

## 2 Why an Animal Needs a Brain

Essentially only one thing in life interests us: our psychical constitution. The considerations which I have placed before you employ a scientific method in the study of these highest manifestations in the dog, man's best friend.

—Ivan Pavlov, Nobel lecture, 1904 (edited for brevity)

Brain books generally begin at the lowest levels—neurons, axons, synapses, and ion channels. But that approach ill suits our goal of reverse engineering. One cannot explain a B-29 by starting with the nuts and bolts. So we postpone the parts lists and detailed schematics to consider first a larger question: why do we *need* a brain?

One's first thought, of course, is that we need it for the magical activities and feelings it confers: art, music, love . . . consciousness. But although these features arouse intense curiosity—as Pavlov emphasized—we shall see that they are merely baroque decorations on the brain's fundamental purpose and should not be mistaken for the purpose itself. What we identify here as the brain's purpose, especially because we are seeking principles, should apply not only to humans but as well to the nematode worm, *C. elegans*, and to flies. The deep purpose of the nematode's brain of 302 neurons, the fruit fly's brain of  $10^5$  neurons, and our own brain of  $10^{11}$  neurons (Azevedo et al., 2009) must be the same. By identifying the basic purpose, we set a context for later considering the “decorations.” We expect that research on the mammalian cerebral cortex will not reveal many new principles—rather it will elaborate the core ones. In general, it should be easier to discover them in simpler brains.

The brain's purposes reduce to regulating the internal milieu and helping the organism to survive and reproduce. All complex behavior and mental experience—work and play, music and art, politics and prayer—are but strategies to accomplish these functions. Sharing these fundamental tasks, the brains of worms, flies, and vertebrates show significant

similarities—which will be discussed. But first, consider that a tiny bacterium, *E. coli*, and a much larger single-celled protozoan, *Paramecium*, manage these two tasks quite well without a brain. How?

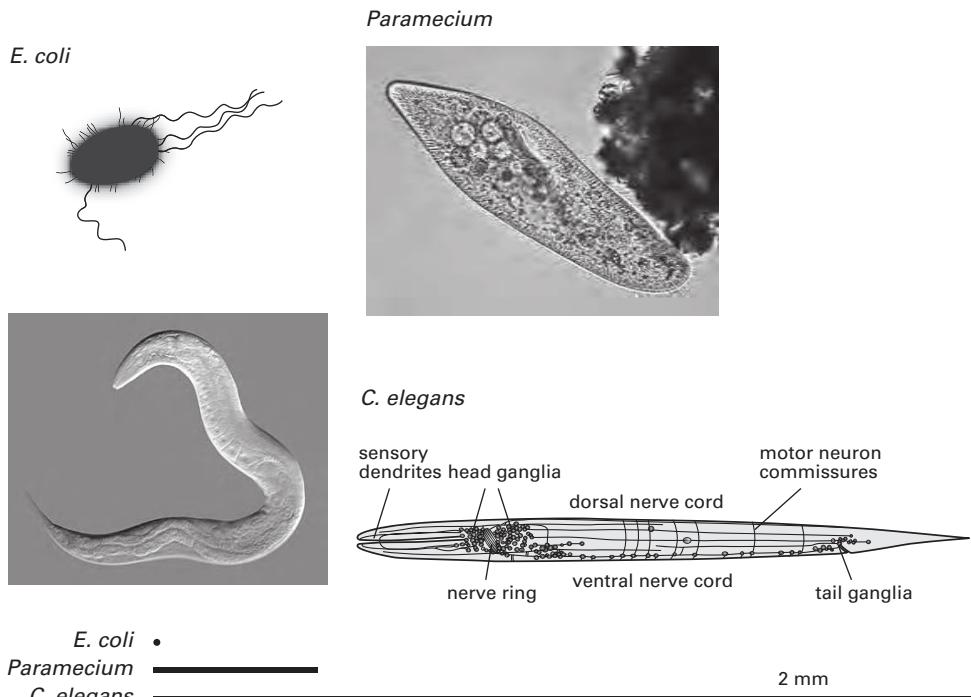
## Lives of the Brainless

### A bacterium foraging

*E. coli* is minuscule ( $1 \times 3 \mu\text{m}$ ) and thrives in a nutritive soup—adrift in the intestinal digests of a large animal (figure 2.1; Alberts et al., 2008). The microbe is equipped with “taste” receptors, a battery of proteins each of which specifically binds an attractant (such as an amino acid or sugar) or a repellent. These receptor proteins cluster on the surface membrane and form signaling complexes within which they cooperate to increase sensitivity and response speed. The largest cluster is at the forward end ready to taste what comes as the bacterium ploughs through the soup. Although each cluster comprises thousands of molecules—to increase the chance of catching a taste—there are only five types of receptor molecule, each responding to a range of related compounds.

The first function of these receptors is to evaluate the *soup du jour*. Each potential nutrient (amino acid, sugar, etc.) requires its own specific transporter (*permease*) for uptake into the bacterium, plus a particular enzyme or even a whole set of enzymes to process it for energy and materials for growth. It would be uneconomical to maintain high levels of all possible transporters and processing enzymes when only a subset is needed at a given moment. Therefore, a cell refrains from synthesizing proteins for uptake and digestion until a taste receptor binds the target molecule. A receptor’s binding affinity determines the concentration at which protein synthesis becomes economical.

For its default fuel *E. coli* uses glucose. But when glucose is off the menu, it can use lactose. This requires lactose detectors to call for two proteins: a permease to admit lactose and an enzyme, galactosidase, to split it. The genes coding these proteins are adjacent in *E. coli*’s DNA, comprising an *operon* (genes that work together). Their expression is blocked by a repressor protein that binds to this stretch of DNA and blocks the entry of RNA polymerase, the molecular machine that transcribes DNA to RNA (*RNA polymerase*) to initiate protein synthesis (figure 2.2). The repressor is the lactose detector which, upon binding allolactose (an isomer that always accompanies lactose) changes shape and releases from the DNA. This allows RNA polymerase to move off and transcribe the operon (figure 2.2; Phillips et al., 2009).



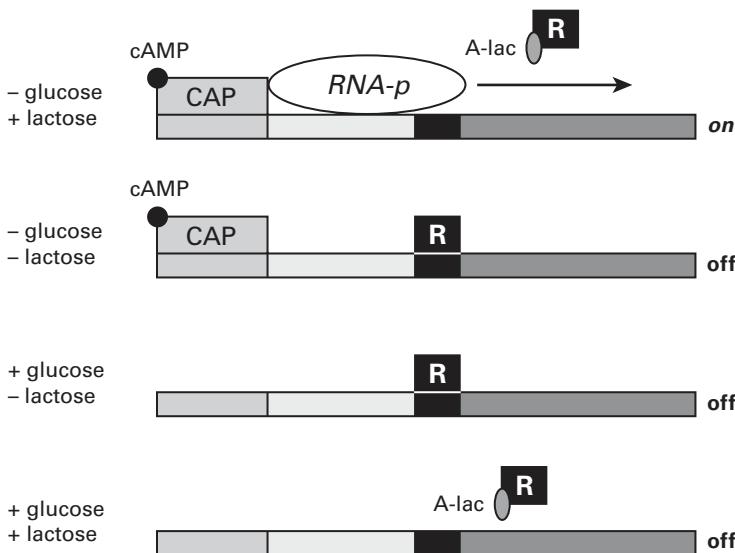
**Figure 2.1**

**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

network controlling the lac operon enables a single cell to detect specific patterns of events and to mount concerted patterns of response that promote survival and reproduction. Of course, this is what a brain does on a larger scale, and in doing so it builds upon the capacities for executing logic that reside in the molecular control systems of single cells (Bray, 2009).

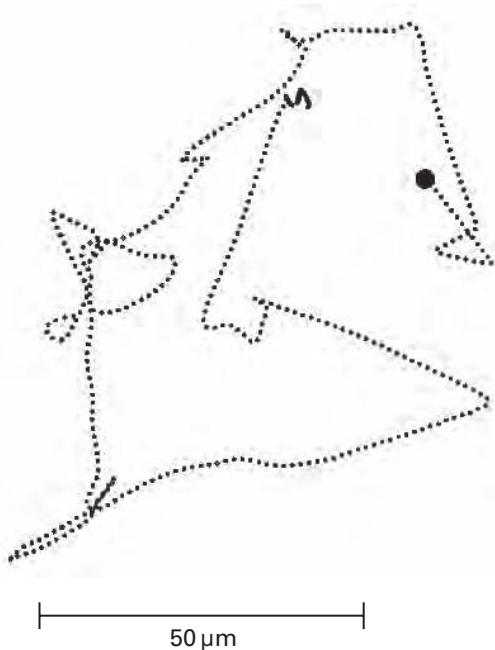
*E. coli* does more than just taste the soup and reprogram its digestive enzymes. The taste receptors also direct the cell to forage, that is, to discover and migrate to regions of higher nutrient concentration. To execute this process, *chemotaxis*, the bacterium propels itself with flagella, which are helical screws that rotate at 6,000 rpm. Their beating sends it tumbling off in random directions for brief periods, each followed by a short, straightish run. A surface receptor, sensing the instantaneous concentration of a nutrient, compares it to the past concentration—"past" lasting 1 s. If the new concentration is higher, the motor apparatus holds the forward course for a bit longer.

This search strategy (*biased random walk*, figure 2.3) resembles the party game where an object is hidden and a searcher is simply told "warmer . . . cooler . . . warmer, warmer . . ." The mechanism can sum signals from several attractants—maintaining the direction of motion for a longer time. Or, it can sum antagonistic signals (attractant + repellent) and change direction sooner. Thus, with a sensor, plus a "working memory" that controls a propeller, a microbe's wandering eventually delivers it to a greener pasture (Berg, 1993).

### A microbe's memory

*E. coli*'s working memory is simple: it is imprinted on the receptor protein by means of a negative feedback loop. The activated taste receptor causes an enzyme to attach methyl groups to the receptor complex, decreasing its sensitivity. The number of methyl groups on a receptor indicates how strongly it has been activated, and because the feedback loop is sluggish, the record stretches back into the bacterium's frantic past—1 s. The mechanism, by using the past to set receptor sensitivity, determines the bacterium's response in the present—a reasonable definition of memory. Thus, a single cell can store information cheaply through chemistry—by covalently modifying a signaling molecule.

In accomplishing the basics (preserve internal milieu and reproduce), this single cell uses mechanisms that are either optimal or highly economical: just the right number and distribution of taste receptors, just the right ratios of transporters and digestive enzymes, just the right levels of protein expression to match costs versus resources, plus the smallest signaling



**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  $\mu\text{m}/\text{s}$ . 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/](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.

### Limitations to life as a microbe

Given that bacteria accomplish the basics so well, one must consider the limitations. First, their ability to respond to environmental challenge resides largely in genetic memory. A *population* thrives by reproducing rapidly and exchanging genetic material—so that when the environment changes, at least one individual in the population will contain a gene to deal with it. Thus, a population can “learn” to exploit new resources—such as potentially delicious industrial waste. However, an individual microbe, suddenly losing glucose in a lactose-rich medium, can respond only if its genome already contains the lac operon.

Second, an individual microbe cannot actively move very far. It can neither return to the site of its last meal nor deliberately transfer to a new host. This confines each species of microbe to the restricted environment for which it has specialized: a termite’s gut or the skin of a human inner elbow (Grice et al., 2009)—where the bacterial genome is prepared for what it will likely encounter, and where surprises are relatively few. But this leaves a wider world unexplored and thus unexploited.

To explore would certainly increase the chances of encountering a more favorable medium—but there is a limiting challenge: size. For such a minuscule object, water is tremendously viscous. Top speed for *E. coli* is 30  $\mu\text{m}$  per second, and when its effort ceases, there is insufficient inertia to carry it forward, so it abruptly stops within 0.01 nm (chapter 5; Purcell, 1977; Nelson, 2008). For a human it would be like swimming in thick molasses—agonizingly slow and energetically expensive. Consequently, to move over long distances, bacteria have evolved other methods, for example, by being sticky and hitching rides on animals.

In short, a bacterium inhabits a tiny universe—barely a few centimeters—where the critical factors are beyond its control. When transportation relies on random, energetically expensive self-propulsion or the kindness of strangers, life is precarious. A cell that could propel itself more rapidly and cheaply could forage more widely, but to overcome the effects of Brownian buffeting and high viscosity it must enlarge. And it need not get very large before motor coordination becomes an issue—as we now explain.

### Protozoa: bigger and faster but still brainless

*Paramecium*, the familiar single-celled protozoan, measures up to 350  $\mu\text{m} \times 50 \mu\text{m}$ . Being 300,000-fold larger than *E. coli*, it is less subject to viscous forces. *Paramecium* propels itself with cilia that cover its surface and coordinate their beating to send synchronous waves from head to tail. Cruising

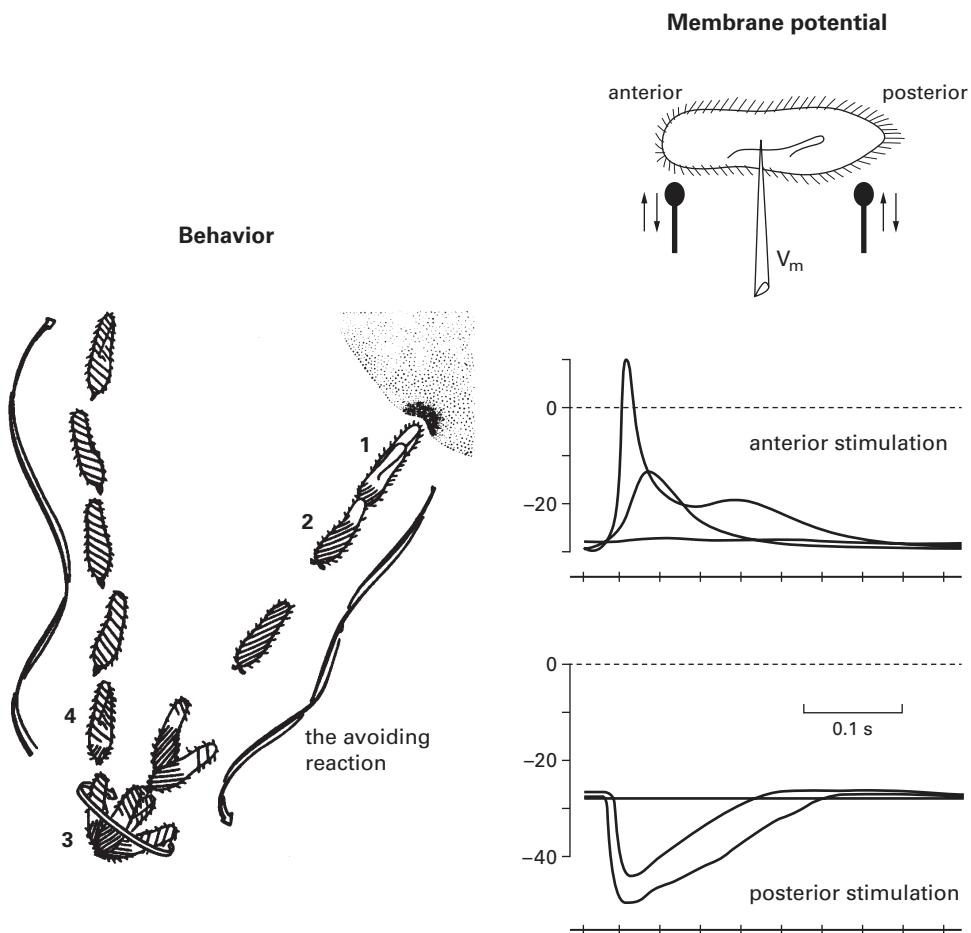
speed can reach roughly 1,400  $\mu\text{m}$  per second, 50-fold faster than *E. coli* and with lower relative energy cost. In human terms this is the difference between exploring on foot at 4 mph and racing a car at 200 mph. Consequently, *Paramecium* can explore relatively enormous volumes of pond water and harvest bacteria by sweeping them into its “mouth.” This microshark is guided by a variety of taste receptors to approach sites where bacteria proliferate, for example, clumps of rotting vegetation. It also has nociceptors to detect toxic sites, such as overripe sludge contaminated with hydrogen sulfide.

In its cluttered environment *Paramecium* inevitably encounters immovable obstacles, and to avoid the futility of continual ramming, *Paramecium* has evolved a useful response (figure 2.4; Jennings, 1904; Eckert, 1972). At the first bump it throws its cilia into reverse and backs off by a few millimeters. Then it does a quick twiddle, switches to forward, and sets off in a new direction. This avoidance response is fast—completed within a fraction of a second—and it has to be. Futile activity wastes time and energy; moreover, the immovable object might be a predator!

*E. coli*’s chemical signaling systems could not trigger and coordinate this rapid response. Diffusion suffices for *E. coli* because the distance is short—a small intracellular messenger molecule diffuses throughout the bacterium in about 4 ms. But diffusion time increases as the distance squared (Nelson, 2008), so for a *Paramecium* that is 100-fold longer than *E. coli*, diffusion from “head” to “tail” would be 10,000-fold slower, about 40 s. Obviously, this is far too slow for receptors at the head to call “Reverse!” to the tail cilia. Electrical signals spread much faster: a change in membrane voltage initiated at the head reaches the tail in milliseconds.

Electrical signaling for this avoidance response requires several new components. First, a mechanoreceptor is needed to detect the bump. This involves a specialized cation channel inserted into the cell membrane. Stretch on the membrane deforms the channel, opening it to sodium ions that rapidly depolarize the membrane ( $<100 \mu\text{s}$ ). Depolarization opens voltage-sensitive calcium channels that admit a rush of calcium ions—further depolarizing the membrane, opening still more calcium channels, and so on. This positive feedback produces a robust response that recruits calcium channels across the entire membrane (figure 2.4). They open briefly, then close and inactivate. Thus, the two components—stretch-gated sodium channel plus voltage-gated calcium channel—cooperate to deliver a synchronous pulse of calcium over the cell’s entire surface.

The reason to spread the electrical signal via a calcium channel, rather than a voltage-gated sodium channel (such as used by nerve and muscle), is

**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.

that a calcium ion can also serve intracellularly as a chemical messenger. In this case the chemical message arrives synchronously at the base of all cilia, saying “*Reverse beat*,” and their simultaneity adds power to the reversal. As *Paramecium* backs up, calcium pumps in the membrane vigorously reduce the calcium level, allowing patches of cilia to slip back into “forward”—explaining the indecisive twiddle. Once most of the calcium has been extruded and all cilia again beat forward, *Paramecium* heads off in a new direction (figure 2.4).

The system is polarized. The stretch channels are at the head, ensuring that the calcium pulse that reverses the cilia will also reverse the animal. The decision to reverse is structured as a simple threshold: when a bump is sharp enough, stretch channels open sufficiently to depolarize the membrane smartly enough to kick the calcium channels into their regenerative cycle. The numbers and sensitivities of stretch channels are adjusted to discriminate a truly immovable obstacle from a yielding one. Conceivably, they are even tuned by experience via the attachment of some chemical group as with *E. coli*’s working memory.

Finally, the twiddle that sets *Paramecium* off in a new direction occurs because some patches of cilia enter forward gear before others, perhaps by the molecular noise in calcium pumps (chapter 6). Whatever the exact mechanism, the twiddle generates a random direction—which is good. Lacking distance receptors, *Paramecium* cannot predict which search direction is most likely to be best, so random behavior is optimal (Reynolds & Rhodes, 2009). Also, random motion prevents a predator from predicting *Paramecium*’s next move, thus making it harder to catch.

### Where brains emerge

Despite the advantage of its fast control system for locomotion, *Paramecium*’s behavioral repertoire is limited. One impediment to richer behavior is that there is only one cell membrane and thus only one line for fast (electrical) communication. But more deeply, the cell is still so small that locomotion must be slow, and the environment remains so evanescent that richer behavior and longer memory offer no advantage. *Paramecium*’s exploitable world remains sufficiently restricted that one communication channel is plenty. Multicellularity can pay—but only when an animal becomes slightly larger and lives slightly longer in an environment where clues to food and danger persist.

The crossover—where multicellular animals arise and dominate (eat the unicellular)—occurs at a size of around 1 mm and a lifetime of days.<sup>1</sup> Then

cells specialize and associate to form tissues, tissues form systems, and systems cooperate to form a more versatile organism. Thus, multicellularity follows the engineering principle *complicate* (Glegg, 1969/2009a). The many tasks performed by a single cell are now divided among many specialized components. Naturally, coordination is required at each level (cell, tissue, organ, system, and organism) and across levels.

Coordination demands some mechanism with an overview that enables it to weigh alternatives, set priorities, and then exert ultimate authority to execute. Fortunately, the multicellular design that demands such integration also provides a special class of cells to accomplish it. These cells—neurons—now do what *Paramecium* could not: provide multiple fast lines for communication. In short, for a multicellular organism a brain becomes necessary, possible, and profitable.

### **Worm with tiny brain**

The nematode worm, *C. elegans*, measures about  $1 \times 0.1$  mm (figure 2.1) and in its predominant hermaphroditic form comprises exactly 959 somatic cells (Herman, 2006). It lives close to the soil surface and feeds on bacteria in rotting vegetable matter. Unlike *Paramecium*'s pond water chemicals in soil and humus are not swept away by convective currents—they move by diffusion and capillarity through a matrix, so traces persist (Félix & Braendle, 2010). The matrix and surface film provide firmer substrates for locomotion, and these allow the worm's sinuous crawl to open up whole new continents for exploitation.

The worm's enlarged territory and its locomotion through a labyrinthine matrix with persistent chemical traces warrant an upgrade. The worm improves the chemotaxis system and adds diverse sensors (of current state, opportunity, and danger), plus a larger repertoire of behavioral responses and a longer memory (de Bono & Maricq, 2005). Because bacteria-rich patches are oases where many species compete, the worm's success requires that it move smartly across a patch to efficiently find and exploit the productive regions, meet, mate, and lay eggs.

Improved foraging must be matched by more efficient systems for digestion, absorption, metabolic storage, and elimination. And as the behavioral repertoire expands, there is more need to evaluate and prioritize. For example, upon encountering a good hunting ground, how much heat or acidity should it tolerate? Upon encountering two chemical traces, which should it follow? When to search and when to graze? When to mate and when to be

stilled by “satisfaction”? In short many of the choices posed for humans by Ecclesiastes arise even for this apparently simple worm—which decides with its tiny brain.

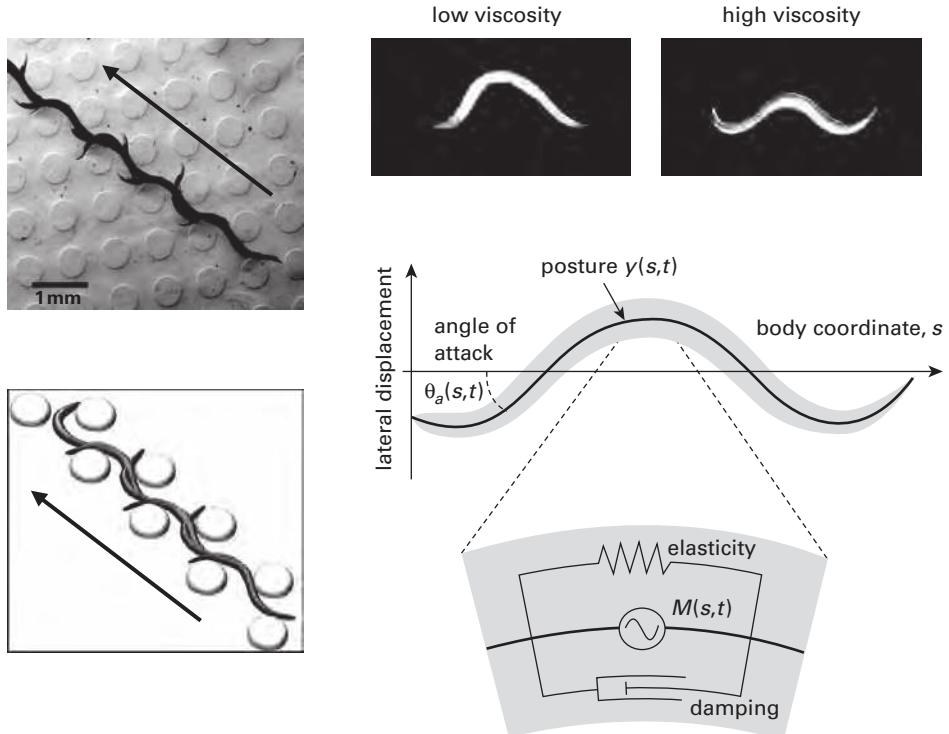
The worm’s brain may be small, but its 302 neurons plus 56 glial and support cells comprise nearly 40% of its body’s entire complement. The figure in humans is close to 1%. So we first consider some behavioral advantages that justify its immense investment. Then we consider the brain’s design, noting the features shared with larger brains that suggest they are governed by principles of neural design.

### Locomotion

Grazers must keep on the move. The worm moves forward by bending just behind the head and then propagating the bend toward the tail. Driven by this sinusoidal wave, it threads its way through soil and rotting vegetable matter, swims through pools of fluid, and crawls across moist surfaces (e.g., decaying fruits, agar plates in laboratories). A worm travels fastest when rigid objects are regularly spaced at 0.5 mm (figure 2.5), and if this spacing is changed by just 10%, their forward speed halves. A worm seems designed to cope best with the average particle size in its preferred habitat, like a pickup truck designed for rough roads (Park et al., 2008).

But *C. elegans* is both truck and driver, continually adapting its propulsion to cope with changing conditions. When the worm goes from swimming in a pool to crawling across a wet surface, the surface tension increases viscous forces 10,000-fold, and the worm adjusts its undulations accordingly (figure 2.5). Frequency falls tenfold, wavelength shortens threefold, and more muscular power is transferred to the viscous medium. The worm continuously adjusts its drive train over a wide range of conditions, maintaining the wave’s angle of attack at an efficient value, close to 45° (figure 2.5). To understand how, we must examine the integrated locomotor system: brain, muscles, body, and substrate.

A sequence of muscular contractions produces the moving wave (Sengupta & Samuel, 2009). Muscle cells on the upper side of the body contract to bow out the lower side, and when the upper cells relax, the body springs back, driven by an internal hydrostatic pressure of 0.5 atmospheres. The wave is propagated by sending two opposite bends along the body, one after the other (figure 2.6), and this sequence repeats at the frequency of undulation. When the head leads the tail, the wave moves down the worm, pushing it forward, and when the tail leads, the worm moves backward. The head also wags from side to side, and when the worm decides to

**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).

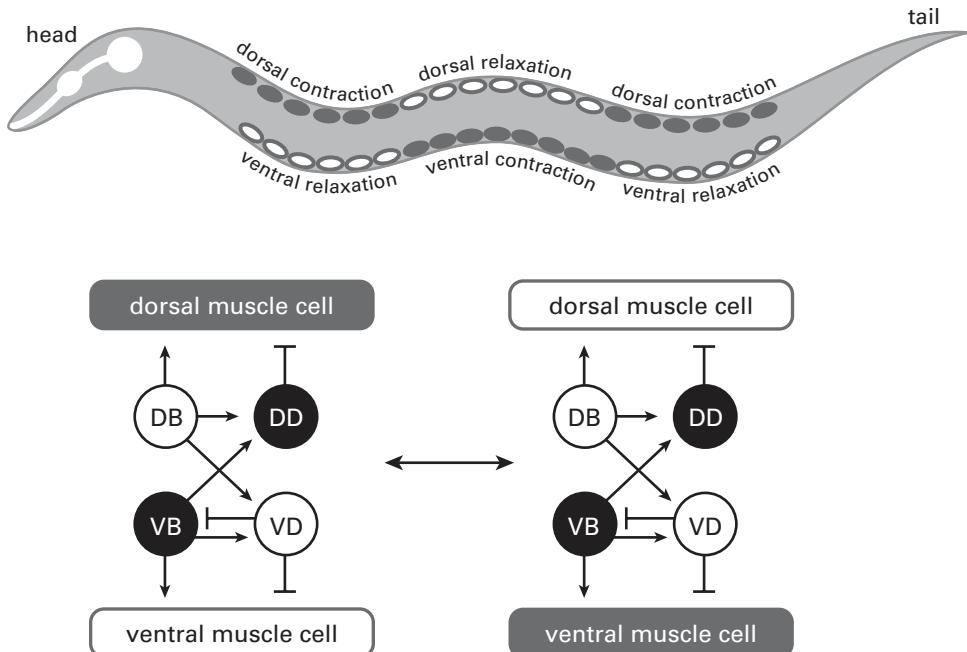
suddenly change direction, it bends the whole body and then springs back—a good tactic for evasion and escape.

These four distinct patterns (forward, reverse, wag, and turn) are produced by 75 motoneurons that control 95 muscle cells. Each muscle cell receives input from one excitatory and one inhibitory neuron which are activated in strict alternation (Bullock, Orkand, & Grinnell, 1977). To bend the head, an excitatory motor neuron on one side of the body activates a muscle, and an inhibitory motor neuron suppresses the corresponding muscle on the other side. To propagate the bend as a wave, motor neurons activate sequentially along the body. Their output frequency determines the frequency of the undulation, and their phase determines its waveform. Excitatory motoneurons on one side activate with inhibitory motoneurons on the opposite side and alternate with excitatory motor neurons on that side (figure 2.6). Where should one look for the oscillators that produce these cycles of motor neuron activity?

### Search for the oscillators

Early studies of animal locomotion were fraught with bitter argument about the origins of cyclical activity—such as stepping. Oscillations might be produced within the nervous system by local circuits (*central pattern generators*). Or they might be produced outside the nervous system by cycling sensory feedback (Marder & Bucher, 2001; Goulding, 2009). The feedback mechanism was proposed early for vertebrate stepping. One set of motor neurons excites muscles that extend the limb. This activates sensors that inhibit the extensor motor neurons and excite the flexor motor neurons, thus retracting the limb. Flexion activates sensors that inhibit the flexor motor neurons and excite the extensor neurons, and so on.

Many animals combine the two mechanisms. A central pattern generator sends cyclical commands to the motor neurons, and sensory feedback adjusts their phase, frequency, and amplitude to match changes in external load (Burrows, 1996). But the worm's circuitry seems not to use a central pattern generator. No intrinsically oscillating neurons have been found, nor does the brain's wiring diagram (see below) show the typical oscillatory circuit—a small group of neurons that send signals around a closed loop. Worms are capable of making central pattern generators—some of their cells use internal biochemical oscillators to control the rhythmical movements of ingestion, defecation, and copulation. That the worm can make central pattern generators but does not do so for locomotion suggests that it might have found a better way. Rather than relying on a pattern generator in its brain, the worm exploits its body.

**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.

So by using its biomechanics the worm can dispense with a central pattern generator, thus freeing up brain space. Here, then, is a useful design principle for motor systems: lighten the brain's load by using the body. Engineers call this *embodied computation* (also embodied intelligence or cognition; Pfeifer & Bongard, 2006).

In the early days of robots, crawling and stepping movements were generated by an all-powerful central computer—an omniscient central pattern generator. This artificial intelligence collected sensory information and fed it into a complicated program that, by modeling the robot's mechanics, worked out the necessary commands and sent them to slavish limbs. To implement this top-down design required the robot to drag around a heavy computer, which, in turn, meant thicker limbs and stronger actuators—the result, a power-hungry behemoth. It was eventually realized that the robot and its limbs *are* a computer, an analogue computer that runs its mechanics in real time (Brooks, 1990). This analogue computer comes for free and can be set up to process information for control by, for example, being part of an oscillator. This insight inspired a new generation of small, efficient, and adroit stepping machines that blew away the behemoths. Thus, the worm exemplifies embodied computation with a neuromechanical system that matches and integrates a few basic components to meet specifications efficiently.

### **Neural circuits coordinate patterns of movement**

Despite the contribution of body mechanics to the oscillator, neural circuits are still essential—they close the loop inside the worm. The neural circuits must be correctly configured and tuned to work with the biomechanics. Sensors must give the right feedback to motor neurons, and motor neurons must send the right signals to the right muscles with the right timing. Circuits are constructed to make this happen by ensuring that as muscles on one side of the body contract, the antagonistic muscles on the other side relax: motor neurons on one side inhibit the excitatory motor neurons for the antagonists and also excite their inhibitory motor neurons (figure 2.6). Here, then, is a circuit motif, *reciprocal inhibition* (Sherrington, 1906), that is widely employed in brains because it simply and effectively solves a common problem.

### **Changing direction**

The brain produces motor rhythms for “forward” and “backward” using two separate sets of motor neurons. Each set has its own circuit: one works with the biomechanics to send the undulatory wave head-to-tail and the

other works to send the wave tail-to-head. This is not a popular design. Most animals use a single set of motor neurons as the final common pathway for all commands to muscle. Using two independent sets, each with a full complement of connections and synapses to muscles, seems wasteful, so why does the worm do this? We speculate that for a small brain with neuromechanical oscillation, two sets of motor neurons are cheaper than a complicated central pattern generator.

### Directing action

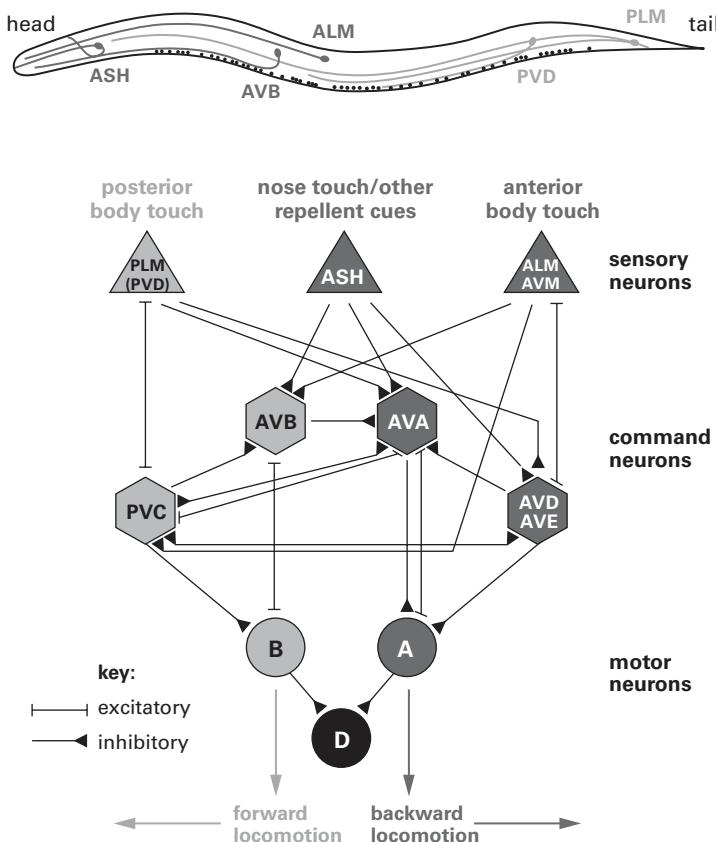
Like *E. coli* and *Paramecium*, the worm acts to improve its chances of completing its production on the ecological stage. Equipped to move further and faster, its costs are higher and the risks greater, but so are the opportunities and rewards. So the acts must be directed appropriately (de Bono & Maricq, 2005; Lockery, 2011).

The simplest acts are aversive responses, similar in purpose and effect to *Paramecium*'s avoidance response. Tap the worm's head, and it immediately wriggles backward; tap its tail, and it wriggles forward. Two simple circuits generate this behavior (figure 2.7). Mechanosensory neurons at the front drive interneurons that activate the "backward" set of motor neurons, and mechanosensory neurons at the rear drive interneurons that activate the "forward" set. The two sets have cross connections to prevent their working in opposition.

Just as the purpose of *E. coli*'s actions is laid out in chemical circuits in a single cell, so the purpose of the worm's behavior is laid out in the connections between neurons. Naturally a brain with many neurons can generate richer behavior because, by forming connections between cells, it makes more circuits. How has the worm's brain harnessed this potential and moved its behavior beyond the simple reactions of *E. coli* and *Paramecium*?

### Brain and behavior

Like the single-celled organisms the worm retreats from noxious chemicals, but its decision is more finely judged. A single sensor, the neuron labeled ASH in the brain's wiring diagram, controls this behavior by driving a "retreat" command interneuron, AVA, which shuts down the "forward" motor neurons and activates the "backward" motor neurons (figure 2.8). The sensor ASH expresses molecular receptors and detectors for a variety of potential threats, such as heavy metals, detergents, acids, or high temperature. Each input contributes to ASH activity, and when their sum suffices to trigger the command neuron, the worm backs off. Thus, a single neuron ASH serves as lawyer, jury, judge, and enforcer. It defines what constitutes



**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,

temperature 13°–25° C, oxygen concentration 7%–14%, moderate pH, ample bacteria, and so on. To find these conditions, the worm needs a signal to warn it of imminent departure from the range—“bacteria depleted,” “temperature dropping,” and so forth. This search signal activates forward crawl. Foraging now for bacteria by taste and smell, the first whiff activates gradient ascent. Upon reaching favorable conditions, the worm needs a stop signal to announce “satisfaction”—what was sought is found. This signal activates a sequence of turns that places the worm in graze mode. But the worm remains vigilant. If at any moment sensors for noxious conditions are activated, they suppress the forward movement and turning, and they activate reverse.

The worm retains *E. coli*'s basic strategy for moving up or down a gradient, the biased random walk. As conditions improve, the worm turns less and runs ahead more; as conditions worsen, it turns more and runs ahead less. The mechanism is also similar: molecular receptors that drive the forward run adapt, and the decay of their output signals allows a turn. Stronger signals decay more slowly, prolonging the run.

However, with multicellularity comes an advance: ascending the gradient with paired sensors. For salt, a sensor on the right side of the head is excited by *increasing* salt, and a sensor on the left side is excited by *decreasing* salt. The right sensor excites the “forward” circuit and inhibits turning. Once the worm finds the peak concentration, this cell falls silent. If the worm moves off the peak, the left cell, excited by decreasing salt, reduces forward motion and excites turning. This search pattern, brief forward motion followed by turning, continues until the concentration starts to rise again.

The worm uses head wagging to expose both sensors to new territory and combines this action with forward thrust. This exemplifies a motor output modulated by sensing. This system also provides a case where two communication channels collect *identical* information, by sensing the same gradient, but extract different patterns and use them to drive opposite motor responses. Here is something else that a brain offers—new forms of pattern recognition that improve foraging.

Improved sensing and control are needed because *C. elegans* is to *E. coli* as a supertanker is to a rowboat. To steer a whole organism in random directions with gradual correction works on a small scale, but on a larger scale it becomes wasteful. Better for the worm to be more discriminating, to search with its *head* and inform the body once a course can be plotted. In still larger animals the sensors themselves are motorized—an insect antenna, a cat external ear, a human eye (chapter 4).

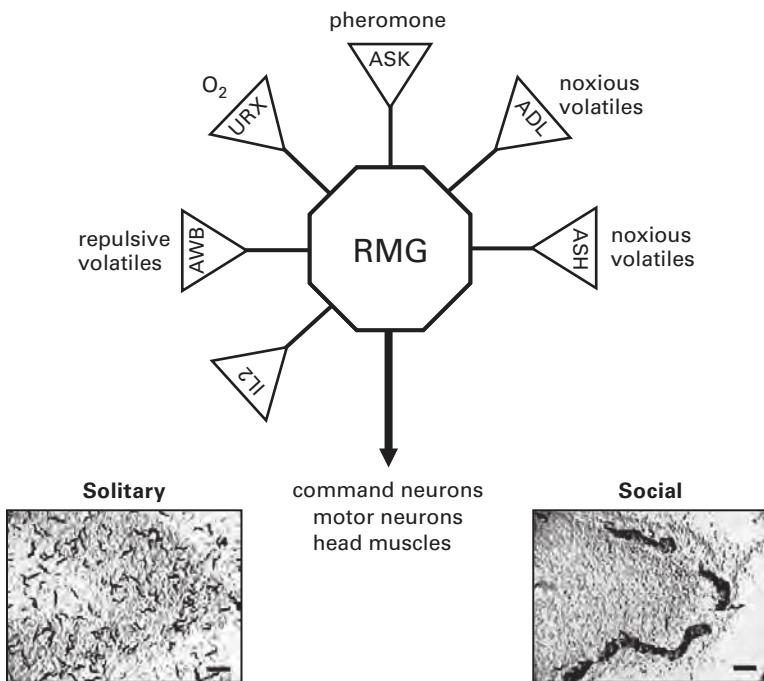
Because most worms use the same foraging circuits, they accumulate at the same sites—like undergraduates at a good café. And the subtext is similar: a place to feed is also a place to find mates. Moreover, the worms, unlike most undergraduates, are commonly hermaphroditic, so doubling their chances of a satisfying encounter. Even so, many worms enhance their attractiveness by releasing a pheromone to which intrinsically social worms are attracted. Movement toward the pheromone is controlled by a single neuron, RMG, a network hub that collects and integrates inputs from a suite of sensors and pheromones and drives the appropriate command interneurons (figure 2.8). A worm's degree of sociality is adjusted by a particular peptide released within the brain in response to changing conditions. The peptide, one member of a class of *neuromodulators*, binds to receptor proteins on specific neurons to change their activity—and hence behavior (Bargmann, 2012).

### Stick and carrot

When local conditions begin to deteriorate, some definite signal is needed for the worm to move on. One such signal is the neuromodulator, octopamine. When food reserves fall, certain neurons release octopamine, which binds to receptors on particular target neurons, modifying their excitability and changing their synapses. This inhibits turning and activates the forward motor pattern. Thus, a single agent, released in response to a change in conditions, acts on specific neurons to alter circuits and switch the worm's program from "graze" to "roam."

When food is found, roaming stops and grazing resumes. This involves a second neuromodulator, dopamine. In mammalian brain, dopamine signifies (among other things) that a reward has exceeded its expected value. In worm, dopamine is released by the presence of food when, for example, mechanosensors touch particles the size of bacteria. Dopamine binds to receptors on target neurons, turning off the octopamine receptors and restoring the circuit to its previous configuration. This switches the worm from roaming to collecting its food reward. Thus, two neuromodulators, octopamine and dopamine, provide this tiny brain with a primordial stick and a primordial carrot to mediate, as they do in larger brains, "anxious" searching and "pleasurable" repetition (de Bono & Maricq, 2005).

Imminent starvation is not the only stress. Others include low oxygen, high CO<sub>2</sub>, acidity and overcrowding. All suggest an exhausted patch—time to move on. As with humans, stress increases urgency. A comfortable worm



**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.

### Associative learning and memory

When life is good, the worm completes its life cycle (egg to egg) in 3.5 days and lives for several weeks. With a life span extending beyond the next mitotic cycle, allowing a past and a future, it now pays to recall what was good and what was bad. Far from living in the moment like *E. coli*, the worm uses its brain to associate events over time and thus draw on its experience (Ardiel & Rankin, 2010).

A worm remembers the temperature at which it was well fed and later seeks this temperature by moving up or down a thermal gradient. Finding the preferred temperature, it hangs there, searching along the isotherm. But dopamine decays promptly, so if the cupboard is bare, preference turns to aversion and the worm crawls off. Upon finding food and thus earning another shot of dopamine, the worm resets its temperature preference.

The mechanism for this learning resides within the thermal sensor that drives oriented crawling. This neuron senses changes of  $0.003^{\circ}\text{C}$ . Its response is minimal at the preferred temperature and rises on either side. The temperature for this minimum is reset by adjustments to the neuron's internal signaling; this requires protein synthesis and takes several hours. This learning process—chemical reprogramming within a single neuron—changes protein molecules but not synaptic connections.

Chemical preferences can also become associated with particular signals. For example, NaCl (salt) normally attracts worms, but when a worm has been starved in the presence of salt for only 10 minutes, it later avoids salt. A particular neuron downstream from the salt sensor releases another neuromodulator (insulin) that feeds back to an insulin receptor on the salt sensor to activate an internal signaling pathway (involving PIP3-kinase) to suppress attraction. Again, reprogramming a signaling pathway *within* a neuron allows experience to change the balance between attraction and repulsion. This mechanism also serves odorants. *C. elegans* even learns to avoid odorants from a particular pathogenic strain of bacteria that has made it sick.

These memory traces promote survival by extending the time over which an animal can identify and use patterns. The number of trials needed to establish an association is modest, five to ten repeats over 20 minutes. This makes sense in an environment where conditions are sufficiently shifty that to be useful, an association must establish rapidly and decay rapidly. In short, the worm's behavior demonstrates its reliance on information from three distinct sources: outside, inside, and the past. Its brain integrates these streams to select behaviors that, reflecting a wider context, improve the worm's vitality and reproductive success.

## Some design aspects of this tiny brain

*C. elegans'* brain may be small, but it is not simple. To achieve its panoply of behaviors, the worm draws on a large catalog of molecular parts. This includes diverse proteins for intracellular chemical and electrical signaling, plus numerous parts for processing information at synapses. For example, signaling proteins occupy 20% of the worm's genome, and its 300+ synaptic parts amount to one third the number for mammals (Emes et al., 2008). In fact the worm brain uses many of the same components present in larger brains. Since parts are shared, one might expect some design rules to be shared as well. If some rules were not shared, that would also be instructive, for it might suggest costs and benefits of scaling up.

Here then are some design features gleaned from considering the worm's brain and what they might imply for bigger brains.

### Computes as much as possible within a single cell

This feature is exemplified by the worm's *receptors* and their *sensors*. We distinguish these terms: "receptor" refers to an individual *protein molecule* that responds to a specific event—like stretch, temperature, protons, or chemical binding; "sensor" refers to an individual *neuron* that expresses one or more types of receptor. Although neuroscientists understand this difference perfectly well, for historical reasons they often use "receptor" for both the molecule and the neuron. We use different terms to reduce confusion for readers unfamiliar with the jargon, and also because they raise two design problems.

First, a single receptor molecule is subject to stochastic fluctuations, such as thermal noise. Therefore a neuron might need to improve the signal-to-noise ratio of signals conveyed by one receptor by averaging over a population of the same type. This raises the following design question: How many receptors of the same type should be expressed by each sensor? The answer will be given in chapter 6.

Second, receptors are more diverse than the sensor neurons that express them. Therefore, how should diverse receptor types be apportioned among sensors? For this problem *C. elegans* has a rule. If a set of receptors all lead to the same final action, they share a common sensor. For example, the sensor ASH collects signals from various types of receptor for noxious stimuli that require an aversive response; ASH couples its output to a single neuron that executes a command: *Scram!*

This rule explains receptor grouping generally. The worm uses more than 1,700 different types of receptor molecule for chemoreception (taste

and olfaction). This considerably exceeds the 800 or so used in mammals, but unlike mammals where each receptor type is typically assigned its own sensor, the worm provides only about 30 separate sensor neurons. Like sensors of noxious stimuli, each chemosensor sends its signal to a specific command neuron. So the signals from 1,700 different input channels (receptors for taste and olfaction) are assembled for action, not by circuits higher in the brain, but by a few dozen sensory neurons.

Computing *within* a cell economizes on neuron numbers. The worm meets all basic requirements for behavior (sensory pattern recognition, sensorimotor integration, and motor control) with small numbers of neurons. Thirty-eight sensors connect to 82 interneurons (whose processes are confined within the brain) that contact 119 motor neurons (cells whose processes leave the brain to contact the worm's 100 muscle cells). This reserves about 70 neurons for internal regulation and mating.

Yet there is a downside to performing several operations in a single cell. A cell's capacity to handle information is limited by factors such as internal noise, dynamic range, and energy supply. So a sensor that processes inputs from several types of receptor compromises its ability to handle the information from any one receptor type. A dedicated sensor can devote more receptors to its particular modality and thus improve sensitivity and signal-to-noise. This is the engineer's principle from chapter 1: to prevent one component from doing two tasks suboptimally, complicate.

Complication goes up the line. Better sensors warrant better sense organs: eyes for vision, ears for hearing, and so on. To benefit from these more accurate and discriminating sense organs, specialized sensory systems evolve in larger brains, each devoted to processing a single modality. The conclusion is obvious: as brains scale up to improve behavior, neurons specialize. Chapter 3 will suggest how and why, but now we consider a related question, how does a worm's tiny neuron manage to compute efficiently?

### Uses chemistry wherever possible

Many worm neurons use internal molecular circuits to perform functions that in larger brains use a circuit of several neurons. For example, a single sensory neuron, AFD, determines the worm's temperature preference by adding new proteins to its intracellular signaling network. Another neuron, AWC<sup>ON</sup>, changes a behavioral response to suit the situation. When an odorant is present *without* food, AWC<sup>ON</sup>'s molecular receptors adapt and chemotaxis declines. However, when the same odorant is present *with* food, its receptors are sensitized, and chemotaxis increases (de Bono & Maricq, 2005). These competing responses are controlled by an intracellular

mechanism that switches the connection between sensor and behavioral output to reverse the control of chemotactic turning behavior (Pereira & van der Kooy, 2012).

These examples show that chemical computing by circuits *within* a neuron can manage behavior. Moreover, this can be very efficient because chemical signals are orders of magnitude cheaper than electrical signals (chapters 5 and 6). Chemical diffusion is slow for long distances, but the worm *is* small and slow. Thus, the worm's size and speed well suit its reliance on cheap chemical signaling. In addition, chemical signals can be broadcast to specific targets, which brings us to another design feature.

### Uses neuromodulators to switch behaviors

Three neuromodulators were mentioned (octopamine, serotonin, and dopamine) that switch the worm's behavior in response to stress or the prospect of reward. But this is just page one from the parts catalog since the worm expresses 250 small peptides with known neuromodulatory functions. Their diversity and ubiquity is understandable because neuromodulation is so ingenious (Harris-Warrick & Marder, 1991). A neuromodulator can be broadcast widely yet still act locally and specifically, affecting only neurons that express an appropriate receptor. The receptors often couple to a protein that modulates intracellular signaling, so in effect a neuromodulator uses *transcellular* chemistry to modulate *intracellular* chemistry.

A neuromodulator's reach is further enhanced because its receptor diversifies into multiple subtypes that couple to different intracellular signaling networks. Consequently, one small molecule can retune and reconfigure a whole neural circuit without altering the anatomical connections. This allows every circuit to always be doing something and then to be recruited for something else as required. Thus, neuromodulators allow the brain to use components to their fullest.

### Conserves synapses

The worm brain makes only about 6,400 chemical synapses. This is roughly the number that in a mammal contact a single retinal ganglion cell or a single cortical pyramidal cell. How can a worm operate with so few synapses? The neurons are far smaller and therefore can be driven by fewer synapses. But since a single synapse is unreliable, how can so few synapses signal reliably?

One answer is: *slowly*—a neuron can improve reliability by averaging over time. This can be tolerated because, compared to many animals, the worm lives in the slow lane. For example, its olfactory sensor uses a

chemical amplifier, a G protein signaling cascade that integrates for more than 20 s (chapter 5, figure 5.6). This sensor drives a synapse that integrates over several minutes. By comparison, a fly's olfactory system acts in less than 1 s. Locomotor waves descend the worm's body at 1 Hz, but an insect moves its legs faster than 10 Hz. So the worm can prosper with few synapses because it is slow. This suggests another feature: *send information as slowly as possible* because this uses fewer synapses, smaller cells, and less energy. Later chapters explain more.

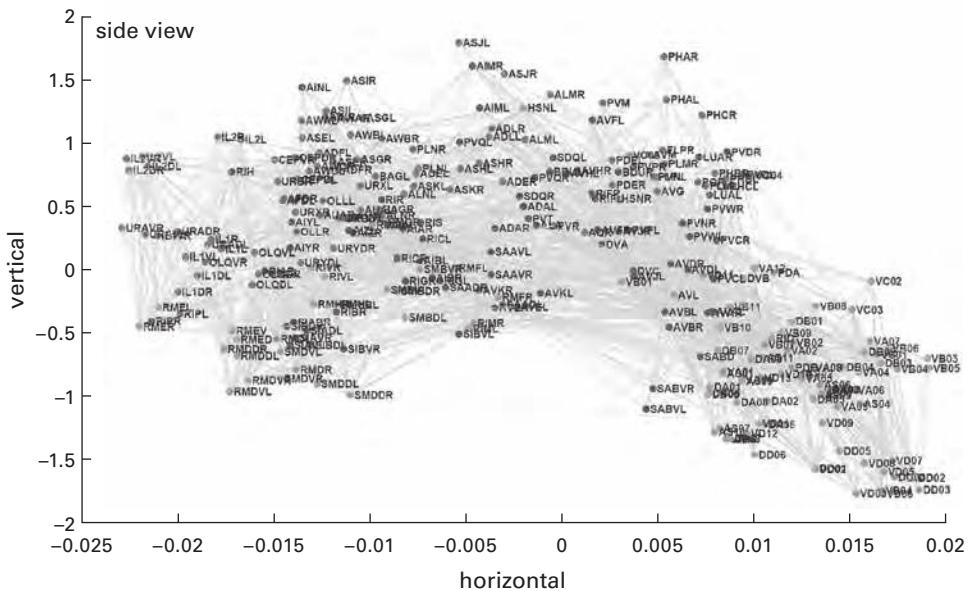
### Uses stereotyped components

Efficient design gives every component a definite task. Once all components are optimized for their tasks and optimally fitted together, it is efficient to repeat them across individuals. Similarly, every neuron in *C. elegans* has a definite role optimized by natural selection to meet a specified level of performance. Correspondingly every neuron is "identified," meaning that it exhibits a stereotyped morphology, chemistry, and location in every animal (White et al., 1986). The circuits are also identified, meaning that the synaptic connections are essentially identical across animals. This was established by reconstructing the entire nervous system from thousands of electron micrographs of serial sections—to produce the worm's *connectome* (figure 2.9). Identified neurons and circuits are consistently found in small brains: worm and water flea, leech and lobster, and so on.

### Minimizes wiring costs

The layout of *C. elegans'* neural wiring suggests that all 302 neurons are located as near as possible to the sites where they are needed (Varshney et al., 2011). Chemical and thermal sensors concentrate at the head; tactile sensors that guide locomotion distribute along the body axis; motor neurons that propel the worm forward distribute along the rear half of the body, and motor neurons for reverse locomotion distribute along the front half (figure 2.6). But does the layout approach the optimum sought by chip designers—the unique set of placements that minimizes the total length of connections in the brain?

Designers of silicon chips have developed algorithms to optimize component placement. Their rule: place the most densely interconnected components close together and the more sparsely connected components further apart (figure 2.9). This algorithm applied to the worm's brain shows that 90% of neurons are optimally positioned (Cherniak, 1995; Chen et al., 2006; Pérez-Escudero & de Polavieja, 2007). The 10% of neurons not in their optimal position suggests competing needs. For example, neurons

**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

(Sarpeshkar, 1998). Even its motor neurons operate in analogue mode. Over these short distances, analogue signaling transmits more information per neuron and at lower cost (chapter 7). So firmly does *C. elegans* hold to this feature that it has abandoned the gene that encodes the voltage-gated sodium channel used by larger, faster species to produce spikes.

### Conclusions

Three organisms of ascending size, *E. coli*, *Paramecium*, and *C. elegans*, show why an animal needs a brain to process information on a larger scale. It is to increase opportunities for survival and reproduction in a competitive and variable environment.

The small single cell, *E. coli*, survives with surface receptors that relay information to the internal chemical signaling networks that determine metabolism, growth, reproduction, and movement. However, *E. coli* is a mere speck in space and time with most opportunities beyond its reach. A larger cell, *Paramecium*, moving more briskly travels farther, expanding opportunities, but is ultimately limited by its chemical signaling networks—diffusion and internal communication by intracellular motors are both too slow. Voltage-gated ion channels added to the cell membrane allow fast electrical signaling, but trapped in a viscous world, a single cell can only do so much.

The multicellular worm, *C. elegans*, overcomes viscosity by enlarging, and it moves faster and farther by specializing cells. This leads it to more opportunities and dangers—richer sources of information to be gathered and processed that finally need a brain. The key innovation is the neuron, a cell type specialized to collect, process, and communicate. Each neuron links its rich web of internal chemical communication to the electrical network at the surface membrane and thence to other neurons via synapses. Neuromodulators retune selected neurons to reconfigure whole circuits. Thus, a brain of only 302 neurons extends the worm's horizon by providing a behavioral repertoire that adapts to changing contexts.

The worm accomplishes the same tasks as a bacterium or protozoan—finds growth conditions and mates while avoiding unproductive or toxic sites. And it does so with similar behaviors, such as gradient ascent by biased random walk and avoidance. But with its brain *C. elegans* can cover more territory, and with its longer lifespan (weeks instead of minutes), it can adapt to nasty surprises as an *individual* rather than as a minuscule part of an adapting *population*.

Here emerges another design principle. Life span and lifestyle are related to the appearance of particular types of memory and particular decay times. Nothing should be remembered that is unlikely to enhance survival and reproduction. Nor should memories exceed the typical time constants of useful correlations—because when correlations decay, memory ceases to predict anything useful. But it *is* useful to establish the memory trace rapidly before it is outdated—and that seems to occur—few trials, closely spaced. This suggests that the longest and deepest human memories are not mere decoration but serve to shape character over a lifetime, promoting survival in our complex social fabric (chapter 14).

Finally, given that *C. elegans* does so well with only 302 neurons, one might look critically at an assumed truth—that it is better to have a bigger brain. So why *have* animals evolved still bigger brains?