

Dynamic Coarse-Grained Models for Simulations of Large-Scale Biophysical Phenomena

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THE UNIVERSITY OF
CHICAGO



Who we are

- Voth Group (PI Prof. Gregory A. Voth):
 - University of Chicago
 - Dept. of Chemistry
 - Computation Institute
 - James Franck Institute
 - Institute for Biophysical Dynamics
 - ...



What we do

- Condensed matter theory / modeling / simulation ...
 - Biomolecular systems
 - Energy storage
- Algorithmic design / development
 - Enhanced sampling
 - Parallel simulation software
- Computer simulations
 - Quantum
 - Atomic resolution
 - “Coarse-grained” (CG)
 - Mesoscopic particle techniques



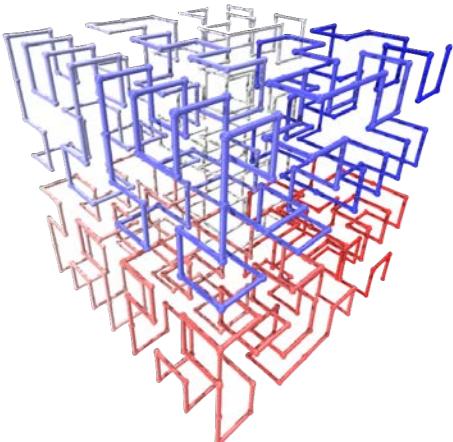
Current work on Blue Waters

- Viral systems
 - HIV-1 immature lattice self-assembly, viral “budding”
 - RNA-driven nucleation and growth of the viral capsid
 - Cleavable models of Gag protein
- Membrane / protein systems
 - Integrin dynamics, focal adhesion complexes
 - BAR domains and membrane remodelling
- Complement “conventional” experimental techniques

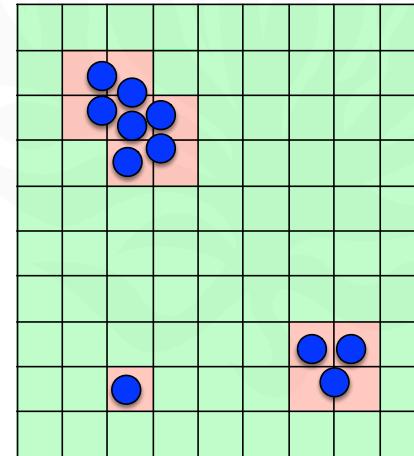


Why Blue Waters?

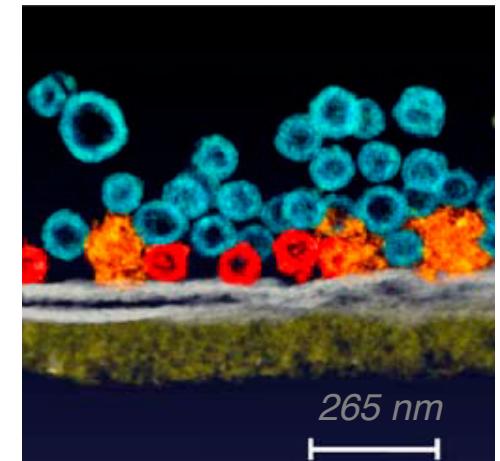
- Critical for developing our software & algorithms
 - Custom parallel simulation code for CG models
 - Highly dynamic CG molecular representations
 - Developed under a Blue Waters PRAC sub-award, in collaboration with Blue Waters technical staff



Load balance: SFCs



Sparse data techniques

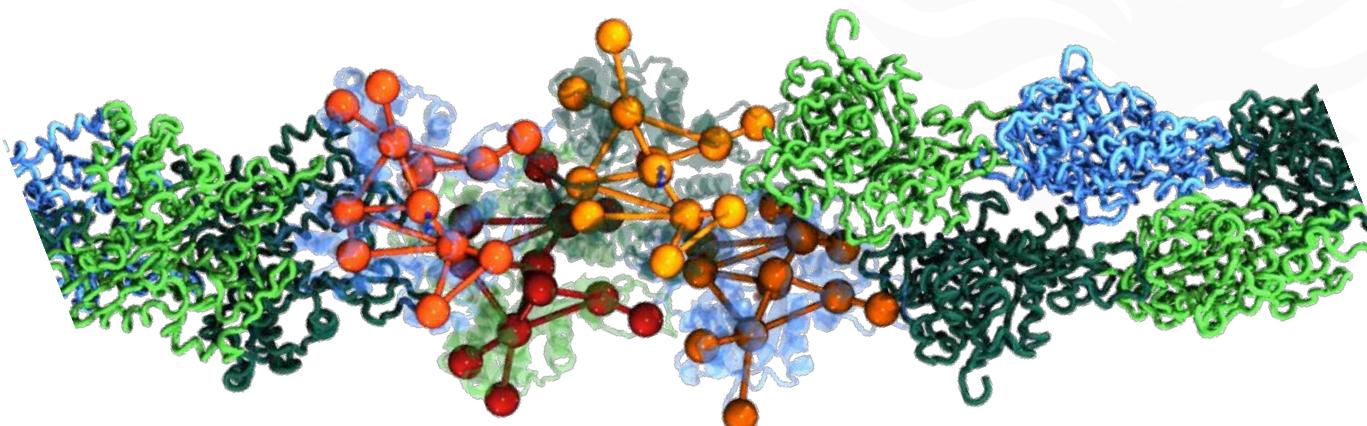


Large-scale systems



Coarse-grained (CG) models

- Remove degrees of freedom!
- Highly coarse grained solvent free model
- Coarse grained solvent free model
- Atomistic solvent free model
- Atomistic model with solvent



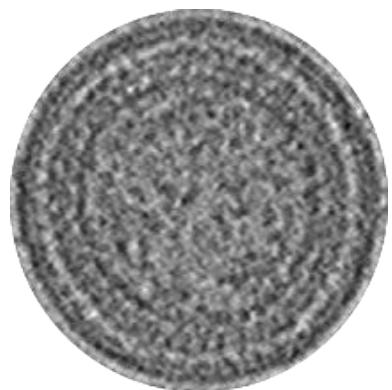
CG



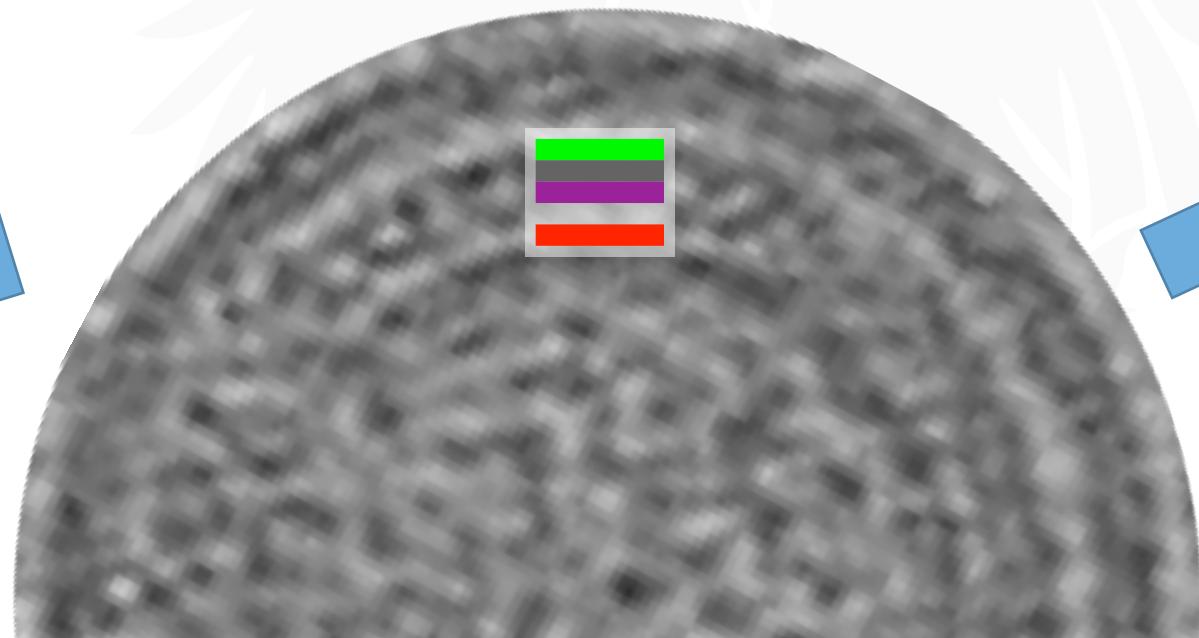
**“Full” atomic
resolution**



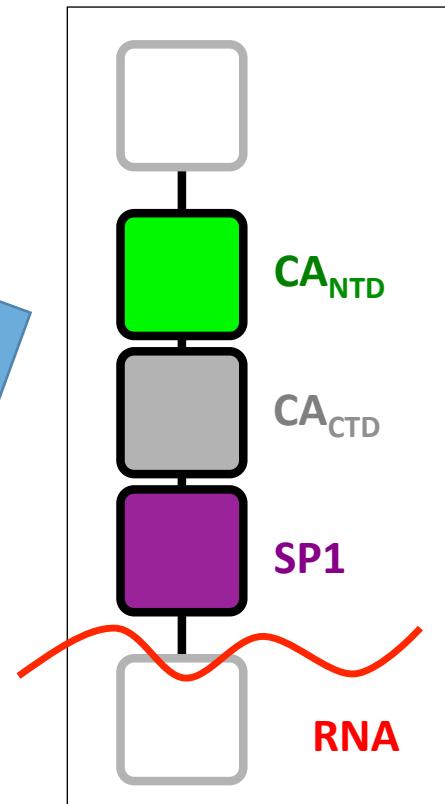
Coarse-grained (CG) models



Viral particle:
“virion”

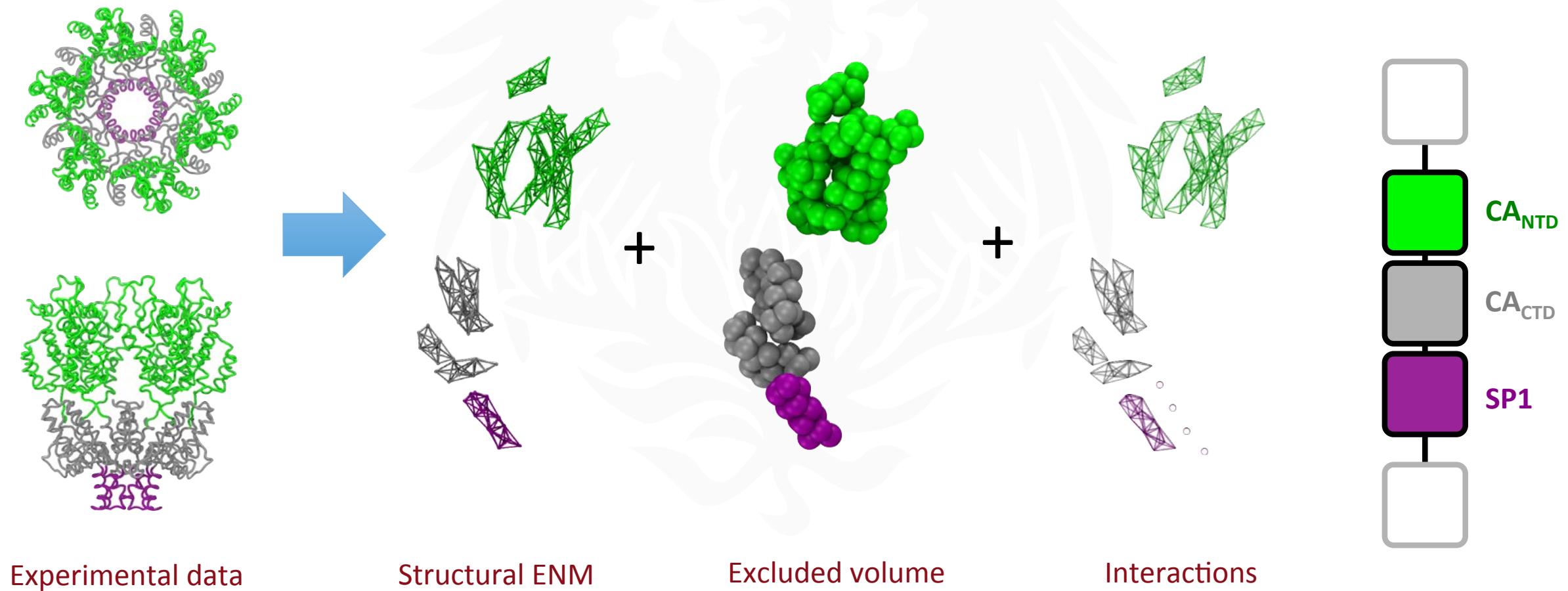


Radial array of Gag molecules,
containing several protein domains

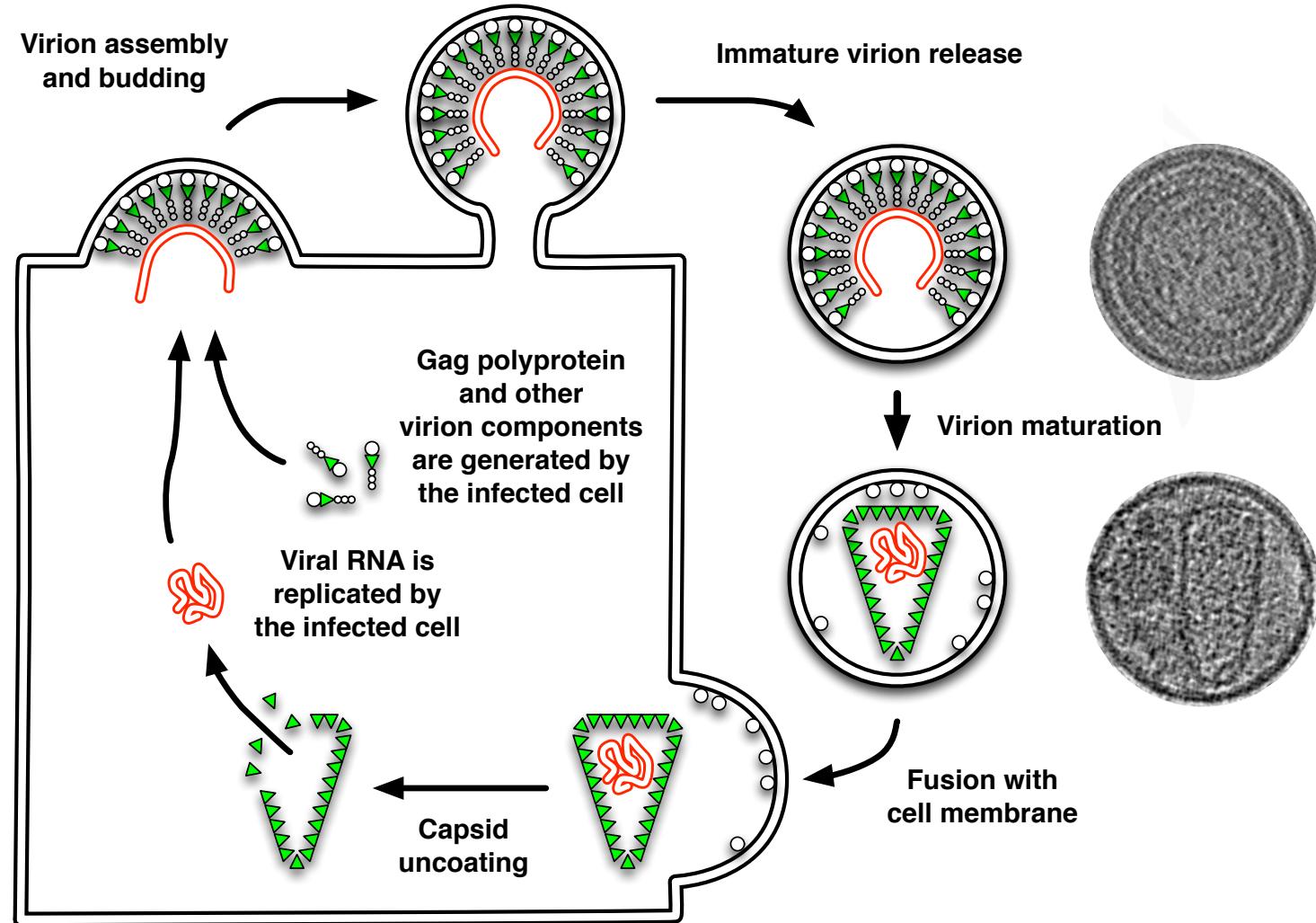




Coarse-grained (CG) models

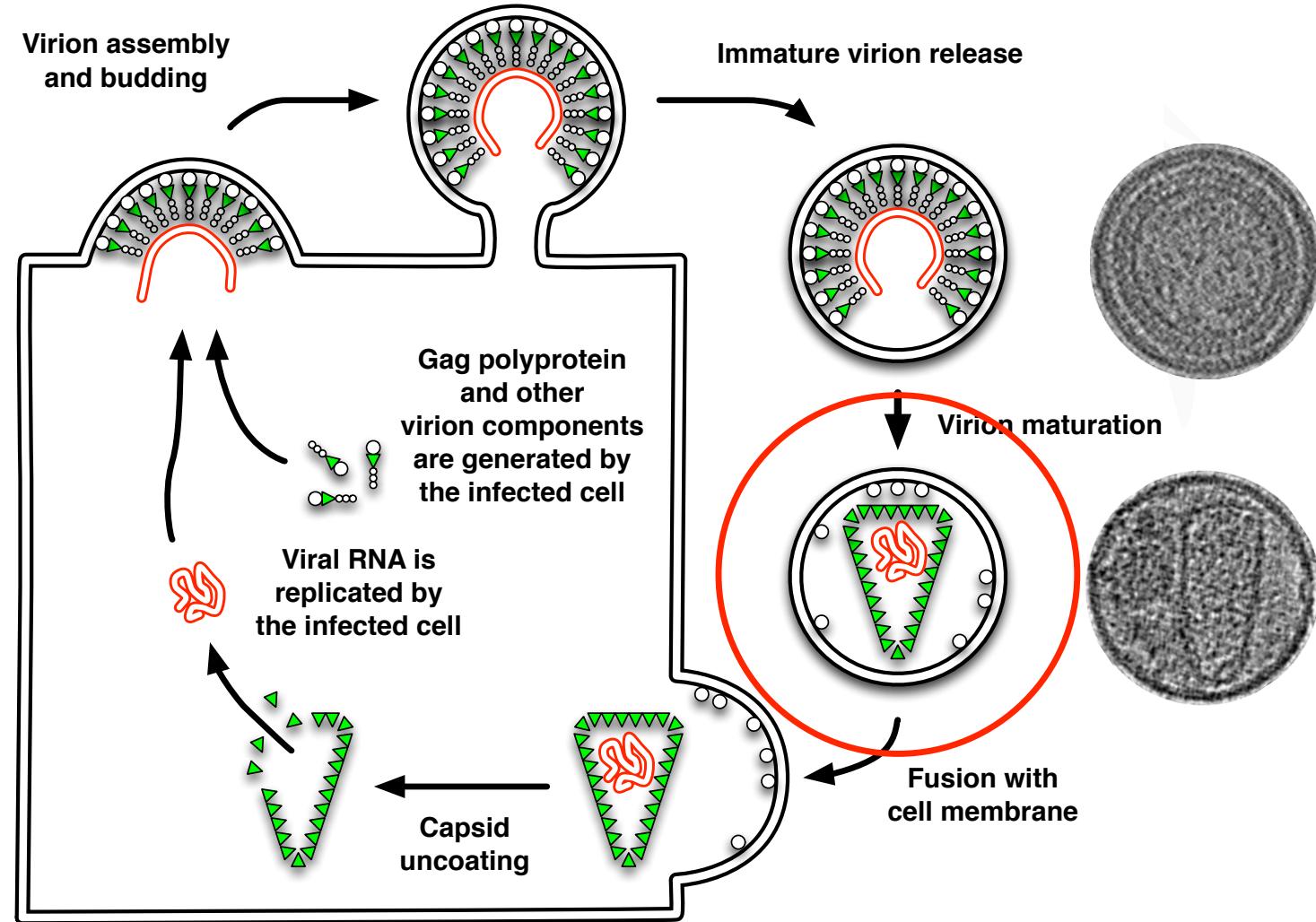


Example: HIV capsid protein self-assembly

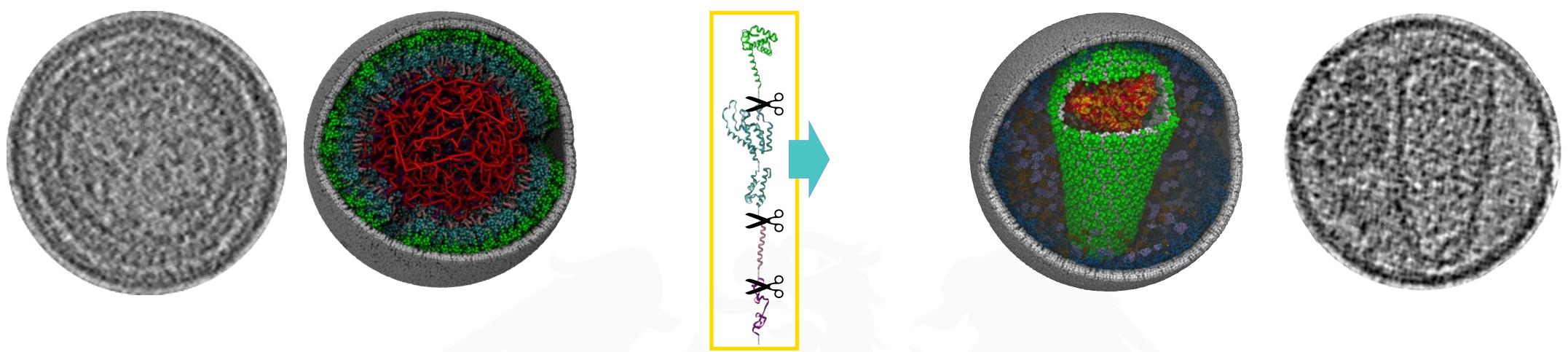


Ganser-Pornillos et al, *Curr. Op. Struct. Biol.* 2008, 18:203

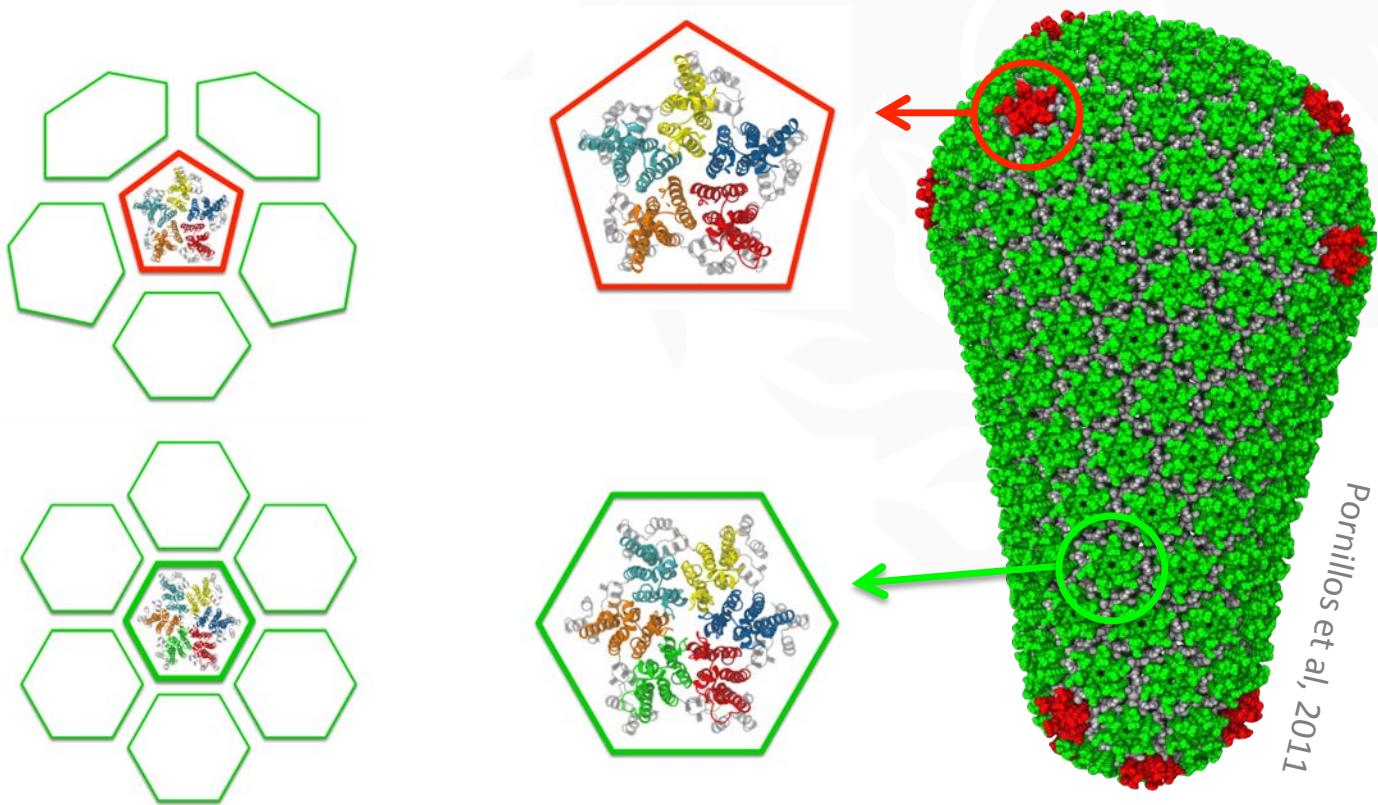
Example: HIV capsid protein self-assembly



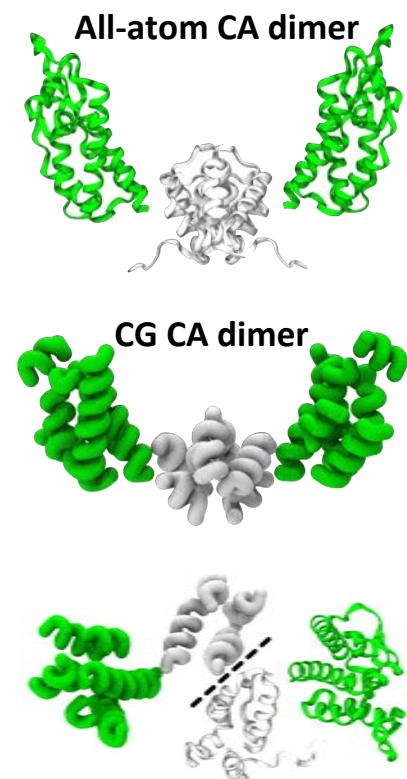
Ganser-Pornillos et al, *Curr. Op. Struct. Biol.* 2008, 18:203



HIV-1 “maturation”: no capsid formation, no viral infection

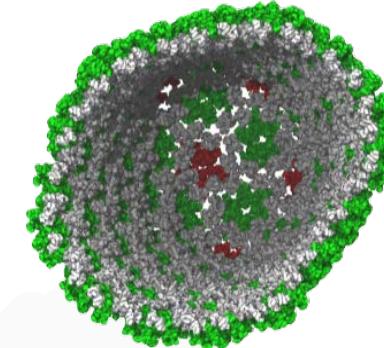


Pornillos et al, 2011

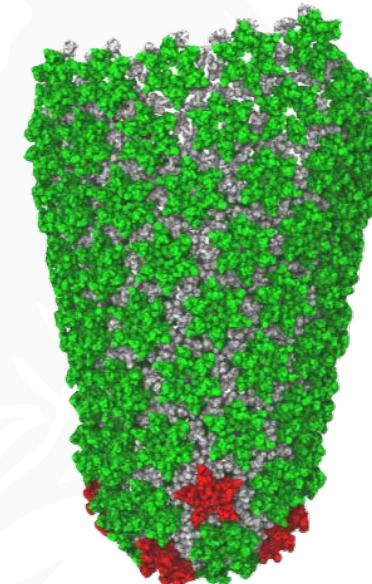




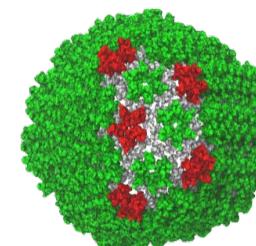
(only aggregated protein shown!)



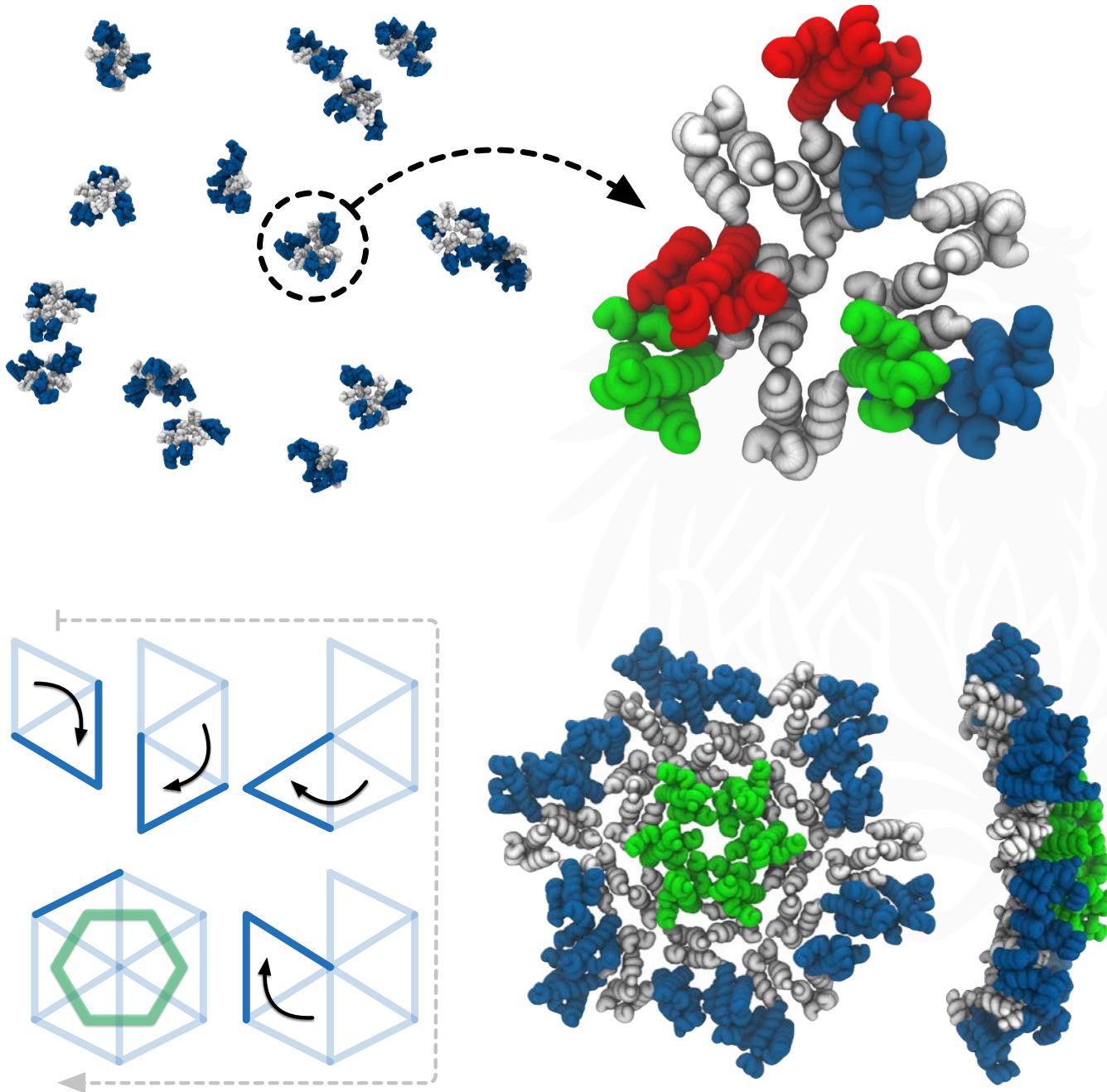
Top



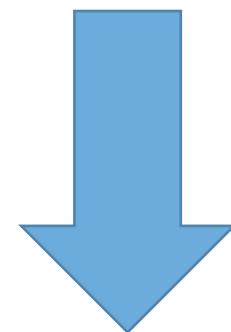
Side



Bottom



Triangles appear! Formed from three protein dimers
(red, blue, green)

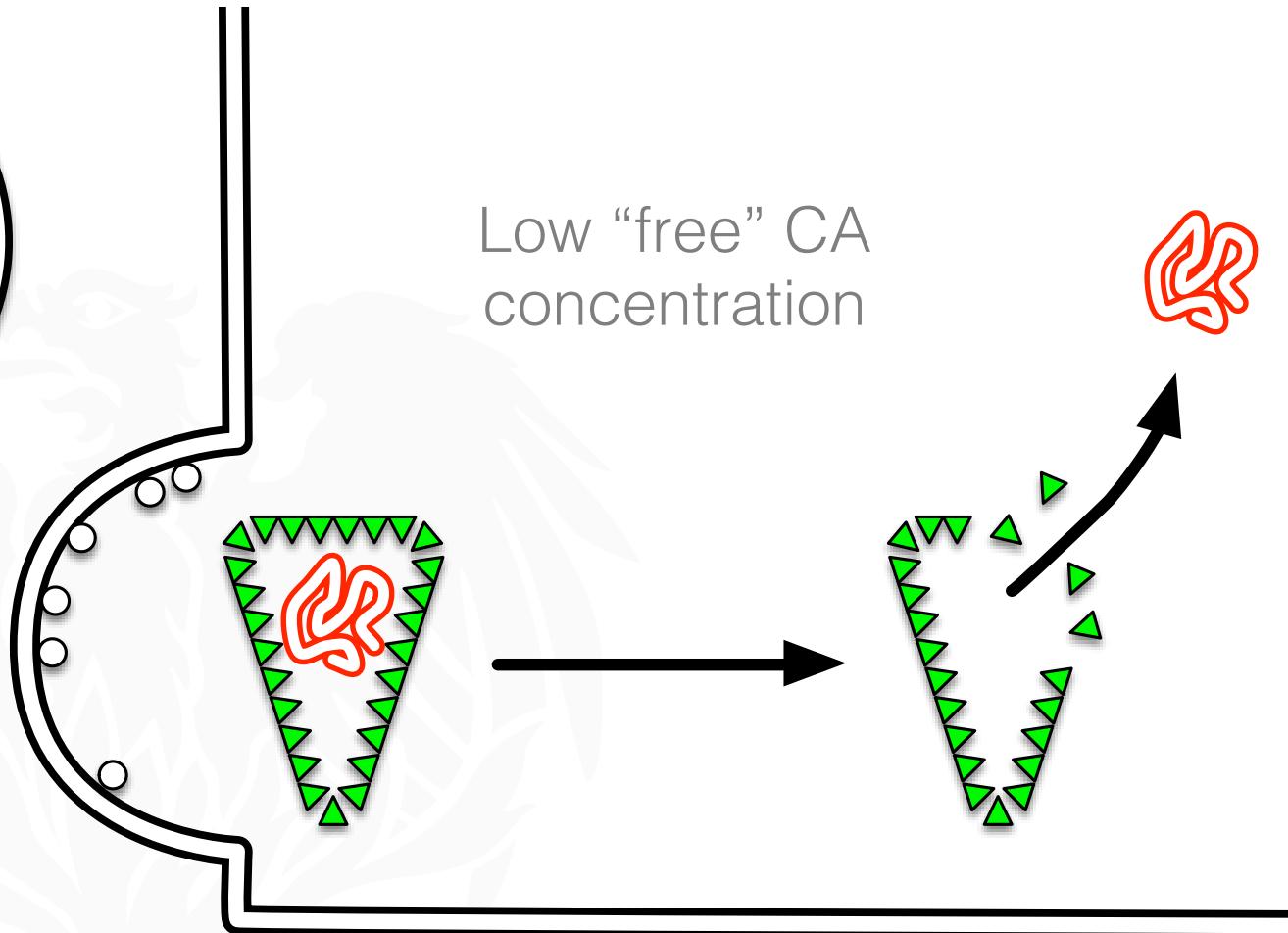


Dimers add to existing triangle, eventually forming a stable hexagon **(green)**

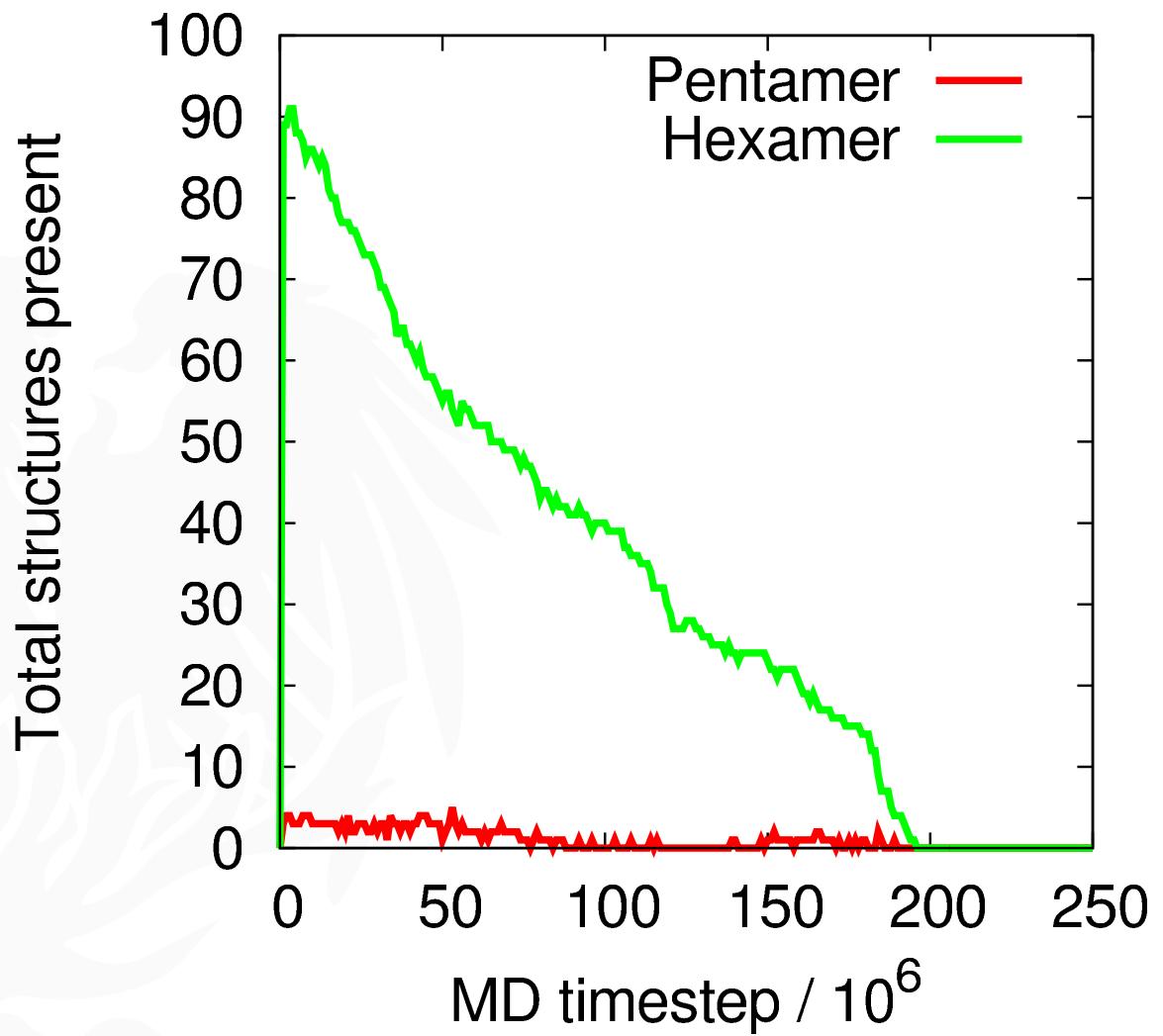
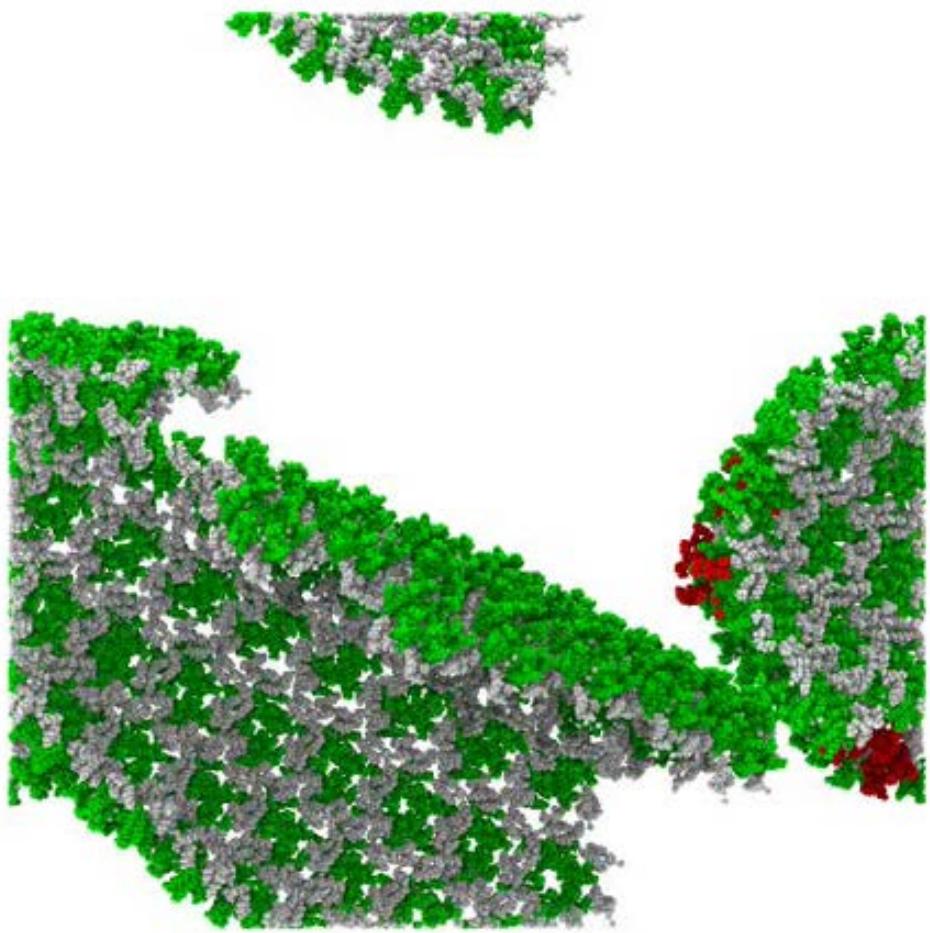
High “free” CA concentration



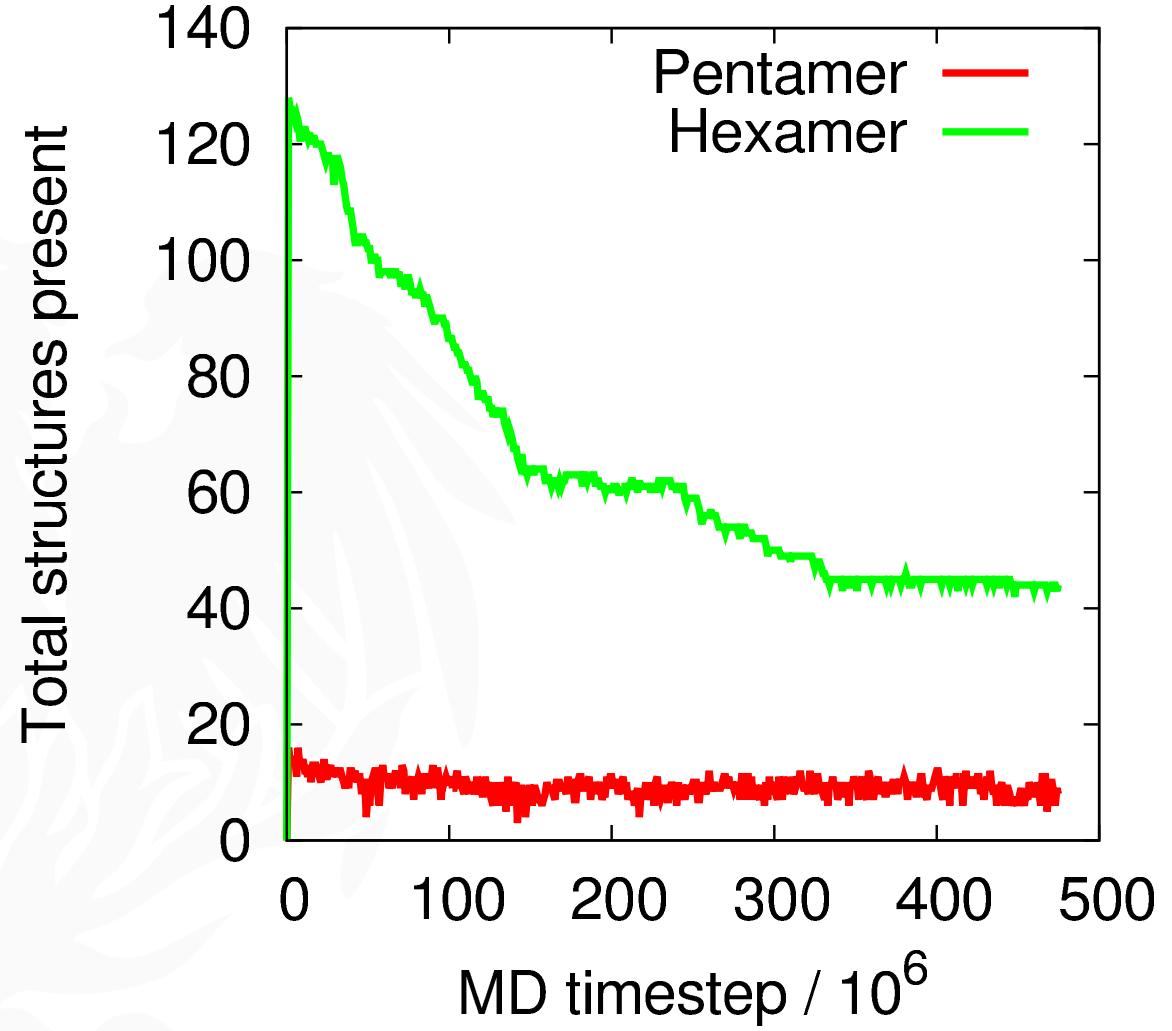
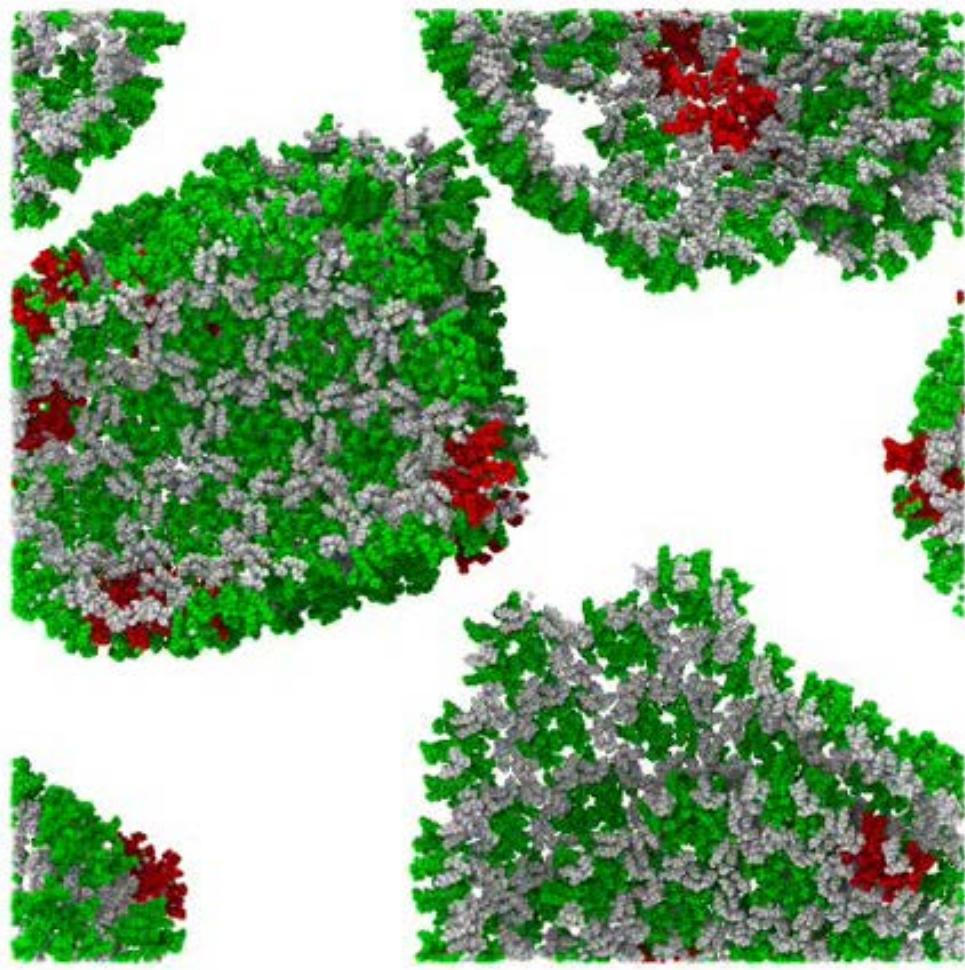
Low “free” CA concentration



Relatively high solution [CA] inside a virion: fusion with cell is effectively a rapid dilution in the new environment. How might this affect stability of self-assembled structures, like the viral capsid?



Structures with **exposed edges** appear **less stable**: protein dissolves from the edges of the lattice under conditions of rapid dilution



Structures with sealed edges appear more stable under rapid dilution:
relevant for cellular defense mechanisms (e.g. TRIM restriction)



Final words

- Thanks to:
 - Our experimental collaborators, including:
 - Grant Jensen (Cal Tech)
 - Mark Yeager (U Virginia)
 - Owen Pornillos (U Virginia)
 - Barbie Ganser-Pornillos (U Virginia)
 - NSF (naturally!)
 - Blue Waters support staff: Robert Brunner, Greg Bauer
 - Voth Group members

