



LEFT \_ DRAWING ON COMPUTER POWER FROM VOLUNTEERS WORLDWIDE, DAVID BAKER SEES "A COMMUNITY-BASED SOLUTION TO A LONG-STANDING SCIENTIFIC PROBLEM."

# Protein Detectives

*To discern the twists and folds of these basic biological machines, David Baker relies on the kindness of strangers.*

**MOST SCIENTISTS CULTIVATE COLLABORATIONS** to advance their work. But we're betting only David Baker has colleagues in Andorra, Belarus, and the Pitcairn Islands. Not to mention the rest of the world.

An HHMI investigator at the University of Washington, Baker relies on collaborators worldwide to help him uncover nature's rules for protein folding—the process by which a protein shapes itself to fulfill its function. Determine a protein's structure, researchers believe, and you can learn how this essential biological machine works. But getting to that point, from a mere amino acid sequence, requires computer power on a gargantuan scale. That's where Baker's far-flung friends come in.

Software that Baker and colleagues created taps participants' PCs during downtime—the computers perform protein-folding calculations while their owners, in effect, sleep. Harnessing that vast capacity, Baker has made considerable progress in the quest to compute protein structures from their sequences of amino acids. Progress has been so good, in fact, he now predicts that many, if not most, protein structures and interactions will one day be computable—a level of confidence that protein researchers have previously lacked.

Three recent accounts from the Baker lab (published in the September 16 and October 28, 2005, issues of *Science* and the August 1, 2005 issue of *Proteins*) report that given enough computing power his protein-modeling software, called Rosetta, can produce protein models that look like their natural counterparts at least about a third of the time. And Baker's results with determining the structure of a protein once it "docks" onto a partner are even better. Together, the papers demonstrate that it's possible to achieve high-

resolution prediction of protein structure by first sampling a large number of potential variations at low resolution and then refining the best candidates with modeling that accounts for all of the atoms in the molecule.

"These results suggest not that the critical problems of protein-structure prediction are solved," says Baker, "but rather that accurate modeling now

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DAVID BAKER

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## BACK STORY: ROSETTA

The Rosetta Web site (<http://boinc.bakerlab.org/rosetta/>) details how participants can volunteer their computers in the hunt for low-energy protein structures. Once they sign up from the site, a server in Baker's lab automatically sends out jobs to participants' computers, which run protein-folding calculations in the background.

Predicting protein structure involves finding a structure that has lower energy than any other structures the protein could adopt. So each individual computer is on a search for the lowest energy structure. "Each computer is like an explorer parachuting into a particular place on a huge landscape, exploring the neighborhood, and reporting back on the lowest elevation point it found," Baker says.

appears to be an achievable goal." To take it to the next level of accuracy, he says, will require still more computing power and better understanding of how linear sequences of amino acids transform into fully functional folded proteins.

Some kinds of proteins resist prediction more than others, however. "It's very difficult right now to accurately calculate interactions involving charged atoms," Baker says. "These are often in places like the active sites of enzymes, so this is a critical problem to solve. But more computing power will definitely help us search these landscapes better."

Even before Rosetta is refined to the point that it can accurately predict the structures of large proteins, it can be used to create altogether new proteins (see [www.hhmi.org/news/baker3.html](http://www.hhmi.org/news/baker3.html)).

"There's no reason to rely strictly on what nature has provided through evolution," says Baker. "For example, we are interested in designing novel enzymes that catalyze reactions not catalyzed by naturally occurring proteins, and new endonucleases—proteins that can cleave DNA at a specific place—which could be useful in controlling pathogens. And we are very excited about our work using computational design methods to try to design a vaccine for HIV. You can imagine that the perfect vaccine might be a very stable, carefully designed protein that would guide the immune system to the Achilles heel of the virus, and that you could make in large amounts and ship all over the world." ■

-Karyn Hede-