PhD Studentship in Using Crystal Data to Address the Solubility of Pharmaceutical Compounds

University of St Andrews 600th Anniversary Studentship

University of St Andrews in collaboration with the Cambridge Crystallographic Data Centre and the University of Strathclyde

Project: Hydrate Crystal Structures, Pair Distribution Functions & Computing Solubility.

Supervisors: Dr John Mitchell (St Andrews), Dr Colin Groom (CCDC), Professor Maxim Fedorov & Dr David Palmer (Strathclyde),

This 3.5 year PhD research project, due to start Oct 2013, is a collaboration between the University of St Andrews, the Cambridge Crystallographic Data Centre (CCDC), a University Partner Institute of the University of Cambridge (www.ccdc.cam.ac.uk), and University of Strathclyde. The doctoral student will be formally based at St Andrews but will spend some of their time at the CCDC. Prof. Fedorov and Dr Palmer will be academic collaborators. The successful candidate will be registered as a postgraduate student at the University of St Andrews, with the expectation of submitting a PhD thesis at the conclusion of the project.

Poor aqueous solubility remains a major cause of attrition in the drug development process. Despite theoretical developments, solubility of drug-like molecules still eludes truly quantitative computation. We have recently [1] shown that accurate first principles calculation is now becoming possible – provided that both the crystalline and solution phases are described by accurate theoretical models. This project aims to make use of experimental crystal data of organic hydrates to compare the distribution functions in the crystalline and solution phases. We will firstly use the Cambridge Structural Database (CSD) to obtain and analyse the distributions of water molecules in organic molecular hydrate crystal structures. We will compare these with the theoretical, solution phase data available for distributions of water around drug-like organic solutes. We will then use the crystal data to improve our understanding and models of the crystalline and solution states. We will subsequently develop better 1D and 3D RISM (Reference Interaction Site Model) [2] parameterized models for computing the aqueous solubility of drug-like molecules and also a specific methodology for computing the solubility of crystalline hydrates. In extensions of this work, we plan to model crystal nucleation, kinetic solubility, the hydrophobic effect [3] and the role of water in protein-ligand binding.

The studentship offers the opportunity for a gifted individual to work on a problem of great significance, supported by two scientific groups of world standing. The candidate should have a first or upper second Bachelor or Master of Science degree, or equivalent, in chemistry, physics, biochemistry, computer science or a similar discipline. A familiarity with molecular modelling, or computer programming ability, would be useful additional experience. The successful candidate will gain experience of a wide variety of computational methods, database searching tools, and statistical analysis methodologies in a discipline which is of direct relevance to the pharmaceutical industries.

The 3.5 year project is funded jointly by a University of St Andrews 600th Anniversary PhD Scholarship and by the CCDC, with a stipend £2000 per year above the standard research council level. **To be eligible for a full award, applicants must satisfy UK or EU residency criteria**.

Please submit a full CV and covering letter to Dr John Mitchell, Purdie Building, University of St Andrews, North Haugh, St Andrews, Scotland KY16 9ST. For informal enquiries contact Dr John Mitchell (jbom@st-andrews.ac.uk). The Deadline for applications is 31st May.

[1] DS Palmer, JL McDonagh, JBO Mitchell, T van Mourik & MV Fedorov, *J. Chem. Theor. Comput.*, **8**, 3322 (2012).
[2] EL Ratkova, GN Chuev, VP Sergiievskyi & MV Fedorov, *J. Phys. Chem. B*, **114**, 12068 (2010)
[3] MC Stumpe, N Blinov, D Wishart, A Kovalenko & VS Pande, J. Phys. Chem. B, 115, 319 (2011)

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