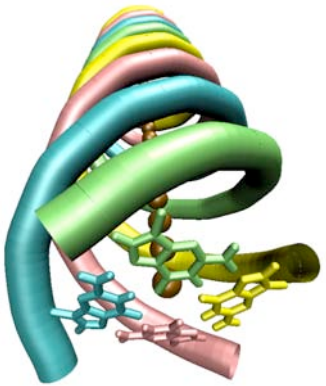
CNMS user meeting, Oak Ridge National Laboratory, TN, USA
September 14th, 2010

Computational investigation of modified DNAs



Rosa Di Felice

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S3 Center, CNR Institute of Nanoscience

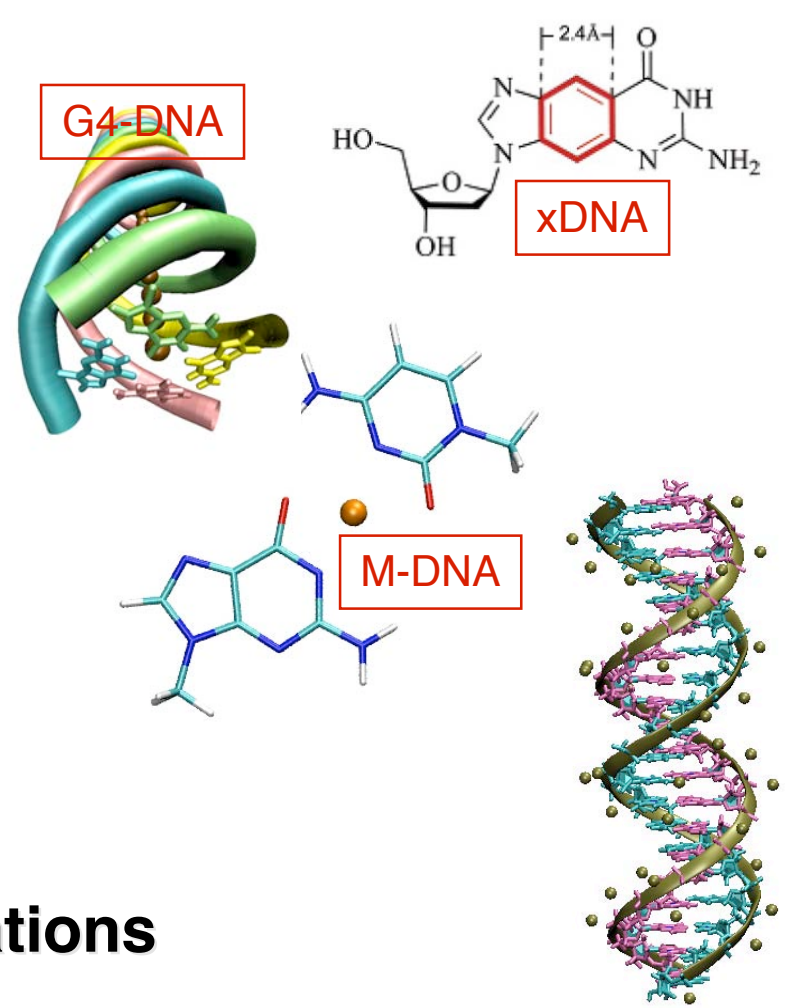
Modena, Italy

Message

- **Traditional approaches: frozen structures**
  - Few evidences that this is not satisfactory
- **New trends: conformational and environmental effects**
  - Our own multi-scale approach

Outline

- **DNA for molecular electronics?**
  - Better measurements
  - Synthetic DNA-derivatives
- **Candidates**
  - G4-DNA, xDNA, M-DNA, dsDNA
  - Intercalators and sequence alterations
- **dsDNA: what do we learn?**
  - Small transfer integrals
  - Importance of conformational flexibility
- **Strategy to account for conformations**
- **Summary**

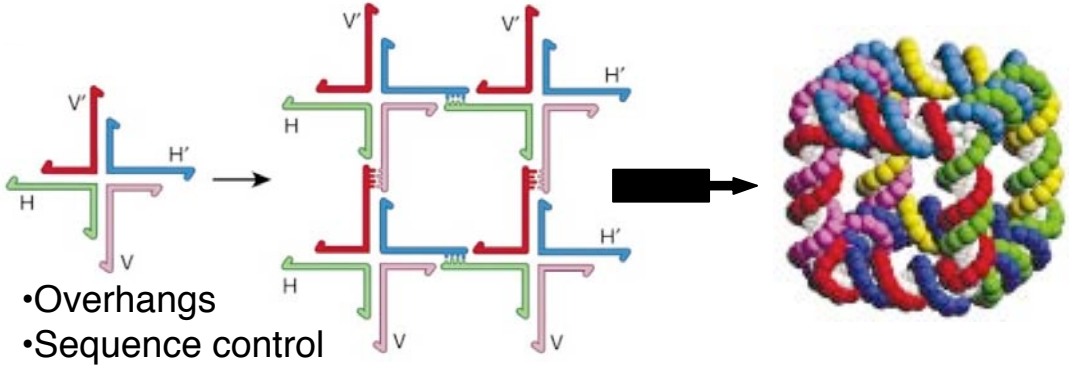


Why DNA for Biomolecular Electronics?

- **Molecules for nanodevices need to express 3 main traits: sructuring, recognition, conductivity**

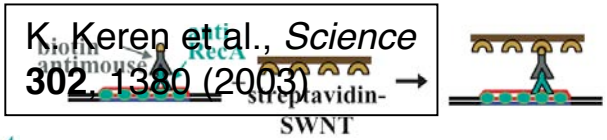
- **DNA**
  - Fantastic structuring

    N. Seeman, *Nature* **421**, 427 (2003)



  - Inter-strand & inter-partner recognition

    K. Keren et al., *Science* **302**, 1380 (2003)

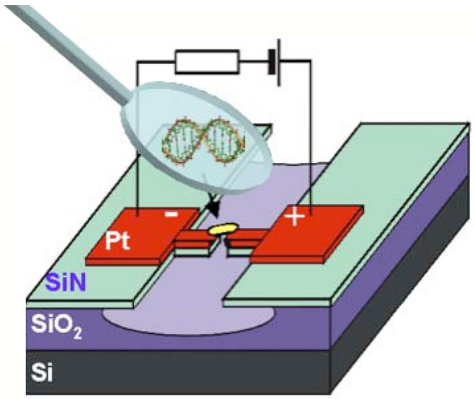


  - Controversial conductivity

Is DNA a viable electrical *material*?

D. Porath, G. Cuniberti, R. Di Felice, *Topics in Current Chemistry* **237**, 183 (2004)

- **Experiments on native-DNA charge mobility show poor conductivity for long (>40 nm) molecules deposited on substrates**



- **Improve measurement setups**
  - Stiffer molecules (G4-DNA?)
  - Softer surfaces (alkanethiol monolayers?)
  - Avoiding non-specific DNA-substrate interaction & controlling DNA-electrode covalent binding

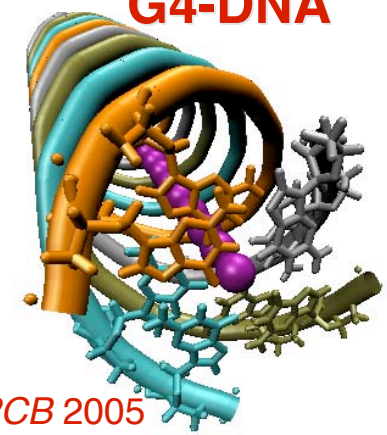
- **Improve intrinsic conductivity**
  - Metal insertion
  - Base modification
  - Helical conformation

How can the difficulty in measuring conductivity be bypassed?
& relevance in the biological context

•Exploring DNA-derivatives

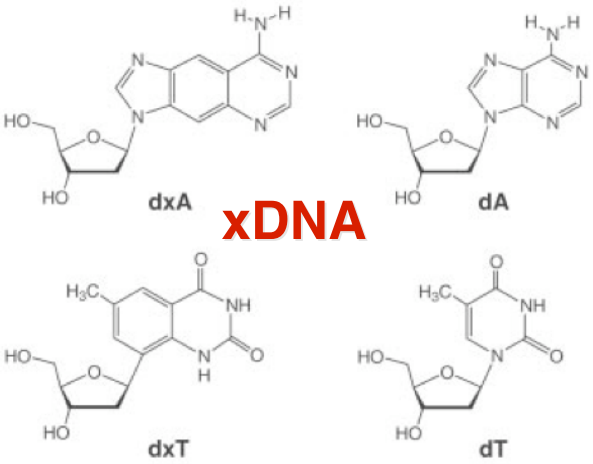
Guanine quadruplex
Aromatic base expansion
Metal complexation

G4-DNA



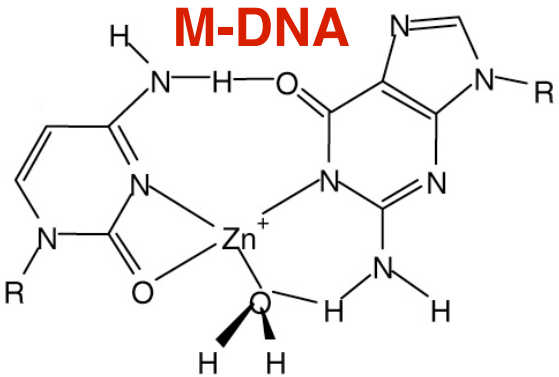
Di Felice, *JPCB* 2005

xDNA



Kool, *Science* 2003

M-DNA



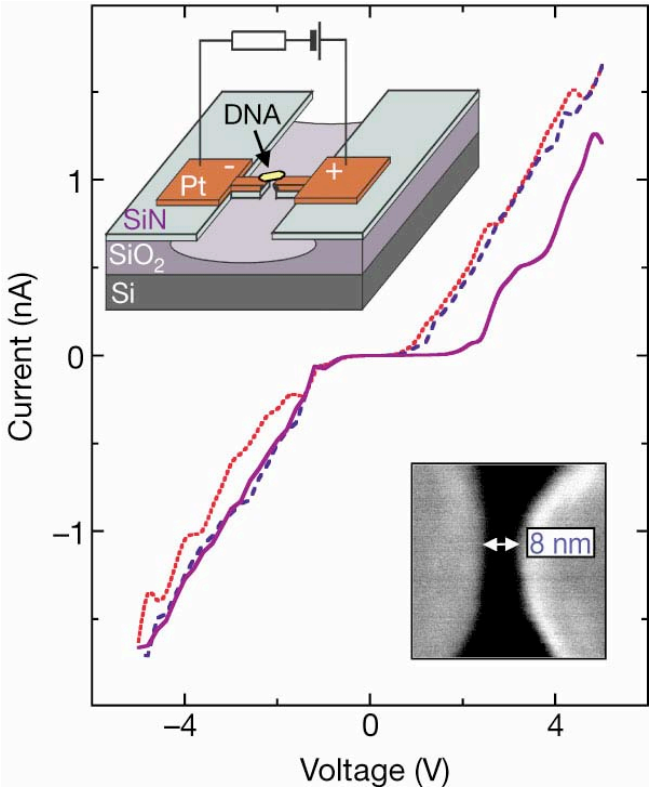
Lee, *PRL* 2001

Properties of interest & methods

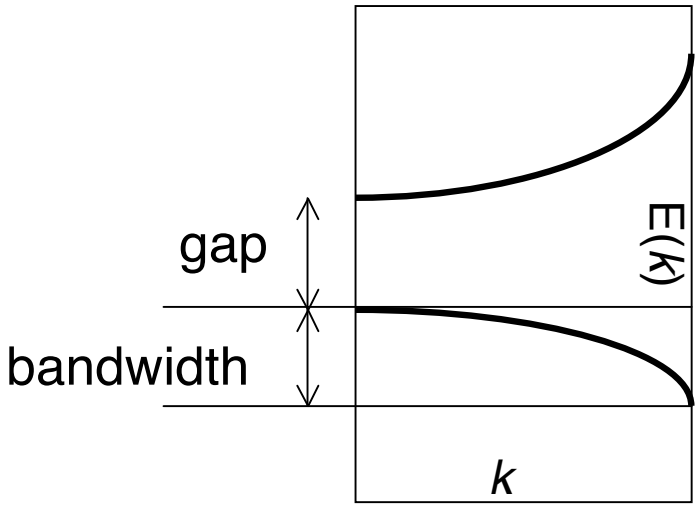
- **Electronic structure by DFT**
  - PWSCF: Plane-wave pseudopotential DFT (LDA, PW91, PBE) http://www.quantum-espresso.org
  - NWChem, Gaussian: DFT with gaussian basis sets http://www.emsl.pnl.gov/docs/nwchem/nwchem.html, www.gaussian.com
- **Optical absorption and circular dichroism**
  - `Octopus`: www.tddft.org/programs/octopus
- **Classical molecular dynamics**
  - NAMD, AMBER: http://www.ks.uiuc.edu/Research/namd/, http://ambermd.org/
- **Transfer integrals**
  - A. Migliore et al., *J. Chem. Phys.* **124**, 064501 (2006)

dsDNA

Bandstructure calculations

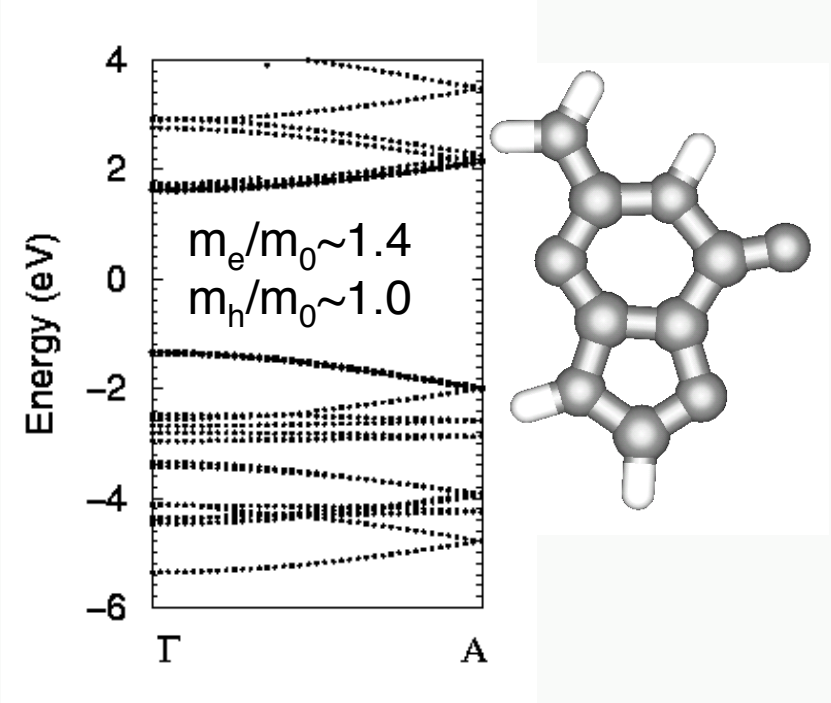


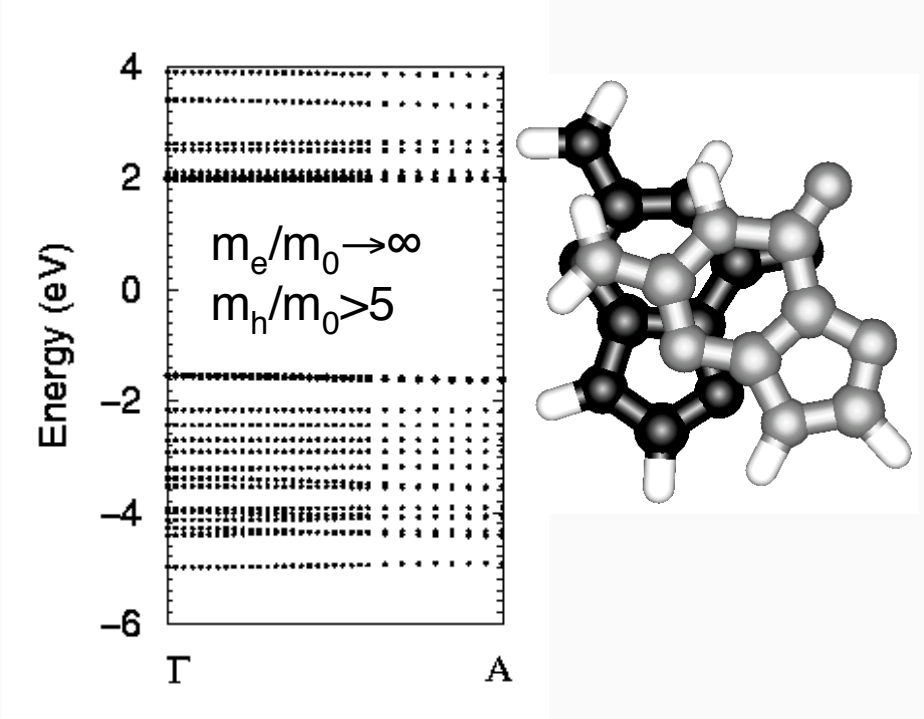
- **Inspiration**
  - D. Porath et al., *Nature* **403**, 635 (2000)
  - **"Semiconductor"** behavior due to the **bands** of the material
- **Semiconductor**
  - **Bandgap**
  - Finite bandwidth: E(*k*) **dispersion** relation



DFT with plane-wave basis set on Guanine stacks

R. Di Felice et al., Phys. *Rev. B* **65**, 045104 (2002)





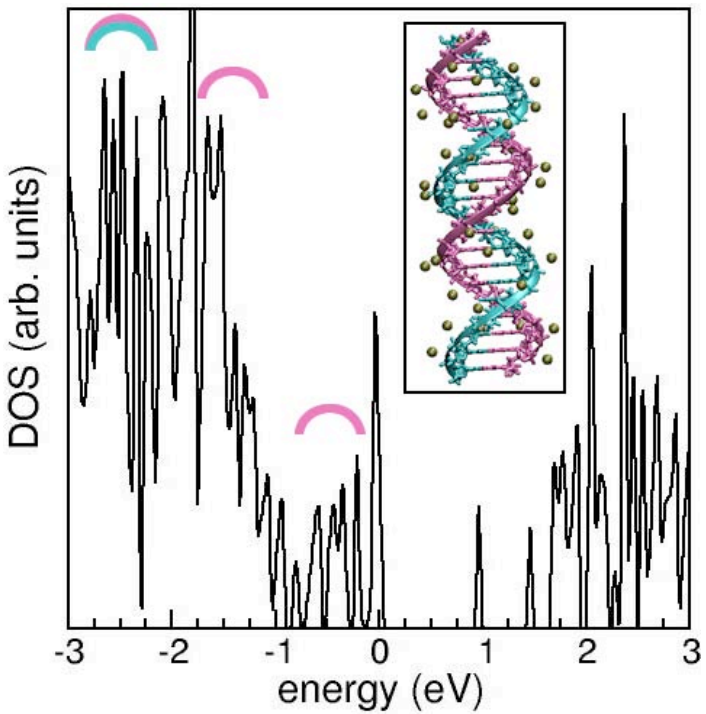
- Band dispersion and small effective masses for eclipsed guanines
- Poor band dispersion and huge effective masses for twisted guanines by 36 degrees as in B-DNA

Density of states of poly(dG)-poly(dC)

E. Shapir, A. Calzolari, C. Cavazzoni, D. Ryndyk, G. Cuniberti, A. B. Kotlyar, R. Di Felice, D. Porath, *Nature Mater.* **7**, 68 (2008)

D. Ryndyk, E. Shapir, A. Calzolari, D. Porath, R. Di Felice, G. Cuniberti, *ACS Nano* **3**, 1651 (2009).

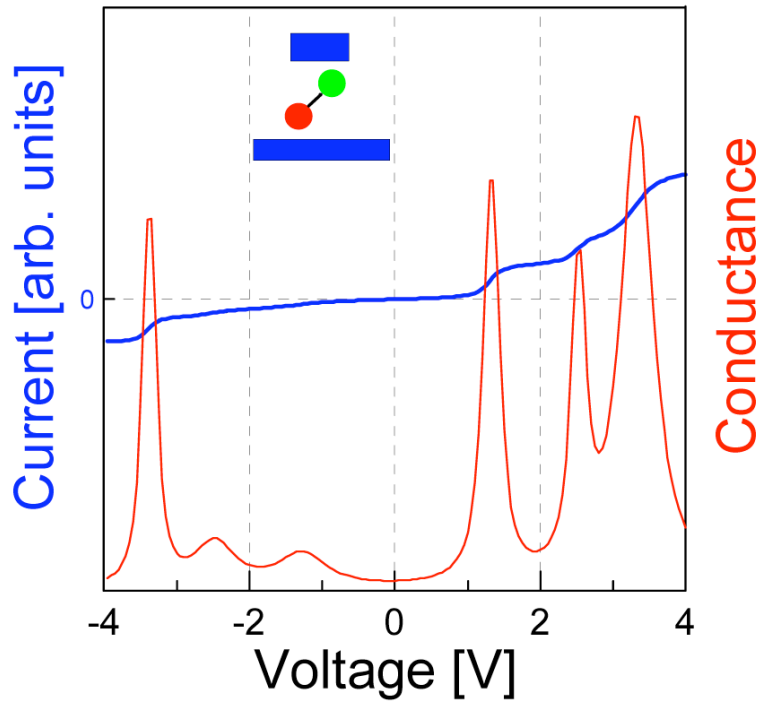
Ab initio



$$dI/dV \propto D_s(r,eV)D_t(0)$$

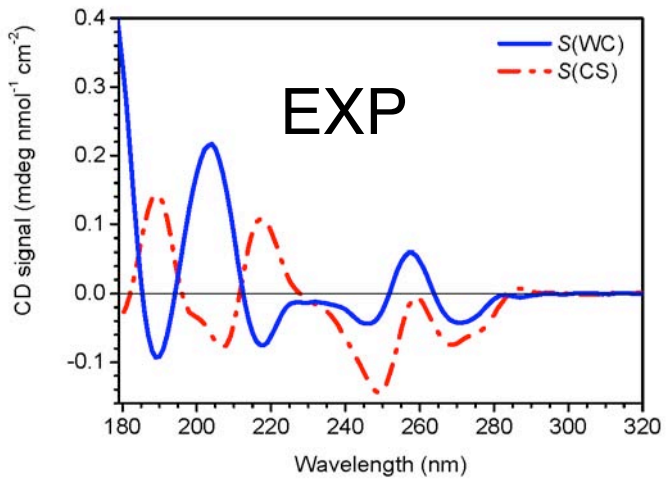
$$I = A\int_0^{eV} D_s(r,E)D_t(E-eV)|T(E,V,r)|^2 dE$$

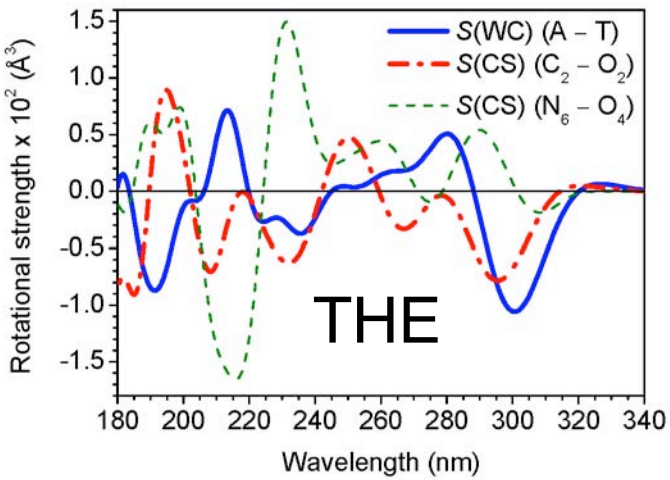
Model hamiltonians



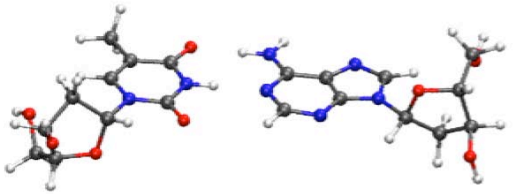
Parameters from ab initio or experiments

Circular dichroism in A-tracts by TDDFT

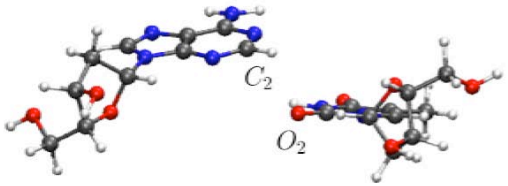




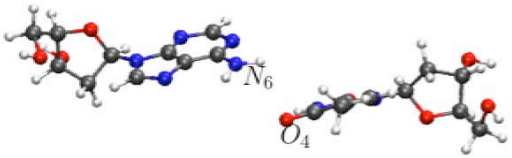
Data by Steen Nielsen, Aarhus University



WC



CS C_2...O_2



CS N_6...O_4

What do we learn for dsDNA?

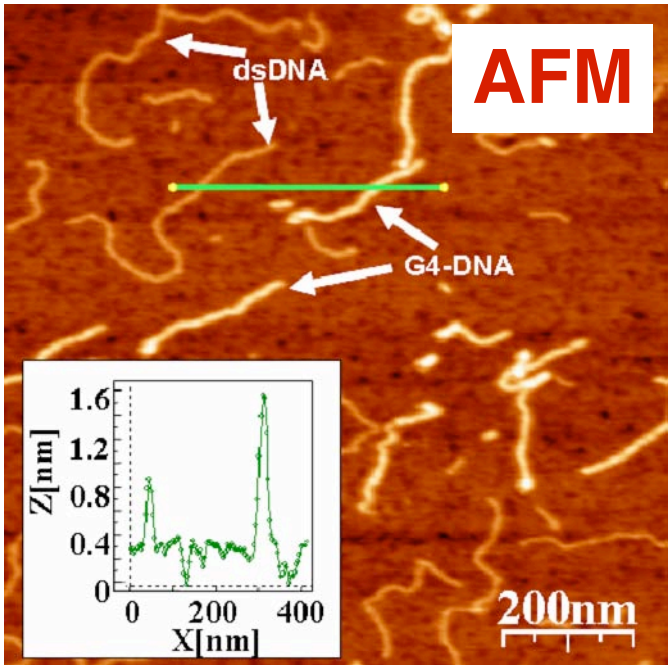
- **Small band widths**
- **Small measured currents, and even smaller from theoretical predictions**
- **DFT and TDDFT useful instruments**

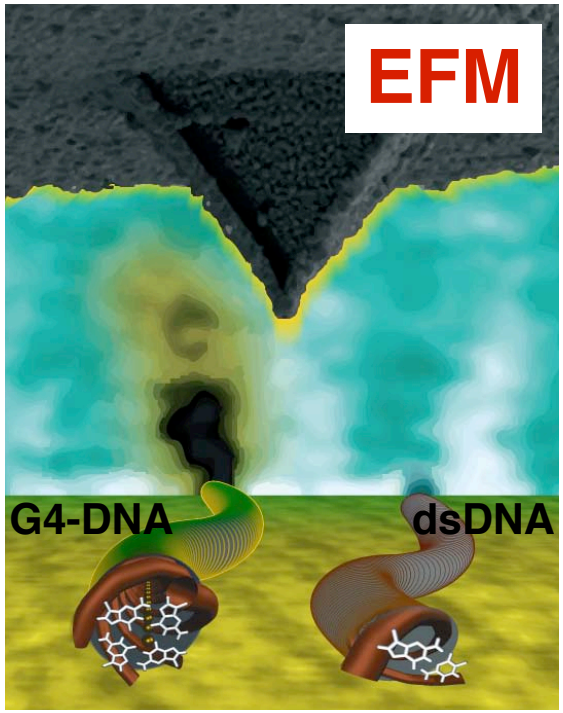
G4-DNA and xDNA

Novel long guanine quadruplexes (G4-DNA wires)

A. B. Kotlyar et al., *Adv. Mater.* **17**, 1901 (2005)

H. Cohen et al., *Nano Lett.* **7**, 981 (2007)

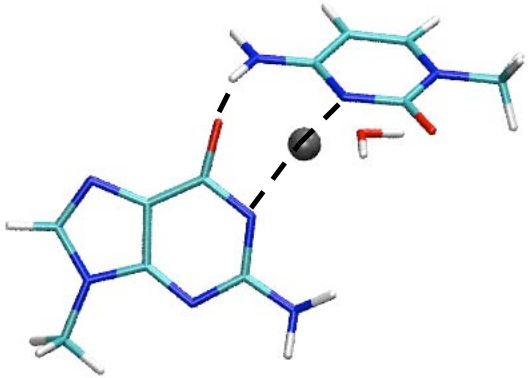




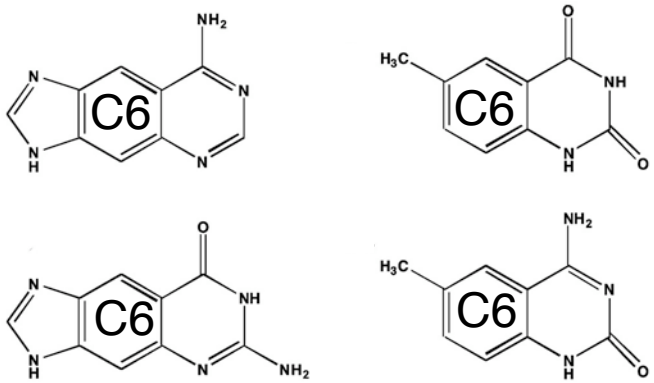
- AFM topography: Higher **stiffness** (brighter, thicker) and **persistence length** than duplex DNA → may improve resistance against deformation on hard surfaces
- EFM phase map: Polarizable G4-DNA against non-polarizable dsDNA

Other appealing candidates

- **MDNA**
  - Complexation of 1 transition metal cation per base pair (Zn, Ag, Cu???)
  - Perspectives: enhanced electron transfer capabilities, detection of single base pairs

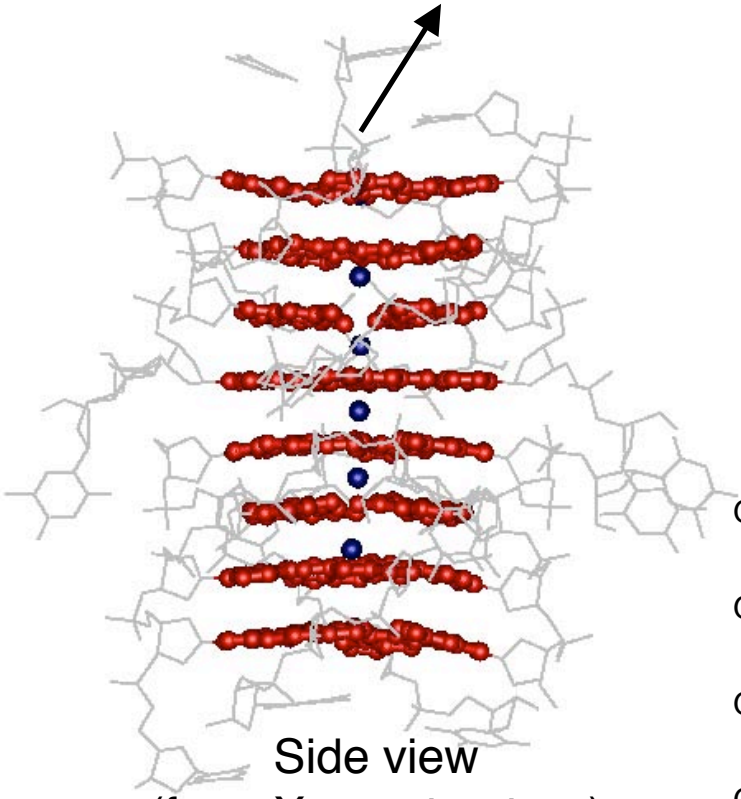


- **xDNA**
  - Size expansion of each natural base with a benzene ring → increased aromaticity
  - Evidence of higher thermal stability for suitable sequences
  - Perspectives: enhanced electron transfer capability, augmented genetic alphabet



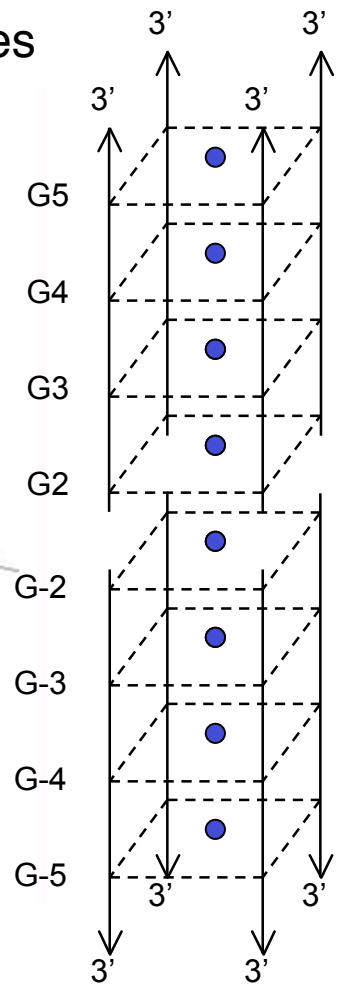
Guanine quadruple helices (G4-DNA molecules)

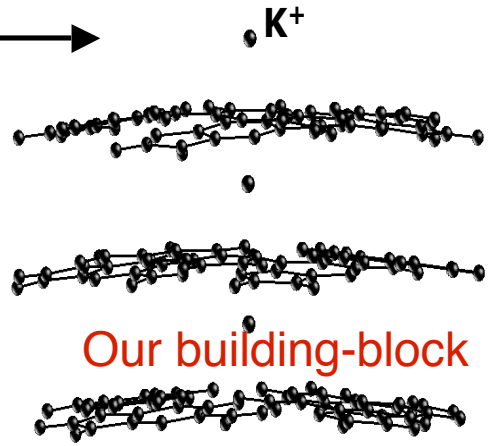
Backbone neglection
Square+translation symmetries



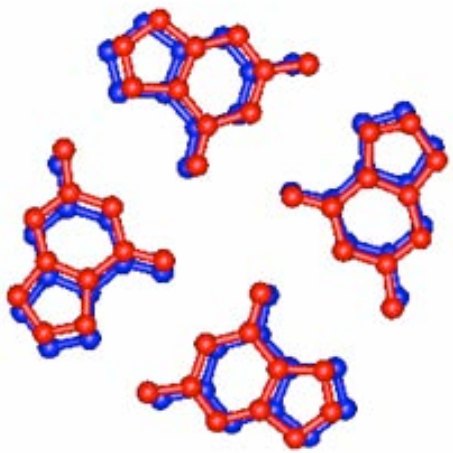
Side view
(from X-ray structure)

B. Luisi et al. *Science* **265**, 520 (1994)





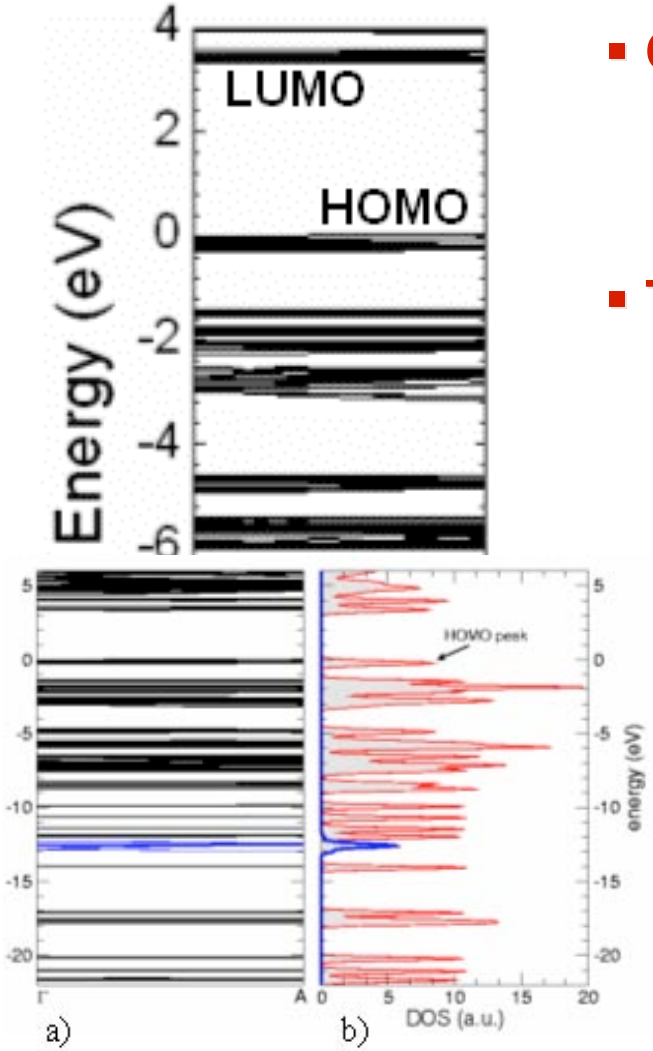
Our building-block



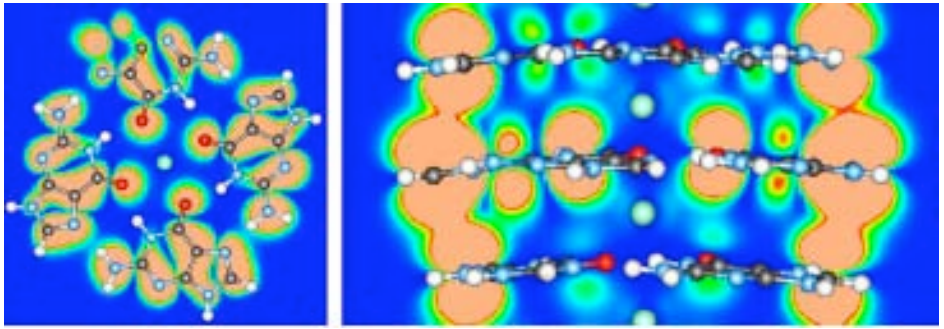
Superposition between
1st and 4th planes

K(I)-G4 Electronic Structure

A. Calzolari et al., *Appl. Phys. Lett.* **80**, 3331 (2002); *J. Phys. Chem. B* **108**, 2509 & 13058 (2004)

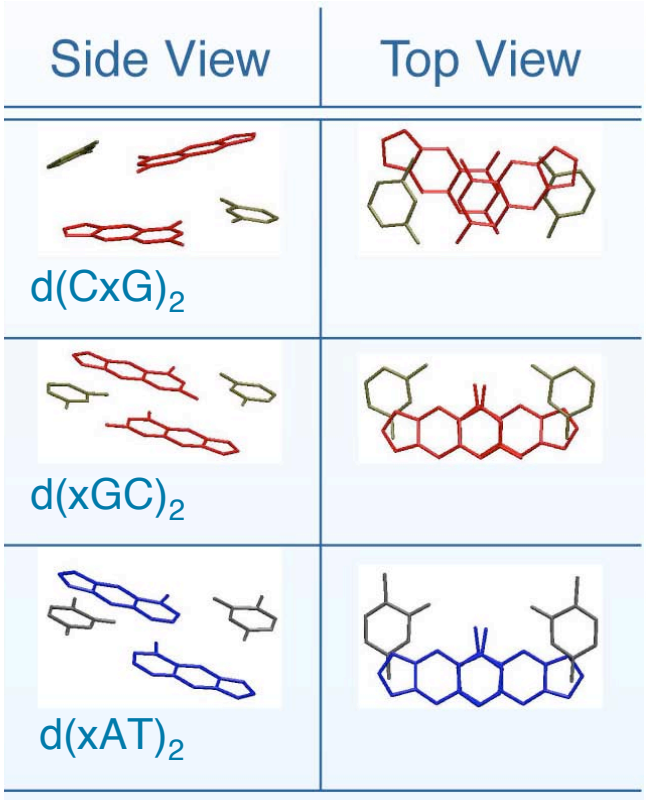


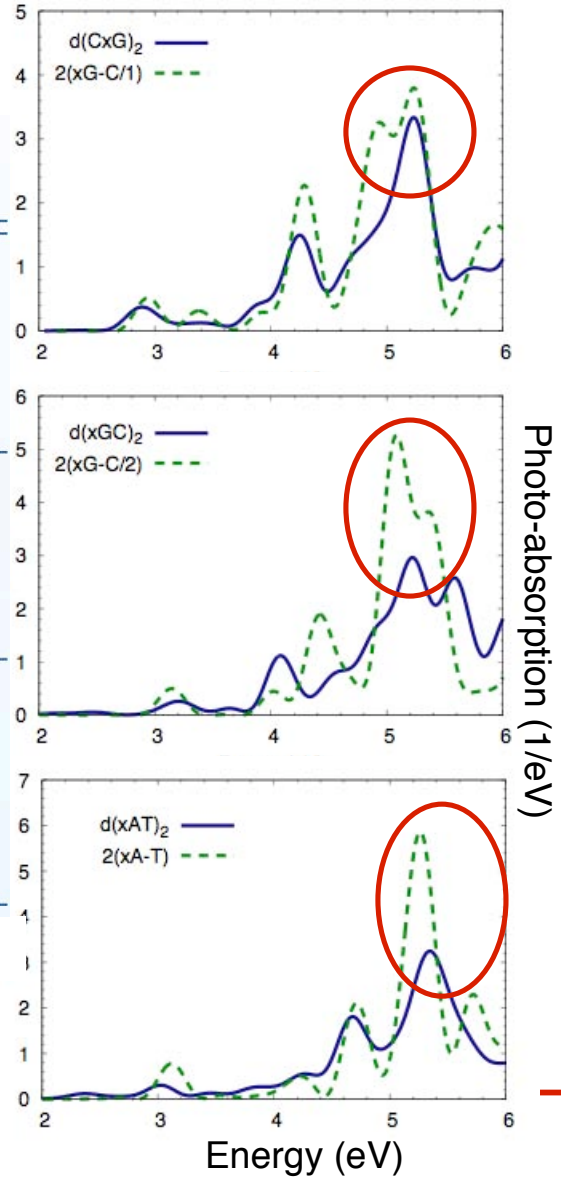
- **Ground-state electronic structure**
  - Manifolds → effective semiconductor with higher band widths than dsDNA
- **Transport**
  - Higher conductance than dsDNA: P.B. Woiczikowski et al., *J. Chem. Phys.* **133**, 035103 (2010)



Optical absorption of x-base stacks

D. Varsano, A. Garbesi, R. Di Felice, *J. Phys. Chem. B* **111**, 14012 (2007).



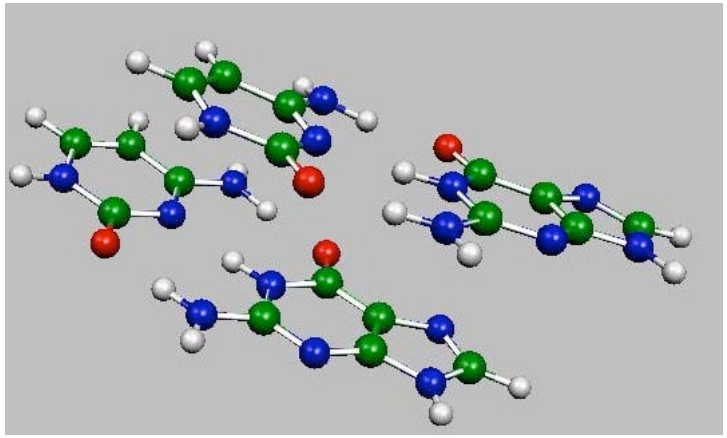


- H-bonding → **redshift** of low-energy excitations (not visible here)
- Stacking → pronounced **hypochromicity**
- Hypochromicity is stronger for structures with regular overlap between x-pairs
- Overall: qualitative behavior similar to stacks of natural pairs, but with **strong structural dependence** of the fine details

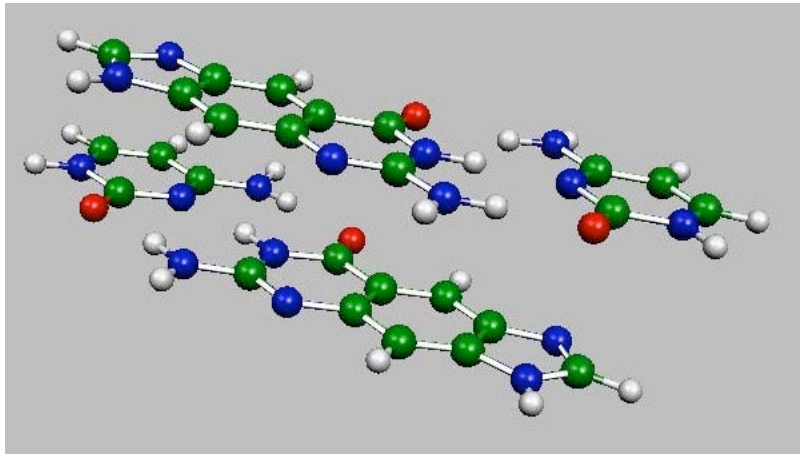
Transfer integrals between x-pairs

A. Migliore, S. Corni, R. Di Felice, E. Molinari, *J. Chem. Phys.* **124**, 64501 (2006) [METHOD]

Native base-pairs



Expanded base-pairs



- Comparison to post-HF results for natural DNA base pairs [accurate testing of computational ingredients such as basis sets, xc functionals, DFT schemes]

- Does the aromatic expansion enhance the transfer integral as a consequence of enhanced π–π stacking?

Natural versus size-expanded base pairs

GC-GC		xGC-xGC		AT-AT		xAT-xAT	
Real	Ideal	Real	**Ideal**	Real	Ideal	Real	**Ideal**
0.058	0.075		**0.205**	0.003 0.059-0.091	0.008-0.017	0.060	**0.040-0.054**

Real: taken from pdb files of oligomers
Ideal: constructed with nucleic acid builders with average parameters

- **Importance of structural fluctuations:** difference between “real” and “ideal”
- Net increase upon size-expansion, less remarkable if structural changes are considered

What do we learn for G4-DNA and xDNA?

- **Maybe faster charge transfer**
- **Relevance of conformational flexibility**

Hybrid computational approach

Computational strategy

- **Force-field parametrization for new derivatives**
  - DFT calculations of small fragments
  - Validation of force-field
- **Molecular dynamics calculations for ~50-100 ns in explicit solvent**
  - Oligomers of realistic size
  - Extraction of temporal snapshots or selected conformations (sorting) from the trajectories
  - (only conformational effects of solvent are included with this approach)
- **Calculation of electronic structure for MD-extracted structures**
  - Small fragments or real oligomers, depending on property and method
  - Coordination water molecules or implicit PCM solvent may be included at this level

Experimental facts for Z-including sequences

- Majima and co-workers addressed the limitations to charge transfer through DNA molecules in A-T tracts by replacing some adenines in A-tracts with Z.
- Deazaadenine (Z) has an ionization potential similar to that of guanine.
- By serially introducing Z in their sequences in the place of A, Majima and co-workers observed an increase of the transport rate by orders of magnitude with respect to the corresponding sequences with natural A.
- What is the mechanism?

Experimental facts

a

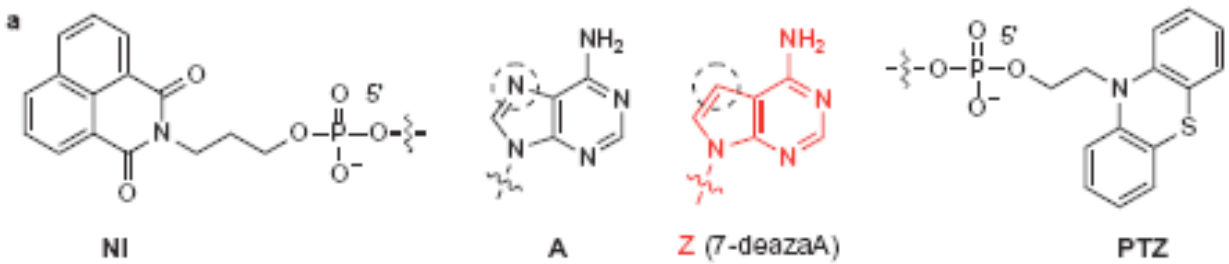
a0 NI-ATTTTTCTCTATATCT
TAAAAAGAGATATAGA-PTZ

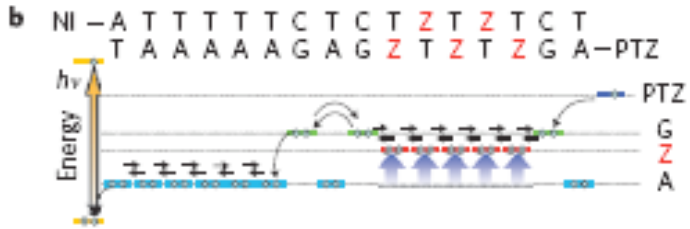
a2 NI-ATTTTTCTCTZTZTCT
TAAAAAGAGATATAGA-PTZ

a3 NI-ATTTTTCTCTATATCT
TAAAAAGAGZTZTZGA-PTZ

a5 NI-ATTTTTCTCTZTZTCT
TAAAAAGAGZTZTZGA-PTZ

A→Z: replacement of N7 atom with a CH group



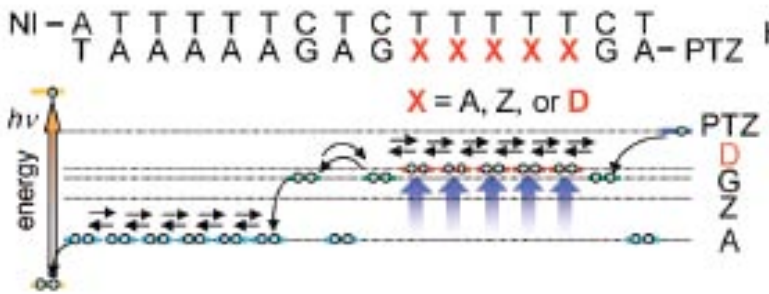


	HOMO level (eV)	Oxidation potential (V vs NHE)
PTZ		0.76
G	−4.93	1.31
Z	−5.25	1.39
A	−5.66	1.63

T. Majima et al., *Nature Chem.* **1**, 156 (2009)

Facts and strategies for Z and D

T. Majima et al. *JACS* **132**, 627 (2010)



	HOMO-level (eV)	Oxidation potential (V vs NHE)
PTZ		0.76
D	−4.90	1.20
G	−4.93	1.31
Z	−5.25	1.39
A	−5.66	1.63

A→D: addition of a NH_2 group

X = Z or D

a0 NI–ATTTTTCTCTTTTTCT
TAAAAAGAGAAAAAGA–PTZ

a2 NI–ATTTTTCTCTTTTTCT
TAAAAAGAGAXAXAGA–PTZ

a5 NI–ATTTTTCTCTTTTTCT
TAAAAAGAGXXXXXGA–PTZ

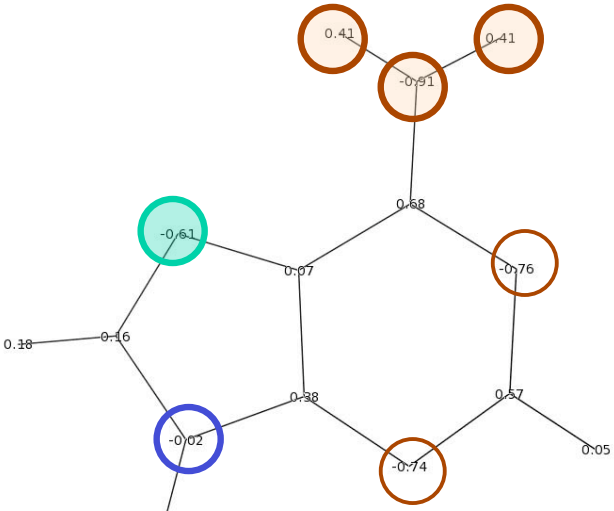
Table 1. Melting Temperatures of Duplexes (T_m)

DNA	X	T_m (°C)
a0		48.2
a5	Z	41.6
a5	D	52.1

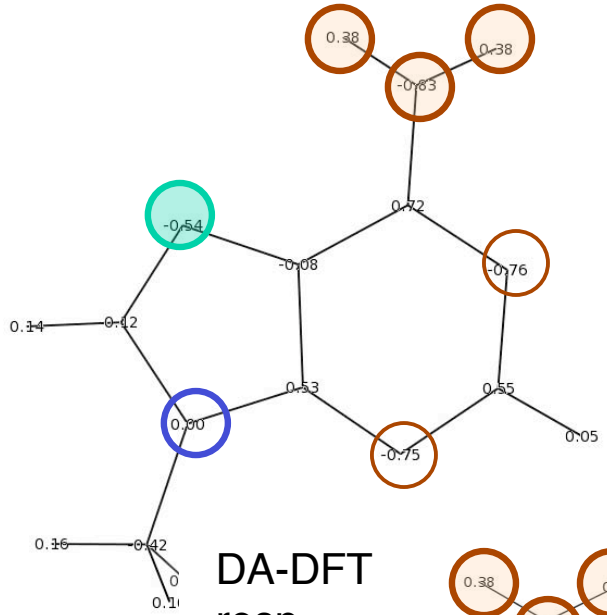
- D-T gives more stable duplexes than Z-T and even A-T
- But… charge transfer ~20 times slower that with Z-T in the same sequence

Z-T or D-T ???

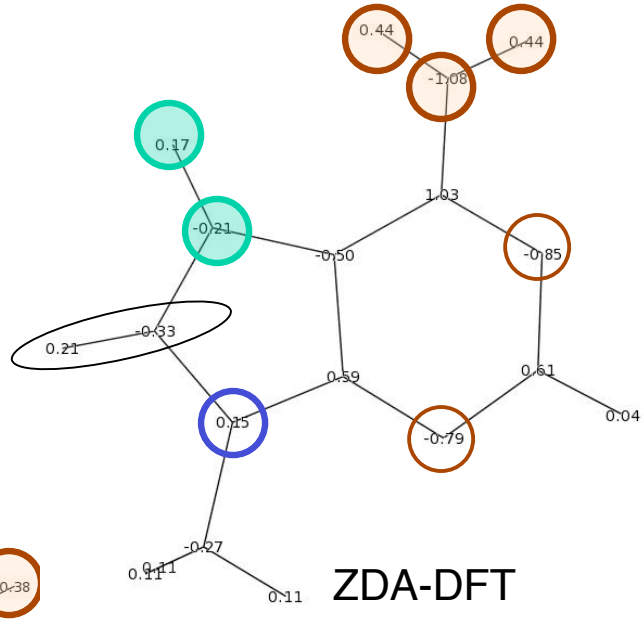
Parametrization from *ab-initio*



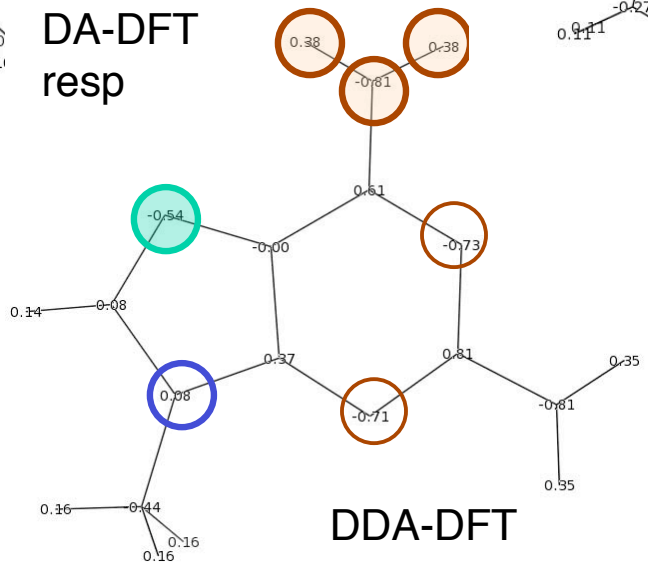
DA-AMBER
parm99



DA-DFT
resp



ZDA-DFT
resp



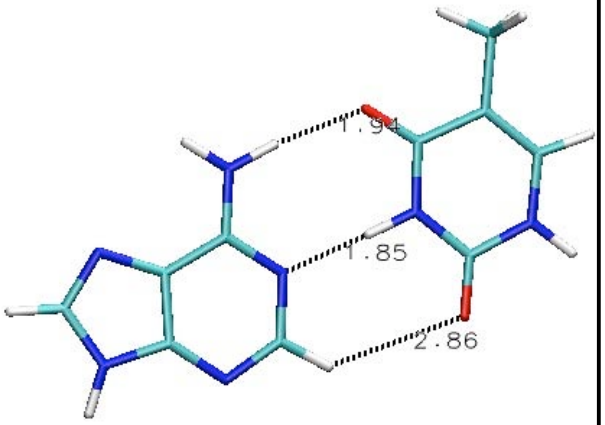
DDA-DFT
resp

Parameters were taken from Amber parm99 force field with exception of charges.
Charges were derived from ESP grid points and from these a set of RESP atomic charges was derived.
Missing parameters were built using tools of the AMBER package, using the geometries relaxed from DFT calculations

DFT: BHH/cc-pVTZ

AMBER: parm99

H-bonding interactions

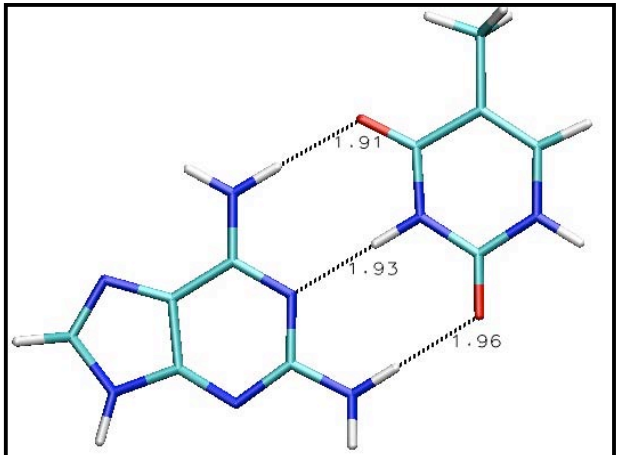


A - T (opt)

$\Delta E_{(DFT)}$= -13.14

$\Delta E_{(AMBER)}$= -16.56

$\Delta E_{(MP2)}$= -14.57

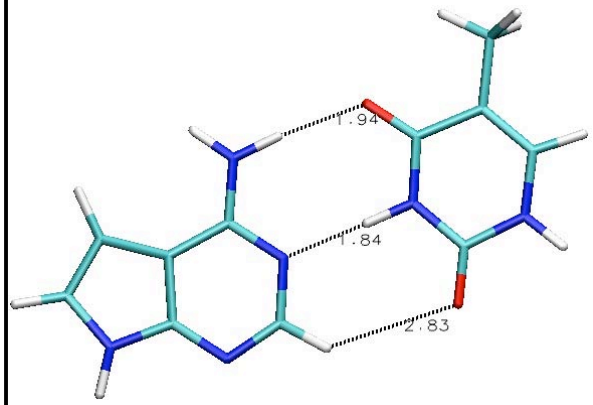


D - T (opt)

$\Delta E_{(DFT)}$= -15.84

$\Delta E_{(AMBER)}$= -18.75

$\Delta E_{(MP2)}$= -17.47



Z - T (opt)

$\Delta E_{(DFT)}$= -13.46

$\Delta E_{(AMBER)}$= -16.90

$\Delta E_{(MP2)}$= -14.94

Interaction Energies (Kcal/mol)
DFT: BHH/cc-pVTZ; MP2: MP2/6-31G(d,0.25) and AMBER: parm99

J. R. Blas, F. J. Luque, M. Orozco *JACS* Vol. 126, No. 1 (2004)

Complex systems in Solvent

1♦ Effects induced on stacking interactions

2♦ Effects induced on H-bonding

3♦ Effects of structural fluctuations

4♦ Modifications induced by the water solvent

Molecular Dynamics (MD)

Multi-scale Approach

1. **Structure**: compute the dynamical trajectory of the chosen DNA-based compound oligomer in a **octahedral box** of water molecules over **20 ns** → **snapshots at selected times** → Electronic Structure DFT *ab-initio*

MD Simulation Protocol

(i) Minimize water

(ii) minimize all system

(iii) 20 ps MD (T =100K) of system with restrains in DNA (K=100 Kcal/mol A)

(iv) as (iii) but T =300K (K=100 Kcal/mol A)

(iv) 25 ps MD (T =300K) of system with restrains in DNA (K=50 Kcal/mol A)

(v) 25 ps MD (T =300K) of system with restrains in DNA (K=25 Kcal/mol A)

(vi) 25 ps MD (T =300K) of system with restrains in DNA (K=10 Kcal/mol A)

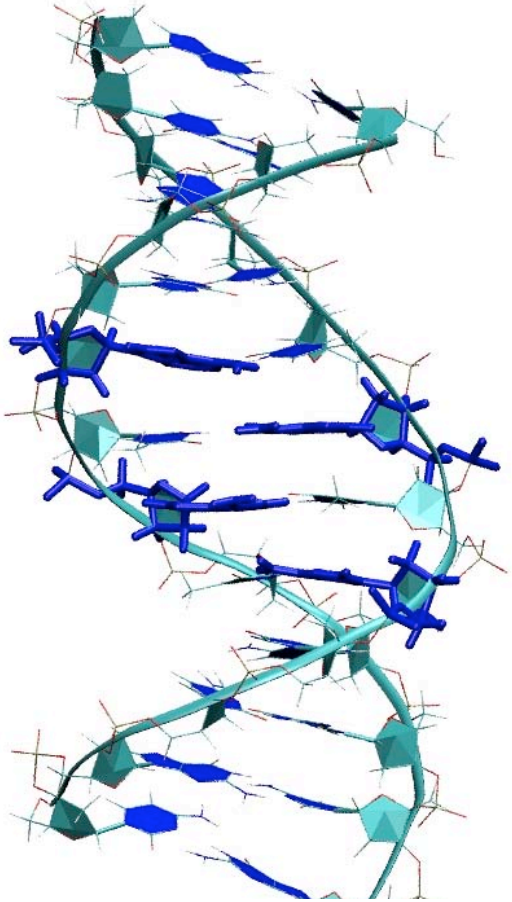
(vii) 25 ps MD (T =300K) of system with restrains in DNA (K=5 Kcal/mol A)

(viii) 25 ps MD (T =300K) of system with restrains in DNA (K=0.2 Kcal/mol A)

Final system is the starting point for 20 ns, unrestrained MD (T= 300 K)

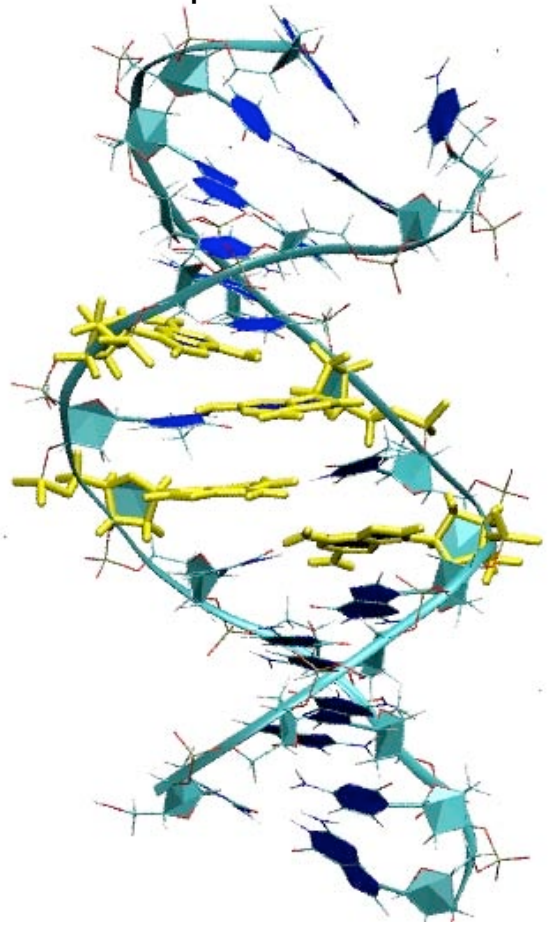
MD in fully explicit water

Snapshot at 20 ns



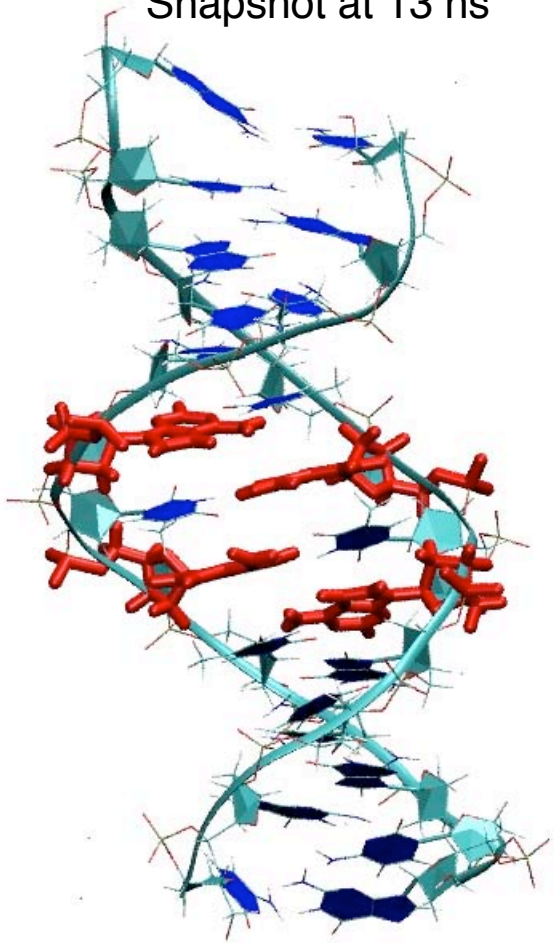
5’-CGCGATATCGCG-3’
3’-GCGCTATAGCGC-5’

Snapshot at 14 ns



5’-CGCGDTDTCGCG-3’
3’-GCGCTDTDGCGC-5’

Snapshot at 13 ns



5’-CGCGZTZTCGCG-3’
3’-GCGCTZTZGCGC-5’

Computational supercell neutralized with Na+

Perspective work..

…once the FF params are checked and validated …

Electronic and Conductivity Properties:

1 We study Duplexes with 12 bp composed of A/Z/D-T base-pair with G-C at the ends

2 We Extract a 5bp duplex from the center and we compute conductivity (SIESTA, c/o M. Fuentes-Cabrera)

3 Electronic properties we could get the whole 12 bp duplex (NWCHEM, G. Brancolini)

Summary

Summary

- **Density functional theory**
  - From the ground state to the excited states (transport and optics)… the road is opening up
  - Predictive potentiality
- **Modified DNAs with better charge transfer are viable**
- **Role of conformational flexibility and environment**

People

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Daniele
Varsano

HouYu Zhang

Giorgia
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Elisa Molinari

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Stefano Corni
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HouYu Zhang (M-DNA)
Daniele Varsano (TDDFT, xDNA, G4/A4)
Manuela Cavallari (molecular dynamics of G4)
Agostino Migliore (electron transfer, xDNA)
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