IRRADIATION OF MATTER FROM FIRST-PRINCIPLES: DNA AND OTHER MATERIALS

CP2K USERS MEETING

Lincoln, 12 January 2018

Jorge Kohanoff
Atomistic Simulation Centre
Queen’s University Belfast
Northern Ireland, UK

Irradiation: application areas

- Biological tissue (damage, radiotherapies)
- Nuclear industry (waste, fusion, fission)
- Electronic components (semicond., detectors)
- Ices on interstellar dust particles (astrobiology)
- Materials processing (e.g. polymers, semicond.)

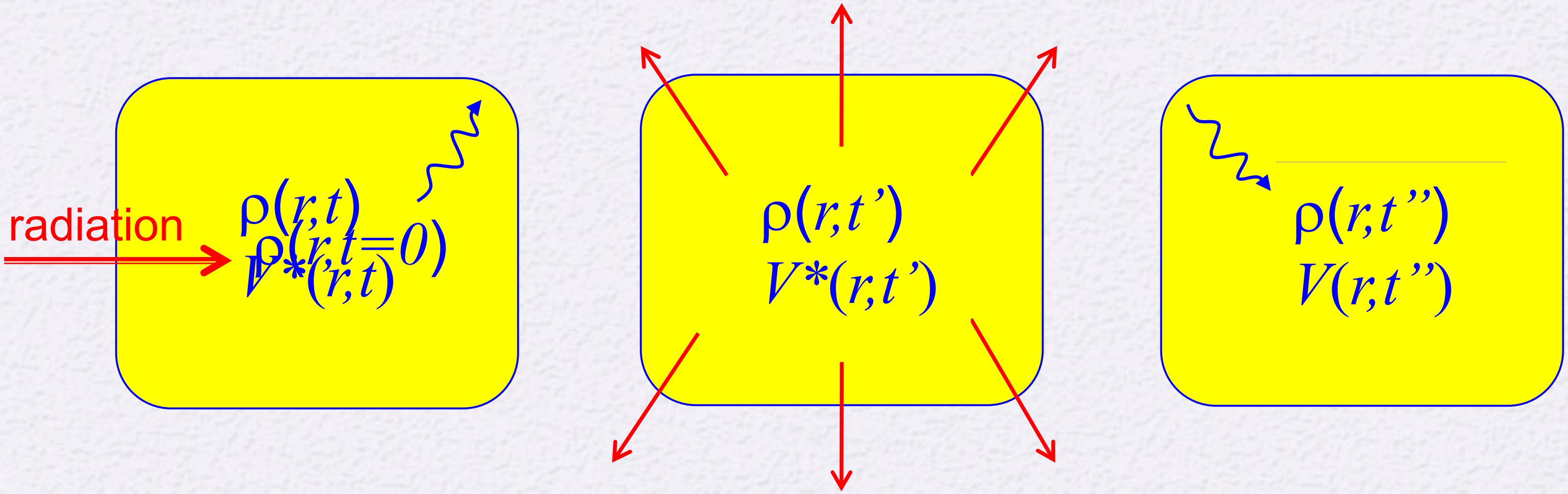
Irradiation:
A multi-scale phenomenon

- Physical stage (~fs to ns)
  - Ionization: secondary electrons and holes. Excitations.
  - Electron, hole and excitation transport: elastic and inelastic.
  - Electron capture, impact ionization, recombination, …

- Chemical stage (~ps to ms)
  - Bond breaking and formation
  - Heating, diffusion
  - Damage

- Biological/Engineering scale (~ns to hours/days)
  - Functional and structural modifications, phase transformations.
  - Failure: death, fracture, explosion.

The physical stage



radiation

$\rho(r,t)$

$\rho(r,t=0)$

$V^*(r,t)$

$\rho(r,t')$

$V^*(r,t')$

$\rho(r,t'')$

$V(r,t'')$

Secondary electron generation

Electronic (heat) transport

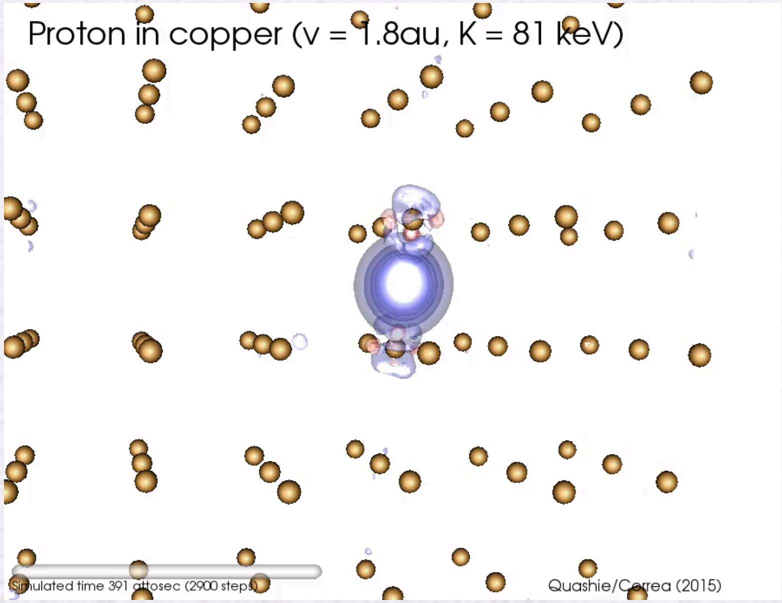
Phonon emission

Inelastic electron transport

Non-adiabatic dynamics: TDDFT, Ehrenfest and beyond

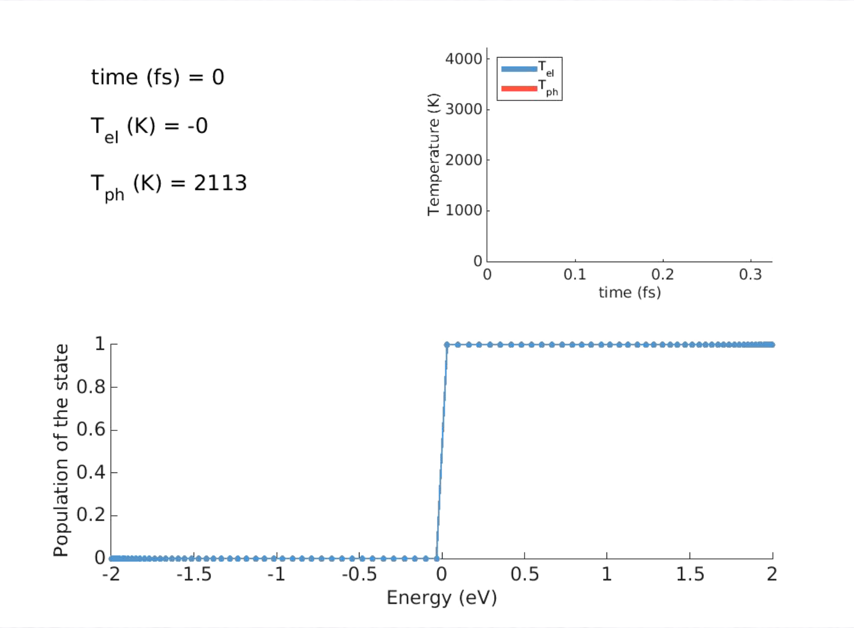
The physical stage

- **Electronic excitation (TDDFT-Ehrenfest -- SIESTA)**
  - 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).



The physical stage

- **Inelastic transport (Beyond Ehrenfest-ECEID – TB models)**
  - V. Rizzi, T. N. Todorov, J. Kohanoff, and A. A. Correa, ***Electron-phonon thermalization in a scalable method for real-time quantum dynamics***, Phys. Rev. B **93**, 024306 (2016).
  - V. Rizzi, T. N. Todorov, and J. Kohanoff, ***Inelastic electron injection in a water chain***, Scientific Reports **7**, 45410 (2017).



The chemical stage

- We want to describe ***chemical modifications*** due to reactive species: ***electrons, holes, radicals***, e.g. ***bond breaking and formation.***
- We will assume ***adiabatic dynamics.*** This is not always the case, but it encompasses a large class of phenomena.
- Modeling ***chemical reactions*** requires explicit electrons (or reactive force fields). Therefore we use ***first-principles methods.***
- Activated processes occur in ***long timescales,*** inaccessible to standard first-principles MD. ***Rare-event sampling*** is necessary.

We want to know where do electrons and holes go, and what do they do.

Methodology

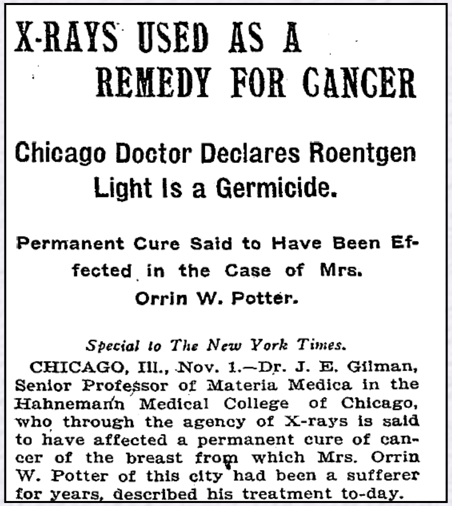
- First-principles molecular dynamics (CP2K)
  - Electronic structure via DFT (GGA-PBE + VDW, SIC, Hybrids)
  - Pseudopotentials + GPW, All-electron + GAPW
  - Gaussian basis sets: DZVP, TZVP, TZV2P
  - Spin density shows excess (unpaired) electron
- Realistic fluctuating environment
  - Up to 3000 atoms, for up to 10 ps
  - Fully first-principles, no QM-MM
- Rare events
  - Constrained MD + thermodynamic integration
  - Metadynamics

Origins of Radiotherapy

- **Wilhelm Röntgen** (Würzburg, 1895): discovers X-rays and proposes medical uses.
- **John Hall-Edwards** (Birmingham, 1896): first radiograph for diagnostic purposes. Experiments on his own arm and contracts dermatitis.

If they cause harm, they can also cure

- **L. Freund** (Vienna, 1898): first therapeutic use of X-rays (birthmark removal).
- **J. E. Gilman** (Chicago, 1901): first use of X-rays in cancer therapy.
- Widespread use of radiotherapy for cancer after WW2



X-RAYS USED AS A REMEDY FOR CANCER

Chicago Doctor Declares Roentgen Light Is a Germicide.

Permanent Cure Said to Have Been Effected in the Case of Mrs. Orrin W. Potter.

Special to The New York Times.

CHICAGO, Ill., Nov. 1.—Dr. J. E. Gilman, Senior Professor of Materia Medica in the Hahnemann Medical College of Chicago, who through the agency of X-rays is said to have affected a permanent cure of cancer of the breast from which Mrs. Orrin W. Potter of this city had been a sufferer for years, described his treatment to-day.

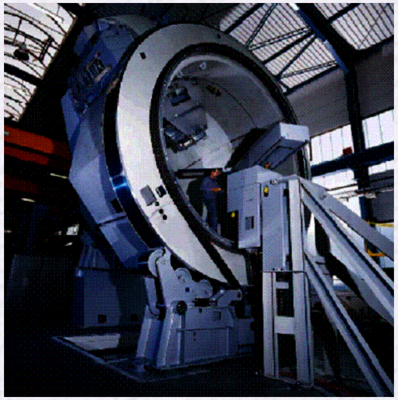
Radiotherapies

“Cancer is the second biggest killer in the Western world”

“40% of patients are cured with radiotherapy”

“Only 11% are cured with just chemotherapy”

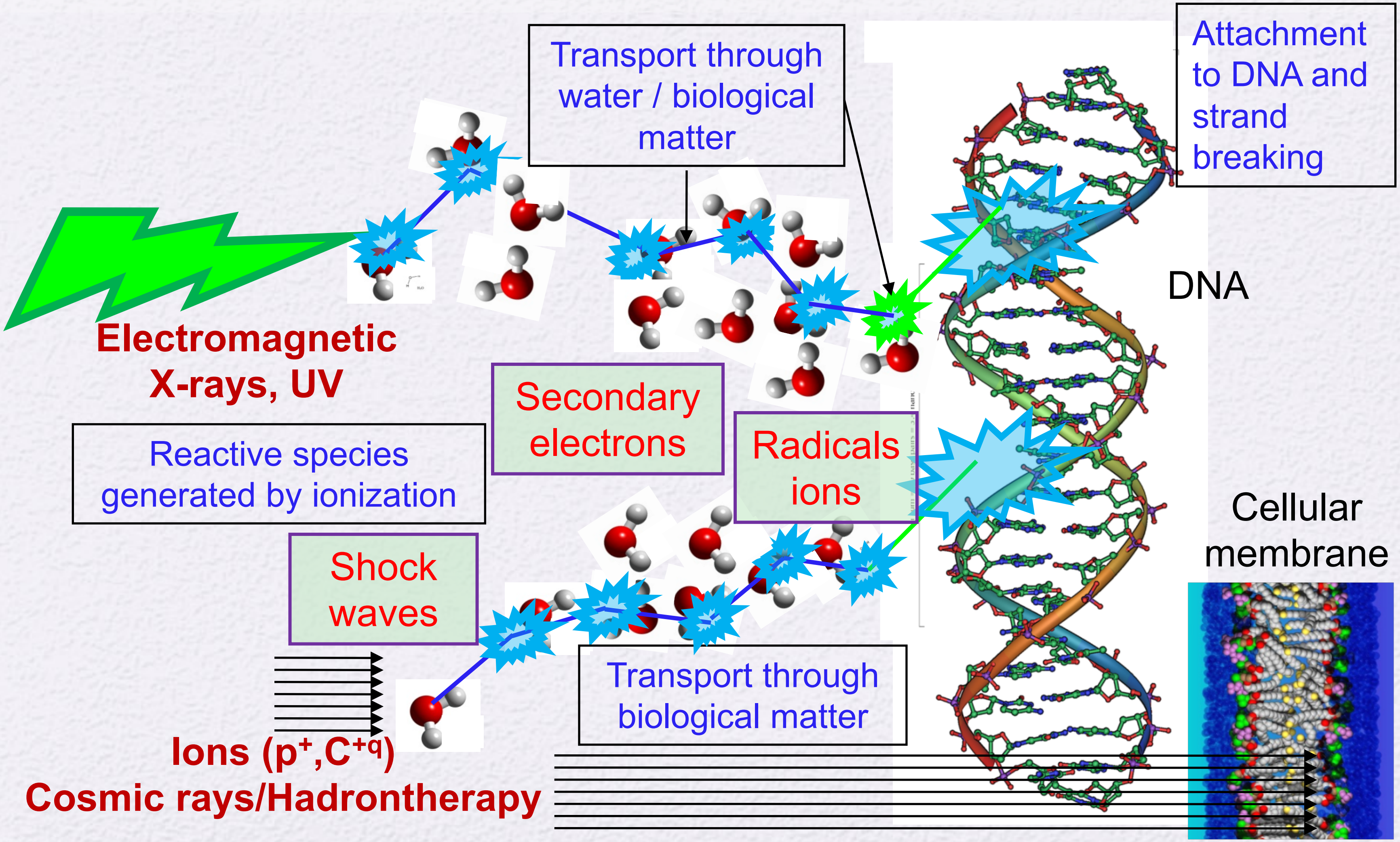
“Radiotherapies are inexpensive – 6% of cost of cancer care”



How do they work?

DNA damage

Maeve McAllister, Maeve Smyth, Gareth Tribello



Transport through water / biological matter

Attachment to DNA and strand breaking

DNA

Electromagnetic X-rays, UV

Reactive species generated by ionization

Secondary electrons

Radicals ions

Cellular membrane

Shock waves

Transport through biological matter

Ions (p^+,C^{+q})
Cosmic rays/Hadrontherapy

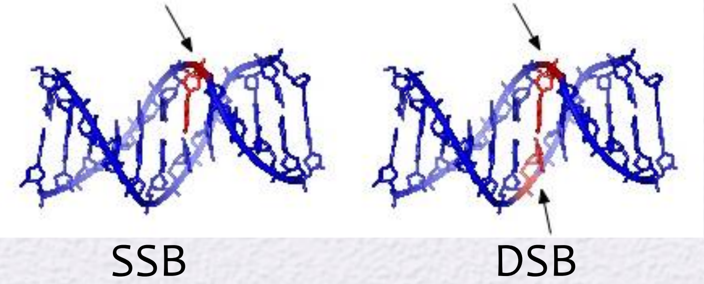
Lesions to biomolecules

- Radiation causes lesions to any biomolecule, especially DNA
  - Directly
    - Ionization (X-rays, UV) → holes
    - Electronic excitation (UVB)
    - Impact fragmentation
  - Indirectly by generating reactive species
    - Ionization → Low-energy electrons (<20 eV)
    - 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



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

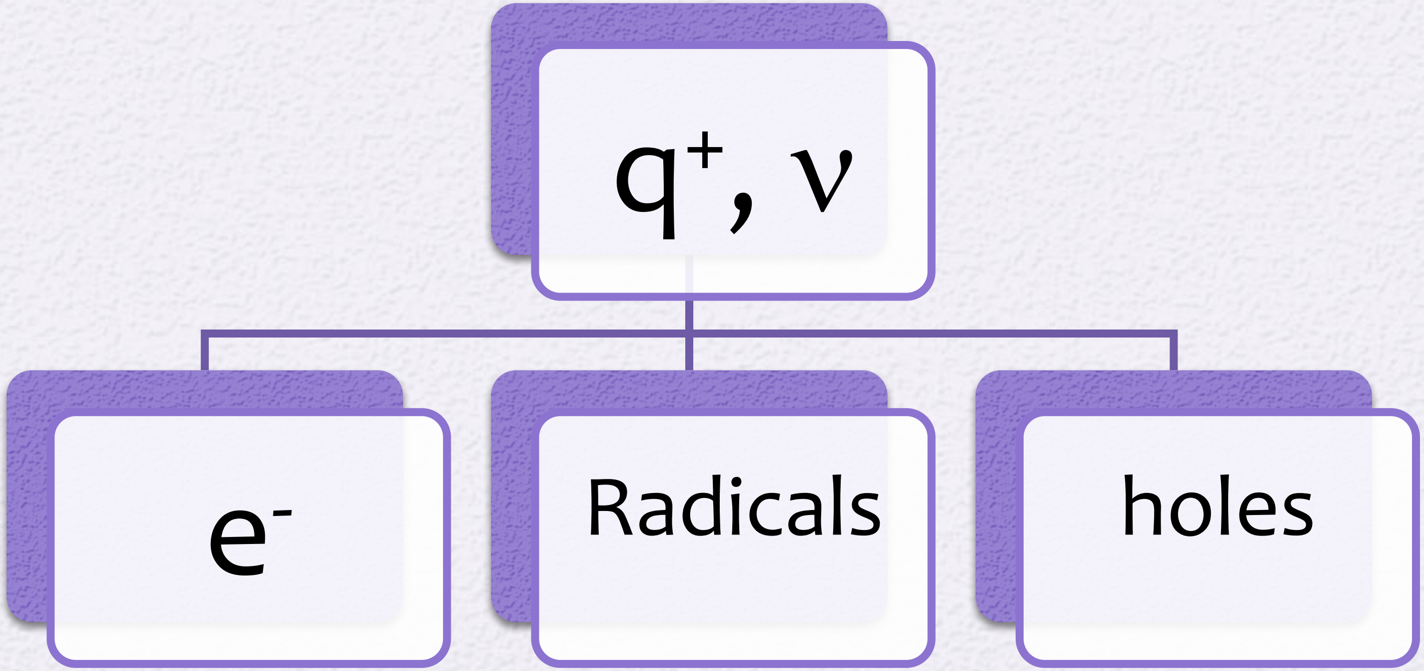
Dissociative electron attachment (DEA)

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

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

To break or not to break: That's the question!

Do low-energy electrons induce damage to DNA in the physiological environment?



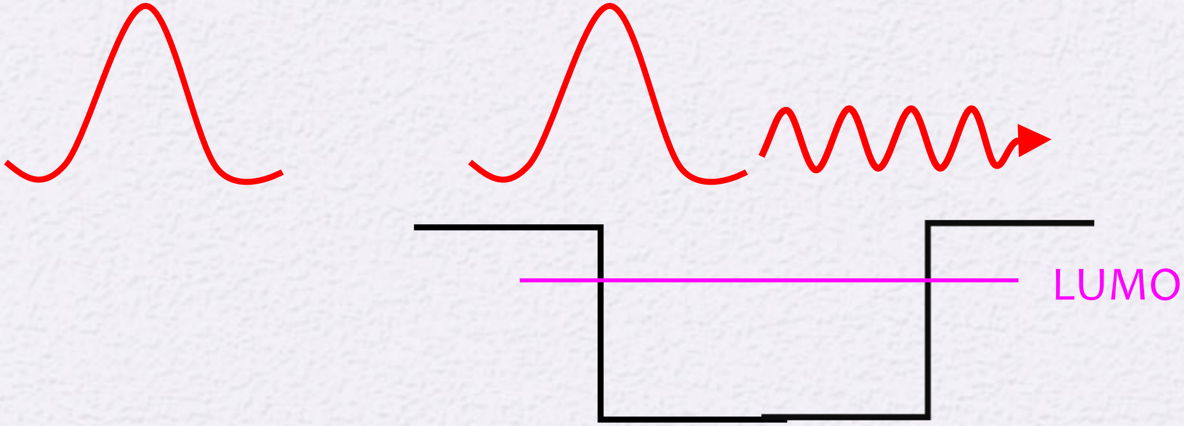
q^+, ν

e^-

Radicals

holes

Dissociative electron attachment



Vibrational excitation

↓

Leading to bond cleavage

Inelastic electron scattering

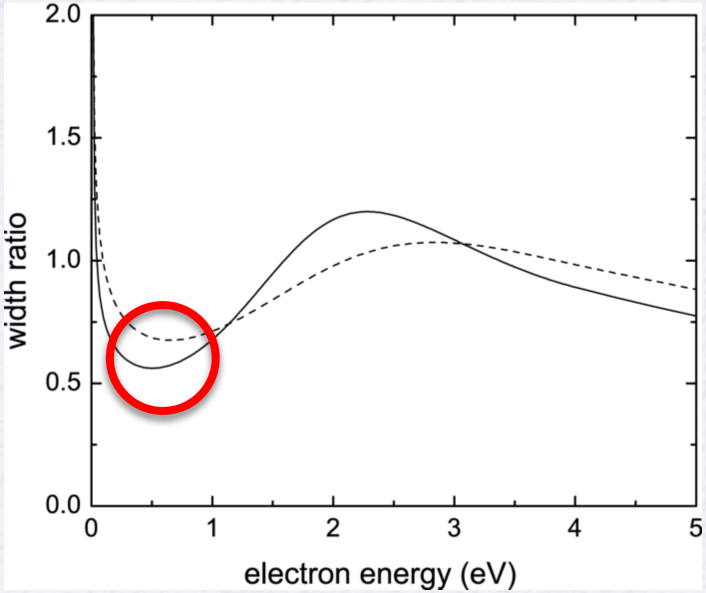
R-matrix: DEA cross section is enhanced by water environment

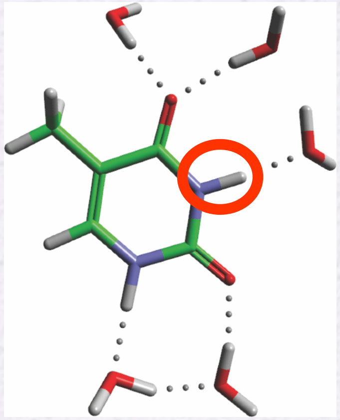
M. Smyth, J. Kohanoff and I. Fabrikant, J. Chem. Phys. **140**, 184313 (2014)

Dissociative electron attachment (DEA)

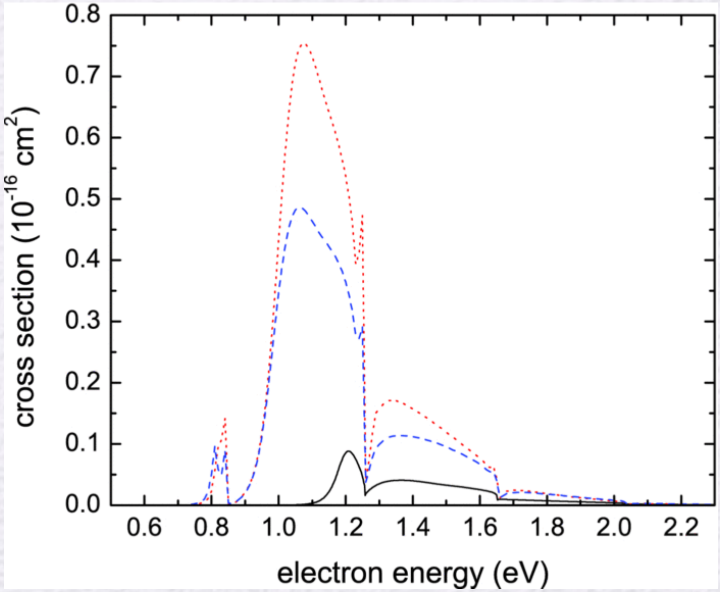
M. Smyth, J. Kohanoff and I. Fabrikant, J. Chem. Phys. **140,** 184313 (2014)

R-matrix: Ratio of resonance widths



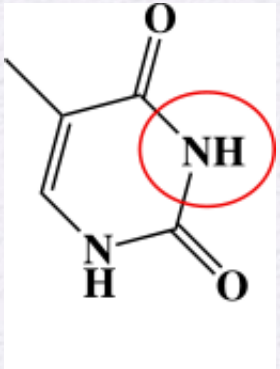


DEA cross section for Thymine: x **6 increase**
VAE shift = −0.326 eV
Solid black: gas-phase
Dotted red: scattering from all molecules
Dashed blue: scattering only from waters



What happens after DEA?

Nucleobases (Thymine)



Thymine

Gas phase: $E_H = 1.7$ eV

Bond cleavage above ~ 1.7 eV

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

What happens after DEA?

Nucleobases (Thymine)

Condensed Phase: E_H = 3 eV

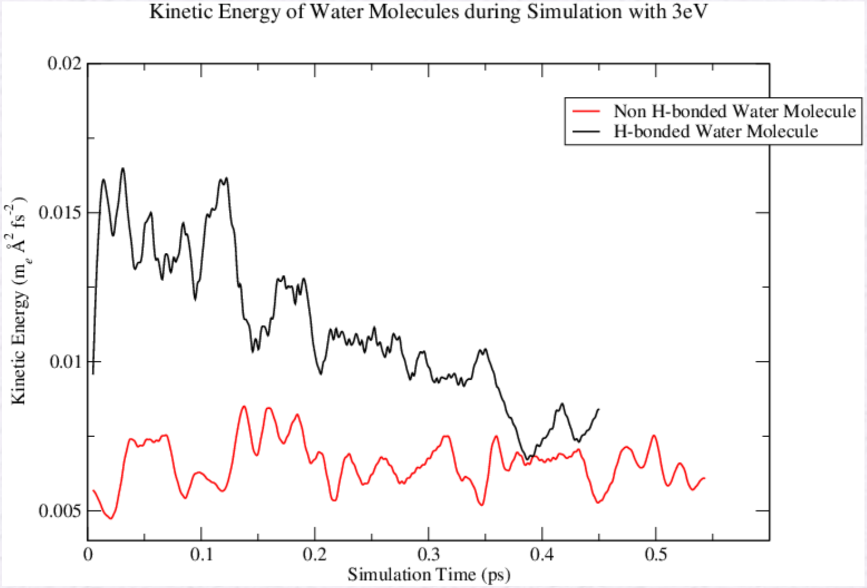
No H-bonding: Cleavage

H-bonding: Caging

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

How likely it is that the base is H-bonded?

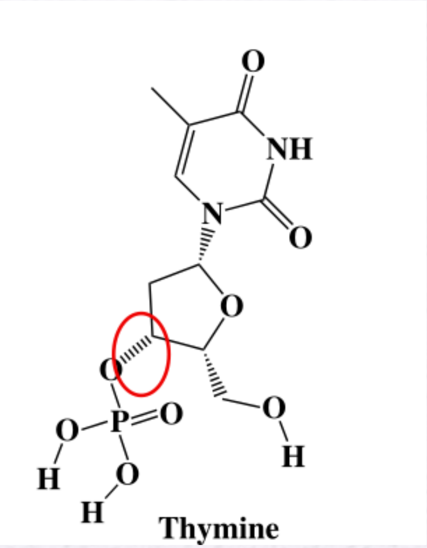
M. McAllister (PhD Thesis, 2016), N. Kazemigazestane (in progress)



- Energy is transferred to the water molecules via H-bonds
- Therefore, more energy is needed to break the bond in water
- Is it also the case for nucleotides and larger fragments?

What happens after DEA?

Nucleotides (Thymidine monophosphate)



Gas Phase: $E_P = 0.7$ eV

- $H_2PO_4^-$ leaves as a closed-shell stable ion
- Nucleoside (B+S) remains as a neutral radical
- Very low dissociation energy if doubly protonated (0.08 eV)

J. Kohanoff et al, J. Phys. Condens. Matter **29,** 383001 (2017)

What happens after DEA?

Nucleotides (Thymidine monophosphate)

Condensed Phase: $E_p = 3$ eV

Condensed Phase: $E_p = 1$ eV

Single protonation: Caging

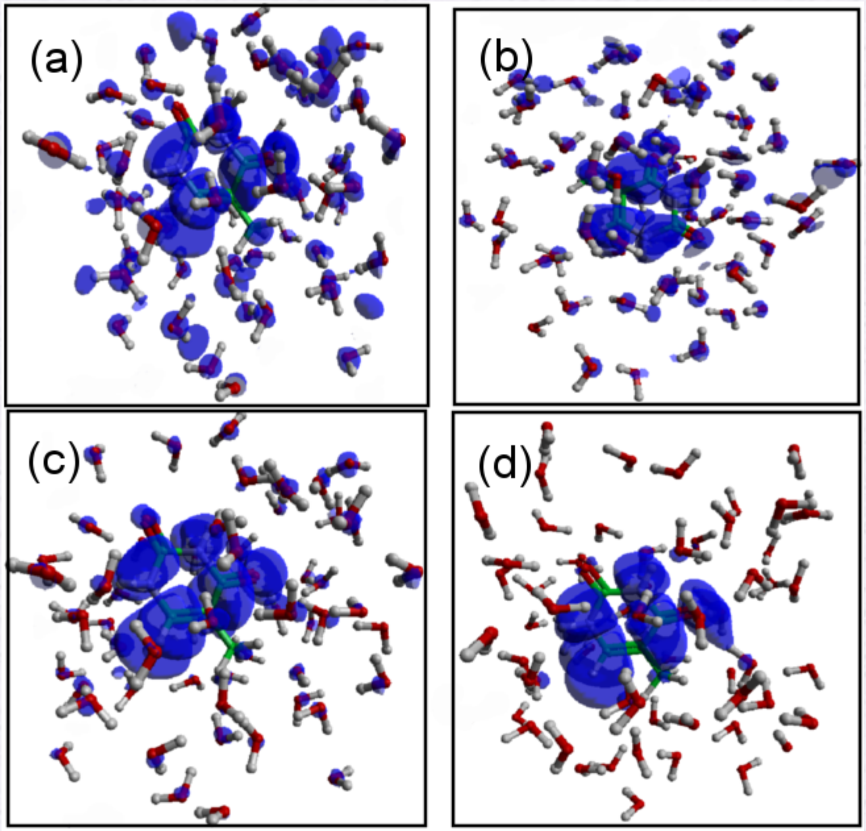
Double protonation: Cleavage

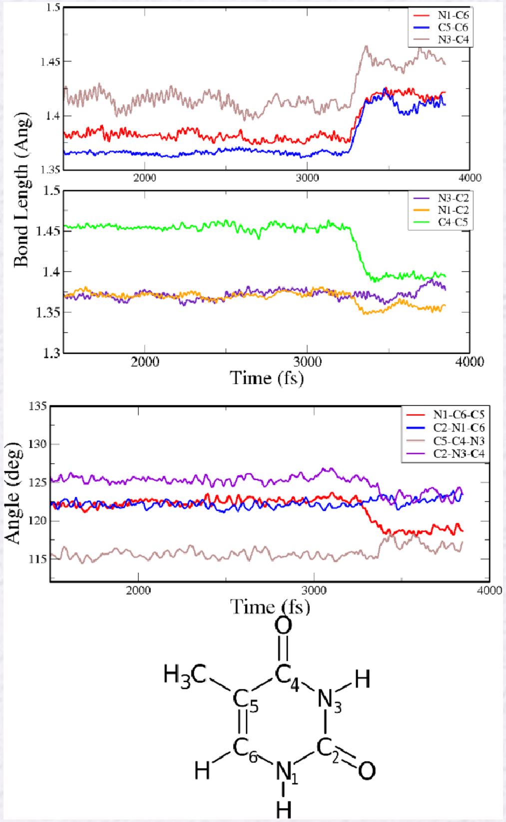
J. Kohanoff et al, J. Phys. Condens. Matter **29**, 383001 (2017)

DEA and Strand breaks

- **Phosphate groups** in solvated DNA are generally **singly protonated and negatively charged.**
- Therefore, for electron **energies < 3 eV**, nucleotides are likely to **dissipate their excess energy into the environment**, remaining as ground state anions, and retaining the **excess electron in the LUMO.**
- In that case **strand breaks** can be treated as **thermally activated events**. Must be studied with **rare event sampling** techniques.
- For **higher energies** it looks like C-O **bond cleavage is possible for nucleotides** … but in DNA it is part of a more complex scaffold ...

Electron localization in thymine





Injected electron localizes quickly (~20 fs) in the base

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

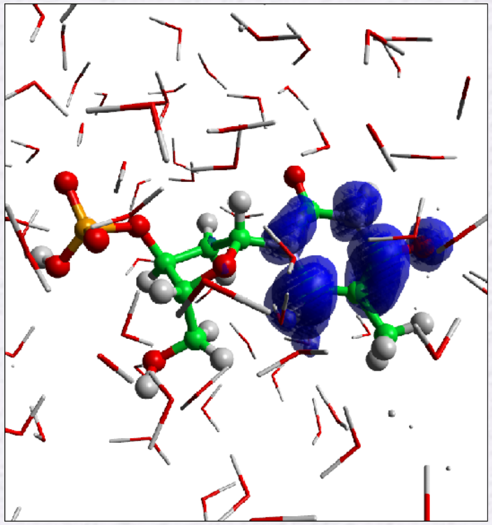
Strand breaks:
phosphodiester bond cleavage in nucleotides

- We assume that electrons lose all their kinetic energy before reaching the nucleotide, and are captured in the LUMO, located in the base. Nucleotides become **Ground state anions**.

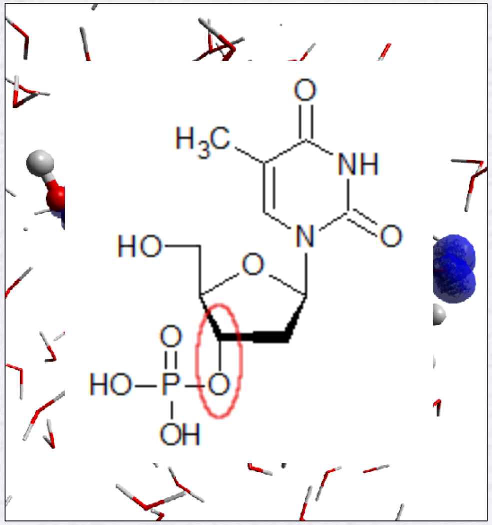
- **Strand breaks** are treated as **thermally activated events**.

- Since they don't occur spontaneously in the simulations (*rare events*) we use **Constrained MD simulations**: stretch bond and compute free energy by integrating the potential of mean force (*Equilibration and statistics*).

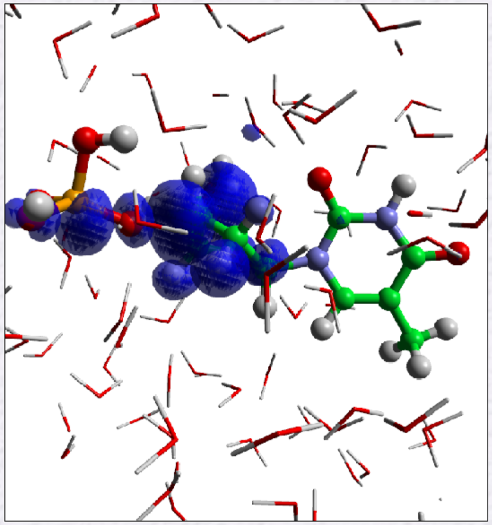
Activated strand breaks



GS



TS

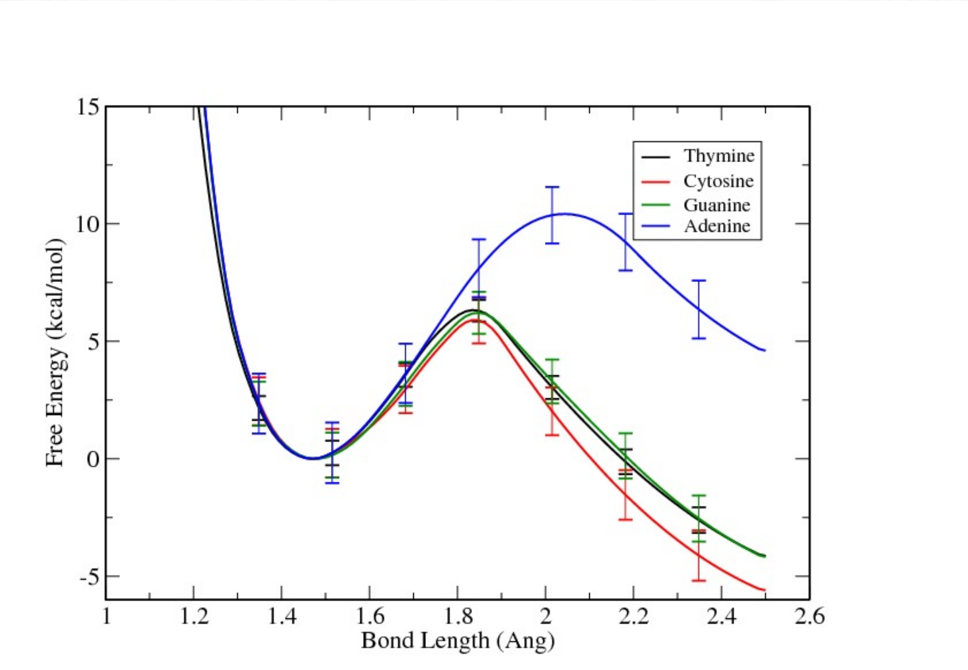


PS

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

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

Strand break barriers

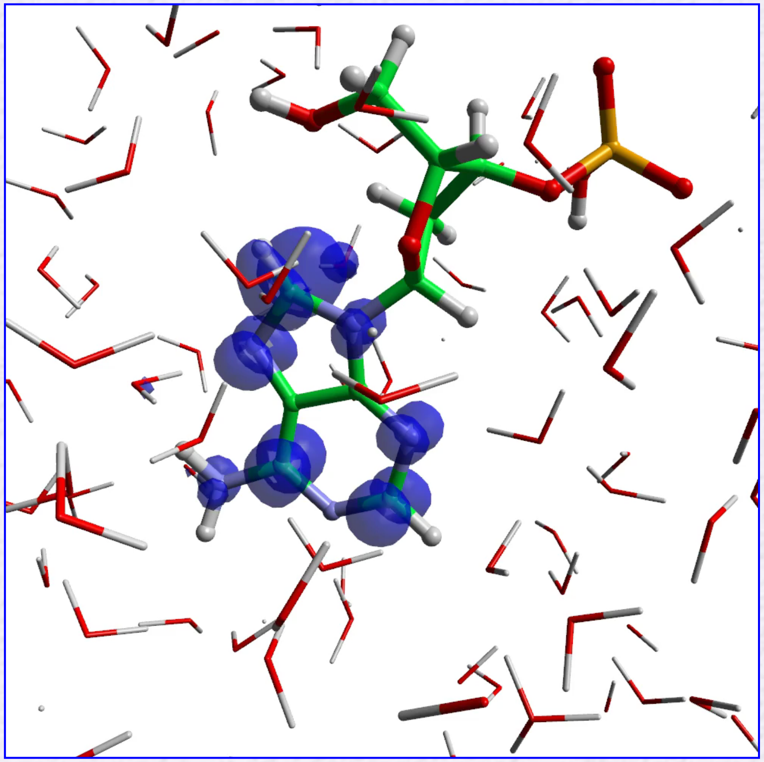


Low barriers imply that SSB are easy at room temperature

Perhaps too easy?

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

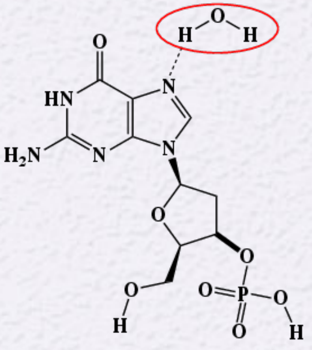
dAMP: Protonation



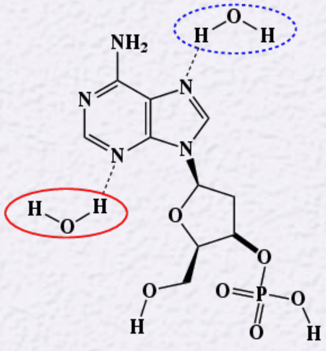
Protonation of the base increases barriers

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

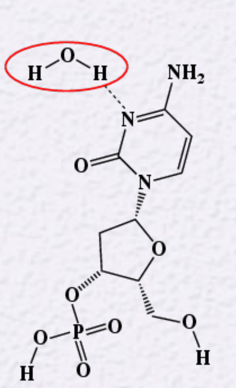
Protonation vs strand breaks



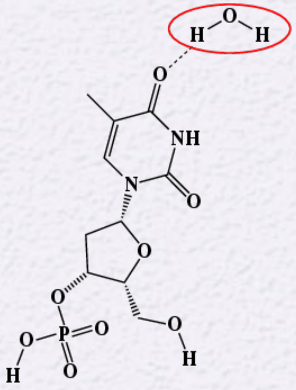
Guanine



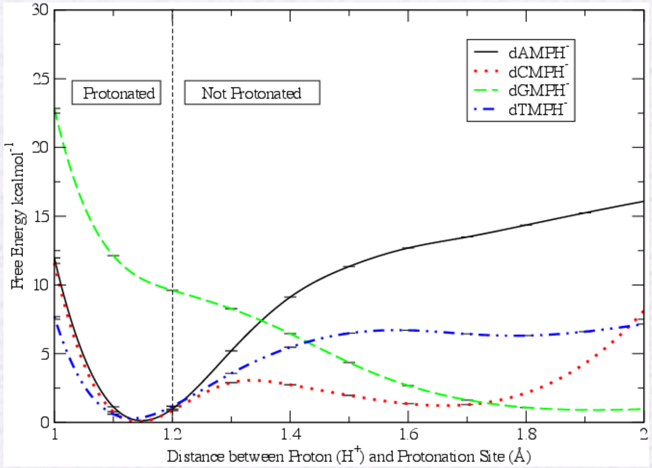
Adenine

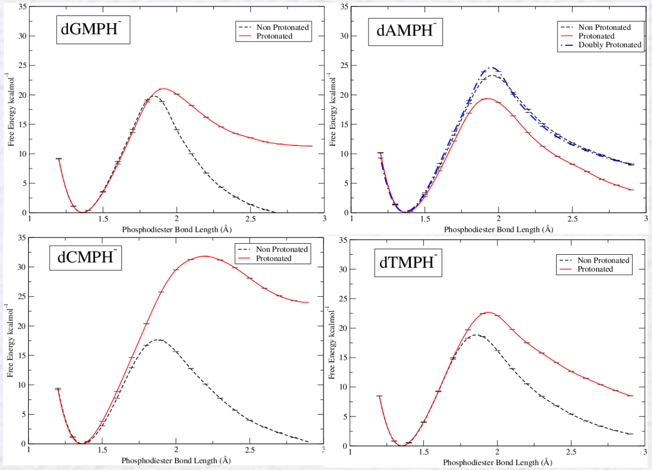


Cytosine



Thymine

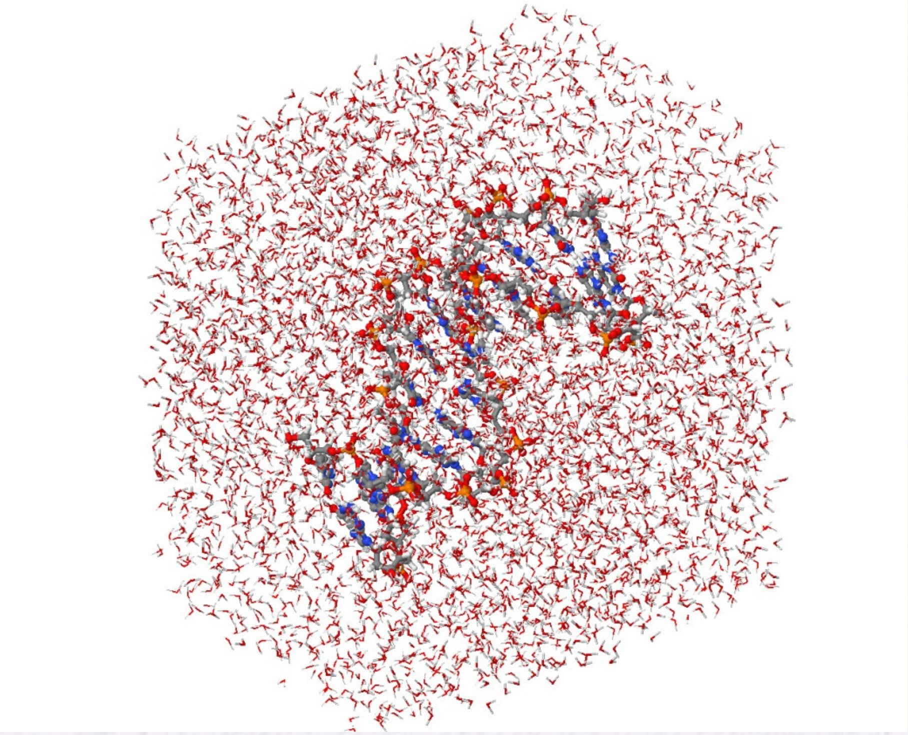




Protonation protects nucleotides against bond cleavage

M. McAllister, M. Smyth, B. Gu, G. Tribello, and J. Kohanoff, J. Phys. Chem. Lett. **6**, 3091 (2015)

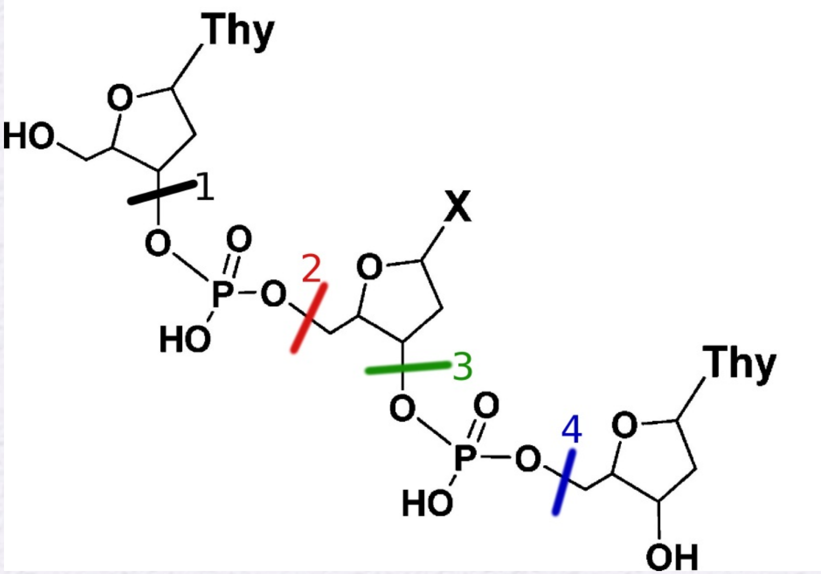
Towards reality: larger DNA fragments in in Physiological environment



- **Are there specific sequences that favour strand breaks?**
- **What is the role of base pairing (duplex DNA)?**
- **What is the role of histones?**
- **Radiosensitation (Cis-Pt)**

Trinucleotides: TXT

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

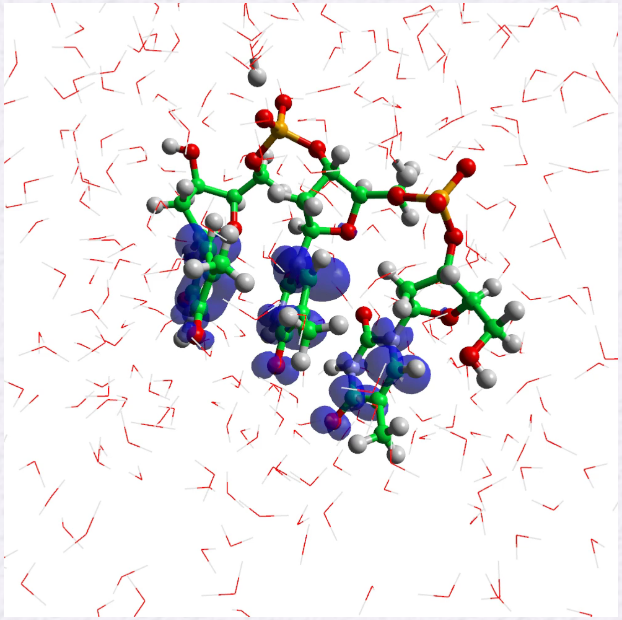


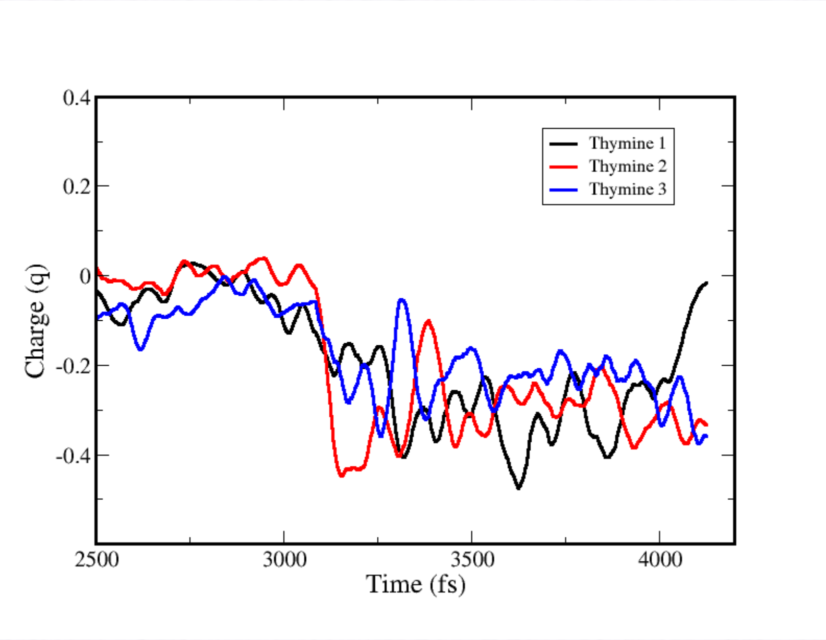
There are 4 possible bonds to break

Experiment suggests 1 ($C_{3'}$-$O_{3'}$) for TTT

Trinucleotides: TTT

L. Bouessel Du Bourg, Bin Gu, M. Smyth, J. Kohanoff (unpublished)

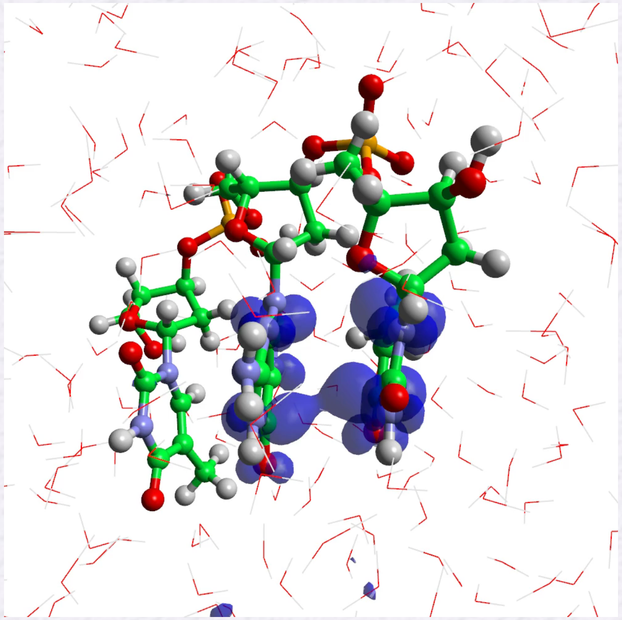


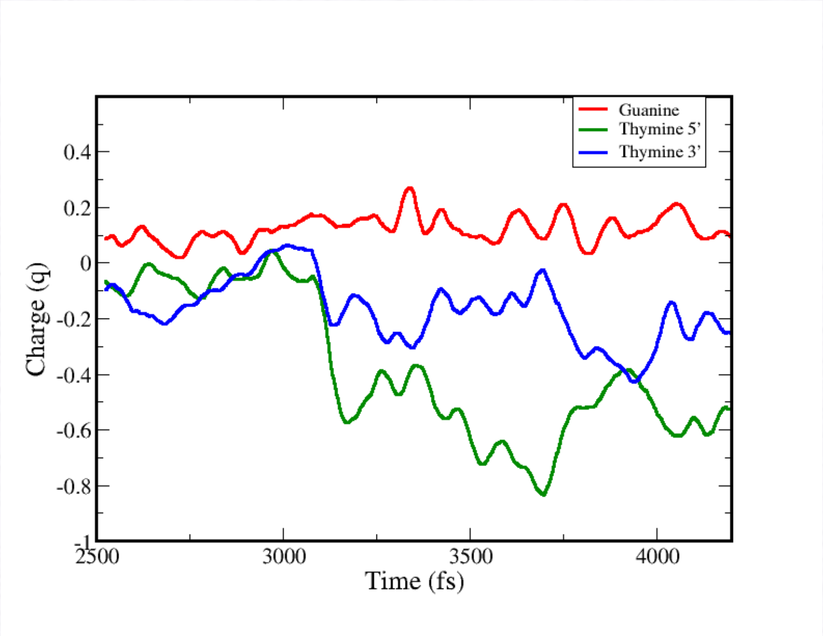


Excess electron fluctuates between the three Thymines

Trinucleotides: TGT

L. Bouessel Du Bourg, Bin Gu, M. Smyth, J. Kohanoff (unpublished)





Excess electron fluctuates between the two Thymines

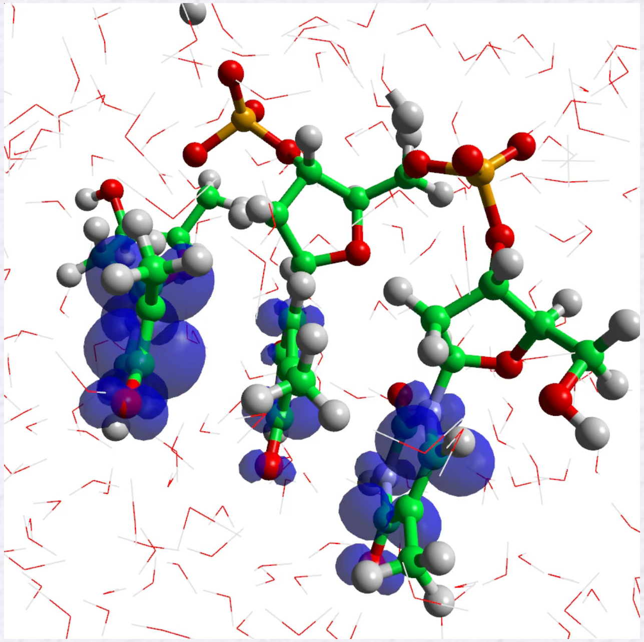
Metadynamics

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

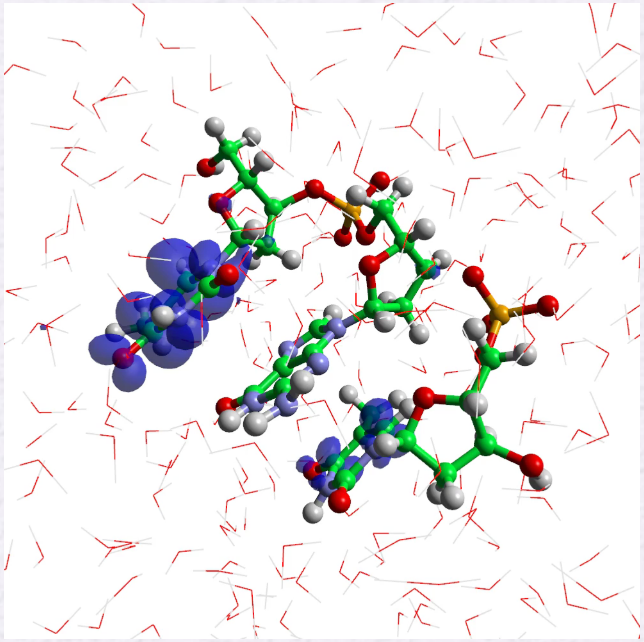
Trinucleotides: TTT vs TGT

L. Bouessel Du Bourg, Bin Gu, G. Tribello, J. Kohanoff (unpublished)

TTT

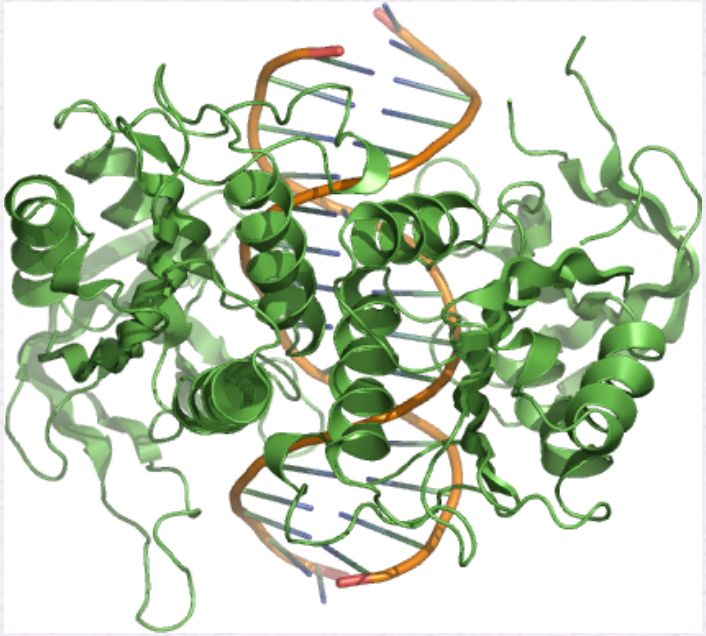


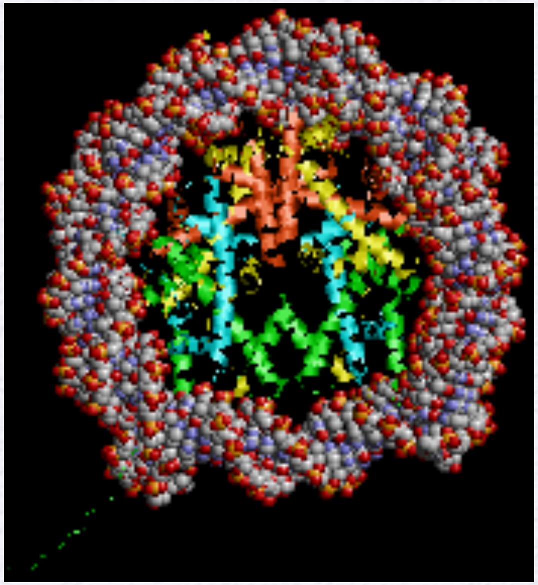
TGT



Strand breaks seem to occur in different places depending on sequence

The nuclear cell environment: Histones



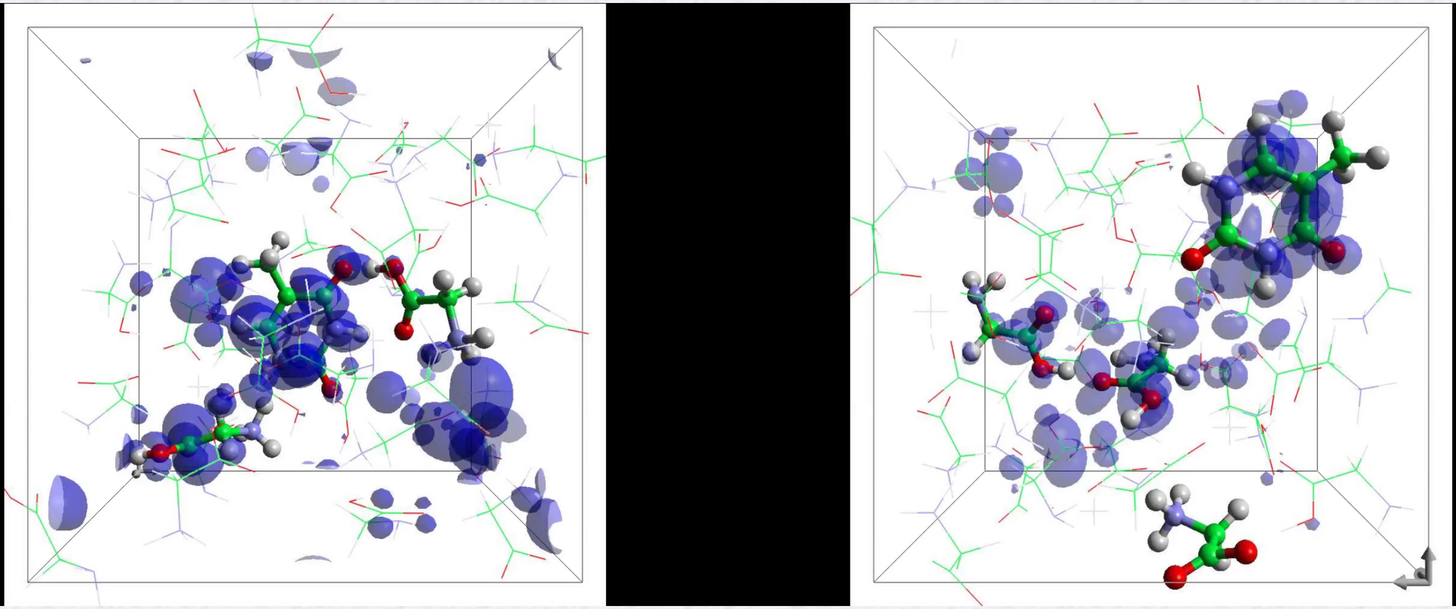


Does the proximity of histones protect DNA against electron attachment and radical attack?

If so, how?

Protective role of aminoacids: Glycine

Bin Gu, M. Smyth and J. Kohanoff, PCCP 16, 24350 (2014)



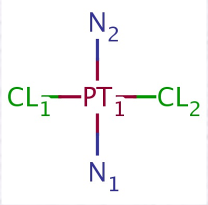
Dynamical mixture of canonical and zwitterions forms of glycine

- **Canonical glycine: scavenges electrons from nucleic acids**
- **Zwitterionic glycine: protonates nucleic acids**

Both are protective mechanisms against low-energy electrons

Chemoradiation: combining Radio- and Chemotherapy

Cisplatin



Is the most commonly used drug in Chemoradiation treatments (CRUK 2015)

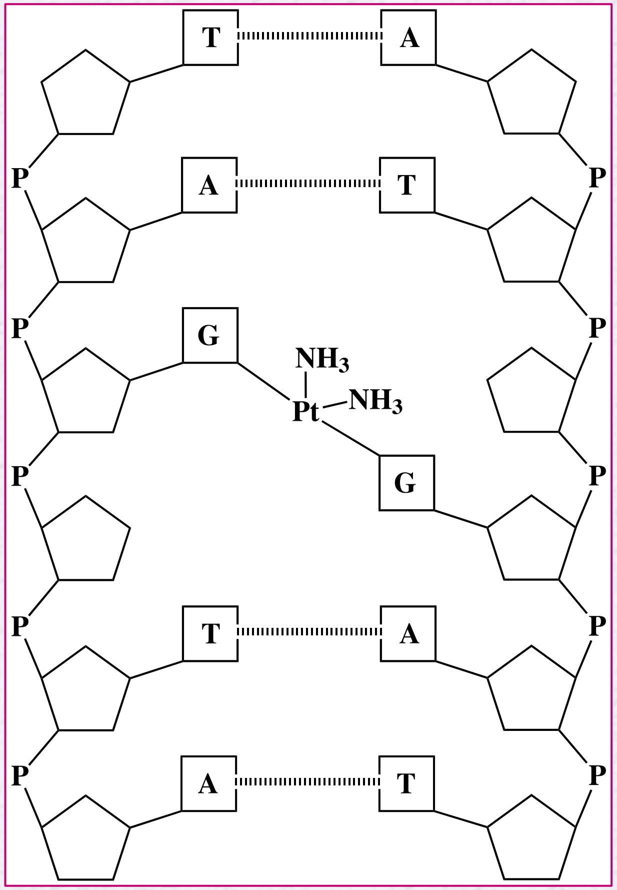
Most significant damage enhancements by low energy electrons (10eV)

(Rezaee 2013)

Ultra-low energy electrons induce **Double strand breaks** only in Pt-modified DNA

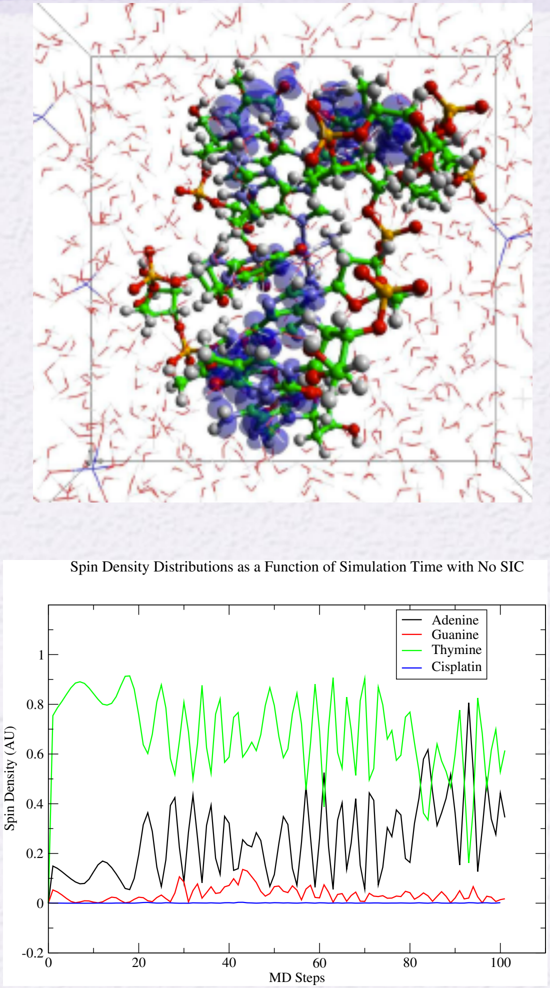
How do these double strand breaks happen?

Radiosensitation:
Cis-Pt + low-energy electrons

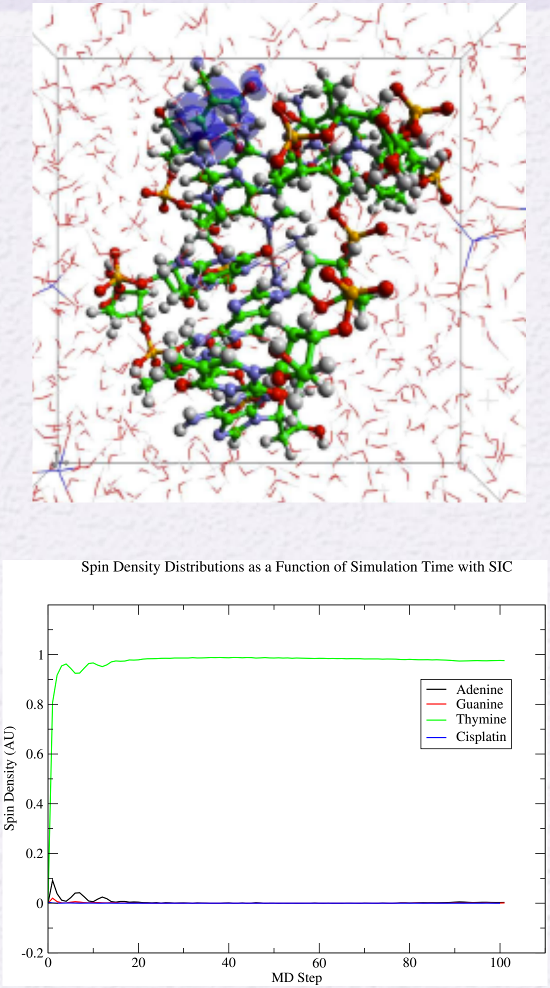


- System : 5-base-pair, double stranded DNA , interstrand cross-linked Cisplatin (adjusted from PDB)
- Explicit water molecules added to 30A box. System Size = 2696 atoms
- Structure and Solvent stabilised using Forcefield MD (CHARMM DL_POLY)
- Electronic Structure Calculations DFT-MD using CP2K on Archer

Cis-Pt + low-energy electrons Self-interaction corrections (SIC)

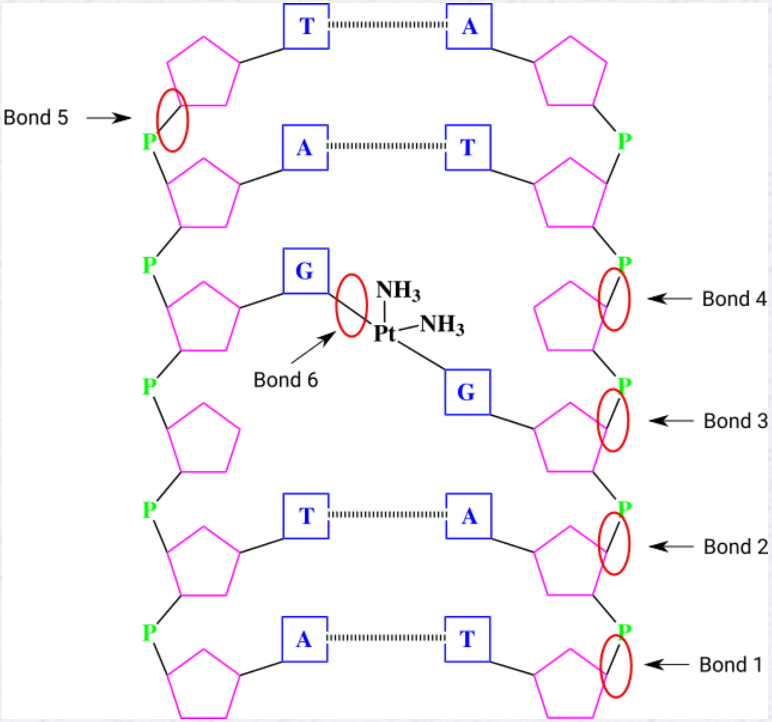


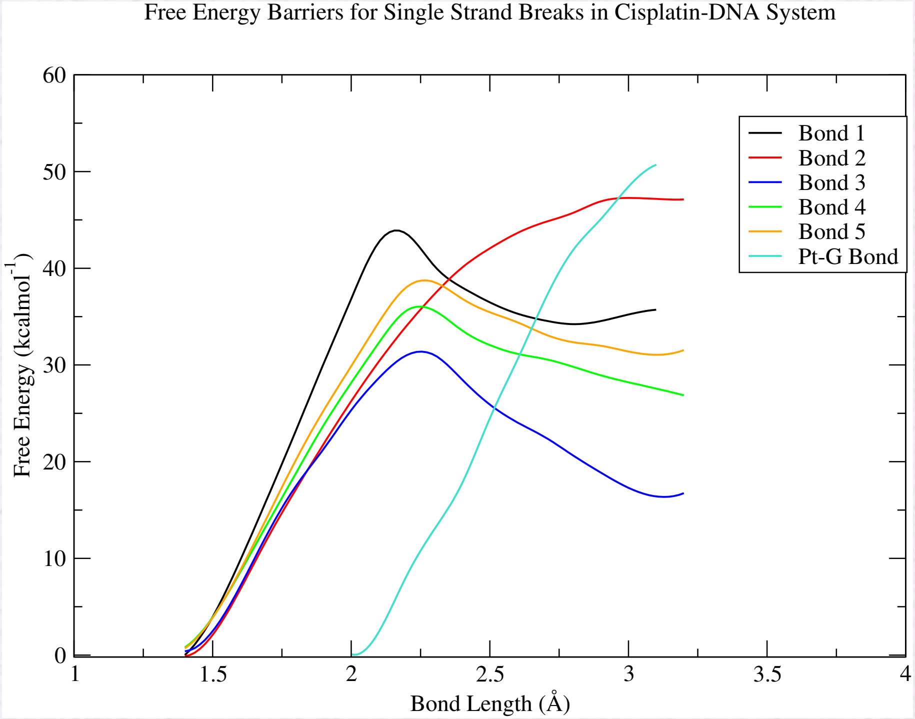
PBE Functional



PBE+SIC Functional

Cis-Pt + low-energy electrons: The weakest link

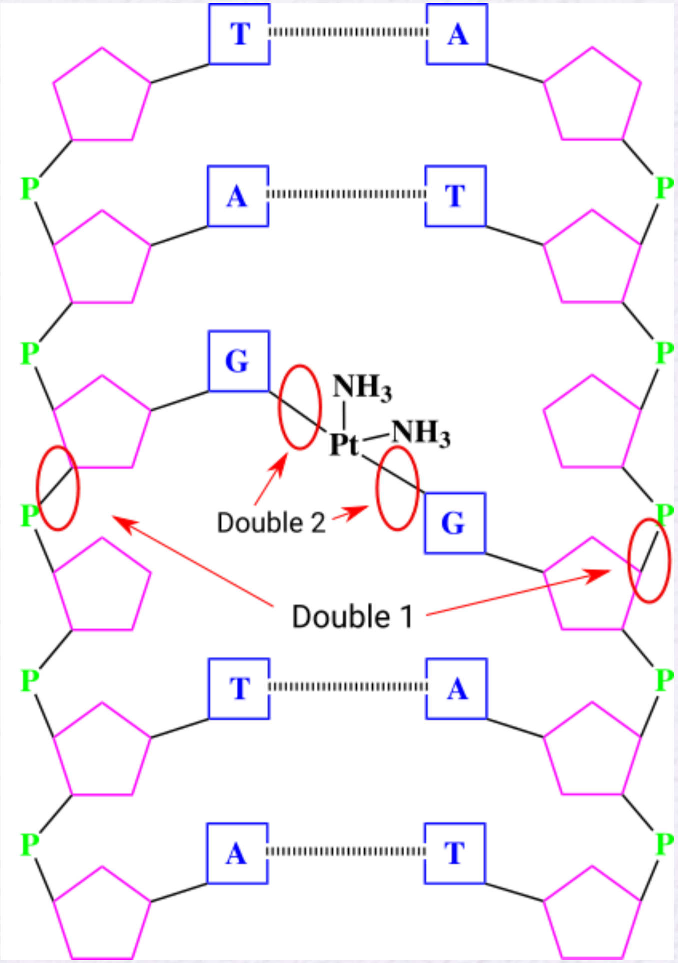




Bond 3 is the weakest (lowest barrier)

How do we investigate double strand breaks?

Cis-Pt + low-energy electrons: Double strand breaks



- Break the weakest bond and its complement simultaneously (Double 1)
- Break the 2 Pt-G bonds, as suggested will break first in the experimental literature (Double 2)

Some reflections on DNA

- Irradiation of biological matter produces ***direct*** and ***indirect*** damage to DNA and other structures. ***Is indirect damage more important?***
- Indirect damage proceeds by ionization of the surrounding medium, generating low-energy (E≤20eV) electrons, holes, and radicals. ***We have focused on the role of electrons*. *What about holes and radicals?***
- Electrons quickly lose energy to the medium (~10 nm, few fs) and are either:
    - ***Captured resonantly by DNA bases.***
    - ***Solvated in the medium*. *Are they inactive when solvated?***
- If captured in DNA, they may:
    - ***Form transient negative ions that dissociate via DEA***
    - ***Transfer excess energy to the medium and become GS anions***

Some reflections on DNA

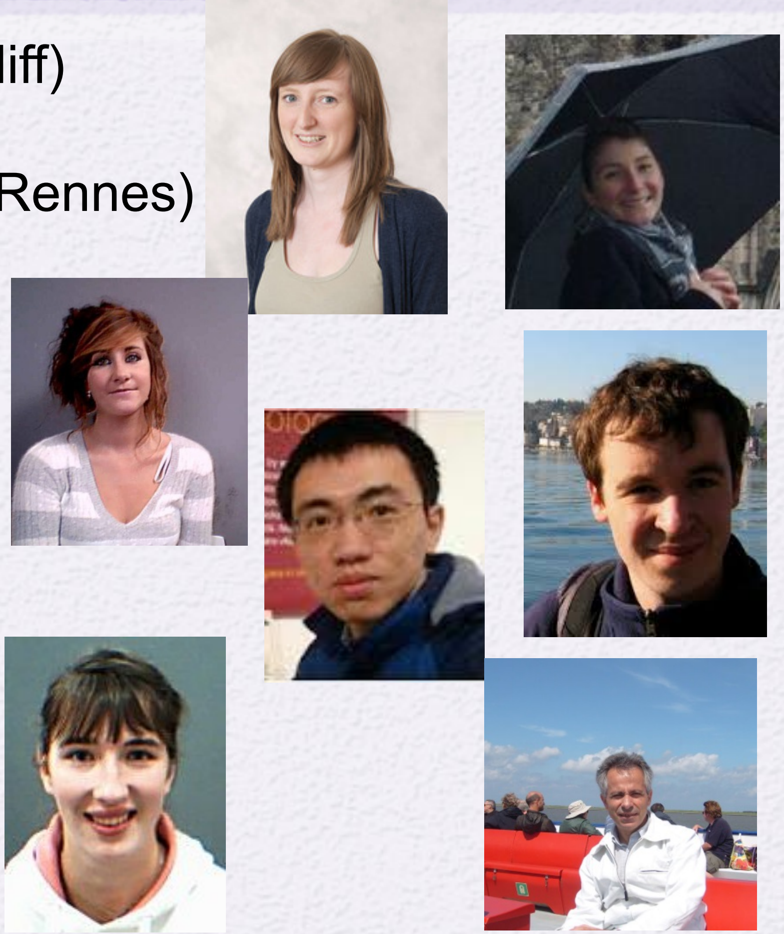
- At high electron energies, TNI nucleotides dissociate easily. ***Will the DNA backbone keep it together?***
- At low electron energies nucleotides become GS anions. Hence, ***strand breaks can only occur via thermal activation***. Barriers are not too low (~20 kcal/mol) and also …
- There is a wide range of ***protection mechanisms***: caging, protonation, amino-acid scavenging [Bin Gu, M. Smyth, and J. Kohanoff, PCCP 16, 24350 (2014)], which make strand breaks even more difficult.
- So **…**

Are low-energy electrons an important source of damage?

See review: J. Kohanoff et al, J. Phys. Condens. Matter **29**, 383001 (2017)

Collaborators

- Maeve Smyth (QUB → NHS Cardiff)
- Lila Bouëssel du Bourg (Paris → Rennes)
- Maeve McAllister (QUB, Randox)
- Gareth Tribello (QUB)
- Bin Gu (Nanjing, China)
- Ilya Fabrikant (Nebraska, USA)
- Amy Williamson (QUB)
- Nazila Kazemigazestane (QUB)



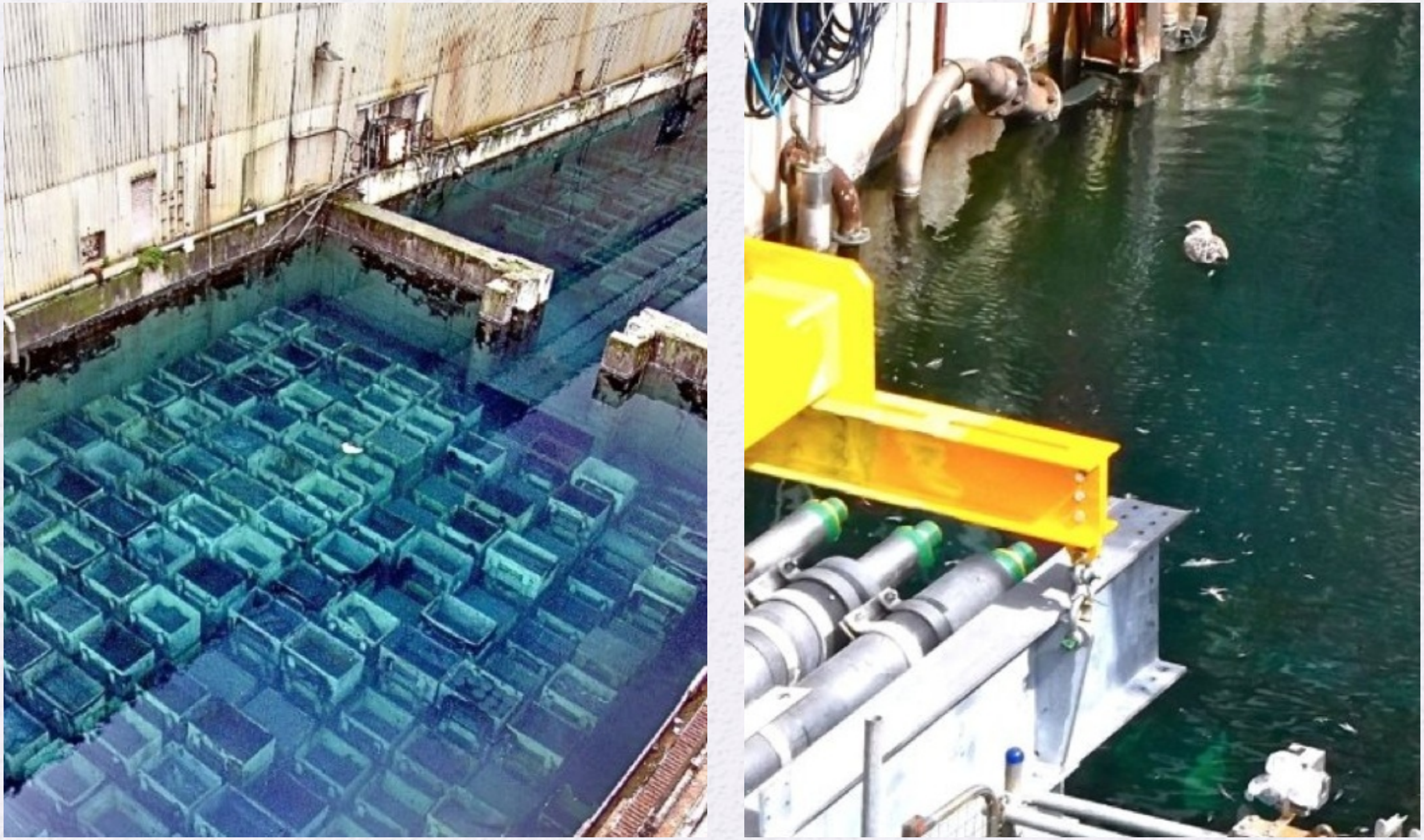
Nuclear materials

- **Fission reactors: Generation III and IV**
  - Structural: Steel vessel (Fe-Cr-Ni), Zircaloy, **Magnox cladding**
  - Coolant: water, L-Na, L-Pb, He gas, F salts (Gen IV)
  - Fuel: UO_2, U compounds, Pu (Fast reactors)
- **Magnetic Confinement Fusion (ITER)**
  - Blanket: LiPb, Li silicate, SiC, Steels (no Nb/Mo. V ok)
  - Divertor: Carbon fibre, W, W-C-Be
- **Fuel reprocessing and waste disposal**
  - Short lifetime waste (100 years): Borosilicate glasses
  - Long term waste: Oxides; Perovskite, Monazite, Pyrochlores
  - **Cement**
- **Chemical separation:**
  - Water/hydrocarbon mixtures (kerosene)
  - **Room-temperature ionic liquids (RTIL)**

UK nuclear power:
Calder Hall (1953)

Magnox power reactors at Sellafield

Nuclear waste: The Sellafield ponds



First Generation Magnox Fuel Storage Pond now – The Guardian

Magnox sludge

Conrad Johsnton, Gareth Tribello, JK

- Corroded Magnox alloy - still corroding
- Mainly Brucite mineral – $\mathbf{Mg(OH)_2}$
- Formed by the reaction:

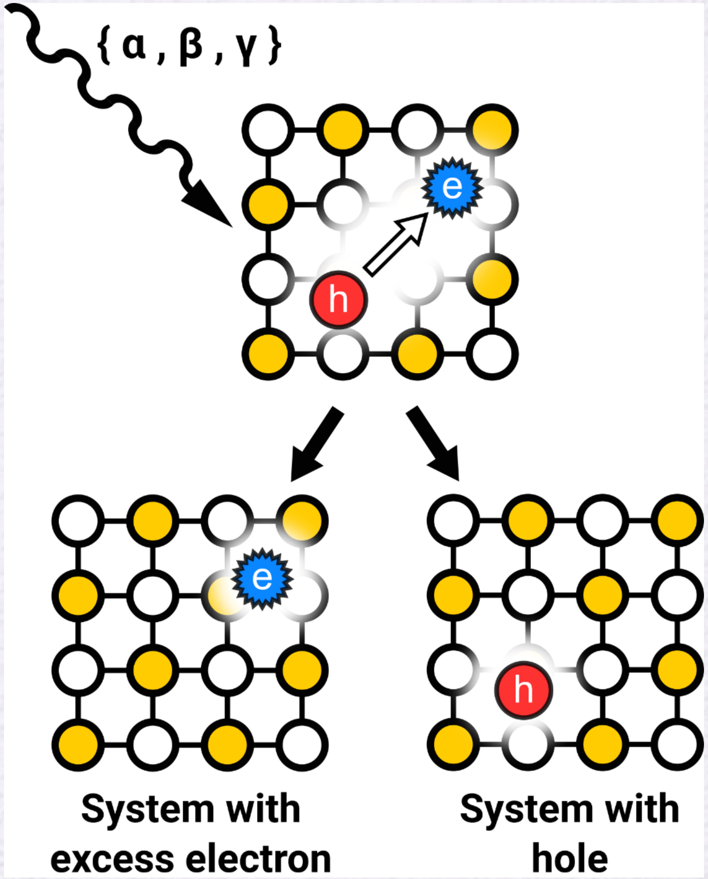
$$Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2$$

- Sludge also contains metal and fuel fragments, organic material, fission products, actinides
- Highly radioactive
- 1,350m^3 in existence
- ***Generates and retains hydrogen gas pockets***

Magnox sludge challenges

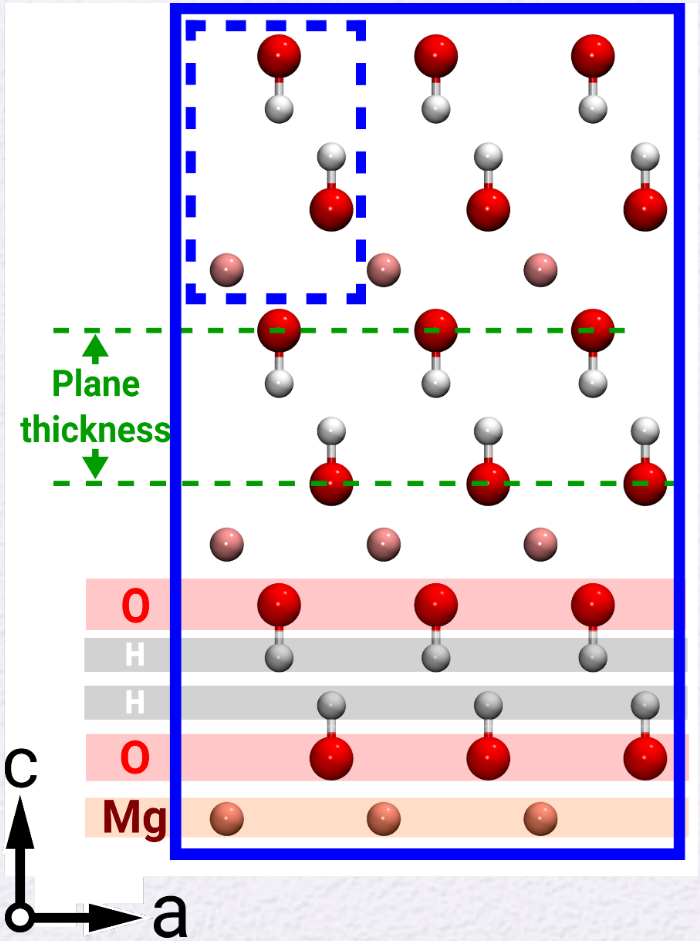
Conrad Johnston, Gareth Tribello, JK

- Bulk or surface phenomenon?
- Diffusion limitations
- Effect of the aqueous environment
- ***Mechanism of radiolysis***
- ***Role of electrons and holes***
- ***Is radiolytic hydrogen possible?***



Brucite mineral

Conrad Johnston, Gareth Tribello, JK

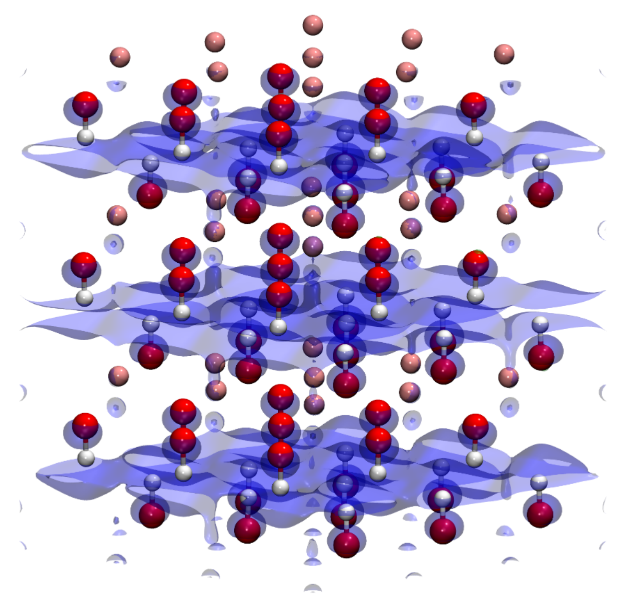


Mg layers separated by double hydroxide layers

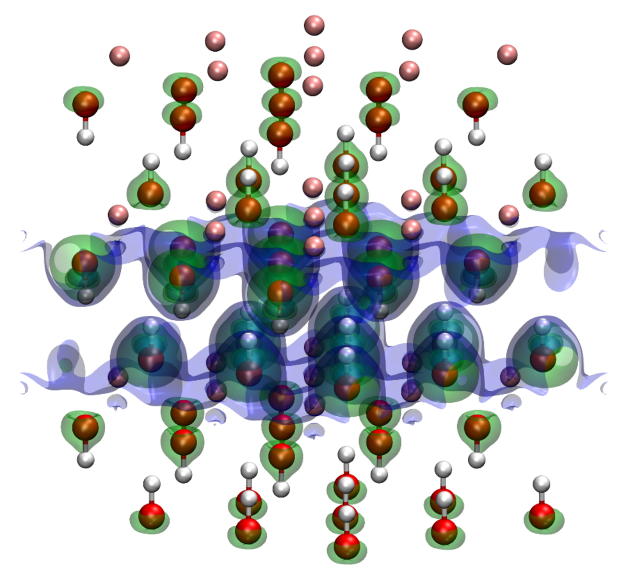
Excess electron in brucite

Conrad Johnston, Gareth Tribello

PBE



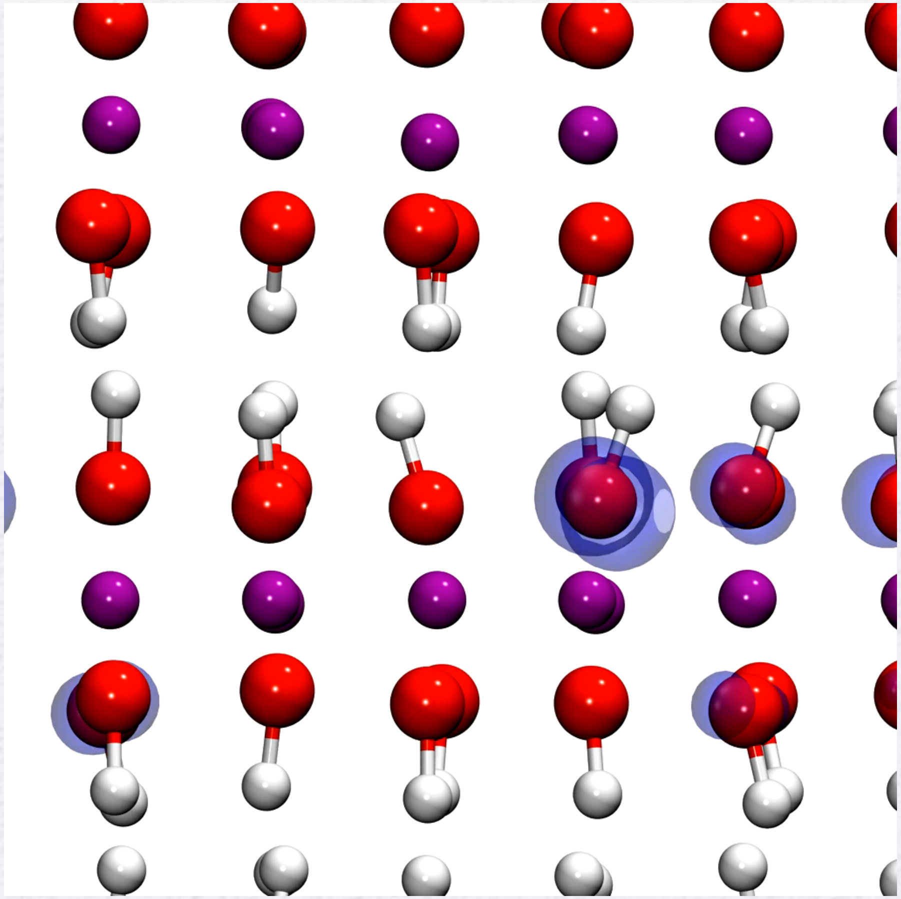
M06-2X (54% HF)



Electron localized in hydroxide layers. A 2-D electron gas?

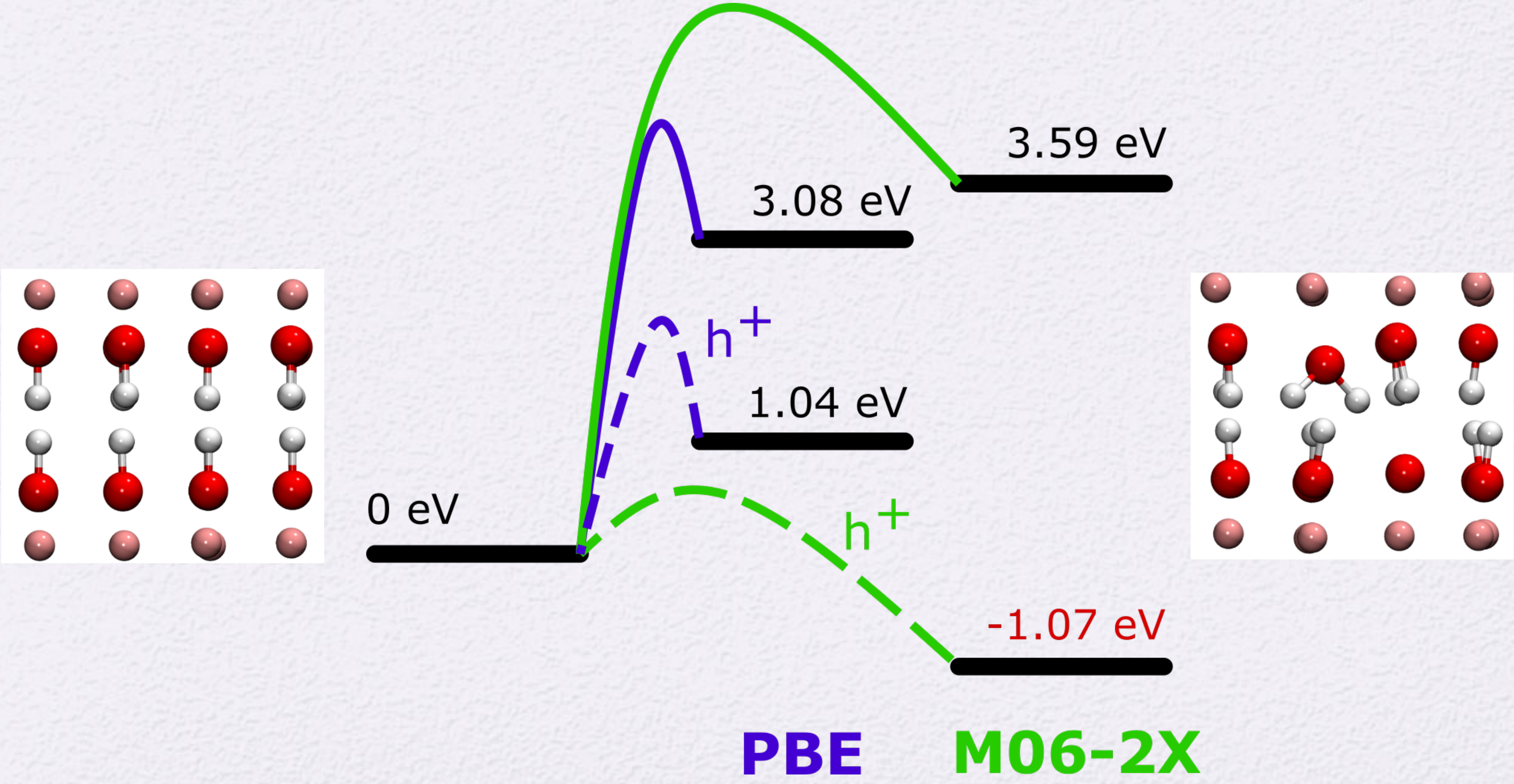
MD hole in brucite: M06-2X

Conrad Johsnton, Gareth Tribello



Hole localized in an OH, promotes bond cleavage and generates hydrogen atoms. ***Precursor of H_2***

Proton transfer profiles



Waste disposal: cement

Ryan Kavanagh, Conrad Johnston, Khaoula Boukari, Andrés Saul, Gareth Tribello, JK

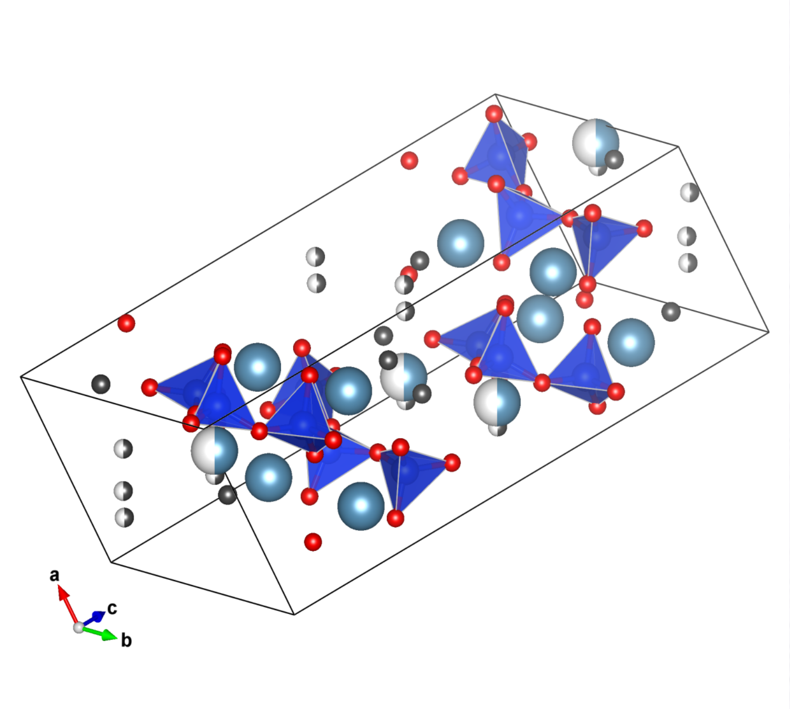
- Second most used resource in the world (after water) worth over $100 billion in 2015 (7 billion m^3)
- Used in the Civil Nuclear industry **to store radioactive waste**, and as a barrier for diffusion.
- Composite material made from aggregates (sand, gypsum…), cementing materials and water.
- Everything matters – in particular **Ca content and short-range order.**

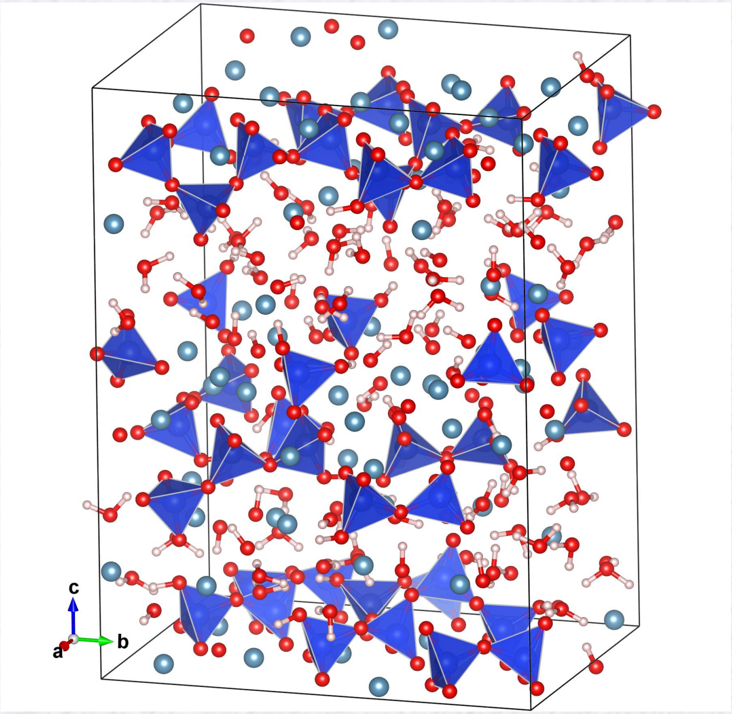
Models for cement

- 14 Å Tobermorite
- C/S = 0.83

CSH “MIT” model

C/S = 1.7



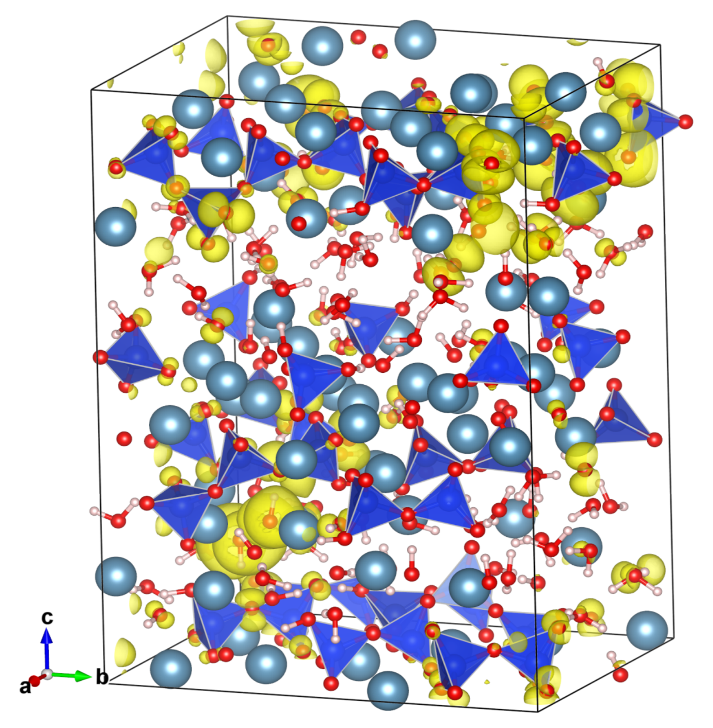


Excess electron in CSH

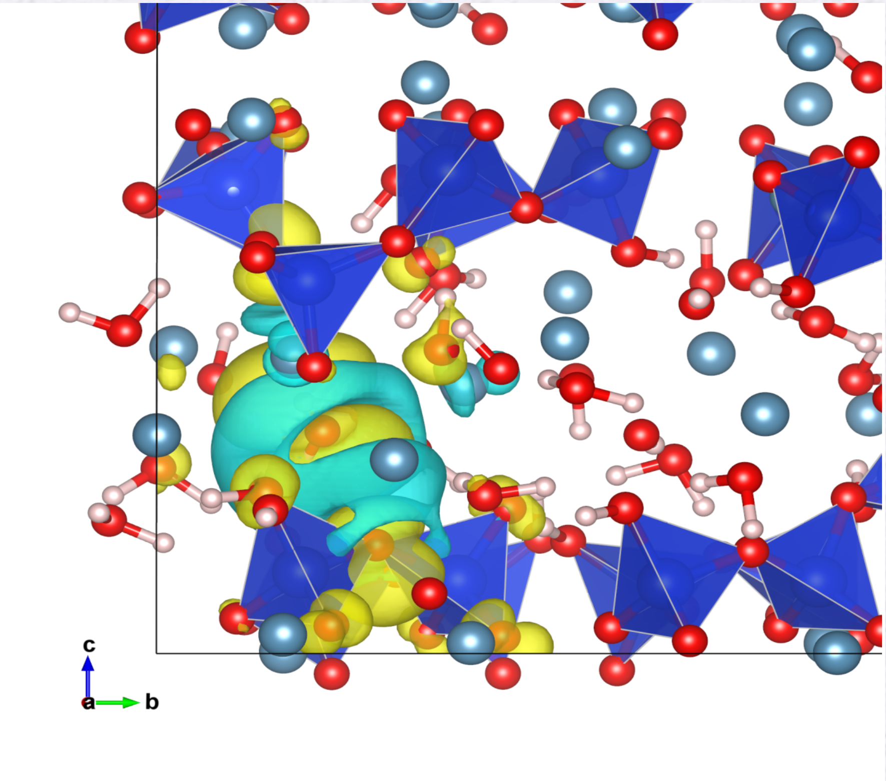
Excess electron localised in voids, and very mobile

Excess hole in CSH

PBE



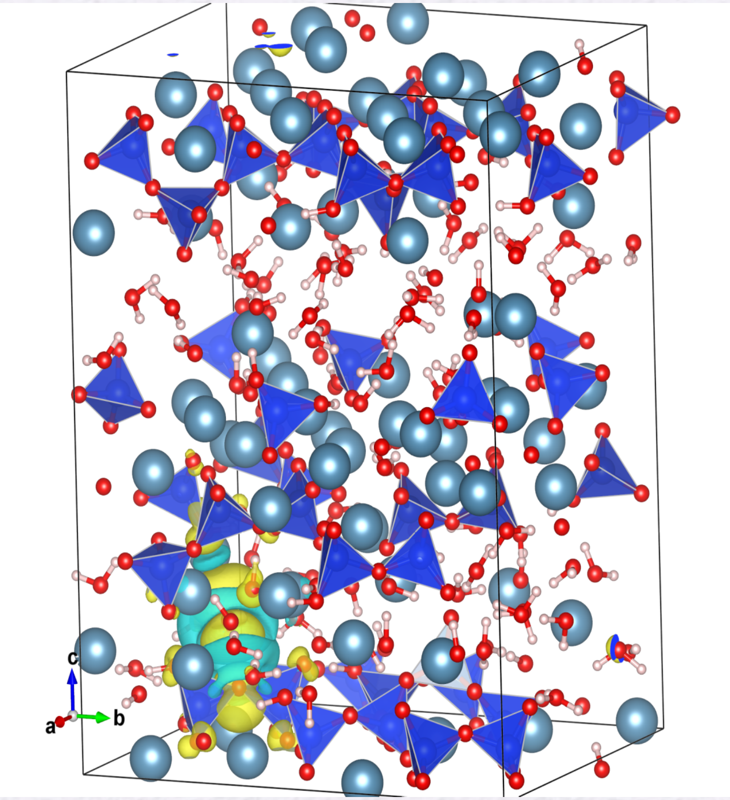
M06-2X (54% HF)

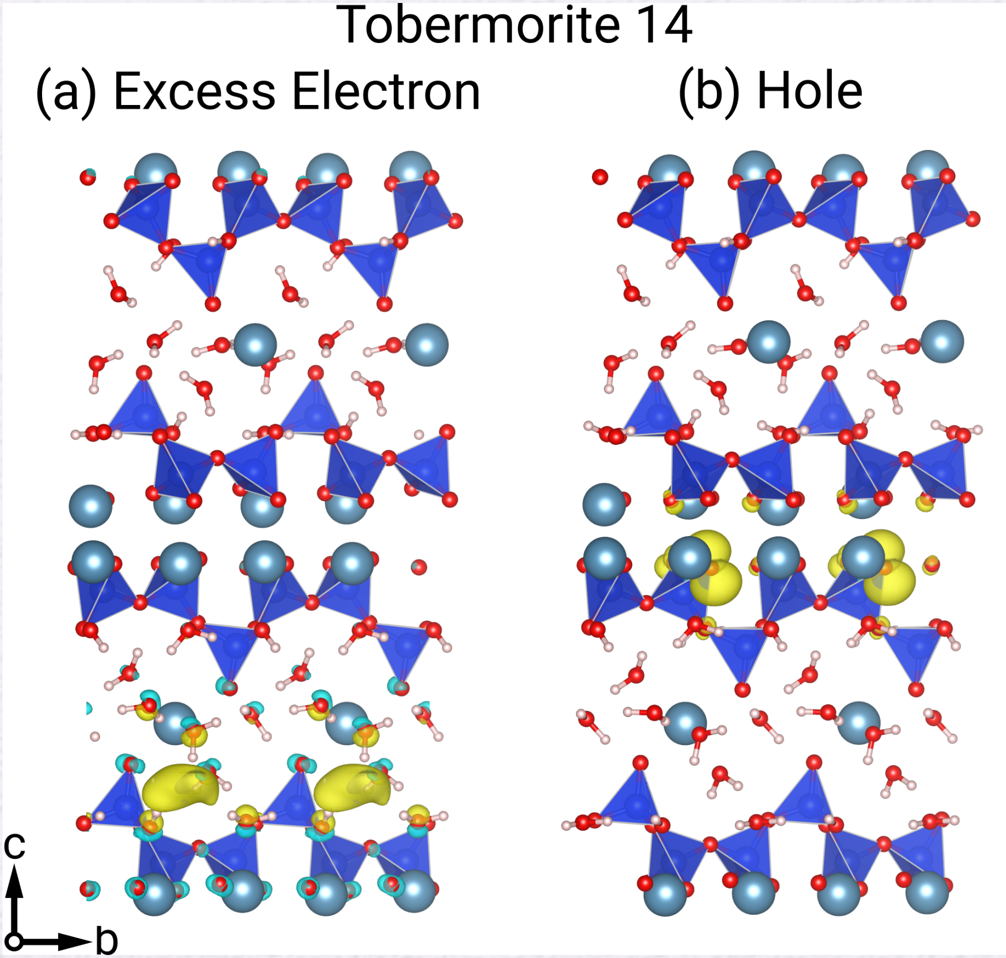


Radiation removes an electron from OH^- creating an $OH^\bullet$

CSH vs Tobermorite 14

CSH hole



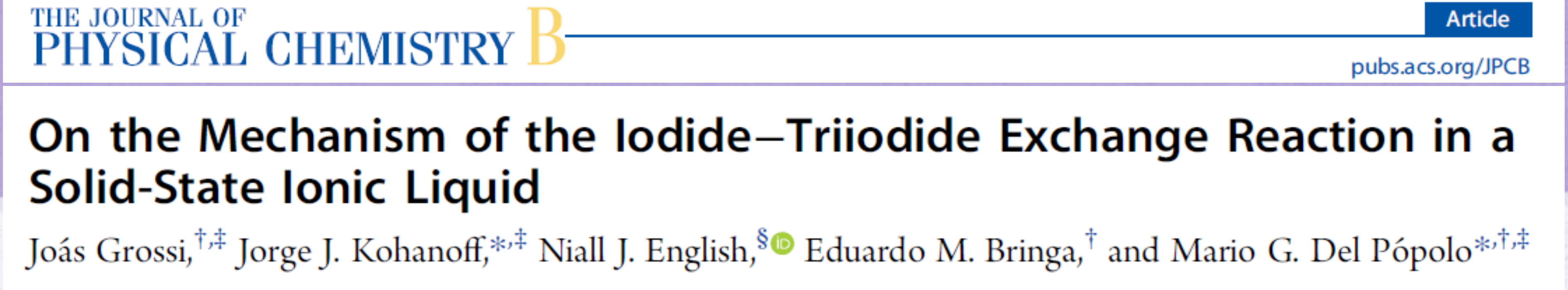

Tobermorite 14

(a) Excess Electron

(b) Hole

Summary

- Ionizing radiation produces electrons, holes and radicals.
- These diffuse through the material and may react producing some chemical modifications.
- Excess electrons tend to localize in acidic groups in biological matter, and in voids in oxides and hydroxides.
- Holes are generally created in OH groups, localizing in oxygen p-orbitals, and can induce OH bond breaks. In DNA holes localize in guanines.



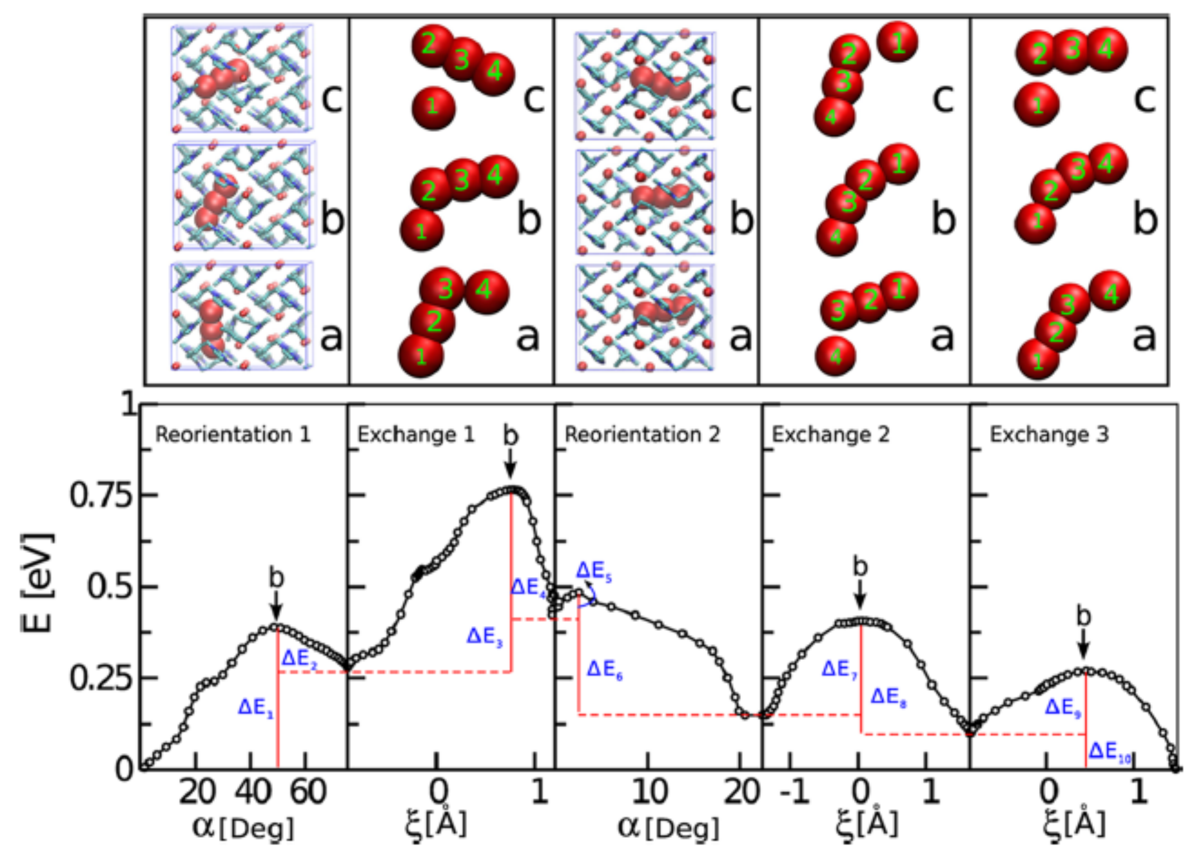
THE JOURNAL OF
PHYSICAL CHEMISTRY B

Article

pubs.acs.org/JPCB

On the Mechanism of the Iodide–Triiodide Exchange Reaction in a Solid-State Ionic Liquid

Joás Grossi,[†,‡] Jorge J. Kohanoff,[*,‡] Niall J. English,[§] Eduardo M. Bringa,[†] and Mario G. Del Pópolo[*,†,‡]



[Bmim][I] liquid phase

QM-MM: classical cations + quantum anions

288 ionic pairs