Health and Fitness

UWM scientists develop techniques to unravel proteins' mysteries

By Mark Johnson of the Journal Sentinel

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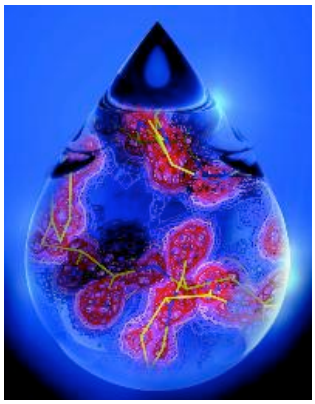

Courtesy of Abbas Ourmazd

This is an artist's impression of a protein that has been inserted into a droplet of water. The illustration shows what the protein's structure might look like once it has been reconstructed from simulated snapshots an X-ray laser would produce.

Proteins, the work-horse molecules necessary for virtually every human action from breathing to thinking, have proved an almost ghostly presence, daring scientists to fully grasp their structure and behavior.

Now, physicists at the University of Wisconsin-Milwaukee have developed powerful imaging techniques that promise to tell us much more about what proteins are and what they do, how they change shapes and how they work together in a cell.

Such questions go to the heart of our quest to understand diseases and find effective drugs.

"The vast majority of diseases are caused by impairment in some kind of protein function - too much or not enough of a certain protein, or a protein that's not working properly," said Andy Greene, director of the Biotechnology and Bioengineering Center at the Medical College of Wisconsin, who was not involved in the UWM work.

Using X-rays, lasers, powerful microscopes and mathematical equations, the UWM scientists have attacked the task of protein-watching on two fronts, publishing papers in the journals Nature Physics and Nature Photonics.

One group led by Valerica Raicu, an assistant physics professor, has discovered a novel way to eavesdrop on the interactions between one protein and another. These communications between proteins are considered vital to understanding what happens inside a living cell.

A second group, led by Abbas Ourmazd, professor of physics and electrical engineering, has developed what may be a vastly improved method of viewing the atomic structure of a single protein.

"This is important because when you know the shape and structure of a protein, you know how it works," Ourmazd said. "These things are really like lock and key."

The two UWM projects, though distinct, are part of an international effort to unravel the story of proteins, a daunting task. Greene said that while discovering the human gene sequence was important and complicated work, "studying proteins is at least 10 times more complicated."

'Juice of life'

If DNA is the book of life, "then proteins are the juice of life," Ourmazd said. "And the book of life is a recipe book for making these juices. Literally every function that occurs in your body is triggered, mediated or performed by some kind of protein."

Our bodies contain about 100,000 different proteins.

"For about half of them, we have a pretty good idea of the structure. The other half, we don't know much about," said George N. Phillips Jr., a professor of biochemistry and computer sciences at UW-Madison who was not involved in the UWM work.

In the 1950s, pioneering scientists Max Perutz and John Kendrew beamed X-rays into crystallized proteins and succeeded in determining the structures of two, hemoglobin and myoglobin. Yet half a century later, important questions remain.

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"As far as drug development is concerned, or as far as understanding how a cell interacts with the outside," Ourmazd said, "we're flying blind to a large extent."

And that runs counter to the whole idea of developing drugs based on biochemistry rather than random screening, a principle known as intelligent drug design. Once researchers have a good picture of the structure, they may be able to take a misshapen protein causing a specific disease and stretch it back to its correct shape.

Scientists have determined some structures by condensing millions of copies of the protein into a crystal and then bombarding it with X-ray photons, or tiny particles of invisible light. To build a three-dimensional picture, scientists rotate the crystal and repeat the process, firing photons from various angles.

Ourmazd compared the crystal with a large stadium in which billions of proteins have joined voices, turning the soft whisper of each one into a loud, collective song. That song tells the protein's story.

But the technique is time-consuming. It can take up to a decade to coax one protein to form a crystal, and sometimes the effort fails.

"For some proteins, we haven't found a recipe that causes them to form a crystal. Some just glop out like egg white," said Phillips, of UW-Madison.

An alternative method - placing proteins in solution and subjecting them to strong magnetic fields - works, but only with small proteins.

Later this year, however, scientists will gain a powerful new imaging tool built for the task of protein-watching. Designed to glimpse the very small and very fast, the Linac Coherent Light Source in California will produce pulses of X-ray light more than a billion times brighter than any made by existing equipment.

Imaging a single protein

The new $420 million device will fire a trillion photons at a protein molecule encased in a frozen drop of water. Despite the massive bombardment, only 100 of the photons actually will capture a snapshot of the protein. Moreover, the pulse of light sent by the device is so powerful that it will destroy the very protein it is trying to reveal. As a result, scientists will have to repeat the process with fresh protein molecules one at a time until they can assemble a complete picture.

Even then, Ourmazd and his team discovered a problem. According to their calculations, the intensity of light generated by the costly device would be 1,000 times too weak to capture the full structure of key proteins - if scientists followed the prescribed method.

So Ourmazd, professor Dilano Saldin and research scientists Russell Fung and Valentin Shneerson developed what they believe to be a solution. Their method takes the massive jumble of photons, digs out the few with snapshots of the protein and simultaneously assembles all the pieces into the full image. Information is gathered so efficiently that the weaker light is sufficient.

Ourmazd compared his team's mathematical sorting technique to a tool familiar to most Internet users. It works in much the same way that a misspelled Google search for "Milwaukea" comes back in one-tenth of a second: "Did you mean *Milwaukee*?"

"When you put in this string of letters, they look for the amount of overlap between what you've put in and the key words of all the documents," he said. "That's called correlation. What our algorithm does is to exploit the correlations between the random snapshots of the protein to give you the right protein structure."

Although the method has yet to be applied to actual proteins, it worked when the physicists tested it on another material.

Physicist Bruce Patterson at the University of Zurich in Switzerland said Ourmazd is one of few people in the world who are optimistic that the Linac Coherent Light Source will succeed in providing high-resolution images showing the structure of key proteins.

"If he's right, it would be terribly important," Patterson said.

Scientists are still examining various ways of using the Linac, said physicist Sebastien Boutet who works on the device at the SLAC National Accelerator Laboratory in Menlo Park, Calif. But the technique developed by Ourmazd and his colleagues "certainly looks like the leading candidate today," Boutet said.

"If successful, it would be revolutionary in this field."

Watching reactions

While Ourmazd studied the individual protein, Raicu focused on the group.

Proteins work together in complexes, passing on messages and starting the chain reactions that enable a cell to respond to change. When a pathogen is threatening at the cell's gate, for example, proteins can summon a response from the immune system.

But little is known about how all of this works.

The intricate dance between different proteins has proved a difficult target for scientists and their microscopes. Researchers have tried to map the position of different proteins and their relationships by tagging them with a green fluorescent protein found in jellyfish. The tag causes the protein to emit a colorful glow.

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Modern instruments called two-photon microscopes excite the protein molecules with laser light. Researchers then watch the way one protein transfers this light to its neighbor, the glow changing in the process from green to yellow.

Although two-photon microscopes provide crisp images of a single slice from a cell, they cannot capture the full array of colors, the spectral fingerprint of each protein.

"Without the array of colors, you don't know the combination of protein molecules," Raicu said. "They don't emit smell. They don't emit sound. To distinguish one molecule from another, you need to see the colors."

Previous methods required scientists to take multiple scans of the same sample in order to pick up all the information. The technique was problematic because proteins constantly change positions.

Raicu and his colleagues built a new type of two-photon microscope that captures a complete slice of a cell frozen in time, all of the spectral fingerprints. There is no need for multiple scans.

Now for the first time, scientists have been able to determine the structure of a protein complex in a living cell. Soon, they might even be able to glimpse a critical cascade of protein actions as it unfolds by taking a series of snapshots in rapid succession, Raicu said.

"We believe that our method has made this possible," he said.

The UWM scientists focused on one complex and saw four protein molecules, each situated in a corner of a structure that resembled a parallelogram. The complex they examined is part of a crucial family of proteins found along the cell membrane and targeted by many drugs.

Researchers believe there is much to be learned by watching the interactions between such proteins.

"We look at differences in protein interactions that occur due to mutations," said Kalina Hristova, an associate professor of materials science and engineering at Johns Hopkins University. "If you can understand how these interactions are changed, you can probably come up with a way to treat the disease."

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