Weighing particles at the attogram scale

New device from MIT can measure masses as small as one millionth of a trillionth of a gram, in solution.

Anne Trafton, MIT News Office
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Press Inquiries

MIT engineers have devised a way to measure the mass of particles with a resolution better than an attogram — one millionth of a trillionth of a gram. Weighing these tiny particles, including both synthetic nanoparticles and biological components of cells, could help researchers better understand their composition and function.

The system builds on a technology previously developed by Scott Manalis, an MIT professor of biological and mechanical engineering, to weigh larger particles, such as cells. This system, known as a suspended microchannel resonator (SMR), measures the particles ' mass as they flow through a narrow channel.

By shrinking the size of the entire system, the researchers were able to boost its resolution to 0.85 attograms —more than a 30-fold improvement over the previous generation of the device.

" Now we can weigh small viruses, extracellular vesicles, and most of the

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engineered nanoparticles that are being used for nanomedicine, ” says Selim Olcum, a postdoc in Manalis ’ lab and one of the lead authors of a paper describing the system in this week ’ s issue of the *Proceedings of the National Academy of Sciences*.

Graduate student Nathan Cermak is also a lead author of the paper, and Manalis, a member of MIT ’ s Koch Institute for Integrative Cancer Research, is the paper ’ s senior author. Researchers from the labs of MIT professors and Koch Institute members Angela Belcher and Sangeeta Bhatia also contributed to the study.

A small sensor for small particles

Manalis first developed the SMR system in 2007 to measure the mass of living cells, as well as particles as small as a femtogram (one quadrillionth of a gram, or 1,000 attograms). Since then, his lab has used the device to track cell growth over time, measure cell density, and measure other physical properties, such as stiffness.

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 mass of the particle can be calculated from that change in frequency.

To make the device sensitive to smaller masses, the researchers had to shrink the size of the cantilever, which behaves much like a diving board, Olcum says. When a diver bounces at the end of a diving board, it vibrates with a very large amplitude and low frequency. When the diver plunges into the water, the board begins to vibrate much faster because the total mass of the board has dropped considerably.

To measure smaller masses, a smaller “ diving board ” is required. “ If you ’ re measuring nanoparticles with a large cantilever, it ’ s like having a huge diving board with a tiny fly on it. When the fly jumps off, you don ’ t notice any difference. That ’ s why we had to make very tiny diving boards, ” Olcum says.

In a previous study, researchers in Manalis ’ lab built a 50-micron cantilever — about one-tenth the size of the cantilever used for measuring cells. That system, known as a suspended nanochannel resonator (SNR), was able to weigh particles as light as 77 attograms at a rate of a particle or two per second.

The cantilever in the new version of the SNR device is 22.5 microns long, and the channel that runs across it is 1 micron wide and 400 nanometers deep.

This miniaturization makes the system more sensitive because it increases the cantilever ' s vibration frequency. At higher frequencies, the cantilever is more responsive to smaller changes in mass.

The researchers got another boost in resolution by switching the source for the cantilever ' s vibration from an electrostatic to a piezoelectric excitation, which produces a larger amplitude and, in turn, decreases the impact of spurious vibrations that interfere with the signal they are trying to measure.

With this system, the researchers can measure nearly 30,000 particles in a little more than 90 minutes. " In the span of a second, we ' ve got four or five particles going through, and we could potentially increase the concentration and have particles going through faster, " Cermak says.

Particle analysis

To demonstrate the device ' s usefulness in analyzing engineered nanoparticles, the MIT team weighed nanoparticles made of DNA bound to tiny gold spheres, which allowed them to determine how many gold spheres were bound to each DNA-origami scaffold. That information can be used to assess yield, which is important for developing precise nanostructures, such as scaffolds for nanodevices.

The researchers also tested the SNR system on biological nanoparticles called exosomes — vesicles that carry proteins, RNA, or other molecules secreted by cells — which are believed to play a role in signaling between distant locations in the body.

They found that exosomes secreted by liver cells and fibroblasts (cells that make up connective tissue) had different profiles of mass distribution, suggesting that it may be possible to distinguish vesicles that originate from different cells and may have different biological functions.

The researchers are now investigating using the SNR device to detect exosomes in the blood of patients with glioblastoma (GBM), a type of brain cancer. This type of tumor secretes large quantities of exosomes, and tracking changes in their concentration could help doctors monitor patients as they are treated.

Glioblastoma exosomes can now be detected by mixing blood samples with magnetic nanoparticles coated with antibodies that bind to markers found on vesicle surfaces, but the SNR could provide a simpler test.

" We ' re particularly excited about using the high precision of the SNR to quantify microvesicles in the blood of GBM patients. Although affinity-based approaches do exist for isolating subsets of microvesicles, the SNR could potentially provide a label-free means of enumerating microvesicles that is

independent of their surface expression, ” Manalis says.

The research was funded by the U.S. Army Research Office through the Institute for Collaborative Biotechnologies, the Center for Integration of Medicine and Innovative Technology, the National Science Foundation, and the National Cancer Institute.

Topics: Nanoparticles | Biological engineering | Mechanical engineering

Comments

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Hope fruits of science and technology are shared with entire humanity.