

# THE COMPUTATIONAL MICROSCOPE

**Allocation:** NSF/30 Mnh, BW Prof./0.24 Mnh

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## SCIENTIFIC GOALS

Bridging the gap between single protein simulations and organelle or cell-scale simulations is challenging on many levels. Because molecular dynamics simulations on the order of hundreds of millions of atoms require substantial computational power, efficient codes as well as appropriate analysis and visualization techniques must be developed. Simulations interpret data, suggest new experiments, and do what experiments cannot, which is to give an atomic-level picture of what is going on inside living systems.

The HIV capsid project aimed to produce the first ever atomic-level structure of a native, mature HIV capsid. HIV is composed of two copies of single-stranded RNA inside a cone-shaped capsid made of a viral protein called p24.

The photosynthetic chromatophore project aimed to create the first all-atom model of a cellular organelle. Chromatophores are spherical organelles in photosynthetic bacteria which allow the bacteria to absorb sunlight and turn it into chemical fuel that drives many processes in the cell. The chromatophore is composed of about 200 proteins and carries out about 20 processes.

## ACCOMPLISHMENTS TO DATE

We have explored the interactions of the full HIV capsid with small molecules, including the controversial Pfizer PF74 drug (which interferes with host cell binding to the capsid), the PF1385801 drug (which results in ultra-stable capsids), and compounds BI01/02 (which trigger premature disassembly). In the early stages of the replication cycle, the HIV capsid interacts with various host cell factors, such as cyclophilin A (which stabilizes and assists capsid assembly), and TRIM family factors (which disrupt the capsid and assist in nuclear import). Together with experimental collaborators, computational scientists were

able to describe the action of cyclophilin A on the capsid and are presently working on the mechanism of restriction by TRIM family proteins. Such studies may help scientists understand better how the HIV capsid infects the host cells and could lead to new HIV therapies. The capsid model also has continued to be used to analyze the dynamics of motion of the HIV capsid subunits and has been used to explore the interactions of the capsid with drugs and host cell factors.

Also, a published model of the spherical chromatophore organelle revealed, for the first time, the locations not only of the light-harvesting complexes, but of the bc1 complex and ATP synthase, two other critical proteins whose locations were previously unknown.

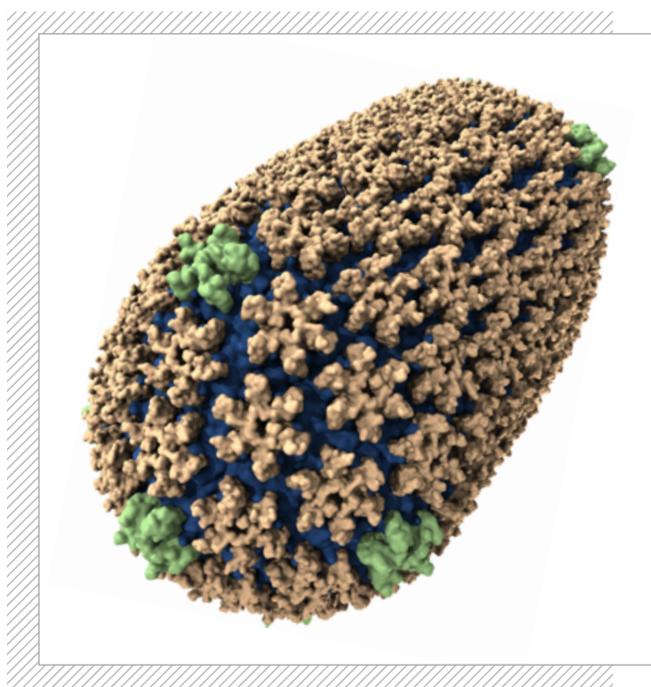


Figure 1. Klaus Schulten's group at the University of Illinois at Urbana-Champaign was able to construct and simulate the first atomic-resolution model of a mature HIV capsid. This capsid model is now being simulated on Blue Waters to test the interactions of HIV drugs and host cell factors with the capsid, which could help lead to the design of new HIV therapies.

## HOW BLUE WATERS PROJECT STAFF HELPED

The Blue Waters staff directly assisted our team by improving a variety of aspects of the Blue Waters scheduling system, by improving the system software to allow use of the Cray XK7 nodes for GPU-accelerated visualization, and by providing a range of tips and guidance on achieving higher I/O performance during all phases of simulation, analysis, and visualization with our software NAMD and VMD.

## WHY THE RESEARCH MATTERS

The ability to explore living systems via the “computational microscope” of molecular dynamics simulations has a profound impact not only on the progress of basic science, but also in the treatment of disease, development of drugs, and development of new energy technologies. The HIV capsid project may help scientists understand better how the HIV capsid infects the host cells and could lead to new HIV therapies.

By modelling the full organelle in the chromatophore project, it is possible to see how the 20 processes that the chromatophore carries out interlock, much like the gears in a fine Swiss watch, and see how they allow the bacteria to make ATP fuel out of sunlight. Deciphering the inner workings of this model photosynthetic system can guide the development of bio-hybrid green energy devices to help address mankind’s energy needs.

## WHY BLUE WATERS

Without Blue Waters and other petascale computing resources, neither the HIV nor the chromatophore project would be possible. The HIV project involves simulations of about 65 million atoms, and the chromatophore project requires simulations of up to 100 million atoms. Both simulations require thousands of nodes on Blue Waters in order to run effectively. These projects are examples of how Blue Waters enables bold, new projects that push the limits of what can be done with scientific computing. In our case, that means expanding molecular dynamics simulation capabilities from simulating just a few proteins to simulating full organelles.

## PRE-PETASCALE PREPARATION

We spent several years redesigning our NAMD and VMD programs to improve their scalability, adapting them for runs on very large node counts, improving their usage of large core count multi-core CPUs and GPU accelerators, and designing several new molecular structure and trajectory file formats that are suited to the needs of petascale molecular dynamics simulations.

## LOOKING FORWARD TO THE NEXT TRACK-1 SYSTEM

With current Track-1 computational resources, breakthroughs are being made in how viruses, in particular

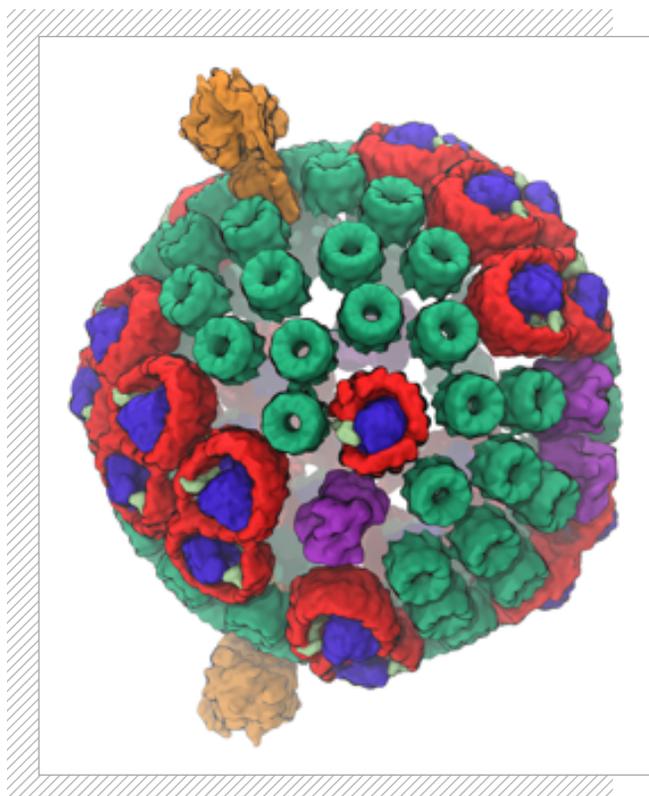


Figure 2. Scientists in Schulten’s group have also constructed an atomic-resolution model of a whole photosynthetic organelle, called a chromatophore. With Blue Waters and other petascale computers, scientists are no longer limited to looking at one or two proteins at a time. It is becoming possible to look at all of the interlocking processes inside an organelle made of many proteins.

HIV, infect cells; how antibiotic and cancer drug resistance occurs; how to efficiently create biomass fuels; and how sunlight is converted to chemical energy in photosynthetic organelles. Many of these simulations require integration of complex experimental data, but at the same time, they create insights that are unachievable by experiment alone since multiple sets of experimental data need to be interpreted. The use of multiple sets of experimental data requires computation, and critical information must come from simulations. The simulations reveal all-atom structures and often entirely unknown physical and chemical mechanisms underlying cellular processes targeted for treatment through new drugs.

Best-of-breed simulations today are covering 60 million to 200 million atoms that span one microsecond of simulated time (for example, simulation of HIV). While impressive, this is only a single step toward the ultimate goal of full-atom scale simulations of an entire cell. An organelle such as a photosynthetic chromatophore is only about 0.1% of even a small cell, which, in the case of human cells, typically has about 100 billion atoms and 300 billion independent proteins. Future Track-1 systems can make the goal of simulating full cells a reality within 10 years or less. Full-cell simulation would guide

unprecedented treatments and have huge potential economic benefits as they enable highly controlled synthetic biology. Similarly, the examples of best-of-breed simulations today of HIV or drug resistance can lead to new and much more effective treatments but require many simulated “drug trials” in order to reach effective solutions. In these and many other cases, future Track-1 level systems are essential.

## COMMUNITY IMPACT

NAMD is an award-winning, widely used molecular dynamics code and further development of the software suite supports many teams’ discoveries on computing systems of all sizes. Discoveries come about not only in basic science, but also in the treatment of disease, development of drugs, and development of new energy technologies. These can lead to economic benefits, spared and improved lives, and reduced pollution.

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