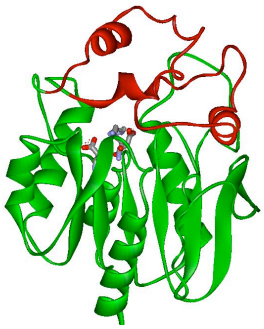
Dr Aaron Oakley

Structural biology lies at the nexus between chemistry, biology, and medicine. The three dimensional structures of biological molecules such as proteins and DNA yield a great deal of information about how they work, and can give rise to new hypotheses about its function that can be further probed through mutagenesis, kinetic and other biochemical analyses. Understanding the structure and function of proteins is of primary importance to medicine, biochemistry, and molecular genetics, since proteins drive and regulate these processes. Protein crystallography is our method of choice for structure determination efforts. We gather additional information about proteins from computational approaches such as molecular dynamics. We are investigating the structure and function of several proteins:

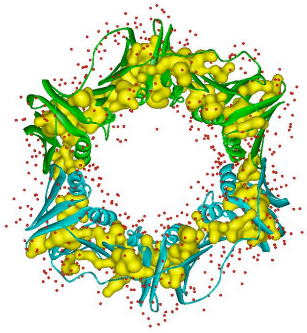
LinB



Haloalkane dehalogenase LinB

Bacteria produce enzymes that bind and degrade organic pollutants. These enzymes have potential for use in the remediation of contaminated industrial sites. We have determined the structure of a haloalkane dehalogenase called LinB at atomic resolution. This enzyme was originally isolated from a soil bacterium that was able to degrade the pesticide lindane. It has activity against a broad range of pollutants called haloalkanes. The structure tells us how the protein might be modified in order to change its range of substrates. Our studies are complimented by *ab inito* QM calculations that provide insight into the reaction mechanism and its energetics.

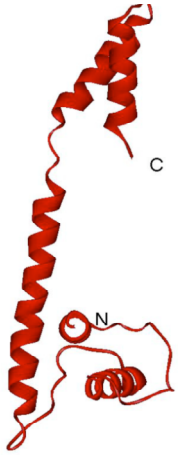
PolIII Beta



E. coli polIIIbeta

This protein, from the bacterium *E. coli* is one of many that are involved in the complicated process of DNA replication, and is part of the DNA polymerase holoenzyme. It is a ring-shaped molecule that wraps around DNA and slides along it. This protein binds to the catalytic subunit of DNA polymerase, preventing it from detaching from DNA. By disrupting this enzyme, DNA replication in bacteria can be halted. Thus this protein is a target for the design of novel antibiotics. With Dr Dixon's group, we have determined the structure of this protein at 1.85 Å resolution.

DnaB and DnaG



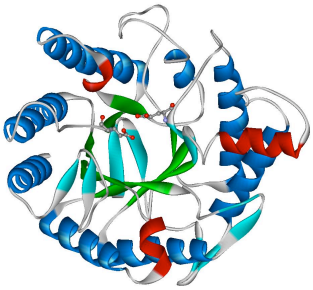
E. coli DnaG

The molecular machine that drives the replisome and separates the two strands of DNA at the apex of the replication fork is a ring-shaped protein called DnaB. With Dr Dixon's group, are working to determine the three-dimensional structure of this protein. Success has been achieved in determining the structure of part of another protein called DnaG. This protein binds to DnaB and synthesises the RNA primers required for DNA synthesis on the lagging strand. We recently determined the three-dimensional structure of the DnaB binding domain of DnaG. Remarkably, this protein has the same fold as the N-terminal domain of DnaB, suggesting an ancient evolutionary relationship between the two proteins. Models of this protein

are being subjected to MD studies to understand the role of flexibility in DnaB-binding.

Mannanase

With researchers at Guelph University in Canada, we recently determined the structure of a carbohydrate-degrading enzyme from tomato fruit called mannanase. The enzyme cleaves chains of mannan sugars, which are found in plant cell walls. This enzyme appears to be involved in softening during fruit ripening. We are now using modelling and molecular dynamics to understand how the substrate, mannan binds to the enzyme prior to cleavage. This will enable us to understand how mannanase and similar enzymes recognise their substrates. The long-term goal is to be able to tailor make carbohydrate cleaving enzymes for industrial processes and research.



Endo-β-mannanase from tomato

Glutathione S-transferases from Mosquitos

I collaboration with workers at Mahidol University in Thailand, we are investigating the structure and function of glutathione S-transferases (GST) from the mosquito *Anopheles dirus* species B, an important malaria vector in South-East Asia. These enzymes are important, because they can break down pesticides used to control mosquitos. We have so far determined the structure of two isozymes from an unusual gene that gives variants through alternate splicing. In the long term, we aim to understand how the enzymes bind and detoxify pesticides and how this might be ameliorated.

A glutathione S-transferase from *Anopheles dirus*

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