Argonne NATIONAL LABORATORY

Biosciences

New study may shed light on protein-drug interactions

Proteins, the biological molecules that are involved in virtually every action of every organism, may themselves move in surprising ways, according to a recent study from the U.S. Department of Energy's Argonne National Laboratory that may shed new light on how proteins interact with drugs and other small molecules.

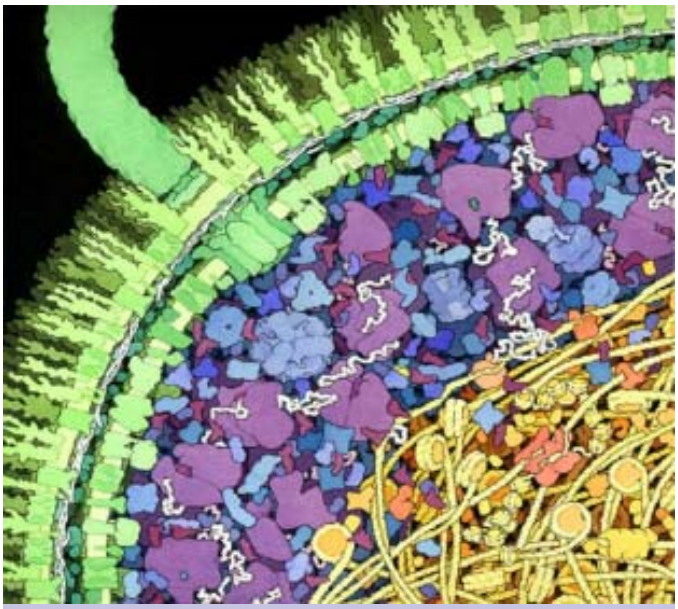
This study, which relied on the intense X-ray beams available at Argonne's Advanced Photon Source, uses a new approach to characterize the ways in which proteins move around in solution to interact with other molecules, including drugs, metabolites or pieces of DNA.

"Proteins are not static, they're dynamic," said Argonne biochemist Lee Makowski, who headed the project. "Part of the common conception of proteins as rigid bodies comes from the fact that we know huge amounts about protein structures but much less about how they move."

The study of proteins had long focused almost exclusively on their structures, parts of which can resemble chains, sheets or helices. To determine these, scientists use high-energy X-rays to take snapshots of proteins frozen in a single conformation within a highly ordered crystal. However, biologists had made relatively little progress in using these pictures to show how proteins can reconfigure themselves in different environments.

While scientists had expected proteins to behave similarly in regions of high and low protein concentration – from as high as 30 percent protein to less than 1 percent protein, respectively – they instead found that proteins had a much larger range of motion and could contort themselves into many more configurations in the dilute solutions. "The difference is comparable to skipping through an open field or being crammed into a crowded elevator," Makowski said.

For more than a century, the standard model of protein behavior depicted them as inflexible "locks" that could interact only with a small set of equally rigid molecular "keys." Even today's introductory biology courses rely



In this e-coli *cell, the proteins (shown in blue) crowd around ribosomes (purple). These regions have a high concentration of protein, typically greater than 30 percent, which limits the ensemble of states into which the proteins can bend themselves.*

on descriptions of protein behavior that require them to swivel and pivot very little as they interact with other biological molecules, according to Makowski. "That's a very powerful image but it's not the whole story," he said. "We've learned that proteins in solution can take on an entire ensemble of slightly different structures and that, for most proteins, this ensemble grows much larger as you go to lower and lower concentrations."

Makowski and his colleagues were also surprised to discover that environmental conditions strongly influence which state in this "ensemble" of conformations a protein prefers to enter. Most of a protein's common configurations have a functional purpose, he said, as it is "not likely to twist itself into something completely irrelevant to its function."

For example, one of the five proteins examined in the study, hemoglobin, has two favored conformations: one in which it binds oxygen very readily and one in which it

does not. When hemoglobin is placed in a solution that contains a great deal of available oxygen, it spends most of the time in the former state, but when oxygen is not easily accessible, it usually flips into the latter. “We now know that in dilute solutions, hemoglobin can actually take on both conformations — even in the absence of oxygen,” he added.

By keeping all of the environmental factors the same save for the protein concentration in the solution, Makowski and his team discovered another surprising result. Scientists had known for many years that when proteins are too concentrated, they aggregate and fall out of solution. However, biochemists previously had difficulty explaining why a similar effect also occurs in overly dilute solutions.

Proteins have hydrophobic – or “water-hating” – core regions that try to avoid touching water if at all possible. Because of this characteristic, proteins will rearrange themselves to protect these regions from coming into contact with water. In dilute solutions, however, Makowski’s team discovered that proteins fluctuate far more than in concentrated solutions, and these fluctuations expose the proteins’ hydrophobic core, making them more likely to stick to one another or to the container walls.

The results of the research appear in the January 11 issue of the Journal of Molecular Biology.

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