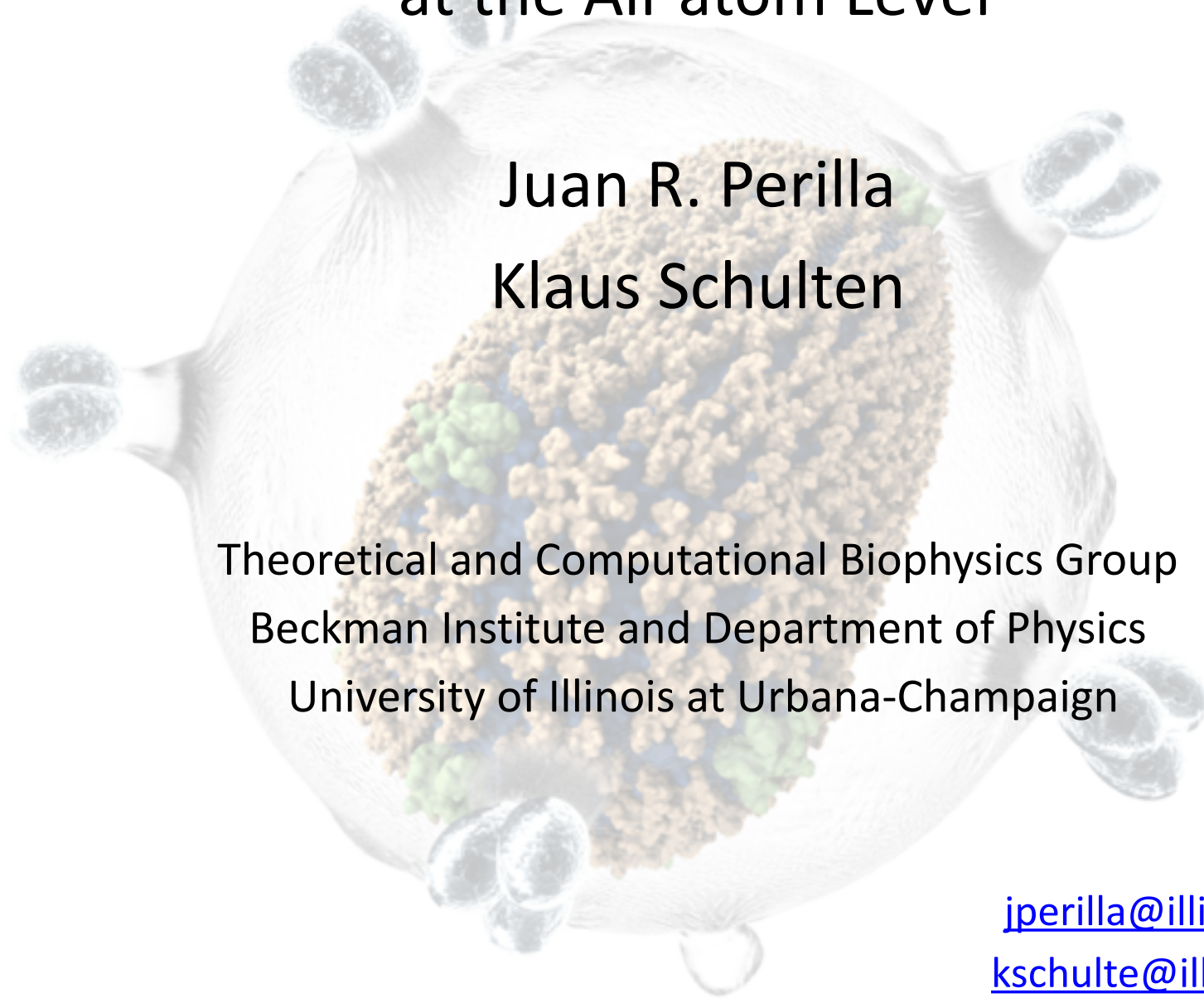


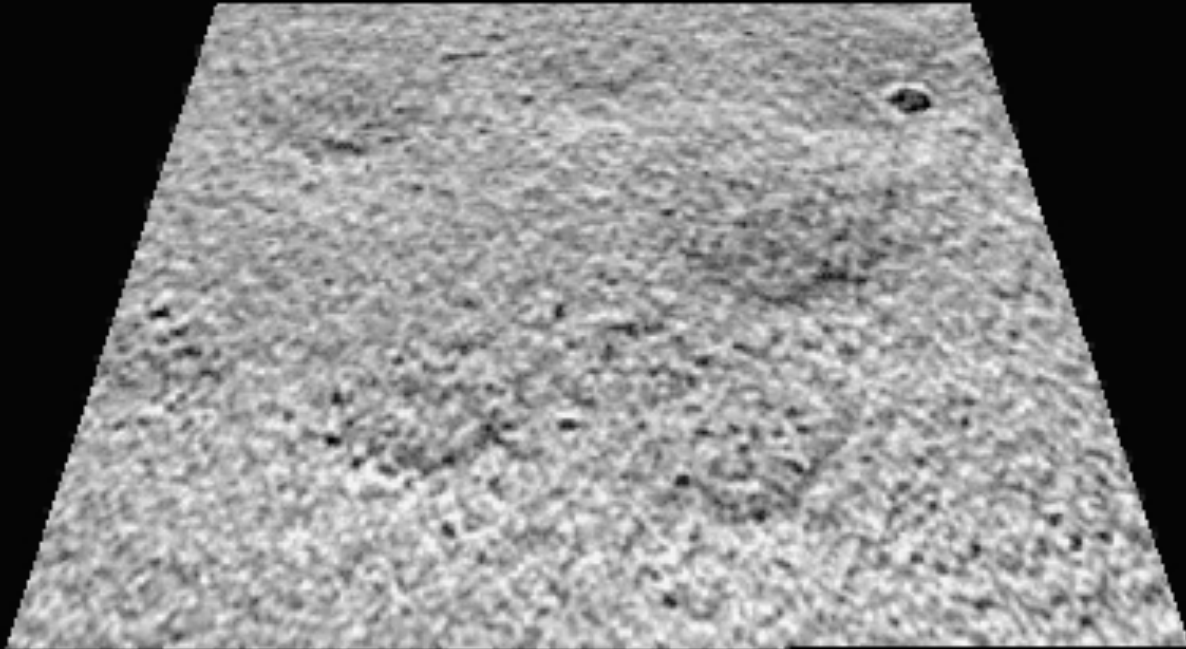
Structure, Dynamics, and Function of the HIV Capsid at the All-atom Level

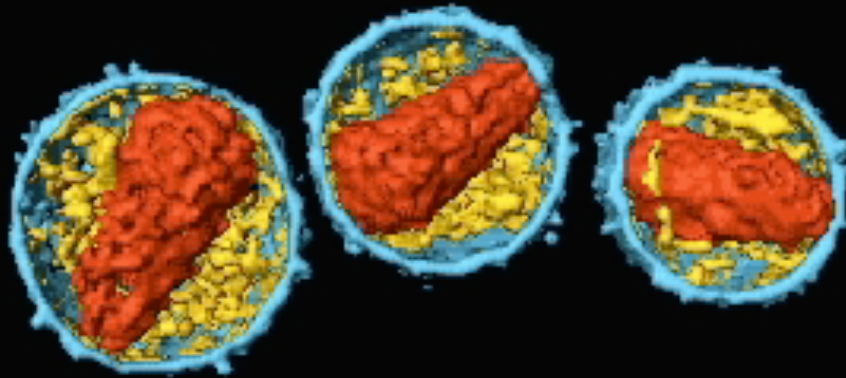
Juan R. Perilla
Klaus Schulten

Theoretical and Computational Biophysics Group
Beckman Institute and Department of Physics
University of Illinois at Urbana-Champaign

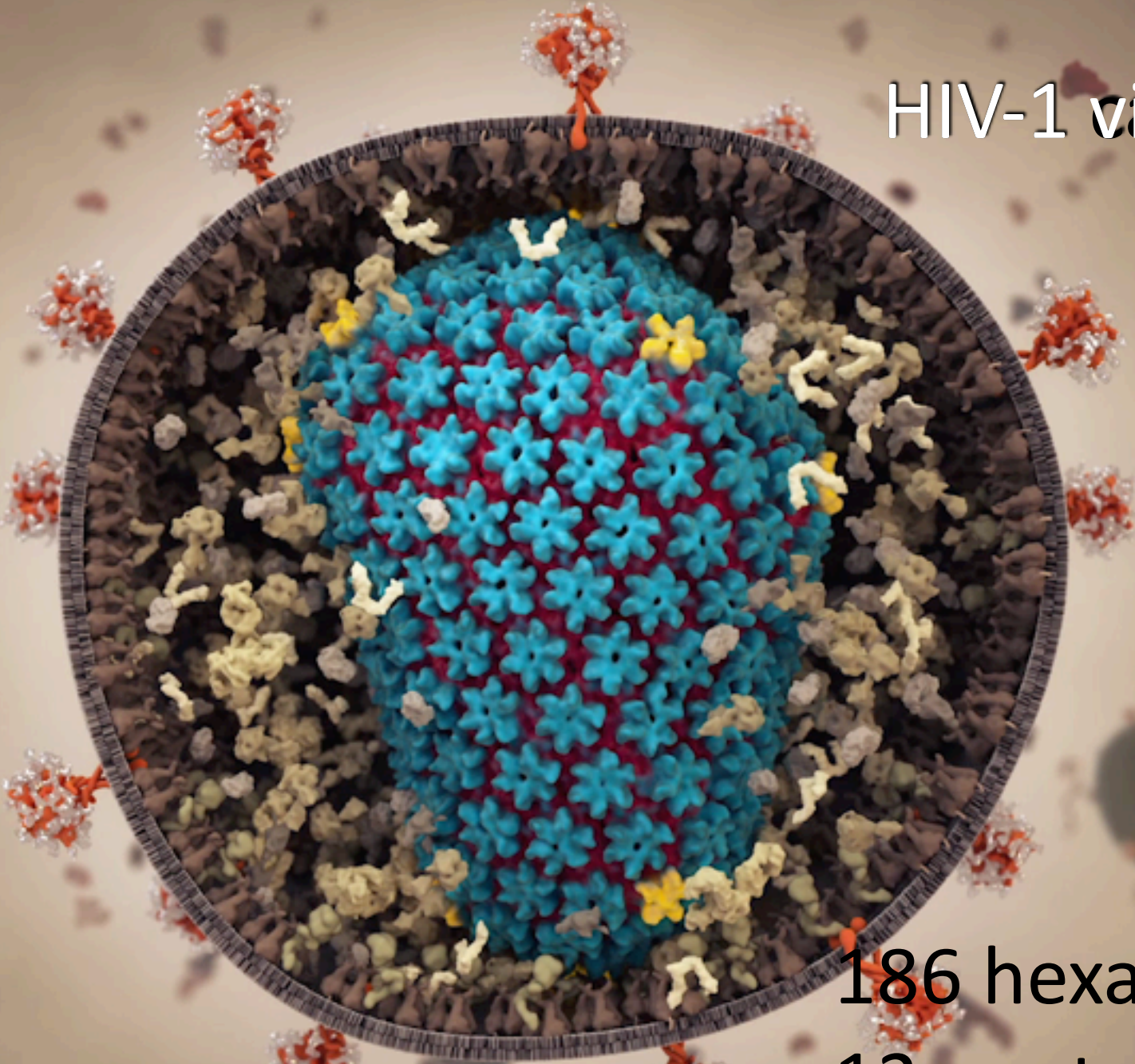
jperilla@illinois.edu
kschulte@illinois.edu





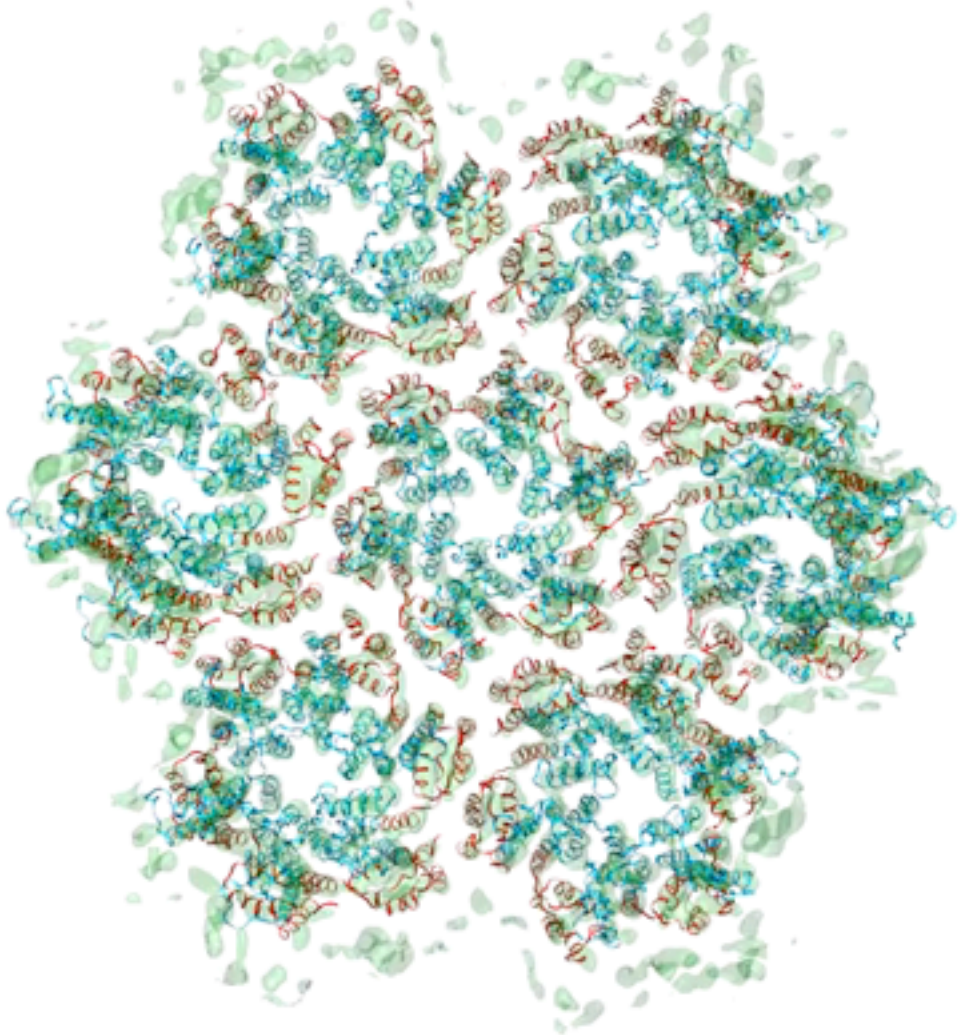
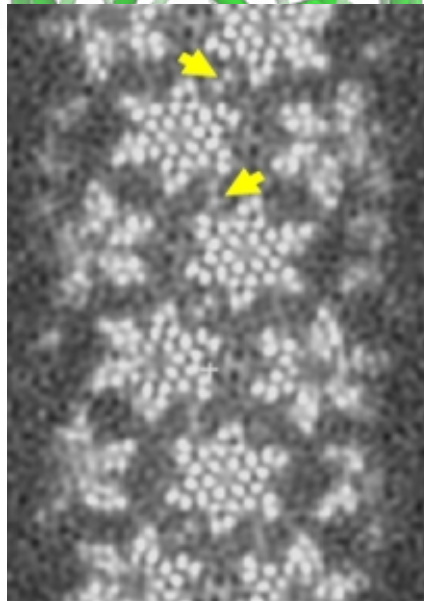
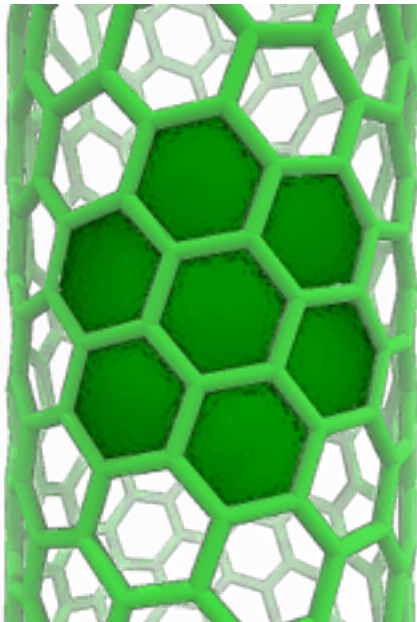


HIV-1 virion

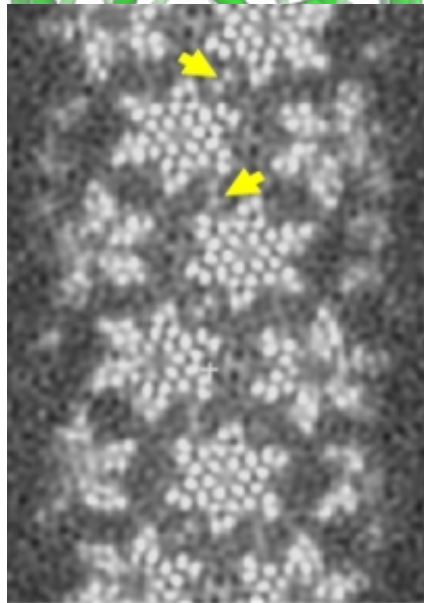
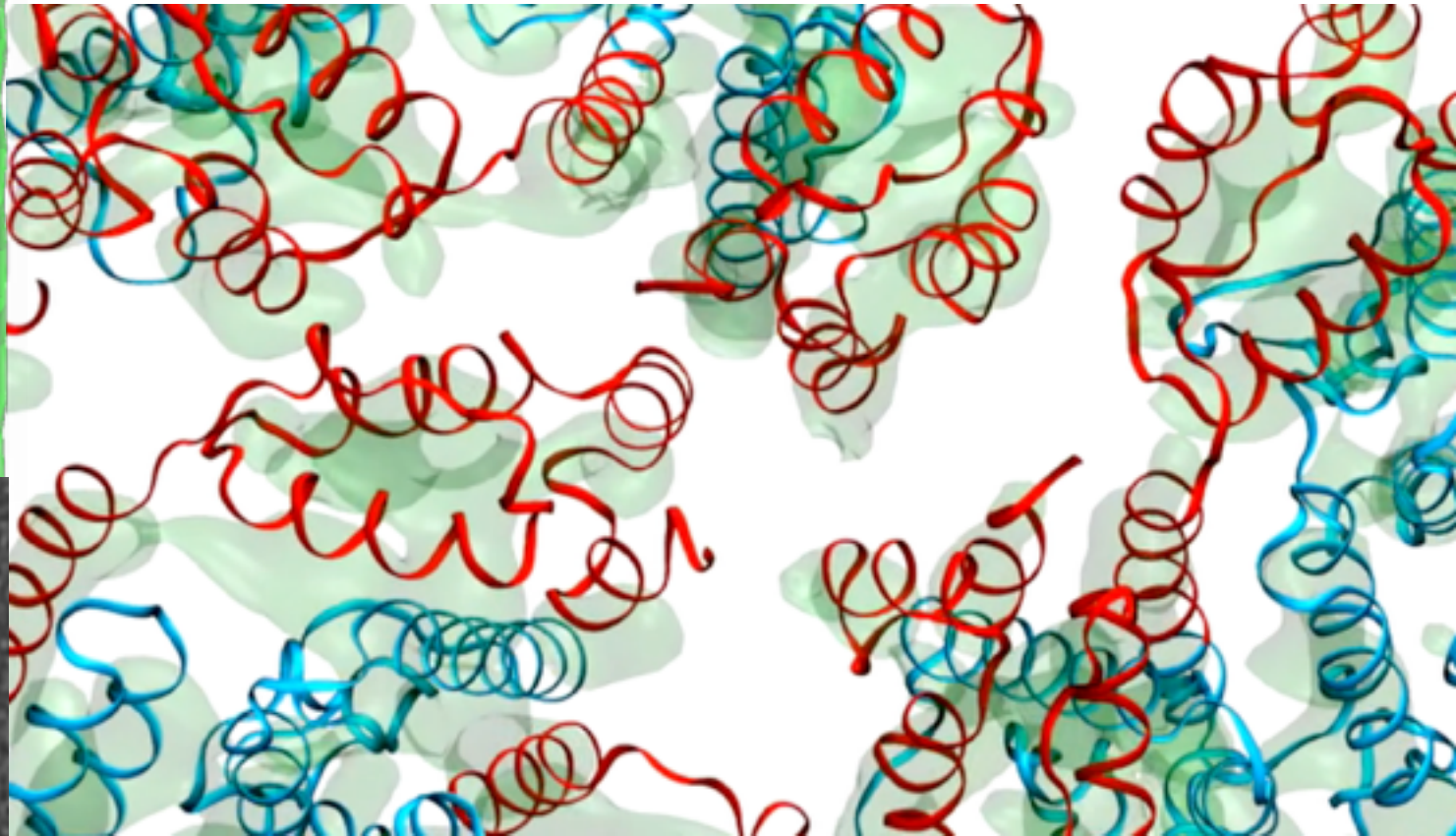
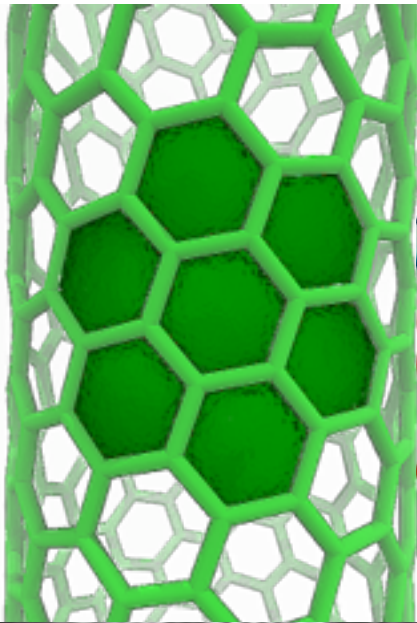


186 hexamers
12 pentamers

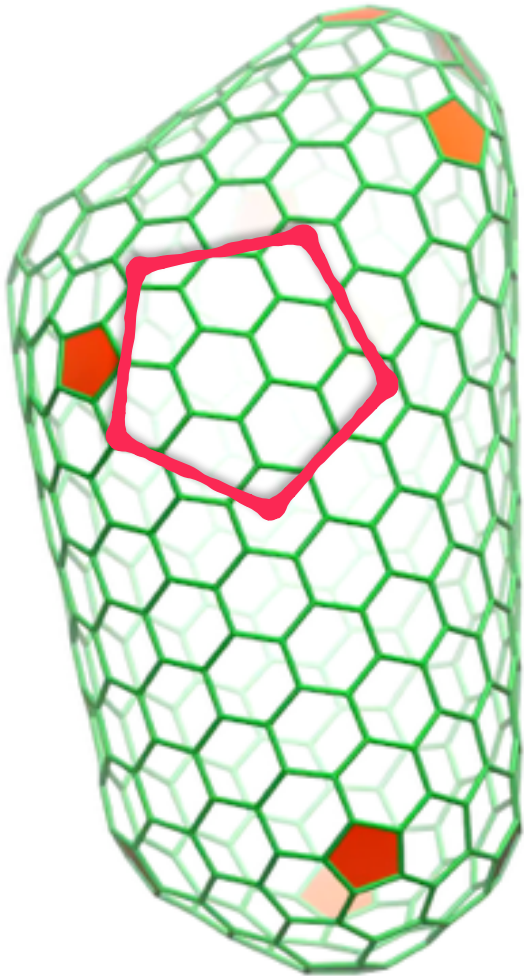
Modeling of the Hexameric Lattice using MDFF



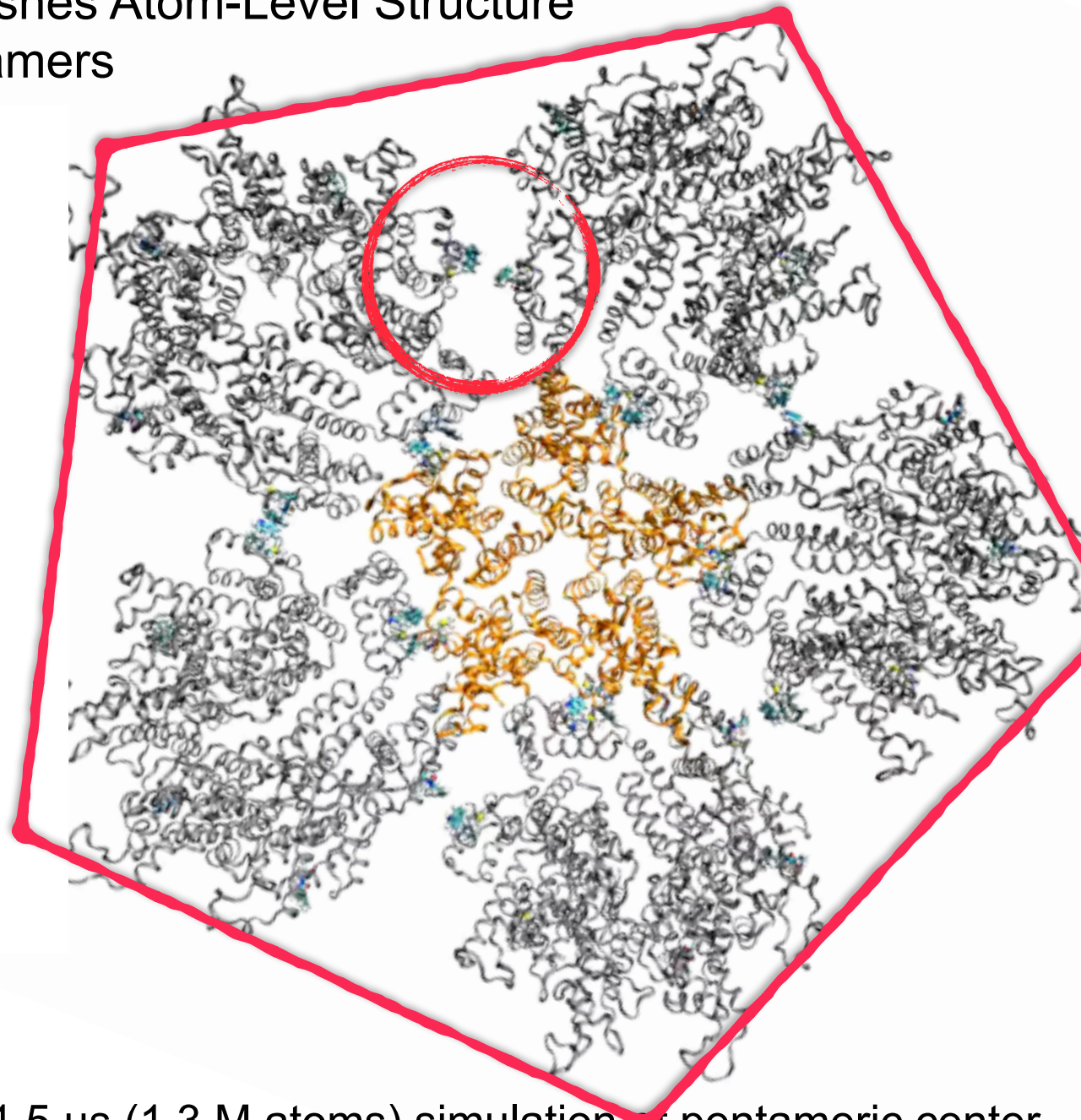
Modeling of the Hexameric Lattice using MDFF



MD Simulation Furnishes Atom-Level Structure of Pentamer-of-Hexamers

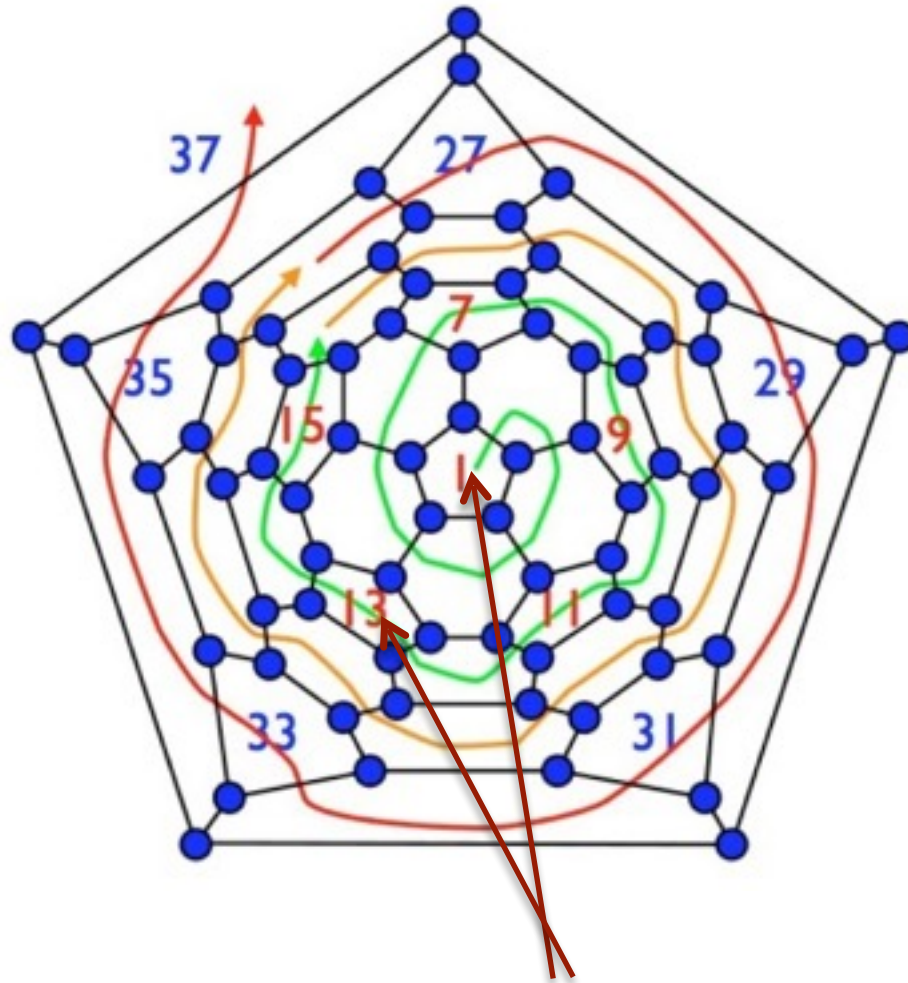


Closed capsid is made of
hexamers-of-hexamers
pentamers-of-hexamers



1.5 μ s (1.3 M atoms) simulation of pentameric center

Isomer search and geometry optimization



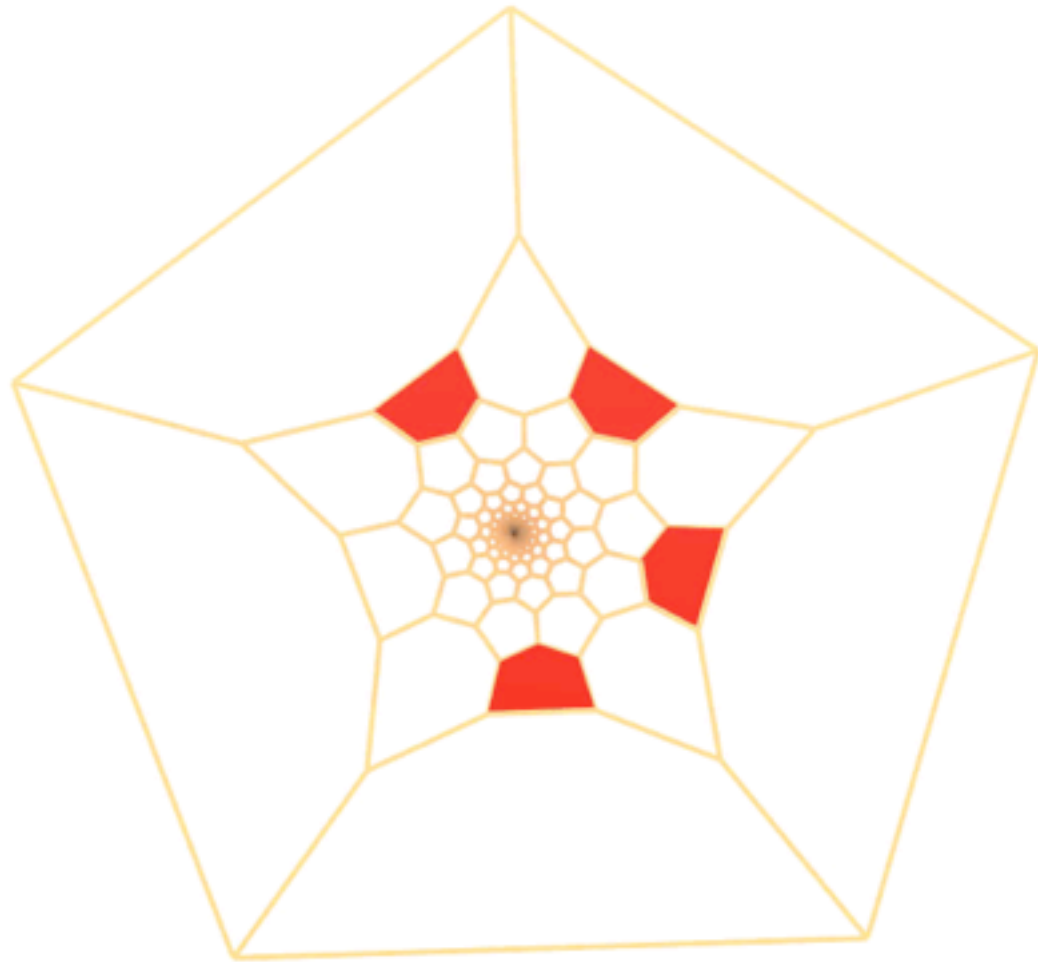
Ring Spiral Pentagon Indices dictate location of pentamers

Fowler-Manolopoulos spiral algorithm

Nature **355**, 428-430 (1992)

RSPI: 1, 7, 14, 51, 55, 79, 116, 145, 176, 180, 191, and 195

Isomer search and geometry optimization



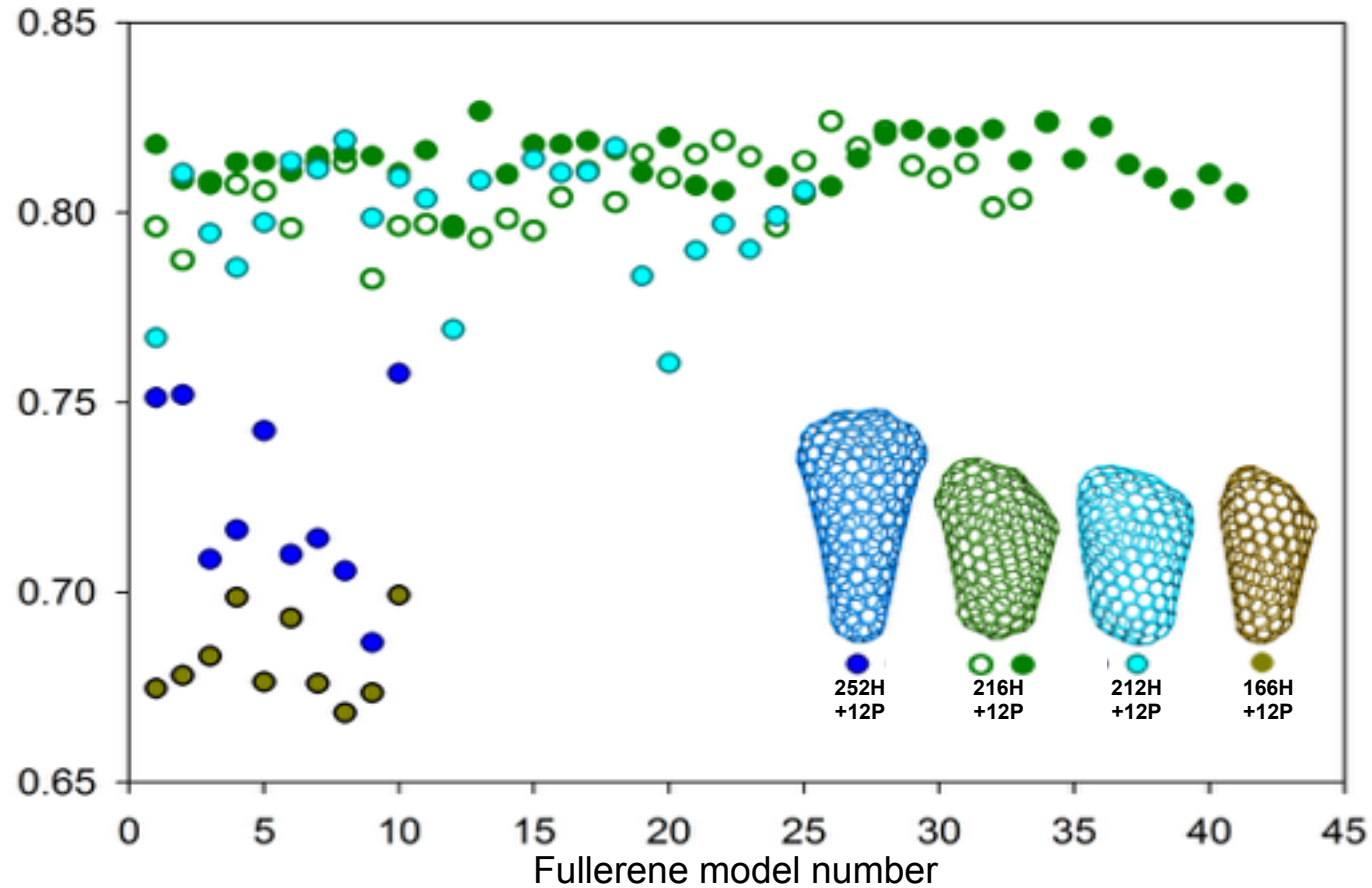
Ring Spiral Pentagon indices dictate location of pentamers

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Isomer search and geometry optimization



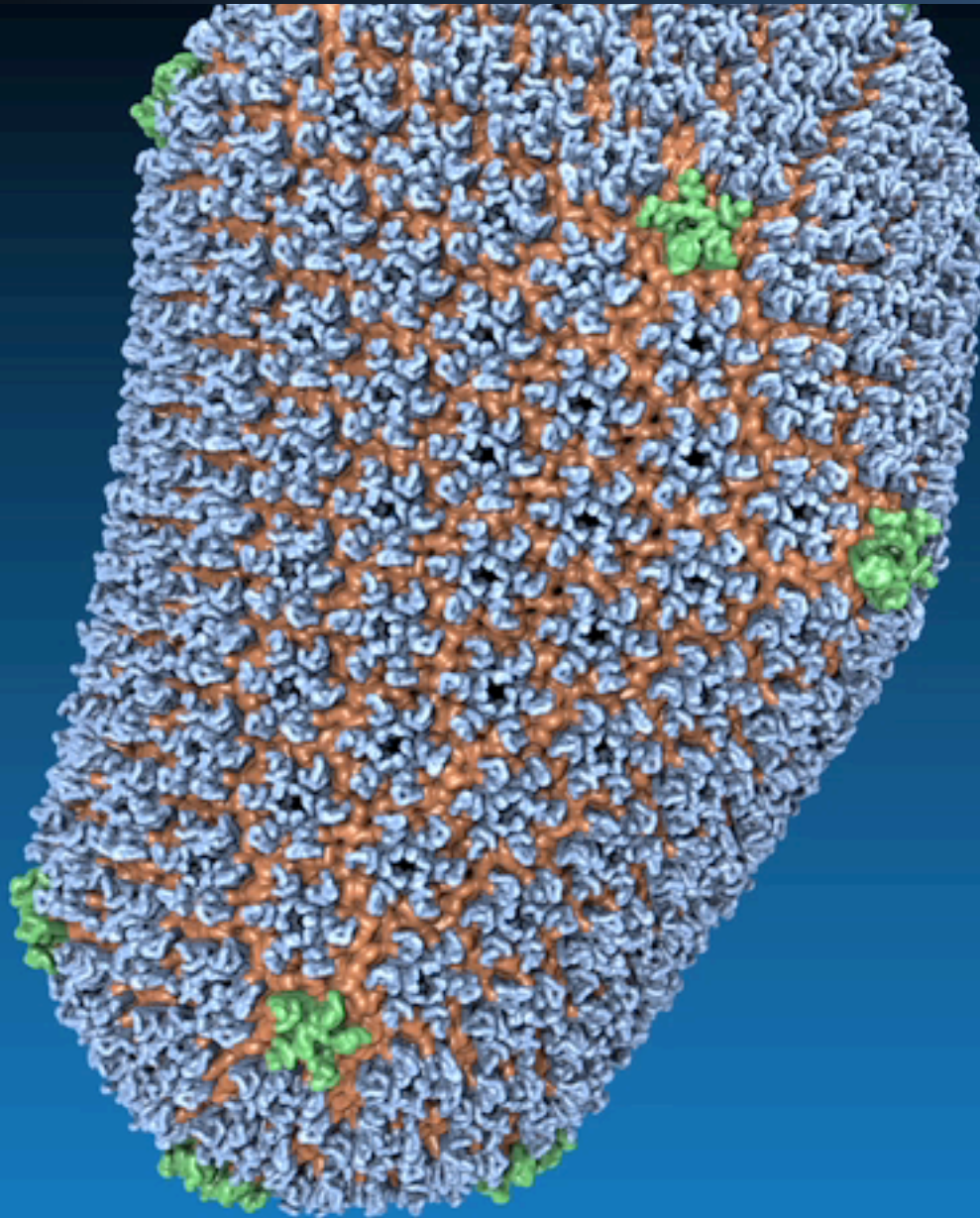
Ring Spiral Pentagon Indices dictate location of pentamers

Fowler-Manolopoulos spiral algorithm

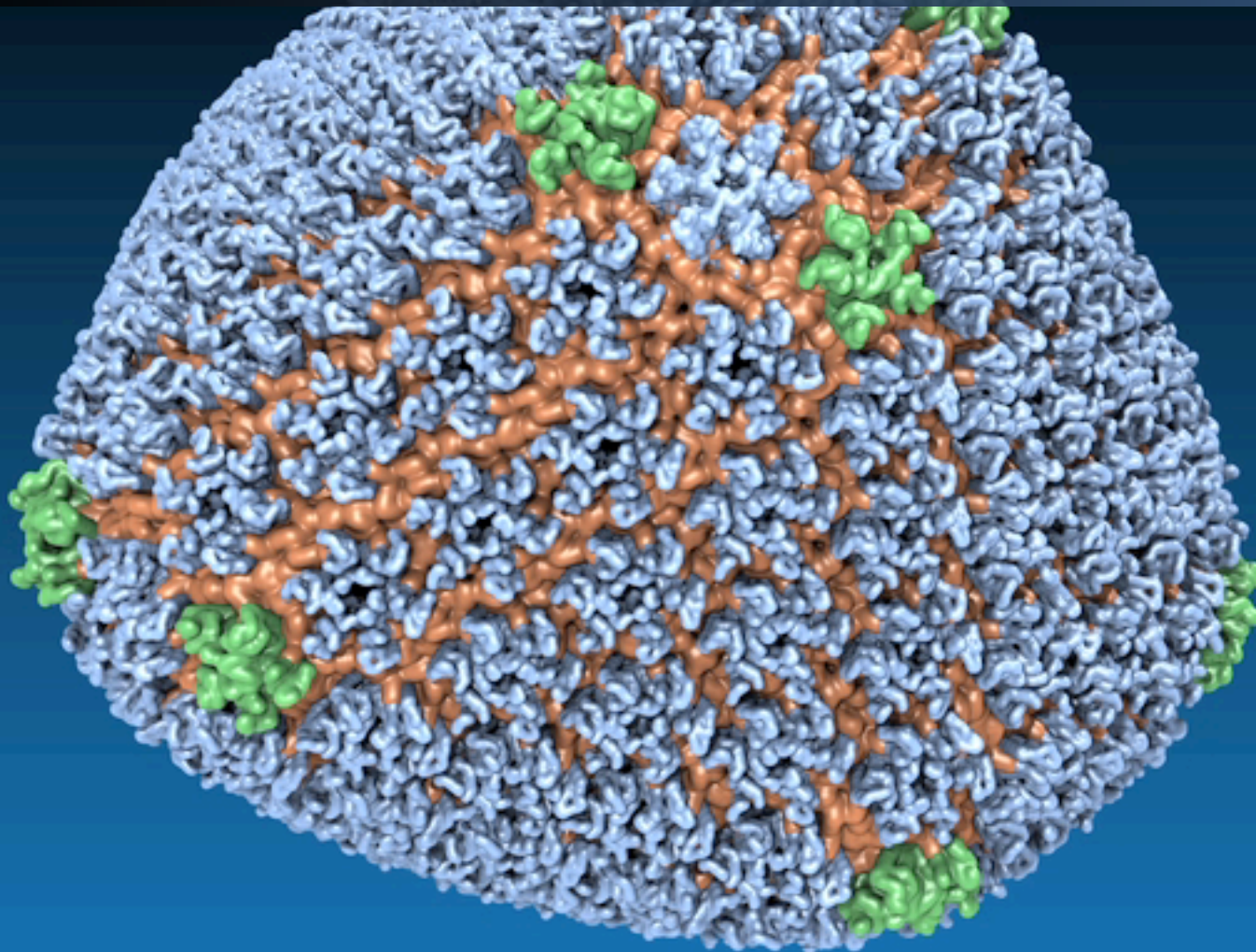
Nature **355**, 428-430 (1992)

RSPI: 1, 7, 14, 51, 55, 79, 116, 145, 176, 180, 191, and 195

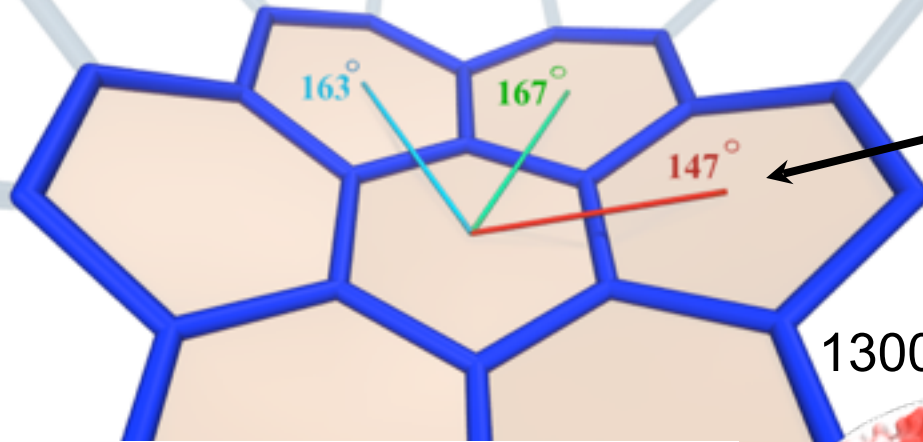
HIV capsid contains 186 atoms, 1300+ proteins



Complete simulation includes 64 million atoms
NSF Blue Waters, NCSA and DOE Titan, ORNL

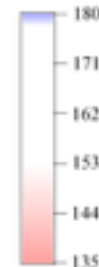
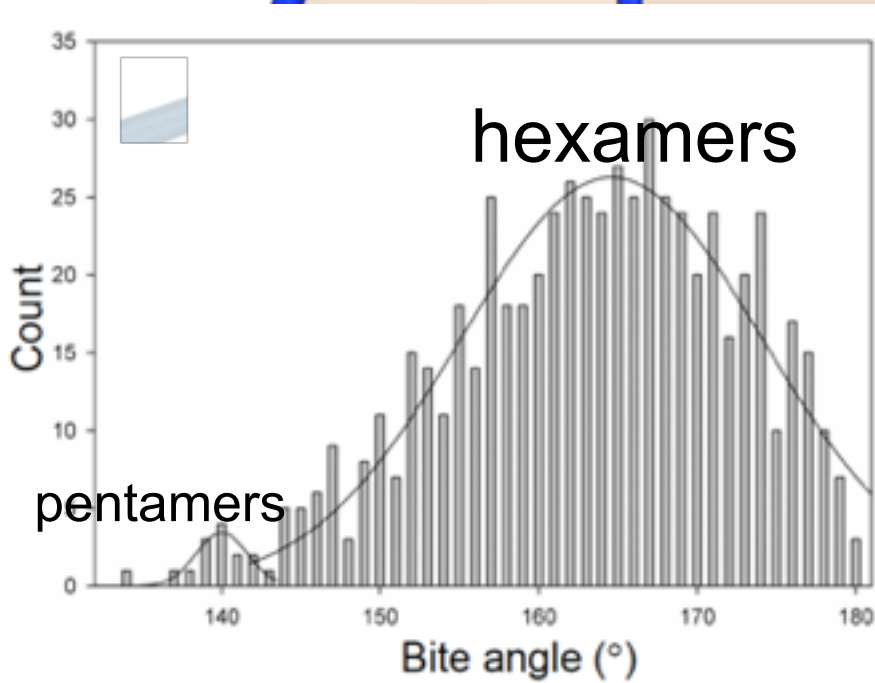
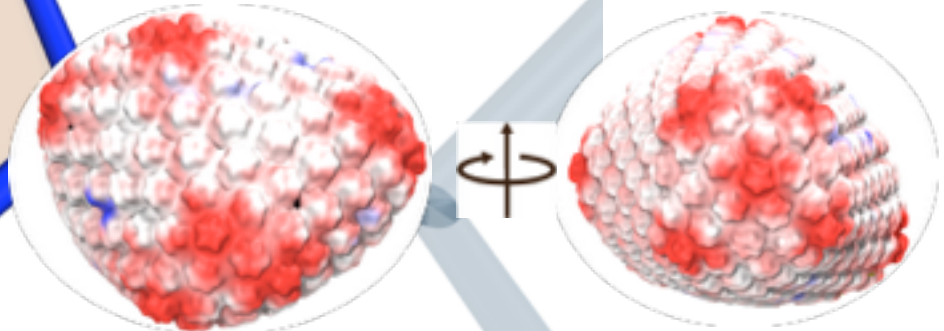


Malleability of HIV-1 CA



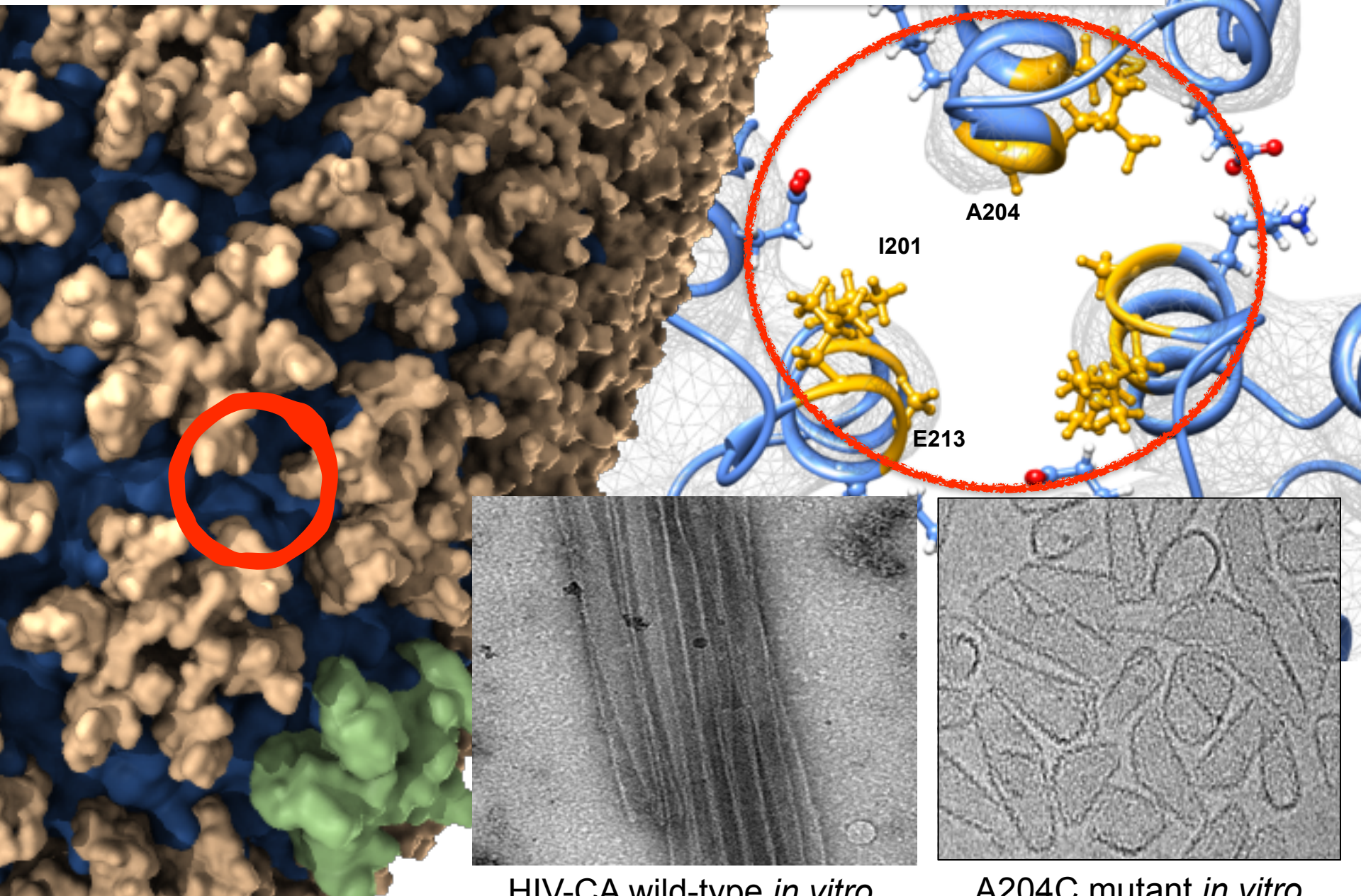
Hexamer of hexamers bite angles along chiral axis

1300 proteins in different conformations



Native capsid bite angle distribution

Curvature is regulated by the trimer interface



Nature **497**, 643-646 (2013)

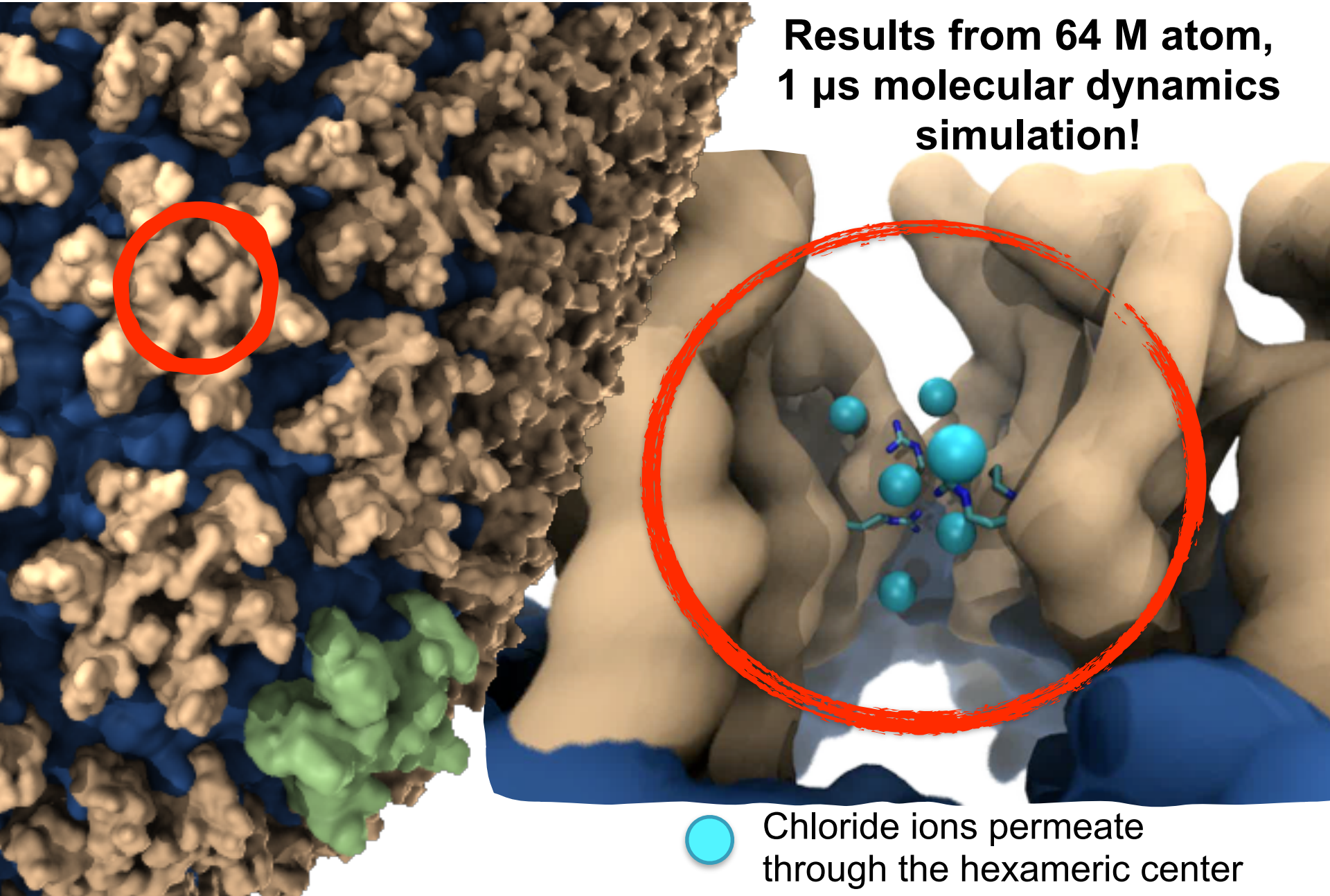
HIV-CA wild-type *in vitro*

A204C mutant *in vitro*

Peijun Zhang - U. Pittsburgh

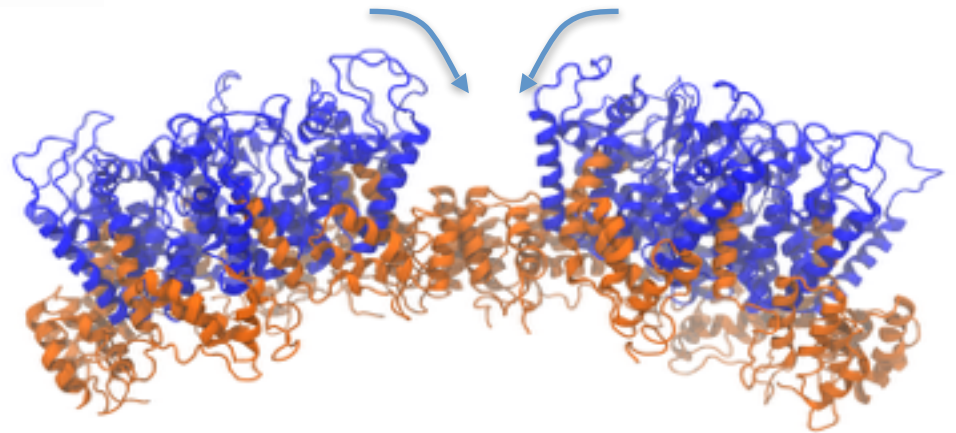
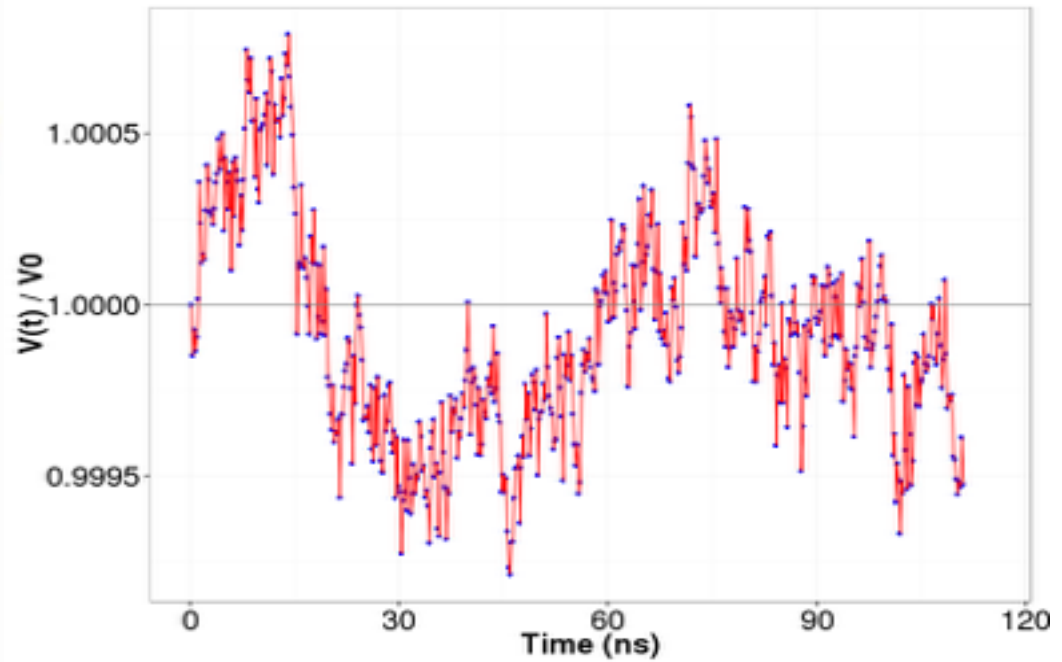
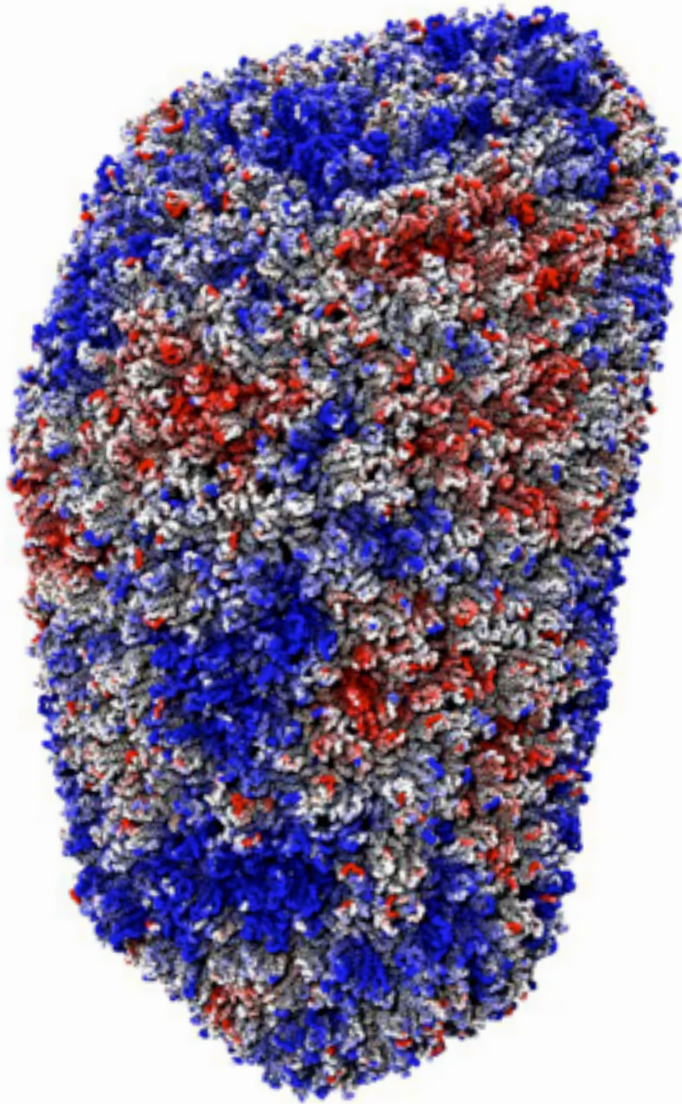
Capsid acts as an osmotic regulator

Results from 64 M atom,
1 μ s molecular dynamics
simulation!



Chloride ions permeate
through the hexameric center

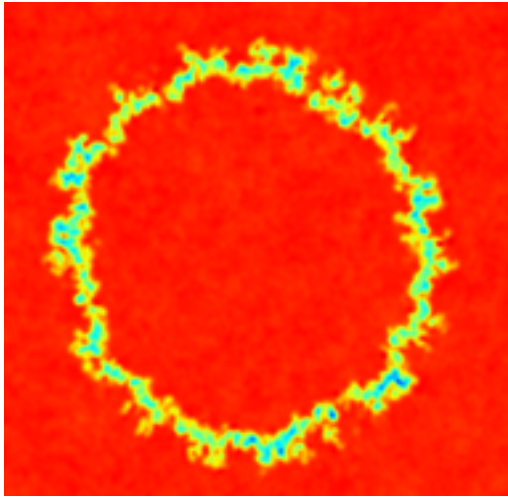
HIV Capsid is highly cooperative



Global motion
Mean (white), inwards (blue),
outwards (red)

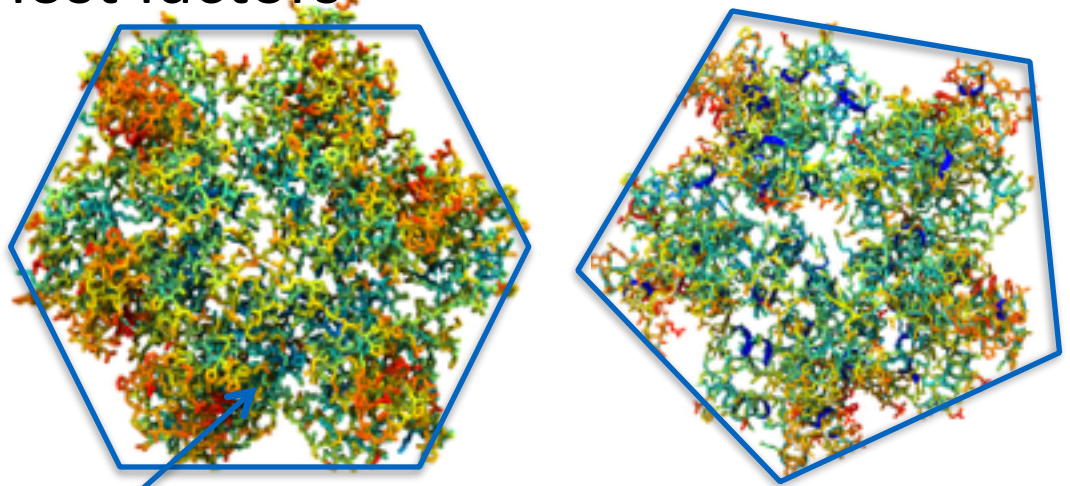
Key motion involved in PCA
mode

Electrostatic potential suggest favorable binding sites for host factors



Electrostatic potential inside and outside, $\Delta\phi = 0$ V.
Averaged over 240ns of molecular dynamics simulation.

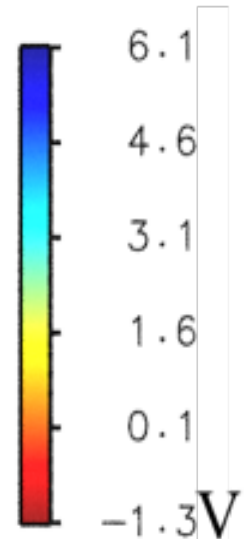
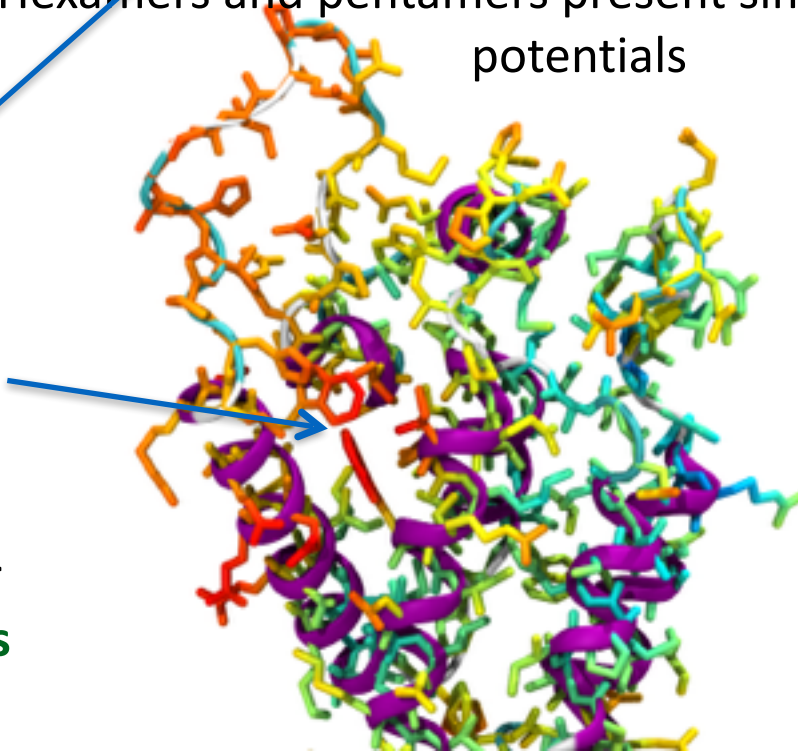
host factors



Hexamers and pentamers present similar electrostatic potentials

The potential differential between the **interior** of the hexamers/pentamers and the **CypA binding site** is $\Delta\phi = 7$ V.

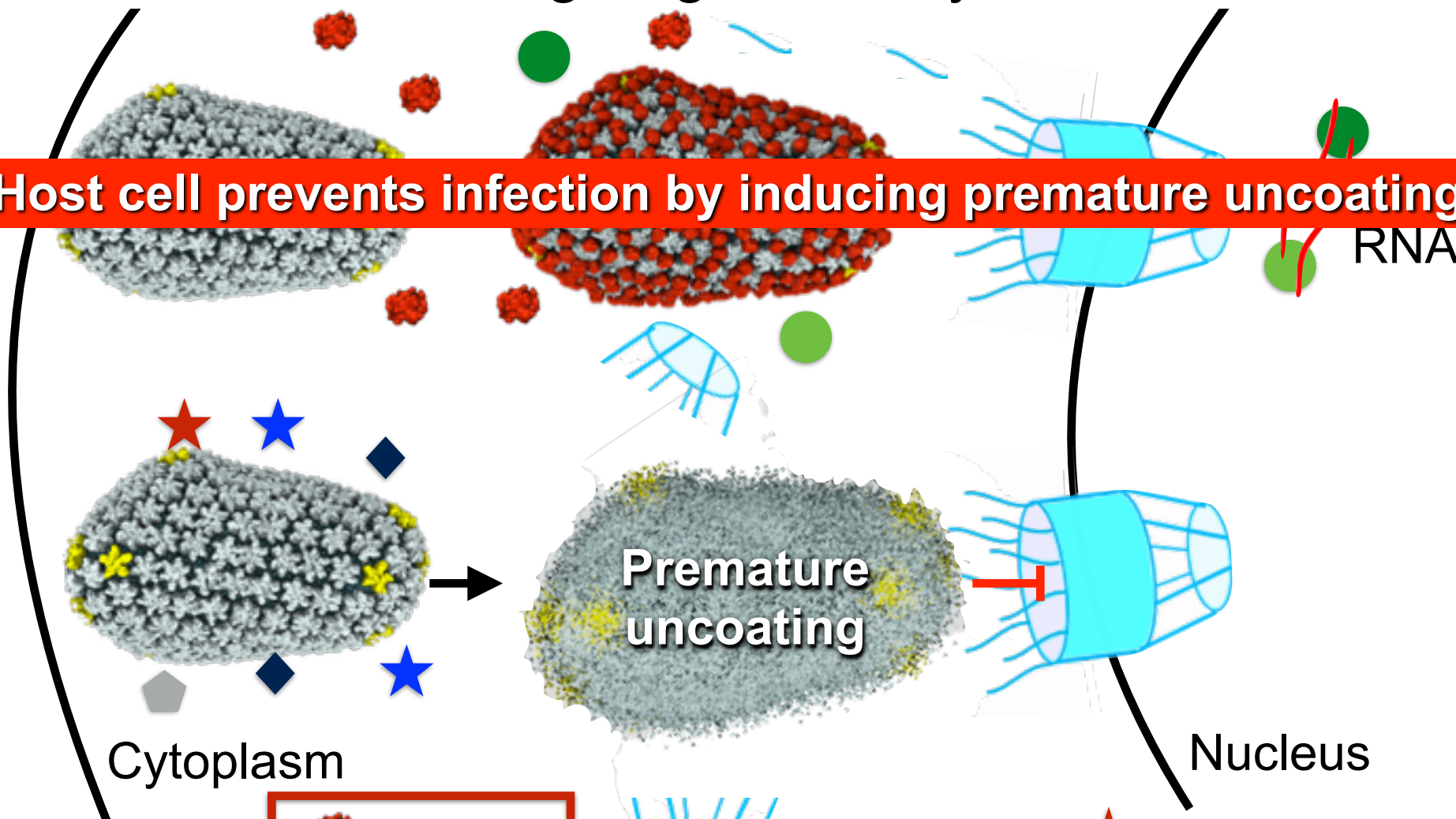
Such electrostatic signature suggests a novel binding site for host cell factors between **helices 4, 5 and 7**.



HIV-1 infection

HIV-1 uncoating: regulation by host factors

Host cell prevents infection by inducing premature uncoating



-  CypA
-  TNPO3
-  CPSF6
-  Inhibitor
-  NUP153
-  NUP358
-  TRIMCyp
-  rhTRIM5α
-  MX2

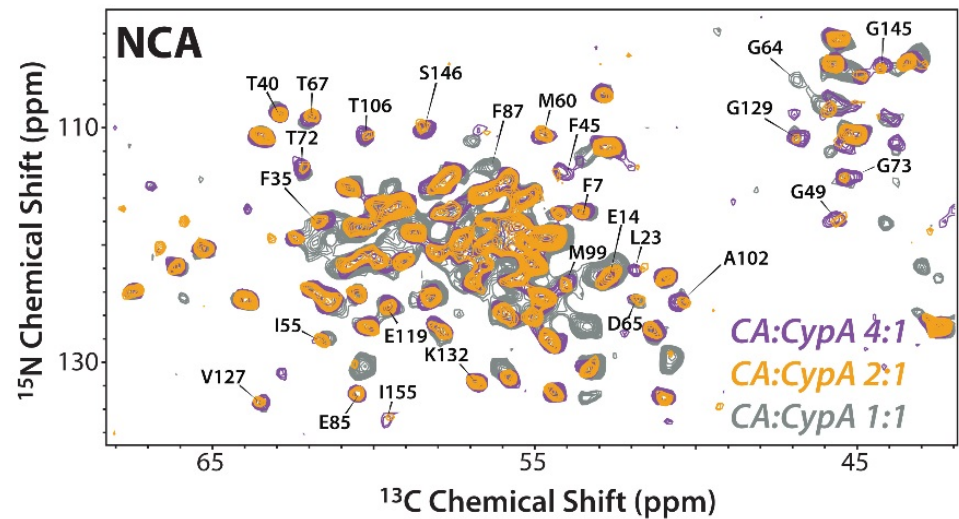
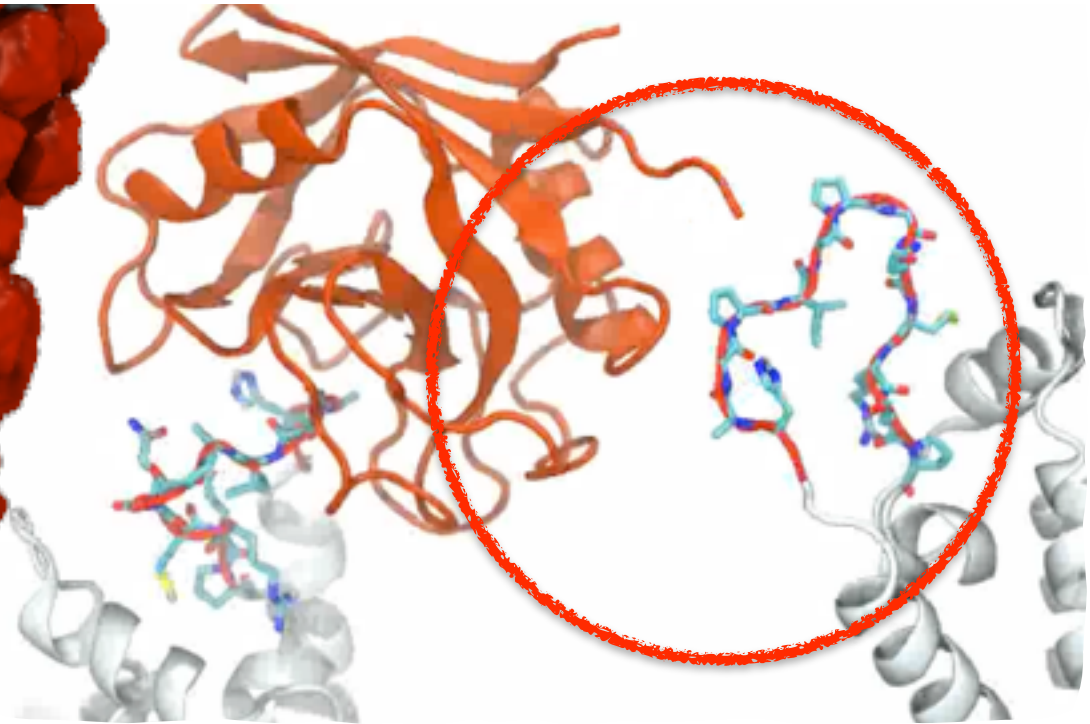
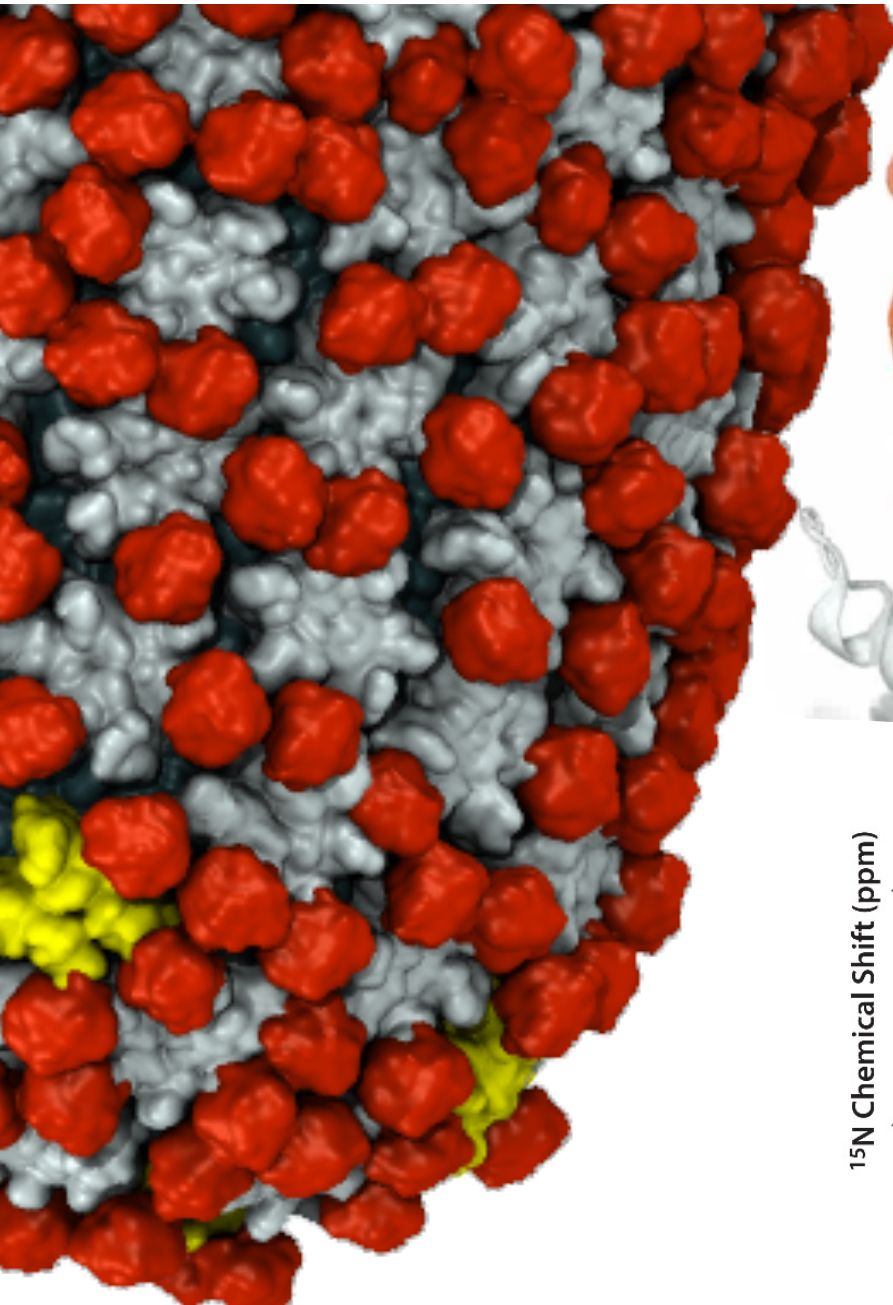
RNA

Premature uncoating

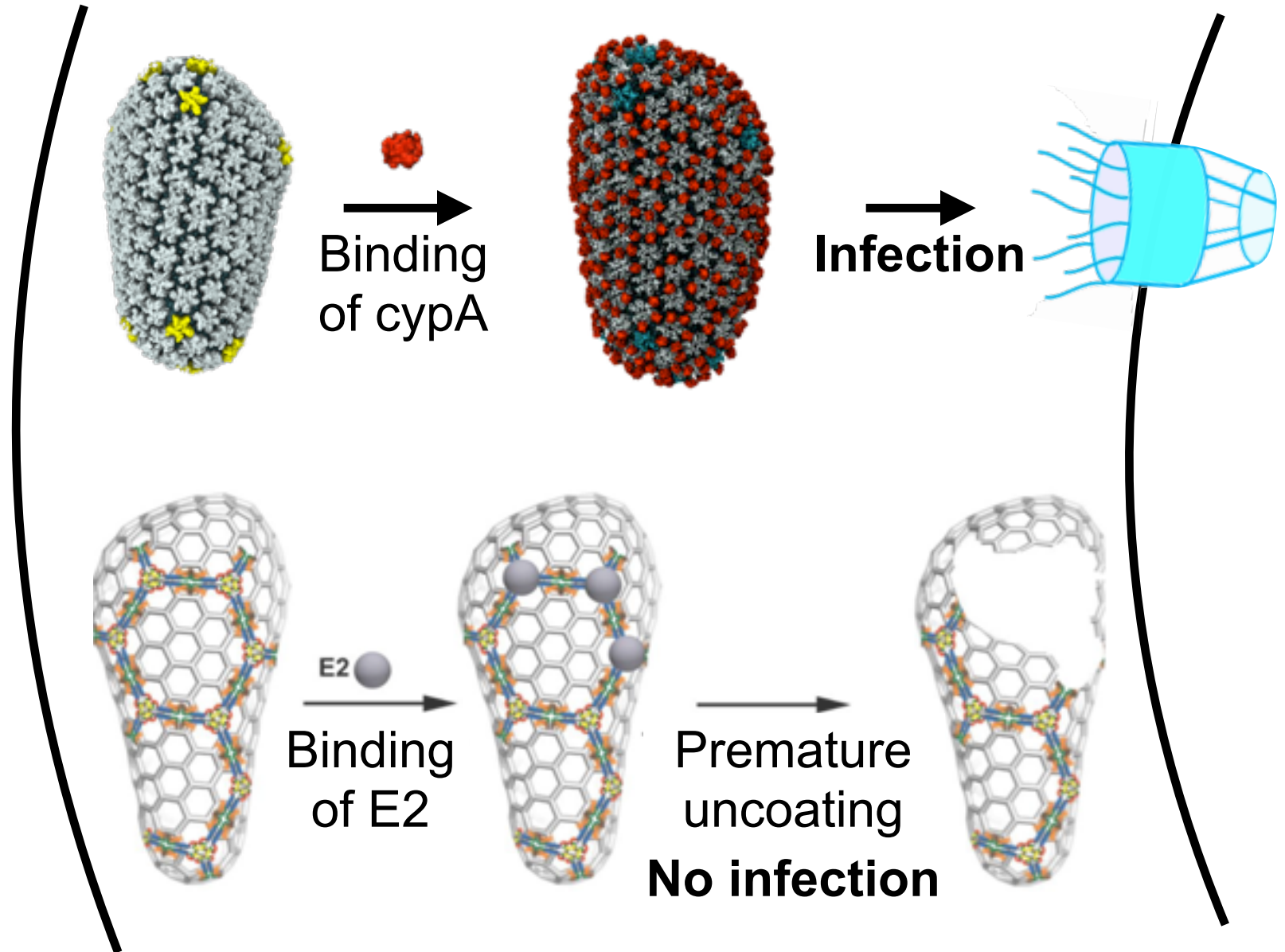
Cytoplasm

Nucleus

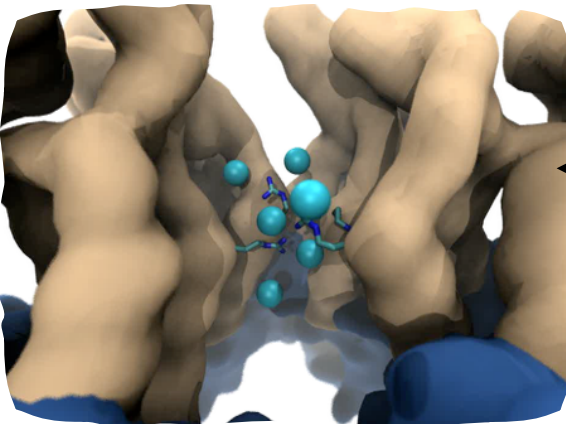
CypA bridge model MD simulations identify a novel catalytic site



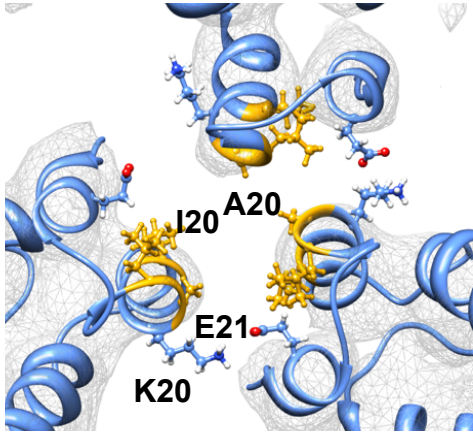
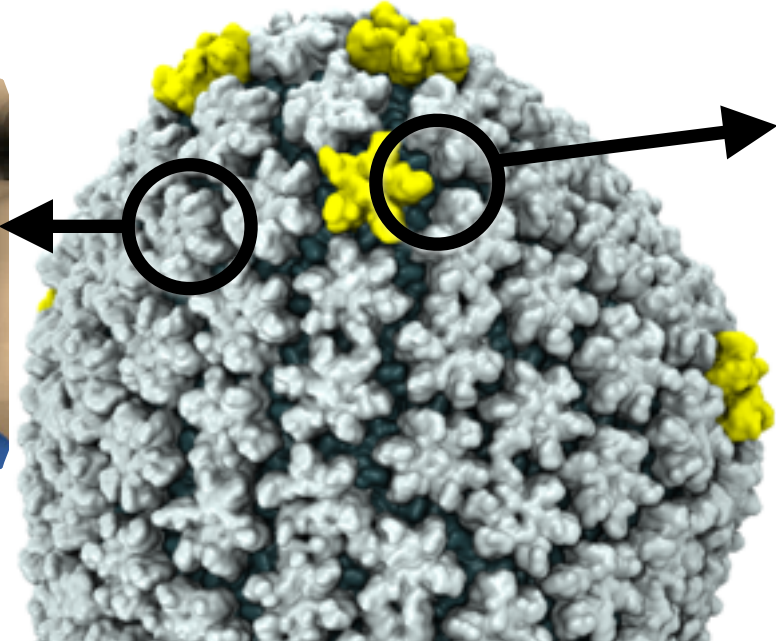
Competitive binding between CypA and Trim



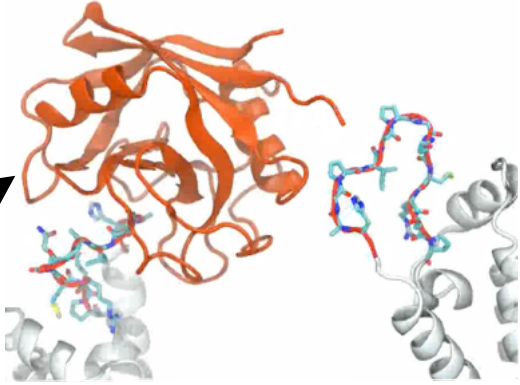
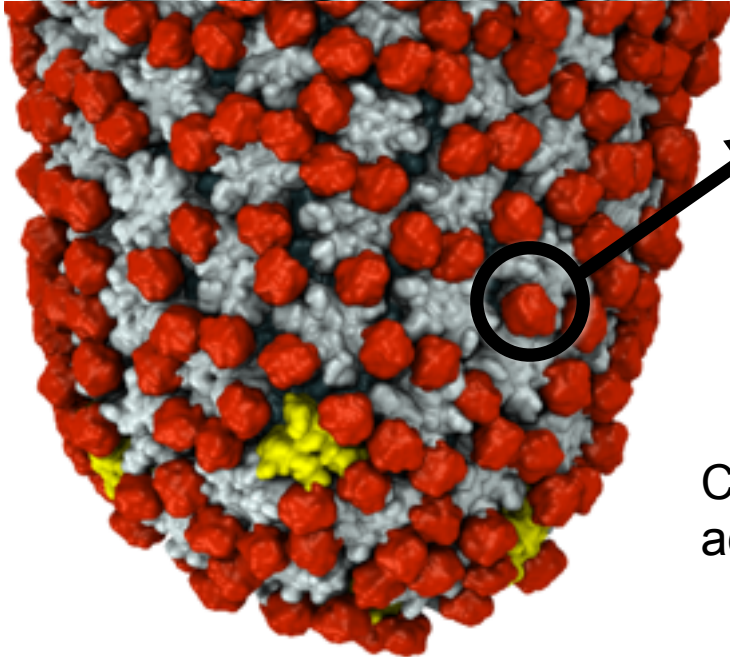
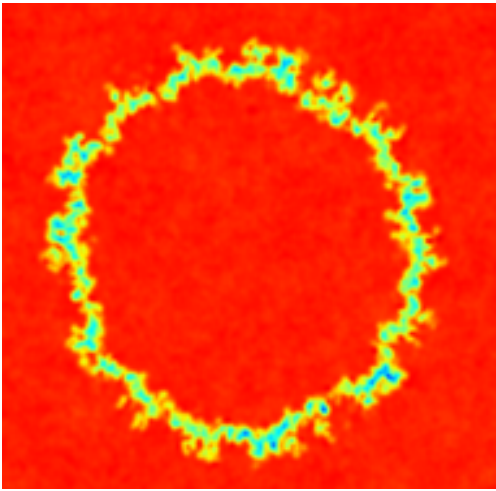
Every atom is needed to study the capsid



Ions permeate through the capsid



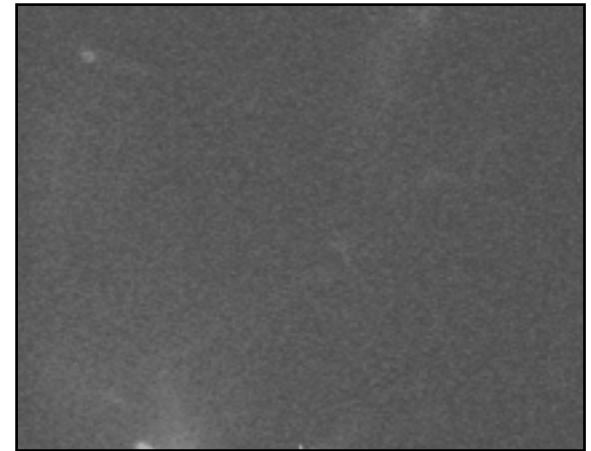
Curvature regulated by trimeric interface



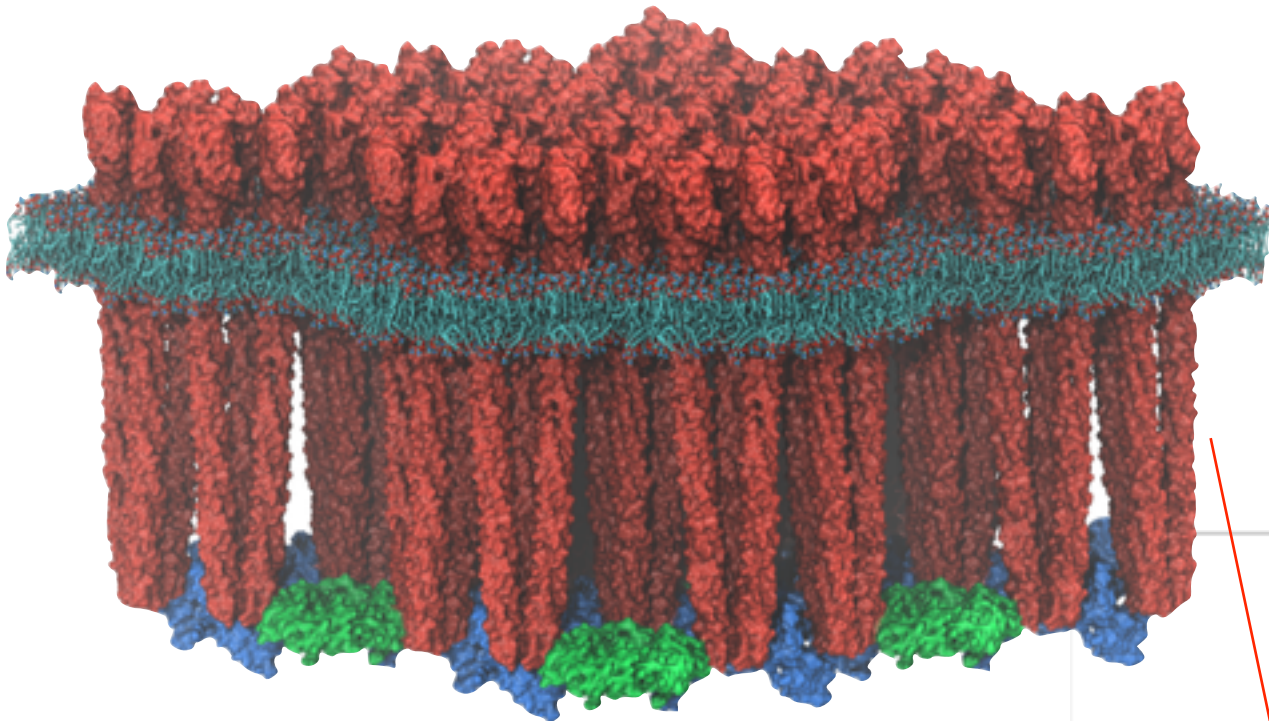
CypA bridges adjacent capsid subunits

The Bacterial Brain: Membrane-bound Chemosensory Array

Array controls signal transduction ultimately regulating cell motility



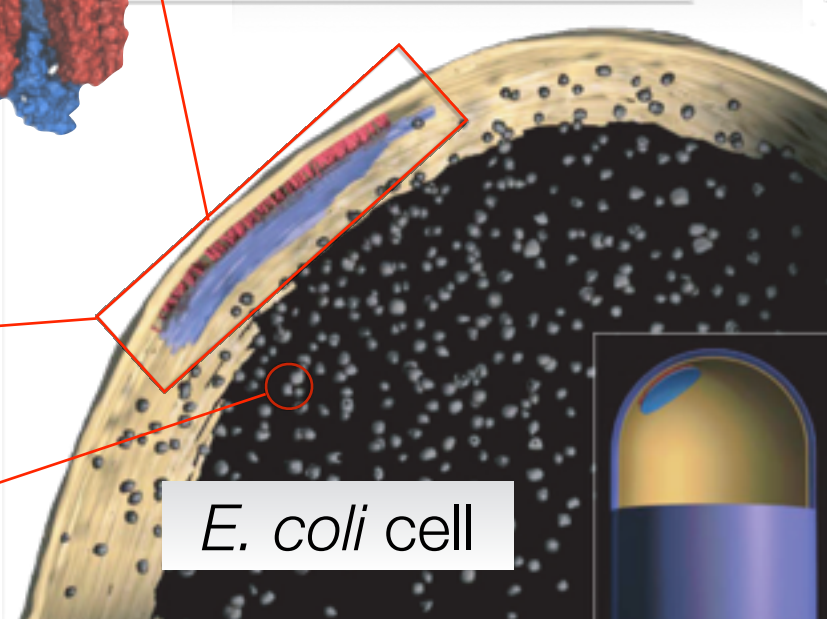
free-swimming *E. coli*



Atomic structure of chemosensory array

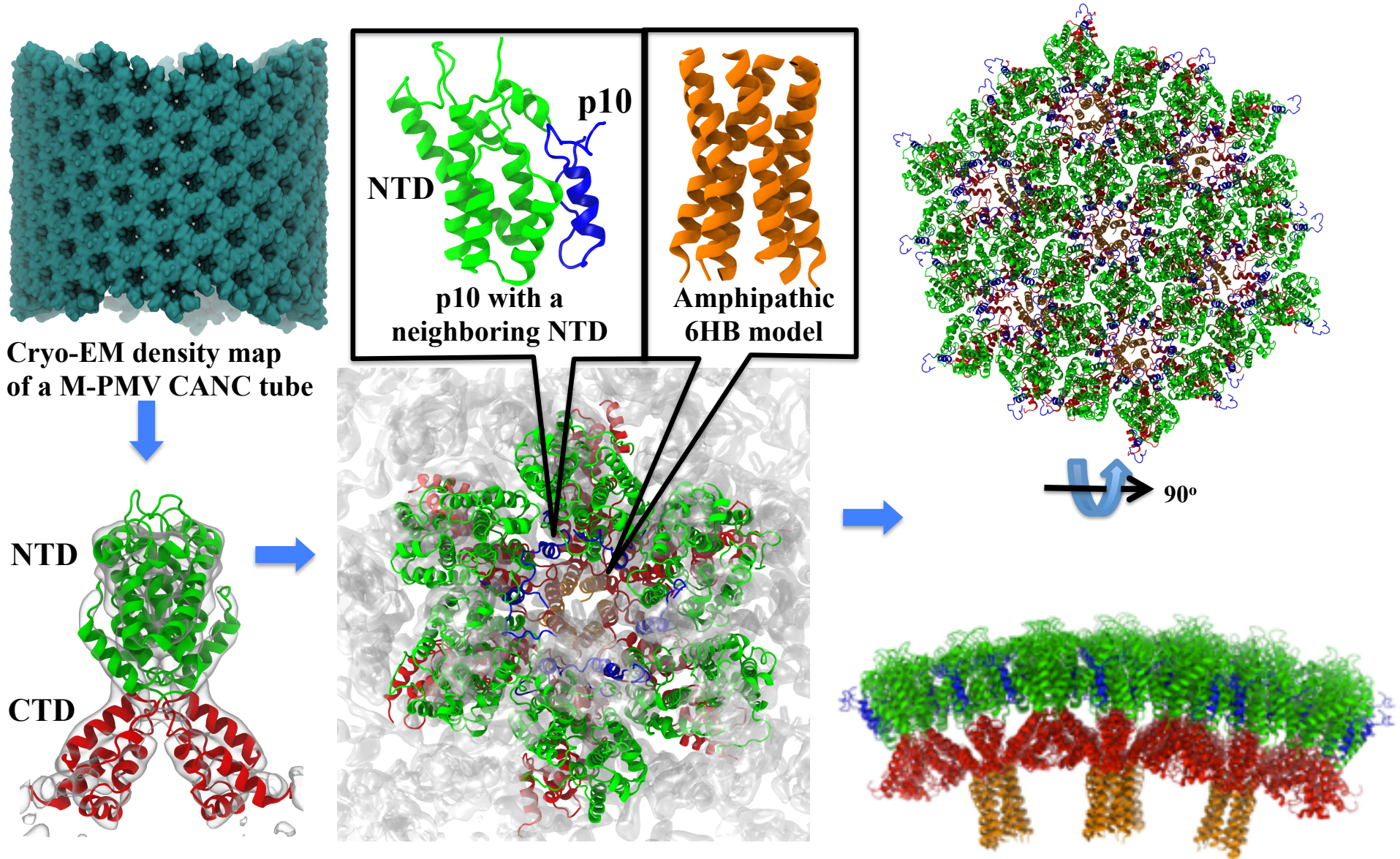
40 million atoms

Ribosome
~3 million atoms



E. coli cell

Immature retroviral lattice



Acknowledgments

Angela Gronenborn

Peijun Zhang

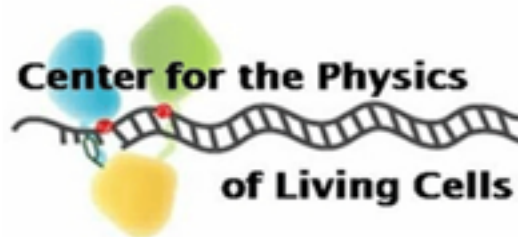
Department of Structural Biology
University of Pittsburgh School of Medicine

Christopher Aiken

Department of Pathology and Immunology
Vanderbilt University School of Medicine

Tatyana Polenova

Department of Chemistry and Biochemistry
University of Delaware



Theoretical and Computational Biophysics Group
University of Illinois Urbana-Champaign

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London

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Homotopia



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exploring the HIV syndemic

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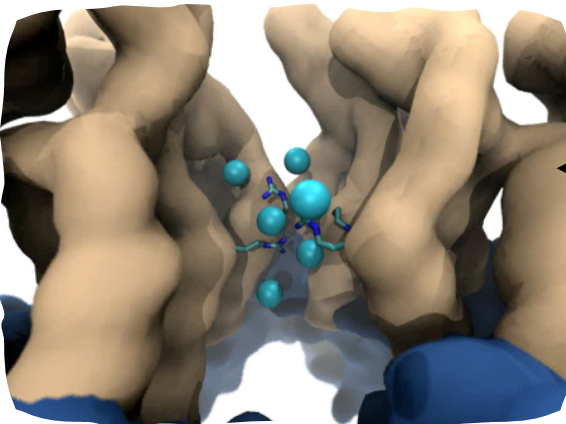
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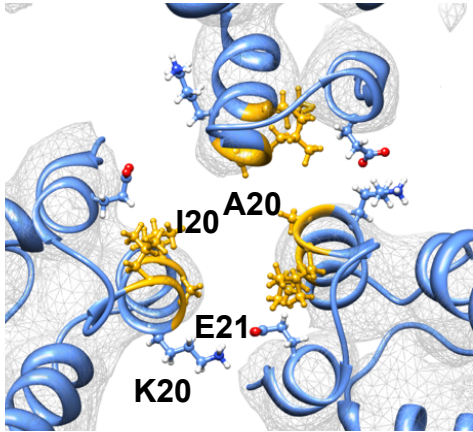
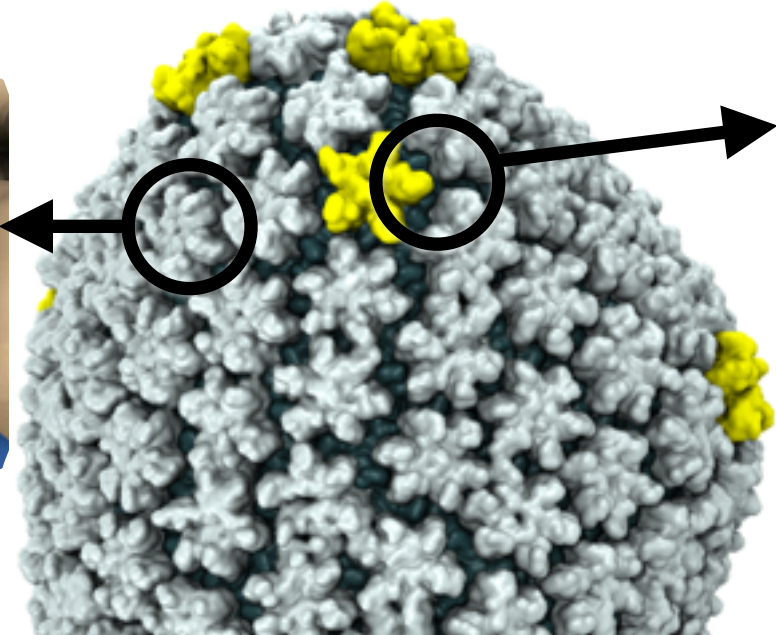




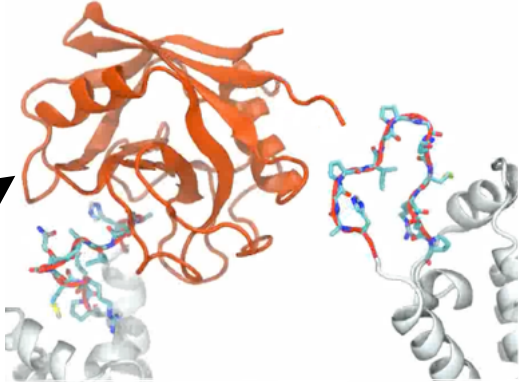
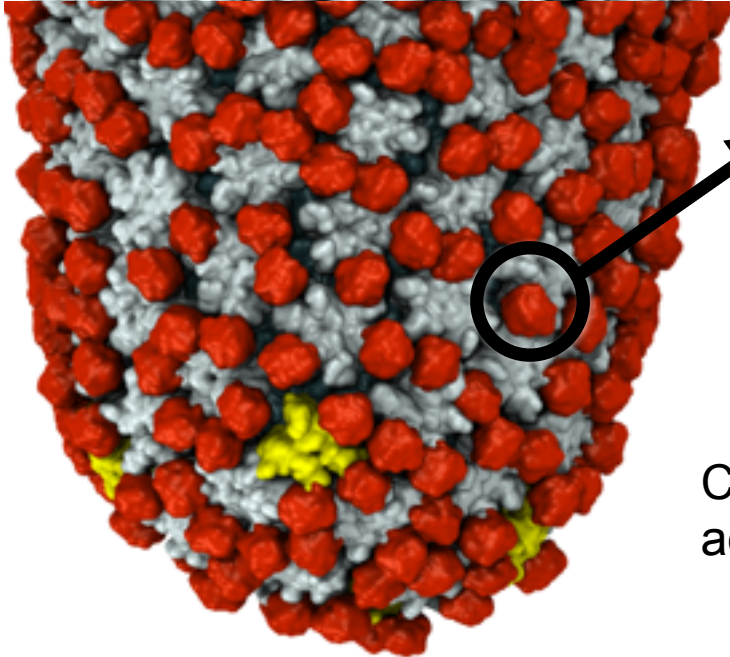
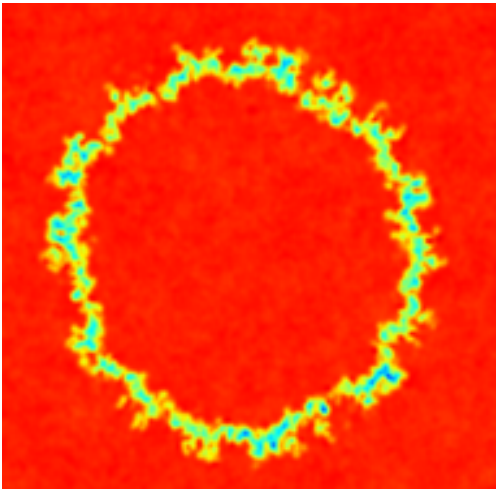
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