PHYSICS TODAY

Watching biomolecules fold and unfold

High-resolution measurements capture brief but informative moments in a molecule's structural evolution.

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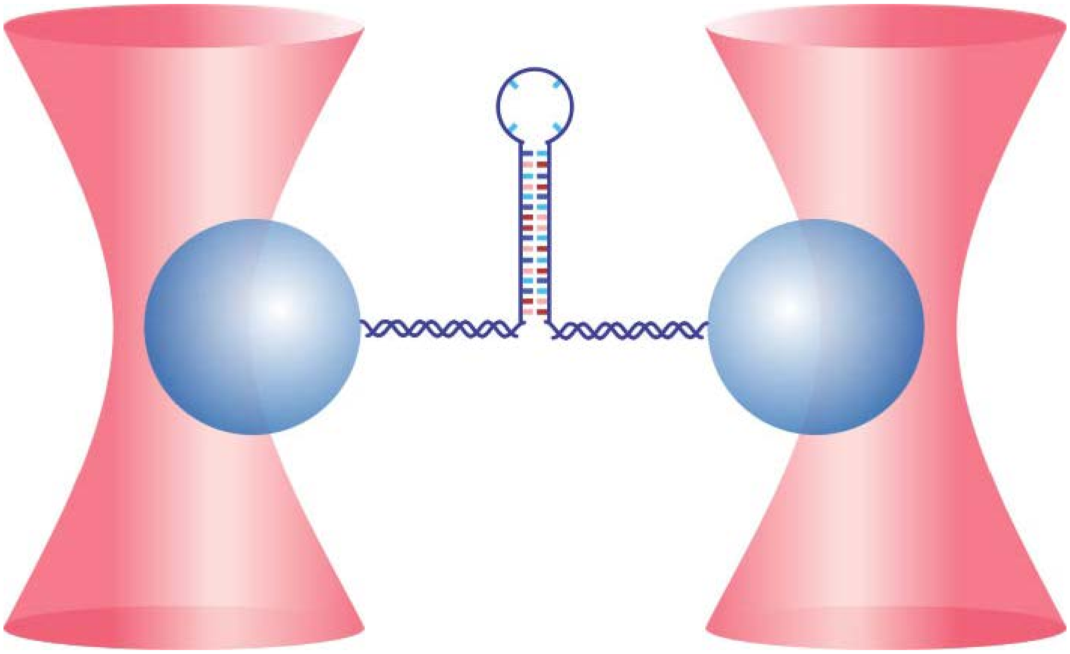
Protein folding is a central puzzle of biophysics. How does a chain of thousands of amino acids find its way so quickly and reliably to a preordained three-dimensional shape? Some things are known: On the way to its final folded structure, the molecule hops among metastable, partially folded states. The metastable states, which typically persist for tens to hundreds of milliseconds, are relatively easy to study experimentally. But the hops between them, which may harbor important clues about how proteins are guided to the correct structure, last just microseconds and are much trickier to probe. Most of what is known about those fleeting transitions comes from computational studies and a few indirect measurements.

Now Michael Woodside and colleagues of the University of Alberta in Edmonton have used single-molecule force spectroscopy to observe biomolecular transition paths directly. As shown in the figure, they attached each end of a molecule to a bead held in an optical trap. The tug of the traps caused the molecule to continually flip-flop between its folded and unfolded states; from the beads' positions at any given instant, the researchers could deduce whether the molecule was folded, unfolded, or on a transition path.

For their proof-of-principle experiment, Woodside and company used a DNA hairpin—whose structure is simpler than a protein's—and watched it fold and unfold more than 24 000 times. That's enough to measure not just the average transition time (around 30 μs) but also the distribution of transition times, which has a smooth exponential tail that extends to at least 140 μs. So far, those results are nothing out of the ordinary—the exponential distribution is just what's expected for folding trajectories traversing a harmonic energy barrier. The researchers are now working on analyzing the shapes of the transitions, which may tell them more. (K. Neupane et al., *Science* **352**, 239, 2016.)



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