Unlocking the function of enzymes

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Fitting a key into a lock may seem like a simple task, but researchers at Texas A&M University are using a method that involves testing thousands of keys to unlock the functions of enzymes, and their findings could open the door for new targets for drug designs.

Texas A&M researcher Frank Raushel is part of a team of scientists who modified a technique called “molecular docking” to predict which molecule, called a substrate, triggers an enzyme into action, enabling them to decipher an enzyme’s function based on its structure alone.

The team’s paper was published in the journal *Nature*.

Most biological processes depend on enzymes, which are proteins that speed up chemical reactions, but the function of many enzymes remains a mystery.

“There are thousands of molecules that could be substrates [for a specific enzyme], and it would take too long to physically test them all,” Raushel said. “So we decided there was a need for a new method to determine the function of enzymes.”

The team started with the three-dimensional X-ray structure of an enzyme and then used a computer to try to fit different smaller molecules into the active site of the enzyme like pieces in a puzzle.

“Each enzyme has a specific size and shape,” Raushel said, “and you can use a computer to take small molecules and fit them into the active site

of an enzyme one by one and score them on how well they fit. It's more or less like fitting a key into a lock, but a lot more difficult since both the enzyme and the substrate are conformationally flexible."

After the computer scores the molecules on how well they fit the enzyme, it ranks their order, and the researchers can then use the prioritized list to decide which molecules to physically test.

"As far as we know, this is the first time anybody has used molecular docking to predict the function of an enzyme," Raushel said. "And it was verified by both experiment and X-ray crystallography."

Other methods researchers use to try to determine an enzyme's function or substrate specificity include physically testing thousands of possible molecules, gathering information from the nearby genes, and comparing the structure of the enzyme to that of other enzymes with known functions. "I think that in the end, we'll have to use all of these methods together," Raushel said. "One single method just won't suffice."

Raushel and his team plan to continue using their molecular docking method to find the function of other enzymes.

"We're looking at other X-ray structures of proteins that have unknown functions, and we're working to fill the gap," Raushel said. "We're trying to see how general this method is going to be or if we were just lucky in this particular case."

Raushel and Texas A&M post-doctoral associate Ricardo Marti-Arbona work in conjunction with Brian Shoichet at the University of California, San Francisco, and Steven Almo from the Albert Einstein College of Medicine in New York.

Raushel hopes that over the next five years, the team can start to use its

findings to locate potential targets for new drugs.

“Understanding the substrate specificity of certain enzymes could allow researchers to differentiate enzymes that catalyze one reaction in pathogenic organisms and a slightly different reaction in human systems,” Raushel said. “This would allow scientists to design [drugs] that would specifically target a pathogenic organism while not affecting the human enzyme.”

Source: Texas A&M University