Title: Harnessing the predictive power of large-scale first principles quantum mechanical calculations in the life sciences

Applications are invited for a prestigious EPSRC industrial CASE PhD studentship in the Skylaris research group to work on applying large-scale first principles quantum mechanical simulations to problems in the life sciences.

Biomolecular simulations of properties and processes such as the interactions between proteins, DNA and potential drugs play a major role in applied life science research as they augment and guides experimental investigations. These interactions are governed by electrostatics, electronic polarisation and charge transfer and by purely quantum effects such as Pauli repulsion. Thus, to provide an accurate description of these interactions it is evident that the quantum theory of electronic structure must be used. However biomolecular simulations are commonly carried out with classical (molecular mechanics) atomistic force fields which provide a “ball and spring” description of molecules with fixed charges and lack the ability to explicitly capture electronic rearrangements. This choice is made out of necessity because the computational effort associated with accurate quantum methods such as Density Functional Theory (DFT) scales as the third power of the number of atoms and is prohibitive for calculations with thousands of atoms, as required for proteins and other biomolecular entities. Recently this situation has started to change due to the ever-increasing power of supercomputers and new developments in theory such as linear-scaling DFT.

This PhD project will aim to apply DFT calculations to current biomolecular problems relevant to the pharmaceutical industry to demonstrate accuracy and predictive capabilities way beyond the possibilities of classical approaches. The ONETEP program for linear-scaling DFT calculations will be used as it is capable of calculations with thousands of atoms and retains the near-complete basis set accuracy of conventional cubic-scaling DFT. A prominent role in this work will be played by recent and ongoing developments in ONETEP such as exchange correlation functionals which have dramatically higher accuracy than the commonly used GGA functionals, advanced solvent models, and methods for decomposing the interactions to quantities that have chemical relevance. These quantum methods will be further developed and validated in test cases from the pharmaceutical industry. Free energies of binding rather than energies are required to evaluate the thermodynamic stability of biomolecular complexes and this poses an additional challenge as the entropic contribution to the free energies requires (often) extensive configurational sampling. For this a hierarchy of approaches of increasing sophistication will be developed, ranging from methods which average configurations to rigorous statistical mechanics approaches that compute the change from a classical to a quantum description. Another direction that will be explored, which is relevant to drug design, concerns the calculations of protonation states of biomolecules and of drugs, which is important for ensuring that the correct protonation state is selected in drug design studies. Preliminary work in this area has shown that DFT calculations produced consistently better results than classical methods. The pioneering applications of quantum methods during this PhD will be formulated into workflows that will provide robust generally applicable frameworks suitable for future applications of these methods on biomolecular problems. The project will also explore ways of extracting “added value” from the DFT calculations such as visual representations that provide insight into the mechanism of interactions and ways for simpler but less computationally expensive modes of DFT operation for quick qualitative comparisons.

The project will be co-supervised by Professor Chris-Kriton Skylaris (University of Southampton) and Dr Adrian Stevens (BIOVIA). It will be based in the group of Professor Chris-Kriton Skylaris in Southampton. BIOVIA will provide periods of placement in their research headquarters in Cambridge where the PhD student will be able to get first-hand experience in case studies from the pharmaceutical industry and in other methods for
simulations in the Life Sciences from the Discovery Studio suite of BIOVIA to integrate ONETEP within this framework.

This is a fully funded PhD studentship. Applications are encouraged from top-level graduates in Chemistry, Physics or related subject. Experience with first principles quantum mechanical calculations and/or classical molecular dynamics simulations is desirable but not essential. If you wish to discuss any details of the project informally, please contact Professor Chris-Kriton Skylaris, Email: c.skylaris@soton.ac.uk

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