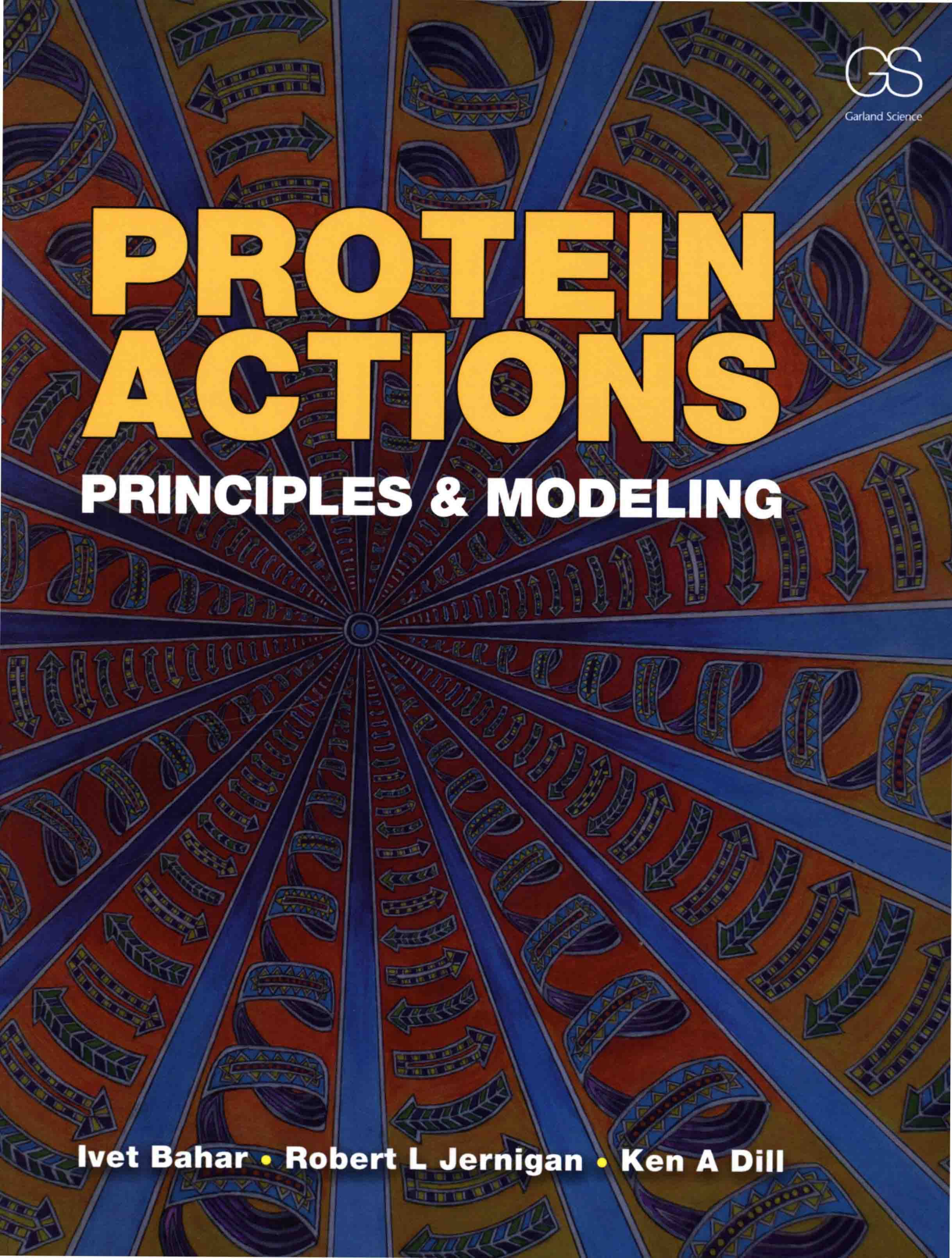

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PROTEIN ACTIONS

PRINCIPLES & MODELING

Ivet Bahar • Robert L Jernigan • Ken A Dill

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Protein Actions: Principles and Modeling describes the basic principles of protein molecules – their structures; their folding, binding and aggregation; their dynamics and mechanisms; and their evolution – as well as the methods of modeling them, including bioinformatics, physics-based computer simulations, and the tools of drug discovery. It is intended for a one-semester course for biological scientists learning quantitative foundations and for physical scientists learning the biology and chemistry. This text is ideal for graduates, advanced undergraduates, and any professional who seeks an introduction to the biological, chemical, and physical properties of proteins.

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Cover Image: This image, by artist Ashley Yevick, shows the helices and beta sheets that are key building blocks of protein structure. And, it captures an aesthetic beauty of proteins – the localized symmetries of these components and the global symmetry of their overall assembly within some proteins.

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Protein Actions

Principles and Modeling

To our families,
Ivet dedicates this book to Izzet, Yosi, and Avi.
Bob dedicates it to Craig, Alex, Julie, Eva, and Mila.
And Ken dedicates it to Ryan, Tyler, and Jolanda.

PREFACE

This is a textbook about the physical principles of protein molecules. It describes protein structures; their folding, binding, and aggregation equilibria and kinetics; their dynamics and mechanisms; and their role in drug discovery. We emphasize principles and models, as well as computational methods for simulating protein actions.

This book is aimed at graduate students and advanced undergraduates. We hope it will have value for a spectrum of readers from biologists, chemists, drug designers, and modelers who seek foundations and quantitative methods to physicists, engineers, material scientists, and computer scientists in other quantitative disciplines who seek an introduction to the biological and chemical properties of proteins. In some chapters, we provide appendices with advanced or embellishing material.

The 13 chapters are organized as follows. Chapter 1 introduces protein structure. Chapter 2 is a survey of some of the fascinating actions and mechanisms of proteins that will be taken up in more detail later in the book. In Chapter 3, we describe protein folding equilibria and the forces that drive folding and other actions. Chapter 4 gives the principles of binding. One of the most important principles of living systems is that the binding of a ligand can be modulated and influenced by the coupled binding of another ligand. This is the basis for molecular motors, regulation, signaling, and transduction. Chapter 5 presents some of the best-known cooperative conformational transitions: the helix–coil transformation, protein folding, and amyloid aggregation. A historical driver of protein physical chemistry was Levinthal's paradox, which puzzles over how proteins can fold so quickly to find their native states. Chapter 6 describes experiments and modeling of the mechanism and kinetics of protein folding. In Chapter 7, we consider how proteins evolve, leading to Darwinian descent with modification and even to new species.

Beginning in Chapter 8, we present the basic principles and applications of computational modeling and simulations. Chapter 8 describes the methods of bioinformatics—how to align and analyze amino acid sequences, leading to insights into structure and function. Chapter 9 introduces how protein structures and energetics are modeled in computer simulations. Chapter 10 describes molecular simulation methods such as Monte Carlo and molecular dynamics, which provide a way to explore conformational ensembles, free energies, dynamics, and mechanisms of actions. In Chapter 11, we survey some of the methods of protein-structure prediction. Chapter 12 describes the collective motions involved in protein actions, principally through the lens of simple structure-based elastic network models. Finally, Chapter 13 gives an overview of computational drug discovery, where proteins play a central role not only as targets, but also as therapeutic agents.

Our intention has been to provide the basic foundations needed for those who are—or are becoming—practitioners in the art, science, and engineering of proteins.

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In 1676, Isaac Newton said: "*If I have seen further than others, it is by standing on the shoulders of giants.*" Some of the many giants to whom we three co-authors owe a great debt of gratitude are shown on this genealogical tree. (Genealogy provided by Academictree.org/chemistry. Image created by Ashley Yevick.)

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