Mechanistic insights into HBV capsid assembly and its inhibition revealed by all-atom MD simulations

Carolina Pérez-Segura[1], Michael F. Hagan[2], Stephen C. Jacobson[3], Adam Zlotnick[3], and Jodi A. Hadden-Perilla[1]

1. University of Delaware, Newark, DE 19716
2. Brandeis University, Waltham, MA 02453
3. Indiana University, Bloomington, IN 47405

Hepatitis B virus (HBV) infection is a major global health concern, with over 250 million individuals affected worldwide. The viral capsid self-assembles from 120 copies of core protein (Cp) homodimer to form predominantly T=4 icosahedral particles. Assembled Cp include both intra- and inter-dimer interfaces, which are allosterically linked. Although the capsid is structurally and biophysically well-characterized, atomistic details of its dynamics and allostery remain largely unresolved. Using all-atom molecular dynamics (MD) simulations, we examine the capsid's response to assembly-altering mutations and assembly-modulating small molecules on the microsecond timescale. We reveal the structural basis by which mutations alter assembly kinetics and confer resistance to assembly inhibitors. We extensively characterize the inhibitor binding site, providing the first statistical description of its topology and dynamics at equilibrium. We provide new insights into allosteric communication between the intra- and inter-dimer Cp interfaces. We collaborate with experimentalists, as well as computationalists specializing in coarse-grain assembly models, to provide the atomistic resolution needed to bridge gaps between theory and experiment. Our results, based on sampling the motion of the intact HBV capsid in simulations encompassing six million atoms, are relevant to the development of new capsid-targeting antivirals that disrupt and misdirect HBV particle assembly.