ME – PhD Thesis Defence

Mechanobiology of cell-substrate interactions

Mr. Siddhartha Jaddivada, PhD Student, Department of Mechanical Engineering, IISc, Bangalore

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ABSTRACT

Adhesion of cells to substrates is a complex process facilitated by focal adhesion complexes (FA) that help them perform vital cellular functions like migration, growth, and division. Cells probe their mechanical milieu through contractile stresses generated via cross-bridge cycling between actin and myosin. These stresses induce exquisite feedback between the substrate and acto-myosin stress fibers, remodeling the cytoskeleton and FA. A repertoire of signaling molecules, including calcium and a mechanosensitive protein, talin, in FA complexes, facilitate these interactions. cells remodel under dynamic mechanical loads in tissues such as arteries? How do individual components of the FA regulate cell adhesions? I use computational models to address these questions.

As a first study, I quantified the cell tractions using micropatterned pillar array detectors (mPAD) created using soft lithography. Results from our study show that mPAD topography resulted in the persistent migration of fibroblasts. Image analysis was used to quantify the micropillar deflection and computed tractions using a neo-Hookean constitutive model to report traction distribution along the cell length. We next developed a multi-scale computational cell model, to investigate the effects of cyclic stretch and substrate stiffness on cell-substrate interactions. We used the modified Hill model and reaction-diffusion equations to model stress fiber contractility in the presence of calcium. The attachment of adaptor proteins, representing FA, was simulated using a Gillespie algorithm in tandem with finite element analysis. The model shows that adhesions and tractions vary along the cell length under static and cyclic stretch conditions; the maxima occurred behind the cell edge. Cell tractions and adhesion initially increased with substrate stiffness and ligand density but decreased beyond an optimum substrate stiffness. Stretch enhanced tractions and adhesions on compliant substrates; in contrast, they were reduced on stiff substrates.

Finally, I simulated the mechanical response of talin while transmitting force in FAs through the combined worm-like chain model. The model incorporates the kinetics of talin unfolding and multivalent actin and vinculin bonds between the cell cytoskeleton and talin. I assessed the variation in force transfer by talin by simulating its extension under varying substrate stiffness, 0.1 and 50 kPa, and actin flow rates, 3, 10, and 100 nm/s. The mean force and lifetimes of the talin-actin bond varied in the ~1-12 pN range and ~2-50s, respectively. Both these parameters magnitude peaked at intermediate actin flow. Analysis of the model output revealed that actin attachments predominantly transfer force at slow and rapid actin flows, and vinculin bonds significantly contribute to force at intermediate actin flow. Additionally, I show that vinculin binding induces a gradient across talin, which stabilizes the interactions at binding sites proximal to the C-terminal of talin.

ABOUT THE SPEAKER

Siddhartha Jaddivada is a Ph.D. student in the Dept. of Mechanical Engineering, IISc. His research interests include biomechanics, solid mechanics, finite element methods, and microfabrication. He works with Prof. Namrata Gundiah in the Biomechanics Lab, IISc.