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Protein-Folding Game Taps Power of Worldwide Audience to Solve Difficult Puzzles

A cooperative online game that puts volunteer “gamers” to work folding proteins has attracted 50,000 players whose “distributed thinking” has, in some cases, proven more powerful than computers in predicting the three-dimensional structure of proteins. Extension of these efforts could one day pay off in the design of new proteins that help fight disease, sequester carbon, or clean up the environment.

The free game, called Foldit, is the brainchild of David Baker, a Howard Hughes Medical Institute biologist, and colleagues Zoran Popovic and Seth Cooper, who are in the computer science department at the University of Washington. The online community of Foldit players is now helping the researchers as they attempt to crack “the protein-folding problem,” one of molecular biology’s toughest challenges.

“The positive response to Foldit makes me very optimistic for getting the general public involved in science,” says Baker. “There’s a lot of creativity and energy out there that is being spent on computer games that could go into solving scientific problems. I’m very pleased we’ve been able to harness some of that energy.”

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Proteins are the miniature machines that carry out almost all the important functions in the body. Scientists have long known that the three-dimensional structures of proteins are completely determined by their linear amino acid sequence. Amino acids are the building blocks of proteins. Researchers now know the amino acid sequence of every protein encoded in the human genome. Until recently, however, it seemed nearly impossible to compute the

structures of proteins from their amino acid sequences, and solving this problem has been one of Baker's obsessions.

In creating Foldit, the researchers partly drew inspiration from "World of Warcraft" and other online games that have attracted millions of players who compete and cooperate to solve puzzles. Baker calls Foldit a success in "distributed thinking" – presenting scientific problems to the masses and attracting a talented crowd that contributes new solutions. An article describing Foldit is published in the August 5, 2010 issue of the journal *Nature*.

Foldit presents players with the challenge of folding proteins into their lowest energy shape. A set of online tools built into the game lets players tug, twist, and otherwise tweak individual segments of each protein, and they can direct traditional computer algorithms to carry out fine-tuning. As the target protein scrunches into a lower energy shape, the player's score rises. Players can compete individually or in teams, and a chat window lets players communicate as they wrestle with their structures. These social aspects of the game have helped draw a crowd: Not only do players enjoy the rewards of solving puzzles, they do so while interacting with other like-minded people. "The cooperative aspect really adds to the appeal of the game," Baker says.

An informal survey of 150 Foldit players revealed that many are non-scientists. For instance, the top five solo players contacted by Baker's team each reported no more than a high-school level biochemistry background. Non-scientists can excel at Foldit because the game requires no previous knowledge of protein folding. Instead, the game draws on visualization skills. "It's a bit like three-dimensional Tetris," Baker says.

With programming and game design provided by University of Washington computer scientists Seth Cooper (lead author of the *Nature* paper), Adrien Treuille (now at Carnegie Mellon University) and Zoran Popovic along with Firas Khatib and other researchers in Baker's group, Foldit debuted in May 2008 as an interactive extension of Rosetta, a computer program Baker developed to predict protein structures. Solving protein structures is one of the preeminent challenges in biology, requiring expensive, labor-intensive x-ray crystallography to divine the arrangement of the thousands of atoms that comprise each protein. Rosetta, in contrast, relies on a large scale search for the lowest energy shape of each protein – a computer-hungry process that requires trillions of calculations. Baker quickly realized that Rosetta was limited by the amount of supercomputer time he could secure. So in 2004 he developed a distributed version of Rosetta that individuals could load on their home or office computers to help perform some of Rosetta's calculations.

Some 200,000 volunteers have downloaded and installed Rosetta@home, which displays possible protein configurations as a screensaver. Foldit got its start when some of the Rosetta@home users told Baker that they wished they

had the ability to manipulate the proteins that their computers were helping to shape. “People saw that Rosetta was making obvious mistakes, and they were getting frustrated that they couldn’t manipulate the proteins themselves,” Baker says.

Now that they can, some players have proven themselves better than Rosetta at certain tasks. In a “blind challenge” run last year, Foldit players competed directly with the Rosetta program in establishing the shapes of 10 proteins whose structures were, at the time, unknown. Humans outperformed Rosetta in five of the 10 trials, and performed just as well as Rosetta in three other trials. Baker says that humans are particularly good at seeing holes in a developing protein that need to be filled with dangling bits called side chains.

“There’s this class of problems where a residue should be sticking into the core of the protein but it isn’t, it’s sticking out,” says Baker. “Rosetta moving that residue at random is not going to stick it into the core of the protein. But people can look at the protein, see that there’s a hole, look at the side chain, see that it’s sticking out, and put it in the right place. They’re very good at that type of problem.”

After soliciting e-mail feedback from top players – some of whom devote six or more hours to each protein puzzle – Baker says he’s overwhelmed by the sheer creativity displayed. “People wrote back these very, very sophisticated descriptions of algorithms they had come up with, how they had combined the tools we provided in very novel ways.”

Next up: Getting Foldit players to design proteins from scratch. Baker works with other scientists who are searching for new proteins that will act as drugs or contribute to environmentally-friendly projects such as making biofuels from carbon dioxide and sunlight.

“Designing new proteins to fit a desired shape is something that Foldit players should be very good at,” says Baker. While it may be years before a new crowd-sourced virtual protein helps solve a real-world problem, Baker is convinced that day will arrive. “The moment we test a protein design in the lab that came from one of the Foldit players and find it carries out the desired new function will be an amazing day for science,” he says.