DNA damage from first principles

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CP2K UK Users Meeting

London, 29th January 2014

Queen's University Belfast
Northern Ireland

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Contents

- Introduction
- Low-energy electrons
  - Electronic capture
  - C-O bond cleavage in nucleotides
  - Strand breaks in polynucleotides
  - Electronic capture in aminoacid-DNA
- Conclusions
- (Shock waves)

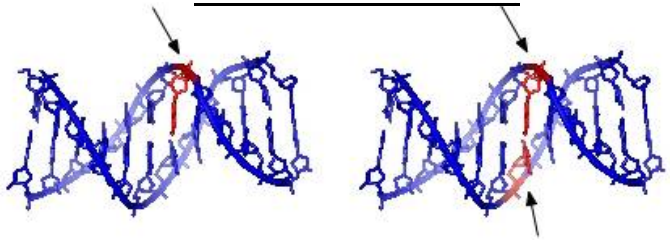
Radiation damage of biological systems

- Radiation causes lesions to any biomolecule, especially **DNA**
  - **Directly**
    - Ionization (X-rays, UV)
    - Impact fragmentation
  - **Indirectly** by generating reactive species
    - Low-energy electrons by ionization
    - free radicals: e.g. $OH^{\cdot}$ from water
  - **Thermo-mechanically**

Types of DNA Damage

- Base Damage
- Single Strand Breaks
- Double Strand Breaks
- Clustered Damage

Strand Breaks



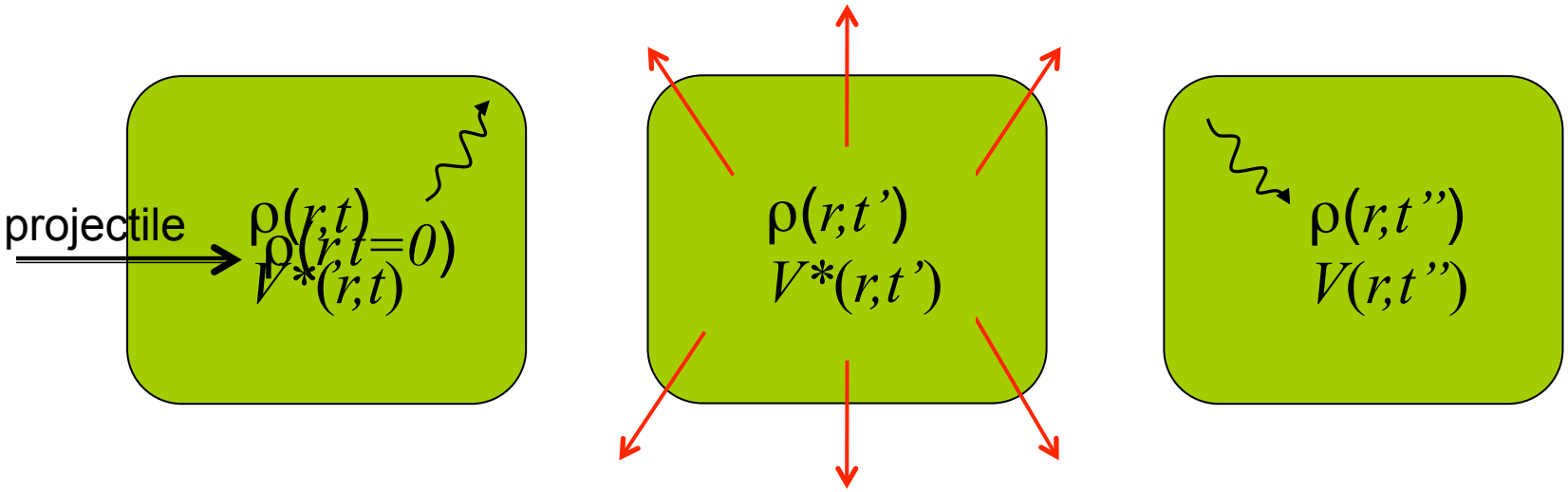
SSB DSB

Low-energy electrons (1-20 eV) cause SSB and DSB in plasmid DNA

B. Boudaïffa et al, Science 287, 1659 (2000)

P. Swiderek, Angew. Chem. Int.. Ed. **45**, 4056 (2006)

The irradiation process



Multiscale phenomenon

- **Secondary electron generation (TDDFT-Ehrenfest)**
  - A. A. Correa, J. Kohanoff, E. Artacho, D. Sánchez-Portal, and A. Caro, ***Non-adiabatic forces in ion-solid interactions: the initial stages of radiation damage***, Phys. Rev. Lett. **108**, 213201 (2012).
  - M. Ahsan Zeb, J. Kohanoff, D. Sánchez-Portal, A. Arnau, J. I. Juaristi, and E. Artacho, ***Electronic stopping power in gold: The role of d electrons and the H/He anomaly***, Phys. Rev. Lett. **108**, 225504 (2012).

- **Inelastic transport (Beyond Ehrenfest)**
- **Capture/localization (Ground state DFT)**
- **Chemical stage: strand breaks (Ground state DFT)**

…

- **Radiobiololgical effects**

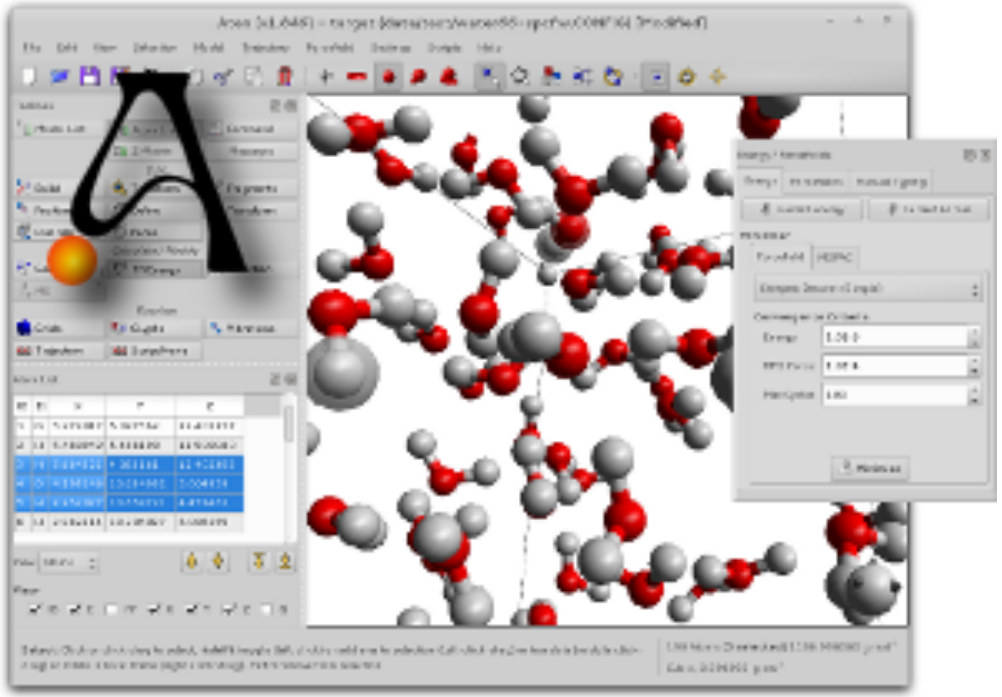
Damage due to low-energy electrons

- **Ab initio molecular dynamics simulations**
  - Quickstep module of **CP2K**
  - Electronic structure via DFT (**GGA-PBE + VDW**, **higher level**)
  - **GTH** pseudopotentials
  - **GPW** method, **TZVP-GTH** basis set
  - Up to **1,000 atoms** and **10 ps** (HECToR) **10,000 atoms**
  - **Spin density** shows excess (unpaired) electron

- REALISTIC ENVIRONMENT + THERMAL FLUCTUATIONS
  - Increasingly large solvated DNA fragments

Molecular builder and visualiser:

Aten (www.projectaten.org)
by Tristan Youngs (RAL – former QUB)

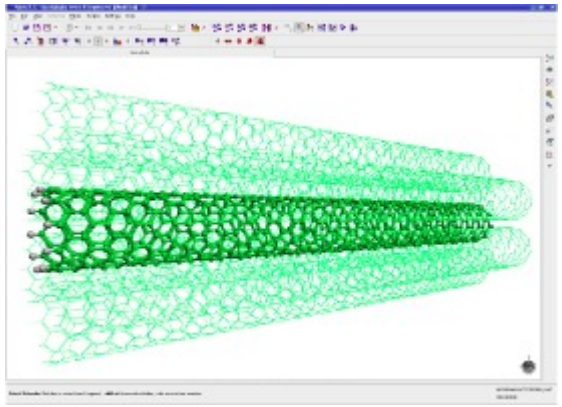


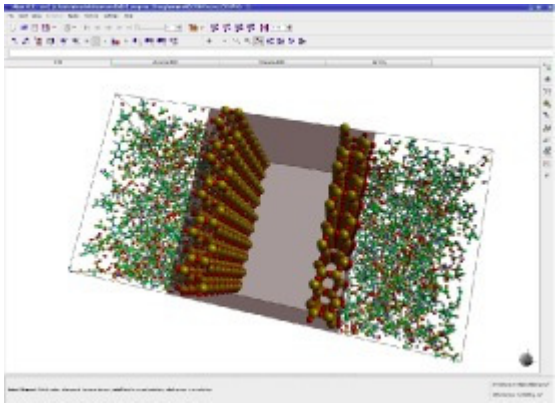
It generates input files for many codes, e.g. quantum-espresso, Siesta, DL_POLY, MOPAC, … **Do we want CP2K as well? (Ask Tristan)**

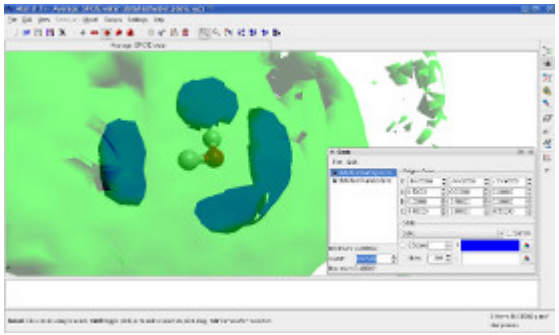
Molecular builder and visualiser:

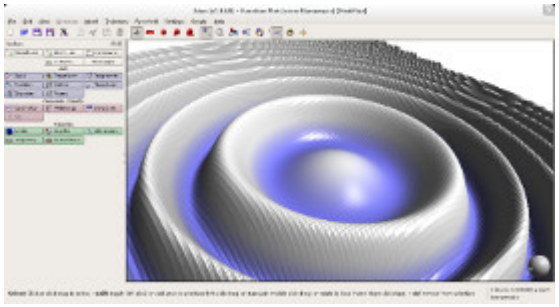
Aten (www.projectaten.org)

by Tristan Youngs (RAL – former QUB)







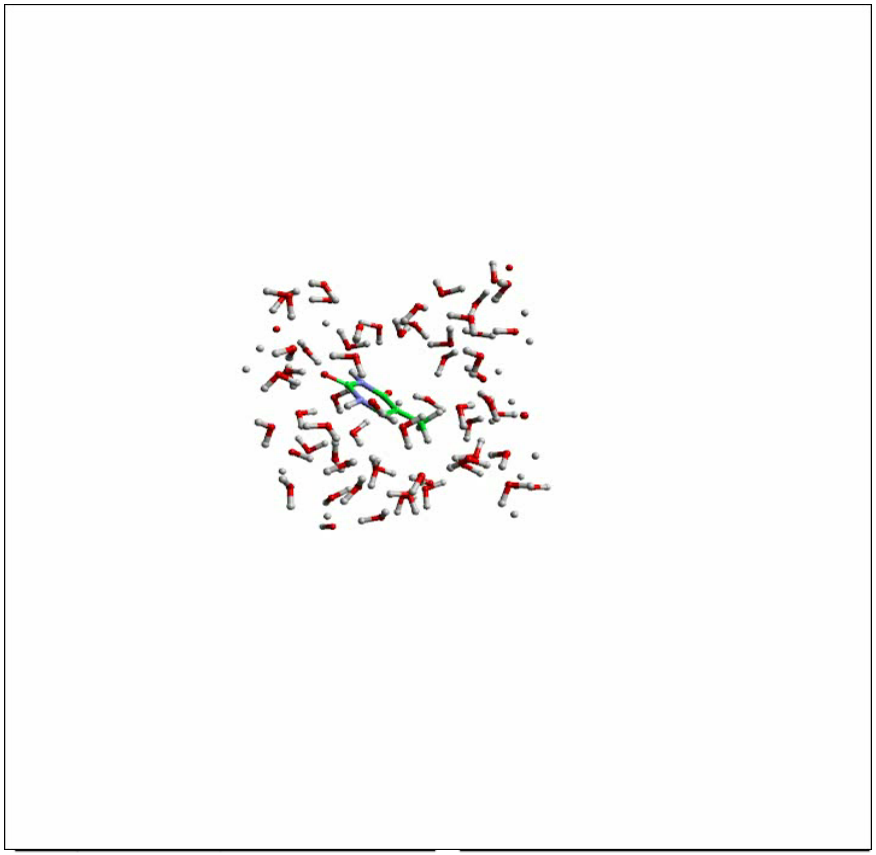


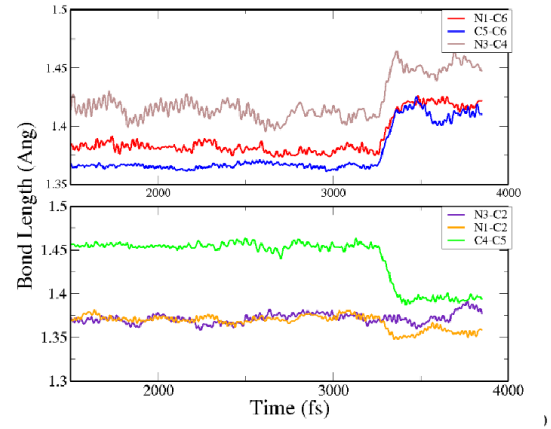
Electron localization

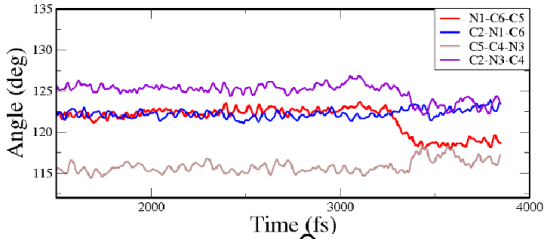
Nucleobases: Thymine

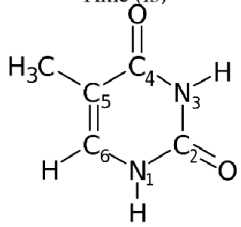
First-principles Molecular Dynamics Simulations

M. Smyth and J. Kohanoff, Phys. Rev. Lett. **106**, 238108 (2011)



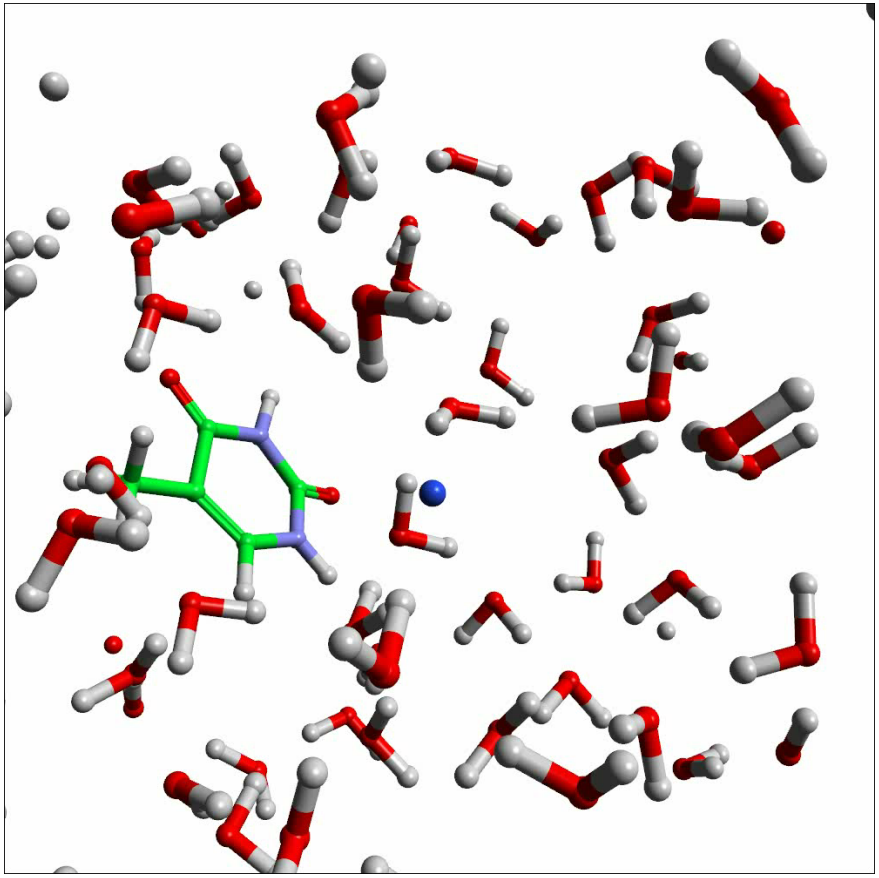






Nucleobases vs cavity

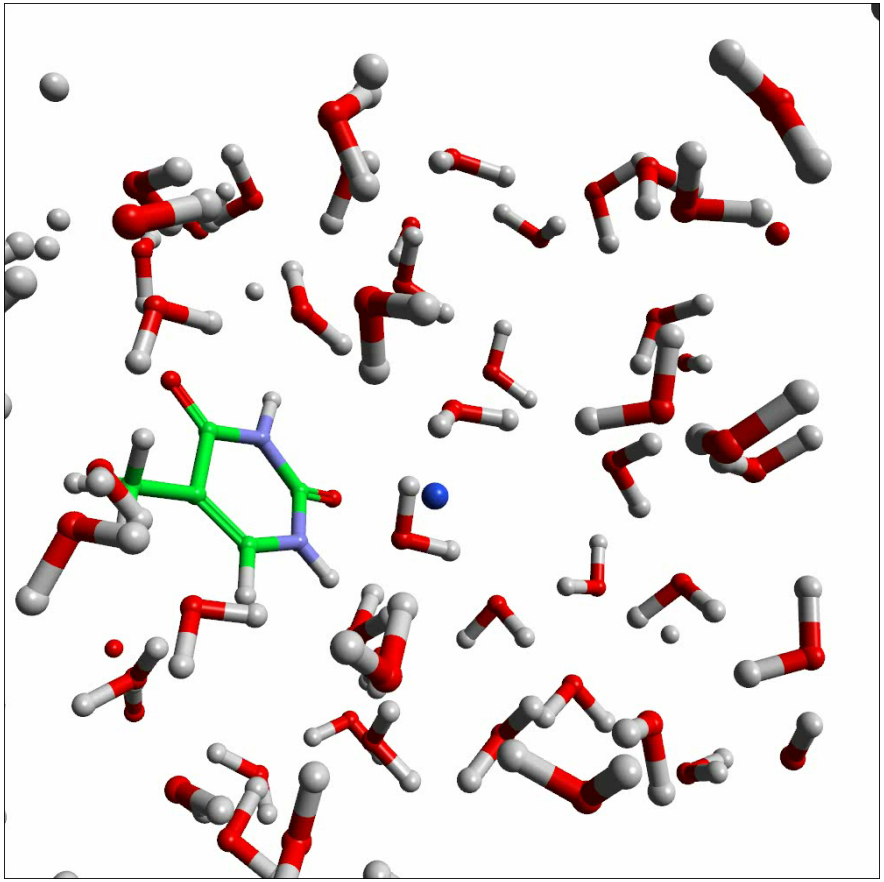
Self-interaction



PBE

Nucleobases vs cavity

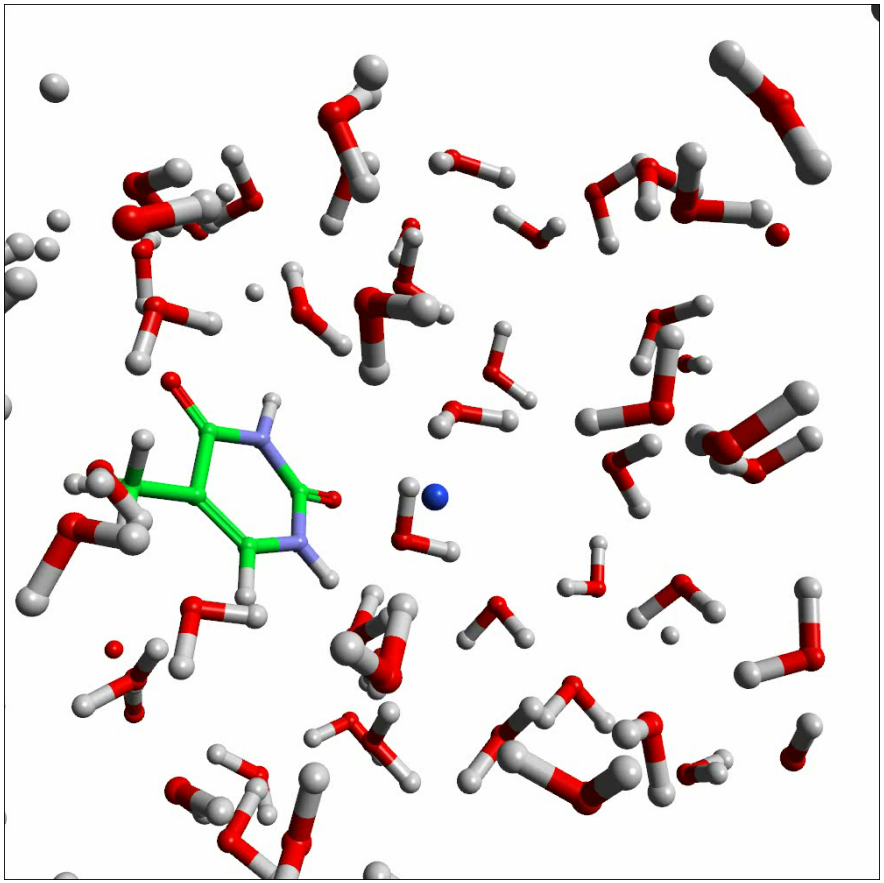
Self-interaction



SIC
a=0.2, b=0

Nucleobases vs cavity

Self-interaction

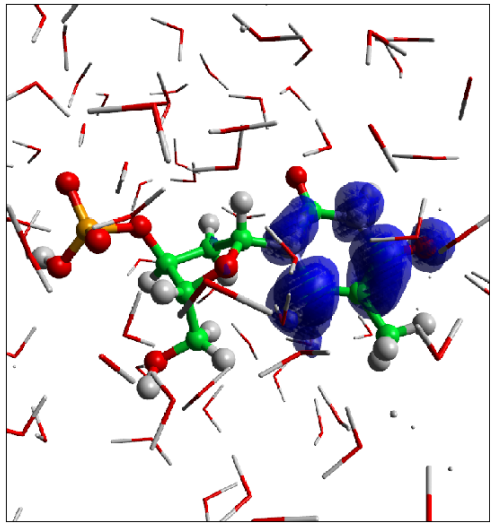


SIC
a=0.8, b=0.5

Nucleotides: dTMP

First-principles constrained Molecular Dynamics

M. Smyth and J. Kohanoff, J. Am. Chem. Soc. **134**, 9122 (2012)



Excess electron still localized in the base

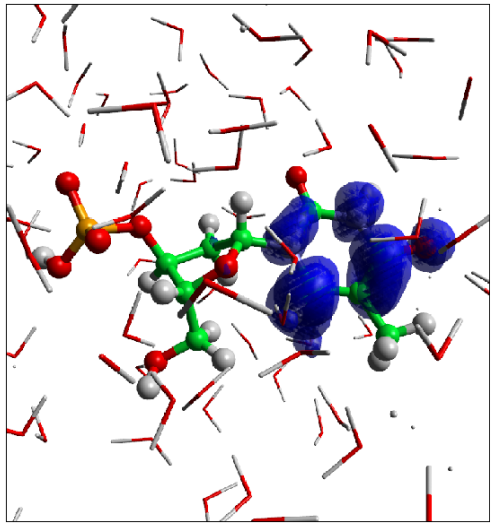
Strand breaks

- Don't occur spontaneously
- Rare event
- **Constrained MD simulations**: stretch bond and compute free energy by integrating the potential of mean force. *Equilibration and statistics*.

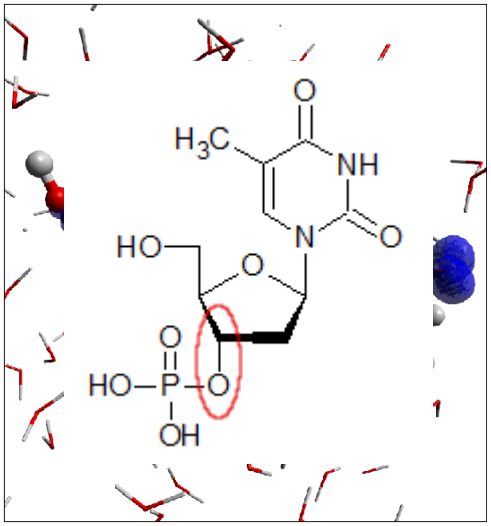
Nucleotides: dTMP

First-principles constrained Molecular Dynamics

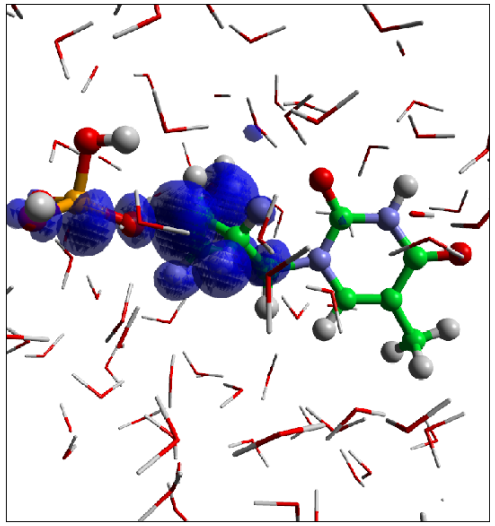
M. Smyth and J. Kohanoff, J. Am. Chem. Soc. **134**, 9122 (2012)



GS



TS



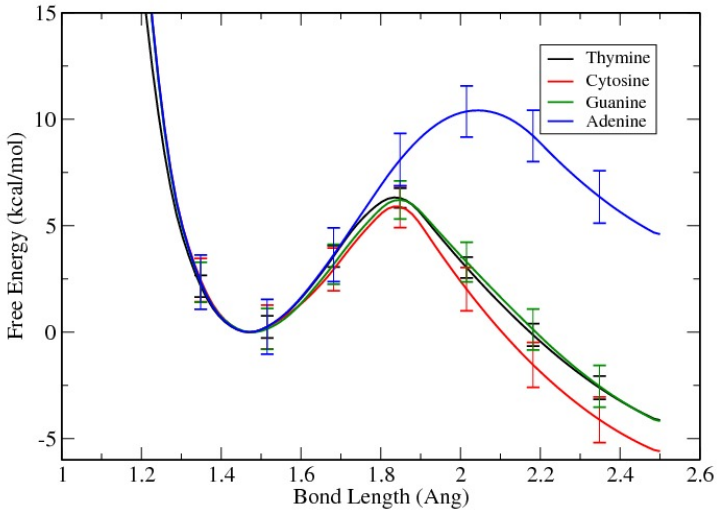
PS

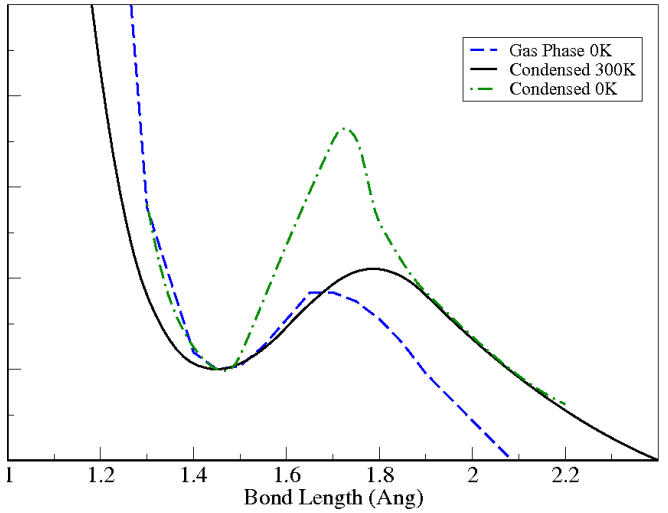
By stretching the $C_{3'}$-$O_{3'}$ phospodiester bond, the excess electron is transferred from the base to the sugar

Single Strand Breaks

$C_{3'}$-$O_{3'}$ phosphodiester bond cleavage in nucleotides

M. Smyth and J. Kohanoff, J. Am. Chem. Soc. **134**, 9122 (2012)





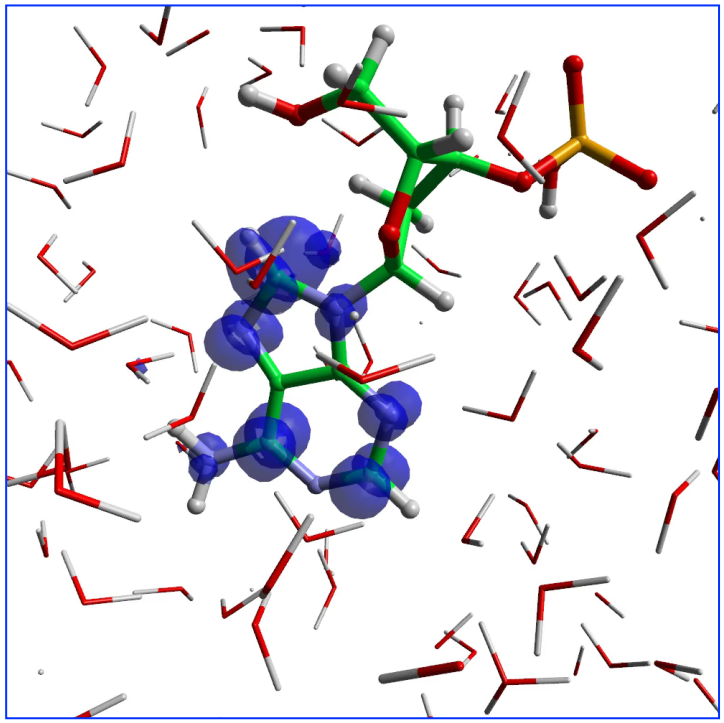
Condensed Phase **From Gas to Condensed Phase**

- **Barriers are about 5 kcal/mol ⇒ spontaneous SSB is feasible**
- **Environmental fluctuations are crucial to lower the barriers**

Nucleotides: dAMP

First-principles constrained Molecular Dynamics

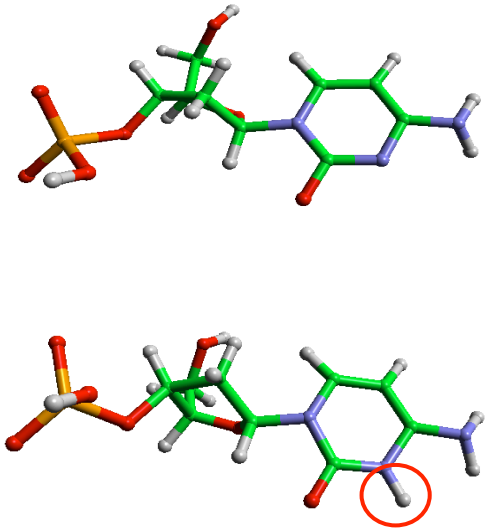
M. Smyth and J. Kohanoff, J. Am. Chem. Soc. **134**, 9122 (2012)

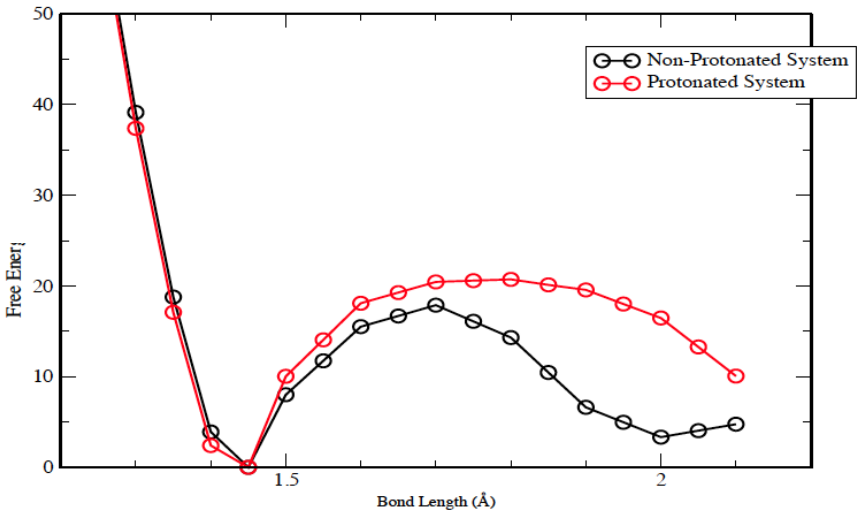


Protonation

Protonation vs strand break
in dCMP

M. McAllister, M. Smyth, G. Tribello, and J. Kohanoff (unpublished)

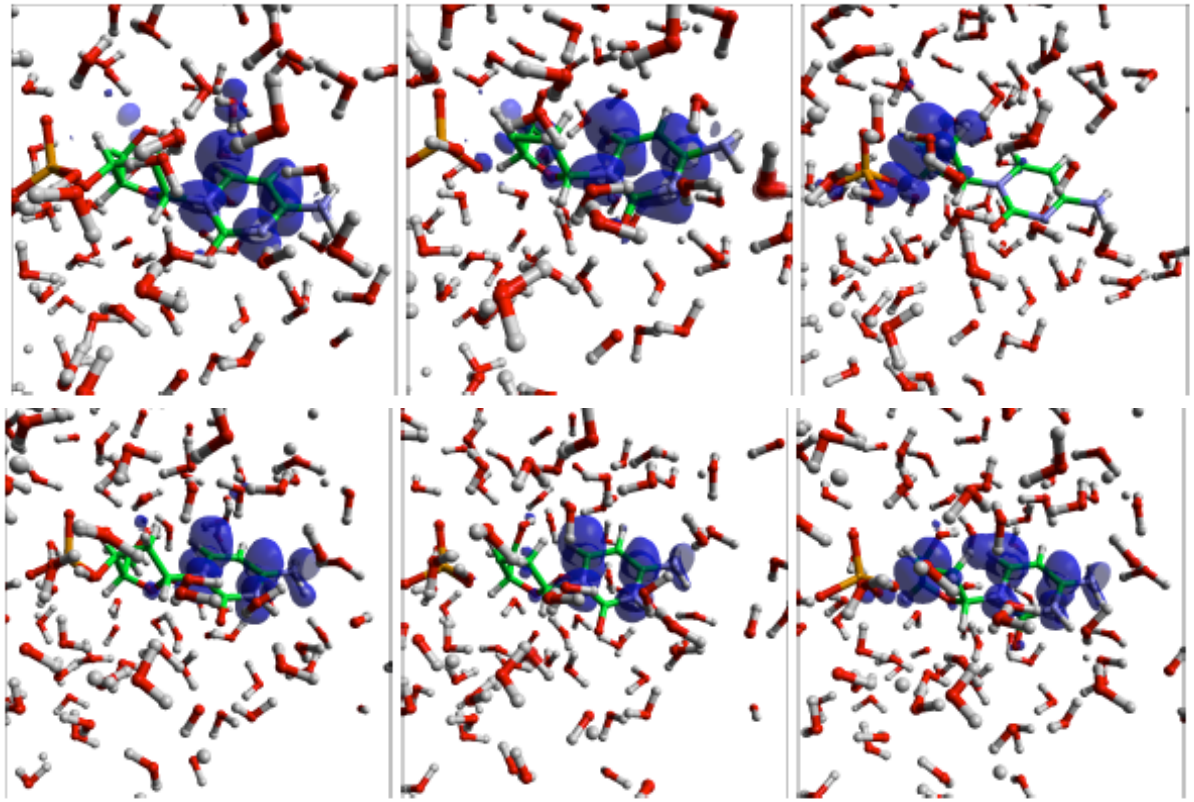




Experimentally, LEE in dAMP and dCMP do no lead to bond cleavage

Protonation vs strand break
in dCMP

M. McAllister, M. Smyth, G. Tribello, and J. Kohanoff (unpublished)

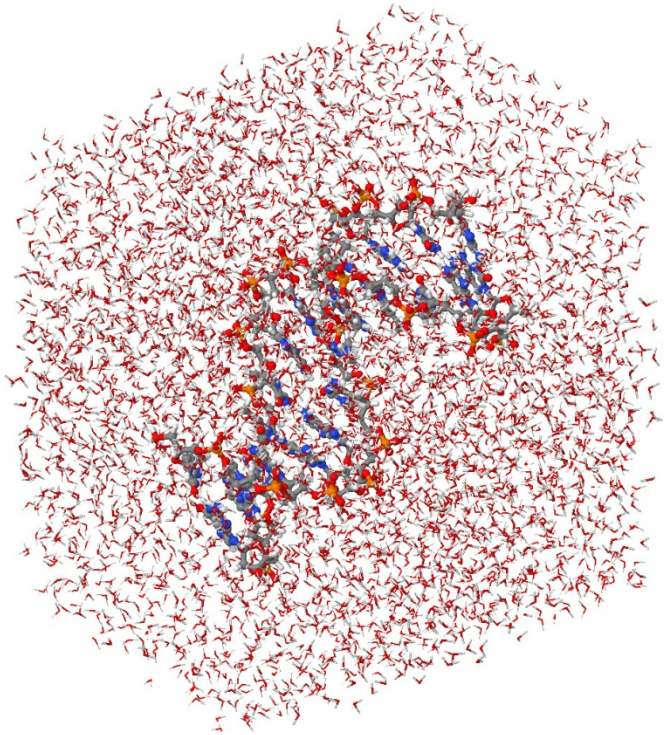


(a) 1.4 Å (b) 1.8 Å (c) 2.2 Å

Non-Protonated

Protonated

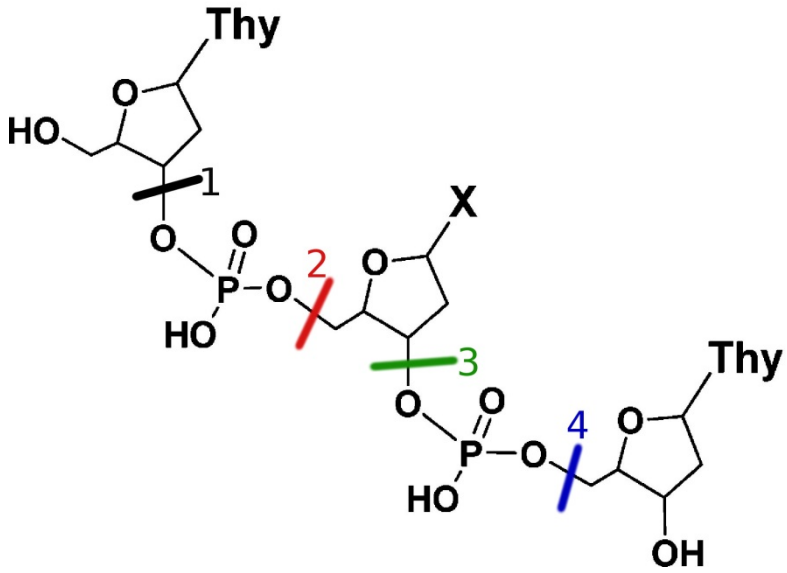
Towards reality: larger DNA fragments



- **Are there specific sequences that favour strand breaks?**
- **Role of base pairing (duplex DNA)**

Trinucleotides
TXT

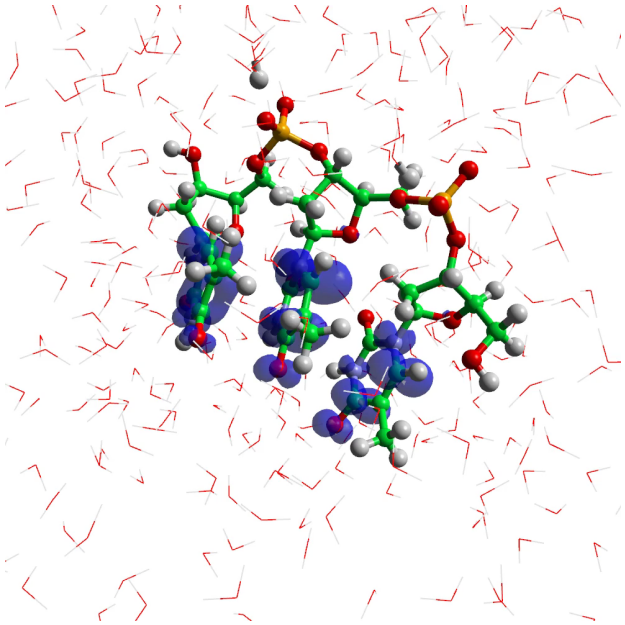
Z. Li, P. Cloutier, L. Sanche and J. R. Wagner, JACS **132**, 5422 (2010)

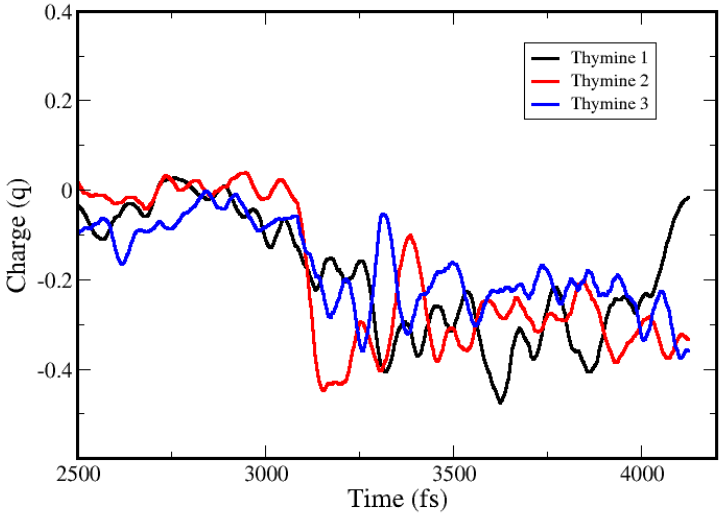


There are 4 possible bonds to break
Experiment suggests 1 ($C_{3'}$-$O_{3'}$) for TTT

Trinucleotides
TTT

L. Bouëssel du Bourg, M. Smyth and J. Kohanoff (unpublished)

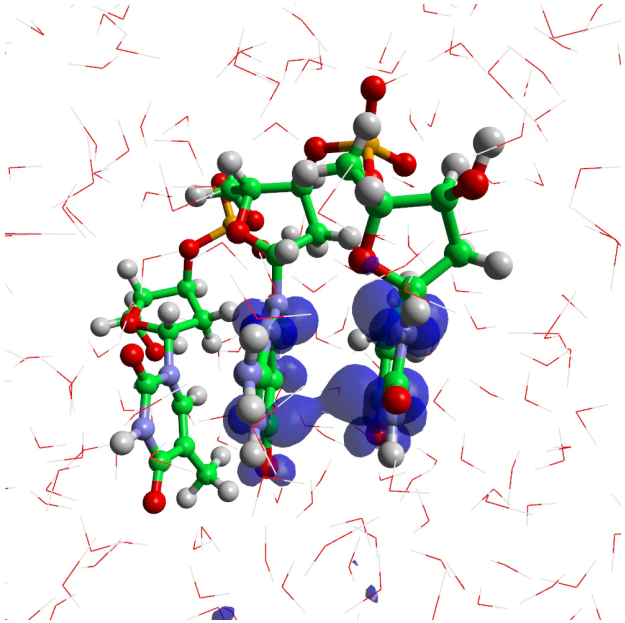


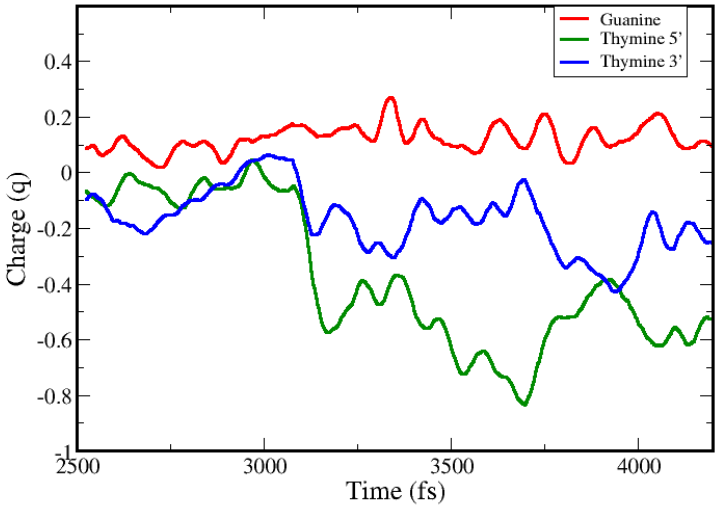


Excess electron fluctuates between the three Thymines

Trinucleotides
TGT

L. Bouëssel du Bourg, M. Smyth and J. Kohanoff (unpublished)





Excess electron fluctuates between the two Thymines

Self-interaction corrected approaches. Hybrids?

Metadynamics

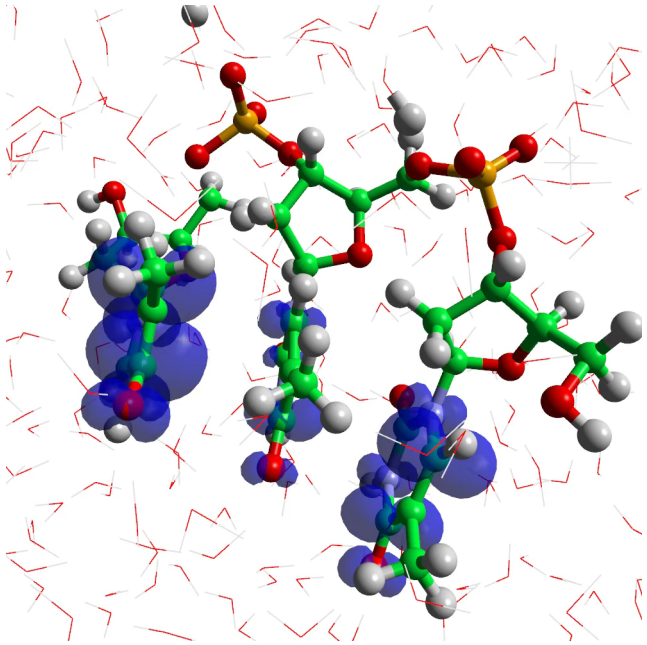
Which path will the system take?
Constrain product of *switching functions* for the 4 bonds

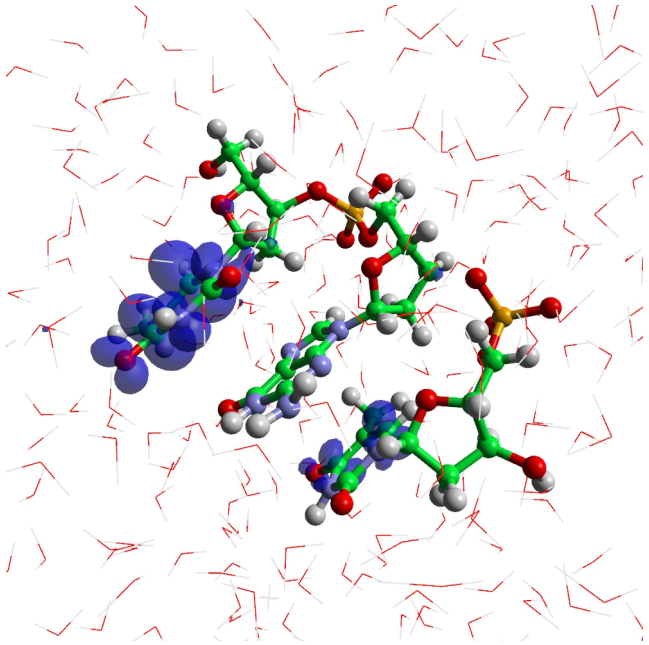
PLUMED (*www.plumed-code.org*): interface with CP2K?

Trinucleotides via metadynamics

TTT vs TGT

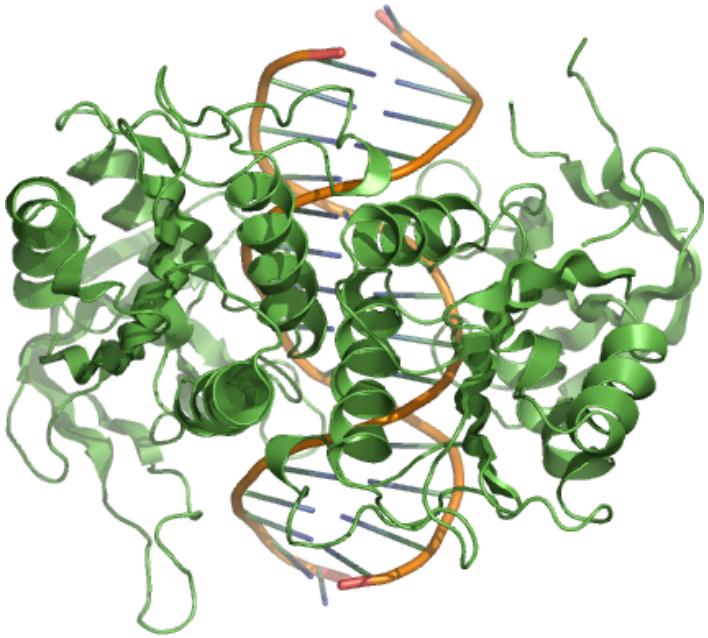
L. Bouëssel du Bourg, M. Smyth, G. Tribello and J. Kohanoff (unpublished)

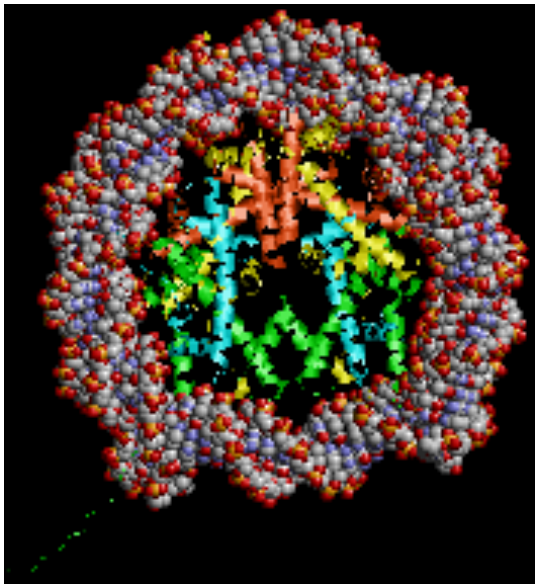




Strand breaks seem to occur in different places depending on sequence

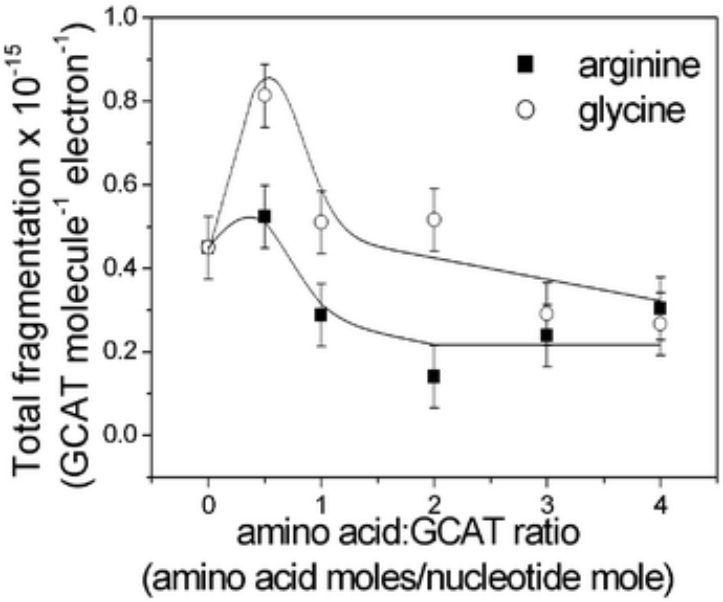
Towards reality:
DNA in the nuclear cell environment



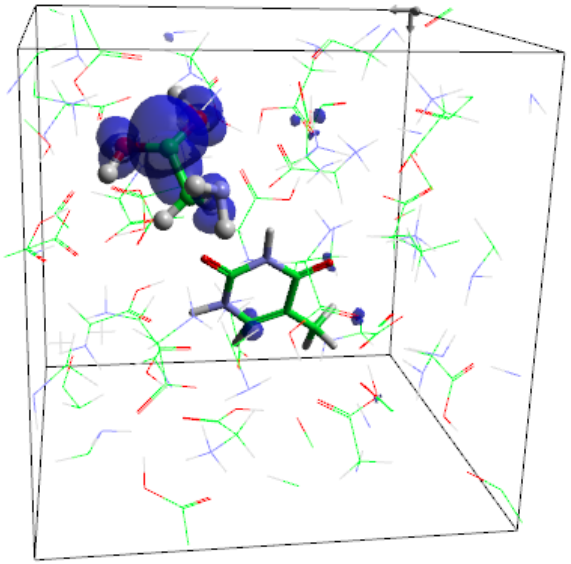


Does the proximity of histones protect DNA against electron attachment and radical attack? If so, how?

A first attempt:
The protective role of Glycine



S. Ptasinska, Z. Li, N. J. Mason and L. Sanche, Phys. Chem. Chem. Phys., 2010, 12, 9367

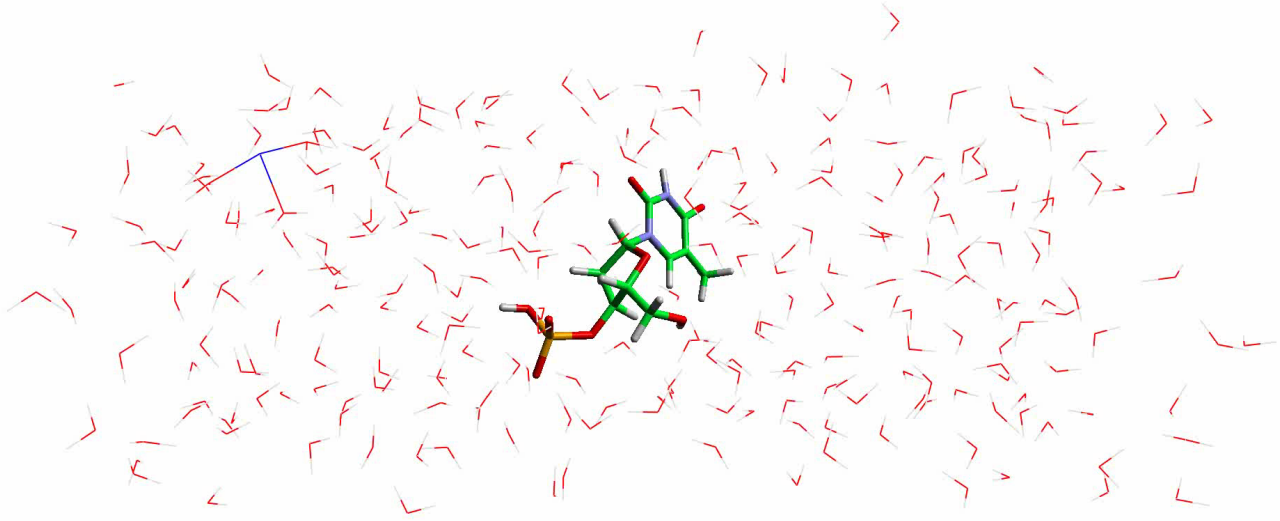


Bin Gu, M. Smyth and J. Kohanoff (unpublished): Thy in pure Gly

Depending on whether it is in the canonical or zwitterion form, Glycine can be more attractive than Thymine for electrons

Shock waves: nucleotide in water

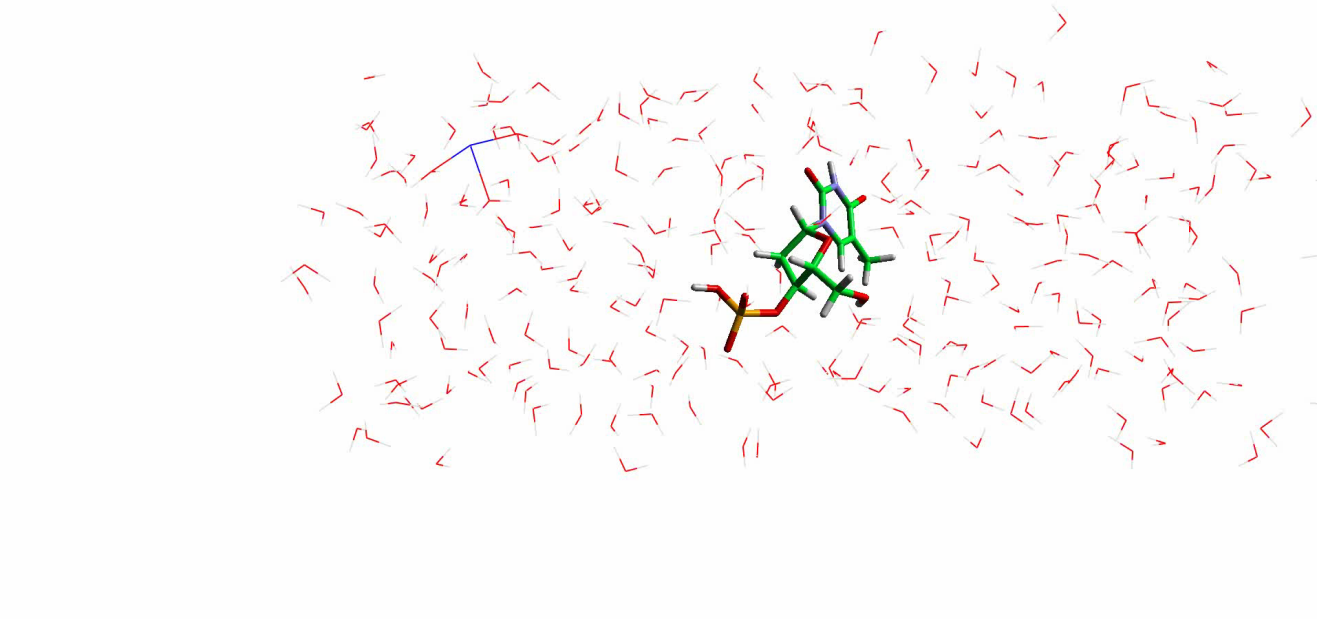
Alberto Fraile and JK (unpublished)



CP2K, v=10 km/s, single shock

Shock waves: nucleotide in water

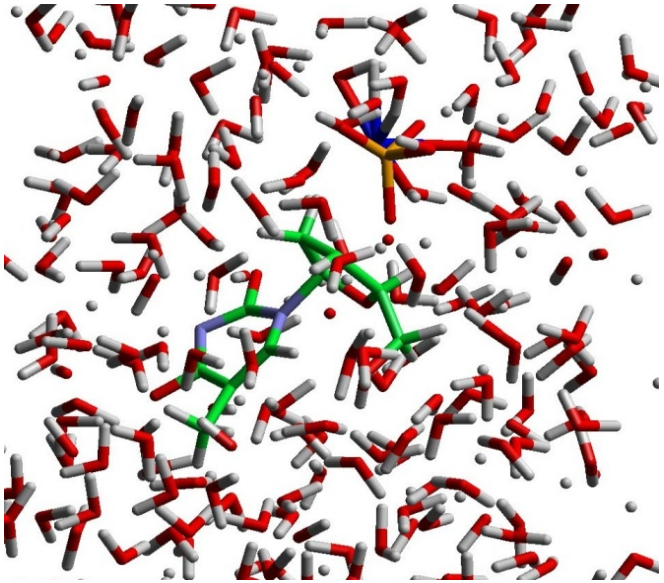
Alberto Fraile and JK (unpublished)

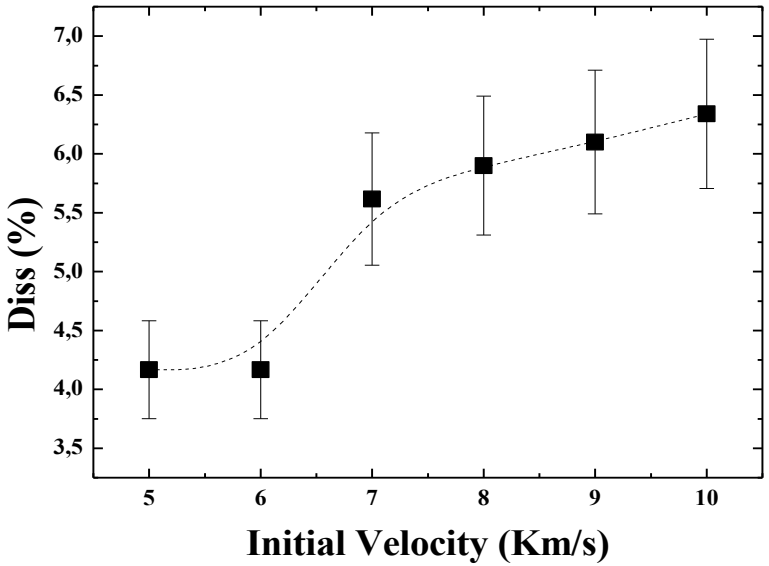


CP2K, v=10 km/s, MSST (Hugoniot)

Water dissociation: enhanced acidity

Alberto Fraile and JK (unpublished)

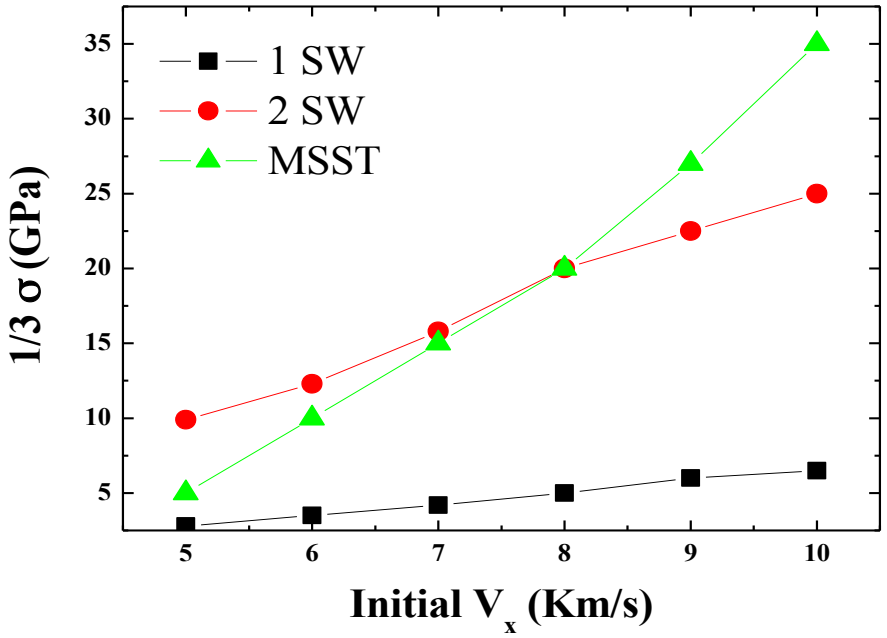




Protons from dissociated water are free to react with the nucleotide

Pressures generated in SW

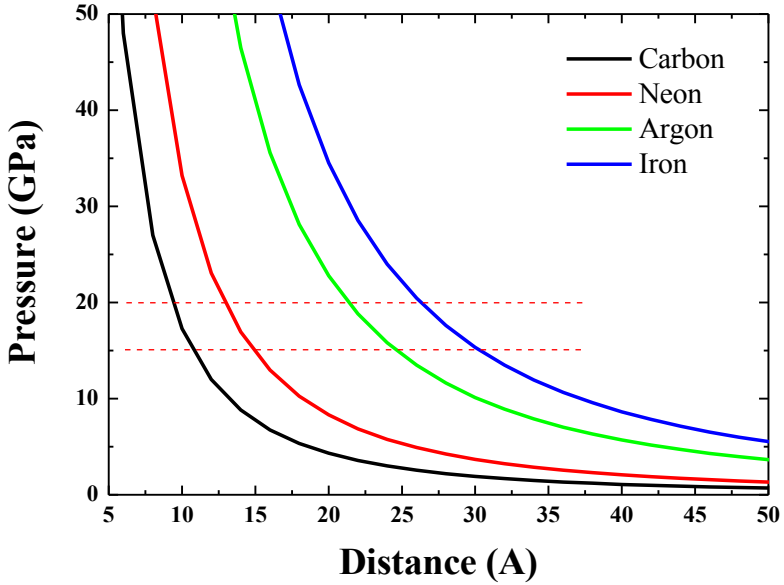
Alberto Fraile and JK (unpublished)



CP2K-MSST. Pressures from 5 to 35 Gpa with v between 5 and 10 km/s

Shock waves: nucleotide in water

Alberto Fraile and JK (unpublished)



- Damage happens at pressures above 15-20 GPa
- Protons don't produce any damage
- Carbon ions must come closer than 10 A
- Only heavy ions produce damage via shock waves

Summary

- When secondary electrons reach zero kinetic energy (vertical attachement), it localizes in the nucleobases in times≈15-25 fs.
- No time to create a cavity as in pure water (time scale ~1.5 ps)
- Nucleotides are stable in water, but excess electrons weaken the C-O (phosphodiester) bond between ribose and phosphate.
- At ambient conditions solvated nucleotides can spontaneously cleave (~5 kcal/mol barriers), thus leading to strand breaks, competing with protonation, which stabilizes the backbone.
- Tri- and tetra-nucleotides. Bond cleaved depends on sequence.
- Neighbouring aminoacids, as present in chromatin, can physically and chemically shield DNA, thus reducing the chances of damage.

Wish list for CP2K

- Integrate the following features:
  - Molecular editor (e.g. aten)
  - Force field for MD equilibration
  - PLUMED for free energies
  - Force field fitting procedure(s)

- Further developments:
  - Real-time electron dynamics beyond Ehrenfest
  - Resonant electronic states
  - Radicals

- Manual !!
  - Tutorials linked to manual sections (e.g. HFX, QMMM, etc)

Collaborators

- Maeve Smyth (QUB → Cardiff)
- Lila Bouëssel du Bourg (ENS-Paris)
- Maeve McAllister (QUB)
- Gareth Tribello (QUB)
- Bin Gu (NUIST, China)
- Alberto Fraile (Madrid → Crete)