ABSTRACT
The introduction of micromechanical resonators with embedded microfluidic channels has enabled mass characterization of nanoparticles in solution with resolution exceeding the femtogram (10^{-15} g) level. By using a correlation analysis of the time-domain mass signal, we were able to recover information on particle size during mass acquisition. The temporal correlation of the mass signal directly depends on the distribution of residence times in the resonator, characteristic of particle size. The validity of the method is corroborated by measurements on known samples of nanoparticles of different materials, ranging from 15 nm to 500 nm.

KEYWORDS: suspended microchannel resonators, residence time distribution, dispersion, particle sizing

INTRODUCTION
Suspended Microchannel Resonators (SMRs) are a class of devices able to characterize the mass of single particles in solution with resolution exceeding the femtogram (10^{-15} g) level [1]. Recently, we have shown that resolution enhancement of over 5 orders of magnitudes can be achieved by use of a correlation analysis of the mass signal [2]. However, regardless of the analysis method employed, these devices have been limited to the characterization of mass and density of particles in solution. Here, we present a refined method of detection able to return particle size information during mass characterization with the SMRs. We call this method Mass Correlation Spectroscopy.

THEORY
SMRs are resonator devices with a microfluidic channel embedded in the vibrating structure. Particles flowing through the resonator affect the effective mass of the device and induce transient variations to its resonance frequency. The buoyant mass of the particles controls the amplitude of the induced frequency shifts, while particle velocity influences the time extension of the effect. Due to the non-uniform velocity profile in the channel, particles move at different velocities according to their position in the cross-section, hence inducing frequency signatures with different durations. However, the residence time distribution (RTD) of the particles in the embedded channel is not fixed, since radial diffusion induces velocity variations and the finite size of the particles prevents them from approaching the channel walls [3].

Figure 1 shows different behaviors of the particles while transiting through the channel: particles of small dimensions quickly diffuse through the whole cross-section and present small axial dispersion and a compact RTD; as the size of the particles increases, radial diffusion reduces and the RTD widens, due to the spread in velocity between the fast and slow moving objects; finally, particles of size comparable to the channel dimensions present a very compact RTD and a high average velocity, as they cannot approach the channel walls, therefore being excluded from the slowest regions of the velocity profile. These effects manifest in the autocorrelation analysis of the time-domain mass signal (Figure 2). Particles of intermediate size are characterized by a long-tailed autocorrelation curve caused by the slow moving objects and the wide RTD. On the contrary, small and large particles present similar autocorrelation shapes, as they are both characterized by compact RTDs in the embedded channel. However, the correlation curves reach zero amplitude at different times, as a consequence of the dissimilar average velocities of the samples.
EXPERIMENTAL

Monodisperse samples of nanoparticles of different sizes and materials suspended in aqueous solutions were characterized with the Mass Correlation Spectroscopy method. For the characterization, we used a torsional SMR device with frequency/mass responsivity of -20 mHz/kg and 3 × 8 µm² cross-section dimensions. 15 nm gold nanoparticles (Nanopartz Inc., P/N A11-15), 30 nm gold nanoparticles (Nanopartz Inc., P/N A11-30) and 490 nm polystyrene particles (Polysciences Inc., P/N 18720) were suspended in milli-Q water at concentrations of, respectively, 1.6 × 10¹² mL⁻¹, 1 × 10¹¹ mL⁻¹ and 4 × 10⁸ mL⁻¹; polystyrene nanoparticles of 85 nm (Polysciences Inc., P/N 16688) and 210 nm (Invitrogen, P/N F8809) diameters were suspended in a solution of 100 mM NaCl, 350 µM SDS and 0.01% w/v NaN₃ at concentrations of 7.7 × 10¹² mL⁻¹ and 1.2 × 10¹¹ mL⁻¹. A small concentration of 1.54 µm polystyrene particles (Polysciences Inc., P/N 64040) of known mass and diameter was added to each sample for calibration of the frequency/mass response of the device and for monitoring the flow velocity during the measurements.

Each sample was measured using different flow velocities and the acquisitions lasted between 30 s and 3 min, according to the stability of the flow. Pressurized inlets and outlets of the chip were used for controlling the flow rates during the measurements.

Resonance frequency values were acquired with a sampling frequency of 1 kHz and 2 kHz, with an acquisition noise of, respectively, 200 mHz and 400 mHz.

RESULTS AND DISCUSSION

Each sample of particles was measured using different flow velocities, ranging from ~0.6 mm/s to ~6 mm/s, to detect the variation of the correlation curve under different diffusion/dispersion regimes of the particles (Figure 3). The use of different flow velocities increases the resolution on the size identification: particles of different sizes might present similar autocorrelation curves for specific flow velocities; however, this ambiguity can be overcome by varying the time allowed for the particles to diffuse in the cross-section. The experimental results for the five different populations of nanoparticles under examination are shown in Figure 4, compared to the manufacturer reported values. The size estimates obtained with our method present an accuracy of about 25 nm with respect to the expected sizes, over the entire range of analysis. Estimates on the buoyant mass of the particles are also shown in Figure 4. Importantly, mass characterization is independent to size detection, and therefore it is not influenced by the accuracy of the size measurement. The uncertainty intervals shown in Figure 4 represents the statistical and measurement error on the estimation of the curve parameters, and do not correspond to the actual distribution of the particles in the sample.
The maximum uncertainty on the size estimation is obtained for the 85 nm polystyrene particles. Under usual working conditions, particles ranging from ~50 nm to ~150 nm do not diffuse considerably in the cross-section of the embedded channel and the average velocities of the sample and of the fluid are practically equal. As a consequence, particles in this range cannot be characterized with precision using devices with similar cross-section dimensions and flow rates.

The average buoyant masses estimated from the amplitude of the correlation curves [2] are shown in Figure 4. As a comparison, single-particle measurements with this SMR presented a detection limit of ~30 fg in a 1 kHz bandwidth, a value more than three orders of magnitude larger than the buoyant mass of the 85 nm polystyrene particles, here detected using our correlation analysis.

CONCLUSION

We have presented here a novel method of characterization with SMR devices, which enables the measurement of the mass and size of free particles in solution in a single experiment. Size characterization is obtained by detecting differences in distribution of residence times of the particles in the microfluidic channel embedded in the resonator structure. The experimental results show that, in combination with the resolution enhancement obtained by correlation analysis, SMR devices can provide mass and size characterization of free nanoparticles in solution, in a single experiment.

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