"*A hybrid molecular simulation/machine-learning framework for rapid and accurate computation of absolute binding free energies of lead-like molecules"*

3.5-year fully funded CASE PhD studentship, September 2021, stipend ca. £15.5k pa

Supervisors: Dr Julien Michel, School of Chemistry, University of Edinburgh ; Dr Daniel Cole, School of Natural and Environmental Sciences, Newcastle University ; Dr Graeme Robb, AstraZeneca, Cambridge.

Applications are invited for a PhD studentship in the Michel lab (http://www.julienmichel.net) in the area of biomolecular simulations and computer-aided drug design. The EaStCHEM school of Chemistry at the University of Edinburgh is among the top ranked departments within the EU. This research project will be carried out in collaboration with the Cole lab at Newcastle University (https://blogs.ncl.ac.uk/danielcole/) and with the pharmaceutical company AstraZeneca. Placements at the partner institutions will be arranged at different stages of the project.

Free Energy Perturbation (FEP) methods are increasingly used to guide *in silico* potency optimisation of preclinical candidate compounds. FEP is most commonly used in the context of Relative Binding Free Energy (RBFE) calculations that are well suited to hit-to-lead or lead optimisation stages of a drug discovery campaign. However, RBFE methods are limited to the calculation of differences in binding affinity between structurally related molecules. It is highly desirable to develop methodologies that achieve accuracy comparable to RBFE but are applicable to a broader class of drug design problems. Examples of high value problems outside the scope of RBFE include: prediction of binding modes; ranking of diverse chemotypes; prediction of binding selectivity profiles. Such problems can in principle be tackled using Absolute Binding Free Energy (ABFE) calculation methods. However ABFE are currently considered too computationally intensive and unreliable to be widely used.

This project will leverage preliminary results from the Michel lab to substantially increase the efficiency of ABFE calculations. In collaboration with the Cole lab, new simulation protocols that combine GPU-accelerated molecular dynamics simulations with machine learning of forcefields and sampling algorithms will be devised. The protocols will be benchmarked on diverse protein-ligand datasets of interest to AstraZeneca. The overall aim is to make ABFE calculations sufficiently rapid and accurate to enable routine use in industrial R&D. This is an exciting opportunity to develop next-generation computer-aided drug design software and methodologies. Upon completion of the studentship, the successful applicant will have gained strong technical expertise in molecular modelling, and worked closely with the pharmaceutical industry sector. This will prepare the student well for a future career in academia or industry.

Applicants with an excellent academic record in a chemistry/biochemistry/physics/high performance computing or related degree are encouraged to apply. The ideal candidate will have: strong knowledge in physical chemistry and/or biophysical chemistry; relevant research experience; excellent written and oral communication skills; enthusiasm for rational drug design, computational chemistry and scientific computing. Previous experience in computer programming (e.g. Python, C++) is desirable but not essential, provided the applicant is keen to develop skills in this area during the studentship.

Applications will be considered until a suitable candidate has been identified. Candidates should have or be about to obtain a 2.i or 1st class degree in a relevant discipline. To apply, please submit initially by email a CV, covering-letter describing your previous research experience and reasons for applying, as well as the names and email address of two referees in pdf format to Dr. Julien Michel julien.michel@ed.ac.uk. Informal enquiries are encouraged.