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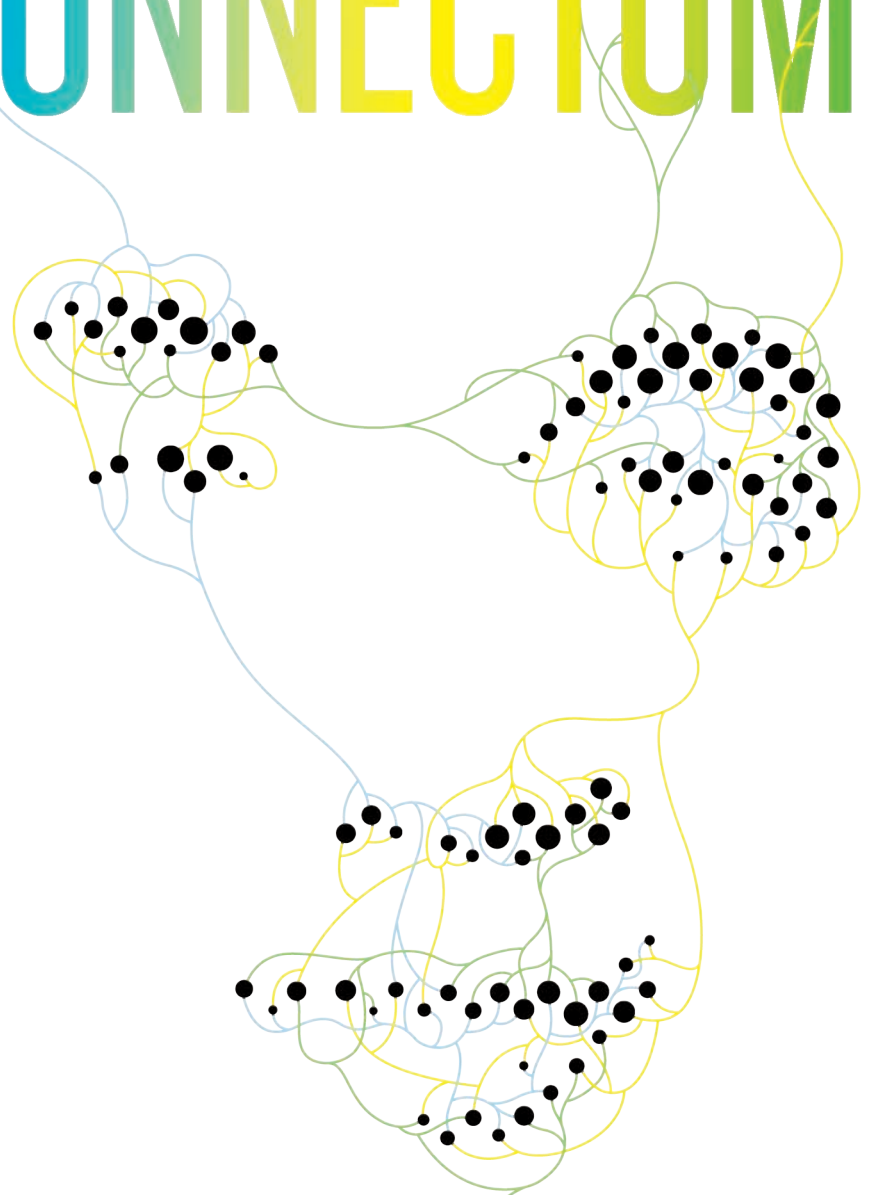

How the Brain's Wiring Makes Us Who We Are

SEBASTIAN SEUNG

THREE

No Neuron Is an Island

THE NEURON IS my second-favorite cell. It's a close runner-up to my favorite: sperm. If you have never looked into a microscope to see sperm swimming furiously, grab your favorite biologist by the lapels of his or her lab coat and demand a viewing session. Gasp at the urgency of their mission. Mourn their imminent death. Marvel at life stripped down to its bare essentials. Like a traveler with a single small suitcase, a sperm carries little. There are mitochondria, the microscopic power plants that drive the whipping motion of its tail. And there is DNA, the molecule that carries the blueprint of life. No hair, no eyes, no heart, no brain — nothing extraneous comes along for the ride. Just the information, please, written in DNA with the four-letter alphabet A, C, G, and T.

If your biologist friend is still game, ask to see a neuron. Sperm impress by their unceasing motion, but a neuron takes your breath away with its beautiful shape. Like a typical cell, a neuron has a boring round part, which contains its nucleus and DNA. But this *cell body* is only a small part of the picture. From it extend long, narrow branches

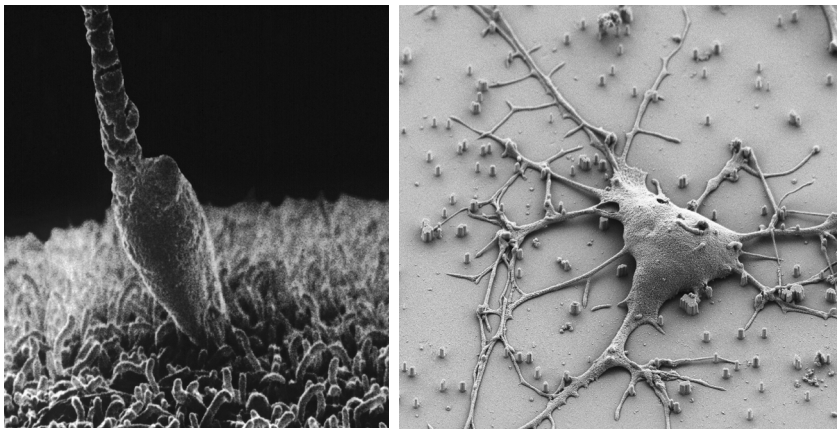

FIGURE 13. *My favorite cells: sperm fertilizing an egg* (left) *and a neuron* (right)

that fork over and over, much like a tree. Sperm are sleek and minimalist, but neurons are baroque and ornate (see Figure 13).

Even in a crowd of 100 million, a sperm swims alone. At most one will achieve its mission of fertilizing the egg. The competition is winner take all. When one sperm succeeds, the egg changes its surface, creating a barrier that prevents other sperm from entering. Whether brought together by a happy marriage or a sordid affair, sperm and egg form a monogamous couple.

No neuron is an island. Neurons are polyamorous. Each embraces thousands of others as their branches entangle like spaghetti. Neurons form a tightly interconnected network.

The sperm and the neuron symbolize two great mysteries: life and intelligence. Biologists would like to know how the sperm's precious cargo of DNA encodes half the information required for a human being. Neuroscientists would like to know how a vast network of neurons can think, feel, remember, and perceive — in short, how the brain generates the remarkable phenomena of the mind.

The body may be extraordinary, yet the brain reigns supreme in its mystery. The heart's pumping of blood and the lung's intake of air remind us of the plumbing in our houses. They may be complex, but they do not seem mysterious. Thoughts and emotions are different. Can we really understand them as the workings of the brain?

A journey of a thousand miles begins with a single step. To understand the brain, why not start with its cells? While a neuron may be a kind of cell, it is far more complex than any other. This is most obvious from its profuse branches. Even after many years of studying neurons, I am still thrilled by their majestic forms. I'm reminded of the mightiest tree on earth, the California redwood. Hiking in Muir Woods, or other redwood forests on the Pacific coast of North America, is a good way to feel small. You see trees that live for centuries or even millennia, enough time to grow to vertiginous heights.

Am I overreaching to compare a neuron to the towering redwood? In absolute size, yes, but consider further how these wonders of nature stack up against each other. The redwood's twigs are as thin as one millimeter, a width 100,000 times smaller than the tree's football-field height. A branch of a neuron, called a *neurite,* can extend from one side of the brain to the other, yet can also narrow to 0.1 micrometer in diameter. These dimensions differ by a factor of one *million.* In its relative proportions, a neuron puts a redwood to shame.

But why do neurons have neurites? And why do they branch to look like trees? In the case of a redwood, the reason for branches is obvious: The redwood's crown captures light, which is a source of energy. A passing sunbeam will almost surely collide with a leaf rather than travel all the way to the ground. Likewise, a neuron is shaped to capture contacts. If a neurite passes through the branches of another neuron, it will likely collide with one of them. Just as a redwood "wants" to be struck by light, a neuron "wants" to be touched by other neurons.

Every time we shake hands, caress a baby, or make love, we may be reminded that human life depends on physical contact. But why do neurons touch? Suppose that the sight of a snake causes you to turn and run. You respond because your eyes are able to communicate a message to your legs: *Move!* That message is conveyed by neurons, but how?

Neurites are much more densely packed than the branches of a forest or even a tropical jungle. Think instead of a plate of spaghetti — or

microscopically fine capellini. Neurites entangle much like the jumbled strands on your plate, allowing one neuron to touch many others. Where two neurons touch, there can be a structure called a *synapse,* a junction through which the neurons communicate.

But contact alone does not make a synapse, which most commonly transmits chemical messages. A molecule known as a *neurotransmitter* is secreted by the sending neuron and sensed by the receiving neuron. Secretion and sensing are performed by still other types of molecules. The presence of such molecular "machinery" signifies that a contact point is actually a synapse, as opposed to a place where one neurite just goes past another.

These telltale signs are blurred in an ordinary microscope, which uses light to make images, but show up nicely with a more advanced microscope based on electrons rather than light. The image shown in Figure 14 is a highly magnified (100,000×) view of a cut through brain tissue. There are two large, round cross-sections of neurites (marked "ax" and "sp"). These are like the cut ends of strands that would be exposed if you sliced through spaghetti. The arrow points to a synapse between the neurites, which are separated by a narrow cleft. Now we see that the term *contact point* is not entirely accurate, as the neurites come extremely close to each other but do not really touch.

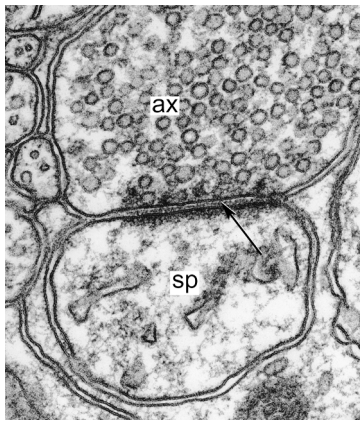

FIGURE 14. *A synapse in the cerebellum*

On either side of the cleft is the molecular machinery for sending and receiving messages. One side is dotted with many little circles, tiny bags called vesicles that store neurotransmitter molecules ready for use. On the other side the membrane holds a dark fuzz called the *postsynaptic density,* which contains molecules known as *receptors.*

How does this machinery transmit a chemical message? The sender secretes by dumping the contents of one or more vesicles into the cleft. The neurotransmitter molecules spread out in the salty water there. They are sensed by the receiver when they encounter receptor molecules embedded in the postsynaptic density.

Many types of molecule are used as neurotransmitters. Each is assembled from atoms bonded to each other, as in the examples shown in Figure 15. (In these "ball-and-stick" models, each ball represents an atom and each stick a chemical bond.) You can see that each type of neurotransmitter has a characteristic shape determined by the specific arrangement of its atoms, a fact that will become important shortly.

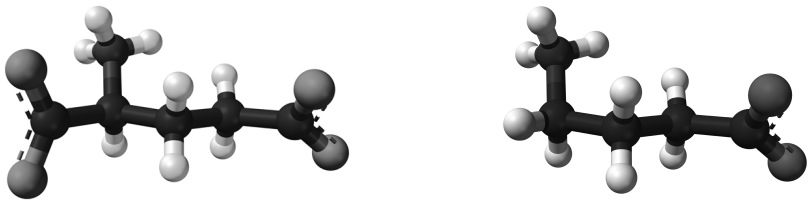

FIGURE 15. *"Ball-and-stick" models of neurotransmitters: glutamate* (left) *and GABA* (right)

On the left is the most common one, glutamate. This is best known to the public in the form of monosodium glutamate (MSG), which is used as a flavor enhancer in Chinese and other Asian cuisines. Few realize that glutamate also plays a crucial role in brain function. Shown on the right is the second most common, gamma-aminobutyric acid, or GABA for short.

More than one hundred neurotransmitters have been discovered so far. The list sounds long. Do you ever feel overwhelmed in the liquor store, when you see the shelves stocked with so many brands of beer

and wine? If you're a creature of habit, you might buy the same one or two brands every time and serve them to your friends at every party you give. That's what neurons do. With few exceptions, a neuron secretes the same small set of neurotransmitters — often only a single neurotransmitter — at all of its synapses. (The synapses in question are those made by a neuron onto others, not those received by a neuron.)

Now let's consider receptor molecules, which are much larger and more complex than neurotransmitters. Part of each molecule sticks out from the surface of the neuron, like the head and arms of a kid using an inner tube to float on water. This protrusion is the part of the receptor that senses neurotransmitter.

A glutamate receptor senses glutamate but ignores GABA and other neurotransmitters. Likewise, a GABA receptor senses GABA but ignores other molecules. Where does this specificity come from? Think of a receptor as a lock and the neurotransmitter as a key. As we saw above, each type of neurotransmitter has a distinctive molecular shape, which is like the pattern of bumps and grooves on a key. Every type of receptor has a location called the binding site, which has a characteristic shape like the innards of a hole in a lock. If the shape of the neurotransmitter matches that of the binding site, it activates the receptor, much as the right key in the right lock opens a door.

Once you know that the brain uses chemical signals, it's no longer surprising that drugs can alter the mind. A drug is a molecule too, and can be shaped like a neurotransmitter. If the mimicry is faithful enough, the drug will activate receptors, much as a copy of a key can open the same lock as the original. Nicotine, the addictive chemical in cigarettes, activates receptors for the neurotransmitter called acetylcholine. Other drugs inactivate receptors, much as an inaccurate copy of a key might turn partially and jam the lock. Phencyclidine or PCP, known on the street as "angel dust" in honor of its recreational use for hallucinogenic effects, inactivates glutamate receptors.

It's worth pausing to consider how we usually perceive secretions. Spit. Sweat. Urine. We suppress the urge to expectorate in polite company, plug glands with antiperspirants, and flush toilets in quiet pri-

vacy. We are embarrassed by secretions, reminders of our flesh and blood. Surely they live in a world apart from entities as ethereal and refined as our thoughts. But the truth is more shocking: The mind depends on an untold number of microscopic emissions. The brain secretes thoughts!

It may seem strange that neurons communicate with chemicals, but we humans do it too. Granted, we rely much more on language or facial expressions. But occasionally we signal each other with smells. While the message of aftershave or perfume is open to interpretation, something along the lines of "I'm sexy" or "Come hither" is a safe guess. Other animals don't have to purchase smell in a bottle. A female dog in heat naturally secretes a chemical signal called a pheromone, which wafts through the neighborhood to bring droves of male dogs by their noses.

Such chemical messages express desire more primitively than Shakespeare's love sonnets. Then again, so do poems that start with "Roses are red, violets are blue." We should distinguish between the medium and the message. Is there something fundamentally primitive about chemical signals as a medium for communication? There are indeed several limitations, but the brain has found a way to circumvent all of them.

Chemical signals are typically slow. If a woman walks into a room, you will usually hear her footsteps and see her clothing well before you catch a whiff of her perfume. A draft in the room might blow the scent toward you more rapidly, but it will still arrive more slowly than sound and light. Nervous systems, however, generate speedy reactions. When you suddenly jump away from a car piloted by a reckless driver, your neurons signal each other quickly. How can they accomplish this with chemical messages? Think of it this way: Even the slowest runner can finish a race in the blink of an eye if the racetrack is just a few strides long. Though chemical signals may move slowly, the distance that they have to travel across the synaptic cleft is extremely short.

Chemical signals also seem crude because it is difficult to send them to specific targets. All the partygoers surrounding a woman can smell

her perfume. Wouldn't it be more romantic if her fragrance could be sensed only by her beloved? Alas, no inventor has managed to create a scent that is focused in this way. So what keeps the chemical messages at one synapse from spreading like perfume and being sensed by others? The answer is that a synapse "recycles" neurotransmitter by sucking it back up, or degrading it into an inert form, leaving the molecules with little chance to wander. It's no trivial matter for the nervous system to minimize crosstalk — as engineers call the spreading phenomenon — because synapses are packed so close to each other. With a billion synapses to a cubic millimeter, the brain is far more crowded than Manhattan, and that island's residents often complain about hearing conversations (and much else) from each other's apartments.

Finally, the timing of chemical signals is not easily controlled. A woman's perfume may linger in a room long after she has left the party. The dawdling of neurotransmitter is averted by the same mechanisms of recycling and degradation that squelch crosstalk. This allows chemical messages between neurons to occur at precise times.

These properties of synaptic communication — speed, specificity, and temporal precision — are not shared by other types of chemical communication inside your body. After you jump away from the car in the street, your heart races, you breathe heavily, and your blood pressure skyrockets. This is because your adrenal gland secreted adrenaline into your bloodstream, which was sensed by cells in your heart, lungs, and blood vessels. The reactions of the "adrenaline rush" may seem immediate, but actually they are tardy. They happened *after* you jumped away from the car, because adrenaline spreads through your bloodstream more slowly than signals jump from neuron to neuron.

Secretion of hormones into the blood is the most indiscriminate type of communication, called broadcasting. Just as a television show is received by many households, and a perfume by everyone in a room, a hormone is sensed by many cells in many organs. In contrast, communication at a synapse is restricted to the two neurons involved, just as a telephone call connects the two people on the line. Such point-to-point communication is much more specific than broadcasting.

In addition to chemical signals between neurons, there are also

electrical signals in the brain. These travel *within* neurons. Neurites contain salty water rather than metal, but they nonetheless resemble, in both form and function, the telecom wires that crisscross the planet. Electrical signals can travel long distances by propagating through neurites, much as they move along wires. (Interestingly, the mathematical equations developed by Lord Kelvin in the nineteenth century to describe electrical signals in undersea telegraph cables have been used in the modeling of neurites.)

In 1976 the legendary engineer Seymour Cray unveiled one of the most famous supercomputers in history, the Cray-1 (see Figure 16). Some called it the "world's most expensive loveseat," and indeed its sleek exterior could have graced the living room of a 1970s playboy. Its interior was anything but sleek, containing 67 miles of tangled wire in lengths spanning 1 to 4 feet. This looked like a chaotic mess to the casual observer, but actually it was highly ordered. Every wire transmitted information between a specific pair of points chosen by Cray and his design team from locations on thousands of "circuit boards" holding silicon chips. As is common in electronic devices, the wires were wrapped with insulating material to prevent crosstalk.

You may think the Cray-1 looks complex, but it's laughably simple compared with your brain. Consider that *millions* of miles of gossamer neurites are packed inside your skull, and they are branched rather than straight like wires. The tangle in your brain is far worse than that of the Cray-1. Nevertheless, the electrical signals in different

FIGURE 16. *The Cray-1 supercomputer, exterior* (left) *and interior* (right)

neurites — even adjacent ones — interfere with each other very little, just as in insulated wires. Transmission of signals between neurites occurs only at specific points, those junctions called synapses. Similarly, signals cross from one wire to another in the Cray-1 only at locations where the insulation is removed and the metals come directly into contact.

I've spoken of neurites generically up to now, but many neurons have two types of neurite — dendrites and axon. The dendrites are shorter and thicker. Several emanate from the cell body and branch in its vicinity. A single axon, long and thin, travels far from the cell body and branches out at its destination.

Dendrites and axons not only look different but play different roles in chemical signaling. Dendrites are on the receiving end of synapses. Their membranes contain the receptor molecules. Axons send signals to other neurons by secreting neurotransmitter at synapses. In other words, the typical synapse is from axon to dendrite.

The electrical signals of dendrites and axons also differ. In axons, electrical signals are brief pulses known as *action potentials,* each lasting about a millisecond (see Figure 17). Action potentials are informally known as "spikes," owing to their pointy appearance, so let's use this nickname for convenience. Neuroscientists often say, "The neuron spiked," much as a financial reporter writes, "The stock market spiked on bank profits." When a neuron spikes, it is said to be "active."

Spikes are reminiscent of Morse code, which you've probably heard in old movies as a sequence of long and short pulses generated by a

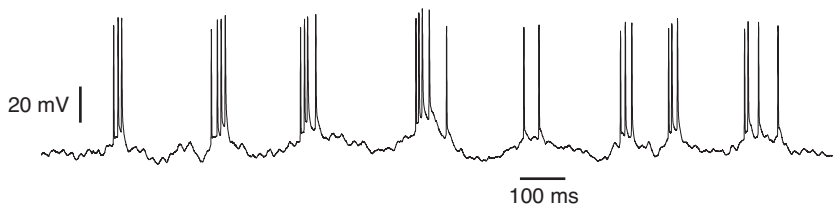

FIGURE 17. *Action potentials, or "spikes"*

telegraph operator pressing a lever. In early telecom systems, pulses were just about the only type of signal that could be heard clearly above the static. Signals tend to become more corrupted by noise as they travel farther. That's why Morse code was still used for long-distance communication even decades after the telephone became popular for local calls. Nature "invented" the action potential for much the same reason, to transmit information over long distances in the brain. Thus spikes occur mainly in the axon, the longest type of neurite. In small nervous systems like that of *C. elegans* or a fly, neurites are shorter and many neurons do not spike.

So how are these two types of neural communication, chemical and electrical, related? Simply put, a synapse is activated when a passing spike triggers secretion. On the other side of the synapse, receptors sense neurotransmitter and then make electrical current flow. In more abstract terms, a synapse converts an electrical signal into a chemical signal and then back into an electrical signal.

Conversion between signal types is common in our everyday technologies. Imagine two people conversing by telephone. Electrical signals travel between them along a continuous wire. (Let's ignore the fact that modern telephone networks additionally use light signals in optical fibers.) But electrical signals do not traverse the narrow gap of air between the handset and the ear; instead, they are converted into acoustic signals. After a journey of a thousand miles as electricity, it is sound that makes the leap to the listener's eardrum. Similarly, an electrical signal may travel far in the brain along an axon, but it does not reach the next neuron directly. Rather, it is converted into a chemical signal, which jumps across the synaptic cleft to the other neuron.

If one neuron can signal a second neuron through a synapse, the second neuron can signal a third, and so on. A sequence of such neurons is known as a *pathway.* This is how neurons can communicate with one another even if they are not directly connected by a synapse.

Unlike the mountain paths that we hike, neural pathways are directional. This is because synapses are one-way devices. When there is a synapse between two neurons, we say that they are connected to

each other, like two friends talking on the telephone. But the metaphor is flawed, because a telephone transmits information in both directions. At any given synapse, the messages travel one way: One neuron is always the sender, the other always the receiver. This is not because one neuron is "talkative" or the other "taciturn." Rather, it has to do with the structure of the synapse. The machinery for secreting neurotransmitter is on one side and that for sensing neurotransmitter on the other.

In principle, neurites are two-way devices along which electrical signals can travel in either direction. In practice, a spike normally travels along an axon away from the cell body, and electrical signals travel along dendrites toward the cell body. Synapses impose this directionality onto neurites. In your circulatory system, blood flows in your veins toward your heart. If a vein were simply a tube, blood could potentially flow in either direction. But a vein also contains valves, which prevent blood from flowing backward. Valves impose directionality on veins in much the same way that synapses impose it on neural pathways.

So a pathway in the nervous system is defined by stepping across synapses from neuron to neuron, respecting the direction of each synapse (see Figure 18). Inside one neuron, electrical signals flow from dendrites to cell body to axon. Chemical signals jump from the axon of this neuron to the dendrite of another neuron. Inside this neuron, electrical signals again flow from dendrites to cell body to axon. They are converted into chemical signals to jump to another neuron, and the process continues. Because the synaptic cleft is extremely narrow, almost all of the distance spanned by the pathway is actually within neurons rather than between neurons. Furthermore, most of this distance runs through axons, which are much longer than dendrites.

If you've eaten poultry, you may have spied bundles of axons on your dinner plate. They are called nerves, and can be recognized as soft whitish strings. They are not to be confused with tendons, which are tougher, or blood vessels, which are darker. Dissecting an uncooked nerve with a very sharp tool causes it to fray, much as a rope unravels into many threads when cut. The "threads" of a nerve are its axons.

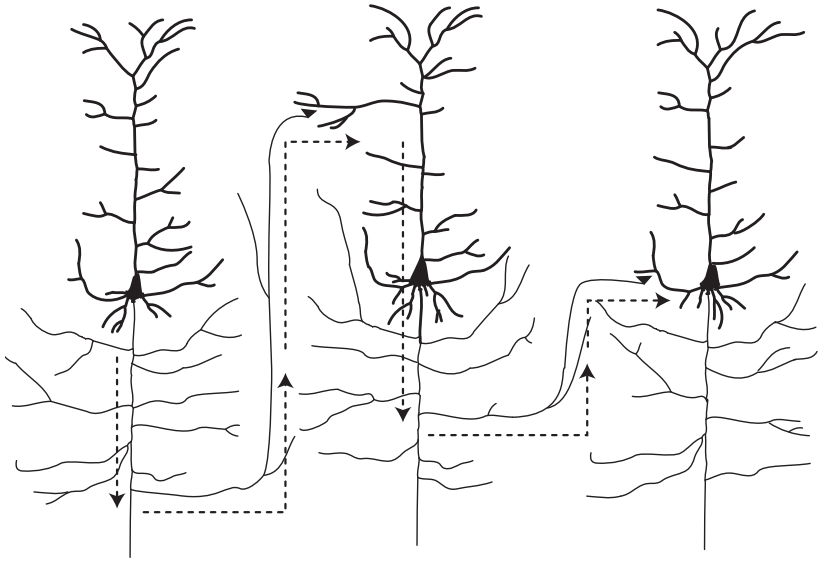

FIGURE 18. *Multineuron pathway in the nervous system*

Nerves are rooted to the surface of the brain or spinal cord, together known as the central nervous system (CNS). Because most nerves extend and branch toward the surface of the body, they are known as the peripheral nervous system (PNS). The axons in nerves come from cell bodies in the CNS or in little outposts of neurons known as peripheral ganglia. The CNS and the PNS together make up the nervous system, defined alternatively as the set of all neurons and the cells that support them. The emphasis on nerves in the term *nervous system* is perhaps misleading, as the brain and spinal cord are its predominant parts.

Now let's return to the question posed earlier: How does the sight of a snake cause you to turn and run? The rough answer is that your eyes signal your brain, which signals your spinal cord, which signals your legs. The first step is mediated by the optic nerve, a bundle of a million axons from the eye to the brain. The second step happens through the pyramidal tract, a bundle of axons from the brain to the spinal cord. (A bundle of axons in the CNS is known as a tract rather than

a nerve.) The third step passes through the sciatic and other nerves, which connect your spinal cord to your leg muscles.

Let's consider the neurons at the beginning and end of the pathways mediated by these axons. At the back of your eye is a thin sheet of neural tissue called the retina. Light from the snake strikes special neurons in the retina called photoreceptors, which respond by secreting chemical messages, which in turn are sensed by other neurons. More generally, every one of your sense organs contains neurons that are activated by some type of physical stimulus. Sensory neurons kick off the journey along neural pathways from stimulus to response.

These pathways end when axons in nerves make synapses onto muscle fibers, which respond to secretion of neurotransmitter by contracting. The coordinated contraction of many fibers causes a muscle to shorten and produce a movement. More generally, every one of your muscles is controlled by axons that come from motor neurons. The English scientist Charles Sherrington, who won a Nobel Prize in 1932 and coined the term *synapse,* emphasized that muscles are the final destination of all neural pathways: "To move things is all that mankind can do . . . for such the sole executant is muscle, whether in whispering a syllable or felling a forest."

Between sensory and motor neurons there are many pathways, some of which we will consider in detail in later chapters. It's clear that these pathways exist; if they didn't, you wouldn't be able to respond to stimuli. But exactly how do signals travel along pathways?

When California joined the United States in 1850, communicating with the eastern states took weeks. The Pony Express was created in 1860 to speed up mail delivery. Along its two-thousand-mile route from California to Missouri were 190 stations. A mailbag traveled day and night, switching horses at every station and changing riders every six or seven stations. After reaching Missouri, messages traveled by telegraph to states farther east. The total transit time for a message between the Pacific and the Atlantic was reduced from twenty-three to ten days. The Pony Express operated for only sixteen months before being completely replaced by the first transcontinental telegraph,

which in turn was succeeded by telephone and computer networks. The technology may have changed, but the underlying principle has not: A communication network must have a means of relaying messages from station to station along pathways.

It's tempting to think of the nervous system as a communication network that relays spikes from neuron to neuron. A neural pathway would behave like dominoes, with each spike igniting the next spike in the pathway in the same way that each falling domino tips over the next one in the chain. This would explain how your eye tells your legs to move when you see a snake. But in fact it's not that simple. While it's true that an axon relays spikes from the cell body to synapses, it turns out that a synapse does not simply relay spikes to the next neuron.

Almost all synapses are weak. The secretion of neurotransmitter causes a tiny electrical effect in the next neuron, far below the level required to cause a spike. Imagine a chain of dominoes spaced too far apart. The falling of one won't have any effect on the next. Likewise, a single neural pathway cannot typically relay a spike on its own — but as I'll explain below, this is a good thing.

"Two roads diverged in a yellow wood / And sorry I could not travel both / And be one traveler, long I stood," wrote Robert Frost in "The Road Not Taken." A spike does not share Frost's dilemma when it comes to a fork in an axon. Not limited to being "one traveler," the spike duplicates itself, giving rise to two spikes that take both branches. By doing this repeatedly, a single spike starting near the cell body becomes many spikes that reach every branch of the axon, amplitude undiminished. All of the synapses made by the axon onto other neurons are stimulated to secrete neurotransmitter.

Through these outgoing synapses, neural pathways diverge like the roads in the poem. That's why stimulating one sense organ can cause multiple responses. The sight of a snake makes you want to run, because of pathways from your eyes to your legs. But the sight of a tasty steak causes your mouth to water, this time thanks to pathways from your eyes to your salivary glands. Because these two types of pathways

diverge from the eyes, it's no mystery that either running or salivation is possible after you see something. The mystery is quite the opposite: Why is there only one response? If signals took all possible pathways, any stimulus would cause every muscle and gland to become activated, and clearly that doesn't happen.

The reason is that signals don't get through pathways so easily. We already saw that single synapses and pathways do not relay spikes. So how do signals ever get through? Although the branches of dendrites look similar to those of axons, their function is completely different. Axons diverge, but dendrites *converge.* Where two branches join, electrical currents can meet as they flow toward the cell body, and can combine like the water of merging streams. And as a lake collects water from many streams, the cell body collects currents from the many synapses converging onto its dendrites.

Why is convergence important? Although a single synapse is typically too weak to drive a neuron to spike, *multiple* converging synapses can do the job. If they are activated simultaneously, they can collectively "convince" a neuron to spike. Because a spike is "all or none," we can regard it as the output of a "neural decision." By this metaphor, I do not mean that a neuron is conscious or thinks in the same way that a human does. I simply mean that a neuron is not wishy-washy. There is no such thing as half a spike.

When we're deciding, we may seek advice from friends and family. Similarly, a neuron "listens" to other neurons through its converging synapses. The cell body sums the electrical currents, effectively tallying the votes of the "advisors." If the tally exceeds a threshold, the axon spikes. The value of this threshold determines whether a neuron decides easily or reluctantly, much as political systems can require a simple majority, a two-thirds majority, or unanimity.

In many neurons, the electrical signals of dendrites are continuously graded, unlike the all-or-none spikes of the axon. This is well suited for representing the entire range of possible vote tallies. A spike in the dendrites would be premature — like calling an election before all the votes are in. Only after the cell body tallies all the votes can spikes occur in the axon. If dendrites lack spikes, they cannot transmit

information over long distances; that's the reason dendrites are much shorter than axons.

One of the basic slogans of a democracy is "One person, one vote." All votes are weighted equally, as in the neural model above. But we may be less democratic when combining the advice of our friends and family, giving more weight to some opinions than to others. Similarly, a neuron actually weights its "advisors" unequally. Electrical currents have magnitudes. Strong synapses produce large currents in the dendrite, and weak synapses produce small currents. The "strength" of a synapse quantifies the weight of its vote in the decision of a neuron. And it's possible for a neuron to receive multiple synapses from another neuron, as if allowing it to cast multiple votes — a further kind of favoritism.

We've arrived at the "weighted voting model" of a neuron. In any type of voting there is some requirement for simultaneity. In politics, this is achieved by asking everyone to go to the polls on a predetermined day. Since synapses can vote at any time, it's always election day in the brain. (Actually, the metaphor is slightly misleading — synaptic votes are tallied over a time period much shorter than a day, ranging from milliseconds to seconds.) The votes of two synapses are counted in the same tally only if their electrical currents are close enough in time to overlap.

Think of synaptic currents as insults being thrown at someone. Any single insult is too weak to excite a temper tantrum (a spike), so if the insults come only infrequently, the person won't get angry. But if there are many simultaneous insults or if they come in quick succession, they can add up — until the "last straw" pushes the person over the threshold.

In the explanation of neural voting I left out an important feature of synapses for the sake of simplicity. It turns out that "yes" votes are not the only kind tallied by neurons. Another kind of synapse registers "no" votes. The yes–no distinction arises because activation of a synapse causes current to flow, and two directions of flow are possible. *Excitatory* synapses say "yes" because they make electrical current

flow *into* the receiving neuron, which tends to "excite" spiking. *Inhibitory* synapses say "no" because they make current flow *out* of the neuron, which tends to "inhibit" spiking.

Inhibition is crucial to the operation of the nervous system. Intelligent behavior is not just a matter of making appropriate responses to stimuli. Sometimes it's even more important to *not* do something—not reach for that doughnut when you're on a diet, or not drink another glass of wine at the office holiday party. It's far from clear how these examples of psychological inhibition are related to inhibitory synapses, but it's at least plausible that there's some sort of connection.

The need for inhibition might be the chief reason why the brain relies so heavily on synapses that transmit chemical signals. There is actually another kind of synapse, one that directly transmits electrical signals without using neurotransmitter. Such electrical synapses work more quickly, since they eliminate the time-consuming steps of converting signals from electrical to chemical and then back to electrical, but there are no inhibitory electrical synapses, only excitatory ones. Perhaps because of this and other limitations, electrical synapses are much less common than chemical ones.

Given that inhibition is a factor, how should our voting model be revised? Earlier I mentioned that a neuron spikes when the number of "yes" votes exceeds a threshold. If we include inhibition, spiking happens when "yes" votes exceed "no" votes by some margin set by the threshold. Like their excitatory brethren, inhibitory synapses can be stronger or weaker, so the vote is weighted rather than totally democratic. Some inhibitory synapses are even strong enough to effectively veto many excitatory synapses.

There's one last thing to know about neural voting. Neurons behave like conformists or contrarians, because they too can be classified as either excitatory or inhibitory. An excitatory neuron makes only excitatory synapses on other neurons, while an inhibitory neuron makes only inhibitory synapses. A similar uniformity does not hold for the synapses *received* by a neuron, which can be a mixture of excitatory and inhibitory.

In other words, an excitatory neuron either says "yes" to all other

neurons by spiking or abstains by remaining silent. Similarly, an inhibitory neuron chooses between "no" and abstaining. A neuron cannot say "yes" to some neurons and "no" to others, or "yes" at some times and "no" at others.

If an excitatory neuron hears many "yes" votes, it also *says* "yes," conforming to the crowd. If an inhibitory neuron hears many "yes" votes, it says "no," bucking the trend. In many brain regions, including the cortex, most neurons are excitatory. You could think of the brain as being like our society, which abounds in conformists but also harbors some contrarians.

Certain sedatives work by increasing the strength of inhibition, empowering the inhibitory neurons to dampen activity. And drugs that weaken inhibition give the upper hand to excitatory neurons, which may go out of control and ignite epileptic seizures. Here you could think of excitatory neurons as rabble rousers who incite the mob to riot, whereas inhibitory neurons are like the police, summoned to dampen the excitement of the crowd.

Many other properties of synapses are under investigation by neuroscientists. But I hope it's clear that saying two neurons are "connected" only begins to describe their interaction. The connection may occur through one or more synapses — chemical or electrical or both. A chemical synapse has a direction, may be excitatory or inhibitory, and may be strong or weak. The electrical currents it produces may be lengthy or brief. All of these factors matter when synapses cause neurons to spike.

I've explained that neural pathways diverge from the eye to both the legs and the salivary glands. To make clear why any given stimulus activates some pathways but not others, I've focused on synaptic convergence, which is crucial for spiking by the voting model. If a neuron doesn't spike, it functions as a dead end for all the pathways converging onto it. The myriad dead ends imposed by nonspiking neurons are essential for brain function. They allow the sight of a snake to *not* trigger the salivary glands, and the sight of a steak to *not* make you run away.

Failing to spike is just as important to neural function as spiking. That's why single synapses and single pathways are not capable of relaying spikes. In the voting model, there are two mechanisms for making neurons choosy about when to spike. I mentioned that the axon spikes only when the total electrical current collected by the cell body exceeds some threshold. Raising the threshold for an axon is a way of making the neuron even choosier. If a neuron receives a "no" vote from an inhibitory synapse, that also increases its selectivity, as now even more "yes" votes are required for a spike. In other words, there are two mechanisms that prevent neurons from spiking indiscriminately: the threshold for spiking and synaptic inhibition.

Spikes have two functions. The generation of a spike near the cell body represents the making of a decision. The propagation of a spike along the axon communicates the result of the decision to other neurons. Communication and decision-making have different goals. The goal of communication is to preserve information, to transmit it without change. But discarding information is fundamental to making decisions. Imagine a friend trying on a coat in a boutique, unable to decide whether to purchase it. There are many inputs to his or her decision, such as the color, the fit, the designer label, the ambiance of the store, and so on. You might listen to your friend go on and on about this information. But at some point you'll lose patience and ask, "Are you buying this coat or not?" In the end, the final decision — not the many reasons for it — is what matters.

Likewise, an outgoing spike indicates that a neuron's tally of votes exceeded its threshold, but does not convey details about the individual votes of its "advisors." So neurons may transmit some information, but they also throw a lot away. (I'm reminded of my father, who likes to say proudly, "Do you know why I'm so smart? It's because I'm so good at forgetting the right things.") That's why the brain is far more sophisticated than a telecom network. It would be appropriate to say that neurons *compute,* not just communicate. We've come to associate the notion of computation exclusively with our desktop and laptop computers, but these are just one type of computational device. The brain is another — albeit a very different kind.

Though we should be cautious about comparing brains to computers, they are similar in at least one important respect. They are both "smarter" than the elements from which they're constructed. According to the weighted voting model, neurons perform a simple operation, one that does not require intelligence and can be performed by a basic machine.

How could brains be so sophisticated when neurons are so simple? Well, maybe a neuron is not so simple; real neurons are known to deviate somewhat from the voting model. Nevertheless, a single neuron falls far short of being intelligent or conscious, and somehow a network of neurons is.

This idea might have been difficult to accept centuries ago, but now we've become accustomed to the idea that an assembly of dumb components can be smart. None of the parts in a computer is by itself capable of playing chess — but a huge number of these parts, when organized in the right way, can collectively defeat the world champion. Similarly, it's the organized operation of your billions of dumb neurons that makes you smart. This is the deepest question of neuroscience: How could the neurons of your brain be organized to perceive, think, and carry out other mental feats? The answer lies in the connectome.