current detection platform, nanopores in these <10 nm-thick HfO2 membranes can detect a wide variety of single biopolymers, including single-stranded DNA at a current blockage level comparable to that of the alpha-hemolysin biological nanopore. These HfO2 pores may be used for hours at a time and translocate tens of thousands of molecules without significant expansion. Interaction with the pore walls results in slow translocation times for nucleic acids. At the same time the thinness of the membrane increases the pore's electric field and confines the region of strong analyte-pore interaction to prevent clogging. These results indicate that HfO2 may be a superior material to SiN for single molecule nanopore experiments.

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Solid-State Nanopore Mapping of DNA with Site-Specific Bound Ligands

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We report the use of solid-state (SS-) nanopores to detect discrete ligands bound to specific sites along the length of double-stranded DNA. Binding to DNA templates is studied initially with electromobility shift assays and atomic force microscopy before SS-nanopore translocation. We find that DNA containing as few as 1-2 bound ligands can be resolved, demonstrating the feasibility of mapping tagged regions of genomic DNA at the single-molecule level.

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Hardware Implementation of Denoising Algorithms for Nanopore Sensing

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Effective biosensors continue to be a research area of great interest for both defense and medical applications. In particular, silicon pores with diameters in the range of micro/nano-meters have demonstrated the ability to detect an array of analytes. Typically, these sensors make use of the Coulter counter set-up where a drop in current across the chamber is observed when a biomaterial passes. The duration and amplitude of this drop is indicative of the biomaterial's size and shape.

In order to effectively use such sensors, however, robust denoising and classification algorithms must also be developed. Recently, Non-Positive Go Decomposition (NpGoDec) was shown to be an effective denoising method for biological data, correctly classifying simulated controlled data for Immunoglobulin G biomolecule with 96 percent accuracy.

In this work, a research team for Arizona State University programmed the NpGoDec algorithm onto a Field Programmable Gate Array (FPGA) for on-chip, biosensor processing. There are several benefits to such a system. First, denoising the signal on an FPGA reduces processing time by avoiding the transmission of the raw data into off-line processing software such as MATLAB and brings biological sensing one step closer to real time. In addition, performing much of the signal processing work on the FPGA moves the sensor closer to being a portable device. The system is carefully investigated for accuracy and processing time as compared to the original, simulated signal. Our approach also enables the integration of a classifier onto an FPGA, which will allow the system to quickly identify the biomaterials passing through a nanopore.

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Graphene Nanopore with Self-Aligned Plasmonic Optical Antenna

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The atomically thin nature of graphene makes it an ideal translocation membrane for high resolution, high throughput, single-molecule DNA sequencing based on nanopores. The conventional approach to creating nanopores on graphene requires a high-resolution electron beam sculpting/drilling process, which often suffers from process variability, precluding the platform from being scalable. Here, we report the formation of integrated graphene nanopores with self-aligned plasmonic optical antennae by photothermal sculpting. We show that a nanometer-sized heated spot created by photon-to-heat conversion (i.e., photothermal effect) of a gold nanorod resting on a graphene membrane forms a nanoscale pore with a self-integrated optical nanoantenna in a single step. The unique interface of graphene nanopore-plasmonic optical antenna is composed of a nanopore with a smallest achievable dimension of a few nanometers and a hemispherical gold nanoparticle located adjacent to the nanopore. The distinct plasmonic traits of metal nanoparticles, which concentrate micron-sized light into nanoscale regions, yield the significant advantage of parallel nanopore fabrication compared to the conventional sequential process using an electron beam. In addition, we achieve tunability of both the nanopore dimensions and the optical characteristics of plasmonic nanoantennae by controlling laser fluence and the dimension of nanoparticles. Finally, the optical function of our self-aligned plasmonic nanoantenna on graphene nanopore is manifested by multifold fluorescent signal enhancement during single lambda phage DNA translocation through a graphene nanopore. We believe our approach to forming an integrated graphene nanopore with self-aligned optical antenna could potentially offer a new avenue and advances for nanopore-based simultaneous electrical and optical DNA sequencing.

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Ion Conductivity, Structural Dynamics and the Effective Force in DNA Origami Nanopores

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Nanopores have emerged as convenient tools for single molecule manipulation and analysis. In a typical measurement, a charged biomolecule-DNA or a protein-is transported through a narrow pore in a biological or synthetic membrane by external electric field. The presence and, in some cases, the chemical structure of the biomolecules is detected by measuring changes in the ionic current that flows through the nanopore. Recently, it has become possible to combine solid-state nanopores with self-assembled DNA nanostructures, the so-called DNA origami, into hybrid pores of advanced functionality. In such systems, a DNA origami plate partially covers the solid-state nanopore, providing both a nanopore of well-defined chemical structure and a platform for incorporation of auxiliary systems such as processive molecular motors and/or metallic nanoparticles. Here, we report molecular dynamics simulations of DNA origami nanopores that characterized the microscopic properties of such systems with unprecedented resolution. First, we built accurate all-atom models of DNA origami nanopores based on the honeycomb and square lattices and simulated the models using the molecular dynamics method. Next, we determined the ionic conductivity of different DNA origami designs by performing the simulations under applied electric field. For some square lattice designs, we observed reversible changes in the DNA origami structures responsive to the magnitude of the applied electric field. In the final set of simulations, we studied the electrophoretic transport of double-stranded DNA through DNA origami nanopores and characterized the effective force exerted by the applied field on both the permeating DNA molecule and the DNA origami structure. Our simulations demonstrate the utility of the molecular dynamics method for rational engineering of DNA origami nanopores into nanoscale sensors of advanced detection functionality.

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Tailoring Nanoprobes for Single-Cell Surgery

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Physiological and pathological processes within the human body are controlled by complex cell-cell interactions within the context of a dynamic microenvironment. Current methods are inadequate to monitor the multiple interactions and dissect the contributions of single cells to these processes. We will present the development of nanoprobes based on nanopipettes for manipulating living cells. We will describe the integration of these nanoprobes with scanning probe microscopy techniques to allow the delivery of biomolecules to individual cells and to biopsy minute amounts of cytoplasmic material and organelles from within living cells. In particular, we will discuss recent developments regarding the fabrication of carbon nanoelectrodes whose size can be precisely tuned with nanometer precision. Nanoelectrodes as small as 3 nm in radius can be functionalized with platinum using established electrochemical methods. The electrochemical deposition of platinum only slightly increases the surface area of the nanoelectrode but dramatically enhances its catalytic activity toward oxygen reduction and hydrogen peroxide oxidation. We will discuss their application for measurement of metabolic activity inside brain slices. Furthermore, the nanoelectrode can be precisely inserted into an individual neuron within the brain tissue with minimal disturbance to the biological milieu. We will present data showing the ability of the functionalized nanoelectrodes to measure intracellular endogenous molecules. Current studies in our group are trying to link the measured current with pathogenic conditions.