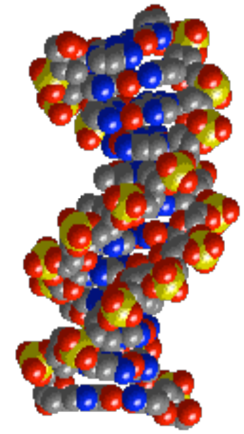


The Geant4-DNA project and its applications

Slides provided by Sebastien Incerti
on behalf of the
Geant4-DNA collaboration

Low Energy Electromagnetic Physics working group,
Geant4 collaboration

Modelling radiation biology

- Modelling biological systems and Physics processes down to the nanometer / ~eV scale is a **challenge**
- Several specialized Monte Carlo codes have been developed for radiobiology and microdosimetry

However

  - Typically each one implementing models developed by its authors
  - Limited application scope
  - Not publicly distributed
  - Legacy software technology (FORTRAN, procedural programming)

Organisation of low energy electromagnetic Physics in Geant4

- coordinator : S. Incerti (IN2P3/CENBG)
- steering-board representative :
  - G. Cuttone (INFN/LNS)
- contains 20 members who are members of the Geant4 collaboration
  - ANSTO (Australia), CERN, CNSTN (Tunisia), CUH (Denmark), ESA (The Netherlands), FAMAF (Argentina), Hampton Univ. (USA), IN2P3 (France), INFN (Italy), IRSN (France), Karolinska (Sweden), NTUA (Greece)
- in collaboration with 15 « external » members
  - having their own expertise on specific items/activity
  - they are not yet members of the Geant4 collaboration
  - they will have the possibility to join the Geant4 collaboration after contribution to the low energy EM working group
- in full collaboration with Standard Electromagnetic Physics working group

6 « mini » working groups

- Low-energy EM processes **including new processes (Geant4-DNA)**
  - coordinator : S. Incerti (IN2P3/CENBG)
- Debugging of existing models
  - coordinator : G. Santin (ESA/ESTEC)
- Computing performance
  - coordinator : N. Karakatsanis (National Tech. Univ. of Athens)
- Testing
  - coordinator : P. Guèye (Jefferson Lab/Hampton U.)
- Validation
  - coordinator : P. Cirrone (INFN/LNS)
- Documentation
  - coordinator : C. Zacharatou (Copenhagen University Hospital)

Geant4 for microdosimetry

- History : initiated from 2000 by Dr Petteri Nieminen (ESA/ESTEC – chairman of the Geant4 Oversight Board) in the framework of the « Geant4-DNA » project

- Objective : adapt the general purpose Geant4 Monte Carlo toolkit for the simulation of interactions of radiation with biological systems at the cellular and DNA level (« microdosimetry »)

- A full multidisciplinary ongoing activity of the Geant4 low energy electromagnetic Physics working group, involving physicists, theoreticians, biophysicsts…

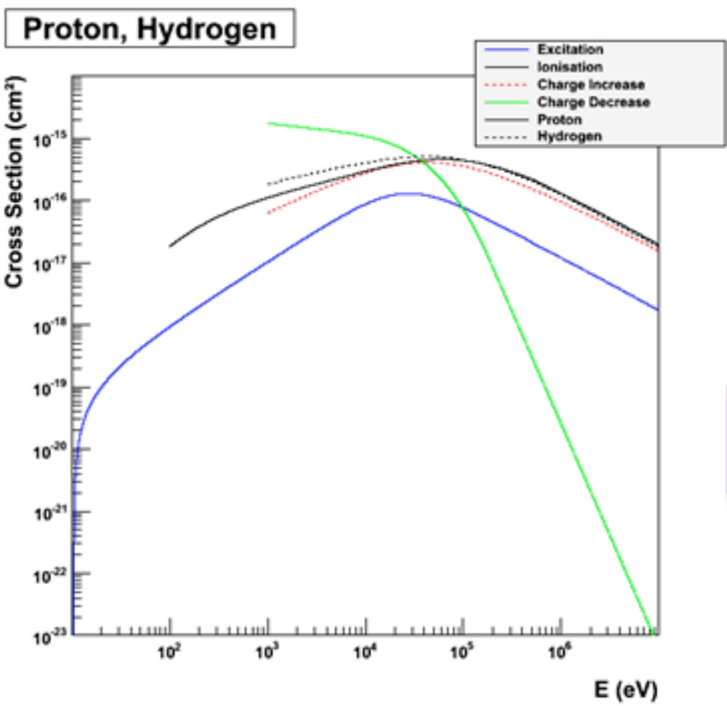
- Applications :
  - Radiobiology, radiotherapy and hadrontherapy (eg. prediction of DNA strand breaks from ionising radiation)
  - Radioprotection for human exploration of Solar system
  - Not limited to biological materials (ex. Silicon)

Down to the eV scale !

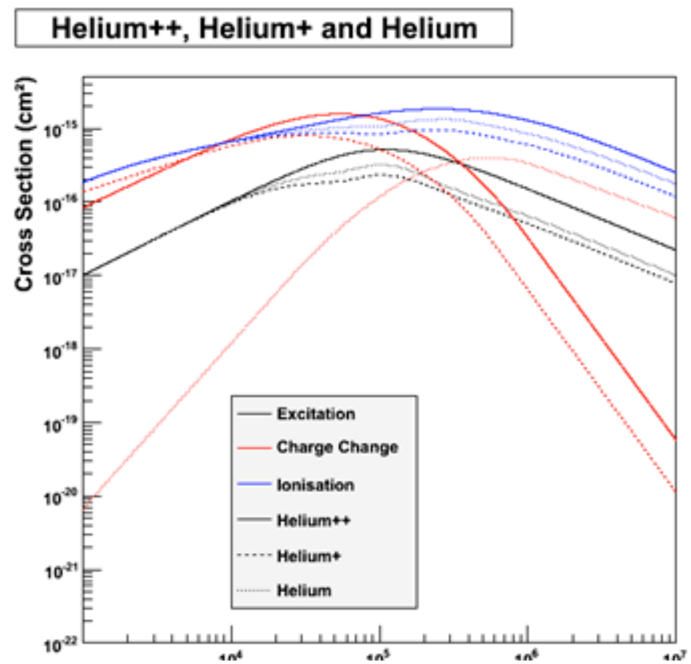
- Models available for liquid water only
- Models in black are analytical
- Models in purple use interpolated data

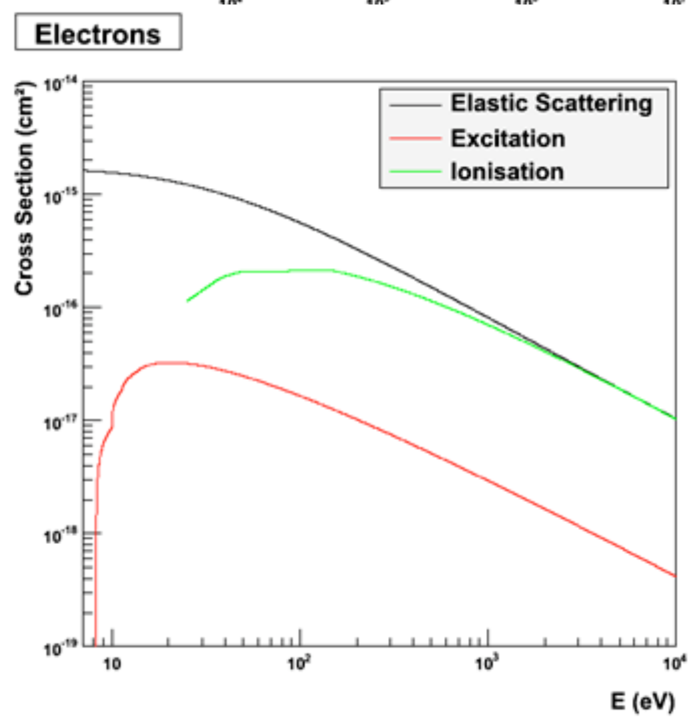
Physics models in Geant4 DNA

	e	p	H	α, He+, He
Elastic scattering	> 7.4 eV Screened Rutherford > 7 eV Champion	-	-	-
Excitation A_1B_1, B_1A_1, Ryd A+B, Ryd C+D, diffuse bands	7.4 eV – 10 MeV Emfietzoglou	10 eV – 500 keV Miller Green 500 keV – 10 MeV Born	-	Effective charge scaling from same models as for proton
Charge Change	-	1 keV – 10 MeV Dingfelder	1 keV – 10 MeV Dingfelder	
Ionisation $1b_1$, $3a_1$, $1b_2$, $2a_1$ + $1a_1$	12.6 eV – 30 keV Born	100 eV – 500 keV Rudd 500 keV – 10 MeV Born	100 eV – 100 MeV Rudd	



Total cross sections vs Incident energy





- Each physics process is characterized by one or several complementary or alternative models

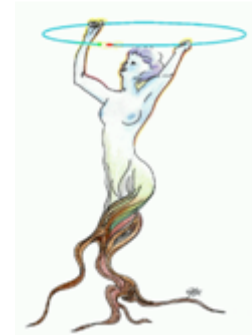
- Each model provides :
  - a computation of the total cross section
  - a computation of the final state : kinematics, production of secondaries involved

Availability

- This is the first time that a general-purpose Monte Carlo simulation toolkit is equipped with open functionality for radiobiology
- These Physics processes are already available in the Geant4 toolkit
- All details about these processes are available on the Low Energy Electromagnetic working group web site
- See **http://cern.ch/geant4**

Highlights of Geant4 microdosimetry applications

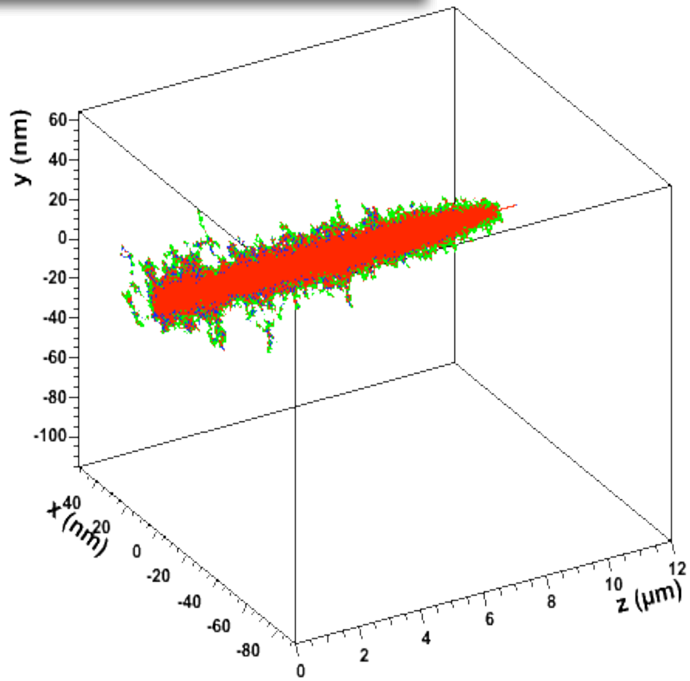
The microdosimetry Geant4 « advanced example »



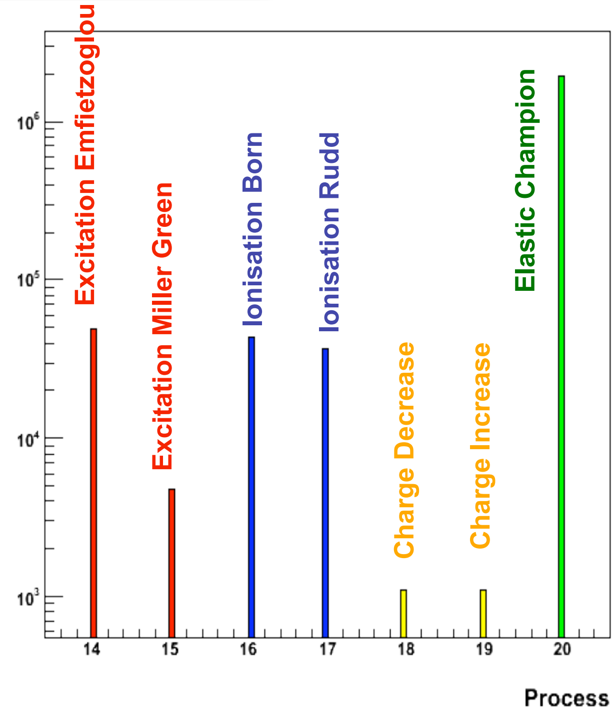
- Purpose
  - explain to users how to use Geant4 very low energy electromagnetic processes for microdosimetry
  - calculation of track structure of a He+ particle in liquid water, ROOT macro provided (http://root.cern.ch)
- Available to users in the Geant4 toolkit
- Located in the Geant4 directory
  - $G4INSTALL/examples/advanced/microdosimetry

The microdosimetry
Geant4 « advanced example »

3D track structure displayed with ROOT macro file



List of Physics processes



E.g. : incident 2.37 MeV He^+ in liquid water, as delivered by the CENBG microbeam irradiation faciltity

Nanodosimetric modelling of low energy electrons in a magnetic field

Centre for Medical Radiation Physics

University of Wollongong

- Purpose : investigate possible biological effect enhancement of low energy electrons in a magnetic field

- Simulated setup
  - Two target geometries :
    - **DNA-segment :** represented by water cylinder of diameter 2.3 nm and height 3.4 nm
    - **Nucleosome :** represented by water cylinder of diameter 6 nm and height 10 nm
  - Incident particle : 50 eV – 10 keV electrons
  - Magnetic field : 1-10 T
  - Physics processes : Geant4 DNA

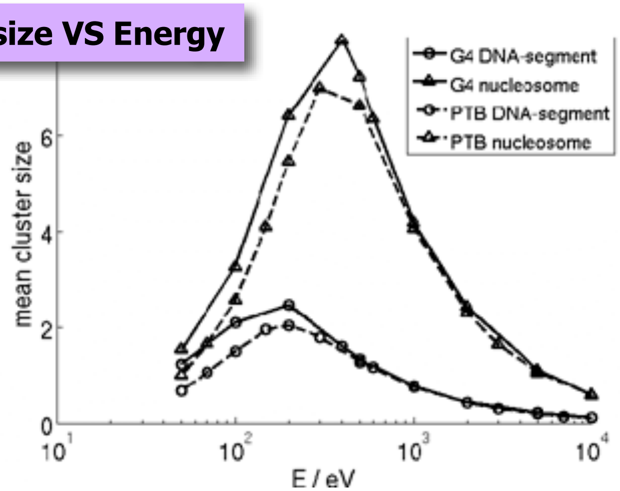
- Comparison between Geant4-DNA and PTB code (B. Grosswendt *et al.*, PTB Braunschweig)

Kindly provided by Marion Bug, Anatoly Rosenfeld and colleagues
Centre for Medical Radiation Physics
University of Wollongong, Australia
Presented at the 13th Geant4 collaboration workshop

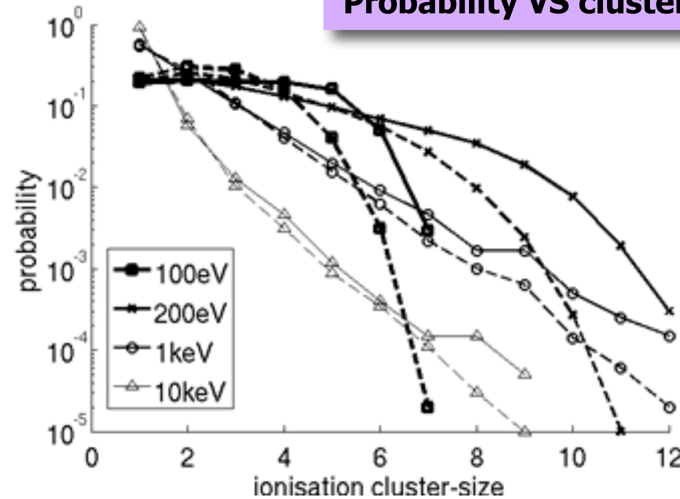
Comparison of cluster-size distribution

- Good agreement between the two codes for both volumes
- PTB-code shows lower mean cluster-size for electrons < 1 keV (left)
- Confirmed in probability distribution (right):
  higher number of large cluster-sizes produced in G4-code than in PTB-code
- Due to different cross-sections, statistical error (?)
- RBE enhancement in magnetic field under investigation

Cluster size VS Energy



Probability VS cluster size



Mean ionisation cluster-size vs. electron energy, comparison of our data (G4) with the MC-code from PTB

Probability of cluster size. Comparison of G4-code (solid lines) with MC-code from PTB (dashed lines)

Kindly provided by Djamel Dabli & Gérard Montarou
Laboratoire de Physique Corpusculaire
Université Blaise Pascal, IN2P3/CNRS, Aubière, France

Predicting cell lesions

- The mean number of lethal lesions in a biological nucleus can be expressed with a linear quadratic formula (Kellerer *et al.* 1978)

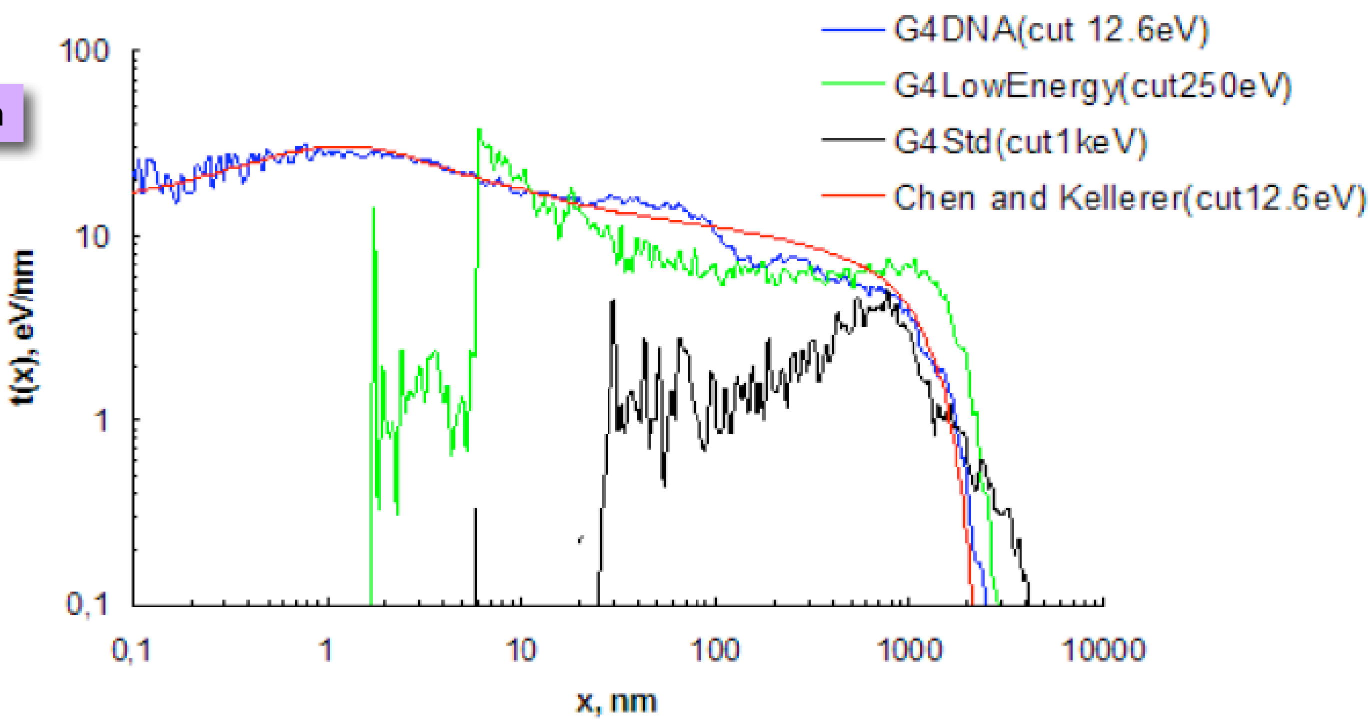
$$< nbr(lesions) >= k\left(D\int_0^\infty \frac{\gamma(x)t(x)}{4\pi x^2}dx + D^2\right)$$

  - sub-lesions can combine in pairs to induce lethal lesions
  - $t(x)$ is the is the physical proximity function, representing the probability distribution of all distances between pairwise energy transfer points in the track
  - $\gamma(x)$ is the biological proximity function representing the distribution of sensitives sites in a nucleus.
- $t(x)$ can be calculated from Geant4 electromagnetic interactions (Standard, Low Energy, Geant4 DNA) in liquid water

Proximity functions

- good agreement between Geant4-DNA physics models and the estimation of Chen and Kellerer (2006).

Proximity function



Perspectives

- Geant4 is currently being extended and improved for the modelling of radiation biology in the framework of the Geant4-DNA project

- Expected developments include :

  - Physics : complementary/additional theoretical models, for other target materials (DNA, Silicon,…)

  - Physico-chemical and chemistry for the production of radical species

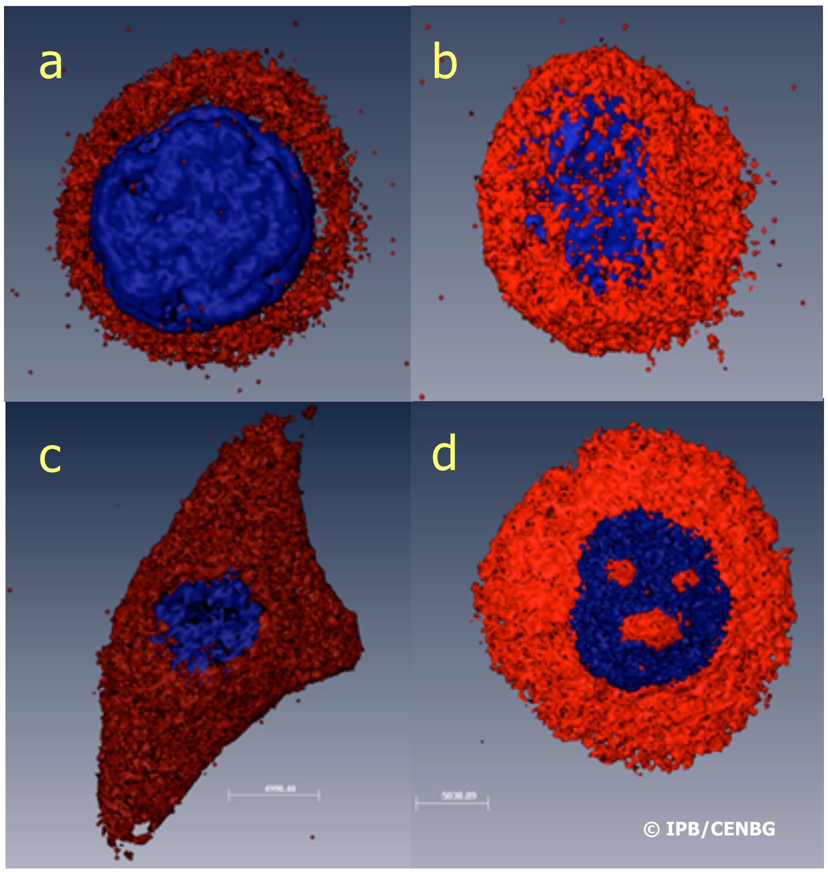
  - Geometry : atomistic approach (Protein Data Bank), voxellized approach

  - Biological damage stage, benefiting from experimental validation (ex. microbeam cellular irradiation at CENBG)

  - New examples will be delivered for Geant users

Perspective 1 :
Simulation of molecular geometries

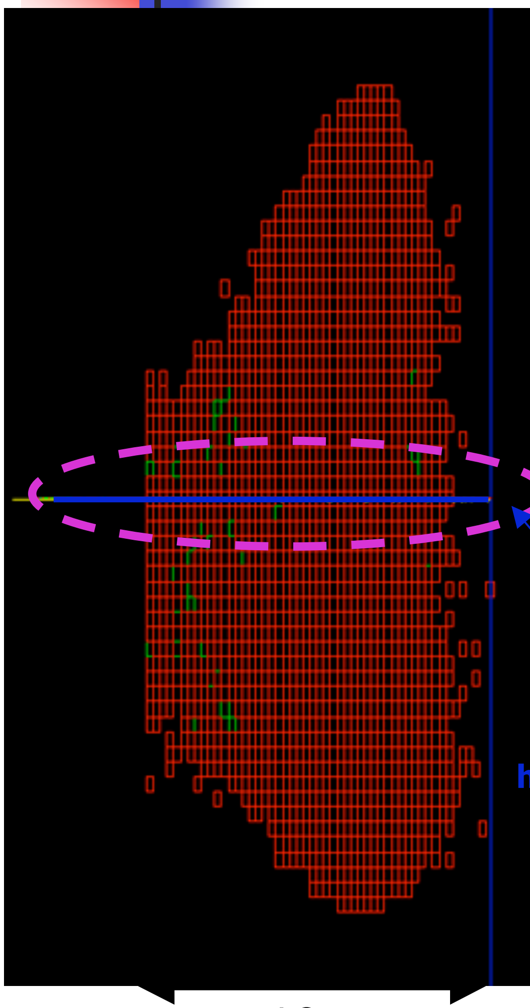
Building cellular models

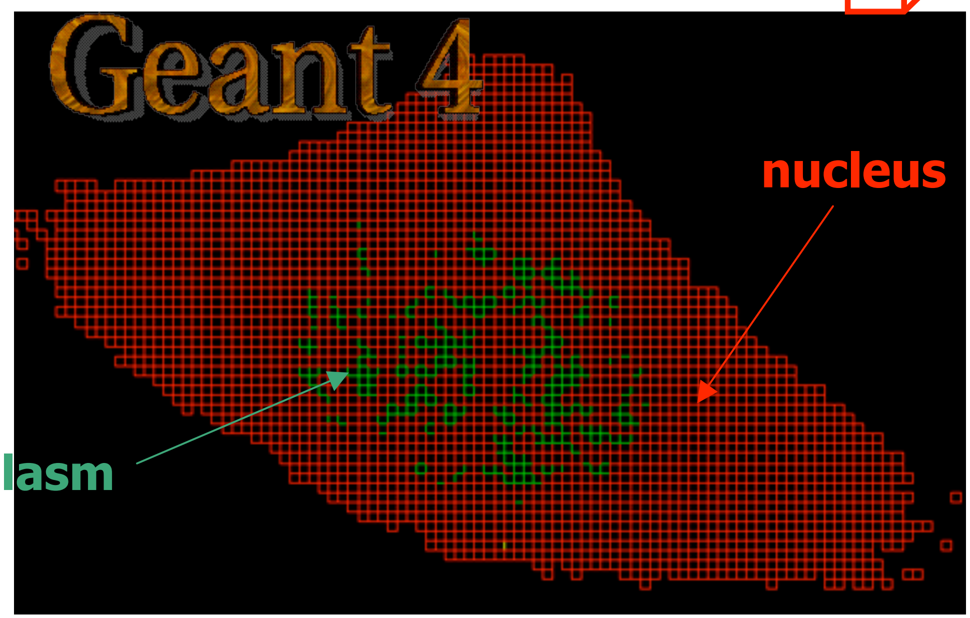


- Selection of four "phantoms" reconstructed from 128×128 2D confocal imaging.
- Incubation :
  - 4 hours for cells a and b
  - 24 hours for cells c and d
- The cytoplasm and nucleoli appear in red while the nucleus is shown in blue.

Cellular phantom model

- 24h incubated cell
- Irradiated with a 2.37 MeV alpha+ beam
- 64 x 64 x 60 resolution
- 0.36 x 0.36 x 0.16 µm^3 voxel size



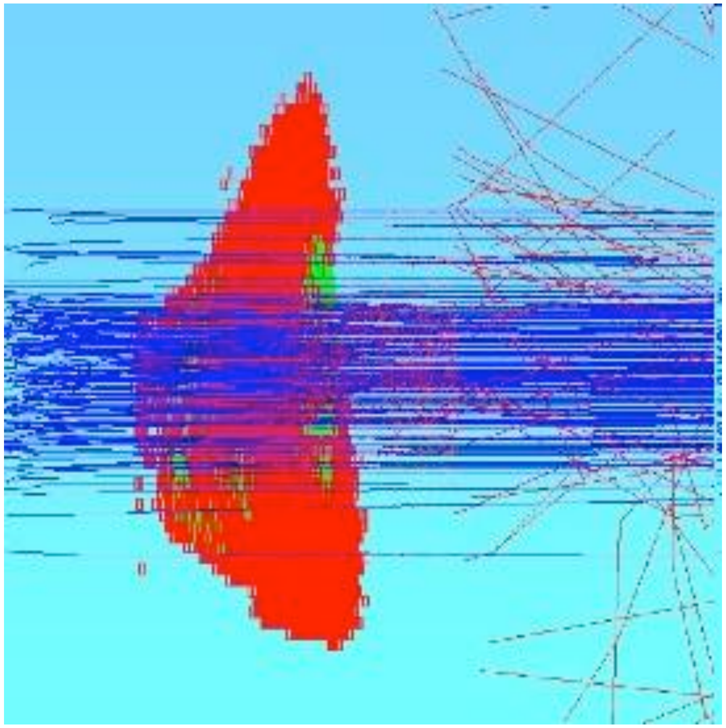


Example of cellular irradiation

- Example of single cell irradiation by 3 MeV alpha particles in a high-resolution cellular phantom

- Full CENBG microbeam irradiation setup simulated

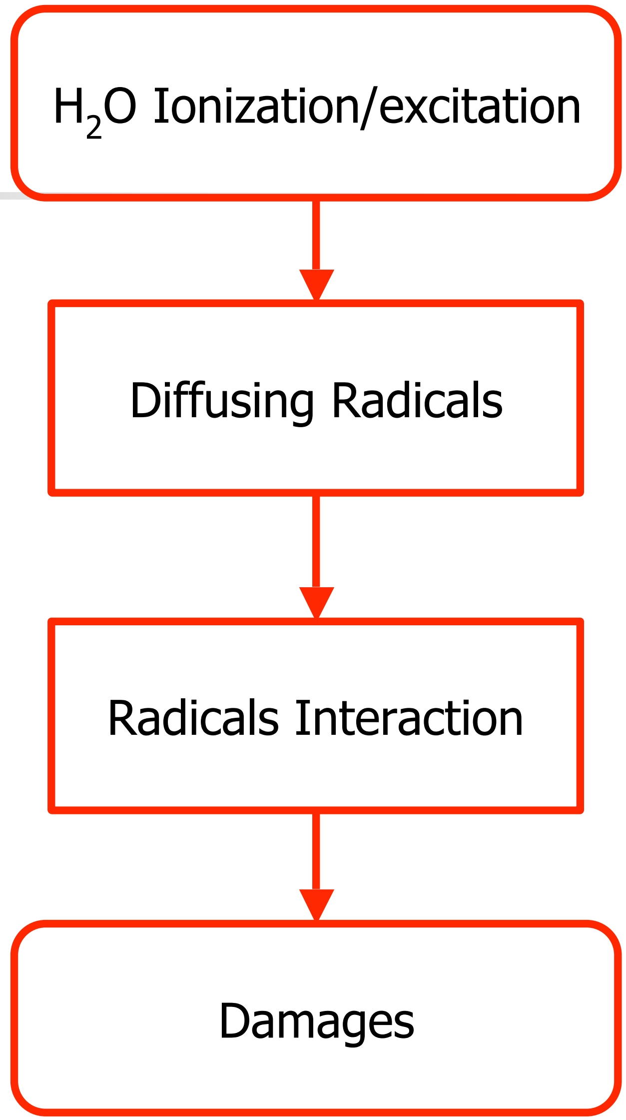
- Available as Microbeam « advanced example » in Geant4



Perspective 2 :
chemistry species & processes

Chemistry

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



PARTRAC

Physico-chemical stage

- à la PARTRAC, written by W. Friedland (GSF)
- There is the production of chemical species, from 10^{-15} s to 10^{-12} s after Physics stage from excited and ionised water molecules
- Ionised molecules convert immediately

$$H_2O^+ + H_2O \blacktriangleright H_3O^+ + OH\bullet$$

Physico-chemical stage

- Excited molecules relax or dissociate according to:

Excited state	Decay channel	Relative percentage
A^1B_1	$H_2O + \Delta E$	35%
	$H^{\bullet} + OH^{\bullet}$	65%
B^1A_1	$H_2O + \Delta E$	52%
	$H_2 + 2\,OH^{\bullet}$	14.5%
	$H_3O^+ + OH^{\bullet} + e^-_{aq}$	33.5%
Ryd A+B, Ryd C+D diffuse bands	$H_2O + \Delta E$	40%
	$H_3O^+ + OH^{\bullet} + e^-_{aq}$	60%

- Low energy electrons (too low to excite water molecules) thermalise and become solvated

Species needed

- These species are produced during the physico-chemical stage
  - H•, H_3O^+, OH•, H_2, e^-_{aq}
- Species produced during chemical stage
  - OH-, H_2O_2
- We are now implementing them as molecules in Geant4

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 behaviour 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

Chemistry in Geant4

"Geant4 is a toolkit for the simulation of the passage of particles through matter"

- **No Molecules in G4**
- **No Diffusion in G4**
- **No interactions between particles (or molecules) in G4**

G4Mo

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         H20
    :     -50 m    -27.6 m    6.97 m     13.4 eV         H20
    :     -50 m    -27.6 m    6.97 m     13.4 eV         H20
    :----------------------------------------------------------------- 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         H20
    :     -50 m    -27.6 m    6.97 m     13.4 eV         H20
    :     -50 m    -27.6 m    6.97 m     13.4 eV         H20
    :----------------------------------------------------------------- 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         H20
    :     -50 m    -27.6 m    6.97 m     10.8 eV         H20
```

IT WORKS!

Perspective 3 :
Simulation of biological effects

Simulation of strand breaks and DNA fragments (ex. of protons)

Direct and quasi-direct effects (non-scavengable)

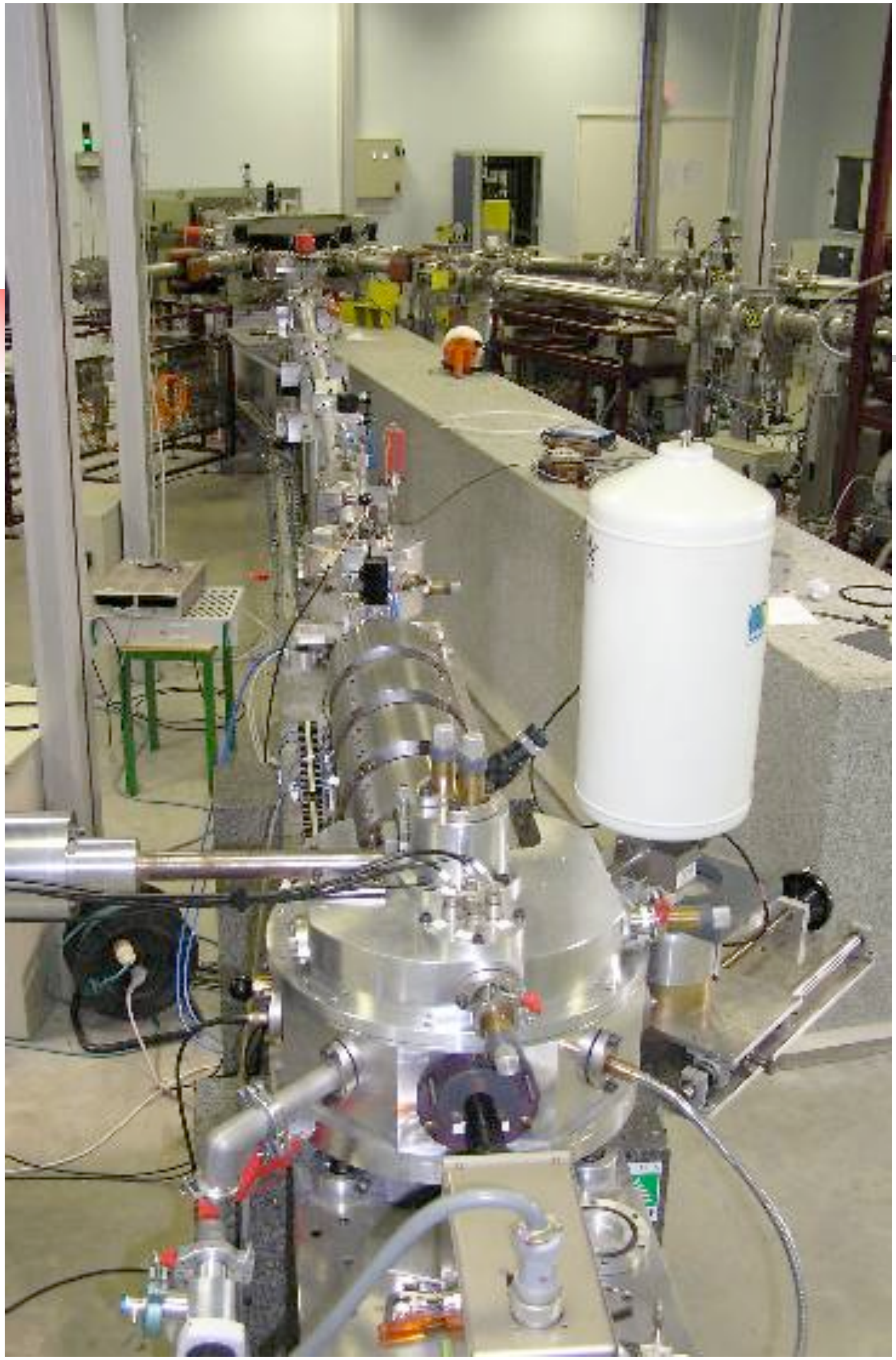
- calculated from a **superposition of the track structure of inelastic events with the DNA model**
- the target volume is a union of the atoms in the sugar-phosphate backbone of the helix applying a Van der Waals radius multiplied by 2 to include 10 water molecules per nucleotide in the target volume.
- lower limit of 5 eV

Indirect effets

- Look at **energy deposition events and thermalized electrons occuring inside a cylinder with a 25 nm diameter positioned around the chromatine fiber containing only water**

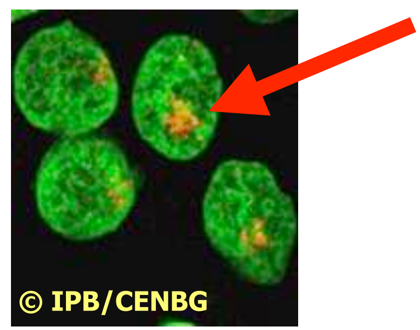
- Water molecule excitation and ionisation
- Reactive species produced : e- aq, H_3O+, OH., H., H_2
- Dissociation scheme, relaxation probabilities, parameters for diffusion and interactions taken from Ballarini et al. and Buxton et al.
- Jump-through corrections (Hamm et al.) for reaction among species and with DNA
- Occurred within the time limit of 10 ns

Validation by experimental facilities: microbeams

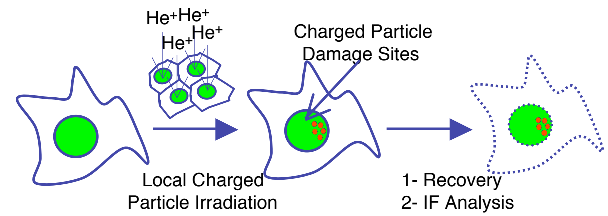


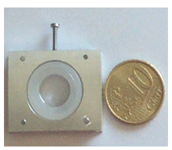
CENBG AIFIRA irradiation facility in Bordeaux, France

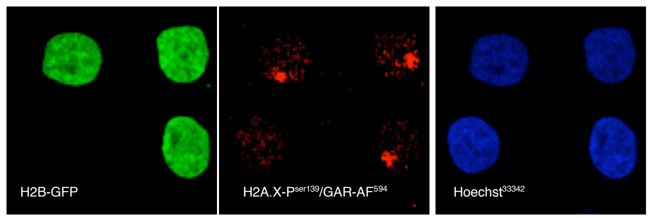
- AIFIRA equipped with a cellular irradiation microbeam line
- 3 MeV proton or alpha beam
- **single cell & single ion mode**
- Targeting accuracy on living cells **in air** : a few µm
- Able to quantify DNA damages like double strand breaks



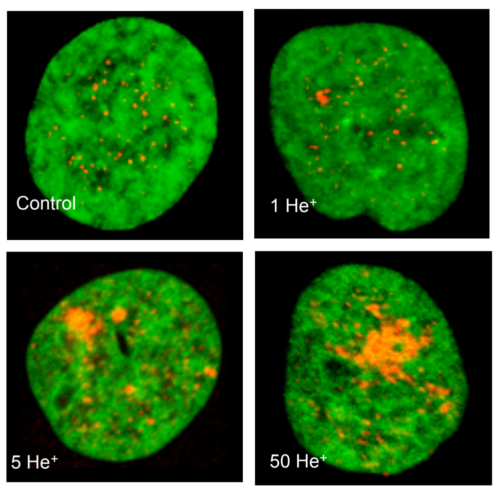
Experimental validation

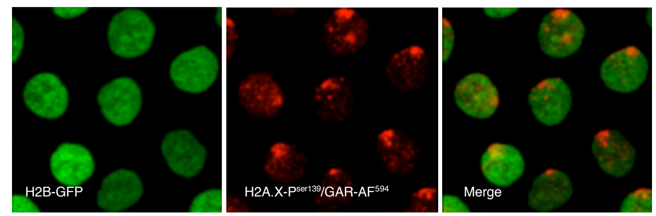




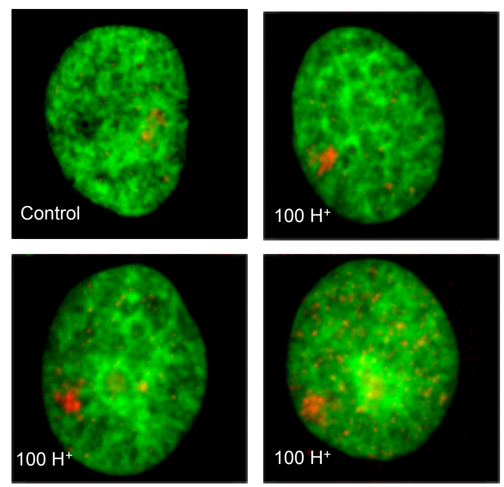


3MeV He^{+}, 2H00





3MeV H^{+}, 2H00



DNA double strand breaks damage quantification

If you want to learn more…

- **A free-parameter theoretical model for describing the electron elastic scattering in water in the Geant4 toolkit,**
  C. Champion, S. Incerti, H. Aouchiche, D. Oubaziz, Rad. Phys. Chem., in press (link)
- **Monte Carlo dosimetry for targeted irradiation of individual cells using a microbeam facility,**
  S. Incerti, H. Seznec, M. Simon, Ph. Barberet, C. Habchi, Ph. Moretto,
  accepted in Rad. Prot. Dos. (link)
- **Microdosimetry in high-resolution cellular phantoms using the very low energy electromagnetic extension of the Geant4 toolkit,**
  S. Chauvie, S. Incerti, P. Moretto, M.G. Pia, H. Seznec,
  Nuclear Science Symposium Conference Record, 2007. NSS '07. IEEE Volume 3, Oct. 26 2007-Nov. 3 2007 Page(s):2086 - 2088 (link)
- **Evaluation of phase effects in Geant4 microdosimetry models for particle interactions in water,**
  S. Chauvie, S. Incerti, P. Moretto, M.G. Pia,
  Nuclear Science Symposium Conference Record, 2007. NSS '07. IEEE Volume 1, Oct. 26 2007-Nov. 3 2007 Page(s):898 - 900 (link)
- **Geant4 physics processes for microdosimetry simulation : design foundation and implementation of the first set of models,**
  S. Chauvie, Z. Francis, S. Guatelli, S. Incerti, B. Mascialino, P. Moretto, P. Nieminen, M. G. Pia, IEEE Trans. Nucl. Sci. 54 (6-2) (2007) 2619-2628 (link)
- **Models of biological effects of radiation in the Geant4 Toolkit,**
  S. Chauvie, Z. Francis, S. Guatelli, S. Incerti, B. Mascialino, G. Montarou, P. Moretto, P. Nieminen, M.G. Pia, ,
  Nuclear Science Symposium Conference Record, 2006. IEEE Volume 2, Oct. 29 2006-Nov. 1 2006 Page(s):803 - 805 (link)
- **Monte Carlo simulation of interactions of radiation with biological systems at the cellular and DNA levels : The Geant4-DNA Project,**
  S. Chauvie, Z. Francis, S. Guatelli, S. Incerti, B. Mascialino, G. Montarou, Ph. Moretto, P. Nieminen, M. G. Pia (The Geant4-DNA Collaboration),
  Rad. Res. Vol. 166 (4) (2006) 652-689 (link)
- **Cellular geometry modeling for Monte Carlo microdosimetry,**
  T. Pouthier, H. Seznec, S. Incerti, O. Boissonnade and Ph. Moretto,
  Rad. Res. Vol. 166 (4) (2006) 652-689 (link)
- **A comparison of cellular irradiation techniques with alpha particles using the Geant4 Monte Carlo simulation toolkit,**
  S. Incerti, N. Gault, C. Habchi, J.L. Lefaix, Ph. Moretto, J.L. Poncy, T. Pouthier and H. Seznec,
  Rad. Prot. Dos. (2006) 1-3 (link)
- **Simulation of cellular irradiation with the CENBG microbeam line using Geant4,**
  S. Incerti, Ph. Barberet, R. Villeneuve, P. Aguer, E. Gontier, C. Michelet-Habchi, Ph. Moretto, D.T. Nguyen, T. Pouthier and R.W. Smith,
  IEEE Trans. Nucl. Sci. 51 (4) (2004) 1395-1401 (link)

Conclusion

- The Geant4-DNA project is expected to run till 2013
- Detailed workplan and schedule is available
- We have access to dedicated irradiation facilities for validation, like the microbeam cellular irradiation facility in CENBG, Bordeaux
  - Biologists for DNA damage quantification
- Funding is already available:
  - ANR « Geant4-DNA »
  - Région Aquitaine (computing farm),
  - ESA proposal submitted for 2010-2013
- Large domain of applications in perspective : radiobiology, radiotherapy/hadrontherapy, radioprotection for aerospace & astronautics, exobiology…
- We are open to worldwide NEW collaborators