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Researchers find way to study proteins moving (relatively) slowly

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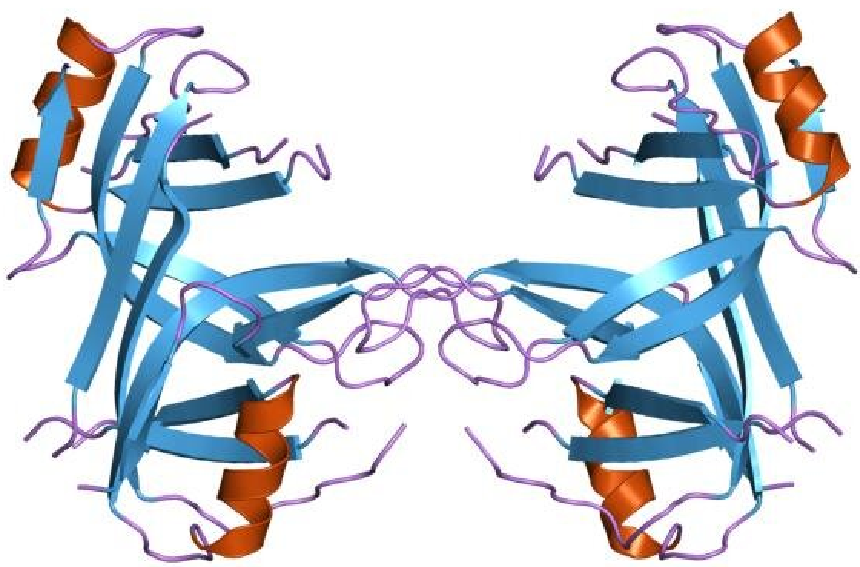

Scientists have not been able to see proteins move at speeds slower than a nanosecond. That changed with a discovery by a team at The Ohio State University. Credit: Wikimedia Commons

Proteins are the workhorses of our bodies. They keep our organs functioning. They regulate our cells. They are the targets for medications that treat a number of diseases, including cancers and neurological diseases. Proteins need to move in order to function, but scientists still know very little about such motions at speeds slower than a nanosecond.

The reason for that gap in knowledge might seem like a strange problem: Proteins sometimes move too slowly for some key technology scientists use to watch them—so slowly that the technology cannot pick up their movements. These proteins are still moving very fast—nanoseconds to microseconds. But before a new study, researchers could view only proteins moving faster than a nanosecond.

The research, published last month in the journal *Science Advances* by a team of biophysical chemists at The Ohio State University, changed that. The researchers found a way to measure the ways proteins move at slower speeds—hundreds of nanoseconds to microseconds. The discovery, a fundamental breakthrough, could open a new line of research for scientists trying to understand how proteins behave in the body.

"We know very little about what proteins do on timescales into the microseconds. Traditional experiments provide very little information, because the way we test proteins now loses sensitivity at those speeds—there is a window, depending on how fast a protein is moving, at which we cannot see what the protein is doing and how it is behaving," said Rafael Brüschweiler, Ohio Research Scholar and professor of chemistry and biochemistry at Ohio State. "Our goal here was to open up this window. To come up with a tool to measure how proteins function on these timescales that we have not been able to watch before."

Brüschweiler has been working on ways to better study proteins for decades, starting when he was a graduate student in Switzerland. He and his research group at Ohio State focus on nuclear magnetic resonance (NMR), a tool that helps scientists understand how proteins behave in the body. But the tool—widely accepted in the scientific community as the definitive tool for studying proteins—was, until this discovery, incapable of measuring fundamental protein behavior at speeds slower than a nanosecond.

"On this slower timescale, the information about those proteins is just washed away—it is there, but our tools could not see it," Brüschweiler said. "We thought there was slower motion present, but it was not observable."

For this discovery, Brüschweiler and his team added nanoparticles—silica, or glass—to a solution containing water and proteins, and used the same tool, NMR—essentially magnetic pods as big as two stories high—to see how the proteins responded. The proteins bonded to the silica, making them all of a sudden visible to scientists analyzing their movements.

It was, Brüschweiler said, akin to developing a new microscope that could see something scientists hadn't been able to see before.

"It's a bit like if you have a telescope, and you look at the visible light from the stars," he said. "Now you have an infrared detector, so you can look for the infrared light that we cannot see with the naked eye. It provides a whole new window of information."

That additional information is the building block of science, allowing researchers who study proteins to ask deeper, better questions.

"This will help us look at a protein and ask, how does it behave? What happens when it interacts with another protein or a drug?" Brüschweiler said. "That's the type of information we need in order to understand the function of these proteins. Each protein has its own function in the body, and with this new tool, we get a glimpse of what they are actually doing and start to better understand why."

The ability to evaluate protein behavior at these speeds had flummoxed Brüschweiler for decades. He had attempted to find a solution 25 years ago. That study was "rigorous and nice," he said, "but ultimately a spectacular failure." He began to believe it just might not be possible to study proteins moving at speeds slower than a nanosecond with our tools.

His lab had begun experiments that worked on nanoparticles in biofluids—urine, cell extracts, serum—and he started to wonder if the nanoparticles—which, though very small, are larger than proteins—could help make dynamic protein behavior visible to scientists. And it worked.

"Science really deals with these unpredictable things that no one saw coming," he said. "That's what this is."

More information: Mouzhe Xie et al. Functional protein dynamics on uncharted time scales detected by nanoparticle-assisted NMR spin relaxation, *Science Advances* (2019). DOI: 10.1126/sciadv.aax5560

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