Folding Phenoms

Some computer gamers are proving to be valuable partners for protein biologists.

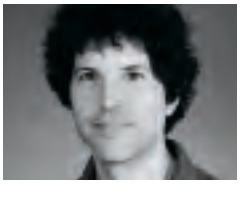
STEVE PLETSCH ISN'T A BIOCHEMIST. THE 32-YEAR-OLD ELECTRICAL designer from Mesa, Arizona, spends his working hours planning how to wire fire alarms and security systems. So it might seem surprising that researchers at the University of Washington in Seattle invited him to show them how to fold proteins. ¶ Though not a scientist, Pletsch is a whiz at "Foldit," a computer game designed by HHMI investigator David Baker and colleagues in which players rack up points for sculpting an on-screen protein into the most stable conformation.

The Foldit team has been analyzing the skills and strategies of prodigies like Pletsch—so-called folding savants—for guidance on how to teach computers better ways to predict protein structure. And through a new version of the game, these virtuosos and other Foldit fans now have a chance to take on a bigger task: designing proteins that might become the next generation of treatments against diseases such as influenza, cancer, and HIV/AIDS.

Every protein folds into a characteristic shape that dictates what job it can perform. Like the seating arrangement at a dinner party, the conformation reflects attractions and repulsions. Water-shy amino acids, for example, huddle in the interior of the molecule. Some pairs of amino acids make good neighbors, whereas others don't mesh because of their bulky side chains. Scientists often nail down a protein's shape experimentally through x-ray crystallography and nuclear magnetic resonance spectroscopy, but these laborious techniques can't keep up with all the new proteins being discovered, says Baker.

As an alternative, researchers often hand the job over to a computer, which can make folding predictions based on the amino acid sequences of proteins. Over the past decade, Baker's team has devised some of the best algorithms for making these forecasts, consistently topping a biennial fold-off called CASP (Critical Assessment of Techniques for Protein Structure Prediction). But predicting the shape of a protein that comprises hundreds, or maybe thousands, of amino acids can overwhelm even a supercomputer.

To speed up the work, Baker and colleagues parceled out the analysis in 2005 through Rosetta@home, a project in which some 200,000 people have allowed their computers, during downtime, to perform a portion of the folding calculations. Baker says that the inspiration for Foldit came from Rosetta users who watched the program's progress on their screen savers and reported that it wasted time testing obviously incorrect configurations. The researchers wondered whether humans could do better. Computers are stuck with a big limitation, says Baker—they select the



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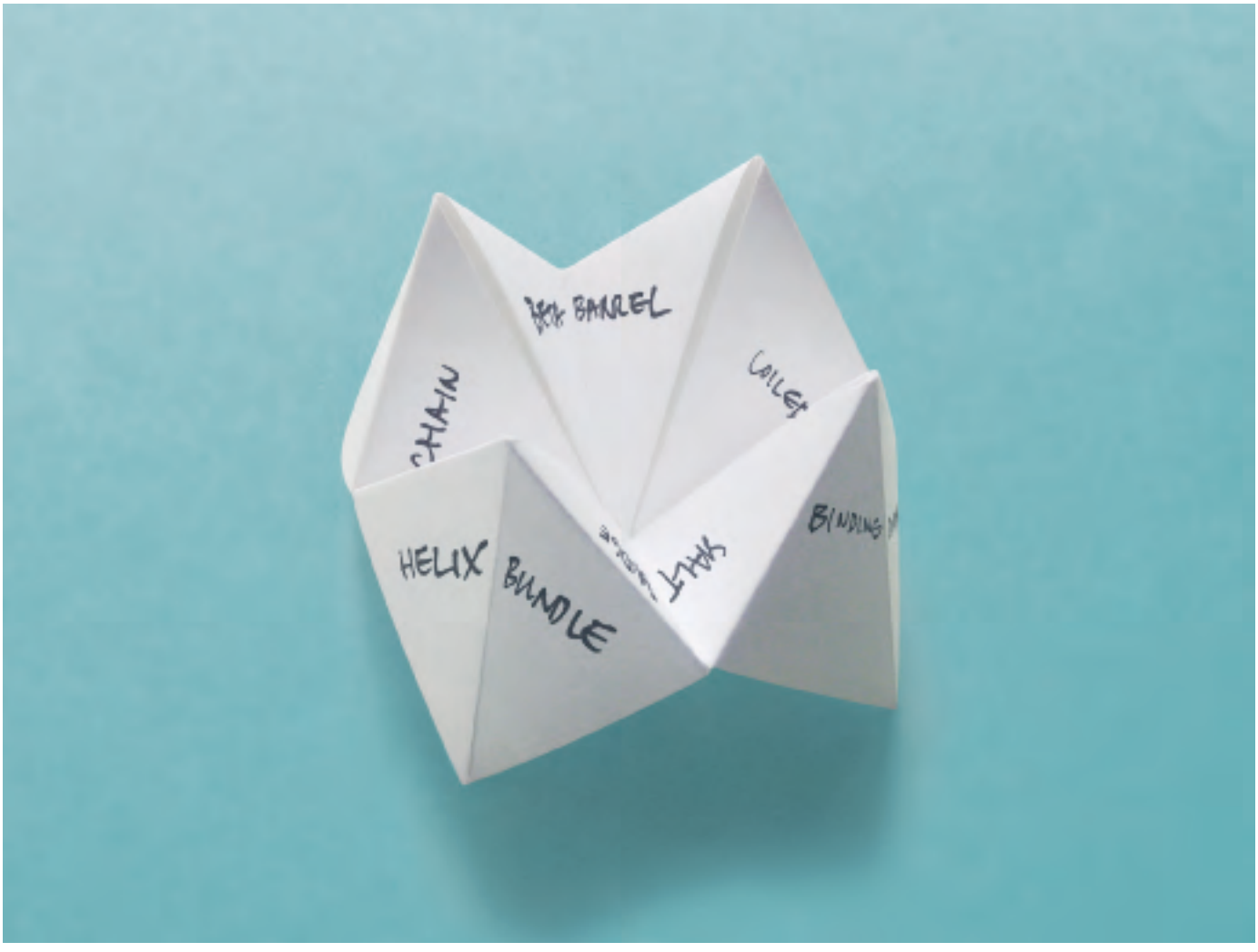
DAVID BAKER

University of Washington



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next step at random. "People won't be moving around randomly. They will use insight to find the best step."

Pletsch says he started playing Foldit shortly after its Internet release in May 2008. Folding solo, he has set the top score on more than 30 of the challenges posted on the website, and he's one of the star performers on the "Another Hour Another Point" team.

Over the last year, Baker and colleagues have invited a handful of Foldit savants, including several Another Hour members, to Seattle for debriefings. In two 20- to 30-minute computer sessions last October, Pletsch showed off his best moves. He says he doesn't stick to a script when he folds, but he does follow a rough plan. For example, he usually starts by giving the protein a few good shakes, which can jostle the molecule into a more efficient configuration.

What impressed Baker about Pletsch's play was his facility for breaking up the molecule onscreen and piecing it back together in a more efficient shape. According to Baker, that requires "phenomenal visual ability."

Baker won't say that humans are better than computers at folding proteins. But he and his colleagues are poring over the savants' play to reveal steps that a computer could emulate. Some attributes of these master players are already clear, though, such as having really good three-dimensional visualization skills. "Being a scientist doesn't help at all," says Baker, who admits his own performance on the game is middling—his 13-year-old son trounces him.

The team recently provided the savants and other Foldit aficionados with a new way to tickle their brains: designing compounds that could possibly furnish treatments for AIDS, malaria, and other diseases. The first challenge, which the team plans to release soon, will ask players to craft a molecule that can jam the flu virus and prevent it from entering cells to start an infection. Pletsch says he's eager to give the design feature a try. "It allows someone with a casual interest to take a crack at some usable solutions." ■

–MITCH LESLIE