NewsBytes

Unraveling the Complex Functions of Proteins

At the birth of a new field, a conference can act as a midwife, making sure the infant enters the world smoothly. Such was the case for the Automated Function Prediction (AFP) conference held at the University of California, San Diego, at the end of August 2006. The field, in which researchers try to computationally determine a protein's function, appears to have arrived in good health.

"I feel we went quite far in creating an identity for this field," says **Adam Godzik, PhD**, program director in bioinformatics and systems biology for the Burnham Institute for Medical Research in La Jolla, California. The conference drew independent researchers who worked together for the first time to establish a common language, Godzik says, as well as a compilation of available methods and a way to evaluate the success of various techniques.

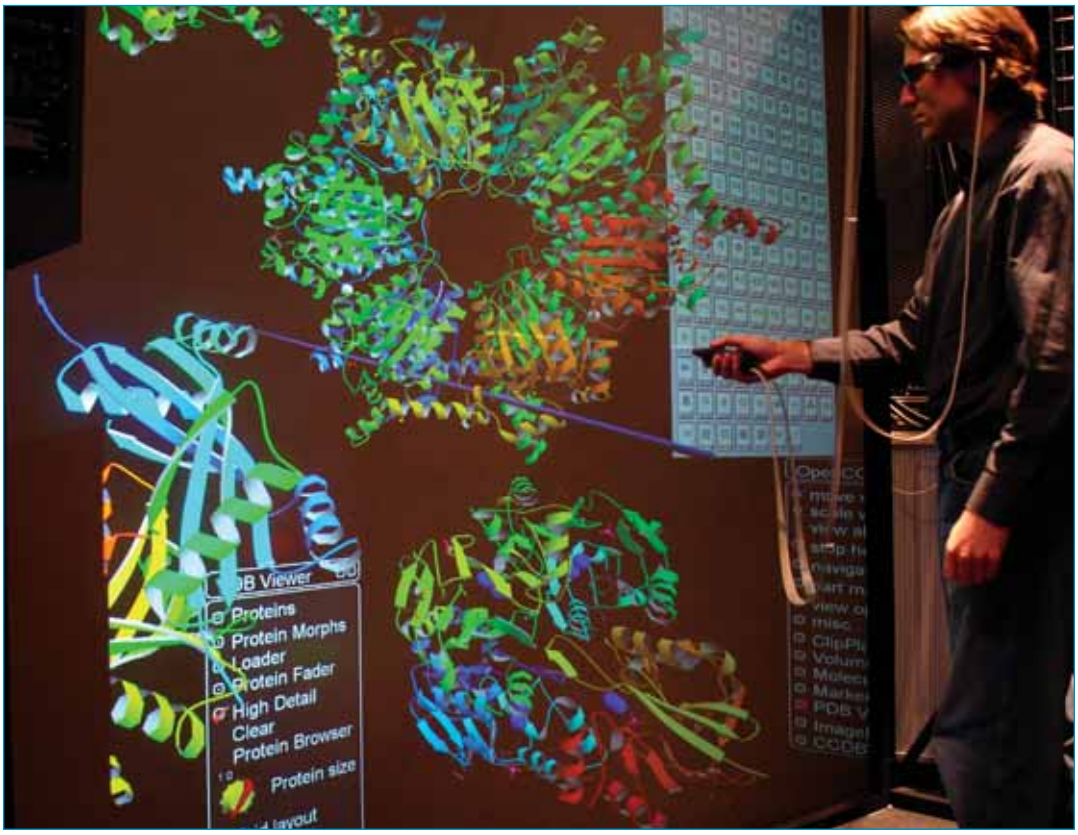
For decades, biochemists have tried to solve the riddle of what individual proteins do. They've done this in the lab, painstakingly slowly. But scientists now sequence genomes far faster than they can assign functions to the corresponding proteins. When there were only a few sequenced genomes, this problem was relatively small in scale and seemed manageable. But, says **Iddo Friedberg, PhD**, the conference organizer and a postdoctoral associate in Godzik's lab, "By sheer scale the problem has changed."

Now, using computational methods, researchers can tease through to answers much more quickly. At the AFP conference, those adept at the process charted the future of this discipline.

Their approach weaves together methods biologists have used for years. They include physical analysis of a protein's structure; genomic context, in which researchers compare a protein's position in a gene to those of similar genes elsewhere with known functions; and what Friedberg calls "guilt by association," or information gleaned in the laboratory about what the protein does when a cell undergoes a particular process. But because they're using computers and high-level algorithms, AFP researchers can now analyze more information faster and come to more robust conclusions about the workings of previously mysterious proteins. Visit http://BioFunctionPrediction.org for more information.

Godzik was pleased with the progress the conference made in crystallizing the field. "Until now," he says, "automated function prediction has been a black art."

—Brittany Grayson



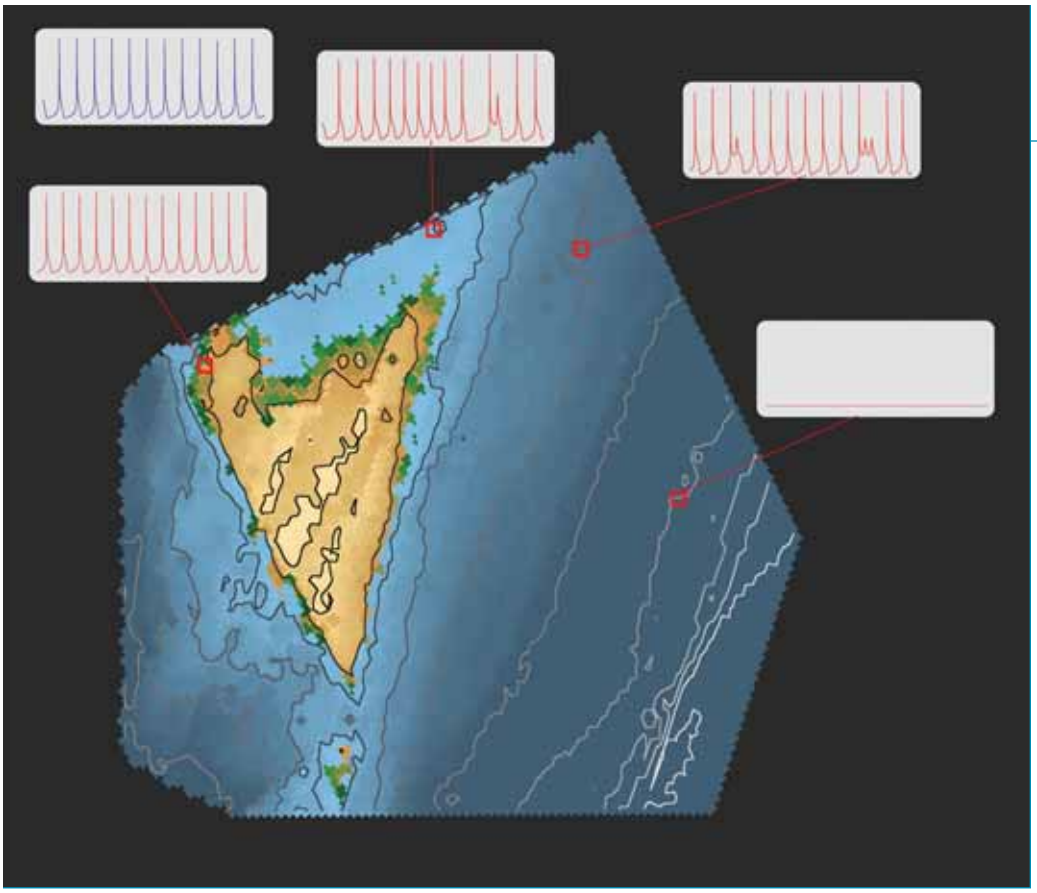
AFP conference participant* Jurgen Schulze, PhD*, receiving an immersive experience of protein functional sites in the virtual reality cave at California Institute for Telecommunications and Information Technology. The software supports collaborative viewing of proteins at multiple sites on the internet. Courtesy of Jurgen P. Schulze.

Neurons Seek Their Own Solution

Each cell in our nervous system is an instrument in a complex symphony of electrophysiologic communication. A neuron's signaling abilities arise from its array of ion channels—tunnels within the cell's membrane that act as gatekeepers of electrical charge. But how does a cell determine the types of channels it needs and where in its membrane they should sit? The results of a new computer model suggest that even with markedly different patterns of ion channels, neurons still can come to play the same tune.

The work supports a growing paradigm shift in neurophysiology, says **Erik De Schutter, MD, PhD**, professor of neurobiology at the University of Antwerp, Belgium, lead author of the study. "We used to think of [ion channels] as LEGO blocks," he explains—with a predetermined number, type and position regulating how the neuron fires.

More recently, physiological experiments have suggested that cells with wildly different ion channel compositions could have similar firing patterns. But researchers have consistently attributed such variability to



One neuron firing pattern can be produced in a variety of ways. Here, typical voltage traces of different computational models (red) have to be compared with the experimental data (blue). The image shows a view of a small slice of the complex landscape for which thousands of parameter sets have been tested. Fitness has been color coded: Good models form a brown island surrounded by a blue sea of bad models. In other parts of parameter space (not shown) similar isolated islands of good models can be found.

experimental error, clinging to the notion of a "platonic ideal" of a neuron with an unchangeable firing pattern.

To look at the problem more closely, De Schutter and **Pablo Achard, PhD**, a postdoc in his lab, computationally modeled the Purkinje cell, an especially complex type of neuron best known for forming as many as 200,000 synapses. The team's model specified 10 types of ion channels and broke the cell into four different regions that the channels could occupy. Using a mathematical approach called the phase-plane method, the model neurons were permitted to evolve their ion channel densities to produce all four firing patterns that Purkinje cells display. To the researchers' surprise, about 20 possible combinations of ion-channel densities fit the bill. The results were published in the July 2006 issue of *PloS Computational Biology*.

The work suggests, De Schutter says, that neurons are preprogrammed for a particular type of firing pattern. Each cell then decides locally how to distribute ion channels to achieve its signaling goal. How well the model predicts real biological properties is not clear and is difficult to test experimentally. Neurophysiologists can record impulses from just a few neurons at a time; the sheer quantity of recordings needed for a thorough comparison with the model doesn't yet exist. "My estimate is you'd need about two people working full time for a year for that data," De Schutter says.

> "This paper is a beautiful example showing that we shouldn't be thinking about a single solution to capture what a neuron is doing," says Eve Marder, "but a family of solutions."

Regardless, the model provides a more nuanced version of how physiologists should conceive of their cells, says **Eve Marder, PhD**, a professor of biology at Brandeis University who studies both physiology and modeling in neurons. "The assumption has been that there was a single solution and the variance was your fault," Marder says. "This paper is a beautiful example showing that we shouldn't be thinking about a single solution to capture what a neuron is doing, but a family of solutions."
—Alla Katsnelson

Two Ways to Merge

Cell membranes fuse with other membranes to allow material in and out. If incoming material includes invading viruses, that can be bad news for the cells. Until recently, the process of membrane fusion has been poorly understood. Now, a powerful computer model shows that neighboring membranes can merge in two distinct ways—a fact that was previously unknown. The work could help researchers clarify how viruses invade cells, and possibly lead to ways to fight viral infections.

"Ultimately we'd like to be able to control fusion in biological systems and induce or inhibit it for therapeutic purposes," says **Peter Kasson, PhD**, a chemistry postdoctoral scholar at Stanford University and leader of the study. This paper takes steps in that direction. "Our model helps provide an explanation for how you get these two fusion processes," he says.

Previously, scientists debated whether membranes fuse by joining directly from