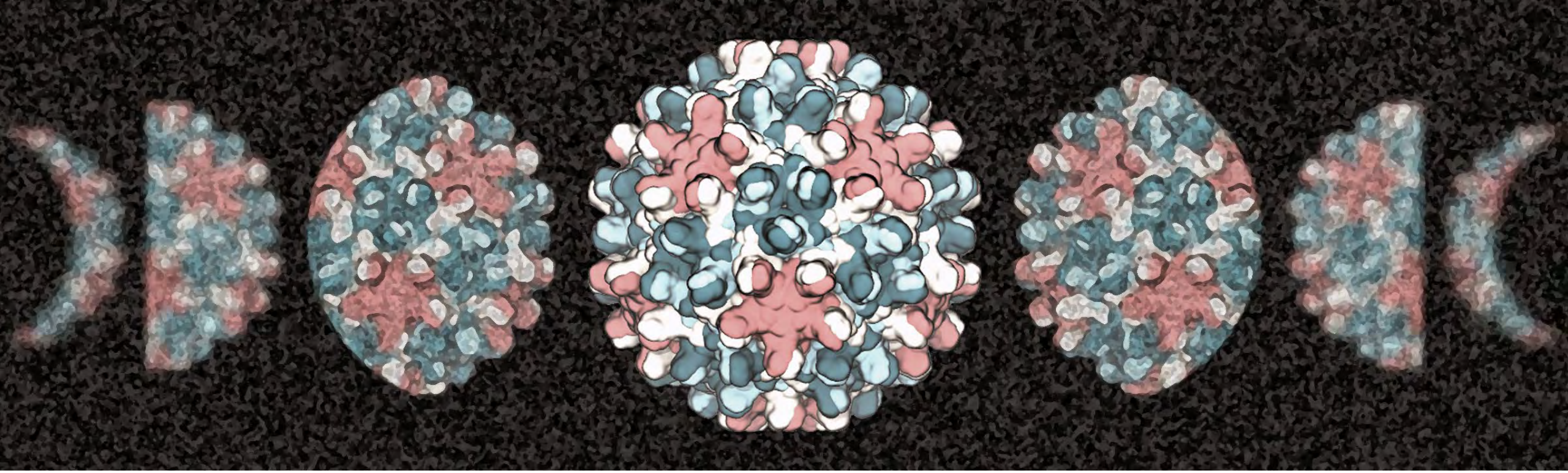


The Hepatitis B Capsid through the Computational Microscope

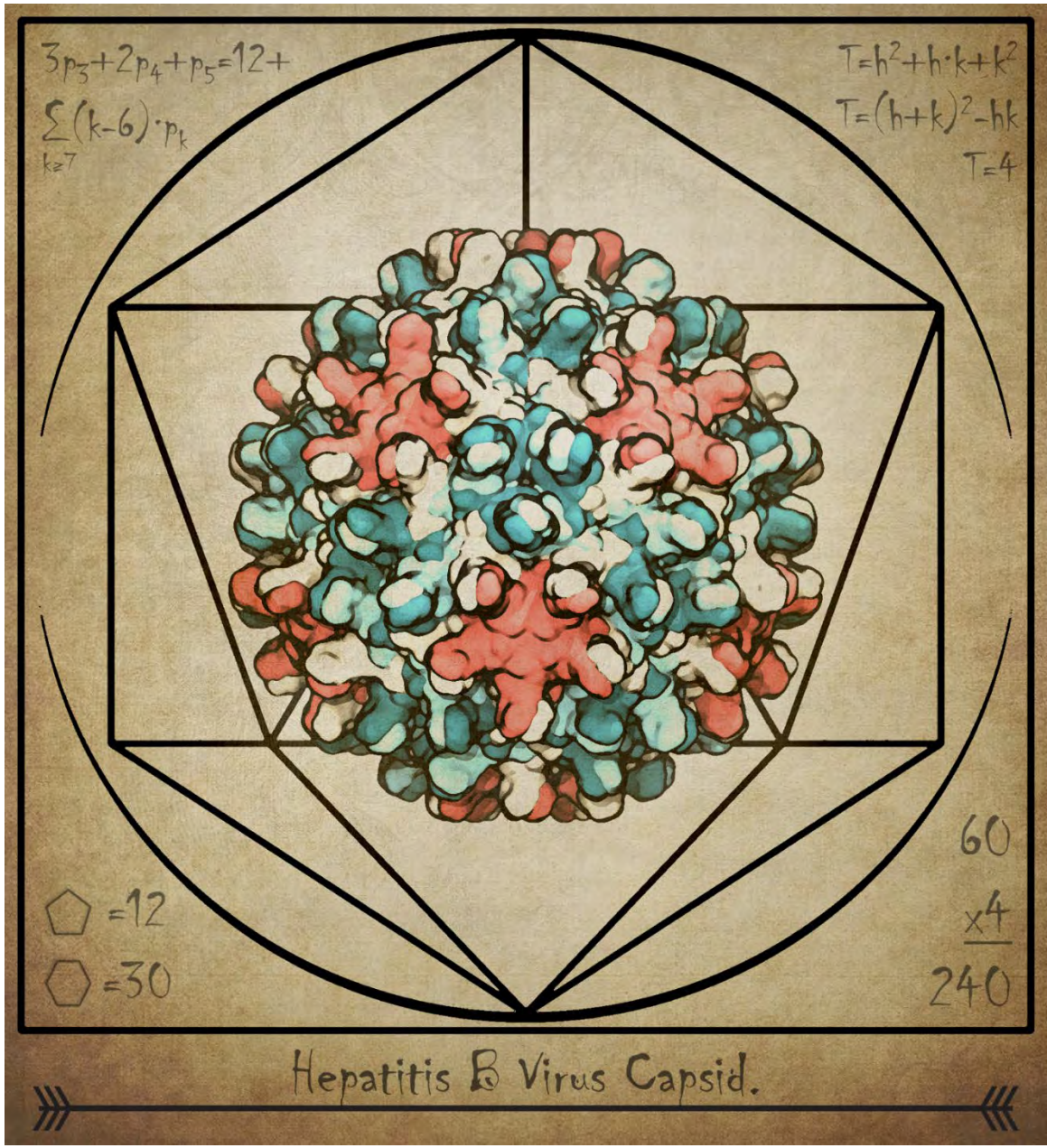
Jodi A. Hadden
University of Delaware

Blue Waters Symposium 2019

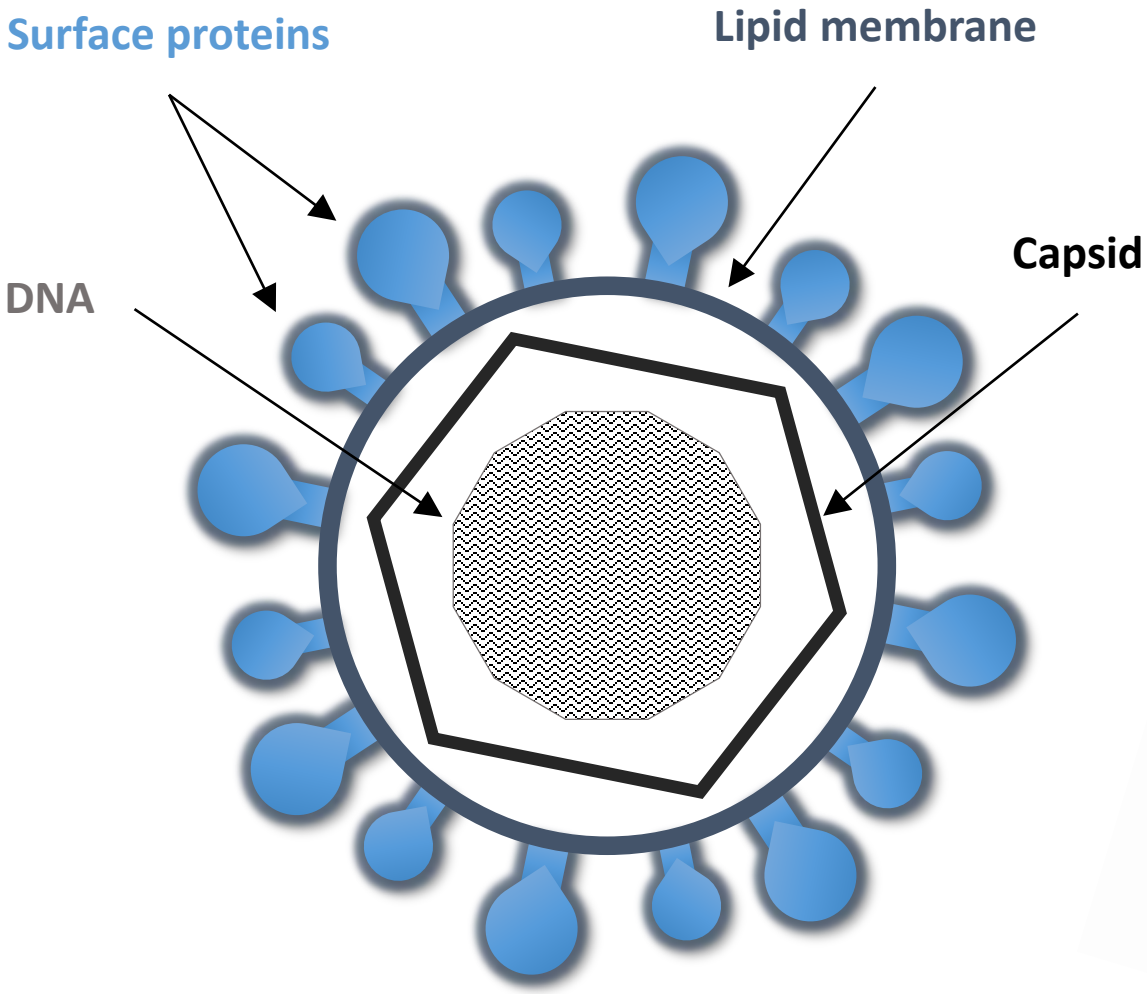
I use Blue Waters to…

- Study HBV capsid as a drug target

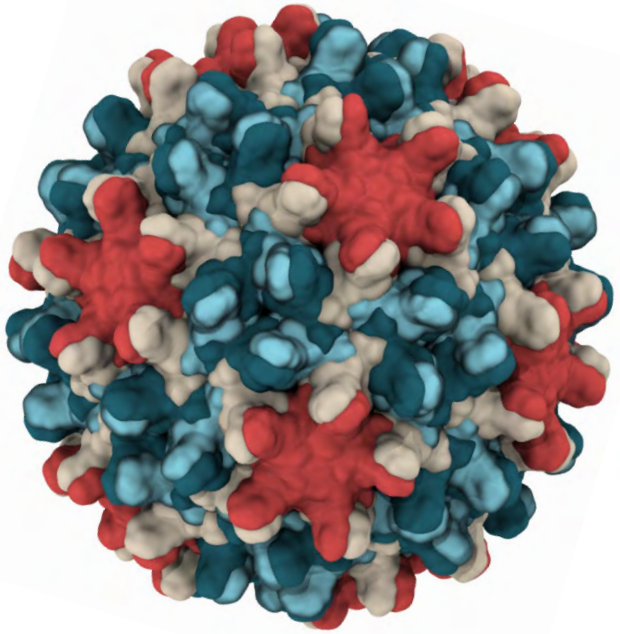
- HBV causes severe liver disease
- 250 million people infected
- Vaccine, but no cure
- Capsid is attractive drug target

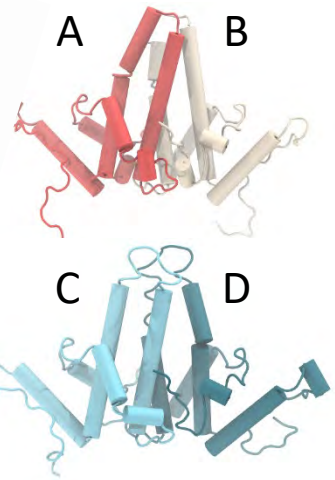


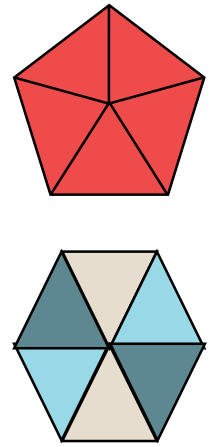
Hepatitis B Virus Capsid



12 vertices
20 faces
30 edges







Microsecond simulation at native conditions

Capsid subunit

Assemble using symmetry rules;
Model in missing protein fragments

Complete capsid

Drug molecule

Parameterization

Drug molecule with force field parameters

Crystallography

Drug-bound capsid

Assign protonation states for environmental pH of 7.0

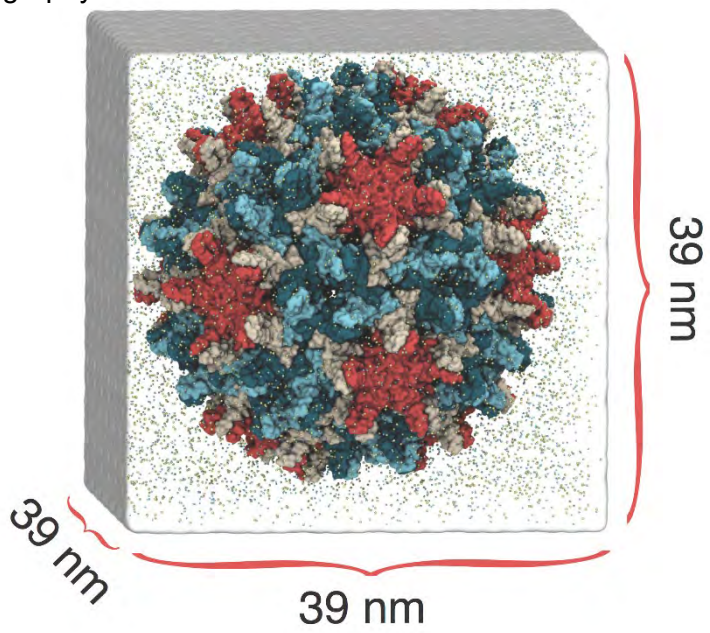
Native drug-bound capsid

Place ions around capsid based on electrostatics

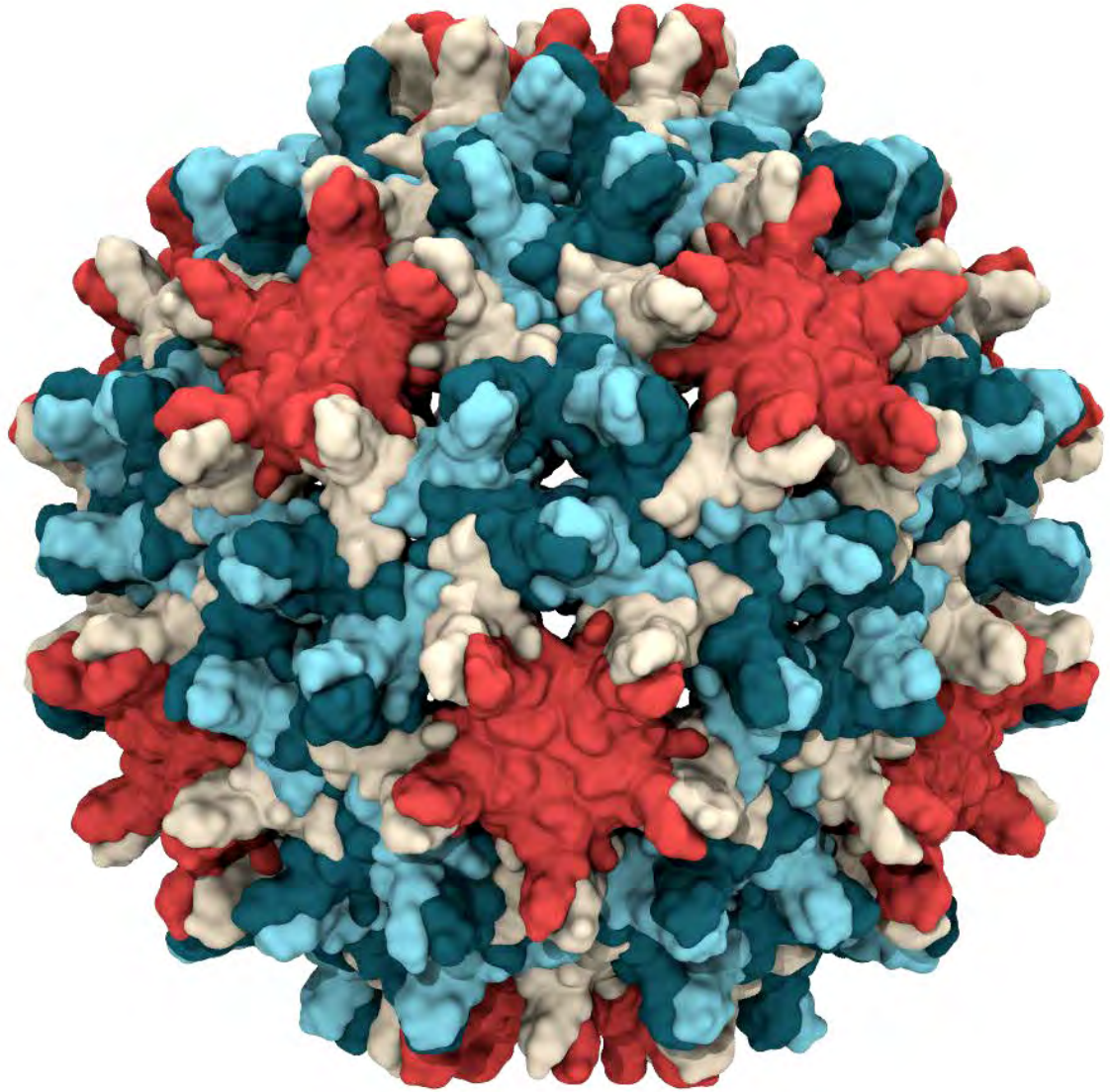
Native drug-bound capsid with neutral charge

Add bulk water and ions

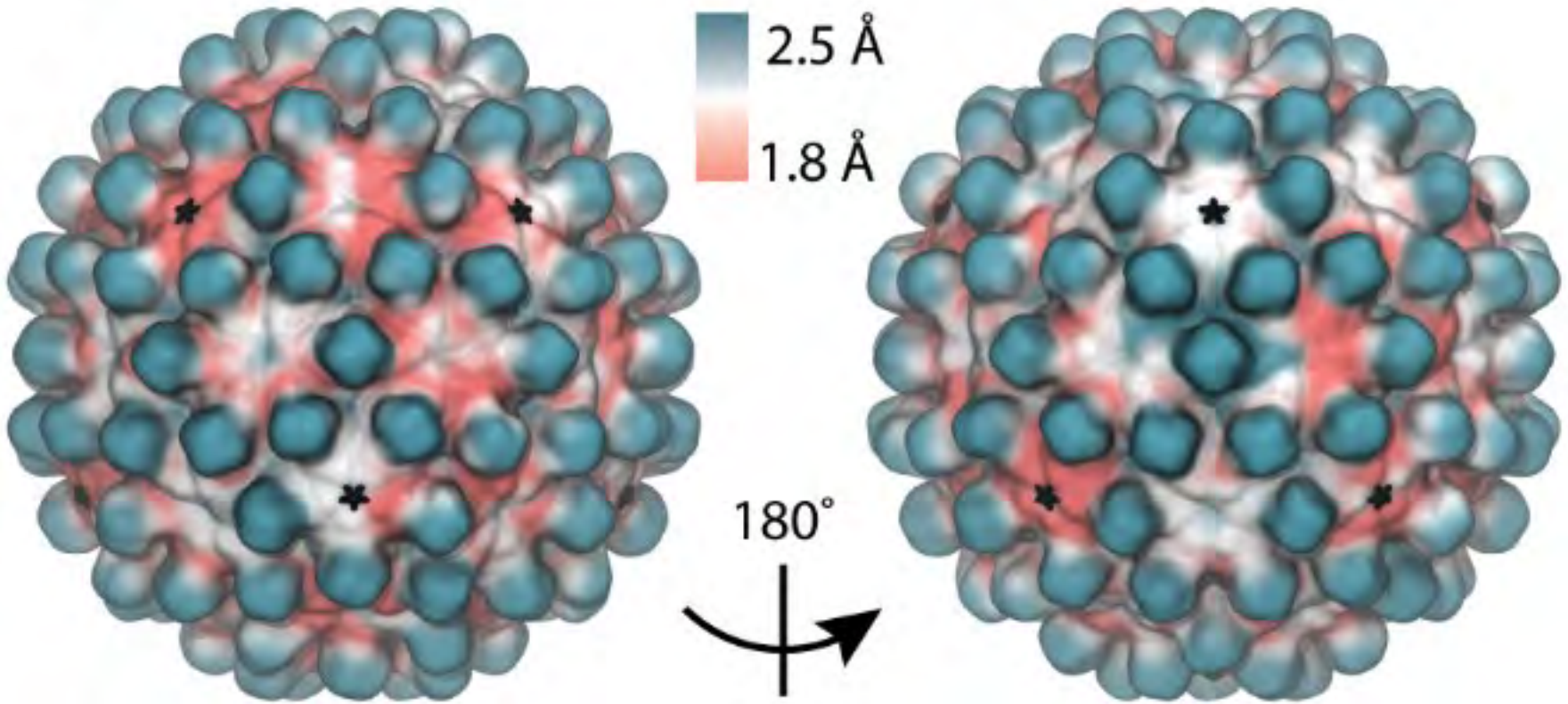
Native drug-bound capsid in 150 mM NaCl solvent box



MD simulation of 6 M atoms for 1 μs without restraints

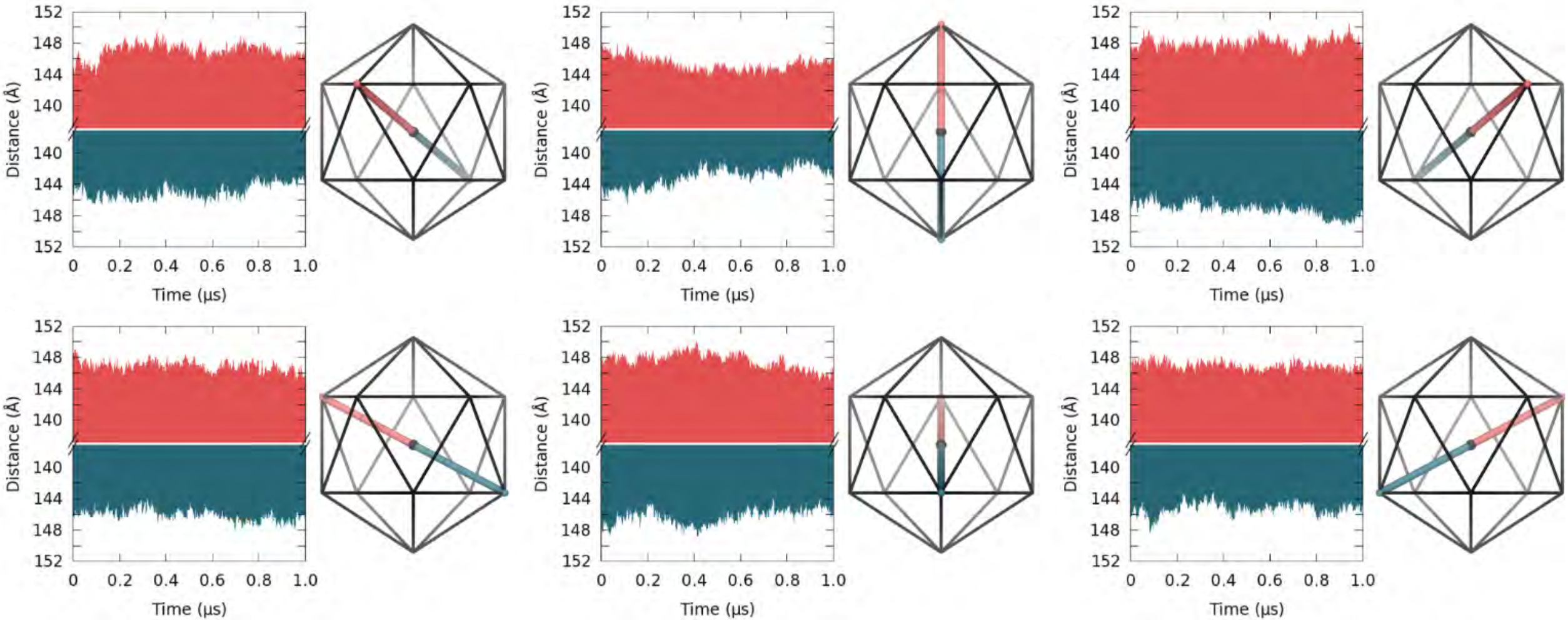


Global Capsid Flexibility



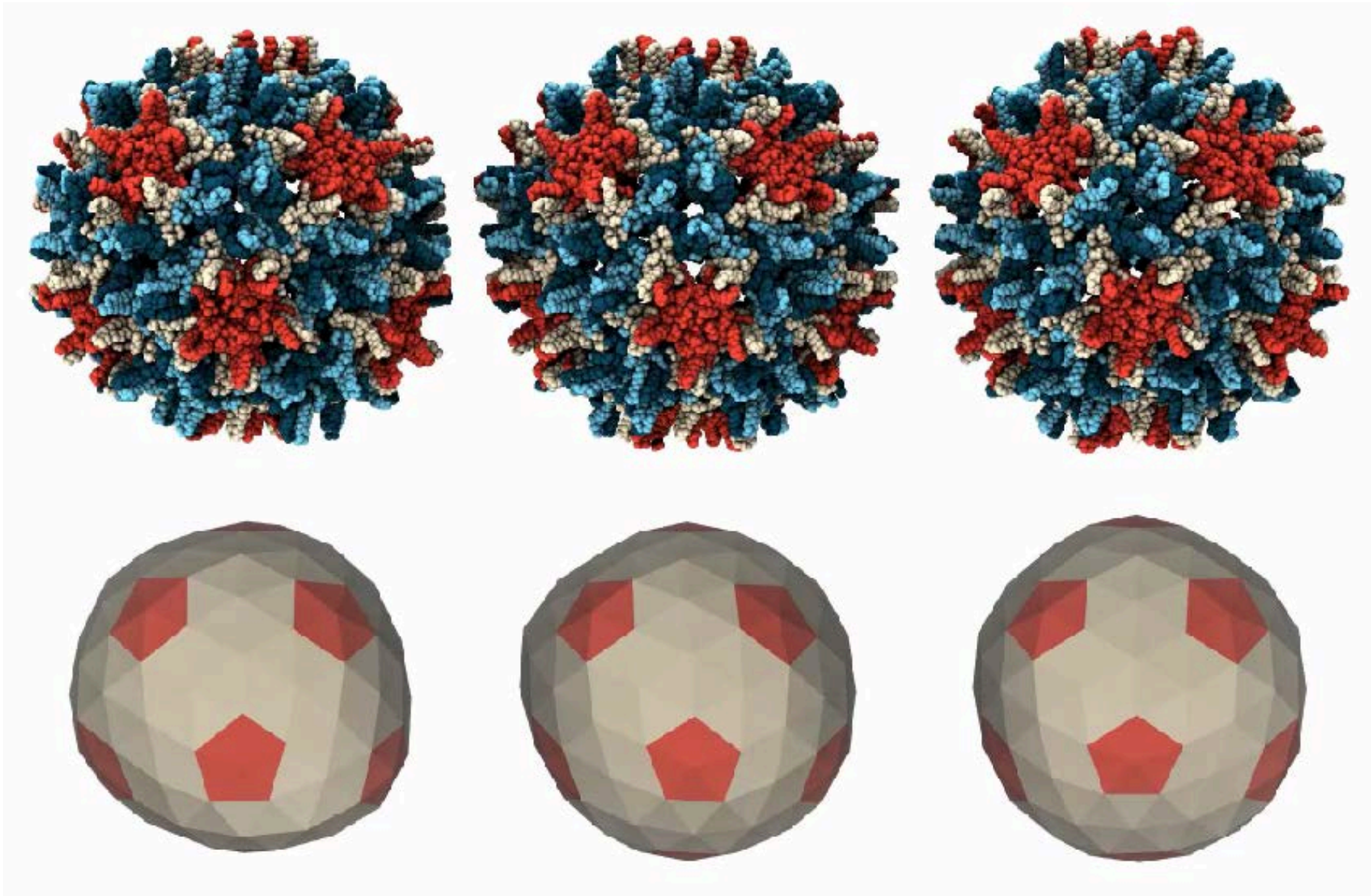
Hadden (2018)

Capsid Asymmetry



Hadden (2018)

Capsid Collective Motions

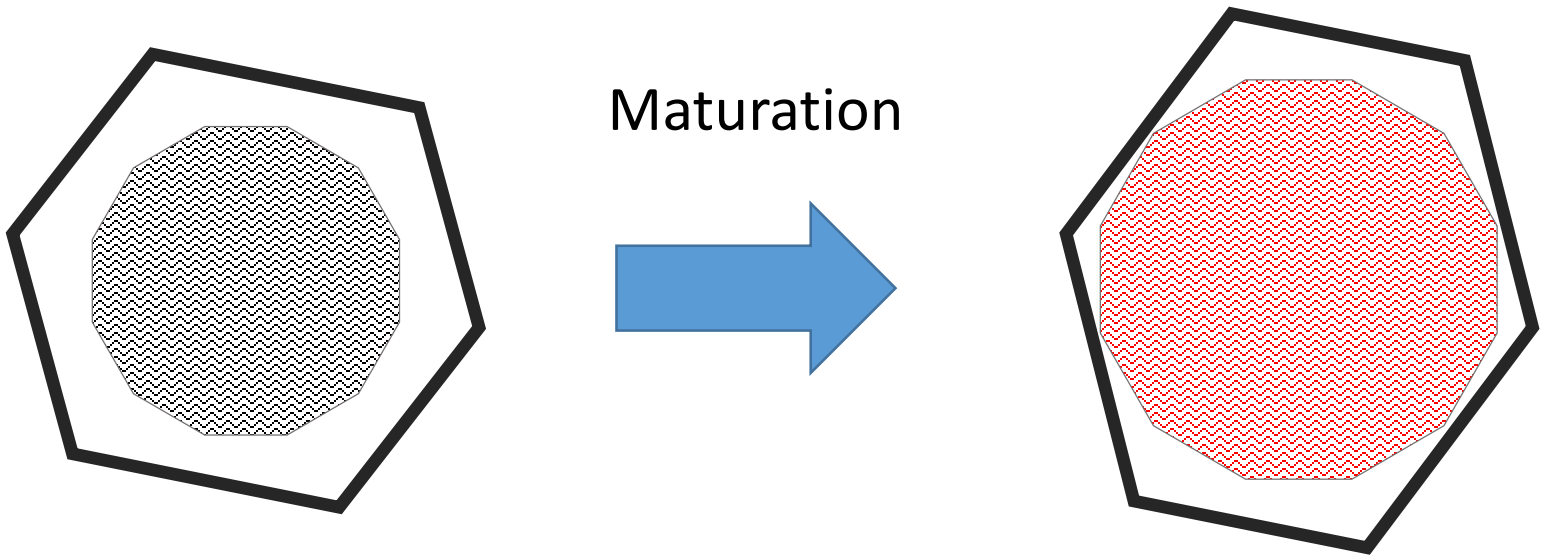


Hadden (2018)

Capsid distortion may be a functional feature

Immature (pgRNA)

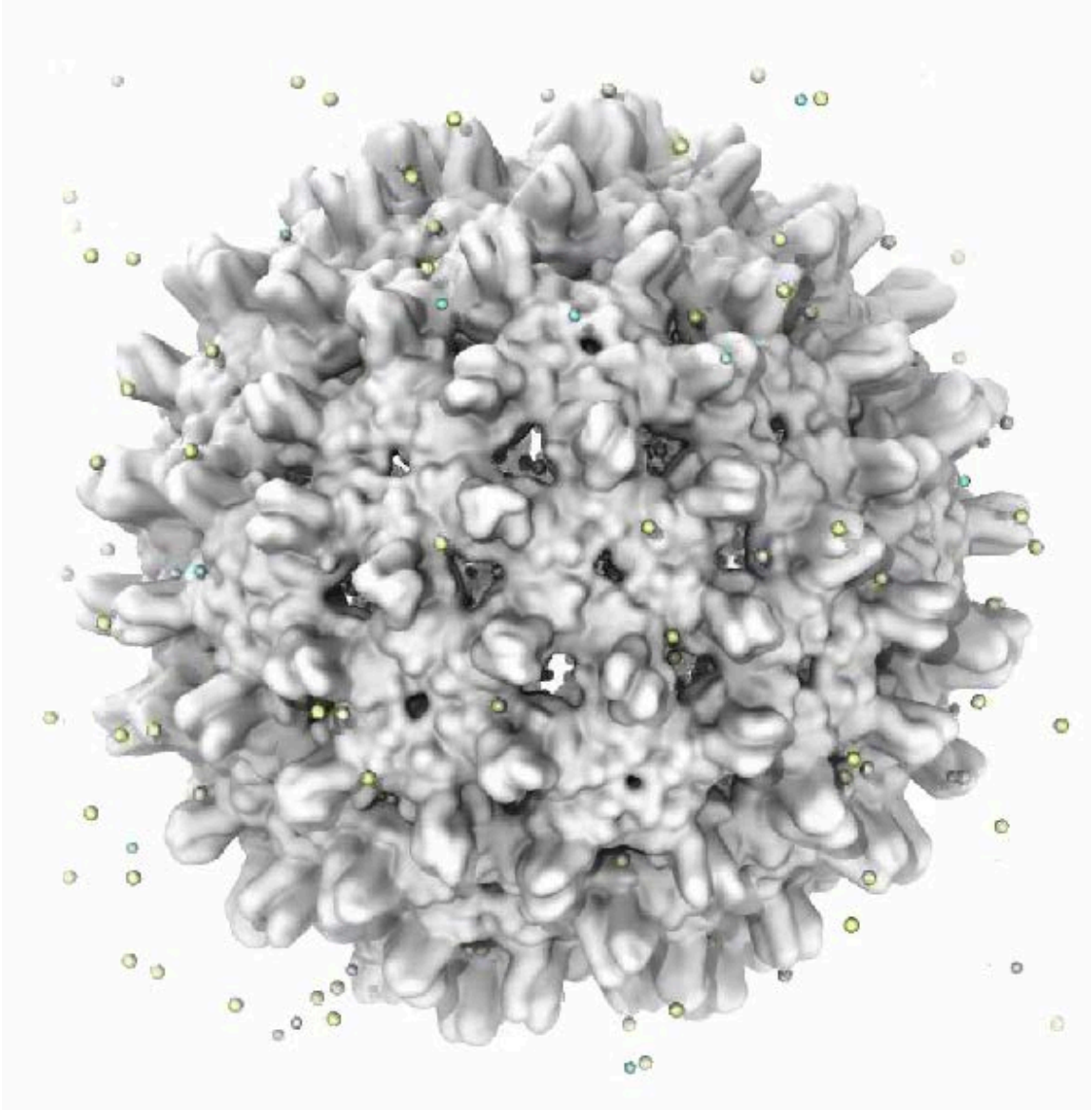
Mature (dsDNA)



Solvent and Ion Exchange

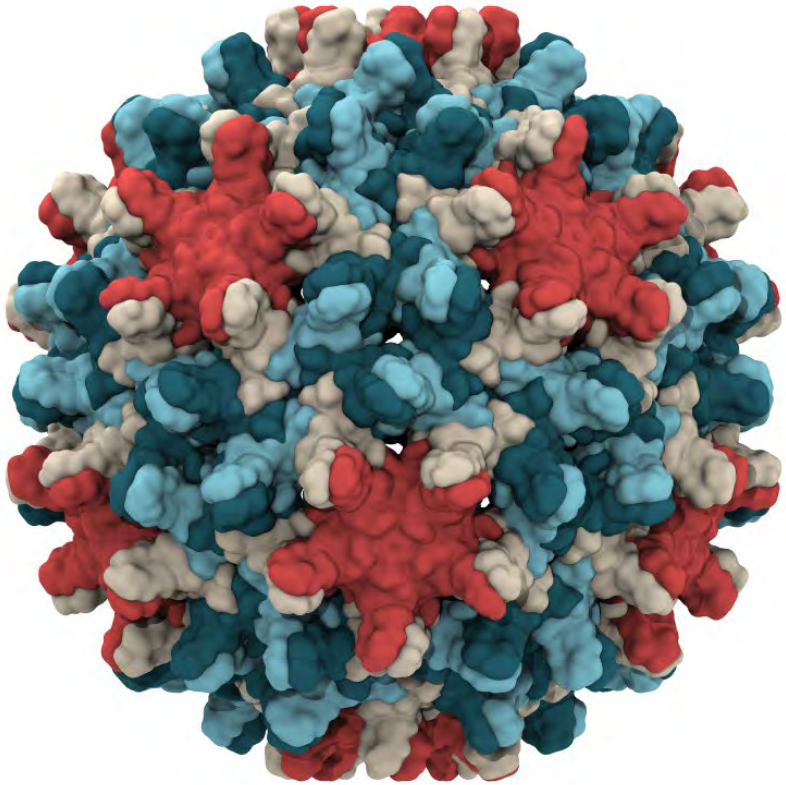
Exchange Rates (ns^{-1})

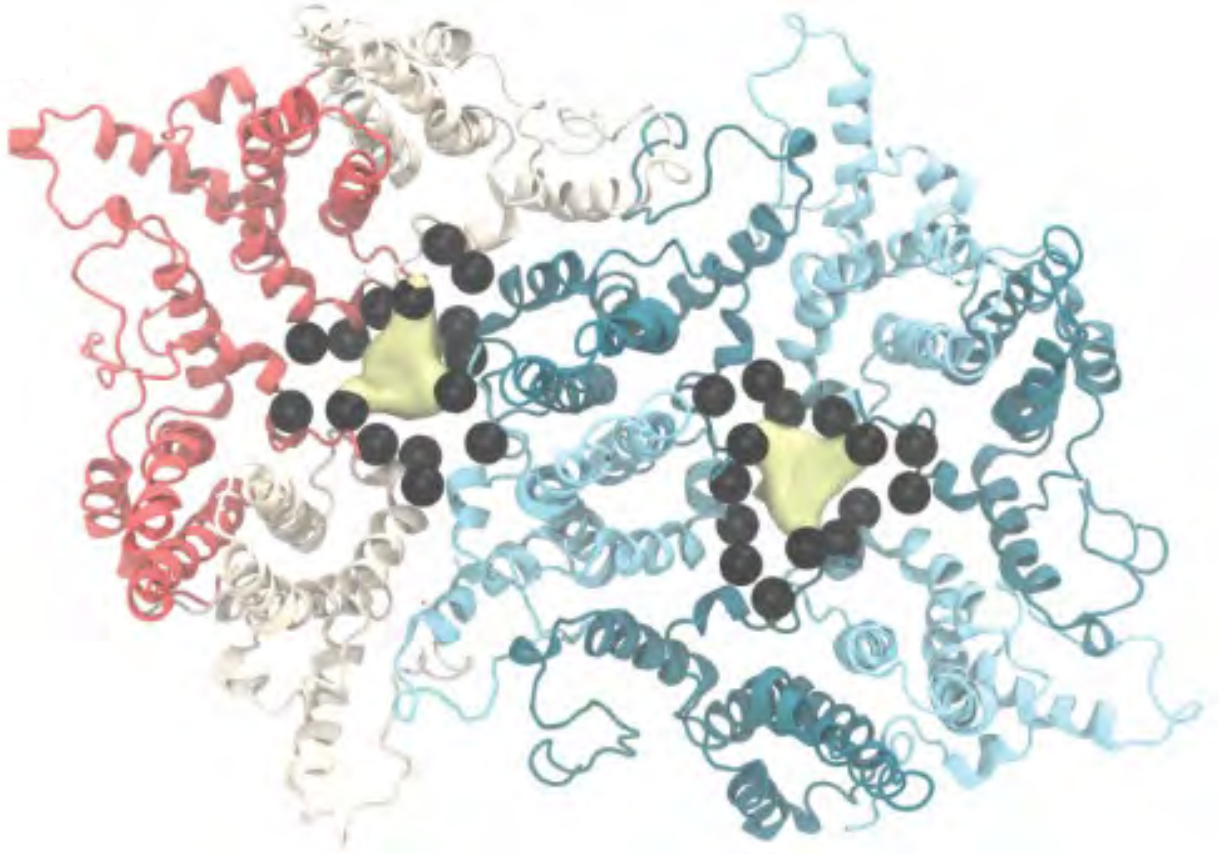
	Water	Sodium	Chloride
Inward	4700	8.4	1.8
Outward	4700	8.5	1.7



Hadden (2018)

Sodium translocate through triangular pores



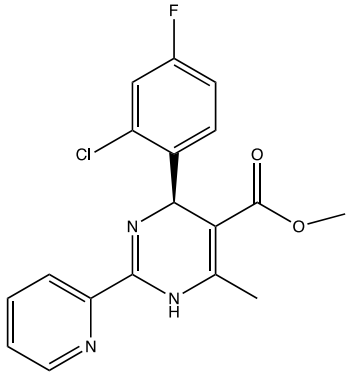


ΔG = -1.00 kcal/mol

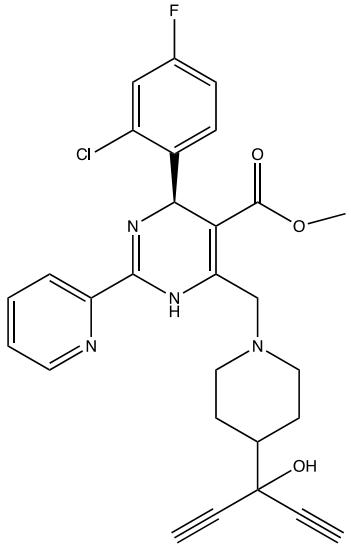
Hadden (2018)

Capsid-disrupting drugs

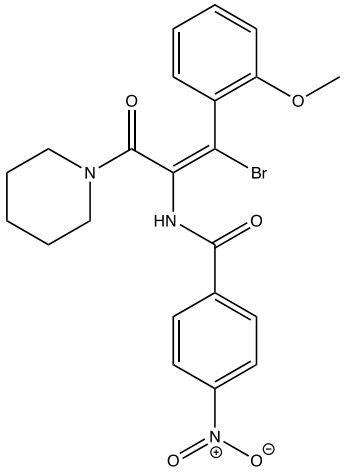
HAP1

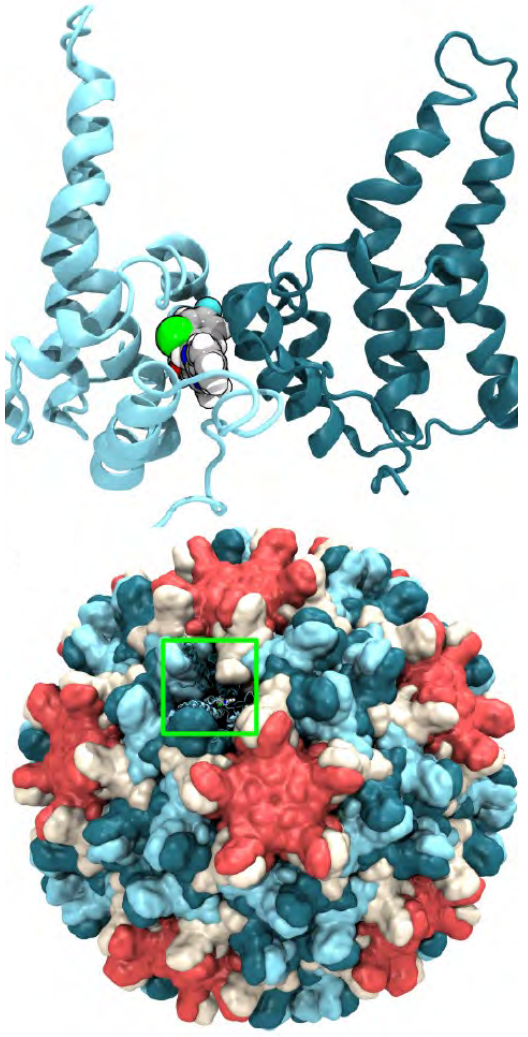


HAP18

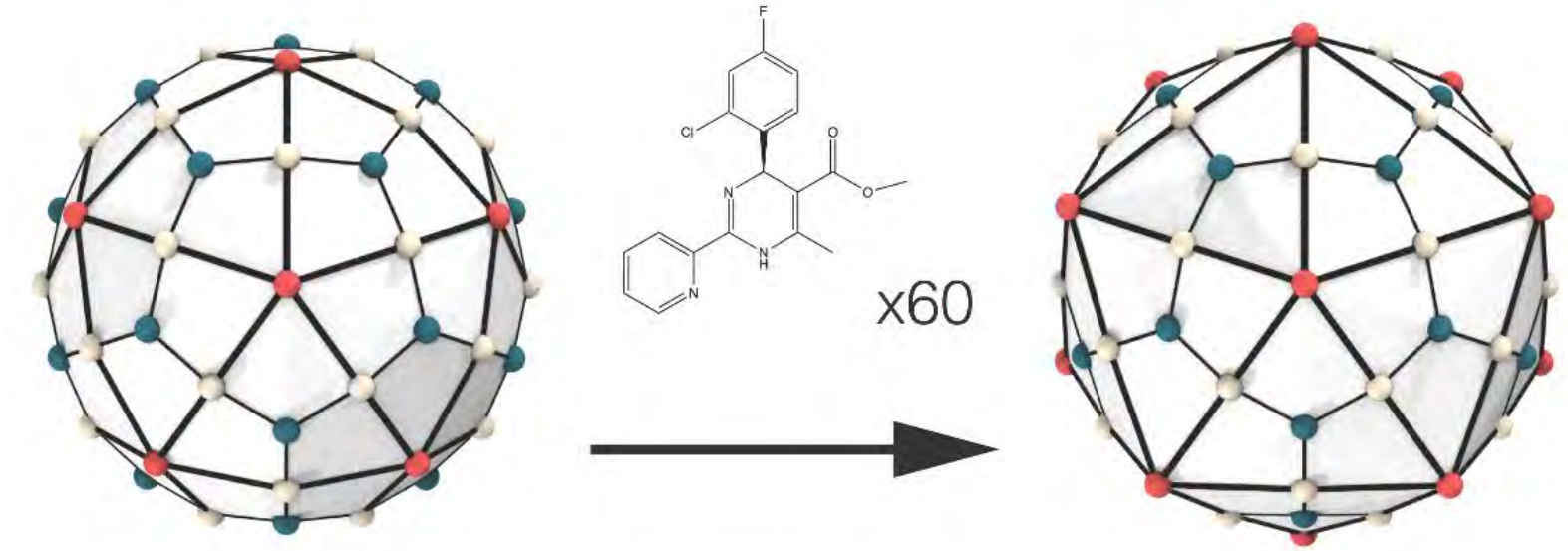


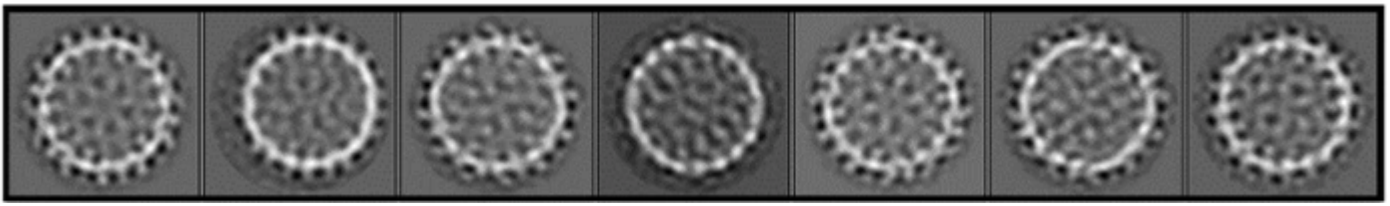
AT130

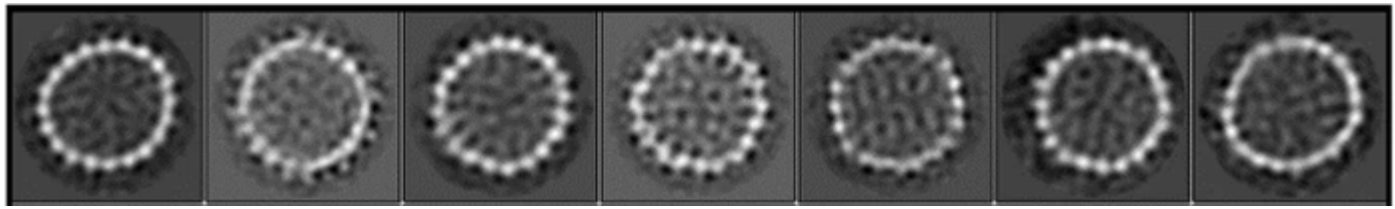




Capsid Morphology: Simulations vs. Experiments

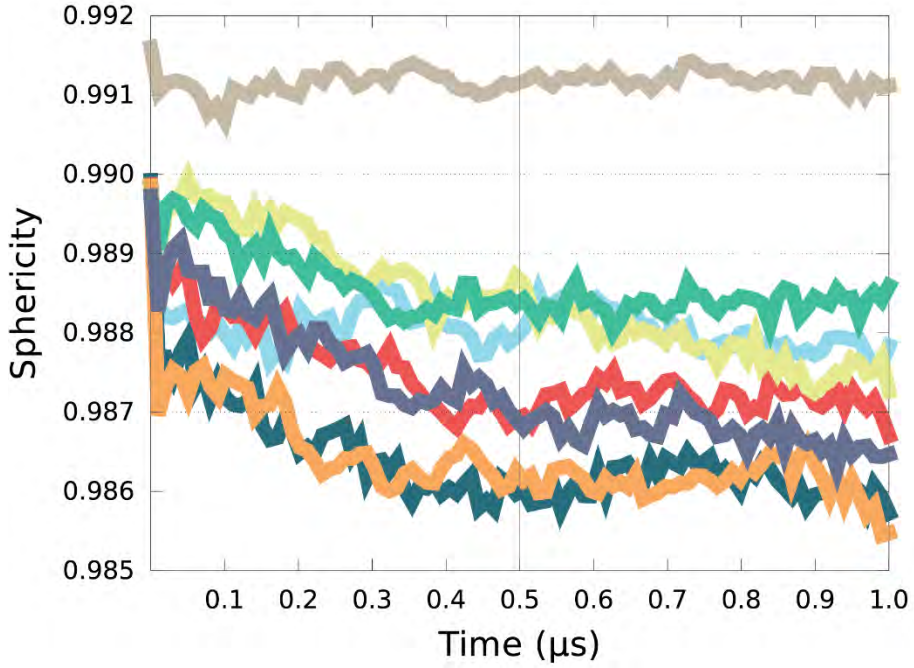


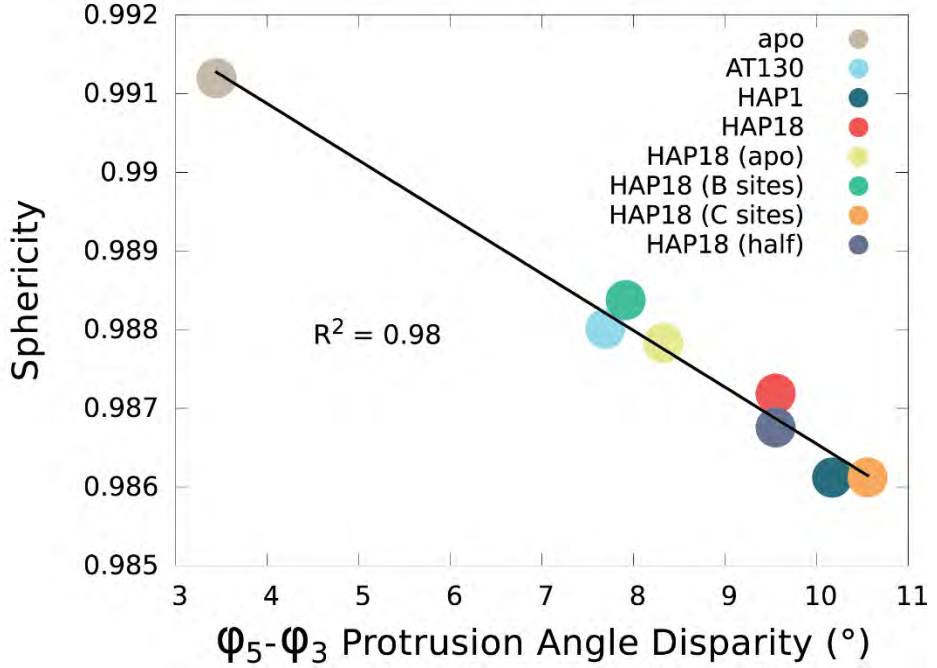


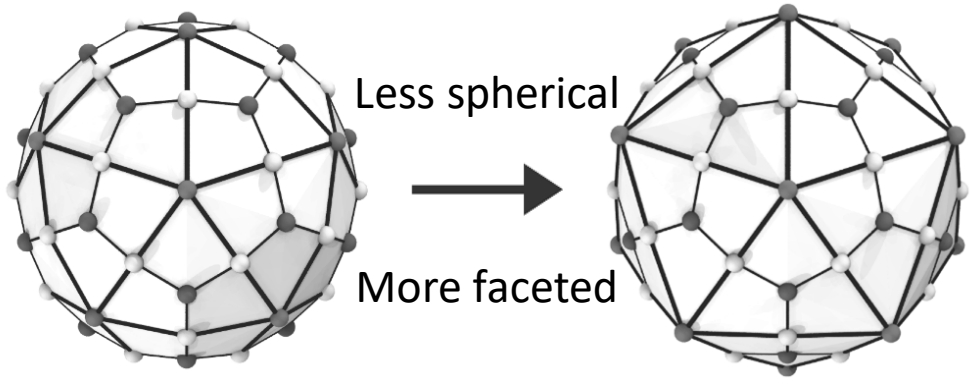


Perilla, Hadden (2016)
Schlicksup, Zlotnick (2018)

Drugs alter capsid morphology





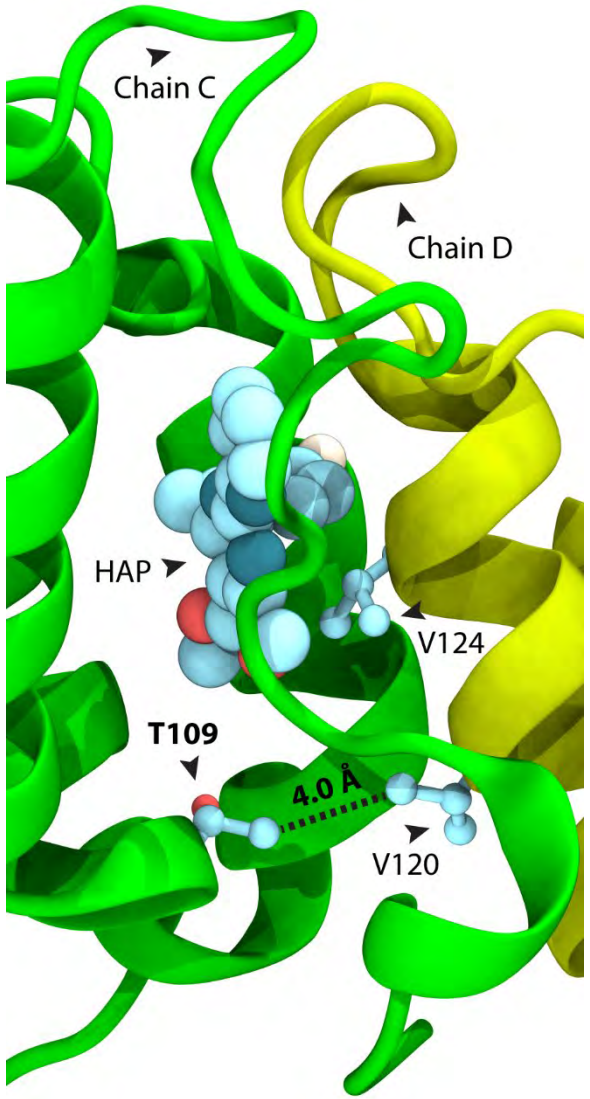


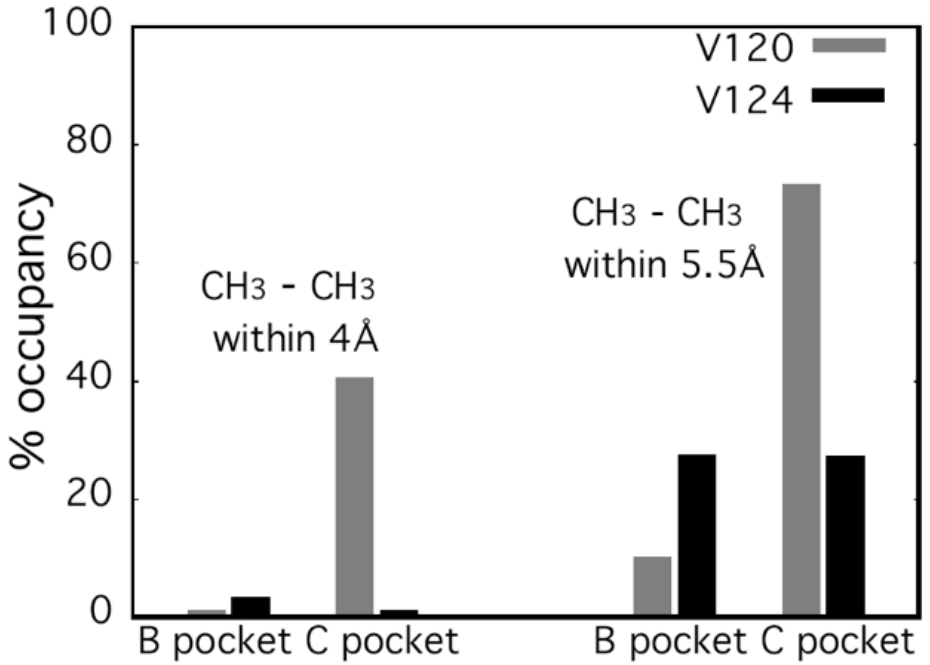
Simulations facilitate interpretation of experiments

- Mutation introduces larger hydrophobic sidechain
  - Enhances capsid assembly
  - Increases drug resistance

- But experimental structures do not explain these observations
  - Residue does not participate in subunit-subunit interaction
  - Residue is at the mouth of the drug binding pocket, not inside it

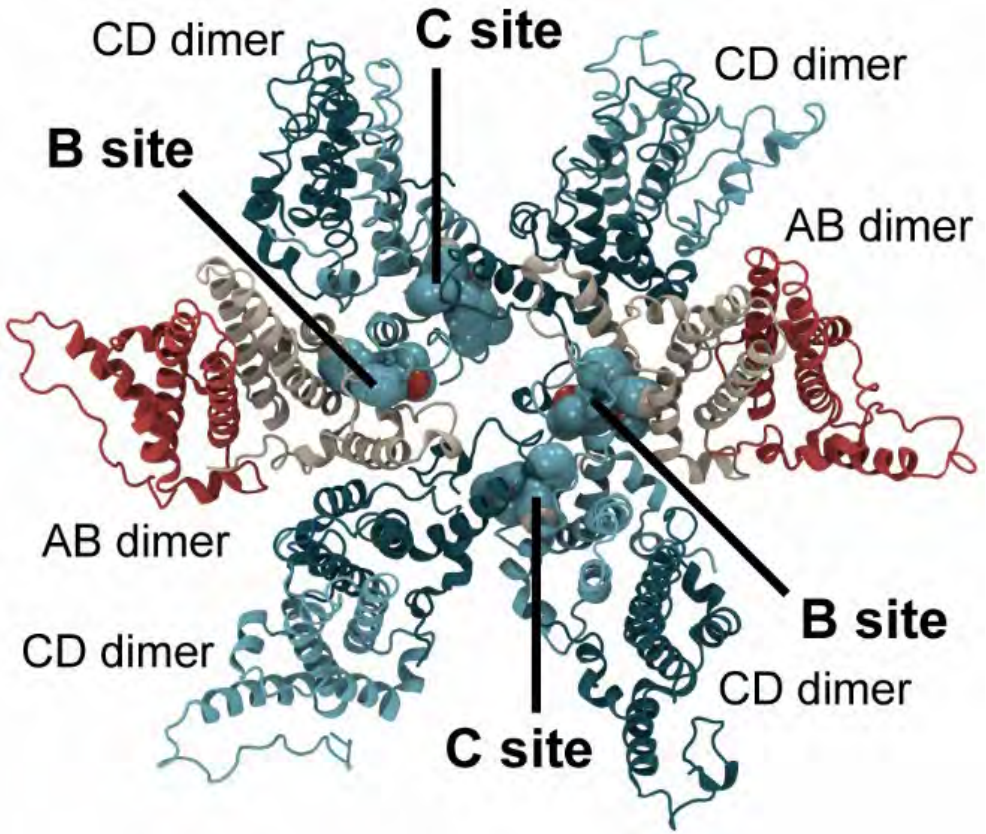
Simulations facilitate interpretation of experiments

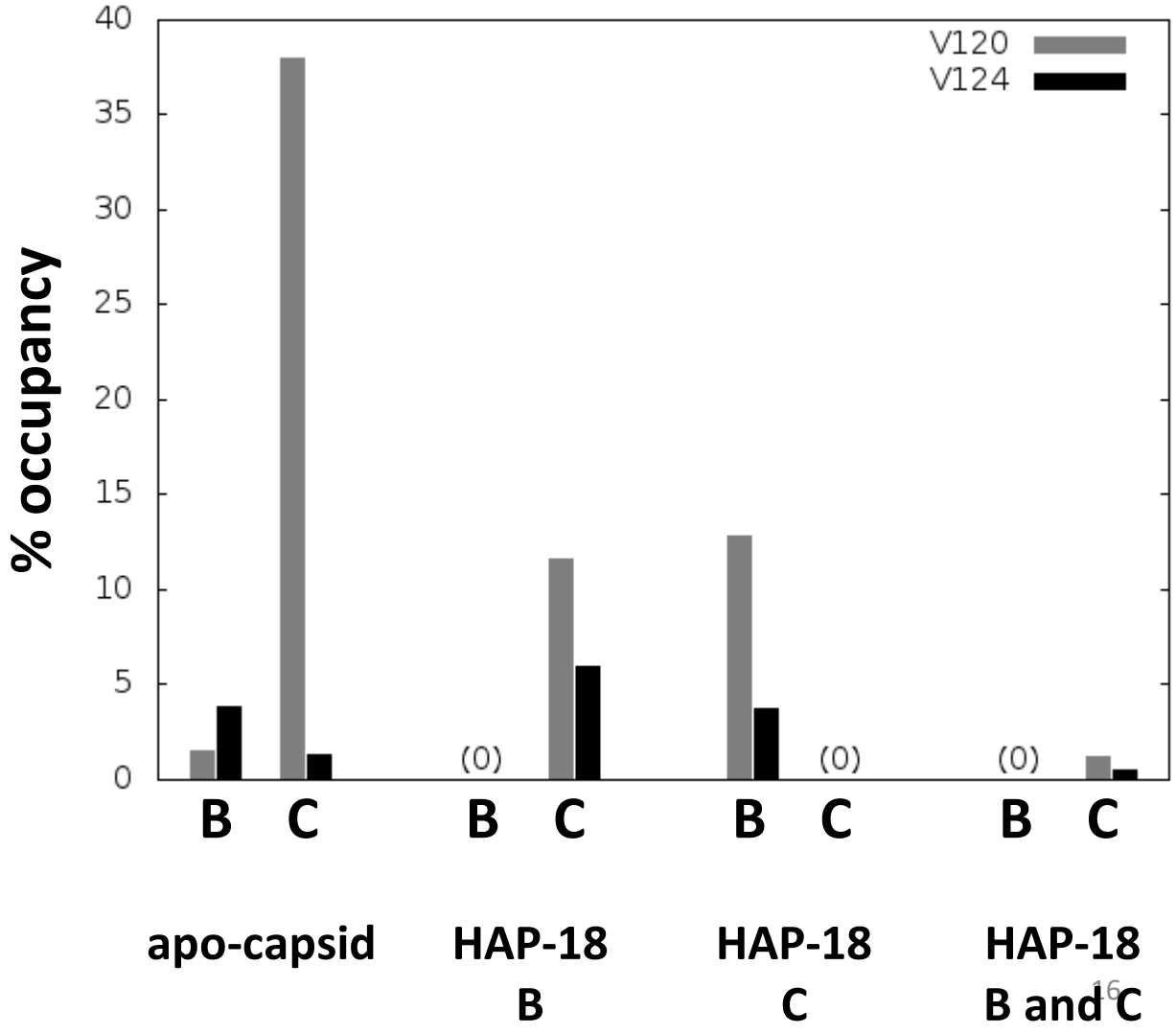




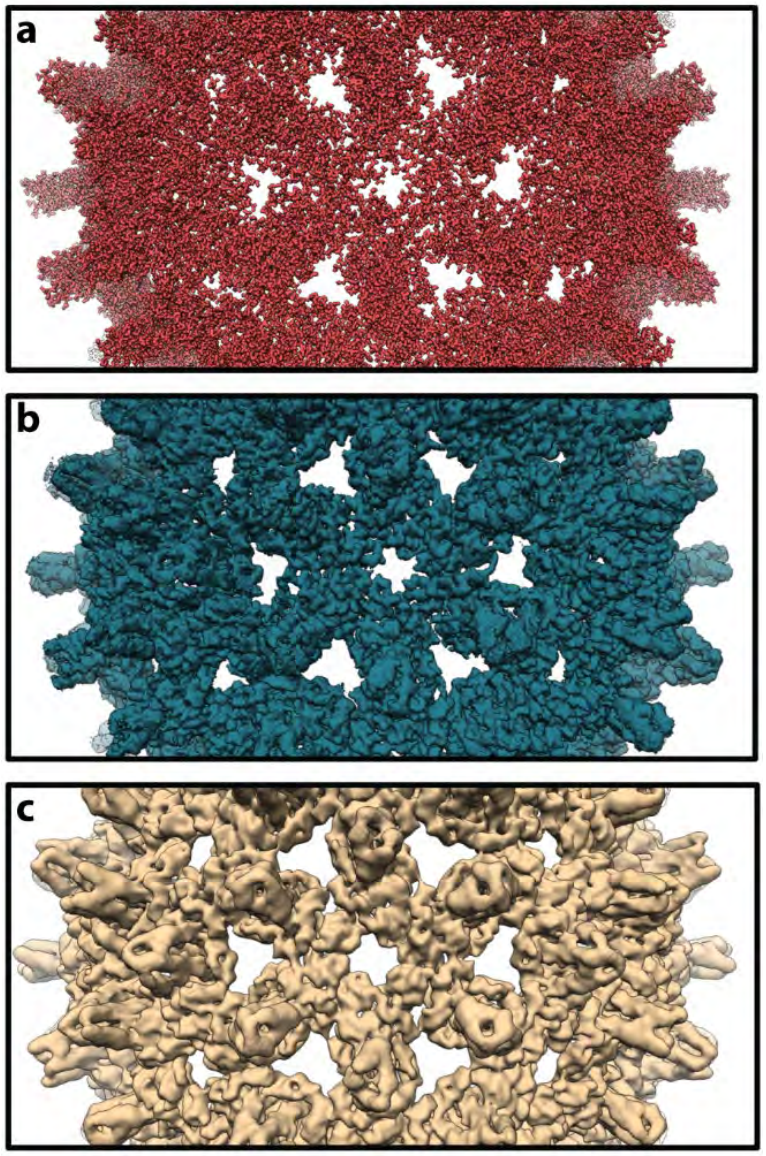
Ruan, Hadden, Zlotnick (2018)

Simulations reveal basis of drug-binding cooperativity





Capsid dynamics limit cryo-EM resolution



Hadden (2018)

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PI, Blue Waters Broadening Participation Allocation 2018
PI, Blue Waters GLCPC Allocation 2019