My current projects in general

- RNA aptamers: classical MD studies
- CYP: docking, semiempirical QC
- Arthritis proteins: classical MD studies

Molecular Modelling of Nucleic Acids:
How Quantum Chemistry Might Help

- Frontier orbitals in DNA
- Nature of excited states in DNA
- Nature of disorder in DNA

Molecular Modelling of Nucleic Acids:
How Quantum Chemistry Might Help

- Electron-phonon coupling in DNA
- Electron correlations in DNA
- DNA doping

Molecular Modelling of Nucleic Acids:
How Quantum Chemistry Might Help

General aim:

Relationship between DNA electronic structure and its properties

Molecular Modelling of Nucleic Acids:
How Quantum Chemistry Might Help

Methods

Extended Hückel: YAeHMOP

Semiempirical: MOPAC (PM3-CI)

Hartree-Fock *ab initio*: GAUSSIAN-98, GAMESS-US

DFT: FIREBALL

FIREBALL

Authors: Prof. O.F. Sankey, Prof. J.P. Lewis *et. al.*

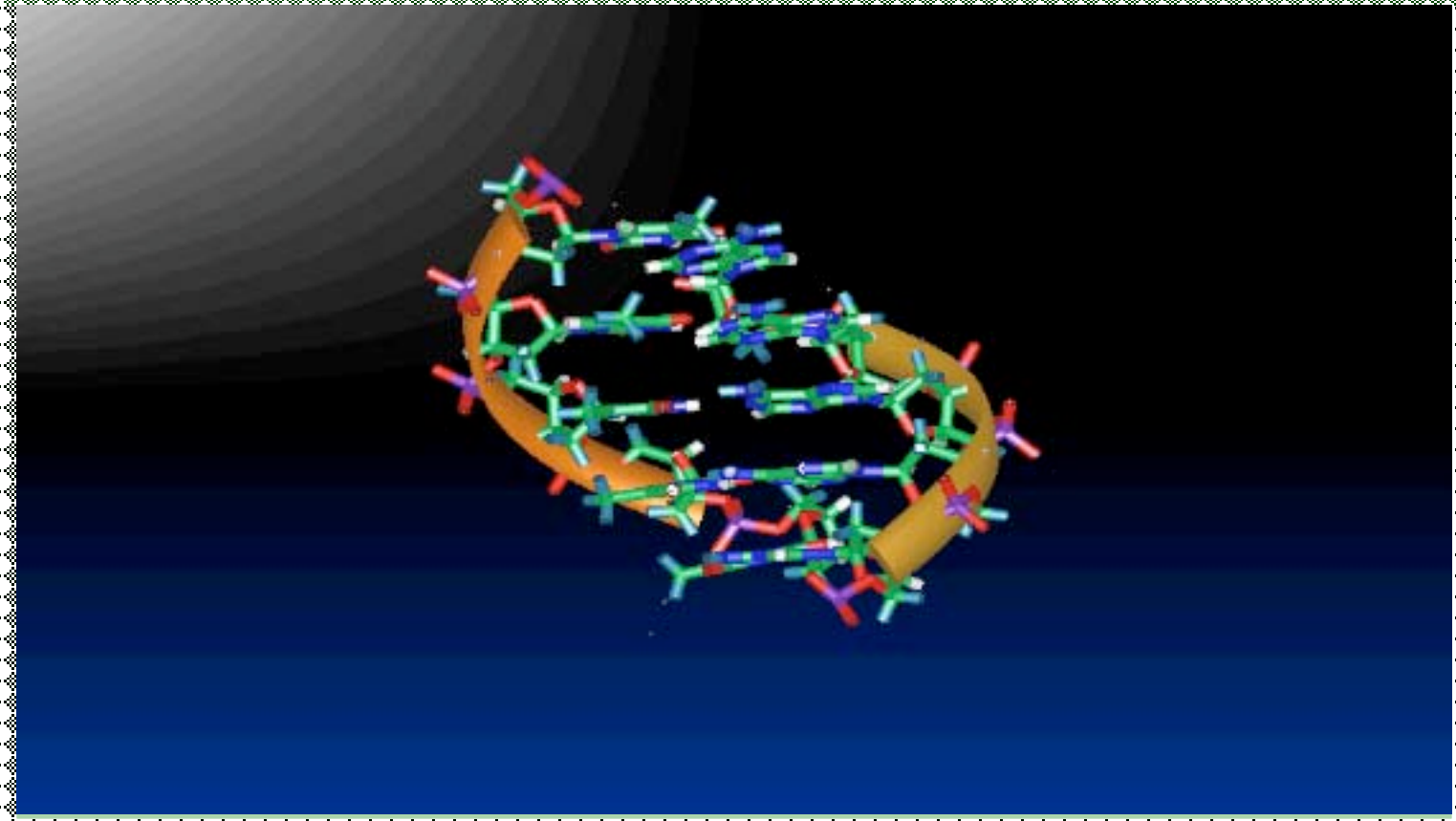
2 Main Features:

-Kohn-Sham functional -> Harris-Foulkes functional (faster achievement of self-consistency)

-One-electron Schrödinger equation in terms of slightly excited atomic orbitals (***„fireballs“***)

-> N-scaling instead of conventional N^3-scaling

Poly(dA)-poly(dT) fiber, +Na & H_2O



Poly(dA)-poly(dT) density of states

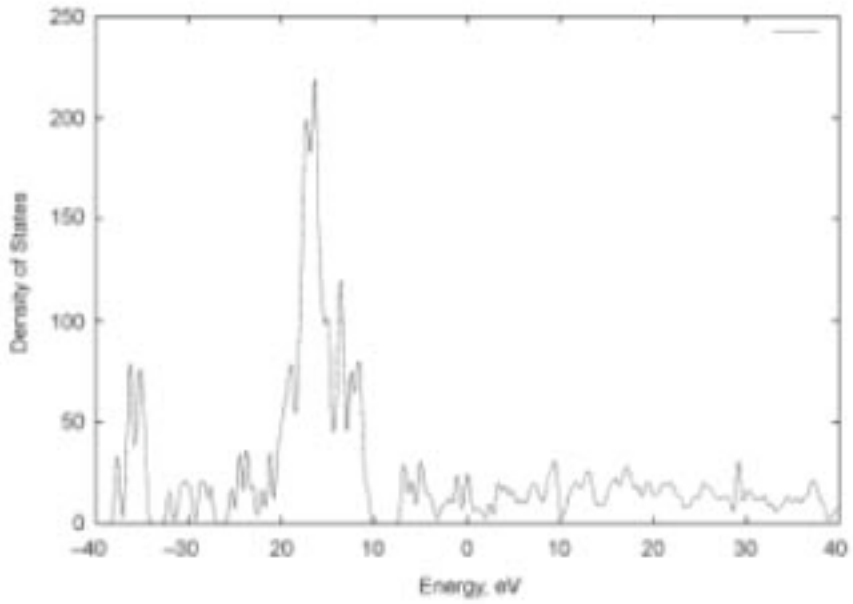


Fig. 1 Total density-of-states plot for polycrystalline poly(dA)–poly(dT) fiber. The energy gap between the valence and conduction band tails is 2.7 eV. The Fermi energy is −10.77 eV.

DNA +

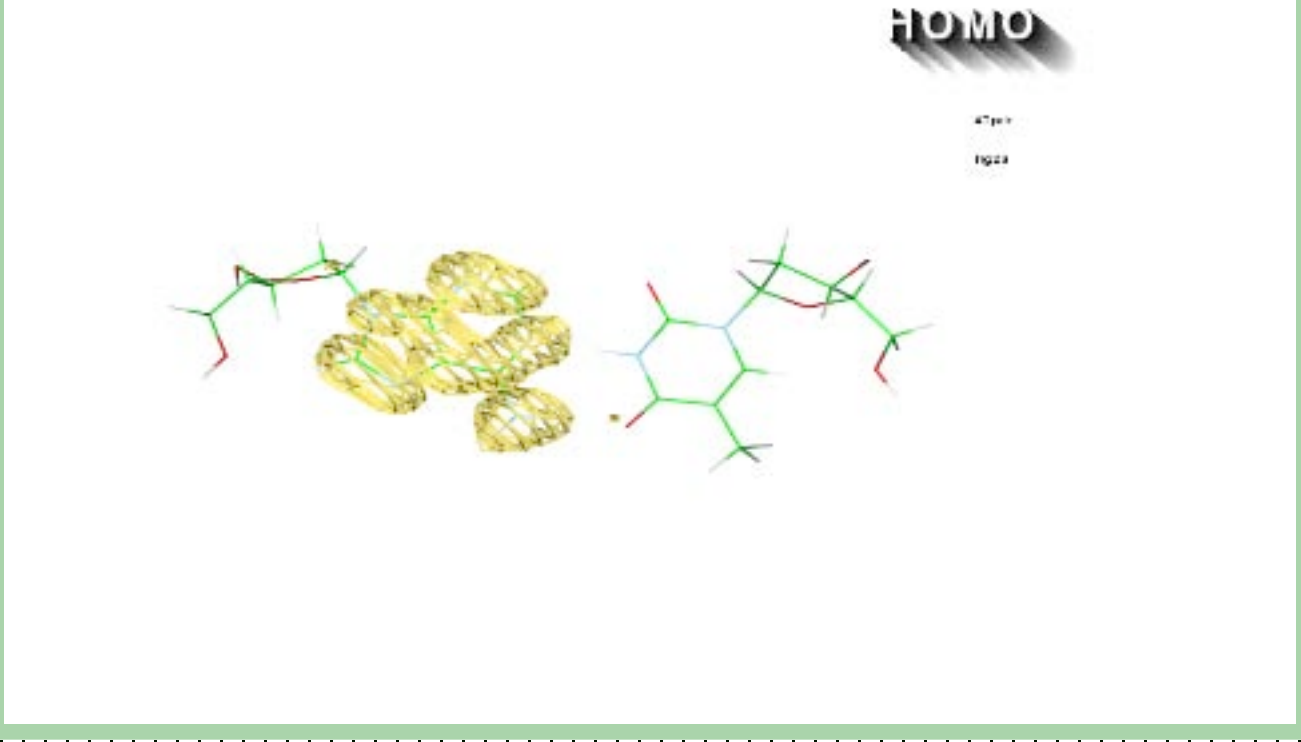
water +

Na cations,

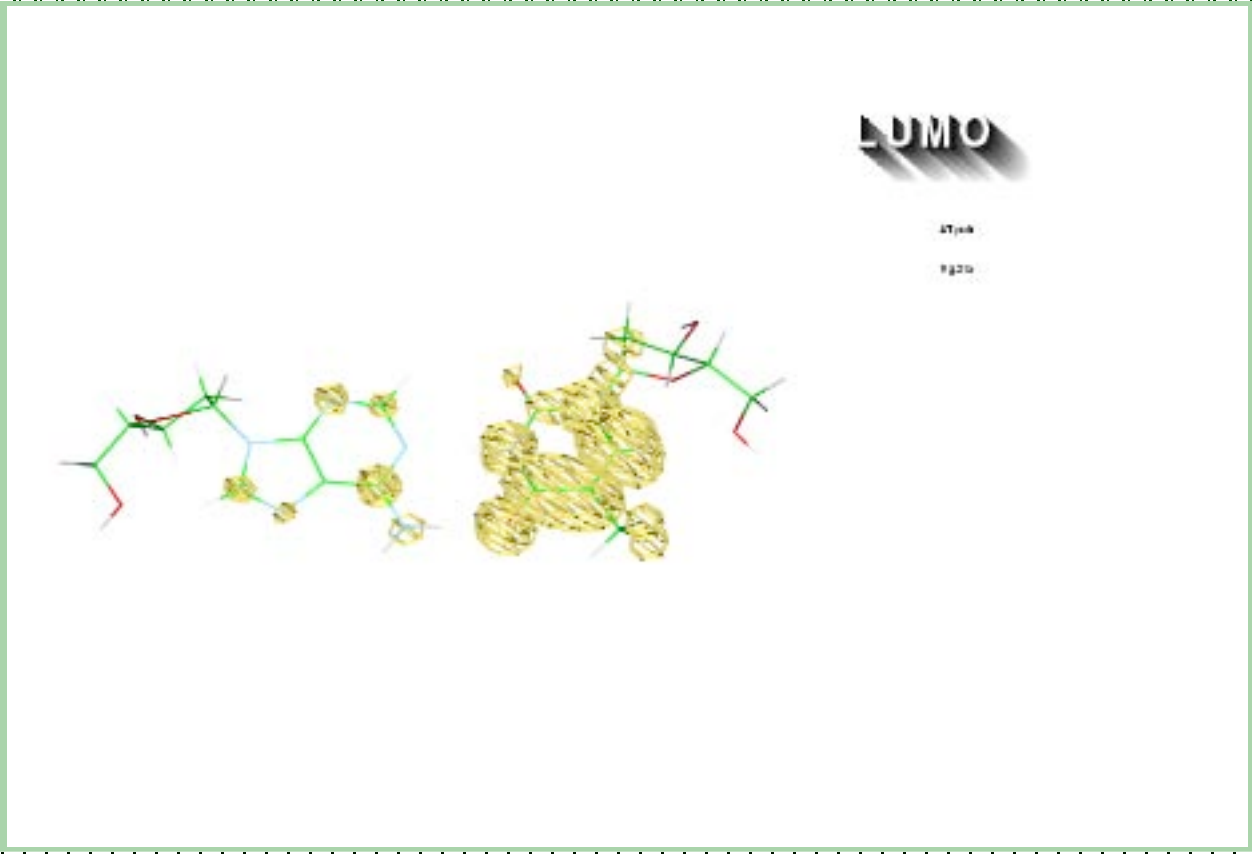
true 3D crystal,

extended Hückel

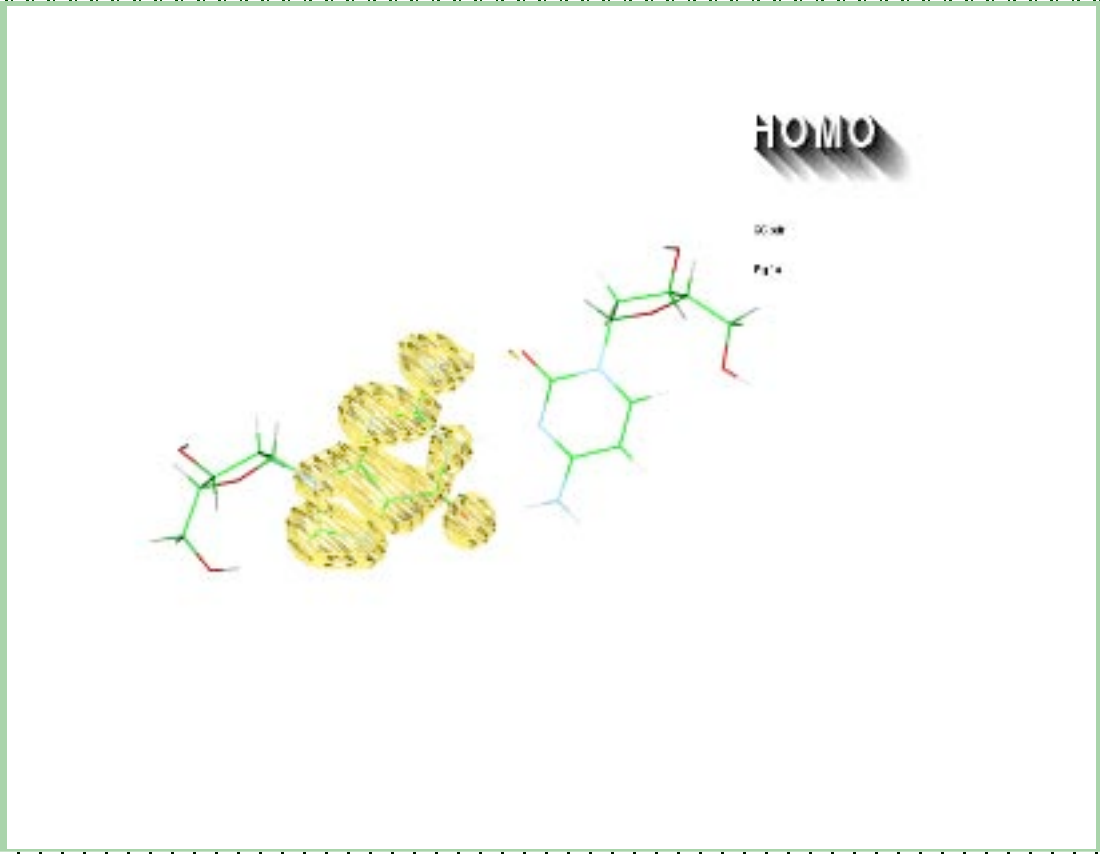
dA-dT Watson-Crick base pair, HOMO



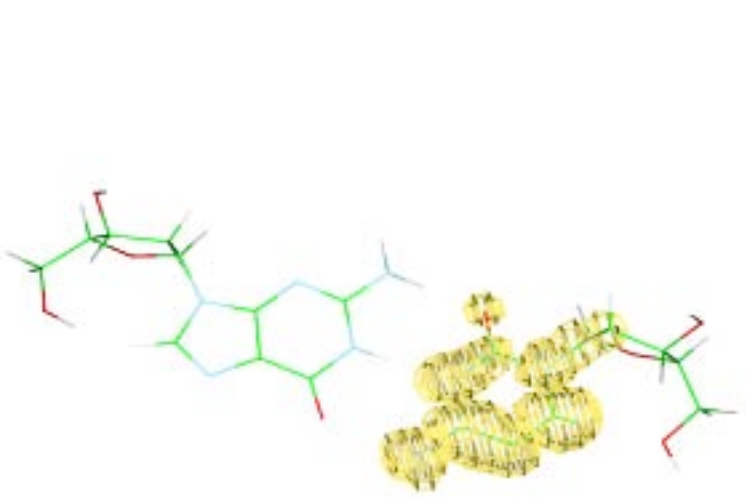
dA-dT Watson-Crick base pair, LUMO



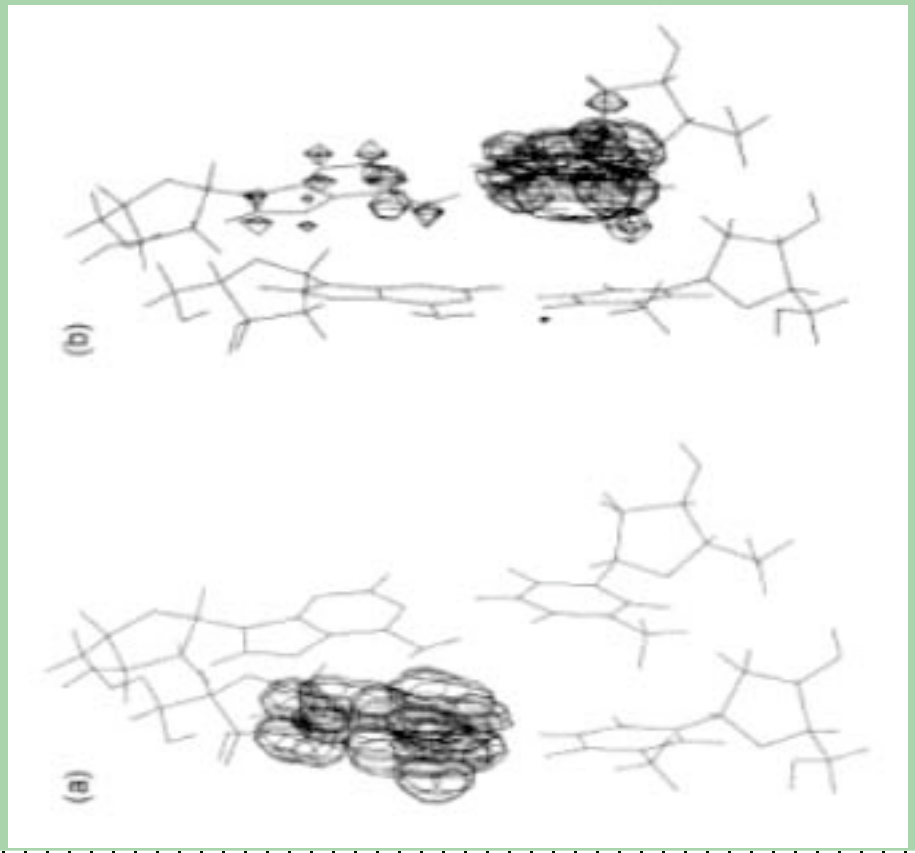
dG-dC Watson-Crick base pair, HOMO



dG-dC Watson-Crick base pair, LUMO



dAdT/dAdT bp step: Frontier orbitals

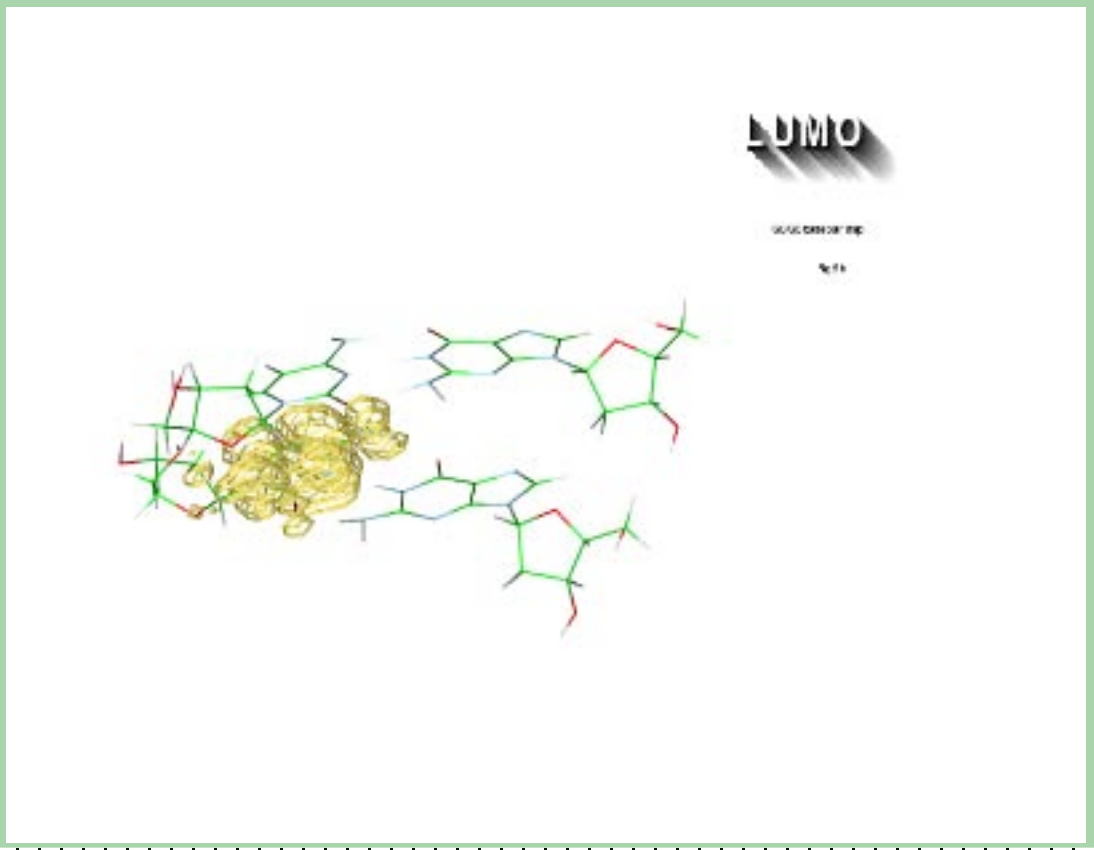


LUMO

HOMO

dGdC/dGdC base pair step, HOMO

dGdC/dGdC base pair step, LUMO



DNA DISORDER

„Marriage“

between FIREBALL and classical MD

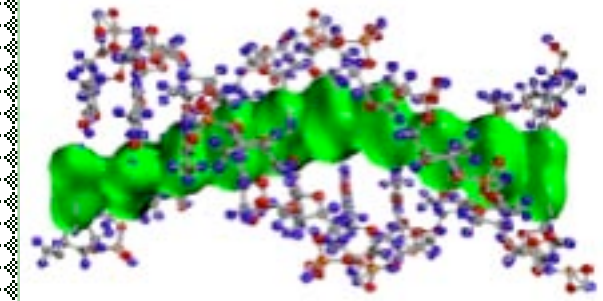
System under study:

poly(dA)$_{10}$-poly(dT)$_{10}$

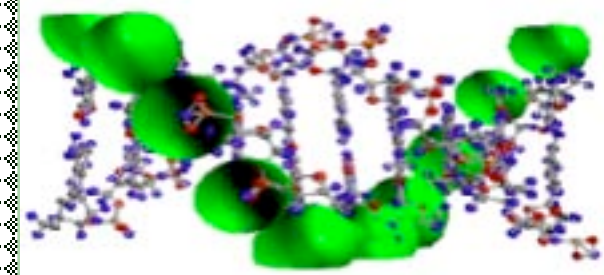
With water of hydration, but without counterions

Ordered, B-DNA:

Disordered, after 2 ns MD:

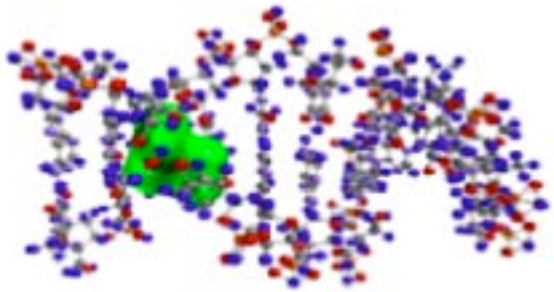


HOMO

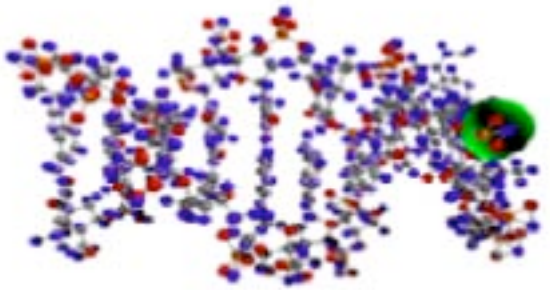


LUMO

->



HOMO



LUMO

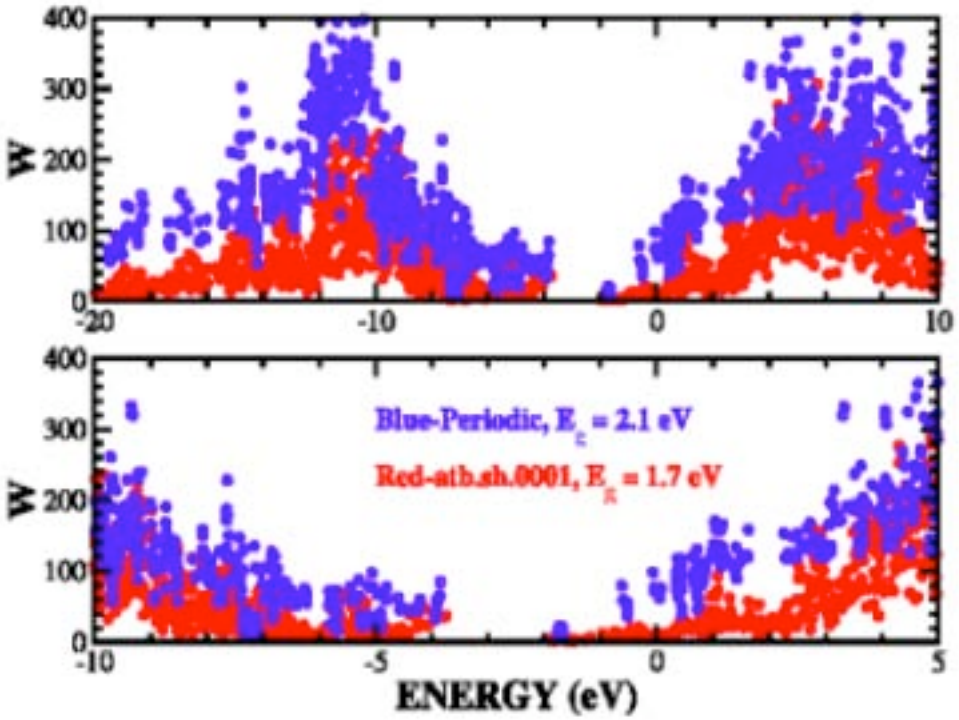
From a particular state ν,
Mulliken population $p_i(\nu)$ on atom i,

$$\sum_i p_i(\nu) = 1.$$

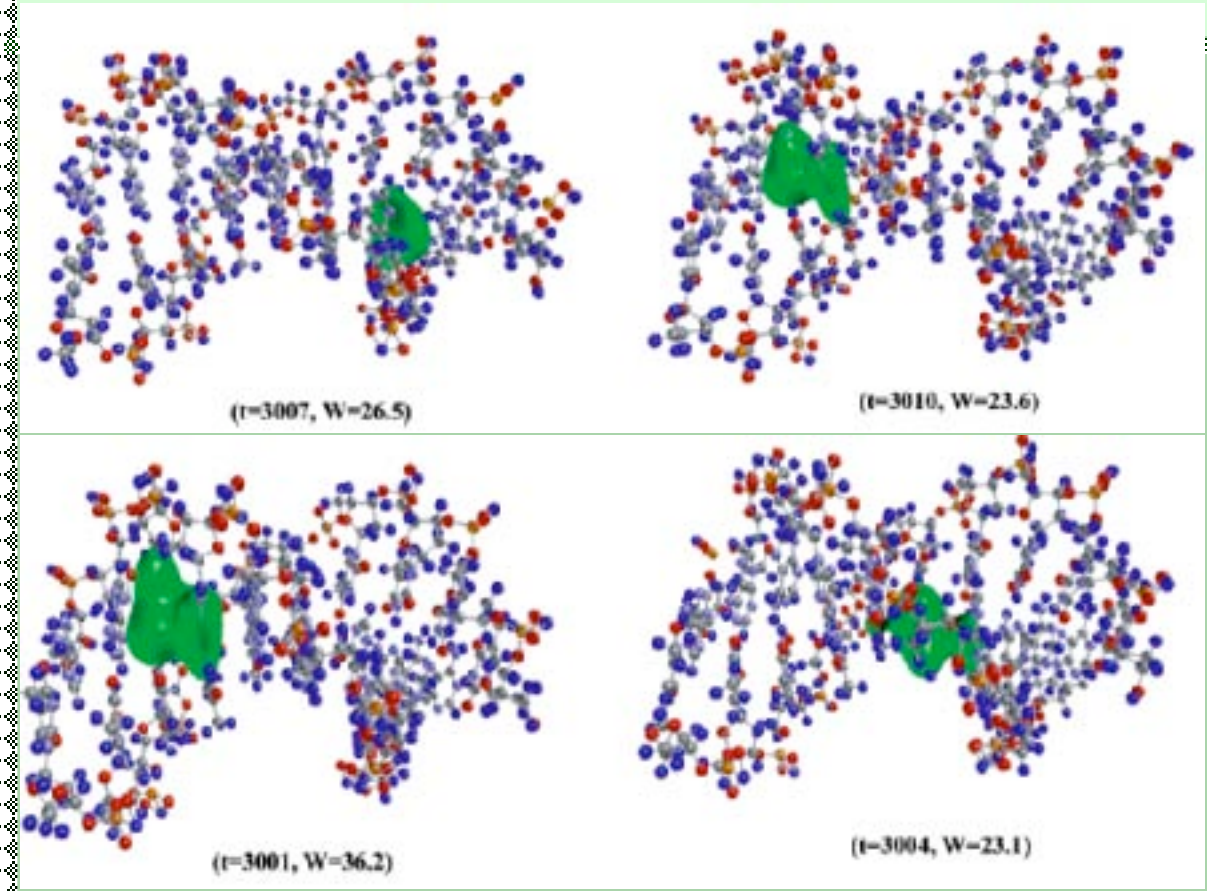
$$S(\nu) = -\sum_i p_i(\nu) \ln p_i(\nu) .$$

$$W(\nu) = e^{S(\nu)} .$$

Quantifying DNA Disorder



Time evolution of HOMO (Ade residue)



Time Step

1.5 ps

Dynamical disorder in DNA: Sources ?

Dynamical attenuation of base coupling

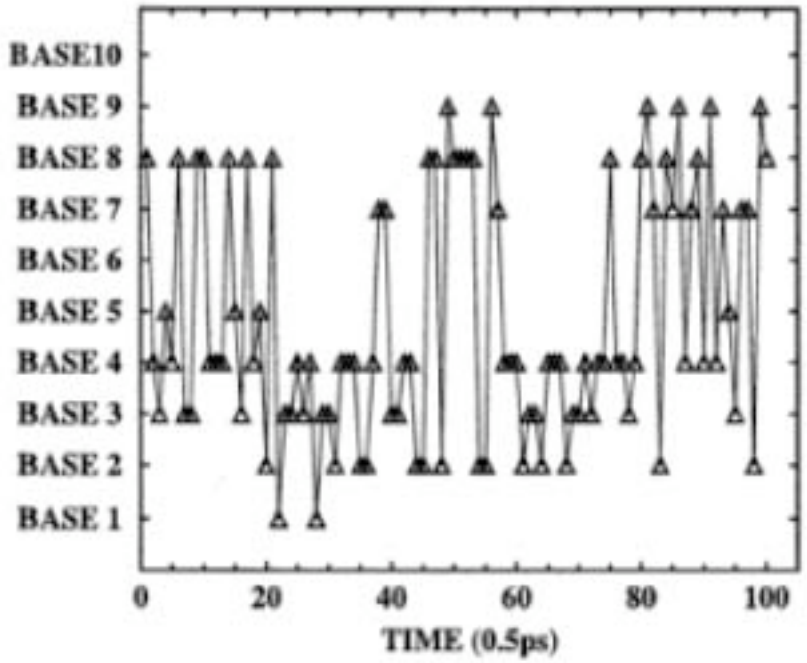


Figure 8. Location of the HOMO as function of time. The 10 bases are the 10 adenine bases on one strand of the DNA. The HOMO is located only on adenine bases.

Thermal fluctuations of counterion-water environment

Electron-phonon coupling in DNA

$$H = H_{el} + H_{vib}\,,$$

$$H_{el} = \sum_n E_n\,|c_n|^2 - V_{n\,n-1}\left(c_n^* c_{n-1} + c_n c_{n-1}^*\right).$$

$$H_{vib} = \frac{1}{2}\sum_n \left[\frac{1}{2M}\left(p_n^r\right)^2 + M\,\Omega^2\,r_n^2\right].$$

Tight binding for electrons,

linear harmonic approximation for vibrations

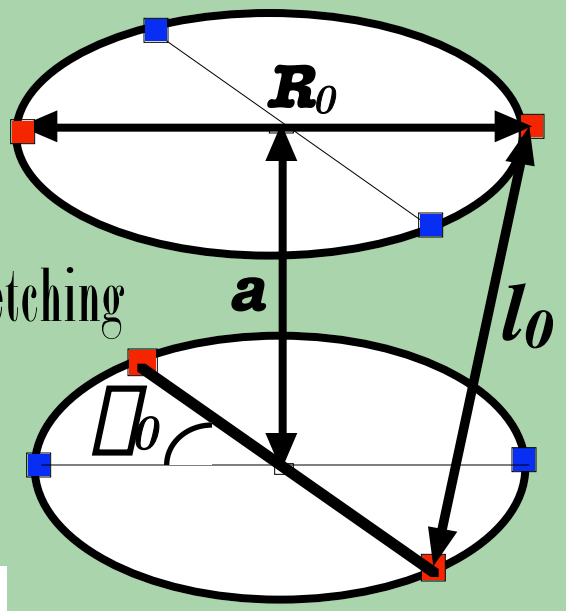
Electron-phonon coupling in DNA

$$E_n = E_0 + k\, r_n \,.$$

$$V_{n\,n-1} = V_0 \,(1 - \alpha\, d_{n\,n-1}) \,.$$

$d_{n\ n-1}$ - changes in l_0

r_n - changes in R_0 due to H-bond stretching

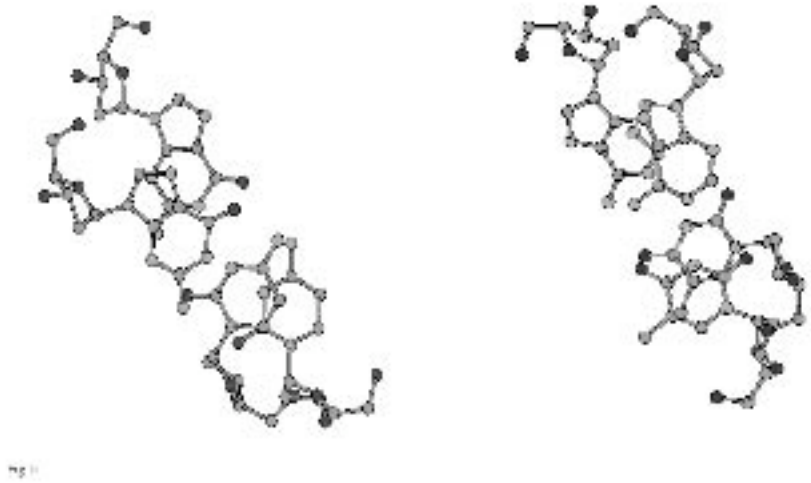


$$l_0 = \sqrt{a^2 + 4R_0^2 \sin^2(\theta_0/2)} \,,$$

$$d_{n\,n-1} = \frac{R_0}{l_0}\,(1 - \cos\theta_0)\,(r_n + r_{n-1}) \,.$$

Electron-phonon coupling in DNA

dGdC/
dGdC



dAdT/
dAdT

Electron-phonon coupling in DNA

poly(dA)-poly(dT)

$k = 0.0778917\,eV/\,\AA$ and $\alpha = 0.053835\,\AA^{-1}$.

- *The helical twist and pitch dynamics is not so strongly coupled to electron degrees of freedom, as compared to the Watson-Crick H-bonds stretching.*

- *The coupling coefficients for the latter one to on-site electron energies in poly(dA)-poly(dT) and poly(dG)-poly(dC) are of the same absolute value, but with opposite signs.*

- *The coupling coefficient for the latter one to electron-hopping matrix elements in poly(dA)-poly(dT) is one order of magnitude less than that in poly(dG)-poly(dC).*

poly(dG)-poly(dC)

$k = -0.090325\,eV/\,\AA$ and $\alpha = 0.383333\,\AA^{-1}$.

Electron-phonon coupling in DNA

The set of coupled equations of motion read as

$$
\begin{aligned}
i\tau\dot{c}_n &= (E_0 + k\,r_n)\,c_n \\
&- (1-\alpha\,d_{n+1,n})\,c_{n+1} - (1-\alpha\,d_{nn-1})\,c_{n-1} \\
\ddot{r}_n &= -r_n - k\,|c_n|^2 - \frac{R_0}{l_0}\,(1-\cos\theta_0) \\
&\times \alpha\left([c^*_{n+1}c_n + c_{n+1}c^*_n] + [c^*_n c_{n-1} + c_n c^*_{n-1}]\right)
\end{aligned}
$$

These equations describe polaron motion in DNA

Electron-phonon coupling in DNA

- Poly(dA)-poly(dT) polaron is less localized than that in poly(dG)-poly(dC).
- Polaron deformations in poly(dA)-poly(dT): H-bond contractions, in poly(dG)-poly(dC) they are H-bond stretchings.

- Generally, poly(dA)-poly(dT) is possessed of worse polaron conductive properties than poly(dG)-poly(dC).

Electron-electron correlations in DNA

$$\hat{H} = h\sum_{\sigma}(\hat{n}_{1,\sigma} + \hat{n}_{2,\sigma}) - t\sum_{\sigma}(\hat{a}^{\dagger}_{1,\sigma}\hat{a}_{2,\sigma} + \hat{a}^{\dagger}_{2,\sigma}\hat{a}_{1,\sigma})$$
$$+ U(\hat{n}_{1,\alpha}\hat{n}_{1,\beta} + \hat{n}_{2,\alpha}\hat{n}_{2,\beta})$$
$$+ V\sum_{\sigma,\sigma'}\hat{n}_{1,\sigma}\hat{n}_{2,\sigma'}$$
$$+ X\sum_{\sigma}(\hat{a}^{\dagger}_{1,\sigma}\hat{a}_{2,\sigma} + \hat{a}^{\dagger}_{2,\sigma}\hat{a}_{1,\sigma})(\hat{n}_{1,-\sigma} + \hat{n}_{2,-\sigma})$$
$$+ \frac{W}{2}\sum_{\sigma}(\hat{a}^{\dagger}_{1,\sigma}\hat{a}^{\dagger}_{1,-\sigma}\hat{a}_{2,-\sigma}\hat{a}_{2,\sigma} + \hat{a}^{\dagger}_{2,\sigma}\hat{a}^{\dagger}_{2,-\sigma}\hat{a}_{1,-\sigma}\hat{a}_{1,\sigma})$$
$$+ \frac{W}{2}\sum_{\sigma,\sigma'}(\hat{a}^{\dagger}_{1,\sigma}\hat{a}^{\dagger}_{2,\sigma'}\hat{a}_{1,\sigma'}\hat{a}_{2,\sigma} + \hat{a}^{\dagger}_{2,\sigma}\hat{a}^{\dagger}_{1,\sigma'}\hat{a}_{2,\sigma'}\hat{a}_{1,\sigma})$$

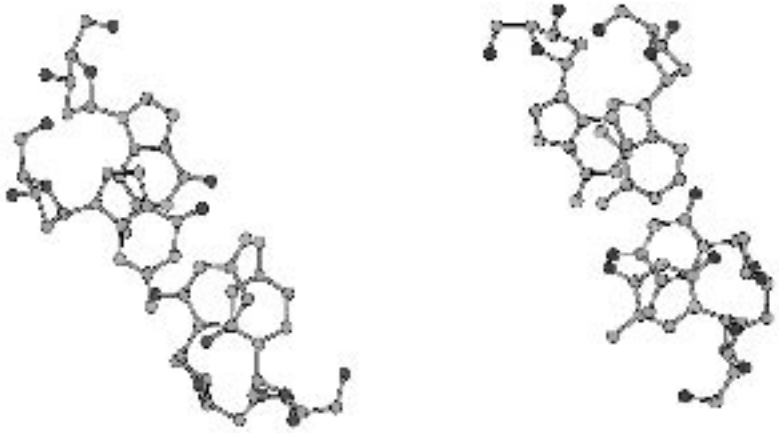
General Hubbard Hamiltonian

Only one frontier orbital per molecular unit is assumed

Electron-electron correlations in DNA

Both A- and B-DNA conformations

dGdC/
dGdC



dAdT/
dAdT

Both excess electrons and holes

Electron-electron correlations in DNA

$$(a)\ E_1^0 - E_1^4 = 4h + 2U + 4V - 2W$$

$$(b)\ E_1^1 - E_1^4 = 3h + U + 2V - W - (t - 2X)$$

$$(c)\ E_2^1 - E_1^4 = 3h + U + 2V - W + (t - 2X)$$

$$(d)\ E_1^2 - E_1^4 = 2h + V + W + \frac{U - V - \sqrt{(U-V)^2 + 16(t-X)^2}}{2}$$

$$(e)\ E_2^2 - E_1^4 = 2h + U - W$$

$$(f)\ E_3^2 - E_1^4 = 2h + V + W + \frac{U - V + \sqrt{(U-V)^2 + 16(t-X)^2}}{2}$$

$$(g)\ E_4^2 - E_1^4 = 2h + V - W$$

$$(h)\ E_1^3 - E_1^4 = h - t$$

$$(i)\ E_2^3 - E_1^4 = h + t$$

E_1^4 *is set to the zero of energy.*

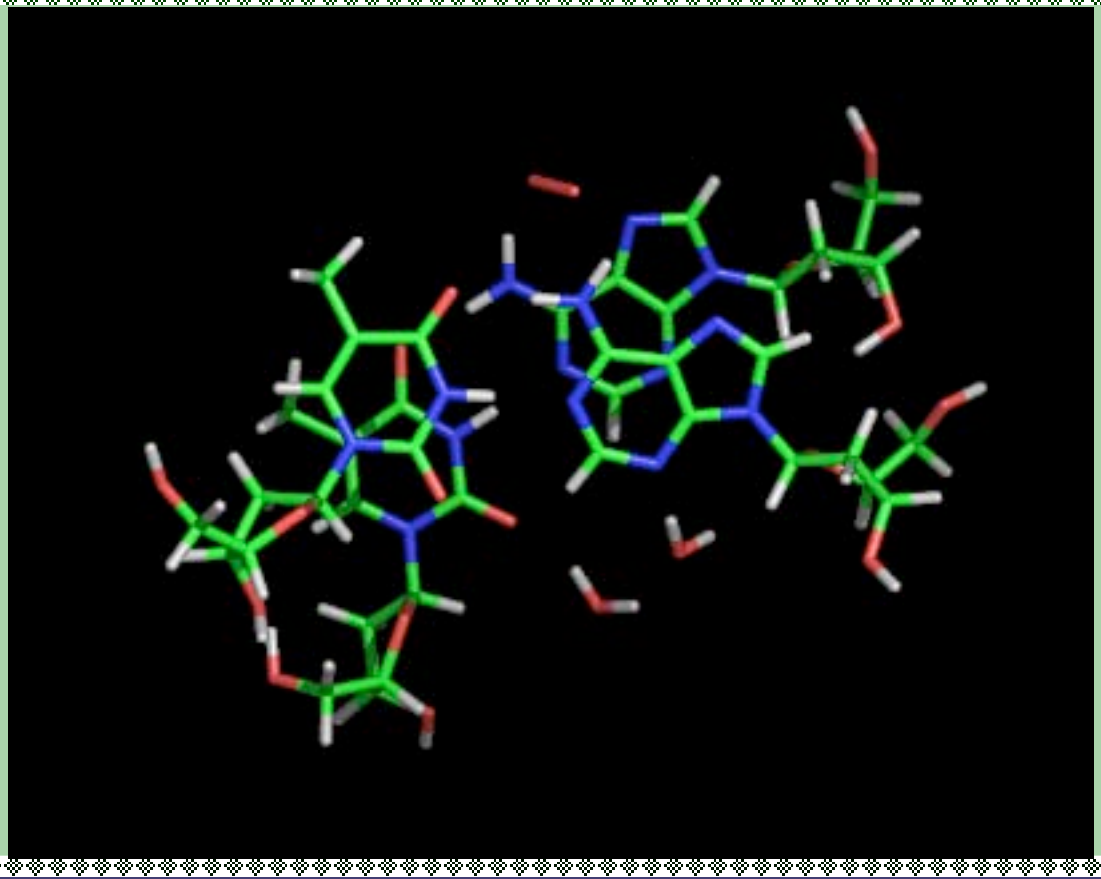
Fortunelli-Painelli method, PM3-CI Hamiltonian.

Electron-electron correlations in DNA

Holes: *U* is lower for GC/GC than for AT/AT, *V* is almost the same. There is significant conformation dependence for *t* in GC/GC.

Excess electrons: *U* is negative ! The *t* values in GC/GC are extremely low. *V* is almost the same as for the holes.

DNA docking with molecular oxygen

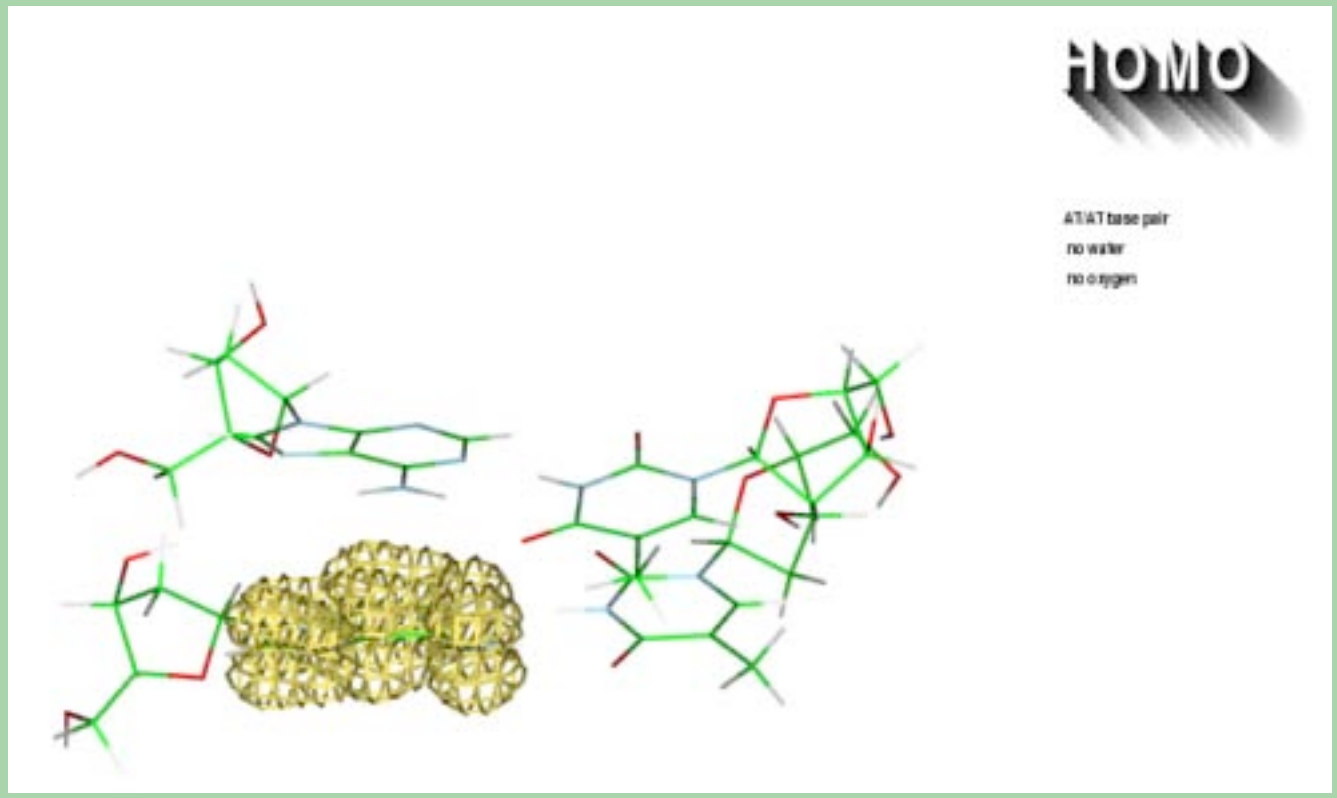


AT/AT, B-form, O_2 in the major and water in the minor groove

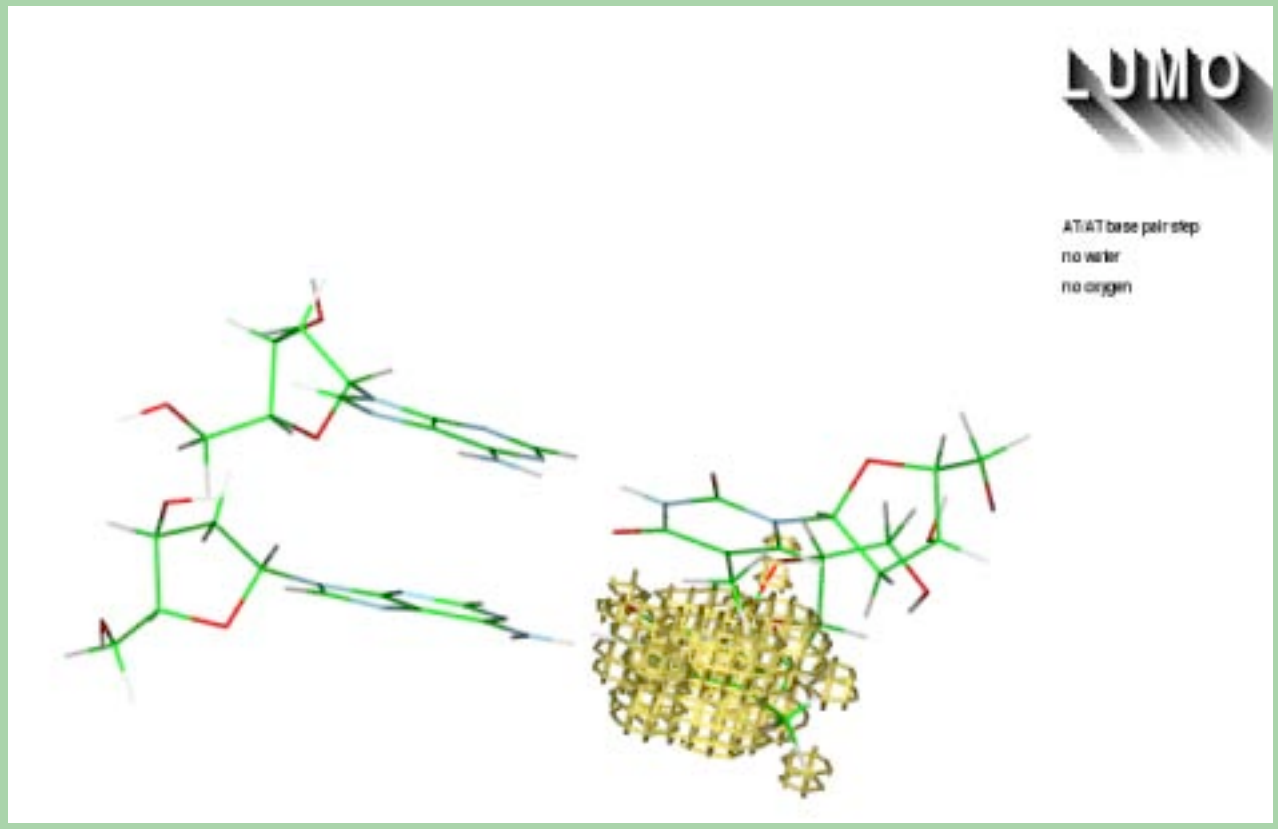
DNA docking with molecular oxygen

GC/GC, B-form, O_2 both in the minor and in the major groove

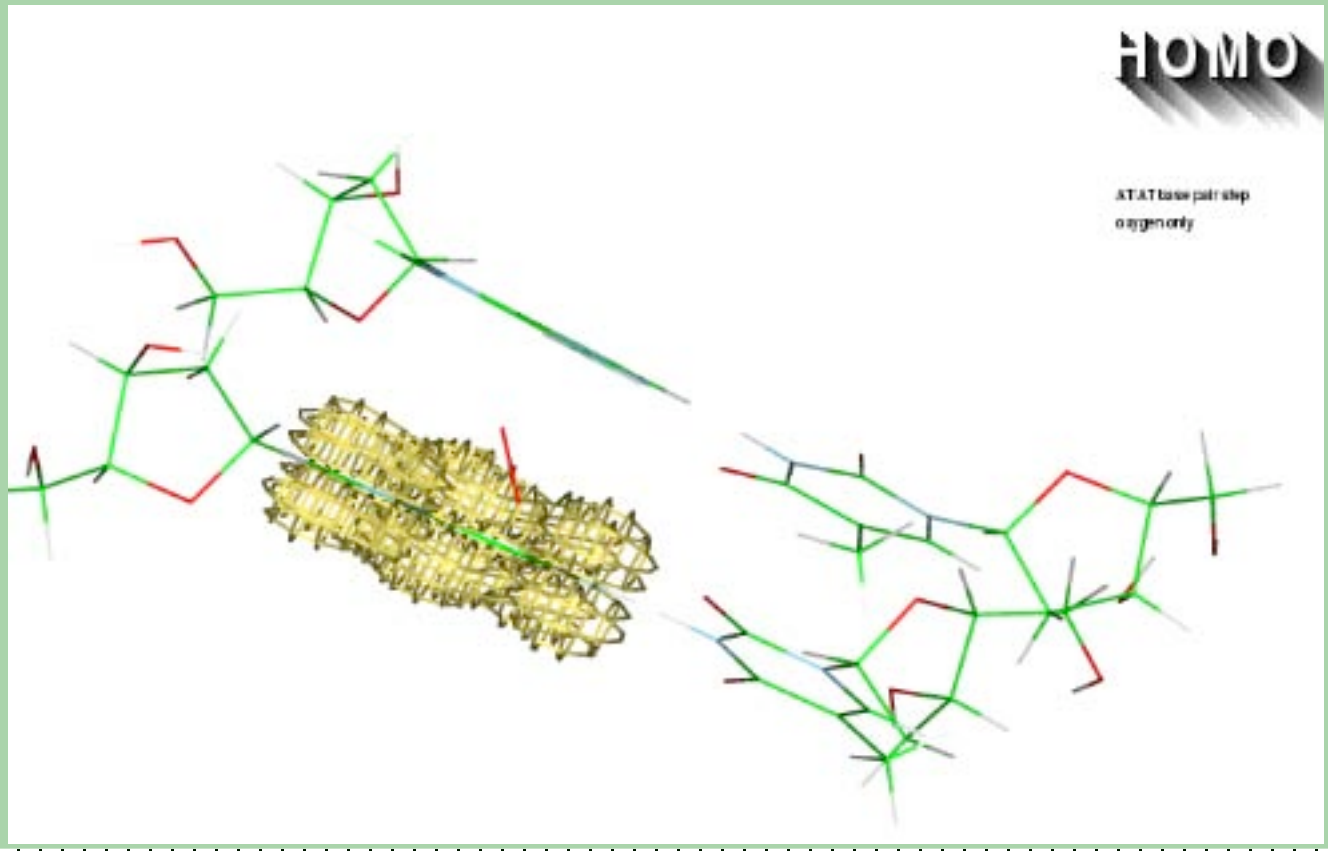
DNA docking: ATAT, no molecular oxygen



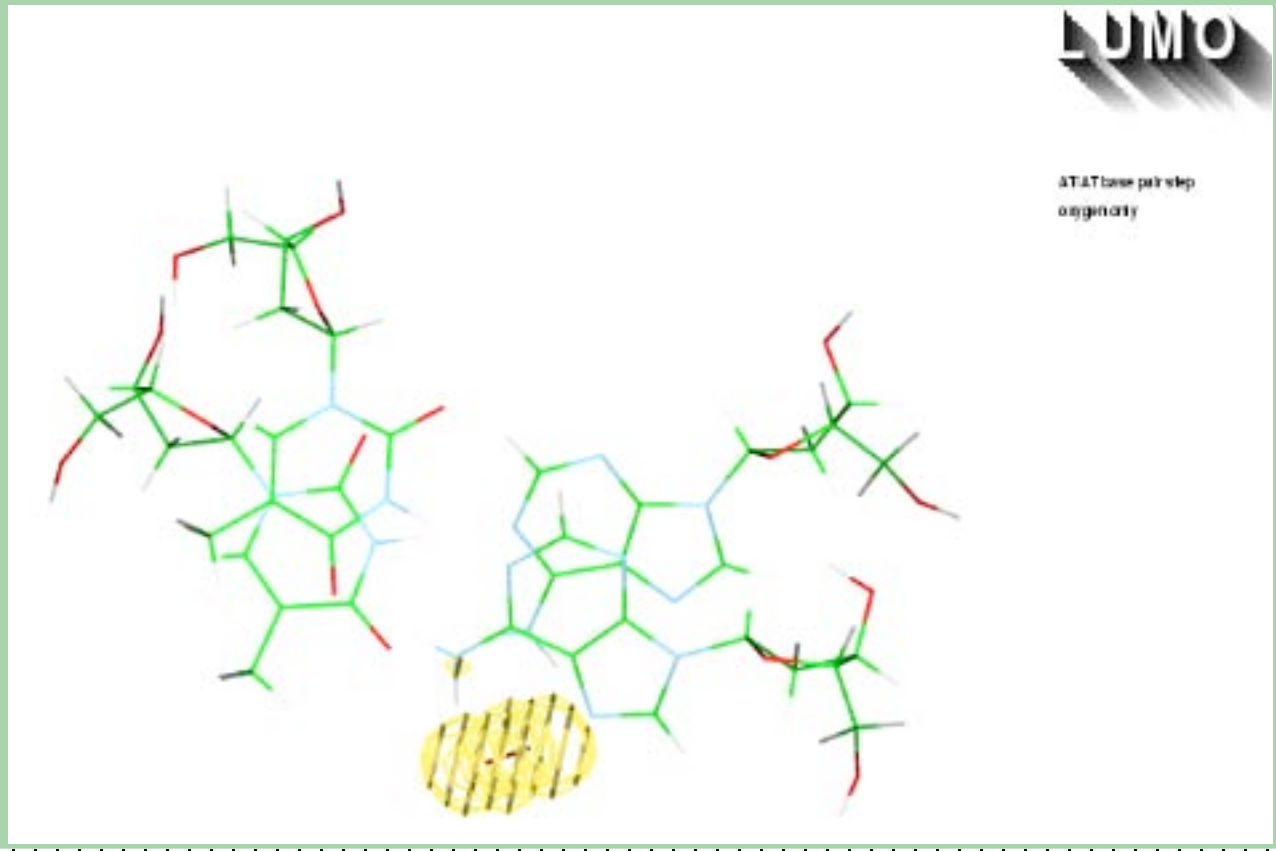
DNA docking: ATAT, no molecular oxygen



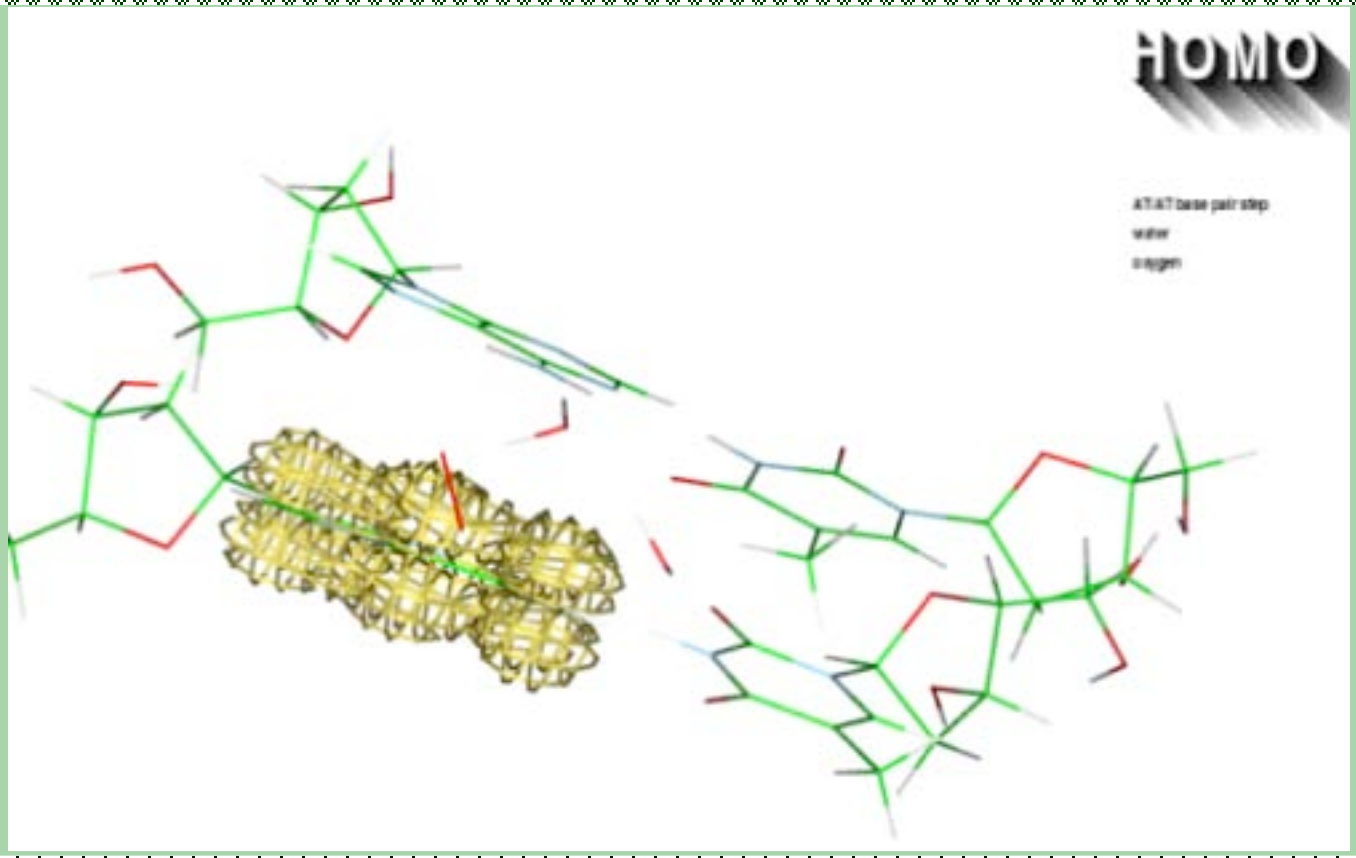
DNA docking: ATAT, molecular oxygen



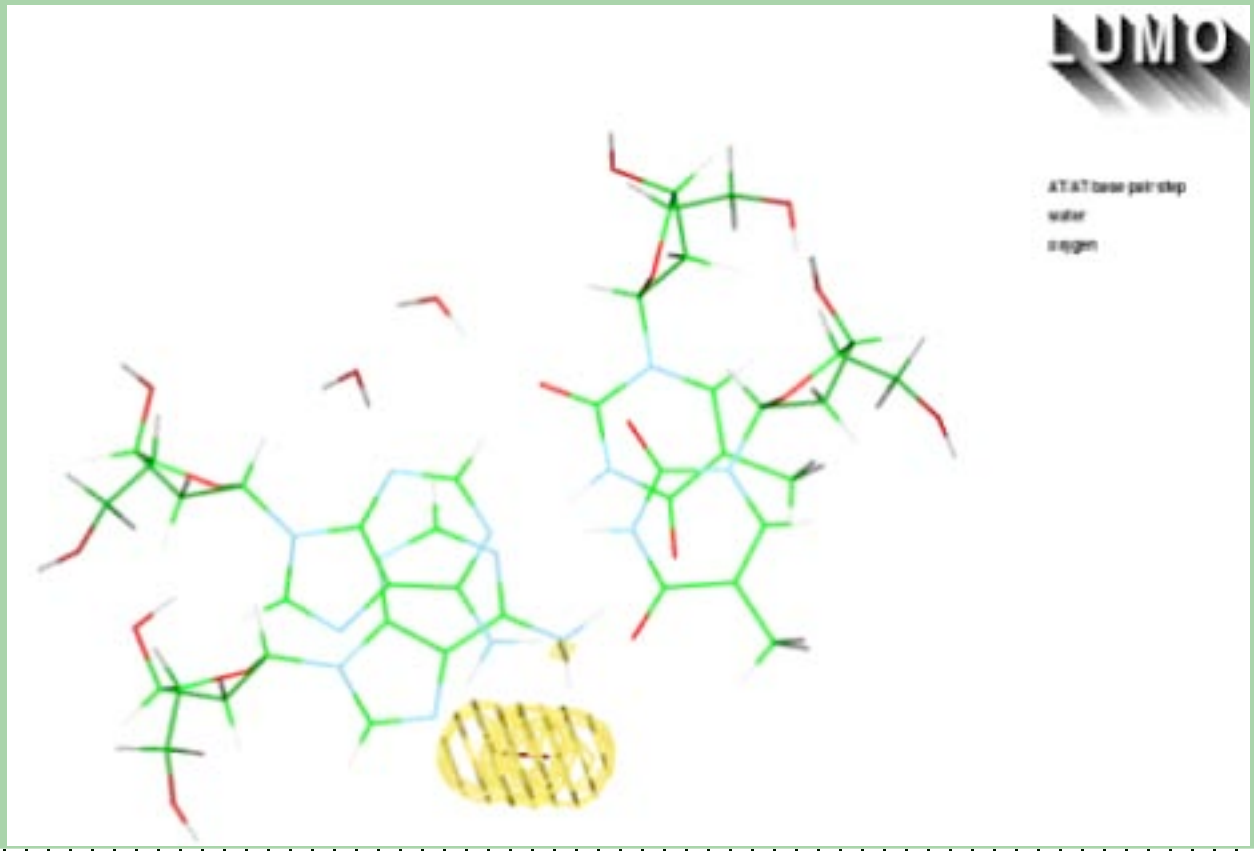
DNA docking: ATAT, molecular oxygen



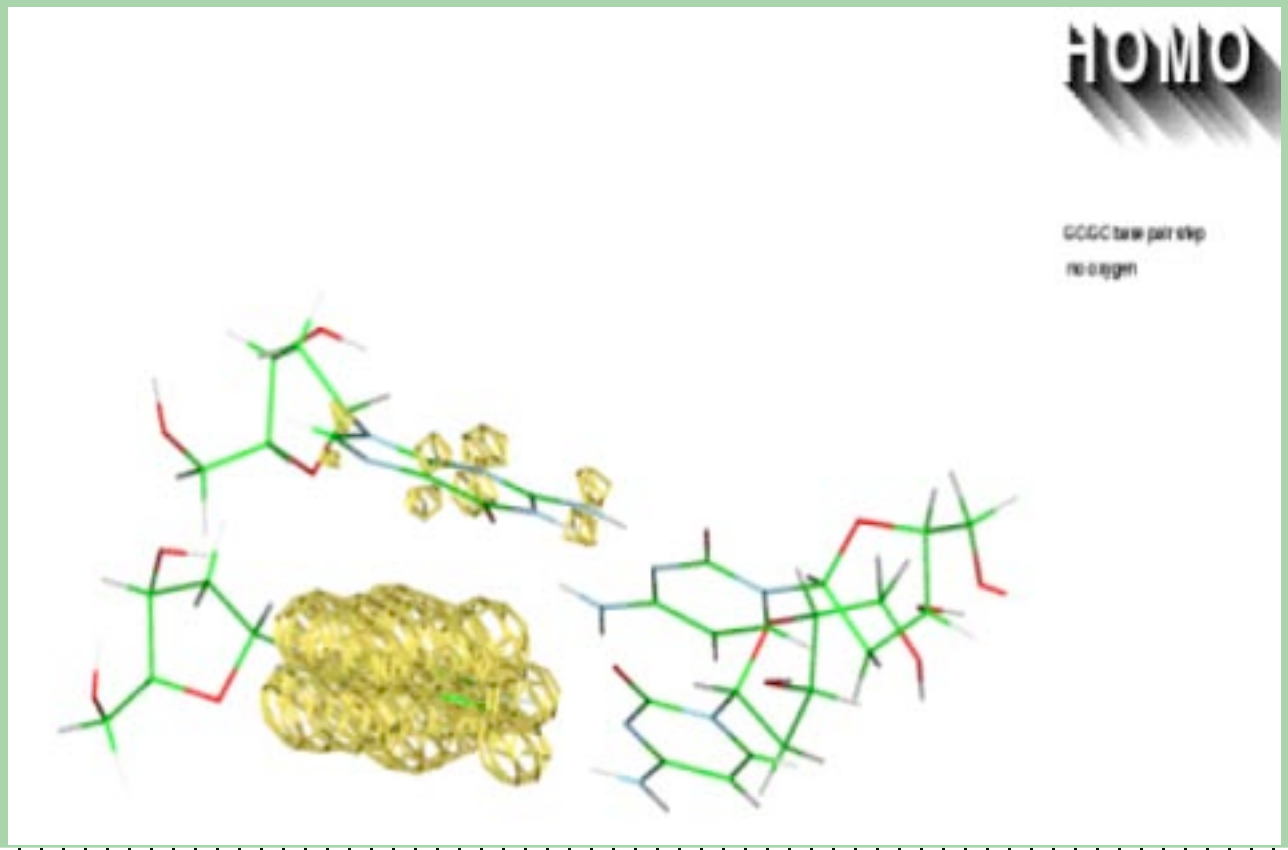
DNA docking: ATAT, oxygen and water



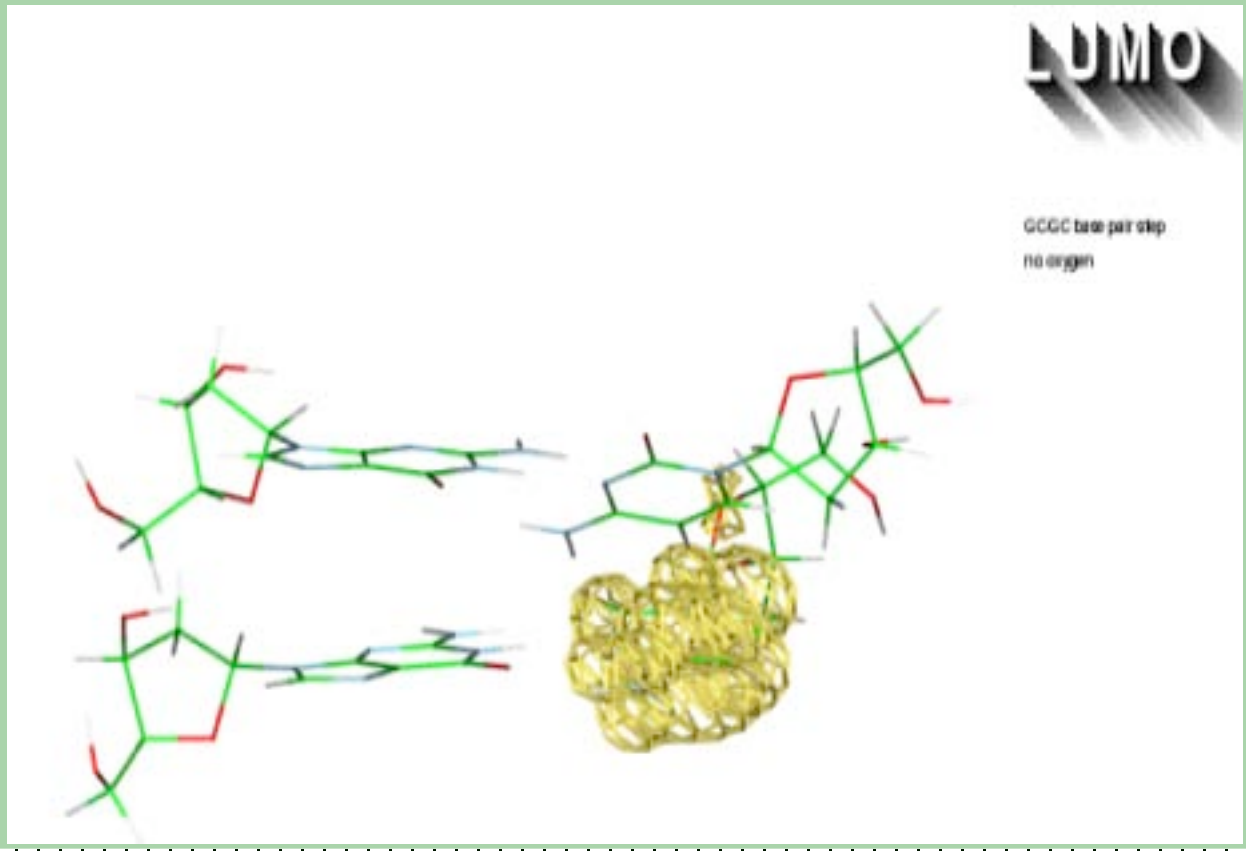
DNA docking: ATAT, oxygen and water



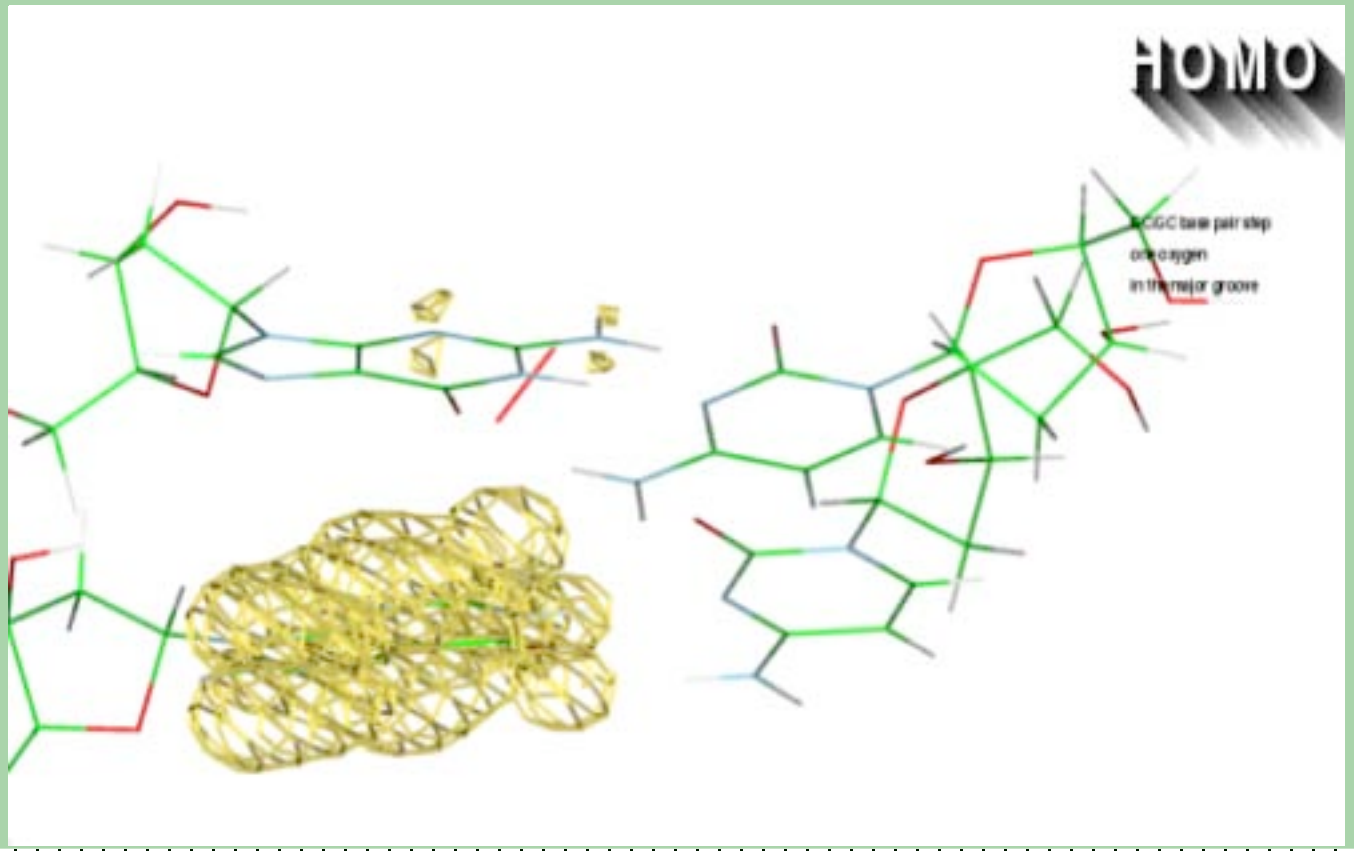
DNA docking: GCGC, no molecular oxygen



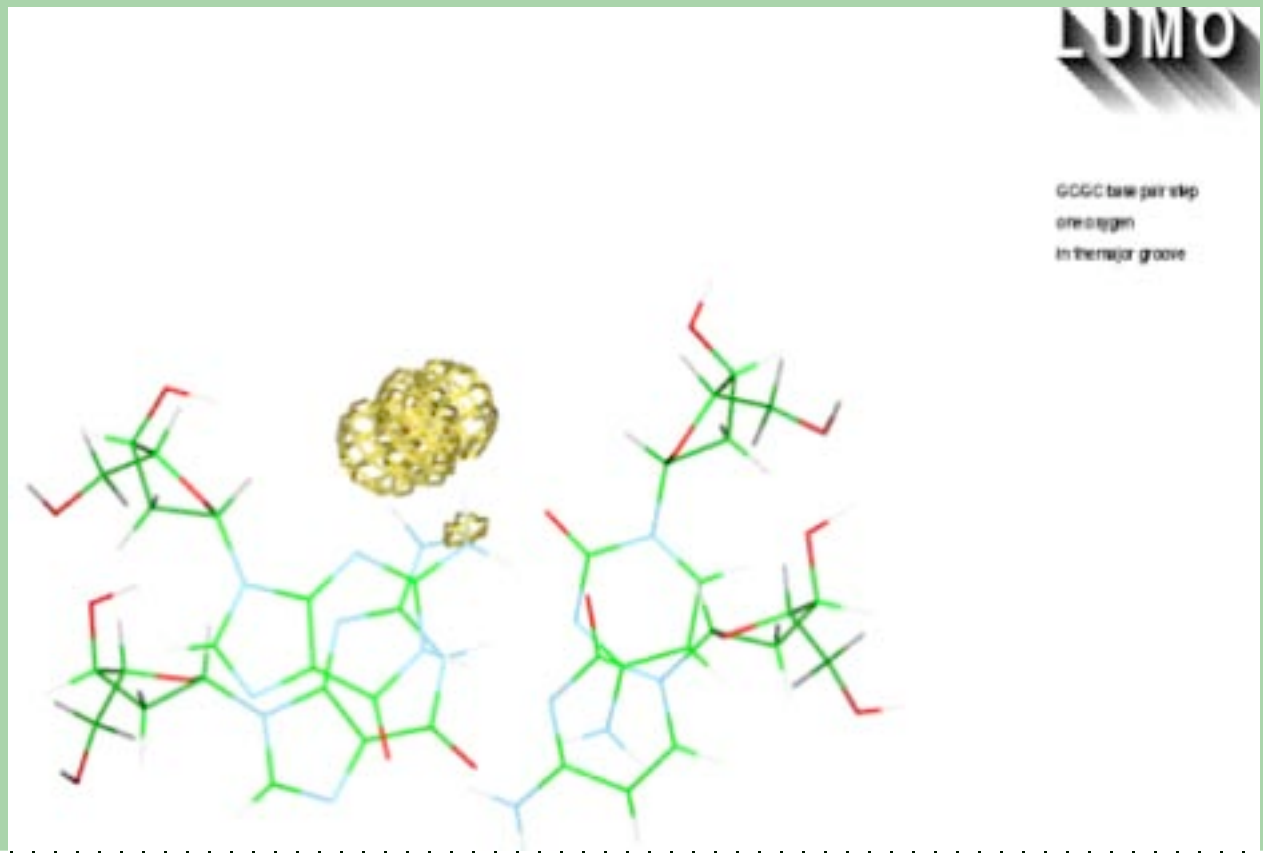
DNA docking: GCGC, no molecular oxygen



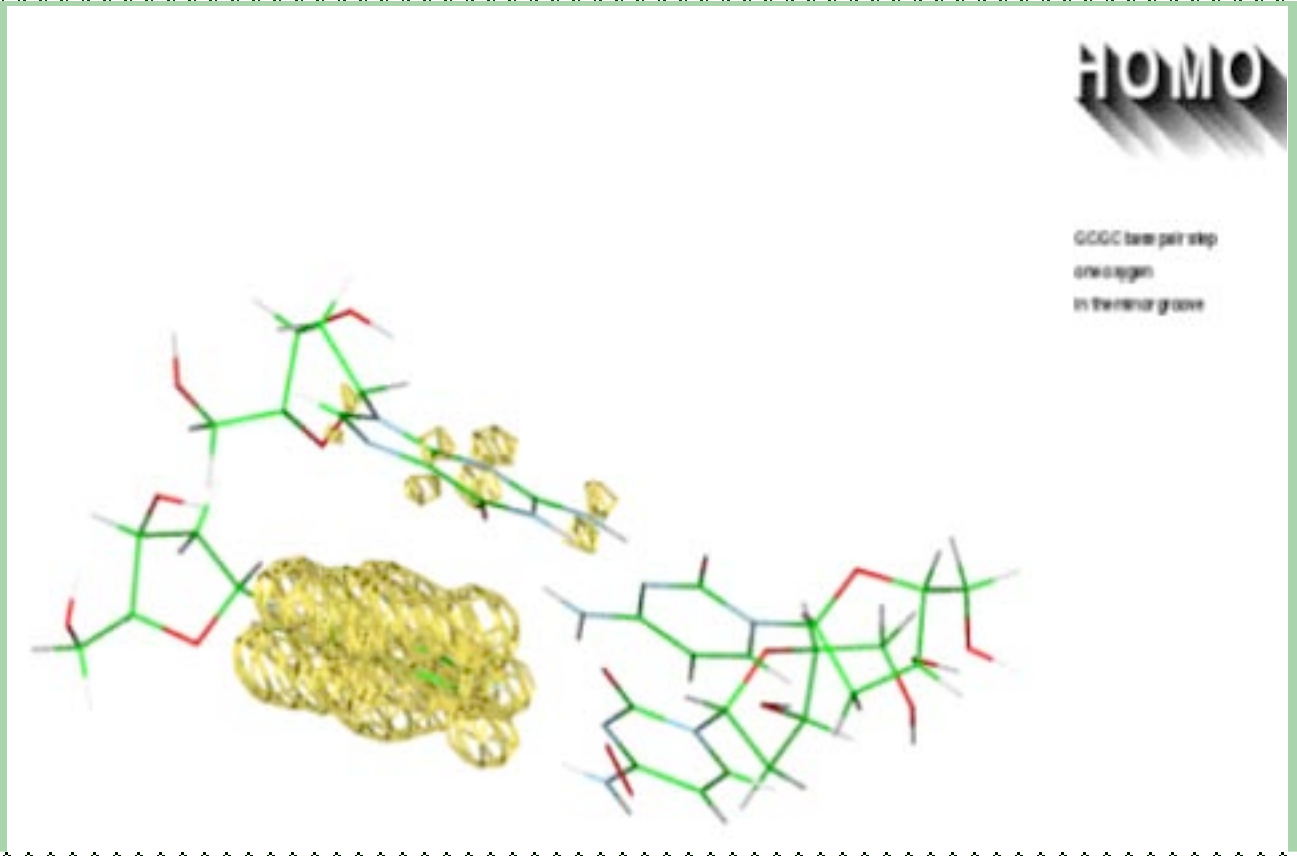
DNA docking: GCGC, O_2 in minor groove



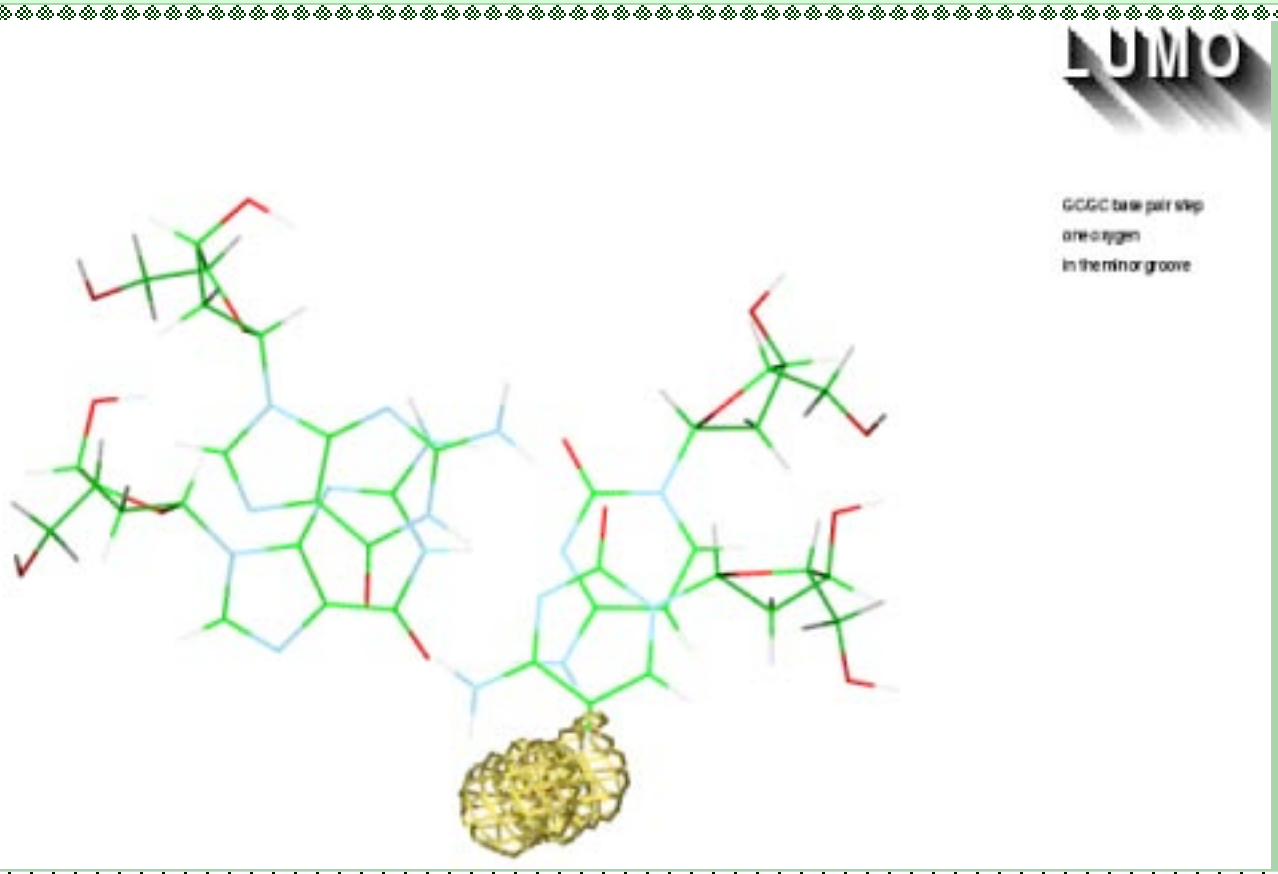
DNA docking: GCGC, O_2 in minor groove



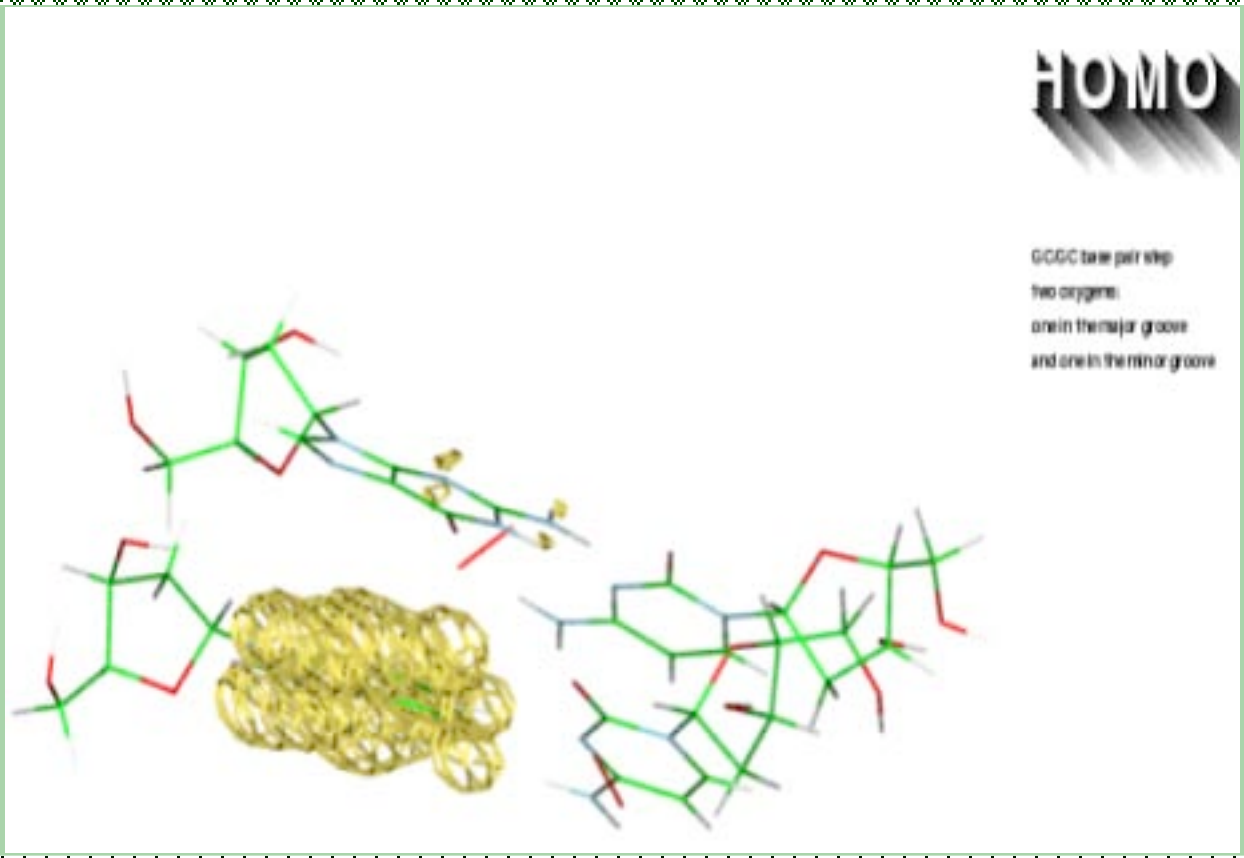
DNA docking: GCGC, O_2 in major groove



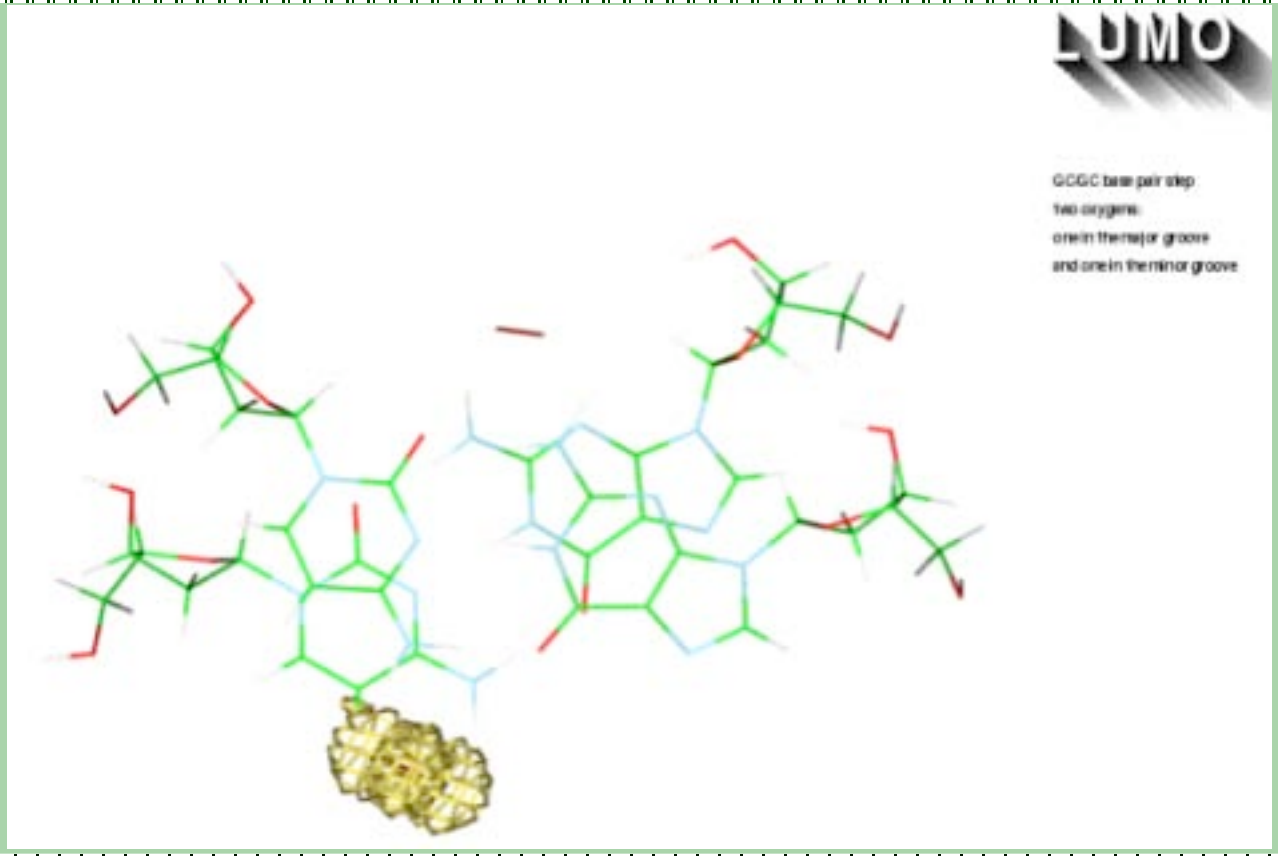
DNA docking: GCGC, O_2 in major groove



DNA docking: GCGC, O_2, the both grooves



DNA docking: GCGC, O_2, the both grooves



Future prospects

- Base pair sequence effects
- Longer DNA fragments
- Ab initio QC vs. semiempirical QC

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