



# Foldit

## Has Scientists and Laymen Alike Predicting Protein Structure

By Terri Yablonsky Stat, MA



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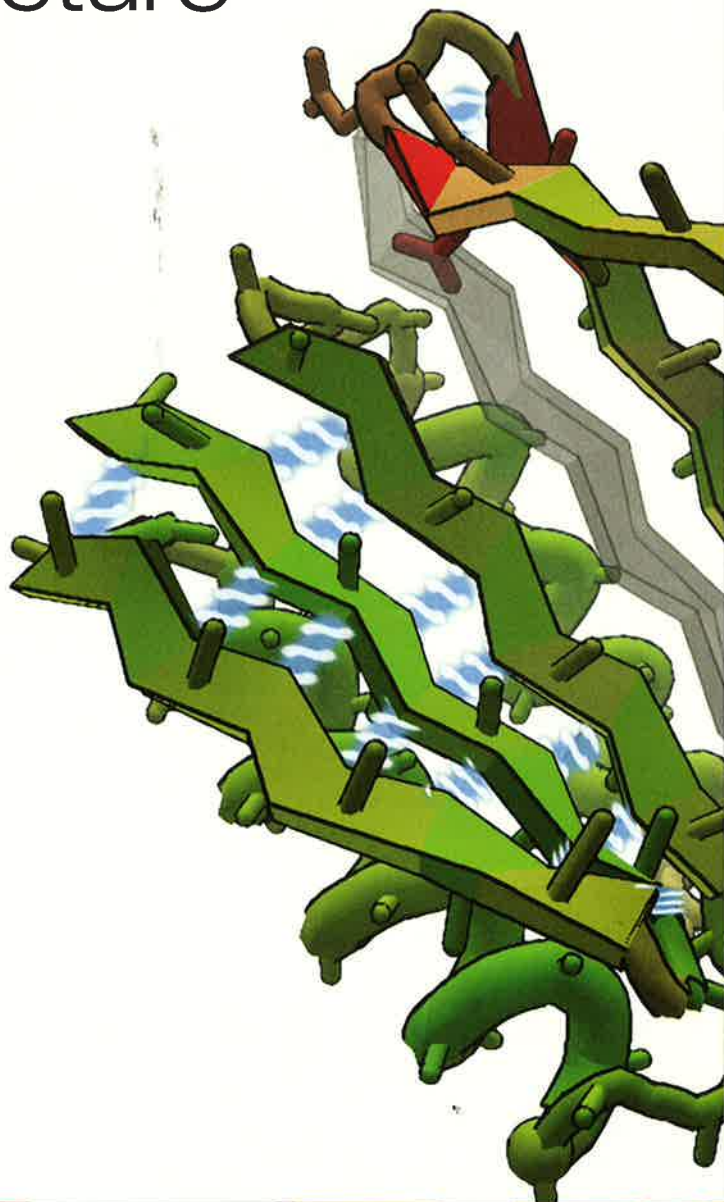
**A** revolutionary online protein folding game has taken hold worldwide and in the process may help scientists design better drugs. It allows nonscientists—the general public—to contribute to scientific research and potentially find cures for major diseases.

In May 2008, David Baker, PhD, a professor of biochemistry at the Howard Hughes Medical Institute at the University of Washington, launched Foldit, a free game in which players around the world compete to predict the structure of proteins. Baker is world-renowned for his efforts to predict the three-dimensional structures of proteins from their sequences of amino acids.

By predicting the structure of a protein, scientists can better understand how it works and eventually create new drugs and therapies. Proteins fold into unique three-dimensional shapes in infinite ways. Baker and his colleagues have spent the last decade developing computer algorithms to predict how certain proteins fold into their characteristic shape.

In 2005, Baker and his colleagues developed a software program called Rosetta@home, which uses the computers of hundreds of thousands of volunteers around the world to determine the three-dimensional shapes of proteins. Rosetta@home is based on SETI@home, which uses Internet-connected computers to search for signs of extraterrestrial life.

“With Rosetta@home, we’ve made huge strides in quite a few areas,” said Baker. “We have predicted protein structure accurately and the interactions between proteins, have designed new proteins and new enzymes, and are working to develop new vaccines. My group is interested



in predicting structures in naturally occurring proteins and in designing new proteins that can do things for society, such as help repair mutations that cause disease, create new protein inhibitors to block pathogens, and design new vaccines for HIV. They essentially involve search problems. The more explorers you have, the better you do. Rosetta does this with 200,000 explorers, and everyone radios back their results."

When volunteers participate in Rosetta@home, the course of their search is visible online. "The Rosetta volunteers wrote in and said their computer was going in one direction but this other direction is better," said Baker. So Baker and University of Washington computer scientist Zoran Popovic began to think of ways to make Rosetta more interactive and to speed up structure prediction using humans' puzzle-solving abilities. They created Foldit, in which people compete to fold the best proteins. "Foldit works the same as Rosetta with protein structure prediction, but the computer isn't running the whole show," said Baker. "The person comes in and can affect whether to move right or left."

Until now Foldit has focused on structure prediction. "The question we're trying to answer is, 'Can people do a better job of predicting structural proteins than computers?'" said Baker. "The results aren't totally clear but appear to indicate that people are better than computers."

The next class of Foldit puzzles will be design-type problems. Gamers soon will be able to design all new proteins that could help create an HIV vaccine, block the flu virus, or clean up the environment. "The problems that we pose are ones that have a major impact on quality of life," Baker explained.

## Kids Can Play

Anyone, including children, can play Foldit. The Web site teaches users the basics of protein folding before letting them tackle real proteins from nature. Users can download the program for free and learn to play in about 20 minutes. "We've found people with definite spatial reasoning ability," said Baker. "Some are incredibly good at it, and the game has become an exciting, fun, interactive, competitive, and social experience."

Users' ability to network with other people only adds to the game's popularity. "We've learned a lot about how people work best in groups and what sorts of problems seem best suited to being solved by people," said Baker. "We've made a lot of progress but haven't answered the key question, which is, How much better are people than computers at solving these problems? We haven't figured out the optimal way of tying into human intelligence and that's what we're trying to do."

Steve Pletsch, who designs commercial low-voltage systems in Mesa, Arizona, has been playing Foldit since its creation. "I started during CASP (Critical Assessment of Techniques for Protein Structure Prediction, which are blind international challenges), more or less to see if it was possible to produce results comparable to those of the scientific community.

"It's challenging," said Pletsch. "I really enjoy puzzles, and this is one of the most advanced puzzles one could try to tackle in my opinion. It's also very competitive at times, since the puzzles and players are scored and ranked according to their score.

"Ultimately, the results may help to further meaningful research. It gives people with only a casual interest in the field the opportunity to contribute to a very worthwhile experiment. So far the results have been promising, and I am hopeful that some new breakthrough or the basis of a novel pharmaceutical with wide impact will come from this game."

Foldit has caught the eye of others in the scientific community. "My students certainly play with it and they are amused," said Rohit Pappu, PhD, associate professor in the Department of Biomedical Engineering and Director of the Center for Computational Biology at Washington University in St. Louis. "My 9-year-old daughter played with it and had a lot of fun. I don't think she has submitted a successful prediction yet. The overall goal, as I see it, is to develop better potential functions that will be able to discriminate correct protein structure from incorrect structure."

"The biggest challenge is that potential functions that are developed using information gathered about small molecules or pairwise contacts of amino acids aren't very good for folding proteins because they largely miss the correlations imposed by the polymeric nature of proteins," Pappu continued. "The premise of Foldit is to see if an uninitiated person making random and perhaps intuitive guesses can propose structural alternatives that serendipitously yield more accurate predictions. If these random successes can be catalogued, then one can imagine the development of machine learning tools that are trained not only to recognize successful random moves, but also to learn why these moves were successful.

"Using the device of a game is a very clever idea. You get the larger community invested in a problem that is very important and a game is probably the best way to do this. Based on the amount of excitement my daughter has experienced, it's a good thing. I'd rather she play this game than any others. It's good to get young, uninitiated minds involved in the process because it increases outreach for scientists. I intend to introduce this game to my class next semester, and I think it will be useful as a teaching device as well.

"One of the positive outcomes is likely to be the realization that, in devising scoring functions, we need to start thinking about constraints imposed by chain connectivity. For someone like me, the direction this would head to a better understanding of how the well-known driving forces work in concert to generate well-defined three-dimensional structures. If Foldit were to provide greater precision in structure prediction, then we might end up with a detailed understanding of why some sequences are more prone to correct folding.

"The big challenge is not only protein folding but also understanding how folding solves the solubility problem," said Pappu. "How is it some sequences fold and remain soluble and most others don't? To ask that question in the realm of a game is enormously beneficial for finding a way to keep some of these molecules soluble. Research into this area could have important implications for a range of problems in neurodegenerative diseases and in the biotechnology industry."

"Exercises or games that involve the broader community are good for science and society in general," Pappu said. "Getting scientists to play games to hone their intuition is going to be huge."

**Users can access the game at [www.fold.it](http://www.fold.it)**

*Ms. Yablonsky Stat is a freelance health writer in Northbrook, IL.*

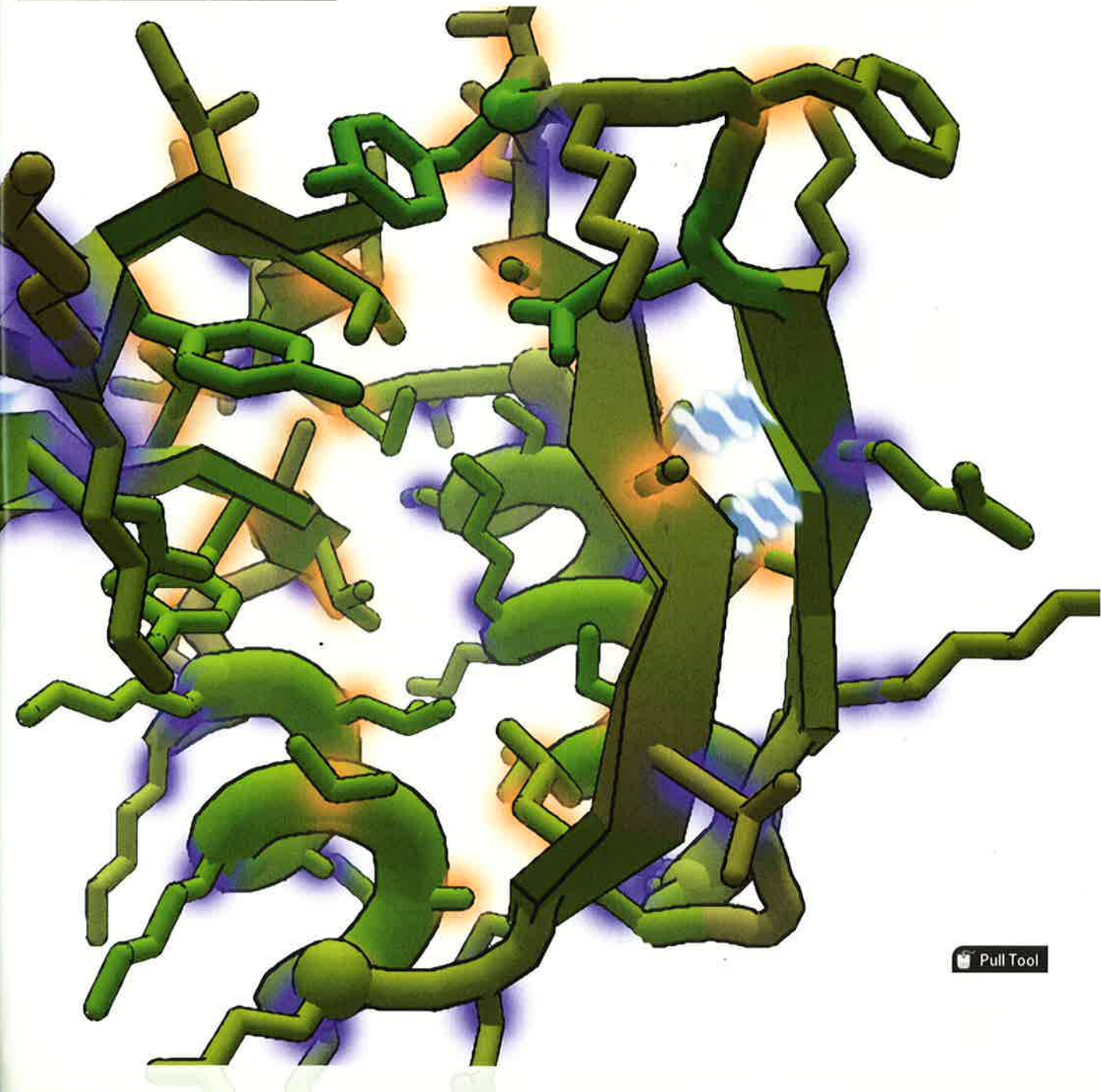




 Shake Sidechains  
 Wiggle Backbone  
 Clear Locks  
 Reset Puzzle

▲ Actions   ► History   ► File

Progress: 8899 of 10000  
 Level 4-2: A Sheet Out of Place  
 ► Chat



 Pull Tool


 What's New  
**Puzzle 48 Wins!**  
 Congratulations to the top scorers and their physics skills!

Rank	Name	Score	Time
1	Shankha	10,000	1:00:00
2	...	...	...

Several users are pulling upon this protein, but none is out of place. Pull the misaligned loop back to its home position. Once I target you successfully to lock, you'll get credit and points.

Progress: 8899 of 10000  
 Level 4-2: A Sheet Out of Place

Level 4-2: A Sheet Out of Place  
 Progress: 8899 of 10000