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Nematode locomotion: dissecting the neuronal–environmental loop

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With a fully reconstructed and extensively characterized neural circuit, the nematode *Caenorhabditis elegans* is a promising model system for integrating our understanding of neuronal, circuit and whole-animal dynamics. Fundamental to addressing this challenge is the need to consider the tight neuronal–environmental coupling that allows the animal to survive and adapt to changing conditions. Locomotion behaviors are affected by environmental variables both at the biomechanical level and via adaptive sensory responses that drive and modulate premotor and motor circuits. Here we review significant advances in our understanding of proprioceptive control of locomotion, and more abstract models of spatial orientation and navigation. The growing evidence of the complexity of the underlying circuits suggests that the intuition gained is but the first step in elucidating the secrets of neural computation in this relatively simple system.

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Introduction

To survive, animals process sensory information to drive motor behaviors and to move about their environment. Among locomotion strategies, undulations are remarkably effective across scales and in a variety of environments [1–3]. Common to most locomotion and to undulation-based strategies, in particular, is the tight neuronal–environmental loop, in which the shape of the body and the way in which the sensory organs sample the environment are integral to the neural dynamics. The nematode *Caenorhabditis elegans* (*C. elegans*) is a powerful system in which to study this loop, due to its small nervous system and experimental tractability. Indeed, with a largely specified neural circuit and rapidly advancing technologies for recording and manipulating neuronal activity [4••,5], significant progress is being made in deciphering the dynamics this neural circuit supports.

Here we review recent progress in understanding the motor programs underpinning undulatory locomotion as well as higher level command of locomotion primitives and sensorimotor programs in *C. elegans*. We discuss how progress in understanding the neuronal–environmental loop is contributing to the ongoing effort and fundamental challenges in assembling a whole animal model of *C. elegans* behavior.

The ventral nerve cord

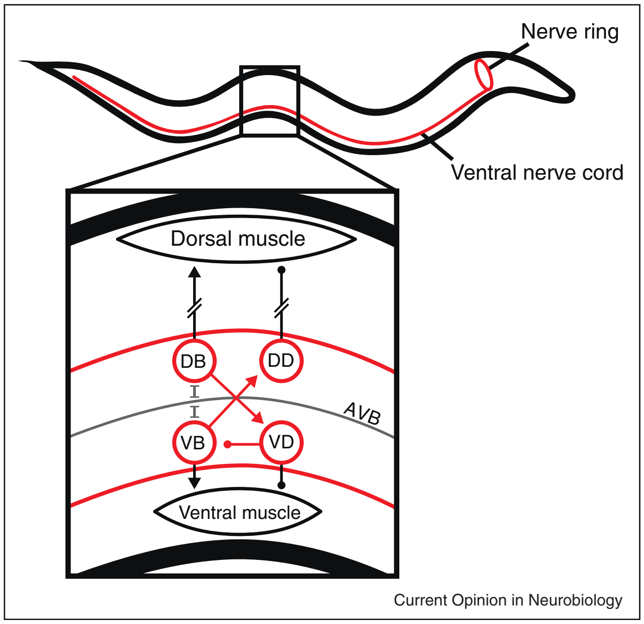
C. elegans is a small (~1 mm long) unsegmented worm with 302 nerve cells [6–8]. The animal's undulations are controlled by head and ventral nerve cord (VNC) circuits. Extensive characterization of defects (through ablation of individual classes of neurons) [9–11] has provided a strong basis for an intuitive understanding of the operation of this otherwise irregular circuit architecture [12••,13]. Indeed, evidence suggests that semi-independent VNC subcircuits control forward and backward locomotion [6,14,15,16•,17••,18•,19•] and are gated by distinct premotor (so-called command) interneurons.

The forward locomotion circuit in the ventral nerve cord

In forward locomotion, cholinergic motor neurons excite muscles on either side of the body while indirectly inhibiting muscles on the other side via excitation of GABAergic inhibitory motor neurons [3,20,21] (Figure 1). Surprisingly, locomotion can be generated even in the absence of inhibitory neurons [11,22], raising fundamental questions about the rhythm generating mechanisms. The conspicuous absence of candidates for a half-center oscillator motif in the VNC circuit [6,23–25] has led to alternative models of the rhythm generating mechanism along the body.

Most models to date [23,25,26,27••,28••] have adopted the assumption that proprioception forms an integral part of the rhythm generating mechanism in *C. elegans* [15,28••,29]. By entirely lacking a central pattern generating (CPG) circuit along the body (although some models rely on the existence of an oscillator in the head), these models differ substantially from other central–peripheral pattern generating mechanisms in which proprioception from stretch receptors entrains or modulates a neuronal CPG circuit, from leech swimming [30] through insect stepping [31] to human walking [32]. As we see below, models assigning different roles to the physical forces acting on the body lead to distinct predictions that have resulted in major progress in our understanding of this system.

Figure 1



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The ventral nerve cord subcircuit associated with forward locomotion contains four main classes of motor neurons: 11 neurons of class VB, 7 DB, 13 VD, and 6 DD as well as two key pairs of command interneurons (classes AVB and PVC). Longitudinal body wall muscles line the body, contracting and relaxing in the dorso-ventral plane. The schematic depicts a reduction in the complexity of the circuit to a series of repeating units, each consisting of one neuron of each class. AVB is coupled to VB and DB motor neurons via gap junctions. DBs and VBs are excitatory (arrow heads), whereas DD and VD are inhibitory (circle heads).

In one approach [23] the environment was sufficiently stiff that it effectively imposed the waveform of the undulations so the neural circuit needed only to generate thrust, as each part of the body pushed backwards rhythmically against the medium. Reducing the resistivity of the environment in such a model (to match more realistic conditions, such as agar gels) would lead to a flaccid worm, unable to locomote. An alternative model [25] introduced neural control, but now with an abstract embodiment and in the absence of physical forces. This approach demonstrated that proprioceptively patterned control could in principle be responsible for the generation of a sinusoidal waveform of undulations (in this case with no thrust, as the physics was entirely neglected). These two complementary views of the respective roles of the neural dynamics and external forces in locomotion could only be resolved by closer investigation of the biomechanics.

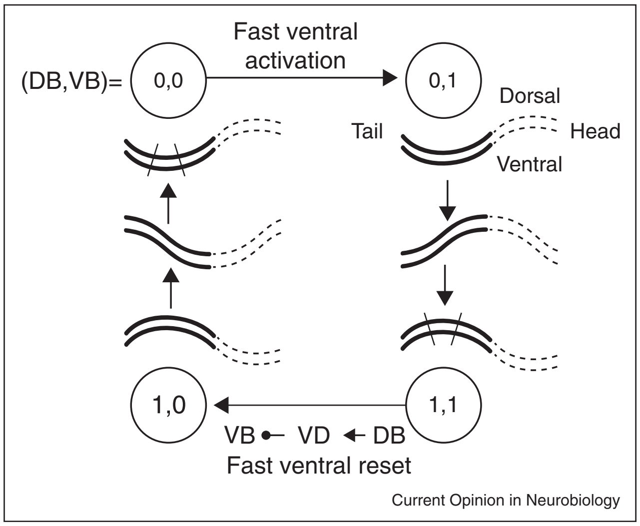
The crucial hint came from observations of swimming patterns, when the worm is placed in liquid. Unlike the slow sinuous undulations characteristic of crawling motion on agar, swimming consists of much faster, longer wavelength undulations. Until recently swimming and crawling were considered to be distinct biomechanical gaits that the animal switches between in response to the environment [33], although Niebur and Erdös already hypothesized that a single underlying circuit generates both swimming and crawling [23]. Berri *et al.* [34] and a large body of work that followed [17••,35,36] now give a strong indication that the two behaviors are extremes of a continuous spectrum, calling for a computational model that would account for the entire range of behaviors.

Indeed, in a computational model by Boyle *et al.* [27••], a single fixed-parameter and 'headless' model worm could produce both swimming and crawling, as well as undulations in intermediate linear viscoelastic and obstacle-rich environments. Crucially, the modulation of the neural control as a function of the resistivity of the environment was accomplished solely via proprioceptive integration of the different body shapes. A basic intuition of the pattern generating mechanism is given in Figure 2. This model suggests that gait modulation (at least in the wild type) can be achieved even in the absence of any chemical neuromodulation. In fact, ample evidence exists for a range of neuromodulators, monoamines and peptides acting in this system [18•,37,38•,39]. In particular, recent evidence that ciliated sensory neurons help determine the worm's locomotion pattern [17••,38•] points to added levels of complexity in the motor control of forward locomotion [17••,40,41].

In Boyle *et al.*'s model [27••], as the resistivity (or viscosity) of the environment increases, mechanical load by the external medium helps to support the body shape and facilitates the generation of thrust. Thus, this model predicts that sufficiently minor defects in the locomotion nervous system that may be masked or disguised in crawling worms may be more apparent in liquid. For example, the model predicts a role for inhibitory neurons in forward locomotion (Figure 2): whereas GABA-defective crawling worms (biological and simulated) can exhibit near wild-type locomotion [11,22], model worms lacking inhibition fail to generate swimming patterns in liquid [27••]. Indeed, the model suggests that GABAergic motor neurons serve a dual role in the robustness of the motor system: ensuring smooth undulations by inhibiting muscles on the opposite side of the body and resetting the neural circuit by inhibiting excitatory motor neurons on the same side of the body (Figures 1 and 2). A further model prediction is an increased dependence on the mechanosensitive receptive field in less resistive media: an effectively local receptive field suffices for simulated crawling, but not for swimming [27••].

Interestingly, excitatory motor neurons along the VNC have long been postulated to express mechanosensitive stretch receptors. However, the morphology of the neurons suggested that motor neurons integrate sensory information from the tail when moving forward, and vice versa during reversals, despite general agreement that

Figure 2



The forward locomotion pattern generator based on [27••]. The schematic depicts a simplified neural subcircuit representing a local unit along the VNC with binary and bistable DB and VB excitatory motor neurons and implicit DD and VD inhibitory motor neurons (with the head to the right). An input drive (assumed constant) from forward locomotion command interneurons onto VB and DB motor neurons is required to switch the circuit on and induce an oscillatory response. This input must be within a given range, implying the existence of two bifurcations (not shown). Starting from a dorsally bent configuration over the appropriate proprioceptive receptive field, and assuming both DB and VB are initially off, denoted by state (0,0), stretch input on the ventral side will activate VB (0,1); ventral bending will gradually increase stretch on the dorsal side, eventually activating DB (1,1), which automatically resets VB via indirect inhibition (1,0). Dorsal bending continues until the stretch input to the dorsal side falls below threshold, releasing VB from inhibition. This mechanism will sustain stable rhythmic oscillations, starting from any initial condition. Modeling VB and DB as bistable binary elements provides robustness, dynamic range to support a range of frequencies and amplitudes of undulations, and perfectly coordinated ON/OFF driving of muscles on either side of the body, which overcomes inefficiencies associated with gradually varying and opposing inputs. Binary muscle input (from VB/DB motor neurons) implies that gait modulation is achieved by modulating the ON/OFF timing of these motor neurons, rather than the bending or muscle force; the latter would require alternative models to be investigated.

forward undulations are initiated in the head and propagated backwards along the animal. For approximately sinusoidal undulations, of course, undulations anterior and posterior to a reference point differ only by phase, and so are mathematically interchangeable. However, to support turning, as directed by the head, an anteriorly facing receptive field would offer a better engineering solution. Experimental support for anterior stretch control in forward locomotion motor neurons is growing [15,28••] and may pave the way for integrated models of head and VNC motor control.

The beauty of the worm's control, as captured by integrated biomechanical models, is the natural exploitation of the body's interaction with the environment via the proprioceptive loop to achieve robust and adaptive locomotion across a wide range of physical environments. If this intuition holds — and given the short neuronal time constants compared to the relevant physical ones — then a minimal mechanical model, short-circuiting the neural circuit, should also qualitatively account for the swim-crawl transition. Indeed, Wen *et al.* modeled the body as an elastic beam, with an oscillator harmonically driving one end (the head) [28••,35]. A feedback mechanism representing the proprioceptive response to stretch (or curvature) activates bending forces along the body, amplifying and entraining the otherwise passive undulations.

The neuronal–environmental loop, as captured above, need not be restricted to microswimmers at low Reynolds number [3]. Indeed, the concept of feedback-driven control is appealing even for robotic navigation of complex terrains [42]. Exclusively feedback (reflex or proprioceptive) driven motor control, if it exists in the VNC, is unheard of in the animal kingdom. Even in *C. elegans*, feedforward control is likely to play a major part in other motor programs [43], and the head motor circuitry is highly suggestive of containing at least one CPG circuit. The alternative, of course, is that the VNC does generate endogenous rhythmic patterns. If so, such patterns could emerge from the distributed, recurrent architecture of the circuit, possibly with approximately repeating structures [12••,13], that may further facilitate the propagation of signals down the body.

Navigation

What roles do neuronal–environmental loops play in sensory processing, and how might they impact on locomotion behavior? One hint is given by the remarkably wide dynamic range in the sensitivity of the animal to different chemical cues [44–46] that is highly suggestive of underlying adaptive sensory perception and responses. The inherently adaptive nature of sensory processing is in fact fundamental to achieving robust motor behavior. In nematodes this form of the neuronal–environmental loop manifests itself most clearly in navigation.

To explore and navigate its environment, *C. elegans* integrates over a wide variety of physical and chemical cues [47,48]. On food, *C. elegans* mostly dwells in the same area, occasionally roaming to seek a better patch of food [49,50]. Off food, the animal may perform an area restricted search, consisting of bouts of forward locomotion, interrupted by reversals and turning events called pirouettes [49]; it will follow gradients by modulating this pirouette rate, in a biased random walk, as well as by more deterministic steering [49,51,52]. While steering occurs on timescales of undulations, the frequency of pirouettes is low (1–2/min, excluding rapidly evoked pirouettes in response to nociceptive stimuli) and its modulation can be even slower. When sufficiently starved, the animal will gradually suppress turns and accelerate away, exhibiting so-called dispersal behavior [49,50].

In a series of modeling papers on *C. elegans* navigation, Lockery and coworkers [53–56] embraced a modeling approach in which the adaptive behavior of an agent is harnessed to artificially evolve robust neural circuits [57]. Fundamental premises of this approach are first that the situatedness of the agent matters: hence a model should include a full sensorimotor pathway in a situated worm to mimic responses to realistic inputs over time; and second, that the neuronal and circuit dynamics are themselves adaptive (in these models, neuronal self-connections, denoting, e.g., slow conductances, can be thought of as encoding an adaptive internal state). Navigation was implemented via a nonlinear modulation of the pirouette rate [53,54], or via steering [55,56], in a point worm. The models consisted of abstract feedforward neuronal circuits, with simplified neural dynamics (justified by the sparseness of reliable recordings of the neuronal activities).

These computational models have led to a compact intuition about sensorimotor control in *C. elegans*, consisting — for each sensory signal — of a single three-stage pipeline: first, a time derivative detecting changes over time in sensory signals such as temperature or chemical concentrations; second, a linear filter, and third, some nonlinear input–output transformation [58,59]. Recent evidence increasingly points to the time derivatives and filtering as being performed in a largely cell autonomous manner within sensory neurons [4••,52,55,59,60]. While the detailed biophysical mechanisms underpinning the derivative response are as yet unknown, the form of the response (a depolarization in the membrane potential, followed by a slow relaxation back to baseline) is suggestive of two opposing and time-scale separated forces, for example, a faster depolarizing conductance, and a delayed rectifier. In this way, the change of concentration is always calculated relative to a baseline (background concentration), that may itself be adaptive, to allow for dynamic range.

An alternative activator–inhibitor combination, suggested for chemotaxis in unicellular eukaryotes (reviewed in [61]), relies on a fast local activator signal and a slow globally diffusing inhibitor. Perhaps surprisingly, the decay times for at least some sensory neurons in *C. elegans* appear to be remarkably slow (60 s and more) [59,60]. Thus, the small cell sizes and slow time scales of the neuronal responses appear to rule out such an intracellular diffusion-based mechanism. Slow neuronal time scales are particularly surprising for a number of reasons. First, they suggest significant information loss in the encoding of the concentration change. Moreover, the response time scales can be significantly slower than the motor responses they control (e.g., steering occurs on time scales of undulations, of the order of seconds), suggesting strong constraints on the efficacy of fast sensorimotor responses. Indeed it is easy to confirm that steering could work significantly better with faster sensory neurons (e.g. [53–56]).

The slow responses of *C. elegans* sensory neurons and their ability to calculate concentration changes over time point to extensive cell-autonomous information processing that in other systems may be associated with circuit-level computation. A further example is the above-mentioned ability of the animal to navigate over a wide range of concentrations [44]. In some behavioral experiments, indices measuring the effectiveness of navigation suggest a logarithmic response to attractive as well as to repulsive sensory cues [45]. Recent calcium imaging experiments explicitly show robust responses of sensory cells to up to six orders of magnitude in concentration changes [46]. While these data describe only a small sample of sensory neurons, they could all be accounted for by approximately logarithmic responses of these sensory cells. Such a response may be captured by the Weber–Fechner law, typically expressed as $R \propto \log S$, where R and S are the response (relative to some baseline) and signal, respectively. The incremental form of the law $\Delta R \propto \log \Delta S/S$ describes a threshold response to a minimal stimulus change, also consistent with calcium imaging recordings in *C. elegans* [60].

To summarize, the picture that emerges is of extensive computation by sensory neurons. Furthermore, sensory computation is likely to be complemented by the extensive recurrent connections within the sensory layer. Thus, for all practical purposes, the earlier intuition of a three-step pipeline dispenses altogether with the need for a head navigation circuit, as any nonlinear dynamics could then be compressed into the sensory layer, or the premotor circuit [4••]. Indeed, from an engineering perspective, placing nonlinear adaptation relatively upstream and the nonlinear encoding of the output downstream (in the premotor or motor circuit) could enhance robustness. A key question for future experiments and theoretical investigations, therefore, is pinning down the computational role of the extensive navigation circuit (in particular, the 79 head interneurons downstream of head sensory neurons).

Integrated and adaptive sensorimotor control of locomotion

The complexity of the interneuron network in the head is suggestive of a role in decision making. One appealing conjecture is that this circuit plays a role in sensory integration. Support for this conjecture is lent by chemosensory integration experiments in which animals were faced with an aversive barrier that had to be crossed to reach an attractant [45]. There, the number of worms across the barrier was shown to be a nonlinear function of both the attractant and repellent concentrations. Furthermore, a specific pair of head interneurons was directly implicated in this sensory integration [45]. Despite the nonlinearity of the computation, these results can be accounted for with a purely linear integration unit, assuming that the motor circuit and/or motor system downstream introduces nonlinearities. Nonetheless, the existence of an integration unit (even if linear) provides a target for neuromodulation (of synaptic weights, of the resting potential, etc.) that can give rise to adaptive behavior. Indeed, the synaptic weights onto the integration site (transmitting these antagonistic sensory signals), as well as the resting potential of a linear integration unit, could determine or bias the tendency of the animal to cross the barrier.

Importantly, the inclusion of a complete sensorimotor pathway allows one to close the neuronal–environmental loop. In fact, the likelihood that nonlinear transformations are implemented within the nematode motor circuits once again highlights locomotion as an important bottleneck in dissecting the neuronal–environmental loop: a better and more complete understanding of the animal's premotor and motor control is likely to impose different constraints on the computation that must be performed by the navigation circuit, and vice versa.

Above, neuromodulation was mentioned as a mechanism for tuning responses. For example, dopamine and serotonin have been reported to modulate speed [39] and turn probability in *C. elegans* [62••]. In fact, neuromodulation has been implicated in drastic reconfiguration of circuits, and the view of the *C. elegans* nervous system is gradually transforming from one specified by a single connectome to a set of overlaid circuits, of which only one is the synaptic wiring diagram and others represent chemical extrasynaptic circuits. Similarly to the neural circuit, these circuit interactions can be fast and point-to-point, due to specific pairings of signal producing neurons and those expressing the matching receptor proteins [62••,63–67]. One example is the monoamine tyramine that has lately been shown to orchestrate touch-evoked escape behavior by sequentially recruiting distinct motor programs: beginning with rapid relaxation of the head and neck muscles, followed by a brief reversal (backward undulations) and ending with a ventral bend that allows the animal to perform a sharp turn [63–65]. The extrasynaptic tyramine-mediated activation of a single class of VNC motor neurons (on the ventral side) was the key to unraveling the secret of the ventral bend that could not be accounted for by the neural circuitry alone.

Another example of neuromodulation, from the sensory layer, describes a context-dependent circuit reconfiguration by the insulin-like INS-6 neuropeptide [67]. For high — but not low — salt concentrations, a gustatory sensory neuron (ASEL) recruits an olfactory sensory neuron (AWC^{ON}). When recruited, the synapse connecting AWC^{ON} onto a downstream interneuron switches from being inhibitory to excitatory. In so doing, ASEL effectively extends the dynamic range of the response to high concentrations that is transmitted to the downstream interneuron.

Yet other examples challenge our most basic intuitions about synaptic circuits. One such study identifies and maps an extensive extrasynaptic subcircuit within the head navigation circuit that regulates the initiation and regulation of two behavioral states: dwelling and roaming [68]. This extrasynaptic circuit bears no resemblance to, and nearly no overlap with, the synaptic circuit it overlays, and the intuitive directionality of synaptic control — from sensory, through interneuron to motor neurons — is not obeyed: One signal (serotonin, promoting dwelling) is released by two motor neurons (NSM and HSN), whereas the other signal (the neuropeptide PDF, promoting roaming) is released by interneurons; targets include sensory neurons (ASI) and multiple interneurons.

These examples, and many more, illustrate the profound effect neuromodulators can have on neuronal computation. The high number (~250) of predicted neuropeptides in *C. elegans* warrants further research into the multitude of overlaid circuits they may control.

Conclusions and future directions

The last decade has witnessed a significant increase in theory-driven computational and quantitative approaches to the study of *C. elegans* behavior and its neural control, resulting in insights into the tight coupling between neuronal dynamics and the environment. In forward locomotion, we have learned how proprioception has afforded the animal a 'cheap' way to maneuver through complex and variable environments. In navigation, highly simplified models of sensory responses and motor outputs already capture key findings in relatively simple assays. And yet, little progress has been made in explicitly including adaptation and plasticity mechanisms in the environmental-sensory loop, or its downstream effects on the navigation and locomotion motor circuits.

Suggestions that locomotion can be described at a high level as a dynamical system that may be continuously modulated (e.g., in response to food deprivation [50]), or may be driven by stochastic transitions between quasi-stable states, such as forward and backward locomotion [16•,69•], provide clues about the possible computations different subcircuits perform. But open questions remain, even in understanding the neural control of undulations, such as mechanisms for backward locomotion [18•,19•], the modulation of speed during forward locomotion [39], and the role of sensory neurons in gait modulation [17••,33].

Recent insights into more complex locomotion behaviors [70,71], the orchestration of sequential behaviors

[16•,62••,63,64], and the variety of modulation pathways [71,72] suggest that extrasynaptic circuit mechanisms should be given more prominence in future models. Indeed what emerges is a much richer view of the *C. elegans* nervous system, as a dynamic, reconfigurable and overlaid circuit, in which neuronal–environmental loops act in a variety of mechanisms across a wide range of time scales. Studying all these circuits (both synaptic and extrasynaptic) should bring us closer to our ultimate goal of fully understanding decision making and motor control along the sensorimotor pathway, with the hope that insights into neural computation in this system may translate to other invertebrate and vertebrate systems [66,73].

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