Simulations describe HIV's 'diabolical delivery device'

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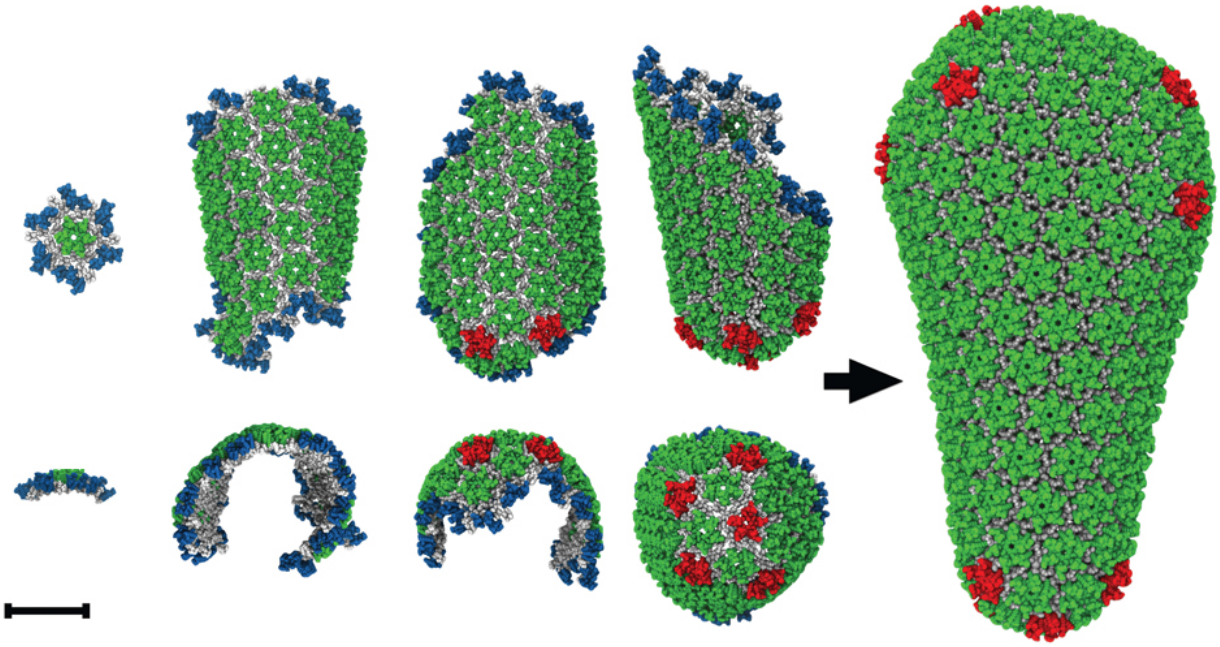

These snapshots from a computer simulation shows steps in the assembly of the HIV-1 capsid, a pear-shaped capsule made of proteins that the virus needs in order to mature and become infective. The scale bar represents 20 nanometers, which is less than a tenth the size of the smallest bacterium. A model of a complete capsid suggested previously is shown on the far right of the image for comparison. Credit: John Grime and others, *Nature Communications*, doi: 10.1038/ncomms11568 and Nature 469:424-427 2011

From a virus's point of view, invading our cells is a matter of survival.

The virus makes a living by highjacking cellular processes to produce more of the proteins that make it up.

From our point of view, the invasion can be a matter of survival too: surviving the virus. To combat viral diseases like HIV-AIDS, Ebola, and Zika, scientists need to understand the "life cycle" of the virus and design drugs to interrupt it. But seeing what virus proteins do inside living cells is extremely difficult, even with the most powerful imaging technologies.

Now University of Chicago scientists and their colleagues have developed an innovative computer model of HIV that gives real insight into how a virus "matures" and becomes infective. In doing so, it offers the prospect of help developing new anti-viral drugs and greatly extends what has been possible with computer simulations of biological systems. Their findings appeared in the May 13 edition of *Nature Communications*.

"Understanding the details of viral maturation is considered a holy grail," said Gregory Voth, UChicago's Haig P. Papazian Distinguished Service Professor in Chemistry, who built the model with research scientist John Grime. "It has a set of processes that are incredibly hard to stop. With our model, we've discovered a key set of dynamical steps in the maturation process. And we think we've identified two core aspects of HIV."

To mature and become infective, a virus must grow a little pear-shaped capsule called the capsid, which is made of proteins that wrap themselves around the RNA that will allow the virus to replicate. "This is the thing that's going to get shot into a new cell and release its contents," said Voth. "The capsid is like a little armor-plated container that carries with it the genetic material of the virus. And it is a diabolical delivery device."

Capsid growth details

Voth and Grime's model illuminates in detail how the capsid grows in HIV, something difficult to examine in real life because the capsid is tiny and surrounded by other material. "That's where computer simulations are so powerful," Voth said. "And in computer simulations you can turn things on and off, which you can't do in reality. It makes a huge difference in what you learn. It's not reality, but if the model's good it can be pretty darn close."

Voth and Grime worked with data and real-world images from experimental collaborators at the University of Virginia and the California Institute of Technology to make sure that their model was consistent with experimental findings. "Their important work helped us to build the model and validate it," Voth said.

After the HIV virus infects a cell it forms a "bud" on the cell's surface—a virus particle that contains some cell membrane, proteins, and the virus's RNA. The bud breaks free of the cell as the "virion" and travels in the body. During that travelling period, critical proteins inside the bud are cut into bits by the enzyme HIV protease—the target of many of today's anti-HIV drugs. Some 1,200 of these protein bits pair up and assemble themselves into the capsid, enclosing the RNA.

Conditions inside the virion are crowded. And that crowding turns out to be critical to whether a capsid can form or not. "With our simulations we can make it more and less crowded and you see a remarkable sensitivity to that," Voth said. Too little crowding, and the proteins are likely to speed past each other without interacting. Too much, and they grow useless bits and pieces.

But Voth and Grime found that even with a Goldilocks-like "just right" amount of crowding in their model, the capsid didn't grow properly.

"We'd grow too much. Or we'd start growing multiple pieces of the shell and they wouldn't stick together in the right way, so you'd get a bunch of crazy-looking structures," Voth said. "We were fundamentally missing something."

Flipping and dancing

After a year of further work, they realized that before the protein bits pair up and add themselves to the growing capsid shell they are in constant motion, flipping and dancing around. For them to connect to each other and to the capsid they had to be oriented properly. This meant that only a few of them could participate in building the structure at any given time.

"We discovered that the contortions of these proteins are very important to limiting how fast these structures can grow, so it's just right," Voth said. "When we built that into the model, guided by published experimental data, that was the secret."

A large part of building a computer model is deciding what to leave out of it so that it is computationally tractable. "We develop methods to simplify the calculations while retaining their physical essence," said Voth. "And that opens up very broad frontiers of what can be studied that hasn't been possible before."

But even though it is simpler than what exists in nature, the HIV capsid model is tremendously complex. It took millions of hours of computer time on the National Science Foundation supercomputer Blue Waters in Urbana-Champaign to run the simulations.

"I don't think anyone's got close to simulating something of this complexity before," said Grime, who did most of the nuts and bolts construction. "I think it's a very significant advance in terms of what you

can do with these sorts of models."

Voth envisions making similar models for other dangerous viruses, helping scientists discern the points in the cycle that might be good prospects for disruption by a drug.

"We could do this for Zika virus, for Ebola," he said. "Viruses have a capsid and that capsid contains their genetic material. So these sets of methodologies could be applied to any of them. We just need enough information and computer power."

More information: John M. A. Grime et al, Coarse-grained simulation reveals key features of HIV-1 capsid self-assembly, *Nature Communications* (2016). DOI: 10.1038/NCOMMS11568

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