New drug design technique could dramatically speed discovery process

April 13 2010

Scientists here are taking the trial and error out of drug design by using powerful computers to identify molecular structures that have the highest potential to serve as the basis for new medications.

Most drugs are designed to act on proteins that somehow malfunction in ways that lead to damage and disease in the body. The active ingredient in these medicines is typically a single molecule that can interact with a protein to stop its misbehavior.

Finding such a molecule, however, is not easy. It ideally will be shaped and configured in a way that allows it to bind with a protein on what are known as "hot spots" on the protein surface - and the more hot spots it binds to, the more potential it has to be therapeutic.

To accomplish this, many drug molecules are composed of units called fragments that are linked through chemical bonds. An ideal drug molecule for a specific protein disease target should be a combination of fragments that fit into each hot spot in the best possible way.

Previous methods to identify these molecules have emphasized searching for fragments that can attach to one hot spot at a time. Finding structures that attach to all of the required hot spots is tedious, time-consuming and error-prone.

Ohio State University researchers, however, have used computer simulations to identify molecular fragments that attach simultaneously to

multiple hot spots on proteins. The technique is a new way to tackle the fragment-based design strategy.

"We use the massive computing power available to us to find only the good fragments and link them together," said Chenglong Li, assistant professor of medicinal chemistry and pharmacognosy at Ohio State and senior author of a study detailing this work.

Li likens the molecular fragments to birds flying around in space, looking for food on the landscape: the protein surface. With this technique, he creates computer programs that allow these birds - or molecular fragments - to find the prime location for food, or the protein hot spots. The algorithm is originated from a computation technique called particle swarm optimization.

"Each bird can see the landscape individually, and it can sense other birds that inform each other about where the foods are," Li said. "That's how this method works. Each fragment is like a bird finding food on the landscape. And that's how we place the fragments and obtain the best fragment combination for specific protein binding sites."

Li verified that the technique works by comparing a molecular structure he designed to the molecular base of an existing cancer medication that targets a widely understood protein.

"My method reconstructed what pharmaceutical companies have already done," he said. "In the future, we'll apply this technique to protein targets for diseases that remain challenging to treat with currently available therapies."

The research appears online and is scheduled for later print publication in the *Journal of Computational Chemistry*.

Li said this new computer modeling method of drug design has the potential to complement and increase efficiency of more time-consuming methods like nuclear magnetic resonance and X-ray crystallography. For example, he said, X-ray fragment crystallography can be hard to interpret because of "noise" created by fragments that don't bind well to proteins.

With this new computer simulation technique, called multiple ligand simultaneous docking, Li instructs molecular fragments to interact with each other before the actual experimental trials, removing weak and "noisy" fragments so only the promising ones are left.

"They sense each other's presence through molecular force. They suppress the noise and go exactly where they are supposed to go," he said. "You find the right fragment in the right place, and it's like fitting the right piece into a jigsaw puzzle."

Before he can begin designing a molecule, Li must obtain information about a specific protein target, especially the protein structures. These details come from collaborators who have already mapped a target protein's surface to pinpoint where the hot spots are, for example, through directed mutations or from databases.

Li starts the design process with molecular fragments that come from thousands of existing drugs already on the market. He creates a computer image of those molecules, and then chops them up into tiny pieces and creates a library of substructures to work with - typically more than a thousand possibilities.

That is where computational power comes into play.

"To search all of the possibilities of these molecular combinations and narrow them down, we need a massive computer," he said. Li uses two

clusters of multiple computers, one in Ohio State's College of Pharmacy and the other in the Ohio Supercomputer Center, to complete the simulations.

The results of this computation create an initial molecular template that can serve as a blueprint for later stages of the drug discovery process. Medicinal chemists can assemble synthetic molecules based on these computer models, which can then be tested for their effectiveness against a given disease condition in a variety of research environments.

Li already has used this technique to identify molecules that bind to known cancer-causing proteins. He said the method can be applied to any protein that is a suspected cause of diseases of any kind, not just cancer.

Provided by The Ohio State University