Proteins Sequence Alignment with Progressive Strategy based on mutual information

Gamil Abdel-Azim[1,2] , Zaher Abo-Eleneen[3,4] and Mohamed Tahar Ben Othman[1,5]
G. A. Azim, IEEE Member: gazim3@gmail.com , abdaladiem@qu.edu.sa
Z. A. Abo-Eleneen: zaher_aboeleneen@yahoo.com
M.B.Othman, IEEE Senior Member: mothman@gmail.com
College of Computer, Qassim University, Saudi Arabia.[1]
College of Computer & Informatics, Suez Canal University, Ismailia, Egypt [2]
Qassim University College of sciences, Saudi Arabia[3]
College of Computer & Informatics, Zagazig University, Egypt [4]
The EMAT Rresearch Group- Électromagnétisme appliqué et télécommunications-Moncton Université (Canada) [5]

Abstract*—Alignment of biological sequences such as DNA, RNA or proteins is one of the most widely used tools in computational bioscience. One of the important research topics of bioinformatics is the multiple proteins sequence alignment. Since the exact methods for MSA have exponential time complexity, the heuristic approaches and the progressive alignment are the most commonly used in multiple sequences alignments. In the progressive alignment strategy, choosing and merging of the most closely (similarly) sequences is one of the important steps. The information theory provides such a similarity measure using the mutual information (MI). In this paper, we propose a progressive alignment strategy modification based on mutual information. To measure this similarity we define a distance between the sequences based on mutual information, and then we construct a distance matrix. The elements of a row of this matrix correspond the distance between a sequence and all other sequences. A guide tree is built using the distance matrix. We obtain preliminary distance matrix without pairwise alignment in the first step. The principle contribution in this paper is the modification of the first step of the basic progressive alignment strategy i.e. the computation of the distance matrix which yields to a new guide tree. Such guide tree is simple to implement and gives a good result's performance. The results of our testing in all dataset BAliBASE 3.0 data base show that the proposed strategy is as good as Clustalw in most cases.

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Gamil. Abdel Azim was working in the College of Computer, Qassim University, Saudi Arabia and College of Computer & Informatics, Suez Canal University, Ismailia, Egypt. (Corresponding author to provide phone: 00966 509781525 e-mail: Gazim3@gmail.com).
Zaher Abo-Eleneen is with College of Computer & Informatics, Zagazig University, Egypt and College of sciences Qassim University. (e-mail: zaher_aboeleneen@yahoo.com
Mohamed Tahar Ben Othman is Associate Prof. in the College of Computer, Qassim University, Saudi Arabia and a Researcher with The EMAT Rresearch Group- Électromagnétisme appliqué et télécommunications-Moncton Université (Canada) e-mail: mothman@gmail.com

***Index Terms*—** Proteins sequences; Alignment; Progressive methods; Mutual information.

I. INTRODUCTION

Multiple sequence alignment (MSA) of DNA, RNA and proteins sequences is one of the most common and important tasks in Bioinformatics. It is one of the most important and challenging task in computational biology because the time complexity for solving MSA grows exponentially with the size [1]. Finding the optimal alignment of given sequences is known as a nondeterministic polynomial-time (NP)-complete problem [2]. The solution of MSA using dynamic programming requires $O((2^m)^n)$ time complexity (n is the number of sequences, and m is the average sequence length) and O(m n) memory complexity [3-5]. Therefore, carrying out MSA by dynamic programming (DP) becomes practically intractable as the number of sequences increases. Multiple alignment methods can be divided into two main categories: methods aligning sequences over their entire length (global) and methods aligning regions of only high similarity (local). In this paper we focus in global alignment. The fact that the MSA problem is of high complexity has led to the development of different algorithms. In addition, the MSA of proteins sequences offers important tools in studying proteins. This is very useful in designing experiments to test and modify the function of specific proteins, in predicting the function and structure of proteins, and in identifying new members of protein families. The search for the best possible alignment for a set of sequences is not trivial. Finding a global optimal alignment of more than two sequences that include matches, mismatches, and gaps and that take into account the degree of variation in all sequences at the same time is especially difficult. The DP algorithm is used to obtain optimal alignment of a pair of sequences and can be extended to global alignment of three sequences, but for more than three sequences, only a small number of relatively short sequences may be treated. One of the most widely used heuristic searches for multiple sequence alignments is known as progressive technique (also known as tree method). It combines pairwise alignments

beginning with the most similar pair and progressing to the most distantly related, which finally builds up a MSA solution. The basic progressive alignment strategy is summarized in the following (see fig 1):

a) Compute D, a matrix of distances between all pairs of sequences

b) From D, construct a "guide tree" T

c) Construct MSA by pairwise alignment of partial alignments ("profiles") guided by T.

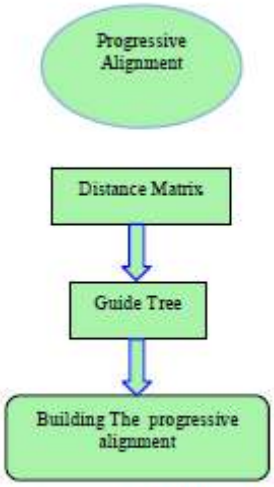


Fig. 1: Progressive Alignment Strategy

Progressive alignments solution cannot be globally optimal. Firstly, the main problem is that any error made at any stage in building the MSA, this error is propagated through to the final result. Secondly, the performance is also particularly bad when all of the sequences in the set are rather distantly related. Progressive alignment methods are efficient enough to implement on a large scale for many (100s to 1000s) sequences. The most popular progressive alignment method has been implemented in the Clustal family [13], especially the weighted variant ClustalW [14]. Some early works on multiple sequence alignment can be found on [15-27]. The guide tree in the basic progressive strategy is determined by an efficient clustering method such as neighbor-joining, or un-weighted average distance (UPGMA).

In this paper we propose a measurement of the similarity between the sequences, which play an important role in the building of the guide tree, then in the performance of the quality of the MSA solution. The measurement of the similarity between the sequences is defined by a new distance between the sequences that is based on mutual information. We obtain preliminary distance matrix without pairwise alignment in the first step.

Our proposed algorithm consists of 3 phases similar to Clustalw. The only different part from Clustalw is how to build distance matrix (see fig 2). The 3 phases are: a) building the Distance Matrix b) calculating the guide tree from the distance matrix using a neighbor joining algorithm [6], and c) processing the progressive alignment. The guide tree defines the order in which the sequences are aligned in the next stage.

There are several methods for building trees, including distance matrix methods and parsimony methods. In this paper, we are using 'neighbor-joining' and un-weighted average methods as distance matrix approach. The sequences are, then, progressively aligned following the guide tree.

The rest of the paper is organized as follows: In the next section, the description of multiple protein sequence alignment is presented. Section 3 will briefly review the existent optimization algorithms and section 4 shows a mutual information concepts and the proposed distance between the sequences. Our algorithm called GEneral Methodology of Progressive Alignments (GEMPA) is decrypted in Section 5 with illustration by examples. The data set and results are discussed in section 6. Finally, concluding remarks and further research to be developed are presented.

II. . PROTEINS SEQUENCES ALIGNMENTS

Let S = $\{S_1, S_2, \ldots, S_n\}$ be the input sequences and assume that n is at least 2. Let $\sum$ be the input alphabet that form the sequences; we assume that $\sum$ does not contain the character '–', which can be used to denote a gap in the alignment. A set S'= $\{S'_1, S'_2, \ldots, S'_n\}$ of sequences over the alphabet $\sum' = \sum \cup \{-\}$, is called an alignment of S if the following two properties satisfied :

1. The strings in S' have the same length.
2. Ignoring gaps, sequence $S_i^{'}$ is identical with sequences S_i.

An alignment can be interpreted as an array with n rows and m columns, one row for each Si. Two letters of distinct strings are called aligned under S if they are placed into the same column. See Figure (1) with three proteins sequences.

$$AP = \begin{bmatrix} A\ R\ N\ -\ D\ C\ Q\ E\ G\ H\ I\ L\ \ M\ F\ -\ W\ T\ W\ Y\ V \\ -\ \ R\ \ -\ N\ D\ C\ Q\ E\ G\ H\ I\ L\ \ M\ F\ S\ -\ T\ W\ Y\ V \\ A\ R\ N\ -\ D\ C\ Q\ E\ G\ H\ I\ L\ \ M\ F\ S\ -\ T\ W\ Y\ V \end{bmatrix}$$

Fig. 1: Example of multiple alignments of three proteins sequences

III. . ENTROPY AND MUTUAL INFORMATION

Information theory [1] provides an intuitive tool to measure the uncertainty of random variables and the information shared by them, in which the entropy and the mutual information are two critical concepts.

The entropy H is a measure of the uncertainty of random variables. Let X be a discrete random variable with alphabet X and $p(x) = P(X = x),\ x \in X$ be the probability mass function, the entropy of X is defined as

$$H(\mathrm{X}) = -\sum_{x \in \mathrm{X}} p(x) \log p(x) \qquad (1)$$

While the mutual information is a measure of information shared by two random variables, defined as

$$I(\mathrm{X},Y) = \sum_{x \in \mathrm{X}} \sum_{y \in Y} p(x,y) \log \frac{p(x,y)}{p(x)\,p(y)}$$

$$= H(Y) - H(Y \mid X), \qquad (2)$$

Where $p(x, y)$ represents the joint probability distribution of X, Y and $p(x)$, $p(y)$ are the marginal distributions of X and Y, respectively and $H(Y \mid X)$ is the conditional entropy of Y in the case of X is known, and can be represented as

$$H(Y \mid \mathrm{X}) = -\sum_{x \in \mathrm{X}} p(x,y) \log p(y \mid x) \qquad (3)$$

For the continuous random variables, the entropy and the mutual information are defined as in (1), (2) and (3) after replaced the summation by integration.

The mutual information is zero if and only if X and Y are statistically independent, i.e. vanishing mutual information does imply that the two variables are independent. This shows that mutual information provides a more general measure of dependencies in the data, in particular positive, negative and nonlinear correlations.

We can compute the mutual information between two variables if we have explicit knowledge of the probability distributions. In general these probabilities are not known. Various methods are used to estimate the probability densities from the observed data. Consider a sequences (SI) and (SJ) of n simultaneous observations of two random variables (SEQUENCES). Since entropy is computed using discrete probabilities, we estimate probability densities using the widely used [30 - 34] histogram method.

Let $\mathrm{f}_{\mathrm{X}}(i)$ denote the number of observations of X falling in the bin a_i. The probabilities $\mathrm{p}(a_i)$ are then estimated as:

$$\mathrm{p}(a_i) = \frac{f_X(i)}{n}$$

Let $\mathrm{f}_{\mathrm{Y}}(j)$ denote the number of observations of Y falling in the bin b_j. The probabilities $\mathrm{p}(b_j)$ are then estimated as

$$\mathrm{q}(b_j) = \frac{f_Y(j)}{n}$$

Let $f_{XY}(i; j)$ denote the number of observations such that X falls in bin a_i and Y falls in bin b_j. Then the mutual information between X and Y is estimated as

$$I(\mathrm{X},Y) = \log n + \frac{1}{n} \sum_i \sum_j f_{XY}(i,j) \log \frac{f_{XY}(i,j)}{f_X(i) f_Y(j)} \qquad (4)$$

IV. . MUTUAL INFORMATION DISTANCE

The definition of a distance measure plays a key role in multiple sequences alignments progressive's algorithms such as ClustalW program. Most algorithms that are progressive depend on guide phylogenetic tree. Which is depend on distance between the sequences

The mutual information between two variables X and Y satisfies the flowing properties:

• MI(X; Y) = MI(Y ;X) symmetric, MI(X; Y) ≥ 0: knowing Y cannot make describing X more difficult and MI(X; Y) = 0 if X, Y are independent. MI is dissimilarity measure. The distance between X and Y is define by

• d(X; Y) = 1 −MI(X; Y)/H(X, Y) is distance (triangle inequality) , where H(X,Y) =H(X)-H(X|Y).

Based on this distance we are calculated the distance between the proteins sequences so the phylogenetic guide tree.

V. EXISTENT OPTIMIZATION ALGORITHMS

There exist three categories of the optimization algorithms for multiple alignment [7]; exact, progressive and iterative. Numerous MSA programs have been applied using many techniques and algorithms. Most commonly used techniques are progressive and iterative techniques. The exact method [1,8] suffers from inexact sequence alignment. Most progressive alignment methods heavily rely on dynamic programming to perform multiple alignments starting with the most related sequences and then progressively adding fewer related sequences to the initial alignment. The existence of several progressive programs has broadened up the aligning techniques. This approach has the advantages of speed and simplicity [7]. They have the advantage of being fast and simple as well as reasonably sensitive. The main drawback is the 'local minimum' problem that stems from the greedy nature of the algorithm. Also the major problem with progressive alignment method is the errors in the initial alignments are the most closely related sequences propagated to the multiple alignments [7]. Algorithms that construct multiple sequence alignment require a cost function as a criterion for constructing an optimal alignment. We are using Gonnet Matrix as a cost function [10].

In this paper, we interested on the progressive technique improvement by proposing a new guide tree based on mutual distance definition.

VI. General Methodology of Progressive Alignments

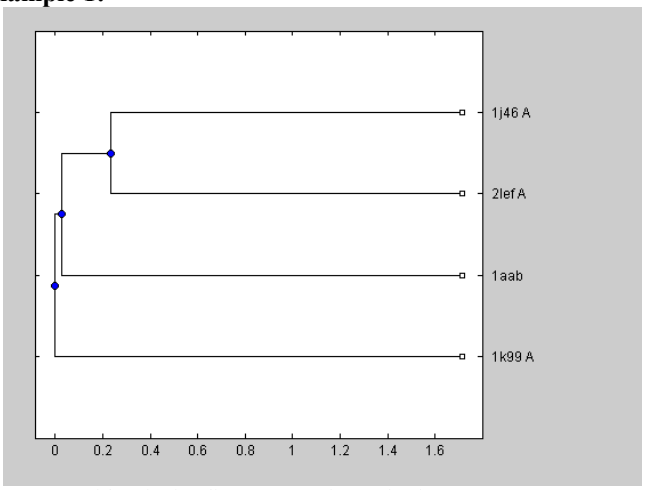
We briefly describe the General Methodology of Progressive Alignments (GEMPA) as following (see fig. 2):

1- Read the set of proteins sequences
2- Construct the distance between all sequences. (Distance Matrix)
3- Build the phylogenetic tree using distance matrix Method
4-Apply the progressive alignment methods with phylogenetic tree.
5- Output the resulting sequence alignment.

Now we will illustrate the GEMPA using two examples, 4 and 9 proteins sequences with minimum length of 390, 385 and maximum length of 456, 457 respectively. First, we calculate the distance matrix, second we build the phylogenetic tree. For each example, the guide trees are built using the proposed mutual distance and the pairwise distance . We are implemented the two guide trees using Matlab functions as following:

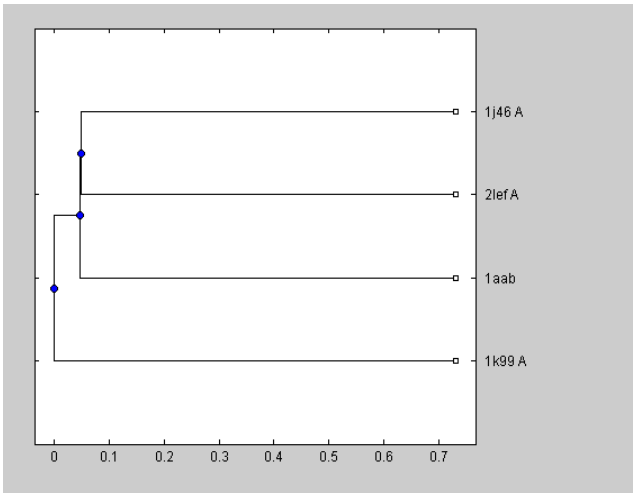
TreePW = seqlinkage (DistancePW,'single',seqs), where seqlinkage is a matlab function, that implements Neighbor-joining algorithm. And, DistancePW = seqpdist (seqs,'ScoringMatrix', pam250), TreePro = seqlinkage (PDM,' single', seqs), where PDM is the proposed distance matrix and seqs are the proteins sequences. (see Figs (4,5)).

Example 1:



TreePW: with Pairwise distance. Scoring Value is 392.6

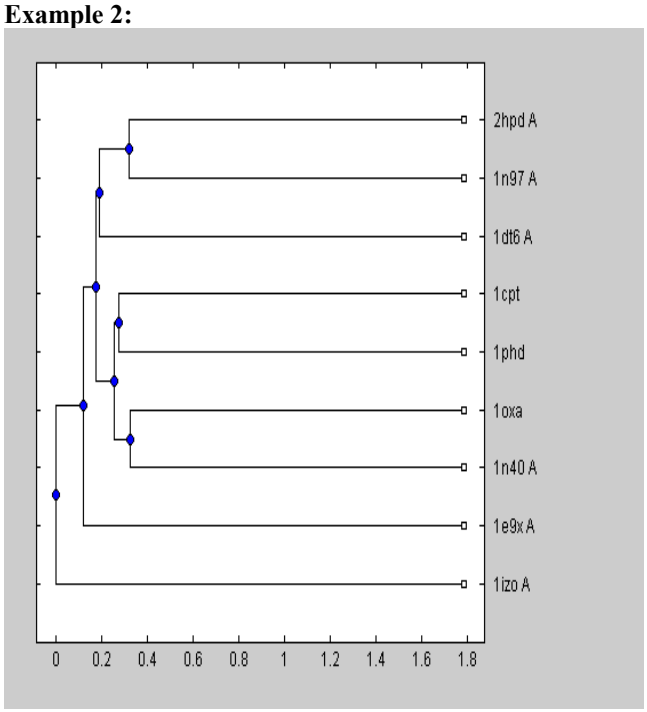
Fig. 2a: TreePW (Example 1 of the data base RV11G)



TreePro with proposed distance. Scoring Value is 392.6

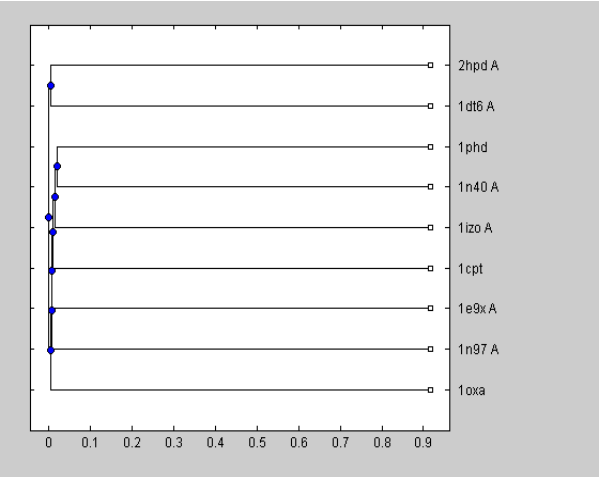
Fig. 3b :TreePro (Example 1 of the data base RV11G)

Example 2:



TreePW: with Pairwise distance.

Fig. 4a: TreePW and TreePro



TreePro with proposed distance
Fig. 5b: TreePW and TreePro

The Scoring Value of the solution alignments using Gonnet matrix is = 2.7752e+003 for Pairwise distance matrix, and is 2.1112e+003 for the proposed distance matrix.

VII. . RESULTS AND DISCUSSIONS

We used the protein database BAliBASE 3.0 for testing our strategy performance. The information concerning the data set taken from the database is summarized as following:

Reference 1: Equi-distant sequences with 2 different levels of conservation.

Reference 2: Families aligned with a highly divergent "orphan" sequence.

RV11: Reference 1, very divergent sequences (20 identities).

RV12: Reference 1, medium divergent sequences (20-40 identity).

RV20: Reference 2. See[9-12]. Also we are comparing the results between the two distances used in progressive algorithm; the progressive algorithm appears to have the best performance in various research papers. It was implemented by multialign in Matlab function with the following options:

PW=multialign (Seqs, TreePW,'ScoringMatrix',{'pam150','pam200','pam250'});

To compare the solutions alignments given by our progressive strategy, this is implemented as following.

Pro=multialign (Seqs, TreePro, 'ScoringMatrix',{'pam150','pam200','pam250'});

Where TreePW and TreePro are Phylogentics guide trees that are built using pairwise distance and Mutual information distance matrix respectively. PW and Pro are alignments solutions obtained using Phylogentic TreePW, and Phylogentic TreePro respectively. Note that the Gonnet scoring matrix is used to measure the two alignments solutions PW and Pro. Figs 6-9 give the comparison between PW and Pro (Solution Alignment Scoring Value) of over the dataset RV11 using different methods such as centroid, compete, Single and weighted with Gonnet substitution matrix.

Table I summarizes the set of figures attached in the appendix for the results of the ClastalW and our strategy using different methods centroid , compete, Single and weighted to build the guide tree with different substitution matrices Gonnet, Pam150, Pam200, and Pam250 over the data set RV11.

Table I: summary of figures for different methods and substitution matrices

Substitution Matrix	Method			
	Centroid	Complete	Single	Weighted
Gonnet	Fig. 6	Fig.7	Fig.8	Fig.9

The obtained results show that for the single method over data set RV11 our strategy is as good as ClastalW in 86% of the examples. Over the data set RV12 and RV20 our strategy is similar than ClastalW. However, using the average method the performance of our strategy is better than ClastalW in some examples and similar over the rest.

VIII. CONCLUSION

The choosing and merging of the most closely (similarly) sequences is one of the important steps in the progressive alignment strategy. A similarity measure based on mutual information distance is used for choosing and merging the sequences. We propose a modified progressive alignment strategy based on a modified distance matrix which is built using mutual information between the sequences. This can be summarized into two steps: 1) find the mutual information between every two sequences and 2) build the guide tree using the distance defined and based on mutual information. We, then, obtain preliminary distance matrix without pairwise alignment in the first step.

The principle contribution in this paper is the modification of the first step of the basic progressive alignment strategy i.e. the computation of the distance matrix which yields to a new guide tree. Such guide tree is simple to implement and gives a good result's performance. The comparison between the proposed strategy and ClastalW is analyzed and the obtained results are reported. The results of our testing on all the dataset show that the proposed strategy obtains good quality solutions. The obtained solutions using the proposed strategy are as good as those obtained by ClastalW.

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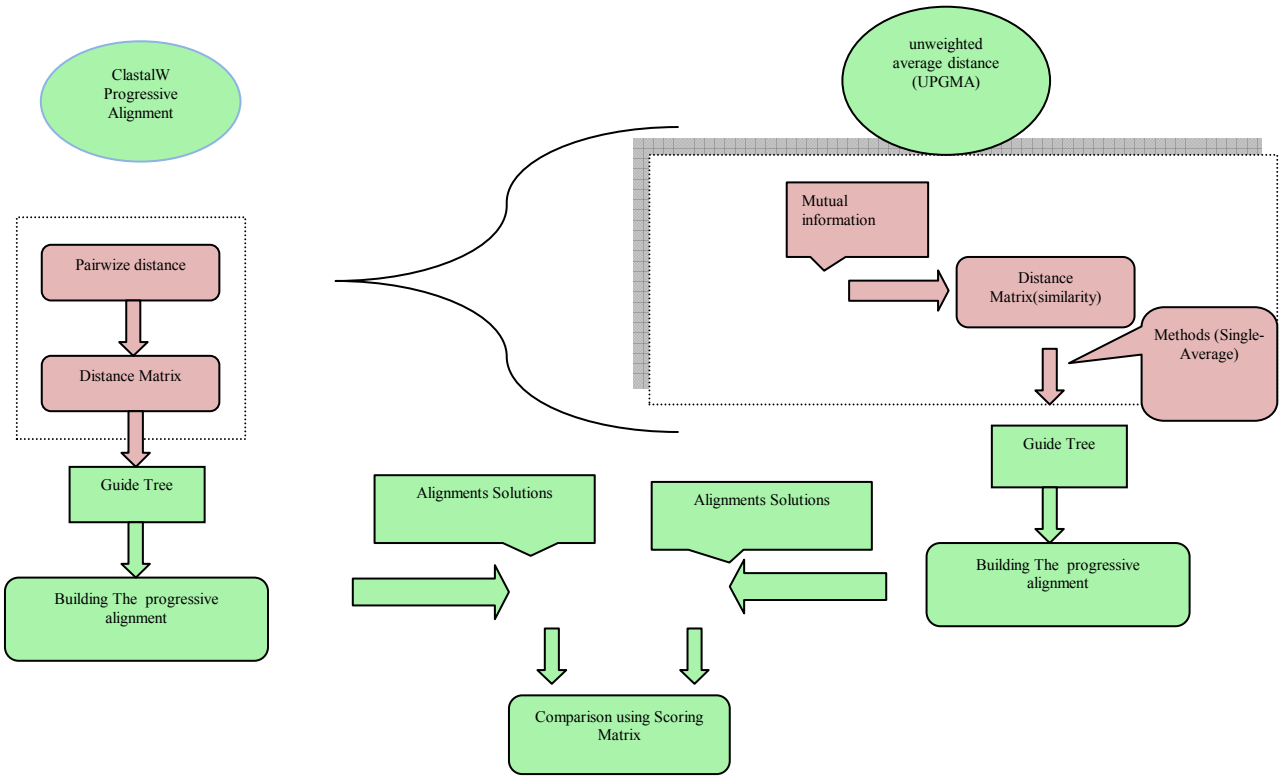

Fig. 6: Proposed Progressive Strategy

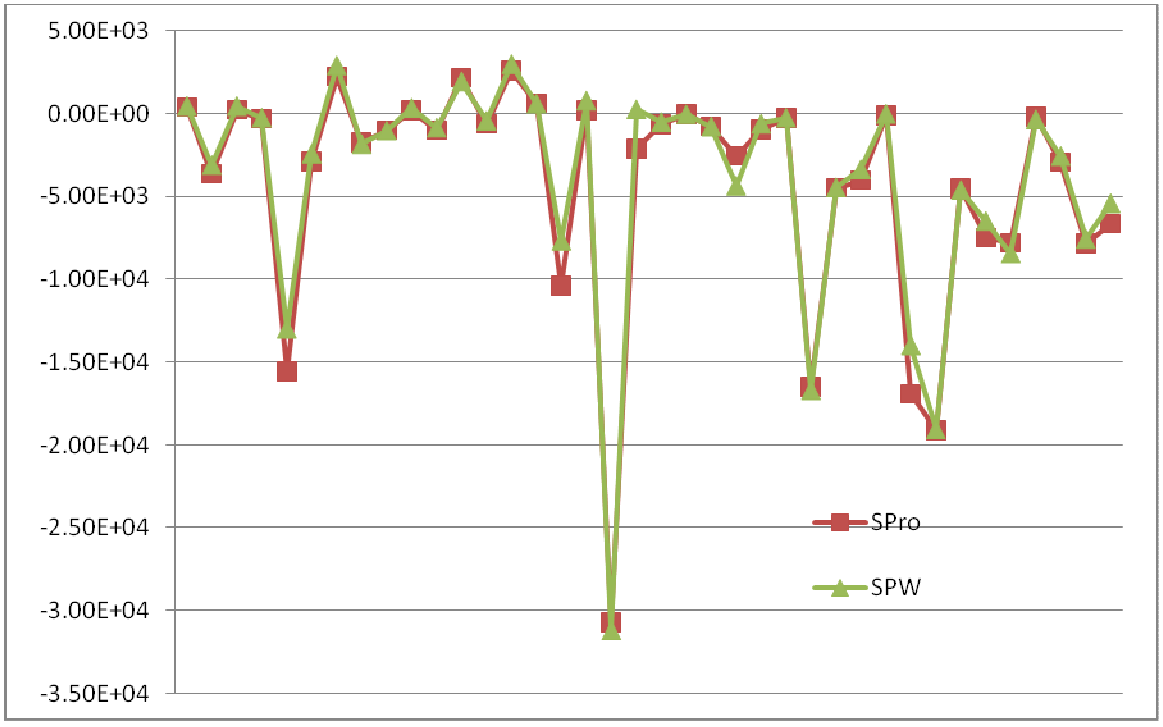

Fig. 7: Performance using centroid_ method Gonnet matrix (1-38 RV11)

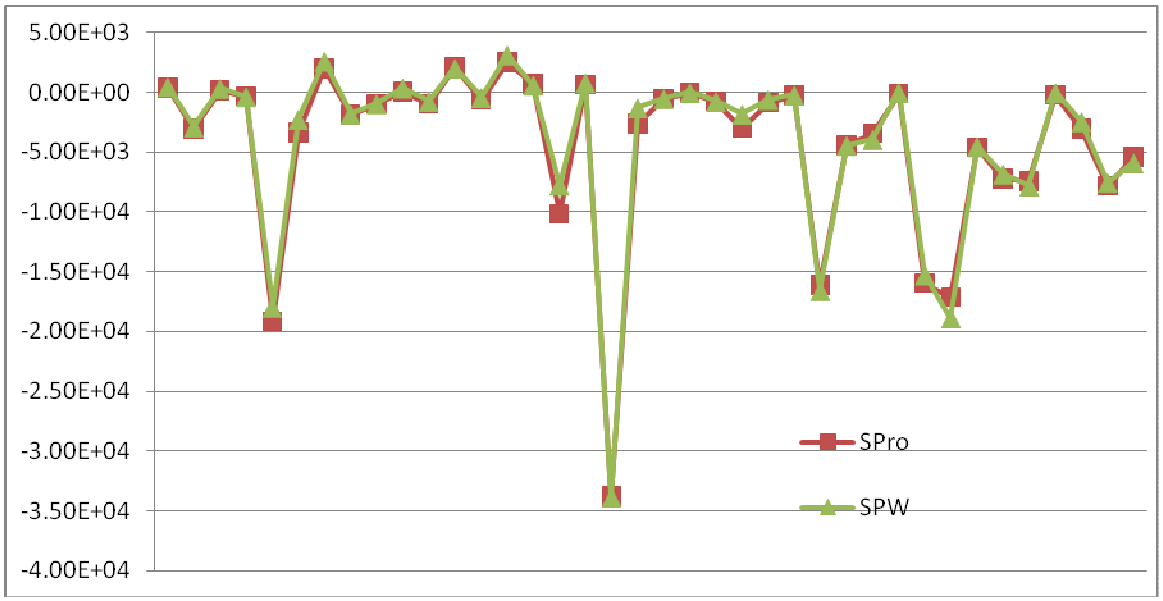

Fig.8: Performance using complete method and gonnet matrix (1-38- RV11)

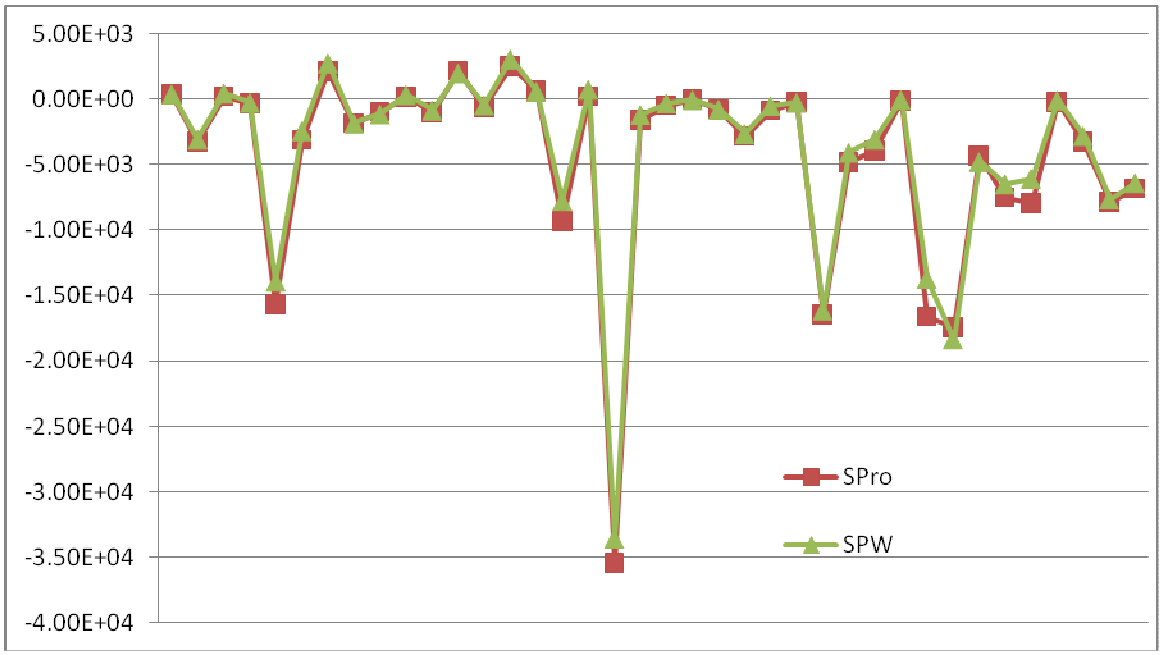

Fig. 9: Performance using single method and gonnet matrix (1-38- of RV11)

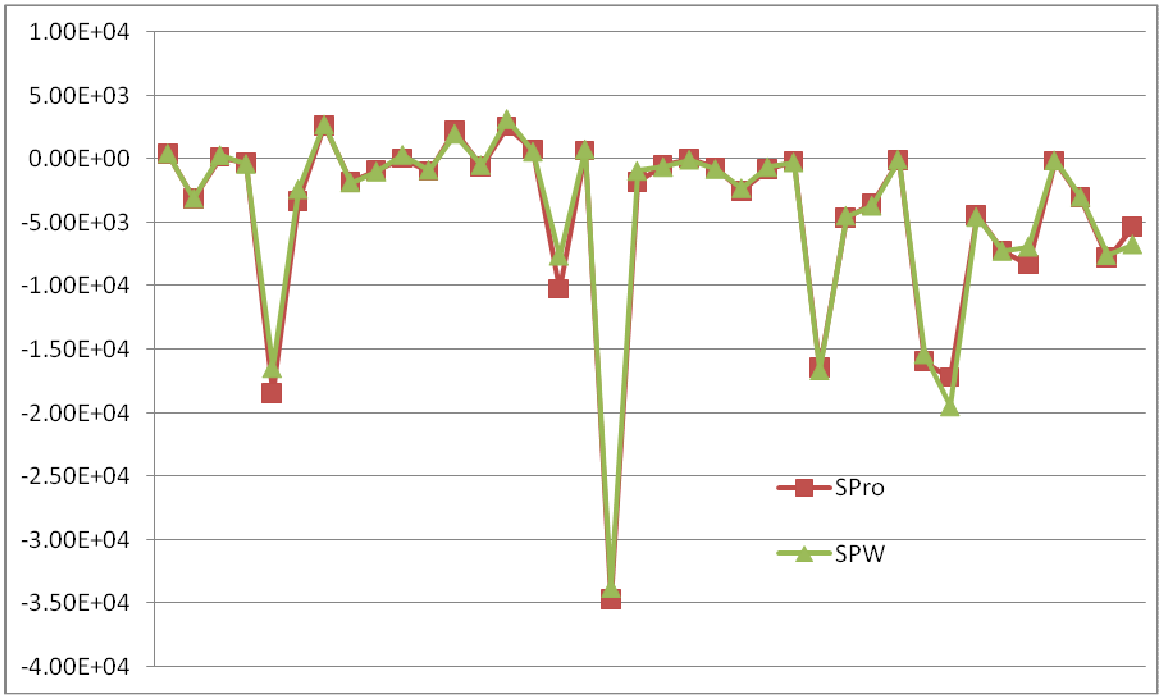

Fig. 10: Performance using weighted method and gonnet matrix (1-38 0f RV11)

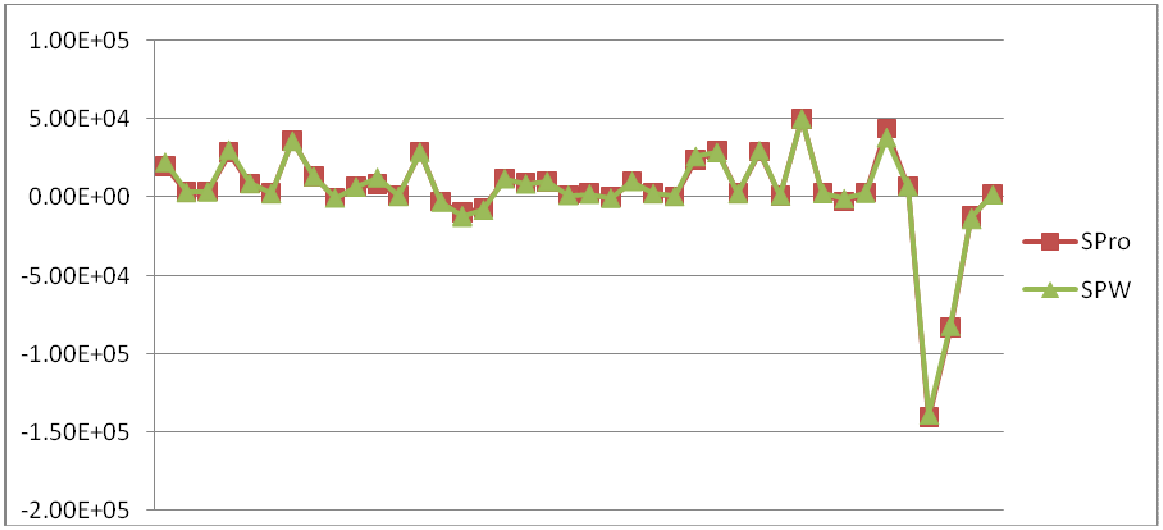

Fig. 11: Performance using single method and gonnet matrix (1-40 0f RV21)

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Dr Gamil Abdel Azim was born in Beni Seuf, Egypt. He received his BSc in Mathematics from Cairo University 1979 and a DEPS (Diplôme des Etudes Pratiques Supérieures) from Poitiers, France. He received MSc. and Ph.D. degrees in Computer Science from Paris Dauphine University, France, in 1988 and 1992, respectively. He worked as Associate Professor in the Department of Computer Sciences, College of Computer and Informatics, Canal Suez University, Egypt. He is currently an Associate Professor at Computer Science Department, Computer College, and Qassim University, Saudi Arabia. His Current research interests include Neural Networks, Combinatorial Optimization, Pattern Recognition, Evolutionary Computation (Genetic algorithms and Genetic Programming), and Bioinformatics. He supervised about 20 BSc student projects. Dr. Gamil is Member of IEEE.

Dr Mohamed Tahar Ben Othman Associate professor, received his Ph.D. in Computer Science from The National Institute Polytechnic of Grenoble INPG France in 1993, His Master degree in Computer Science from ENSIMAG "École Nationale Supérieure d'Informatique et de Mathématiques Appliquées de Grenoble" in 1989. He received a degree of Senior Engineer Diploma in Computer Science from Faculty of Science of Tunis. This author became a Member (M) of IEEE in 1997, and a Senior Member (SM) in 2007. He worked as post-doc researcher in LGI (Laboratoire de Genie Logiciel) in Grenoble, France between 1993 and 1995, Dean of the Faculty of Science and Engineering between 1995 and 1997 at the University of Science and Technology in Sanaa, Yemen, as Senor Software Engineer in Nortel Networks, Canada, between 1998 and 2001 and Assistant Professor in Computer College at Qassim University in Saudi Arabia from 2002 until present. His research interest areas are wireless networks, Adhoc Networks, communication protocols, and bioinformatics.

Dr Abo-Eleneen, Z. A. received the B.Sc., M.Sc. and Ph.D. from Zagazig University, Zagazig, Egypt in 1988, 1994, and 2001,respectively. From 1999 to 2001 he was a Visiting Scholar, University of The Ohio State University, USA. He joined the Faculty of Computers and Informatics at Zagazig University, where he held the position of Associate Professor. His research interests include order statistics, estimation theory, information theory, mathematical modeling, and bioinformatics.