BIOPHYSICS

Following the fold

A specialized supercomputer allows molecular dynamics simulations to be carried out for much longer periods of time than previously possible, yielding new insights into protein folding and dynamics.

Three-dimensional structural reconstructions are extremely useful for understanding protein function, for sure, though they may give a casual observer a false impression that proteins are static, locked into a single conformation. In reality, folded proteins are in constant motion, and these motions are crucial for biological activity, but experimentally observing all but the most stable states is essentially impossible.

Molecular dynamics simulations can help to fill in the gaps between the static snapshots that can be taken experimentally. All-atom simulations are also particularly useful for modeling how proteins fold from an unfolded state because a continuous trajectory of the behavior can be recorded. However, a timing discrepancy exists between simulations and experiments. Whereas experimental techniques are limited to observing the valleys in the protein folding landscape—those states that exist for long enough to be detected—continuous molecular dynamics simulations have been generally limited to modeling events with very short timescales, on the order of about a microsecond. All-atom molecular dynamics simulations are incredibly computationally expensive, making longer simulations basically impossible. Protein folding and other dynamic events often occur on timescales much slower than a microsecond, however, so computational constraints have been a real limitation for the field.

Now, using a specialized supercomputer named Anton, David Shaw of D.E. Shaw Research in New York and his team recently reported the first results from all-atom molecular dynamics simulations of protein dynamics over 1 millisecond, about 100 times longer than was previously possible.

Anton is a specialized machine designed for carrying out molecular dynamics simulations only. What Anton lacks in flexibility, however, it makes up for in impressive speed. A 1-millisecond simulation of a small protein took about 100 days to run on Anton, whereas a general-purpose supercomputer typically could only carry out a 10-microsecond simulation in the same amount of machine time. Anton's speed, explains Shaw, is "attributable in large part to custom chips we designed specifically for molecular dynamics calculations, together with hardware and algorithms that reduce the time required to transfer data among these chips."

Shaw's team put Anton's power to the test to follow the folding and unfolding of a small Trp-Trp (WW) domain protein called FiP35. Two 100-microsecond simulations allowed the researchers to observe a sequence of events—from the unfolded state to the native state and back again—that were in agreement with experimental evidence. They found that FiP35 consistently folded via the same route, suggesting the existence of a single dominant folding pathway, something that could not be gleaned from experiments alone. They also simulated the native state dynamics of bovine pancreatic trypsin inhibitor for 1 millisecond, which allowed them to observe several structurally distinct states with lifetimes between 6 and 26 microseconds. Previously, only the two most stable states of this protein had been experimentally observed. Shaw notes that they could perform simulations even longer than 1 millisecond on Anton. "It's just a matter of when you run out of patience," he says.

Other researchers in the field will also have the opportunity to use Anton to address questions about dynamics in their systems of interest. Shaw and his colleagues have donated a machine to the National Resource for Biomedical Supercomputing in Pittsburgh, and 47 scientific proposals have been awarded simulation time on the machine by the National Academies. "Anton is used routinely in our lab, and for our problems it's been a very valuable tool," says Shaw. "How valuable it is in the hands of other researchers remains to be seen."

With Anton, the time barrier limiting the usefulness of molecular dynamics simulations has been broken, but this certainly does not mean that experimentalists should put away their traditional toolbox. "It's a tool for experimentalists to use as one extra source of data in trying to solve the various mysteries that all of us are interested in," Shaw concludes.

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RESEARCH PAPERS
Shaw, D.E. *et al.* Atomic-level characterization of the structural dynamics of proteins. *Science* **330**, 341–346 (2010).