Biophysics: Searching for Principles

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This is a draft, not complete but hopefully not embarrassing either. I would be very happy to receive feedback at `wbialek@princeton.edu`. Please note the caveats in the section "About this draft," which includes an explanation for the red ellipses.

CONTENTS

INTRODUCTION

Like all authors, I hope that this book will find wide readership. At the same time, I believe that good books are intensely personal objects. As readers, we have our favorite books, and this is an emotional statement, laden with context.[1] Similarly, writers bring not just their knowledge and their technical skill to the creation of a book, but also their personalities. In writing something which might be used as a textbook, I feel a responsibility to provide a fair view of the field. But I won't apologize for giving you *my* view, which surely is not a consensus view. Indeed, perhaps by the time there is a clear consensus the field won't be quite as much fun.

A. About our subject

When a PhD student in Physics picks up a textbook about elementary particle physics, or cosmology, or condensed matter, there is little doubt about what will be found inside the covers. There are questions, perhaps, about the level and style of presentation, or about the emphasis given to different subfields, but the overall topic is clear. The situation is very different for books or courses that attempt to bring the intellectual style of physics to bear on the phenomena of life. The problem is not just in how we teach, but also in how we do research. The community of physicists interested in biological problems is incredibly diverse, it spills over into more amorphously defined interdisciplinary communities, and individual physicists often are more connected to biologists working on the same system than they are to physicists asking the same conceptual question in other

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[1] The book which gave me my first taste of real quantum mechanics has a special place in my library, even though it isn't a book I would recommend to my students. Translated from the Russian, it looks like it was typed rather than typeset. An important part of the story is that I found it for sale on a remainder table in a department store. It must have been the only quantum mechanics book ever sold by the *Emporium*.

systems. None of this is necessarily good or bad, but it can be terribly confusing for students.

Ours is not a new subject, but over its long history, "biophysics" or "biological physics" has come to mean many different things to different communities.[2] At the same time, for many physicists today, biophysics remains new, and perhaps a bit foreign. There is an excitement to working in a new field, and I hope to capture this excitement. Yet our excitement, and that of our students, sometimes is tempered by serious concerns, which can be summarized by naive questions: Where is the boundary between physics and biology? Is biophysics really physics, or just the application of methods from physics to the problems of biology? My biologist friends tell me that 'theoretical biology' is nonsense, so what would theoretical physicists be doing if they got interested in this field? In the interaction between physics and biology, what happens to chemistry? How much biology do I need to know in order to make progress? Why do physicists and biologists seem to be speaking such different languages? Can I be interested in biological problems and still be a physicist, or do I have to become a biologist? Although there has been much progress over the last decade, I still hear students (and colleagues) asking these questions, and so it it seems worth a few pages to place the subject of this book into context.[3] The discussion will start by reacting to the history of our subject, but by the end I hope to outline a view of the field which stands on its own as a guide to what we would like to accomplish, both on the time scale of working through this book and on the longer time scale of our research agendas [not quite sure about that last phrase, but want to say something in this spirit].

There is an old saying that "physics is what physicists do." This doesn't sound very helpful, but it may be getting at an important point. Academic disciplines have a choice to define themselves either by their objects of study or by their style of inquiry. Physics (at its best, I would like to think) is firmly in the second camp. Physicists make it their business to ask certain kinds of questions about Nature, and to seek certain kinds of answers. "Thinking like a physicist" means something, and we are proud to do it; it is this, above all else, that we try to convey to our students. We are the intellectual heirs of Galileo, taking seriously his evocative claim that the book of Nature is written in the language of mathematics.

Biology surely is defined by the objects of study—if it's not alive, biologists aren't interested. The style of inquiry may change, from studies of animal behavior and anatomy to genetics and molecular structure, but the objects remain the same. It is especially important for physicists to appreciate the vastness of the enterprise that is labeled 'biology,' and the tremendous divisions within biology itself. A geneticist, for example, studying the dynamics of regulatory networks in a simple organism such as yeast, may know absolutely nothing about the dynamics of neural networks for the regulation of movement in higher organisms, and vice versa. Not only is biology defined by the objects of study, but the subfields of biology are similarly defined, so that networks of neurons and networks of genes are different subjects.

Differences in our view of the scientific enterprise translate rather directly into different educational structures. In physics, we (try to) teach principles and derive the predictions for particular examples. In biology, teaching proceeds (mostly) from example to example. Although physics has subfields, to a remarkable extent the physics community clings to the romantic notion that Physics is one subject. Not only is the book of Nature written in the language of mathematics, but there is only one book, and we expect that if we really grasped its content it could be summarized in very few pages. Where does biophysics fit into this view of the world?

There is something different about life, something that we recognize immediately as distinguishing the animate from the inanimate. But we no longer believe that there is a fundamental "life force" that animates a lump of inert stuff. Similarly, there is no motive force which causes superfluid helium to crawl up the sides of a container and escape, or which causes electrical current in a superconducting loop to flow forever; the phenomena of superfluidity and superconductivity emerge as startling consequences of well known interactions among electrons and nuclei, interactions which usually have much more mundane consequences. As physicists studying the phenomena of life, we thus are not searching for a new force of Nature. Rather we are trying to understand how the same forces that usually cause carbon based materials to look like rocks or sludge can, under some conditions, cause material to organize itself and walk (or swim or fly) out of the laboratory. What is special about the state of matter that we call life? How does it come to be this way? Different generations of physicists have approached these mysteries in different ways.

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[2] The use of these two different words is also problematic. I think that, roughly speaking, "biophysics" can be used by people who think of themselves either as physicists or biologists, while "biological physics" is an attempt to carve out a subfield of physics, distinct from biology. The difficulty is that neither word really points to a set of questions that everyone can agree upon. So, we need to dig in.

[3] The intellectual questions about biophysics and its relation to the larger, separate, activities of physics and biology easily become entangled with political and sociological problems—one does not have to be a fanatic to realize that the setting of research agendas and the parcelling out of resources involves the exercise of political power. All of us who pursued interests at the interface of physics and biology before it became popular have some personal perspectives on these issues. I will try to avoid these political entanglements and focus on our intellectual goals.

Looking back

Some of the giants of classical physics—Helmholtz, Maxwell, and Rayleigh, to name a few—routinely crossed borders among disciplines that we now distinguish as physics, chemistry, biology, and even psychology. Some of their forays into the phenomena of life were driven by a desire to test the universality of physical laws, such as the conservation of energy. A very different motivation was that our own view of the world is determined by what we can see and hear, and more subtly by what we can reliably infer from the data that our sense organs collect. These physicists thus were drawn to the study of the senses; for them, there was no boundary between optics and vision, or between acoustics and hearing. Helmholtz in particular took a very broad view, seeing a path not just from acoustics to the mechanics of the inner ear and from the properties of light to the optics of the eye, but all the way from the physical stimuli reaching our sense organs to the nature of our perceptions, to our ability to learn about the world, and even to what makes some sights or sounds more pleasing than others. Reading Helmholtz today I find myself struck by how much his insights still guide our thinking about vision and hearing, and by how the naturalness of his cross–disciplinary discourse remains something which few modern scientists achieve, despite all the current fanfare about the importance of multidisciplinary work. Most of all, I am struck by his soaring ambition that physics should not stop at the point where light hits our eyes or sound enters our ears, and that we should search for a physics that reaches all the way to our personal, conscious experience of the world in all its beauty.

The rise of modern physics motivated another wave of physicists to explore the phenomena of life. Fresh from the triumphs of quantum mechanics, they were emboldened to seek new challenges and brought new concepts. Bohr wondered aloud if the ideas of complementarity and indeterminacy would limit our ability to understand the microscopic events that provide the underpinnings of life. Delbrück was searching explicitly for new principles, hoping that a modern understanding of life would be as different from what came before as quantum mechanics was different from classical mechanics. Schrödinger, in his influential series of lectures entitled *What is Life?*, seized upon the discovery that our precious genetic inheritance was stored in objects the size of single molecules, highlighting how surprising this is for a classical physicist, and contrasted the order and complexity of life with the ordering of crystals, outlining a strikingly modern view of how non–equilibrium systems can generate structure out of disorder, continuously dissipating energy.

In one view of history, there is a direct path from Bohr, Delbrück and Schrödinger to the emergence of molecular biology. Certainly Delbrück did play a central role, not least because of his insistence that the community should focus (as the physics tradition teaches us) on the simplest examples of crucial biological phenomena, reproduction and the transmission of genetic information. The goal of molecular biology to reduce these phenomena to interactions among a countable set of molecules surely echoed the physicists' search for the fundamental constituents of matter, and perhaps the greatest success of molecular biology is the discovery that many of these basic molecules of life are universal, shared across organisms separated by hundreds of millions of years of evolutionary history. Where classical biology emphasized the complexity and diversity of life, the first generation of molecular biologists emphasized the simplicity and universality of life's basic mechanisms, and it is not hard to see this as an influence of the physicists who came into the field at its start.

Another important idea at the start of molecular biology was that the structure of biological molecules matters. Although modern biology students, even in many high schools, can recite 'structure determines function,' this was not always obvious. To imagine, in the years immediately after World War II, that all of classical biochemistry and genetics would be reconceptualized once we could see the actual structures of proteins and DNA, was a revolutionary vision—a vision shared only by a handful of physicists and the most physical of chemists. Every physicist who visits the grand old Cavendish Laboratory in Cambridge should pause in the courtyard and realize that on that ground stood the 'MRC hut,' where Bragg nurtured a small group of young scientists who were trying to determine the structure of biological molecules through a combination of X–ray diffraction experiments and pure theory. To make a long and glorious story short, they succeeded, perhaps even beyond Bragg's wildest dreams, and some of the most important papers of twentieth century biology thus were written in a physics department.

Perhaps inspired by the successes of their intellectual ancestors, each subsequent generation of physicists offered a few converts. The idea, for example, that the flow of information through the nervous system might be reducible to the behavior of ion channels and receptors inspired one group, armed with low noise amplifiers, intuition about the interactions of charges with protein structure, and the theoretical tools to translate this intuition into testable, quantitative predictions. The possibility of isolating a single complex of molecules that carried out the basic functions of photosynthesis brought another group, armed with the full battery of modern spectroscopic methods that had emerged in solid state physics. Understanding that the mechanical forces generated by a focused laser beam are on the same scale as the forces generated by individual biological molecules as they go about their business brought another generation of physicists to our subject. The sequencing of whole genomes, including our own, generated the sense that the phenomena of life could, at last, be explored comprehensively, and this inspired yet another group. These examples are far from complete, but give some sense for the diversity of challenges that drew physicists toward problems that traditionally had been purely in the domain of biologists.

Through these many generations, some conventional views arose about the nature of science at the borders between physics and biology. First, there is a strong emphasis on technique. From X–ray diffraction to the manipulation of single molecules to functional imaging of the brain, it certainly is true that physics has developed experimental techniques that allow much more direct exploration of questions raised by biologists. Second, there is a sense that in some larger classification system, biophysics is a biological science. Certainly when I was a student, and for many years afterwards, physicists would speak (sometimes wistfully) of colleagues who were fascinated by the phenomena of life as having "become biologists." For their part, biologists would explain that physicists were successful in these explorations only to the extent that they appreciated what was "biologically important." Finally, biophysics has come to be organized along the lines of the traditional biological subfields. As a result, the biophysics of neurons and the statistical mechanics of neural networks are separate subjects, and the generation of physicists exploring noise in the regulation of gene expression is disconnected from the previous generation that studied noise in ion channels.

Without taking anything away from what has been accomplished, I believe that much has been lost in the emergence of the conventional views about the nature of the interaction between physics and biology. By focusing on methods, we miss the fact that, faced with the same phenomena, physicists and biologists will ask different questions. In speaking of biological importance, we ignore the fact that physicists and biologists have different definitions of understanding. By organizing ourselves around structures that come from the history of biology, we lose contact with the dreams of our intellectual ancestors that the dramatic qualitative phenomena of life should be clues to deep theoretical insights, that there should be a physics of life and not just the physics of this or that particular process. It is, above all, these dreams that I would like to rekindle in my students and in the readers of this book.

Looking forward

At present, most questions about how things work in biological systems are viewed as questions that must be answered by experimental discovery. The situation in physics is very different, in that theory and experiment are more equal partners. In each area of physics we have a set of general theoretical principles, all interconnected, which define what is possible; the path to confidence in any of these principles is built on a series of beautiful, quantitative experiments that have extended the envelope of what we can measure and know about the world. Beyond providing explanations for what has been seen, these principles provide a framework for exploring, sometimes playfully, what *ought* to be seen. In many cases these predictions are sufficiently startling that to observe the predicted phenomena (a new particle, a new phase of matter, fluctuations in the radiation left over from the big bang, ...) still constitutes a dramatic experimental discovery.

Can we imagine a physics of biological systems that reaches the level of predictive power that has become the standard in other areas of physics? Can we reconcile the physicists' desire for unifying theoretical principles with the obvious diversity of life's mechanisms? Could such theories engage meaningfully with the myriad experimental details of particular systems, yet still be derivable from succinct and abstract principles that transcend these details? For me, the answer to all of these questions is an enthusiastic "yes," and I hope that this book will succeed in conveying both my enthusiasm and the reasons that lie behind it.

I have emphasized that, in the physics tradition, our subject should be defined by the kinds of questions we ask, but I haven't given you a list of these questions. Worse yet, this emphasis on questions and concepts might leave us floating, disconnected from the data. It is, after all, the phenomena of life which are so dramatic and which demand our attention, so we should start there. There are so many beautiful things about life, however, that is can be difficult to choose a concrete starting point. Before explaining the choices I made in writing this book, I want to emphasize that there are many equally good choices. Indeed, if we choose almost any of life's phenomena—the development of an embryo, our appreciation of music, the ability of bacteria to live in diverse environments, the way that ants find their way home in the hot desert—we can see glimpses of fundamental questions even in the seemingly most mundane events.

It is a remarkable thing that, pulling on the threads of one biological phenomenon, we can unravel so many general physics questions. In any one case, some problems will be presented in purer form than others, but in many ways everything is there. Thus, if we think hard about how crabs digest their food (to choose a particularly prosaic example), we will find ourselves worrying about how biological systems manage to find the right operating point in very large parameter spaces. This problem, as we will see in Chapter Three, arises in many different systems, across levels of organization from single protein molecules to short–term memory in the brain. Thus, in an odd way, everything is fair game. The challenge is not to find the most important or "fundamental" phenomenon, but rather to see through any one of many interesting and beautiful phenomena to the deep physics problems that are hiding underneath the often formidable complexity of these systems.

The first problem, as noted above, is that there really is something different about being alive, and we'd like to know what this is—in the same way that we know what it is for a collection of atoms to be solid, for a collection of electrons to be superconducting, or for the vacuum to be confining (of quarks). This "What is life?" question harkens back to Schrödinger, and one might think that the molecular biology which arose in the decades after his manifesto would have answered his question, but this isn't clear. Looking around, we more or less immediately identify things which are alive, and the criteria that we use in making this discrimination between animate and inanimate matter surely have nothing to do with DNA or proteins. Even more strongly, we notice that things are alive long before we see them reproduce, so although self–reproduction might seem like a defining characteristic, it doesn't seem essential to our recognition of the living state. Being alive is a macroscopic state, while things like DNA and the machinery of self–reproduction are components of the microscopic mechanism by which this state is generated and maintained.[4] While we have made much progress on identifying microscopic mechanisms, we have made rather less progress on identifying the "order parameters" that are characteristic of the macroscopic state.

Asking for the order parameters of the living state is a hard problem, and not terribly well posed. One way to make progress is to realize that as we make more quantitative models of particular biological systems, these models belong to families: we can imagine a whole class of systems, with varying parameters, of which the one we are studying is just one example. Presumably, most of these possible systems are not functional, living things. What then is special about the regions of parameter space that describe real biological systems? This is a more manageable question, and can be asked at many different levels of biological organization. If there is a principle that differentiates the genuinely biological parts of parameter space from the rest, then we can elevate this principle to a theory from which the properties of the biological system could be calculated a priori, as we do in other areas of physics.

If real biological systems occupy only a small region in the space of possible systems, we have to understand the dynamics by which systems find their way to these special parameters. At one extreme, this is the problem of the origin of life. At the opposite extreme, we have the phenomena of physiological adaptation, whereby cells and systems adjust their behavior in relation to varying conditions or demands from the environment, sometimes in fractions of a second. In between we have learning and evolution. Adaptation, learning and evolution represent very different mechanisms, on different but perhaps overlapping time scales, for accomplishing a common goal, tuning the parameters of a biological system to match the problems that organisms need to solve as they try to survive and reproduce. What is the character of these dynamics? Are the systems that we see around us more or less "equilibrated" in these dynamics, or are today's organisms strongly constrained by the nature of the dynamics itself? Put another way, if evolution is implementing an algorithm for finding better organisms, are the functional behaviors of modern biological systems significantly shaped by the algorithm itself, or can we say that the algorithm solves a well defined problem, and what we see in life are the solutions to this problem?

In order to survive in the world, organisms do indeed have to solve a wide variety of problems. Many of these are really physics problems: converting energy from one form to another, sensing weak signals from the environment, controlling complex dynamical systems, transmitting information reliably from one place to another, or across generations, controlling the rates of thermally activated processes, predicting the trajectory of multidimensional signals, and so on. While it's obvious (now!) that everything which happens in living systems is constrained by the laws of physics, these physics problems in the life of the organism highlight these constraints and provide a special path for physics to inform our thinking about the phenomena of life.

Identifying all the physics problems that organisms need to solve is not so easy. Thinking about how single celled organisms, with sizes on the scale of one micron, manage to move through water, we quickly get to problems that have the look and feel of problems that we might find in Landau and Lifshitz. On the other hand, it really was a remarkable discovery that all cells have built Maxwell demons, and that our description of a wide variety of biochemical processes can be unified by this observation (see Section II.D). Efforts in this direction can be very rewarding, however, because we identify questions that connect functionally important behaviors—things organisms really care about, and for which evolution might select—with basic physical principles. Physics shows us what is hard about these problems, and where organisms face real challenges. In some cases, physics also places limits on what is possible, and

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[4] More precisely, all the molecular components of life that we know about comprise *one way* of generating and maintaining the state that we recognize as being alive. We don't know if there are other ways, perhaps realized on other planets. This remark might once have seemed like science fiction, and perhaps it still is, but the discovery of planets orbiting distant stars has led many people to take these issues much more seriously. Designing a search for life on other planets gives us an opportunity to think more carefully about what it means to be alive.

this gives us an opportunity to put the performance of biological systems on an absolute scale. This makes precise our intuition that organisms are really very good at solving some very difficult problems.

[I would like this paragraph to be better, but will come back to this.] To summarize, the business of life involves solving physics problems, and these problems provide us with a natural subject matter. In particular, these problems focus our attention on the concept of "function," which is not part of the conventional physics vocabulary,[5] but clearly is essential if we want to speak meaningfully about life. Of the possible mechanisms for solving these problems, most combinations of the available ingredients probably don't work, and specifying this functional ensemble provides a manageable approach to the larger question of what characterizes the living state. Adaptation, learning and evolution allow organisms to find these special regions of parameter space, and the dynamics of these processes provide another natural set of problems.

If you are excited about problems at the interface of physics and biology, you must read Schrödinger's "little book" *What is Life?*. To get a sense of the excitement and spirit of adventure that our intellectual ancestors brought to the subject, you should also look at the remarkable essays by Bohr (1933) and Delbrück (1949). Delbrück reflected on those early ideas some years later (1970), as did his colleagues and collaborators (Cairns et al 1966). For a more professional history of the emergence of modern molecular biology from these physicists' musings, see Judson (1979).

Bohr 1933: Light and life. N Bohr, *Nature* **131,** 421–423 (1933).

Cairns et al 1966: *Phage and the Origins of Molecular Biology*, J Cairns, GS Stent & JD Watson, eds (Cold Spring Harbor Press, Cold Spring Harbor NY, 1966).

Delbrück 1949: A physicist looks at biology. M Delbrück, *Trans Conn Acad Arts Sci* **38,** 173–190 (1949). Reprinted in Cairns et al (1966), pp 9–22.

Delbrück 1970: A physicist's renewed look at biology: twenty years later. M Delbrück, *Science* **168,** 1312–1315 (1970).

Judson 1979: *The Eighth Day of Creation* HF Judson (Simon and Schuster, New York, 1979).

Schrödinger 1944: *What is Life?* E Schrödinger (Cambridge University Press, Cambridge, 1944).

B. About this book

This book has its origins in a course that I have taught for several years at Princeton. It is aimed at PhD students in Physics, although a sizable number of brave undergraduates have also taken the course, as well as a handful of graduate students from biology, engineering, applied math, etc.. Bits and pieces have been tested in shorter courses, sometimes for quite different audiences, at the Marine Biological Laboratory, at Les Houches, at the Boulder Summer School on Condensed Matter Physics, at "Sapienza" Universitá di Roma, and at the Rockefeller University.

In early incarnations, the course consisted of a series of case studies—problems where physicists have tried to think about some particular biological system. The hope was that in each case study we might catch a glimpse of some deeper and more general ideas. As the course evolved, I tried to shift the balance from examples toward principles. The difficulty, of course, is that we don't know the principles, we just have candidates. At some point I decided that this was OK, and that trying to articulate the principles was important even if we get them wrong. I believe that, almost by definition, something we will recognize as a theoretical physics of biological systems will have to cut across the standard subfields of biology, organizing our understanding of very different systems as instantiations of the same underlying ideas.

Although we are searching for principles, we start by being fascinated with the *phenomena* of life. Thus, the course starts with one particular biological phenomenon that holds, I think, an obvious appeal for physicists, and this is the ability of the visual system to count single photons. As we explore this phenomenon, we'll meet some important facts about biological systems, we'll see some methods and concepts that have wide application, and we'll identify and sharpen a series of questions that we can recognize as physics problems. The really beautiful measurements that people have made in this system also provide a compelling antidote to the physicists' prejudice that experiments on biological systems are necessarily messy; indeed, I think these measurements set a standard for quantitative experiments on biological systems that should be more widely appreciated and emulated.[6]

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[5] This isn't quite fair. In thermodynamics we distinguish "useful work," provides a notion of function, at least in the limited context of heat engines. But we need something much more general if we want to capture the full range of problems that organisms have to solve.

[6] Perhaps surprisingly, many biologists share the expectation that their measurements will be noisy. Indeed, some biologists insist that physicists have to get used to this, and that this is a fundamental difference between physics and biology. Certainly it is a difference between the sciences as they are practiced, but the claim that there is something essentially sloppy about life is deeper, and deserves more scrutiny. One not so hidden agenda in my course is to teach physics students that it is possible to uncover precise, quantitative facts about biological systems in the same way that we can uncover precise quantitative facts about non–biological systems, and that this precision matters.

Another crucial feature of the photon counting problem is that it cuts across almost all levels of biological organization, from the quantum dynamics of single molecules to the macroscopic dynamics of human cognition.

Having introduced ourselves in some detail to one particular biological phenomenon, we proceed to explore three candidate principles: the importance of noise, the need for living systems to function without fine tuning of parameters, and the possibility that many of the different problems solved by living organisms are just different aspects of one big problem about the representation of information. Each of these ideas is something which many people have explored, and I hope to make clear that these ideas have generated real successes. The greatest successes, however, have been when these theoretical discussions are grounded in experiments on particular biological systems. As a result, the literature is fragmented along lines defined by the historical subfields of biology. The goal here is to present the discussion in the physics style, organized around principles from which we can derive predictions for particular examples.

My choice of candidate principles is personal, and I don't expect that everyone in the field will agree with me (see above). More importantly, the choice of examples is not meant to be canonical, but illustrative. In choosing these examples, I had three criteria. First, I had to understand what was going on, and of course this biases me toward cases which my friends and I have studied in the past. I apologize for this limitation, and hope that I have been able to do justice at least to some fraction of the field. Second, I want to emphasize the tremendous range of physics ideas which are relevant in thinking about the phenomena of life. Many students are given the impression, implicitly or explicitly, that to do biophysics one can get away with knowing less 'real physics' than in other subfields, and I think this is a disastrous misconception. Finally, if the whole program of finding principles is going to work, then it must be that a single principle really does illuminate the functioning of seemingly very different biological systems. Thus I make a special effort to be sure that the set of examples for each principle cuts across the subfields of biology, in particular across the great divide between molecular and cellular biology on the one hand and neurobiology on the other.

In trying to provide some perspective on our subject, in the previous section, I mentioned a number of now classic topics from across more than a century of interaction between physics and biology. I don't think it's right to teach by visiting these topics one after the other, for reasons which I hope are clear by now. On the other hand, it would be weird to take a whole course on biophysics and come out without having learned about these things. So I have tried to weave some of the classics into the conceptual framework of the course, perhaps sometimes in surprising places. There also are many beautiful things which I have left out, and again I apologize to people who will find that I neglected matters close to their hearts. Sometimes the neglect reflects nothing more than my ignorance, but in some cases it is more subtle. I felt strongly that everything I discuss should fit together into a larger picture, and that it is almost disrespectful to give a laundry list of wonderful but undigested results. Thus, much was left unsaid.

I assume that readers (as with my students) have a strong physics background, and are comfortable with the associated mathematical tools. While many different areas of physics make an appearance, the most frequent references are to ideas from statistical mechanics. In practice, this is the area where at least U.S. students have the largest variance in their preparation. As a result, in places where my experience suggests that students will need help, I have not been shy to include (perhaps idiosyncratic) expositions of relevant physics topics that are not especially restricted to the biophysical context, since this is, after all, a physics course. Some more technical asides are presented as appendices. Throughout the text, and especially in the appendices, I try very hard to avoid saying "it can be shown that;" the resulting text is longer, but I hope more useful.

No matter how much we may be searching for deep theoretical principles, in the physics tradition, we do need a grasp of the facts. But when we teach particle physics we don't start by reading from the particle data book, so similarly I don't start by reciting the "biological background." Rather, we plunge right in, and as we encounter things that need explaining, I try to explain them. I do want to emphasize (maybe this is especially meaningful coming from a theorist!) the importance of mastering the experimental facts about systems that we find interesting. I think we should avoid talking about how "physicists need to learn the biology," since "biology" could mean either the study of living systems or the academic discipline practiced in biology departments, and these need not be the same thing. We must know what has been measured, assess these data with informed skepticism, and use the results to guide our thinking as we ask our own new and interesting questions. I hope I manage to strike the right balance.

The most important comment about the structure of the book concerns the problems. I cannot overstate the importance of doing problems as a component of learning. One should go further, getting into the habit of calculating as one reads, checking that you understand all the steps of an argument and that things make sense when you plug in the numbers or make order of magnitude estimates. For all these reasons, I have chosen (following Landau and Lifshitz) to embed the problems in the text, rather than relegating them to the ends of chapters. In some places the problems are small, really just reminding you to fill in some missing steps before going on to the next topic. At the opposite extreme, some problems are small research projects. Because progress in biophysics depends on intimate interaction between theory and experiment, some of the problems ask you to analyze real data, which can be found at `http://www.princeton.edu/∼wbialek/PHY562/data`.

Let me also say a few words about references. References to the original literature serve multiple functions, especially in textbooks. Most obviously, I should cite the papers that most influenced my own thinking about the subject, acknowledging my intellectual debts. Since this text is based on a course for PhD students, citations also help launch the student into the current literature, marking the start of paths that can carry you well beyond digested, textbook discussions. In another direction, references point back to classic papers, papers worth reading decades after they were published, papers that can provide inspiration. Importantly, all of these constitute subjective criteria for inclusion on the reference list, and so I think it is appropriate to collect references with some commentary, as you have already seen at the end of the previous section. Let me note that the reference list should *not* be viewed as a rough draft of the history of the subject, nor as an attempt to establish objective priorities for some work over others.

C. About this draft

This is not the final draft of the book. I know there are things that need to be fixed, but I have been pushing to get the text to the point where I won't be embarrassed by letting other people look at it (I hope!). My own concerns about the state of the text include the following:

1. All the figures are placeholders. Some are grabbed from published papers, while others are bad photographs of what I sketched on the blackboard. There is work to be done in bringing all of this up to a standard of clarity and consistency.

2. I have pushed through the text several times, but I haven't really had a chance to look at the balance of topics. I worry that things which I know best have grown out of proportion to other topics, and I could use some advice. There is a related question about which things belong in the main text and which can be safely pushed to the Appendices.

3. There are places where I just haven't finished, even if I am pretty sure what needs to be done. This has been a very long project, but I fully expect readers to give advice that will necessitate further revision. Thus, I thought it might be OK to let people see things even with the gaps—perhaps you even have ideas about how to fill them in. These problem areas of the text are flagged in red. In some places these are small (I think) nagging questions, while in other areas there are bigger sections missing.

4. I have been working hard on the opening parts of chapters and sections, trying to provide more context and a guide to what is coming. The ends of many sections still seem a bit abrupt, however, suggesting that I might have stopped when I was exhausted by the topic rather than when I reached a conclusion. This will get fixed.

At this stage of the project, all input is welcome. I hope you will read sympathetically as well as critically, but getting things right is important, so feel free to bash away.

ACKNOWLEDGMENTS

Even if I had the perfect idea for teaching a course, it would be meaningless without students. By now, hundreds of students have listened to the whole set of lectures and worked through the problems, providing feedback at every stage, as have several very able teaching assistants. At least as many students have heard pieces of the course, in different venues, and every time I taught I learned something—at least, I hope, about how to say things more clearly. Less tangible, but even more important, the liveliness and engagement of the students have made teaching a pleasure.

The views of the field which I present here are personal, and I don't want anyone else held responsible for my foibles. On the other hand, these views did not emerge in isolation. I am especially grateful to Rob de Ruyter van Steveninck, who introduced me to the wonders of close collaboration between theory and experiment. What began as a brief discussion about the possibility of measuring the precision of computation in a small corner of the fly's brain has become half a lifetime of friendship and shared intellectual adventure.

My good fortune in finding wonderful experimental collaborators began with Rob, but certainly didn't end there. A decade of conversations with Michael Berry, Allison Doupe, Steve Lisberger and Leslie Osborne, sometimes reflected in joint papers and sometimes not, have all influenced important parts of this book, in ways which I hope they will recognize. After I moved to Princeton, David Tank, Eric Wieschaus and I began a very different adventure, soon joined by Thomas Gregor. I have been amazed by how these interactions have so quickly reshaped my own thinking, leaving their mark on my view of the subject as a whole and hence on this text.

Theory itself is more fun in collaboration with others, even when we aren't engaged with our experimental friends. Different parts of the text trace their origins to joint work with N Brenner, WJ Bruno, CG Callan, M DeWeese, AL Fairhall, S Kivelson, R Koberle, T Mora, I Nemenman, JN Onuchic, SE Palmer, M Potters, FM Rieke, DL Ruderman, E Schneidman, S Setayeshgar, T Sharpee, GJ Stephens, S Still, SP Strong, G Tkačik, N

Tishby, A Walczak, D Warland and A Zee. I am hugely grateful to all of them.

It is almost embarrassing to admit that I first taught PHY 562 a very long time ago, while I was still a member of the NEC Research Institute, and a visiting lecturer at Princeton. Dawon Kahng and Joe Giordmaine were responsible for creating the enlightened environment at NEC, which lasted for a marvelous decade, while David Gross and Stew Smith made it possible for me to teach those early versions of the course at Princeton. The opportunity to interact with students while still enjoying the support of an industrial research laboratory dedicated to basic science was quite magical. During this period, frequent discussions with Albert Libchaber were also important, as he insisted that explorations at the interface of physics and biology be ambitious but still crisp and decisive—a demanding combination.

Although the wonders of life in industrial labs have largely disappeared, the pleasures of teaching at Princeton have continued and grown. I am especially grateful to my colleagues in the Physics department for welcoming the intellectual challenges posed by the phenomena of life as being central to physics itself, rather than being "applications" of physics to another field. The result has been the coalescence of a very special community, and I hope that some of what I have learned from this community is recorded faithfully in this book. John Hopfield's role in making all this happen—by setting an example for what could be done, by being an explicit (and horrifyingly witty) provocateur, and by being a quiet but persistent catalyst for change—cannot be overestimated; it a pleasure to thank him. I don't think that even John imagined that there would eventually be a "biophysics theory group" at Princeton, but with Curt Callan and Ned Wingreen, we have managed to do it, and we have been joined by a succession of young colleagues who have held the Lewis–Sigler Fellowship—M Desai, J England and M Kaschube—all of whom have added enormously to our community. Curt deserves special thanks, for his leadership and even more for the energy and enthusiasm he brings to seminars and discussions, engaging with the details but also reminding us that theoretical physics has lofty aspirations.

Everyone who has tried to write a book based on their teaching experience knows the enormous difference between a good set of lecture notes and the final product. I very much appreciate Arthur Wightman's suggestion, long ago, that this transition would be worth the effort. Ingrid Gnerlich, my editor at Princeton University Press, has consistently provided the right combination of encouragement and gentle reminders of looming (and passing) deadlines. The idea of actually finishing (!) started to crystallize during a wonderful sabbatical in Rome, and has been greatly helped along by visiting professorships at the Rockefeller University and most recently at The Graduate Center of the City University of New York. Both in Rome and in New York, stimuli from colleagues and from the surrounding cities have proved delightfully synergistic.

Despite my reservations (see above), I am much more comfortable with this draft than I was with the previous one, and this is the result of wonderful input on short notice from several colleagues. Rob Phillips brought objectivity, and the proper amount of scathing humor, alerting me to a variety of problems. Thomas Gregor, Justin Kinney and Fred Rieke gave generously of their expertise, and Rob de Ruyter provided yet more of the insight, craftsmanship and knowledge of scientific history that I have so much enjoyed in our long collaboration. My thanks to all of them.

It often is remarked that theory is a relatively inexpensive activity, so that we theorists are less dependent on raising money than are our experimentalist friends. But theory is a communal activity, and all the members of the community need salaries. Because I have benefited so much from the stimulation provided by the scientists around me, I am especially grateful for the steady support my colleagues and I have received from the National Science Foundation, and for the generosity of Princeton University in bringing all of us together. In particular, Denise Caldwell, Kenneth Whang and especially Krastan Blagoev deserve our thanks for helping to insure that this kind of science has a home at the NSF, even in difficult times. The Burroughs–Wellcome Fund, the WM Keck Foundation, and the Swartz Foundation have also been extremely generous, sometimes leaping in where the usual angels feared to tread.

Finally, while the product of the scientific enterprise must have meaning outside our individual feelings, the process of science is intensely personal. When we collaborate or even just learn from one another, we share not just our ideas about the next step in a small project, but our hopes and dreams for efforts that could occupy a substantial fraction of a lifetime. To make progress we admit to one another how little we understand, and how we struggle even to formulate the questions. For want of a better word, collaboration is an intimate activity. Colleagues become friends, friendships deepen, we come to care not just about ideas and results but about one another. It is, by any measure, a privileged life. If this text helps some readers to find their way to such enjoyment, I will have repaid a small fraction of my debt.

William Bialek
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