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Preface

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PREFACE

The ability of proteins to fold rapidly and efficiently into their intricate and highly specific structures following their synthesis on ribosomes is an essential part of the conversion of genetic information into cellular activity. But in contrast to our understanding of the transcription and translation events, little is understood in detail about how this occurs. In the cell folding is now recognized to be a highly controlled process, with a cascade of proteins involved in ensuring that it occurs in the right place at the right time, and that the newly formed polypeptide chains do not fall victim to unproductive and irreversible events. Many proteins, however, are able to fold *in vitro* in the absence of all of these factors, indicating that the information necessary for folding is encoded in the amino acid sequence. This also allows folding to be investigated *in vitro*, and enables physical and chemical methods to be used to probe the structural transitions involved. The role of individual cellular factors can then be explored by examining their influence on the *in vitro* process, and by comparison with studies of the *in vivo* events themselves.

The meeting on which this volume of papers is based focused strictly on the molecular basis of the folding processes, and brought together a wide range of experimental and theoretical scientists who are leaders in this field. The first group of papers is concerned with the experimental elucidation of the pathways of protein folding. In the opening paper, Creighton discusses the value of studying disulphide-coupled folding pathways, illustrating this particularly with studies of BPTI, a protein with one of the best characterized folding pathways. In the next two papers, Fersht discusses experimental strategies for mapping the structures of transition states and intermediates in folding using protein engineering methods, and Radford and Dobson describe the use of physical techniques, particularly nuclear magnetic resonance spectroscopy, to characterize the structures of species formed during the folding of proteins. The use of spectroscopic methods is discussed further in the paper by Shortle and colleagues who describe approaches to defining folding pathways by studying time averaged structures of denatured proteins under equilibrium conditions. The description of folding intermediates in terms of their thermodynamic as well as structural properties is one of the subjects of the paper by Ptitsyn *et al*., who discusses the concept of the 'molten globule' state which has had a marked influence on the development of ideas as to how folding takes place. This topic is extended in the paper by Kim and colleagues, in which studies of the structure of one of the classic molten globules, that of α-lactalbumin, by 'protein dissection methods' are described.

The next group of papers is concerned with theoretical approaches to the folding problem, including those which link an understanding of protein folding with the prediction of three-dimensional structures from sequence information and the design of new proteins. Van Gunsteren *et al*. describe the methods of molecular dynamics to probe the unfolding of a variety of proteins in computer simulations, and compare the results of these with experimental findings. Dill and coworkers use lattice models to examine the manner in which the tertiary structure of a protein is encoded in its sequence, and to explore the nature and significance of cooperativity in protein folding. Thornton *et al*. provide a rather different perspective on the folding problem by asking how inspection of the database of protein structures can provide clues as to the interactions that stabilize the final folded states of proteins and how this might provide insight into the folding pathways by which these are attained. Finally in this section, De Grado and colleagues describe synthetic approaches to understanding the structural basis for the interaction of helices in coiled coils, and discuss *de novo* design of proteins based on the rules and concepts believed to be important for protein folding and stability.

The final group of papers address the issue of how proteins fold *in vivo*, and how this relates to the situation found during *in vitro* folding. Goldberg and colleagues address the complex issue of the structural properties of nascent polypeptide chains during synthesis on ribosomes, using a strategy based on the use of conformation dependent monoclonal antibodies. The thorny question of misfolding and aggregation, which can compete with proper folding and association of proteins is addressed by Jaenicke, who also touches on the role of molecular chaperones in preventing and controlling such interactions. This aspect of folding is pursued in detail by Hartl, who describes the hierarchical action of chaperone complexes by which newly formed polypeptide chains are passed from one class of helper proteins to another. The last paper in the volume, by Sigler and Horowitz, describes the crystal structure of one of the most studied of molecular chaperones, GroEL from *E. coli*, and discusses the extent to which this has allowed insights to be gained into its mechanism of action. This paper emphasizes particularly clearly that the description of folding at a molecular level, the theme of the meeting, is no longer the preserve of *in vitro* folders alone.

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