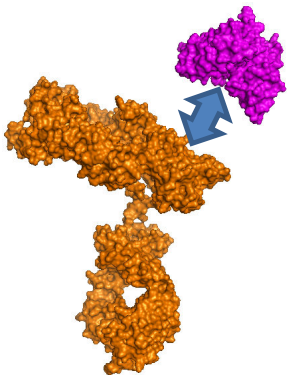
PhD opportunities in Computational Biology / Chemistry at the Manchester Institute of Biotechnology (MIB)

October 2013 start

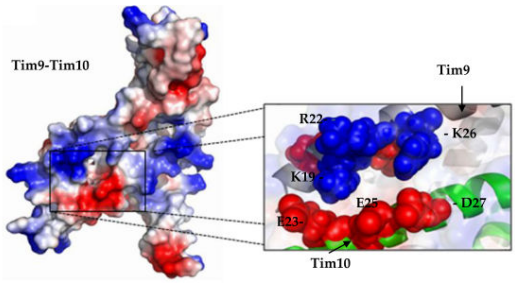
Deconstructing and reconstructing proteins: a combined experimental and computational approach to protein solubility. (Jim Warwicker, Robin Curtis, Jeremy Derrick, Alan Dickson)



It is becoming common practice to make use of biological activities in proteins domains, or combinations of domains, that have been excised from parent molecules. An obvious example lies in the engineering of antibodies and their fragments, but there are many others. The philosophy of modular function is one of the driving forces for synthetic biology. However, protein domains have not evolved to be soluble in combinations other than those found in naturally occurring proteins. Thus stability and solubility problems are often encountered with protein fragmentation. This problem arises in the analysis of protein function, where a divide and conquer approach to characterise multi-domain proteins is often used. It is also the case in the development of biological molecules (biologics), such as humanised antibodies, for therapeutic purposes. Since biologics are of increasing importance in the pharmaceutical sector, the time is right to improve our fundamental understanding of the molecular determinants of stability and solubility. The project will concentrate on solubility, which plays a major role in the development of biologics. Directly relevant to this project is the case where parts of an antibody are excised. In order to be able to reconstruct these deconstructed proteins, engineering increased solubility into the framework structure, we will need to improve our tools for predicting solubility. Importantly, some of the computational groundwork is already in place, with a physico-chemical model for protein solubility being developed in JW's group. The project will focus on experimental tests using model systems with poor solubility, and model-based improvement in designed solubility. This information will feed back into the model, to develop a prediction package for installation and use by other groups, as well as a web server allowing the research community to make predictions and re-designs online.

Specificity determinants within families of protein-protein interactions. (Jim Warwicker and Chandra Verma, BII, Singapore)

Specificity in protein-protein interactions determines biological process, and discovery of these interactions still drives much cellular biochemistry. As a complement to experimental methods (both large- and small-scale), bioinformatics has a role to play, particularly when based on structures or models. Analysis of comparative models of protein complexes is an area of growing importance, where the use of sequence databases linked to homology-based modelling allows users to ask the question of whether a particular complex observed in one case, is likely to be maintained in other cases. The project will address three key aims in this area: (A) Development of a comparative model-based procedure that gives a statistical assessment of the likelihood of complex formation; (B) How much does modelling the flexibility of a potentially interacting pair improve performance?; (C) Where a set of interactions are formed between two homologous protein families, what relative roles are played by polar and non-polar interactions in determining specificity? The groups in this collaboration, under the joint Manchester-A*STAR/Singapore training programme, have expertise in the structural bioinformatics techniques that underpin the project, particularly studies of molecular interactions and molecular dynamics/flexibility. Progress in these areas will be coupled to existing databases of protein-protein complexes, such as SCOPPI, and to biological systems of particular interest to the Manchester and Singapore supervisors and their experimental collaborators.



PhDs may suit candidates from range of science backgrounds, further information is available from:

jim.warwicker@manchester.ac.uk MIB, tel: +44 (0)161-306-4490
http://www.ls.manchester.ac.uk/phdprogrammes/ 1st project is BBSRC DTP, 2nd is A*STAR