Preface

Or, how physical science methods help us understand "life"

> And the whole is greater than the part.
>
> **Euclid elements, Book I, Common Notion 5, ca. 300 BC**

This book concerns one simple question:

> What is life?

If only the answer were as simple! In this book, you will find a comprehensive discussion of the experimental and theoretical tools and techniques of biophysics, which can be used to help us address that most innocuous question.

The creation of this second edition was guided mainly by two imperatives: include the feedback from students and teachers made in the classroom, tutorial offices, practical labs, and lecture theaters from the first edition, and to freshen up some key areas and include some new emergent ones in light of recent developments in Physics of Life research. So, a number of sections have been reorganized, condensed, and expanded as appropriate, and the narrative improved in response to reader comments. Several additional worked examples and problem questions are now included. The title has been marginally revised to reflect the intersection of "biophysics" and "biological physics" into a single discipline of the "Physics of Life."

"Interdisciplinary" research between the physical and biological sciences is now emerging as one of the fastest growing fields within both the physical and biosciences—a typical search for "biophysics" in any major Internet search engine now generates several million hits. The trend toward greater investment in this interfacial area is reflected in the establishment of centers of excellence across the world dedicated to interdisciplinary science research and graduate student training that combine the elements of both physical and life sciences. Biophysics/biological physics is now a standard teaching component option in undergraduate biochemistry and physics courses, and the significant direction of change over the past few years in terms of research direction has been a shift toward a smaller length scale and a far greater physiological realism to highly challenging bioscience experiments—experiments are getting better at imaging molecular processes. On the other hand, there are some theorists who feel that we need biophysical concepts and theories at higher length scales to combat the sometimes suffocating reductionism of modern biology.

Physical science methods historically have been key to providing enormous breakthroughs in our understanding of fundamental biology—stemming from the early development of optical microscopy for understanding the cellular nature of life to complex structural biology techniques to elucidate the shape of vital biomolecules, including essential proteins and DNA, the coding molecule of genes. More recently, physical science developments have involved methods to study single cells in their native context at the single-molecule level, as well as providing ground-breaking developments in areas of artificial tissue bioengineering and synthetic biology, and biosensing and disease diagnosis. But there is also a tantalizing theme emerging for many of the researchers involved to, in effect, reframe their questions across the interface between the physical and life sciences, through a process of "co-creation"; biologists and physicists interacting to generate transformative ways of studying living matter that neither in isolation could achieve. The tools and techniques described in this book resonate with those chords.

This book concisely encompasses the full, modern physical science "toolbox" of experimental and analytical techniques that are in active use. There is an enormous demand for literature to accompany both active research and taught courses, and so there is a compelling, timely argument to produce a concise handbook summarizing the essential details in this broad field, but one which will also focus on core details of the more key areas. This book can be used to complement third- and fourth-year undergraduate courses in physical science departments involving students who are engaged in physical/life sciences modules—there are several of these internationally involving biological physics/biophysics, bioengineering, bionanotechnology, medical/healthcare physics, biomedical sciences, natural sciences, computational biology, and mathematical biology. Similar stage undergraduates in life sciences departments doing physical/life science interfacial courses will also benefit from this text, to accompany lectures covering biophysics, bionanotechnology, systems biology, and synthetic biology. Also, PhD and master's students engaged in physical/life sciences courses and/or research will find significant utility for structuring and framing their study, and expert academics will find this text to be an

excellent concise reference source for the array of physical science tools available to tackle biological problems.

In this book I focus specifically on the purpose, the science, and the application of the physical science tools. The chapters have been written to encapsulate all tools active in current research labs, both experimental and analytical/theoretical. Bulk ensemble methods as well as single-molecule tools, and live-cell and test tube methods, are discussed, as all are different components available in the physical scientist's toolbox for probing biology. Importantly, this broad material is comprehensively but concisely mapped into one single volume without neglecting too much detail or any important techniques. Theoretical sections have been written to cover "intermediate" and "advanced" ability, allowing levels of application for students with differing mathematical/computational abilities. The theory sections have been designed to contrast the experimental sections in terms of scale and focus. We need theories not only to interpret experimental techniques but also to understand more general questions around evolution, robustness, nonequilibrium systems, etc., and these are not tied to molecular scales.

Future innovators will need to be trained in multidisciplinary science to be successful, whether in industry, academia, or government support agencies. This book addresses such a need—to facilitate educating the future leaders in the development and application of novel physical science approaches to solve complex challenges linked to biological questions. The importance of industrial application at the physical/life sciences interface should not be underestimated. For example, imaging, tracking, and modeling chemical interactions and transport in industrial biological/biomedical products is an emergent science requiring a broad understanding and application of biophysical sciences. One of the great biopharma challenges is the effective delivery of active compounds to their targets and then monitoring their efficacy. This is pivotal to delivering personalized healthcare, requiring biological processes to be understood in depth. This is also a good example of scales: the necessary molecular scale of target, binding site, etc., and then the much larger organismal scale at which most candidate drugs fail—that of toxicology, side effects, etc. Physically based methods to assess drug delivery and model systems facilitating *in vitro* high-throughput screening with innovative multilength scale modeling are needed to tackle these challenges.

Also, the need for public health monitoring and identifying environmental risks is highly relevant and are key to preventative medicine. An example is exposure to ionizing radiation due to medical imaging, travel, or the workplace. Detecting, monitoring, and understanding radiation damage to DNA, proteins, and cellular systems during routine imaging procedures (such as dental x-rays or cardiothoracic surgery) are key to understanding noncancer effects (e.g., cataracts in the lens of the eye) and the complications of radiation-based cancer therapy. These are core global public health issues.

Understanding the science and application of new instrumentation and analysis methods is vital not only for core scientific understanding of biological process in academia but also for application in many sectors of the industry. Step changes in science and healthcare sectors are always preceded by technological advances in instrumentation. This requires the integration of specialist knowledge with end-users' requirements alongside an appreciation of the potential commercialization process needed to exploit such innovation in both public and private sectors via both multinational companies and small- to medium-sized business enterprises (SMEs). Such real-world challenges require individuals who are skilled scientists and experts in their own field, but who are also equipped to understand how to maximize impact by utilizing the full investigative power of the biophysical sciences. Specific advances are needed in advanced optical microscopy and instrumentation, single-molecule detection and interactions, atomic force microscopy (AFM), image processing, polymer and synthetic chemistry, protein crystallography, microfabrication, and mathematical and finite element modeling to then interface with current biological and healthcare problems.

This book is structured as nine concise chapters, navigating the reader through a historical background to the concepts and motivation for a physical science toolbox in understanding biology, and then dedicating a chapter to orienting readers from a physical science area of expertise to essential biological knowledge. Subsequent chapters are then themed into sections involving experimental biophysical techniques that primarily detect biological components or measure/control biological forces. These include descriptions of the science and application of the key tools used in imaging, detection, general quantitation, and biomolecular interaction studies, which span multiple length and time scales of biological processes, ranging from biological contexts both in the test tube and in the living organism. I then dedicate a chapter to theoretical biophysics tools, involving computational and analytical mathematical methods for tackling challenging biological questions, and end with a discussion of the future of this exciting field.

Each chapter starts with a "General Idea," which is a broad-canvas description of the contents and importance of the chapter, followed by a nontechnical overview of the general area and why it is relevant. Case examples are used throughout for the most popular physical science tools, involving full diagrams and a précis of the science involved in the application of the tool. "Key Points" are short sections used to reinforce key concepts, and "Key Biological Applications" are used to remind the reader of the general utility of different biological questions for the different biophysical tools

and techniques discussed. To aid revision, several exam-style questions are also included at the end of each chapter, pitched at a general audience that can consist of readers with a background in either physical or life sciences. Solved exercises are also used and are associated with worked case examples in which study questions are solved in clearly defined steps. Summary bullet points are also used at the end of each chapter to summarize the key concepts.

The writing of this book went through several iterations, not least in part due to the several anonymous expert reviews that came my way, courtesy of Francesca McGowan at Taylor & Francis Group. I am indebted to her and her team, and to the anonymous reviewers who invested their valuable time to improve this textbook. Also, I am indebted to several of my students and academic peers who generated a range of valuable feedback from their own areas of expertise, whether wittingly or otherwise. These include Pietro Cicuta, Jeremy Cravens, Domi Evans, Ramin Golestanian, Sarah Harris, Jamie Hobbs, Tim Newmann, Michelle Peckham, Carlos Penedo, Ehmke Pohl, Steve Quinn, Jack "Emergency Replacement Richard" Shepherd, Christian Soeller, and Peter Weightman.

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Special thanks also go to the other members of my own research team who, although not being burdened with generating feedback on the text of this book, were at least generous enough to be patient with me while I finished writing it, including Erik "The Viking" Hedlund, Helen "The Keeper of the Best Lab Books Including a Table of Contents" Miller, Adam "Lens Cap" Wollman, and Zhaokun "Jack" Zhou.

Finally, you should remember that this emergent field of interfacial physical/life science research is not only powerful but genuinely exciting and fun, and it is my hope that this book will help to shine some light on this highly fertile area of science, and in doing so captivate your senses and imagination and perhaps help this field to grow further still.

Perhaps the most important fact that the reader should bear in mind is that the use of physical science methods and concepts to address biological questions is genuinely motivated by *ignorance*; biophysical enquiry is not a box-ticking exercise to confirm what we already know, but rather it facilitates a genuinely new scientific insight. It allows us not only to address the *how*, but more importantly is driven by the most important word in science—*why?*

The most important words in science are "we don't know."

There is no such thing as a stupid question, only fools too proud to ask them.

Additional material is available from the CRC Press website: www.crcpress.com/product/isbn/9781498702430.

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Building Bridges and removing barriers. Not just 'decorating the boundaries.'
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