

tors in the plasma membrane is slow. Application of intracellular IP₃ takes several minutes to activate plasma membrane IP₃ receptors; yet activation of Ca²⁺ release through ER IP₃ receptors is within a few seconds. Could this reflect a time-dependent insertion of IP₃ receptors into the plasma membrane or perhaps their time-dependent activation? Application of adenosine phosphatase, a nonmetabolizable, high-affinity IP₃ receptor agonist, gave a much faster effect, suggesting instead that some change in the metabolism of IP₃ occurs in the vicinity of the plasma membrane IP₃ receptors. This implies local regulation of IP₃ concentrations to control opening of these channels.

Ca²⁺ entry at the cell surface mediated by IP₃ receptors contrasts dramatically with another Ca²⁺ entry process occurring almost universally among cell types, known as “store-operated” Ca²⁺ entry (9, 10). Ca²⁺ stores have a finite release capacity, and activation of ER IP₃ receptors causes rapid Ca²⁺ store depletion. The decrease in luminal Ca²⁺ triggers store-operated channels (SOCs) present in the plasma membrane, which mediate the exceedingly Ca²⁺-selective Ca²⁺ release-activated Ca²⁺ current (I_{CRAC}) observable in many cell types (10). Yet the identity of these channels, and the coupling process between the ER and the plasma membrane that triggers their activation, have eluded understanding. Novel high-throughput screens recently identified the single transmembrane-spanning ER protein STIM1 as the likely sensor of Ca²⁺ in the ER by virtue of its luminal-facing EF-hand domain, which binds to Ca²⁺ (11–15).

But STIM1 is not the only essential protein. New studies show that the Orail protein is also crucial for SOC activation (3, 4, 7). This revelation came from a combination of elegant studies including genome-wide RNA interference screening and modified linkage analysis identifying an Orail mutation as the cause of severe combined immune deficiency. T cells of the immune system in such patients have ablated Ca²⁺ entry which can be restored by Orail expression (3). Dramatically, coexpression of both Orail and STIM1 in any cell reconstitutes store-dependent coupling and I_{CRAC} function that is almost indistinguishable from that in normal T cells (5–7). Orail is expressed in the plasma membrane, and it seems certain to constitute the channel moiety itself. The structure of Orail does not appear to be a “typical” cation channel. For example, the IP₃ receptor has six transmembrane domains with a pore-forming loop between transmembrane segments 5 and 6, and exists as a tetramer. But the function of SOCs is itself rather unusual – highly inwardly rectifying, non-voltage-gated, and with a very small but exceedingly selective Ca²⁺ conductance. So the atypical structure of Orail may not be so surprising.

Whereas the IP₃ receptor and Orail both mediate receptor-induced Ca²⁺ entry signals, the

function, appearance, and physiological significance of the two proteins provide some sharp distinctions (see the figure). The IP₃ receptor has a large single-channel conductance (in the 200-pS range under normal physiological conditions), and although its relative ion nonselectivity would predominantly facilitate Na⁺ ion movement, substantial Ca²⁺ entry is predicted even though cells express only one or two in the plasma membrane (2). In contrast, Orail-mediated I_{CRAC} has an estimated single-channel conductance at or below 1 pS (16). However, the high Ca²⁺ selectivity of Orail and the likely presence of thousands of these channels per cell predict an even larger entry of Ca²⁺ than through the IP₃ receptors. The scenario described by Dellis *et al.* is a torrent of Ca²⁺ through just one or two isolated IP₃ receptors in the plasma membrane, as opposed to a more evenly distributed trickle of Ca²⁺ through the many Orail channels across the cell surface. This may have profound consequences for Ca²⁺ signaling events in cells.

Certainly, uncovering the molecular identity of the Ca²⁺ entry machinery at the cell surface has crucial importance for pharmacological targeting to control cellular signaling. It would be premature to generalize about the universality of plasma membrane IP₃ receptors, because so far their function has been observed only in B cells of the immune system (2). However, the function and

wide cellular distribution of the three mammalian Orail gene products and their ancillary coupling machinery, including the two mammalian STIM proteins, indicates that this process may have broad functional significance in the mediation of Ca²⁺ signal generation in many cell types.

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10.1126/science.1130811

PHYSICS

Controlling Friction

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Nanometer-scale friction can be altered electronically or mechanically. The results may lead to more reliable nanometer-scale devices.

According to Plato, necessity is the mother of invention. Scientists and engineers working on small-scale mechanical devices may be relieved to find this idea starting to take effect at the nanometer scale. There is a critical need to control the effect of friction at this scale, and in this issue, two groups (1, 2) provide independent and precise means of doing just that.

Control of tribological interactions—friction, adhesion, and wear—is desirable at all length scales. Estimated annual expenses attributable to friction and wear across the U.S. economy run up to hundreds of billions of dollars (3). But researchers working on small-scale devices such as micro- and nanoelectromechanical systems (MEMS/NEMS) are not

even counting dollars yet. Devices with sliding interfaces, such as certain actuators, positioning devices, and microgears, cannot be commercialized because the surfaces of these devices wear out and seize too rapidly (4).

In these small-scale devices, many or even most atoms reside at surface and interface sites (rather than in the bulk of the material). Surface forces such as friction and adhesion therefore dominate over the available actuation and restoring forces; furthermore, the high friction and adhesiveness of silicon (a common MEMS material), coupled with its brittle nature, lead to high rates of wear and debris generation. Surface treatments, such as self-assembled monolayers, can overcome the adhesion problem and reduce friction, but wear persists, and device lifetimes and reliability remain inadequate (5).

On page 207 of this issue, Socoliuc *et al.* (1) show that friction can be reduced more than 100-fold in a nanometer-scale contact by

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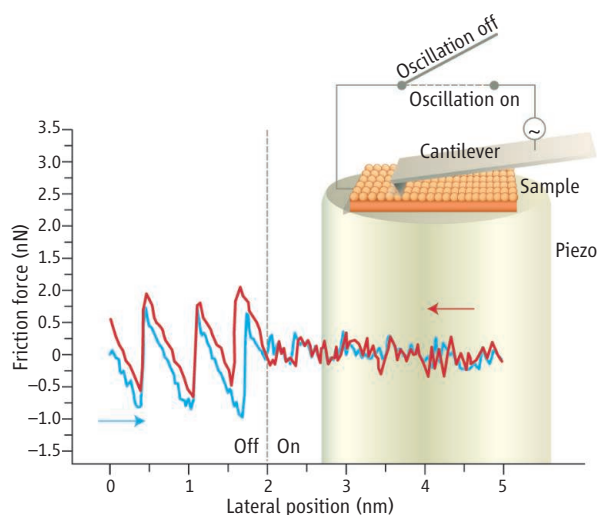
applying a small vibrating normal force to the interface. The authors formed a contact between the silicon tip of an atomic force microscope (AFM) cantilever and atomically flat alkali halide surfaces under ultrahigh-vacuum conditions. When the sample is displaced laterally with respect to the cantilever, the tip sticks and slips in a series of instabilities. The effect, known as atomic-scale stick-slip friction (6), can be thought of as an atomic-scale analog to the macroscopic stick-slip effect responsible for squeaking door hinges and bowed violin strings.

The atomic-scale instability occurs because high static friction leads to a buildup of energy during sliding in the springlike elastic compliances of the system. This energy is partially stored in the elastic deformation of the cantilever, but some of it builds up at and around the interface. This elastic energy is suddenly released when the magnitude of the negative lateral force gradient in the sliding direction exceeds the combined lateral stiffness of the cantilever and the contact. Because the lateral interaction force is periodic by virtue of the symmetry of the crystal surfaces, the stick-slip behavior repeats once every lattice site, creating lateral-force images that match the lattice periodicity of the sample (see the figure). This leads to the buildup and dissipation of substantial amounts of energy.

This effect has been known for years (7) and was anticipated much earlier (8, 9). What is new here is that the instability can be completely suppressed, and energy dissipation dramatically lowered, by cleverly navigating the available energy landscape. Socoliuc *et al.* have previously shown that the instability is suppressed when very small (tensile) normal forces are applied (10). This is because under tension, the separation between the tip and the sample is slightly increased even though they remain in contact. Consequently, the corrugation of the interfacial potential energy is reduced. The gentler slopes of this landscape ensure that the magnitude of the negative lateral force gradient never exceeds the lateral system stiffness, and hence, no instability occurs.

However, working at such small forces is not always practical. So instead, Socoliuc *et al.* have now used a range of higher (compressive) normal forces (1). A sinusoidal modulation of this normal force about its average value leads to brief periods where the gentler energy landscape is found; the tip takes advantage of this and smoothly slides over the next position in the laterally periodic system.

The process can be thought of in terms of a modified version of the story of Sisyphus, the tragic figure of Greek mythology who was condemned to push a rock up a mountainside, only to have it roll back to the bottom over and over again. Imagine that Sisyphus succeeded in pushing his rock to the top of the mountain. It would then begin to roll down the other side. Because the mountain is steep, he would not be able to keep up, and the rock would crash down to the next valley below. Sisyphus would then have to push the rock up the next mountain. This is like the stick-slip instability: Tremendous potential energy is built up (in the AFM, it is the elastic potential energy in the cantilever and contact; with Sisyphus, it is



A method for reducing friction. Friction in a nanometer-scale contact, in the form of atomic-scale stick-slip instabilities (left), is dramatically reduced (right) when a modulation in the normal force is applied to the interface (sketch, top right).

gravitational potential energy). Then, just as the landscape becomes easier to navigate at the top of the mountain, the energy is rapidly released and dissipated as the rock rolls down the steep downward slope. If the mountains were not so tall, Sisyphus could push the rock to the top of each one more easily, requiring less energy. Once at the top, he would be strong enough to hold on to the rock and control it as he continues down the gentle hill.

What Socoliuc *et al.* have done is to make the “mountain,” that is, the corrugation of the lateral potential energy, less tall for brief periods of time. Because the corrugation is reduced at lower normal forces, oscillating the normal force will lead to short time spans when the tip can move forward in a stable manner without the stick-slip instability. The lateral force to slide, with the modulation turned on, is therefore reduced compared to the nonmodulated case by at least a factor of 100 (see the figure).

It is not clear whether the total amount of energy required to slide is reduced (because some energy is required to drive the cantilever),

but smoother sliding unquestionably occurs. If this effect can be put to use in MEMS and NEMS devices with contacting interfaces, for example, by using actuators that are integrated into the devices, it could enable these devices to function reliably.

On page 186 of this issue, Park *et al.* (2) report another method for controlling friction in a nanometer-scale contact: the use of electric fields. The authors worked with a silicon sample with well-defined regions of n- and p-doping. The differently doped regions had distinct friction forces even when no bias voltage was applied between the sample and a conducting AFM tip. When a bias of +4 V was applied to the sample, an increase in friction by up to a factor of 2 was observed in the p-doped region. The mechanism for this increase is not clear, but estimates of the contribution due to electronic friction (the drag force that results when charge carriers move in an electric field) are far too low to explain the result.

Biases of a few volts can be easily applied in MEMS and NEMS devices. Thus, this also appears to be a feasible method to control friction. The frictional control knob in this case goes up and not down, but that, too, could be of use. Sliding MEMS actuators that depend on alternately holding and releasing interfaces have the potential for extremely high positional precision, but are limited by the ability to exert high enough friction to hold the device steady (11).

Both studies provide beautiful and enticing scientific insights into the origin of atomic-scale friction. At the Gordon Research Conference on Tribology (12), the conference chairman, J. Thomas Dickinson, commented that “these fascinating studies are examples of how nanotribology research is maturing from just investigating friction to now providing prescriptions to control it.” Plato might be pleased to know that the discoveries were driven not only by necessity, but also by tremendous scientific curiosity, creativity, and skill.

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10.1126/science.1130420