Up-conversion nanoparticles measure medium-sized forces in hard-to-reach places

Squeezing the tiny crystals can dramatically change their photophysics.

Caenorhabditis elegans, illustrated in figure 1, is a well-studied worm. Since the pioneering work of biologist Sydney Brenner in 1965, it's been featured in tens of thousands of research papers and has had connections to four Nobel Prizes. In Brenner's own Nobel lecture, in 2002, he called the organism "without doubt the fourth winner of the Nobel Prize this year . . . but, of course, it will not be able to share the monetary award."

A big part of *C. elegans*'s appeal is that it occupies a useful middle ground between small and large: It's simple enough to study thoroughly but sufficiently complex to have salient features in common with humans. It's a millimeter long and comprises less than a thousand cells, but it contains differentiated organ systems, including muscle, a digestive tract, and a central nervous system. Its rudimentary brain was the first of any organism to have all its connections mapped. And in its brief two- to three-week lifespan, it experiences age-related muscle and neurological degeneration, often with striking biochemical similarity to the same phenomena in humans.

But something has been missing from the intermediate-scale measurements researchers can make: mechanical forces. Molecular tools exist for measuring the forces exerted by single proteins. And macroscale forces can be probed by piezoelectric transducers, among other technologies. Largely unmeasured is the in-between regime of forces exerted by several cells working together, whether to squeeze food through *C. elegans*'s digestive tract or to pump blood through human arteries.

Now two interdisciplinary research groups—one led by Jennifer Dionne at Stanford University[1] and the other by P. James Schuck at Columbia University[2]—have developed new force sensors for bridging that scale gap. The details of their implementations differ: Schuck's focus so far has been on dynamic range, whereas Dionne's has been on biocompatibility. But both groups used lanthanide-doped up-conversion nanoparticles (UCNPs), a versatile platform for optically probing inside living organisms. Indeed, Dionne and colleagues have already used their sensors to measure how hard *C. elegans* chomps on the bacteria it eats.

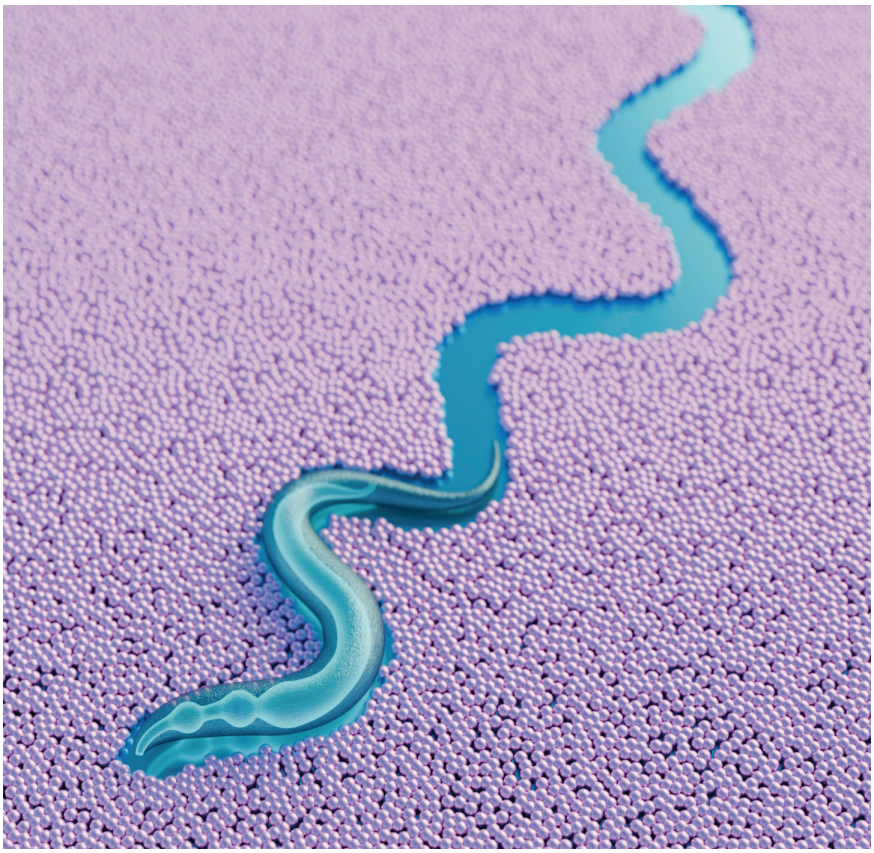

FIGURE 1. LOOKING FOR A MEAL, *Caenorhabditis elegans* slithers through a field of what, for all it can tell, are nutrient-rich bacteria. But actually, they're polystyrene spheres embedded with force-sensitive nanoparticles. Tricking the millimeter-long worm into eating the micron-size pressure gauges is the first step toward measuring the forces exerted in its pharynx—the region from the front of the worm to the back of the second bulbous structure, where *C. elegans* crushes up its food—and other parts of its digestive tract. (Image courtesy of Jason Casar.)

Up with up-conversion

UCNPs turn low-frequency light into high-frequency light. That by itself is not so unusual: Many nonlinear optical materials can do the same. One of the things that makes UCNPs so special is that their excitation wavelength, in the near-IR, is one where biological tissues are nearly transparent. Another is that they can perform the conversion efficiently even when the input light is relatively dim.

Typically, for a nonlinear optical material to convert two low-energy photons into one higher-energy one, it needs to absorb those photons at almost exactly the same time. The probability of that happening is low and scales with the

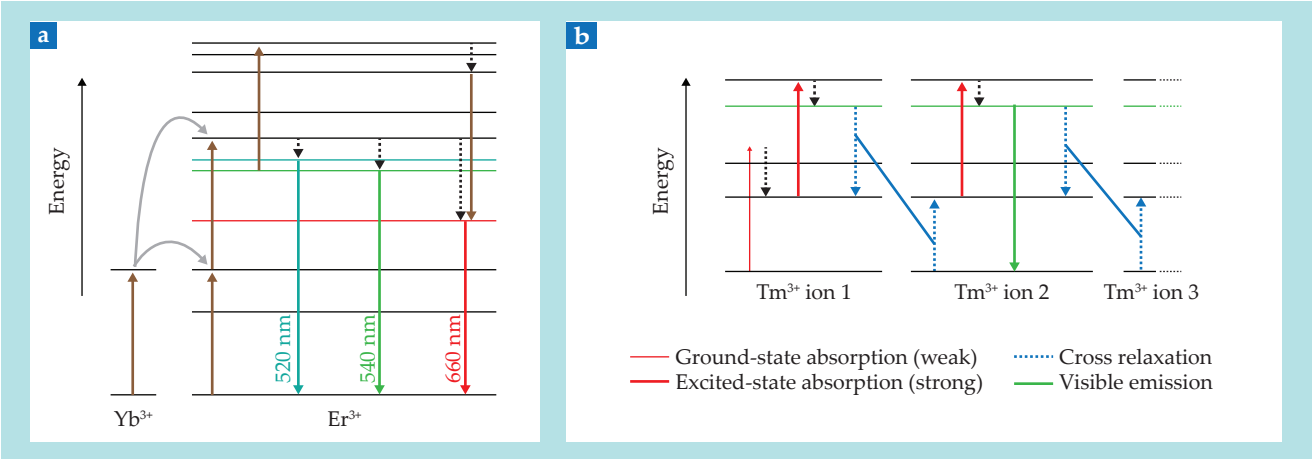

FIGURE 2. MECHANISMS OF UP-CONVERSION. (a) In a nanoparticle doped with ytterbium and erbium, Yb^{3+} ions absorb near-IR photons and transfer their energy to nearby Er^{3+} ions. Through a complicated network of photophysical pathways—sensitive to pressure, as it turns out—the Er^{3+} ions emit a combination of green and red photons. (Panel adapted from ref. 3.) **(b)** In a thulium-doped nanoparticle, one Tm^{3+} ion absorbs two photons and then shares part of its energy with a second ion. If the conditions are right for the absorption and sharing to continue—again, a pressure-sensitive matter—the excitations spread exponentially across the nanoparticle, until all the excited Tm^{3+} ions emit visible photons. (Panel adapted from ref. 4.)

square of the illumination power. That's why, for example, nonlinear operations had been considered prohibitively difficult for low-power optical computing (see Physics Today, October 2024, page 12).

But ions of the lanthanides—elements 57 through 71, usually depicted as the upper of the two rows floating below the body of the periodic table—have excited electron states with rather long lifetimes: milliseconds, rather than picoseconds. So a lanthanide ion in a crystalline matrix can absorb one photon, linger for a while in its excited state, and then catch a second photon that arrives later. It can also use its excited-state dwell time to transfer energy to another lanthanide ion with a different spectrum of excited states. From a single input wavelength, lanthanide-doped UCNPs can produce a rich and tunable array of output colors, depending on how they're designed. (For more on the design and application of UCNPs, see the article by Marco Bettinelli, Luís Carlos, and Xiaogang Liu, Physics Today, September 2015, page 38.)

What does any of that have to do with measuring forces? The mechanism of mechanosensitivity is complicated—and not always completely understood—but the key aspect of it seems to be the lanthanide–lanthanide energy transfer. Squeezing a lanthanide-doped UCNP brings its dopant ions closer together and alters the spectrum of vibrational modes that ions use to couple to one another. So a nanoparticle under pressure, both research groups reasoned, could display a significantly different pattern of optical emission than an uncompressed particle. And they were right.

Belly of the beast

Dionne and colleagues, including biologist Miriam Goodman and Dionne's student Jason Casar, used a tried-and-true UCNP formulation based on erbium and ytterbium. As sketched in figure 2a, the Yb^{3+} ions absorb near-IR light and transfer energy to Er^{3+} ions, which emit some combination of red and green photons, depending on the conditions.

Those conditions, as Dionne and colleagues showed in 2017, include mechanical force: Compressed particles emit more red, whereas uncompressed particles emit more green.[3] In the years since then, they've been working out the details in preparation for biological experiments. What other factors influence the up-conversion output, and how could they calibrate the sensors to account for those? How could they coat the particles to make them nontoxic to living organisms, and would that coating also affect the calibration? How could they get the particles into the target region of the organism to begin with?

That last part required a *C. elegans*–specific solution. The worm eats bacteria, which it recognizes by their size: Anything smaller than 200 nm gets filtered out before it reaches the digestive tract, and the nanoparticles are an order of magnitude smaller than that. So the researchers embedded the nanoparticles in micron-sized lumps of polystyrene, the same size as bacteria. And the worms ate them up.

Chain reaction

Meanwhile, Schuck and colleagues, including chemist Emory Chan, biologist Bruce Cohen, and Schuck's postdoc Natalie Fardian-Melamed, were exploring a different up-conversion mechanism, illustrated in figure 2b: the photon avalanche.[4] The name is a slight misnomer because the avalanche builds on itself inside the nanoparticle before the photons ever come out.

The researchers used nanoparticles doped only with thulium, chosen because the coupling between its ground and first excited states is especially weak when the particles are illuminated with near-IR light. The Tm^{3+} ion struggles to absorb its first photon, but once it does, it absorbs a second one easily. Moreover, once it's absorbed two quanta of energy, it can share one of them with another Tm^{3+} ion—so two dopant ions get promoted to the first excited state for the price of just one sluggish ground-state absorption.

From there, the avalanche grows—two become four, four become eight, and so on—but only if the excited ions keep absorbing and sharing photons faster than they can relax back to the ground state. Typically, the photon avalanche

manifests as an extremely nonlinear dependence on the power of the excitation laser: Below a threshold brightness, there's no avalanche and little up-conversion; above it, the avalanche switches on and the particle lights up.

But what if the avalanche depends on more than just laser power? "This is a chain reaction that spreads over 30 different levels before photons come out," says Schuck. "If the particles are even slightly sensitive to anything in the environment that changes how energy is transferred, that gets raised to the 30th power. So it's potentially very sensitive."

The researchers hypothesized that the photon avalanche would be sensitive to force, but they weren't sure how sensitive until they probed the nanoparticles with an atomic force microscope (AFM), whose pointy cantilever acts like a finger to feel the contours of a surface. "Just with the AFM tip tapping on the particles, their emission changed drastically," says Schuck. "It was such a big change that we almost didn't believe it at first."

In general, tapping on the photon-avalanching particles made their emission dimmer. But when particles were carefully crafted with a Tm^{3+} concentration just below the threshold needed for a photon avalanche, mechanical force could squeeze the ions closer together, initiate the avalanche, and make the emission much brighter. Through the combination of the two phenomena, the nanoparticles respond to forces over four orders of magnitude: from hundreds of piconewtons to several micronewtons.

Powerful bite

Dionne and colleagues' work has so far focused on the high end of the force range. When they fed their polystyrene-wrapped nanoparticles to *C. elegans*, they found that the particles experienced forces of around 10 μN in the worm's pharynx, the first part of its digestive tract. That may sound like a small number, but it's equivalent to a pressure of 80 MPa—the same pressure felt by a 1 cm cube under the weight of a large male polar bear. The human bite, in contrast, exerts just over 1 MPa of pressure.

The proof-of-concept measurement shows that UCNPs work for measuring forces *in vivo*. But at the same time, as Goodman points out, "The thing we chose to measure was completely unknown. We knew that *C. elegans* gets nutrition from bacteria, but we didn't know how hard it needed to chew, and now we do."

And it's not just an isolated measurement. Like humans, *C. elegans* grows frailer with age, and the weakening muscles in its pharynx have been studied as a model for such human conditions as muscular dystrophy and cardiac disease. The goal is to screen potential drugs: If some chemical compound can restore lost function in *C. elegans*, it might do the same in humans. Previously, researchers measured electrical signals as a proxy for muscle strength, but the UCNPs make it possible to measure the muscle forces directly. "This paper is the capstone of our work in many ways," says Dionne, "but in other ways, it's just the beginning."

Schuck and colleagues also have their sights on biophysical measurements, including the force involved in embryo development. It's known that mechanical forces help to govern how tissues grow (see Physics Today, April 2007, page 20). But so far, researchers have largely been limited to inferring 3D force patterns from optical images of the cells on the surface. "They don't have great ways of looking inside," says Schuck. "But these pressure sensors can do that."

Beyond biology, Schuck is also working with roboticists to see if an array of nanoparticles could be the basis for a touch-sensitive robot fingertip. The forces would be measured optically, so Schuck envisions that the fingertips would also contain tiny LEDs to excite the nanoparticles and cameras to record their output. That is, for future robots, touch may be a second sight.

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References

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Water's hydrogen bonds are seen like never before

With a new spectroscopy approach, researchers observed how charge redistributes through hydrogen bonds when water becomes acidic or basic.

Liquid water has a dynamic atomic-scale structure, which gives rise to many of the unique properties of water, such as its extraordinarily high boiling and freezing points. Water's hydrogen bonding—the interaction that attracts a hydrogen atom on one molecule to an oxygen atom on another—facilitates the transfer of a small amount of electric charge, about one-fiftieth that of a single electron, between molecules.

No two molecules have identical sets of hydrogen bonds, because each hydrogen bond affects the formation of others on the same molecule and beyond (see figure 1). The behavior yields a complex network of hydrogen bonds that are constantly forming and breaking on time scales of a millionth of a millionth of a second. Hydrogen bonds are complicated further by nuclear quantum effects (NQEs)—the position of a hydrogen atom, because of its low mass, is delocalized. Computations predict that NQEs can weaken hydrogen bonds.[1]

What is known about hydrogen bonds in liquid water comes predominantly from molecular dynamics simulations. Because the bonds carry a small amount of delocalized charge, which is transferred when the bonds are broken or formed, changes in pH could affect charge transfer in liquid water.[2] Theorists have proposed that in a cluster of three water molecules, excess protons decrease or hydroxide ions increase the amount of electronic charge that is shifted across the hydrogen-bond network. NQEs should also affect charge transfer, but that possibility has not been well observed.

The lack of experimental data on charge transfer and NQEs is caused by the structural complexity of water and