



Modelling of Radiation Effects on DNA

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Our goal

To set up a computer model to evaluate radiation damage at the DNA level, in order :

- to increase the knowledge of mechanisms
- to support interpretation of experimental results
- to test hypothesis
- to predict radiation risk
- to suggest experiments

Initial damage modelling

Ionisation or radical attack
on 'ribose-phosphate'

$T < 10^{-15}$ s : Direct
ionisation

SSB

Radical attack on hydration shell
is transferred in DNA

$T < 10^{-8}$ s : Indirect
radical

Indirect effect
(Bases, strands)

Other direct events
or
OH attack in external shells

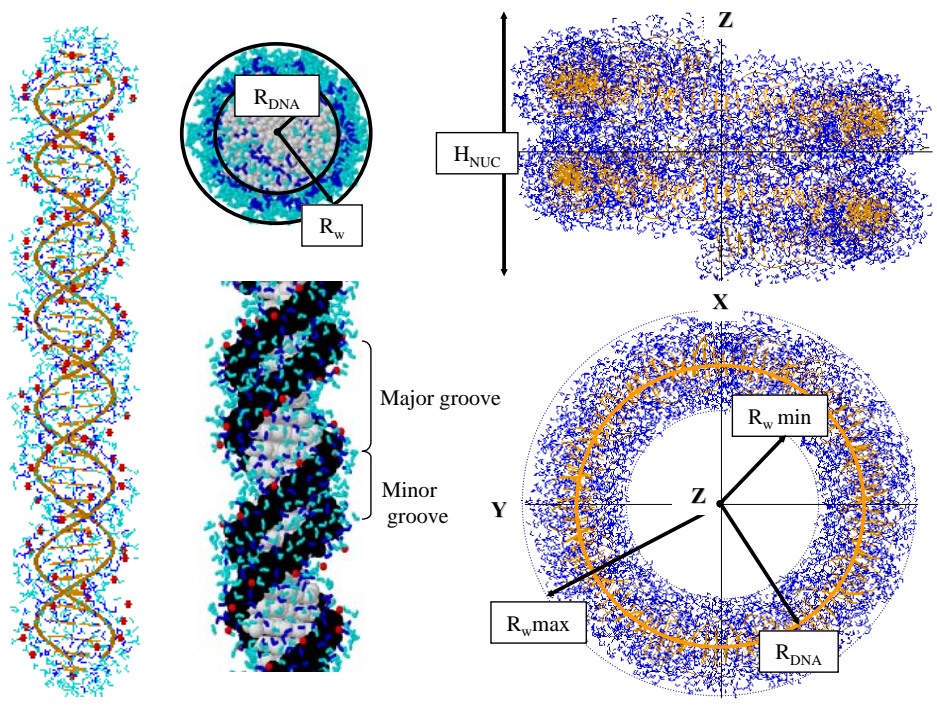
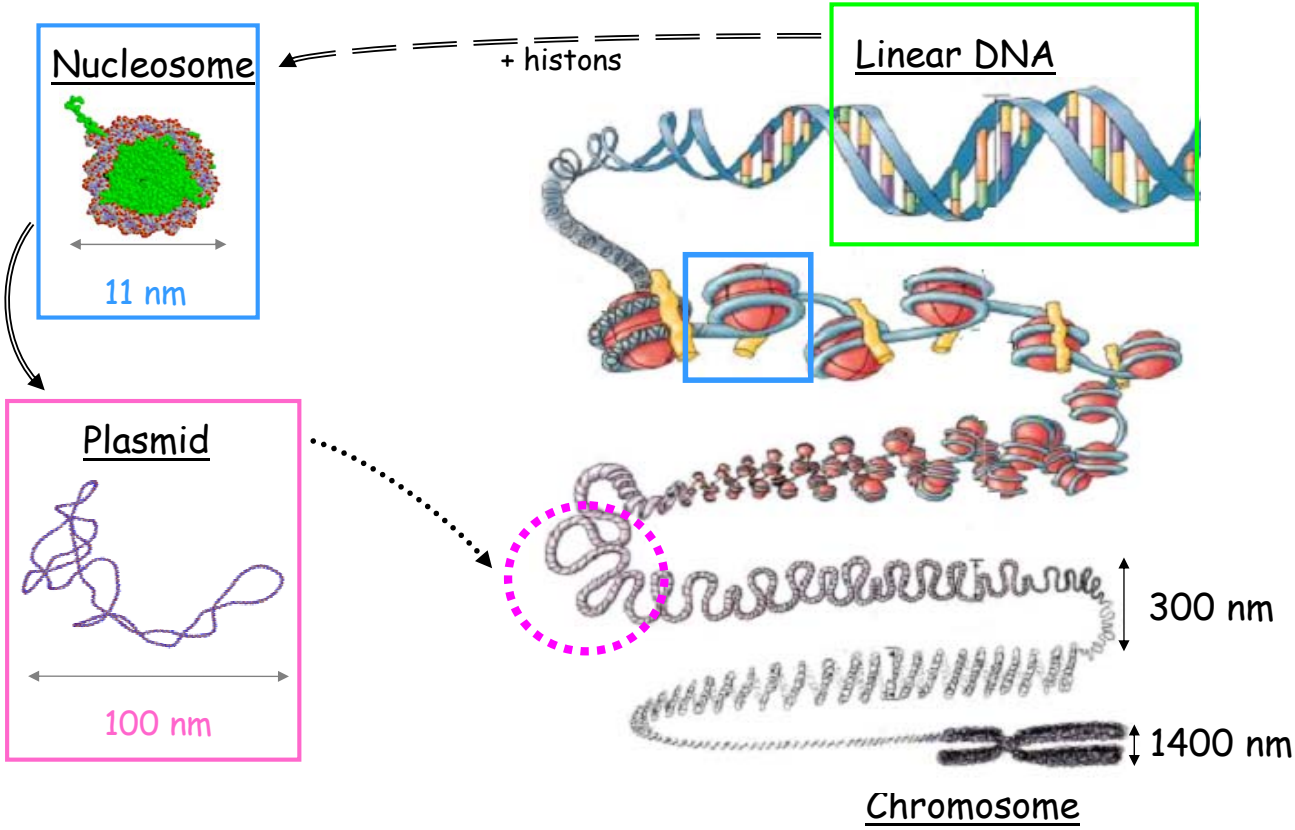
Non altered
released bases

+ Oxidative stress modelling

Why molecular structure ?

- Photons \Rightarrow interact mainly with core electrons
Molecular structure \rightarrow Auger and fluorescence
characteristic spectra
- Electrons \Rightarrow interact mainly with outer electrons
Molecular structure \rightarrow energy depositions and
transfers
- Chemistry : between **molecules**
- More realistic **cross-sections** in orbital energy range

Basic structures

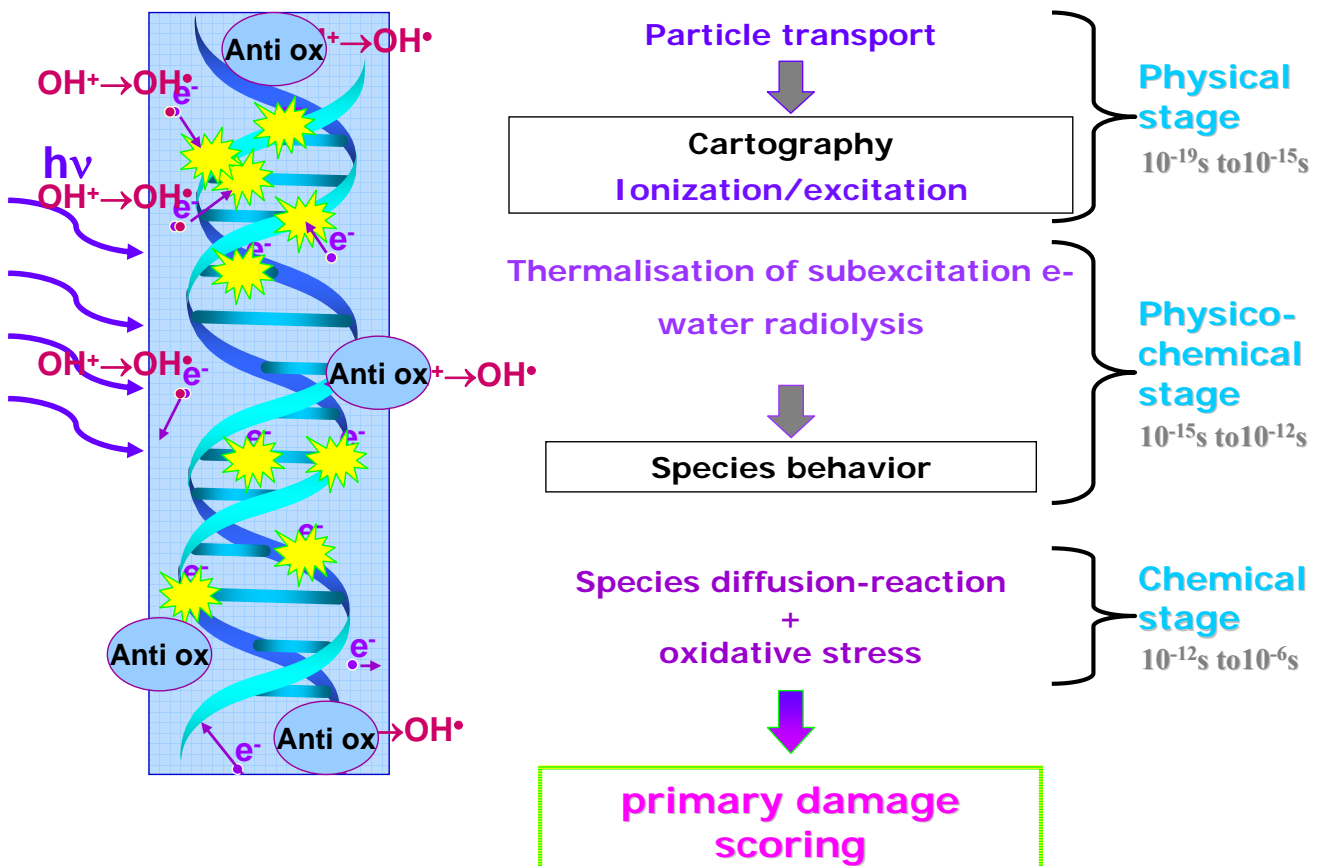
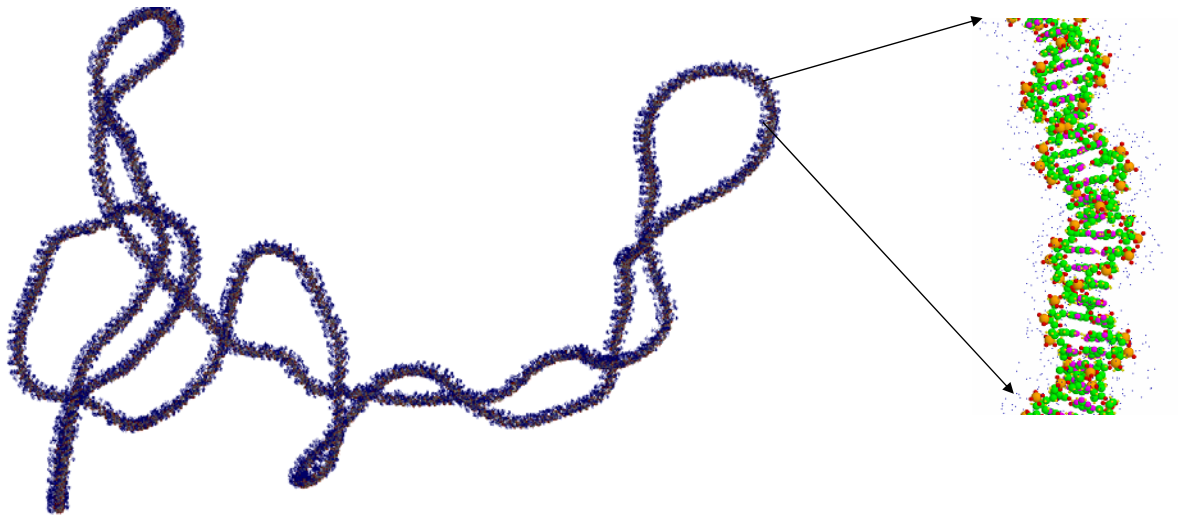


Number of atoms of the hydrated nucleosome: 27955

TARGET : Plasmid

Plasmid pBR322 simulated by Kummerle E. A. and Pomplun E.

- 8722 base pairs
- ≈ 446000 atoms once hydrated ($20 \text{ H}_2\text{O} / \text{basepair}$)
- 3 different configurations were used



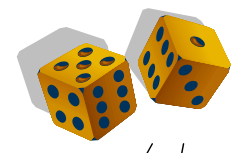
Simulation features

- Monte Carlo transport photons & electrons $E < 150$ keV
4 dimensions x, y, z, t
- Molecular or atomic targets, non homogeneous medium
- Includes reorganisation radiative (fluorescence) and non radiative (Auger)
- Includes charge transfer within the biomolecules
- Includes species reaction-diffusion together and with DNA about 130 reactions
- Includes primary chemical repair

Transport
modelling

PARTICLE PATH THROUGH A COMPOSITE MEDIUM

Particle path sampling...(Kalos & Whitlock, 1986)



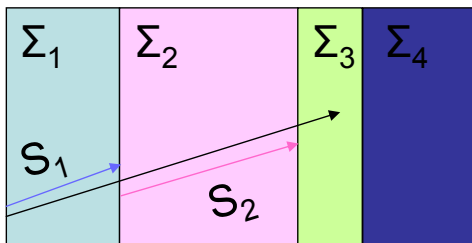
HOMOGENEOUS medium

$$\Sigma_k$$

$$\Sigma_k(E) = \sum_{i=1}^j n_i \cdot \sigma_i(E)$$

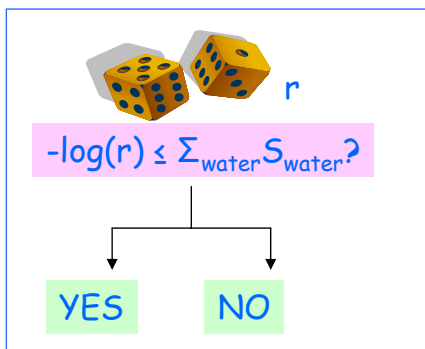
$$S_k(E) = \frac{-\log(r)}{\Sigma_k(E)}$$

SUCCESSION OF HOMOGENEOUS media

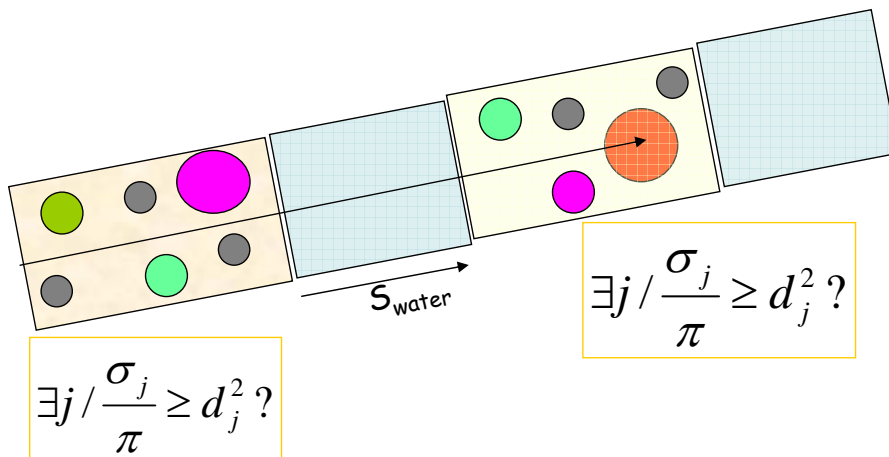


$$S = \sum_{j=1}^{m-1} S_j - \frac{\sum_{j=1}^{m-1} \Sigma_j S_j + \log(r)}{\Sigma_m}$$

How to sample particle path in plasmids?



σ_j : -> entity total cross section



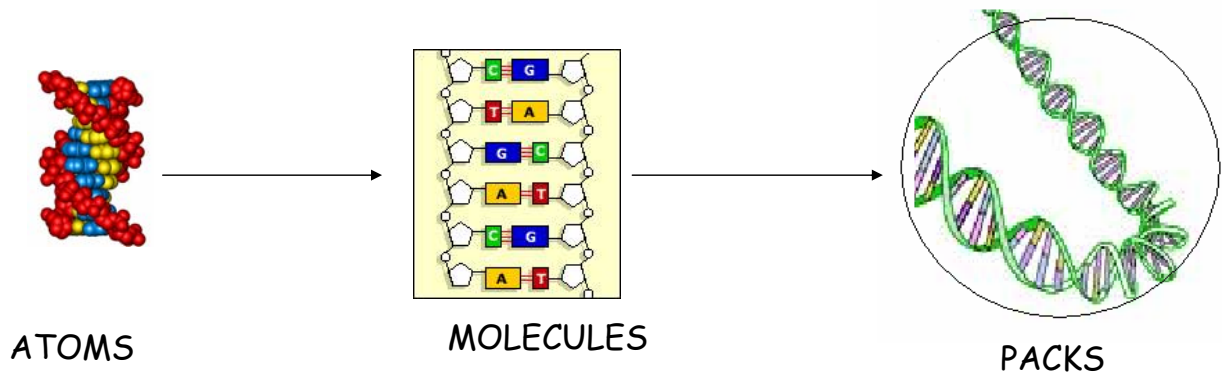
$$\exists j / \frac{\sigma_j}{\pi} \geq d_j^2 ?$$

$$\exists j / \frac{\sigma_j}{\pi} \geq d_j^2 ?$$

INVERSE ZOOM METHOD

*Since
A, T, C, G
have comparable
cross-sections*

We can group in various entities :
molecules, bases, packs,.....



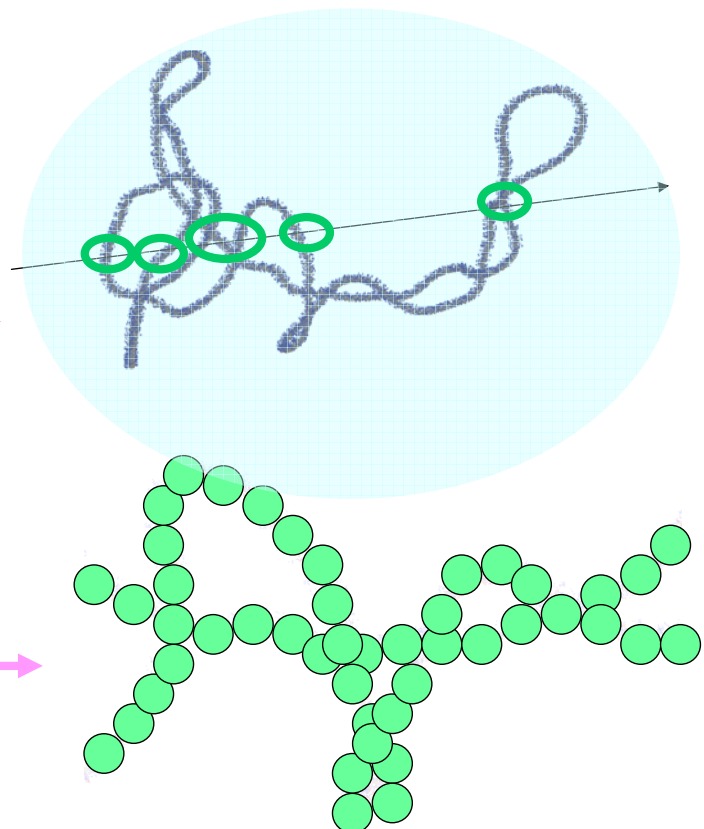
How to sample paths in the plasmid-water medium ?

$$\exists j / \frac{\sigma_j}{\pi} \geq d_j^2 ?$$

300000
atoms



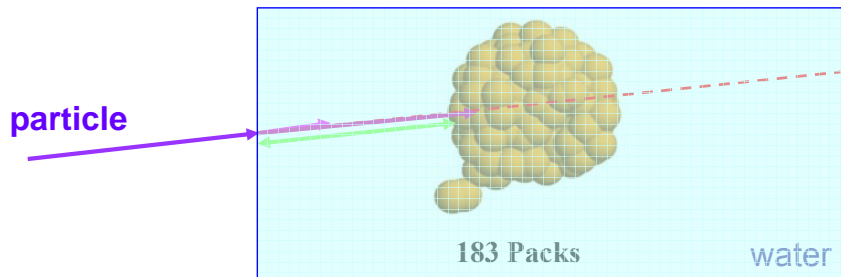
1000
packs



Is there a pack
on the trajectory ?

At wich distance (**dm**)
stay this pack ?

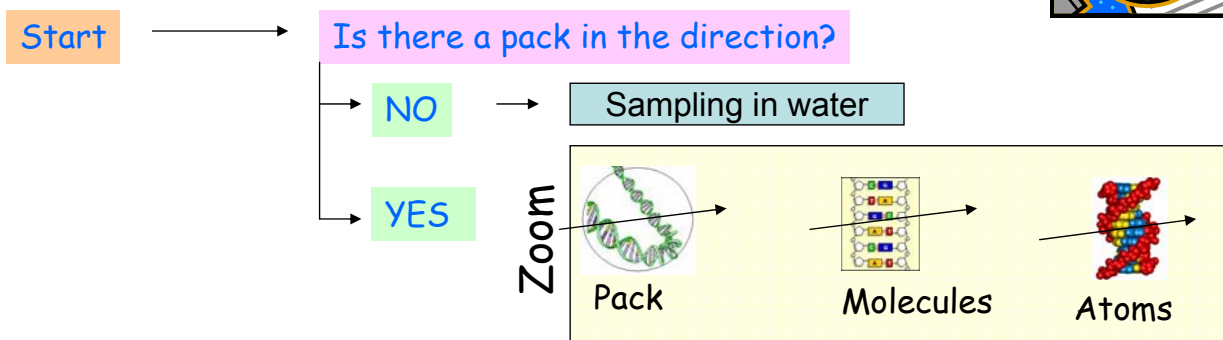
Sample a path in water (**dd**)



if $dd < dm$
interaction with water

if $dd > dm$
interaction with a pack
inverse zoom
gives the entity

INVERSE ZOOM METHOD

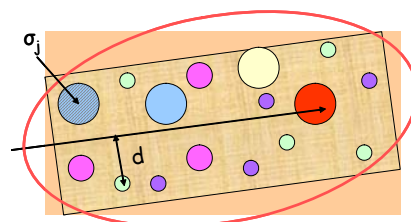


$$\exists j / \frac{\sigma_j}{\pi} \geq d_j^2 ?$$

YES → DNA interaction

NO → DNA crossed

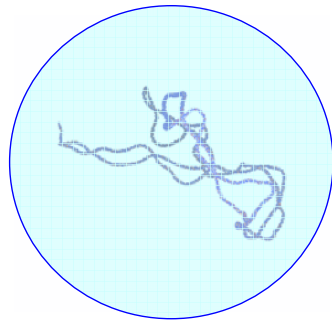
Start



EXPERIMENT / MODEL

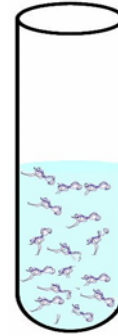
range of 10 keV electron \rightarrow 0.0002 cm \rightarrow 1 plasmid

range of 10 keV photon \rightarrow 0.2 cm \rightarrow 10^4 plasmids



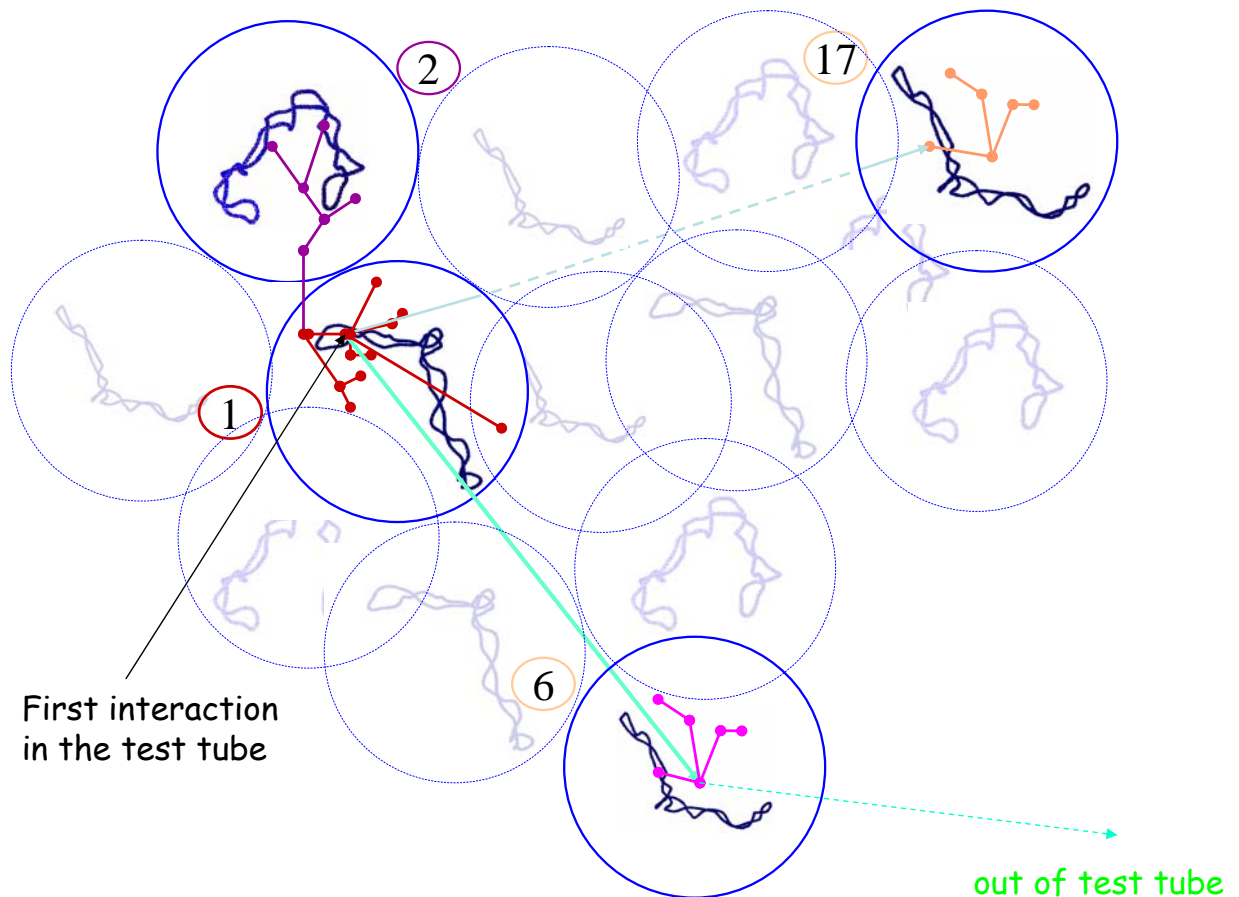
$\approx 0.35 \mu\text{m}$

for [ADN] = 50 $\mu\text{g/ml}$



several mm

for [ADN] = 50 $\mu\text{g/ml}$



Cross-sections and parameters

Molecular basic data calculation

"Ab initio" calculations:

- 27 entities : 20 histon amino-acids + 4 bases + sugar + phosphate + water
- Number of Molecular Inner Shells and Shells of Valence
- Energy of Molecular orbits
- Population Analysis in the Molecular Orbit



Chem3D Ultra with GAMESS or GAUSSIAN 98

MO Binding Energy

Comparison

Sanche and Mozejko,
Paretzke and Bernhardt

Adenine

MO	Energy (Sanche)	Energy calculated	number of e-
1	425,60	426,64	2,00
2	424,10	424,73	2,00
3	424,00	424,56	2,00
4	423,80	424,52	2,00
5	423,50	424,23	2,00
6	309,10	310,39	2,00
7	308,60	309,74	2,00
8	308,50	309,26	2,00
9	308,20	308,68	2,00
10	306,80	307,67	2,00

10 Internal MO



20,00

MO	Energy (Sanche)	Energy (Paretzke)	Energy calculated	number of e-
11	37,99		36,64	1,89
12	36,13		34,96	1,81
13	34,46		33,44	1,91
14	32,79		31,74	1,88
15	31,82		30,80	1,87
16	28,90		27,68	2,04
17	24,89		24,66	2,12
18	24,30		23,80	2,02
19	23,33		23,25	2,10
20	21,70		20,95	2,12
21	20,51		19,80	2,07
22	17,23		18,87	2,13
23	16,52		17,91	2,11
24	15,60		17,18	2,15
25	15,52		16,88	2,05
26	15,13		16,63	1,82
27	14,31		15,70	1,87
28	13,60		14,85	1,92
29	12,14		13,33	1,89
30	11,02		13,12	1,84
31	10,23	11,73	12,41	1,86
32	9,98	11,38	11,58	1,84
33	9,28	10,56	11,07	1,83
34	8,99	10,00	10,65	1,85
35	8,26	8,44	8,12	2,00

25 MO of Valence



49,00

Mulliken Population Analysis

Glycine Results

Glycine C2 N O H3

MO	Energy calculated	Atom							number of e-
		N 1	C 2	C 3	O 5	H 6	H 8	H 9	
1	-559,918	0,000	0,000	0,000	2,000	0,000	0,000	0,000	2,000
2	-423,107	2,000	0,000	0,000	0,000	0,000	0,000	0,000	2,000
3	-310,784	0,000	0,000	2,000	0,000	0,000	0,000	0,000	2,000
4	-307,121	0,000	2,000	0,000	0,000	0,000	0,000	0,000	2,000
5	-32,5231	1,209	0,389	0,084	0,027	0,126	0,021	0,018	1,874
6	-26,7923	0,273	0,722	0,809	0,107	0,087	0,050	0,076	2,124
7	-19,6357	0,088	0,186	0,575	1,379	0,050	0,033	0,061	2,374
8	-19,3364	0,203	0,290	0,610	0,650	0,046	0,000	0,124	1,923
9	-18,4929	0,103	0,413	0,715	0,476	0,022	0,220	0,069	2,018
10	-17,0724	0,488	0,043	0,345	0,452	0,349	0,000	0,000	1,677
11	-16,5173	0,390	0,525	0,190	0,366	0,043	0,362	0,000	1,877
12	-15,6357	0,459	0,410	0,307	0,293	0,167	0,000	0,033	1,670
13	-14,9091	0,326	0,585	0,115	0,202	0,095	0,039	0,546	1,908
14	-12,6751	0,047	0,288	0,220	2,021	0,000	0,037	0,033	2,646
15	-10,958	1,413	0,148	0,030	0,025	0,016	0,238	0,039	1,909
		7,000	6,000	6,000	8,000	1,000	1,000	1,000	30,000

4 Internal MO

11 MO Of Valence

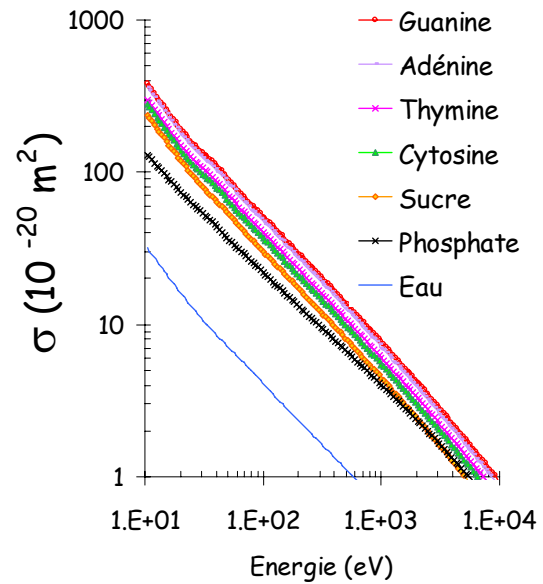
ELECTRONIC MOLECULAR CROSS-SECTIONS

Elastic cross-section

INDEPENDANT ATOM MODEL (MOTT & MASSEY)

$$\frac{d\sigma}{d\Omega} = \sum_{j=1}^N \frac{d\sigma^A}{d\Omega_j} + \sum_{i \neq j=1}^N \frac{\sin(sr_{ij})}{sr_{ij}} [f_i(\theta) f_j^*(\theta)]$$

$f(\theta)$ and $f^*(\theta)$ are calculated with the phase-shift method, solving the Mott-Dirac equation



ELECTRONIC MOLECULAR CROSS-SECTIONS

Ionisation cross-sections

BINARY-ENCOUNTER-BETHE (KIM & RUDD)

$$\sigma_{OM}^{BEB} = \frac{S}{t + \frac{u+1}{v}} \left[\frac{Q \ln(t)}{2} \left(1 - \frac{1}{t^2}\right) + (2-Q) \left(1 - \frac{1}{t} - \frac{\ln(t)}{t+1}\right) \right]$$

Parameters for molecular orbit n :

- B : binding energy
- U : mean kinetic energy
- N : occupation probability
- $Q = 1$ (optical oscillator)

v is an empirical adjustment parameter for atomic principal quantum number $n > 3$

T : incident energy

$$t = \frac{T}{B} \quad u = \frac{U}{B} \quad S = \frac{4\pi a_0^2 N R^2}{B^2}$$

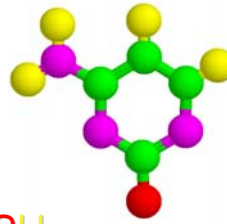
$$a_0 = 0.5292 \text{ \AA (Bohr)}$$

$$R = 13.61 \text{ eV}$$

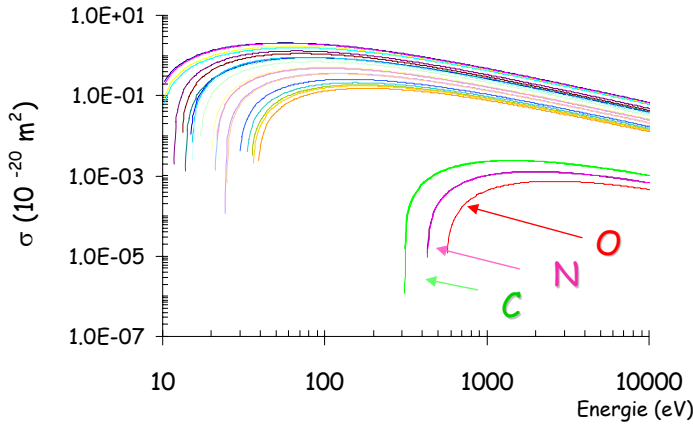
ELECTRONIC MOLECULAR CROSS-SECTIONS

Ionisation cross-sections per MO

U, B and N are calculated with GAMESS



Cytosine $C_4N_3OH_4$



	U	B	N		
16 e- internes	1	794.00	558.57	2.00	O
	2	601.50	425.51	2.00	N
	3	601.40	424.26	2.00	
	4	601.60	424.06	2.00	
	5	435.90	310.68	2.00	C
	6	435.90	309.69	2.00	
	7	435.80	308.15	2.00	
	8	435.60	306.24	2.00	
41 e- de valence	9	67.91	39.32	1.97	
	17	38.94	20.60	2.00	
	27	49.86	11.94	1.85	
	28	40.18	10.76	1.72	
	29	42.94	9.41	1.83	

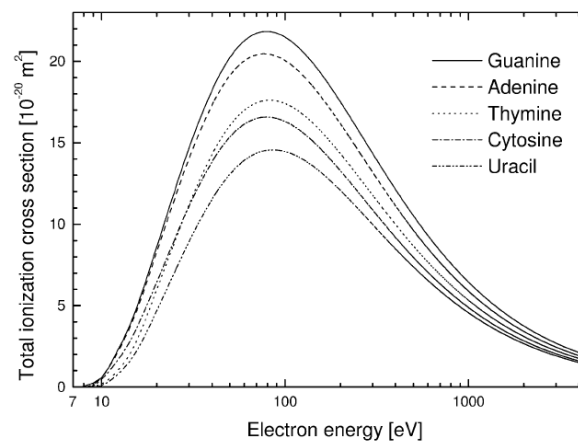
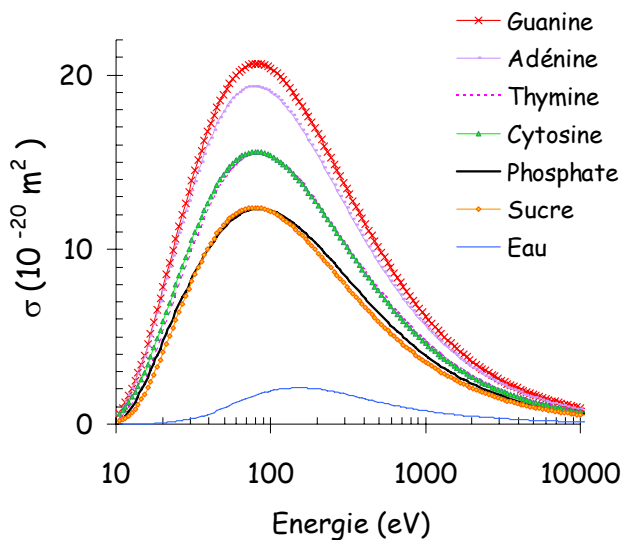
57 electrons, 29 MO

ELECTRONIC MOLECULAR CROSS-SECTIONS

Total ionisation cross-section per entity

$$\sigma_{ion} = \sum_{i=1}^{n_{OM}} \sigma_i^{BEB}$$

Total cross-section is the sum of orbital cross-sections

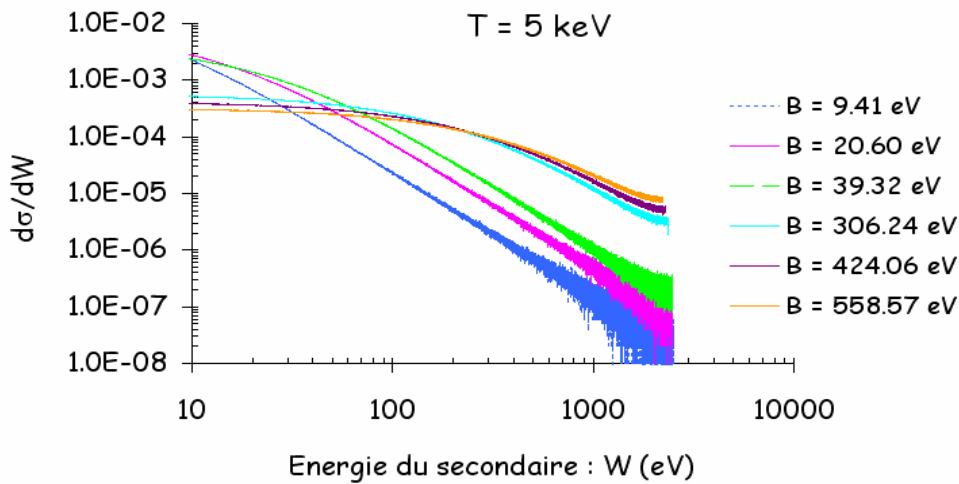


Mozejko & Sanche (2003)

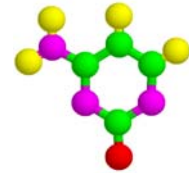
ELECTRONIC MOLECULAR CROSS-SECTIONS

Differential ionisation cross-section

$$\frac{d\sigma}{dw} = \frac{S}{t+u+1} \left[-\frac{1}{t+1} \left(\frac{1}{w+1} + \frac{1}{t-w} \right) + \frac{1}{(w+1)^2} + \frac{1}{(t-w)^2} + \ln(t) \left(\frac{1}{(w+1)^3} + \frac{1}{(t-w)^3} \right) \right]$$

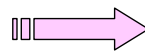


Example :
cytosine $C_4N_3OH_4$



DNA cross-sections

• Lack of data



hypothesis

La Verne Pimblott (1995)

$$\rho_{DNA} \cdot \lambda_{DNA} = \rho_{water} \cdot \lambda_{water}$$

$$\Sigma_{Base} = \Sigma_{water} \cdot \frac{A_{Base}}{A_{water}}$$

Our work

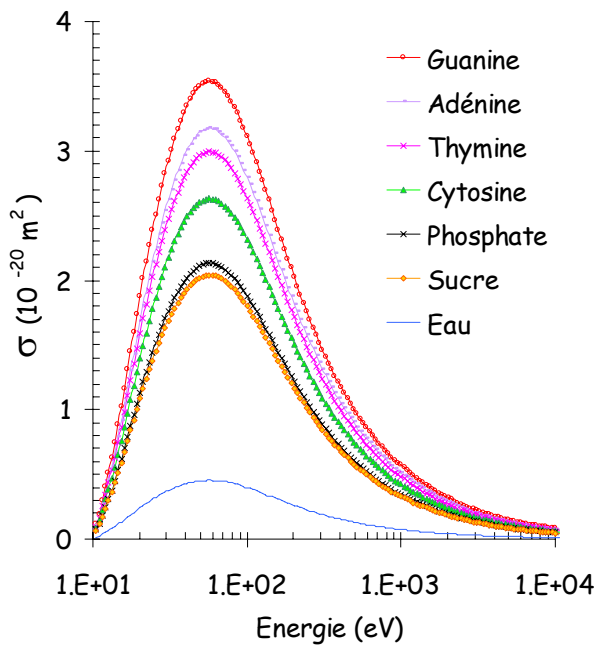
$$\sigma_i(E) = \sigma_{Base}(E) \cdot \frac{R_{VDW_i}}{\sum_{Base} R_{VDW_i}}$$

$$\sigma_i(E) = \frac{R_{VDW_i}}{\sum_{Base} R_{VDW_i}} \cdot \frac{A_{Base}}{A_{water}} \cdot \sigma_{water}(E)$$

σ_{water} from DINGFELDER *ET AL* (1998)

ELECTRONIC MOLECULAR CROSS-SECTIONS

Excitation cross-sections

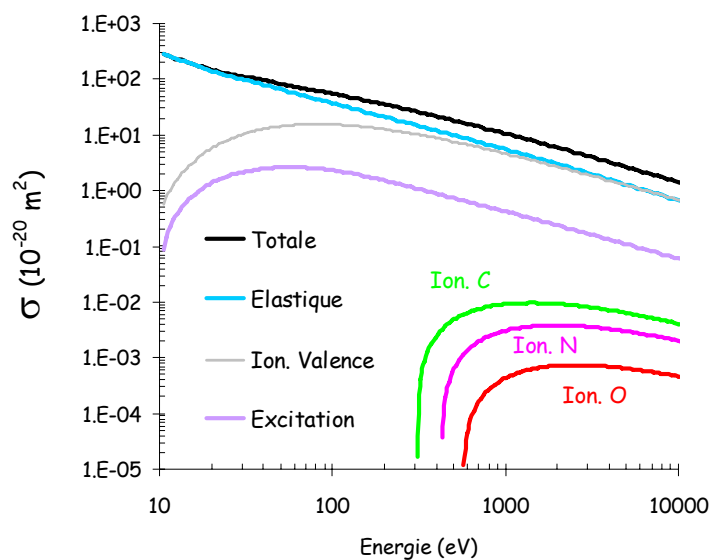
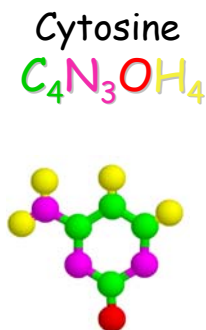


When necessary there are estimated with :

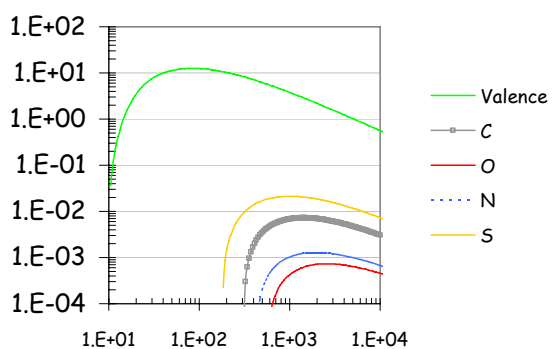
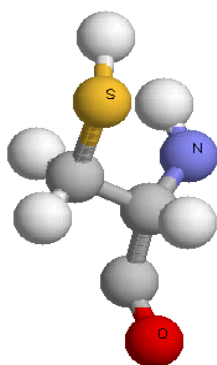
$$[\sigma_{exc}]_{DNA} \approx [\sigma_{ion}]_{DNA} \left[\frac{\sigma_{exc}}{\sigma_{ion}} \right]_{water}$$

BEB
Dingfelder

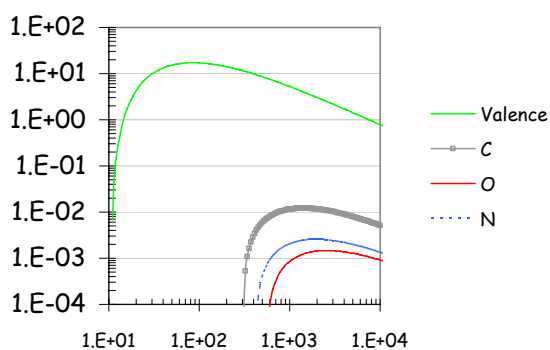
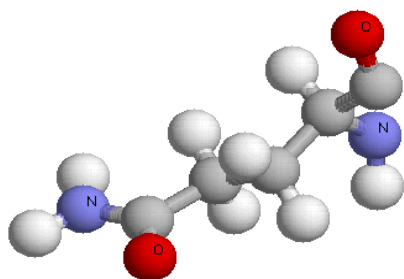
ELECTRONIC DNA CROSS-SECTIONS



CYSTEINE S C3 N O H5

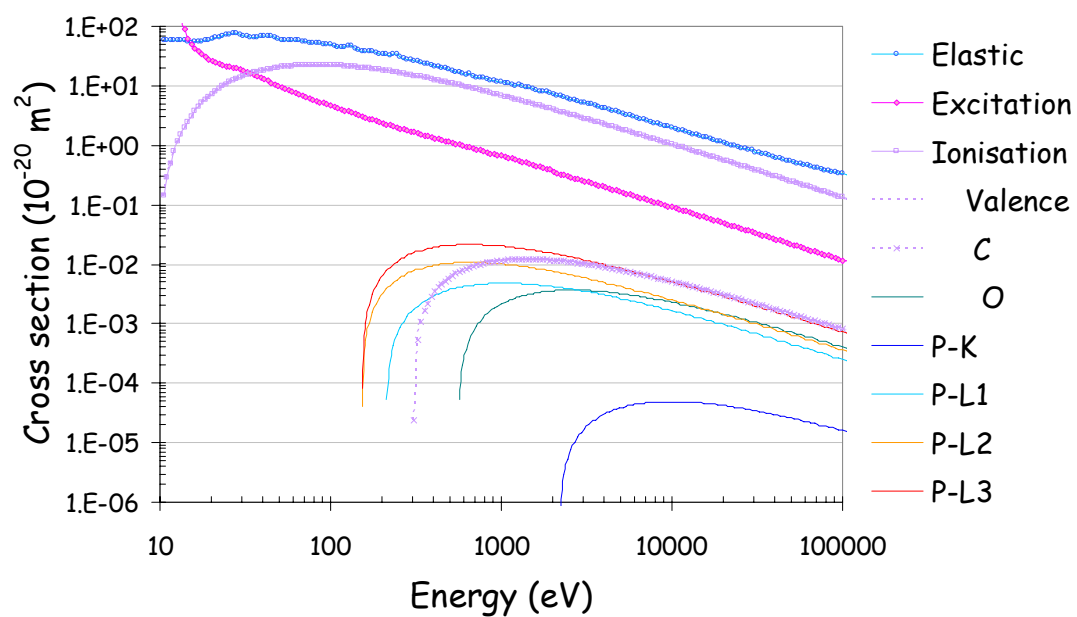


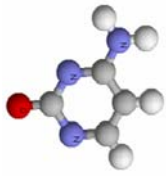
GLUTAMINE C5 N2 O2 H8



ELECTRON TOTAL CROSS SECTIONS IN DNA

BACKBONE TOTAL CROSS SECTION





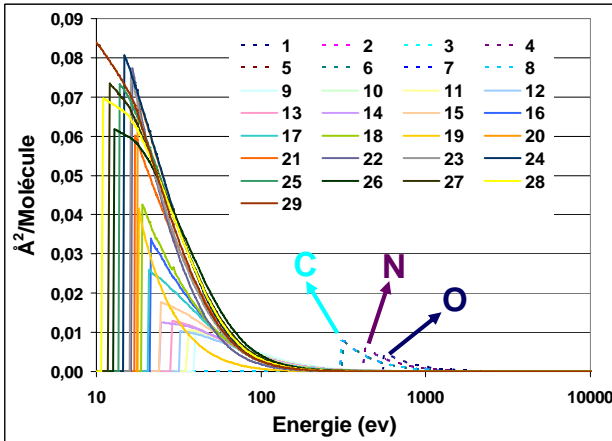
Photon cross-section

Photoelectric cross-section

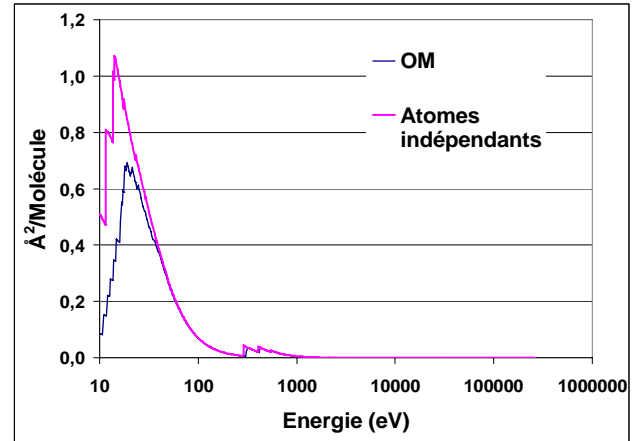
Cytosine : C4 N3 O H4

$$(\sigma_{\text{pho}})_i = \sum_{j=1}^{N_{\text{at}}} p_j \cdot (\sigma_{\text{pho}})_j$$

$$(\sigma_{\text{pho}})_{\text{tot}} = \sum_{i=1}^{nc} (\sigma_{\text{pho}})_i$$



Photoelectric cross-section per MO



Total photoelectric cross-section

H₂O Molecule

Ionization energy

From GAMESS

Molecular Orbital	Energy (eV)	Mulliken Population Analysis			Number of e-
		O 1	H 2	H 3	
1	-559,21	2,000	0,000	0,000	2,00
2	-37,19	1,541	0,208	0,208	1,96
3	-19,54	1,136	0,622	0,622	2,38
4	-15,71	1,579	0,170	0,170	1,92
5	-13,88	1,745	0,000	0,000	1,74
		8,000	1,000	1,000	10,00

H₂O Molecule

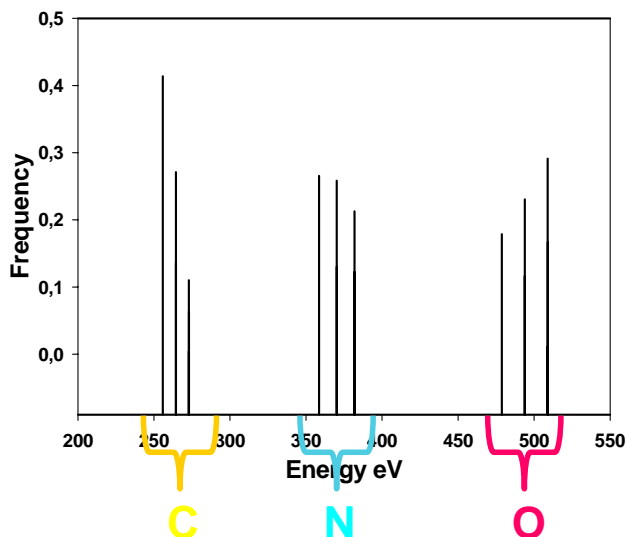
Auger Probabilities

Transition	Masaki Mitani (2003)			This Work		
	Energy	Relative intensity	Probability	Energy from GAMESS	Pop[L _i]*Pop[L _j]	Probability
155	497,7	0,5	0,079	531,45	1,300	0,078
145	495,9	1	0,158	529,62	2,755	0,166
144	492,6	0,5	0,079	527,78	0,913	0,055
135	492,0	0,84	0,133	525,79	1,982	0,119
134	489,7	0,83	0,131	523,96	1,793	0,108
133	484,4	0,35	0,055	520,14	0,154	0,009
125	470,7	0,74	0,117	508,14	2,689	0,162
124	469,4	0,72	0,114	506,31	2,432	0,147
123	463,0	0,59	0,093	502,49	1,750	0,105
122	448,0	0,26	0,041	484,83	0,833	0,050

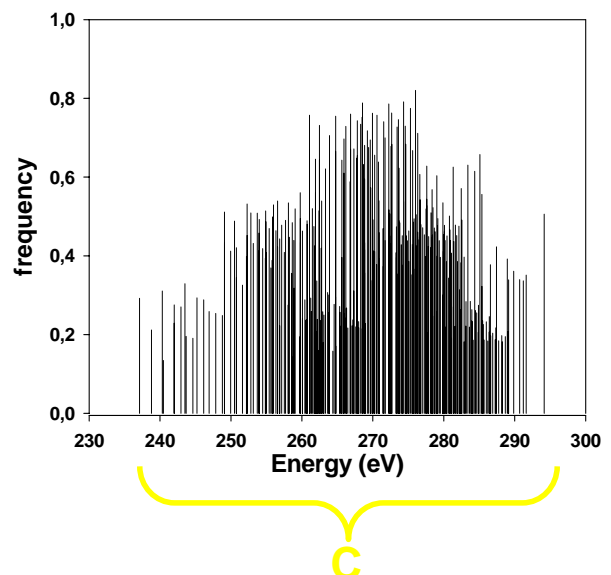
DNA Molecule

Auger Transitions

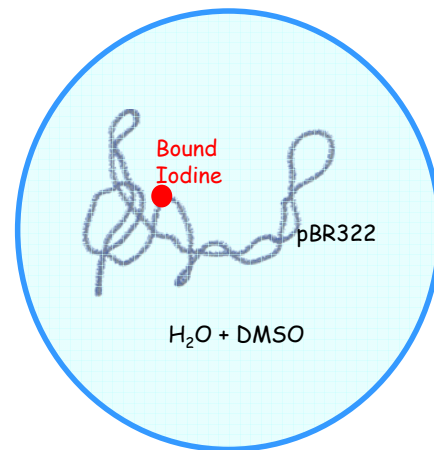
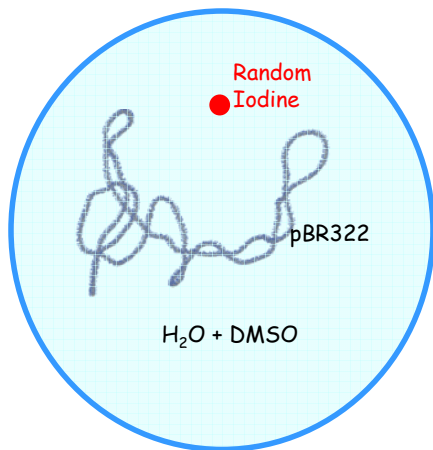
Augers from C, N, O



Augers from adenine-Ck



Experiment / Model

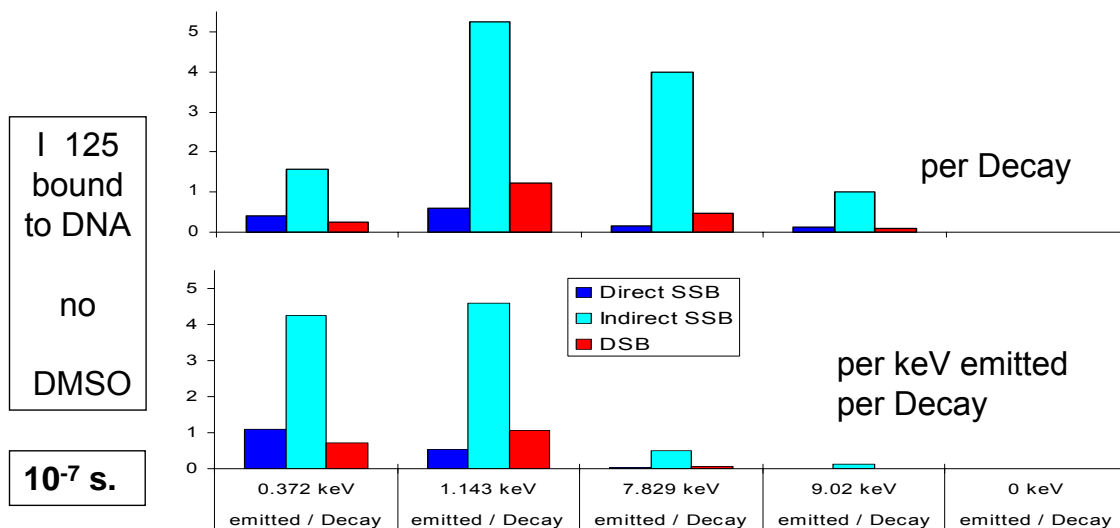
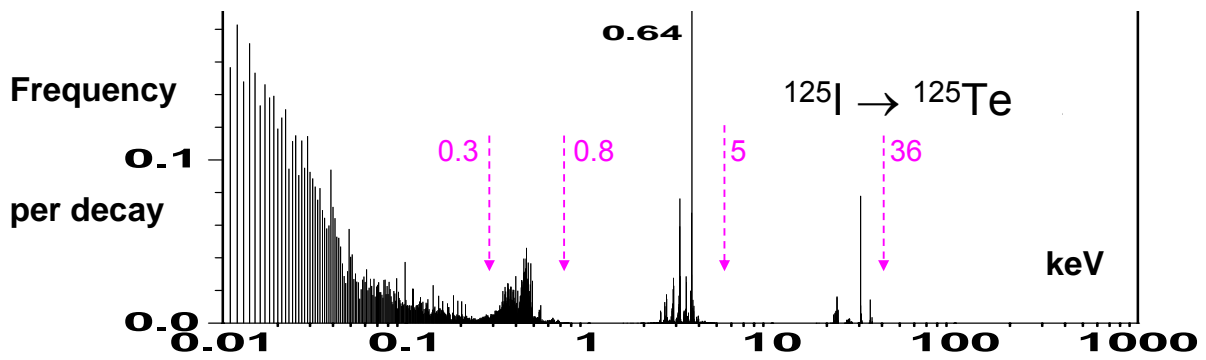


DNA concentration = 5 pBR322/ μ^3
Lobachevsky et al (2005)

Sphere of 362 nm radius

8722 base pairs
+ hydration

total : 446000 atoms



Thank you for attention