niche between the macroscopic mechanics of the Fung book (Biomechanics: Mechanical Properties of Living Tissues, Y.C. Fung, Springer-Verlag, 1993) and the molecular mechanics of the Howard book (Mechanics of Motor Proteins and the Cytoskeleton, Jonathan Howard, Sinauer Associates, 2001). In addition, Boal deals with membrane mechanics and cell-cell adhesion, which are critical aspects at the cellular, but not the higher or lower levels.

The topic of cytoskeletal mechanics, from filament persistence length to three-dimensional networks, is considered in a format adapted to the characteristics of cells. There are multiple references to relevant literature, such as the effect of avidin crosslinking of biotinylated actin filaments on the mechanics of the actin gel. The treatment of DNA and RNA mechanics is brief. However, there is enough basic description of the mechanics to enable one to adapt the equations to other biological materials such as DNA or RNA. To gain a real understanding of the material, it is important for the reader to try and solve or at least consider the problems at the end of each chapter. To be successful in solving the problems, you may want to dust off your college calculus book, particularly if it has had time to collect significant dust.

Biological membranes are unusual in their mechanical properties in that they are essentially two-dimensional inelastic fluids constrained by attachment to the cytoskeleton. Membrane mechanics chapters have a particularly good description of the factors that lead to the formation of a bilayer. In the section on cell-cell interactions, there are good treatments of the critical events of cell-cell binding. The details on membrane fluctuations are probably of greater interest to physicists than biologists. Overall, the treatment of membranes is excellent and it can be of great benefit to all to have a better physical feel for membranes. This is especially important in light of popularly held misconceptions such as membrane flow driving motility, membrane stretching, or even large membrane rafts that are inconsistent with the physical properties of membranes.

In terms of possible improvements, additional figures would be useful, as would further tables of properties such as those provided for the membrane chapter. Expansion of the discussion of experimental problems as case examples would also help. As a text for a course, the essentials are present in this book, from the basic explanations of the equations to a good set of sample problems.

In general, this book provides a good introduction to the physical description of the mechanical properties of cells and membranes. Readers will benefit from a background in calculus, although some topics can be understood without complex mathematics. All who deal with the cytoskeleton and membranes are encouraged to increase their understanding of the physical properties of those materials, since the physical properties can influence or control biochemical activities in integrated cell functions.

Michael P. Sheetz
Department of Biological Sciences
Columbia University
New York, New York 10027

Toward Single Molecule Biochemistry

Biology at the Single Molecule Level
Edited by S.H. Leuba and J. Zlatanova
New York: Pergamon Press (2001).
284 pp. $149.50

Our understanding of nature and biological systems depends on the previous knowledge that has been accumulated and on the current tools available. The history of science has shown that new concepts frequently emerge and interpretations of the data become modified as more sophisticated and accurate measuring systems are developed. New data allow us to emphasize different aspects of biological systems and to reveal aspects of those systems that had not previously been unveiled. While static measurements have given us information on the static aspects of a system, in the last decade, a wave of new technologies has emerged. These technologies, collectively called single molecule detection, are expected to revolutionize the field of life sciences. With these techniques, it is possible to determine the behavior of single biomolecules working in complicated systems. This is in direct contrast to the conventional ensemble measurements which involved averaging the results from a large number of molecules, thus obscuring the dynamic behavior of individual molecules.

This emergent technology has successfully allowed single molecules to be visualized and manipulated and has taken the scientific community by surprise. While scientists marveled at how this was possible, the structure of single molecules was right there in front of their eyes. Single molecules were moving and being captured and handled by human hands. Despite such a sensational debut, single molecule detection is still in the early stages of development, but its use is growing rapidly. A new book, *Biology at the Single Molecule Level*, edited by Leuba and Zlatanova, summarizes some of the major topics in single molecule measurements. Editing a book such as this is a challenge because developments have occurred very rapidly. Thus, it is not easy to select topics, briefly describe all recent technical developments (some of which are highly complex), summarize the results obtained so far, and discuss the implications for future research. However, many readers will have been waiting for such a synopsis of the recent developments in these techniques. Some readers will be scientists in various fields. Some will be students who are investigating a research field they may want to devote their careers to in the future. Others will be purely interested in the technological aspects of the field. In this book, they will try to find the answers to their questions. Although this single book will not be able to satisfy all readers, it will provide a solid base for future publications.

A wide range of techniques dealing with single molecules have been collectively called "single molecule measurements," and therefore some techniques have not been discussed. Of those which are covered, many of the techniques have been developed independently. Thus, each chapter is treated as an independent piece

of work. As the editors stated in the preface, each author was asked not only to review the topic but also to answer many of the questions they feel readers may ask, to provide his or her own viewpoint, and to speculate on future developments. As the authors have been given this freedom of writing, the chapters reflect the authors' work and the atmosphere of their fields. This gives each chapter a style, flare, and individuality that readers can enjoy.

Fluorescence imaging is widely used in biological systems, including recently in living cells, and thus is a methodology of great importance to those interested in visualizing single molecules. Given the broad potential of this technique, it is likely that many readers will want to know specific details of fluorescence imaging techniques in order to determine if it is feasible to image single molecules in their own field of interest. However, despite these general expectations, the editors and authors have focused this discussion in a single chapter solely on the fluorescence polarization method, one of the most challenging and difficult measurements in single molecule fluorescence imaging. They concisely describe the basic background, instrumentation, preparation, and data analysis of fluorescence polarization measurements based on their own experience. Although not as comprehensive a treatment of this topic as expected, we are sure that those who are interested in other aspects of fluorescence imaging will still find this information useful.

The manipulation of actin filaments by a laser trap is discussed in a separate chapter. Here, the authors have focused on the analysis of the mechanical measurements obtained from actin filaments. At the single molecule level, the work done is on the same order of magnitude as thermal energy. In fact, single actin molecules may harness the effects of thermal energy for the processes they perform. Thus, these types of measurements are inevitably influenced by thermal noise. How are the real data extracted from the thermal fluctuations that are also recorded? The authors have described the history of trial and error attempts to analyze data in which the real signals are hidden among a large background of noise. This is a valuable lesson that all researchers who perform single molecule measurements will face. The discussion of how such problems have been overcome has applications in a wide variety of fields and is certainly more useful to the readers than a general description of the manipulation methods of molecular motors.

The data on single molecule measurements presented in papers, books, and lectures appears fascinating. However, the techniques involved in detecting the dynamic behavior of single molecules, which is rather a complex, and at times tedious, process. Sophisticated data collection equipment is necessary, and the resulting data require complicated analysis. Consequently, we doubt the effort and time invested by researchers in the field to achieve these results will be fully understood by many readers, as this technology bridges the fields of physics and biology. However, while some progress is being made to merge these disciplines, there is still a considerable gap between them. Physicists do not want to handle biological materials and find it difficult to distinguish living molecules from physical and chemical materials. On the other hand, many biologists do not appreciate the finer details of complex measurements and data analysis. When biologists read this book, they will find that the chapters have been organized around different technologies rather than by the biological systems, in which measurements may have been obtained using several different techniques. The chapter on titin, for example, provides an excellent review and is a fine example of the communications between modern technology and biology, and reveals how new questions have been raised by the advances in experimental techniques. Another chapter addresses the relationship between single molecule technology and protein engineering.

This new technology has been made possible by integrating research methods from physical and biological backgrounds. At the same time, researchers in both fields found hurdles to clear. A comparison can be made to nanotechnology, which developed from the fields of physical and chemical sciences. Nanotechniques allow us to visualize, manipulate, and create materials in the size range of nanometers. As nanotechnologies have expanded, many researchers have realized that the laws that govern materials of nanometer size are very different to those applied to macroscopic machineries with which we are more familiar. Nature, however, has already developed and utilized nanotech. Life is full of nanomachines, and their functions are very different from artificial nanomachines. Thus, the unique operations of biomolecules and their assembly draws attention. Advances in the fields of biological sciences, molecular biology, biotechnology, and cell biology have enabled us to identify particular proteins of interest, sequence them from information in a genomic DNA database, and determine their role in cells. In this postgenomic era, researchers have started to address questions on the structure and function of protein molecules. Researchers now know that protein molecules are more complex than the simple design the DNA information implies. Studying the mechanism underlying protein functions is intriguing, and prerequisite are the techniques that allow us to monitor the dynamic structure of protein molecules and directly detect the functions of proteins.

At this point, with the range of different single molecule technologies available, it is difficult to find a common message in all the different topics of this book. Although physicists and biologists have acknowledged the possibility that single molecule measurements may solve many basic questions, complete answers have not yet been achieved. The editors of *Biology at the Single Molecule Level* have used the word "single molecule biochemistry," while other researchers have coined the terminology "single molecule physiology," "single molecule physics," and "single molecule cell biology." These words give us hope that single molecule detection will provide a breakthrough for the life sciences. At this stage, we cannot say if these technologies will be possible in living systems; however, it remains a goal and a dream. We have always believed that single molecule detection is not only a technique to solve individual questions, but one which will provide information on the functioning of complex living systems. We feel that this book will offer a significant contribution to the further

development of the single molecule technology and science in general.

Yoshiharu Ishii and Toshio Yanagida
Single Molecule Processes Project
ICORP, JST
2-4-14 Senba-higashi, Mino
Osaka, Japan 562-0035

Putting the Cell Biology Establishment on the Stand

Cells, Gels and the Engines of Life
By G.H. Pollack
Seattle, WA: Ebner & Sons (2001).
305 pp. $27.95

When I was a graduate student, I set out to get a handle on cell biology by carrying out an extensive review of the literature, beginning with the earliest citations I could find. By observing how the field progressed over time, I hoped to get a better sense for where the field would move in the future. I read the preface of the first edition of a biochemistry textbook from the early 1900s which explained that, for simplicity, it was assumed that all reactions took place in a well-stirred solution in a test tube in the section on thermodynamics and kinetics. The authors clearly recognized that life was not a structureless chemistry and thus, they explicitly warned the reader that this limitation must be addressed in the future. However, when I read the preface of the second and third editions of the same textbook, this warning was nowhere to be found. I realized that generations of scientists were being trained without any awareness of this fundamental flaw in their understanding of what governed chemical reactions within a living cell. For this reason, I was not shocked when the cell biology "establishment" was taken aback by the suggestion that structural (cytoskeletal) scaffolds and mechanical forces play critical roles in virtually all aspects of cell regulation; they just never read the preface. In *Cells, Gels and the Engines of Life*, Gerald Pollack has done us all a service: he has provided us with a 305 page preface to the future of cell biology which warns us all—students and establishment alike—that there will always be a fine line between understanding and assumption.

While our knowledge of the molecular widgets that comprise living cells has exploded beyond our wildest dream, our understanding of cell architecture and the relation between structure and function still remain rudimentary. For example, one mainstream cell biology textbook defines the cell as "a small membrane-bounded compartment filled with a concentrated aqueous solution of chemicals," like a balloon filled with molasses. In fact, many biologists who work with molecules in isolation still share this view, as do virtually all lay people, including the congressmen and women who decide which science projects the government will invest in. Pollack views this image as a dragon that must be slain and I cannot agree more.

The living cell is a chemo-mechanical machine and it uses all forces and devices at its disposal—physical as well as chemical and electrical—to carry out its miraculous tasks. The reality is that the cytoplasm is a molecular lattice, known as the cytoskeleton, that is permeated and insufflated by an aqueous solution. The different molecular filaments that comprise the cytoskeleton—microfilaments, microtubules, and intermediate filaments—position the cytoplasmic organelles. But this is not a passive support system. The same scaffolds orient many of the enzymes and substrates that mediate critical cell functions, including signal transduction, glycolysis, protein synthesis, transport, and secretion; analogous insoluble scaffolds mediate RNA processing and DNA replication within the nucleus. This use of "solid-state" biochemistry greatly increases the efficiency of chemical reactions because they are no longer diffusion limited, and it provides a means to compartmentalize different cellular activities. The cytoskeletal system also can dynamically grow and shrink within different microcompartments as a result of the action of specific molecular regulators. Finally, the entire cytoskeleton is always mechanically tensed as a result of the action of contractile forces that are generated within cytoskeletal microfilaments. Because thermodynamic and kinetic parameters are sensitive to changes in molecular mechanics, physical distortion of load-bearing molecules can directly alter biochemical activities. Thus, both changing the level of the tension in the cytoskeleton and chemically modifying cytoskeletal architecture can significantly impact cell form and function. Indeed, it is through these varied functions of the cytoskeleton that living cells can exhibit behaviors that are far beyond anything observed in man-made materials. The abilities of a cell to move its entire mass upstream against the flow of blood or contract against hundred pound weights are two simple examples.

Given these novel features of the cytoskeleton and the global orchestrating role that it plays in cell regulation, it is surprising that none of these features are ever mentioned by Pollack. In fact, he rarely uses the term cytoskeleton when discussing the cytoplasm. Instead, the revolutionary concept he presents is that the cytoplasm is a gel. At first glance, it would seem that we have merely changed the model of the cell from a balloon filled with molasses to one filled with jello. However, there is something deeper and much more important in his message. While cell biology focuses on the molecular components that comprise living cells, Pollack centers his attention on the water molecules that swell the cytoskeletal gel and which, up to now, have been virtually absent from the cell biology radar screen.

In the beginning of the book, we are introduced to new and important findings from fields as wide as engineering, drug delivery, and nanoscale chemistry that demonstrate previously unexpected properties of water when it is in a bound state. Pollack explains that much, if not most, of cellular water exists in a highly structured state in tight association with the hydrophilic surfaces of cytoskeletal proteins. This state lies somewhere between ordinary liquid water and ice. In fact, water molecules assemble into higher order geodesic structures