IITB-Monash Research Academy

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Project Title:	**Understanding the physical response of cells to force by simulating the mechanics of sticky biopolymer networks**
Project Number	**IMURA0802**
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Highlight which of the Academy's CLUSTERS this project will address? *(Please nominate JUST **one.** For more information, see www.iitbmonash.org)*		**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)*	
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The research problem

The mechanical properties of biological cells play a central role in cell locomotion, embryonic tissue formation, and tumour migration among many other processes [1-4]. Cells exhibit a complex nonlinear response to mechanical perturbation that is not yet well understood. Cells are observed to stiffen as well as soften, depending on the type of stimulus [5-7]. Many studies of cell mechanics and dynamics have shown that the cell is a viscoelastic, glassy, fragile and inelastic body, and it is an intriguing question to what extent such mechanical behaviour can be understood in terms of relatively simple polymer physics models [5,6].

Cells derive their mechanical strength from fibrous protein scaffolds, which typically have a complex hierarchical structure. Essentially, the mechanical properties are governed by the cytoskeleton, a dynamic and active cross-linked biopolymer network based on three different biopolymers: actin, microtubules, and intermediate filaments [8], as displayed in Figs.1 and 2.

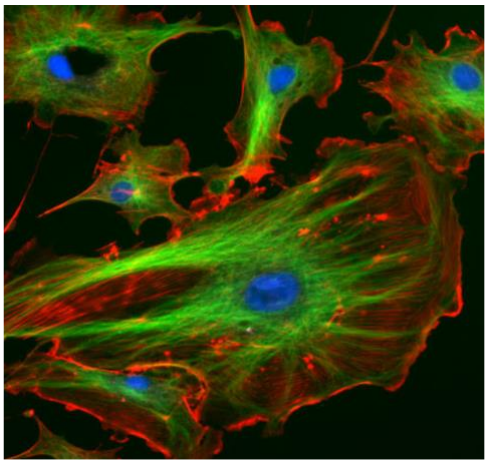

Fig. 1. Fluorescence microscopy image of bovine pulmonary artery endothelial cells. Reproduced from Ref. [8].

The cytoskeleton ensures cell mechanical stability and adaptability, and its dynamic nature enables a cell to exhibit a mechanical response on different timescales. The mechanical properties of single cells have been investigated in detail through a number of different techniques, shown schematically in Fig.3. In the case of small-amplitude oscillatory experiments, it is widely agreed that linear viscoelastic cell moduli exhibit power law rheology, i.e., they increase with frequency as a power law with a small exponent. However, the understanding of nonlinear aspects of rheological cell response remains elusive. In this regime, cells have highly contradictory mechanical properties: they are malleable and adaptive, yet rigid enough to maintain their integrity under large mechanical loads. Cells exhibit reversible nonlinear stiffening, which allows them to increase their resistance to deformation as the applied stress is increased. This property arises from the intrinsically nonlinear elastic response of networks of stiff fibres. They also appear to undergo plastic or inelastic deformation, with nature effectively utilizing plasticity to toughen cells against the mechanical demands of their environment [5-7]. The balance of elastic nonlinearity and plasticity across a large range of strains encountered physiologically is poorly understood. The complicated properties of cells emerge from the unique characteristics of cellular components. Thus, understanding the molecular origins of the dynamics and mechanics of cell components is a prerequisite for illuminating the complicated mechanical properties of cells.

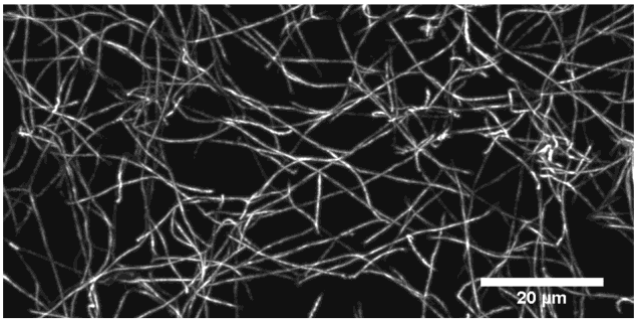

Fig. 2. Confocal microscopy image of a fluorescently labelled collagen network. Reproduced from Ref. [8].

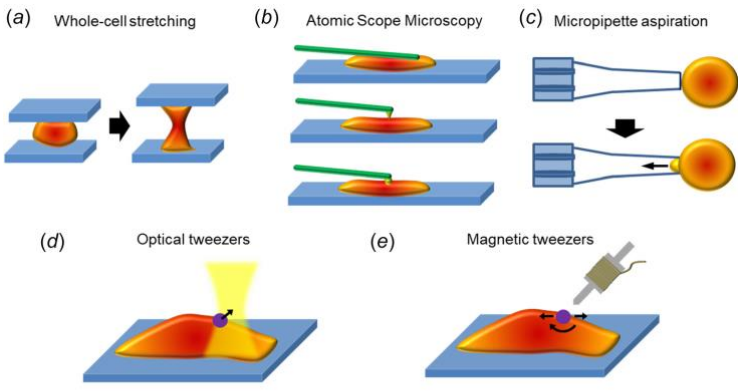

Fig. 3. Rheological techniques designed for measuring cell mechanical properties. Reproduced from Ref. [2].

Biopolymers are far more rigid than most synthetic polymers, and they constitute prime examples of semiflexible polymers [8]. Over the past decades, semiflexible polymers and their assemblies in the form of solutions and networks have emerged as model systems for the study of the cytoskeleton [8,9]. Their rigidity results in conformations, at both the single polymer and network levels, that are very far from the random coil configurations common in polymer physics, as a result of which they exhibit qualitatively different elastic and viscoelastic properties. The dynamics of semiflexible polymers is essentially governed by a competition between entropic and energetic effects. The semiflexible nature of the polymers also has major implications for how they interact with each other to form entangled or cross-linked networks, and for the linear and nonlinear elastic and flow properties of such networks. A predictive understanding of the physics of such networks is a daunting theoretical challenge due to their disordered many-body nature, and the role of bending and entropy in these systems. The key to modelling biopolymer systems is to develop a systematic way to account for interactions of the semiflexible polymers within the crowded cellular environment.

Rheological experiments on cells have provided evidence that suggest that cells behave as soft glassy materials which cannot be understood within existing simple theories for semiflexible polymer networks or solutions and appears to suggest that the cytoskeleton and its polymer constituents may be surrounded by a glassy environment [10]. Such a glassy environment has been modelled as a collection of traps distributed in space, with a broad power-law distribution in strength locally pinning the polymer [11-13]. Various predictions of the glassy wormlike chain model agree favourably with the rheology of actin solutions as well as live cells and suggest that despite the underlying variety of molecular mechanisms, all such glassy systems have one feature in common--structural rearrangements that are slow, localized and inelastic. Current glassy semiflexible chain models are, however, approximate mean field models that neglect important molecular phenomena such as hydrodynamic interactions.

The goal of this project is to understand how the microscopic topology and the strength & number of intermolecular interactions control the rheological behaviour of a cell, modelled as a sticky semiflexible polymer network. This aim will be achieved by the development of a novel multi-particle mesoscopic simulation algorithm for describing the dynamics of a solution of sticky semiflexible polymers that can form reversible associations with each other. Predictions will be compared with known rheological observations on cells.

Project aims

There are two significant challenges to simulating semiflexible polymer networks. First, cell interiors are typically semidilute solutions, a regime of concentration which necessitates modelling multi-body hydrodynamic interactions between polymer chain segment pairs. Importantly, this consideration converts the simulation to a many-body one, which is computationally complex. The second challenge arises due to the presence of extensional deformation in cell stretching experiments. The simulation boxes need to deform with high fidelity in order to maintain periodicity and allow simulations to proceed for sufficiently long times. Our group has recently overcome both of these challenges in the context of Brownian dynamics (BD) simulations, and successfully predicted both static and dynamic equilibrium properties, and non-equilibrium flow properties of semidilute solutions of *linear* polymers [14-16]. 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.

Semidilute solutions of sticky semiflexible polymers can be modelled as an ensemble of coarse-grained bead-spring chains with a bending potential between springs along with several generic stickers which form reversible bonds by association. By selectively labelling some beads as attractive, a family of sticky semiflexible network polymer models will be created, ranging from telechelic semiflexible polymers with attractive beads only at the chain ends, to multi-sticker polymers with increasing numbers of attractive beads distributed along the chain backbone. The family of coarse-grained models used in the simulations will mimic molecular architectures examined in experiments. The new multi-particle algorithm, which will be unique in the world, will give an unprecedented opportunity to examine the influence of (i) chain architecture and flexibility, (ii) the strength and location of attractive groups on chains, (iii) the concentration and polydispersity of polymers, and (iv) the deformation strength, systematically. The creation and destruction of transient chain conformations in the presence of extensional deformation can

be directly visualised, and their relation to the development of macroscopic stress in the network can be explored.

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Expected outcomes

The outcomes of the project will include:

1) A hydrodynamic coarse grained molecular model of cell deformation that captures the experimentally observed macroscopic rheological behaviour.
2) Elucidation of the general principles relating the segment level structure of cells to their soft glassy rheology.

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

The research in this project addresses the Academy cluster “Bio, Stem Cells, Bio Chem, Pharma, Food”. The major benefit is an understanding of the rheology of cells. This is important both on fundamental scientific and on practical levels because understanding the molecular processes involved in cell deformation is crucial for developing an adequate description of the mechanical properties of biological cells. This Project offers research training to a post-graduate student, exposing them to a broad range of advanced computer simulation techniques. The proposed research will build expertise in India and Australia in advanced simulation methods that are currently the domain of a select few research groups across the world.

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 (Either MSc in Physics or BTech/BE in Mechanical/Chemical Engg)

Potential Collaborators

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.

Modelling and Simulation, Computational Fluid Dynamics and Mechanics, Bioscience, Biomedical Engineering.