IITB-Monash Research Academy

Indian Institute of Technology Bombay | MONASH University

An Indian-Australian research partnership

Project Title:	**Development of novel methods for prediction of transmembrane protein structure and drug binding**
Project Number	**IMURA0197**
Monash Supervisor(s)	Prof. Patrick Sexton, Prof. Arthur Christopoulos, Dr. John Simms
Monash Primary Contact:	Patrick.sexton@med.monash.edu.au, +61 3 9903 9069
IITB Supervisor(s)	Prof. Santosh Noronha
IITB Primary Contact:	noronha@iitb.ac.in, (022)25767238

Full names and titles / *Email, phone* / *Full names and titles* / *Email, phone*

Research Academy Themes:

Highlight which of the Academy's Theme(s) this project will address?
(*Feel free to nominate more than one. For more information, see www.iitbmonash.org)*

1. Advanced computational engineering, simulation and manufacture
2. Infrastructure Engineering
3. Clean Energy
4. Water
5. Nanotechnology
6. Biotechnology and Stem Cell Research

The research problem

Define the problem

Although much progress has been made in understanding proteins in the absence of direct knowledge of 3D-structure, the ability to elucidate high resolution structure has provided major advances in understanding the molecular basis of protein function. High resolution structures also provide a key framework for experimental planning and interpretation of data and have been used for understanding how drugs bind and, indeed, for drug discovery. Recent advances in technology and automation have led to an ever increasing number of protein structures from x-ray crystallography and nuclear magnetic resonance analyses. Despite this, the elucidation of structure for some of the most important protein families has been extremely difficult, as is the case for membrane proteins that constitute the largest group of drug targets. The absence of individual structures for GPCRs has led to a need for alternate methods for deriving high resolution structural information; particularly in the application of molecular modelling methods to generate predictive models of the receptors. To date, most transmembrane spanning protein models have been built through homology modelling. However, such models are generically most closely related to the template structure. Therefore, at best, such models can only be considered low resolution approximates of the true protein structure, and while these may be useful in understanding aspects of protein function and in experimental planning, they are insufficient to allow meaningful interpretation of the likely side chain interactions that contribute to drug binding.

An alternate to homology modelling is the ab initio prediction of protein structure. In the case of TM helical proteins, which are a major group of drug targets, the problem can essentially be broken up into 3 major tasks. 1) the prediction of helical secondary structure, 2) packing of the helices and 3) prediction of the structure of the interconnecting loops. In addition to this, we require methods that can allow refinement of potential drug binding pockets in the protein, as this is often a key to use of such models for prediction of drug binding. Within Monash University, the project supervisors have developed new methods to address

key elements of TM helical prediction and packing for the 7TM domain G protein-coupled receptors, as well as for prediction of drug binding pockets that reside principally in the TM region of the receptor. The IITB supervisors are working on methods to improve interconnecting loop modelling; this latter methodology is likely to be very important for prediction of drug binding to receptor regions that involve key interactions with loop residues.

Project aims

The aims of the current project are to 1) improve the efficiency and automation of existing methods for TM folding and packing; 2) improve the performance of TM packing with an aim to reduce reliance on low resolution structural information for derivation of packing solutions; 3) develop methods to improve modelling of interconnecting loops; 4) improve the prediction of drug binding to TM proteins.
Method development would be applied to G protein-coupled receptors and also to an alternate TM spanning protein, that of P. falciparum TGS1 protein.

Expected outcomes

The development of novel procedures for improved prediction of protein structure; particularly that of transmembrane helical proteins that form a major target grouping for drug development.
The development of methods for prediction of novel compounds that bind to modelled proteins.
The identification of novel lead compounds that may be developed as either research tools, or potentially as lead candidates for drug development.

How will the project address the Goals of the above Themes?

Under Themes 1 and 6. The project will develop novel computational methods for simulating protein structure and drug binding. It has the potential to lead to improved understanding of protein structure and to identify new tools for study of protein function.