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Caenorhabditis elegans: a model system for systems neuroscience

Piali Sengupta[1] and Aravinthan DT Samuel[2]

The nematode *Caenorhabditis elegans* is an excellent model organism for a systems-level understanding of neural circuits and behavior. Advances in the quantitative analyses of behavior and neuronal activity, and the development of new technologies to precisely control and monitor the workings of interconnected circuits, now allow investigations into the molecular, cellular, and systems-level strategies that transform sensory inputs into precise behavioral outcomes.

Addresses
[1] Department of Biology and National Center for Behavioral Genomics, Brandeis University, Waltham, MA 02454, United States
[2] Department of Physics and Center for Brain Science, Harvard University, Cambridge, MA 02138, United States

Corresponding author: Sengupta, Piali (sengupta@brandeis.edu) and Samuel, Aravinthan DT (samuel@physics.harvard.edu)

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Introduction

The aim of systems neuroscience is to understand how assemblies of neural circuits generate coordinated motor outputs, and how these motor outputs are modified in response to sensory input and experience to effect coherent behavior. *Caenorhabditis elegans* has long been an ideal animal in which to explore the genetic basis of behavior, due to its experimental amenability, and its small and well-defined nervous system. Here, we review recent advances that are now allowing the use of *C. elegans* to pursue long-standing questions in systems-level neuroscience. These advances include the development of new behavioral assays that quantify worm motor outputs in defined stimulus environments with high precision, as well as new methods to monitor and manipulate the sensorimotor circuits that produce these behaviors. Thus, the goal of achieving a comprehensive description of the pathways by which a sensory stimulus is transformed through multiple circuit layers into a defined motor response might now be within reach in *C. elegans*.

How the motor circuit drives locomotion

Except for simple reflex arcs, sensory inputs do not generate motor outputs in a deterministic manner. Instead, sensory inputs modulate ongoing patterns of neuromuscular activity that regulate motor behavioral outcomes such as locomotion. Thus, understanding the control and production of the motor output is a starting point, and not the last step, in the study of sensory-evoked behaviors. The rhythmic locomotory gait of *C. elegans* has long been an area of intense focus, informed by classic studies that sought the structure and function of the motor circuits that produce oscillation and undulation in swimming leech and lamprey [1,2]. Unlike in animals with larger nervous systems, however, *C. elegans* offers an opportunity for a complete understanding of motor circuit function and modulation within the freely moving animal.

C. elegans is the only animal whose complete wiring diagram has been anatomically mapped by serial section electron microscopy [3]. (We are referring to the hermaphrodite; the wiring diagram in the male is not yet complete.) Although parts of the motor circuit — in particular, the set of synaptic connections between 58 motor neurons in the ventral nerve cord — were not actually completed in the original reconstruction, these have now been mapped [4•]. The motor circuit for forward movement consists of four types of motoneurons with a consistent connectivity motif along the animal's length (Figure 1). The pattern of connectivity within the motif suggests an elegant mechanism for contralateral inhibition: DB/VB neurons excite dorsal/ventral muscles, and VD/DD neurons in turn inhibit the opposing ventral/dorsal muscles. Contralateral inhibition mediated by this repeating motif helps to coordinate sinusoidal bending by prohibiting simultaneous contraction of the ventral and dorsal musculature.

Beyond contralateral inhibition, a systems-level understanding of the motor circuit is needed to explain the detailed dynamics of the locomotory rhythm. Worms swim in fluids or crawl on agar surfaces with different locomotory gaits [5,6]. Swimming is characterized by large amplitude, high frequency, long wavelength undulations, whereas crawling is characterized by small amplitude, low frequency, short wavelength undulations. When nematodes navigate environments that pose intermediate amounts of mechanical load than those experienced during swimming (low load) or crawling (high load), they display intermediate gaits with continuous variation in amplitude, frequency, and wavelength [7•,8].

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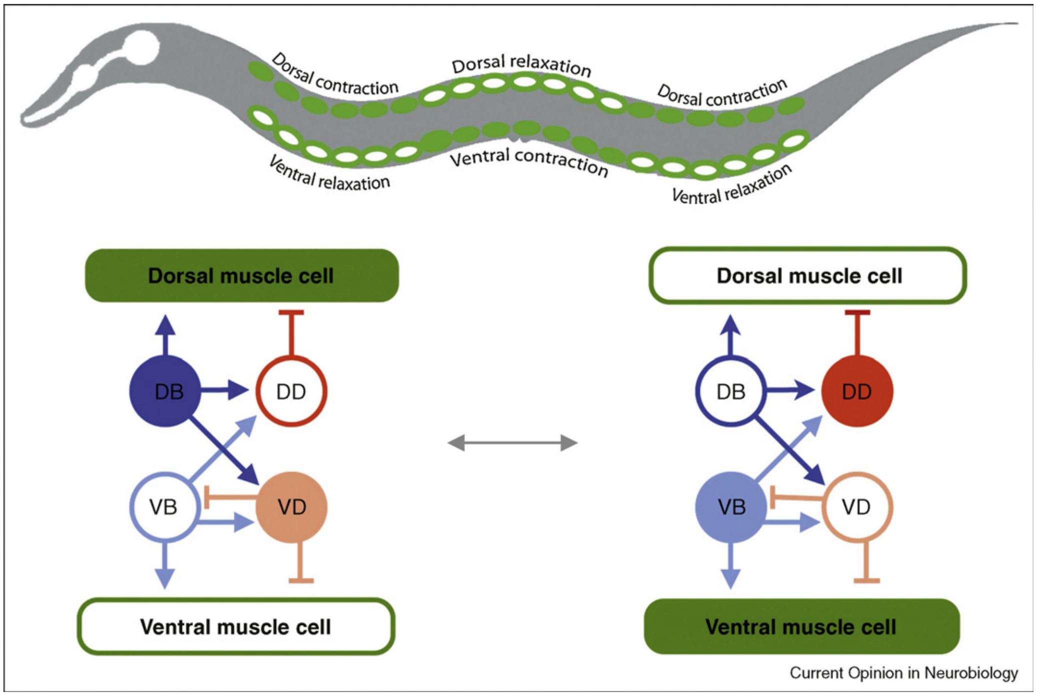
Figure 1



Current Opinion in Neurobiology

Forward movement is driven by the propagation of contraction and relaxation of rows of muscle cells that line the dorsal and ventral sides of the animal. The activity of each muscle cell on the dorsal (ventral) side of the animal is driven by input from cholinergic DB (VB) motor neurons or inhibited by GABAergic input from DD (VD) motor neurons. Activity (inactivity) of each cell type is schematized by filled (open) shapes. Excitatory (inhibitory) connections are shown by arrows (bars). A motif of connectivity between motor neurons and muscle cells repeats along the length of the worm, and shows pathways for contralateral inhibition. For example, DB motor neurons can simultaneously excite a dorsal muscle cell while exciting VD motor neurons that inhibit the opposing ventral muscle cell. Not shown are gap junctions between identical cell types between adjacent motifs. Based on data from [2,3].

Thus, a full understanding of the locomotory rhythm is a multilevel problem in biomechanics, sensory feedback, and the rhythmic activity of neuronal ensembles that produce and propagate rhythmic activity [9,10]. The entry point in a detailed study of the locomotory gait is that it is eminently quantifiable experimentally, and can be modeled mathematically. Progress has been made on both these fronts recently [9,11,12], leading toward a more a detailed description of gait dynamics and the operation of the motor circuit.

The next step in dissecting the motor circuit is to define the contributions of individual neurons or neuronal ensembles to defined aspects of motor output. The transparent, genetically tractable worm is ideal for implementing optogenetic assays for monitoring neuronal or muscle cell activity [13], or directly manipulating their activity with light-activated ion channels [14,15,16•]. In a recent study, activity patterns within the muscles of crawling and swimming worms were visualized by calcium imaging in freely moving worms, and it was shown that their distinct gaits correspond to distinct spatiotemporal patterns of activity in the ventral and dorsal musculature [5]. Using light-activated channels and electrophysiology, Liu *et al.* [17•] simultaneously measured the electrical current evoked in muscle cells upon depolarization or hyperpolarization of motor neurons, and found that levels of neurotransmission at the neuromuscular junction were continuously graded [17•]. This finding indicates that the motor circuit is analog rather than digital, perhaps allowing continuous variation of contraction and relaxation within muscle cells during the propagation of an undulatory wave, or the continuous adaptation of locomotory gait in different mechanical environments.

To date, optogenetic probes have been used to globally alter the locomotory patterns of freely moving animals. Thus, an entire worm has been paralyzed by simultaneous contraction or relaxation of all muscle cells, or by activation of entire classes of motor neurons [14,16•]. However, given that the locomotory gait is generated by precise spatiotemporal patterns of activity in different circuit elements, progress will be driven with the development of new techniques to microstimulate the motor circuit at different points in space and time [18].

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Locomotory behavior in an isotropic environment

Worms do not swim or crawl continuously in a given direction, but instead exhibit spontaneous transitions between locomotory modes: periods of forward movement (runs), periods of backward movement (reversals), and sharp turns that redirect forward movement without pause [19,20]. These outputs of the motor circuit are governed by command interneurons, whose roles in directing locomotion were elegantly mapped functionally via laser-mediated ablations [3,21]. These command interneurons are stochastically active, and drive spontaneous behaviors even in the absence of incoming sensory inputs [19,20].

The space of possible motor outputs that drive navigation is remarkably small, recently demonstrated in a mathematically rigorous way by Stephens *et al.* [22••] who used principal component analysis to demonstrate that any attainable posture of a crawling worm could be reconstructed from just four fundamental worm shapes, what they called eigenworms. Thus, given any state of motor output, a multiplicity of states of underlying neural activity might correspond to that motor state. Nevertheless, a statistical analysis of transitions between observable states of motor activity — between runs, reversals, and turns — can shed light on the transitions between underlying states of neural activity that correspond to those motor states. For example, Srivastava *et al.* [23••] analyzed the intervals of forward movement exhibited by swimming worms, where successive intervals were separated by the spontaneous occurrence of a sharp turn. A swimming worm will exhibit turns at random points in time, sometimes exhibiting several turns in rapid succession, sometimes waiting long intervals between turns. Detailed analysis of motor statistics using a Hidden Markov Model showed that the spontaneous run/turn behavior of the swimming worm could be described with two run states and one turn state: one run with a high rate of transition to a turn; another run state but with a low rate of transition to a turn; along with 'hidden' transitions between the two run states.

In *C. elegans*, one does not have to settle for inferring hidden transitions between states of neural activity based on observable motor activity. It is now possible to simultaneously monitor neuronal activity and locomotory behavior in behaving nematodes [24,25•]. Microfluidic devices may greatly facilitate the simultaneous imaging of behavior and calcium dynamics in behaving animals. Chronis *et al.* measured intracellular calcium dynamics in the backward command AVA interneurons of worms trapped in the so-called 'behavior' chip with concurrent measurements of propagated body waves [26••]. This work showed that responses in this neuron type were correlated with the initiation, and maintained through the duration, of anterior-traveling waves (and thus, backward locomotion), providing a one-to-one correlation between activity of this neuron and reversal. Additional such measurements can readily generate a correlation map between command interneuron activity and specific behavioral transitions, inferred previously solely from behavioral measurements.

Navigation behavior is modulated by sensory inputs

It has long been known that faced with a gradient of a chemical on an agar plate, *C. elegans* will end up at the peak (if it is an attractive chemical), or at the trough (if it is a repulsive chemical) [27]. When *C. elegans* navigates gradients in its environment, it modulates the ongoing pattern of runs, reversals, and sharp turns according to rules that yield migration up or down gradients or aggregation near preferred conditions. These rules constitute the computational underpinning of navigational behavior, the mapping of sensory inputs onto motor outputs that enables the worm to reach its goals. Insights into the underlying decision mechanisms that allow animals to move toward or away from the stimulus only arose following high resolution tracking of behaving *C. elegans* on sensory gradients, along with improvements in the methodologies used to deliver different types of sensory stimuli [28,29•,30–33].

Although the activity patterns of command interneurons are deterministically coupled to motor output, the relationship between sensory neuronal activity and motor output is more subtle. Worms climb up or down gradients in their environment by using a biased random walk, a behavioral strategy similar to that used by bacteria to navigate gradients [34]. If the worm encounters improving conditions during a run, it lengthens that run (i.e. it postpones any reorientation maneuvers). If it encounters declining conditions, it shortens that run by turning [28,32]. Thus, the activity of a sensory neuron that is responding to an ambient gradient is related to the probability of stochastic transitions between run states and reorientation states. In other words, the nervous system of the worm drives spontaneous and stochastic dynamics of the motor system even in an isotropic environment, and ambient or past sensory cues simply modulate the statistics of these dynamics [35–38].

The basic computation in performing a biased random walk strategy is the time derivative of the sensory input; the worm has to know whether life is getting better or worse during each run in order to adjust the probability of transitions between run and reorientation. Sensory systems that encode time derivatives — from bacterial chemotaxis to vertebrate phototransduction — commonly exploit the dynamics of short-term adaptation. In the worm, the locus of short-term adaptation for temporal changes in sensory input appears to be in the sensory neurons themselves. When worms are subjected to step

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changes in temperature, ambient chemicals, or gases, recordings of calcium dynamics in the primary sensory cells exhibit adaptive dynamics with similar time course as the change in reorientation rate of behaving animals [39••,41,42,43•,44•,45•,46•]. In some cases, upsteps or downsteps in sensory inputs can both raise or lower calcium levels within a single sensory neuron [26••,43•]. In these cases, sensory neuron activity itself may be sufficient to modulate activity of the downstream navigation circuit to generate biased random walks. However, in other cases, integration must occur at other loci in the circuit. For example, the left/right members of a sensory neuron pair (the ASE chemosensory neurons), or different sensory neurons (BAG and URX) sense upsteps or downsteps in chemical or oxygen concentrations, respectively [40••,44•,45•], suggesting that sensory information is integrated further downstream in the circuit in the calculation of motor decisions.

During navigation via the random walk strategy, not only is the probability of turns random, the direction of reorientation following the turn is also random. In other words, the animal does not steer itself toward a specific direction, but navigates toward its preferred direction by simply modulating the frequency of turns. However, a weak biasing of the turn angle was noted in early analyses of the random walk strategy performed by *C. elegans* on a chemical gradient [32]. Recent detailed analyses of locomotory behavior data also suggest that, in some cases, the worm can orient itself in a deterministic manner [47••]. In chemotaxis, a gradual steering strategy toward higher concentration appears to work together with the biased random walk strategy to efficiently allow navigation up gradients. In this 'weathervane strategy', the worm will gradually curve its trajectories to better align itself with the gradient direction during long runs [47••]. A steering strategy is also used by worms to track isotherms at their preferred temperature in thermotaxis behavior [48]. To remain on a track, the worm markedly lowers the probability per unit time of generating a reorientation maneuver that would throw it off the track, and uses temporal variations in temperature recorded at its nose to steer itself along the track [30]. Subsets of the same circuits that mediate random walk behaviors appear to also regulate steering on both chemical and thermal gradients [47••,49].

Almost certainly, more sophisticated patterns of behavior will require more sophisticated computations at the level of sensory and downstream neurons. For instance, on an oxygen gradient, worms navigate not to the peak of the gradient, but to an optimum experience-dependent concentration [50,51]. In a theoretical study, Dunn *et al.* [52••] showed that distinct behavioral strategies are optimal for gradient climbing and goal seeking behaviors, in which an animal seeks the highest or an intermediate point on a gradient such as in chemotaxis or aerotaxis behaviors, respectively. This analysis suggested that these strategies may be encoded in different motifs downstream of the sensory neurons. Examination of neuronal activity in first-layer and second-layer interneurons, and simultaneous imaging of multiple circuit components may provide hints regarding the mechanisms by which more sophisticated behavioral strategies are encoded by the navigation circuit.

Navigation outcomes are deterministic, but not fixed

Behavioral responses to stimuli are not always hardwired into the nervous system. Worm navigation behavior is highly flexible and adaptive, and can be modulated by experience. If removed from food and placed in an isotropic environment, the probability of runs and turns made by an animal is dictated by the length of time the animal has been food-deprived [35–38], providing a clear example of modulation of the locomotory circuit by past experience. Similarly, turn rates and run lengths can be modulated to result in avoidance of a normally attractive chemical by prolonged exposure to high concentrations of the chemical, starvation, or coupling with an aversive chemical or experience [53,54•,55–57].

Where does this plasticity occur in the circuit? The answer appears to be largely at the level of neurons upstream of the command interneurons that directly regulate locomotory behavior. Thus, both the input and/or the output of chemosensory, and first-layer or second-layer interneurons are altered by experience to modulate the stochastic dynamics of the downstream core locomotory circuit [36,54•,55–60,61••]. Of particular interest is a recent study that indicates that experience-dependent altered neurotransmission of a single sensory neuron type is sufficient to switch an attractive response to an aversive one [61••]. Although the mechanism of this switch has not yet been fully elucidated, not surprisingly, neuromodulation via neuropeptides and hormones has been implicated in the regulation of experience-dependent plasticity [54•,57,58,60,62].

Conclusions

Recent technical developments and increased sophistication in behavioral analyses and quantification of neuronal activity have been used to describe the neural ensembles that generate motor outputs, and identify the mechanisms by which sensory stimuli modulate these outputs to achieve a defined behavior. To fulfill the promise that the worm system holds to understand behavior at the molecular, cellular, and systems levels, we will need to continue to enhance the resolution of experimental measurements at all levels, as well as enhance the sophistication of the statistical analyses that are used to describe and understand these measurements. We will also need to continue to elucidate the contributions of individual neurons to a behavior via high-resolution behavioral

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analyses, and implement methods to simultaneously image all components of interconnected circuits in live, behaving animals. While a reasonable and practical goal is to investigate these issues in the 2D space of a channel in a nanodevice or on the agar surface of a petri plate, the ultimate goal will be to understand how the nervous system directs behavior in the complex 3D environment of the worm's soil habitat. To paraphrase Barack Obama — it took a lot of blood, sweat, and worms to get to where we are today, but we have just begun.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest
•• of outstanding interest

1. Marder E, Calabrese RL: **Principles of rhythmic motor pattern generation**. *Physiol Rev* 1996, **76**:687-717.

2. Grillner S, Kozlov A, Dario P, Stefanini C, Menciassi A, Lansner A, Hellgren Kotaleski J: **Modeling a vertebrate motor system: pattern generation, steering and control of body orientation**. *Prog Brain Res* 2007, **165**:221-234.

3. White JG, Southgate E, Thomson JN, Brenner S: **The structure of the nervous system of the nematode *Caenorhabditis elegans***. *Philos Trans R Soc Lond B* 1986, **314**:1-340.

4. • Chen BL, Hall DH, Chklovskii DB: **Wiring optimization can relate neuronal structure and function**. *Proc Natl Acad Sci U S A* 2006, **103**:4723-4728.

The layout of the worm nervous system could be derived from first principles using the concept of wire minimization, reducing the amount of neuronal fiber that is required to produce the pattern of synaptic connectivity in worm neuronal circuits. Additional synaptic connectivity that was not completed in the original wiring diagram was found in the motor circuit.

5. Pierce-Shimomura JT, Chen BL, Mun JJ, Ho R, Sarkis R, McIntire SL: **Genetic analysis of crawling and swimming locomotory patterns in *C. elegans***. *Proc Natl Acad Sci U S A* 2008, **105**:20982-20987.

6. Croll NA: *The Behavior of Nematodes*. New York: St. Martin's; 1970

7. • Berri S, Boyle JH, Tassieri M, Hope IA, Cohen N: **Forward locomotion of the nematode *C. elegans* is achieved through modulation of a single gait**. *HFSP J* 2009, **3**:186-193.

Worms swim in fluids and crawl on solid surfaces with distinct locomotory gaits. By putting worms in environments that posed intermediate amounts of mechanical load, it was shown that the worm continuously adjusts its gait between the extremes of swimming and crawling.

8. Wallace HR: **Movement of eelworms II: a comparative study of the movement in soil of *Heterodera schachtii schmidt* and of *Ditylenchus dipsaci (Kuhn) Filipjev***. *Ann Appl Biol* 1958, **46**:86-94.

9. Bryden J, Cohen N: **Neural control of *Caenorhabditis elegans* forward locomotion: the role of sensory feedback**. *Biol Cybern* 2008, **98**:339-351.

10. Korta J, Clark DA, Gabel CV, Mahadevan L, Samuel AD: **Mechanosensation and mechanical load modulate the locomotory gait of swimming *C. elegans***. *J Exp Biol* 2007, **210**:2383-2389.

11. Karbowski J, Schindelman G, Cronin CJ, Seah A, Sternberg PW: **Systems level circuit model of *C. elegans* undulatory locomotion: mathematical modeling and molecular genetics**. *J Comput Neurosci* 2008, **24**:253-276.

12. Boyle JH, Cohen N: ***Caenorhabditis elegans* body wall muscles are simple actuators**. *Biosystems* 2008, **94**:170-181.

13. Kerr R, Lev-Ram V, Baird G, Vincent P, Tsien RY, Schafer WR: **Optical imaging of calcium transients in neurons and pharyngeal muscle of *C. elegans***. *Neuron* 2000, **26**:583-594.

14. Zhang F, Wang LP, Brauner M, Liewald JF, Kay K, Watzke N, Wood PG, Bamberg E, Nagel G, Gottschalk A *et al.*: **Multimodal fast optical interrogation of neural circuitry**. *Nature* 2007, **446**:633-639.

15. Nagel G, Brauner M, Liewald JF, Adeishvili N, Bamberg E, Gottschalk A: **Light activation of channelrhodopsin-2 in excitable cells of *Caenorhabditis elegans* triggers rapid behavioral responses**. *Curr Biol* 2005, **15**:2279-2284.

16. • Liewald JF, Brauner M, Stephens GJ, Bouhours M, Schultheis C, Zhen M, Gottschalk A: **Optogenetic analysis of synaptic function**. *Nat Methods* 2008, **5**:895-902.

Optogenetic techniques were devised to manipulate neurotransmission between specific cell types in the motor circuit of freely moving worms, providing bidirectional optical control to contract or relax the muscles that drive locomotion.

17. • Liu Q, Hollopeter G, Jorgensen EM: **Graded synaptic transmission at the *Caenorhabditis elegans* neuromuscular junction**. *Proc Natl Acad Sci U S A* 2009, **106**:10823-10828.

Simultaneous electrical recording of muscle cells and optogenetic stimulation of motor neurons showed that synaptic transmission at the neuromuscular junction varies continuously in strength. Thus, the motor circuit operates as an analog device.

18. Farah N, Reutsky I, Shoham S: **Patterned optical activation of retinal ganglion cells**. In *Proceedings of the 29th Annual International Conference on IEEE EMBS*; *Lyon, France: 2007:6368-6370*.

19. Zheng Y, Brockie PJ, Mellem JE, Madsen DM, Maricq AV: **Neuronal control of locomotion in *C. elegans* is modified by a dominant mutation in the GLR-1 ionotropic glutamate receptor**. *Neuron* 1999, **24**:347-361.

20. Brockie PJ, Mellem JE, Hills T, Madsen DM, Maricq AV: **The *C. elegans* glutamate receptor subunit NMR-1 is required for slow NMDA-activated currents that regulate reversal frequency during locomotion**. *Neuron* 2001, **31**:617-630.

21. Chalfie M, Sulston JE, White JG, Southgate E, Thomson JN, Brenner S: **The neural circuit for touch sensitivity in *Caenorhabditis elegans***. *J Neurosci* 1985, **5**:956-964.

22. •• Stephens GJ, Johnson-Kerner B, Bialek W, Ryu WS: **Dimensionality and dynamics in the behavior of *C. elegans***. *PLoS Comput Biol* 2008, **4**:e1000028.

The detailed postures of freely crawling worms were analyzed at high resolution using a tracking microscope, and discovered to be describable using a small number of dimensions. Despite the large number of individual components in the motor circuit, motor control in the worm is achieved through a small number of degrees of freedom.

23. •• Srivastava N, Clark DA, Samuel AD: **Temporal analysis of stochastic turning behavior of swimming *C. elegans***. *J Neurophysiol* 2009, **102**:1172-1179.

The spontaneous turning movements of individual swimming worms were quantified over long periods of time, and shown to be describable using a simple Markov model involving two run states, with distinct probabilities of transition to the turn state.

24. Faumont S, Lockery SR: **The awake behaving worm: simultaneous imaging of neuronal activity and behavior in intact animals at millimeter scale**. *J Neurophysiol* 2006, **95**:1976-1981.

25. • Clark DA, Gabel CV, Gabel H, Samuel AD: **Temporal activity patterns in thermosensory neurons of freely moving *Caenorhabditis elegans* encode spatial thermal gradients**. *J Neurosci* 2007, **27**:6083-6090.

A tracking microscope was used to follow calcium transients within individual thermosensory neurons of worms navigating temperature gradients, allowing simultaneous measurements of unrestrained behavior and neuronal activity.

26. •• Chronis N, Zimmer M, Bargmann CI: **Microfluidics for *in vivo* imaging of neuronal and behavioral activity in *Caenorhabditis elegans***. *Nat Methods* 2007, 4:727-731.

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Intracellular calcium dynamics in the AVA command interneurons were correlated with initiation and duration of forward propagating waves by trapping worms in microfluidics devices. These devices also permit optical imaging of sensory neurons in the absence of confounding variables of other immobilization methods.

27. Dusenbery DB: **Analysis of chemotaxis in the nematode *Caenorhabditis elegans* by countercurrent separation**. *J Exp Zool* 1974, **188**:41-47.

28. Ryu WS, Samuel AD: **Thermotaxis in *Caenorhabditis elegans* analyzed by measuring responses to defined thermal stimuli**. *J Neurosci* 2002, **22**:5727-5733.

29. • Luo L, Gabel CV, Ha HI, Zhang Y, Samuel AD: **Olfactory behavior of swimming *C. elegans* analyzed by measuring motile responses to temporal variations of odorants**. *J Neurophysiol* 2008, **99**:2617-2625.
An olfactory assay was designed for swimming worms that allowed precise and robust quantification of attractive and repulsive olfactory responses with single worm resolution.

30. Luo L, Clark DA, Biron D, Mahadevan L, Samuel AD: **Sensorimotor control during isothermal tracking in *Caenorhabditis elegans***. *J Exp Biol* 2006, **209**:4652-4662.

31. Zariwala HA, Miller AC, Faumont S, Lockery SR: **Step response analysis of thermotaxis in *Caenorhabditis elegans***. *J Neurosci* 2003, **23**:4369-4377.

32. Pierce-Shimomura JT, Morse TM, Lockery SR: **The fundamental role of pirouettes in *Caenorhabditis elegans* chemotaxis**. *J Neurosci* 1999, **19**:9557-9569.

33. Ramot D, MacInnis BL, Lee HC, Goodman MB: **Thermotaxis is a robust mechanism for thermoregulation in *Caenorhabditis elegans* nematodes**. *J Neurosci* 2008, **28**:12546-12557.

34. Berg HC, Brown DA: **Chemotaxis in *E. coli* analysed by three-dimensional tracking**. *Nature* 1972, **239**:500-504.

35. Wakabayashi T, Kitagawa I, Shingai R: **Neurons regulating the duration of forward locomotion in *Caenorhabditis elegans***. *Neurosci Res* 2004, **50**:103-111.

36. Gray JM, Hill JJ, Bargmann CI: **A circuit for navigation in *Caenorhabditis elegans***. *Proc Natl Acad Sci U S A* 2005, **102**:3184-3191.

37. Hills T, Brockie PJ, Maricq AV: **Dopamine and glutamate control area-restricted search behavior in *Caenorhabditis elegans***. *J Neurosci* 2004, **24**:1217-1225.

38. Tsalik EL, Hobert O: **Functional mapping of neurons that control locomotory behavior in *Caenorhabditis elegans***. *J Neurobiol* 2003, **56**:178-197.

39. •• Chalasani SH, Chronis N, Tsunozaki M, Gray JM, Ramot D, Goodman MB, Bargmann CI: **Dissecting a neural circuit for food-seeking behavior in *Caenorhabditis elegans***. *Nature* 2007, **450**:63-70.
Imaging of temporal dynamics of intracellular calcium responses described information flow between the AWC sensory neurons, and their postsynaptic partners, the AIY and AIB interneurons. Removal of olfactory stimuli activates the AWC and AIB neurons, but inhibits the AIY interneurons. The parallel ON/OFF channels of stimulus transmission through the circuit may regulate the generation of probabilistic navigation behavior.

40. •• Suzuki H, Thiele TR, Faumont S, Ezcurra M, Lockery SR, Schafer WR: **Functional asymmetry in *Caenorhabditis elegans* taste neurons and its computational role in chemotaxis**. *Nature* 2008, **454**:114-117.
Navigation on a salt gradient is regulated by asymmetric sensory responses in the ASE chemosensory neurons. The left ASE neuron responds to upsteps in salt concentration and lengthens runs, whereas the right ASE neuron responds to salt downsteps and increases turns. ON/OFF information from the left and right ASE neurons converges downstream to provide a time derivative of the salt concentration.

41. Hilliard MA, Apicella AJ, Kerr R, Suzuki H, Bazzicalupo P, Schafer WR: ***In vivo* imaging of *C. elegans* ASH neurons: cellular response and adaptation to chemical repellents**. *EMBO J* 2005, **24**:63-72.

42. Kimura KD, Miyawaki A, Matsumoto K, Mori I: **The *C. elegans* thermosensory neuron AFD responds to warming**. *Curr Biol* 2004, **14**:1291-1295.

43. • Clark DA, Biron D, Sengupta P, Samuel ADT: **The AFD sensory neurons encode multiple functions underlying thermotactic behavior in *C. elegans***. *J Neurosci* 2006, **26**:7444-7451.
The stimulus–response properties of the AFD thermosensory neuron were mapped using calcium imaging and subjecting worms to a wide range of temperature waveforms. AFD responds to both increases and decreases in temperature, effectively calculating the time derivative of thermosensory input, and the temperature range of its sensitivity encodes thermotactic memory.

44. • Zimmer M, Gray JM, Pokala N, Chang AJ, Karow DS, Marletta MA, Hudson ML, Morton DB, Chronis N, Bargmann CI: **Neurons detect increases and decreases in oxygen levels using distinct guanylate cyclases**. *Neuron* 2009, **61**:865-879.
Sensory neurons sense increases or decreases in ambient oxygen levels with distinct temporal dynamics, and contribute to the different locomotory behaviors exhibited by *C. elegans* upon shifts away from, or toward, its preferred oxygen concentration.

45. • Persson A, Gross E, Laurent P, Busch KE, Bretes H, de Bono M: **Natural variation in a neural globin tunes oxygen sensing in wild *Caenorhabditis elegans***. *Nature* 2009, **458**:1030-1033.
Sensory neurons sense increases or decreases in ambient oxygen levels with distinct temporal dynamics, and contribute to the different locomotory behaviors exhibited by *C. elegans* upon shifts away from, or toward, its preferred oxygen concentration.

46. • Biron D, Wasserman SM, Thomas JH, Samuel AD, Sengupta P: **An olfactory neuron responds stochastically to temperature and modulates *C. elegans* thermotactic behavior**. *Proc Natl Acad Sci U S A* 2008, **105**:11002-11007.
The AWC sensory neurons respond stochastically, but in a stimulus-correlated manner to thermal stimuli and contribute to turning behavior on thermal gradients. Deterministic responses of the AFD thermosensory neuron type and stochastic responses of the AWC neurons to thermal stimuli may be integrated downstream in the circuit to regulate navigation on spatial thermal gradients.

47. •• Iino Y, Yoshida K: **Parallel use of two behavioral mechanisms for chemotaxis in *Caenorhabditis elegans***. *J Neurosci* 2009, **29**:5370-5380.
When *C. elegans* navigates chemical gradients, it not only modulates the rate of abrupt turns to execute a biased random walk, but also gradually steers the direction of its runs to orient itself toward its navigational goals. Simulations show that this additional sophistication in behavioral strategy is an integral part of the fidelity of *C. elegans* chemotaxis.

48. Hedgecock EM, Russell RL: **Normal and mutant thermotaxis in the nematode *Caenorhabditis elegans***. *Proc Natl Acad Sci U S A* 1975, **72**:4061-4065.

49. Mori I, Ohshima Y: **Neural regulation of thermotaxis in *Caenorhabditis elegans***. *Nature* 1995, **376**:344-348.

50. Cheung BH, Cohen M, Rogers C, Albayram O, de Bono M: **Experience-dependent modulation of *C. elegans* behavior by ambient oxygen**. *Curr Biol* 2005, **15**:905-917.

51. Gray JM, Karow DS, Lu H, Chang AJ, Chang JS, Ellis RE, Marletta MA, Bargmann CI: **Oxygen sensation and social feeding mediated by a *C. elegans* guanylate cyclase homologue**. *Nature* 2004, **430**:317-322.

52. •• Dunn NA, Conery JS, Lockery SR: **Circuit motifs for spatial orientation behaviors identified by neural network optimization**. *J Neurophysiol* 2007, **98**:888-897.
Optimum computational strategies were derived in *C. elegans* for climbing spatial gradients or for remaining within a particular location in the environment based on calculations that could be carried out by motifs in the neural circuits for navigation.

53. Saeki S, Yamamoto M, Iino Y: **Plasticity of chemotaxis revealed by paired presentation of a chemoattractant and starvation in the nematode *Caenorhabditis elegans***. *J Exp Biol* 2001, **204**:1757-1764.

54. • Tomioka M, Adachi T, Suzuki H, Kunitomo H, Schafer WR, Iino Y: **The insulin/PI 3-kinase pathway regulates salt chemotaxis learning in *Caenorhabditis elegans***. *Neuron* 2006, **51**:613-625.

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Prolonged exposure to a normally attractive salt stimulus paired with starvation results in avoidance of salt upon subsequent exposure. This plasticity is mediated via insulin secretion from an interneuron which feeds back on a salt-sensing neuron (ASER) that senses downsteps in salt concentration to modulate its functions and alter navigation behavior.

55. Ishihara T, Iino Y, Mohri A, Mori I, Gengyo-Ando K, Mitani S, Katsura I: **HEN-1, a secretory protein with an LDL receptor motif, regulates sensory integration and learning in *Caenorhabditis elegans***. *Cell* 2002, **109**:639-649.

56. Hukema RK, Rademakers S, Dekkers MP, Burghoorn J, Jansen G: **Antagonistic sensory cues generate gustatory plasticity in *Caenorhabditis elegans***. *EMBO J* 2006, **25**:312-322.

57. Zhang Y, Lu H, Bargmann CI: **Pathogenic bacteria induce aversive olfactory learning in *Caenorhabditis elegans***. *Nature* 2005, **438**:179-184.

58. Chao MY, Komatsu H, Fukuto HS, Dionne HM, Hart AC: **Feeding status and serotonin rapidly and reversibly modulate a *Caenorhabditis elegans* chemosensory circuit**. *Proc Natl Acad Sci U S A* 2004, **101**:15512-15517.

59. Kano T, Brockie PJ, Sassa T, Fujimoto H, Kawahara Y, Iino Y, Mellem JE, Madsen DM, Hosono R, Maricq AV: **Memory in *Caenorhabditis elegans* is mediated by NMDA-type ionotropic glutamate receptors**. *Curr Biol* 2008, **18**:1010-1015.

60. Harris GP, Hapiak VM, Wragg RT, Miller SB, Hughes LJ, Hobson RJ, Steven R, Bamber B, Komuniecki RW: **Three distinct amine receptors operating at different levels within the locomotory circuit are each essential for the serotonergic modulation of chemosensation in *Caenorhabditis elegans***. *J Neurosci* 2009, **29**:1446-1456.

61. •• Tsunozaki M, Chalasani SH, Bargmann CI: **A behavioral switch: cGMP and PKC signaling in olfactory neurons reverses odor preference in *C. elegans***. *Neuron* 2008, **59**:959-971.

Mutations in an AWC sensory neuron-expressed receptor guanylyl cyclase and PKC result in avoidance of a normally attractive olfactory stimulus. Although sensory responses are unaffected by these mutations, these molecules may act to regulate the synaptic output of one of the bilateral AWC neuron pair in an experience-dependent manner to direct avoidance or attraction behavior. Thus, altered activity of a single sensory neuron can switch olfactory preferences via effects on navigational strategy.

62. Macosko EZ, Pokala N, Feinberg EH, Chalasani SH, Butcher RA, Clardy J, Bargmann CI: **A hub-and-spoke circuit drives pheromone attraction and social behavior in *C. elegans***. *Nature* 2009, **458**:1171-1175.

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