A Coarse Grained DNA Model: Twist/Writhe Partitioning in DNA Minicircles

Mehmet Sayar
College of Engineering, Koç University, İstanbul, Turkey

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Supercoiling in DNA

Understanding the supercoil formation energetics/dynamics in DNA molecule is key to resolving several important features of DNA such as the structure-function relationship, the melting behaviour, twist-writhe interplay.

- Computer simulations can play a major role in tackling these problems.

- Current elastic rod models cannot properly account for the helical nature and hybridization of the DNA molecule.

- Computationally efficient coarse-grained models are essential for simulating large enough systems for long enough times.

DNA minicircle

Length 90 bps

Full atomistic MD simulation using a 400 core cluster

AMBER-99 force field

\[ \sigma = \frac{(Lk - Lk_0)}{Lk_0} \]


msayar@ku.edu.tr http://home.ku.edu.tr/~msayar
DNA under Torsion

Coarse-Grained Model of DNA

- Two bead model: Phosphate bead (P), Base bead (B)
- Intra-strand bonded and Inter-strand nonbonded interactions
- Force constants extracted from full-atomistic MD simulations via Boltzmann Inversion
- Generic base model: no A, T, G, C specificity


Amber (parm94 force field)

msayar@ku.edu.tr
Four different bonds
Two dihedrals
Two interstrand interactions
Harmonic potentials are fitted to the Boltzmann inverted potentials.
Generic base model: no A, T, G, C specificity
Electrostatic interactions are not explicitly included
Slight departure from harmonic behaviour

Good agreement between the fitted functions and observed PMF from coarse-grained simulations

No significant coupling among CG interactions
Equilibrium Distributions

Inter-strand interactions

- Non-harmonic behaviour is observed.
- H-bonds within basepairs lead to stiff potentials
- Inter PP interaction displays GC – AT basepair specificity
Equilibrium Structure

Directionality
Minor and Major groove
Double helical structure
Persistence Length

- Correlations of the PP bond vectors follow the helical pitch of the DNA
- 11.08bp pitch at finite temperature
- 96 bps persistence length ($l_p$)
- Persistence length is shorter than experimental value (~150 bps)
Supercoil Formation

\[ \sigma = \frac{(Lk - Lk_o)}{Lk_o} \]

- \( L/l_p = 1.2 \), \( \sigma = 0.00 \)
- \( L/l_p = 2.9 \), \( \sigma = 0.05 \)
- \( L/l_p = 5.8 \), \( \sigma = 0.13 \)

msayar@ku.edu.tr

http://home.ku.edu.tr/~msayar
Supercoiled Formation

- $L_k = W_r + T_w$

- DNA mini-circles ($L/l_p = 1.2$) exhibit a non-linear behaviour.

- For small $\sigma$, $T_w$ absorbs all deformation, the minicircle remains planar.

- Buckling instability of the planar state is observed.

- Beyond the transition $T_w$ and $W_r$ absorb the excess linking number equally.

$$\sigma = \frac{(L_k - L_k^o)}{L_k^o}$$
Supercoil Formation

- For longer chains the planar regime slowly disappears.
- The buckling instability is only observed in short chains.
- Majority of the excess linking number is absorbed by the Wr.
Conclusions

- The coarse-grained DNA model mimics local geometric properties successfully.
- This model enables us to reach the relevant length scale for supercoil formation.
- Buckling instability is observed for short chains.
- Once planarity of the minicircles is lost, for short chains the excess linking number is absorbed equally by twist and writhe.
- For long chains the buckling instability disappears, and the writhe absorbs majority of the excess linking number.

Hydrophobically Modified PEs

M. Bockstaller et al., Macromolecules, 34, 6353 (2001)
Hydrophobically Modified PEs

- Micellar PPP aggregates in solution
- 10-19 PPP molecules/cross-section (Na\(^+\) counterion)
- 60 PPP molecules/cross-section (Ca\(^{2+}\) counterion)
- 4-5 PPP molecules in length
- Double micelle length with double PPP length
- Rich phase diagram
Preform the Bundle

top view

side view

- No self-assembly
- 1000 water / PPP
- Gromos 96 Force Field
- SPC water model
Simulation Results

Monovalent counterions
Sodium, Na
8 PPP Molecules

- Basic packing idea is OK.
- Hydrophobic side chains in the core.
- Charged \( \text{SO}_3 \) groups remain on the surface.
- Condensed counterions
- Small fraction in the hydrophobic core
- Counterions move with their hydration shell
- Water inside the core
Bundle Stability

8 PPP Molecules

10 PPP Molecules

14 PPP Molecules

20 PPP Molecules
Bundle Size from Simulations

Comparison of Experimental and Simulated SAXS Results

Scattering intensity

Bundles of 8-10 PPPs yield the closest match to the experimental SAXS results.


msayar@ku.edu.tr

http://home.ku.edu.tr/~msayar
Multivalent Counterions

Divalent counterions
Calcium, Ca

Experimentally bundles of size 60 PPPs is observed with Ca$^{+2}$
Bundle Stability with Ca$^{+2}$

- 8 PPP molecules
- 10 PPP molecules
- 20 PPP molecules
• 10-14 molecules /bundle
• Counterions penetrate the hydrophobic core for big bundles
• Beyond 20 molecules the bundle forms two separate cores.
• Packing of the side chain
• Coulomb energy of the bundle
• Hydrophobic energy of the side chains
• No fundamental difference in bundle size with Na vs. Ca ions
Bundle Size


msayar@ku.edu.tr

http://home.ku.edu.tr/~msayar
Comparison of Na$^+$ and Ca$^{+2}$
Coarse-Grained Model of PPP

Bead spring model

PPP backbone mapped on three beads (blue)

PPP backbone is semi flexible

Hydrophobic side chain mapped on to a flexible chain (green)

Na⁺ Ions (yellow)

Preformed bundle of PPPs in Cell Model

Simulation Model

Molecular dynamics
Langevin Thermostat
Cell Model
Full electrostatics ($N^2$-loop) with explicit counterions
Espresso Package

msayar@ku.edu.tr

http://home.ku.edu.tr/~msayar
Bundle Simulation


counterions both in and around the bundle
only a fraction of counterions condense
net charge on the micelle

msayar@ku.edu.tr

http://home.ku.edu.tr/~msayar
Phase Diagram

non-monotonic dependence on $\ell_B$ and $\epsilon$

stable finite size bundles decreased stability with increasing $\ell_B$, upto $\ell_B \approx 2.0\sigma$.

increasing $\ell_B$ increases attractive ion correlations leads to increased stability

Can we use iterative Boltzmann inversion in the presence of an interface?

\[ V_{i+1}(r) = V_i(r) - k_B T \ln \left( \frac{g_i(r)}{g(r)} \right) \]
LENNARD-JONES MODEL SYSTEM

- System composed of two types of particles (A and B)
- Same type of particles attract each other (i.e. A-A and B-B)
- A-B interaction is repulsive Lennard-Jones
- Iterative Boltzmann Inversion is applied to obtain all potentials simultaneously in the presence of the interface.

- The radial distribution functions do not converge to 1 (i.e. bulk density) in the presence of an interface.
Lennard-Jones Model System Results

★ IBI successfully reproduces the actual RDFs and potentials

RDF for attractive particles

RDF for repulsive particles

★ Insufficient statistics for the A-B interaction destabilizes the convergence of IBI.
★ This can be overcome by a scaling factor for the A-B interaction.
Hydrophobically Modified PEs

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Application to a Real System: Propane & Water

- Propane-water system also phase separates
- Map each propane and water molecule onto a single bead
- Target radial distribution functions are acquired from atomistic simulations.
- Iterative Boltzmann inversion simulations are performed for propane and solvent separately to obtain propane-propane and solvent-solvent interactions.
Potential for propane-propane interaction

Potential for solvent-solvent interaction

RDF for propane-propane

RDF for solvent-solvent
Propane-solvent interaction is also obtained by IBI.
The propane-propane and solvent-solvent interactions are kept fixed as obtained from the IBI simulations of homogeneous systems.
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