Monash_IITB_masterhead

Project Title:	**Simulating polymer dynamics in a crowded nucleus**	
Project Number	**IMURA0901**	
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Monash Co-supervisor(s) (Name, Email, Phone)		
Monash Head of Dept/Centre (Name,Email)	Mark M. Banaszak Holl, mark.banaszakholl@monash.edu	*Full name, email*
Monash Department:	Chemical Engineering	
Monash ADGR (Name, Email)	Assoc. Professor Timothy Scott, timothy.scott@monash.edu	*Full name, email*
IITB Main Supervisor (Name, Email, Phone)	Ranjith Padinhateeri, ranjithp@iitb.ac.in,	*Full name, Email*
IITB Co-supervisor(s) (Name, Email, Phone)		*Full name, Email*
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IITB Department:	Biosciences and Bioengineering Department	

Research Clusters:

Highlight which of the Academy's CLUSTERS this project will address? *(Please nominate JUST **one.** For more information, see www.iitbmonash.org)*	
1	*Material Science/Engineering (including Nano, Metallurgy)*
2	*Energy, Green Chem, Chemistry, Catalysis, Reaction Eng*
3	***Math, CFD, Modelling, Manufacturing***
4	*CSE, IT, Optimisation, Data, Sensors, Systems, Signal Processing, Control*
5	*Earth Sciences and Civil Engineering (Geo, Water, Climate)*
6	***Bio, Stem Cells, Bio Chem, Pharma, Food***
7	*Semi-Conductors, Optics, Photonics, Networks, Telecomm, Power Eng*
8	*HSS, Design, Management*

Research 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***
7	*Humanities and social sciences*
8	Design

The research problem

DNA in our cells is a long polymer that is folded and packaged into chromatin. Parts of the genetic code in the DNA is switched ON (made accessible) and switched OFF (made inaccessible) depending how the DNA is folded into chromatin. Understanding the time-dependent 3D organization of chromatin – understanding time evolution of chromatin architecture – is a problem in the interface of Physics, Engineering and Biology. One needs to use ideas from statistical physics, chemical/mechanical engineering (polymer physics) to simulate the chromatin polymer. Moreover, chromatin polymer is in a highly crowded environment inside the nucleus interacting with multitudes of other polymer chains, namely proteins. In this work, the aim is to simulate chromatin accounting for the crowding and multi-polymer environment using physics and engineering principles.

Project aims

The aim of this project is to develop a multi-scale model that can predict the dynamics of chromatin packaging accounting for crowding in the nucleus. In particular, the following questions will be investigated using computer simulations and polymer theory

1. How does a crowded environment influence the folding of chromatin?

2. How does one computationally mimic conditions that similar to those in the nucleus? How important are hydrodynamic interactions (that describe solvent mediated momentum propagation between polymer segments) when realistic conditions similar to that of the nucleus are mimicked?

The work will build on and extend recent work published by the IITB-Monash research academy student Kiran Kumari [1].

[1] K. Kumari, B. Dünweg, R. Padinhateeri, J. R. Prakash, Computing 3D chromatin configurations from contact probability maps by Inverse Brownian Dynamics. In Press, Biophysical Journal (2020) (available on the arXiv online repository: https://arxiv.org/abs/2002.09171).

How do skills/experience of the IITB and the Monash supervisor(s) support the proposed project?

Highlight the purpose of the collaboration and/or the complementary skills/experience that you bring to the project. List any joint or independent publications and joint funding in the area of the proposed project.

Ravi Jagadeeshan brings expertise in molecular modelling and Brownian dynamics (BD) simulations. In a major recent advance, his group has developed a multi-particle BD algorithm capable of quantitatively describing the properties of flowing macromolecular solutions at finite concentration, spanning the dilute and semi-dilute regime. This is a significant improvement on earlier models that are based on the behaviour of isolated chains in solution, since many-body interactions between multiple chains can now be taken into account. Consequently, he provides the analytical and numerical tools for tackling the proposed problem.

Ranjith Padinhateeri has expertise in solving problems in cell biology using ideas from physics. His group has been studying self-assembly of chromatin, using computational tools. His expertise will bridge biology experiments with theoretical studies of chromatin as a polymer.

This unique team has the capabilities to deliver a significant advance in the understanding of chromatin dynamics.

Jagadeeshan and Padihateeri have together supervised one PhD student (Kiran Kumari) under the auspices of the IITB-Monash research academy. A paper based on this work has recently been published in the Biophysical Journal [1].

What is expected of the student when at IITB and at Monash?

Highlight how the project will gain from the students stay at IITB and at Monash

Expected work at IITB

At IITB, the student would complete his/her course work and will start working on the project. The student will be asked to reproduce some known results using her own codes. For example, Langevin dynamics of two particles connected with a spring, quantifying its fluctuations. The student can also learn equilibrium statistical mechanics of polymers like the end-to-end vector distribution with different persistence length. Next task would be to study the dynamics of a polymer chain, which can be viewed as many dumbbells connected to form the chain. This will make the student ready for the next stage where he/she actually starts working on the specific project. For this, it is planned that the code developed in Prof. Jagadeeshan's group at Monash will be the one on which he/she should build upon his Brownian Dynamics code. However, this should start during student's visit at Monash and would continue in IITB after he/she comes back from Monash.

Contributions and supervision responsibilities of IITB supervisor

IITB supervisor will take care of the student's course work at IITB. With the mutual consent of the supervisor at Monash, he will chalk out the courses to be taken by the student. The student will be advised to take a set of courses from Physics, Chemistry, Chemical engineering and biosciences departments. In addition, it is IITB supervisor's responsibility to connect the student with the research problem and start training the student with the toy problem mentioned above. The long-term task would be to supervise and guide the student towards the completion of his/her project after he/she comes back from Monash. It is expected that he/she would spend a year in Monash either in two terms or in a single term.

Expected work at Monash

In the first stages, the student will get familiar with the multi-particle Brownian dynamics simulation algorithm that has been developed in Jagadeeshan's group. Subsequently, the code will need to be modified to account for chain stiffness through the incorporation of bending potentials. Some benchmark problems will be examined to ensure the developed code is valid. Once these tasks are completed, the work on the actual research problem will begin. Based on the progress achieved, the student will continue to work on the project after returning to IITB.

Contributions and supervision responsibilities of Monash supervisor

Jagadeeshan brings expertise in molecular modeling and Brownian dynamics simulations. The protocol for the development of Brownian dynamics simulations algorithms is well established in his group, and consequently, the analytical and numerical tools for tackling the proposed problems are readily available. His role is to provide the technical expertise, to guide the student, to coordinate the various activities of the project, to manage the budget, and to ensure that the aims and objectives of the project are met.

Expected outcomes

The key outcomes of the PhD work will be essentially answering the above-mentioned questions and other questions associated with it. That is, we would write simulations to how protein-bound DNA would fold itself in a time-dependent manner under crowded environment. The simulation can examine the role hydrodynamic interactions in conditions similar to that of a cell nucleus.

These outcomes will result in high quality journal publications within the fields of polymer dynamics and soft matter, with exemplar outputs demonstrated in recent publications from the participating academics.

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

Describe how the project will address the goals of one or more of the 6 Themes listed above.

Using theory and simulation we ultimately aim at understanding the dynamics of chromatin packaging on the scale of many genes, which is a problem of fundamental importance in the field of biophysics. Only a combination of computer simulation and theoretical techniques can shed light onto such complex dynamical process. This project will firstly enhance our ability to understand mechanisms in biological systems such as biological cells. The outcome of this project 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.

Potential RPC members from IITB and Monash

Provide names of the potential research progress committee members (RPC) and describe why they are most suited for the proposed project.

Dr Prabhakar Ranganathan (Monash) - expert in soft matter and computer simulations.
Dr Rajarshi Chakrabarti (IITB) - expert in polymer physics.

Capabilities and Degrees Required

List the ideal set of capabilities that a student should have for this project. Be as specific or as general as you like. These capabilities will be input into the online application form and students who opt for this project will be required to show that they can demonstrate these capabilities.

The following capabilities are essential:
1. Excellent training in mathematics and numerical methods (biology knowledge is not mandatory)
2. Proven experience with computer programming in high level languages
3. Ability to write and communicate fluently
4. Strong background in Engineering/Physics (Either M Sc in Physics or B Tech/BE in Mechanical/Chemical/Electrical Engineering).

While the topic has a biological context, students **without a background in physics or engineering will not be considered**.

This is not a complete list. However, the student should read these papers before he/she starts working on the PhD project.

- Tom Misteli. Higher-order Genome Organization in Human Disease. Cold Spring Harb. Perspect. Biol. 2 (8), 1–17 (2010)
- Erez Lieberman-aiden, et al, Comprehensive Mapping of Long-Range Interactions

Reveals Folding Principles of the Human Genome. Science, 326, 289–294 (2009)

- Eran Segal and Jonathan Widom. What controls nucleosome positions? Trends Genet 25, 335–343 (2009).
- G.V. Shivashankar. Mechanosignaling to the Cell Nucleus and Gene Regulation. Annu. Rev. Biophys. 40 (1), 361–378 (2011).
- Hsieh TH, et al. (2015) Mapping Nucleosome Resolution Chromosome Folding in Yeast by Micro-C. Cell 162:108–119.
- Langowski J (2006) Polymer chain models of DNA and chromatin. Eur. Phys. J. E. Soft Matter 19:241–249.

Necessary Courses

List three tentative core courses relevant to the project that the student should complete during his/her coursework at IITB (the student will require to secure 8 point in these courses)

The student will need to do courses in advanced mathematical methods, statistical mechanics and computational methods. There are several courses offered at IITB that meet these requirements. For instance, the following are examples of courses that IITB-Monash Academy students of Jagadeeshan have completed previously:

CH 814 Fundamentals of Molecular Energetics and Dynamics
CH 576 Statistical Mechanics
CL 613 Special Topics in Complex Fluids
CL-602 Mathematical and Statistical Methods in Chemical Engineering
BB-619 Mathematics for Biologists

The student will be advised to take similar courses in order to pick up the required background.

Potential Collaborators

Please visit the IITB website www.iitb.ac.in OR Monash Website www.monash.edu to highlight some potential collaborators that would be best suited for the area of research you are intending to float.

N/A

Select up to **(4)** keywords from the Academy's approved keyword list **(available at http://www.iitbmonash.org/becoming-a-research-supervisor/)** relating to this project to make it easier for the students to apply.

Computer Simulation, BioScience, Modelling and Simulation, Computational and Theoretical Chemistry