Towards Reliable Automatic Protein Structure Alignment

Xuefeng Cui¹, Shuai Cheng Li², Dongbo Bu³, and Ming Li¹ *

University of Waterloo, Ontario, Canada
 City University of Hong Kong, Hong Kong, China
 Chinese Academy of Sciences, Beijing, China

Abstract. A variety of methods have been proposed for structure similarity calculation, which are called structure alignment or superposition. One major shortcoming in current structure alignment algorithms is in their inherent design, which is based on local structure similarity. In this work, we propose a method to incorporate global information in obtaining optimal alignments and superpositions. Our method, when applied to optimizing the TM-score and the GDT score, produces significantly better results than current state-of-the-art protein structure alignment tools. Specifically, if the highest TM-score found by TMalign is lower than 0.6 and the highest TM-score found by one of the tested methods is higher than 0.5, there is a probability of 42% that TMalign failed to find TM-scores higher than 0.5, while the same probability is reduced to 2% if our method is used. This could significantly improve the accuracy of fold detection if the cutoff TM-score of 0.5 is used.

In addition, existing structure alignment algorithms focus on structure similarity alone and simply ignore other important similarities, such as sequence similarity. Our approach has the capacity to incorporate multiple similarities into the scoring function. Results show that sequence similarity aids in finding high quality protein structure alignments that are more consistent with eye-examined alignments in HOMSTRAD. Even when structure similarity itself fails to find alignments with any consistency with eye-examined alignments, our method remains capable of finding alignments highly similar to, or even identical to, eye-examined alignments.

1 Introduction

Proteins function in living organisms as enzymes, antibodies, sensors, and transporters, among myriad other roles. The understanding of protein function has great implications to the study of biological and medical sciences. It is widely accepted that protein function is determined mainly by structure. Protein structures are often aligned for their common substructures, to discover functionally

^{*} Email: mli@cs.uwaterloo.ca

or evolutionarily meaningful structure units. A very large amount of data is available for such studies; the number of known protein structures (the Protein Data Bank) has exceeded 90,000 [1]. Research in structure alignments has intensified recently to enable efficient searches of such databases.

Protein structures are usually modeled as 3-dimensional coordinates of atoms. Thus, the alignment of two protein structures can be modeled as an optimization problem to minimize the distance between two protein structures after a specific rotation and translation. One problem with such comparisons is that the time complexity is typically high. As a result, current methods for the problem are heuristic in nature [2,3,4,5,6,7,8,9,10,11,12].

For example, TMalign [13] creates an initial alignment through sequence and secondary structure alignments and extracts an initial rotation and translation (ROTRAN) accordingly. Then, the ROTRAN is improved iteratively until convergence. This approach suffers from possibly dissatisfactory initial alignments and from a lack of optimality guarantees in the final results. TMalign was improved by the fragment-based approach in fr-TM-align [14], in which local structure alignments are computed and represented by the fragment alignments. A dynamic programming technique is then employed to optimize the score function. However, this method only guarantees the quality of the local alignment rather than of the global alignment.

An alignment of two subsets of residues (or C_{α} atoms) corresponds to a RO-TRAN. Unlike fr-TM-align, we also consider the situation in which the small sets contain remote residues. In addition, to overcome the problem of computational inefficiency, we choose to filter the ROTRANs by clustering rather than by using an exhaustive method.

Experimental results suggest that both local fragments and remote fragment pairs show significant contribution to finding higher TM-scores [15] and to finding higher GDT scores [16], as stated in Sections 3.1 and 3.2, respectively. Specifically, if the highest TM-score found by TMalign [13] is lower than 0.6 and the highest TM-score found by one of the tested methods is higher than 0.5, there is a probability of 42% that TMalign failed to find TM-scores higher than 0.5, while the same probability is reduced to 2% with our method. Our method is also capable of finding alignments with significantly (up to 0.21) higher TM-scores. This could significantly improve the accuracy of fold detection if the cutoff TM-score of 0.5 is used.

Another limitation of current protein structure alignment scoring functions, the TM-score [15] and the LG-score [17], is that only protein structure similarity is taken into consideration, while other important protein similarities, such as sequence similarity, are ignored. It has been observed that many protein structure alignments, based only on protein structure similarity are highly sensitive to conformational changes [18]. Recently, sequence similarity has been incorporated into the scoring function [19,20]. In this paper we introduce a new scoring function incorporating a variety of protein similarities.

In Section 3.3, we demonstrate that sequence similarity enables discovery of high quality protein structure alignments that are more consistent with eyeexamined alignments. Even when structure similarity itself fails to find alignments with any consistency with eye-examined alignments in HOMSTRAD [21], our method is nevertheless able to find alignments highly similar to, or even identical to, the eye-examined alignments. When the aligned protein structures contain a high percentage of helices, TM-score [15] involving only structure similarity sometimes cannot avoid shifting the HOMSTRAD alignment by a few residues. In our experiment, such shifting tends to be avoided by our scoring function, which involves both structure and sequence similarities.

2 Method

Our protein structure alignment search method can be divided into two parts: the search algorithm and the scoring function. In Section 2.1, we describe our search algorithm, which samples and selects near optimal alignments reliably and efficiently. In Section 2.2, we describe our scoring function for evaluating the quality of an alignment accurately.

2.1 Protein Structure Alignment Search Algorithm

Given a protein structure alignment scoring function, finding the optimal alignment involves finding the optimal ROTRAN that maximizes the alignment score. Assume that there exists a near optimal ROTRAN that minimizes the RMSD of two small sets of C_{α} atoms. We find the near optimal structure alignment by sampling ROTRANs in four steps: (1) ROTRANs are initially sampled from local fragment alignments and from remote fragment pair alignments; (2) noise ROTRANs are filtered out by clustering; (3) one representative alignment for each ROTRAN cluster is selected based on alignment scores; (4) the selected alignments are refined by random ROTRAN sampling. Steps one through four are discussed in this section and our scoring function is discussed in Section 2.2.

First, an initial set of ROTRANs must be sampled. Here, the primary concern is to have several good candidates, instead of to have a high signal-to-noise ratio, which is addressed in the next step. Finding good candidates is done by calculating the optimal ROTRAN that minimizes RMSD between one or two fragments from each protein structure. In case of a single fragment from each protein structure, we call it local fragment. In case of two fragments from each protein structure, we call them remote fragment pair. Here, we require the pair of remote fragments to be of the same size and to be at least three residues away from each other to avoid modeling information redundant to the local fragments. In practice, a significantly large number of ROTRANs with the lowest RMSDs are kept for the next step, and the actual number of ROTRANs is selected empirically as stated in Section 3.1.

Since the initial set of ROTRANs may contain a great deal of noise, we try to filter out most of the noise with a star-like k-median clustering algorithm in the second step. Assuming that we know the maximum distance ϵ between the

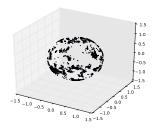
median of a cluster and any member of the same cluster, an approximate clustering is applied using a neighbor graph: each vertex represents a rotation matrix, and two vertices are connected if and only if the distance between them is at most ϵ . For each iteration, the vertex with the highest degree and its neighbors are grouped into a cluster, and are removed from the neighbor graph. The iteration repeats until either there are no vertices of degree higher than one or until the maximum number of clusters is reached. The unclustered ROTRANs are treated as noise. Similar approximate clustering algorithms have been used [22] and studied [23].

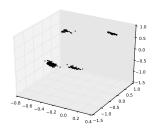
To complete the clustering algorithm, we need a distance function between ROTRANs. The Riemannian distance is a widely used distance metric measuring the length of the shortest geodesic curve between two rotation matrices [24]. Since the transition vector can be calculated by the rotation matrix and the weight centers of the aligned residues, we use Riemannian distances between rotation matrices to avoid using redundant information when clustering ROTRANs.

For each cluster, we find the representative alignment defined by the RO-TRAN that yields the highest alignment score within the cluster. The alignment score is defined in Section 2.2, and is calculated by the Needleman-Wunsch dynamic programming algorithm [25]. Since dynamic programming is computationally expensive, the number of clusters in the previous step must be carefully determined to avoid wasting computation on clusters of noise. After all alignment scores have been calculated, the top scored alignments are selected for the refinement step.

Finally, we refine the selected representative alignments by random ROTRAN sampling. Specifically, for each alignment to be refined, six aligned residue pairs are randomly selected from the alignment, the ROTRAN that minimizes RMSD of the aligned residue pairs is calculated, the alignment score of the alignment defined by the sampled ROTRAN is also calculated, and the previous steps are repeated until there are no improvements after l_1l_2 iterations, where l_1 and l_2 are the number of residues of the two aligned protein structures.

The example shown in Figure 1 demonstrates the efficiency of our protein structure alignment search algorithm, when aligning SCOP domains d3k2aa_and d2cufa1 [26]. In the figure, each coordinate represents a ROTRAN because the coordinate is calculated by applying the rotation matrix of the ROTRAN on the coordinate (1,0,0). By looking at the initially sampled ROTRANs shown in Figure 1(a), we can see that the ROTRANs have a non-uniform distribution, and the ROTRANs with a small number of neighbors are potential noise candidates. After clustering, the four largest clusters include 19% of the initially sampled ROTRANs, as shown in Figure 1(b). Note that the optimal ROTRAN that maximizes the alignment score is located in the largest cluster, which includes 13% of the initially sampled ROTRANs. Therefore, our search algorithm is highly efficient because the alignment score calculation (by the computationally expensive dynamic programming algorithm) for noise ROTRANs is mainly





- (a) ROTRANs initially sampled
- (b) ROTRANs of the four largest clusters

Fig. 1. ROTRANs before and after clustering when aligning SCOP domains d3k2aa and d2cufa1: each ROTRAN is represented by a coordinate that is calculated by applying the rotation matrix of the ROTRAN on coordinate (1,0,0).

eliminated. It is also possible to trade accuracy for speed by reducing the number of sampled ROTRANs and reducing the number of clusters.

Our search algorithm is both efficient and reliable. Since similar protein structures tend to have many local fragments, or remote fragment pairs with small RMSDs, and similar rotation matrices, these rotation matrices tend to form to a large cluster in our method. Since the rotation matrix space is limited and we assume that the maximum distance between two rotation matrices within a cluster is a constant, the maximum number of clusters within the rotation matrix space is limited. This implies that the number of ROTRANs required to accurately identify large clusters is also limited. Therefore, it is only necessary to sample a limited number of ROTRANs, which is sufficient to identify the large cluster containing near optimal ROTRANs.

2.2 Protein Structure Alignment Scoring Function

TM-score [15], based on LG-score [17], is one of the most successful protein structure alignment scoring functions. However, one limitation of TM-score and LG-score is that they use only protein structure similarity while they ignore other protein similarities, such as the sequence similarity. It has been observed that many protein structure alignments, based only on protein structure similarity, are highly sensitive to conformational changes [18]. This suggests the incorporation of other protein similarities, such as the sequence similarity, in the protein structure alignment scoring function. Here, we introduce a new scoring function incorporating variety kinds of protein similarity as follows:

$$S = \frac{1}{L_r} \sum_{i < l} \frac{1}{1 + f_a(D_1(i), D_2(i), \dots, D_n(i))},$$

where L_r is the reference protein size; l is the number of aligned residue pairs of the alignment; f_a is the weighted averaging function (e.g. arithmetic, geometric or harmonic average); $D_k(i)$ is the normalized distance of the i-th aligned residue pair using the k-th distance function; and n is the number of distance functions incorporated. If there is n = 1 and $D_1(i) = (d_i/d_0)^2$, where d_i is the distance between the C_α atoms of the i-th aligned residue pair and d_0 is a normalization factor, our scoring function is identical to the LG-score [17]. If there is also $d_0 = 1.24(L_r - 15)^{1/3} - 1.8$, our scoring function is identical to the TM-score [15]. Thus, LG-score and TM-score are two special cases of our scoring function.

As an initial study on our new scoring function, we focus on the geometric average of the normalized C_{α} distance $D_1(i)$ and the normalized amino acid distance $D_2(i)$ as follows:

$$S = \frac{1}{L_r} \sum_{i < l} \frac{1}{1 + \sqrt[1+w]{D_1(i)D_2^w(i)}},$$

where w is a weighting factor. As with TM-score [15], we define the normalized C_{α} distance as

$$D_1(i) = (\frac{d_i}{d_0})^2,$$

where $d_0 = 1.24(L_r - 15)^{1/3} - 1.8$. Based on the popular BLOSUM62 matrix [27,28], we define the normalized amino acid distance as

$$D_2(i) = 2^{-M(P_i,Q_i)} = 2^{-\lambda \log \frac{P(P_i,Q_i)}{P(P_i)P(Q_i)}} = (\frac{P(P_i)P(Q_i)}{P(P_i,Q_i)})^{\lambda},$$

where M is the BLOSUM62 matrix, (P_i, Q_i) is the i-th aligned residue pair, λ is a scaling factor, $P(P_i, Q_i)$ is the probability of amino acid P_i aligning to amino acid Q_i , and $P(P_i)$ and $P(Q_i)$ are the probabilities of amino acid P_i and amino acid P_i and amino acid P_i respectively. Instead of using the default scaling factor λ , it is treated here as a parameter to control the rate of mutation.

An appealing property shared between TM-score [29] and our scoring function is that the in-favored protein structure alignments tend to have scores higher than 0.5. If the C_{α} distance between the *i*-th aligned residue pair is in-favored, there is $d_i < d_0$ and thus $D_1(i) < 1$. If the amino acid distance between the *i*-th aligned residue pair is in-favored, there is $P(P_i, Q_i) > P(P_i)P(Q_i)$ and thus $D_2(i) < 1$. Then, for the *i*-th aligned residue pair, there is $D_1(i)D_2(i) < 1$ and thus $1/(1+\sqrt[1+w]{D_1(i)D_2^w(i)}) > 0.5$. Therefore, if many in-favored aligned residue pairs occur in the alignment, our protein structure alignment score tends to be higher than 0.5.

3 Result

We included three experiments to demonstrate that the protein structure alignments found by using our method are not only higher scored but are also more consistent with those alignments examed visually by human-beings. In Section 3.1, we compared our search algorithm to current state-of-the-art search algorithms, TMalign [13] and fr-TM-align [14], to demonstrate that our method tends to find alignments with higher TM-scores [15]. In Section 3.2, we compared our search algorithm to SPalign [30] to demonstrate that our method tends to find alignments with higher GDT scores [16]. In Section 3.3, we compared our scoring function to TM-score [15] to demonstrate that our method tends to find alignments more consistent with the eye-examined alignments in HOMSTRAD [21].

3.1 Search Algorithm Evaluation on TM-score

To demonstrate reliability, we repeated the alignment experiment for the 200 non-homologous protein structures, which have sizes of between 46 and 1058, have a sequence identity cutoff of 30%, and are used by TM-align [13]. We compared our results with that of current methods, TM-align and fr-TM-align [14]. Here, we used TM-score [15] normalized by the smaller protein size as the scoring function. Since fr-TM-align does not support normalization by the smaller protein size, TM-score normalized by the smaller protein size is calculated based on the rotation matrix returned by fr-TM-align. Since biologists tend to be more interested in similar protein structures within the same protein fold, and the

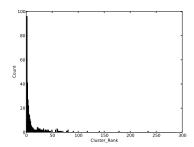
TM-score of 0.5 is a good approximate threshold for protein fold detection [29], only the 350 protein structure alignments with TM-scores higher than 0.5 (found by at least one of the tested methods) are included in this analysis.

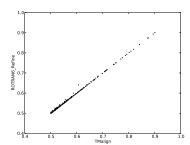
For the experiment settings in the algorithm described in Section 2.1, we used local fragments of size 12, and remote fragment pairs of size 3. Such experiment settings are called L12R3align. To study the contributions of using local fragments and using remote fragment pairs, we simplified our method to two variants: L12align, that used only local fragments of size 12, and R3align, that used only remote fragment pairs of size 3. For consistency, we selected 1,536 local fragments of size 12 and 1,536 remote fragment pairs of size three in the sampling step, used $\epsilon = 10^{\circ}$ in the clustering step, stopped clustering when 288 clusters were found, and selected eight clusters in the refinement step in all experiments for this section. With L12R3align, the elapsed time required to finish this experiment was approximately 4.5 hours on a computer with dual Intel Xeon X5660 2.8GHz CPUs and dual Nvidia GeForce GTX 670 GPUs. Thus, each pairwise alignment took approximately 0.8 seconds on average.

First, we would like to evaluate the ROTRAN filtering step described in Section 2.1. Figure 2(a) shows the cluster rank that contains the optimal ROTRAN with the highest TM-score [15]. Here, we focus on the results of using local fragments because the results of using remote fragment pairs draws similar conclusions. Specifically, 28% of the optimal ROTRANs are from the largest cluster and 72% of the optimal ROTRANs are from the largest ten clusters. Moreover, only 1% of the optimal ROTRANs are not from the largest 100 clusters. This demonstrates that the optimal ROTRAN tends to have many similar ROTRANs that minimize the RMSD of local fragment alignments, and that these ROTRANs tend to form a large cluster, which can be identified easily by clustering the sampled ROTRANs.

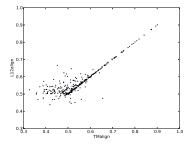
Next, we will demonstrate that our refinement step using randomly selected ROTRANs, as described in Section 2.1, is able to consistently find protein structure alignments with similar or higher TM-scores [15]. Figure 2(b) shows the TM-score before and after refining the optimal alignment found by TMalign [13]. It can be seen that the TM-scores are mostly similar, while our refinement occasionally improves the TM-score by up to 0.10. Specifically, after refinement, all TM-scores are at most 0.0029 lower, while 3% of the TM-scores are at least 0.01 higher. Recall that the random ROTRANs used in the refinement step are generated by finding the ROTRAN that minimizes the RMSD of size randomly selected aligned residue pairs from the alignment. Thus, this result also verifies our assumption that there exists a near optimal ROTRAN that minimizes the RMSD of two small sets of C_{α} atoms.

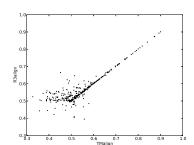
To support our choices of local fragment size and of remote fragment pair size, the highest TM-scores found by L12align and R3align are compared to those found by TMalign in Figures 2(c) and 2(d), respectively. For protein structure pairs that have TMalign TM-scores higher than 0.6, both L12align and R3align can reliably find high quality alignments with similar TM-scores. For the other protein structure pairs, both L12align and R3align tend to improve TM-scores,



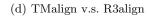


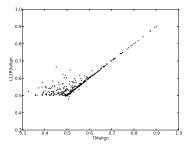
(a) Cluster rank containing the optimal (b) TM-score before and after refine-ROTRAN $\,$ ment

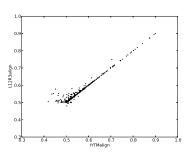




(c) TMalign v.s. L12align







although there may be some reductions of TM-scores. This demonstrates that both L12align and R3align are capable of finding high quality alignments that are comparable to or even better than those found by TMalign. In fact, the local fragment size of 12 has also been used by fr-TM-align [14].

The improvements of TM-scores found by L12R3align over those found by TMalign are shown in Figure 2(e). We see that TM-scores found by L12R3align are mainly higher than those found by TMalign for the 284 protein structure pairs that have TMalign TM-scores lower than 0.6. Specifically, L12R3align improves TM-scores by 0.03 on average and by 0.21 in the best case. Moreover, 14% of the TM-scores are improved by at least 0.1, 30% of the TM-scores are improved by at least 0.05, and only 2% of the TM-scores are reduced by at most 0.03. Comparing to Figures 2(c) and 2(d), the number of TM-scores found by our method that are lower than those found by TMalign is significantly reduced using both local fragments and remote fragment pairs.

If the highest TM-score found by TMalign is lower than 0.6 and the highest TM-score found by one of the tested methods is higher than 0.5, there is a probability of 42% that TMalign failed to find TM-scores higher than 0.5. In such cases, L12R3align tends to discover better protein structure alignments with (possibly significantly) higher TM-scores, with a probability of only 2% that L12R3align failed to find TM-scores higher than 0.5. This could significantly improve fold detection results. Interestingly, L12R3align tends to improve TM-scores more for α -proteins, while never reduces TM-scores for β -proteins.

In addition to comparison with TMalign, the TM-scores found by L12R3align are also compared with those found by fr-TM-align [14] as shown in Figure 2(f). Note that TM-scores found by L12R3align are also mainly higher than those found by fr-TM-align for protein structure pairs that have fr-TM-align TM-scores lower than 0.6. Specifically, L12R3align improves TM-scores by up to 0.13, while it reduces TM-scores by at most 0.02. Moreover, L12R3align finds 28 more TM-scores that are higher than 0.5.

3.2 Search Algorithm Evaluation on GDT Score

In addition to TM-score [15], GDT [16] score is also one of the most popular protein structure alignment scoring function [31]. Thus, we repeated the experiment in Section 3.1, but compared the GDT scores found by our method to those found by SPalign [30], which is a new protein structure alignment tool that uses a search algorithm similar to that of TMalign. SPalign aims to find one of the highest SP-score, the highest TM-score, or the highest GDT score. If we included SPalign in the previous experiment in Section 3.1, it would perform slightly better than TMalign on average. Thus, SPalign has a effective search algorithm and it should be a candidate for finding the highest GDT score for comparison. Again, only the 339 protein structure alignments with GDT scores higher than 0.5, found by at least one of the tested methods, are included in this analysis.

Comparing the GDT scores found by L12R3align and SPalign as shown in Figure 3(a), we find that L12R3align consistently finds similar or higher GDT

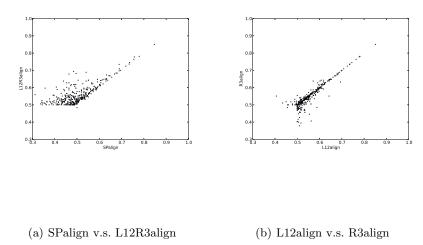


Fig. 3. Comparisons of the highest GDT scores found by SPalign and by using our method

scores than SPalign. Specifically, L12R3align improves GDT scores by 0.06 on average and by 0.25 in the best case. It is seen that 25% of the GDT scores are improved by at least 0.09 and that 75% of the GDT scores are improved by at least 0.02. Moreover, SPalign finds 145 alignments with GDT scores higher than 0.5, while L12R3align finds 314 alignments with GDT scores higher than 0.5. Thus, 169 more alignments with GDT scores higher than 0.5 are discovered, with an average GDT score improvement of 0.09. These results again supports that our protein structure alignment search algorithm can reliably find high quality alignments.

To further study the contributions of local fragments and remote fragment pairs to the GDT score improvements of L12R3align over SPalign, the GDT scores found by L12align and R3align are compared in Figure 3(b). It can be seen that both L12align and R3align find similar GDT scores when one of the GDT scores found by L12align and R3align is higher than 0.65. For the remaining protein structure pairs, both L12align and R3align are capable of discovering some better GDT scores than is the other method. Generally, 47% of the GDT scores found by L12align are up to 0.16 higher and 30% of the GDT scores found by R3align are up to 0.14 higher. Therefore, local fragments have a greater contribution in finding the highest GDT scores, while remote fragment pairs still have a significant contribution in finding the highest GDT scores.

3.3 Scoring Function Evaluation on Consistency with Eye-Examed Alignments

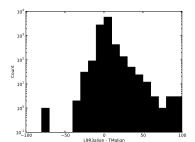
In this experiment, we would like to show that our scoring function is capable of finding protein structure alignments that are significantly more consistent with alignments examed visually by human-beings. Thus, we used protein structure alignments from the HOMSTRAD database [21] as a benchmark and compared the alignment quality of our protein structure alignment with that of TMalign [13]. Here, the quality of the alignment is evaluated by the F-score, the harmonic mean of recall and precision, of aligned residue pairs.

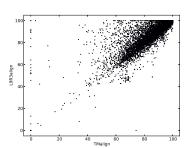
The HOMSTRAD database has been widely used in protein research, including sequence-sequence alignment [32], sequence-structure alignment [33], and structure-structure alignment [34], among others. The database contains structure alignments of 3,454 homologous protein structures from 1,032 protein families [21]. Since different sequences were read from alignment files and from PDB structure files for some proteins, only 9,429 out of 9,535 protein structure alignments from HOMSTRAD were included in this experiment.

For our experiment settings, we chose $\lambda=0.25$ and w=1.9, empirically. Unlike previous experiment settings, we used local fragments of size 9 and remote fragment pairs of size 3. Such experiment settings are balanced between the accuracy and the speed of our protein structure alignment algorithm because only a minor improvement on accuracy is gained by increasing the sizes, while slowing down the running time. The local fragment size of 9 was previously shown to be the optimal balance between the complexity of the model and the amount of data required to train the model [35,36]. Other experiment settings remained the same as in the previous experiment.

The F-score differences between L9R3align and TMalign are shown in Figure 4(a). Using L9R3align, 47% of the F-scores are improved, and the average F-score is improved from 88% to 90% compared to using TMalign. Moreover, there are 663 L9R3align F-scores that are at least 10% higher and there are 1,342 L9R3align F-scores that are at least 5% higher than the TMalign F-scores. For comparison, 31% of the TMalign F-scores are higher, and only 124 TMalign F-scores are at least 10% higher. In total, TMalign finds 5,560 protein structure alignments with F-scores higher than 90%, while L9R3align finds 6,114 such alignments. Therefore, the protein structure alignments found by L9R3align are 10% more likely to be highly consistent (with F-score higher than 90%) with eye-examined alignments, and tend to have similar or higher F-scores compared to the protein structure alignments found by TMalign.

Among the 34 pairs of protein structures that have TMalign F-scores equal to zero as shown in Figure 4(b), the L9R3align F-scores reach 36% on average. Specifically, two L9R3align F-scores equal to 100% and 19 L9R3align F-scores are higher than 50%. For the two cases that L9R3align F-scores are equal to 100%, the aligned protein structures contain a high percentage of helices, and TMalign shifts the HOMSTRAD alignment by a few residues, which has also been previously observed [37]. Such shifting is difficult to avoid by evaluating only structure similarities. However, the shifting is avoided by our scoring function, involving





(a) F-score difference between L9R3 align (b) TMalign F-score v.s. L9R3 align F-and TMalign score

 ${\bf Fig.\,4.}$ Comparisons of the F-scores of the aligned residue pairs found by L9R3align and TMalign

both structure and sequence similarities, in this experiment. Therefore, sequence similarity does aids in finding high quality protein structure alignments that are highly consistent with eye-examined alignments, even if structure similarity itself fails to do so.

There is also one pair of protein structures in Figure 4(b) that the L9R3align F-score equals to zero, while the TMalign F-score equals to 74%. Here, the HOM-STRAD alignment can be represented by protein "AB-" aligning to protein "-CD", where each character represents a protein fragment and "-" represents a gap region. One possible reason for this is that the weight parameters of our scoring function are not yet optimized to completely break the dependency between the alignment score and the protein size. We have observed that such cases can be eliminated by using different weight parameters, and this problem will be addressed in our future work.

4 Discussion and Conclusion

Therefore, our protein structure alignment method is not only reliable in finding the optimal alignment with the highest alignment score, but is also capable of discovering new alignments missed by current stat-of-art alignment search algorithms and scoring functions. Our result verifies our assumption that there exists a near optimal ROTRAN that minimizes the RMSD of two small sets of C_{α} atoms. Our result also verifies that although structure similarity may be efficient in many cases, sequence similarity helps to find better protein structure alignments that are (possibly significantly) more consistent with eye-examined alignments. This is the result of incorporating both local fragments and remote fragment pairs in the alignment search algorithm, and of incorporating both structure similarity and sequence similarity in the scoring function.

Our protein structure alignment algorithm is still subject to improvement and application. Our scoring function remains capable of modeling more types of protein similarities, such as the (ϕ, ψ) dihedral angle distance and the secondary structure distance. Unknown protein domain length problems when aligning multi-domain proteins should also be addressed in the future as proposed by SPalign [30]. It should be interesting to allow flexible ROTRANs within the same cluster to find flexible structure alignments as seen in FATCAT [38] and to find flexible multi-structure alignments as seen in Matt [39]. Moreover, the alignment quality can be further studied by evaluating CASP protein structure prediction [31], by checking self-consistency [37], and by simulating the SCOP fold detection [26]. All these aid in fully automating protein structure alignment process as good as or even better than human experts in the short future.

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