The Whole Worm: Brain-Body-Environment Models of *C. elegans*

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Abstract

Brain, body and environment are in continuous dynamical interaction, and it is becoming increasingly clear that an animal's behavior must be understood as a product not only of its nervous system, but also of the ongoing feedback of this neural activity through the biomechanics of its body and the ecology of its environment. Modeling has an essential integrative role to play in such an understanding. But successful whole-animal modeling requires an animal for which detailed behavioral, biomechanical and neural information is available and a modeling methodology which can gracefully cope with the constantly changing balance of known and unknown biological constraints. Here we review recent progress on both optogenetic techniques for imaging and manipulating neural activity and neuromechanical modeling in the nematode worm *Caenorhabditis elegans*. This work demonstrates both the feasibility and challenges of whole-animal modeling.

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Introduction

What is a nervous system for? To integrate and process sensory information? To represent the world? To perform computations? To predict the future? These may all be things that a nervous system *does*, but what it is *for* is to coordinate the behavior of a multicellular animal so as to further the reproductive success of that animal's species. This shifts the emphasis from neural activity alone to the behavioral consequences of this activity as it plays through the body and environment to eventually return as sensory feedback. A central challenge for 21st century systems neuroscience is to move beyond the study of individual neurons and small circuits and even brain regions to understand how an entire brain-body-environment system operates as an integrated whole [1, 2]. Here we argue that the best animal with which to pursue this ambitious but essential goal is the nematode worm *Caenorhabditis elegans*. We briefly summarize the general state of experimental knowledge regarding this animal and argue for the crucial role that modeling must play in such an endeavor. We review recent modeling work on nematode locomotion and spatial orientation. Along the way, we emphasize both neuromechanical modeling in general and a specific modeling methodology, involving constrained stochastic optimization and ensemble analysis, that nicely complements both current gaps and future trends in experimental technology. We end with some brief comments about future challenges and opportunities.

C. elegans is perhaps the best characterized animal in the world. It was the first animal to have its genome fully sequenced (1998; [3]) and remains the only animal to have its complete developmental cell lineage (1977; [4]) and neural connectome (1986; [5]) mapped. The adult hermaphrodite on which this review will focus is composed of only 959 somatic cells. Despite its simplicity, *C. elegans* exhibits a relatively rich behavioral repertoire, including withdrawal from aversive stimuli, crawling, swimming, a variety of taxes, egg-laying, social feeding. Some of these behaviors are plastic, exhibiting not only habituation, but also associative conditioning [6]. These behaviors are driven by 95 body wall muscles

operating on the nematode's hydrostatic skeleton. This musculature is in turn activated by a total of 302 nerve cells [Figure 1]. Of these, 20 constitute a largely independent subcircuit devoted to the pharynx and 3 form no synapses with other neurons. The most recent published analysis lists a total of 8,693 connections involving the remaining 279 neurons, with 6,393 chemical synapses, 890 gap junctions and 1,410 neuromuscular junctions [7], but refinement of the connectome is ongoing [8, 9]. In addition, extensive graph theoretic analysis of the structure of the *C. elegans* connectome has been performed [7, 10].

[Figure 1]

The Electrophysiological Challenge

Of course, connectivity alone is insufficient for understanding neural activity and its role in behavior [11]; electrophysiological and neuromodulatory information is also required and the data here are much less complete. Although electrophysiological analysis of *C. elegans* has been difficult due to the small size of its neurons and its pressurized body, considerable progress has been made in whole-cell patch clamping techniques over the last decade [12, 13, 14*]. In addition, functional properties can sometimes be inferred from gene expression mapping, behavioral genetics and laser ablation [15].

Perhaps the most exciting recent development in *C. elegans* electrophysiology is the increasingly sophisticated ability to optically image and manipulate large-scale neural activity at the cellular level in the intact worm. When light sensitive ion channels are genetically inserted, specific wavelengths of light can be used to selectively excite or inhibit neural or muscle cells with millisecond precision in freely-behaving nematodes [16]. On the other hand, when genetically-encoded calcium indicators are combined with high-resolution imaging, it is possible to image calcium activity (a proxy for neural activation) at whole-brain scale and cellular resolution in both immobilized [17, 18**] and freely-moving [19, 20] worms. For example, Kato et al. [18**] have recently identified a low-dimensional intrinsic neuronal oscillation whose segments may encode distinct action sequences and their parameters, and which is

modulated by ongoing sensory input. As such techniques become increasingly common, they will provide unprecedented access to the ongoing whole-brain dynamics of a behaving animal. But, despite such exciting progress, much work still remains to be done in understanding the electrophysiological details of individual cells and synapses and the role played by feedback through the body and environment onto neural activity in shaping behavior.

Models of Locomotion

Modeling plays an essential part in any nontrivial integrative endeavor. All too often, however, modeling is seen merely as a capstone of an experimental program, a final confirmatory step that all the essential pieces have been identified. But models embody theories and, as such, they should be an equal partner with experiment from the very beginning of a research program. The very act of formulating a model helps to identify gaps in the experimental knowledge that need to be filled. Analysis provides insights into the operation of the system, allowing us to generate hypotheses about the relationship between neuroanatomical structure, neural dynamics, and biomechanical behavior. Calculating the consequences of model manipulations leads to hypotheses to be experimentally tested. Experimental results challenge the model, leading to its refinement or revision. In this theory/experiment cycle of improved understanding, models are made to be broken and replaced. A model is a failure only if it teaches us nothing new. Here we review the current state of locomotion models in *C. elegans*, which highlights the important role played by closed-loop interaction between neural models and biomechanical models.

C. elegans locomotes in an undulatory fashion, generating thrust by propagating dorso-ventral bends along its body with a wavelength that depends on the properties of the medium through which it moves [21-25]. Models of locomotion can be broadly divided into those that include a neuronal central pattern generator in the head and those that rely primarily on sensory feedback mechanisms to generate

the rhythmic pattern. The majority of models, however, rely on sensory feedback to propagate the wave along the length of the body.

Some models of locomotion have focused purely on the nervous system, without a physical component. Niebur and Erdös [26] were the first to develop a purely neural computational model of locomotion in the worm. There have been a number of models since that have continued to investigate the role of neural dynamics in locomotion [27, 28]. For example, Kunert et al. [29*], recently developed a neural network model of the full connectome using a biophysically-realistic neuron model and showed that oscillations arise in the network when input to some of the motor neurons are stimulated. Even though the model used the same biophysical parameters for all neurons, it is interesting that the period of the oscillations is similar to that observed in the worm. Portegys [30*] used an evolutionary algorithm to search for parameters of the full connectome that generate global oscillatory patterns.

Other models of nematode locomotion have focused on the biomechanics of the nematode body. Some models have focused on the kinematics of movement only [31], but most incorporate forces in some form. Because *C. elegans* lives at a scale at which viscous forces dominate inertial forces, a linear drag approximation is typically employed [32, 33]. Erdös and Niebur [34] were again the first to study *C. elegans* locomotion using a biomechanical model that included drag forces from the environment, initiating a sequence of more recent models [35, 36]. For example, Majmudar et al. [37] developed a mechanical model consisting of a number of elastically linked spherical particles, subject to forces and torques in a richer environment than most typically modeled (i.e., containing obstacles in the form of a square lattice of micropillars). Their model demonstrates how some aspects of the locomotive behavior, including turns, are a product of the interactions of the mechanical body with a rich environment alone, even before sensing and behavior are factored in.

Finally, there have been a series of models that integrate neural dynamics and body mechanics. Niebur and Erdös [38] were once again the first to create an integrated neuromechanical model of forward locomotion. More recent models have varied greatly in their degree of idealization, from minimal bodies

[39] to more complex biomechanical structures that use realistic environmental forces [40]. For example, Deng et al. [41*] developed a highly idealized biomechanical model controlled using a neuroanatomically-grounded model of the nervous system to produce locomotion. The paper demonstrates how the rhythmic pattern can be generated in the head and propagated along the body. The only downside of biomechanical models that do not take into consideration environmental forces is that thrust production is not modeled, and thus forward motion is described only kinematically. Most recently, Boyle, Berri and Cohen [42] developed a neuromechanical model of locomotion using realistic environmental forces (Figure 2A, B). The model was designed to produce and propagate the waves using proprioceptive feedback. The results of the model lead to experiments that have strengthened the evidence for the role of proprioception in the control of undulations [43]. The model reproduced the transition from swimming to crawling using a single gait, providing testable predictions about the modulation of neuromuscular control as a function of the resistivity of the environment, some of which have been verified [24].

Different models have taken into consideration different aspects of nematode locomotion: Some have focused on the neuroanatomy, some have focused on the biophysics of the neural model, some have focused on the biomechanics, and some have taken into consideration environmental forces. The majority of models have employed sensory feedback for the generation and/or propagation of the rhythmic pattern. Collectively these models have pushed the understanding of the role of proprioception and the transition between swimming and crawling during forward locomotion. The challenge for future work is combine these various lines of research to build and analyze a model that includes the most recent neuroanatomical data from the reconstructed connectome [44], and new details about the directionality and length of stretch reception [43], all embedded in a biomechanical model that incorporates environmental forces. So far, models of locomotion have been hand-designed to show the plausibility of a limited number of specific mechanisms for generating and propagating the dorsoventral rhythmic wave. It would be

particularly useful if future integrated neuromechanical models could be used to systematically explore different hypotheses [22].

[Figure 2]

Models of Spatial Orientation

Spatial orientation behaviors are fundamental for any animal. The worm orients to locate food, mating partners, and habitat, using a wide range of different sensory modalities [14*, 45*, 46]. Within the context of odorants, tastants, and temperatures, two main strategies have been studied: klinokinesis and klinotaxis [47]. The role of the sensory neurons involved in these strategies has been explored in some depth. Gradients are sensed at a single point in space by one or more head amphid neurons that respond to increases and/or decreases in stimuli [48]. There have been some modeling efforts to study the performance of the two strategies acting simultaneously [47]. These models have attempted to reproduce statistical properties of the behavior at the level of populations of organisms, treating the organism as a point in space with either an algorithmic or a highly idealized neural network controller. Most recently, Appleby [49*] analyzed the performance of the two strategies under different environments, suggesting that under shallow gradients klinokinesis is more effective than klinotaxis; whereas for steep gradients all mechanisms are equally effective. These predictions have yet to be tested in the worm. How the sensory information is transformed by the nervous system to produce orientation behaviors in interaction with the body and environment has not yet been addressed by any model.

Klinokinesis involves a biased random walk. On agar, a forward crawl is interrupted by sharp turning events called “pirouettes.” In order to orient, the rate of pirouette initiation is modulated by sensory activity, increasing or decreasing when the animal is moving in a favorable or unfavorable direction, respectively [50]. Some of the neuronal circuitry involved in klinokinesis has been studied, in particular the role of the command motor neurons that promote forward and reverse locomotion, since pirouettes occur during changes in the direction of locomotion [51, 52]. A series of highly idealized

computational models of klinokinesis have been developed [53-56]. Most of these models do not incorporate details of the *C. elegans* connectome. Most recently, Roberts et al., [57**] developed a stochastic model involving two highly idealized populations of the forward and command motor neurons that reproduces the kinematics of the biased random walk using a point model of the worm's body. After adjusting the model to reproduce behavior, the model predicted key aspects of the functional connectivity between the neurons involved. These predictions were then confirmed using photoactivation and electrical recordings from the key motoneurons.

Klinotaxis involves gradual turns toward the line of steepest ascent up a gradient [47] by modulating rhythmic head oscillations as a result of changes in stimuli that must be detected by sensory neurons within the timescale of a head sweep [45*, 58**]. Recently, the role of certain interneurons, such as AIY and RIA, have been studied in detail [59-61], but how the strategy is realized in the worm is not yet understood. Modeling work in klinotaxis provides a particularly good example of how integrative brain-body-environment modeling of *C. elegans* leads to particular opportunities and challenges. Strong modeling constraints arise from behavior, general anatomy and the neural connectome, while far weaker constraints are available from current electrophysiological data. This suggests a modeling methodology in which a brain-body-environment model constrained by what is known and parameterized by what is unknown is optimized for a performance measure related to observed behavior [62]. Since the models are underconstrained, stochastic optimization can be rerun many times. This results in sampling the space of possible models consistent with a given set of experimental data and theoretical assumptions. Analysis of this model ensemble then allows us to explore the breadth of different hypotheses for the neural basis of a behavior and experiments that can distinguish between them. As new data become available, the models can be expanded and the search can be further constrained. We review below the current state of klinotaxis models in *C. elegans*, which highlight the important role played by the use of stochastic optimization techniques and ensemble analysis.

The first model of the sensorimotor basis of klinotaxis utilized a highly idealized biomechanics and neural circuitry [63], focusing on demonstrating a minimal circuit capable of modulating the dorsoventral oscillatory pattern required for steering during locomotion. The solution found using stochastic optimization employed a clever symmetry-breaking mechanism exploiting the dorsoventral antiphase nonlinearities in the motor neurons. Recently, support for this view has been provided through an understanding of the compartmentalized activity of RIA [61]. The first model to include interneuronal circuitry was described in [64], which proposed a minimal circuit determined by the shortest and strongest connectome pathways between select sensory neurons and neck motor neurons. The interneurons in the proposed circuit have been shown to be involved in a number of different steering behaviors [14*, 16, 46, 65, 66*]. Since little is known about the electrophysiological properties of the interneurons or the strengths of the chemical synapses and gap junctions, the parameters of the model were explored using multiple runs of a stochastic optimization technique and the resulting model ensemble analyzed. Despite large variations in the neural parameters of individual circuits, the information flow of the circuits was consistent across the ensemble [67**]. The same minimal circuit was recently combined with the Boyle et al. [42] model of forward locomotion to produce the first integrated neuromechanical models of spatial orientation in the worm [68*] (Figure 2C). The model predicted how the worm's directional bearing changes as a function of the undulatory phase in which sensory stimuli is applied. Elements of this prediction have since been confirmed through phasic stimulation of the sensory neurons [59; 66*]. More generally, the work demonstrated that large-scale parameter optimization is possible on biologically-constrained brain-body-environment models.

There are a number of directions for future work. Models of klinokinesis will need to consider the neuronal circuitry modulating stochastic switching [69], the circuitry from the command motor neurons to the ventral cord motor neurons, and the biomechanics of the body, particularly for the switching between forward and backwards motion and the generation of sharp turns. Similarly, models of the neural basis of klinotaxis will need to be integrated with updated models of forward locomotion, as well as with a better

understanding of the neural basis of steering [61]. Neural and neuromechanical models of klinokinesis also need to be developed and combined with klinotaxis models. In addition, integration between different sensory modalities [14*, 45*], variations of steering behavior such as isothermal tracking [68], and the modulation of these behaviors through experience [46, 66*, 70] will all need to be considered.

Conclusions

Over the past several years, a great deal of progress has been made on integrated neuromechanical modeling of *C. elegans* locomotion and orientation behavior, and both optogenetics and stochastic optimization techniques are poised to open the floodgates on the scope of biologically-constrained whole-animal models that can be constructed. However, many challenges remain to be addressed, including high-throughput analysis of single-neuron electrophysiology, a better understanding of force development in the body wall muscles and its interaction with the hydrostatic skeleton and surrounding medium, and the incorporation of neuromodulatory effects into electrophysiological models. In addition, open source integrative efforts such as the OpenWorm initiative [71] have an essential role to play in coordinating and supporting multiple modeling efforts. Yes, these challenges are daunting, but, just as almost every other major breakthrough in biology has been led by work on simpler systems, it is unlikely that these challenges will be any less difficult in more complicated animals. Once again, *C. elegans* can lead the way on a fundamental biological problem, this time to the development of a systems neuroscience that does full justice to the brain-body-environment interactions that underlie the operation of animals as integrated wholes.

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Figure Captions

Figure 1: A schematic image of the neuroanatomy and surrounding body wall musculature of *C. elegans*. Image courtesy of the OpenWorm Browser (<http://browser.openworm.org>).

Figure 2: Integrated neuromechanical model of forward locomotion and klinotaxis, adapted from [67*]. (A) Model of forward locomotion adapted from [42]. The forward locomotion neural units affect all muscles along the body (blue). The steering circuit affects only the anterior most muscles in the body (magenta). (B) Neuromuscular model for forward locomotion adapted from [42]. One of 12 repeating units making up the circuit for forward locomotion. The circuit includes a pair of B-class excitatory neurons (light blue), a pair of D-class inhibitory neurons (dark blue), and four muscles (gray) on each side. Synapses are excitatory (arrowhead) or inhibitory (circle head). Posteriorly directed lines from B-class neurons denote the stretch receptor input (brown). (C) Steering neuromuscular model adapted from [65]. Chemosensory class, ASE (yellow). Interneuron classes: AIY (orange) and AIZ (red). Neck motor neuron class: SMB (magenta). Dorsal and ventral muscles (gray). All classes have left and right cells. Motor neurons have additional dorsal and ventral pairs of cells. Chemical synapses shown as black arrows. Gap junctions shown as red undirected connections.

Figures

Figure 1

Figure 2