Biophysics: Searching for Principles[1]

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[1] These notes are based on lectures in a course for PhD students (Physics 562) at Princeton University. The plan is for them to appear as a book, to be published by Princeton University Press. For more information see `http://www.princeton.edu/~wbialek/PHY562.html`. If you would like to cite or use any of the material in these notes, please contact me directly: `wbialek@princeton.edu`. I would be especially happy to receive feedback on the utility or clarity of the presentation!

Preface

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 (hence opening me to charges of corrupting the youth), I feel a responsibility to provide a fair view of my 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.

What is biophysics?

This question ought to have a short answer. The problem is that our subject has a long history, and through this history "biophysics" has come to mean many different things to different communities.[2] At the same time, for many physicists, biophysics remains new and perhaps a bit foreign. There is an excitement to working in a new field, and I would like to capture this excitement. But there are also legitimate concerns, often 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

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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 sold by the *Emporium.*

[2] Some of my colleagues have hoped that we could use different words for these different things—hence the use of "biological physics" as an alternative to "biophysics." In practice, I think that each different term still has multiple meanings.

biology' is nonsense, so what would theoretical physicists be doing if they got interested in this field? 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? Because the simple question at the start of this section quickly becomes so many different questions, many of them quite urgent for students embarking on their scientific careers, it seems worth a few pages to place the subject of this book into context.[3]

There is an old saying that physics is what physicists do. In many ways this isn't 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. 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,

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[3] It should be clear that many 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. In trying to explain what I mean by biophysics, however, I will try to avoid these political entanglements and focus on our intellectual goals.

to a remarkable extent the physics community clings to the romantic notion that Physics is one subject. All of us are trying to understand Nature, and to the extent that we have separate understandings of different parts of Nature we should not be satisfied. 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?

It seems obvious that 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 individual electrons and atoms, 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. Different generations of physicists have approached this mystery in different ways.

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, our ability to learn about the world, and even 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. Some of their motivation must have been hubris; fresh from the triumphs of quantum mechanics, they were emboldened to seek new challenges. But they also brought new concepts. Bohr wondered aloud if the ideas of complementarity and indeterminacy wouldn't limit our ability to understand the microscopic events that provided 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 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 the central phenomena of life, 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. Thus 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 would matter. 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 forbearers, 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 suggest that much has been lost in the emergence of these conventional views. By focusing on methods, we miss the fact that, faced with the same phenomena, physicists and biologists will ask different questions. By focusing on biological relevance, 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.

In teaching a course for PhD students, I took it as my responsibility not just to convey what has been accomplished under the banner of biophysics, but to point toward some vision of what the field could be. Inevitably, this second part of the task will be accomplished with less reliability. To overstate what has been done would be dishonest, and certainly a disservice to the students. At the same time, to limit our imaginations about what *could be* done might be an even more serious disservice.

At present, most questions about how things work in biological systems are viewed as questions that must be answered by experimental discovery. Implicitly, the assumption is that things are as they are, tied together only by evolutionary history. 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 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 this level of predictive power? 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 "yes."

About this book

This book has its origins in a course, PHY 562, which 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. 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 the Universitá di Roma, La Sapeinza, 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. In particular, 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.[4] 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. 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). The choice of examples is not meant to be canonical, but illustrative. In choosing these examples, I had three goals. 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 disastrous advice. 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

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[4] 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 much stronger. 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.

biology on the one hand and neurobiology on the other.

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. The result is a tad unsystematic, but maybe that's OK.

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 (as Landau and Lifshitz did) 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`.

Acknowledgments

Even if I had the perfect idea for teaching a course, it would be meaningless without students. By now, more than two hundred 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, I Nemenman, JN Onuchic, SE Palmer, M Potters, FM Rieke, DL Ruderman, E Schneidman, S Setayeshgar, S Still, SP Strong, G Tkačik, N Tishby, A Walczak, D Warland and A Zee.

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 more ambitious (again, principles not examples) 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.

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 deadlines. The final push (not quite done as I write this) began with a wonderful sabbatical in Rome, and has been greatly helped along by a visiting professorship at the Rockefeller University. In both places, stimuli from colleagues and from the surrounding cities have proved delightfully synergistic.

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 paid a small fraction of my debt.

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