Abstract:
Resonant nanoelectromechanical systems (NEMS) are being actively investigated as sensitive mass detectors for applications such as chemical and biological sensing. We demonstrate that highly uniform arrays of nanomechanical resonators can be used to detect the binding of individual DNA molecules through resonant frequency shifts resulting from the added mass of bound analyte. Localized binding sites created with gold nanodots create a calibrated response with sufficient sensitivity and accuracy to count small numbers of bound molecules. The amount of nonspecifically bound material from solution, a fundamental issue in any ultra-sensitive assay, was measured to be less than the mass of one DNA molecule, allowing us to detect a single 1578 bp DNA molecule.

Summary:
The drive toward ultra-sensitive biochemical assays has motivated significant efforts in single molecule detection and identification. Resonant nanomechanical devices [1-3] provide an alternative approach to techniques such as those using fluorescent labels. The mechanical approaches also have the possibility of quantification of the bound molecules, and can be incorporated in array-based systems for multiplexed biochemical analyses. Carbon nanotubes, attractive because of their uniform diameters and small mass have also been considered as biomolecular detectors, but remain difficult to incorporate in device architectures and have not yet been able to quantify specifically bound biomolecules.

We have detected the binding of functionalized 1578 base pair long double-stranded deoxyribonucleic acid (dsDNA) molecules to nanomechanical oscillators by measuring the resonant frequency shift due to the added mass of the bound molecules. The binding of a single DNA molecule could readily be detected [4]. The resonant frequency of individual oscillators in an array of resonator devices was measured by thermo-optically driving the individual devices and detecting their motion by optical interference. The number of bound molecules on each device was quantified as proportional to the measured frequency shift with a proportionality constant determined experimentally and verified by modeling of the mechanical response of the system. For the smallest and most sensitive cantilevers the mass sensitivity was 194Hz/attogram. The resonant frequency shift of the oscillators can be measured with high accuracy, having a practical experimental uncertainty of ~10 Hz corresponding to ~0.05ag. The nonspecific binding of material to the oscillator throughout the process, however, limits the quantification of the specifically bound compounds for a particular analytical process.

We measured the effects of non-specific binding of material other than the DNA from our solutions and found this to be approximately 0.43 ± 0.23ag for an oscillator of length L = 3.5 µm, with 0.23ag therefore being the approximate limiting mass resolution resulting from uncontrolled binding to the surface in our particular process. For the smallest (L = 3.5 µm), most sensitive oscillator this mass uncertainty corresponds to the mass of ~ 0.26 DNA molecules, enabling us to be able to resolve a single molecule. With the most sensitive devices and dilute DNA concentrations, we have detected a single dsDNA molecule.

References:
Enumeration of Single DNA Molecules Bound to a Nanomechanical Oscillator

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Figure 1, top right:
Micrographs (a & b) showing arrays of cantilevers of varying lengths. (c) SEM of the 90 nm thick SiN cantilever with a 40 nm circular Au dot.

Figure 2, below right:
Schematic of the optical measurement setup and binding strategy of the thiolated dsDNA molecules to the Au dots.

Figure 3, below left:
Frequency spectra before and after the binding events show a frequency shift due to a single dsDNA molecule bound to the Au surface of the cantilever.