structure, we find that despite the chirality of the ciliary structure, cilia can in principle generate clockwise as well as anticlockwise twirling beat patterns. However, our results show that the axoneme's chirality leads to one sense of rotation being selected dynamically for given parameter values and properties of dynein motors. This dynamic selection of asymmetric states is analogous to how the direction of motion of a motor protein moving along a filament.

3236-Pos Board B283

Cellular Potts Modeling of Matrix-Dependent Endothelial Cell Networking

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Networking of endothelial cells during fetal and post-natal development relies upon dynamic remodeling and subsequent stabilization of cell-cell and cell-extracellular matrix (ECM) interactions. Herein, we investigate lung endothelial cells network dynamics on thin films of engineered ECM. These systems adhere to the Differential Adhesion Hypothesis and their behaviors are well reproduced with a Cellular Potts Model. In order to gain insight on the profound effect external environment has on cell behavior, our model explicitly includes the ECM, as we explore particular changes in networking dynamics with changes in substrate parameters. Further, we describe specifics of the system Hamiltonian governing the Monte Carlo methods with addition of experimentally derived rules that can simulate both normal and non-networking cells systems. The biological significance of derived cell-cell and cell-matrix adhesion and cohesion energies that most appropriately model our experimental data is discussed.

3237-Pos Board B284

Accelerated Proliferation and Migration of Keratinocytes, Fibroblasts and Macrophages Isolated from H2-Calponin Knockout Mice

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Calponin is a family of actin-associated regulatory proteins that play a role in modulating smooth muscle contractility and actin cytoskeleton functions. The h2 isoform of calponin is found in smooth muscle and certain non-muscle cells. Keratinocytes, fibroblasts, and macrophages express h2-calponin at significant levels. To investigate the function of h2-calponin in these cell types that are key players in wound healing, we studied primary cultures of epidermal keratinocytes, dermal fibroblasts and peripheral macrophages isolated from h2-calponin knockout mice recently developed in our laboratory (Huang et al., *J. Biol. Chem.* 283:25887-99, 2008). Cell proliferation studies revealed faster growth rates of all of the three cell types from h2-calponin knockout mice as compared with that of wild type control cells. Similarly, the three types of cells exhibited faster migration in in vitro wound healing experiments when h2-calponin is absent. The results suggest that h2-calponin may be a regulatory factor in the balance of cell proliferation and migration during wound healing. We have previously observed that mechanical tension built in the cytoskeleton regulates h2-calponin expression and degradation in cells including keratinocytes and fibroblasts (Hossain et al., *J. Biol. Chem.* 280:42442-53, 2005; *Biochemistry* 45:15670-83, 2006). Therefore, experiments are underway to investigate the role of h2-calponin in the effect of mechanical tension on keratinocyte differentiation and skin wound healing.

3238-Pos Board B285

How deep cells feel: Mean-field Computations and Experiments

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Most cells in solid tissues exert contractile forces that mechanically couple them to elastic surroundings and that significantly influence cell adhesion, cytoskeletal organization, and even cell differentiation. However, strains within the depths of matrices are often unclear and are likely relevant not only to the fact that some matrices such as so-called basement membranes are thin relative to cell dimensions but also to defining how far cells can 'feel'. Here we present experimental results for cell spreading on thin, ligand-coated gels and for prestress in stem cells in relation to gel stiffness. Spread area on thin and soft gels was found to resemble cells on thick and stiff gels. Matrix thickness also affects focal adhesions and cytoskeleton organization in stem cells, which we will compare to differentiated cells. We introduce a finite element computation in which a cell is placed on an elastic matrix, while matrix elasticity and thickness are varied in order to compute and compare elastostatic deformations within the matrix. Average interfacial strains between cell and matrix show large deviations only when soft matrices are a fraction of the height and width of a cell, proving consistent with experiments. Three-dimensional (3D) cell morphologies that model stem cell-derived neurons, myoblasts, and osteoblasts show that a cylinder-shaped myoblast induces the highest strains, consistent with the prominent contractility of muscle. Groups of such cells show a weak crosstalk in matrix strains, but the cells must be much closer than a cell-width - experimental tests of this are emerging. Cells thus feel on length scales closer to that of adhesions than on cellular scales or larger.

3239-Pos Board B286

Interactions Between Lipid Bilayer And Protein Skeleton In Erythrocyte Deformations

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We study mechanics of a red blood cell in large deformations by using a multi-scale modeling approach, in which the interactions between the lipid bilayer and the protein skeleton are considered as two parts: vertical contact and lateral sliding. The sliding is caused by the mobility of the transmembrane proteins (e.g. band 3 and glycophorin C). Our model consists of a complete-cell model which depicts the cell membrane as two continuous shells, and a molecular-detailed model of a junctional complex (JC) that provides the constitutive properties of the inner layer (the skeleton). The folding/unfolding reactions of the spectrin are also considered and incorporated into the JC model. This multi-scale model is validated by comparisons with other modeling approaches and experiments about micropipette aspirations and optical tweezer stretching. Applying this method, we numerically duplicated the boundary-value problem associated with cell deformation in a flow channel. The critical contact force, i.e. the maximum contact force that can exist between the bilayer and the skeleton without inducing skeleton-bilayer disassociation, is extracted. This critical force is then applied to predict conditions of vesiculation in other mechanically-induced cell deformations.

3240-Pos Board B287

Measurement of Adhesion Force between a Human Neutrophil and a *Candida albicans* Hyphae Using a Micromanipulation Technique

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Yeast infection (candidiasis) is a common and persistent threat to human health. Normally harmless, the fungus *Candida albicans* is present in 40-80% of normal human beings, but in immune-compromised individuals, it can proliferate and cause a variety of health problems including pneumonia, septicemia, or endo[[Unsupported Character - Codename -]]carditis. The fundamental mechanism towards the control of candidiasis and other fungal infections involves understanding how human neutrophils interact with β-Glucan, a polysaccharide present in fungal cell walls, at the single cellu[[Unsupported Character - Codename -]]lar level. We hypothesize that the complement receptor 3 (CR3), a member of the integrin family, can recog[[Unsupported Character - Codename -]]nize the β-Glucan on the *C. albicans* hyphae, initiating neutrophil adhesion and caus[[Unsupported Character - Codename -]]ing a respiratory burst. We test this hypothesis using a two-pipette micromanipulation technique to measure the adhesion force between a single neutrophil and a *C. albicans* hyphae. A micromanipulator attached to a suction pipette is used to trap a single *C. albicans* hyphae that is attached by a single neutrophil to a second, flexible pipette. The micromanipulator slowly pulls up on the hyphae, exerting an increasing force and causing the flexible pipette to bend until the hyphae detaches from the neutrophil. By measuring the deflection of the flexible pipette at the instant the hyphae detaches, Hooke's law can be used to calculate the adhesion force between the hyphae and the neutrophil. By measuring the average adhesion force of neutrophils from knock-out mice missing CR3 and compare with that from the wild type animals expressing CR3, we can determine the mechanical role the receptor plays in neutrophil adhesion.

3241-Pos Board B288

Mechanical Computation in Neurons

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Motility is a major function of cells, playing a fundamental role in development and embryogenesis. Growth cones are the major motile structures usually located at the tip of neurites and are composed of a lamellipodium from which thin filopodia emerge. We have analyzed the kinetics and dynamics of growth cones from a computational point of view with the aim to understand two major issues: firstly, the strategy used by filopodia and lamellipodia during their exploration and navigation; secondly, which kind of mechanical problems neurons need to solve during their operation. Filopodia grow and retract following

statistical patterns nearly optimal for an efficient exploration of the environment. This exploratory motion is at the basis of contact formation and the establishment of appropriate synaptic connections. Filopodia and lamellipodia can also avoid obstacles and occasionally lamellipodia can displace them. From this point of view, filopodial and lamellipodial motion can be described as a random process in which errors are corrected by efficient feed-back loops. We argue that neurons not only process sensory signals, but also solve mechanical problems throughout their entire lifespan, from the early stages of embryogenesis to adulthood.

3242-Pos Board B289
Assessing the Dynamics and Mechanics of the Cell Membrane
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Thermally and actively driven cell membrane fluctuations are known to be readouts for the nanomechanical interaction between the cortical cytoskeleton and the plasma membrane and the membrane. In this study, we developed a non-contact method to measure cell surface fluctuations through measurements of resistance between a microelectrode tip and the cell membrane. The system resolution was < 2 nm tested by using 2-10 Hz sinusoidal piezo stage motion with amplitudes ranging from 2 nm to 100 nm. We found that endothelial cells exhibited local membrane fluctuations of ~20 nm at a number of characteristic frequencies. To determine the role of actin in membrane fluctuation, we treated cells with 2 μM of actin depolymerizing drug, cytochalasin D, and we found that actin depolymerization increased in fluctuation amplitude up to 2 times at all frequencies. Finally, to determine role of ATP in membrane fluctuations, we treated cells with ATP depletion drug cocktail which consisted of 25nM Antimycin A + 2mg/ml 2-Deoxy-D-Glucose, and we found that ATP depletion abolished all membrane fluctuations. Therefore, actin cytoskeleton and dynamic processes facilitated by ATP may modulate membrane functions through mechanical effects on membrane fluctuations

3243-Pos Board B290
Cell Coat Mediated Cell Migration
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Cell migration depends on a sequence of adhesion and detachment events. These events arise during the cyclic migration process, which involves the integrin-dependent adhesion machinery, the acto-myosin system and the signaling pathways between them. Migration appears to rely on a delicate spatio-temporal regulation of cell adhesion to the surrounding substrate. Studies of cell migration in physiological contexts have shown that a pericellular coat, a thickened polymer matrix attached to many cell surfaces, often is required to facilitate cell migration, including that of aggressively spreading cancers. Cell motility in these systems directly depends on the formation of a large, hyaluronan-rich cell coat with an asymmetric distribution around the polarized migrating cell. Removal or alteration of the coat substantially decreases motility - to the point that such treatments have been proposed as therapies for some types of cancer. The hyaluronan biology community often speculates that cell migration requires the 'insulation' and/or the mechanical properties provided by the cell coat. However, little has been done to substantiate this claim. A bigger problem yet is that the lubricating effect of hyaluronan has been shown to oppose adhesion, which leads to a conundrum in the present context: How is it possible that inhibition of adhesion can help a cell migrate, when adhesion is absolutely necessary to gain traction and exert the force to move the cell forward? We have developed a microfluidics-based cell migration assay capable of presenting several surface gradients of fibronectin of different slopes to induce cell migration within the same device. We study the ability of these gradients to induce cell migration and their influence on the cell coat phenotype and mechanical properties using a combination of fluorescent labeling, particle exclusion assays, and optical tweezer force probe experiments.

3244-Pos Board B291
Biophysics of Tumor Cell Adhesion: From single molecules to multi-cellular interactions
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Cell adhesion plays a critical role in tumor formation, invasion and metastasis. The complex processes underlying adhesion to other cells and the extra-cellular matrices are dynamic and inherently multi-scale. Unfortunately, computational and mathematical models aimed at understanding adhesion have traditionally focused on a single length-scale and have been unable to link events at the atomic and molecular scale to bulk behaviors seen in experiments. In addition, most adhesion models have been blind to the effects of matrix structure and mechanics, molecular sequence and conformations and hence can only make qualitative predictions. Using a combination of molecular dynamics to generate conformations, coarse-graining of these results for single-chain mean field theory and then further coarse graining too study processes at the bulk level, we have developed a fully multi-scale model of cell-matrix and cell-cell interactions. Our models are rooted in principles of thermodynamics, statistical and continuum mechanics and are able to capture cell-matrix and cell-cell adhesion events at a single molecular, cellular, multi-cellular and tissue level. We are also able to study the effects of soluble and insoluble ligands, functionalized nano-particles and tethered surfaces. Thus our model is able to make quantitative predictions in both in vivo and in vitro environments.

3245-Pos Board B292
Professor
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The free energy that drives growth, resorption and sliding of focal adhesions includes mechanical and chemical contributions. We have identified a competition among four effects that control focal adhesion dynamics: (1) work done during addition of complexes, (2) the chemical potential inherent to focal adhesions, (3) the elastic free energy associated with deformation of focal adhesions, and (4) work done on a molecular conformational change. A theoretical treatment of focal adhesion dynamics developed in the framework of rate processes driven by thermodynamics demonstrates that the mechanisms governed by these four effects allow focal adhesions to exhibit a rich variety of behavior without the need to introduce special constitutive assumptions. In this treatment, the structural unit of focal adhesions is a complex consisting of a ligand such as fibronectin, an integrin molecule, and associated plaque proteins. The binding and unbinding of these complexes causes focal adhesion growth and resorption, respectively. The reaction-limited case is considered. Our central findings are that growth, resorption and sliding are all predicted by a very simple chemo-mechanical model. Sliding requires symmetry breaking and is achieved via (1) above; (4) promotes symmetric growth, and (2) and (3) cause symmetric desorption. The role of kinetic modulation is also examined.

3246-Pos Board B293
Micromechanical Properties Of Fixed And Living Vascular Pulmonary Endothelial Cells Following Exposure To Barrier Enhancing And Barrier Disrupting Agents
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Disruption of pulmonary endothelial cell (EC) barrier function is a critical pathophysiologic event that occurs in multiple inflammatory disease processes. The actin cytoskeleton, an essential regulator of endothelial permeability, is a dynamic structure whose stimuli-induced rearrangement is linked to barrier modulation. We used atomic force microscopy (AFM) to characterize structural and mechanical changes in the F-actin cytoskeleton of cultured human pulmonary artery EC in response to both barrier-enhancing and barrier-disrupting conditions. The mechanical properties of both fixed and live cells were evaluated. Elastic modulus values in the range of 50-1000 kPa were typically measured for fixed cells, while much lower values of 1-40 kPa were characteristic of live cells. In fixed cells, a differential distribution of elasticity was observed after exposure to the barrier-enhancing compound S1P (sphingosine 1-phosphate) compared to that produced by the barrier-disrupting agonist, thrombin. After S1P, the elastic modulus was elevated primarily at the periphery, while thrombin treatment increased elasticity in the central region of the cell. These observations correspond with the distribution of F-actin in parallel-treated EC as detected by immunofluorescence. In living cells, thrombin generally increased the average elastic modulus over 60 minutes; however, the S1P response was more varied and subtle. Experiments are under way to confirm these preliminary observations. These results provide novel insights into the structural and mechanical properties that dynamically regulate pulmonary EC barrier function.

3247-Pos Board B294
Adaptive-Control Model for Neutrophil ORIENTATION in the Direction of Chemical Gradients
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Directional movement of neutrophils in spatial chemical gradients is the result of complex intracellular signaling mechanisms that are not yet fully understood. Although many of the signaling molecules that participate in the mechanisms of gradient detection in neutrophils are already known, current models still cannot provide satisfactory explanation for the initial orientation in the direction of chemical gradients. To address these challenges, we propose a new biophysical model for neutrophil orientation in the direction of chemical