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Introduction

How does life work? This question may seem overwhelming, or even preposterous. How could any answer do justice to both a sprinting cheetah and a stationary tree, to the unique *you* along with the trillions of bacteria that live inside you? The experiences of even a single organism are breathtakingly varied: consider a chick's emergence from its egg, the first flap of its wings, the racing of its heart at the sight of a fox, and its transformation of food and water into eggs of its own. Could any intellectual framework encompass all of this?

The search for an answer—for some kind of unity amid the diversity of life—is reflected in our ancient urge to categorize living things based on similarities of appearance or behavior. Aristotle partitioned animals into groups using attributes such as laying eggs or bearing live young. Ancient Indian texts applied a variety of classifiers, including, similarly, manner of origin: “those born from an egg, those born from an embryonic sac, those born from moisture, and those born from sprout.” Modern taxonomy emerged from the eighteenth-century work of Carl Linnaeus, who systematized the naming of organisms and developed a hierarchical classification scheme based on shared characteristics that we continue to find useful. Classification in itself, however, is not very satisfying. We want to know the *why*, not just the *what*, of the commonalities that unify living things.

In this book, we look for that *why* through the lens of physics, revealing a surprising elegance and order in biology. Of course, this isn't the only perspective that offers deep insights into life. There is the viewpoint of biochemistry, with which we understand how atoms join together to form the molecular components of organic matter, how energy is deposited in and extracted from chemical bonds, and how the incessant flux of matter and energy in chemical reactions constitutes

the metabolism of living things. But it is difficult to use chemistry alone to zoom out from the scale of molecules to the scales of the animals and plants around us, or even the scale of single cells, and make sense of shape and form.

Another all-encompassing perspective is that of evolution. Since the mid-nineteenth-century epiphanies of Charles Darwin and Alfred Russel Wallace, we can see the traits of living creatures as manifestations of deeper historical processes. Similarities, whether of visible characteristics of anatomy or more hidden patterns in DNA sequences, can reflect shared ancestry with which we can deduce a tree of relationships linking all of life together. Differences emerge due to random chance and the varied pressures on survival imposed by creatures' environments; again, present forms reflect past history. Evolution provides a powerful framework for understanding life. It is not, however, one that we focus on in this book. In part, this is because there is already a large popular literature on the subject. More importantly, however, evolutionary principles alone don't illuminate the *why* as much as the *how*.

To illustrate what I mean by "why," consider the swim bladder, a pair of gas-filled sacs possessed by many, but not all, species of fish. Comparing creatures both extant and extinct reveals this organ's evolutionary history, with connections to the emergence of lungs in air-breathing animals that Darwin himself remarked upon. Understanding the function of a swim bladder, however, requires a bit of physics: the low density of the enclosed gas offsets the high density of bone in bony fishes, allowing the animal to maintain the same average density as its watery surroundings and thereby easily position itself at whatever depth it likes. A swim bladder is just one solution to the challenge of matching density. The fish might instead contain large amounts of low-density oil, or a skeleton composed of cartilage rather than bone, both of which are strategies adopted by sharks, which lack a swim bladder. The last common ancestor of cartilaginous and bony fish lived over 400 million years ago. Since then, the distinct evolutionary paths of the two groups have led to different solutions to the shared physical challenges of aquatic locomotion. We can state, with a point of view echoed throughout this book, that understanding the *why* of these anatomical

features, related to control of density, highlights a hidden unity that fish share that transcends their evolutionary divergence. We should keep in mind, however, that the machinery of variation and natural selection—the enhanced odds of survival that accrued over generations to those creatures better able to navigate their aquatic world—provides the paths by which the forms we see arise.

There are other vantage points besides those of biochemistry and evolution from which to survey the breadth of life. Rather than list all the approaches we won't be exploring, however, let's turn to the one we will.

I've already hinted at the view of nature the rest of this book expands upon, which I identify as *biophysical*. The term implies a unification of biology and physics. It encapsulates the notion that the substances, shapes, and actions that constitute life are governed and constrained by the universal laws of physics, and that illuminating the connections between physical rules and biological manifestations reveals a framework upon which the dazzling variety of life is built. The notion of universality is central to the utility of physics, and to its appeal. The same principles of gravity apply to an apple falling from a tree and to planets orbiting the sun, and current work aims to further expand this framework to encompass the strange behavior of the quantum world. Biophysics extends to the living world the quest for unity that lies at the heart of physics.

To say that living things obey the laws of physics may seem trivial. After all, organisms are made up of the same fundamental particles that make up everything else and are therefore governed by the same rules. But one might expect the explicit role of physics to be over after physical forces set up the formation of atoms and molecules, with complex chemistry giving shape to further molecular rearrangements and the idiosyncratic predilections of cells and organisms being responsible for larger features. This is, however, incorrect. Just as physical forces direct the intricate branching of frost on a winter window and the rhythmic curves of vast desert dunes, and do so in ways that don't require subatomic particles for their explanation, physical mechanisms shape life at all scales. One of the great triumphs of physics, especially

over the last half century, has been an understanding of how broad rules arise in all sorts of natural phenomena, clearing the underbrush of complexity to reveal deep principles. Magnets, for example, become nonmagnetic if heated above some specific “critical” temperature; though magnets can be made of many different elements and alloys, each with their own unique atomic-scale structure, the magnetic field of every magnet decays with exactly the same form as it approaches its critical temperature. Being a three-dimensional arrangement of interacting atoms, it turns out, suffices to determine the consequences of these interactions, regardless of atomic details. As another example, consider a shaken container of mixed nuts. One typically finds that the larger nuts rise to the top, giving this well-known phenomenon its name: the Brazil nut effect. The effect isn’t particular to nuts, of course, and occurs in mixtures of cereal grains, rocks on riverbeds, and any collection of agitated, disordered objects. Its explanation involves general notions of what are called granular flows, and the ways in which any ensemble of colliding particles must create and fill in interstitial spaces in order to move.

Biophysics applies this quest for broadly applicable physical rules to the world of living things. This endeavor, though still incomplete, has already been far more successful than we might have dreamed even a few decades ago. Using physics, we can understand the bursting of DNA from viruses, fundamental limits on the speed of thought, and the regular spacing of our vertebrae. We can apply our insights to grow organs on slabs of plastic and read genomes using pulses of light. We uncover a simplicity and an elegance in the living world that is otherwise hidden. Simplicity emerges because a handful of principles rather than a morass of detail suffices for many explanations; elegance because of the unity shared by the living and nonliving world. This is an unusual point of view; I hope the pages to come will convince you of it.

Every quest for unity amid complexity risks the pitfall of hubris, however. There is the temptation to ignore the lessons that variety provides, or to force motley data into unreasonably simple frameworks. A physical perspective is especially prone to these missteps, perhaps because of the elegance of its theories and perhaps because of their

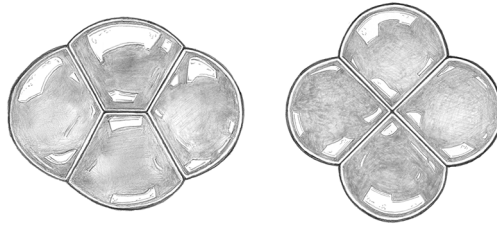
historical successes. Despite being a physicist myself, I note that the caricature of physicists as blithely trampling, elephant-like, through adjacent fields of inquiry without adequately appreciating the treasures underfoot is not wholly inaccurate. Though this book is a celebration of biophysics, I'll describe some of its stumbles as well; chapter 12 in particular examines contentious issues of metabolism against which a biophysical approach may have failed.

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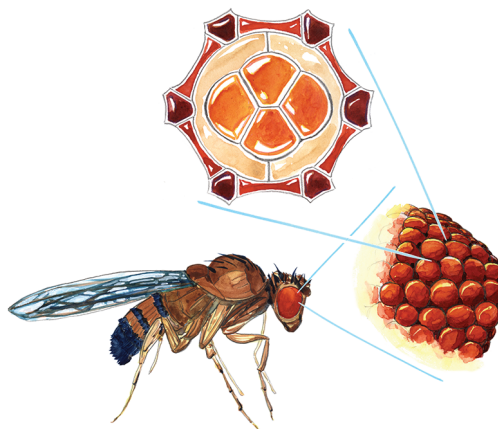
What are the physical principles that govern living things? We could refer to laws related to fundamental forces, thermodynamics, probability, and so on, amenable to precise mathematical formulation. While rigorous, this would be rather dry, and would moreover obscure the overarching lessons that biophysicists have drawn from nature. Instead, I direct our attention to four concepts or motifs that arise repeatedly in biophysical explorations.

The first is *self-assembly*, the idea that the instructions for building with biological components—whether molecules, cells, or tissues—are encoded in the physical characteristics of the components themselves. It may seem obvious that an organism contains its own instructions. After all, one doesn't need to carve a tree into a tree shape or paste five arms on a starfish; the creatures organize their own forms. Their internal instructions, however, need not take the form of a task list written into one set of components and executed by another. Rather, the physical characteristics of biological materials often *are* the instructions. Features like size and shape can guide the arrangement of pieces into a larger whole, as can less visible attributes such as electrical charge, harnessing the laws of physics.

I'll illustrate with an example. If you've ever blown soap bubbles and watched them come together, you may have noticed that there's never a junction at which more than three bubbles meet. Four adjoining bubbles may look like the drawing on the left of the figure below (page 6), with boundaries like a bent letter H, but never like the drawing on the right, with boundaries like an X. Physical forces drive soap films to minimize their surface area, leading to incontrovertible rules for



sets of bubbles that have been appreciated since their nineteenth-century elaboration by Belgian physicist Joseph Plateau. These rules prohibit any junction of four bubbles, as such a junction could never be part of a minimal-area surface. The arrangements of bubbles aren't haphazard. No external hand, however, is needed to guide them into their stereotyped pattern; the rules for their organization are embedded in their physical nature. For well over a century, scientists have noticed that arrangements of adjoining cells in all sorts of tissues resemble the arrangements of soap bubbles, and have investigated whether this is coincidence or a reflection of similar underlying mechanisms. In 2004, for example, Takashi Hayashi at the University of Tokyo and Richard Carthew at Northwestern University looked at the cluster of photoreceptor cells situated in each of a fruit fly's compound eyes. Normally, there are four, with exactly the same arrangement as four soap bubbles. Using mutant flies that developed 1, 2, 3, 5, and 6 photoreceptor cells per group, they found the same arrangements that one finds in assemblies of 1, 2, 3, 5, and 6 adjoining soap bubbles. The fly, it seems, relies on general physical mechanisms of surface area minimization to organize these crucial cells of its retina. Rather than painstakingly positioning cells, the fly makes the cells and lets them sort out their contacts, minimize their areas, and pattern themselves on their own. The cells, like the soap bubbles, assemble themselves. In countless other contexts as well, we similarly find that structure isn't drawn explicitly into the blueprints of an organism; rather, nature places the raw materials at the site and trusts that the laws of physics will put them together properly. Thankfully, the laws of physics are reliable workers.



The second recurring motif is that of a *regulatory circuit*. The ubiquity of computers makes us familiar with the idea that machines can use rules of logic to transform inputs into outputs, making decisions based on signals from sensors or controllers. We're also comfortable with the idea that living creatures, ourselves included, make behavioral choices based on the stimuli in their environment, though the details of the computations are more mysterious. We'll see that decision-making circuitry is not just a feature of the large-scale world but is manifested in the microscopic activities of life's molecules, built in to their very structure and modes of interaction. The wet, squishy building blocks of life assemble into machines that can sense their environment, perform calculations, and make logical decisions.

A migrating cell in a developing embryo, for example, must stop its wandering when it reaches the appropriate destination, a decision determined in part by assessing the mechanical stiffness of the neighboring tissue. Cells adhere using proteins that jut out from their surfaces, and through these proteins they can tug on their surroundings. Some adhesion proteins can serve as sensors as well as anchors, with these two roles inexorably linked: for stiff surroundings, the protein molecules are stretched, as your arm would be if tugging on a thick tree branch from a few feet away; for soft surroundings, the proteins are bent, as your arm would be if pulling a towel on a clothesline, easily

dragged toward you. The cell contains other components that can bind to sites on the adhesion protein only if those sites are exposed, which occurs only if the molecule is stretched—imagine the inside of your elbow, accessible as you tug on the tree but not the towel. This binding triggers events that culminate in the cell's decision to stop its wandering. The physical conformation of the protein, therefore, underpins a cell-scale machine that senses, calculates, and decides.

Our third concept is that of *predictable randomness*. The physical processes underlying the machinery of life are fundamentally random but, paradoxically, their average outcomes are reliably predictable. In the nonliving world, randomness is central to activities as diverse as the shuffling of cards and the collisions of gas molecules. Physics has long tackled the question of how robust features emerge from underlying chaos. We know, for example, why steady, consistently colored light shines from stars despite their churning interiors, and how energy can be extracted from the violent combustion of gasoline. The microscopic world is subject to incessant, vigorous, and fundamentally random motion that DNA and other cellular components must deal with, and even exploit. We can deduce the probable outcomes of random processes, which in many cases provide simple explanations of superficially complex phenomena. A virus reaching a cell that it may infect, for example, doesn't need to think (even if it were capable of thought) about how to find the specific surface proteins to which it can bind; it is buffeted by random forces that drag it everywhere, ensuring that its chaotic trajectory will intersect its target. Your immune system also makes use of randomness, generating an enormous variety of receptor proteins that might, by chance, recognize invaders that have never before been encountered. We devote all of chapter 6 to the randomness of microscopic motion, which finds echoes in discussions of genes and traits where randomness is also built into the way life works.

Our final recurring biophysical motif is that of *scaling*, the idea that physical forces depend on size and shape in ways that determine the forms accessible to living, growing, and evolving organisms. That size, shape, and physics are related is well appreciated for artificial structures. It's hard to build big buildings, for example. Before the advent

of steel frames and other modern inventions, to attempt great heights or large interior spaces was to tempt collapse, as the weight of a structure could overwhelm the support its walls could provide. Simply scaling up a small building, maintaining the proportionality of its dimensions, fails. In modern language that we elaborate in chapter 10, gravity and other forces *scale* with size in different ways that we need to account for when designing buildings. Scaling concepts are similarly reflected in the sizes and shapes of animals but extend to much more than mechanical concerns. Scaling illuminates aspects of living forms, from the existence of lungs to (perhaps) the rate of our metabolism.

These four themes don't exist in isolation but can interact with and even depend on each other, as we'll see in the chapters to come. The precision of biological circuits often depends on the statistics of random motion. Random motion nudges the positions of biological components to facilitate their self-assembly. Self-assembly into larger structures is subject to the dictates of scaling laws. All these processes and principles together create the explanatory framework of biophysics.

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Understanding life brings with it the ability to influence life. This isn't in itself a new insight. Our knowledge of the immune system and the behavior of microorganisms, among other topics, has enabled us to triumph over a multitude of diseases that ravaged humanity in the past. In the twentieth century alone, for example, more than 300 million people died of smallpox, a disease that has now vanished thanks to the invention of vaccines. Our knowledge of genetics, biochemistry, and many other subjects lets us coax plants and animals to produce enough food for over seven billion people, four times as many as inhabited the planet just a hundred years ago. In recent years, we've learned how to alter organisms at their core, directly reading the information carried in genomes and rewriting it to modify form and function. As we'll see, these contemporary advances required taking seriously a biophysical view of life, acknowledging the tangible, physical character of DNA and other molecules to design tools that quite literally push, pull, cut, and connect life's pieces.

A biophysical perspective also helps us make sense of the implications of these new biotechnologies and the difficult choices they bring. We'll encounter, for example, methods to engineer the extinction of the mosquitoes that spread malaria, dengue fever, and other diseases, bringing to mind both the dismal legacy of human-induced extinctions and the uplifting histories of past eradications of disease. The decision whether to deploy such methods requires understanding how they work and how they differ from past tools. At a more personal level, our ability to read our own genetic code brings with it the prediction of likelihoods of various illnesses in ourselves or in our children; our nascent ability to edit genomes offers the chance to alter these likelihoods. What would it mean to alter the genome of an unborn child to try to avoid cystic fibrosis, or cancer, or depression? Whether to take such an action is both a deeply personal decision and one with serious ethical and societal implications. Making such decisions can, and should, be aided by an understanding of what genes, genomes, cells, and organisms actually are, and the processes that shape the relationships among them. As we'll see, the physical nature of life's materials, as well as fundamental issues related to randomness and uncertainty, influence what we can and cannot do with our new technologies.

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Our exploration of biophysical themes includes examples spanning the variety of life. We consider the normal workings of organisms, including ourselves, as well as the pitfalls of disease and the intersections of biology and technology. In part I ("The Ingredients of Life"), our journey begins inside cells. We delineate the pieces that make up living things, materials like DNA and proteins that also exemplify a sort of universality, as they make up every living thing ever discovered. The molecular characters in this first part of the story will likely be familiar from high school biology, but we focus on the physical traits that guide their functions. We find stiff strands of DNA, two-dimensional liquids that define cell boundaries, and three-dimensional sculptures made of single molecules. In part II ("Living Large"), we expand our horizons to look at communities of cells, including embryos, organs, and the consortia

of bacteria that live inside each of us. We also explore scaling relationships that govern the shapes of animals and plants, revealing why an elephant can never be as athletic as an antelope. In part III (“Organisms by Design”), we return to the microscopic world of DNA, but now, having developed deeper connections between molecules and organisms, we tackle the genome. We learn what it means to read, write, and edit DNA, learn how nature itself pointed us toward the tools that make these feats possible, and examine the opportunities and challenges these technologies present for our future.

As interesting as these topics and examples may be, their cumulative effect is greater than the sum of their parts. Biophysics transforms the way we look at the world. At the end of *On the Origin of Species*, Darwin writes:

There is grandeur in this view of life, with its several powers, having been originally breathed into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved.

I hope to convince you that Nature has a grandeur even deeper than what Darwin discerned. Rather than a contrast between the fixed, clockwork laws of physics and the generation of endless and beautiful forms, the two are inextricably linked. We can identify the crucial “simple beginning” not as the origin of life, nor the formation of our planet, but as the primeval emergence of the physical laws that characterize our universe. The influence of these laws on life didn’t end billions of years ago, but rather shaped and continues to shape all the wonderful forms around us and within us. To discern simplicity amid complexity and to draw connections between life’s diverse phenomena and universal physical concepts gives us a deeper appreciation of ourselves, our fellow living creatures, and the natural world that we inhabit. I hope you’ll agree.

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