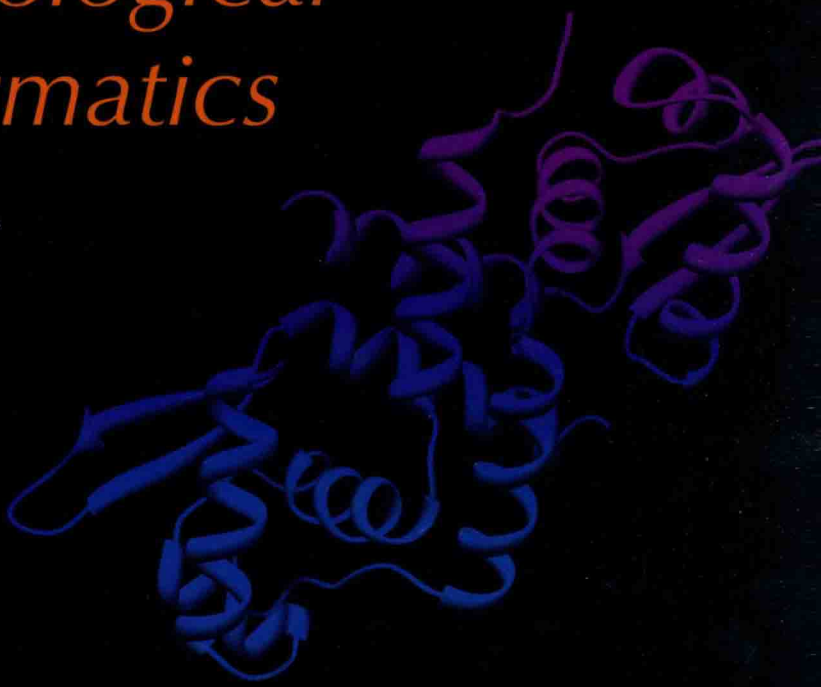
WILEY SERIES ON BIOINFORMATICS
Yi Pan and Albert Y. Zomaya, Series Editors

Computational Intelligence and Pattern Analysis *in Biological Informatics*



Ujjwal Maulik
Sanghamitra Bandyopadhyay
Jason T. L. Wang

WILEY

COMPUTATIONAL INTELLIGENCE AND PATTERN ANALYSIS IN BIOLOGICAL INFORMATICS

Edited by

UJJWAL MAULIK
Department of Computer Science and Engineering, Jadavpur University, Kolkata, India

SANGHAMITRA BANDYOPADHYAY
Machine Intelligence Unit, Indian Statistical Institute, Kolkata, India

JASON T. L. WANG
Department of Computer Science, New Jersey Institute of Technology, Newark, New Jersey

WILEY
A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey.
Published simultaneously in Canada.

ISBN 978-0-470-58159-9

Library of Congress Cataloging-in-Publication Data is available.

Printed in Singapore

10 9 8 7 6 5 4 3 2 1

COMPUTATIONAL INTELLIGENCE AND PATTERN ANALYSIS IN BIOLOGICAL INFORMATICS

Wiley Series on

Bioinformatics: Computational Techniques and Engineering

A complete list of the titles in this series appears at the end of this volume.

To Utsav, our students and parents
—U. Maulik and
S. Bandyopadhyay

To my wife Lynn and
daughter Tiffany
—J. T. L. Wang

PREFACE

Computational biology is an interdisciplinary field devoted to the interpretation and analysis of biological data using computational techniques. It is an area of active research involving biology, computer science, statistics, and mathematics to analyze biological sequence data, genome content and arrangement, and to predict the function and structure of macromolecules. This field is a constantly emerging one, with new techniques and results being reported every day. Advancement of data collection techniques is also throwing up novel challenges for the algorithm designers to analyze the complex and voluminous data. It has already been established that traditional computing methods are limited in their scope for application to such complex, large, multidimensional, and inherently noisy data. Computational intelligence techniques, which combine elements of learning, adaptation, evolution, and logic, are found to be particularly well suited to many of the problems arising in biology as they have flexible information processing capabilities for handling huge volume of real-life data with noise, ambiguity, missing values, and so on. Solving problems in biological informatics often involves search for some useful regularities or patterns in large amounts of data that are typically characterized by high dimensionality and low sample size. This necessitates the development of advanced pattern analysis approaches since the traditional methods often become intractable in such situations.

In this book, we attempt to bring together research articles by active practitioners reporting recent advances in integrating computational intelligence and pattern analysis techniques, either individually or in a hybridized manner, for analyzing biological data in order to extract more and more meaningful information and insights from them. Biological data to be considered for analysis include sequence, structure, and microarray data. These data types are typically complex in nature, and require advanced methods to deal with them. Characteristics of the methods and algorithms

reported here include the use of domain-specific knowledge for reducing the search space, dealing with uncertainty, partial truth and imprecision, efficient linear and/or sublinear scalability, incremental approaches to knowledge discovery, and increased level and intelligence of interactivity with human experts and decision makers. The techniques can be sequential or parallel in nature.

Computational Intelligence (CI) is a successor of artificial intelligence that combines elements of learning, adaptation, evolution, and logic to create programs that are, in some sense, intelligent. Computational intelligence exhibits an ability to learn and/or to deal with new situations, such that the system is perceived to possess one or more attributes of reason, (e.g., generalization, discovery, association, and abstraction). The different methodologies in CI work synergistically and provide, in one form or another, flexible information processing capabilities. Many biological data are characterized by high dimensionality and low sample size. This poses grand challenges to the traditional pattern analysis techniques necessitating the development of sophisticated approaches.

This book has five parts. The first part contains chapters introducing the basic principles and methodologies of computational intelligence techniques along with a description of some of its important components, fundamental concepts in pattern analysis, and different issues in biological informatics, including a description of biological data and their sources. Detailed descriptions of the different applications of computational intelligence and pattern analysis techniques to biological informatics constitutes the remaining chapters of the book. These include tasks related to the analysis of sequences in the second part, structures in the third part, and microarray data in part four. Some topics in systems biology form the concluding part of this book.

In Chapter 1, Das et al. present a lucid overview of computational intelligence techniques. They introduce the fundamental aspects of the key components of modern computational intelligence. A comprehensive overview of the different tools of computational intelligence (e.g., fuzzy logic, neural network, genetic algorithm, belief network, chaos theory, computational learning theory, and artificial life) is presented. It is well known that the synergistic behavior of the above tools often far exceeds their individual performance. A description of the synergistic behaviors of neuro-fuzzy, neuro-GA, neuro-belief, and fuzzy-belief network models is also included in this chapter. It concludes with a detailed discussion on some emerging trends in computational intelligence like swarm intelligence, Type-2 fuzzy sets, rough sets, granular computing, artificial immune systems, differential evolution, bacterial foraging optimization algorithms, and the algorithms based on artificial bees foraging behavior.

Chakraborty provides an overview of the basic concepts and the fundamental techniques of pattern analysis with an emphasis on statistical methods in Chapter 2. Different approaches for designing a pattern recognition system are described. The pattern recognition tasks of feature selection, classification, and clustering are discussed in detail. The most popular statistical tools are explained. Recent approaches based on the soft computing paradigm are also introduced in this chapter, with a brief representation of the promising neural network classifiers as a new direction toward dealing with imprecise and uncertain patterns generated in newer fields.

In Chapter 3, Byron et al. deal with different aspects of biological informatics. In particular, the biological data types and their sources are mentioned, and two software tools used for analyzing the genomic data are discussed. A case study in biological informatics, focusing on locating noncoding RNAs in Drosophila genomes, is presented. The authors show how the widely used Infernal and RSmatch tools can be combined to mine roX1 genes in 12 species of Drosophila for which the entire genomic sequencing data is available.

The second part of the book, Chapters 4 and 5, deals with the applications of computational intelligence and pattern analysis techniques for biological sequence analysis. In Chapter 4, Rani et al. extract features from the genomic sequences in order to predict promoter regions. Their work is based on global signal-based methods using a neural network classifier. For this purpose, they consider two global features: n-gram features and features based on signal processing techniques by mapping the sequence into a signal. It is shown that the n-gram features extracted for $n = 2, 3, 4,$ and 5 efficiently discriminate promoters from nonpromoters.

In Chapter 5, Masulli et al. deal with the task of computational prediction of microRNA (miRNA) targets with focus on miRNAs' influence in prostate cancer. The miRNAs are capable of base-pairing with imperfect complementarity to the transcripts of animal protein-coding genes (also termed targets) generally within the 3' untranslated region (3' UTR). The existing target prediction programs typically rely on a combination of specific base-pairing rules in the miRNA and target mRNA sequences, and conservational analysis to score possible 3' UTR recognition sites and enumerate putative gene targets. These methods often produce a large number of false positive predictions. In this chapter, Masulli et al. improve the performance of an existing tool called miRanda by exploiting the updated information on biologically validated miRNA gene targets related to human prostate cancer only, and performing automatic parameter tuning using genetic algorithm.

Chapters 6–10 constitute the third part of the book dealing with structural analysis. Chapter 6 deals with the structural search in RNA motif databases. An RNA structural motif is a substructure of an RNA molecule that has a significant biological function. In this chapter, Wen and Wang present two recently developed structural search engines. These are useful to scientists and researchers who are interested in RNA secondary structure motifs. The first search engine is installed on a database, called RmotifDB, which contains secondary structures of the noncoding RNA sequences in Rfam. The second search engine is installed on a block database, which contains the 603 seed alignments, also called blocks, in Rfam. This search engine employs a novel tool, called BlockMatch, for comparing multiple sequence alignments. Some experimental results are reported to demonstrate the effectiveness of the BlockMatch tool.

In Chapter 7, Bhattacharya et al. explore the construction of neighborhood-based kernels on protein structures. Two types of neighborhoods, and two broad classes of kernels, namely, sequence and structure based, are defined. Ways of combining these kernels to get kernels on neighborhoods are discussed. Detailed experimental results are reported showing that some of the designed kernels perform competitively with the state of the art structure comparison algorithms, on the difficult task of classifying 40% sequence nonredundant proteins into SCOP superfamilies.

The use of protein blocks to characterize structural variations in enzymes is discussed in Chapter 8 using kinases as the case study. A protein block is a set of 16 local structural descriptors that has been derived using unsupervised machine learning algorithms and that can approximate the three-dimensional space of proteins. In this chapter, Agarwal et al. first apply their approach in distinguishing between conformation changes and rigid-body displacements between the structures of active and inactive forms of a kinase. Second, a comparison of the conformational patterns of active forms of a kinase with the active and inactive forms of a closely related kinase has been performed. Finally, structural differences in the active states of homologous kinases have been studied. Such studies might help in understanding the structural differences among these enzymes at a different level, as well as guide in making drug targets for a specific kinase.

In Chapter 9, Smalter and Huan address the problem of graph classification through the study of kernel functions and the application of graph classification in chemical quantitative structure–activity relationship (QSAR) study. Graphs, especially the connectivity maps, have been used for modeling chemical structures for decades. In connectivity maps, nodes represent atoms and edges represent chemical bonds between atoms. Support vector machines (SVMs) that have gained popularity in drug design and cheminformatics are used in this regard. Some graph kernel functions are explored that improve on existing methods with respect to both classification accuracy and kernel computation time. Experimental results are reported on five different biological activity data sets, in terms of the classifier prediction accuracy of the support vector machine for different feature generation methods.

Computational ligand design is one of the promising recent approaches to address the problem of drug discovery. It aims to search the chemical space to find suitable drug molecules. In Chapter 10, genetic algorithms have been applied for this combinatorial problem of ligand design. The chapter proposes a variable length genetic algorithm for *de novo* ligand design. It finds the active site of the target protein from the input protein structure and computes the bond stretching, angle bending, angle rotation, van der Waals, and electrostatic energy components using the distance dependent dielectric constant for assigning the fitness score for every individual. It uses a library of 41 fragments for constructing ligands. Ligands have been designed for two different protein targets, namely, Thrombin and HIV-1 Protease. The ligands obtained, using the proposed algorithm, were found to be similar to the real known inhibitors of these proteins. The docking energies using the proposed methodology designed were found to be lower compared to three existing approaches.

Chapters 11–13 constitute the fourth part of the book dealing with microarray data analysis. In Chapter 11, Saha and Maulik develop a differential evolution-based fuzzy clustering algorithm (DEFC) and apply it on four publicly available benchmark microarray data sets, namely, yeast sporulation, yeast cell cycle, Arabidopsis Thaliana, and human fibroblasts serum. Detailed comparative results demonstrating the superiority of the proposed approach are provided. In a part of the investigation, an interesting study integrating the proposed clustering approach with an SVM classifier has been conducted. A fraction of the data points is selected from different clusters based on their proximity to the respective centers. This is used for training an SVM.

The clustering assignments of the remaining points are thereafter determined using the trained classifier. Finally, a biological significance test has been carried out on yeast sporulation microarray data to establish that the developed integrated technique produces functionally enriched clusters.

The classification capability of SVMs is again used in Chapter 12 for identifying potential gene markers that can distinguish between malignant and benign samples in different types of cancers. The proposed scheme consists of two phases. In the first, an ensemble of SVMs using different kernel functions is used for efficient classification. Thereafter, the signal-to-noise ratio statistic is used to select a number of gene markers, which is further reduced by using a multiobjective genetic algorithm-based feature selection method. Results are demonstrated on three publicly available data sets.

In Chapter 13, Maulik and Sarker develop a parallel algorithm for clustering gene expression data that exploits the property of symmetry of the clusters. It is based on a recently developed symmetry-based distance measure. The bottleneck for the application of such an approach for microarray data analysis is the large computational time. Consequently, Maulik and Sarker develop a parallel implementation of the symmetry-based clustering algorithm. Results are demonstrated for one artificial and four benchmark microarray data sets.

The last part of the book, dealing with topics related to systems biology, consists of Chapters 14–16. Jeong and Chen deal with the problem of gene prioritization in Chapter 14, which aims at achieving a better understanding of the disease process and to find therapy targets and diagnostic biomarkers. Gene prioritization is a new approach for extending our knowledge about diseases and potentially about other biological conditions. Jeong and Chen review the existing methods of gene prioritization and attempt to identify those that were most successful. They also discuss the remaining challenges and open problems in this area.

In Chapter 15, Bagchi discusses the various aspects of protein–protein interactions (PPI) that are one of the central players in many vital biochemical processes. Emphasis has been given to the properties of the PPI. A few basic definitions have been revisited. Several computational PPI prediction methods have been reviewed. The various software tools involved have also been reviewed.

Finally, in Chapter 16, Bhattacharyya and Bandyopadhyay study PPI networks in order to investigate the system level activities of the genotypes. Several topological properties and structures have been discussed and state-of-the-art knowledge on utilizing these characteristics in a system level study is included. A novel method of mining an integrated network, obtained by combining two types of topological properties, is designed to find dense subnetworks of proteins that are functionally coherent. Some theoretical analysis on the formation of dense subnetworks in a scale-free network is also provided. The results on PPI information of *Homo Sapiens*, obtained from the Human Protein Reference Database, show promise with such an integrative approach of topological analysis.

The field of biological informatics is rapidly evolving with the availability of new methods of data collection that are not only capable of collecting huge amounts of data, but also produce new data types. In response, advanced methods of searching for

useful regularities or patterns in these data sets have been developed. Computational intelligence, comprising a wide array of classification, optimization, and representation methods, have found particular favor among the researchers in biological informatics. The chapters dealing with the applications of computational intelligence and pattern analysis techniques in biological informatics provide a representative view of the available methods and their evaluation in real domains. The volume will be useful to graduate students and researchers in computer science, bioinformatics, computational and molecular biology, biochemistry, systems science, and information technology both as a text and reference book for some parts of the curriculum. The researchers and practitioners in industry, including pharmaceutical companies, and R & D laboratories will also benefit from this book.

We take this opportunity to thank all the authors for contributing chapters related to their current research work that provide the state of the art in advanced computational intelligence and pattern analysis methods in biological informatics. Thanks are due to Indrajit Saha and Malay Bhattacharyya who provided technical support in preparing this volume, as well as to our students who have provided us the necessary academic stimulus to go on. Our special thanks goes to Anirban Mukhopadhyay for his contribution to the book and Christy Michael from Aptara Inc. for her constant help. We are also grateful to Michael Christian of John Wiley & Sons for his constant support.

U. MAULIK, S. BANDYOPADHYAY, AND J. T. L. WANG

November, 2009

CONTRIBUTORS

Ajith Abraham, Machine Intelligence Research Labs (MIR Labs), Scientific Network for Innovation and Research Excellence, Auburn, Washington

G. Agarwal, Molecular Biophysics Unit, Indian Institute of Science, Bangalore, India

Angshuman Bagchi, Buck Institute for Age Research, 8001 Redwood Blvd., Novato, California

Sanghamitra Bandyopadhyay, Machine Intelligence Unit, Indian Statistical Institute, Kolkata, India

Chiranjib Bhattacharyya, Department of Computer Science and Automation, Indian Institute of Science, Bangalore, India

Malay Bhattacharyya, Machine Intelligence Unit, Indian Statistical Institute, Kolkata, India

Sourangshu Bhattacharya, Department of Computer Science and Automation, Indian Institute of Science Bangalore, India

S. Durga Bhavani, Department of Computer and Information Sciences, University of Hyderabad, Hyderabad, India

Kevin Byron, Department of Computer Science, New Jersey Institute of Technology, Newark, New Jersey

Miguel Cervantes-Cervantes, Department of Biological Sciences, Rutgers University, Newark, New Jersey

Basabi Chakraborty, Department of Software and Information Science, Iwate Prefectural University, Iwate, Japan

Nagasuma R. Chandra, Bioinformatics Center, Indian Institute of Science, Bangalore, India

Jake Y. Chen, School of Informatics, Indiana University-Purdue University, Indianapolis, Indiana

Swagatam Das, Department of Electronics and Telecommunication, Jadavpur University, Kolkata, India

Alexandre G. de Brevern, Université Paris Diderot-Paris, Institut National de Transfusion Sanguine (INTS), Paris, France

D. C. Dinesh, Molecular Biophysics Unit, Indian Institute of Science, Bangalore, India

Jun Huan, Department of Electrical Engineering and Computer Science, University of Kansas, Lawrence, Kansas

Jieun Jeong, School of Informatics, Indiana University-Purdue University, Indianapolis, Indiana

Francesco Masulli, Department of Computer and Information Sciences, University of Genova, Italy

Ujjwal Maulik, Depatment of Computer Science and Engineering, Jadavpur University, Kolkata, India

Anirban Mukhopadhyay, Department of Theoretical Bioinformatics, German Cancer Research Center, Heidelberg, Germany, on leave from Department of Computer Science and Engineering, University of Kalyani, India

B. K. Panigrahi, Department of Electrical Engineering, Indian Institute of Technology (IIT), Delhi, India

S. Bapi Raju, Department of Computer and Information Sciences, University of Hyderabad, Hyderabad, India

T. Sobha Rani, Department of Computer and Information Sciences, University of Hyderabad, Hyderabad, India

Stefano Rovetta, Department of Computer and Information Sciences, University of Genova, Italy

Giuseppe Russo, Sbarro Institute for Cancer Research and Molecular Medicine, Temple University, Philadelphia, Pennsylvania

Indrajit Saha, Interdisciplinary Centre for Mathematical and Computational Modeling, University of Warsaw, Poland

Anasua Sarkar, LaBRI, University Bordeaux 1, France

Soumi Sengupta, Machine Intelligence Unit, Indian Statistical Institute, Kolkata, India

Aaron Smalter, Department of Electrical Engineering and Computer Science, University of Kansas, Lawrence, Kansas

N. Srinivasan, Molecular Biophysics Unit, Indian Institute of Science, Bangalore, India

Jason T. L. Wang, Department of Computer Science, New Jersey Institute of Technology, Newark, New Jersey

Dongrong Wen, Department of Computer Science, New Jersey Institute of Technology, Newark, New Jersey

CONTENTS