PHYSICS TODAY

October 2019 • volume 72, number 10

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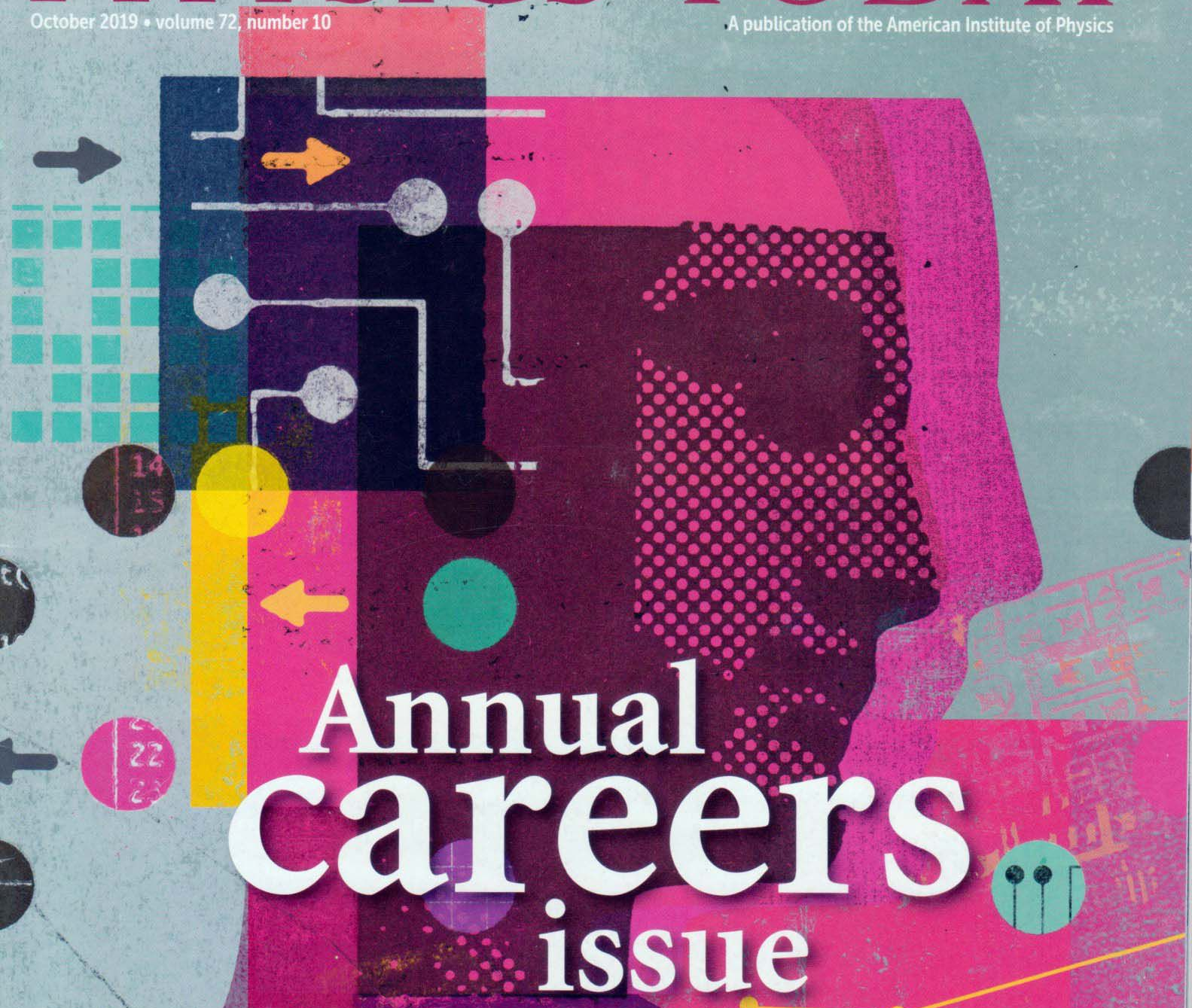

Annual careers issue

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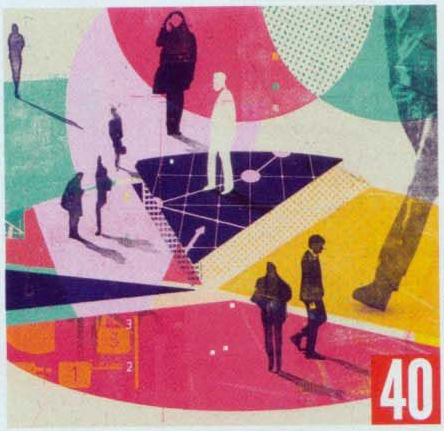
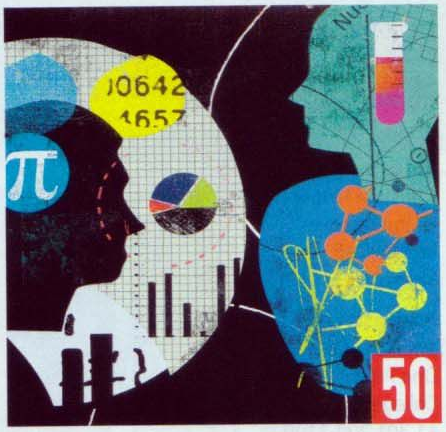
The paths from PhD to job





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Careers issue

ON THE COVER: Our first annual careers issue focuses on three aspects of becoming and being a physicist: the paths that physical scientists pursue 10 years after obtaining their PhD, the case for including innovation and entrepreneurship in the undergraduate physics curriculum, and the efforts of a consortium of California colleges and universities to boost the number of women and underrepresented minorities in graduate school. Be sure also to turn to Elizabeth Frank's commentary on **page 10** and the news stories starting on **page 24**. (Image by Stuart Kinlough/Alamy Stock Photo.)

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Nobel season

The 2019 Nobel Prizes will be announced 7–14 October, and PHYSICS TODAY has them covered. Before the awards, explore an in-depth analysis of the pioneering physics papers that have garnered Nobel recognition. Then on 8 October, visit physicstoday.org for a full report on the newly announced physics laureates.

physicstoday.org/Oct2019a

MICHELLE MILNE

Fostering inclusivity

Nearly 75% of undergraduate women in physics experience sexual harassment, according to one study. Education in the classroom can help combat the problem. PHYSICS TODAY's Heather Hill profiles efforts by physics faculty at St Mary's College of Maryland to create a welcoming environment.

physicstoday.org/Oct2019b

OAK RIDGE NATIONAL LABORATORY

Element hunters

The addition of new elements to the periodic table garners much publicity. Yet the technicians who produce the ultrapure ingredients that are forged together are often overlooked and underappreciated. Claire Jarvis highlights the work that makes superheavy element production possible.

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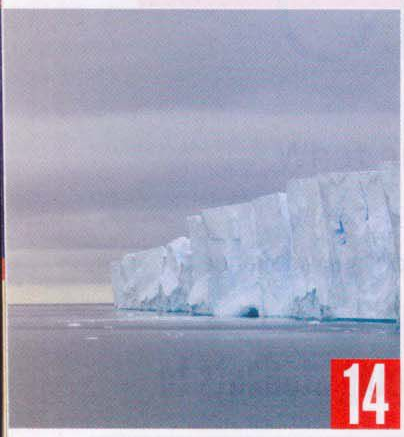

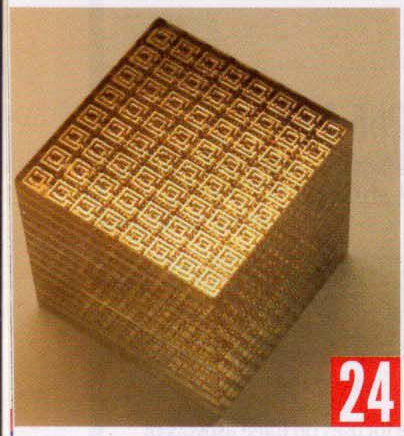

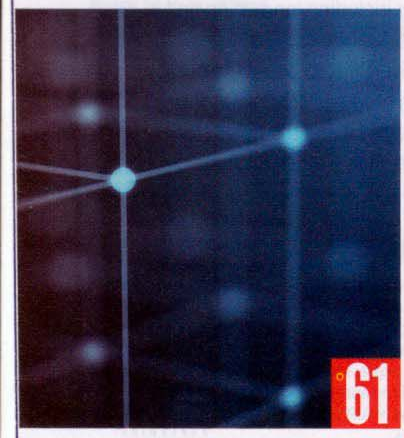

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Wind analysis links West Antarctic ice loss to humans

Anthropogenic warming is reversing the predominant winds over the region and could explain the ice sheet's destabilization.

The thinning of the West Antarctic Ice Sheet (WAIS) is contributing to global sea-level rise at a current rate of about 0.5 mm per year,[1] and the situation will probably only get worse (see PHYSICS TODAY, July 2014, page 10). Ice from Pine Island Glacier (see figure 1), the Thwaites Glacier, and others drain the WAIS into the sea. The glaciers melt more quickly than usual if winds diverted eastward by human activity drive warmer circumpolar water onto the continental shelf and underneath the floating ice.

Given rising greenhouse gas concentrations, that chain of events could already be under way. Average global temperatures have risen by about 0.8 °C since 1880. In the Arctic, warm air temperatures are directly responsible for the increased melting of glaciers. But for West Antarctica, determining the rate of ice loss is difficult because of episodic fluctuations. The region's climate swings between warm and cold cycles. The air pressure at sea level over the Amundsen varies more than any other place in the Southern Hemisphere.[2] And over a 10-year period, the amount of warm ocean water reaching the glacier there can fluctuate by about 50%.

The natural climate variability in the Amundsen Sea stems from year-to-year change associated with the tropical Pacific Ocean's El Niño–Southern Oscillation (ENSO; see the article by David Neelin and Mojib Latif, PHYSICS TODAY, December 1998, page 32). When tropical sea-surface temperature anomalies alter the prevailing wind patterns, the winds around West Antarctica also change. Records lack enough years of data to clearly separate how natural variability and human activity cause West Antarctic winds to change and consequently increase the rate of ice loss.

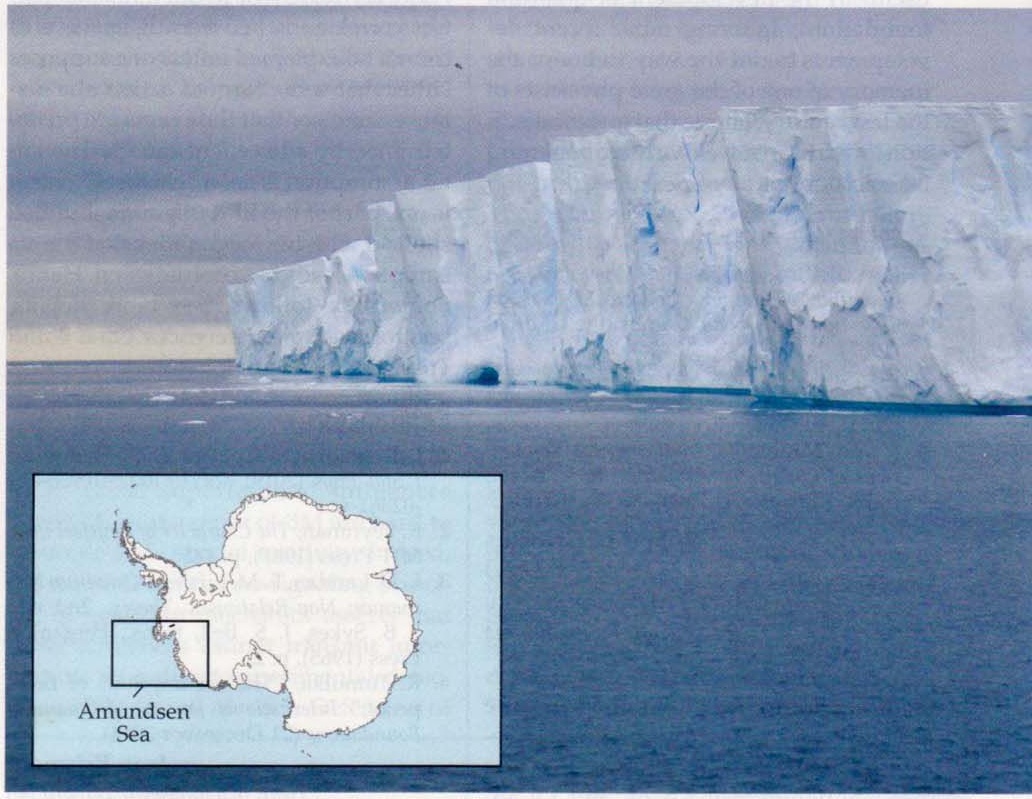

FIGURE 1. PINE ISLAND GLACIER, at the edge of the Amundsen Sea in West Antarctica, shown in the inset. More eastward winds caused by human activity drive warm, circumpolar water onto the continental shelf, where the underside of the glacier can become destabilized, lose mass, and accelerate sea-level rise. (Photo by Pierre Dutrieux; inset by Polargeo/Wikimedia Commons.)

Now Paul Holland of the British Antarctic Survey and his colleagues have disentangled the causes and established a clear connection between WAIS loss and human-induced climate change.[3] The researchers combined satellite-derived data and model simulations so they could study trends over the 20th century. Their analysis indicates that an anthropogenic reversal in the direction of local winds is accelerating the ice-loss rate of the WAIS.

Tropical data mining

On-the-ground climate data around the Amundsen Sea are limited. "It was in the early 1990s that serious observations really began," says Eric Steig, a glaciologist and geochemist at the University of Washington and a coauthor of the new paper. "And that is not a very long time in terms of climate change." The available wind data over the Amundsen Sea came from an analysis by the European Centre for Medium-Range Weather Forecasts, which uses a meteorological model to blend satellite observations from 1979 to the present.

To extend the wind record back before the satellite era, Holland and his colleagues took advantage of a climate connection between West Antarctica and the tropical Pacific Ocean. Water-temperature data have been collected by ships since at least the mid 19th century, with relatively reliable coverage and frequency starting in the early 20th century.[4] Wind speed over West Antarctica is significantly correlated with tropical Pacific sea-surface temperature because ENSO brings tropical wind patterns to the poles by atmospheric Rossby waves.

Climate models can use the connection to fill in the gaps where past wind observations are lacking. At the National

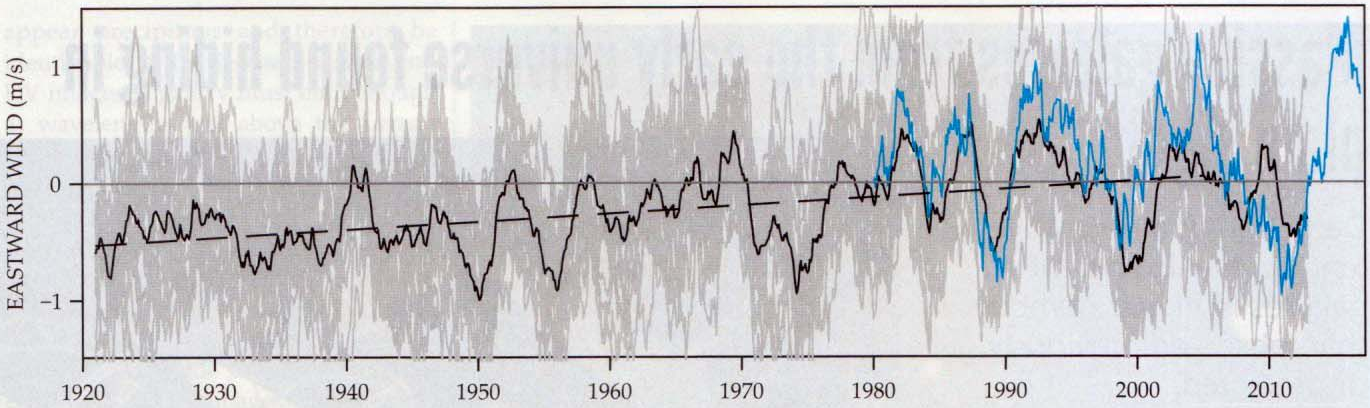

FIGURE 2. A REVERSAL OF THE PREDOMINANT WINDS over the Amundsen Sea may be thinning the West Antarctic Ice Sheet. The average winds (black solid line) of 20 climate simulations (gray) from the Community Earth System Model agree with observed winds (blue solid line) obtained from an analysis by the European Centre for Medium-Range Weather Forecasts. The trend (dashed black line) of 0.7 m/s over much of the 20th century shows that the winds changed from westward-flowing (negative values) to predominantly eastward-flowing (positive values). Rising greenhouse gas concentrations contributed 0.5 m/s to the eastward winds. (Adapted from ref. 3.)

Center for Atmospheric Research (NCAR) in Boulder, Colorado, the Community Earth System Model (CESM) incorporates historical ocean data to simulate the wind speed and direction back to 1920. There's nothing specific to how the CESM physically models the atmosphere, land, and ocean that makes it more accurate at simulating Antarctic climate than other models. Researchers have run the CESM repeatedly to more clearly separate human activity from natural variability in West Antarctica.[5]

"I've been trying to think of a way of writing this paper," says Holland, and the CESM was the tool he needed. The first 20 simulations Holland and his colleagues analyzed were constrained by the historical tropical Pacific sea-surface temperature data. Using the same data for each simulation means that the average of those 20 runs is reflective of both natural and human climate variability.

Which way the wind blows

The results of the 20 simulations, plotted in figure 2, show the strong decadal variability in the simulated wind speed and the observations. The simulations' average speed increased at a rate of 0.7 m/s per century. That change corresponds to a decrease in westward winds and an increase in eastward winds over the 20th century. The reversal in direction brings more warm water to the glaciers and consequently more WAIS ice loss.

To separate the long-term anthropogenic trend from the noisy natural variability in the time series, Holland and his colleagues analyzed a second set of 40 simulations that was not constrained by the historical sea-surface temperature data.[6] In those runs, the average only indicates the anthropogenic warming because the natural variability is random and cancels out.

Holland and his colleagues determined that the once-predominant westward winds have weakened by about 0.5 m/s over the past 100 years because of human activity. "Many studies have hypothesized that a link might exist" between anthropogenic climate change and the winds around West Antarctica, says Nerilie Abram of the Australian National University. "This study now clearly demonstrates the link."

The magnitude of the anthropogenic effect is about the same as the natural variability of the winds, estimated by the spread in the simulations. The result underscores the necessity of the model simulations. Observations alone didn't cover enough time, and measurements of winds and ice loss will continue to be strongly influenced by natural variability from the tropical Pacific for decades to come. Humans are changing the climate in West Antarctica to be sure, but until now the natural variability has been large enough to obscure the signal.

The not-so-distant future

Now that there's clear evidence that eastward winds in West Antarctica have increased, Holland wants to better understand how the Amundsen Sea responds to the atmosphere on a longer time scale. Using an ocean model that precisely simulates the dynamics of each ocean layer in the region, he is exploring what happens to the flows when they are forced by the eastward winds simulated in the CESM. Once the observed rate of ice loss is reproduced, he can test whether the same atmosphere–ocean processes that operate on decadal time scales also apply to centennial time scales.

Knowledge of the processes that control ice loss on decadal and longer time scales can inform future climate change forecasts. Holland and his colleagues suggest that if humans continue to increase carbon dioxide emissions in a business-as-usual scenario, the Antarctic wind trend they found for the 20th century will continue into the 21st century.

However, the worst effects of climate change may be averted if such a trend can be avoided. In a 21st-century scenario in which greenhouse gas emissions are rapidly reduced, the Antarctic winds stabilize to the present-day state. "Reversing the change," says Holland, "is a much bigger challenge."

Alex Lopatka

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Massive galaxies from the early universe found hiding in plain sight

Detection at a new wavelength reveals ancient galaxies in higher numbers than observed previously or predicted.

FIGURE 1. ANTENNAS FROM THE ATACAMA LARGE MILLIMETER/SUBMILLIMETER ARRAY are on an elevated desert plateau ideal for measuring wavelengths from the far-IR to radio. The 66 antennas can cluster together for higher-sensitivity measurements or spread over tens of kilometers to zoom in on details. (Courtesy of W. Garnier/ALMA/ESO/NAOJ/NRAO.)

Opened in 2012, the Atacama Large Millimeter/Submillimeter Array (ALMA), shown in figure 1, measures the portion of the spectrum straddling the boundary between radio and IR—a range which is easily absorbed by water in Earth's atmosphere. The array's location is ideal. Not only is Chile's Atacama Desert the driest place on Earth (excluding the poles) but it also has a wide plateau whose 5000 m elevation reduces absorption by water vapor and whose flatness allows the array's 66 large antennas to be easily moved around and reconfigured. ALMA researchers have published numerous results in the intervening seven years (see, for example, PHYSICS TODAY, December 2016, page 22). The array is also part of the network of facilities that make up the Event Horizon Telescope, which recently captured the first image of a black hole (see "What it took to capture a black hole," PHYSICS TODAY online, 11 April 2019).

Now Tao Wang of the University of Tokyo and his colleagues have used ALMA to find a missing link in the story of galaxy formation.[1] Before he and his team made their discovery, the low number of massive galaxies, with masses above 10^{10} solar masses, observed from the first 2 billion years after the Big Bang could not account for the significantly higher number observed from the next billion years. ALMA's wavelength range is perfect for finding those ancient massive galaxies not visible in previous measurements, and Wang and his team did just that.

Redshift your perspective

Because the universe is expanding, emitted radiation from galaxies redshifts to longer wavelengths the farther away it starts from Earth. A wave's journey to us takes time, so to observe a redshifted wave is to look into the past. Redshifts are determined by identifying an emission line in a galaxy's spectrum and measuring how far its peak wavelength, λ_{obs}, has shifted from its rest-frame value, λ_0. Redshift z is defined as $(\lambda_{obs} - \lambda_0)/\lambda_0$. Although spectral features broaden in their long journey across the universe, the redshift is still identifiable. Radiation with $z = 3$ was emitted when the universe was 2 billion years old.

In its rest frame, a galaxy's visible-to-UV emission spectrum drops off suddenly for wavelengths shorter than 912 Å. Light with shorter wavelengths than that limit ionizes hydrogen gas in and around the galaxy before it escapes. As the radiation gets redshifted, the sudden break in the spectrum shifts to higher wavelengths—even into the UV range measurable from Earth. Astronomers identify high-redshift galaxies, with $z > 3$, by filtering the emission and comparing its higher signal in the visible range with its much lower signal in the UV. Galaxies discovered using that method are known as Lyman-break galaxies (LBGs).

Previous measurements performed with the *Hubble Space Telescope* and at Las Campanas Observatory in Chile found many massive galaxies with redshifts z of 2–3, which existed 2 to 3 billion years after the Big Bang.[2] But far fewer have been found from earlier stages in the universe's evolution, with $z > 3$. Those found thus far either are LBGs with much smaller stellar populations than later galaxies or are extreme starburst galaxies, which have high star-formation rates and are brighter than a typical massive galaxy. Together they are too small or too few to have made all the galaxies seen with a z of 2–3.

The Lyman-break selection method overlooks some galaxies. For the break to

appear precipitous and therefore be identifiable in Earth-based visible and UV images, a galaxy must emit enough at wavelengths just above the Lyman break. That condition is unlikely to be met by massive galaxies because the surrounding dust dims the outgoing emission or because their stars are older and emit less right above the break to begin with. Detectors that have higher sensitivity and are able to measure into the mid- and far-IR provide a higher signal to compare with UV images. But the exact wavelength ranges one compares are important. Galaxies at lower redshifts can mimic those with higher redshifts if their spectrum is pushed to a redder color by attenuation from high levels of dust or is intrinsically redder because it comes from an active galactic nucleus rather than stars.

Hiding in plain sight

A few years ago, Wang and his team hunted for those missing massive galaxies in the mid-IR.[3] They found a specific combination of filters capable both of finding galaxies too faint for Lyman-break selection and of distinguishing between older galaxies and younger mimics. Using the *Spitzer Space Telescope*'s Infrared Array Camera, they captured an image at 4.5 μm, which they subtracted from existing *Hubble Space Telescope* measurements in the near-IR. A difference in the intensity above a certain threshold indicated the location of a potential galaxy in the distant universe. Through that method, Wang and company identified 63 potential ancient massive galaxies not found using *Hubble*'s measurements alone.

But the galaxies are still very faint at 4.5 μm, and measurements with better spatial resolution and at multiple wavelengths would reveal more about their properties. The researchers knew they needed a facility such as ALMA, with detection in the far-IR. Taken in the summer of 2016, their ALMA images resolved the galaxies and confirmed that 39 of the previously identified objects are

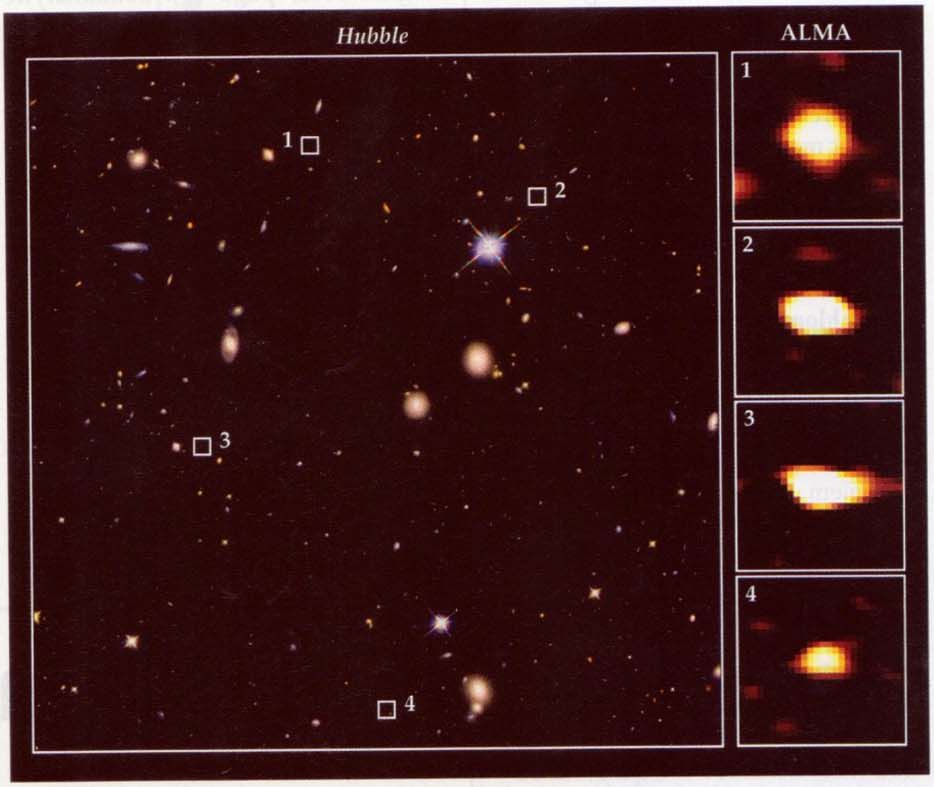

FIGURE 2. ANCIENT MASSIVE GALAXIES visible with the Atacama Large Millimeter/Submillimeter Array (right) in the far-IR are invisible to the *Hubble Space Telescope* (left). (Courtesy of Tao Wang.)

star-forming massive galaxies invisible in the *Hubble* images: Four are shown in figure 2. "While we did expect that many of these galaxies would be at high redshift, the high detection rate with ALMA is still surprising," says Wang.

Once older massive galaxies are identified, there's still the question of figuring out their exact redshift. It's much harder to measure a full spectrum, so many observatories stick with radiation that is detected through a broad filter and not spectrally resolved. Such a measurement gives just one number—the intensity—rather than the individual spectral lines necessary to calculate the redshift. Instead, the data need to be fitted with an expected spectral energy distribution to find what is called the photometric redshift, which has a larger uncertainty than redshifts found from spectroscopy.

Corentin Schreiber of Oxford University in the UK was in charge of figuring out the redshift in the team's ALMA measurements—a tricky task because most photometric methods use measurements in the UV to visible rather than in the far-IR. By combining different photometric methods and cross-correlation with galaxies known to be of the same age, Schreiber found that the median redshift was $z = 4$, corresponding to radiation emitted about 1.5 billion years after the Big Bang.

The galaxies are faint, below the detection limit of a single antenna, and massive, with most in the range from 10^{10} to 10^{11} solar masses, an order of magnitude larger than the average LBG. The shape of their spectral energy distribution indicates the rate at which they produce stars, and on average they churn out 200 solar masses' worth of stars per year—that's about 10% of the rate previously

found for LBGs and starburst galaxies of the same age but one to two orders of magnitude higher than LBGs of similar masses. Their star-formation rate coupled with their densities of 2×10^{-5} galaxies per cubic megaparsec, two orders of magnitude higher than starbursts', mean the new galaxies are responsible for the majority of the stars produced by massive galaxies in the early universe.

The problem for theorists

Although the newly found ancient galaxies help explain the presence experimentally of so many, and such large, massive galaxies at lower redshifts, they present a problem for most galaxy-formation theories (see the article by Jeremiah Ostriker and Thorsten Naab, PHYSICS TODAY, August 2012, page 43). Semianalytic models—those that tune simple phenomenological descriptions of astrophysical processes to match the abundance, clustering, redshift, and other observed properties of the galaxy population—underestimate the density of massive galaxies in the early universe by one to two orders of magnitude. And hydrodynamic simulations of galaxy merger rates predict no massive galaxies at all. Although previously observed LBGs and starburst galaxies already challenged those theories, the abundance and star-formation rates of the new galaxies render the disagreements harder to ignore.

"More and more observations show that a large population of massive galaxies and supermassive black holes has already been established in the young universe," says Wang. "In general, the young universe is more efficient in forming big things than we thought." To reconcile theory with observations, astronomers will need more accurate redshift measurements and better characterization of the physical properties for a larger sample of galaxies so they can put more stringent constraints on galaxy-formation models.

Heather M. Hill

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A molecular clock for testing fundamental forces

The vibrational frequencies of trapped ultracold molecules can serve as a check on what we think we know about the universe.

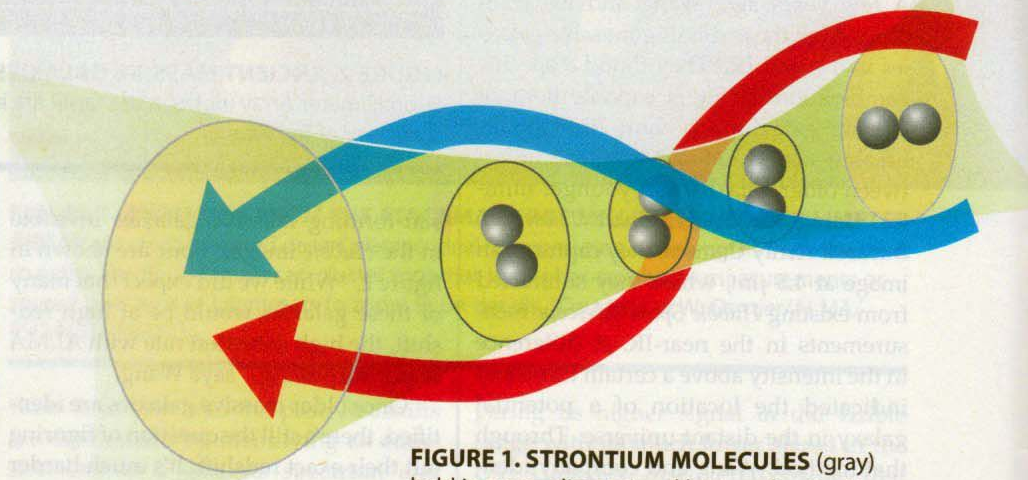

FIGURE 1. STRONTIUM MOLECULES (gray) held in a one-dimensional lattice of optical traps (yellow) are probed by a pair of Raman lasers (red and blue). Ultraprecise measurements of their vibrational frequencies reflect the fundamental forces acting on the nuclei and electrons.

Gravity over macroscopic distances is well understood. The simple inverse-square law, proposed centuries ago by Isaac Newton, continues to accurately describe the force at scales across the nonrelativistic regime, from laboratory-scale torsion balance experiments to the motions of stars and galaxies. It's been especially well tested at the scale of the distance from Earth to the Moon.

Short distances—microns or less—are another matter. In microscopic experiments, electromagnetic forces are so overwhelmingly dominant that the force of gravity at small scales has never been directly measured. All we have are upper bounds on its strength, some of which are astonishingly large. According to the best experimental constraint so far, the gravitational attraction between two objects 1 nm apart is no more than 10^{21} times what Newton's law says it is.[1]

It's not so outlandish to imagine that the force of gravity could follow the inverse-square law over large distances but deviate from it over small ones. Theories of extra dimensions through which only gravity can propagate, for example, allow just such a functional form. (See the article by Nima Arkani-Hamed, Savas Dimopoulos, and Georgi Dvali, PHYSICS TODAY, February 2002, page 35, and the Quick Study by Lisa Randall, PHYSICS TODAY, July 2007, page 80.) To help test and constrain those theories, experimenters have been working for decades to chip away at the possible parameter space of short-range non-Newtonian gravity. Their techniques include measurements of the Casimir force (see the Quick Study by Jeremy Munday on page 74 of this issue) and neutron scattering off atomic nuclei.

Now Columbia University's Tanya Zelevinsky and colleagues are adding a new experimental method to the mix with their ultraprecise measurements of molecular vibrations.[2] Because their experiment, shown schematically in figure 1, is similar to that of an atomic optical-lattice clock (see PHYSICS TODAY, March 2014, page 12), they call it a molecular lattice clock, even though precision timekeeping isn't among their immediate goals. Although theoretical details remain to be worked out, the researchers estimate that with their current experimental ca-

pabilities—measuring a 25 THz vibrational resonance to within just 1 Hz—they'll be able to constrain predictions of nanometer-scale gravity to within 10^{18}–10^{19} of its Newtonian value.

Cold-molecule spectroscopy

Relative to atoms, molecules are complicated. Not only can their electrons be excited into more energetic states, but their vibrations and rotations are also quantized. The resulting hierarchy of quantum levels lends itself to probing many aspects of fundamental physics (see the article by Dave DeMille, PHYSICS TODAY, December 2015, page 34). But it also makes molecules hard to control. Whereas it's straightforward to optically cool atoms to a fraction of a kelvin, doing the same for molecules means keeping track of a vast tangle of states to make sure the cooling lasers aren't inadvertently pumping energy into the molecules instead of pulling it out. (See PHYSICS TODAY, January 2010, page 9.)

Molecular-physics experiments don't always require ultracold samples; sometimes it suffices to use a molecular beam, in which collisions cool the molecules to a relatively balmy few kelvin. Zelevinsky and colleagues needed lower temperatures than that, though, so they used an established trick in the cold-molecule field. Rather than cooling the molecules directly, they first cooled a gas of atoms, then optically coaxed the atoms into diatomic bound states. (See the article by Debbie Jin and Jun Ye, PHYSICS TODAY, May 2011, page 27.)

That approach is limited to the elements compatible with cold-atom techniques, though, so their molecule—the strontium dimer, Sr_2—isn't one that's often found outside of cold-molecule experiments. It's held together not by a covalent bond but by the weaker van der Waals force, so it's an order of magnitude larger than a covalently bound molecule such as nitrogen or oxygen, and its binding energy and vibrational-level spacing are accordingly smaller. Otherwise, it behaves much like any other diatomic molecule.

To probe the energy difference between two vibrational states, shown in blue and orange in figure 2, the researchers use Raman spectroscopy, a two-photon process that connects the two states by way of a higher-energy virtual state. The difference between the Raman laser frequencies can be stabilized to better than 0.1 Hz. The technique's precision is thus limited by molecular, not optical, effects.

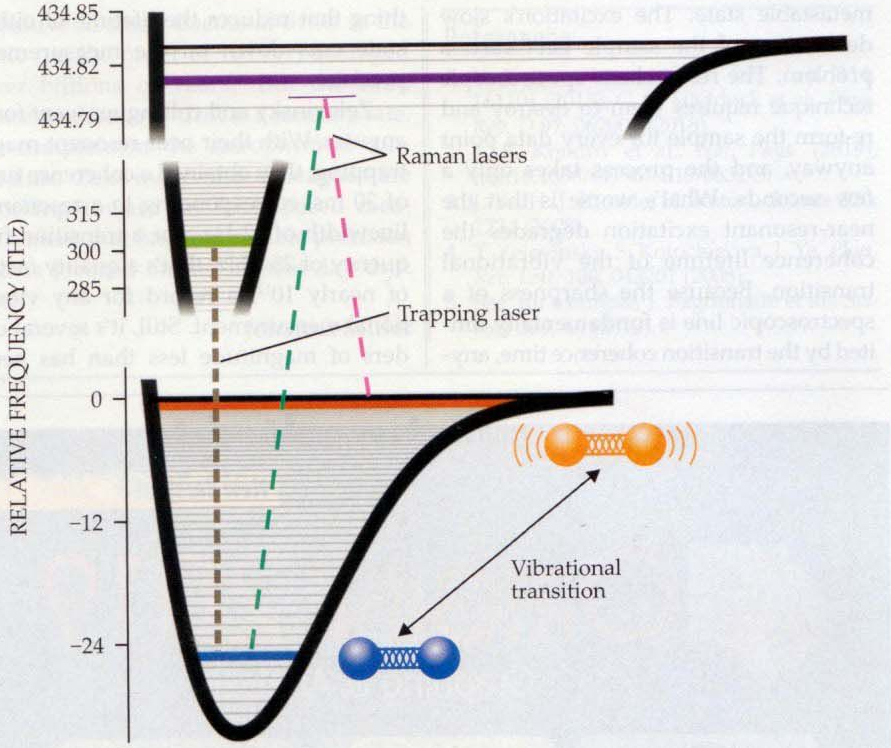

FIGURE 2. IN THE HIERARCHY OF MOLECULAR QUANTUM STATES, each electronic state (thick black curves) contains a series of vibrational levels (horizontal lines). To probe the frequency of the vibrational transition between the levels marked in blue and orange, Tanya Zelevinsky and colleagues use a pair of Raman lasers that drive the transition by way of a higher-energy virtual state (thin purple line). To eliminate both Doppler broadening and AC Stark shifts, they optically trap the molecules at a so-called magic frequency that's nearly resonant with yet another excited state (green solid line). (Adapted from ref. 2.)

Magic trapping

One potential source of uncertainty comes from Doppler broadening. Molecules moving toward or away from the source of the Raman lasers are excited at slightly different frequencies. Cooling slows their relative motion, but even at 2 μK, the molecules move enough to broaden the resonance by 30 kHz. So the researchers confine the molecules to a one-dimensional optical lattice formed by the standing wave of a near-IR trapping laser, shown in yellow in figure 1.

Lattice trapping eliminates Doppler broadening, but it introduces its own problem. Through the AC Stark effect, the trapping laser field separately shifts each vibrational state's energy by an amount that depends on the state's frequency-dependent electric polarizability and the trapping light's intensity. Molecules in different parts of the lattice can have their transition energies shifted by different amounts, and the overall resonance can be broadened by tens or hundreds of kilohertz.

Fortunately, the cold-atom community had already worked out a solution: Set the trapping laser to a so-called magic frequency at which the two states have the same polarizability. The Stark shifts then cancel, and the transition frequency can be measured with high precision.[3]

It's not always possible to find a convenient magic frequency, especially for a pair of molecular vibrational states, whose polarizabilities tend to parallel each other without crossing. The exception is for frequencies close to a resonance between one of the states of interest and a higher-energy electronic state (shown in green in figure 2). Near-resonant fields make a molecule's polarizability fluctuate rapidly as a function of frequency, so crossing points become plentiful.

But near-resonant trapping is risky, because the trapping laser can slowly excite molecules out of the vibrational state of interest and into the higher-energy

metastable state. The excitation's slow destruction of the sample isn't such a problem: The researchers' spectroscopic technique requires them to destroy and re-form the sample for every data point anyway, and the process takes only a few seconds. What's worse is that the near-resonant excitation degrades the coherence lifetime of the vibrational transition. Because the sharpness of a spectroscopic line is fundamentally limited by the transition coherence time, anything that reduces the lifetime of either state cuts down on the measurement precision.

Zelevinsky and colleagues went for it anyway. With their near-resonant magic trapping, they obtained a coherence time of 30 ms, corresponding to a resonance linewidth of 32 Hz. For a transition frequency of 25 THz, that's a quality factor of nearly 10^{12}, a record for any vibrational measurement. Still, it's several orders of magnitude less than has been achieved in atomic measurements—where quality factors have reached 10^{16}—and less than Zelevinsky was hoping for. "We were surprised that the near-resonant trapping shortened the coherence time as much as it did," she says. "There's clearly something that's not very well understood, and we take it as our new challenge to figure it out." Because the molecules have so many excited states, there are many more near-resonant magic frequencies to explore that could perform better.

The hunt for new physics

A linewidth of 32 Hz doesn't mean that the measurement precision is limited to 32 Hz. Zelevinsky and colleagues estimate that with a reasonable integration time, they can find the center of the line to within 1 Hz. That's enough for them to start making meaningful measurements of fundamental forces. Strontium has several stable spin-0 isotopes that range in mass number from 84 to 88. Looking at each of them in turn should allow the researchers to isolate what observable effect, if any, gravitational mass has on interatomic forces.

Before they do those experiments, though, they want to have a good handle on all the other ways vibrational frequencies can depend on mass. Heavier nuclei have more inertia, so they respond more sluggishly to the forces of the surrounding atoms (see, for example, PHYSICS TODAY, September 2018, page 17). To help isolate the influence of gravity, the experimenters are working with theorist Robert Moszyński and colleagues at the University of Warsaw to calculate contributions to that isotope effect that are usually ignored, including the effects of relativity and coupling between nuclear and electronic motion.

Non-Newtonian gravity isn't the only fundamental-physics measurement the experimenters have in their sights. They're also interested in testing the stability of the proton–electron mass ratio over time.[4] The ratio could change if, for example, the strong nuclear force is not constant: The proton, unlike the electron, is not a fundamental particle, and its mass depends on how its constituent quarks interact. So far, there's been no sign of such a drift in the proton mass, but as Zelevinsky explains, "It's not strictly ruled out, and therefore scientists are actively looking for it, since there are many things

about the universe we know we don't understand."

If the proton–electron mass ratio does change, one natural place to look for it is in molecular vibrational frequencies, which straightforwardly depend on both bond stiffness (a consequence of the quantum mechanical behavior of electrons) and nuclear inertia. Most constraints to date have come from astrophysical spectra of distant galaxies, which are sensitive to small fractional drifts in the ratio (on the order of 10^{-16}/yr) averaged over billions of years.[5] But the ratio doesn't necessarily drift at a constant rate. To complement the astrophysical constraints, Zelevinsky and colleagues are working toward an Earth-based measurement that has comparable precision but is focused on the present-day drift rate.

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A folding protein gets caught in the act

Time-resolved NMR spectra paint a picture of structural transformation with millisecond resolution.

To transform from linear chains to three-dimensional structures, *in vivo* proteins somehow navigate tortuous free-energy landscapes. Their final configurations must be just right for them to function properly; protein misfolding is thought to underlie some allergies as well as neurodegenerative diseases such as Parkinson's and Alzheimer's.

X-ray crystallography and NMR are well-established methods for accessing the detailed structure of a protein's final folded configuration. Gathering dynamical information about the folding process itself requires real-time techniques such as fluorescence, circular dichroism, and hydrogen exchange; acquiring information that quickly, however, comes at the expense of structural detail. Molecular dynamics simulations are also a valuable tool for studying protein configurations (see PHYSICS TODAY, December 2013, page 13), but because of computational limitations they fail to capture either the complete atomistic detail of real proteins or the complete process of folding.

Now Jaekyun Jeon, Robert Tycko, and coworkers at the National Institutes of Health in Bethesda, Maryland, have introduced a new way to track a protein's folding.[1] Their experimental setup, shown in figure 1, can start and stop the folding process quickly enough to trap proteins in transitory configurations. With the help of a signal-enhancing NMR technique, the researchers generated 2D spectra to track the formation of helices and dimers by melittin, a protein found in bee venom.

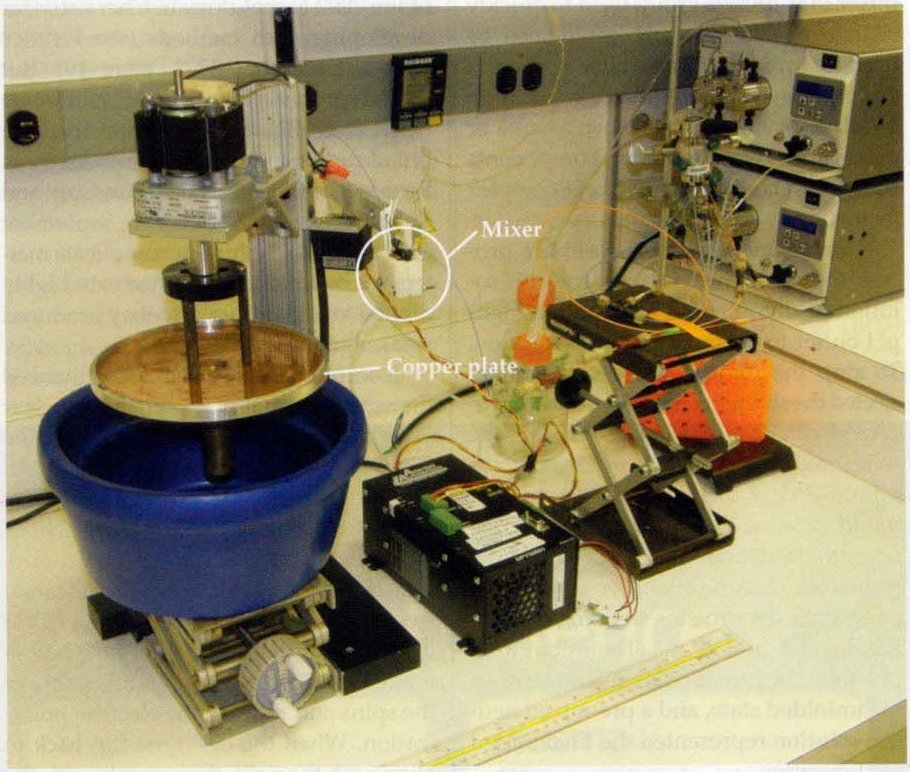

FIGURE 1. A RAPID-MIXING DEVICE starts and stops the protein-folding process with millisecond resolution. The mixer combines two pumped solutions, producing a high-velocity jet that freezes when it hits a liquid-nitrogen-cooled rotating copper plate. The frozen samples are subsequently analyzed using solid-state NMR. (Adapted from ref. 1.)

Their data, which have both high spatial and temporal resolution, challenge the previously accepted picture of melittin's structural development.

One moment in time

Melittin is a small protein—a peptide—with only 26 amino acids. At low pH, the peptides are linear chains, but in neutral to high pH, each peptide forms a bent helix. The helices form antiparallel dimers, which pair to make tetramers, melittin's native configuration.[2] The entire transition happens in less than 10 ms, so whether those steps happen concurrently or sequentially has been hard to discern.

Tycko's group developed a rapid mixer to change the solution's pH and initiate the protein-folding process. It mixes two solutions in just 1.6 ms—not quite instantaneous on the protein-folding time scale, but fast enough to capture a narrow spread of folding times. Although it's conceptually simple, the mixer is a critical part of their technique. "We've been working on these kinds of experiments

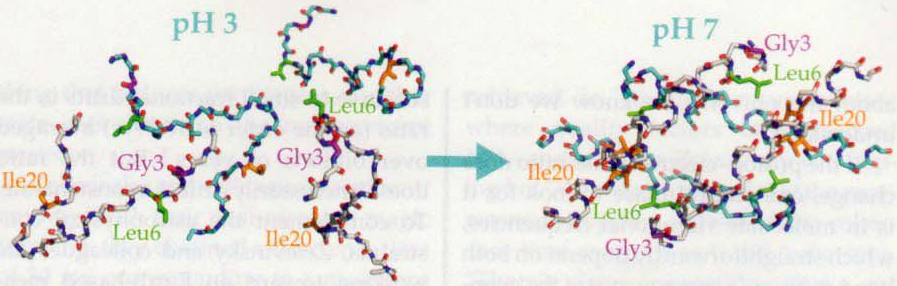

FIGURE 2. MELITTIN PEPTIDES FOLD AND UNFOLD in response to changing pH. At low pH they are extended chains (left), but at neutral to high pH they form ordered structures (right). Each chain forms a helix, the helices form antiparallel dimers, and the dimers pair into tetramers. The blue and white backbones indicate dimer pairs. Helix formation brings two labeled amino acids on a single peptide, glycine-3 (Gly3; purple) and leucine-6 (Leu6; green), closer together. When dimers form, the labeled isoleucine-20 (Ile20; orange) on one peptide gets close to the Leu6 on the other. (Adapted from ref. 1.)

for a while, and that was always one of our stumbling blocks," says Tycko. The microfluidic devices the researchers tried previously were expensive and had to be discarded when they inevitably became clogged. In addition to being inexpensive, their small homemade mixer, made from standard chromatography fittings, is reliable and can be easily disassembled and rebuilt if it becomes clogged. And, importantly, it yields reproducible results.

The device will likely be useful for a wide range of future experiments because rapid mixing is a versatile way to trigger protein structural changes. The same mixer that Tycko's group used to quickly change a solution's pH could also be used for rapid dilution to alter a protein's structure by changing the concentration of salt or of a denaturant such as urea or guanidine. Two interacting components could also be mixed to initiate complex formation.

To start melittin's self-assembly process, the researchers mixed a low-pH solution of unfolded melittin with a high-pH buffer to produce a neutral solution. To stop the folding process, the mixer ejected the solution onto a liquid-nitrogen-cooled rotating copper plate that froze the solution—and the protein's configuration—in less than 0.5 ms. The speed of the fluid leaving the mixer and the distance to the copper plate determined the protein's structural evolution time. In experiments, the proteins were frozen after 2.2, 4.6, 9.4, and 29 ms. The initial low-pH solution provided measurements of the unfolded state, and a pre-mixed neutral solution represented the final folded configuration.

The researchers used carbon-13 isotope labeling to track the locations of three amino acids on each peptide: glycine-3, leucine-6, and isoleucine-20. Helix formation in melittin brings Gly3 and Leu6 close together, and dimer formation brings Leu6 and Ile20 close together, as illustrated in figure 2. The proximities of those amino acids therefore served as proxies for structural developments.

Freeze frame

Once they had a time series of frozen protein configurations, the researchers still faced the challenge of extracting structural information from their samples. Using NMR to discern the structures of biological molecules is a tried-and-true technique; Kurt Wüthrich received half of the 2002 Nobel Prize in Chemistry for developing such methods (see PHYSICS TODAY, December 2002, page 19). But frozen proteins necessitate solid-state NMR (ssNMR), and those spectra have broad peaks compared with those from liquids (see the article by Clare Grey and Robert Tycko, PHYSICS TODAY, September 2009, page 44). To further complicate matters, the melittin solutions had to be highly diluted to fold properly, so they produced weak signals.

Jeon, Tycko, and coworkers enhanced the ssNMR signal with dynamic nuclear polarization. DNP takes advantage of the fact that electrons are much easier to polarize than nuclei; the gyromagnetic ratio of an electron is about 2500 times that of a carbon nucleus. The electrons are irradiated with microwaves at the resonant frequency of their precession—263 GHz in the 9.4 T field from the lab's homemade NMR setup—which flips some of the spins and reduces the electron polarization. When the electrons flip back to align with the field, they couple with the nuclear spins and, because they're preferentially flipping in one direction, increase the nuclear polarization.

DNP is not a new technique—the underlying nuclear Overhauser effect was postulated and experimentally demonstrated[3] in lithium metal in 1953. But, as Tycko explains, it has had a renaissance in the past 10–15 years because of its newfound utility in biologically relevant experiments and improvements in microwave sources.[4] Applying DNP to time-resolved ssNMR made detailed protein measurements feasible: Previous experiments without DNP could not follow the evolution of intermediate structures.[5] The researchers achieved adequate NMR spectra in less than eight hours, whereas without DNP the same measurements would have taken a month or longer.

Come together

Jeon, Tycko, and coworkers used 2D NMR to track the development of helices and dimers in the melittin samples. They used a pulse sequence that transferred nuclear spin polarization between ^{13}C atoms so that at the beginning of a measurement they observed the nuclear resonance from one atom, and at the end they observed that from another nearby atom. That's what gives the technique its two dimensions—polarization transferring from one nucleus to another. The nuclei in different locations resonate at different frequencies, so the signal shows up as an off-diagonal peak, or crosspeak, in a two-dimensional NMR spectrum. The NMR pulse sequence was tailored such that nuclear polarization transfer between atoms in the labeled amino acids happened only when they were close enough (see PHYSICS TODAY, October 2016, page 19). Because the labeled amino acids were chosen such that their proximity indicated helix and dimer formation, the amount of transfer between them grew as those structures developed.

Figure 3 shows the buildup of nuclear polarization transfer between the labeled amino acids, which is quantified by the crosspeak volume ratio. Growth of the Gly3–Leu6 crosspeak indicates helix formation; the Leu6–Ile20 crosspeak shows antiparallel dimer formation. Exponential fits to the data give buildup times of 8.7 ± 4.1 ms and 6.1 ± 2.8 ms, consistent with the two processes happening concurrently instead of sequentially. Helices in monomeric proteins typically form much faster than that, which suggests that for melittin, intermolecular interactions are necessary to stabilize the helical

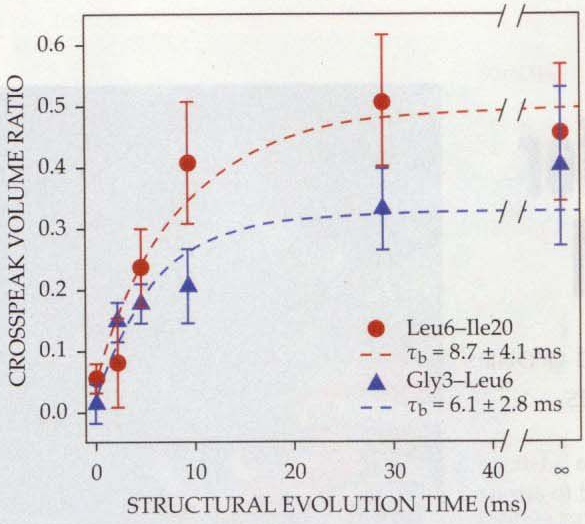

FIGURE 3. HELIX AND DIMER FORMATION increase the transfer of nuclear spin polarization between labeled amino acids glycine-3 (Gly3), leucine-6 (Leu6), and isoleucine-20 (Ile20); the polarization transfer is quantified by the crosspeak volume ratio. The Gly3–Leu6 crosspeak, which indicates helix formation, and the Leu6–Ile20 crosspeak, which indicates dimer formation, both grow with the protein's structural evolution time. The buildup times τ_b from exponential fits (dashed lines) are consistent with concurrent development of the two structures. (Adapted from ref. 1.)

structures. That prerequisite could have to do with the hydrophobic core created by melittin's full tetrameric structure—shielding each peptide's hydrophobic side chains may partially drive the folding process.

Time-resolved ssNMR was not used to track the protein's full tetrameric structure. That experimental choice highlights one of the NMR technique's limitations: The 2D spectra can be hard to interpret because the peaks are broad, particularly early on, when the protein is more disordered. Labeling more sites exacerbates the problem; the number of structural features that can be studied at once before the spectra become intractable is therefore limited. Although they could have done additional time-resolved ssNMR measurements with different labeled sites, the authors instead monitored tetramer formation using a less precise real-time fluorescence technique. Those measurements were consistent with tetramers forming along with the helices and dimers instead of the previously accepted sequential folding pathway. The unexpected result will inform theoretical models of protein folding dynamics.

Tycko sees time-resolved ssNMR as complementary to existing ways of studying protein folding. "There are a lot of other great techniques," he says, "but they don't give you the same kind of detailed molecular structural information that NMR can give you." Now that they've demonstrated their method, the researchers are extending it to other protein-folding problems, such as complex formation by calmodulin (see PHYSICS TODAY, May 2006, page 18), a ubiquitous protein that can bind to various target proteins in response to changes in calcium concentration.

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