Contents

1 How Can We Understand Living Matter?

There is something at work in my soul, which I do not understand.

—Mary Shelley, *Frankenstein*

1.1 The Vital Challenge of Living Matter

The world around us is teeming with life. A lone traveler sits upon a cliff top, looking down upon the glassy waters that gave the Pacific Ocean its name. Our traveler notes a large brown patch of fish, undulating slowly under the curious eye of a sea lion swimming in their midst, as seen in figure 1.1. As the sea lion moves, the shape of the school of fish deforms, sometimes frothing as the predator speeds into the school. The traveler wonders, What are the rules that govern the shape of the fish school? How far within the school does the impinging sea lion's motion propagate? Science begins with curiosity about the mysteries of the world around us. Perhaps no mystery crowds in upon us as much as does the mystery of life itself.

Probably for as long as humans have been trying to understand the world around them, it has been clear that the living parts of the material world are qualitatively different from their inorganic counterparts. Ancient cave paintings already convey the dynamism of living beings with hunters in pursuit of their prey, illustrating a world vastly different from the rock upon which those images are painted. Alongside these commonplace observations have run a parallel scientific instinct to understand what they mean and how those phenomena work. What gives living matter its dynamic and malleable nature? Are biological materials truly governed by the same physical laws as lifeless, inorganic ones? A catchall concept that has been invoked and refuted over and over again is "vitalism," the idea that living matter is endowed with some special "force" that lies outside the purview of the laws of inanimate matter.

Though we skip over centuries of experimentation and scientific thinking on what makes living matter so different from its inorganic counterparts (such as the work of William Harvey on the active pumping of blood through the human body), our starting point is the microscopic observations of cytoplasmic streaming by the Italian priest and natural scientist Bonaventura Corti. Figure 1.2 shows the title page and a few surviving drawings from Corti's 1774 book on fluid flow within cells of the green alga *Chara*, a phenomenon we return to several times throughout the book as one of our principal case studies in the field theory of materials. The central mystery is very easily stated and parallels the questions that surrounded the nature of motion in nonliving matter that began with the thoughts of Aristotle on the relation between force and velocity. It led to the discredited idea that heavy objects fall faster than light objects. From there, our understanding of dynamics made major leaps forward with Galileo's

Figure 1.1

The wonder of a sea lion swimming through a huge collection of fish. The large brown blob that covers almost the entire field of view is a school of fish. To the left, a lone sea lion has "indented" the school by swimming into it. The fish have moved out of the way of the frolicking sea lion, and as it continues to swim, there is an ever-changing zone of clearance in the vicinity of the graceful predator. From the video "Mesmerizing Moment Sea Lion Swims through Giant School of Fish." Photograph by Nick Holton.

articulation of the law of inertia (i.e., bodies at rest or in uniform motion will stay that way) and Newton's formulation of the famed law of motion, $F = ma$, that takes center stage in our own analysis in later chapters. The key point is that the persistent streaming motions within an algal cell such as *Chara* seem to be quite at odds with our usual experience of mechanics, since that persistence leads to the uncomfortable feeling of some alliance with the otherwise discredited idea of a perpetual motion machine. How do these steady and interminable motions work?

Figure 1.2

Historical origins of the study of active matter. (A, B) The Italian natural scientist Bonaventura Corti is credited with the first observation of cytoplasmic streaming, or active intracellular flow, for his descriptions of flow within cells of the green alga *Chara* in 1774. (C) Streaming patterns in a *Chara braunii* cell. (A) and (B) from *Osservazioni microscopiche sulla Tremella e sulla circolazione del fluido in una pianta acquajuola*, by Bonaventura Corti (Apresso G. Rocchi, 1774). (C) from "Plasmolysis in *Characeae*" by T. Hayashi and E. Kamitsubo (*Shokubutsugaku zasshi*, 1959, vol. 72: 853–854) © The Botanical Society of Japan.

At nearly the same time as Corti's investigation of cytoplasmic streaming, another Italian, Luigi Galvani, puzzled over similar mechanistic questions in biological dynamism. In Galvani's case, it was the phenomenon of muscle action that focused his experiments, with one of the most famous insights being his ability to animate the muscles of dead frogs when in contact with an electrical source, as seen in figure 1.3. In his publication *De viribus electricitatis in motu musculari commentarius*, translated in English as *Commentary on the Effect of Electricity on Muscular Motion*, he dubbed this phenomenon "animal electricity," revealing the deep puzzles attending the inner workings of electricity that remained in the eighteenth and early nineteenth centuries. Indeed, another Italian, Alessandro Volta, adopted a view in which animal electricity should be viewed as just another manifestation of the broad phenomenon of "metallic electricity," foreshadowing centuries of debate about the extent to which a given phenomenon is uniquely lifelike. Some readers will recognize in the work of Galvani and Volta the seeds of an early classic of science fiction, *Frankenstein* by Mary Shelley. Muscles have been much more deeply understood as a molecular active matter phenomenon in which highly ordered molecular assemblies of motors and filaments can be made to spontaneously contract in the presence of ATP, as seen in figure 1.3(B, C).

In the nineteenth century, the study of metabolism unearthed deep insights into the way that living organisms perform chemical reactions to convert molecules from some raw form, such as a sugar, into usable substrates to provide both energy and building blocks for cells. Once again, the specter of vitalism reared its head, this time with Pasteur representing the perspective that fermentation, for example, was part of the life process revealing something special and different about the chemical transformations within living organisms, while the Buchner brothers argued that the fermentative process involved the ordinary goings-on of enzyme-mediated catalysis. As with the Galvani-Volta debate, viewed from the modern perspective, this debate seems now almost surprising since in a sense both parties to the debate had a correct but incomplete picture of what was really happening. Specifically, Pasteur was right that fermentation is indeed a key part of the story of how yeast cells make a living, harvesting energy from their environment to give rise to their apparent vitalistic qualities. On the other hand, the Buchner brothers were also correct in a sense that is played out over and over again in increasingly complex ways in the biochemist's lab to this day. Specifically, though the enzyme reactions that power the life of a yeast cell are part of what makes it lifelike, those same reactions can be carried out in a test tube with the only necessary living thing nearby being the human that pipetted in the relevant reagents.

These musings on vitalism have continued unabated in one form or another until the present day. Over 75 years ago, in a famed series of popular lectures that then became the inspiring book *What Is Life?*, Erwin Schrödinger formulated the active matter question as "How can the events in *space and time* which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?" More recently, a turn of the millennium opinion piece by Kirschner, Gerhart, and Mitchison on "molecular vitalism" asked the same questions, musing thus: "We do not question the importance of genetics, nor dispute the role of DNA as the blueprint for all the components of living systems, but we think it worth asking to what extent the postgenomic view of modern biology would convince a nineteenth century vitalist that the nature of

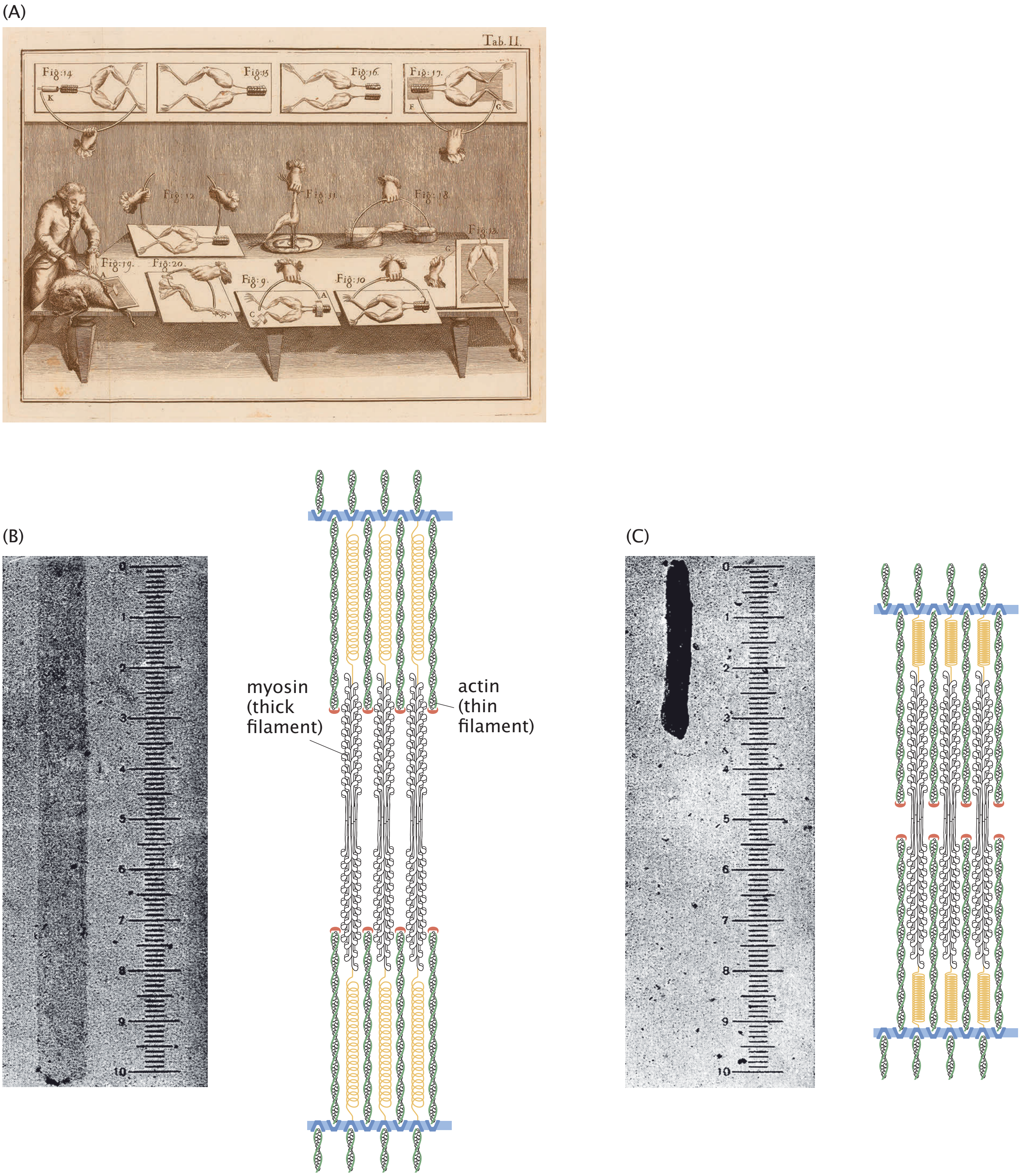

Figure 1.3

The development of understanding of muscle contraction. (A) The experiments of Luigi Galvani on the electrical stimulation of muscle twitching. Using a dead frog, Galvani discovered that he could use an electrical current to induce muscle twitching, lending credence to the idea that nervous impulses are electrical. Adapted from Galvani's book *De viribus electricitatis in motu musculari* (1792). (B) The work of Albert Szent-Györgyi showed that contraction of muscle fibers could be induced by ATP. The uncontracted fiber is shown here. (C) Muscle fiber after addition of ATP. Parts (B) and (C) adapted from "Discussion" in *Studies from the Institute of Medical Chemistry University of Szeged*, edited by A. Szent-Gyorgyi (vol. I, pp. 67–71), New York: Karger, 1941.

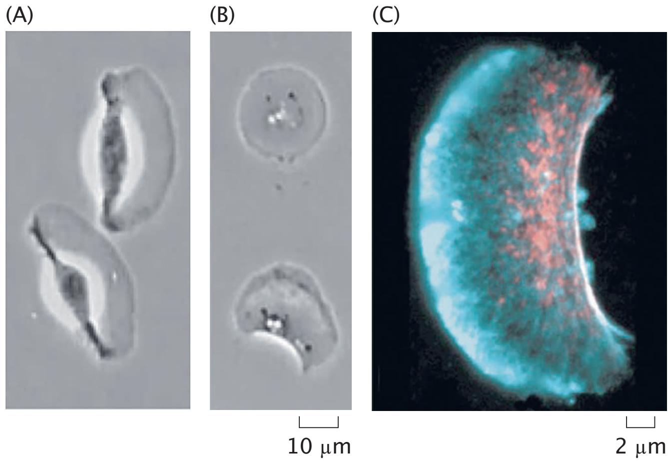

Figure 1.4

Keratocyte motion without a nucleus. (A) Image of keratocytes as they appear during motion. (B) Cellular fragments from keratocytes. The cell fragment at the top is nonpolarized and sessile. The cell fragment at the bottom is polarized and moving. (C) Distribution of myosin (red) and actin (cyan) in a motile fragment. Adapted from Verkhovsky, Svitkina, and Borisy (1999).

life was now understood. How close are we to understanding how a single cell functions or how an embryo develops? If the answer is not so close, will true understanding of living systems come from further annotating the database of genes, or must we explore the physicochemical nature of living systems?" In the same playful vein, figure 1.4 shows the motion of a keratocyte cell that has had its nucleus removed. At this point, the cell has become a physicochemical, active matter engine whose behavior raises precisely the kinds of questions that a field theory of living materials should be able to address.

All told, we hold that these questions about what makes living organisms life-like that have persisted across the generations remain fascinating and critical. Further, as we argue in this book, we believe that the fledgling field of active matter provides one route to better answering these questions.

1.2 The Active Matter Landscape

In recent decades, broad efforts to understand the mathematical and physical basis of living matter, reconciling theory and experimental data, have come together under the modern moniker *active matter*. These efforts ask how complex biological structures and phenomena emerge from rules governing individual energy-consuming agents, and seek to answer that question in firm mathematical and predictive language. For example, the 1995 work of Vicsek and then Toner and Tu on collective motions of animals sought to understand the emergence of two-dimensional ordered structures (flocks) by active agents (birds) and is considered by some the modern birth of active matter theory. At a million-fold smaller length scale, the work of Leibler, Nédélec, Surrey, and others in the late 1990s on self-organizing systems of molecular motors and filaments, like those shown in figure 1.5, illustrated the wondrous complexity of structure that emerges even from minimal, well-characterized active agents, where a mixture of microtubules, motors, and ATP suffice to drive the rich and beautiful structures seen in the figure. These kinds of clever in vitro experiments have been carried to an ever-increasing level of sophistication to the present day.

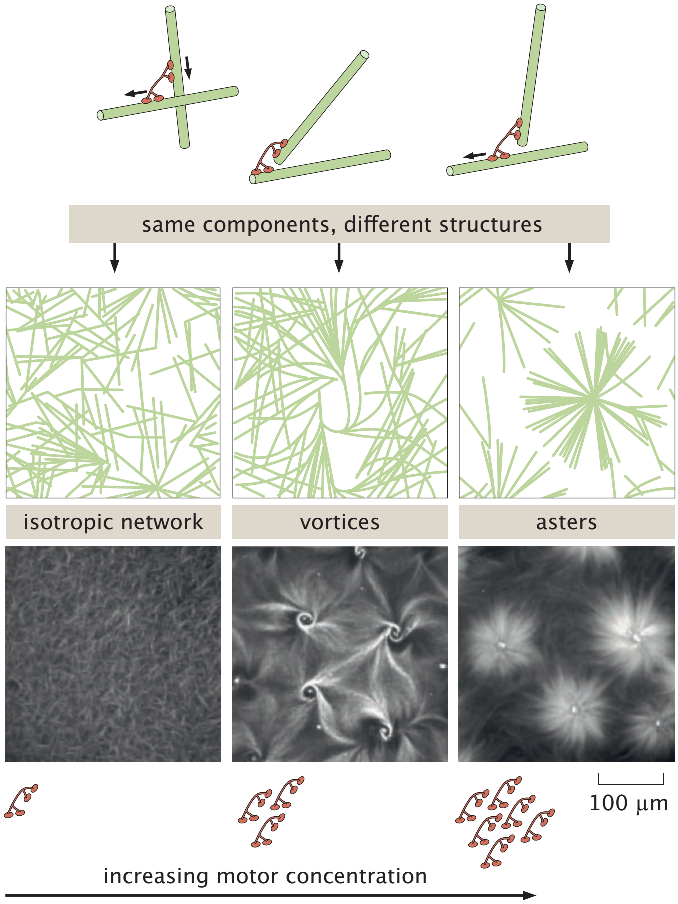

Figure 1.5

Motors orient and move microtubules to build different structures. As motor complexes walk on microtubules, they can reorient, slide, and cluster microtubules. The same molecular components (motors, microtubules, and ATP) can build different macroscopic structures. In the example shown, the microtubule structure that emerges is isotropic and uniform in density when few motors are present. As the ratio of motors to microtubules increases, the system self-organizes into vortices. At an even higher ratio of motors to microtubules, the system self-organizes into a different steady-state structure: asters. Adapted from Nédélec and Surrey (2001) (top) and Surrey, Nédélec, Leibler, and Karsenti (2001) (bottom).

Such simplified active systems with defined, microscopic energy-consuming agents, such as molecular motors or swimming bacteria, have proved a fertile testing ground for the development of active matter theories. These theories can explain the emergence of a very diverse set of phenomena, including topological defects, turbulent states, and intricate flows. While it can be tempting to confuse the study of these fertile active matter systems with the subject of active matter itself, we note that insights gained in these microscopic models have implications across much broader swathes of biology. Analogously, the subject of genetics is broader than the study of *Drosophila*, despite that system's utility in deciphering general genetic principles. The same active matter spirit and tools used in the microscopic context have been applied to understand the behavior of wildebeest herds crossing the Serengeti, the collective movement of cells in tissues, the contraction of cytoskeletal nets in starfish oocytes, and how flows across worm embryos contribute to developmental patterning, as shown in figure 1.6.

At this point, the subject of active matter has a vast and exciting literature, showcasing beautiful phenomena, incredibly clever experimental approaches, puzzling observations and measurements, and a variety of interesting models and theoretical principles. As such, as is noted by many authors attempting to survey a field, we cannot hope to even scratch the surface of this vast literature.

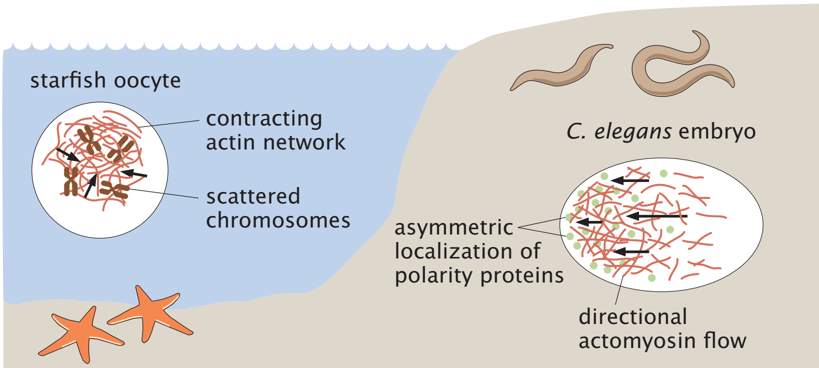

Figure 1.6

Active matter in context. Two classic examples of active actin networks. (Left) A contractile actin network in a starfish oocyte collects chromosomes scattered around this large cell, positioning them for efficient spindle assembly. (Right) Directional flows of actin and myosin at the cortex of a one-cell *C. elegans* embryo asymmetrically distribute PAR proteins, which break the embryo's anterior-posterior symmetry.

Here we provide a feeling for the different kinds of theoretical ideas that have been set forth in broad-brush strokes and point the reader to the Further Reading section at the end of the chapter.

Theoretical approaches to active matter often fall within two categories: discrete "agent-based" approaches and field-theoretic continuum approaches, as illustrated with a cytoskeletal example in figure 1.7. Discrete theories keep track of individual agents as they move or act over time. At each step forward in time, the properties of an individual agent (speed, position, state) update according to governing rules or equations. Continuum theories, on the other hand, zoom out to describe the system's properties of interest (speeds, concentrations, states) and their time evolution at a coarse-grained level. A continuum theory may keep track of a field of velocity vectors, each of which is a summary of the velocity of many individual agents. At each step forward in time, these velocity vectors update according to governing field equations, which are derived from fundamental physical laws and from a knowledge of the system's material properties. For example, as shown in figure 1.7, the changing organization of microtubules can be described either as a continuum of orientations (headless vectors) or at finer-grained resolution, tracking the movement of each individual microtubule. Readers are invited to explore a number of excellent reviews to get contrasting perspectives on the many achievements of the active matter field in the Further Reading section at chapter's end.

In the mid-1990s, the field of active matter can be said to have been actively born as a result of the surprising results of a discrete simulation model of moving active entities such as shown in figure 1.7, but this time in the context of large-scale animal motions. Though this work has now seen action in many different contexts, we are excited about its interpretation in the context of animal herding or bird flocking. The idea of these pioneering numerical studies was to construct an array of active agents that live within a square domain of dimension L and move at constant speed at all times. However, as a result of measuring the orientations of their neighbors, there is an update rule for figuring out the orientation of the flocking animal at the next time step that is of the form

$$\theta(t+\Delta t) = \langle\theta(t)\rangle_r + \Delta\theta. \tag{1.1}$$

The symbol $\langle\theta(t)\rangle_r$ means taking the average of the orientations of all the other agents within a radius of interaction r. We discuss these dynamics more deeply in chapter 15, (p. 316) where we will see that this update rule reflects a kind of

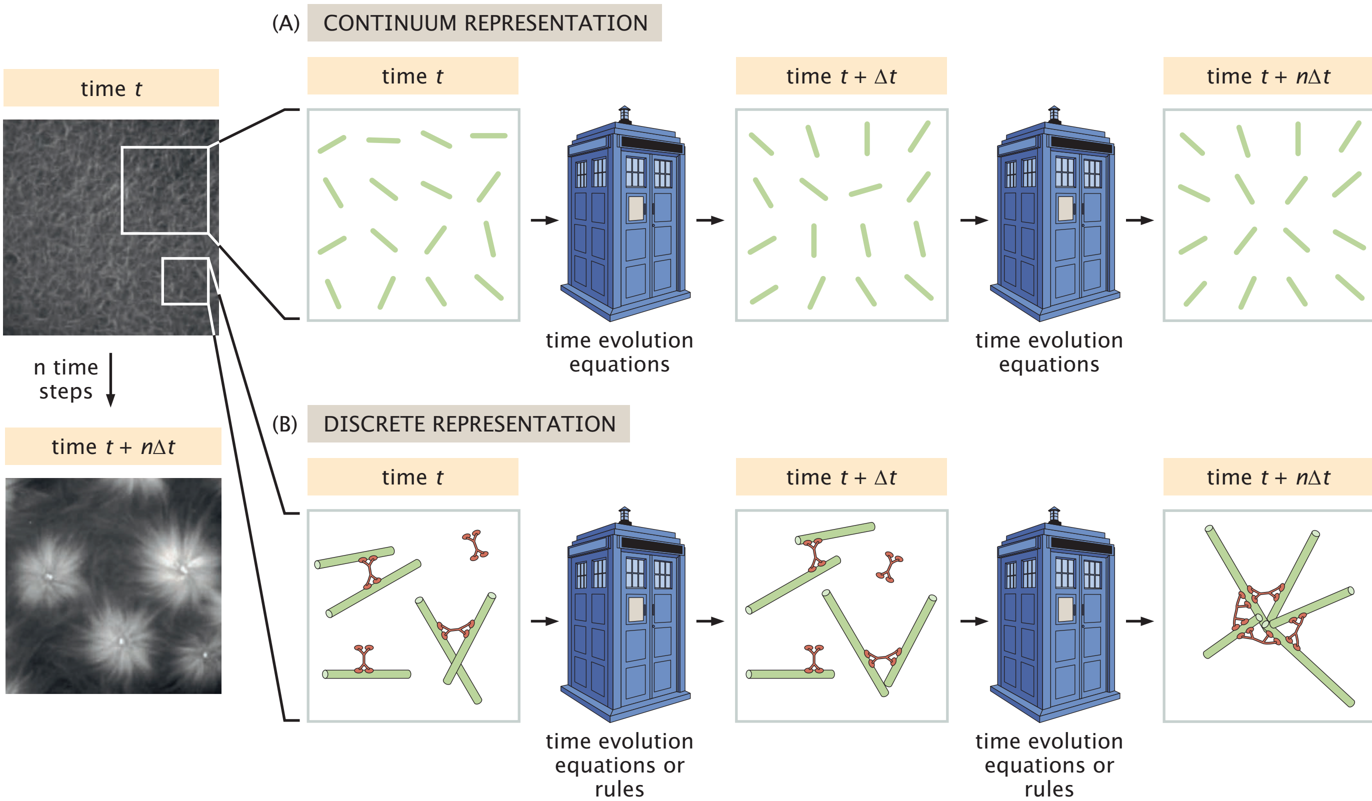

Figure 1.7

Inside the time machine. The dynamics of active matter can be thought of from either the continuum or discrete perspective. (A) Time steps in the evolution of the vector field describing orientation of filaments. (B) Time steps in the evolution of individual filaments. Adapted from Surrey, Nédélec, Leibler, and Karsenti (2001).

angular democracy, but for now we content ourselves with the simple concept highlighted above. Once the angle has been determined, the new position of each agent can be calculated using the time machine by recourse to the simple dynamical law

$$\mathbf{x}_i(t+\Delta t) = \mathbf{x}_i(t) + \mathbf{v}_i(t)\Delta t. \tag{1.2}$$

This simply tells each agent to go to a new position, which is gotten by adding the displacement $\mathbf{v}_i(t)\Delta t$ to its previous position. The term $\Delta\theta$ is a "noise" term that means that the angular democracy, like all democracies, is imperfect. Though the rule is to reorient precisely based on averaging over neighbors, the noise term perturbs that precise angular reorientation. The results of these kinds of simulations are shown in figure 1.8. As is often the case in statistical physics, we characterize the state of the system by evaluating key averages. The absolute value of the normalized velocity is given as

$$v_a = \frac{1}{Nv}\left|\sum_{i=1}^{N} \mathbf{v}_i\right| \tag{1.3}$$

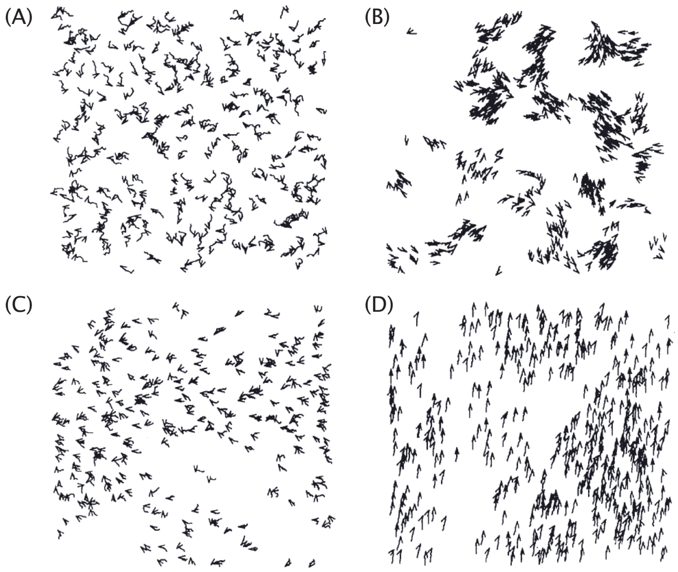

Figure 1.8

Simulation results from the Vicsek model. The arrowheads characterize the current direction of motion, and the squiggly lines behind each arrowhead show the agent's trajectory over the last 20 time steps. Adapted from Vicsek, Czirók, Ben-Jacob, and Choen (1995) © 1995 The American Physical Society.

and serves as a readout of herding behavior since, as is clear from the equation, when each animal points in a random direction, the parameter v_a is nearly zero, while for the case in which there is coherent motion, it has a nonzero value. Some of our readers might immediately think of the behavior of magnets, where the magnetic state is revealed by the presence of a nonzero magnetization corresponding to the sympathetic alignment of the different spins. That analogy holds here as well, though we must part with that analogy in recognizing that this is a dynamical effect and not an equilibrium phenomenon.

A series of results of this Vicsek model are shown in figure 1.8. From one frame to the next, the governing parameters that are being tuned are the density of agents, $\rho = N/L^2$, and the magnitude of the noise term introduced above $\Delta\theta$. Intuitively, we suspect that as the density gets sufficiently high without too much noise to perturb it, the ordered state will emerge as seen in figure 1.8(D). Though the coming chapters almost exclusively focus on the continuum field theory approach to problems in active matter, it is critical to remember that often the kinds of discrete approaches described briefly here provide mechanistic, numerical experiments that help us see how systems work in ways that the largely phenomenological field theory approaches may not.

Examples like those given above and the series of case studies from across scales that occupy center stage later in the book together demonstrate how the rise of the subject of active matter and its corresponding theories have served as a source rich in biological insights. We focus the opening chapters of our book on a pedagogical introduction to the continuum theory approach and its application to living systems. We hope to (1) convince our readers of the power of field theories, such as elasticity and fluid mechanics, which emerged shortly after Newton showed the world how to study dynamics; (2) provide the tools, building from the ground up, for life scientists to use field theory approaches to study their living systems; and (3) take the reader on a tour of the wonder of living matter, glimpsed through the natural language of mathematics.

Chapter Summary

This, our first chapter, sets the stage for all that follows. At the most fundamental level, the questions addressed here focus on what gives living organisms their lifelike properties and what kind of theoretical machinery is required to describe those properties. In this chapter, we began with a caricature of the way that the scientific perception of active matter has emerged over the millennia, with questions ranging from the apparent perpetual motion of flows within single cells to the twitching of frog legs in the presence of an electric potential. The point of view adopted here is that we are living through a wonderful and exciting period of discovery in which categories of matter that have traditionally fallen outside the purview of physics are now beginning to be considered in earnest. As the book unfolds, certain themes and principles appear over and over—ideas such as the coarse graining of discrete agents to yield field variables, the continuum theory protocol that shows us how to formulate field theories of matter both inanimate and living, and the ways in which symmetry can help us understand the terms that appear in those field theories. The chapters that follow aim to give our readers the tools to turn their imaginations loose in response to the mystery and wonder of the living world.

Further Reading

This list gives only a smattering of the many important and interesting places our readers can turn to learn more about the topic of our book.

Barnett, JA (2000). A history of research on yeasts 2: Louis Pasteur and his contemporaries, 1850–1880. *Yeast* 16: 755–771. Barnett wrote a wonderful series of articles on the place of yeast in our understanding of biochemistry, genetics, and cell biology, only two of which are highlighted here. This article examines the contributions of Pasteur, who argued that the metabolic reactions of cells were a critical part of maintaining the state we call alive.

Barnett, JA (2001). A history of research on yeasts 3: Emil Fischer, Eduard Buchner and their contemporaries, 1880–1900, *Yeast* 18: 363–388. This article takes the point of view of those scientists studying metabolism who rejected the vitalistic perspective and instead argued that the reactions of metabolism are just that—ordinary chemical reactions between different molecules.

Gross, P, Kumar, KV, Grill, SW (2017). How active mechanics and regulatory biochemistry combine to form patterns in development. *Annu. Rev. Biophys.* 46: 337–356. This excellent article shows how ideas from active matter physics can be used specifically in the context of developmental patterning.

Keener, JP (2021). *Biology in Time and Space: A Partial Differential Equation Modeling Approach*. American Mathematical Society, Providence, RI. This great book complements what we have done here.

Kirschner, M, Gerhart, J, and Mitchison, T (2000). Molecular "vitalism." *Cell* 100: 79–88. This inspiring article is full of interesting ideas and perspectives. As

the quote in the chapter illustrates, these authors believe that there is something more to explaining the apparently vitalistic aspects of living organisms than appealing to the genome sequence.

Marchetti, MC, Joanny, JF, Ramaswamy, S, Liverpool, TB, Prost, JM, Rao, M, and Simha, RA (2013). Hydrodynamics of soft active matter. *Rev. Mod. Phys.* 85: 1143–1189. This article is in many ways the definitive statement of the various problems and approaches in the field of active matter. The level is very high and thus the article is a difficult read. Our hope is that, after reading our book, much of this great article will be accessible to our readers.

Mukherjee, S (2022). *The Song of the Cell: An Exploration of Medicine and the New Human*. Scribner, New York. This book, while not explicitly about active matter, gives an excellent overview of the wide and varied lives of cells. Amusingly, we discovered after submission of our own book that Mukherjee also found the notion of the restless cell a fitting one, since that is the title of one of his chapters.

Phillips, R (2000). *Crystals, Defects and Microstructures*. Cambridge University Press, Cambridge, UK. This book, written by Rob long ago, represents the power of continuum thinking in the context of nonliving materials. Specifically for the purposes of the present book, ideas from the continuum theory of solids might help our readers see how the same approaches work in biological contexts.

Pismen, L (2021). *Active Matter within and around Us: From Self-Propelled Particles to Flocks and Living Forms*. Springer, Cham, Switzerland. This thoughtful book is full of insights into active matter phenomenology and how to think about it. The author turns his back on his natural inclination to talk about the subject quantitatively, giving a captivating narrative reflecting his very worthwhile take on the subject.

Prost, J, Jülicher, F, and Joanny, JF (2015). Active gel physics, *Nat. Phys.* 11: 111–117. This article is another interesting commentary by some of the most thoughtful creators and practitioners of the active matter art.

Rall, JA (2018). Generation of life in a test tube: Albert Szent-Györgyi, Bruno Straub, and the discovery of actin. *Adv. Physiol. Educ.* 42: 277–288. This article gives a compelling story of the work of Albert Szent-Györgyi in working out the molecular basis of muscle action, revealing the “active matter” character of the process.

Ramaswamy, S (2010). The mechanics and statistics of active matter. *Annu. Rev. Condens. Matter Phys.* 1: 323–345. This excellent article gives the perspective of one of the founders and masters of the field. We consider it mandatory reading.

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Verkhovsky, AB, Svitkina, TM, and Borisy, GG (1999). Self-polarization and directional motility of cytoplasm. *Curr. Biol.* 9: 11–20.

Vicsek, T, Czirók, A, Ben-Jacob, E, and Choen, I (1995). Novel type of phase transition in a system of self-driven particles. *Phys. Rev. Lett.* 75: 1226–1229.

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