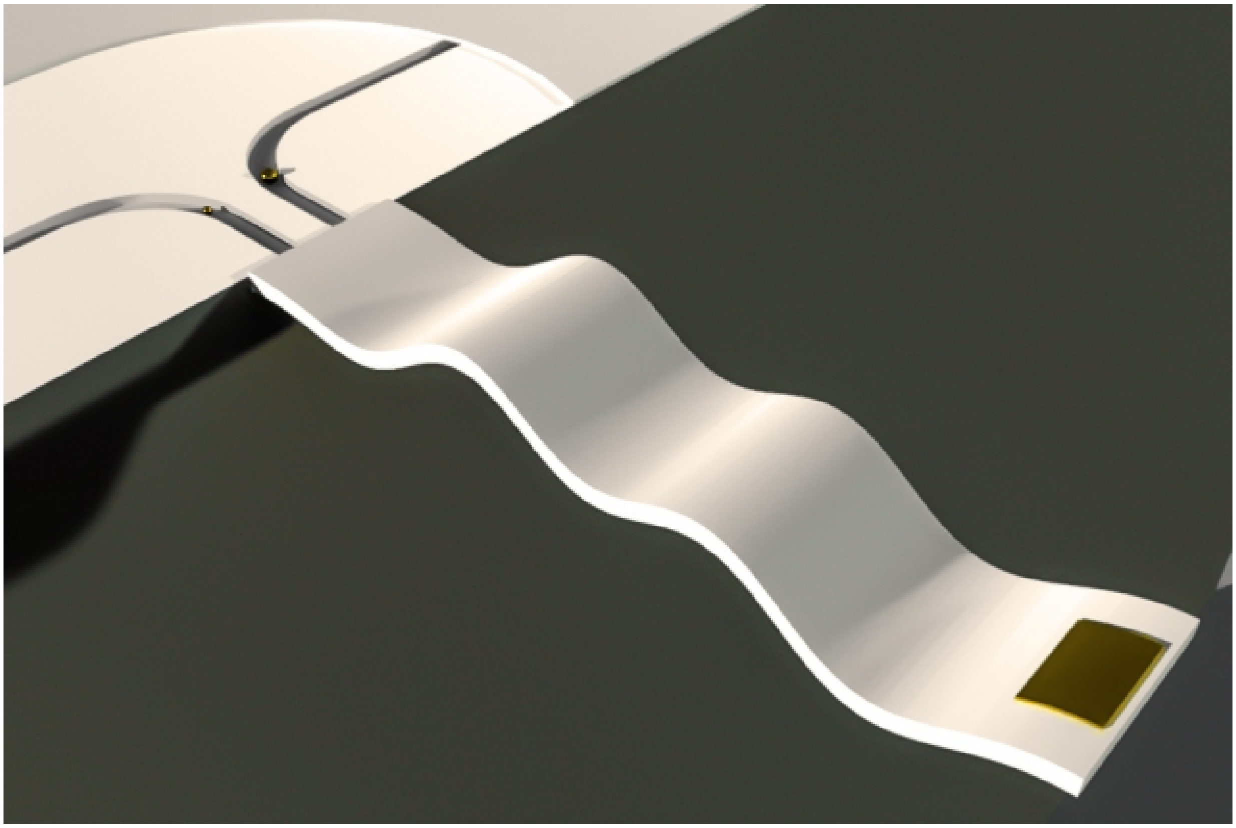
Device measures the distribution of tiny particles as they flow through a microfluidic channel

May 12 2015, by Anne Trafton



A suspended microchannel resonator (SMR) measures particles' masses as they flow through a narrow channel. The original mass sensor consists of a fluid-filled microchannel etched in a tiny silicon cantilever that vibrates inside a vacuum cavity. As cells or particles flow through the channel, one at a time, their mass slightly alters the cantilever's vibration frequency. This illustration depicts a snapshot of a cantilever vibrating at its first four resonant modes. Credit: Selim

Olcum

A new technique invented at MIT can measure the relative positions of tiny particles as they flow through a fluidic channel, potentially offering an easy way to monitor the assembly of nanoparticles, or to study how mass is distributed within a cell.

With further advancements, this technology has the potential to resolve the shape of objects in flow as small as viruses, the researchers say.

The new technique, described in the May 12 issue of *Nature Communications*, uses a device first developed by MIT's Scott Manalis and colleagues in 2007. That device, known as a suspended microchannel resonator (SMR), measures particles' masses as they flow through a narrow channel.

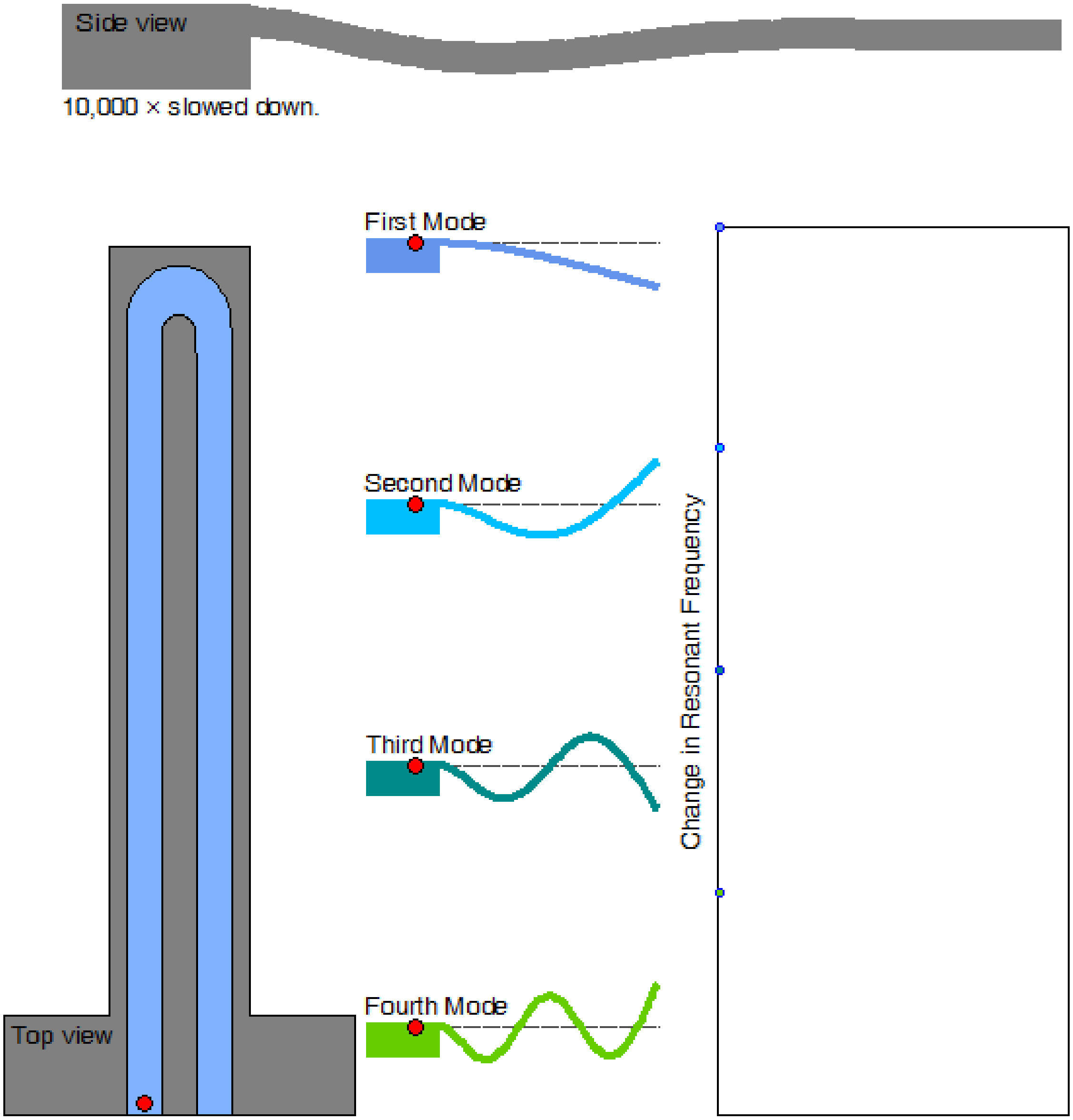
The original mass sensor consists of a fluid-filled microchannel etched in a tiny silicon cantilever that vibrates inside a vacuum cavity. As cells or particles flow through the channel, one at a time, their mass slightly alters the cantilever's vibration frequency. The masses of the particles can be calculated from that change in frequency.

In this study, the researchers wanted to see if they could gain more information about a collection of particles, such as their individual sizes and relative positions.

"With the previous system, when a single particle flows through we can measure its buoyant mass, but we don't get any information about whether it's a very small, dense particle, or maybe a large, not-so-dense particle. It could be a long filament, or spherical," says grad student Nathan Cermak, one of the paper's lead authors.

Postdoc Selim Olcum is also a lead author of the paper; Manalis, the Andrew and Erna Viterbi Professor in MIT's departments of Biological Engineering and Mechanical Engineering, and a member of MIT's Koch Institute for Integrative Cancer Research, is the paper's senior author.

Many frequencies



This animated image demonstrates multiple vibration modes. The top panel depicts a cantilever simultaneously oscillating in its first four vibrational modes. The bottom left panel shows a particle flowing through the microfluidic channel integrated into the cantilever. Next to that is an animation of the four vibrational mode shapes. The bottom right panel demonstrates the deviations of the resonant frequencies of these modes. Credit: Selim Olcum

To obtain information about the mass distribution, the researchers took advantage of the fact that each cantilever, much like a violin string, has many resonant frequencies at which it can vibrate. These frequencies are known as modes.

The MIT team came up with a way to vibrate the cantilever in many different modes simultaneously, and to measure how each particle affects the vibration frequency of each mode at each point along the resonator. The cumulative sum of these effects allows the researchers to determine not only the mass, but also the position of each particle.

"All these different modes react differently to the distribution of mass, so we can extract the changes in mode frequencies and use it to calculate where the mass is concentrated within the channel," Olcum says.

The particles flow along the entire cantilever in about 100 milliseconds, so a key advance that allowed the researchers to take rapid measurements at each point along the channel was the incorporation of a control system known as a phase-locked loop (PLL). This has an internal oscillator that adjusts its own frequency to correspond to the frequency of a resonator mode, which changes as particles flow through.

Each vibration mode has its own PLL, which responds to any changes in the frequency. This allows the researchers to rapidly measure any changes caused by particles flowing through the channel.

In this paper, the researchers tracked two particles as they flowed through a channel together, and showed they could distinguish the masses and positions of each particle as it flowed. Using four vibrational modes, the device can attain a resolution of about 150 nanometers. The researchers also calculated that if they could incorporate eight modes, they could improve the resolution to about 4 nanometers.

High-resolution mass imaging

This advance could help spur the development of a technique known as inertial imaging, which makes use of several vibration modes to image an object as it sits on a nanomechanical resonator.

Inertial imaging could allow scientists to visualize very small particles, such as viruses or single molecules. "Multimode mass sensing has previously been limited to air or vacuum environments, where objects must be attached to the resonator. The ability to achieve this dynamically in flow opens up exciting possibilities," Manalis says.

The new MIT technology could enable very high-speed inertial imaging as cells flow through a channel.

"The suspended nanochannel technology pioneered by the Manalis group is remarkable," says Michael Roukes, a professor of physics, applied physics, and bioengineering at Caltech, who is pioneering the development of inertial imaging but was not part of this study.

"Their application of our approach for simultaneous monitoring position and mass of the fluidic analytes opens up many new possibilities," Roukes says. "Extension of their efforts to fully employ our recently developed method of inertial imaging will also permit characterizing the shape of analytes, in addition to their mass and position, as they flow through the nanochannels."

Manalis' lab is also using the new technique to study how cells' densities change as they pass through constrictions. This could help them to better understand how cancer cells behave mechanically as they metastasize, which requires squeezing through small spaces. They are also using the PLL approach to increase throughput by operating many cantilevers on a single chip.

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