Tools and Algorithms for Protein Structures Comparison with Various Initial Configurations

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Abstract. *Comparison of protein structures provide the opportunity to recognize homology that is undetectable by sequence comparison, and it represents a powerful means of discovering functions, yielding direct insight into the molecular mechanisms. Currently, there are several techniques available in attempting to find the optimal alignment of shared structural motifs between two proteins.*

In this paper, we propose algorithms and develop tools for local alignment between two protein structures by means of local adjustment. In our previous work [18], we show that the trigonometric series approximation is appropriate for estimating the good isometric transformations of one structure and aligning it to the other structure. Based on these results, here we propose algorithms to refine the given alignment by stepwise finding better alignments of the protein pairings using minimum bipartite matching method on geometric distance space and several other adjustment strategies. The proposed methods are used to improve the given initialized alignment of two structures.

Furthermore, we also propose several preliminary initialization algorithms to examine the effectiveness of the proposed local refinement algorithms. We show the effectiveness of the proposed refinement methods and initial algorithm by a set of experiments, which improve several previous results. Furthermore, some of our preliminary result is accessible through the web interface.

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1 Introduction

Protein structures play critical roles in vital biological functions [10]. With more than 59,000 protein structures determined by the advances in X-ray crystallography and NMR spectroscopy to date, molecular biologists these days proceed in the direction of analyzing and classifying these protein structures in order to discover the structural relationships with protein functions [7].

Detection of proteins with a similar fold can suggest a common ancestor, and often a similar function [6]. Comparison of 3D structures makes it possible to establish distant relationships, even between protein families distinct in terms of sequence comparison alone. This is why structural alignment of proteins increases our understanding of more distant evolutionary relationships [3, 13].

There have been several methods proposed to compare protein structures and measure the degree of structural similarity based on alignment of secondary structure elements as well as alignment of intra and inter-molecular atomic distances. The basic ideas are rapid identification of pair alignments of secondary structure elements, clustering them into groups, and scoring the best substructure alignment. For examples, the VAST system [5] is based on continuous distribution of domains in the fold space. The FSSP/DALI system

[12] provides two levels of description – a coarse-grained one and one with a fine-grained resolution. The method, CATH, provides the complete PDB fold classification by domains and links to other sources of information. The two methods, CE and LGscore2 [19] focus on the local geometry rather than global features such as orientation of secondary structures and overall topology (as in the case of VAST or DALI). VAST has been used to compare all known PDB domains to each other. The results of this computation are included in NCBI's Molecular Modelling Database at `http://www.ncbi.nlm.nih.gov/Structure/-VAST/vast.html`.

Note that there must be an atom-pairing scheme before one can do the structure alignment computation. The first atom of the first selection is compared to the first atom of the second selection, fifth to fifth, and so on. Incorporating with ideas of bipartite matching and 3-parameter isometric transformation, Lin *et al.* [14] proposed methods of using parametric searching strategies with adaptive controls, and demonstrated that more accurate and similar protein structure pairings are possible comparing to previous known results like VAST [5] or CE [19].

One of the crucial steps of these algorithms is finding a good isometric transformation, which leads to the best atom-pairing alignment between two proteins. In this paper, we propose algorithms of for efficiently locating more suitable isometric transformations of one structure and aligning it to the other structure. Based upon the periodical property of the parametric settings, we propose parametric searching strategies by approximations with power series and trigonometric series. We show the effectiveness of the proposed parametric searching strategies by a set of experiments, which leads to better alignments of structure pairing in general.

2 Background and Terminology

The main idea of our local refinement algorithm for finding a suitable matching between two sets of points before utilizing the RMSD procedure to fine-tune the final result is by adjusting the suitable parameter sets by ways of searching the underlying parametric space.

Root mean squared deviation

The smallest *root mean squared deviation (rmsd)* is a least-squares fitting method for two sequences of points [12]. The idea is to align atom vectors of the two given (molecular) structures, and use the common least averaged squared errors as a measurement of differences between these two (paired) sequences. Formally, let $P = \langle p_1, \ldots, p_n \rangle$ and $Q = \langle q_1, \ldots, q_n \rangle$ be two sequences of points. We assume that P is translated so that its centroid $(\frac{1}{n}\sum_{k=1}^{n} p_k)$ is at the origin. We also assume that Q is translated in the same way. For each point or vector x, let $(x)_i (i = 1, 2, 3)$ denote the i-th (X, Y, Z) coordinate value of x, and $\|x\|$ denote the length of x. Let

$$\text{RMSD}(P, Q, R, \mathbf{a}) = \sqrt{\frac{1}{n}\sum_{k=1}^{n} \|Rp_k + \mathbf{a} - q_k\|^2},$$

where R is a rotation matrix and $\mathbf{a}$ is a translation vector. Then, the *rmsd* value $d(P, Q)$ between P and Q is defined by $d(P, Q) = \min_{R,\mathbf{a}} d(P, Q, R, \mathbf{a})$. Schwartz [17] showed that $d(P, Q, R, \mathbf{a})$ is minimized when $\mathbf{a} = 0$ and

$$R = (A^t A)^{\frac{1}{2}} A^{-1},$$

where the matrix $A = (A_{ij})$ $i, j = 1, 2, 3$ is given by

$$A_{ij} = \sum_{k=1}^{n} (p_k)_i (q_k)_j,$$

where $A^{\frac{1}{2}} = B$ means $BB = A$, and $\mathbf{o}$ denotes the zero vector. Thus, $d(P, Q)$, R and $\mathbf{a}$ can be computed in $O(n)$ time [15].

We use the the McLachlan algorithm [15] as the RMSD fitting method and write a program in C language to calculate the *rmsd* between C-α atoms of paired protein backbones.

After locating the appropriate suggested points, the minimum bipartite matching algorithm is used to find the best matching between two sets to decide the best matching alignment, which is needed for the RMSD procedure. Let $P' = T \circ P$, and Q being translated to Q' such that the mass center of Q' is located at the origin. We construct a weighed graph $G = (V, E)$ with V being labelled with points of P' and Q', and each (p, q) in E being weighted with the squared Euclidean (3D) distance; i.e., $w(p, q) = \|p, q\|^2$. We then solve the weighted *minimum bipartite matching* problem [9]

to obtain the best matching of P' and Q'. By the matched pairing, we perturb and refine the final alignment to obtain a prosbably lower *rmsd*.

Isometric rotation transformation

According to Euler's rotation theorem [8], any rotation about the origin point can be described by using three angular parameters. The rotation is determined by 3 consecutive rotations with 3 *Euler angles* (α, β, γ). The first rotation is done by the angle α around the z-axis, the second is done by the angle β around the x-axis, and the third rotation is done by the angle γ around the z-axis. See [11] for more detailed discussions about the transformation.

Similar to Euler's rotation transformation, our 3-parameter method (α, β, γ) can be summarized as the following:

- **Rotation around z-axis:**

  Given a unit vector $\mathbf{p} = (x, y, z)^T$, $\mathbf{p}$ is transformed into $\mathbf{p}'$ by a rotation around the z-axis by angle α. That is, let

  $$\mathbf{p}' = \begin{pmatrix} x_\alpha \\ y_\alpha \\ z_\alpha \end{pmatrix} = \begin{bmatrix} \cos\alpha\pi & \sin\alpha\pi & 0 \\ -\sin\alpha\pi & \cos\alpha\pi & 0 \\ 0 & 0 & 1 \end{bmatrix} \cdot \mathbf{p}$$

  Since $\sin\theta = \alpha$ and thus, $\cos\theta = \sqrt{1-\alpha^2}$.

- **Rotation around x-axis:**

  The vector, $\mathbf{p}' = (x_\alpha, y_\alpha, z_\alpha)^T$, is transformed into the probe $\mathbf{p}''$ by a rotation around the x-axis by angle β. That is, let

  $$\mathbf{p}'' = \begin{pmatrix} x_\beta \\ y_\beta \\ z_\beta \end{pmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos\beta\pi & -\sin\beta\pi \\ 0 & \sin\beta\pi & \cos\beta\pi \end{bmatrix} \cdot \mathbf{p}'$$

  then we will get new coordinate of $(x_\beta, y_\beta, z_\beta)^T$.

- **Rotation around the probe $\mathbf{p}''$:**

  The last rotation matrix, R_γ, do the body rotation around the probe $\mathbf{p}''$ by angle γ; see [11] for related discussions about the transformation. That is, let

  $(x, y, z) = (x_\beta, y_\beta, z_\beta)^T$.
  $c = \cos\gamma\pi, s = \sin\gamma\pi, h = 1 - c$.

  $$R_\gamma = \begin{bmatrix} c + x^2h & xyh - zs & xzh + ys \\ xyh + zs & c + y^2h & yzh - xs \\ xzh - ys & yzh + xs & c + z^2h \end{bmatrix}$$

As a result, we reduce the problem of finding the good rotation matrix to the new problem of finding a good 3-parameter setting. The rotation matrix is thus characterized by just adjusting the 3 uniformly distributed parameters.

Minimum bipartite matching

We use the minimum bipartite matching to find the best matching between two sets of points to decide the best matching for the *rmsd* procedure. We adopted the Munkres [16, 2] algorithm. The public available implementation is written with the Perl language. To improve the efficiency of computation, we implement the Munkres algorithm and write hundreds lines of C Codes.

2.1 Parametric adjustment with trigonometric series

In our previous work [18], the trigonometric series estimation method, the three parameters are assumed to be independent. We adjust the three parameters one by one and increase the power of the estimated function. The trigonometric series function is described as the following:

$$\begin{aligned} f(\theta) = C_1 &+ C_2\cos\pi\theta + C_3\sin\pi\theta \\ &+ C_4\cos 2\pi\theta + C_5\sin 2\pi\theta \\ &+ C_6\cos 3\pi\theta + C_7\sin 3\pi\theta + \ldots \\ &+ C_{2k}\cos k\pi\theta + C_{2k+1}\sin k\pi\theta. \end{aligned} \quad (1)$$

where $f(\theta)$ denote the corresponding value of *rmsd* with respect of one of the three parameters, (α, β, γ). The k usually reflects the numbers of local maximal points in the approximated curve.

2.2 VAST

It performs all-on-all structure comparisons using the VAST algorithm. VAST is based on aligning secondary structure elements using an algorithm from the field of graph theory .The output is a neighbors D list. It also contains the complete PDB representative structure comparison structure alignments and a structure superposition tool. The search space for alternative secondary structure elements depends on the length of proteins. All pairs of secondary structure elements (one from each structure) that have the same type are represented as nodes of a graph. Two nodes are connected by an edge

if the distance and angle between the corresponding pairs of secondary structure elements from the two proteins are within some threshold. The graph therefore represents correspondences between pairs of secondary structure elements that have the same type, relative orientation, and connectivity. This correspondence graph is then searched to find the maximal subgraph such that every node in the subgraph is connected to every other node in the subgraph and is not contained in any larger subgraph with this property. This is referred to as clique detection in graph theory and is basis of finding the initial secondary structure alignment. VAST extends this initial alignment to a residue level alignment using a Gibbs sampling [4] technique. VAST places considerable emphasis on defining the statistical significance of an alignment. For each pairwise alignment, the algorithm computes an alignment score as well as a P-value for the best substructure superposition. The P-value assigned to the alignment is calculated as the probability that its score would be seen by chance in drawing secondary structure pairs at random from the database multiplied by the number of possible alternative substructure alignments for the given pair of structures. The program only reports alignments that yield a P-value less than 0.05. A P-value of 0.05 indicates that VAST expects to find an alignment with the same degree of similarity by chance in 5% of all pair-wise comparisons. VAST uses a threshold of 0.05 to limit the noise in the hit lists, thus allowing repeated iterations of double neighboring in Entrez . VAST has been used to compare all known PDB domains to each other. The results of this computation are included in NCBI's Molecular Modeling Database at `http://www.ncbi.nlm.nih.gov/Structure/VAST/vast.html`.

2.3 Initialization by Main Vector Method

The initial method, such as VAST and CE, supports the trigonometric series estimation method to improve the *rmsd* value. A better initial alignment is very important for the trigonometric series estimation method to adjust a better result. Therefore, we try to develop a initial method according to the shape of protein structure. The main vector method is to find a main vector about protein structure in 3-dimension and a second main vector in 2-dimension. We apply the inner and outer product to find the rotation and vertical vector. Let $\mathbf{x}$, $\mathbf{y}$ be two vectors and θ be the included angle of $\mathbf{x}$ and $\mathbf{y}$. We can have $\theta = \cos^{-1} \frac{\langle \mathbf{x} \cdot \mathbf{y} \rangle}{\|\mathbf{x}\| \cdot \|\mathbf{y}\|}$, then we use the outer product to find the vertical vector, $\mathbf{v}$, which is defined as $\mathbf{v} = \mathbf{x} \times \mathbf{y}$, then we use θ and $\mathbf{v}$ to rotate the protein structure. The algorithm is shown in Figure **??**. In this algorithm, we have a first main vector and a second main vector. If we assume $\mathbf{a}$, $\mathbf{b}$ to stand for the two points of first main vector and $\mathbf{c}$, $\mathbf{d}$ to to stand for another. There are totally four possible combinations for them, $(\overrightarrow{\mathbf{ab}}, \overrightarrow{\mathbf{cd}}), (\overrightarrow{\mathbf{ba}}, \overrightarrow{\mathbf{cd}}), (\overrightarrow{\mathbf{ab}}, \overrightarrow{\mathbf{dc}}), (\overrightarrow{\mathbf{ba}}, \overrightarrow{\mathbf{dc}})$. We choose the minimum *rmsd* of them to be the initial rotation. Besides the main vector method, we also use a random initial rotation to execute the trigonometric series estimation method. The experimental results of those two different settings are discussed in next section.

2.4 Initialization by segment alignment

Comparing to the more sophisticated methods like CE or VAST, the main-vector initialization position [18] does have the advantage of saving valuable computation resources. Yet the initial orientation found by the main-vector method does not produce satisfactory final orientation even after the fine-tune procedures. The idea here is trying to find more suitable starting positions and still conserve enough computation time for later adjustment. Since the protein structure is just a chain sequence of atoms, we can subdivide the sequence and use the subsequence matching information to find the better alignment. Thus, the atom chains of a structure is divided into several (consecutive) segments.

Given a list of (consecutive) atoms obtained from the PDB file [1], one way of dividing protein chains of a structure is by using the secondary structural information of the given protein. That is, for the secondary structural partition method, the segments of structures is determined by partition the protein sequence by the secondary structural information of the given protein. Another possible division scheme is obtained by slicing a fixed number of atoms of the given protein. Thus, for the fixed number partition method, the segments of structures is determined by partition the protein sequence by a fixed number of atoms of the given protein.

After the segments of structures is decided, the

segment alignment uses the standard dynamic programming technique to obtain feasible pairings between segments by maintaining a suitable score table. The dynamic programming evaluation function is described as the following:

$$score(s, \lambda) = Ump \cdot \mid s \mid$$
$$score(\lambda, t) = Ump \cdot \mid t \mid$$
$$score(sx, ty) =$$
$$\min \begin{cases} \textsc{Rmsd}(L(s,t) \circ \textsc{Match}(x,y)) \cdot \ell \\ \quad + Ump \cdot (\mid sx \mid + \mid ty \mid -2\ell) \\ score(sx, t) + Ump \cdot \mid y \mid \\ score(s, ty) + Ump \cdot \mid x \mid \end{cases}$$

here λ denotes the empty list; s and t are two prefix segment lists. $L(s,t)$ is the alignment between segment lists s and y, and n_L denotes the number of atoms in L; $\ell = \mid L(s,t) \circ \textsc{Match}(x,y) \mid$.

The recurrence relation for evaluating the value *score* relies on three possible alignments between sx and ty. Here s and t are two prefix *segment lists*, and x and y are the two currently (last) considered segments. The first alignment, L is the pairing list from $L(s,t)$ merging with $\textsc{Match}(x,y)$ which stands for the match between segment x y. Since $\textsc{Rmsd}()$ returns the average precalculated *rmsd* value, the number is multiplied by the number of matched pairs ℓ. However, if one can not find any match for an atom, a given punishment constant, Ump, must be added to encourage most atom be aligned with some atoms on the other sequence. Another possibility is the case of $score(sx,t)$; in that case, the segment y is not able to match with segment on the other list. Thus we need to add in the punishment values for all atoms of the y segment. The case of $score(s,ty)$ is also treated similarly.

3 Methodology

In this section, first we introduce the motivation about why we want to use the local refinement algorithm to find the better list between two proteins. Secondly, we show the initial algorithm according to the structure of protein. The detail experimental result is showed in next section.

3.1 Motivation

In our previous works, the trigonometric series estimation method is used to find a better position in protein structure comparison. Let PA and PB denote two protein structures. The proposed method partitions atoms of a given protein by a fixed length, forming a list of *segments*. By using the dynamic programming technique, the algorithm aligns segments of PA to segments of PB to obtain the initial configuration; then the algorithm proceeds with trigonometric series estimation method to further improve the control parameters of the 3D isometric transformation in order to further refine the final alignment list. We also develop another initial methods, *main vector* as an substitute for the well-known methods, such as the VAST and CE. In the following we introduce the segment alignment initialization algorithm.

3.2 Initialization by New Segment Alignment

Let $A = \{a_1, a_2, a_3 \ldots, a_i\}$ and $B = \{b_1, b_2, b_3 \ldots, b_i\}$ are two list of 3D coordinates of point, and $C = \{c_1, c_2, c_3 \ldots, c_i\}$ are center of gravity of A and B. The p is not match point with segment. $W(p) = \min\{d(p, C_i)\}$ is weight of point p.

$$score(s, \lambda) = Ump \cdot \mid s \mid$$
$$score(\lambda, t) = Ump \cdot \mid t \mid$$
$$score(sx, ty) =$$
$$\min \begin{cases} \textsc{Rmsd}(L(s,t) \circ \textsc{Match}(x,y)) \cdot \ell \\ \quad + \sum_{p \in sx \cup ty \setminus L'} \min_{q \in \textsc{Center}(L')}\{d(p,q)\}) \\ score(sx, t) + \sum_{p \in y} \min_{q \in \textsc{Center}(L)}\{d(p,q)\} \\ score(s, ty) + \sum_{p \in x} \min_{q \in \textsc{Center}(L)}\{d(p,q)\} \end{cases}$$

$L(s,t)$ is the alignment between segment lists s and y, and n_L denotes the number of atoms in L; $\ell = \mid L(s,t) \circ \textsc{Match}(x,y) \mid$.

3.3 Parametric adjustment with trigonometric series

By incorporating with the two key concepts, parameterized-rotation as well as bipartite matching, the main algorithm can compare paired protein structures once given a reasonable good initial setting of the 3 parameters. Since the best parametric settings can be very difficult to locate, our previous methods concentrate on using randomized perturbation method in searching sufficiently large number of parametric probes over the parameter spaces and let each probe searching its own proximity in a randomized greedy manner. It is shown that the underlying corresponding *rmsd*

SEG-ALIG ▷Segment Alignment algorithm

Input: Two segment list of protein atoms, namely $(A[1], A[2], \dots), (B[1], B[2], \dots)$.

```
 1  for i ← 0 to n_s                                  ▷ initiate the table
 2      do score[i, 0] ← Ump · lenAs[i]               ▷ Ump : unmatched penalty
 3  for j ← 0 to n_t
 4      do score[0, j] ← Ump · lenBs[j]
 5  for i ← 1 to n_s
 6      do for j ← 1 to n_t
 7             do L ← L[i − 1, j − 1] ∘ MATCH(i, j)
 8                r ← RMSD(L)
 9                s ← r · n_L + UM(i, j, L)        ▷ n_L = (n_{L_[i−1,j−1]} + n_{M_[i,j]})
10                u ← UM(i, j − 1)
11                l ← UM(i − 1, j)
12                if s ≤ score[i, j − 1] + u and s ≤ score[i − 1, j] + l
13                   then score[i, j] ← s; L[i, j] ← L
14                elseif score[i, j − 1] + u ≤ s and score[i, j − 1] + u ≤ score[i − 1, j] + l
15                   then score[i, j] ← score[i, j − 1] + u; L[i, j] ← L[i, j − 1]
16                else
17                         score[i, j] ← score[i − 1, j] + l; L[i, j] ← L[i − 1, j]
```

UM(i, j, L)

Input: The L is the pairing list.

```
1  D ← A[1, ..., i] ∪ B[1, ..., j] − L
2  C ←COFG(L)
3  p ←UMP(C, D)
4  return p
```

COFG(L) return the center of gravity of L list pairs.

UMP(C, D) return the weight of minimum distance sum of center of gravity C and dropped point set D.

Figure 1: The new segment alignment .

values associated with the parametric sets are related to each other in periodical and *continuous* manner; thus seeking reasonable approximation of the underlying *rmsd* values distributions is possible by some suitable mathematical models, especially by trigonometric series [14].

Here we further improve our previous results and propose an algorithm that further exploit more phases of the trigonometric series estimation methodology. As shown in Figure 2, the algorithm consists of 3 phases. The algorithm first spreads g *guessing points* uniformly over the underlying normalized parameter space ranged $(-0.5, +0.5)$; secondly, the algorithm proceeds with h *estimation points* by trigonometric series estimation function. These $g + h$ phases are repeated over all three parameters searching spaces. Finally, these parametric searching processes are performed by exactly f rounds. Each parametric searching process usually alternates one of these three parameters space; once the isometric transformation is set, the atoms of one protein are transformed and matched (by bipartite matching method) with the other protein. Thus, there are totally $3f(g + h)$ MBM operations performed for the structure alignment refinement algorithm.

4 Experimental Results And Web System

In this section, we introduce the target of experimental data set first. Then we show the difference with dividing protein chains of a structure depends on the different secondary structures of the given protein. Finally, we show the Web enable user can use our system through the network.

4.1 Data Set

We choose the PDB for our experimental sample source, and we randomly pick 14,400 protein structures in the PDB database as our experimental subjects by the uniform distribution sampling out of totally 59,618 protein structures as of 2009. For each chosen protein structures we randomly choose one structure alignments listed on the database of VAST as the tested targets. We use the term, P, to stand for one of the 14,400 randomly picked protein structures, and we use Q to stand for one of the neighbors of each P. Note that P and Q include all un-aligned and aligned atoms. We use the term, PA, to stand for the aligned atoms of P by VAST, and we use PB to stand for one of the neighbors of each PA. Totally, there have 14,400 protein pairings can test by our previous experiment. The distribution of them is shown in Figure 3. In this paper we randomly pick 1,000 protein pairings from 14,400 protein pairings to test our experiment.

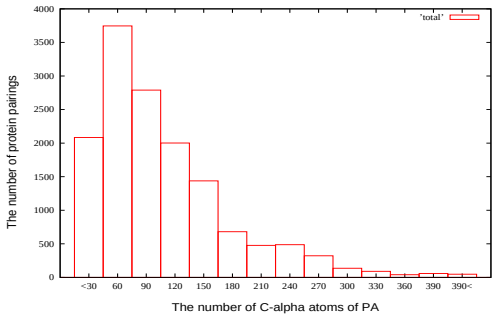


Figure 3: The distribution of the 14,400 randomly picked protein structures in PDB and their one neighbor structures. The total number of protein pairs is 14,400.

4.2 Web System

We make a web system, the *Providence University Protein Structure Comparison Web System*, for users who are interested in our structures comparison system at `http://bioinfo.cs.pu.edu.tw/pupsc.html`. The user of our web service usually provides two protein PDB IDs. We provide three initial methods, and two parametric adjustment methods. Our web system searches and obtains the corresponding PDB data from the Protein data bank database [1] and perform the desired protein structure alignment/comparison using the chosen set of algorithms. To avoid the time delay, our web service provides user access keys for user to check the result later. Users can come back and check the comparison result after the computation is completed by the system servers; parts of our web entry interface are shown in Figure 7.

5 Concluding Remarks

In this paper, we propose algorithms to improve the *rmsd* value between a protein structure pair

STRUC-ALIGN$(P, Q, \alpha_I, \beta_I, \gamma_I, \mathbf{p})$

Input: Two set of 3D coordinates of points $P = \{p_1, p_2, \ldots, p_n\}$ and $Q = \{q_1, q_2, \ldots, q_m\}$; $n < m$.
The α_I , β_I and γ_I are real numbers that are between -0.5 to 0.5.
▷ These inputs control the initial position of 3 parameters box and affect the explored area.
▷ $\mathbf{p}$ is the vector $(x, y, z)^T$, explained in section 2.4.

Output: $(s, \alpha, \beta, \gamma)$ is a sufficiently low RMSD s and (α, β, γ).
▷ (α, β, γ) is the best position of 3 parameters box.

Global : f, g, h, θ_{max}.
The threshold F,G,H are integer numbers.
▷ F is number of uniformly spreading probes.
▷ G is number of adaptively estimating probes.
▷ H is number of adjustment rounds.
θ_{max} is real numbers of control the parametric perturbation variances between -0.5 to 0.5.

```
1  (α, β, γ) ← (α*, β*, γ*) ← (α_I, β_I, γ_I)
2  Q' ← TRANS(Q,ROT-M(α, β, γ, p))        ▷ Q' is a temp array of atoms set of protein.
3  L ← MBM(P, Q') ; (R, a) ←MS-FIT(L, P, Q') ; s* ←RMSD(P, Q', R, a)
4  for t ← 1 to h
5       do for i ← 1 to 3
6            do (θ[1], θ[2], θ[3]) ← (α, β, γ)        ▷Reset parameters θ[i]s.
7               S[1] ← s ; U[1] ← θ[i]
8               for k ← 2 to f + 1        ▷Spreading f probes.
9                    do θ[i] ← U[k] ←RAND(−θ_max, θ_max)
10                      Q' ← TRANS(Q,ROT-M(θ[1], θ[2], θ[3], p))
11                      L ← MBM(P, Q') ; (R, a) ←MS-FIT(L, P, Q') ; s ← S[k] ←RMSD(P, Q', R, a)
                                                  ▷ S is an array to save the rmsd.
12                      if s ≤ s*
13                        then s* ← s ; (α, β, γ) ← (α*, β*, γ*) ← (θ[1], θ[2], θ[3]) ;
14              z ← f + 1
15              for j ← 1 to g/2        ▷Estimating g probes.
16                   do z ← z + 1
17                      θ[i] ← U[z] ←LOWEST(z, U, S)
18                      Q' ← TRANS(Q,ROT-M(θ[1], θ[2], θ[3], p))
19                      L ← MBM(P, Q') ; (R, a) ←MS-FIT(L, P, Q') ; S[z] ←RMSD(P, Q', R, a)
20                      if s ≤ s*
21                        then s* ← s ; (α, β, γ) ← (α*, β*, γ*) ← (θ[1], θ[2], θ[3]) ;
22                      z ← z + 1
23                      (U', S') ←DELMIN(U, S)
24                      θ[i] ← U[z] ←LOWEST(z, U', S')
25                      Q' ← TRANS(Q,ROT-M(θ[1], θ[2], θ[3], p))
26                      L ← MBM(P, Q') ; (R, a) ←MS-FIT(L, P, Q') ; S[z] ←RMSD(P, Q', R, a)
27                      if s ≤ s*
28                        then s* ← s ; (α, β, γ) ← (α*, β*, γ*) ← (θ[1], θ[2], θ[3]) ;
29 return (s*, α*, β*, γ*)
```

MBM(P, Q) returns the minimum bipartite matching of two point sets P and Q.

DELMIN(U, S) returns two arrays U', S' such that the largest element in S, and it's corresponding element.

LOWEST(z, U, S).
Input: The z is number of probes.
The U is an array of angles.
The S is an array of $rmsd's$.
Output: (θ^*)

```
1   for i ← 1 to z
2     Matrix[i][1] ← 1
3     for j ← 1 to (z−1)/2
4       Matrix[i][2j] ← cos(jπU[j]) ; Matrix[i][2j + 1] ← sin(jπU[j])
5   C ←GaussElim(Matrix, S)      ▷The estimated function is f(θ) = C[1] + C[2]cosπθ + C[3]sinπθ + ...
6   θ* ← arg min_{−0.5≤θ≤0.5} f(θ)      ▷f(θ) is the estimated function.
7   return (θ*)
```

RAND(a, b) is a random function returning a real number uniformly distributed between a and b.

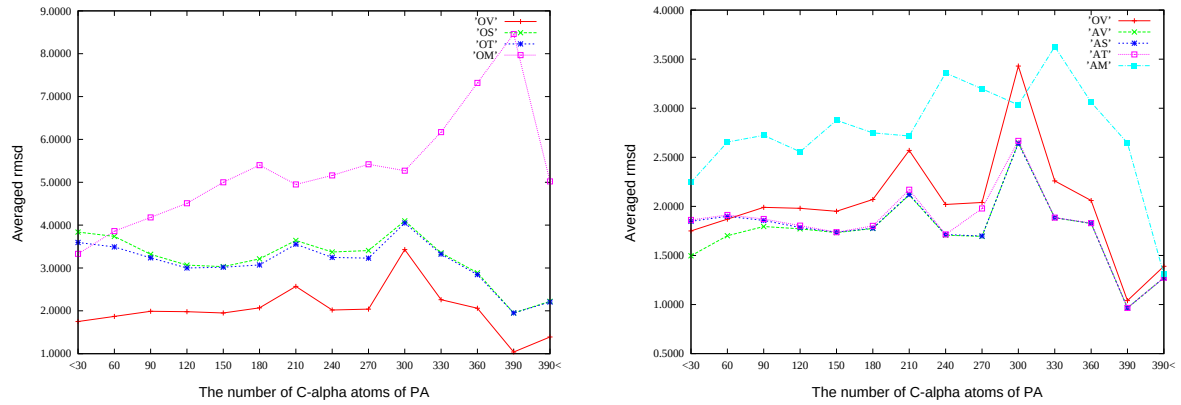
TRANS(A, R).
Input: A is an array of 3D points with size n.
R is the rotation matrix.
Output: An array of 3D points,B.

```
1  for i ← 1 to n do
2        B[i] ← R · A[i]      ▷ B is the array containing the transformed n points.
3  return B
```

Figure 2: Aligning two sets of atoms with low *rmsd* by pairing points according to the minimum bipartite matching measurement .

The number of C-α atom of PA	The numbers of protein pairings	The average *rmsd* after VAST	The average *rmsd* after adjust VAST	The average *rmsd* after adjust Seg-Alig	The average *rmsd* after adjust New Seg-Alig	The average *rmsd* after adjust Main Vector
12-30	161	1.75	1.50	1.85	1.86	2.24
31-60	249	1.87	1.70	1.90	1.91	2.66
61-90	202	1.99	1.80	1.86	1.87	2.72
91-120	143	1.98	1.77	1.78	1.80	2.56
121-150	88	1.95	1.73	1.74	1.74	2.88
151-180	46	2.07	1.77	1.78	1.80	2.75
181-210	41	2.57	2.12	2.12	2.17	2.72
211-240	27	2.02	1.71	1.71	1.71	3.36
241-270	14	2.04	1.69	1.70	1.98	3.20
271-300	10	3.43	2.65	2.64	2.67	3.03
301-330	9	2.26	1.88	1.89	1.89	3.63
331-360	4	2.06	1.83	1.83	1.83	3.06
361-390	3	1.04	0.97	0.97	0.97	2.65
390-1200	3	1.39	1.27	1.27	1.27	1.31
total	1000	1.96	1.73	1.85	1.87	2.65

Table 1: The result is to execute the algorithm of three initial method and VAST. This table show initial method *rmsd* and after adjustment *rmsd*. The unit of *rmsd* values is measured by Angstrom($\mathring{A} = 10^{-8}cm.$).

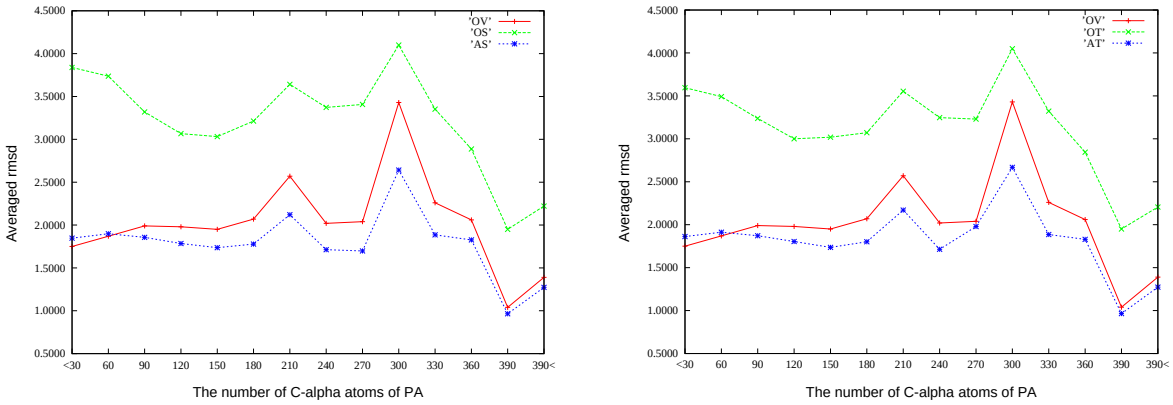


(a) (b)

Figure 4: (a) The average of *rmsd* value for original VAST(OV), original Seg-Alig(OS), original New Seg-Alig(OT), original Main Vector(OM). (b) The average of *rmsd* value for original VAST, adjustment of VAST(AV), adjustment of Seg-Alig(AS), adjustment of New Seg-Alig(AT) and adjustment of Main Vector(AM).

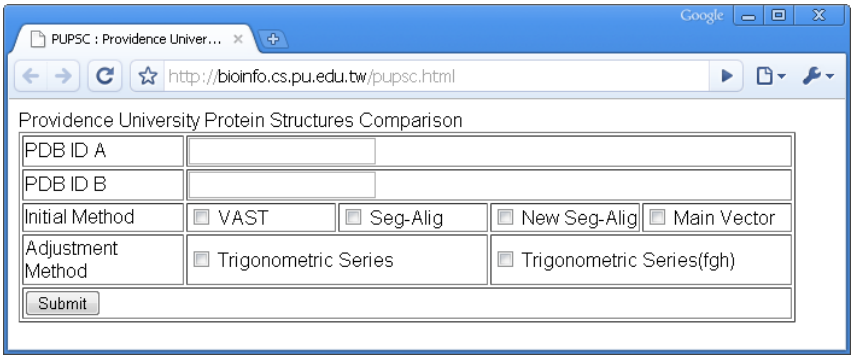
The initial method method	The average *rmsd* after initial method	The average *rmsd* after old trigonometric	The average *rmsd* after new trigonometric
VAST	1.9572	1.7329 (11.46%)	1.7285 (11.69%)
Seg-Alig	3.4563	1.8526 (5.34%)	1.8496 (5.50%)
New Seg-Alig	3.3109	1.8508 (5.44%)	1.8684 (4.54%)
Main Vector	4.2697	2.5907 (-32.37%)	2.6518 (-35.49%)

Table 2: The result is to execute the algorithm of trigonometric series with initial alignment of VAST, Seg-Alig, New Seg-Alig and Main vector. These percentages are express improvement of original Vast.



(a) (b)

Figure 5: (a) The average of *rmsd* value for original VAST(OV), original Seg-Alig(OS) and adjustment of Seg-Alig(AS). (b) The average of *rmsd* value for original VAST, original New Seg-Alig(OT) and adjustment of New Seg-Alig(AT).



(a)

Figure 7: The web window of input and user menu. User submits can get a access key. After the system obtain all analyzed results, user can get the result later on through the use of access key.

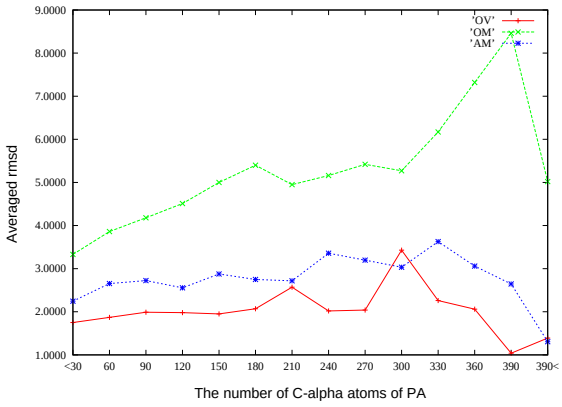


Figure 6: The average of *rmsd* value for original VAST(OV), original Main Vector(OM) and adjustment of Main Vector(AM).

by finding better alignment list. A set of experiments is designed to test the parameters; these adjusted parameters are set to perform the experiments over over a thousand of protein pairs, which are uniformly random sampled from the PDB database. As the results shown that our methods improve the alignment computed by the VAST by an averaged improvement ratios about 11%. The results demonstrate that the method of using 3D Euclidean distance minimum bipartite matching with trigonometric series estimated parametric searching scheme indeed improves existed known system like the VAST. It remains interesting to further explore the underlying best suited parameters for our method.

The experiments show that a good initial rotation is very important before the parametric adjustment. The idea of our segment alignment ini-

tial setting methods is to slice a fixed number of atoms and by matching segments of two structures using the dynamic programming technique; the proposed segment alignment method does obtain feasible starting configurations. It is shown that, by further incorporated with our proposed trigonometric series estimation method, the combined method performs better than the original VAST method by an averaged improvement ratios about 5%. Furthermore, some of our preliminary result is accessible through the our web interface to provide molecular biologists and other bioinformatic researchers the use of our service.

Finally, since the structure comparison problem, like many scientific computation/simulation problem, is very time-consuming under cases of large structures and large number of paired structures, it is desirable to implement the system under massive parallel machines cluster, e.g., the grid-environment, to increase the throughput of the system.

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