Rhythmic movements, such as walking, breathing, and swimming, are coordinated by neural networks called central pattern generators (CPGs) (Marder and Calabrese, 1996). CPGs can produce a rhythmic motor output when isolated from both descending signals from high-order centers and sensory feedback signals from the musculoskeletal system. Traditionally, it was believed that the CPG provided commands for rhythmic movements, such that the musculoskeletal system was entrained to oscillate at the endogenous CPG frequency (Brown, 1914). It is now appreciated, however, that both the passive and active mechanical properties of the musculoskeletal system greatly contribute to the control of rhythmic movements.

Studies on a variety of vertebrate and invertebrate systems have indicated several roles for the natural body dynamics in rhythmic motor control. For instance, the metabolic cost or energy expenditure for walking in humans (Holt *et al.,* 1995; Jeng *et al.,* 1997) and swimming in a variety of animals including jellyfish (DeMont and Gosline, 1988), scallops (DeMont, 1990), and hagfish (Long *et al.,* 2002) is minimized by performing the movement at the natural or resonant frequency of the body mechanics, not at the endogenous CPG frequency. Both humans (Abe and Yamada, 2003) and some fish species (Pabst, 1996) actively change mechanical properties, like stiffness, to match the body's resonant frequency to a range of movement frequencies. Theoretical models of cat locomotion have also shown an increased stability of the movement when the nonlinear force-velocity and force-length muscle properties are included in the musculoskeletal dynamics (Prochazka *et al.,* 1997). These examples show that by using the inherent musculoskeletal dynamics, the necessary neural contribution to the control of movement is simplified.

For the CPG to take advantage of the musculoskeletal dynamics, however, the neural and mechanical systems must be intimately linked. This coordination is accomplished, in part, by movement-related sensory feedback signals from the musculoskeletal system to the CPG. Removal of sensory feedback has been shown to significantly affect the frequency of locust flight (Wilson, 1967) and lamprey swimming (Guan *et al.,* 2001). However, the influence of sensory feedback connectivity on the frequency of rhythmic movements has been largely unexplored. **In this work, our objective is to elucidate how the nature of the sensory feedback connections influences the steady-state, unperturbed frequency of rhythmic movements.**

To meet this objective, we developed a generalized computational model based on the neuromechanical configurations that are found in one segment of the lamprey swim system. The lamprey is ideal for studying neuromechanical interactions because the CPG is well-characterized (Grillner and Wallen, 2002), the mechanical properties of similar swimmers have been studied (Ekeberg, 1993; Jordan, 1996; Long and Nipper, 1996) and the sensory feedback connections between the body and the CPG are known (Viana Di Prisco *et al.,* 1990). Our neuromechanical model includes a generalized half-center oscillator for the CPG and an underdamped, one-degree-of-freedom system for the mechanical component. The CPG generates a torque that drives the mechanics and receives a feedback current related to the position of the mechanics. By using a computational model, we are able to manipulate parameters that are difficult, if not impossible, to change *in vivo* and to consequently determine how these parameters affect the frequency of the closed-loop system.

We have divided our objective into four aims. A general introduction, a summary of the work accomplished, and the future goals for each of the four aims are given below.

1. Characterize the synchronization of a neuromechanical system when two *negative* sensory feedback connections are individually and concomitantly implemented. The lamprey simultaneously uses two negative feedback configurations to coordinate the neuromechanical dynamics during swimming. We describe the two negative feedback connections as ipsilateral inhibition and contralateral excitation. Thus far, the functional significance of the dual negative feedback connections and the relative conductances of the two types of feedback synapses are not known. *We hypothesize that by using two sensory feedback configurations concomitantly, the neuromechanical system synchronizes to greater range of mechanical resonant frequencies than if either one configuration is individually implemented.*

We have shown that the closed-loop system tunes to different ranges of mechanical resonant frequencies depending on the sensory feedback connectivity. Overall, the neuromechanical system tuned to a greater range of resonant frequencies with ipsilateral inhibition, but only when large maximal conductances were used. With contralateral excitation, the closed-loop system tuned to a smaller range of resonant frequencies (only those much greater than the endogenous CPG frequency), but this occurred with relatively small

maximal conductances. We have also shown that the neuromechanical system tunes to a greater range of mechanical resonant frequencies when both negative feedback connections are symmetrically and simultaneously applied than when either connection is individually implemented. Thus far, we have only run simulations when the two negative feedback connections are symmetrically implemented. We have begun to systematically vary the relative contributions of the two negative configurations. In doing so, we will determine if there is an optimal weighting of these configurations for resonance tuning.

We have also made several general conclusions about the behavior of the closed-loop system with negative sensory feedback. First, with any individual or combination of *negative* feedback synapses, the neuromechanical system only tuned to resonant frequencies that were *greater* than the endogenous CPG frequency. Second, higher feedback gains and higher maximal conductances increased the range of mechanical resonant frequencies to which the neuromechanical system would synchronize.

We have also confirmed that our results are true when living neurons are used as the CPG. Here, we used a dynamic clamp to connect two, isolated *Aplysia californica* bursting neurons with reciprocally inhibitory synapses. With the living cells as the CPG, we also saw a different activity with ipsilateral inhibition vs. contralateral excitation. As with previous studies, the neuromechanical system would only tune to mechanical resonant frequencies that were greater than the endogenous CPG frequency.

2. Characterize the synchronization of the neuromechanical system when two *positive* sensory feedback connections are individually and concomitantly implemented. Although the lamprey is known to have negative sensory feedback connections, it is also possible to synchronize a closed-loop system using positive feedback. We describe the two possible positive feedback synapses as ipsilateral excitation and contralateral inhibition. In this aim, we are trying to determine what advantages negative feedback provides to the neuromechanical system. *We hypothesize that the closed-loop system will synchronize to a smaller range of resonant frequencies with positive feedback than with negative feedback.*

As with negative feedback, the closed-loop system tuned to a different range of resonant frequencies depending on the connectivity of the positive sensory feedback. With ipsilateral excitation, the system tuned to resonant frequencies that were immediately below the endogenous CPG frequency, whereas with contralateral inhibition, the system tuned to resonant frequencies that were much lower than the endogenous CPG frequency. When both configurations were symmetrically and simultaneously implemented, the neuromechanical system tuned to a greater range of resonant frequencies than when either configuration was individually implemented.

There are several major differences between the behaviors of the neuromechanical system with positive vs. negative feedback. First, with *positive* feedback, the system would only tune to resonant frequencies that were *lower* than the endogenous CPG frequency. This is in direct contrast to *negative* feedback, which would only *increase* the CPG frequency. We have also shown that these trends are true when the mechanical system is non-resonant or overdamped: with positive feedback, the system only operates at frequencies below the endogenous CPG frequency and with negative feedback, the system only operates at frequencies above the endogenous CPG frequency. Second, with positive feedback, the lower feedback gains were more effective in synchronizing the system to resonance, whereas higher feedback gains were more effective with negative feedback. These results show a duality in the activity of a closed-loop system when positive vs. negative feedback is used to connect the mechanical and neural components.

Contrary to our hypothesis, we have not determined that positive feedback is less effective in synchronizing the system to mechanical resonance. Instead, we found that positive and negative feedback tune the system to two distinct frequency ranges. However, we are currently analyzing the negative and positive feedback simulations for several stability metrics. We hypothesize that while both positive and negative feedback are effective in synchronizing the closed-loop system to resonance, the movement may be more stable with negative feedback.

3. Characterize how the CPG's cellular properties affect the ability of the neuromechanical system to synchronize to the mechanical resonant frequency. Several models of the lamprey CPG have been presented in the literature. These models differ in both the number of cells that are used to represent one segment of the swim CPG and in the ionic current detail that is included to model each of the individual neurons. In this aim, our objective is to determine how (1) the *intercellular* dynamics amongst the cells in the

CPG and (2) the *intracellular* ionic dynamics of individual cells affect the ability of the neuromechanical system to synchronize to the mechanical resonant frequency. In other words, we are trying to determine if our results from Aims 1 and 2 are general to a broad class of neural oscillators that are coupled to a mechanical system or if they are specific to the combination of CPG and mechanical system that are used. *We hypothesize that the general trends observed for negative and positive feedback will be true for all CPGs. However, we hypothesize that the CPG dynamics will influence which sensory feedback connection is most effective in tuning the neuromechanical system to resonance.*

We have analyzed the resonance tuning of the neuromechanical system when the same CPG is activated by two different simulated drug applications: NMDA and non-NMDA. The CPG will only fire action potentials when activated by one or a combination of these drugs, and it has a different bursting pattern depending on the activation. Thus far, we have shown that our general results from Aims 1 and 2 are true independent of how the CPG is activated. Surprisingly, though, the neuromechanical system seems to track the mechanical resonant frequency within 30% both above and below the endogenous CPG frequency when non-NMDA activation was used with negative feedback. This suggests that there may be a combination of CPG and feedback parameters such that the neuromechanical system synchronizes to the mechanical resonant frequency both above and below the endogenous CPG frequency. This would be an important result for engineers who build robotic systems (i.e. Williamson [MIT], Ferris [Michigan]) with artificial neural controllers. Previously, the endogenous CPG frequency was the lower frequency limit where resonance tuning would occur. Our results suggest that the energy minimization benefits of resonance tuning can be extended beyond this boundary by choosing an appropriate sensory feedback/CPG combination. To this end, I am trying to classify the interactions between the sensory feedback connections and the neural properties.

4. Characterize the synchronization of the neuromechanical system when force-velocity and force-length nonlinearities are included in the musculoskeletal model. The first three aims are performed with a mechanical system that only possesses passive musculoskeletal dynamics. *By including the active muscle dynamics in our computational system, we hypothesize that the closed-loop system will synchronize more quickly, and may, therefore, synchronize to a slightly increased range of mechanical resonant frequencies with all sensory feedback configurations.* Obtaining results for this aim will be much of our focus for the next few months. Thus far, we have implemented the nonlinear musculoskeletal model, but we have not run enough simulations to formulate results.

By using engineering (control systems) methods to analyze biological locomotion, we have shown that the frequency of a rhythmic movement can be dramatically altered by the nature of the sensory feedback connections. Our results have implications for both biologists and engineers. In particular, we suggest that in animals, like the lamprey, multiple sensory feedback connections may minimize the animal's energy expenditure for movement over a wider range of frequencies than if only one connection was used. We also suggest that engineers can further decrease the energy requirements of robotic locomotion by optimizing the connectivity of sensory feedback from the robotic device to the artificial neural controller. Overall, this work emphasizes that the sensory feedback connections are as important as the nervous and musculoskeletal systems in determining the frequency of a rhythmic movement.

Academic Coursework

I completed my course work in the Fall of 2003, and I will not take any classes next year. My completed course work is listed below.

- Cellular Engineering, Biomedical Engineering
- Tissue Engineering, Biomedical Engineering
- Systems Pathophysiology, Biomedical Engineering
- Feedback Control of Biological Systems, Biomedical Engineering
- Orthopedic and Injury Biomechanics, Biomedical Engineering
- Cardiovascular Biomechanics, Biomedical Engineering
- Fundamentals of Digital Signal Processing, Electrical and Computer Engineering
- Numerical Methods in Mechanical Engineering, Mechanical Engineering
- Math Methods in Engineering, Math
- Biochemistry, Interdisciplinary Biological Sciences (EMORY)

- Advances in Molecular Biology, Biology
- Cellular Neuroscience, Neuroscience (EMORY)
- Introduction to Nonlinear Dynamics and Chaos, Physics
- Control Systems, Electrical and Computer Engineering

Usage of Educational Funds

During the 2002-2003, I used the professional development funds for travel to two conferences: Society for Neuroscience in November 2004 and Neural Control of Movement in April 2005.

Other Relevant Information

In December 2004, I proposed my thesis. My thesis committee consists of:

- Stephen DeWeerth (BME, Georgia Tech)
- Lena Ting (BME, Georgia Tech)
- Rob Butera (ECE, Georgia Tech)
- Bob Lee (BME, Georgia Tech)
- Paul Katz (Biology, Georgia State)

With the proposal completed, I should graduate no later than Summer 2006. In addition to the proposal, I presented a poster at three conferences: Whitaker Foundation in August 2004, Society for Neuroscience in November 2004, and Neural Control of Movement in April 2005. My poster abstracts for these conferences are included in the progress report package. Although I do not have a manuscript to include at this time, I am running the final simulations that I will need to combine the results from my first two specific aims into a paper. Tentatively, we plan to submit these results to IEEE Transactions on Neural Systems and Rehabilitation Engineering.

Advisor: Stephen P. DeWeerth, Ph.D.   Student: Carrie A. Williams

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