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The computational worm: spatial orientation and its neuronal basis in *C. elegans*

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Abstract

Spatial orientation behaviors in animals are fundamental for survival but poorly understood at the neuronal level. The nematode *Caenorhabditis elegans* orients to wide range of stimuli and has a numerically small and well-described nervous system making it advantageous for investigation the mechanisms of spatial orientation. Recent work by the *C. elegans* research community has identified essential computational elements of the neural circuits underlying two orientation strategies that operate in five different sensory modalities. Analysis of these circuits reveals novel motifs including simple circuits for computing temporal derivatives of sensory input and for integrating sensory input with behavioral state to generate adaptive behavior. These motifs constitute hypotheses concerning the identity and functionality of circuits controlling spatial orientation in higher organisms.

Introduction

Most animals are able to orient their locomotion with respect to a variety of cues in the environment (Fig. 1). Typical cues include local gradients, landmarks, compass bearings related to the Earth's magnetic field or the position of celestial bodies such as the Sun, and internalized maps of the environment [1]. These abilities – collectively known as spatial orientation behaviors – are of scientific interest because they are fundamental to survival and goal directed. In addition, spatial orientation behaviors are unusually well suited to investigations of sensorimotor integration in the nervous system because the sensory cues that signal the goal, and the motor performance required to attain it, are directly observable and easily quantified.

Despite the interest and tractability of orientation behaviors, our understanding of their neuronal basis remains rudimentary. It is notable, therefore, that considerable progress has been made in understanding the neuronal mechanisms of spatial orientation in the nematode *Caenorhabditis elegans*. *C. elegans* exhibits a diverse repertoire of orientation behaviors in response to a variety of gradients by which it locates food, mating partners, and habitat. These behaviors include chemotaxis to salts and other soluble compounds [2,3], chemotaxis to odorants associated with food and mates [4,5], thermotaxis to preferred temperatures [5], aerotaxis to preferred levels of oxygen [6] and aerotaxis to low levels of carbon dioxide [7]. In most of these behaviors, the gradient is sensed predominantly by one or more pairs of left-right symmetric neurons. These neurons contact the environment through a pair of sensory pores in the head. Although the right and left sensory pores are separated by 10 μ m [8], the worm effectively samples the gradient at a single point in space. This is because the worm crawls on its right or left side which places the axis defined the pores orthogonal to the plane of the substrate. The fact that the worm samples the environment at a single point entails that orientation behaviors are guided by either absolute stimulus strength or by the time derivative of sensory input as the animal moves through the environment. As discussed below, the physiology of *C. elegans* chemosensation supports the latter view.

C. elegans is an advantageous experimental system for the neuronal and theoretical analysis of behavior. The adult hermaphrodite has a compact nervous system of only 302 neurons, for which there exists an essentially complete anatomical reconstruction, the celebrated "wiring diagram" of the worm [9,10]. The genetic tractability of *C. elegans* together with recent technical advances in nematode neurophysiology – including patch clamp recording [11], calcium imaging [12], and optogenetics [13] – has accelerated the pace of research into the neuronal basis of behavior in this organism. *C. elegans* is also remarkably amenable to mathematical and computational modeling. The great majority of its neurons are morphologically simple, with just one or two processes which in most cases are unbranched [9]. Neuronal processes are likely to be short relative to the predicted length constant of *C. elegans* neurons [11] suggesting that many *C. elegans* neurons are probably isopotential [11], or nearly so. Consequently, individual neurons can often be modeled as single electrical compartments. Consistent with their electrical compactness, and the absence of voltage gated sodium channels in the *C. elegans* genome [14], most *C. elegans* neurons probably do not fire classical, sodium-dependent action potentials [11,15] and synaptic transmission between *C. elegans* neurons is likely to be graded [16]. Thus, the widely-used formalism of real-time recurrent neural networks [17], which is formally equivalent to networks of single compartment neurons with graded synaptic input-output functions, is a better approximation of network-level function in *C. elegans* than in most other systems.

Two main behavioral strategies have been identified for spatial orientation behaviors in *C. elegans*. These are klinokinesis and klinotaxis, also known, respectively, as the pirouette [18–20] and weathervane mechanisms in *C. elegans* [21]. Both strategies were first identified in gradients of tastants such as inorganic salts and other soluble compounds [2]. As discussed below, essential neuronal elements of both strategies have been delineated.

Klinokinesis behavior

The klinokinesis strategy involves a biased random walk up the gradient (Fig. 2A). In the laboratory, *C. elegans* orientation behaviors are mainly studied in the aqueous environment of the surface of a moist agar filled plate. Locomotory thrust is generated by via snake-like undulations. These undulations occur in the dorsoventral plane because worms crawl on their sides. In a uniform concentration of a chemoattractant, locomotion in *C. elegans* consists of periods of relatively straight forward movement, called "runs." Runs are punctuated by bouts of large-scale reorientation events called "pirouettes" which occur stochastically with an average rate of approximately 2 events/min [19,22]. Pirouettes involve one or more brief periods of reverse locomotion lasting about 2 sec. followed in most cases by a deep body bend and resumption of forward locomotion. In the presence of a chemoattractant gradient, however, pirouette frequency is strongly modulated by the rate of change of attractant concentration $dC(t)/dt$ as the worm moves through the environment (Fig. 2B). When $dC(t)/dt < 0$, pirouette probability is increased whereas when $dC(t)/dt > 0$, pirouette probability is decreased, resulting in a biased random walk up the gradient. A computer model of klinokinesis using the empirical function shown in Fig. 2B indicated that this mechanism is only partially sufficient to generate the full extent of chemotaxis [19]. The discrepancy between model and data predicted the existence of another mechanism which was later found to be a form of klinotaxis [21]. In addition to tastants, klinokinesis has been implicated in chemotaxis to olfactants [23,24] as well as in thermotaxis [25–28], and aerotaxis [7,29].

Neuronal mechanisms of klinokinesis

A candidate neural circuit for klinokinesis in gradients of tastants has been identified (Fig. 2C). Although earlier modeling studies provided existence proofs for circuits of *C. elegans*-

like neurons sufficient to compute $dC(t)/dt$ at the network level [30,31], subsequent neurophysiological experiments demonstrated that this quantity is actually computed jointly at the cellular and network levels [32,33]; for a possible exception to this rule, see [34]. Three left-right pairs of chemosensory neurons are known both to respond to various salts and to be required for the full extent of chemotaxis, pirouette behavior, or both: ASE, ASH, and ADF [3,32,33]. Calcium imaging of their somata suggests that each of these chemosensory neurons functions as either an on-cell (ASE-left, ADF) or an off-cell (ASE-right, ASH), exhibiting a transient increase in activation in response to maintained increases or decreases in concentration, respectively (Fig. 2D). In response to a stepwise change in concentration, these transients rise to their half-maximum value in 1.2 to 1.4 sec [32]. By comparison, the duration of a complete excursion between the dorsal and ventral extremes of a head sweep is approximately 0.6 sec [35]. Thus, the worm may be able to detect the direction of the gradient during a single head sweep. This analysis probably underestimates the extent to which chemosensory neurons respond during head sweeps because calcium transients are low pass filtered by the kinetics of genetically targeted calcium probes [36]. The transduction mechanisms leading to on-cell and off-cell functionality in chemosensory neurons for tastants in *C. elegans* remains to be determined.

Anatomical reconstructions indicate that the outputs of on-cells and off-cells converge on a small network of pre-motor command interneurons that regulates the relative probability of pirouettes and forward locomotion (Fig. 2C) [37,38]. Chronic hyperpolarization or depolarization of command interneurons decreases or increases pirouette probability, respectively, thereby providing a possible mechanism whereby chemosensory neurons exert their effects on behavior [38]. In support of this mechanism, direct activation of chemosensory neurons shows that on-cells and off-cells decrease and increase pirouette probability, respectively [32]. Thus, the on and off components of $dC(t)/dt$ are computed at the cellular level whereas their outputs are summed at the network level to complete the derivative computation. Note that when re-expressed in terms of the probability of forward locomotion (i.e., of not pirouetting), the behavioral output of the circuit approximates the time derivative chemosensory input with deviations from ideal performance likely attributable to temporal filtering at the neuronal level (Fig. 2D). At present, the two main gaps in our understanding of the klinokinesis circuit are the identities of the interneurons that mediate the polysynaptic connections between chemosensory neurons and command interneurons, and the nature of the synaptic mechanisms that give rise to observed sigmoidal relationship between pirouette initiation frequency and $dC(t)/dt$ (Fig. 2B).

Similar circuitry is likely to be involved in the other forms of klinokinesis in *C. elegans*. On-cells have been reported for sensation of temperature changes [39–41], off-cells have been reported for detection of changes in odorant concentration [42], and both types of neurons have been reported for detection of changes in the partial pressure of oxygen [43,44] and carbon dioxide [7]. In most cases, ablation or direct activation of these neurons implies that on-cells required for klinokinesis up the gradient reduce pirouette probability [32,33], whereas on-cells required for klinokinesis down the gradient increase pirouette probability [7,44–47]. As would be expected, off-cells required for klinokinesis up or down the gradient have the opposite effects on pirouette probability relative to on-cells [4,7,32,33,46].

Klinotaxis behavior

In the klinotaxis strategy, by definition, the animal's course is continuously corrected toward the line of steepest ascent up the gradient (Fig. 3A). Klinotaxis is therefore a deterministic rather than a stochastic strategy. *C. elegans* steers by adjusting the angle of its head with respect to the rest of body [48,49]. Course corrections in klinotaxis take place during the side-to-side movements of the worm's head that occur as part of normal undulatory

locomotion in nematodes. Klinotaxis behavior can be quantified in terms of variables such as turning bias, i.e., the angular change in velocity of the worm's center of mass (COM) from one complete undulation cycle to the next [50].

Graphical analysis of worm trajectories reveals that klinotaxis, like klinokinesis, is probably driven by $dC(t)/dt$. Plotting turning bias against the magnitude of the component of the gradient normal to the COM velocity vector reveals a linear relationship showing that the latter predicts the former [21] (Fig. 3B). This relationship has two properties that provide further insight into the mechanism of klinotaxis in *C. elegans*. First, the relationship is antisymmetric, indicating that a worm can correct its course equally well in the clockwise or counterclockwise direction. Second, turning bias scales with the normal component of the gradient. Such scaling is significant because it ensures that course corrections occur not only when the normal component is positive on one side of the animal and negative on the other, but also when it has the same sign on both sides. The latter situation occurs when the animal is moving obliquely up or down the gradient, which appears to be the normal state of affairs as the worm is rarely oriented perfectly to the gradient [21]. Computer models of klinotaxis using the function shown in Fig. 3B indicate that this mechanism is only partially sufficient to generate chemotaxis [21]. However, when models of klinotaxis and klinokinesis are combined, the full extent of chemotaxis is reproduced indicating that the two mechanisms are jointly sufficient [21]. Klinokinesis and klinotaxis probably act in concert in real worms, except in dilute gradients where concentration changes over the spatial extent of a head sweep are very small. A klinotaxis-like strategy called isothermal tracking has been identified during thermotaxis near the animal's preferred temperature [48,51], but whether klinotaxis is used to orient to stimuli other than chemical or thermal gradients is unknown.

Neuronal mechanisms of klinotaxis

Neuronal ablations together with anatomical reconstructions imply the circuit shown in Fig. 3C. The ASE neurons provide almost all of the chemosensory input to the klinotaxis circuit [21]. The off-cell, ASE-right, is the dominant member of the ASE class in that ablating it produces a strong deficit in klinotaxis, whereas ablation of the on-cell, ASE-left, has little or no effect unless combined with ablation of its sister cell [21]. However, when both ASE neurons are ablated, the relationship between turning bias and gradient amplitude retains its positive slope, indicating that other chemosensory neurons make a modest contribution to klinotaxis. Candidate motor neurons in the circuit can be identified by noting which motor neurons predominantly innervate either dorsal or ventral neck muscles and also receive significant synaptic input from the chemosensory on-cells and off-cells mentioned above [9]. Synaptic pathways from the chemosensory neurons to candidate dorsal and ventral neck muscle motor neurons are polysynaptic [9] and a pair of interneurons that may mediate some of these connections has been identified [21]. Importantly, the combined number and strength of these pathways is approximately balanced with respect to dorsal and ventral motor neurons, consistent with the antisymmetry of the turning bias curve (Fig. 3B).

The dorso-ventral balance in synaptic input to the motor neurons (Fig. 3C) raises an intriguing functional paradox. Although balanced connectivity is required to enable course corrections up or down the gradient in both the clockwise and counterclockwise directions, it interferes with the steering movements required for course corrections. For example, consider a worm encountering an increase in concentration during a clockwise head sweep. This stimulus activates the on-cells which in turn simultaneously excite dorsal and ventral muscles. However, the ensuing increments in dorsal and ventral muscle tension cancel out; an analogous problem occurs with off-cell activation. Thus, the logic of the klinotaxis strategy requires a means of breaking the dorso-ventral symmetry of the chemosensory projections to neck motor neurons.

Symmetry breaking in klinotaxis

A model of symmetry breaking in *C. elegans* klinotaxis based on the principle of phasic sensory gating [52,53] has been proposed [50]. The model is based on two main assumptions. First, it assumes that undulations of the neck are produced by antiphase synaptic inputs to dorsal and ventral neck muscle motor neurons (Fig. 3C). Such inputs might originate from a central pattern generator, for example. Second, the model assumes a nonlinear relationship between motor neuron synaptic input and muscle tension with a low-gain and a high-gain region (Fig. 3D). Such a relationship could be implemented by a synaptic nonlinearity such as that observed at the neuromuscular junction in the nematode *Ascaris suum* [54]. By the first assumption, when motor neurons on one side are in the high-gain region of the nonlinearity, motor neurons on the other side are in the low-gain region. Given the signs of sensory-motor connections in Fig. 3C, the model generates orientation responses constitutive of klinotaxis. For example, if during a dorsal head sweep (Fig. 3D, circles) the worm encounters a higher concentration of attractant, the on-cells activate (filled arrows), moving the motor neurons to the two points labeled *a*. As a result, the difference between dorsal and ventral muscle tension increases, causing the neck to bend more deeply to the dorsal side during that cycle of locomotion. Similarly, activation of off-cells (open arrows) moves the motor neurons to the points labeled *b*, causing the difference between dorsal and ventral tension to decrease and the neck to bend less deeply to the dorsal side. Both scenarios correct the worm's course in accordance with recent sensory information. Similar rules apply during ventral bends (Fig. 3D, diamonds and points *c* and *d*).

Computer simulations show that the model accurately reproduces the main features of klinotaxis, including approach to, and persistence at, the peak of a radial gradient [50]. A remarkable emergent property of the model is that it reproduces the differential effects of on-cell and off-cell ablations mentioned above, suggesting that the model and biological circuit may be operating according to similar principles. The simulated ablations also show that a circuit in which there are only off-cells is sufficient to produce efficient klinotaxis. This finding suggests that the circuit for chemotaxis to olfactants, in which there appear to be only off cells[42], is not necessarily incomplete.

Evolution of on-off coding

Why is on-off coding pervasive in *C. elegans* sensory neurons required for spatial orientation behavior? In the early visual system of vertebrates and insects, where on-off coding is well known [55,56], it has been suggested that this coding scheme reflects a requirement for energy efficiency [57]. The alternative strategy, in which single neurons code increases and decreases in the stimulus, requires high basal rates of activity to achieve a similar dynamic range. On-off coding can also be seen as a solution to the problem of maximizing signal to noise ratio in a system with a small number of neurons. For example, assuming a pair of sensory neurons with intrinsic noise and zones of maximal sensitivity at the center of their individual dynamic ranges, it can be shown that the optimal solution is a so-called split-range code [58], in which each neuron spans only one half of the input range to be encoded. This configuration allows for higher sensitivity than the alternative in which single neurons cover the full range of inputs. Both types of constraint may have contributed to the evolution of on-off coding in *C. elegans* given that the benefits of energy efficiency are universal and, with only 302 neurons at its disposal, *C. elegans* is almost certainly faced with the problem of coding a wide range of input values with a small number of neurons.

Phylogenetic considerations

Spatial orientation has been investigated in a wide range of aquatic organisms in addition to *C. elegans*. These include prokaryotes, unicellular organisms, insect larvae, crustaceans, and fish. Despite this diversity in species, only two main types of sampling strategies have been identified: single-point sampling as described above for *C. elegans*, and stereo sampling in which the organism simultaneously makes use of a widely separated pair chemosensory structures. Comparison of orientation strategies across species is facilitated by the two-dimensional allometric analysis shown in Fig. 4. The x -axis indicates the organism's fluidic regime, quantified in terms of its Reynolds number (R_e). Fluid flow is laminar at low R_e and turbulent at high R_e . The y -axis indicates the organism's characteristic speed (S_C) which is defined as the speed of locomotion normalized to the distance between the organism's chemosensory structures. Characteristic speed enables direct comparison of locomotion speeds in organisms that differ greatly in body size and the disposition of sensory structures.

The allometric analysis reveals that the two sampling strategies are clustered in the R_e - S_C plane. Organisms that rely on single-point sampling live at low R_e and move at comparatively high speeds relative to organisms that rely on stereo sampling. Segregation of sampling strategies along the x -axis is believed to reflect an evolutionary response to the differences in the stability of chemical gradients in the two fluidic regimes [59]. Because single point sampling entails sequential sampling through time, it is effective only in the laminar regime where gradients are relatively stable over the characteristic time interval of the sampling process. By contrast, stereo sampling is advantageous in the turbulent regime where chemoattractants are distributed discontinuously in filamentous plumes and patches. With $R_e = 0.2$, *C. elegans* clearly operates in the laminar regime. Sampling strategies are also segregated along the y -axis. This segregation may reflect the fact that higher locomotion speeds result in improved signal-to-noise ratio in single point sampling. The characteristic speed of *C. elegans* is similar to that of *E. coli* and *Paramecium*. Interestingly, all three organisms utilize similar forms of klinokinesis. *Drosophila* larvae are anomalous. When situated in the aqueous environment of rotting fruit, they operate low R_e yet they have been shown to use stereo sampling [60]. A possible explanation for this anomaly is that *Drosophila* larvae also occur in non-aqueous environments such as the surface of fruit. Thus, their sensory structures may be adapted primarily for the high R_e regime of airborne odorants.

Outlook

Spatial orientation behaviors in *C. elegans* are well suited to investigations of sensory processing and sensorimotor integration. The neuronal analysis of klinokinesis has yielded a simple circuit motif for computing the time derivative of sensory information that can be applied other sensory modalities. Theoretical analysis of klinotaxis has provided a model of how representations behavior are integrated with biological outcomes to generate adaptive responses. These findings lead to testable hypotheses concerning the neuronal basis of behavior in higher organisms.

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Abbreviations

COM center of mass

References

1. Schone, H. The spatial control of behavior in animals and man. Princeton: Princeton University Press; 1984.
2. Ward S. Chemotaxis by the nematode *Caenorhabditis elegans*: identification of attractants and analysis of the response by use of mutants. *Proc Natl Acad Sci U S A*. 1973; 70:817–821. [PubMed: 4351805]
3. Bargmann CI, Horvitz HR. Chemosensory neurons with overlapping functions direct chemotaxis to multiple chemicals in *C. elegans*. *Neuron*. 1991; 7:729–742. [PubMed: 1660283] •• This compendious paper laid the foundations for the cellular analysis of chemosensory processing in *C. elegans*. It focusses on chemotaxis to soluble compounds
4. Bargmann CI. Odorant-selective genes and neurons mediate olfaction in *C. elegans*. *Cell*. 1993; 74:515–527. [PubMed: 8348618] •• This paper complements reference [3] by laying the foundations for the cellular analysis of olfactory processing in *C. elegans* •• This paper complements reference [3] by laying the foundations for the cellular analysis of olfactory processing in *C. elegans*
5. White JQ, Nicholas TJ, Gritton J, Truong L, Davidson ER, Jorgensen EM. The sensory circuitry for sexual attraction in *C. elegans* males. *Curr Biol*. 2007; 17:1847–1857. [PubMed: 17964166]
6. 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. [PubMed: 15220933]
7. Bretscher AJ, Kodama-Namba E, Busch KE, Murphy RJ, Soltesz Z, Laurent P, de Bono M. Temperature, Oxygen, and Salt-Sensing Neurons in *C. elegans* Are Carbon Dioxide Sensors that Control Avoidance Behavior. *Neuron*. 69:1099–1113. [PubMed: 21435556] • An unusually complete investigation of the neuronal basis of spatial orientation behavior in *C. elegans*
8. Ward S, Thomson N, White JG, Brenner S. Electron microscopical reconstruction of the anterior sensory anatomy of the nematode *Caenorhabditis elegans*. *Journal of Comparative Neurology*. 1975; 160:313–338. [PubMed: 1112927]
9. 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 Biol Sci*. 1986; 314:1–340. [PubMed: 22462104] •• This paper reports the celebrated wiring diagram of *C. elegans* central nervous system
10. Varshney LR, Chen BL, Paniagua E, Hall DH, Chklovskii DB. Structural properties of the *Caenorhabditis elegans* neuronal network. *PLoS Comput Biol*. 7:e1001066. [PubMed: 21304930] • This paper fills in most of the gaps in the work reported in reference [9] using new serial section electron microscopy reconstructions as well as updates and corrections of the original reconstruction
11. Goodman MB, Hall DH, Avery L, Lockery SR. Active Currents Regulate Sensitivity and Dynamic Range in *C. elegans* Neurons. *Neuron*. 1998; 20:763–772. [PubMed: 9581767]
12. Kerr, R. Imaging Excitable Cell Activity in *C. elegans*. San Diego, CA: University of California; 2002.
13. 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. [PubMed: 16360690]
14. Bargmann CI. Neurobiology of the *Caenorhabditis elegans* genome. *Science*. 1998; 282:2028–2033. [PubMed: 9851919]
15. Lockery SR, Goodman MB. The quest for action potentials in *C. elegans* neurons hits a plateau. *Nat Neurosci*. 2009; 12:377–378. [PubMed: 19322241]
16. Lindsay TH, Thiele TR, Lockery SR. Synaptic Transmission between identified neurons in the central nervous system of the nematode *C. elegans*. *Nature Communications*. 2011 (In press).

17. Beer RD. Parameter space structure of continuous-time recurrent neural networks. *Neural Comput.* 2006; 18:3009–3051. [PubMed: 17052157] • This paper provides a concise and rigorous introduction to what is perhaps the most commonly used formalism for modeling and analysis of idealized dynamical neural networks
18. Dusenbury DB. Responses of the nematode *Caenorhabditis elegans* to controlled chemical stimulation. *Journal of Comparative Physiology.* 1980; 136:127–331.
19. Pierce-Shimomura JT, Morse TM, Lockery SR. The fundamental role of pirouettes in *Caenorhabditis elegans* chemotaxis. *J Neurosci.* 1999; 19:9557–9569. [PubMed: 10531458] •• Building on the work of Dusenbury [18], this paper firmly established klinokinesis as a major contributing factor in *C. elegans* spatial orientation
20. Dusenbury DB. Analysis of chemotaxis in the nematode *Caenorhabditis elegans* by counter current separation. *Journal of Experimental Zoology.* 1974; 188:41–47. [PubMed: 4822548]
21. Iino Y, Yoshida K. Parallel use of two behavioral mechanisms for chemotaxis in *Caenorhabditis elegans*. *J Neurosci.* 2009; 29:5370–5380. [PubMed: 19403805] •• This paper demonstrated that *C. elegans* uses both klinokinesis and klinotaxis in chemotaxis to soluble compounds and identified fundamental elements of the klinotaxis circuit using a combination of neuronal ablations and quantitative behavioral analysis
22. Rutherford TA, Croll NA. Wave forms of *C. elegans* in a chemical attractant and repellent and in thermal gradients. *Journal of Nematology.* 1979; 11:232–240. [PubMed: 19300640]
23. Hills T, Brockie PJ, Maricq AV. Dopamine and glutamate control area-restricted search behavior in *Caenorhabditis elegans*. *J Neurosci.* 2004; 24:1217–1225. [PubMed: 14762140]
24. Bargmann CI. Chemosensation in *C. elegans*. *WormBook.* 2006; 1:29.
25. Ryu WS, Samuel AD. Thermotaxis in *Caenorhabditis elegans* analyzed by measuring responses to defined Thermal stimuli. *J Neurosci.* 2002; 22:5727–5733. [PubMed: 12097525]
26. 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. [PubMed: 17553981]
27. 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. [PubMed: 19020047]
28. Zariwala HA, Miller AC, Faumont S, Lockery SR. Step response analysis of thermotaxis in *Caenorhabditis elegans*. *J Neurosci.* 2003; 23:4369–4377. [PubMed: 12764126]
29. 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. [PubMed: 15916947]
30. Dunn NA, Lockery SR, Pierce-Shimomura JT, Conery JS. A neural network model of chemotaxis predicts functions of synaptic connections in the nematode *Caenorhabditis elegans*. *J Comput Neurosci.* 2004; 17:137–147. [PubMed: 15306736]
31. Dunn NA, Conery JS, Lockery SR. Circuit motifs for spatial orientation behaviors identified by neural network optimization. *J Neurophysiol.* 2007; 98:888–897. [PubMed: 17522174]
32. 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. [PubMed: 18596810] •• Using calcium imaging and direct activation of individual chemosensory neurons in intact animals, this paper demonstrated on-off coding in the *C. elegans* chemosensory system and elucidated its relationship to spatial orientation behavior
33. Thiele TR, Faumont S, Lockery SR. The neural network for chemotaxis to tastants in *Caenorhabditis elegans* is specialized for temporal differentiation. *J Neurosci.* 2009; 29:11904–11911. [PubMed: 19776276]
34. Macosko EZ, Pokala N, Feinberg EH, Chalasani SH, Butcher RA, Clardy J, Bargmann CI. A hub-and-spoke circuit drives pheromone attraction and social behaviour in *C. elegans*. *Nature.* 2009; 458:1171–1175. [PubMed: 19349961]
35. 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. [PubMed: 19074276]

36. Reiff DF, Ihring A, Guerrero G, Isacoff EY, Joesch M, Nakai J, Borst A. In vivo performance of genetically encoded indicators of neural activity in flies. *J Neurosci*. 2005; 25:4766–4778. [PubMed: 15888652]
37. 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. [PubMed: 3981252]
38. 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. [PubMed: 10571229]
39. Kimura KD, Miyawaki A, Matsumoto K, Mori I. The *C. elegans* thermosensory neuron AFD responds to warming. *Curr Biol*. 2004; 14:1291–1295. [PubMed: 15268861]
40. Biron D, Wasserman S, Thomas JH, Samuel AD, Sengupta P. An olfactory neuron responds stochastically to temperature and modulates *Caenorhabditis elegans* thermotactic behavior. *Proc Natl Acad Sci U S A*. 2008; 105:11002–11007. [PubMed: 18667708]
41. Kuhara A, Okumura M, Kimata T, Tanizawa Y, Takano R, Kimura KD, Inada H, Matsumoto K, Mori I. Temperature sensing by an olfactory neuron in a circuit controlling behavior of *C. elegans*. *Science*. 2008; 320:803–807. [PubMed: 18403676]
42. Chalasani SH, Chronis N, Tsunozaki M, Gray JM, Ramot D, Goodman MB, Bargmann CI. Dissecting a circuit for olfactory behaviour in *Caenorhabditis elegans*. *Nature*. 2007; 450:63–70. [PubMed: 17972877] • Using calcium imaging in intact animals, this paper provided the first demonstration of off-cells the *C. elegans* chemosensory system
43. 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. [PubMed: 19262507]
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. [PubMed: 19323996]
45. Mori I, Ohshima Y. Neural regulation of thermotaxis in *Caenorhabditis elegans*. *Nature*. 1995; 376:344–348. [PubMed: 7630402]
46. Gray JM, Hill JJ, Bargmann CI. A circuit for navigation in *Caenorhabditis elegans*. *Proc Natl Acad Sci U S A*. 2005; 102:3184–3191. [PubMed: 15689400] • This paper presents a comprehensive analysis of the contributions of sensory neurons, interneurons, and motor neurons to kinesis behavior
47. Kuhara A, Sasakura H, Kimata T, Mori I. [Neural circuit mechanism underlying thermotaxis behavior in *C. elegans*]. *Tanpakushitsu Kakusan Koso*. 2008; 53:580–586. [PubMed: 21089340]
48. 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. [PubMed: 17114399]
49. Kim D, Park S, Mahadevan L, Shin JH. The shallow turn of a worm. *J Exp Biol*. 214:1554–1559. [PubMed: 21490263]
50. Izquierdo EJ, Lockery SR. Evolution and Analysis of Minimal Neural Circuits for Klinotaxis in *Caenorhabditis elegans*. *J Neurosci*. 2010; 30:12908–12917. [PubMed: 20881110] • This modeling paper used a neural network optimization algorithm that mimics evolution to identify circuit motifs capable of generating klinotaxis given on-off sensory coding and biological constraints that follow from the anatomical reconstructions of White et al 1986. Models in the paper were based on the formalism of continuous-time recurrent neural networks described in [17]
51. Hedgecock EM, Russell RL. Normal and mutant thermotaxis in the nematode *Caenorhabditis elegans*. *Proceedings of the National Academy of Science*. 1975; 72:4061–4065.
52. Reichert H, Rowell CH. Integration of nonphaselocked exteroceptive information in the control of rhythmic flight in the locust. *J Neurophysiol*. 1985; 53:1201–1218. [PubMed: 2987432]
53. Dickinson MH. Haltere-mediated equilibrium reflexes of the fruit fly, *Drosophila melanogaster*. *Philos Trans R Soc Lond B Biol Sci*. 1999; 354:903–916. [PubMed: 10382224]
54. Davis RE, Stretton AOW. Signaling properties of *Ascaris* motoneurons: graded active response, graded synaptic transmission, and tonic transmitter release. *Journal of Neuroscience*. 1989; 9:415–425. [PubMed: 2563763]

55. Wassle H. Parallel processing in the mammalian retina. *Nat Rev Neurosci.* 2004; 5:747–757. [PubMed: 15378035]
56. Joesch M, Schnell B, Raghu SV, Reiff DF, Borst A. ON and OFF pathways in *Drosophila* motion vision. *Nature.* 468:300–304. [PubMed: 21068841]
57. Schiller PH. The ON and OFF channels of the visual system. *Trends Neurosci.* 1992; 15:86–92. [PubMed: 1373923]
58. von der Twer T, MacLeod DI. Optimal nonlinear codes for the perception of natural colours. *Network.* 2001; 12:395–407. [PubMed: 11563536]
59. Dusenbery, DB. *Life at Small Scale: The Behavior of Microbes.* New York: Scientific American Library; 1996.
60. Louis M, Huber T, Benton R, Sakmar TP, Vosshall LB. Bilateral olfactory sensory input enhances chemotaxis behavior. *Nat Neurosci.* 2008; 11:187–199. [PubMed: 18157126]
61. Locsei JT. Persistence of direction increases the drift velocity of run and tumble chemotaxis. *J Math Biol.* 2007; 55:41–60. [PubMed: 17354016]
62. Gee CC, Zimmer-Faust RK. The effects of walls, paternity and ageing on sperm motility. *J Exp Biol.* 1997; 200:3185–3192. [PubMed: 9364024]
63. Kaupp UB, Kashikar ND, Weyand I. Mechanisms of sperm chemotaxis. *Annu Rev Physiol.* 2008; 70:93–117. [PubMed: 17988206]
64. Hamel A, Fisch C, Combettes L, Dupuis-Williams P, Baroud CN. From the Cover: Transitions between three swimming gaits in *Paramecium* escape. *Proc Natl Acad Sci U S A.* 108:7290–7295. [PubMed: 21464291]
65. Van Houten J. Chemosensory transduction in eukaryotic microorganisms. *Annu Rev Physiol.* 1992; 54:639–663. [PubMed: 1562186]
66. Cobb M, Bruneau S, Jallon JM. Genetic and developmental factors in the olfactory response of *Drosophila melanogaster* larvae to alcohols. *Proc Biol Sci.* 1992; 248:103–109. [PubMed: 1352888]
67. Berrigan D, Pepin DJ. How maggots move: allometry and kinematics of crawling in larval diptera. *Journal of Insect Physiology.* 1995; 41:329–337.
68. Kraus-Epley KE, Moore PA. Bilateral and unilateral antennal lesions alter orientation abilities of the crayfish, *Orconectes rusticus*. *Chem Senses.* 2002; 27:49–55. [PubMed: 11751468]
69. Sherman ML, Moore PA. Chemical orientation of brown bullheads, *Ameiurus nebulosus*, under different flow conditions. *J Chem Ecol.* 2001; 27:2301–2318. [PubMed: 11817083]
70. Bardach JE, Todd JH, Crickmer R. Orientation by taste in fish of the genus *Ictalurus*. *Science.* 1967; 155:1276–1278. [PubMed: 6018651]
71. Horner AJ, Weissburg MJ, Derby CD. Dual antennular chemosensory pathways can mediate orientation by Caribbean spiny lobsters in naturalistic flow conditions. *J Exp Biol.* 2004; 207:3785–3796. [PubMed: 15371486]
72. Devine DV, Atema J. Function of chemoreceptor organs in spatial orientation of the lobster, *Homarus americanus*: differences and overlap. *Biological Bulletin.* 1982; 163:144–153.
73. Anderson EJ, McGillis WR, Grosenbaugh MA. The boundary layer of swimming fish. *J Exp Biol.* 2001; 204:81–102. [PubMed: 11104713]
74. Gardiner JM, Atema J. The function of bilateral odor arrival time differences in olfactory orientation of sharks. *Curr Biol.* 20:1187–1191. [PubMed: 20541411]
75. Johnsen PB, teeter JH. Behavioral responses of bonnet-head sharks (*Sphyrna tiburo*) to controlled olfactory stimulation. *Marine and Freshwater Behaviour and Physiology.* 1985; 11:293–291.

Figure 1. Examples of spatial orientation behaviors

A. Taxis behavior. Orientation to a local gradient in temperature, luminance, or chemical concentration. B. Piloting behavior. A swimming animal locates a submerged platform by reference to visible landmarks. C. Compass orientation behavior. Migratory birds are guided by the angle of the Sun and knowledge of the time of day. D. Map-and-compass orientation. Homing pigeons travel directly to their loft from arbitrary release points *a* and *b*. The observation that pigeons correct their course as a function of starting location whereas migrating birds do not, implies a combination of compass orientation and map-like knowledge of the individual's location in the case of homing behavior.

Figure 2. Klinokinesis behavior in *C. elegans*

A. Path of a worm's center of mass in a planar gradient of a chemoattractant. Concentration rises in the direction of the arrow; dashed lines are isoconcentration contours. The filled dot indicates the end of the path. Open dots show the location of pirouettes. Scale bar: 1 cm. B. Empirical relationship between pirouette frequency and the rate of change of concentration during klinotaxis. C. Candidate neural circuit for klinokinesis. Solid and dashed lines indicate monosynaptic and polysynaptic pathways, respectively. Plus and minus signs are excitatory and inhibitory connections, respectively. Body wall motor neurons that generate locomotory thrust have been omitted for clarity. D. Mechanism for computation of the time derivative of chemosensory inputs during klinokinesis. A step-wise increase in attractant

concentration $C(t)$ produces positive-going on and off transients in on-cell and off-cells, respectively. These transients are usually monitored by changes in intracellular calcium concentration which is used as a surrogate for changes in membrane potential. At the level of the command interneurons shown in C, the effect of on-cell activation is inverted and added to the effect of off-cell activation to regulate pirouette probability ($P_{\text{Pirouette}}$). The probability of forward locomotion (P_{Forward}) varies in the opposite direction and represents a lowpass filtered version of the derivative $dC(t)/dt$, shown by the gray trace. A and B are redrawn from [19].

Figure 3. Klinotaxis behavior in *C. elegans*

A. Paths of the center of mass of three worms orienting to a radial gradient of chemoattractant. The peak of the gradient is indicated by the diamond; dashed lines are isoconcentration contours. Filled dots indicate the ends of the paths. The arrow shows the direction normal to the worm's velocity, defined as the vector that is clockwise-orthogonal to the worm's instantaneous velocity. Scale bar: 1 cm. B. Empirical relationship between turning bias and the component of the concentration gradient normal to the worm's velocity. When the normal component of the gradient is positive, turning bias as seen from above is clockwise. C. Candidate neural circuit and network model for klinotaxis. Chemosensory on-cells and off-cells respectively excite and inhibit neck muscle motor neurons. Connection strengths of a given sign to the motor neurons are equal. In the biological network, these connections are polysynaptic. Motor neurons in the model receive antiphase inputs from a presumptive pattern generator (sine wave symbol) that drives undulatory locomotion. Other symbols as in Fig. 2C. D. Symmetry breaking in the model network for klinotaxis. Circles

and diamonds indicate the state of the motor neurons during dorsal and ventral bends, respectively. Oncells in the model are excitatory and cause a rightward shift in net motor neuron input to the right (filled arrows); off-cells are inhibitory and cause a leftward shift net motor neuron input (open arrows). Points y -values of points a and b indicate how neck muscle tension is perturbed by on-cell and off-cell activation, respectively, during a dorsal bend; points c and d indicate analogous perturbations during ventral bends. The model assumes that turning bias is proportional to the difference between dorsal and ventral muscles tension. A and B are redrawn from [21]; C and D are redrawn from [50].

Figure 4. Allometric analysis of spatial orientation behaviors in aquatic environments

Characteristic speed is plotted against Reynolds number (Re). Marker color indicates sampling strategy as shown in the key. The transition between laminar and turbulent fluidic regimes occurs at $Re \approx 2000$ (vertical black line). Reynolds numbers were calculated as $Re = \rho UL/\mu$, where U is the organism's typical speed, L is its length, ρ is the density of water (1000 kg/m^3) and μ is its dynamic viscosity ($9 \times 10^{-4} \text{ Pa}\cdot\text{s}$). Characteristic speeds were calculated by dividing U by the maximum possible separation between the organism's sensory receptors. For example, *E. coli* travels at speeds of $\sim 20 \mu\text{m/s}$ and the maximum possible separation between receptors is equal to its length ($2 \mu\text{m}$), yielding a characteristic

speed of 10 s^{-1} . Sampling strategies as well as numerical values for length, separation of receptors, and speed for each organism, were obtained from the following sources: *E. coli* [61], sperm [62,63]; *C. elegans* [19], *Paramecium* [64,65]; *Drosophila* [60,66,67]; crayfish [68], catfish [69,70], lobster [71,72], shark [73–75].