UNVEILING THE FUNCTIONS OF VIRUS CAPSIDS THROUGH THE COMPUTATIONAL MICROSCOPE

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EXECUTIVE SUMMARY

Virus capsids play critical roles in viral infection and are, therefore, promising molecular targets for antiviral drugs. Blue Waters enables all-atom modeling and molecular dynamics (MD) simulations of these remarkable molecular machines, exposing details underlying their biological functions and potential vulnerabilities to drug compounds. This project specifically studied the viruses that afflict humans with hepatitis B liver disease and T-cell leukemia.

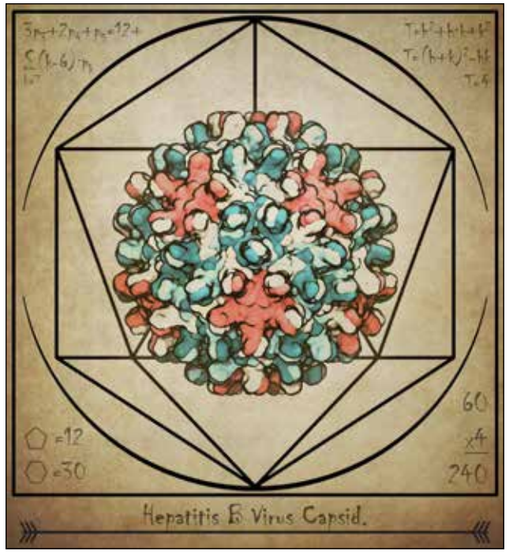

Figure 1: The HBV capsid is an icosahedral protein shell composed of 240 identical proteins. Although experimentally determined structures suggest that the capsid is rigid and symmetric, our simulations on Blue Waters reveal that the capsid is highly flexible and can distort asymmetrically.

RESEARCH CHALLENGE

Viral pathogens are a major risk to public health; millions of people die annually due to a lack of effective antiviral treatments. The development of novel drug compounds that can target viruses depends heavily on characterizing the components of virus structure and the roles these components play in facilitating infection. One such structural component key to virus function is the capsid, a protein shell that packages the viral genome and regulates its delivery to the host cell nucleus. Virus capsids are currently of great pharmacological interest as drug targets.

METHODS & CODES

MD simulations provide a powerful technique to investigate the dynamical structure and chemical–physical properties of virus capsids [1]. Our work has demonstrated that, when performed at the all-atom level of detail, simulations are capable of capturing even subtle effects on capsid structure and dynamics induced by bound drug molecules [2]. Our simulations employed NAMD [3], a highly scalable MD code, optimized specifically for Blue Waters, that boasts a long and successful track record of deployment on the machine. While all-atom simulation of virus capsids comes at great computational expense, access to NAMD on Blue Waters has enabled us to reveal critical new insights into the structure and function of capsids, as well as to suggest mechanisms by which drug molecules can disrupt them. Importantly, our discoveries were inaccessible to state-of-the-art experimental methods and were made possible only through access to the petascale computing power of Blue Waters.

RESULTS & IMPACT

HBV. Hepatitis B virus (HBV, Fig. 1) is a leading cause of liver disease worldwide, including cancer. The capsid of HBV is icosahedral. To reduce computational expense and increase resolution in experimental structure determination, studies of icosahedral capsids commonly constrain them to be symmetric. We previously utilized Blue Waters to perform the first simulations of the HBV capsid without symmetry constraints [2]. At present, we have leveraged Blue Waters to investigate the unconstrained capsid on the microsecond timescale, representing the most extensive unbiased simulations for the largest icosahedral virus capsid achieved to date.

Our simulations reveal that the HBV capsid is highly flexible and capable of asymmetric distortion, even under equilibrium conditions. Experiments suggest that the capsid's ability to flex and distort may be important during reverse transcription or nuclear import. Our simulations also reveal that triangular pores in the capsid surface selectively filter the passage of ionic species. This observation implicates the triangular pores as the openings through which the capsid exposes charged peptides that signal nuclear localization; this observation further suggests that the capsid controls signal exposure based on experimentally determined changes in peptide charge. Drugs designed to rigidify the capsid to prevent distortion, or to block triangular pores to prevent signal exposure, could inhibit key stages of viral infection.

We also used capsid conformers sampled during simulations on Blue Waters to perform a theoretical single-particle image reconstruction, mimicking structure determination by cryo-electron microscopy (EM). Our analysis indicated that capsid flexibility and asymmetry significantly lowered the resolution of the image reconstruction. Thus, even in this era of advancing cryo-EM technology, our simulations reveal that protein flexibility likely remains a major limiting factor to achieving true atomic resolution for virus capsids and other large biological structures.

HTLV-1. Human T-cell leukemia virus type 1 (HTLV-1, Fig. 2), which causes cancer, is a cousin of the HIV-1 virus, which causes AIDS. HTLV-1 assembles as an immature particle. In the immature state, the proteins destined to become the mature capsid are incorporated into a polyprotein known as Gag, which packs into a spherical lattice. Leveraging our previous experience using Blue Waters to determine the structure of the mature HIV-1 capsid [3] and immature Rous sarcoma virus capsid lattice [4], we have now utilized Blue Waters to construct a model of the immature HTLV-1 capsid lattice.

Mutagenesis experiments indicated a series of residues critical to HTLV-1 assembly, and our simulations reveal that these residues mediate key interactions at dimer and trimer interfaces between proteins within the immature capsid lattice. Our results also demonstrate that the HTLV-1 lattice is more structurally similar to that of HIV-1 than Rous sarcoma virus, although all three are retroviruses with similar capsid morphologies. Drugs designed to interfere with the key protein interactions identified by our study could disrupt the capsid structure or assembly of HTLV-1, representing a novel treatment approach.

WHY BLUE WATERS

Due to their formidable computational expense, simulations of virus capsids are only feasible on a petascale machine like Blue Waters. Capsid systems encompass millions of atoms, and computing the interactions among such large numbers of particles over microsecond timescales can take months, even on thousands of processors. Further, analysis of the colossal data sets generated by capsid simulations is enabled through access to the massively parallel computing power and high-performance Lustre filesystem provided by Blue Waters. The exciting discoveries revealed by our research underscore an essential role for petascale resources like Blue Waters in the development of antiviral treatments, and demonstrate that access to leadership-class computing facilities holds the potential for significant impact on public health.

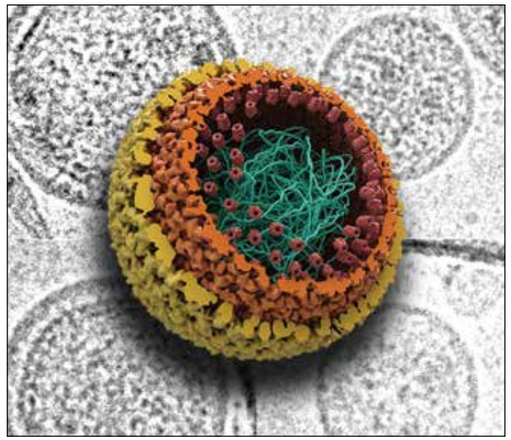

Figure 2: HTLV-1 assembles as an immature particle, with the polyprotein Gag packed into a spherical lattice with the viral genome at its center. We used Blue Waters to determine the structure of the capsid component of HTLV-1 Gag.

PUBLICATIONS & DATA SETS

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