microenvironment. The fluid flux through the membrane is governed by the difference of chemical potential across the membrane. The osmotic pressure is obtained from the ion diffusion and flux and the hydrostatic pressure is obtained from the fluid dynamics inside the cell. The flux of cations and anions across the cell membrane is determined by the properties of the ion channels as well as the external electric field. Results show that without the contribution from actin network and myosin contraction, water permeation can also drive non-polarized cells with the presence of an external electric field. The direction of migration is affected by the properties of ion channels which are cell-type dependent. The results suggest that external voltages can be used to sort cells.

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Circular Dorsal Ruffles Increase Directional Persistence of Cell Migration by Actin Diffusion from Ruffles to Lamellipodia

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Circular dorsal ruffles (CDRs) are transient actin structures which have been linked to cell motility but the exact mechanism is still unclear. CDRs appear and grow in size after cells are stimulated with growth factors, such as the platelet-derived growth factor, eventually disappearing tens of minutes after stimulation. The role of CDR formation in cell motility is investigated for NIH 3T3 fibroblasts seeded on compliant polyacrylamide substrates. We found that CDR formation increases cell migration directional persistency but did not affect the migration speed. Furthermore, an increase in the localization of lamellipodial protrusion at the cell edge in the vicinity of the CDRs was observed. Relocalization of lamellipodia occured 1 to 6 min after CDR formation at the cell edge closest to the site of CDR formation. The time lag between peak CDR formation and the peak lamellipodial protrusion is then correlated with the spatial distance between the CDR and the lamellipodia; this time scale is consistent with the diffusive time scale of cytosolic globular actin (G actin). Using green to red photoswitchable Dendra2-conjugated actin, we photoconverted CDR actin from green to red and observed the subsequent appearance of red fluorescent actin in the lamellipodia at the cell leading edge. These findings help shed light on the interconversions between mesoscopic actin structures in cell behavior.

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Modeling Transmigration of Malaria Infected Red Blood Cells through Inter-Endothelial Slits in Human Spleens using Dissipative Particle Dynamics

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We simulate the transmigration of malaria-infected red blood cells (RBCs) through the inter-endothelial slits in the human spleen by using Dissipative Particle Dynamics based two-component RBC model. We modeled the spectrin-actin network and the lipid bilayer separately and considered the real number of the structural proteins in the model. The mechanical properties of the bilayer-cytoskeletal interactions, such as stiffness and friction, are calibrated by comparing with membrane fluctuations and tank-treading experiments. First, we further validated our numerical model by comparing the predicted retention rates of healthy and pathological cells in an 'artificial spleen' consisting of micro beads with the experimental measurements. To explore the possibility of the bilayer-cytoskeletal detachment during this transmigration process, which is strongly related to RBC aging and hereditary spherocytosis, we predicted the maximum interaction force between the spectrin-actin cytoskeleton and the lipid bilayer and compared the value with the previously predicted bilayer-cytoskeletal bond strength. Furthermore, we systematically studied the effects of cell rigidity, cell shape and inter-endothelial slit dimensions on the critical pressure gradient for RBCs to pass through the spleen. We found that the cell shape plays a much more important role than the cell rigidity in the transmigration process, which may guide the future experiments and the drug design for eradicating malaria and treating anemia such as hereditary spherocytosis.

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Restricted Exchange Environment Chambers for Creating and Manipulating Diffusive Gradients in 2D Cell Culture

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Diffusive exchange between capillaries and the tissues they serve generates concentration gradients of a significant number of soluble molecules, creating heterogeneous microenvironments on the length scale of single cells. This heterogeneity is not well captured in 2D cell culture models, and it is not easily controlled or studied in spheroid models. Here we describe a simple chamber in which diffusive gradients similar to those found in vivo can be formed and manipulated. In restricted exchange environment chambers (REECs), cells are grown in a narrow gap formed by two coverslips, and diffusive exchange occurs via one or more small openings machined into one coverslip – through which the cells exchange nutrients and metabolic waste with the bulk medium. Based on a concept similar to the sandwich assay (Hlatky and Alpen, Cell Tissue Kinet., 18:597, 1985) and compatible with multiwell plate formats used in high-throughput investigations, REECs improve experimental control of gradient structure in cell culture. Because diffusive concentration gradients vary as a function of distance from a source or sink, the dimensions of the chamber (e.g. height of the gap) and the number, shape, and size of openings create the gradient structure. For example, in REECs with a single round opening (order 200 μm diameter), concentration gradients form radially. Only cells within a several hundred micrometers of the opening exchange sufficient metabolites to survive - similar to diffusive exchange near a capillary in a tissue. Alternatively, cells cultured in REECs with two parallel bar-shaped openings produce the 1-dimensional equivalent of a spheroid. Using these restricted exchange environment chambers, we find that fibroblasts align themselves along the axis of diffusion while MDCK cells do not. MDCK cells do, though, exhibit morphological variations along the diffusive gradient.

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Coupling a Mechanosensitive Channel with a Vesicle under Shear Flow

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Mechanosensitive channels enable cells to respond to their local environment. Continuum mechanical models have been proposed to describe how bilayer deformation induced by the transmembrane protein and the membrane tension influence the free energy of channel gating under static conditions. The dynamics of mechanosensitive channels under flow conditions however remains largely unexplored. Cells under flow display interesting features not observed under static environments. Here we present a model coupling a mechanosensitive channel with the dynamics of a vesicle under shear flow to investigate how the channel gating responds to hydrodynamic stress. The model could be used to investigate the release of signaling molecules, transport of ions or drugs across cell membranes under flow in biological systems, as well as the design and control of channel gating in synthetic cells.

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Perturbing the Active Process of Hair Cells: Self Recovery of Spontaneous Oscillations Following Overstimulation

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In the inner ear, hair cells perform the transduction of mechanical input into electrical output. An energy-consuming process enhances their sensitivity to incoming auditory and vestibular stimuli. One manifestation of this active process is spontaneous oscillation of the mechano-sensitive organelle, the hair bundle, which is at the apical surface of each hair cell. To attain this increased sensitivity, the hair bundle is postulated to operate near a bifurcation, where an internal control parameter vital to the active process determines whether the bundle shows limit cycle oscillations or is quiescent. This control parameter may be linked to adaptation in vertebrate hair cells and could help explain how prolonged high-level sounds cause a temporary threshold shift in mammalian hearing. High amplitude, prolonged deflection of bullfrog sacculus bundles have been shown to temporarily suppress spontaneous oscillations, suggesting a readjustment of the control parameter through a bifurcation. The transition back from quiescence to limit cycle oscillations has been shown to depend on the duration of the imposed deflection and on calcium ion concentration around the mechanically gated transduction channels.

Here, we present experiments where we identify other environmental factors that affect this control of the active process. We introduce various pharmacological agents to manipulate the mechano-sensitive transduction channels and the myosin motors inside the hair bundles. We compare how these agents affect particular components of the internal control parameter by measuring the duration of the induced quiescent intervals and the time scales associated with the return of the bundle's position to equilibrium. Additionally, we attach magnetic bead particles to the hair bundles and deflect with a strong magnetic field. Thus, hair bundles avoid physical contact with the stimulus probe, and experience no external hydrodynamic effects. Selected results are discussed.