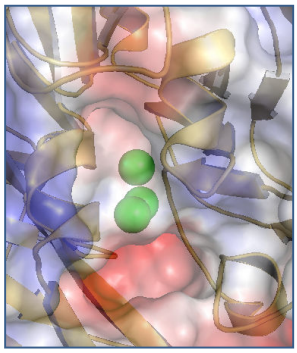
Funded PhD projects available in Jim Warwicker's group (MIB) jim.warwicker@manchester.ac.uk

Suitable for Biologists interested in Bioinformatics, Chemists, Chemical Engineers

Developing a computational tool for modulation of redox potential in enzymes.
DTP: Co-Supervisors Sam DeVisser, Chris Blanford (University of Manchester)

The next stage of enzyme biotechnological development will include a coupling of theoretical understanding with experimental measurements. Electron transfer is central to many enzyme reactions, and modulation of redox potential is used to optimise catalysis in evolved catalytic systems. The hypothesis of this project is that theoretical methods, combined with experimental redox data for a wealth of naturally occurring enzymes, will allow predictive methods to be constructed for engineering enzyme activity, for example through directed evolution. Our supervisory team reflects three elements of the project. First, the role of protein in modulating redox potentials can be described by continuum electrostatics methods that Jim Warwicker's group has contributed to developing [1,2]. Second, the effect of substituents on redox cofactors is handled with quantum mechanics/molecular mechanics (QM/MM) methods, in which Sam de Visser's group has expertise [3]. Third, Chris Blanford has experience in measuring the redox and electrocatalytic properties of enzymes [4], particularly in the biotechnologically relevant laccases [5]. This experimental outlet will provide an important element of validation and iterative development with the computational part of the project. One of the challenges in the era of data-rich biology and biotechnology is making best use of existing measurements in developing predictive models. For heme groups [2] and laccases [5] alone there exist many structure – redox potential pairs. Combined with further data from the literature and our theoretical expertise, a novel tool will be delivered to the biocatalysis research community.

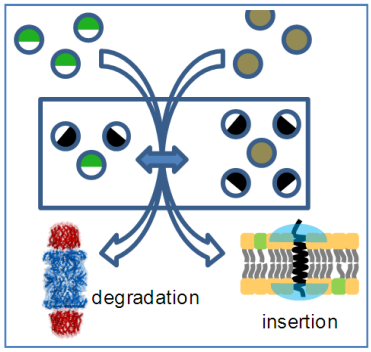


[1] Moutevelis E & Warwicker J (2004) *Protein Sci* **13**:2744. **[2]** Zheng Z & Gunner MR (2009) *Proteins* **75**:719. **[3]** Kumar D et al (2011) *J Am Chem Soc* **133**:3869. **[4]** Cracknell JA & Blanford CF (2012) *Chem Sci* **3**:1567. **[5]** Rodgers CJ et al (2009) *Trends Biotech* **28**:63.

http://www.dtpstudentships.manchester.ac.uk/ **Application deadline Friday 6 December 2013**

Investigating the recognition and interactions of non-polar helices in biology.
A*STAR: Co-Supervisors Frank Eisenhaber, Birgit Eisenhaber (Bioinformatics Institute, Singapore)

Bioinformatics is playing a crucial role in the post-genomic era of biology. This project will use bioinformatics to leverage data from sequence, structure and interaction databases in making models for protein function. The focus will be on non-polar helices, most familiar as mediators of a large proportion of transmembrane (TM) segments in membrane proteins. Cell biologists are discovering that trafficking and quality control complexes are recognising TM segments alongside non-polar helices from water-soluble proteins, and then sending these elements to different fates (Leznicki et al 2013). This is reminiscent of work in Frank and Birgit Eisenhaber's group identifying different types of non-polar helix, according to hydrophobicity and sequence complexity (Wong et al 2012). The first part of this project will use cell biological and structural data, alongside bioinformatics analysis and protein-protein interaction databases (e.g. Chatr-Aryanmontri et al 2013), to make models for recognition and differential targeting of non-polar helices by quality control and trafficking machinery. These models will be tested and iterated by collaborations with our experimental colleagues.



A second part of the project again looks to build on the separation of non-polar helix types, but this time in terms of functional differentiation for TM segments that have been correctly membrane inserted. We know a lot about amino acid non-polarity dictating, on average, helix embedding in a membrane (e.g. Hessa et al 2007), but we know less about the instances where charge is forced into the membrane, often to mediate function. This part will identify membrane-embedded charge clusters (including hydrogen-bonding groups) in known membrane protein structures, and characterise these with sequence and structural bioinformatics methods, including algorithms for calculating charge-charge interactions developed in Jim Warwicker's group. Then sequence databases of families related to the known structures will be probed for charge clusters, models made, and predictions of potentially functional regions compared with the experimental literature.

Chatr-Aryanmontri A et al. (2013) The BioGRID interaction database: 2013 update. *Nucl Acids Res* **41**:D816-23.
Hessa T et al (2007) Molecular code for transmembrane-helix recognition by the Sec61 translocon. *Nature* **450**:1026-30.
Leznicki P et al. (2013) The association of BAG6 with SGTA and tail-anchored proteins. *PLoS One* **8**:e59590.
Wong, W.-C. et al. (2012) Transmembrane helix: simple or complex. *Nucl Acids Res* **40**:W370-W375.

http://www.ls.manchester.ac.uk/phdprogrammes/singaporeastar/ **Application deadline: see URL**