A Different Type of "Computer Virus"

Blue Waters Symposium 2017

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Overview

- For this talk, our uses of Blue Waters will be grouped into two major aspects:
  - Development of custom software for molecular simulations
  - CG simulations of biomedically relevant systems; in this case, aspects of viral lifecycle of influenza & HIV-1

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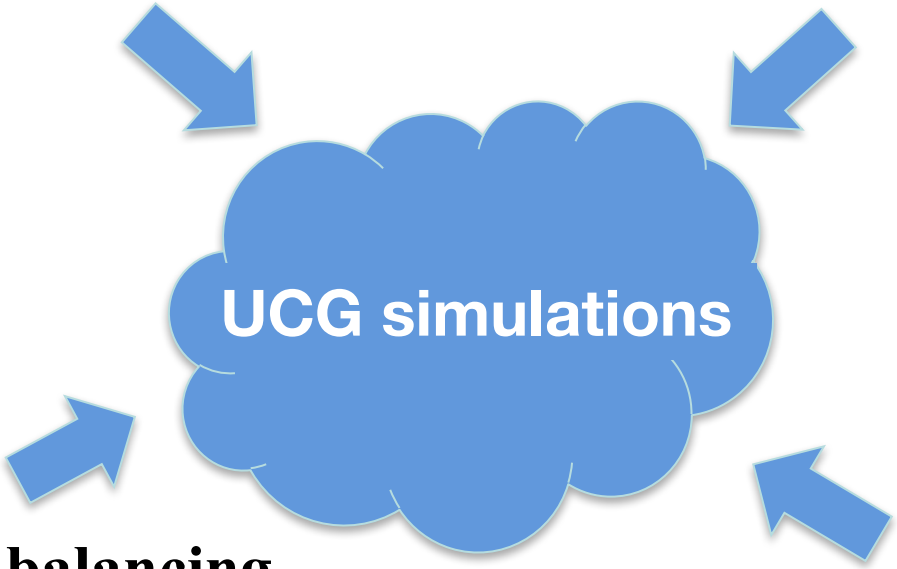
"Ultra-coarse-grained" MD *

UCG-MD: what do we need?

Dynamic system components
(significant runtime changes)

Low memory requirements
(very large simulations)



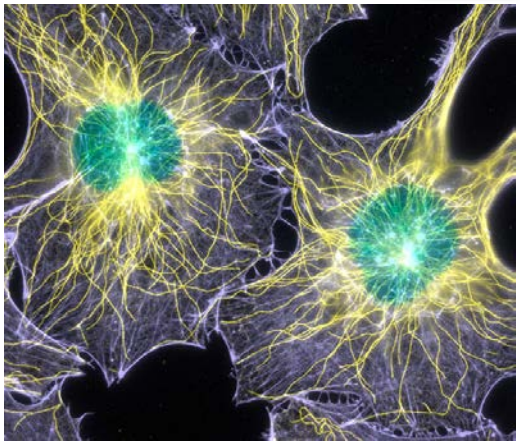
Dynamic load balancing
(implicit solvent etc)

Flexibility
(ease of modification)

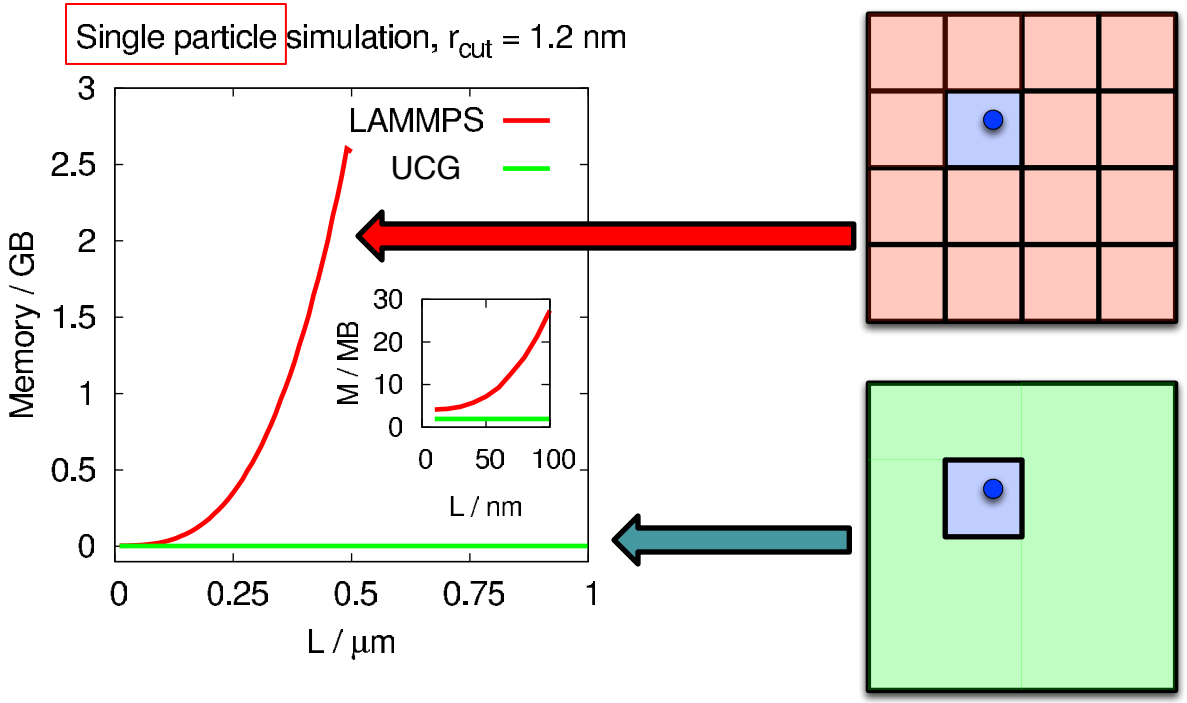
* **Grime** and Voth, JCTC **10**:423 (**2014**)

UCG-MD: "Sparse" Data

(Bio)material sims may span *many orders of magnitude: e.g.* **Å → µm**



Mouse fibroblast cells, Torsten Wittman, The Scripps Research Institute



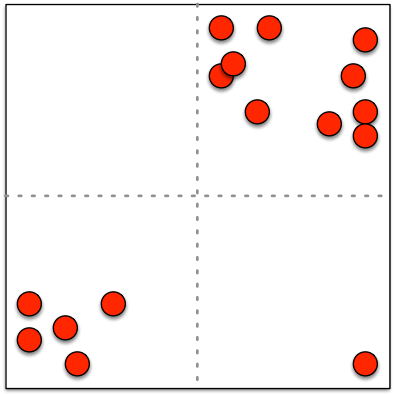
Trivial example: **single particle** with conventional algorithm: can use *huge* amounts of memory, even though the simulation is basically empty!

UCG-MD algorithms* are much better behaved in large-scale sims

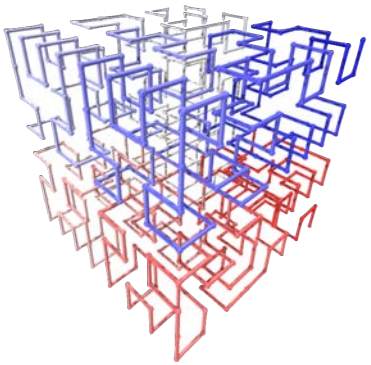
* dynamic spatial tree structures, indexed with *x,y,z* link cell lattice coordinate

UCG-MD: Load Balancing

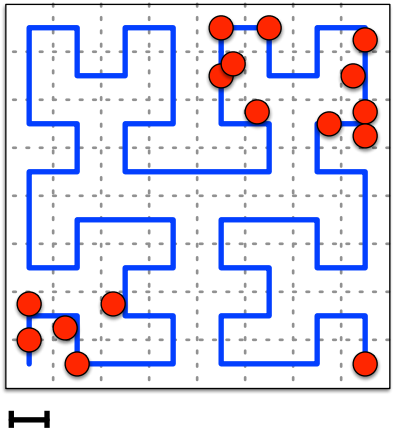
Hilbert space-filling curve (SFC):



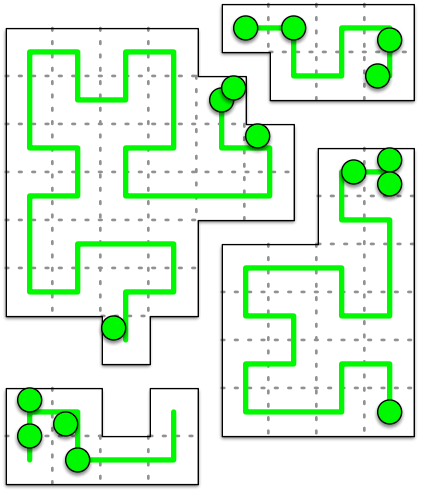
Unbalanced system



Apply SFC



Map particles into SFC



Section SFC

Inspired by colleagues in astrophysics: reversible mapping of 3D lattice coordinates ⟹ 1D “curve index”. Curve then sectioned for roughly equal loads

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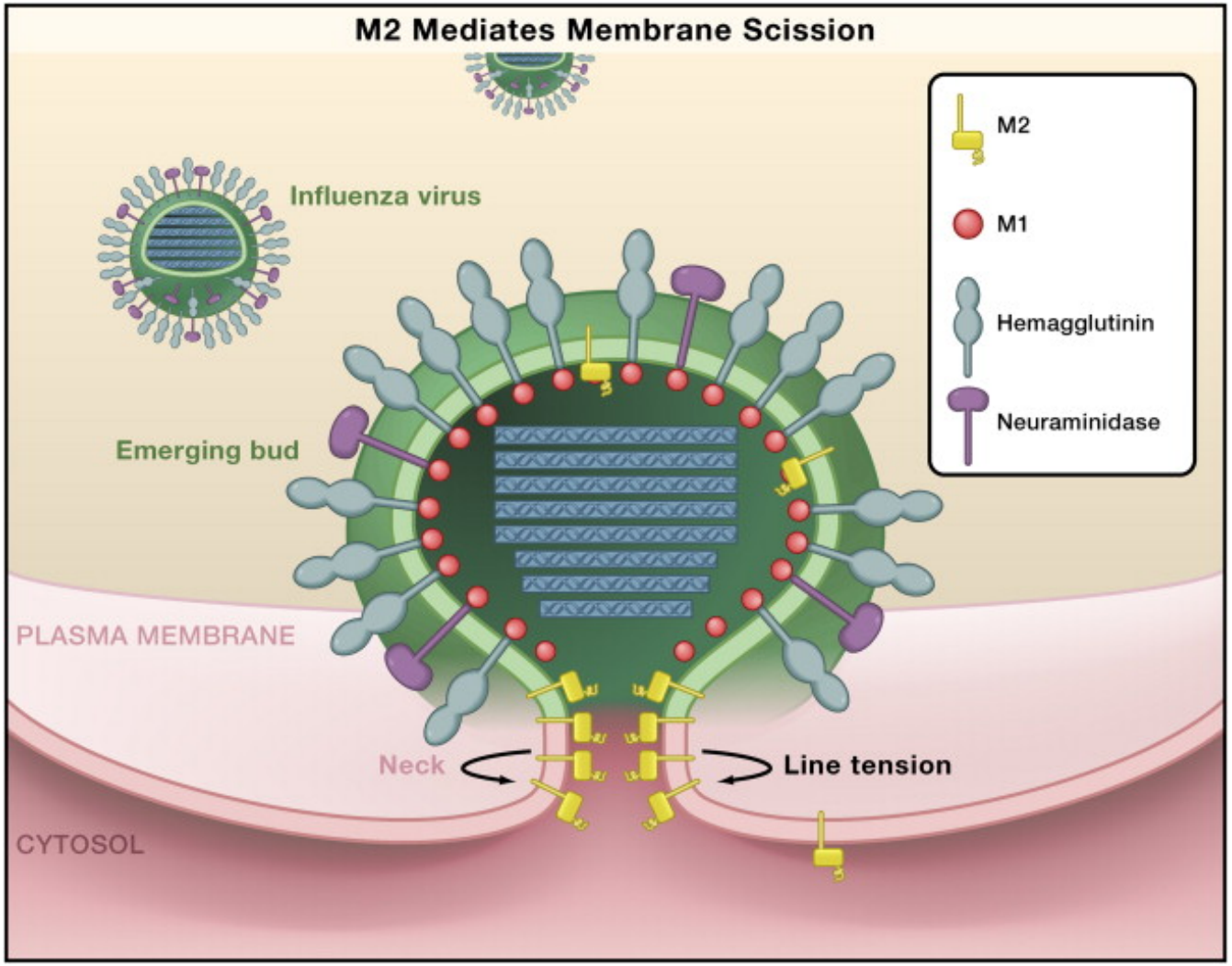
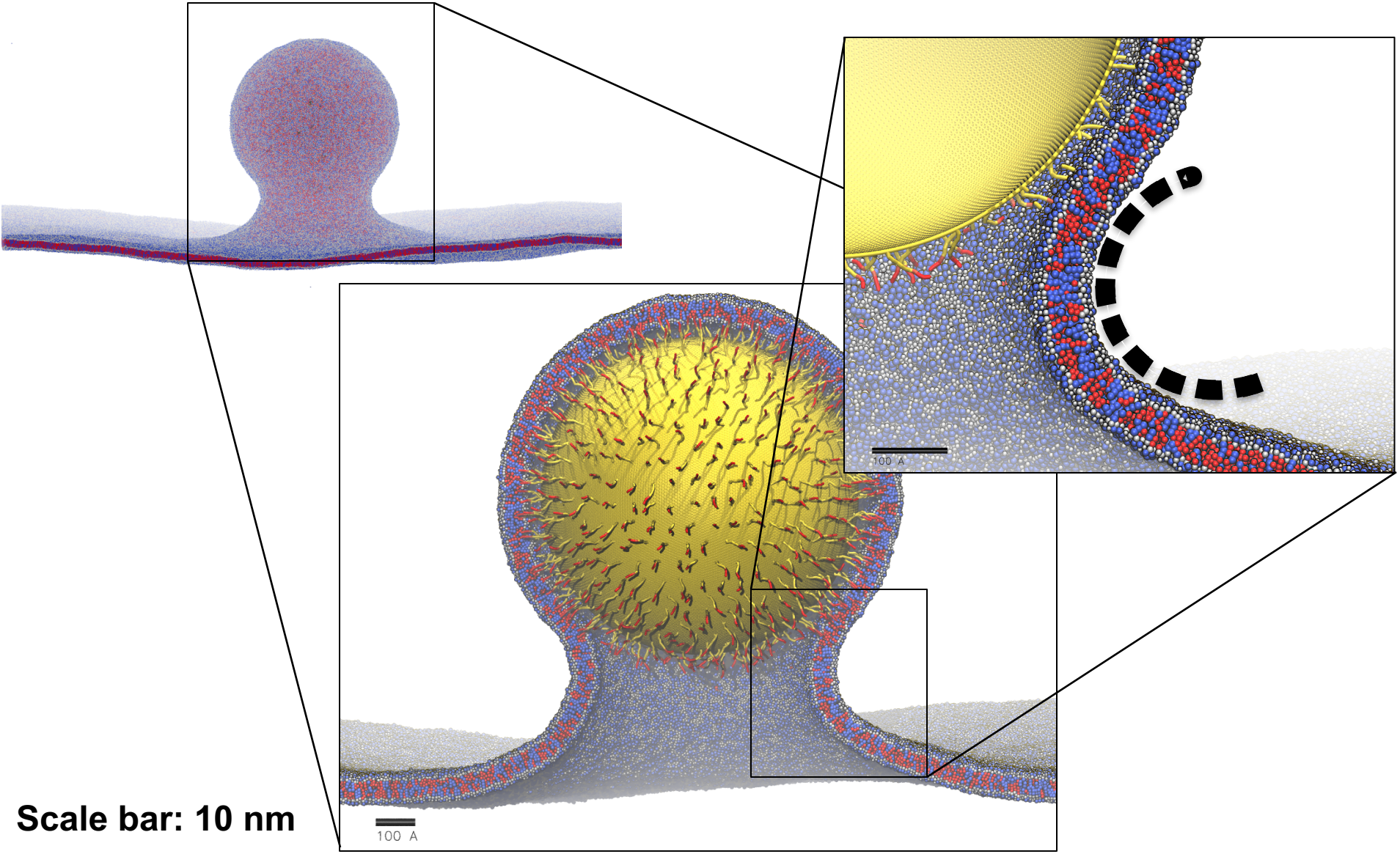
Influenza "budding"



Preview: Influenza Exits the Cell without an ESCRT. H. G. Göttlinger. **Cell** 2010; 142 (6), 839–841. http://dx.doi.org/10.1016/j.cell.2010.08.036

Influenza Virus M2 Protein Mediates ESCRT-Independent Membrane Scission. J. S. Rossman, X. Jing, G. P. Lesser, R. A. Lamb. **Cell** 2010; 142(6), 902-913. http://dx.doi.org/10.1016/j.cell.2010.08.029

Influenza "budding"



Scale bar: 10 nm

J. J. Madsen, J. M. A. Grime, G. A. Voth. In preparation.

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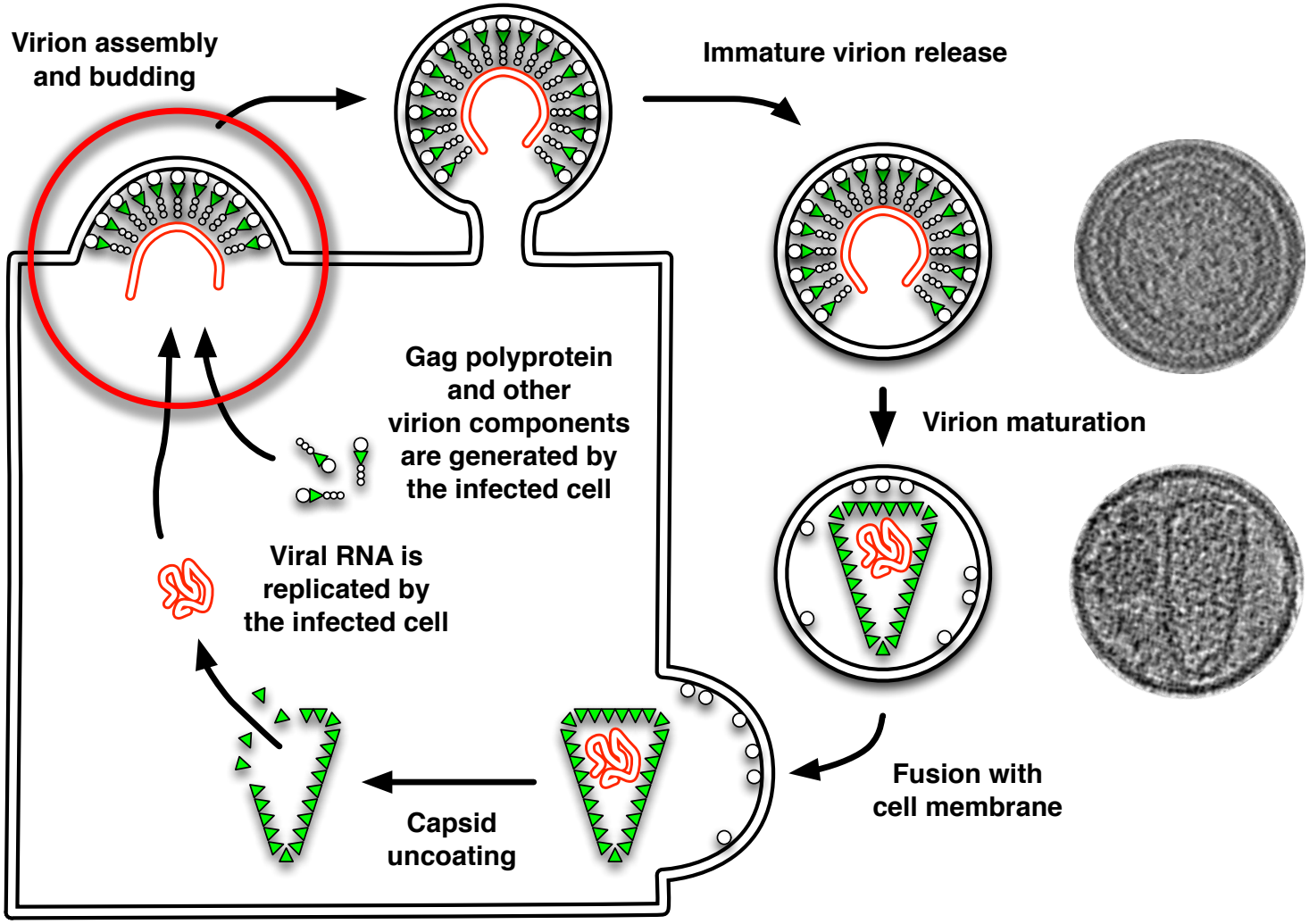
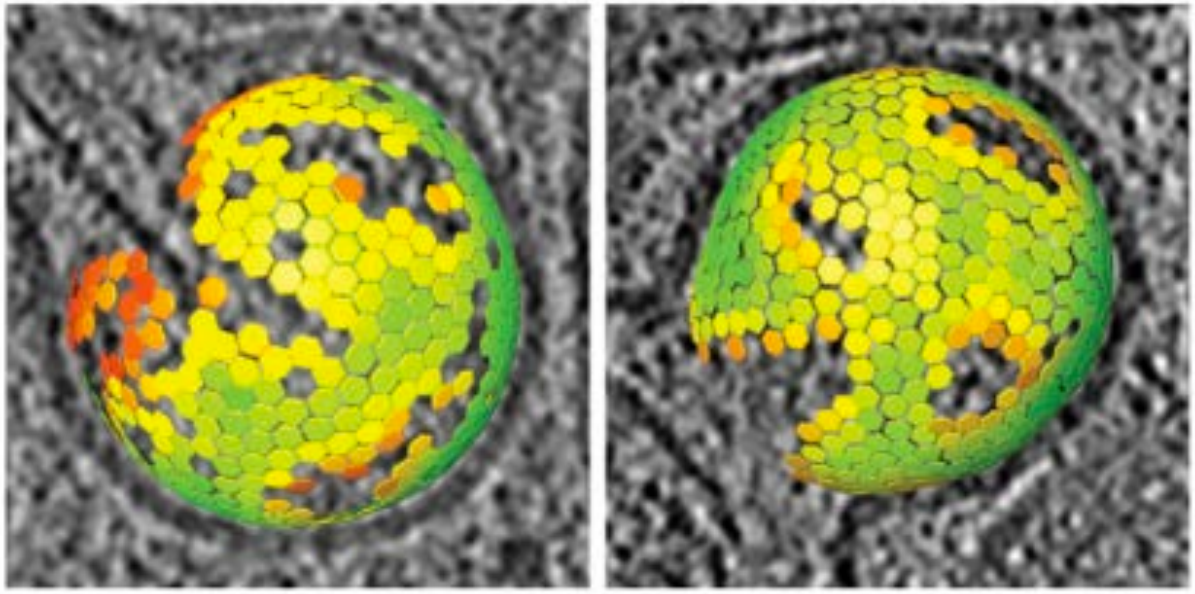
HIV: "immature" lattice, budding



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

HIV: hexameric immature lattice

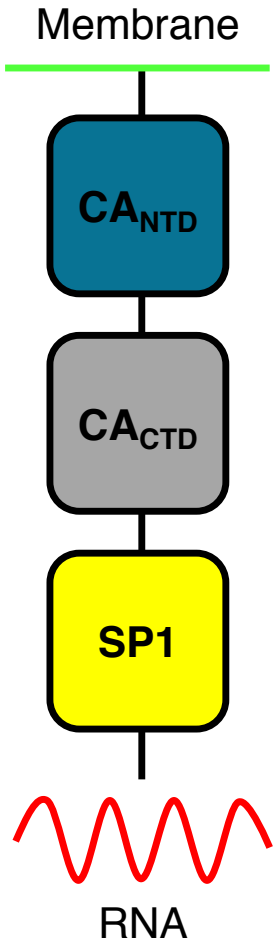


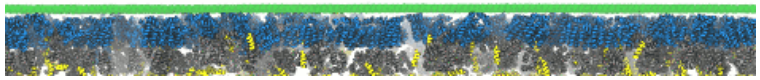
Note: Green (high) to Red (low) indicates hexameric ordering

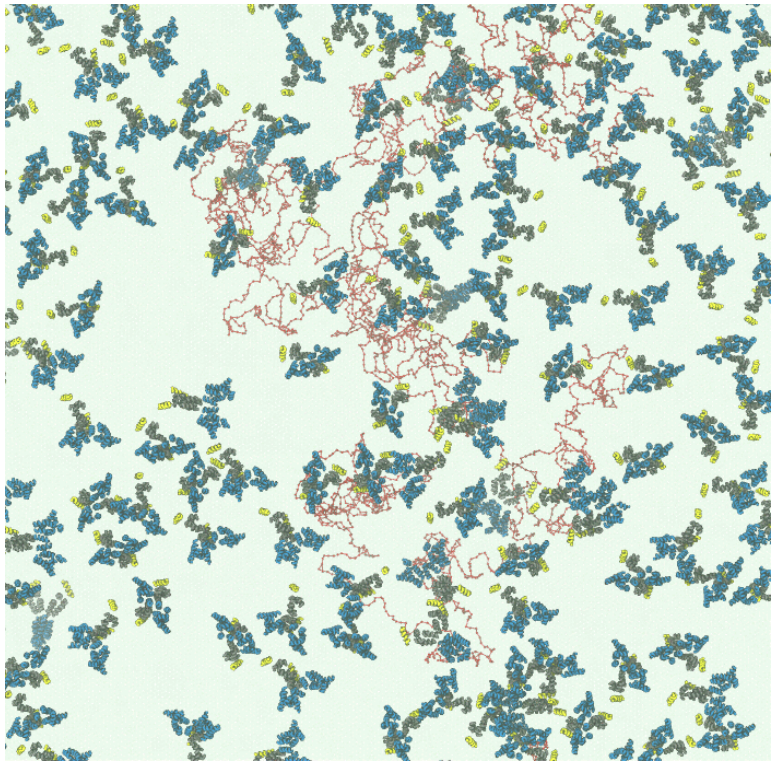
Immature protein lattice: **sub-units are believed to be strictly hexamers** with **curvature accommodated by lattice defects.**

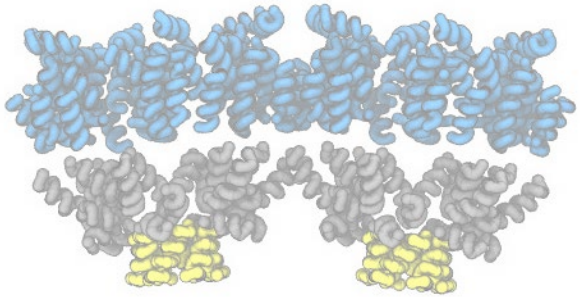
Carlson et al, *PLoS Pathogens* ***6***:1001173 (**2010**)

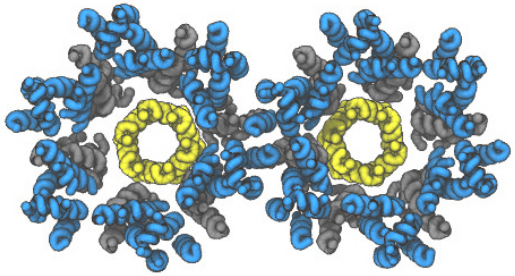
HIV: hexameric immature lattice







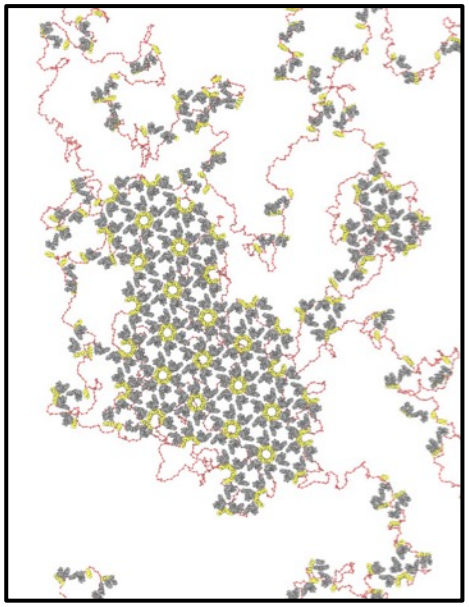




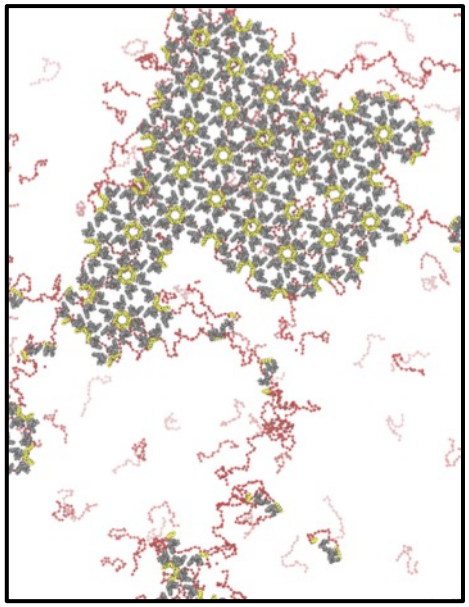
* Pak, **Grime,** et al., in review

HIV: hexameric immature lattice

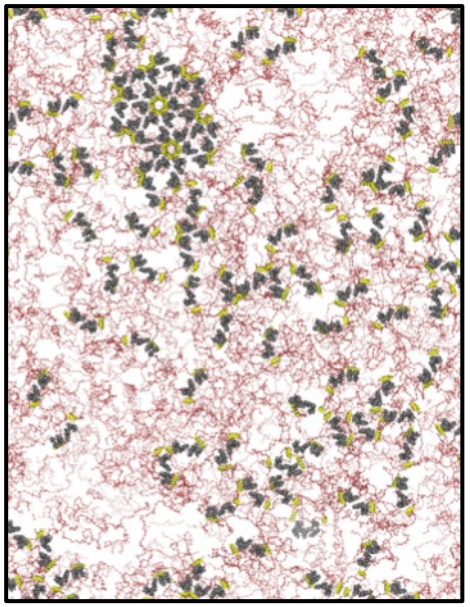
3500-nt RNA



3500-nt RNA +
100x 20-nt miRNA
($\rho_{Gag}/\rho_{miRNA} \approx 3$)



3500-nt RNA +
2000x 20-nt miRNA
($\rho_{Gag}/\rho_{miRNA} \approx 0.1$)



Critical concentrations of miRNA restrict immature lattice assembly

* Pak, **Grime,** et al., in review

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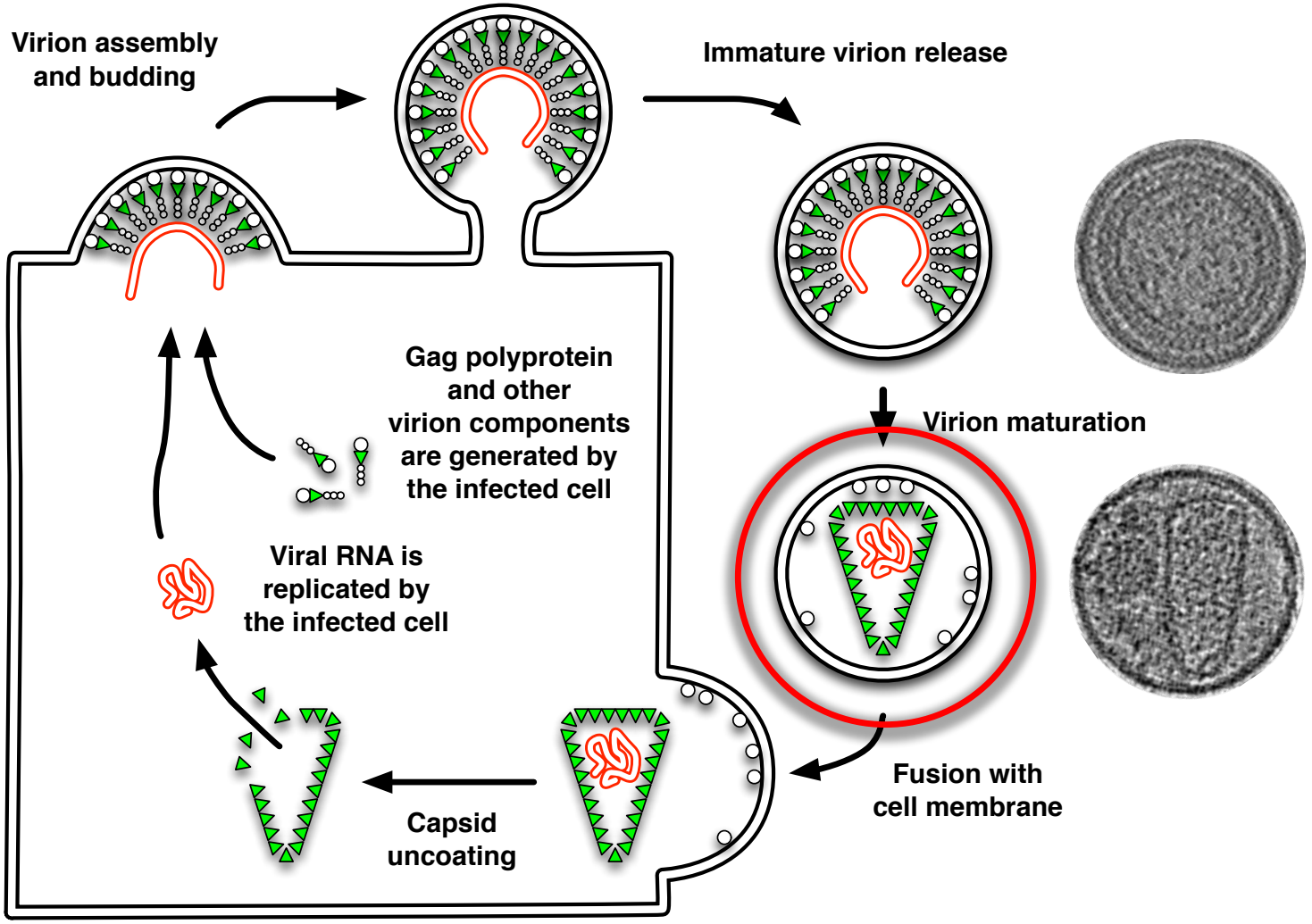
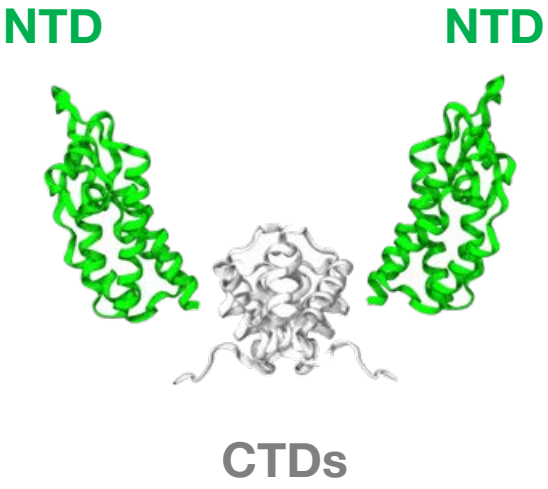
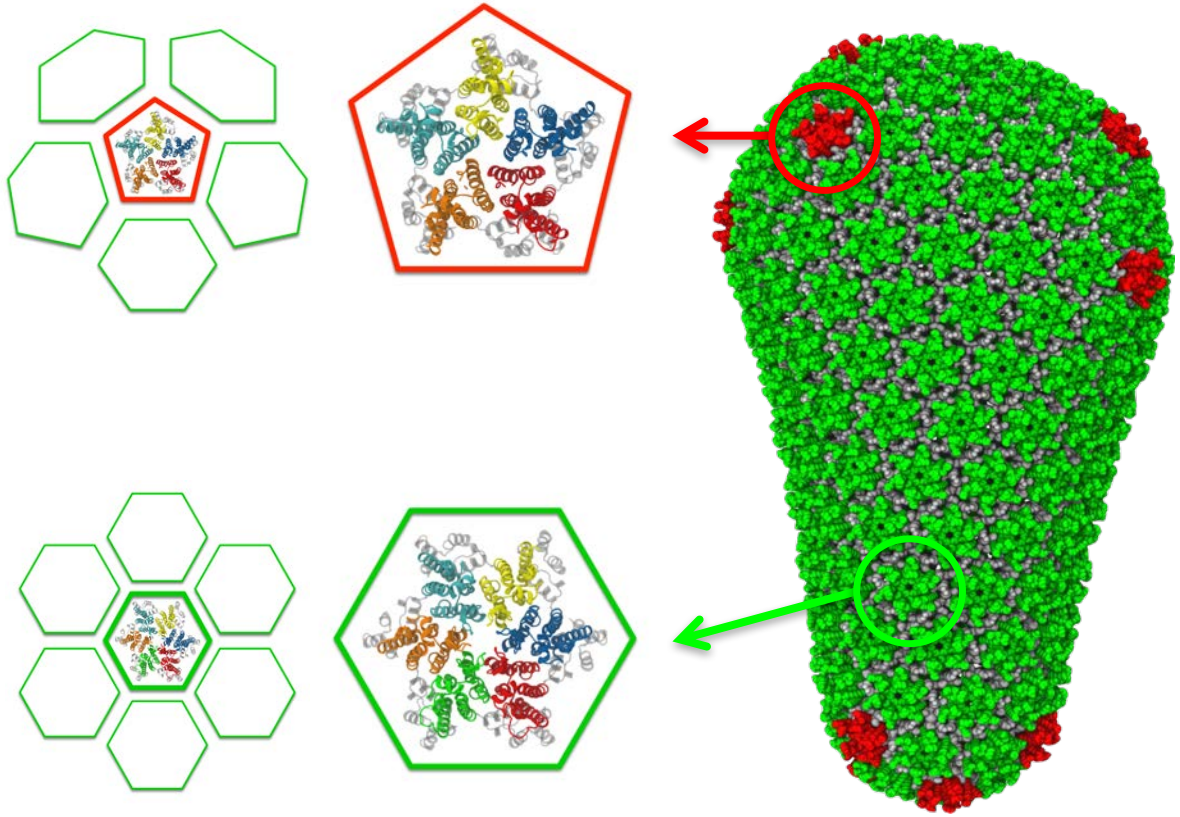
HIV: "mature" capsid lattice



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

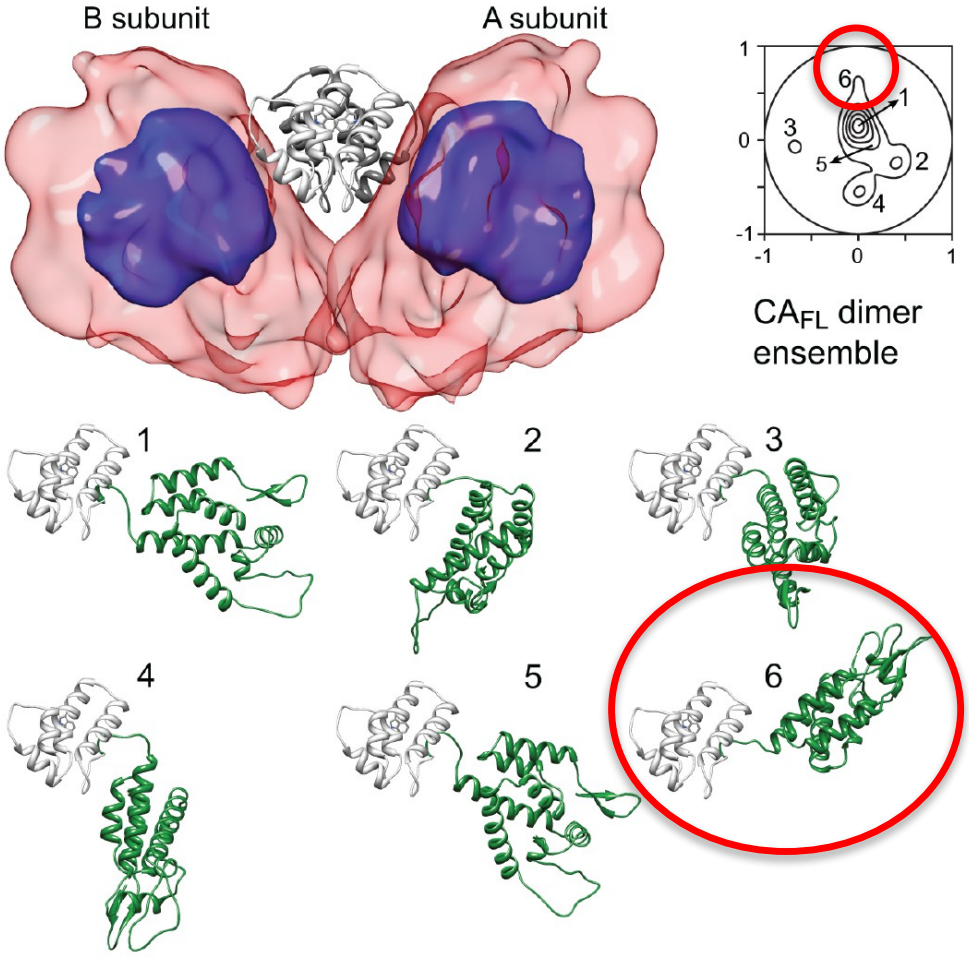
HIV Capsid Protein (CA)





Structure: CA mainly **protein dimers in solution**, can self-assemble into a mature capsid lattice with **quasi-equivalent hexagons and pentagons**

HIV Capsid Protein (CA)

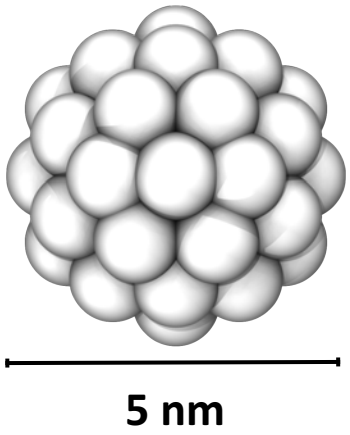


Relatively small amount of CA in "native-style" NTD/CTD conformation in solution (≈ 5%),[1] due to flexible linker region between domains.

Ultra-coarse-grained (UCG) style "switching" model for CA …

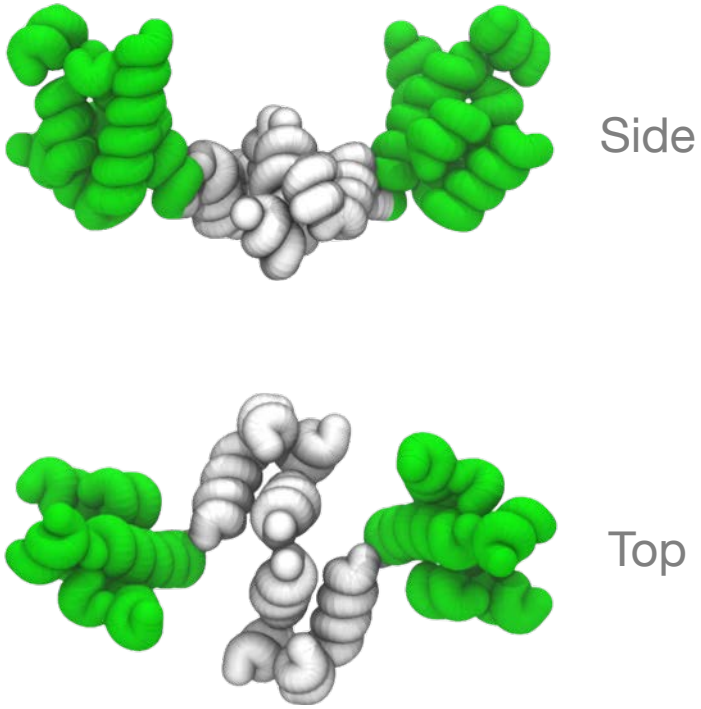
[1] Deshmukh et al, *JACS* **135**:16133-16147 (**2013**)

UCG-MD Style Model of CA*



Inert crowding agent: pure excluded volume. Based on Ficoll-70 [1]

[1] del Alamo et al, *J. Virol.* **79**:14271-14281 (**2005**)



CG capsid protein dimer. Based on experimental structural data [2,3]

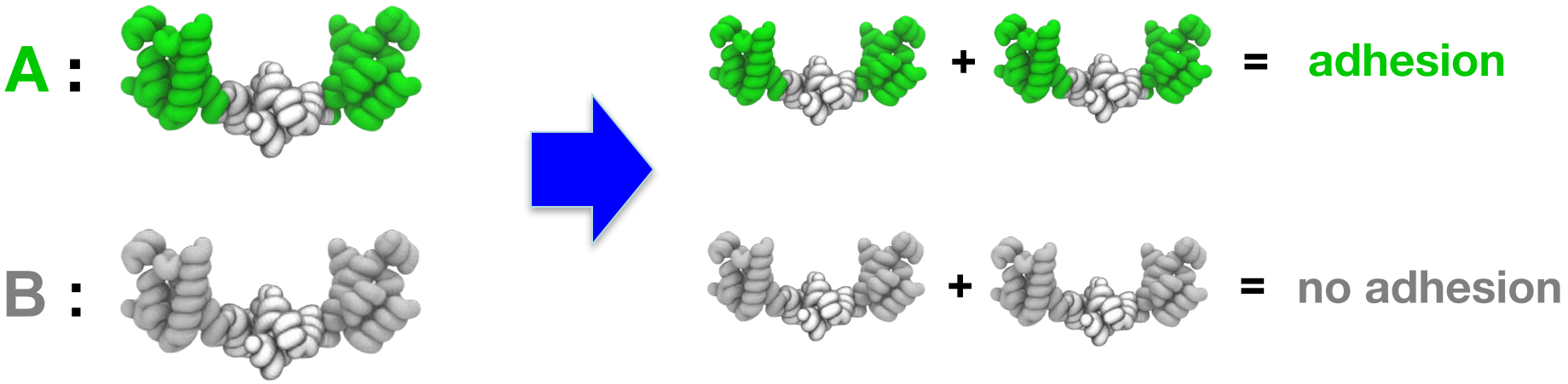
[2] Pornillos et al, *Nature* **469**:424-427 (**2011**)

[3] Byeon et al, *Cell* **139**:780-790 (**2009**)

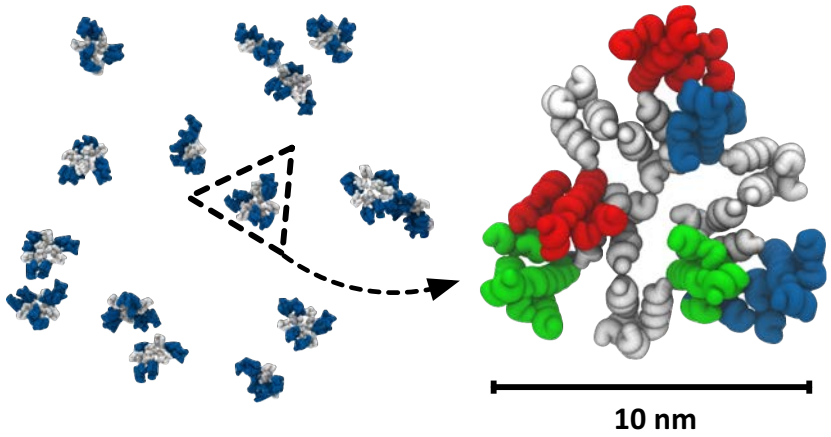
* **Grime**, Dama, Ganser-Pornillos, Woodward, Jensen, Yeager, Voth. *Nature Communications* **7:**1156 (**2016**)

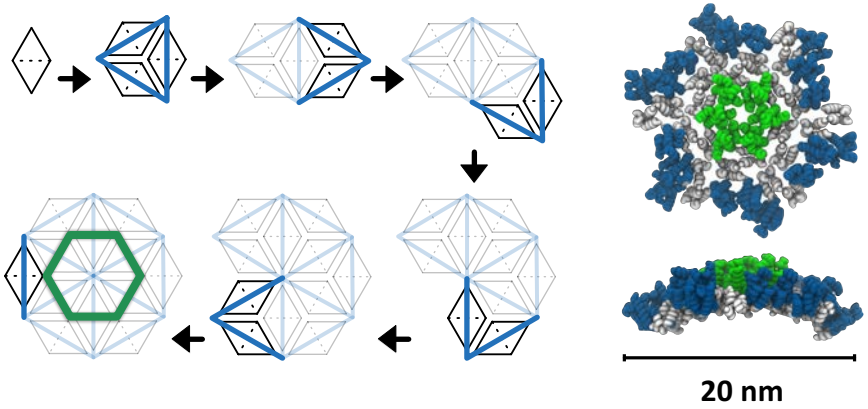
UCG-MD Style Model of CA

Simple two-component system: **A** and **B** protein dimers with identical internal structure but different interactions:

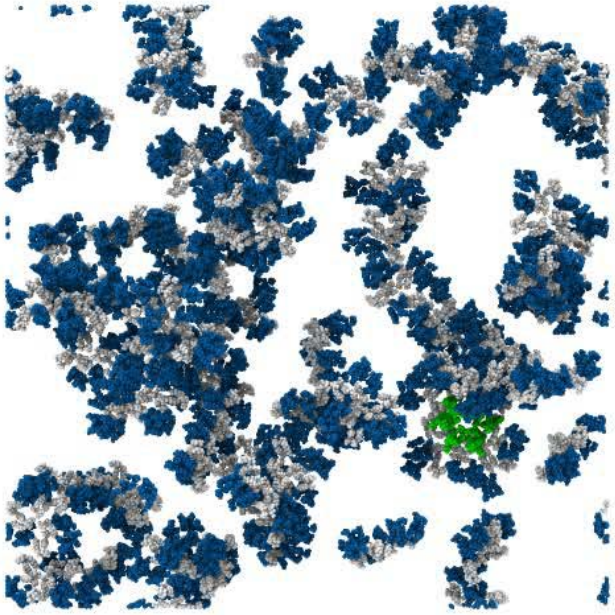


Fixed overall **[CA]** (4mM, 200 mg/mL crowder), *solution-state* proportion **A** stochastically (re)assigned. Examine effects of conformational plasticity on controlled self-assembly …

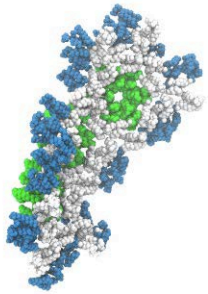




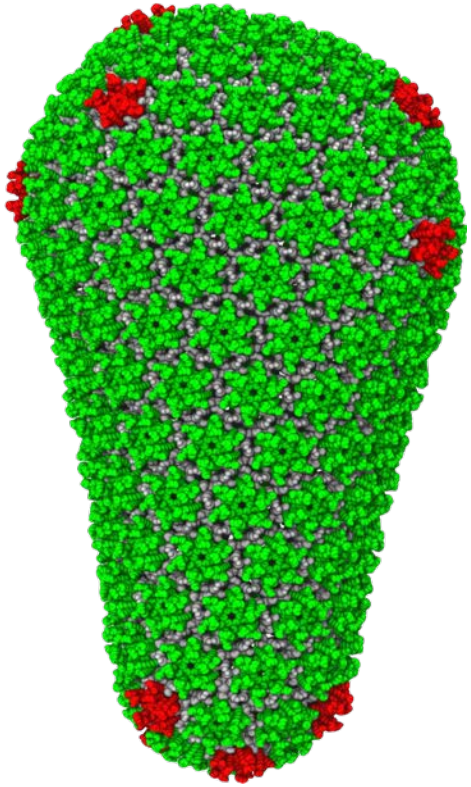
Controlled CA self-assembly via simple UCG-style model



No UCG switching



UCG switching



Acknowledgments

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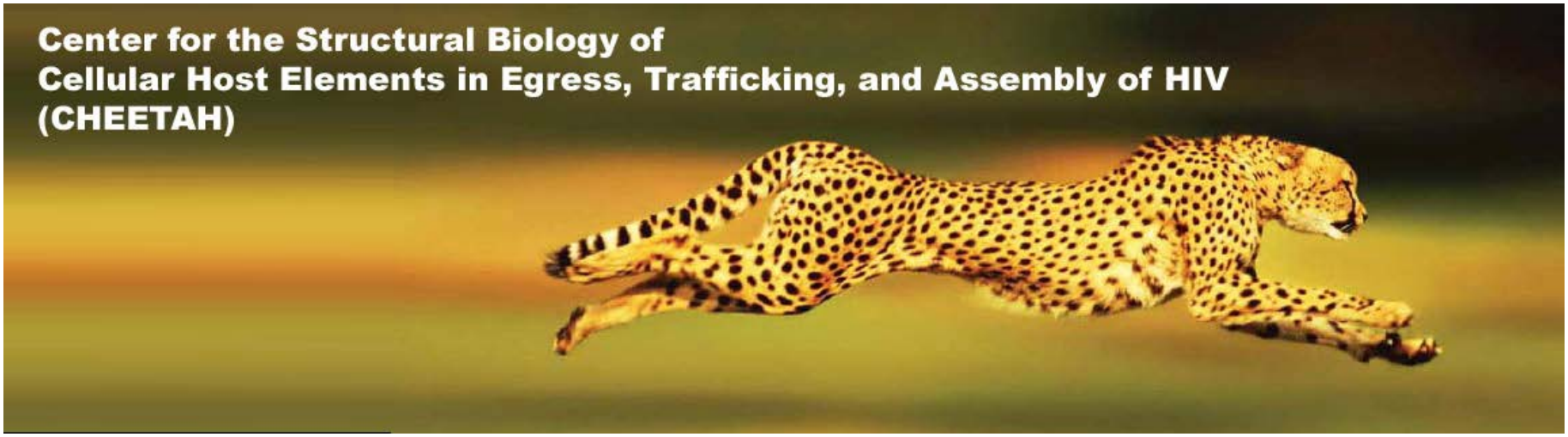
Special thanks to Robert Brunner, our BW PoC!