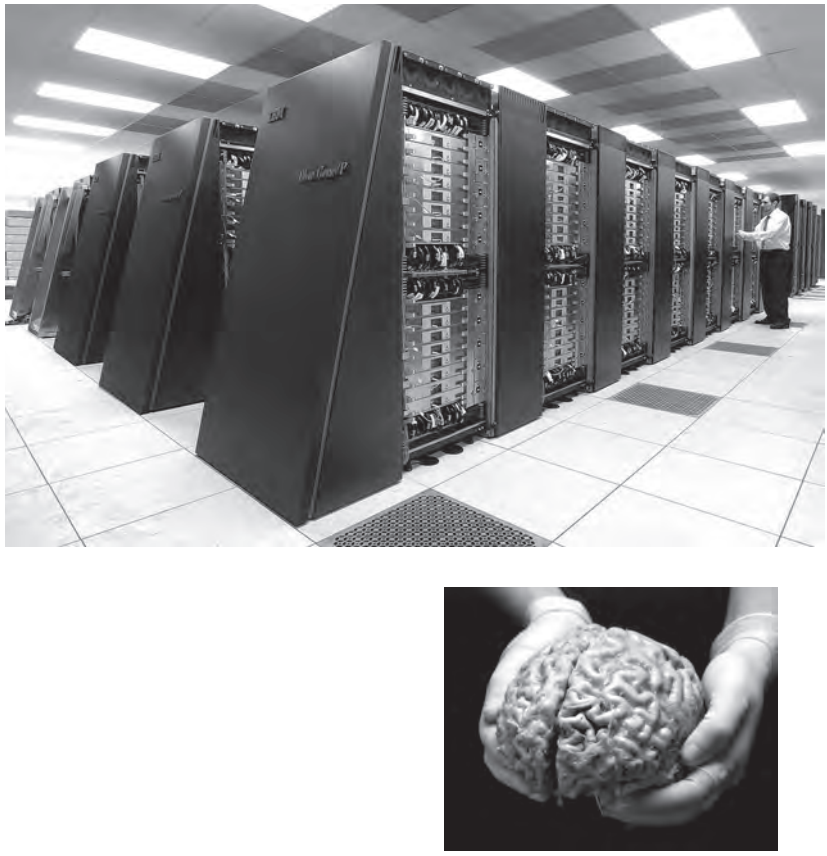

Figure I.1
How do neural circuits use space and power so efficiently? Computer: Image http://upload.wikimedia.org/wikipedia/commons/d/d3/IBM_Blue_Gene_P_supercomputer.jpg. Brain: Photo by UW-Madison, University Communications © Board of Regents of the University of Wisconsin System.

Consequently, the idea of pausing to distill principles from facts has lacked appeal. Moreover, to many who ferret out great new facts for a living, it has seemed like a waste of time.

Yet, we draw inspiration from Charles Darwin, who remarked, "My mind seems to have become a kind of machine for grinding general laws out of large collections of facts" (Darwin, 1881). Darwin, of course, is incomparable, but this is sort of how our minds work too. So we have written a small book—relative to the great compendia—intending to beat a rough path up "Data Mountain" in search of organizing principles.

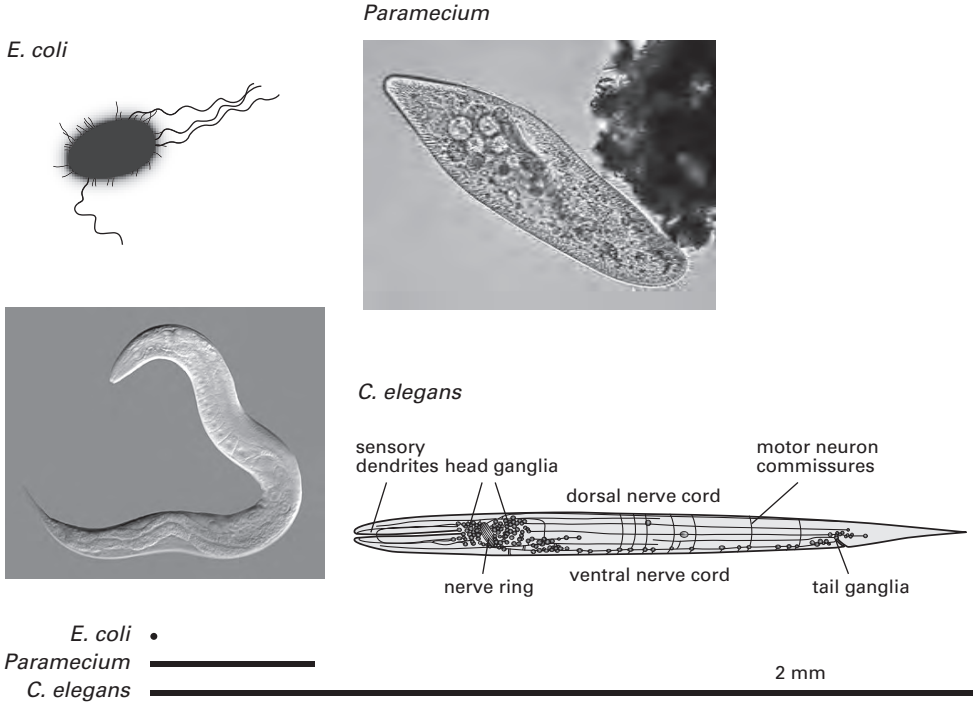

Figure 2.1

Three organisms of increasing size: bacterium, protozoan, and a nematode worm. Note the different scales: micrometers to millimeters. Body lengths are drawn to the same scale at the bottom of the diagram. *Paramecium caudatum* and *C. elegans* photos are light micrographs of live specimens. Diagram of worm indicates the positions of neurons that form the brain. Light micrographs from Wiki commons. *C. elegans* from Wikimedia Commons, CC BY-SA 3.0 / Bob Goldstein, UNC Chapel Hill, http://bio.unc.edu/people/faculty/goldstein/. *Paramecium* by Alfred Kahl, public domain, from Wikimedia Commons.

In effect, the lactose receptor *predicts* for the organism what it will need to exploit this new resource. By encoding the permease and the digestive enzyme together, one sensory signal can evoke all necessary components in the correct ratios. Thus, a given level of lactose in the soup calls for the proper amount of permease which is matched by the proper amount of galactosidase. This design principle—matching capacities within a coupled system—is a key to the organization of multicellular animals where it is called "symmorphosis" (Weibel, 2000). We see here that symmorphosis begins in the single cell.

The lac operon

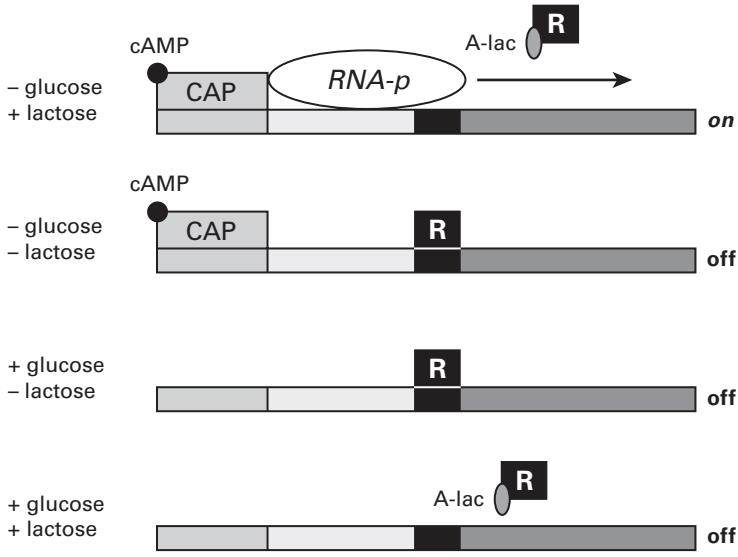

Figure 2.2

The lac operon: a molecular mechanism that discriminates between patterns of input and determines action. To transcribe the lac operon's genes, RNA polymerase (*RNA-P*) must bind to its site and move into the operon's DNA. Its movement is blocked by the repressor R, but R cannot bind and block when holding a molecule of allolactose (A-lac). To start moving, *RNA-p* must be activated by the protein CAP. This activator protein only binds to its site on the DNA when it is binding cAMP, and cAMP is eliminated in the presence of glucose. Thus, *RNA-p* only transcribes the lac operon when glucose is absent and lactose is present.

On occasions, such as when its host has eaten an ice cream, *E. coli* is presented with both lactose *and* glucose. Now the bacterium need not metabolize lactose and so need not build machinery to process it. To block this futile activity, there is a second molecular switch. RNA polymerase, to step along the DNA transcribing the lac operon, must be activated by the protein CAP, and CAP must be binding a small signaling molecule, cAMP. Biochemical pathways couple the production of cAMP to the concentration of glucose. As glucose rises, cAMP falls; this turns off the RNA polymerase (figure 2.2), and *E. coli* stops producing unneeded machinery.

Thus, a molecular control system combines information from two inputs to compute the correct conditions for processing lactose: IF lactose AND NO glucose, then GO; IF lactose AND glucose, then NO GO. The chemical

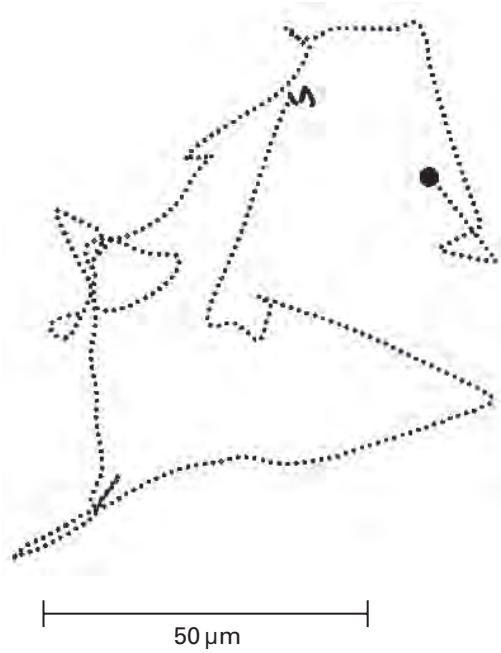

Figure 2.3
***E. coli*'s biased random walk**. By moving forward more and turning less, as the concentration of attractant increases, *E. coli* approaches the attractant's source. Tracing shows 26 runs over about 30 s with a mean speed of 21.2 µm/s. Reprinted with permission from Berg and Brown (1972). For videos of *E. coli* swimming see http://www.rowland.harvard.edu/labs/bacteria/index_movies.html/.

network for chemotaxis that could provide sufficiently robust performance. Moreover, its working memory suffices to steer the motor toward food and mates. Although a memory lasting only 1 s may not seem impressive, realize that to store a long history of lactose concentrations would be pointless—because they are themselves evanescent. Given its lifestyle, the bacterium's memory is just about as long as it *should* be.

This microbe easily lives like a Zen master—in the moment. Feed the cell, and in an hour it is gone, divided among its progeny. But once an organism becomes large enough for a brain, the Zen injunction—"Live in the moment"—itself becomes a Zen koan. A brain provides the organism with a more significant individual past and a more extended future with which to exploit it. But so equipped, staying in the moment becomes as unimaginable as the sound of one hand clapping.

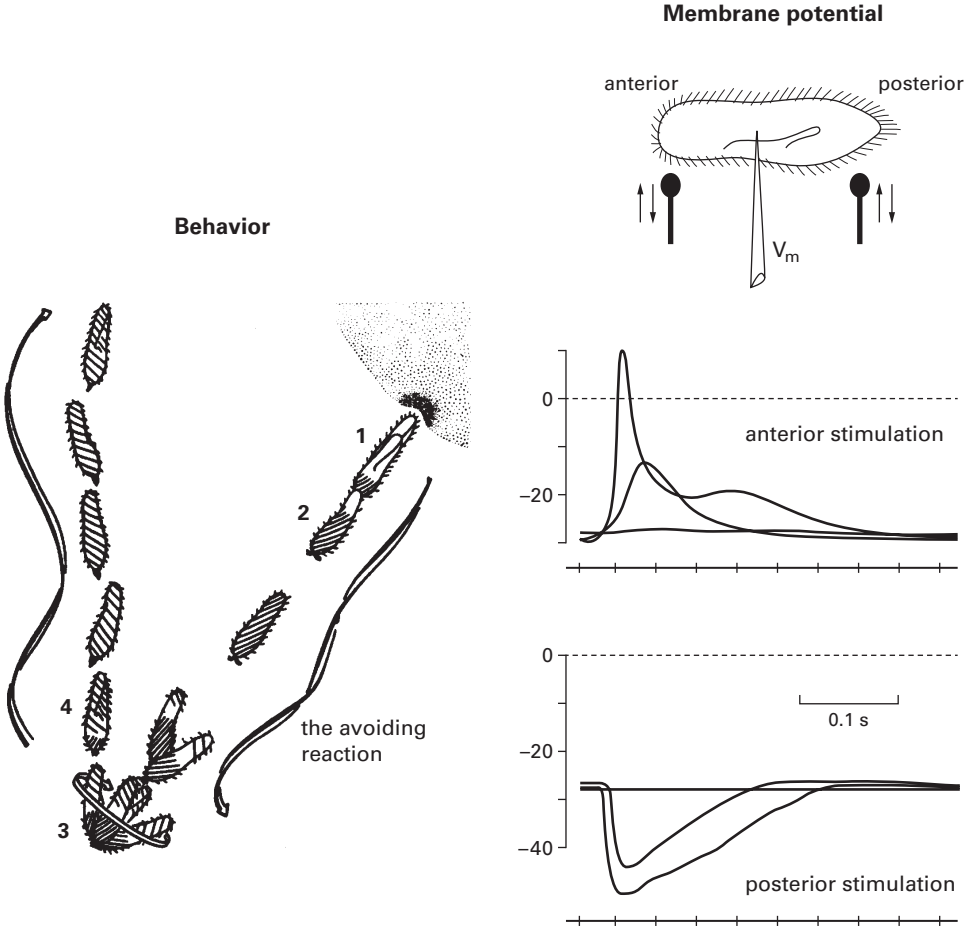

Figure 2.4

***Paramecium*'s avoidance response: behavior and electrical mechanism**. **Left**: The four stages of behavior. (1) Bumps up against immovable object, (2) backs off by reversing cilia, (3) gyrates while cilia switch from reverse to forward, and (4) sets off in a new direction. **Upper right**: Measuring electrical response to mechanical stimuli. Intracellular microelectrode records membrane potential and probes prod the membrane. **Middle right**: Membrane potential recorded following stimulation with anterior probe. A weak prod depolarizes membrane for 300 ms (lower trace). A strong prod generates a short calcium action potential followed by longer depolarization (upper trace). **Lower right**: Posterior prod hyperpolarizes. The response to the weaker prod is smaller and has a longer latency. Adapted from Eckert (1972), with permission.

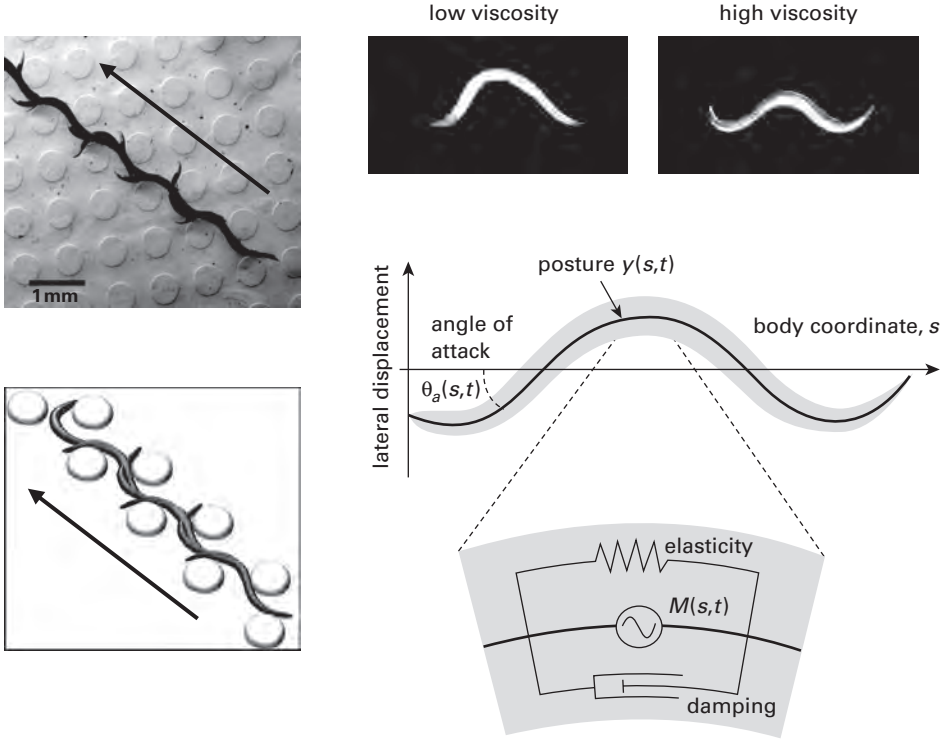

Figure 2.5

***C. elegans* locomotion matches the terrain and adapts to viscosity**. Spacing of soil particles affects forward speed, as shown when worm crawls through a regular array of agar posts of given spacing. **Upper left**: Superposition of 10 photos taken at 200-ms intervals as a worm traversed the array in which it moved forwards at maximum speed. **Lower left**: Tracings of five of the above photos, taken at 400-ms intervals, show why speed is maximum: body wavelength matches post spacing to distribute thrust efficiently. **Upper right**: The wavelength of undulation is longer in a low-viscosity medium and shorter in high viscosity. **Middle right**: Body posture is described by $y(s,t)$, the lateral displacement, y, changing with position along body, s, and time, t. The angle of attack at a given position and time, $\theta_a(s,t)$, is critical for determining thrust against the substrate. **Lower right**: The factors determining body posture and its dependence on viscosity. These vary with position along the body, s, and change with time t. In a simple biomechanical model the muscle force $M(s, t)$ interacts with body elasticity and viscous damping by the medium, to determine lateral displacement $y(s, t)$ and the angle of attack $\theta_a(s, t)$. Left reprinted with permission from Park et al. (2008). Right reprinted with permission from Fang-Yen et al. (2010).

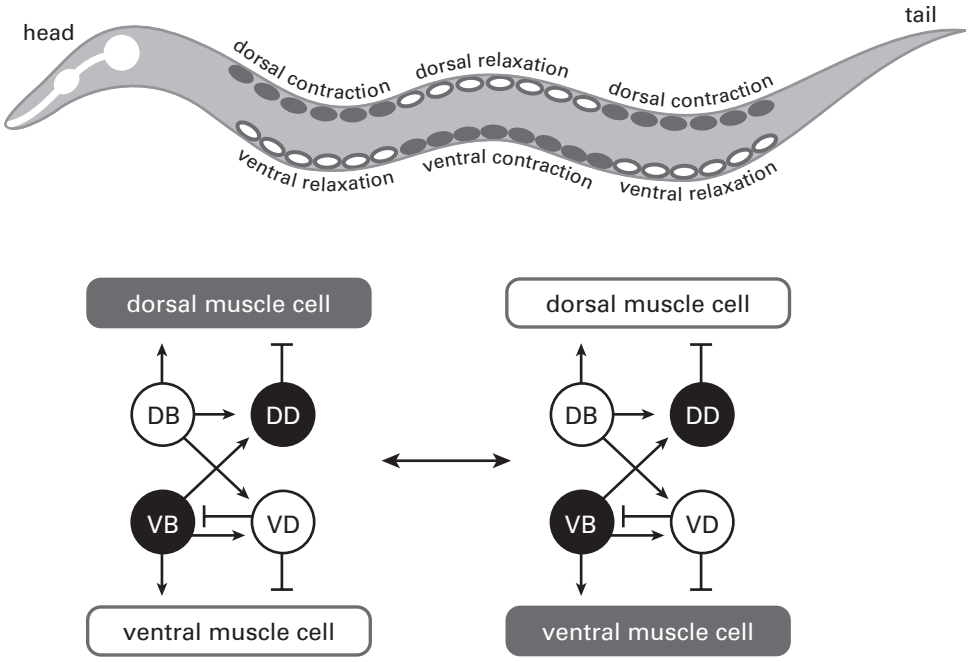

Figure 2.6

Neural circuit that bends the worm. Excitatory motor neurons (DB, VB) alternately cause dorsal and ventral muscles to contract, whereas inhibitory motor neurons (DD, VD) alternately cause them to relax. The excitatory motor neuron on one side drives the inhibitory neuron on the other side so that the body bows downward (DB and VD active), or upward (VB and DD active). This cross-inhibitory circuit repeats along the worm to promote a traveling wave. Modified from Sengupta & Samuel (2009), with permission.

Cycling with the body

The worm builds its oscillator by combining feedback with body mechanics. A burst of activity in motor neurons drives the muscles on one side. Their contraction bends the body and tensions the body's intrinsic spring—internal hydrostatic pressure. Sensors excited by these forces feed back to inhibit motor neurons, whereupon the muscles relax and the body springs back. This terminates the negative feedback, allowing the motor neurons to reactivate and start a new cycle (figure 2.6). Because the spring is damped by viscous forces (figure 2.5), the oscillation is well behaved. Also, it automatically adjusts to changes in viscous load, smoothly shifting the worm's gait to match operating conditions.

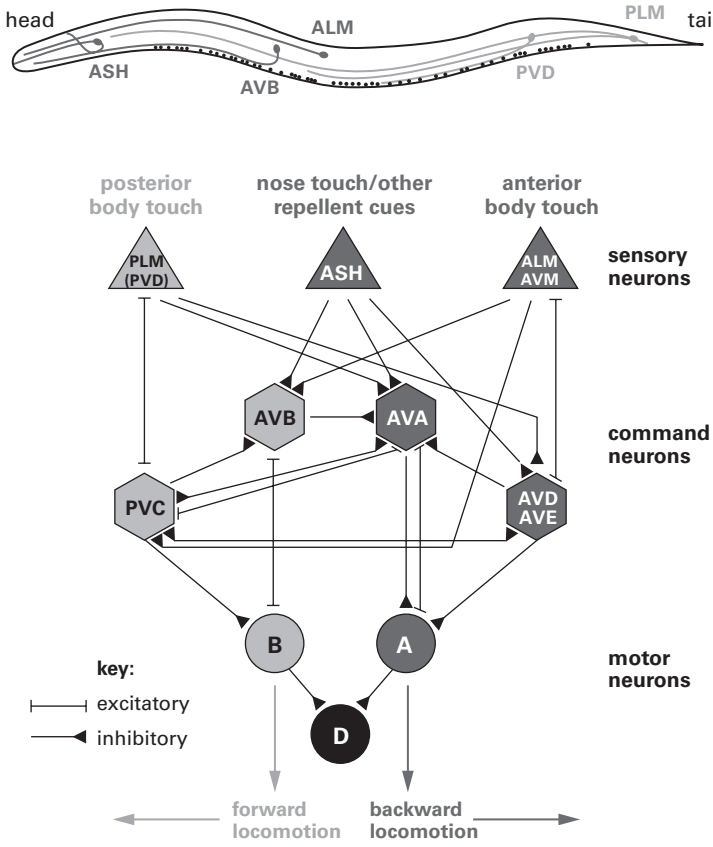

Figure 2.7
The circuit for aversive behavior. Mechanosensory neurons in the nose and in other anterior parts of the body drive command neurons for "backward" motor neurons. Mechanosensory neurons at the posterior end drive command neurons for "forward" motor neurons. These two pathways cross inhibit at the levels of command neurons and motor neurons. Adapted from de Bono & Maricq (2005), with permission.

evidence by selecting which receptors to express on its surface, collects the evidence, weighs it, judges if it warrants escape, and mandates the decision. The worm has several such sensory neurons, collecting other lines evidence for other actions.

Finding warmth, food, and mates

The worm seeks congenial places to feed, grow, and mate. *C. elegans* thrives and reproduces in a fairly narrow range of conditions: dim light,

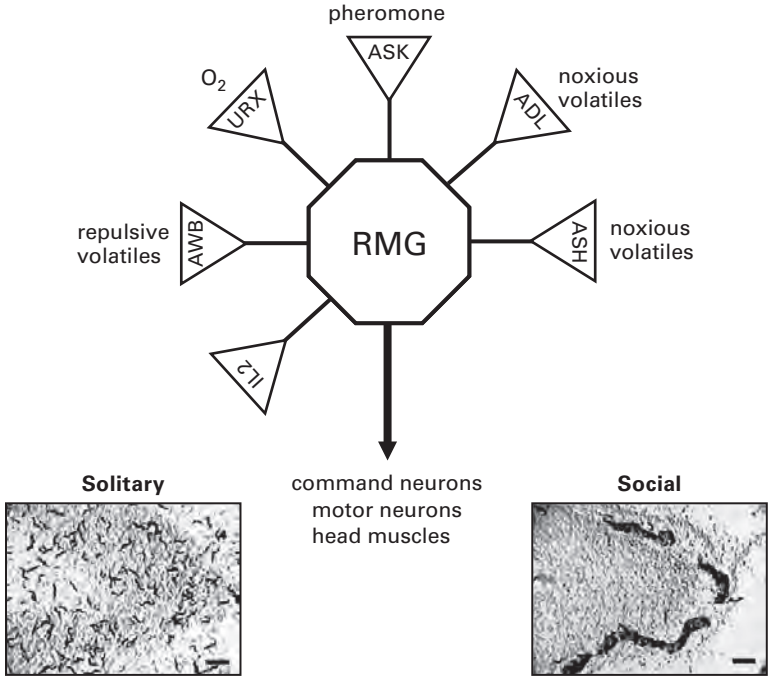

Figure 2.8

C. elegans. **Spoke and hub circuit controls solitary versus social behavior (dispersed vs. huddled). Upper**: The neuron RMG integrates social cues sensed by particular sensory neurons, ASK etc., and drives neurons that implement behavior. **Lower**: Social behavior. Solitary worms disperse and keep apart. Social worms huddle in groups. Each worm appears as a dark speck. Diagram adapted from Sokolowski (2010). Solitary and social worms from de Bono & Bargmann (1999), with permission.

moves leisurely up a promising chemical gradient, but a worm subjected to low oxygen for several hours ascends quickly. To change from stroll to rush, neuromodulators reconfigure the circuit for gradient ascent (Bargmann, 2012). For example, the sensors ADF and ASG respond to low oxygen by releasing another neuromodulator, serotonin.

Just as "carrot and stick" oversimplify human motivation, so it is for the worm. Competing for limited resources requires many factors to be weighed in deciding whether to roam or graze. A rich suite of neuromodulators allows the worm's brain of 302 neurons to evaluate contextual factors, such as nutritional status, food availability, crowding, and social signals, and then reconfigure accordingly.

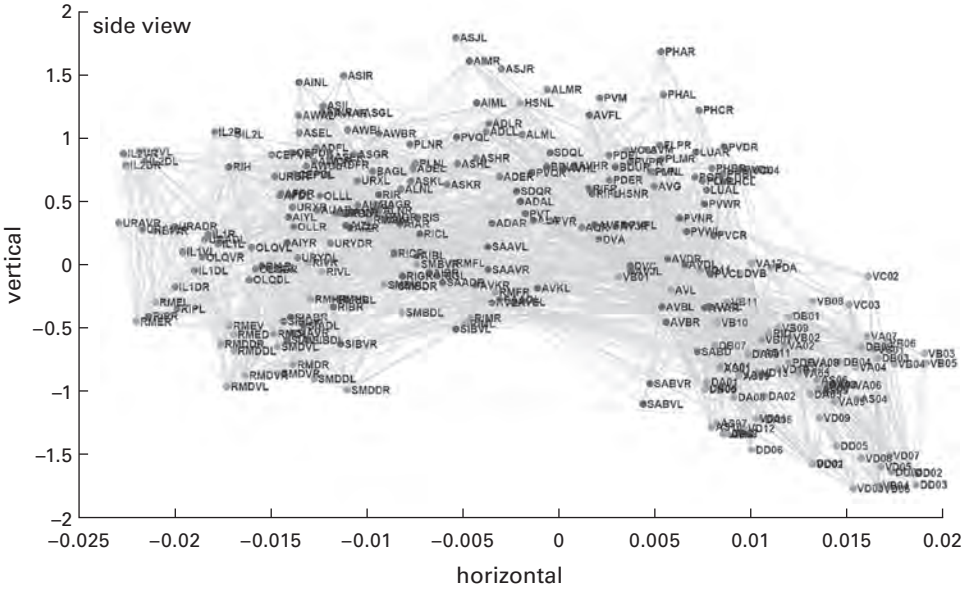

Figure 2.9

***C. elegans* connectome reconstructed from serial sections photographed in the electron microscope.** Each neuron is identified, and its synaptic connections are shown in gray. At the time of writing this is one of the most complete wiring diagrams established for any part of any brain (the other is the fly lamina cartridge, figures 9.2 and 9.3). Careful estimates suggest that this worm connectome is 93% accurate. Such are the technical difficulties of tracing neurons' thin connections that, after two decades of work on 302 neurons, 7% of connections are "missing." Reprinted with permission from Varshney et al. (2011).

that communicate most frequently with each other may be placed closer together to save energy and reduce conduction delays between them. Although layouts in larger brains certainly reflect this, conduction delay may be less relevant for *C. elegans* because the distances are so short, and the worm is so slow. "Short and slow" suggests another design feature.

Favors analogue over pulsatile

Because electrical signals in the worm travel less than a millimeter, neurons can conduct passively, as graded (analogue) changes in electrical potential. The brief, sharp, energy-intensive action potentials that dominate long-distance signaling in larger brains are unneeded, so the worm can rely solely on analogue computations, which are direct and energy efficient