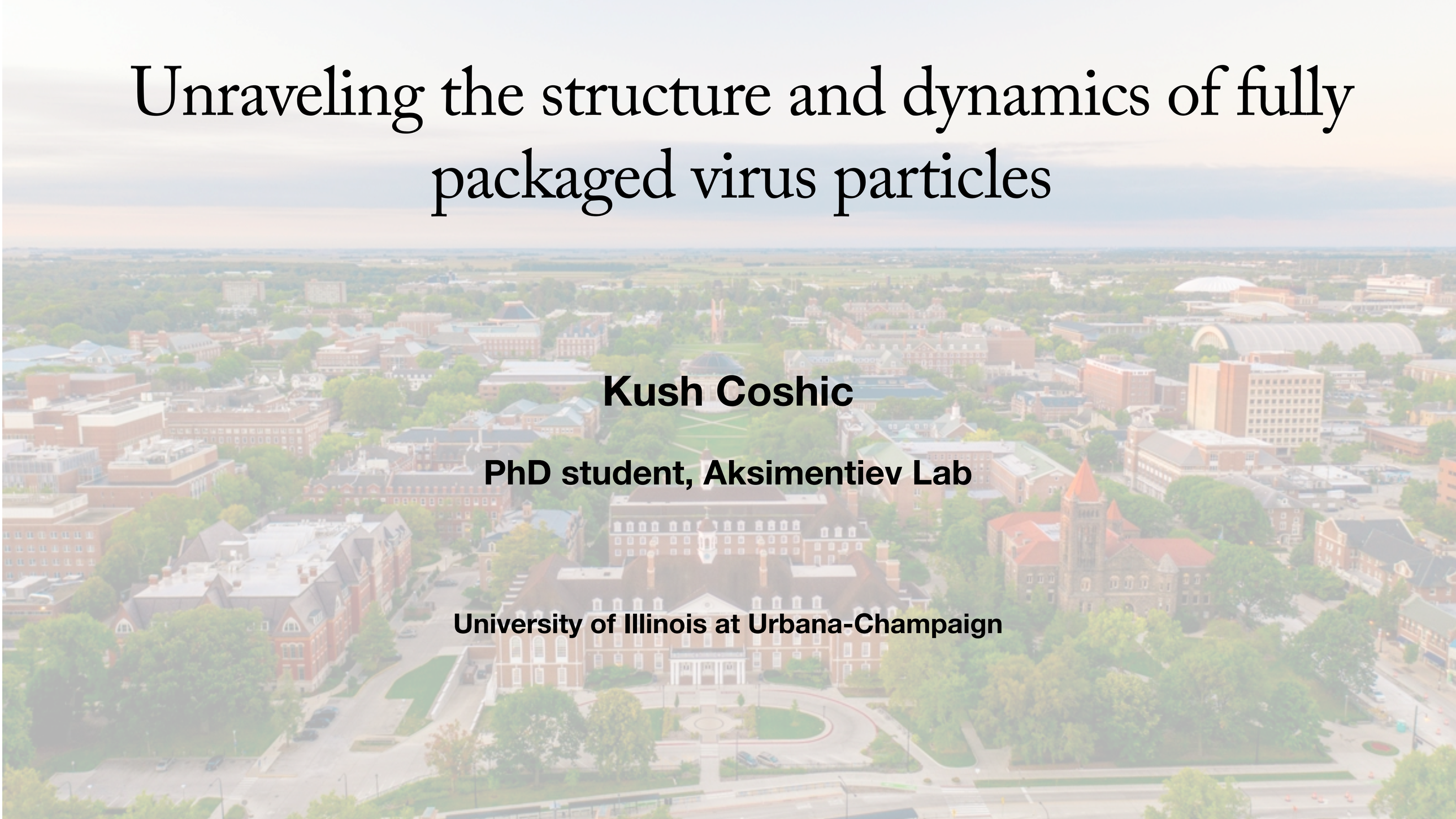
# Unraveling the structure and dynamics of fully packaged virus particles

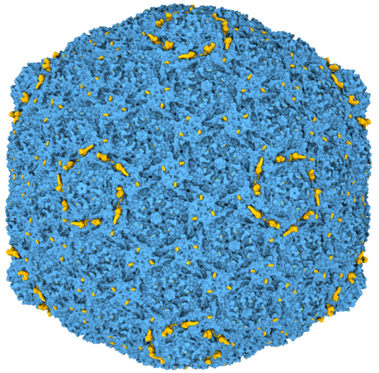


**Kush Coshic**

**PhD student, Aksimentiev Lab**

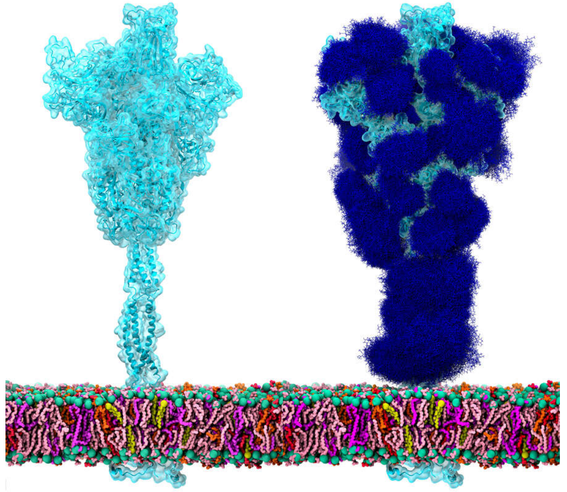
**University of Illinois at Urbana-Champaign**

# Target: the 3D organization of genomes in individual virions

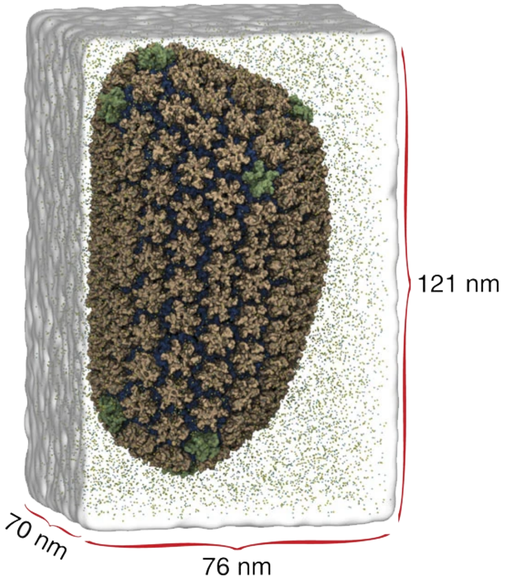


Gan, Lu, et al. Structure 14: 1655 (2006)

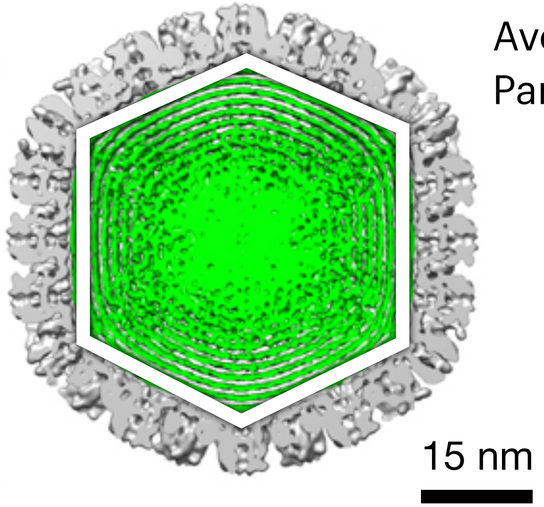
**Protein capsid:**
Atomic structures are available for many species



Casalino et al. ACS Cent. Sci. (2020)




Perilla et al. Nat Comm. (2017)




Evilevitch et al, 2014
(Lund university)

**Genome:**
Averaged cryoEM density
Partial density for select species

**DNA is a highly charged and stiff polymer**

**Internal pressure ~60 atm**

## Open questions:

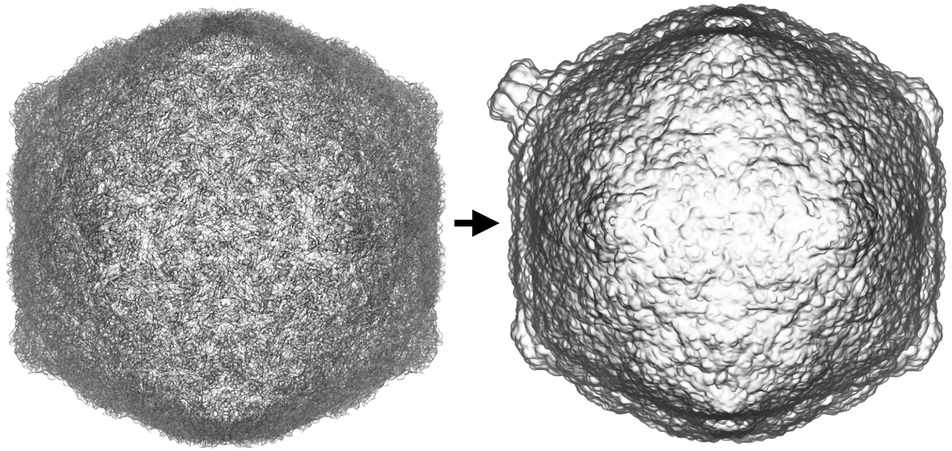
- What is the 3D structure of the packaged genome?
- How genome ejection is triggered and sustained?
- Can the structure of the genome and/or genome—capsid interface be used as drug target?

Experiments currently cannot resolve the genome structure at atomic resolution

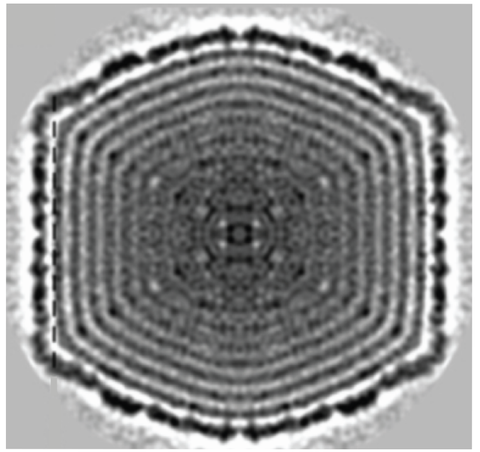
# Multi-resolution packaging of dsDNA genomes (HK97)

**HK97 Bacteriophage Capsid, Head II**
Gan, Lu, et al. Structure 14.11 (2006): 1655-1665.

**PDB ID: 2FT1**

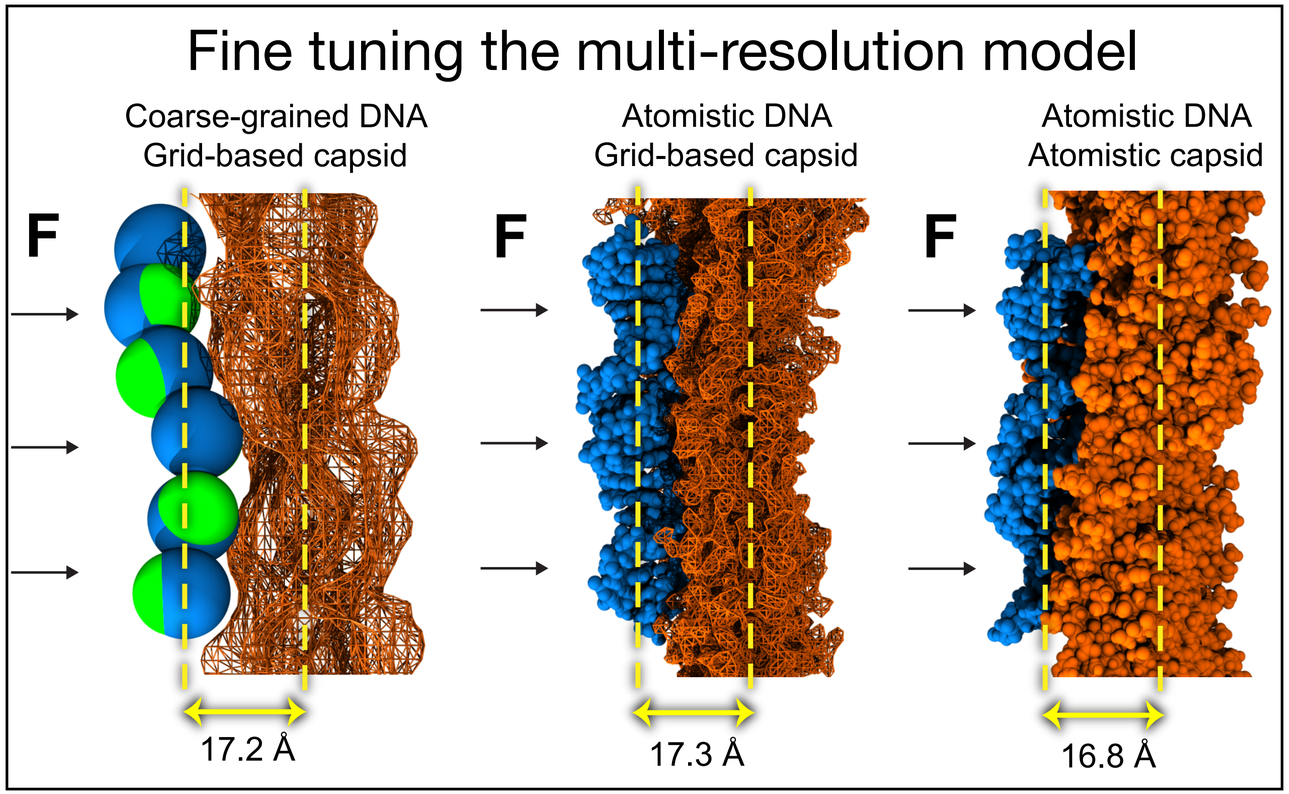


Smooth, purely repulsive volumetric map
Volmap, VMD: capsid+portal (3KDR)



Duda, Robert L., et al. *Journal of molecular biology* 391.2 (2009): 471-483.

## Fine tuning the multi-resolution model




THE JOURNAL OF PHYSICAL CHEMISTRY C
Article
pubs.acs.org/JPCC

**Predicting the DNA Sequence Dependence of Nanopore Ion Current Using Atomic-Resolution Brownian Dynamics**

Jeffrey Comer and Aleksei Aksimentiev*

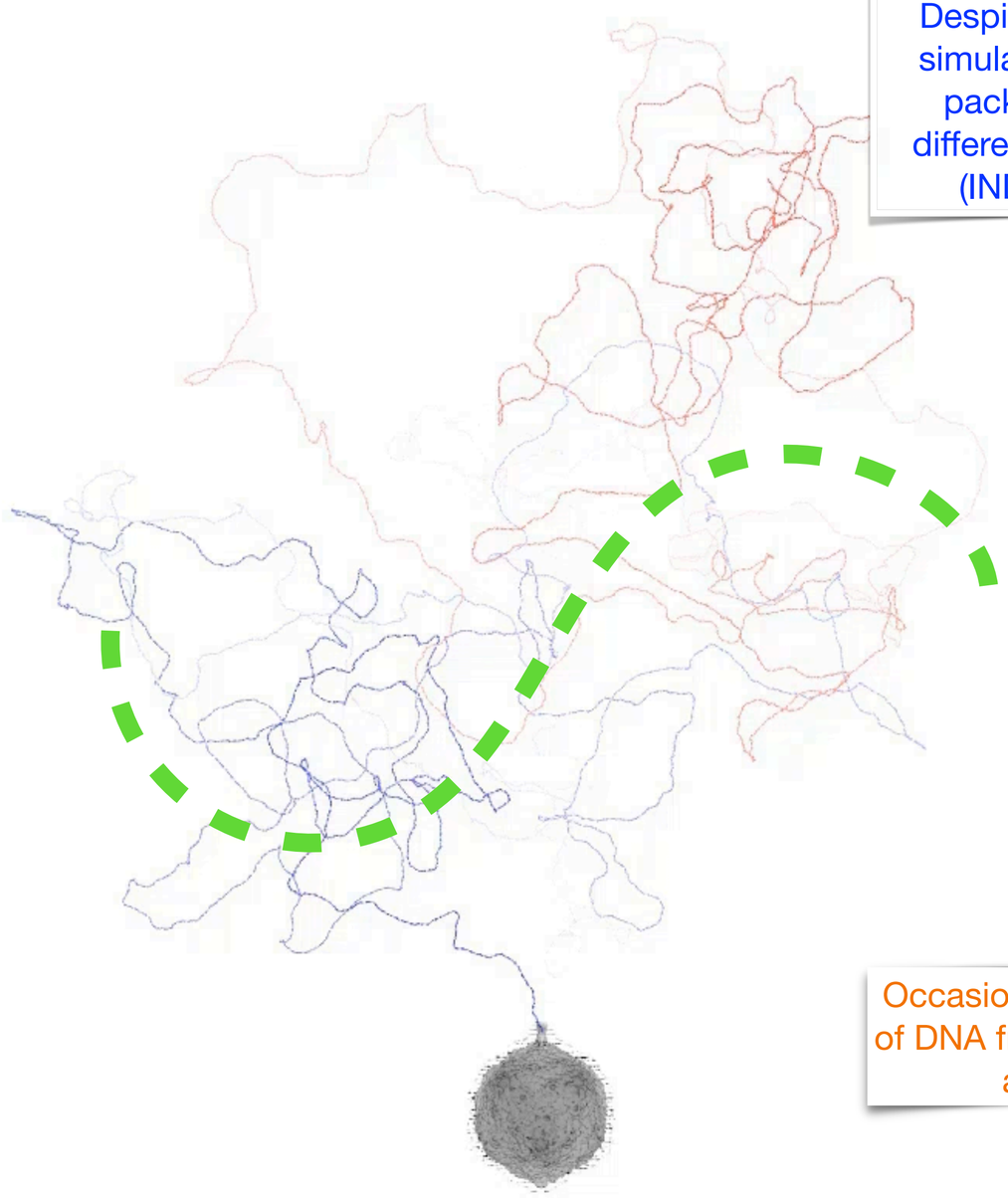
*Published online 31 March 2020*
*Nucleic Acids Research, 2020, Vol. 48, No. 9* ***5135–5146***
*doi: 10.1093/nar/gkaa200*

**MrDNA: a multi-resolution model for predicting the structure and dynamics of DNA systems**

Christopher Maffeo [1,*] and Aleksei Aksimentiev [1,2,*]

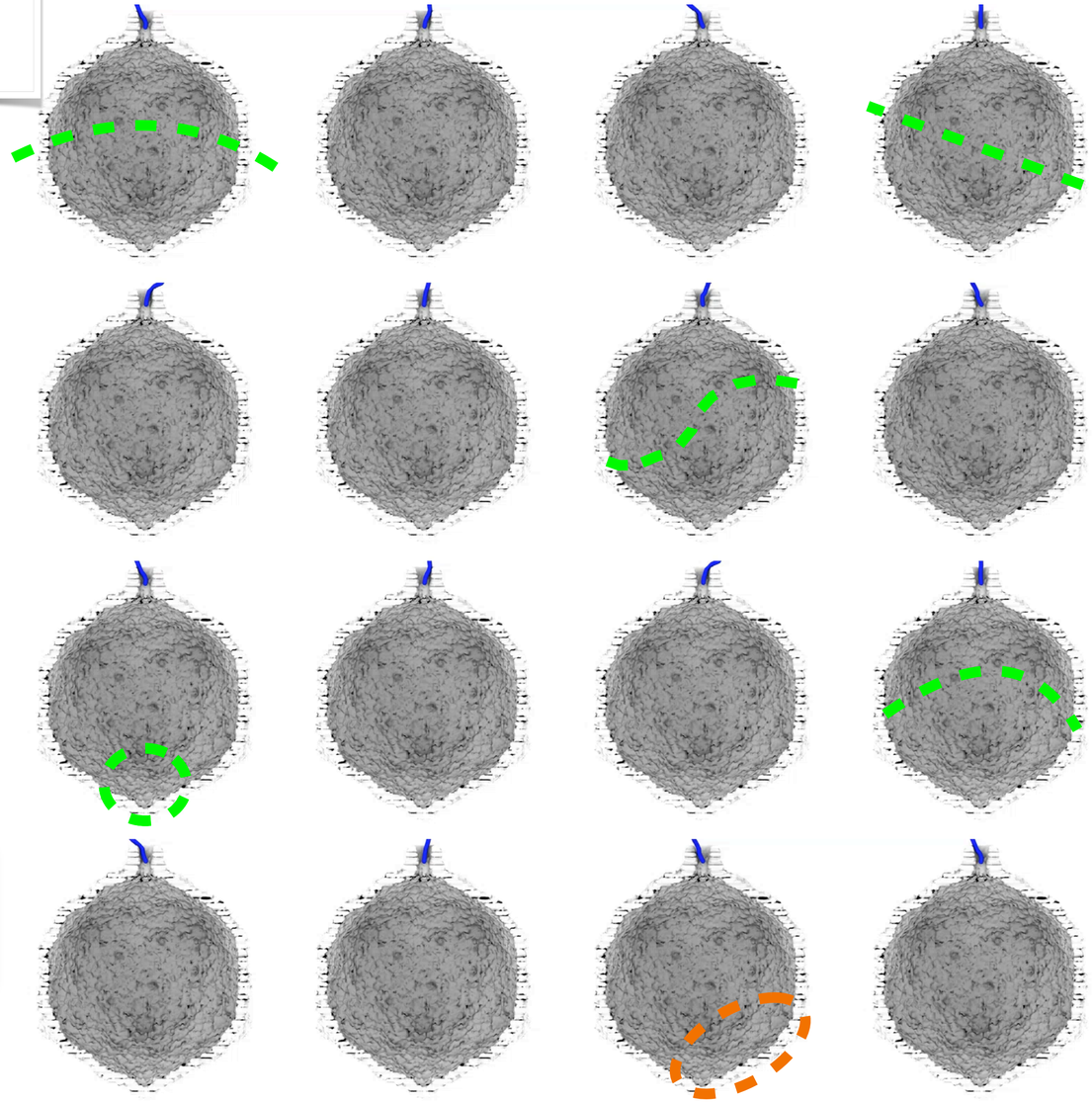
# Packaging a model herpes-like virus

Trajectories lasted >1 ms
with 40-fs timestep, requiring ~4 months of simulation
**Only feasible with Frontera GPU-nodes!**



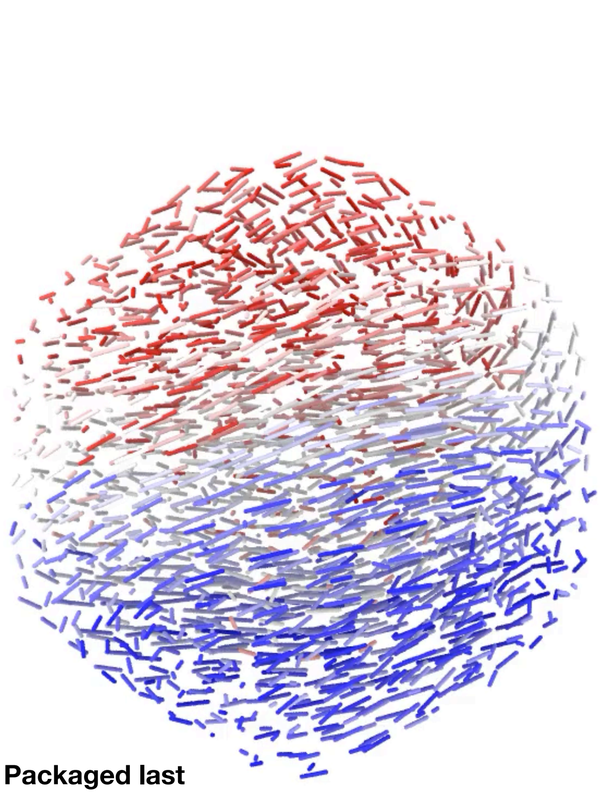
Despite near-identical simulation conditions, packaged genome differed in each capsid (INDIVIDUALITY)

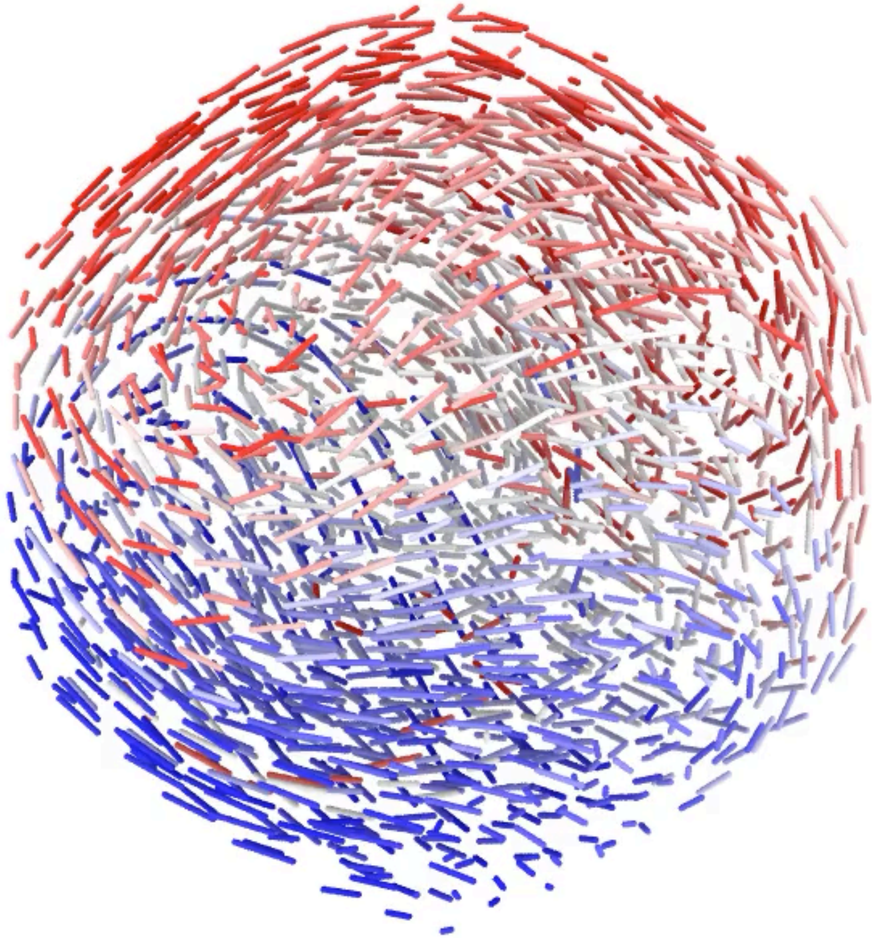
Occasional protrusions of DNA from one side to another

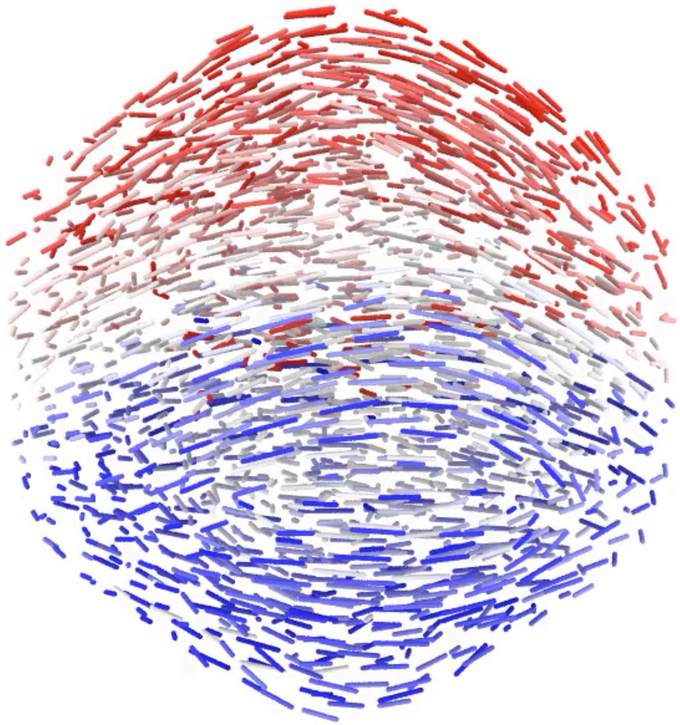


# Packaged genome configurations are unique

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







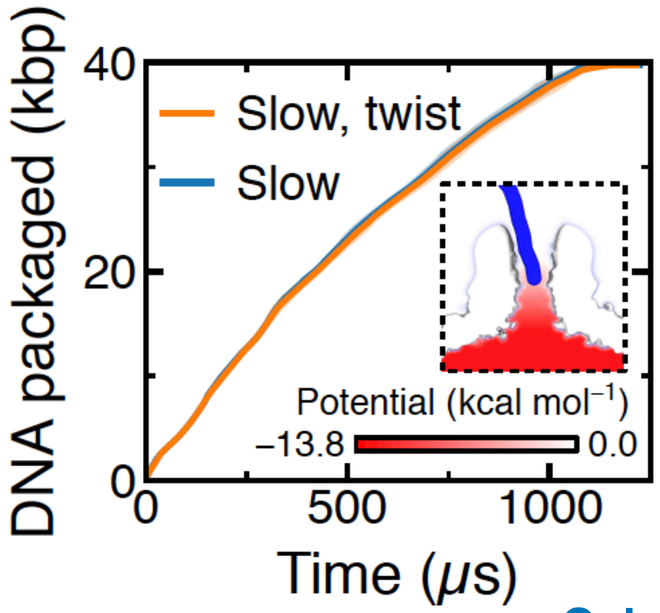
**Packaged last**

**Packaged first**

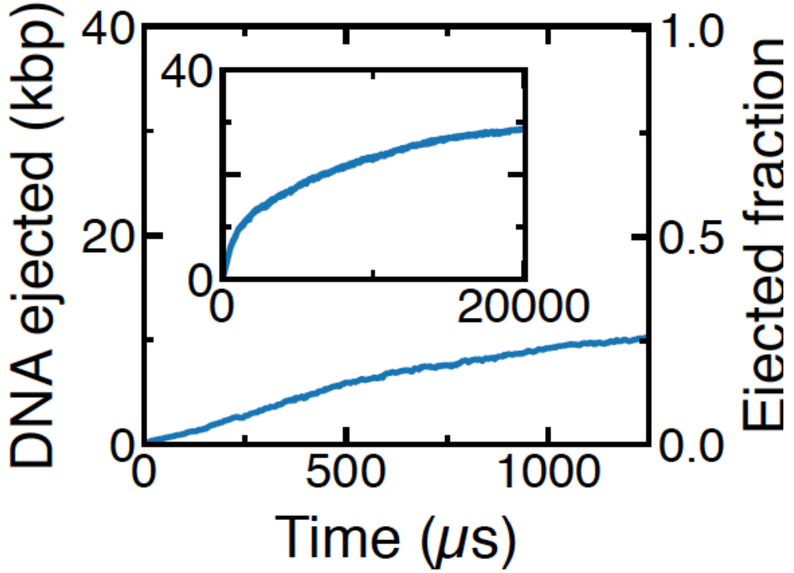
Baseball-like order at surface, with two cupped halves having orthogonal order at the poles

Order in the same-direction at the poles

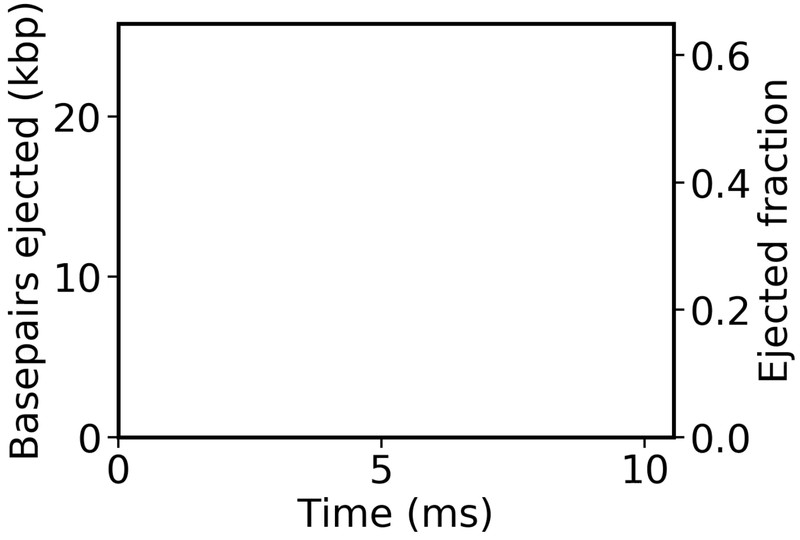
# DNA is packaged near the speed of spontaneous ejection




**Only 4 times slower!**



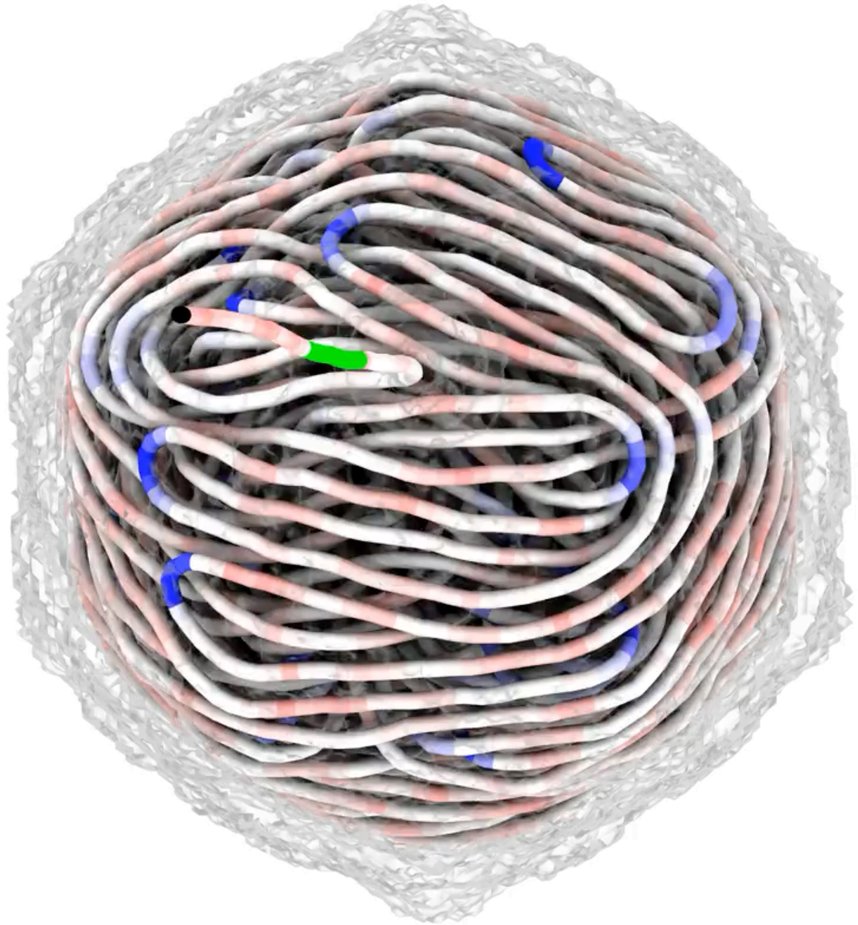

Capsid is not shown for clarity



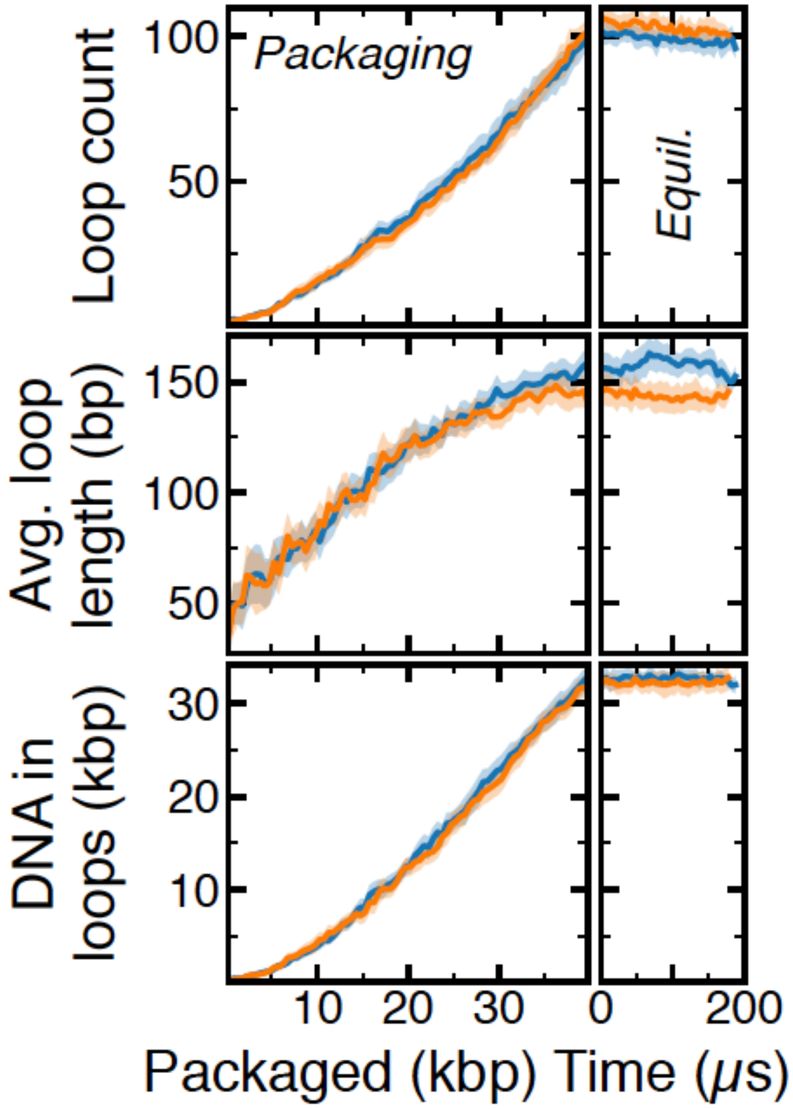

Spontaneous ejection of DNA from a bacteriophage capsid
~ 1 year's simulation!!

# DNA is packaged in switchback loops

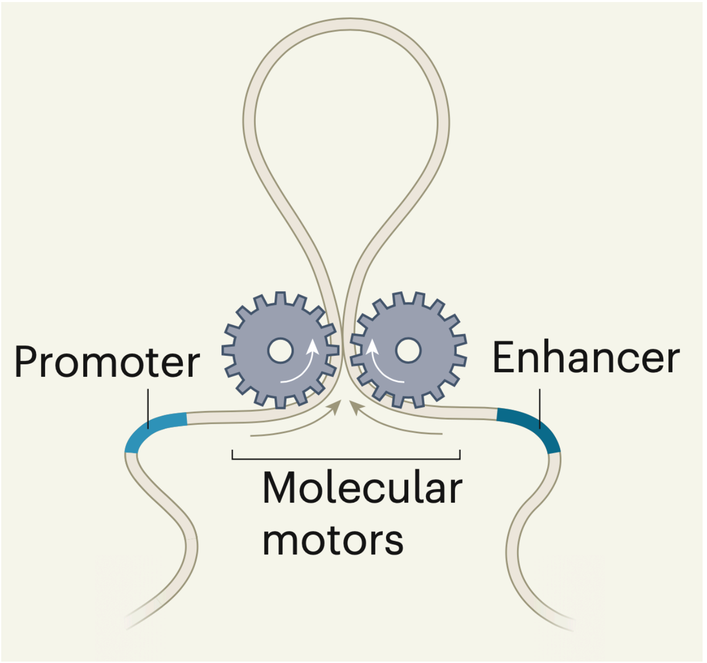
DNA is colored according to local bending energy



The three loops are shown in green, magenta, and violet

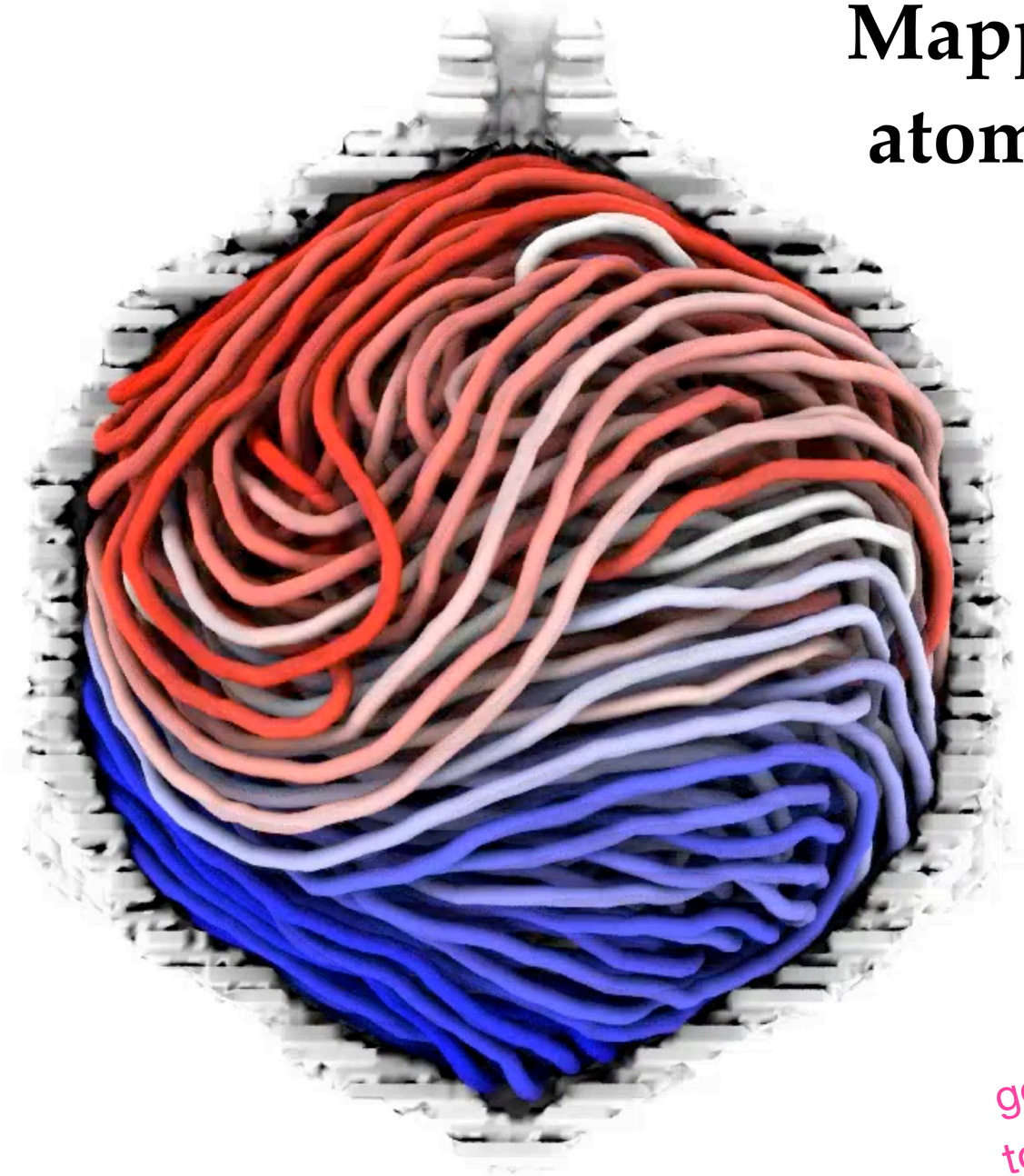



Loop-extrusion




Cells use loop extrusion to weave and tie the genome

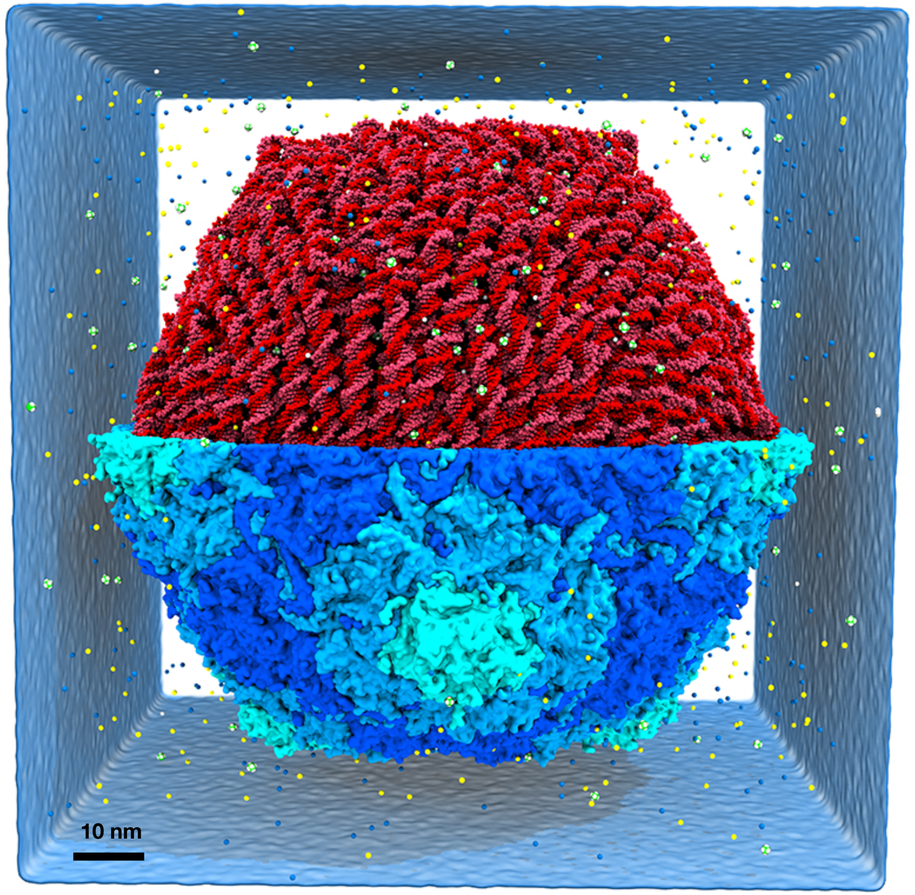
Mirny, Nature (2021)



# Mapping to all-atom structure

## Bacteriophage HK97

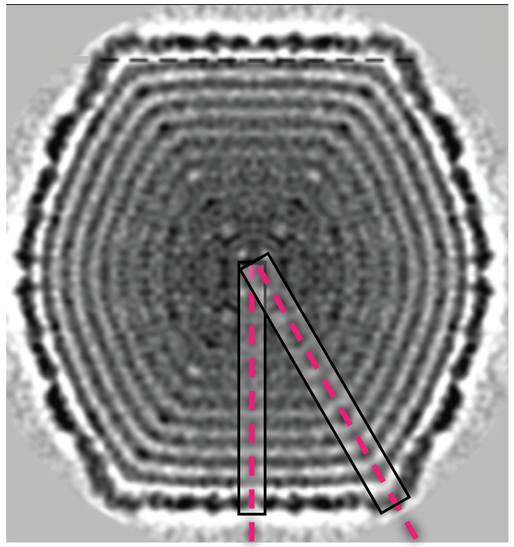
39,732 bp DNA genome
(~ 60nm diameter)
Fully solvated system: 27 M atoms




Method generalizable to any dsDNA virus

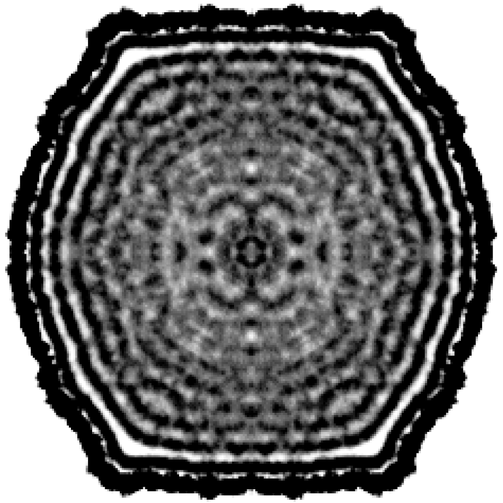
**"The structure and physical properties of a packaged bacteriophage particle"**
Kush Coshic, Christopher Maffeo, David Winogradoff and Aleksei Aksimentiev.
*Under peer review*

Experiment



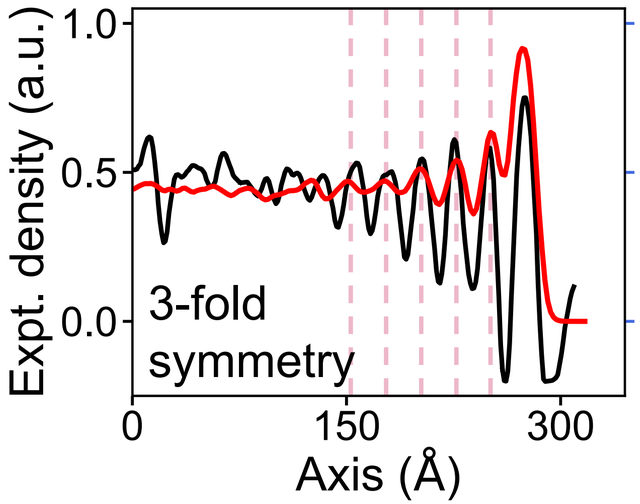

1300 structures

All-atom simulation

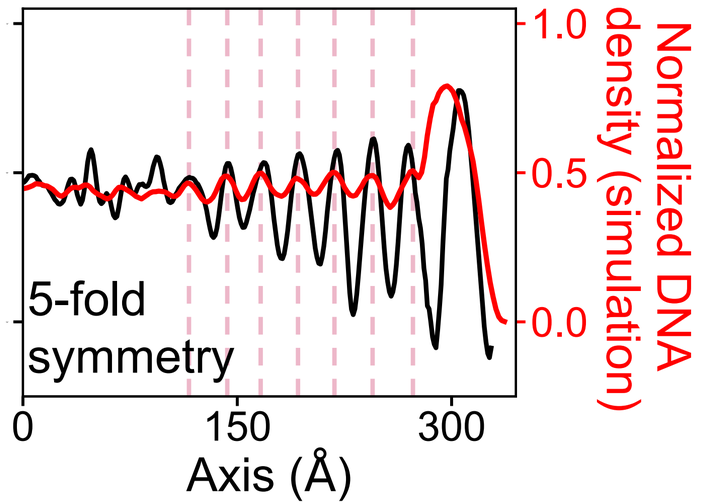


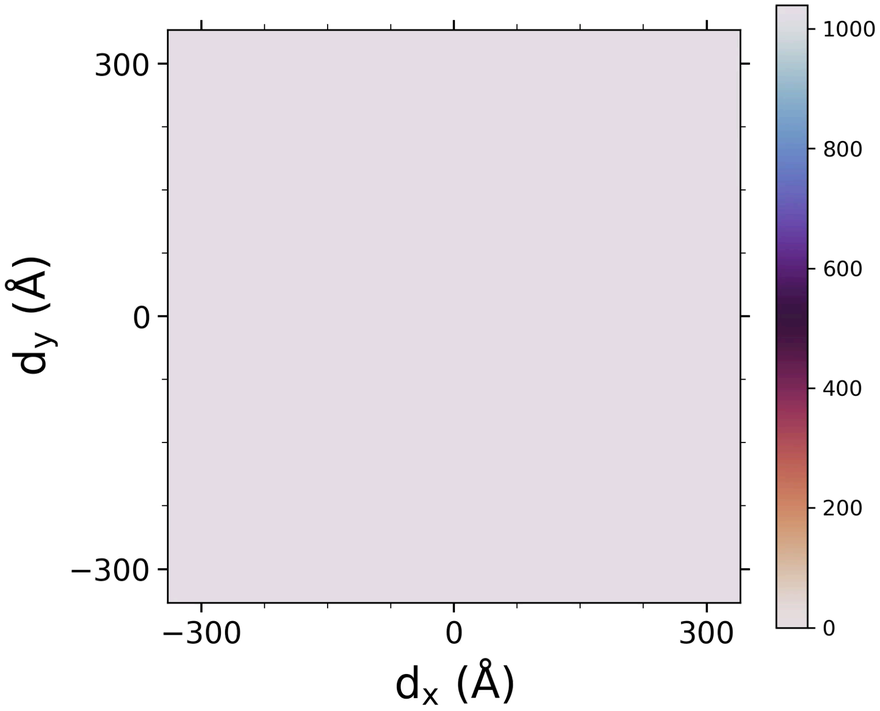
1 structure (60 icosahedron symmetries)

Face

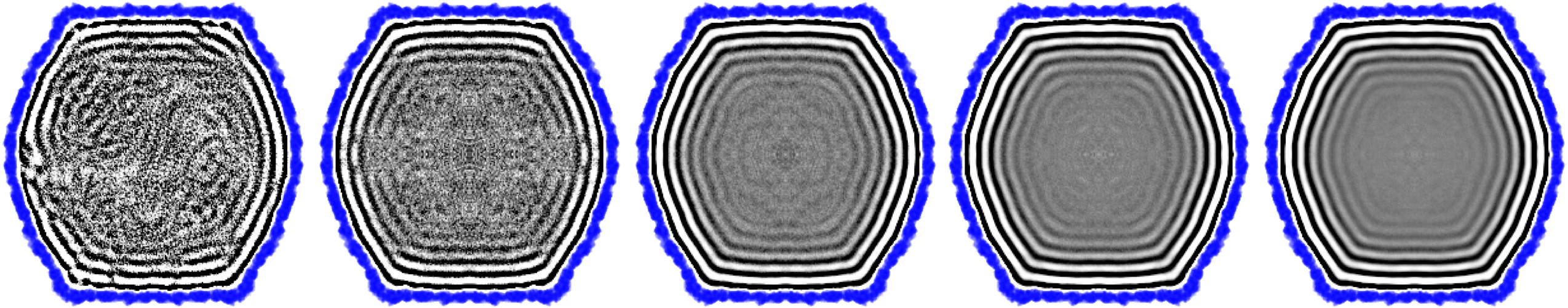



Vertex



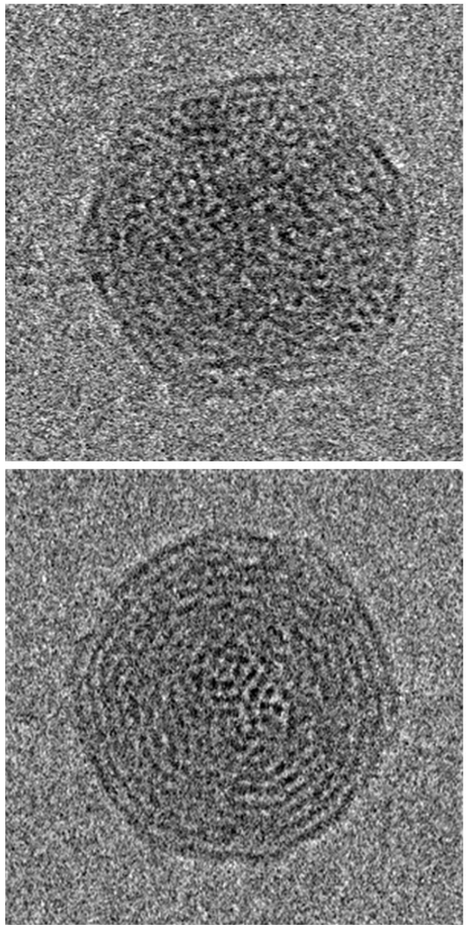



# Coarse-grained simulations

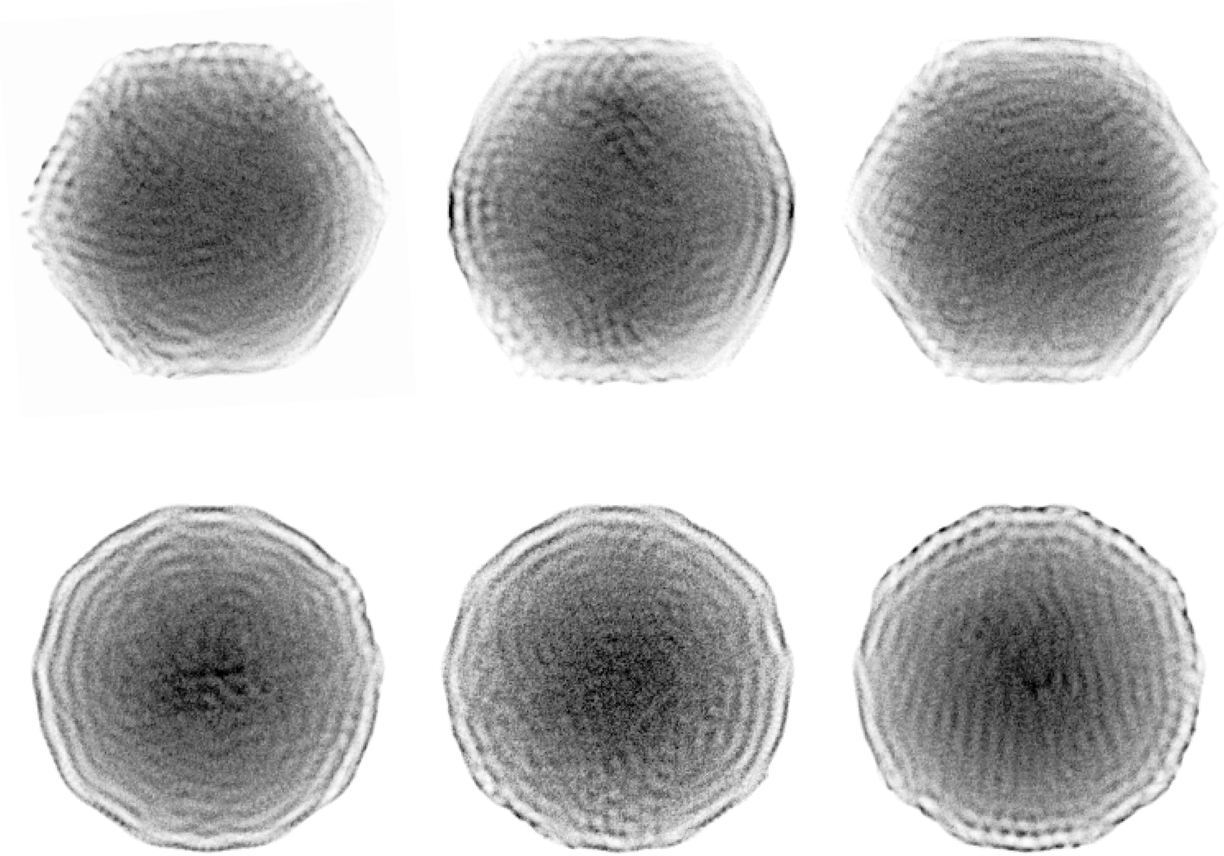


No symmetrization | 4 symmetry axes | 60 symmetry axes | 4 replicas | 16 replicas

# TEM-like analysis of packaged HK97 genome



Journal of Molecular Biology, vol. 391, no. 2, pp. 471–483, 2009

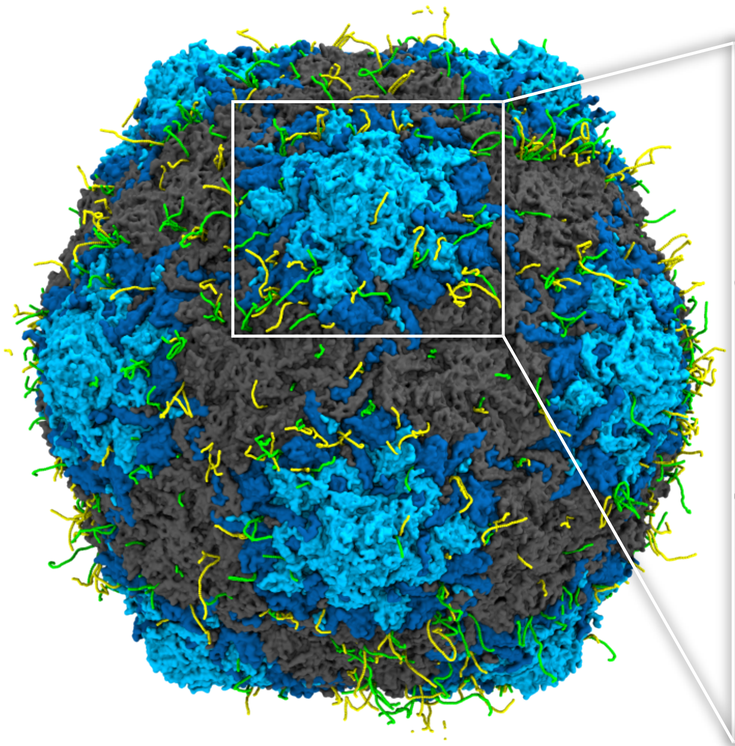


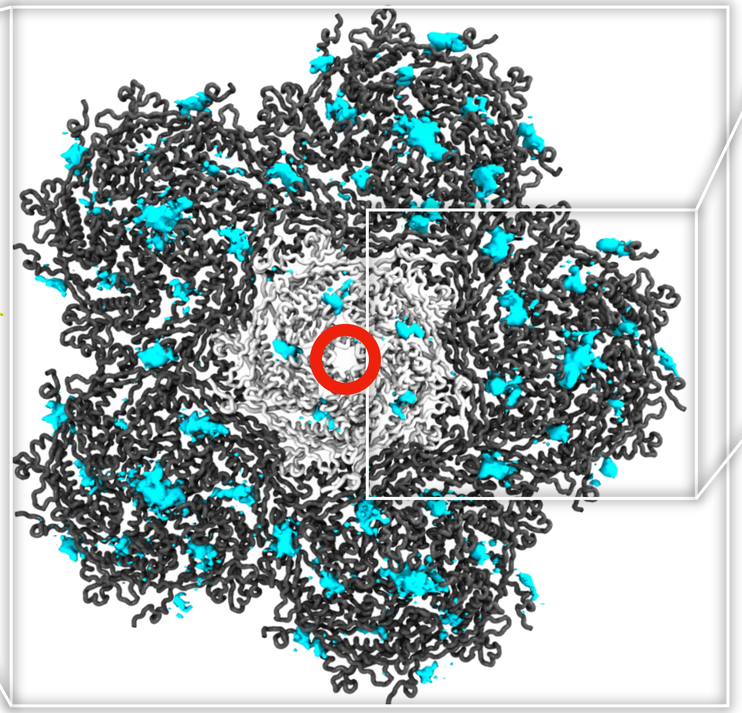
DNA mass density obtained from the coarse-grained packaging simulations projected along several axes

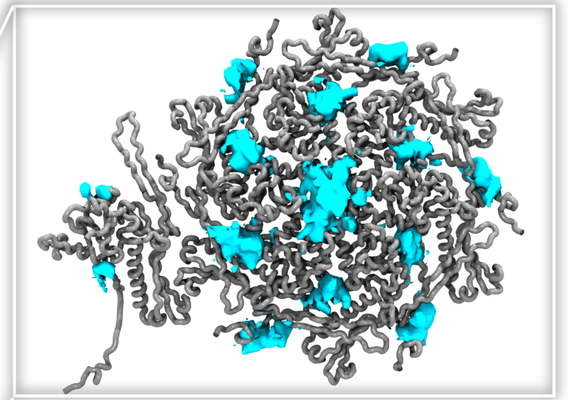
# Frontera enables unprecedented high throughput analysis

A microsecond trajectory of the 27 M atom system => Around 30 Terabytes data

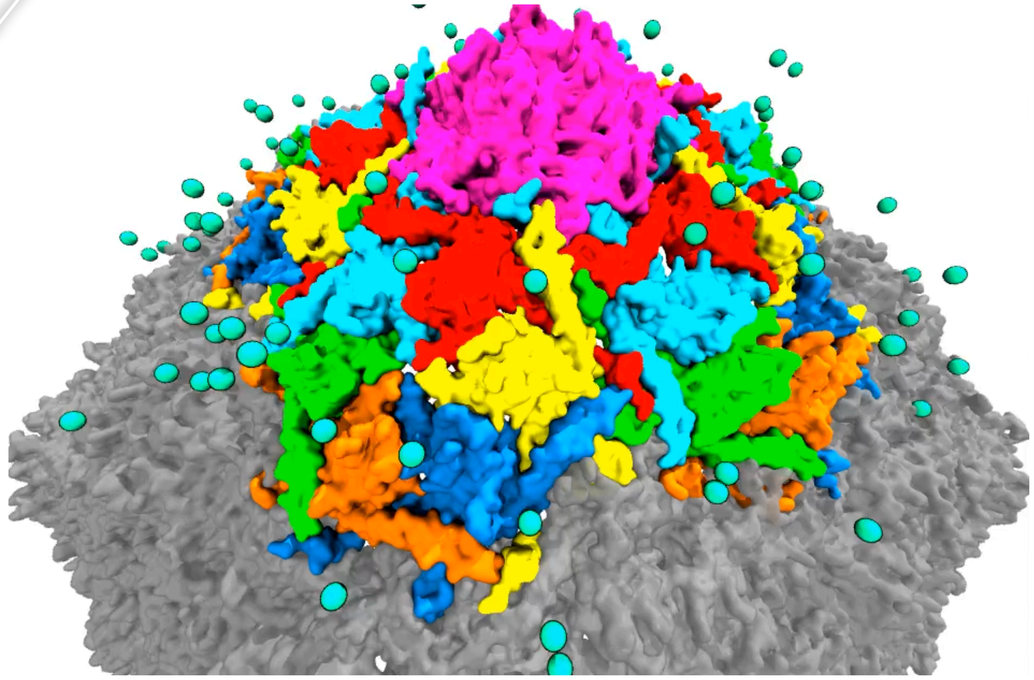
We have 8 such replicas

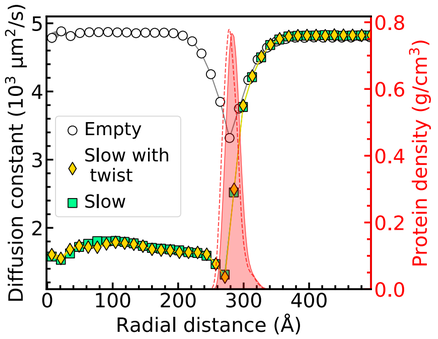


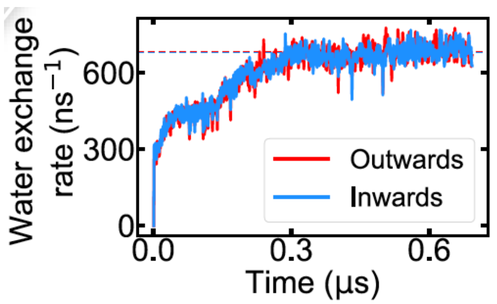


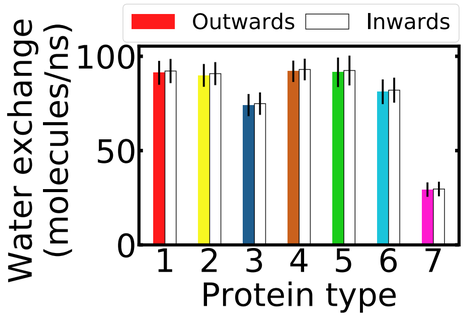


**Water and ion exchange**

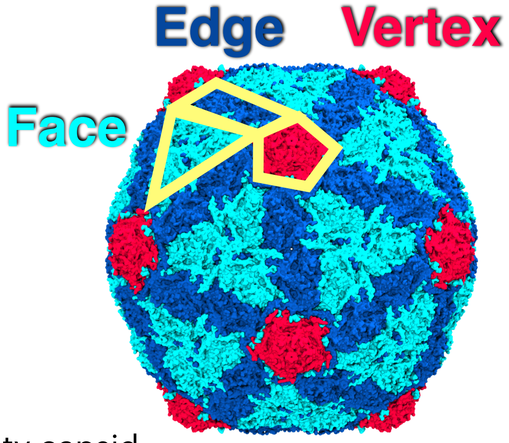




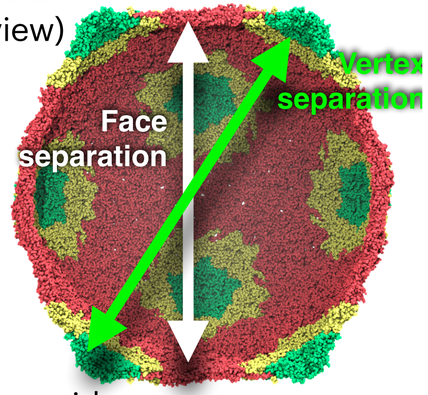



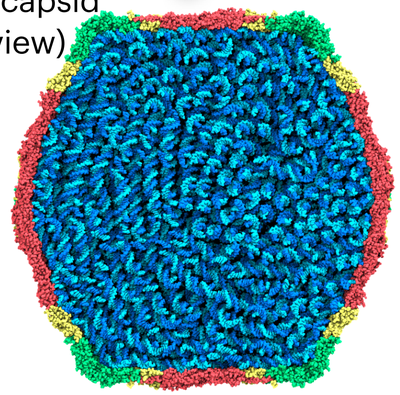
# DNA matters: Capsid structure and dynamics

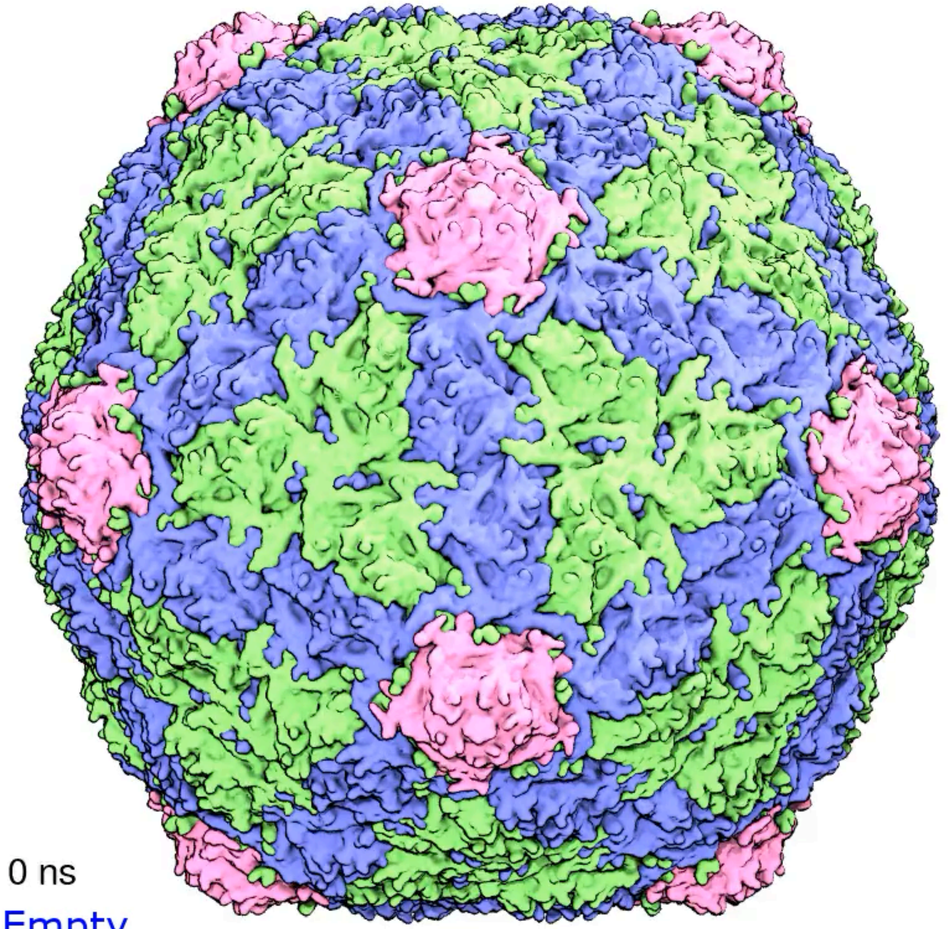



Empty capsid
(cut-away view)

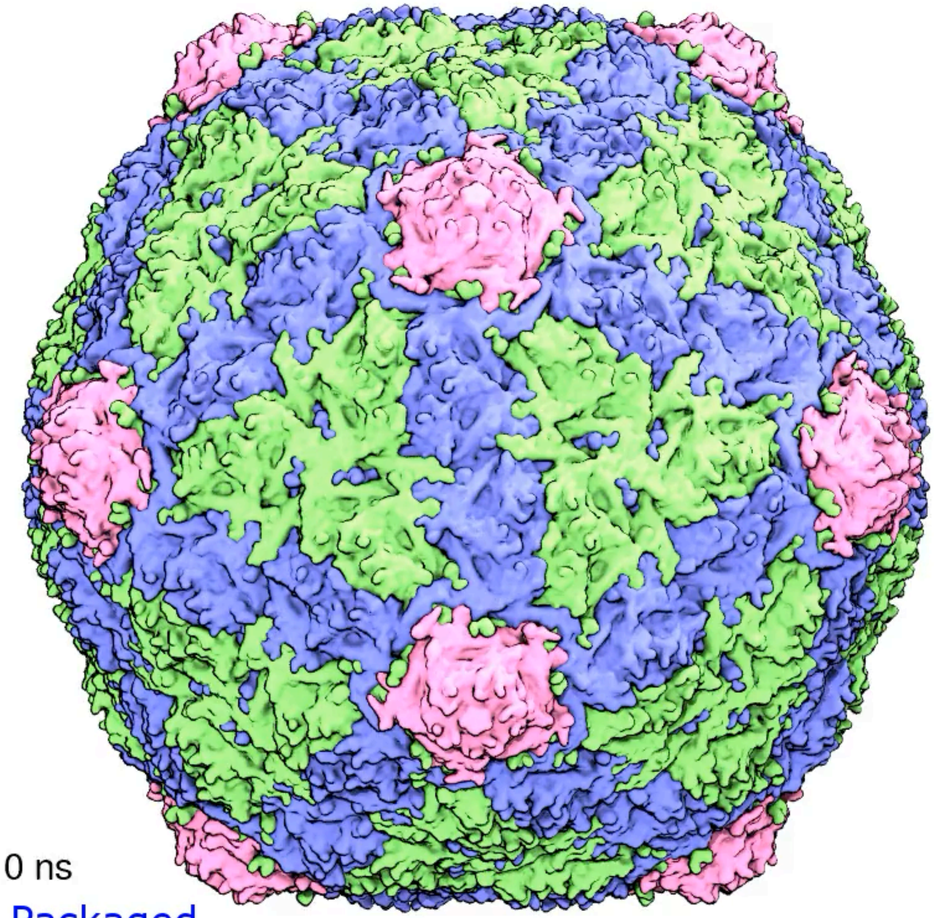



DNA-filled capsid
(cut-away view)





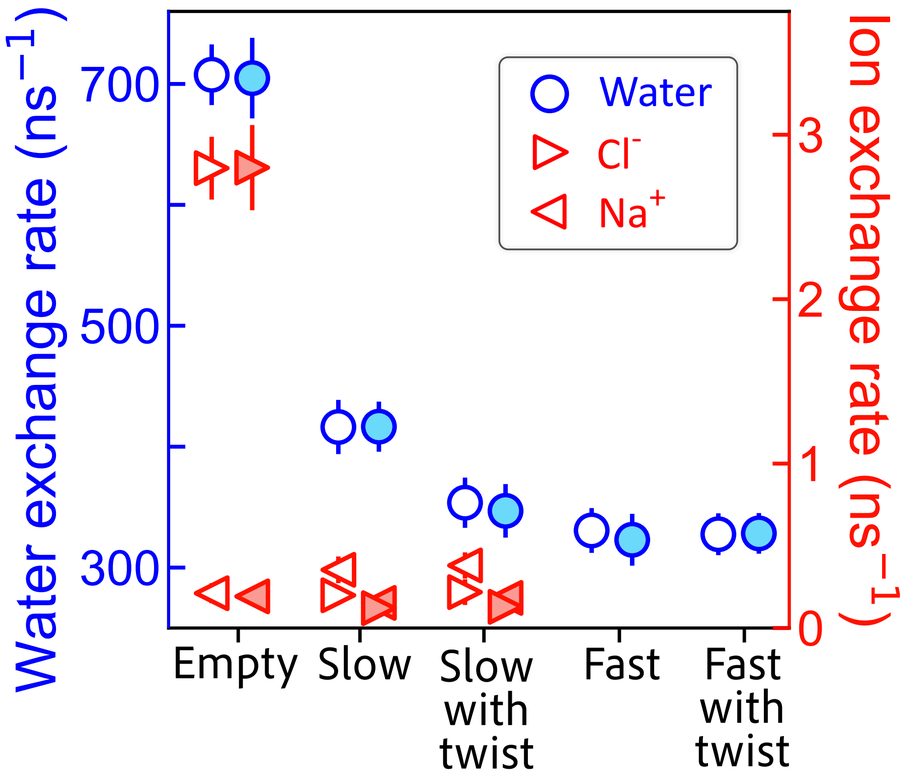
0 ns
Empty



0 ns
Packaged

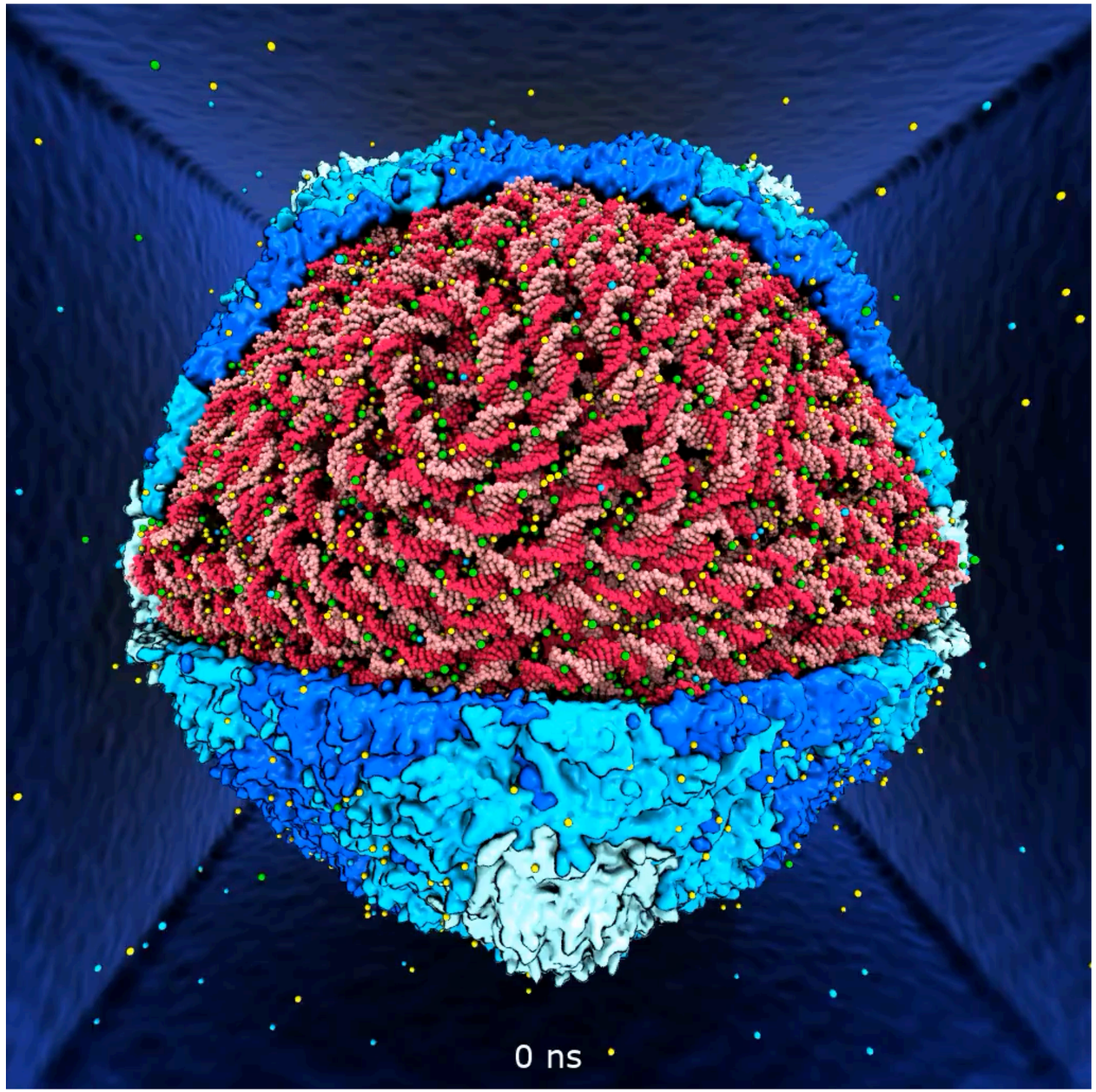
Locally correlated but globally
asynchronous breathing motion

# Effect of DNA on water and ion exchange

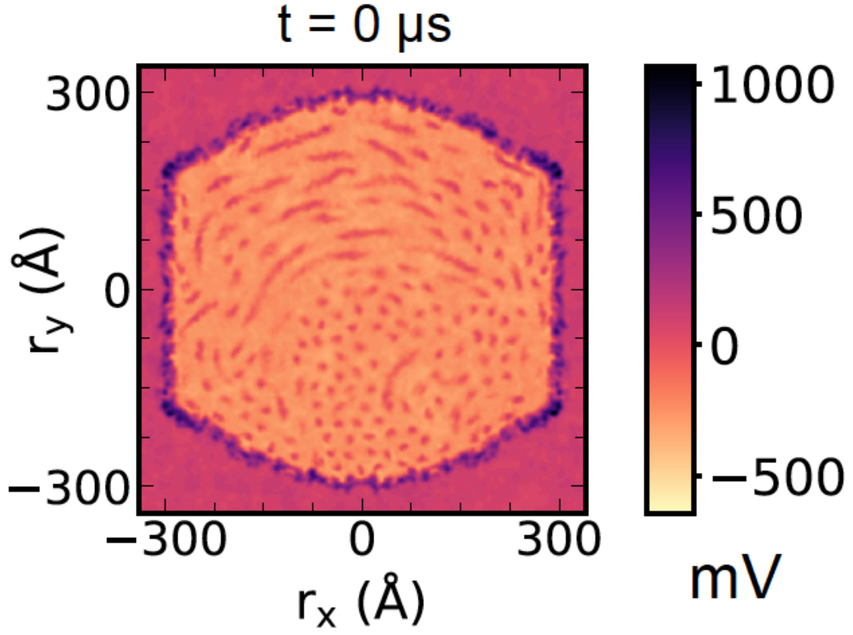


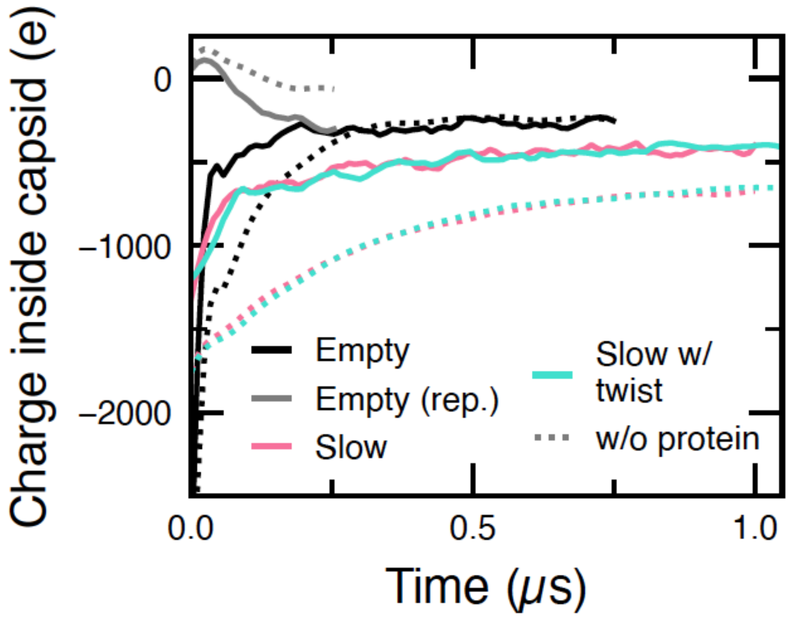

DNA makes water exchange slower by twofold because of reduced volume of water filled cavities and reduced diffusivity

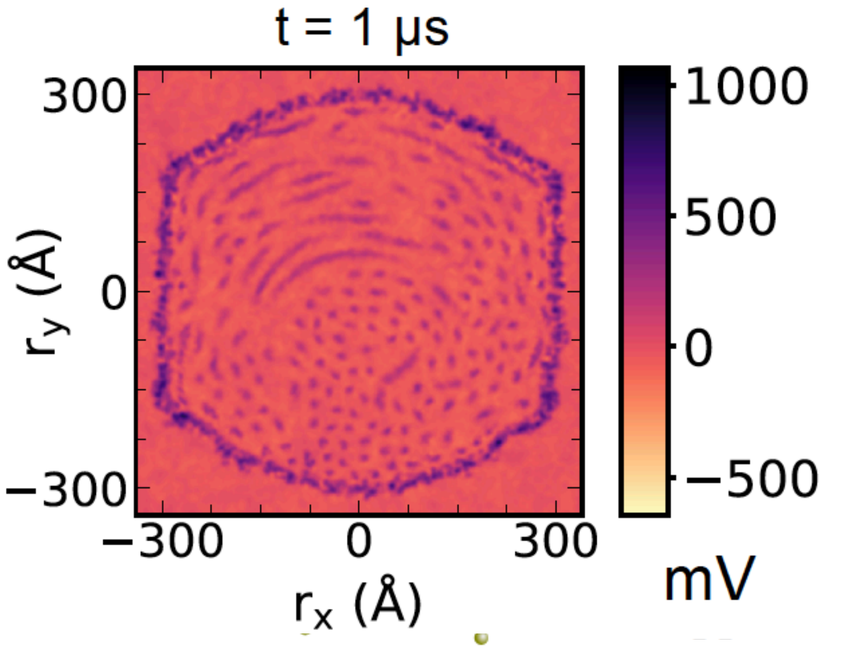
Empty capsid is anion selective (5 fold). DNA doubles the rate of cation exchange and lowers (5 fold) the rate of chloride exchange



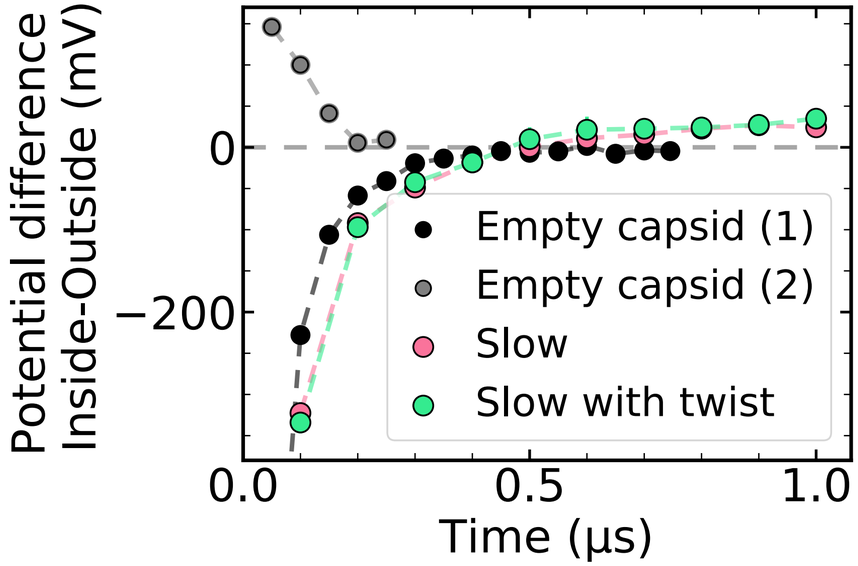
# Electrostatics in a fully packaged virion (HK97)

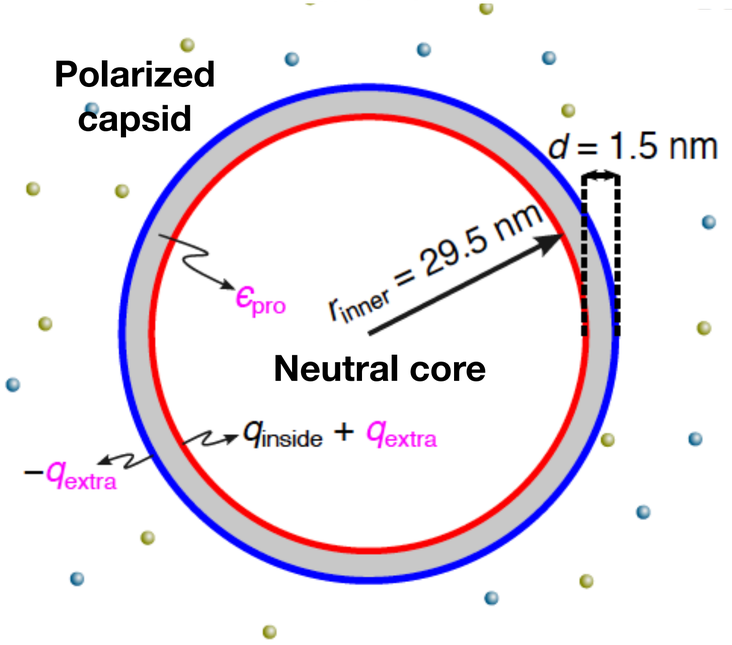



**The capsid interior starts with a lower electrostatic potential**



# Summary

Multi-resolution simulation can deliver complete all-atom structures of packaged virions

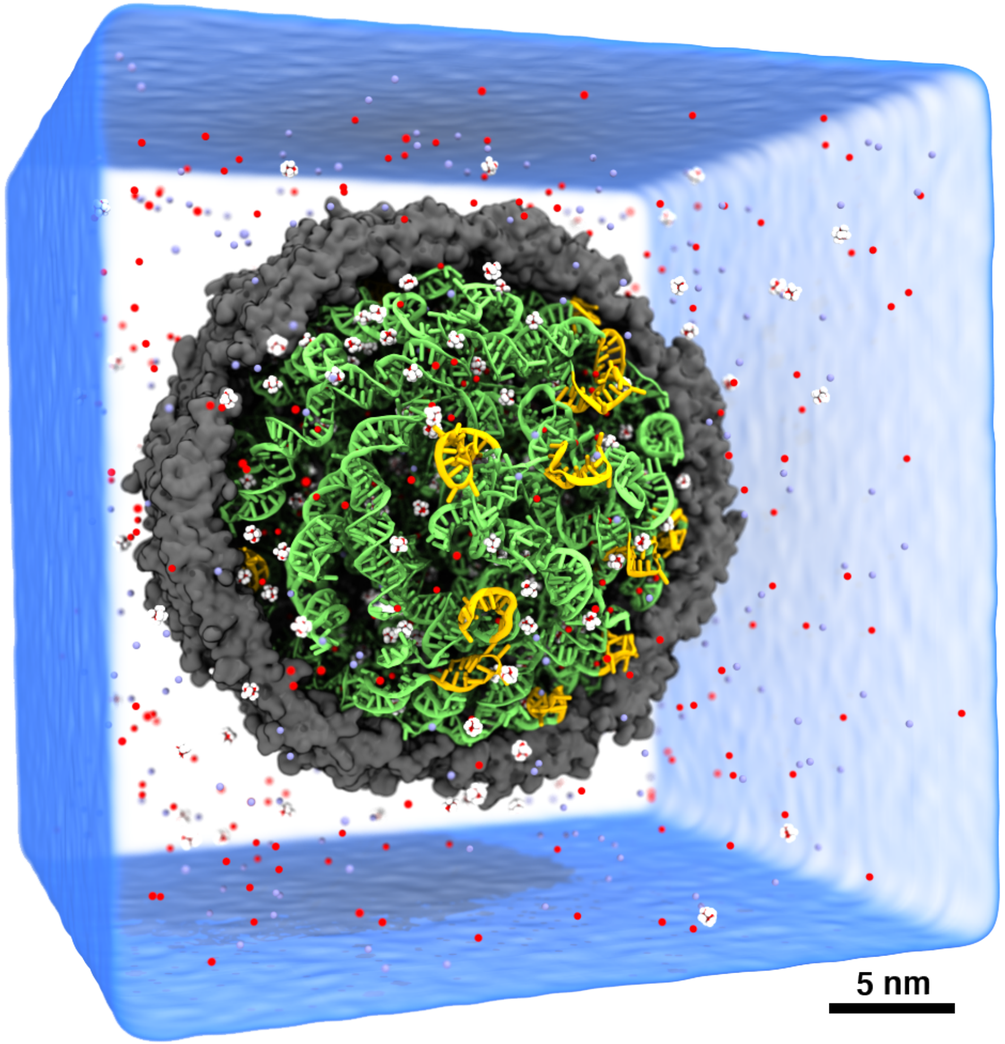
DNA packaging occurs via a loop extrusion mechanism

Each packaged particle is unique because of the topology of its packaged genome, and thus the concept of **individuality** goes all the way to the most primitive forms of life

Twisting DNA while packaging did not produce major differences in the structure and physical properties of packaged particles

Packaged DNA affects the structure and fluctuation of the capsid as well as diffusion of water and ions inside and through the capsid

# The structure and dynamics of a fully packaged RNA virus




4 M atoms
90 ns/day with 256 nodes

Multiple replicas
2.5 μs each

**“The structure and dynamics of a fully packaged RNA virus”**
Kush Coshic and Aleksei Aksimentiev.
*In preparation*

# RNA genomes of self-assembled viruses

LETTER

doi:10.1038/nature20589

## *In situ* structures of the genome and genome-delivery apparatus in a single-stranded RNA virus

Xinghong Dai[1,2], Zhihai Li[2,3,4], Mason Lai[3], Sara Shu[1], Yushen Du[1], Z. Hong Zhou[2,3] & Ren Sun[1,2]

BIOINFORMATICS

## Hierarchical natural move Monte Carlo refines flexible RNA structures into cryo-EM densities

2 RNA structures

JENG-YIH CHANG,[1,2] ZHICHENG CUI,[1,2] KAILU YANG,[1,2,5] JIANHUA HUANG,[3] PETER MINARY,[4] and JUNJIE ZHANG[1,2]

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[3]Department of Statistics, Texas A&M University, College Station, Texas 77843, USA
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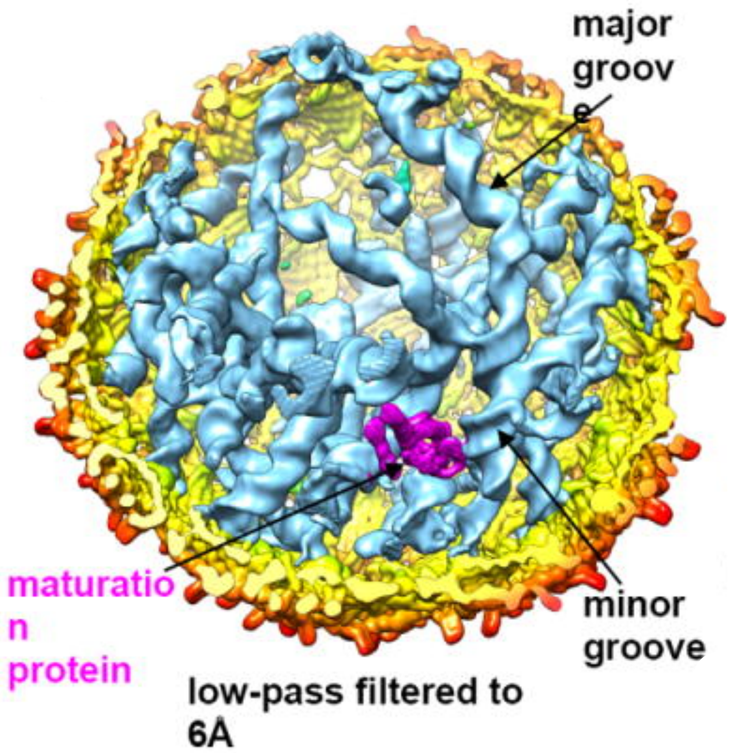
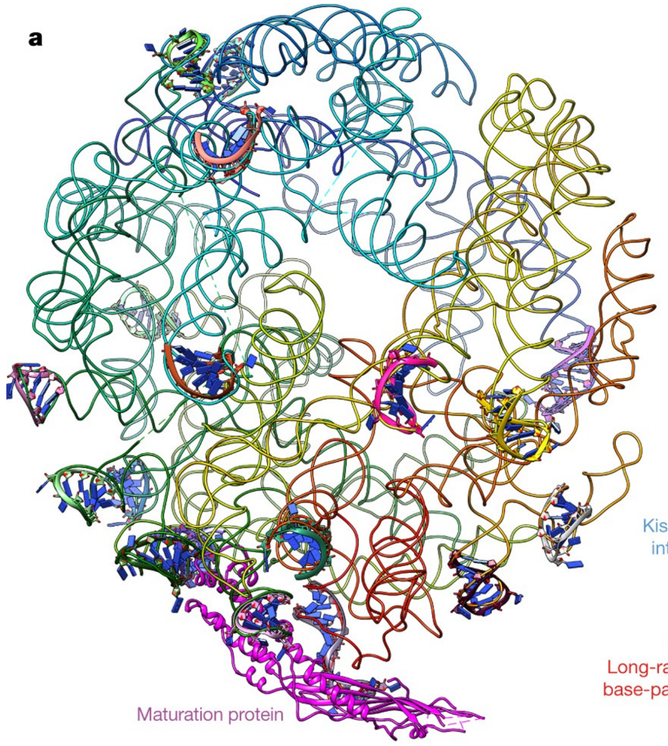
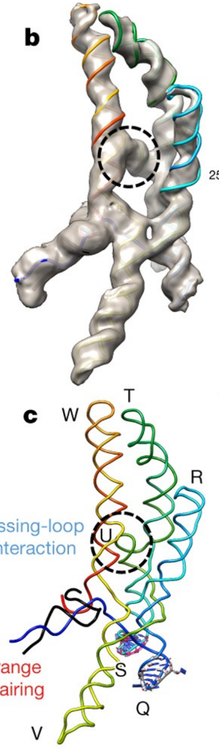
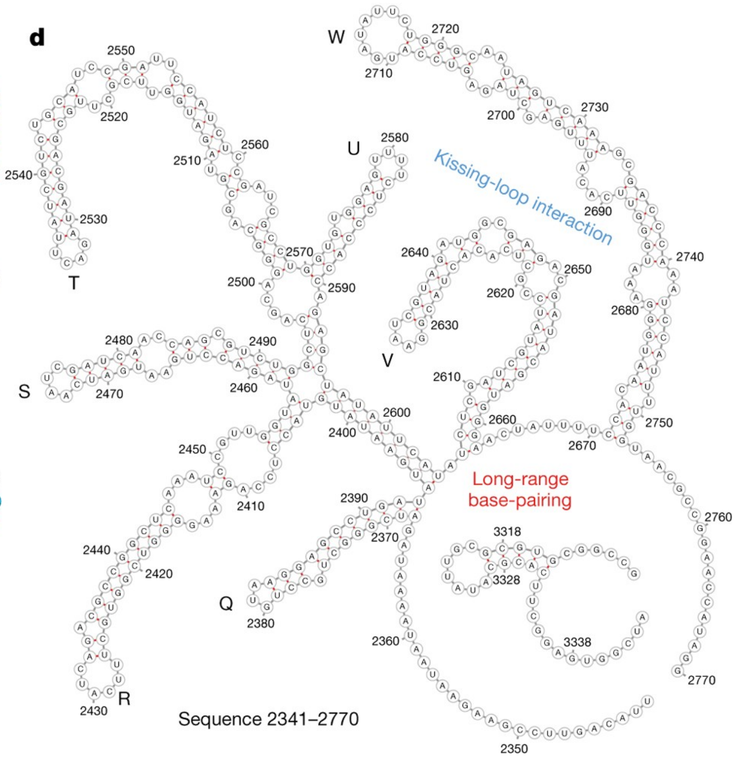
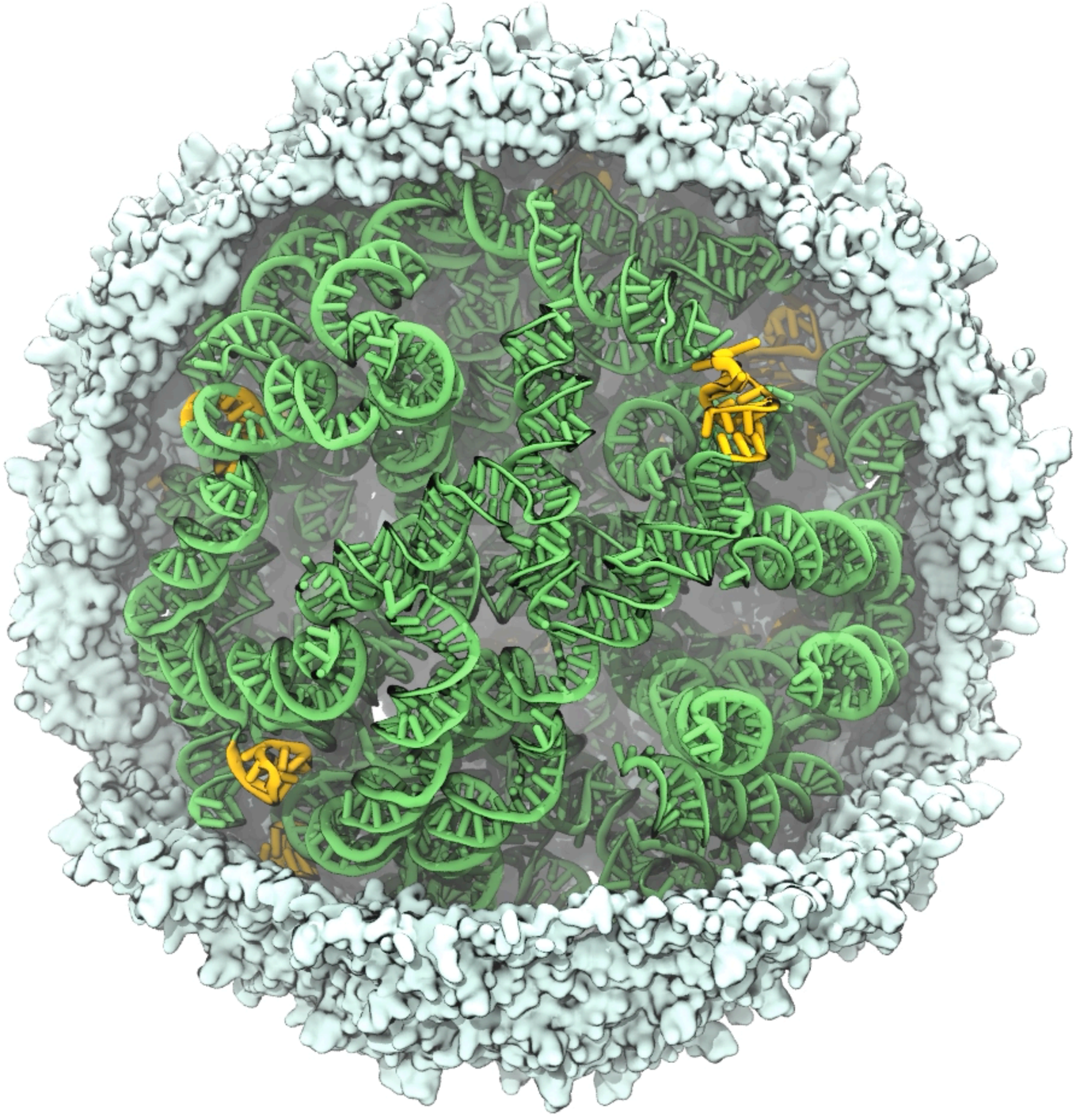


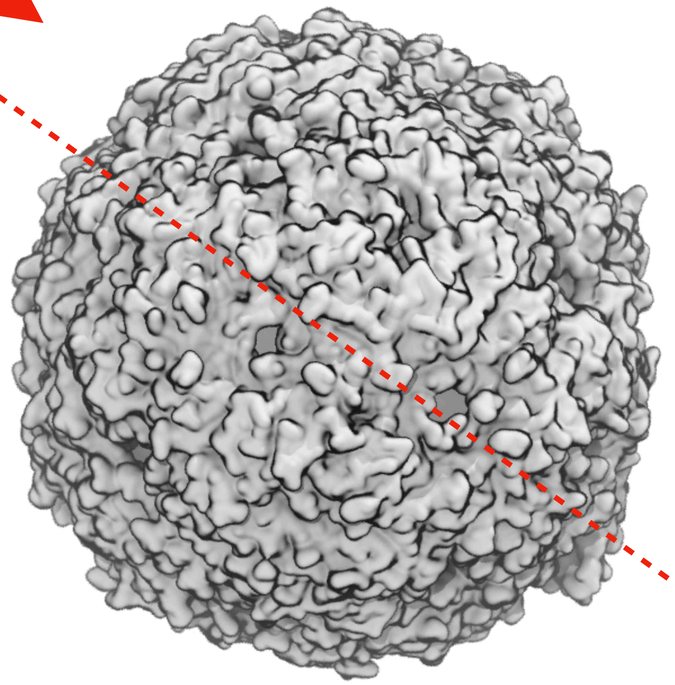





# Measuring the electrophoretic mobility of mature vs immature virions

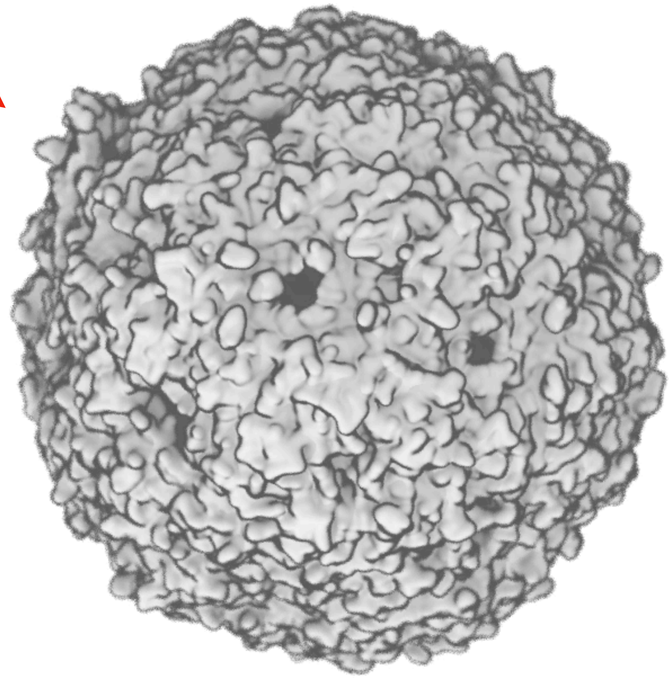
**1 V**

**E** = 0.0033 V/Å



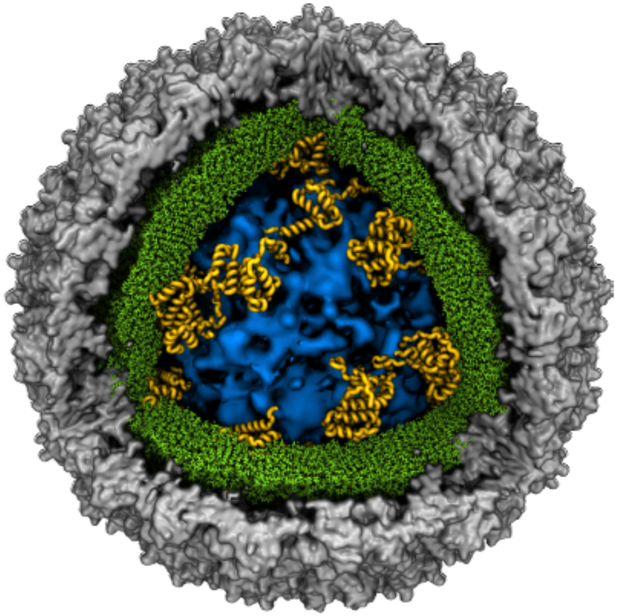
Constant electric field

**v** = ~ 0.5 Å/ns



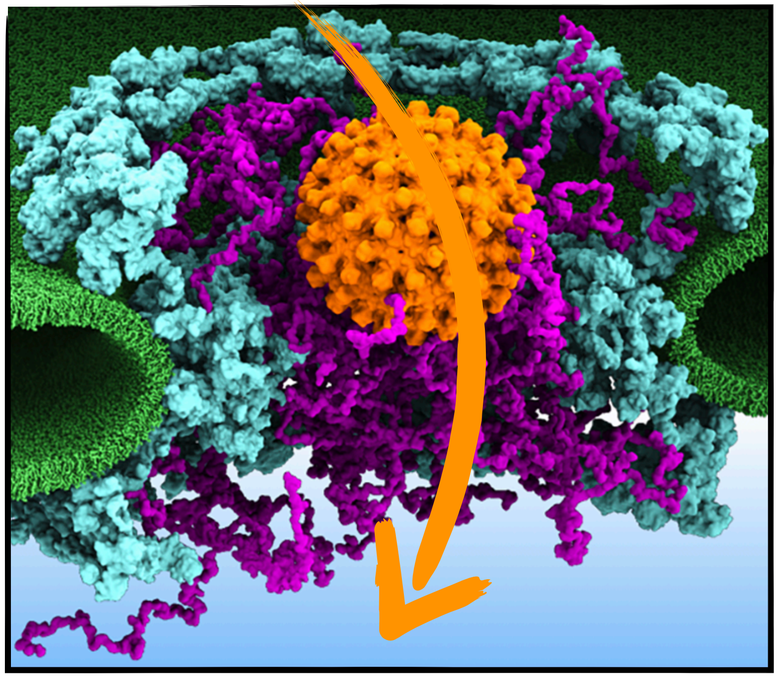
**SMD** (constant velocity)

# Coming soon



Mature Dengue virion

Passage through the nuclear pore complex



Probing mechanical properties of capsids

Ejection *in-vivo*