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Scientists make major advance in structural biology

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Scientists from Baylor College of Medicine (BCM) and Rice University have discovered a new way to analyze the moving parts of large proteins – a breakthrough that will make it easier for structural biologists to classify and scrutinize the active sites of proteins implicated in cancer and other diseases.

The breakthrough research will appear online this week and in an upcoming edition of the *Proceedings of the National Academy of Science*. In involves a new mathematical algorithm that narrows down all the possible ways a protein might flex and bend. The math is used in conjunction with information captured via X-ray crystallography, a technique in which protein crystals are bombarded with X-rays, producing a diffraction pattern that reveals the precise three-dimensional arrangement of every atom in the protein.

"Increasingly, our discipline is faced with deciphering the structure of large, complex proteins in which some parts are constantly moving, even when the protein is locked in a crystal form," said lead researcher Jianpeng Ma, who holds joint appointments at both BCM and Rice. "We expect our method to be particularly useful in refining very large and flexible supramolecular complexes with limited diffraction data."

Nobel laureate William Lipscomb of Harvard University, one of the founding fathers of protein crystallography in the North America, said, "This recent success in X-ray crystallographic refinement is revolutionary for the field of structure biology in terms of improving large and flexible complex structures that are becoming far more abundant nowadays. It is one of the largest technical leap-forwards in X-ray refinement in the last two decades. It will fundamentally change the way people do structural refinement for large and flexible complexes."

Each protein is a chain of amino acids strung end-to-end, and Ma said current techniques are good at deciphering all but the most flexible parts of proteins. But since form and function are inextricably linked in every protein, the most flexible parts are often those most vital to the protein's function – like the site where a enzyme catalyzes a reaction or where a signaling protein docks with its partners.

"Where proteins move, they do it for a reason," Ma said. "It is perhaps ironic that current techniques give us the fuzziest detail in the regions where we desire the most clarity."

Ma, who was born in China, earned degrees at Shanghai's Fudan University and at Boston University before pursuing postdoctoral studies at Harvard. He joined BCM and Rice in 2000 and was recognized with the Welch Foundation's prestigious Norman Hackerman Award in 2004 for his outstanding contributions to biophysics and biochemistry.

Ma said he first imagined developing a new mathematical algorithm to zero in on these mobile sites about a decade ago, and after four years of working the problem himself, with very little progress, he assigned it to Rice graduate student Billy Poon in mid-2001.

"The success of this project is really a story about Billy's perseverance and determination," Ma said.

In most cases, scientific discovery moves forward in increments, offering a chance for scientists and graduate students to publish their latest findings every once in a while. Ma said Poon's project was the exception that it offered a potentially large payoff at the end with no option for publication in between.

"His fellow students in the research group published tons of material during the years that he worked on this," Ma said. "He didn't have anything to show for his efforts, and he was under enormous pressure."

Poon said he never lost faith the basic premise of the project.

"All indications were that it should work," Poon said. "I did start to get worried in the fourth and fifth years because I needed to finish."

Ma said the break in the project came last fall. The pieces started to fall into place for Poon, but a huge hurdle remained – the protein Ma and Poon were using as a test case had to be "fitted" to the map that Poon's program had produced. This final step is like an enormous puzzle, and to solve it, students put on special goggles that allow them to look at a computer and see 3-D representations of both the map and the protein. They grab hold of the protein and twist it to fit within the mapped area, but in so doing they may inadvertently move a different part of the protein out of alignment somewhere else. The problem is magnified by the fact that only a small fraction of the entire puzzle can ever be shown on the screen at one time.

The problem of fitting the protein fell to BCM student Xiaorui Chen, a recent graduate of Tsinghua University in China, who joined Ma's group as part of her medical school rotation at BCM in December. Ma said protein fitting is an art, and he said Chen has an enormous gift for it, in part because she has studied proteins for many years, having who won a gold medal in the Chinese national competition of the International Biology Olympiad (IBO) while still in high school.

"The process requires a deep understanding of proteins and an intuitive sense about how they behave at the atomic level," Ma said. "Xiaorui mastered this art at a very young age while she was still in high school."

Chen attacked the problem, working googled at her screen for hours on end. Taking minimal breaks – she even learned to eat meals with the googles on – she chipped away at the enormous puzzle hour after hour, bit by bit.

Poon recalls the exact moment, just before Christmas, when he realized the problem was finally solved. He said he was overjoyed when he realized he'd be able to publish the results of his long years of study.

"If anything I was even happier," Ma said. "Nobody was sure it would work out before that, and it's a rare treat when a scientist gets to witness a success like this one, which was pivotal not only for myself and my students but also for every other scientist in this field."

"We can use this method to improve many other systems in our lab." Ma said "We are indeed working on a bunch of other important systems, such as membrane proteins, that will demonstrate the breadth of applicability of the method."

Co-author and BCM faculty member Qinghua Wang, who was responsible for the the technical supervision of Poon and Chen, said, "Both Billy and Xiaorui are outstanding students. We wish to have more students like them."

Source: Rice University

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