Dynamic Protein Design

Supervisory team:
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Collaborators: Prof Richard Chahwan (University of Zurich)

Host institution: University of Exeter (Streatham)

Project description:
The student will pioneer a new interdisciplinary approach to discover the dynamic features within protein structures that underpin their ability to switch between functionally distinct states: allostery. Despite allostery appearing in the biochemistry textbooks for decades now, the mechanisms that enable proteins to act as biosensors remain unknown. Ultimately, we anticipate that this project will provide molecular mechanisms to explain allostery and demonstrate proof of principle that we can now design not only proteins, but functional proteins.

The project aims to uncover the molecular mechanisms of allostery. The goal is to identify the structural dynamics that underpin allostery in two important proteins (glycogen phosphorylase and CRISPR-Cas9) and test this new understanding with targeted molecular engineering at these precise locations. This is the key step towards a scalable approach to identify general principles of allostery throughout the proteome and so give rise to next generation AI tools for dynamic protein design. First, you will show proof of principle with the first ever allosteric enzyme to be described, glycogen phosphorylase, which we have previously characterised. Next, you will apply your growing expertise to decipher and engineer allostery of substrate recognition in genome editing enzymes (e.g. CRISPR-Cas9). The transient molecular structural changes that occur during enzyme allostery will be identified, using an in-house coarse-grained mathematical model that has been shown to be predictive of allosteric pathways. This will reveal the precise structural locations that alter during the enzyme activation process. State-of-the-art structure prediction and protein design tools will be used to create an in silico library of designed enzyme variants by making mutations at these identified sites. The impact of the sequence changes on allosteric function will be assessed by the coarse-grained model. A representative sample of enzymes with a range of predicted behaviours will be selected to be recombinantly produced and analysed by millisecond time-resolved non-equilibrium hydrogen/ deuterium-exchange mass spectrometry (HDX-MS) using in-house prototype robotics.

In this way, we will take a step forward in our understanding of the precise sub-molecular pathways and the dynamic molecular architecture that underpins functional switching in proteins. We will provide proof of principle for rational design of the structurally dynamic function of enzymes.

You will gain expertise in cutting edge structure prediction and protein design tools (RosettaFold; AlphaFold2, Rosetta, protein MPNN, RFdiffusion), major programming languages (MatLAB; Python), coarse-grained protein dynamics simulation, recombinant bacterial expression and purification and structural proteomics techniques including hydrogen/deuterium-exchange mass spectrometry.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.