IRSN
INSTITUT
DE RADIOPROTECTION
ET DE SÛRETÉ NUCLÉAIRE

New physics processes dedicated to **nanometric** scale track structure in the Geant4 toolkit

On behalf of the Geant4-DNA collaboration

And the Low Energy group

Ziad FRANCIS IRSN/SDE

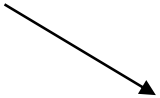
Institut de Radioprotection et de Sureté Nucléaire, Fontenay-aux-Roses FRANCE.

ROSIRIS : RadiobiOlogie des Systèmes Integrés pour l'optimisation des traitements utilisant des rayonnements ionisants et évaluation du RISque associé

IRSN-Inserm collaboration.

Objective: Develop and study irradiation related models revealing the different biological effects resulting from different radiation types.

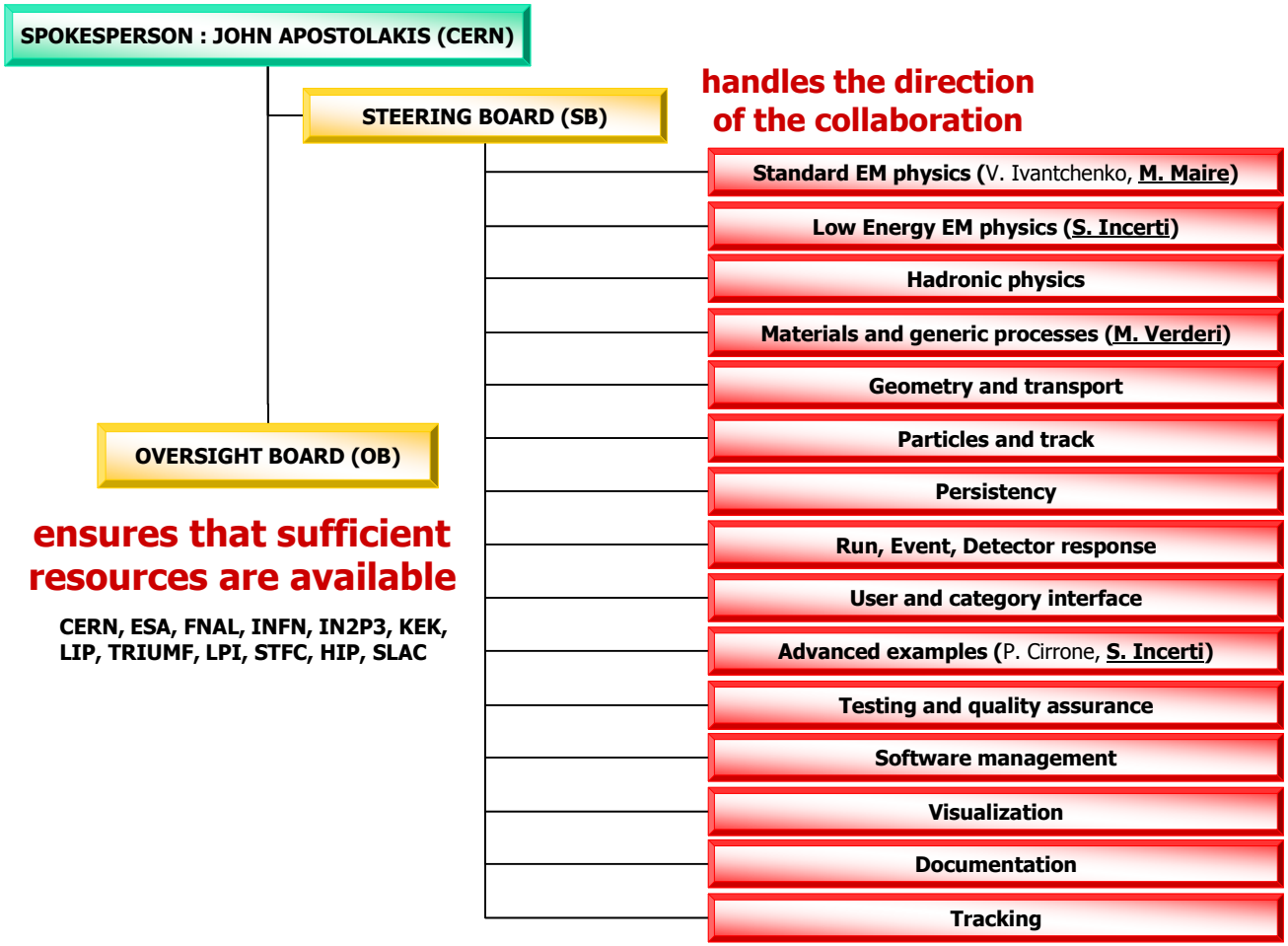
Many interest points and activities (biological experiments on DNA damage, repair Focis, Radiotherapy purposes…)



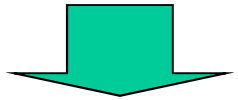
Particle track structure simulation is a common interest start

86 members

The Geant4 collaboration



• On the molecular scale we need a detailed step by step track structure simulation



Monte-Carlo codes (Partrac, Triol, PITS, KURBUC, OREC, NOREC, …)

Physical, physio-chemical and chemical phase. Even REPAIR models (PARTRAC)

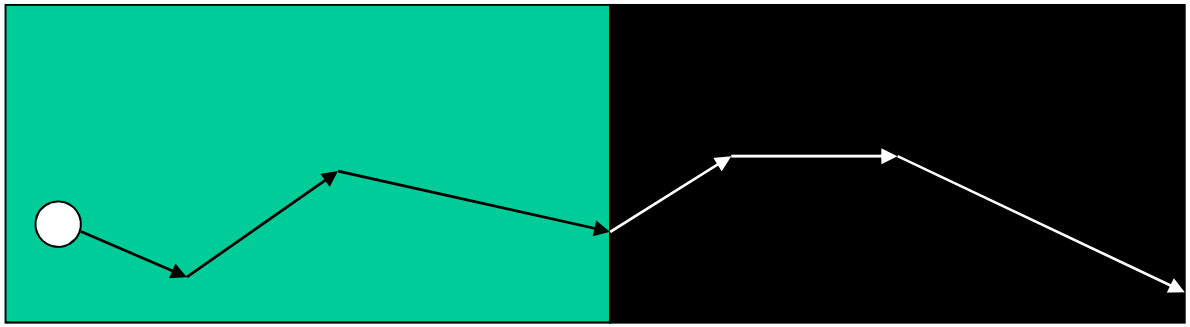
Accessible General purpose tools?

To expand **accessibility** and avoid **« reinventing the wheel »**, track structure codes should be made available to all users via the internet from a central data bank. *H. Nikjoo in his paper Int. J. Rad. Bio. 1998*

• **GEANT4** offers an exceptional flexibility for users, presenting a common platform which is totally accessible and opened for development.
• The user can access the source code « easily » can make modifications to adapt the tool for his own application.

Geant4-DNA

The Step



$$\sigma(Z,E,T_{cut}) = \int_{T_{threshold}}^{T\,\max} \frac{d\sigma(Z,E,T)}{dT}\,dT$$

Calculus time decreases if $T_{Threshold}$ increases

$$\sigma(Z,E,T_{\min}) = \int_{T\,\min}^{T\,\max} \frac{d\sigma(Z,E,T)}{dT}\,dT$$

Microdosimetry

On the molecular scale **all possible interactions** need to be taken into account

Physics processes summary

Particle	process	Model	validity
Electrons	Ionisation	Born (with corrections)	12.61 eV - 35keV (1 MeV)
	Elastic scattering	Rutherford & Champion	0 eV - 10 MeV
	Excitation	Emfietzoglou	8.23 eV - 10 MeV
Protons	Excitation	Miller & Green	8 eV - 500 keV
		Born	500 keV - 16 MeV (100 MeV)
	Ionisation	Rudd	100 eV - 500 keV
		Born	500 keV - 16 MeV (100 MeV)
	Charge transfer	Dingfelder	100 eV - 10 MeV

Particle	process	Model	validity
Hydrogen	Ionisation	Rudd	100 eV - 100 MeV
	Charge transfer (Stripping)	Dingfelder	100 eV - 10 MeV
Alpha+	Excitation	Miller & Green	1 keV - 10 MeV
&	Ionisation	Rudd	1 keV - 10 MeV
Helium	Charge transfer (decrease and increase)	Dingfelder	1 keV - 10 MeV
Alpha++	Excitation	Miller & Green	1 keV - 10 MeV
	Ionisation	Rudd	1 keV - 10 MeV
	Charge transfer (decrease)	Dingfelder	1 keV - 10 MeV

* See Thesis of Ziad FRANCIS for calculation details (**http://cdsweb.cern.ch/record/1100426/files/cer-002754058.pdf**

The First Born Approximation
Inelastic Cross sections

The doubly differential cross section for inelastic collisions:

$$\frac{d^2\Sigma}{dE.dK} = \frac{1}{\pi.a_0.T}\frac{1}{K}\eta_2(E,K)$$

Energy transfer

Momentum transfer

$$T = \frac{m_{e-}}{M}\tau$$

Dielectric response function or the Bethe term

Kinetic energy of incident particle

M incident particle mass

Energy differential cross section:

$$\frac{d\Sigma}{dE} = \int_{k\,\min}^{k\,\max} \frac{d^2\Sigma}{dE.dK}\frac{dK}{K}$$

$$K_{\min} = \frac{\sqrt{2M}}{\hbar}(\sqrt{\tau} - \sqrt{\tau - E})$$

$$K_{\max} = \frac{\sqrt{2M}}{\hbar}(\sqrt{\tau} + \sqrt{\tau - E})$$

Total cross section:

$$\Sigma = \int_{0}^{E\,\max} \int_{K\,\min}^{K\,\max} \frac{d^2\Sigma}{dE.dK}\frac{dK}{K}dE$$

Linear energy transfer (1st momentum):

$$\frac{dE}{dX} = \int_{0}^{E\,\max} E\frac{d\Sigma}{dE}dE$$

Straggling (2nd momentum):

$$S = \int_{0}^{E\,\max} E^2\frac{d\Sigma}{dE}dE$$

Bethe surface for liquid water

$$\frac{d^2\Sigma}{dE.dK} = \frac{1}{\pi.a_0.T}\frac{1}{K}\eta_2(E,K)$$

$$\eta_2(E,K) = \mathrm{Im}\left[-\frac{1}{\varepsilon(E,K)}\right]$$

Exp data *Hayashi et al. (J. Chem. Phys. 108 - 2001) AND Heller et al.*

(J. Chem. Phys. 60 – 1974)

$$\mathrm{Im}\left[\frac{-1}{\varepsilon(E,q)}\right] = \frac{\pi}{2}\frac{E_p^2}{(q^2/2m)}\frac{1}{Z}\sum_f \left|\left\langle f\left|\sum_{j=1}^{Z}\exp(iqr_j/\hbar)\right|i\right\rangle\right|^2$$

5 discrete states (corresponding to electronic excitation of water molecule)
→ fit using experimental data and « Drude » equations

$$\varepsilon_{2,Exc}(E,0) = E_P^2\sum_j^{exc} f_j \frac{2(\gamma_j E)^3}{[(E_j^2-E^2)^2+(\gamma_j E)^2]^2}$$

$$\varepsilon_{1,Exc}(E,0) = 1+E_P^2\sum_j^{exc} f_j \frac{(E_j^2-E^2)[(E_j^2-E^2)^2+3(\gamma_j E)^2]}{[(E_j^2-E^2)^2+(\gamma_j E)^2]^2}$$

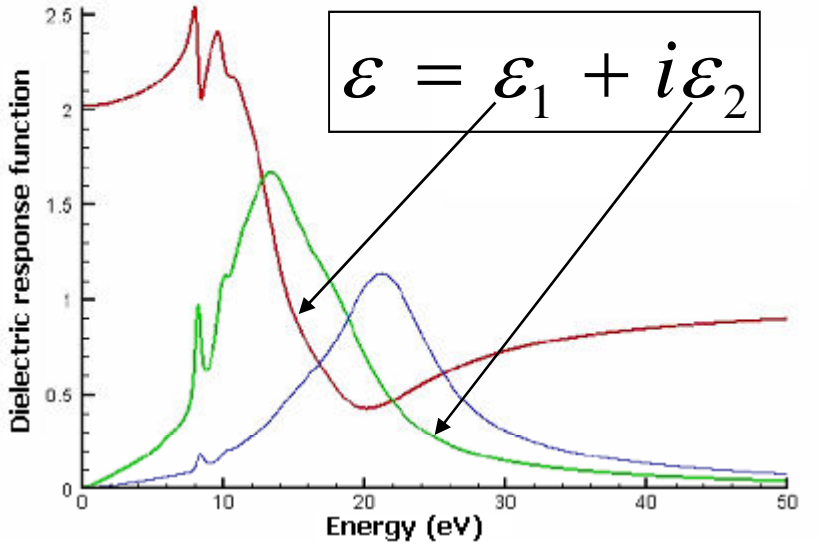
$$E_p = \hbar\sqrt{\frac{4\pi Ne^2}{m}} = 28.816\cdot(\rho\frac{Z}{A})^{1/2}$$

$$\varepsilon_{2,Ioni}(E,0) = E_P^2\sum_j^{Ioni} f_j \frac{\gamma_j E}{(E_j^2-E^2)^2+(\gamma_j E)^2}$$

$$\varepsilon_{1,Ioni}(E,0) = 1+E_P^2\sum_j^{Ioni} f_j \frac{E_j^2-E^2}{(E_j^2-E^2)^2+(\gamma_j E)^2}$$

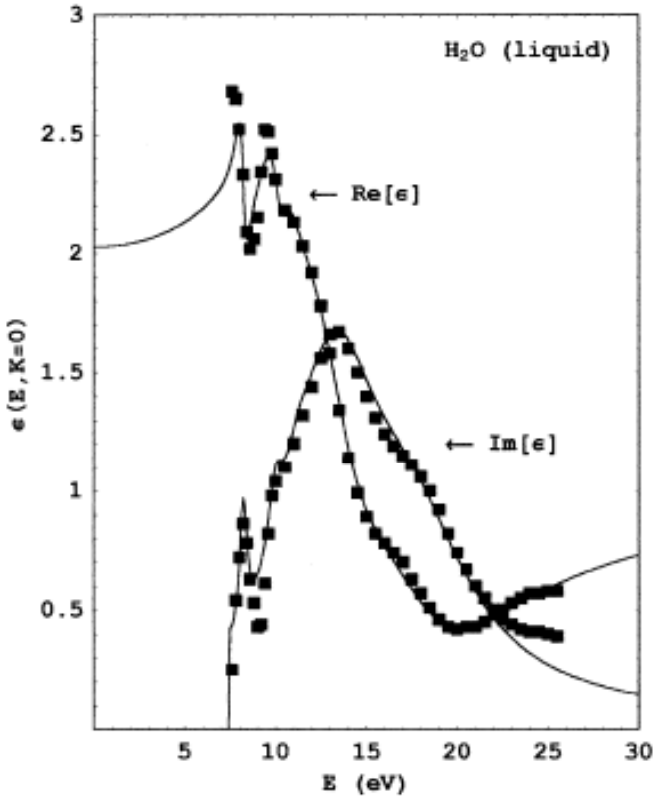
5 continuum states (ionisation)

Bethe surface for liquid water



Real part and Imaginary part of the DRF for water on the optical limit **K = 0** Vs energy transfer

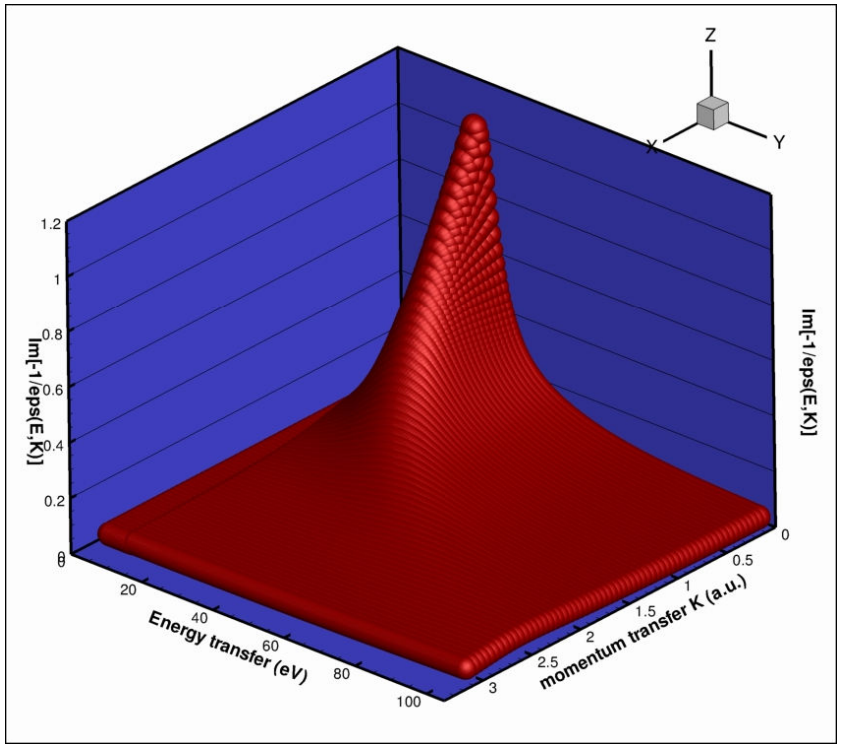
K = 0 (No momentum transfer)



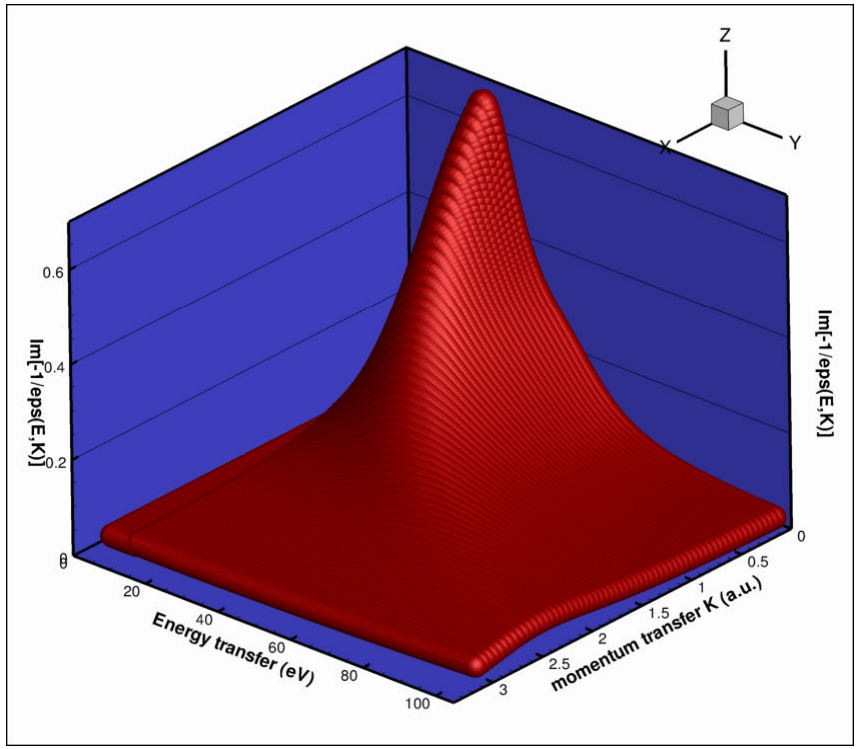
from D. Emfietzoglou (NIMB 193 2002 71-78) compared to data from Heller et al. (J. Chem. Phys. 60 - 1974)

Bethe surface for liquid water

By applying the dispersion schemes proposed by D. Emfietzoglou (NIMB 256 2007 141-147) for **K > 0**

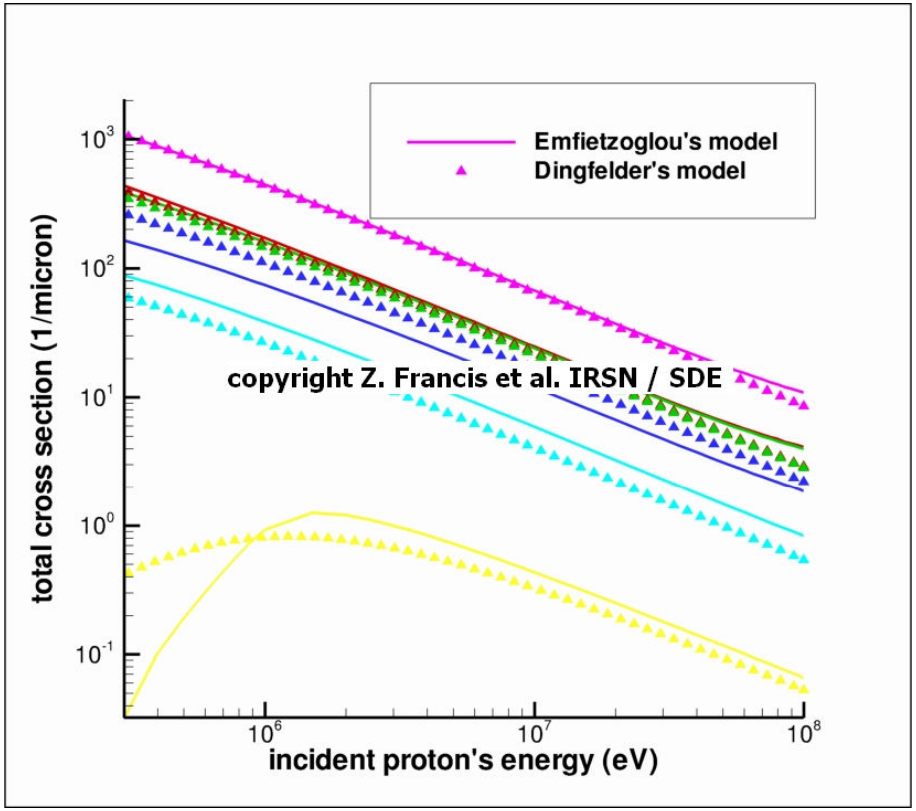


Bethe surface using data from de Heller et al. *(J. Chem. Phys. 60 – 1974)*



Bethe surface based on data from Hayashi et al. *(J. Chem. Phys. 108 - 2001)*

Inelastic protons cross sections comparison



Protons cross sections in liquid water obtained according to models described by M. Dingfelder (PARTRAC) and

D. Emfietzoglou (OREC)

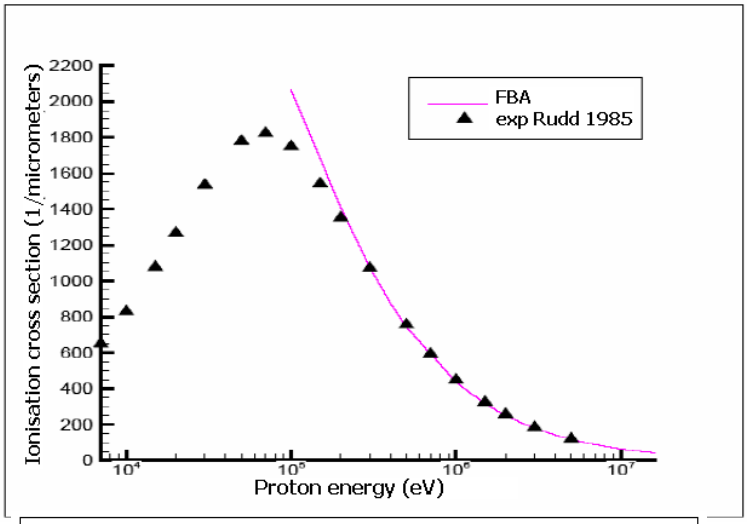
- K-shell ionisation → hydrogen model of the generalized oscillator strength

(M. Dingfelder et al. Rad. Phys. and Chem. 59 – 2000)

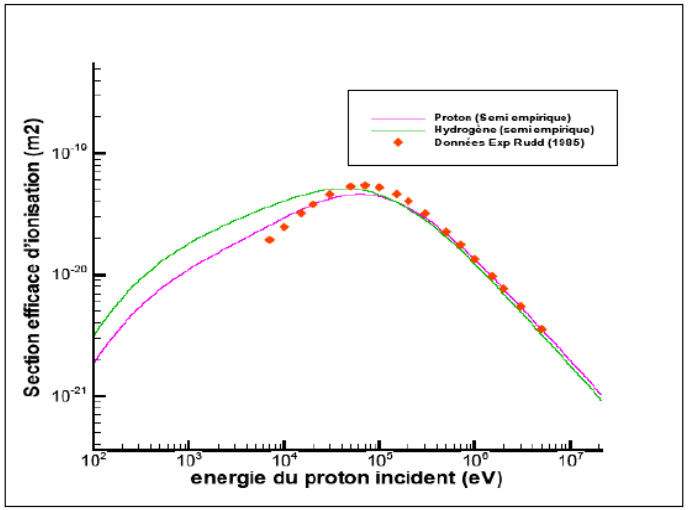
Cross sections in Geant4 are actually available up to 16 MeV, higher energies Will be available in December 2009 release

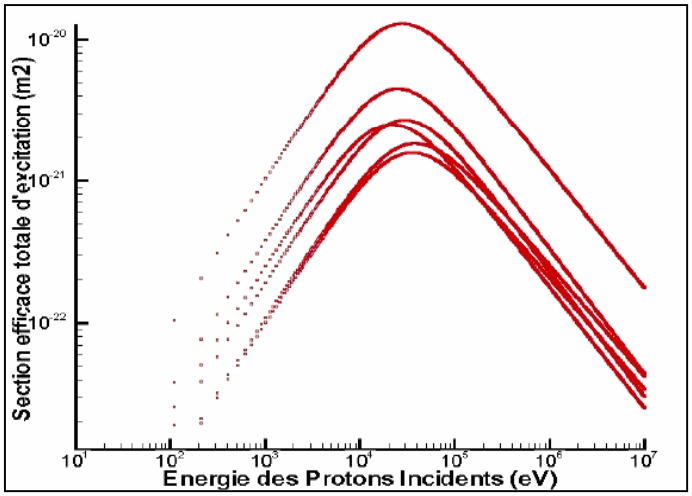
FBA Fails for low incident energies

Born approximation works only for protons above a certain energy threshold **~300 keV**



Ionisation cross section (FBA) compared to experimental data of *Rudd et al. (Phys. Rev. A 31 – 1985)*



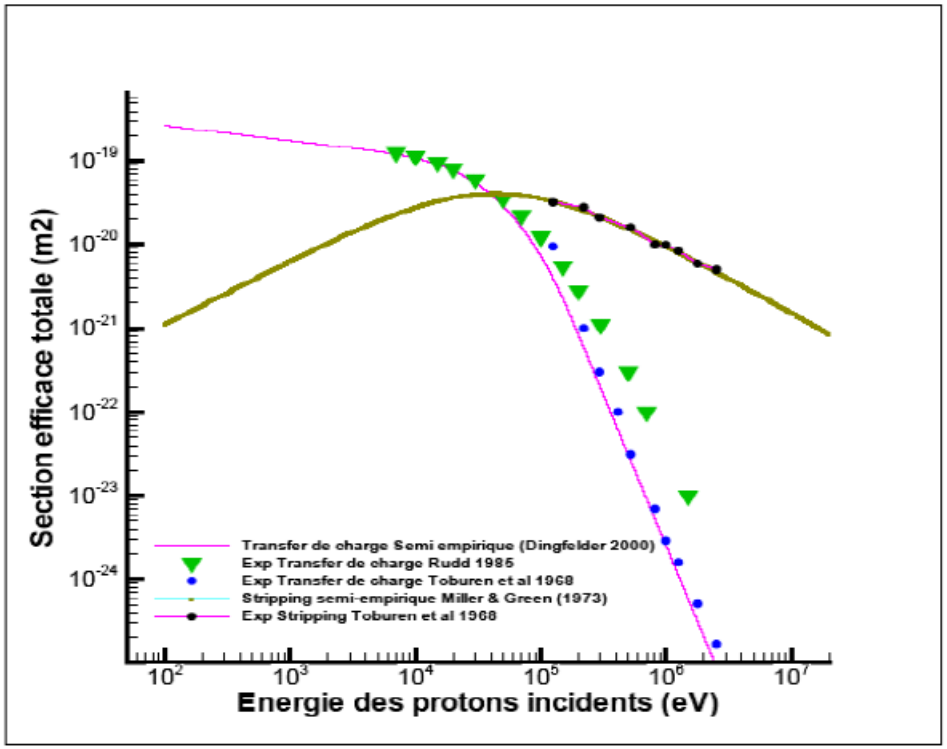


Excitation Miller & Green

Ionisation Rudd (Rev. Mod. Phys. 64 - 1992) between 100 eV – 300 keV

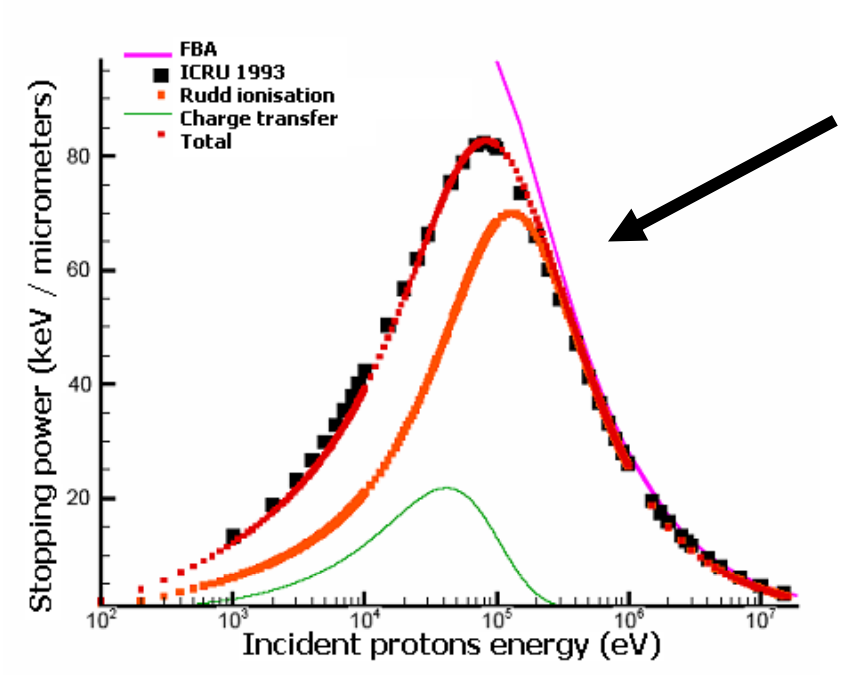
Charge transfer (protons)

- Incident protons can capture an electron and become a neutral hydrogen atom
- The hydrogen atom can undergo ionisation processes in water and can also lose his boundary electron to become a proton again (« Stripping process »)
- Excitations by hydrogen can be safely neglected

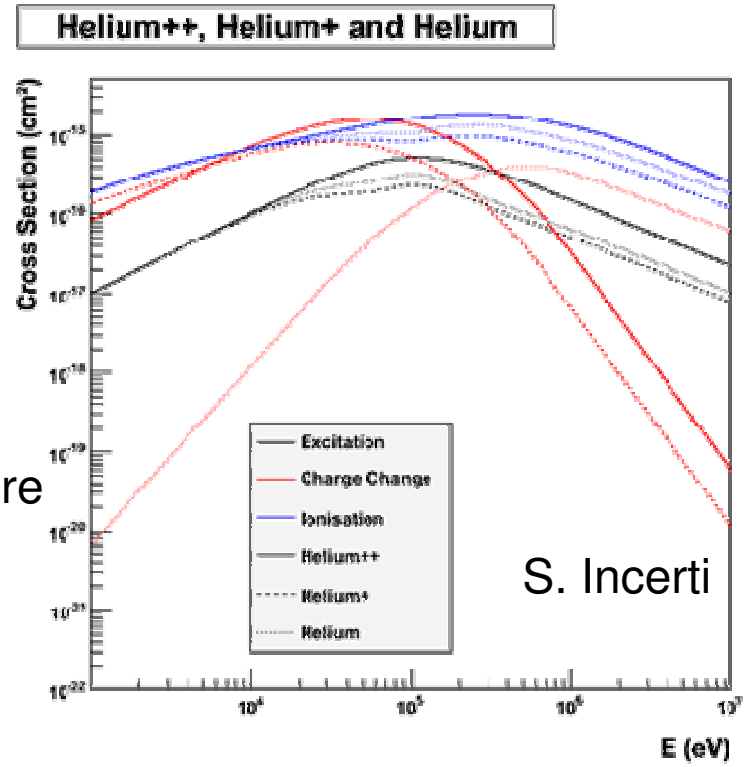


Charge transfer cross sections compared to some experimental data of Toburen and Rudd

Stripping cross section compared to data from Toburen et al.



Protons total stopping power (Dingfelder model set) compared to ICRU data



For Alpha particles a speed scaling procedure is used for protons cross sections:

$$\frac{d\sigma_{ion}}{dE.dq}(v) = Z_{eff}^2(E)\frac{d\sigma_{protons}}{dE.dq}d(v)$$

Zeff is the effective charge, it depends on energy transfer and also on incident particle velocity.

Electrons high impact energies, relativistic approach

$$\Sigma_j = \Sigma_j^L + \Sigma_j^T$$

$$\Sigma_j^L = \frac{2}{\pi \alpha_0 \beta^2(T) mc^2} \left\{ \int_{E\min}^{E\max} dE \int_{k\min}^{k\max} \mathrm{Im}\left[-\frac{1}{\varepsilon(E,K)} \right]_j \frac{dK}{K} \right\}$$

longitudinal Interactions

$$\Sigma_j^T = \frac{1}{\pi \alpha_0 \beta^2(T) mc^2} \left\{ \int_{E\min}^{E\max} \mathrm{Im}\left[-\frac{1}{\varepsilon(E,0)} \right]_j dE \right\} \times \left[\ln\left(\frac{1}{1-\beta^2(T)} \right) - \beta^2(T) \right]$$

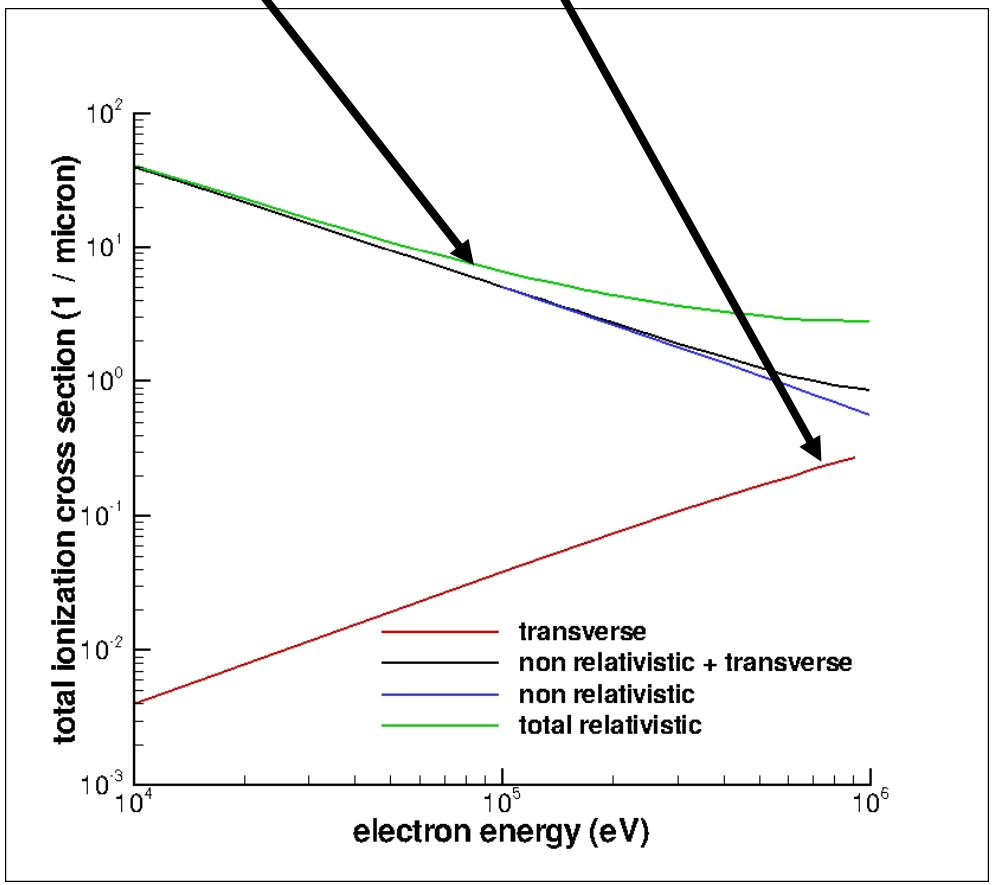
Transverse Interactions

(C. Bousis et al. 2008)

Not available in Geant4 yet … will be in December 2009 release

Electrons relativistic cross section

$$\Sigma_j = \Sigma_j^L + \Sigma_j^T$$



Total ionisation cross section for relativistic e- in water

Low energy electrons cross section in water

Dielectric formalism (FBA) used for inelastic collisions

Born approximation becomes inapplicable at very low energies (~ 1 keV) !!!

Several corrections are proposed:

- Coulomb field correction by Vriens (Phys. Rev. 141 - 1966)
- Ashley correction (phys. Rev. B5 – 1972)
- D. Emfietzoglou (Rad. Prot. Dos. 99 – 2002)
- M. Dingfelder (adjusted to data on water vapor) (Rad. Phys. Chem. 53 - 1998)

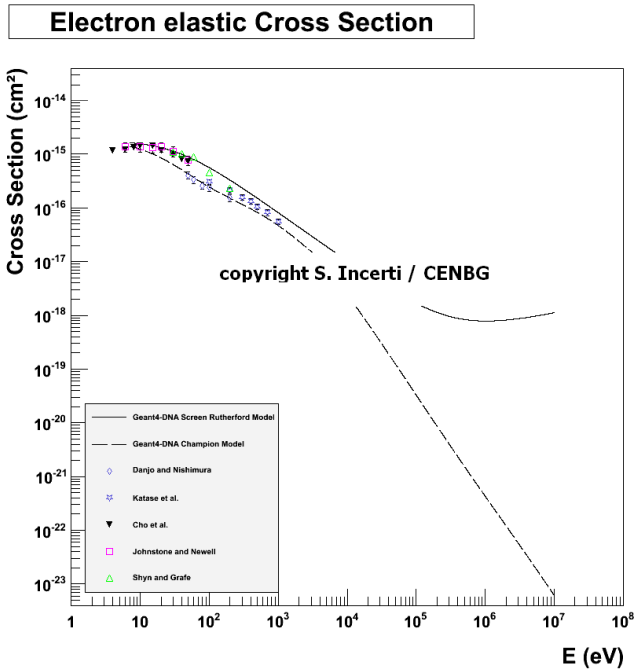
Exchange cross section term taken into account, (Phys. Med. Biol. 48 - 2003):

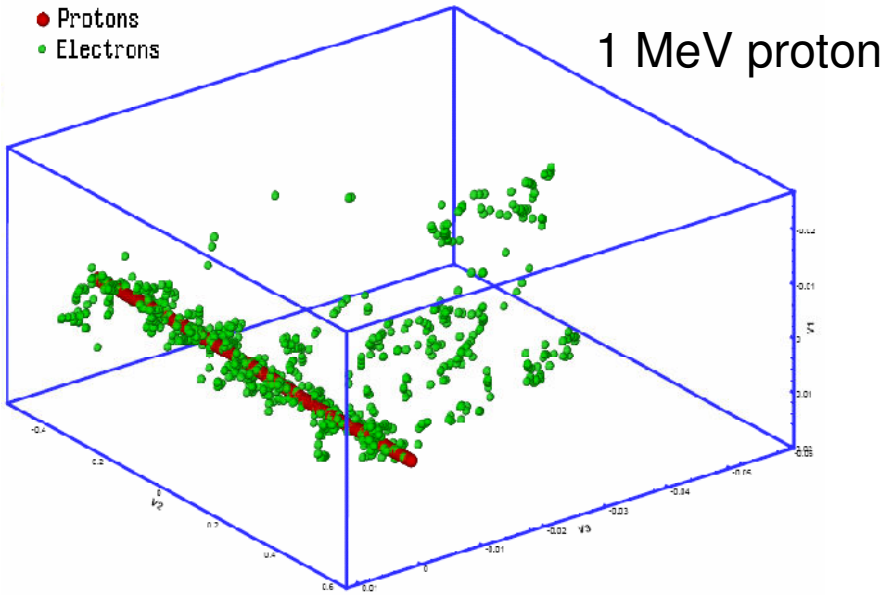
$$\frac{d\Sigma_{ech}^{(j)}(W,T)}{dW} = \frac{d\Sigma^{(j)}(T-W-E_j,T)}{dW} - \left[\frac{d\Sigma^{(j)}(W,T)}{dW} \times \frac{d\Sigma^{(j)}(T-W-E_j,T)}{dW}\right]^{1/2}$$

Electrons elastic scattering

2 different models → 2 different choices:

- Screened Rutherford model
- Champion et al. model (Geant4 collaboration member)





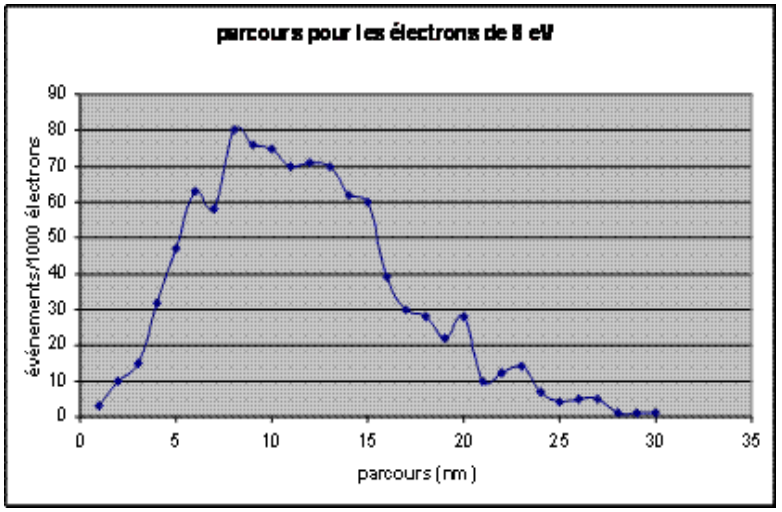
In conclusion we are able to follow:

In WATER !!!

Electrons 8.23 eV - 1 MeV Protons 100 eV - 100 MeV Alpha 1 keV - 10 MeV

In water using the GEANT4DNA package **FOR MICRODOSIMETRY**

- Preliminary results for Sub-excitation electrons thermalization
- e- can be followed down to **0.025 eV** using "Michaud & Sanche" cross sections (in progress, it works on **local home made** G4 version, not available for public yet)

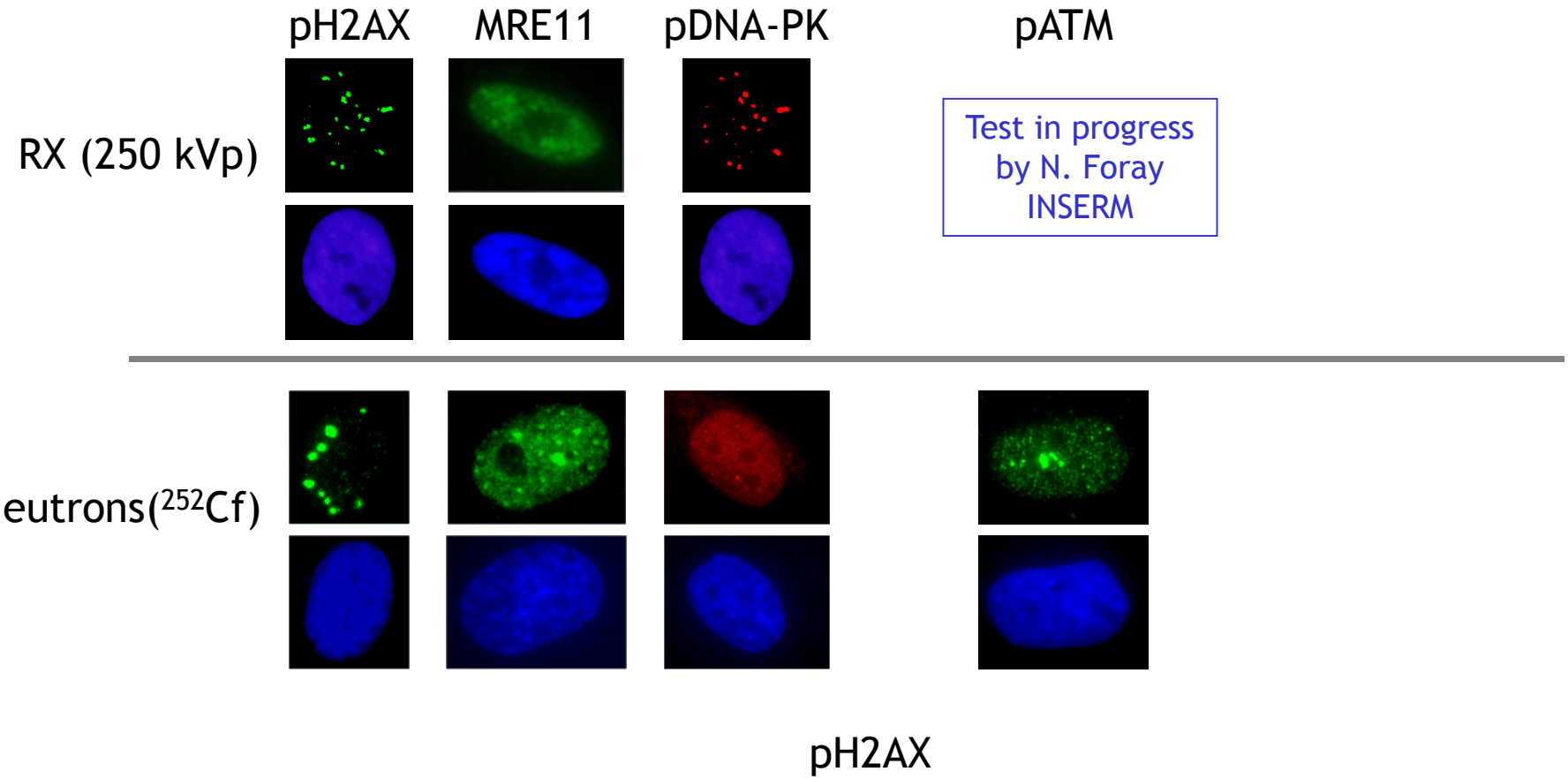


- **Part of G4DNA (< 35 kev for electrons, < 15 MeV for protons) cross section tables already available in the actual GEANT4 releases.**
- **The whole energy range tables will be available in the release of December 2009**

- **first time that a general-purpose Monte Carlo simulation toolkit is equipped with open functionality for radiobiology on the molecular level**

Available experiments and Cell damage Applications

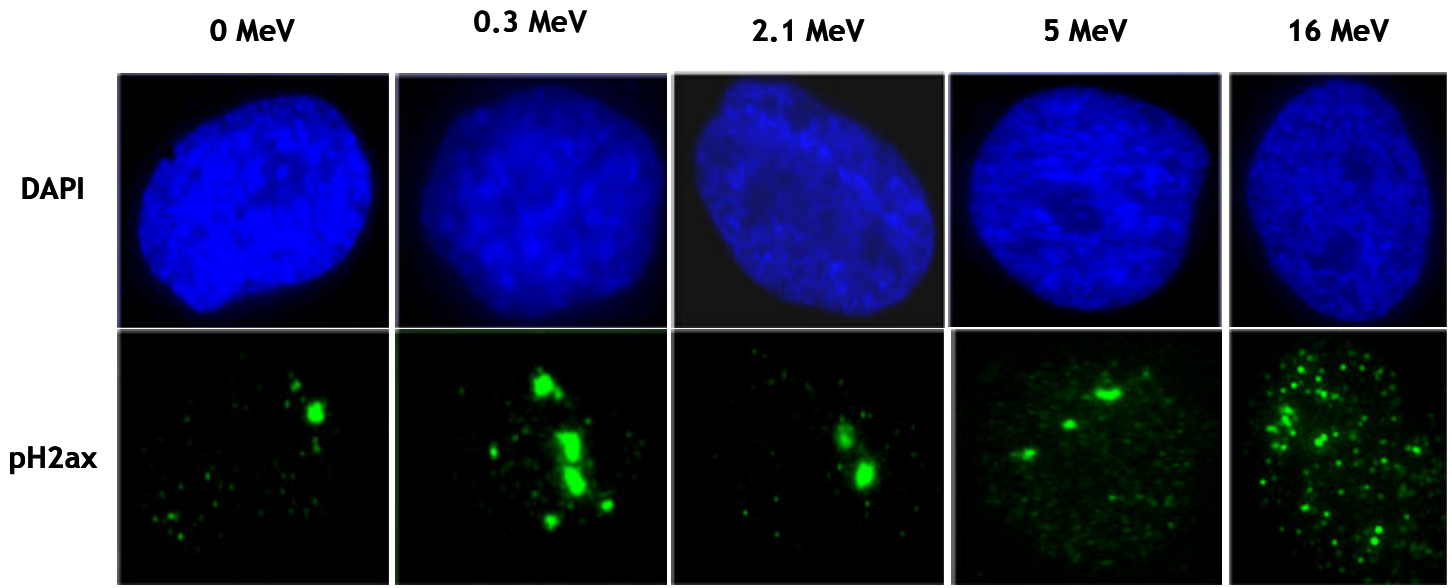
Different markers were tested at IRSN for XRays and neutrons



A. Joubert, et N. Foray. DNA double-strand break repair in syndromes associated with acute radiation response: a balance between DNA-PK- and MRE11-dependent pathways. *IJRB* (2008).

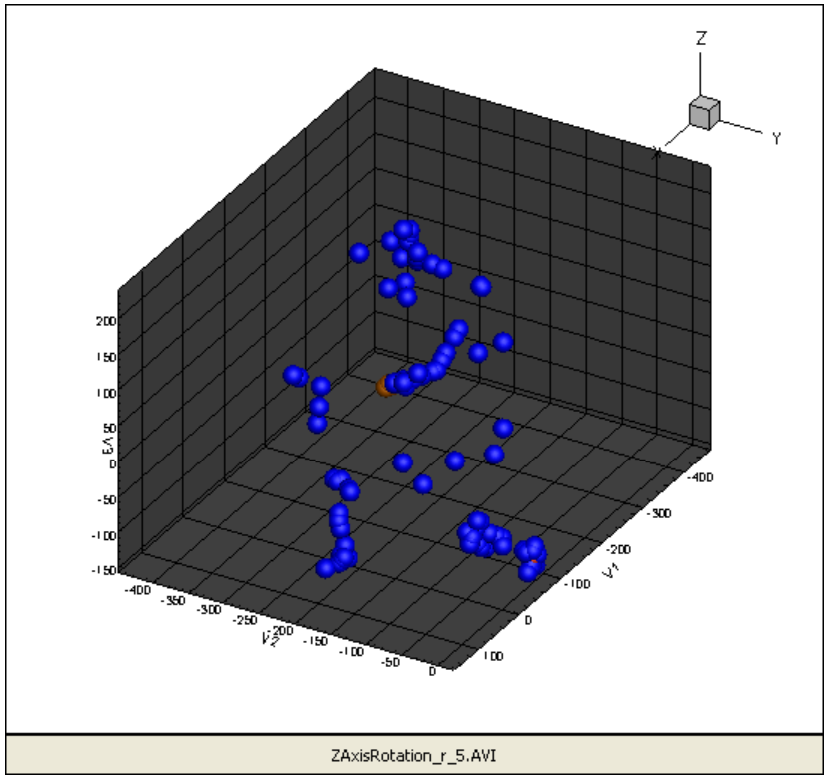
Spatial distribution depends on neutrons energy

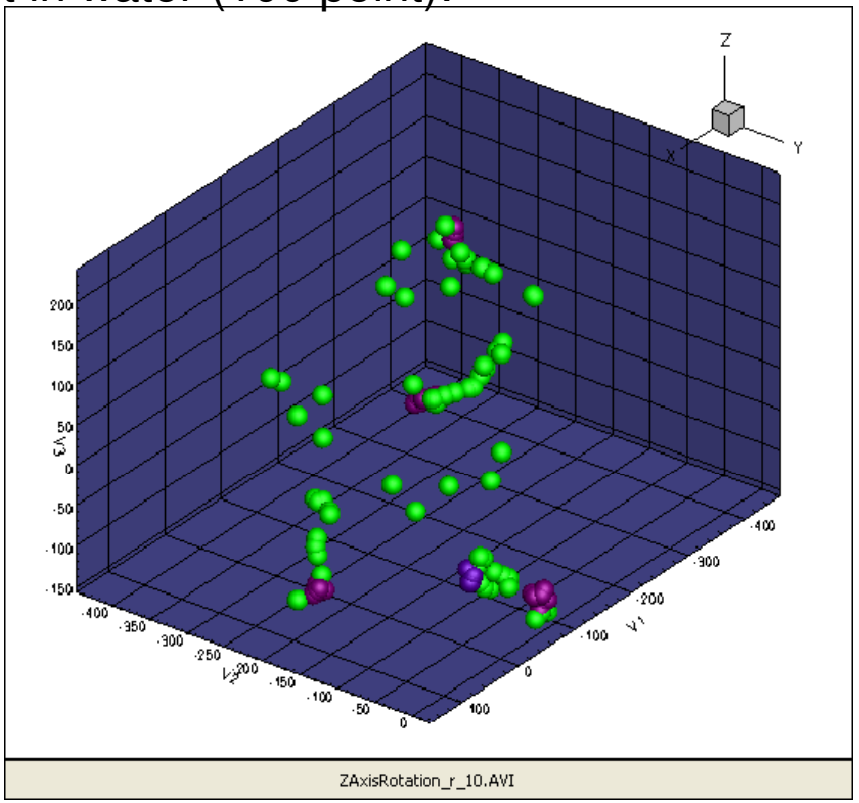
AMANDE (IRSN) irradiation facility for mono-energétic neutrons irradiations



Data mining & Clustering algorithms:

DBSCAN for a proton track fragment in water (100 point):





Density = 3 points

Radius = 5 nm

(Input parameters)

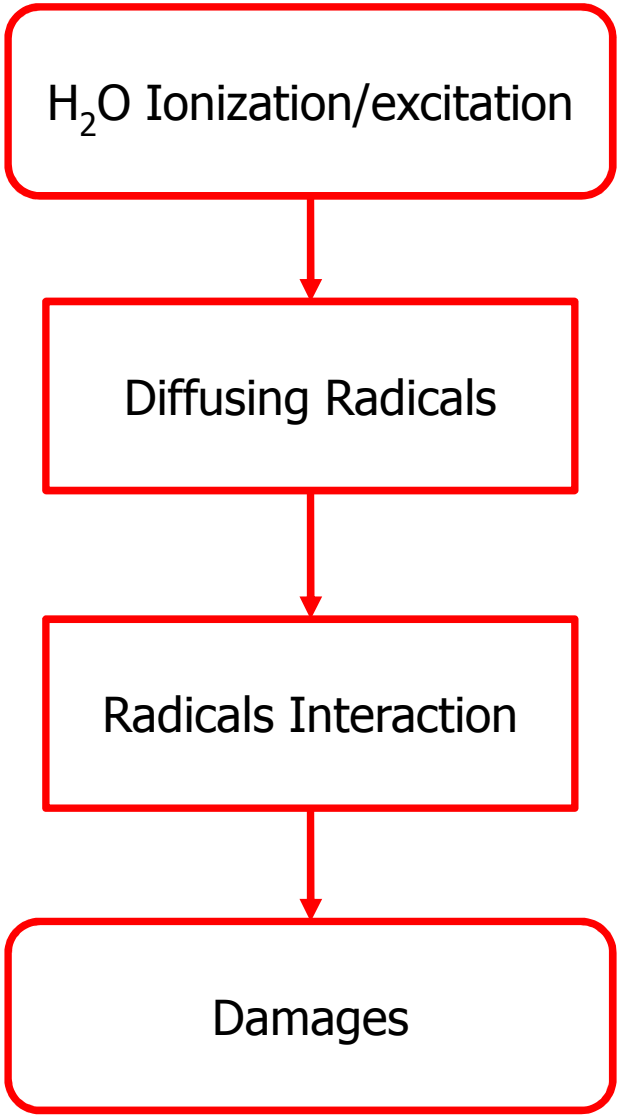
Density = 3 points

Radius = 10 nm

Perspectives
chemical species & processes

Chemistry

- Damages are given by diffusing radicals, interacting with DNA molecule.
- Creation, diffusion and interaction of these chemical species is required



PARTRAC

Chemical stage

- Concerns the reaction and diffusion of chemical species, from 10^{-12} s to 10^{-6} s, after physico-chemical stage

- The reactions included are (with rates)

Reaction	k (10^{10} $M^{-1}s^{-1}$)
$e^-_{aq} + e^-_{aq} + H_2O \rightarrow H_2 + 2\ OH^-$	0.5
$e^-_{aq} + OH^\bullet \rightarrow OH^-$	3.0
$e^-_{aq} + H^\bullet + H_2O \rightarrow H_2 + OH^-$	2.5
$e^-_{aq} + H_3O^+ \rightarrow H^\bullet + H_2O$	2.4
$e^-_{aq} + H_2O_2 \rightarrow OH^- + OH^\bullet$	1.2
$OH^\bullet + OH^\bullet \rightarrow H_2O_2$	0.45
$OH^\bullet + H^\bullet \rightarrow H_2O$	2.0
$H^\bullet + H^\bullet \rightarrow H_2$	1.0
$H_3O^+ + OH^- \rightarrow 2\ H_2O$	14.3

Chemical stage

- Diffusion of radicals assumes a pure diffusion behavior with short time steps (0.1 ps to 30 ps) and uses these parameters:

Species	D (10^{-9} m^2 s^{-1})	$\sqrt{\langle l^2 \rangle}$ (nm)
e^-_{aq}	4.5	0.16
$OH^\bullet$	2.8	0.13
$H^\bullet$	7.0	0.20
H_3O^+	9.0	0.23
H_2	5.0	0.17
OH^-	5.0	0.17
H_2O_2	1.4	0.09

- After each diffusion step, distances between each pair of radicals are checked : if radicals are closer than their reaction radius, they are allowed to interact and replaced by their products

G4Molecule

G4MolecularDecay

Under Development

```
---> Begin of Event: 0

*****************************                                    ***
* G4Track Information:   Part                                    =
*****************************                                    ***

Step#      X          Y          Z         KineE     dEStep    StepLeng  TrakLeng    Volume     Process
    0    -50 m    -27.6 m    6.97 m    1e+03 eV       0 eV       0 fm       0 fm        Water    initStep
    1    -50 m    -27.6 m    6.97 m      986 eV    13.4 eV    9.59 Ang   9.59 Ang        Water  DNAIonisation
    :----- List of 2ndaries - #SpawnInStep=  4(Rest= 0,Along= 0,Post= 4), #SpawnTotal=  4 ---------------
    :    -50 m    -27.6 m    6.97 m    0.417 eV          e-
    :    -50 m    -27.6 m    6.97 m     13.4 eV         H2O
    :    -50 m    -27.6 m    6.97 m     13.4 eV         H2O
    :    -50 m    -27.6 m    6.97 m     13.4 eV         H2O
    :-------------------------------------------------------------- EndOf2ndaries Info ---------------
    2    -50 m    -27.6 m    6.97 m      972 eV    13.4 eV     2.8 nm    3.75 nm        Water  DNAIonisation
    :----- List of 2ndaries - #SpawnInStep=  4(Rest= 0,Along= 0,Post= 4), #SpawnTotal=  8 ---------------
    :    -50 m    -27.6 m    6.97 m    0.638 eV          e-
    :    -50 m    -27.6 m    6.97 m     13.4 eV         H2O
    :    -50 m    -27.6 m    6.97 m     13.4 eV         H2O
    :    -50 m    -27.6 m    6.97 m     13.4 eV         H2O
    :-------------------------------------------------------------- EndOf2ndaries Info ---------------
    3    -50 m    -27.6 m    6.97 m      961 eV    10.8 eV    1.75 nm     5.5 nm        Water  DNAIonisation
    :----- List of 2ndaries - #SpawnInStep=  4(Rest= 0,Along= 0,Post= 4), #SpawnTotal= 12 ---------------
    :    -50 m    -27.6 m    6.97 m    0.374 eV          e-
    :    -50 m    -27.6 m    6.97 m     10.8 eV         H2O
    :    -50 m    -27.6 m    6.97 m     10.8 eV         H2O
```

...

IT WORKS!

…More perspectives:

- Extending electrons follow till **0.025 eV** for electrons in GEANT4 (vibrational excitations processes).
- DNA Geometry (level of details? Not decided)
- Are DNA cross sections necessary ???
- How far can clustering algorithms and data mining be useful ? Can they reveal potential lethal damages in the cell ?
    - Open PhD position at IRSN (Fontenay-aux-Roses) on GEANT4 chemical phase, DNA geometry and Cell damage quantification