Resource Letter:
Biological Physics

Raghuveer Parthasarathy

Department of Physics, The University of Oregon, Eugene, OR 97403

Email: raghu@uoregon.edu

June 5, 2021

NOTE: The following is a pre-submission preprint of an invited "Resource Letter" for *The American Journal of Physics* (AJP). AJP asks for "... an annotated bibliography, along with critical commentary, on a particular topic. Their primary purpose is to provide a survey for the non-specialist of a topic that is treated in an introductory or intermediate physics course... Resource Letters also can serve as a bridge for someone who is moving into a new area of teaching or research."

Symbols: "All references should be designated by E (Elementary), I (Intermediate), or A (Advanced)." – AJP

Abstract

This resource letter provides an overview of the literature in biological physics, a vast, active, and expanding field that links the phenomena of the living world to the tools and perspectives of physics. While no survey of this area could be complete, this list and commentary are intended to help provide an entry point for upper level undergraduates, graduate students, researchers new to biophysics, or workers in subfields of biophysics who wish to expand their horizons. Topics covered include subcellular structure and function, cell-scale mechanics and organization, collective behaviors and embryogenesis, genetic networks, and ecological dynamics.

I. Introduction

Life is full of variety, vigor, and clever solutions to daunting challenges. Physics provides deep, elegant insights into how nature works, and tools with which to gain ever-greater insights. In biological physics we find the merger of physics and biology. The resulting combination of diversity and depth, together with a wealth of practical applications, contributes to the vitality and size of the field.

The terms biological physics and biophysics are hard to define. I return to the possible distinction between the two terms below, but for now I'll note that one might consider either to denote the intersection of biology and physics, containing the systems and approaches of interest to both biologists and physicists, but this simply sidesteps the questions of what occupies that intersection and why. Moreover, since every living system obeys the laws of physics, it is hard to escape the conclusion that all of biology could fall under the umbrella of biological physics. Biophysicists do in fact consider scales ranging from ions to ecosystems; there is no shortage of topics to attract our attention. Nonetheless, one can state a few principles that, even if they don't quite define biological physics, at least unite many of its inquiries and methods.

One such principle is the notion that the physical properties of biological materials are central to their function. It is not surprising that bone strength influences the agility of animals, but this sort of connection extends to all the components of the living world. The mechanical stiffness of DNA governs how each of our cells pack about a meter of this molecule into every cell nucleus, while still managing to read out the code it carries. The nature of cellular membranes as two-dimensional liquids is integral to the activity of membrane-anchored proteins. Tissues and developing embryos can adopt solid- or fluid-like phases with different consequences for their dynamics. Understanding these and countless other systems requires more than information about genes or biochemical interactions; it requires a grasp of the physics at work.

A second principle is the notion that fluctuations, noise, and entropy are central to life. This is in some sense obvious – living things obey laws of physics, and statistical mechanics is central to these laws – but the extent to which it is embedded in the workings of life often comes as a surprise to those new to biophysics. Proteins explore complex free energy landscapes; genes are expressed in stochastic bursts; diffusion dictates the molecular distributions that pattern developing limbs. The tools that help us make sense of randomness give us insights into life, and conversely, life illustrates the potential of guided randomness to generate function.

A third principle is that the living world obeys general laws, transcending often complicated details, that are amenable to quantitative analysis. Making and testing numerical predictions, and assessing the mathematical forms of natural phenomena, have long been hallmarks of physics. Biological data are quantitative and precise in a large and expanding number of contexts, made possible in many cases by new biophysical tools, and in general facilitating the application of biophysical analyses. We can investigate the single protein molecules and untangle signatures of active motion and universal diffusive dynamics, observe the stochasticity of gene expression and relate it to dictates of probability theory, map the positions of thousands of cells in an embryo and identify characteristics of collective phases of matter, and more.

Is there a distinction between "biological physics" and "biophysics"? About twenty years ago, Frauenfelder, Wolynes, and Austin identified biological physics as "the field where one extracts interesting physics from biological systems" [1]. Aside from the impossibility of defining "interesting physics," the authors themselves noted that the differences between biological physics and biophysics "represent only psychological style and current attitude; the same person at different times could be thinking as a biophysicist or as a biological physicist." There are certainly many areas in which studies of biological phenomena have advanced our understanding of physical concepts, for example in studies of active and non-equilibrium systems and complex networks of various sorts. However, given the principles above, it is hard to imagine "biophysical" topics from which one could not also extract "biological physics." I believe there is little to gain by thinking about the distinction.

The following list of resources for biological physics is necessarily incomplete and idiosyncratic – it could not be otherwise. It is informed by my experiences in the field, many discussions with colleagues over many years, and biophysics courses I have designed for both graduate students and non-science-major undergraduates. Biophysicists have very diverse perspectives, and I encourage the reader to seek out other views as well. I have divided these resources into three primary sections: General Resources, including textbooks and online seminars; Biological

Physics Within the Cell, on the goings-on inside the basic building block of all organisms, Biological Physics Beyond the Cell, on larger-scale organization and activity from organs to ecosystems.

1. "Biological Physics," H. Frauenfelder, P. G. Wolynes, and R. H. Austin, Rev. Mod. Phys. **71**, S419-430 (1999).

II. General Resources

The following resources each span a wide range of topics and can serve, especially in the case of the textbooks, as valuable introductions to the field.

A. Textbooks

Thorough, well-written, and captivating textbooks exist on the topic of biological physics. Each of the books listed below, written by and for physicists, provides biological information, physical insights, abundant examples of contemporary research, and exercises that help build the reader's skills.

2. Biological Physics Student Edition: Energy, Information, Life, P. Nelson (Chiliagon Science, 2020). Aimed at undergraduates and beginning graduate students, this clear and well-structured text emphasizes the connections between statistical mechanics and biophysical phenomena. (E)

3. Physical Biology of the Cell, R. Phillips, J. Kondev, J. Theriot, and H. Garcia (Garland Science, London: New York, 2nd edition., 2012). Aimed at undergraduates and beginning graduate students, this text spans a vast range of cellular systems, conveying the power of quantitative and physical perspectives to provide insights. (E)

4. Biophysics: Searching for Principles, W. Bialek (Princeton University Press, Princeton, NJ, 2012). This graduate-level text takes a rigorous, information-centric approach, using noise, fluctuations, and other statistical-mechanical concepts to explore phenomena like developmental pattern formation, chemotaxis, and signaling. (I)

B. Internet Resources

Many recorded talks, blog posts, and short comments are available in various venues online. The following are a few resources for seminars and reference information.

5. Biological Physics/Physical Biology Virtual Seminars, https://iyerbiswas.com/outreach/bppbseminars/schedule/, accessed May 15, 2021. Given and recorded during the 2020-21 Covid-19 pandemic, these Zoom-based virtual seminars cover a wide variety of biophysical topics. (I)

6. iBiology talks, https://www.ibiology.org/, especially on Biophysics (https://www.ibiology.org/research-talks/biophysics/) and microscopy (https://www.ibiology.org/online-biology-courses/microscopy-series/), accessed May 15, 2021. The large collection of iBiology videos is produced by the American Society for Cell Biology, with the aim of conveying topics in science as well as the process of how science works to a wide audience. (E)

7. Molecular Biology of the Cell, B. Alberts, A. D. Johnson, J. Lewis, D. Morgan, M. Raff, K. Roberts, P. Walter, (Garland Science, 2002). A standard undergraduate molecular biology textbook. It doesn't provide a physical perspective, but it gives a wealth of useful information about the components, functions, and activities of cells. The fourth edition is freely available online: https://www.ncbi.nlm.nih.gov/books/NBK21054/, accessed May 15, 2021. (E)

8. bioRxiv, https://www.biorxiv.org/, accessed May 15, 2021. A widely used biology preprint server, with a large biophysics section. Receiving its emails alerts provides access to a steady stream of cutting-edge reports. (I).

9. Cell Biology by the Numbers, http://book.bionumbers.org/, accessed May 15, 2021. Useful quantitative information about many aspects of biology at cell-scales and smaller. (E)

C. Popular Science Books

There are remarkably few popular science books on biological physics (spurring me to write my own, noted below). Nonetheless, a handful of excellent works intersecting topics of biophysical interest exist.

10. Sync: How Order Emerges from Chaos in the Universe, Nature, and Daily Life, Steven H. Strogatz (Hachette Books, 2003). A fascinating look at spontaneous order and synchronization, with many examples from the living world including the choreographed flashing of certain fireflies. (E)

11. How to Walk on Water and Climb Up Walls: Animal Movement and the Robots of the Future, David L. Hu (Princeton University Press, 2018). About some of the clever tactics animals have devised to move in challenging environments, and technologies that can mimic these feats. (E)

12. So Simple a Beginning: How Four Physical Principles Shape Our Living World, Raghuveer Parthasarathy (Princeton University Press, 2022). On biophysics, and how a physical perspective on life illuminates wonders spanning scales from viruses to elephants, and also spawns technologies for altering cells, organs, and even whole organisms. (E)

13. The Vital Question: Energy, Evolution, and the Origins of Complex Life, Nick Lane (W. W. Norton, 2015). One of several excellent books by Nick Lane, this focuses especially on the roles of energy in cellular activity and the origins of life. (E)

14. The Machinery of Life, David Goodsell (Springer; 2nd ed. 2009). An illustrated survey of the molecules and molecular machines that make up cells. (E)

15. The Self-Made Tapestry: Pattern Formation in Nature, Phillip Ball (Oxford University Press, 2001). On pattern formation, spanning both the non-living world (e.g. rippling sand dunes) and the living (e.g. animal coats). (E)

III. Biological Physics Within the Cell

The resources in this section consider the structures, activities, and guiding principles at play inside cells.

A. DNA

No molecule exemplifies our modern understanding of life as much as DNA. DNA is, of course, the carrier of genetic information. It is also a tangible thing whose physical properties are deeply connected to its function. Physicists have been central to the investigation of DNA for well over half a century, with contributions to our understanding of its structure from well-known names like Erwin Schrodinger (cited below) that even precede the discovery of the double helix. Around the turn of century, methods for manipulating single molecules of DNA and RNA provided unprecedented insights into the interplay between microscopic mechanics, statistical thermodynamics, and function. More recently, the advent of contemporary experimental and theoretical tools to probe the dynamic three-dimensional architecture of DNA in living cells contributes to ongoing excitement about the biophysics of DNA. Basic aspects of

DNA mechanics are covered well in the Nelson and Phillips *et al.* textbooks noted earlier. The following papers are landmarks or good entry points to the biophysics of DNA or entire genomes.

16. "Ten years of tension: single-molecule DNA mechanics," C. Bustamante, Z. Bryant, and S. B. Smith, Nature **421**, 423-427 (2003). A brief review of experimental methods for manipulating single molecules and measuring their physical properties, and what we've learned from applying these tools to DNA. (E)

17. "Stretching DNA with optical tweezers," M. D. Wang, H. Yin, R. Landick, J. Gelles, and S. M. Block, Biophysical Journal **72**, 1335-1346 (1997). A pioneering experimental study of single DNA molecules. (E).

18. "Osmotic pressure inhibition of DNA ejection from phage," A. Evilevitch, L. Lavelle, C. M. Knobler, E. Raspaud, and W. M. Gelbart, Proc. Natl. Acad. Sci. **100**, 9292-9295 (2003). Elegant experiments revealing the high-pressure packaging of DNA in viruses. (E)

19. "Higher-order chromatin structure: bridging physics and biology," G. Fudenberg, L. A. Mirny, Current Opinion in Genetics & Development **22**, 115–124 (2012). On the intermediate scale of DNA organization, between the double helix and complete chromosomes, especially highlighting polymer physics perspectives. (I)

20. "Comprehensive mapping of long-range interactions reveals folding principles of the human genome," E. Lieberman-Aiden, N. L. van Berkum, L. Williams, M. Imakaev, T. Ragoczy, A. Telling, I. Amit, B. R. Lajoie, P. J. Sabo, M. O. Dorschner, R. Sandstrom, B. Bernstein, M. A. Bender, M. Groudine, A. Gnirke, J. Stamatoyannopoulos, L. A. Mirny, E. S. Lander, and J. Dekker, Science, **326**, 289–93 (2009). Describes a method to map the structure and topology of the human genome in cells, revealing a "fractal globule" organization of our nuclear DNA. This "Hi-C" method, like several other twenty-first century tools, is enabled by DNA sequencing technologies. (I)

21. "Nonequilibrium Biophysical Processes Influence the Large-Scale Architecture of the Cell Nucleus," A. Agrawal, N. Ganai, S. Sengupta, and G. I. Menon, Biophysical Journal, **118**, 2229–2244 (2020). On physical principles related to non-equilibrium activity that may govern genome architecture in cells. (A).

22. What Is Life? The Physical Aspect of the Living Cell, E. Schrödinger (Cambridge University Press, 1944). Schrödinger muses on how physical and chemical principles can make life work. Perhaps most notably, he suggests that genetic material may take the form of an "aperiodic crystal" to provide both robustness and information content, presciently anticipating the as-yet-undiscovered form of DNA. (E)

23. The Eighth Day of Creation, H. F. Judson (Cold Spring Harbor Laboratory Press, 1996). An account of the early history of molecular biology, with a clear and detailed description of the discovery of DNA's structure, and the people involved. (E)

B. Proteins, Protein Structure, and Protein Folding

Protein molecules shape themselves into specific three-dimensional forms, with form and function intimately connected. The characterization of protein structure via crystallography was one of physics' most important contributions to biology, and its methods are now well established. Current topics of particular interest to physicists include the challenge of predicting protein structure, known as the "protein folding problem," understanding the landscape of possible forms, and experimentally probing the paths taken as proteins explore these landscapes.

24. The Physics of Proteins: An Introduction to Biological Physics and Molecular Biophysics, Hans Frauenfelder (Springer, 2010). Short chapters, based on lecture notes, on the basics of protein structure as well as more advanced topics. (I)

25. The Protein Data Bank, https://www.rcsb.org/, accessed May 15, 2021. A repository of molecular structures for over 150,000 proteins, along with tools and descriptions. Particularly notable is the "Molecule of the Month" series, which showcases and describes important proteins. (E)

26. "A rotary molecular motor that can work at near 100% efficiency," K. J. Kinosita, R. Yasuda, H. Noji, and K. Adachi, Philos. Trans. R. Soc. Lond. B Biol. Sci. **355**, 473-489 (2000). Remarkable experiments measuring the efficiency of F1-ATPase, a molecular motor that forms part of an essential protein complex. (I)

27. "The physics of molecular motors," C. Bustamante, D. Keller, and G. Oster, Acc. Chem. Res. **34**, 412-420 (2001). Describes the theory underlying the operation of molecular motors, with the F0 rotary motor as an example. (I)

28. "Thermodynamics and kinetics of molecular motors," R. D. Astumian, Biophysical Journal **98**, 2401–2409 (2010). On the principles governing molecular motors, especially those that transform chemical energy into linear motion. (I)

29. "The biophysicist's guide to the bacterial flagellar motor," J. A. Nirody, Y.-R. Sun, and C.-J. Lo, Advances in Physics: X **2,** 324-343 (2017). A short review article on the bacterial flagellar motor, including the chronology of our understanding of it. (E)

30. "Torque-generating units of the flagellar motor of Escherichia coli have a high duty ratio," W.S. Ryu, R. M. Berry, and H. C. Berg, Nature **403,** 444-447 (2000). An example of precision measurements of the performance of molecular motors, in this case a bacterial flagellar motor. (I)

31. "Mechanical processes in biochemistry," C. Bustamante, Y. R. Chemla, N. R. Forde, and D. Izhaky, Annu. Rev. Biochem. **73**, 705-748 (2004). On how mechanical forces influence molecular activities. (I).

32. "The protein folding problem," K. A. Dill, S. B. Ozkan, M. S. Shell, and T. R. Weikl, Annual Review of Biophysics **37**, 289-316 (2008). A review article describing the problems of protein folding, and strategies for solving them. (I)

33. "Single-molecule fluorescence spectroscopy maps the folding landscape of a large protein," M. Pirchi, G. Ziv, I. Riven, S. S. Cohen, N. Zohar, Y. Barak, and G. Haran, Nature Communications **2**, 493 (2011). An example of a study using fluorescence-based methods to examine the dynamics of single, folding proteins. (A)

34. "Protein folding studied by single-molecule FRET," B. Schuler, W. A. Eaton, Current Opinion in Structural Biology **18**, 16-26 (2008). A review article on how single-molecule fluorescence studies can give insights into protein folding. (I)

35. "'The game has changed.' AI triumphs at protein folding," R. F. Service, Science **370**, 1144-1145 (2020). Deep learning methods have recently proven to be remarkably successful at predicting protein structures, as noted in this news article. Whether such methods can illuminate the underlying physics remains to be seen. (E)

C. Supramolecular organization

Biological molecules often organize themselves into larger scale structures. Proteins, for example, link into all sorts of shapes from one-dimensional chains to regular three-dimensional polygons to phase-separated blobs. Lipids form into membranes;

DNA is increasingly being artificially crafted into techniques appropriately described as "origami." Both the principles of supramolecular organization and its natural and artificial functions are of interest to biological physicists.

36. "The cell as a material," K. E. Kasza, A. C. Rowat, J. Liu, T. E. Angelini, C. P. Brangwynne, G. H. Koenderink, and D. A. Weitz, Current Opinion in Cell Biology **19,** 101-107 (2007). A short review article on the complex mechanical properties of cellular cytoskeletal networks, especially as probed in cell-free, *in vitro* experiments. (I)

37. "Mechanotransduction by the actin cytoskeleton: Converting mechanical stimuli into biochemical signals," A. R. Harris, P. Jreij, and D. A. Fletcher, *Annual Review of Biophysics*. **47**, 617-631 (2018). Actin and associated molecules form one of the major cytoskeletal networks in cells, giving rise to mechanical properties that dynamically respond to internal and external stimuli. (A)

38. "Large-scale vortex lattice emerging from collectively moving microtubules," Y. Sumino, K. H. Nagai, Y. Shitaka, D. Tanaka, K. Yoshikawa, H. Chaté, and K. Oiwa, Nature **483,** 448-452 (2012). On experiments showing that protein filaments and motors, reconstituted outside of cells, can self-organize into dynamic, self-organized patterns. (I)

39. "MreB filaments align along greatest principal membrane curvature to orient cell wall synthesis," S. Hussain, C. N> Wivagg, P. Szwedziak, F. Wong, K. Schaefer, T. Izoré, L. D. Renner, M. J. Holmes, Y. Sun, A. W. Bisson-Filho, S. Walker, A. Amir, J. Löwe, and E. C. Garner, eLife **7,** e32471 (2018). It was only recently discovered that bacteria have cytoskeleton. This paper describes a remarkable relationship between bacterial filament organization and cellular curvature. (I)

40. "Protein self-organization: Lessons from the Min system," M. Loose, K. Kruse, and P. Schwille, Annual Review of Biophysics **40,** 315-336 (2011). On the self-organization of the bacterial Min system, which makes patterns in space and time. (I)

41. "Liquid-liquid phase separation in biology," A. A. Hyman, C. A. Weber, and F. Jülicher, Annual Review of Cell and Developmental Biology **30,** 39-58 (2014). A review paper on a rapidly developing topic of when and how proteins can phase separate into distinct liquid zones. (A)

42. "Advancing biophysics using DNA origami," W. Engelen and H. Dietz, Annual

Review of Biophysics **50,** 469-492 (2021). A recent review paper on the biophysics of DNA origami, and also new biophysical tools that DNA origami makes possible. (I)

D. Membranes, Surfaces, and Interfaces

Much of life takes place at interfaces – gas exchange at the surfaces of leaves and lungs, for example, and cell-cell signaling at the membranes that demarcate cell boundaries. The physics of these environments is fascinating, as their nature as quasi-two-dimensional materials in a three-dimensional world influences how principles of electrostatics, statistical mechanics, and mechanics are manifested.

43. Intermolecular and Surface Forces, J. Israelachvili (Academic Press, New York, 1991). Clear and comprehensive, its treatment of electrostatics in liquids is especially useful. (I)

44. Statistical Thermodynamics of Surfaces, Interfaces, and Membranes, S. A. Safran (Westview Press, Boulder, CO, 2003). On the rich statistical physics of two-dimensional materials in a three-dimensional world. (I)

45. Structure and Dynamics of Membranes, edited by R. Lipowsky and E. Sackmann (North Holland, 1995). Stand-alone chapters on a variety of fundamental aspects of membrane biophysics. (I)

46. "Separation of liquid phases in giant vesicles of ternary mixtures of phospholipids and cholesterol," S. L. Veatch, S. L. Keller, Biophys. J. **85**, 3074-3083 (2003). Lipid membranes can spontaneously separate into coexisting two-dimensional liquid phases, analogous to miscibility phase transitions in non-biological materials and likely an important tool with which cells can organize their surfaces. (I)

47. "Curvature and spatial organization in biological membranes," R. Parthasarathy and J. T. Groves, Soft Matter **3,** 24–33 (2007). A review article on the physics of membrane curvature, and its manifestations. (I)

48. "Principles and applications of biological membrane organization," W. F. Zeno, K. J. Day, V. D. Gordon, and J. C. Stachowiak, Annual Review of Biophysics **49,** 19-39 (2020). A review paper on the maintenance and utility of heterogeneity in membranes. (I)

E. Genetic Networks and Systems Biology

A hallmark of life is adaptability, implemented at all its scales. At the level of DNA, the activation or repression of the expression of individual genes is tied to all sorts of stimuli, including the expression of other genes. Genes thereby form networks of activity, made possibly by the specificity of protein and DNA interactions but also by general principles of dynamical systems that give rise to motifs like feedback loops, oscillations, and memory. The study of genetic networks intersects the broad field of systems biology, which also encompasses the engineering of new genetic circuits.

49. An Introduction to Systems Biology: Design Principles of Biological Circuits, 2nd edition, U. Alon (Chapman and Hall / CRC Press, 2019). A textbook on systems biology. Both this and the book by Voit listed below are clear and engaging. (E)

50. A First Course in Systems Biology, Eberhard Voit (Garland Science, 2nd edition, 2017). A textbook on systems biology. (E)

51. Physical Models of Living Systems, P. C. Nelson (W. H. Freeman, 2015). A short textbook exploring gene regulation and networks from the perspective of physics and dynamical systems. (E)

52. "A synthetic oscillatory network of transcriptional regulators," M. B. Elowitz and S. Leibler, Nature **403**, 335-338 (2000). An elegant example of designing and building a circuit from biological components, in this case an oscillator (I).

IV. Biological Physics Beyond the Cell

The resources in this section consider the scales greater than that of individual cells, involving for example microscopic motion and navigation, the organization of tissues and embryos, and even the largest scales of activity spanning whole ecosystems.

A. Motility and Sensing

Motion has always been a central concern of physicists. The motion of living objects provides amazing, beautiful, and important illustrations of how mechanisms for generating movement and directing it to particular ends is governed by physical principles. (See especially the textbook by Bialek, noted above, for physical constraints on cellular information processing.) Notably, physicists' explorations of organismal motion span scales from the microscopic behaviors of individual cells to the macroscopic dynamics of flocks, swarms, and schools of animals.

53. Random Walks in Biology, H. C. Berg (Princeton University Press, Princeton, NJ, 1993). A classic and very readable book on the properties of random walks and their importance in biology. (E)

54. "Life at low Reynolds number," Purcell, E. M., American Journal of Physics **45**, 3-11 (1977). A highly influential paper on how basic principles of fluid mechanics have an enormous impact on microbial motion. (E)

55. "Physics of chemoreception," H. C. Berg and E. M. Purcell, *Biophys J.* **20**, 193-219 (1977). Elegant, fundamental physical constraints on how well microscopic creatures can sense molecular cues. (E)

56. "Live from under the lens: exploring microbial motility with dynamic imaging and microfluidics," K. Son, D. R. Brumley, and R. Stocker, Nature Reviews Microbiology **13,** 761-775 (2015). A review article mostly describing microfluidic tools for studying microbial motion and navigation, but also discussing the biophysics of these activities. (I)

57. "Hydrodynamics and Phases of Flocks," J. Toner, Y. H. Tu, and S. Ramaswamy, *Annals of Physics.* **318**, 170-244 (2005). On theories of flocking, or directed self-driven collective motion. (A)

58. "Scale-free correlations in starling flocks," A. Cavagna, A. Cimarelli, I. Giardina, G. Parisi, R. Santagati, F. Stefanini, and M. Viale, *Proc. Natl. Acad. Sci.* **107**, 11865-11870 (2010). Experiments on flocking, with impressive imaging and detailed analysis. (A)

B. Embryos, Tissues, and Other Collections of Cells

The transformation of a single cell into a complete organism is one of nature's most stunning feats. Multicellular development has fascinated scientists for centuries, and though it involves considerable biochemical and genetic complexity, it also reflects universal physical principles governing pattern formation and mechanics that are increasingly amenable to quantitative understanding. These issues are also central to other multi-cellular systems such as tissues and organs, either in their natural state or in newly engineered construction such as organoids. I also include here a recent resource letter on physics and neuroscience; the two have had a long and rich history of intersections.

59. “Matrix elasticity directs stem cell lineage specification,” J. Engler, S. Sen, H. L. Sweeney, and D. E. Discher, Cell **126**, 677-689 (2006). A highly influential paper on the discovery that the mechanical stiffness of a substrate can influence what type of cell a stem cell turns into. (I)

60. “A density-independent rigidity transition in biological tissues,” D. Bi, J. H. Lopez, J. M. Schwarz, and M. L. Manning, Nature Physics **11**, 1074-1079 (2015). A model of a phase transition governing tissue mechanics. (I)

61. “Organoids by design,” T. Takebe and J. M. Wells, Science **364**, 956-959 (2019). A brief review of principles guiding organoid formation. (E)

62. “Fluid flows and forces in development: functions, features and biophysical principles,” J. B. Freund, J. G. Goetz, K. L. Hill, and J. Vermot, Development **139**, 1229-1245 (2012). On fluid flows in organismal development. (E)

63. “3 minutes to precisely measure morphogen concentration,” T. Lucas, H. Tran, C. A. P. Romero, A. Guillou, C. Fradin, M. Coppey, A. M. Walczak, and N. Dostatni, *PLOS Genetics*. **14**, e1007676 (2018). Quantitative measurements of molecular dynamics in a developing embryo. (I)

64. “Optimal decoding of cellular identities in a genetic network,” M. D. Petkova, G. Tkačik, W. Bialek, E. F. Wieschaus, and T. Gregor, *Cell*. **176**, 844-855.e15 (2019). Experiments, analysis, and theory showing how the expression of four genes suffices to specify positions in a developing embryo to an accuracy of 1%. (A)

65. “Positional information, in bits,” J. O. Dubuis, G. Tkačik, E. F. Wieschaus, T. Gregor, and W. Bialek, *PNAS*. **110**, 16301–16308 (2013). Connecting randomness and diffusion in a developing embryo to insights from information theory. (I)

66. “Villification: How the Gut Gets Its Villi,” A. E. Shyer, T. Tallinen, N. L. Nerurkar, Z. Wei, E. S. Gil, D. L. Kaplan, C. J. Tabin, and L. Mahadevan, *Science*. **342**, 212–218 (2013). On how physical forces generate the ridges, bumps, and zigzags of the gut. (A)

67. “In Toto Imaging and Reconstruction of Post-Implantation Mouse Development at the Single-Cell Level.,” K. McDole, L. Guignard, F. Amat, A. Berger, G. Malandain, L. A. Royer, S. C. Turaga, K. Branson, and P. J. Keller, *Cell*. **175**, 859–876 (2018). An example of contemporary imaging advances that allow tracking every cell in a developing embryo in model organisms like zebrafish or, as in this case, mice. (A)

68. "Embryonic tissues as active foams," S. Kim, M. Pochitaloff, G. A. Stooke-Vaughan, and O. Campàs, *Nature Physics*, 1–8 (2021). Embryonic tissues have properties reminiscent of solids, liquids, and glasses. Here, the authors show that actively driven fluctuations of mechanical tension at cell boundaries can fluidize collections of cells. (A)

69. On Growth and Form, D. W. Thompson (Cambridge University Press, Cambridge, UK, 1942). A massive, imaginative exploration of the geometry of animal and plant forms, and how they might be generated. (A)

70. "Resource Letter PB-1: The physics of the brain," C. G. Fink, American Journal of Physics, **86**, 805-817 (2018). A Resource Letter, like this one, but focused entirely on physics and neuroscience. (E)

C. Organism-scale Biophysics

Biophysics and biological physics typically focus on microscopic scales. Physics, of course, applies much more broadly, for example to the function of organ systems, whole organisms, and even ecosystems. Much of the study of organismal function falls under the classic headings of biomechanics and animal and plant physiology, vast fields in themselves. The references below give a few examples that may be of particular interest to physicists.

71. Environmental Physiology of Animals, P. Willmer, G. Stone, I. Johnston (Wiley-Blackwell, 2004). A textbook on animal physiology. (E)

72. Life in Moving Fluids: The Physical Biology of Flow, S. Vogel (Princeton University Press, Princeton, N.J., 2nd Revised edition., 1996). An influential and engaging book on the intersection of fluid mechanics and biology. (I)

73. Life's Devices: The Physical World of Animals and Plants, S. Vogel (Princeton University Press, Princeton, NJ, 1988). A captivating look at the physics and engineering underlying many amazing aspects of animals and plants, from shark skeletons to spider silk.

74. "Transporting water to the tops of trees," N. M. Holbrook and M. A. Zwieniecki, Phys. Today **61**, 76-77 (2008). On the surprisingly difficult question of how trees get water to their tips. (E)

75. Dialogues Concerning Two New Sciences, G. Galilei (Cosimo Classics, New

York, 2010). First published in 1638, Galileo discusses the physics governing bone size. (E)

76. On Being the Right Size and Other Essays, J. B. S. Haldane (Oxford University Press, Oxford; New York, 1985). On the scaling relationships that govern animal form. (E)

D. Medical Physics

Physics finds many powerful applications in health and medicine, including radiation therapies and many varieties of medical imaging. Medical physics is a large field in itself, with devoted professional organizations and publications.

77. "Resource Letter MP-2: Medical physics," R. K. Hobbie and B. J. Roth, American Journal of Physics, **77**, 967-978 (2009). A Resource Letter, like this one, but focused entirely on medical physics. (E).

78. Intermediate Physics for Medicine and Biology, 4th ed., R. K. Hobbie and B. J. Roth (Springer, New York, 2007). A textbook on many aspects of medical physics, as well as biological physics more broadly. An associated blog contains a wealth of information (http://hobbieroth.blogspot.com/). (I)

79. Introduction to Physics in Modern Medicine, 3rd ed., S. A. Kane and Boris Gelman (CRC Press, 2020). This textbook covers lasers, ultrasound, nuclear medicine, magnetic resonance imaging, and more. (E)

E. Ecology and Evolution

The existence of general rules describing collections of species, or whole ecosystems, has long been debated. In influential work, Robert May in the 1970s applied random matrix theory to generic models of inter-species interactions to explore questions of stability. In recent years, a growing number of physicists have examined issues of coexistence and cooperation in strongly interacting living systems. The topic also intersects that of evolutionary dynamics, especially in the interplay between random and non-random processes.

80. Stability and Complexity in Model Ecosystems, R. M. May (Princeton University Press, Princeton, Reprint edition., 2001). Classic work on instability in ecosystems. (I)

81. "Metabolic trade-offs promote diversity in a model ecosystem," A. Posfai, T. Taillefumier, and N. S. Wingreen, Phys. Rev.

Lett. **118,** 028103 (2017). A theoretical model of how stability in ecosystems can arise. (I)

82. "The transition between the niche and neutral regimes in ecology," C. K. Fisher and P. Mehta, Proc. Natl. Acad. Sci. 111, 13111-13116 (2014). Phase transitions in ecological dynamics. (I)

83. "Evolutionary dynamics and statistical physics," D. Fisher, M. Lässig, and B. Shraiman, J. Stat. Mech. **2013**, N01001 (2013). The introduction to a special issue on evolutionary dynamics and statistical physics, giving a sense of questions in the field. (E)

84. "Range expansions transition from pulled to pushed waves as growth becomes more cooperative in an experimental microbial population," S. R. Gandhi, E. A. Yurtsev, K. S. Korolev, and J. Gore, Proc. Natl. Acad. Sci. **113,** 6922-6927 (2016). On how microbial communities expand in space. (I)

85. "Genetic drift at expanding frontiers promotes gene segregation," O. Hallatschek, P. Hersen, S. Ramanathan, and D. R. Nelson, *Proc. Natl. Acad. Sci.* 104, 19926-19930 (2007). On connections between how communities expand in space and signatures of random genetic fluctuations. (I)

86. "Emergent simplicity in microbial community assembly," J. E. Goldford, N. Lu, D. Bajić, S. Estrela, M. Tikhonov, A. Sanchez-Gorostiaga, D. Segrè, P. Mehta, and A. Sanchez, Science **361**, 469-474 (2018). Experiments uncovering unexpected simplicity in multi-species communities. (A)

Acknowledgments

I thank Nancy Forde, Eric Dufresne, Jayanth Banavar, and Jayson Paulose for suggestions, and the authors of the textbooks noted above for their work in organizing a sprawling field. In books and in many conversations, Philip Nelson especially has provided valuable perspectives.