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# RNA-RNA interaction prediction using genetic algorithm

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## Abstract

**Background:** RNA-RNA interaction plays an important role in the regulation of gene expression and cell development. In this process, an RNA molecule prohibits the translation of another RNA molecule by establishing stable interactions with it. In the RNA-RNA interaction prediction problem, two RNA sequences are given as inputs and the goal is to find the optimal secondary structure of two RNAs and between them. Some different algorithms have been proposed to predict RNA-RNA interaction structure. However, most of them suffer from high computational time.

**Results:** In this paper, we introduce a novel genetic algorithm called GRNAs to predict the RNA-RNA interaction. The proposed algorithm is performed on some standard datasets with appropriate accuracy and lower time complexity in comparison to the other state-of-the-art algorithms. In the proposed algorithm, each individual is a secondary structure of two interacting RNAs. The minimum free energy is considered as a fitness function for each individual. In each generation, the algorithm is converged to find the optimal secondary structure (minimum free energy structure) of two interacting RNAs by using crossover and mutation operations.

**Conclusions:** This algorithm is properly employed for joint secondary structure prediction. The results achieved on a set of known interacting RNA pairs are compared with the other related algorithms and the effectiveness and validity of the proposed algorithm have been demonstrated. It has been shown that time complexity of the algorithm in each iteration is as efficient as the other approaches.

**Keywords:** RNA secondary structure, Minimum free energy, Fitness function

## Background

Major successes have been achieved in the treatment of some cancers, including colon, breast and pancreatic by suppressing the gene expression involved in the development of these diseases using RNA-RNA interaction. The interaction between two RNAs is known as the newest and the most efficient method for gene silencing. It has been shown that the small interfering RNAs (siRNAs) can be used for silencing their target mRNAs [1]. Furthermore, small RNAs (sRNAs) play an important role in the regulation of gene expression. They usually bind to their target mRNAs to prevent their translation [2].

In RNA-RNA Interaction Prediction (RRIP) problem, two RNA sequences are given as inputs and the goal is to find the minimum free energy Secondary Structure of Interacting RNAs (SSIR). To tackle this problem, some algorithms have been proposed by research groups. Andronescu et al. [3] proposed a method based on dynamic programming in which two RNA sequences are concatenated as a single sequence and its secondary structure is calculated [3]. Another approach calculates the partition function of a secondary structure complex of multiple interacting RNAs [4]. This method rigorously extends those models of secondary structure to the multi-stranded case. The tools such as RNAhybrid [5], UNAFold [6] and RNAduplex from *ViennaRNA package* [7] reduce computational time complexity by ignoring all the internal base pairings in both RNAs. RNAup [8,9] extends the standard partition function approach to RNA secondary structures and employs the single (unpaired) regions on each RNA to find the interaction between them. RNApplex

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In this example, each RNA has one stem. In the left hand RNA, one stem is found by the production of bonding between *CGG* and the reverse *CCG* (*GCC*). There are two hybrid regions between the sequences  $R_1$  and  $R_2$ . The first one is produced by binding between *UUUU* and the reverse *AAAA* (*AAA*). The second one is generated by binding between *GGU* and the reverse *ACC* (*CCA*).

### A new genetic algorithm for RNA-RNA interaction prediction

Genetic algorithm is an optimization method based on evolutionary biology that is widely used to solve search and optimization problems [20-22]. In this section, a new genetic algorithm, GRNAs, is presented to predict RNA-RNA interaction. In the following, initial population, fitness function, crossover and mutation operations are introduced.

#### Initial population

In the proposed algorithm, two RNA sequences  $R' = r'_1 r'_2 \dots r'_n$  ( $|R'| = n$ ) and  $R'' = r''_1 r''_2 \dots r''_m$  ( $|R''| = m$ ) are given as inputs. The two RNAs  $R'$  and  $R''$  are converted to the sequence  $R = r_1 r_2 \dots r_l$  as follows;

$$r_i = \begin{cases} r'_i & 1 \leq i \leq n, \\ r''_{i-n-1} & n+2 \leq i \leq l, \\ N & i = n+1, \end{cases}$$

where  $N$  is an arbitrary character to distinguish between two sequences and  $l = m + n + 1$ .

A dot matrix  $M^R_{l \times l}$  is made, where the axes in the dot matrix correspond to the two sequences  $R$  and reverse  $R$ , as follows;

$$M^R[i, j] = \begin{cases} 1 & \text{if } (r_i, r_{l-j+1}) \in \{(A, U), (U, A), (C, G), \\ & (G, C), (U, G), (G, U)\}, \\ 0 & \text{else,} \end{cases}$$

where  $r_i$  and  $r_{l-j+1}$  ( $1 \leq i, j \leq l$ ) are the  $i$ -th and  $l-j+1$ -th nucleotides in the sequence  $R = r_1 r_2 \dots r_l$ , respectively. Each right-skewed consecutive value of 1's which is parallel to the main diagonal in the dot matrix is selected as a sub-diagonal. Each sub-diagonal shows a possible stem in each RNA or hybrid region between two RNAs. Set  $D^R$  shows all sub-diagonals in the dot matrix as follows;

$$D^R = \{ \langle i, j, t \rangle \mid 1 \leq i \leq l \& 1 \leq j \leq l \& 1 \leq t \leq l-1 \},$$

where  $i$  and  $j$  indicate the start position of the row and the column of a sub-diagonal with  $t+1$  consecutive 1's,

respectively. Hence, each  $\langle i, j, t \rangle$  is a set of consecutive base pairs as follows;

$$\langle i, j, t \rangle = \{ (r_i, r_{l-j+1}), \dots, (r_{i+t}, r_{l-j-t+1}) \},$$

According to the prior knowledge, we know that Watson-Crick base pairs occur more than Wobble in RNA structures. In this regard, we compute the percent of  $G-U$  pairs on our dataset approximated 14%. So,  $G-U$  pairs are removed from the sub-diagonals including more than 14%  $G-U$  pairs. For each  $d_1 = \langle i_1, j_1, t_1 \rangle \in D^R$  and  $d_2 = \langle i_2, j_2, t_2 \rangle \in D^R$ ,  $d_1 \propto d_2$  is defined as;

$$d_1 \propto d_2 = \{ (r_i, r_j) \in d_1 \mid \exists (r_k, r_g) \in d_2, i = kv, j = gv, k = kv, g = gv \},$$

where  $d_1 \propto d_2$  represents all base pairs in  $d_1$  overlapping with  $d_2$ .

For each individual  $P$ , a  $|D^R|$ -tuple is randomly made as;

$$I = \langle x_1, x_2, \dots, x_{|D^R|} \rangle, x_k \in \{0, 1\},$$

where  $x_k$  ( $1 \leq k \leq |D^R|$ ) indicates the  $k$ -th sub-diagonal in  $I$ . In other words, individual  $P$  contains those sub-diagonals that their related  $x$  in  $I$  is equal to 1. Here,  $x_k = 1$  means sub-diagonal  $d_k \in P$ , while  $x_k = 0$  points to  $d_k \notin P$ . Then, the individual  $P$  is constructed as follows;

$$P = \{ C_k \mid x_k = 1, C_k \neq \emptyset \}, \quad (1)$$

where the set  $C_k$  (modified  $k$ -th sub-diagonal) is obtained as follows;

$$C_k = \{ (r_i, r_j) \in d_k \} - \bigcup_{C_t \in P, 1 \leq t \leq k-1} d_k \propto C_t.$$

Here,  $C_k \in P$  is a set of base pairs in  $d_k$  without any common base pairs in the previous sub-diagonals,  $d_t$  ( $1 \leq t < k$ ), of individual  $P$ . Finally,  $C_k$  is modified by removing the lonely base pairs from it as follows;

$$C_k = C_k - \{ (r_i, r_j) \in C_k \mid (r_{i+1}, r_{j-1}) \notin C_k \& (r_{i-1}, r_{j+1}) \notin C_k \}.$$

Notice that a set of the produced individuals creates an initial population.

#### Fitness function

For each individual  $P$ , let  $S$  and  $H$  represent two RNAs secondary structures and binding sites between the two RNAs, respectively. Therefore, the fitness function is defined as follows;

$$Fitness(P) = MFE(S) + MFE(H),$$

where for  $C \in \{S, H\}$ ,  $MFE(C)$  denotes the minimum free energy of structure  $C$ . We apply RNAeval.exe [7] to compute minimum free energies of secondary structures and binding sites separately.

### Crossover

Crossover operation is performed between the individuals with the rate of 0.9. The good and mediocre individuals are transferred to the next population. The remaining individuals are consecutively selected for crossover operation.

Let  $P_1$  and  $P_2$  are selected as parents. For each individual  $P_i$ ,  $1 \leq i \leq 2$ , a  $|D^R|$ -tuple is defined as follows:

$$I_i = \langle x_{i1}, x_{i2}, \dots, x_{i|D^R}| \rangle, \quad x_{ij} = \begin{cases} 1 & \text{if } C_j \in P_i, \\ 0 & \text{else.} \end{cases}$$

In this procedure, a random position  $k$ ,  $1 \leq k \leq |D^R|$ , is selected and  $I_1$  and  $I_2$  are crossed. Then,  $I'_1$  and  $I'_2$  are formed as follows:

$$I'_1 = \langle x_{11}, x_{12}, \dots, x_{1k}, x_{2(k+1)}, \dots, x_{2|D^R}| \rangle, \\ I'_2 = \langle x_{21}, x_{22}, \dots, x_{2k}, x_{1(k+1)}, \dots, x_{1|D^R}| \rangle.$$

In the following, two new individuals  $P'_1$  and  $P'_2$  are generated from  $I'_1$  and  $I'_2$  similar to the described method in the initial population (refers to the Equation 1), respectively.

### Mutation

Mutation operation is done with the rate of 0.1 on a few randomly selected individuals in each generation. Assume that  $P$  is an individual selected for mutation. For the individual  $P$ , a  $|D^R|$ -tuple is obtained by:

$$I = \langle x_1, x_2, \dots, x_{|D^R}| \rangle, \quad x_i = \begin{cases} 1 & \text{if } C_i \in P, \\ 0 & \text{else.} \end{cases}$$

An item  $x_p$ , where  $x_j = 1$  is randomly selected and replaced to 0. Then, another  $x_k$  ( $x_k = 0$ ) is replaced to 1. The new individual,  $P$ , is obtained from the changed  $I$  based on the proposed method in initial population (refers to the Equation 1). Finally, if  $C_k \notin P$  (all the base pairs of  $d_k$  have overlapping with the existence sub-diagonals in  $P$ ), the other  $x_i$  ( $x_i = 0$ ) is selected to replace with 1. This process continues until  $C_k \in P$  or the defined number of generations is reached. When mutation is performed on a number of individuals, they will be increasingly sorted based on their fitness values.

### Termination of the GRNAs algorithm

The GRNAs algorithm terminates when the best individual in definite generations will not be changed or the defined number of generations be reached. After the termination of the algorithm, one of the best individuals is selected as the best folding of two RNAs and the best interaction between the two RNAs.

### Time and space complexity

We have obtained the time and space complexity of GRNAs in each iteration. Making the dot matrix needs the complexity of  $O(l^2)$  where  $l$  exposes sum of the length of the two RNAs. Let  $h$  and  $|P|$  be the number of individuals and the length of an individual  $P$ . The time complexity of creating the initial population is  $O(h \cdot |P|^2)$ . We set  $h = 40$  and  $|P| = \max\{|R^1|, |R^2|\}$ , so  $h$  can be ignored. Sorting individuals based on their fitness values requires  $O(|P| \cdot h \cdot \log h)$ . Crossover and mutation operations take  $O(|P|^2)$  and  $O(|P|)$ , respectively. Thus, the time complexity in each iteration in the proposed algorithm is  $O(h \cdot |P|(|P| + \log h))$ . The maximum number of iteration is at most  $I = 20$ . Therefore, the time complexity of the algorithm is  $O(I \cdot h \cdot |P|(|P| + \log h) + I^2)$  that is simplified with  $O(I^2 + |P|)$ .

On the other hand, for storing the  $h$  individuals of length  $|P|$  we need  $O(h \cdot |P|)$  space complexity. Furthermore, the population in the algorithm uses both dot matrix and an array of sub-diagonals. Hence, the storage complexity of these two types is  $O(l^2)$ , where  $l$  denotes sum of the length of the two RNAs. Thus the total space complexity of GRNAs is  $O(h|P| + l^2)$  which is simplified with  $O(l^2 + |P|)$ .

### Results and discussion

The GRNAs has been performed on a machine with two-Core Intel(R) Duo processor T6670 2.20 GHz and 4 GB RAM to predict the interaction structure between two RNAs. The proposed genetic algorithm is performed on two well-known datasets of RNA-RNA interactions. The first set contains: R1inv-R2inv, Tar-Tar\*, DIS-DIS, CopA-CopT and lncRNA<sub>54</sub>-RepZ in the *Escherichia coli* bacteria [12]. The joint secondary structures of this dataset include kissing hairpins. We evaluate the performance of joint secondary structure prediction of this dataset.

Also, this algorithm is carried on the second set of datasets with their binding sites including some RNA pairs called: DsrA-Rpos, GcvB-argT, GcvB-dppA, GcvB-gltI, GcvB-livK, GcvB-livJ, GcvB-oppA, GcvB-STM4351, IstR-tisAB, MicA-ompA, MicA-lamB, MicC-ompC, MicF-ompF, OxyS-fhlA, RyhB-sdhD, RyhB-sodB, SgrS-ptsG and Spot42-galK [14]. This dataset is used to appraise the performance of RNA-RNA interaction prediction in binding sites.

To evaluate the prediction accuracy of the GRNAs, F-measure ( $F$ ) and Matthews Correlation Coefficient ( $MCC$ ) [18] are calculated using sensitivity ( $Sn$ ) and positive predictive value ( $PPV$ ). Assume that the number of correctly predicted base pairs, the number of false predicted base pairs and the number of unpredicted base pairs are indicated by  $TP$ ,  $FP$  and  $FN$ , respectively. So,  $Sn$ ,  $PPV$ ,  $F$ , and  $MCC$  are defined as follows:

**Table 1 The results of joint secondary structure prediction of GRNAs in MCC in comparison to the PETcofold and other joint structure prediction methods such as RNAcofold, inteRNA, Pairfold and RactIP**

RNA-RNA pairs	GRNAs	PETcofold	RNAcofold	inteRNA	Pairfold	RactIP
MicA-ompA	67	87	80	49	86	57
OxyS-fhlA	60	80	61	64	61	48
RyhB-uof-fur	56	13	21	12	21	19
RyhB-sodB	74	67	65	70	65	65
Average	64	62	57	49	58	47

$$Sn = TP/(TP + FN), \quad PPV = TP/(TP + FP),$$

$$F = (2 \times Sn \times PPV)/(Sn + PPV),$$

$$MCC = \sqrt{Sn \times PPV}.$$

Table 1 shows the results of joint secondary structure prediction of our algorithm, GRNAs, in Matthews Correlation Coefficient [18]. It is also compared to the state-of-the-art methods such as PETcofold [18], the sparsified version of inteRNA [19], Pairfold [3], RactIP

[17] and RNAcofold [7]. The MCC evaluates the joint structure, i.e. both the binding sites between the two RNAs and the secondary structure of each single RNA. In two pairs MicA-ompA and OxyS-fhlA, PETcofold has the best MCC value and in other two pairs RyhB-uof-fur and RyhB-sodB, GRNAs has the highest MCC value.

We also compared GRNAs with four state-of-the-art methods: inRNAs, IntaRNA, RNAup and RactIP. Table 2 shows the results of prediction in binding sites in sensitivity and positive predictive values on the datasets

**Table 2 The results of binding sites prediction of GRNAs in sensitivity and positive predictive value on the datasets [12,14] in comparison to inRNAs, IntaRNA, RNAup and RactIP**

Sensitivity RNA-RNA pairs	PPV					GRNAs	inRNAs	IntaRNA	RNAup	RactIP
	GRNAs	inRNAs	IntaRNA	RNAup	RactIP					
Tar-Tar*	100	100	100	100	81.5	100	83.3	83.3	83.3	57.9
R1inv-R2inv	100	100	100	100	100	100	77.8	100	77.8	100
DIS-DIS	100	100	100	100	75	100	100	100	100	78.3
CopA-CopT	89.47	88.9	100	55.6	100	80.95	82.8	39.1	65.2	100
IncRNA <sub>54</sub> -RepZ	71.44	100	73.8	75	100	100	88.9	85	85.7	83.3
DsrA-Rpos	73.08	80.8	80.8	80.8	65.4	100	77.8	77.8	77.8	73.9
GcvB-argT	87.5	95	95	90	95	100	86.4	95	94.7	100
GcvB-dppA	94.12	100	100	100	94.1	100	85	58.6	45.9	59.3
GcvB-gltI	91.67	75	0	0	100	95.65	50	0	0	100
GcvB-livK	70.83	54	54.2	54.2	95.5	89.47	57	56.5	56.5	95.5
GcvB-livJ	95.45	63.4	95.5	95.5	95.8	95.45	82.4	95.5	95.5	95.8
GcvB-oppA	90.91	100	100	100	100	100	73.3	95.7	95.7	100
GcvB-STM4351	72	76	76	88	88	100	100	90.5	95.7	100
IstR-tisAB	69.44	72.2	87.9	66.7	77.8	100	100	96	100	100
MicA-ompA	93.75	100	100	100	87.5	100	100	100	100	87.5
MicA-lamB	82.61	100	100	82.6	56.5	90.48	100	82.1	70.4	86.7
MicC-ompC	90.91	100	100	72.7	72.7	100	100	53.7	41	88.9
MicF-ompF	100	96	96	80	83.3	100	96	96	95.2	76.9
OxyS-fhlA	80	81.3	50	37.5	56.3	86.96	100	100	100	81.8
RyhB-sdhD	58.82	61.8	58.8	79.4	82.4	95.24	95.5	100	79.4	82.4
RyhB-sodB	100	100	100	100	100	100	100	81.8	90	39.1
SgrS-ptsG	60.87	56.6	73.9	73.9	83.9	87.5	76.5	100	100	100
Spot42-galK	61.36	43.2	40.9	52.3	68.2	87.1	76	64.3	52.3	69.8
Average	84.1	84.5	81.9	77.6	84.7	96.03	86.5	80.5	78.4	85.1



[12,14] using the proposed approach and mentioned methods. Here, only external base pairs are considered to measure accuracy. According to the second half of Table 2, the average positive predictive value on datasets [12,14] is 96.03%. This table shows that our method is comparable with the existing methods. Table 3 indicates the accuracy of GRNAs in F-measure with considering binding sites. In GRNAs, the average F-measure is 89%. The results shown in Tables 2 and 3 indicate that GRNAs works as efficient as the other methods in average sensitivity, positive predictive value and F-measure.

Our genetic algorithm randomly selects the sub-diagonals to make individuals. Therefore different individuals with variety sub-diagonals are constructed. Due to the nature of proposed genetic approach, some of the RNA-RNA interactions can be predicted more accurate than the other algorithms. For example the accuracy rate of Tar-Tar\* is obtained 100%, while maximum accuracy of the other approaches is 90.9%.

We compare the computational time complexity of GRNAs and state-of-the-art methods. The time and space

complexity of several algorithms (TIRNA [15], App (approximation algorithm to predict SSIR) [14], ripalign [23], and other methods in the Tables 1, 2 and 3) are given in Table 4. As it is shown, the time complexity of GRNAs in each iteration is  $O(l^2 + |P|)$ , where  $l$  and  $|P|$  indicate sum of the length of the two RNAs and the length of an individual, respectively. Also, Space complexity of the proposed method is  $O(l^2 + |P|)$ .

## Conclusion

In this paper, a new genetic algorithm was introduced for solving RNA-RNA interaction prediction problem. In this algorithm, all possible stems in each RNA and hybrid regions between two RNAs are extracted from a dot matrix showing all possible base pairs. Initial population is formed based on some stems and hybrid regions of the dot matrix. Minimum free energy is considered as a fitness function. Crossover operation is done between some consecutive individuals in the population. Mutation is taken on a few randomly selected individuals. Population generation continues until the minimum free energy of the best individual becomes minimal enough. Finally, one of the best individuals is selected to form RNA-RNA interaction structure. The proposed algorithm was tested on several RNA-RNA interaction datasets. The experimental results indicate a high accuracy of GRNAs. Furthermore, time and space complexity of GRNAs is as efficient as the other related studies.

## Availability

The program of GRNAs is available at <http://mostafa.ut.ac.ir/grnas>.

**Table 3 The results of binding sites prediction of GRNAs in F-measure on the datasets [12,14] in comparison to inRNAs, IntaRNA, RNAup and RactIP**

RNA-RNA pairs	GRNAs	inRNAs	IntaRNA	RNAup	RactIP
Tar-Tar*	100	90.9	90.9	90.9	67.7
R1inv-R2inv	100	87.5	100	87.5	100
DIS-DIS	100	100	100	100	76.6
CopA-CopT	85	85.7	56.2	60	100
IncRNA <sub>54</sub> -RepZ	82.92	94.1	79	80	90.9
DsrA-Rpos	84.44	79.3	79.3	79.3	69.4
GcvB-argT	93.33	90.5	95	92.3	97.4
GcvB-dppA	96.97	91.9	73.9	62.9	72.2
GcvB-gltI	93.62	60	0	0	100
GcvB-livK	76.07	55.5	55.3	55.3	95.5
GcvB-livJ	95.45	71.7	95.5	95.5	95.8
GcvB-oppA	95.24	84.6	97.8	97.8	100
GcvB-STM4351	83.72	86.4	82.6	91.7	93.6
IstR-tisAB	81.96	83.9	91.8	80	78.5
MicA-ompA	96.77	100	100	100	87.5
MicA-lamB	86.36	100	90.2	76	68.4
MicC-ompC	95.24	100	69.9	52.4	80
MicF-ompF	100	96	96	86.9	80
OxyS-fhlA	83.33	89.7	66.7	54.5	66.7
RyhB-sdhD	72.73	75	74.1	79.4	82.4
RyhB-sodB	100	100	90	94.7	56.3
SgrS-ptsG	71.79	65.1	85	85	85
Spot42-galK	72	55.1	50	52.3	69
Average	89	84.5	79.1	76.3	83.6

**Table 4 Comparison of time and space complexity of some algorithms**

Algorithm	Time complexity	Space complexity
GRNAs	$O(l^2 +  P )$	$O(l^2 +  P )$
TIRNA	$O(k^2 \log k^2)$	$O(k^2)$
SPM	$O(n^3 m^3)$	$O(n^2 m^2)$
LM	$O(n^3 m^3)$	$O(n^2 m^2)$
inRNAs	$O(k^4 w)$	$O(k^2)$
RNAup	$O(n^3 m)$	$O(n^2)$
EBM	$O(n^3 m^3)$	$O(n^2 m^2)$
App	$O(n^3 m^3)$	$O(n^2 m^2)$
Pairfold	$O(k^3)$	$O(k^2)$
IntaRNA	$O(nm + n^3)$	$O(nm)$
ripalign	$O(N^6)$	$O(N^4)$
PETcofold	$O(Ml^3)$	
RactIP	$O(n^5)$	

Here,  $l$  and  $|P|$  indicate the sum of the length of two RNAs and the length of an individual, respectively.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

SM participated in the design of the algorithm, performed the experiments and drafted the manuscript. FZM contributed in the design of the algorithm, performed the experiments, drafted the manuscript and supervised the project. NMC contributed in the design of the algorithm and drafted the manuscript. All authors contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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