A Model Reveals Proteins' Bold Fold

To live, every organism looks to its genes for guidance. From its DNA, it receives instructions that tell it how to make proteins.

Those proteins — big, crumpled molecules — serve as an organism's biological workhorses. Starting out as long sequences of amino acids, proteins fold into unique shapes that enable them to perform their very specific tasks.

But exactly how they fold has remained mysterious. What folding rules do proteins follow to transform a certain sequence into a specific shape? Could one learn those rules and use them to predict how a protein actually folds?

Addressing this issue, chemist Peter G. Wolynes of the University of Illinois at Urbana-Champaign, physicist Jose N. Onuchic of the University of California, San Diego, and their colleagues describe a method to explain some of the intricacies of protein folding.

To do this, they merge a theoretical model with experimental data to show how an unfolded protein starts out with many possible shapes and, through a series of steps, narrows down its options to obtain a final natural structure.

"Folded proteins are marvels of molecular engineering," the scientists say in the March 17 SCIENCE. "A protein navigates with remarkable ease . . . as it explores many possible physical configurations. This feat is beginning to be quantitatively understood by means of statistical mechanics and simplified computer models."

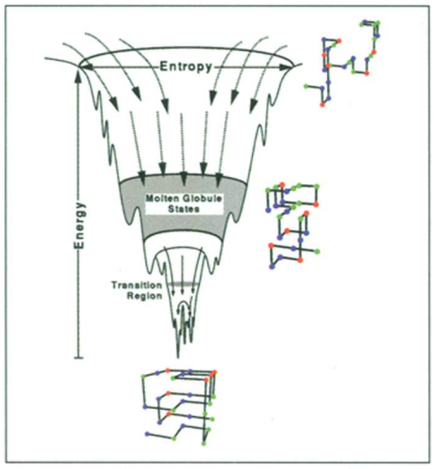
An elaboration of their work will appear in the April 11 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

Before folding, a protein faces so many possible shapes — about 10^{60} options for a protein with 60 amino acids — that to evaluate every one is impossible. "An unguided search, like a drunk playing golf, would take practically forever," the scientists say.

So they looked at the problem from a different angle, asking how the molecule settles into its most stable shape.

In stabilizing itself, the protein moves through an energy "funnel" (diagram), which guides it through many potential shapes to the one that minimizes its energy, Wolynes says. While folding, the molecule runs the risk of getting stuck, so to speak, in a relatively stable (but not the most stable) shape. To prevent that, the team finds, the funnel sides must be fairly steep, helping the molecule to get through bottlenecks.

To hone the model, the scientists introduced laboratory data from real folded proteins into a computer program that represents unfolded molecules as "necklaces of beads." After cross-checking the model against natural proteins, they expect that under the right circumstances, a bead model will effectively show how and why a protein collapses into its natural structure.



Nicholas D. Socci/UCSD

An energy "funnel" moves a protein from randomness (top) to a partly folded, or molten globule, state (middle) to a properly folded shape (bottom).

"Obviously, a real protein isn't as simple as these little beads in the model," Wolynes says. "Real proteins have special structural features, like hydrogen bonds and side chains. But when you include all of those details in the model, it becomes too complicated computationally."

"Even though this model has relatively few parameters, we could still see a correspondence between what happens in the model and what happens in real proteins," he says. "The model allowed us to dissect the folding process."

Previous attempts to make such models focused more on qualitative than quantitative aspects of folding, he says.

— R. Lipkin

Italians discover mouse model for ulcers

Bacteria known to cause ulcers in people now wreak gastric havoc in mice as well. This mouse model of persistent infection may help pave the way for development of a vaccine to protect humans from the microbe, which has also been linked to stomach cancer.

The corkscrew-shaped bacterium in question — *Helicobacter pylori* — infects an estimated 50 percent of the world's population.

Researchers had previously infected monkeys and pigs with *H. pylori,* enabling scientists to study the disease. But these animals are large, expensive, and sometimes hard to handle. Now Rino Rappuoli of the Immunobiological Research Institute of Siena in Italy and his colleagues have created a cheap, easy-to-use rodent model of ulcers.

The Italian team first infected mice with a strain of *H. pylori* known as type I. Those mice soon resembled their suffering human counterparts, exhibiting ulcers and severe stomach inflammation.

"The beauty of this model is that we reproduce the full-blown disease," Rappuoli says. This finding fits with the observation that type I *H. pylori* predominates among humans with ulcers.

The team also reports that mice infected with the type II strain of *H. pylori* showed signs of mild gastric inflammation but did not develop ulcers.

The researchers then turned their attention to the development of a vaccine. They knew that type I *H. pylori* produces a protein called vacuolating cytotoxin (VacA) that, with long-term exposure, ulcerates the lining of the stomach. Could they harness this powerful protein to provoke an immune response that would shield uninfected mice from *H. pylori* infection?

Rappuoli's team gave healthy mice two doses of VacA in solution 14 days apart and then challenged them with type I bacteria. The researchers found no evidence of *H. pylori* infection or ulcers in the mice.

To see if they could ward off type II infection in the animals, the researchers turned to another protein — urease — that is produced by both strains of *H. pylori.* They discovered that a solution of urease generated a response that protected mice from infection with either type I or type II *H. pylori.*

All told, the team has conducted 13 separate experiments with more than 300 mice. In the March 17 SCIENCE, they report that 79 percent of vaccinated mice resisted *H. pylori* infection.

The findings raise the prospect of developing a vaccine that could be given to human infants to ward off *H. pylori* infection, remarks infectious disease specialist Lucy S. Tompkins of the Stanford University School of Medicine, who wrote an accompanying comment in SCIENCE.

She believes researchers can use this mouse model to delve into the mystery of how *H. pylori* evades the human immune system to cause a lifelong infection. "The development of a small rodent model — where you could examine how the organism causes the disease — is critically important," she adds. *— K. Fackelmann*