Nanofluidic Systems for Biomolecular Analysis

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We have used nanofabrication methods to create fine-scale fluid channels and optical devices with spatial confinement in a variety of material systems. With these systems we have explored new approaches for biochemical separation and analysis. Functional fluid systems have been embossed, etched and created by use of sacrificial layer techniques.[1-6] With these approaches we can fabricate structures with controlled dimensions down to the tens of nanometer range. Applications of such systems range from capillary electrophoretic separations to manipulation and analysis of individual molecules in molecular-scale channels and constrictions.

By controlling the time and spatial dependence of electric fields one can drive, sort and separate molecules by a variety of physical mechanisms. Asymmetric barriers to driven molecular motion have been used for continuous sorting of molecules by differential diffusion rate.[7] We have created nanoconstrictions in fluid channels that act as entropic barriers to electrophoretically driven molecular motion and used the size dependence of these entropic effects to separate DNA fragments by size.[8-10] Time varying electric fields can be used in conjunction with spatially generated entropic barriers to create high-speed molecular sorting systems exploiting the ability of nanostructures to apply controlled femtoNewton forces on molecular ensembles.[11] With these nanosystems we can control the application of small forces on molecules and observe the response in motion through confined geometries. These approaches give us access to the mechanical properties of molecules that may enable molecular separation approaches based on the *mechanical* properties of large molecules in a way that was previously inaccessible in engineered devices. The ability to integrate these with lab-on-a-chip systems and microfluidic systems may be exploited for improved device performance.

Nanostructures have also been used to enhance optical effects for molecular analysis. We have explored devices for optical confinement in 1 to 3 dimensions. Channels with thickness smaller than optical wavelengths in one dimension can be used, for example, to create an refractive index-based sensor using photon tunneling.[5] Fluid channels have been created with physical confinement in 2 dimensions with optical excitation confined to volumes less than a femtoliter. These devices have been used for DNA fragment sizing by single molecule spectroscopy and used for fluorescence correlation spectroscopy with improved signal-to-noise ratios.[6,12] Related fabrication approaches have been used to create regions of confined optical excitation in 3 dimensions using metallic nanoconstrictions. These devices enable practical studies of biochemical processes at the single molecule level.[13]

Nanofabricated systems allow us to create devices to experimentally access the mechanical and optical properties of individual molecules. The understanding derived from these measurements is motivating a new set of molecular analytical approaches based on single molecule analysis and properties inherent in nanoscale systems.

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