HIV Shell Structure Cracked With Help Of Supercomputer

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A new study that features on the cover of *Nature* this week describes how researchers in the US have for the first time cracked the chemical structure of the capsid or protein shell of the human immunodeficiency virus (HIV). The breakthrough, which likely opens the way to powerful new drugs against the virus that causes AIDS, was made possible with the help of a new "petascale" supercomputer.

Scientists have been trying for some time to crack the precise chemical structure of HIV's cone-shaped capsid, a protein shell that protects the virus's genetic material. The capsid is thought to be the key to virulence of HIV and has become an attractive target for new antiretroviral drug development.

As senior author of this new *Nature* study, Peijun Zhang, an associate professor of structural biology at the University of Pittsburgh School of Medicine, says in a statement:

"The capsid is critically important for HIV replication, so knowing its structure in detail could lead us to new drugs that can treat or prevent the infection."

"This approach has the potential to be a powerful alternative to our current HIV therapies, which work by targeting certain enzymes, but drug resistance is an enormous challenge due to the virus' high mutation rate."

Previous studies have described attempts to chip away at the capsid structure bit by bit. To try and see the atomic-level detail of the shell, made of over 1,300 identical proteins, researchers have used a range of sophisticated lab tools, from nuclear magnetic resonance spectroscopy and X-ray crystallography, to cryo-electron microscopy and cryo-EM tomography.

But it was only when they added the processing power of the new petascale Blue Waters supercomputer at the National Center for Supercomputing Applications at the University of Illinois, to the already impressive array of tools, that Zhang and colleagues were able to fathom the chemical structure of the entire capsid.

A petascale computer has a number-crunching rate measured in "petaflops", or petas (quadrillions, 10^{15}) of floating point instructions per second. To put this into context, a petascale computer can perform in one second the same number of instructions as it would take everyone on Earth doing one calculation per second for 1.5 days.

The simulations that added the missing pieces to the HIV capsid puzzle were conducted during testing of Blue Waters by co- authors Klaus Schulten, a physics professor, and Juan R. Perilla, a post-doc researcher, both at the University of Illinois.

Commenting on the HIV capsid challenge, Schulten says:

"This is a big structure, one of the biggest structures ever solved."

"It was very clear that it would require a huge amount of simulation - the largest simulation ever published - involving 64 million atoms," he adds.

From previous studies that had found the HIV capsid contains a number of identical proteins, the researchers already knew these proteins are arranged as pentagons and hexagons, and they had a hunch that the pentagons formed the tight round corners of the cone-shaped capsid they could see under an electron microscope.

But exactly how many of these proteins it takes to make the capsid, or how the pentagons and hexagons fit together, remained a mystery.

Zhang and the structural biology team at Pittsburgh found that when exposed to high concentrations of salt, the protein building blocks assemble into tubes made only of hexagons.

From further experiments they found that certain regions of the proteins interact with one another in a way that is "critical for capsid assembly and stability, and for viral infectivity," they note.

They then managed to get a rough idea of the overall shape of the capsid by taking cryo-electron tomographs of it sliced into sections.

From these results, and their own simulations of how the hexamers and pentamers might interact, Schulten and Perilla carried out a series of large-scale computer simulations.

Schulten says that they could only match the 64-million-atom capsid structure to the "diverse" experimental data using a unique approach they developed themselves that they call **"molecular dynamic flexible fitting"**.

"You basically simulate the physical characteristics and behavior of large biological molecules but you also incorporate the data into the simulation so that the model actually drives itself toward agreement with the data," he explains.

With these techniques the researchers found that the HIV protein shell comprises 216 hexagons and 12 pentagons arranged in the way the experimental data suggested.

The proteins in the hexagons and pentagons were identical but the angles through which they attached to each other were different among different regions of the structure.

Schulten says this is what puzzled them: such a protein would have to be inherently flexible to form such a varied structure.

By having pentagons as well as hexagons, the capsid can form a closed structure, explain the researchers, describing the property the pentagons bring as "induced acute surface curvature". (A quick look at the structure of fullerenes, or even soccer balls for that matter, and you get an idea of what they are talking about).

Schulten says that knowing more about the detailed structure of the HIV capsid will help researchers understand how it functions, and this helps drug developers work out how to disrupt those functions.

He explains how the HIV capsid has to perform two opposing functions. It has to remain intact to protect its genetic material, but it also has to be able to release it in a timely manner once inside the host cell so it can replicate.

"That has to happen with really good timing - too quick is not good, too slow is not good. And this is a moment when you can throw a wrench into the system," says Schulten.

"**The timing of the opening of the capsid is essential for the degree of virulence of the virus**. This is where we could perhaps best interfere with HIV infection," he adds.

Funds for the study came from the National Institute of General Medical Sciences at the National Institutes of Health and the National Science Foundation, which also funds the Blue Waters supercomputer.

Earlier this year, scientists in the UK developed a vaccine against foot and mouth disease that uses a synthetic virus capsid to provoke an immune response.

To determine the structure of that virus shell, and identify mutations that would improve it, they used Diamond Light Source, the UK's national synchrotron facility.

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"Mature HIV-1 capsid structure by cryo-electron microscopy and all-atom molecular dynamics"; Gongpu Zhao, Juan R. Perilla, Ernest L. Yufenyuy, Xin Meng, Bo Chen, Jiying Ning, Jinwoo Ahn, Angela M. Gronenborn, Klaus Schulten, Christopher Aiken and Peijun Zhang; *Nature* 497, 643-646, published online May 2013; DOI:10.1038/nature12162; Link to Abstract.
Additional sources: University of Pittsburgh Schools of the Health Sciences; and University of Illinois News Bureau.