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Conference on Molecular Aspects of Cell Biology: A Perspective from Computational Physics

11 - 15 October 2010

Simplified Models to Simulate DNA Dynamics

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Simplified Models to Simulate DNA Dynamics

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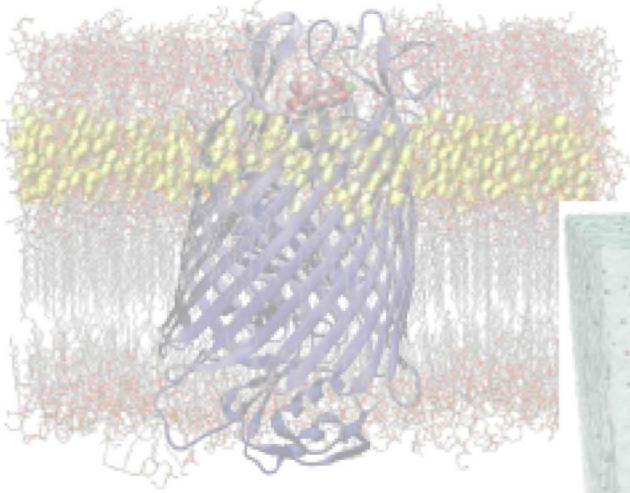
fs | 100 fs - ps | μs | ms

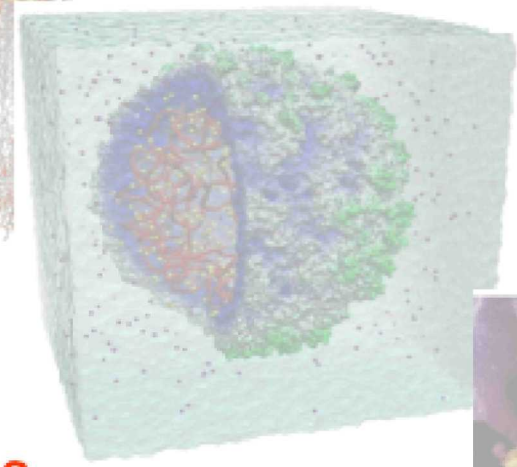
Electronic exitations | Vibrations | Rotations | Conformational Transitions

Small molecules
~ 1.000 atoms

Macromolecular complexes
~ 50.000 to ~ 1.000.000 atoms



Virus
several millions of atoms



Bacteria/cells?
7e+9 carbon atoms

ps

e-tranfer reactions | Enzymatic reactions

ns | μs - s

Peptide folding | Protein folding

μs

DNA melting

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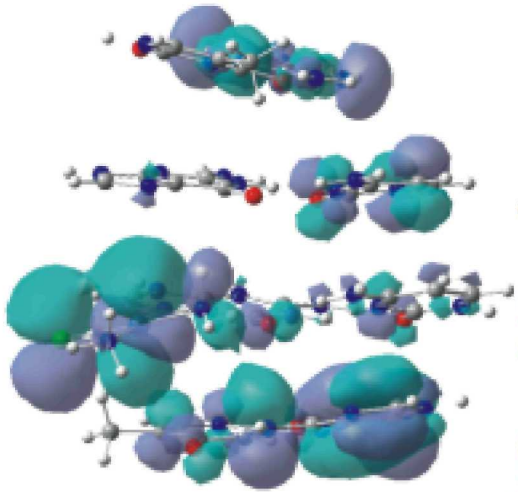
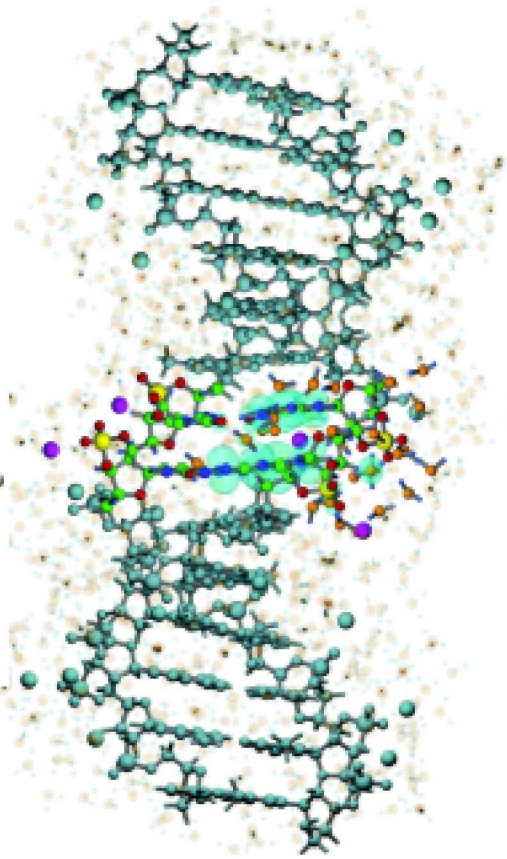


Quantum Mechanics

Dozens to hundreds of atoms

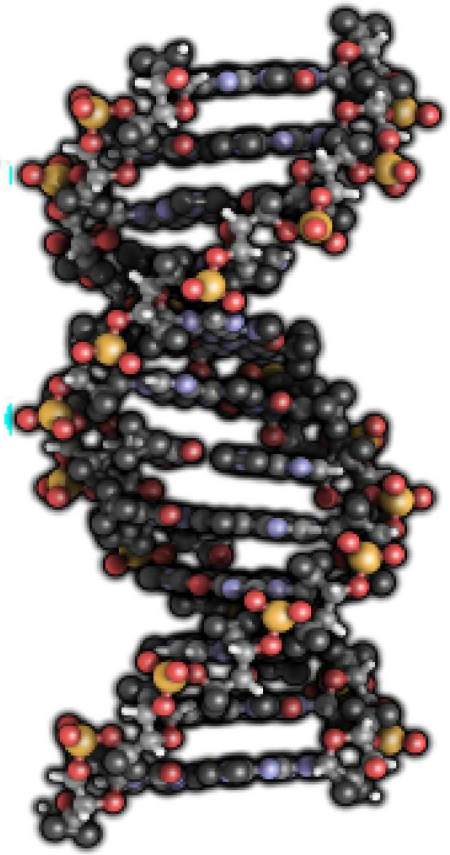
Few ps



QM/MM

Dozens to thousands of atoms

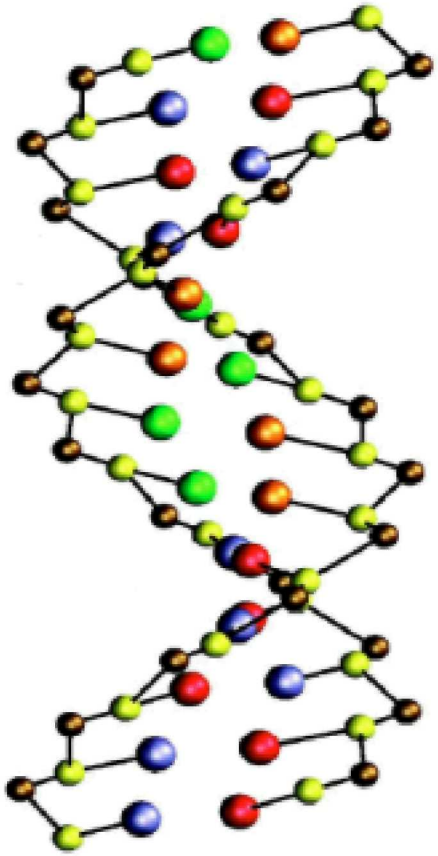
Dozens of ps



Molecular Mechanics/Dynamics

Thousands to (if) few millions of atoms

Hundreds of ns to μs



Coarse Grained

Millions of "atoms"

μs to ms

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Coarse Grain Methods:

1.Mapping

R = T • r

2. Parameters

(Systematic Derivation)

1. Boltzmann Inversion
2. Iterative MonteCarlo
3. Force Matching
4. Etc.

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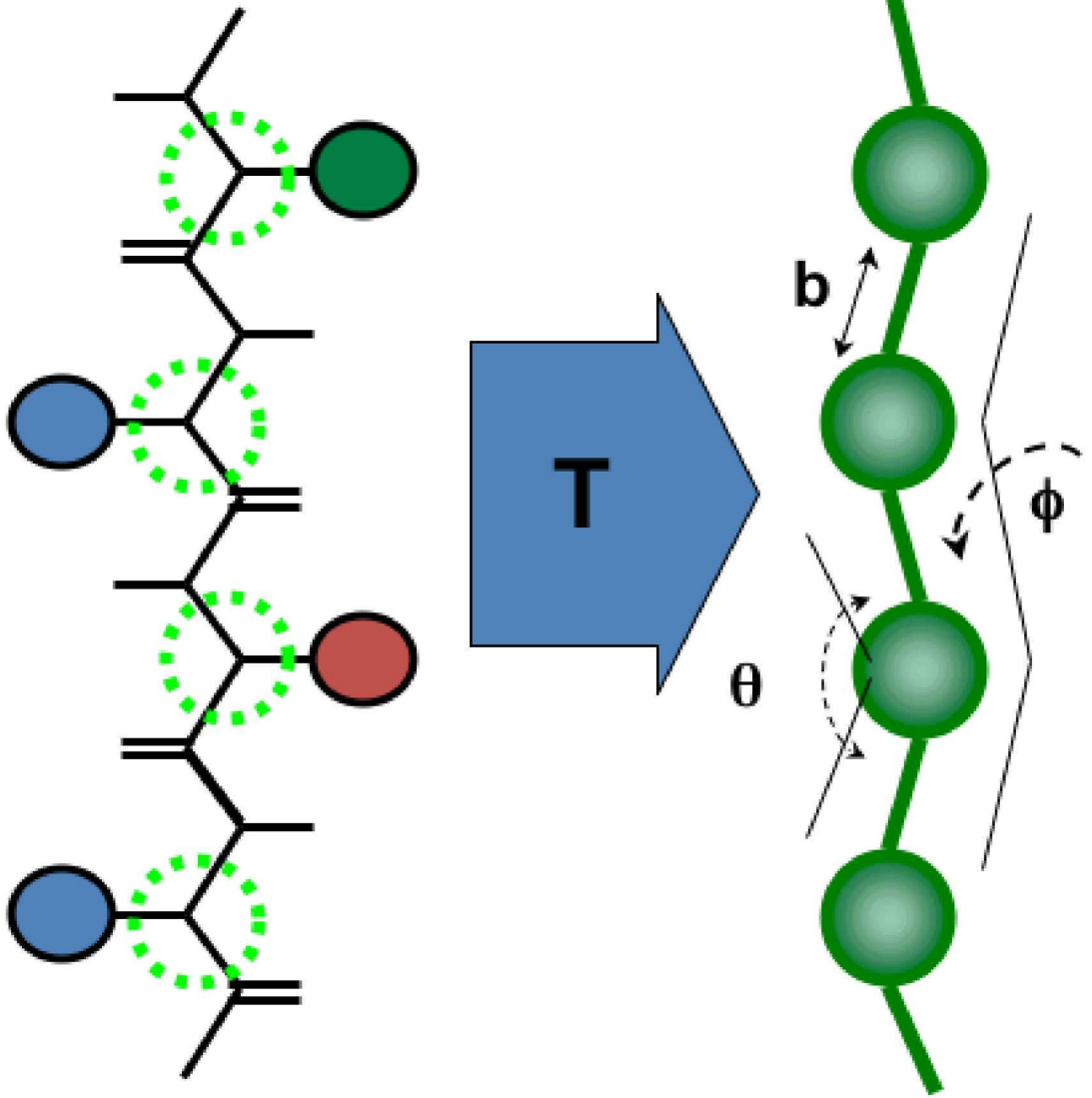
AA → CG Mapping:

Hypothesis:

$\mathbf{r}_{(i)}$ (high detail)

$\mathbf{R}_{(j)}$ (low detail)

$$\mathbf{R}_{(j)} = \mathbf{T} \cdot \mathbf{r}_{(i)}$$



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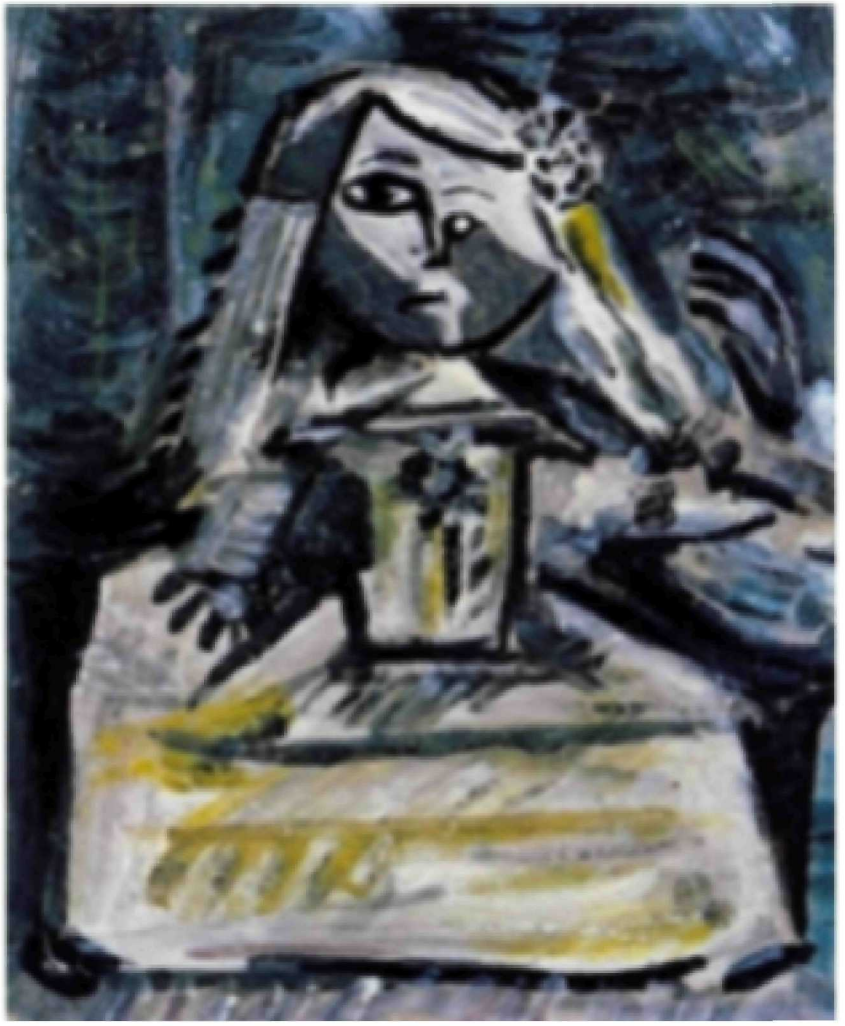
"Las Meninas"

Diego Velázquez 1656



Pablo Picasso 1957

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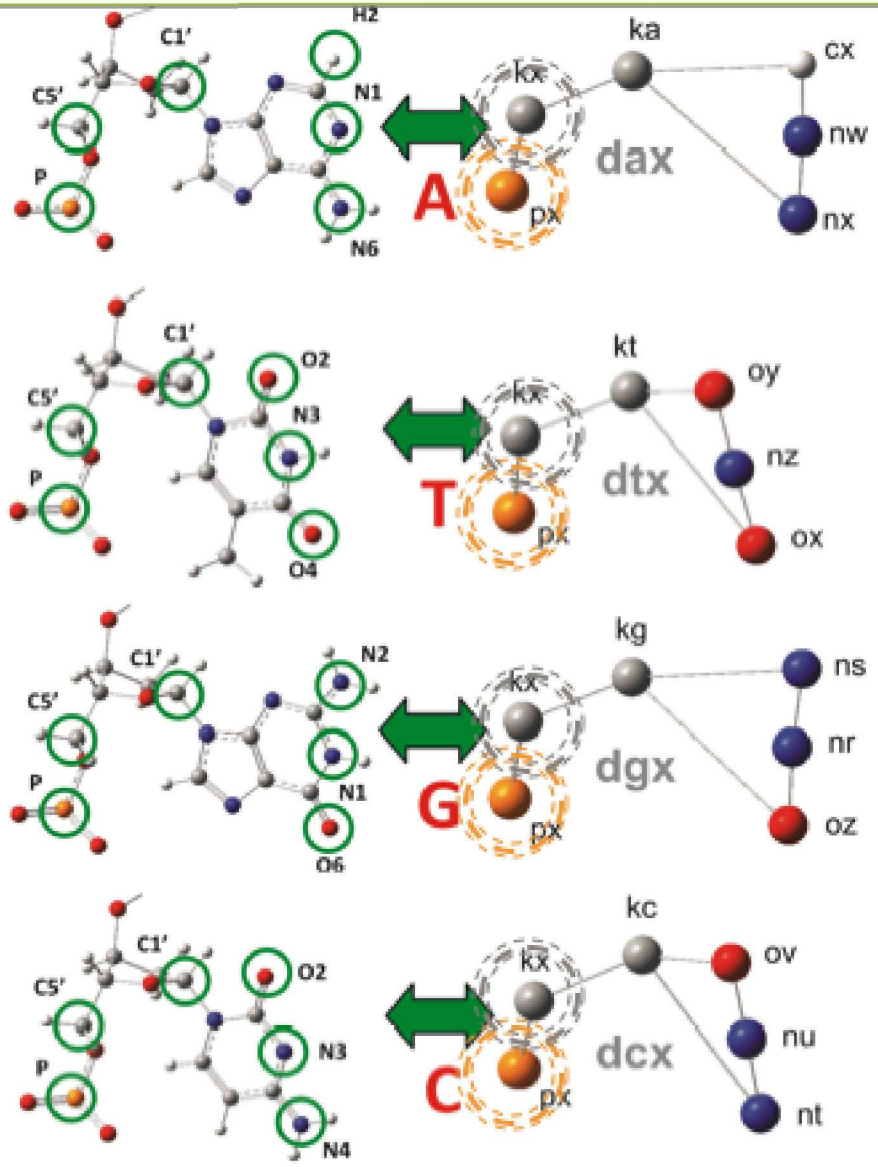
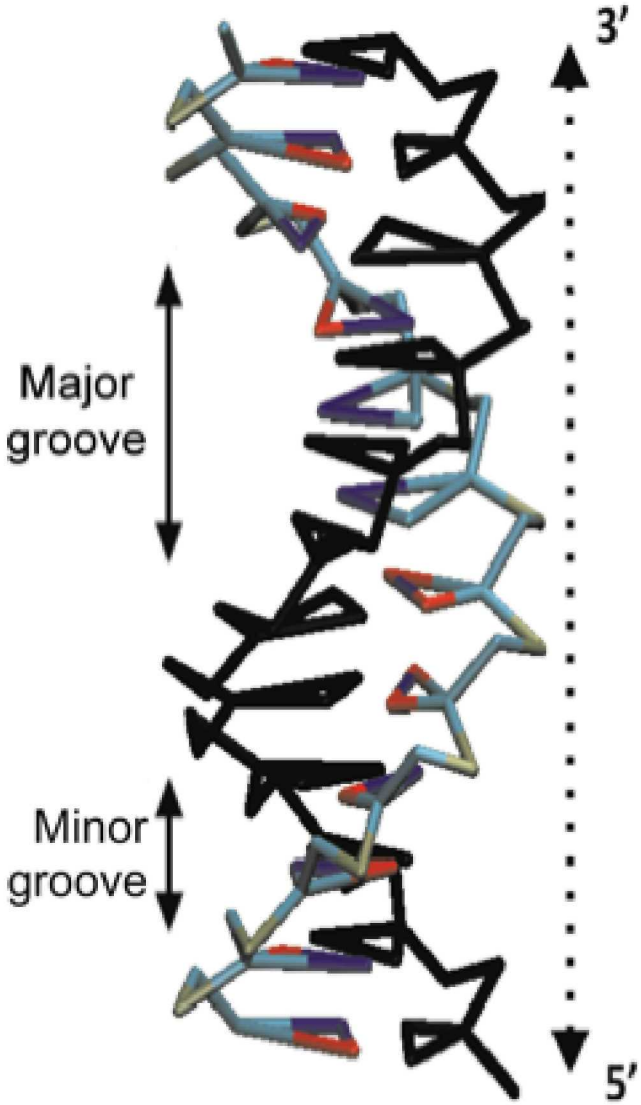
CG and Mapping / Back-mapping scheme





Dans et al JCTC 2010

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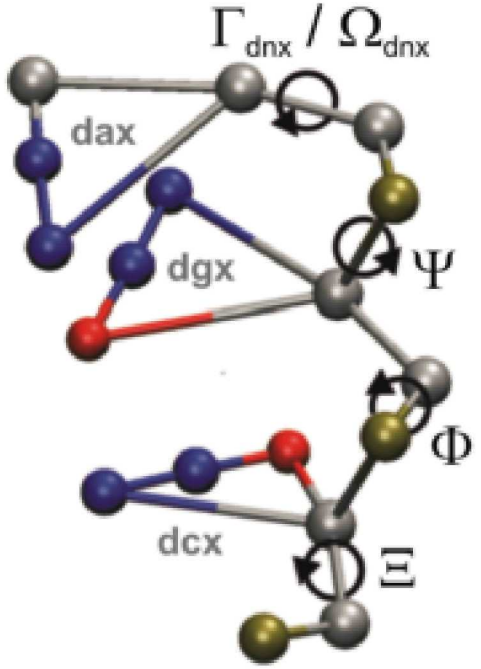
Classical Hamiltonian for Interactions (Plug & Play)

$$U = \sum_{bonds} k_b \left(r_{ij} - r_{eq}\right)^2 + \sum_{angles} k_\theta \left(\theta - \theta_{eq}\right)^2 + \sum_{dihedrals} \frac{V_n}{2}\left[1 + \cos\left(n\phi - \gamma\right)\right]$$

$$+ \sum_{i}^{atoms} \sum_{j>i}^{atoms} \left\{ 4\varepsilon \left[\left(\frac{\sigma}{r_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}}\right)^{6} \right] + \frac{q_i q_j}{\in r_{ij}} \right\}$$

Electrostatics via Generalized Born model for implicit solvation

Harmonic Interactions for Bonding terms (four Dihedral angles)



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Classical Hamiltonian for Interactions (Plug & Play)

Parameters Available:

Bonds **1 €**

Angles **5 €**

VdW **50 €**

Electrostatic **500 €**

Torsional terms **50000 €**

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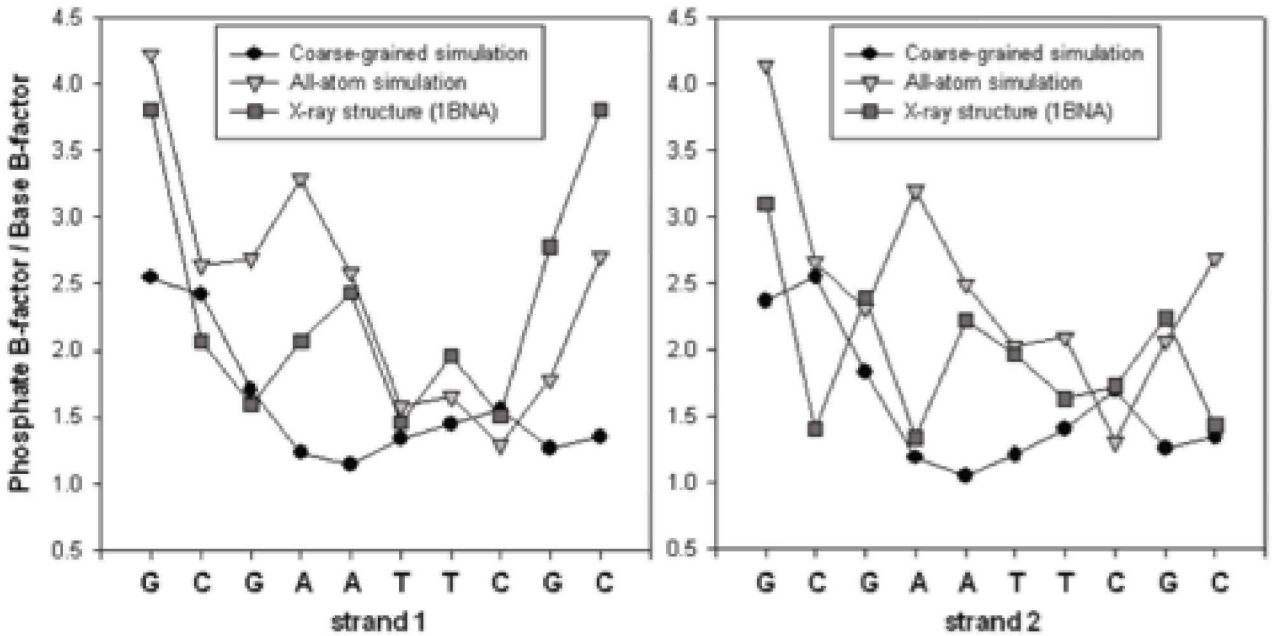
Structure and Dynamics

Table 3. Structural comparison between CG and all-atoms simulations. RMSD are calculated over 5 μs and 50 ns for the CG and all-atoms trajectories, respectively. Values are reported in Angstroms.

	Mean during MD trajectory	Starting conformer (B form)	X-ray (1BNA)	NMR (2DAU)
Coarse-Grain	1.0 ± 0.3	1.8 ± 0.3	2.3 ± 0.3	3.1 ± 0.3
All-Atoms	1.6 ± 0.4	2.8 ± 0.4	2.6 ± 0.4	2.7 ± 0.4



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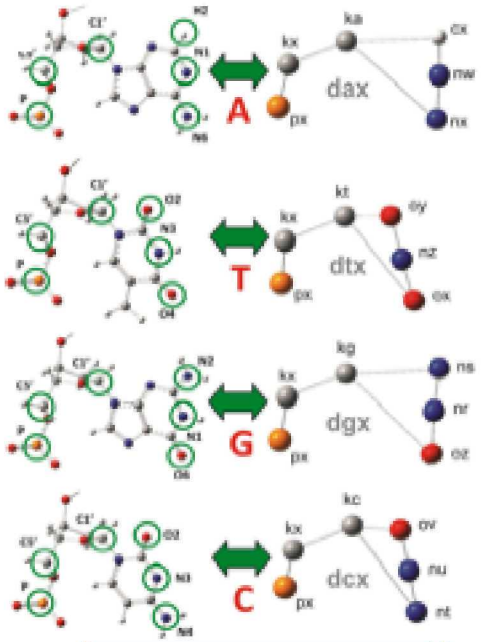
Back-Mapping

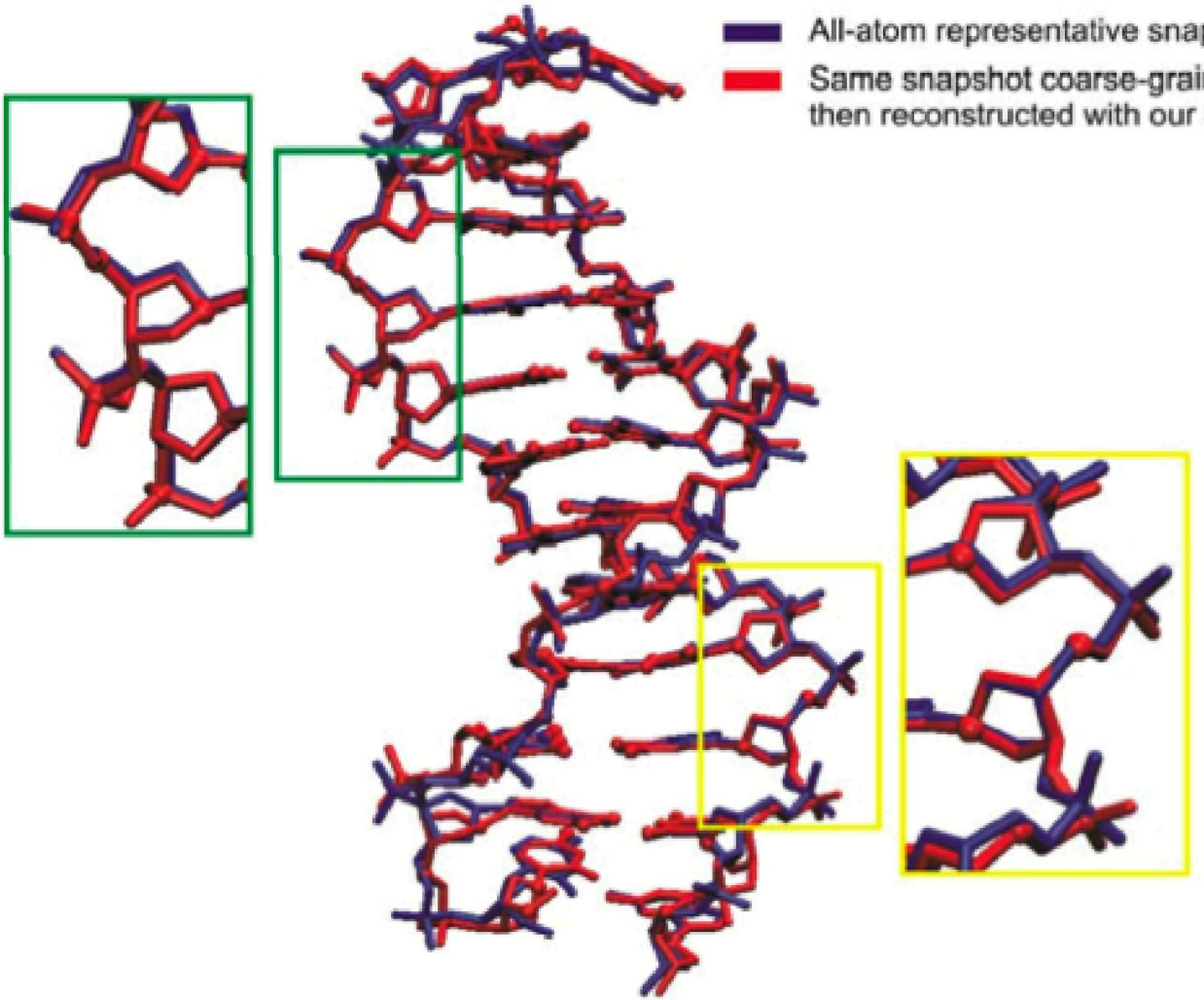


Mapping

Back-Mapping

Minimization

RMSD Fitting



Accuracy of the reconstruction in terms of RMSD = 1.0 ± 0.1 Å
(calculated over 1000 structures)

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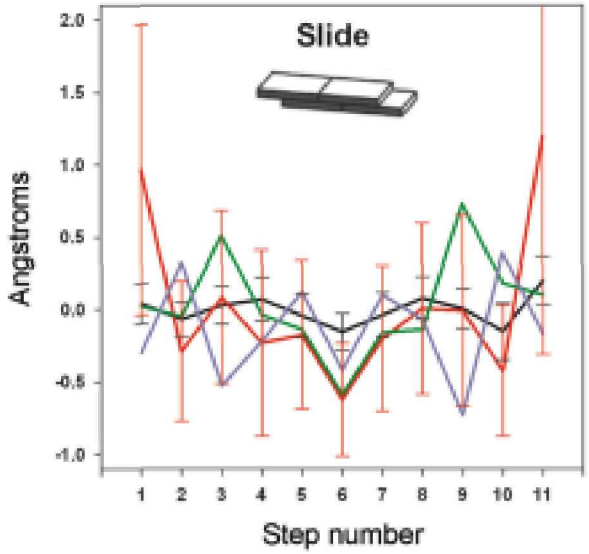
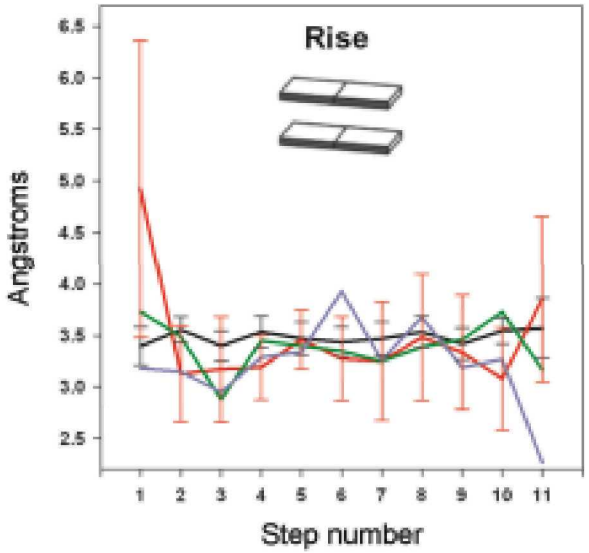
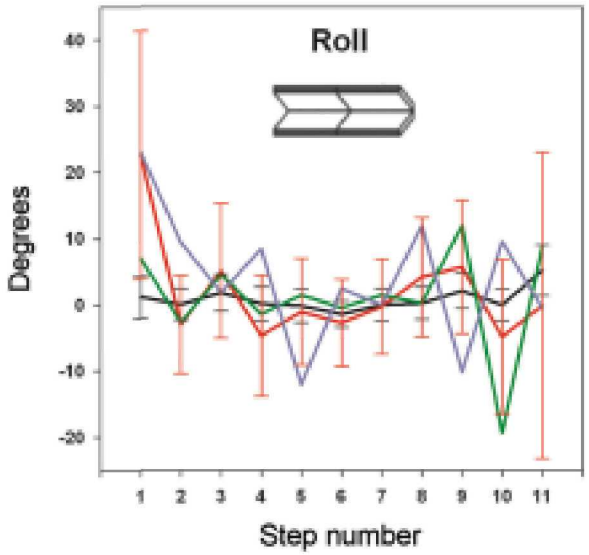
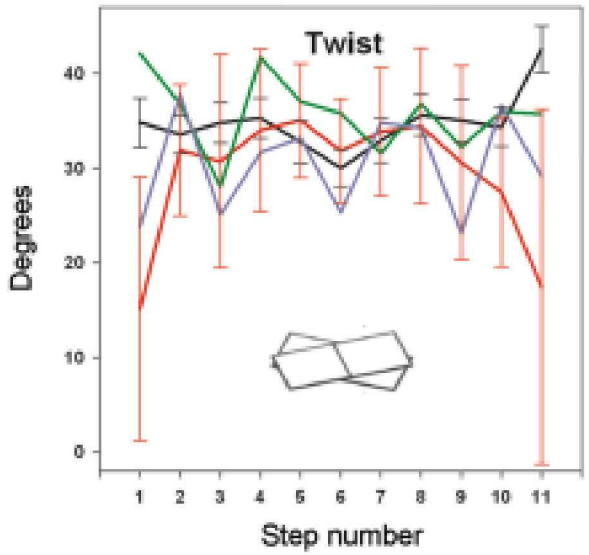
Structre and Dynamics of DNA

RMSF









CG
All-atom
1BNA
2DAU

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Structre, Dynamics (and perhaps Energetics) of DNA

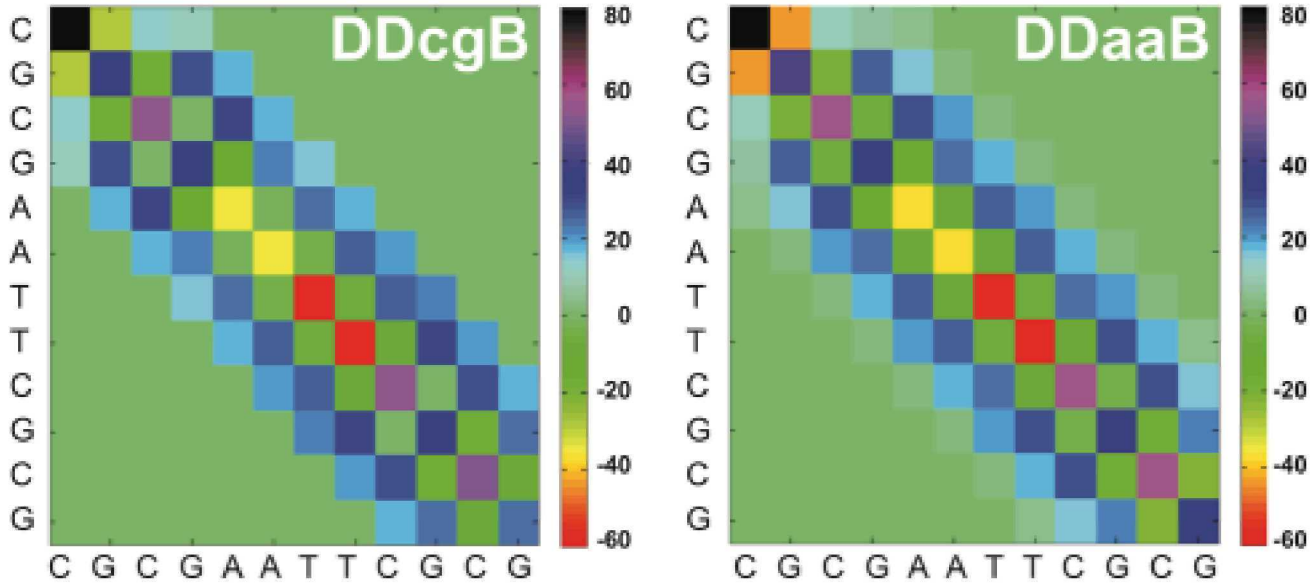

Table 5. Comparison of averaged[a] electrostatic and van der Waals (VdW) interactions.

	Electrostatic (Kcal/mol)		*VdW* (Kcal/mol)	
	DDcgB	DDaaB	DDcgB	DDaaB
St1[b] *vs.* St2	1449 ± 38	1434 ± 68	-66 ± 5	-72 ± 8
G4-C21 bp	4 ± 3	6 ± 2	-2 ± 1	-1 ± 1
A5-T20 bp	19 ± 2	11 ± 2	-2 ± 1	-1 ± 1

[a] The averages were calculated over 50 contiguous (DDaaB) or non-contiguous (DDcgB) ns. [b] St1 stands for strand 1 and St2 for strand 2.

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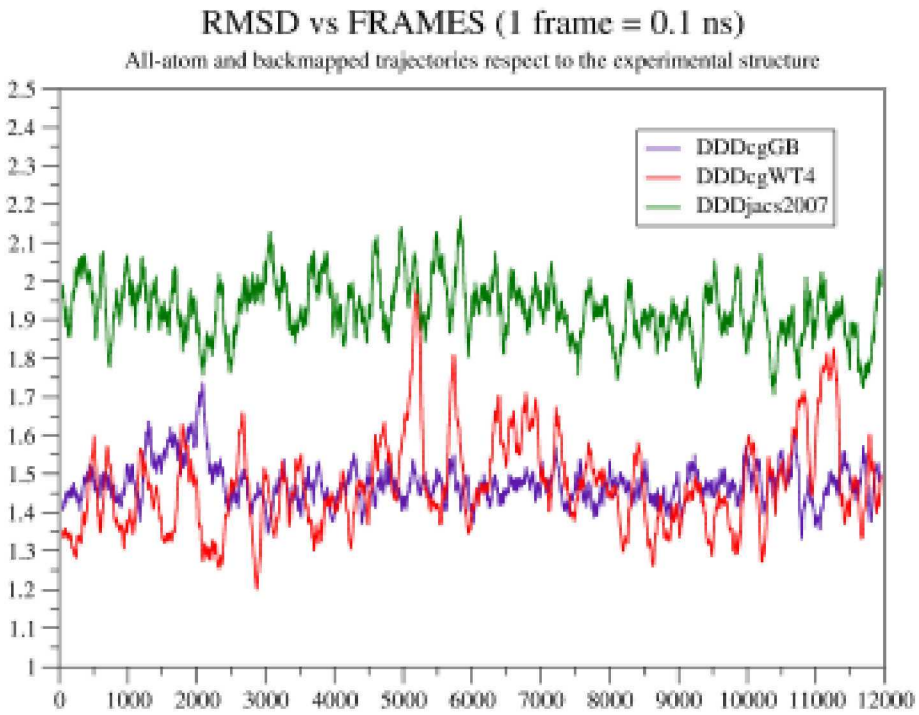
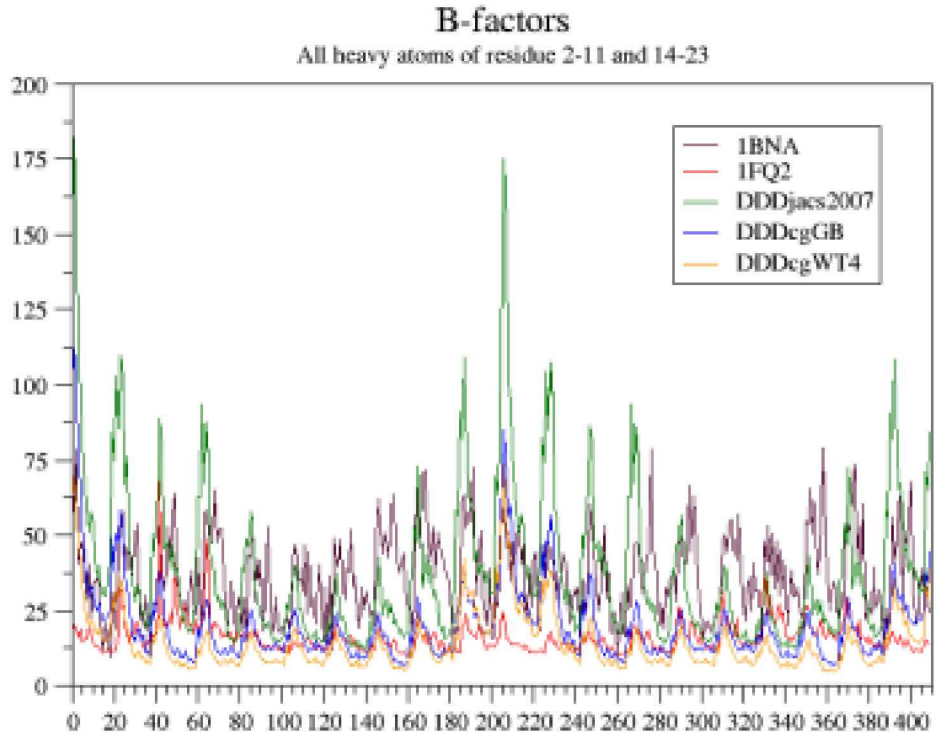
Comparison against atomistic simulations*





RED line: see poster by Dans et al.

*Pérez, *et al. J. Chem. Theory Comput.* **2005**, *1*, 790–800.

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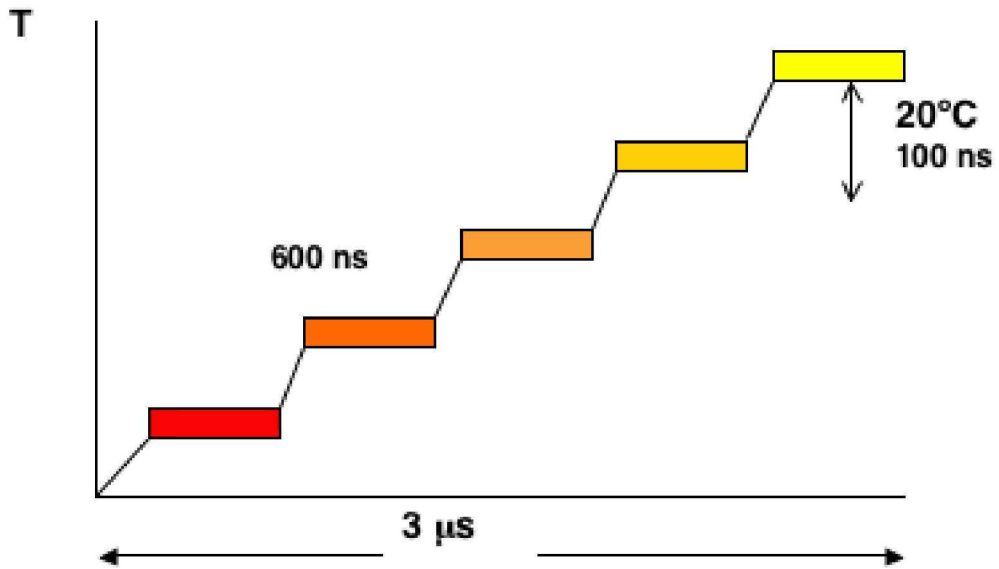
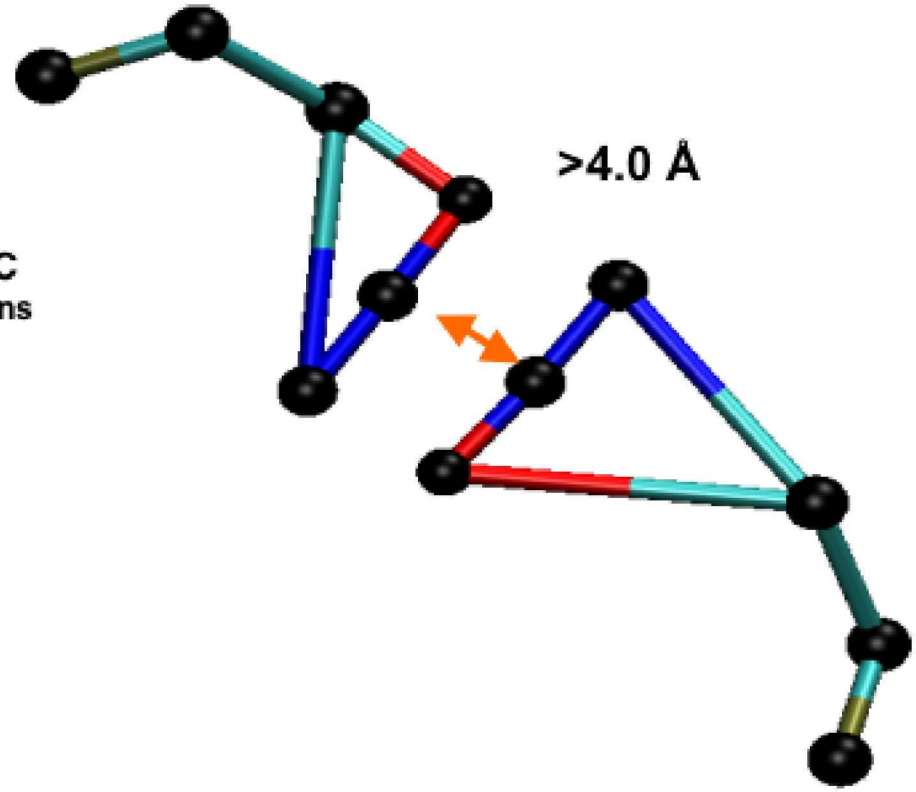
Salt, Length, and GC%-dependent Melting

i) 5'-d(ATCGTCTGGA)-3' (seq10)
ii) 5'-d(TACTAACATTAACTA)-3' (seq15a)
iii) 5'-d(GCAGTGGATGTGAGA)-3' (seq15b)
iv) 5'-d(GCGTCGGTCCGGGCT)-3' (seq15c)
v) 5'-d(AGCTGCAGTGGATGTGAGAA)-3' (seq20)





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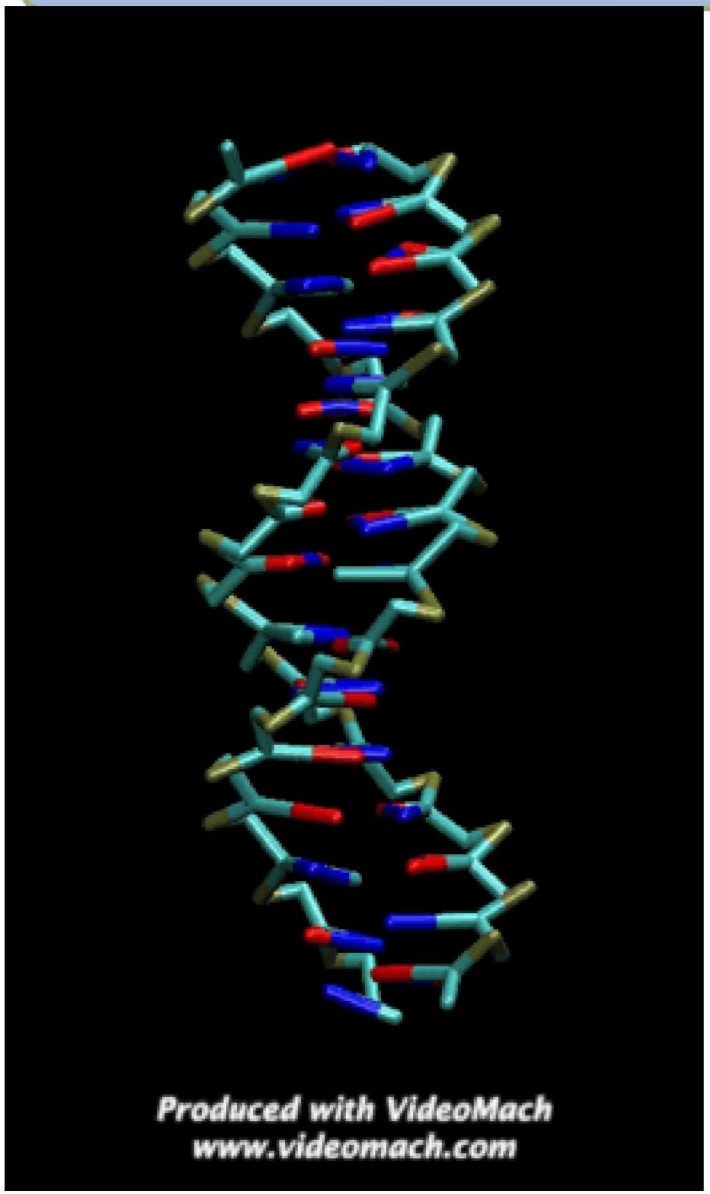
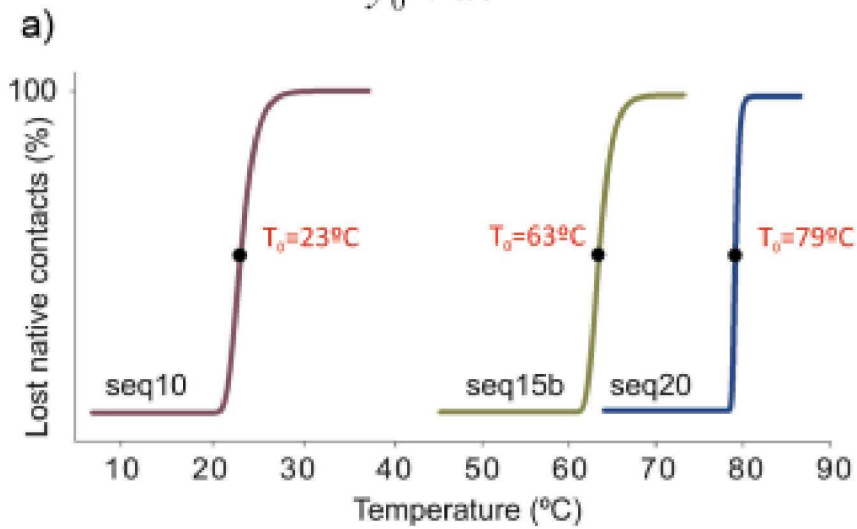
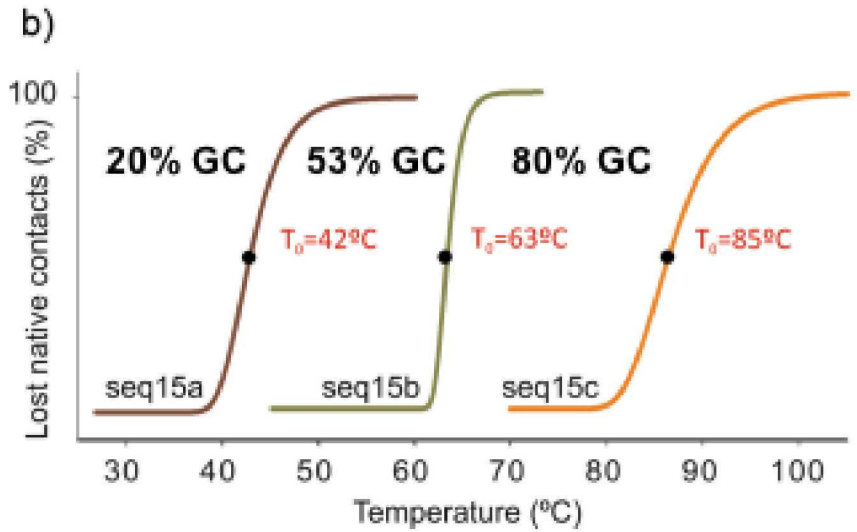
Salt, Length, and GC%-dependent Melting



$$y_0 + ae^{-e^{\frac{-(T-T_0)}{b}}}$$





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Experimental evidence for characteristic times in DNA dynamics (along ~8 orders of magnitude in time scale):

Small conformational changes
ps timescale

Moderate conformational changes
ns timescale

Large? conformational changes
μs timescale

1. Time-resolved Stokes shifts (TRSS) spectroscopy using coumarin. **Helix fraying occurs in a few ps time scale. Base pair opening in the multi-ps time scale.**
   Andreatta *et al. J. Am. Chem. Soc.* **2006**, 128, 6885-6892.
2. ^{1}H NMR measurement of imino-proton/water exchange. **According to this methodology the rate for the closing of an unbounded base pair is from hundreds of ps to dozens of ns.**
   Deva Priyakumar, MacKerell Jr. *J. Am. Chem. Soc.* **2006**, *128*, 678-679.
3. Fluorescence spectroscopy, using fluorophore and quenchers. **The dynamics of bubble formation has a life time between 20 to 100 μs.**
   Altan-Bonnet, Libchaber, Krichevsky. *Phys. Rev. Letters* **2003**, *90*, 138101.

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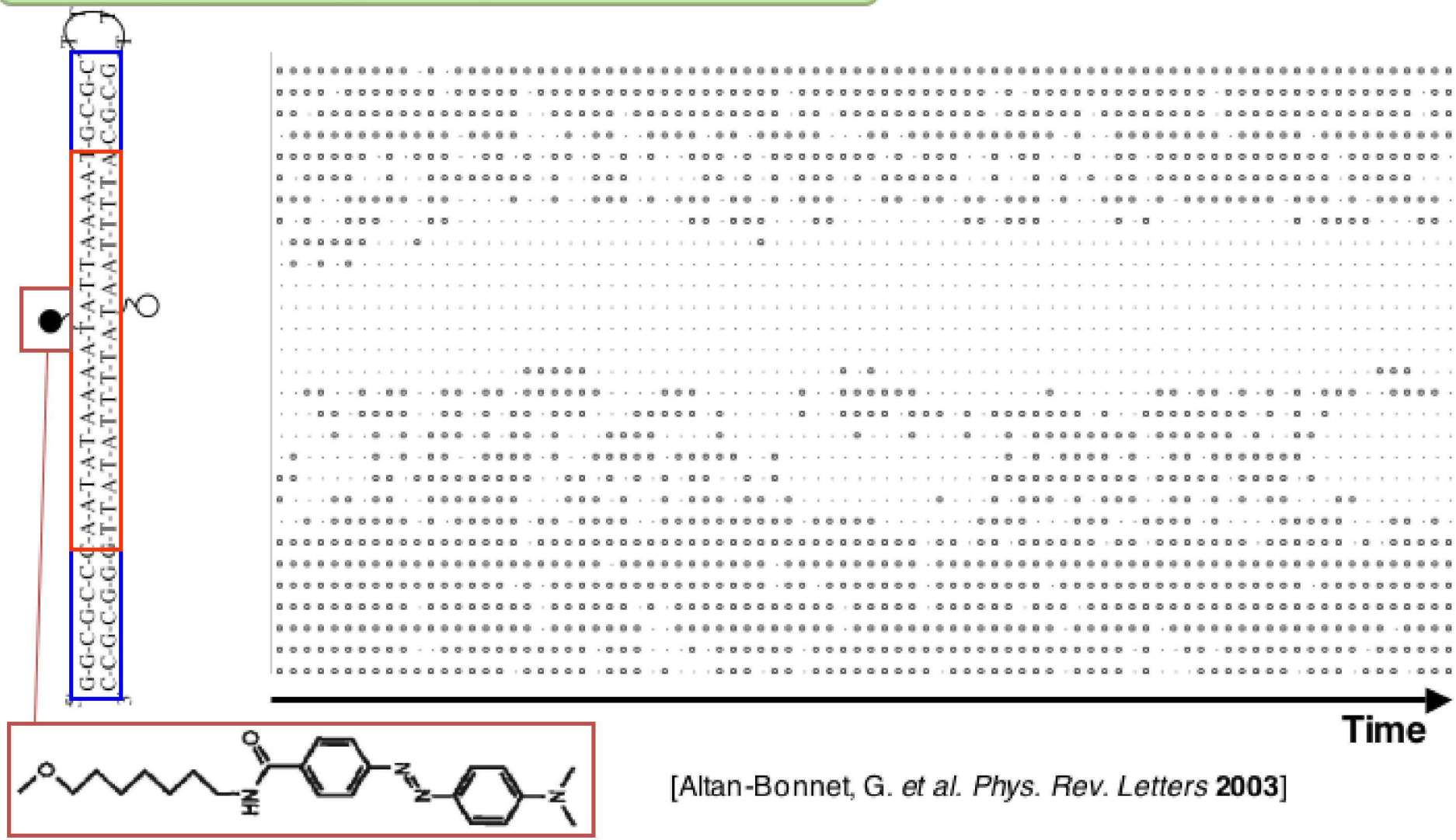
Breathing dynamics and timescale



[Altan-Bonnet, G. *et al. Phys. Rev. Letters* **2003**]

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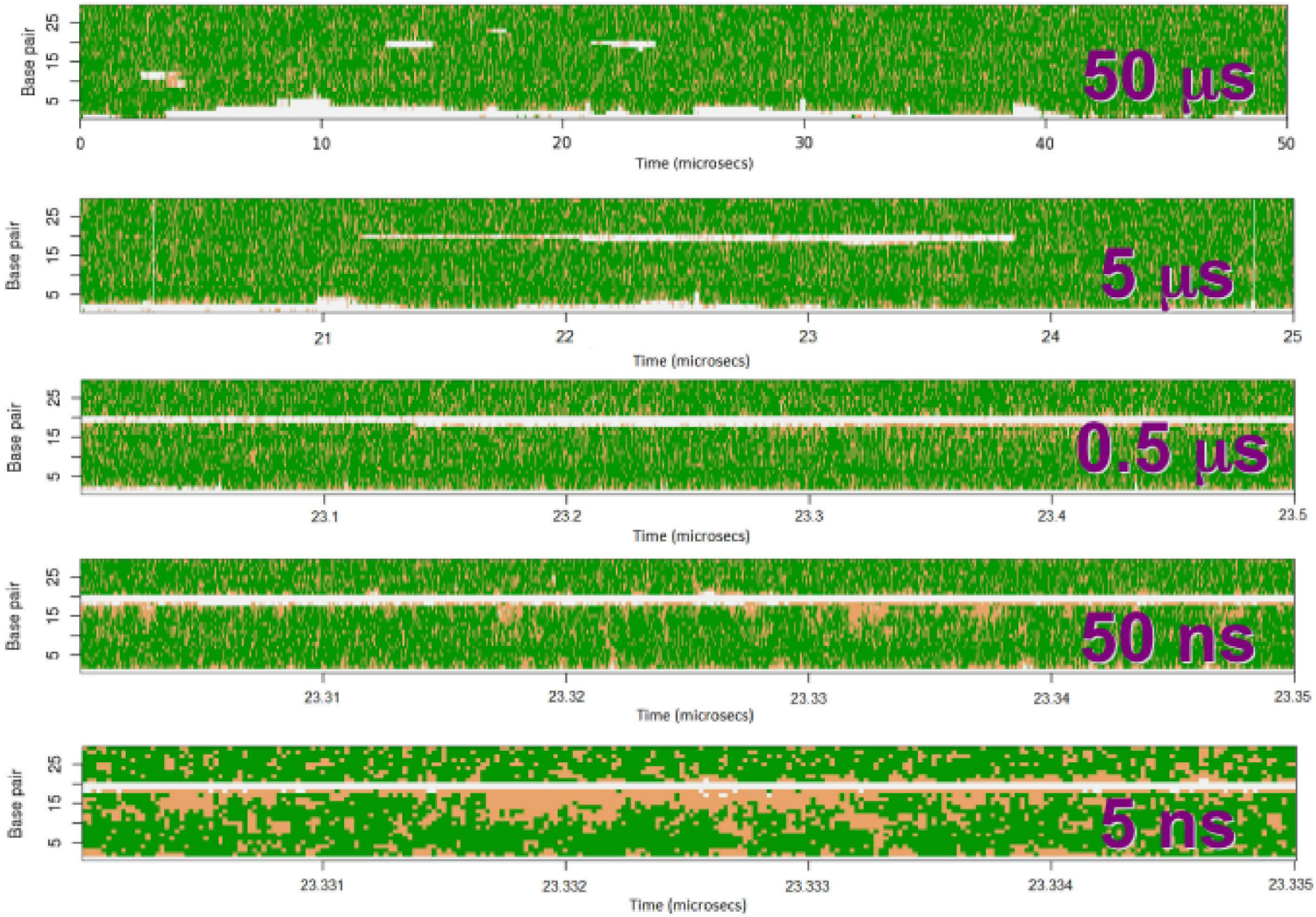

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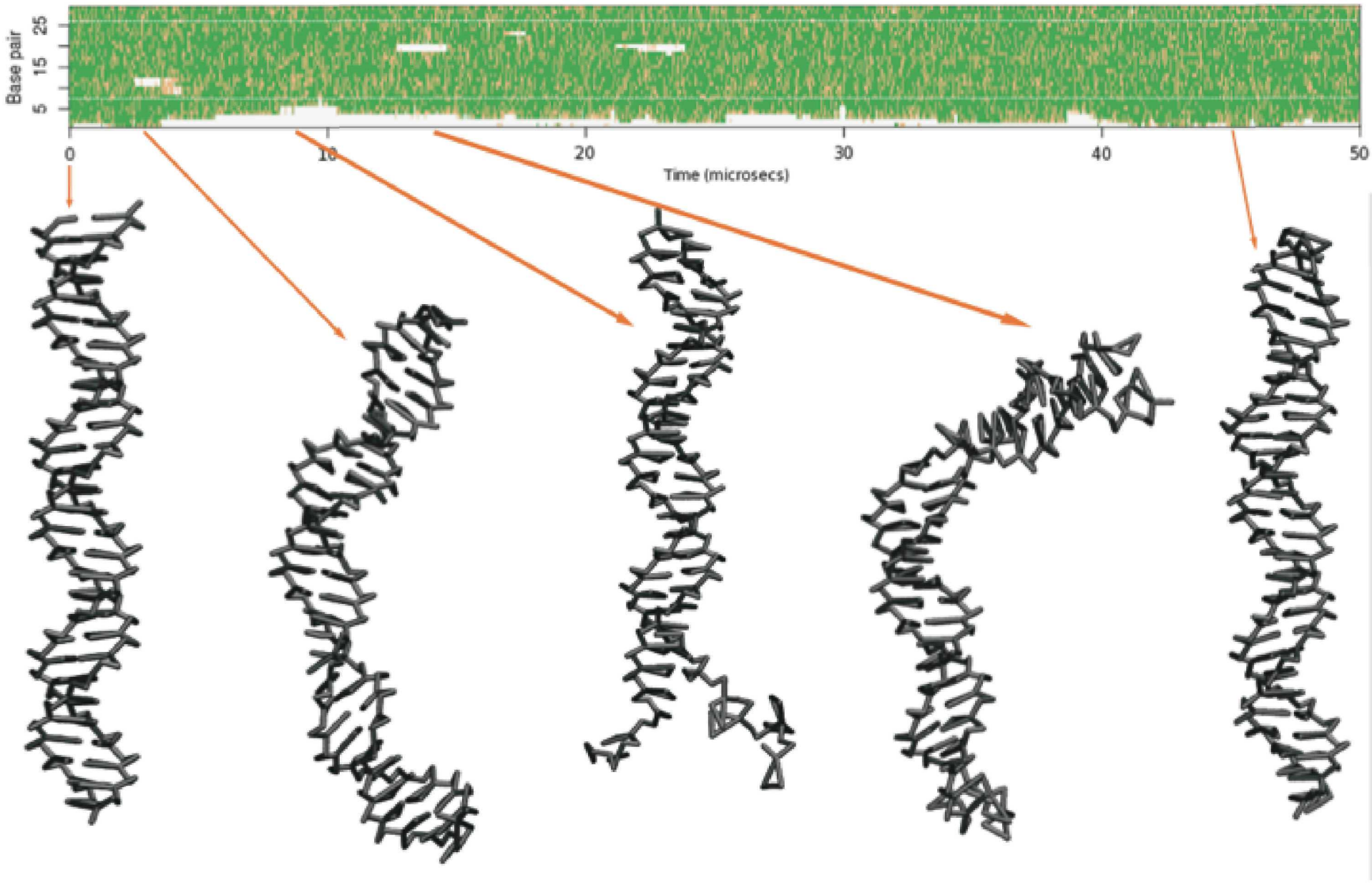

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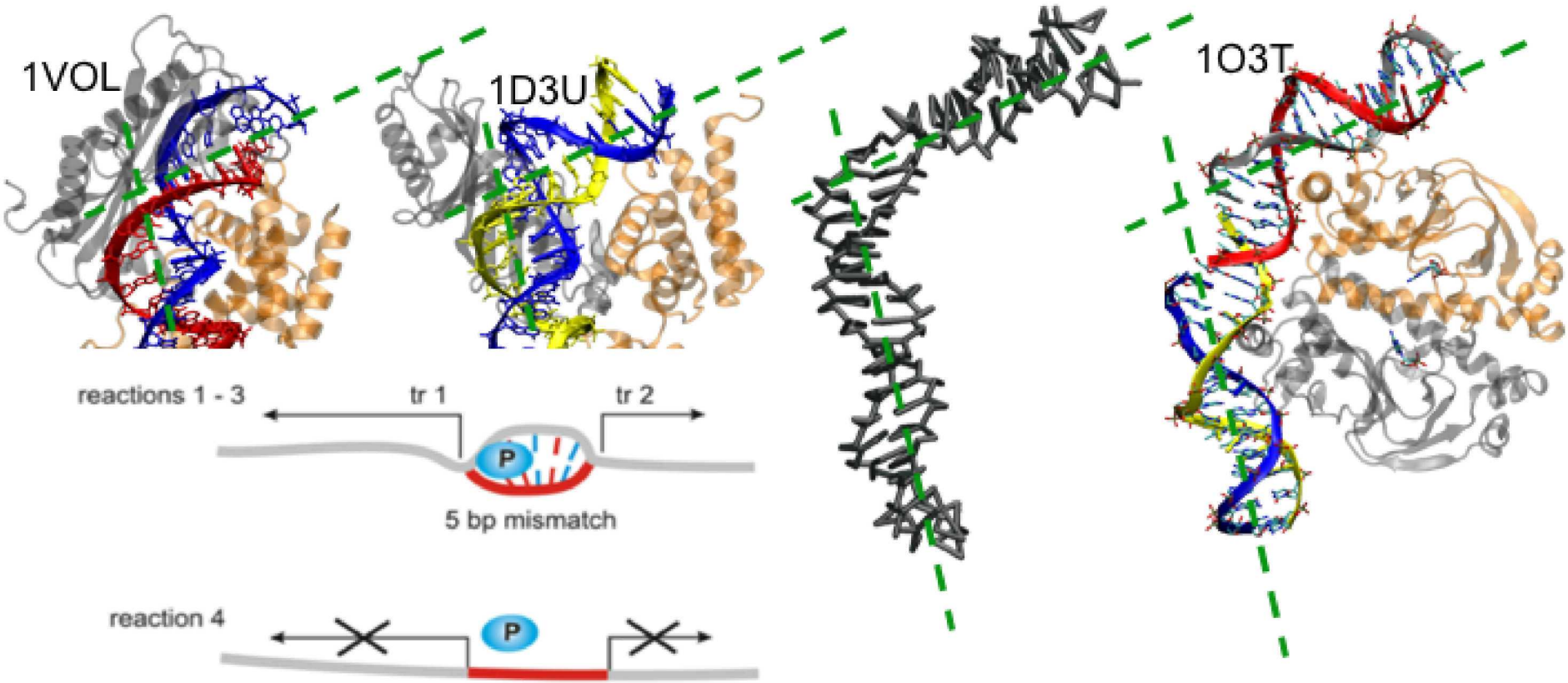

Alexandrov et al PLOS Comp. Biol. 2009

The existence of these long-lived fluctuating bubbles adds a new and interesting dimension to the dynamical picture of DNA behavior and of DNA-protein interactions." Altan-Bonnet et al. PRL 2003

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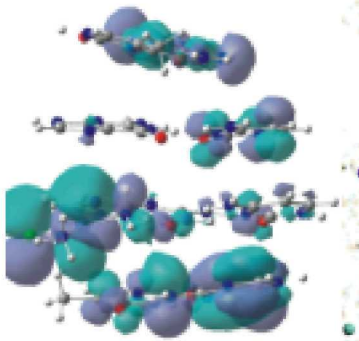
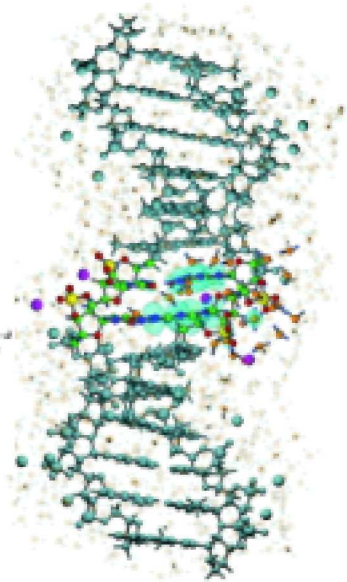
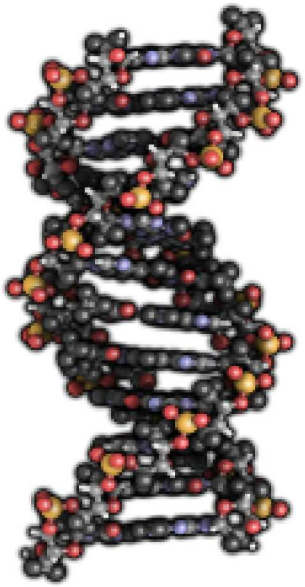


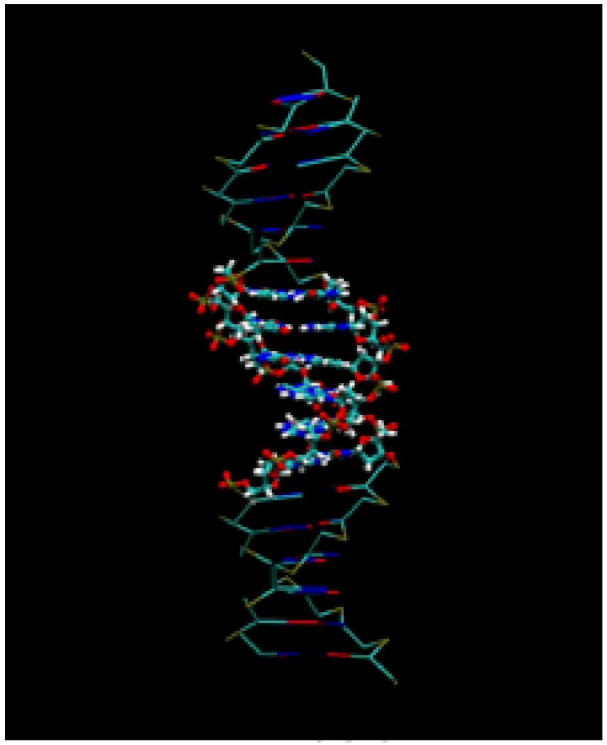
QM

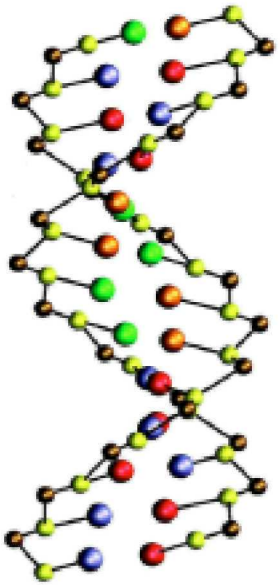


QM/MM



MM





CG