In-line picogram-resolution microchannel resonator for protein adsorption measurement operating at atmospheric pressure

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Novelty. This paper reports on an in-line microchannel resonator for protein adsorption measurement with a resolution of 19 pg. The sensor eliminates the need for complex measurement sequences, vacuum environment or delicate external (optical) components.

Background. Measurement of mass can be done down to the scale of zeptogram samples using nanomechanical resonators [1]. However, these methods suffer from complex measurement sequences of immersion and drying of bio-molecules, measuring in vacuum and high sensitivity to environmental influences during handling. In [2], a solution to some of these problems was found by integrating a microchannel in a cantilever resonator. However, this solution still requires vacuum packaging and external optical read-out. Here, we present a microchannel resonator for sensitive mass measurement without the need of vacuum conditions or external apparatus. Due to the relatively large channel diameter of approximately 40 µm, the sensor can be used for detection of bio-molecules in continuous flow with relatively high throughput.

Design and fabrication. The sensor is made using microchannel technology described in [3]. The resonating structure consists of a freely suspended rectangular tube with semi-circular cross-section (see figure 1). The diameter of the channel is approximately 35 µm to allow for high throughput at low pressure drop. Due to the thin channel wall of 1.5 µm, the resonance frequency is highly sensitive to the presence of molecules whose mass density differs from that of the solution. This way, bio-molecular mass sensing by means of surface adsorption can be measured by a frequency shift. The sensor is operated as two-port resonator with Lorentz force actuation using permanent magnets (see figure 2) and measurement of the induction voltage across a second metal track on the tube (see figure 3). The phase shift between actuation signal and induced voltage is exactly zero degrees at resonance, so that including the resonator in the feedback loop of an amplifier is sufficient to realize an oscillator.

Experimental results. To measure the sensitivity to mass, solutions of Albumin (5 mg/5 ml) and Avidin (2.5 mg/50 ml) in phosphate buffered saline (PBS) are flushed through the sensor while the resonance frequency is monitored. The pressure containers with the solutions are connected to the sensor by a three-way valve. Prior to the measurement, the channel has been rinsed using Helmanex. Figure 4 shows the measurement results of several cycles of applied Albumin and Avidin flows. Due to a difference in density between the two solutions, the resonance frequency changes each time the solution is switched. After compensation for the change in density, it can be seen that the frequency change is approximately 0.25 Hz per cycle. Assuming monolayer coverage (1 pmol/cm2), the sensitivity of the sensor can be calculated to be 4.5 ng/Hz with a resolution of 19 pg.

References
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[2] T.P. Burg, et al. 2007. Nature 446:7139: 1066-1069
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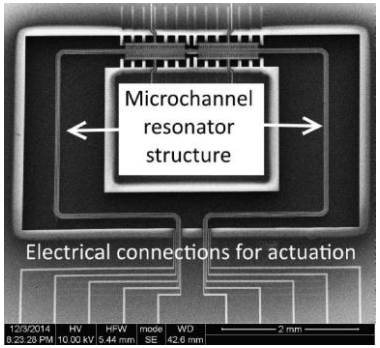

Figure 1. SEM image of the microchannel resonator. The electrical tracks for actuation and detection are visible at the bottom. The fluid inlets are at the backside of the chip and not visible in the image. Integrated comb-structures can be used for capacitive detection of the tube movement.

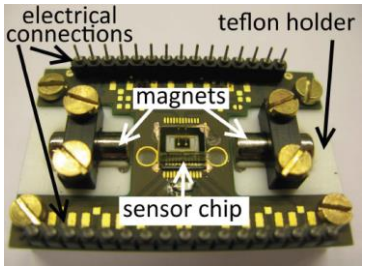

Figure 2. The sensor chip is mounted on a Teflon holder with fluidic connections and a printed circuit board (pcb) for the electronic connections. The fluid connections are made using o-rings through holes in the pcb. Permanent magnets are mounted at either side of the chip.

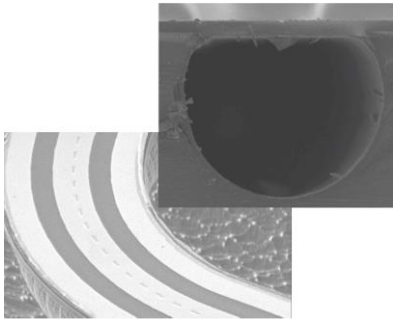

Figure 3. SEM images. Top: cross-section of the channel with a diameter of 35 µm and wall thickness of 1.5 µm. Bottom: top view showing the metal tracks for actuation and detection on one of the corners of the channel.

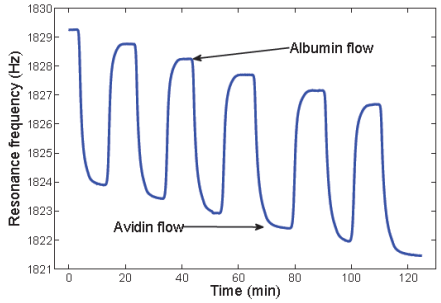

Figure 4. Measured change in resonance frequency when an alternating flow of Albumin in PBS and Avidin in PBS is applied. The large steps when the fluid is switched is caused by the difference in density of the fluids. Per monolayer of either albumin or Avidin, the frequency decreases approximately 0.25 Hz.