Modeling Radiation Chemistry and Biology in the Geant4 Toolkit

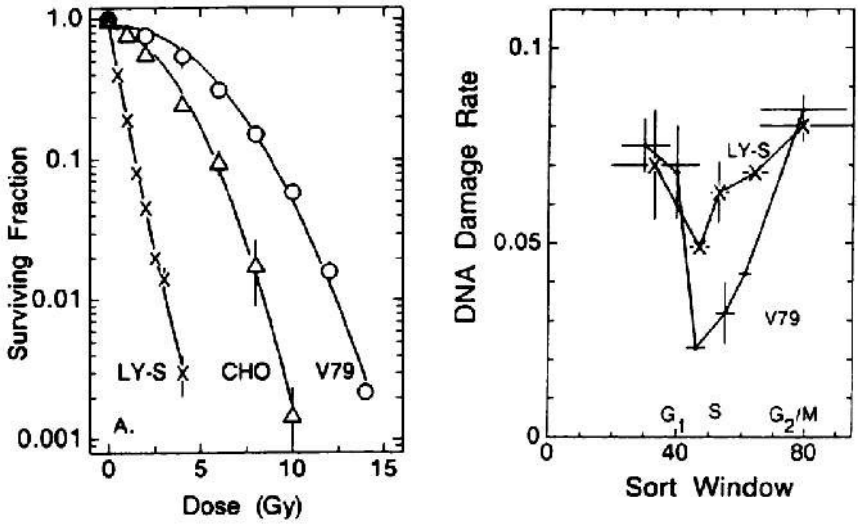
A. Mantero on behalf of the Geant4-DNA consortium

MC2010, Tokyo

Context & motivation

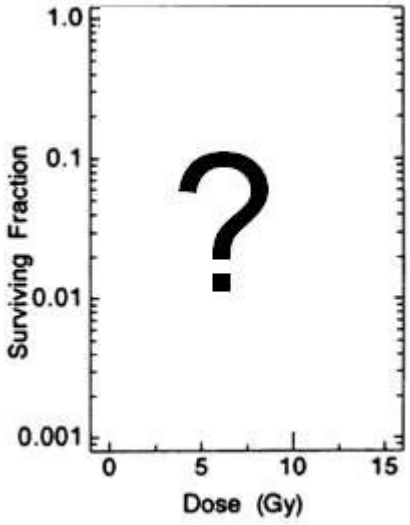
Modeling radiation biology

Experimental data



Source :
« DNA Double-Strand Breaks Measured in Individual Cells Subjected to Gel Electrophoresis »,
Olive, Wlodek, Banath 1991

Simulation results at cellular and sub-cellular scale



Forerunner codes :
PARTRAC,
RADACK,
CPA100 …

Modeling radiation biology

Today validated simulation tools are of primary importance for radioprotection

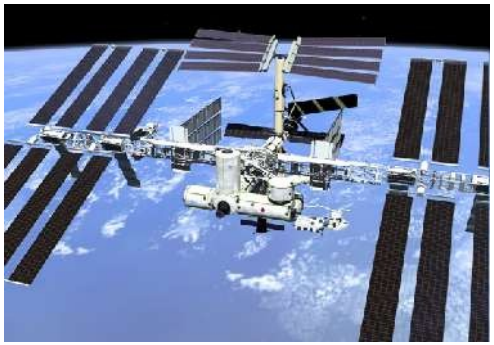
Not only in the low dose regime (< ~200 mSv)

- "nuclear" workers (nuclear plants, health-care, particle accelerators)
- general public (radon, medical exams…)

But also at high doses

- new therapeutic techniques based on ionising radiation (ion therapy)
- long duration manned space exploration missions (ISS, Mars…)

Biological effects can only be extrapolated from epidemiological surveys (Hiroshima and Nagasaki bombings)



Modeling radiation biology

Several specialized Monte Carlo codes have been developed for "track structure" modeling of ionizing radiation at the molecular scale.

Traditionally these codes are not open source are not publicly distributed

We have adopted an alternative approach based on Geant4 : open-source, done for general purpose

Table I – Monte Carlo Track Codes in Radiation Research.

Code	Author	Medium	Particle	Energy Range	ref
ETRAN	Berger & Seltzer	all	e & phot	10 keV - 1 GeV	[1]
EGS4	Nelson	all	e^- & phot	10 keV - 1 GeV	[2]
PTRAN	Berger	H_2O	proton	50 - 250 MeV	[3]
MCNP	Briemeister	all	neutron	eV – MeV	[4]
PENELOPE	Salvat	all	e– & e+	1keV-100MeV	[5]
PREGRINE	Hartmann Siantar	tissue	phot. & e–	Therapy beam	[6]

Table II – Monte Carlo Track Codes in Radiation Biology.

Code	Author	Medium	Particle	Energy Range	Ref
ATRACK	Katz *et al*	all	e & ions	up to GeV	[7]
MOCA8	Paretzke	H_2O (v, l)	e^-	10 eV – 100 keV	[8]
OREC	Turner *et al*	H_2O (l)	e^-	10 eV – 1 MeV	[9]
			p & a	0.3 – 4 MeV/u	
STBRGEN	Chatterjee & Holley	H_2O (l)	e^-	0.1 - 2 keV	[10]
			ions	0.3 – GeV	
CPA100	Terrissol	H_2O (l)	e^-	10 eV – 100 keV	[11]
DELTA	Zaider & Brenner	H_2O (v,l)	e	10 eV - 10 keV	[12]
			p & a	0.3 – 4 MeV/u	
ETRACK	Ito	H_2O (v)	e	10 eV - 10 keV	[13]
TRION	Lappa *et al*	H_2O (v,l)	e^-	10 eV – 1MeV	[14]
			p & a	0.3 - 4 MeV/u	
KURBUC	Uehara & Nikjoo	H_2O (v)	e^-	10 eV – 10 MeV	[15]
TRACEL	Tomita *et al*	H_2O (v, l)	e^-	10 eV - 1 MeV	[16]
PARTRACK	Paretzke *et al*	H_2O (v, l)	ions	0.3 – GeV	[17]
MOCA14	Wilson & Paretzke	H_2O (v)	p & a	0.3 - 4 MeV/u	[18]
PITS	Wilson & Nikjoo	Biological	Ions	0.3 – GeV MeV/u	[19]
LEPHIST	Uehara & Nikjoo	H_2O	P	1keV-1MeV	[20]

Source : *"Monte Carlo track structure for radiation biology and space applications"*, Nikjoo et al., 2000

The Geant4 Monte Carlo toolkit

The Geant4 toolkit:

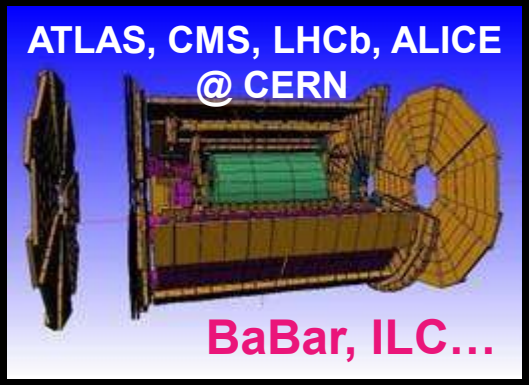
GEometry ANd Tracking

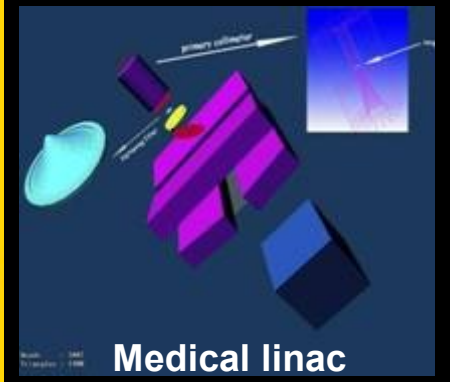
- Libraries to simulate interactions of particles with matter
- Initiated by CERN in 1994 for HEP (LHC)
- Successor of Geant3 (20 years)
- R&D 1994-1998, 1st release in December 1998
- International collaboration (~100 members)
- Object-Oriented technology (C++)
- Constantly updated
- Entirely open source and free
- Two public releases / year

Geant 4

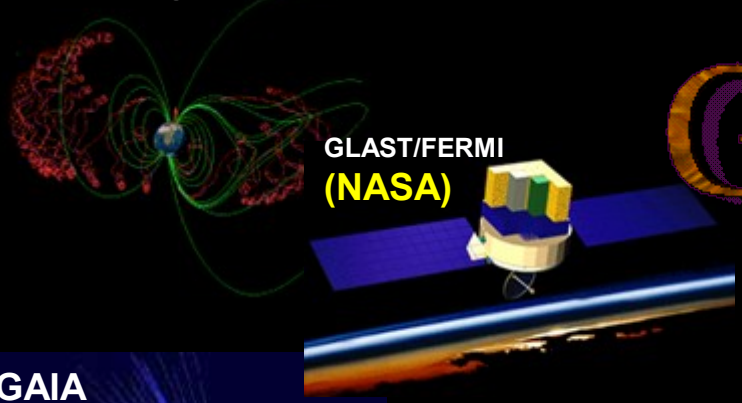
- Flexible geometry
- Interaction processes (electromagnetic, hadronic)
- Follow intial and secondary particles within the geometry
- Save physics quantities and analyze them
- Visualization
- Interactivity
- Extensibility

http://www.geant4.org

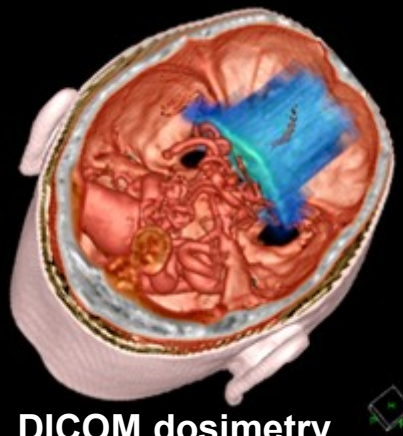




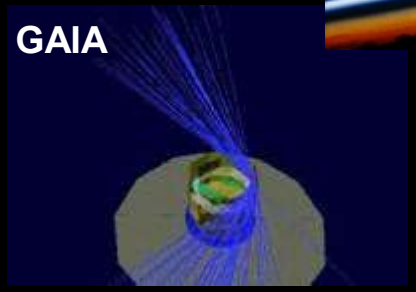
Earth magnetosphere



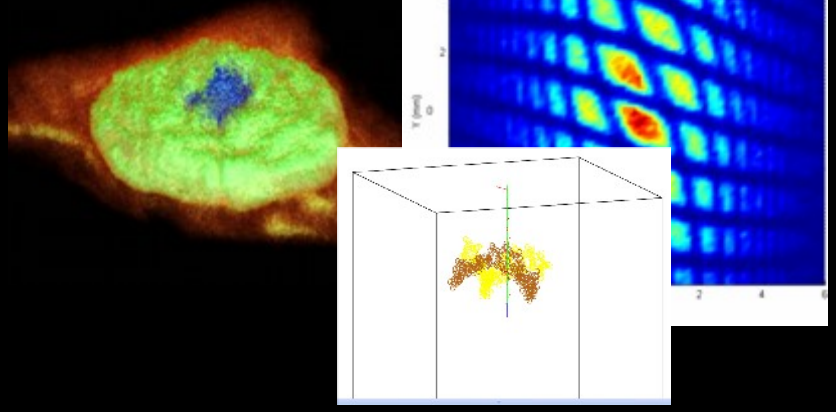
Geant 4

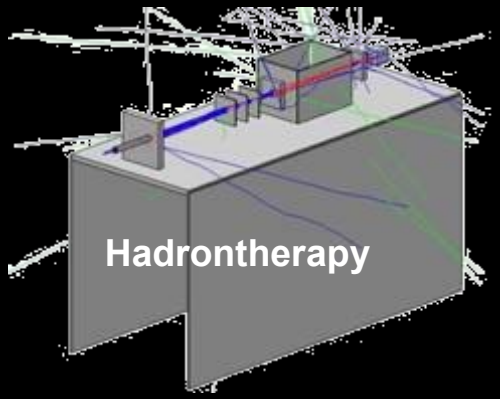


DICOM dosimetry



Physics-Biology





ISS

The Geant4-DNA project

The Geant4-DNA project : Geant4 for nanodosimetry in biological medium

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**

2001: initiated by Dr Petteri Nieminen at the ESA

- Delivered work package reports and a user requirement document

2004: design and implementation

- First Physics models were added to Geant4 in late **2007** for the discrete modelling of light particle interactions down to the eV scale
- Chemistry developments started end of **2009**

Currently an on-going interdiciplinary activity

- Developed by the Geant4 low energy electromagnetic Physics working group.
- Coordinated by CNRS/IN2P3/CENBG since **2008**

How can Geant4-DNA model radiation biology ?

Physics stage
step-by-step modelling of **physical interactions** of ionizing radiation with biological medium (water)

- Excited **water molecules**
- Ionised **water molecules**
- Solvated **electrons**

Physico-chemistry/chemistry stage
- **Molecular** species production
- Diffusion
- Mutual interactions

Geometry stage
DNA strands, chromatine fibers, chromosomes, whole cell nucleus, individual cells…

Biological damages (SSB&DSB)
DIRECT DNA damages

Biological damages (SSB&DSB)
INDIRECT DNA damages

t=0 t=10-15s t=10-6s

Physics stage :
Physics models available in Geant4-DNA

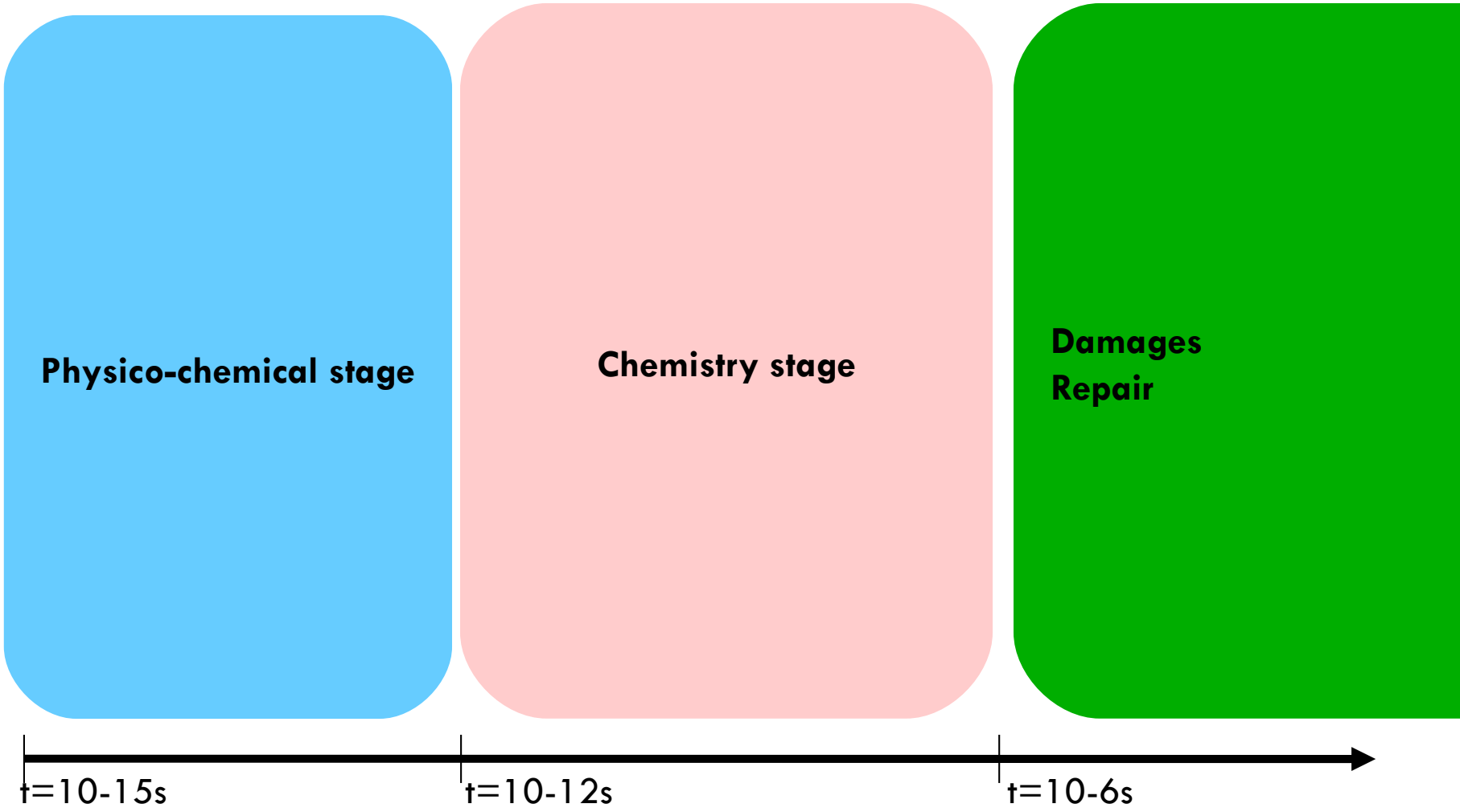
- Can reach the **eV limit**
  - 8.23 eV lower energy limit for excitation (by electrons)
  - Compatible with molecular interactions
- Applicable to **liquid water only** (for now…)
  - Purely **discrete**
  - Simulate **all** elementary interactions on an event-by-event basis
- No condensed history approximation
- Models can be purely **analytical and/or use interpolated data tables**
- Use the **same software design** as all electromagnetic models available in Geant4 (standard EM and low energy EM)
- Extension is on-going…

Physics stage :
status of Physics models in Geant4 9.4

	e	p	H	α, He+, He	C, O, Fe,...
Elastic scattering	> 8.23 eV Screened Rutherford > 8.23 eV Champion	-	-	-	-
Excitation A_1B_1, B_1A_1, Ryd A+B, Ryd C+D, diffuse bands	8.23 eV – 10 MeV Emfietzoglou	10 eV – 500 keV Miller Green 500 keV – 100 MeV Born	-	Effective charge scaling from same models as for proton **improved**	**Ionisation ready but not delivered**
Charge Change	-	100 eV – 10 MeV Dingfelder	100 eV – 10 MeV Dingfelder		
Ionisation $1b_1$, $3a_1$, $1b_2$, $2a_1 + 1a_1$	11 eV – 1 MeV Born	100 eV – 500 keV Rudd 500 keV – 100 MeV Born	100 eV – 100 MeV Rudd **improved**	**1 keV – 400 MeV**	
Vibrational excitation	**0.025 – 100 eV**	-			
Attachment	**4 – 13 eV**				

Radiation Chemistry

Modeling water radiolysis ?



Physico-chemical stage

Physico-chemistry

Dissociation:
$H2O^{*/+} \rightarrow (H3O^+, OH^-, e_{aq}, H, H2)$

Thermalization:
products slow down to diffusion energy
(cf. Kreipl et al, REB, 2009)

Ionised molecules convert into :
$H2O^+ + H2O \blacktriangleright H3O^+ + OH\bullet$

Excited molecules relax or dissociate

	Process	Decay channel	Fraction (%)
Ionisation (H_2O^+)			
$1b_1$, $3a_1$, $1b_2$, $2a_1$, K	Dissociative decay	$H_3O^+ + {}^\bullet OH$	100
Excitation (H_2O^*)			
A^1B^1	Dissociative decay	${}^\bullet OH + H^\bullet$	65
	Relaxation	$H_2O + \Delta E$	35
B^1A^1	Auto-ionisation	$H_3O^+ + {}^\bullet OH + e^-_{aq}$	55
	Dissociative decay	$H_2 + {}^\bullet O^\bullet$	15
	Relaxation	$H_2O + \Delta E$	30
Ryd, diff bands	Auto-ionisation	$H_3O^+ + {}^\bullet OH + e^-_{aq}$	50
	Relaxation	$H_2O + \Delta E$	50

(From Kreipl et al, Radiat Environ Biophys, 2009)

t=10-15s → t=10-12s

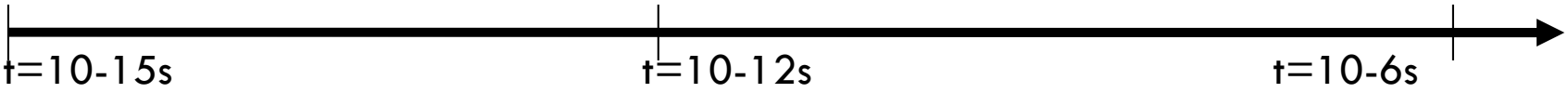
Chemistry stage

Physico-chemistry stage

Chemistry stage

Radiolytic species

- diffuse
- interact
  - amongst themselves
  - with the DNA



Chemistry stage

Physico-chemistry stage

Chemistry stage

Two models available in the literature:

- Step By Step (SBS)
  - Accurate
  - Resource usage
- Independent Reaction Time (IRT)
  - Faster
  - Accuracy?

t=10-15s t=10-12s t=10-6s

Chemistry stage: Step By Step Model

Physico-chemistry stage

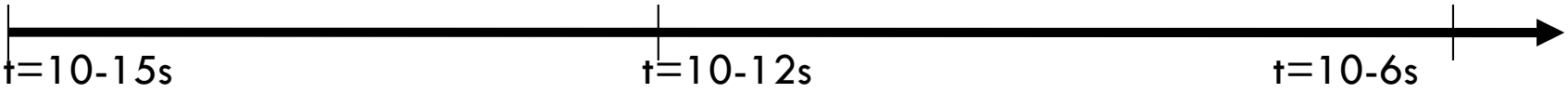
Chemistry stage

<u>Step by step model</u>

1.Check if molecules are "close enough" to react

2.Reactions (if any)

3.Make one diffusion step for all the molecules, go to point 1



Step By Step model: Interaction Process

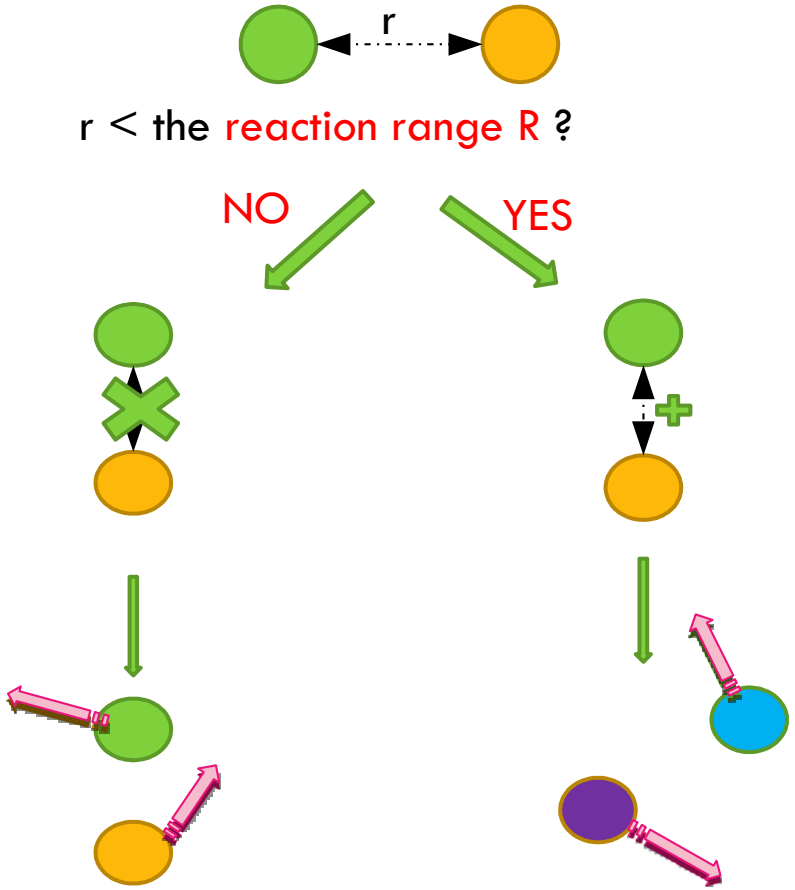
Chemistry stage

Step by step model

1.Check if molecules are "close enough" to react

2.Reactions (if any)

3.Make one diffusion step for all the molecules, go to point 1



t=10-12s

t=10-6s

Step by Step model: Diffusion process

Chemistry stage

Step by step model

1.Check if molecules are "close enough" to react

2.Reactions (if any)

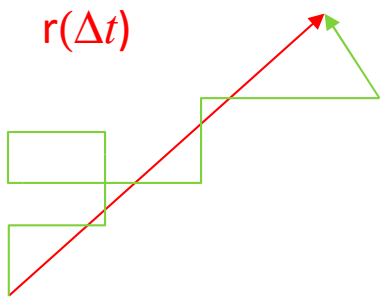
3.Make one diffusion step for all the molecules, go to point 1

t=10-12s

t=10-6s

Physics: in a given interval of observation Δt we have a succession of different steps

Geant4: A molecule "jumps" for a calculated distance in a random direction



Step by Step model: Diffusion process

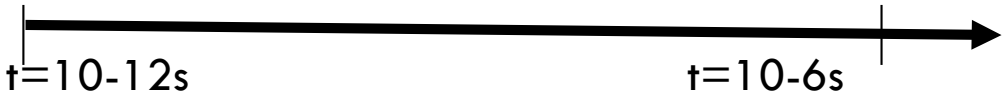
Chemistry stage

Step by step model

1.Check if molecules are "close enough" to react

2.Reactions (if any)

3.Make one diffusion step for all the molecules, go to point 1



To calculate r(Δt) (i.e. step size) we need:

- Δt
- D(mol), the diffusion coefficient

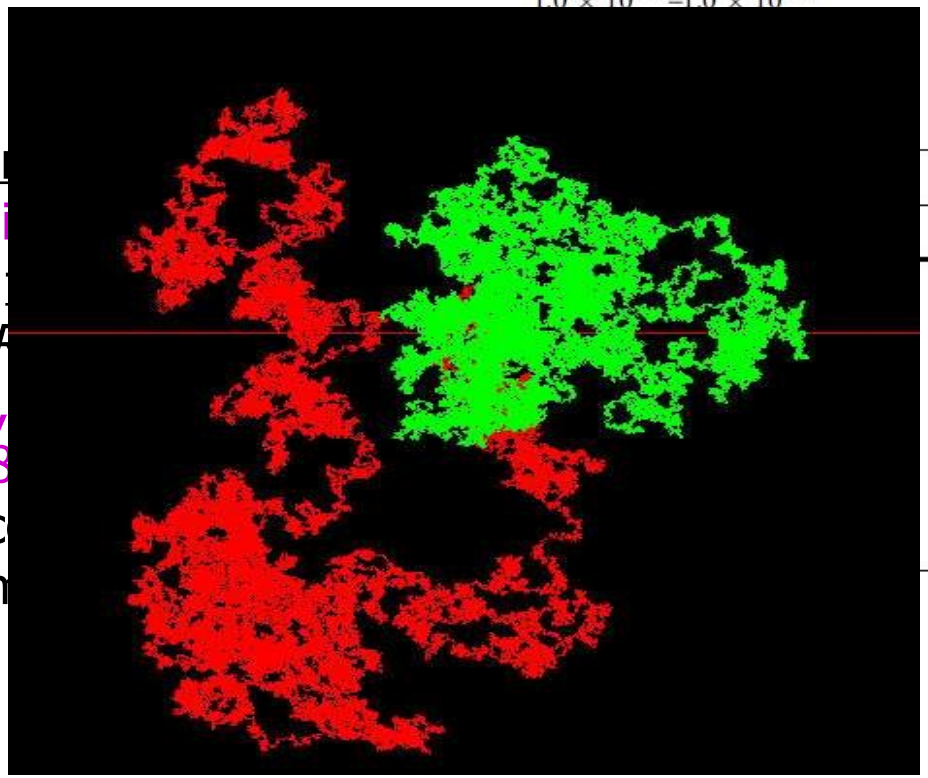
Following this formula:

$$\sqrt{\langle r^2 \rangle} = \sqrt{2\,D\,\Delta t}$$

Step by Step model: PARTRAC approach

The time step is used to calculate the space step.
How to define the

- Δt = User defi
  approach (Krei
- Δt =Minimum
  encounter → A
  (Michalik et al,
  Research,1998
- Δt = Time enc
  computed from
  approach



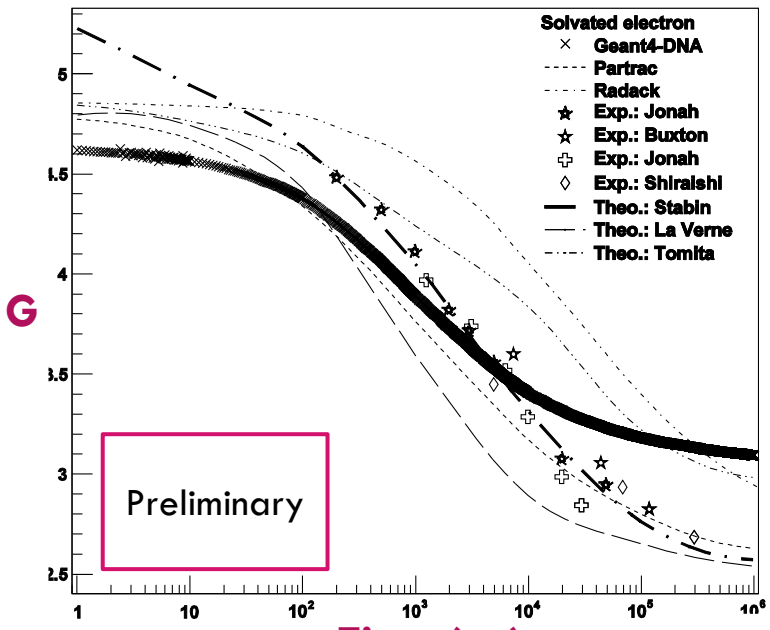
Time interval (s)	Δt (ps)
Until 1.0×10^{-11}	0.1
1.0×10^{-11}–1.0×10^{-10}	1
	3
	10
	100

D ($\times 10^{-9}$ m^2 s^{-1})
4.9
2.8
7.0
9.0
4.8
5.0
2.3

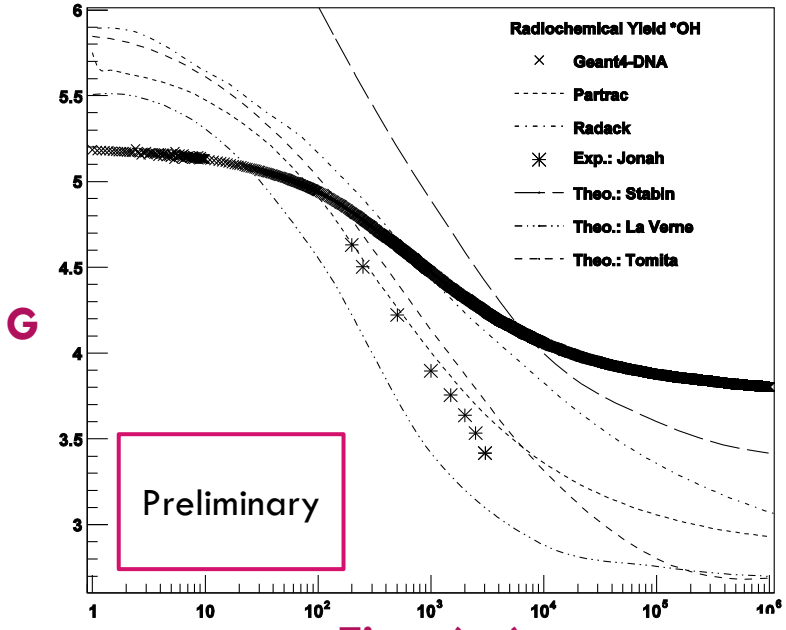
G values against time

G : **radiochemical yield** for a given species
(number of molecules created for 100 eV of deposit energy)

Solvated Electron



Hydroxyl OH°



Incident particle : e- 750 keV

Expected developments

Physics :

- add complementary/additional theoretical models
- other incident particles (C, O, …)
- other target materials (DNA, …)
- down to the sub-eV range
- allowing the simulation of direct DNA damages

Chemistry :

- Implement new models of diffusion & interaction :
  - the Independent Reaction Time (IRT) model → fast model of diffusion and interaction
  - Implement a multithread approach

Cellular and sub-cellular geometries :

- model realistic geometries down to the DNA scale following two approaches
- atomistic approach
- voxellized approach (phantoms)
- biological damage prediction -SSBs, DSBs (using geometry)

Comparison to experimental measurements:

For **water radiolysis** validation : LRad, CEA, Saclay, France, G. Baldacchino
For **cellular irradiation** : microbeam irradiation facility at CENBG

Conclusion

Geant4-DNA **Chemistry status** :

M**olecular mechanisms** have been implemented in G4:

- Molecules
- Decay process and product thermalization
- Diffusion
- Molecular interaction

Two years for completion, verification and validation of the code (expected delivery end **2012)**

Open source package of Geant4

Thank you For your attention

Where to find more information

Geant4-DNA :

Internet & recent publications

Geant4 web site
Low Energy Electromagnetic Physics Working group page
www.geant4.org

Geant4-DNA:
ESA / AO6041 project
geant4.in2p3.fr

Molecular scale track structure simulations in liquid water using the Geant4-DNA Monte-Carlo processes
Z. Francis *et al.*, Applied Radiation and Isotopes (2010) (link)

Comparison of GEANT4 very low energy cross section models with experimental data in water,
S. Incerti *et al.*, Med. Phys. 37 (2010) 4692-4708 (link)

The Geant4-DNA project
S. Incerti *et al.*, Int. J. Model. Simul. Sci. Comput. 1, (2010) 157–178 (link)

A free-parameter theoretical model for describing the electron elastic scattering in water in the Geant4 toolkit
C. Champion *et al.*, Rad. Phys. Chem. 78 (2009) 745-750 (link)