

Preface

*Whoever cannot seek
the unforeseen sees nothing,
for the known way
is an impasse.*

Heraclitus, sixth century B.C.

The biological functionality of a soluble protein can only be fully grasped when its aqueous interface becomes an integral part of the structural analysis. Furthermore, the acknowledgment of how exquisitely the structure and dynamics of proteins and their aqueous environment are related attests to the overdue recognition that biomolecular phenomena cannot be grasped without dealing with interfacial behavior at multiple scales. This is essentially the *dictum* that guided the writing of this book.

The book focuses primarily on the biological and pharmacological role of interfacial forces determined by the embedding of protein structure in a physiological aqueous environment. By providing a suitable statistical mechanical apparatus to handle epistructural (“around the structure”) interfacial phenomenology, the book becomes uniquely positioned to address core problems in molecular biophysics. It highlights the importance of interrelated concepts like water hydrogen-bond frustration, interfacial tension and non-Debye dielectrics in delineating a solution to the protein folding problem, in unraveling the physicochemical basis of enzyme catalysis and protein associations, in delineating the molecular etiology of aberrant protein aggregation, and in rationally designing molecular-targeted therapies.

The book incrementally builds upon a statistical mechanical apparatus to deal with epistructural interfaces in a biological context. As it extends previous work in interfacial physics to the biological context, the book strives to maintain the level of rigor expected from a researcher devoted to interfacial physics, notwithstanding the daunting complexities of biomolecular systems. In the biological/biomedical context, the book introduces the necessary controls and experimental corroborations to validate the physical treatment. Furthermore, molecular dynamics and quantum

mechanics computations are used to validate the theoretical advances. Such computations fulfill the tenets of statistical physics.

Grounded in recent advances in the statistical mechanics of epistructural aqueous interfaces, the book develops a technological platform for drug design termed *epistructure-based design*, above and beyond the prevailing paradigm of structure-based drug design. The book is set to inspire scientists at any level in their careers determined to address some of the major challenges in molecular biophysics and pharmacological engineering. Thus, the book is essentially interdisciplinary and covers vast conceptual territory, from statistical physics to molecular-targeted therapy. As a measure of its intellectual latitude, Chap. 1 introduces a statistical thermodynamics framework to handle the aqueous interface of a protein, while Chap. 17 describes the epistructure-based design of kinase inhibitors with controlled multi-target activity to treat cancer metastasis and overcome drug resistance. In spite of this diversity, the conceptual progression remains smooth throughout the presentation. For this reason, the book can serve as a textbook, as originally intended, and also as an advanced monograph for practitioners in drug design or molecular-targeted therapy interested in the translational aspects of their art. Fruitful reading requires a background in physical chemistry and some notions of biophysics. 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, physics, bioengineering, or related disciplines.

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