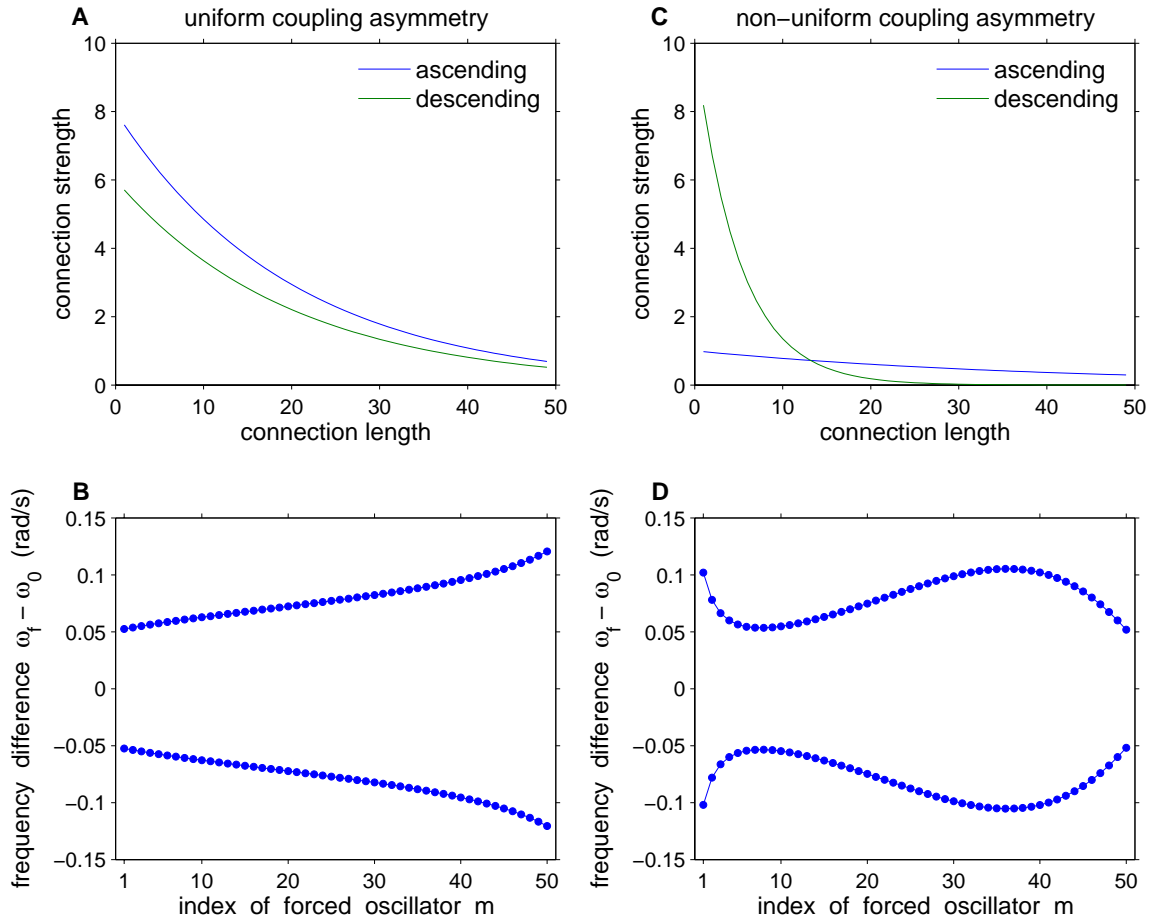


Figure 4. Entrainment ranges for examples with uniform and non-uniform coupling asymmetry. A: Connection strengths for an example with uniform coupling asymmetry. Parameter are $n = 50$, $A_a = 8$, $A_d = 6$, $\lambda_a = \lambda_d = 20$, and $\alpha_f = 4$. B: Resulting entrainment ranges. C: Connection strengths for an example with non-uniform coupling asymmetry. Parameter are $n = 50$, $A_a = 1$, $A_d = 10$, $\lambda_a = 40$, $\lambda_d = 5$, and $\alpha_f = 4$. D: Resulting entrainment ranges.