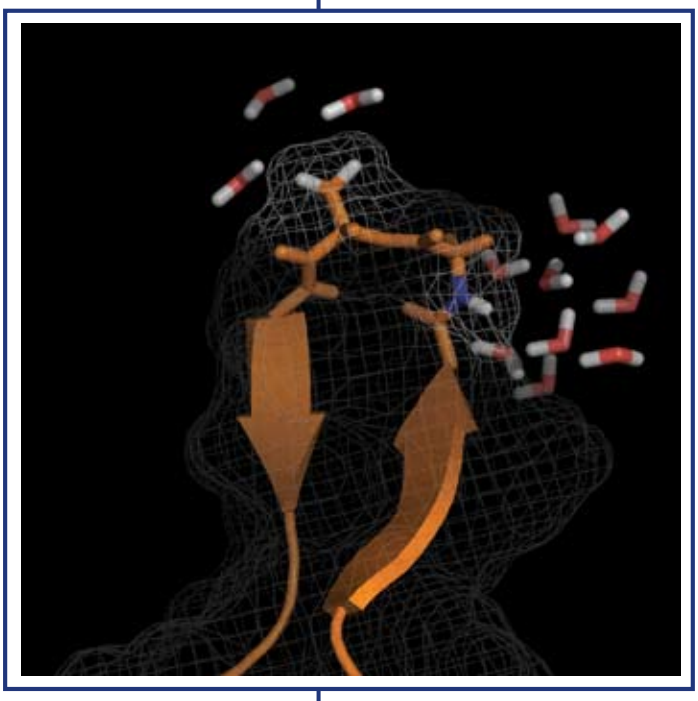
Simulation Helps Unlock the Secrets of Protein Folding



Simulation model of a peptide surrounded by V-shaped, red-and-white water molecules. How the water hydrates the peptide is found to decide the shape the peptide adopts.

A team led by biophysicist Jeremy Smith of the University of Tennessee (UT) and Oak Ridge National Laboratory (ORNL) has taken a significant step toward unrav-eling the mystery of why proteins fold into unique, three-dimensional shapes.

Using ORNL's Cray XT4 Jaguar supercomputer as well as computer systems in Italy and Germany, the team revealed a driving force behind protein folding involv-ing the way its constituents interact with water. The team's results are being pub-lished in the September 18 edition of the Proceedings of the National Academy of Sciences.

Proteins are the workhorses of the body, taking on a wide variety of tasks. They fight infections, turn food into energy, copy DNA, and catalyze chemical reactions. Insulin is a protein, as are antibodies and many hormones.

Nevertheless, scientists are still deciphering how proteins work. A protein is a string of amino acids, but what it does is determined by the shape it takes, which is itself determined by the sequence of the amino acids. Like a piece of biological origami, the protein folds itself into the form necessary to carry out its job. Without the shape the protein would be worthless.

"Understanding the mechanism by which proteins fold up into unique three-dimensional architectures is a holy grail in molecular biology," explained Smith, who holds the first Governor's Chair at UT and ORNL. "If you give me the se-quence of amino acid building blocks in the protein, I cannot tell you what the structure would be. If I had been able to do that with a computer a while ago, the work behind about a dozen Nobel prizes—those awarded for experimental work on protein structure determination— would not have been necessary."

Working on a smaller chain of amino acids known as a peptide, the group showed that the folding is determined largely by the aversion of some parts of the peptide to water. Areas that shun water are said to be hydrophobic, and the team's results show how the way in which water wets these hydrophobic areas determines the ul-timate shape and behavior of the peptide.

In particular, the team determined that small hydrophobic areas of the peptide, up to the size of a water molecule, induce different behavior in water than larger hydro-phobic areas, and that this difference is crucial for the folding. This insight builds on the work of another team, based at the University of California–Berkeley.

"David Chandler and his colleagues at Berkeley have a theory stating that hydro-phobicity is qualitatively different on different length scales." said Smith. "If you have small hydrophobic molecules or groups that are roughly the size of a water molecule, the water doesn't seem to be too bothered by these

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groups. When you get big enough hydrophobic entities that cover several water molecules of length, how-ever, then the water molecules have a problem with that. They can't cloak them-selves around the hydrophobic surface anymore, and there is a dewetting or drying effect as they move away from the surface.

"Our simulations have shown that Chandler's theory works for peptides, and, moreover, that the drying effect determines which structure the peptide adopts."

Smith said his team's achievement was made possible by the computing muscle brought to the task by high-performance computing, noting that Jaguar is currently rated the second most powerful computing system in the world. Smith also noted that his team will need increasingly powerful supercomputers for additional simula-tions. While the team so far has been able to simulate peptides for a matter of mi-croseconds, it must eventually be able to increase that time a thousand-fold, to mil-liseconds, and simulate proteins that are ten to 100 times as large as the peptides.

"The runs were a couple of microseconds, which was adequate for the peptide that was simulated," Smith explained. "But the team is looking forward to increased computing capacity as it moves forward. The technique used is molecular dynamics simulation and it needs high-performance leadership supercomputing to reach the length and timescales needed to fold a complete functional protein in the computer. With the projected capability improvements in Jaguar over the next couple of years we will soon be approaching that goal."

Smith made it clear that the achievement would represent a watershed in the field.

"When we do eventually find out how to calculate protein structure from sequence" he said, "then a major revolution will come upon us, as we will have the basis to move forward with understanding much of biology and medicine, and the applica-tions will range from rationally designing drugs to fit clefts in protein structures to engineering protein shapes for useful functions in nanotechnology and bioenergy."

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