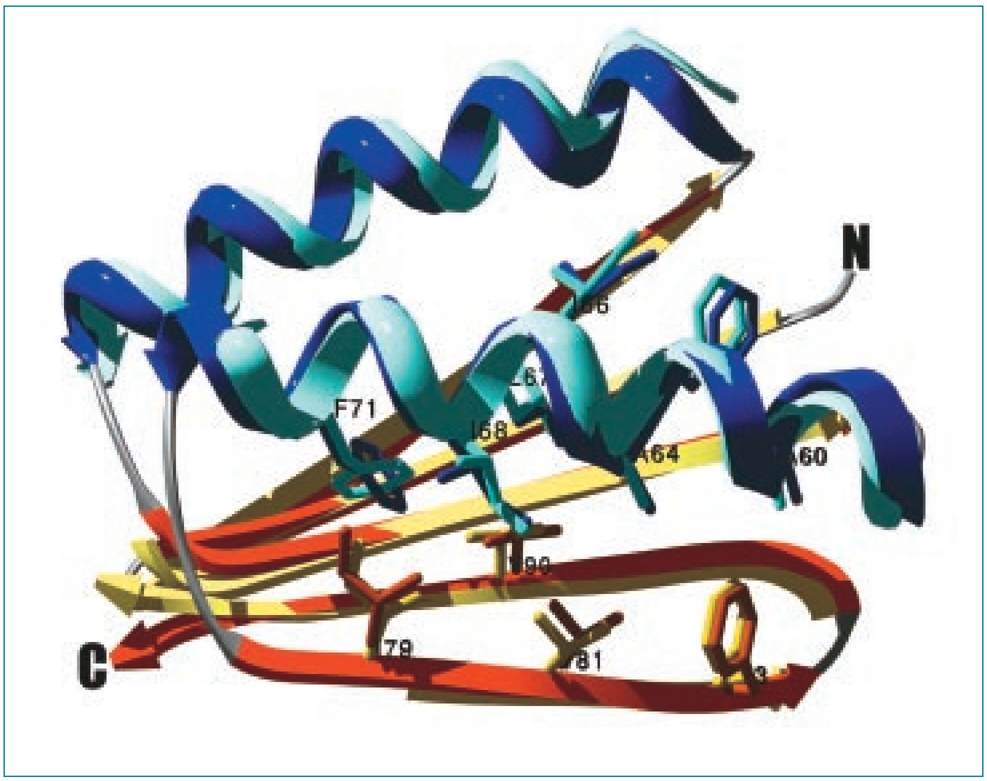
NewsBytes

And the Winner Is... Computer Aided Protein Design

Each year, the American Association for the Advancement of Science (AAAS) gives an award to an outstanding paper that appeared in the pages of *Science*. This year the award—the Newcomb Cleveland Prize—went to researchers who computer-designed and then synthesized a protein that matched the design. The paper was published in the November 2003 issue of *Science*.



The Top7 computational model superimposed on the x-ray structure. The backbones are represented as ribbons (computational model: helices - dark blue, strands - red; x-ray structure: helices - light blue, strands - yellow), while selected amino-acid side chains in the protein core are represented as sticks. Courtesy: David Baker

"You see all these marvelous structures in nature and there has always been a question of whether there could be a larger set of proteins that don't exist in nature," says David Baker, PhD, associate professor of biochemistry at the University of Washington and one of the paper's authors. "This paper showed such proteins do exist and people can make them with very high accuracy."

Baker and his colleagues designed their novel protein using an iterative process. They started with a three-dimensional cartoon of a structure and used an existing design program to find the lowest energy sequence of amino acids to fit that structure. Like fitting puzzle pieces within an abstract shape, the sequence wasn't a perfect fit for the pre-designed structure. So they perturbed the structure to fit the sequence and then tried again to generate the lowest energy sequence of amino acids to fit the new structure. They went through this process ten times, and ended up with a protein they called Top7.

When they then produced that same protein sequence in the lab, Top7 folded into a shape that very closely matched the computer design. And the shape is unlike anything found in nature.

The work has helped researchers who struggle with the protein structure prediction problem, Baker says. "The prediction and design problems are closely related. The insights from the Top7 design have been helpful in developing methods for prediction, and the reverse is also true."

Ultimately, Baker hopes to come up with novel protein machines and therapeutics. He's working on making enzymes that will catalyze reactions that aren't catalyzed in nature, and he's also trying to make better vaccines. It's

> When produced in the lab, Top7 folded into a shape that very closely matched the computer design. And the shape is unlike anything found in nature.

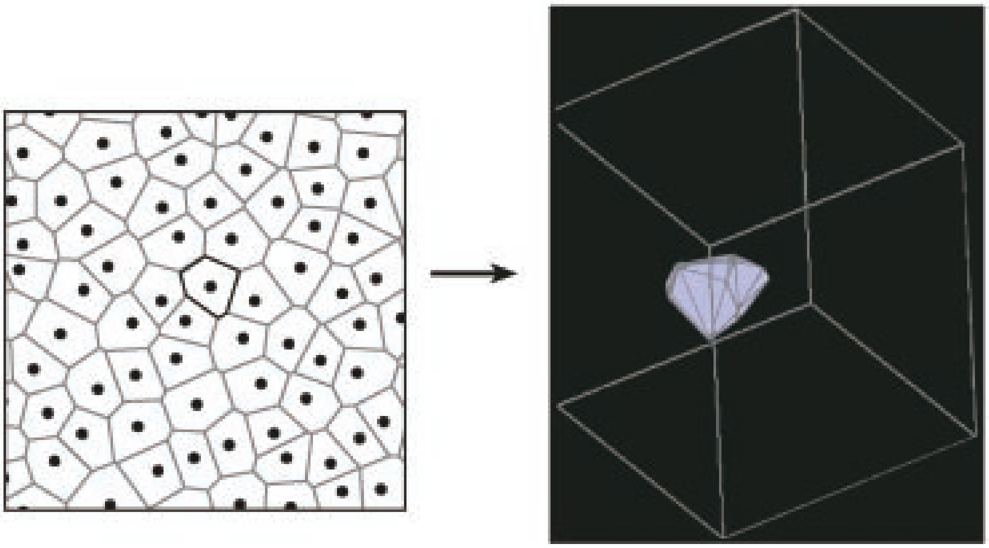
an open question whether vaccines might be best designed using a scaffold that doesn't occur in nature, Baker says. "Nature hasn't ever come up with a vaccine on its own."

Baker foresees a time when computer-designed therapeutics will become a reality, so long as they aren't too immunogenic. The AAAS award suggests that Top7 marks an important step in that direction.

Spaced-Out Neurons

Do neurons need personal space like people in an elevator? Are they influenced by their neighbors or do they randomly find a home in the brain? If the arrangement is patterned, what is the cause of the pattern?

These are all unanswered questions



Measuring the geometrical relationships defined by the position of neurons in 3-D, as shown on the right, is far more computationally demanding than doing so for the 2-D version on the left.

in developmental neurobiology, but that may soon change as a result of a National Institute of Mental Health grant to a group of multi-disciplinary researchers at the University of California, Santa Barbara and the University of Cambridge.

"We're creating software tools to analyze how neurons distribute themselves within the brain," says Benjamin Reese, PhD, principal investigator on the grant and a professor of psychology at UCSB. "We understand how neurons are born, the instructions governing their fate and how they then migrate, but virtually nothing about how they distribute themselves in three-dimensional space."

Reese and his colleagues have found that many types of neurons in the retina (essentially a two-dimensional space) respect one rule: they avoid being positioned near one another. This rule results in neurons being spread evenly across the retina, providing a uniform sampling of the visual scene—a characteristic required for good eyesight.

But neurons in other parts of the brain might function under additional or completely different rules. Moreover, 3-D space is harder to model using current software. "The algorithms we've created for studying the distribution of cells in two dimensions are all Matlab-based scripts," Reese says. "Once we add the depth dimension, they become extremely cumbersome." So he and his colleagues, including co-principal investigator Steven Eglen, DPhil, a lecturer at the University of Cambridge, are re-writing portions of the scripts in a lower-level language to improve computational efficiency.

"By July of 2006, we expect to have a website up and running with both two- and three-dimensional software available for others to download and use."

—Benjamin Reese.

The software will both simulate neuronal populations and compare the simulations to real biological data. The first simulation step: throw virtual cells into a defined space with various constraints (e.g., a specified vicinity to similar, or other types of, cells) until the cells achieve the same density as is found within a region in the brain. The researchers will also generate experimental data using transgenic animals that express fluorescently marked populations of nerve cells. They will measure those neurons' x-y-z coordinates and feed them into the software program. The software can then determine the geometry of the simulations repeatedly, looking for the best fit to the real biological data.

The group plans to make the software available to the public. "By July of 2006, we expect to have a website up and running with both two- and three-dimensional software available for others to download and use," says Reese.

Eventually, Reese would like to understand both cell spacing and its causes: "Is what spaces them apart a diffusible factor emitted by the cells, or is it contact-based, mediated by outgrowing dendrites?" Reese asks.

The understanding of neuron spacing may enlighten us about developmental disorders of the brain, Reese says. Mutations in genes that influence neuronal spacing may, in turn, alter the synaptic connectivity and circuit formation within the nervous system, altering brain function.

Binary Breathing

In September 2004, researchers at Pacific Northwest National Laboratory (PNNL) in Richland, Washington, received a $10 million grant to create a three-dimensional imaging and computer model of how the respiratory tract interacts with particles carried in the air. Ultimately, the researchers hope the effort will lead to a better understanding of what happens when