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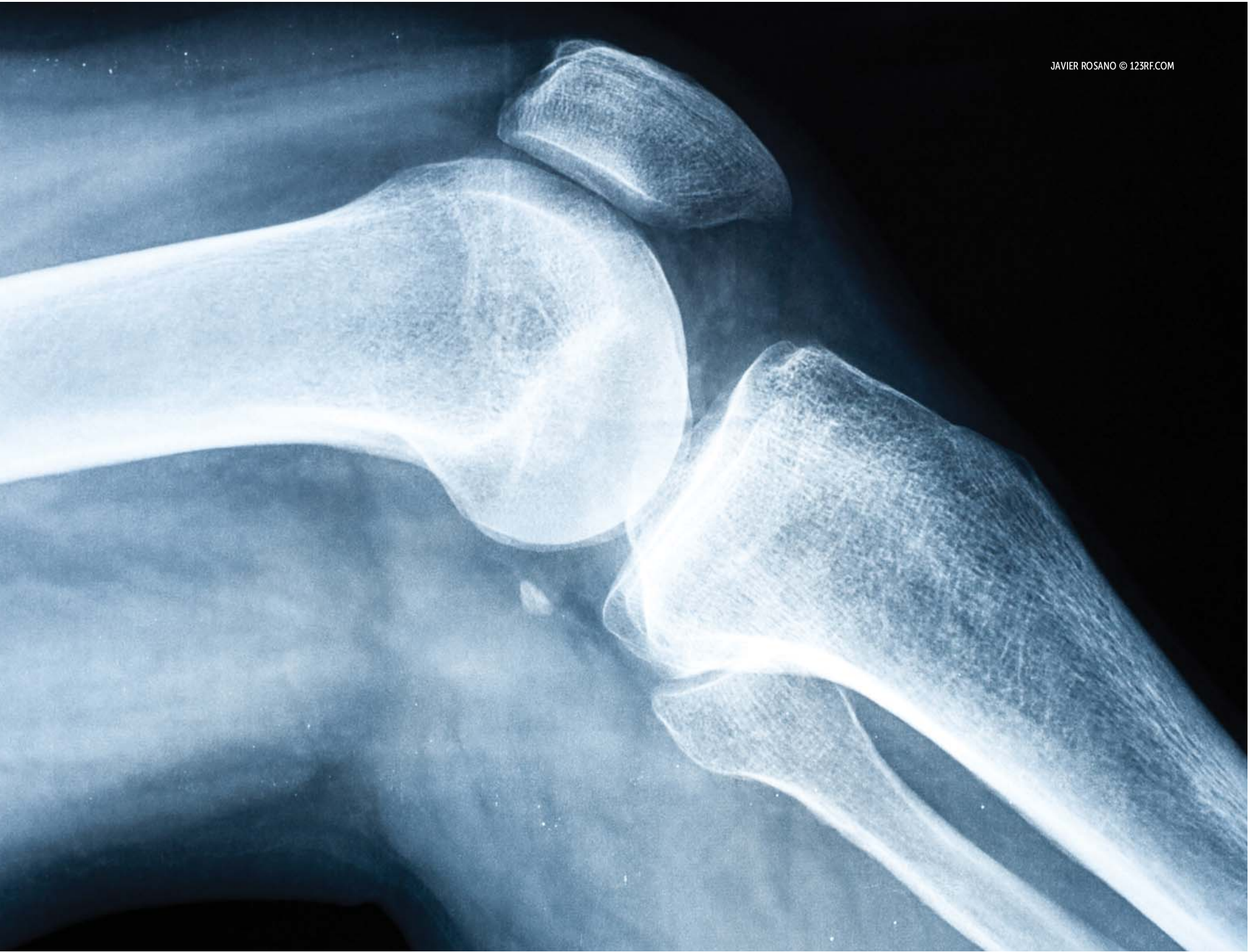
LUBRICATION *of* articular cartilage

Sabrina Jahn
and Jacob Klein

A mix of proteins, polymers, lipids, and tightly bound but fluid shells of water molecules may account for a healthy joint's ultralow friction.

Imagine supporting a 1-ton weight on your hand and then sliding it along the palm with a slight push of a finger. Pulling off that trick would require, roughly, the level of lubrication that is provided by cartilage surfaces in the major joints of our bodies. Those joints, which enable rotation (or more precisely, articulation) at shoulders, elbows, hips, and knees, are remarkable structures. Indeed, the articular cartilage layers that coat the ends of the bones and slide past each other as we flex our joints are the most efficiently lubricated surfaces in nature. No manmade material can match the ultralow sliding friction, which is a consequence of the lubrication, that cartilage provides at the high pressures and low velocities that our joints experience. Such low friction is essential for their health, as they withstand varied harsh and complex loading, day after day, over a human lifetime.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What is the origin of the lubrication that exists between cartilage surfaces? And can we exploit our knowledge of it to alleviate common and debilitating joint diseases? One example is osteoarthritis, a condition in which high friction is associated with cartilage degradation. Both questions are topics of current research, not least because osteoarthritis imposes a huge burden on society,[1] affecting some 30 million people in the US alone. Deeper insight into how cartilage lubrication relates to disease progression may lead to treatments that ameliorate the condition.

The layers coating our joints

To appreciate the frictional processes that occur at a cartilage surface, consider the basic anatomical structure and composition of our major joints, also called synovial joints. As shown in figure 1a, a synovial joint is enclosed by a flexible, fibrous, protective capsule, called the synovial membrane, whose inner surfaces are lined with tissue, the synovium. The synovium helps produce synovial fluid, the liquid in which the joint is bathed. (With its viscous consistency, synovial fluid resembles egg whites, and its name comes from the Latin ovum for egg.) The ends of the articulating bones are covered with a 1- to 4-mm-thick layer of smooth, whitish tissue, the articular cartilage—essentially a water-filled network of collagen fibers permeated by highly charged macromolecules and other molecules.[2] The osmotic pressure of those molecules gives the cartilage its mechanical resilience. (See PHYSICS TODAY, September 2002, page 21.)

Cartilage possesses four distinct zones, shown in figure 1b. The outermost, superficial zone is composed of a fine fibrillar network that's in contact with both the synovial fluid and the opposing cartilage layer that slides past the superficial zone when joints are flexed and extended. That outer zone, whose thickness is just tens of microns, contains no cells. The properties of that outer, boundary layer at the cartilage surface determine the boundary friction during articulation, and the nature and conformations of the surface macromolecules are crucial to understanding the friction there.

The main macromolecules that permeate the collagen network and have been implicated in its lubrication include proteoglycans, polymers, noncollagenous proteins, and lipids.[2] Proteoglycans are highly charged, bottlebrush-like molecules. In cartilage they are called aggrecans. The ends of those molecules are attached to hyaluronan—also known as hyaluronic acid or HA—a long, linear, negatively charged polysaccharide. The composite structure is shown schematically in figure 1c. Typical lengths of the central HA backbone range from 100 nm to 10 μm, and the aggrecans dangling from it are about 100–200 nm long.

Another molecule implicated in cartilage lubrication is lubricin, a flexible, rodlike protein with a charged, carbohydrate-rich backbone.[3–5] Together, phospholipids, HA, and lubricin reside both in the synovial fluid and in the superficial zone of the cartilage. Importantly, phospholipids, in which two hydrophobic chains of CH_2 monomers are attached to a hydrophilic phosphocholine head group, form the largest group of lipids in cartilage and its surrounding fluid, the so-called PC, or phosphatidylcholine, lipids.[6] As discussed below, such lipids have been proposed as central to the low friction experienced by flexing joints.

Articular cartilage contains a low density of specialized cells, called chondrocytes, which synthesize the components of the cartilage itself. As the only cells in the cartilage, they are central to cartilage and joint well-being. Crucially, chondrocytes are sensitive to mechanical stresses through a process known as mechanotransduction, which affects how the cells' genes respond to the stresses. Chondrocytes thus require pressure—or more accurately, normal stress—to function optimally and produce cartilage-maintaining molecules.[7] When subjected to shear stress, however, the cells respond very differently: They overproduce enzymes that may degrade the cartilage network or the molecular components permeating it.[8]

That undesirable effect makes the chondrocytes especially vulnerable to high friction. It also provides a direct link between the health of the cartilage and the level of lubrication at its surface. The low friction of healthy

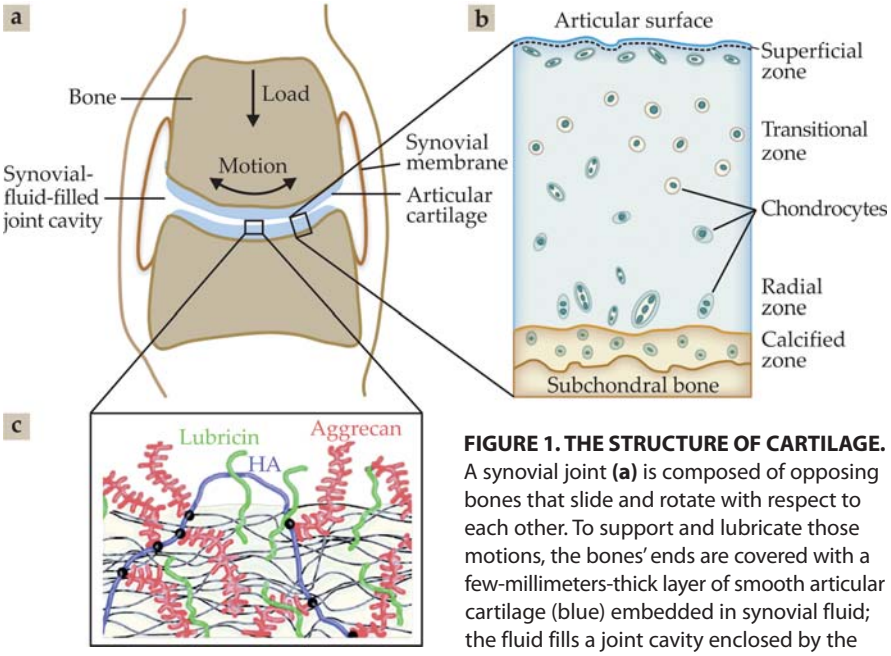


FIGURE 1. THE STRUCTURE OF CARTILAGE. A synovial joint **(a)** is composed of opposing bones that slide and rotate with respect to each other. To support and lubricate those motions, the bones' ends are covered with a few-millimeters-thick layer of smooth articular cartilage (blue) embedded in synovial fluid; the fluid fills a joint cavity enclosed by the synovial membrane. **(b)** The cartilage is organized into four main zones. A few tens of microns thick, the superficial zone exposes the articulating, lubricated surface. Water makes up about 70% of cartilage tissue by volume, and cells known as chondrocytes, which produce all the molecules that make up the tissue, occupy less than about 5% of it. **(c)** The outer boundary of articular cartilage is composed of numerous macromolecules. Among ones that are thought to participate in lubrication are hyaluronic acid (HA), lubricin, and aggrecans. Lipids, much smaller than those macromolecules, are ubiquitous but not shown. (Adapted from ref. 2.)

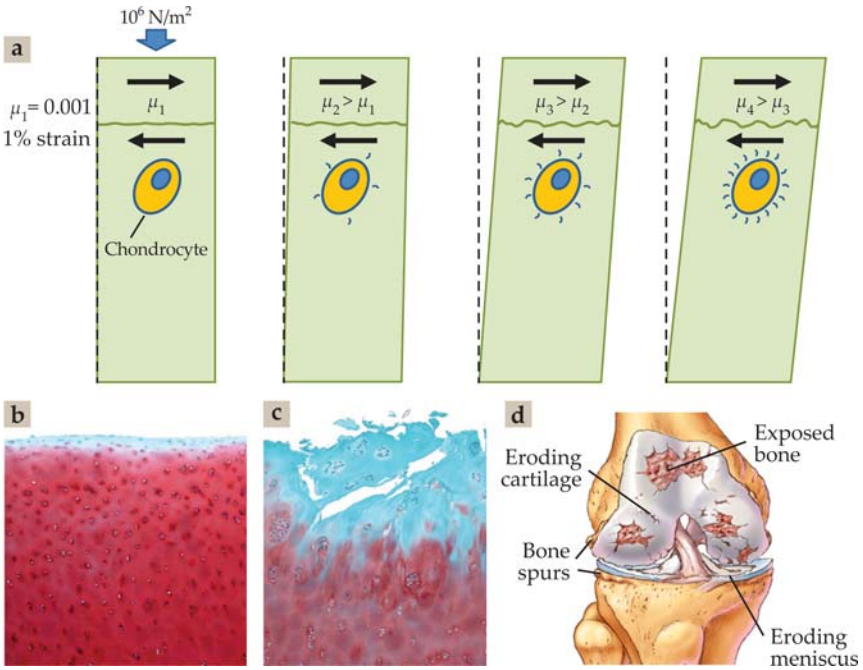


FIGURE 2. THE TRANSITION FROM HEALTHY TO DISEASED CARTILAGE. The shear strain on cartilage cells—chondrocytes—is linearly proportional to the product of the friction coefficient μ and the applied pressure. **(a)** An increase in the friction at the boundary between two surfaces sliding in opposite directions (arrows) can degrade the cartilage through the increase in shear experienced by embedded chondrocytes. The cells respond to increased strain in each panel (from left to right) by producing more cartilage-degrading enzymes (tick marks), which further increases the friction and can lead to osteoarthritis. (Adapted from J. Klein, *Nat. Rev. Rheumatol.*, in press.) **(b)** A thin histological section normal to an articular cartilage surface shows healthy tissue. **(c)** An osteoarthritic section exhibits fissures that extend from the cartilage surface into deeper zones. (Adapted from K. P. H. Pritzker et al., *Osteoarthritis Cartilage* **14**, 13, 2006.) **(d)** This schematic of a knee joint shows degraded cartilage in fully developed osteoarthritis. (Courtesy of stoneresearch.org.)

cartilage ensures that there is little shear stress at its surface during articulation. However, if the friction increases unduly—due to a traumatic event, such as a sporting accident, or with age—the higher shear stress at the cartilage surface leads to higher shear strain on the chondrocytes embedded in it. That strain in turn leads in a self-reinforcing manner to overall wear of the tissue and eventually osteoarthritis, as illustrated in figure 2.

Frictional energy dissipation

Friction arises from energy dissipation as two surfaces slide past each other, and lubrication is the process by which that dissipation is minimized. The main dissipation processes on cartilage surfaces concern fluid-film and boundary frictions. Fluid-film friction is the viscous dissipation when two surfaces separated by a thin liquid film slide past each other. For a sliding velocity v across a roughly uniform film of thickness D and effective viscosity η, the surfaces experience a shear stress per unit area $\sigma \approx (v/D)\eta$. In that case, the friction depends linearly on the sliding velocity.

Boundary friction, by contrast, arises when the boundary layers coating the two surfaces are in actual molecular contact. Energy in the form of heat is then dissipated as molecular bonds across the interface between the contacting layers repeatedly form and break as the layers slide past each other. Unlike with fluid films, boundary friction is very weakly dependent on velocity. The upshot: To determine whether sliding is dominated by fluid-film or boundary lubrication, one examines how its friction depends on sliding velocity.

That boundary friction takes place at the slip plane between surfaces has another consequence: The friction is largely independent of the underlying substrates, which are not themselves in contact. Rather, it depends mostly on the structure of the contacting boundary layers. Experiments that measure friction between model substrates coated with given boundary layers can thus provide insight into the friction between living cartilage, so long as the model substrates are coated with similar boundary layers.

Friction in joints

Frictional processes between boundary layers are complicated, and understanding them requires knowing the detailed molecular interactions. Even so, one can use the sliding friction coefficient μ as a descriptive surrogate to quantify their effects. The ratio of the force required to slide two surfaces past each other to the load compressing them, μ is a simple scalar and contains little direct information on the complex physics of energy dissipation. It is, however, useful as a comparative measure between different systems and experiments.

Measurements in synovial joints reveal friction coefficients[2] between roughly 0.001 and 0.03. The weak velocity dependence of friction in such measurements suggests that the dominant mechanism is boundary lubrication, with outer boundaries of opposing cartilage layers in molecular contact. Moreover, by placing sensors in artificial hip implants in living subjects[9] or inserting pressure-sensitive paper between cartilage surfaces in cadaver joints, researchers have measured local pressures as high as 10–20 MPa between cartilage surfaces. The hypothetical scenario that opens this article—a 1-ton load distributed on the palm of one's hand—would produce a pressure of roughly 1 MPa and is thus a realistic analogy of what our joints experience; and for a surface with a μ of 0.001, a 10-newton nudge from a finger is enough to slide the huge weight.

When the friction between cartilage surfaces is so low, measuring its value in living joints is extremely challenging. Apart from the practical difficulty of manipulating the limbs of living animals to order, the distortion of tissues and ligaments associated with flexing a joint also dissipates energy. Those viscoelastic energy losses manifest themselves as a resistance to

the joint's motion and can mask the very low frictional dissipation from cartilage–cartilage sliding.

Most measurements have been carried out on cartilage in whole joints or excised from joints—so-called explants. Alternatively, researchers have used model surfaces whose boundary layers mimic those on living cartilage.[2,5] Both methods have advantages and disadvantages. Cartilage explants more closely reproduce the mechanical properties and surface topography of articular cartilage, but the precise molecular structure of their outer boundary layers is difficult to control and may differ significantly from that in living joints. Model substrates such as glass or mica, on the other hand, have the advantage that any molecular layers attached to them can be carefully controlled. And the controllable attachment of suitable boundary layers can provide molecular insight into boundary friction, even when the substrate differs from cartilage itself, as explained in the last section.

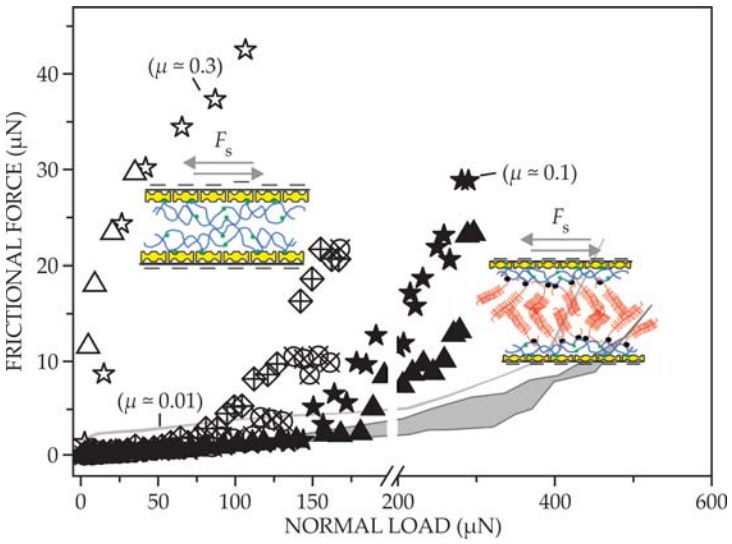


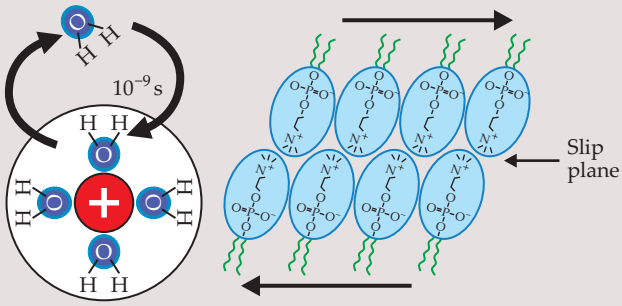
FIGURE 3. PLOTS OF FRICTIONAL FORCE VERSUS NORMAL FORCE as measured by a surface force balance when two mica surfaces slide past each other. The mica surfaces bear boundary layers of either hyaluronic acid (HA, open stars and triangles) or HA complexed with aggrecans (all other symbols). The two cases are sketched to the right of their plotted data. The different curves demonstrate that neither of the boundary layers provides the ultralow friction level measured on articular cartilage, whose friction coefficient is about 0.001 at physiological pressures of 1 MPa or more. (Adapted from J. Seror et al., *Biomacromolecules* **13**, 3823, 2012.)

Measuring and modeling

Efforts to understand the lubrication of natural joints date back to the 16th century, when Swiss physician Paracelsus described the oily nature of the synovial fluid in the joint cavity. The complex structure and composition of cartilage, including its high water content, make both fluid-film and boundary processes likely contributors to the overall frictional dissipation. The earliest models were based on lubrication in machines, whereas later ones were based on the fluid films exuded by cartilage between its sliding, pressurized surfaces. In that second class of models, the fluid between the surfaces reduced the friction and supported much of the load via its own pressure.[10,11] Most frictional dissipation in joints arises from boundary contact, however, and most research has striven to identify the characteristic structure and molecular composition of the boundary layer at the cartilage surface.

HYDRATION LUBRICATION

Hydration lubrication is an emergent paradigm for understanding friction and lubrication processes in aqueous media, including at articular cartilage surfaces. Because of their large electric dipoles, water molecules in the vicinity of a charge or polar group can surround it to form a so-called hydration shell, as shown in the left panel of the figure (adapted from J. Klein, *Nat. Rev. Rheumatol.*, in press). A large energy is required to break up the shells. And yet individual water molecules in each shell can exchange positions with surrounding bulk water or with water in adjacent shells. The time scale for that exchange can be as short as a nanosecond, depending on the central ion being hydrated.



That combination of being strongly held—and therefore difficult to squeeze out even under a heavy load—while remaining fluid under shear makes hydration shells extremely effective molecular-scale lubricants. And their formation accounts for the extremely low friction provided by hydrated ions and charged polymers, surfactants, and lipids on cartilage surfaces. The hydrated head groups of one class of phospholipid—comprising a negative charge, PO_4^-, next to a positive charge, $N^+(CH_3)_3$, are especially good lubricants.[17] A close-packed array of opposing head groups has been proposed to reside at the slip plane between two cartilage surfaces, as shown in the right panel. Those head groups are thought to suppress frictional dissipation via the hydration lubrication mechanism. During that suppression, the strong attraction of the head groups' hydrophobic CH_2 tails keep the lipid bilayers robust enough to withstand high pressures. The phase state of those bilayers—as either a disordered liquid or an ordered solid—and their self-healing ability when worn may be modified by changing the lengths of the tails. The hope is that such modifications can optimize the lubricating properties of such hydration shells for eventual biomedical applications.

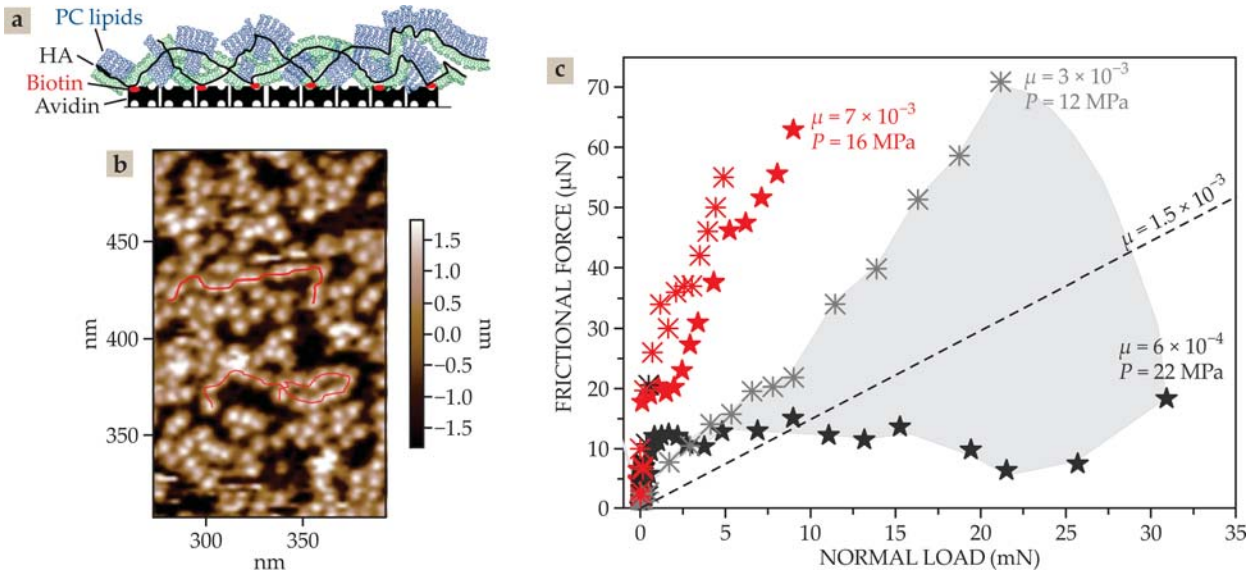


FIGURE 4. COMPLEXES OF LIPIDS and a hyaluronic acid (HA) layer exhibit friction coefficients on par with those measured on articular cartilage. **(a)** In one experiment, PC lipids (blue and green), whose phosphocholine head groups are each joined to two C_{16} chains, are attached to HA molecules (black). The HA molecules in turn are functionalized with chemical groups (biotin, red) that anchor the HA–lipid complex to a mica surface, which is coated with avidin groups that strongly attract the biotins. **(b)** In this atomic force micrograph of the complex on the mica substrate, the meandering red lines highlight strings of HA coated with lipids. **(c)** Experimental data obtained by surface force balance experiments show variations in friction force with load between mica surfaces that are coated with HA–lipid complexes and slid under water (black symbols) or a salt solution (red symbols); friction coefficients μ and local pressures P label select data, and the dashed line shows the mean of the data taken under water. (Adapted from ref. 13.)

One molecule identified in the early 1930s as a possible lubricating candidate is HA. The charged polysaccharide is largely responsible for the highly viscous nature of synovial fluid and is routinely injected into patients' joints to relieve symptoms of osteoarthritis. But in 1970, researchers at Harvard Medical School showed that removing the HA from synovial fluid barely affected lubrication,[3] and in later studies, the glycoprotein lubricin was implicated as the lubricating molecule. Additional molecular components of the synovial joint, including PC lipids, aggrecans, and other proteins, have also been proposed as lubricants, either alone or in combination, and as components of the synovial fluid or in boundary layers coating the cartilage.[2]

Experimental methods for probing cartilage lubrication have ranged widely—from macroscopic measurement of friction in whole joints or cartilage explant surfaces to microscopic methods. The latter include surface force balance (SFB) methods and colloidal probe scanning techniques, whereby a colloidal particle attached to the cantilever of an atomic force microscope slides past molecular layers on substrates, such as glass.[12] Widely used by our group and others, SFBs can directly measure the normal and frictional surface forces between boundary layers composed of the various molecules of interest, which are attached to atomically smooth mica surfaces.[13,14] SFBs provide state-of-the-art sensitivity, force/area resolution, and control over the boundary layers, which can be precisely deposited on the mica surfaces; they also reveal, to within a few angstroms, the thickness of those layers.

Clearly, a prerequisite for understanding the boundary lubrication of cartilage is to reproduce the material's astonishingly low friction—with coefficients as low as 0.001 at physiological contact pressures of up to 10 MPa. (But keep in mind that a portion of that pressure may be borne by the fluid between the cartilage surfaces.[10,11]) Figure 3 shows typical SFB measurements of friction between boundary layers of HA and of HA complexed with aggrecans—in both cases with the layers attached to mica. The data, plotted as the friction force F_s versus the normal load F_n, reveal that both kinds of layers lead to a sliding friction coefficient as much as two orders of magnitude higher than that in joints. Studies of the boundary friction on other macromolecules reveal similar results. Indeed, boundary layers of HA, aggrecans, lubricin, and other proteins found in joints all fail to reduce the friction to a level typical of healthy cartilage.[5,12–14] Moreover, the role of phospholipids, widely present in joints and also thought to work as cartilage lubricants,[15] has long been unclear. What, then, underlies the remarkable lubrication of articular cartilage?

Watery shells around charges

The concept of hydration lubrication, a key finding outlined in the box on page 52, answers that question. The concept is based on so-called hydration shells, water molecules that cluster around a central positive charge or ion in aqueous media. Such shells are tenaciously bound to the enclosed charge because of the reduction in self-energy or, more precisely, the Born energy of the charge, provided by the dipoles of the water molecules oriented about it. Due to that strong binding, the hydration shells can withstand high pressures without a net loss of water molecules. And yet individual water molecules inside the shells can rapidly diffuse out while water molecules in the bulk diffuse in, a process that keeps the hydration shell fluid. That combination—resistance to normal forces

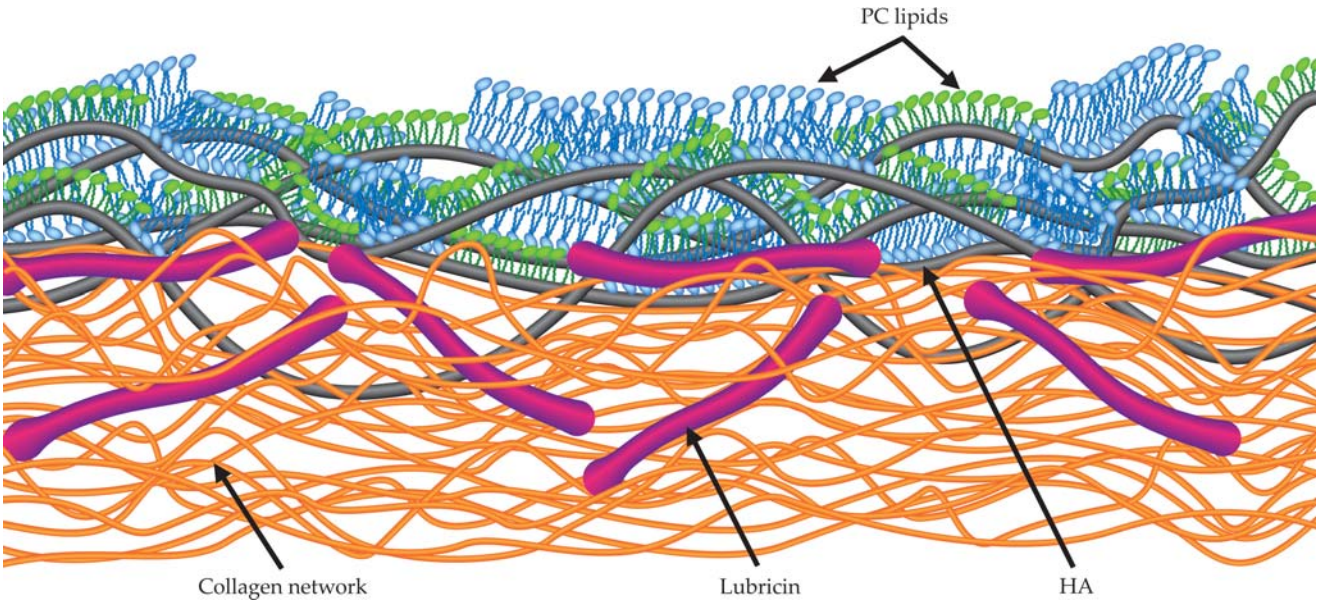


FIGURE 5. STRUCTURE OF A PROPOSED BOUNDARY LAYER at the articular cartilage surface. Lubricin molecules (red), known to reside in the outer superficial zone of cartilage and to be attached to its surface, interact with and immobilize hyaluronic acid molecules (HA, black) at the surface. Together, the HA and lubricin molecules form a complex with PC lipids whose outer exposed and highly hydrated phosphocholine head groups reduce friction via the hydration lubrication mechanism outlined in the box on page 52. (Adapted from ref. 2.)

while remaining fluid under shear—results in extremely effective lubrication.[16]

It turns out that the phosphocholine head groups of the most common phospholipids in our joints, the PCs, are extremely hydrated—that is, densely surrounded by hydration shells. Thus they constitute especially effective lubrication units. Boundary layers exposing close-packed arrays of such head groups—for example, the PC lipid bilayers forming vesicles known as liposomes—have sliding friction coefficients less than 10^{-4} at contact pressures of 10 MPa or more.[17]

Three years ago one of us (Klein) and postdoc Jasmine Seror led a project showing that HA molecules attached to a surface could interact with PC lipids to produce a boundary layer with nearly such low friction,[13] as shown in figure 4. The complexes form because of the charge-dipole attraction between the dipolar phosphocholine head groups and the negatively charged HA backbone. The results, and the known interaction of lubricin molecules with HA,[13,14] led us and our colleagues to propose that the lubricating boundary layer at articular cartilage surfaces consists broadly of all three main suspects: HA, PC lipids, and lubricin, each playing a different role.

Figure 5 illustrates that proposed boundary layer, its outermost lipids oriented such that their highly hydrated head groups point outward. When the layer slides against a similar boundary layer on the opposing cartilage surface, the interaction reduces frictional dissipation via hydration lubrication, as illustrated in the box.

Wear between sliding surfaces is inevitable, no matter how well they are lubricated. Thus it is essential that the cartilage boundary layers regenerate themselves. The regeneration is enabled by the fact that the layers' main components are pervasive in the outer cartilage region and in the synovial fluid bathing the joints. What's more, because the molecules' interactions are physical rather than chemical and likely due to charge–charge, charge–dipole, or van der Waals forces, their assembly is essentially spontaneous. The emerging picture of cartilage surfaces—as coated by molecular assemblies that expose continually regenerating layers of robust yet fluid hydration shells—suggests possible new treatments for alleviating osteoarthritis. To name one example, physicians could inject suitable PC lipid vesicles directly into the joint cavity (see figure 1a), where they may augment the cartilage boundary lubricating layer, reduce friction, and thus help to suppress cartilage degradation and osteoarthritis.

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REFERENCES

1. D. J. Hunter, D. Schofield, E. Callander, *Nat. Rev. Rheumatol.* **10**, 437 (2014).
2. S. Jahn, J. Seror, J. Klein, *Annu. Rev. Biomed. Eng.* **18**, 235 (2016).
3. E. L. Radin, D. A. Swann, P. A. Weisser, *Nature* **228**, 377 (1970).
4. A. R. C. Jones et al., *J. Orthop. Res.* **25**, 283 (2007).
5. T. A. Schmidt et al., *Arthritis Rheum.* **56**, 882 (2007).
6. M. K. Kosinska et al., *Arthritis Rheum.* **65**, 2323 (2013).
7. M. Jin et al., *Arch. Biochem. Biophys.* **395**, 41 (2001).
8. T. L. Vincent, *Curr. Opin. Pharmacol.* **13**, 449 (2013).
9. W. A. Hodge et al., *Proc. Natl. Acad. Sci. USA* **83**, 2879 (1986).
10. C. W. McCutchen, *Nature* **184**, 1284 (1959).
11. G. A. Ateshian, *J. Biomech. Eng.* **119**, 81 (1997).
12. D. P. Chang et al., *Soft Matter* **5**, 3438 (2009).
13. J. Seror et al., *Nat. Commun.* **6**, 6497 (2015).
14. S. Das et al., *Biomacromolecules* **14**, 1669 (2013).
15. B. A. Hills, B. D. Butler, *Ann. Rheum. Dis.* **43**, 641 (1984).
16. L. Ma et al., *Nat. Commun.* **6**, 6060 (2015).
17. R. Goldberg et al., *Adv. Mater.* **23**, 3517 (2011).

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