Determining mass of individual micron-sized particles using PicoBalance and FluidFM® probes

Micron-sized particles are commercially available in a wide range of materials such as polymers, (magnetic) metals, glass and ceramics. They have applications in biology, medicine, material science and various fields of engineering. These particles are used for targeted delivery or timed release of drugs, changing the viscosity of slurries in the casting-industry, as filler materials, as contrast agents in e-displays or to produce dentures, to name a few. The physical properties of the particles, in particular their size distribution and density, are key to control specific functionalities including magnetic properties, packing density, or flow dynamics. Careful characterization of the surface area, composition, and size or mass of these beads is a critical factor to their function.

In this article, we present unprecedented mass/size measurements of micrometer sized particles using the synergetic combination of two state-of-the-art technologies: PicoBalance and FluidFM®. Specifically, we used hollow cantilevers that are commercially available (FluidFM probes) to reliably aspirate, hold, and subsequently release individual particles. To measure the mass of the particles, we employed PicoBalance, a technology that measures the mass of beads by measuring the frequency shift of a resonating cantilever.

PicoBalance

PicoBalance is a cantilever-based method that can be used to determine the mass of a sample that is attached to the free end of the cantilever (see Fig. 1). Typically, the particle is attached to a tipless cantilever and the shift in resonance frequency before and after attachment is determined to measure the mass[1-3]. To calculate the mass, three parameters are required: (1) the shift in resonance frequency (see Fig. 2), (2) the cantilever's spring constant, and (3) the position of the attached mass on the cantilever.

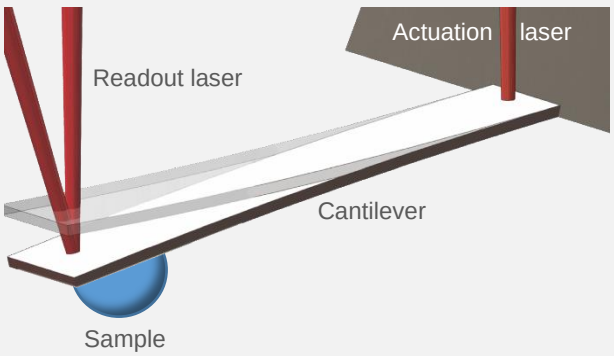

Figure 1. PicoBalance schematic. The mass of a sample is measured by determining the mass-induced shift in resonance frequency of an oscillating cantilever. Actuation and readout are done via near-infrared lasers.

For accurate mass measurements, a clean and stable actuation of the cantilever is required. With acoustic (piezo) actuation, clean and stable actuation is challenging especially in liquids, where a phenomenon called the "forest of peaks"[4,5] obscures the cantilever resonance. To avoid this artifact, PicoBalance uses photothermal actuation (CleanDrive) of the cantilever, the resulting textbook like amplitude and phase response, allows accurate tracking of the resonance frequency.

The spring constant can be measured in various ways before the experiment if it is not already pre-calibrated. Generally, the best results are obtained using the Sader

method[6]. This method uses the planar dimensions of the cantilever. Its damping and resonance frequency are measured in air, either by a thermal spectrum or by actuating the cantilever.

As the mass sensitivity varies with position, the position of the attached mass has to be accounted for. It can be determined optically, however, when FluidFM probes are used, it is well defined.

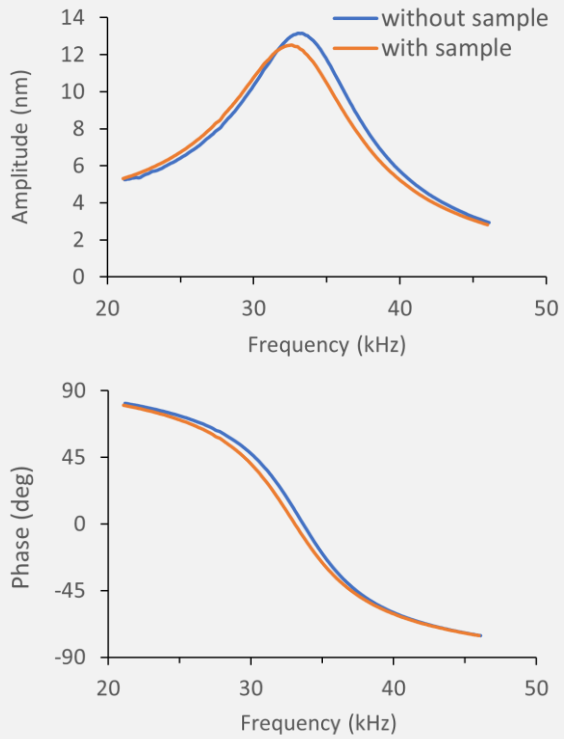

Figure 2, Attachment of a bead to the cantilever leads to a resonance frequency shift that allows the mass determination of the bead.

FluidFM®

The basis of the FluidFM technology is a hollow cantilever with an aperture at the free end (Fig. 3). Using a reservoir that is controlled by a precision pump, the hollow cantilever functions like a micropipette[7]. Particle attachment is quick and reversible. In practice, the cantilever is brought in the vicinity (~10 µm) of the particle that is to be attached and a slight underpressure

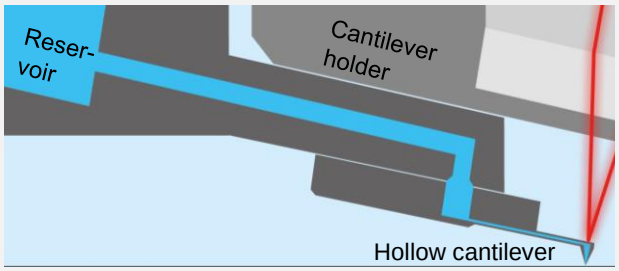

Figure 3. Schematic of FluidFM. A hollow FluidFM cantilever is connected to a pressurized fluid reservoir.

(- 50 mbar) is applied to attach the particle by suction onto the cantilever. After the mass of the particle has been measured, an overpressure can release the particle. The position of the attached particle is known and repeatable, and corresponds to the position of the aperture. In the case shown (Fig. 4), the aperture is 8 µm in diameter and 4.4 µm from the free end. Without FluidFM, attaching particles relies on glue or chemical functionalization. These techniques can give rise to uncertainties in the particle mass and the attachment process is irreversible such that a new cantilever is required for each measurement. However, for some biological samples, a chemical functionalization might be more appropriate.

In air or vacuum environments, small beads are challenging to manipulate and aggregate due to strong electrostatic interactions. Working in liquids at proper pH (i.e. in their storage buffer solution) aggregation can be inhibited, and FluidFM technology easily allows selection of individual particles The smallest detectable shift in the resonance frequency of the FluidFM probe was found to be 15 Hz, which equates to a mass resolution of 0.12 ng

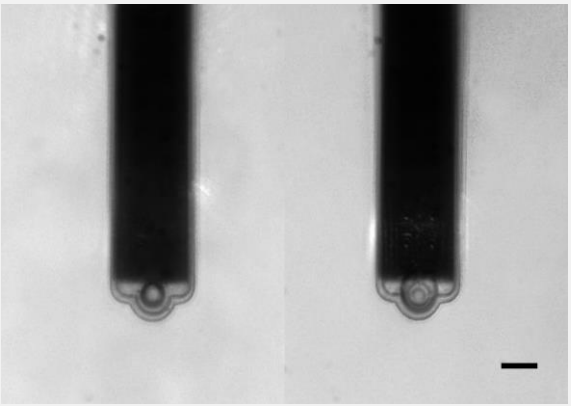

Figure 4. Left, 10 µm bead attached to FluidFM probe. Right, 15 µm bead attached to FluidFM probe. Scale bar is 15 µm.

Mass distribution of silicon dioxide and polystyrene beads

As a model system, silicon dioxide (SiO_2) beads with nominal diameters of 10, 11, 13, 14, and 15 µm and polystyrene beads (PS) with diameters of 10 and 15 µm were measured using PicoBalance with FluidFM probes. 25 different specimens of each type of bead have been measured sequentially.

The results of all 175 measurements are shown in Figure 5. The expected mass (x-axis) and uncertainty was deduced by the manufacturers specifications for the density and nominal diameter[9,10]. The masses found with the PicoBalance-FluidFM combination (y-axis) exhibited an uncertainty of only 0.1 ng. To improve this value further, smaller cantilevers can be used. The strong correlation between the expected and measured mass indicates that the frequency shift directly gives the total mass of the beads and does not measure the buoyant mass (mass of the bead minus the mass of the displaced liquid).

The observed mass corresponds with the expected mass based on the diameter of the bead and given density by the manufacturer. In fact, the mass uncertainty provided by the manufacturer

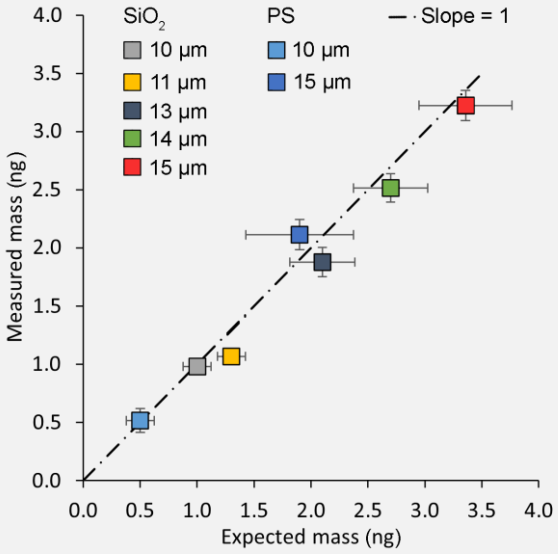

Figure 5. Results of 175 mass measurements on different beads. The uncertainty as represented by the error bars is lower than expected from the manufacturer specifications. A straight line of slope 1 indicates the expected behaviour for an accurate, linear measurement. n=25 per datapoint.

specifications is higher than the uncertainty in the PicoBalance measurements, suggesting that the cantilever-based mass sensing technique is more accurate.

Summary

The combination of FluidFM and PicoBalance technologies enables precise mass measurements of colloidal beads in solution and provides a userfriendly platform for aspirating and dispensing particles. PicoBalance, enabled by photothermal excitation (CleanDrive), is an accurate technique to measure the total bead mass. Using the FluidFM technology, the measurement process is quick and highly repeatable.

The PicoBalance is the only commercially available solution to measure the total mass of samples in the range of picograms to nanograms. Other, non-commercial mass

measurement techniques that are cantilever-based have one of two drawbacks: measuring just the buoyant mass (total mass minus the mass of the sample displaced liquid) or poorer mass and time resolution. They also lack simultaneously acquired, supportive optical information.

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