Project Title: Modelling protein covalent modifications with molecular simulation and machine learning

Application Reference: SAC21-17

Applications are invited for a collaborative PhD studentship to develop molecular simulation methodologies and software to model the effect of protein covalent modifications on molecular recognition mechanisms. Research supervision will be provided by the academic supervisor Julien Michel (School of Chemistry, The University of Edinburgh; http://julienmichel.net/) and the industrial supervisor Mark Mackey (Cresset, https://www.cresset-group.com). The student will be based at the University of Edinburgh, School of Chemistry and placements at Cresset will be arranged at different stages of the project.

Project Summary

Free Energy Perturbation (FEP) methods are increasingly used in preclinical drug discovery research to guide the optimisation of small molecules into potent protein ligands. Relative Binding Free Energy (RBFE) calculations are frequently applied to calculate differences in binding affinity between structurally related molecules, whereas Absolute Binding Free Energy (ABFE) calculation methods may be used to calculate binding affinities for series of structurally diverse molecules. To date FEP methodologies have been primarily used to model the interactions of non-covalent small molecule ligands with biological molecules.

This project will focus on developing and validating FEP methodologies to model the effect of protein structure modifications on molecular recognition mechanisms. Efforts will focus on biologics, peptidomimetic ligands, and covalent ligands for which robust simulation protocols are currently lacking. These classes of ligands present challenges for conventional FEP approaches tailored for small molecules because the ligands are often larger, more flexible, and can covalently bind to their target proteins. To address these issues this research will couple state of the art FEP simulation methodologies available in open-source software with advances in machine learning of potential energy functions to enable accurate modelling of binding energetics. The overall aim is to deliver a suite of protein FEP protocols 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 life sciences softtware 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 the first instance, informal enquiries (accompanied by a CV) should be directed to:
Julien Michel, School of Chemistry, University of Edinburgh, David Brewster Road, Edinburgh EH9 3FJ, UK.

Email: julien.michel@ed.ac.uk

The position will remain open until filled.

References

1) ''Assessment of Binding Affinity via Alchemical Free-Energy Calculations'' Maximilian Kuhn, Stuart Firth-Clark, Paolo Tosco, Antonia S. J. S. Mey, Mark Mackey, and Julien Michel *Journal of Chemical Information and Modeling* **2020** *60* (6), 3120-3130

2) ''Mechanism-Based and Computational-Driven Covalent Drug Design'' Yun Lyna Luo *Journal of Chemical Information and Modeling* **2021** *61* (11), 5307-5311

Equality and Diversity

The School of Chemistry holds a Silver Athena SWAN award in recognition of our commitment to advance gender equality in higher education. The University is a member of the Race Equality Charter and is a Stonewall Scotland Diversity Champion, actively promoting LGBT equality. The University has a range of initiatives to support a family friendly working environment. See our University Initiatives website for further information. University Initiatives website: https://www.ed.ac.uk/equality-diversity/help-advice/family-friendly

Funding Notes

The studentship is fully funded for 48 months from September 2022 and covers tuition fees and an annual stipend (starting at £15,609 per annum) for a candidate satisfying UKRI eligibility criteria.