tein p53 for degradation, show that Mdm2 inhibition can be attained by blocking interaction with its substrate. Yang *et al*. show that a stable complex forms between TRAF6 and Akt, suggesting that this approach may be a good way to block TRAF6-mediated Akt activation. The potential effectiveness of this approach for tumor therapy is highlighted by the point in the signaling cascade at which TRAF6 contributes to Akt activation—downstream of common mutations observed in the clinic that affect phosphatidylinositol 3-kinase (PI3K) or the phosphatase PTEN, both of which cause hyperactivation of Akt. In support of this, the tumor cell line depleted of TRAF6 that was injected into mice by Yang *et al*. did not express PTEN and displayed strong Akt activation.

TRAF6 could be used to augment the effectiveness of rapamycin analogs (rapalogs), drugs that inhibit the mammalian target of rapamycin complex 1 (mTORC1). Rapalogs are approved for limited antitumor therapy because they may temporarily stabilize tumors in clinical trials but rarely elicit a full response in terms of tumor ablation. Preclinical studies indicate that rapalogs have a cytostatic effect on tumors, due at least in part to increased Akt activation, because a negative feedback loop that normally prevents PI3K signaling is lost. As Yang *et al*. show, cells lacking TRAF6 display increased spontaneous apoptosis (programmed cell death). Thus, TRAF6 inhibition in conjunction with rapalogs could shift the response of tumors to rapalogs from cytostatic to cytotoxic, increasing the efficacy of these drugs in cancer therapy.

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PHYSICS

Coupling Strongly, Discretely

Mechanical systems acting as electronic quantum dots can be tuned at the level of single electrons.

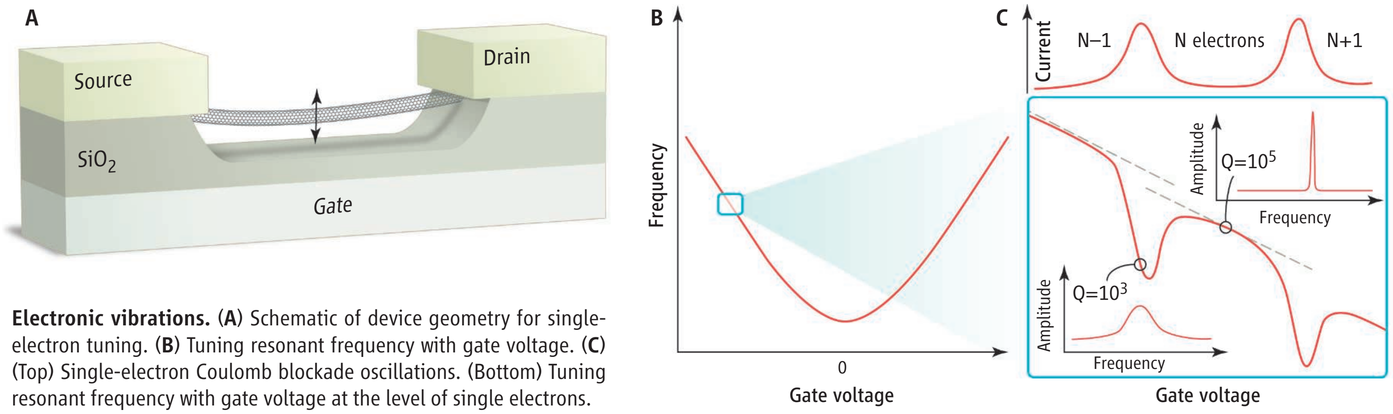
James Hone[1] and Vikram V. Deshpande[2]

The fields of electronics and mechanics have made impressive progress toward true quantum mechanical devices. Through improvements in device performance and measurement techniques, nanoelectromechanical systems (NEMS) have enabled high-sensitivity detection of charge, mass, and spin, and have steadily approached the quantum limit of mechanical motion (*1*). Similarly, the ability to manipulate individual electrons in quantum dots has led to developments in solid-state quantum computing (*2*). On pages 1107 and 1103 of this issue, Lassagne *et al*. (*3*) and Steele *et al*. (*4*) bring together these two fields to study the influence of charge transport on nanomechanical motion in high-performance carbon nanotube mechanical resonators that simultaneously act as quantum dots. They find that the resonant frequency and dissipation in the nanotubes are both highly sensitive to the charge state at the level of single electrons.

Carbon nanotubes are a model system for nanoelectronics. Adding even a single electron to this small system carries a large energetic cost; thus, at low enough temperatures, electrical transport in carbon nanotubes can take place through the tunneling of electrons one at a time. This manifests itself in peaks in the current as a function of the voltage on a nearby gate (which modulates the chemical potential of the nanotube), a phenomenon known as Coulomb blockade. Advances in the growth and fabrication of nanotubes (*5*) have enabled the development of clean, freely suspended devices that have been used to observe electronic phenomena such as correlated electron states (*6*, *7*) and spin-orbit coupling (*8*).

Because of their small size, high stiffness, and low density, nanotubes are also excellent materials for NEMS. But they may also have an additional advantage. They circumvent the surface dissipation mechanism known, in bulk-etched NEMS, to decrease the quality factor *Q* (which quantifies the sharpness of the resonance peak) with decreasing device size. However, nanotubes have until recently shown *Q* values of only 100 to 1000 (*9*–*12*), in keeping with the trend for etched devices. Steele *et al*. now show that clean nanotubes do in fact beat the trend, achieving a *Q* of 100,000 at ultralow temperatures.

The two reports take advantage of these parallel improvements in device performance to examine in detail the coupling



Electronic vibrations. (**A**) Schematic of device geometry for single-electron tuning. (**B**) Tuning resonant frequency with gate voltage. (**C**) (Top) Single-electron Coulomb blockade oscillations. (Bottom) Tuning resonant frequency with gate voltage at the level of single electrons.

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between the electrical and mechanical properties of nanotube NEMS in the Coulomb blockade regime. In both studies, a nanotube is suspended above a substrate, which acts as a gate (see the figure, panel A). Lassagne *et al*. use an electromechanical mixing scheme that takes advantage of the change in current with gate voltage. This scheme is particularly well suited to the Coulomb blockade regime, in which conductance oscillations lead to a large signal, providing single-atom mass sensitivity (*12*). Steele *et al*. measure the dc conductance, which is sensitive to the second derivative of the current with gate voltage. Motion of the nanotube modulates the capacitance to the gate, and therefore the charge state (and conductance) of the nanotube.

As voltage is applied to the gate, electrostatic force induces tension in the nanotube and increases the resonant frequency (see the figure, panel B). However, the frequency does not change smoothly, but shows discrete jumps (see the figure, panel C), which are correlated with the charge state as determined by the Coulomb blockade measurement. This occurs because the charge on the nanotube, and therefore the electrostatic tension, changes in discrete amounts; Steele *et al*. term this effect "single-electron tuning," as the mechanical analog to single-electron tunneling. In addition, the resonance softens and broadens at each jump. Both effects are a direct result of the fluctuating charge at the boundary between states with N and $N \pm 1$ electrons.

Although the discussion so far has addressed the effects of charge transport on the mechanical measurement, the opposite also can be interesting. Steele *et al*. find that in the regime of strong coupling to the leads (rate of tunneling larger than resonant frequency), electron tunneling may spontaneously drive the nanotube into resonance, and consequently distort the dc transport features.

The work of Lassagne *et al*. and Steele *et al*. beautifully demonstrates the rich physics that arises from the coupling of NEMS and electron transport in quantum dots. In addition to the results described in these two studies, such strong electronic-vibrational coupling may be used to investigate interesting physics such as negative charging energy (*13*). Moreover, the newly achieved high Q's make nanotubes very attractive candidates for detecting the quantum limit of motion and subsequent manipulation of quantum states at macroscopic scales.

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ATMOSPHERE

Antarctica's Orbital Beat

Peter Huybers

What do Antarctic ice core records really record?

Alternating glacial and interglacial conditions have dominated Earth's climate for at least the past 800,000 years (*1*, *2*). Such a global rhythm of glaciation is surprising—at least if summer solar radiation controls glaciation (*3*)—because variations in Earth's orbit cause opposite changes in the intensity of northern and southern summer radiation. Deciphering the origins of the orbital period variations found in Antarctic proxies of climate may tell us why glaciations are global.

Earth's orbit around the Sun is not steady. The tilt of its spin axis varies with a period of 41,000 years, the eccentricity of its orbit changes at time scales of 100,000 to 400,000 years, and the orientation of the eccentric orbit precesses with respect to the seasons about once every 21,000 years. One implication of the orbital geometry is that at the time when precession aligns Earth's closest approach to the Sun (perihelion) with Northern Hemisphere summer, Earth is farthest away from the Sun (at aphelion) during Southern Hemisphere summer. But if the north and south are alternately near and far from the Sun during summer, why has glaciation been globally synchronous?

A clue lies in Antarctica's ice, as illustrated by the δD record from Dome C (see the figure) (*4*). δD is the normalized deuterium to hydrogen ratio of the ice and is sensitive to air temperature over Antarctica, as can be roughly understood in that colder temperatures lead to greater distillation of heavy isotopes out of atmospheric moisture. The exact δD of the snow accumulated at Dome C depends on detailed evaporation and precipitation histories (*5*), but similarities between the δD variability and other Southern Hemisphere climate records (*6*, *7*) suggests that this signal represents regional and hemispheric climate variations.

The Dome C δD record (*4*) indicates that Antarctic temperature increases with the tilt of Earth's spin axis. This is as expected, because greater tilt increases the annual incoming solar radiation (insolation) at high latitudes. More puzzling is that temperature also seems to be higher when aphelion occurs during Antarctic summer (*1*, *2*, *4*, *6*). This contrasts with the Northern Hemisphere, which warms when perihelion aligns with northern summer (*2*, *3*). The northern response can be understood as more intense summer insolation reducing ice cover, leading to lower surface reflectivity and higher temperatures (*2*, *3*), but what mechanism governs the southern temperature response?

The answer to this question may also tell us why glacial/interglacial cycles are global. There are at least five possibilities.

Perhaps the most basic prediction can be traced from Milankovitch (*3*), who used simple radiative equilibrium calculations to explore how orbital variations influence temperature and ice volume. He dismissed Antarctica as too cold for changes in southern insolation to influence its ice volume, but applying his radiative equilibrium approach to mean annual temperature does suggest that Antarctica will be warmest when aphelion coincides with Southern Hemisphere summer (*8*). Aphelion is associated with less intense summer insolation, but it also corresponds to a longer summer and shorter winter, as follows from Kepler's second law. Simple radiative equilibrium indicates that the longer summer more than compensates for a lower intensity, giving temperature variations that are consistent with—albeit smaller in amplitude than—those derived from the ice core records (*9*).

Alternatively, if increased Southern Hemisphere spring insolation drives a reduction in sea

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