

An updated guide to enzyme and protein folding mechanisms

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Structure and mechanism in protein science: A guide to enzyme catalysis and protein folding by Alan Fersht. Published by W.H. Freeman Company, 41 Madison Avenue, New York, New York 10010, USA; 1999. 614 pages, US \$67.95. ISBN 0-7167-3268-8.

Protein structure and dynamics are intimately linked with biological activity. Understanding the physical basis for this activity requires knowledge of the equilibrium and kinetic properties of the protein in solution, in various free and ligand bound states. For example, conformational changes in enzymes may be crucial for optimal function and may result from subtle movements, such as the rotation of a peptide bond; from large scale fluctuations, such as the folding of regions of a protein around a prosthetic group, or from changes in the relative orientation of domains (proteins) with respect to one another in a multidomain (multiprotein) complex. Thus, understanding the interplay between structure, dynamics and function of enzymes in solution is an important goal in modern biochemistry.

Generations of students have been introduced to this subject with the first and second editions of *Enzyme structure and mechanism* by Alan Fersht. The detailed introductory descriptions of stopped-flow, rapid quench, steady and pre-steady state kinetics included in this text have made it a classic in graduate level courses in mechanistic enzymology. Rapid advances in protein engineering and structure elucidation over the past decade in addition to the rebirth of interest in the protein folding question require a modernized text that includes strategies and analyses of protein engineering and its effects on folding and activity. In an admirable effort, Fersht has expanded his original text to include discussions on the impact of advances in protein engineer-

ing combined with efforts directed towards understanding protein folding and catalysis. The foundation of the text is grounded on solid principles encompassing chemical reactivity, kinetics and thermodynamics in the context of the three-dimensional structure of the system under investigation.

While the scope of the book is broad, the unifying reliance on simple chemical principles in discussing enzyme mechanism and protein folding makes it a coherent work from start to finish. Thus it remains an excellent text for modern graduate courses in biochemistry and biophysics. Much of the subject matter from the original work has been retained while some chapters have been extensively updated and new sections that focus on protein stability, folding pathways and energy landscapes have been added. A particularly appealing aspect of this text is the author's writing style, which is engaging and rigorous not only in discussing the key topics of interest in protein engineering today, but also in his insistence on the importance of using correct terminology when discussing important concepts in enzymology and protein chemistry.

The systems that Fersht has chosen for a detailed examination of the benefits and limitations of applying a protein engineering approach to elucidating an enzyme reaction or folding mechanism generally come from detailed studies in his own laboratory. The discussion of studies on tyrosyl-tRNA synthetase highlights the principles of overcoming very unfavorable equilibrium by the use of

binding energy in the enzyme-product complex; facilitating a reaction by lowering the transition state energy by virtue of increased favorable interactions in the enzyme-transition state species and the process of stopping unwanted side reactions during catalysis by the favorable interactions between the enzyme and highly reactive intermediates in a process known as enzyme-intermediate complementarity. The new focus on the protein folding problem, which includes a discussion on the kinetic consequences of rapid pre-equilibria and the relevance of transition state theory in light of advances in theoretical methods for the analysis of folding mechanisms, is an especially noteworthy addition to this text. While the discussions of key concepts in protein folding and stability focus mostly on barnase and chymotrypsin inhibitor 2 and are technically sound, a more inclusive overview of contributions from leaders in the field would have been appropriate. Nonetheless, his discussions on energetics of structure formation, propensity for structure in the denatured state and thermodynamics/kinetics of protein folding provide a wonderful transition for the beginning student from introductory biochemistry to a more advanced understanding of structure formation and stabilization.

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