

BlueFern HPC PhD Scholarship Application (application no longer than 2 pages)

1. Title of Research project: **Understanding enzyme inhibition by tracking molecular motion using computational studies**

2. Project Outline including an explanation of the nature of the project and benefit to the student :

In recent years there has been a growing understanding of the intimate relationship between molecular motion and enzyme function. One of the most powerful techniques to explore the nature of these molecular motions of a large macromolecular system is by carrying out all atom molecular dynamics calculations. These calculations enable the relative motions of individual atoms to be tracked with respect to time and the interaction of the enzyme with its binding partners to be explored in detail. In this project we will use computational molecular dynamics calculations to explore the motion of a key metabolic enzyme.

3-Deoxy-D-*arabino*-heptulosonate 7-phosphate (DAH7PS) is the first enzyme of the shikimate pathway, which is responsible for the biosynthesis of essential aromatic amino acids in plants and microorganisms. This enzyme has been identified as a possible target for antibiotic development. In this project calculations will be performed to gain insight into the usual modes of inhibition of this enzyme.

This project will involve computational studies with two forms of the enzyme, one from *Thermotoga maritima*, which undergoes a major domain movement on inhibitor binding, and the DAH7PS from *Mycobacterium tuberculosis* undergoes no obvious large changes in its structure. Our preliminary modelling studies using the BlueFern Super Computer suggest that small dynamic fluctuations may be responsible for the inhibition of this enzyme by aromatic amino acids.

This project will involve the investigation of both of these two systems and another related enzyme using the molecular dynamics programme NAMD and the molecular docking programme AUTODOCK running on the BlueFern Super Computer. The following studies are proposed:

1. The molecular dynamics of the *T. maritima* DAH7PS system will be explored. Structures of the inhibited and uninhibited forms of the protein will be used as the starting points for the simulations. These simulations will help determine the trajectory associated with the major domain movement.
2. Initial molecular dynamics calculations on the *M. tuberculosis* DAH7PS system will be performed to investigate how coupled or correlated motions relate to the function of the enzyme and its response to inhibitors. These molecular dynamics simulations will focus on the dynamics of *in silico* mutants of the protein and comparisons will be made to the wild-type protein.
3. Docking studies will be carried out on the *Helicobacter pylori* DAH7PS model structure in order to identify possible inhibitors. The initial stages of this project will involve homology modelling of the *H. pylori* DAH7PS using the *M. tuberculosis* DAH7PS as a starting point.

All atom MD simulations will be carried out using the complete tetrameric structures, solvated with explicit TIP3 water molecules in a box using VMD, and ionized by adding Na⁺ and Cl⁻ ions to balance the net charge of the water box. Molecular dynamics simulations will be conducted with the CHARMM force field parameter specifications at a constant temperature and pressure. AUTODOCK is also available on BlueFern for predicting allosteric binding partners.

This project tackles an area of considerable international interest: The role of protein dynamics in determining biological function. The combination of using a high performance computing facility and performing calculations on an important potential antibiotic target will ensure high quality research is carried out, and provide an excellent training environment for doctoral research.

3. Brief description of the research record of the proposed Senior Supervisor that is relevant to the proposed project:

The senior supervisor, Dr Emily Parker, has used the Bluefern recently in conjunction with PhD student Wanting Jiao. Molecular dynamics calculations have been carried out using NAMD on both small peptide systems and the large M. tuberculosis enzyme system. This work has paved the way for the studies described in this project proposal. One paper has been published featuring entirely computational studies carried out on the BlueFern. One other is under review. Emily also has extensive experience in understanding protein structure and function. This work will be complemented by experimental studies taking place in her laboratory. This will help to ensure that publications featuring computational work are accepted in the highest quality journals, as any functional predictions from our computational studies will be able to be experimentally verified.

4. Indication of how research expenses will be met (computing time is free) :

Only modest consumable costs will be incurred as the PhD student will be spending the majority of time performing calculations. A small allowance for these consumables will be provided through funding for the Biomolecular Interaction centre (\$2500).

5. Approval of the relevant Head of Department, School, Institute or Centre in which the research will take place:

Name Department

Signature

6. Please indicate which type of HPC architecture the project intends to use and an estimation of amount of HPC time required:

Architecture	CPU time (cpu hours)
Blue Gene	
Power 7	