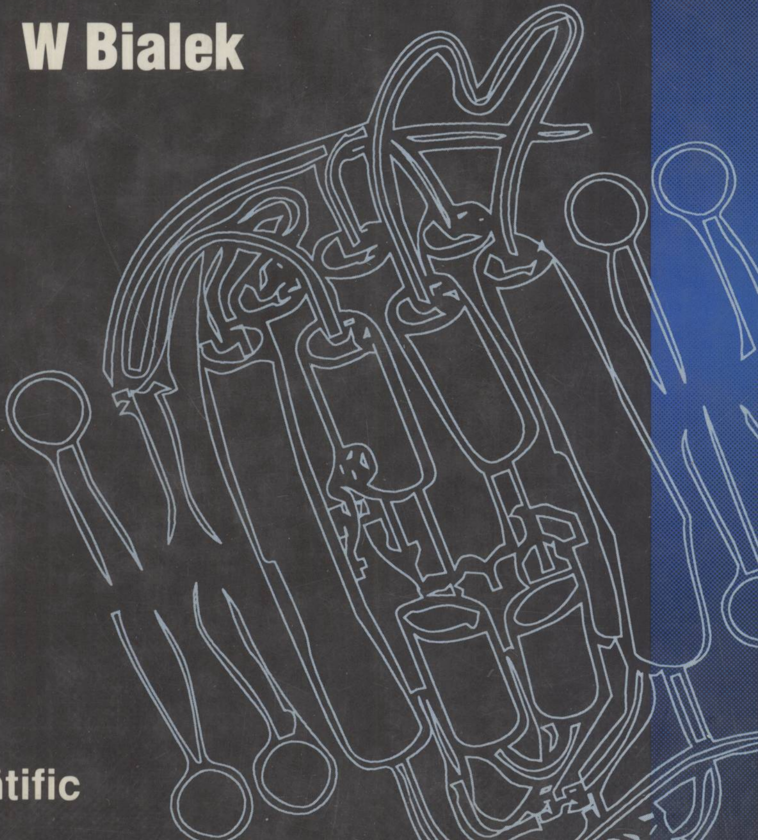
PRINCETON LECTURES ON BIOPHYSICS

Edited by

W Bialek



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Preface

A Little bit of History

Physics and biology were not always separate subjects. In the 19th century, Helmholtz, Maxwell, Ohm and Rayleigh all made great contributions to what we would now call the biological sciences. To these physicists, understanding the mechanics of the ear and the perception of sound were parts of acoustics, muscles constituted a perfectly sensible testing ground for the laws of thermodynamics, and so on. In the intervening century, physicists have often been drawn back to biology.

One historical thread tying physicists to biology is an interest in uncovering the molecular basis of life. Bohr inherited an interest in the subject from his physiologist father, and passed his thoughts on to a young colleague named Delbruck, who became one of the founders of molecular biology. A whole generation of physicists were influenced by Schrodinger's little book *What is Life?*. The early work on the structure of biological molecules --- Crick and Watson on DNA, Perutz and Kendrew on proteins --- was carried out in a small shed outside the Cavendish laboratory, under the watchful eye of Bragg himself. Ideas on the feedback mechanisms which regulate gene expression were developed by Monod in conversations with Szilard.

A second thread begins with the experiments of Galvani and Volta on "animal electricity," and continues through Helmholtz' work on the propagation of the nerve impulse and the quantitative investigation of the sense organs. This thread is picked up in this century with the British physiologists Hill, Hodgkin, Huxley, and Katz, who provided a quantitative description of the dynamics of nerves, muscles and synapses. Attempts to test Helmholtz' ideas about the mechanics of the inner ear have driven the development of beautiful experimental techniques for the measurement of small motions, beginning with the work of von Bekesy.

Despite these frequent interactions, physics and biology have developed separate intellectual traditions. Biology is taught largely as a celebration of the diversity and complexity of life on earth, a complexity which seems to exist even at the molecular level. Physics is taught as a search for simple and universal principles. Biology is divided in many different slices: molecular, cellular, organismal and population, neurobiology, immunology, developmental biology and genetics. A budding Delbruck would have a hard time learning about biology from modern texbooks, which are often written in a "headline" style more familiar to medical students than to physics students. In addition, the systems which provide the greatest inspiration for a physicist may be off the beaten track of the biologist.

As physics has matured, boundaries between sub-disciplines have tended to dissolve. We know that the nuclear reactions which make the stars shine are the same ones which we can reproduce here on earth, that broken symmetries in many-body systems can be understood in the same framework whether we are talking about electrons in solid state physics or the Higgs field in elementary particle physics. The ideas of scaling unify the equilibrium statistical mechanics of phase transitions both with the high-energy behavior of quarks and gluons and with the chaotic dynamics of systems far from equilibrium. In this context, the exclusion of living things from the provenance of physics would seem arbitrary.

About the Lectures

The Princeton Lectures on Biophysics are meant to be a place where physicists can come and learn about the phenomena of biology and about the attempts of other physicists to understand these phenomena. The ground rules are that, no matter how abstract we may end up, the discussion has to be grounded in the (sometimes harsh, but often inspiring) realities of life. You will notice that all of the chapters in this book have at least one figure with real data. Part of what makes this an exciting time to work at the interface of physics and biology is that so many biological systems have been characterized to the point where quantitative, "physics-style" experiments are possible. This is good news for both theorists and experimentalists, and the topics for the first set of lectures were chosen to highlight some of these particularly ripe areas, although obviously not in an exhaustive fashion.

The lectures themselves were held at the NEC Research Institute for one week in June 1991. The students were primarily advanced Ph.D. students and postdocs from physics departments, although there were exceptions. A relatively small fraction were already working in some area of biophysics. Many came unsure about whether one could reconcile an interest in biology with the desire to remain a part of the tradition and community of physicists; some left committed to follow precisely this path. It was an intense an lively week, and perhaps the most remarkable fact was that the activities seemed to peak on Thursday, which is very unusual for a one week event.

The format of the lectures was intended to maximize discussion, with long breaks and strong coffee. Each lecture was two hours long, and some lecturers gave two talks. Many of the students had taken their last biology course sometime in high school, yet I think that in most cases the lecturers managed to avoid jargon and fill in enough background to make things comprehensible. Because we covered a very broad range of topics, everyone (including the lecturers) was ignorant of the background for some of the talks, and in an important way this helped the communication process.

About this Book

This volume is not a precise record of the lectures. Several of the lecturers were unable to write up their notes, and in one case a lecturer from the 1992 installment agreed to pinch hit. The result is a book (coincidentally) evenly divided, with four articles following the molecular thread and four following the sensory systems. We begin with Hong *et al.*, who describe a heroic experiment in which they pump excitations into a protein molecule at relatively low energies and observe the resulting changes in the rate at which the molecule makes transitions between different states, states which are actually part of the cycle through which the protein carries out its biological function. This is a sort of resonant activation spectroscopy which provides a window into a little-studied (but much speculated) energy range for protein dynamics. The chapter captures some of the wit and irreverence of Austin's lecture, and the experiments have become much clearer with time. They challenge us to think about the "elementary excitations" of these complex molecules, and the way in which these excitations couple to the biologically significant dynamics.

The spectroscopic theme continues with Loppnow, who describes the dynamics of the visual pigments. The response of these molecules to the absorption of a photon is ultimately what triggers our perception, and this response turns out to be astoundingly fast; time-resolved studies of the visual pigments have been among the first experiments done with each new generation of fast pulse lasers. Loppnow explains how Raman spectroscopy allows the direct measurement of the forces of the molecule in the instant after the photon is absorbed, and develops a scenario for the molecular dynamics in the crucial first 50 femtoseconds of vision.

Proteins are large, complex and heterogeneous molecules. They are not random, displaying several repeating structural motifs, but they are not crystalline either. Understanding how these structures arise --- and ultimately predicting the structures of particular proteins --- is the protein folding problem. For biologists this is a central issue, since they would like to know in advance how new genetically engineered molecules will behave. For physicists, as Chan *et al.* describe, there are wonderful statsitical mechanics problems which can be attacked with both analytical and numerical techniques. This chapter, pieced together from two recent articles, provides as authoritative and up-to-date a view of this exciting area as I have seen anywhere.

One of the simplest of chemical reactions is electron transfer between donors and acceptors fixed in space. Biology uses these reactions in a variety of energy converting systems, notably photosynthesis. Here the simplicity hides tremendous subtlety --- how do you control the electron's path, to insure that the photon's energy is really trapped in a state sufficiently long-lived to do useful chemistry? Betts *et al.* tackle the problem of electron pathways through proteins, approximating it down to a managable combination of quantum mechanics and graph search. The simple theory is sufficient to organize and predict the results of a long series of experiments on specially modified proteins. These arguments point the way toward rigorous tests of the theory in which one attempts to design new proteins which have certain specified electron transfer reactions.

The study of unicellular organisms provides a bridge between the molecular and the macroscopic. Here the problems being solved are familiar from our own experience --- how do we find our way to a desirable location --- but bacteria have to answer these questions by examining only a handful of molecules in their environment, and their behavior is in turn controlled by only a handful of molecules inside the cell. Kruglyak gives an introduction to these issues in the context of bacterial chemotaxis, the system whereby bacteria can swim toward higher concentrations of useful molecules (or away from aversive ones). There is the tantalizing possibility that much of bacterial behavior will be understandable as a strategy for dealing for the physics of the bacterial environment.

In the 1991 lectures the subject of chemotaxis was covered by Steve Block, who gave two lectures on the mechanism and control of biological motors, including the remarkable rotary engine of bateria. One of the important emerging techniques for studying biological motors is the optical trap, which allows the experimenter to apply foces comparable to those produced by single motor molecules. This work points the way toward quantitative physics experiments on force generation by single molecules, and many groups are now working toward this goal. For a recent example see the article by Block *et al.* in *Nature* **348,** 348-352 (1990).

The nervous system is, in part, a machine for processing incoming information. Information theory tells us that even the simpler problem of moving information from one place to another is not trivial; there are limits, analagous to the limits on heat engines in thermodynamics, on the ability of systems, including nerve cells, to transmit information. Atick provides a self-contained introduction to these deep ideas, and then proceeds to explore their application in the early stages of visual processing. The focus is on making optimal use of the available capacity through the construction of efficient representations, where efficiency is given a precise mathematical definiton. This leads to predictions about what different pieces of the visual system, from flies to goldfish to monkeys, should be doing if they are to provide the maximally efficient represenations of the world as it varies in space, time and color. These predictions are in striking agreement with experiment, suggesting that the brain may indeed have found the optimal solution to its information transmission problems.

One of the problems in testing the information-theoretic ideas is that the efficiency with which the nervous system represents information is not measurable by experiments on any single neuron. Instead one needs methods which allow simultaneous recording of the activity of many individual cells. In the 1991 Lectures Jon Art discussed high resolution optical imaging techniques which can be used with dyes that are sensitive to the electrical activity of an array of cells. In the 1992 installment, Markus Meister returned to the problem, describing multi-electrode arrays which have be used to record activity from up to one hundred cells at once in the retina. Both of these approaches are developing quickly. For review of optical recording methods see the article by Grinvald in *Ann. Rev. Neurosci.* **8,** 263-305 (1985) or the recent contribution by Chien and Pine in *Biophys. J.* **60,** 697-711 (1991). The methods of Meister *et al.* are described (in part) in *Science* **252,** 939-943 (1991).

Our experience of the world is dominated by our visual system, but of course this is not the case for all animals. A dramatically different view of the world is provided by the bat's echolocation or sonar system, described in Simmons' contribution. Rather than scanning the world with a narrow beam, as in man-made systems, the bat broadcasts widely and uses his computational power to synthesize an image of the three-dimensional world. Simmons reviews the latest in a long series of experiments which aim to characterize this image and the remarkable way in which the bat constructs it out of the different clues in the echo waveform. I cannot resist pointing out that Jim held his audience at full attention for a solid three hours straight, alternately pulling out some remarkable experimental result and telling amusing stories about bats. I hope that some of the excitement we all experienced comes through in the text.

Part of what made Thursday such a remarkable day was that Simmons' lecture was followed by Nicolas Franceschini's. Nicolas descibed a series of beautiful experiments which have gradually elucidated various parts of the fly's visual system, from the optics and and pigment molecules [see N. F. in *Photoreceptors,* Borsellino and Cervetto, eds., pp. 319-350 (Plenum Press 1984)] to the neurons which compute motion across the visual field and provide a signal to guide the bug's flight [see N. F. *et al.* in *Facets of Vision,* Hardie and Stavenga, eds., pp. 360-390 (Springer-Verlag 1989)]. At the end he described a robot which was designed using some of the principles of visual processing which had been learned from the fly [Pichon *et al., SPIE* **1195,** 44-53 (1989)], and showed how the attempt to build this robot focused attention on new questions about the fly itself.

The chapters by Atick and Kruglyak introduced the idea that sensory systems operate at or near fundamental limits imposed by physics and information theory. I take up this theme in the last chapter, reviewing the evidence for optimal performance in a wide variety of different systems, and developing the theory of optimal signal processing to the point where we can make successful predictions about the dynamics of real neural circuits on the hypothesis that these circuits are optimized for particular tasks.

Acknowledgements

Many of the participants in the Lectures kindly pointed out that it was probably the best organized workshop they had attended. Starting with the tentative list of speakers and vague ideas about where to house the students, Cynthia Woodhull created a real organization. Angela Cramer joined her in the month or so before the Lectures, and together they had responsiblity for most everything. Getting more than sixty people together, keeping them fed, housed, transported, and generally happy is an amazing accomplishment. Cynthia and Angela also hounded the lecturers into producing enough notes and reprints to fill a thick binder, which we all keep as the real record of what happened that week.

Seemingly all of the adminstrative staff at NECI joined at one time or another, helping with everything from contracts to xeroxing. As a scientist at NEC I have an easy life in large part because the vice-president for physical science, Joe Giordmaine, believes that the administration exists to help the scientists. This is an uncommon perspective, and it extends to the sponsorship of events like the Lectures. Joe took an interest in every aspect of the project, providing much needed advice and support.

Producing this book was a large effort. I am writing this quite late at night, and Mary Anne Rich has just gone home, having put in overtime for yet

another day. She has not only worked hard on the manuscript, but kept all the other things running so that I was free to think about the editing. Most of the figures were scanned and then incorporated into the compuscript, and this was made possible by Brad Gianulis and the facilities of the graphics lab. The difference between the 'almost final' and the true final version of the manuscript was substantial, and Allan Schweitzer and Nick Socci deserve much of the credit for this tranformation.

When we started I didn't realize that the funds for this event were coming directly from the president of the Research Institute, Dawon Kahng. Dawon was very excited about bringing so many new faces to the Institute, and he attended almost all the lectures. He attended the banquet, but only after I had promised that there would be no speeches. Dawon's style as president could be annoying. He didn't sit in his office and administer. He once confided to me that adminstration wasn't very interesting; he wished he could be back in the lab. He would wander the halls, bothering us with his ideas and telling us what was wrong with our latest papers. During the week of the lectures, and for months after, we had many enjoyable conversations about what we both had learned. Shortly before the 1992 installment of the lectures, Dawon died. As a small token of my appreciation, this book is dedicated to him.

W. B.

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