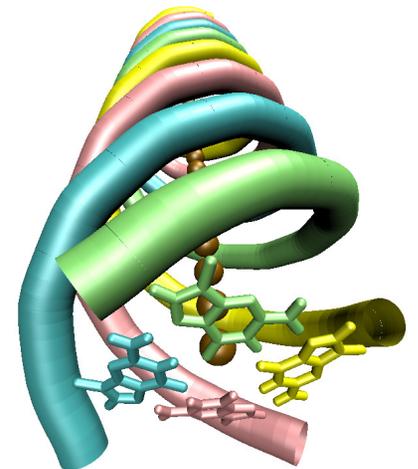


Density functional theory and molecular dynamics of DNA-derivatives for nano-electronics

Rosa Di Felice
rosa.difelice@unimore.it

Natl Center on nanoStructures and bioSystems
at Surfaces (**S3**) of INFM-CNR
Modena, Italy



Outline

▪ Current understanding and further needs

- Better measurements
- Towards synthetic DNA-derivatives

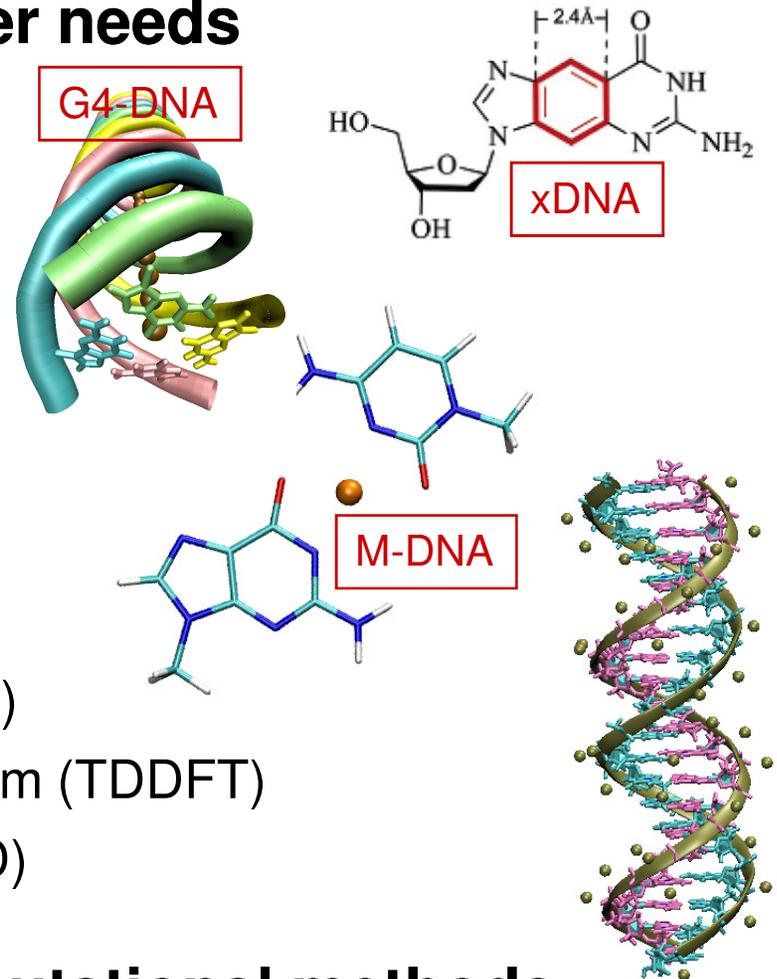
▪ Candidates

- G4-DNA, xDNA, M-DNA, dsDNA
- Intercalators and sequence alterations

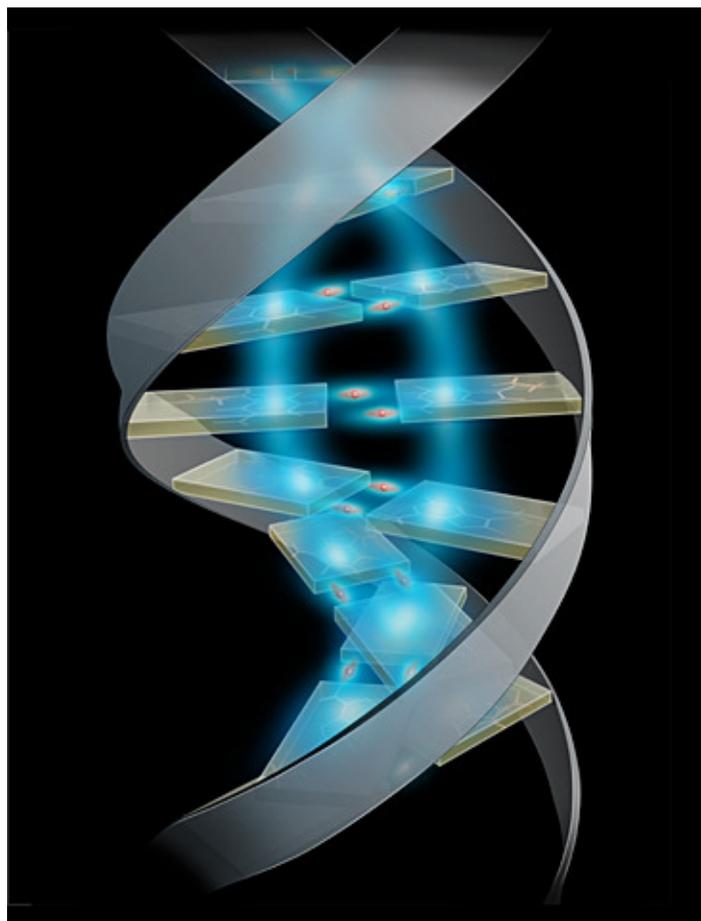
▪ Properties of interest

- Structure and electronic structure (DFT)
- Optical absorption and circular dichroism (TDDFT)
- Dynamics and energetics (classical MD)

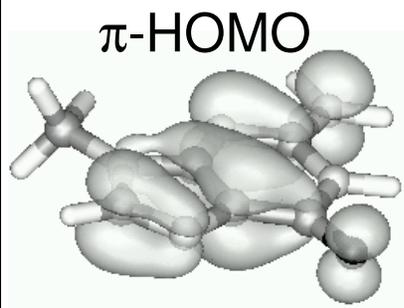
▪ Selected results by various computational methods



Rationale: the Π -way?



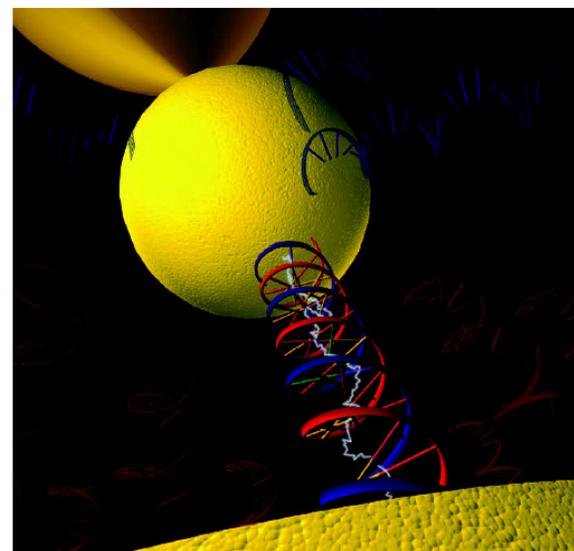
<http://www.energyislife.org/?paged=2>



Faraday Discussions

Vol 131

Molecular Wires and Nanoscale Conductors



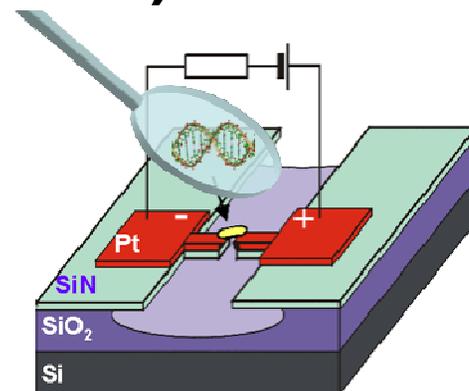
RSC Publishing

D. Porath, PNAS 2005,
Faraday Disc. 2006

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

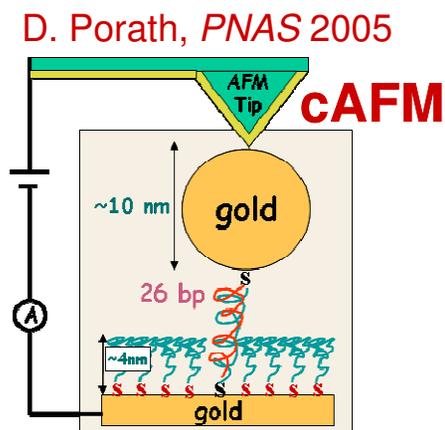
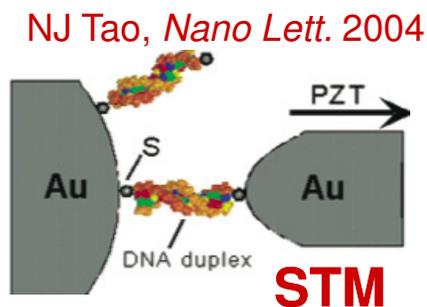
- Improve intrinsic conductivity

- Metal insertion
- Base modification
- Helical conformation

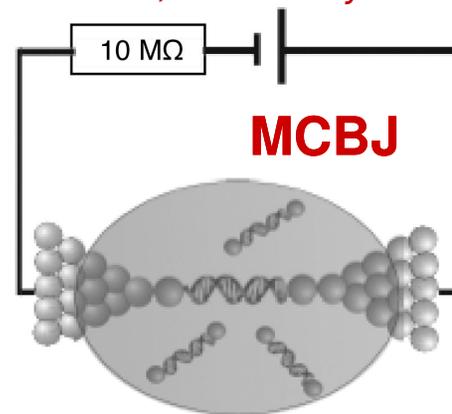
How can the difficulty in measuring conductivity be bypassed?

• Improving measurement setup

Avoiding non-specific molecule-substrate contact
Optimizing covalent molecule-electrode contact



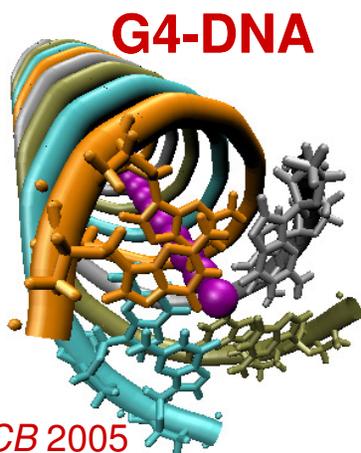
E. Scheer, *New J. Phys.* 2008



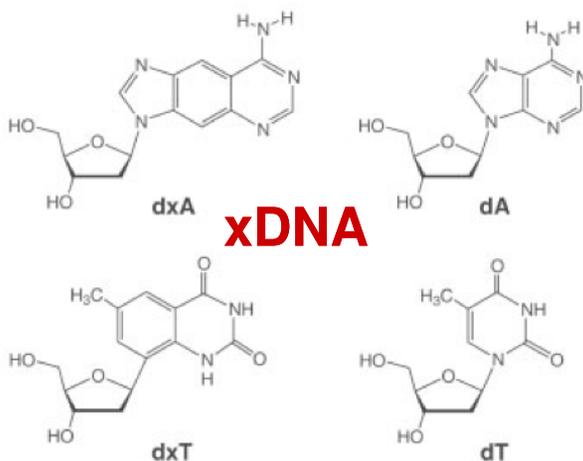
How can the difficulty in measuring conductivity be bypassed?

• Exploring DNA-derivatives

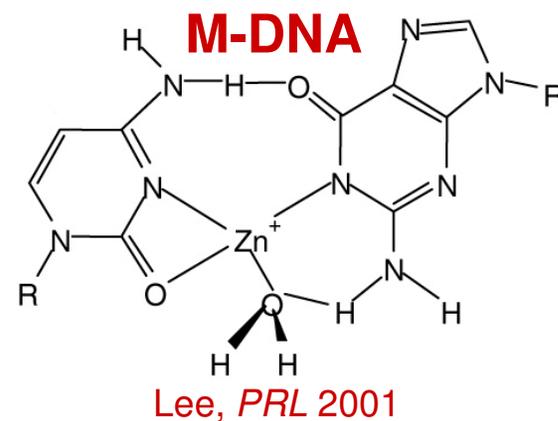
Guanine quadruplex
Aromatic base expansion
Metal complexation



Di Felice, *JPCB* 2005



Kool, *Science* 2003

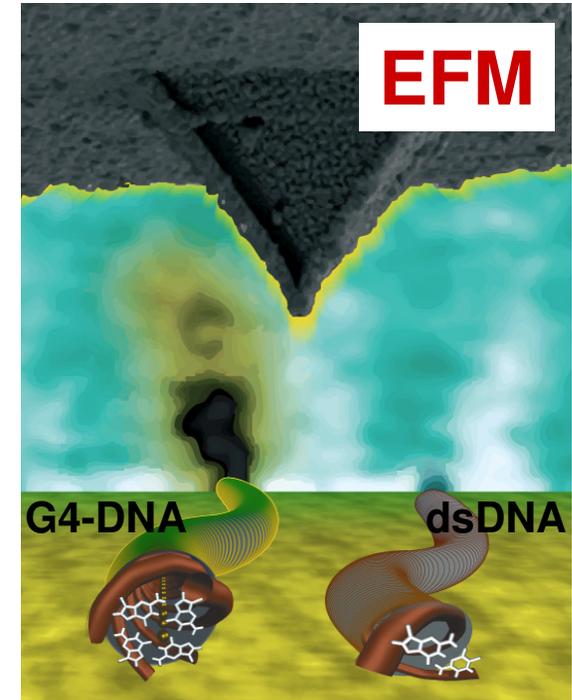
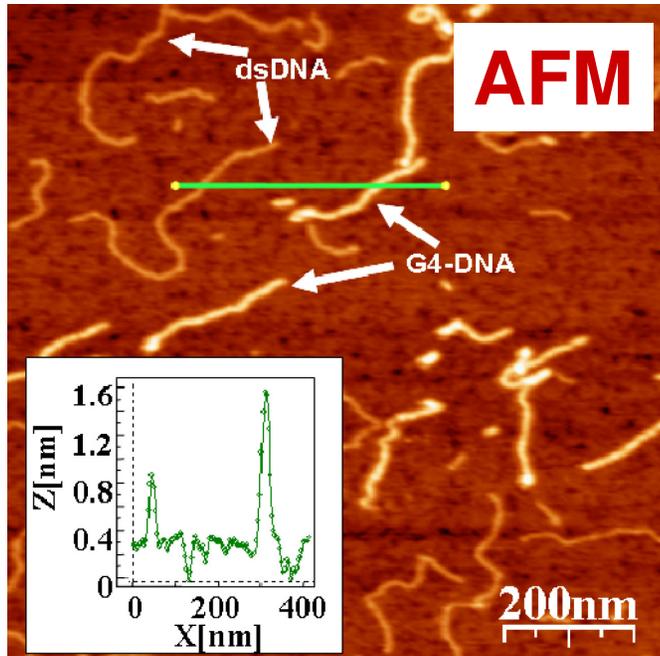


Lee, *PRL* 2001

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)

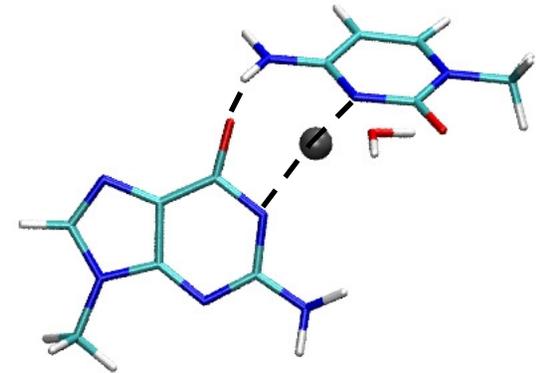


- **AFM topography**: Higher **stiffness** (brighter, thicker) and **persistence length** than duplex DNA → may improve resistance against deformation on hard surfaces
- **EFM phase map**: Polarizable G4-DNA against non-polarizable dsDNA

Other appealing candidates

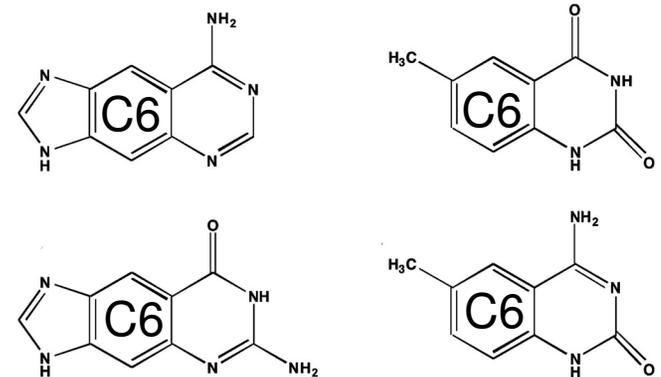
▪ MDNA

- 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



Properties of interest

Electronic structure by DFT

▪ Why?

- Transport measurements
- Scanning tunneling spectroscopy measurements

▪ General procedure

- Hypothesize viable initial *model* conformations and annihilate atomic forces until convergence
 - X-ray or NMR structures; chemical intuition
- Compute the self-consistent electronic structure for the optimized geometry
- Analyze energy levels, density of states, charge density distribution, individual wave functions → interpretation of possible conduction behavior
- Compute transfer integrals when possible

Method: DFT

electronic structure

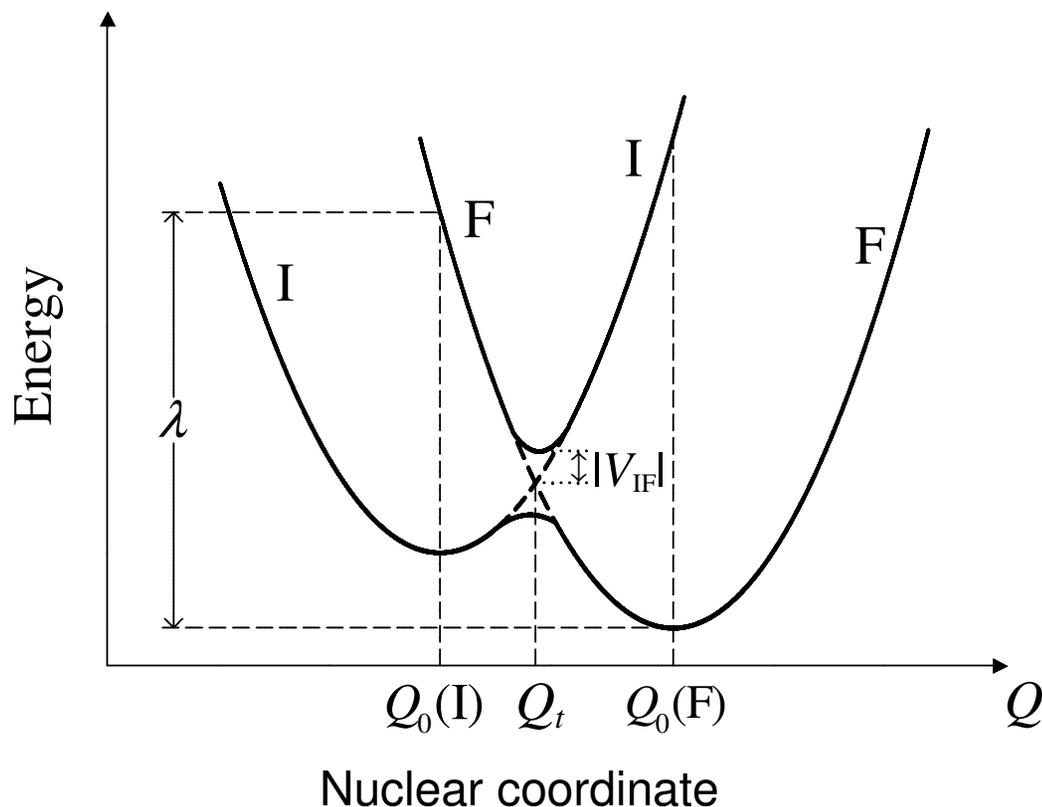
▪ Structural Optimization and electronic structure

- PWSCF: Plane-wave pseudopotential DFT (LDA, PW91, PBE)
<http://www.quantum-espresso.org>
 - Particularly suitable to describe structures with long-range order
- NWChem, Gaussian: DFT with gaussian basis sets
<http://www.emsl.pnl.gov/docs/nwchem/nwchem.html>,
www.gaussian.com

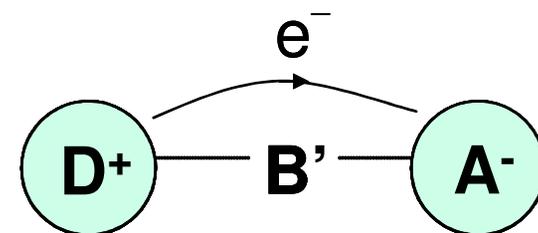
▪ Analysis of the electronic properties

- Bandstructure: $\epsilon_{i,k}$
- Isosurface plots of Bloch orbitals: $\Psi_{i,k}$
- Density of States: $D(E) = \sum_{i,k} \langle \Psi_{i,k} | \Psi_{i,k} \rangle \delta(\epsilon_{i,k} - E)$ $D_\phi(E) = \sum_{i,k} \langle \phi | \Psi_{i,k} \rangle \delta(\epsilon_{i,k} - E)$
- Transfer integrals

Electron transfer rates from DFT



Potential energy surfaces of the initial and final states in a typical ET reaction: **interaction** \Rightarrow **splitting at transition coordinate**



Marcus' formula for ET rate

$$k = \frac{2\pi}{\hbar} |V_{IF}|^2 \frac{e^{-\frac{(\lambda + \Delta G^0)^2}{4k_B T \lambda}}}{\sqrt{4\pi k_B T \lambda}}$$

λ = nuclear reorganization energy

V_{IF} = electronic coupling

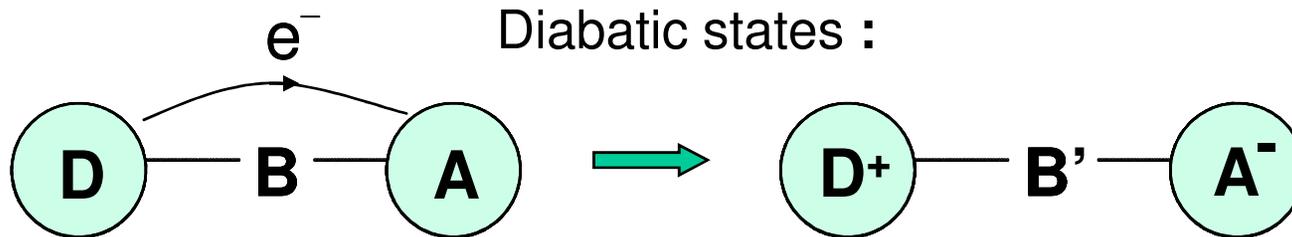
Theoretical approach to ET

$$V_{\text{IF}} = \frac{1}{1 - S_{\text{IF}}^2} \left| H_{\text{IF}} - \frac{H_{\text{II}} + H_{\text{FF}}}{2} S_{\text{IF}} \right| = \left| \frac{ab}{a^2 - b^2} \Delta E_{\text{IF}} \right|$$

$\Delta E_{\text{IF}} = E(\psi_{\text{I}}) - E(\psi_{\text{F}})$ energy difference between the initial and final diabatic electronic states

a, b : overlaps between diabatic states and ground state

ground state: $|\psi\rangle = a|\psi_{\text{I}}\rangle + b|\psi_{\text{F}}\rangle + c|\psi_{\text{T}}\rangle, \quad |c| \ll |a|, |b|$



$$|\psi_{\text{I}}\rangle = |D\rangle|A\rangle$$

$$|\psi_{\text{F}}\rangle = |D^+\rangle|A^-\rangle$$

CDFT: $|\psi_{\text{I}}\rangle = |D, A\rangle$

$$|\psi_{\text{F}}\rangle = |D^+, A^-\rangle$$

Optical absorption by TDDFT

▪ Why?

- Tool for structural characterization of chiral biomolecules

▪ Calculation of linear absorption spectra using OCTOPUS

(www.tddft.org/programs/octopus)

- Real-space uniform-grid implementation
- Ground state calculated within DFT
- Kohn-Sham equations are propagated in real time

$\tilde{\phi}_j(\mathbf{r})$: ground state

$$v(\mathbf{r}, t) = -k_0 x_\nu \delta(t) \quad x_\nu = x, y, z$$

Time Evolution

$$i \frac{\partial}{\partial t} \phi_i(\mathbf{r}, t) = \left[\frac{-\nabla^2}{2} + v_{KS}(\mathbf{r}, t) \right] \phi_i(\mathbf{r}, t)$$

Polarizability:

$$\alpha_\nu(\omega) = -\frac{1}{k} \int d^3 r x_\nu \delta n(\mathbf{r}, \omega)$$

photo-absorption cross-section:

$$\sigma(\omega) = -\frac{4\pi\omega}{c} \Im \sum_n \alpha_\nu(\omega)$$

Circular dichroism by TDDFT

▪ Why?

- Powerful spectroscopic tool to reveal the conformation of chiral molecules
- Clear-cut experimental data available for A strands
- Protection against **UV damage**: Delocalization through multiple bases? De-excitation mechanism?

THEORY

Time propagation of angular momentum by TDDFT with $\delta(t)$ perturbation

$$L_\nu(t) = \sum_i \langle \psi_i(t) | -i(\mathbf{r} \times \nabla)_\nu | \psi_i(t) \rangle$$

Fourier transform and imaginary part $R(E) = \text{Im} \frac{\Re(E)}{\pi}$

$R(E)$ is proportional to the measured signal (difference between left and right refraction indexes)

Gauge-invariance and other technical issues

Structure by MD and MM

▪ Why?

- Describe more complete systems and environment, though not the quantum features
- Motion of ions, rigidity and flexibility, resistance against unfolding, intercalation, conformational effects on electronic structure

▪ General procedure

- Hypothesize viable initial conformations that take into account the solvent
 - X-ray or NMR structures; chemical intuition, various electrostatic rules
- Solve the equations of motion for the “classical” ions
- Analyze the trajectories: selected distances and angles, hydrogen bonds, other structural features depending on the specific system
- Root-mean-square deviations and variance histograms

Method MD

trajectories in real time at finite temperature

$$H_I(R_I)\Psi_I\Psi_e + E_e(\{R_I\})\Psi_I\Psi_e = E_I\Psi_I\Psi_e$$

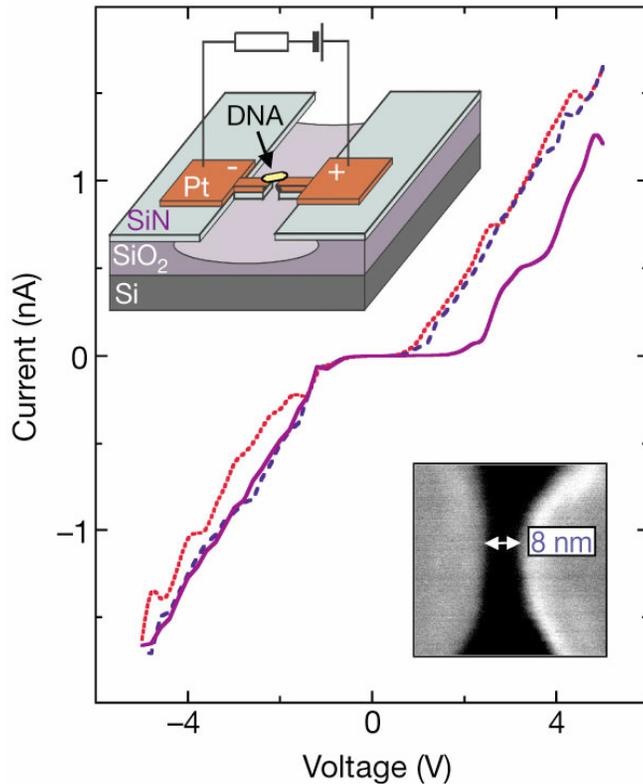
- Slow nuclei → replaced by classical particles

$$M_I \ddot{\mathbf{R}}_I = -\frac{\partial E}{\partial \mathbf{R}_I} = \mathbf{F}_I[\{\mathbf{R}_I\}]$$

- Total energy derived from quantum electronic structure calculations → quantum Molecular Dynamics (**Car-Parrinello**)
- Total energy parametrized by two-body potentials (or other forms) → classical Molecular Dynamics with a variety of force fields (**CHARMM**, **AMBER**, etc.)

Selected results

Bandstructure calculations

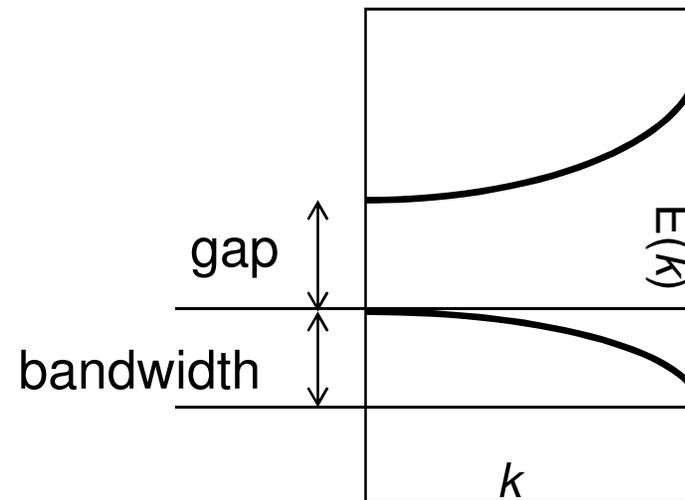


■ Inspiration

- D. Porath et al., *Nature* **403**, 635 (2000)
- “**Semiconductor**” behavior due to the **bands** of the material

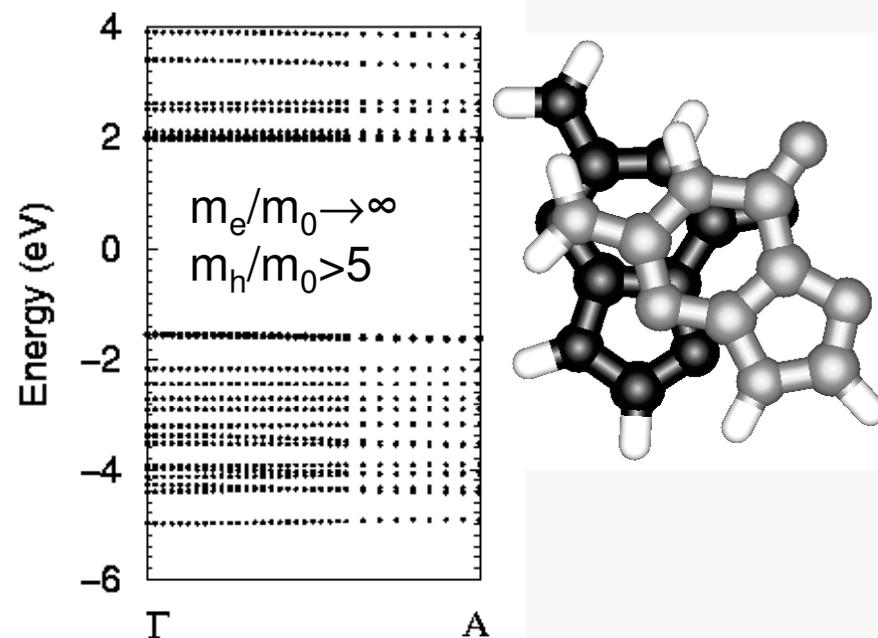
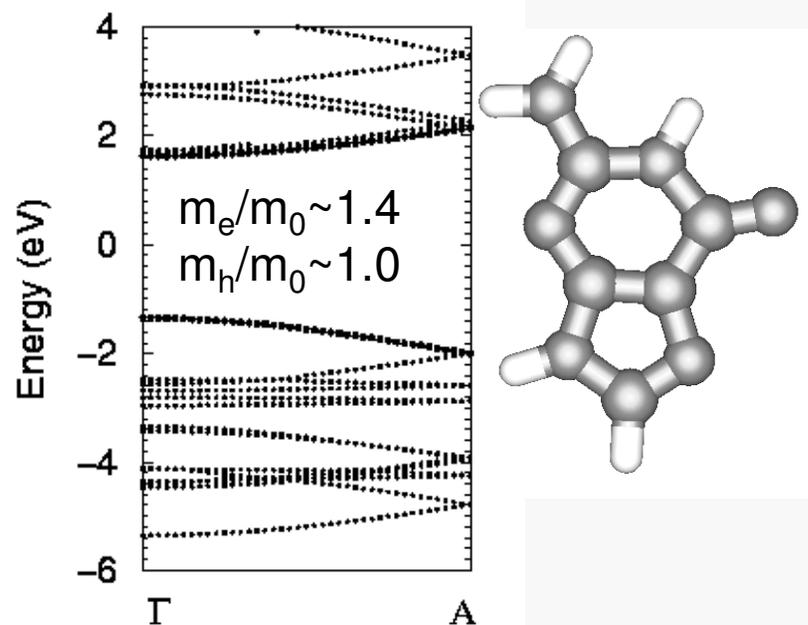
■ Semiconductor

- **Bandgap**
- Finite bandwidth: $E(k)$ **dispersion** relation



DFT with plane-wave basis set on Guanine stacks

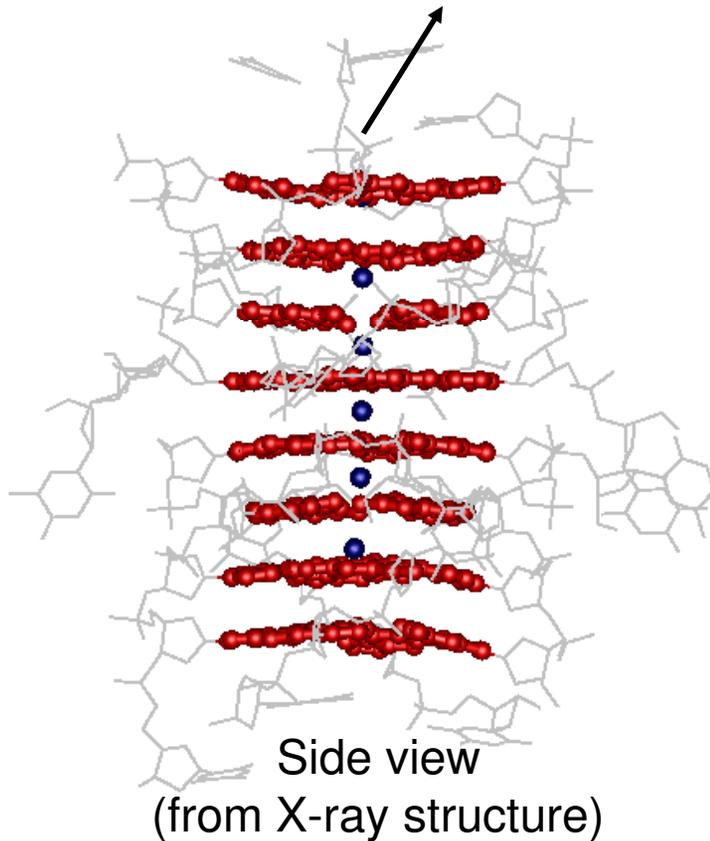
R. Di Felice et al., *Phys. Rev. B* **65**, 045104 (2002)



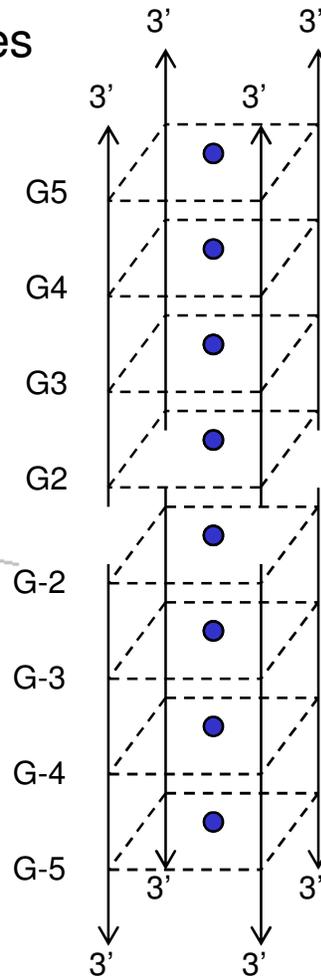
- Band dispersion and small effective masses for eclipsed guanines
- Poor band dispersion and huge effective masses for twisted guanines by 36 degrees as in B-DNA

Guanine quadruple helices (G4-DNA molecules)

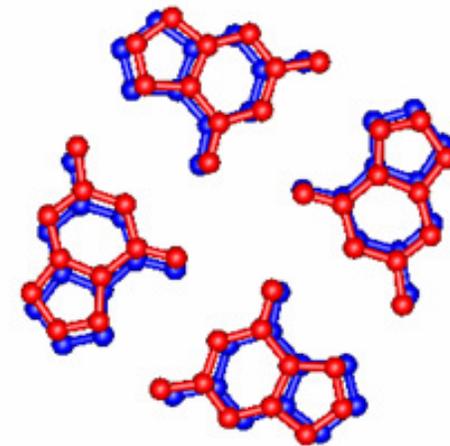
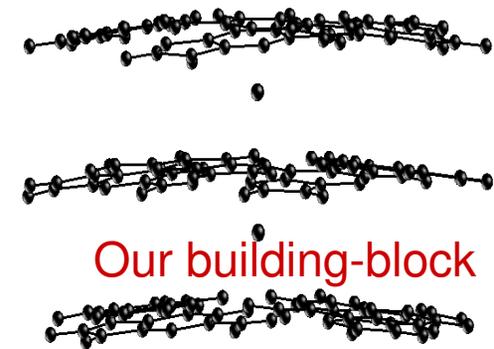
Backbone neglection
Square+translation symmetries



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



K^+

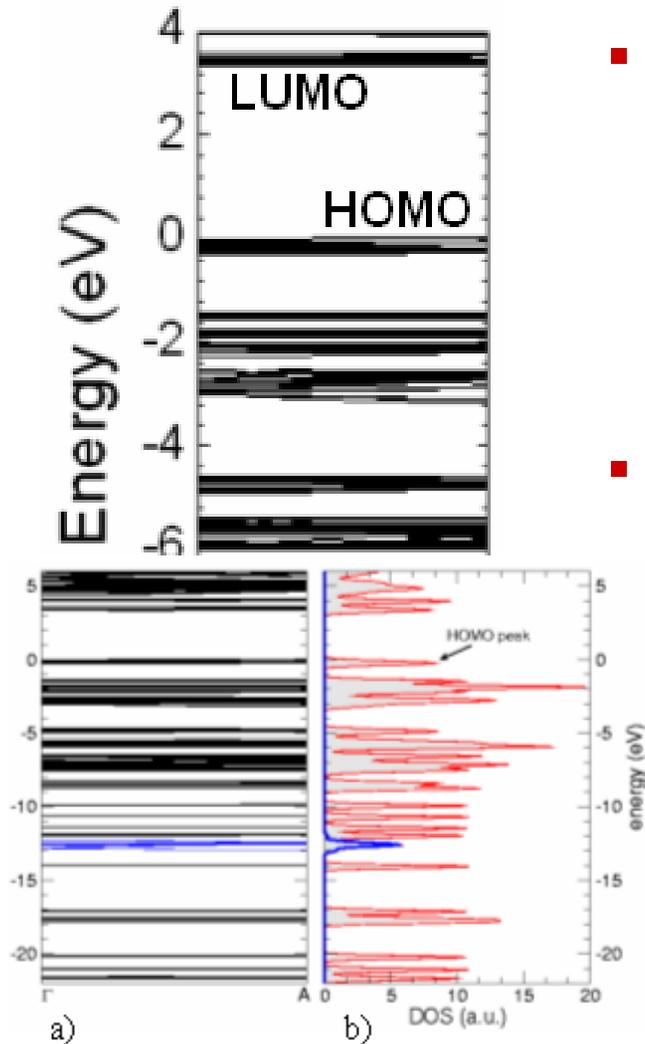


Superposition between
1st and 4th planes

DNA NANODEVICES

K(I)-G4 Electronic Structure

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

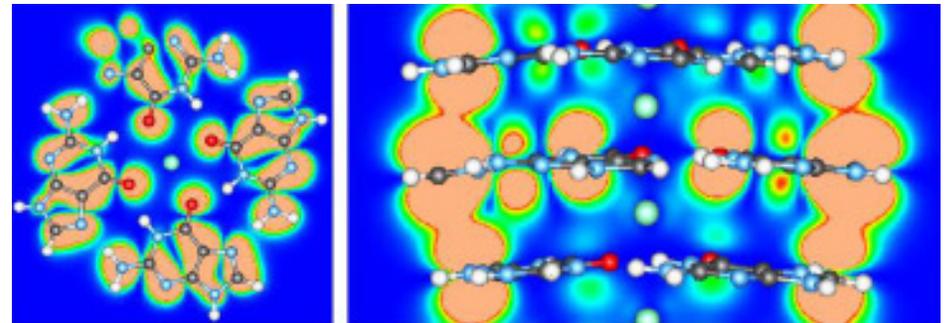


▪ Bandstructure

- Flat bands gathered in manifolds
- No dispersion along wire axis (Γ A)
- No backbone effects
- Manifolds \rightarrow effective semiconductor

▪ Contour plots

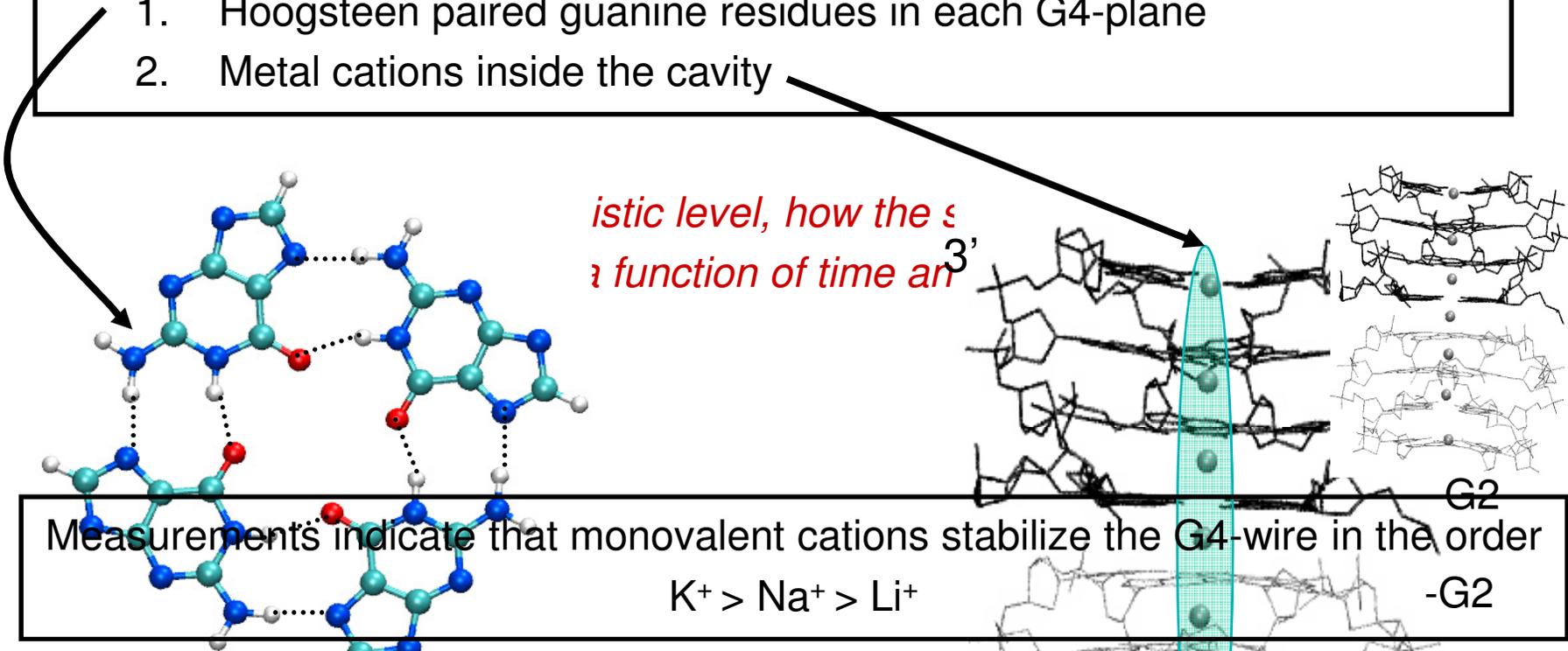
- Channels for charge motion through the bases
- Poor potassium-guanine coupling



Molecular Dynamics simulations of G4-wires

G4-wires are primarily stabilized by

1. Hoogsteen paired guanine residues in each G4-plane
2. Metal cations inside the cavity



What do MD simulations say in this context?

Can metal cations penetrate an empty or partially occupied G4-cavity?

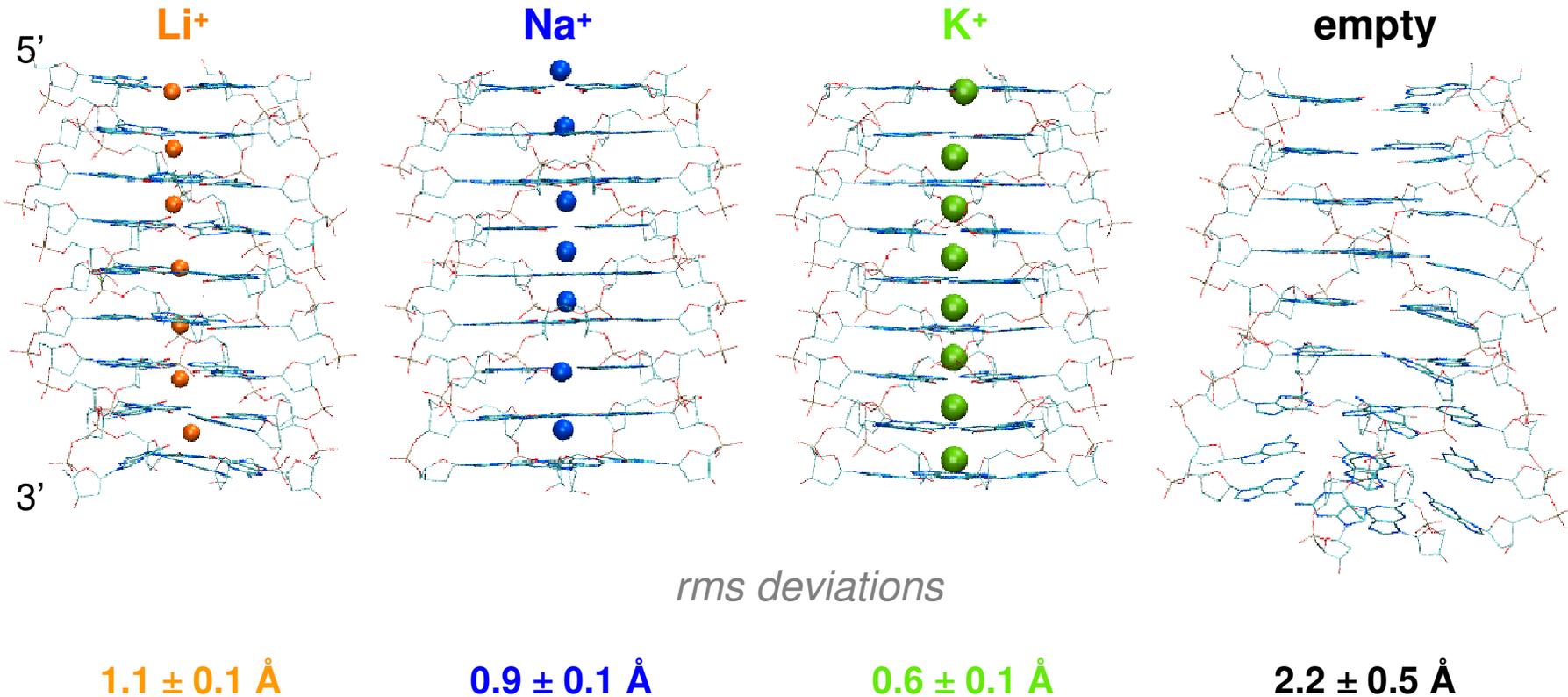
Can cations move and how efficiently inside such a cavity?

Do different ionic species perform differently with respect to the above actions?

Can empty channels exist?

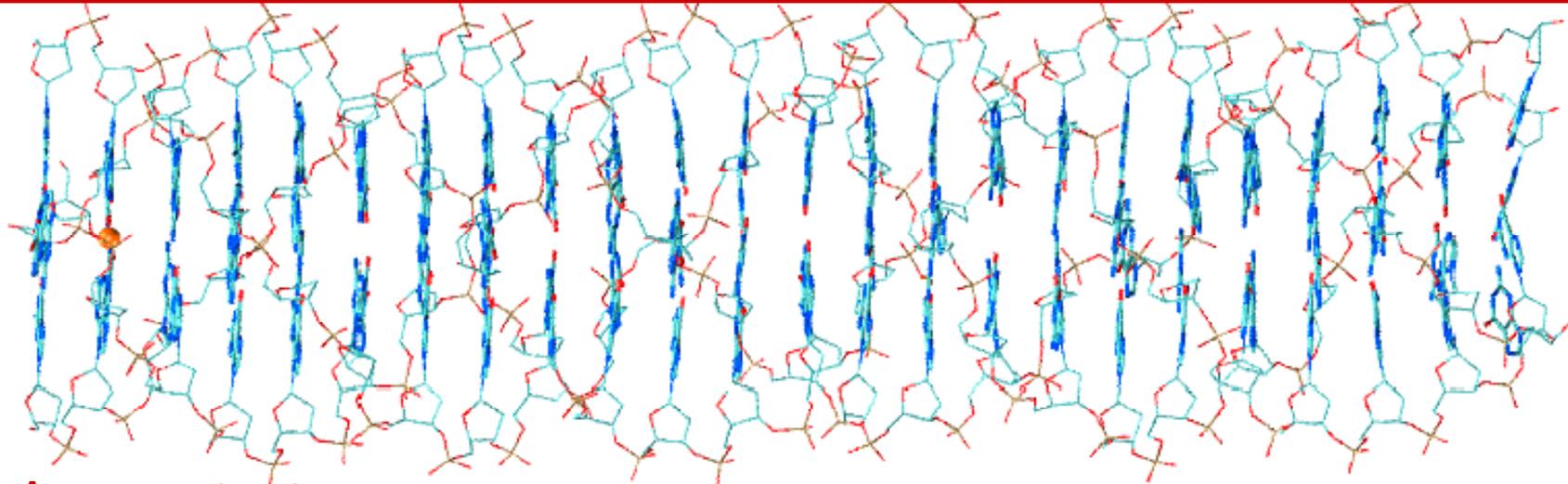
Average Structures on 5ns MD:

G4-wire Mobility



- Confirmed “stability” trend $K^+ > Na^+ > Li^+$
- Empty quadruplexes are less deformed than shorter molecules → stability is likely to improve with increasing length

A longer simulation (20 ns) of a longer helix (24 planes)



Average structure

Tetrad stacking and base co-planarity are almost precisely preserved

M. Cavallari, A. Calzolari, A. Garbesi, R. Di Felice, *J. Phys. Chem. B* **110**, 26337 (2006)

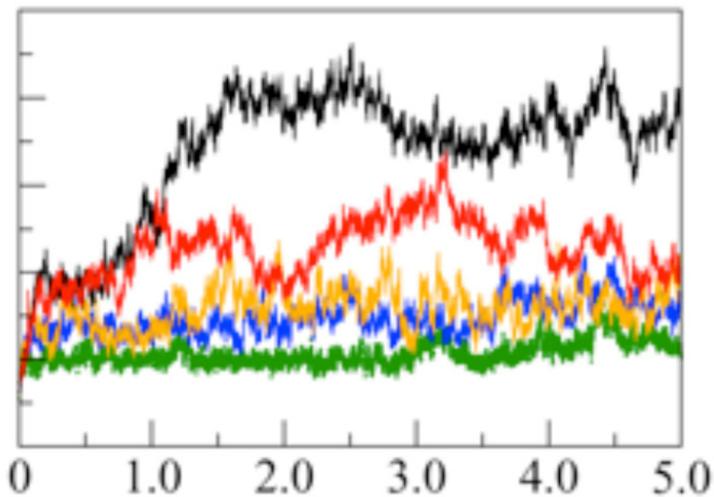


Increasing the number of stacked tetrads helps preserve the G4-wire structure against unfolding in the absence of cation coordination

Statistical analysis from MD

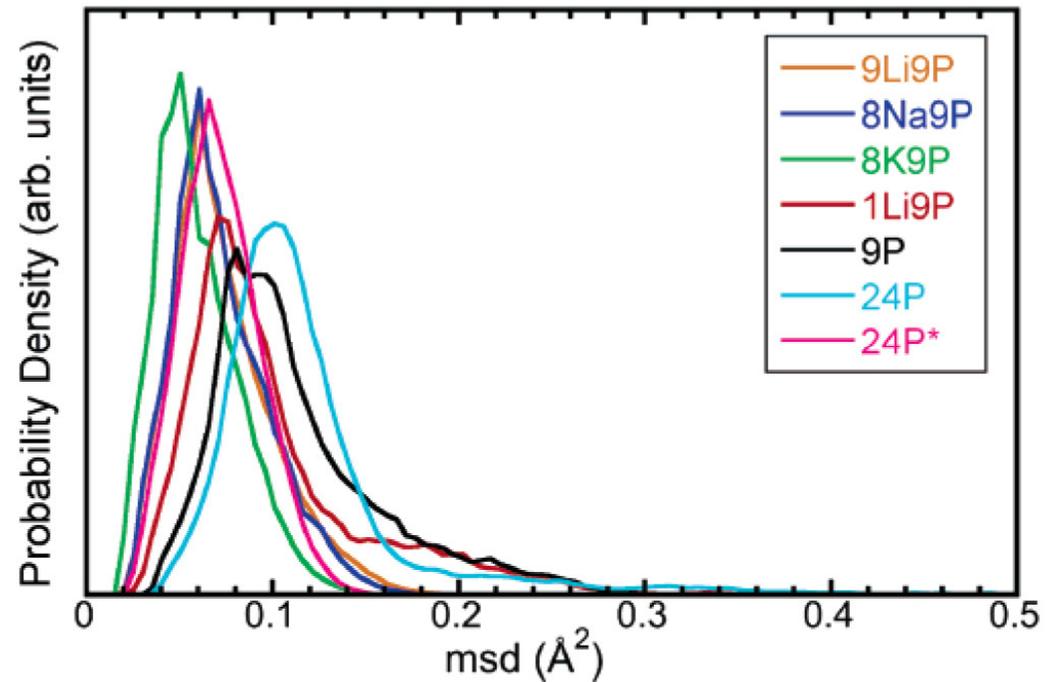
M. Cavallari, A. Calzolari, A. Garbesi, R. Di Felice, *J. Phys. Chem. B* **110**, 26337 (2006)

G-base rms deviations (Å)



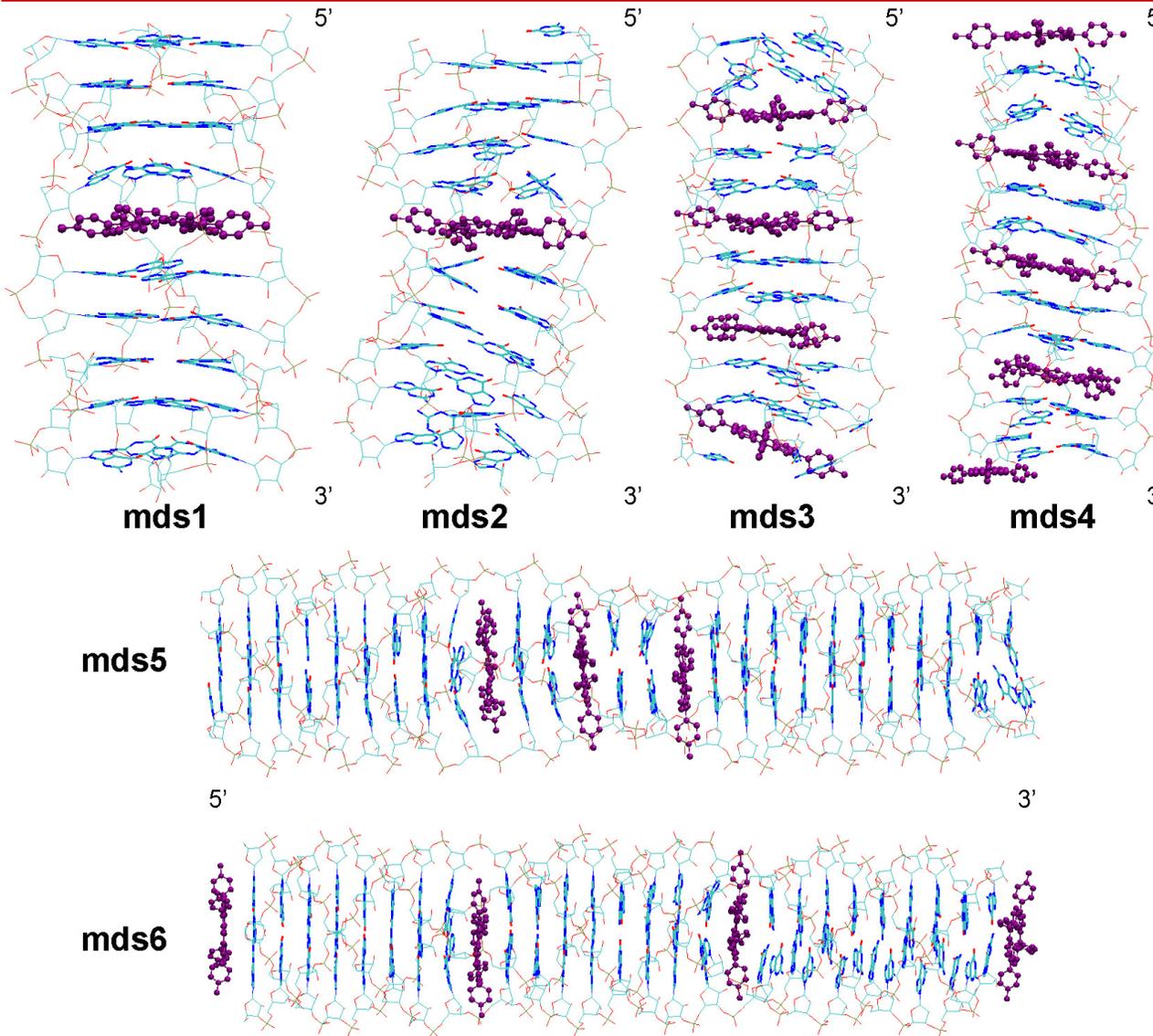
$$RMSD(t) = \left[\frac{1}{N} \sum_{i=1}^N [r_i(t) - \langle r_i \rangle_T]^2 \right]^{1/2}$$

- N=total number of atoms
- T=total simulation time (after equilibration)
- $\langle \rangle$ =average



Analysis of the variance after:
L. Maragliano et al., *Biophys. J.* **86**, 2765 (2004)

Porphyrim intercalation



Average structures from 10-ns (mds, mds, mds3, mds5) and 20-ns (mds4, mds6) runs

Major deformations in mds2 and mds3

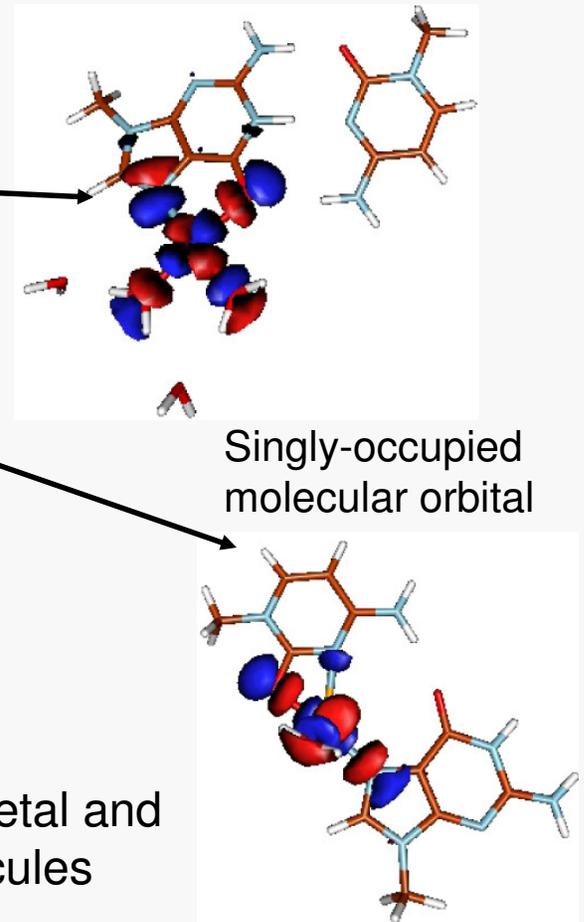
Larger 1/8 TMPyP/tetrad ratio in mds6 more regular than the smaller 1/2 ratio in all other structures

TMPyP intercalation in long G4-DNA quadruplexes viable

DFT on MDNA base-pairs

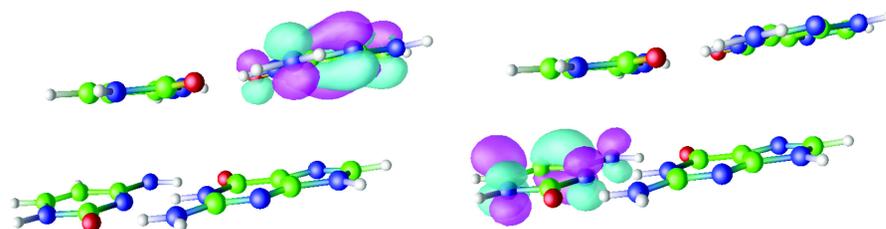
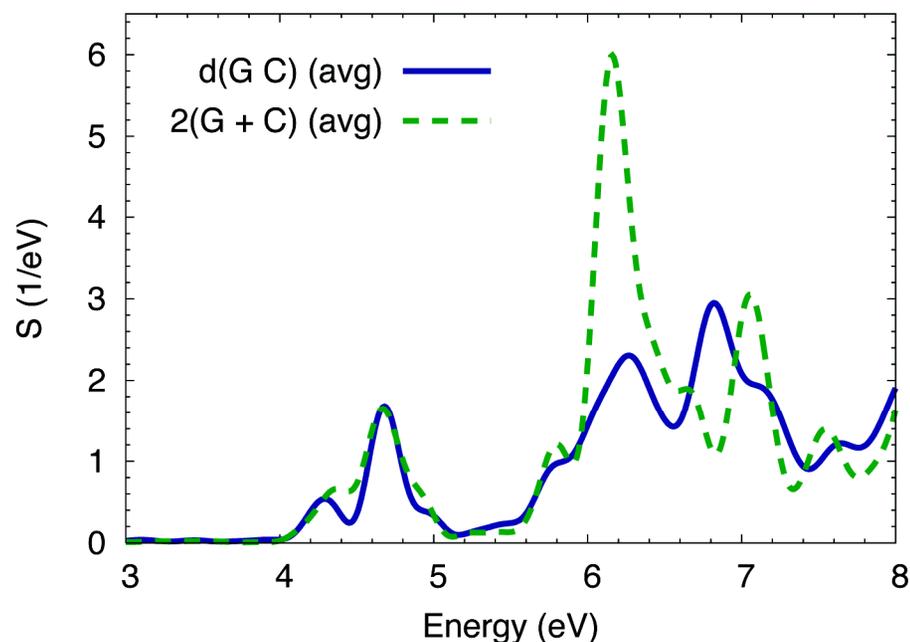
G. Brancolini and R. Di Felice, *J. Phys. Chem. B* **112**, 14281 (2008).

Structure	HOMO-LUMO gap
Natural GC	3.78, 3.79, 3.75
Cu(II)-N7-4aH2O	1.01 [3.32]
Cu(II)-N7	0.65
Cu(II)-lipsyn-2H2O	1.76 [3.73]
Cu(II)-imino	1.77 [3.87]
Cu(II)-imino-2H2O	1.21 [3.23]
Cu(I)-imino	3.23
Zn(II)-imino-H2O	3.36
Zn(II)-N7-5H2O	4.17
Zn(II)-lipsyn-2H2O	4.47
Ag(I)-N7	3.39
Ag(I) imino	3.36



- Modulation of the HOMO-LUMO gap depending on the metal and its coordination to the surrounding bases and water molecules
- Possible metal-base hybridization in the frontier orbitals, strongest with Cu and weakest with Zn

Optical absorption of GC pairs: combined effect of **stacking** and **H-bonding**



- Main effect of **H-bonding**: small redshifts at low energies
- Main effect of **stacking**: hypochromicity at higher energies (~62% for most intense peak)
- H-bonding and stacking act separately

Optical absorption of x-bases

Recent DFT studies of electronic properties

- Role of π -ring
- M. Fuentes-Cabrera & coworkers, *J. Phys. Chem B* **109**, 21135 (2005); *J. Phys. Chem. B* **110**, 6379 (2006); *J. Phys. Chem. A* **110**, 12249 (2006)

Consequences on optics?

Relation to natural bases?

- Shifts and hypochromicity

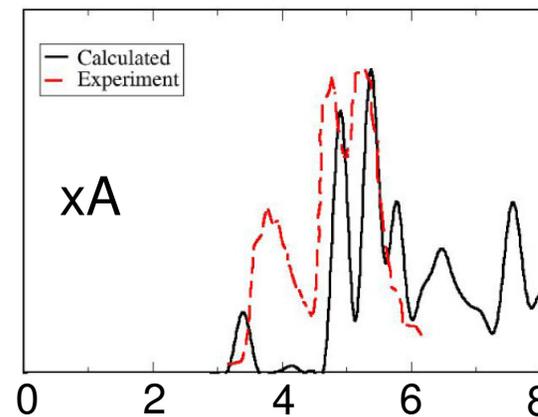
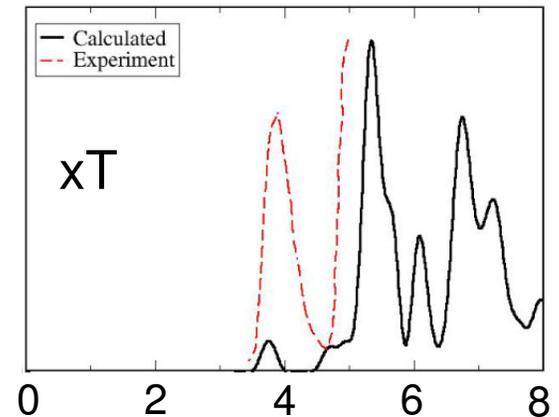
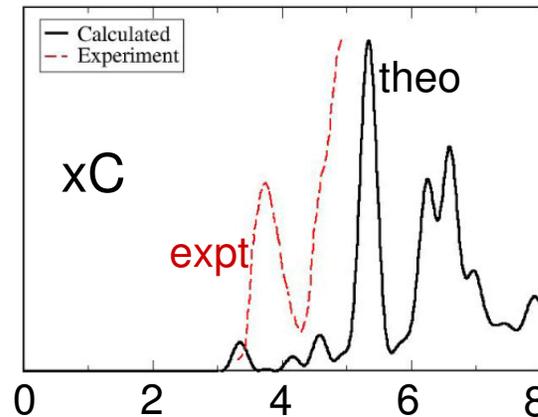
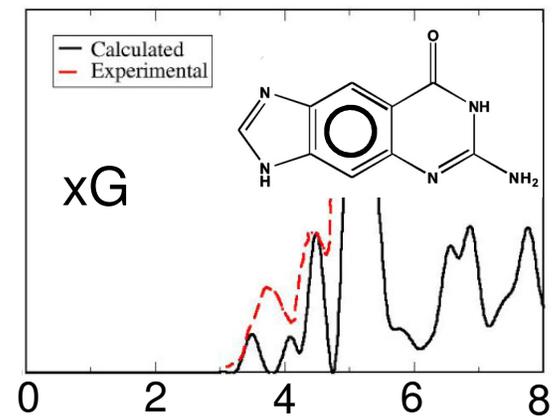


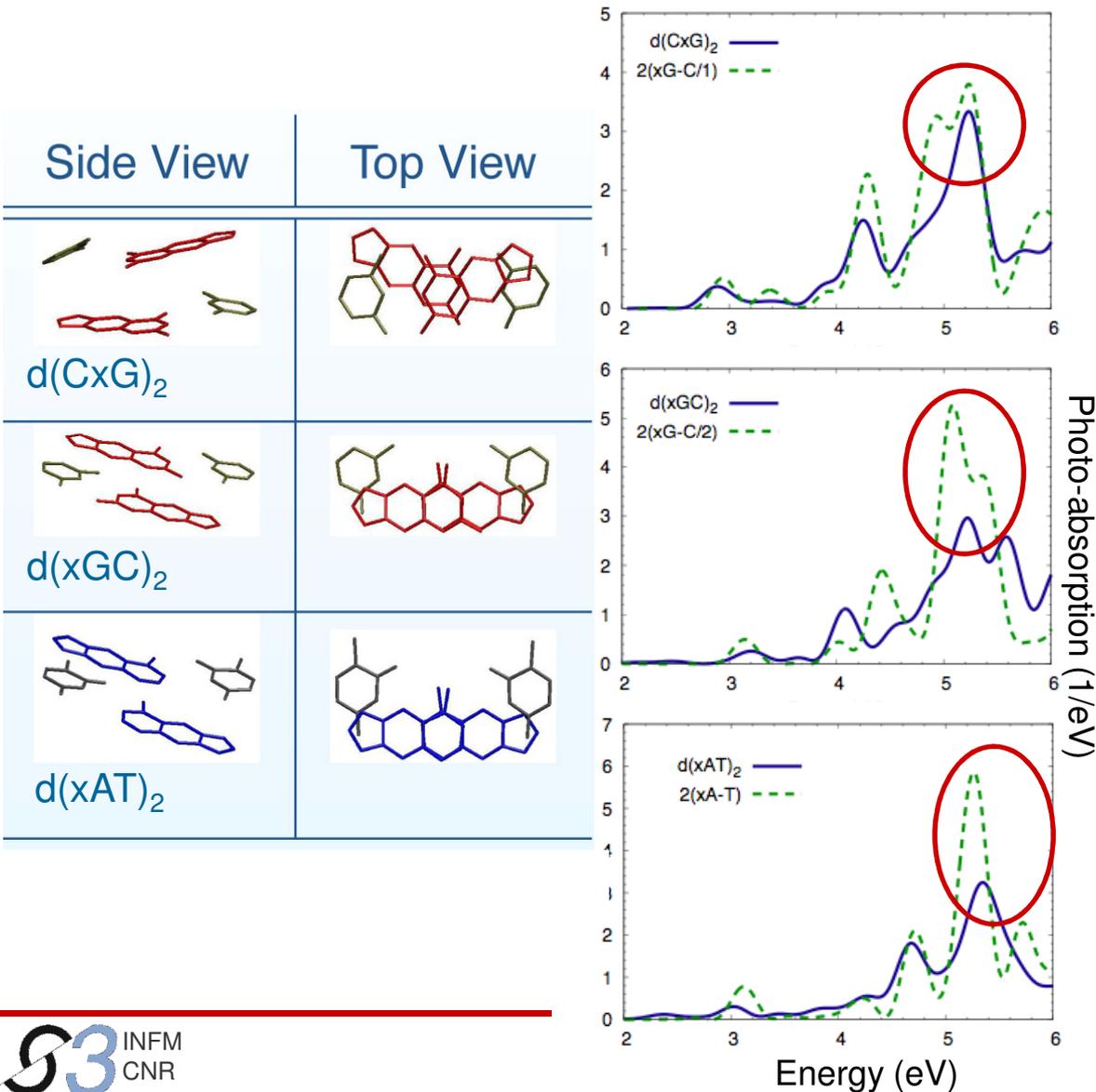
Photo-absorption



Energy (eV)

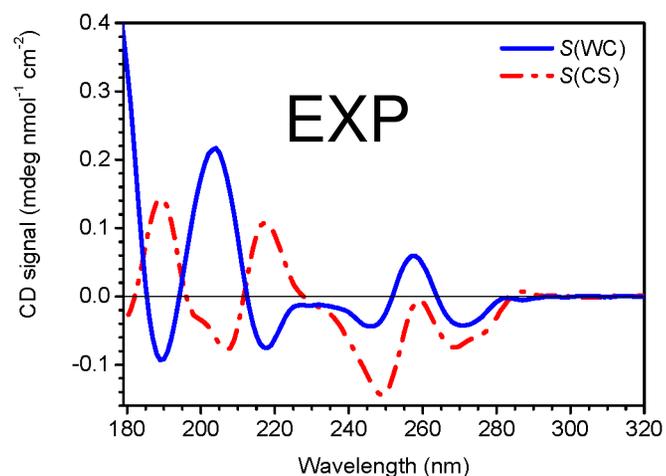
Optical absorption of x-base stacks

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

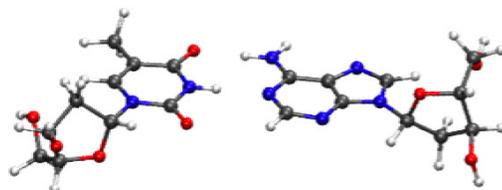


- H-bonding → **redshift** of low-energy excitations (not visible here)
- Stacking → pronounced **hypochromicity**
- Hypochromicity is stronger for structures with regular overlap between x-pairs
- Overall: qualitative behavior similar to stacks of natural pairs, but with strong structural dependence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

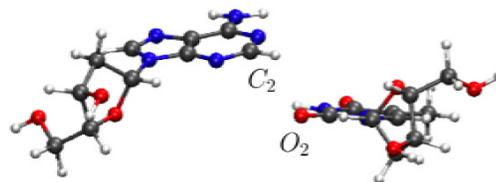
Early circular dichroism attempts



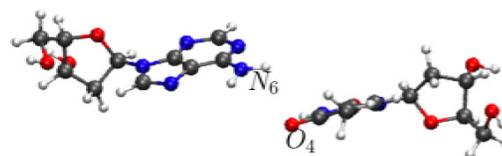
Data by Steen Nielsen, Aarhus University



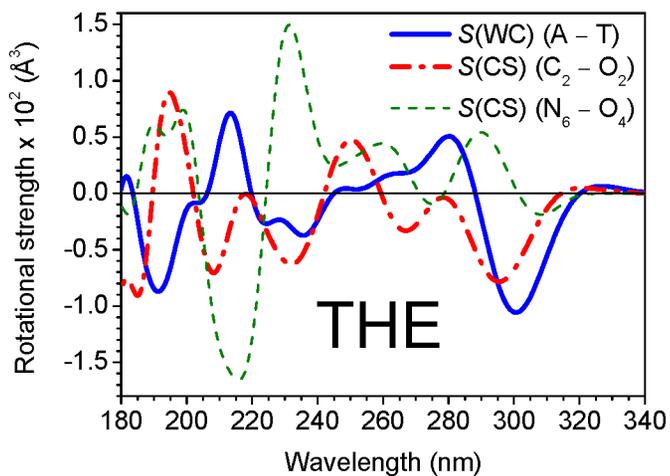
WC



CS C₂...O₂



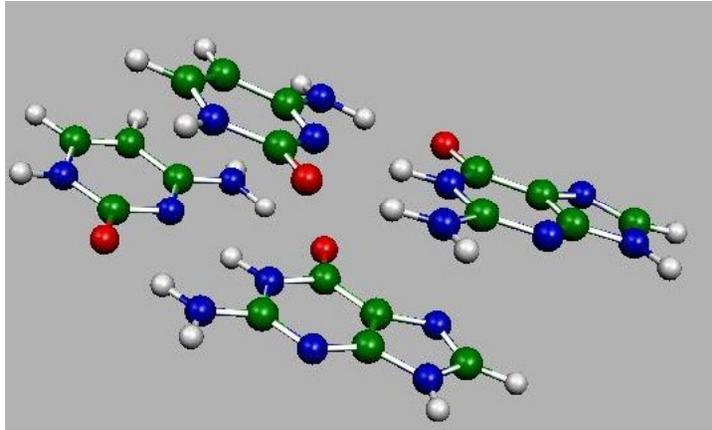
CS N₆...O₄



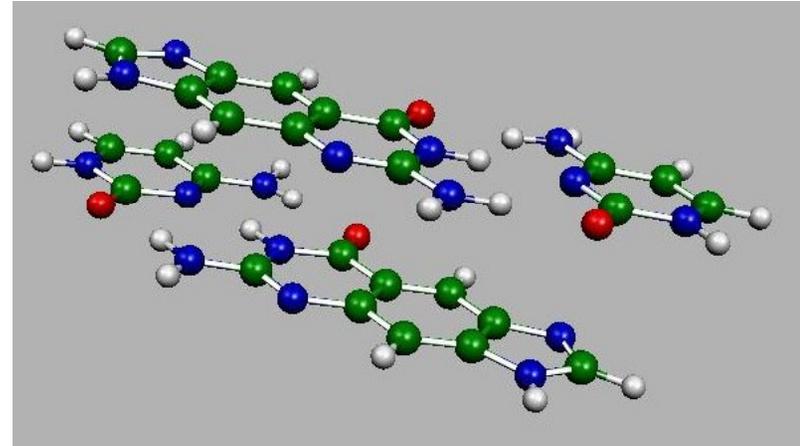
Transfer integrals between x-pairs

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?

Methodological tests on GG stacks

	Method	(eV)	(eV)	(eV)
	6-31g*	0.498	0.141	0.129
	6-311++g**	0.441	0.075	
Our work with the BHH exchange-correlation functional	6-311++g(3df,3pd)	0.426	0.065	
	cc-pVTZ	0.439	0.076	
	TZVP	0.446	0.076	0.069
	TZVP + BSSE	0.446	0.076	
Our work with other exchange-correlation functionals	6-31g*, PBE0			0.619
	6-31g*, B97-3			0.627
	6-31g*, B3LYP			0.726
	6-31g*, B97			0.751
Other DFT-based works	SCC-DFTB		0.061 (0.087)	
	DFT, TZ2P in ADF		0.053 (0.119)	
HF-based works	KTA, HF/6-31g*		0.081-0.084	
Post-HF-based work	CASSCF(7,8), 6-31g*	0.414	0.067	
	CASSCF(11,12), 6-31g*	0.370	0.049	
	CASPT2(11,12), 6-31g*	0.392	0.051	

Good performance relative to post-Hartree-Fock methods

Natural versus size-expanded base pairs

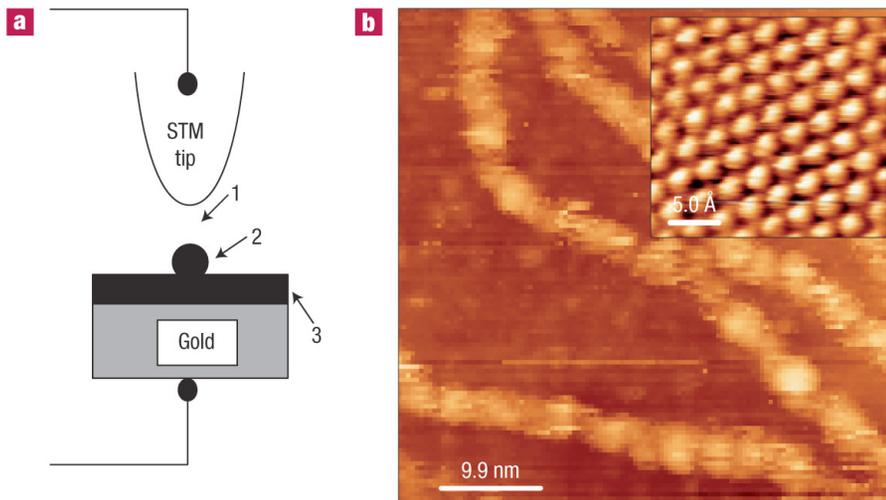
GC-GC		xGC-xGC		AT-AT		xAT-xAT	
Real	Ideal	Real	Ideal	Real	Ideal	Real	Ideal
0.058	0.075		0.205	0.003 0.059-0.091	0.008-0.017	0.060	0.040-0.054

Real: taken from pdb files of oligomers

Ideal: constructed with nucleic acid builders with average parameters

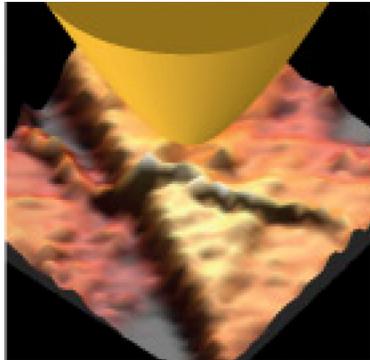
- **Importance of structural fluctuations:** difference between “real” and “ideal”
- Net increase upon size-expansion, less remarkable if structural changes are considered

Complementary look at the electronic structure: scanning tunneling spectroscopy (STS)

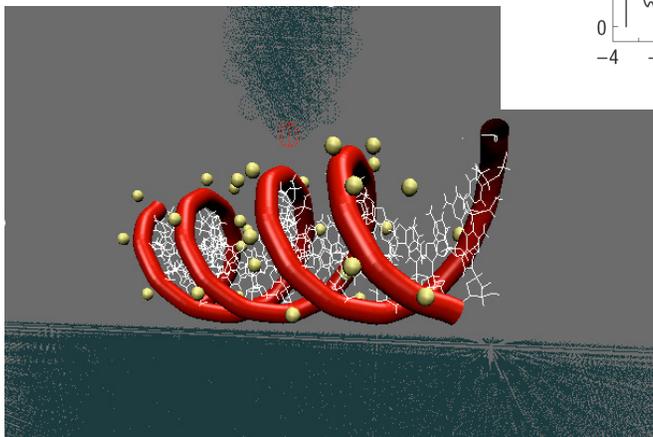
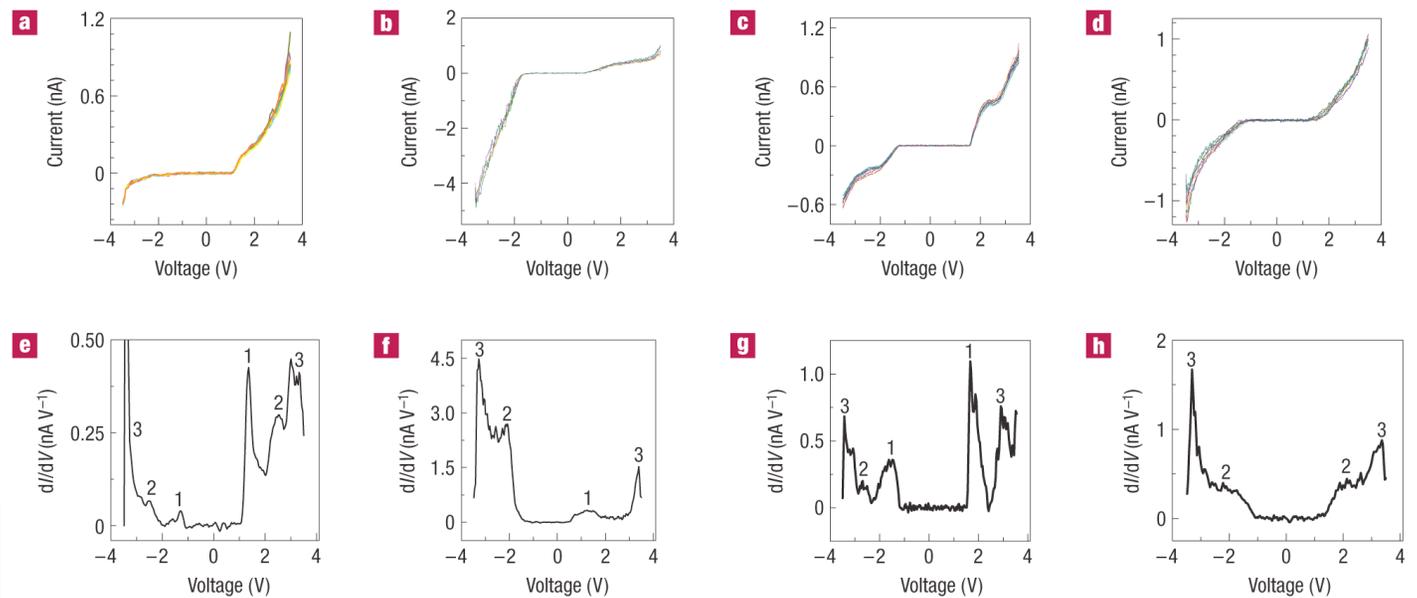


STS: experiment

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



Conductance peaks with a gap

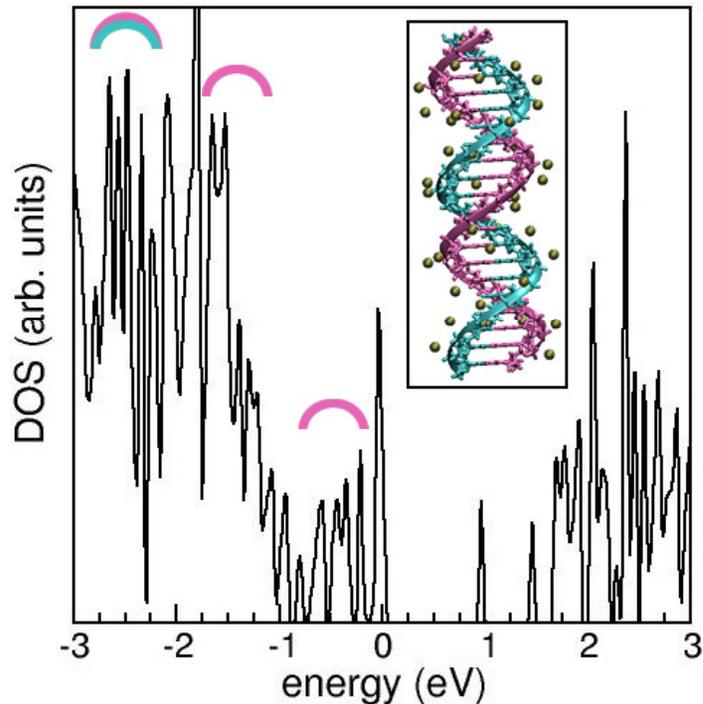


Desired but unfeasible ab initio
computational setup

STS: theoretical interpretation

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

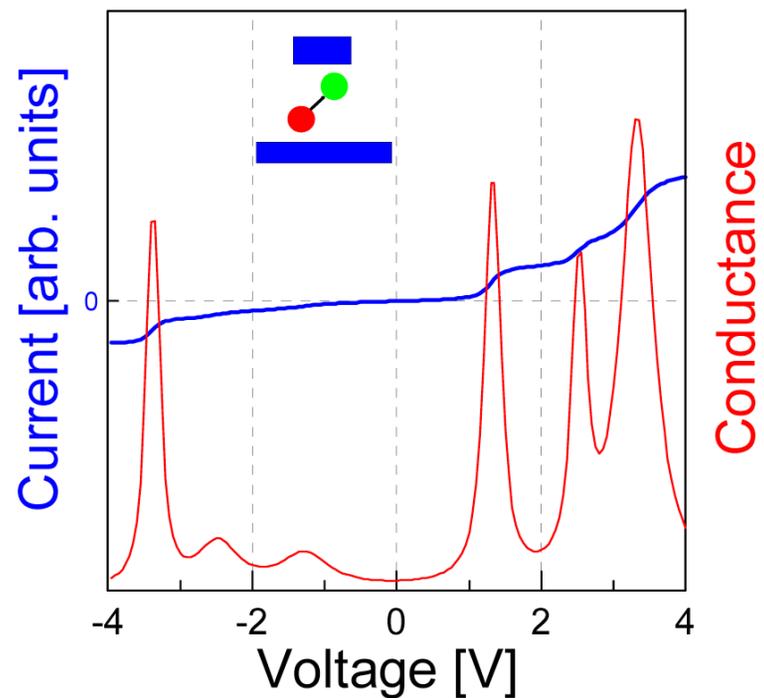
Ab initio



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

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

Model hamiltonians



Parameters from ab initio or experiments

Summary of methods

▪ Experiment

- Charge transfer rates in solution
- Current-voltage measurements
- STM spectroscopy
- Optical spectroscopy

▪ Theory

- Electron transfer theory (transfer integrals)
- Ab initio electronic structure: ground-state and excitations
- Model Hamiltonians
- Molecular dynamics

Summary

▪ Density functional theory

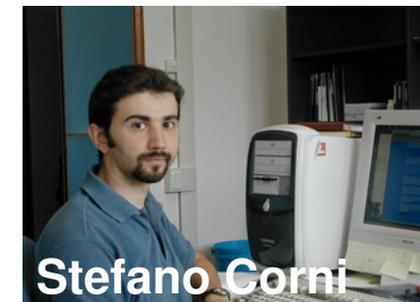
- From the ground state to the excited states (transport and optics)... the road is opening up
- Predictive potentiality

▪ Molecular dynamics

- Structural flexibility
- Powerful tool to complement electronic structure theory

**Relevance of dynamical fluctuations
in electronic structure issues**

People



Collaborators at S3

Elisa Molinari

Anna Garbesi

Stefano Corni

Andrea Ferretti

Arrigo Calzolari (G4)

HouYu Zhang (M-DNA)

Daniele Varsano (TDDFT, xDNA, G4/A4)

Manuela Cavallari (molecular dynamics)

Agostino Migliore (electron transfer, xDNA)

Giorgia Brancolini (M-DNA)

External Collaborators (experiment)

Danny Porath (HUJI Jerusalem, Israel) Sasha Kotlyar (TAU Tel Aviv, Israel)

External Collaborators (theory)

Joshua Jortner (TAU Tel Aviv, Israel) Gianaurelio Cuniberti (TU Dresden, Germany)

Angel Rubio (UPV/EHU San Sebastian, Spain)

Miguel Fuentes-Cabrera (ORNL, Oak Ridge, TN, USA)

Acknowledgements

Funding: CNR-INFM, EC projects “DNA-based Nanowires” (2002-2006) & “DNA-based Nanodevices” (2006-2009), EC Marie Curie Network “EXC!TING”, MIUR (Italy) “FIRB-NOMADE”

Computer time: CINECA Bologna, ORNL Oak Ridge, NERSC Berkeley