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CHEME 7770 Final Project – Project Update

Project 4: Kinetic Monte Carlo simulation of traction force dynamics

In this update I will investigate the first two major questions for considerations: What is the molecular clutch and how does it function, and what is force transduction, what role do key element play in force transduction networks. In addition, I would like to present some key questions and concerns and also describe the current state of the project and my expectation and goals.

It's well known that substrate stiffness and compliance can play a large role in the morphology of cells, population growth characteristics, and metastatic capability in cancer. Chan and Odde describe the system by which the cells sense their external environment by with can they call a "motor clutch". In their paper, they seek to explain one method by which cells utilize their glycocalyx for this endeavor, using a computational model to describe the molecular interactions of the outer membrane proteins and structures.

In order to provide a holistic view of the force transduction framework and 'motor clutch' and in-depth description of the force transduction network is needed. Force transduction is a process integral to the function of cells, luckily recent work has served to illuminate some of these structures in the transduction network. It is believed that force transduction is achieved through three possible methods: Protein, lipid-initiated protein, and spacial alteration of signal centers. External forces induce a change in confirmation of crucial cytoskeleton crosslinkers such as a-actinin and vinculin exposing active sites. On the outer membrane and cytoskeleton of the cell an intricate network of proteins forms the force transduction network of which proteins like myosin and actin play a role. These proteins are commonly known for their action in inducing muscle contracture. Myosin binds to actin fibers and can generate a pulling force on them. Meanwhile the actin fibers polymerize and elongate at the + end. This action of myosin binding and pulling is what would lead to the contraction in muscles but here it forms of the basis for force transduction. Lipid-mediated mechanosensing arises due to the compressional forces generated by the lipid bilayer on transmembrane proteins during a force event results in a reconfirmation of the protein and activation. Decrease and increase in the distance between signal centers and substrates during contracture or expansion in response to external forces may also result in signal transduction.

In general, the system Chan and Odde describe as a "motor clutch" acts in some ways like that in a car. Cars utilize a system of springs and rely on tension to either isolate the engine from the drive train or allow its continued motion. This tension can be likened to the molecular friction experienced by the F-actin bundle and substrate surface. With this friction engaged there is a resistance to retrograde motion of the F-actin bundle but as it weakens and eventually breaks there is a retrograde in the F-actin. Chan and Odde model this system a series of springs. It is not clearly explained what exactly these clutches are. It is possible they could be chemical bonds or Van der Waals/charge attractions to the substrate or simply physically interlocking interactions. In either case these 'clutches' are capable of sustaining a certain amount of stress before moving disengaging. This is described by a Kon and a Koff which describes the frequency to which the 'clutches' are engaged. As tension increases so does Koff exponentially according to Bell's Law.

$$\mathrm{k\_exp}\left(\frac{\gamma F}{kTN_b}\right)$$

There are a series of clutches which engage the F-actin to the substrate and these form a spring-spring dynamic system where the elasticity of the substrate acts as the connecting string that lowers the load on the 'molecular clutches'. An interesting occurrence predicated by Chan and Odde in their computational model is a 'frictional slippage' behavior with noncompliant substrates and 'Load-and-Fail' behavior with soft substrates. Frictional slippage refers to retrograde of the actin fiber at a constant rate as 'clutches' detach and reattach constantly. In this case the stiff substrate is unable to provide much additional help to lower the burden of the load so 'clutches' detach faster. In the case of the soft substrate, 'clutches' engage the substrate and remain attached for long periods of time due to the sharing of stress by the compliant substrate. As this continues more 'clutches' engage and remain engage further helping to manage the load. Eventually, the stress experienced is so high all of the 'clutches' disengage leading to a sudden rapid increase in F-actin retrogradation.

The next step in the project is to begin development of an optimized computational model to mimic and reproduce the results obtained by Chan and Odde. To this effect I would like to request access to the full article from Science including supplementary figures and materials to better understand their computational model. While the written article in itself was provided in the Cornell Box access to the Science article is not available through the school and my present resources at hand.

After developing a thorough model for the molecular mechanics, it would be interesting to see how viscoelastic substrates would differ in response to elastic substrates. Chan and Odde actively mention that they excluded tension dependent strengthening of adhesions which I take to refer to viscoelastic behavior. Time should be taken to see what substrates are more common biologically and assess the mechanics in the viscoelastic system which is defined by their rate of deformation and loading rate. I would predict that at high rates of deformation the viscoelastic substrates would begin to perform similarly to a stiff substrate and at lower deformation rates the behavior would be likened to a softer gel substrate. I would also like to see if the addition of new parameters as described in Elosequi-Artola et al. would result in any major differences in the results of the computational model if so, to what degree.

References:

1. Chan and Odde (2008), Traction dynamics of filopodia on compliant substrates, Science, DOI: 10.1126/science.1163595
2. Elosegui-Artola et al. (2016), Mechanical regulation of a molecular clutch defines force transmission and transduction in response to matrix rigidity, Nature Cell Biology, doi:10.1038/ncb3336
3. P. Bieling et. al Force Feedback Controls Motor Activity and Mechanical Properties of Self-Assembling Branched Actin Networks. Cell VOLUME 164, ISSUE 1-2, P115-127, JANUARY 14, 2016. DOI:https://doi.org/10.1016/j.cell.2015.11.057
4. Paul A. Janmey David A. Weitz. Dealing with mechanics: mechanisms of force transduction in cells. Cell VOLUME 29, ISSUE 7, P364-370, JULY 01, 2004. DOI:https://doi.org/10.1016/j.tibs.2004.05.003