

Understanding protein motion could greatly aid new drug design

By Jenny Green, ASU News
March 27, 2026

For many of us, “protein” is the key element of a food order. However, beyond your preferred choice of meats or plant-based alternatives, proteins encompass a large class of complex biomolecules whose chemical structure is encoded in our genes.

Proteins have critical functions in living cells: They help repair and build body tissues, drive metabolic reactions, maintain pH and fluid balance, and keep our immune systems strong.

To perform their important functions, many proteins have a dynamic molecular structure capable of adopting multiple conformations. For a long time, scientists have suspected that proteins don’t change shape at random. Instead, they seem to move according to deep, slow rhythms — like a building that sways gently in the wind rather than shaking violently.

Those slow rhythms guide how a protein bends, twists and shifts between its different forms. If one could understand those rhythms, one might be able to predict — and even hurry along — the protein’s movements.

The problem is that many tools scientists have to make predictions of molecular motion were built for simpler cases. They work well for fast, tiny vibrations, like the quick trembling of a guitar string. But the slow, sweeping motions of proteins are different. They’re messy, uneven and irregular.

Recently, members of the research group of Associate Professor [Matthias Heyden](#) in Arizona State University’s [School of Molecular Sciences](#) have found a new way forward. They developed a method that can tease out these slow, important motions from short computer simulations — snapshots lasting only billionths of a second.

Even better, the method is remarkably reliable: Run it again and again, and it tells the same story each time. They have recently published this work in *Science Advances*.

Better understanding protein fluctuations in turn predicts which larger motions the protein is capable of, and that knowledge can greatly improve drug design, enable more effective cancer treatments and help find a solution to antibiotic resistance.

“In short, we resurrected a long-standing idea that conformational transitions in proteins are tied to low-frequency vibrations,” Heyden says of the approach of his team.

“We developed a method to identify these vibrations through natural fluctuations caused by molecular collisions. The natural motions stand out if analyzed with the right tools.

“This can be compared to an unlocked door: We can feel quickly if we need to push or pull, while trying to yank the door up and off of its hinges is always hard. The key is that we don’t need to execute the full motion to realize these differences. On a molecular scale, it is even enough to observe tiny fluctuations that are always present at room temperature.”

Heyden said that knowing the low-frequency vibrations of a protein “should enable us to speed up the sampling of conformational transitions in molecular dynamics simulations.”

Once they had uncovered these hidden rhythms, the researchers used them like guide rails. In simulations of five very different proteins, they gently nudged each protein to move along its natural pathways, encouraging it to explore all the shapes it prefers to adopt. This approach allowed them to map the protein’s landscape — where it likes to linger, where it resists change and how much energy it takes to move from one form to another — with impressive accuracy.

What makes this especially exciting is speed. By harnessing powerful graphics processors on ASU’s [Sol supercomputer](#), they can now watch proteins undergo meaningful shape changes in less than a day. What once required weeks or even months of computation can now happen overnight.

That matters because most designed proteins today are rigid and dull compared with nature’s creations. They hold their shape well, but they don’t do much. By understanding motion and change, scientists could design proteins that switch on when a small molecule binds, act as sensitive detectors or perform chemical reactions like natural enzymes.

There’s another payoff, too. Many important drug targets work through subtle, long-distance communication within the protein — touch it in one place, and something changes far away. These “allosteric” effects are notoriously hard to study. With faster, more revealing simulations, researchers can finally watch these internal conversations unfold, paving the way for drugs that fine-tune protein behavior with fewer side effects.

By learning to listen to the slow music proteins move to, scientists are beginning to understand not just what proteins are, but how they live. What once took deep intuition and careful manual selection of variables could now be done systematically and efficiently.

This high-throughput generation of conformational ensembles has opened a new door. With richer and more diverse datasets, researchers could train next-generation machine learning models capable of understanding the intertwined relationships between protein sequence, structure and dynamics.

This work was supported by the National Science Foundation (CHE-2154834) and the National Institutes of Health (R01GM148622).

This story originally appeared on [ASU News](#).

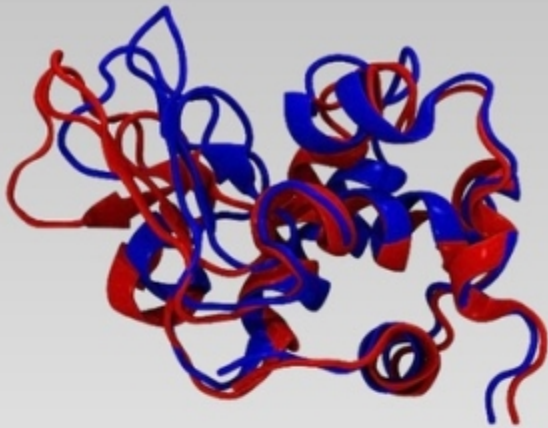
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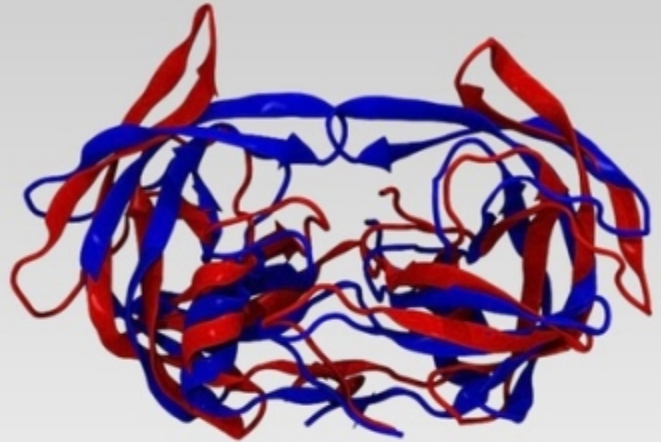
Associate Professor Matthias Heyden from the School of Molecular Sciences. Photo by David Rozul/ASU

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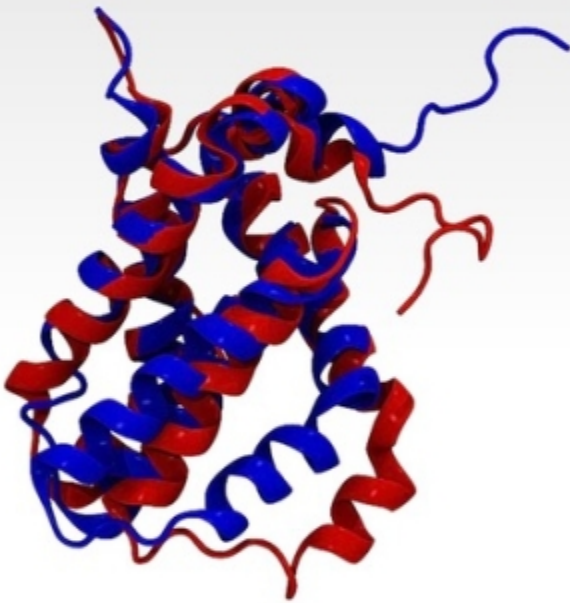
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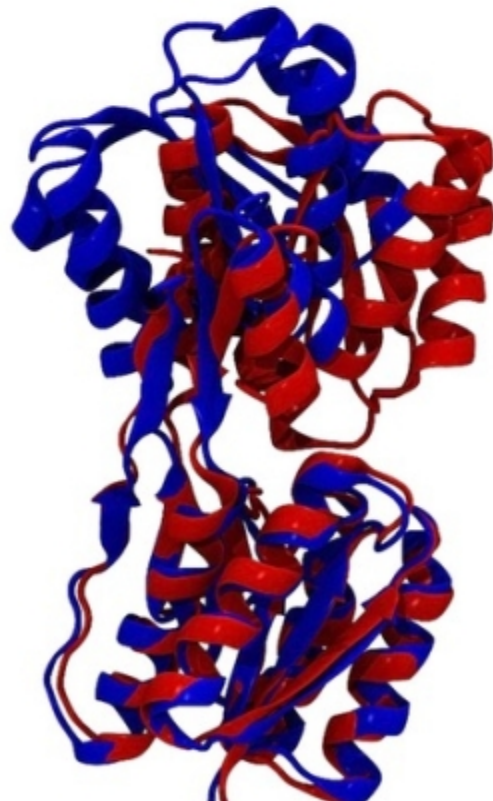
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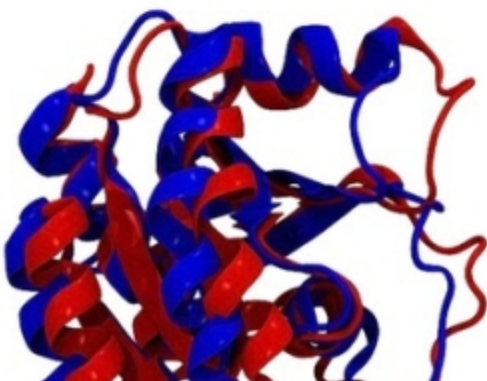
MCL-1



**Ribose
Binding
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KRAS



The five proteins part of this research and the conformational changes.