

phase continuously as long as the atoms are suspended in the lattice.

The longer the hold time, the more the vibrations average out. The 20 seconds that Müller achieved reduces the interferometer's phase sensitivity to vibrations by up to four orders of magnitude. He was surprised to discover that as the lattice hold times kept increasing, his team stopped needing any vibration isolation.

Despite its advantages, the new device still falls short of state-of-the-art atom interferometers. In the Berkeley group's proof-of-principle demonstration, the gravitational potential-energy difference from just 4 μm of vertical separation generates 1.6 megaradians of phase accumulated in the two arms. But there's room to improve that performance. An interferometer's precision increases with both longer hold times and larger wavepacket separations.

The 4 μm separation between the arms

was achieved using the momentum kick from just a single two-photon Raman transition. In a separate experiment, Müller and coworkers have demonstrated laser pulses strong enough to generate 10-photon momentum kicks and almost 9 mm of separation. No fundamental barrier limits increasing the separation and hold times, but maintaining the coherence of such large spatial superpositions remains a huge technical challenge.

The compact nature of the new interferometer makes it ideal for measuring short-ranged interactions, such as Casimir forces and those hypothesized to be responsible for dark energy. And the different nature of the new approach—holding atoms to probe the potential-energy difference rather than dropping them to measure accelerations—has Müller particularly intrigued.

Measuring the phase of atoms from different gravitational potentials but in a gravitational-force-free setting—for ex-

ample, inside a spherical shell of uniform mass—would be tantamount to observing the gravitational analogue of the Aharonov–Bohm effect. The experiment, which Müller proposed with the University of Vienna's Anton Zeilinger in 2012, would constitute the first demonstration of a force-free gravitational redshift.⁵ It would also provide a new measurement of Newton's constant G , the least accurately known fundamental constant in nature.

Mark Wilson

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A supercooled protein refolds unexpectedly

A small simulated peptide's structure is shaped by the surrounding water's anomalous dynamics.

Human bodies have a narrow range of temperatures at which they function properly. Proteins behave similarly: At ambient temperatures they fold as needed for their biological purposes, but if they get too hot or too cold, their structures unravel. The details of what happens to proteins away from their conformational sweet spot and how or why they denature could provide insight into how they manage to find their functional forms at physiological conditions in the first place.

Proteins found in nature don't exist in a vacuum, and the molecules surrounding them affect their behavior (see the article by Diego Krapf and Ralf Metzler, *PHYSICS TODAY*, September 2019, page 48). It's therefore not enough to consider only how interactions within a protein change with temperature; to fully understand a protein's behavior, the dynamics and structure of the solvent—typically water—must also be taken into account.

At the intersection of protein folding and water's molecular dynamics Daniel

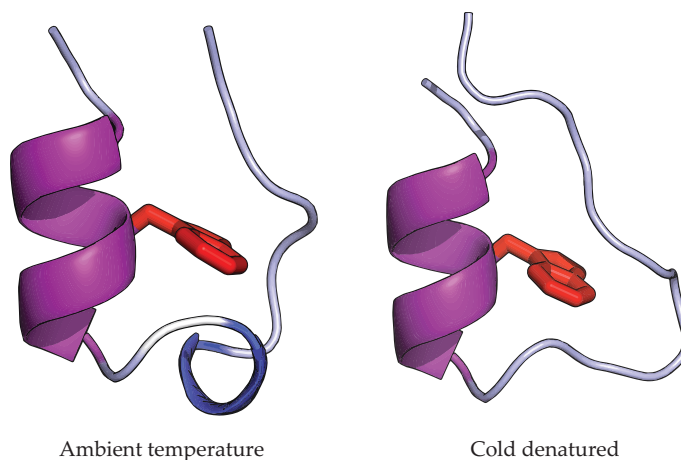


FIGURE 1. AMBIENT AND LOW-TEMPERATURE STRUCTURES for the protein Trp-cage reflect its cold denaturation. The α -helix (purple) remains stable, but the 3_{10} -helix (blue) seen at ambient temperatures unfolds at 224 K. A tryptophan amino acid (red) sits in the protein's core. (Adapted from ref. 1.)

Kozuch, Frank Stillinger, and Pablo Debenedetti of Princeton University noticed something unexpected in their simulations.¹ Earlier work² led by Debenedetti had investigated the cold denaturation of Trp-cage, a 20-amino-acid model protein, in liquid water supercooled to 210 K. Those simulations, as expected, had shown a peak in the fraction of folded pro-

teins at room temperature followed by a steep drop-off as the temperature decreased. But when the researchers lowered the temperature even further in their latest study, they found a surprising result: At 194 K, the proteins refolded.¹

The well-tempered ensemble

Experimental studies of protein folding

are challenging because of the short length and time scales on which the folding occurs (see *PHYSICS TODAY*, October 2019, page 21). Molecular dynamics simulations and theory—the tools employed by DeBenedetti's group—are therefore indispensable because they can provide otherwise inaccessible details.

Fast folding may be an impediment for experiments, but it's a boon for simulations because it makes them more time efficient and less computationally expensive. Trp-cage, illustrated in figure 1, normally folds in less than 4 μ s, which is relatively fast. For comparison, melittin, a similarly sized protein, folds on millisecond time scales.

Molecular dynamics simulations mimic the stochastic motion of a physical protein; they evolve a protein from an initial to a final configuration by navigating through the protein's free-energy landscape and finding a global minimum. Each computational step represents a small, random physical fluctuation in the protein's conformation that happens on the femtosecond time scale. But a protein's free-energy landscape is vast and complex. If the simulated protein randomly explored that entire space in femtosecond steps, it would take an impractically long time to find its final state.

To bridge the gap between experimental and simulation time scales, computational scientists use enhanced sampling methods that guide the protein's steps through the free-energy landscape to help it explore more efficiently.³ In their 2016 paper on simulating Trp-cage, DeBenedetti and his group used parallel tempering—a technique originally developed to deal with slow dynamics in simulations of low-temperature spin glasses—to sample the protein's conformational states. Also known as replica exchange molecular dynamics, parallel tempering helps the evolving protein access more states by running multiple copies of the simulation simultaneously and by periodically exchanging configurations at different temperatures. Basically, it helps each copy avoid getting stuck.

Parallel tempering enabled the re-

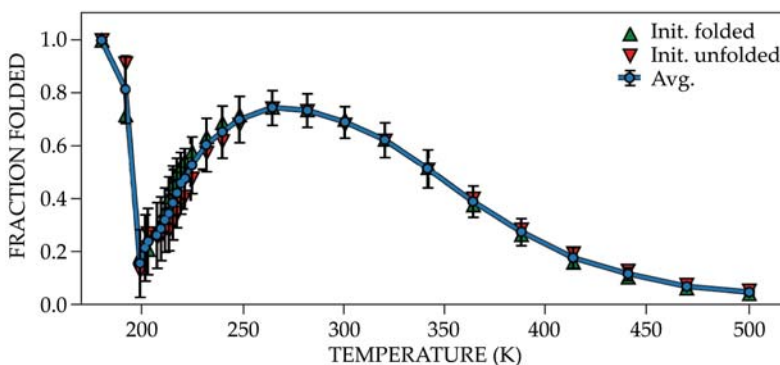


FIGURE 2. LOW-TEMPERATURE REFOLDING OF SIMULATED TRP-CAGE occurs below 200 K as the surrounding water molecules become increasingly tetrahedrally coordinated. Above that temperature, the simulated protein behaves as expected: The fraction of proteins in folded states peaks at ambient temperature decreases as the protein gets too hot or cold. (Adapted from ref. 1.)

searchers to simulate the protein at temperatures down to 210 K. But, says DeBenedetti, "at low enough temperatures it was just impossible to equilibrate the system in reasonable times." Thermal fluctuations had just gotten too small. He and his collaborators therefore turned to an enhanced version of parallel tempering that employs the well-tempered ensemble.⁴ The updated technique reweights configurations to help the simulated protein overcome large free-energy barriers in fewer, more efficient steps.

Protein variations

DeBenedetti's previous study of the cold denaturation of Trp-cage showed the unfolding of the small helix (blue) shown in figure 1. The process was quantified by the average distance between the protein structure and a reference structure, the latter determined by NMR. If the distance was less than 0.3 nm, the protein was deemed folded; otherwise, it was considered unfolded.

Proteins are known to denature at low temperatures, so that result wasn't a surprise; the researchers were focused on delineating the protein's low-temperature thermodynamic properties, such as the free energy of unfolding and the heat capacity. But when Kozuch and cowork-

ers looked at the fraction of folded proteins at even lower temperatures, things unexpectedly changed. The cold denatured configuration from the previous simulations appeared again, but at the lowest temperatures the folded fraction quickly increased, from around 10% at 200 K to nearly 100% at 180 K, as shown in figure 2.

The results of Kozuch's simulations were initially met with skepticism. "I really pushed back," says DeBenedetti. "This study took a long time. I had Daniel repeat the calculations many times." But the results were robust. That the protein arrived at the same state regardless of whether it began folded or unfolded confirmed that the result reflected the underlying energy landscape and was not just an artifact.

The supercooled folded structure was remarkably similar, though not identical, to that at ambient temperature. Water molecules hydrated the folded protein's core at room temperature, whereas the supercooled structure had a more compact hydrophobic core.

To seek an explanation for that structural difference, the researchers turned to the surrounding water molecules. Unlike most liquids whose densities increase as they get colder, water reaches



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its maximum density at 4 °C and then becomes less dense with cooling. The formation of short-lived hydrogen bonds at low temperatures generates transient connections between molecules, thereby increasing the average volume per molecule. By the time water reaches its minimum density, nearly all of the molecules are tetrahedrally coordinated. In the simulations, water's minimum density and the protein refolding occurred synchronously at 195 K. (For more on the unusual behavior of supercooled water, see the article by Pablo Debenedetti and Gene Stanley, *PHYSICS TODAY*, June 2003, page 40.)

It's no accident that the protein's cold refolding coincided with water's evolution to that low-density state. The researchers attribute the compact core's formation to water's increased order. Although the simulated water remained liquid and had no long-range order, on short length and time scales, the molecules were tetrahedrally coordinated. Solvating the protein's core would have disrupted that order, so instead the water was expelled; hence the core's collapse. Water's role in reforming the helix is less clear, but it's likely a factor. "Biology happens in water," points out

Debenedetti. "I would be really surprised if water played no role."

Aqueous oratorio

Accurately capturing water's low-temperature dynamics is a challenge. Many computational models for water exist, and although none are perfect, the TIP4P/2005 model used by Kozuch and coworkers is considered one of the best among classical models. It still has its shortcomings; for example, it places the water's ambient-pressure melting temperature at 252.1 K, more than 20 K below its actual value. That means the researchers' simulations at 200 K are actually only 52 K below freezing, not 73 K. But, importantly, the model has been shown to capture much of water's known behavior—particularly its anomalous dynamics far from ambient conditions—and its complex crystalline phase diagram.

The researchers knew water could influence the protein's behavior, which is why they wanted to capture its dynamics as accurately as possible. In fact, Debenedetti originally wanted to study how Trp-cage's behavior would change around a liquid-liquid phase transition that has been seen in previous simulations of water.⁵ But simulating the protein

at the low temperature and high pressure necessary to reach that transition was unexpectedly difficult because the system took an extraordinarily long time to equilibrate. Luckily for the researchers, decreasing only the temperature was enough to uncover unexpected and intriguing behavior.

Although proteins don't run the risk of becoming supercooled *in vivo*, the simulated temperatures and cooling rates are physically relevant for preparing cryo-electron microscopy and cryopreservation samples. Now that they know where to look, the researchers are repeating their calculations on other proteins to see whether the refolding effect is more general.

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Twisted bilayer graphene enters a new phase

Improved device quality is the key to seeing a whole series of superconducting, correlated, and magnetic states in two layers of graphene assembled at a magic angle.

For years many graphene researchers pursued superconductivity. In 2018 Pablo Jarillo-Herrero of MIT and his colleagues found it in so-called magic-angle bilayer graphene (see *PHYSICS TODAY*, May 2018, page 15). A single layer of graphene, a two-dimensional sheet of carbon atoms, is not superconducting on its own. But two sheets (blue and black in figure 1) vertically stacked at just the right, "magic" angle θ —about 1.1° with respect to each other—have a superconducting transition around 1.7 K.

Now Dmitri Efetov of the Institute of Photonic Sciences in Barcelona, Spain, and his colleagues have replicated Jarillo-Herrero's results and discovered a rich landscape of competing states in magic-angle graphene.¹ By preparing a more homogenous device, Efetov's team could

establish and resolve previously hidden electronic states.

Quest for superconductivity

Researchers long suspected graphene could have correlated states, described by collective rather than individual charge-carrier behavior. Those states, such as superconducting and Mott insulating states, are likely to occur in materials with many electrons sharing the same energy. Such conditions occur in flat regions of the band structure—around a saddle point, for instance. Monolayer graphene has a saddle point in its band structure, but it's several electron volts higher in energy than the Fermi level, the highest occupied state of the material. Raising the Fermi level up to the saddle point isn't feasible with an applied voltage alone. In his grad-

uate work from 2007 to 2014 with Philip Kim, then at Columbia University and now at Harvard University, Efetov tried electrolytic gates, and other groups investigated intercalation to reach higher levels of charge-carrier doping. But none quite reached the saddle point.

A different route to correlated behavior² was proposed by Rafi Bistritzer and Allan MacDonald at the University of Texas at Austin back in 2011. Two layers of graphene at different relative angles form a quasiperiodic structure, or moiré lattice, at a larger length scale than graphene's lattice constant—see the larger hexagons in figure 1, in which the graphene sheets nearly align at their centers and increasingly misalign toward their edges. The periodicity of the moiré lattice tunes the band structure from that of independent monolayers for large angles to that of normal bilayer graphene, which is also not superconducting, when the layers are aligned.

For two layers of graphene mis-