

**IRSN**

INSTITUT  
DE RADIOPROTECTION  
ET DE SÛRETÉ NUCLÉAIRE

*Enhancing nuclear safety*

## ***First results on DNA clustered damage combining direct and indirect effects with Geant4-DNA***

**MCMA-2017**

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Naples, Italy

**Carmen Villagrasa**

**IRSN**

**representing the efforts of the  
Geant4-DNA Collaboration**

<http://geant4-dna.org>

## Outlook

1. **Main recent developments of the Geant4-DNA extension of the Geant4 Monte Carlo simulation toolkit**
2. **First results on DNA clustered damage combining direct and indirect effects with Geant4-DNA**

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# Geant4-DNA : Modelling biological effects

**Geant4 for radiobiology? LIMITATIONS** prevent its usage for the modelling of biological effects of ionising radiation **at the sub-cellular & DNA scale**

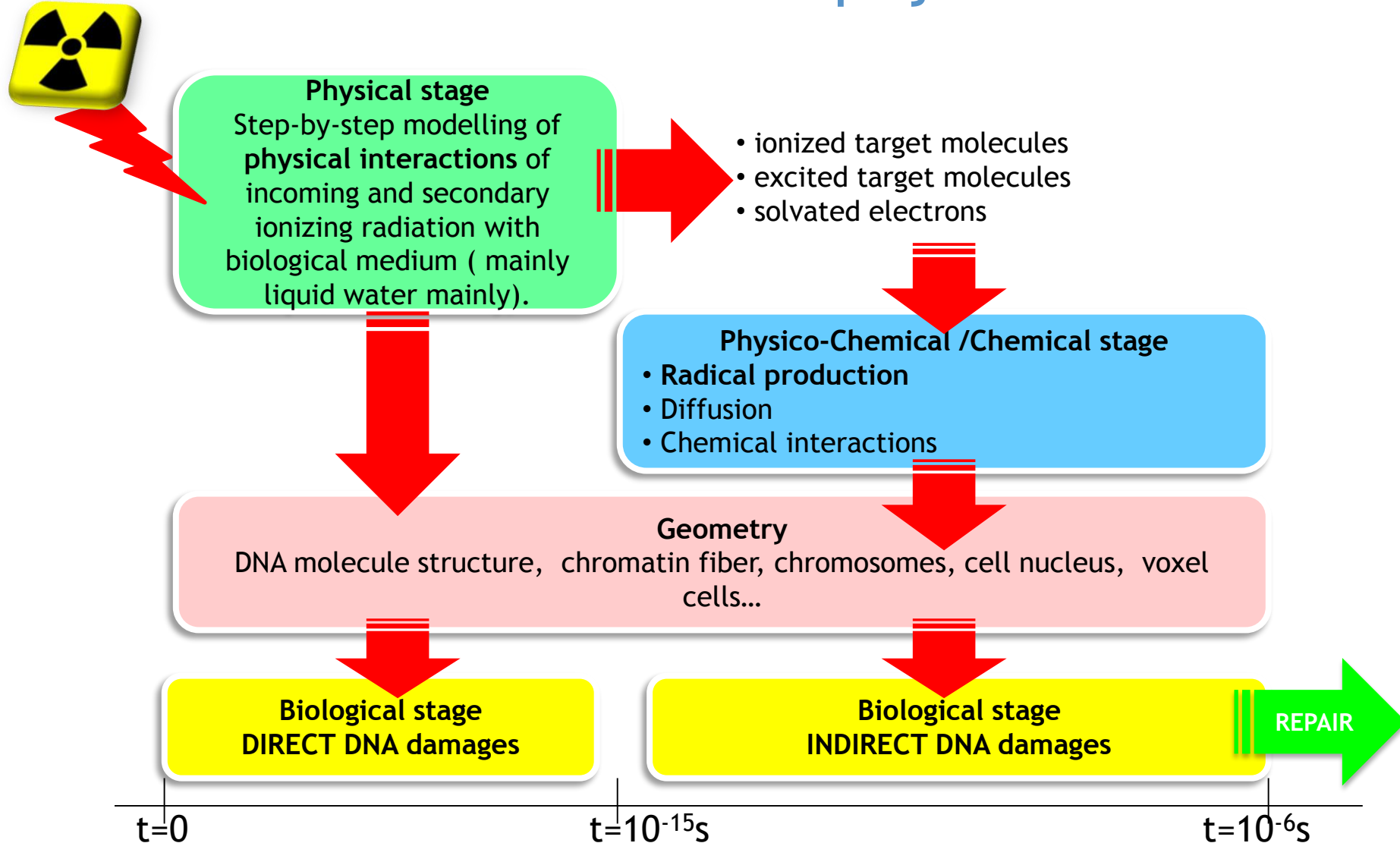
- **Condensed-history approach**
  - No step-by-step transport on small distances, a key requirement for micro/nano-dosimetry
- **Low-energy limit applicability of EM physics models is limited**
  - « Livermore » Low Energy EM models can technically go down to 10 eV but accuracy limited < 250 eV
  - 100 eV for « Penelope 2008 » Low Energy EM models, accurate down to 1 keV
- **No description of target molecular properties**
  - Liquid water, DNA nucleotides, other ?
- **Only physical particle-matter interactions**
  - At the cellular level, physical interactions are NOT the dominant processes for DNA damage at low LET...

## Geant4-DNA: Main objective

Extend the general purpose Geant4 Monte Carlo toolkit for the simulation of interactions of radiation with biological systems at the cellular and DNA level in order to predict early and late DNA damage in the context of manned space exploration missions (« bottom-up » approach).

Designed to be developed and delivered in a FREE software spirit under Geant4 license, easy to upgrade and improve.

# The Geant4-DNA project



## Simulation of the Physical stage

# Overview of physics models for liquid water

## Electrons

- **Elastic scattering**
  - Screened [Rutherford](#) and [Brenner-Zaider](#) below 200 eV
  - Updated alternative version by [Uehara](#)
  - Independent Atom Method (IAM) by [Mott et al.](#) & VLE data in ice from [CPA100 TS code](#)
  - Partial wave framework model by [Champion et al.](#), 3 contributions to the interaction potential



- **Ionisation**
  - 5 levels for H<sub>2</sub>O
  - Dielectric formalism & FBA using [Heller](#) optical data up to 1 MeV, and low energy corrections, by [Emfietzoglou et al.](#)



- Improved alternative version by [Emfietzoglou and Kyriakou](#)
- Relativistic Binary Encounter Bethe (RBEB) by [Terrissol](#) from [CPA100 TS code](#)

- **Excitation (\*)**
  - 5 levels for H<sub>2</sub>O
  - Dielectric formalism & FBA using [Heller](#) optical data and semi-empirical low energy corrections, derived from the work of [Emfietzoglou et al.](#)



- Improved alternative version by [Emfietzoglou and Kyriakou](#)
- Dielectric formalism by [Dingfelder](#) from [CP100 TS code](#)

- **Vibrational excitation (\*)**
  - [Michaud et al.](#) xs measurements in amorphous ice
  - Factor 2 to account for phase effect

- **Dissociative attachment (\*)**
  - [Melton](#) xs measurements

Med. Phys. 37 (2010) 4692 ([link](#))  
 Appl. Radiat. Isot. 69 (2011) 220 ([link](#))  
 Med. Phys. 42 (2015) 3870 ([link](#))  
 Phys. Med. 31 (2015) 861 ([link](#))  
 Nucl. Instrum. and Meth. B 343 (2015) 132 ([link](#))  
 Phys. Med. 32 (2016) 1833 ([link](#))

PhD theses of H. N. Tran (2012), Q. T. Pham (2014), J. Bordes (2017)

## Protons & H

- **Excitation (\*)**
  - Miller & Green speed scaling of e<sup>-</sup> excitation at low energies and Born and Bethe theories above 500 keV, from [Dingfelder et al.](#)

- **Ionisation**
  - Rudd semi-empirical approach by [Dingfelder et al.](#) and Born and Bethe theories & dielectric formalism above 500 keV (relativistic + Fermi density)

- **Charge change (\*)**
  - Analytical parametrizations by [Dingfelder et al.](#)

- **Nuclear scattering**
  - Classical approach by [Everhart et al.](#)

## He<sup>0</sup>, He<sup>+</sup>, He<sup>2+</sup>

- **Excitation (\*) and ionisation**
  - Speed and effective charge scaling from protons by [Dingfelder et al.](#)

- **Charge change (\*)**
  - Semi-empirical models from [Dingfelder et al.](#)

- **Nuclear scattering**
  - Classical approach by [Everhart et al.](#)

## Li, Be, B, C, N, O, Si, Fe

- **Ionisation**
  - Speed scaling and global effective charge by [Booth and Grant](#)

## Photons

from EM « standard » and « low energy »

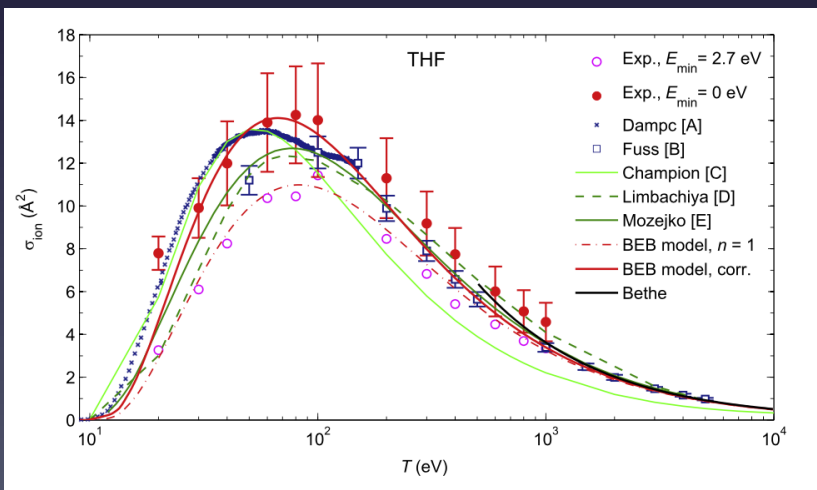
- Default: « Livermore » ([EPDL97](#))

(\*) only available in Geant4-DNA

# Other bio-materials (1)

- Part of the effort to extend Geant4-DNA models to other materials than liquid water
- Cross sections for biological materials are proposed since Geant4 10.4 Beta by IRSN team (C. Villagrasa, S. Meylan), applicable to DNA constituents
  - tetrahydrofuran (THF), trimethylphosphate (TMP), pyrimidine (PY) and purine (PU)
  - serving as precursors for the deoxyribose and phosphate groups in the DNA backbone as well as for bases
- For the following incident particles
  - electrons (12 eV-1keV, elastic + excitation + ionisation) : from measurements @ PTB, Germany
  - protons (70 keV-10 MeV, ionisation) from the HKS approach

Eg. total electron ionisation cross sections in THF



See ICSD extended example

More details in  
Rad. Phys. Chem. 130 (2017) 459-479



## Other ongoing developments for the physical stage

- **New models** describing ionisation of the **four bases of DNA** (adenine, thymine, cytosine and guanine) by incident protons, by Z. Francis (St Joseph U., Lebanon) large energy coverage: **1 keV – 10<sup>8</sup> keV**; based on the **relativistic analytical Rudd approach**, fitted to experimental data will be publicly released in the near future. *J. Appl. Phys.* **122** (2017) 014701
- **Extension of Geant4-DNA** for the modelling of radiosensitization from **gold nanoparticles**. Activity initiated in 2016 by D. Sakata (Bordeaux U., France). **Discrete processes for electrons**: elastic (ELSEPA), ionization (modified RBEBV), electronic (4 channels) and bulk plasmon (Quinn's) excitation. *Nucl. Instrum. Meth. B* **373** (2016) 126 & *J. Appl. Phys.* **120** (2016) 244901
- **Accelerating simulations: variance reduction**. An new extended example, "splitting", provided by J. Ramos-Mendes (UCSF) is provided to illustrate variance reduction technique in the Geant4-DNA ionisation process *Phys. Med. Biol.* **62** (2017) 5908-5925

## Simulation of the Physico-chemical stage & Chemical stage

## Simulation of the Physico-chemical stage

- During this stage, water molecules
  - **Dissociate if ionized**
  - **Relax or dissociate if excited**

J. Comput. Phys. 274 (2014) 841

Electronic state	Dissociation channels	Fraction (%)
All single <b>ionization</b> states	$\text{H}_3\text{O}^+ + \bullet\text{OH}$	100
<b>Excitation</b> state A1B1: (1b1) $\rightarrow$ (4a1/3s)	$\bullet\text{OH} + \text{H}\bullet$	65
	$\text{H}_2\text{O} + \Delta\text{E}$	35
<b>Excitation</b> state B1A1: (3a1) $\rightarrow$ (4a1/3s)	$\text{H}_3\text{O}^+ + \bullet\text{OH} + \text{e}^-_{\text{aq}} (\text{AI})$	55
	$\bullet\text{OH} + \bullet\text{OH} + \text{H}_2$	15
	$\text{H}_2\text{O} + \Delta\text{E}$	30
<b>Excitation state</b> : Rydberg, diffusion bands	$\text{H}_3\text{O}^+ + \bullet\text{OH} + \text{e}^-_{\text{aq}} (\text{AI})$	50
	$\text{H}_2\text{O} + \Delta\text{E}$	50
Dissociative attachment	$\bullet\text{OH} + \text{OH}\cdot + \text{H}_2$	100

- Products thermalize down to their energy of diffusion at equilibrium

# Simulation of the Chemical stage

J. Comput. Phys. 274 (2014) 841

Species	Diffusion coefficient D ( $10^{-9} \text{ m}^2 \text{ s}^{-1}$ )
$\text{H}_3\text{O}^+$	9.0
$\text{H}\bullet$	7.0
$\text{OH}^-$	5.0
$\text{e}^-_{\text{aq}}$	4.9
$\text{H}_2$	5.0
$\bullet\text{OH}$	2.8
$\text{H}_2\text{O}_2$	1.4

We propose by default the set of parameters published by the authors of the PARTRAC software (Kreipl et al., REB 2009). However, these parameters can be modified by the user.

Reaction	Reaction rate ( $10^7 \text{ m}^3 \text{ mol}^{-1} \text{ s}^{-1}$ )
$\text{H}_3\text{O}^+ + \text{OH}^- \rightarrow 2 \text{H}_2\text{O}$	14.3
$\bullet\text{OH} + \text{e}^-_{\text{aq}} \rightarrow \text{OH}^-$	2.95
$\text{H}\bullet + \text{e}^-_{\text{aq}} + \text{H}_2\text{O} \rightarrow \text{OH}^- + \text{H}_2$	2.65
$\text{H}_3\text{O}^+ + \text{e}^-_{\text{aq}} \rightarrow \text{H}\bullet + \text{H}_2\text{O}$	2.11
$\text{H}\bullet + \bullet\text{OH} \rightarrow \text{H}_2\text{O}$	1.44
$\text{H}_2\text{O}_2 + \text{e}^-_{\text{aq}} \rightarrow \text{OH}^- + \bullet\text{OH}$	1.41
$\text{H}\bullet + \text{H}\bullet \rightarrow \text{H}_2$	1.20
$\text{e}^-_{\text{aq}} + \text{e}^-_{\text{aq}} + 2 \text{H}_2\text{O} \rightarrow 2 \text{OH}^- + \text{H}_2$	0.50
$\bullet\text{OH} + \bullet\text{OH} \rightarrow \text{H}_2\text{O}_2$	0.44

# Simulation of the Chemical stage with Geant4-DNA

- Four examples are available in Geant4 in the « [extended examples/medical/dna](#) » category of Geant4 examples
  - CHEM1:** activating chemistry
  - CHEM2:** how to set minimum time step limits
  - CHEM3:** user interactivity and visualization
  - CHEM4:** extraction of time dependent radiochemical yields (G) in a range of deposited energy. Number of molecules of a given species for 100 eV of deposited energy

$$G(t) = \frac{N(t)}{E_{dep}} \text{ with}$$

N(t) number of molecules at time t

Edep Deposited energy scaling to 100 eV

## Note

- Examples can be run in **MultiThreading mode**
- Chemistry works in with **G4\_WATER** material

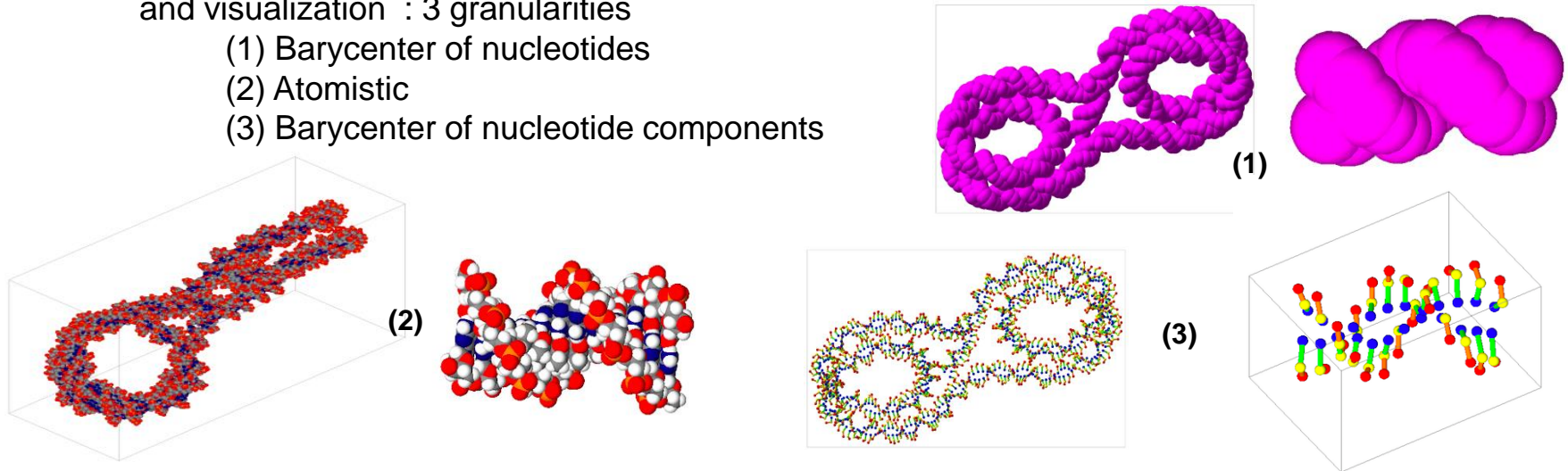
# Geometrical models

# Geometrical models examples

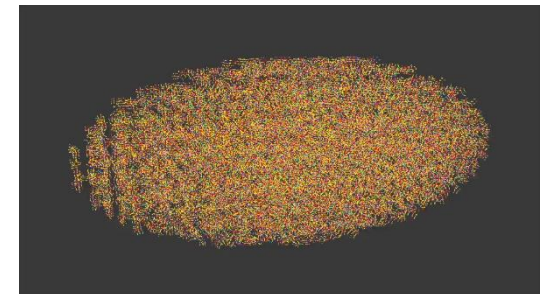
- **PDB Protein data bank interface.** <http://pdb4dna.in2p3.fr>.

**pdb4dna extended example:** Comput. Phys. Comm. 192 (2015) 282. Reading of PDB files  
 Build bounding boxes from atom coordinates, Search for closest atom from a given point, Geometry and visualization : 3 granularities

- (1) Barycenter of nucleotides
- (2) Atomistic
- (3) Barycenter of nucleotide components

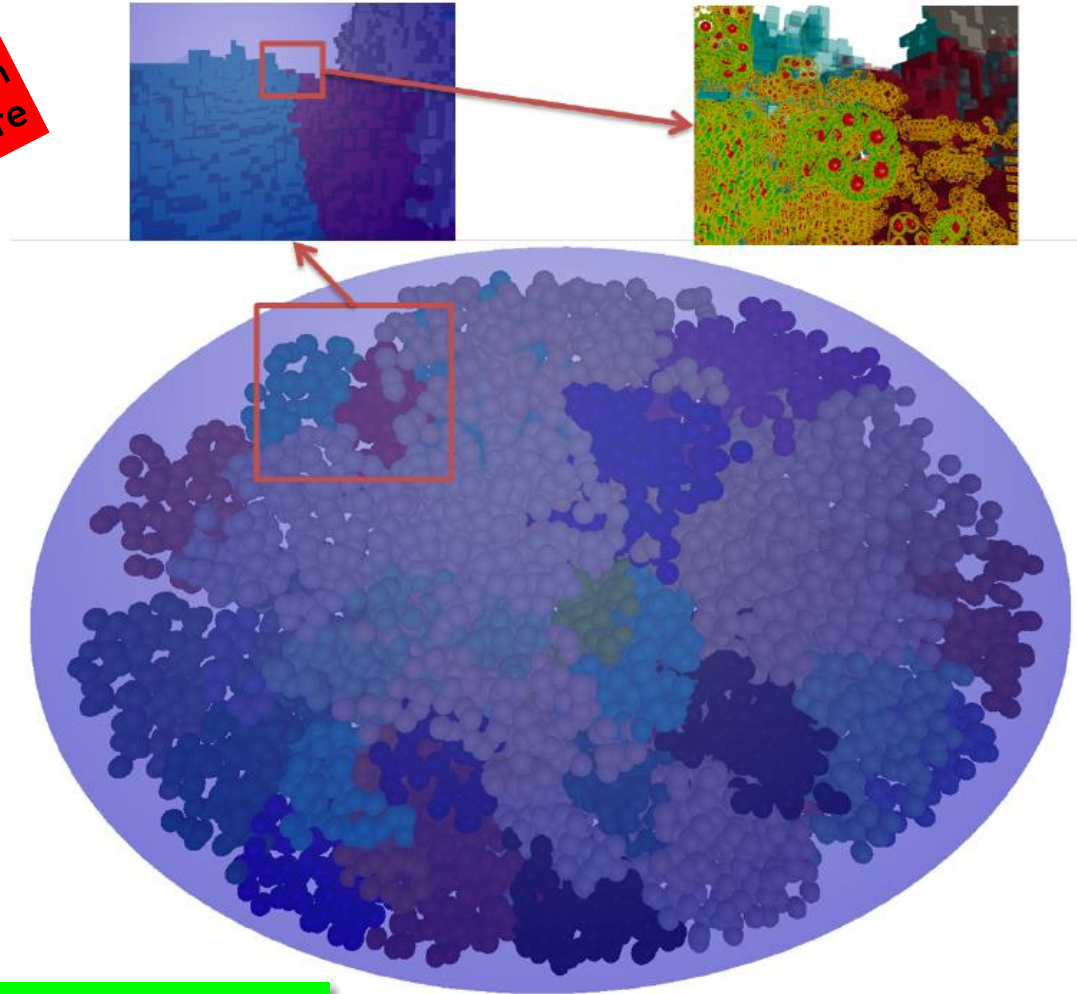


- **Modeling E coli bacteria.** PhD thesis of N. Lampe (2017) (in press). "integral" simulation & scoring of early damage fully driven by UI commands



# ...and the first relaxed human fibroblast cell

Alternative on-going approach  
using the DNAFabric software



Comput. Phys. Comm. 204 (2016) 159



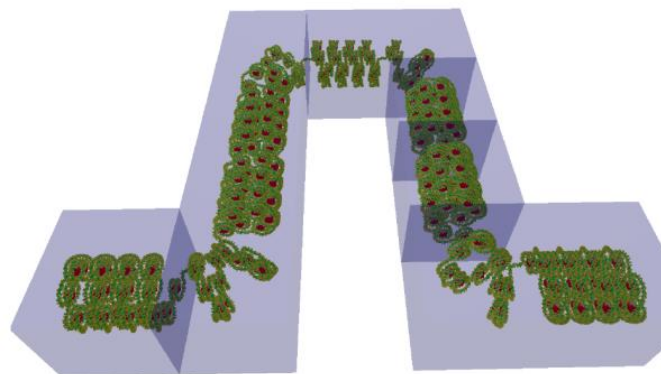
## Outlook

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2. **First results on DNA clustered damage combining direct and indirect effects with Geant4-DNA**

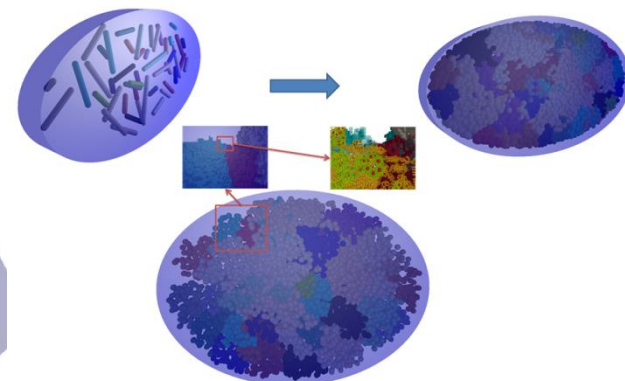
# DnaFabric - Generation of a cell nucleus model

**DNAFabric: C++ software : generation, modification and 3D geometries that can be exported to Geant4.** Comput. Phys. Comm. 204 (2016) 159

1. Choice of **shape** (ellipsoid, sphere, elliptical cylinder...) and nucleus **size**.
2. Generation of an **empty** nucleus phantom.
3. Choice and placement of the **genome** inside the nucleus in a **condensed** form.
4. **Relaxation** step allowing a modelling of the genome domains in G0/G1 phase of the cell cycle.
5. **Filling** step of the genome domains with different voxels containing chromatin fibers with a molecular definition of DNA volumes.
6. **Export** of the nucleus geometry towards the simulation chain based on Geant4-DNA

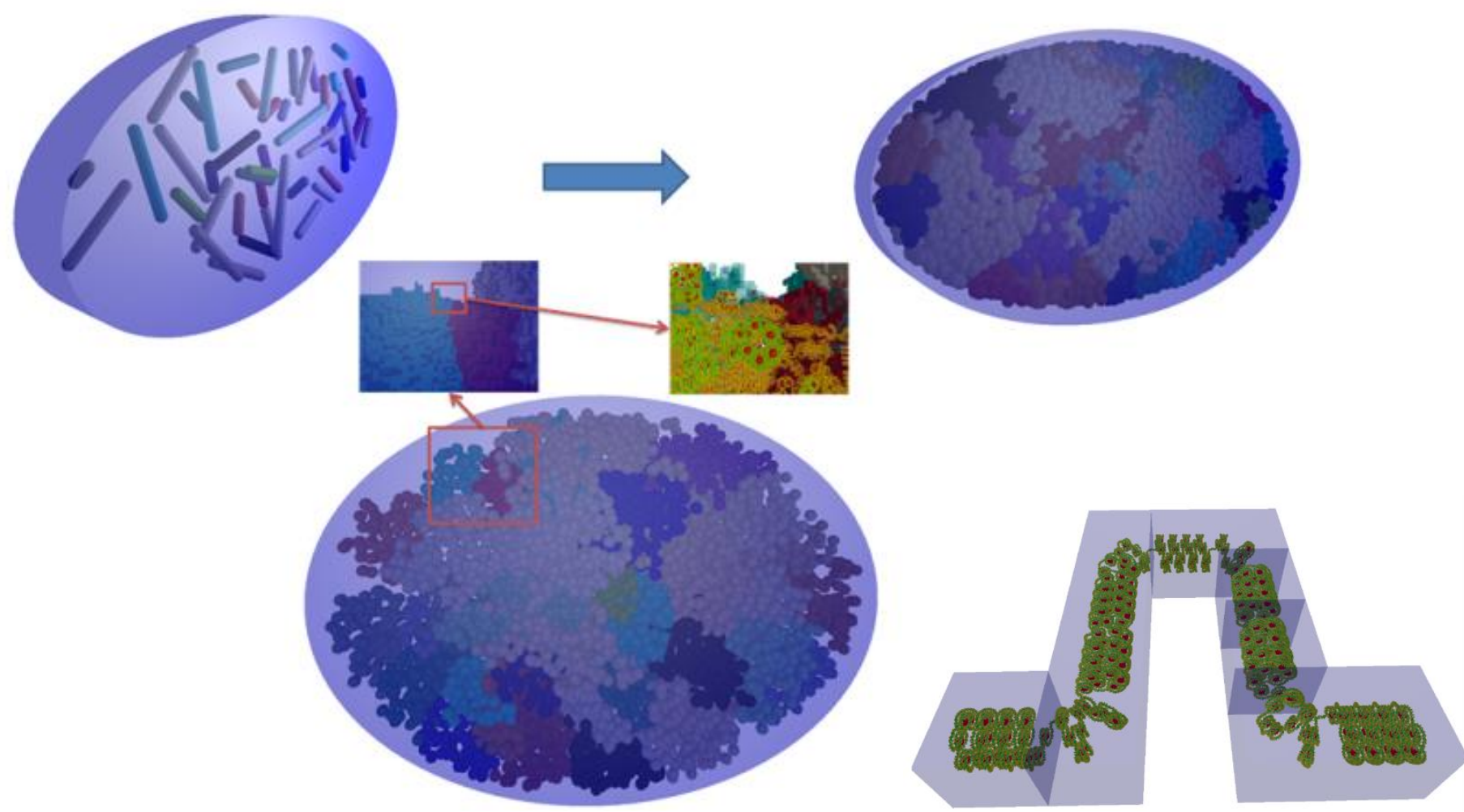


*Different types of voxels*

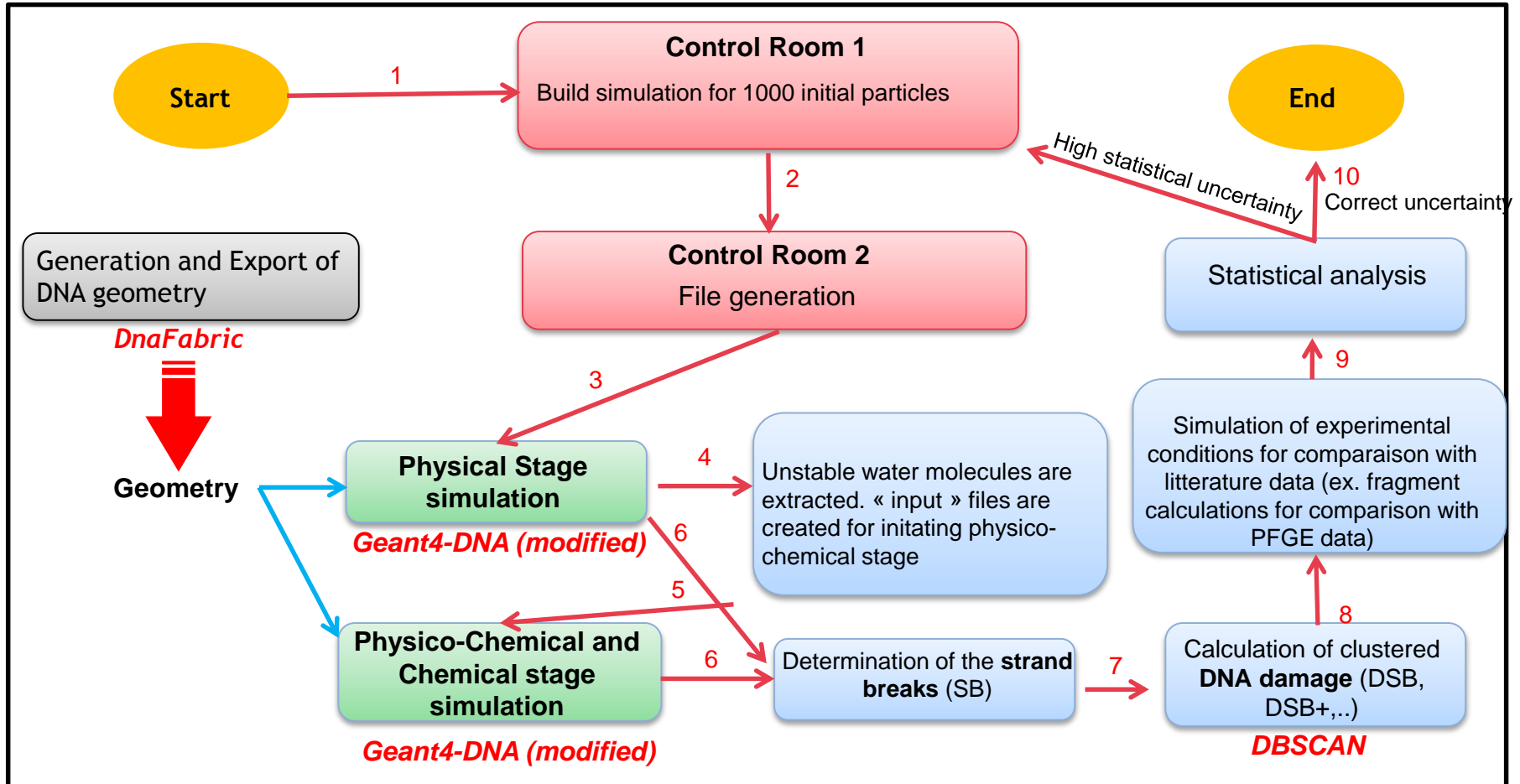


*Example of a generation of a fibroblast cell nucleus*

# DnaFabric - Generation of a cell nucleus model



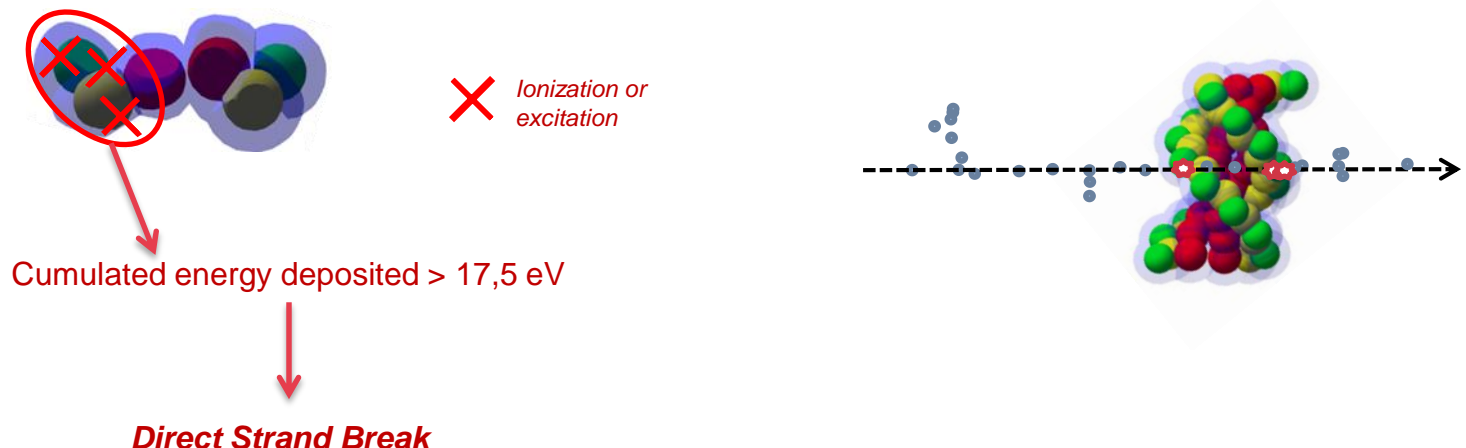
# Simulation chain for clustered DNA damage calculation



# Simulation using Geant4-DNA and SB criteria: Direct effects

## Physical stage using the Geant4-DNA (V10.01) models

- Use of G4EmDNAPhysics (V10,01, defaults)
- Complete cell nucleus:  $\sim 36 \cdot 10^9$  molecular volumes
- **Specificities of the simulation chain :**
  - **Modified Parameterization** used for the  $\sim 2$  million voxels of the DNA geometry (5 different types of voxels: straight, left, right, up and down)
  - **Modifications** of Geant4 allowing the **multithreaded calculation** in such parameterization
- **Direct SB:** Use a **threshold value** on the cumulated energy deposited in the backbone region: **17.5 eV**



# Simulation of the physico-chemical and chemical stages

The DNA target geometry volume are treated as ‘static’ chemical species (no diffusion) and their chemical product is recorded:

- histone proteins make “disappear” any radical diffusing at a distance < the histone radius (sphere)
- OH· radicals interacting with DNA bases give rise to a base damaged
- **40% OH· radicals interacting with deoxyribose are registered as an indirect SB .**

Chemical species	Diffusion coefficient (m <sup>2</sup> /s)	Chemical reactions	Reaction rate (10 <sup>-3</sup> m <sup>3</sup> /mole*s)
H2	$5 \times 10^{-9}$	$e_{aq} + e_{aq} + 2H_2O \rightarrow H_2 + 2OH^-$	$0.5 \times 10^{10}$
H2O	$2 \times 10^{-5}$	$e_{aq} + OH^* \rightarrow OH^-$	$2.95 \times 10^{10}$
H2O2	$1.4 \times 10^{-9}$	$e_{aq} + H^* + H_2O \rightarrow H_2 + OH^-$	$2.65 \times 10^{10}$
H3Op	$9 \times 10^{-9}$	$e_{aq} + H_3O^+ \rightarrow H^+ + H_2O$	$2.11 \times 10^{10}$
OH	$2.8 \times 10^{-9}$	$e_{aq} + H_2O_2 \rightarrow OH^- + OH^*$	$1.41 \times 10^{10}$
OHm	$5 \times 10^{-9}$	$OH^* + OH^* \rightarrow H_2O_2$	$0.44 \times 10^{10}$
$e_{aq}$	$4.9 \times 10^{-9}$	$OH^* + H^* \rightarrow H_2O$	$1.44 \times 10^{10}$
H	$7 \times 10^{-9}$	$H^* + H^* \rightarrow H_2$	$1.20 \times 10^{10}$
Desoxyribose	0	$H_3O^+ + OH^- \rightarrow 2H_2O$	$14.3 \times 10^{10}$
Adenine	0	$^1Desoxyribose + OH^*$	$2.5 \times 10^9$
Guanine	0	$^1Adenine + OH^*$	$6.10 \times 10^9$
Thymine	0	$^1Guanine + OH^*$	$9.20 \times 10^9$
Cytosine	0	$^1Thymine + OH^*$	$6.40 \times 10^9$
		$^1Cytosine + OH^*$	$6.10 \times 10^9$

<sup>1</sup>B. Aydogan et al. Rad. Res. 169 (2008) 223-231

# Simulation of the physico-chemical and chemical stages

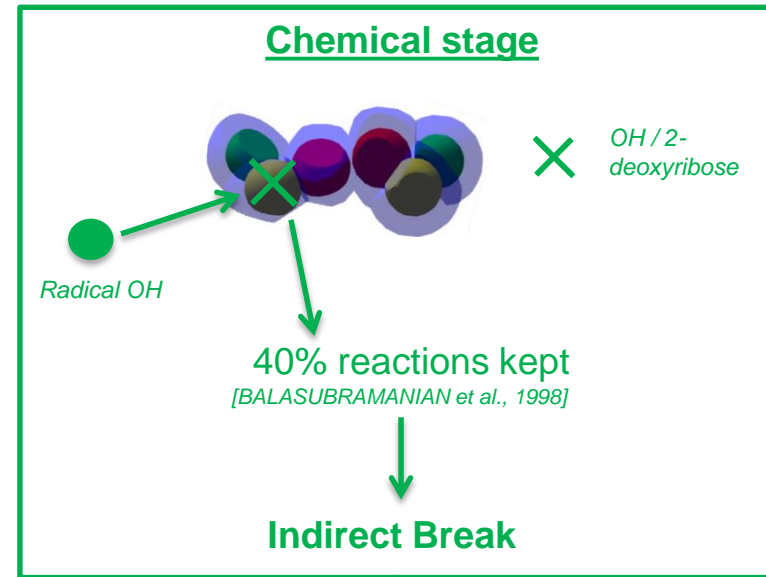
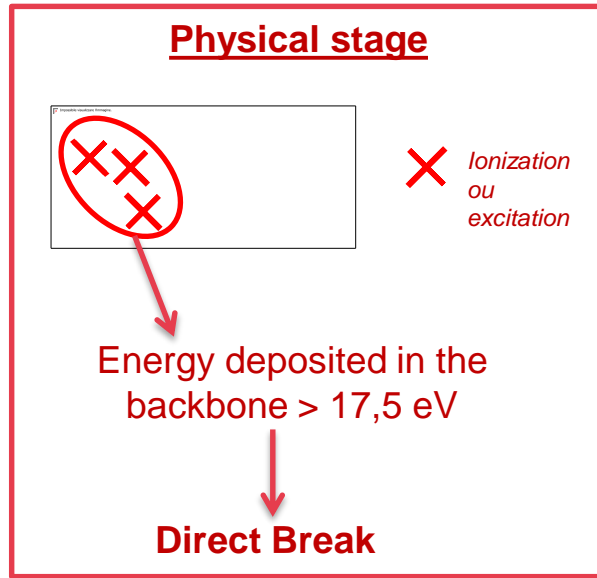
The DNA target geometry volume are treated as ‘static’ chemical species (no diffusion) and their chemical product is recorded:

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- OH• radicals interacting with DNA bases give rise to a base damaged
- **40% OH• radicals interacting with deoxyribose are registered as an indirect SB .**

Chemical species	Diffusion coefficient (m <sup>2</sup> /s)	Reaction	Reaction rate (10 <sup>-3</sup> m <sup>3</sup> / (mol.s))
H2	$5 \times 10^{-9}$	2-deoxyribose + OH•	1.8
H2O	$2 \times 10^{-5}$	Adenine + OH•	6.1
H2O2	$1.4 \times 10^{-9}$	Guanine + OH•	9.2
H3Op	$9 \times 10^{-9}$	Thymine + OH•	6.4
OH	$2.8 \times 10^{-9}$	Cytosine + OH•	6.1
OHm	$5 \times 10^{-9}$	2-deoxyribose + e <sup>-</sup> <sub>aq</sub>	0.01
e <sub>aq</sub>	$4.9 \times 10^{-9}$	Adenine + e <sup>-</sup> <sub>aq</sub>	9.0
H	$7 \times 10^{-9}$	Guanine + e <sup>-</sup> <sub>aq</sub>	14.0
Desoxyribose	0	Thymine + e <sup>-</sup> <sub>aq</sub>	18.0
Adenine	0	Cytosine + e <sup>-</sup> <sub>aq</sub>	13.0
Guanine	0	2-deoxyribose + H•	0.029
Thymine	0	Adenine + H•	0.10
Cytosine	0	Guanine + H•	-
		Thymine + H•	0.57
		Cytosine + H•	0.092
		Histone + molecule → histone <sub>modified</sub>	-

The **clustering algorithm DBSCAN** is then used on the results **combining SB produced by direct effects and indirect effects** to reveal **DSB**

# Scoring of DNA clustered damage



**Clustering algorithm (at least 2 SB located in opposite strands and separated by less than 10 bp)**

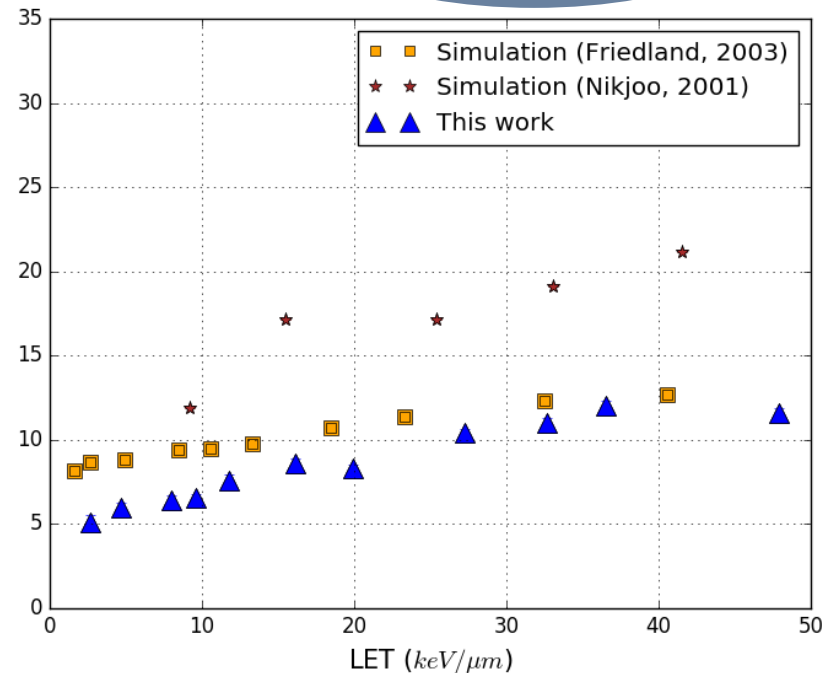
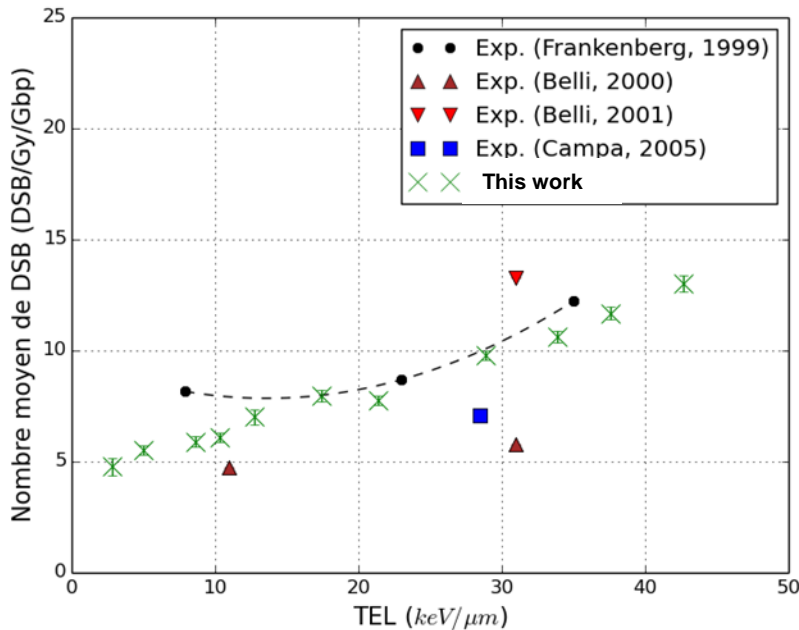
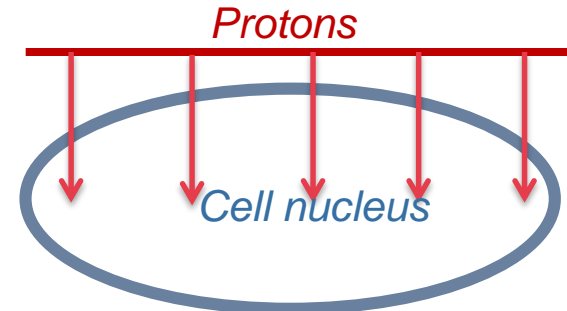




# Results on the number of DSB/Gy/Gbp for protons for a fibroblast cell nucleus

DSB/pp → fragments /pp →  $N_{\text{DSB/event}}(S_{\text{bp}})$

$$N_{\text{DSB/Gy/Gbp}}(s_{\text{bp}}) = N_{\text{DSB/event}}(s_{\text{bp}}) \cdot \frac{E_{1\text{Gy}}}{\bar{l} \cdot \text{TEL}(E_n) \cdot n}$$



\*Meylan S., Incerti S., Karamitros M., Tang N., Bueno M., Clairand I., Villagrasa C., accepted in Scientific Reports (2017)

## Conclusions-> Simulation Chain

- **First results of DSB** simulations using **Geant4-DNA** (Physical +Chemical stages). Others are ongoing
- Importance of a **realistic DNA geometrical model**
- **Great influence of the criteria chosen for the quantification of the direct SB and indirect SB**
  
- **Update of the simulation chain to the late version of Geant4-DNA-> Public release**
- **Including a library of geometries built using DNAFabric**

# Thank you for your attention... and a special thank you to

## Our main developers

Marie-Claude Bordage (INSERM, France)  
Julien Bordes (INSERM, France) - PhD on-going  
Ziad Francis (St Joseph U., Lebanon)  
Vladimir Ivantchenko (G4AI Ltd, UK)  
Mathieu Karamitros (Bordeaux, France)  
Ioanna Kyriakou (Ioannina U., Greece)  
Nathanael Lampe (Melbourne, Australia)  
Sylvain Meylan (Paris, France)  
Shogo Okada (Kobe U., Japan)  
Dosatsu Sakata (Bordeaux U., France)  
Wook-Geun Shin (Bordeaux U., France) - PhD starting  
Nicolas Tang (IRSN, France) - PhD on-going  
Hoang N. Tran (CEA, Saclay & Ton Duc Thang U., Vietnam)  
Carmen Villagrasa (IRSN, France)

Marion Bug (PTB, Germany) (alumni)  
Morgane Dos Santos (IRSN, France) (alumni)  
Yann Perrot (Paris, France) (alumni)  
Trung Q. Pham (HMH, Vietnam) (alumni)  
Vaclav Stepan (NPI Prague, Czech Rep.) (alumni)

Theory & MC

Our  
users !

Michael Dingfelder (ECU, USA)  
Dimitris Emfietzoglou (Ioannina U., Greece)  
Werner Friedland (Helmholtz Z., Germany)  
Francesc Salvat (Barcelona U., Spain)

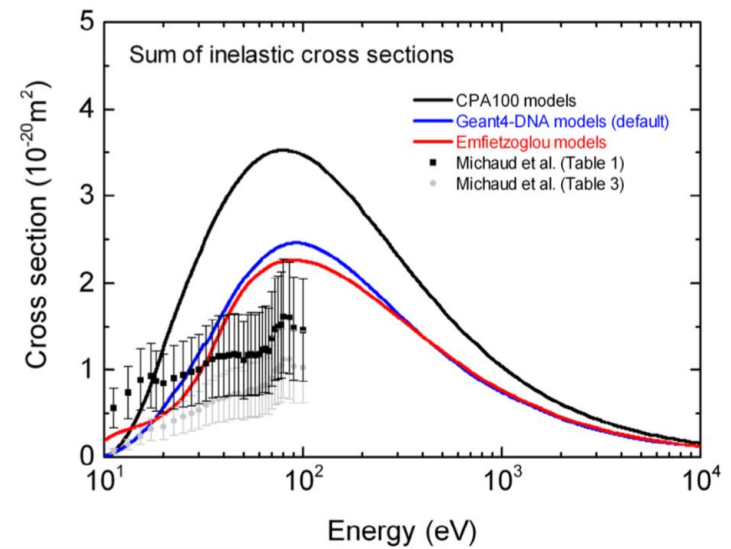
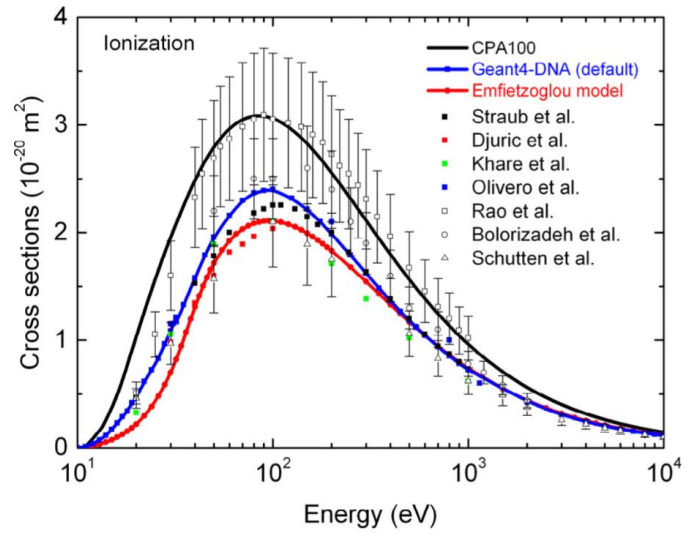
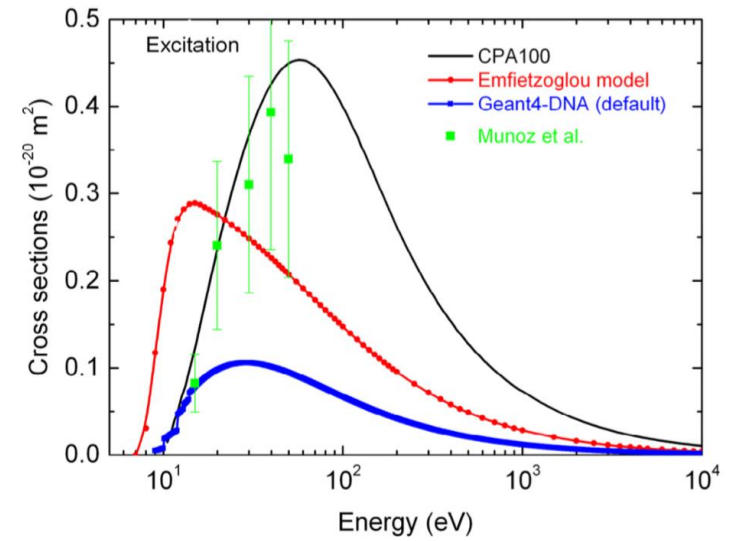
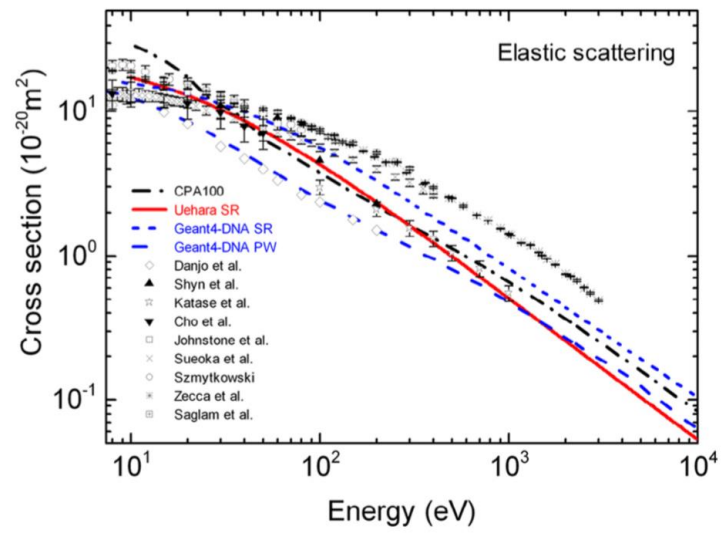


<http://geant4-dna.org>

If you use Geant4-DNA, please be kind to cite in your work our **two** collaboration papers

Phys. Med. 31 (2015) 861-874 ([link](#))  
Med. Phys. 37 (2010) 4692-4708 ([link](#))

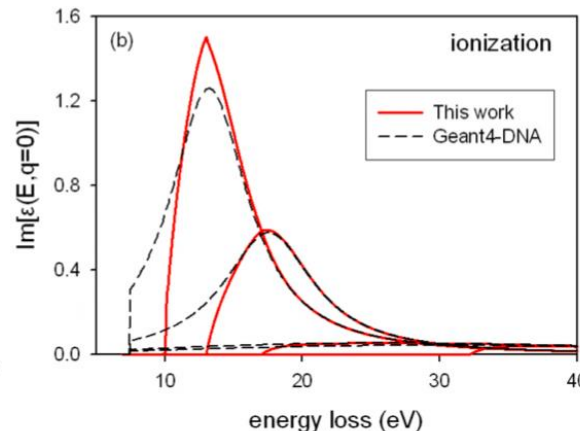
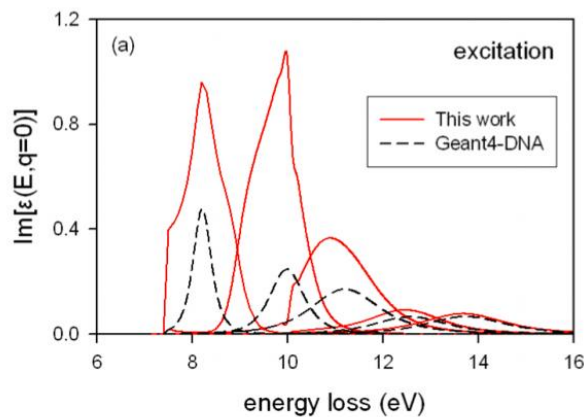
# Cross section models for electrons



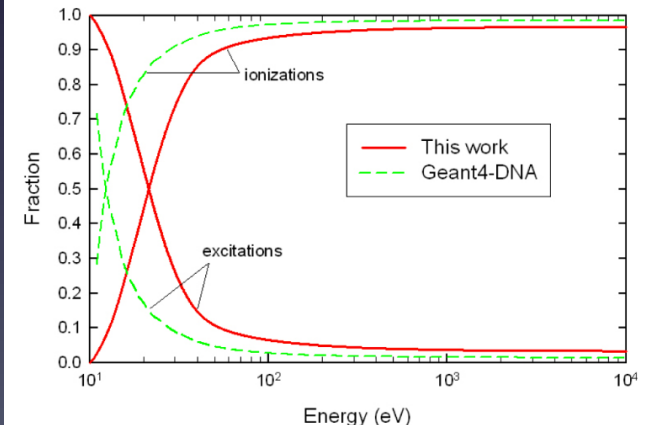
# Ioannina models (1)

- A new set of alternative models improving the accuracy of electrons interactions, developed by I. Kyriakou and D. Emfietzoglou, Ioannina U., Greece
- Main improvements
  - truncation algorithm modifies imaginary part of the dielectric function model :
    - enhance the contribution of the excitation states [see (a)]
    - while eliminating the contribution of each ionization state below the corresponding binding energy with a concomitant smoothing at the near-threshold region [see (b)]
  - low energy corrections for exchange and correlation in electron–electron interactions and corrections for the departure from the plane-wave 1st-order perturbation theory
  - elastic sc.: screening factor proposed by Uehara from vapor experimental data, instead of Grosswendt-Waibel

Imaginary part of the dielectric function model



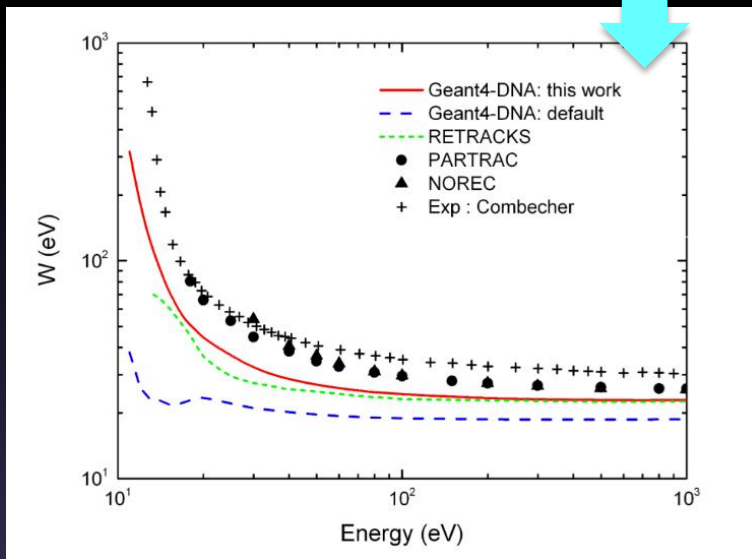
Contribution of ionizations and excitations to the total inelastic cross section



# Ioannina models (2)

Example of verification & validation in liquid water

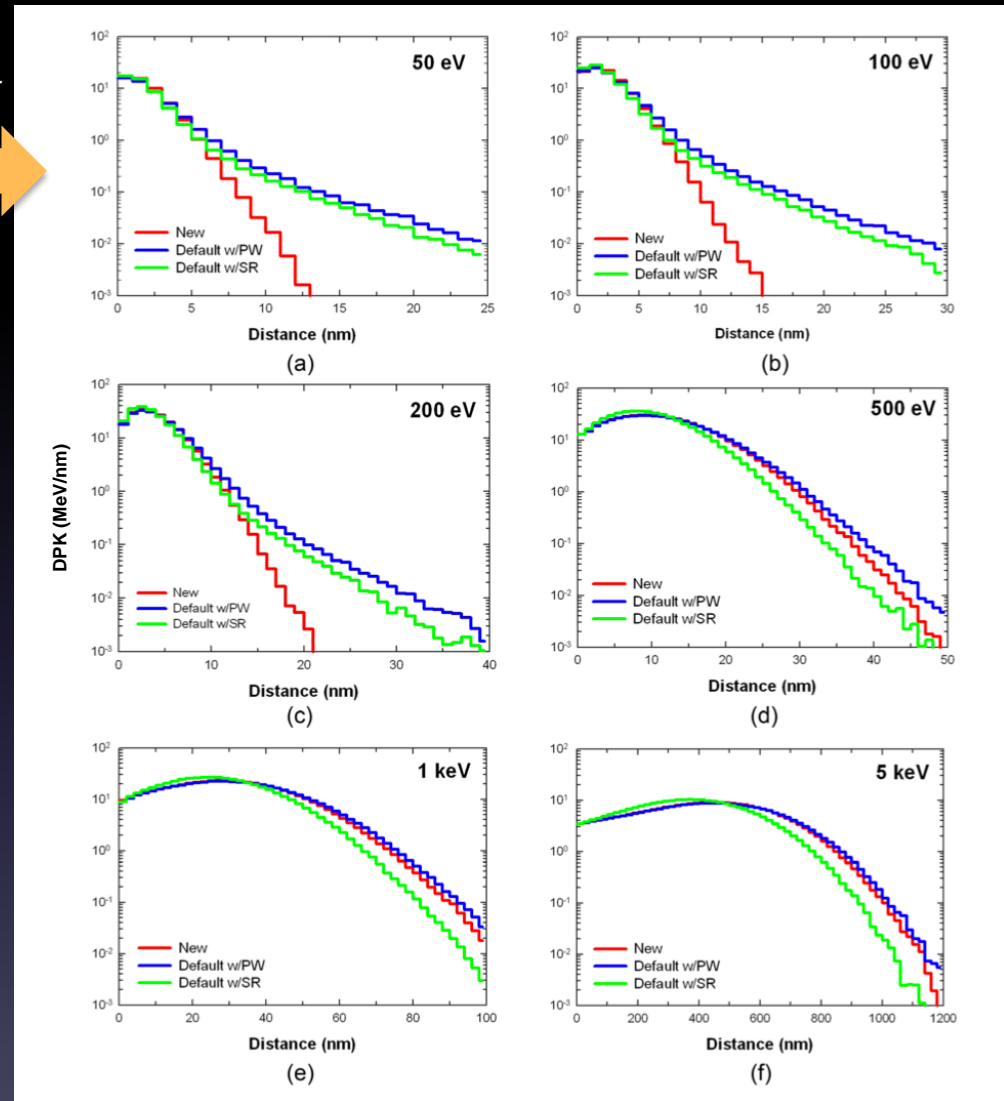
- Dose Point Kernels
- W-value (mean energy to create an ion pair)



The larger the excitation-to-ionization cross section ratio is, the higher the W-value since a smaller number of ion pairs will be formed (for the same electron energy dissipated)

Some difference with the experimental data for gaseous water is expected and confirms the well-established higher ionization yield of the liquid phase compared to the gas phase.

Med. Phys. 42 (2015) 3870 ([link](#))  
J. Appl. Phys. 32 (2016) 119, 194902 ([link](#))



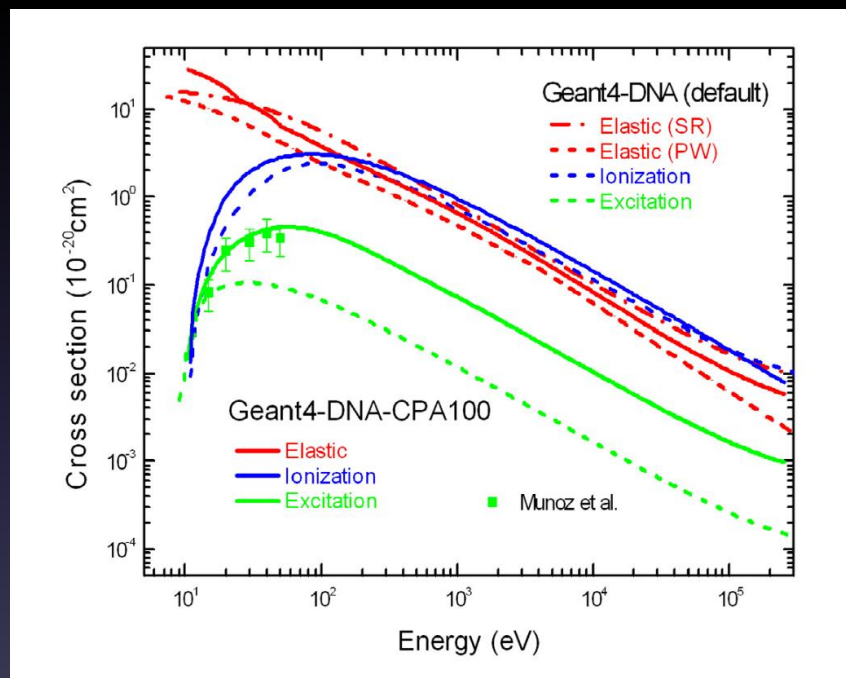
Much less diffusive DPKs with the new inelastic model. With the default model, small excitation cross sections (dominant at large distance and low energy) allow these very low energy electrons to diffuse much longer distances in the medium before their energy falls below the cut-off

# CPA100 models (1)

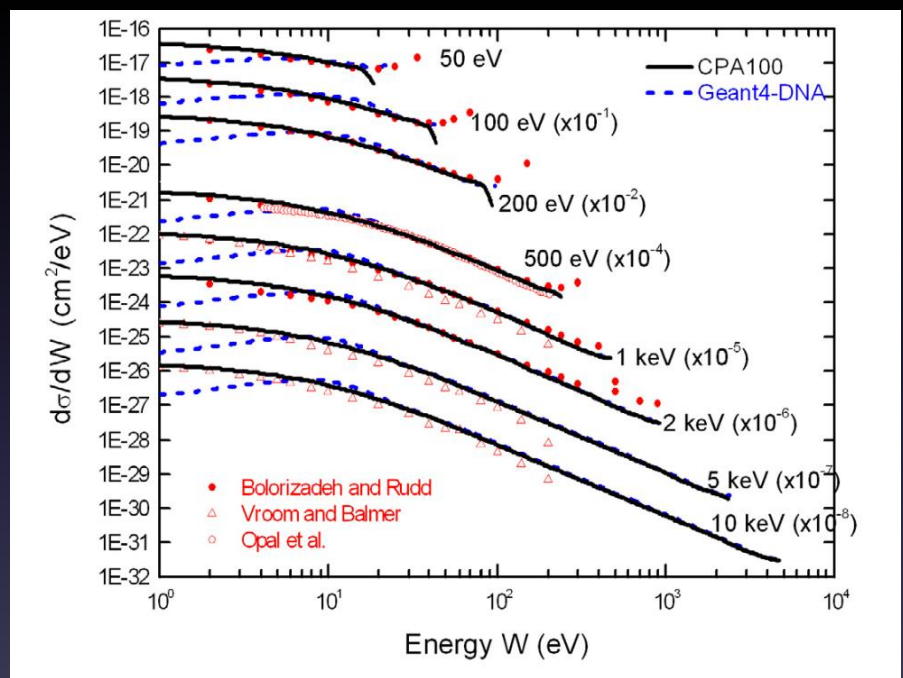
An alternative set of models for electrons (10 eV – 255 keV)  
from the CPA10 Track Structure code (M. Terrissol, M. C. Bordage, Toulouse U., France)

Software  
preservation

Integral cross sections for electrons



Differential ionisation cross section

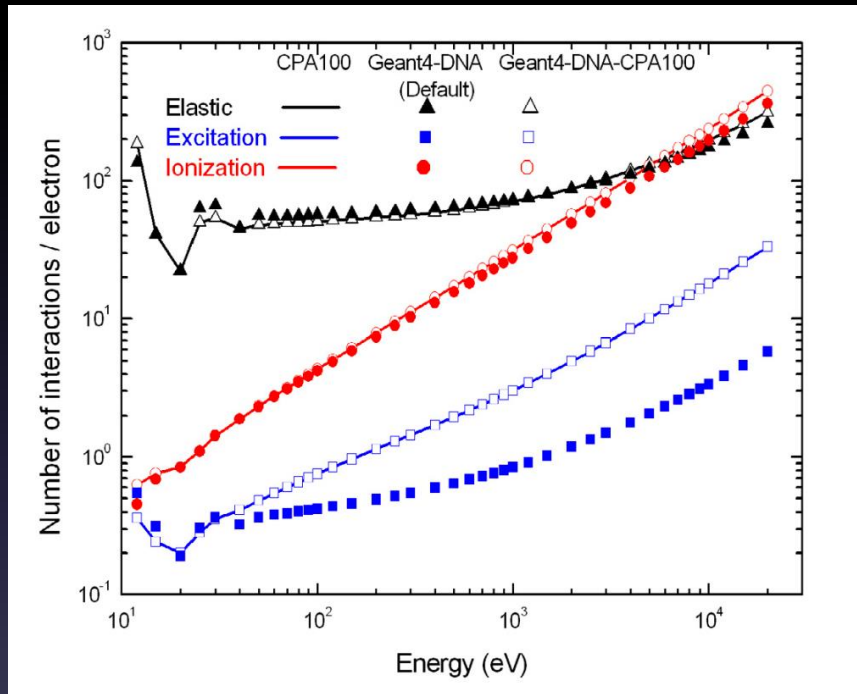


- CPA100 **excitation model** is in better agreement with the only experimental data in the gaseous water by Munoz et al.
- **one order of magnitude**, between the CPA100 model and the Geant4-DNA default model for each excitation state

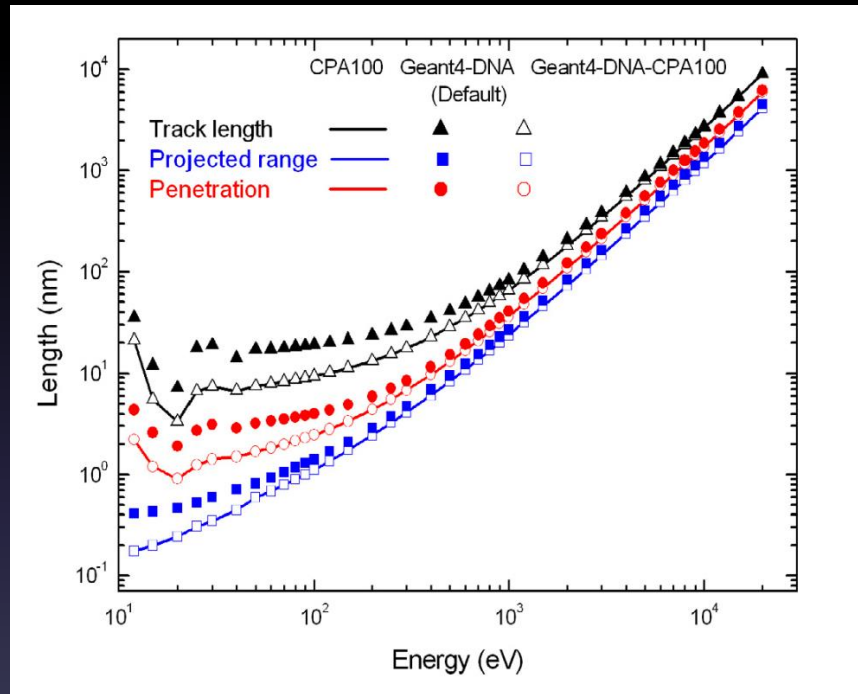
- **good agreement** between **data and CPA100 cross sections**, especially at low ejected kinetic energies (where the differential cross section is the largest).
- **main differences** between Geant4-DNA default model and the experimental data are observed **at ejected electron energy W lower than 10 eV**.

# CPA100 models (2)

## Numbers of interactions



## Track length, penetration & projection range



The main differences appear in the **number of excitations** from 20 keV down to 20 eV, originating from the difference of magnitude between CPA100 and Geant4-DNA default excitation cross sections

- differences between the models are larger when considering **track length**, rather than the number of collisions, especially at low energies (<1 keV) (eg. 50% at 50 eV)
- **electrons lose less energy and consequently travel larger distances** in liquid water when simulated using **Geant4-DNA default models** compared to CPA100 (CPA100 inelastic cross sections are larger)



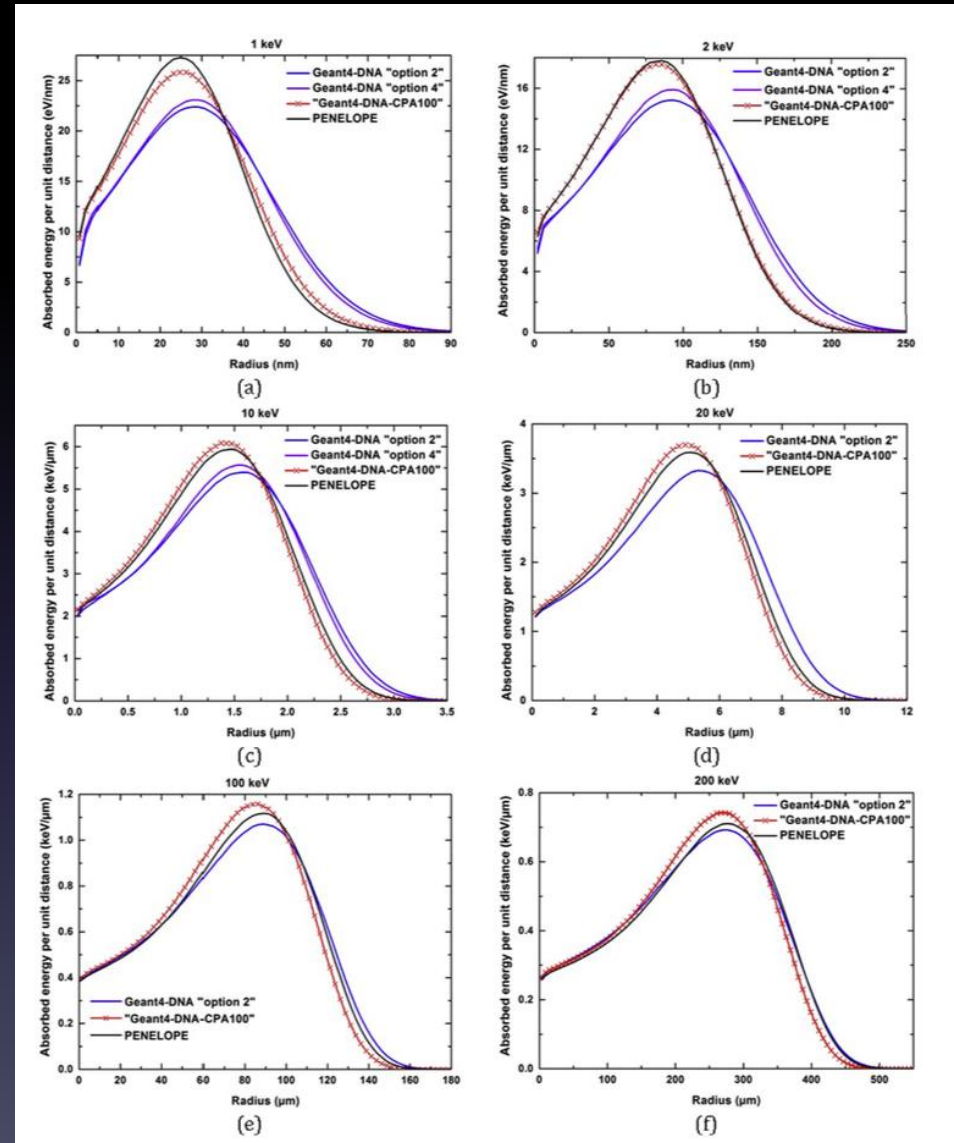
# CPA<sub>100</sub> models (3)

Example of Dose Point Kernel comparison in liquid water between

- Geant4-DNA option 2 (default)
- Geant4-DNA option 4 (Ioannina)
- Geant4-DNA CPA<sub>100</sub> models
- PENELOPE 2011

The comparison with the reference Monte Carlo code **PENELOPE**, set to perform step-by-step simulation, showed **very good agreement**.

For all tested energies, the maximum relative difference between simulated DPK, which occurs for 1 keV electrons, is less than 10 %.



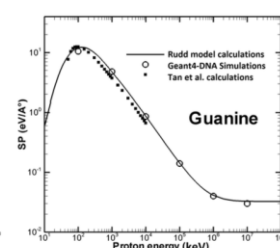
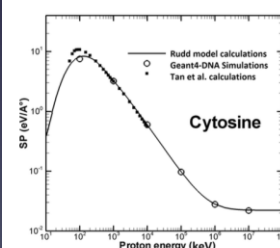
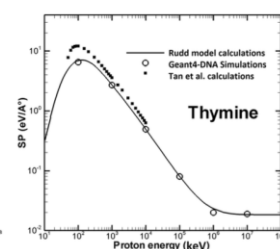
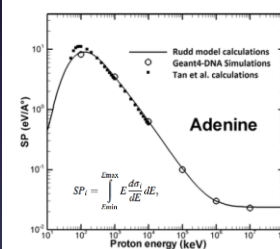
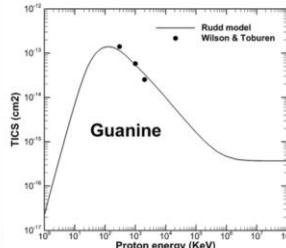
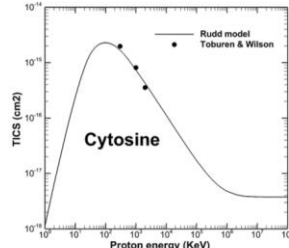
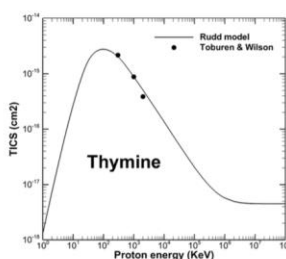
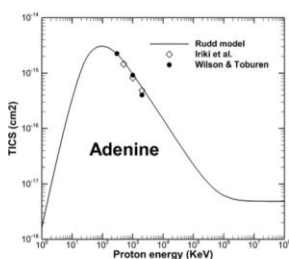
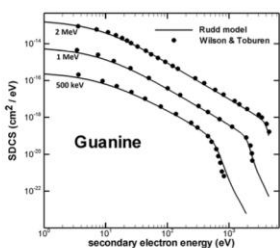
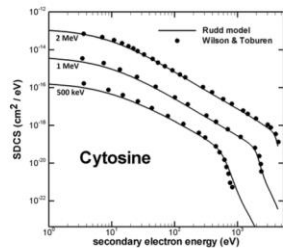
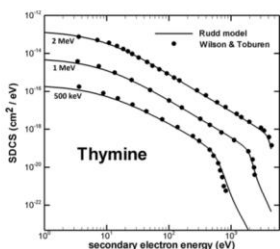
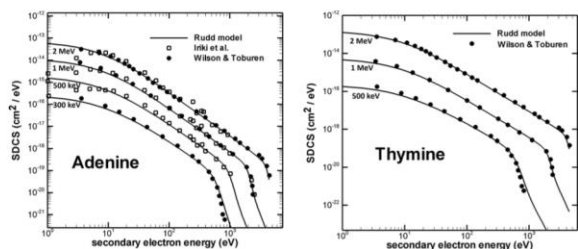
# Other bio-materials (2)

- New model describing **ionisation** of the **four bases of DNA** (adenine, thymine, cytosine and guanine) by **incident protons**, by Z. Francis (St Joseph U., Lebanon)
- large energy coverage: 1 keV –  $10^8$  keV
- based on the **relativistic analytical Rudd approach**, fitted to experimental data
- will be publicly released in the near future

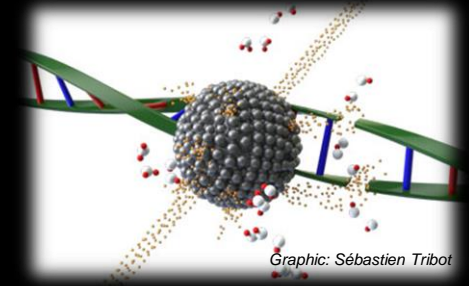
Single **differential** cross section

**Total** cross section

**Stopping power**

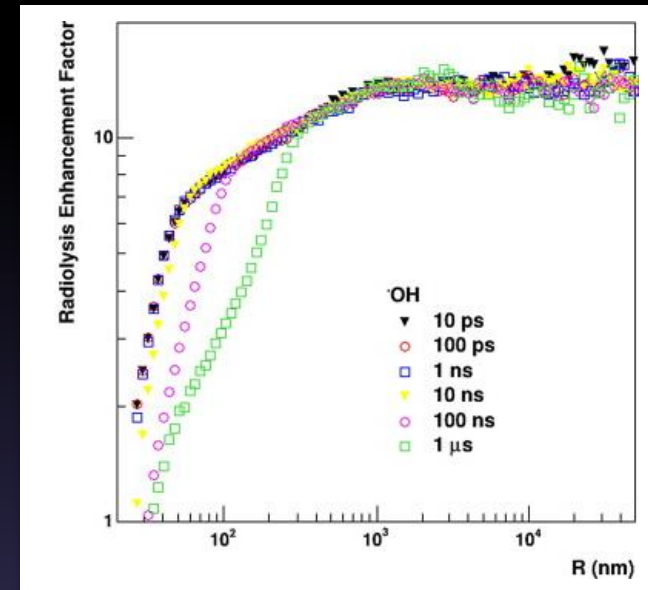


# Investigation of radiotherapy **sensitization** using high-Z nanoparticles



Graphic: Sébastien Tribot

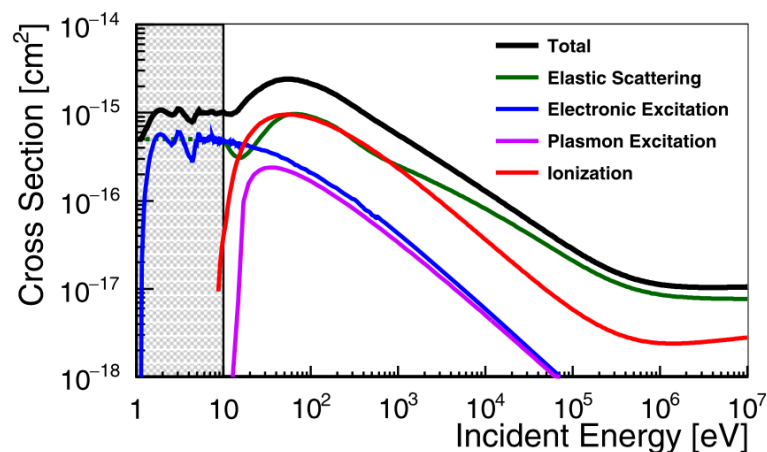
- "Hot" topic: high-Z NP internalized in cells could **boost energy deposition** and increase the efficacy of radiotherapy
- Well established for **photon beams** (photoelectric effect), not so clear for proton beams...
- Still a **challenge** to perform mechanistic simulations
  - We initiated a specific Geant4-DNA activity on the subject in 2015
  - Simulation of physics + physico-chemistry + chemistry around NP (using Livermore for Gold)
  - Eg. **Radiolysis Enhancement Factor** as a function of distance from GNP compared to WNP
  - Underlined the necessity to extend Geant4-DNA models to high-Z metals



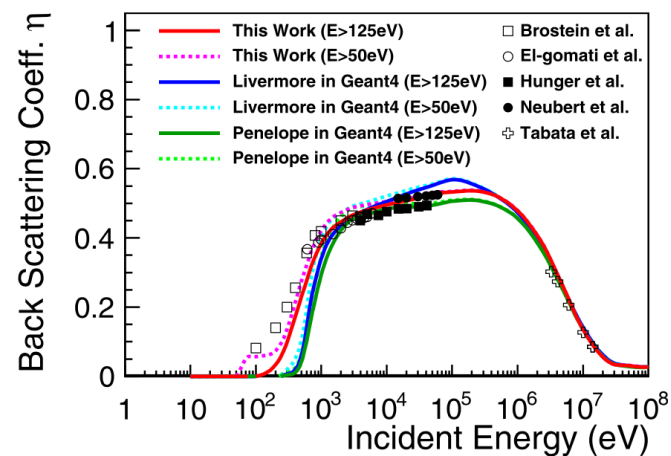
# High-Z materials : gold

- Extension of Geant4-DNA for the modelling of **radiosensitization** from **gold nanoparticles**
- Activity initiated in 2016 by **D. Sakata (Bordeaux U., France)**
- Discrete processes for electrons: **elastic** (ELSEPA), **ionization** (modified RBEBV), **electronic** (4 channels) and **bulk plasmon** (Quinn's) **excitation**
- Models will be delivered in the near future (probably 2018) - **See D. Sakata's talk (Friday)**

Integral **cross sections** for electrons

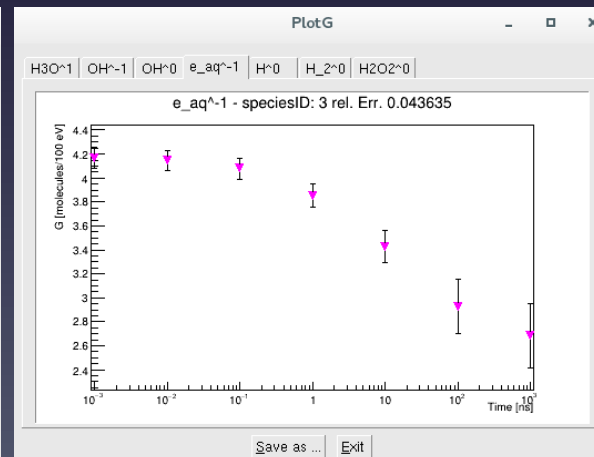
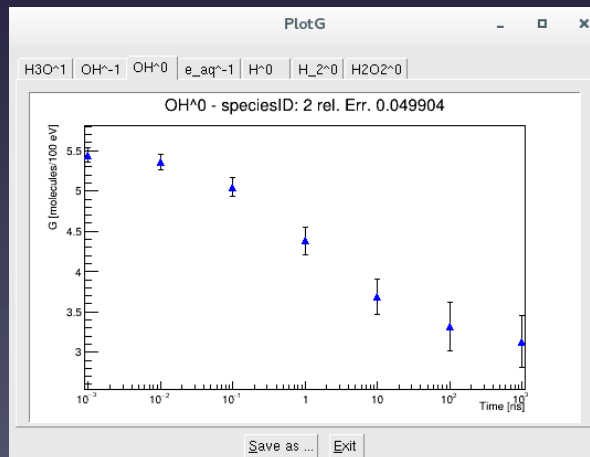


Eg. of validation (5 cm gold plate)



# Simulation of G-values

- A new extended example is provided: "chem4", my P. Piersimoni and M. Karamitros
- Hypotheses
  - infinite volume: the energy lost by the primary equals the deposited energy since all secondary particles slow down to thermal energy
  - two thresholds
    - The primary is killed once it has deposited more energy than a selectable minimum threshold,  $T_1$
    - When the primary particle loses more energy in few interaction steps than a maximum allowed threshold,  $T_2$ , the event is aborted
    - this allows to calculate G-values on the deposited energy range  $[T_1, T_2]$
    - can be set using UI commands :
      - `/primaryKiller/eLossMin 1 keV # primary is killed if deposited E is greater than this value`
      - `/primaryKiller/eLossMax 2 keV # event is aborted if deposited E is greater than this value`
- Can run in MT mode
- Results are stored in ROOT format and can be visualised using a dedicated ROOT interface (plotG)



Eg. : species by 10 incident electrons of 100 keV (beam.in)

# Perspectives

- **PHYSICS**

- Inclusion of alternative or improved **cross section models** for **electrons and ions**
  - Liquid water + DNA-like materials + gas materials for nanodosimeters + metals

- **PHYSICO-CHEMISTRY/CHEMISTRY**

- **Alternative approach** for the simulation of radiolysis
- **Combination of geometry & chemistry** : two approaches
  - Granular approach
  - Composite material & voxelized approach
- Addition of **scavenger species and reactions**

- **BIOLOGY**

- Multi-scale **geometrical models** of biological targets, including « **deformable** » geometries
- Prediction of **direct and non-direct** DNA simple & complex damages in **plasmids** and **realistic cells**
- **Time** evolution of damage: repair processes for the simulation of late damage

- **COMPUTING ACCELERATION: GPU FOR CHEMISTRY**

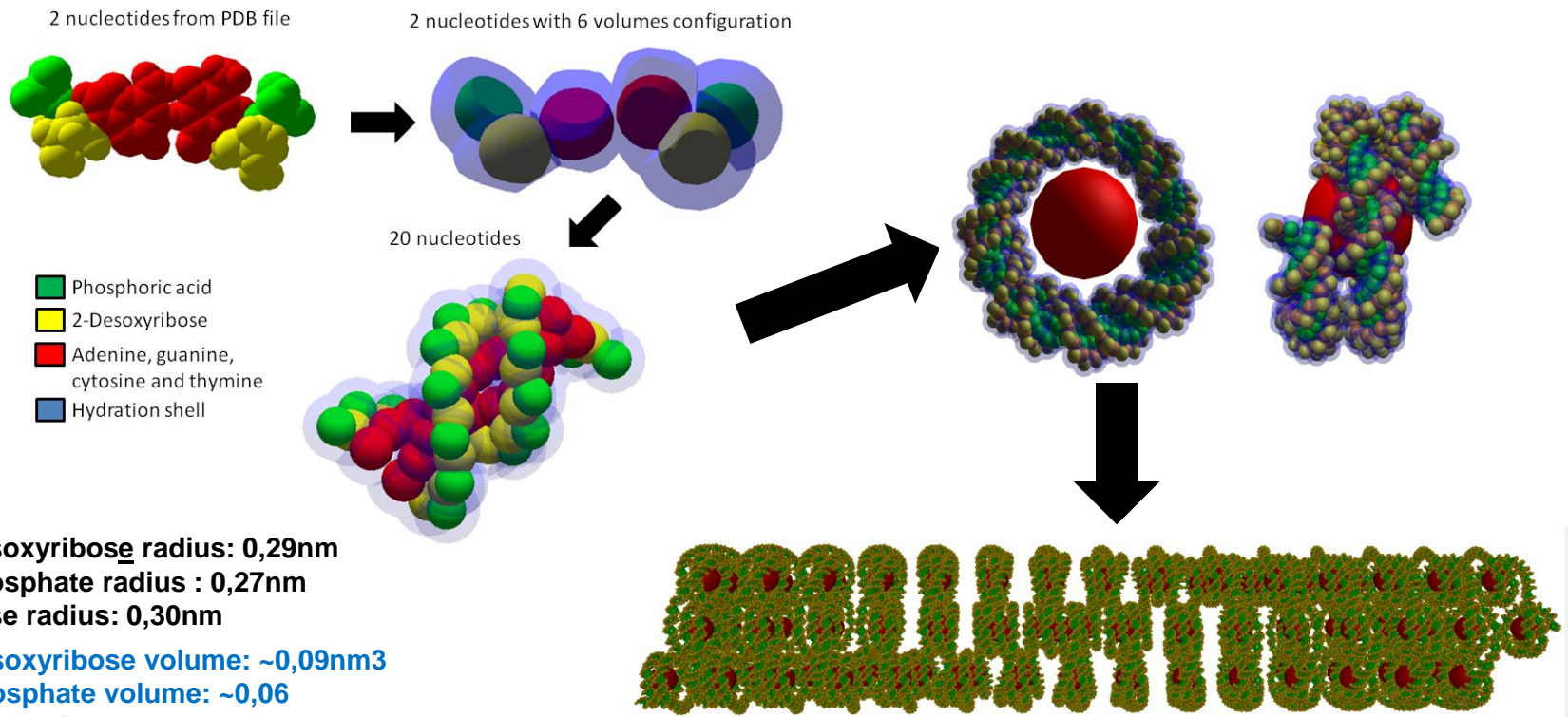
- **VERIFICATION (WITH OTHER CODES) AND VALIDATION (WITH EXPERIMENTAL DATA)**

All these developments take time – once published, they are delivered publicly in Geant4

# DNA geometrical model used in the simulation

DNA target geometry : Molecular **description of the DNA target** to simulate the physical and chemical interaction between the radical species and the DNA.

*S. Meylan PhD work, IRSN*

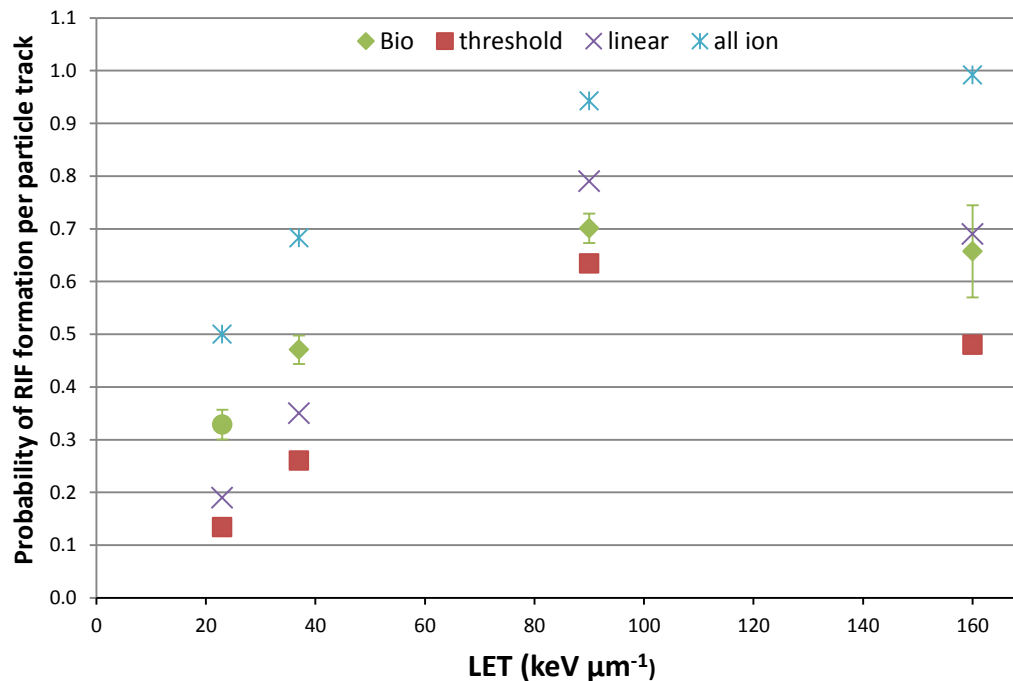
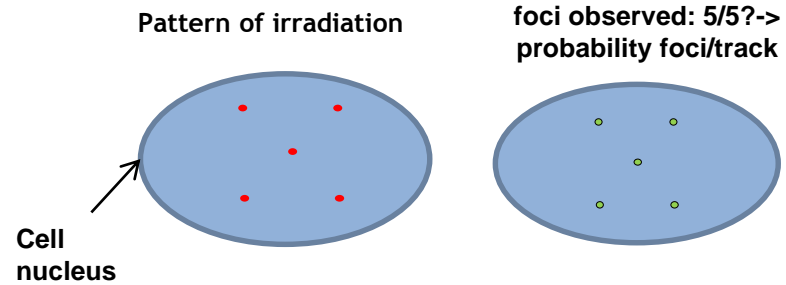


We take into account the hydration shell ( $\Gamma = 12$ ) by using a water envelop.

# Comparison between experimental results and simulation

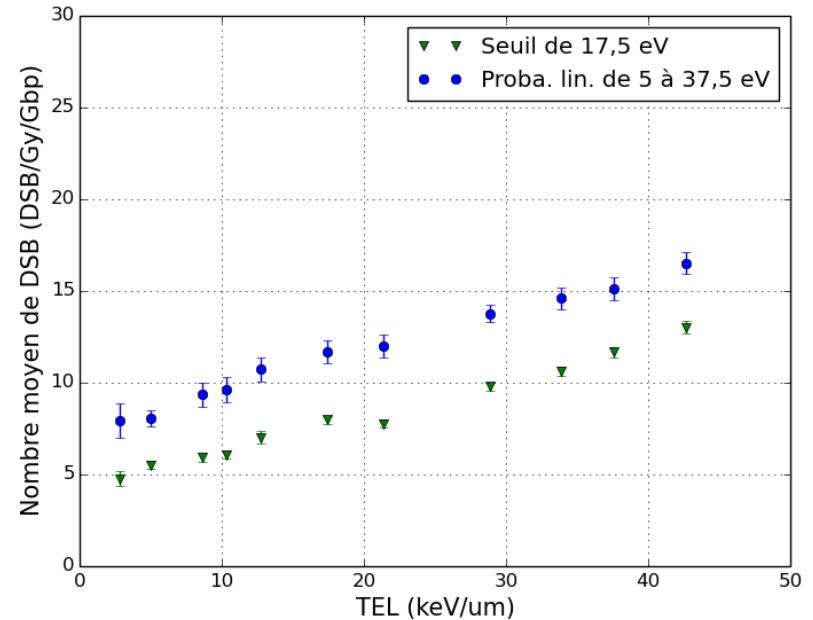
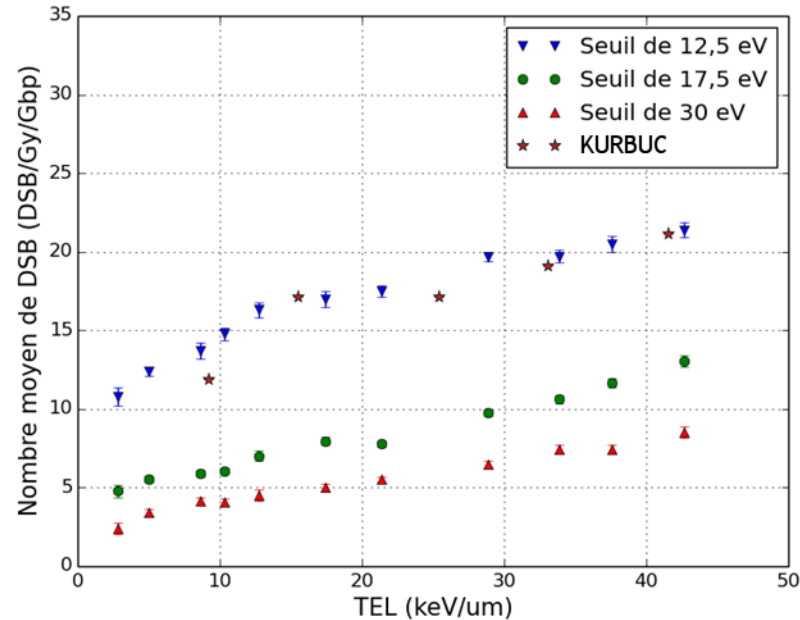
$\alpha$ 8 MeV (160 keV/ $\mu$ m)	$p$ 3 MeV (23 keV/ $\mu$ m)
$\alpha$ 20 MeV (37 keV/ $\mu$ m)	$\alpha$ 10 MeV (90 keV/ $\mu$ m)

**Simulation:** At least 1 DSB compared to Foci probability





## IV.2) Variation du critère de sélections



- Bon accord avec KURBUC lorsque le seuil de 12,5 eV est utilisé
- Critère de sélection ++
- Cassures directes ++