DI
GA
BW
MP
CI
BI

MULTISCALE SIMULATIONS OF COMPLEX SELF-ASSEMBLING BIOMOLECULES: TARGETING HIV-1

Allocation: NSF PRAC/200 Knh
PI: Gregory Voth[1]

[1]University of Chicago

EXECUTIVE SUMMARY

Biomolecular proteins are capable of performing extraordinary microscopic processes that are used to accomplish the useful macroscopic biological functions of the cell. From changing conformations (shape) to self-assembling into large microcompartments, these nanomachines are at the heart of the cellular machinery that underlies all living activity. The research team's overarching research goal is to develop advances in theoretical and computational methodology that couple microscopic-scale phenomena to higher-scale descriptions. A key element of the team's strategy is to systematically coarse-grain or reduce the representations of atomic-scale systems in a manner that is rigorously consistent within the framework of statistical mechanics. The team applies the computational tools it developed to understand biophysical phenomena that pose major public health risks. In the present research, the research team unraveled the mechanisms by which innate immune sensors assemble to block human immunodeficiency virus type-1 (HIV-1) infection and how capsid inhibitor drugs might perturb capsid assembly processes

RESEARCH CHALLENGE

HIV-1 is the causative agent of autoimmune deficiency syndrome (AIDS), which has affected millions of individuals worldwide and resulted in approximately one million AIDS-related deaths in 2017 [1]. Understanding the molecular-scale mechanisms and physical principles that govern viral processes such as the self-assembly of HIV-1 capsids is critical to the effective treatment of the disease. Retroviruses subvert normal cellular processes in order to replicate viral genetic information and assemble micrometer-sized nanostructures (viral capsids) that contain the genetic material, which is transmitted to new host cells. From a computational point of view, these large-scale viral components and the biophysical processes they are involved in consist of the concerted action of thousands of interacting proteins. Molecular simulations require not only large system sizes but also long timescale dynamics on the order of minutes to hours. Clearly, novel simulation methodologies need to be developed to tackle the intrinsic difficulties in computation at these time and length scales.

METHODS & CODES

The research group has made significant strides in developing new multiscale simulation methods to push the boundaries of phenomena that can be studied [2–5]. By combining atomic-level simulations with multiscale coarse-grained (CG) simulation algorithms, the team was able to investigate the dynamical properties of virus capsid assembly, capsid inhibitor drugs that perturb the maturation process, and intriguing innate immune proteins that wrap around the capsid to block HIV infection. The atomic-scale simulations employed NAMD, a parallel molecular dynamics code designed for high-performance simulation of large biomolecular aggregates, while the coarse-grained simulations use the research team's custom ultra-coarse-grained software, which was designed and optimized for the Blue Waters machine.

RESULTS & IMPACT

Viral Capsid Assembly. During the HIV-1 lifecycle, immature viral particles are converted into mature, infectious particles in a process called maturation. Proteolytic cleavage of the Gag polypeptide releases capsid proteins (CA) that self-assemble into conical capsids that enclose the viruses' genetic material. The team's investigations into the self-assembly properties of the CA protein reveal that the slow kinetic growth of the capsid is carefully regulated within the viral membrane envelope. Changes to the concentration of CA, molecular crowding agents, and capsid protein interaction strengths were found to cause the growth of aberrant capsid morphologies. The results suggest that conformational changes available to structurally flexible CA domain dimers are essential for capsid assembly.

Capsid Inhibitor Drugs. The viral capsid is also an attractive therapeutic drug target, owing to significantly less genetic flexibility in altering the composition of the capsid as compared to other essential viral proteins such as protease, for which there already exist a wide class of inhibitors. Using CG models, the team simulated how capsid inhibitor drugs that significantly stabilize metastable intermediates in the capsid assembly process can perturb the resulting morphologies of the assembled capsid.

Viral Capsid Restriction. Innate immune sensors target the viral capsid and are potent restriction factors that cause the premature destruction of the capsid, thereby blocking HIV-1 infection. In particular, the tripartite-motif-containing proteins, TRIM5α and TRIMCyp, are cytoplasmic proteins that confer species-specific resistance to HIV-1. The research team's recent simulations of TRIM5α revealed how they form hexagonally patterned nets on the surface of the capsid to encage the core of the virus and restrict viral activity. These results show how the coupling between two interaction sites of TRIM5α can give rise to self-assembling behavior, in which a critical balance of interaction strengths must be maintained.

These advances in multiscale simulation have opened up remarkable opportunities to study the dynamics of biomedically relevant problems that were largely intractable until now. Technological advances in computational methods that increase the accuracy, predictive power, and range of phenomena under study contribute directly to public health by elucidating the fundamental chemistry underlying infectious diseases.

WHY BLUE WATERS

Multiscale simulations of viral processes are inherently computationally expensive, requiring the evaluation of interactions among many proteins and millions of particles. An immediate advantage of CG models is that their reduced representations are very computationally efficient, allowing leadership petascale resources such as Blue Waters to probe the dynamics of molecular systems that are many orders of magnitude in both length and time scales and would otherwise be inaccessible to conventional molecular simulations. The team's highly scalable, custom molecular dynamics software was developed with the expertise of Blue Waters staff to perform CG simulations across thousands of computer processors and has been made available to the broader scientific community. The researchers' atomic-scale and coarse-grained simulations were made possible thanks to the massively parallel computing infrastructure of Blue Waters. These exciting advances in fundamental simulation methodology and novel discoveries in self-assembly phenomena highlight an essential role for access to state-of-the-art leadership-class computing resources.

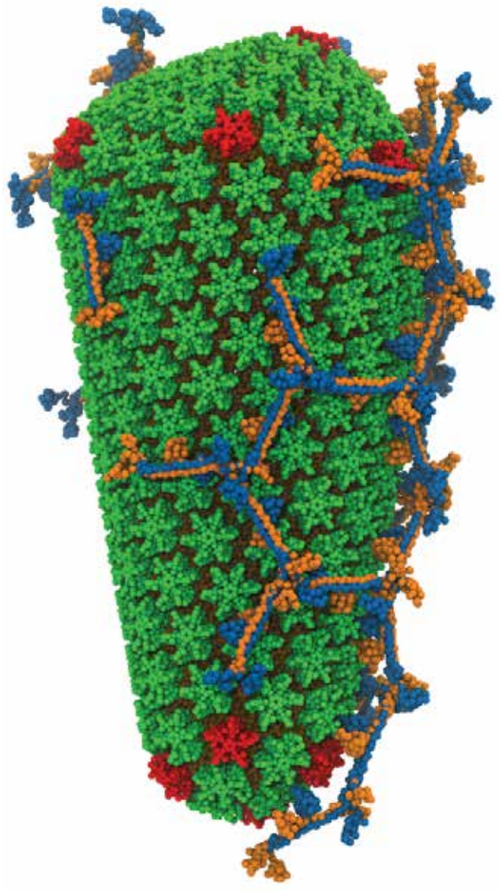

Figure 1: TRIM5α, an innate immune sensor, encases the core of the HIV-1 virus to restrict viral activity.

PUBLICATIONS & DATA SETS

J. M. A. Grime and G. A. Voth, "Highly scalable and memory efficient ultra-coarse-grained molecular dynamics simulations," *J. Chem. Theory Comput.*, vol. 10, no. 1, pp. 423–431, Jan. 2014.

J. M. A. Grime *et al.*, "Coarse-grained simulation reveals key features of HIV-1 capsid self-assembly," *Nat. Commun.*, vol. 7, p. 11568, May 2016.

A. J. Pak, J. M. A. Grime, A. Yu and G. A. Voth, "Supercharged assembly: A broad-spectrum mechanism of action for drugs that undermine controlled HIV-1 viral capsid formation," *JACS*, in review, 2019.

A. Yu, B. K. Ganser–Pornillos, O. Pornillos, and G. A. Voth, "TRIM5α self-assembly and compartmentalization of the HIV-1 viral capsid," in preparation, 2019.