Multiscale Simulations of DNA and Nucleosome Core Particles

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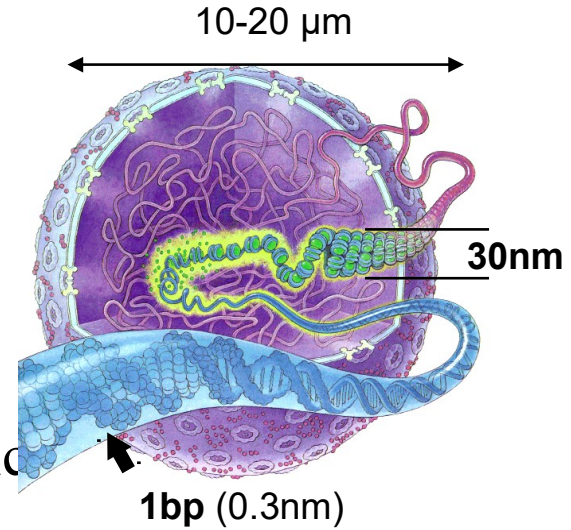
DNA in a cell

DNA length ~ 2m : present in every cell of a body

... even inside a cell nucleus, of size ~ 0.01 mm



How it find place there?

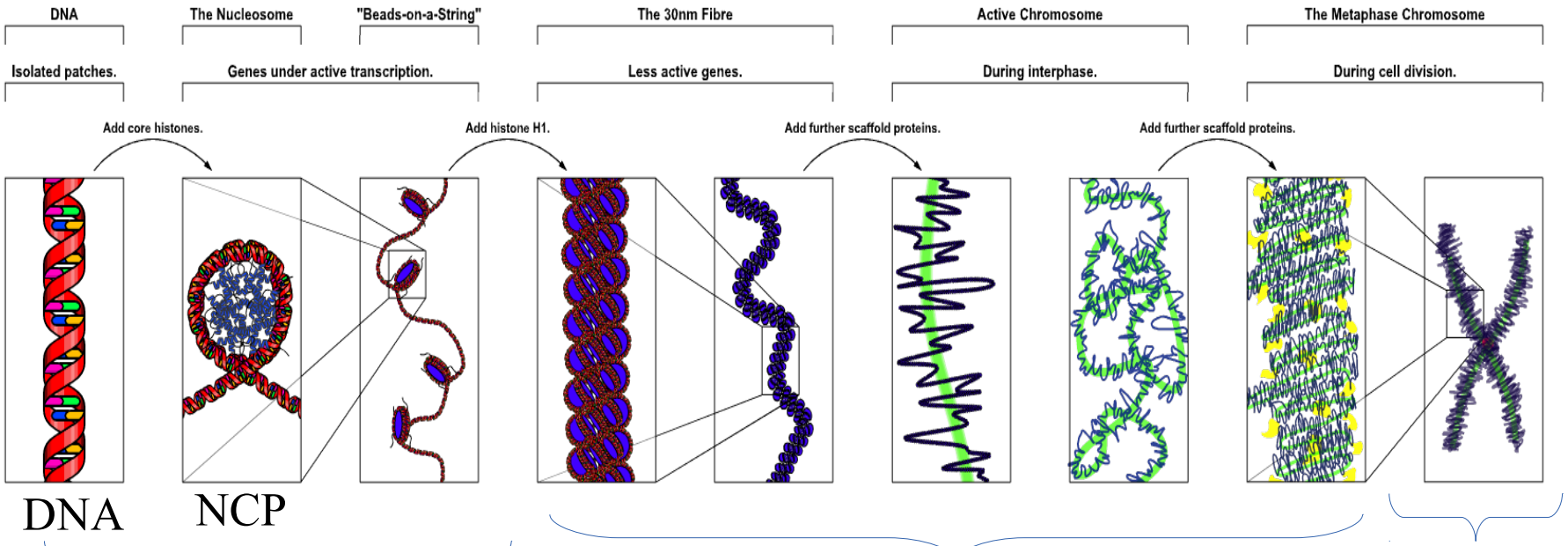
Problems:

- Size: less than "random coil" -
  Overcome entropy barrier and electrostatic
- we often need access ***to specific fragments*** of the DNA (transcription)
- All cells have the same DNA sequence, but work differently!

Chromatin

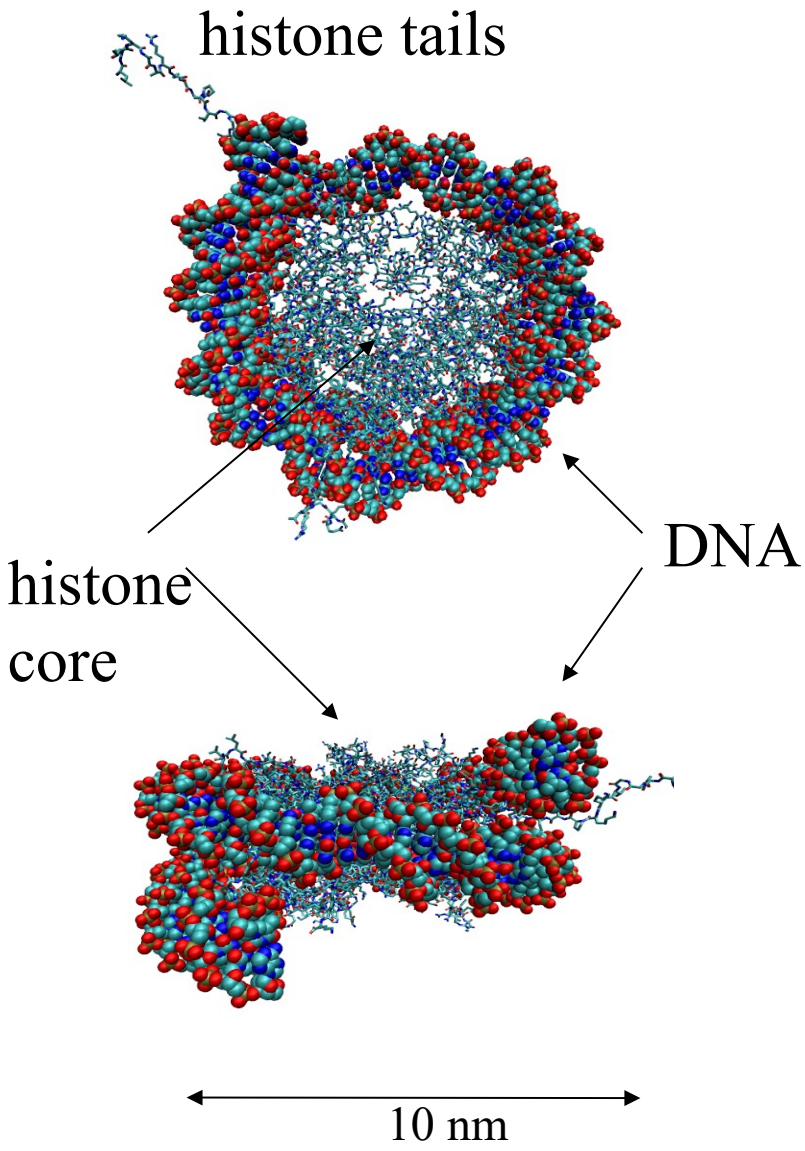
The Nature solves this by several levels of structural organization of DNA
Hierarchical complex of DNA and proteins in the cell nucleus

DNA in chromatine (adopted from Wikipedia)



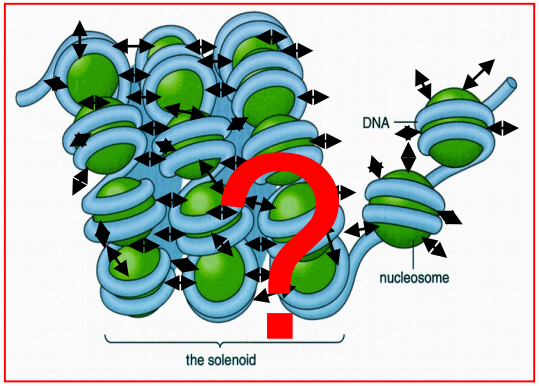
DNA folding determines active / inactive genes

Nucleosome core particle



DNA is wrapper (1.75 turns) around histone octamer core
with 8 positively charged histone tails.
DNA charge: around -300e
Histone charge: around +150 e
DNA-NCP complex – still strong negatively charged polyelectrolyte

Nucleosome core particles form higher hierarchical structures



Challenges in DNA - NCP - chromatine folding modeling

- Atomistic simulations not feasible
  (1 NCP : box ~20 nm , num of atoms approaching 1 mln,
  and time scale > 1 μs)

- "Primitive model" simulations do not include:

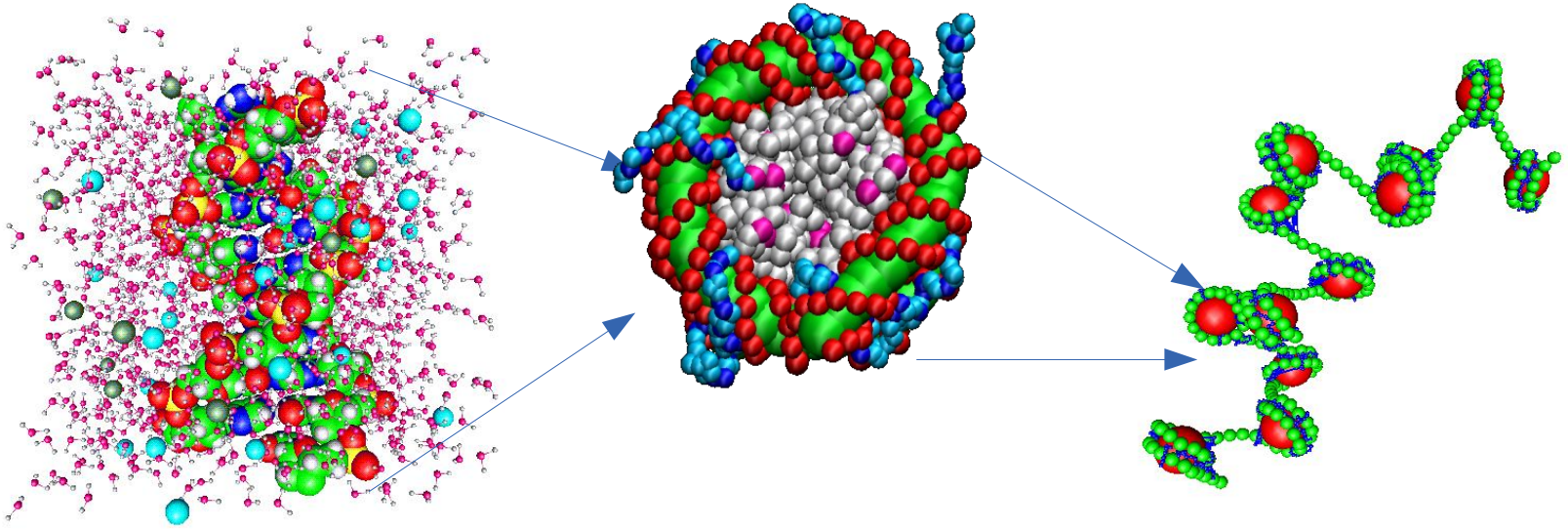
- hydration: hydrogen bonding / hydrophobic effect
- dielecric permittivity is not 78 in crowded environments

- Even at "primitive electrolyte model" coarse-graining too much interaction centers (with explicit treatment of ions)

Solution: ***Systematic Multiscale Modeling***

Systematic Multiscale Modeling of DNA-chromatin

The idea:



Atomistic

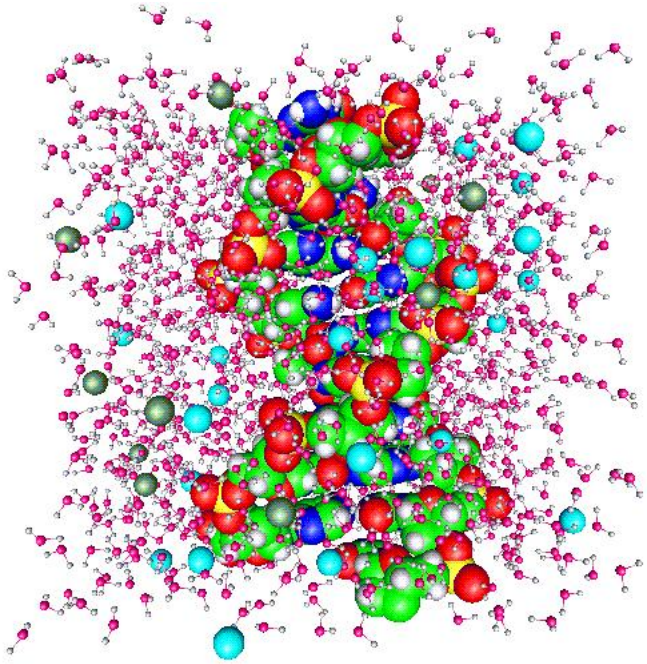
CG level 1
implicit solvent
CG site ~ 10 atoms

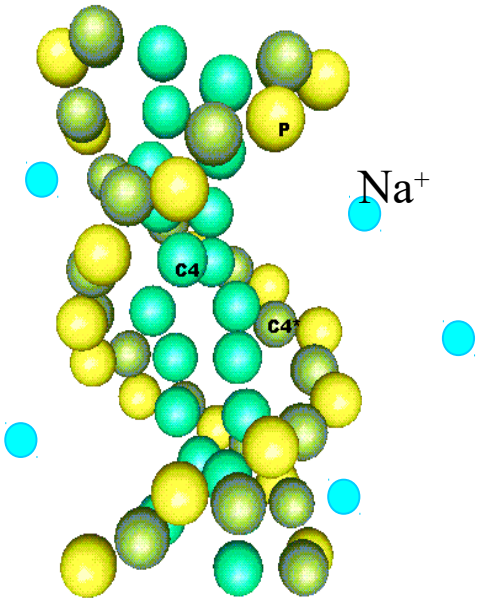
GC level 2
implicit ions
CG site ~100 atoms

How determine parameters / potentials for CG models?

Bottom-up multiscale modeling

reducing the number of degrees of freedom





$$H^{at}(r_1, r_2, \ldots, r_n)$$

$$R_j = \theta(r_{1,\ldots}, r_J), \quad J \ll N$$

$$H^{CG}(R_1, R_2, \ldots, R_J) = ?$$

The task:

to find CG potentials which reproduce properties of the atomistic model

An inverse problem : find interaction potentials from properties

Structure-based multiscale approach

Structural properties
(from atomistic simulations)

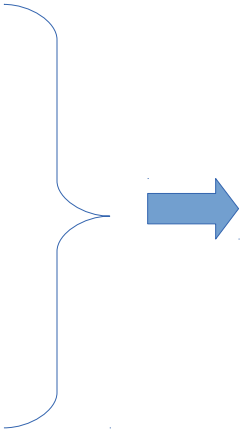
Effective potentials
(for coarse-grained models)

R D F $g_{ij}(r)$

bond length distribution

angle distribution

torsion distribution



pair CG potentials $V_{ij}(r)$

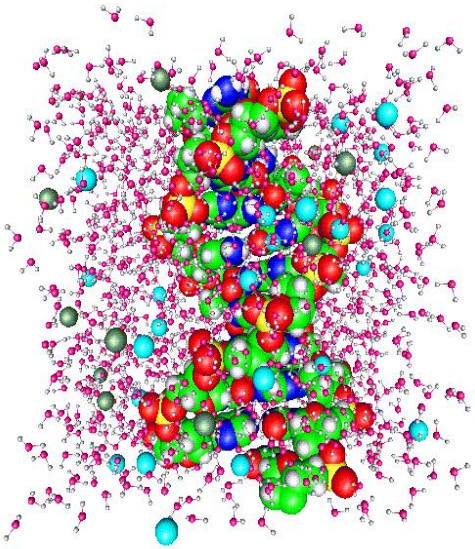
bond potentials

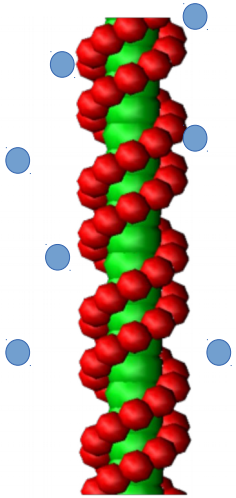
angle potentials

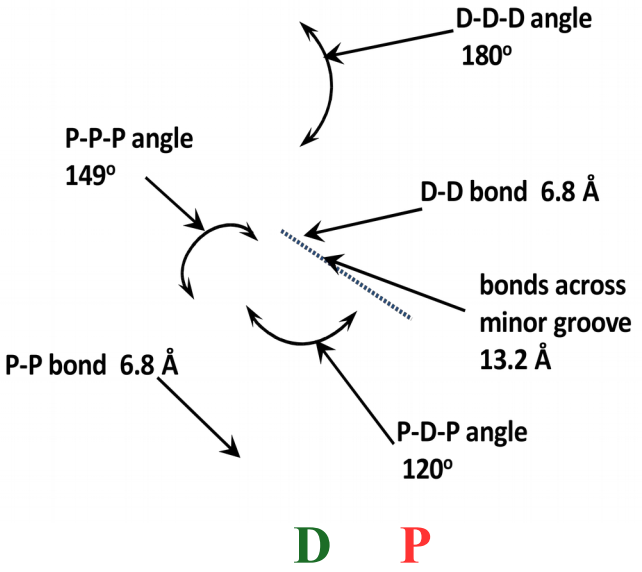
torsion potentials

Henderson theorem (1974): solution of the inverse problem is unique
How to find solution: Inverse Monte Carlo
(Lyubartsev&Laaksonen, Phys.Rev.E, 52, 3730 (1995))
Implementation: MagiC software (Mirzoev&Lyubartsev, JCTC, 9, 1512 (2013)
http://bitbucket.org/magic-su/magic-2

Coarse-grained DNA model







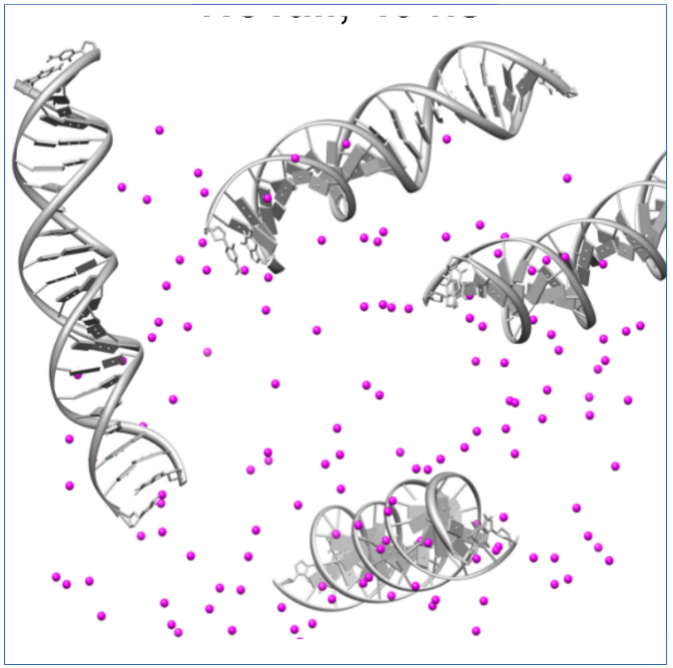
one CG site per each 2 base pairs
and for each phosphate

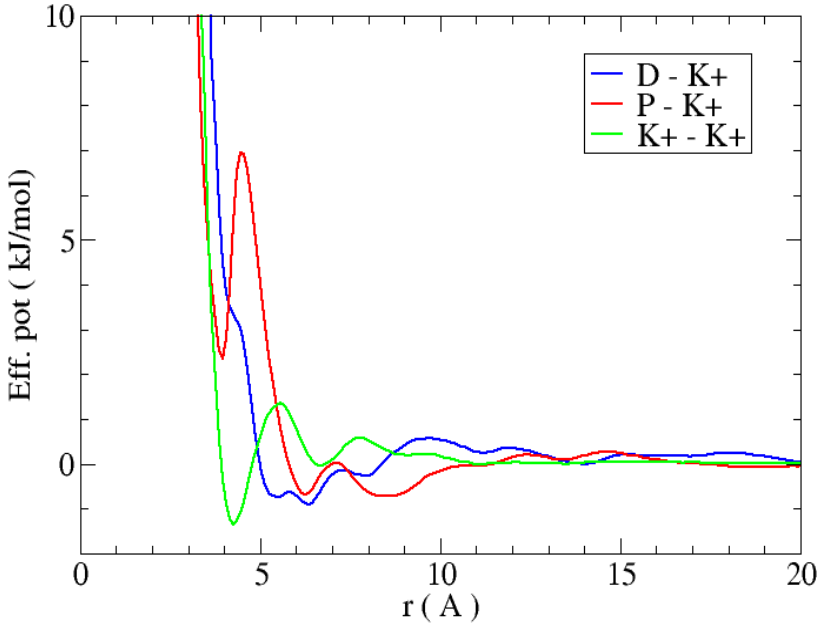
Internal structure is described by 3 bond (D-D; D-P and P-P)
and 3 angular (D-D-D: P-D-P and P-P-P) interactions

Coarse-grained DNA and ions potentials

Atomistic simulations:
4 DNA 22bp oligonucleoties, 21200 H_2O, 168 K+ ions, box 88 Å

(N.Korolev, D.Luo, A.P.Lyubartsev, L.Nordenskiöld, Polymer, 6, 1655-1675 (2014))

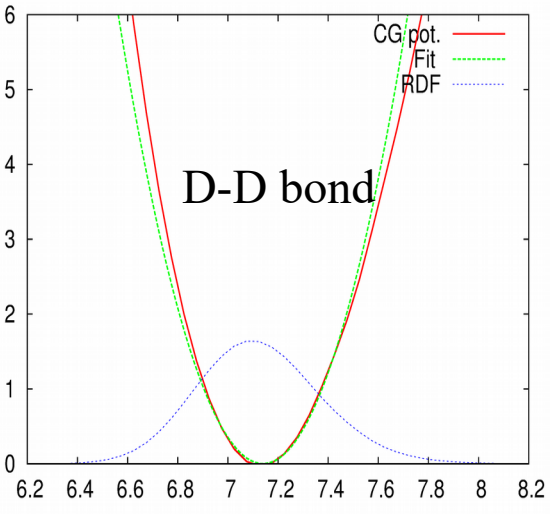


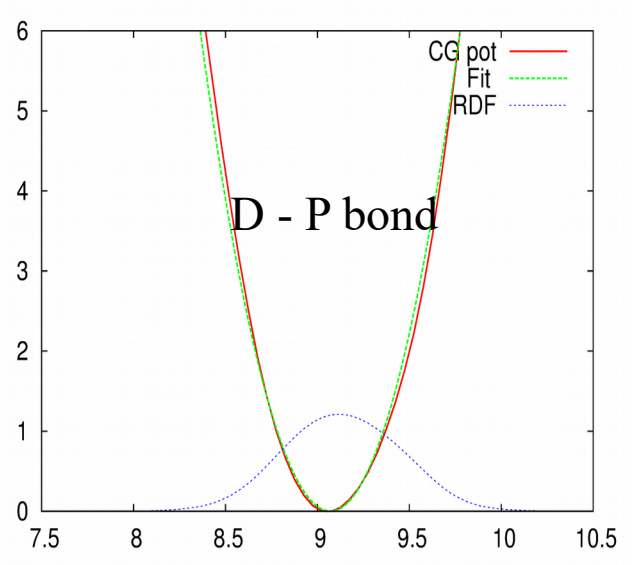


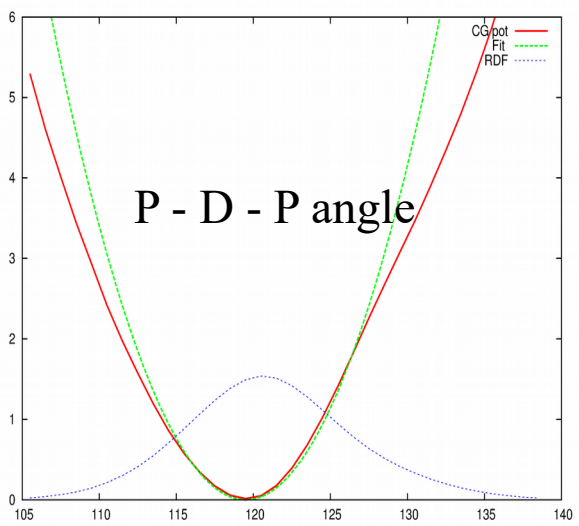
ion-DNA CG potentials

Software: MagiC

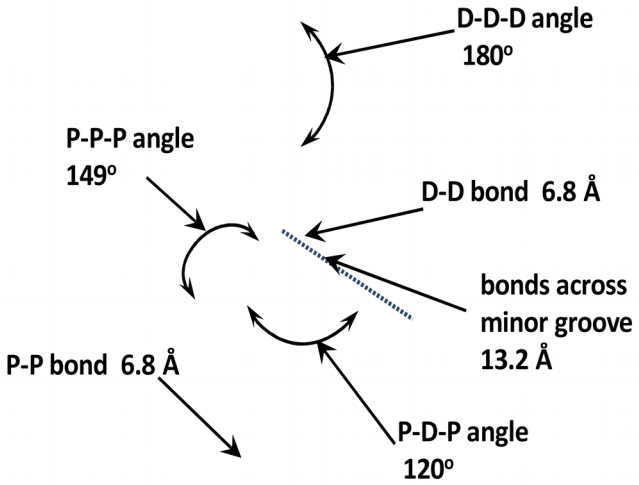
Harmonic approximation of the internal DNA potentials







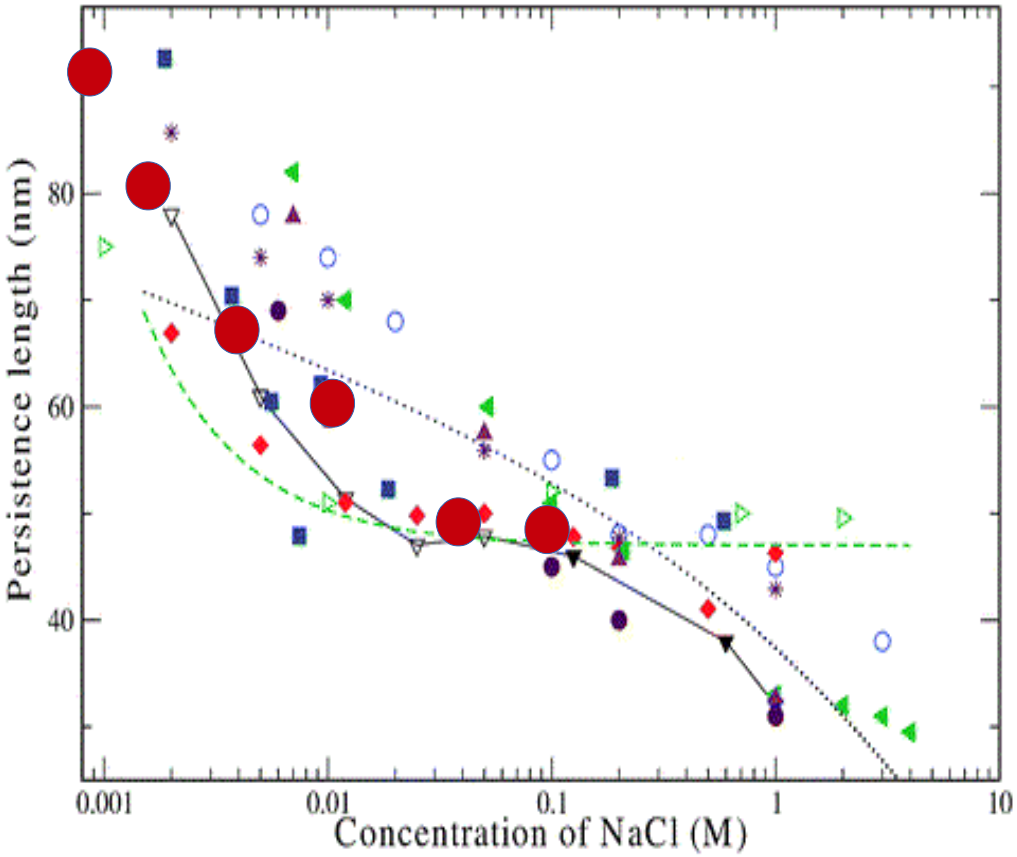
Type of bond/angle	Equilibrium distance / angle	Force constant ($k_BT/Å^2$ or k_BT/rad^2)
D-D bond	7.14 Å	14.8
D-P bond	9.04 Å	9.7
P-P bond	6.88 Å	19.4
D-D-D angle	166°	37.0
P-D-P angle	119.5°	100
P-P-P angle	165°	32.0

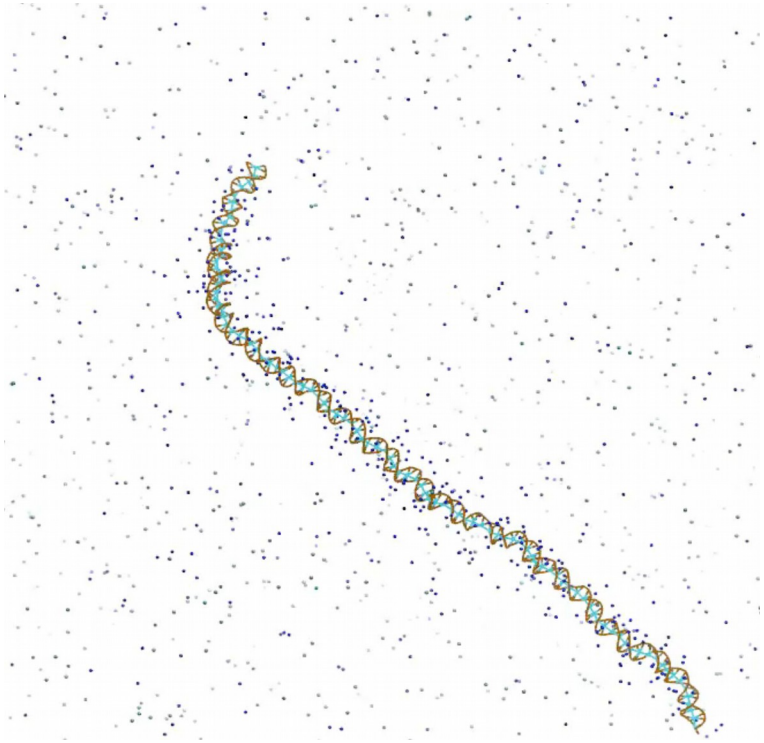


DNA persistence length: CG simulation

200 bp DNA + 1:1 ions

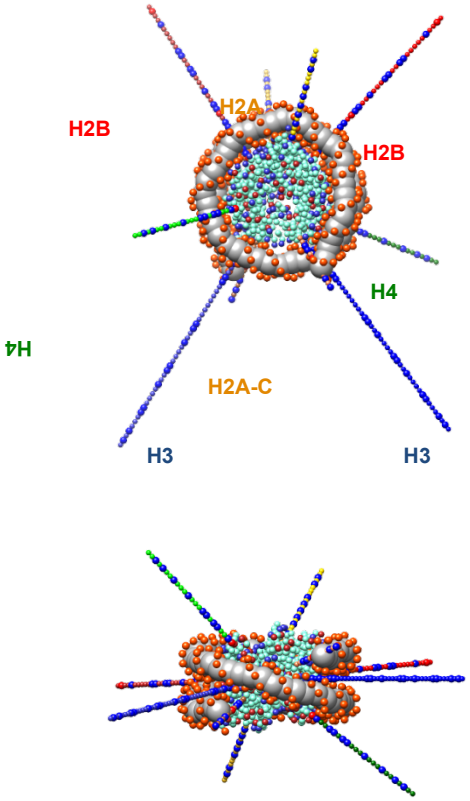
$$L_p = \frac{L_c}{\ln\langle \cos\alpha \rangle}$$





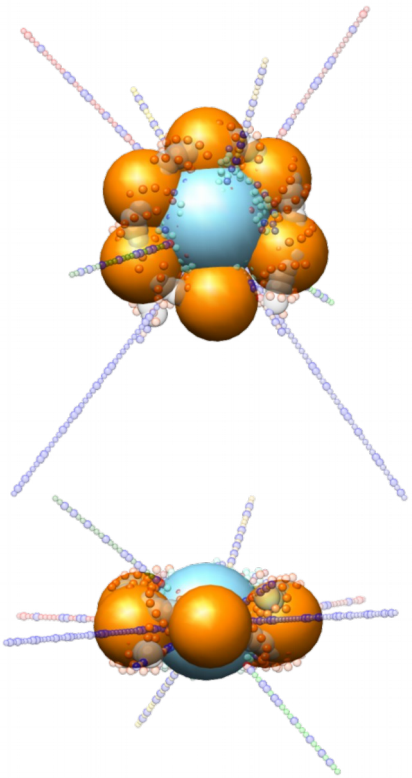
“Second-level” coarse-grained NCP

high-resolution CG



1350 CG sites + ions

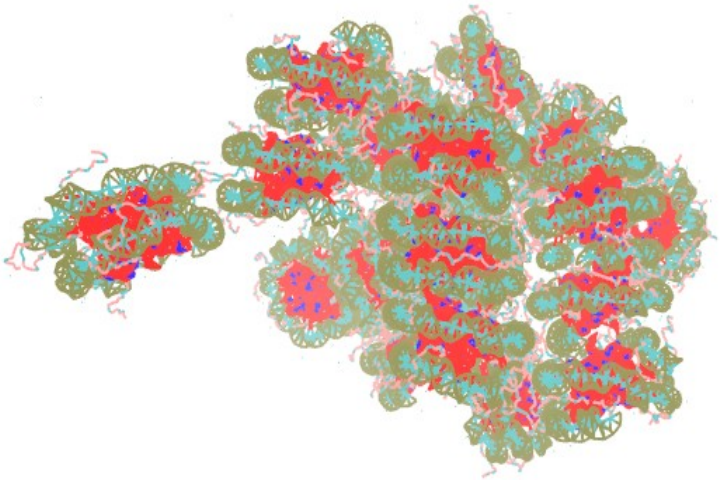
2-nd level CG

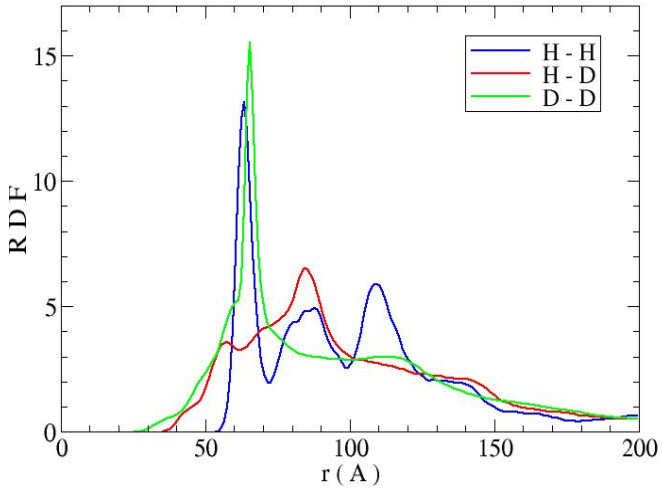


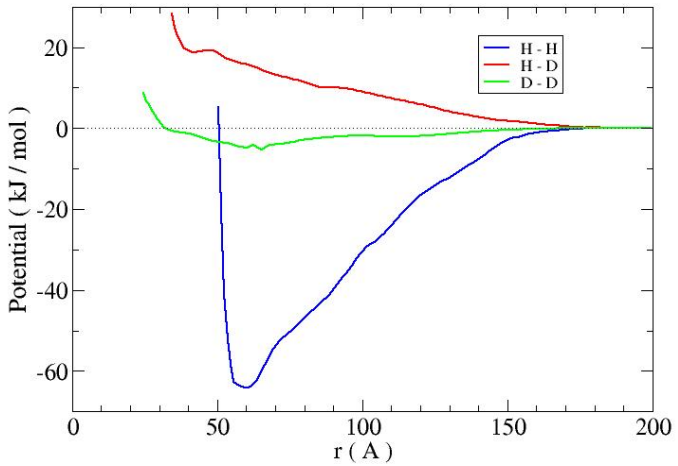
7 sites

Langevin MD simulations of high resolution NCP CG model

20 NCP with 1000
3+ counterions



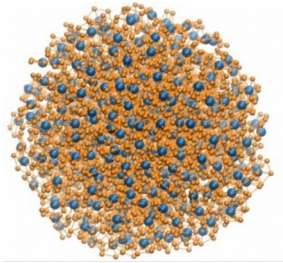




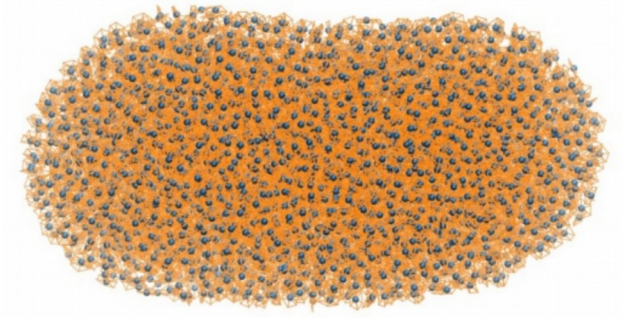
Large-scale simulations of 2-nd level NCP

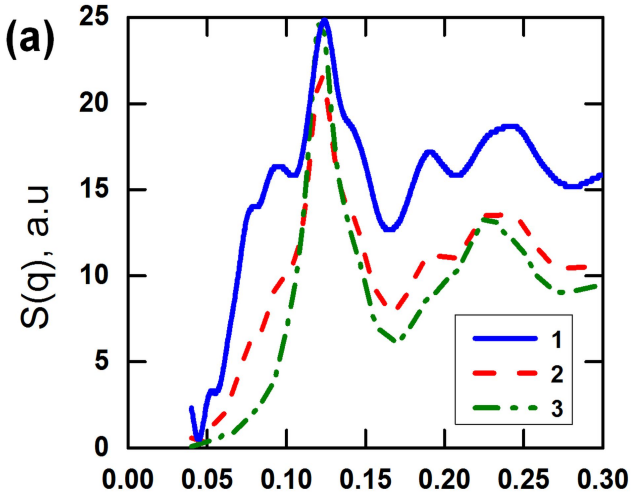
Simulation 500 and 5000 “super-coarse-grained” NCPs
Comparison with experimental structure factor

500 NCP

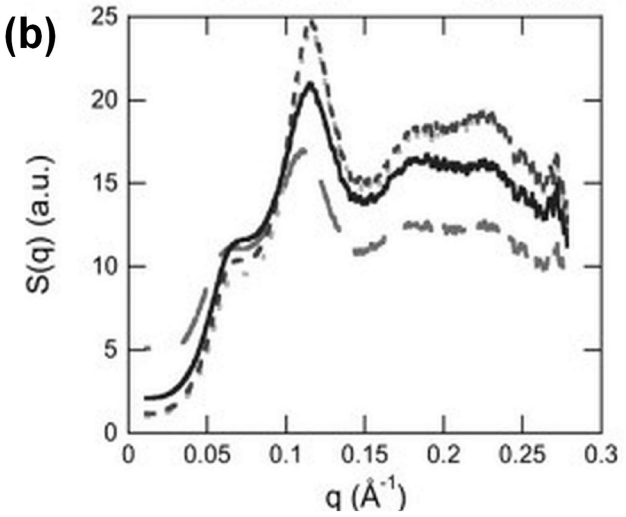


5000 NCP





Sim:
1- 500 NCP
2- 5000 NCP
3- continuous (PBC)



Exp:
(Bertin A. ,...Livolant F., Biophys.J., 93, 3652 (2007)
7 - 40 mM conc. +3 Spd counterions)

Nanoparticles toxicity: Effect on DNA folding in chromatin

Nanoparticles (size 1 – 100 nm):
many important technological applications, but also a matter of actual health and environmental concern

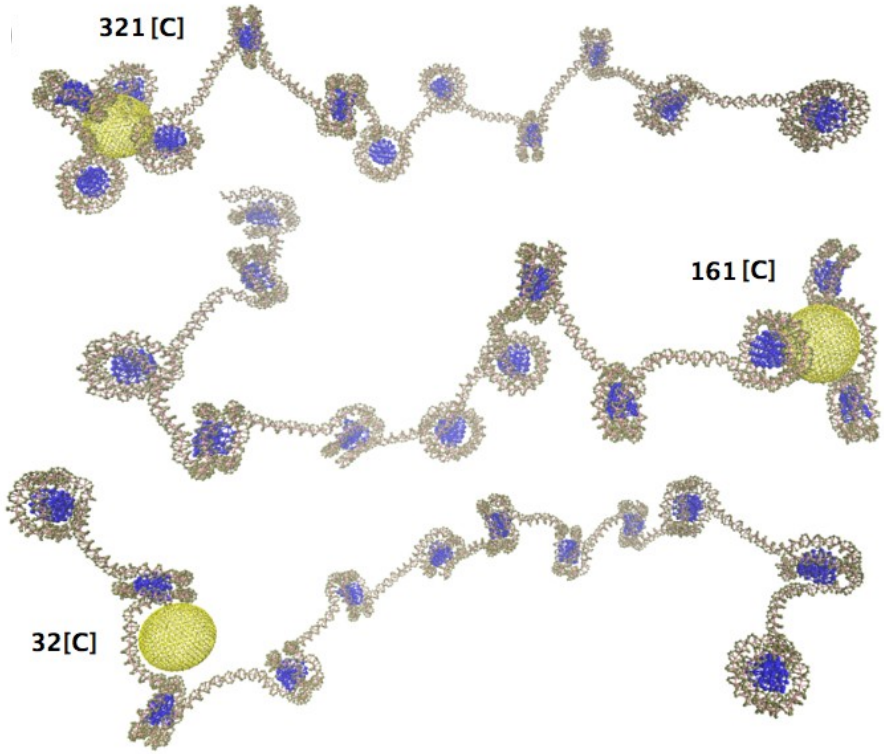
Affect living systems in variety of ways: immune system not ready

One of toxicity pathways: affect gene expression (genotoxicity)

Many nanoparticles have surface charge: may interfere DNA folding in chromatin

Coarse-grained modeling of DNA-NCP-NP system

DNA, ions:
IMC-derived CG model
Nanoparticle:
Generic positively charged sphere with short-range (r^{-12}) repulsion
100 mM KCl solution



NP of different charge / size affect DNA folding in chromatine in different ways: implication for genotoxicity

Conclusions

- Modeling of DNA packing in chromatin is inherently multiscale problem requiring considering several levels of DNA-NCP organization
- Systematic multiscale coarse-graining using inverse MC method allows to build several levels of coarse-grained models starting from atomistic simulations
- Coarse-grained DNA model parametrized exclusively from atomistic potentials shows consistent with experiment behaviour of DNA persistence length
- Next level of coarse-graining (with implicit ions) shows consistent with experiment behaviour of NCPs
- The IMC-derived CG DNA model can be used for evaluation of possible toxic effects of charged nanopartices

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