Mulitiplexed Molecular Assays Using Nanoelectronically Barcoded Beads

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We introduce the concept of electronically barcoded micron-sized beads, which to the best of our knowledge, is the first time an impedance based barcoding technique for beads has been used with the potential of achieving high barcode density. Nanoelectronic barcoding works by fabricating tunable nano-capacitors on the micro-particle surface, effectively modulating the frequency dependent dielectric properties of the particles allowing one bead barcode to be distinguished from another, potentially on the scale of 100. Multi-frequency lock-in measurements of the real to imaginary impedance ratio allows for bead differentiation. Barcoding of microparticles has been widely used for performing multiplex genomic and proteomic assays. The most common methods of barcoding are optical and plasmonic which requires large and bulky instrumentation for performing the readout, which is unsuitable for portable devices requiring small instrumentation footprint. Electronic barcoding is advantageous to optical barcoding because it can significantly reduce the cost and size of the readout instrumentation.

The barcoded structures have a metal layer on one half of the bead covered by a thin dielectric layer, similar to Janus particles. The bead capacitance is tuned by controlling the thickness of the oxide and the surface area of the bead. This results in modulation of the electrical impedance of the bead at high frequencies. By performing high-speed multi-frequency lock-in amplification measurements on the tuned particles as they transit across the impedance sensor, one can determine the precise location of the transitions in the CM factor (where CM is zero) and compute both the diameter of the beads and also the capacitive properties, effectively recognizing one bead barcode from another. Fig. 2 explains the fabrication process. The polystyrene beads are coated with a layer of gold and a 10 nm layer of Atomic Layer Deposited (ALD) Al_2O_3.

Fig. 3 shows microscopic images of the barcoded particles deposited on a Si surface (Fig. 3B) and flowing through an impedance cytometer (Fig. 3C). Fig. 4 shows that when using two-dimensional clustering, three bead types (PS, Bare metal Janus Particle, and Oxide covered Janus Particle) with nearly the exact same diameter can be easily distinguished from each other, despite the fact that the diameters only differ by less than 10 nm.

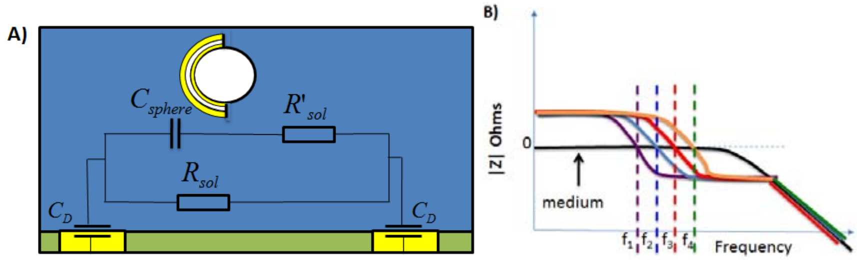

Figure 1: A) Equivalent circuit model for impedance sensor with electronically barcoded microparticle. B) The cross over frequency at which particle impedance is equal to medium impedance.

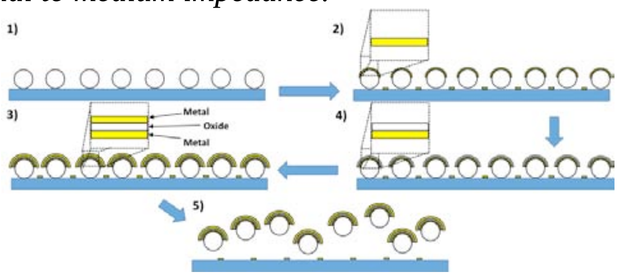

Figure 2: Process for fabricating electronically barcoded particles. 1) Dip coat a single layer of polystyrene beads on Silicon Dioxide. 2) Evaporate gold on top-half of particles. 3) Use ALD to coat thin oxide layer on top of metal. 4) Evaporate thin film of gold on resulting in a parallel plate capacitor. 5) Ultrasonicate to re-suspend the particles in solution.

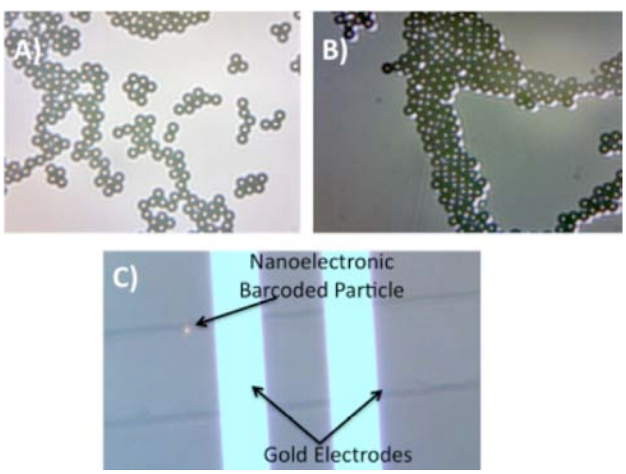

Figure 3: A) Bare Polystyrene particles. B) Al2O3/Gold coated particles on substrate before ultrasonication. C) Nanoelectronic barcoded particle flowing through microfabricated impedance cytometer.

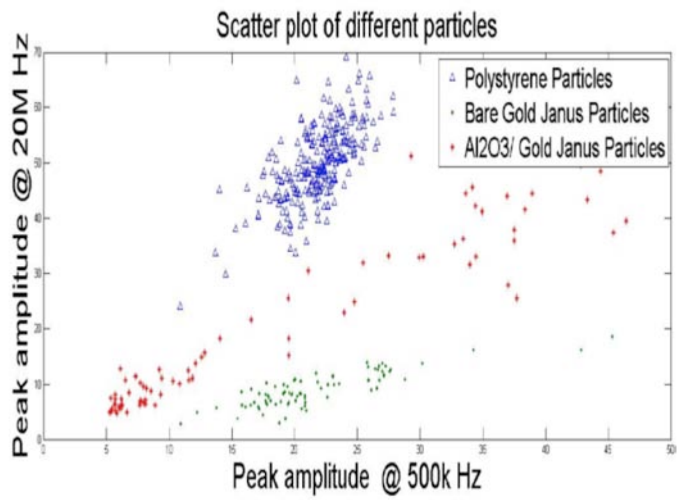

Figure 4: Plotting normalized peak size @500k Hz vs. normalized peak size @20M Hz for three different types particles.