Research Statement

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One of the grand challenges of Neuroscience is to understand how behavior arises from the dynamical interaction of an organism's nervous system, its body, and its environment. My research aims to address this challenge by *constructing and analyzing computational models of complete brain-body-environment systems*.

There are an increasing number of funding initiatives to address the challenges of understanding the human brain (e.g., BRAIN Initiative and the European Human Brain Project). A key stepping stone to this ultimate goal is to understand how behavior is produced in a simpler model organism. In order to accomplish this, we need access to an organism where we can theoretically and experimentally study the complete brain-body-environment system. A major challenge is finding an animal system for which such an integrated model is at all feasible. The nematode *Caenorhabditis elegans* is a highly qualified target for this endeavor.

My approach involves developing mathematical models grounded in the known neurophysiology, neuroanatomy, and biomechanics of the organism. Optimization techniques are used to search through the space of unknown parameter configurations of the model, such that the internal dynamics of the system result in the desired behavior, when coupled through sensory motor interactions with its environment. The emphasis of the approach is to study the ensemble of successful solutions that reproduce the behavior of interest. Beyond the broader theoretical issues that computational models allow us to address, having access to models that reproduce the behavior of an organism help us investigate the breadth of possible hypotheses about the operation of the circuit, while data is still missing. It also helps us devise experimental assays that can efficiently discern between those different hypotheses, and thus help generate more meaningful data from experiments. Part of the challenge involves developing the mathematical tools from dynamical systems theory and information theory to analyze such complex systems.

Given the increasing availability of biological data and computational power, it is becoming realistic to achieve the neuroscientific goal of constructing a comprehensive brain-body-environment model of a complete organism. Such a model has the potential to completely transform our understanding of how integrated behavior arises from the ongoing interaction of an animal's nervous system, its body, and its environment. It also has the potential to accelerate the development of conceptual frameworks, mathematical tools of analysis, and innovative technologies, and to pave the way for our understanding of more complex organisms. My background puts me in in a favorable position to accomplish that goal.

Past work

One of the most interesting aspects of biological organisms is their ability to learn. Yet an embodied understanding of the mechanisms of learning behavior has remained largely unexplored. The dominant view in neuroscience is that learning occurs exclusively in the synapses. This is reflected in neural models of learning, where neuronal activity is usually responsible for the behavior and the changes in synaptic strength are usually in charge of changes to the behavior. Such a view of learning behavior fails to take into account 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. The focus of my PhD was to study how learning behavior arises from: (a) neural activity without synaptic plasticity; (b) the organism's body; and (c) the organism's feedback through the environment. I employed optimization techniques to synthesize brain-body-environment systems performing tasks that required learning behavior under different conditions. 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 served, thus, as a hypothesis generator, allowing us to explore the space of possible, and often counterintuitive, solutions.

In order to study the role of the neurons, the body, and the feedback through the environment independently, I created a series of different tasks and conditions. First, to study learning behavior as a result of the richness in the dynamics of the nervous system alone, I evolved neural networks without synaptic plasticity to produce a number of different learning behaviors, including Hebbian learning (Izquierdo and Harvey, 2007) and imprinting (Izquierdo, Harvey, and Beer, 2008). Second, to study learning behavior as a result of the organisms' body alone, I evolved the same neural network to perform entirely different behaviors when embodied in different bodies (Izquierdo and Buhrmann, 2008). Finally, to study how learning can arise purely from an agent's interaction with its environment, I evolved embodied and situated agents with a stateless (reactive) network in a perceptual categorization (Izquierdo and Di Paolo, 2005) and a relational categorization task, that required the agent to distinguish between same and differently sized objects in relation to an object seen earlier (Izquierdo and Harvey, 2006). For each task, I went into some depth analyzing how the learning behavior was produced by the most successful networks. In all of these studies, the models were abstract, with little or no specific biological instantiation, driven purely by theoretical questions. Although it would be unjustified to claim that the modeling experiments gave us direct insight into the physical mechanisms of a biological organism, they did teach us something in the form of existence proofs. We demonstrated a cognitive capacity to learn under clearly specified conditions and constraints, hence showing that these provide sufficient conditions for that cognitive phenomenon. The approach goes one step further. By analyzing the specific ways in which the solutions accomplish the cognitive phenomenon, we provide guiding principles for studying it in model organisms.

Current work

Since finishing my PhD, the main focus of my work has been to tackle some of the challenges of embodied cognition and adaptive behavior within the context of a specific model organism for which we can test the underlying hypotheses. The nematode worm *Caenorhabditis elegans* is a uniquely qualified target for integrated brain-body-environment computational modeling for two main reasons. First, despite the relative simplicity of its nervous system, the nematode exhibits a rich behavioral repertoire, including a range of different spatial orientation strategies operating under different timescales and a different sensory modalities. The worm also shows the ability to learn. Both habituation and associative conditioning have been observed. Moreover, the list of behaviors that have been studied continues to grow. Only recently have researchers begun to study more complex behaviors involving the integration of simpler ones, like decision making in the context of an aversive stimuli and an attractive one. Second, knowledge about the organisms' developmental lineage, its genetics, and neuroanatomy is one of the most complete. Furthermore, the variety of techniques available to characterize and manipulate the freely-moving intact worm at the neuronal and behavioral level are simply unprecedented in any other organism. The combination of these factors make the nematode, which is already a major model organism in experimental biology, also an ideal model organism for brain-body-environment computational modeling.

Evolution and analysis of minimal but biologically-grounded neural circuits. Chemotaxis during sinusoidal locomotion in nematodes captures in simplified form the general problem of how dynamical interactions between the nervous system, body, and environment are exploited in the generation of adaptive behavior. One of my recent accomplishments involved using an evolutionary algorithm to generate neural networks that exhibit klinotaxis, a common form of chemotaxis in which the direction of locomotion in a chemical gradient closely follows the line of steepest ascent (Izquierdo and Lockery, 2010). Sensory inputs and motor outputs of the model networks were constrained to match the inputs and outputs of the *C. elegans* klinotaxis network. We found that a minimalistic neural network, comprised of an ON-OFF pair of chemosensory neurons and a pair of neck muscle motor neurons, is sufficient to generate realistic klinotaxis behavior. Importantly, emergent properties of model networks reproduced two key experimental observations that they were not designed to fit, suggesting that the model may be operating according to principles similar to those of the biological network. A dynamical systems analysis of all successful networks revealed a novel neural mechanism for spatial orientation behavior. This mechanism provides a series of testable hypotheses that have accelerated the discovery and analysis of the biological circuitry for chemotaxis in *C. elegans*.

Connecting a connectome to behavior. One of the main goals of my current work has been to make sense of the fast-growing availability of experimental data about *C. elegans* within the context of a specific behavior. The availability of a nearly complete connectome is obviously an outstanding resource for such an endeavor. Most of the analysis of the connectome has been graph-theoretic. Linking the connectome to behavior requires a more fine-grained analysis and a strategy for integrating it with behavioral experiments. One of the accomplishments of my current research has involved developing novel connectome data-mining tools, strategies for combining connectome analysis and ablation studies to incrementally identify circuits underlying specific behaviors, constructing a computational model grounded in the available neurophysiology and neuroanatomy, optimizing the unknown parameters to produce the desired behavior, and analyzing the clusters of solutions, each of which represents a hypothesis for the neural basis of that behavior (Izquierdo and Beer, 2013).

Information flow through a sensorimotor circuit. One of the advantages of having access to an empirically-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. A major challenge in neuroscience is to understand how information flows through a circuit. 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 (Izquierdo, Williams, and Beer, in revision PLoS Comp. Biology). 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 experimental 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.

Integrated neuro-mechanical model of steering. Although a detailed electrophysiological model of a neuronal circuit is often taken to be the end goal of a complex systems project in neuroscience, my current work has aimed a step further. In order to capture the closed-loop interaction through the world between motor neurons and sensory neurons, an integrated understanding of the mechanisms of behavior must include an understanding of how the biomechanical structure of an animal's body transforms motor neuron activity into behavior. Fortunately, significant progress is being made in *C. elegans* on characterizing the anatomical structure of its body and the biomechanics of its movement. My most recent accomplishment involves integrating the model of klinotaxis with the model of musculature developed for studies of locomotion (abstract and presentation given at ESF-EMBO meeting, Nov. 2014; paper in preparation for PNAS). By integrating the model into the biomechanics of the worm, we (a) demonstrate that modulation of the activity of the neck muscles is sufficient to steer the full nematode body, producing the characteristic changes in wavelength and amplitude of the worm track that have been observed experimentally during turns, (b) predict the specific relationship between the ON/OFF sensory cells and the neck motor neurons, and (c) provide a hypothesis for steering in *C. elegans* that is common to other sensory modalities.

Future work

As the acquisition of time series data from cellular recordings and the efforts to characterize the biophysical properties of nervous systems and bodies of a range of model organisms accelerates, the need for a theoretical framework to understand behavior becomes more pressing. Indeed, even if complete biophysical knowledge about an organism were available, the problem of understanding the general principles by which it operates would remain unaddressed. By building and analyzing models of relatively simple but complete brain-body-environment systems we can begin to address some of the central theoretical challenges in neuroscience. In what remains, I provide a brief overview of the research themes I plan to develop over the medium and long term.

Integrated neuro-mechanical models of behavior. As experimental work continues to identify circuits for different behaviors in *C. elegans*, it would be extremely pertinent and complementary to develop and analyze computational models of them in parallel. The models can be grounded in what is known about the neurophysiology and neuroanatomy, and embedded into our biomechanical model of the worm. Such models could help test hypotheses about the proposed roles for the different components in the circuit. In addition to specific experimental questions, such models will allow us to explore broader theoretical questions about the neural basis of behavior (e.g., How do the biomechanics of the organism shape behavior? How does the circuit process information about the environment, and how is the circuit modulated?)

Recurrent control. For simplicity, the circuits that have been identified for *C. elegans* behavior are usually idealized to only feedforward connections. Indeed, the role of recurrent connections in the neural basis of behavior in biological networks remains largely unexplored. The *C. elegans* connectome is highly interconnected, including many recurrent connections, making it an ideal organism to study the role of such complex networks in the generation of behavior.

Beyond the connectome. Most computational models of the *C. elegans* behaviors 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. How do neuromodulators shape neural circuits? While the effect of neuromodulators is being actively studied in a number of *C. elegans* behaviors, a complimentary computational approach can help explore their role in modifying the information processing of neural circuits.

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.

Integration of multiple strategies and sensory modalities. How do different circuits in the worm work together to produce coherent behavior? When it comes to spatial navigation, the worm can use multiple strategies to approach or avoid a source (e.g., klinotaxis and klinokinesis). The worm can also use similar strategies in different sensory modalities: odors, chemicals, temperature. Each of these strategies/modalities involves a different timescales of activity, different neuronal components, and different motor programs. Having worked out individual circuits for each of the strategies, we can begin to explore how these circuits interact within the same body to produce coordinated behavior.

Multifunctional circuits. The ability of biological circuits to generate multiple behaviors is widespread. How does a circuit dynamically reconfigure itself to process information differently during its interaction with the environment? The 'overconnected' nature of many nervous systems, including that of *C. elegans*, may represent latent circuits for alternative modes of information processing. Adaptive mechanisms in the circuit, as well as the circuit's embodied and embedded contexts, can provide many degrees of freedom for reconfiguring the circuit's information processing. The size and connectedness of the *C. elegans* network provides an ideal system to study multifunctional circuits and to generate testable hypotheses on the organism.

Ecological models of behavior. One of the goals of neuroscience is to be able to understand the neural basis of behavior within its ecological context. Access to complete brain-body-environment models of the worm allow us to predict its behavior under different simulated conditions (e.g., multiple gradients, patchy environments). Different hypotheses for the neural basis of behavior in the worm are likely to result in different behaviors under different environmental conditions. Computational models could be used to help design assays to test different hypotheses. Moreover, advances in the experimental techniques to study the freely-moving worm under an increasingly diverse set of conditions make access to such models invaluable.

Similar activity from disparate system 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 will allow us to explore the relationship between the levels of description and to study the role the functional roles of variability in the system.

A comprehensive brain-body-environment model of a complete organism. Although detailed reductionist analyses of the individual molecular, cellular and organismal components of biological systems have led to a remarkable wealth of data and insights throughout biology, a complementary synthetic approach that reintegrates these components into an understanding of whole systems has been lacking. Computer modeling will play a central role in any such integrative endeavor. For the first time it is becoming realistic to achieve the neuroscientific goal of constructing a comprehensive brain-body-environment model of a complete organism. Such a model is likely to completely transform our understanding of how integrated behavior arises from the ongoing interaction of an animal's nervous system, its body, and its environment. Ultimately, progress on this front will pave the way for our understanding of complex systems, including the human brain.