MANCHESTER 1824

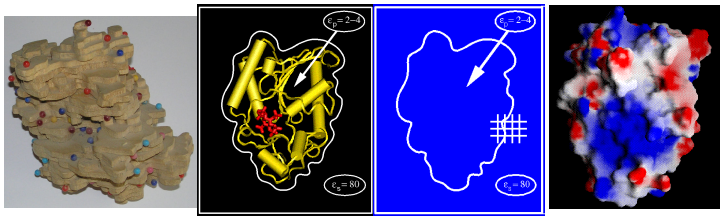
The University of Manchester

Computational Biology and Chemistry in Jim Warwicker's group at the MIB.

Structure/Function relationships in biological molecules, from algorithm development to genomic application and hypothesis discovery, in a collaborative environment with experimental colleagues. (jim.warwicker@manchester.ac.uk)

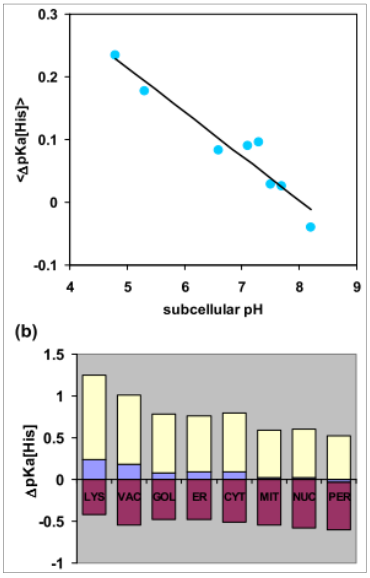
Algorithms: Charges, Interactions and pH-Dependence

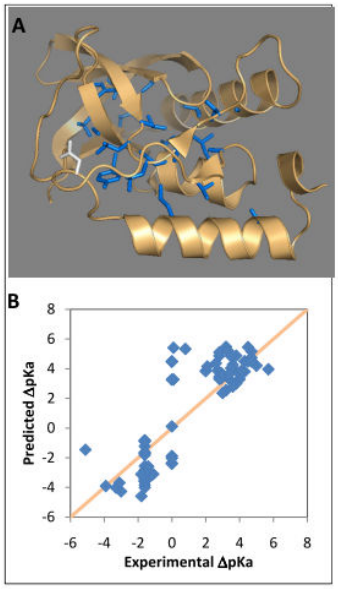
Continuum models for charge interactions in proteins and other biological molecules.



Models are developed to improve prediction of pH-dependent properties e.g. below right, staphylococcal nuclease engineering as a test-bed.

Models are applied proteome-wide e.g. below left, entire PDB analysed in terms of subcellular location, environmental pH. Histidine positioning has evolved to reflect subcellular location.

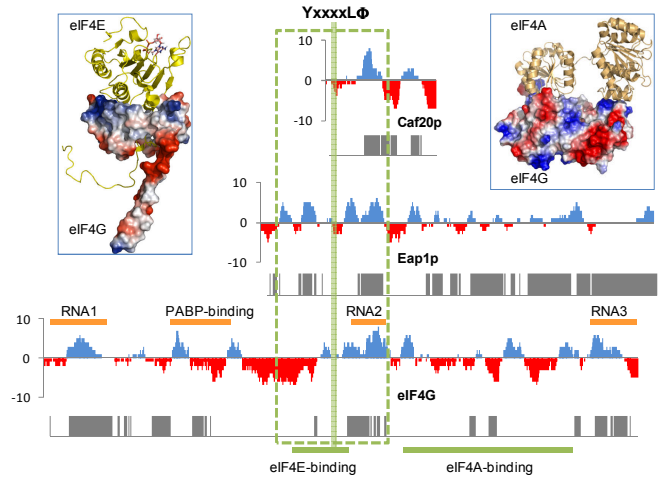




References: BMC Biology (2009) 7:69.
Proteins (2011) 79:3374-3380.

Algorithms: Disorder and Post-Translational Modifications

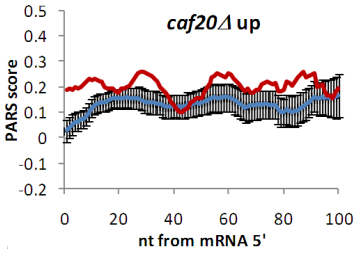
Many proteins contain disordered regions. These vary in their charge and we can map these variations to functional differences, e.g. with Gene Ontology. A recurring theme is the complementarity of charge interactions between binding partners. Two areas of particular interest are the tuning of interactions by phosphorylation, and the use of charge density to select for secondary structure-dependent nucleic acid binding (below).



Above: Properties of 4E-BPs and eIF4G. Plots of (windowed) predicted structural disorder and net charge, are shown for each of Caf20p, Eap1p, and eIF4G (Tif4631p).

Right: The mRNA binding proteins have been deleted in yeast, and associated sets of up- and down-regulated mRNAs recorded. Combining these sets with transcriptome-wide measurement of secondary structure, (the PARS score), reveals mRNA secondary structure specificities for the binding proteins.

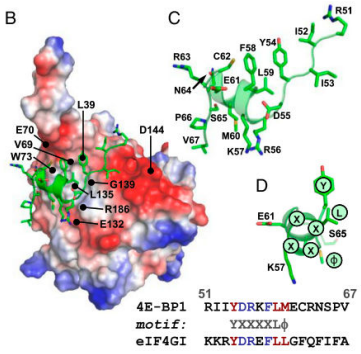
This has implications for assessing the results of high-throughput measurement of protein – RNA binding, since we predict that ordered RNA binding domains will be supplemented by disordered regions.



Reference: Nucleic Acids Research (2012) 40:7666-7675.

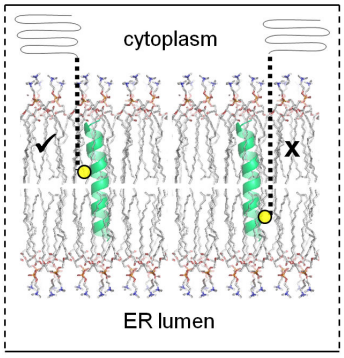
Collaboration Examples

A disorder/order transition regulates eIF4E-mediated translation.



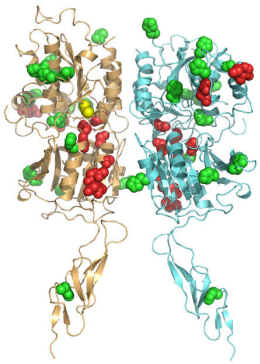
PNAS (2010) 107:17627-17632

Tuning the membrane partitioning of PEGylated tail anchor proteins.



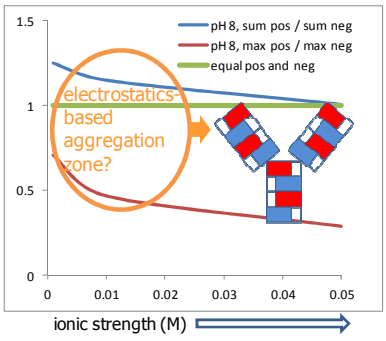
Biochem J (2011) 436:719-727.

pH-dependence of channels and receptors. Examples: Calcium Sensing Receptor, ASIC.



In preparation

Solubility prediction - collaborations with colleagues in Manchester and Industry.



Ongoing

Current Group

Ivan Sazanavets	PhD student	pH-dependence of ion channels; redox energetics in proteins (BBSRC CASE with Astra Zeneca)
Rose Keeling	PhD student	Phase separation in antibody solutions (with Robin Curtis and MedImmune, BBSRC BRIC funded)
Alejandro Carballo	PhD student	Improving protein solubility and expression (with Alan Dickson, CONACYT funded)
Spyros Charonis	PhD student	Computational models for protein solubility (with Robin Curtis, EPSRC funded via UCL network in Emerging Therapeutics)
Stefan Ivanov	PhD student	Modelling specificity in protein-protein interactions
Max Hebditch	PhD student	Antibody structure in solution (with Robin Curtis)

Grants with experimental group PDRAs: Steve High – membrane protein biosynthesis; Robin Curtis/James Austerberry – protein solubility