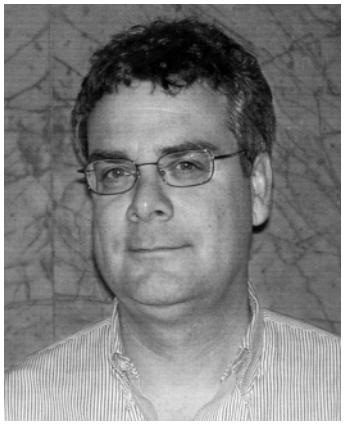
CHEMICAL REVIEWS

Volume 106, Number 5



Josh Wand was born and raised in Ottawa, Canada. He received his B.Sc. (Honors) in biochemistry from Carleton University in Ottawa. Working under the direction of Stan Tsai, he also received a M.Sc. in bioorganic chemistry from Carleton University. He received his Ph.D. in biophysics from the University of Pennsylvania under the guidance of Walter Englander. After a short postdoctoral stint in solid state NMR at the National Research Council of Canada with I. C. P. Smith, he joined the faculty of the Institute for Cancer Research. He subsequently spent time on the faculties of the University of Illinois at Urbana-Champaign and the State University of New York at Buffalo. He is currently the Benjamin Rush Professor of Biochemistry and chair of the graduate group in biochemistry and molecular biophysics at the University of Pennsylvania, where he continues to employ novel applications of solution NMR to questions in protein biophysics.

Introduction: Protein Dynamics and Folding

Without motion, there cannot be life. This is particularly true for proteins, as exemplified by the now classic work of Petsko and co-workers.[1] The tremendous conformational flexibility of the amino acids forces one to admit an incredibly large number of members to the landscape of structures available to proteins of even modest size. The nature of the landscape and how proteins move across it is the focus of this thematic issue of *Chemical Reviews*. The structural taxonomy of proteins has been intensely studied by crystallography and nuclear magnetic resonance (NMR) spectroscopy for decades. In contrast, the experimental exploration of motion across the conformational landscape of proteins is only now coming into focus with sufficient clarity to be able to guide theoretical descriptions. It is from this perspective that contributions to this issue have been assembled. To set the theoretical stage upon which experiment can be interpreted, we open with three reviews representing the major vistas of the protein conformational ensemble. The statistical thermodynamic evaluation of the protein conformational landscape is described by a concise and thoughtful review by Hilser and co-workers. This contribution illustrates a variety of mechanisms for how perturbation of the manifold states accessible to a protein can potentially influence and even guide its function. A statistical mechanical view of the protein conformational landscape is provided by Shakhnovich where he presents an analysis of the utility of various approaches to problems in protein dynamics and folding. The temporal view is represented by a comprehensive review by Adcock and McCammon of the methods of computational molecular dynamics. These three reviews set the stage for exploration of dynamics across the protein energy landscape.

We begin at the bottom of the energy landscape of proteins, near the native structure. Prabhu and Sharp present a detailed discussion of the current view of protein hydration and the structural and dynamic role of water as the "21st amino acid". Fast motion between structures not far removed

[1] Rasmussen, B. F.; Stock, A. M.; Ringe, D.; Petsko, G. A. *Nature* **1992**, *357*, 423.

10.1021/cr030460l CCC: $59.00
Published on Web 05/10/2006

from the native lowest energy state, visualized by structural methods, is probed by a variety of spectroscopic methods. This special issue attempts to take full advantage of the exceptional range of time scales that can be accessed by NMR spectroscopy. Jarymowycz and Stone review the techniques and contributions of NMR relaxation in probing the nature and functional role of sub-nanosecond motion of the polypeptide backbone. Igumenova, Frederick, and Wand provide a similar review of the analogous but somewhat less mature use of NMR relaxation techniques to probe fast motion of amino acid side chains in proteins. Palmer and Massi present a concise and insightful review of the emerging tools of relaxation in the rotating frame to access protein dynamics in the millisecond to microsecond time regime. Tolman and Ruan present a detailed description of the potential of partial alignment of proteins and the residual dipolar couplings that result to report on motion within proteins. We conclude our focus on dynamics around the native state with a review of the potential for computational methods to reveal the role of protein motion in enzymatic catalysis. Long a central question of enzymology, the illumination of the detailed dynamical contributions to enzyme catalysis is critically evaluated by Olsson, Parson, and Warshel.

The mechanism(s) underlying protein folding have fascinated biochemists and biophysicists for decades. Basic principles have emerged, and unifying views may be close at hand. Large excursions from the native state of proteins have historically been extensively probed by hydrogen exchange (HX) methods. Bai presents an authoritative summary of the use of HX in the study of protein refolding pathways. Royer summarizes the potential of fluorescence spectroscopy for characterization of protein dynamics and focuses on its use in studying the large conformational transitions associated with protein refolding. Similarly, Michalet, Weiss, and Jäger introduce the potential of emerging single-molecule fluorescence methods to illuminate local and large-scale protein motion including protein refolding. Akasaka describes the re-emergence of high pressure NMR to promote and probe both low energy and large scale structural transitions in proteins. Roder and co-workers contribute a concise review of the methods of rapid mixing and their use in meeting the tremendous experimental challenge of the early events in protein folding. Sosnick and co-workers then review the basis of an exciting recently introduced methodology for illuminating fundamental characteristics of the protein folding transition state. Kallenbach and coauthors examine the "other side" of the folding problem—the unfolded state—and explore in some detail the controversy over the existence of residual persistent structure in the unfolded ensemble. To close our focus on the mechanism of spontaneous protein refolding, Daggett presents an overview of efforts to use computational methods to describe and dissect critical features of protein folding. We then turn to the role of protein-assisted refolding of misfolded proteins. Horwich and co-workers present an authoritative review of the mechanism of protein refolding by the GroEL−GroES machine. Finally, MacKenzie presents an impressive review of what may be the final frontier in protein folding—the incorporation and folding of integral membrane proteins.

I hope that you, the reader, will find this special issue of *Chemical Reviews* a significant and useful resource. Many of the contributions are provocative, and some may even be considered controversial. All seek to poke and prod existing paradigms and suggest future paths. Though the field of protein dynamics is itself dynamical and rapidly changing, what you will find in the following pages should remain as a foundation for understanding new developments for years to come.

In organizing this thematic issue, memories from my time at Urbana-Champaign surfaced regularly. I was particularly reminded of my arrival in 1990 when a wonderful mixture of giants and then emerging giants in protein dynamics and folding were present. Hans Fraunfelder, Klaus Schulten, Peter Wolynes, and Gregorio Weber dominated the flat landscape of that small piece of central Illinois. In particular, Gregorio Weber was a significant inspiration to my own work in protein dynamics and his passing nearly a decade ago still leaves a void. This issue is dedicated to his memory.

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