

of intracellular mechanical stresses and plaque protein concentrations on cell and focal adhesion shapes. The cell is treated as a hypoelastic actively-deforming continuum and the substrate is modeled as a linearly elastic continuum. The active deformation, captured by the addition of an active rate of deformation tensor, models local cytoskeletal reorganization. Focal adhesions connecting the cell and the substrate are modeled as a collection of discrete elastic springs. The model allows for the focal adhesion complexes to grow and shrink depending on mechanical forces that are acting on them and local concentrations of plaque protein. A model of stress-induced plaque protein dynamics, which is based on earlier work of Besser and Safran (2006), is coupled to the model of cell-substrate mechanics. Finite element simulations of the model allow us to explore the effects of original focal adhesion configuration, cytoskeletal dynamics, and focal adhesion strength on the shape evolution of individual focal adhesions and on overall cell shape.

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Dynamics of Focal Adhesions

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Focal adhesions (FA) are the cells machinery to sense the environment and help in migration. They are macromolecular complexes which link the actin to the integrins and are extremely dynamic in nature. The mechanism of FA movement in the cell is unclear. Treadmilling and sliding are the two modes in discussion. Recent experimental results for force velocity relationship in focal adhesions show a biphasic relationship between F-actin speed and traction force.

In our study, an FA complex is modelled as a one dimensional array of point masses connected laterally to each other and to the substrate by springs. Binding and unbinding of molecules to the substrate corresponds to sliding and adding/deleting from the ends corresponds to treadmilling in the system. Through Gillespie simulations, we sought to understand the mechanism of FA movement by comparing the force velocity curves generated to the experimental data. From our preliminary results, for a one layer model in a small range of forces, we see that there is a range of possible velocities for a given force depending on the ratio of rate constants for treadmilling and sliding mechanisms. Another observation is that on increasing the stiffness of the substrate, the slope of these curves decreases significantly only in the sliding dominated mechanisms.

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Focal Adhesion Size Uniquely Predicts Cell Migration

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Focal adhesions are large protein complexes organized at the basal surface of cells, which physically connect the extracellular matrix to the cytoskeleton and have long been speculated to mediate cell migration. However, whether clustering of these molecular components into focal adhesions per se is actually required for these proteins to regulate cell motility is unclear. Here, we use quantitative microscopy to characterize large families of focal adhesion and cell motility descriptors across a wide range of matrix compliance, following genetic manipulations of focal adhesion proteins. This analysis revealed a tight, biphasic relationship between mean size of focal adhesions - not their number, surface density, or shape - and cell speed. The predictive power of this relationship was comprehensively validated by disrupting non-focal adhesion proteins and subcellular organelles (mitochondria, etc.) not known to affect either focal adhesions or cell migration. This study suggests that mean size of focal adhesions robustly and precisely predicts cell speed independently of focal adhesion surface density and molecular composition.

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Mechanosensing of Cells in Laminin-Functionalized Biomembrane-Mimicking Substrates

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¹Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany, ²Indiana University-Purdue University, Indianapolis, IN, USA. Adherent cells actively probe and respond to the mechanical properties of their environment. Studies of cellular mechanosensing are mostly conducted on polymeric substrates of adjustable elasticity with immobilized cell-substrate linkers that neglect the dynamic and viscoelastic nature of tissues. Here, we study cell migration on a polymer-tethered multi-lipid bilayer substrate with mobile linkers and dissipative material properties. The substrates are functionalized with laminin, which replicates the linkages of cells to the extracellular matrix. The polymer-tethered lipids connecting the bilayer stacks do not hinder the lateral mobility of individual cell linker molecules in the fluid lipid bilayer matrix, but obstruct or even prevent the free lateral diffusion of clusters of cell

linkers. These biomembrane-mimicking substrates therefore exhibit a viscous response with respect to individual linkers, and an elasto-plastic response in the presence of linker clusters, allowing the cells to rearrange and recruit ligands. Moreover, the mechanical properties of the substrate can be tuned by stacking multiple bilayers. Experiments with mouse embryonic fibroblasts confirm that cells can sense linker mobility and dissipative mechanical properties of the substrate. Cells respond to decreasing linker mobility, decreasing substrate elasticity, and increasing substrate plasticity with a reduction in spreading area, cell stiffness, traction magnitude, and focal adhesion size, but with an increase in focal adhesion number density. In conclusion, the results illustrate that cells change their morphological and mechanical properties in response to changes in substrate elasto-plasticity and linker mobility.

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Probing Mechanosensitivity of Myoblasts on Cadherin-Functionalized Biomembrane-Mimicking Substrates

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There is a growing recognition that cells not only respond to biological signals, but also to those of mechanical nature. Cellular mechanosensing is exemplified by the cell's ability to respond to changes in substrate viscoelasticity. Traditionally, experiments about cellular substrate sensitivity were conducted on polymeric substrates with immobilized linkers. Here we present an alternative strategy based on biomembrane-mimicking cell substrates with E-cadherin cell linkers. This substrate design allows a systematic variation of viscoelastic properties by changing the number of lipid bilayers in a polymer-tethered multi-bilayer system. Importantly, individual cell linkers within this type of cell substrate are laterally mobile, thus leading to a viscous substrate behavior. In contrast, clusters of linkers, which are immobilized, cause an elasto-plastic substrate response. By using E-cadherin linkers, multi-bilayer substrates can be seen as a mimetic of a cell-cell linkage. The functionality of the multi-bilayer substrate for cellular mechanosensing studies is illustrated in terms of specific cell parameters, including cell morphology, migration speed, cytoskeletal organization, and size of cell adhesions. Furthermore, the influence of linker density on cell adhesion and spreading is discussed.

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Role of Integrin in Cellular Mechanotransduction

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Chemical and physical cues from the extracellular matrix (ECM) are used as input for an integrated mechanochemical sensory system that controls cell behavior. Forces derived from the ECM have been implicated in various biological systems, including mesenchymal stem cell differentiation and tumor growth. Integrin transmembrane receptors connect the ECM network to the intracellular actomyosin network and are expected to play an important role in force sensing. Our group has previously shown that switching between two different integrin heterodimers ([α 5] β 1 vs [α v] β 3), that bind the same ECM protein (fibronectin), causes remarkably distinct actin cytoskeletal organization. To investigate the role of these integrins in cellular mechanotransduction, we used fibronectin coated polyacrylamide substrates with varying rigidities and micropillar arrays. Data obtained thus far point to distinct rigidity thresholds for spreading and different distribution of ECM pulling forces for cells expressing either of these integrins. In order to further unravel the role of these integrins in cellular mechanotransduction we developed cyclic substrate stretcher technology coupled to real time confocal imaging.

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Viscoelastic Cell Adhesion Model (VECAM)

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Circulating leukocytes and tumor cells deform during their interactions with vascular endothelium and other adhesive substrates under physiological flow conditions. We studied the effect of cytoplasmic viscosity on these interactions using our novel three-dimensional computational algorithm that treats the cell as a compound droplet in which the core phase (nucleus) and the shell phase (cytoplasm) are viscoelastic fluids. This algorithm, known as viscoelastic cell adhesion model (VECAM), includes the mechanical properties of the cell cortex by cortical tension and considers cell microvilli that deform viscoelastically and form viscous tethers at supercritical force. Stochastic binding kinetics describes binding of cell adhesion molecules. VECAM predicts that the cytoplasmic viscosity plays a critical role in cell rolling on an adhesive substrate. High-viscosity cells are characterized by high mean rolling velocities, increased temporal fluctuations in the instantaneous velocity, and a high probability for detachment from the substrate. A decrease in the cell velocity, drag