Simulation-led redesign to generate enantioselective biocatalysts

Supervisory team:
Main supervisor: Dr Marc van der Kamp (University of Bristol)
Second supervisor: Prof Matthew Crump (University of Bristol)
Dr Paul Race (University of Bristol), Prof Chris Willis (University of Bristol)

Collaborators: Prof Sheryl Tsai (University of California, Irvine)

Host institution: University of Bristol

Project description:
Enzymes are remarkable biocatalysts that can work under mild conditions and with high specificity and selectivity. If enzymes could be engineered in a designed way, they could provide an efficient route to new molecules such as pharmaceuticals. In pharmaceuticals (and many other applications), it is crucially important to control the precise stereochemical structure. Differences in stereochemistry result in molecules that are different like your right and left hand are different, and this can make the difference between medicine or poison. In this project, the aim is to develop ways to control how polyketide synthases, an important class of natural biocatalytic machinery, set the stereochemistry of their products, polyketides. This will be done by modifying – or redesigning – a key enzyme in polyketide synthase systems that sets stereochemistry in the polyketide product chain, a ketoreductase. In particular, in the so-called polyketide synthase type II systems, an acyl-carrier protein (ACP) will bring the evolving polyketide chain to a ketoreductase, which will subsequently set a stereochemical center. Existing structural information defines how the ACP and the ketoreductase are involved in making the polyketide actinorhodin (a natural antibiotic), and this will guide the development of computational prediction protocols. This will be the bulk of the work, involving QM/MM reaction simulations, molecular dynamics and protein-protein docking. The simulations will predict new ketoreductase variants that alter the stereochemical outcome. To test and improve these computational predictions, experimental characterisation of promising enzyme variants (product outcome, kinetics and structural biology) will be performed. Once successful, the atomic detail of new variants will be confirmed through structural biology techniques (NMR, X-ray crystallography). This interdisciplinary project is thus combining the expertise in computational simulation of enzymes in Bristol and the expertise from an internationally leading academic team with multidisciplinary expertise of polyketide systems and the relevant experimental techniques (enzymology, molecular biology, chemistry and structural biology). Combining simulation and experiment in this way is still developing, but will become increasingly important. The strategies and protocols developed in this project will therefore be of general use for similar modification of biosynthetic activities. The multidisciplinary environment ensures the student will acquire a range of skills that will arm them for a future career in academic or industrial bioscience (including pharmaceutical science). The student will be embedded in the vibrant research environment in Bristol, including the Centre for Computational Chemistry and the Bristol BioDesign institute, ensuring a wide range of interactions, seminar programmes and courses.