

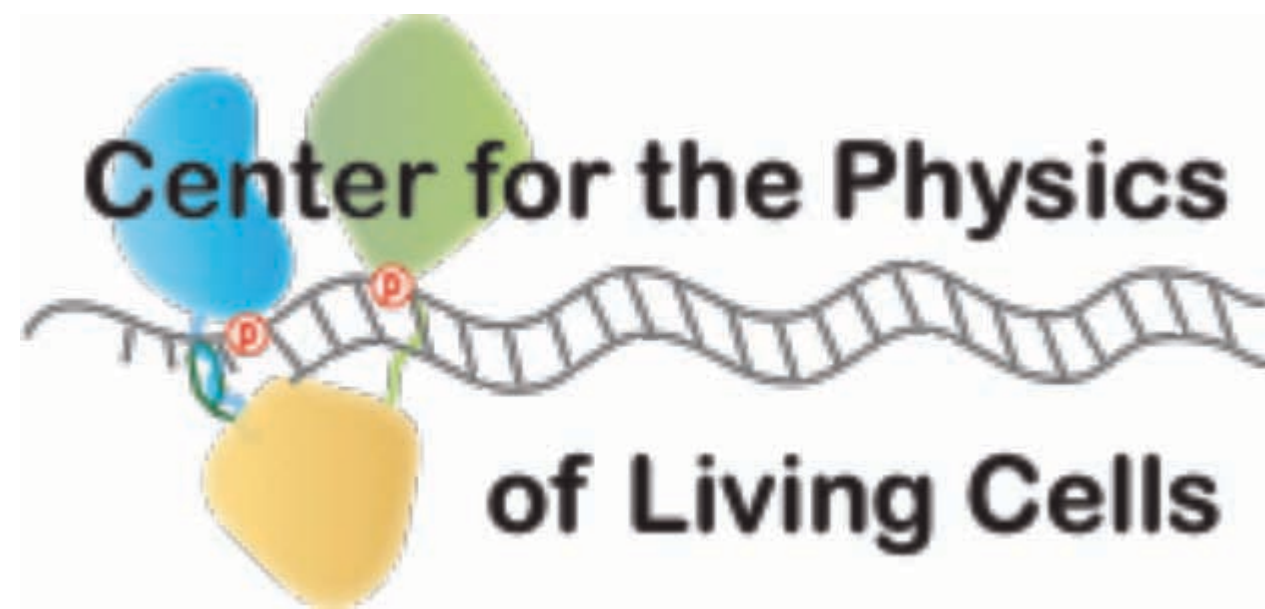
Exploring Nanoscale Frontiers with Frontera

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Department of Physics

University of Illinois at Urbana-Champaign

Frontera allocation: MCB20012



PHY-1430124
DMR-1827346



R01-GM137015
P41-GM104601



University of Illinois, Urbana-Champaign, USA

University College, London, UK

University of Cambridge, UK

TU Munich, Germany

TU Delft, Netherlands

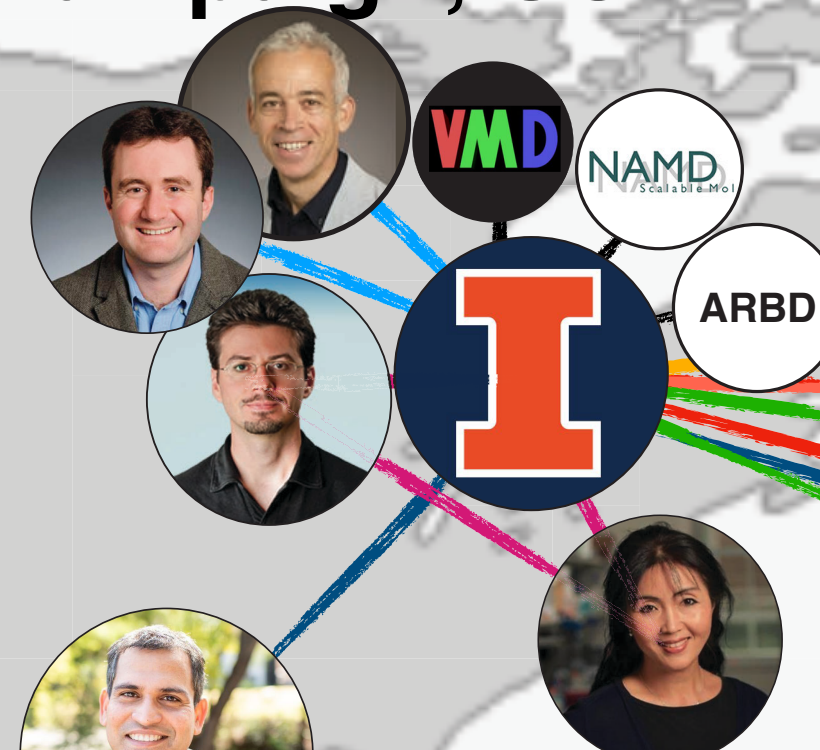
UT Austin, USA

Johns Hopkins University, Maryland, USA

University of Manchester, UK

IISc Bangalore, India

A*STAR, Singapore



Artificial water channels (NSF DMR)

Human Frontier Science Program (Viral Fusion)

Frontier DNA in the 2D world (NSF)

Center for Physics of Living Cells (NSF)

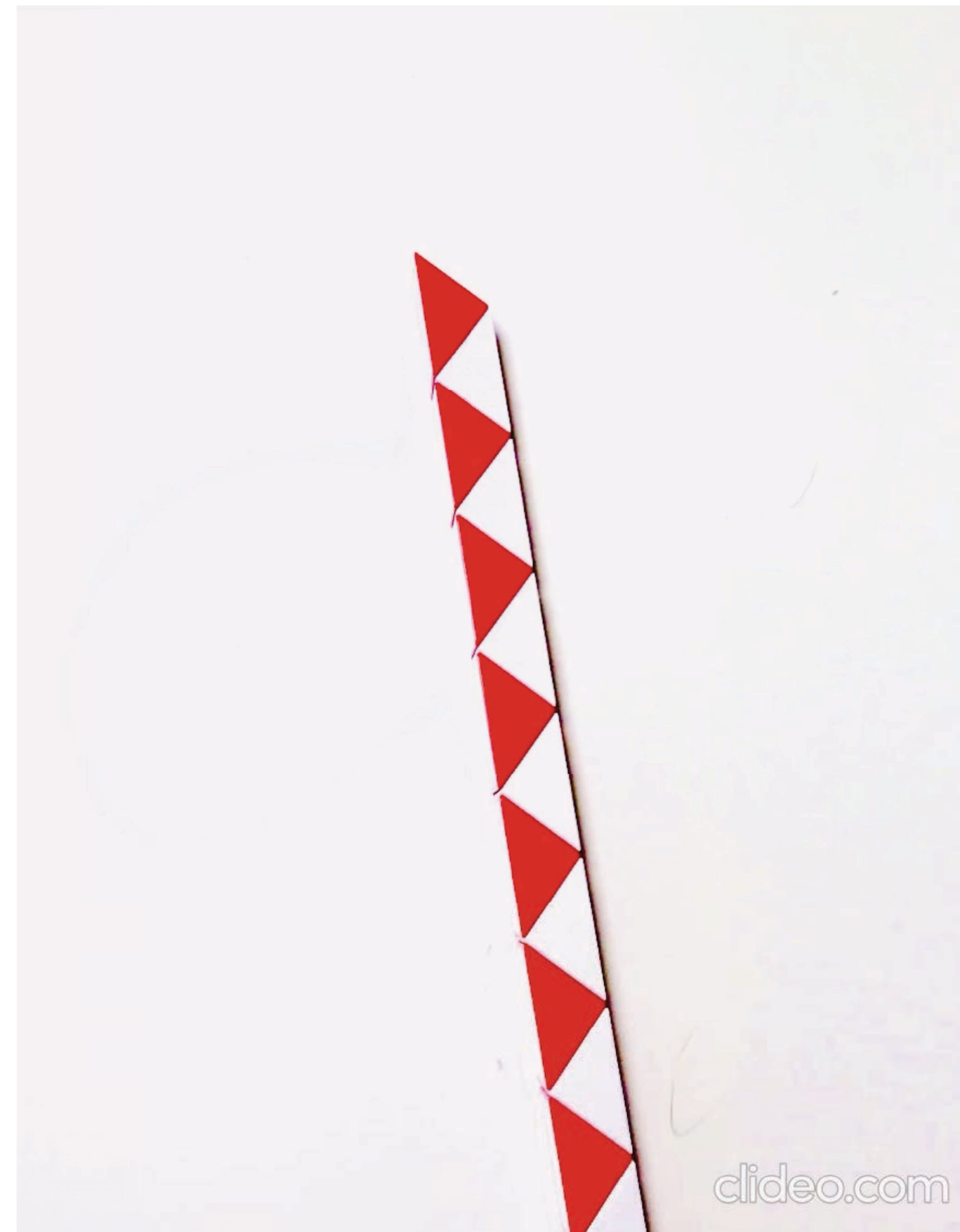
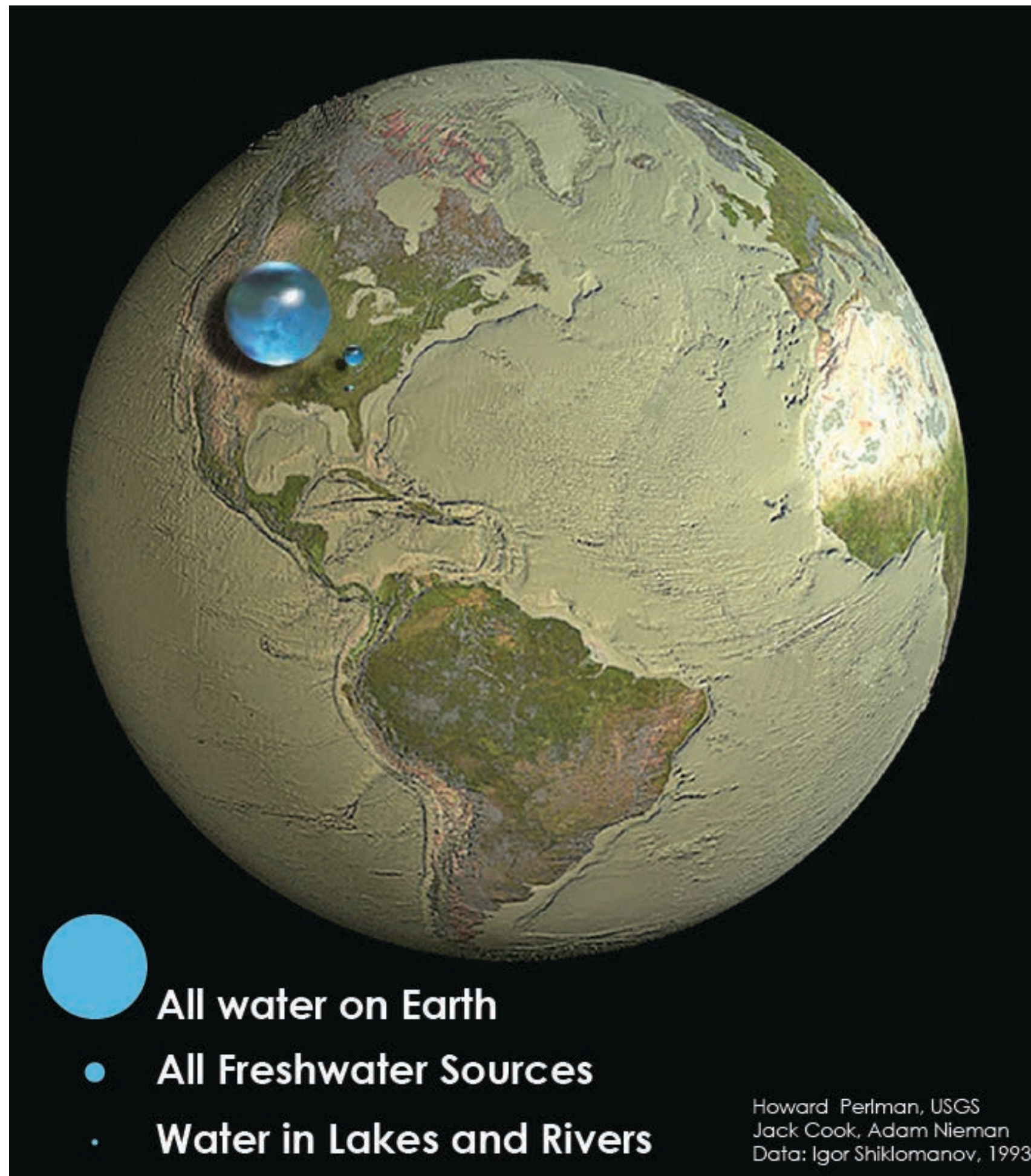
Viral genomes/ NPC (NIH R01)

DNA Nano Systems (NSF)

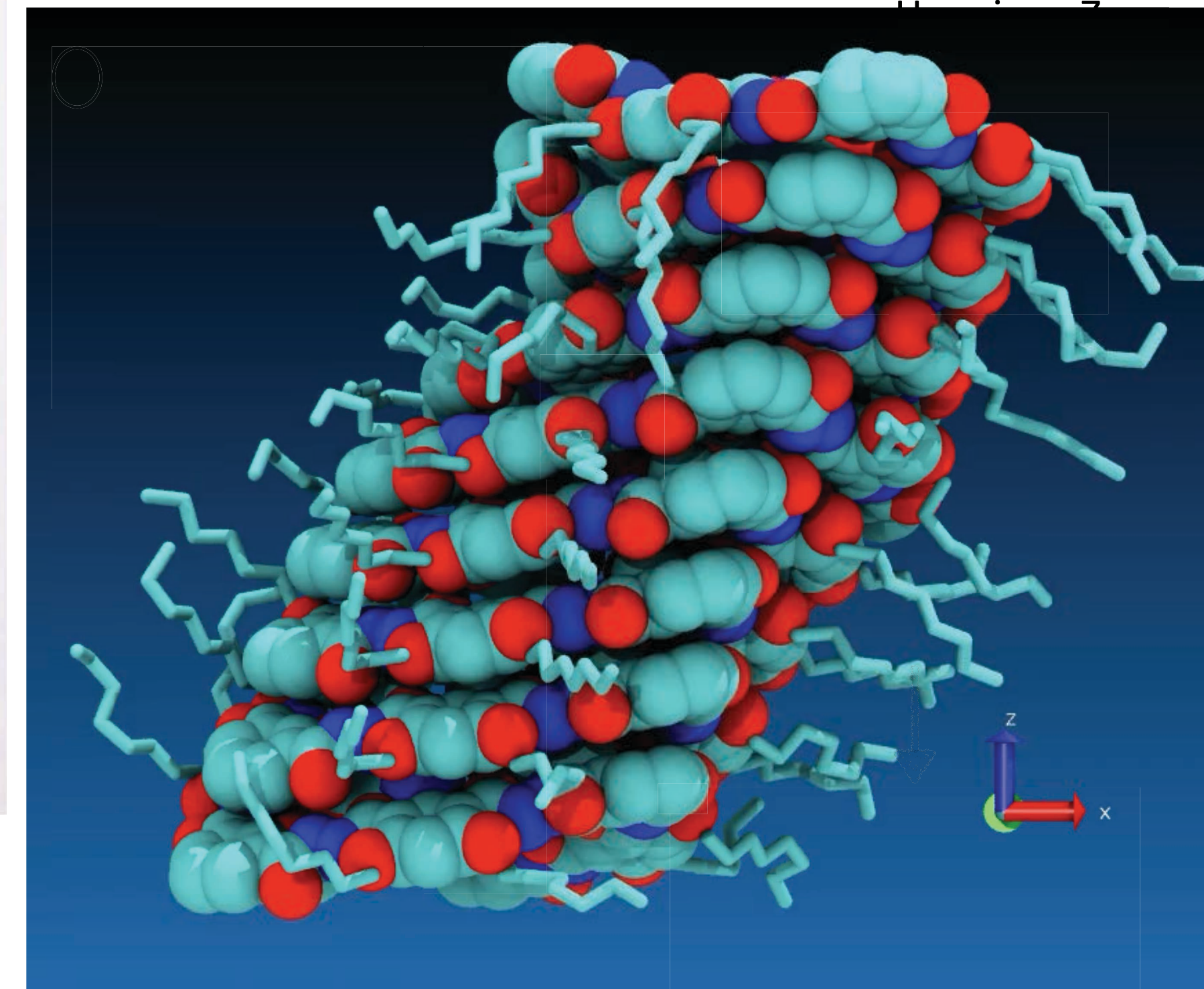
DNA Nano Systems (NFS)

NIH Center for Macromolecular Modelling and Bioinformatics

Artificial self-folding water channel that reject ions and protons



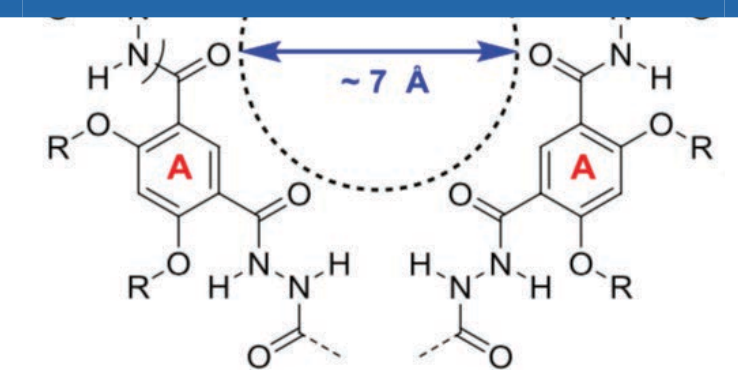
A race is on to develop robust, synthetic channels reproducing or exceeding performance of aquapoins



Less than 1% of the total water is available for drinking
 3.4M people die every year due to water related diseases
 11% of the world population lack the access to clean water

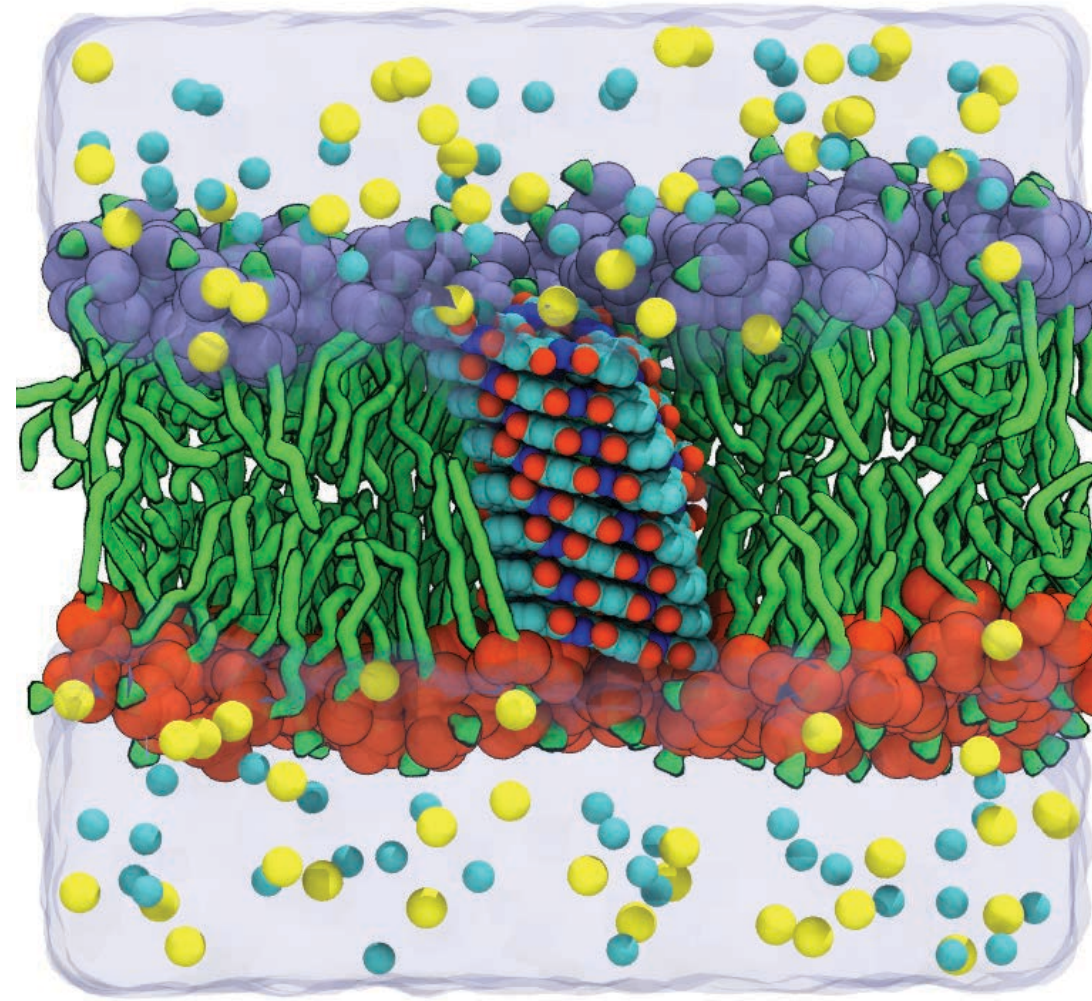
... a foldamer

Noworyta.
Nature **414**:188-190,
 2001.

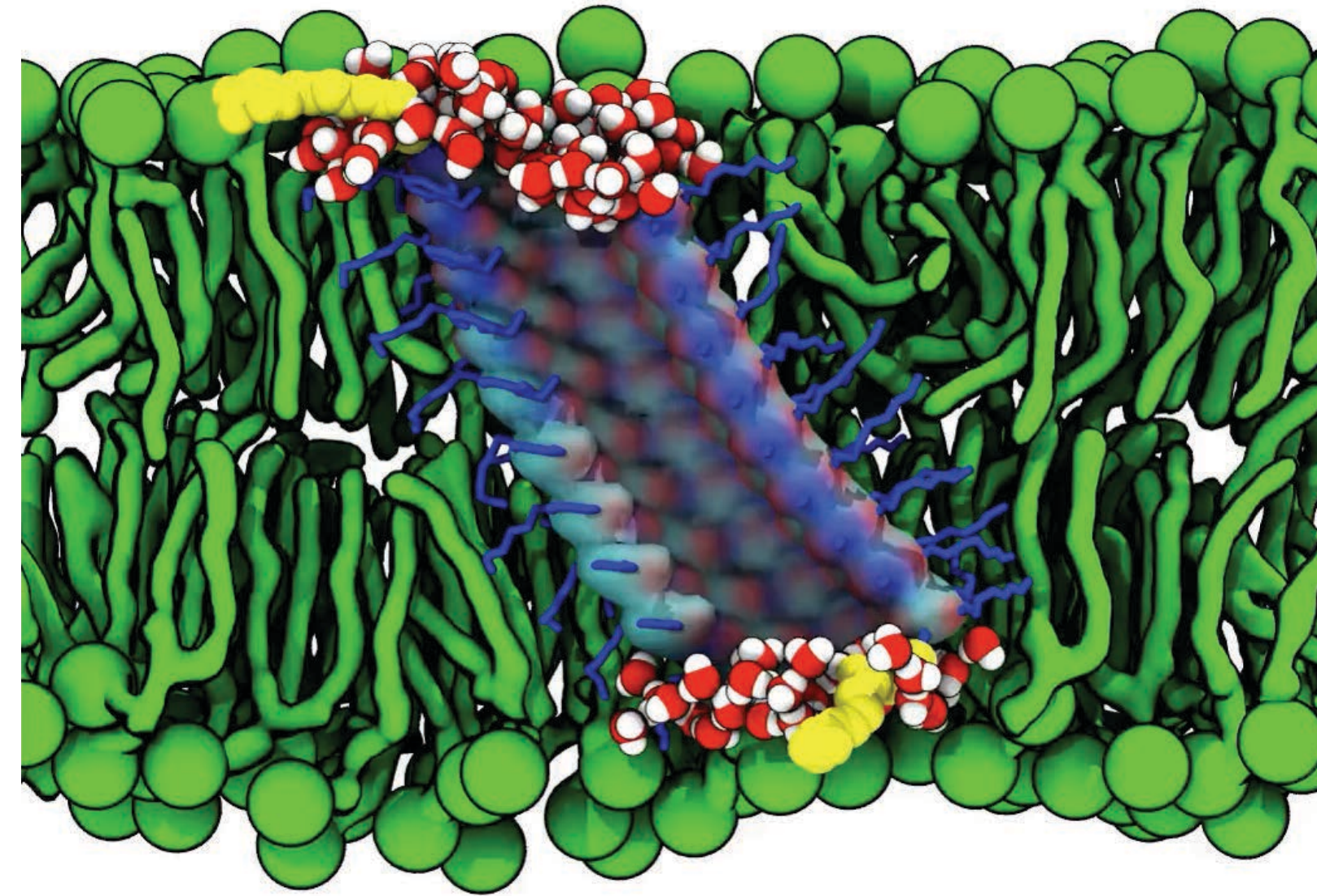
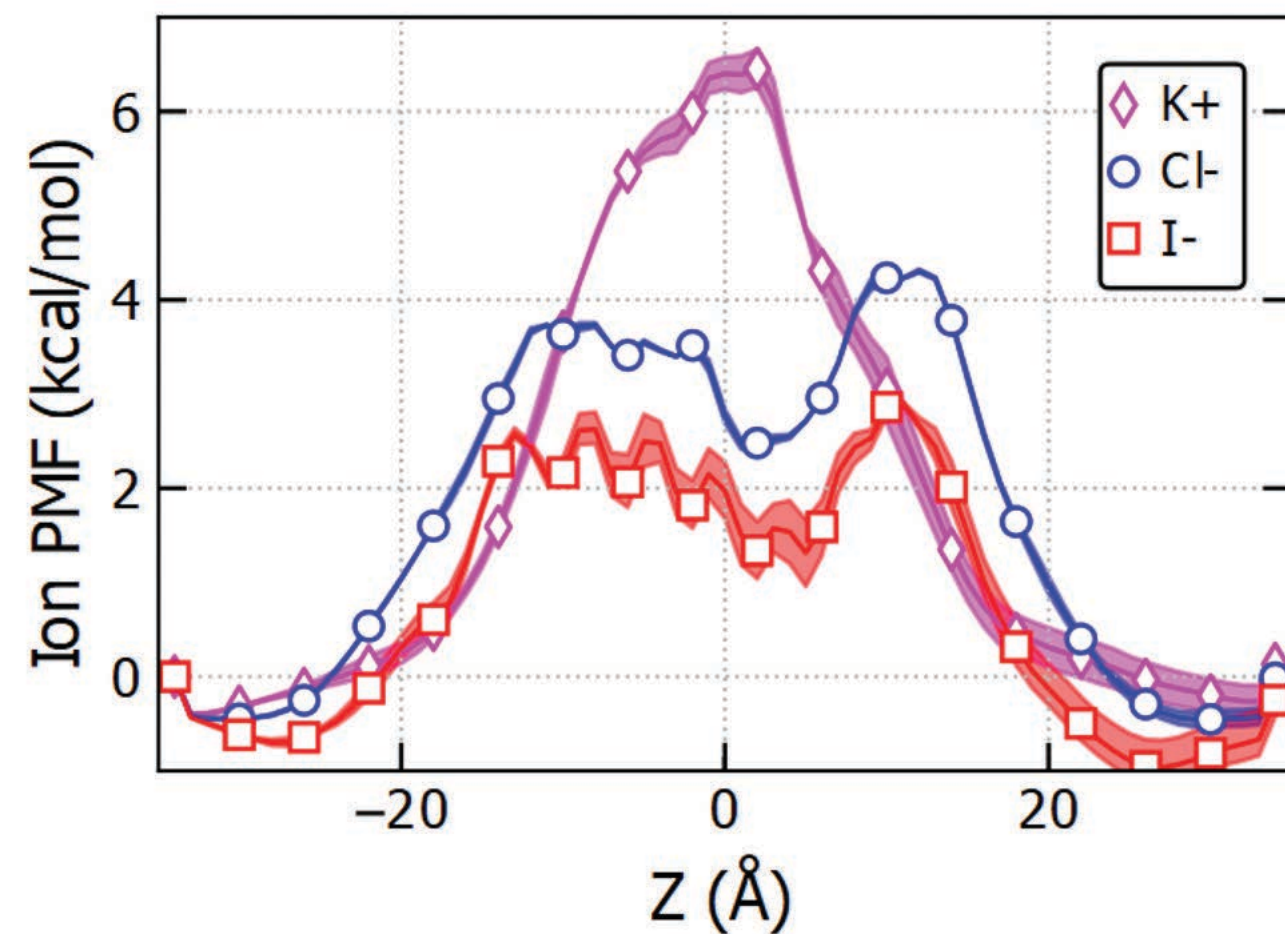


Artificial self-folding water channel that reject ions and protons

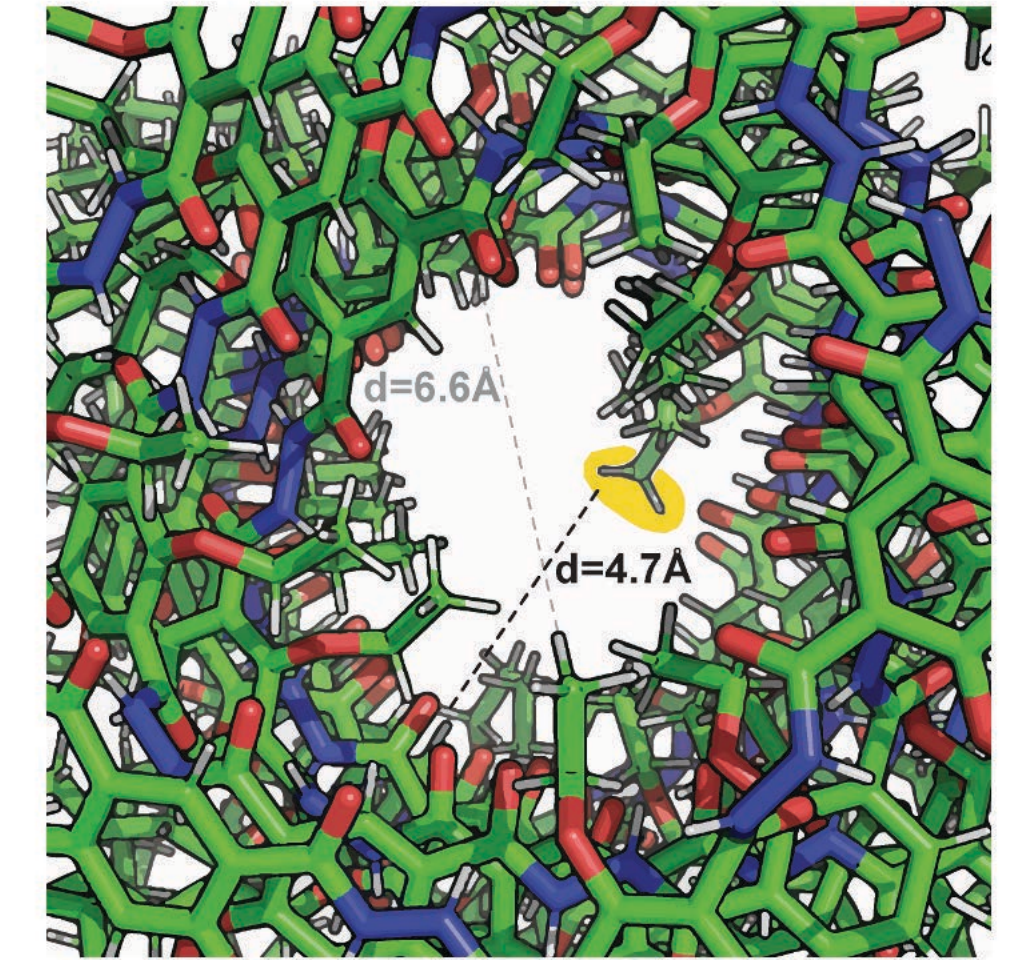
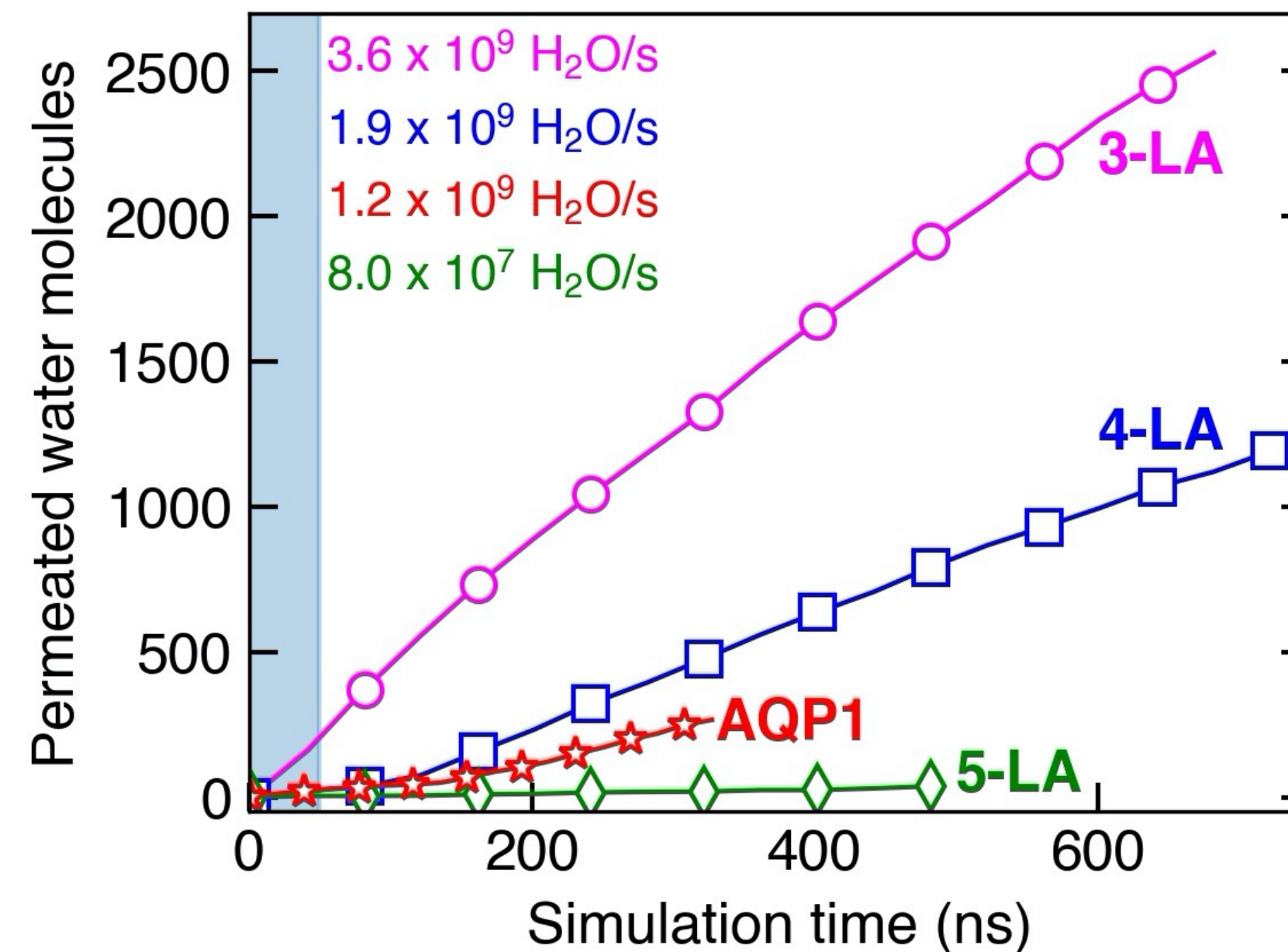
2019 allocation: First synthetic iodide channel



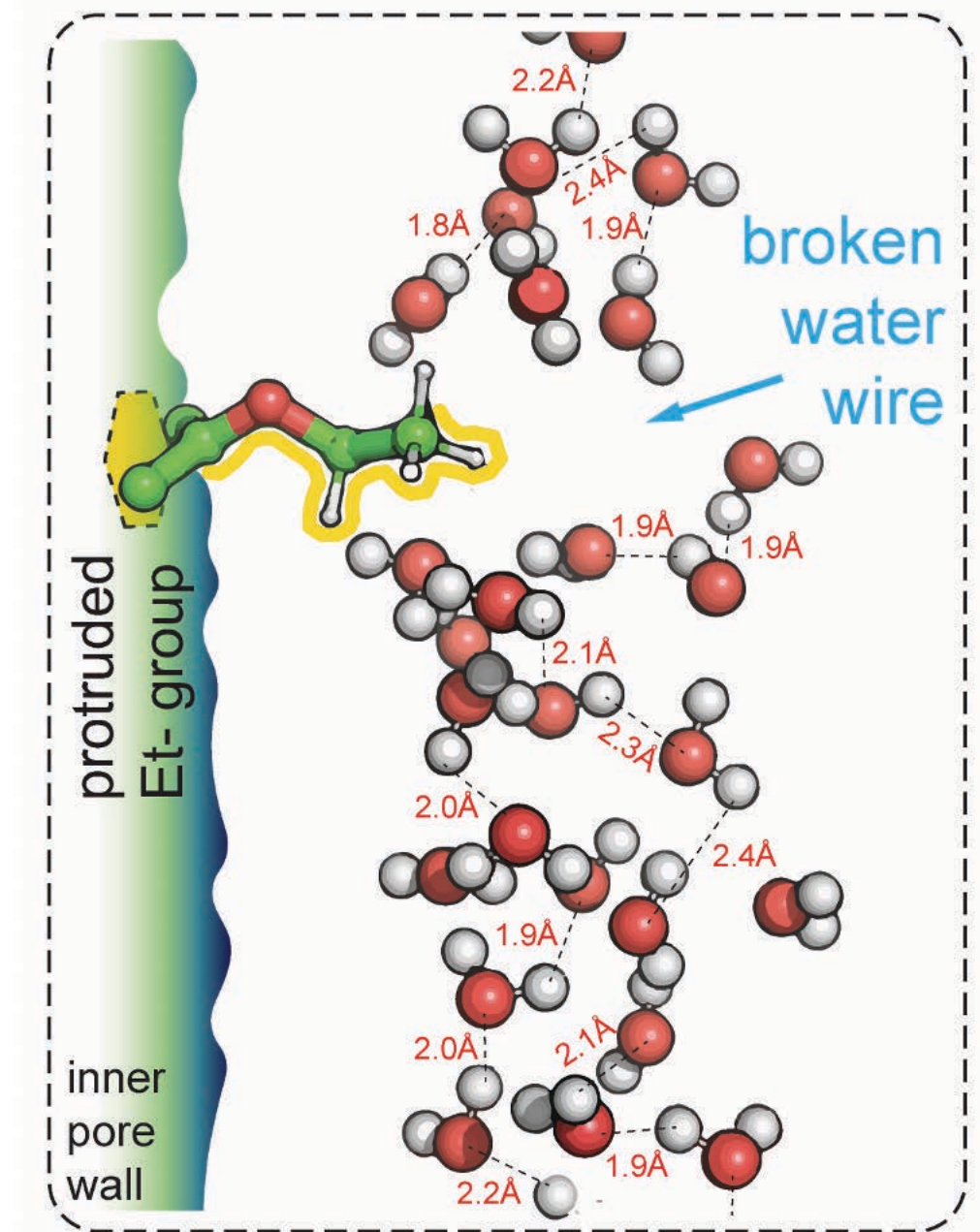
Replica-exchange PMF calculation



Ultra-fast water transport

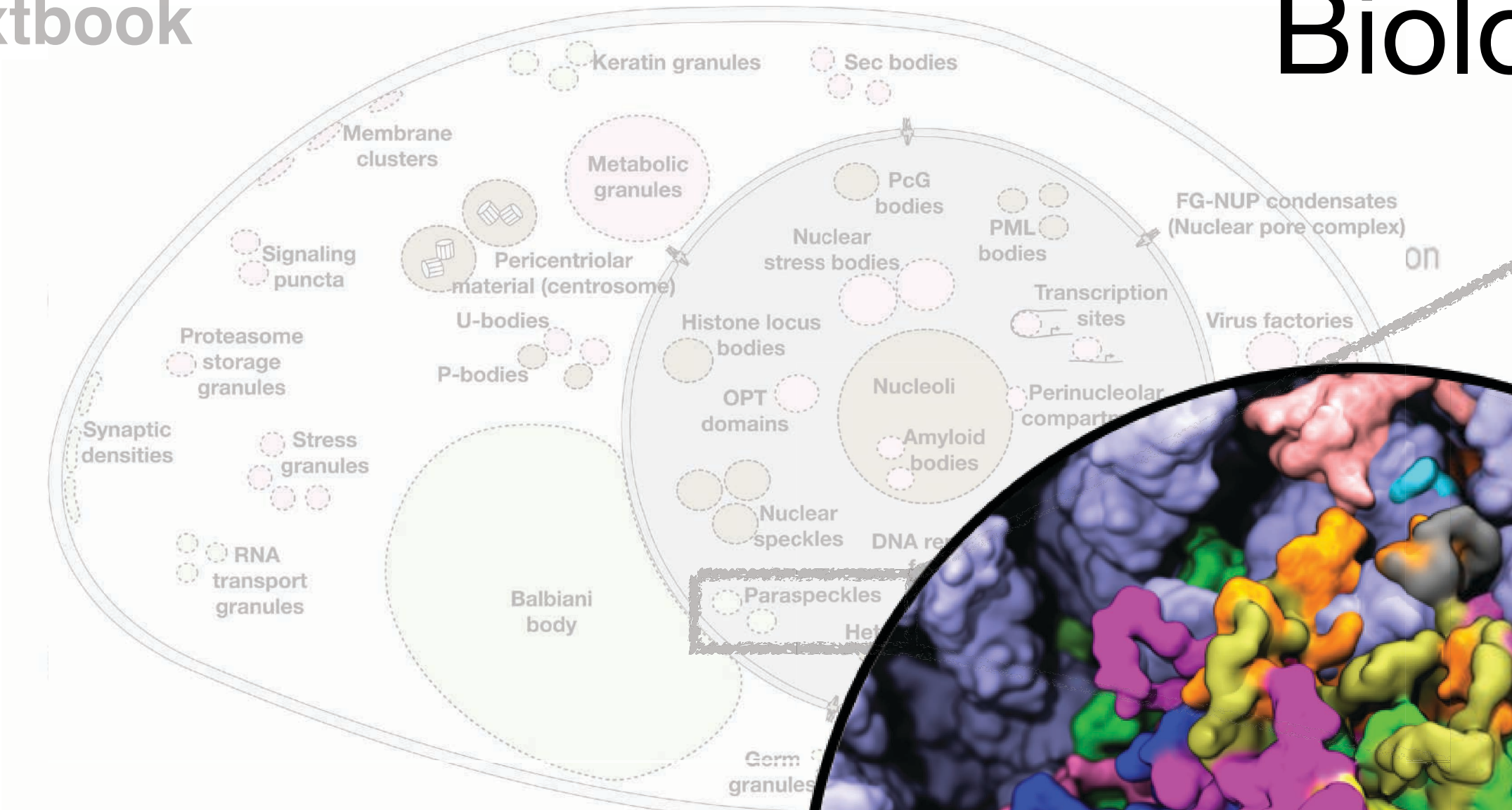


Proton rejection mechanism

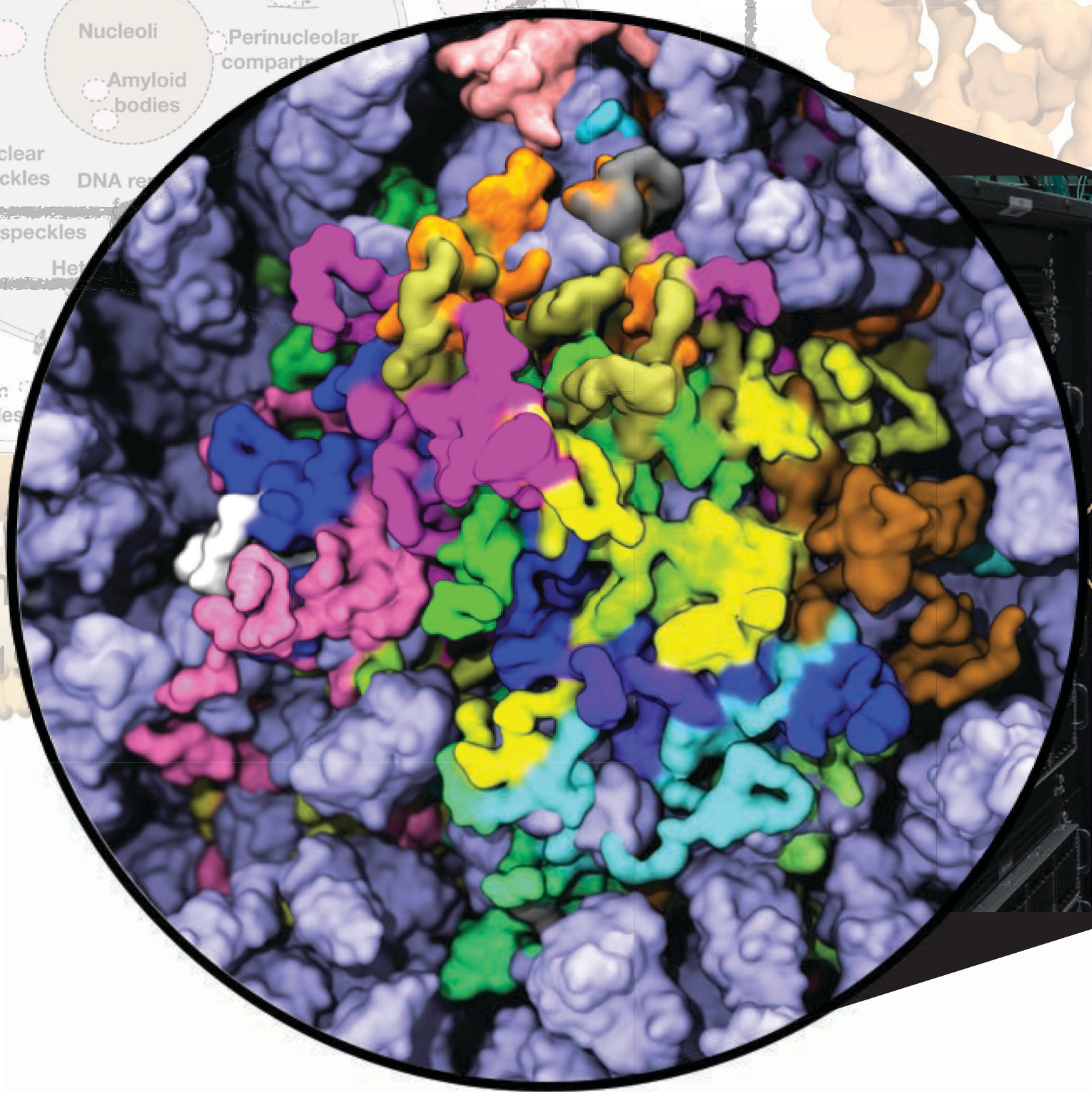


Et-containing channel 4

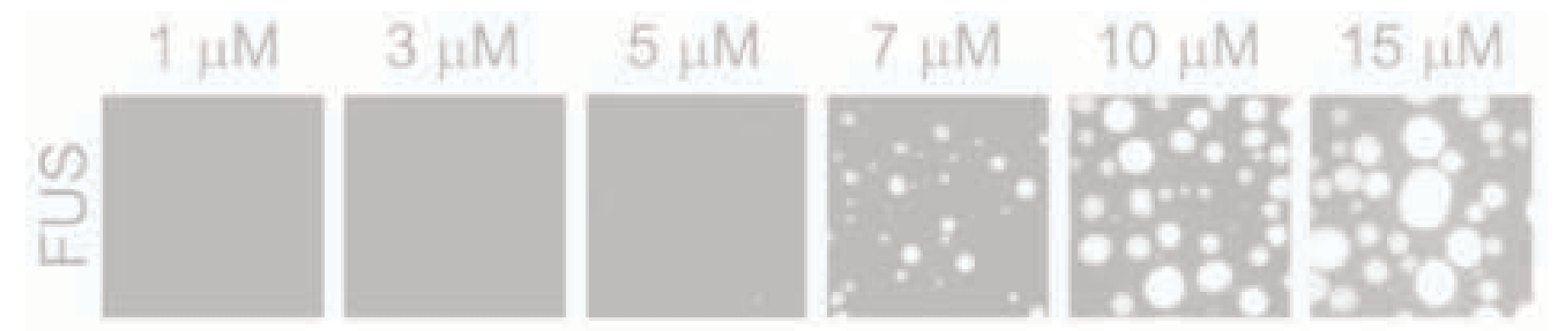
Biological condensates



Various membrane-less org...
 nucleic acids to organize r...
 Smooth endoplasmic reticulum
 Spann et. al., *Traffic*, 201...



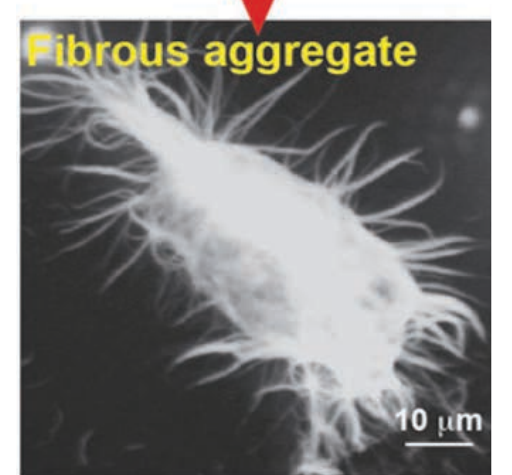
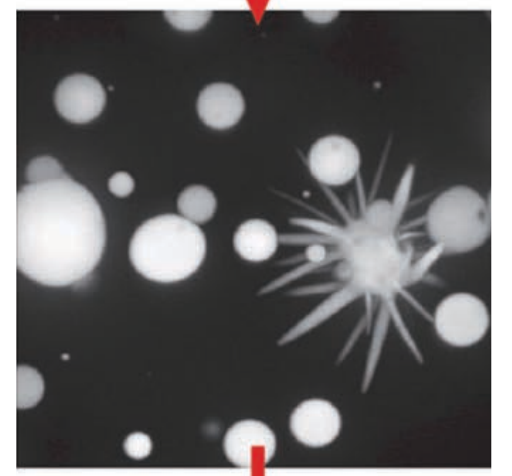
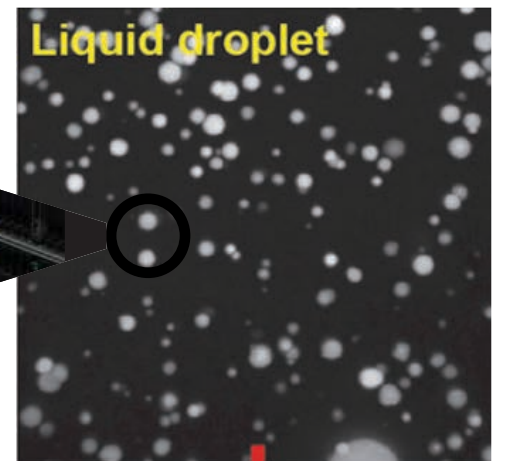
FUS condenses to form liquid like structures



Increasing concentration leads to
 "Liquid-Liquid Phase Separation"
 Wang et al., 2018, *Cell* 174, 688

FRONTERA

Biological state seen in
 patients of neurodegenerative
 diseases, most commonly
ALS



What is the molecular origin of liquid-liquid phase separation?

What is the role of protein/RNA in the phase behavior?

What causes aggregation of the condensates?

We use the Frontera-powered
computational microscope to uncover
 molecular information

5,000+ people are diagnosed per year

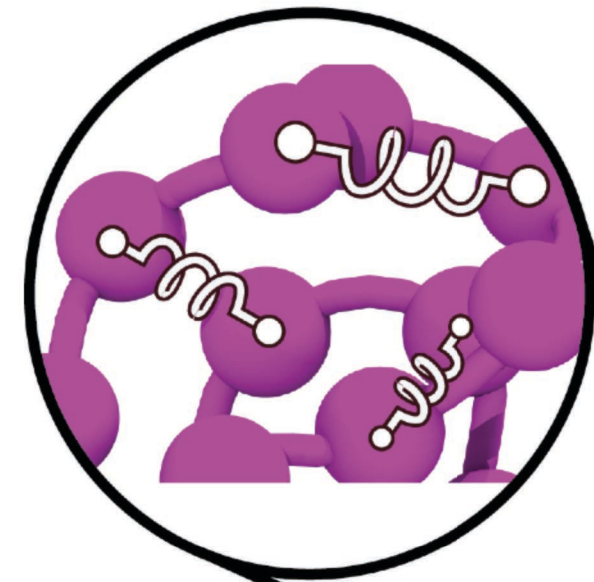
2-5 YEARS is the average life expectancy

\$2 BILLION is the estimated cost to develop a drug to slow or stop the progression of ALS

\$250,000 is the estimated out-of-pocket cost for caring for a person with ALS

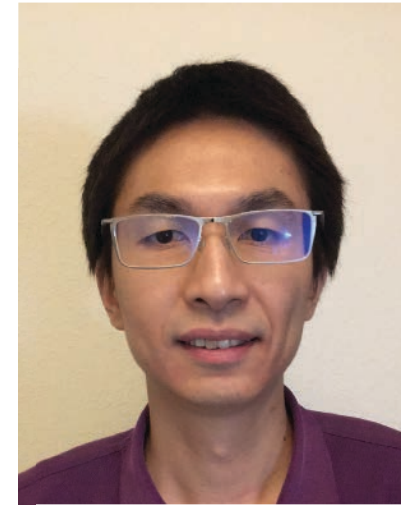
There is NO CURE for ALS

Single-Protein Collapse Determines Phase Equilibria of a Biological Condensate

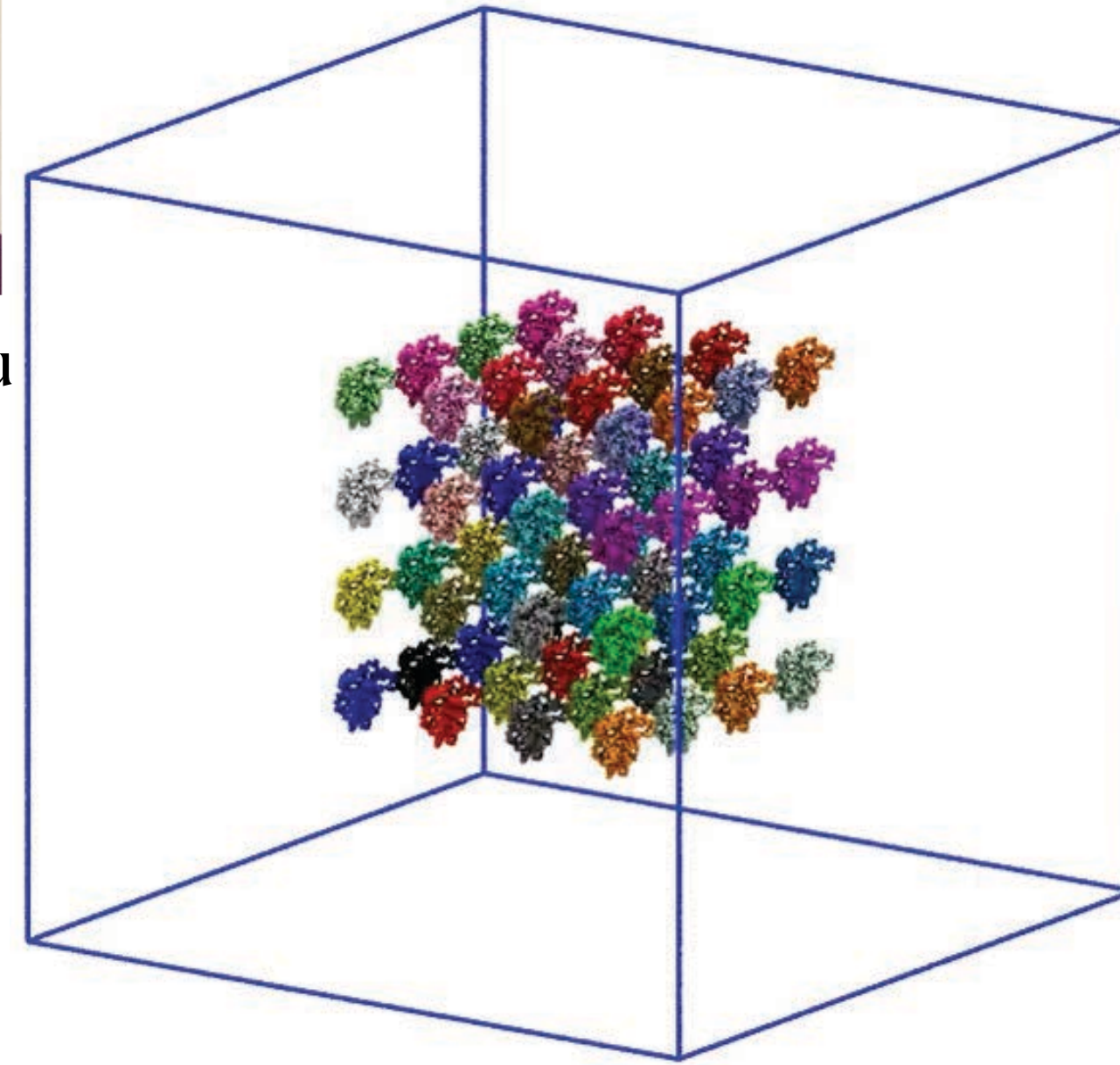


Spatial restraints applied to structured domains

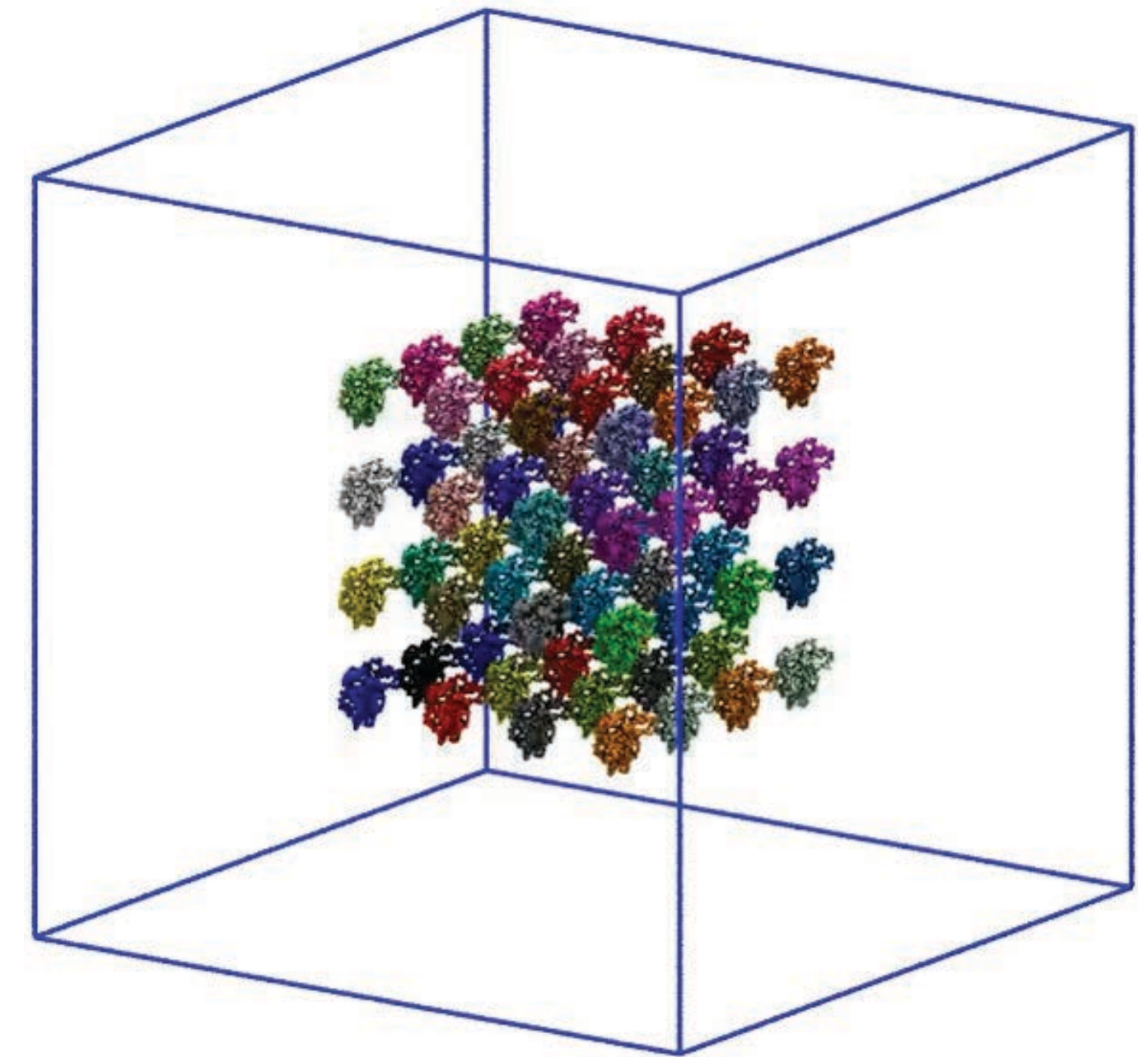
HK Model (Hummer lab)
J. Mol. Biol. 375:1416



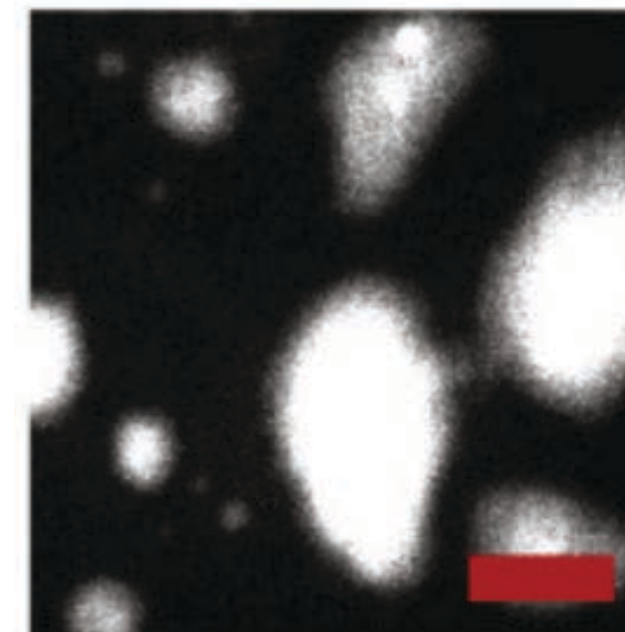
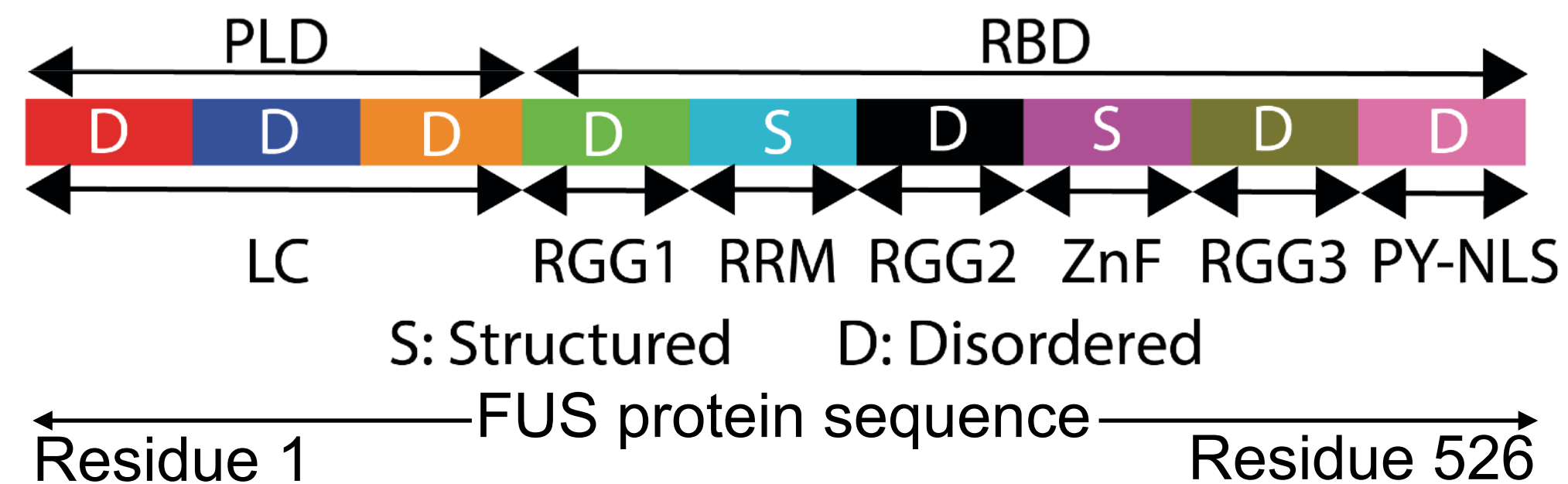
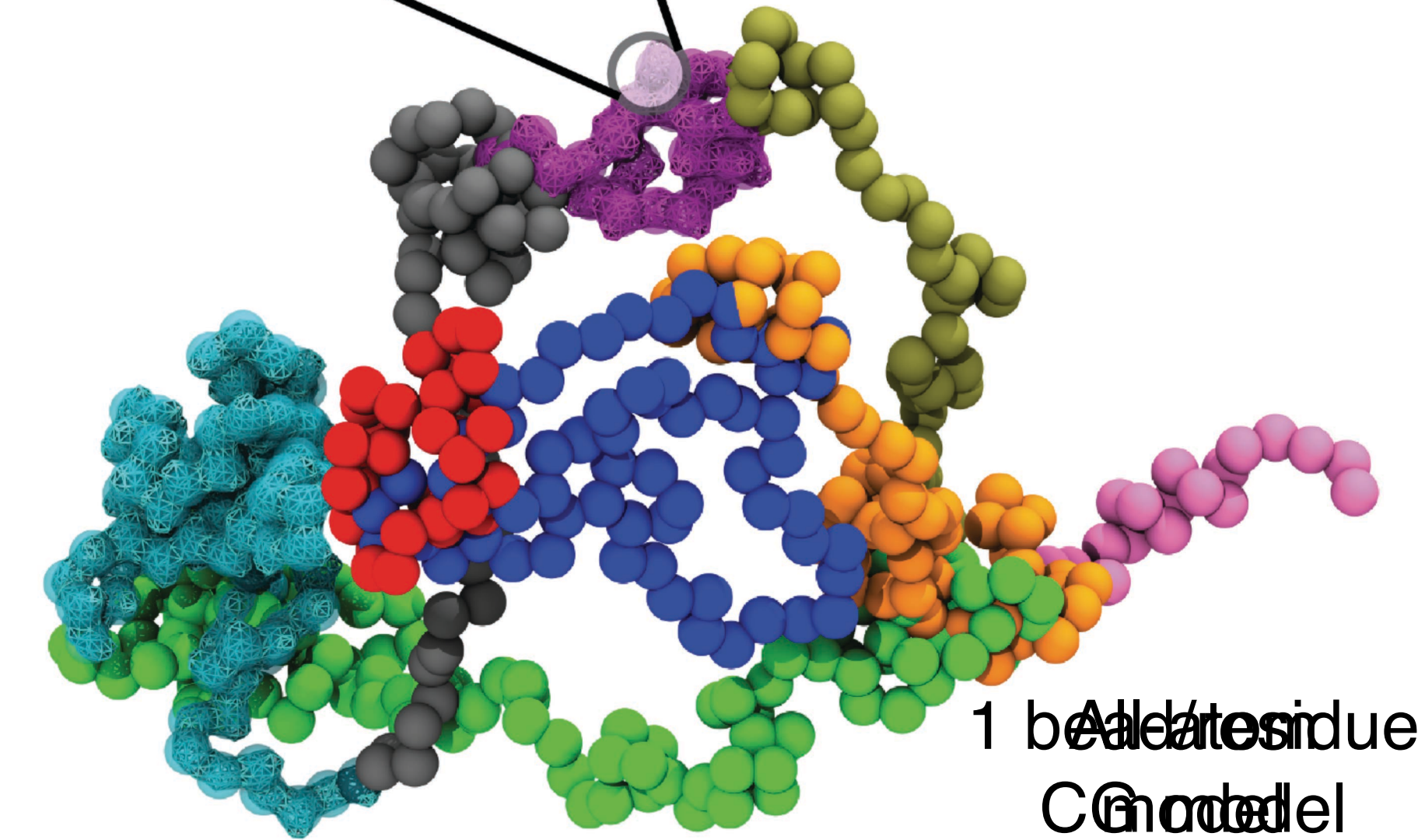
Han-Yi Chou



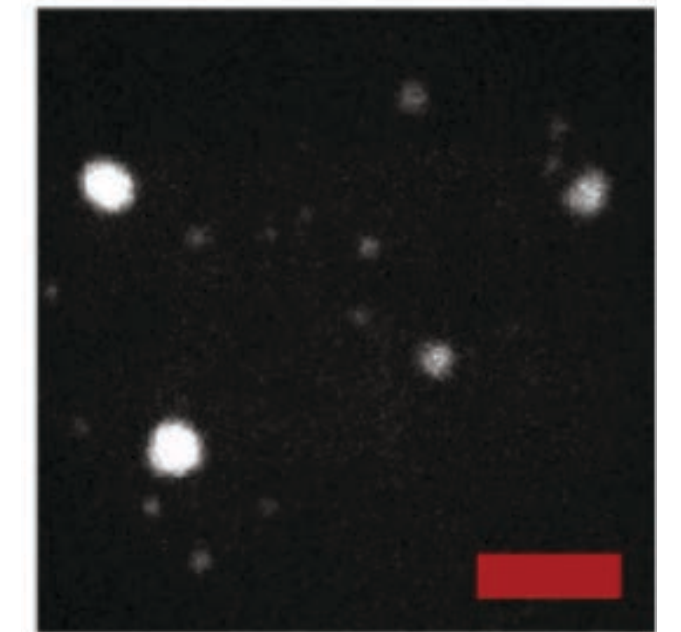
CG simulation of wild type FUS shows phase separation to form spherical condensates



CG simulation of R-to-K mutant FUS shows loss of phase separation



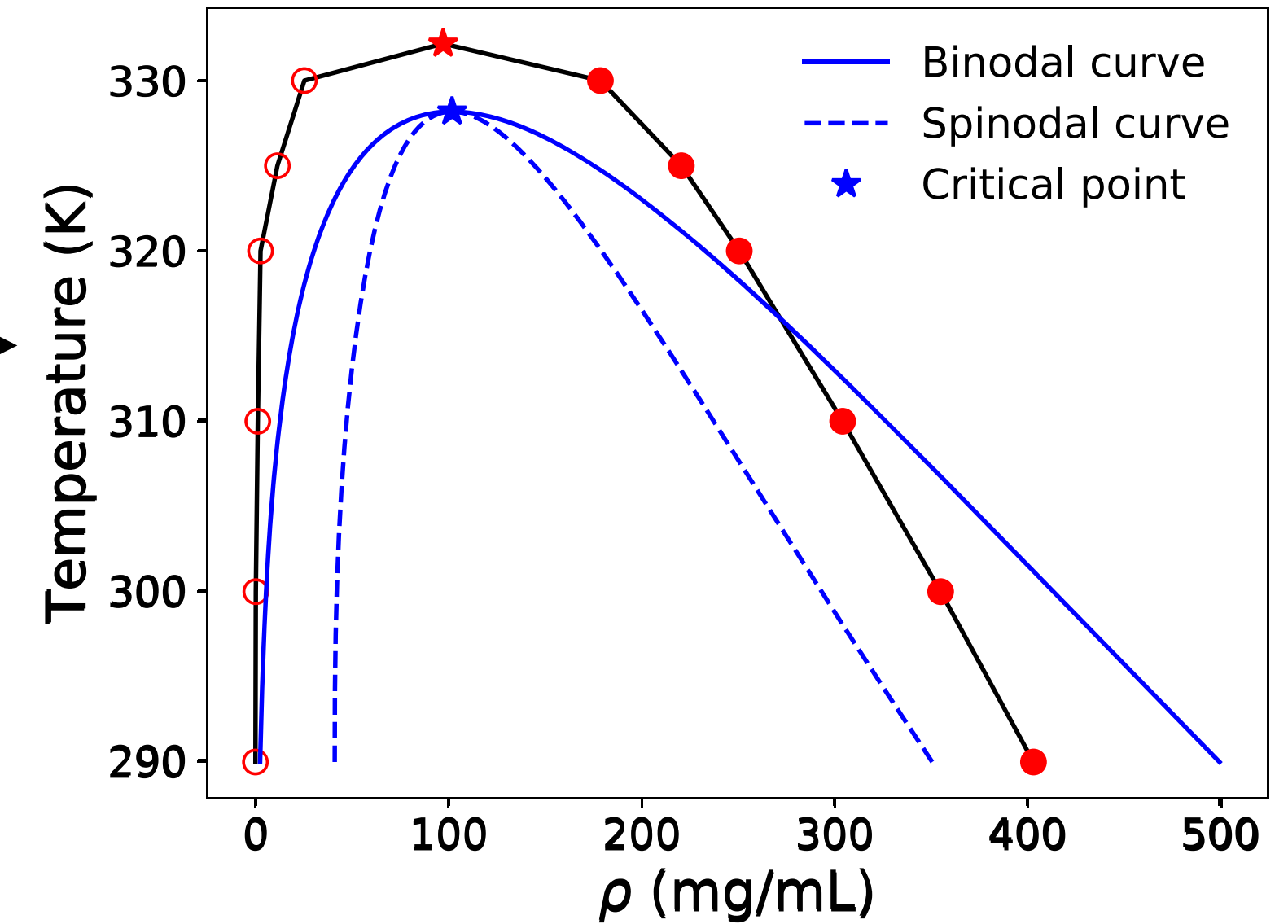
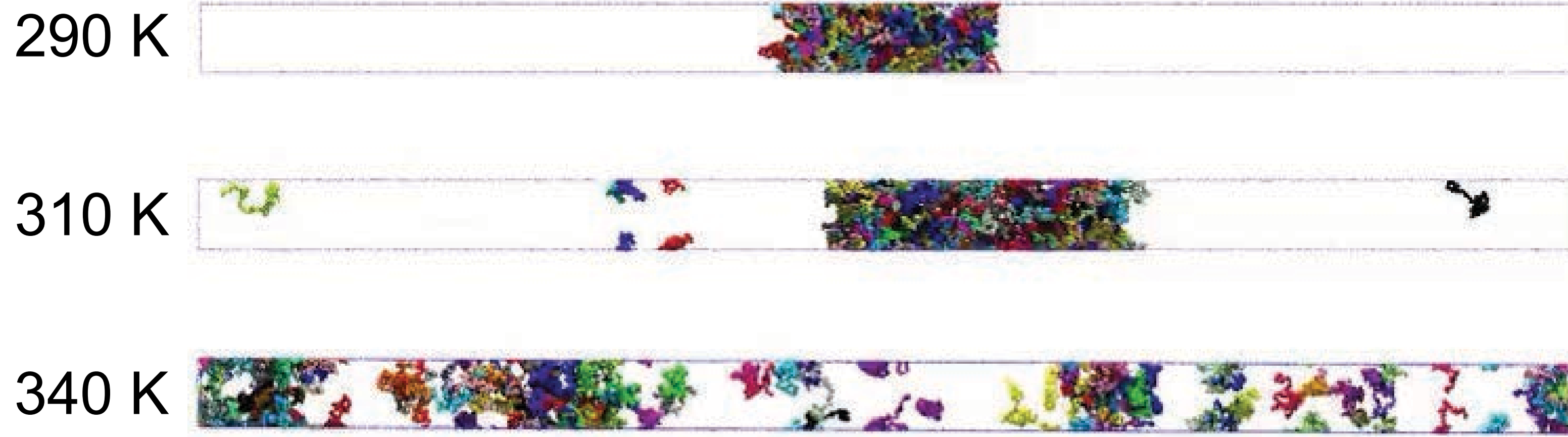
Experimental data
Wang et al. (2018), *Cell* 174, 688



Single-Protein Collapse Determines Phase Equilibria of a Biological Condensate

Brute force simulations of phase diagram (Frontiera GPUs)

Phase diagram of FUS condensate

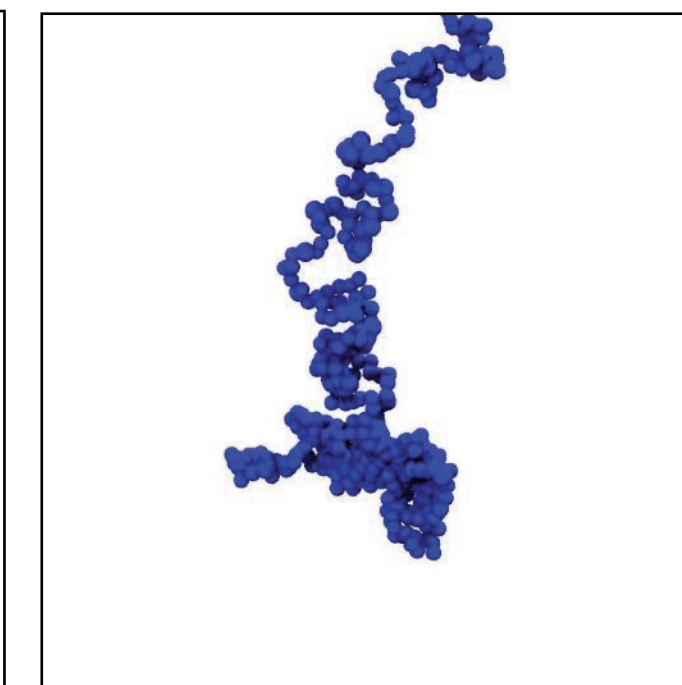
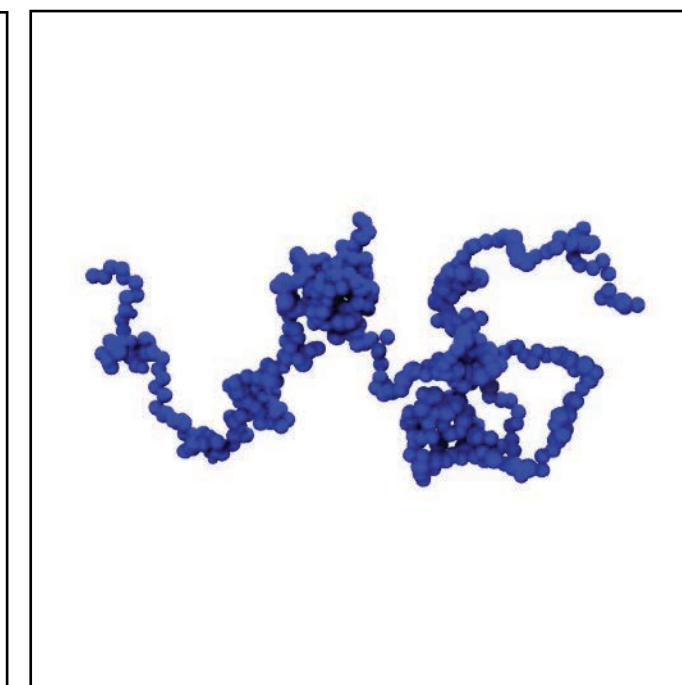


300 K

350 K

400 K

Single chain collapse theory
(Raos & Allegra, JPC 1996)
(Pappu Lab, BJ 2020)



Phase behavior of a biological condensate is determined by the behavior of just one condensate molecule in isolation!

Highlights:

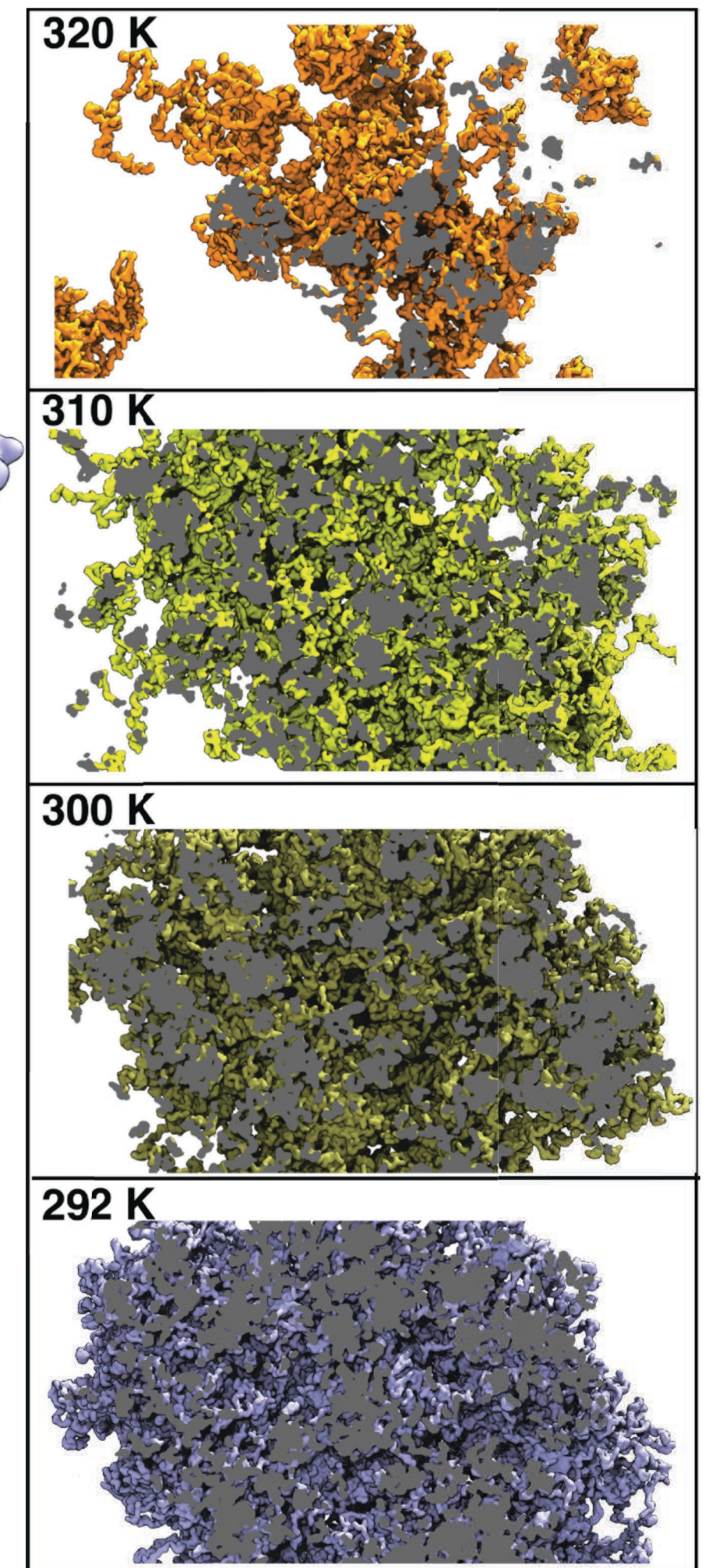
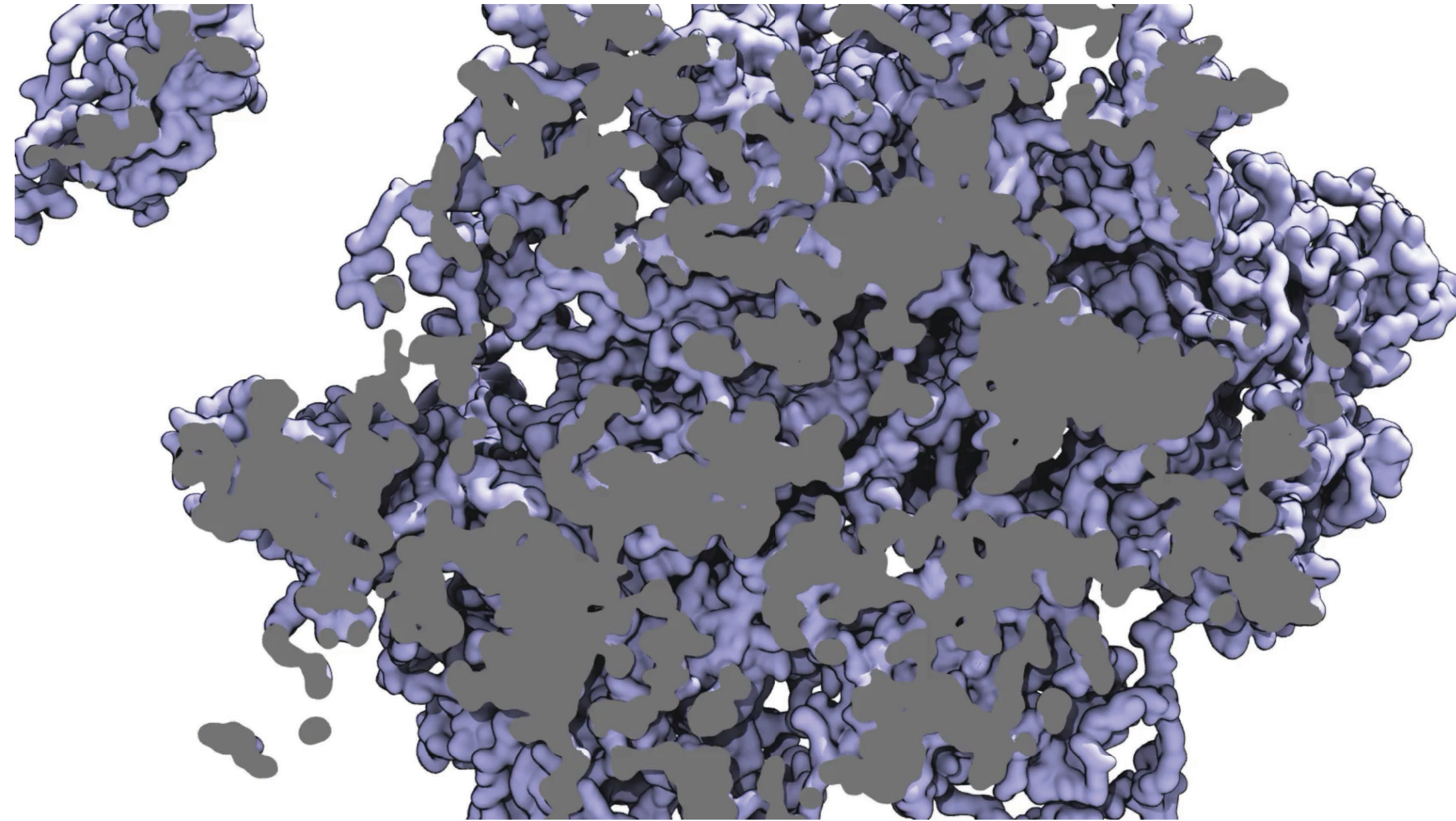
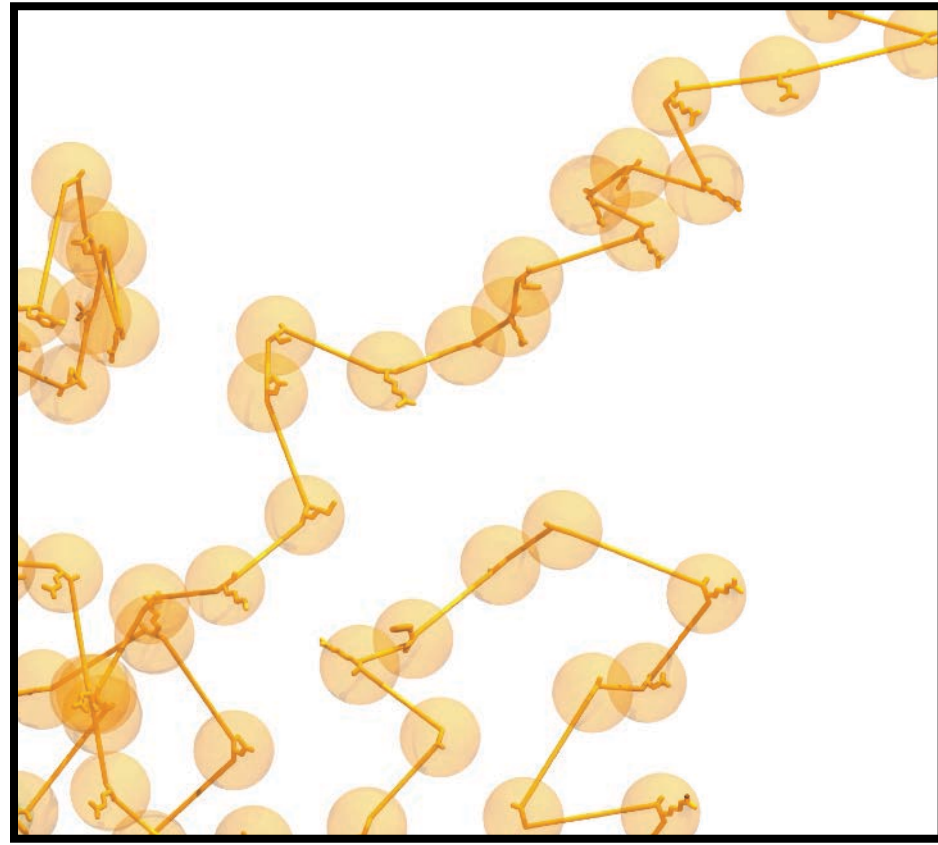
TACC: Mysterious cellular droplets come into focus

From page of NSF

All-atom simulations reveal internal structure of the condensates

Configurations from CG simulations were converted to all-atom representation

64 proteins
10 million atoms



Temperature ↑

Simulations reveal a network of channels formed by water inside the condensate

The channels are dynamically formed and broken as the simulation progresses

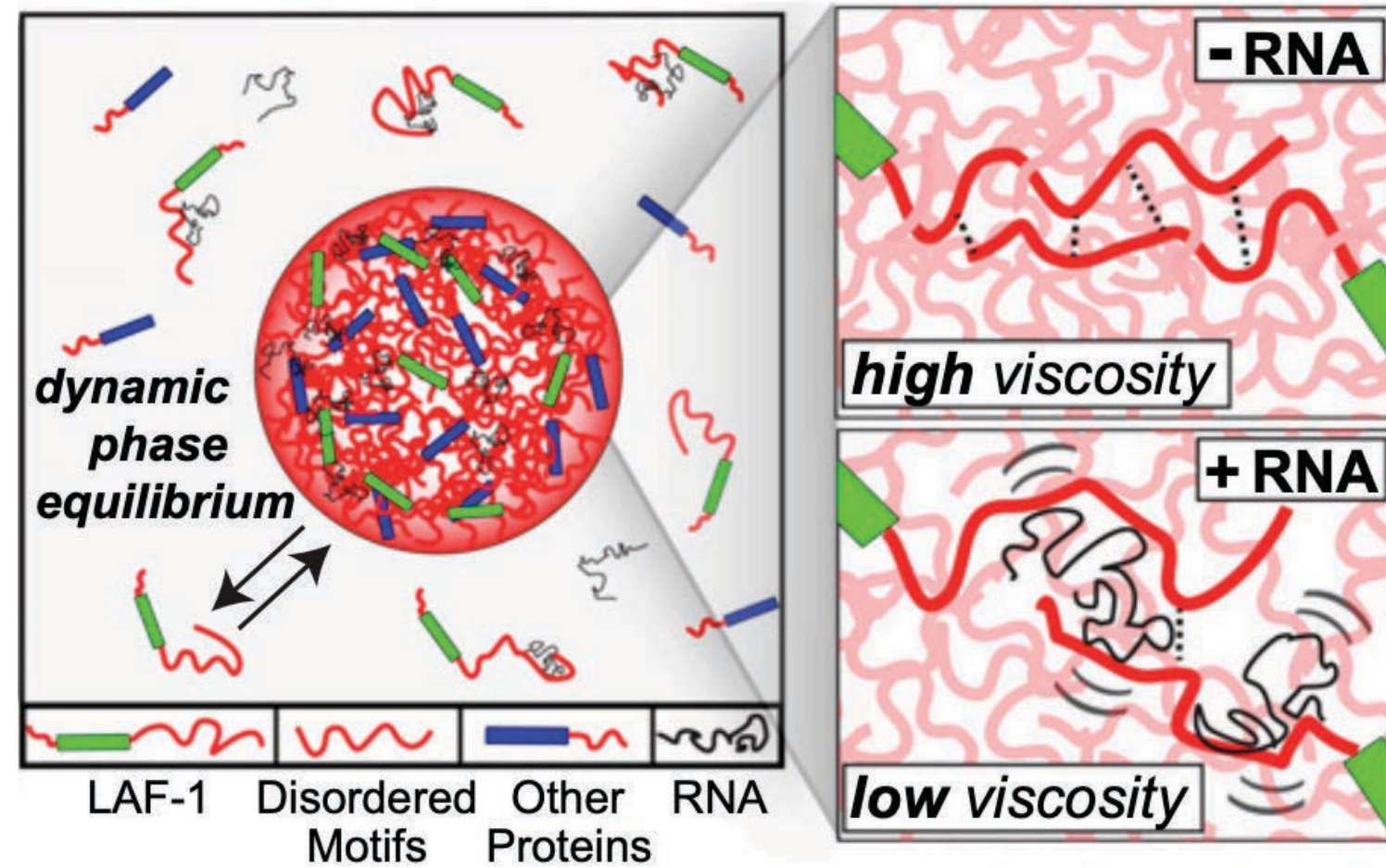
Simulations suggest a mechanism for recruitment of molecules into the condensates

Temperature regulates both abundance and size of the channels

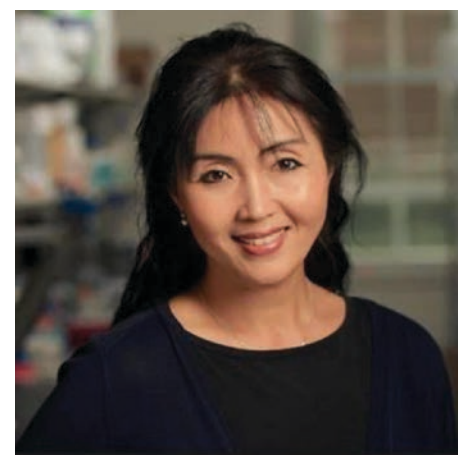
H.-Y. Chou, S. Htun, K. Sarthak, D. Winogradoff, and A. Aksimentiev, *To be published* (2021)

RNA modulates phase behavior of FUS condensates

Experiment: RNA affects thermodynamics and fluidity of condensate droplets

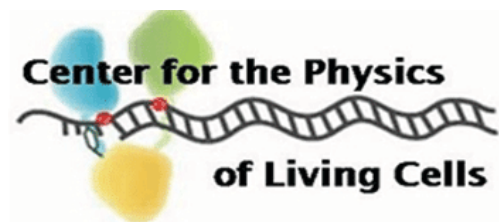


Elbaum-Garfinkle et al. (2017) *PNAS* 112.23, 7189

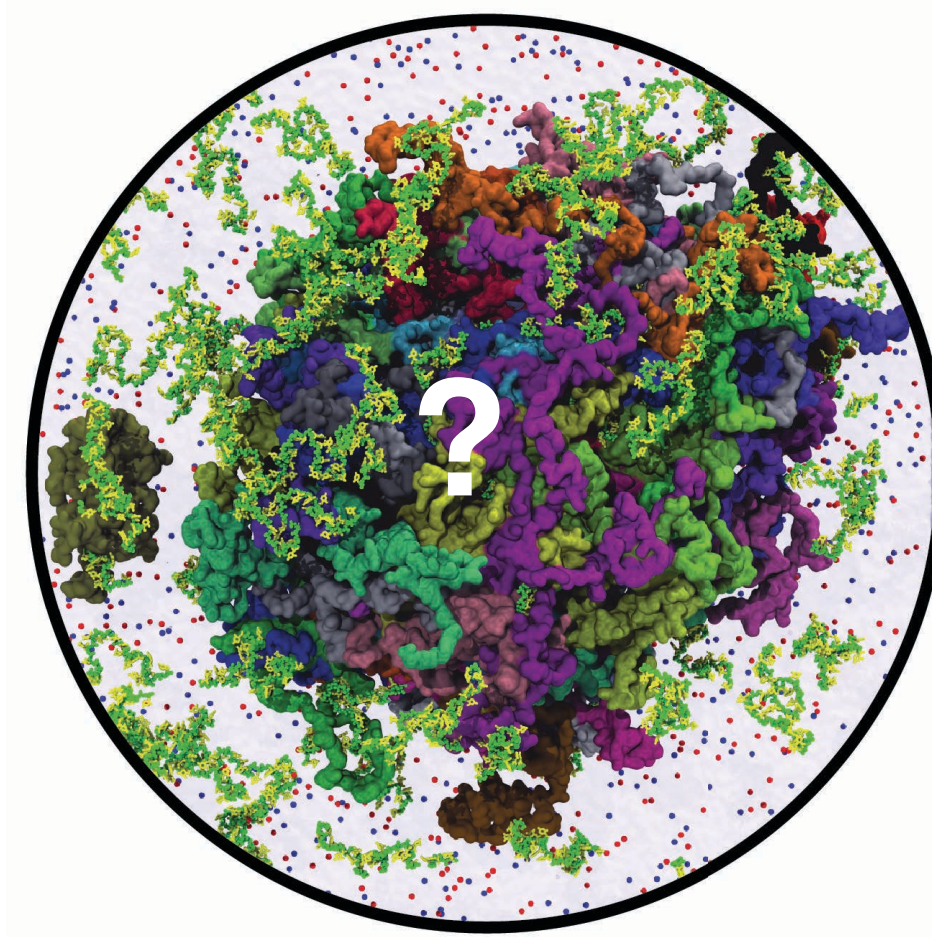


Sua Myong Lab
Johns Hopkins University

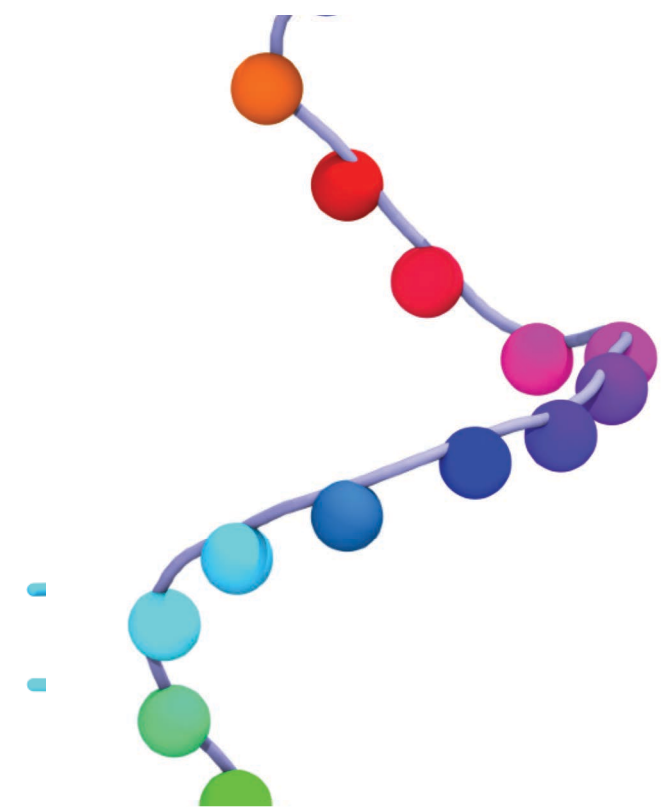
Ongoing experimental efforts at CPLC



Yann Chemla Lab
University of Illinois



Molecular mechanism is not known

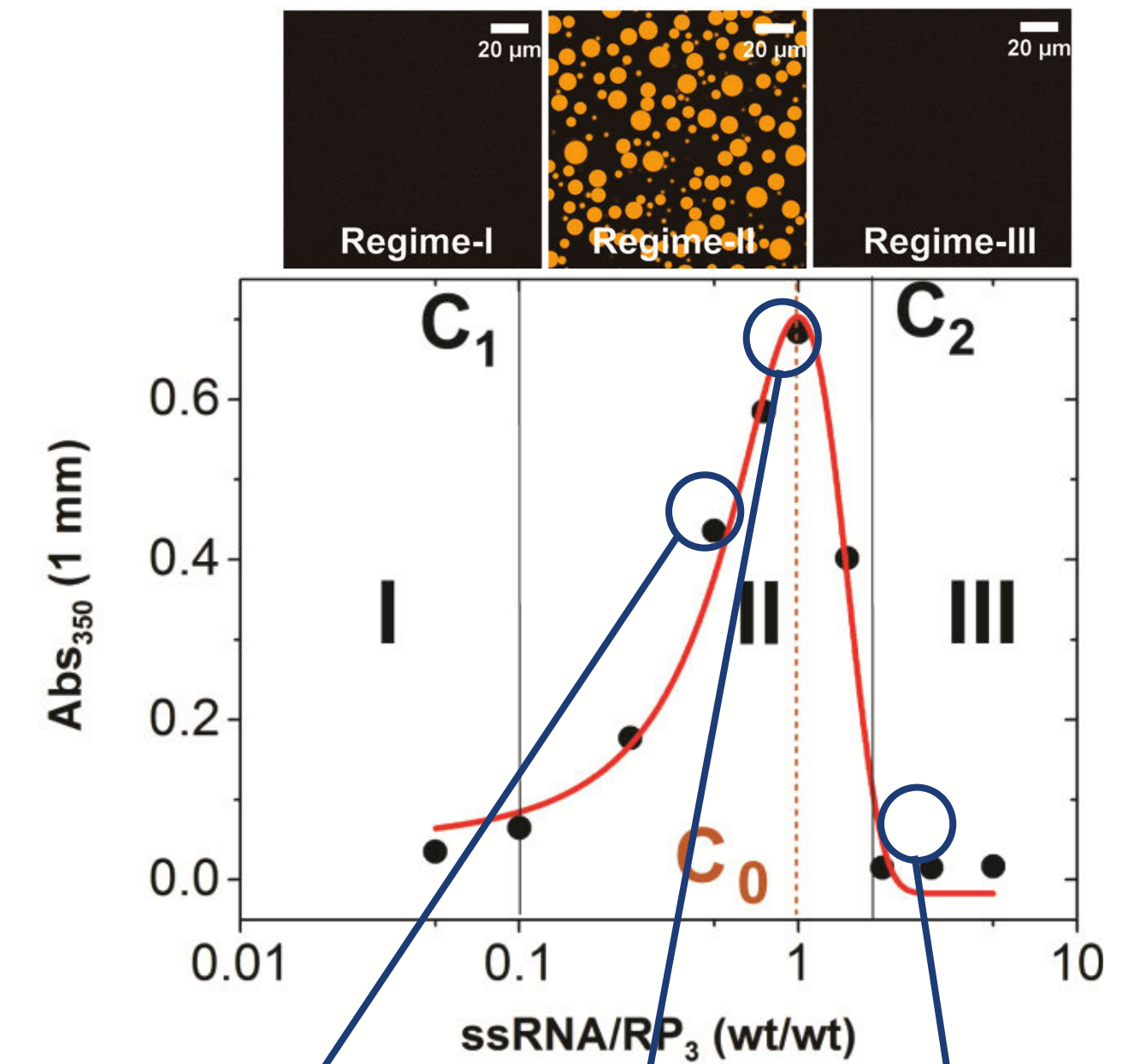


Fragment of ssRNA

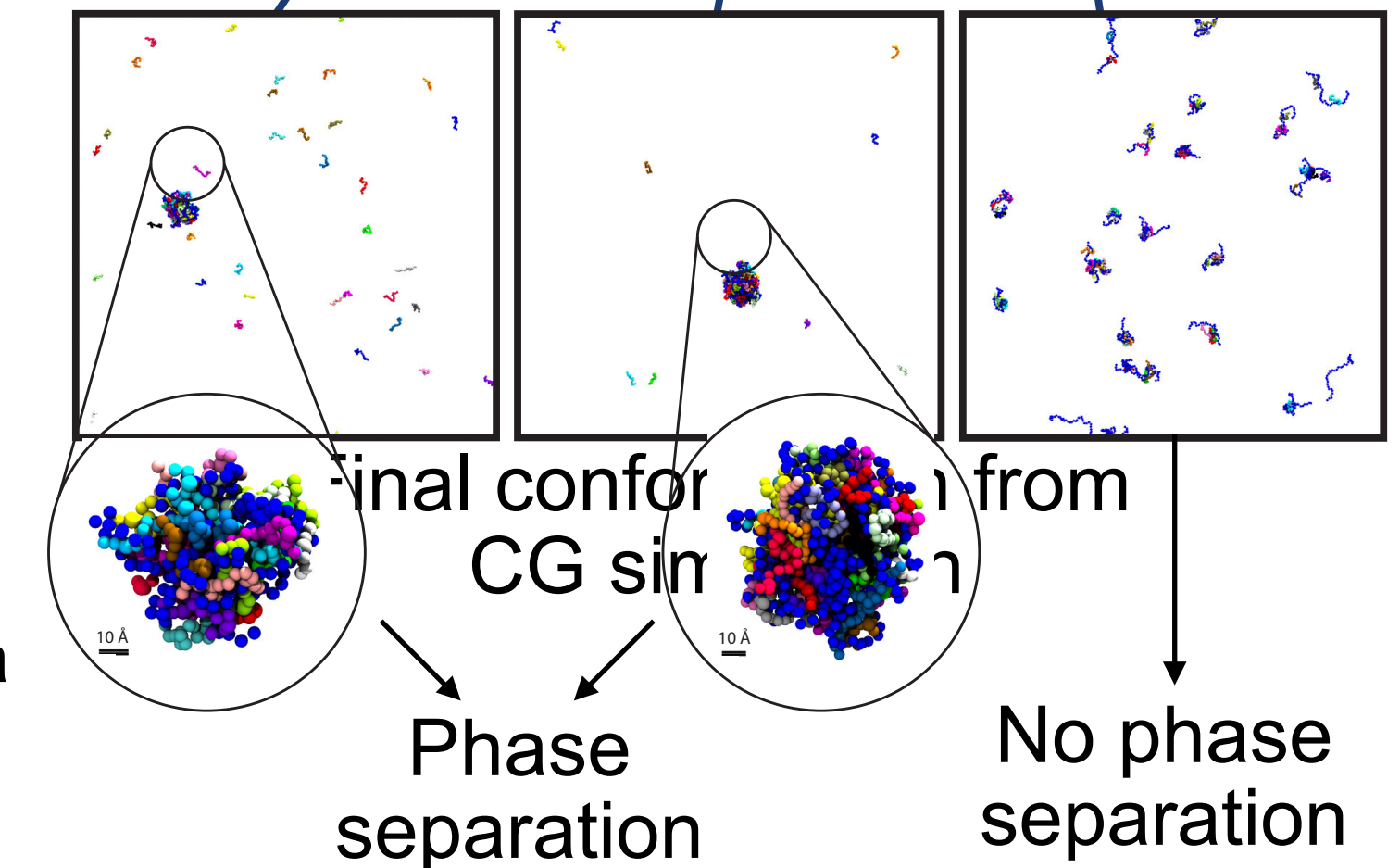
One charged bead represents one nucleotide

We developed a custom CG model of ssRNA using FRET and protein affinity data

Experiment: FUS-RNA condensates show re-entrant phase behavior



Priya R. Banerjee et al. *Angew. Chem. Int. Ed.* (2017)



RNA modulates phase behavior of FUS condensates

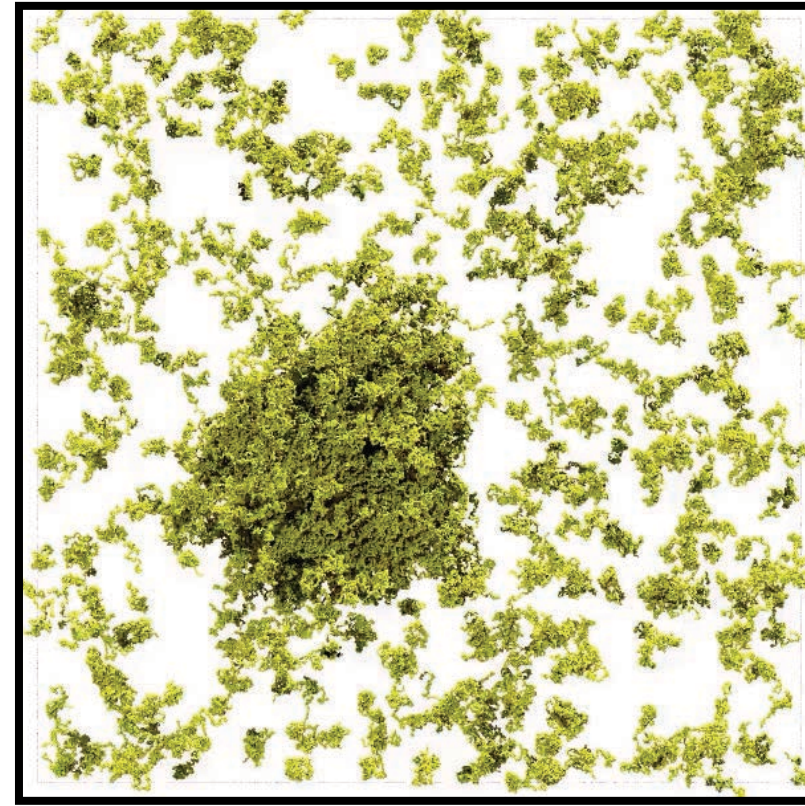
Simulations run on Frontera GPU

Each system contains 1,728 proteins and 672 RNA molecules

T = 292 K

T = 320 K

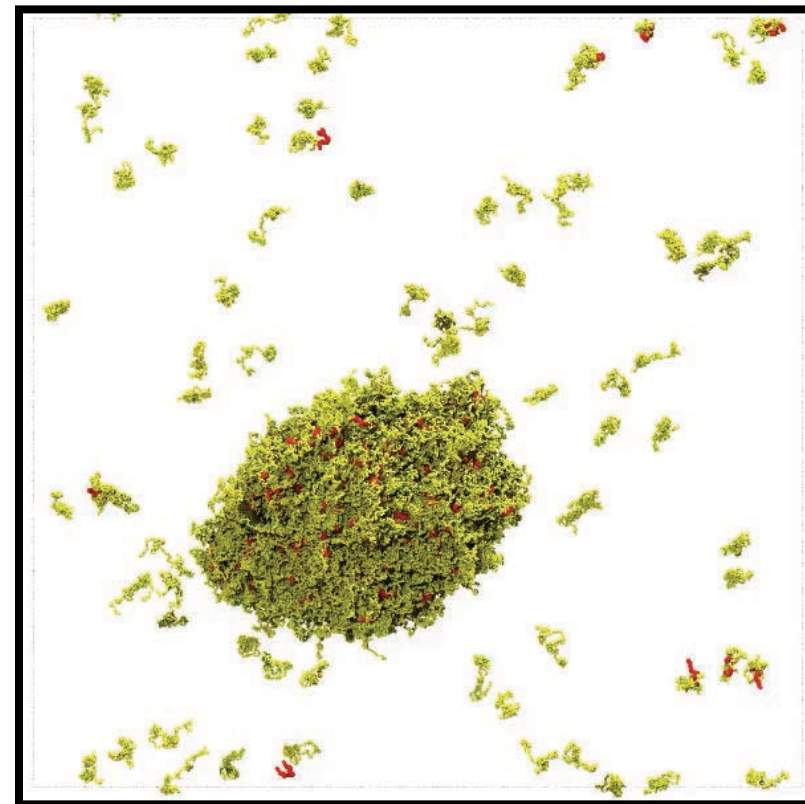
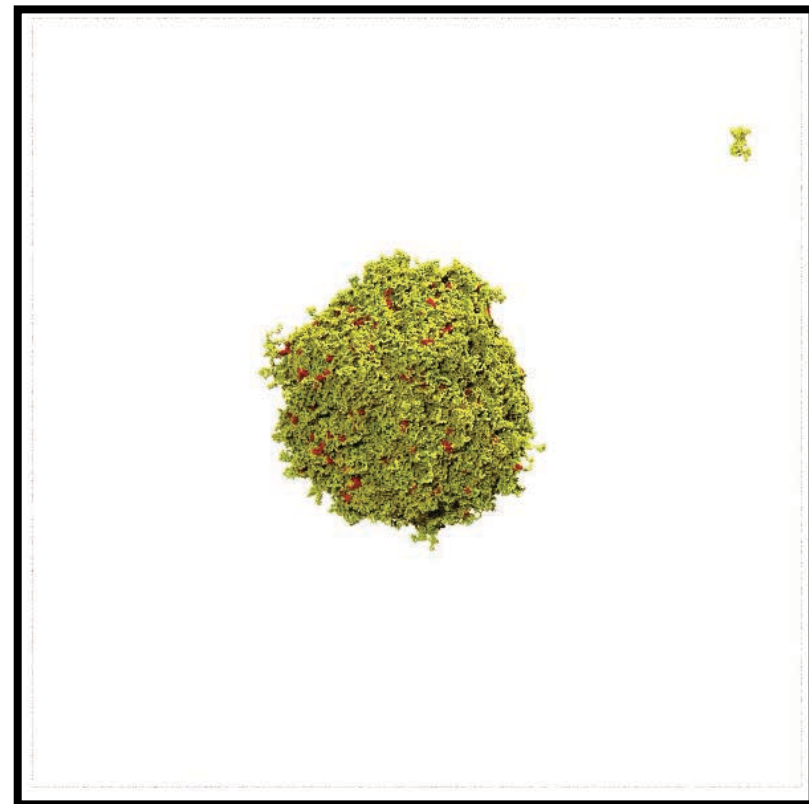
FUS
only



T = 292 K

T = 320 K

FUS
+
RNA



RNA inhibits exchange of biomolecules with dispersed phase

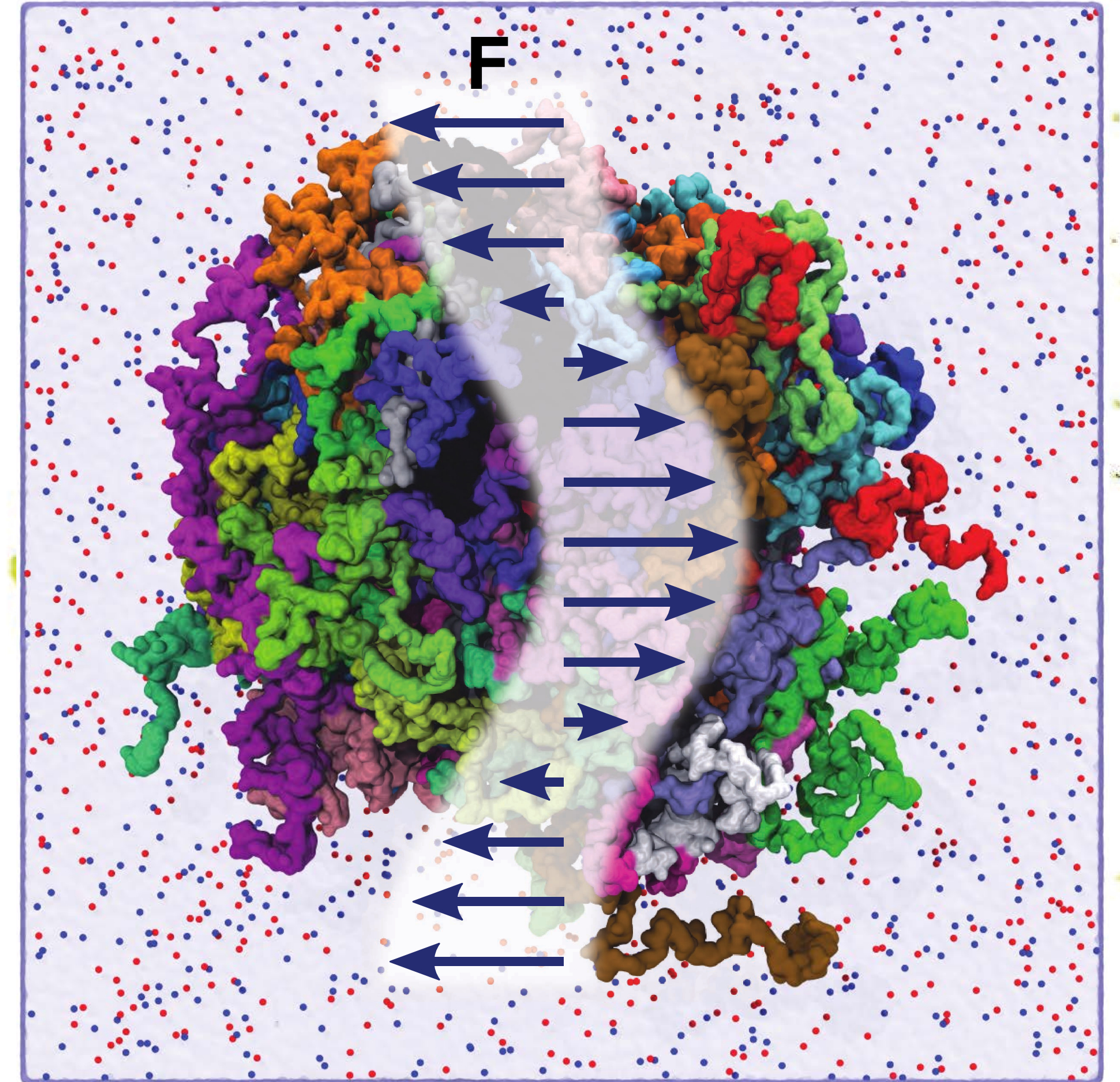


Swan Htun



Kumar Sarthak

Probing the condensate viscosity by applying time and position dependent shear force



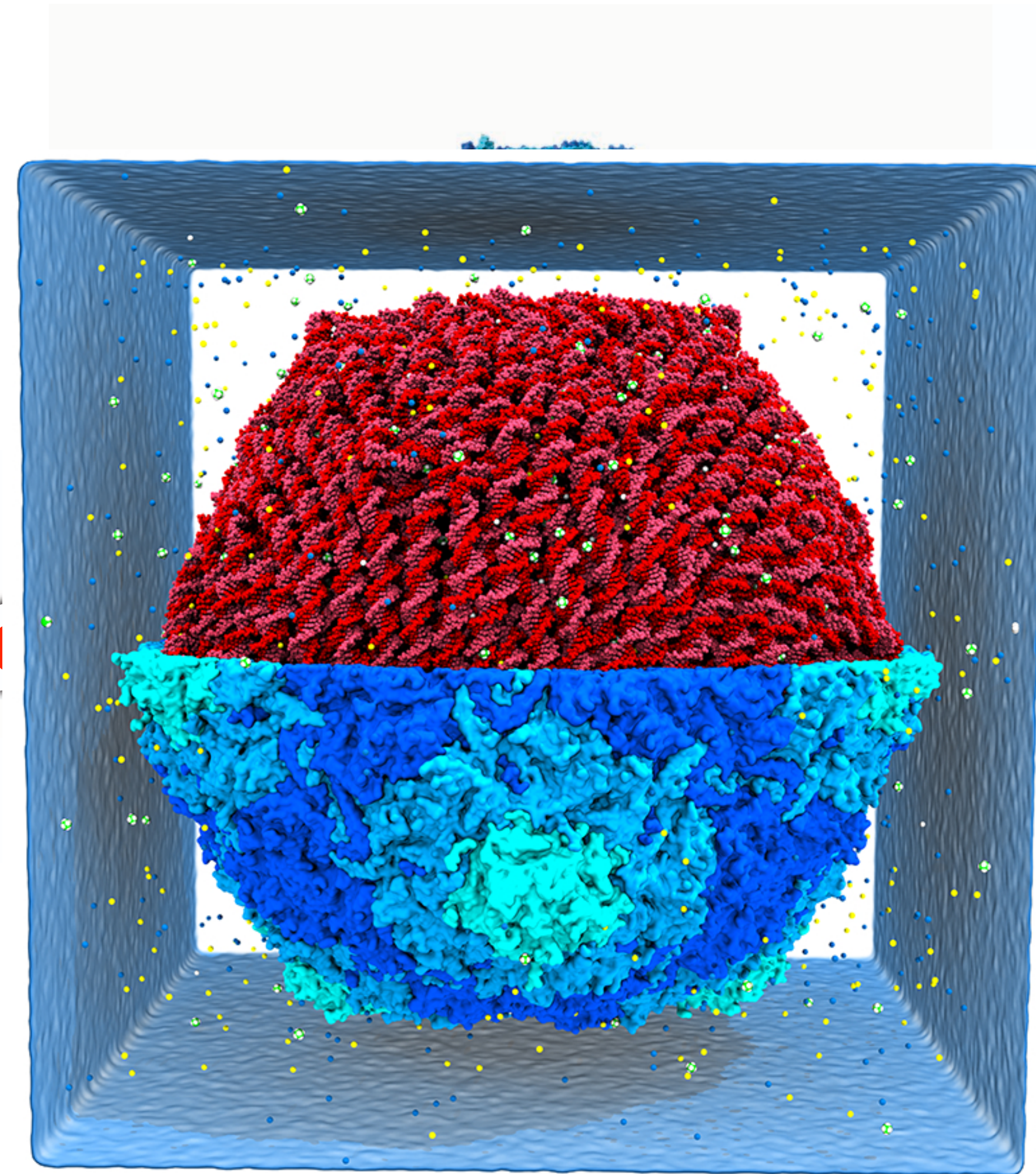
Viscosity calculation will reveal how RNA modulates the fluidity of the condensate

First all-atom structure of a complete packaged virus



Alex
Evelevich
(UIUC)

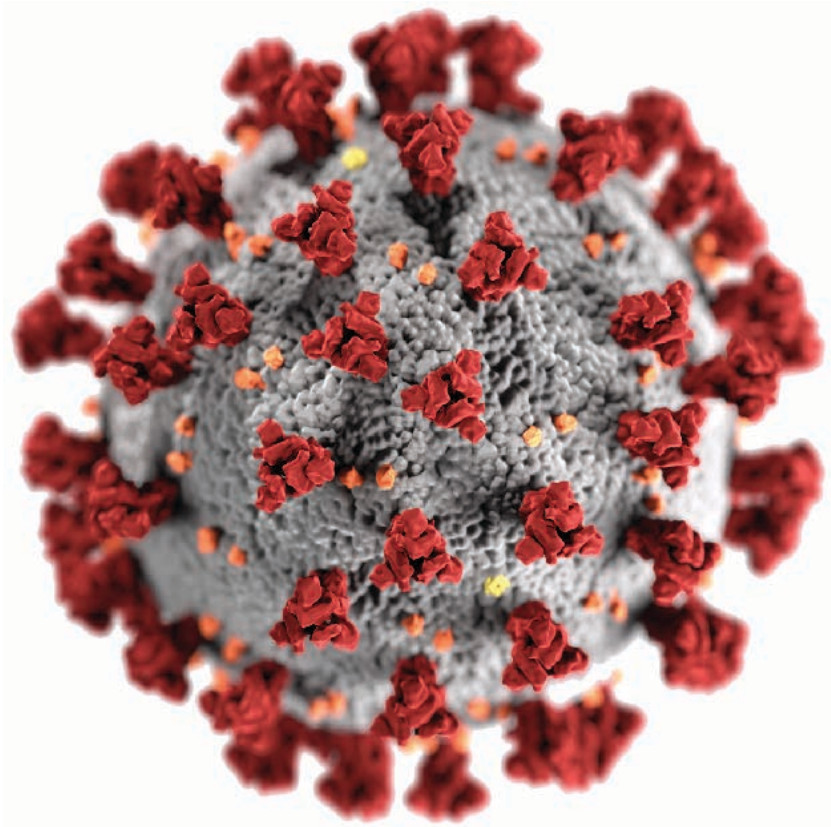
Genome of HK97:
~38,000 nucleotides
(long molecule ever
simulated)
~ 2.5M atoms



Complete solvated system contains ~ 26M atoms

1 μ s long simulation on Frontera is ~30 days on
512 nodes; 15% boost in performance in 2020!

Not possible anywhere else



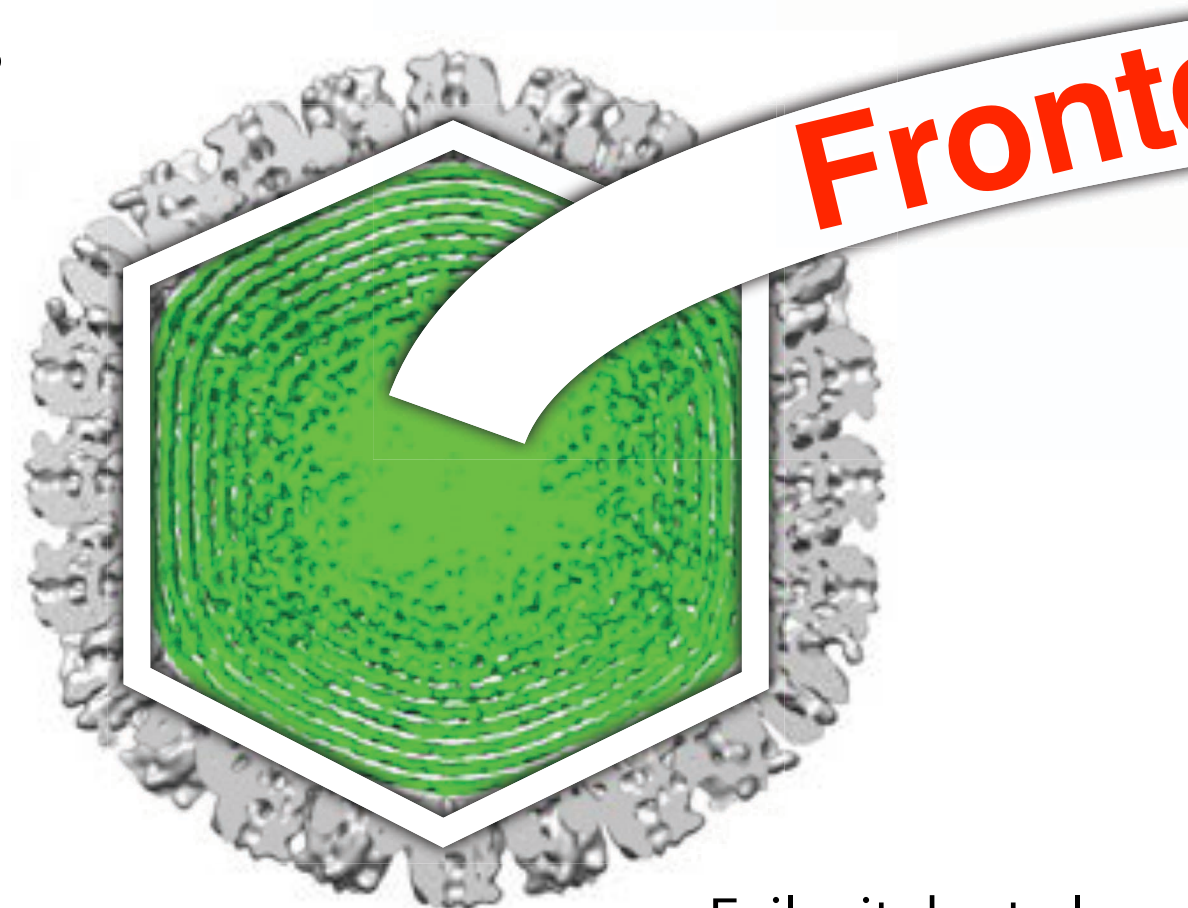
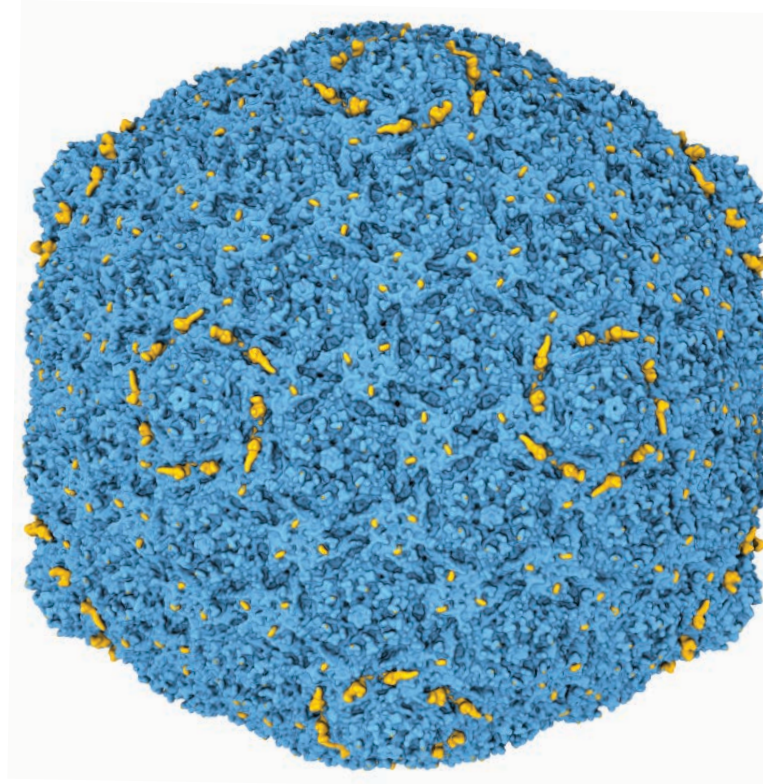
Virus particle

Protein capsid

Atomic structures are
available for several
viruses

Genome

Partially resolved cryoEM density



Evilevitch et al

Gan, Lu, et al.
Structure 14.11
(2006): 1655-1665.

Experiments cannot resolve the genome
structure with atomic resolution

Open questions:

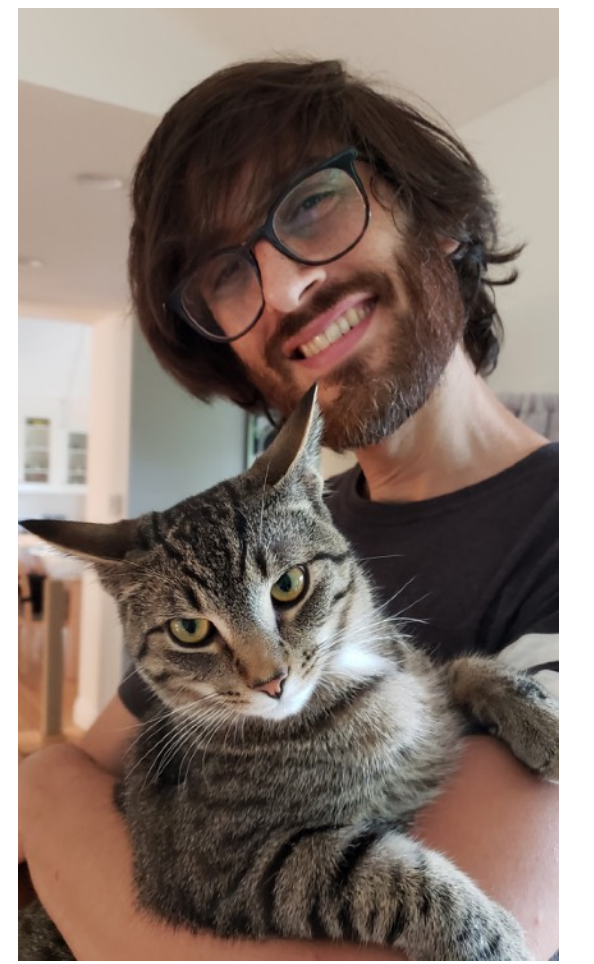
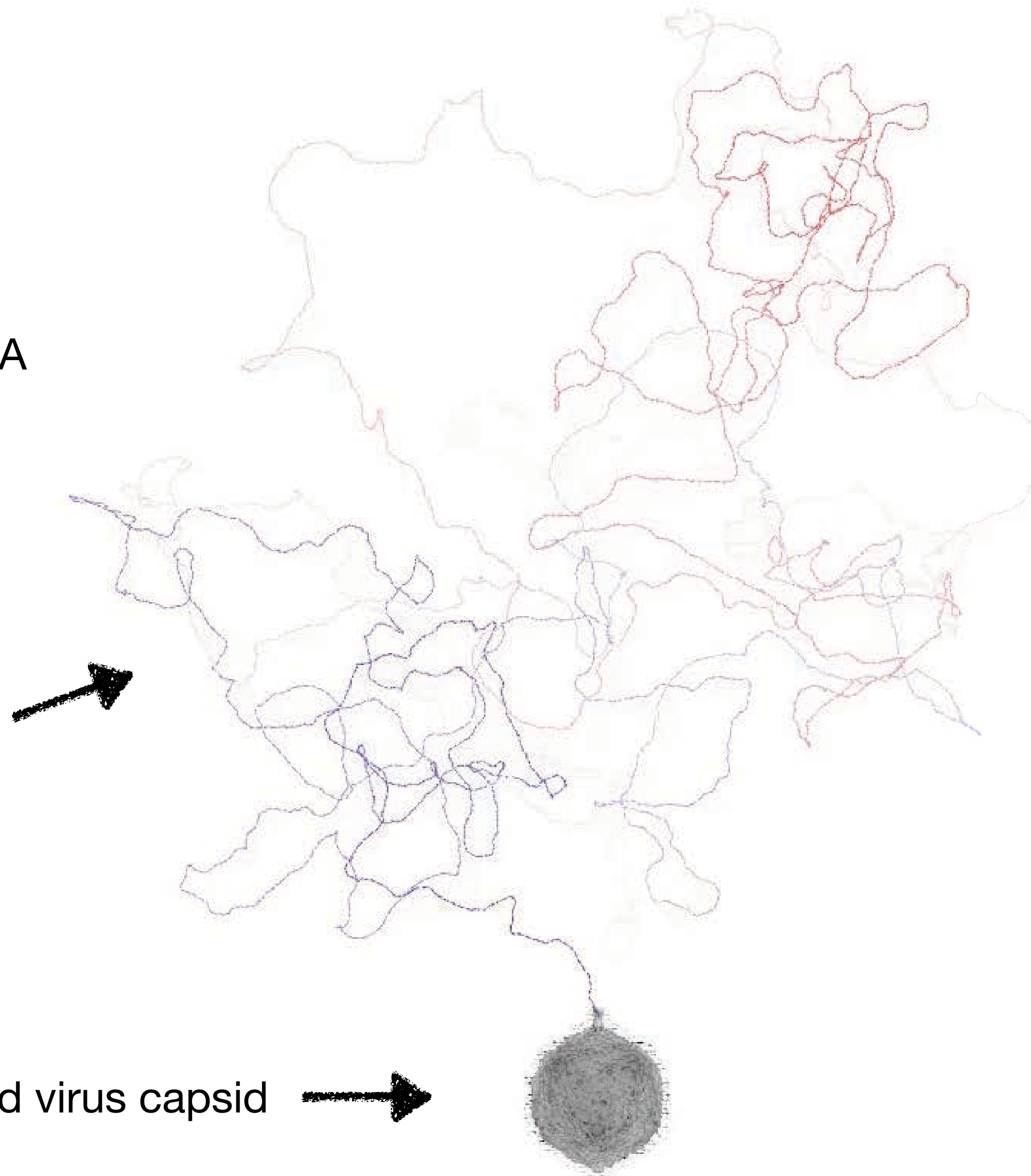
- What is the 3D structure of the genome?
- How genome ejection is triggered and sustained?
- Can genome be used as a drug target?

Packaging a model herpes-like virus

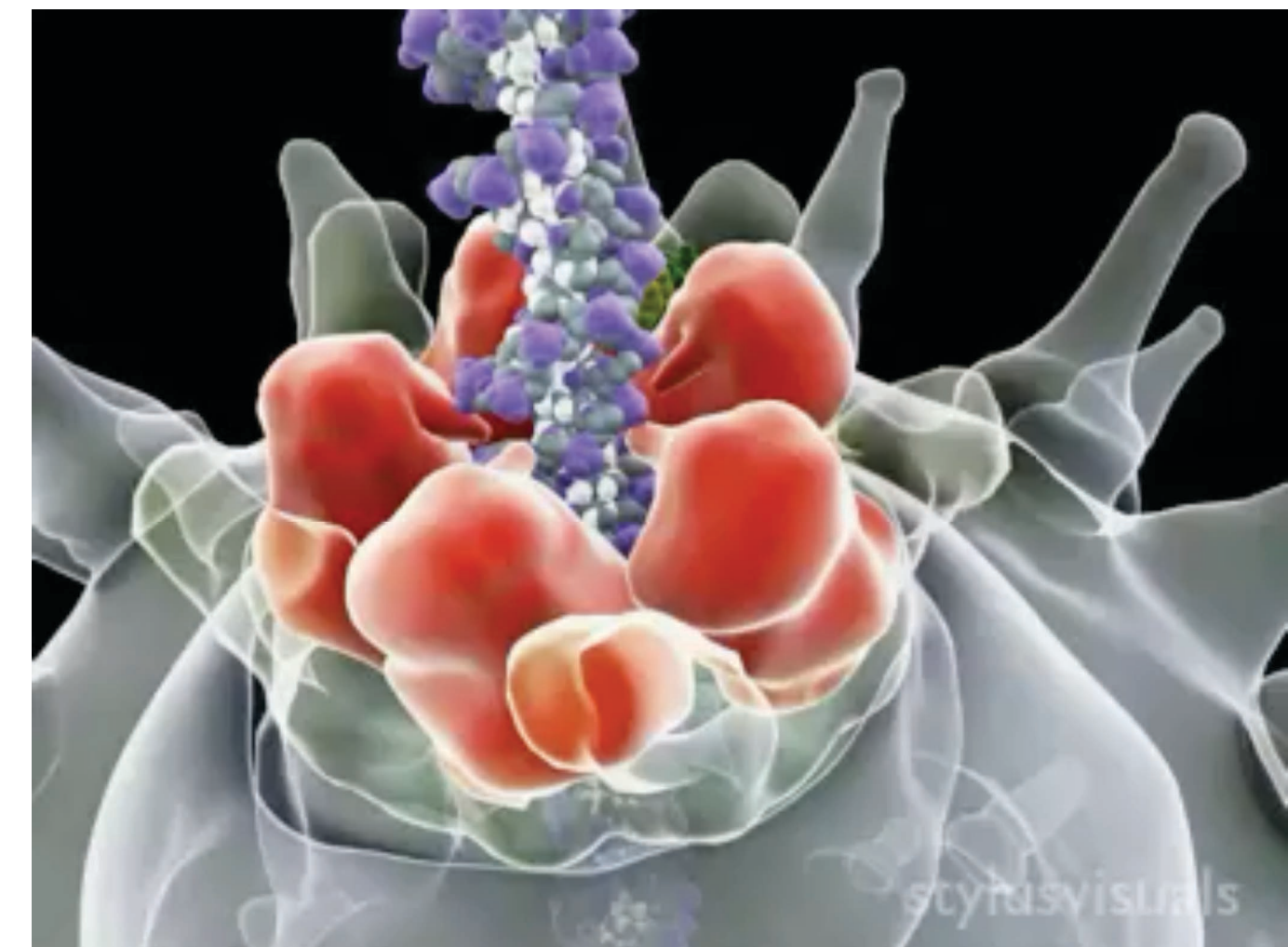
HK97 dsDNA virus infects bacteria and is a model system for pressurized dsDNA viruses like herpes

Unpackaged viral genome

Fixed virus capsid



Chris Maffeo



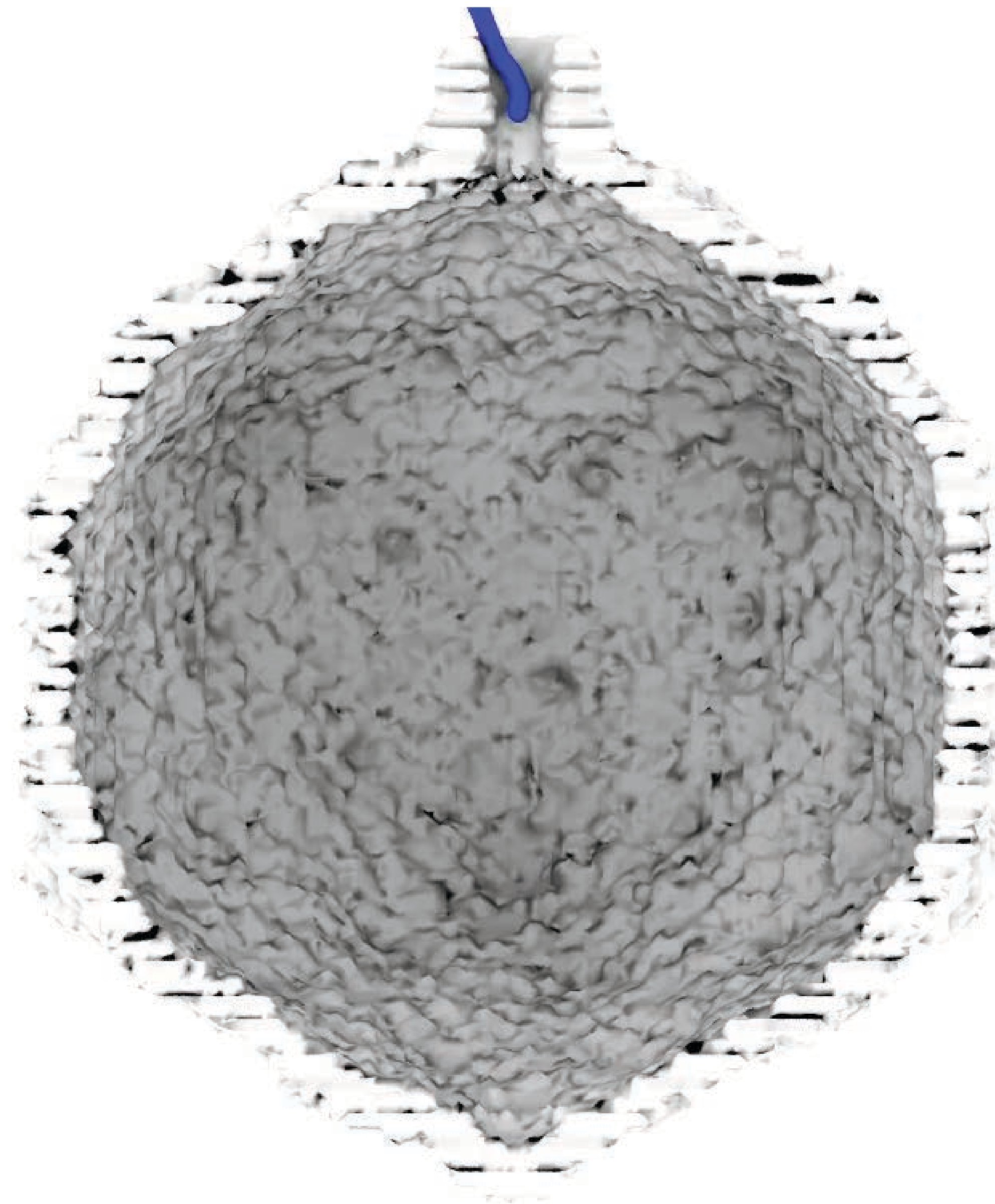
Takes about 3 minutes to pack DNA 130 times longer than the capsid !

Movie: Carlos Bustamante Lab

Packaging a model herpes-like virus

Packaging done with ARBD, our own GPU-accelerated coarse-grained BD package

bionano.physics.illinois.edu/arbd



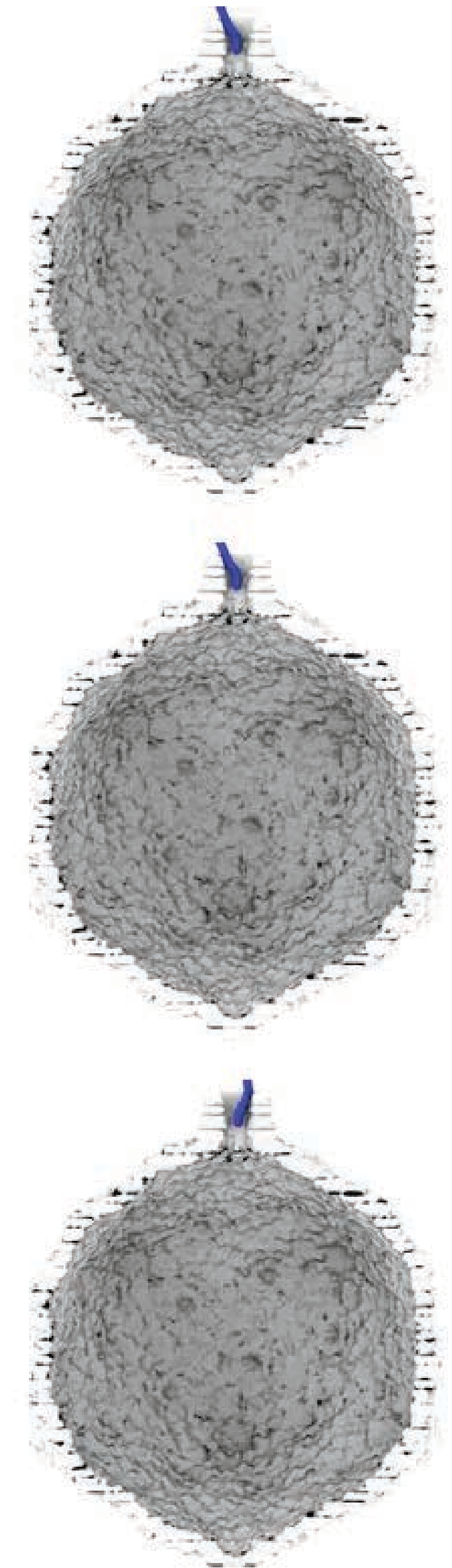
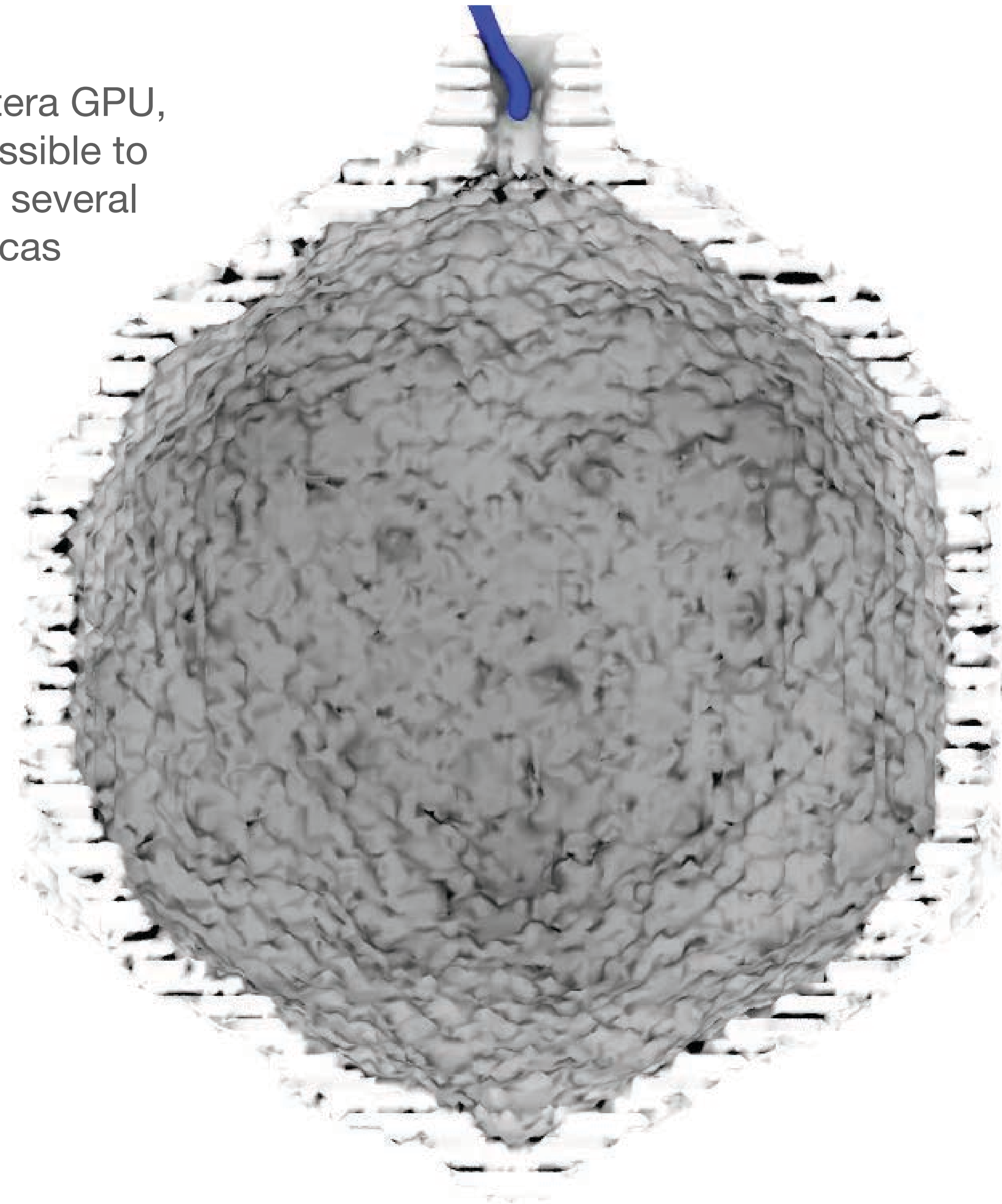
Trajectories lasted >1 ms with 40-fs timestep, requiring ~4 months of simulation

Frontera GPU-nodes rock!

Packaged last
Packaged first

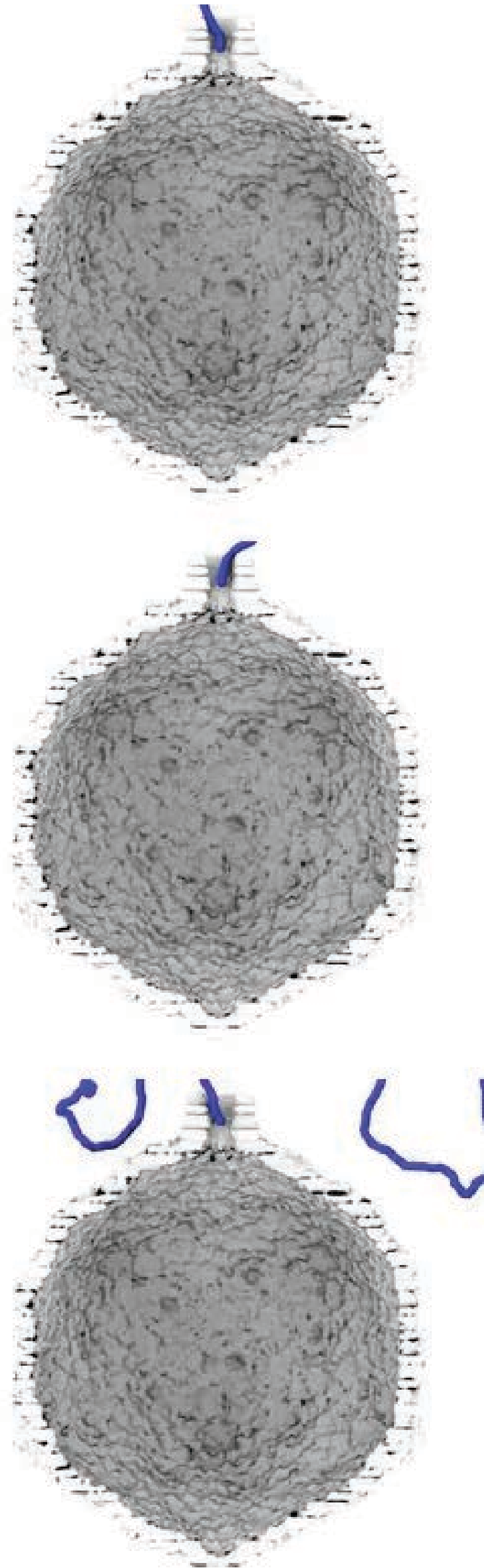
Packaging a model herpes-like virus

With Frontera GPU,
it was possible to
package several
replicas

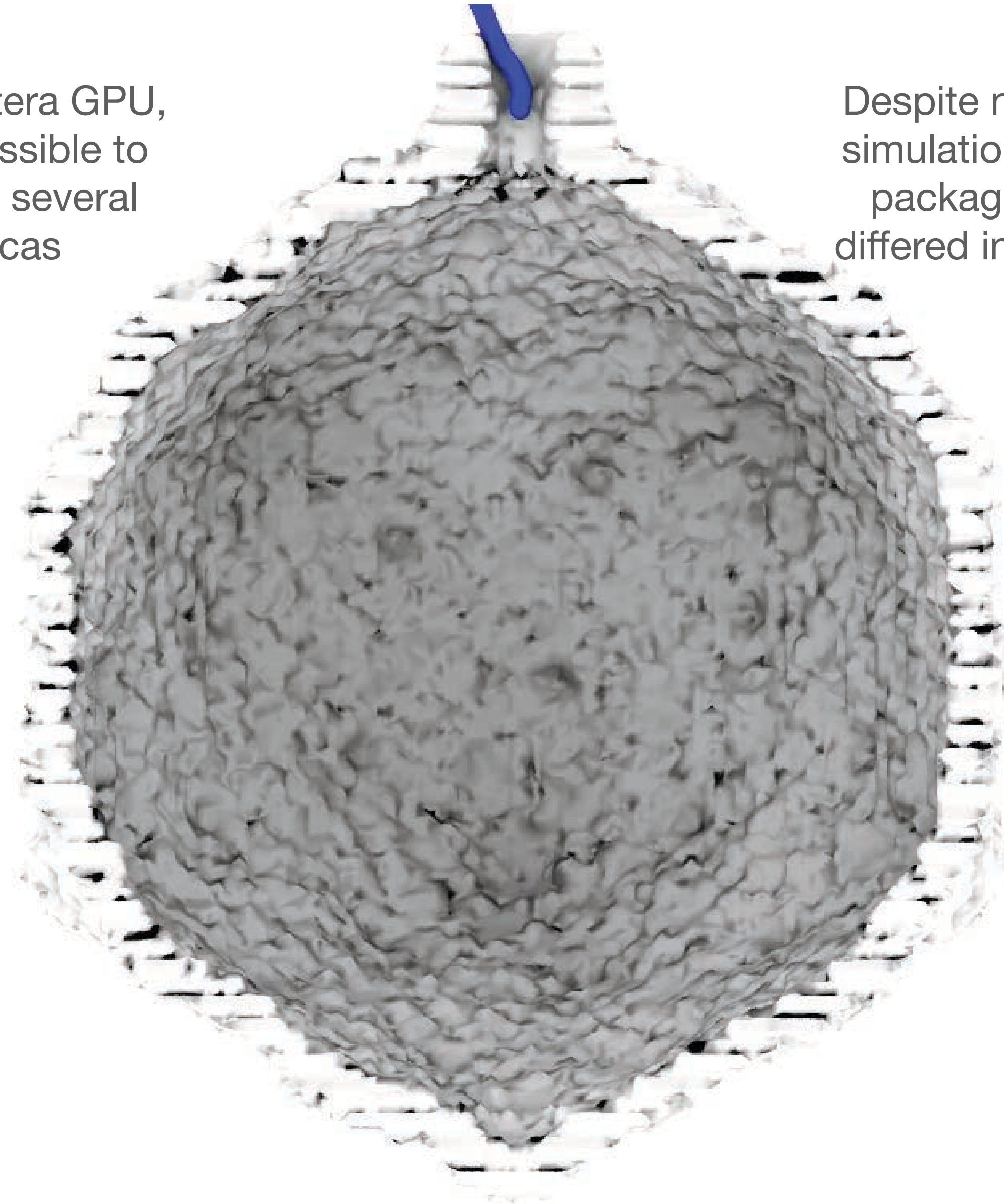


Packaged last
Packaged first

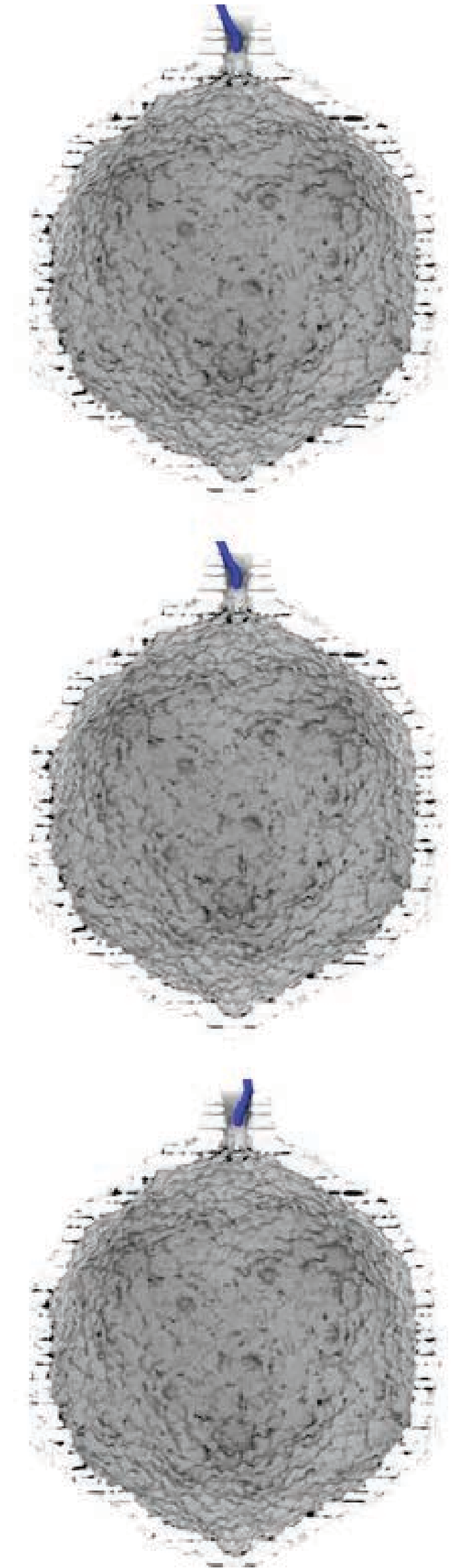
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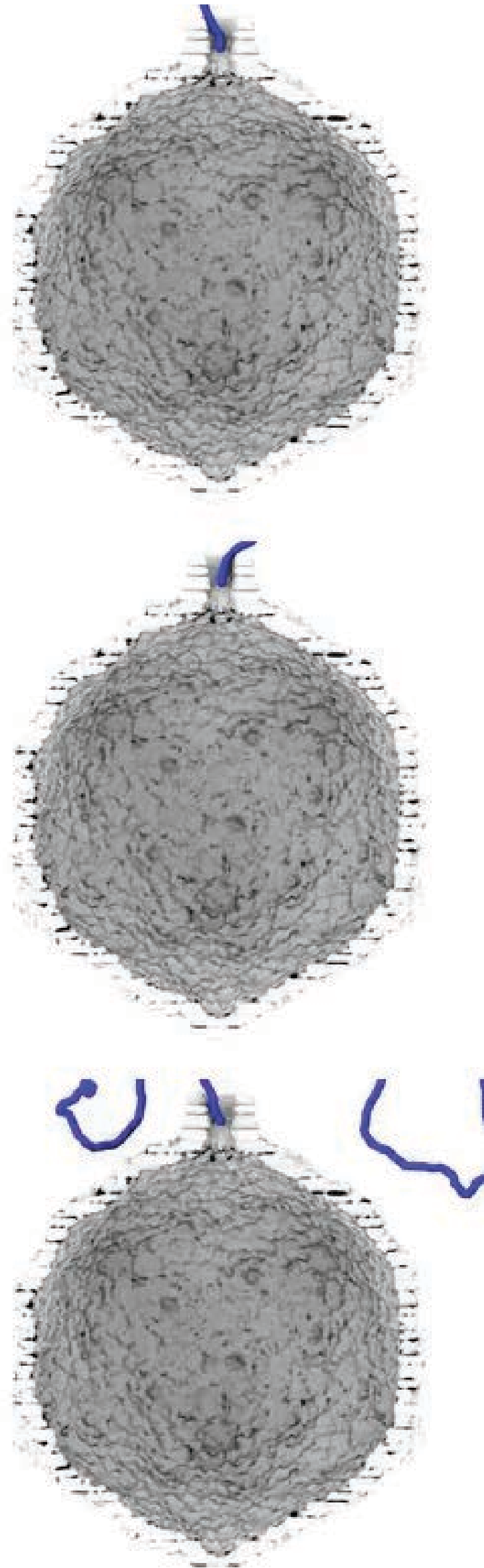


Despite near-identical
simulation conditions,
packaged genome
differed in each capsid

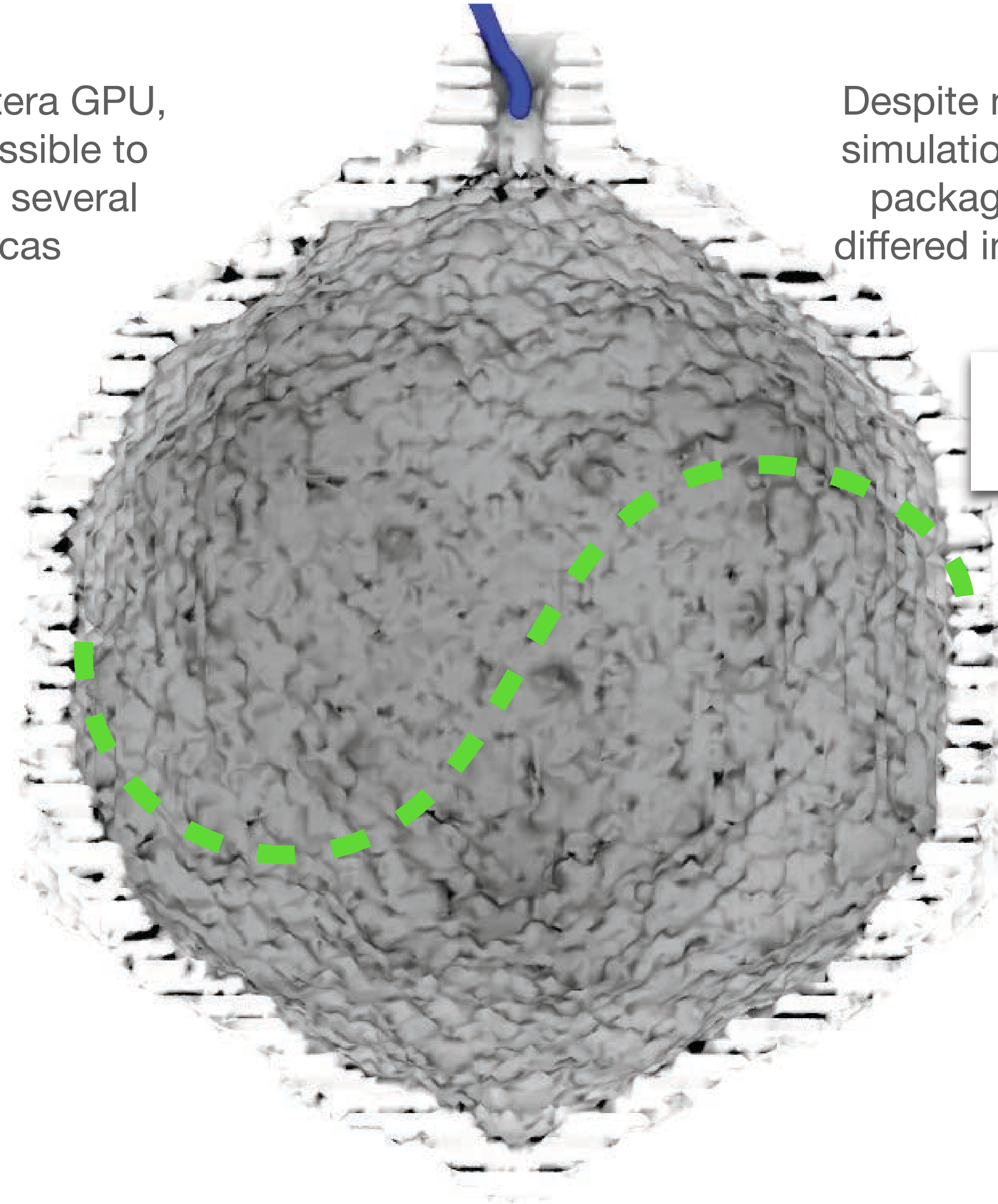


 Packaged last
Packaged first

Packaging a model herpes-like virus



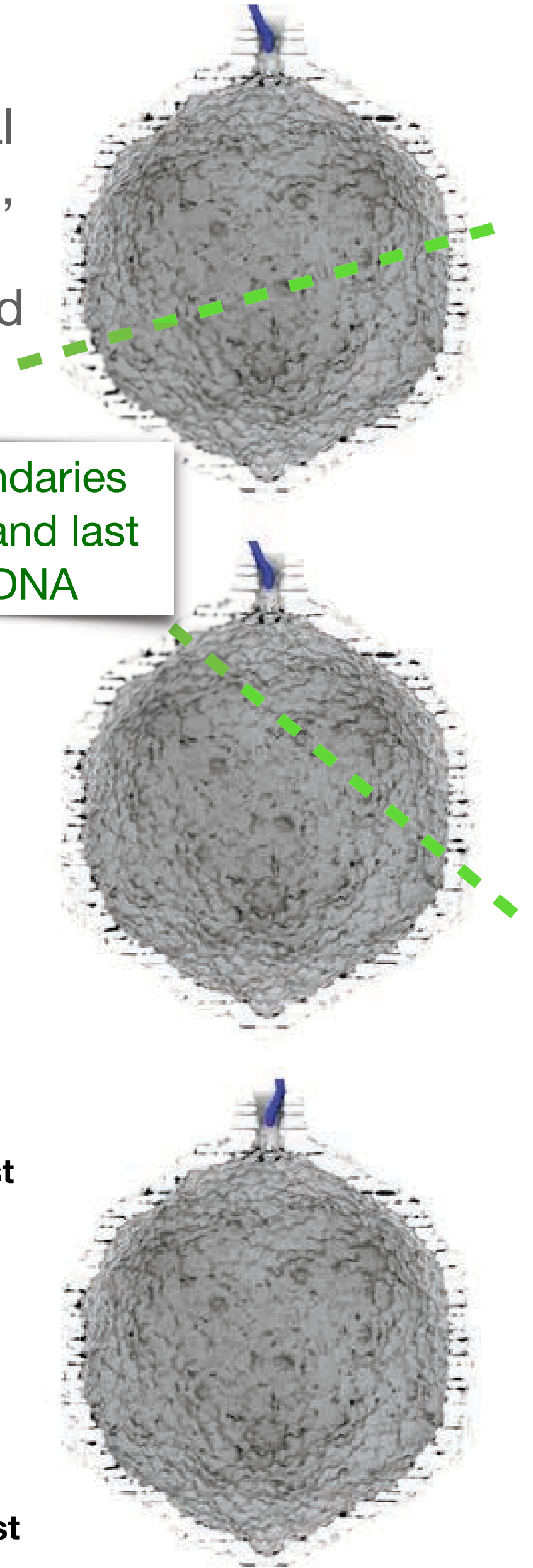
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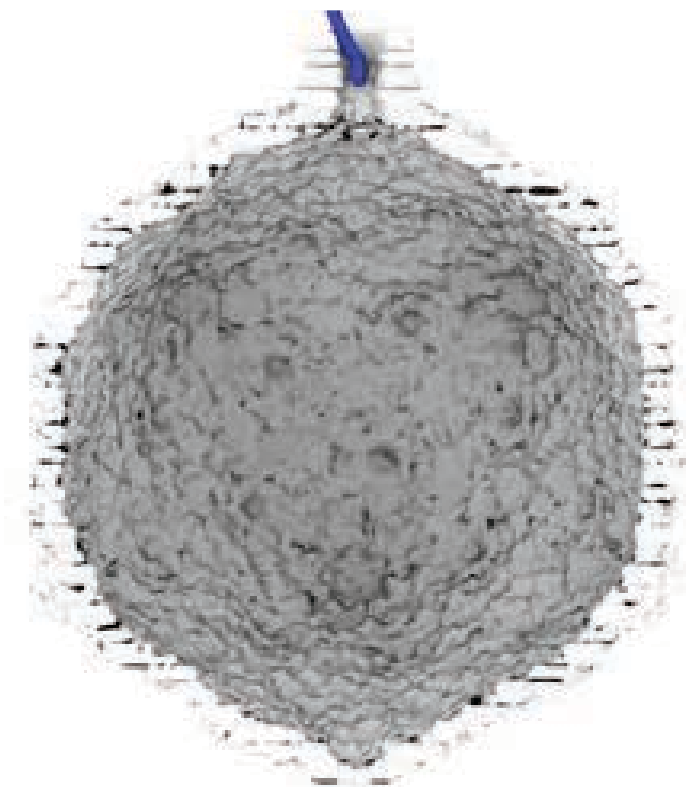
Despite near-identical
simulation conditions,
packaged genome
differed in each capsid

Different boundaries
between first and last
packaged DNA

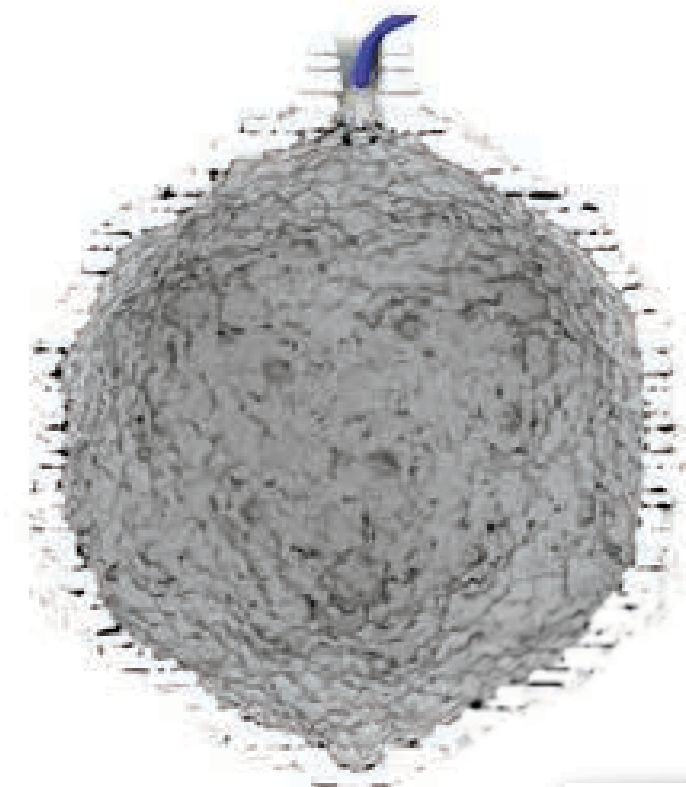
Packaged last
Packaged first



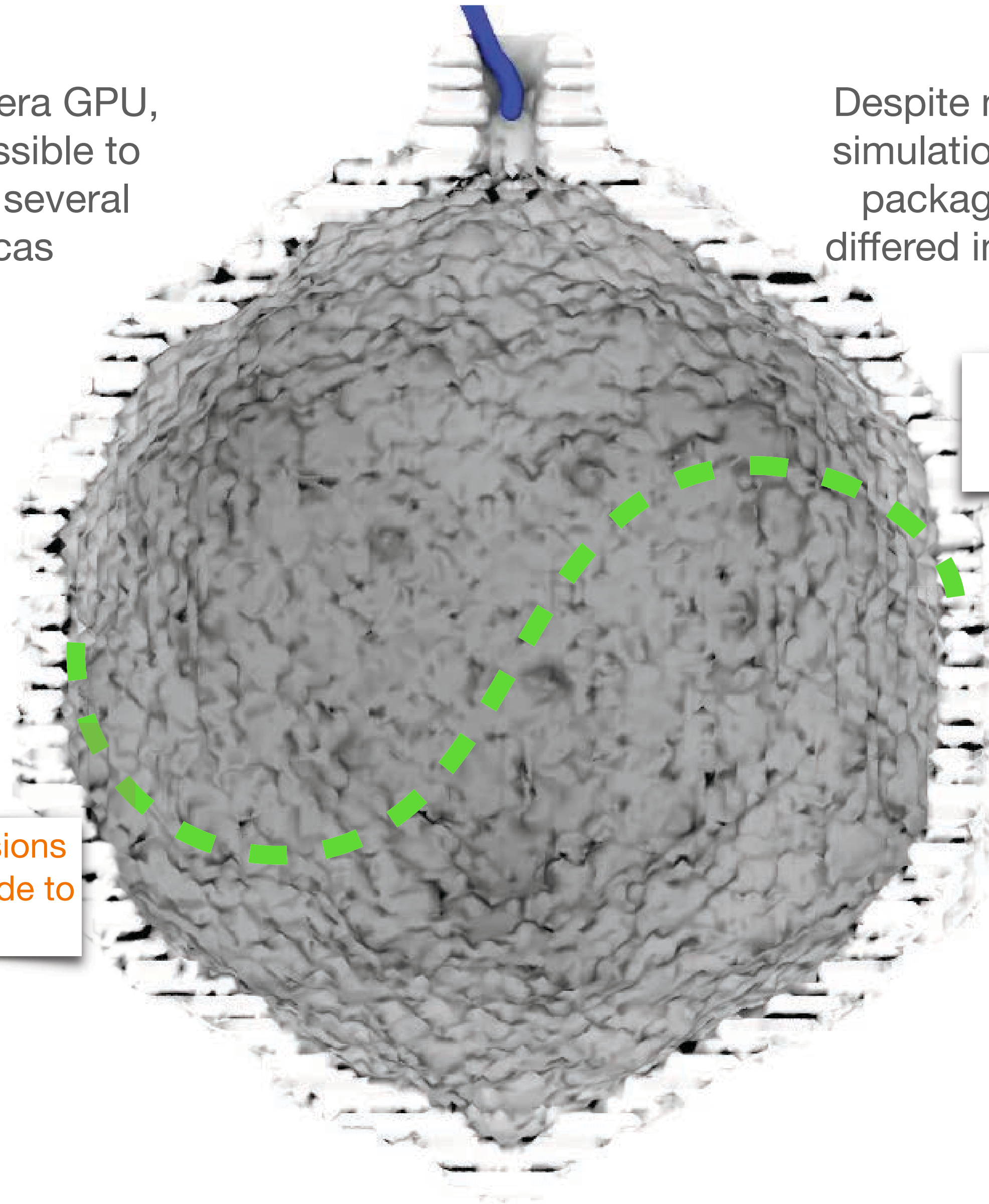
Packaging a model herpes-like virus



With Frontera GPU,
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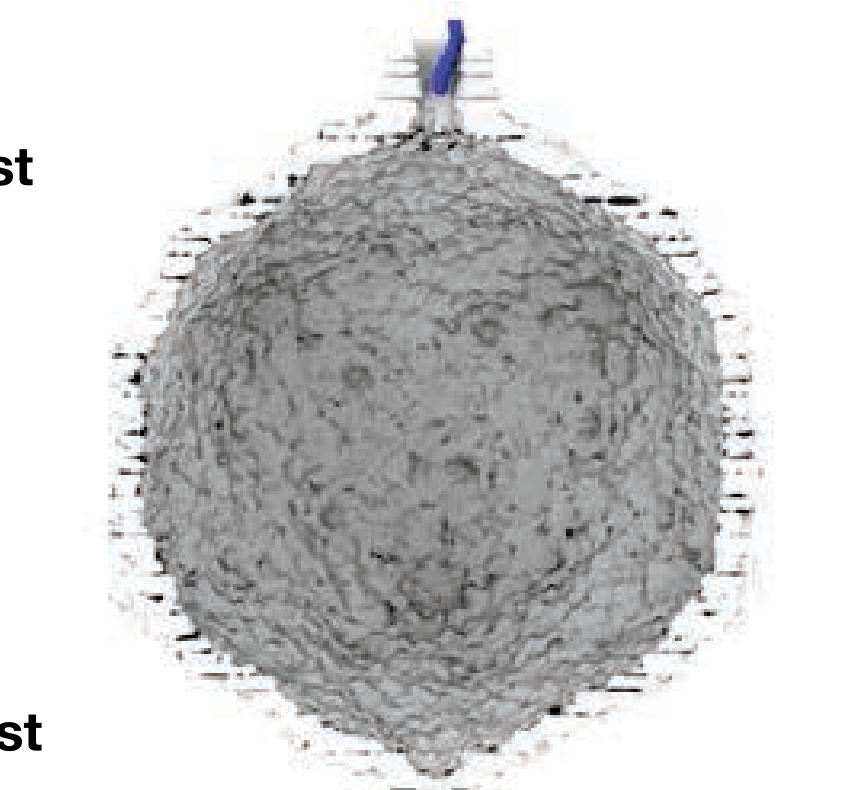
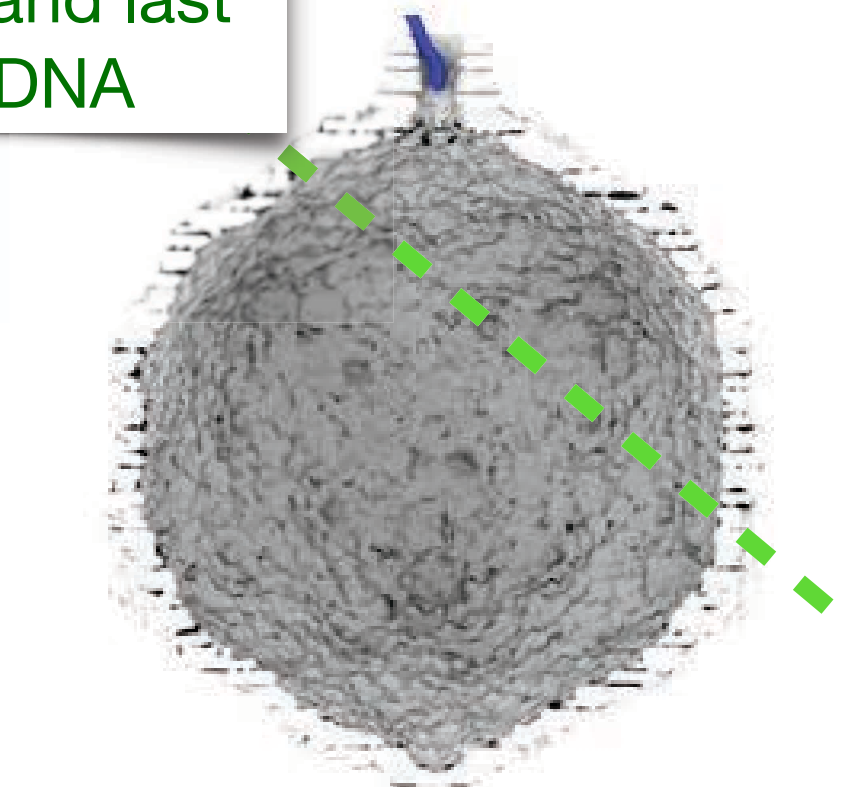
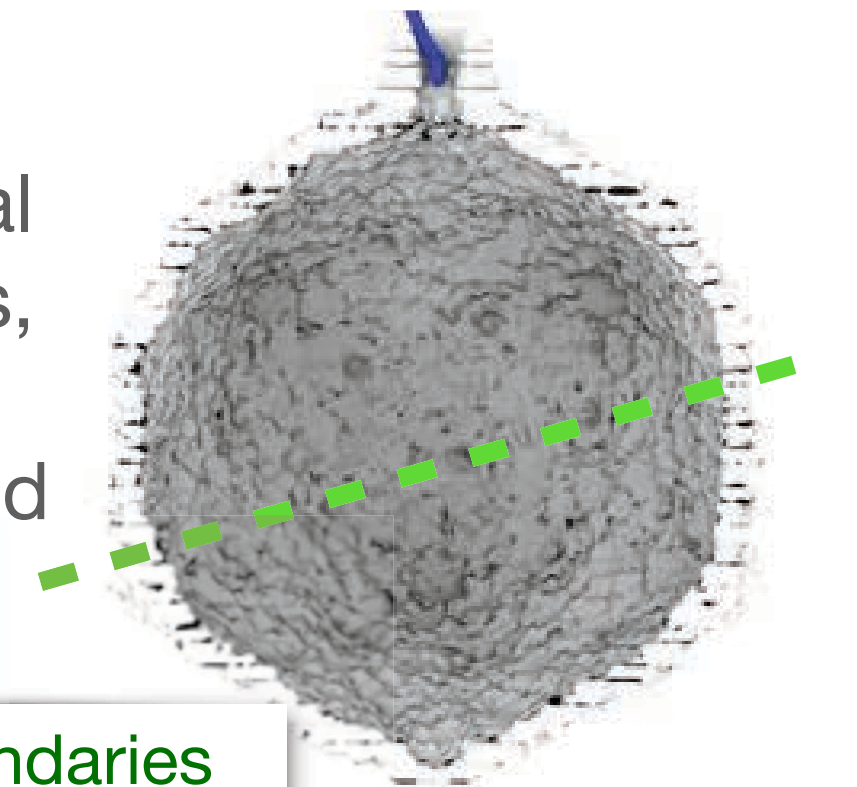
Occasional protrusions
of DNA from one side to
another



Despite near-identical
simulation conditions,
packaged genome
differed in each capsid

Different boundaries
between first and last
packaged DNA

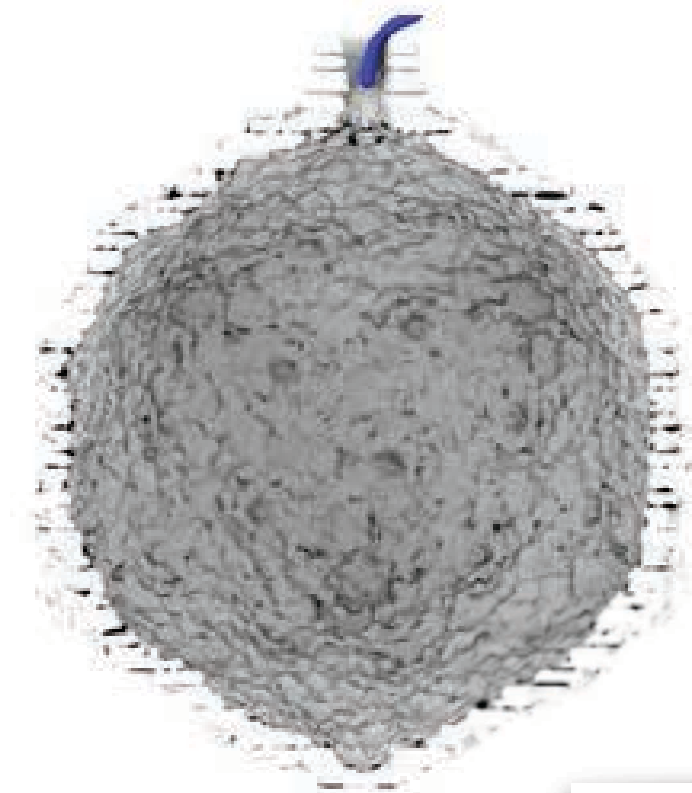
Packaged last
Packaged first



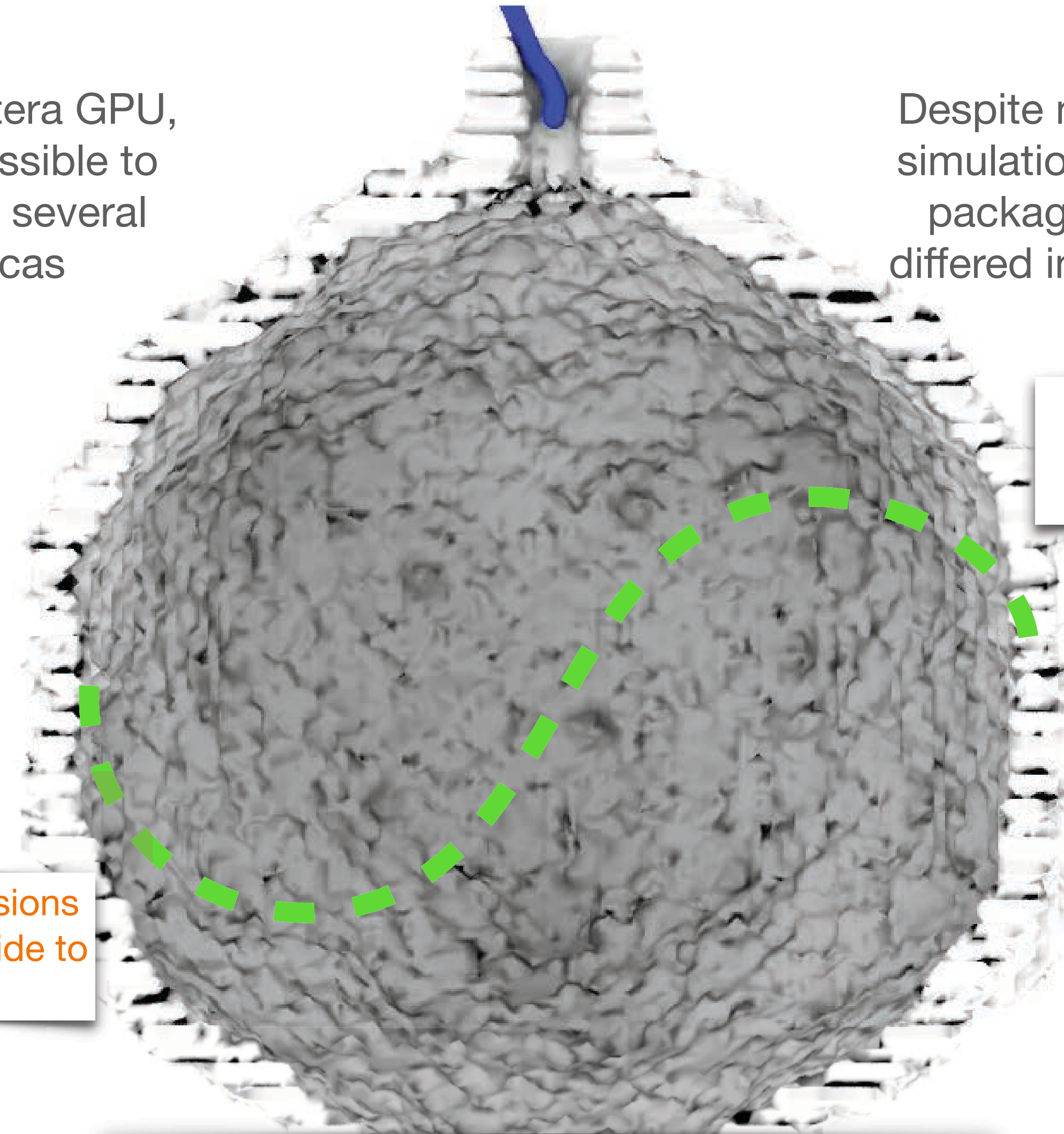
Packaging a model herpes-like virus



With Frontera GPU, it was possible to package several replicas

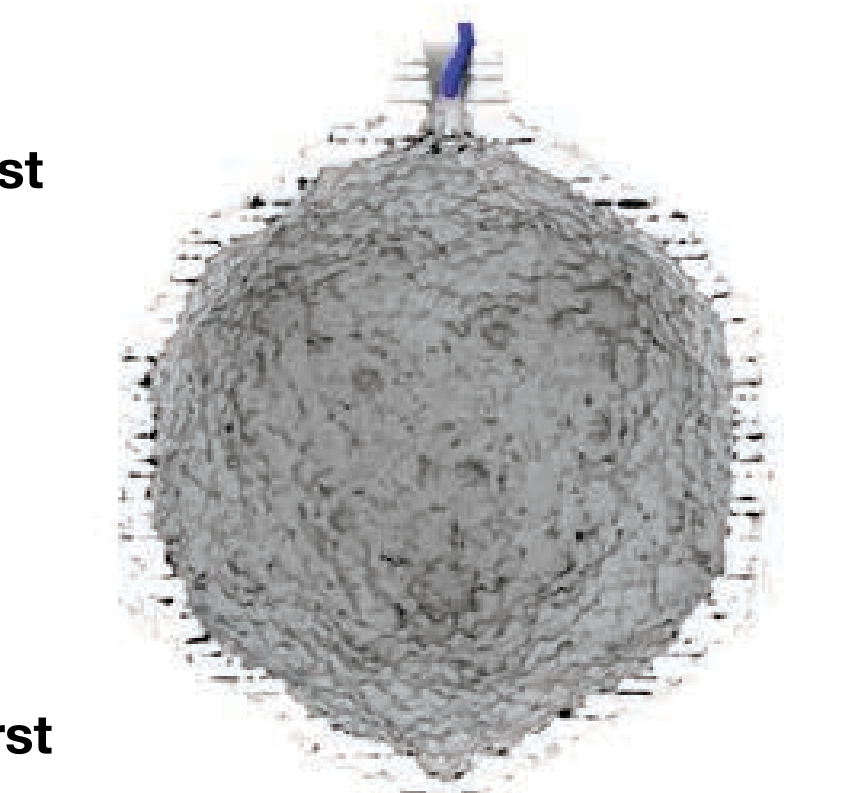
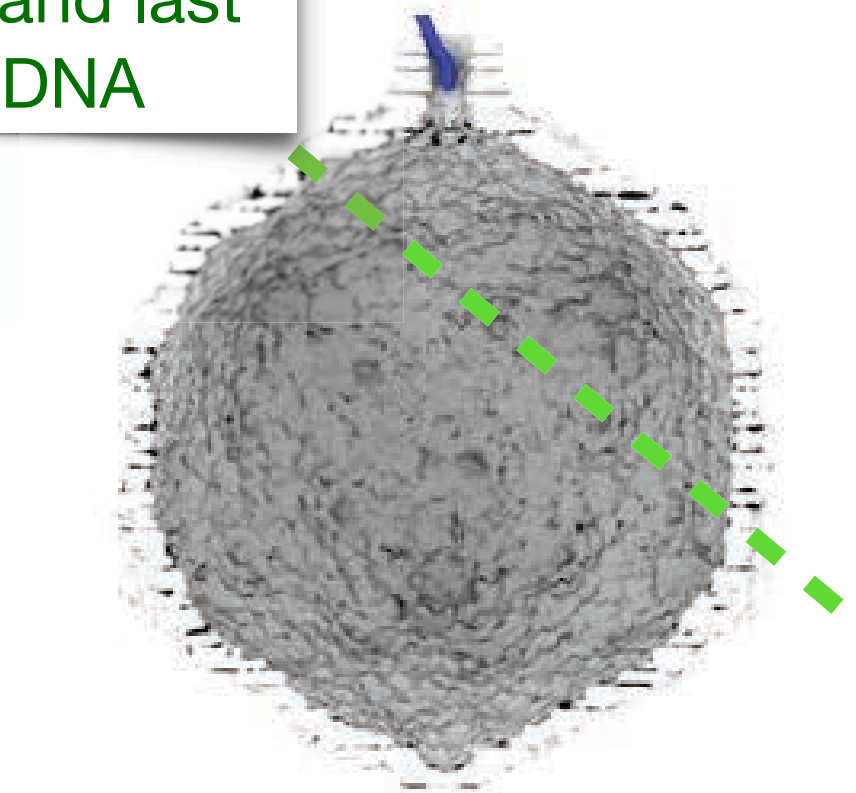
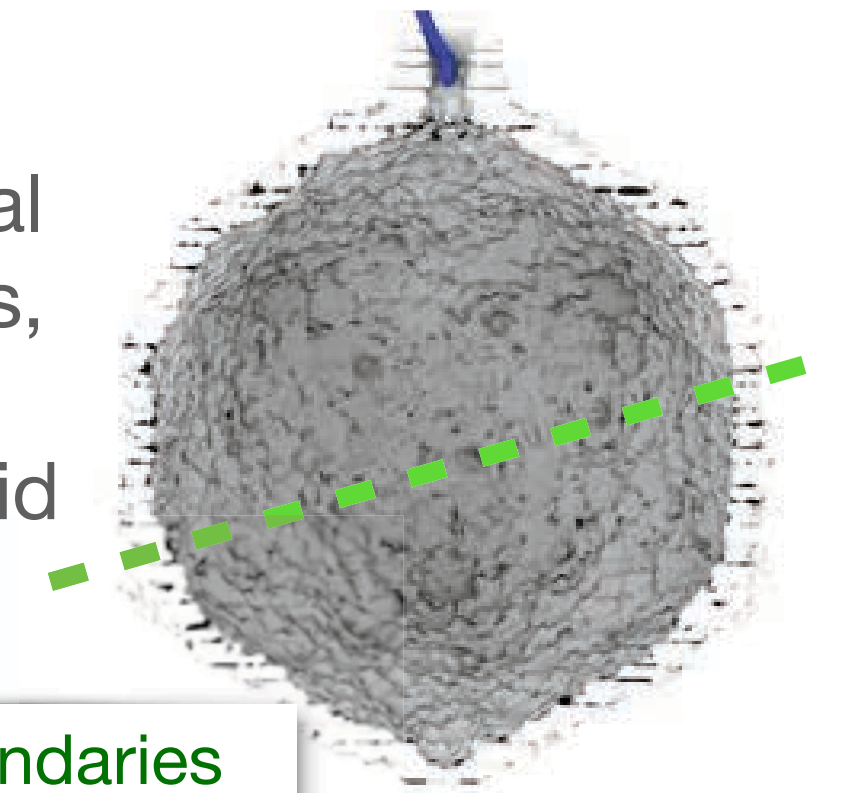


Occasional protrusions of DNA from one side to another



Despite near-identical simulation conditions, packaged genome differed in each capsid

Different boundaries between first and last packaged DNA

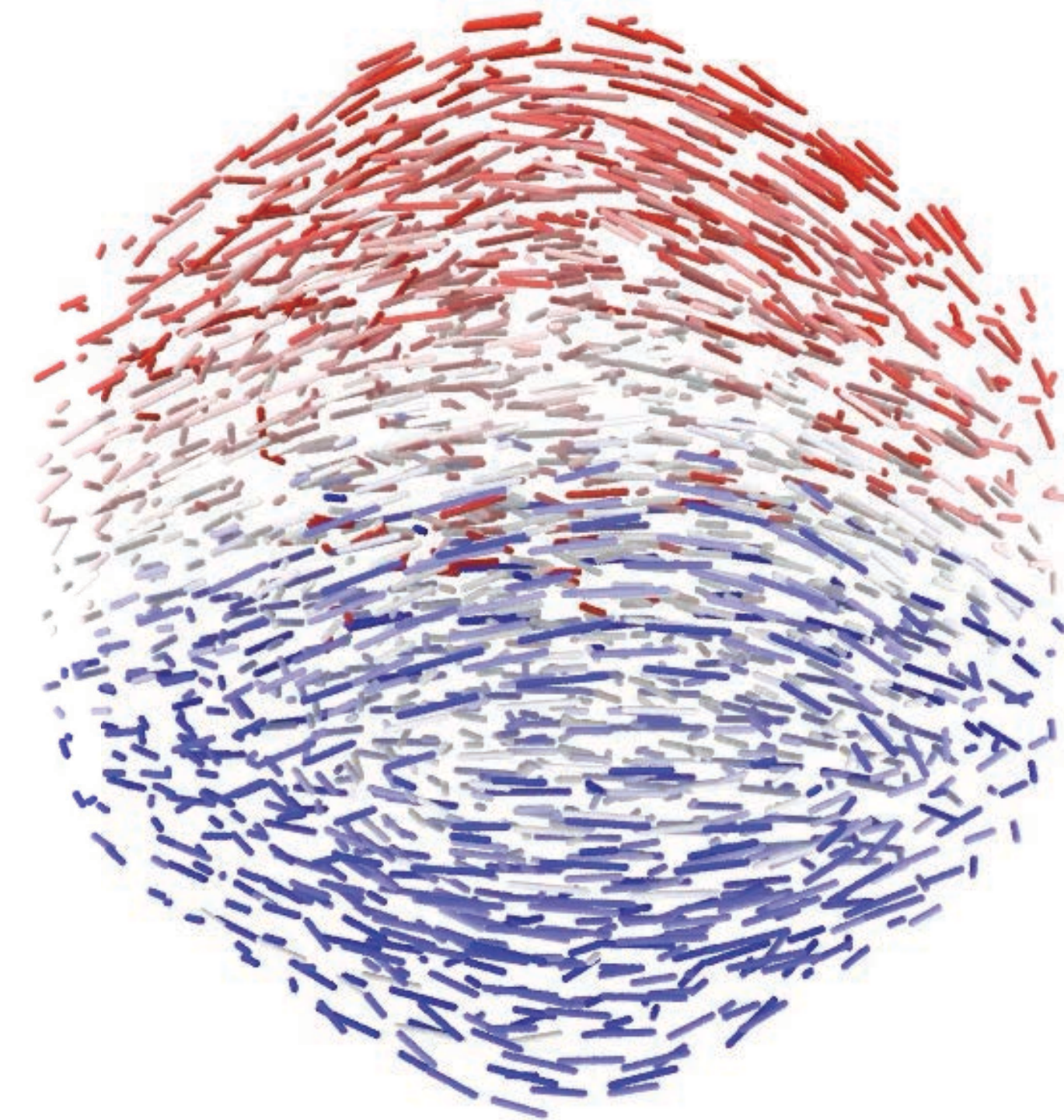
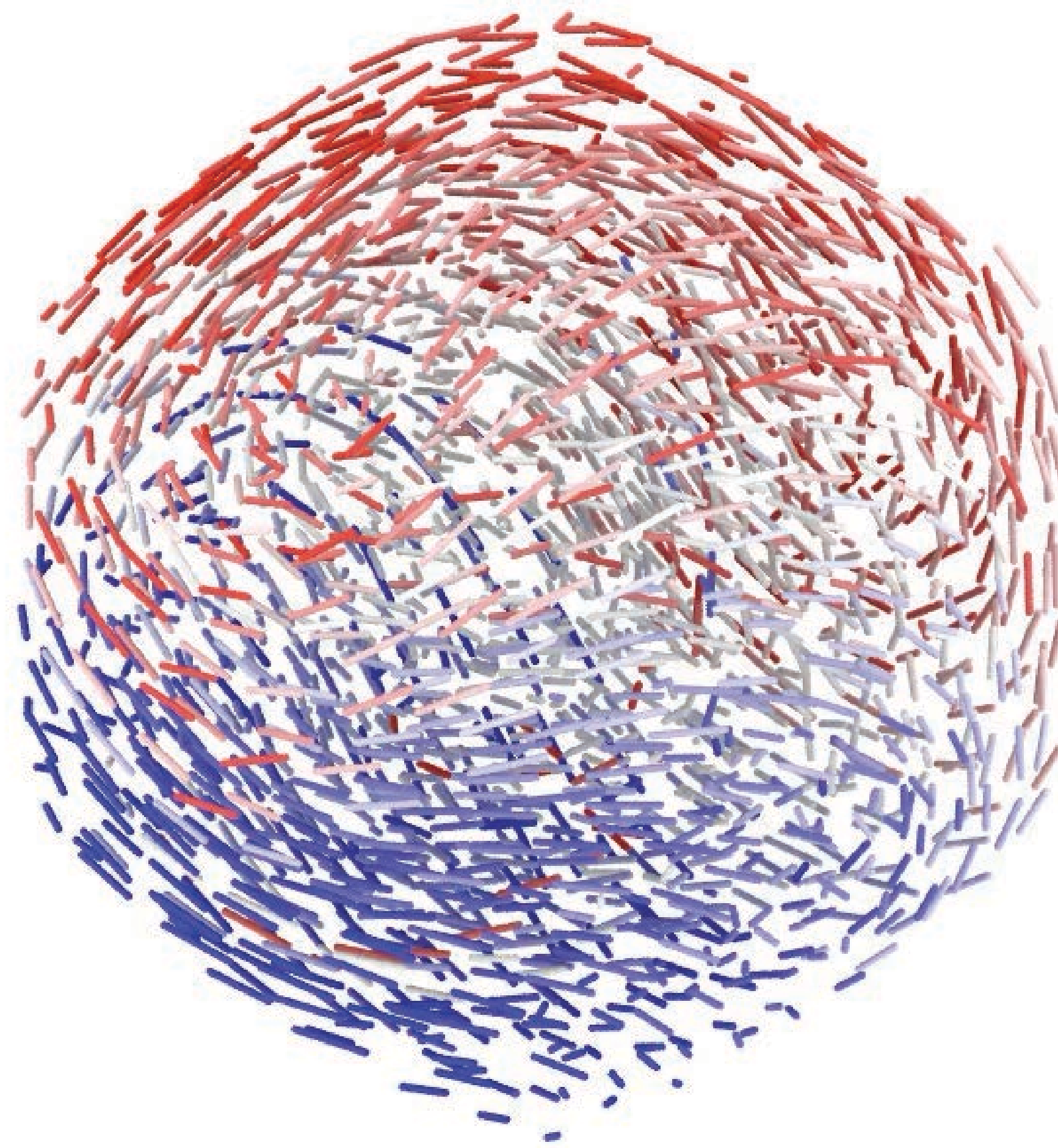
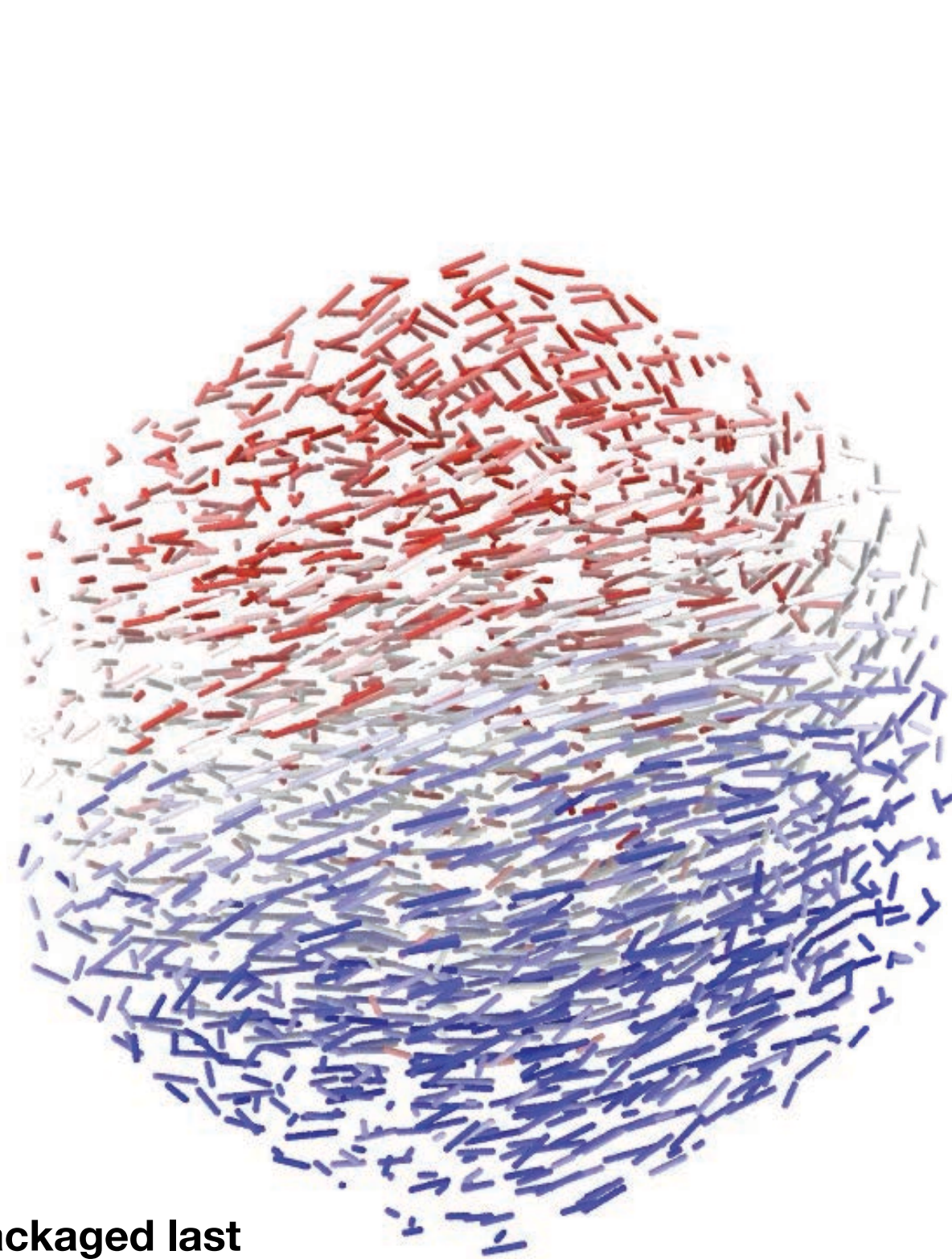


Despite common organizing principle of keeping DNA helices aligned, we did not observe textbook spooling of genome

Packaged last
Packaged first

Packaged genome configurations are unique

Local helical axis of DNA, shown here, winds around the packaging axis near the equator



Packaged last

Packaged first

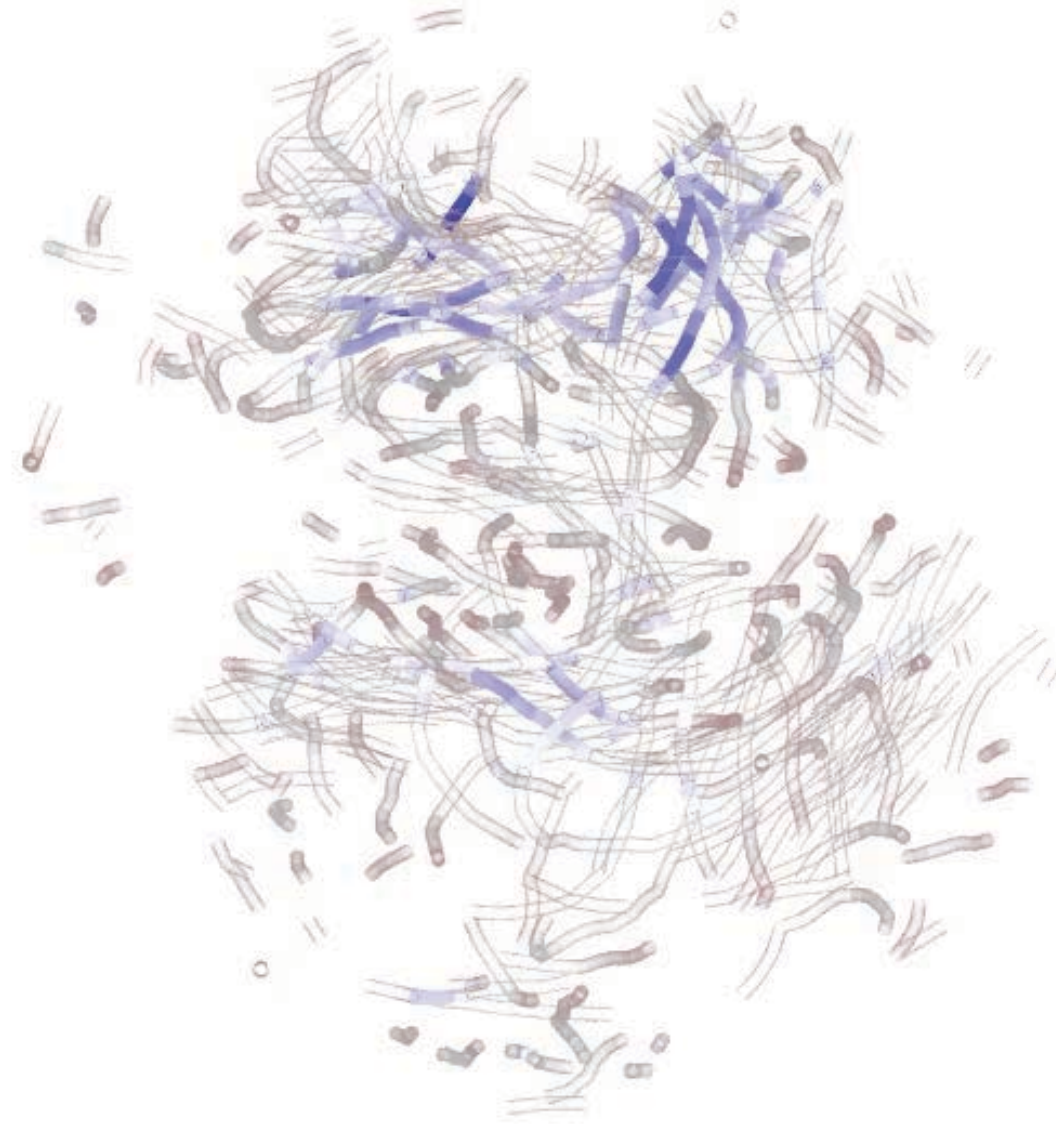
Baseball-like order at surface, with two cupped halves having orthogonal order at the poles

Order in the same-direction at the poles

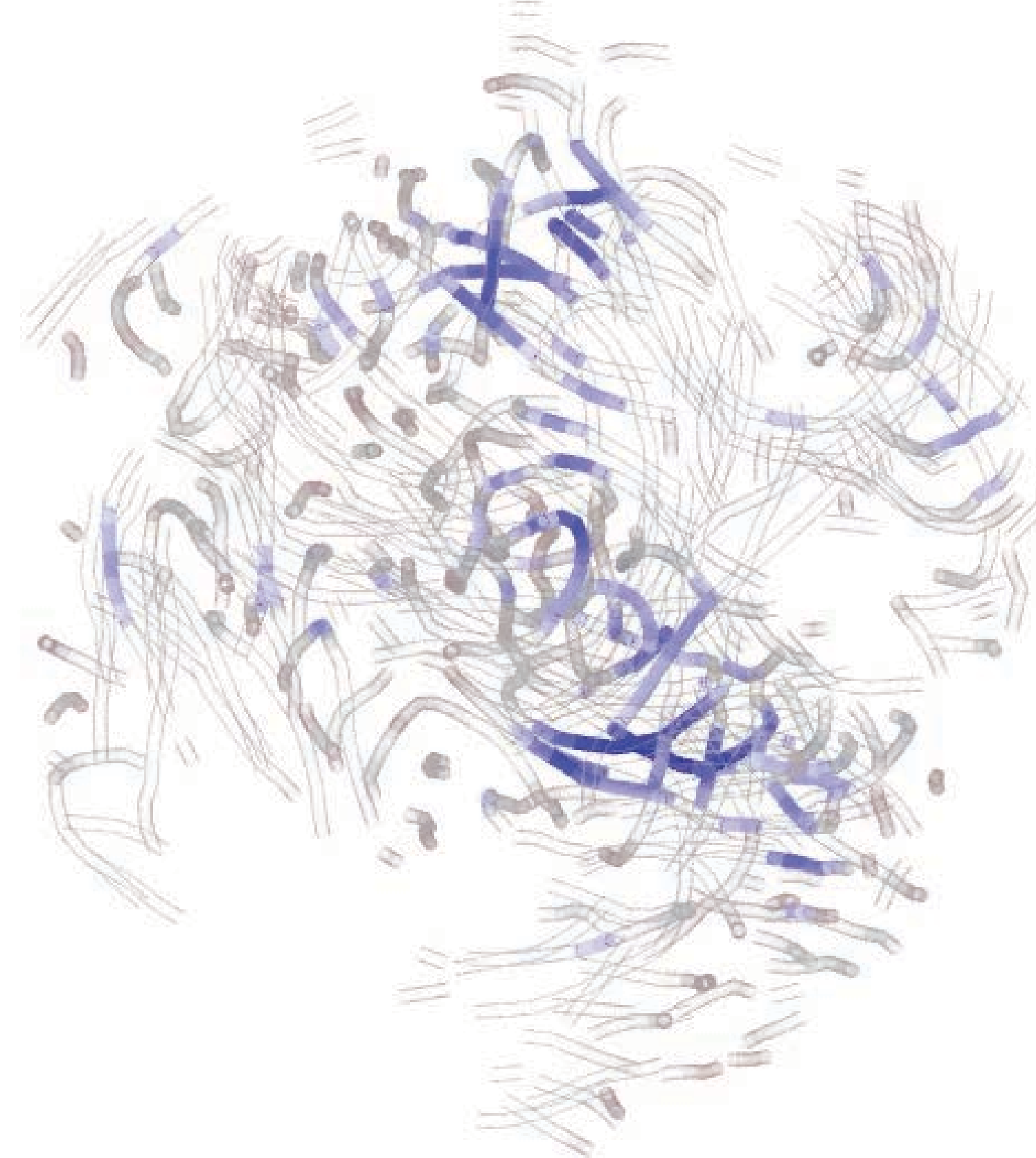
Diverse patterns of topological defects in liquid crystal ordering of genome

Local helical axis of DNA, shown here, winds around the packaging axis near the surface, but is more diverse in the interior

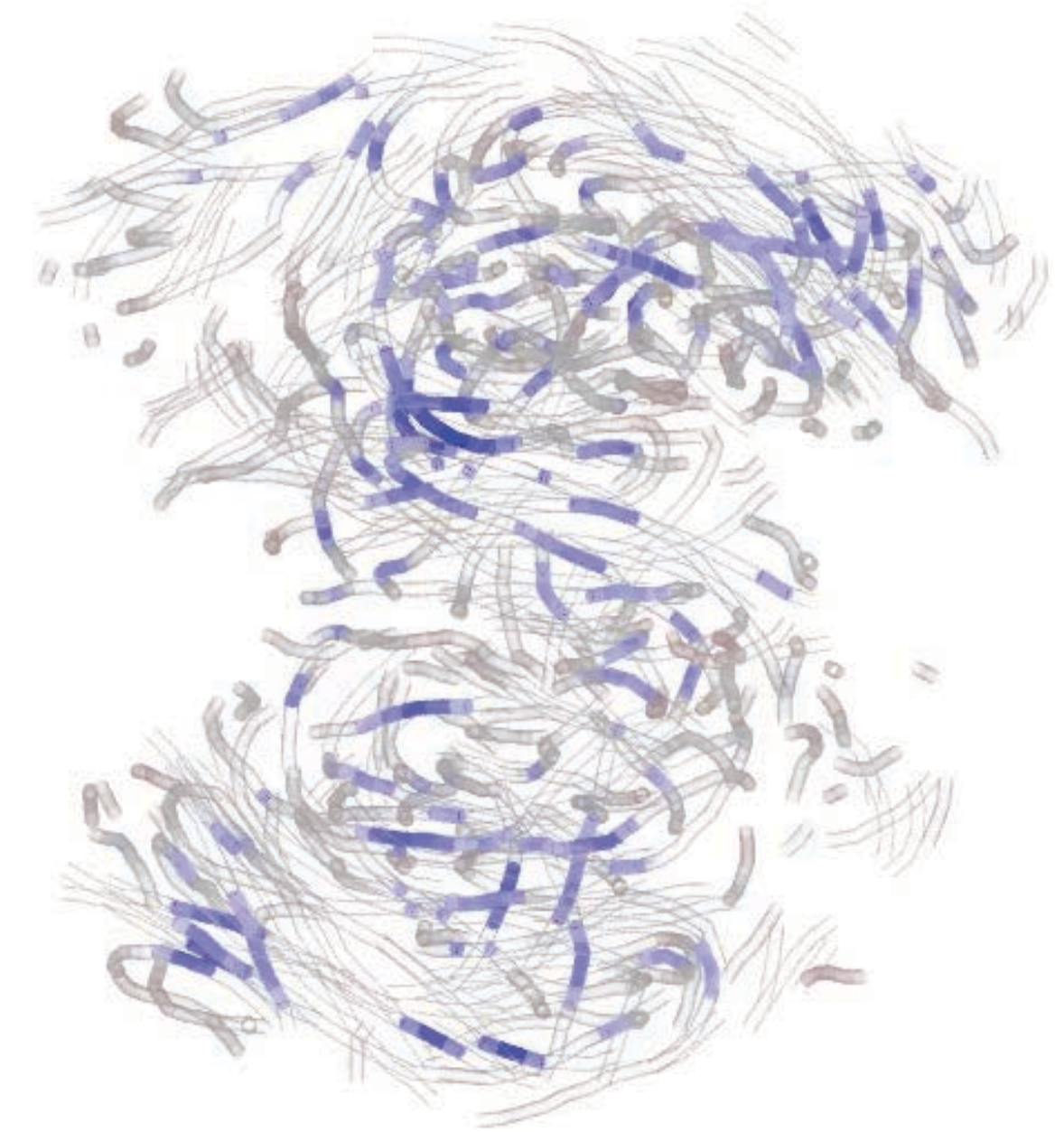
Relatively localized defects



Branching defects



Loop of defects



High alignment energy → Defects

Low alignment energy

Mapping to all-atom model



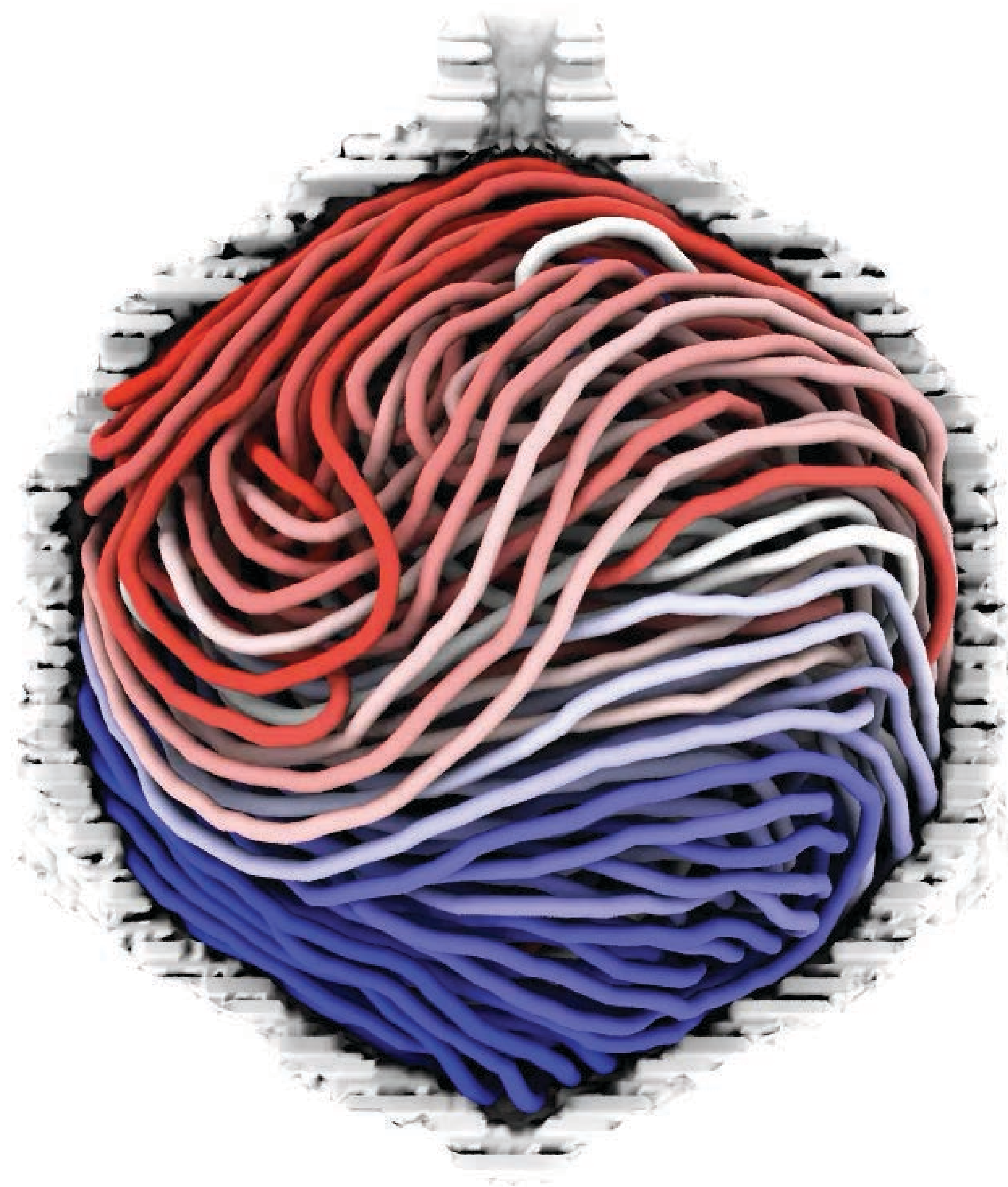
Kush Coshic

Splines are fit through the beads to facilitate “back-mapping” to higher resolution

First, a simulation is performed with a 1 bead/bp model

Next, a simulation is performed with a 2 bead/bp model

Finally, atomic coordinates are generated



Mapping to all-atom model

Splines are fit through the beads to facilitate “back-mapping” to higher resolution

First, a simulation is performed with a 1 bead/bp model

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Finally, atomic coordinates are generated



All-atom relaxation performed in vacuum with grid-based capsid and restraints applied to DNA

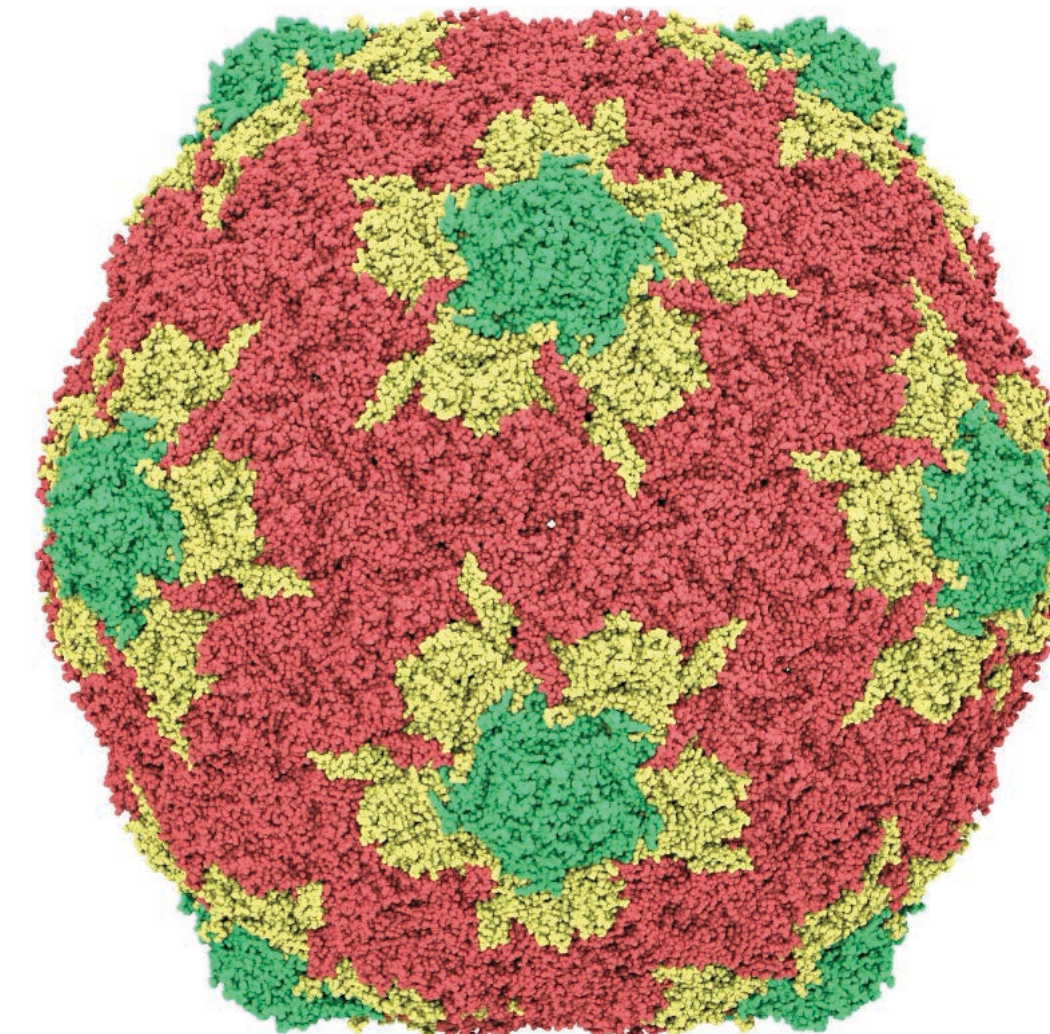
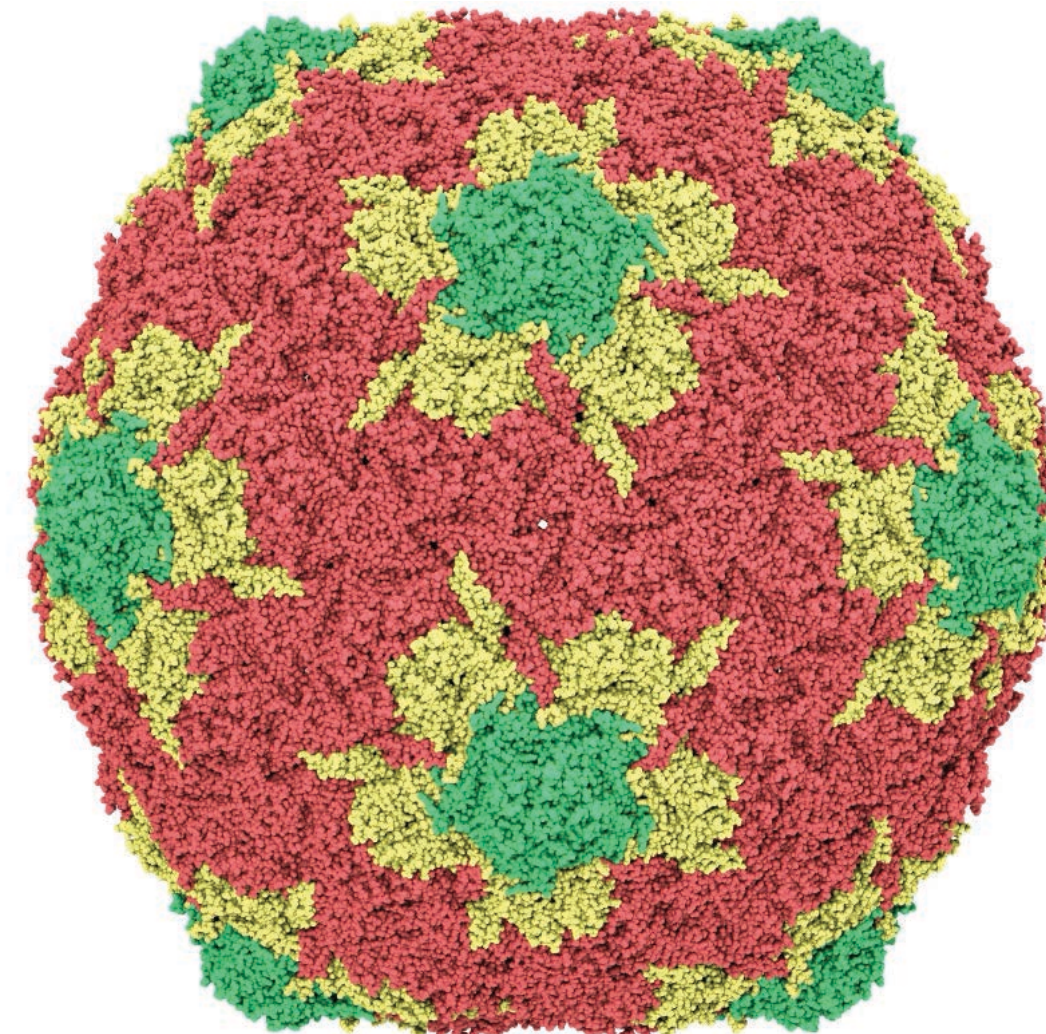
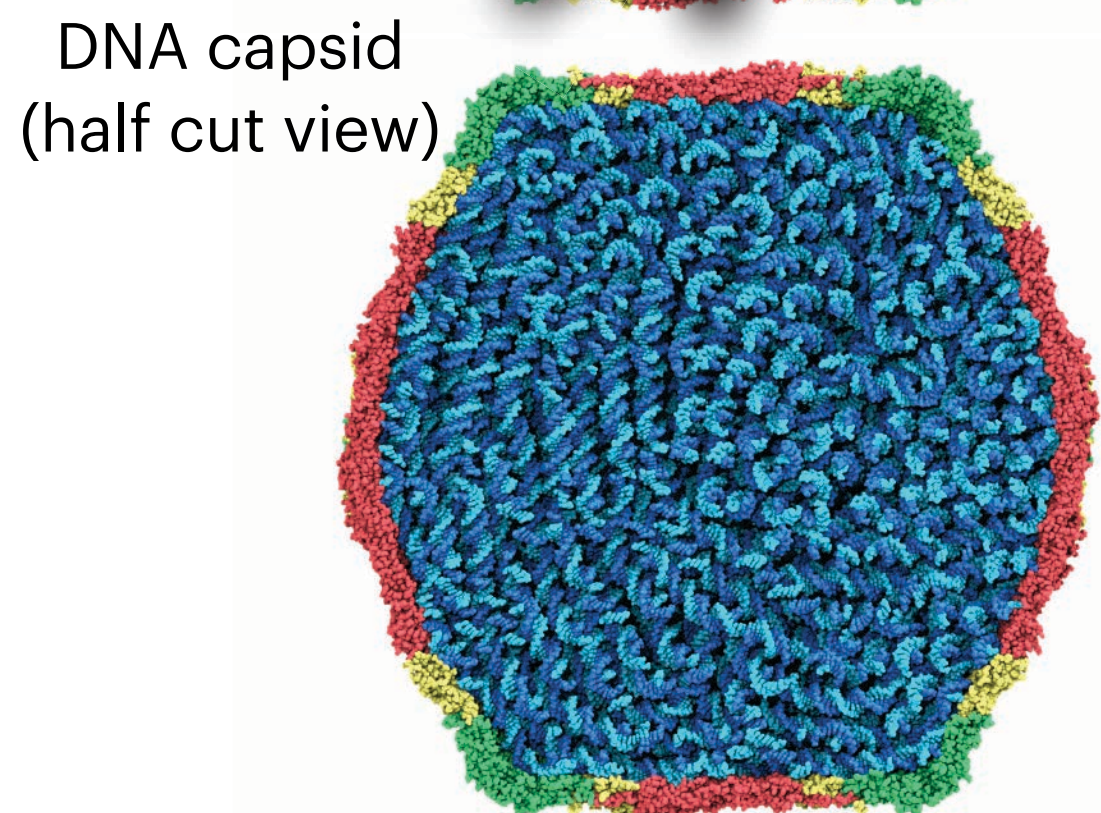
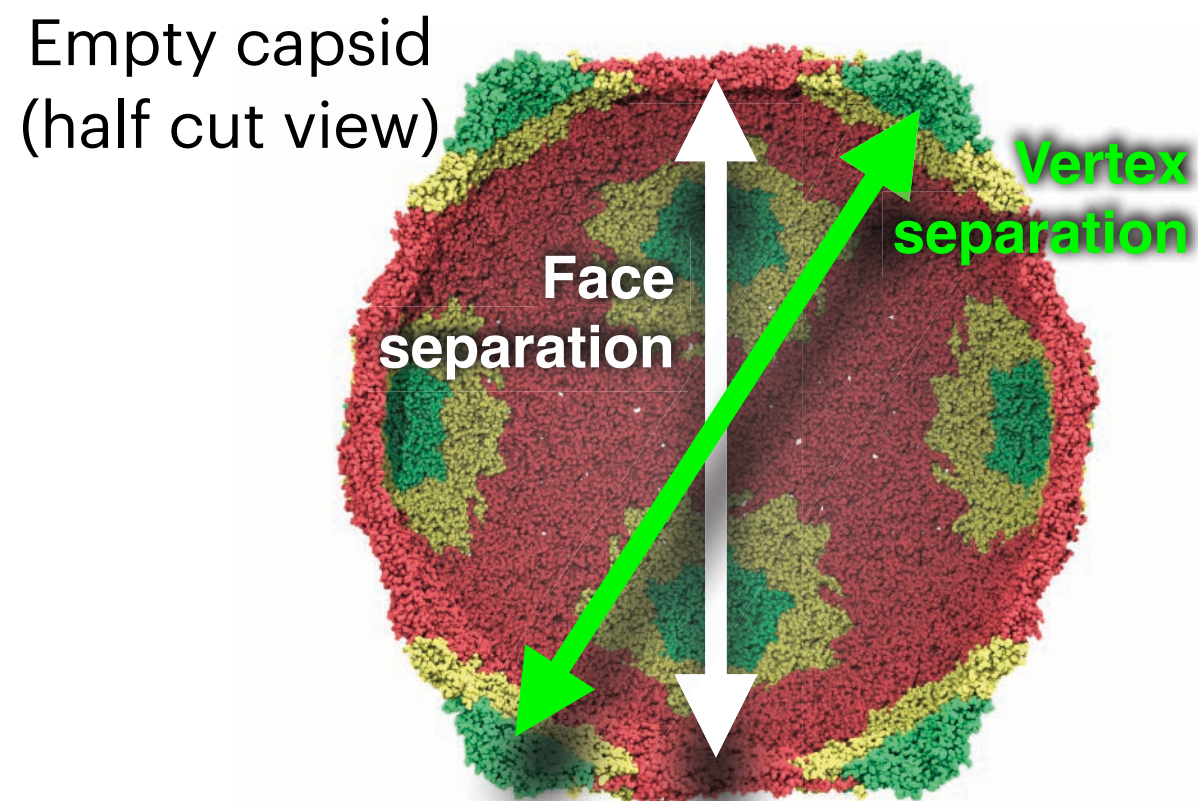
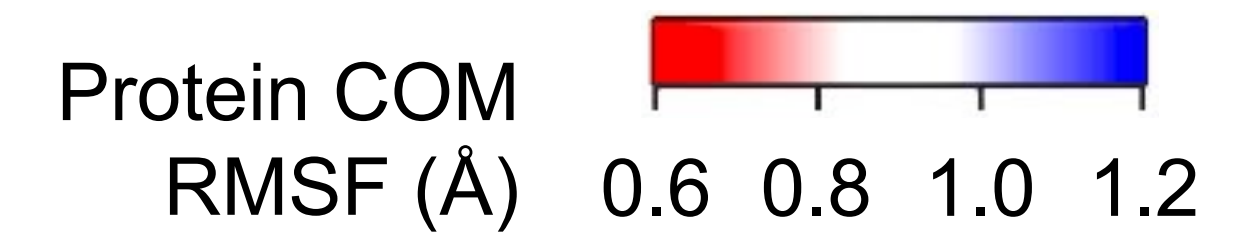
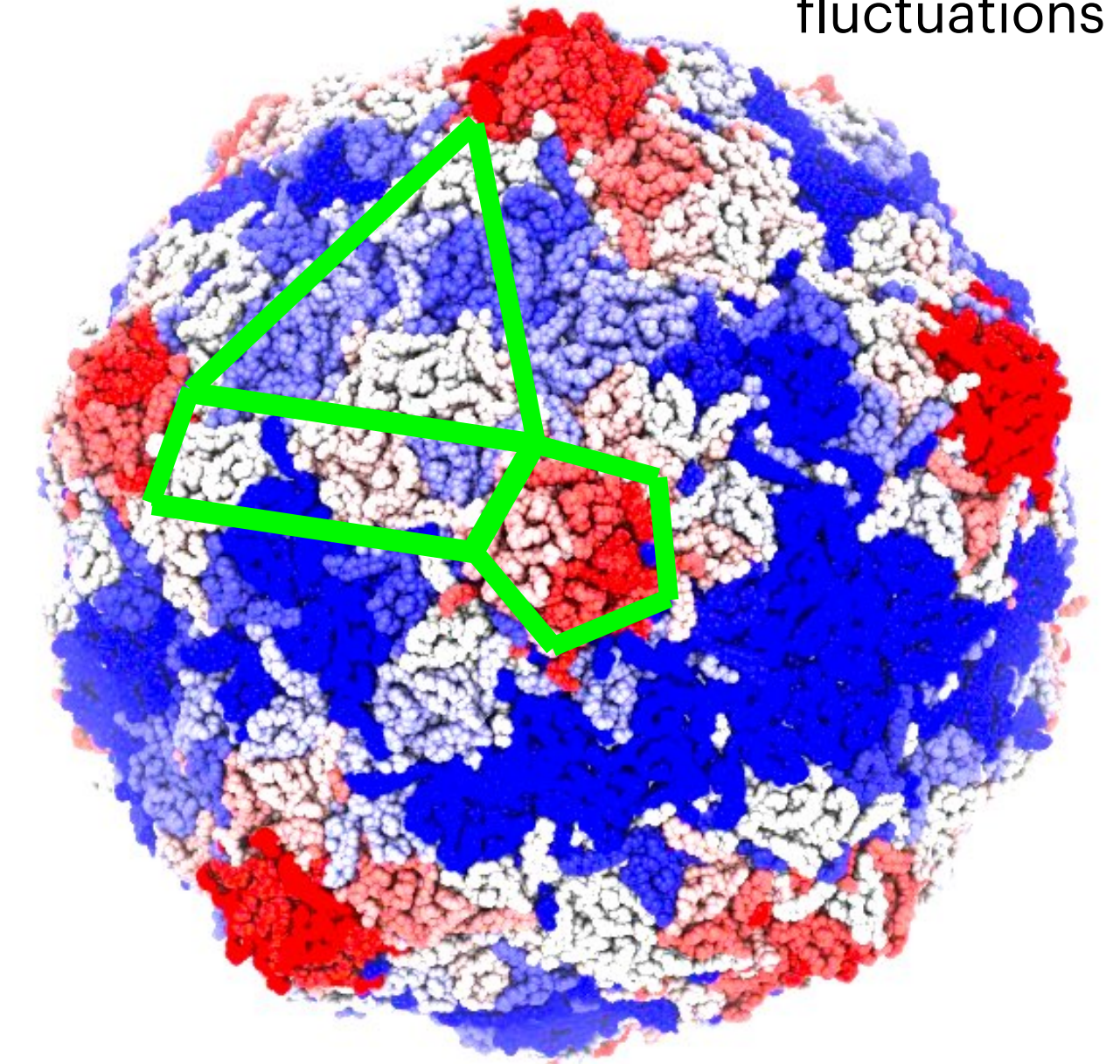
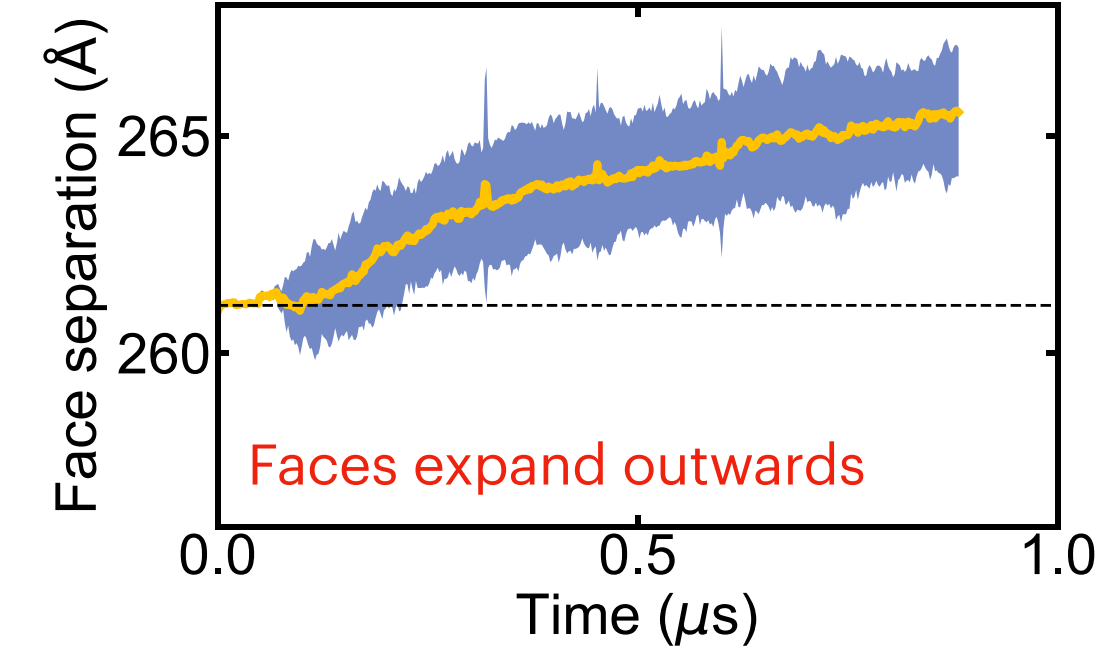
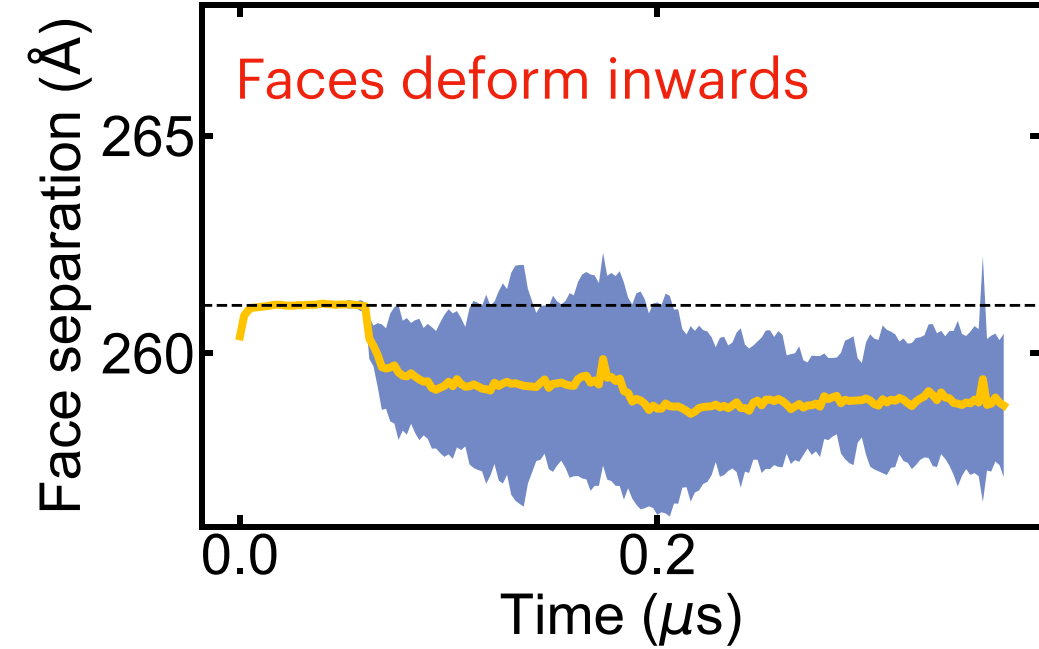
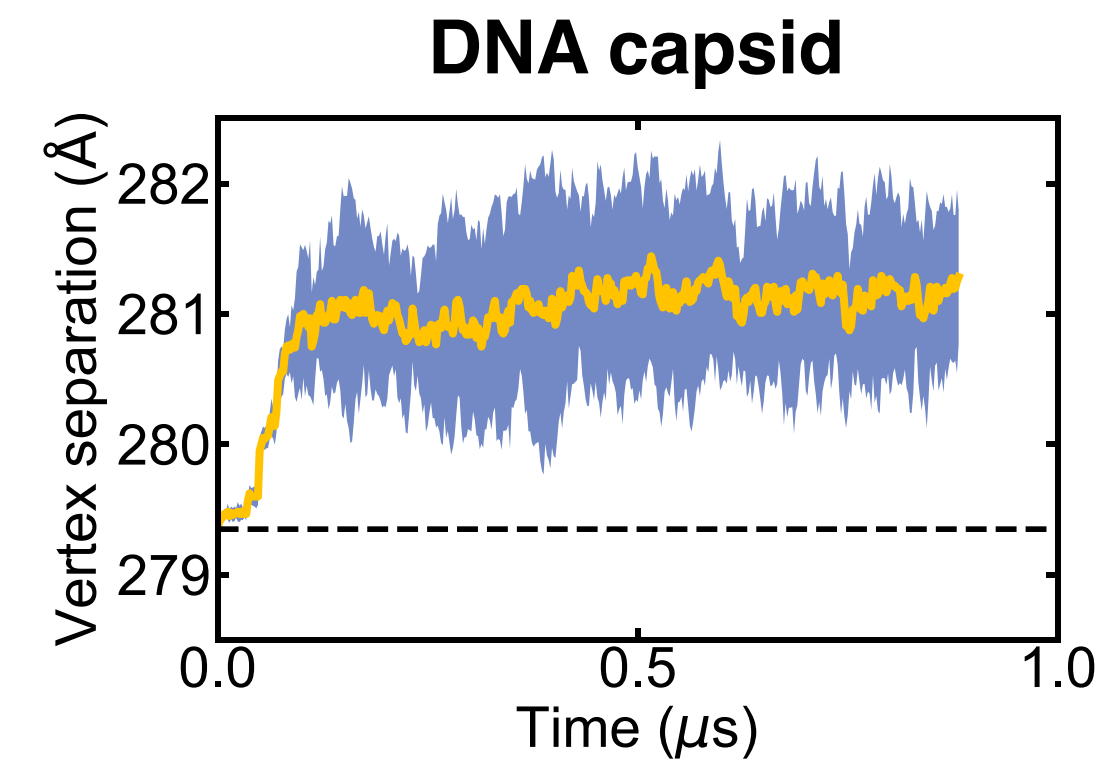
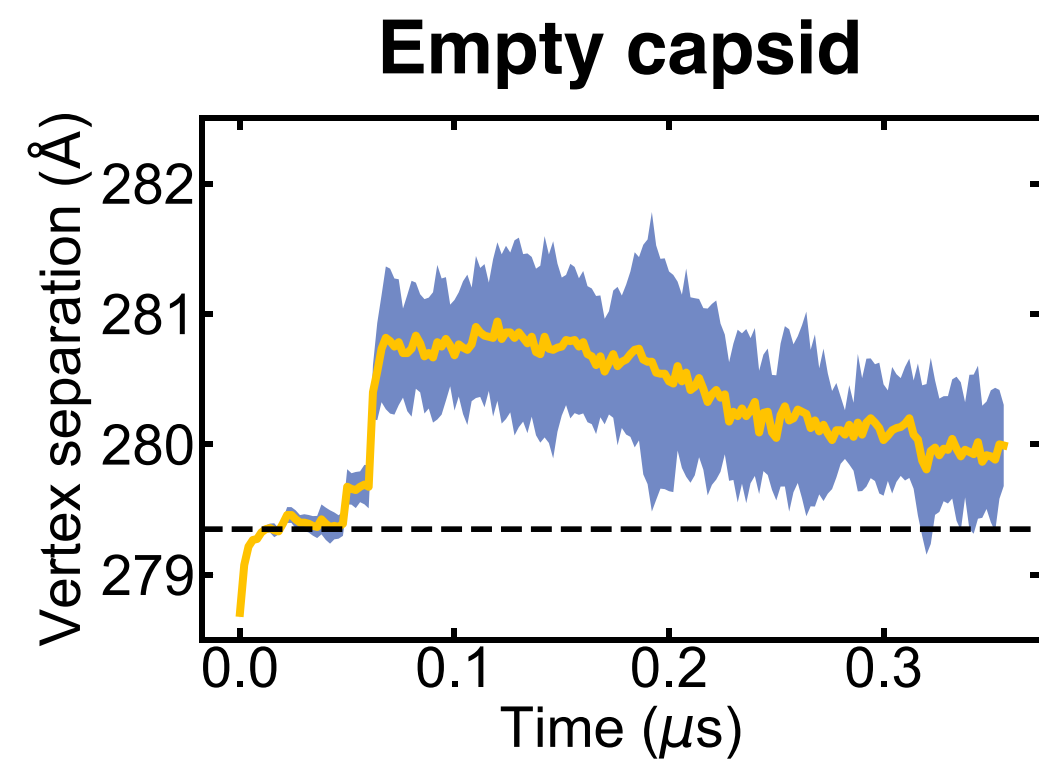
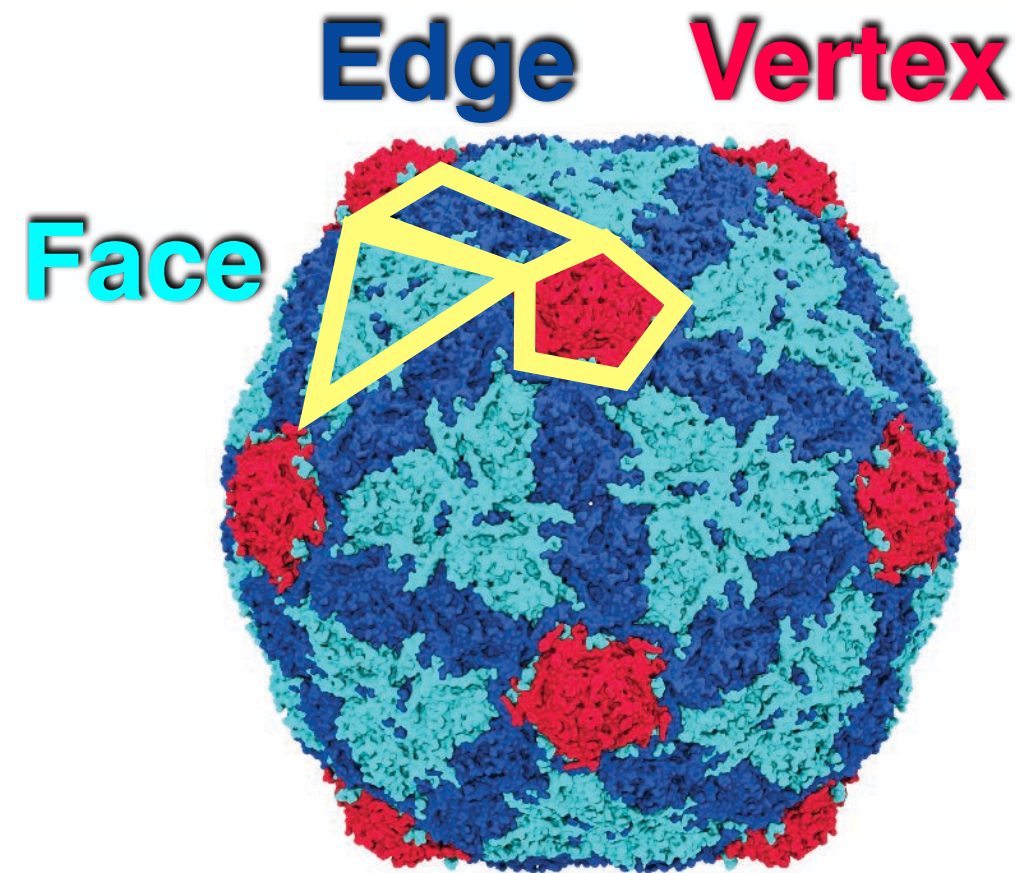
Protein replaces the capsid potential

Solvent is added with ion distribution from prior equilibration with DNA

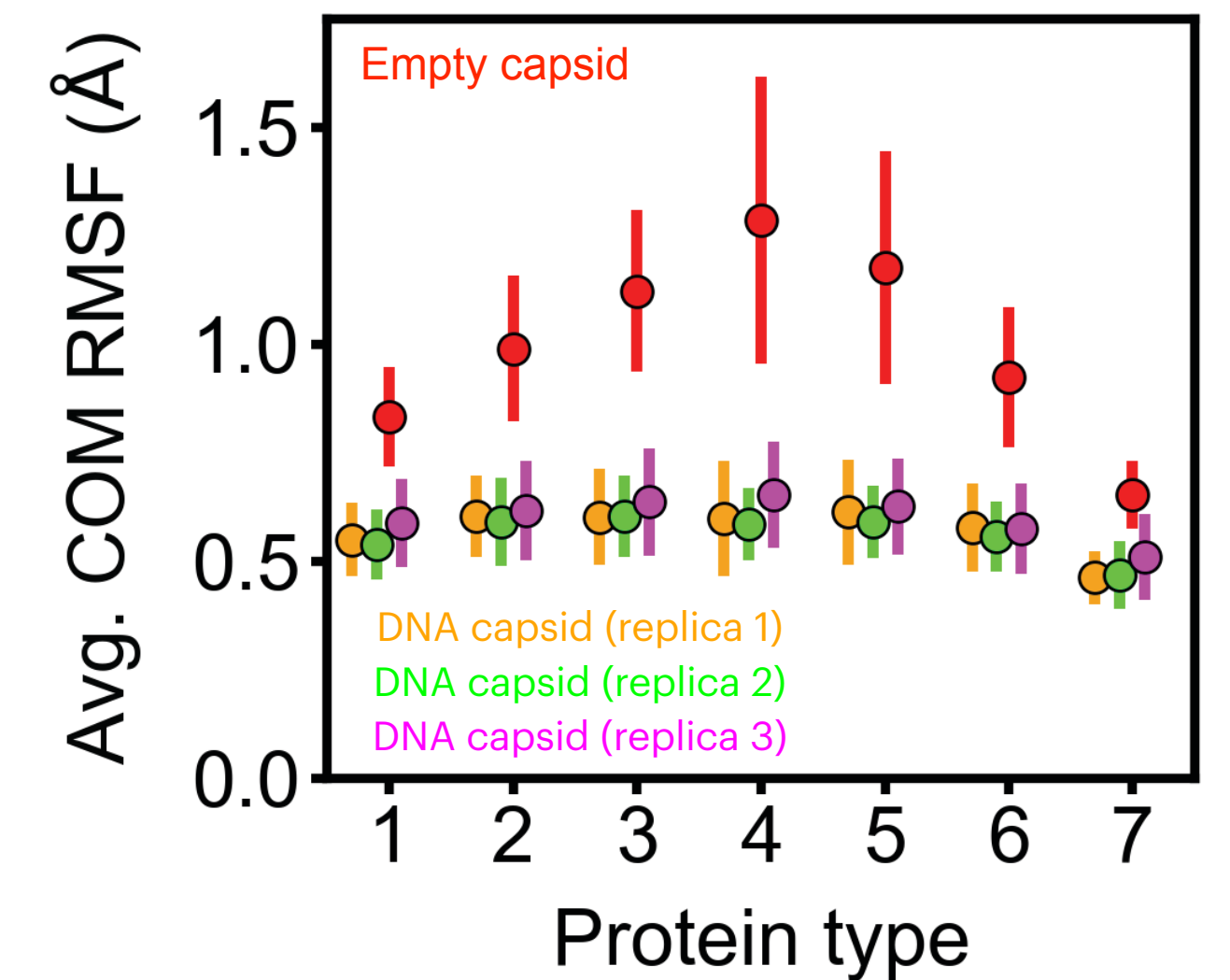
Restraints are slowly released

DNA matters: Capsid structure and dynamics

Presence of DNA
reduces capsid
fluctuations

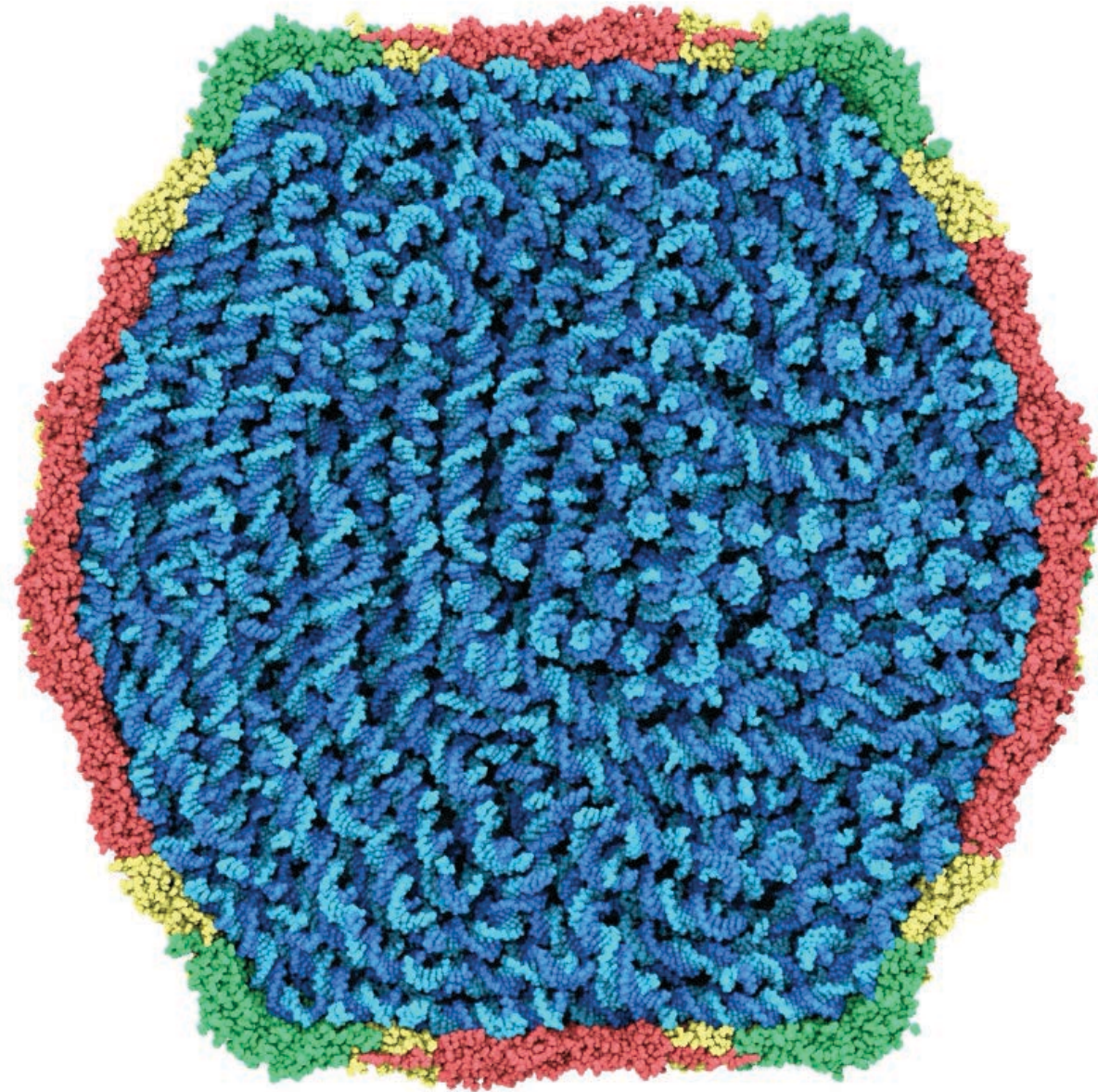


Pronounced breathing motion in empty capsid

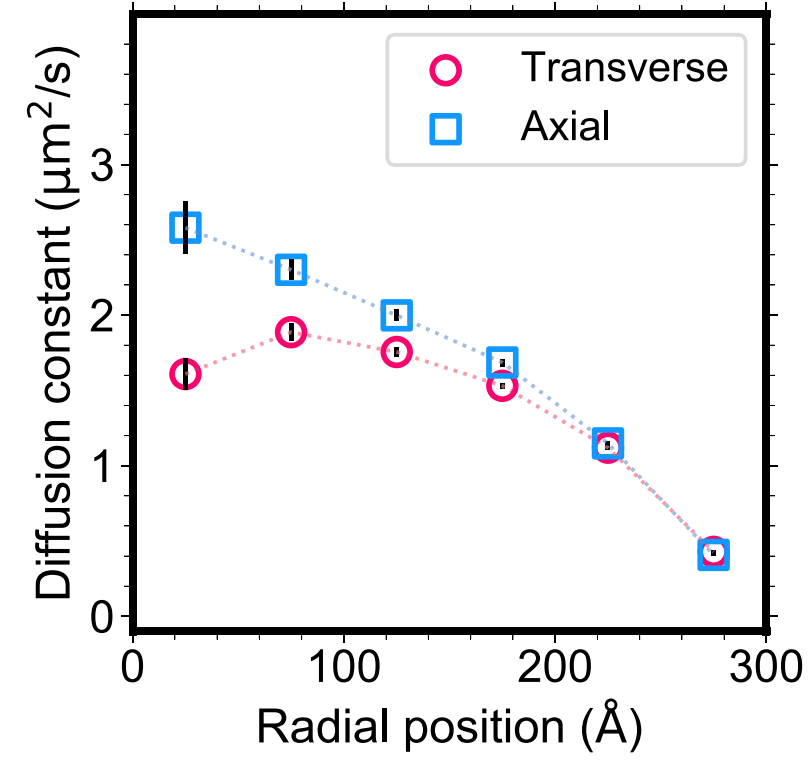


Confined DNA remains fluid!

Half-cut view

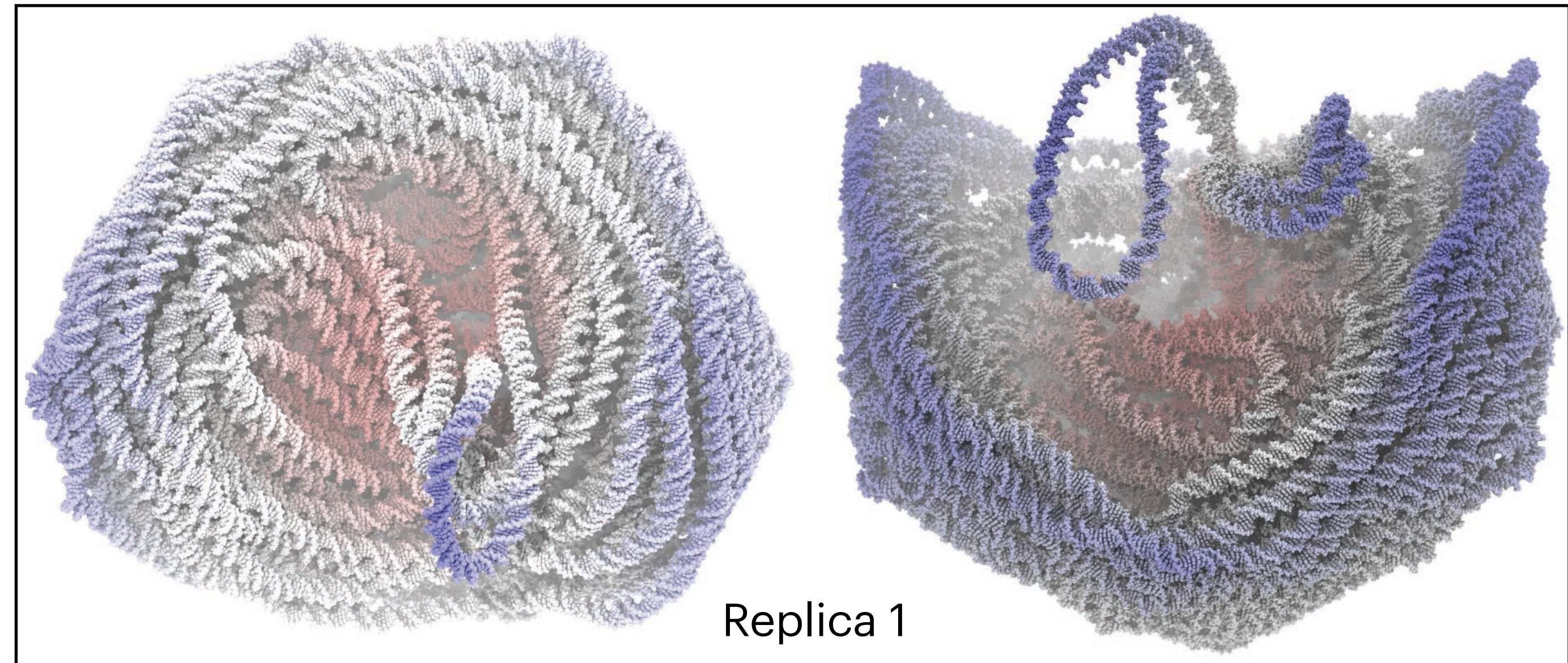


DNA in the inner regions is more mobile

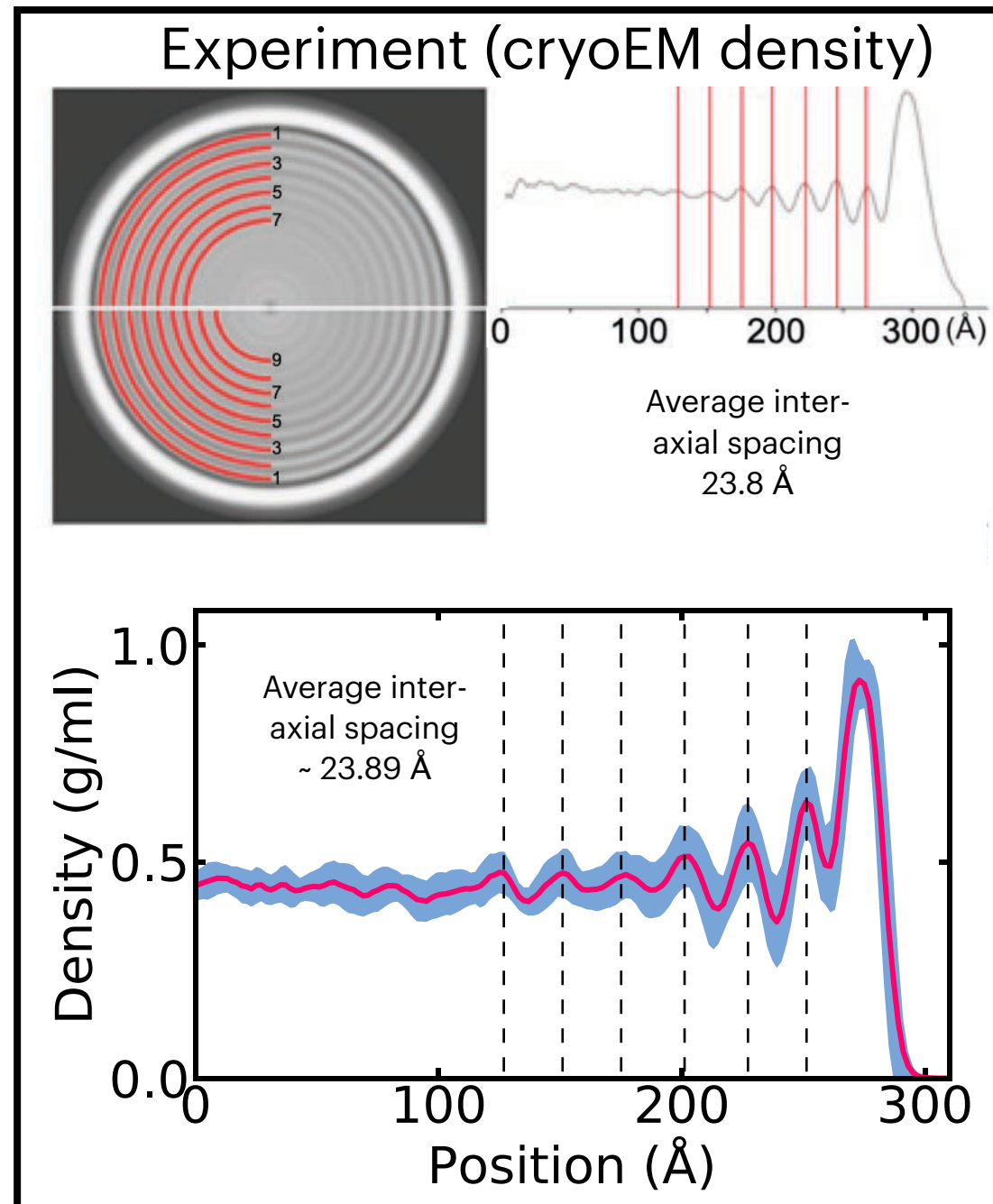


First half of genome

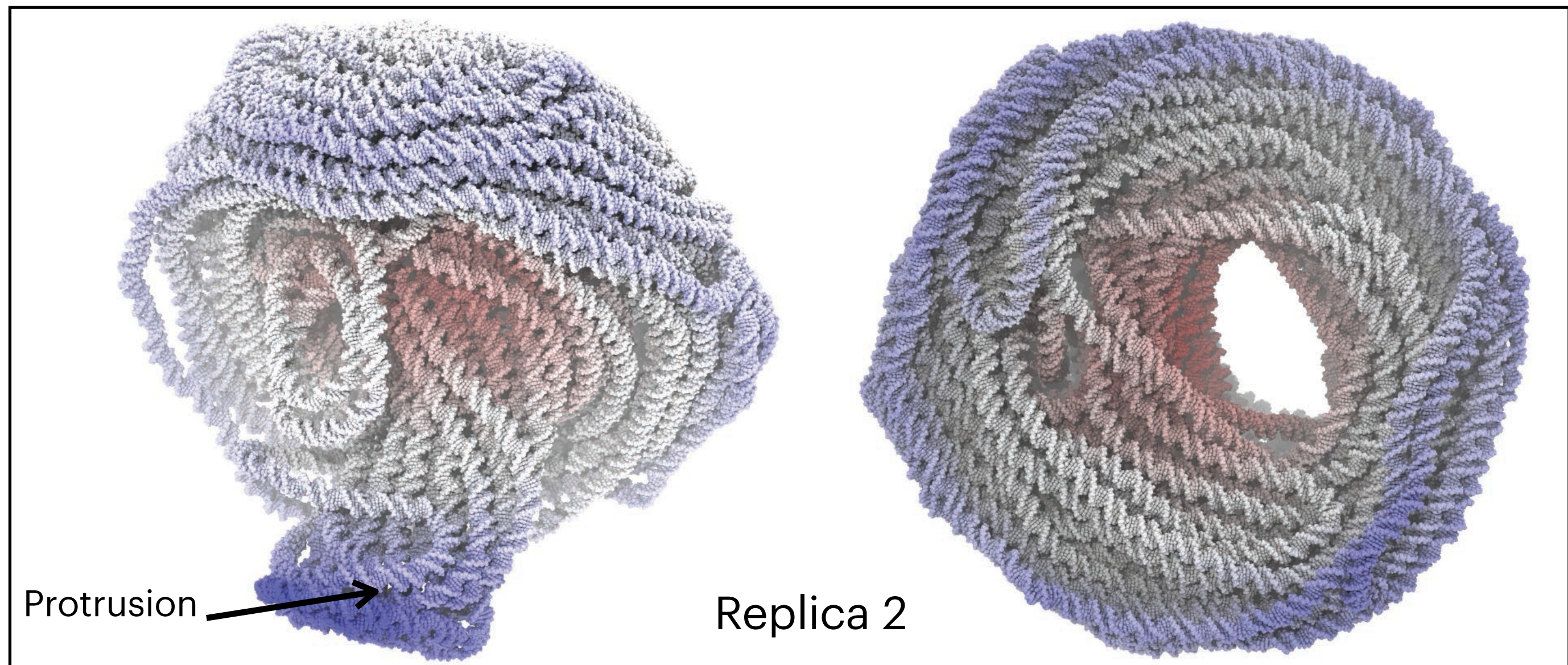
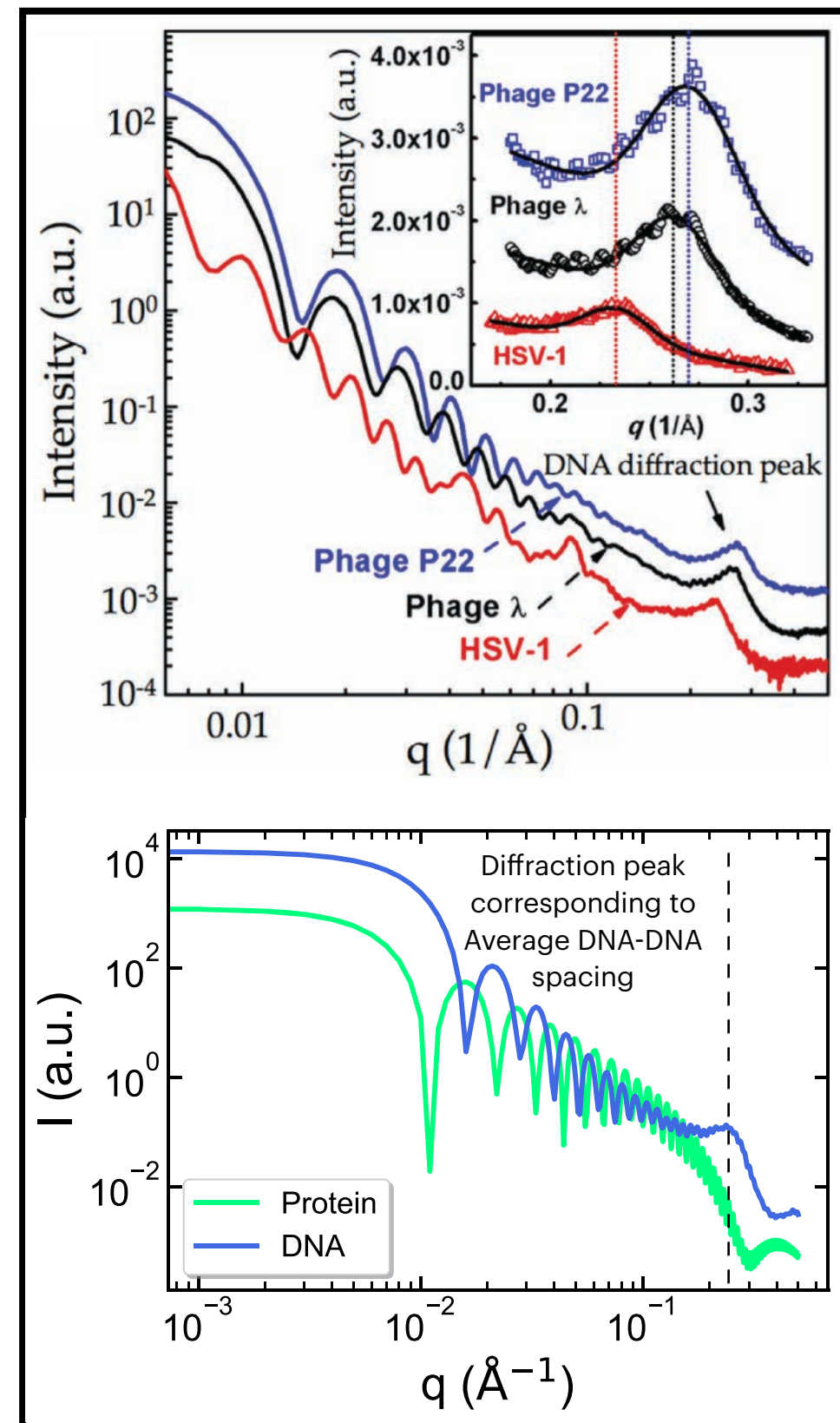
Second half of genome



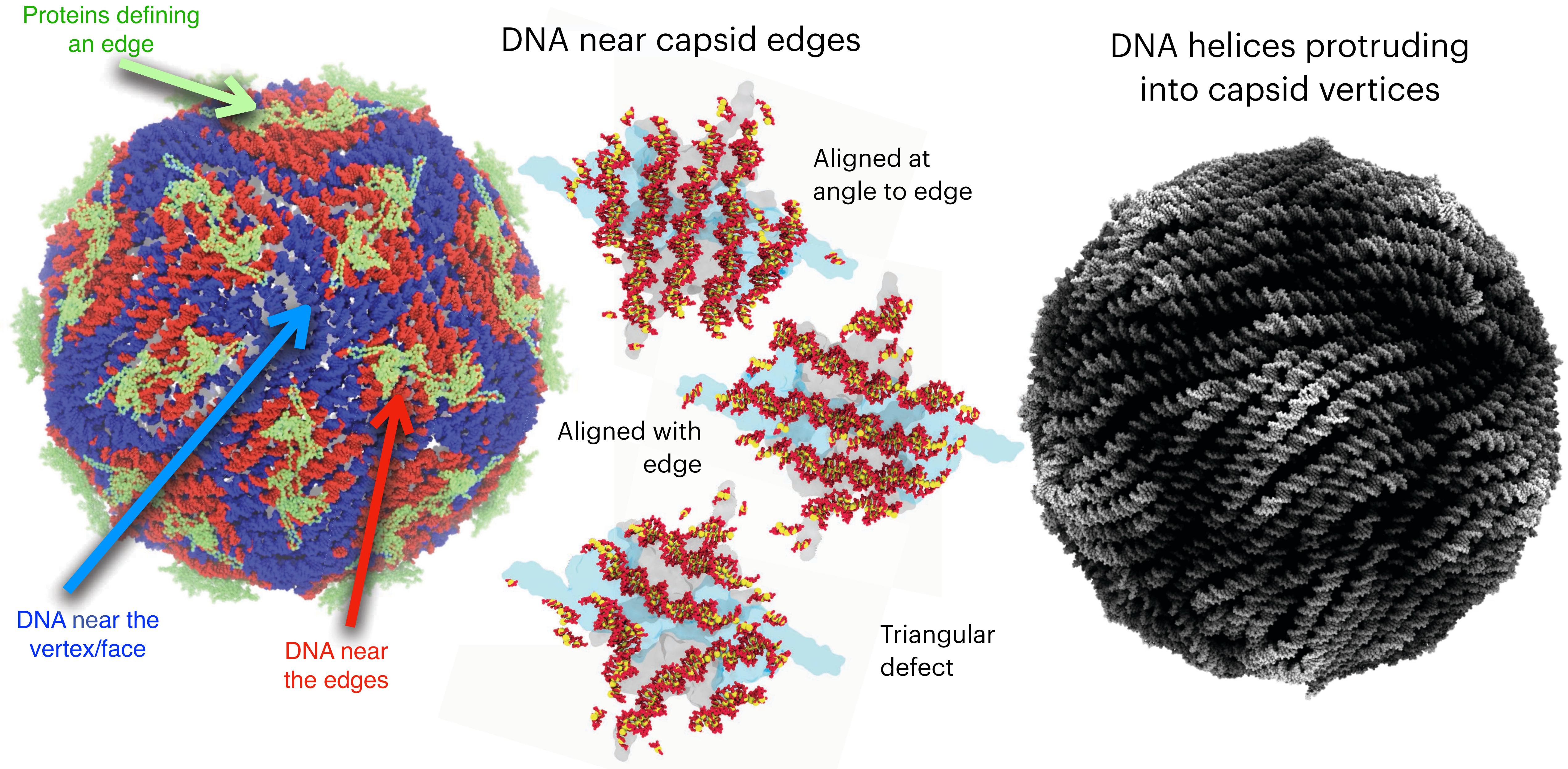
Averaged DNA density



Scattering profile



Capsid confinement imprints structural features



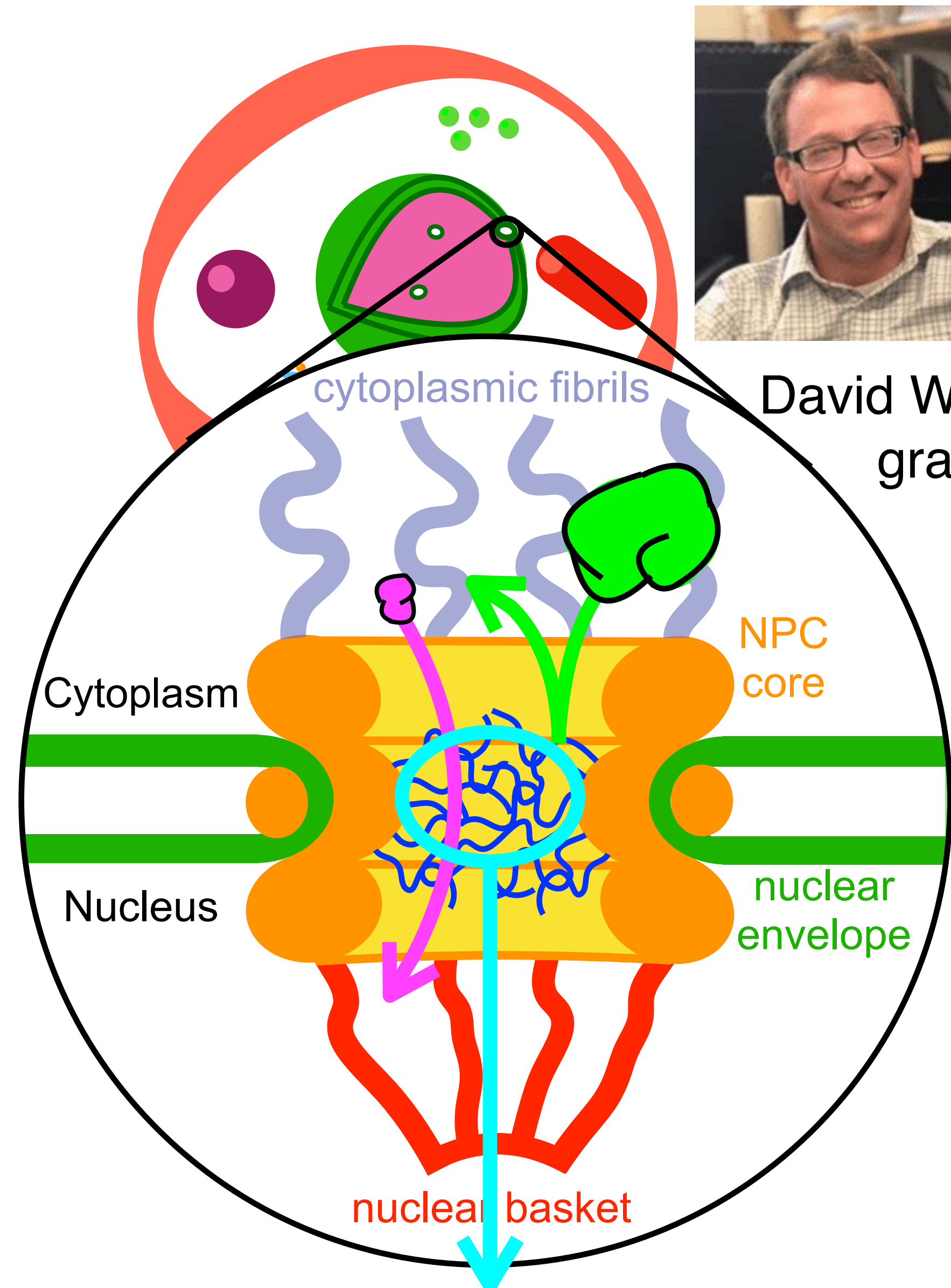
Multi-resolution modeling of the nuclear pore complex (NPC)



Starting from experimental data for the nuclear envelope (gray), and the NPC's scaffold (colors)

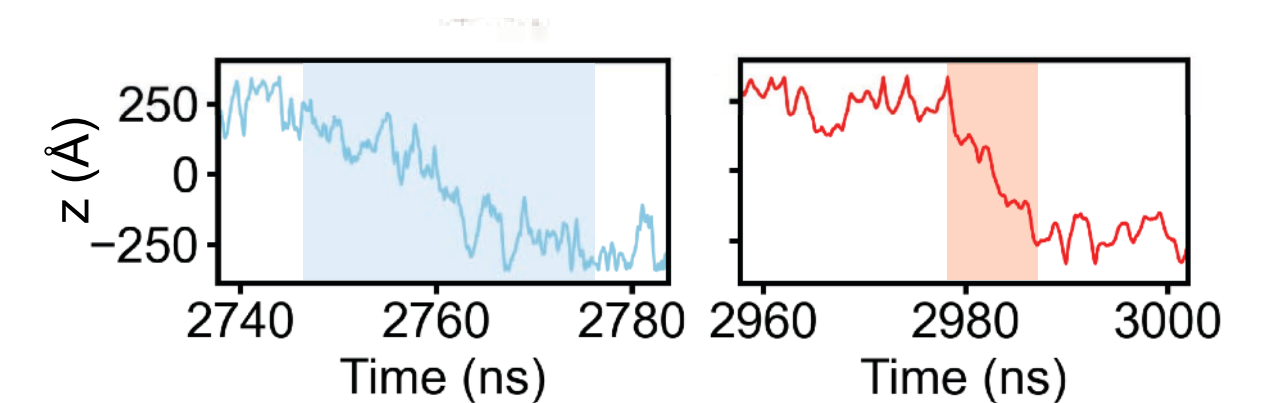
Passive diffusion across NPC. ARBD run on Frontera GPUs.

David Winogradoff



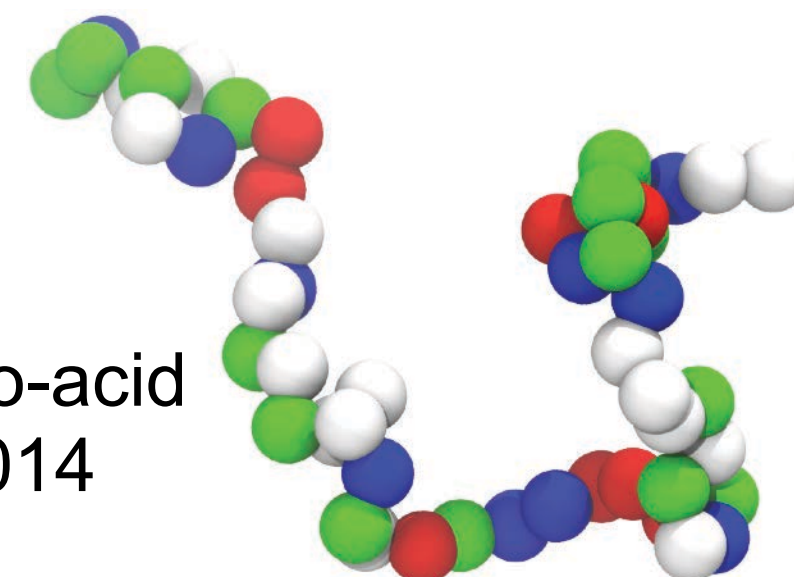
We built a coarse-grained model of the NPC

- Nuclear envelope (von Appen, Nature, 2015),
- Protein scaffold (Lin, Science, 2016),
- FG-domains of nups (colors) with a CG force-field



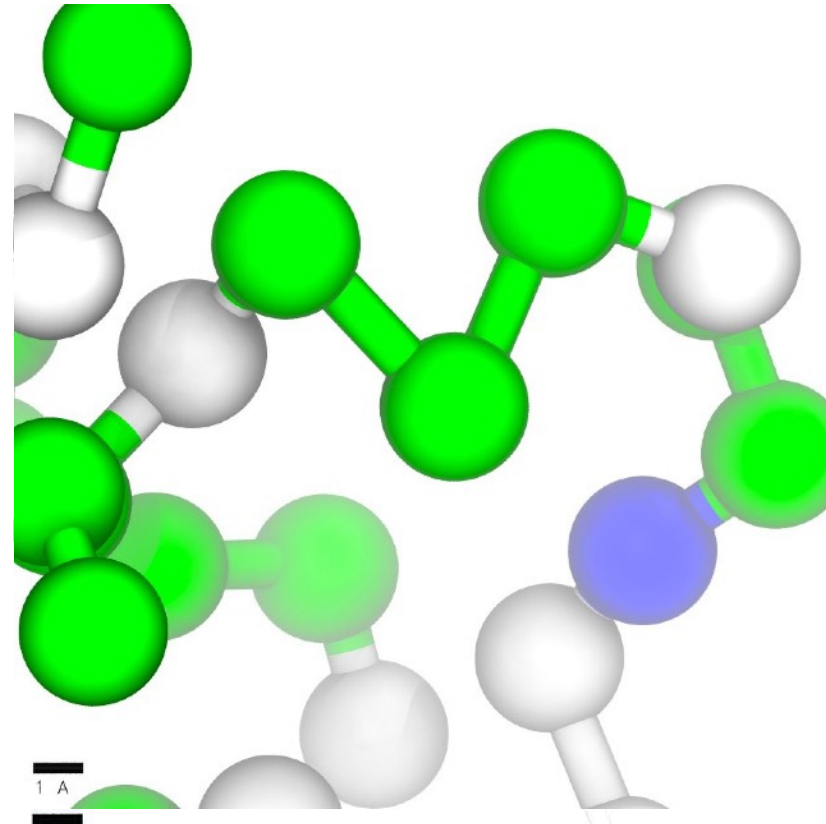
What mechanism governs transport across the nuclear pore complex?

One-bead-per-amino-acid
Onck et al, BJ, 2014

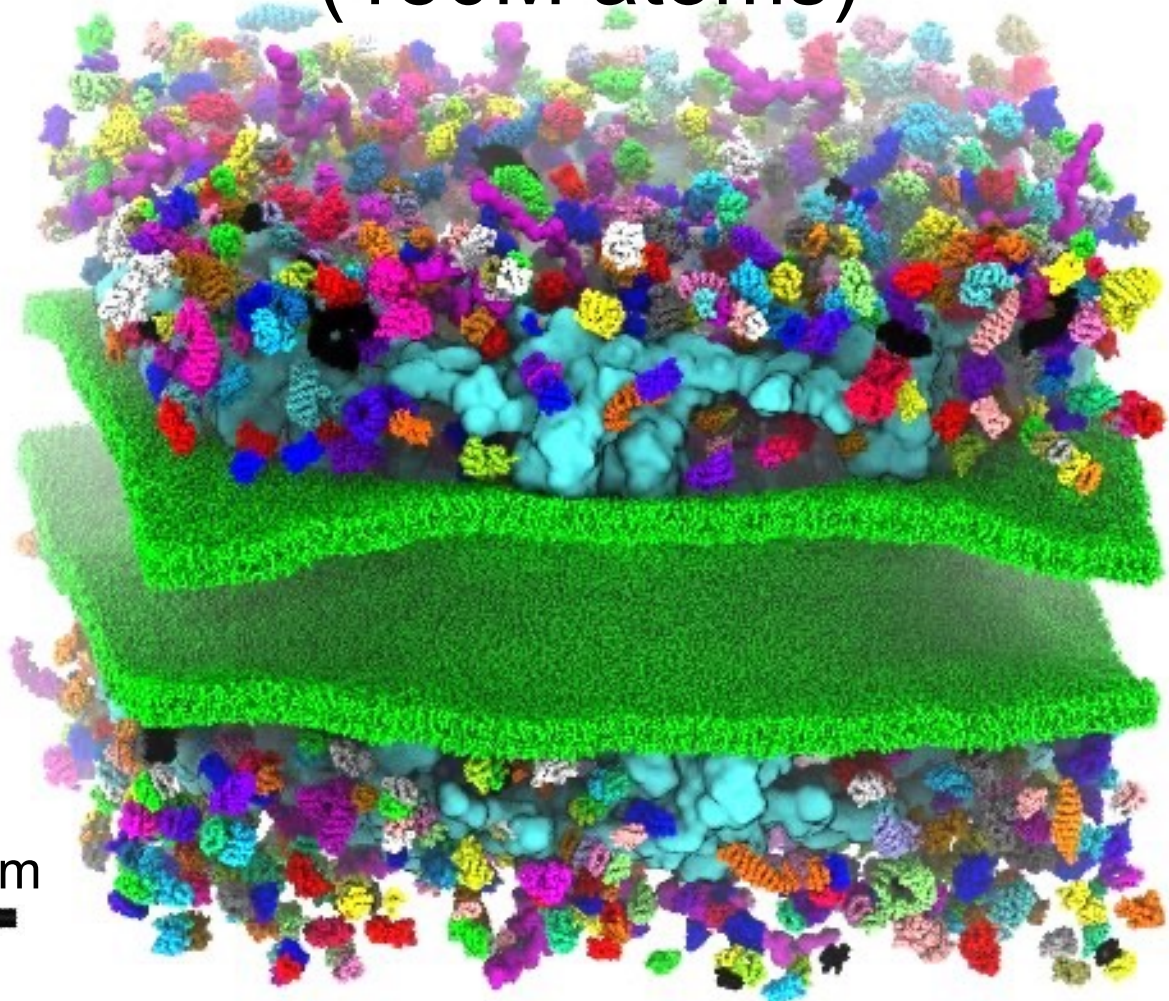


Multi-resolution modeling of the nuclear pore complex (NPC)

CG conformations were mapped to all-atom resolution



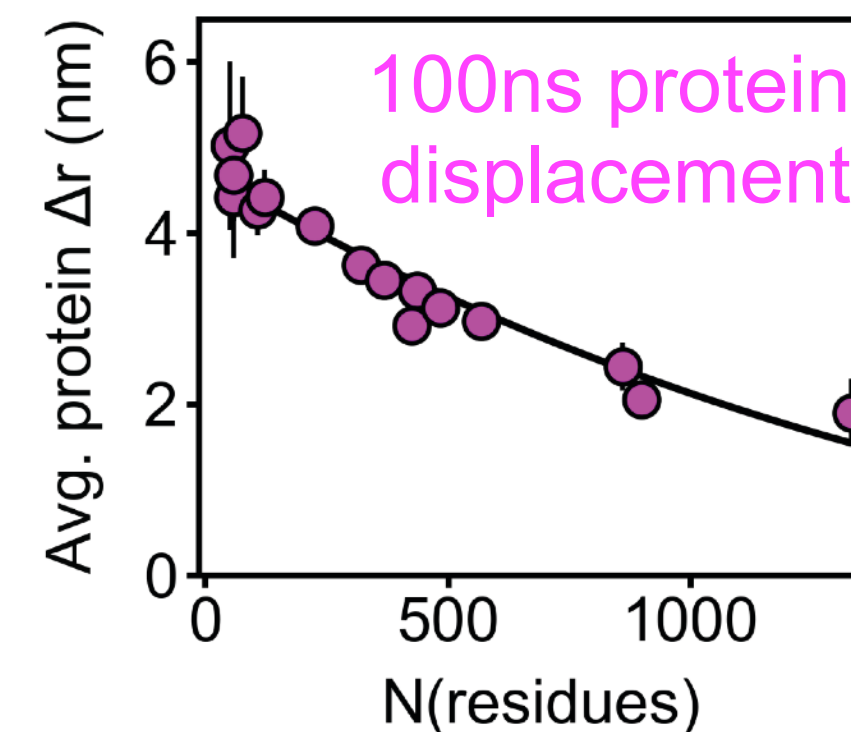
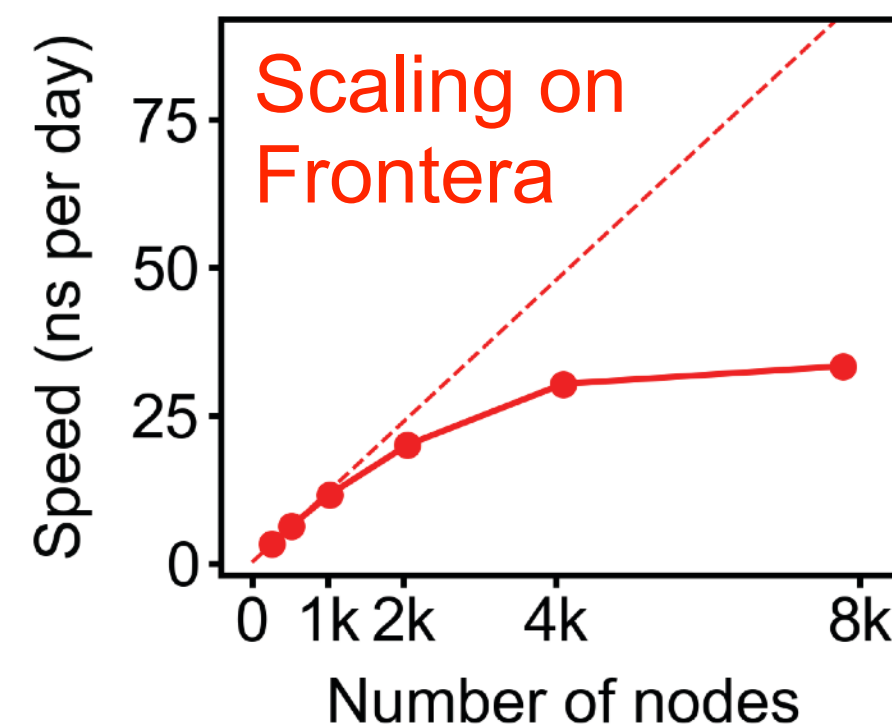
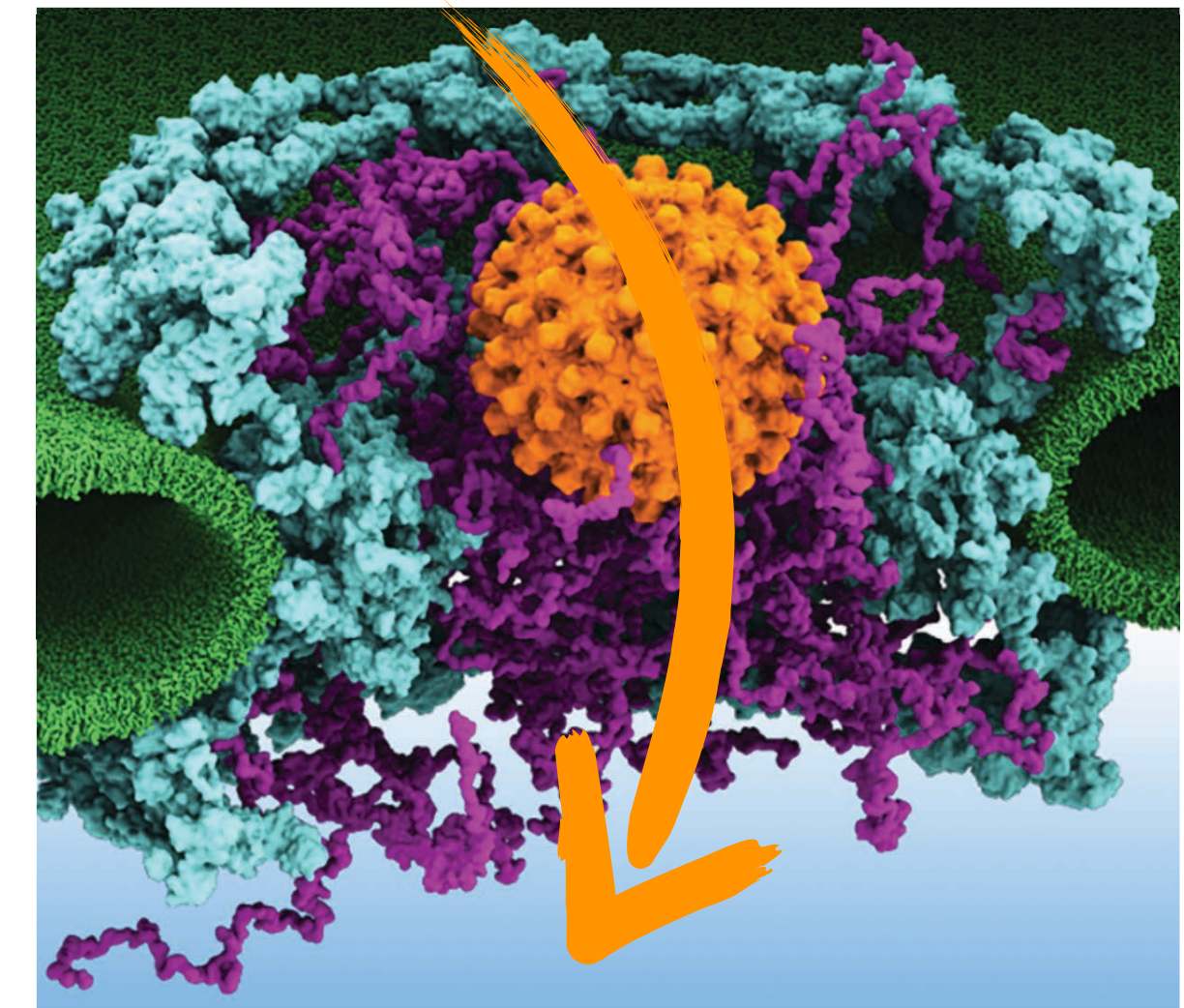
Obtained a fully atomistic model (150M atoms)



Lipid bilayer, von Appen, 2015, *Nature*
scaffold, Lin, 2016, *Science*
central channel from CG simulation

All-atom NPC + cytoplasm.
Run for 100ns on Frontera.

Future direction: modeling viral passage through an NPC



What is both big and small?

The 2D World!



Andre Geim
University of Manchester, UK



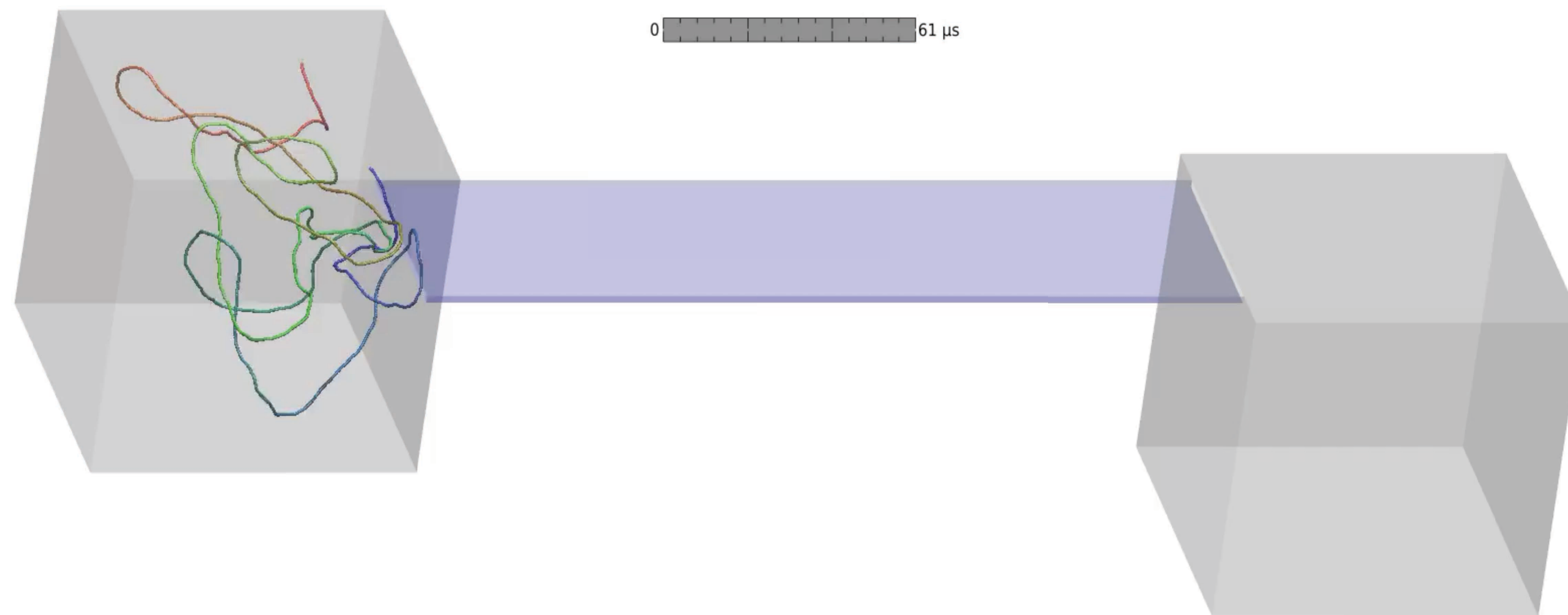
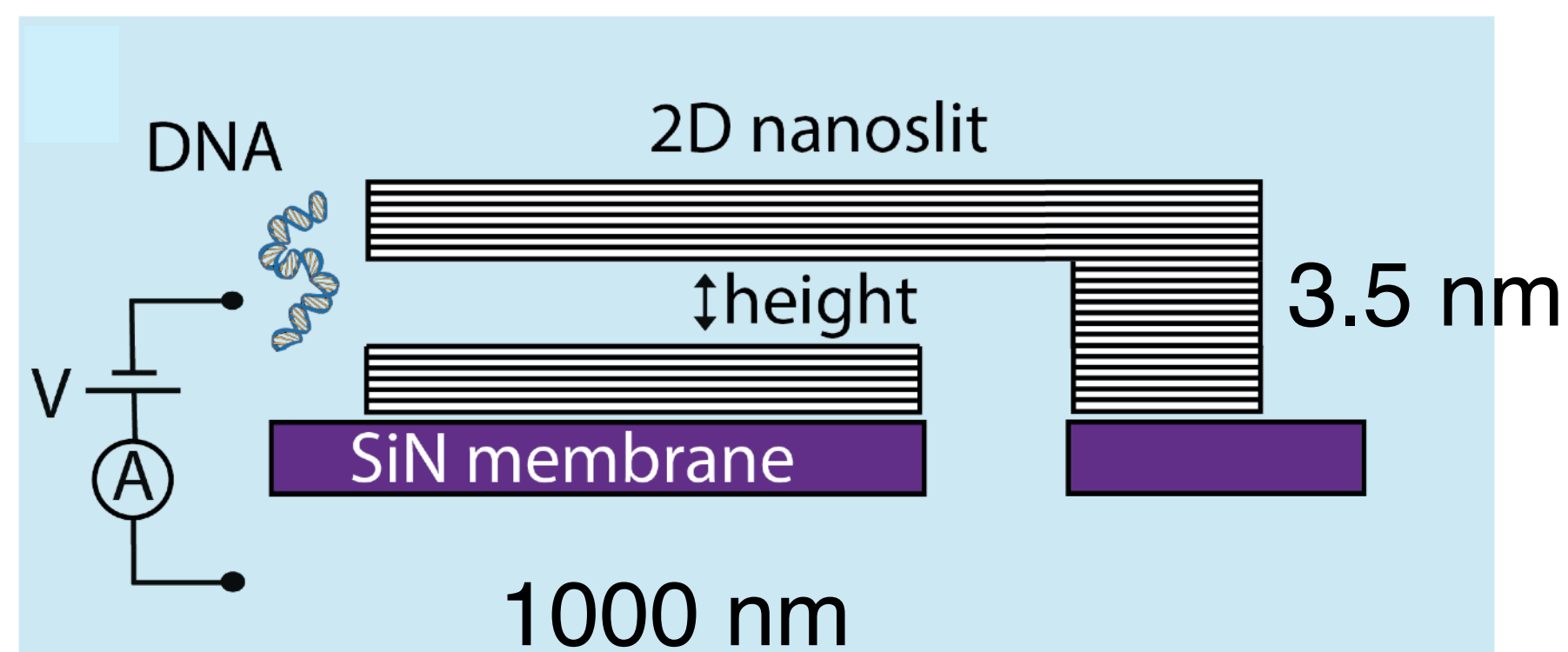
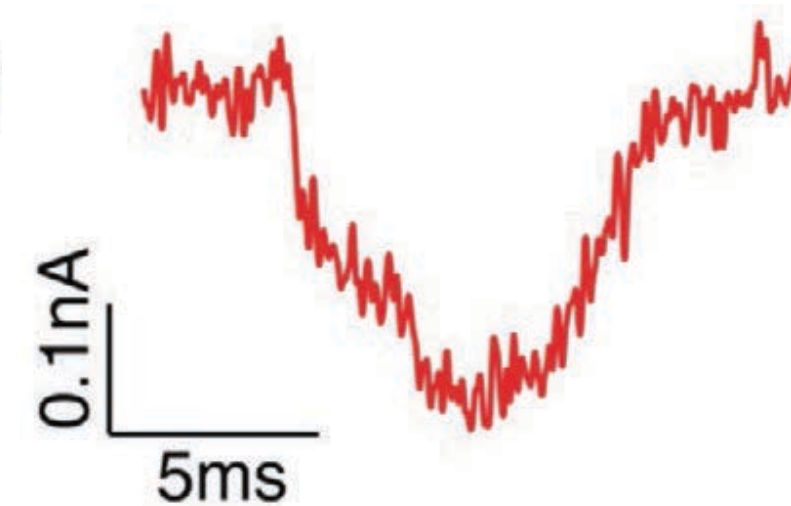
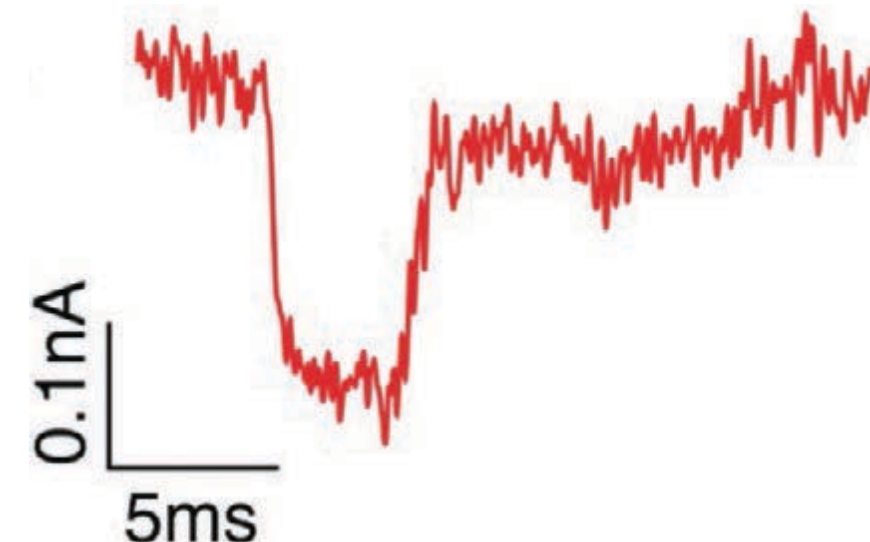
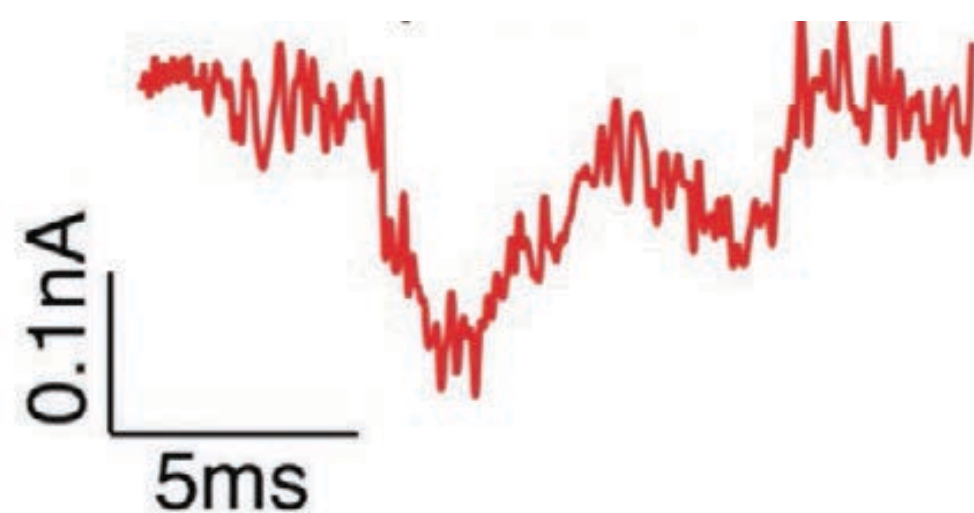
Ashok Keerthi



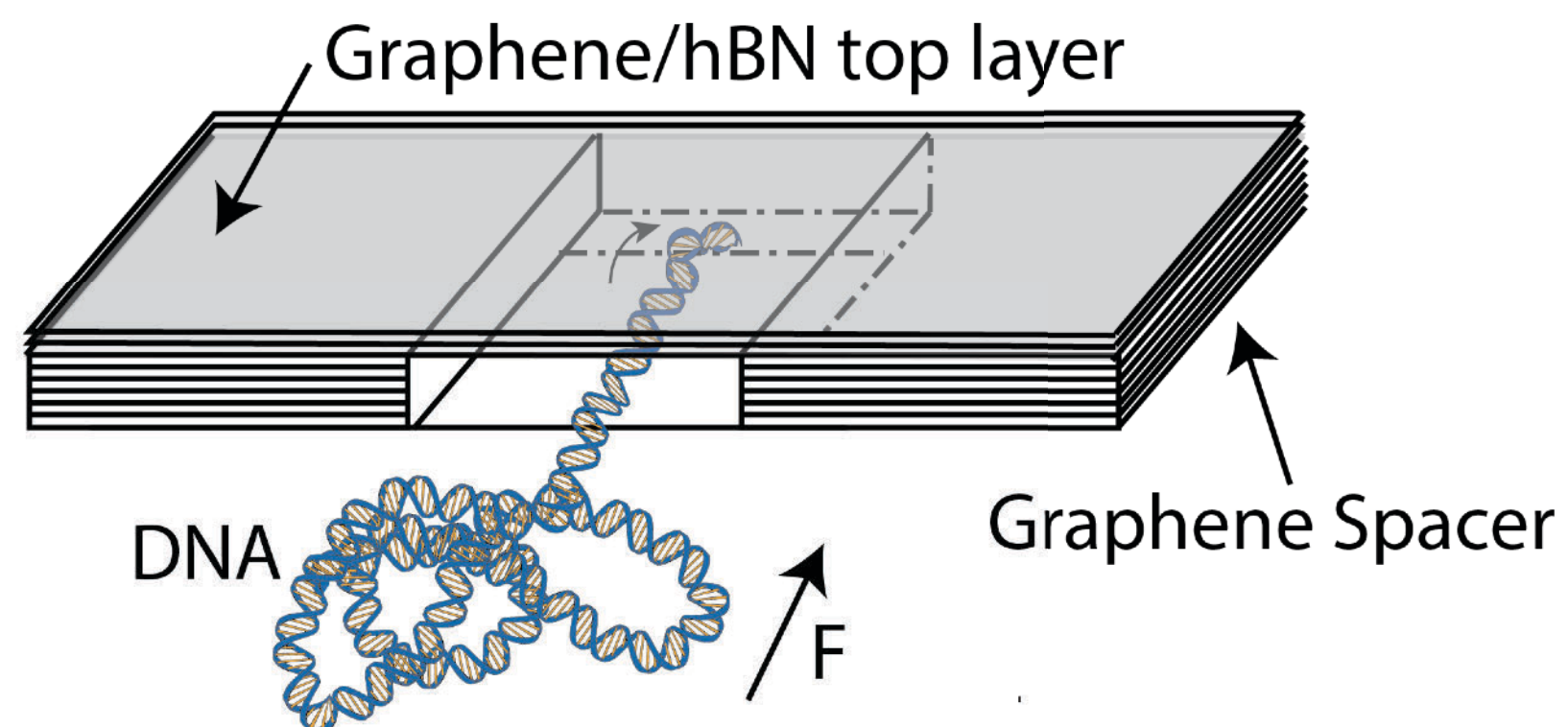
Cees Dekker,
TU Delft, Netherlands



Adnan
Choudhary



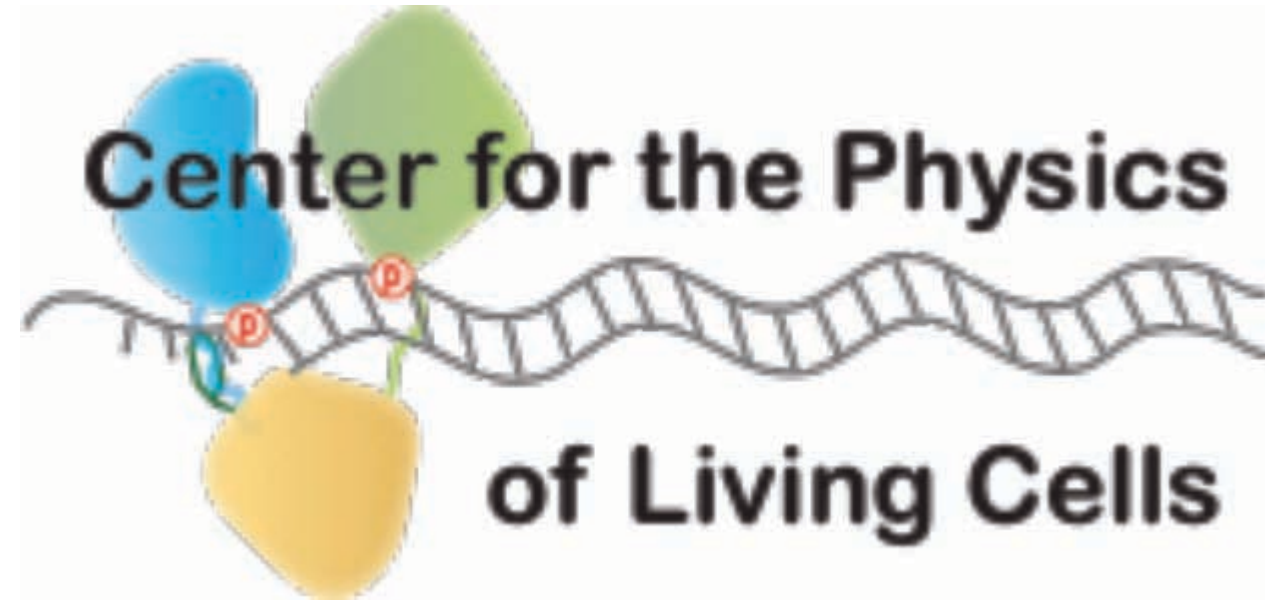
The nanoslit graphene device captures and freezes DNA topology, potentially enabling precise characterization of its genome-scale structure



Advanced Materials, doi: 10.1002/adma.202007682 (2021)

Acknowledgements

Funding



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R01-GM137015
P41-GM104601



People (Aksimentiev lab and collaborators)

TACC



NSF

Terascale, Petascale, Exoscale ... Heroscale!