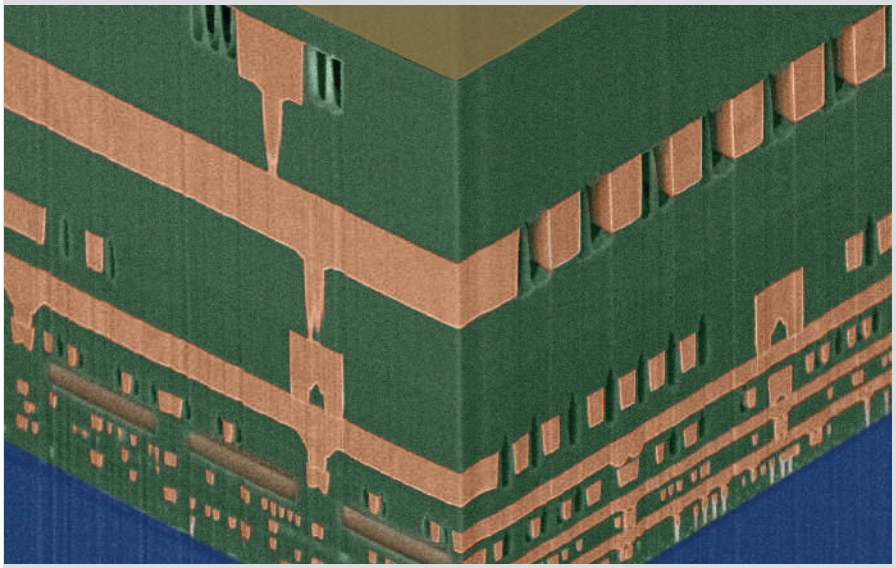
SEMICONDUCTORS

Chip maker turns to self-assembly



IBM

IBM has introduced a self-assembly process into chip manufacture — a first for the semiconductor industry. The company reports that the new chips consume 15% less energy than conventional devices. Electrical signals can also travel 35% faster in the new chips.

Dan Edelstein and co-workers exploit self-assembly to create air gaps — which are actually regions of vacuum — that act as insulators between the copper wires on the chip. A typical chip contains miles of wires, and as chips have become smaller, the wires inside them have become closer, making insulation more difficult. At first, semiconductor companies tried to solve this problem by introducing new materials with better insulating properties, but these materials tended to be fragile.

The IBM team has now developed a completely new solution that involves pouring a polymer onto a silicon wafer that has already been patterned with copper wires and a carbon silicate glass insulator, and then baking it to form a layer that contains trillions of holes, all measuring about 20 nanometres across. This array of holes then acts as a mask for a standard plasma etching process that drills vertical nanocolumns in the insulator. Subsequent steps dissolve the partitions between the nanocolumns to form continuous air gaps between the wires. Finally, the air is pumped out and another insulating layer is deposited to seal the vacuum gaps between the wires (www-03.ibm.com/press/us/en/presskit/21463.wss).

The gaps can be seen beside the copper-coloured wires in the image, which measures about 15 micrometres across. The insulating layers are shown in green. The new process, which has been patented, has already been integrated into a manufacturing line at IBM's East Fishkill site in New York state, and is expected to be included in all the company's production lines by 2009.

Peter Rodgers

NANOMECHANICAL SYSTEMS

Inside track weighs in with solution

The performance of biosensors that rely on tiny vibrating cantilevers suffers when they are operated in a liquid. The solution is to place the liquid inside the cantilever.

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Laboratories around the world are competing to measure the smallest possible masses with sensors based on tiny cantilevers that are fixed at one end and vibrate at the other. The concept is simple: when an object lands on the cantilever, its resonant frequency decreases by an amount that is proportional to the mass of the object. The sensitivity of the device is inversely proportional to the active mass of the cantilever, and as advances in fabrication techniques have allowed sensors to become smaller, the masses measured have evolved from picograms to zeptograms[1–3]. Improvements in transduction techniques — which convert the vibration of the cantilever into a signal that can be measured — have also been central to this progress.

One of the driving forces in this field is the demand for biological sensors that are faster, more sensitive and capable of higher throughputs than current techniques[4]. Cantilever-based sensors offer many advantages: they can detect samples directly, whereas most existing techniques involve labelling the sample with fluorescent dyes, which is time-consuming and prone to false positives. Moreover, they can be reduced in size quite easily, which decreases the sample volumes. Finally, the ability to make devices with multiple cantilevers allows complex biochemical analysis. There is, however, one main disadvantage: biology tends to happen in aqueous solutions, whereas cantilever-based sensors perform best in a vacuum.

The key parameter is the quality or Q factor, which is significant in two ways: first

it is inversely proportional to the mechanical power dissipated by the vibrating cantilever; second, it is also inversely proportional to the width of the resonant peak. In a vacuum, the energy dissipated by a resonant cantilever is very small, arising from internal material losses, so the vibration response is sharply peaked at the resonant frequency. However the immersion of a cantilever in liquid degrades the Q factor by several orders of magnitude (up to five) owing to viscous damping, which severely reduces the sensitivity for detecting frequency changes (Fig. 1a,b). So far, various approaches have been explored to enhance the Q factor— such as measuring higher-frequency vibration modes[5], designing new resonant structures[6], and using feedback loops to change the Q factor[7] — but none of these has been able to approach the levels of performance obtained in a vacuum.

Writing in *Nature*, Scott Manalis, Thomas Burg and co-workers at the Massachusetts Institute of Technology and two companies — Innovative Micro Technology and Affinity Biosensors — demonstrate an approach that avoids viscous damping of the cantilever[8,9] by fabricating cantilevers with built-in microfluidic channels that can confine the liquid. By placing the liquid inside the cantilever, the device can then be operated in a vacuum and achieve a Q factor of about 150,000, which is at least three orders of magnitude higher than is possible with conventional cantilevers immersed in water[10] (Fig. 1c,d).

Using this approach and coating the walls of the microchannels to strongly attach a particular antibody, Manalis and co-workers were able to measure the kinetics of an antibody–antigen reaction at an antigen concentration of about 100 ng ml^{-1}. This level of sensitivity is comparable to that offered by the best quartz crystal microbalance, which is currently the instrument of choice for such measurements. Moreover, there is room for major improvement by further miniaturization of the device. A very attractive feature of the new approach is that the microchannel has a volume of just 10 picolitres or so, which ensures minimal sample consumption. This is critical for many biomedical applications in which the sample is precious or the reagents are costly.

A unique aspect of this device is the ability to track individual nanoparticles. When a single particle is injected into the microchannel, the resonant frequency decreases by an amount that depends on the position of the particle along the cantilever, as well as the usual dependence on the extra mass, and the maximum change occurs when the particle is near the free end of the cantilever. Manalis and co-workers are able to exploit this to weigh single live bacteria, and also to distinguish between two bacteria, *Escherichia coli* and *Bacilus subtilis*, which have different masses. These experiments bring us closer to the goal of counting and categorizing biological molecules contained in a sample by their individual mass, and perhaps their transit time (which should be related to their size). However, weighing biomolecules such as proteins and DNA will require nanoscale rather than microscale channels.

As the authors point out, their device might also be able to count CD4 cells for AIDS monitoring. Today this task is done with flow cytometers that are bulky and too expensive for developing countries. By borrowing fabrication technology from the semiconductor industry, combined with optical transduction methods, it may be possible to mass-produce inexpensive cantilever-based sensors that can count CD4 cells. Moreover, these devices should be small enough to be suitable for point-of-care applications in remote regions.

These results, together with previous results from a number of laboratories, highlight that nanomechanical sensing is a promising technique for medical diagnosis, biological research, functional genomics and pharmacological research. However, there is still a long way to go because, in common with other nanosensors, reproducibility is still problematic. The efficient biofunctionalization of devices, a full understanding of the sensor response mechanisms (including the effects of undesired external stimuli) and the convergence between nanofluidics and nanomechanics are just some of the areas in which further research is needed. However, if these challenges can be overcome, nanomechanical sensors could have a major impact on many areas of science.

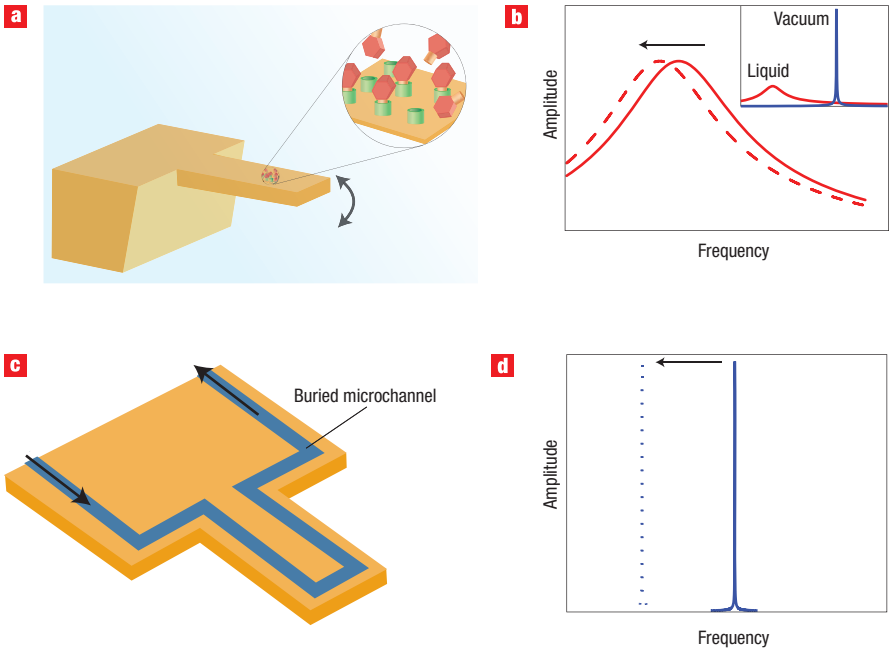

Figure 1 Mass sensing in liquids with nanomechanical devices. **a**, Schematic of a conventional microcantilever immersed in liquid. The target molecules we are interested in measuring (shown in red, inset) become attached to molecular receptors (green) on the surface of the cantilever. **b**, The resonant peak of the cantilever can be seen when the amplitude of the vibrations is plotted as a function of frequency. When the cantilever is vibrating in a vacuum (blue line, inset), the resonant peak is very sharp and the Q factor is very high. In a liquid, however, viscous damping makes the peak much broader (solid red line, inset and main figure). When the target molecules become attached to the cantilever and increase its mass, the resonance is shifted to lower frequencies (dashed red line), but this shift is difficult to detect because of the low Q factor. **c**, Schematic of a microcantilever with a built-in microfluidic channel (blue) in vacuum. **d**, The very high Q factor of such cantilevers means that the amount of shift shown in **b** can be easily detected.

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Abstractions

FIRST AUTHOR

Predicting whether a non-native invasive plant species is likely to overtake a given ecosystem can be tricky. But being able to make such predictions would be valuable, because invasive species can have serious ecological and economic consequences. Researchers generally believe that invasive plants thrive best when resource levels — nutrients, water and sunlight — are plentiful. But as an undergraduate visiting Hawaii, Jennifer Funk, now a postdoc at Stanford University in California, found this puzzling. Despite having low-nutrient volcanic soils, the islands are overrun with invasives. She and colleague Peter Vitousek compared the resource-use efficiency of 19 invasives with that of 19 evolutionarily related natives. They report, on page 1079, that invasives are as efficient as or more so than native plants at using limited resources. Funk tells *Nature* about her trek across paradise to study these plants.

Why have there been so few studies of invasives in low-resource environments?

Most invasive species are found in disturbed habitats, which are often characterized by high resource availability. For example, if you harvest some of the trees in a forest, you increase the amount of light available to the remaining trees and plants. Research in disturbed systems suggests that invasive plants are able to exploit high-resource conditions. But it's widely thought that natives in low-resource environments should be able to outcompete invasives, because the natives have traits that allow them to persist there.

How did you decide which species to look at?

I used evolutionarily related pairs of native and invasive plants, comparing an invasive and native plant from either the same genus or the same plant family. Closely related species have more traits in common, which makes it easier to identify the trait or traits making an invasive plant more aggressive.

How did you determine the performance of natives versus invasives?

We looked at resource-use efficiency, which is the amount of carbon that a plant assimilates through photosynthesis per amount of resource used to acquire that carbon.

What further studies might help determine better ways to manage invasives?

It would be interesting to look at how resource-use efficiency operates at different phases of invasion. For example, if a grass invading an arid environment has very high water-use efficiency, you might want to target the removal of that invasive plant before it becomes problematic, because it's likely to outcompete the native vegetation for the most limited resources. ■

MAKING THE PAPER

Scott Manalis

Microfluidics boosts the resolution of tiny mass measurements in liquid.

Finding ways to make very sensitive measurements of biological molecules has long been of interest to Scott Manalis's group at the Massachusetts Institute of Technology in Cambridge. But they didn't want to use fluorescent or radioactive labelling techniques that require multistep sample preparation methods and relatively large sample volumes. "We wanted to develop methods for label-free detection that could be as sensitive as fluorescence," says Manalis. One way of detecting molecules is by their mass. But how do you weigh really tiny things?

Nanoscale mechanical resonators can measure the mass of particles weighing as little as several zeptograms (a zeptogram is 10^{-21} grams). These instruments are designed to vibrate at a given frequency, known as the resonant frequency. When a molecule lands on the resonator's surface, the resonant frequency changes by an amount that correlates to the mass of the molecule. However, these instruments do not work as well when they are placed in a solution, because fluids dampen the mechanical vibrations. This often limits their biological applications, because these frequently require fluid.

In 2002, Manalis and his team came up with an approach to overcome the problem. Why not try putting the fluid in microchannels inside the resonator? Thomas Burg, a graduate student in Manalis's lab at the time, set about making a prototype. Although it worked, it didn't take very sensitive or reliable measurements. This was partly because Manalis and Burg had not been able to make it in such a way that it could be contained within a vacuum, one of the requirements for measuring really small weights. "A well-known challenge in the MEMs [micro-electro-mechanical systems] field is packaging," says Manalis. "In many cases, the details of packaging are known only by the graduate student who developed the process. Once the student graduates, it can be difficult to advance the project beyond the initial demonstration."

To prevent this from happening, Manalis joined forces with the Santa Barbara-based labs of Innovative Micro Technology (IMT), a Californian company with expertise in manufacturing MEMs. "Collaborating with IMT has given us access to state-of-the-art packaging and microfluidic processes that have allowed us to develop highly robust and sensitive mass detectors," says Manalis. Burg, who had by this time almost completed his thesis, decided to continue on the project as a postdoc. After about three years' further development, the group had a vacuum-packaged resonator that could weigh individual nanoparticles, single bacteria and protein monolayers in solution with a resolution of 10^{-15} grams (see page 1066).

In addition to weighing particles that bind to the sides of the channels, the instrument can measure samples as they flow through it. The idea of designing the instrument in this way came about almost by accident. "Once the device had been designed with three-micrometre-tall channels, it occurred to us that we could flow bacteria through them and weigh individual cells one by one," says Manalis. Using this flow-through mode, they could weigh a wide variety of particles, as ways to bind particles to the instrument's surface were not needed.

The instrument works better than Manalis and his co-workers could have ever anticipated, but the proof lies in what it will be able to do. "We know we can weigh nanoparticles and cells. Now we need to focus on useful applications," says Manalis. ■

KEY COLLABORATION

What's the best that can happen when a scientist sits in on a course from another discipline? For Robert MacPherson, a mathematician based at Princeton in New Jersey, and materials scientist David Srolovitz, it led to a collaboration that hit a theoretical jackpot and has broad practical applications.

"Bob attended my graduate course at Princeton because he'd heard there were some great geometry problems in materials science," says Srolovitz, now dean of Yeshiva University in New York. MacPherson's hunch proved correct when Srolovitz spoke about the von Neumann grain growth problem, which predicts how cells grow in two dimensions but can't describe how they grow in three.

Within months they were able to take some abstract concepts from geometric probability theory and measurement theory to evaluate the integral curvature in three dimensions (3D). "After we saw that the idea worked in 3D and reduced to the von Neumann 2D result, we realized the solution could be extended to all dimensions," Srolovitz says (see page 1053).

But perhaps the most valuable result of their collaboration is the identification of a quantity they term the 'mean width', a 1D measurement that they believe will become the standard measurement of length or size for 3D objects. ■