Extremophilic enzymes: investigating structural adaptation through rapid physics-based geometric simulation

Supervisory team:
Main supervisor: Prof Alison Walker (University of Bath)
Second supervisor: Dr Marc van der Kamp (University of Bristol)
Dr Christopher Pudney (University of Bath)

Collaborators: Dr Tom Williams (University of Bristol), Dr Stephen Wells (University of Bath)

Host institution: University of Bath

Project description:
The relationship between the structure of a protein and its function is vital to understanding how molecules give rise to biological effects. We will study structural adaptation of extremophilic enzymes to their ambient temperature through their flexibility and dynamics. Experimental structure determination is time-consuming and costly so is not practical for the many variants of a protein under optimization, nor is ab initio modelling of protein structure yet tractable. This project will develop a modelling tool combining two complementary modelling methods developed at Bath Physics and Bristol Biochemistry. The tool will be used by an experimental group in Bath Biology and Biochemistry who develop experimental approaches to rapidly test proteins for their native function based on accurate detection of their dynamics and flexibility, termed the dynamic profile. There are industrial applications and potential for use in a clinical setting.

The dynamics and flexibility of a protein are key to its function: many enzymes undergo substantial, reversible conformational changes during chemical operation. We will use simulation methods taking as input a protein structure, obtained through protein crystallography, and explore its motions from small local rearrangements such as side chain reorientations, to large domain motions such as hinge motion. This project combines a code that undertakes geometric simulations of intrinsic flexible motion in enzymes with enhanced sampling molecular dynamics on these structures that focus on picosecond timescales. Molecular dynamics is used to study how effective the enzyme is as a catalyst.

Enzyme stability and flexibility in different conditions is a crucial aspect for enzyme activity and durability, both for extremophilic life-forms as well as biocatalysts for industrial biotechnology. The rigidity of enzyme structures needs to be finely balanced to allow for sufficient stability (e.g. at high temperature, high salt concentration) as well as maintaining the flexibility required for activity (turn-over).

The project will examine structural adaptations that can change the rigidity of enzyme structures, e.g. salt-bridges, hydrogen bonding and hydrophobic interactions. Code development will take place to make improvements to its description of the physics and to become more user friendly.

The student will acquire an in-depth knowledge and training in enzyme structure and function, interpretation of experimental measurements, and programming skills and techniques using C++ and Python.

A degree in any of physics, chemistry, biology, or natural sciences is required, along with a strong interest in coding.