Viral Morphogenesis Through the Lens of Large-Scale Coarse-Grained Simulations

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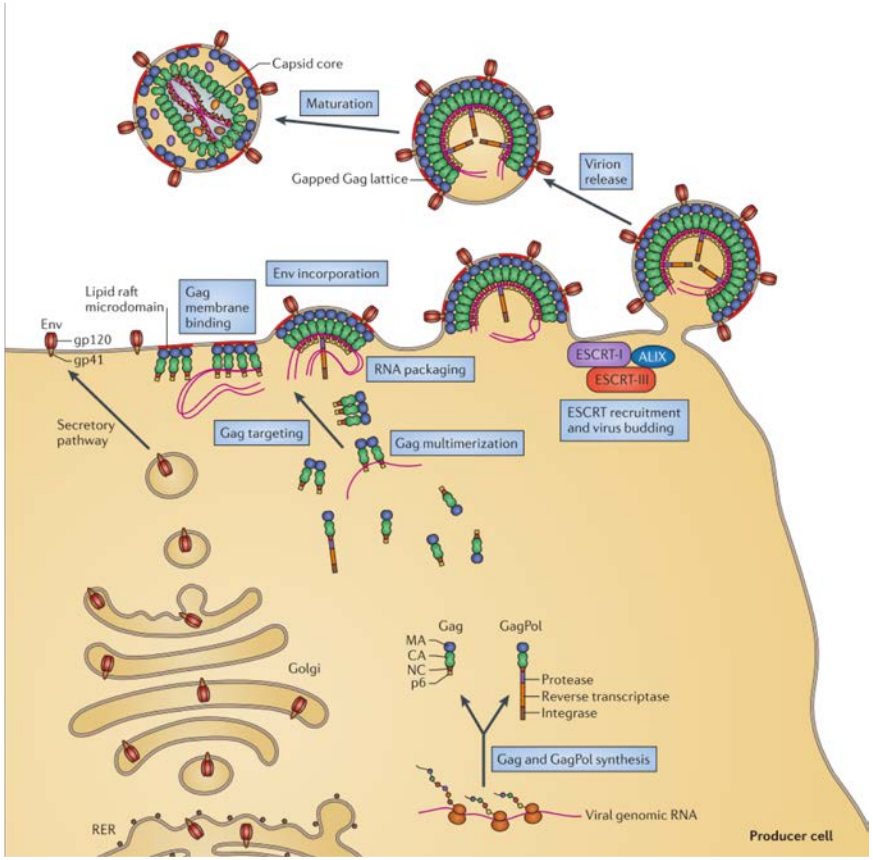
Blue Waters Symposium, June 5th, 2018

Molecular mechanisms that dictate the viral lifecycle are therapeutic targets



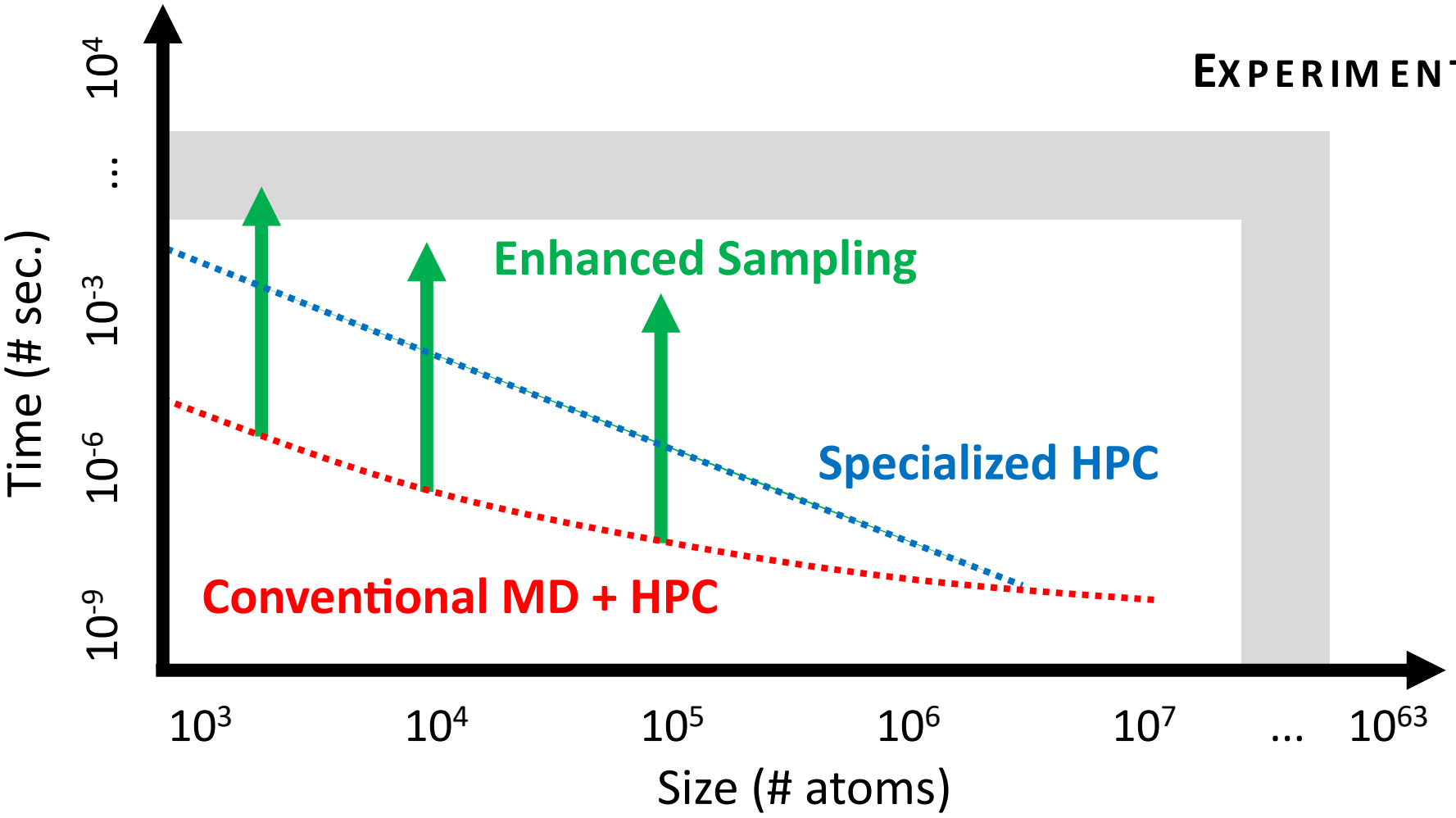
Electron Microscopy
(e.g., cryoEM/cryoET)

Fluorescence Microscopy
(e.g., spt-PALM/STORM)

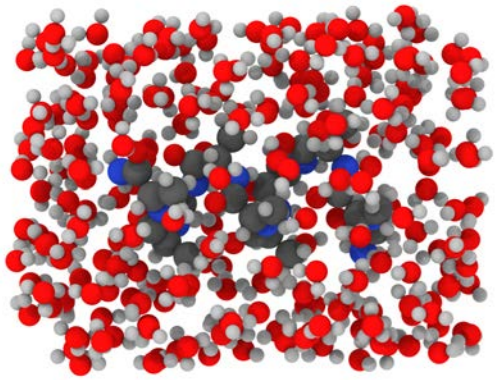
Computer Simulations
(e.g., Molecular Dynamics)

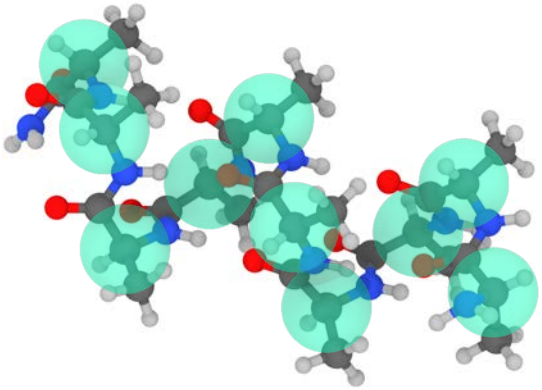
The Goal: Fundamental molecular insights into highly dynamical, out-of-equilibrium biophysical processes

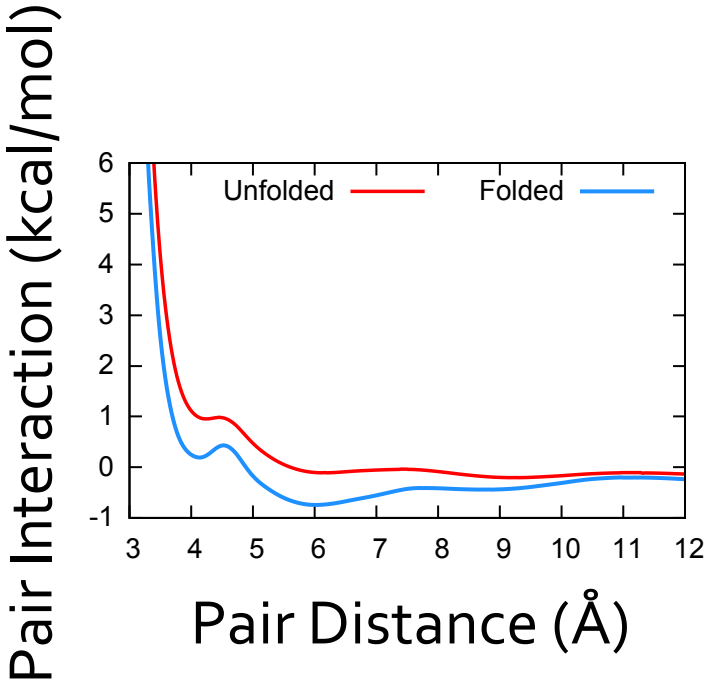
The challenge: Overcoming untenable molecular dynamics simulations



Our approach: Coarse-grained modeling and simulation







MAPPING

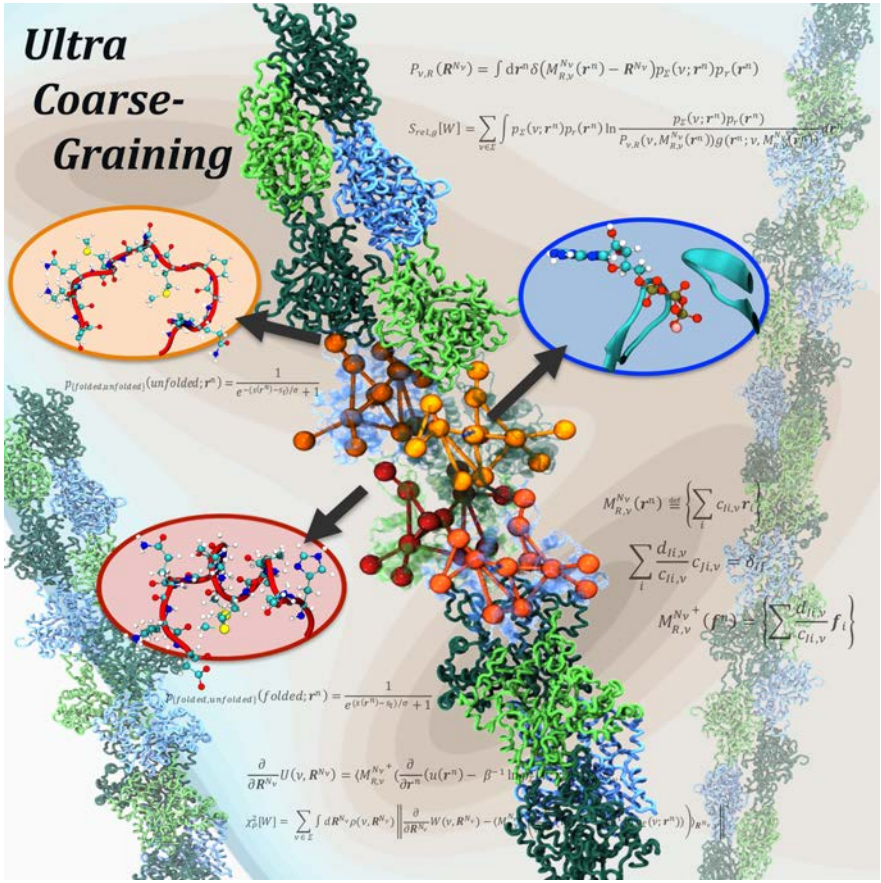
PARAMETERIZATION

A new general framework: ultra-coarse-graining (UCG)

States within UCG "beads"

— physical —
disorder transition
ligand binding
loop folding/unfolding

— chemical —
nucleotide hydrolysis
redox reaction
protonation

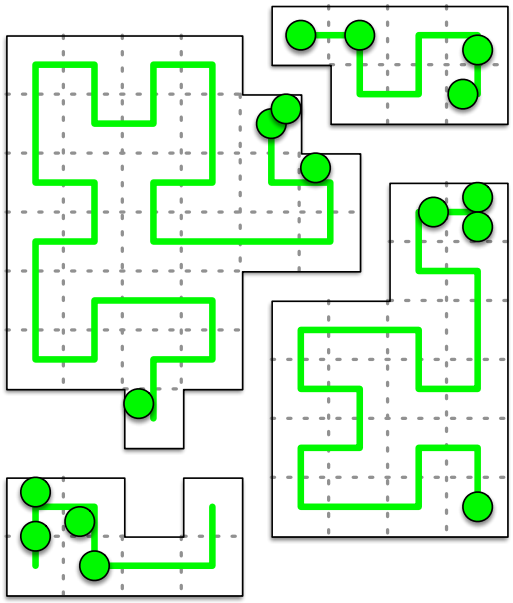


Dama, … and Voth, *JCTC* 9:2466 (2013); Davtyan, ... and Voth, *JCTC* 10:5265 (2014); Dama, … and Voth, *JCTC* 13:1010 (2017).

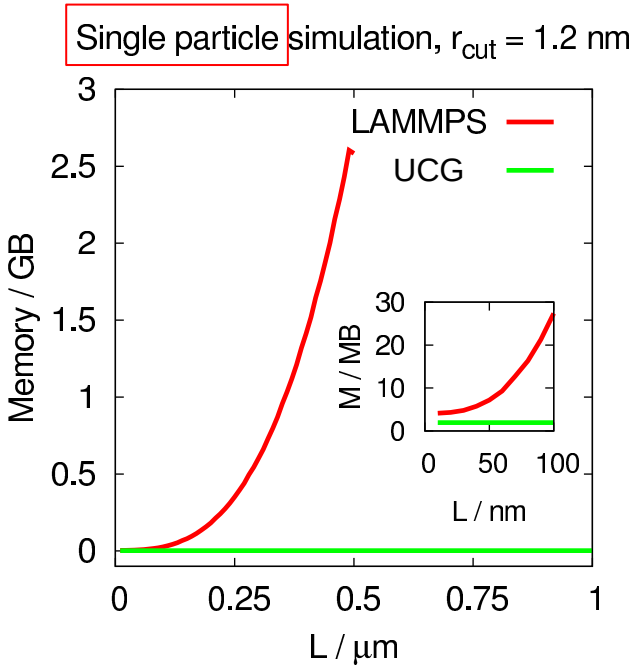
Custom-tailored software on Blue Waters enables UCG-MD simulations

The heterogeneous nature of implicit-solvent UCG models requires MD engine customization:

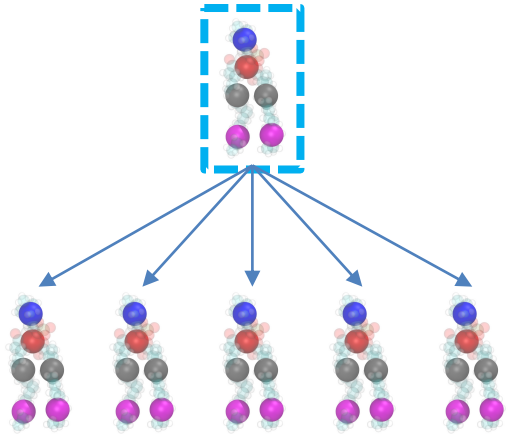
Load Balancing via Hilbert Space Filling Curves



Sparse Data Structures for Efficient Memory Usage

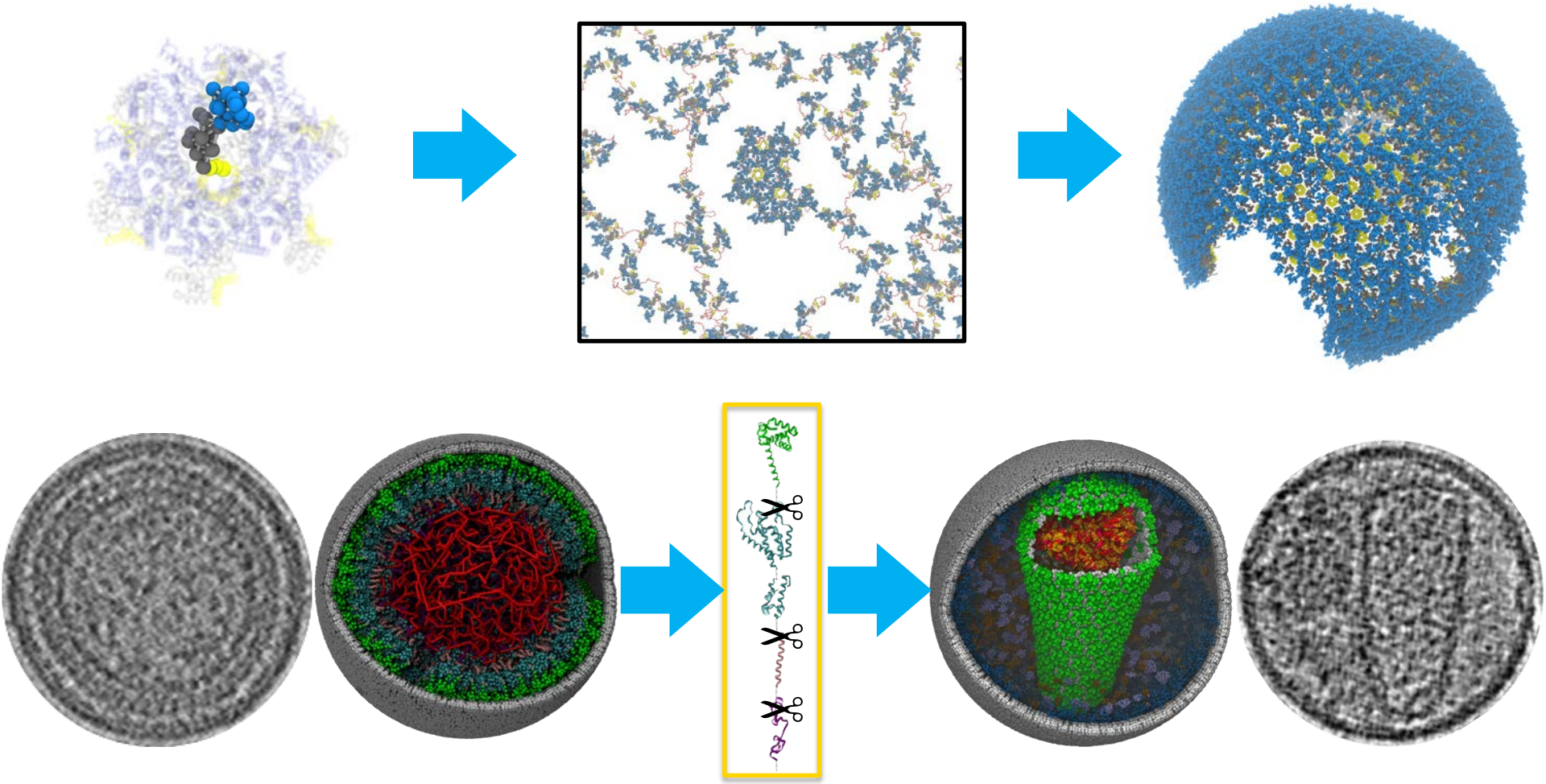


Dynamic Assignment During Runtime



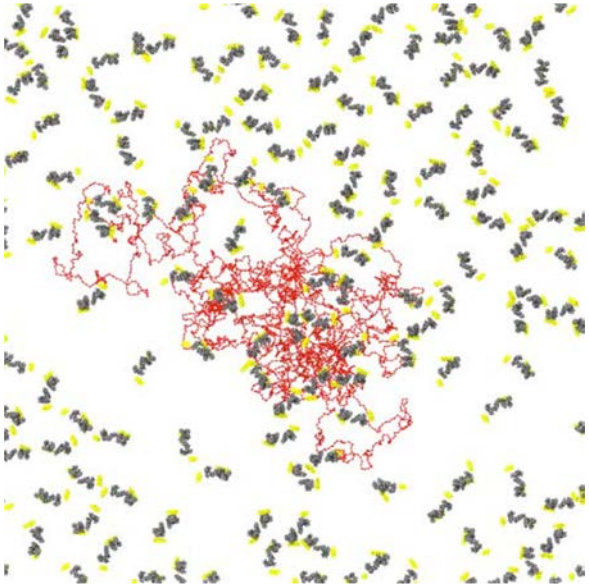
Grime and Voth, *JCTC*, 10:214 (2018)

Our focus: Late-stages of HIV-1

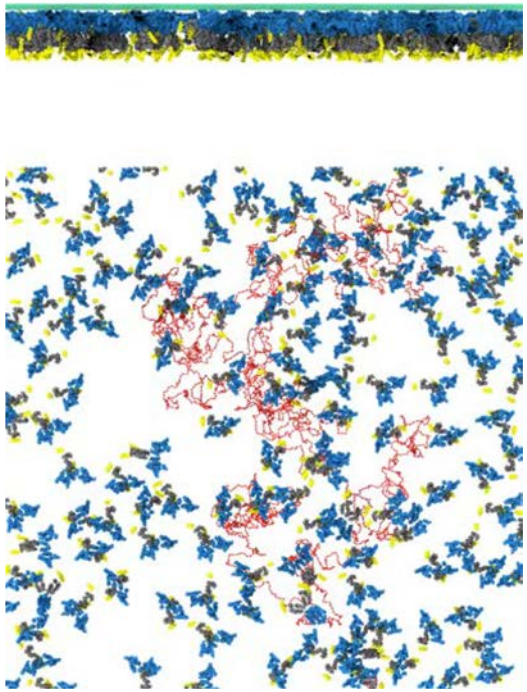


The immature lattice assembly process is catalyzed by scaffolds

RNA co-localizes protein and promotes assembly

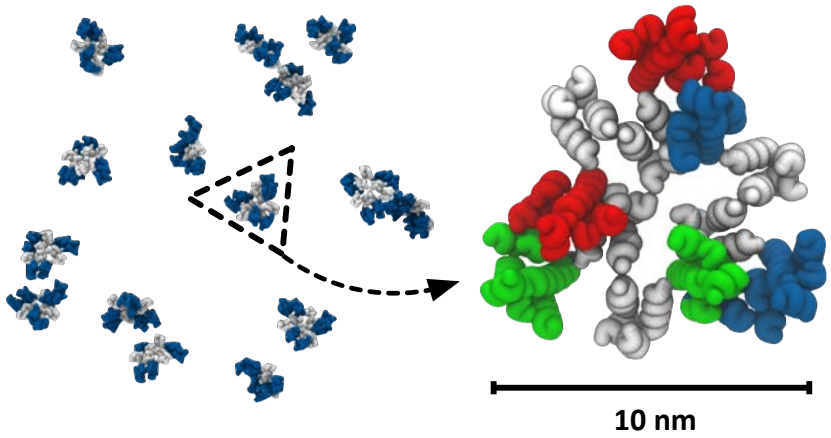


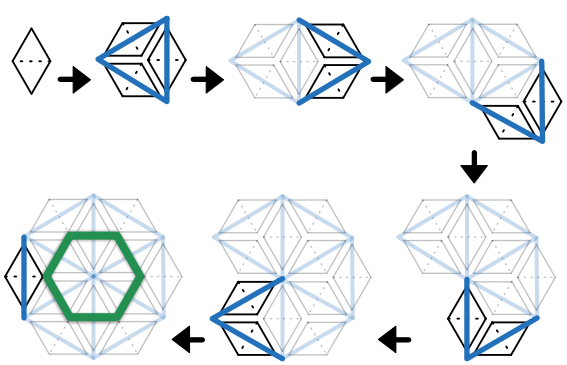
Membrane deformation also serves to co-localize and promote assembly

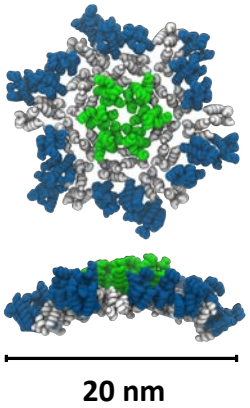


Pak, Grime, … and Voth. *PNAS* 114:E10056 (2017)

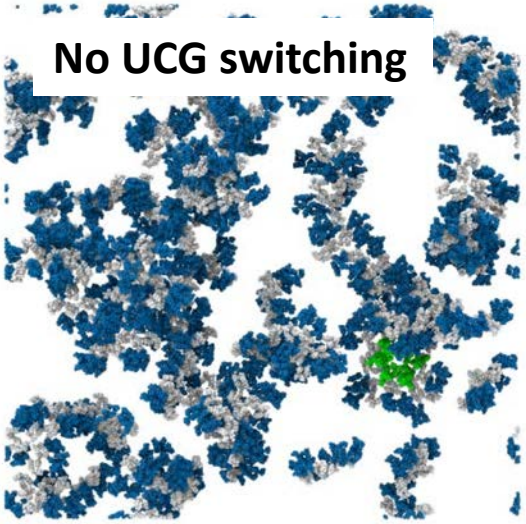
The mature capsid also requires precise conditions for assembly



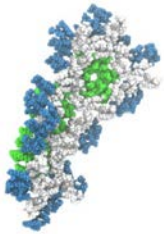


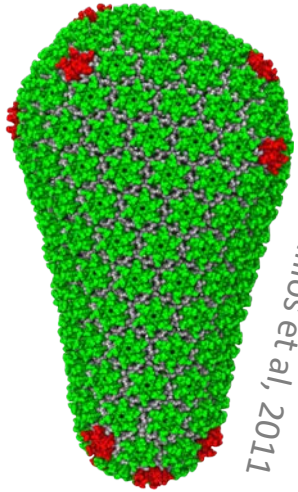


No UCG switching



UCG switching





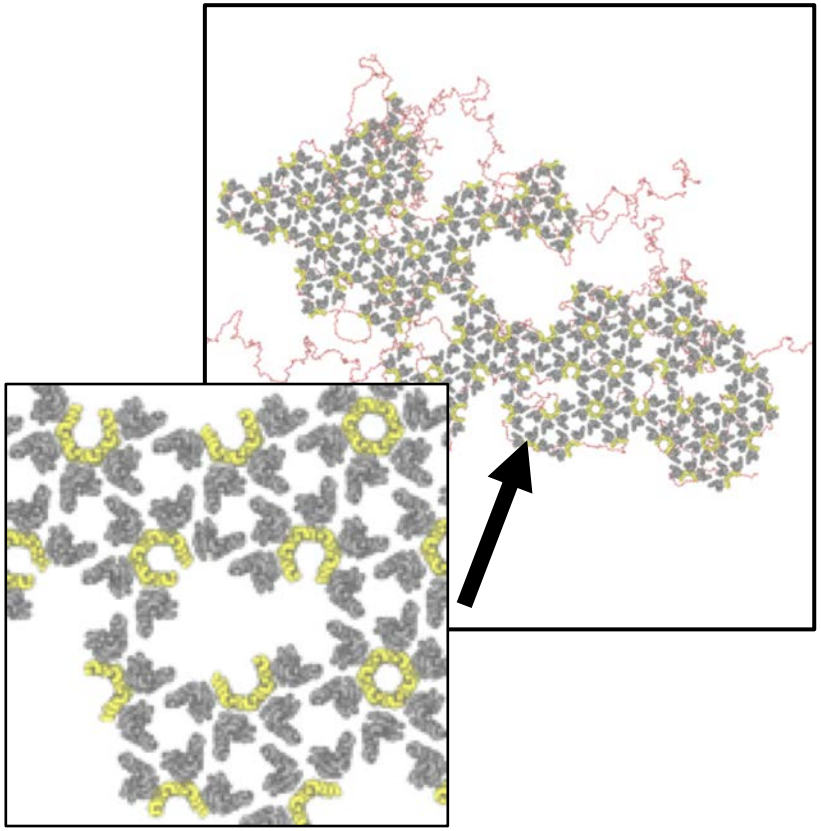
Grime, Dama … and Voth. *Nat. Comm.* 7:11568 (2016)

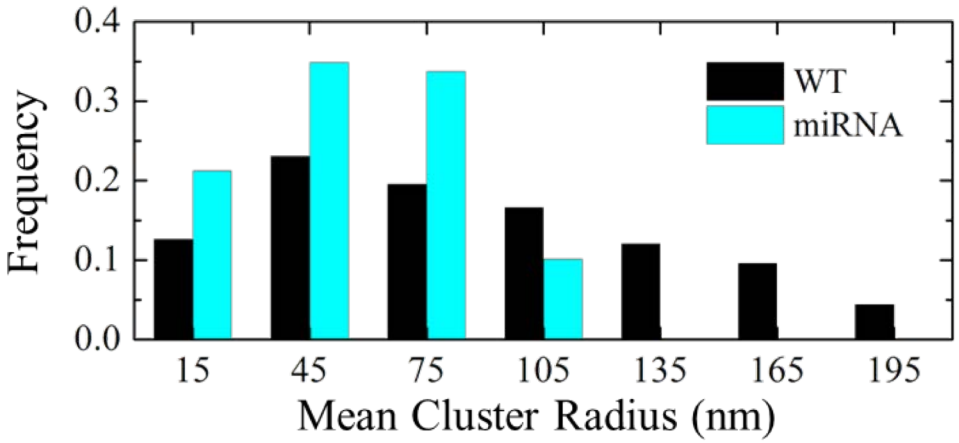
Nature seems to call for a balance between strength (E) and specificity (S)

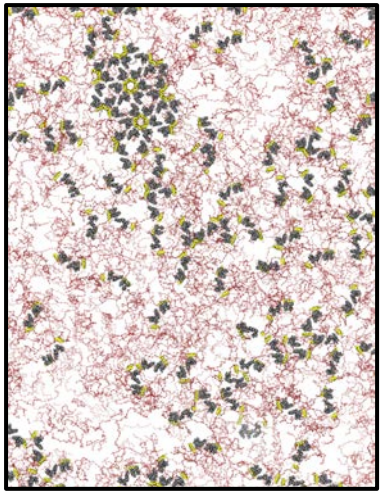
Perturbing this balance may lead to reduced infectivity

(in collaboration with Lippincott-Schwartz (NIH))

Enhancing protein-protein interactions







Pak, Grime, … and Voth. *PNAS* 114:E10056 (2017)

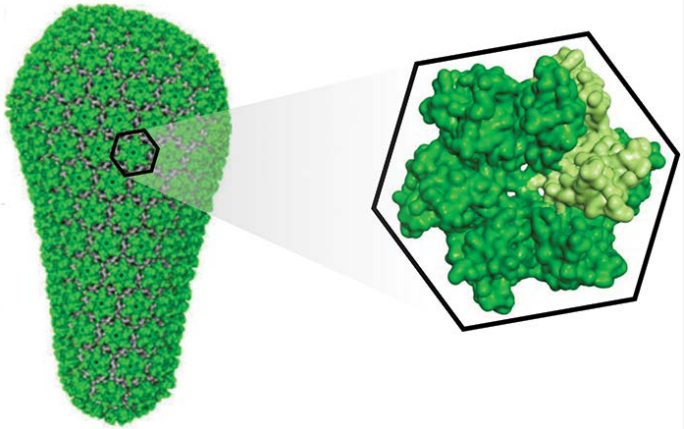
GS-CA1: A new type of HIV drug

Volume 95 Issue 31 | pp. 23-25
Issue Date: July 31, 2017

Conquering HIV's capsid

After a dozen years, researchers have struck upon a molecule that can disrupt an elusive HIV target

By **Lisa M. Jarvis**



The HIV capsid (left) protects the viral genome so it can be delivered into host cells. Gilead's tool compound, GS-CA1 (light green, right), binds between two capsid proteins in the pinwheel-like hexamer.

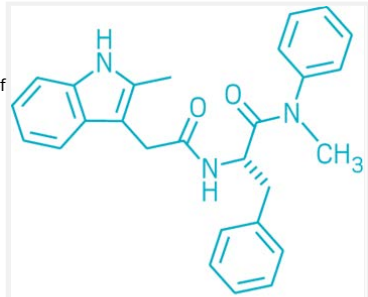
Credit: Gilead Sciences

For most of his career at Gilead Sciences, medicinal chemist Winston Tse has lived and breathed one thing. While his peers at other companies hopped from project to project, Tse has spent the past decade obsessing over a single target: the HIV capsid.

HIV's capsid is a complex, protein-rich shell that protects the genetic payload the virus is

C&EN of 1,500 capsid proteins that organize themselves into hexamers and pentamers to form an eggplant-shaped shell. HIV researchers had no close-ups of the full capsid; a crystal structure had captured only the monomeric protein.

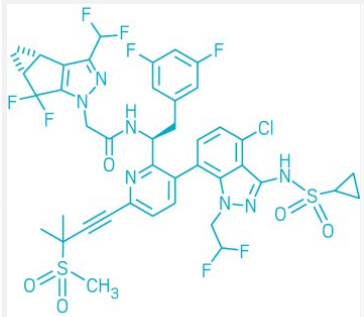
Moreover, scientists weren't—and still aren't—sure how the capsid assembles. Many envision something like a molecular knitting project that begins at the stem end of the eggplant and gets wider as rows of hexamers are added.



Pfizer's PF-3450074

Yet one thing was clear: Those 1,500 proteins need to knit together with just the right geometry and kinetics. "There is a real beauty in how geometrically structured it is," says Tomas Cihlar, vice president of biology at Gilead.

The shell needs to be stable enough to come together during virus maturation but still disassemble to expose its genetic payload once it is inside the host cell. That leads to a "delicate equilibrium in the whole capsid shell, which we thought could really be its Achilles' heel," Cihlar, who conceived of the capsid program back in 2006, adds.



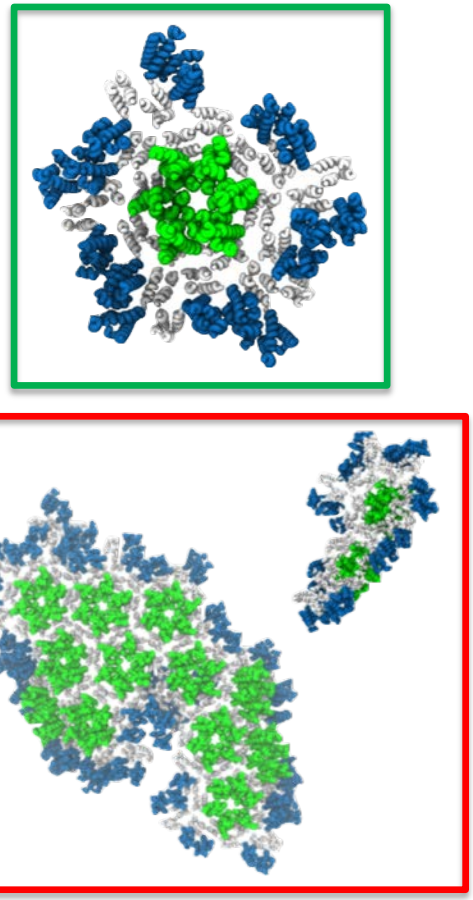
Gilead's GS-CA1

In addition to having limited structural information about the shell, Gilead researchers knew of no molecules that could convincingly bind to the capsid protein. The only clues in the literature were "some really

Simulating GS-CA1 effects induces assembly

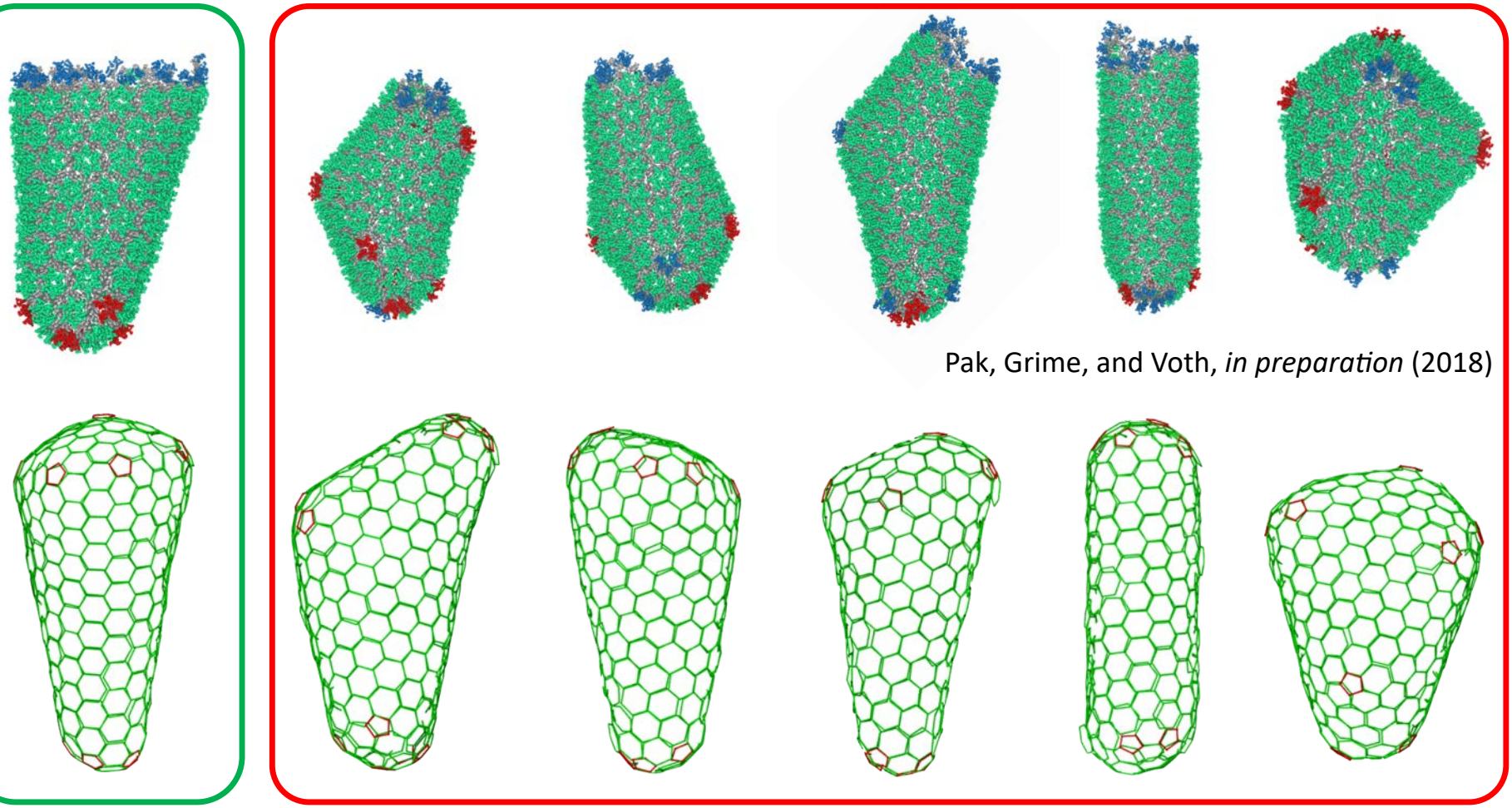
(notably, under conditions that **do not produce self-assembly)**

Initial "stabilized" CA	Result
≈ 0.5%	No effect
≈ 1.0%	No effect
≈ 1.5%	No effect
≈ 2.5%	No effect
≈ 5.0%	**Single nucleation**
≈ 10.0%	**Multiple nucleation**



Self-assembly process appears sensitive to even small localized "boosts"

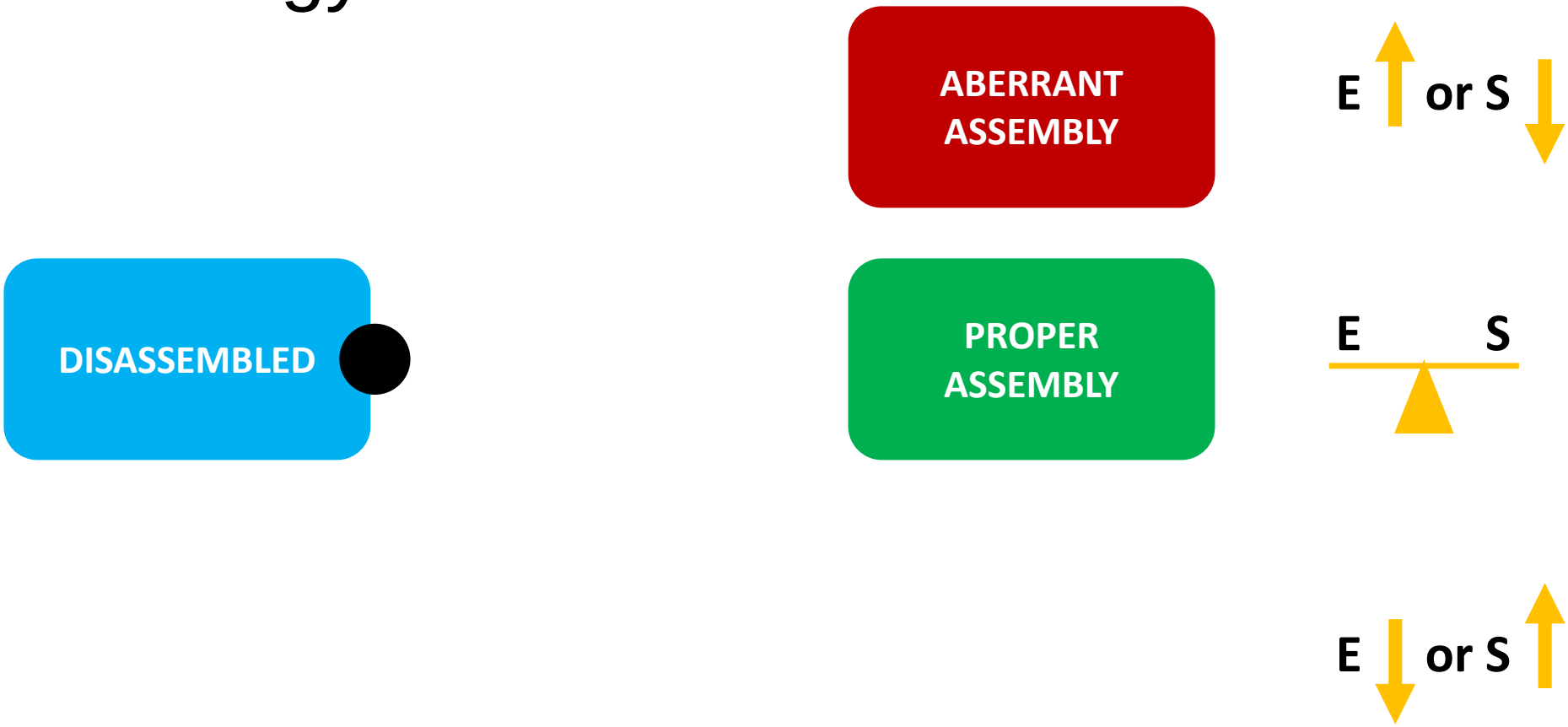
Enhanced morphological diversity with defective end-points



Pak, Grime, and Voth, *in preparation* (2018)

Mattei, Glass, Hagen, Krausslich, and Briggs, *Science* 354:6318 (2016)

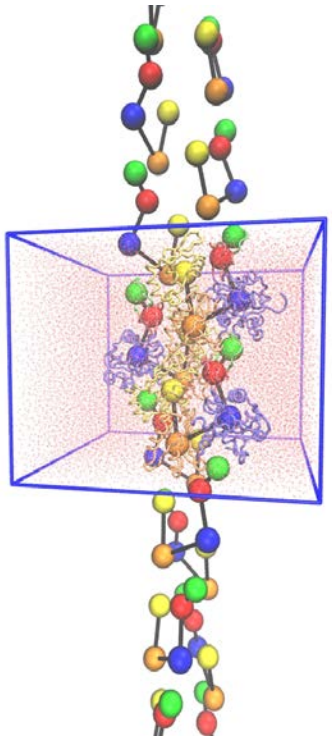
Increasing strength (E) or decreasing specificity (S) is a viable therapeutic strategy



Future direction: Coarse-grained directed simulations (CGDS)

Full system with 3N+3M atoms has coordinates $\vec{r} = (\vec{q}_1, \vec{q}_2)$, subsystem has coordinates has coordinates $\vec{q}_1$. Integrate out $\vec{q}_2$ leaving PMF acting on subsystem:

$$F(\vec{X}) = -k_B T \ln\left(\frac{\int d\vec{q}_1 d\vec{q}_2 \delta(\vec{q}_1 - \vec{X}) e^{-\beta U(\vec{r})}}{\int d\vec{r}\ e^{-\beta U(\vec{r})}}\right)$$



Then the average value of any observable f of the subsystem coordinates ($f(\vec{r}) \equiv f(\vec{q}_1)$) can be recovered just simulating the subsystem:

$$\langle f \rangle = \frac{\int d\vec{r}\, f(\vec{r}) e^{-\beta U(\vec{r})}}{\int d\vec{r}\, e^{-\beta U(\vec{r})}} = \frac{\int d\vec{X}\ f(\vec{X}) e^{-\beta F(\vec{X})}}{\int d\vec{X} e^{-\beta F(\vec{X})}}$$

Practical alternative!

$$\Rightarrow P(X) = \frac{e^{-\beta(H(X)+H'(X))}}{\int dX e^{-\beta(H(X)+H'(x))}} \quad \boxed{H'(x) = \lambda f(x)}$$

PLUMED

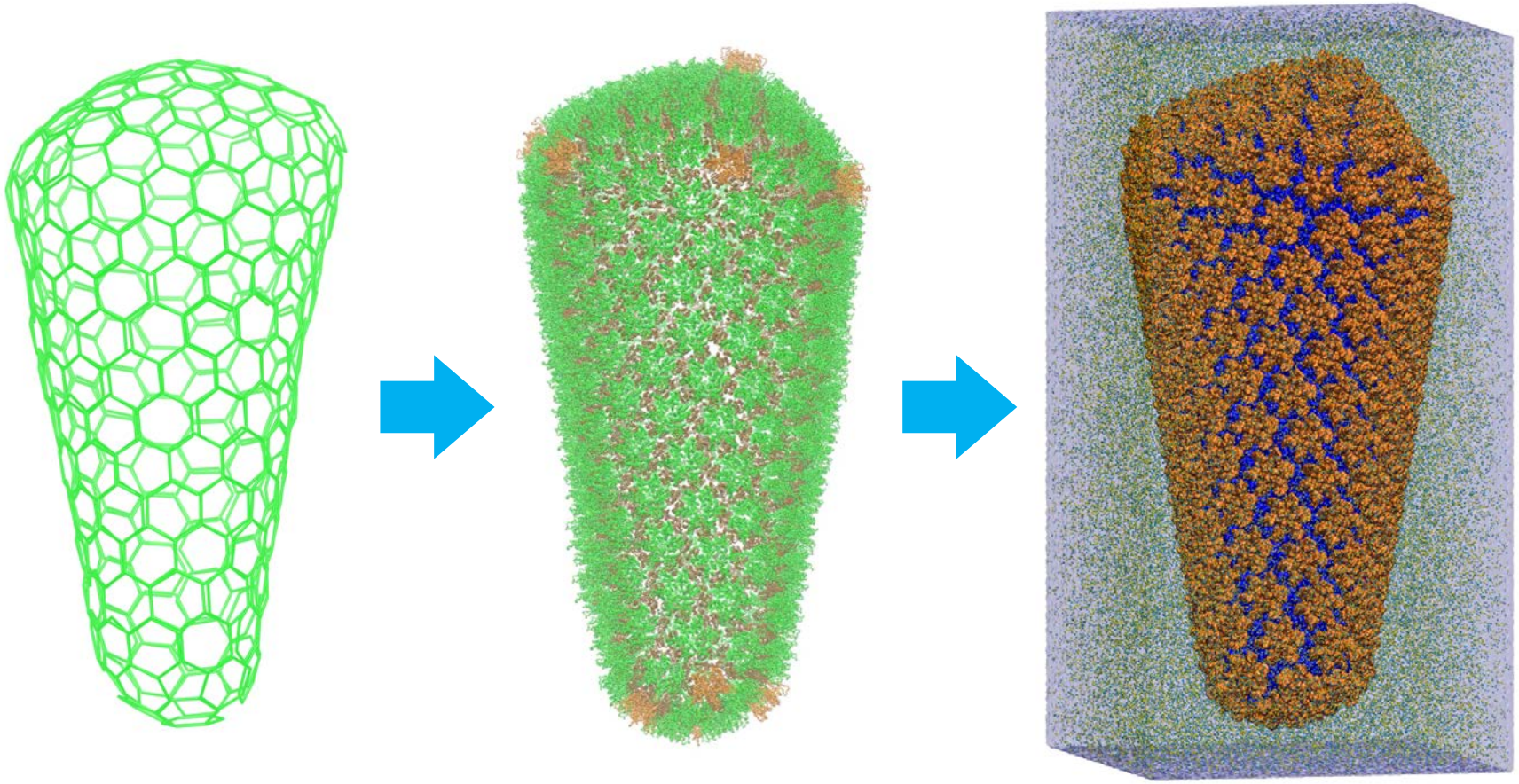
Hocky, Dannenhoffer-Lafage, and Voth, *JCTC* 18:4593 (2017)

Toward a high-throughput multi-scale workflow

cryoET (e.g., Briggs Group)

CG MD

AA MD



~220 capsomers

~300K particles

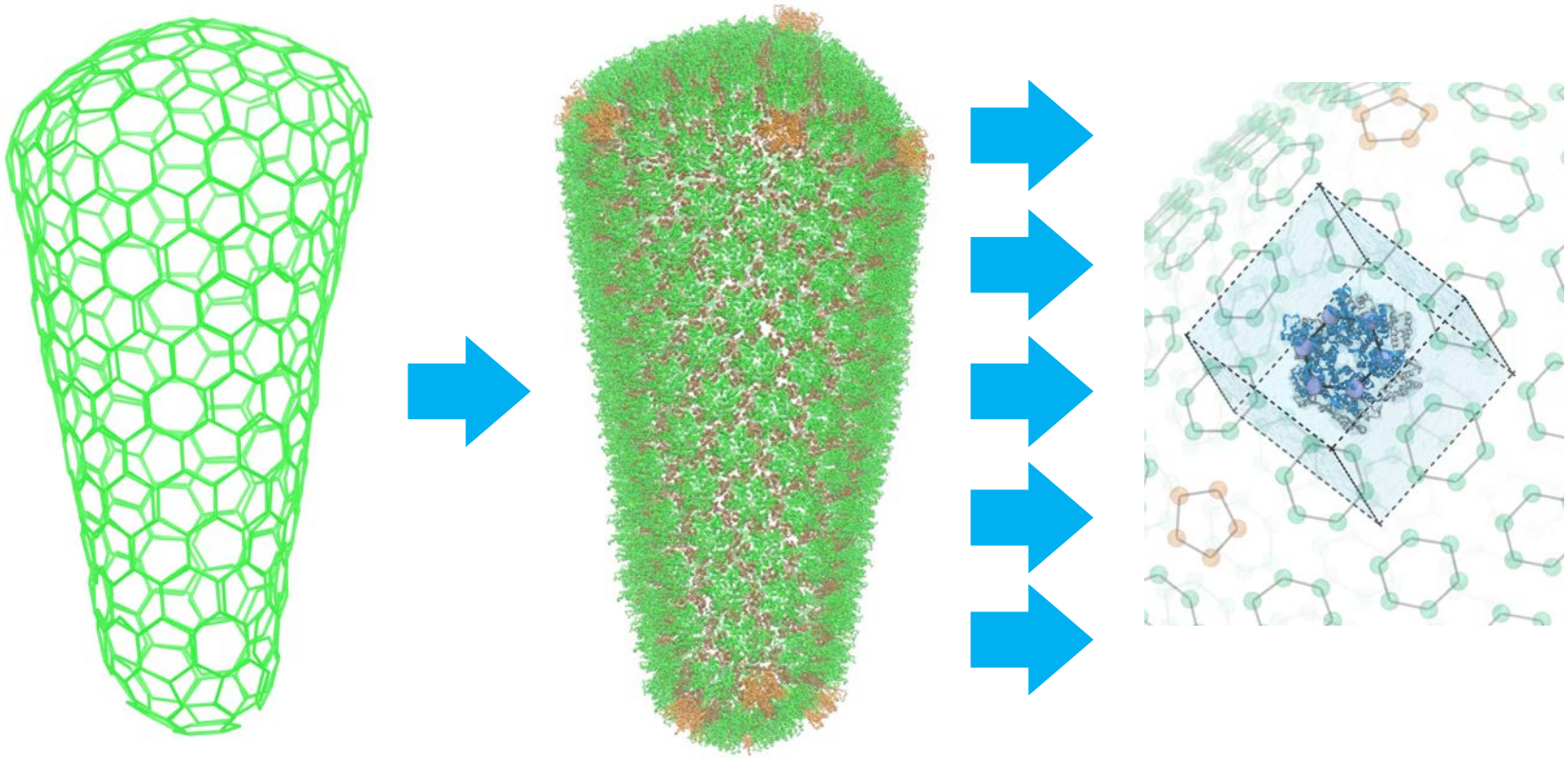
~75M atoms

Toward a high-throughput multi-scale workflow

cryoET (e.g., Briggs Group)

CG MD

CGDS (AA MD)



~220 capsomers

~300K particles

~250-750K atoms

Thank you for your attention!

University of Chicago
Voth Group

University of Virginia
Mark Yeager
Barbie Ganser-Pornillos

NIH
Jennifer Lippincott-Schwartz

MRC-LMB
John Briggs