64-million atom simulation – a new weapon against HIV

University of Illinois physics professor Klaus Schulten and postdoctoral researcher Juan Perilla recently used molecular simulations on the Blue Waters supercomputer to determine the chemical structure of the HIV capsid. The capsid protects the virus's genetic material and plays a key role in debilitating the immune system. However, although the capsid is an attractive target for antiretroviral drugs, researchers have struggled to understand its structure.

Researchers have used various lab techniques to look at individual parts of the capsid. (In fact, the Blue Waters simulations integrate data from experiments performed at the University of Pittsburgh, Pennsylvania, and Vanderbilt University, Tennessee.) Until now, they were unable to simulate the entire capsid, which consists of more than 1,300 identical proteins at the atomic level.

"This is a big structure, one of the biggest structures ever solved," said Schulten. "It was very clear that it would require a huge amount of simulation – the largest simulation ever published – involving 64 million atoms."

Targeting the HIV Virus: Researchers Use Supercomputer to Solve the Structure of the HIV-1 Capsid. Video courtesy Beckman Institute for Advanced Science and Technology at the University of Illinois.

"The work of matching the overall capsid to the diverse experimental data can only be done through computer simulation using a methodology we have developed called molecular dynamic flexible fitting," explains Schulten. "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."

Previous research revealed that the proteins are arranged into pentagons and hexagons. To create large-scale simulations on Blue Waters, Perilla and Schulten combined that data with their results from simulated interactions between the pentamers and hexamers. A report appears in the journal Nature .

"An important aspect of Blue Waters is how its design allows researchers to examine complicated molecular structures such as the capsid," said Robert Brunner, Blue Waters applications support. "The research starts with experimental data, which gives a picture of the molecular structure – but the limitations of the experimental procedures result in a picture that is a little out-of-focus, so the finest details cannot be seen directly."

The computational challenge is to create a detailed model of the structure (without knowing the actual structure of the molecule), then run simulations to see how well it fits the experimental data. The simulation then adjusts the model, to improve how well the model matches the data. For a molecule as complex as the capsid, only a machine the size of Blue Waters can refine the model within a practical amount of time to match the experimentally observed results.

"Blue Waters is especially well suited to performing the kinds of irregular calculations required for this problem – mainly because it is designed to be a balanced system, with a fast network connecting the parts of the machine and good input/output performance to complement the high processing speed," notes Brunner.

Brunner is a member of the Blue Waters Science and Application Support team at the National Center for Supercomputing Applications (NCSA) at the University of Illinois at Urbana-Champaign, US. He assists science teams with running calculations, locating and addressing problems, and tuning code – not to mention finding and installing software, and helping researchers find the best ways to process the big data that simulations produce.

"The sustained petascale performance of Blue Waters is precisely what enabled these talented researchers to explore new methods combined with structural and electron microscopy data to reliably model the chemical structure

of the HIV capsid in great detail," says Irene Qualters, NSF program manager for Advanced Cyberinfrastructure. "This knowledge will allow researchers to infiltrate that membrane with HIV-fighting drugs."

Simulations on the structure of the HIV capsid use highly scalable NAnoscale Molecular Dynamics (NAMD) software, developed at the University of Illinois by Schulten and computer science professor Laxmikant 'Sanjay' Kale. NAMD's parallel scalability is based on the prioritized message-driven execution capabilities of the Charm++/Converse parallel runtime system. These efficiencies enable far better simulations: in 2006, the first million-atom simulation fully characterized the structure of the tiny satellite tobacco mosaic virus. Running on a petascale computer, NAMD now allows biomolecular modeling like Schulten's and Perilla's 64 million-atom simulation of the full HIV capsid.

Such capabilities are key to developing potent new antiretroviral drugs that suppress the HIV virus and stop the progression of AIDS. Armed with the detailed capsid structure, researchers can investigate how to disrupt its functioning – effectively interfering with the timing of its opening to prevent HIV infection.

"The HIV capsid has actually two completely opposite properties," says Schulten. "It has to protect the genetic material, but once it gets into the cell it has to release the genetic material. 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."

You can read the University of Illinois news release here.

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