Resolving the Structure of Viral Genomes with Atomic Resolution

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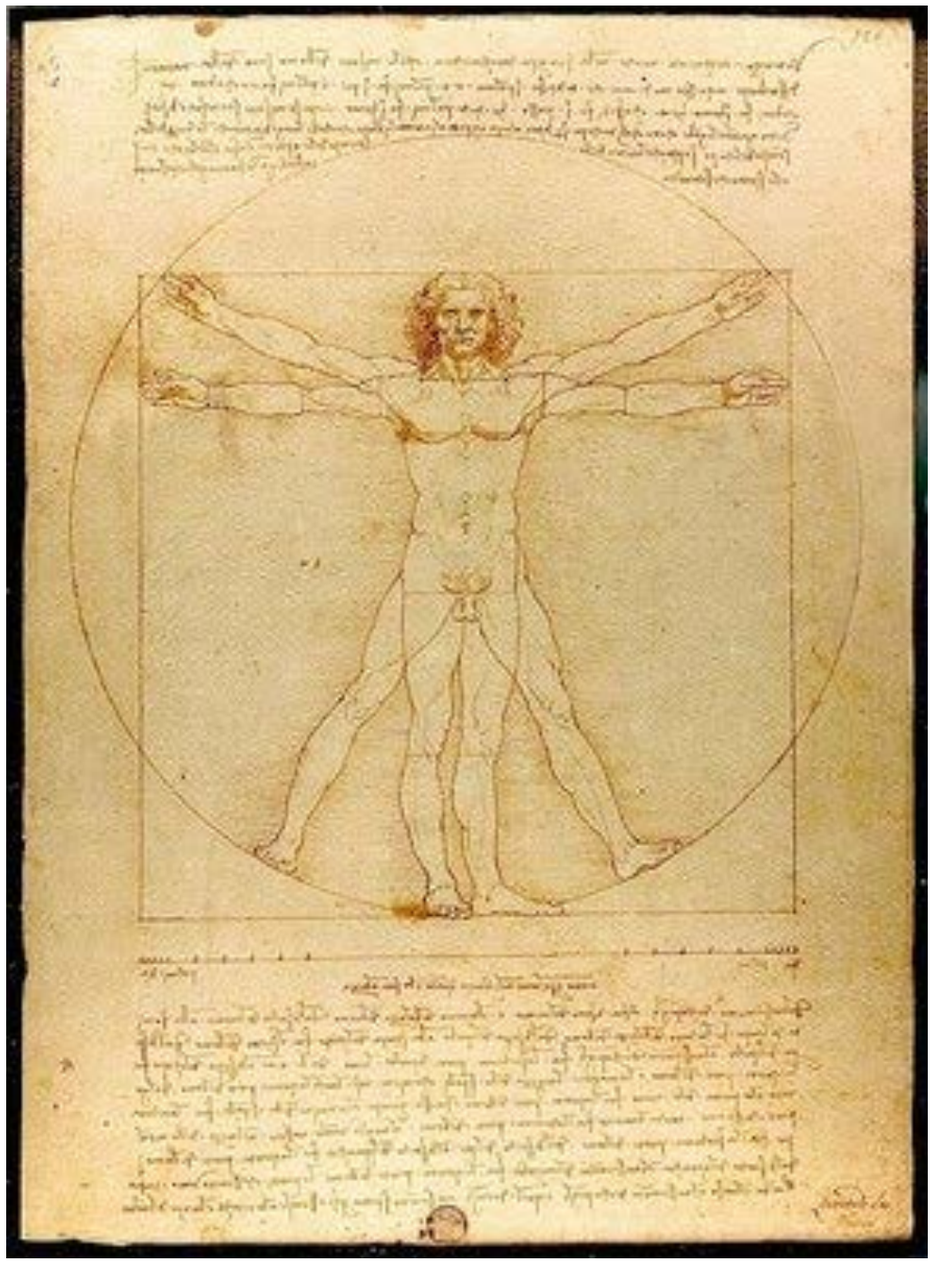
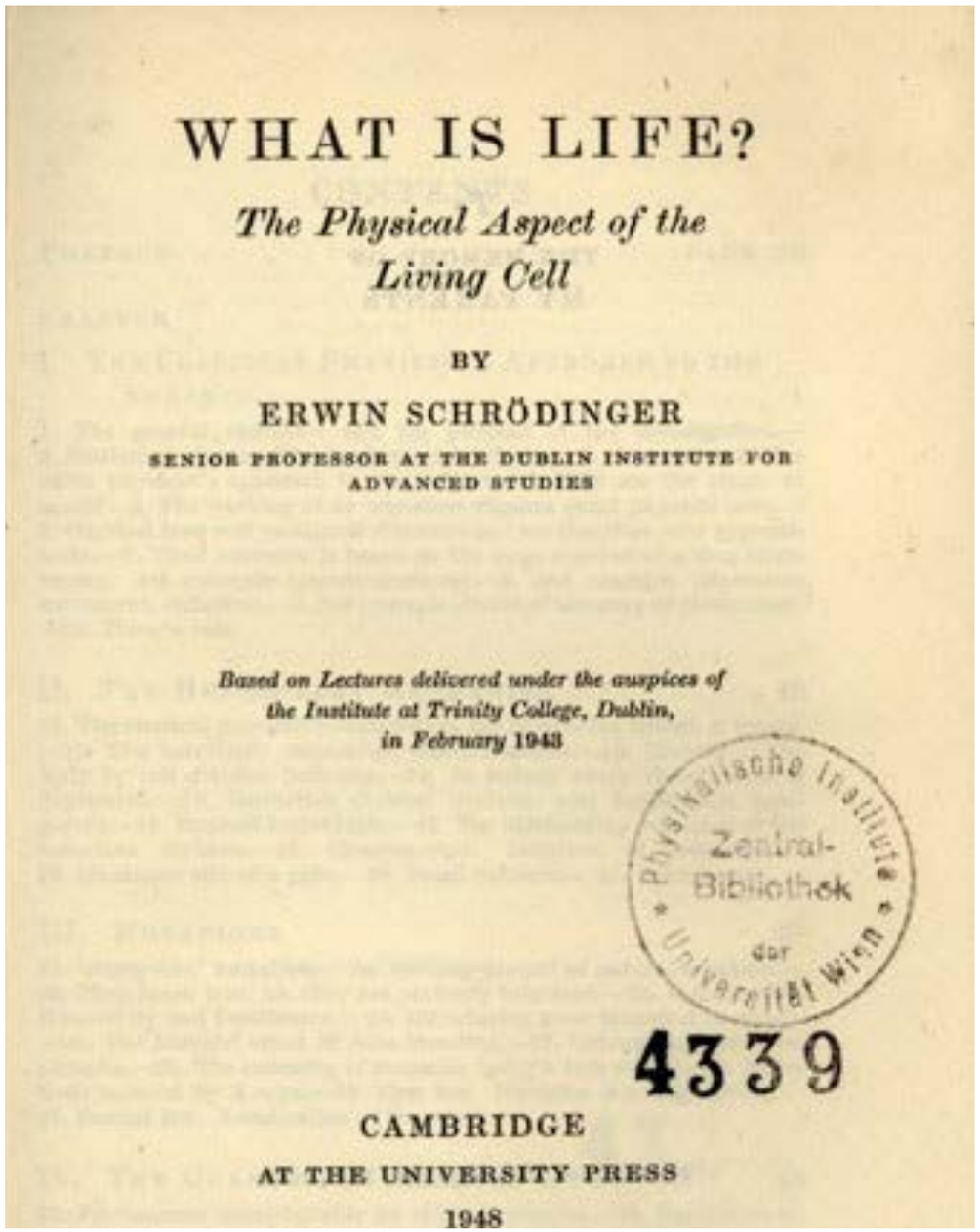
I use Blue Waters to …





WHAT IS LIFE?

The Physical Aspect of the Living Cell

BY

ERWIN SCHRÖDINGER

SENIOR PROFESSOR AT THE DUBLIN INSTITUTE FOR ADVANCED STUDIES

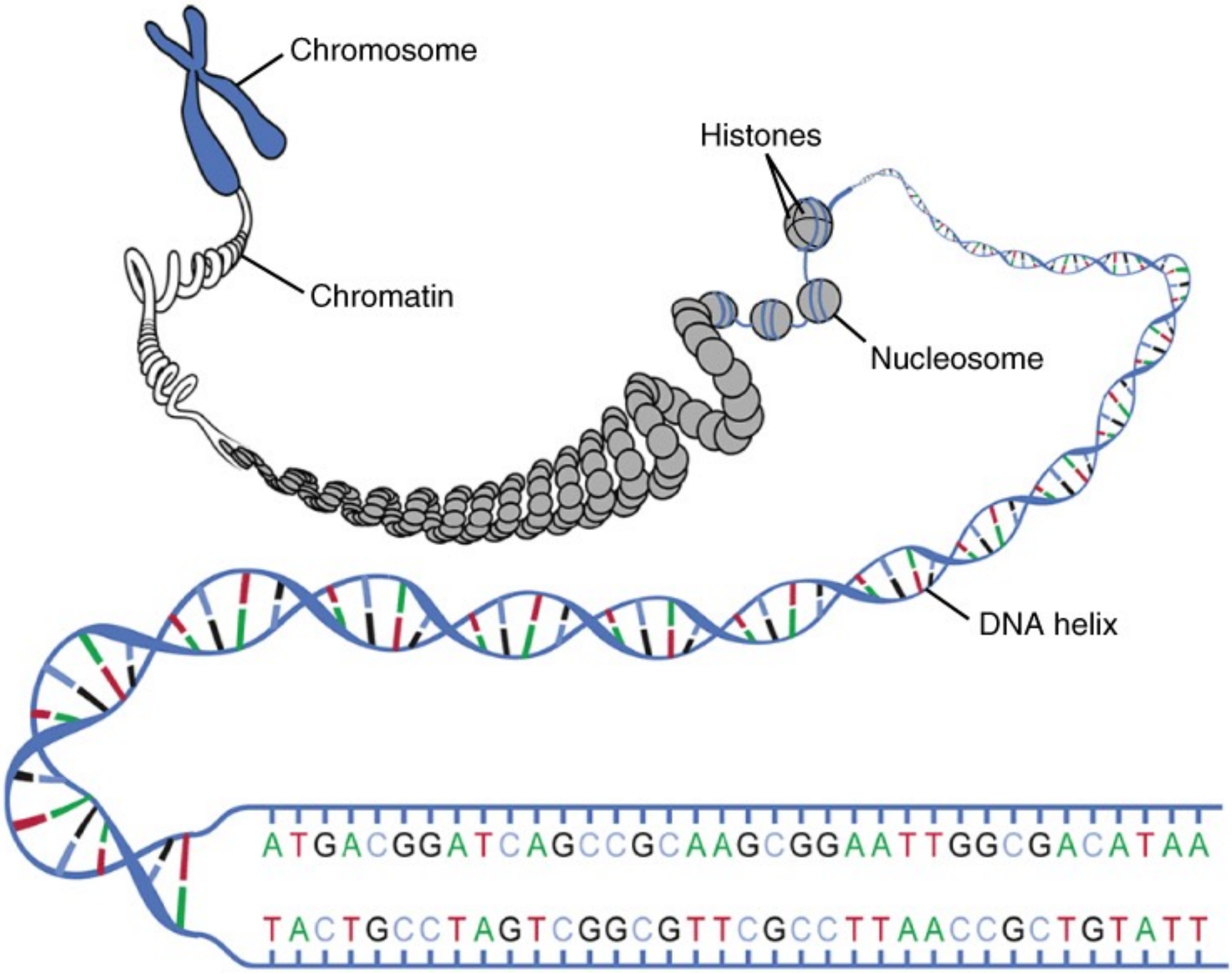
Based on Lectures delivered under the auspices of the Institute at Trinity College, Dublin, in February 1943

CAMBRIDGE
AT THE UNIVERSITY PRESS
1948

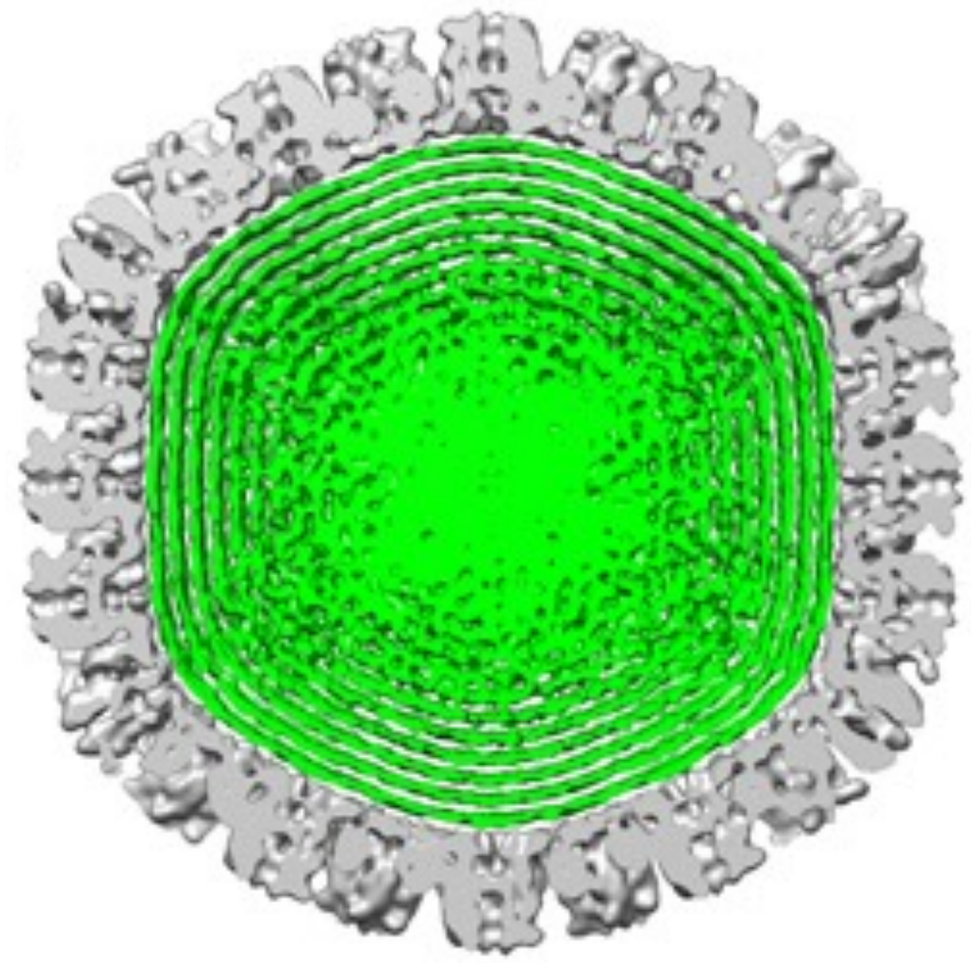
… understand molecular underpinnings of life

… build biologically inspired systems

DNA, the blueprint

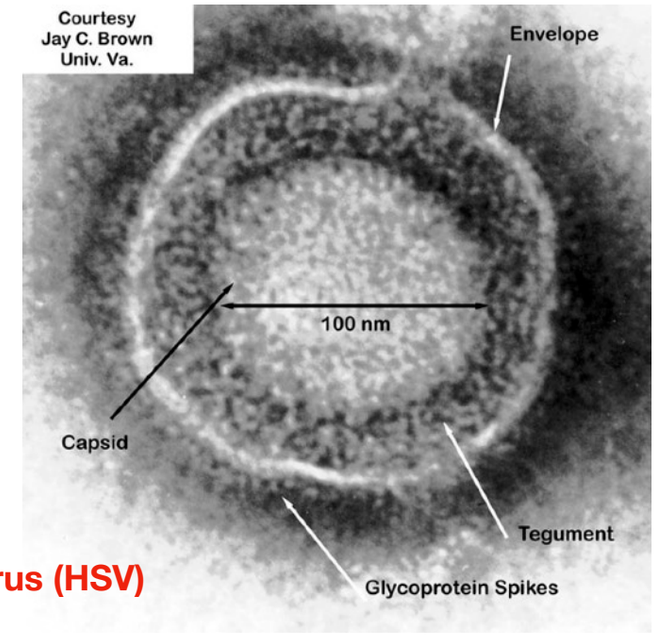


Viral genome, the program of infection

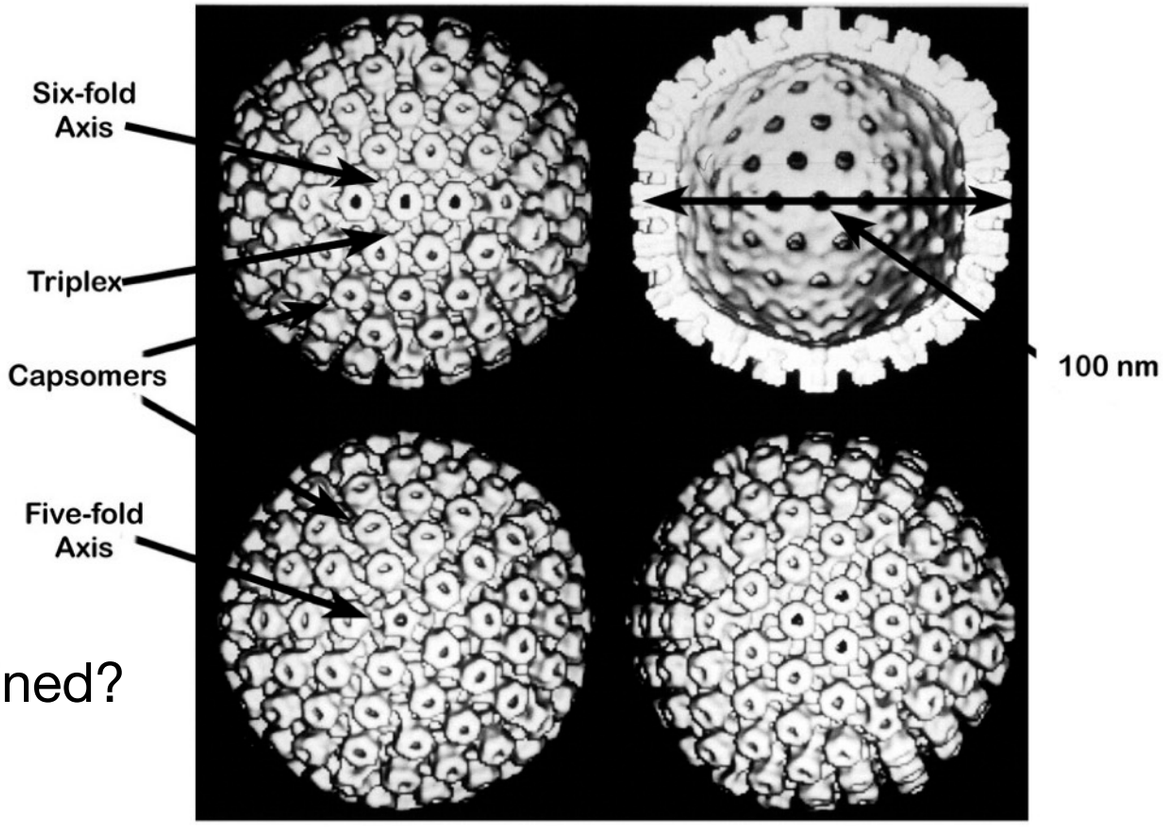


Cryoem reconstruction with concentric rings
(Evilevitch et al, UIUC)

DNA is a highly charged polymer!



Herpes virus (HSV)



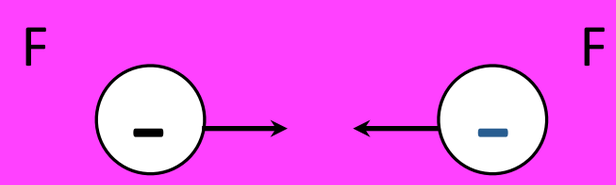
http://darwin.bio.uci.edu/~faculty/wagner/hsv2f.html

Open questions:

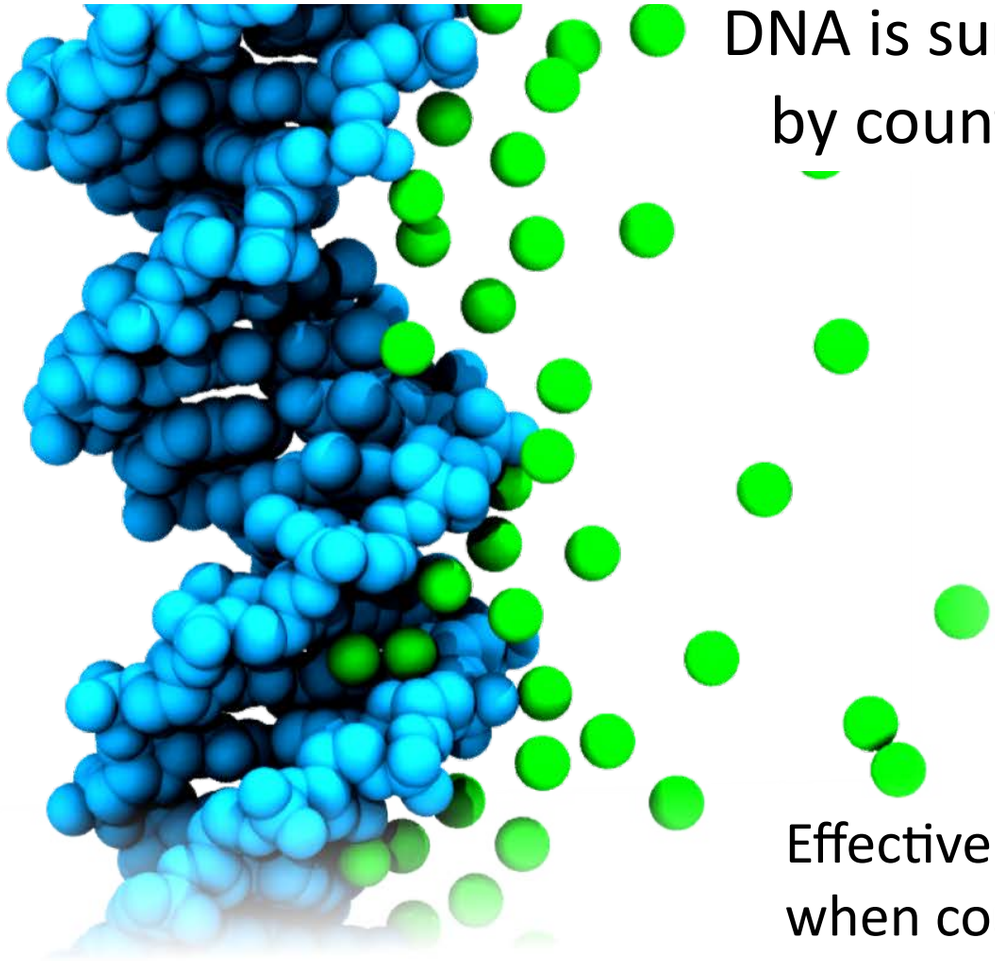
- What is the 3D structure of the genome?
- How genome ejection is triggered and sustained?
- Can it be used as a drug target?

Same sign charges ….

Same sign charges repel
(in vacuum)

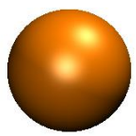


Same sign charges can
attract (in a medium)

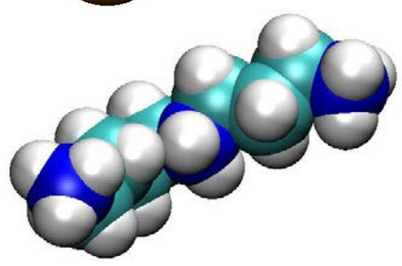


DNA is surrounded
by counter ions

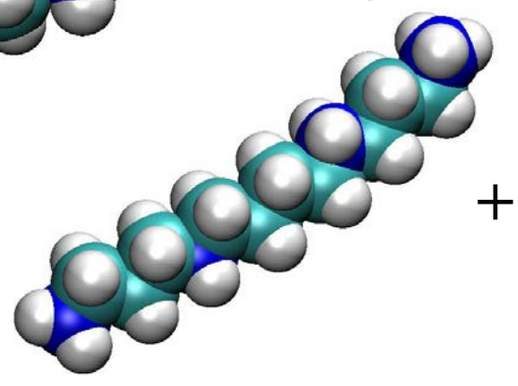
+1e, sodium or potassium



+2e, magnesium or calcium



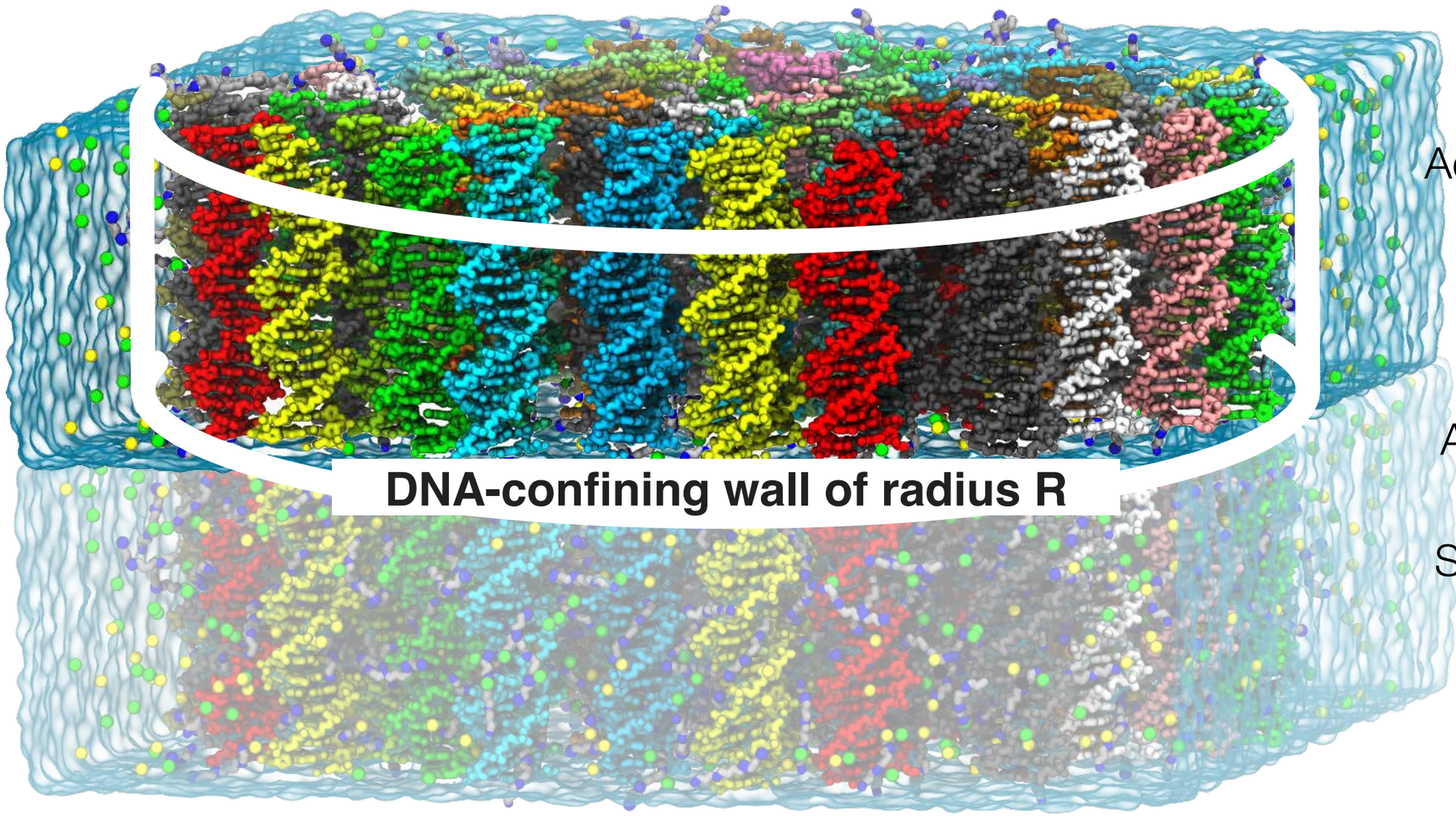
+3e,spermidine



+4e,spermine

Effective attraction between DNA is observed
when counterions have charge ≥ 2e

All-Atom Molecular Dynamics Simulation of DNA Condensates



Add **64 DNA** helices

Add **polyamine cations (+4)**

Add 150 mM **NaCl**

Add explicit **water**

Apply a half-**harmonic wall potential** only to DNA

Solve the equation of motion (F= ma) under **periodic boundary condition** in all directions

Classical **Force Field**

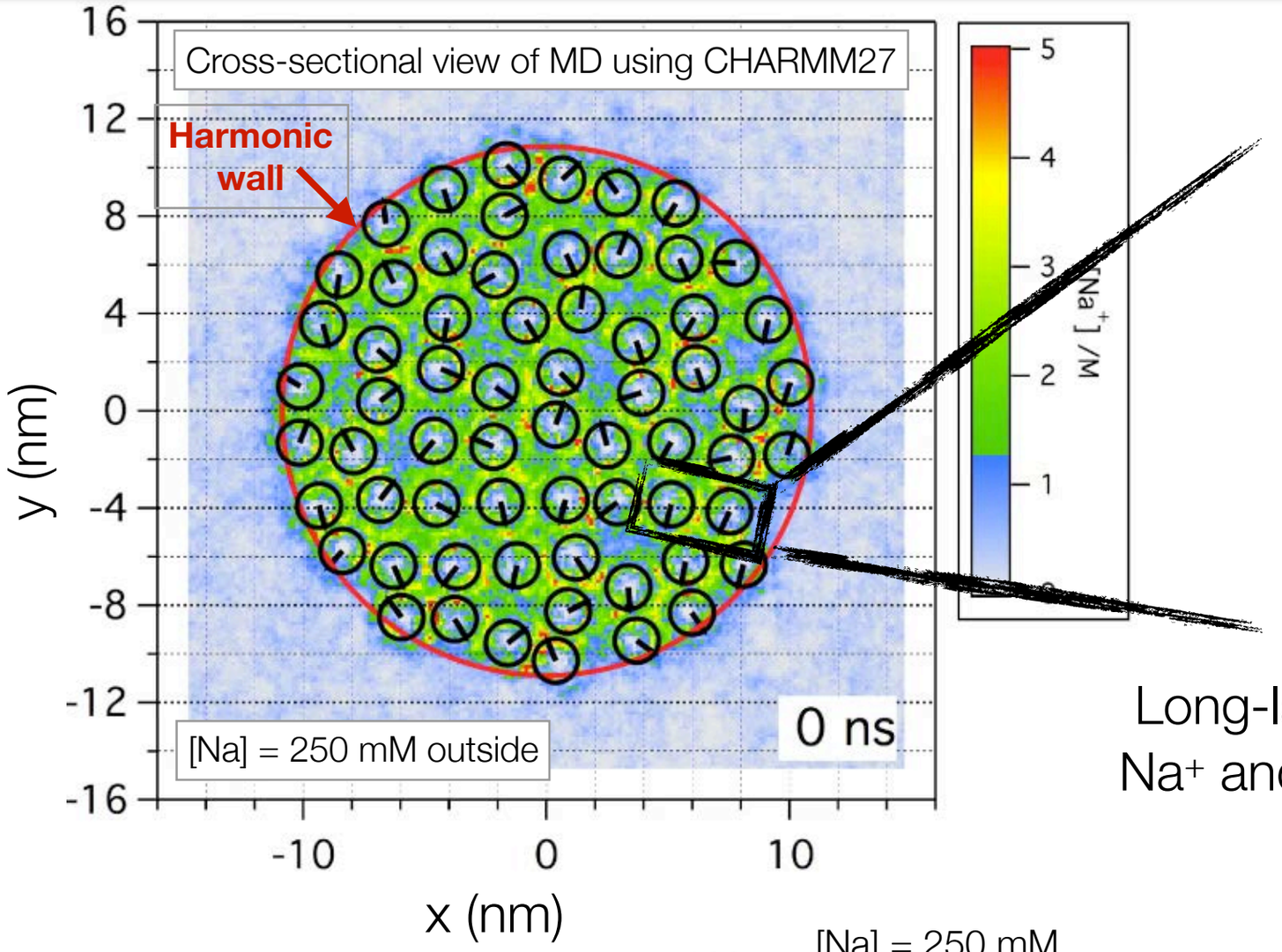
$$U(r) = \sum_{\text{bonds}} k_b(b - b_0)^2 + \sum_{\text{angles}} k_\theta(\theta - \theta_0)^2 + \sum_{\text{dihedrals}} k_\phi(1 + cos(n\phi - \phi_0)) + \sum_{\text{non-bonded pairs } i,j} \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} + \sum_{\text{non-bonded pairs } i,j} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right]$$

Partial charges from quantum mechanics

LJ parameters from experiments

Bonded parameters from quantum mechanics

Standard CHARMM & AMBER Force Fields Are Not Perfect for the Simulation of DNA Condensates

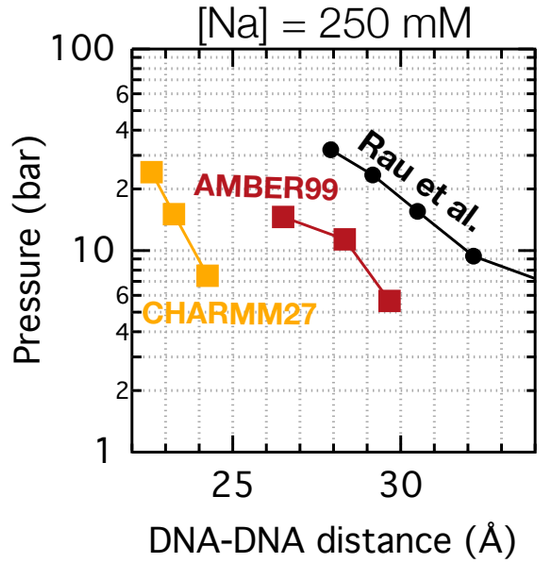


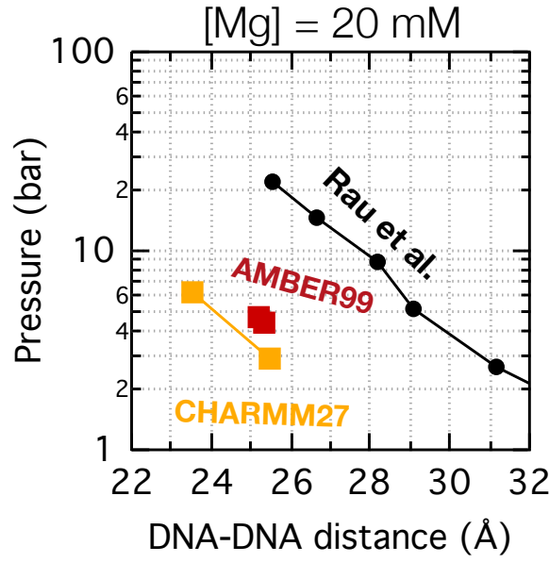
Na

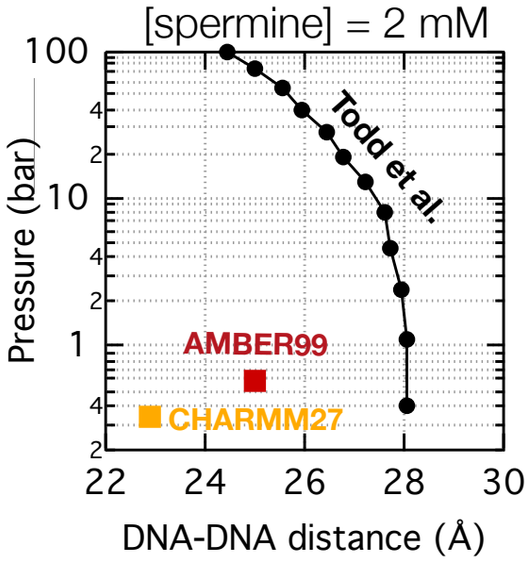
15-ns MD

Long-lasting **contact ion pairs** (CIP) between Na^+ and phosphate stabilize contact DNA pairs.

Due to excessive CIP formation, the simulations underestimate both inter-DNA distance and pressure in DNA array systems.



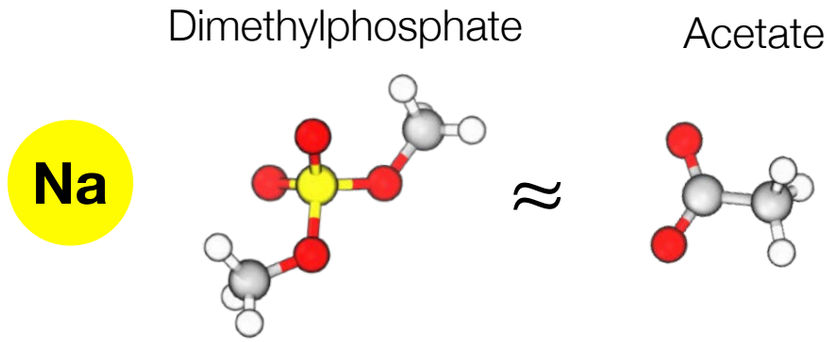


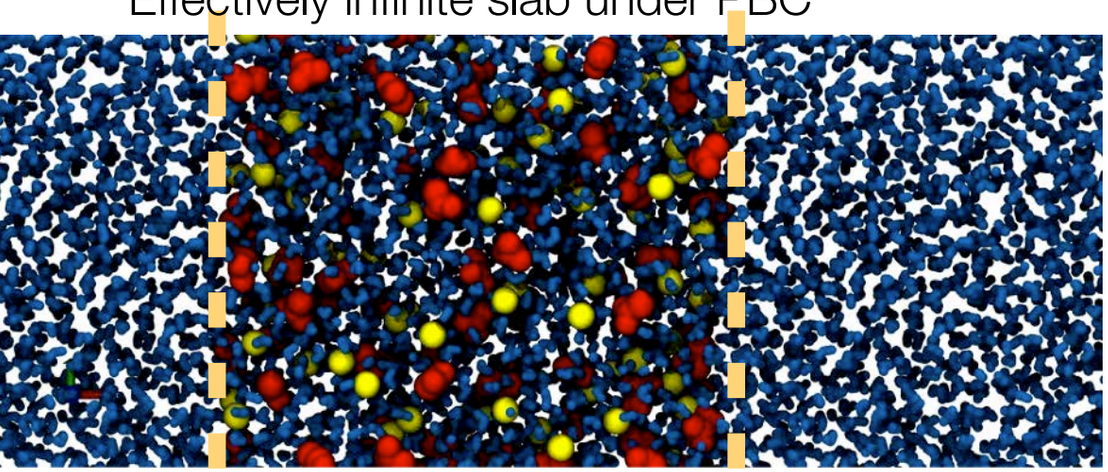


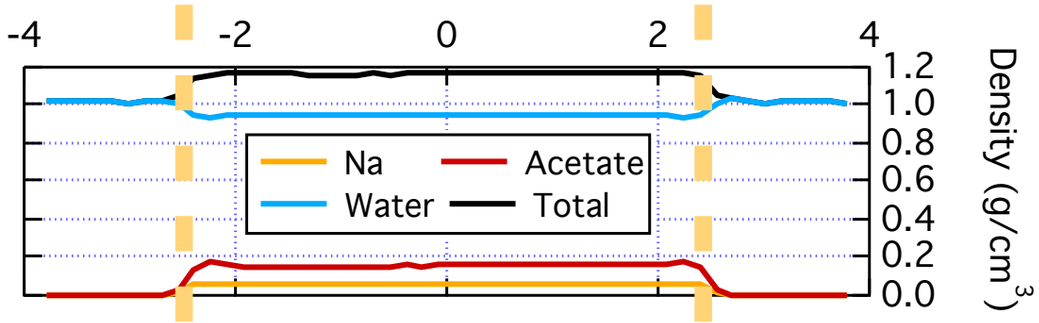
Rau et al, *PNAS* 1984 Todd et al, *BJ* 2008 Yoo & Aksimentiev, *JPCL* 2012

Champaign-Urbana Non-Bonded FIX (CUFIX): Improved Lennard-Jones Parameters for CHARMM & AMBER

"Much of what is known about association and dissociation of solutes and ions comes from measurements of **colligative properties**" — Molecular driving forces by Dill & Bromberg.

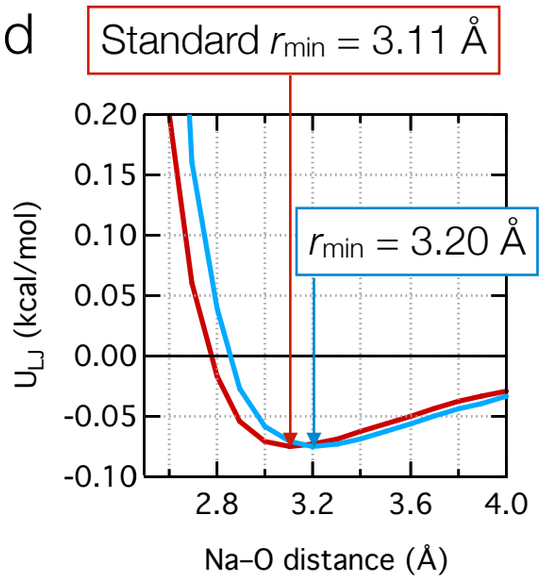


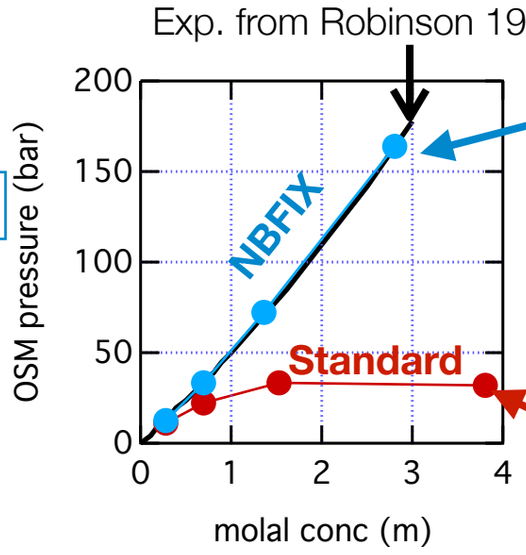


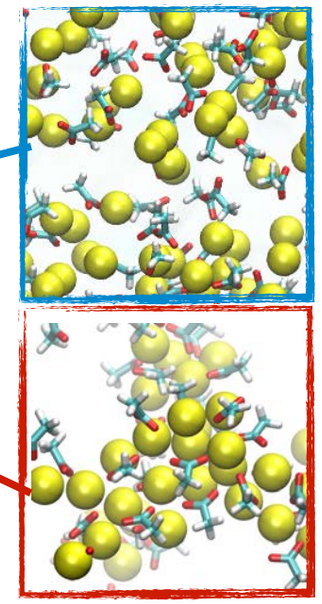


Yoo & Aksimentiev, *JPCL* 2012

Murad & Powles, *JCP* 1993
Luo & Roux, *JPCL* 2010

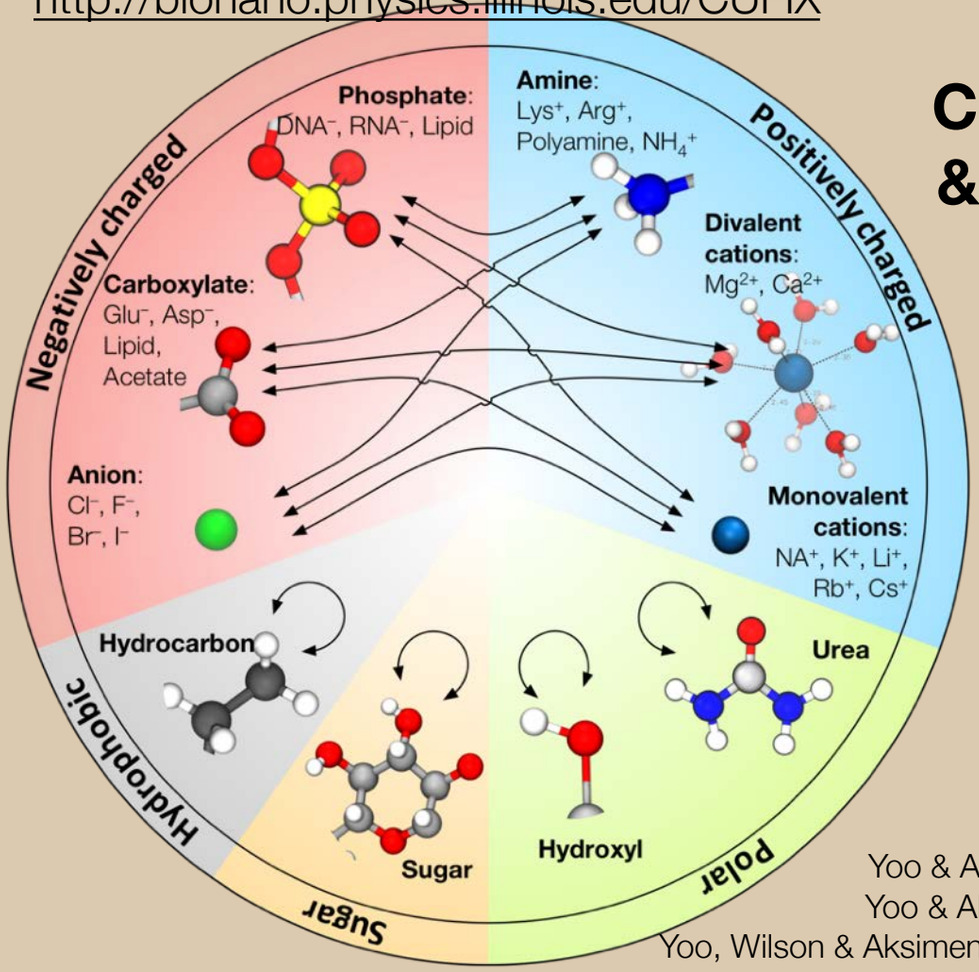






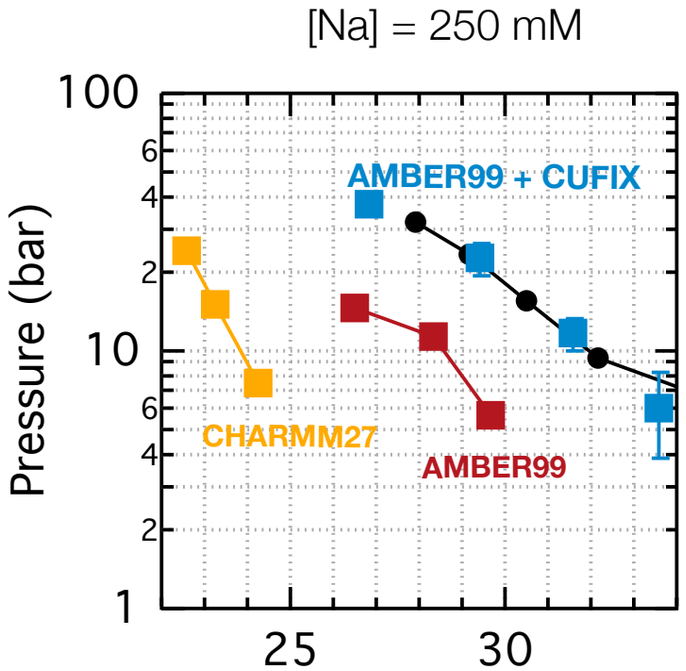
http://bionano.physics.illinois.edu/CUFIX

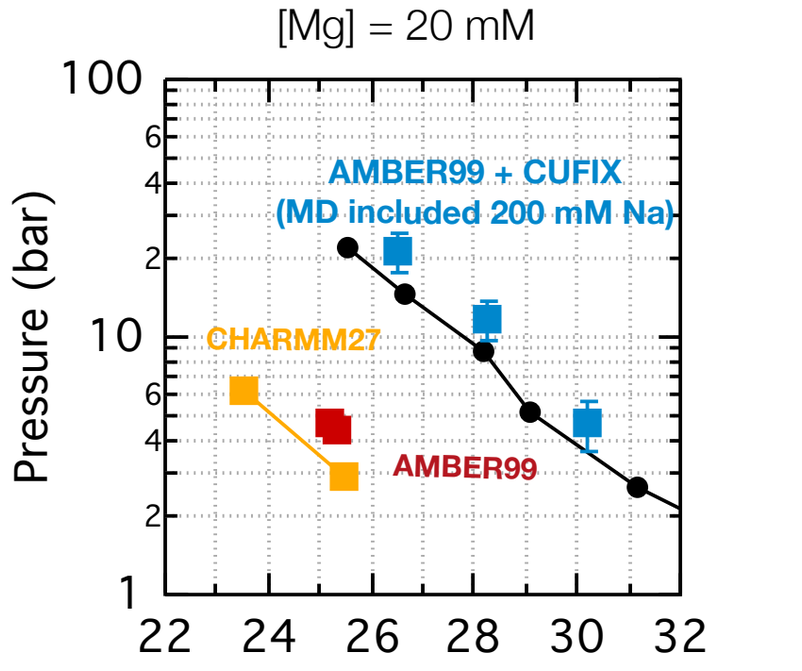
CUFIX for CHARMM36 & AMBER99

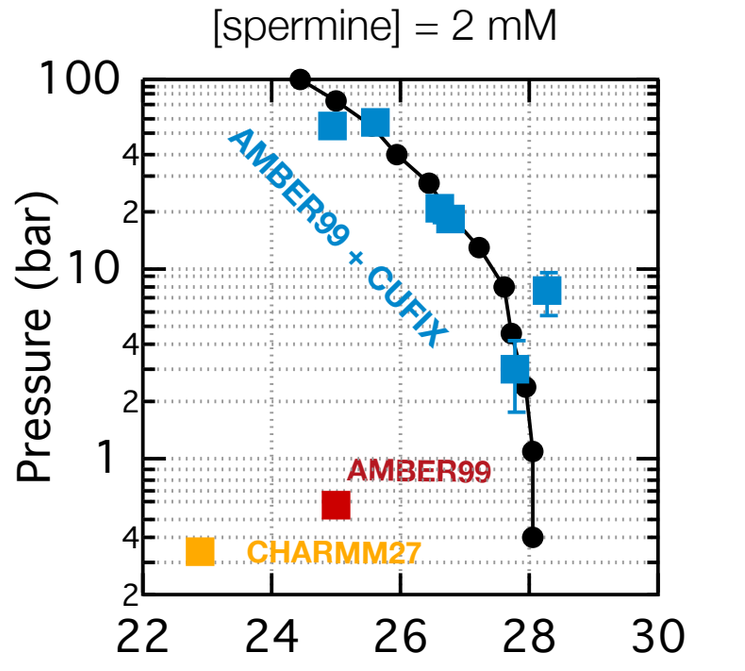


Yoo & Aksimentiev, *JPCL* 2012
Yoo & Aksimentiev, *JCTC* 2016
Yoo, Wilson & Aksimentiev, *Biopolymers* 2016

CUFIX Improves Simulations of DNA Condensates

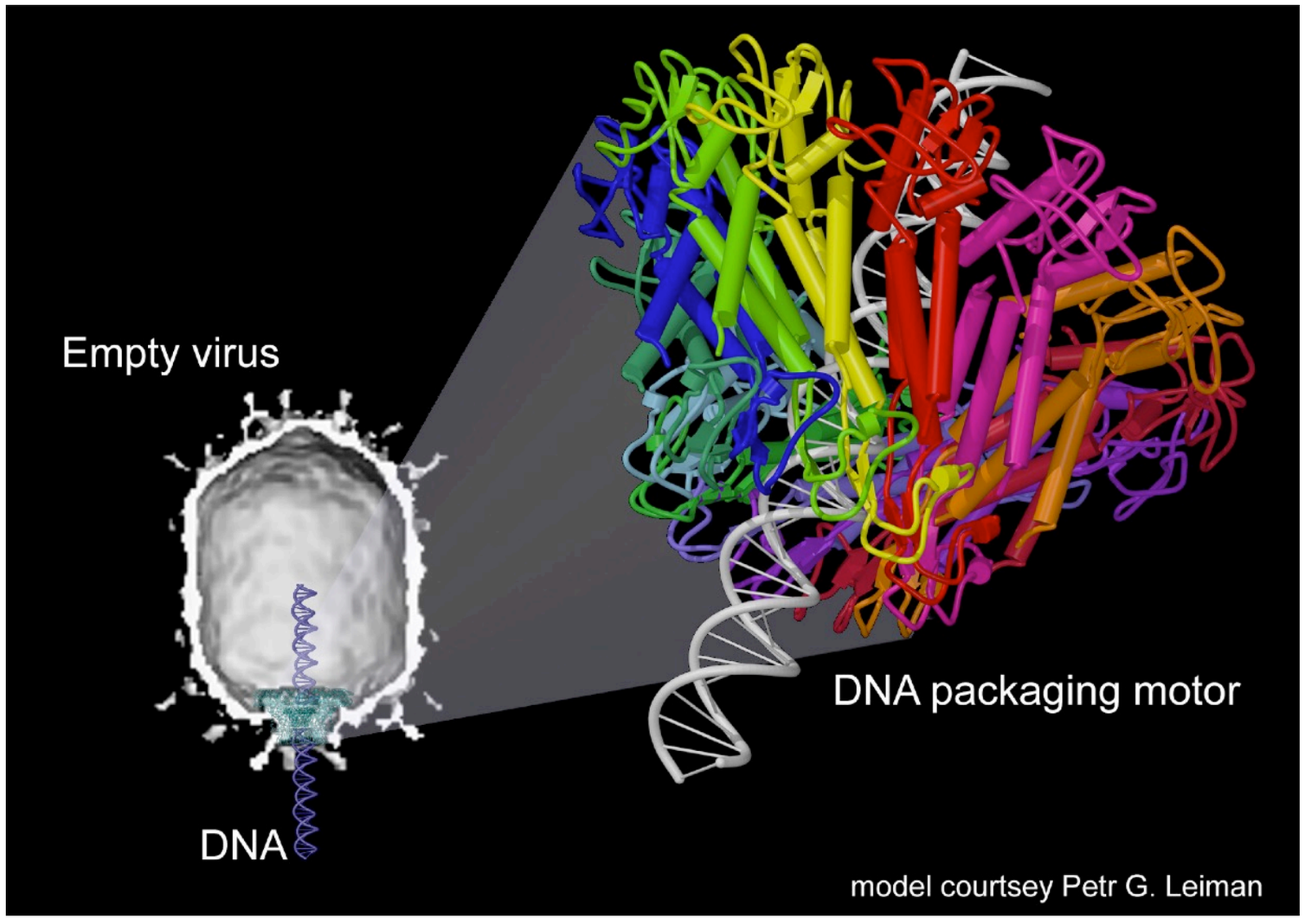


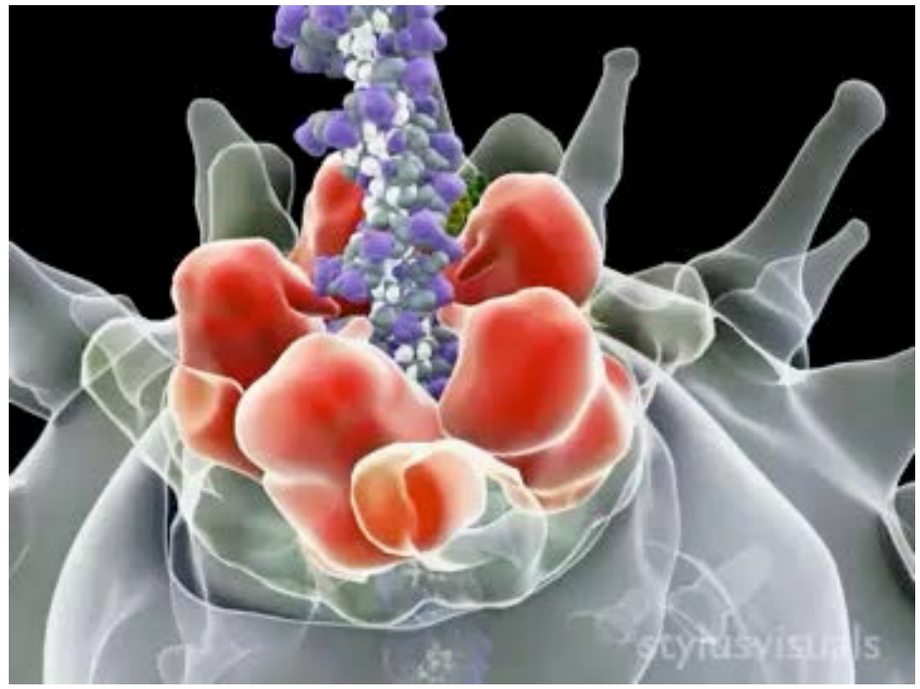




Yoo & Aksimentiev, *NAR* 2016

DNA is packaged by a motor





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

Max Force: 100pN

Movie: Carlos Bustamante Lab

Can one simulate the process?

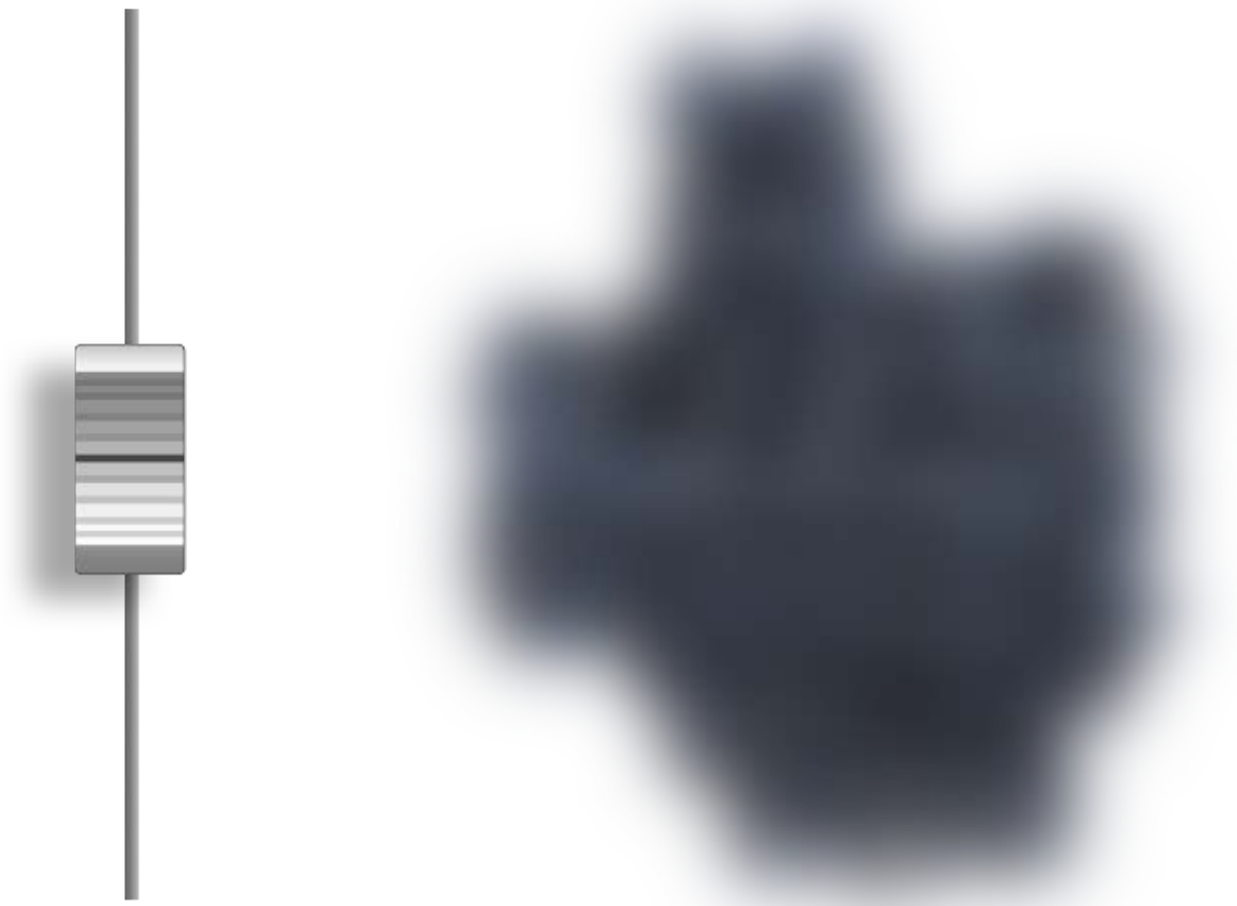
Packaging process is slow (~min), all-atom simulation at physiological forces is not possible

At higher forces, DNA will deform

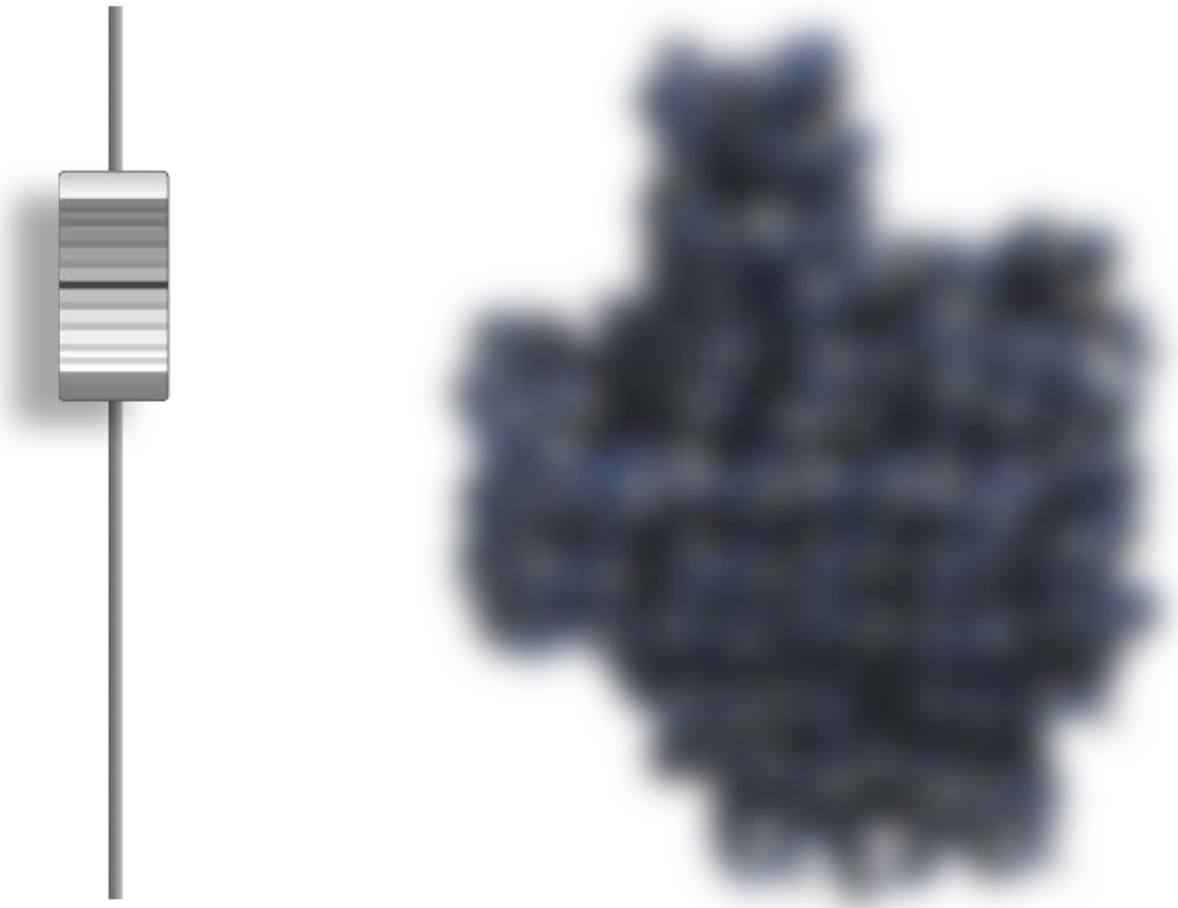
Strategy: change resolution for speed and detail

Strategy: change resolution for speed and detail

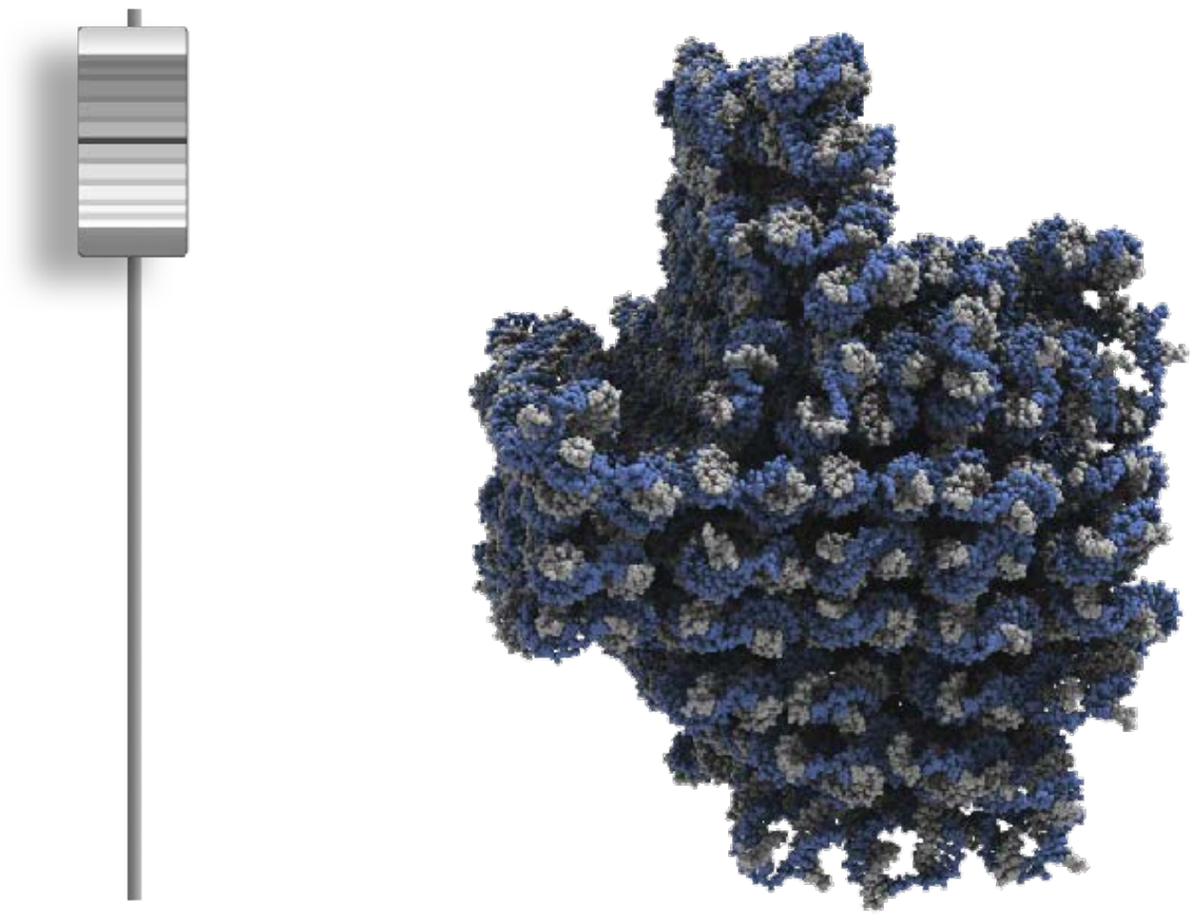
Strategy: change resolution for speed and detail



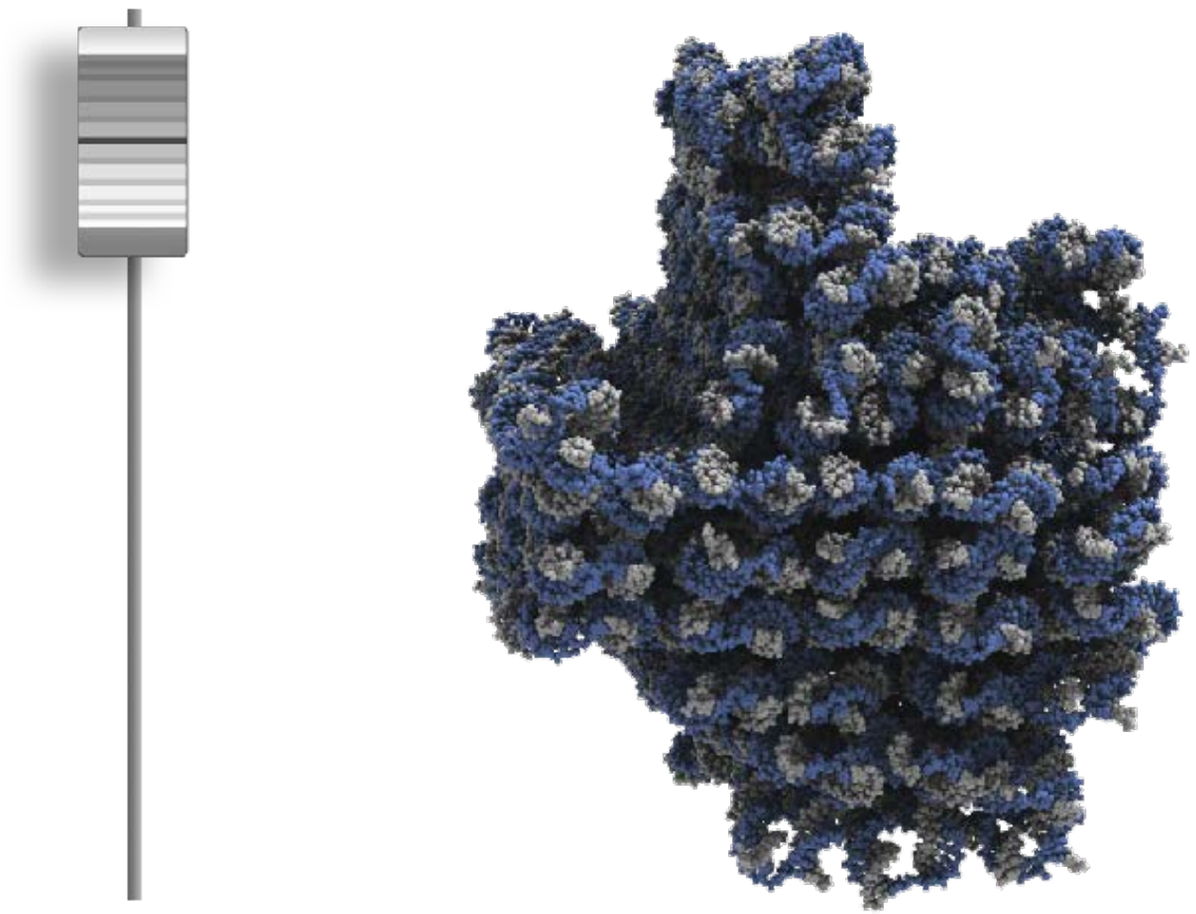
Strategy: change resolution for speed and detail



Strategy: change resolution for speed and detail

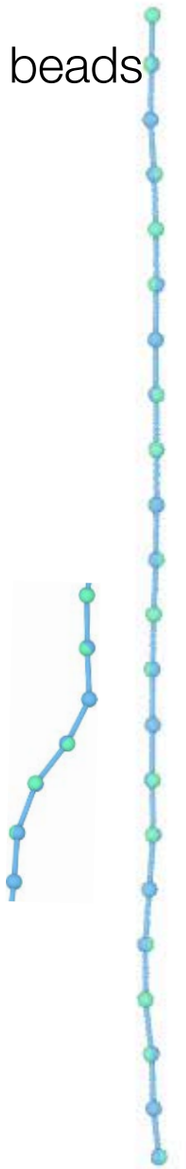


Strategy: change resolution for speed and detail



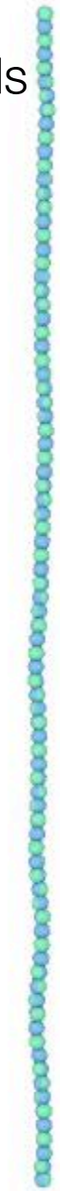
500 bp dsDNA fragment modeled at different resolutions

24 bp/2 beads



12 bp/2 beads

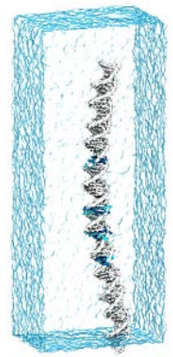
6 bp/2 beads



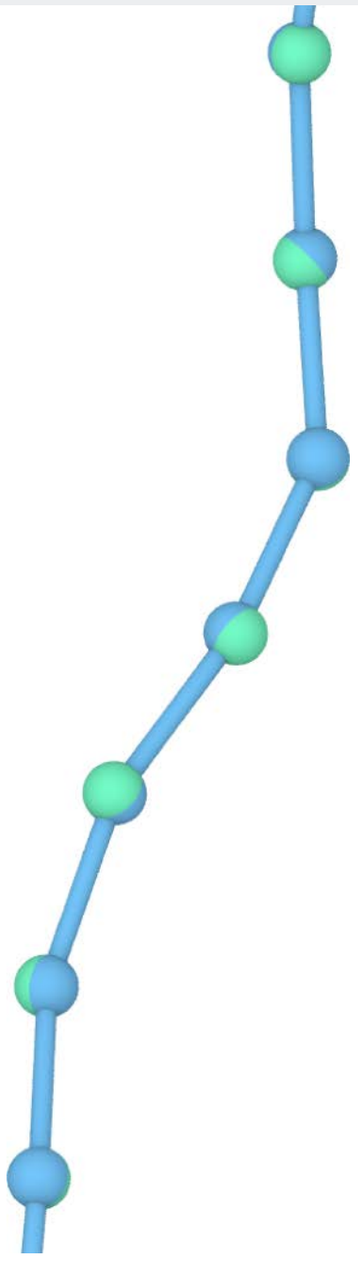
3 bp/2 beads

1 bp/2 beads

All-atom, ~100 bp



Interactions in a simple coarse-grained DNA model



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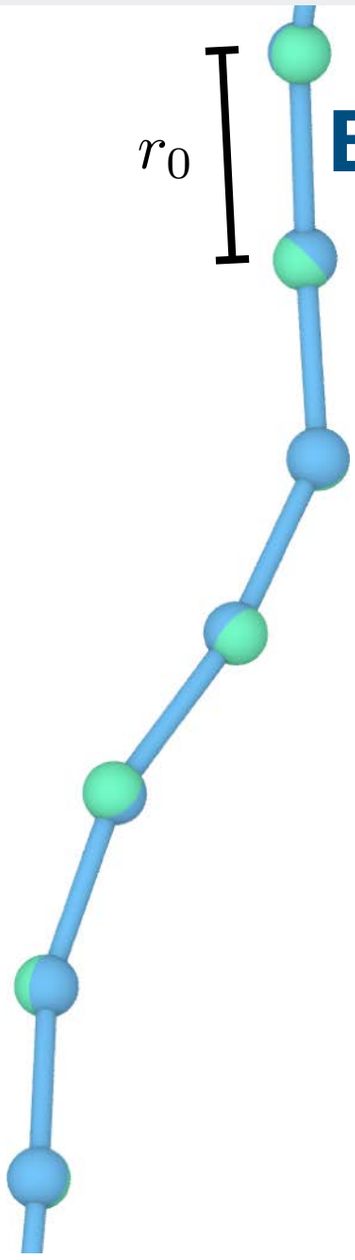
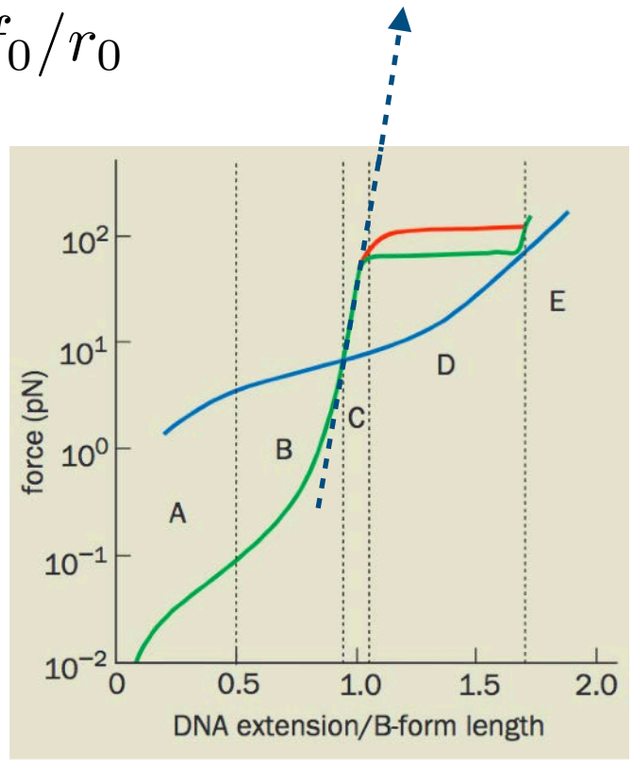


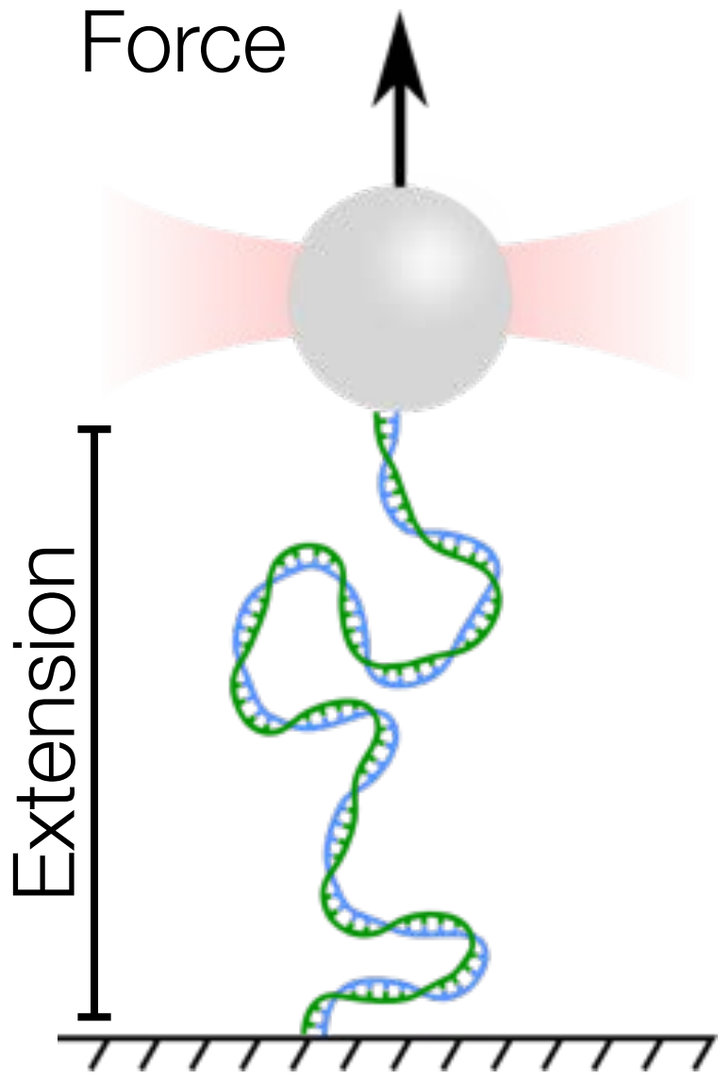
Bond potential

$$r_0 = n_{\mathrm{bp}} \times 3.4\ \text{Å}$$

$$f_0 = 1000\mathrm{pN} \leftarrow \textbf{Elastic constant}$$

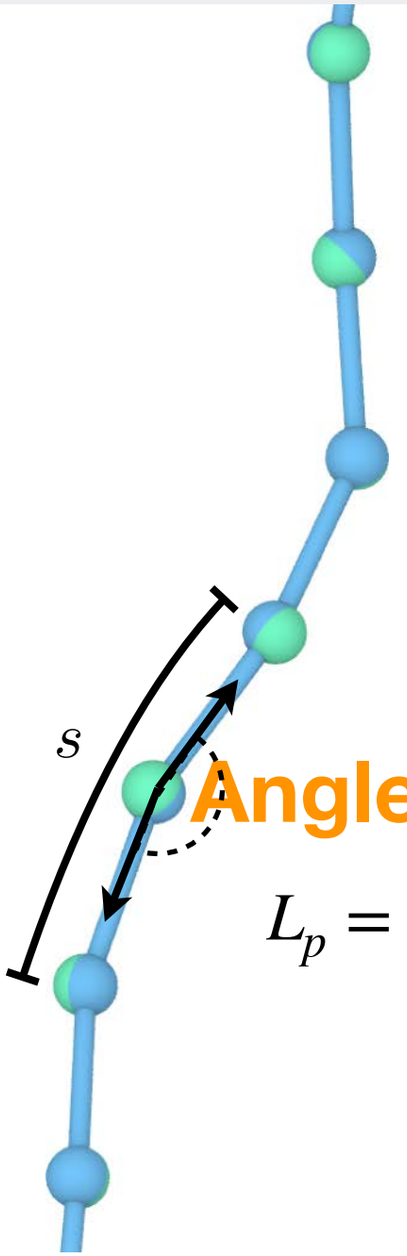
$$k_{\mathrm{spring}} = f_0 / r_0$$





http://www.phys.ens.fr/~cocco/Art/24physworld.pdf

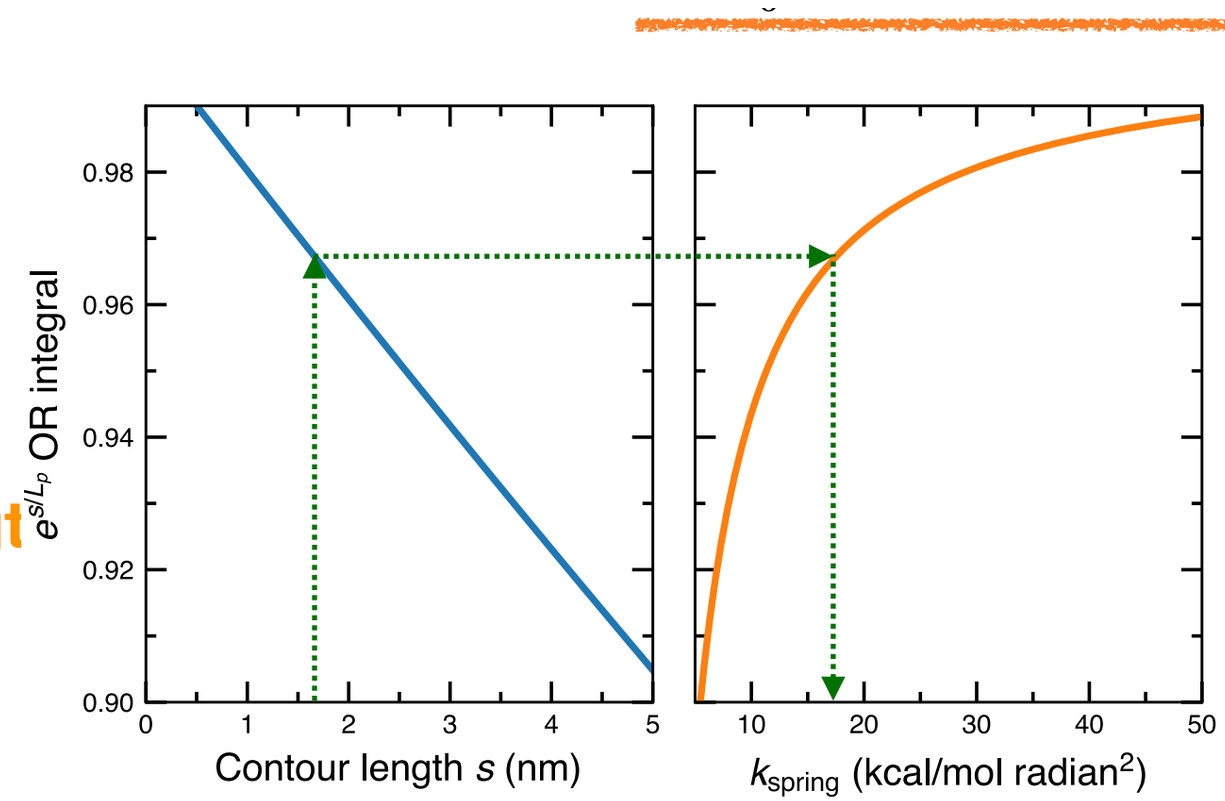
Interactions in a simple coarse-grained DNA model



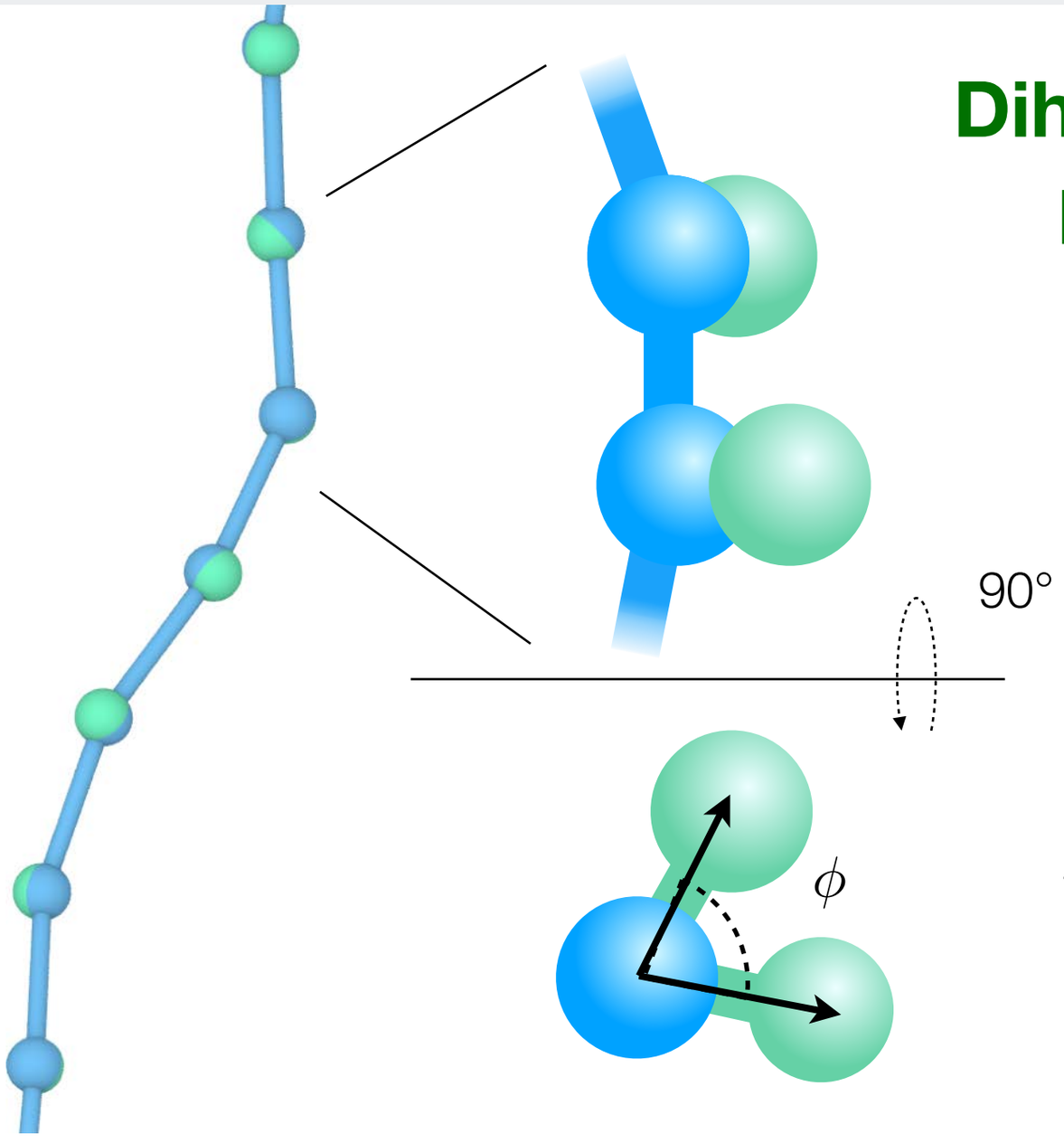
$$e^{-s/L_p} = \langle \cos\theta \rangle$$

Angle potential

$L_p = 50$ nm ← **Persistence length**



Interactions in a simple coarse-grained DNA model



Dihedral angle potential

Twist persistence length

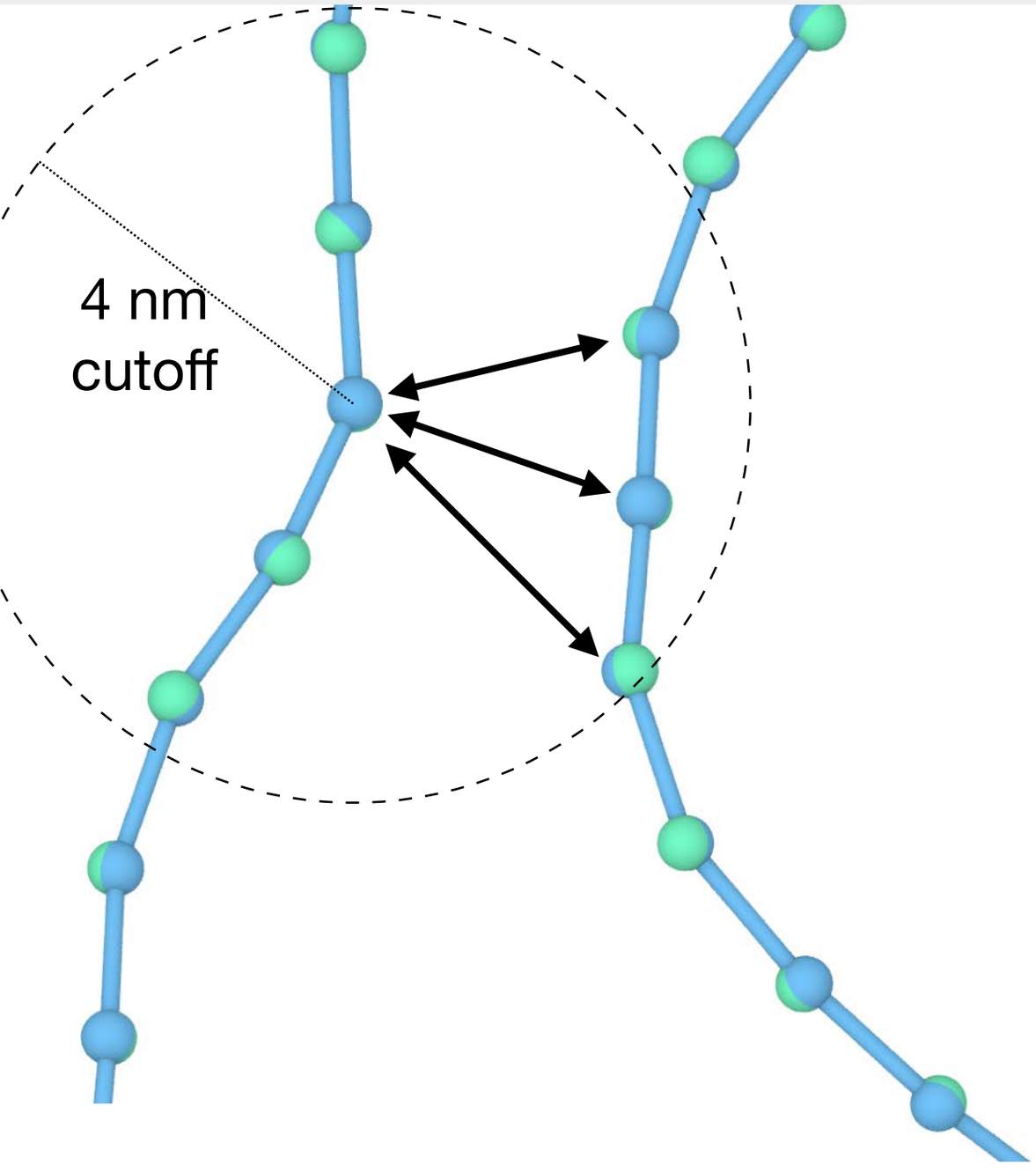
$$L_{tw} = 90 \text{ nm}$$

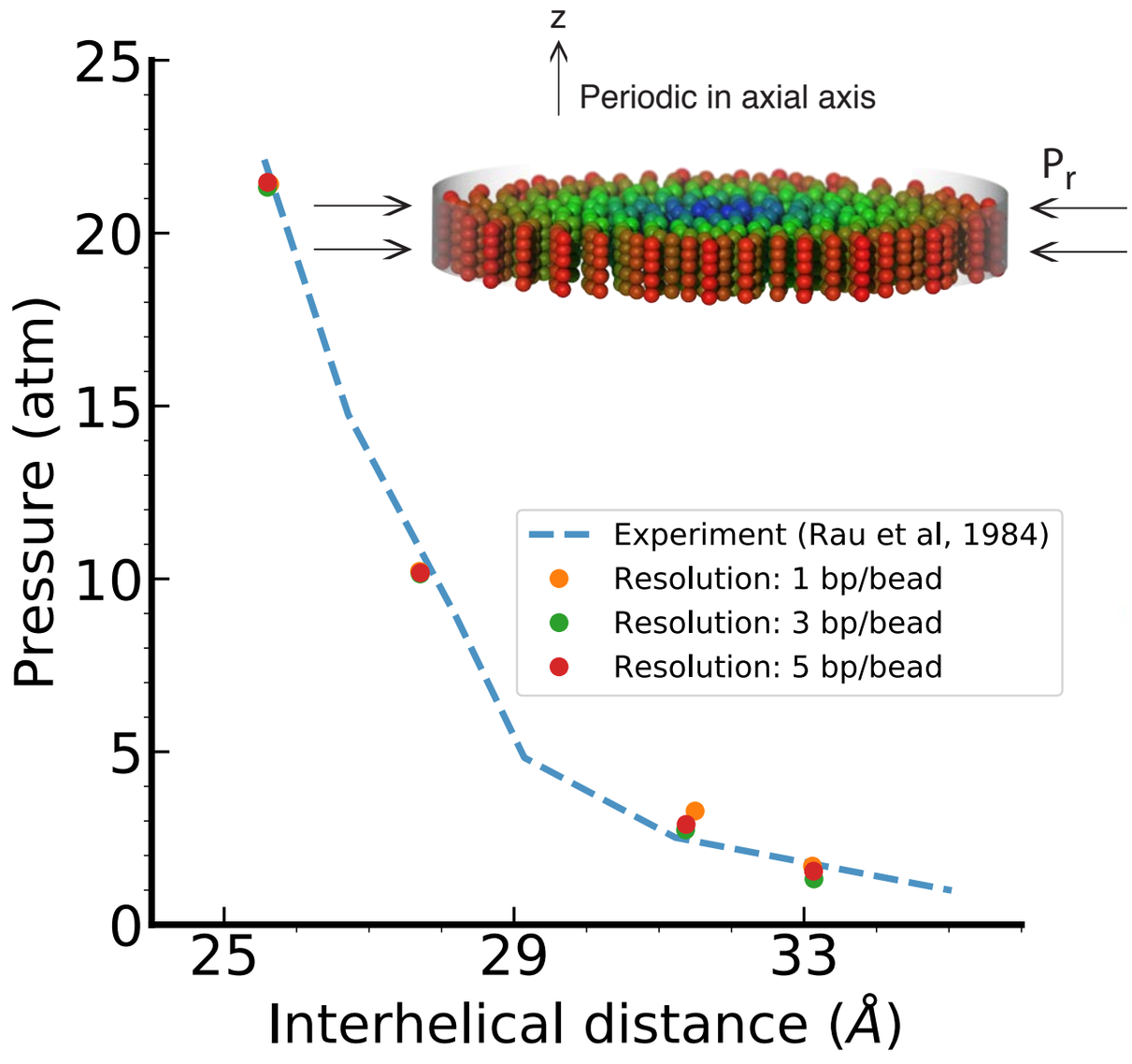
$$\langle \cos\phi \rangle = e^{-s/L_{tw}}$$

$$\int_0^\pi d\phi \ \cos\phi \ e^{-\frac{k_{\text{dihed}}(\phi-\phi_0)^2}{2k_BT}} = e^{-s/L_{tw}}$$

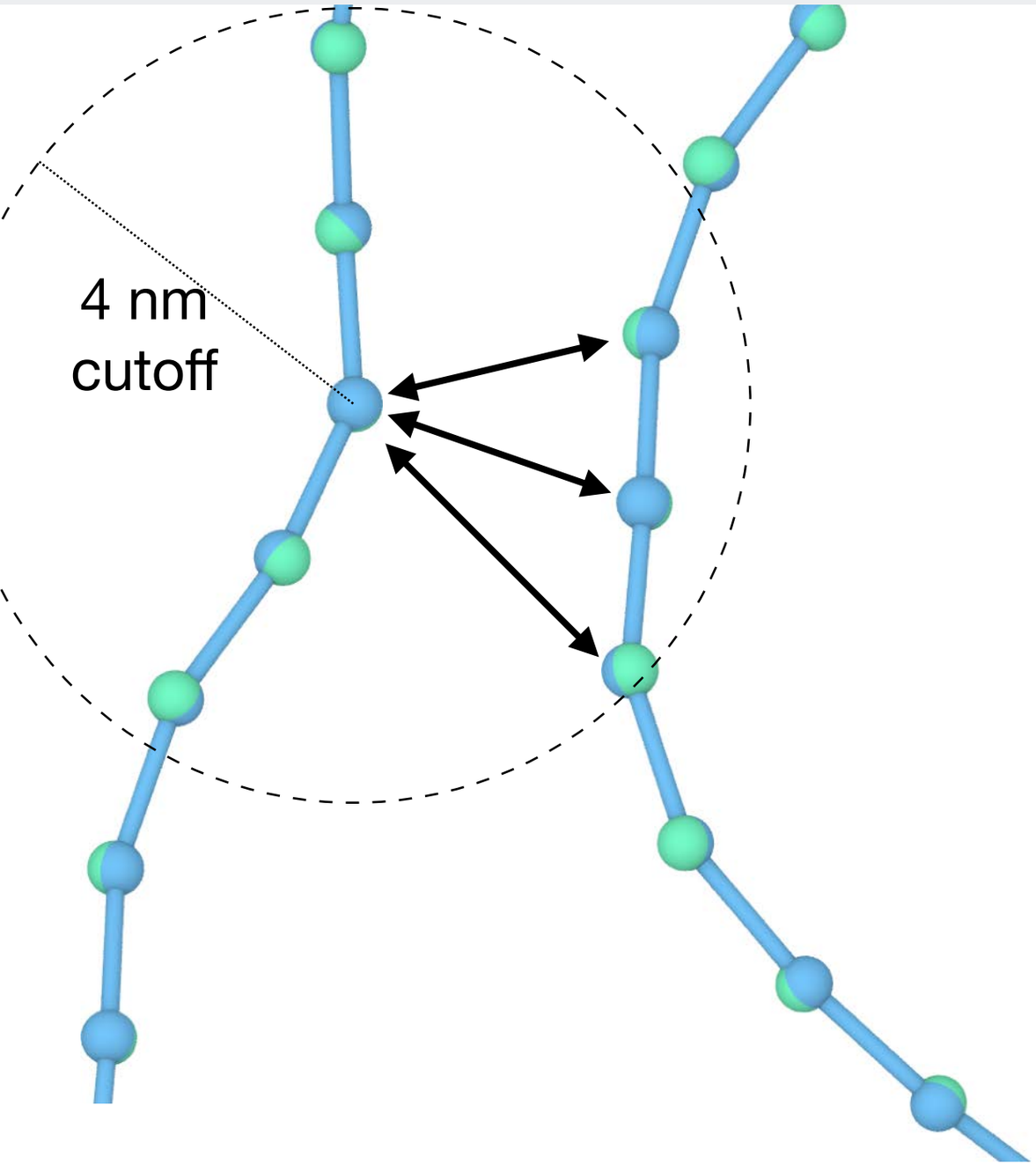
$$\phi_0 = s \times \ 10.14°/\text{Å}$$

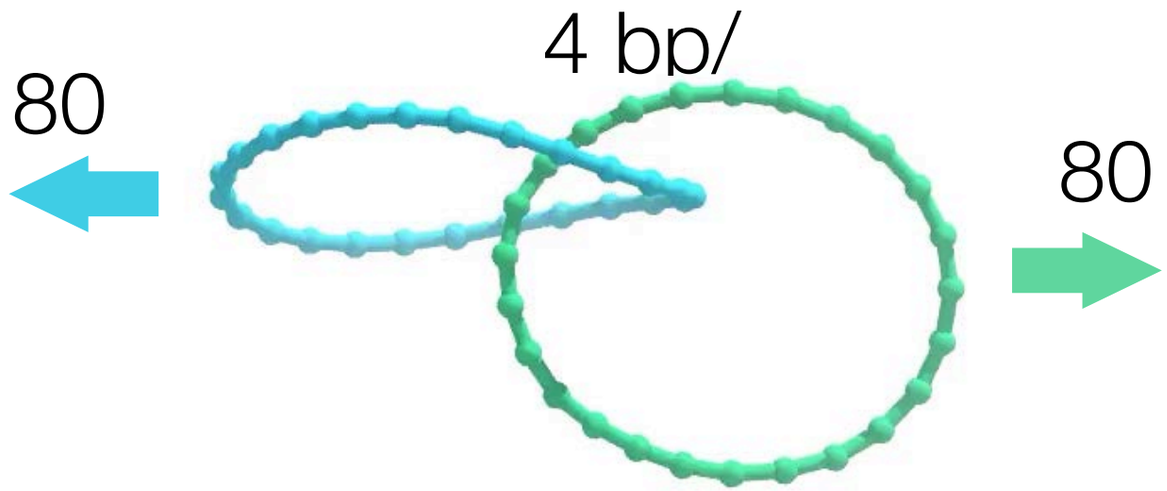
Interactions in a simple coarse-grained DNA model

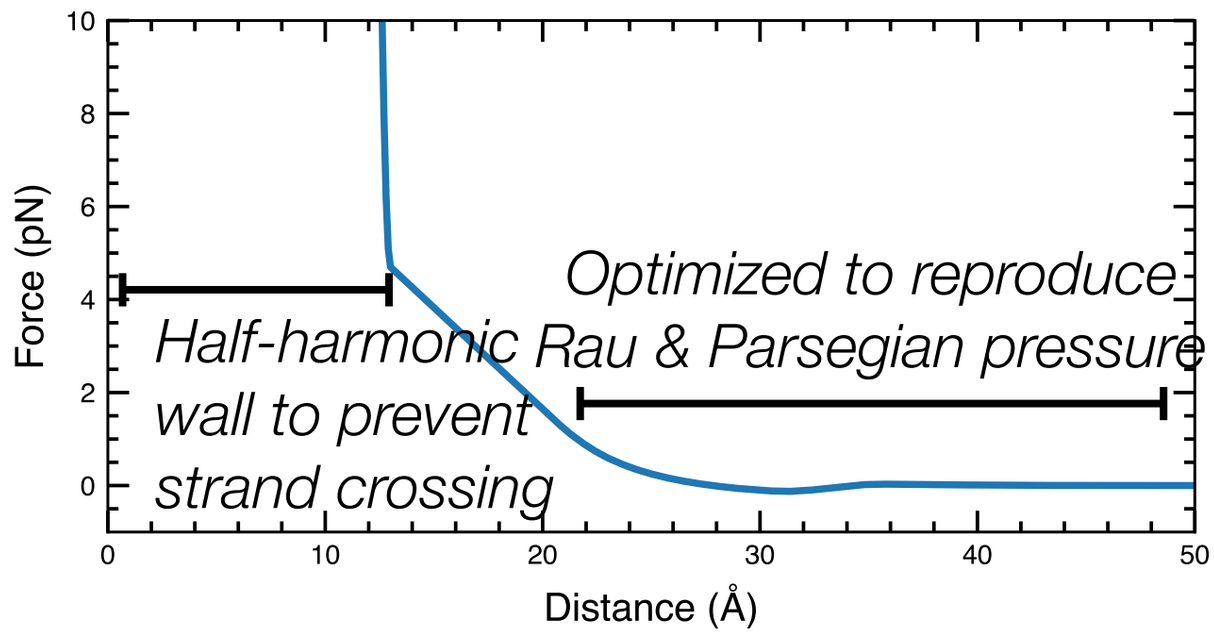




Interactions in a simple coarse-grained DNA model

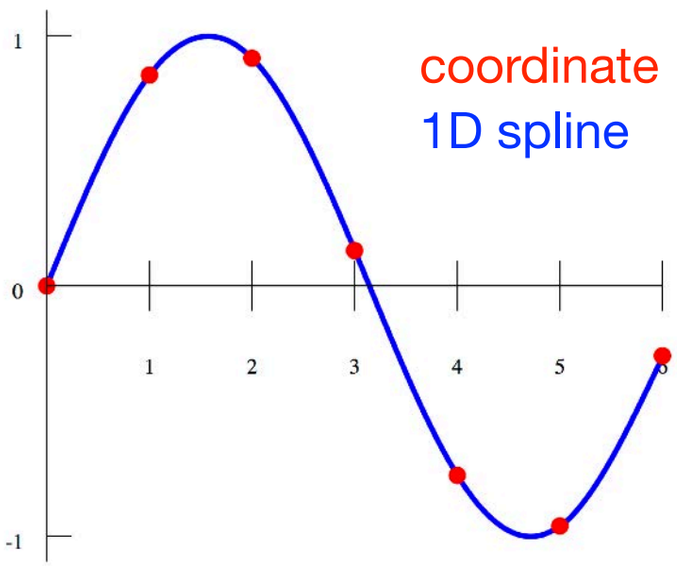




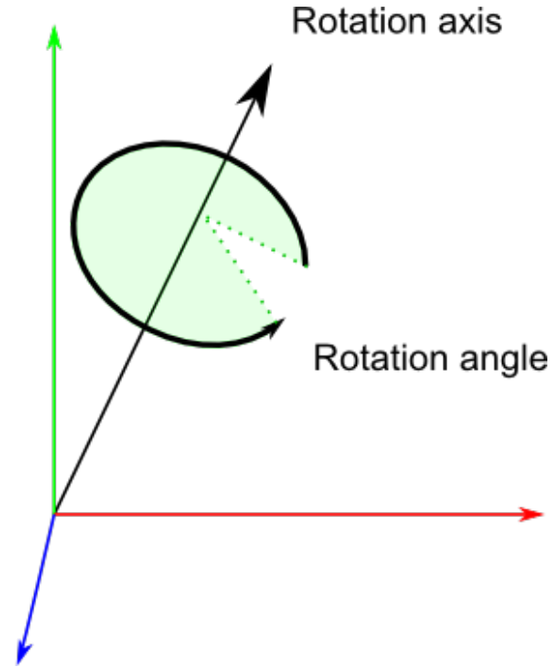


Mapping between coarse-grained resolutions

For each helix,
fit a 3D spline through bead coordinates
at end of simulation



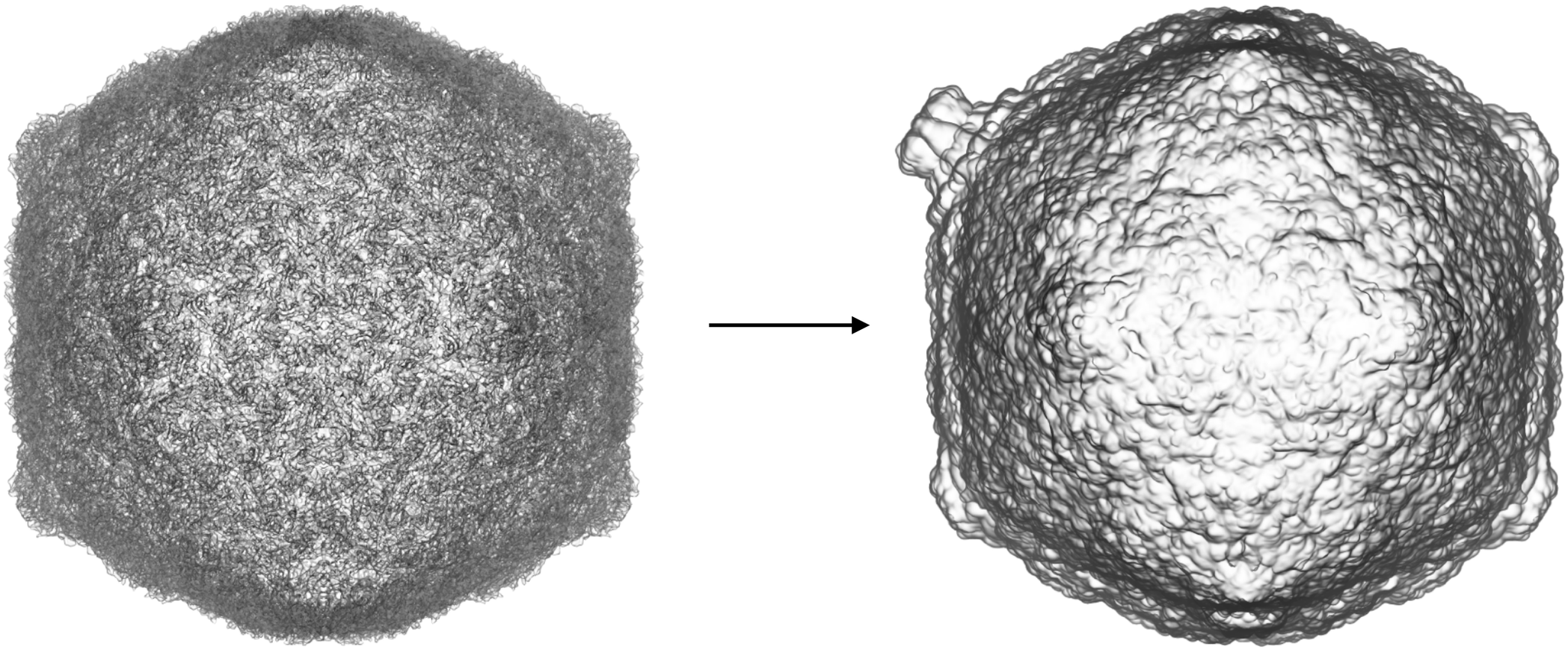
Fit a spline between
quaternion representation of
rotations



Packaging viruses with ARBD

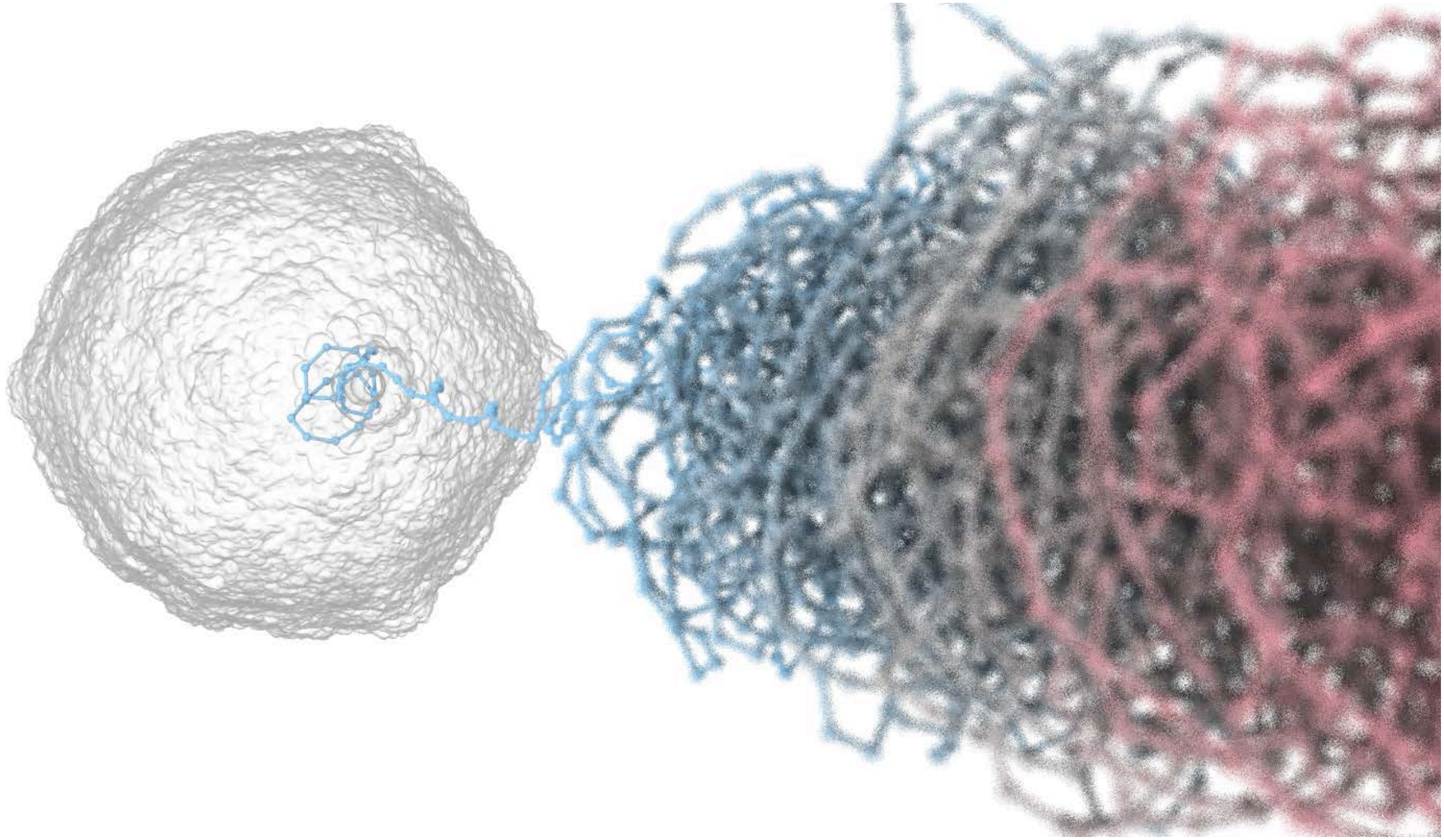
ARBD: Atomic Resolution Brownian Dynamics (multi-resolution)

Package DNA (CG) with ARBD, into CryoEM reconstruction of a HK97 bacteriophage capsid. A cryoEM map of the portal is fitted into the original capsid reconstruction, and DNA is packaged through the portal.

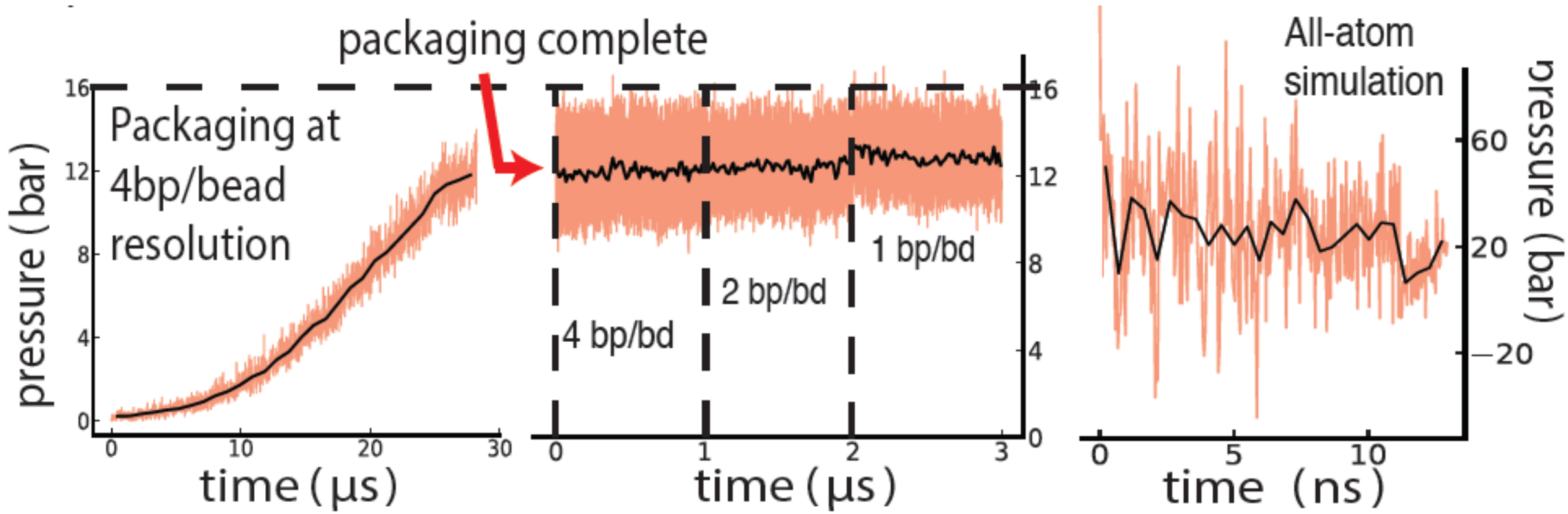


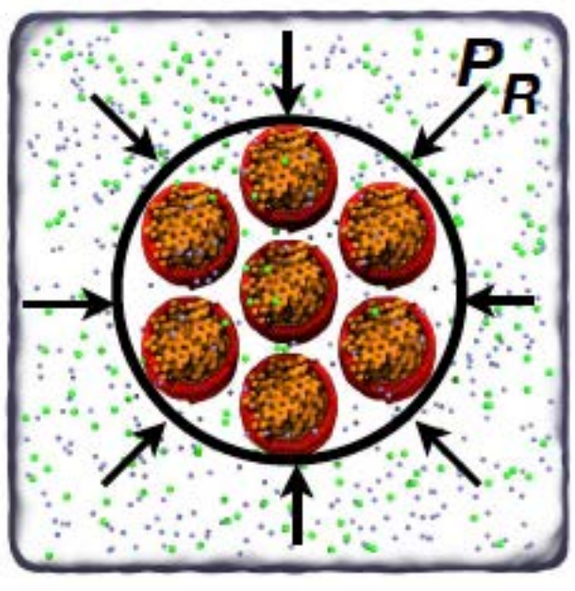
Smooth, purely repulsive grid-based potential obtained by blurring cryoEM density and adding the portal

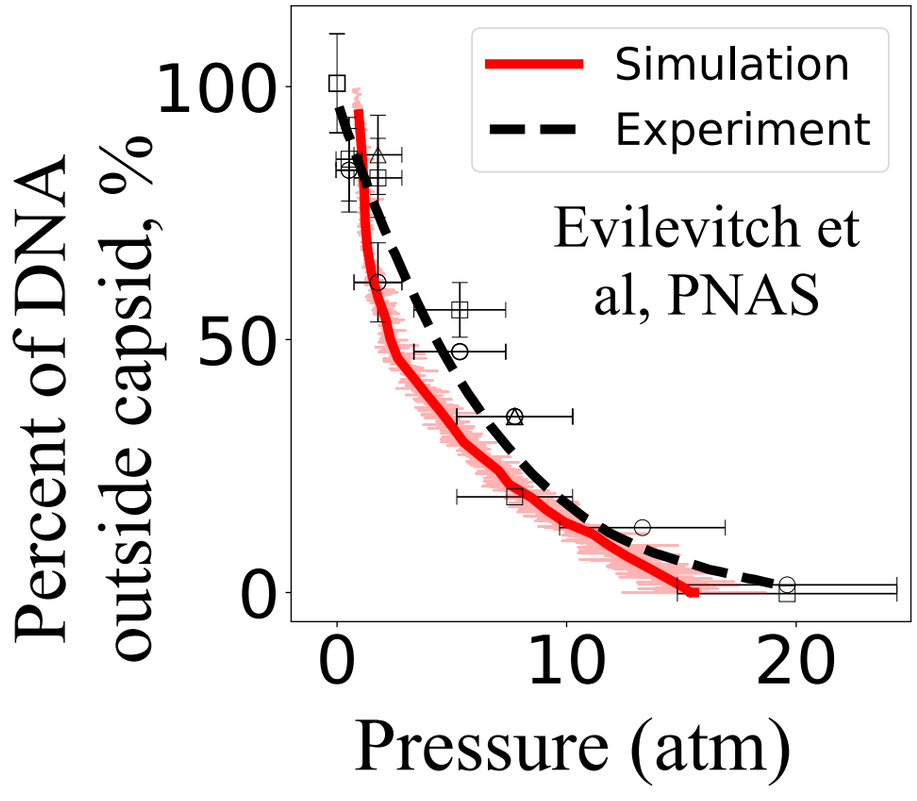
Multi-resolution packaging dsDNA viruses



Internal pressure during packaging

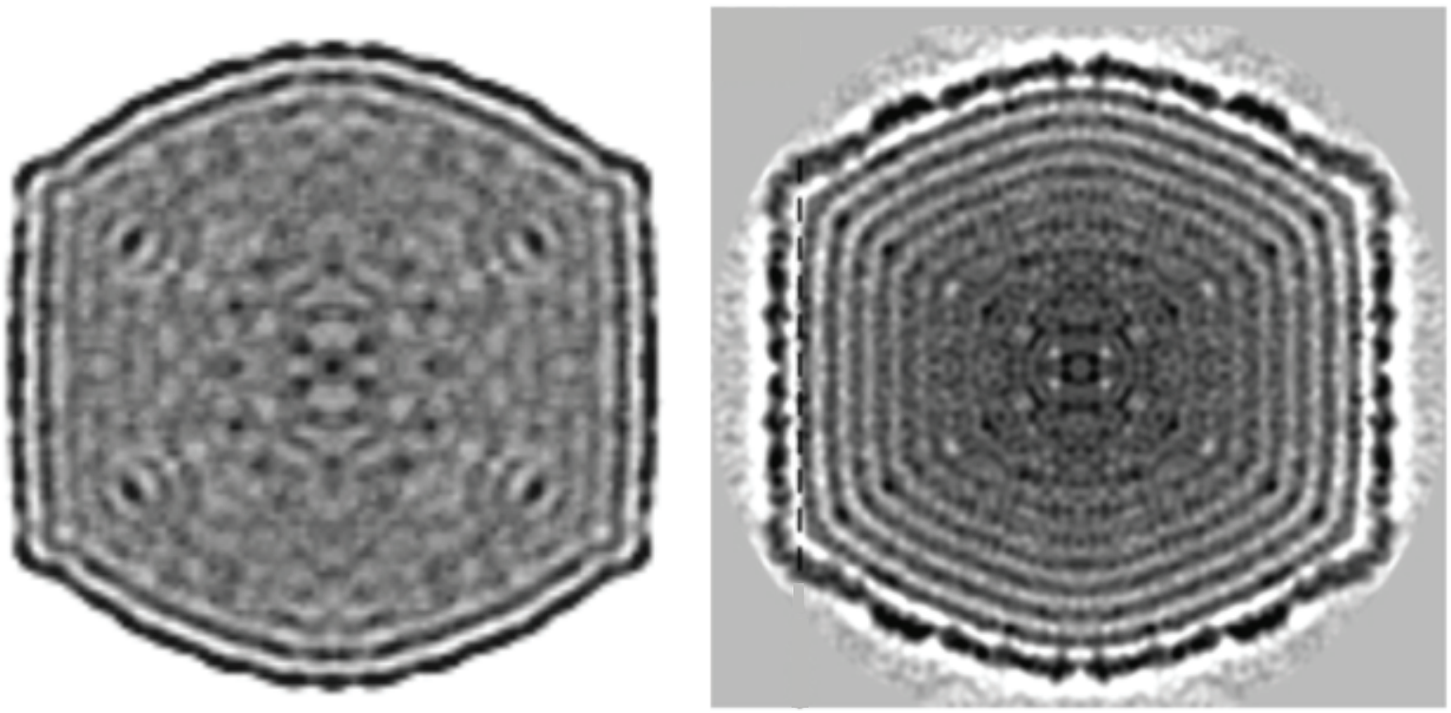






Comparison to structural data

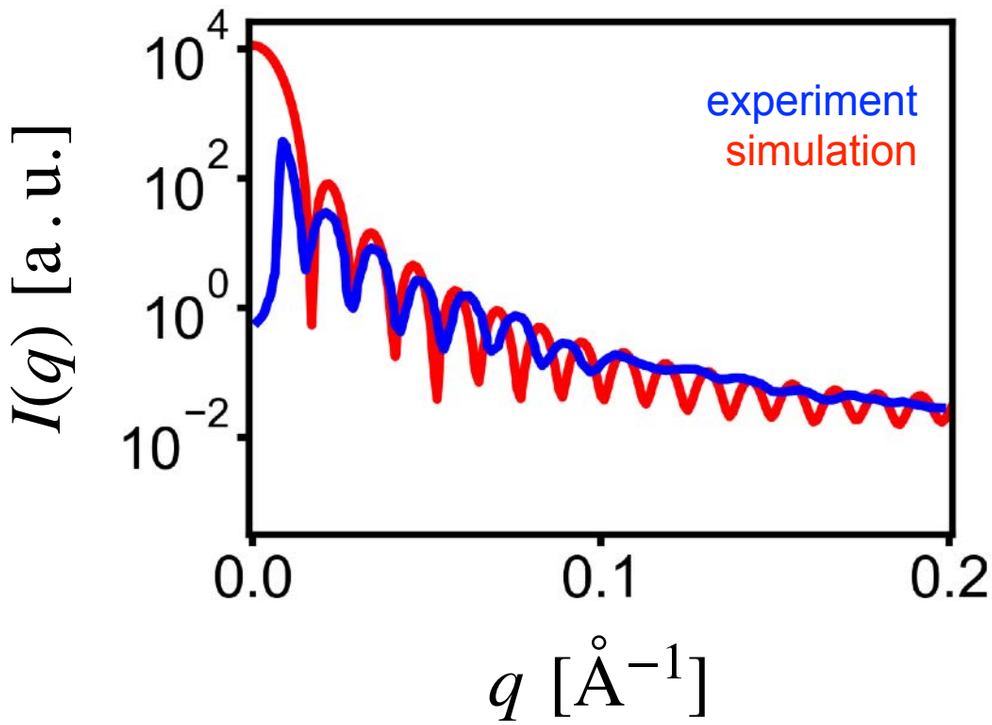
Cryo-electron microscopy



Simulation Experiment

J. Mol. Biol. (2009) 391, 471-483, Hendrix et al

Small Angle X-ray Scattering



Experiment:

Journal of molecular biology, 408: 541 (2011)

Simulation SAXS data were generated from CRYSOL, using an atomistic PDB of the protein coat and packaged DNA

Conclusions and outlook

Obtained first atomic-resolution structure of packaged viral particle

Developed accurate multi-resolution representation of DNA—DNA and DNA—protein interactions

To do: Extend the model to ssRNA and ssDNA viruses

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- Computations

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