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CHAPTER 1

Introduction

ENTER SPIKES

Midafternoon is the devil's time. The ebbing of your circadian rhythms collides with the digestion of an ill-considered lunch of hot dog and hummus to dull your mind and bring thoughts of a cheeky nap. But there's an all-hands meeting in the conference room in ten minutes, at which you've discovered that snoring loudly enough to drown out the CEO's "always be coding" speech is a no-no. Eat something, says inner you. On the desk abutting yours is the box for some homemade ginger, pear, and chocolate cookies that Dietrich brought for the 10:00 a.m. conference call with the South Africa office—strangely delicious, definitely tempting, disappointingly gone.

No, wait. Your eyes glimpse a rounded, crumbly edge. There's one left. Your brain sparks to life, as you glance around to clock your coworkers' locations and think—*could I take that?* After a moment's hesitation, weighing the ethical dilemmas and more importantly confirming that no one has line of sight, you extend a hand.

In those few moments your brain is abuzz with electricity. Vital, surreptitious-cookie-obtaining electricity. Why?

Your brain uses electricity to communicate. Each nerve cell, each of the eighty-six billion neurons in your brain, talks to other neurons by sending a tiny blip of voltage down a gossamer thin cable. We neuroscientists call that blip "the spike." These tiny pulses of electricity stream endlessly, ceaselessly across your brain. Spikes are seeing, hearing, and

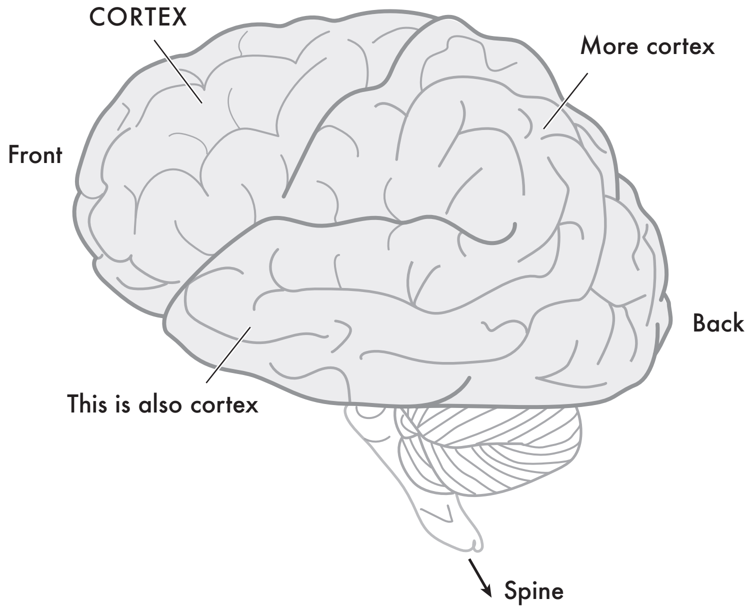

FIGURE 1.1. Basic anatomy of the human brain. Most of the outside of your brain is the cortex.

feeling; thinking, planning, and doing. Spikes are how neurons talk to each other. And neurons talking to each other is how you do anything.

A LIFE IN SPIKES

The uniquely human things you do are thanks to the chatter of spikes in your cortex (figure 1.1). This outer layer of the brain contains more neurons in you than in any other animal, ever.[1] So many in fact that we have to divide the cortex into a constellation of areas, each with its own name, to make sense of it all. (Few of these names are exciting—the area with the most neurons that talk directly to the spine, and so has the most control over movement, is called the primary motor cortex; the areas next door are the premotor cortex and, wait for it, the supplementary motor area. Inspired.) These areas all share the same types of neurons but do wildly different things with the spikes sent between them.

Many of these areas are dedicated to seeing, from the areas breaking down the world into its simplest components—edges and lines and corners—to the areas dealing with motion, colors, objects, and faces. Some areas do hearing and touch; some control your movement.

There are areas for uniquely human things, like reading, speaking, and understanding the spoken word. And at the front of the cortex we find areas that do mysterious things with information from the outside world, somehow using it to plan, anticipate, and predict. All of it done by spikes.

The numbers are vertiginous. Of the eighty-six billion neurons in the adult human brain, about seventeen billion of those are found in the cortex. Each of those sends at most one spike per second, on average.[2]

The United Nations tells us the expected lifespan of a human on this planet is about seventy years. That's more than two billion seconds, each of which contains about seventeen billion spikes in cortex. All told, your lifespan is about thirty-four billion billion cortical spikes.

The cry you emitted on your appearance in the world. Your first tottering, uncertain steps. The pain when Susan's wildly swinging arm knocked out your wobbly tooth in primary school. Recognizing that cluster of trees in the distance, and the relief of knowing you'll now find your way across the damp, foggy hills back to the welcome warmth of the car. Plucking up the courage to ask for a date, and blurting it all out in a rush. The flush of embarrassment. The quiet euphoria of a yes. Deciding you just have to do something about the clash between the purple sofa and the lime green curtains. Remembering the smell of your mom's bread and dad's roast chicken. Cradling your baby. Reading this sentence. And this one.

All spikes.

From the magnificent to the mundane, everything you've done is in those thirty-four billion billion spikes that have streamed across your cortex. If I were to write the story of your life with one word for every spike, your biography would be longer than the combined length of all novels in English ever published.[3] Yes, ever, since Gutenberg introduced movable type to Europe in 1439. And not just a bit longer—seventy-six million times longer. Even with the combined efforts of Tom Wolfe, Neal Stephenson, and George R. R. Martin to deliver novels that are also handy for weighting down small children in a storm, novelists still have at least another 380 million years or so to publish as many words in English as spikes in your cortex in your lifetime. And below the cortex, billions upon billions more neurons, sending billions upon billions more spikes.

You'll excuse me if I attempt something a little less daunting.

THE JOURNEY OF A SPIKE

In this book, I'm going to tell you the story of just two of those seconds. Of a simple act: you spot that last cookie in the office tray, and think—*no one will mind if I take that, right*?

A spike's journey from the eye that receives the light bouncing from the cookie, through the seeing parts of cortex turning patterns of light and shade into the edges, curves, crumbs, and colors of the cookie, on to cortical areas for perceiving, deciding, and remembering, plunging into the depths of the motor system, and out, out through the spine and on to the muscles, finally moving your hand to what your eye can see. A journey from seeing to deciding to moving, from eye to hand.

This is the story of everywhere the spike was sent, and of everything it saw on the way—the twinkling galaxy of neurons, the deep darkness of the cortex, the loneliest neuron. Of splitting into a thousand clones. Of spontaneous birth and instant death. An epic journey, all in but a moment of time, a story replayed two billion times over.

THE GOLDEN AGE

That I can tell you this story at all is thanks to a remarkable convergence of technologies.

One of these is brain imaging, especially functional MRI (fMRI). Relied on heavily in popular accounts of neuroscience, fMRI can tell us much about the broad picture, of how a group of brain areas may process vision, but not hearing; create emotional responses to faces, but not chocolate; or paradoxically only turn on when your mind goes blank. Yet fMRI tells us nothing about how neurons work. Each tiny pixel on a fMRI image, each dot of color, contains 100,000 neurons. fMRI measures the flow of oxygen-rich blood around those 100,000 neurons, a flow that increases as those 100,000 neurons send more spikes, for making spikes needs energy, and creating energy needs oxygen. Each dot of color shows us only where the demand for such energy-giving blood has changed around 100,000 neurons. So fMRI cannot see or record individual neurons, let alone the spikes emitted from them.

It is a wonderful technology, the only way to peer at the moment-to-moment activity inside the living human mind, and with great potential for our assault on neurological disorders, where diagnosis and treatment perhaps take precedence over a deep understanding of what each neuron is doing. But alone it is of no use to us here. Trying to understand how neurons work using fMRI is like trying to follow a soccer match through the roar of the crowd. The crowd's crescendos and groans will tell you when something exciting is happening, and with luck which part of the crowd is baying will tell you roughly at which end of the field the excitement is happening in. But you'll be oblivious to the match itself, to the intricacies of what the players and the ball whizzing between them have been doing for ninety minutes. To understand a match, we need to watch the players. To understand the brain, we need to watch the spikes.

We caught our first glimpse of the spike from a single neuron in the 1920s.[4] Since then, tens of thousands of neuroscientists have recorded spikes from every imaginable part of the brain. And from almost every imaginable brain, from the giant tentacle neurons of the squid, to the deciding neurons of the rat, even to the neurons in an awake, chatty, lucid human. But now we can go further, for we are in the midst of the golden age of systems neuroscience, the pursuit of how neurons are wired and work together.

For decades we could record the spikes of only one neuron at a time. Now we can record the spikes of hundreds or thousands at the same time with standard equipment, and the cutting edge is growing exponentially year on year.[5]

We used only to be able to trace the broad outlines of where neurons in one area of the brain sent their cables outward. Now we can trace the wiring of each single neuron to find out precisely where spikes will be sent.

We can now record not just the spikes coming out of a neuron but also the tiny effect they have on the next neuron, at a connection smaller than a bacterium. We can even do so at multiple sites on a single neuron at once.

More than just record them, we can now turn neurons on and off with light, either forcing them to send spikes on command, or stopping them from sending spikes altogether.[6] So we can at last test directly what spikes are for, by seeing what happens when they are sent, or, just as importantly, not sent.

Combined, these tools let us record the spikes sent from hundreds of separate neurons, stop or start spikes at will, and give us some idea of the destinations of the wires along which they travel. Combined, these tools can now tell us the journey of spikes.

There's a catch to this smorgasbord of technological triumphs. None of them can be used in humans. Tracing the wiring between neurons would mean injecting fluorescent chemicals directly into a region of your brain, then taking out your brain, slicing it up, and sticking the slices under a microscope to find out where the fluorescent chemicals ended up. Can't do that to you. To turn neurons on and off with light we have to make them sensitive to light in the first place, by inserting DNA from light-sensitive plants or bacteria into the neuron's DNA. Can't do that to you either. And to record the spikes from hundreds of neurons at the same time means either filling your neurons with a toxic chemical that glows according to how active the neuron is, or sticking tens of long tungsten or carbon-fiber electrodes through your skull and into your brain, attached to long wires. Ethically speaking, the slicing, gene-fiddling, and electrode-poking are right out.

Except in fascinating rare cases. On rare occasion, we do get to record spikes from electrodes implanted into a live human brain. Sometimes these are from patients with Parkinson's disease who are undergoing surgery for deep brain stimulation. This treatment for Parkinson's targets electrical stimulation at regions deep in the brain (hence, "deep brain stimulation"—neurologists are some of the most literal-minded people on the planet). It requires a permanently implanted electrode, attached to a battery pack installed under the collarbone. The surgery to implant the electrode happens in two stages. The electrode is inserted first, into approximately the right place, but its leads are left dangling outside the skull so that the position of the electrode can be fine-tuned. During the tuning, the neurologist will pass stimulation down these leads into the electrode, and out into brain. If the electrode is in slightly the wrong place, then slightly the wrong thing will happen: if the patient salutes you, this is wrong, move the electrode a little; if the patient starts weeping uncontrollably, this is wrong, move the electrode a little. If the patient's tremulous arm suddenly becomes still, this is right; so now the electrode can be secured in place, and the second stage of surgery commences to run the leads under the skin and down to the battery pack, and to close up the hole in the skull.

But this slow fine-tuning means there is a window of time, about a week, in which these leads hanging out of the skull can also be used to record from the electrode, record the neurons next to it.[7] Creative researchers spend this week asking the patient to do a whole bunch of tasks, which hopefully will involve the tiny deep brain structure in some way. Along similar lines, people whose severe epilepsy is not responding to drugs can also have implanted electrodes, targeting stimulation at the small region of brain—typically in the hippocampus or cortex—where the seizure activity starts. Again, while getting the electrode into position, the researchers can record from neurons next to those electrodes during tasks in these patients.[8] From both rare occurrences we get precious rare recordings of single neurons from a live human. A valuable resource, but one limited to a handful of brain regions in a handful of people—and still no slicing or gene manipulation allowed.

With humans literally off the table in the quest to understand spikes, neuroscientists gather much of their data from a wide range of nonhumans. Some are our close cousins, evolutionarily speaking—the rat and mouse, in particular, for their combination of smarts and well-studied DNA. Others are studied for the unique ways they can tell us about the fundamentals of how neurons talk to each other. Salamanders, zebrafish, leeches, sea slugs, even the maggots of vinegar flies, will all appear in the pages that follow. For neurons are extraordinarily preserved from deep evolutionary time. Neurons are recognizably neurons in practically everything with some kind of brain. If you can see it, and it moves, it lives a life of spikes.

HOW WE CAN INTERPRET SPIKES

Our interpretation of these reams of data from nonhumans, data on spikes and where and when they are sent, relies on casting it into what we know about the human brain. From brain imaging we can get confirmation that similar brain regions in humans are active, at similar times and places, in response to similar things in the world, as the spikes we record in nonhumans. From psychology and the cognitive sciences we can get an understanding of what processes are happening in the human mind when those spikes are observed in nonhumans.

The face code is a beautiful example of this interplay between psychology, brain imaging, and spikes. Humans pay a lot of attention to faces. Psychology tells us that our preference for looking at faces is there from our earliest childhood, that as adults we can remember around five thousand faces,[9] and that we can recognize faces from exceptionally impoverished information: from an extraordinary variety of angles, with just a glimpse, and using the most basic of visual clues. Even this :-o. Or this ;-). Our deep ability to process faces is perhaps not surprising when you consider that recognizing faces and their expressions is the basis of many social interactions, for knowing who is kin and who is not, who is above us and who below in the pecking order, and who is pleased to see us—and who is really not. But the depths to which our minds process faces implies our brains must dedicate some serious processing power to the face problem.

Brain imaging showed us that indeed the human brain takes this problem so seriously it dedicates a whole area just to faces. The now-named “fusiform face area” lights up in humans when shown a face, at whatever odd angle you choose, but not when shown objects or scrambled faces. It really does care only about faces.[10]

Doris Tsao, Winrich Freiwald, and colleagues then sought out some nonhumans that also care about faces—monkeys—to venture into this area of their brains, record spikes, and find out the actual messages being passed between neurons.[11] They found a mass of dedicated neurons that all sent spikes in responses to pictures of faces.[12] There turned out to be six separate patches of face neurons in this one area, and these patches were linked together. Stimulation of one patch activated neurons in some of the others,[13] which suggested a face was represented by the joint activity between neurons in different patches. That joint activity code was revealed nine years later in 2017: each neuron sends spikes in response to some abstract feature common to faces—like the curve formed by the eyebrow and nose. The combination of neurons with different abstract features sending spikes together adds up to a whole face.[14]

Psychology tells us how much humans care about faces, and how deeply they process them. Brain imaging shows us a brain region dedicated to processing faces. Spikes show us the face code—how that region sends messages about faces. Recording spikes alone in response to faces would not tell us that these spikes correspond to "seeing" faces, for "seeing" is a subjective human experience. We interpret spikes in nonhumans through our own experience as humans.

WHERE WE WILL GO

In this golden age, cutting-edge technologies have only just begun to draw back the curtain on the neuronal drama of the brain. Seemingly every day of the past ten years brought new research that upended our understanding of how neurons talk to each other. And so upended our understanding of what makes us tick—of how we see, of how we decide, of how we move. But each cluster of neuroscientists working feverishly on their favorite brain region or type of neuron cannot see the big picture, cannot know all the ways in which our understanding of the inner workings of the brain has radically changed. That's my challenge.

By taking you on the journey of a spike from eye to hand, this book will tell the story of what we know about spikes, about what they mean for us as humans, and of what we have left to understand. Journeying with the spike will let us rip apart misconceptions about how brains work and about how they fail, many of these held by neuroscientists themselves.

A textbook neuron has a defined function, a defined reason why it sends spikes, based on some external cause in the world. But we will meet the dark neurons, the literal silent majority, who sit unmoved by anything and everything going on around them. They are invisible to brain imaging and challenge our most deeply held theories of what neurons do. Evolution tolerates no waste, so why would it allow there to be billions of neurons that apparently do nothing?

And we will meet the spontaneous spikes. Spikes mysteriously created by neurons without any input from the outside world; spikes created solely by the myriad feedback loops between neurons that drive each other to spike endlessly. They carry no message from the world, or to the world through movement. Crazier still are spikes born without any input even to the neuron that created them, spikes created solely by the internal cycling of molecules inside a neuron. Yet on our journey from seeing to moving, we will meet these spikes everywhere.

Meeting the spontaneous spikes leads to one of the new ideas I will advance in this book: that spontaneous spikes are an inevitable consequence of wiring up a big bag of neurons into a brain—and evolution has co-opted them for survival. Rather than waiting for spikes to make their journey through the myriad areas of cortex to work out what is being seen, to decide what to do about it, and then to act—rather than wait for all that, we have harnessed spontaneous spikes to give us the power of anticipation. Spontaneous spikes predict what we'll see next, what we'll hear next, what our next decision is likely to be. They prepare for our next movements. All so we can react faster, move quicker—and survive longer.

Clinging to a spike as it speeds from your eye through your brain to your hand, from seeing the cookie to deciding to nab it to reaching it, we will trace torturous paths, be cloned, and fail badly. We will wander through the splendor of the richly stocked prefrontal cortex and stand in terror before the wall of noise emanating from the basal ganglia. All of this is yet to come. For we start with the thing we understand best of all: the spike itself.

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