Resolving the Structure of Viral Genomes with Atomic Resolution

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I use Blue Waters to...

... understand molecular underpinnings of life
... build biologically inspired systems
DNA, the blueprint
Viral genome, the program of infection

DNA is a highly charged polymer!

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?

Herpes virus (HSV)

http://darwin.bio.uci.edu/~faculty/wagner/hsv2f.html
Same sign charges repel (in vacuum)

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

Classical Force Field

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

Bonded parameters from quantum mechanics

Partial charges from quantum mechanics

LJ parameters from experiments

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

DNA-confining wall of radius \(R\)
Standard CHARMM & AMBER Force Fields Are Not Perfect for the Simulation of DNA Condensates

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.

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.

<table>
<thead>
<tr>
<th>Compound</th>
<th>OSM Pressure (bar)</th>
<th>Molal Conc (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Acetate</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Water</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Sodium Dimethylphosphate Acetate</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Effectively infinite slab under PBC

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

CUFIX for CHARMM36 & AMBER99

Yoo & Aksimentiev, JPC 2012
Luo & Roux, JPC 1993

Yoo & Aksimentiev, JPC 2012
Yoo & Aksimentiev, JCTC 2016
Yoo, Wilson & Aksimentiev, Biopolymers 2016
CUFIX Improves Simulations of DNA Condensates

[Graphs showing pressure vs. DNA-DNA distance for different ion concentrations: Na, Mg, spermine. Each graph compares AMBER99, AMBER99 + CUFIX, and CHARMM. The graphs illustrate the improvement in simulations using CUFIX, especially with the inclusion of MD (molecular dynamics) with 200 mM Na.]

Yoo & Aksimentiev, NAR 2016
DNA is packaged by a motor

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

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

Max Force: 100pN

Movie: Carlos Bustamante Lab
Strategy: change resolution for speed and detail
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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
Interactions in a simple coarse-grained DNA model

Bond potential

\[ r_0 = n_{bp} \times 3.4 \, \text{Å} \]
\[ f_0 = 1000 \text{pN} \]
\[ k_{spring} = \frac{f_0}{r_0} \]

Elastic constant

http://www.phys.ens.fr/~cocco/Art/24physworld.pdf
$e^{s/L_p} = \langle \cos \theta \rangle$

$P = 50 \text{ nm}$

$\int \cos \theta \delta (\theta - \theta') d\theta = \int_0^{\pi} \sin \theta d\theta \cos \theta e^{-\beta 1/2 k_{\text{spring}} \theta^2}$
Interactions in a simple coarse-grained DNA model

Dihedral angle potential

Twist persistence length

\[ L_{tw} = 90 \text{ nm} \]

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

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

\[ \phi_0 = s \times 10.14^\circ/\text{Å} \]
Interactions in a simple coarse-grained DNA model

4 nm cutoff

Pressure (atm)

Interhelical distance (Å)

Periodic in axial axis

Experiment (Rau et al, 1984)
- Resolution: 1 bp/bead
- Resolution: 3 bp/bead
- Resolution: 5 bp/bead
Interactions in a simple coarse-grained DNA model

- 4 nm cutoff
- Optimized to reproduce Rau & Parsegian pressure
- Half-harmonic wall to prevent strand crossing

Force (pN) vs. Distance (Å) graph

- Optimized to reproduce Half-harmonic Rau & Parsegian pressure
- Wall to prevent strand crossing
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

Packaging at 4bp/bead resolution

Percent of DNA outside capsid, %

Evilevitch et al, PNAS
Comparison to structural data

Cryo-electron microscopy

Simulation

Experiment

Small Angle X-ray Scattering

Experiment: 

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
Acknowledgements

• Funding through CPLC

• Computations

Jejoong Yoo  Chris Maffeo  Kush Coshic  David Winogradoff