

X-ray scattering shines light on protein folding

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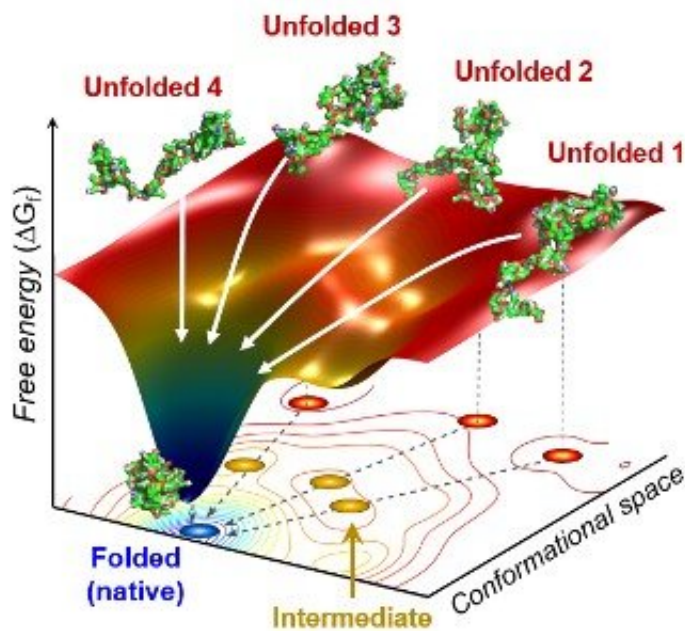


Figure. The scientists found that non-functional unfolded forms of the protein cytochrome c follow different pathways and timelines to reach a stable functional folded state. Credit: The Korea Advanced Institute of Science and Technology (KAIST)

KAIST researchers have used an X-ray method to track how proteins fold, which could improve computer simulations of this process, with implications for understanding diseases and improving drug discovery. Their findings were reported in the *Proceedings of the National Academy of Sciences* of the United States of America (*PNAS*) on June 30.

When proteins are translated from their DNA codes, they quickly transform from a non-functional, unfolded state into their folded, functional state. Problems in folding can lead to diseases like Alzheimer's and Parkinson's.

"Protein folding is one of the most important biological processes, as it forms the functioning 3-D protein structure," explained physical chemist Hyotcherl Ihee of the Department of Chemistry at KAIST. Dr. Tae Wu Kim, the lead author of this research from Ihee's group, added, "Understanding the mechanisms of protein folding is important, and could pave the way for disease study and drug development."

Ihee's team developed an approach using an X-ray scattering technique to uncover how the protein cytochrome c folds from its initial unfolded state. This protein is composed of a chain of 104 amino acids with an iron-containing heme molecule. It is often used for protein folding studies.

The researchers placed the protein in a solution and shined ultraviolet light on it. This process provides electrons to cytochrome c, reducing the iron within it from the ferric to the ferrous form, which initiates folding. As this was happening, the researchers beamed X-rays at very short intervals onto the sample. The X-rays scattered off all the atomic pairs in the sample and a detector continuously recorded the X-ray scattering patterns. The X-ray scattering patterns provided direct information regarding the 3-D protein structure and the changes made in these patterns over time showed real-time motion of the protein during the folding process.

The team found cytochrome c proteins initially exist in a wide variety of unfolded states. Once the folding process is triggered, they stop by a group of intermediates within 31.6 microseconds, and then those intermediates follow different pathways with different folding times to

reach an energetically stable folded state.

"We don't know if this diversity in folding paths can be generalized to other proteins," Ihee confessed. He continued, "However, we believe that our approach can be used to study other [protein folding](#) systems."

Ihee hopes this approach can improve the accuracy of models that simulate protein interactions by including information on their unstructured states. These simulations are important as they can help identify barriers to proper folding and predict a protein's folded state given its amino acid sequence. Ultimately, the models could help clarify how some diseases develop and how drugs interact with various [protein](#) structures.

More information: Tae Wu Kim et al. Protein folding from heterogeneous unfolded state revealed by time-resolved X-ray solution scattering, *Proceedings of the National Academy of Sciences* (2020). [DOI: 10.1073/pnas.1913442117](https://doi.org/10.1073/pnas.1913442117)

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