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BCL3 19q13.1 B-cell lymphoma
CBLC 19q13.2 Ectopic CAS
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PVRL2 19q13.2 poliovirus receptor
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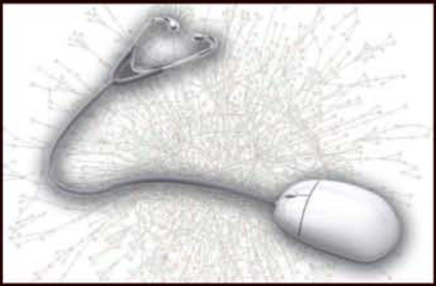

Edited by
Jake Y. Chen
Stefano Lonardi

CRC Press
Taylor & Francis Group
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Biological Data Mining

Chapman & Hall/CRC
Data Mining and Knowledge Discovery Series

SERIES EDITOR

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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business
A CHAPMAN & HALL BOOK

Chapman & Hall/CRC
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number: 978-1-4200-8684-3 (Hardback)

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Library of Congress Cataloging-in-Publication Data

Biological data mining / editors, Jake Y. Chen, Stefano Lonardi.
p. cm. -- (Data mining and knowledge discovery series)
Includes bibliographical references and index.
ISBN 978-1-4200-8684-3 (hardcover : alk. paper)
1. Bioinformatics. 2. Data mining. 3. Computational biology. I. Chen, Jake. II. Lonardi, Stefano. III. Title. IV. Series.

QH324.2.B578 2010
570.285--dc22 2009028067

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Preface

Modern biology has become an information science. Since the invention of a DNA sequencing method by Sanger in the late seventies, public repositories of genomic sequences have been growing exponentially, doubling in size every 16 months—a rate often compared to the growth of semiconductor transistor densities in CPUs known as Moore's Law. In the nineties, the public–private race to sequence the human genome further intensified the fervor to generate high-throughput biomolecular data from highly parallel and miniaturized instruments. Today, sequencing data from thousands of genomes, including plants, mammals, and microbial genomes, are accumulating at an unprecedented rate. The advent of second-generation DNA sequencing instruments, high-density cDNA microarrays, tandem mass spectrometers, and high-power NMRs have fueled the growth of molecular biology into a wide spectrum of disciplines such as personalized genomics, functional genomics, proteomics, metabolomics, and structural genomics. Few experiments in molecular biology and genetics performed today can afford to ignore the vast amount of biological information publicly accessible. Suddenly, molecular biology and genetics have become data rich.

Biological data mining is a *data-guzzling turbo engine* for postgenomic biology, driving the competitive race toward unprecedented biological discovery opportunities in the twenty-first century. Classical bioinformatics emerged from the study of macromolecules in molecular biology, biochemistry, and biophysics. Analysis, comparison, and classification of DNA and protein sequences were the dominant themes of bioinformatics in the early nineties. Machine learning mainly focused on predicting genes and proteins functions from their sequences and structures. The understanding of cellular functions and processes underlying complex diseases were out of reach. Bioinformatics scientists were a rare breed, and their contribution to molecular biology and genetics was considered marginal, because the computational tools available then for biomolecular data analysis were far more primitive than the array of experimental techniques and assays that were available to life scientists. Today, we are now witnessing the reversal of these past trends. Diverse sets of data types that cover a broad spectrum of genotypes and phenotypes, particularly those related to human health and diseases, have become available. Many interdisciplinary researchers, including applied computer scientists, applied mathematicians, biostatisticians, biomedical researchers, clinical scientists, and biopharmaceutical professionals, have discovered in biology a *gold* *mine* of knowledge leading to many exciting possibilities: the unraveling of the tree of life, harnessing the power of microbial organisms for renewable energy, finding new ways to diagnose disease early, and developing new therapeutic compounds that save lives. Much of the experimental high-throughput biology data are generated and analyzed "in haste," therefore leaving plenty of opportunities for knowledge discovery even after the original data are released. Most of the bets on the race to *separate the wheat from the chaff* have been placed on biological data mining techniques. After all, when easy, straightforward, first-pass data analysis has not yielded novel biological insights, data mining techniques must be able to help—or, many presumed so.

In reality, biological data mining is still much of an "art," successfully practiced by a few bioinformatics research groups that occupy themselves with solving real-world biological problems. Unlikely data mining in business, where the major concerns are often related to the bottom line—profit—the goals of biological data mining can be as diverse as the spectrum of biological questions that exist. In the business domain, association rules discovered between sales items are immediately actionable; in biology, any unorthodox hypothesis produced by computational models has to be first red-flagged and is lucky to be validated experimentally. In the Internet business domain, classification, clustering, and visualization of blogs, network traffic patterns, and news feeds add significant values to regular Internet users who are unaware of high-level patterns that may exist in the data set; in molecular biology and genetics, any clustering or classification of the data presented to biologists may promptly elicit questions like "great, but how and why did it happen?" or "how can you explain these results in the context of the biology I know?" The majority of general-purpose data mining techniques do not take into consideration the prior knowledge domain of the biological problem, leading them to often underperform hypothesis-driven biological investigative techniques. The high level of variability of measurements inherent in many types of biological experiments or samples, the general unavailability of experimental replicates, the large number of hidden variables in the data, and the high correlation of biomolecular expression measurements also constitute significant challenges in the application of classical data mining methods in biology. Many biological data mining projects are attempted and then abandoned, even by experienced data mining scientists. In the extreme cases, large-scale biological data mining efforts are jokingly labeled as *fishing expeditions* and dispelled, in national grant proposal review panels.

This book represents a culmination of our past research efforts in biological data mining. Throughout this book, we wanted to showcase a small, but noteworthy sample of successful projects involving data mining and molecular biology. Each chapter of the book is authored by a distinguished team of bioinformatics scientists whom we invited to offer the readers the widest possible range of application domains. To ensure high-quality standards, each contributed chapter went through standard peer reviews and a round of revisions. The contributed chapters have been grouped into five major sections.

The first section, entitled *Sequence, Structure, and Function*, collects contributions on data mining techniques designed to analyze biological sequences and structures with the objective of discovering novel functional knowledge. The second section, on *Genomics, Transcriptomics, and Proteomics*, contains studies addressing emerging large-scale data mining challenges in analyzing high-throughput "omics" data. The chapters in the third section, entitled *Functional and Molecular Interaction Networks*, address emerging system-scale molecular properties and their relevance to cellular functions. The fourth section is about *Literature, Ontology, and Knowledge Integrations*, and it collects chapters related to knowledge representation, information retrieval, and data integration for structured and unstructured biological data. The contributed works in the fifth and last section, entitled *Genome Medicine Applications*, address emerging biological data mining applications in medicine.

We believe this book can serve as a valuable guide to the field for graduate students, researchers, and practitioners. We hope that the wide range of topics covered will allow readers to appreciate the extent of the impact of data mining in molecular biology and genetics. For us, research in data mining and its applications to biology and genetics is fascinating and rewarding. It may even help to save human lives one day. This field offers great opportunities and rewards if one is prepared to learn molecular biology and genetics, design user-friendly software tools under the proper biological assumptions, and validate all discovered hypotheses rigorously using appropriate models.

In closing, we would like to thank all the authors that contributed a chapter in the book. We are also indebted to Randi Cohen, our outstanding publishing editor. Randi efficiently managed timelines and deadlines, gracefully handled the communication with the authors and the reviewers, and took care of every little detail associated with this project. This book could not have been possible without her. Our thanks also go to our families for their support throughout the book project.

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Dr. Chen received PhD and MS degrees in computer science from the University of Minnesota at Twin Cities and a BS in molecular biology and biochemistry from Peking University in China. He has extensive industrial research and management experience (1998–2003), including developing commercial GeneChip microarrays at Affymetrix, Inc. and mapping the first human protein interactome at Myriad Proteomics. After rejoining academia in 2004, he concentrated his research on "translational bioinformatics," studies aiming to bridge the gaps between bioinformatics research and human health applications. He has over 60 publications in the areas of biological data management, biological data mining, network biology, systems biology, and various disease-related omics applications.

Stefano Lonardi is associate professor of computer science and engineering at the University of California, Riverside. He is also a faculty member of the graduate program in genetics, genomics and bioinformatics, the Center for Plant Cell Biology, the Institute for Integrative Genome Biology, and the graduate program in cell, molecular and developmental biology.

Dr. Lonardi received his "Laurea cum laude" from the University of Pisa in 1994 and his PhD, in the summer of 2001, from the Department of Computer Sciences, Purdue University, West Lafayette, IN. He also holds a PhD in electrical and information engineering from the University of Padua (1999). During the summer of 1999, he was an intern at Celera Genomics, Department of Informatics Research, Rockville, MD.

Dr. Lonardi's recent research interests include designing of algorithms, computational molecular biology, data compression, and data mining. He has published more than 30 papers in major theoretical computer science and computational biology journals and has about 45 publications in refereed international conferences. In 2005, he received the CAREER award from the National Science Foundation.

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Part I

Sequence, Structure, and Function

Chapter 1

Consensus Structure Prediction for RNA Alignments

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1.1 Introduction

RNA secondary structure prediction has been studied for quite awhile. Many minimum free energy (MFE) methods have been developed for predicting the secondary structures of single RNA sequences, such as mfold [1], RNAfold [2], MPGAfold [3], as well as recent tools presented in the literature [4, 5]. However, the accuracy of predicted structures is far from perfect. As evaluated by Gardner and Giegerich [6], the accuracy of the MFE methods for single sequences is 73% when averaged over many different RNAs.

Recently, a new concept of energy density for predicting the secondary structures of single RNA sequences was introduced [7]. The normalized free energy, or energy density, of an RNA substructure is the free energy of that substructure divided by the length of its underlying sequence. A dynamic programming algorithm, called Densityfold, was developed, which delocalizes the thermodynamic cost of computing RNA substructures and improves on secondary structure prediction via energy density minimization [7]. Here, we extend the concept used in Densityfold and present a tool, called RSpredict, for RNA secondary structure prediction. RSpredict computes the RNA structure with minimum energy density based on the loop decomposition scheme used in the nearest neighbor energy model [8]. RSpredict focuses on the loops in an RNA secondary structure, whereas Densityfold considers RNA substructures where a substructure may contain several loops.

While the energy density model creates a foundation for RNA secondary structure prediction, there are many limitations in Densityfold, just like in all other single sequence-based MFE methods. Optimal structures predicted by these methods do not necessarily represent real structures [9]. This happens due to several reasons. The thermodynamic model may not be accurate. The bases of structural RNAs may be chemically modified and these processes are not included in the prediction model. Finally, some functional RNAs may not have stable secondary structures [6]. Thus, a more reliable approach is to use comparative analysis to compute consensus secondary structures from multiple related RNA sequences [9].

In general, there are three strategies with the comparative approach. The first strategy is to predict the secondary structures of individual RNA sequences separately and then align the structures. Tools such as RNAshapes [10,11], MARNA [12], STRUCTURELAB [13], and RADAR [14,15] are based on this strategy. RNA Sampler [9] and comRNA [16] compare and find stems conserved across multiple sequences and then assemble conserved stem blocks to form consensus structures, in which pseudoknots are allowed.

The second strategy predicts common secondary structures of two or more RNA sequences through simultaneous alignment and consensus structure inference. Tools based on this strategy include RNAscf [17], Foldalign [18], Dynalign [19], stemloc [20], PMcomp [21], MASTR [22], and CARNAC [23]. These tools utilize either folding free energy change parameters or stochastic context-free grammars (SCFGs) and are considered derivations of Sankoff's method [24].

The third strategy is to fold multiple sequence alignments. RNAalifold [25, 26] uses a dynamic programming algorithm to compute the consensus secondary structure with MFE by taking into account thermodynamic stability, sequence covariation together with RIBOSUM-like scoring matrices [27]. Pfold [28] is a SCFG algorithm that produces a prior probability distribution of RNA structures. A maximum likelihood approach is used to estimate a phylogenetic tree for predicting the most likely structure for input sequences. A limitation of Pfold is that it does not run on alignments of more than 40 sequences and in some cases produces no structures due to under-flow errors [6]. Maximum weighted matching (MWM), based on a graph-theoretical approach and developed by Cary and Stormo [29] and Tabaska et al. [30], is able to predict common secondary structures allowing pseudo-knots. KNetFold [31] is a recently published machine learning method, implemented using a hierarchical network of k-nearest neighbor classifiers that analyzes the base pairings of alignment columns in the input sequences through their mutual information, Watson–Crick base pairing rules and thermodynamic base pair propensity derived from RNAfold [2]. The method presented in this chapter, RSpredict, joins the many tools using the third strategy; it accepts a multiple alignment of RNA sequences as input data and predicts the consensus secondary structure for the input sequences via energy density minimization and covariance score calculation.

We also considered two variants of RSpredict, referred to as RSefold and RSdfold respectively. Both RSefold and RSdfold use the same covariance score calculation as in RSpredict. The differences among the three approaches lie in the folding algorithms they adopt. Rse-fold predicts the consensus secondary structure for the input sequences via free energy minimization, as opposed to energy density minimization used in RSpredict. RSdfold does the prediction via energy density minimization, though its energy density is calculated based on RNA substructures as in Densityfold, rather than based on the loops used in RSpredict.

The rest of the chapter is organized as follows. We first describe the implementation and algorithms used by RSpredict, and analyze the time complexity of the algorithms (see Section 1.2). We then present experimental results of running the RSpredict tool as well as comparison with the existing tools (see Section 1.3). The experiments were performed on a variety of datasets. Finally we discuss some properties of RSpredict, possible ways to improve the tool and point out some directions for future research (see Section 1.4).

1.2 Algorithms

RSpredict, which can be freely downloaded from http://datalab.njit.edu/biology/RSpredict, was implemented in the Java programming language. The program accepts, as input data, a multiple sequence alignment in the FASTA or ClustalW format and outputs the consensus secondary structure of the input sequences in both the Vienna style dot bracket format [26] and the connectivity table format [32]. Below, we describe the energy density model adopted by RSpredict. We then present a dynamic programming algorithm for folding a single RNA sequence via energy density minimization. Next, we describe techniques for calculating covariance scores based on the input alignment. Finally we summarize the algorithms used by RSpredict, combining both the folding technique and the covariance scores obtained from the input alignment, and show its time complexity.

1.2.1 Folding of a single RNA sequence

1.2.1.1 Preliminaries

We represent an RNA secondary structure as a fully decomposed set of loops. In general, a loop L can be one of the following (see Figure 1.1):

i. A hairpin loop (which is a loop enclosed by only one base pair; the smallest possible hairpin loop consists of three nucleotides enclosed by a base pair)

ii. A stack, composed of two consecutive base pairs

iii. A bulge loop, if two base pairs are separated only on one side by one or more unpaired bases

iv. An internal loop, if two base pairs are separated by one or more unpaired bases on both sides

v. A multibranched loop, if more than two base pairs are separated by zero or more unpaired bases in the loop

We now introduce some terms and definitions. Let S be an RNA sequence consisting of nucleotides or bases A, U, C, G. $S[i]$ denotes the base at position i of the sequence S and $S[i, j]$ is the subsequence starting at position i and ending at position j in S. A base pair between nucleotides at positions i and j is denoted as (i, j) or $(S[i], S[j])$, and its enclosed sequence is $S[i, j]$. Given a loop L in the secondary structure R of sequence S, the base pair (i^*, j^*) in L is called the *exterior pair* of L if $S[i^*](S[j^*]$, respectively) is closest to the $5'$ ($3'$, respectively) end of R among all nucleotides in L. All other nonexterior base pairs in L are called *interior pairs* of L. The length of a loop L is the number of nucleotides in L. Note that two loops may overlap on a base pair. For example, the interior pair of a stack may be the exterior pair of another stack, or the exterior pair of a hairpin loop. Also note that a bulge or an internal loop has exactly one exterior pair and one interior pair.

We use the energy density concept as follows. Given a secondary structure R, every base pair (i, j) in R is the exterior pair of some loop L. We assign (i, j) and L an energy density, which is the free energy of the loop L divided by the length of L. The set of free energy parameters for nonmultibranched loops used in our algorithm is acquired from [33]. The free energy of a multibranched loop is computed based on the approach adopted by mfold [1], which is a linear function of the number of unpaired bases and the number of base pairs inside the loop, namely $a + b \times n_1 + c \times n_2$, where a, b, c are constants, n_1 is the number of unpaired bases and n_2 is the number of base pairs inside the multibranched loop. We adopt the loop decomposition scheme used in the nearest neighbor energy model developed by Turner et al. [8]. The secondary structure R contains multiple loop components and the energy densities of

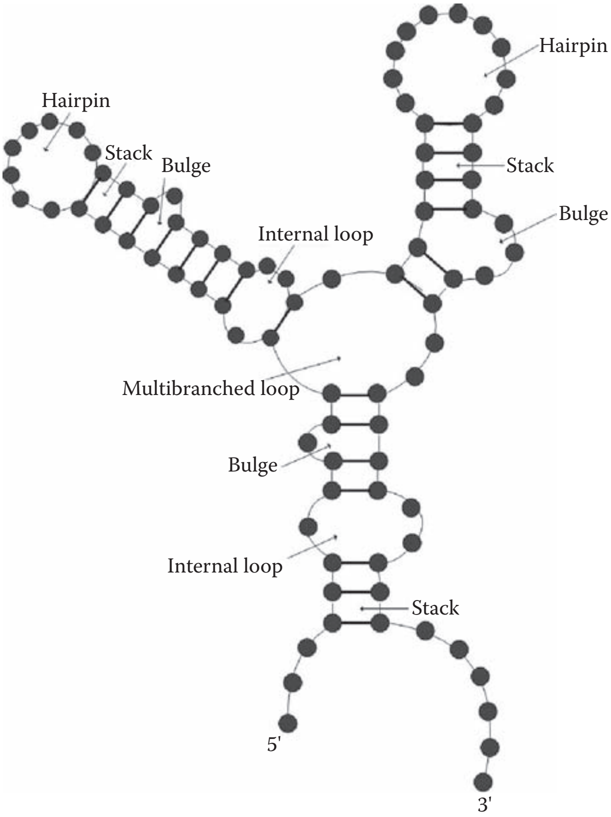


FIGURE 1.1: Illustration of the loops in an RNA secondary structure. Each loop has at least one base pair. A stem consists of two or more consecutive stacks shown in the figure.

the loop components are additive. Our folding algorithm computes the total energy density of R by taking the sum of the energy densities of the loop components in R. Thus, the RNA folding problem can be formalized as follows. Given an RNA sequence S, find the set of base pairs (i, j) and loops with (i, j) as exterior pairs, such that the total energy density of the loops (or equivalently, the exterior pairs) is minimized. The set of base pairs constitutes the optimal secondary structure of S.

When generalizing the folding of a single sequence to the prediction of the consensus structure of a multiple sequence alignment, we introduce the notion of refined alignments. At times, an input alignment may have some columns each of which contains more than 75% gaps. Some tools including RSpredict delete these columns to get a refined alignment [28]; some tools simply use the original input alignment as the refined alignment. Suppose the original input alignment A_o has N sequences and n_o columns, and the refined alignment A has N sequences and n columns, $n \leq n_o$. Formally, the consensus structure of the refined alignment A is a secondary structure R together with its sequence S such that each base pair $(S[i], S[j])$, $1 \leq i < j \leq n$, in R corresponds to the pair of columns i, j in the alignment A, and each base $S[i]$, $1 \leq i \leq n$, is the representative base of the ith column in the alignment A. There are several ways to choose the representative base. For example, $S[i]$ could be the most frequently occurring nucleotide, excluding gaps, in the ith column of the alignment A. Furthermore, there is an energy measure value associated with each base pair $(S[i], S[j])$ or more precisely its corresponding column pair (i, j), such that the total energy measure value of all the base pairs in R is minimized.

The consensus secondary structure of the original input alignment A_o is defined as the structure R_o, obtained from R, as follows: (i) the base (base pair, respectively) for column C_o (column pair (C_o1, C_o2), respectively) in A_o is identical to the base (base pair, respectively) for the corresponding column C (column pair ($C1$, $C2$), respectively) in A if C_o ((C_o1, C_o2), respectively) is not deleted when getting A from A_o; (ii) unpaired gaps are inserted into R, such that each gap corresponds to a column that is deleted when getting A from A_o (see Figure 1.2). In Figure 1.2, the RSpredict algorithm transforms the original input alignment A_o to a refined alignment A by deleting the fourth column (the column in red) of A_o. The algorithm predicts the consensus structure of the refined alignment A. Then the algorithm generates the consensus structure of A_o by inserting an unpaired gap to the fourth position of the consensus structure of A. The numbers inside parentheses in the refined alignment A represent the original column numbers in A_o.

In what follows, we first present an algorithm for folding a single RNA sequence based on the energy density concept described here. We then generalize the algorithm to predict the consensus secondary structure for a set of aligned RNA sequences.

1.2.1.2 Algorithm

The functions and parameters used in our algorithm are defined below where $S[i, j]$ is a subsequence of S and $R[i, j]$ is the optimal secondary structure of $S[i, j]$.

i. NE(i, j) is the total energy density of all loops in $R[i, j]$, where nucleotides at positions i, j may or may not form a base pair.

ii. $\mathrm{NE}_p(i, j)$ is the total energy density of all loops in $R[i, j]$ if nucleotides at positions i, j form a base pair.

iii. $e_H(i, j)(E_H(i, j)$, respectively) is the free energy (energy density, respectively) of the hairpin with exterior pair (i, j).

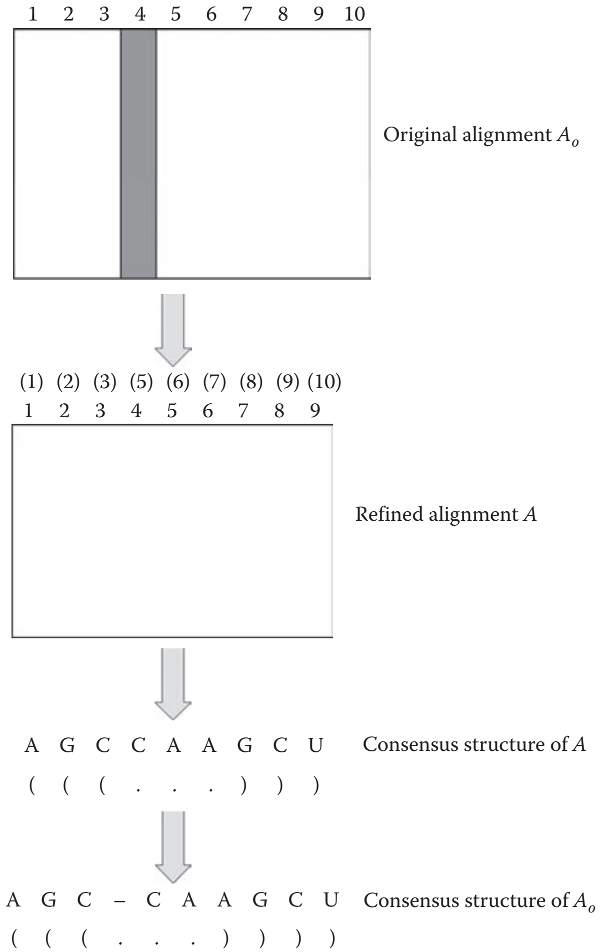


FIGURE 1.2: Illustration of the consensus structure definition used by RSpredict.

iv. $e_S(i,j)(E_S(i,j)$, respectively) is the free energy (energy density, respectively) of the stack with exterior pair (i,j) and interior pair $(i+1,j-1)$.

v. $e_B(i,j,i',\ j')$, $(E_B(i,j,i',\ j')$, respectively) is the free energy (energy density, respectively) of the bulge or internal loop with exterior pair (i,j) and interior pair (i',j').

vi. $e_J\left(i,j,i_1',j_1',i_2',j_2',\ldots,i_k',j_k'\right)$ $E_J\left(i,j,i_1',j_1',i_2',j_2',\ldots,i_k',j_k'\right)$ respectively, is the free energy (energy density, respectively) of the multibranched loop with exterior pair (i,j) and interior pairs $\left(i_1',\ j_1'\right),\ \left(i_2',\ j_2'\right),\ldots,\ \left(i_k',\ j_k'\right)$.

It is clear that

$$E_H\left(i,j\right) = \frac{e_H\left(i,j\right)}{j-i+1} \tag{1.1}$$

$$E_S(i,j) = \frac{e_S(i,j)}{4} \tag{1.2}$$

$$E_B\left(i,j,i',j'\right) = \frac{e_B\left(i,j,i',j'\right)}{i'-i+j-j'+2} \tag{1.3}$$

$$E_J(i,j,i'_1,j'_1,i'_2,j'_2,\ldots,i'_k,j'_k) = \frac{e_J(i,j,i'_1,j'_1,i'_2,j'_2,\ldots,i'_k,j'_k)}{n_1+2\times n_2} \tag{1.4}$$

Here n_1 is the number of unpaired bases and n_2 is the number of base pairs in the multibranched loop in (vi).

Thus, the total energy density of all loops in $R[i,j]$ where (i,j) is a base pair is computed by Equation 1.5:

$$\mathrm{NE}_P\left(i,j\right) = \min \begin{cases} E_H(i,j) \\ E_S\left(i,j\right) + \mathrm{NE}_P\left(i+1,j-1\right) \\ \min\limits_{i<i'<j'<j} \{E_B\left(i,j,i',j'\right) + \mathrm{NE}_P\left(i',j'\right)\} \\ \min\limits_{i<i'_1<j'_1<i'_2<j'_2<\cdots<i'_k<j'_k<j} \{E_J\left(i,j,i'_1,j'_1,i'_2,j'_2,\ldots,i'_k,j'_k\right) \\ \qquad + \sum_{r=1}^{k} \mathrm{NE}_P\left(i'_r,j'_r\right)\} \end{cases} \tag{1.5}$$

That is, the energy density is calculated by taking the minimum of the following four cases:

i. (i,j) is the exterior pair of a hairpin, in which case the energy density $\mathrm{NE}_P(i,\ j)$ equals $E_H(i,j)$, which is the energy density of the hairpin

ii. (i,j) is the exterior pair of a stack, in which case $\mathrm{NE}_P(i,j)$ equals the energy density of the stack, i.e., $E_S(i,j)$, plus $\mathrm{NE}_P(i+1,j-1)$

iii. (i,j) is the exterior pair of a bulge or an internal loop, in which case $\mathrm{NE}_P(i,j)$ equals the minimum of the energy density of the bulge or internal loop $E_B(i,j,i',j')$ plus $\mathrm{NE}_P(i',j')$ for all $i<i'<j'<j$

iv. (i,j) is the exterior pair of a multibranched loop, in which case $\mathrm{NE}_P(i,j)$ equals the minimum of the energy density of the multibranched loop $E_j\left(i,j,i'_1,j'_1,i'_{2,}j'_2,\ldots,i'_k,j'_k\right)$ plus $\sum_{r=1}^{k}\mathrm{NE}_P\left(i'_r,j'_r\right)$, for all $i<i'_1<j'_1<i'_2<j'_2<\cdots<i'_k<j'_k<j$

Equation 1.6 below shows the recurrence formula for calculating $\mathrm{NE}(i,j)$:

$$\mathrm{NE}\left(i,j\right) = \min \begin{cases} \mathrm{NE}\left(i,j-1\right) \\ \mathrm{NE}\left(i+1,j\right) \\ \mathrm{NE}_P\left(i,j\right) \\ \min_{i<h<j}\{\mathrm{NE}\left(i,h-1\right) + \mathrm{NE}\left(h,j\right)\} \end{cases} \tag{1.6}$$

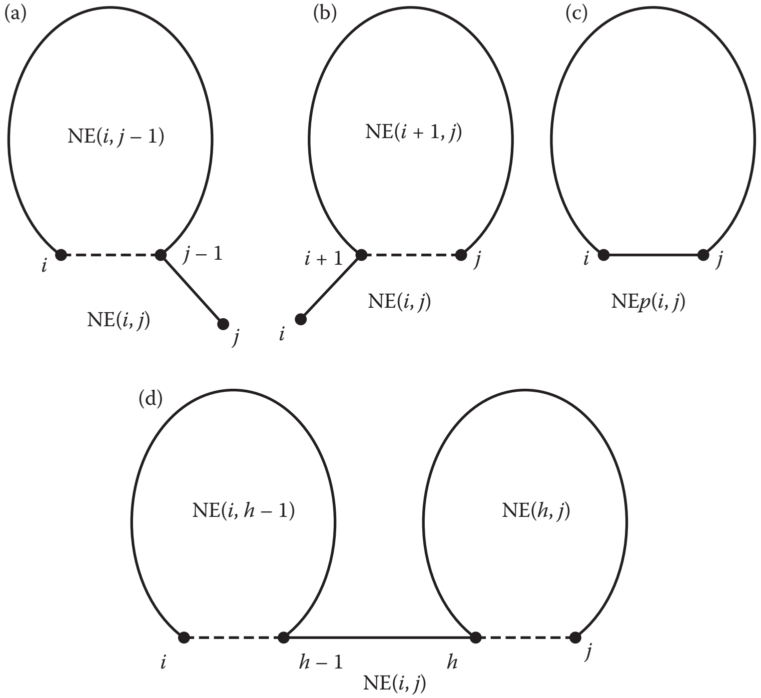


FIGURE 1.3: Illustration of the cases in Equation 1.6. a) the total normalized energy of all loops in the optimal secondary structure $R[i, j-1]$ of subsequence $S[i, j-1]$; b) the total normalized energy of all loops in the optimal secondary structure $R[i+1, j]$ of subsequence $S[i+1, j]$; c) the total normalized energy of all loops in the optimal secondary structure $R[i, j]$ of subsequence $S[i, j]$, where $S[i]$ and $S[j]$ form a base pair; d) the minimum of $\mathrm{NE}(i, k-1)$ plus $\mathrm{NE}(k, j)$ for all $i < k < j$; The dashed line between two nucleotides means that the two nucleotides may or may not form a base pair. The solid line between two nucleotides means that the two nucleotides form a base pair.

That is, the energy density is computed by taking the minimum of the following four cases:

i. The total energy density of all loops in the optimal secondary structure $R\,[i, j-1]$ of subsequence $S\,[i, j-1]$ (Figure 1.3a)

ii. The total energy density of all loops in the optimal secondary structure $R\,[i+1, j]$ of subsequence $S\,[i+1, j]$ (Figure 1.3b)

iii. The total energy density of all loops in the optimal secondary structure $R[i, j]$ of subsequence $S[i, j]$, where $S[i]$ and $S[j]$ form a base pair (Figure 1.3c)

iv. The minimum of NE$(i, h-1)$ plus NE(h, j) for all $i < h < j$ (Figure 1.3d)

Note that case (iii) of Equation 1.6 is not considered when the nucleotides at positions i, j are forbidden to form a base pair, i.e., $(S[i], S[j])$ is a nonstandard base pair. A standard base pair is any of the following: (A,U), (U,A), (G,C), (C,G), (G,U), (U,G); all other base pairs are nonstandard.

In calculating the time complexity of the folding algorithm, there is a need to check for finding the optimal i', j' where $i < i' < j' < j$ in case (iii) (the optimal $i'_1, j'_1, i'_2, j'_2, \ldots, i'_k, j'_k$ where $i < i'_1 < j'_1 < i'_2 < j'_2 < \cdots < i'_k < j'_k < j$ in case (iv), respectively) of Equation 1.5. It can be shown that it takes linear time to compute NE$_P(i, j)$ in Equation 1.5. Hence, the time complexity of the folding algorithm is $O(n^3)$ since we need to calculate NE$_P(i, j)$ for all $1 \le i < j \le n$, where n is the number of nucleotides in the given sequence S. The energy density of the optimal secondary structure R for the sequence S equals NE$(1, n)$.

1.2.2 Calculation of covariance scores

When applying the above folding algorithm to a multiple sequence alignment A_o, we take into consideration the correlation between columns of the alignment. In many cases, the sequences in the alignment may have highly varying lengths. We refine the alignment A_o by deleting columns containing more than 75% gaps to get a refined alignment A [28]. We will use this refined alignment throughout the rest of this subsection.

1.2.2.1 Covariance score

We use the covariance score introduced by RNAalifold [25, 26, 34] to quantify the relationship between two columns in the refined alignment. Let $f_{ij}(XY)$ be the frequency of finding both base X in column i and base Y in column j, where X, Y are in the same row of the refined alignment. We exclude the occurrences of gaps in column i or column j when calculating $f_{ij}(XY)$. The covariation measure for columns i, j, denoted C$_{ij}$, is calculated by Equation 1.7:

$$C_{ij} = \frac{\sum XY, X'Y' f_{ij}(XY)\, D_{ij}(XY, X'Y')\, f_{ij}(X'Y')}{2} \tag{1.7}$$

Here, $D_{ij}(XY, X'Y')$ is the Hamming distance between the two base pairs (X, Y) and (X', Y') if both of the base pairs are standard base pairs, or 0 otherwise. The Hamming distance between (X, Y) and (X', Y') is calculated as follows:

$$D_{ij}(XY, X'Y') = 2 - \delta(X, X') - \delta(Y, Y') \tag{1.8}$$

where

$$\delta(X, X') = \begin{cases} 1 & \text{if } X = X' \\ 0 & \text{otherwise} \end{cases} \tag{1.9}$$

Observe that the information acquired from the two base pairs (X, Y) and (X', Y') is the same as that from (X', Y') and (X, Y). Thus, we divide the numerator in Equation 1.7 by two so as to obtain the non-redundant information between column i and column j in the refined alignment.

For every pair of columns i, j in the refined alignment, the covariance score of the two columns i and j, denoted Cov_{ij}, is calculated in Equation 1.10:

$$\mathrm{Cov}_{ij} = C_{ij} + c_1 \times \mathrm{NF}_{ij} \tag{1.10}$$

Here, C_{ij} is as defined in Equation 1.7, c_1 is a user-defined coefficient (in the study presented here, c_1 has a value of -1), and

$$\mathrm{NF}_{ij} = \frac{\mathrm{NC}_{ij}}{N} \tag{1.11}$$

where N is the total number of sequences and NC_{ij} is the total number of conflicting sequences in the refined alignment. A conflicting sequence is one that has a gap in column i or column j, or has a nonstandard base pair in the columns i, j of the refined alignment. A sequence with gaps in both columns i, j is not conflicting.

1.2.2.2 Pairing threshold

We say that column i and column j in the refined alignment can possibly form a base pair if their covariance score is greater than or equal to a pairing threshold; otherwise, column i and column j are forbidden to form a base pair. The pairing threshold, η, used in RSpredict is calculated as follows.

It is known that, on average, 54% of the nucleotides in an RNA sequence S are involved in the base pairs of its secondary structure [35]. We use this information to calculate an alignment-dependent pairing threshold, observing that the base pairs in the consensus secondary structure of a sequence alignment represent the column pairs with the highest covariance scores. Given that different structures contain different numbers of base pairs, we consider two different percentages of columns, namely, 30% and 65%, in the sequence alignment. For each percentage p, there are at most T_p possible base pairs, where

$$T_p = \frac{(p \times n) \times (p \times n - 1)}{2} \tag{1.12}$$

and n is the number of columns in the sequence alignment.

Now, we calculate the covariance scores of all pairs of columns in the given refined alignment, and sort the covariance scores in descending order. We then select the top T_p largest covariance scores and store the covariance scores in the set ST_p. Thus, the set $\mathrm{ST}_{0.65}$ contains the top largest covariance scores that involve 65% of the columns in the refined alignment; the set $\mathrm{ST}_{0.30}$ contains the top largest covariance scores that involve 30% of the columns in the refined alignment; and $\mathrm{ST}_{0.65} \backslash \mathrm{ST}_{0.30}$ is the set difference that contains covariance scores in $\mathrm{ST}_{0.65}$ but not in $\mathrm{ST}_{0.30}$ (see Figure 1.4). The pairing

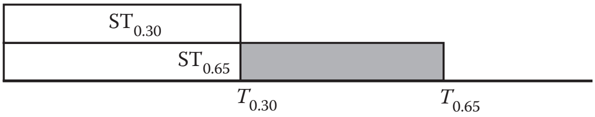


FIGURE 1.4: Illustration of the pairing threshold computation. The pairing threshold used in RSpredict is computed as the average of the covariance scores inside the shaded area.

threshold η used in RSpredict is calculated as the average of the covariance scores in $\mathrm{ST}_{0.65} \backslash \mathrm{ST}_{0.30}$, as shown in Equation 1.13:

$$\eta = \frac{\sum \mathrm{Cov}_{ij} \in \mathrm{ST}_{0.65} \backslash \mathrm{ST}_{0.30} \mathrm{Cov}_{ij}}{|\mathrm{ST}_{0.65} \backslash \mathrm{ST}_{0.30}|} \tag{1.13}$$

where the denominator is the cardinality of the set difference $\mathrm{ST}_{0.65} \backslash \mathrm{ST}_{0.30}$.

If the covariance score of columns i and j is greater than or equal to η, then column i and column j can possibly form a base pair, and we refer to (i, j) as a pairing column. If the covariance score of the columns i and j is less than η, we will check the covariance scores of the immediate neighboring column pairs of i, j to see if they are above a user-defined threshold [31] (in the study presented here, this threshold is set to 0). The immediate neighboring column pairs of i, j are $i + 1$, $j - 1$ and $i - 1$, $j + 1$. If the covariance scores of both of the immediate neighboring column pairs of i, j are greater than or equal to $\max\{\eta, 0\}$, then (i, j) is still considered as a paring column.

1.2.3 Algorithms for RSpredict

Given a refined multiple sequence alignment A with N sequences, let (i, j) be a pairing column in A. Let X_i^S (Y_j^S, respectively) be the nucleotide at position i (j, respectively) of the sequence S in the alignment A. $\left(X_i^S, Y_j^S\right)$ must be the exterior pair of some loop L in S. We use $e\left(X_i^S, Y_j^S\right)$ to represent the free energy of that loop L. If $\left(X_i^S, Y_j^S\right)$ is a nonstandard base pair, $e\left(X_i^S, Y_j^S\right) = 0$. We assign the pairing column (i, j) a pseudo-energy e_{ij} where

$$e_{ij} = \frac{1}{N} \sum_{S \in A} e\left(X_i^S, Y_j^S\right) + c_2 \times \mathrm{Cov}_{ij} \tag{1.14}$$

Here, c_2 is a user-defined coefficient (in the study presented here, $c_2 = -1$). Thus, every pairing column in the refined alignment A has a pseudo-energy. We then apply the minimum energy density folding algorithm described in the beginning of this section to the refined alignment A, treating each pairing column in A as a possible base pair considered in the folding algorithm.

Notice that when calculating the energy density for the loop L, the sequence S is in the refined alignment A, which may have fewer columns than the original input alignment A_o (cf. Figure 1.2). RSpredict computes all energy densities based on the refined alignment, and the program uses loop lengths from the refined alignment A rather than the original input alignment A_o. Let R be the consensus secondary structure, computed by RSpredict, for the refined alignment A. We obtain the consensus structure R_o of the original input alignment A_o by inserting unpaired gaps to the positions in R whose corresponding columns are deleted when getting A from A_o (cf. Figure 1.2). The following summarizes the algorithms for RSpredict:

1. Input an alignment A_o in the FASTA or ClustalW format.
2. Delete the columns with more than 75% gaps from A_o to obtain a refined alignment A.
3. Compute the pseudo-energy e_{ij} for every pairing column (i, j) in A as in Equation 1.14.
4. Run the minimum energy density folding algorithm on A, using the pseudo-energy values obtained from step (3) to produce the consensus secondary structure R of the refined alignment A. The base at position i of the consensus secondary structure R is the most frequently occurring nucleotide, excluding gaps, in the ith column of the refined alignment A.
5. Map the consensus structure R back to the original alignment A_o by inserting unpaired gaps to the positions of R whose corresponding columns are deleted in Step (2).

Notice that Equation 1.6 is used to compute the NE values only. To generate the optimal structure R in Step (4), we maintain a stack of pointers that point to the substructures of loops with minimum energy density as we compute the NE values. Once all the NE values are calculated and the energy density of the optimal secondary structure R is obtained, we pop up the pointers from the stack to extract the optimal predicted structure. In step (5), we map the bases (base pairs, respectively) for the columns (column pairs, respectively) in A to their corresponding columns (column pairs, respectively) in A_o. For example, consider Figure 1.2 again. In the figure, the refined alignment A is obtained by deleting column 4 from the original input alignment A_o. The bases for columns 1, 2, 3, 4 in A are mapped to columns 1, 2, 3, 5 in A_o. The base pair between column 1 and column 9 in A becomes the base pair between column 1 and column 10 in A_o; the base pair between column 2 and column 8 in A becomes the base pair between column 2 and column 9 in A_o. An unpaired gap is inserted to the position corresponding to the deleted column 4 in A_o.

Let N be the number of sequences and n_o be the number of columns in the input alignment A_o. Step (2) takes $O(Nn_o)$ time. Step (3) takes $O\left(n_o^2\right)$ time. Step (4) takes $O\left(n_o^3\right)$ time. Step (5) takes $O(n_o)$ time. Therefore, the time complexity of RSpredict is $O\left(Nn_o + n_o^3\right)$, which is approximately $O\left(n_o^3\right)$ as $N$is usually much smaller than n_o.

1.3 Results

We conducted a series of experiments to evaluate the performance of RSpredict and compared it with five related tools including KNetFold, Pfold, RNAalifold, RSefold, and RSdfold. We tested these tools on Rfam [36] sequence alignments with different similarities. The Rfam sequence alignments come with consensus structures. For evaluation purposes, we used the Rfam consensus structures as reference structures and compared them against the consensus structures predicted by the six tools. The similarity of a sequence alignment is determined by the average pairwise sequence identity (APSI) of that alignment [6]. In the study presented here, a sequence alignment is of high similarity if its APSI value is greater than 75%, is of medium similarity if its APSI value is between 55% and 75%, or is of low similarity if its APSI value is less than 55%. The data sets used in testing included 20 Rfam sequence alignments of high similarity and 36 Rfam sequence alignments of low and medium similarity. These data sets were chosen to form a collection of sequence alignments with different (low, medium and high) APSI values, different numbers of sequences, as well as different sequence alignment lengths. More specifically, the data sets contained sequence alignments that ranged in size from 2 to 160 sequences, in length from 33 to 262 nucleotides and had APSI values ranging from 42% to 99%.

The performance measures used in our study include sensitivity (SN) and selectivity (SL) [6], where

$$\mathrm{SN} = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FN}} \tag{1.15}$$

$$\mathrm{SL} = \frac{\mathrm{TP}}{\mathrm{TP} + (\mathrm{FP} - \xi)}. \tag{1.16}$$

Here, TP is the number of correctly predicted base pairs ("true positives"), FN is the number of base pairs in a reference structure that were not predicted ("false negatives") and FP is the number of incorrectly predicted base pairs ("false positives"). False positives are classified as inconsistent, contradicting or compatible [6]. When predicting the consensus secondary structure for a multiple sequence alignment, a predicted base pair (i, j) is inconsistent if column i in the alignment is paired with column $q, q \neq j$, or column j is paired with column $p, p \neq i$, and p, q form a base pair in the reference structure of the alignment. A base pair (i, j) is contradicting if there exists a base pair (p, q) in the reference structure of the alignment, such that $i < p < j < q$. A base pair (i, j) is compatible if it is a false positive but is neither inconsistent nor contradicting. The ξ in SL represents the number of compatible base pairs, which are considered neutral with respect to algorithmic accuracy. Therefore ξ is subtracted from FP. Finally, we used the Matthews correlation coefficient (MCC) to combine the sensitivity and selectivity, where MCC is approximated to the geometric mean of the two measures, i.e., MCC $\approx \sqrt{\mathrm{SN} \times \mathrm{SL}}$ [18]. The larger MCC, SN, SL values a tool has, the better performance that tool achieves and the more accurate that tool is.

1.3.1 Performance evaluation on Rfam alignments of high similarity

The first data set consisted of seed alignments of high similarity taken from 20 families in Rfam. The APSI values of these seed alignments ranged from 77% to 99%. The alignments ranged in size from 2 to 160 sequences and in length from 33 to 159 nucleotides. Table 1.1 presents the accession number, description, number of sequences, and length of the seed alignment of each of the 20 Rfam families used in the experiment. The seed alignments of the 20 families are of high similarity; their APSI values are shown in the last column of the table. The families are sorted, from top to bottom, in ascending order on the APSI values. All six tools including RSpredict, KNetFold, RNAalifold, Pfold, RSefold and RSdfold were tested on this data set.

The graphs in Figure 1.5 show the trend of the MCC, SN, and SL, which are sorted in descending order for each tool under analysis. The X-axis shows, therefore, the rank of the MCC (SN and SL, respectively) from highest to lowest. For example, number 1 in the X-axis corresponds to the highest score achieved by each tool. The Y-axis represents the MCC, SN, and SL, respectively.

It can be seen from Figure 1.5 that RSpredict performed the best while RSdfold performed the worst among the six tools. The Pfold tool had good performance in selectivity but did not perform well in sensitivity and as a result in MCC. It also suffered from a size limitation (the Pfold web server can accept a multiple alignment of up to 40 sequences). Only 17 out of the 20 sequence alignments used in the experiment were accepted by the Pfold server; the other three alignments (RF00386, RF00041, and RF00389) had more than 40 sequences and therefore could not be run on the Pfold server. RSpredict had stable performance with the best mean 0.85 (standard deviation 0.16, respectively) in MCC, while the other methods' MCC values varied a lot and had means (standard deviations, respectively) ranging from 0.37 to 0.82 (0.24 to 0.34, respectively).

1.3.2 Performance evaluation on Rfam alignments of medium and low similarity

In the second experiment, we compared RSpredict with the other five methods on multiple sequence alignments of low and medium similarity. The test dataset included seed alignments of 36 families taken from Rfam [36]. The APSI values of the seed alignments ranged from 42 to 75%, the number of sequences in the alignments ranged from 3 to 114, and the alignment lengths ranged from 43 to 262 nucleotides. Table 1.2 presents the accession number,

TABLE 1.1: Rfam alignments of high similarity.

Accession	Description	Number of sequences	Length	APSI
RF00460	U1A polyadenylation inhibition element (PIE)	8	75	77%
RF00326	Small nucleolar RNA Z155	8	81	79%
RF00560	Small nucleolar RNA SNORA17	38	132	82%
RF00453	Cardiovirus cis-acting replication element (CRE)	12	33	82%
RF00386	Enterovirus 5′ cloverleaf cis-acting replication element	160	91	83%
RF00421	Small nucleolar RNA SNORA32	9	122	84%
RF00302	Small nucleolar RNA SNORA65	8	130	84%
RF00465	Japanese encephalitis virus (JEV) hairpin structure	20	60	86%
RF00501	Rotavirus cis-acting replication element (CRE)	14	68	87%
RF00041	Enteroviral 3′ UTR element	60	123	87%
RF00575	Small nucleolar RNA SNORD70	4	88	89%
RF00362	Pospiviroid RY motif stem loop	16	79	92%
RF00105	Small nucleolar RNA SNORD115	23	82	92%
RF00467	Rous sarcoma virus (RSV) primer binding site (PBS)	23	75	93%
RF00389	Bamboo mosaic virus satellite RNA cis-regulatory element	42	159	93%
RF00384	Poxvirus AX element late mRNA cis-regulatory element	7	62	93%
RF00098	Snake H/ACA box small nucleolar RNA	22	150	93%
RF00607	Small nucleolar RNA SNORD98	2	67	98%
RF00320	Small nucleolar RNA Z185	2	86	98%
RF00318	Small nucleolar RNA Z175	3	81	99%

description, number of sequences, and length of the seed alignment of each of the 36 Rfam families used in the experiment. The seed alignments of the 36 families are of low and medium similarity; their APSI values are shown in the last column of the table. The families are sorted, from top to bottom, in ascending order on the APSI values.

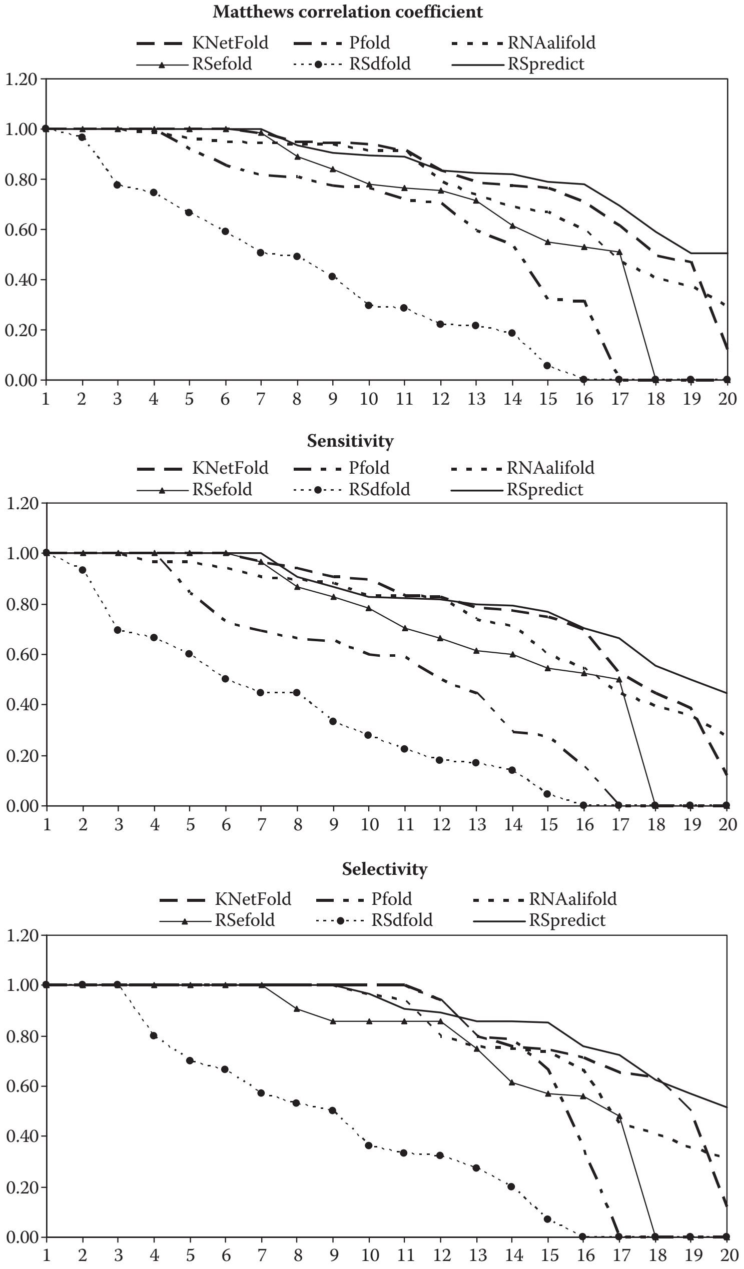
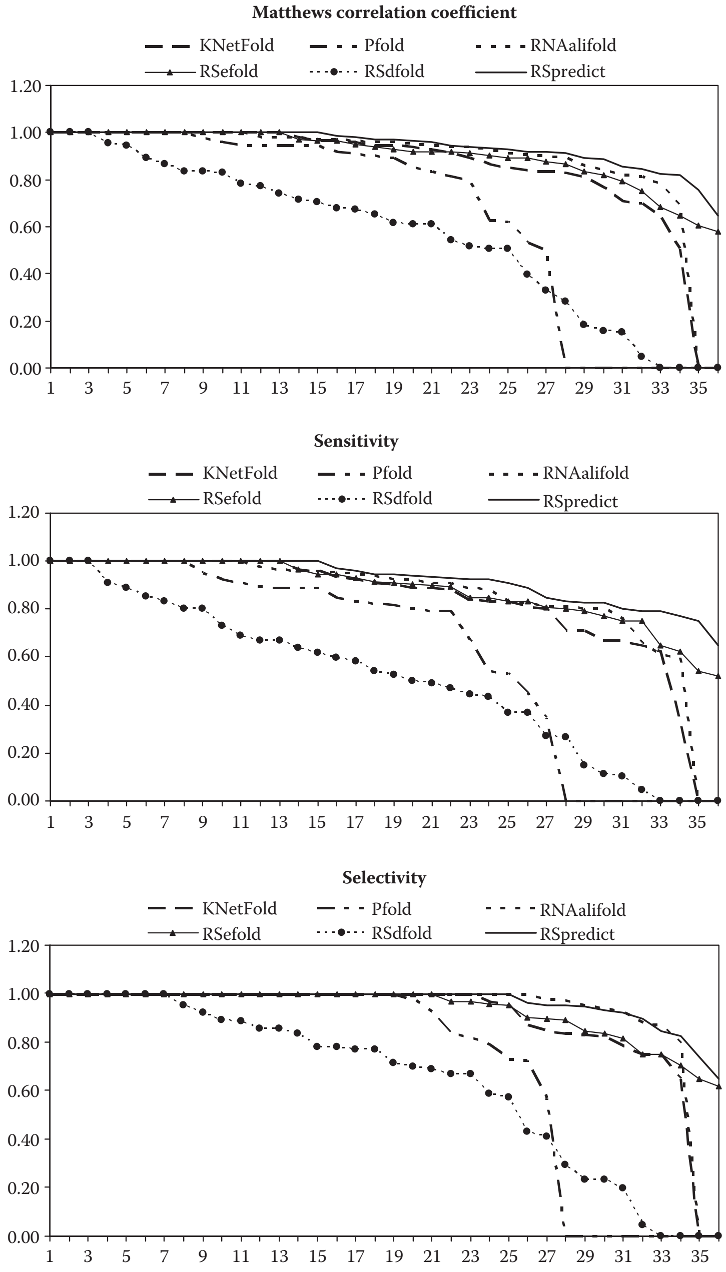


FIGURE 1.5: Comparison of the MCC, SN, and SL values of the six tools under analysis on the seed alignments of high similarity taken from the 20 families listed in Table 1.1.

TABLE 1.2: Rfam alignments of low and medium similarity.

Accession	Description	Number of sequences	Length	APSI
RF00230	T-box leader	103	262	42%
RF00080	yybP-ykoY leader	50	131	44%
RF00515	PyrR binding site	72	125	47%
RF00557	Ribosomal protein L10 leader	66	149	48%
RF00504	Glycine riboswitch	93	111	50%
RF00029	Group II catalytic intron	114	94	52%
RF00458	Cripavirus internal ribosome entry site (IRES)	7	203	54%
RF00559	Ribosomal protein L21 leader	33	81	54%
RF00234	glmS glucosamine-6-phosphate activated ribozyme	11	218	55%
RF00556	Ribosomal protein L19 leader	24	43	55%
RF00519	suhB	13	80	56%
RF00379	ydaO/yuaA leader	25	150	58%
RF00380	ykoK leader	36	172	59%
RF00445	mir-399 microRNA precursor family	13	119	59%
RF00522	PreQ1 riboswitch	22	47	59%
RF00095	Pyrococcus C/D box small nucleolar RNA	25	59	60%
RF00442	ykkC-yxkD leader	11	111	60%
RF00430	Small nucleolar RNA SNORA54	5	134	60%
RF00521	SAM riboswitch (alpha-proteobacteria)	12	79	61%
RF00049	Small nucleolar RNA SNORD36	20	82	63%
RF00513	Tryptophan operon leader	11	100	63%
RF00309	Small nucleolar RNA snR60/ Z15/Z230/Z193/J17	23	106	63%
RF00451	mir-395 microRNA precursor family	21	112	64%
RF00464	mir-92 microRNA precursor family	33	80	64%
RF00507	Coronavirus frameshifting stimulation element	23	85	66%
RF00388	Qa RNA	5	103	70%
RF00357	Small nucleolar RNA R44/ J54/Z268 family	19	105	70%
RF00434	Luteovirus cap-independent translation element (BTE)	17	108	71%
RF00525	Flavivirus DB element	111	76	71%
RF00581	Small nucleolar SNORD12/ SNORD106	8	91	71%
RF00238	ctRNA	48	88	72%
RF00477	Small nucleolar RNA snR66	5	105	72%
RF00608	Small nucleolar RNA SNORD99	3	80	72%
RF00468	Heaptitis C virus stem-loop VII	110	66	74%
RF00489	ctRNA	14	80	74%
RF00113	QUAD RNA	14	150	75%

The MCC, SN, and SL values are sorted in descending order for each tool under analysis and placed in the graphs in Figure 1.6. The X-axis shows, therefore, the rank of the MCC (SN and SL, respectively) from highest to lowest. For example, number 1 in the X-axis corresponds to the highest score achieved by each tool. The Y-axis represents the MCC, SN, and SL, respectively.


Matthews correlation coefficient

Sensitivity

Selectivity

FIGURE 1.6: Comparison of the MCC, SN, and SL values of the six tools under analysis on the seed alignments of low and medium similarity taken from the 36 families listed in Table 1.2.

Comparing Figures 1.5 and 1.6, we see that the methods under analysis generally performed better on sequence alignments of medium and low similarity than on sequence alignments of high similarity. Like what was observed in the previous experiment, RSdfold performed the worst (cf. Figure 1.5). The structures predicted by RSdfold tend to be stem-like structures; therefore, many structures, particularly those containing multibranched loops, were mispredicted. For this reason, RSdfold yielded very low MCC, SN and SL values.

RSpredict outperformed the other five methods based on the three performance measures used in the experiment. The tool achieved a high mean value of 0.94 in MCC, better than those of KNetFold (0.86), Pfold (0.88) and RNAalifold (0.89). Similar results were observed for sensitivity and selectivity values. Furthermore, RSpredict exhibited stable performance across all the families tested in the experiment. The tool had an MCC, SN and SL standard deviation of 0.08, 0.09 and 0.08, respectively. These numbers were better than the standard deviation values obtained from the other five methods, which ranged from 0.11 to 0.34. Pfold suffered from a size limitation; it could not generate a structure for the large seed alignments with more than 40 sequences in 9 families, including RF00230, RF00080, RF00515, RF00557, RF00504, RF00029, RF00525, RF00238 and RF00468.

1.4 Conclusions

In this chapter we presented a software tool, called RSpredict, capable of predicting the consensus secondary structure for a set of aligned RNA sequences via energy density minimization and covariance score calculation. Our experimental results showed that RSpredict is competitive with some widely used tools including RNAalifold and Pfold on tested datasets, suggesting that RSpredict can be a choice when biologists need to predict RNA secondary structures of multiple sequence alignments, especially those with low and medium similarity. Notice that RSpredict differs from KNetFold [31] in that KNetFold is a machine learning method that relies on precompiled training data derived from existing RNA secondary structures. RSpredict, on the other hand, is based on a dynamic programming algorithm for folding sequences and does not utilize training data.

Given a multiple sequence alignment A_o, our work is focused on predicting the consensus structure of the aligned sequences in A_o, rather than folding each individual sequence in A_o. Our approach is to first transform A_o to a refined alignment A by deleting columns with more than 75% gaps from A_o, then predict the consensus structure for A, and finally extend the consensus structure by inserting gaps to the positions corresponding to the deleted columns in A_o (cf. Figure 1.2). The predicted structure may not correspond exactly to any individual sequence in the original alignment A_o. As an example, assume for simplicity that A_o is the same as A, i.e., no columns are deleted when getting A from A_o. Consider a particular sequence S in A_o. Assume that the position (column) i of S has a gap due to the alignment with the other sequences in A_o. On the other hand, the position i in the consensus structure of A_o has the most frequently occurring nucleotide in column i of A_o, which cannot be a gap. As a result, the consensus structure of A_o, which is at least one nucleotide longer than S, cannot be mapped exactly back onto S. In future work we plan to look into ways for improving on consensus structure prediction. Possible ways include the utilization of evolutionary information [37], more sophisticated models of covariance scoring, and training data for more accurate pairing thresholds.

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