Preface

The primary structure of a protein containing sequence of amino acids has the blueprint for the complete stable and functional tertiary structure. However, there is a huge gap in our knowledge of how we move from protein sequence to function in living organisms. Lots of efforts are being made to predict three-dimensional structure of the protein from its primary structure. It is strongly believed that deep understanding of protein folding would be the way to solve the problem. Further, it would also help to understand diverse cellular processes; *viz*. transfer of information by the ligand through specific receptor toward cell's interior, generation of antibodies against specific antigens, etc. as well as giving solution to the problem of protein misfolding leading to number of diseases. The present book focuses on major challenges in protein folding, approaches made, and it's till date research updates. This will help in improved understanding of the route that a protein takes from its synthesis to the correct folded form.

Chapter 1: The principle guiding protein to fold into its native conformation has been searched by biochemists, structural biologists, molecular biologists and recently by bioinformaticians. The problem is not new but it is being worked for approximately 100 years. There are various challenges, most importantly short-lived folding intermediates and formation of inter-residual interactions including disulfide linkages. Various experimental and theoretical models are being generated to decipher the pathways and principles of protein folding but none have the complete solution to the problem. The present chapter is the compilation of important research contributions in the arena of protein folding made till date.

Chapter 2: The protein is functionally active in its three-dimensional native state. Almost all cells' machinery is based on the involvement of number of proteins. Native state of the protein is the most active and stable state with a specific conformation determined by polypeptide backbone and intermolecular interactions. Efficient protein folding is the prerequisite of proper functioning of cell machinery which depends on coordinated functioning of chaperones, chaperonins, and various auxiliary cofactors. The failure of a specific protein to adopt its native and active state is called "protein misfolding". Protein misfolding has wide range of pathological implications due to loss of normal cellular functions. The present chapter is based on the criteria determining proper protein folding based on their structural and kinetics studies.

Chapter 3: Protein folding has now been accepted to be a self assembly process with favorable environmental parameters. Native state of the protein has lowest free energy due to various interactions (ionic, covalent, and hydrogen bonds and hydrophobic interactions). From last decades, researchers are trying to predict *de novo* three-dimensional structure of a protein from its amino acid sequence using parameters of folding energetics. Further, efforts are also being made to understand protein–protein and protein–ligand interactions based on folding energetics studies. However, it is not clear which is the most crucial interaction leading to major free energy change and responsible for changing from unfolded to folded states. The present chapter has discussed various factors involved in protein folding and their contribution toward folding energetics.

Chapter 4: Energy landscape theory and funnel concept have been recently introduced in finding solution of protein folding. They are being used to design various motifs present in the protein using their primary structure, prediction of order of native contact formation during folding, etc. Here protein folding is not characterized by single pathway but enormously large number of equivalent folding pathways reaching to the point of native state with single conformation of the backbone. The present chapter is based on understanding energy landscape and its significance toward prediction of three-dimensional structure of the real protein based on various topological parameters and native inter-residual contacts.

I have been introduced with the problem of protein folding by two academicians: Prof Arvind M. Kayastha (School of Biotechnology, Banaras Hindu University) and Prof. M. V. Jagannadham (Molecular Biology Unit, Banaras Hindu University). Their guidance and unflinching encouragement have generated keen interest in me to thoroughly understand the problem. I was so fascinated with the problem that I am still stuck to it and expecting to give some solution to it. Prof. Dinakar M. Salunke (Structural Biology Unit, UNESCO-Regional Centre for Biotechnology) has introduced me with all the recent tools and techniques used to find suitable solution to the problem. His involvement with his originality has triggered and nourished my intellectual maturity in the field. Further, I would like to thank my parents and hubby (Dr Yogesh K. Sharma) for their emotional and motivational support in writing this book. I have tried my best to make this book; simple and easier so that it can be approached by all the classes (students, academicians, and researchers) to understand the problem and creating enthusiasm towards finding suitable solutions.

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