mechanism of cell migration in confined spaces is still unclear. Here we propose a jet propulsion model of the cell motility when cells migrate through heterogeneous structures in tissues, such as lymphatic vessels, vasculature and nerves. We show that as long as the cell is polarized so that an ion concentration gradient along the elongated cell body can be maintained, water molecules can be ingested into the cell at the leading end and emitted at the trailing end of the cell. Therefore, cells can migrate forward at a high speed. Our model also predicts that an osmotic shock can reverse the direction of cell migration in microchannels. These predictions were verified by our microfluidic experiments. The effects of actin, mysoin, microtubules and ion transporters were studied theoretically and experimentally.

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**Amoeboid Cells Migrate by Alternating Between Modes with Distinct Adhesion Dynamics and Contractility**

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Directional cell migration is involved in a broad range of biological phenomena, ranging from the metastatic spreading of cancer to wound healing. Chemotaxing *Dictyostelium* cells adapt their morphology and speed to external conditions like the stiffness and adhesive properties of their substrate. The mechanism by which they control both their shape and speed remains largely unknown. Using Traction Force Microscopy measurements, we construct traction tension kymographs to examine the spatio-temporal dynamics of both the adhesions and the traction stresses during migration. We show that wild-type cells control their motility by switching between two motility modes with distinct adhesion and contractility dynamics. In the "*Stepping-Stepping"* mode, the adhesion sites remain stationary while the cell moves forward by periodic axial contractions. The back adhesions break after new frontal adhesions are formed. In the *"Stepping-Gliding"* mode, the cell reduces the magnitude of the traction stresses, increases the frequency of axial contractions and its migration speed, and keeps the frontal adhesion stationary while sliding the back adhesion forward. These two modes are not conserved when cells move on adhesive poly-L-Lys coated substrates, where cells alternate between a *"Nearly Stationary"* mode, characterized by strong lateral contractions and extremely low migration speed and a *"Gliding-Gliding"* mode, where multiple weak and transient adhesions are formed which are gliding forward as the cell moves by barely adhering to the substrate. In summary, our findings have contributed to a more precise understanding of how the coordination of traction stresses together with the adhesion dynamics result in efficient amoeboid cell migration. We propose that these are highly conserved mechanisms, which function in a range of amoeboid cells, including leukocytes, as well as other forms of cell motility.

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**Cellular Contact Guidance through Dynamic Sensing of Surface Topography**

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We investigate the directed migration of the amoeba Dictyostelium discoideum on nano-topographical gratings. We observe significant contact guidance of Dictyostelium along ridge-shaped and groove-shaped nano- and microtopographic surface features, even though Dictyostelium lack Focal Adhesion Complexes which had been associated with contact guidance mechanisms in other studies. More specifically, we find that cells that move parallel to ridges are faster and more elongated than cells that move perpendicular to ridges. Cells that move parallel to ridges are also more protrusive at their fronts than cells that move perpendicular to ridges. Quantification of contact guidance efficiency shows that ridges with a spacing of about 1.5 μm have optimal contact guidance efficiency. Because Dicty cells exhibit rhythmic protrusions and retractions, we model contact guidance on nanogratings in terms of stochastic cellular harmonic oscillators that couple to the periodicity of the ridges. The wavelength and speed of the oscillations that best couple to the surface are consistent with those of the protrusive dynamics and with actin polymerization waves, which have been associated with both cell migration and cell spreading. Thus our results suggest that actin waves may facilitate a dynamic contact guidance process. Finally we describe our efforts to utilize the wave-like nature of contact guidance to design optimal guidance strategies.

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**Reverse Engineering the Euglenoid Movement**

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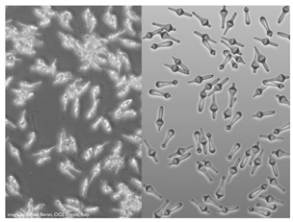
Euglenids exhibit an unconventional motility strategy amongst unicellular eukaryotes, consisting of large amplitude highly concerted deformations of the entire body (euglenoid movement or metaboly). A plastic cell envelope called pellicle mediates these deformations. Unlike ciliary or flagellar motility, the biophysics of this mode is not well understood. We examine quantitatively video recordings of four euglenids executing such motions with statistical learning methods, revealing strokes of high uniformity. We then interpret the observations with a theory for the pellicle kinematics, providing a precise understanding of the link between local actuation by pellicle shear and shape control. We find that two of our euglenids execute their stroke at constant body volume, the other two exhibit deviations of about 20% from their average volume, challenging current models of low Reynolds number locomotion.The active pellicle shear deformations can reach 340%. Moreover, we find that metaboly accomplishes locomotion at hydrodynamic efficiencies comparable to those of ciliates and flagellates. Our results suggest new quantitative experiments, provide insight into the evolutionary history of euglenids, and suggest that the pellicle may serve as a model for engineered active surfaces with applications in micro-fluidics.



Arroyo, Heltai, Millán and DeSimone, PNAS (in press).

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**Extrinsic Forces: How they Reprogram Cell Motility**

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While moving on a culture substrate, a cell can respond to two types of forces. Intrinsic force helps to maintain the cell persistence. Extrinsic force involves repulsive or attractive signals exerted by an external stimulus. Extrinsic is the stronger force, since it can overcome the intrinsic force and cause the cell to change direction. The studies were designed to determine whether these forces are associated with different protrusions. We studied fibroblasts that met a barrier while moving in a chemokinesis system. The prevalence of various protrusions was determined after movement was halted along the original trajectory. We computed latent factors corresponding to cell features: factor 4 values to filopodia, factor 7 to a nascent neurite, and factor 5 values to centrifugal mass displacement. The data showed that as cells moved further and further from the barrier, they had progressively lower values of factor 5 ($R^2 = 0.25$). Factor 4 values rose slightly, whereas factor 7 values showed little tendency to change with distance from the barrier. A different experimental system, designed to investigate intrinsic force in epithelial cells, was also studied. Here, the frequency of various combinations of factor 4, factor 5, and factor 7 differences was obtained by using different treatments. In table 1, there are 10 combinations of changes (1 is increment, 0 is no effect, and −1 is decrement). The single most common effect of treatment was an enhancement of factor 5 values without a corresponding change in factor 4 or factor 7 values. The results, taken together, suggest that the protrusion associated with exploratory motility is factor 5. As in guidance model systems, factor 4 may be representative of persistence. Learning how the protrusive features are regulated may help investigators to understand persistence.

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**The Matrix Stiffness Regulates Morphology, Direction and Persistence of Motiles Cells**

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Cell motility is a fundamental process for embryonic development, wound healing, immune responses and for pathological processes such as cancer metastasis. During past few decades, the influence of the extracellular matrix stiffness, known as durotaxis, has been extensively studied on stationary cells. However, the impact of the matrix stiffness on the motion of motile cells is still unclear. By using a wide range of ECM stiffnesses with a contant cell-ligand density, we have investigated morphological and dynamical parameters of fish keratocytes in response to a wide range of matrix stiffnesses. We have found that modifying the matrix rigidity of the underlying substrate has a dramatic effect on keratocyte motility and directional persistence. To elucidate the mechanisms by which the matrix stiffness determines moving cell behavior, we examined the organization of adhesions, myosin II, and the actin network in keratocytes migrating on substrates with a wide range of stiffnesses and a constant surface chemistry. Our results are consistent with a quantitative physical model in which keratocyte shape and migratory behavior emerge from the self-organization of actin, cell-substrate adhesions and myosin II activity.