concentrations using nanoapertures (Fig. 1a) have been those in which the action of an immobilized enzyme can be followed directly. This method has been used, for instance, to monitor the activity of the enzyme polymerase[1] and follow DNA sequencing in real time; and for visualizing a ribosome in action[6]. But to place a functional enzyme exactly in the hot spot of the nanoantenna-in-box will be challenging. To solve this problem, an approach that takes advantage of a recently developed DNA-scaffolded, gap-nanoantenna might represent a viable solution[7]. Here, two nanoparticles forming the gap-nanoantenna are attached to a self-assembled DNA nanostructure (so-called DNA origami) that provides handles to place the biomolecule of interest in the hot spot. Matching the size of the DNA/gap-nanoantenna to that of the nanoaperture might enable an antenna-in-box with handles for targeted enzyme placement. Whatever direction the research field might take, it seems as though the development of sophisticated coverslips in which nanophotonic structures such as the antenna-in-box set-up are incorporated may unlock more potential for single-molecule detection than developing more powerful microscopes. ❐

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NANOMECHANICS

Sensing from the bottom up

Ultrasensitive nanomechanical transducers based on carbon nanotubes can be fabricated using a bottom-up assembly method.

Martino Poggio

The measurement of weak forces is typically carried out using cantilevers that are fabricated with top-down lithographic methods. Despite considerable effort over the past decade and the optimization of materials and detection schemes[1–3], the resolution of such devices has not improved beyond several hundred zN Hz$^{-1/2}$. Writing in *Nature Nanotechnology*, Adrian Bachtold and colleagues at the Institute of Photonic Sciences and Institut Català de Nanotecnologia in Barcelona, and Michigan State University, now describe a force sensor with a sensitivity of 12 zN Hz$^{-1/2}$ limited only by the thermal noise acting on the cantilever (ref. 4). This record force sensitivity is achieved by using ultrasensitive measurements of electrical noise to detect the low-amplitude thermal vibrations of a carbon nanotube oscillator down to a temperature of 1.2 K. The approach could, in principle, allow a single nuclear spin to be mechanically detected or allow ultrasensitive magnetometry of single molecular magnets.

The minimum detectable force of the most sensitive transducers is set by their intrinsic thermomechanical noise, which, at a given temperature, can be improved by reducing mechanical dissipation. Mechanical dissipation can be reduced by shrinking the dimensions of mechanical transducers, so that the ultimate resolution of state-of-the-art devices is limited by the dissipation produced by surface imperfections because of their large surface-to-volume ratios. These surface defects and adsorbates are mostly introduced during the top-down fabrication processing, which typically involve optical or electron-beam lithography, chemical or plasma etching, and a release step.

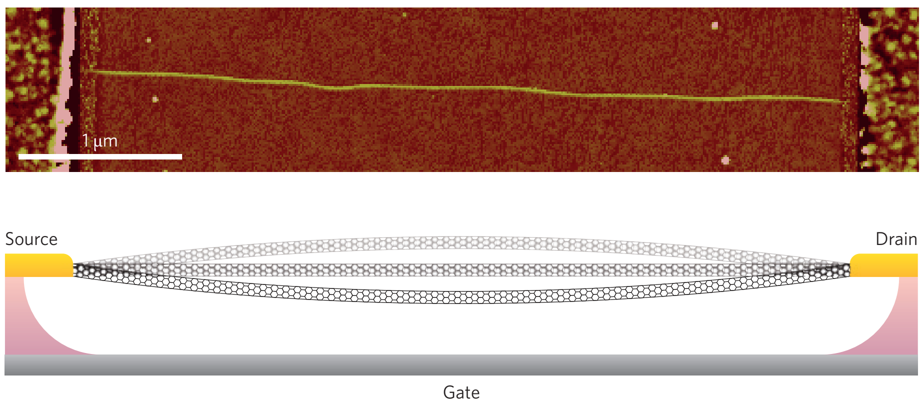

Figure 1 | A carbon nanotube resonator. Top: atomic force microscope image of a single-walled carbon nanotube spanning the source and drain contacts taken before its suspension. It is suspended by removing the silicon oxide layer. Bottom: a nanotube spanning two contacts vibrates around its equilibrium position due to its thermal energy, that is, it undergoes Brownian motion. In the Coulomb blockade regime, this motion excites electrons so that they can escape from their electrostatic traps, producing a small electron current. The resulting electric current noise is a measure of the nanotube's thermal motion. Top panel reproduced from ref. 4, © 2013 NPG.

To produce tiny, defect-free mechanical nanostructures with perfectly terminated surfaces, researchers are now turning to bottom-up fabrication methods, in which resonators are built molecule-by-molecule. The process is typically driven by self-assembly or directed self-assembly. The most prominent examples of such mechanical resonators include suspended carbon nanotubes[5,6], suspended graphene sheets[7] and nanowire cantilevers[8]. Until now, the central challenge facing mechanical transducers built by bottom-up fabrication methods has been the difficulty of detecting their miniscule displacements. Various techniques exist for detecting the displacement of traditional micromechanical oscillators including optical, microwave, capacitive, magnetic and piezoelectric schemes. However, the sensitivity of these schemes tends to suffer as the dimensions of the mechanical resonator shrink.

The detection method reported by Bachtold and colleagues achieves an impressive force resolution in a resonator consisting of a carbon nanotube, which is several micrometres long, suspended between two contact electrodes over a gate electrode. By operating the device in the Coulomb blockade regime, the motion of the carbon nanotube is converted into a tiny electron current. To overcome electronic noise, the researchers amplify the signal with two independent low-noise amplifiers and cross-correlate their output. The voltage noise of the amplifiers cancels out and the weak signal due to the thermal vibrations of the carbon nanotube is extracted. Having solved the challenge of detecting the low-temperature thermal motion of the carbon nanotube, the researchers take advantage of its special mechanical properties, that is, the combination of an extremely small mass with one of the softest spring constants of any resonator, and a high mechanical quality factor.

The frequency of the fundamental mode of the carbon nanotube (4.2 MHz) is high compared with traditional ultrasensitive cantilevers and this provides further advantages. In high-frequency resonators, the effects of external sources of noise can be mitigated because, when the resonant frequency is much higher than the characteristic frequency of the external noise, the resonator can be effectively decoupled from the noise. Furthermore, for mass-sensing applications, the minimum detectable mass depends on the inverse square of the resonator frequency.

Despite their many advantages, carbon nanotubes are not the only promising transducers fabricated using bottom-up approaches. Epitaxially grown inorganic nanowires, for example, have recently been used in a low-temperature force-detected form of nanometre-scale magnetic resonance imaging, achieving exquisite spatial resolution[5,6]. Unlike suspended carbon nanotube transducers, these devices have been used as cantilevers, such that their tip can be scanned close to the surface of a sample; this ability makes them well suited to scanning probe applications where doubly clamped carbon nanotube resonators are awkward.

It is clear that mechanical oscillators must be scaled down to simultaneously minimize dissipation and maximize resonance frequency. Moving towards ever-smaller mechanical transducers with ever-fewer defects should optimize their ultimate force and mass resolutions. This trend positions bottom-up techniques as the most promising fabrication methods. The work of Bachtold and co-workers, along with recent results obtained using nanowire cantilevers[9,10], may be the first indications of a new approach to build mechanical transducers. ❐

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SENSORS

Good vibrations for bad bacteria

The response of bacteria to antibiotics can be quickly assessed by monitoring the fluctuations of cantilevers coated with the bacteria.

Rachel A. McKendry and Natascha Kappeler

Infections that are resistant to antibiotics are one of the gravest threats to human health and have recently been classified alongside dangers such as global warming and terrorism[1]. Such drug-resistant strains of bacteria can spread rapidly and unpredictably, and have the potential to cause enormous human and economic losses. The problem is acute because the pipeline of new antibiotics has dried to a trickle, and the widespread misuse of antibiotics has fuelled the rise in bacterial resistance through natural selection. The correct treatment of an infection relies on early detection with accurate diagnostic tests, but current gold-standard methods are slow requiring days to weeks to culture bacteria — a method used in laboratories to grow sufficient bacteria so that their sensitivity to antibiotics can be tested. The inherent delays between tests, results, follow-up appointments and treatment impacts on patient health outcomes and leads to ongoing transmission of serious infections. These delays also hinder public health efforts to tackle new threats. These major unmet clinical needs are driving the development of new rapid diagnostic tests to revolutionize the management of infections and improve the stewardship of antibiotics. Writing in *Nature Nanotechnology*, Giovanni Longo and colleagues have now shown that low-frequency fluctuations of atomic force microscopy cantilevers can be used to characterize bacteria, rapidly test their sensitivity to antibiotics and identify resistance within minutes[2].

Free-standing cantilevers, which function like miniature diving boards, are of interest in a range of diagnostic applications due to their sensitivity and microscopic dimensions, and their ability to be mass manufactured and operated in parallel. Researchers have, for example, previously used cantilevers to study bacteria with high sensitivity[3–5]. However, tests of antibiotic sensitivity have typically relied on culturing cells on the cantilever[6]. Longo and colleagues — who are based at EPFL, University Hospital of Lausanne and the University of Lausanne — have been able to move beyond these limitations by using a novel nanomechanical transduction mechanism to sense bacteria, which they correlate to cell metabolism.

To test their approach, the team optically track the fluctuations of cantilevers coated with *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* in response to stimuli that alter the metabolism of the bacteria (Fig. 1). The bacteria were selected as models of motile and non-motile bacteria, respectively, and are both clinically important targets. *S. aureus* is a common hospital-acquired infection often associated with surgical procedures.