

Research Statement

Introduction

Many experimental tools have been developed to map neural connectivity, to measure and manipulate neural activity, and to characterize behaviors in multiple model organisms; however, the focus of most research has been on characterizing each of these levels individually. Fully understanding the neuromechanical basis of behavior will demand new computational tools that allow us to integrate across these different levels. The goal of my research program is *to bridge the gap between connectome, neural activity, and behavior through the construction and analysis of brain-body-environment models and the development and application of theoretical and computational tools to understand the resulting complex systems.*

When faced with the difficult challenge to understand such complex systems, an ideal approach is to study the simplest instances of the general problem of interest. As part of my research program, I have developed two research directions that focus on two different sets of simplifications: targeted models of a relatively “simple” organism and highly idealized models of more general brain-body-environment systems. The first research direction involves the study of a model living organism with a tractable and well-characterized nervous system, musculature and body, and a rich behavioral repertoire: *Caenorhabditis elegans*. The nematode worm is a particularly ideal organism to target the development of a brain-body-environment computational model and it is the most promising organism where an understanding of the relationship between connectome, neural activity, and behavior will be feasible. The second research direction involves the study of idealized brain-body-environment models that do not target any one specific living organism. This set of idealized models is particularly useful to address theoretical challenges that are common to the generation of behavior across many living organisms. Crucially, by working on both research directions together, I am able to use insights from each to advance the other synergistically.

Interdisciplinary nature of my research program. My research integrates approaches and questions of interest that span across the fields of computer science, intelligent systems engineering, complex systems, informatics, psychological and brain sciences, cognitive science, artificial intelligence, and neuroscience. Yet, the specific approach and focus of my research program sets it apart from the main thrusts of any one of those fields. Like most work in *Computational Neuroscience*, my work focuses on understanding the brain. However, unlike the main thrust in that field, my work considers not just the analysis of brains in isolation, but also the analysis of an embodied neural system in closed-loop interaction with its environment. Like some of the work in *Artificial Intelligence*, my work uses optimization techniques and artificial neural networks and seeks to generate artificial systems that can exhibit the robustness and flexibility of living organisms. However, my work differs from that field in focusing on how the resulting artificial systems operate in a way that can be applied to better understanding intelligence in living organisms. Like most work in *Artificial Life*, my work develops and analyzes models that allow us to address theoretical challenges in understanding life and cognition. However, unlike most of the work in that field that focuses on idealized model systems, an important part of my work is focused on models that target specific behaviors in specific living organisms. Finally, like most of the work in *Complex Systems* and *Intelligent Systems Engineering*, my work focuses on applying systems thinking, reverse engineering, and the development and application of tools of analysis to understand complex systems, but instead of analyzing empirical datasets I develop and apply such tools to computational models. Although this level of interdisciplinarity may not be typical, it is essential for addressing the challenge of understanding how behavior arises from a brain-body-environment system.

Research Direction 1: Targeted models of brain-body-environment systems

The nematode worm is an ideal candidate for such an integrated brain-body-environment modeling of a complete animal [1]. *Caenorhabditis elegans* exhibits a rich behavioral repertoire, including crawling, swimming, withdrawal responses, a variety of taxes, social feeding, male searching, egg-laying, habituation, and associative conditioning. A variety of techniques exist for characterizing and manipulating worm behavior, including automatic visual tracking and microfluidics to finely control the structure of artificial soil-like environments. Its entire genome has been sequenced and the developmental lineage of every one of the 959 somatic cells that make up the adult hermaphrodite is known, allowing for unprecedented genetic and developmental manipulation. Most importantly for my research program, its almost complete “connectome” is available. Its 302 neurons, 6393 chemical synapses, 890 electrical junctions, and 1410 neuromuscular junctions have been mapped out from serial section electron microscopy. The only remaining incompleteness involves the ventral nerve cord motor neurons from the posterior half of the animal, for which extrapolations are available from repeating patterns. Importantly, advances in automation and novel neuroanatomical tools are likely to fill this gap in the data in the very near future and to add more information about different stages of development. Although there is a great deal of current work on the connectomes of other animals, the *C. elegans* connectome is by far the most complete that is currently available and is likely to remain so for some time.

Despite the substantial behavioral, anatomical, and neural connectivity knowledge in *C. elegans*, information about the electrophysiological properties of its nervous system is much less complete. Using single-cell optical recording and whole-cell patch-clamp techniques, researchers have made slow but steady progress. In addition, exciting new techniques such as light-sheet microscopy and optogenetics are becoming increasingly available, which allow simultaneous imaging and manipulation of calcium activity of all neurons in the entire nervous system of a freely behaving worm during behavior. But we are still a long way from knowing in general even which synaptic connections in this nervous system are excitatory or inhibitory, let alone the strengths of all such connections or the response characteristics of the neurons involved.

A core contribution of my research program has been the development and successful demonstration of a methodology for modeling and analyzing biologically grounded brain-body-environment models of the nematode based on constrained stochastic optimization and ensemble analysis [1, 2, 3, 4, 5, 6, 7, 8]. Specifically, I identify and model the neural circuit based on the connectivity derived from the connectome and experimental results associating specific neurons to the behavior of interest, such as locomotion or spatial navigation. I then integrate the neural circuit to a model of the *C. elegans* body, which in turn is situated in a simulated environment. Where available, knowledge of the cellular physiology is incorporated into the model. The remaining unknown parameters, including the sign and strength of the connections, are optimized by running a large set of evolutionary searches aimed at reproducing the worm’s behavior. Because neurobiological models are almost always underconstrained, each successful search produces a distinct set of parameter values, leading to an ensemble of models that are consistent with the known biological constraints.

The properties of this entire ensemble are then analyzed using techniques ranging from model neuron recordings, neural and behavioral manipulation, and lesion studies to parameter clustering, dynamical systems theory, and information theory. The focus of this analysis is to identify different classes of solutions and to thoroughly understand the operation of the highest-performing exemplars of each. This insight can then be used to suggest specific experiments that could decide between the different possibilities. Finally, the results of such experiments can be used to constrain subsequent optimizations and the entire process iterated. Not only does this ensemble analysis allow us to incrementally improve our understanding through a modeling/experiment cycle of refinement, it explicitly addresses the growing realization that individual variability must be recognized by modeling efforts so that not a single model but rather the space of possible models should be the focus of attention.

An important contribution of my research program has been to introduce computational modeling early in the experiment-theory cycle as a hypothesis generator with a reduced bias. When it comes to understanding the neural basis of behavior, empirical experimentation stands as the primary research methodology while

theoretical work, in particular simulation models, play secondary roles. The traditional experiment-theory cycle involves the generation of a hypothesis, the design, development, and execution of experiments that test the hypothesis, and a cycle of adjustments to the hypothesis based on observations to start the cycle again. When they are employed, simulation models are most often used to provide further validation of an existing hypothesis for which supporting evidence is already available, once the experiment-theory cycle has circled through a few times. The limitation of this classical approach is that the hypotheses we generate are heavily biased by the way we (as humans and scientists) can think about complex systems. Such a bias might not hinder progress for relatively simple systems, but as the systems of study become larger and more complex, the bias has the potential to limit the space of possibilities under consideration. By using stochastic optimization to search for multiple possible ways that a neural circuit can use its resources and its interaction with its body and environment to perform a behavior, we are broadening the space of possible hypotheses and including some that may be counterintuitive or that may employ the dynamic interaction between brain, body, and environment in subtle ways. Such an approach has great potential to impact the efficiency and strength of theoretically-driven experimentation.

Although one goal of my research program is to arrive at a whole brain-body-environment model of a living organism, my approach is bottom-up: I study individual microcircuits dedicated to specific behaviors and I gradually integrate these together into the same nervous system and body. With each circuit and each behavior, we are involved in the experiment-theory cycle of understanding the neural and mechanical basis of that behavior, generating hypotheses, and refining assumptions as new experiments reveal new insights. More importantly, understanding each circuit/behavior allows us to begin to address broader theoretical questions that are raised by the generation of behavior by any living organism. Although the repertoire of behaviors *C. elegans* exhibits is relatively large, our approach has been to start with the most fundamental behaviors first: locomotion and spatial orientation. Using these behaviors as platforms, I have focused on the following fundamental questions: *How do organisms integrate proprioceptive feedback with neural activity to produce locomotion behavior? How do organisms integrate sensory information with neural and body state to produce the decision making needed for spatial orientation? And how do different functions integrate within the same nervous system and body to produce different strategies and different behaviors?*

Locomotion: Integrating proprioceptive feedback with neural activity to produce behavior

Locomotion is a rhythmic and flexible motor behavior that enables animals to explore and interact with their environment. In all animals, locomotion results from the coordinated activity of muscles mediated by neural circuits composed of motor neurons which receive information from interneurons and proprioceptors. Although partial maps of circuits for regulating locomotion have been generated for mice, cat, fish, tadpoles, lamprey, leech, crayfish, and *Drosophila* larva, *C. elegans* offers a unique opportunity for the reasons outlined earlier. Importantly, since the entire behavioral repertoire of this organism is expressed through movement, understanding the neuromechanical basis of locomotion and its modulation is especially critical as a foundation upon which analyses of all other behaviors must build. Similar to other nematodes, *C. elegans* locomotes in an undulatory fashion, generating thrust by propagating dorsoventral bends along its body. Although the components involved have been identified, how the rhythmic pattern is generated and propagated is not yet well understood. Several distinct hypotheses have been proposed and to date the majority of models of locomotion have been hand-tuned to demonstrate a specific hypothesis, with little exploration of alternatives. *One of the main threads of my current research has been to examine the feasibility of the full range of hypotheses possible in the worm through the development and analysis of integrated neuromechanical models of C. elegans forward locomotion on agar.* I have constructed a brain-body-environment model that is consistent with experimental evidence and used the stochastic optimization and ensemble analysis approach to systematically explore different possibilities for how locomotion can be produced in the worm. I describe below the main contributions to date.

Locomotion through multiple reflexive pattern generators (RPGs). One of my recent contributions has been to demonstrate how locomotion can be generated in the absence of central pattern generators. To demonstrate how locomotion could be produced in the worm through proprioceptive feedback from the worm's posture, I constructed a model that extended all previous models in a number of important

ways, including particularly the neuroanatomy of the ventral nerve cord from recent analysis and recent evidence of the effect of local body curvature (i.e., stretch receptors) on nearby motorneurons. Unknown parameters were evolved using a genetic algorithm to match the speed of the worm on agar. The searches consistently found electrophysiological configurations that reproduced realistic control of forward movement. Solutions also reproduced key experimental observations that they were not designed to fit. Analysis revealed that the worm's circuit was capable of initiating oscillations in the head using stretch reception, providing a novel hypothesis. Similarly, circuits relied on stretch reception to propagate the dorsoventral oscillation, without the need for bistability in the motorneurons, as had been previously proposed, and with gap junctions across neural units playing only a minor role. I was invited to present this work in a recent meeting titled "Connectome to Behaviour: Modelling *C. elegans* at cellular resolution" in the Royal Society in London. The work is now published in a Special Issue from the *Philosophical Transactions of the Royal Society B: Biological Sciences* [9].

Locomotion through a chain of central pattern generators (CPGs). While central pattern generators (CPGs) are involved in animal locomotion in many organisms, from leech to humans, their presence in *C. elegans* has been questioned, mainly because there has been no evident circuit that supports intrinsic network oscillations. To resolve this question, I took a two-stage approach. First, I used an evolutionary algorithm to find configurations of parameters of the VNC that would allow for an intrinsic oscillation that matched the main features that have been experimentally observed in neural traces of forward and backward locomotion. As the model did not include muscles or mechanical parts of the body, I focused on the patterns in the neural traces of the A- and B-class motorneurons as a proxy for evaluating performance. Through analysis, we identified the minimal circuit consistent with the behavior. In addition to providing an existence proof for the possibility of a CPG in the VNC, we proposed a series of testable hypotheses about its operation. This work was published in *Network Neuroscience* [5]. The goal of the second stage was obvious: given the feasibility of a CPG in the ventral nerve cord, could a chain of them be coupled in a way to drive the body to move forward? I have recently integrated multiple VNC neural units along the length of the worm's body, interconnected via the set of chemical and electrical synapses obtained from the connectome dataset, and embedded the nervous system in a model of the worm's musculature, which in turn drives a 2D physical model of the body in a simulated agar environment. The evolved solutions demonstrated for the first time that the VNC can not only generate intrinsic oscillations, but that those oscillations can propagate throughout the VNC to drive forward locomotion in the absence of stretch-receptor feedback. This manuscript was recently accepted for publication in *Frontiers of Computational Neuroscience* [7].

Spatial orientation: Integrating sensory information with neural and body state

Most animals can orient their locomotion with respect to a variety of cues in their environments. These spatial orientation behaviors are particularly well suited to investigations of sensorimotor integration in the nervous system. For these reasons, the second class of behaviors that I have focused on modeling is spatial orientation. Such behaviors are fundamental for survival but poorly understood at the neuromechanical level. The nematode uses a wide range of signals from the environment to find food, avoid harmful conditions, develop appropriately, and mate, making it an ideal organism for investigating the mechanisms of sensorimotor integration at the neuronal level. *C. elegans* exhibits two strategies for orienting spatially: klinokinesis, a stochastic strategy that involves a biased random walk up the gradient; and klinotaxis, a deterministic strategy whereby the animal's course is continuously corrected toward the line of steepest ascent up the gradient. These strategies operate across a wide range of sensory modalities, including chemicals, odors, and temperature. Both strategies require us to take brain-body-environment interactions seriously, since the stimulus gradient detected by the sensory neurons drives the motion of the body, which in turn changes the perceived gradient distribution. Klinotaxis is a particularly interesting behavior because (unlike klinokinesis) it exhibits state-dependence: the reactions to sensory input depend on the worm's internal state at the time of the stimulus. My work in this area has primarily focused on chemotaxis [2, 3, 4, 10, 11, 12] and more recently also in thermotaxis [8]. Using my approach, I have identified essential elements of the neural circuit and principles of operation underlying klinotaxis that have pushed the field forward. Analysis of these circuits has revealed novel motifs including simple circuits for computing temporal derivatives of sensory input and for integrating sen-

sory input with behavioral state to generate adaptive behavior. These mechanisms constitute hypotheses concerning the identity and functionality of circuits controlling spatial orientation in higher organisms.

Symmetry breaking in klinotaxis. Klinotaxis involves course corrections during the side-to-side movement of the worm's head that occurs as part of its normal undulatory locomotion. Due to the worm's size and the fact that it is laying on its side during locomotion, the worm effectively samples the gradient at a single point in space. Sensory neurons have chemical and electrical pathways that connect them to the dorsal and ventral neck motorneurons, which in turn innervate the dorsal and ventral muscles. Such dorso-ventral balance in synaptic pathways to the motorneurons raises a functional paradox. The klinotaxis strategy requires a means of breaking the dorso-ventral symmetry of the chemosensory pathways to the neck motor neurons. One of my accomplishments involved developing an idealized model of the klinotaxis circuit and using an evolutionary algorithm to generate neural networks that exhibited klinotaxis [2]. Notably, development and analysis of the computational model itself revealed the functional paradox and the symmetry-breaking problem for klinotaxis, which had not been discussed in the literature until then. Dynamical systems analysis of successful solutions revealed a novel hypothesis for symmetry breaking in *C. elegans* klinotaxis based on the principle of phasic sensory gating. A remarkable emergent property of the model is that it reproduced the differential effects of on-cell and off-cell ablations observed in the worm. The simulated ablations also showed that a circuit in which there are only off-cells is sufficient to produce efficient klinotaxis, which is relevant for odortaxis. The suggested mechanism has provided a series of testable hypotheses that have accelerated the discovery and analysis of the biological circuitry for understanding spatial orientation in *C. elegans*.

Klinotaxis circuit. While I provided a sensorimotor account of the operation of klinotaxis in the worm, the neural pathways involved remained poorly understood. In subsequent work [3], I addressed this by constructing a neuroanatomically-grounded model of *C. elegans* klinotaxis. First, I identified the minimal klinotaxis circuit by systematically searching the connectome for pathways linking chemosensory neurons to the neck motor neurons responsible for steering and then pruning the resulting network based on both experimental considerations and several simplifying assumptions. One outcome of this project has been the development a circuit exploration tool that will be available online for anyone to use at wormcircuits.iu.edu before the end of this year. Second, I ran a large set of evolutionary searches for the electrophysiological parameters of this minimal circuit that optimized a measure of chemotactic performance. Although this measure did not specifically reward klinotaxis, I found that a significant fraction of these searches successfully produced klinotaxis in a way that was consistent with both the nematode and the previous model. Next, I analyzed in some detail the operation of the best-evolved circuits. The analysis provided insight into how the observed sensorimotor transformations were implemented interneuronally in the models. I then enlarged the analysis to characterize the similarities and differences between this mechanism and other solutions observed in the ensemble. Finally, I proposed a series of experiments that could be performed to determine which of these alternatives the worm itself may be using. This work has generated new experiments and new insights [13], which in turn have led to current work updating, revising, and extending the model (in conversation with the experimentalists). This includes work proposed in my NSF CAREER.

Information flow through a sensorimotor circuit. A major challenge in neuroscience is to understand how information flows through a circuit. However, until recently there had not been an attempt to analyze the information flow through an entire sensorimotor circuit underlying a particular behavior. One of the advantages of having access to a biologically grounded model that reproduces the organism's behavior is that we can begin to address theoretical challenges that require access to full brain-body-environment systems. One of my recent accomplishments involved characterizing the information flow through such a complete sensorimotor circuit: from stimulus, to sensory neurons, to interneurons, to motor neurons, to muscles, to motion [10]. The information flow analysis revealed several key principles underlying specific mechanisms about the neural basis of the behavior, including what information each of the interneurons carried about the stimuli of interest, the role that the chemical synapses and gap junctions played in the distribution of the information, an information gating mechanism responsible for the circuit's state-dependent response, the preservation of information in the circuit, and the functional information used by the organism to solve the task. Each of the findings corresponded to an experimen-

tal prediction that could be potentially tested in the worm. Also, despite large variations in the neural parameters of individual circuits, the overall information flow architecture circuit was remarkably consistent across the ensemble, suggesting that information flow analysis captures general principles of operation for the klinotaxis circuit.

Spatial orientation across different sensory modalities: Thermotaxis Most recently, a collaborator and I have extended my approach to study thermotaxis [8]. Like many other organisms, *C. elegans* can adapt to changes in the environment. The worm can remember an environmental temperature where there was food, and it can use this memory to steer toward that temperature when presented with a thermal gradient. In addition to constraining the circuit on the connectome and evolving the model worms to match the worm's behavior, we introduced additional constraints for the model worms to match known behavioral variations that arise as a result of genetic and neural manipulations. Our analysis of solutions provides the first and only model for how thermal signals are transmitted from a thermosensory neuron to dorsal and ventral neck motor neurons, regulating the balance of dorsoventral muscle contractions of model worms and generating steering behavior. This collaboration is ongoing, and we are currently working on extending the model to other aspects of this same behavior, including isothermal tracking.

Integrating multiple behaviors within the same system.

Multifunctionality, the ability of a given neural circuit to reconfigure dynamically into distinct functional circuits under various conditions, is widespread among organisms and has been a subject of interest to neuroscience over the past 30 years (and to artificial intelligence increasingly). However, most experimental studies and theoretical models of multifunctional circuitry have focused on the switching between distinct patterns of rhythmic motoneuron activity, with little insights into how circuits integrate sensory inputs with internal states and motor outputs to produce different behaviors. The circuits responsible for spatial orientation behaviors in *C. elegans* span the full breadth of the connectome: from sensors to motors, and have to integrate sensory input with internal state and motor output to successfully operate. However, current research in *C. elegans* has focused largely on isolated neurons and small dedicated subcircuits. *The aim of this research direction has been to integrate the multiple subcircuits that have been identified in isolation back together into an understanding of the whole organism, which will be essential to understand how multifunctionality arises in a living system.*

Integrating different strategies for spatial orientation within the same system. The parallel use of multiple strategies (klinotaxis and klinokinesis) to orient spatially in *C. elegans* provides an ideal substrate to understand the operation of multifunctional circuits because both strategies are processed by a common set of interneurons. I have begun to model the interaction between these two strategies first at the behavioral level. In a recently published model [12], we demonstrated the complementary and synergistic role that the two different strategies offer to the overall behavior across a wide range of different environments. Current work as part of the NSF CAREER involves modeling the implementation of these strategies in the shared neural resources and body where they have to coordinate.

Integrating spatial orientation and locomotion circuits. In the previous research direction, both strategies, although fundamentally different, accomplish the same overall goal for the organism. The second line of my work in this thread involves integrating altogether different behaviors within the same brain-body-environment system. The first step in this direction was to combine multiple models of different lower-level behaviors (specifically locomotion and spatial orientation) within the same nervous system and body to produce more complex behaviors [4]. We integrated our previous model circuit for klinotaxis steering in *C. elegans* to control a more realistic biomechanical model of forward locomotion (discussed in earlier aims). As described in the previous subsection, our original model of steering focused primarily on the neuroanatomical structure and the available neurophysiological properties of the circuit. For simplicity, however, the body and model of movement were highly idealized. By combining the head steering circuit with the locomotion circuit on a biomechanical model of the full body, I could address the assumptions about steering in my original work. More broadly, such a demonstration addressed the capacity of my methodological approach to integrate multiple behavioral circuits cohesively.

Research Direction 2: Idealized models of brain-body-environment systems

There are organisms such as *C. elegans* that make the use of computational models particularly tractable and powerful to address questions of interest in understanding behavior. However, there are certain theoretical questions that can be better addressed from the vantage point of more highly idealized models. These two different kinds of models have been referred to in the literature as “animal” and “animat” models, respectively. More broadly, this is an area of research that is labeled Adaptive Behavior, Artificial Life, and/or Evolutionary Robotics. Like their animal model counterparts, animat models also have a target. The main difference is that the target of animal models is the living organism itself, while the target of an animat model is a theoretical question about living organisms. The first type of model is primarily driven by data, while the second type of model is primarily driven by theory. Data-driven models aim to gain insights through the study of specific systems that can be later generalized. Theory-driven models aim to study general issues by formulating highly simplified models that focus on the commonalities of many specific systems. Both kinds of models are complementary to the goal of understanding any complex systems, in particular the complexities of living systems. In particular, the focus in my work for these highly idealized models is to examine the theoretical consequences of how behavior can be generated by the interaction of brains, bodies, and environments, particularly in scenarios where it might be far too complex to carry out the implications of the assumptions by other means. Crucially, even though the primary aim of these models is the exploration of conceptual issues and not to account for the results of specific experiments, these models have the potential to challenge our ideas about how these complex systems work in a way that can drive novel avenues of empirical research. My focus here has been on answering these fundamental questions: *How is learning behavior generated in brain-body-environment systems? How does lifetime learning interact with evolution to produce adaptive behavior? How can we combine lifetime learning and evolution to produce artificial systems with the robustness and flexibility of living organisms? And how can we develop and better understand neural circuits that can perform many multiple behaviors?*

Learning behavior in embodied systems. One of the most cognitively interesting aspects of living organisms is their capacity to learn. Yet an embodied understanding of the mechanisms of learning behavior has remained largely unexplored. The dominant view in neuroscience is that learning behavior occurs exclusively through the changes in efficacy of synapses. This is reflected in neural models of learning in computational neuroscience and artificial intelligence. However, most computational models of learning do not incorporate demonstrations of ecological forms of behavioral learning. As a result, such a view of learning behavior fails to consider the potential richness in the dynamics of neural circuits, as well as the added dimensions provided by a serious consideration of the organisms’ embodiment and situatedness. *An important area of my research contributions to date have been in understanding how learning behavior can arise from neural activity, even in the absence of synaptic plasticity, purely through the feedback through the environment.* Essentially, I have used optimization techniques to synthesize brain-body-environment systems that can perform tasks that require learning behavior, including: the evolution of neural networks without synaptic plasticity to reproduce basic forms of Hebbian learning [14], imprinting behavior [15], a relational perceptual categorization task [16]. More recently, we systematically explored the topologies of neural networks that facilitated memory capacity in learning tasks to reveal that a neural network’s modular architecture plays a vital role in determining memory performance [17]. By specifying requirements for the outward behavior, but not for the underlying mechanisms, the approach reduced the prior assumptions about how the task must be solved. The optimization technique serves as a hypothesis generator, allowing us to explore the space of possible, and often counterintuitive, solutions. By analyzing the specific ways in which the solutions accomplish the cognitive phenomenon, we provide guiding principles for studying it in living organisms.

Interaction between learning and evolution: synergy between exploration and exploitation. There are two approaches to generating adaptive behavior: evolution and learning. The robustness and flexibility of life on earth demonstrates that there is an advantage to combining the two. However, current approaches in artificial neural network models and artificial intelligence have been focused almost exclusively on lifetime learning through gradient descent algorithms. My goal with this line of work is twofold: to better understand how lifetime learning and evolutionary learning combine to produce adap-

tive behavior, and to improve the computational techniques that allow us to develop artificial systems that can both evolve and learn during their lifetime. There are two contributions that I have made to this area now. In a theoretical approach, I have used the NK fitness landscape framework to characterize systematically the benefit of combining evolution and learning across a broad range of different difficulty levels of environments and different combinations of learning and evolution [18]. In more applied work, we have successfully demonstrated the potential to use the actor-critic paradigm where the critic neural circuit is evolved to provide the training for the actor neural circuit through reinforcement learning [19]. Unfortunately, the current advances in reinforcement learning applied primarily to non-biological neural models and architectures. I have also begun to develop lifetime learning algorithms that work on continuous-time recurrent neural networks. Finally, I have also begun to apply this line of ideas to problems faced by groups of humans. The trade-off between exploration and exploitation lies at the heart of many problems faced by all living organisms, groups of individuals, and organizations, who often need to decide whether to search for new, potentially better solutions or keep using an existing solution that works well. In collaboration with Rob Goldstone (Cognitive Science, Indiana University), we built a computational model of how social learning such as imitation (exploitation) and individual learning (exploration) affect performance in collective problem solving and how the interplay of these strategies interacts with the social or organizational network in which learning takes place [20].

Multifunctionality and neural reuse in brain-body-environment systems. The ability of living organisms to generate multiple behaviors is universal. However, nearly all work in biological and artificial neural networks has focused on understanding single behaviors. The work that does study multiple behaviors tends to limit their analysis to the properties of the neural circuit alone, not the brain-body-environment system. I have now contributed to this area in several different ways. My first contribution to this area involved demonstrating with an embodied neural network model how the exact same circuit could produce entirely different behaviors without any re-wiring or modulation [21]. The work then focused on using dynamical systems theory to explain how the feedback through the environment could drive the same circuit to produce different behaviors. More broadly, this is a demonstration that when organisms must solve multiple tasks, evolution can find ways to do so within the same circuit. This work continues to receive a lot of praise. Researchers in cognitive science that hear about it are still surprised, and I have been encouraged by several in the field to continue to advance it. In a related project, I used information theory instead to identify how the same circuit dynamically reconfigures itself to perform different tasks [22, 23]. In another project, I set out to study how neural re-use evolved under changing environments [24]. Finally, one of my most recent contributions involves an analysis of neural re-use using information theory on agents that can perform multiple embodied control tasks using the same sensory and motor systems across different behaviors, in the absence of modulatory mechanisms [25]. We are currently evolving and analyzing systems that can perform between 5 and 20 different tasks using the same neural circuit and body. The common goal of all these recent efforts is aimed at showing concrete examples of how the interaction between brain, body, and environment enables neural networks to perform multiple behaviors and to elucidate the dynamical and information-theoretic tools that help us to better understand multi-functionality and neural reuse.

Summary of Research Impact

Publications. Throughout my career, my papers have been published in well-respected, peer-reviewed, highly competitive venues, including the *Journal of Neuroscience*, *Philos Trans R Soc Lond B Biol Sci.*, *PLOS Computational Biology*, *Frontiers Computational Neuroscience*, *Network Neuroscience*, *eLife*, *Current Opinion in Neurobiology*, *Journal of Adaptive Behavior*. I've published in some of the top conferences in my field, including particularly the *International Conference of Artificial Life*. I have published a total of 16 journal articles, 22 papers in top peer-reviewed conferences, 3 peer-reviewed non-archival papers, 3 editorial papers, and numerous abstracts and posters. Of those publications, 15 journal articles and 15 conference papers were published since receiving my PhD; and 12 journal articles and 13 conference papers have been published during my time as an Assistant Professor. According to Google Scholar, I have an *h*-index of 13 (which means that I have published 13 papers each of which has been cited at least 13 times) and an *i*10-index of 23 (which means that I have published 23 papers that have been cited at least 10 times).

Funding. One of the most prestigious achievements in my career so far was receiving an NSF CAREER award in 2019 for \$600,000.00. I have also received an NSF/IIS RI award as a Co-PI for \$492,189.00 (2015-2018). Recently, I was asked by NSF program officers to lead the effort to organize an NSF Workshop to determine new areas of funding at the intersection between Computational Neuroscience, Neurobiology, and Artificial Intelligence.

Invited talks and visits. I have devoted substantial time to giving talks about my research to disseminate results, identify collaborators, and encourage students to consider IU for graduate school. Since joining IU, I have given 13 invited talks at conferences and workshops. My students and I have given about 25 talks and posters about our research at some of the top conferences and workshops in my field, including the Society for Neuroscience, the International *C. elegans* conference, the *C. elegans* Neuroscience conference (CeNeuro), the Computational and Systems Neuroscience Conference (COSYNE), and International Artificial Life Conference (ALIFE), as well as several regional meetings.

Future Directions

Research vision. Throughout my career, I have pursued an interest in addressing questions from neuroscience and cognitive science using the quantitative tools of computer science and complex systems. I will continue to seek the synergy of such an interdisciplinary approach. As the amount of data characterizing the structure and activity of neural circuits and the behavior of living organisms continues to increase rapidly, a complementary synthetic approach that reintegrates these components into an understanding of whole systems will continue to play an increasingly central role. I will continue to pursue this direction in my research by employing synergistically the use of both targeted models and highly idealized ones. In what follows, I provide a few of the most prominent threads.

Locomotion and the integration of sensory, proprioceptive, and neural state more generally. There are four main directions for future work in this thread. First, although I have demonstrated the possibility of CPG and RPG configurations, given the importance of locomotion, the worm most likely uses a mixture of both. A current model allows us to study this possibility. Second, for simplicity, I have focused all the analysis of locomotion in one type of environment: agar. However, the characteristic frequency and wavelength of the behavior varies with the viscosity of the environment and has been studied in some detail [26, 27, 28]. I have begun to analyze how feedback through the environment affects the operation of my current models. Third, using certain interneurons, the worm can change between forward and backward movement, and turns. I have extended my current models to include these interneurons and have begun to evolve them to change movement successfully. Finally, I have begun to create an idealized "animat" version of the problem of interest (i.e., combining sensory, proprioceptive, and neural information to produce rhythmically coordinated behavior). The simplicity of this model will allow me to better address the principles of operation of this more general problem.

Constraining models to genetic and neural manipulations. As is common in biology, due to the number of unknown parameters of the system, current models of *C. elegans* are underconstrained. As a result, the feasibility of multiple hypotheses is often demonstrated. However, the quantity and quality of datasets for characterizing the kinematics of the body during different behaviors under hundreds of different mutations, optogenetic manipulations, and different environments continues to improve and expand rapidly [29, 30]. I will be using these datasets to further constrain all of my *C. elegans* models. As a first step, I have begun to create an idealized toy version of this same challenge that will allow me to more efficiently develop a robust methodology for matching multiple constraints.

Connecting the connectome to whole-brain imaging data. The quality and quantity of whole-brain imaging datasets for *C. elegans* (and other model organisms) continues to improve rapidly [31, 32]. These datasets can be used to identify potential candidates for the strengths and signs of the connections in the connectome. This is an avenue of research that I have begun to develop first in an idealized "animat" approach. I am also in conversation with Manuel Zimmer (Research Institute of Molecular Pathology in Vienna), one of the leading experimental researchers in whole-brain imaging, to apply what we learned from the idealized models to the worm data.

Behavioral plasticity. *C. elegans* has demonstrated an extreme sensitivity to experience — every sensory modality studied can mediate learning. They have been shown to habituate to mechanical and chemical stimuli, as well as learn the smells, tastes, temperatures, and oxygen levels that predict aversive chemicals or the presence or absence of food. Although many of the genes required for learning have been identified, there are practically no neural models of learning behavior in the worm yet. This is a thread where I have made several contributions using idealized models [14, 15, 21, 17]. The main next step is to apply what we have learned so far to targeted models in the worm.

Neuromodulation and the multi-layered connectome. Most computational models of the neural basis of behavior consider only the network of chemical synapses and gap junctions. However, these wiring diagrams are incomplete, because functional connectivity is actively shaped by neuromodulators that modify neuronal dynamics, excitability, and synaptic function. There has been recent work mapping out the monoamines and neuropeptides connectomes for the worm [33]. How these neuromodulators shape neural circuits is still poorly understood. Together with Jason Yoder (Rose-Hulman Institute of Technology), I have begun to study how neural networks maintain their function in the face of neuromodulation in the context of highly idealized models [34].

From connectome to behavior over a developmental timescale. All nervous systems undergo postnatal growth, but there is little understanding of how this process affects circuit development and behavioral adaptation. Work is underway to determine the precise worm wiring diagram of the entire nervous system across developmental stages. I have plans to model behavior at different developmental stages. Of particular interest will be to study the principles of operation of the circuit that allow it to continue to function as the number of neurons increases and as the wiring changes. As with the rest of the threads of future work, I plan to address this work using both idealized and targeted models.

Artificial circuits constrained by connectomes, behavior, and evolution: from *C. elegans* to Humans. The approach developed — the use of neural networks constrained by the connectomes of living organisms, and the use of evolutionary learning to match the robustness and flexibility of the behavior of such organism — can be applied to other organisms where the connectome is available. For most organisms, the models can be generated at the level of brain regions instead of neurons without affecting the approach. This is one of the threads that I plan to work on next. Ultimately in the case *C. elegans*, given the increasing availability of biological data, it is becoming realistic to achieve the neuroscientific goal of constructing a comprehensive brain-body-environment model of a complete organism. Achieving such a comprehensive model of a living organism has the potential to completely transform our understanding of the neural basis of behavior for all other organisms.

Similar activity from disparate parameters. Individuality and variation are characteristic of all neural and behavioral processes. Variation can be observed at different levels of description: the parameters of the circuit, the network activity, and ultimately the organism's behavior. How variable can the set of parameters of a circuit be and still produce the same behavior when embodied and embedded in their environment? Having access to an ensemble of model systems where we can study the variability at each of those different levels allows us to explore the relationship between the levels of description and to study the functional role of variability in the system. I have begun to make progress in this area by analyzing the variability across all my *C. elegans* models. I am currently pursuing a more concerted effort to address this question by studying it in idealized toy models as well.

Summary

My research program focuses on building and analyzing computational models of complete brain-body-environment systems to understand how behavior is produced in living organisms. The focus has been on understanding simple but whole systems: some targeted, some idealized. The methodological approach, the theoretical framework, the tools of analysis, and the insights learned from studying these simpler model systems have the potential to pave the way for our understanding of other complex systems, as well as to guide the design of artificial systems with the robustness and flexibility of living organisms. My future research plan focuses on strengthening the strong theoretical and empirical founda-

tions established in my career so far. The result of this research holds great potential for strong impact in science and for society more broadly.

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