Project Proposal for Join A*STAR Graduate Scholarship (Overseas) with the University of Cambridge:

"Identifying Druggable Protein-Protein Interactions by Computational Sampling of Cryptic Binding Pockets"

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Background and Current Situation

Protein-protein interactions (PPIs) mediate the majority of cellular processes and provide a large number of attractive molecular targets for treatment. However, few therapeutics have been targeted at PPIs[1] as it is evident that many PPIs involve large areas of relatively featureless contact and these present a major challenge to disruption by small molecules. It has been established that the contribution of individual surface amino acid residues to the free energy of binding is not uniform and that in many cases the majority of the binding energy is associated with a small number of surface hot spots.[2] A subset of these hot spots then represent suitable binding sites for small molecule inhibitors.[3] At present, the scientific basis for identifying such interactions and locating the hot spots within them that are vulnerable to disruption by small molecules is poorly developed. In particular, recent work has identified the importance of protein flexibility in facilitating small-molecule binding. So called "cryptic pockets" are not present in the unbound structure of the protein, but are revealed upon ligand binding. They are an important phenomena and have been discovered in a number of proteins including PLK1, RNA editing ligase, UDP Galactose Epimerase, Neuraminidase, HIV integrase, and MDM2.[4] However, these pockets are not typically observed in the unbound state of the protein and thus cannot be identified experimentally.

Objective and Approach

Molecular simulations can provide a route to characterize the conformational plasticity of proteins in atomic detail. However, due to the large system sizes and correspondingly large numbers of degrees of freedom, identifying cryptic pockets using computer simulation is challenging. The proposed project is focused on overcoming this challenge and this will be achieved through the completion of four objectives, provisionally one in each year of the project:

1) Understand the free-energy landscapes underlying the opening of cryptic pockets.
2) Develop fast sampling techniques to locate cryptic binding pockets efficiently.
3) Identify an effective multiscale approach to avoid sampling spurious degrees of freedom.
4) Validate the approach by studying proteins, with reference to previously identified cryptic pockets, and/or novel sites for subsequent validation.

Objectives 1-3 will be completed by studying a single well-understood test case. Objective 4 will be achieved by comparison with experimental data from X-ray crystallography for 5-10 test cases. The projects will take advantage of the expertise of the group of Dr David Huggins at the University of Cambridge in the areas of modelling protein surface[5] and free-energy calculations in aqueous environments.[6] Similarly, they will benefit from the expertise of Dr Peter Bond's group at BII A*STAR in modelling multi-component complexes[7] and coarse-grained simulations of biomolecular assembly.[8] Successful completion of these objectives will improve our understanding of the ubiquitous phenomenon of cryptic pockets and provide a basis for their exploitation in structure-based drug design.

References

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