One of the most impressive abilities of animal nervous systems is to quickly coordinate strategies outside their nominal patterns of behavior. In dynamic locomotion, we can observe real-time low-level problem-solving. Responding to perturbations such as unexpected ground height changes requires significant departures from nominal walking patterns, and these changes must be fast and coordinated in order to be effective.

1. How are such responses generated in a dynamic neural hierarchy?
2. How do higher-level networks dynamically interact with functioning low-level control networks to improve performance?
3. How are dozens of muscles coordinated simultaneously?
4. Are known pathways sufficient to explain the full range of behaviors for small and large perturbations?
5. When the animal outperforms our model, what new mechanisms could explain observed behaviors?

To understand the dynamics of hierarchical coordination in biological systems, high-fidelity biomechanical models are needed that accurately reflect the internal dynamics of the animal and its interaction with the physical world. The Quinn lab has experience abstracting components of neurobiological locomotion strategies (e.g. specific behavioral reactions, neural pathways, dynamic oscillators and organizational hierarchies) at tractable levels to validate these strategies in physical and software models [1]–[9], and further applying them in robots [10]–[18]. The Fischer lab experiments provide low-level behavior and performance data, e.g. joint kinematics, electromyograms of leg muscles and ground reaction forces, which are essential for validation and calibration of both mechanical and neurobiological models. In this work, we will combine insights gained from biological experiments in the Fischer lab with a dynamic model developed by the Quinn lab to explain novel behaviors. Our proposed collaboration will holistically test previous research from our labs and others, provide a foundation for addressing deeper questions in biology, neurobiology, and neuroscience, and inspire development of improved robotic control systems for dynamic control of walking and running.

To appreciate an animal’s skill in running, it is helpful to consider the state of the art in legged robots. Current legged machines like BigDog [19] and the 2013 WildCat can calculate slow, statically stable steps on rubble piles and stabilize themselves to run on relatively smooth ground. They are, however, unable to keep up with legged animals over arbitrary natural terrain. In contrast, animals exploit the mechanical advantages of multi-jointed legs by making small adjustments to muscle activation magnitudes and timing for stabilization– often without breaking stride. While these biologically-inspired reflexes can be abstracted as heuristics for robots, we also need biologically-plausible control structures to understand how different competing reflexes interact without overshoot or canceling each other out, how feedforward predictions of limited accuracy are combined with sensory measurements of limited precision, and how coordination of dozens of semi-redundant muscles is performed so that the entire system works together. Because these tasks are difficult for robots, robots are typically more cautious than animals, making them slower and more power demanding (i.e. heavier), and thus even harder to balance. In contrast, small animals adapt their stride based on the substrate and dynamically react to diminishing ground support, loss of traction, or contact with uneven surfaces. We hypothesize that the behavioral and EMG data during nominal and perturbed animal walking can be reproduced by small sets of muscle activation patterns (synergies) that simplify the problem of coordinating the many leg muscles in real time. Accurate computational models of these phenomena will improve our understanding of mammalian spinal cord functional organization and inspire improved robots.

The anatomical hierarchy of the nervous system with the brain at the top and the motor neurons at the bottom has inspired many engineered control systems, however, the fact that engineered hierarchies cannot achieve the complexity and agility of animals suggests that there is much to learn from the functional organization of nervous systems. Examples of hierarchically modeled systems include humans [20], [21], other vertebrates [22], and insects [23], and learning tasks [24]. However, the nature of the hierarchical organization of the neural basis for behavior is debated [25]. Extensive modulation of reflexes by sensory inputs, the presence of both feedback and feedforward loops in the motor system, and the ability to flexibly change limb coordination might all suggest that neurobiological hierarchies can have complex multilevel interactions that are different than typical engineering hierarchies. The construction of neural systems in computational models can challenge and extend our understanding of the neural architectures that produce complex emergent behaviors.

Biological research has provided useful hypothetical control structures for different levels of this hierarchical control scheme. At the highest level, the brain forms decisions based upon internal context and external cues and sends descending commands to the local systems [26]–[29]. Intermediate oscillators (Central pattern generators or CPGs) produce self-sustained oscillations that coordinate behaviors [30]–[35] with sensory feedback [36]–[40]. At low levels, afferent feedback modulates the strength and direction of movement [41]–[48]. Modeling has demonstrated the value of this type of hierarchy in insects [49]. The Quinn group has demonstrated that hierarchically descending signals from a low-parameter higher level can modify neurobiological oscillators and the sensory signals that entrain them to coordinate joints and legs into different gaits such that emergent kinematics matched observed cockroach data [1].

Rats rely on the dynamics and flexibility of their neurobiological coordination in ways that are more challenging than the requirements of insect models [1]. First, the wide stance and minimum of three legs on the ground during normal locomotion make the cockroach inherently stable [50]. Larger animals and robots walk with legs underneath the body to take advantage of better energetics; however, this more upright posture makes balance more difficult [51]. Second, insect muscles are highly damped, making inertial forces from the leg small compared to passive muscles forces, and requiring different control strategies than in mammals [52], [53]. The inclusion of passive muscle properties, and sensitivity to them, significantly affects the performance of robotic and modeled systems [10], [54], [55].

Recent modeling of mammalian nervous systems supports an organization in which coordinated patterns of muscle activation (muscle synergies) are driven by rhythm generators for each leg, which in turn receive inputs from the brain [56]. Muscle synergies are consistent proportions of muscles’ activation that are reused for different tasks [57], [58]. In recorded muscle activations, such synergies have been found in many different walking systems including cats and humans [59]–[61]. These muscle recruitment patterns group muscles that apply forces in particular directions during balancing tasks and can be used to respond to task-level demands regardless of kinematic configuration. In posture control, synergistic muscle activations have been shown to be a function of time-delayed linear feedback of center of mass movement [62]. The degree to which this network is hierarchical or heterarchical, and the types of descending and ascending influences that occur, are highly debated. Our hypothesis is that muscle synergies provide a reduced parameterization that improves adaptation to the environment and perturbations when compared to a system in which all muscles are coordinated independently.

To understand dynamic walking strategies, we have used the literature and biological data collected by Fischer [63]–[66] and others [41], [67]–[70] to construct a control system that is able to coordinate stepping motions of a simulated rat built in AnimatLab [71]. This neurobiologically-based control system coordinates hind leg walking in the sagittal plane with an antagonistic pair of muscles for each joint. This model incorporates both physics-based mechanics and a detailed neural controller with a CPG for each opposing muscle group modified by afferent feedback [38], [56], [72]. We have also developed a method to train this neural system to produce robust, forward walking behavior in the hind legs [8]. The training method sets system parameters to produce desired motoneuron activation patterns based on expected muscular feedback.

This proposed work seeks to answer how complex muscular systems are effectively coordinated in adaptive walking. In particular, we will collect new 3D data from walking rats over a variety of conditions, expand our neuromechanical model of rat hind legs to locomote in a three dimensional world and explore how different neural organization schemes adapt to system perturbations and determine different failure mechanisms associated with each. We hypothesize that there is a set of synergistic muscle groups which will most closely match the animal behavior and EMG data for the proposed perturbation experiments on rats.

We have submitted proposals on this subject to this program previously. Since that time we have published papers that have addressed those previous reviewers’ concerns. We also appreciate the responses of previous reviewers who have suggested that modeling the full body might be too ambitious, while reducing motion to the sagittal plane might be oversimplifying. Focusing on the hind legs in 3D permits a high degree of accuracy while also providing the highest relevance to existing mammalian literature and biped walking. The reviewers also correctly recognized the challenge of training large dynamic networks. We have since developed an optimization method that allows us to match desired outputs with expected inputs and applied this method not only to a physics-based simulated rat but also to a robotic dog model [8], [18]. We are confident that the proposed 3D hind leg model will be relevant for improving our understanding of spinal cord circuits in nominal and perturbed locomotion.

We propose an international Network of interdisciplinary research groups (IRGs) consisting of modelers, engineers, and experimentalists to address the foundational question: **How do biological nervous systems control and execute interactions with the environment?** Animals must solve this problem, whether during walking, grasping, feeding, or other behaviors. Our NeuroNex Network will focus on the *Communication, Coordination, and Control in Neuromechanical Systems* (**C3NS**) to develop a comprehensive model of sensorimotor control and its relationship to the environment, both within individual species, and across the phyla Arthropoda, Mollusca, and Chordata. This comparative analysis of a diversity of organisms is necessary to uncover underlying general principles of sensorimotor control [1]–[3]. The inclusion of modelers and engineers to guide the research of experimentalists will provide a bottom-up, scale-based theory for efficient communication between higher and lower levels of the nervous system. Such a theory will lead to transformative knowledge about how movement is controlled and modulated across the animal kingdom.

The control of behavior is only partially understood for two reasons: the dynamics of downstream networks, and the dynamics of the environment are both extremely complex. First, **the downstream networks that implement motor control are highly dynamic**, containing multiple levels of sensory feedback loops [4], [5], pattern generating networks [3], context-dependent neuromodulation [2], and inter- appendage communication [6]. Such components create a complex context in which the potential simplicity of the descending signals is difficult to understand. For example, when the mollusk *Aplysia californica* feeds, the neuronal networks that control its feeding apparatus naturally generate rhythms to grasp and ingest food in its environment. However, the cerebral ganglion can use ascending sensory information to determine that hard-to-ingest food should be rejected, and this is accomplished by descending commands that alter the phasing of the feeding program. Thus, descending commands may simply modify the phasing of an already-existing program in a dedicated neuronal network, which is economical both in terms of the number of neurons required and the amount of information communicated from the cerebral ganglion to the dedicated neuronal network (buccal ganglion). What is the encoding protocol of these descending commands? What are their exact targets? How does the dynamical nature of these networks affect these commands? We hypothesize that answering these questions will enable us to understand general principles for motor control networks.

Second, **the environment itself is highly dynamic**. For example, as an animal walks through its environment, it must cope with small obstacles, uneven terrain, and other challenges on an instant-to- instant basis. These challenges are solved on multiple levels: passive biomechanics [7]–[9], low-level reflexes, interleg connections [6], and higher-latency ascending pathways to the brain [10], which then forms new descending commands [11]. The higher level command centers make predictions based on past experience, which are updated by ascending information from motor ganglia [12]. What is the protocol used to communicate to the brain the state of the environment as it affects the periphery, and how might reflexes and mechanics simplify these protocols? This is critical to understanding how the brain controls behavior.

**IRG3 will focus on small mammals** (chordates). To investigate how the nervous system coordinates muscle recruitment for different tasks, rejects perturbations while walking, and communicates local and global limb state variables, IRG3 will expand multi-level neuromechanical models of mammalian locomotion. IRG3 will simultaneously record 3D kinematics, 3D dynamics, and electromyography of rats via stereo, high-speed, X-ray camera systems, recording over a dozen muscles’ activity during locomotion. Recordings from large populations of neurons in the spinal cord and brainstem during perturbations will elucidate how subsystems throughout the nervous system coordinate to maintain stability. Calcium imaging of neuronal populations in the neonatal mouse will help to elucidate the neuronal networks in the spinal cord and brainstem responsible for such adaptive behavior.

IRG3 will study how the state of the body and locomotor commands are encoded and communicated between neuronal systems in the spinal cord and brainstem in mammals. Classic work in cats has established the organization of canonical mammalian spinal circuits, such as the Ia reciprocal inhibitory system Renshaw cells, Ib, and group II neurons [50]. Parallel work has focused on elaborating the organization of pattern generating networks in the spinal cord responsible for locomotion in rodents [51]. Much less is known about the nature of descending systems in the brainstem and how they interact with spinal circuits [52], [53]. More fundamentally, the functional role of these networks remains unclear. How do they interact with one another and with the intelligent mechanics of the musculoskeletal system to enable effective motor control? What sensorimotor control principles do they instantiate? The experiments and analysis of IRG3 will examine these issues, using a combination of behavioral, neurophysiological, and computational experiments and exploiting the range of expertise in our research team. C3NS will enhance this investigation, with the experiments of IRG3 being strengthened by parallel and complementary experiments in IRGs 1 and 2.

This IRG will use computational neuromechanical models of quadrupedal mammals and the neurorobot Muscle Mutt [54] to play two central roles in this investigation: generating hypotheses and consolidating findings. First, the neural models will be used as a theoretical framework to guide our experimental approach. Hypotheses on the role of spinal circuits will be generated in the model and then evaluated in behavioral and neurophysiological experiments. Second, these models will be used to integrate information obtained from experiments and generate new hypotheses. This iterative loop between theory and experimentation is central to our approach. IRG3 has the following hypotheses:

***Hypothesis 1:***The spinal cord and brainstem exploit peripheral mechanics to implement a series of hierarchical control strategies that enable the efficient production of effective behavior.

***Hypothesis 2:***Descending systems in the brainstem exploit the simplification of control produced by spinal circuits such that descending signal commands relate to higher-level behavioral goals. *Research goals and intellectual focus:*

***Goal 1****:* To evaluate how mammalian sensorimotor systems maintain robust performance in the face of perturbations due to a continuously changing body and environment.

***Goal 2:***To evaluate how neurons in the spinal cord and brainstem encode the state of the body in response to changes in the environment.

***Goal 3****:* To evaluate how information about limb state is communicated from the spinal cord to brainstem neurons and how activity in brainstem neurons alters behaviors produced by the spinal cord.

*Planned research activities:*

***Goal 1:***To evaluate how the mammalian nervous system maintains robust locomotion in the face of perturbations, Quinn and Hunt have created neuromechanical computational models and robots to investigate sensorimotor control networks producing locomotion [55]–[57]. These models will be integrated with behavioral experiments by Fischer to characterize the control principles implemented by spinal and brainstem systems. Fischer and Andrada have expertise in comparative biomechanics [58]–[61] and have established techniques to measure synchronously detailed kinematics with biplanar high speed fluoroscopy along with EMGs and force plate recordings during locomotion in small mammals [62], [63]. They have also established sophisticated techniques for dynamically perturbing limbs during locomotion. They will extend these experiments using methods developed in the Tresch lab to record EMG activity chronically in large numbers of muscles across the body.

To evaluate the control strategies implemented by spinal and brainstem systems, Fischer and Andrada will work together with Quinn and Hunt to perform a series of perturbation experiments. They will use both transient perturbations (e.g. torque pulses to limbs, ground displacement) and persistent perturbations (e.g. adding a mass to the torso, changing the incline, or paralyzing a muscle) to evaluate the hypothesis that spinal and brainstem systems regulate higher-level aspects of behavior (e.g. center of mass trajectory, or leg stiffness) while allowing lower-level aspects of movement to vary (e.g. individual joint angles or muscle activation). By examining the latencies of reflexes, they will gain insight into whether responses reflect the actions of spinal or descending circuits. They will use the computational model to design additional perturbations to validate or challenge model assumptions and to test potential theories of control principles implemented by spinal and brainstem circuits. These experiments will also provide critical information to interpret and guide the neurophysiological experiments in Goal 2.

***Goal 2:***To determine how spinal and brainstem systems encode the state of the limb during transient and persistent perturbations, Heckman will leverage his extensive expertise in the neurophysiological characterization of sensorimotor systems in the spinal cord [64]–[68]. His lab has recently developed techniques for recording simultaneously from large numbers of motoneurons, sensory afferents, and spinal interneurons in response to different perturbations in the cat. He will record from spinal interneurons and brainstem neurons in experiments with the same perturbations used in the experiments of Goal 1. These experiments will identify how local spinal circuits encode information of limb state and communicate this information to the brainstem. Importantly, he will examine this encoding in a functional context, evaluating how neuronal activity in spinal and brainstem systems is related to the control strategies observed in the experiments of Goal 1. These activity patterns will be integrated with the neuromechanical models developed by Hunt and Quinn, evaluating whether they confirm the predictions of the model or suggest refinements.

To improve the possibilities for data collection in spinal systems, Heckman will also work with Tresch to develop similar techniques for recording activity in rats, exploiting the carbon fiber electrode (CFE) arrays developed by the MINT NeuroNex Network. Tresch has expertise in investigating how animals regulate muscle control under perturbations and characterizing spinal neuronal function [69]–[72]. The improved properties of the carbon fiber electrodes will enable these experiments in rats, despite the animal’s smaller size. They will compare the activity in spinal and brainstem networks between rats and cats to evaluate whether neuronal circuits are organized differentially across mammals. These experiments in rats will also provide more direct integration with the experiments of Goal 1. Heckman and Tresch will also evaluate the exciting possibility that the properties of these electrodes will permit spinal neuronal recordings in behaving animals. A lack of spinal neuronal activity data in intact animals is a fundamental gap in the understanding of the neural control of movement. Although these would be challenging experiments, they have the potential to transform the field’s understanding of motor control.

***Goal 3****:* To evaluate how spinal and brainstem systems communicate with one another to produce adaptations of locomotion, Perreault will leverage her extensive expertise examining the function of spinal and brainstem systems in the production and modulation of locomotion [53], [73]–[76]. She will perform experiments to stimulate and inactivate brainstem systems descending to the spinal cord and evaluate their effects on ongoing locomotion. Exploiting the advantages of the *in vitro* mouse spinal cord, Perreault will image activity in functionally distinct populations of identified motoneurons during the production of locomotion. Using electrical stimulation, selective lesions, and optogenetic manipulations, she will investigate how commands from descending brainstem systems alter the timing and amplitude of locomotor outputs. These experiments will also record the activity of spinal interneurons during locomotion and characterize how they are modulated by descending activity. Perreault will also work with Tresch and Heckman to perform complementary experiments *in vivo*, stimulating brainstem sites or descending tracts and evaluating their effect on locomotion and on spinal interneuronal activity. In particular, they will evaluate how descending systems alter activation of motor neurons across the body to modulate key aspects of ongoing movements (e.g. center of mass trajectory, speed or direction of locomotion)