MANCHESTER 1824

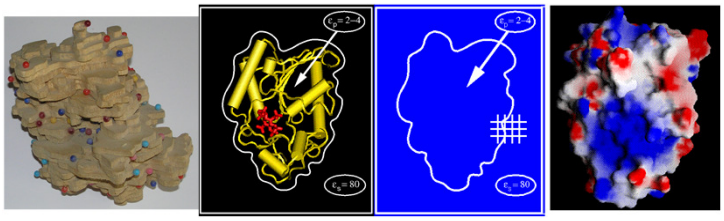
The University of Manchester

# 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)

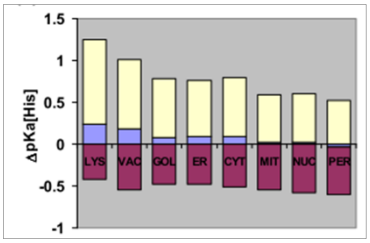
## Algorithms: Charges, Interactions and pH-Dependence

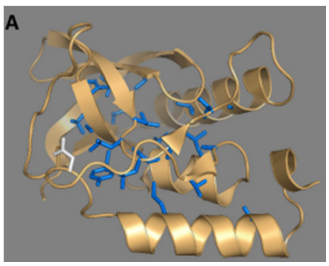
Continuum models for charge interactions in proteins and other biological molecules.



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.

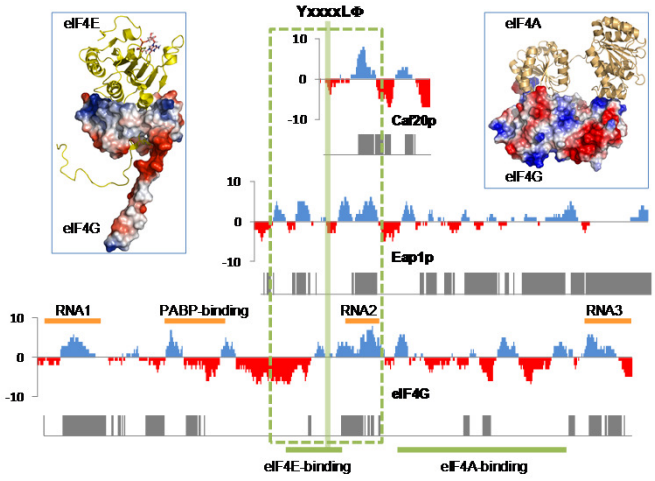



*References: BMC Biology (2009) 7:69; Proteins (2011) 79:3374-3380.*

## Algorithms: Disorder and Post-Translational Modifications

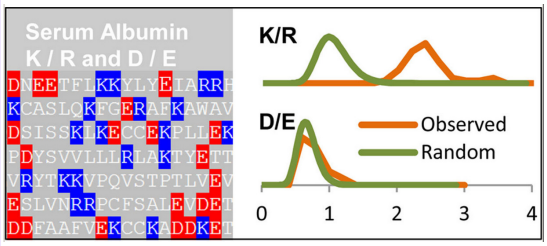
Many proteins contain disordered regions. Variations in charge can be mapped to functional differences, e.g. with Gene Ontology. A recurring theme is the complementarity of charge interactions between binding partners, including modulation by e.g. phosphorylation.




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).

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

## Biotechnology and Bioprocessing

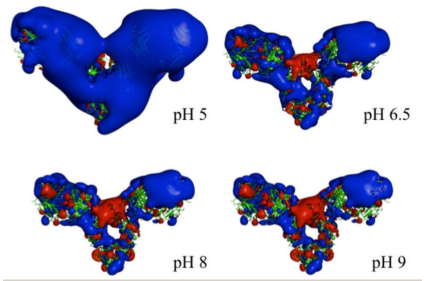



Left: Proteins at high concentrations inside or outside of cells tend towards a higher content of lysine relative to arginine. This observation could be the basis for a conservative modification to improve solubility.

*Mol Pharm (2014) 11:294-303.*

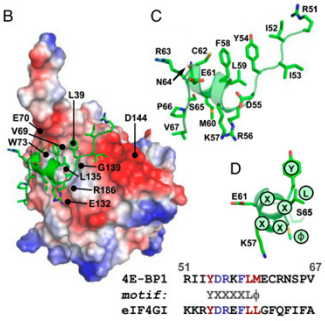
Right: Electrostatic interactions play a key role in the properties of monoclonal antibody solutions at high concentration (and thus in the bioprocessing, formulation, storage and delivery of mAb biologics). Charge calculations allow us to visualise transition between isotropic and anisotropic potential fields.

*Mol Pharm (2014) 11:2475-2489.*



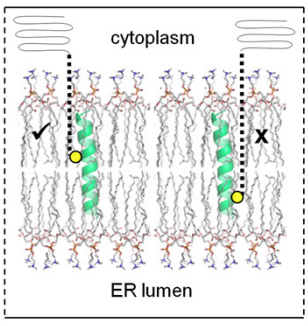

## Collaboration Examples

A disorder/order transition regulates eIF4E-mediated translation.



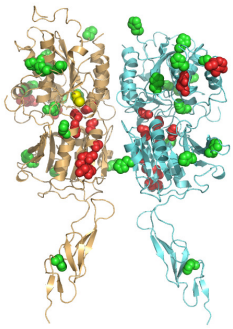

*PNAS (2010) 107:17627-17632*

Tuning the membrane partitioning of PEGylated tail anchor proteins.



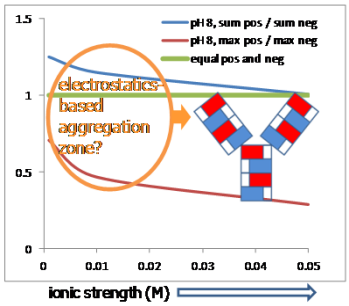

*Biochem J (2011) 436:719-727.*

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



*J Am Soc Nephrol (2015) 26:2163-2171*

Solubility prediction - collaborations with colleagues in Manchester and Industry.




*Ongoing*

## Current Group

| | | |
|---|---|---|
| Rose Keeling | PhD student | Phase separation in antibody solutions (with Robin Curtis and MedImmune, BBSRC BRIC funded) |
| Alejandro Carballo | PDRA | Developing web tools for solubility prediction |
| 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 (joint with BII, Singapore, Peter Bond Co-Supervisor) |
| Max Hebditch | PhD student | Antibody structure in solution (with Robin Curtis) |
| James Baker | PhD student | Sequence analysis of transmembrane helices (joint with BII, Singapore, Frank and Birgit Eisenhaber Co-Supervisors) |
| Nick Fowler | PhD student | Computational and experimental investigation of redox potential (joint with Sam DeVisser and Chris Blanford) |
| Luke Holloway | PhD student | iCASE funding with MedImmune partner, Co-Supervisor in Manchester, Robin Curtis |
| | | PDRA Grants with collaborators: Steve High – protein quality control ; Jeremy Derrick and others – protein solubility |