Heuristic Based Search for Protein Structure Prediction

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Statement of Originality

This work has not previously been submitted for a degree or diploma to any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Mahmood A. Rashid
Brisbane, December 19, 2013
Dedicated to my parents and family for their unconditional love and support
This work has benefited greatly from the input and support of many people over the past four years. I would like to express my gratitude to everyone who contributed to it in one way or other.

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Abstract

This thesis presents our heuristic based search approaches for protein structure prediction. Proteins are essentially sequences of amino acids. Every protein adopts a specific three-dimensional (3D) structure to perform a specific task. The function of a protein depends on its 3D native structure that has the minimum free energy level. Proteins are the fundamental component of all living cells. However, misfolded proteins cause fatal diseases. Therefore, protein structures are very important in biotechnology and drug design. Hence, protein structure prediction (PSP) has emerged as a very important multi-disciplinary research problem.

Given a protein’s amino acid sequence, the protein structure prediction problem is to find a three dimensional structure of the protein such that the total free energy amongst the amino acids in the sequence is minimised. In-vitro laboratory methods used in PSP are very time-consuming, cost-intensive, and failure-prone. On the other hand, computational predictive methods are NP-hard even when conformation models are simplified by using low-resolution energy function and discretised lattice-based structures.

There are three computational approaches for protein structure prediction: homology modeling, protein threading and ab initio approach. The prediction quality of homology modeling depends on the sequential similarity with proteins that have previously known structures. On the other hand, protein threading also known as fold recognition, is based on the structural similarity with the previously known fold families. Our work is based on the ab initio approach that only depends on the amino acid sequence of the target protein. The computational methods found in the literature are largely based on optimisation algorithms. The widely used algorithms in PSP are genetic algorithms, memetic algorithms, ant colony optimisation, particle swarm optimisation, simulated annealing, stochastic local search, and Monte Carlo simulation.

This thesis focuses on genetic algorithms and stochastic local search algorithms because they are found promising in conformational search. A genetic algorithm (GA) is a population based optimisation algorithm inspired from nature. Genetic algorithms mimic genetic mutation, recombination and survival for the fittest principles. On the other hand, local search (LS) algorithms, starting from a single initial solution, move from one solution to another to find a better solution in the vicinity of the current solution. However, for large sequences, the performance of both algorithms deteriorate and the search often get stuck in plateaus and/or local minima. In general, the success of GA and LS methods crucially depends on the balance of diversification and intensification of the search. Any further progress to these algorithms require addressing the above issues appropriately.
In this thesis, we introduce a new population based algorithm (GA\(^+\)) under the GA framework for simplified PSP. We use hydrophobic-polar (HP) energy model on 3D FCC lattice to simplify the problem. In GA\(^+\), we use i) an exhaustive generation approach to diversify the search; ii) a novel hydrophobic core-directed macro-mutation operator to intensify the search; and iii) a random-walk based stagnation recovery technique.

In HP model, protein structures have hydrophobic cores (H-core) that hide the hydrophobic amino acids from water and expose the polar amino acids to the surface to be in contact with the surrounding water molecules. Taking H-core formation as an objective, in this thesis, we present a new spiral search algorithm for PSP. The spiral search algorithm, denoted by SS-Tabu, works in a spiral fashion within a hydrophobic-core directed local search that is guided by tabu meta-heuristic.

In a separate work, we present a parallel processing technique to expedite exploration by starting spiral search from different points. In this approach, a number of random initial solutions are generated and distributed to different threads. We allow each thread to run for a pre-defined period of time. The improved solutions from the threads are merged together and a number of solutions are selected for next round processing.

As we find no single algorithm suits the best for the protein structure prediction problem, we have tried a hybrid search technique to mix the power of stochastic local search and population based genetic algorithms to gain improvements. In this approach, we embed our spiral search algorithm within the GA\(^+\) framework. The spiral search improves the individuals within the GA\(^+\) population and quickly builds a rich population.

A detailed 20 × 20 energy model could better capture the behaviour of the actual energy function than a very simple 2 × 2 HP energy model. In contrast, the HP energy model could effectively bias the search towards certain promising directions. We have used the HP model with a detailed 20 × 20 model in a mixed fashion in GA+ and parallel spiral search frameworks and found that the mixed setting works more effectively than using the energy models separately.

We evaluated our approaches on a set of benchmark proteins using FCC lattice, and the 2 × 2 HP and the detailed 20 × 20 energy models. We experimentally show that our approaches significantly outperform the current state-of-the-art approaches for the same lattice and energy models.

In conclusion, this thesis presents a new local search algorithm, a parallel local search framework, a hybrid search framework and several enhancements made to the GA framework. These algorithms and enhancements improve protein structure prediction in lattice based structures and low resolution energy models.
The scientific contributions of this research have been fully or partly published the following peer-reviewed journals and proceedings:

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**Conference Publications**


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<td>Two Dimensional</td>
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<td>3D</td>
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<td>AA</td>
<td>Amino Acid</td>
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<tr>
<td>ACO</td>
<td>Ant Colony Optimisation</td>
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<td>AIS</td>
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<td>Average</td>
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<td>BH</td>
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<td>BnB</td>
<td>Branch and Bound</td>
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<td>$C_\alpha$</td>
<td>Alpha Carbon</td>
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<tr>
<td>$C_\beta$</td>
<td>Beta Carbon</td>
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<td>CASP</td>
<td>Critical Assessment of Techniques for Protein Structure Prediction</td>
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<td>CBLS</td>
<td>Constraint Based Local Search</td>
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<td>Compact Hydrophobic Core Construction</td>
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<td>Constraint Logic Programming</td>
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<td>H</td>
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<td>H-Core centre</td>
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<td>HCP</td>
<td>Hexagonal Close Pack (lattice)</td>
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<td>HGA</td>
<td>Hybrid Genetic Algorithm</td>
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<td>Description</td>
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<tr>
<td>HP</td>
<td>Hydrophobic-Polar (Hydrophilic)</td>
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<td>Immune Algorithm</td>
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<td>LP</td>
<td>Linear Programming</td>
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<td>Monte Carlo Algorithm</td>
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<td>MH-Tabu</td>
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<td>Nuclear Magnetic Resonance</td>
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<tr>
<td>NP</td>
<td>Non Polynomial</td>
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<tr>
<td>P</td>
<td>Polar (Hydrophilic amino acids)</td>
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<td>PDB</td>
<td>Protein Data Bank</td>
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<td>PPC</td>
<td>Prediction of Protein Complex</td>
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<td>PSO</td>
<td>Particle Swarm Optimisation</td>
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<td>PSP</td>
<td>Protein Structure Prediction</td>
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<td>PSS</td>
<td>Parallel Spiral Search</td>
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<td>RGA</td>
<td>Randomised Genetic Algorithm</td>
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<td>RMSD</td>
<td>Root-Mean-Square Deviation</td>
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<td>RNA</td>
<td>Ribonucleic Acid</td>
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<td>SA</td>
<td>Simulated Annealing</td>
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<td>SAW</td>
<td>Self-Avoiding-Walk</td>
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<td>SVM</td>
<td>Support Vector Machine</td>
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<td>SS</td>
<td>Spiral Search</td>
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<td>SS-Tabu</td>
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<td>TM-score</td>
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