

# 'Snapshots' Shake Up Views about Proteins

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In 2002, University of Maryland biochemist Victor Muñoz observed something about proteins that challenged the generally accepted theory about how proteins assume their biologically active states – a process called folding. Muñoz suggested that, in contrast to the belief that all proteins fold in one sudden movement, some of them in fact fold and unfold gradually, in a random series of steps called downhill folding.

In the June 15 online issue of the journal *Nature*, Muñoz presents clear evidence of the potential of his earlier observation. Using nuclear magnetic resonance spectroscopy, which allowed detection of protein folding events at the level of single atoms, Muñoz and his team produced the equivalent of a sequence of snapshots of the protein folding process. Their findings could change the way scientists look at proteins, the molecular nanomachines that perform most of the body's critical functions.

“We found that some proteins do not fold like popcorn exploding, but do it in a more gradual downhill folding process that can be dissected with modern high-resolution techniques,” says Muñoz. “We were able to see the folding process with such resolution because we could stop it at a certain point, observe a property, then move on to the next step. We can now ask specific questions about the rules of protein folding.”

Understanding protein folding could lead to the ability to manipulate proteins to prevent disease, such as Alzheimer's and Parkinson's Diseases, which result when protein folding goes awry; create proteins that could prevent crops from freezing; or even design simple proteins

that can be used as laundry detergent.

## **The Downhill Fold**

A protein must fold into a specific and unique three-dimensional structure to be functional. The totally scrambled protein and the finished 3-D structure are all scientists have previously been able to see, which led many to believe that folding was a one-step process. “Obviously, the process had to be much more complicated than that,” says Muñoz. “The question was to find the appropriate protein and methods to unveil all this complexity. By analyzing individual atoms in a downhill protein, we were able to resolve the structural events that take place during folding.”

Muñoz compares this process to figuring out how a car is assembled. “It’s very hard to understand how a car is put together by just looking at all the pieces in the storeroom or the complete car exiting the assembly line. You don’t know what the parts do or how they are put together. But if you can look at each step of the assembly process, then you have the blueprint you need to build the car.”

## **Starting With a “Mess”**

Muñoz’s team looked at many atoms in the folding process. “It looks like a mess at first, but with sophisticated statistical tools, you start to see exquisite patterns,” says Munoz. You start to see what is connected to what, how the folding forces are acting to hold atoms together in space. Confirming the atom-by-atom assembly process characteristic of downhill folding gives us a new recipe for studying protein folding.”

Co-authors of the paper are Mourad Sadqi and David Fushman, also of the University of Maryland. The research was supported by grants from the National Science Foundation and the National Institutes of Health.

Source: University of Maryland, College Park

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