Discovery about protein structure opens window on basic life process

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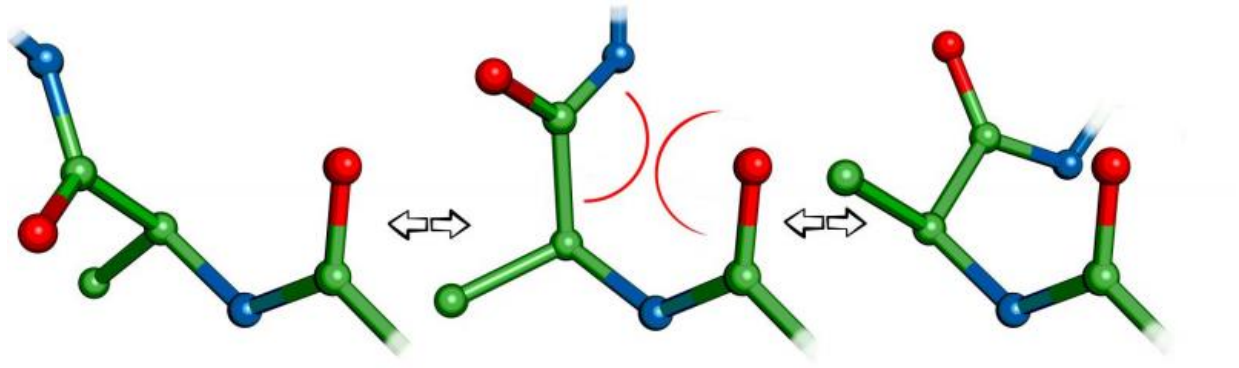

Proteins can go through odd changes as they shift from one stable shape to a different, folded one. Credit: Oregon State University

Biochemists at Oregon State University have made a fundamental discovery about protein structure that sheds new light on how proteins fold, which is one of the most basic processes of life.

The findings, announced today in *Science Advances*, will help scientists better understand some important changes that proteins undergo. It had previously been thought to be impossible to characterize these changes, in part because the transitions are so incredibly small and fleeting.

The changes relate to how proteins convert from one observable shape to

another—and they happen in less than one trillionth of a second, in molecules that are less than one millionth of an inch in size. It had been known that these changes must happen and they have been simulated by computers, but prior to this no one had ever observed how they happen.

Now they have, in part by recognizing the value of certain data collected by many researchers over the last two decades.

"Actual evidence of these transitions was hiding in plain sight all this time," said Andrew Brereton, an OSU doctoral student and lead author on this study. "We just didn't know what to look for, and didn't understand how significant it was."

All proteins start as linear chains of building blocks and then quickly fold to their proper shape, going through many high-energy transitions along the way. Proper folding is essential to the biological function of proteins, and when it doesn't happen correctly, protein folding diseases can be one result—such as Alzheimer's disease, Lou Gehrig's disease, amyloidosis and others.

Proteins themselves are a critical component of life, the workhorses of biology. They are comparatively large, specialty molecules that can do everything from perceiving light to changing shape and making muscles function. Even the process of thinking involves proteins at the end of one neuron passing a message to different proteins on the next neuron.

A powerful tool called X-ray crystallography has been able to capture images of proteins in their more stable shapes, but what was unknown is exactly how they got from one stable form to another. The changes in shape that are needed for those transitions are fleeting and involve distortions in the molecules that are extreme and difficult to predict.

What the OSU researchers discovered, however, is that the stable shapes

adopted by a few proteins actually contained some parts that were trapped in the act of changing shape, conceptually similar to finding mosquitos trapped in amber.

"We discovered that some proteins were holding single building blocks in shapes that were supposed to be impossible to find in a stable form," said Andrew Karplus, the corresponding author on the study and a distinguished professor of biochemistry and biophysics in the OSU College of Science.

"Apparently about one building block out of every 6,000 gets trapped in a highly unlikely shape that is like a single frame in a movie," Karplus said. "The set of these trapped residues taken together have basically allowed us to make a movie that shows how these special protein shape changes occur. And what this movie shows has real differences from what the computer simulations had predicted."

As with most fundamental discoveries, the researchers said, the full value of the findings may take years or decades to play out.

What is clear is that proteins are key to some of the most fundamental processes of life, and this new information has revealed the first direct views of specific details of one aspect of protein folding in a way that had not been considered possible.

"In the 1870s an English photographer named Eadweard Muybridge made some famous photographs that settled a debate which had been going on for decades, about whether horses as they run actually lift all four feet off the ground at the same time," Karplus said.

"His novel series of stop-action photos proved that they did, and opened up a whole new understanding of animal locomotion," he said. "In a similar way, our results change the way researchers can now look at one

of the ways proteins change shape, and that's a pretty fundamental part of life."

More information: Native proteins trap high-energy transit conformations, *Science Advances*, advances.sciencemag.org/content/1/9/e1501188

Provided by Oregon State University