Predicting Model and Algorithm in RNA Folding Structure Including Pseudoknots

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The prediction of RNA structure with pseudoknots is a nondeterministic polynomial-time hard (NP-hard) problem; according to minimum free energy models and computational methods, we investigate the RNA-pseudoknotted structure. Our paper presents an efficient algorithm for predicting RNA structure with pseudoknots, and the algorithm takes $O(n^3)$ time and $O(n^2)$ space, the experimental tests in Rfam10.1 and PseudoBase indicate that the algorithm is more effective and precise. The predicting accuracy, the time complexity and space complexity outperform existing algorithms, such as Maximum Weight Matching (MWM) algorithm, PKNOTS algorithm and Inner Limiting Layer (ILM) algorithm, and the algorithm can predict arbitrary pseudoknots. And there exists a $1 + \varepsilon$ ($\varepsilon > 0$) polynomial time approximation scheme in searching maximum number of stackings, and we give the proof of the approximation scheme in RNA-pseudoknotted structure. We have improved several types of pseudoknots considered in RNA folding structure, and analyze their possible transitions between types of pseudoknots.

Keywords: RNA folding structure; algorithm; PTAS; pseudoknots; BHG.

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1. Introduction

RNA is an important biomacromolecule which performs a wide range of functions in biological systems. RNA is a key component in several vital molecular biological processes. RNAs are three-dimensional molecules. The major driving force of RNA molecule is the set of base pairs of A–U, C–G match, and G–U mismatch; RNA can fold into a three-dimensional structure by forming base pairs; a pseudoknot is two overlapping base pairs; pseudoknots are known to exist in some RNAs²³; some RNA helices contain overlapping base pairs and more pseudoknots are used to refer pairs of substructures. RNA tertiary structure is a more stable structure, and RNA secondary structure prediction is the first step to predict RNA tertiary structure in RNA sequence.

Cross of base pairs form pseudoknots, and cross of stems can form pseudoknotted structure. Now it is difficult to compute large RNA molecules including pseudoknots for existing polynomial time-predicting algorithms. Finding the optimal RNA structures based on combination with stems has become the new method to predict RNA pseudoknotted structures. It is a nondeterministic polynomial-time hard (NP-hard) problem to find an optimal RNA secondary structure if we allow any set of base pairs, and some RNA structures are legal when base pairs obey the minimum separation requirement. For predicting secondary structures with pseudoknots, Nussinov has studied the case where the energy function is minimized when the number of base pairs is maximized, and has obtained an $O(n^3)$ time algorithm for predicting RNA secondary structures,²² but Nussinov algorithm cannot predict pseudoknotted structures. Algebraic dynamic programming algorithm for finding RNA-pseudoknotted structure with simple planar pseudoknots was proposed by Jens and Robert, the algorithm takes $O(n^4)$ time and $O(n^2)$ space.¹² Efficient algorithm for finding optimal folding of an RNA structure has been firstly known by Michael Zuker³⁵; Pknots algorithm for RNA-pseudoknotted structure of predigesting model based on minimum free energy (MFE) has been presented by Rivas and Eddy,²⁸ in which time complexity and space complexity are $O(n^6)$ and $O(n^4)$, respectively. The problem for predicting RNA secondary structure including pseudoknots is NP-complete,²¹ and maximizing the number of stacking pairs allowing pseudoknots in a planar secondary structure makes it NP-hard,¹⁰ so naturally people seek for approximation algorithms in the past. In mimic RNA structure, pseudoknots apparently exist.¹⁵ A heuristic algorithm including pseudoknots for finding RNA-pseudoknotted structures has been presented by Ren.²⁷ Several publications show that extending the RNA structures including arbitrary pseudoknots indicates the problem of finding the optimum structure is NP-hard.¹ People can find the more stable structure with arbitrary pseudoknots if RNA secondary structure is modeled by maximum weighted matching.³⁰ The problem of the time and space complexities of predicting algorithms in the sparse case, sparse-related techniques have also been applied to RNA folding.^{34,5,6}

We analyze the RNA secondary structure. The contribution of this paper is to present an efficient algorithm for predicting RNA-pseudoknotted structure, where the time complexity of the algorithm is $O(n^3)$ and the space complexity is $O(n^2)$, and

we implement the algorithm in VC++ to complete the computation, “the experimental test in PseudoBase and Rfam10.1 of RNA database show that the algorithm is more effective and exact than other algorithms”, and the algorithm can predict arbitrary pseudoknots. Furthermore, we have proposed and proved that $1 + \varepsilon$ ($\varepsilon > 0$) polynomial time approximation scheme (PTAS) exists in searching maximum number of stackings. At last, we investigate the complexity of maximum number for stacking pairs of RNA structures and present a 2-approximation algorithm, analyzing the approximation ratio of the approximation algorithm. This paper also presents several types of pseudoknots considered in RNA folding structures, and analyzes their possible transitions between types of pseudoknots.

2. Predicting Model of RNA Structure

We discuss the model of RNA structure prediction with simple pseudoknots based on MFE through limiting pseudoknotted type.

2.1. Preliminary

- (1) RNA secondary structure S : Let S be a set of base pairs such as $s_i.s_j$, base s_i or $s_j \in \{A, C, G, U\}$, $1 \leq i \leq n$.
- (2) Pseudoknot: if $s_i.s_j$ and $s_{i'}.s_{j'} \in S$, $i < i' < j < j'$, or $i' < i < j' < j$, then the RNA base sequence $s_i \dots s_{i'} \dots s_j s_{j'}$ composes a pseudoknot.
- (3) Stem: the RNA structure closed by base pairs (i, j) and $(k, l) \in S$, and (i, j) , $(I + 1, j - 1), \dots, (k, l)$ are base pairs, $I \leq k < l \leq j$.
- (4) K -stacking pairs: In the RNA secondary structures, we use $(s_i, s_{i+1}, \dots, s_{i+k}; s_{j-k}, \dots, s_{j-1}, s_j)$ to describe k consecutive stacking pairs (s_i, s_j) , (s_{i+1}, s_{j-1}) ; (s_{i+1}, s_{j-1}) ; (s_{i+2}, s_{j-2}) ; $\dots$; (s_{i+k-1}, s_{j-k+1}) , (s_{i+k}, s_{j-k}) .
- (5) PTAS.
- (6) BHG: basin hopping graph.
- (7) Nested structure: if $s_i.s_j$ and $s_{i'}.s_{j'} \in S$, $i < j < i' < j'$, or $i' < j' < i < j$, then the RNA base sequence $s_i, \dots, s_{i'}, \dots, s_j s_{j'}$ composes nested structure.

2.2. Algorithm of dynamic programming

Let $S = s_1 s_2, \dots, s_n$, $s_{ij} = s_i, \dots, s_j$, $V(i, j)$, $W(i, j)$ and $W_M(i, j)$ can be computed as follows: $1 \leq i < j \leq n$.

In the formula, let $V(i, j)$ be the minimum energy for subsequence $s_{i,j}$ and (s_i, s_j) form a base pair, let $W(i, j)$ be the minimum energy for subsequence $s_{i,j}$, the computation of $V(i, j)$ and $W(i, j)$ can be represented as Figs. 1 and 2. E_1 represents the energy of base pair, and E_2 represents the energy of stack. EF represents the minimum energy of sequence F , LF represents the length of sequence F , W_M represents

Fig. 1. The model of V and W .

$$\begin{aligned}
 V(i, j) &= \min \begin{cases} E(i, j) \\ \min_{i < k < l < j, u = (k - i + j - l) - 2 < U} \{E_2(i, k : l, j) + V(k, l)\} \\ \min_{i < h < j-1} \{W_M(i+1, h) + W_M(h+1, j-1) + M + P\} \end{cases} \\
 W(i, j) &= \min \begin{cases} V(i, j), W(i+1, j), W(i, j-1), \min_{i < k < j-1} (W(i, k) + W(k+1, j)) \\ \min_{i \leq k < l < j} (EF(i, k : l) + EF(k+1 : l+1, j) + W_M(k+1 + LF(k+1 : l+1, j), l - LF(i : k, l)) + G_w) \\ \min_{i-1 \leq l \leq j} (EF(i : l, j) + W_M(i + LF(i : l, j), l-1)), \min_{i \leq k \leq j-1} (EF(i, k : j) + W_M(k+1, j - LF(i : k, j))) \\ \min_{i < k \leq l < j} (EF(i : k, l) + EF(i + LF(i : k, l), k-1 : j) + W_M(l+1, j - LF(i + LF(i : k, l), k-1 : j)) + G_w) \\ \min_{i < k \leq l < j} (EF(i : l+1, j - LF(k, l : j)) + EF(k, l : j) + W_M(i + LF(i : l+1, j - LF(k : l, j)), k-1) + G_w) \end{cases}
 \end{aligned}$$

Fig. 2. The model of V , W and W_M .

the energy value of the multi-loop, and the computation of $W(i, j)$ and W_M can be represented as Figs. 1 and 2. P represents the value of every base pair of the multi-loop, M represents the weight value of multi-loop, U represents the value of the length of base pairs, G_w represents the value of the pseudoknots. Based on principle of MFE, we use the thermodynamic parameters of M. Andronescu, A. Condon and Mathews,^{2,3} the algorithm can identify the pseudoknotted type of the query RNA structure, and output the RNA-pseudoknotted structure.

3. Predicting Algorithm of RNA Folding Structure

Based on principle of MFE, we design a polynomial time algorithm PreAlgorithm for predicting the RNA folding structure including pseudoknots. Stem is continuous stacking pairs in Fig. 3.

Fig. 3. RNA folded structure.

3.1. Definition

$$E = mS_b + nP_b + lN_b + u + v,$$

where E is the total energy of an RNA-pseudoknotted structure, S_b is the total number of bases for RNA-pseudoknotted sequences, P_b is the total number of RNA pseudoknots, N_b is the number of the bases which do not match with others, and m is the weight of S_b , n is the weight of P_b , l is the weight of N_b , u is the weight of coaxial stack, v is the weight of dangle bases. cf. Fig. 4.

$C(i, k: k + 1, j)$ represents the bonus value of coaxial stack $V(i, k)$ and $V(k + 1, j)$, the dangle bases function $L(i: I + 1, j)$ decided by the dangle bases s_i and base pair $(I + 1, j)$, the dangle bases function $R(j: i, j - 1)$ decided by the dangle bases s_j and base pair $(i, j - 1)$.

(a)

$$\begin{aligned} & \min_{i < k < j-1} \{V(i, k) + V(k + 1, j) + C(i, k : k + 1, j)\} \\ & L(i: i + 1, j) + V(i + 1, j), R(j: i, j-1) + V(i, j - 1) \\ & L(i: i + 1, j - 1) + R(j: i + 1, j-1) + V(i + 1, j - 1) \end{aligned}$$

(b)

Fig. 4. The representation (a) and formulas (b) of coaxial stack and dangle bases.

Algorithm 1. PreAlgorithm (S, E)

-
- 1: Compute energy E of RNA sequence S , $E = E_1 + E_2$
 E_1 is the energy value of RNA-nested structure, and E_2 is the energy value of RNA-pseudoknotted folding structure. Fill entry of $A[i, j]$ to save energy value of E and stems.
 - 2: $S_1 \leftarrow \emptyset, V_1 \leftarrow \emptyset, P_1 \leftarrow 0$
Define S_1 to save the k -stems which are found in RNA structures, define V_1 to save the energy value in m -stems structure, and define P_1 to save the amount of RNA pseudoknots of E_2 .
 - 3: For ($k = 1; k \leq 42; k++$) Search the prefix of i -stem s_i .
For ($l = 1; l \leq 42; l++$), search the suffix of j -stem s_i .
Seek k -stem s_k which is relative maximum of RNA molecule according to the MFE.
 - 4: $v_k = \min\{v_1, v_2, \dots, v_n\}$, v_k is the energy value of s_i ,
 $S_l \leftarrow S_l \cup \{s_l\}, V_l \leftarrow V_l \cup \{v_l\}$.
 - 5: While ($f_d = 1$) do
Mark the i -stem s_i which is relative maximum in RNA structure
 $S, S \leftarrow S - \{s_l\}$.
 - 6: Search the stem s_j which is hypo-maximum in RNA structure S except s_i which is relative maximum.
 - 7: $S_l \leftarrow S_l \cup \{s_l\}$,
 - 8: $V_l \leftarrow V_l \cup \{v_l\}$, until without l -stem in S .
 - 9: $S_e = \{s_1, s_2, \dots, s_n\}, V_a = \{v_1, v_2, \dots, v_n\}$.
 - 10: Compute the number P_1 of pseudoknots in S_l .
 - 11: Compute the energy values E_1 and E_2
 - 12: Compute the energy E according to E_1 and E_2 .
 - 13: Save and output S, E and P_1 .
-

4. PTAS of RNA Folded Structure

RNA structure is used to any set of base pairs for an RNA molecule. cf. Fig. 3. Finding the optimal RNA folded structure based on combination with stems and loops has become new method to predict RNA-pseudoknotted structure, there are substructures in RNA secondary structure, for example, hairpin loop, internal loop, multibranched loop, bulge, stem and so on. In fact, RNAs are three-dimensional molecules. The set of base pairs in the three-dimensional structure of an RNA molecule is denoted by the secondary structure.

We design a PTAS according to the characteristic of stems in the RNA secondary structure, and analyze the optimized structure of stems. The paper divides the stem into several subsegments with the length t , and then searches the optimal structure formed by subsegments with the length less than t as the approximation structure of given sequence.

Fig. 5. The mRNA secondary structure.

4.1. Terminology

Let RNA sequence $S = s_1 s_2, \dots, s_i, \dots, s_n$, $s_i \in \{A, U, G, C\}$,

$$|S| = n, \quad 1 \leq i \leq n.$$

Given a stem I in S , we suppose the RNA optimum structure $\text{OPT}(I) = \{x_1, x_2, \dots, x_m\}$, x_i is stem, and $x_i \in I$, $1 \leq i \leq m$. cf. Fig. 5.

Definition 1. Let $\text{LS}[i, j]$ be the length of stem $S[i, j]$ closed by base pairs (i, j) and $(k, l) \in S$, $i \leq k < l \leq j$, then $\text{LS}[i, j] = (k - i + 1)$ or $\text{LS}[i, j] = (j - l + 1)$.

Definition 2. Let $\text{NPS}(S)$ be the number of stacking pairs in stem $S[i, j]$, then $\text{NPS}(S) = \text{LS} - 1$.

Lemma 1. Let $S[i, j]$ be a stem of length LS , divide the stem $S[i, j]$ into t segment: $s_1, s_2, \dots, s_t$, let L_{s_i} be the length of stem $1 \leq i \leq m$, then $L_{s_1} + L_{s_2} + \dots + L_{s_t} = \text{LS}$, the number of stacking pairs after dividing the stem $S[i, j]$ is $\text{NPS}(S) = \sum L_{s_i} - m = \text{LS} - m$.

Proof. Let (i, j) be external base pair in stem $S[i, j]$, without loss of generality, let (k, l) be internal base pair in stem $S[i, j]$, according to the Definitions 1 and 2, then $\text{LS} = k - i + 1 = j - l + 1 = \text{NPS}(S[i, j]) + 1$. $\square$

Similar. $L_{s_i} = \text{NPS}(s_i) + 1$, $1 \leq i \leq m$, then $\text{NPS}(s_i) = L_{s_i} - 1$, the number of stacking pairs after dividing the stem $S[i, j]$ into m segment in stem $S[i, j]$ is $\text{NPS}(s_1) + \text{NPS}(s_2) + \dots + \text{NPS}(s_t) = (L_{s_1} - 1) + (L_{s_2} - 1) + \dots + (L_{s_t} - 1) = \sum L_{s_i} - t = \text{LS} - t$.

4.2. The analysis of PTAS

Given each $y_q \in \text{OPT}(I)$, let L_q be the length of the stem y_q , $1 \leq L_q \leq n/2$, so the maximum number of stacking pairs for the stem y_q is: $L_q - 1$.

Let $\text{MOP}(y_q)$ be the maximum number of stacking pairs for the stem x_q , then $\text{MOP}(y_q) = L_q - 1$.

If $L_q > l(l > 2)$, we divide the stem y_q with the shorter stem of length l into $\lceil L_q/l \rceil$ segment.

We discuss with two cases as follows:

(a) If $\lceil L_q/l \rceil \neq L_q/l$, so $\lceil L_q/l \rceil = \text{int}(L_q/l) + 1$,

The reduced number of stacking pairs for primary stem x_q is $\text{int}(L_q/l) + 1$

$$\text{So } \text{int}(L_q/l) + 1 < L_q/l + 1.$$

For any stem $x_q \in \text{OPM}(I)$, the number of stacking pairs is more than $L_q - 1 - (L_q/l + 1)$.

$$L_q - 1 - (L_q/l + 1) = L_q - L_q/l.$$

Suppose the approximation scheme is $AS(y_q)$

$$\text{So } AS(y_q) > L_q - L_q/l.$$

Then

$$\begin{aligned} \text{LOP}(y_q)/PT(y_q) &< (L_q - 1)/(L_q - L_q/l) \\ &< L_q/(L_q - L_q/l) \\ &= 1/(1 - 1/l) \\ &= l/(l - 1) \\ &= 1 + 1/(l - 1). \end{aligned}$$

That is, $\text{MOP}(y_q)/AS(y_q) < 1 + 1/(l - 1)$

So we get the results according to the first case:

$$\text{MOP}(y_q)/AS(y_q) < 1 + 1/(l - 1),$$

(b) If $\lceil L_q/l \rceil = L_q/l$, the reduced number of stacking pairs for stem y_q is L_q/l

The number of stacking pairs for the case is

$$(L_q - 1) - L_q/l$$

Suppose the approximation scheme is $AS(y_q)$

$$\text{So, } AS(y_q) = (L_q - 1) - L_q/l$$

We compute the approximation ratio as follows:

$$\begin{aligned} \text{MOP}(y_q)/AS(y_q) &= (L_q - 1)/(L_q - 1) - (L_q/l) \\ &= 1/(1 - L_q/(l(L_q - 1))) \\ &= 1/(1 - (L_q - 1 + 1)/(l(L_q - 1))) \\ &= 1/(1 - (1/l) - 1/(l(L_q - 1))) \\ &< 1/(1 - (1/l) - 1/l) \\ &= 1/(1 - 2/l) \\ &= l/(l - 2) \\ &= 1 + 2/(l - 2) \end{aligned}$$

So, $\text{MOP}(y_q)/AS(y_q) < 1 + 2/(l - 2)$

We get the results according to the second case:

$$\text{MOP}(y_q)/AS(y_q) < 1 + 2/(l - 2), \quad (l > 2)$$

According to (a):

$$\text{MOP}(y_q)/AS(y_q) < 1 + 1/(l - 1)$$

According to (b):

$$\text{MOP}(y_q)/AS(y_q) < 1 + 2/(l - 2)$$

$$2/(l - 2) > 1/(l - 1)$$

According to two cases above, we have

$$\text{MOP}(y_q)/AS(y_q) < 1 + 2/(l - 2)$$

$$\text{Let } \varepsilon = 2/(l - 2)(l > 2)$$

That is, $\text{MGOP}(L_q)/AS(L_q) < 1 + \varepsilon$ ($\varepsilon > 0$)

So we can get the scheme to exist as $1 + \varepsilon$ ($\varepsilon > 0$) PTAS in searching maximum stacking pairs in RNA structure prediction.

5. Types of Pseudoknots Considered in RNA Folding Structure

If a, b are two local minima, then there exists a zigzag path connecting a and b .¹⁴ Reidys provides gfold software that can implement Boltzmann sampling.^{24,25} We can draw the RNA secondary structure with VARNAs,⁸ and the RNA topological structures can be computed.^{25,7} We generalize the RNA-pseudoknotted framework based on BHG and study the differences in predicted folding behavior.¹⁷

For a given RNA sequence S , its energy landscape L is connected. For any base pairs given from secondary structures S_1 and S_2 , $S_1 \in S, S_2 \in S$, there exists a path between S_1 and S_2 , for any two local minimum m_1, m_2 , then there exists a zigzag path connecting m_1 and m_3 . We can define the path as follows: path $P = (v_1, v_2, v_3, \dots, v_k) \in L$, L is the energy landscape structure. If $v_i < v_{i+1} = \dots = v_{n-1} > v_n$, then for any structures $v_{i+1} = \dots = v_{n-1}$ are called peak points. If $v_i > v_{i+1} = \dots = v_{n-1} < v_n$, then for any structures $v_{i+1} = \dots = v_{n-1}$ are called valley points. If a path P fulfills three conditions: (1) $\max f(v_k) = S(x, y)$; (2) if $v_i < v_{i+1} = \dots = v_{n-1} > v_n$, then each v_m with $i + 1 \leq m \leq n - 1$ is a direct saddle separating the nearest valley points that the path P passed before and after v_m ; (3) if $v_i > v_{i+1} = \dots = v_{n-1} < v_n$, then each v_m with $i + 1 \leq m \leq n - 1$, there is a minimal shelf L , we declare the path P is a zigzag path. P can be called BHG, then BHG is connected.

We can generalize the RNA structures with pseudoknots using the BHG and the sampling strategy for local minima. We can create a set for implementing the gradient walk of the class of pseudoknots, it comprises five types of pseudoknots as follows: Type S , Type H , Type K , Type L and Type M . cf. Fig. 6.

Fig. 6. Five types of pseudoknots.

Type *S* refers to structures without pseudoknots

Removing base pairs is relatively simple since they will never result in an invalid structure, the general case involving five types of pseudoknots is rather involved, even with the restriction to structures, with at most one pseudoknot. See Table 1.

Adding base pairs is relatively simple since they will never result in an invalid structure, the general case involving five types of pseudoknots is rather involved, even with the restriction to structures, with at most one pseudoknot. See Table 2.

The paper presents an example named PKB92 of tobacco mild green mosaic virus, we investigate 27 bases with pseudoknots named PK1. Its structure can be correctly predicted with an energy of -4.3 kcal/mol by gfold. cf. Fig. 7.

Table 1. Possible transitions between types of pseudoknots upon removing a single base pair.

Removing	M	L	K	H	S
M	1	1	1	0	0
L	0	1	0	1	0
K	0	0	1	1	1
H	0	0	0	1	1
S	0	0	0	0	1

Table 2. Possible transitions between types of pseudoknots upon adding a single base pair.

Adding	M	L	K	H	S
M	1	0	0	0	0
L	1	1	0	0	0
K	1	0	1	0	0
H	0	1	1	1	0
S	0	0	1	1	1

Fig. 9. (Continued)

According to the principle of the BHG and MFE, the paper provides a path-searching algorithm to connect the graph LM. We investigate the low-energy part of the BHG for PKB92 sequence, the PKB92 is more likely to fold the most stable secondary structure, and refold to form the pseudoknots. We label the LM by “Lx” and

Fig. 10. The secondary structures with pseudoknots based on BHG.

Table 3. Comparison of preAlgorithm algorithm and pknots algorithm.

Sequence	PreAlgorithm Algorithm		Pknots Algorithm	
	Sensitivity	Specificity	Sensitivity	Specificity
Mottle virus	100%	98%	100%	95%
Mosaic virus	89%	97%	90%	96%
Ringspot virus	91%	95%	86%	88%
Sapiens mRNA	72%	81%	63%	67%
Time complexity	$O(n^3)$		$O(n^6)$	
Space complexity	$O(n^2)$		$O(n^4)$	

Table 4. Comparison of preAlgorithm algorithm and ILM, MWM and pknots.

Sequence	ILM		MWM		Pknots		PreAlgorithm	
	Sp%	Sn%	Sp%	Sn%	Sp%	Sn%	Sp%	Sn%
TYMV	82.9	100	63.3	100	96	100	98.9	98.6
Dr7741	96.8	94.5	84.5	91.2	100	100	98.7	99.1
HIV-1-RT	100	100	92.7	100	95.5	100	96.5	99.6
BMV1	84.6	85.4	85.4	87.8	80.4	84.2	97.1	96.3
TMV-3'-up	83.9	81.3	41.6	68.1	59.2	52.1	90.2	89.5
TMV-3'-down	68.5	76.6	51.1	73.6	97.1	97.1	89.3	92.3
HDV	82.5	100	45.3	67.9	75.0	85.8	90.2	89.6
Anti-HDV	66.8	100	38.5	70.9	69.8	95.9	87.1	97.3
Average	82.5	93.8	53.6	83.2	84.6	87.1	91.8	95.9

label the saddles by “Sx”. The paper labels the edges by their energy barriers with [kcal/mol]. Optimal folding pathway of PKB92 sequence based on MFE, and the suboptimal pathways form the stem of pseudoknots which can be drawn in the BHG. Lx, Sx, Saddle points and local minima of the structures are as follows. cf. Fig. 10.

6. Experimental Comparison

The paper selected many sequences of Rfam10.1 and PseudoBase for experiment, and computes the energy value of stems including pseudoknots, according to the energy parameters.^{31,11,29} The polynomial time algorithm can compute RNA-nested structure and pseudoknotted structure in RNA sequences. We randomly picked the RNA subsequence in the Rfam10.1 and PseudoBase to compute the experiment.¹⁹ Many experiments on RNA-pseudoknotted structures indicated that the algorithm has above 83% predicting accuracy averagely. Our algorithm can predict more than 3300 bases of RNA sequences. The predicting accuracy of the algorithm descends with the increasing of the RNA base sequences. We have designed effective ways to improve the prediction accuracy for long sequences.

RNA sequence was generated with bases A,C,G,U, four experiments in family of PseudoBase can be computed in less than 45 seconds with quad-core CPU and 32 G

memory. We have performed experiments, and experiments show that accuracy of these experiments is valuable, the predicting accuracy outperforms existing algorithms, such as MWM algorithm, PKNOTS algorithm, ILM algorithm,^{35,28,21,9} etc. Evolutionary algorithm also provide a kind of important method in the RNA structure prediction.³³ The structural alignment of RNA proves to be a useful computational technique for identifying noncoding RNA (ncRNA).^{32,20} The efficiency of our algorithm is faster than the other related algorithms in the RNA secondary structure and target structure (see Tables 3 and 4).^{33,32,20}

7. Conclusion and Future Work

In this paper, we have presented an efficient algorithm for predicting RNA structure with pseudoknots, and the algorithm takes $O(n^3)$ time and $O(n^2)$ space; the predicting accuracy, the time complexity and space complexity outperform existing algorithms, such as MWM algorithm, Pknots algorithm and ILM algorithm, and the algorithm can predict arbitrary pseudoknots. An $1 + \varepsilon$ ($\varepsilon > 0$) PTAS in searching maximum number of stackings has been presented, and we give the proof of the approximation scheme in RNA-pseudoknotted structure. We have improved several types of pseudoknots considered in RNA folding structure, and analyzed their possible transitions between types of pseudoknots.

It is a good computational method for characterizing the RNA folding structure using BHG.¹⁶ The RNA adopts an unexpected tandem three-way junction structure, and unspliced dimeric genomes are selected by the RNA conformer that directs packaging.¹³

One of the strategies for feature selection that is often applied by brain-computer interface researchers is based on genetic algorithms.²⁶ The fuzzy-rough feature selection and vaguely quantified rough set feature selection are coupled with CLONALG and AIRS for improved detection and computational efficiencies.¹⁸ Interactive segmentation of images has become an integral part of image-processing applications. Several graph-based segmentation techniques have been developed, which depend upon global minimization of the energy cost function. An adequate scheme of interactive segmentation still needs a skilled initialization of regions with user-defined seed pixels distributed over the entire image.⁴ Their algorithm idea is important for our paper in RNA structure prediction.^{26,18,4}

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