IITB-Monash Research Academy

Indian Institute of Technology Bombay | MONASH University

An Indian-Australian research partnership

Project Title:	**Monitoring the interactions of drugs with cellular targets to enhance drug discovery**
Project Number	**IMURA0469**

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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

There is an impending crisis in the practice of medicine, as we know it today. The treatment of routine infections may no longer be possible because of the increasing prevalence of drug resistant bacteria. Humanity may return to the dark ages of mass deaths due to uncontrolled infections because one of the pillars of modern medicine, the antibiotic, perhaps the principal reason for our leading long and healthy lives today, is under threat. These seemingly ominous statements are in fact the considered opinions of leading health experts and organizations around the world. To quote a WHO summary "A post-antibiotic era – in which common infections and minor injuries can kill – far from being an apocalyptic fantasy, is instead a very

real possibility for the 21st Century." (Antimicrobial resistance (AMR): global report on surveillance, WHO, 2014). Public Health England has recently estimated that by 2050 the global cost of AMR will be up to $1 trillion and will account for 10 million extra deaths a year. Indeed, in many countries emergency task forces have been established to recommend courses of action to avoid the catastrophic consequences of drug resistant bacteria.

Finding new drugs with new modes of action is the focus of much of the research to deal with AMR. However, an equally important but lower profile challenge is to develop new analytical methodologies to reliably screen potential drugs against their potential cellular targets. Many of the targets for AMR drugs are high aspect ratio complex assemblies of molecular components such as membranes, cytoskeletal protein fibres, molecular machines, enzymatic clusters and peptidoglycan layers – all of which are challenging to characterise by traditional techniques. Flow linear dichroism (LD) is a technique to characterise binding of drugs to such large, comparatively irregular, assemblies of molecules – precisely what is required for AMR drug development. Sometimes external and occasionally internal calibration can enable LD to be a quantitative measure of drug binding. More commonly, a qualitative or semi-quantitative indication of binding is all that can be deduced because we do not understand how the semi-rigid structures of interest behave in flow, and the LD signal is crucially dependent on the degree of sample orientation.

Project aims

The aim of this project is to develop a predictive theoretical approach to determining how intermolecular interactions control the flow behaviour of polymeric liquids, and determines LD signal magnitude. This will enable LD to be used as a quantitative screen of drug molecule binding to high aspect ratio molecular targets in bacteria. The specific goal of the project is to determine the orientation parameter (and hence the LD spectrum) of semi-dilute semi-rigid polymers using Brownian dynamics methodologies.

The search for new antimicrobial agents needs new quantitative techniques to screen potential drugs with different targets, and to probe molecular mechanisms. Linear dichroism has the potential to be such a technique if the dependence of the signal on the behaviour of semi-rigid semi-dilute polymers in flow can be predicted. This project aims to develop Brownian dynamics simulation methods to predict how polymers behave in flow. The new methods will be tested on DNA and control data will be collected at the University of Warwick to calibrate theoretical methods. The aim is to develop a software tool to compute time-dependent probability density functions for orientation distributions of semi-dilute semi-rigid biomolecular assemblies. The software tool from this project will make linear dichroism a truly quantitative structural tool able to give dynamical information on complex biomacromolecular assemblies such as those involved in the bacterial cell division, DNA replication machinery etc.

Expected outcomes

The outcomes of the project will include:
(i) The development of a validated software tool that can directly compute time-dependent probability density functions for the orientation distributions of semi-dilute semi-rigid biomolecular assemblies.
(ii) Integration of theoretical and experimental approaches (to be carried out at the University of Warwick, UK) to enable the maximum level of dynamic structural binding information to be extracted from LD spectra.
These outcomes will lead to the development of better quantitative assays for the effect of potential drugs on bacterial cell division structures. The capacity to accurately and quantitatively monitor the action of a drug on target cellular processes will greatly enhance our capacity to rapidly screen drug candidates, and will consequently have direct application in the design of new modes of drug action that circumvent bacterial resistance in both clinic and environment.

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

This project will enhance our ability to understand mechanisms in biological systems. The research in this project and the resulting analytical methodologies will contribute to enabling aspects of the Strategic Research Priority "Living in a changing environment" and understanding the fundamental molecular aspects of Biodiversity—all of which is essential for harnessing biomolecular processes whether in health care or biotechnology. The industry is dependent on analytical science for its competitiveness and productivity. Any step-change in performance is going to be dependent both on availability of new techniques with novel capabilities, enhanced sensitivity and selectivity and on a new kind of problem solving scientist who can

work across the theory/experiment “divide”. This project contributes to these goals.

Capabilities and Degrees Required

The following capabilities are essential:

1. Excellent training in mathematics and numerical methods
2. Proven experience with computer programming in high level languages
3. Ability to write and communicate fluently
4. Strong background in Engineering/Physics

Potential Collaborators

The project will be carried out in collaboration with Professor Rodger Alison, Head of the Department of Chemistry, University of Warwick, UK. The research team combines world leaders from Monash in BD simulations and from Warwick in LD and other polarized light spectroscopies. This proposal integrates these unique, but at first sight, disparate areas of expertise to solve a problem that is not possible in either domain or in any other single area.

Please provide a few key words relating to this project to make it easier for the students to apply.

Polymer solution dynamics, Brownian dynamics simulations, Linear dichroism spectroscopy