IITB-Monash Research Academy

Indian Institute of Technology Bombay | MONASH University

An Indian-Australian research partnership

Project Title:	**Understanding chromatin folding dynamics through molecular simulations**	
Project Number	**IMURA0901**	
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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

The fate of a cell is decided by the "state" of its chromatin. Chromatin is a packaged form of DNA – a long polymer that carries genetic information. In humans, the total contour length of DNA is approximately two meters, 10000 times larger than the dimensions of the cell nucleus. The packaging of chromatin in the cell is achieved with a large number of proteins that bend and fold DNA to induce local curvature. The precise structure of the packaged chromatin is still an open question. In order for life processes to go on, chromatin needs to be unfolded and refolded dynamically so that it can be read, repaired and replicated repeatedly. Nearly nothing is known about how the unfolding and folding happens, and the precise sequence of events during folding and unfolding. Understanding and defining the different states of chromatin is a huge task. Some of the major deciding factors are the arrangement and distribution of proteins along the DNA, and the influence of their binding and dissociation dynamics on the transient 3D architecture of the compacted DNA. Existing experiments provide information on contact probabilities between different parts of the chromatin, averaged over many cells. They are consequently only frozen snapshots of protein positioning and 3D DNA architecture. A proper understanding of cellular processes requires the development of a dynamic model that can predict how chromatin is locally folded and unfolded regularly, within the timescale relevant to biological processes such as transcription and gene regulation.

Project aims

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

1. Given a protein arrangement/distribution along the DNA, what is the dynamics of folding? How does the folding dynamics depend on the distribution of proteins/their organisation along DNA. To begin with we may model the bound proteins as intrinsic curvatures along the chain.
2. Can the dynamics of proteins (binding/dissociation dynamics) influence the polymer folding dynamics? Proteins along the DNA can be chemically modified (methylation/acetylation) leading to different physical behaviour (stability and short-range inter-protein interactions) – how does this influence the folding dynamics?
3. For gene expression/gene regulation, certain sites on the DNA (e.g., TATA binding site) need to be accessible (available "open" for binding) for proteins. Given a particular folding, how easy/difficult is it for a protein to access certain specific sites on the polymer?

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).

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. The simulation can predict how two remote regions along the DNA would come close to each other in a time-dependent manner. These predictions are testable in future experiments where one may monitor two regions along the

DNA using appropriate techniques.

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.

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 Engg)
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.

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