1. Project Title: UKCP WP3

2. Title of Case Study: Density functional theory calculations on entire proteins for free energies of binding: Application to a model polar binding site

3. Summary of Case Study:

In drug optimization calculations, the molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) method can be used to compute free energies of binding of ligands to proteins. The method involves the evaluation of the energy of configurations in an implicit solvent model. One source of errors is the force field used, which can potentially lead to large errors due to the restrictions in accuracy imposed by its empirical nature. To assess the effect of the force field on the calculation of binding energies, in this project we used large-scale density functional theory (DFT) calculations as an alternative method to evaluate the energies of the configurations in a "QM-PBSA" approach. Our DFT calculations were performed with a near-complete basis set and a minimal parameter implicit solvent model, within the self-consistent calculation, using the ONETEP program on protein–ligand complexes containing more than 2600 atoms. We applied this approach to the T4-lysozyme double mutant L99A/M102Q protein, which is a well-studied model of a polar binding site, using a set of eight small aromatic ligands. We observed that there is very good correlation between the MM and QM binding energies in vacuum but less so in the solvent. The relative binding free energies from DFT are more accurate than the ones from the MM calculations, and give markedly better agreement with experiment for six of the eight ligands. Furthermore, in contrast to MM-PBSA, QM-PBSA is able to correctly predict a nonbinder

4. Key outputs:

Density functional theory calculations on entire proteins for free energies of binding: Application to a model polar binding site. S. J. Fox, J. Dziedzic, T. Fox, C. S. Tautermann, and C.-K. Skylaris, Proteins 82 (2014) 3335-3346

This work was part of the PhD thesis of Dr Stephen J. Fox and the project was done in collaboration with Boehringer Ingelheim. This work demonstrated the importance of using large scale first principle electronic structure calculations in drug optimisation applications as it allows us to overcome the limitation of force field based approaches (lack of explicit electronic polarisation and sometimes lack of accurate parameterisation). Future extensions will include more sophisticated free energy approaches and more complex proteins.

5. Names of key academics and any collaborators:

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Dr Thomas Fox and Dr Christofer S. Tautermann
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6. Sources of significant sponsorship (if applicable):

BBSRC Industrial CASE studentship supported by Boehringer Ingelheim

7. Who should we contact for more information?

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