STRUCTURAL BIOLOGY

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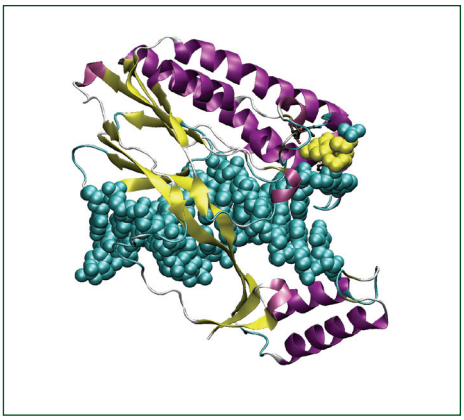
At a fundamental level, living processes are driven by the chemistry of biomolecules such as proteins and DNA. Understanding the chemistry of life requires detailed information about the structures of the molecules involved. Why is this important? Many advances in medicine, biotechnology and industry result from understanding of these processes. Within this broad sphere, my group conducts fundamental and applied research:

Cofactor Free Oxygenases

Divergent evolution in enzymes is poorly understood. While there are numerous examples of related enzymes catalysing identical chemistries, little is known about how novel chemistries arise. We have crystallised an enzyme called QDO, which is a member of the α/β–hydrolase superfamily. Most members of this very large group of enzymes catalyse hydrolysis reactions. QDO however is a cofactor free oxygenase, catalysing a reaction that is fundamentally different from its close relatives. By solving the structure of this enzyme we hope to gain insight into how the α/β–hydrolase fold has been adapted to cofactor free oxygenase chemistry. *(With R Qi, and S Fetzner [U Oldenburg, Germany])*

Termination of DNA Replication in Bacteria

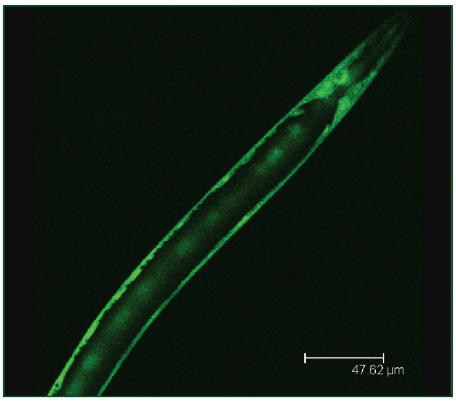
Bacterial DNA replication is halted at specific sites on the chromosome called *Ter* sites. A protein called Tus recognises and binds to these *Ter* sites. Recent work in the Dixon group has shown that by breaking a specific DNA-base-pair interaction, Tus bind more tightly to DNA, preventing the replisome from progressing. We have recently determined the structure of this locked form of the Tus-*Ter* complex. *(With N E Dixon, M D Mulcair, P M Schaeffer)*



Cartoon representation of the "locked" Tus-*Ter* complex.

Nematode Proteins: Potential Drug Targets

Nematodes, commonly known as round worms, are the most numerous multicellular organisms on earth. There are tens of thousands of different species; most are free living and some are significant parasites to animals, humans or plants. As such, there is a need for new drugs against parasitic nematodes. We have identified a number of proteins that are potential drug targets, and are working to solve the structures of these proteins with a view to structure-based drug design. *(With P Lloyd, C Behm [BaMBi])*



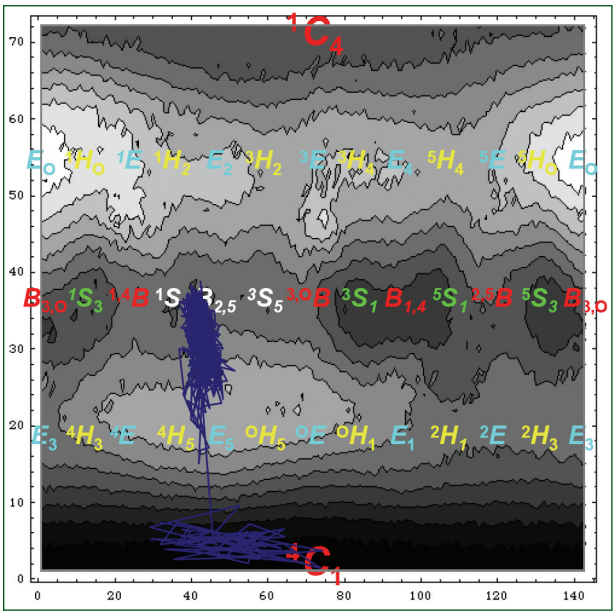
The nematode *C. elegans*.

Human Omega-class Glutathione S-transferases

The omega class glutathione S-transferases (GSTO) play a central role in the metabolism of arsenic and in the recycling of vitamin C in the brain. Genetic polymorphisms may alter their structure and function and cause individual variations in toxicity and response to arsenic. We are examining the structure of GSTO in complex with its substrates as well as the structures of mutants resulting from genetic polymorphisms found in the population. *(With P G Board, R Baker [JCSMR, ANU])*

Conformational Changes in Glucopyranose Rings During Catalysis

Sugars and their polymers are of importance to such diverse areas as immunity and paper bleaching. In order to better understand the enzymes that cleave sugars, we have mapped energy landscapes of glucopyranoses commonly found in nature using empirical force fields. We are using these force fields to examine the transitions that sugar rings undergo when bound to enzymes prior to cleavage. Using molecular dynamics simulations, we have mapped the transition of mannoside residues from $^4C_1$ chair-conformation to $^1S_5$ skew-boat conformation in a bacterial *endo*-β-mannanase. The conformation degrees of freedom of the sugar can be decomposed into two essential degrees of freedom and plotted (see below).



Conformational mapping of a mannoside residues as it transits from $^4C_1$ chair-conformation to $^1S_5$ skew-boat conformation (blue line). Here, the energy ranges from low (black) to high (white).

http://rsc.anu.edu.au/research/oakley.php