EASTBIO Computational design of multi-state proteins using molecular simulations and machine learning

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Funding: This 4 year PhD project is part of a competition funded by EASTBIO BBSRC Doctoral Training Partnership. This opportunity is open to UK and International students and provides funding to cover stipend and tuition fees. Please refer to UKRI website and Annex B of the UKRI Training Grant Terms and Conditions for full eligibility criteria. Applicants must hold a first or upper second class UK honours degree or equivalent.

Closing date for applications: 6th January 2021

Project Details:
The ability to computationally design de novo proteins is a key technology that underpins future progress in synthetic biology and biomaterials discovery. However current *de novo* design methods tend to produce rigid, hyperstable folds that lack functionality. To progress towards truly functional *de novo* protein design it is crucial to design proteins that adopt multiple conformational states. This would enable the design of protein as catalysts, or biosensors or bioswitches that respond to environmental changes such as a variation in pH or temperature.[1]

Such an endeavour is challenging for the energy functions in current protein-design software because it requires designing folds that adopt structurally distinct yet energetically similar states. Rigorous molecular dynamics simulation methods that describe protein dynamics and solvation effects at the atomistic level have shown potential for such 'dynamic design' problems.[2] However current molecular dynamics methods are too slow and complex for routine application to protein design.

This PhD project will validate an interdisciplinary approach that leverages new classes of machine learning algorithms to substantially accelerate the speed of molecular dynamics simulations for *de novo* protein design problems. Throughout the project we will tackle a range of problems of fundamental importance in protein design, ranging from optimising secondary structure preferences of cyclic peptides,[3] to tuning the preferred oligomerisation states of *de novo* □-helical bundles.[4] Such systems are well suited to a combined data-driven/physics-driven molecular modelling approach owing to a large amount of existing experimental data, and validated energy functions for atomistic modelling. The accurate modelling of such multi-state systems will open new routes for the design of versatile building blocks for synthetic biology applications, and for the discovery of new biomaterials. Experimental validation of the design method will be performed by designing switchable □-helical bundles. Designs will be produced in the lab using either molecular biology or solid phase peptide synthesis and will be characterised *in vitro* using a range of biophysical techniques.

Throughout this project the student will receive advanced training in computational biology, structural bioinformatics, biophysical chemistry, machine learning and computer programming, with additional skills in experimental techniques such as protein production and characterisation. The Michel (https://www.julienmichel.net/) and Wood (https://www.wellswoodresearchgroup.com/) labs are committed to open-access research, and software and datasets generated during this project will be made publicly available. Informal enquiries are encouraged. Interested candidates should send to julien.michel@ed.ac.uk and chris.wood@ed.ac.uk a copy of their CV, and a brief description of their previous research experience and current research interests as soon as possible, preferably no later than 18th December 2020

References

(1) ''Towards functional de novo designed proteins'' Dawson et al. Current Opinion in Chemical Biology, 52, 102-111, 2019

(2) ''Dynamic design: manipulation of millisecond timescale motions on the energy landscape of Cyclophilin A'' Juárez-Jiménez et al. Chemical Science , 11, 2670-2680, 2020

(3) ''Designing Stapled Peptides to Inhibit Protein-Protein Interactions: An Analysis of Successes in a Rapidly Changing Field'' Bluntzer et al. ; O'Connell J ; Baker, TS ; Michel, J ; Hulme, AN Journal of Peptide Science, in press, 2020

(3) ''Navigating the structural landscape of de novo α-helical bundles'' Rhys et al. DN Journal of the American Chemical Society, 141, 8787-8797, 2019

Application Process:

To apply for an EASTBIO PhD studentship, follow the instructions below:
Check FindaPhD for our available projects and contact potential supervisors before you apply.
http://www.eastscotbiodtp.ac.uk/how-apply-0

Please send your completed EASTBIO application form, along with academic transcripts to Dr. Julien Michel (julien.michel@ed.ac.uk). Two references should be provided by the deadline using the EASTBIO reference form. Please advise your referees to return the reference form to Dr. Julien Michel (julien.michel@ed.ac.uk)

All EASTBIO (online) interviews will be in the week 8-12 February 2020 with awards made the following week.

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