Ant Colony with Genetic Algorithm Based on Planar Graph for Multiple Sequence Alignment

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Abstract: Multiple Sequence Alignment (MSA), known as NP-complete problem, is among the most important and challenging tasks in computational biology. For multiple sequence alignment, it is difficult to solve this type of problems directly and always results in exponential complexity. In order to effectively solve the MSA problem, in this study, we present a novel algorithm of ant colony with genetic algorithm (ACG) based on the planar graph representation for MSA. Firstly, the planar graph is described a representation for multiple sequences that took every possible aligning result into account by defining the representation of gap insertion, the value of heuristic information in every optional path and scoring rule for the processes of MSA. Secondly, we use an ant colony with genetic algorithm to find the better path that denotes a better aligning result for multidimensional graph. Experimental results show that ACG could bring about a rise in the quality of MSA when compared with standard Clustal algorithm.

Key words: Multiple sequence alignment, planar graph, ant colony algorithm, genetic algorithm, multidimensional graph, local search

INTRODUCTION

Multiple Sequence Alignment (MSA) of nucleotide or amino acid sequences continues to act a very important role in the advancement of understanding in molecular biology. Sequence alignment can be used to determining evolutionary distances between organisms and infer evolutionary history, discover conserved regions among closely related sequences and improve our understanding and prediction of molecular structures (Gusfield, 1997). Therefore, the MSA problem is of great practical interest to biologists.

However, MSA is of very high computational complexity. It is well-known that MSA problems with sum-of-pairs (SP) score can be solved in $O(n^k)$ steps for k sequences of length at most n via Dynamic Programming (DP) (Sankoff, 1972; Carrillo and Lipman, 1988). The size of the MSA problem space increases dramatically with the number of sequences and their lengths. Moreover, it is known that the MSA problem with SP-score is NP-hard (Wang and Jiang, 1994).

Although, DP can guarantee a mathematically optimal alignment, it can only tackle MSA problems with a small number of short sequences. However, this does not exclude the possibility of developing algorithms that produce near optimal MSA in polynomial time. To align multiple sequences within limited resources, a number of align multiple sequences methods have been developed. Many of them use heuristics to find good alignments (Wallace et al., 2005; Feng et al., 1985; Fogel, 1994).

Though, the progressive alignment methods are faster than DP algorithms, its main disadvantage is the found alignments that may be trapped in local optima, which stems from the greedy nature of this algorithm. This means that if mistakes are made in intermediate alignments, they cannot be corrected later when more sequences are added into the alignment process. Furthermore, there is no objective function to evaluate the performance for multiple sequence alignment.

A number of iterative stochastic approaches have been present to alleviate these problems. For example, evolutionary computation techniques especially Genetic Algorithms (GAs) have been successfully applied to the MSA problem (Notredame and Higgins, 1996; Notredame et al., 1997; Chellapilla and Fogel, 1999; Thomsen et al., 2002; Wallace et al., 2005; Lee et al., 2008). It has shown that they can search large solution spaces more efficiently. Nevertheless, when applying GAs to solve complex problems like MSA, they confronted with the conflict between accuracy and speed, GAs sometimes result in an unsatisfactory compromise, characterized by either low solution quality or low

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274
convergence speed. Furthermore, one of the commonest difficulties frequently encountered is premature convergence (Davis, 1981; Fogel, 1994). Recently, GAs with local search have been considered as good alternatives for solving optimization problems (Zhang and Wong, 1997; Jiao and Wang, 2000). The concept of local search is to find a better candidate nearby the current one before moving to the next stage of search. In the study of Burke and Smith (2000), Merz and Freisleben (2000) and Lee et al. (2003a, b), the genetic algorithm equipped with local search is also referred to as the mimetic algorithm, the genetic local search, the hybrid genetic algorithm, or the cultural algorithm. Studies have shown that the early stages of genetic algorithm in search can fastly converge to the optimal solution, but the GA is powerless in backtracking, when the solution in a certain extent, GA often do a lot of redundant iterations to make accurate demand solution and reduce efficiency. The ant colony algorithm in the initial search due to lack of information elements, make the slow search speed, but when the pheromone accumulated to a certain intensity, the optimal solution has been rapidly increased the speed of convergence.

In this study, we use a representation for the processes of MSA. We called it planar graph (Chen et al., 2009). By this representation, we consider the every possible aligning result. We also defined the representation of gap insertion, the value of heuristic information in every optional path and scoring rule. We also introduced the ant colony with genetic algorithm (ACG) (Lee et al., 2008) to explore and exploit search spaces for MSA. It has both the advantage of genetic algorithms, the ability to find feasible solutions and to avoid premature convergence and that of ant colony algorithm, the ability to search over the subspace and then to move out of local optima.

**THE REPRESENTATION OF MULTIPLE SEQUENCES BY USING PLANAR GRAPH**

**The multiple sequence alignment:** Sequence alignment algorithm is to find the best aligning result based on the scoring function, which can calculate the score of any result. The motive is to find the most similar arrangement of several sequences by inserting some gap '·'. Suppose that a family $S = (s_1, s_2, ..., s_k)$ of $k$ sequences of various length $n_i$ to $n_k$ is given. Each sequence element represents a character from a given alphabet $\Sigma$ (for DNA sequences, the alphabet consists of 4 character of nucleotide, i.e., $\Sigma = \{ A, T, C, G \}$), an MSA of $S$ is a new $k \times n$ matrix of sequences $S' = (s_1', s_2', ..., s_k')$ such that all the strings in $S'$ are of equal length and each $s_i'$ is generated from $s_i$ by inserting gaps, where $s_i' \in \Sigma' = \Sigma \cup \{·\}$. While performing MSA, we evaluated the quality of the alignment by giving it a numerical score. The SP function is the most popular scoring method for MSA in bioinformatics. The goal of general MSA algorithms is to find one alignment with the maximum SP score.

**The expression of sequences by using planar graph:** Multidimensional graphical representation of multiple sequences is the graphic dimension and the number of sequences corresponds. Each dimension represents a sequence. The $n$-dimensional graph can be expressed as an $n$-hypercube (Chen et al., 2009). The $n$-dimensional hypercube graph model can be used to describe the $Q_n$ undirected graph, $Q_n = (V, E)$, where $V$ is point set which describe by using all n-bit binary sequence, denoted as $V = \{x_0, x_1, x_2, ..., x_n | x \in \{0, 1\}, i = 0, 1, ..., n-1\}$. If and only if the binary strings of points $x = x_{n+1} x_{n+2} ... x_0$ and $y = y_{n+1} y_{n+2} ... y_0$ have a different bit, points $x$ and $y$ connected by an edge, $E$ is edge set and is defined as follows:

$$E = \{(x, y) \mid \sum_{i=0}^{n} x_i \oplus y_i = 1, x, y \in V\}$$

Figure 1a and b is a three-dimensional and four-dimensional hypercube graph cell.

We describe the hypercube by using the planar graph, which include the vertexes and their adjacency relationship of the hypercube graph. Figure 2a and b show (Chen et al., 2009) the planar graph, where all the serial numbers of vertexes are the result of binary-coded
Fig. 2: The planar graph cell. (a) The three-dimensional planar graph and (b) the four-dimensional planar graph.

decimal, each dimension of graphics and every edge can be described. The various contacted information in the hypercube graph will be not lost in the planar graph. The information also include all space-diagonal because the diagonal is optional, because in sequence alignment the diagonal direction is optional. At this point it has more easily the alignment meaning.

THE PROPOSED ANT COLONY WITH GENETIC ALGORITHM FOR MSA

After we advanced the representation for multiple sequences we will introduce the method of use some heuristic algorithm to find the better aligning result in such graph. And we give an example of find the best aligning result by three-dimensional graph and Ant colony with genetic algorithm.

Representation: Given three sequences $S_0$, $S_1$, $S_2$ respectively, the length of $m$, $n$, $t$. With three axes, x-axis, y-axis and z-axis, respectively, said they are out of the points in space corresponding to $x$, $y$, $z$ coordinates of the values that they value. And then three-dimensional graphics plane, but that in order to distinguish each point and their coordinates retained. To use $k$ to indicate the direction of the transfer option for each point, $k$ values range: 0, 1, 2, 3, 4, 5, 6; they represent seven different alternative directions. Their corresponding binary code is '000-111'; 0 represent '4', 1 represent characters of character set and three representatives of the corresponding x-axis, y-axis, z-axis; such as '101' characters corresponding to said that x-axis is character, y-axis is gap, z-axis is character.

**Fitness evaluation:** Assume that a scoring matrix $C(a, b)$ is defined to score between any two characters $a$ and $b$ in $\Sigma$ with the following characteristics (Chen et al., 2009):

\[
\begin{align*}
C(a, b) &= +2 & \text{if } (a = b \text{ and } a, b \in \Sigma), \\
C(a, b) &= -1 & \text{if } (a \neq b \text{ and } a, b \in \Sigma), \\
C(a, b) &= -2 & \text{if } (a \in \Sigma, b = \cdot \cdot \cdot \text{ or } b \in \Sigma, a = \cdot \cdot \cdot), \\
C(a, b) &= 0 & \text{if } (a = \cdot \cdot \cdot, b = \cdot \cdot \cdot)
\end{align*}
\]

The score between two rows $s'_i$ and $s'_j$ of an alignment $S'$ is defined as follows:

\[
C(s'_i, s'_j) = \sum_{p \in S'} C(s'_i, s'_j)
\]  

The score of an alignment $S'$, shown in Eq. 2, is defined by the sum of scores between all pair-wise sequences in $S'$:

\[
C(S) = \sum_{i < j \in S'} C(s'_i, s'_j)
\]

The fitness value of an alignment is calculated by Eq. 2. Therefore, the optimization task at hand is defined as a maximization problem, such that matching symbols over columns of an alignment are rewarded and gaps are penalized.

**Heuristic information value:** For each point, the enabling transfer of the seven selectable direction was inspired by the corresponding information value. According to rating function we can be deduced own evaluation rules (Chen et al., 2009). The different types of points in a different direction encountered, are given corresponding to the value of heuristic information. Information value is equal to the sum of its inspired score function value and the absolute value of the minimum score value (negative) and one. Also note that is: these points of the three surface of the cube boundary in the $x = m$, $y = n$, $z = t$ have the only three direction to shift, if you select other four direction, you would be beyond the scope of the cube.
than the formation of erroneous results. In order to avoid into the four directions, the heuristic information value of the directions were assigned to 0.

**State transition rule:** For each point, if these inspired information value in these direction is not 0, these directions are the directions of their transition options. We define the integer variable k as the transition direction and its value 0, 1, 2, 3, 4, 5, 6 are corresponding to the seven directions, the probability formula is as follows, at t moment, in the coordinates (i, j, h) of the point of the ants choose the direction of the probability of k forward (Chen et al., 2009).

\[
P_{ijk}(t) = \begin{cases} 
\frac{\tau_{ijk}^\alpha M_{ijk}^\beta}{\sum_{\text{allowed}} \tau_{ijk}^\alpha M_{ijk}^\beta} & \text{if } k \in \text{allowed} \\
0 & \text{else}
\end{cases}
\]  

(3)

where, \(\tau_{ijk}\) is the k direction of the pheromone, \(M_{ijk}\) represent the direction of the heuristic information value, \(\alpha\) and \(\beta\) is the impact factor of these two parameters. Allowed \(\delta\) is the current point of the direction of the transfer of a collection of alternative, namely those inspired by the information value of the transfer direction is not 0.

**Global pheromone update rule:** Each ant has completed a path for the termination condition is to an end (m, n, l), has completed the score after the rules, by definition, a path for each demand points, update the pheromone according to the following formula (Chen et al., 2009).

\[
\tau_{ijk}^{new} = (1-\rho)\tau_{ijk}^{old} + \Delta \tau_{ijk}
\]  

(4)

\[
\Delta \tau_{ijk} = \sum_{s} \Delta \tau_{ijk}^s
\]  

(5)

\[
\Delta \tau_{ijk}^s = \begin{cases} 
Q \cdot \text{score}(n), & \text{if } (i, j) \in \text{route}(n) \\
0, & \text{else}
\end{cases}
\]  

(6)

Among them, \(\rho\) said the pheromone evaporation coefficient, values range from 0 to 1. Q is a positive number, indicating the distribution of pheromone intensity. The route(n) records the path traversed by the nth ant. The score(n) is the ant paths of the nth ant corresponding to a positive number. It is with this path is proportional to the score values. The w is the number of ants.

**The proposed algorithm:** Ant colony with genetic algorithm for the specific processes described below:

**Step 1:** Set the relevant parameters for the ant colony algorithm and genetic algorithm. Cycles NC = 0, set the maximum cycle number NCmax. Plan the establishment of three sequences. Each vertex of the graph representative of an optional side of the direction of the initial amount of information set to a constant and initialize the pheromone concentration.

**Step 2:** Ant colony algorithm iteration number NC = NC + 1; if the iteration satisfy condition, then the algorithm is ended, otherwise the transfer step 3.

**Step 3:** Placed in the source node w ant, ants, each based on Eq. 3 state transition probability k and the choice of the next path forward; record the walking path.

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**Step 5:** Application of crossover operator and mutation operator to complete the iterative evolution of the genetic algorithm.

**Step 6:** Iterative process of genetic algorithm to get the optimal solution, according to pheromone update (Eq. 4-6) to update the amount of information on each path.

**Step 7:** Check to meet the convergence condition, that is, cycles NC=NCmax if satisfied, then the algorithm is completed and outputs the optimal solution; Otherwise, the return flow step 2.

**RESULTS**

We download three sequences from different data sources, respectively and we make an experiment with the sample mentioned in Table 1 and we compare our aligning result with the result of ClustalX (Wallace et al., 2005) and ACO algorithm in ref (Chen et al., 2009).

The CPU and memory size of my computer are 3.0 GHz and 512 MB, respectively. The values of parameters are list in the following:

\[\alpha = 0.5; \beta = 3; \rho = 0.1;\] the amount of information the initial value of 2.0; \(N_{	ext{max}} = 200.\)

We used the customary and acquiescent parameters of ClustalX.

**Experiment 1:** In the first, we make an experiment with the sample shown in Table 1. Moreover, we compare our aligning result with the result of ClustalX and ACO algorithm.

277
We can compute the scores of the two results based on the Eq. 2 in Table 2. The scores of ClustalX, ACO algorithm and present proposed algorithm (ACG) are 149, 158 and 167, respectively. Obviously, present result has the highest score. Then, we can count the number of column that has three identical letters. There are 28 columns in the result of the ClustalX; there are 29 columns in AOC; there are 31 columns in our result. Obviously, we can see that present result has the highest columns.

**Experiment 2:** In addition, we list the sequence segments of three kinds of species and make an experiment. Table 3 shows the original sequences and the aligning results.

We can compute the scores of the two results based on the Eq. 2 in Table 4. The scores of ClustalX, ACO algorithm and our proposed algorithm (ACG) are 345, 348 and 348, respectively. Obviously, present result has a higher score. Then, we can count the number of column that has three identical letters. There are 59 columns in the

| Table 1: The original sequences for experiment one and the aligning results |
|---|---|
| **Results** | **Sequence** |
| S1 | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| S2 | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| S3 | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| ClustalX | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| S1 | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| S2 | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| S3 | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| AOC algorithm | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| S1 | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| S2 | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| S3 | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| ACG algorithm | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| S1 | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| S2 | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |
| S3 | GGGCCCTGCTACCTGAGACTGAGGAGAACATGATCTGCCTCAGGAGCCAGGTGG |

| Table 2: The comparison of the score and same columns for experiment one |
|---|---|---|
| **Method** | **Score** | **The same columns** |
| AOC | 167 | 31 |
| ClustalX | 149 | 28 |
| AOC | 158 | 29 |

| Table 3: The original sequences for experiment two and the aligning results |
|---|---|
| **Results** | **Sequence** |
| Lenmar | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Gorilla | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Mouse | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| ClustalX | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Gorilla | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Mouse | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| AOC | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Lenmar | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Gorilla | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Mouse | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| ACG | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Lenmar | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Gorilla | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Mouse | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| ACG | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Lenmar | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Gorilla | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |
| Mouse | ATGACTTTGCTGATGCTAGGAGAGATCTGATCTGACCTCTCGAGCCAGAGTCGG |

278
result of the ClustalX; there are 60 columns in AOC; there are 62 columns in our result. From the experimental results, we can see that our result has the highest columns.

Experiment 3: We have downloaded the third exon sequences of beta-globin gene of three species and made an experiment. The original sequences and the aligning results are shown in Table 5.

We can compute the scores of the two results based on the Eq. 2 in Table 6. The scores of ClustalX, ACO algorithm and our proposed algorithm (ACG) are 471, 477 and 471, respectively. Present result has a second score. Then, we can count the number of column that has three identical letters. There are 81 columns in the result of the ClustalX; there are 83 columns in AOC; there are 84 columns in our result. From the experimental results, we can see that our result has the highest columns.

**DISCUSSION**

In present experiments, independent runs of present proposed method, ClustalX and AOC and the statistical
outcome of the optimal fitness in each run are calculated as the results. We measure the score and the number of column with three identical letters (The same column). We compare performance of our proposed method with the two methods through three experiments, the Table 1, 3 and 5 show alignment results of three sequences which were the different source, respectively. Table 2, 4 and 6 show the score value and the same column of alignment results of the three methods in different sources sequences. Table 2 shows the results of the experimental one. From the Table 2, we can see that the score and the same columns of our proposed method are higher than the existing method of ClustalX and the AOC. From Table 4, the second experiment, the score and the same columns of the proposed method are significantly higher than ClustalX, although the score of our proposed method and AOC algorithm is the same, but the same columns of the proposed method are significantly more than AOC.

From Table 6, the third experiment, the score of our proposed method and ClustalX is the same, but the same columns of our proposed method are significantly more than ClustalX. The score and the same columns of our proposed method are significantly higher than ClustalX, although the score of our proposed method is lower than AOC algorithm, but in our method, the same columns are more than AOC. As a whole, our approach is superior to the existing two methods.

CONCLUSION

In this study, we described a new representation for multiple sequences at first. And we use this representation to the MSA. On basis of this representation, we can consider every possible aligning result. We also defined the representation of gap insertion, the value of heuristic information in every optional path and scoring rule. In this kind of multidimensional graph, we use an ant colony with genetic algorithm to find the better path that denotes a better aligning result. In present study, we present the instance of three-dimensional graph and four-dimensional graph and bring forth their multidimensional graph and their planar representation. We advanced a special planar representation to analyze MSA. In the end, we give an example of finding the best aligning result by three-dimensional graph and ant colony with genetic algorithm. Experimental results show that the algorithm can improve the solution quality on MSA benchmarks.

In this study, the proposed ACO algorithm is to enhance the performance of genetic algorithm by incorporating local search, ant colony optimization, for multiple sequence alignment. In the future study, we can enhance the interaction of ants by placing some ants on the end of point. Their tours are from the end to the origin point.

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