Preface: Why the physical microbe?

There are no small parts, only small actors.

Constantin Stanislavski

The microbial cell is a sophisticated machine. It builds and maintains itself using an elaborate molecular toolbox that it regulates with precision. It imports and processes nutrients, senses its environment, communicates with its cohort, and turns information into action. It grows and multiplies with alacrity. Leafing through any microbiology text, one cannot help being struck by the difficult technical and physical problems a micron-sized cell has solved in order to thrive: making decisions using chemical circuits, preparing optimally for unpredictable environments, communicating efficiently with competing or cooperating organisms, and growing as rapidly as possible when conditions are favorable. It seems one could reinterpret the standard microbiology text as an overview of the physical problems that a unicellular organism must solve, together with real world examples of how to solve them. In fact there are some excellent biophysics or physical biology textbooks that take this approach, disassembling large parts of biology and then reassembling the subject from a physical perspective.

The goal here is less ambitious. This book does not attempt any kind of comprehensive overview of cell biology, microbiology, or even biophysics. It is not even an introduction to microbiology. Instead it aims to use microbes to introduce a few major themes in physical biology. These themes include gene regulation, networks, noise and heterogeneity, and signaling and information flow. The book tries to give a readable overview of some of the research that has helped to advance these themes in recent years, and thus has shaped biological physics. The book focuses on the application to microbes—mostly bacteria—because the microbial world is such a wonderful laboratory for studying how living cells solve physical problems. Bacteria are easy to grow and to manipulate genetically. Many of their regulatory behaviors, physical structures and functions, and other properties are, although complex, still much simpler than in higher organisms. They are a starting point for testing quantitative models. At the same time, the microbial world is so diverse and rich in special cases that it almost seems that every microbial behavior that is not forbidden does occur in at least some instances. For these reasons many of the biophysical topics that are presented in this book were first developed and demonstrated in bacteria, either in familiar model organisms such as *Escherichia coli* or *Bacillus subtilis*, or in other species less well known.

In earlier epochs (a couple of decades ago) biological physicists certainly had the will to construct quantitative physical models for living systems. The enduring fascination with Kleiber's law, discussed briefly in chapter 1, attests to that.

Unfortunately, upon approaching the molecular level, experimental detail often was lacking and the trail went cold. What has changed is that tools are now available for constructing and testing molecular-level models for biological function. There has also been an influx of physically and mathematically enthused scientists applying these tools. Experimentalists can engineer new genes and circuits into living cells, isolate individual cells and count protein or other molecules within those cells, test stimulus and response, and compare the results to quantitative models and simulation. This book gives an idea of how physically motivated experiments and models are leading to a highly quantitative understanding of the living cell. Much of this understanding can be applied not only to bacteria but also more widely in eukaryotic biology and in particular to biomedical problems such as cancer.

The book arises from an introductory course in biological physics that I have taught for advanced undergraduates in the physical sciences at the University of Florida. The course has evolved over the years, gradually increasing its focus on the above themes in physical biology. Students want exposure to real scientific literature in this area, presented at a level that is accessible to the interested but non-expert physical scientist. Therefore this book attempts to walk the reader through some of the highlights of the literature. It is aimed at advanced undergraduates, beginning graduate students, and others with varying levels of expertise in biology, chemistry, and even physics. Aside from a very basic undergraduate science background, its only significant prerequisite is a willingness to use mathematics, in particular calculus and probability.

The first chapter begins with a very general overview of the microbial world and some terminology, followed by a consideration of size and energy constraints that impact bacteria. The second chapter introduces some basics of bacterial growth that have motivated recent investigations of resource allocation and heterogeneity in cell division. Subsequent chapters discuss gene regulatory networks and feedback, the role of noise or stochasticity in gene expression, and their application to phenotypic switching. Bacterial communication, in particular pheromone signaling and the very new topic of electrical signaling, is then discussed. The final chapter is a case study that involves nearly all of these topics: the sporulation/competence decision circuit in *B. subtilis*. This final example shows how a cell can integrate feedback, noise, heterogeneity, and chemical communication in order to control a phenotypic switch.

Again, the book does not attempt to be comprehensive. Many interesting bacterial behaviors such as motility (including chemotaxis), social behavior (competition and cooperation), and evolution are only briefly mentioned. Furthermore, needless to say, this is not a biology textbook. Although I have tried not to get any biology wrong, I have not tried to explain it authoritatively either. That is the job of a microbiology textbook. Nevertheless, where biological jargon arises that may leave the physical scientist reader at a disadvantage, I have tried to explain it in a footnote.

A few exercises are sprinkled throughout. Most are designed to fill in mathematical or physical details that would bog down the discussion. They vary in difficulty.

Finally I thank the students who have sat in my classes for their interest and enthusiasm. I apologize in advance for any mistakes or serious omissions and accept responsibility for them.