UI supercomputer Blue Waters decodes HIV capsid

By Katherine Boehle | Assistant assignment editor |
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With the help of the University's Blue Waters supercomputer, researchers in the Beckman Institute have determined the chemical structure of the HIV's capsid, the protein shell surrounding the genetic material.

The capsid protects the genetic material until it is disassembled to release the genetic material into a cell to infect it.

"One of the reasons the capsid is so attractive is because in nature there are animals resistant to it (HIV), and the capsid is what their system attacks," said Juan Perilla, a postdoctoral fellow, one of the main investigators of the project.

The capsid is also the target of many other antiviral drugs, said Klaus Schulten, a University physics professor and another primary investigator.

"Now that we know the structure of the capsid, we can now develop an antiviral drug," Schulten said. "Now that the structure is known, we can develop these drugs much more rationally."

The HIV-1 protein capsid is made up of over 1,300 proteins, all of which are the same protein, Schulten said. These proteins make up 216 protein hexagons and 12 protein pentagons, also known as hexamers and pentamers.

Schulten and Perilla said that if the capsid was just hexamers, it would be shaped like a cylinder and would not be closed in like a capsid.

They said that they knew there would be 12 pentamers in the structure because according to the Euler's theorem — a mathematical theorem that relates a polyhedron's edges, vertices and faces — to have a closed structure, no matter how many hexagons you have, you will always have 12 pentagons.

Despite the fact that all of the proteins are the same kind, no one protein is identical, Schulten said.

"Some proteins get close together, other places they're far apart," Schulten said. "This is a very important finding because you would think one protein, one shape, but it was actually one protein, 1,300 shapes."

This is only one of the reasons that the protein capsid is polymorphic, meaning it can take lots of different shapes. Perilla said that although every capsid has the same number of hexamers and pentamers, the placement of these pentamers varies with every capsid, thus giving each capsid an individual shape.

Schulten and Perilla said that it is the medical schools at the University of Pittsburgh and Vanderbilt University who are heading the HIV-1 capsid project, but that researchers at the University are in charge of the computational side.

Schulten said that although it was a big project, it progressed quickly with the research only beginning at the start of 2012, shortly after Perilla started as a postdoctoral fellow and when Blue Waters was developed at the University.

"It was very, very fast work," Schulten said. "We worked very hard."

Before supercomputers, researchers had figured out the individual proteins that make up the capsid and the overall picture of the capsid. Perilla said that it was only in 2009 that it was determined there were hexameric proteins in the capsid, and 2011 when the pentameric proteins were determined.

However, it wasn't until Blue Waters was up and running that researchers could determine how the capsid was

pieced together with these hexagonal and pentagonal proteins.

Perilla said that Blue Waters is not considered a fast computer, but an extremely powerful one, comparing its power to using 2000 computers at once.

According to Schulten and Perilla, Blue Waters is what made determining the protein capsid possible. Schulten said that x-ray crystallography had determined the structure of the individual proteins, while electron microscopy gave researchers an idea of the big picture of the capsid. What Blue Waters was able to do was put the individual proteins into the whole capsid, and see how the capsid is specifically structured.

Perilla said this is done by simulating proteins in the computer so that the proteins are in a solution of water and ions — this way, researchers are properly simulating how the proteins would be in a lab or organism. Otherwise, Perilla said it would be like simulating proteins in a vacuum. Because the proteins are simulated in these conditions, Perilla said they were able to see how the proteins would interact with each other in the capsid.

Using the electron microscopy images as an overall picture, Perilla said they were able to estimate where the 12 pentagonal proteins would be located and then fit the rest of the hexagonal proteins between these pentagons, thus determining how many hexamers were in the capsid.

Perilla said that although the structure of the capsid has now been determined, the group's research doesn't stop there with the HIV-1 virus. The group is currently working on figuring out how the capsid disassembles to release the genetic material. Perilla said this is important because the virus appears to do this at a very specific time.

"If it happens too soon or too late, it (the genetic material) won't be infective," he said.

Perilla also said that it is unknown what triggers disassembly of the capsid and also what stabilizes the capsid before disassembling.

"We opened a new chapter in the book of HIV," Schulten said. "And this chapter is just starting."

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