New computer simulation helps explain folding in important cellular protein

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(PhysOrg.com) -- Most parts of living organisms come packaged with ribbons. The ribbons are proteins—chains of amino acids that must fold into three-dimensional structures to work properly. But when for any reason the ribbons fold incorrectly, bad things can happen, and in humans misfolded-protein disorders include Alzheimer's and Parkinson's diseases.

Scientists have for the past three decades tried to understand what makes proteins fold into functional units and why it happens, and several breakthroughs have occurred through computer modeling—a field that dramatically increases analytical speed.

Now, scientists at the University of Georgia have created a two-step computer simulation (using an important process called the Wang-Landau algorithm) that sheds light on how a crucial protein—glycophorin A—becomes an active part of living cells. The new use of Wang-Landau could lead to a better understanding of the controlling mechanisms behind protein folding.

"Our goal is to present the methodology in a clear, self-consistent way, accessible to any scientist with knowledge of Monte Carlo simulations," said David Landau, distinguished research professor of physics at the University of Georgia and director of the Center for Simulational Physics.

The research was just published in The Journal of Chemical Physics.

Authors of the paper are Clare Gervais and Thomas Wüst, formerly of UGA and now employed in Switzerland; Landau, and Ying Xu, Regents-Georgia Research Alliance Eminent Scholar and professor of bioinformatics and computational biology, also at UGA. The research was supported by grants from the National Institutes of Health and the National Science Foundation. Landau and Xu are in UGA's Franklin College of Arts and Sciences.

"This work demonstrates the power and potential of combining expertise from computational physics and computational biology in solving challenging biological problems," said Xu.

Monte Carlo simulations—the use of algorithms with repeated random samplings to produce reliable predictions—have been around for some decades but have been steadily refined. These simulations are useful for extremely complex problems with multiple variables, and though they often require considerable computer "brain power," they are able to give scientists startlingly accurate predictions of how biological processes work.

In the current paper, the research team developed a two-step Monte Carlo procedure to investigate, for glycophorin A (GpA), an important biochemical process called dimerization. (A dimer in biology or chemistry consists of two structurally similar units that are held together by intra- or intermolecular forces.)

"One particularly promising approach is to investigate the thermodynamics of protein folding through examining the energy landscape," Landau explained. "By doing this, we can learn about the characteristics of proteins including possible folding pathways and folding intermediates. Thus, it allows us to bridge the gap between statistical and experimental results."

Unfortunately, so much is happening physically and biochemically as proteins fold into their functional shapes (called the native state) that the problems must be broken down one by one and studied. That led the team to a question: Could they use a Monte Carlo Simulation along with the Wang-Landau algorithm to discover an efficient simulation method capable of sampling the energy density states that allow such folding?

Perhaps remarkably, they did. The first step in studying the dimerization process was to estimate those states in GpA using Wang-Landau. The second step was to sample various energy and structural "observables" of the system to provide insights into the thermodynamics of the entire system.

The results could be broadly applied to many fields of protein-folding studies that are important to understanding—and treating—certain diseases. (Wang-Landau, named for David Landau and Fugao Wang, is a Monte Carlo algorithm that has proved to be useful in studying a variety of physical systems. Wang was a doctoral student at UGA and now works for the Intel Corp.)

GpA is a 131-amino acid protein that spans the human red-blood cell membrane and is crucial in cell procedures. Because it has been studied in depth for many years, it also serves as an important model system for how similar systems work. That's why the new simulation may open doors in many other areas of inquiry.

"The main advantage of this two-step approach lies in its flexibility as well as its generality," said Landau. "This method is widely applicable to any study of biological systems, such as the folding process of soluble proteins, polymers, DNA or protein complexes. Therefore, it is an excellent alternative to other simulation methods used traditionally in the field of protein-folding thermodynamics."

In the current study, the team discovered something generally important about membrane proteins in general, too. They found that unlike some proteins for which folding is mainly governed by their attraction to or repulsion by water, the process in GpA is driven by a subtle interplay between multiple types of interactions.

Source: University of Georgia (news : web)