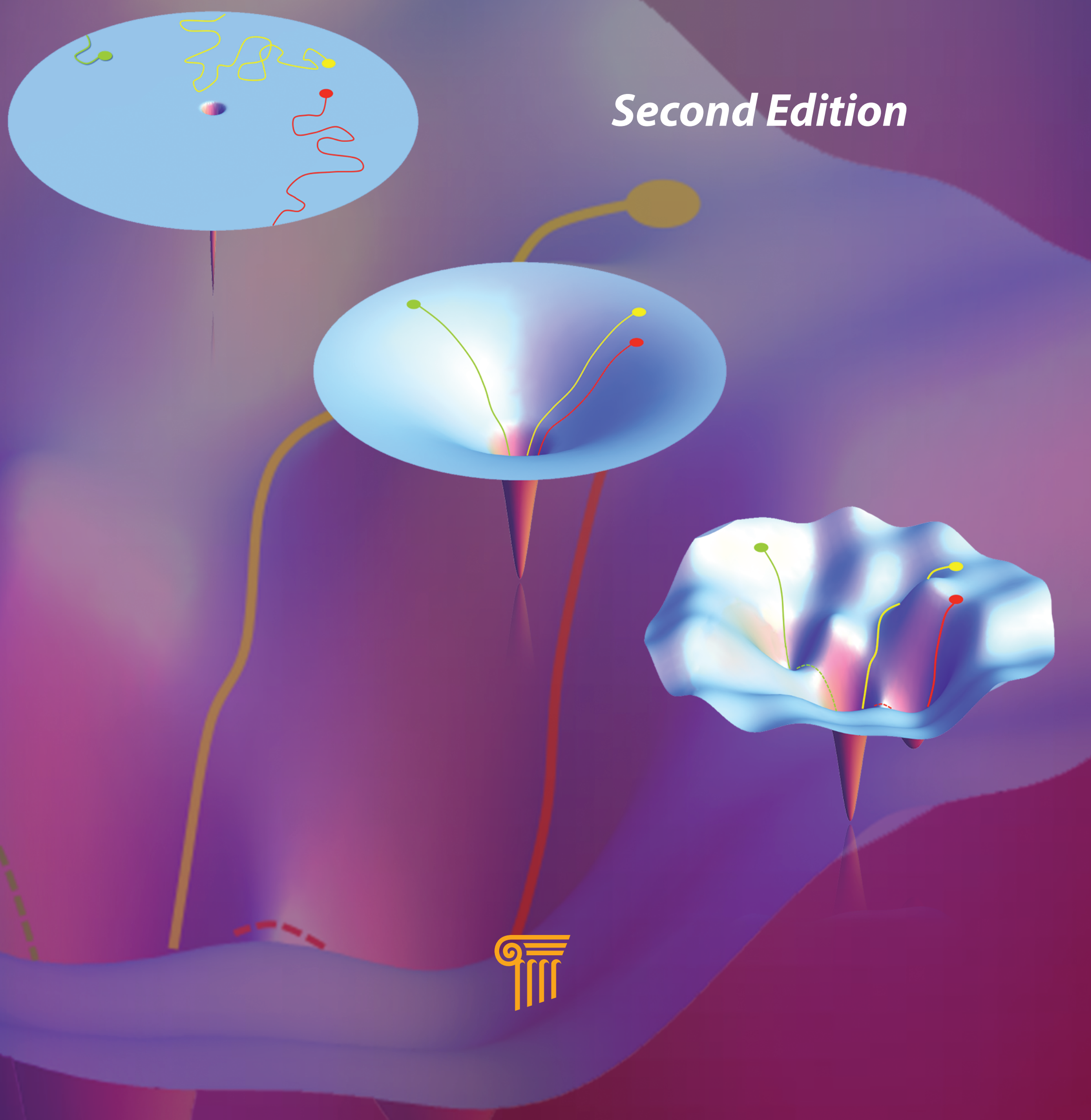
Helmut Schiessel

Biophysics for Beginners

A Journey through the Cell Nucleus

Second Edition



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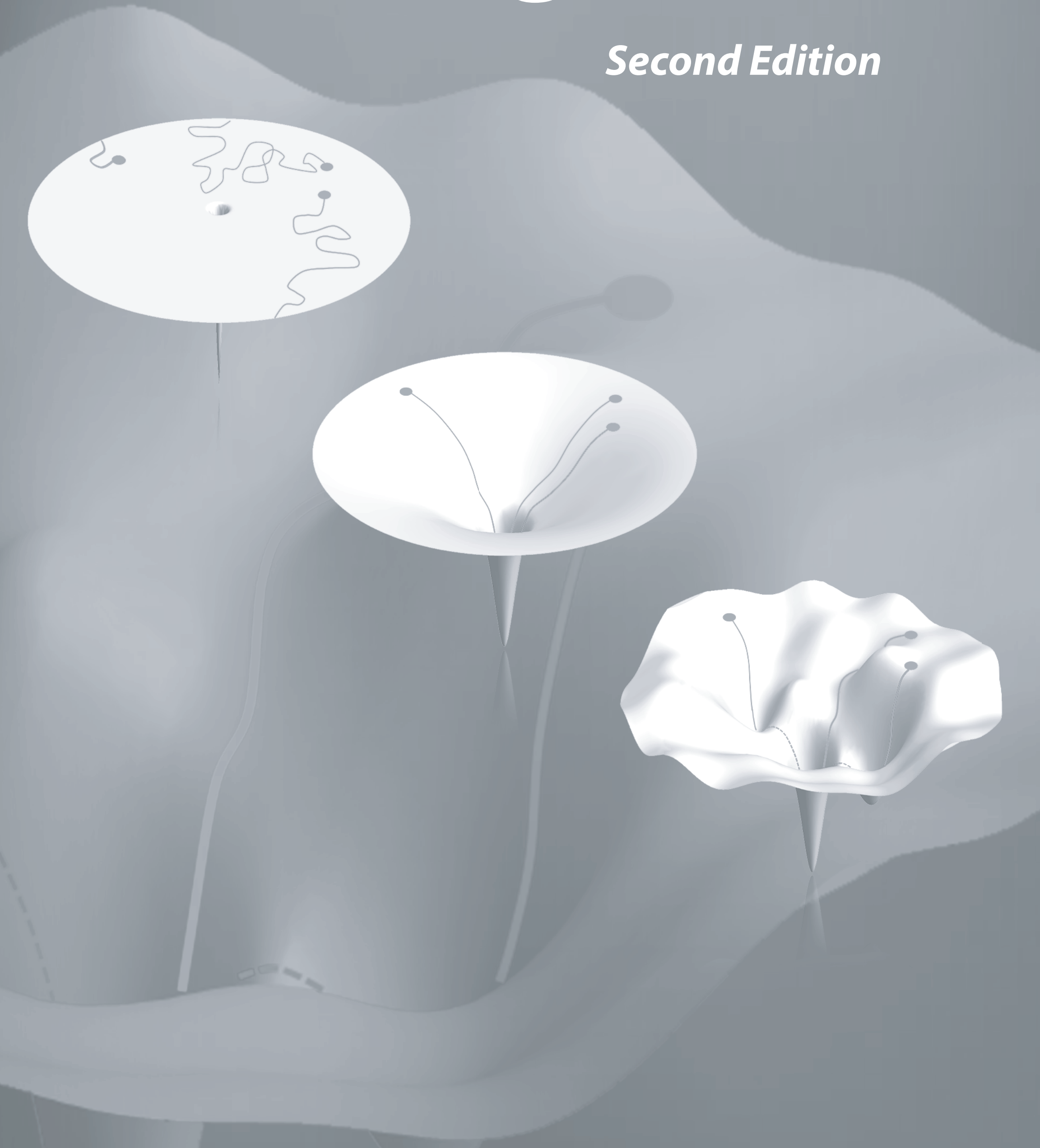

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Biophysics for Beginners: A Journey through the Cell Nucleus
(Second Edition)

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Contents

Preface to the First Edition

Preface to the first edition: Biophysics or biological physics or statistical physics of biological matter or quantitative biology or computational biology is a large and rapidly growing interdisciplinary field with many names on the border between physics, biology and mathematics. It is not clear where this field begins, where it ends, or where it will ultimately lead. However, it is clear that tremendous progress has been made in this area over the past two decades. This book is the result of various attempts to teach the subject in a variety of settings to audiences from diverse backgrounds at different stages in their studies. It started with courses (usually 4 h long) at winter and summer schools in Denmark, the Netherlands, Belgium, South Korea, South Africa, France and Mexico. The material was expanded in a theoretical biophysics course for Physics Masters students at Leiden University. A script that I made for a course at the Casimir Graduate School between Delft and Leiden University was a short first version of the book.

When I decided to write an entire book on the subject, I wanted it to be self-contained (avoiding phrases like "one can show"), especially since I noticed that some students in my classes did not know much about molecular biology while others had no background in statistical physics. In order for the book to reach a certain depth without becoming too thick, some difficult decisions had to be made beforehand. I decided that everything in this book should be related to what I consider the heart of molecular biology of the cell, the central dogma of molecular biology, which states that information flows from DNA to RNA to proteins. By limiting myself to this topic, I only had to deal with three types of molecules, all polymers, all of which are in the nucleus of eukaryotic cells. Using these molecules as examples, I cover a large number of biophysical topics, most of which are also relevant in many other areas of biophysics. I present examples that make it clear what is special about biophysics compared to other areas of physics. A second decision was to restrict myself to "paper and pencil" theories and show how they can be used to understand experimental observations, but not to discuss computer simulations. I stress here that simulations are just as important as theory and experiments, but for this textbook I have selected topics where a purely theoretical treatment is sufficient—as in most textbooks on more classical subjects. [Note: The second edition of this book covers computer simulations.]

The book contains 8 chapters. The first chapters are more introductory, are shorter and contain fewer examples to enable the reader to grasp the structures of the theories. The later chapters bring more and more experimental examples and help the reader to develop the physical intuition necessary to grasp the complex physics behind the systems under consideration. The problems considered are also more recent, and many are still the subject of intense debate in the current literature. I have tested preliminary versions of all the chapters of the book in various courses: Chapters 2 and 7 with physics bachelors students, Chapters 1, 3, 4, 5 and 7 with physics masters students and Chapters 1, 4, 6, 7 and 8 with PhD students and postdocs, most of them physicists, but some with a background in chemistry or biology. I hope that this book will find usefulness in a variety of settings.

I would like to acknowledge the people without whom this book would not have been possible. The late Jonathan Widom had been extremely kind in sharing his deep insights into biological matter with me when I had just started in the field. Never again have I met someone who was able to combine the biological and physical perspectives so seemingly effortlessly. It was Robijn Bruinsma and Bill Gelbart with whom I took my first steps in this new field. Robijn's lecture at a winter school in Vancouver opened my eyes to what is special about biophysics; I tried to preserve some of that excitement in the section on protein-target search in the last chapter of the book [now Chapter 8]. Working with Philip Pincus gave me a more intuitive understanding of electrostatics, which I tried to explain

in the chapter on this subject. Discussions from this time with his student Andy Lau also affected this chapter. John Maddocks had kindly and critically read large parts of the manuscript and had helped clear up inconsistencies in my explanations of Euler elasticas. If there are still any left, it is entirely my fault. My former student Igor Kulić is the person whose work has found its way into this book in more places than anyone else. His clear-cut approaches to problems related to DNA and nucleosomes have proven ideal for a textbook. Martin Depken's work on chromatin fibers and kinetic proofreading during transcription also seemed to fit too well into this book to be left out. Ralf Everaers has greatly influenced my views on chromatin fibers and the organization of chromosomes on large scales.

In addition to John Maddocks, many other people helped me with the book. Peter Prinsen read and corrected large parts of it at an early stage. Marc Emanuel and Giovanni Lanzani had been helpful at several points when I was hopelessly stuck in a calculation. Giovanni also helped with some illustrations. I would also like to thank Behrouz Eslami-Mossallam, Jean-Charles Walter and Raoul Schram and many students in my courses for helpful suggestions. My doctoral supervisor Alexander Blumen helped me to appreciate clarity and precision during my PhD work, which I also wanted to achieve here. Some of the work on polymer dynamics with him and Gleb Oshanin found its way into this book. My favorite course during my studies at Freiburg University was the statistical physics course given by Hartmann Römer; I consulted my old notes from this course as the basis for Chapter 2.

There are many more people I should thank. I mention some of them below (and apologize to those I forgot to mention): Ralf Blossey, Reza Ejtehadi, Ion Cosma Fulga, Stephan Grill, Remus Dame, Markus Deserno, Marianne Gouw, Rosalie Driessen, Arman Fathizadeh, Peter Kes, Kurt Kremer, Jörg Langowski, Ralf Metzler, Farshid Mohammad-Rafiee, Daniela Rhodes, Hervé Mohrbach, Laleh Mollazadeh-Beidokhti, John van Noort, Wilma Olson, Fran Ouwerkerk, Jens-Uwe Sommer, Mario Tamashiro, Rochish Thaokar, Harald Totland, Michelle Wang and Kenichi Yoshikawa. Last but not least, I would like to thank Sabina for her infinite patience.

H. Schiessel

Preface to the Second Edition

This is an updated and expanded version of my textbook *Biophysics for Beginners: A Journey through the Cell Nucleus*. I decided to break with a rule in the first edition, namely to limit myself to "paper and pencil" theories. Most of the chapters now contain extensive computational exercises and there is a new chapter on computational methods (Chapter 9). I hope that the exercises will enable a deeper understanding of various (bio)physical systems (including the ideal and real gas, self-avoiding walks, DNA mechanics, RNA and protein folding and nucleosomes) and various methods (including exact enumeration, transfer matrix method, dynamic programming algorithm as well as molecular dynamics and Monte Carlo simulations).

New sections reflect recent developments such as biomolecular condensates and loop extrusion in chromosomes. The chapter on polymer physics has been expanded and a new appendix has been added on the connection between polymer statistics and critical phenomena. Finally, the text has been improved throughout.

I thank Marco Tompitak for many suggestions on how to improve the book. Martijn Zuiddam developed an analytical approach to describe sequence-dependent DNA mechanics, which was missing in the first edition (new Subsection 4.2.2). Many thanks to him and Ralf Everaers. I thank Michael Wimmer and Lennart de Bruin, with whom I taught computational physics at Leiden University. The interaction with them formed the basis for many changes in the new edition.

Several of the new computational exercises were successfully tested in Leiden: Problem 2.6 "Verifying the ideal gas law" in the Bachelor course on Statistical Mechanics taught by Peter Denteneer (thanks to him and Pascal van der Vaart for improving it), Problem 3.4 "Exact enumeration of self-avoiding walks" in my MSc course

on Theoretical Biophysics and Problems 9.1 "Different phases in a system of Argon atoms" and 9.2 "Phase transitions in the two-dimensional Ising model" in my Computational Physics courses.

Since the first edition of this textbook, I have had the pleasure of interacting with various other people who influenced my thinking. I would like to mention Alain Arneodo, Benjamin Audit, Gerard Barkema, Rhys Bird, Giovanni Brandani, Enrico Carlon, Jamie Culkin, Koen van Deelen, Nicolas Destainville, Ariel Kaplan, Lennard Kwakernaak, Steven Lankhorst, Joshua Lequieu, Kazuhiro Maeshima, Manoel Manghi, John Marko, Alireza Mashaghi, Alexandre Morozov, Jonas Neipel, Alexey Onufriev, Juan de Pablo, Lois Pollack, Rob Phillips, Akihisa Shioi, Andy Spakowitz, Cedric Vaillant, Tetsuya Yamamoto, Takahiro Sakaue, Shelley Sazer, Bahareh Shakiba, Gijs Vermarïen, Michael Wellens, Jesse van Welzenes, Dulcy van der Werff, Joerie Wondergem and Renger Zoonen.

H. Schiessel

"Helmut Schiessel's Biophysics for Beginners is an excellent text for anyone interested in understanding the workings of the cell nucleus from the perspective of physics. The book is unique in providing a deep, authoritative introduction to the physical principles that underlie our current understanding of the packaging and processing of the nucleic acids and proteins within the nucleus and in introducing the reader to key biological questions."

Prof. Wilma K. Olson
Rutgers, the State University of New Jersey, USA

"The book by Helmut Schiessel is a welcome timely addition to the growing but still badly insufficient literature on modern biological physics. This field of science is traditionally difficult for students and teachers alike: students lack either knowledge of physics or background in biology, or both. The attractive feature of the book is that it is self-contained: it starts with a concise description of the main ideas and facts of molecular biology and then continues to introduce the main concepts of statistical physics and polymer physics. Both physics and biology introductions are solid enough for the student to start using these ideas. Do not miss this book!"

Prof. Alexander Grosberg
New York University, USA

"This is a most welcome book showing beautiful applications of physics to polymers in cells. It will clearly be useful as a basis to teach biophysics and more generally to all physicists interested in the properties of cells and their nucleus, and also to biologists interested in the physical properties of biopolymers."

Prof. Jean-François Joanny
Institut Curie, France

"Teaching an introductory course in theoretical biological physics is a major challenge. The lecturer not only needs to introduce a diverse set of theoretical concepts from different areas of physics, but also needs to provide a thorough introduction to molecular biology and a broad set of examples of how to apply the physics concepts to biological systems. This textbook does all of this in a well-balanced mix. It will be an excellent choice both as course material and for self-study."

Prof. Ulrich Gerland
Technical University Munich (TUM), Germany

Biophysics is a new way of looking at living matter. It uses quantitative experimental, theoretical, and computational methods, thereby opening a new window for studying and understanding life processes. This textbook provides a brief introduction to the basics of the field, followed by in-depth discussions of more advanced biophysics subjects, going all the way to state-of-the-art experiments and their theoretical interpretations. The second edition presents some of the newest developments in the field (e.g., biomolecular condensates, loop extrusion), a new chapter on computational methods, and many computer exercises specially designed for this textbook.

Helmut Schiessel studied physics at the Albert-Ludwigs University, Freiburg, Germany. There he earned his PhD under the guidance of Prof. A. Blumen in the Group for Theoretical Polymer Physics. After graduating in 1997, he worked as a postdoc with Prof. P. A. Pincus at the University of California, Santa Barbara. Then, he was a joint postdoc with Profs. W. M. Gelbart and R. Bruinsma at the University of California, Los Angeles. In 2000, he joined the Theory Group of the Max Planck Institute for Polymer Research, Mainz, Germany, where he was in charge of a biophysics research project. From 2005 to 2020, Prof. Schiessel headed the chair of Theoretical Physics of Life Processes in the Instituut-Lorentz at Leiden University, the Netherlands. In 2021, he joined the Cluster of Excellence Physics of Life at the Technical University in Dresden, Germany, where he heads the Theoretical Physics of Living Matter Group.

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