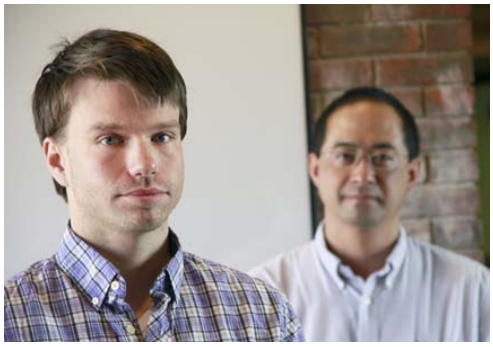
Slicing Proteins with Occam's Razor

Release Date: 09-29-2010

Author: Joshua E. Brown
Email: Joshua.E.Brown@uvm.edu
Phone: 802/656-3039 Fax: (802) 656-3203



Grad student William DeWitt and Professor Kelvin Chu, Department of Physics, have invented a new way to peer into proteins. Their paper in Physical Review Letters pinpoints which atoms within the protein myoglobin hold and release oxygen to meet the unique needs of different animals. (Photo: Joshua Brown)

A cheetah lies still in the grass. Finally, a gazelle comes into view. The cheetah plunges forward, reaches sixty-five miles per hour in three seconds, and has the hapless gazelle by the jugular in less than a minute. Then it must catch its breath, resting before eating.

A blue whale surfaces, blasting water high from its blowhole. It breathes in great gasps, filling its thousand-gallon lungs with air. Then it descends again to look for krill, staying below for 10, 20, even 30 minutes before taking another breath.

Both animals need oxygen, of course. And both depend on the protein myoglobin to store and then release that oxygen within their working muscles. But how they need oxygen differs. The whale must have enough to last a whole dive. Its muscles have a high concentration of myoglobin that delivers oxygen steadily. In contrast, the cheetah's myoglobin must perform like a fast-shooting cannon. The cheetah needs to suddenly take up and release large doses of oxygen to stoke its explosive speed.

How does myoglobin do all that? For decades, biologists have wondered how -- and with what atomic motions, exactly -- the folded structure of myoglobin allows it to hold and release oxygen.

Now, two physicists at the University of Vermont have an answer. They've developed a new way to peer into the inner workings of proteins and detect which specific atoms are at work. Their work was published in the Aug. 27 issue of the journal Physical Review Letters.

Atomic bondage

Using myoglobin as a test, the scientists were able to home in on the critical functional piece of the protein, separating it from the vast number of other "jigglings and wigglings of atoms" says William DeWitt, a UVM graduate student and the lead author on the paper that describes the finding.

"We've been able to identify the motion of one particular amino acid -- this group of atoms called the distal histidine -- that controls the binding process," he says.

Shaped a bit like a tennis racket over a basket, this tiny arm of the protein moves, through thermal fluctuations, to open or close the binding site near the myoglobin's iron-filled center. "As the atoms move in one direction it becomes easier to bind oxygen," says DeWitt, "and as they move in the reverse direction it becomes less easy."

And how this distal histidine moves should vary between the whale and the cheetah. "I would imagine," says Kelvin Chu, associate professor of physics and DeWitt's co-author, "that there has been evolutionary pressure on every species to adapt this motion in the myoglobin for their particular oxygen-binding needs."

"That's a testable hypothesis," Chu says. "What we would expect to see across species is that the tennis rackets are in different places or move different amounts."

DeWitt and Chu's work extends far beyond myoglobin. The two physicists see broad application of their new method in creating custom-crafted proteins.

"Once you know what these motions are and what the important atoms are," says Chu, "you can make mutants of proteins that have different binding attributes." And these different attributes have promise in developing new biotechnologies "ranging from blood substitutes to organic solar cells," he says.

Function follows form

Proteins are a cell's heavy laborers: hauling water, taking out the trash, carrying in the groceries -- and trillions of other tasks that make life. But how the shape of a protein determines its function remains one of the most vexing and important questions in the physics of biology.

Proteins are not the static, Lego-like objects you might see in an x-ray photograph in a biochemistry textbook. Instead, made from long chains of amino acids scrunched into various blobs and globs, a protein is always jumping between slightly different structural arrangements due to thermal motion of its atoms. Even a modest-sized protein like myoglobin has more possible arrangements of its atoms than there are stars in the universe. And each of these arrangements slightly changes a protein's function.

"But what are the important motions that control its function?" asks Chu.

"Relating the structure of a protein to what it is doing is the holy grail," he says. For myoglobin at least, the two UVM scientists seem to have brought the prize a lot closer to hand.

The power of parsimony

Their method -- called temperature derivative spectroscopy or TDS -- involves cooling myoglobin to as low as -450 degrees Fahrenheit, about 18 degrees above absolute zero, and then measuring its oxygen-binding process. At these chilly temperatures, each protein basically gets stuck in just one arrangement. These individual atomic arrangements can't be observed directly, but, using infrared light, a pack of myoglobin molecules does yield a kind of group portrait -- a summing, called a TDS surface -- of the position of all the proteins as they bind to the oxygen in carbon monoxide.

The Vermont scientists' innovation comes largely from what they have been able to do with this group portrait.

"This scenario is called an inverse problem," DeWitt notes, "we have measured the effect but want to determine the cause." Unfortunately, a bit like asking what two numbers add up to ten, there are many solutions.

But, usually, nature does not build wasteful structures -- and though the universe is undoubtedly complex, it does not seem given to capricious complexity. In other words, the scientific principle of parsimony -- what philosophy students encounter as Occam's Razor -- suggests that the least complex explanation is the most likely.

Applying a mathematical version of this idea from Bayesian statistics, called the principle of maximum entropy, DeWitt and Chu went looking for the simplest solution to the TDS surface created by their group of myoglobin molecules. And the answer: the motion of the distal histidine most simply explains how myoglobin regulates oxygen binding.

They followed this prediction by performing a computer simulation of the molecular dynamics of the distal histidine, which confirmed their interpretation.

"Will did a lot of this on his own," says Chu, "He took the data, and the analysis was done on a MacPro," plus some time on the National Science Foundation's high-performance computer network, the TeraGrid.

"He's a clever guy," says Chu.