Applications of the Martini force field for Nucleic Acids

Covering all the bases

Martini Workshop August 21-25 2017

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Overview

- DNA and RNA in Biology
- Martini DNA and RNA models:
  - mapping
  - bonded and non-bonded interactions
- Validation of the models:
  - single strands: analysis
  - double strands: analysis and tools
- Interaction with ions and water
- Applications and future

Martini DNA and RNA models

- Coarse grain Martini models of DNA and RNA
- Parameters for both single- and double-stranded molecules
- Compatible with all other Martini models

- It does not hybridize single stranded molecules
- It cannot be used to study big conformational changes

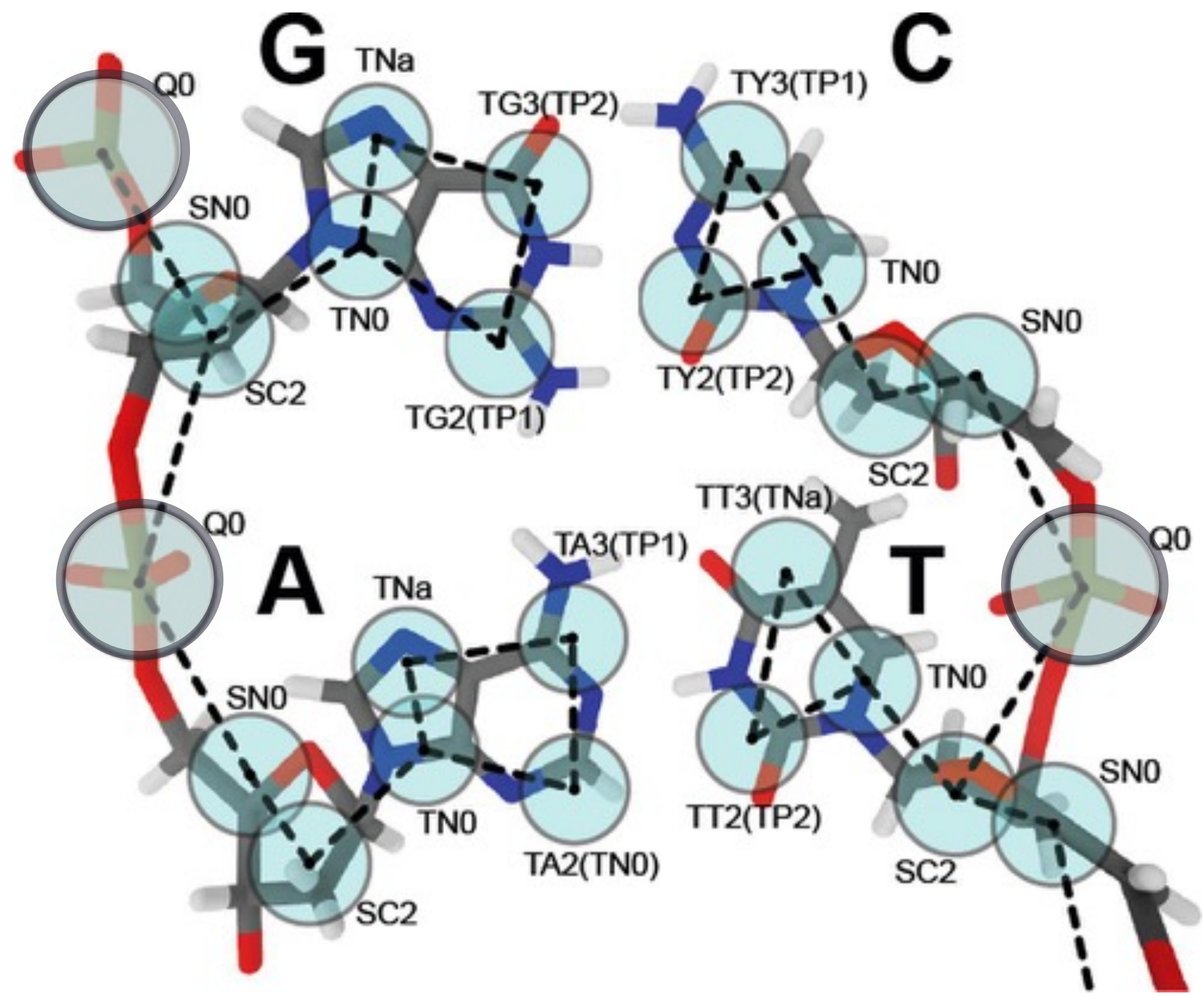
Mapping of DNA and RNA residues
keeping it simple

6 or 7 CG beads per residue

- 3 backbone beads
- 3 or 4 nucleobase beads

Changes in RNA:

- sugar SC2 bead to SNda
- in Uracil: position of TT3 bead



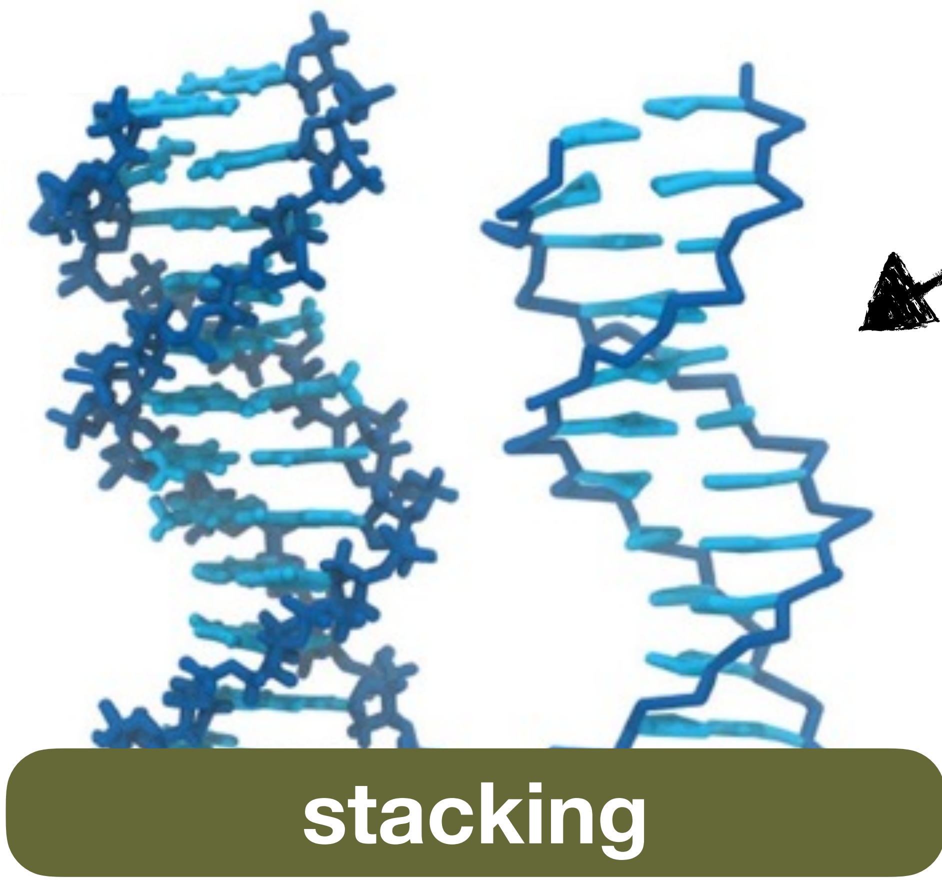
Uusitalo, JJ *et al. J Comp Theo Chem* 2015

Mapping of DNA and RNA residues

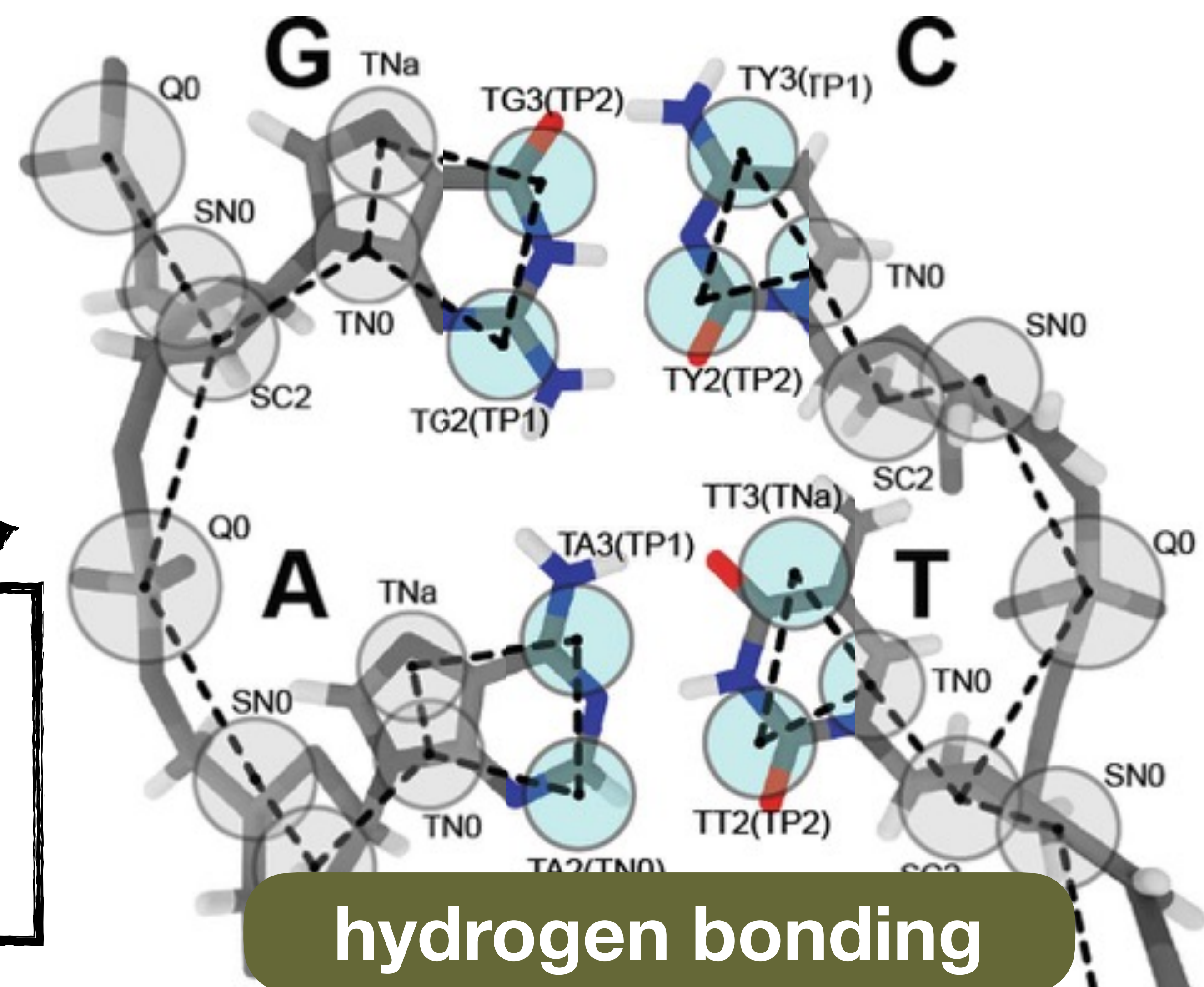
need for special beads and interactions

N beads (σ = 0.47 nm) are too big

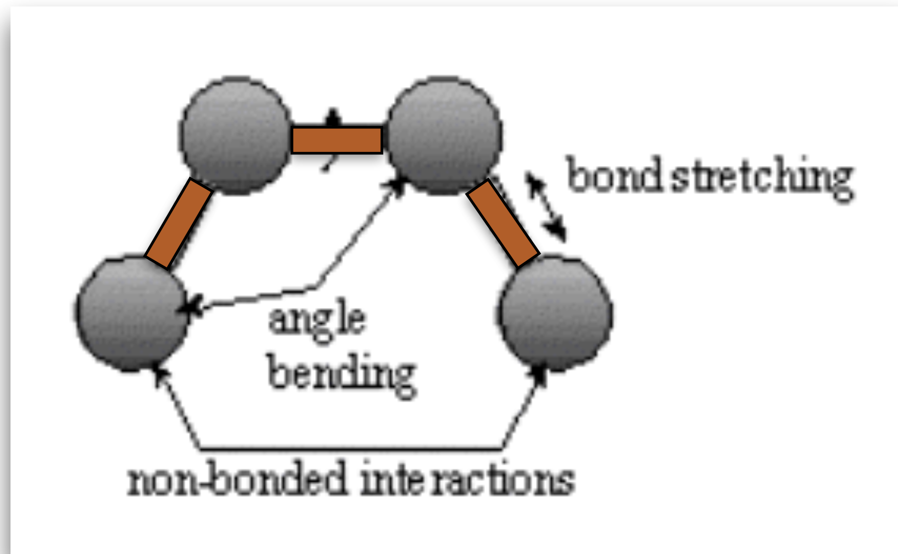
T (σ = 0.32 nm) particles to better fit stacked bases in dsDNA

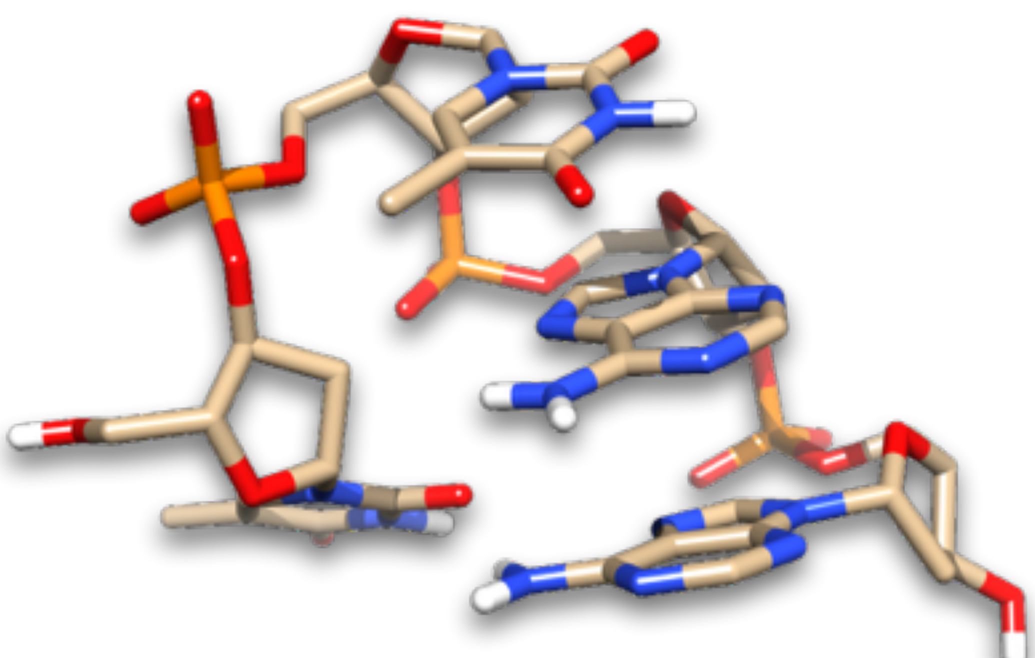


Special interactions to improve hydrogen bonds in dsDNA

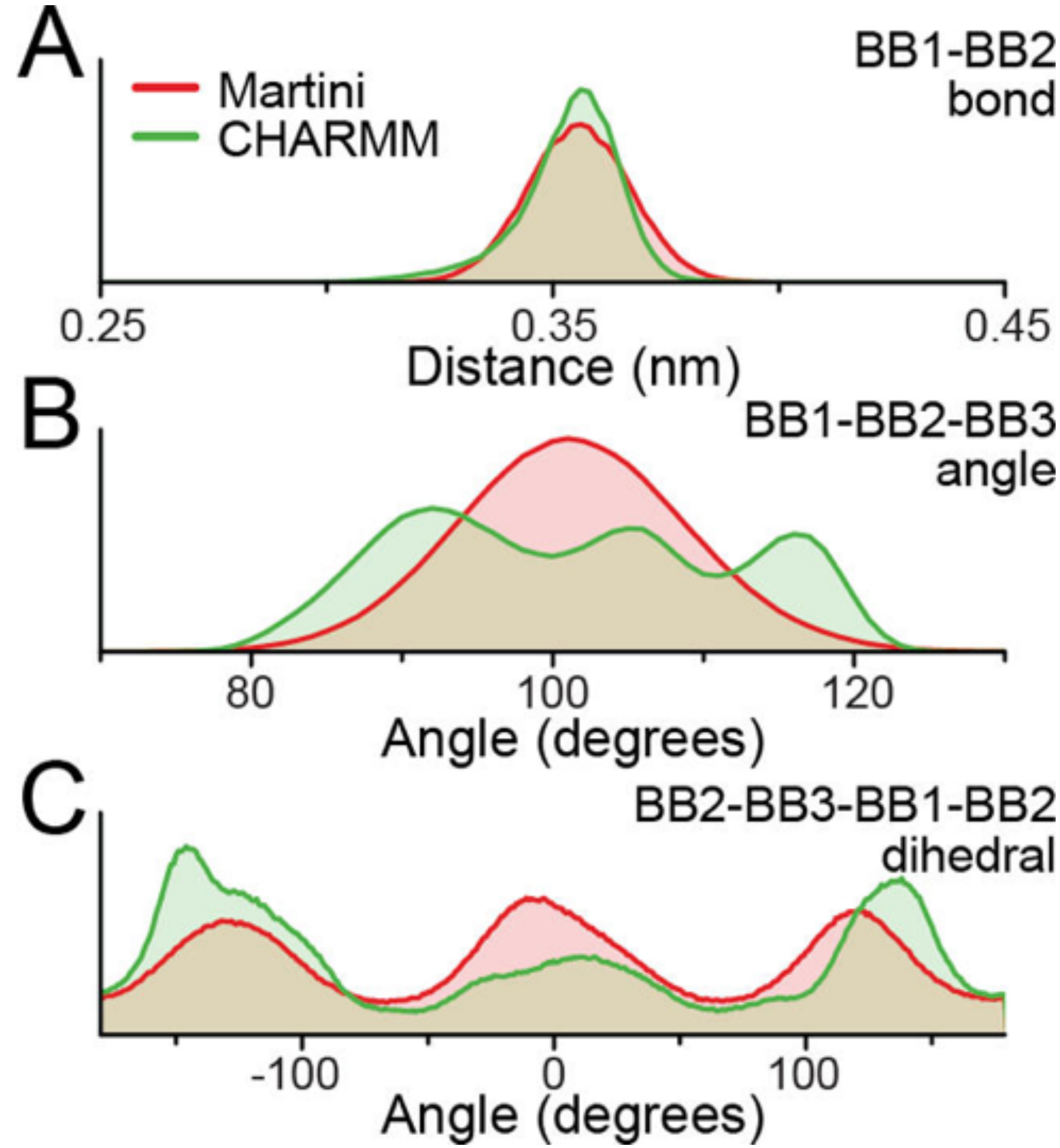


Optimizing bonded parameters
using single-stranded molecules as a reference



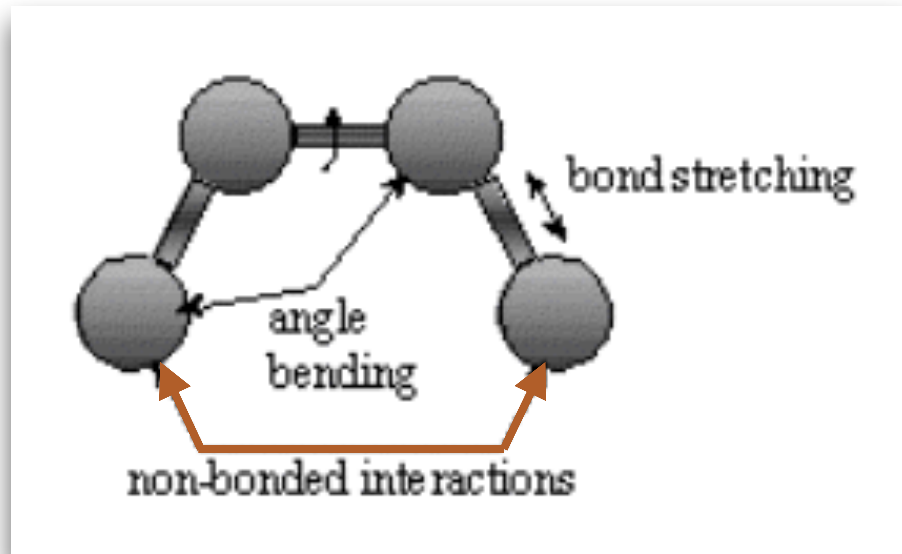


AAMD simulations
of 4-mer nucleotides



Uusitalo, JJ *et al. J Comp Theo Chem* 2015

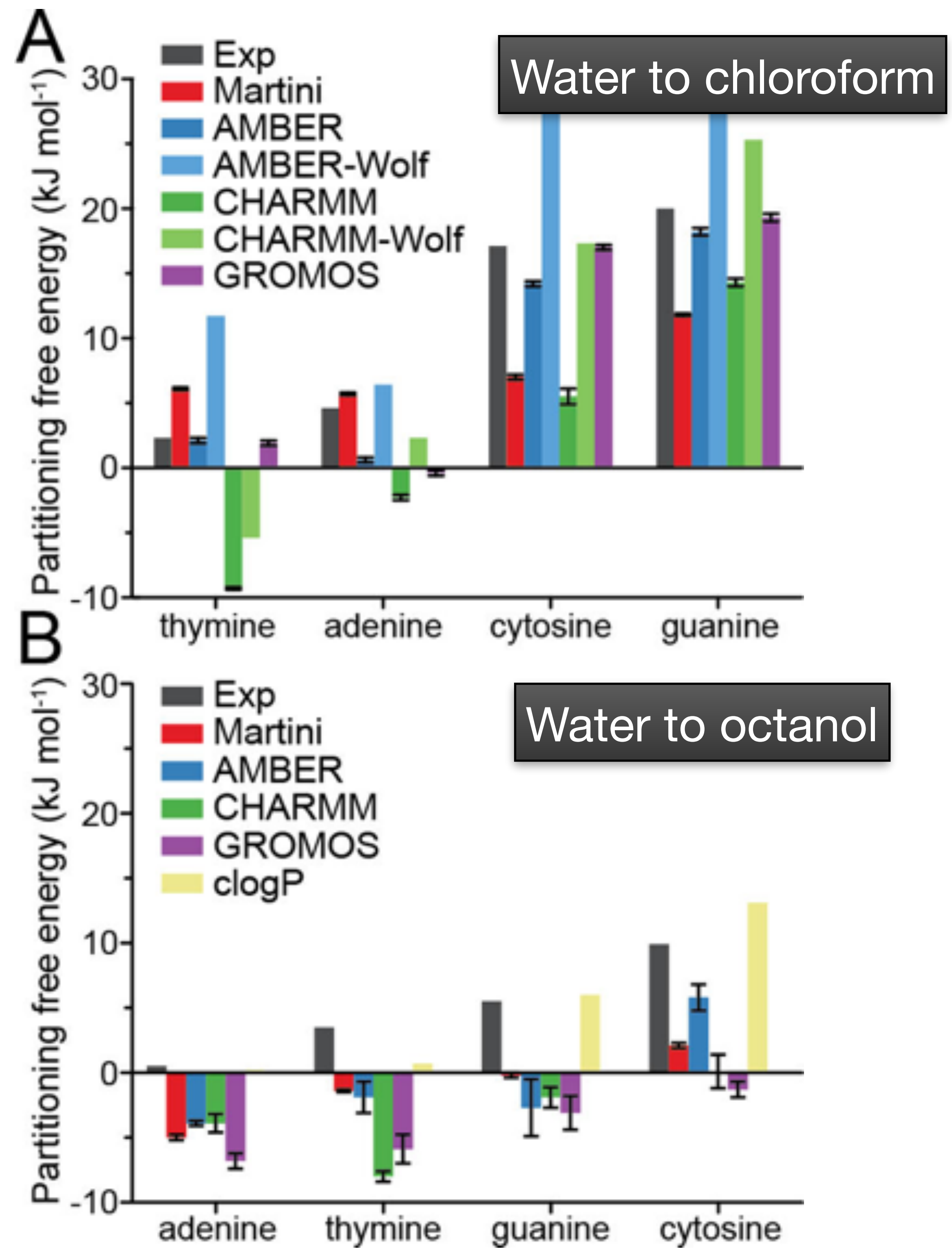
Optimizing non-bonded parameters
comparison with partitioning free energies



High variability of AA data

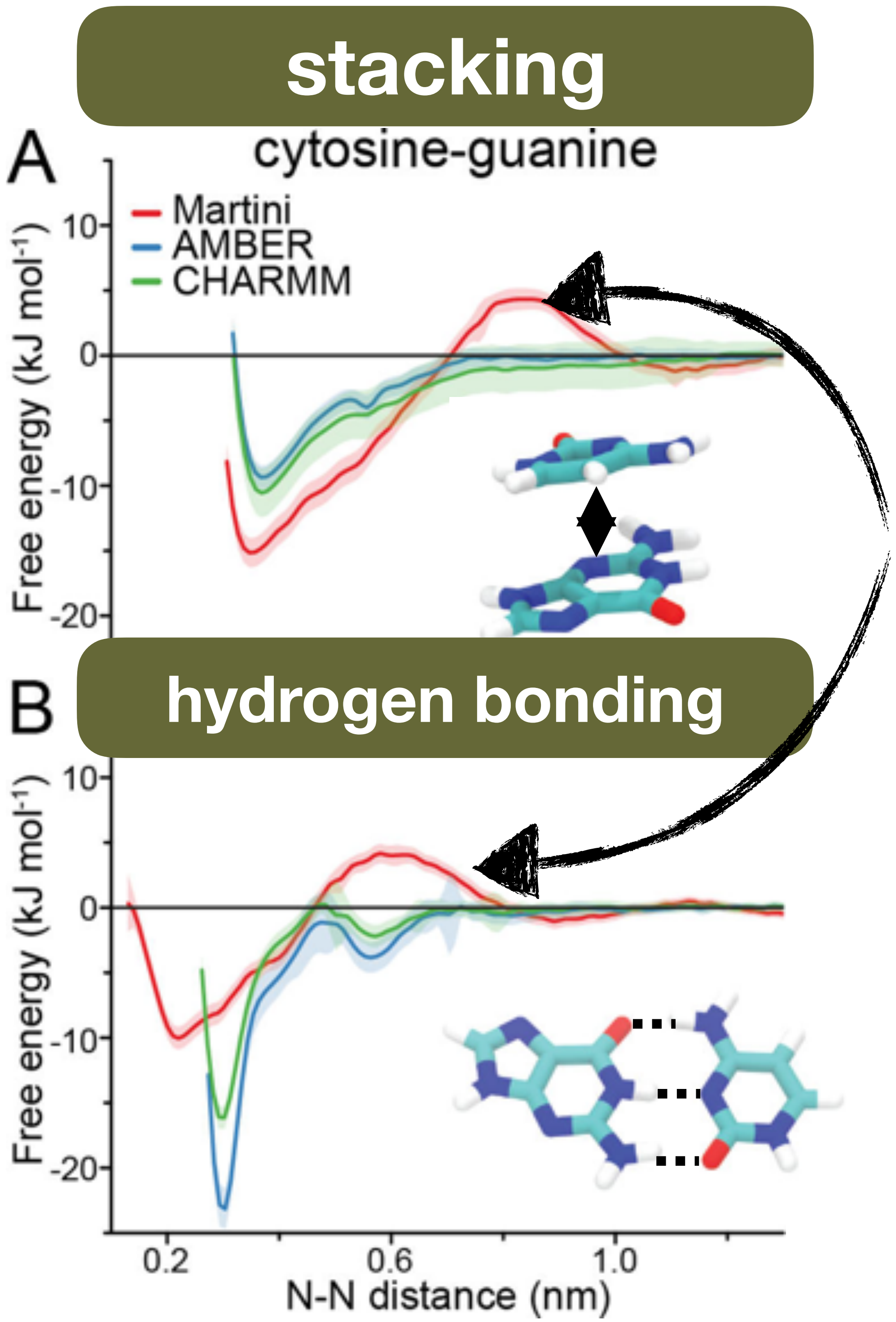
Guanine and cytosine are more hydrophilic than adenine and thymine

Martini trends follow experimental data



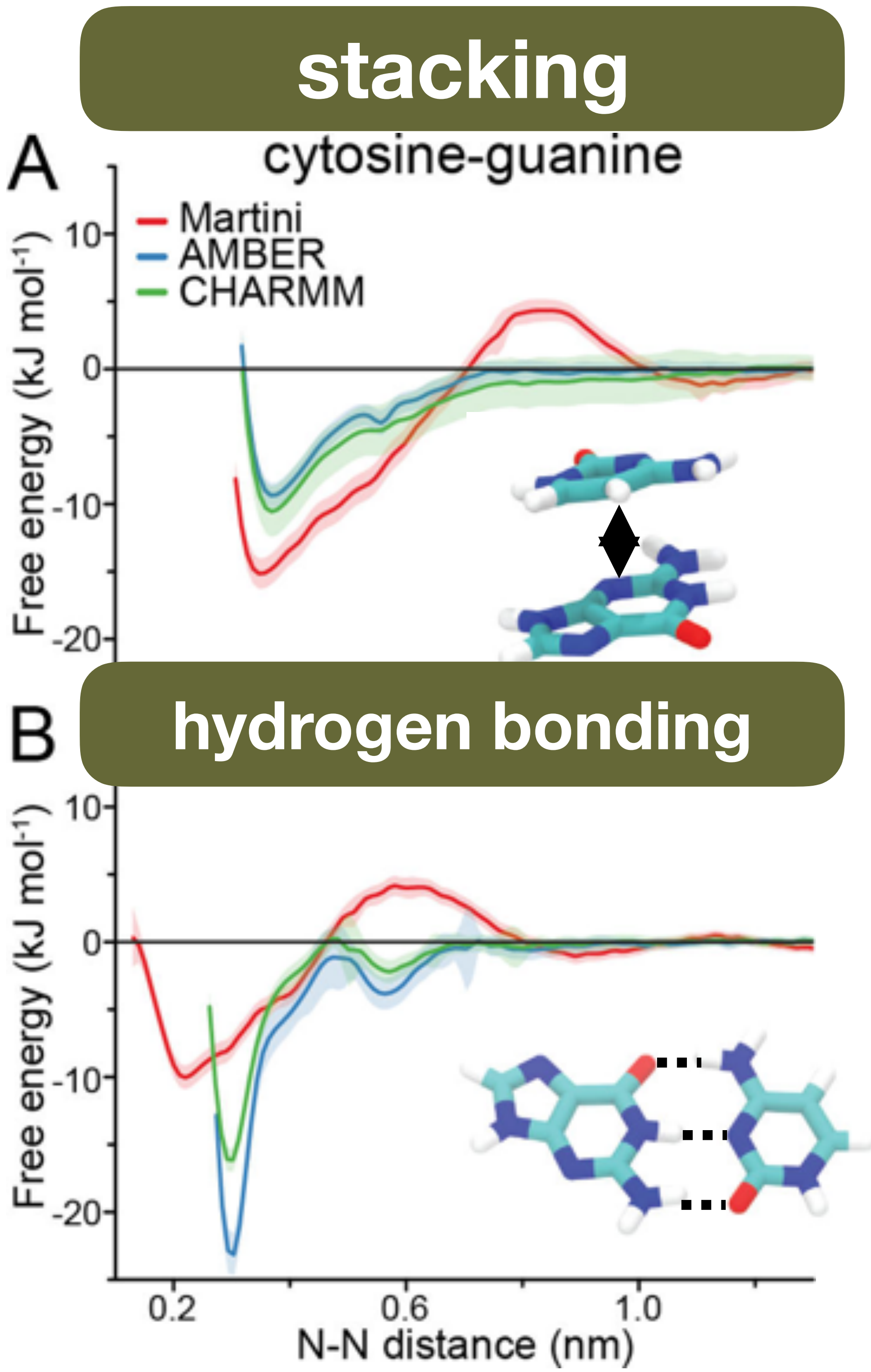
Uusitalo, JJ *et al. J Comp Theo Chem* 2015

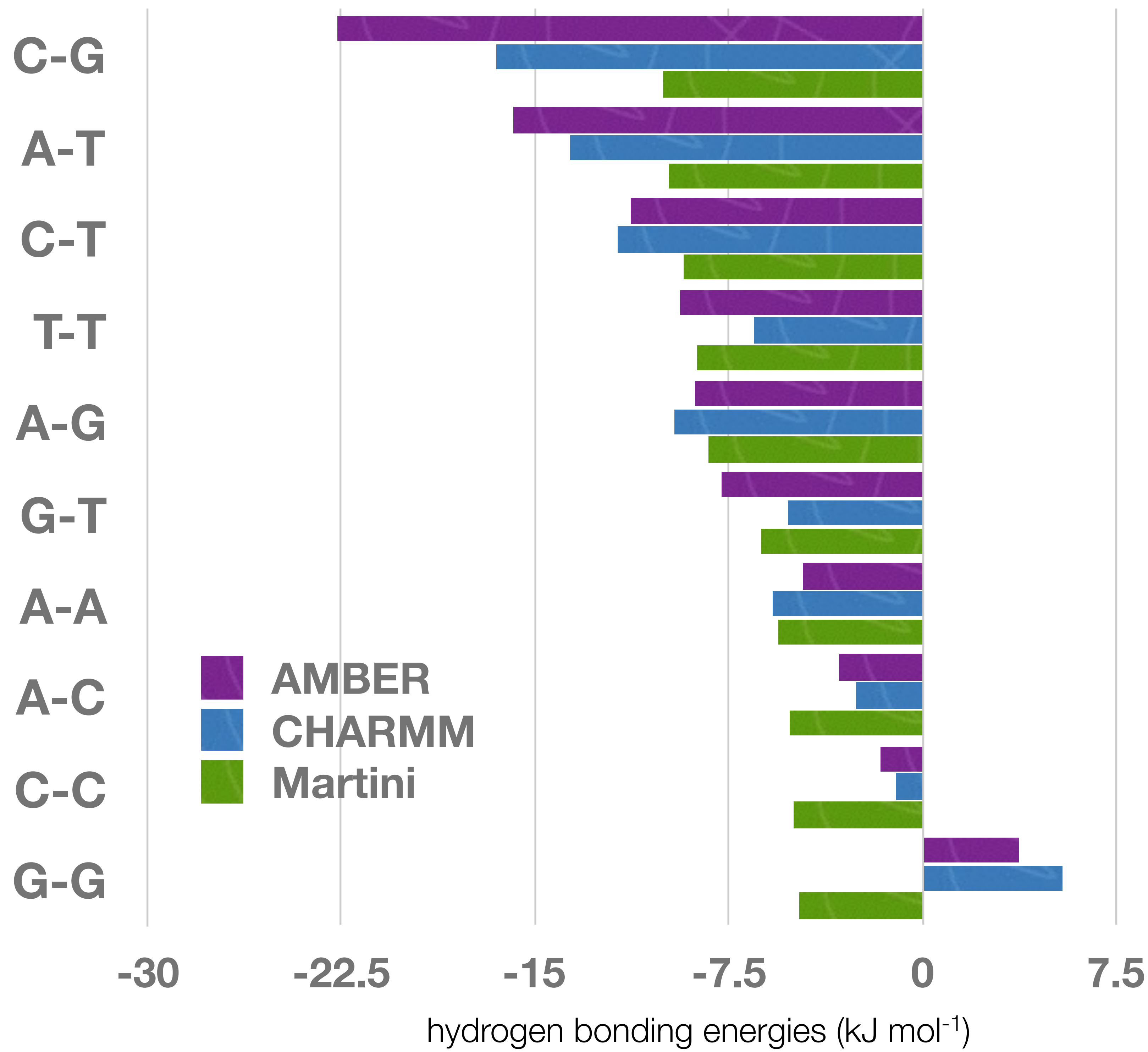
Base-base interactions
stacking and hydrogen bonding



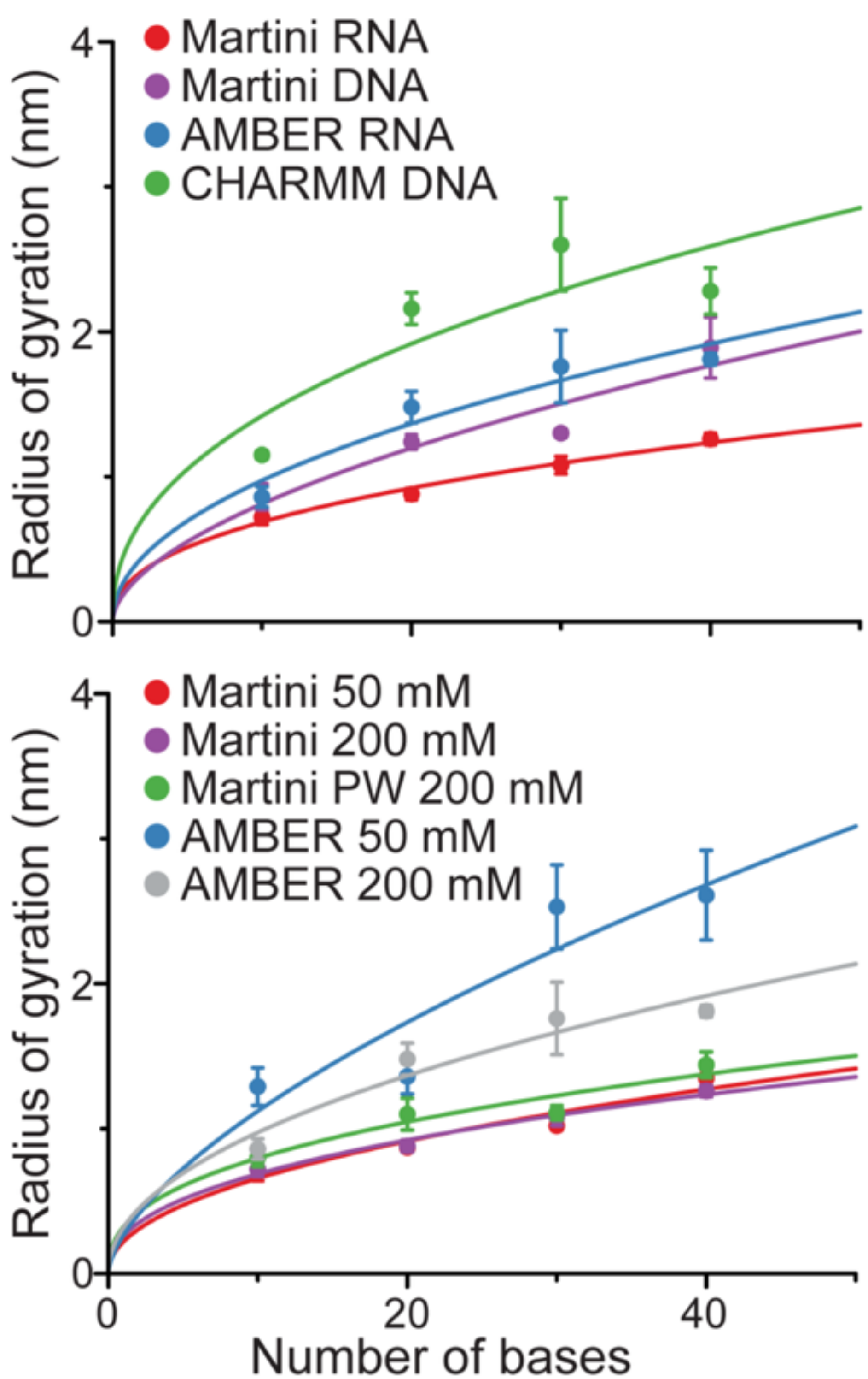
- T particles - need for small beads size
- Artificial kinetic energy barrier
- Special bead types on the Watson-Crick interface
- Specificity difficult to achieve

Base-base interactions
stacking and hydrogen bonding



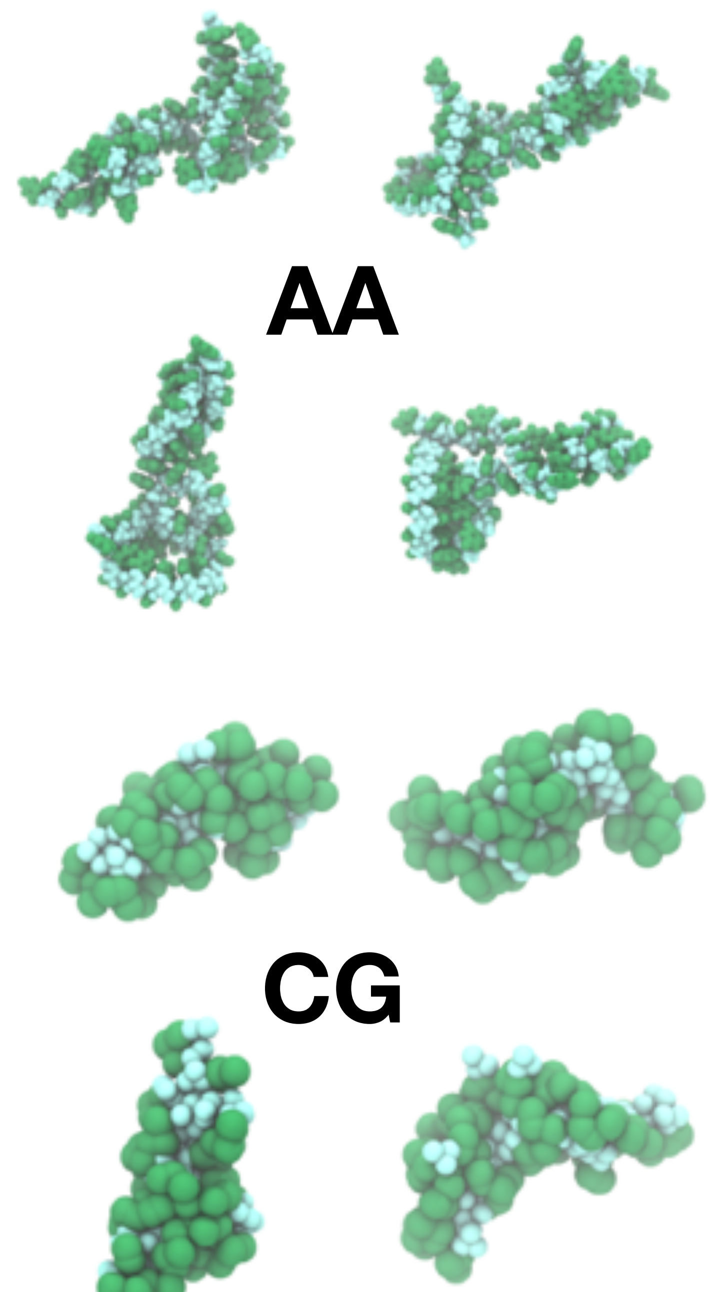


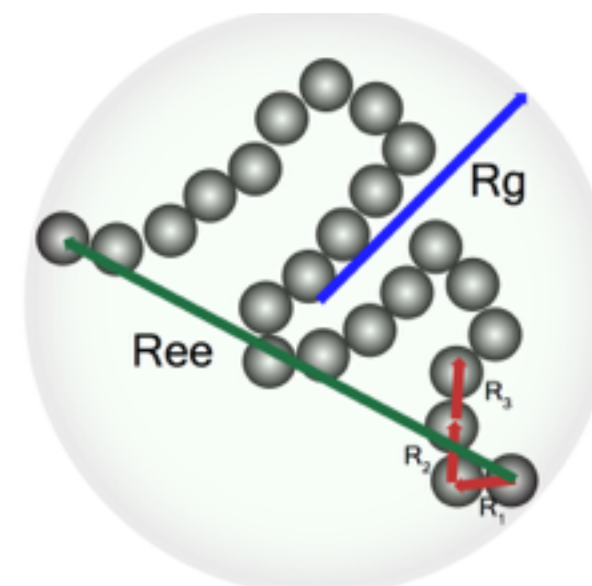
Validating the model for ss molecules
ssRNA is more flexible than ssDNA



Radius of gyration:

$$R_g^2(N) = \frac{1}{N}\Sigma_i(\mathbf{r}_i - \mathbf{r}_{CM})^2$$





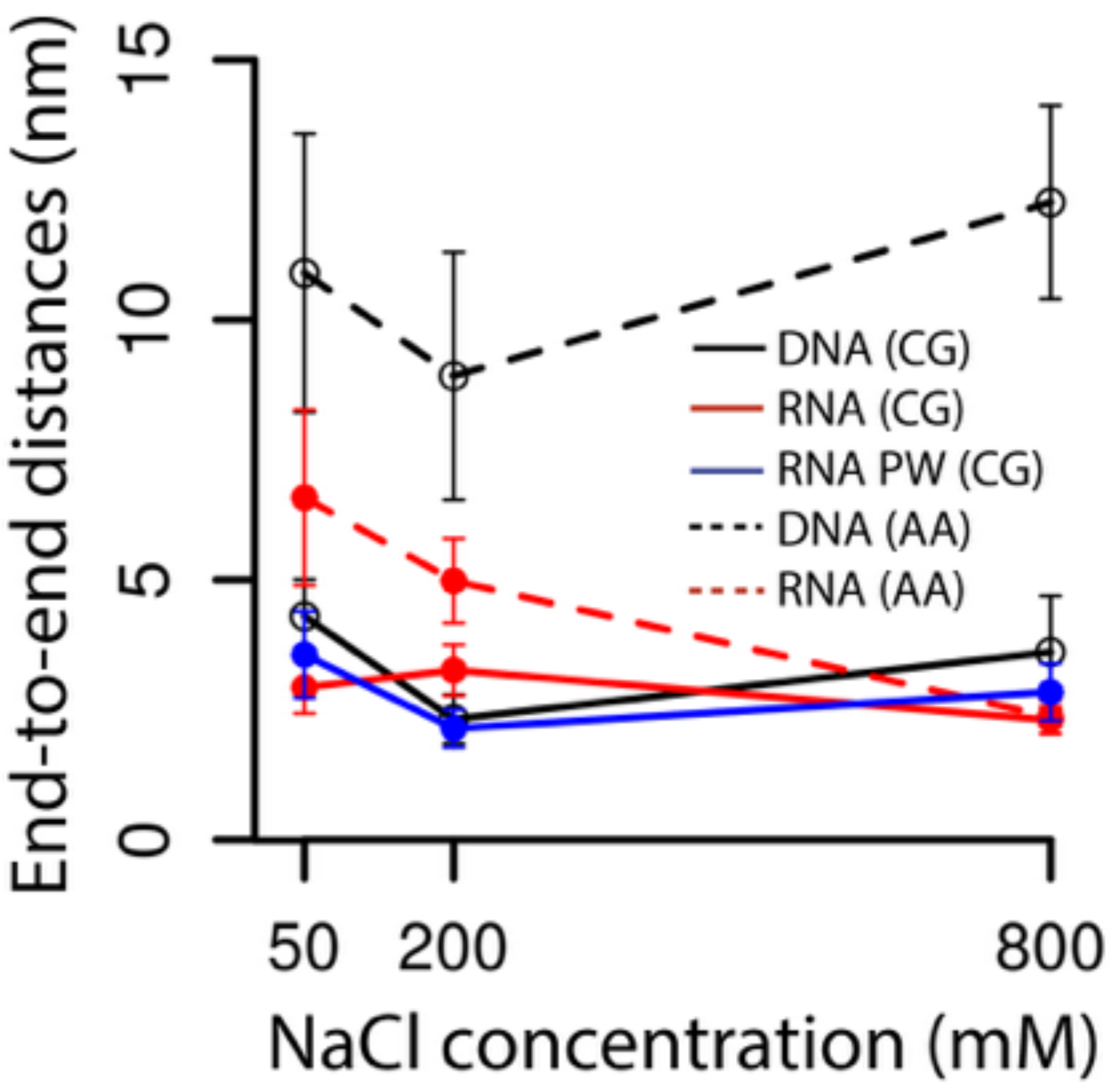
Martini and AA models give similar results

Lower radius of gyration for ss molecules (PW improves this trend)

Uusitalo, JJ *et al. Biophys J* 2017

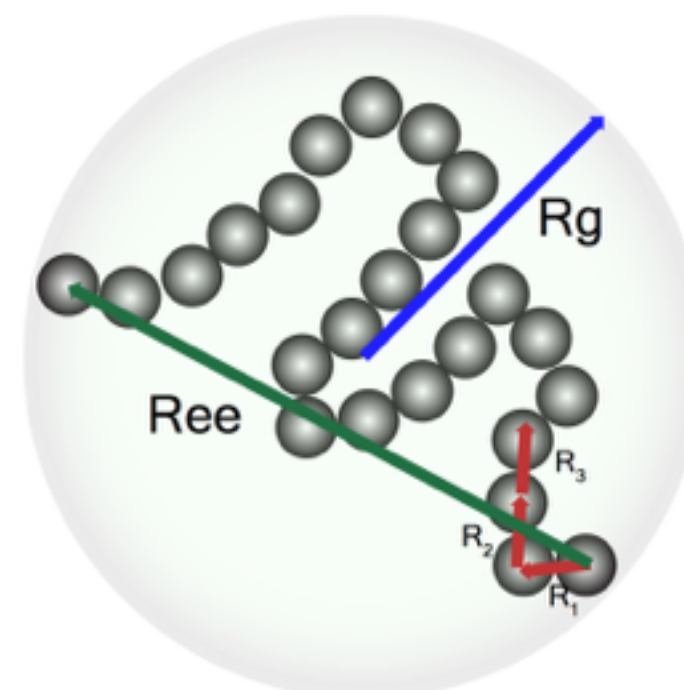
Validating the model for ss molecules

single strand molecules (ssDNA and ssRNA)



End-to-end distance:

$$\mathbf{R}(N) = \sum_{i=1}^{i=N} \mathbf{r}_i$$



Both AA and CG simulations
has little ionic concentration dependency

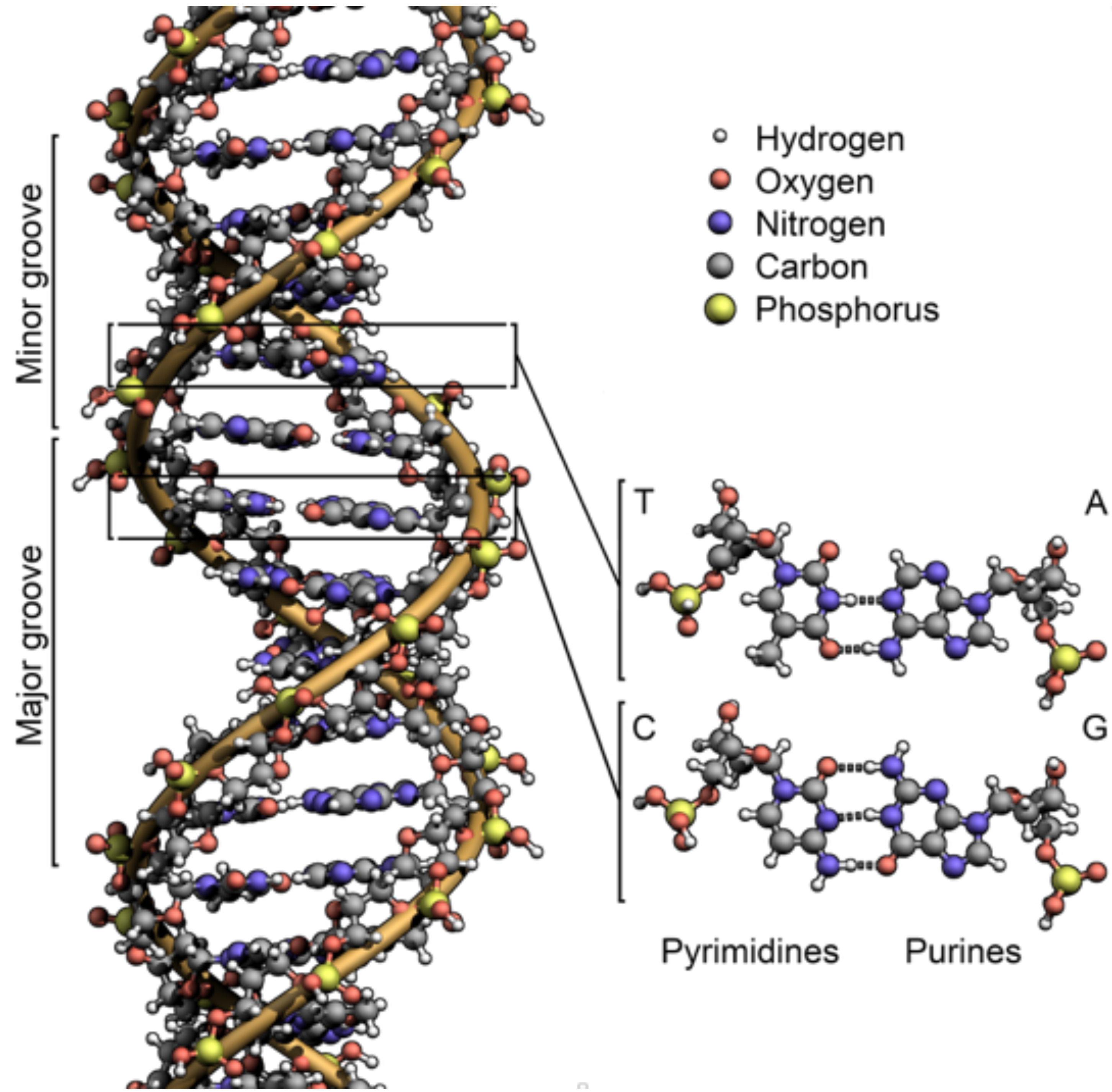
Uusitalo, JJ *et al. Biophys J* 2017

Validating the model for **ds molecules**
helical and structure descriptors

double helix

stores genetic code as a linear sequences of bases

sequence-dependent effects

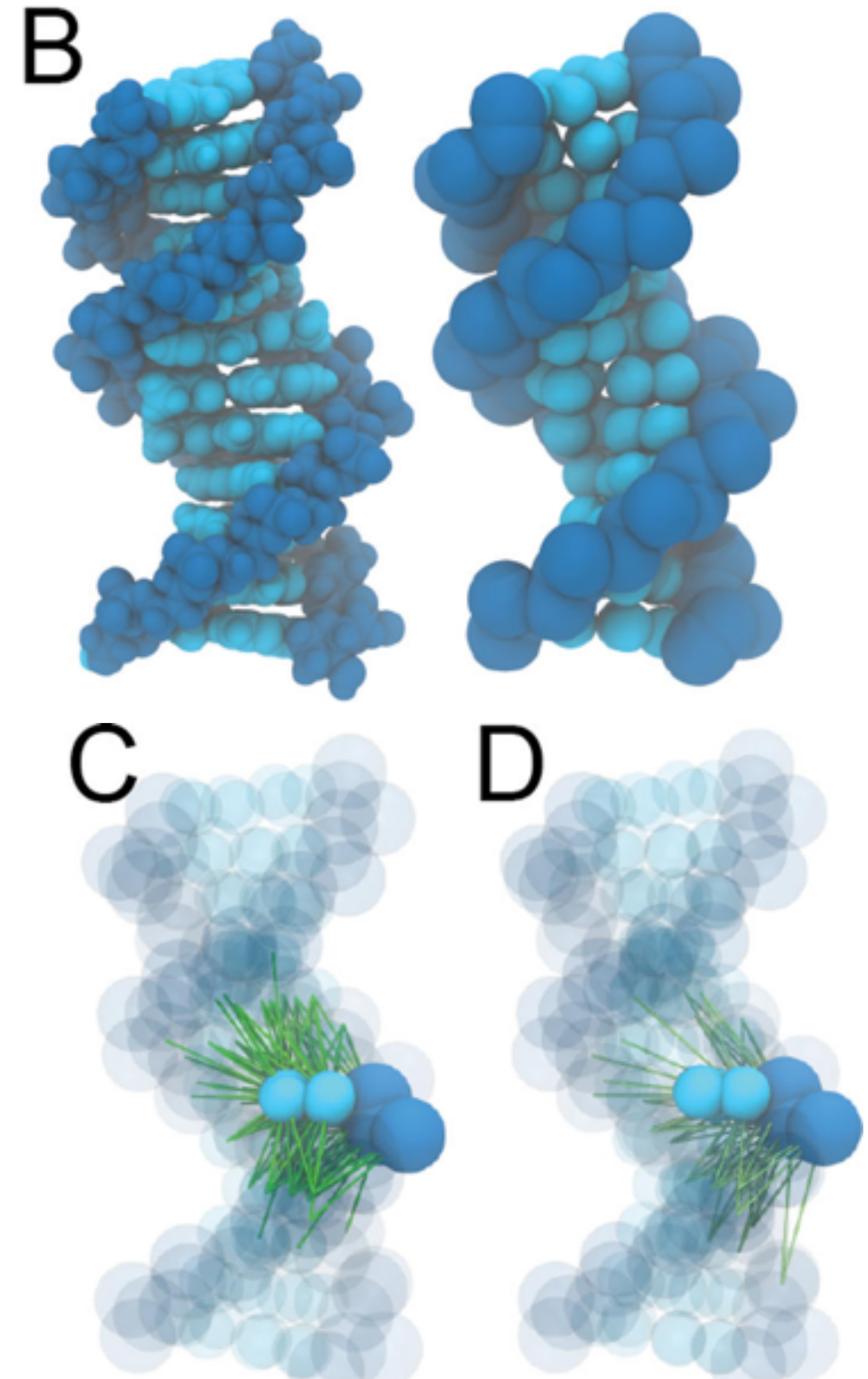


Elastic networks for ds molecules
keeping secondary structure

Stability requires an elastic network:

1. STIFF
   For rigid structures. 20 fs time step

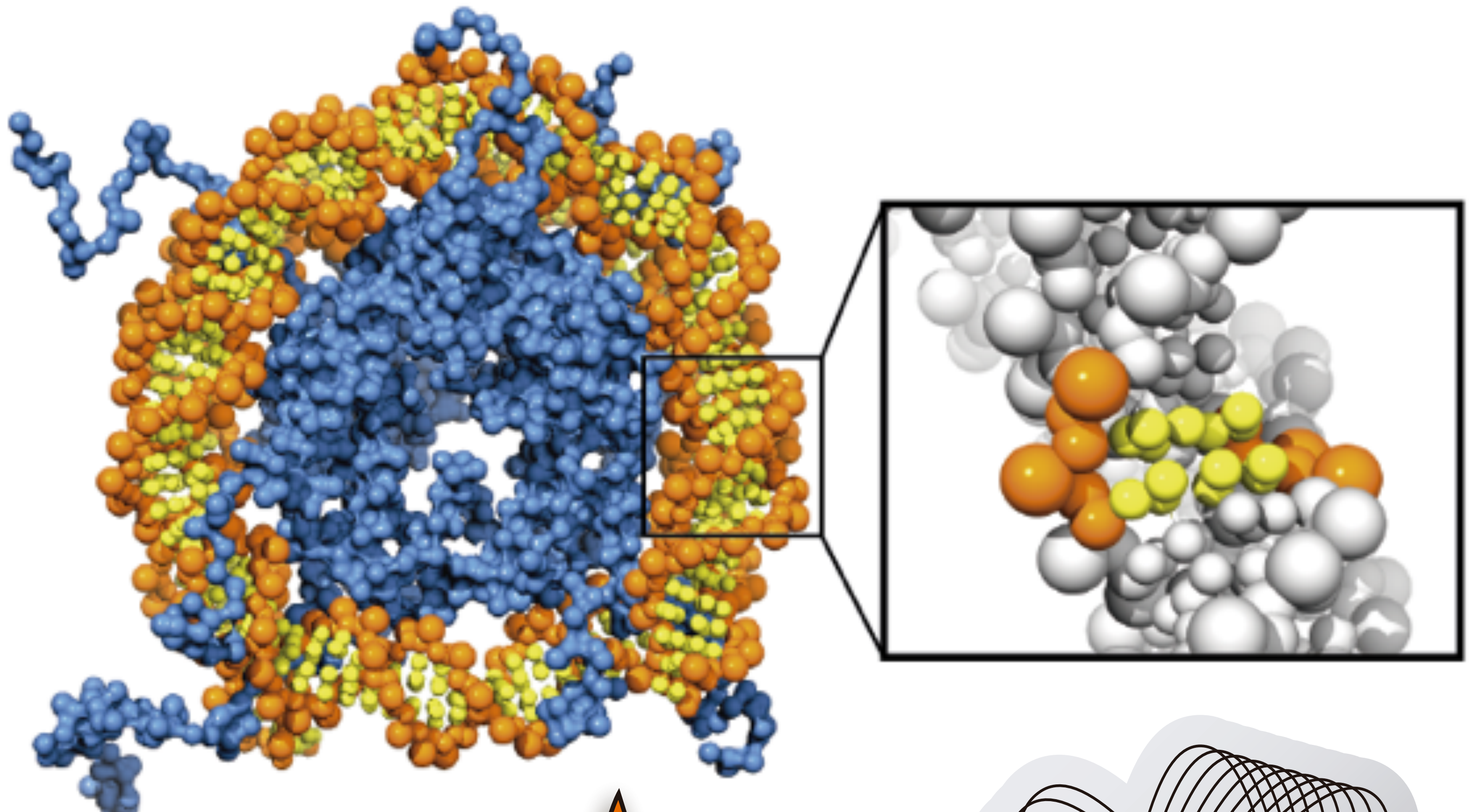
2. SOFT
   For more flexible structures. 10 fs is required

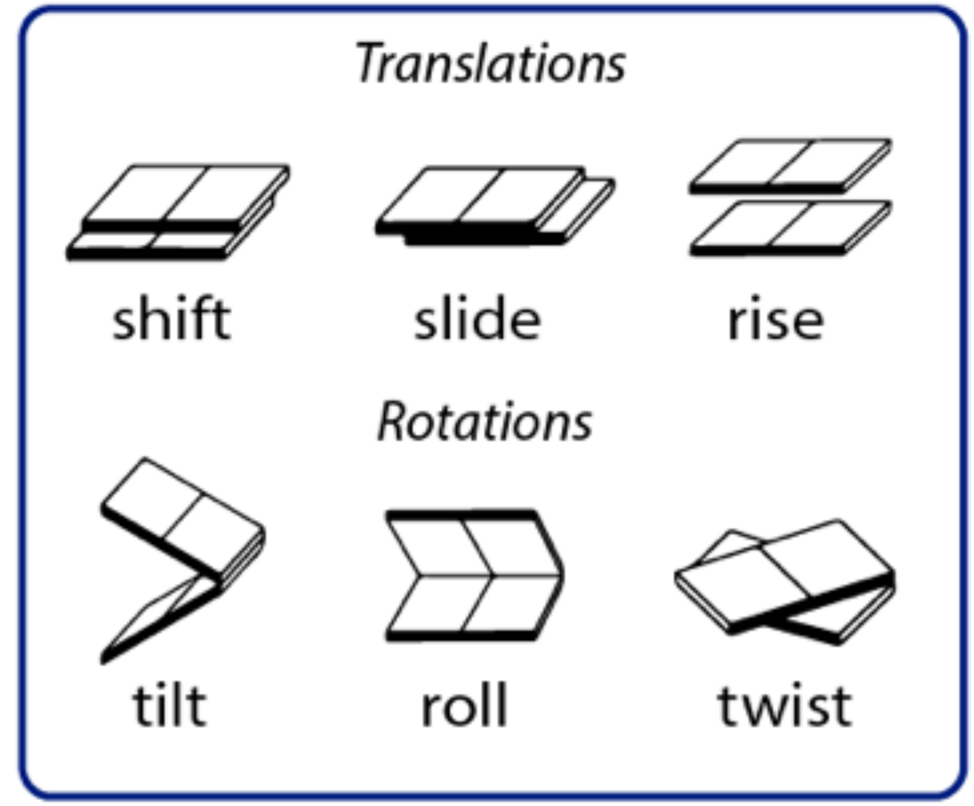


Validating the model for **ds molecules**

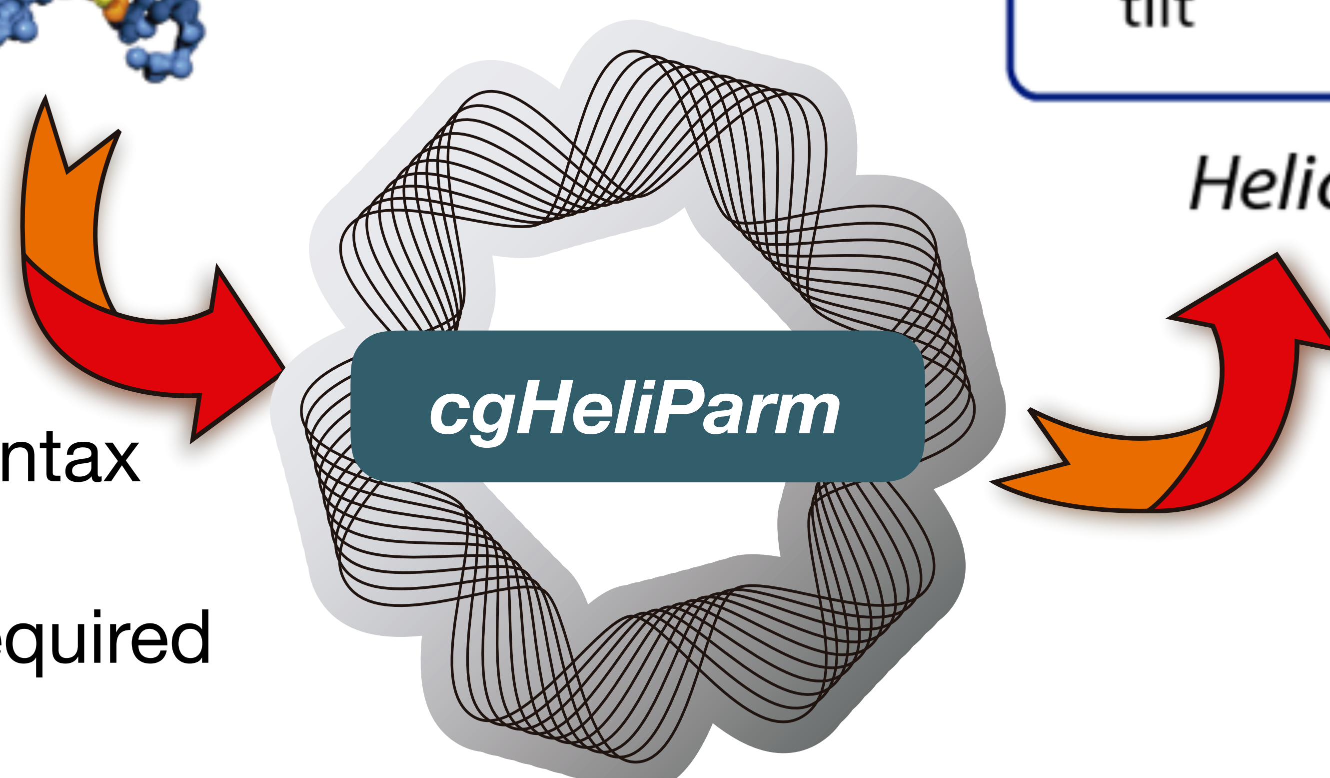
helical and structure descriptors

TUTORIAL





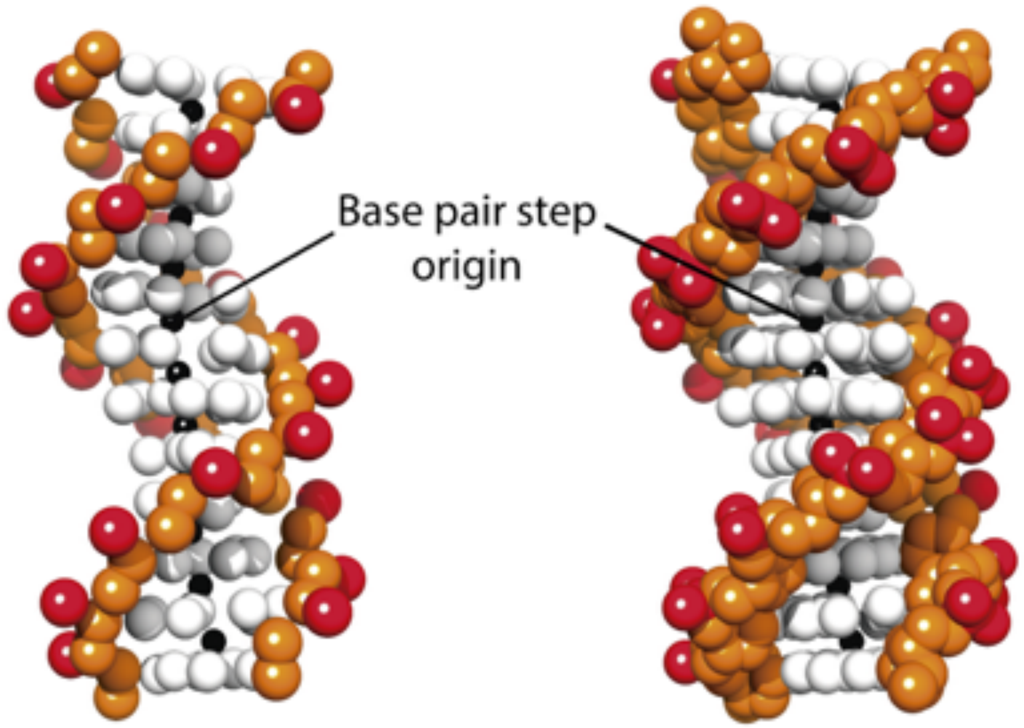
Helical parameters

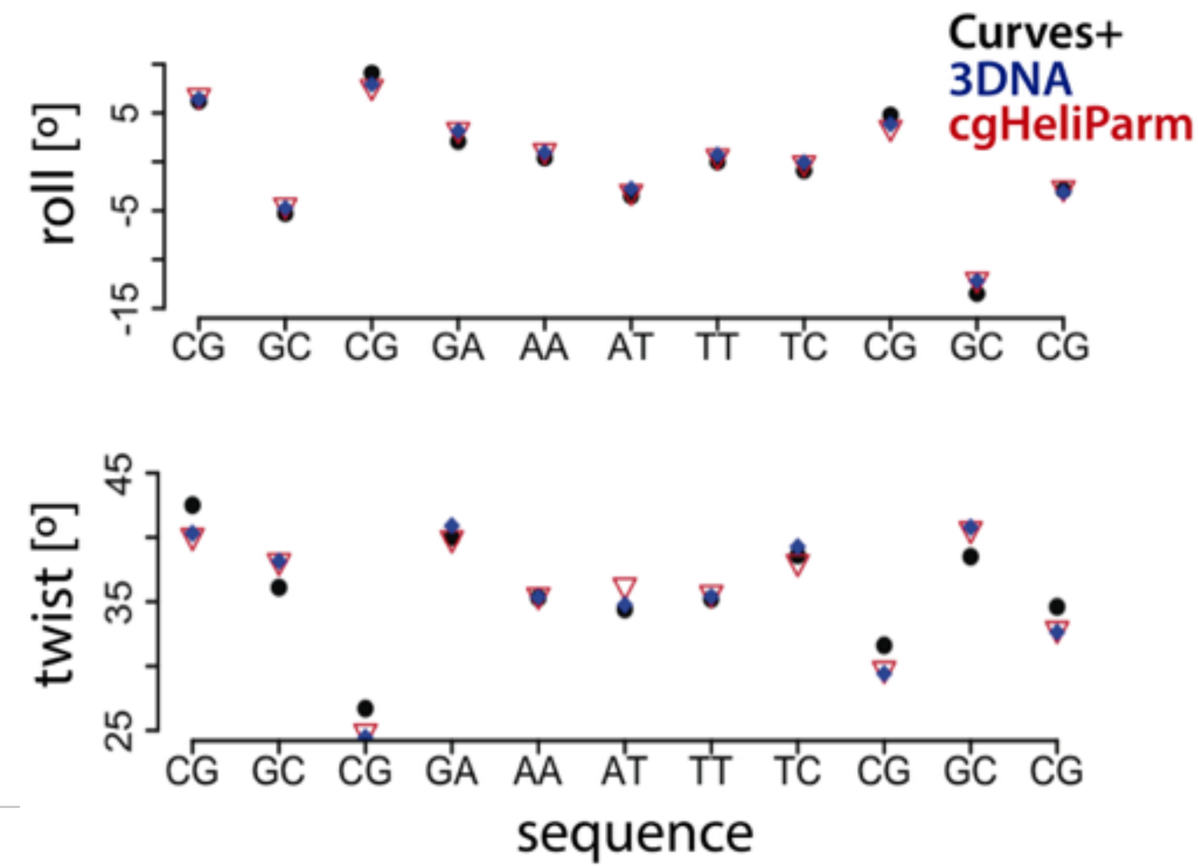


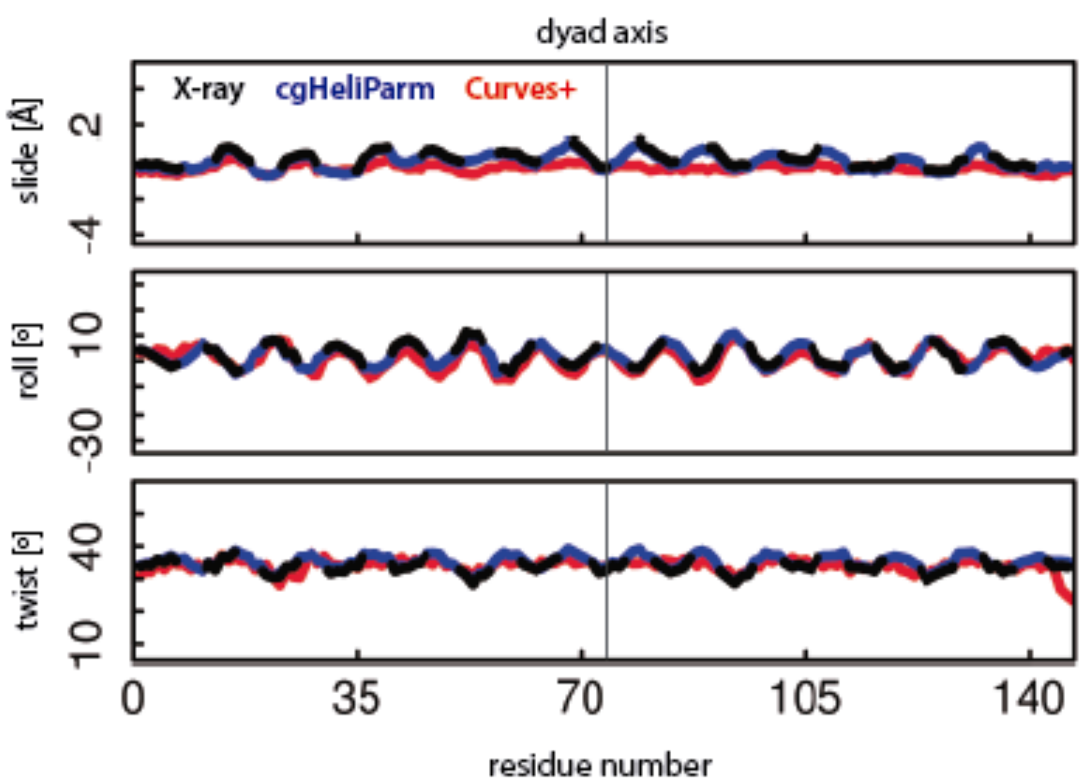
- Python script
- Gromacs tool syntax
- MDAnalysis is required
- Download https://github.com/ifaust83/cgheliparm

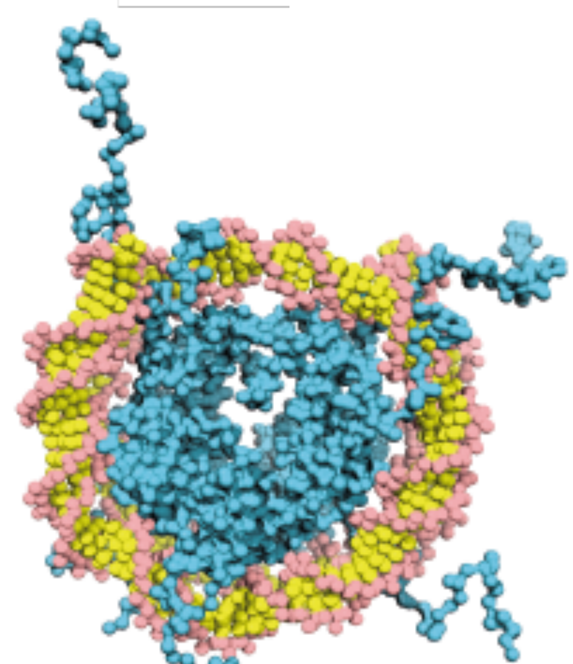
Faustino, I., Marrink, S.J. *Bioinformatics* 2017

Validating the model for **ds molecules**
helical and structure descriptors









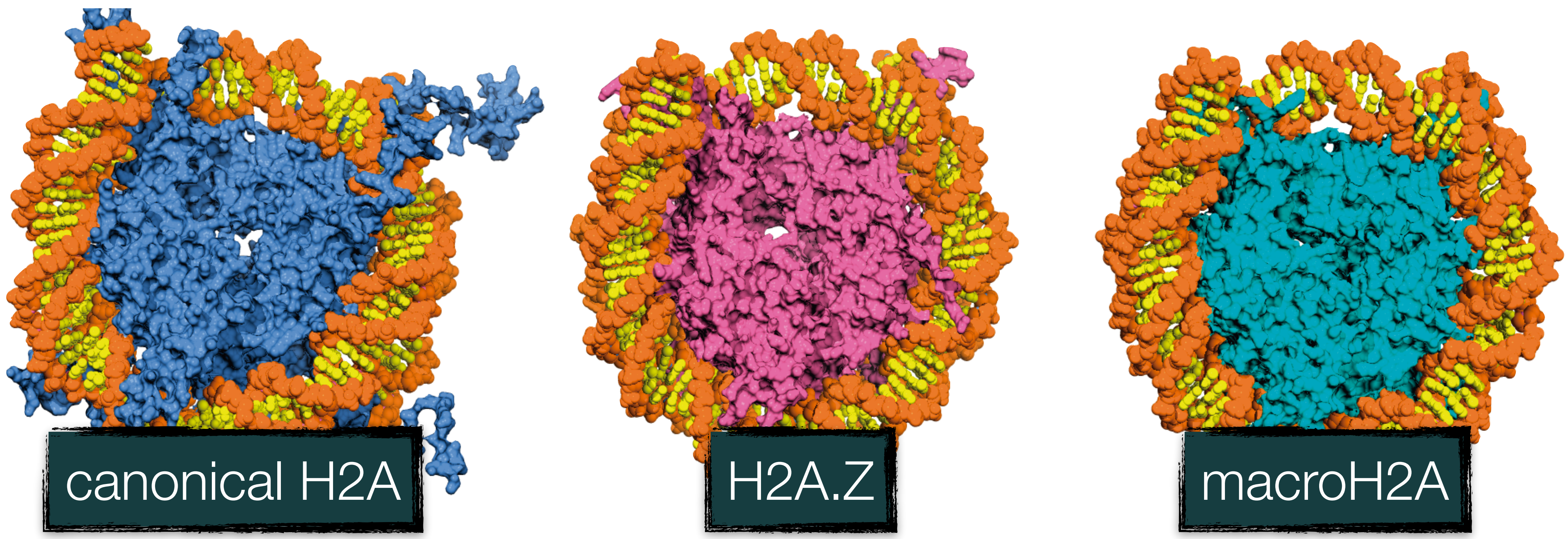
Similar results to AA-based algorithms

Application to bigger systems and longer simulations

Faustino, I., Marrink, S.J. *Bioinformatics* 2017

Validating the model for flexibility of **ds molecules**

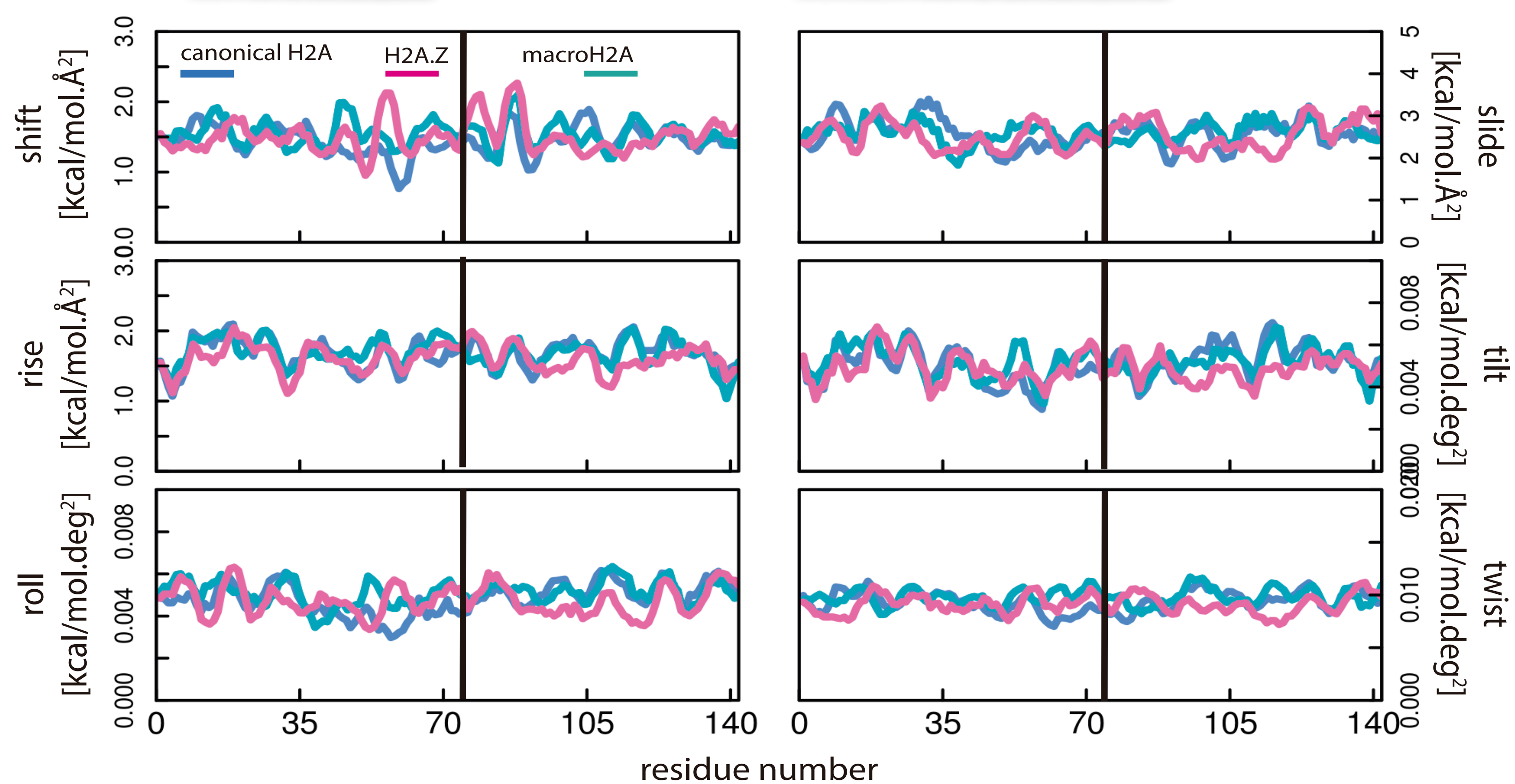
case study: histone variants and DNA flexibility



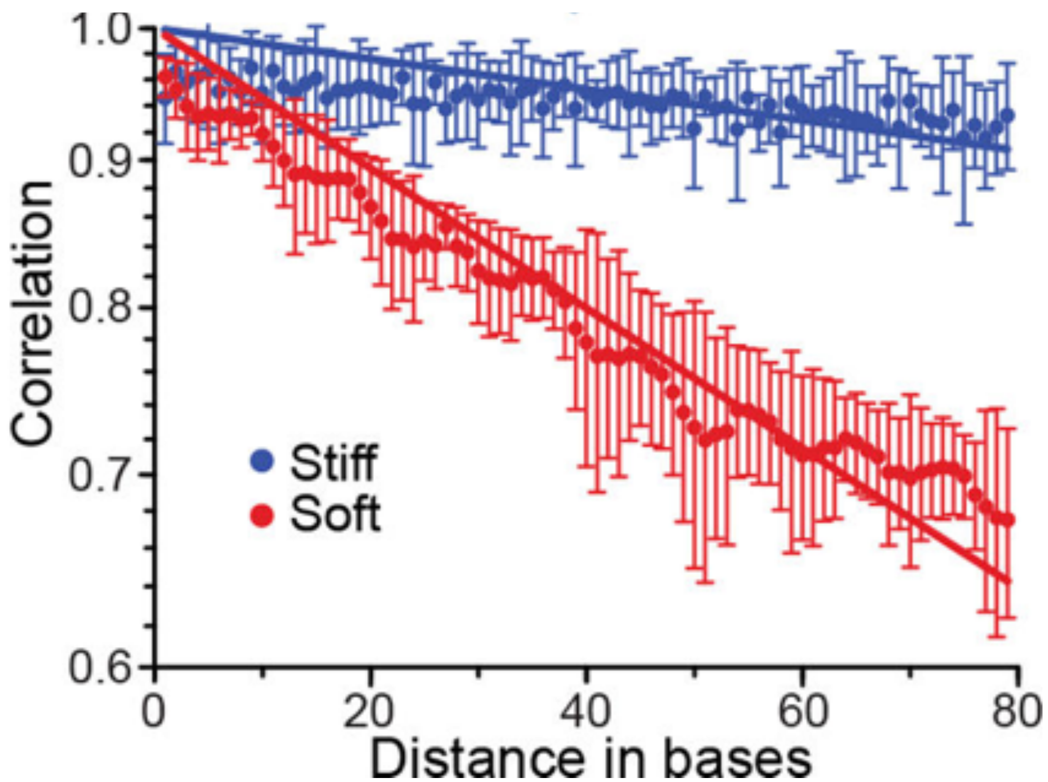
Major differences around the dyad axis

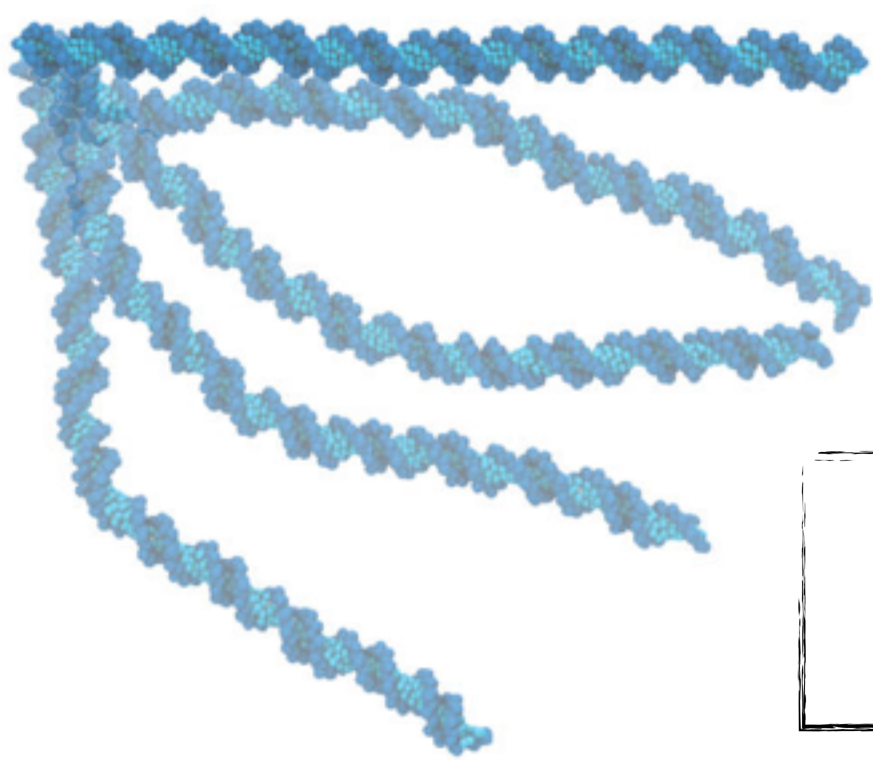
macroH2A associated to stiffer DNA motions

H2A.Z loosens the bound DNA



Validating the model for ds molecules
comparing the global flexibility





Persistence length of a polymer:

$$\langle n_i \cdot n_0 \rangle = e^{-i\langle L_0 \rangle / L}$$

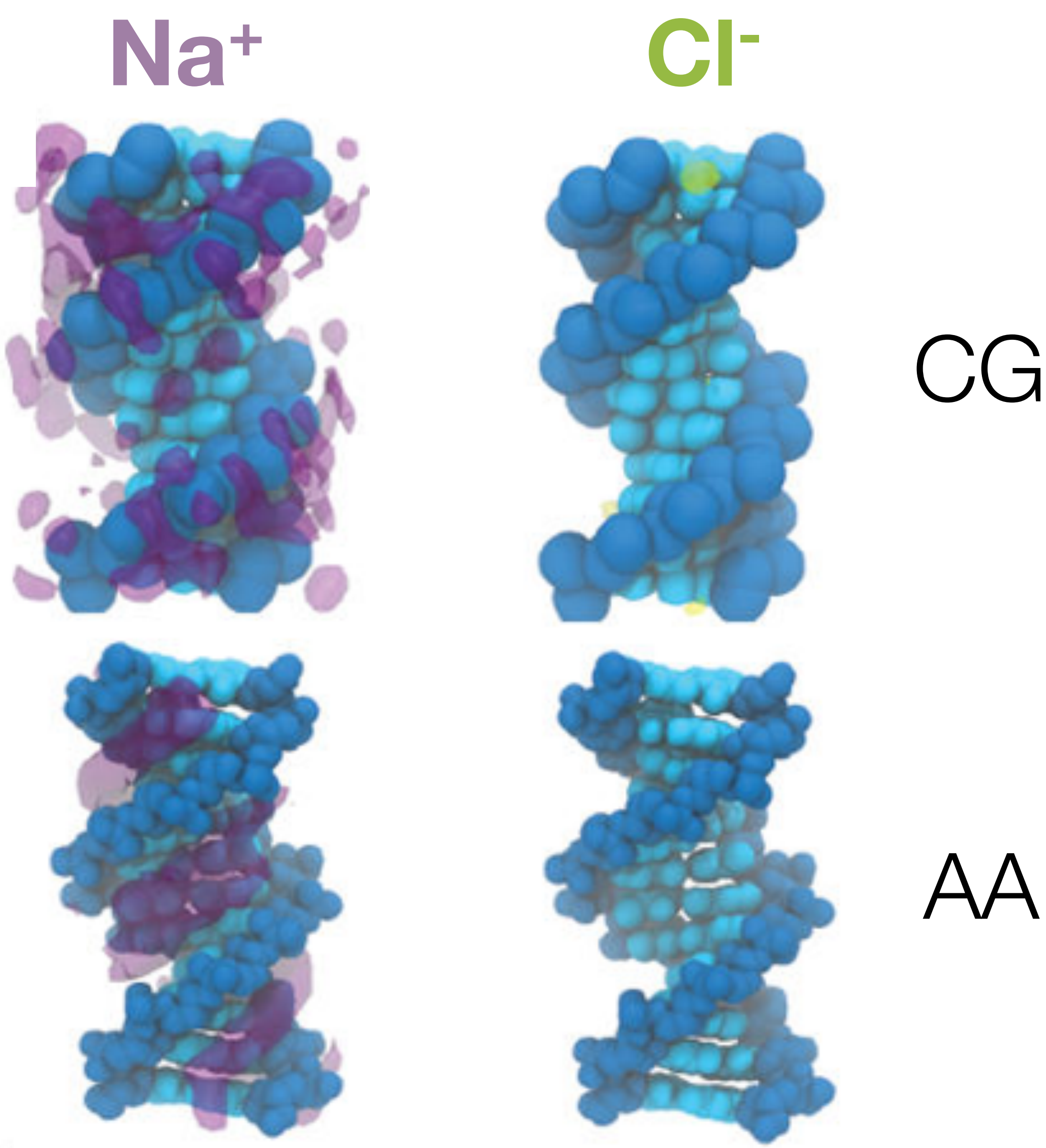
Experimentally about 50 nm for DNA and between 58-80 nm for RNA

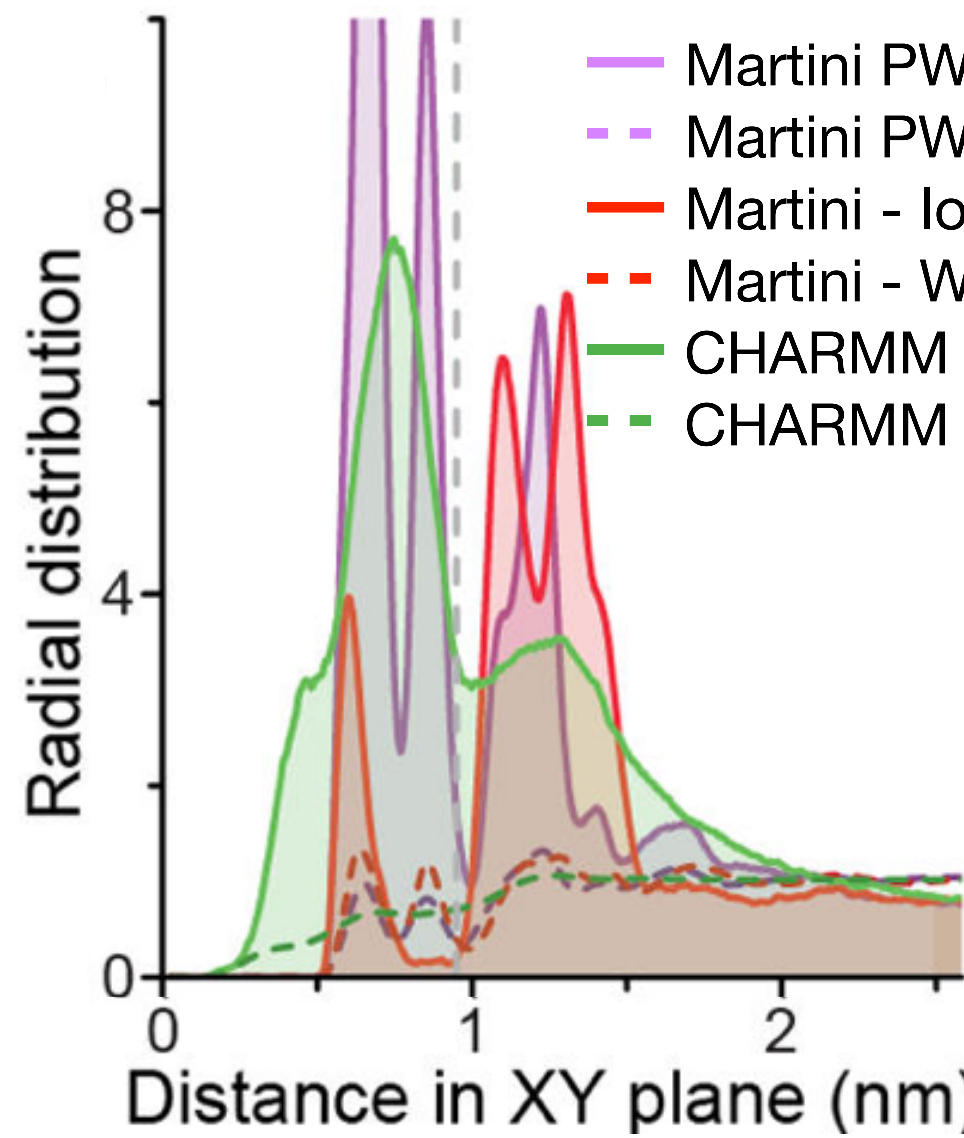
in nm	Persistence length (Soft)	Persistence length (Stiff)
dsDNA	50 ± 6	206 ± 53
dsRNA	62 ± 10	208 ± 52

The soft model is a more realistic model

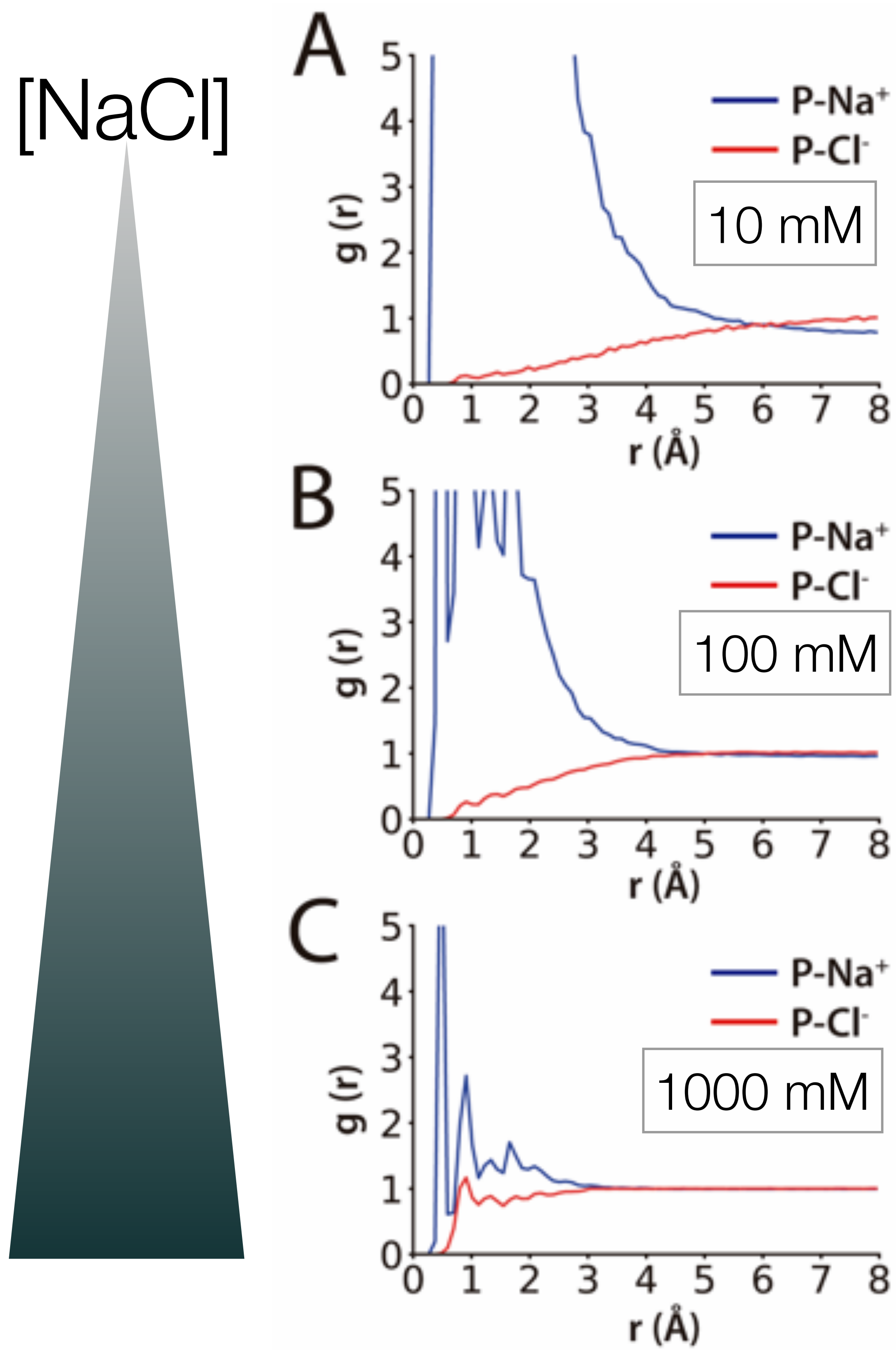
Interactions with other molecules
specific binding of ions

Na+ ions localize further away from DNA than in AA, due to CG bead size





Interactions with other molecules
non-specific binding of ions



Counterion atmosphere around dsRNA correctly reproduced

Agreement with BE-AES experiments:

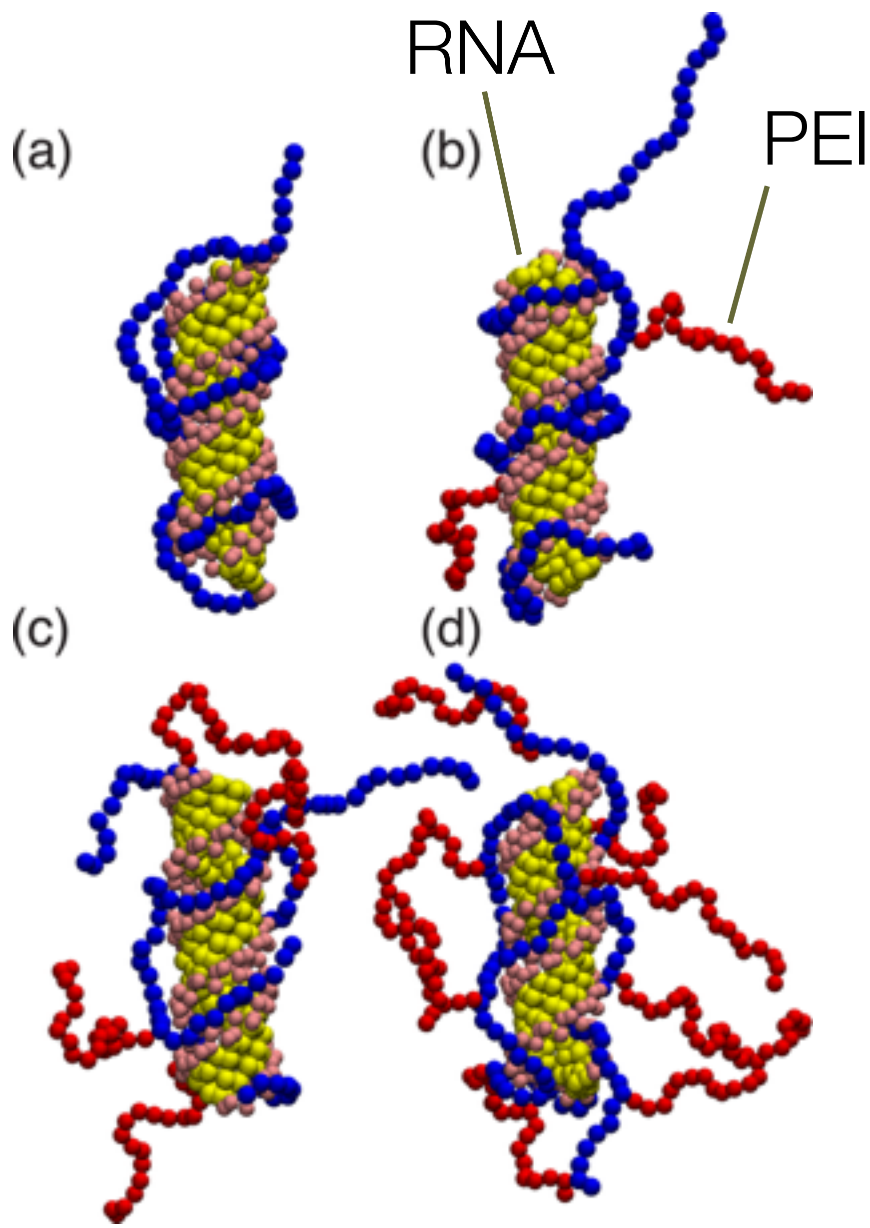
- Accumulation of positive ions
- Depletion of negative ions

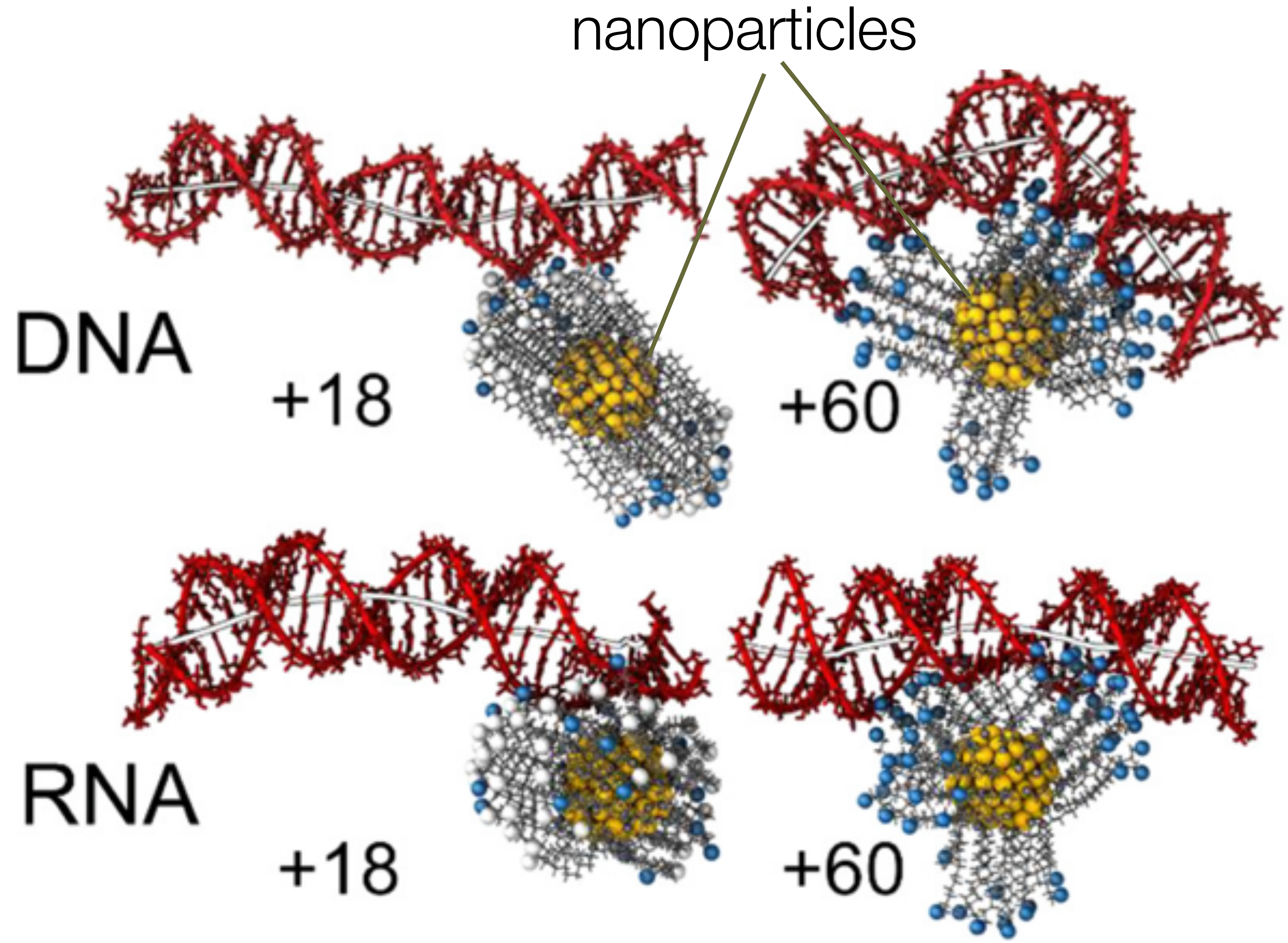
[NaCl] (mM)	$\Gamma_{(Na^+)}$	$\Gamma_{(Cl^-)}$	$\Gamma_{(Na^+)} + \lvert\Gamma_{(Cl^-)}\rvert$
10	15.8 ± 2.0	-1.0 ± 0.8	16.9 ± 2.1
100	19.8 ± 3.1	-3.9 ± 2.9	23.9 ± 3.0
1000	20.8 ± 7.5	-4.4 ± 7.4	27.9 ± 7.0

Values corresponding to a 14 bp dsRNA (-26e)

Uusitalo, JJ *et al. Biophys J.* 2017

Other applications

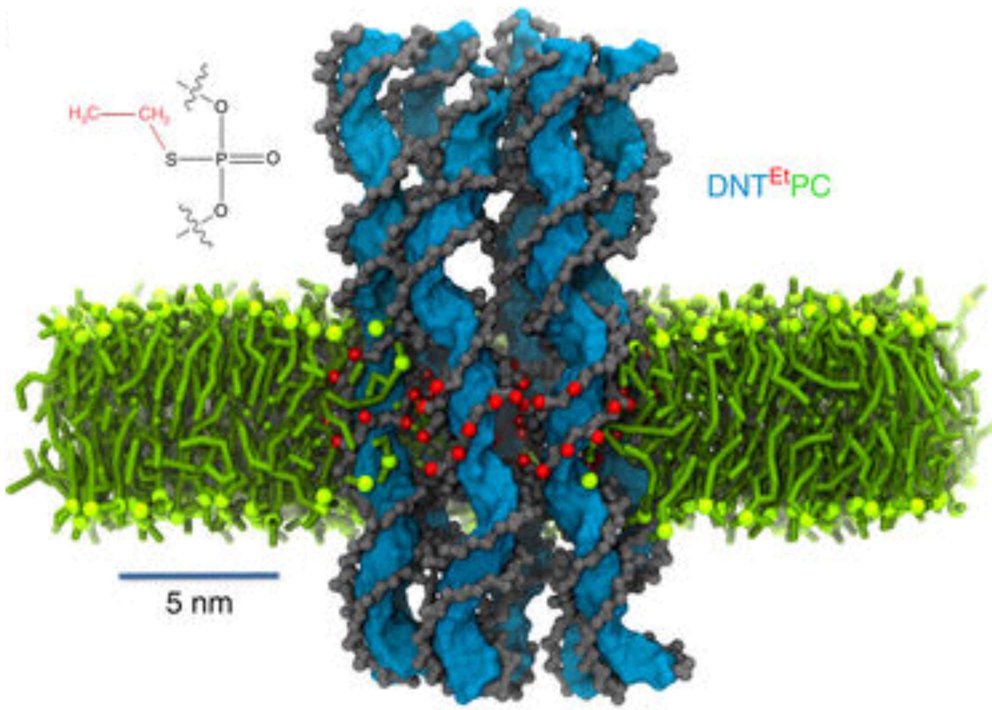




Drug delivery systems

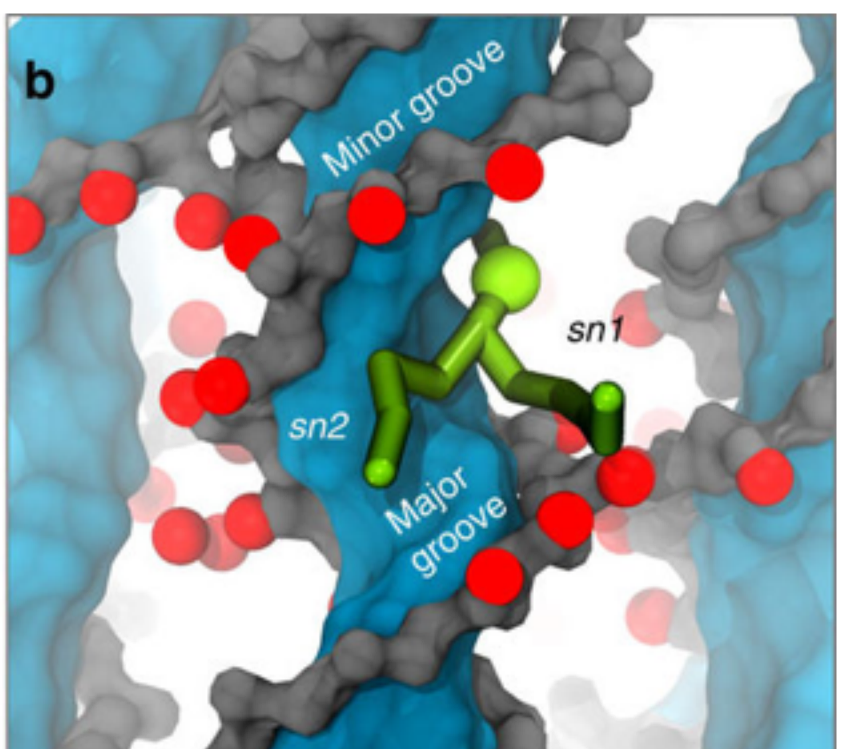
Wei, Z *et al*. *J Chem Phys.*, **2015**, 143 (24)
Nash, JA *et al*. *Bioconjugate Chem.*, **2017**, 28 (1)

Other applications



Nanotechnology

CGMD reveals that the lipids reorganize locally to interact closely with the membrane-spanning section of the DNA tube



Differences in gating properties showed at different ion concentrations

Potential applications in the design of the next generation of nanotubes

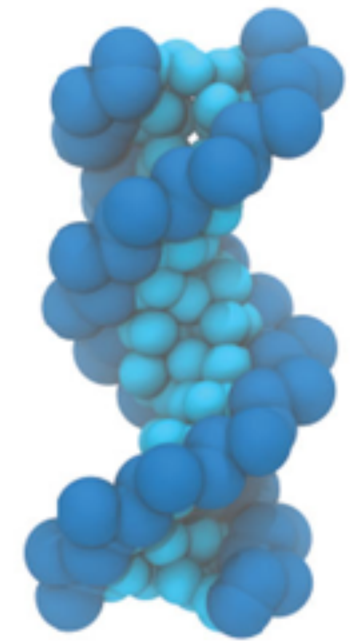
Maingi, V., *et al*. *Nat Commun*. **2017**. 8: 14784

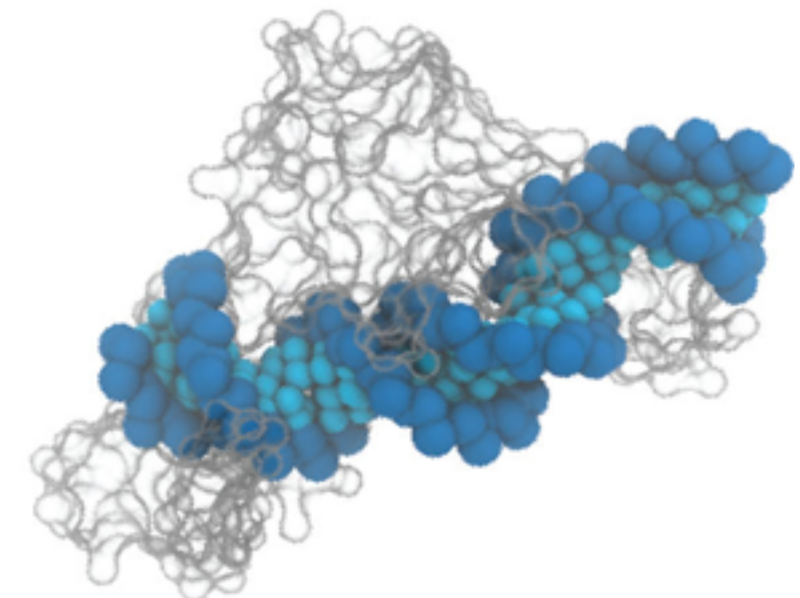
University of Groningen

JU Uusitalo

HI Ingolfsson

SJ Marrink

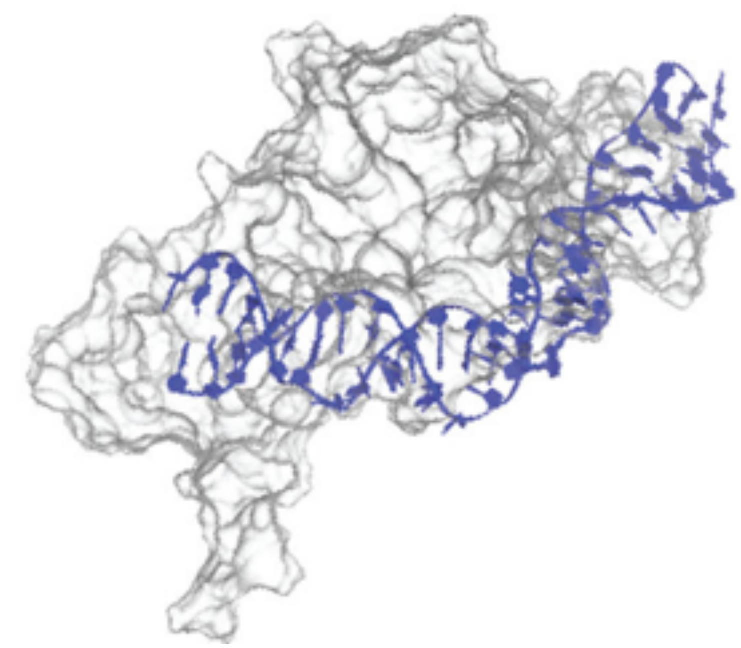




University of Calgary

P Akhshi

DP Tieleman



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Martini

Coarse Grain Forcefield for Biomolecules

More on how to build and analyze your DNA/RNA molecule

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