BENEFITS OF GENETIC ALGORITHM FEATURE-BASED RESAMPLING FOR PROTEIN STRUCTURE PREDICTION

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Abstract: *Protein structure prediction* (PSP) is an important task as the three-dimensional structure of a protein dictates what function it performs. PSP can be modelled on computers by searching for the global free energy minimum based on Afinsen's 'Thermodynamic Hypothesis'. To explore this free energy landscape Monte Carlo (MC) based search algorithms have been heavily utilised in the literature. However, evolutionary search approaches, like Genetic Algorithms (GA), have shown a lot of potential in low-resolution models to produce more accurate predictions. In this paper we have evaluated a GA feature-based resampling approach, which uses a heavy-atom based model, by selecting 17 random CASP 8 sequences and evaluating it against two different MC approaches. Our results indicate that our GA improves both its root mean square deviation (RMSD) and template modelling score (TM-Score). From our analysis we can conclude that by combining feature-based resampling with Genetic Algorithms we can create structures with more *native-like* features due to the use of crossover and mutation operators, which is supported by the low RMSD values we obtained.

1 INTRODUCTION

Critical Assessment of Techniques for Protein Structure Prediction (CASP) is a worldwide experiment that was developed to determine the capabilities and limitations of current *protein structure prediction* (PSP) approaches. There have been numerous CASP experiments starting in 1994 through to 2010, with a 2 year interval between each (Kryshtafovych et al., 2009). PSP methods are evaluated by performing a large amount of blind predictions on soon to be released protein structures.

In PSP numerous search algorithms have been utilised (Bornberg-Bauer, 1997), (Simons and et al., 2001), (Shmygelska and Hoos, 2005). Two of the most popular methods are: Monte Carlo based algorithms (MC) (Simons and et al., 2001) and Genetic Algorithms (GA) (Hoque et al., 2007). GAs provide a way of constructing a generalised search approach, which alleviates the need to change its main search operators for separate sequences. A technique that can be easily applied to the GA search process is feature-based resampling. The intuition behind feature-based resampling is that various PSP approaches generate large amounts of local minima, which may contain features that when combined together create structures that are more uniformly low in free energy (Blum, 2008), (Higgs et al., 2010). A simplistic example of this would be given a predicted protein structure with one domain wrong, by intermixing this with a protein that has the other domain correct a structure that is closer to the native conformation is created.

In this paper we compare a Genetic Algorithm feature-based resampling PSP method (Higgs et al., 2010) against state-of-the-art benchmark sequences used in CASP 8, and demonstrate the potential evolutionary algorithms have over other popular search algorithms like Monte Carlo (MC) based methods. To do this we have picked 17 random CASP 8 sequences and have conducted simulations using Rosetta, our feature-based resampling GA, and a Monte Carlo approach. This MC method was implemented using similar move sets, energy calculations, and scoring methods to allow for a fair comparison.

On average our method performed better than the MC approach by creating more *native-like* structures. It also, in general, did better than Rosetta by obtaining

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an average 10.72% RMSD improvement and 7.76% TM-Score improvement after resampling. From this we observed that the overall topology of the protein formed due to the larger feature-space provided by the GAs population, and the crossover and mutation operators, which allow to easily and efficiently search this feature-space.

The rest of this paper is organised as follows. In Section II we discuss the general background, Section III we will outline our methodology, Section IV presents and analyses the results we gained from our experimentation, and finally in Section V we draw our conclusions and mention possible future work.

2 BACKGROUND

Computational PSP methods have been historically broken up into three categories: *comparative modelling* (Sali and Blundell, 1993), *threading* (Zhang and Skolnick, 2004a), and *ab initio*. Out of these three methods *ab initio* (Simons and et al., 2001) is probably the most difficult as the target protein usually has no structurally related protein in the PDB library.

Two popular search algorithms that have been extensively used in the literature for *threading* and *ab initio* PSP are Monte Carlo based algorithms (Baker, 2006), (Zhang, 2007), and Genetic Algorithms (Hoque et al., 2009). MC algorithms for PSP problems work by conducting a random walk of the energy landscape, using a set of random move sets (e.g. protein fragment replacement). It only accepts a new state if the energy is lower than the current state (i.e. gradient descent) (Brunette and Brock, 2005).

GAs, on the other hand, belong to a specific class of evolutionary algorithms that are bio-inspired. It starts off with a large pool of genetic traits, which by use of genetic operators are reproduced, sometimes with random mutations, and are subjected to natural selection (i.e. the fittest survives). In PSP GAs have proven to be a very successful way of sampling the free-energy conformational landscape (Unger and Moult, 1993), (Pedersen and Moult, 1997), (Jiang et al., 2003), (Arunachalam et al., 2006), (Hoque et al., 2007), (Hoque et al., 2009), (Higgs et al., 2010).

3 METHODOLOGY

In this publication we apply a GA feature-based resampling algorithm (Higgs et al., 2010) to 17 sequences that were used in CASP 8 for our predictions. To gauge the validity of using a GA approach we will also compare our algorithm against a Monte Carlo method, which uses a similar approach as our GA to make it a fair comparison. Both of these methods will be explained briefly in the next two sections.

3.1 Genetic Algorithm Feature-based Resampling Approach

A technique that can be applied to the GA search process is feature-based resampling. Feature-based resampling is concerned with *native-like* features from the previous sampling round. If no models from the previous round of sampling produces a structure close enough with the native structure, they still may contain various *native-like* features, which can be recombined to create new structures that are closer to the native conformation.

Taking this idea of feature-based resampling we applied it to a GA based search, which utilises genetic operators designed for low-resolution lattice models. Our feature-based resampling GA works by taking the initial predicted structures from a complete run of a *protein structure prediction* (PSP) software using an arbitrary target protein. These initial structures are then used as input into our GA for refinement. The PSP software that we use to create these structures is Rosetta (Simons and et al., 2001). The reasons for this is two fold: (1) in Critical Assessment of Techniques for Protein Structure Prediction (CASP) (Bradley et al., 2003) Rosetta outperformed numerous other PSP software suites in high-resolution structure prediction, and (2) Rosetta is open source making it easy to modify and integrate into our GA. For the same reasons we use Rosetta's energy function for fitness calculations.

In regards to our GA search operators we use a roulette wheel procedure for selection. Crossover is carried out by splicing together protein fragments, that have *native-like* features according to the fitness function f, contained within the current population. This is done by using a single point crossover technique that randomly selects a crossover point (n) where $n \in C\alpha(S)$, $C\alpha(S)$ refers to the set of $C\alpha$ atoms contained within the structure S. Let $p1$ be parent 1, and $p2$ be parent two everything from n onwards in $p1$ is replaced with everything from n onwards in $p2$, and vice versa. This process will produce two offsprings.

Mutation is performed by using a random pivot rotation move on either the x, y, or z axis. Pivot rotations work by translating all points to a chosen pivot (n) where $n \in C\alpha(S)$ and rotating the sub-structure around that pivot point ($n+1$ to m). The sub-structure, in this case, refers to all the points in a protein structure from $n+1$ to the end of the structure (m). Finally scoring the output of our algorithm

Table 1: GA and MC Resampled Results.

Protein	GA				MC			
	RMSD	*TM*	*RMSD%*	*TM%*	*RMSD*	*TM*	*RMSD%*	*TM%*
t0389	11.816Å	0.2733	6.18	23.00	15.74Å	0.1976	7.51	-0.05
t0390	12.913Å	0.1667	10.20	-0.12	18.111Å	0.1237	18.82	14.01
t0392	6.994Å	0.2941	19.78	-10.66	14.57Å	0.1988	4.23	6.37
t0393-D1	10.484Å	0.4149	12.43	38.58	14.951Å	0.247	33.96	11.66
t0395	15.248Å	0.1715	4.07	-7.94	19.818Å	0.1544	6.19	6.93
t0397-D1	7.999Å	0.2067	23.62	9.22	9.16Å	0.2978	14.75	19.98
t0398-D1	12.757Å	0.1847	3.88	17.49	13.47Å	0.1554	17.18	13.51
t0399	12.694Å	0.2213	11.05	14.19	17.535Å	0.1628	4.34	-2.28
t0404	4.674Å	0.4185	6.69	-4.67	5.021Å	0.4024	11.07	7.68
t0405-D1	3.58Å	0.5665	33.67	40.54	6.831Å	0.3171	22.48	3.42
t0405-D2	13.945Å	0.2728	8.77	8.69	15.15Å	0.2274	15.94	-4.33
t0406	9.871Å	0.3457	-7.03	5.85	17.44Å	0.2185	5.49	-19.79
t0407-D1	15.537Å	0.2169	6.93	5.75	19.999Å	0.1894	10.02	13.82
t0407-D2	12.684Å	0.2053	0.03	-4.33	14.214Å	0.2066	27.61	15.74
t0409-D2	9.759Å	0.2874	8.86	-22.19	12.689Å	0.3449	14.24	-5.27
t0411	7.742Å	0.405	4.04	18.08	14.271Å	0.2518	9.07	0.92
t0415	6.523Å	0.3606	29.05	0.47	9.616Å	0.3616	18.09	6.86

is taken care of by two structural measures: root mean square deviation (RMSD), and template modelling score (TM-Score) (Zhang and Skolnick, 2004b).

3.2 Monte Carlo Approach

Most Monte Carlo (MC) approaches (Metropolis and Ulam, 1949) apply random variance to improve a solution. It starts with a random conformation S_1 with energy E_1. It then applies some random change to the conformation to make a new solution S_2, which has energy E_2. If the energy improves ($E_2 < E_1$) then accept the change, otherwise the metropolis criterion is applied to decide whether or not to accept the change.

In our approach we have used similar techniques that were applied in our GAs mutation operator to allow for a fair comparison of the two algorithms. Therefore, the random change in the MC algorithm will be conducted by using rotational move sets.

4 RESULTS AND DISCUSSION

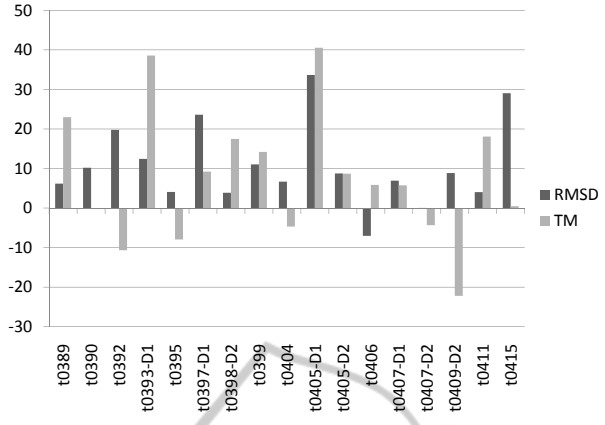
For all of our experiments 17 CASP 8 sequences were chosen to test our algorithms on. Our GA used a 70% crossover rate, 10% mutation rate, twin removal of $>=$ 80% similarity, and the algorithm was run for 100 generations. Output from the GA was saved in 10 generation increments (10, 20, 30, $\cdots$, 100). For each sequence the structure that had the lowest RMSD out of all the structures saved was chosen as a representative for that sequence.

Our MC algorithm was run for 16000 steps, and had a temperature value of 2, which is steadily cooled each step to reach convergence. Starting points for the MC simulations were also decoys created by Rosetta to allow for a fair comparison between our GA approach.

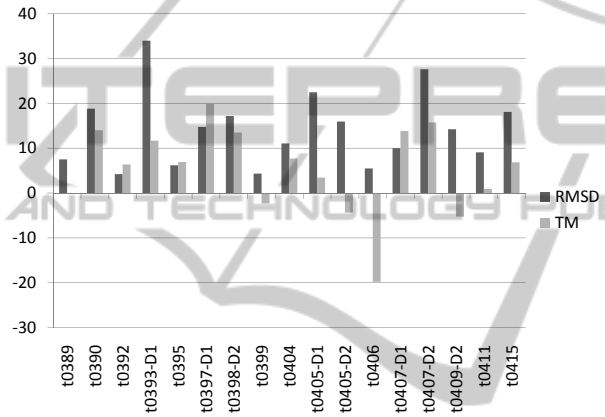
4.1 Empirical Results

A summarisation of our results can be found in Table 1. This table contains the protein's CASP identification, GA resampled RMSD, GA resampled TM-Score, GA resampled RMSD and TM-Score improvement in percent over the best Rosetta model in the initial population, MC resampled RMSD, MC resampled TM-Score, MC resampled RMSD and TM-Score improvement in percent over the starting point created with Rosetta. Improvement is measured the same way as described in (Higgs et al., 2010).

Figures 1(a) and 1(b) show the RMSD and TM-score improvement in percent over the initial starting point/s for our GA and MC algorithms. In Figures 1(a) and 1(b) the x axis is the protein's CASP identification, and the y axis is the improvement percentage over the best Rosetta models used in the GA/MC simulations. We have also depicted a direct comparison of RMSD and TM-score measures between the two algorithms in Figures 2(a) and 2(b). In Figures 2(a) and 2(b) the x axis is the protein's CASP identification, and the y axis is the RMSD/TM-Score value. And finally in Figure 3 we visually depict our improvements for t0405-D1 using our GA approach, and t0393-D1 using our MC approach.



(a) Genetic Algorithm Approach



(b) Monte Carlo Approach

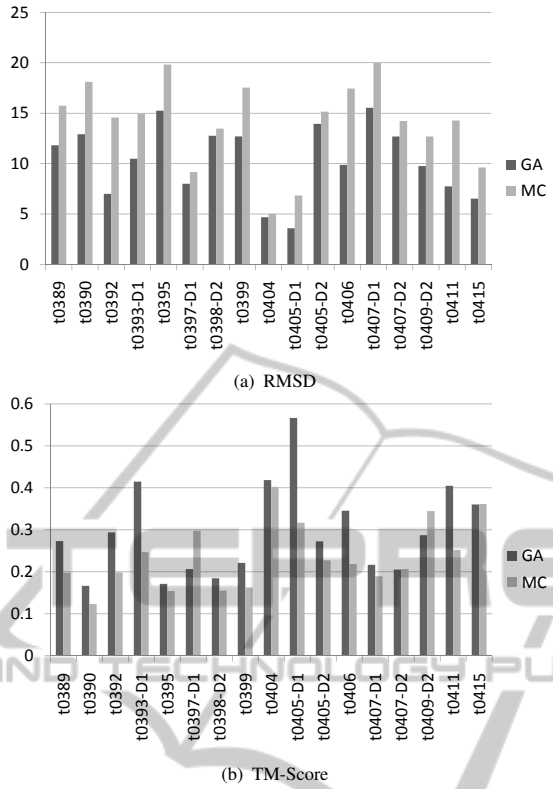
Figure 1: RMSD and TM-Score improvements over the initial starting points.

4.2 Analysis of Results

First of all we will discuss the results and performance of our GA approach in regards to its resampling improvement. From Table 1, and Figure 1(a) you can see that the resampled structures on average improve in either RMSD, TM-Score or both, when compared to the best Rosetta model in the initial population. Over the complete data set we had an average RMSD improvement of 10.72%, and an average 7.76% TM-Score improvement. The lower average TM-Score is attributed to a few structures having an improved RMSD value, but worse TM-Score, which can be seen in Figure 1(a). Out of the 17 sequences we used we had 16/17 improvements in RMSD, and 11/17 improvements in TM-Score. The main reason why it appears that the TM-Score is poor would be due to the formula we use to calculate improvement. As the scale of TM-Score is 0 to 1, 1 being exactly the same as native, the improvement calculation can make simple changes from 0.3 to 0.2 look like a large deterioration (i.e. -50%). Finally, to visually demonstrate the benefits of our GA approach Figure 3 (a)-(c) demonstrates the structural improvements for one of our best predicted structures: t0405-D1.

In comparison to our GA, our MC approach performed about on par at resampling Rosetta starting points (see Table 1, and Figure 1(b)). Out of the 17 sequences we used we had an average 14.18% RMSD improvement, and an average 5.25% TM-Score improvement. Our MC approach had 17/17 structures with RMSD improvements, and 12/17 structures with TM-Score improvements. These results provided us with a similar conclusion as our GA results in regards to the TM-Score deteriorating in some structures when the RMSD improves. This can also be blamed on the bias imposed by the improvement measure we are using. In Figure 3 we show our most improved MC resampled structure (f) compared to its Rosetta starting point (e), and native conformation (d).

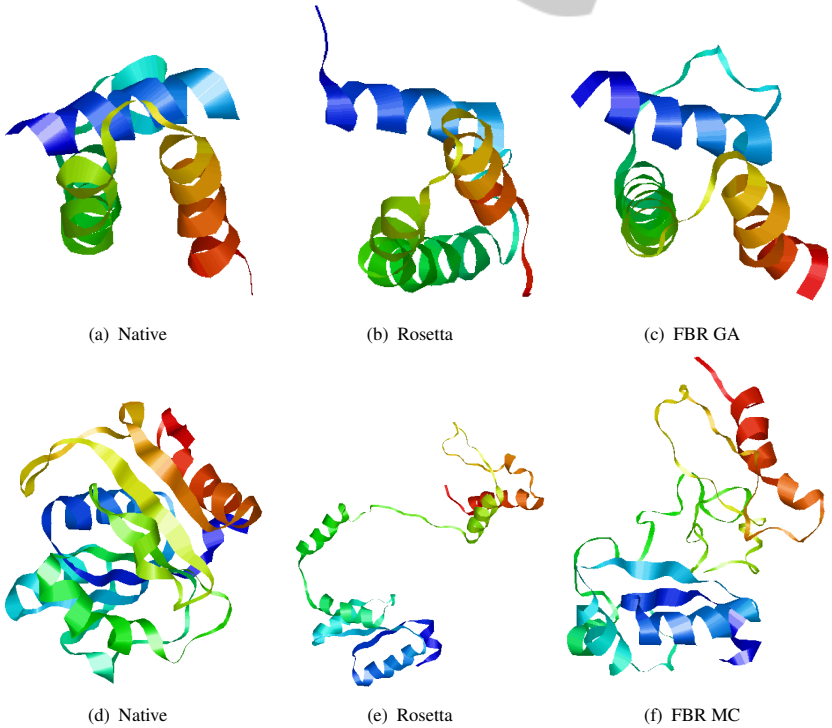
It is obvious from our results that both algorithms perform quite well at resampling structures from Rosetta. However, the major difference between



(a) RMSD

(b) TM-Score

Figure 2: Comparison of RMSD and TM measured values between GA and MC algorithms.



(a) Native (b) Rosetta (c) FBR GA

(d) Native (e) Rosetta (f) FBR MC

Figure 3: In (a)-(c) we compare our GA to Rosetta using protein t0405-D1, and in (d)-(f) we compare our MC implementation to Rosetta using protein t0405-D1. All proteins were generated with the visualisation program Rasmol (Sayle, 2009).

the two algorithms can be seen in Figures 2(a) and 2(b). In Figure 2(a) we show the RMSD values of our resampled structures for each algorithm. All of our GA resampled structures have a lower RMSD value than our MC resampled structures. In Figure 2(b) our GA approach has 13 structures with better TM-Score values, and two that are on par with our MC approach. The lower the RMSD the closer the structure is to the native-conformation, and likewise the higher the TM-Score value is the closer the structure is to the native. This means that our GA approach, on average, is creating structures that are closer to the native conformation. The main reason for this is that it has a larger feature-space to work with due to the GAs ability to contain a library of low energy features in its population, and by using crossover and mutation operators a lot more of the conformational landscape can be explored. In contrast our MC algorithm only uses one Rosetta decoy as a starting point, and therefore it has less features at its disposal. This means it is highly unlikely to find structures that are < 15Å to the native conformation.

Based on the above analysis we have shown that using an evolutionary approach can give better results than other popular algorithms like the Monte Carlo (MC) method. It also indicated that combining feature-based resampling with Genetic Algorithms can create structures with more *native-like* features, which is supported by the lower RMSD values we obtained when compared to our MC approach. Due to this we can infer that more correct features are being added to the search space, and thus guiding our search to more accurate structures.

5 CONCLUSIONS

Critical Assessment of Techniques for Protein Structure Prediction (CASP) is a good way to accurately indicate how far we have come in solving the protein prediction problem. In this paper by randomly selecting 17 CASP 8 sequences we have demonstrated the capabilities of our GA feature-resampling approach. We have also compared it to Rosetta, a state-of-the-art PSP suite, and another MC algorithm which we developed to demonstrate the potential evolutionary algorithms have over other non-deterministic search algorithms.

Both algorithms were run on a set of 17 randomly chosen sequences, which were used in the CASP 8 experiment. Our results showed that our GA performed well overall, obtaining good improvements in both RMSD and TM-Score. This indicated that most of the overall topology of the protein was forming throughout our GA search. We have also shown that evolutionary algorithms have the potential to be more successful than other non-deterministic search algorithms like MC approaches. Our GA performed very similar in resampling Rosetta starting points as our MC approach, however due to having a larger feature-space our GA approach produced more accurate predictions than our MC method.

In regards to future work it would be interesting to look at modelling energy preferences in the fitness function to enforce a bias on certain features or arrangement of features that are observed in native conformations. This could increase the accuracy of our search, and hence produce better predictions.

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