Team identifies universality and specificity in protein motions

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Although proteins have very different function functions, or specialties, in living cells, they share the general characteristics—the same universality—in their motions, say University of Oregon scientists.

Their motion is much like mountain landslides or wildfires, reports the UO team in a paper published in the journal *Physical Review Letters*.

The findings, which relied on theoretical methods developed in the lab of UO chemist Marina Guenza, may help pinpoint where protein binding could occur, and how protein motion is involved in the process.

"Dynamics is often unexplored in the study of protein binding, but it could be a determinant for the way proteins regulate their own biological activity," Guenza said. "Proteins in biological systems are constrained to a maximum size and move within a narrow, temperature-dependent window of time in which they are available to bind with other molecules, so it seems that all proteins should have some universal characteristics guiding their behavior. We sought to find this universal behavior using our theoretical approach."

In that range, where salt concentrations and volume are also important, the researchers found, a critical hydrogen-bonding network delivers random energy fluctuations that make or break a protein's ability to bind to another molecule.

Energy fluctuations and protein motions were investigated by using the

Langevin Equation for Protein Dynamics method developed in the Guenza lab.

"Many well-known theoretical methods attempt to study protein dynamics, but they lack important aspects of the physics involved," said Mohammadhasan Dinpajooh, a postdoctoral researcher. "By incorporating the essential physics, we can unravel biological mechanisms, which are still elusive in well-advanced X-ray or nuclear magnetic resonance experiments."

The work was a result of teamwork started by Jeremy Copperman, a former physics doctoral student in the lab, and continued by Dinpajooh and Eric Beyerle, a third-year graduate student.

"We developed a way to accurately describe the specific functional dynamics of a protein on a protein-by-protein basis. In the process, we noticed a trend—a scaling pattern—which had no reason to be there," said Copperman, now a postdoctoral researcher at the University of Wisconsin-Milwaukee. "We simulated the protein motion on supercomputers, spent months writing analysis codes and found quantities of this simple scaling pattern."

With that information, Guenza said, the team was able to map the equilibrium of proteins that exists in an ever-fluctuating system that moves randomly and similarly to the front line of a wildfire.

The researchers took starting structural information based on nuclear magnetic resonance or X-ray techniques, and simulated 14 behavioral dynamics in 12 proteins in times ranging from 50 nanoseconds to 1.23 milliseconds. In short, the researchers suggest that the motion of proteins may be described by a simple fluctuation subject to random energetic noises, which is like climbing over a mountain range that is constantly shifting and rearranging randomly.

The study's approach to understand protein dynamics could be useful to the pharmaceutical industry, Guenza said.

"Industry researchers test a lot of organic molecules and can see that a molecule stops the function of a protein, but they don't know how it works," she said. "Our approach could allow them to understand these mechanisms and ultimately to manipulate the structure of their drug so that it finds the binding site and ensures a better fit on the target site of the protein."

More information: J. Copperman et al, Universality and Specificity in Protein Fluctuation Dynamics, *Physical Review Letters* (2017). DOI: 10.1103/PhysRevLett.119.158101

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