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STUDYING CELLULAR PROCESSES THROUGH THE COMPUTATIONAL MICROSCOPE

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"In biology and in biomedicine, we have to realize that basically all organisms are large societies of molecules. We need a supercomputer to see that society for the first time."

—Klaus Schulten (1947–2016)

EXECUTIVE SUMMARY

Blue Waters provides a powerful platform at the interface of biology, physics, and computer science that is being leveraged to shed light on cellular processes toward direct impact on public health. Utilizing Blue Waters as a "computational microscope," researchers are revealing key new insights into viral infection and the mechanisms by which it can be disrupted with drugs. Virus capsids represent promising drug targets, and the world's first microsecond molecular dynamics (MD) simulations of these remarkable molecular machines performed at all-atom resolution—a feat made achievable only by the petascale computing resources of Blue Waters—expose details underlying their biological functions and potential vulnerabilities to drug compounds.

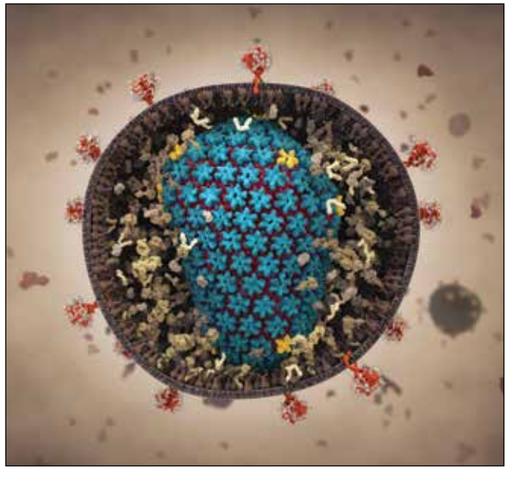

Figure 1: At the core of the HIV-1 virion lies its capsid. Composed of repeating copies of proteins, the capsid protects the viral genome and performs key functions throughout the viral life cycle that are essential to successful infection.

RESEARCH CHALLENGE

Infectious viral pathogens are a major risk to public health, and millions of people die annually due to a lack of effective anti-viral 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 (Fig. 1), 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]. We employed Nanoscale Molecular Dynamics, or NAMD [3] for our simulations, 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

HIV-1. Infection with human immunodeficiency virus type 1 (HIV-1) is classified as a global pandemic by the World Health Organization. Due to the extremely high mutation rate of the virus, new drug treatments must be constantly developed. We previously utilized Blue Waters to solve the all-atom structure of the mature HIV-1 capsid [1], providing an essential platform

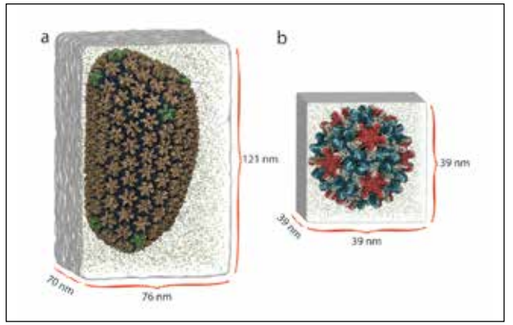

Figure 2: (a) The HIV-1 capsid simulation system contains more than 1,300 proteins immersed in a native solvent environment, totaling over 64 million atoms. (b) The HBV capsid simulation system contains 240 proteins immersed in a native solvent environment, totaling about 6 million atoms.

for study of its dynamical and structural properties, as well as its interaction with host-factors [3] and drug molecules [2]. At present, we have leveraged Blue Waters to perform the most monumental all-atom simulation achieved to date, characterizing the dynamical behavior of the HIV-1 capsid system (64 million atoms, Fig. 2a) over the timescale of one microsecond.

Our simulation reveals charge-specific channels in the surface of the capsid through which solvent ions translocate; these channels are likely capable of regulating translocation of DNA nucleotides, which must travel from the exterior to the interior of the capsid during reverse transcription. Further, analysis of the capsid's collective motions reveals a belt dividing the capsid into two hemispheres, suggesting a potential mechanism by which the capsid may break apart to deliver its genome. Our results, which additionally included characterization of the electrostatic and acoustic properties of the capsid, indicate new avenues for the development of drugs that seek to disrupt the capsid by altering its complex biophysical properties.

HBV. Hepatitis B virus (HBV) is a leading cause of liver disease worldwide, including cancer, and the World Health Organization estimates that 240 million people suffer from chronic infection. The capsid of HBV is icosahedral, and most prior structural studies imposed assumptions of icosahedral symmetry to enhance experimental resolution and reduce computational complexity. We previously utilized Blue Waters to perform the first simulation of the HBV capsid undertaken without symmetry bias and characterized drug-induced structural changes likely related to the drug's mechanism of capsid disruption [2]. At present, we have leveraged Blue Waters to perform the most extensive unbiased simulations achieved for an icosahedral virus capsid to date, characterizing the dynamical behavior of the HBV capsid system (6 million atoms, Fig. 2b) in the presence and absence of three distinct drug compounds over timescales of one microsecond.

Our simulations reveal remarkable asymmetry in capsid motions, supporting hypotheses that the capsid can distort asymmetrically to accommodate unevenly-distributed internal strain resulting from conversion of pgRNA (pre-genomic ribonucleic acid) to DNA during reverse transcription. Further, the localization of ions during simulation provides a structural explanation for experimentally observed enhancement of capsid assembly under high salt concentrations. Finally, our results capture a variety of morphological and allosteric changes induced by bound drug molecules, providing insight into their complex mechanisms of action.

Viral host factors. Integrating the results of additional simulations with experiments performed by our collaborators, we also reveal key details underlying the structures and mechanisms of large host-cell molecules that are implicated in viral infection, including the myxovirus resistance protein B (HIV-1) and cytoplasmic dynein (HIV-1 and HBV).

WHY BLUE WATERS

Due to their formidable computational expense, microsecond simulations of virus capsids are only possible on a petascale machine like Blue Waters. Capsid systems encompass millions of atoms, and computing the interactions among such large numbers of particles over such long timescales can take months, even on tens of thousands of processors. Further, analysis of the colossal data sets generated by our capsid simulations was made feasible only 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 anti-viral treatments, and demonstrate that access to leadership-class computing facilities holds the potential for significant impact on overall public health.

PUBLICATIONS AND DATA SETS

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