Weighing of Biomolecules, Single Cells and Single Nanoparticles in Fluid

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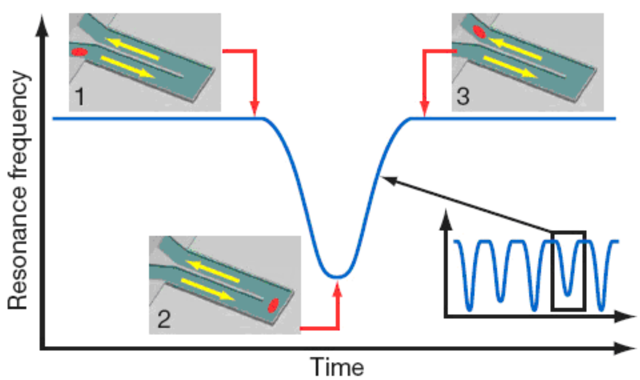
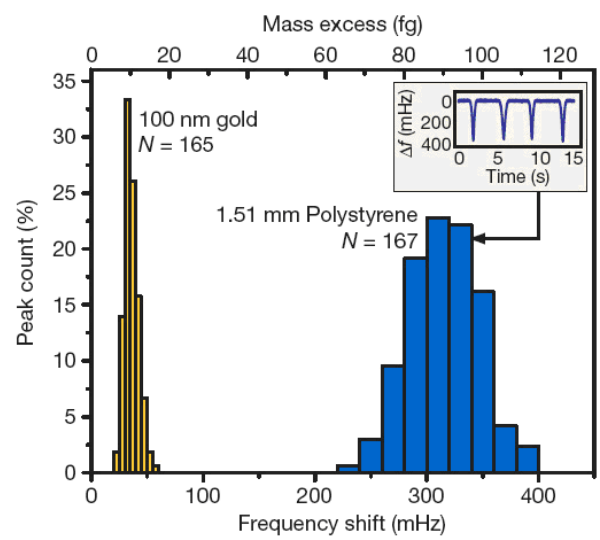
Nanomechanical resonators enable the measurement of mass with extraordinary sensitivity. Previously, samples as light as 7 zeptograms (1 zg = 10^{-21} g) have been weighed in vacuum, and proton-level resolution seems to be within reach. Resolving small mass changes requires the resonator to be light and to ring at a very pure tone—that is, with a high quality factor. In solution, viscosity severely degrades both of these characteristics, thus preventing many applications in nanotechnology and the life sciences where fluid is required. Although the resonant structure can be designed to minimize viscous loss, resolution is still substantially degraded when compared to measurements made in air or vacuum. An entirely different approach eliminates viscous damping by placing the solution inside a hollow resonator that is surrounded by vacuum (Figure 1). We have recently demonstrated that suspended microchannel resonators can weigh single nanoparticles (Figures 2), single bacterial cells. and sub-monolayers of adsorbed proteins in water with sub-femtogram resolution (1 Hz bandwidth). Central to these results is our observation that viscous loss due to the fluid is negligible compared to the intrinsic damping of our silicon crystal resonator. The combination of the low resonator mass (100 ng) and high quality factor (15,000) enables an improvement in mass resolution of six orders of magnitude over a high-end commercial quartz crystal microbalance [1]. This gives access to intriguing applications, such as mass-based flow cytometry, the direct detection of pathogens, or the non-optical sizing and mass density measurement of colloidal particles.



▲ Figure 1: A suspended microchannel translates mass changes into changes in resonance frequency. Fluid continuously flows through the channel and delivers biomolecules, cells. or synthetic particles. Sub-femtogram mass resolution is attained by shrinking the wall and fluid layer thickness to the micrometer scale and by packaging the cantilever under high vacuum. In one measurement mode, particles flow through the cantilever without binding to the surface, and the observed signal depends on the position of particles along the channel (inset 1 – 3). The exact mass excess of a particle can be quantified by the peak frequency shift induced at the apex.



▲ Figure 2: Synthetic particles of known size and density were measured to calibrate the mass sensitivity of the device. Gold nanoparticles (100 ± 8 nm) weighing 10 fg more than the water they displace produced a mean frequency shift of 36 mHz with a standard deviation of 6 mHz. On a different device, we measured a frequency shift of 310 ± 30 mHz for polystyrene microspheres (1.51 ± 0.01 um) with 90.1 fg mass excess.

REFERENCES

[1] T.P. Burg. M. Godin, W. Shen, G. Carlson, J.S. Foster, K. Babcock, and S.R. Manalis, "Weighing of biomolecules, single cells, and single nanoparticles in fluid," *Nature,* to be published.