DI

GA

BW

MOLECULAR DYNAMICS SIMULATIONS OF THE HBV CAPSID AS A DRUG TARGET

Allocation: GLCPC/370 Knh
PI: Jodi A. Hadden–Perilla[1]
Collaborators: Adam Zlotnick[2], Juan R. Perilla[1], Michael F. Hagan[3], Brian Bothner[4]

[1]University of Delaware
[2]Indiana University
[3]Brandeis University
[4]Montana State University

EXECUTIVE SUMMARY

Hepatitis B virus (HBV) is a major cause of liver disease. The World Health Organization estimates that more than 250 million people worldwide suffer from this chronic infection, with no cure available. Researchers aim to develop new treatments targeting HBV's capsid, the protein shell that encloses its viral genome (Fig. 1a). The research team has been leveraging Blue Waters since 2015 as a computational microscope to study the capsid, employing all-atom molecular dynamics simulations to reveal details of structure and function that are inaccessible to experiments.

Currently, the team is endeavoring to further characterize the capsid as a drug target by investigating morphological disruption by heteroaryldihydropyrimidine (HAP) compounds, cooperativity in HAP uptake, and the structural and statistical details of HAP binding modes under physiological conditions. The team's findings go far beyond conclusions that can be drawn from static models derived with crystallography or cryo-electron microscopy. Importantly, simulation of the multimillion-atom capsid system is only possible on a petascale supercomputer such as Blue Waters.

RESEARCH CHALLENGE

The HBV capsid is a complex molecular machine that self-assembles from 120 capsid-protein dimers to package RNA. In addition, it facilitates the maturation of RNA to DNA and hijacks various components of the host cell's own machinery to transport the capsid's genomic cargo throughout the viral infection cycle. Drugs that disrupt the capsid have been identified but have not been approved for human use. Researchers' ability to produce new treatments that target the capsid depends heavily on understanding the capsid's inner workings and the mechanisms by which known drug compounds disrupt it; by determining how the capsid works, researchers can also determine how best to inhibit it.

METHODS & CODES

Molecular dynamics simulations provide a powerful tool to investigate virus capsids such as HBV [1]. The research team's work has demonstrated that when performed at all-atom resolution, simulations are capable of capturing remarkably subtle details of capsid structure and dynamics, including changes induced by bound drugs [2]. These simulations employ NAMD [3], a highly scalable biomolecular simulation code that boasts a long and successful track record of deployment on Blue Waters. While all-atom simulations of the intact HBV capsid come at a great computational expense, access to NAMD on Blue Waters has enabled the team to reveal critical new insights into the capsid's function and to suggest strategies for targeting it with novel therapeutics [4,5].

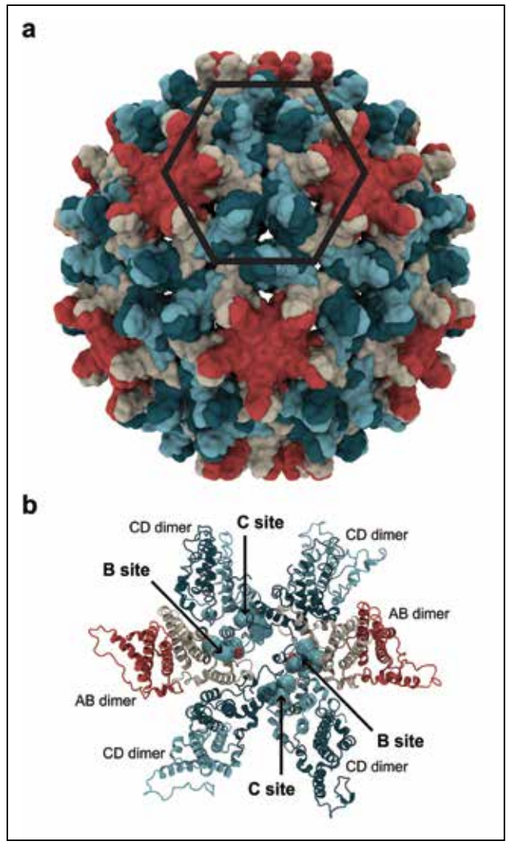

Figure 1: (a) The HBV capsid is composed of 120 capsid-protein dimers. These dimers can occupy either AB (red/beige) or CD (cyan/blue) quasi-equivalent positions. One capsid hexamer is highlighted. (b) The capsid hexamer exhibits four drug binding sites: two B sites and two C sites. Bound HAPs are shown.

RESULTS & IMPACT

The HBV capsid is composed of 120 capsid-protein dimers, arranged according to icosahedral symmetry (Fig. 1a). There are two possible orientations that dimers can occupy within the capsid structure, which are referred to as AB and CD. Drugs known to target the capsid recognize hydrophobic pockets found at the interfaces of B/C and C/D subunits, referred to as B sites and C sites (Fig. 1b). Previously, the research team used Blue Waters to simulate the apo (unbound) form of the HBV capsid on the microsecond timescale [4] and observed differences in the structure and dynamics of B sites versus C sites, despite symmetry [5]. Now, the team has used Blue Waters to study the capsid's response to drug binding in each of these quasi-equivalent locations, furthering characterization of the capsid as a drug target. The simulations of the intact capsid with drugs from the HAP family complexed in B sites, C sites, or both B and C sites reach the microsecond timescale.

Morphology. Preliminary work on HAP-bound capsids demonstrated that the compounds induce changes in the capsid's shape [2] consistent with experimental observations. The presence of drugs causes the spherical capsid to adopt a faceted morphology similar to that of a regular geometric icosahedron (Fig. 2). The latest results reveal that drug binding in C sites leads to more pronounced capsid faceting than drug binding in B sites. Saturation of the capsid with drugs in B and C sites leads to intermediate faceting and increased particle size. Importantly, these findings underscore the capsid's resilience and ability to make structural adjustments to accommodate drug uptake.

Cooperativity. Experiments by the team's collaborators suggest that drug uptake in the capsid is cooperative, meaning that the binding of one drug molecule makes the binding of a second more likely. The research team's findings indicate that within the apo-form capsid, B sites remain mostly open, while C sites spend a significant portion of the time closed and occluded. As such, initial drug binding is most probable in B sites. Using the new simulation data, the team has learned that the presence of drugs in B sites causes C sites to become occluded less often, confirming the existence of a cooperativity mechanism. Further, the presence of drugs in C sites causes B sites to be occluded more often, reducing the likelihood of drugs binding there. Similar to the faceting effect, cooperativity between drug binding sites arises from shifts in interdimer orientations as the capsid makes structural adjustments to accommodate drug uptake.

Binding modes. The research team's simulations of drug-bound capsids have provided the unique opportunity to expand characterization of HAP binding modes far beyond what was previously determined from static crystal structures. Using Blue Waters, the researchers have produced ensembles of six-million samples each for B and C quasi-equivalent binding sites, which capture the dynamical interactions of HAPs with the capsid under native physiological conditions at full chemical resolution. The structural and statistical details revealed by these data sets are invaluable toward the design and optimization of new drug compounds that target the capsid and have the potential to support the discovery of new therapeutics.

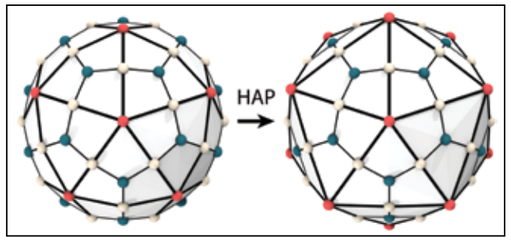

Figure 2: Bound HAPs cause the spherical capsid to adopt a faceted shape, similar to that of a regular geometric icosahedron.

WHY BLUE WATERS

Owing to computational expense, simulations of the intact HBV capsid are only feasible on a petascale supercomputer such as Blue Waters. Investigating the capsid under physiological conditions at full chemical resolution requires calculations involving the interactions of millions of atoms. Simulations exploring the microsecond timescale can take months, even on thousands of processors. The exciting discoveries revealed by this work underscore the essential role for leadership-class computing resources in supporting basic science research toward understanding viruses and developing novel antiviral treatments.

PUBLICATIONS & DATA SETS

A. J. Bryer, J. A. Hadden–Perilla, J. E. Stone, and J. R. Perilla, "High-performance analysis of biomolecular containers to measure small-molecule transport, transbilayer lipid diffusion, and protein cavities," *J. Chem. Inf. Model.*, vol. 59, no. 10, pp. 4328–4338, 2019.

J. A. Hadden–Perilla, B. C. Goh, C. J. Schlicksup, B. Venkatakrishnan, and A. Zlotnick, "Mechanistic insights into the drug-induced disruption of the HBV capsid revealed by all-atom molecular dynamics simulations," submitted, 2019.