
Preface

Almost all aspects of life are engineered at the molecular level, and without understanding molecules we can only have a very sketchy understanding of life itself.

—Francis Crick

The decades that followed the successful forays in structural biology have witnessed a veritable deluge of research publications in the next frontier discipline: molecular biophysics. Despite much effort, the core problems in the field remain stubbornly open and the field has not enjoyed, at least so far, the meteoric level of success of structural biology. The stakes are high, the science is loud, and yet, the signal-to-noise ratio in the conveyance of information remains deceptively low. In spite of enticing promises, it is felt that we are nowhere near cracking the protein folding problem from first principles, that we are far from unraveling the physicochemical basis of enzyme catalysis and protein associations, and that we are still unable to engineer therapeutic drugs based on our understanding of molecular interactions. In regards to the latter problem, drug discovery seems riskier than ever, with projects routinely terminated at mid-stage clinical trials, new targets getting harder to find, and therapeutic agents recalled due to unanticipated health threats or idiosyncratic side effects in patient subpopulations. The vast and seemingly endemic problems of the pharmaceutical industry are not confined to the scientific realm but the latter has much to do them. Properly harvesting and ultimately exploiting the output of structural biology to make more efficacious and safer drugs has proven to be much more difficult than originally thought. This rather grim reality has motivated the writing of this book as it keeps reminding us that conceptual breakthroughs in the realm of molecular biophysics are sorely needed.

The book focuses on a vital area of biophysical research that has been—in the author’s view—substantively overlooked if not relegated, an area from within many of the needed breakthroughs are likely to sprout: *the physics of biomolecular interfaces*. The book advocates its paramount relevance to tackle some of the core problems in molecular biophysics in a unified systematic manner. To this effect, the book introduces powerful theoretical and computational resources and is set to inspire scientists at any level in their careers determined to address the major challenges in the field.

The acknowledgment of how exquisitely the structure and dynamics of proteins and their aqueous environment are entangled attests to the overdue recognition that biomolecular phenomena cannot be effectively understood without dealing with interfacial behavior. There is an urge to grasp how biologically relevant behavior is mediated and affected by the structuring of biomolecular interfaces. This book squarely addresses this need, heralding the advent of a new discipline that the author has aptly named *epistuctural biology*. This field may be broadly described as the physicochemical study of the reciprocal influence between water and biomolecular structure across the interface. Given its scope, the book ends up covering vast intellectual territory. It has to, because the subject is highly demanding and requires a multidisciplinary approach.

With the advent of sophisticated techniques for probing and modeling biomolecular systems, it seems likely that epistuctural biology will emerge as a vigorous area of research, impacting core areas of biophysics, including protein folding, enzyme catalysis, protein associations, and drug/ligand design.

Since the days of J.W. Gibbs or perhaps earlier, physical chemists have realized that where different phases meet, unusual things are likely to happen. Even for interfaces modeled as sharp discontinuities between bulk phases—where, say, a liquid meets a solid—the mere solution of continuity generates surface-associated phenomena such as interfacial tension. The free energy cost of spanning the interface makes the latter a locus for unexpected phenomena. One wonders whether, had the pioneers of surface physics been confronted with the complexity of biological interfaces laid bare in the recent decades, they may not have turned to other projects in despair at their ungainliness.

The closer we look, the greater the complexities of biological interfaces appear to be. *Episteric* (“around the solid”) water relinquishes its bulk-like character and even fails to align with the electrostatic field due to tight geometric confinement coupled with short-range intermolecular forces. These deviations from bulk properties can enhance the chemical inhomogeneity of protein surfaces by altering the dielectric properties of interfaces in unfathomable ways. Furthermore, biological interfaces may be significantly enriched in ions relative to bulk water, an effect with profound consequences for core biophysical phenomena. Even the most basic questions such as whether episteric water is acidic or basic are still subject to contention.

Interfaces have long been recognized as central to the chemical sciences but there has been no systematic, cogent effort to understand them, let alone deal with them in a biochemical context. This book squarely addresses this need and shows that a masterful understanding of epistuctural behavior is of the essence to address the challenges that have proven unyielding to research efforts.

Recognizing that practitioners may not be familiar with biomolecular interfaces, the book first introduces the subject at a reasonably elementary level, exploring its relevance for protein interactions, protein folding, and catalytic function (Chaps. 1–7). The remaining eight chapters are devoted to molecular targeted medicine and therapeutic drug design based on the molecular understanding gained in the first seven chapters. The book first explores biomolecular interfaces from a

physicochemical standpoint, drawing basic relationships between interfacial water and the structure of soluble proteins (Chap. 1). The analysis leads to the concept of dehydron, a protein structural defect that causes interfacial tension. Chapter 2 further deals with the physicochemical underpinnings of interfacial tension, demonstrating its paramount relevance to understand protein associations. Chapter 3 deals with the steering role of the aqueous interface and interfacial tension in the protein folding process, providing the first semiempirical solution to the protein folding problem. Chapter 4 draws relations between interfacial tension and protein hydration patterns that serve as blueprints for epistructure-based drug design. Chapter 5 examines large concentrations of packing defects (dehydrons) as causative of misfolding and aberrant aggregation phenomena and explores the connection between disorder propensity, misfolding, and dehydron concentration. An exercise in this chapter deserves particular attention as it leads the reader to discovering a therapeutic disruption of a protein–protein interface based on rational design, a holy grail in the field. Chapter 6 explores biomolecular interfaces from an evolutionary perspective and highlights its relevance for the overarching goal of achieving specificity in drug design. Chapter 7 deals with the chemical functionality of biomolecular interfaces as enablers and stimulators of enzyme catalysis. This chapter contains the highest level of novelty, as it presents the striking finding that dehydrons prepare the aqueous interface for catalysis. Chapter 8 establishes a selectivity filter for drug design based on the concepts introduced in Chap. 6. Chapter 9 describes the redesign of a powerful anticancer drug guided by the selectivity filter established in Chap. 8. Chapter 10 introduces a bioinformatics analysis of biomolecular interfaces as universal markers for specificity and personalized medicine achieved through the therapeutic interference with signaling pathways. It emphasizes the usefulness of targeting biomolecular interfaces for personalized molecular treatments tailored to cope with somatic or inherited mutations that create constitutively deregulated functions. Chapter 11 deals with dynamic aspects of drug design and drug-induced folding of the protein target, focusing on dehydron induction. The dynamic concepts and their importance for molecular engineering are illustrated by the redesign of imatinib into a JNK inhibitor to treat ovarian cancer. Chapter 12 deals with drug combinations purposely synergized to edit out side effects and constructed based on the dehydron selectivity filters described in Chaps. 8–10. Chapter 13 introduces a systems biology approach to the engineering of wrapping drugs and, consequently, introduces the control of multi-target drug activity based on the selectivity filters previously introduced. Chapter 14 introduces the novel modality of immuno-synergic drugs, that is, anticancer kinase inhibitors redesigned to avoid compromising the immune response while retaining anticancer activity. Finally, Chap. 15 deals with advanced quantum mechanical treatments of biomolecular interfaces that empower the paradigm of “drugs as dehydron wrappers.” These advanced quantum treatments lead to significant improvements for drug design with the incorporation of halogens in the chemical scaffolds.

The book is primarily intended as an advanced textbook that may be adopted at the senior undergraduate level or graduate level and it also reads as a monograph for

practitioners. Fruitful reading requires a thorough background in physical chemistry and biochemistry. The selected problems at the end of the chapters and the progression in conceptual difficulty make it a suitable textbook for a graduate level course or an elective course for seniors majoring in chemistry, biophysics, biomedical engineering, or related disciplines. The material would be especially adequate for courses dealing with the Thermodynamics and Physical Chemistry of Biomolecular Systems, with Fields, Forces and Flows in Biological Systems, and with Biological Engineering Design.

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Interactions, Functions and Drug Design

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