New Argonne study may shed light on protein-drug interactions

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Proteins, the biological molecules 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.

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 one 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," said Argonne biochemist Lee Makowski, who headed the project.

This study represents a novel approach to characterizing the ways in which proteins move around in solution to interact with other molecules, including drugs, metabolites, or pieces of DNA, and relied on the intense x-ray beams available at Argonne's Advanced Photon source.

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.

“Proteins are not static, they’re dynamic,” Makowski said. “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.”

For over 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 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 smaller and smaller 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, while if oxygen is not available, it usually flips into the latter. “We now know that in dilute solutions, hemoglobin actually can take on both conformations - even in the absence of oxygen,” he said.

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 hydrophobic core of the proteins, making them more likely to stick to one another or to the walls of the container.

Source: Argonne National Laboratory