

PREFACE

The universe cannot be understood without first learning the language, and being conversant with the characters with which it is written. It is written in mathematical language, and the characters are triangles, circles and other geometrical figures, without which means it is humanly impossible to comprehend a single word.

—Galileo Galilei, *Opere: Il Saggiatore*

Biology is sometimes disparaged as a subject without far-reaching conceptual ideas. I think this is often the result of the way our understanding of the living world is presented in introductory courses rather than of any flaw in the subject itself. Indeed, for me, biology is a subject that harbors perhaps the most beautiful of phenomena we are aware of in the natural world and the most interesting scientific puzzles of our time. Further, belying the biology portrayed in many survey courses and fact-filled textbooks, it is also a subject with many overarching conceptual ideas, and this claim has been made for decades (see the references at the end of the preface for examples). One of these ideas, namely, that of allostery, has just recently passed its 50th anniversary and serves as an intuitive explanation of how molecules function across all domains of biology, from physiology to neuroscience, from the processes of the central dogma to those of quorum sensing.

My own fascination with the subject was solidified at a meeting at the Institut Pasteur to celebrate the 50th anniversary of the allostery concept, with many of the central fields of biology on display. Neuroscience had its advocates on hand to talk about ion channels from an allostery perspective. The processes of the central dogma were represented on many fronts, with researchers discussing everything from how genes are regulated by allosteric transcription factors to the structural conformations of the ribosome during translation. Human physiology was represented in the form of studies on hemoglobin. G protein-coupled receptors took center stage as an example of how the allostery phenomenon impacts cell signaling. Other examples abounded as well, including conformational changes in viral capsids, the workings of bacterial chemotaxis and molecular motors such as myosin. See the special volume of the *Journal of Molecular Biology*, "Allosteric interactions and biological regulation (Part I)" (Kalogridimos and Edelstein 2013) for the impressive breadth of topics described at that meeting. From my own point of view, the aspect of these talks I found most interesting was that all these seemingly disparate examples were to a first approximation described by the same fundamental equation that serves as the central equation of allostery, namely,

$$p_{\text{active}}(c) = \frac{(1 + \frac{c}{K_A})^n}{(1 + \frac{c}{K_A})^n + e^{-\beta \varepsilon} (1 + \frac{c}{K_I})^n}. \quad (1)$$

This equation tells us the probability of a molecule with n binding sites for ligands being in its active state is a function of ligand concentration c in terms of

the energy difference between the inactive and active conformations ϵ , and the affinity K_A and K_I of these ligands for the active and inactive states, respectively.

Often during the years over which this book was under construction, I have given a talk entitled "The Other Bohr and Biology's Greatest Model," in some sense as a provocation to see if I could get anyone to name for me a model they think has broader reach in helping explain more biology than does the two-state allosteric model of Monod, Wyman, and Changeux (and its model cousins) celebrated at that wonderful Institut Pasteur meeting. I didn't hear many persuasive alternatives.

This book is one in a collection of books entitled *Studies in Physical Biology* with one central aim, namely, to celebrate the deep, quantitative principles that preside over the subject of biology. This series aims to complement an earlier book, *Physical Biology of the Cell*, by taking particular themes laid out there and probing them more deeply, more in research monograph format than in textbook format. The audience for this book is the same as that for *Physical Biology of the Cell* or *Cell Biology by the Numbers*. That list includes biologists interested in seeing how the language of physics and mathematics can sharpen our biological thinking, physicists who want an introduction to some of the most exciting themes of modern biology, and engineers who want to see the scientific underpinnings of their subject. Though it is way too lofty an ideal to ever live up to, I always had the model of the classic series of Landau and Lifshitz in mind as an inspiration for how entire domains of a quantitative field could be revealed and, more recently, the more accessible (at least to me) work of Blandford and Thorne. The idea of this first book in the series is to bring together in one place the rudiments of how to describe the allosteric phenomenon using ideas from statistical physics and to showcase some of the most intriguing usage of these models across a broad spectrum of applications. The book is a caricature of a subject (allostery) that itself is full of caricatures of many important biological problems. I adopt this approach of simplification and abstraction without apology. My argument is that simplified models are often nothing more than a restatement of many of the key cartoons and schematics that dominate the biological literature, recast in a mathematical form that permits us to more rigorously subject those models to corroboration. One of my favorite scientific essays by my friend Jeremy Gunawardena aptly channels the great James Black in noting that our models are "not meant to be descriptions, pathetic descriptions, of nature; they are designed to be accurate descriptions of our pathetic thinking about nature." That in a nutshell is the philosophy that animates the entirety of this book, namely, that the history of science shows us over and over that our impressions of subjects are often naive or just plain wrong, and the idea behind formulating our views in mathematical terms is that we can sharpen those views, making it easier to subject them to scrutiny. To that end, we try to make our pathetic thinking as clear as we possibly can and then use mathematical reasoning to explicate the experimental implications of that thinking.

It is important to be clear from the outset, this is a book about models more than it is a book about biological phenomena. We knowingly make simplifications of many phenomena as a vehicle to introduce the conceptual framework. Of course, this leaves the question of how to best think about the phenomena themselves. To go even further, our ambitions are even more limited because for the most part, the entire book is restricted to one special class of models as described using equilibrium statistical mechanics, though we will make several

forays into the ways in which these ideas have to be generalized when thinking about the dynamical situations that arise out of equilibrium.

I have been particularly inspired by two books that attempt to bring unity to problems of signaling and regulation in biology, namely, *Genes and Signals*, by Mark Ptashne and Alex Gann, and *Cell Signaling*, by Wendell Lim, Bruce Mayer, and Tony Pawson. These excellent books attempt to find overarching principles that describe how molecules can mediate signaling processes. This book tackles some of the same questions but with a change in philosophy in the sense that it argues that by using mathematics to sharpen our thinking, we can sometimes go further in our understanding of the underlying phenomena, gaining precise insights into both the physiological and evolutionary parameters that characterize the phenotypes of the allosteric molecules of the cell.

The book is organized around a series of vignettes, each of which tells a little story about a biological problem which is a caricature of the real biology. With the biological problem in hand, we then show how statistical mechanical models of allostery can be erected for that problem as an explanatory and predictive framework. Signaling has many levels of description, ranging from the ecology and physiology of organisms to the natures of the networks to the molecules that make up those networks. In this book we will tell stories about the higher levels, but the rigorous quantitative discussion will focus on the molecular implementations of these signaling concepts with specific reference to allosteric interactions. The formulation might appear repetitive at times. Why? Because the statistical mechanical states are conceptually the same, and the resulting mathematics ends up often being identical, with the nouns changing but the verbs staying the same. Alfred Hershey once introduced the concept of a perfect experiment. "When asked what his idea of happiness would be, [Hershey] replied, 'to have an experiment that works, and do it over and over again.'" (Hodgkin 2001). In some sense, the statistical mechanical theory of allostery is the perfect theory for the same reason, because we can do it over and over again to shed light on a huge variety of different biological phenomena.

I was surprised to find how many fierce and personal debates and feelings I would uncover during the decade I spent digging deeply into models of allostery. There are still exposed nerves from the 1960s over topics such as the relative merits of the MWC and KNF models. But further, discussions of these ideas in the scientific public and in the reviewing process have exposed the widely divergent views about what it actually means to know something. Opinions on the status of theoretical models of allostery range from the idea that the success of the approach is "well known" to the fact that such models "don't work," with both opinions held with great conviction and stated as fact. MWC seems to be a world fraught with opinions not based on explicitly having a dialogue between theory and experiment, where theory says which knobs to tune, and then experiments are designed to tune those knobs. There is much received wisdom about the applicability or lack thereof of this framework, and part of the goal here is to make that conversation more clear. On that note, because in fact many of the applications of models of allostery to real-world problems have not been subjected to a rigorous theory-experiment dialogue, in some cases the data I appeal to will not be characterized by the same attention to error bars and fits that more modern treatments would. The reader is urged to overcome those shortcomings of my presentation by participating in the next phase of development of the study of allostery.

A subject I am very sensitive to is the enormous contributions made in all corners of science by a veritable army of researchers young and old, of different races and genders. These contributions should be honored, and I am grateful to be the beneficiary of these contributions every day. That said, this book makes no attempt at a scholarly report on the original literature on the many topics that appear throughout the text. As already noted, the book is built around intentional simplifications of the enormous atomic-level complexity found in the macromolecules of life. My main focus is to provide a coherent and pedagogical discussion of how one class of models can answer to diverse biological phenomena. My referencing is idiosyncratic and primarily focused in two directions: those papers that were the basis of some particular case study I am introducing or those papers I found to be particularly accessible for describing some topic.

Acknowledgments

I have always found there are two great and very distinct pleasures in writing a book. The first is personal and solitary and is a pleasure born of sitting and thinking and calculating and trying to come to a deep and rigorous understanding of the topic by myself. The second is quite the opposite and is fundamentally social and involves invoking the generosity of colleagues who are happy to talk about their ideas, to offer critiques of their own, and to provide an education in the subject. Though I have benefited from many such conversations now for decades, for this book I am particularly grateful to Frances Arnold, Tony Auerbach, Rachel Banks, Stephanie Barnes, Nathan Belliveau, Howard Berg, Bill Bialek, Shelby Blythe, Jean-Pierre Changeux, Griffin Chure, Eric Davidson, Julia Duque, Bill Eaton, Tal Einav, Luke Funk, Vahe Galstyan, Hernan Garcia, John Gerhart, Lea Goentoro, Chandana Gopalakrishnappa, Shura Grosberg, Jeremy Gunawardena, Bob Haselkorn, Liz Haswell, Dan Herschlag, Hopi Hoekstra, Christina Hueschen, Kabir Husain, Oleg Igoshin, Zofii Kaczmarek, Marc Kirschner, Tolya Kolomeisky, Jane Kondev, John Kuriyan, Michael Laub, Thomas Lecuit, Heun Jin Lee, Henry Lester, Mitch Lewis, Wendell Lim, Rod MacKinnon, Sanjoy Mahajan, Rodrigo Maillard, Madhav Mani, Sarah Marzen, Linas Mazutis, Chris Miller, Ron Milo, Leonid Mirny, Tim Mitchison, Richard Murray, Arvind Murugan, Brigitte Naughton, Phil Nelson, Elad Noor, Noah Olsman, Arthur Pardee, Isabelle Peter, Niles Pierce, Steve Quake, Rama Ranganathan, Manuel Razo, Doug Rees, Greg Reinhart, Kimberly Reynolds, Tyler Ross, Helmut Schiessel, Clarissa Scholes, Mikhail Shapiro, Boris Shraiman, Parijat Sil, David Sivak, Ed Taylor, Matt Thomson, Denis Titov, Reza Vafabakhsh, Navish Wadhwa, Jon Widom (sorely missed), Ned Wingreen, Shahrzad Yazdi, and Zechen Zhang. Special thanks for Manuel Razo, Griffin Chure, Stephanie Barnes, and Nathan Belliveau, who undertook turning our theoretical musings into a rigorous experimental endeavor. I am deeply grateful to the Benjamin and Donna Rosen Center for Bioengineering, which has supported my work at every turn, and to the NIH for generous support for curiosity-driven research.

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