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UCSB Physicist Devises Way to Observe Protein Folding

Physicists are getting more involved in the fight against diseases by studying the folding of proteins, which they hope will eventually lead to the development of new drugs. Illnesses such as Alzheimer's disease and even some cancers are the result of protein folding that has gone awry. Since proteins in the body perform different functions according to their shape, the folding process is considered a very important area of study.

Everett Lipman, a new assistant professor of physics at the University of California, Santa Barbara, recently co-authored an article in the journal Science, describing an innovative study of how to "see" proteins as they fold, the result of experiments performed with co-workers at the National Institutes of Health.

The machinery of life arises from interactions between protein molecules, whose functions depend on the three-dimensional shapes into which they fold, said Lipman. Although proteins are composed of just 20 different building blocks (the amino acids), the process by which a given sequence of these components adopts its unique structure is complex and poorly understood.

Folding proteins are too small to view with a microscope, so the researchers used a method called Forster Resonance Energy Transfer, or FRET, to study them. Using a microfabricated silicon device and a microfluidic mixing technique, they were able to observe single protein molecules at various times after folding was triggered.

Two small molecules of fluorescent dye (red and green) were applied to amino acids in the protein. When the green dye was excited by a laser, it either emitted green light or transferred the energy to the red dye, causing it to light up. The green dye is a photon donor and the red dye is a photon acceptor. If the two dyes are close together, more red is emitted as the energy is transferred easily to the red. If they are far apart, more green light is emitted. The fraction of red counts shows how efficient the energy transfer is, which shows how close the ends of the molecule are to each other. By taking a sequence of measurements as the protein folds up, scientists can get a "picture" of the folding.

The group was the first to perform these single molecule measurements in microfluidic mixtures.

"Once we have more understanding of the folding process, it will fill in a huge gap in our knowledge of how biological systems work," said Lipman. "However it will be a long time before this knowledge can be applied."

Lipman explained, "The fantastic advances in biology during the last century have brought us to the point where we have working knowledge of many fundamental processes. There remain, however, numerous details and enormous complexity of function and interaction that we have yet to comprehend. It has been the case in the past that the most precise information about biomolecular machinery has been uncovered using techniques of experimental physics, such as magnetic resonance and x-ray crystallography. As we progress toward understanding proteins and nucleic acids as complex physical systems, this will no doubt remain true."

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