Tissue can be soft like brain, stiff like muscle, or rigid like bone. Proteomic profiling of human and mouse tissues and cells reveals that the nucleoskeletal protein lamin-A scales with various collagens and with tissue microelasticity, *E*. Among the many cell structure and nuclear components quantified here, lamin-A acts most clearly as a ''mechanostat'' in scaling with *E*, typical in polymer physics, whereas B-type lamins are nearly constant. Lamin-A dominates in stiff tissues and has been implicated in aging and diseases that impact muscle, bone, and fat but rarely brain or marrow, and nuclei in stiff tissue cells also prove much stiffer than nuclei from softer tissues. Mesenchymal stem cell differentiation *in vitro* further shows that lamin-A amplifies lineage signals from matrix, with low lamin-A favoring a soft tissue fate and high levels favoring stiff tissue. Regulation of lamin-A occurs at multiple levels, with conformational changes in isolated nuclei revealing its direct response to stress. Cells are also motile, and migration through dense matrix or tissue has also been seen to involve large nuclear contortions, which Lamin-A modulates in diverse 3D models in vitro and in vivo. Polymer physics again offers insight into response times. Systematic relations thus exist between tissue stress, stiffness and physics of the nucleus.

45-Subg
Nuclear Mechanics and Genome Regulation
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Mechanical signals from the extracellular matrix impinge on cellular geometry resulting in altered functional nuclear landscape and gene expression. These alterations regulate diverse biological processes including stem-cell differentiation, developmental genetic programs and cellular homeostatic control systems. How such matrix signals are integrated to the 3D spatio-temporal organization of the cell nucleus to elicit differential gene expression patterns are poorly understood. Using a multidisciplinary approach, combining high resolution live-cell imaging, micro-patterned substrates and single-cell mechanics experiments, our laboratory investigates the biophysical principles underlying the coupling between nuclear mechanics and genome regulation during stem-cell differentiation and in differentiated cells. In these projects, we engage in a number of collaborations with both theoretical and experimental groups. I will describe our ongoing work that provides mechanistic links between nuclear mechanics, chromosome organization and genome regulation.

46-Subg
T Cell Receptor-Associated Actin Patches Generated by Wiskott-Aldrich Syndrom Protein
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T cell activation involves massive cytoskeletal remodeling, including dynamic actin polymerization and centripetal flow proximal to T cell-antigen presenting surface synapse (IS). F-actin is required for the formation of signaling T cell receptor microclusters (MCs) and for on-going signaling. Wiskott-Aldrich Syndrome Protein (WASP) is an actin nucleation-promoting factor that is critical for appropriate T cell function. Patients with mutations in WASP experience a severe immunodeficiency and autoimmunity. The role of WASP in actin polymerization at the immunological synapse has been surprisingly cryptic as WASP deficient T cells still display dramatic increases in F-actin at the immunological synapse. Here, with the aid of live cell as well as super-resolution imaging in primary T cells, we identify WASP dependent F-actin patches closely associated with TCR microclusters. The patches also contain phosphorylated HS-1, a cortactin homolog, and phosphorylated Cas-L a mechanotransduction protein, which are recruited down-stream of WASP. Closely related proteins N-WASP and WAVE2 do not participate in TCR-associated F-actin patches. Super-resolution imaging reveals that the patches are composed of multiple actin arrays that are oriented to diverge from TCR microclusters. We conclude that F-actin patches represent a unique mode of actin polymerization in the immunological synapse that integrate the well documented functional defects in WASP deficient T cells to F-actin nucleation activity.
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47-Subg
Plasticity at Synapses:From Super-Resolution to Physical-Chemistry of Receptor Scaffold Interactions
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The variability of the postsynaptic response following a single action potential arises from two sources: the neurotransmitter release is probabilistic, and the postsynaptic response to neurotransmitter release has variable timing and amplitude. At individual synapses, the number of molecules of a given type that are involved in these processes is small enough that the stochastic (random) properties of molecular events cannot be neglected. How the stochasticity of molecular processes contributes to the variability of synaptic transmission, its sensitivity and its robustness to molecular fluctuations has important implications for our understanding of the mechanistic basis of synaptic transmission and of synaptic plasticity. Using single particle tracking and super-resolution imaging, we will address the issue of inhibitory postsynaptic receptors dynamic, their interactions with scaffolding protein and regulations implicated in synaptic plasticity.

48-Subg
Shaping the Embryo: Cellular Dynamics in Development
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A major challenge in developmental biology is to understand how large-scale changes in tissue structure are generated on a cellular and molecular level. Two decades of research in molecular genetics have provided insight into the mechanisms that control cell fate and patterning, but the mechanisms that regulate the mechanical forces that shape cells and tissues are not well understood. A conserved feature of tissue architecture in vertebrates and invertebrates is a body axis that is elongated from head to tail. In the embryo of the fruit fly Drosophila, this elongation is achieved through the coordinated movements of hundreds of cells along a common axis. Several molecules that are asymmetrically localized in the plane of the tissue are crucial for planar polarized force generation and junctional remodeling during axis elongation, including components of the contractile machinery and cell-cell junctions. Using quantitative imaging, we found that these asymmetries at the cellular level result in a collective behavior in which groups of cells assemble into multicellular rosette structures that form and resolve directionally (Blankenship et al., 2006). Rosettes form through a mechanical feedback loop in which an initial asymmetry in myosin II localization is selectively stabilized in regions of increased tension to produce higher-order contractile networks (Fernandez-Gonzalez et al., 2009). This positive feedback loop that is predicted to increase the number of cells engaged in contractile behavior, promoting efficient elongation. Rosette formation has since been shown to occur during epithelial elongation in vertebrates and may represent a general mechanism linking cellular asymmetry to tissue elongation. We are currently using biophysical approaches and large-scale genetic screens to identify the machinery that directs polarized cell behavior and components of the mechanotransduction pathway that is required for tension-dependent myosin dynamics during tissue elongation.

49-Subg
Bacteria are Stressed Out Too: The Physics of Mechanosensation
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Many of the ways that cells talk and listen to the external world center on the presence of proteins on the cell surface. Indeed, the cell membrane is an amazingly diverse lipid environment, riddled in turn with a host of different proteins that perform tasks ranging from sensing and measuring chemical signals to the transport of sugars needed for cell division to the detection of potentially lethal osmotic pressures. This talk will focus on recent progress in the dissection of the mechanisms of mechanosensation in bacteria with special reference to the rich interplay between certain classes of ion channels and the surrounding lipids. Using simple arguments from elasticity theory, I will describe the membrane deformation footprint surrounding ion channels and how this deformation footprint contributes to the free energy of channel gating. In turn, I will show how these ideas can be parlayed into an experimental strategy for better understanding mechanosensation by watching individual cells as they are subjected to controlled levels of osmotic shock.

Subgroup: Biological Fluorescence

50-Subg
Novel Labeling Schemes for Single-Molecule Localization Microscopy
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Single molecule localization-based superresolution microscopy methods, such as PALM or STORM, have been breakthrough techniques of the last years. Until now however, they require special fluorescent proteins to be cloned or high-affinity antibodies to be generated for specific labeling. On the other hand,