INTRODUCTION TO PROTEIN STRUCTURE PREDICTION

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INTRODUCTION TO PROTEIN STRUCTURE PREDICTION

Methods and Algorithms

Edited by

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PREFACE

PROTEIN STRUCTURE PREDICTION

Proteins play a crucial role in governing several life processes. Stunningly complex networks of proteins perform innumerable functions in every living cell. Knowing the function and structure of proteins is crucial for the development of better drugs, higher yield crops, and even synthetic biofuels. As such, knowledge of protein structure and function leads to crucial advances in life sciences and biology. The motivation behind the structural determination of proteins is based on the belief that structural information provides insights as to their function, which will ultimately result in a better understanding of intricate biological processes.

Breakthroughs in large-scale sequencing have led to a surge in the available protein sequence information that has far outstripped our ability to characterize the structural and functional characteristic of these proteins. Several research groups have been working on determining the three-dimensional structure of the protein using a wide variety of computational methods. The problem of unraveling the relationship between the amino acid sequence of a protein and its three-dimensional structure has been one of the grand challenges in molecular biology. The importance and the far reaching implications of being able to predict the structure of a protein from its amino acid sequence is manifested by the ongoing biennial competition on "Critical Assessment of Protein Structure Prediction" (CASP) that started more than 16 years ago. CASP is designed to assess the performance of current structure prediction methods and over the years the number of groups that have been participating in it continues to increase.

This book presents a series of chapters by authors who are involved in the task of structure determination and using modeled structures for applications involving drug discovery and protein design. The book is divided into the following themes.

BACKGROUND ON STRUCTURE PREDICTION

Chapter 1 provides an introduction to the protein structure prediction problem along with information about databases and resources that are widely used. Chapters 2 and 3 provide information regarding two very important initiatives in the field: (i) the structure prediction flagship competition (CASP), and (ii) the protein structure initiative (PSI), respectively. Since many of the approaches developed have been tested in the CASP competition, Chapter 2 lays the foundation for the need for such an evaluation, the problem definitions, significant innovations, competition format, as well as future outlook. Chapter 3 describes the protein structure initiative, which is designed to determine representative three-dimensional structures within the human genome.

PREDICTION OF STRUCTURAL ELEMENTS

Within each structural entity called a protein there lies a set of recurring substructures, and within these substructures are smaller substructures. Beyond the goal of predicting the three-dimensional structure of a protein from sequence several other problems have been defined and methods have been developed for solving the same. Chapters 4–6 provide the definitions of these recurring substructures called local alphabets or secondary structures and the computational approaches used for solving these problems. Chapter 6 specifically focuses on a class of transmembrane proteins known to be harder to crystallize. Knowing the pairs of residues within a protein that are within contact or at a closer distance provides useful distance constraints that can be used while modeling the three-dimensional structure of the protein. Chapter 7 focuses on the problem of contact map prediction and also shows the use of sophisticated machine learning methods to solve the problem. A successful solution for each of these subproblems assists in solving the overarching protein structure prediction problem.

TERTIARY STRUCTURE PREDICTION

Chapters 8–11 discuss the widely used structure prediction methods that rely on homology modeling, threading, and fragment assembly. Chapters 8–9 discuss the problems of fold recognition and remote homology detection that attempt to model the three-dimensional structure of a protein using known structures. Chapters 10 and 11 discuss a combination of threading-based approaches along with modeling the protein in parts or fragments and usually helps in modeling the structure of proteins known not to have a close homolog within the structure databases. Chapter 12 is a survey of the hybrid methods that use a combination of the computational and experimental methods to achieve high-resolution protein structures in a high-throughput manner.

Chapter 17 provides information about the challenges in modeling transmembrane proteins along with a discussion of some of the widely used methods for these sets of proteins.

Chapter 13 describes the loop prediction problem and how the technique can be used for refinement of the modeled structures. Chapters 14 and 15 assess the modeled structures and provide a notion of the quality of structures. This is extremely important from a biologist's perspective who would like to have a metric that describes the goodness of the structure before use. Chapter 19 provides insights into the different conformations that a protein may take and the approaches used to sample the different conformations.

FUNCTIONAL INSIGHTS

Certain parts of the protein structure may be conserved and interact with other biomolecules (e.g., proteins, DNA, RNA, and small molecules) and perform a particular function due to such interactions. Chapter 16 discusses the problem of ligand-binding site prediction and its role in determining the function of the proteins. The approach uses some of the homology modeling principles used for modeling the entire structure. Chapter 18 introduces a computational model that detects the differences between protein structure (modeled or experimentally-determined) and its modeled mutant. Chapter 20 describes the use of molecular dynamic-based approaches for modeling mutants.

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We hope that you as a reader benefit from this book and feel as excited about this field as we are.

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