http://geant4-dna.org

Geant4-DNA Overview

Sébastien Incerti

2015 Geant4-DNA Tutorial

Hiroshima, Japan

August 24-25

Topics

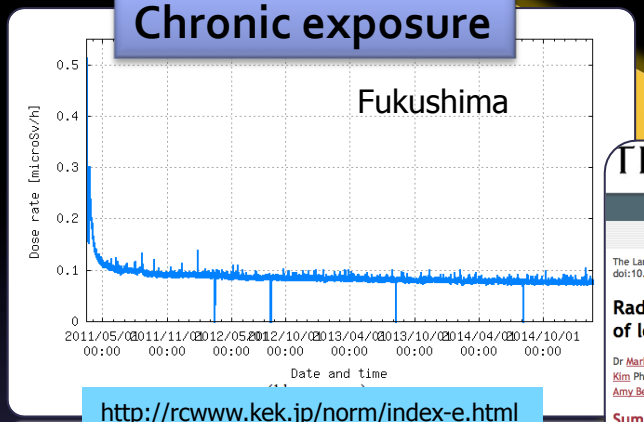
1. Context of the Geant4-DNA project
2. Physical stage
3. Physico-chemical & chemical stage
4. Geometrical models of biological targets
5. Where to find more information ?

See Geant4-DNA reference …(link)

1) CONTEXT

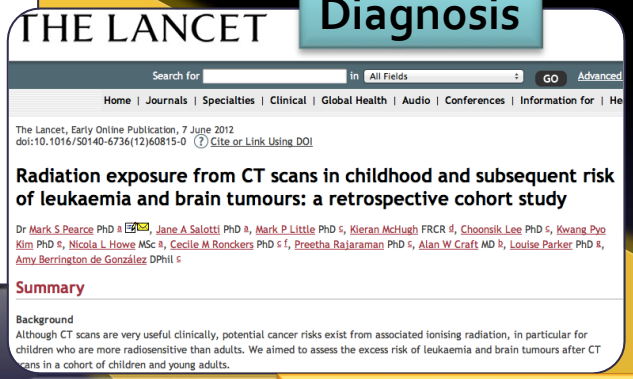
Modelling biological effects of ionising radiation remains a major scientific challenge

Chronic exposure



http://rcwww.kek.jp/norm/index-e.html

Diagnosis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The Lancet, Early Online Publication, 7 June 2012
doi:10.1016/S0140-6736(12)60815-0 Cite or Link Using DOI

Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study

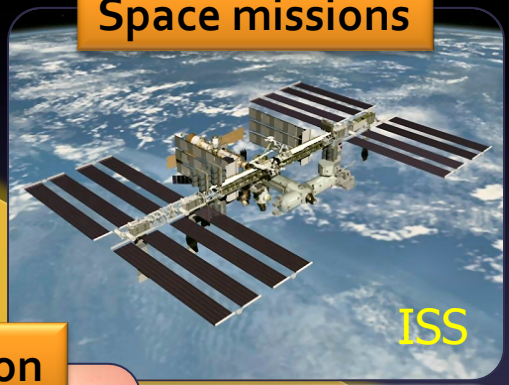
Dr Mark S Pearce PhD a, Jane A Salotti PhD a, Mark P Little PhD c, Kieran McHugh FRCR d, Choonsik Lee PhD c, Kwang Pyo Kim PhD e, Nicola L Howe MSc a, Cecile M Ronckers PhD c f, Preetha Rajaraman PhD c, Alan W Craft MD b, Louise Parker PhD a, Amy Berrington de González DPhil c

Summary

Background

Although CT scans are very useful clinically, potential cancer risks exist from associated ionising radiation, in particular for children who are more radiosensitive than adults. We aimed to assess the excess risk of leukaemia and brain tumours after CT scans in a cohort of children and young adults.

Space missions



Space exploration

Proton & hadrontherapy

« A MAJOR CHALLENGE LIES IN PROVIDING A SOUND MECHANISTIC UNDERSTANDING OF LOW-DOSE RADIATION CARCINOGENESIS »

L. MULLENDERS *ET AL.*

ASSESSING CANCER RISKS OF LOW-DOSE RADIATION

NATURE REVIEWS CANCER (2009)

The Monte Carlo approach

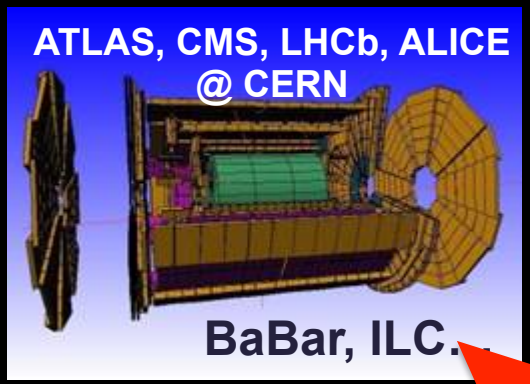
- Can « reproduce » with accuracy the stochastic nature of particle-matter interactions
- Many Monte Carlo codes are already available today in radiobiology for the simulation of track structures at the molecular scale in biological medium
  - E.g. PARTRAC, MC4*, TRIOL, PHITS, KURBUC, NOREC…
  - Include physics & physico-chemistry processes, detailed geometrical descriptions of biological targets down to the DNA size, DNA and chromosome damage simulation and even repair mechanisms (PARTRAC)…
- Usually designed for very specific applications
- Not always easily accessible
  - Is it possible to access the source code ?
  - Are they adapted to recent OSs ?
  - Are they extendable by the user ?

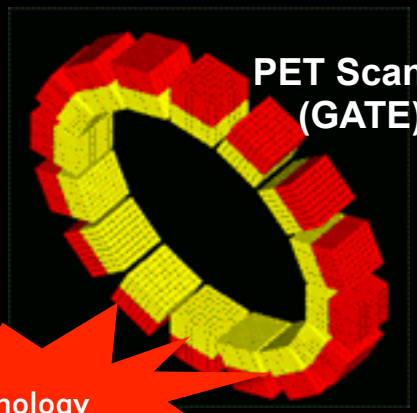
« To expand accessibility and avoid 'reinventing the wheel', track structure codes should be made available to all users via the internet from a central data bank»

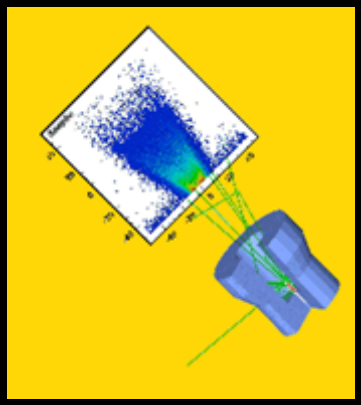
H. Nikjoo, IJRB 73, 355 (1998)

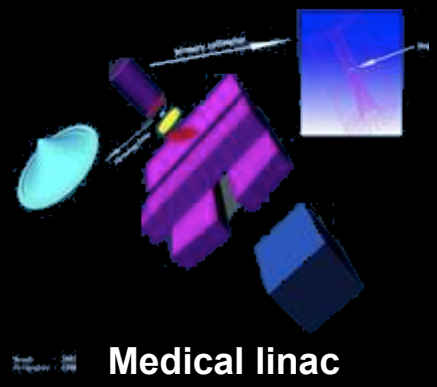
Geant4 for radiobiology

- Can we try to extend Geant4 to model biological effects of radiation ?
- 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
    - 100 eV for Penelope 2008 Low Energy EM models
  - 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…



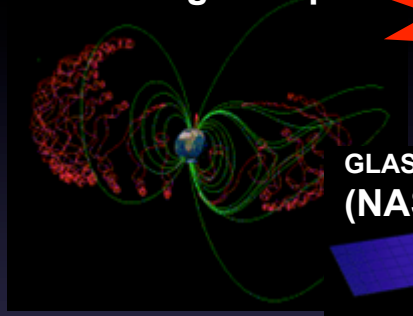




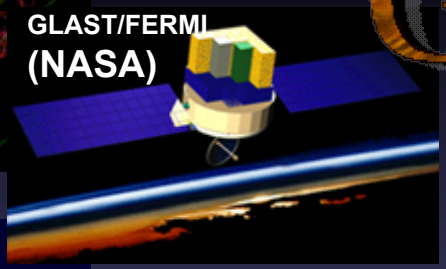


Technology transfer

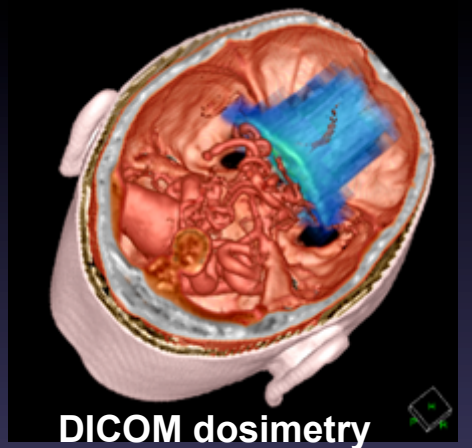
Earth magnetosphere

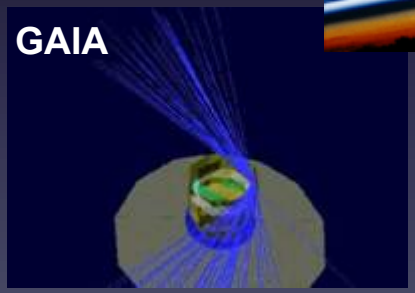


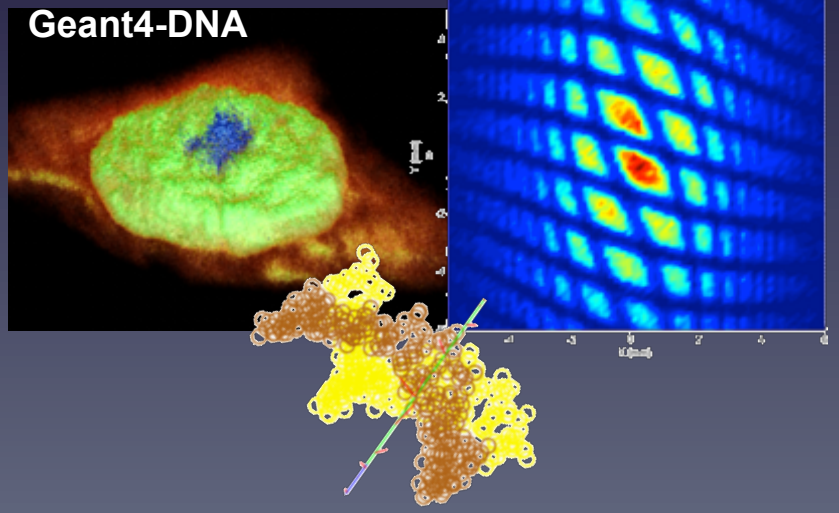
GLAST/FERMI
(NASA)

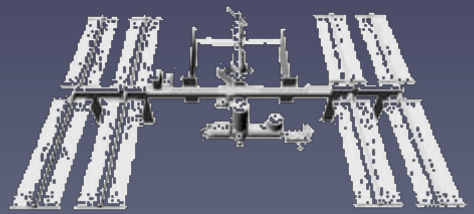


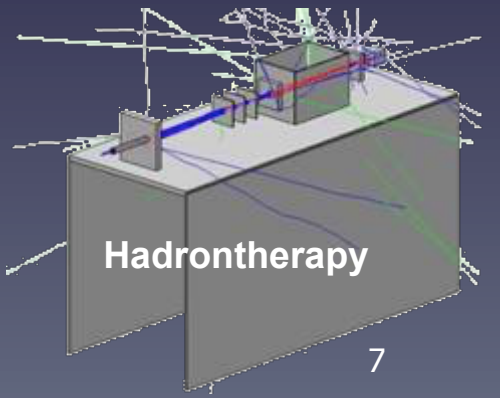
Geant 4











See Int. J. Model. Simul. Sci. Comput. 1 (2010) 157-178 (link)

The Geant4-DNA project

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 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.

2001

Initiated at the **European Space Agency/ESTEC** by Petteri Nieminen

2007

First prototypes of **physics models** for liquid water added to Geant4 **9.1**

W. Friedland
D. Emfietzoglou
M. Dingfelder

2008

Development coordinated by CNRS/IN2P3

(physics, chemistry, geometries)

2014

Chemistry stage extension ready for end users in Geant4 **10.1**

See Int. J. Model. Simul. Sci. Comput. 1 (2010) 157-178 (link)

The Geant4-DNA project

- The code is fully included in Geant4
- It is an independent sub-category of the electromagnetic physics category of Geant4: $G4INSTALL/source/processes/electromagnetic/dna
- An interdisciplinary activity of the Geant4 « low energy electromagnetic physics » working group
- Both are coordinated by CNRS/IN2P3 since 2008
- Integration in Geant4 enables the use of Geant4-DNA physics from inside GATE (2014) and TOPAS (2015)

http://www.topasmc.org

Contact: Joseph Perl @ SLAC

http://www.opengatecollaboration.org

Contact: Irène Buvat @ CNRS

How can Geant4-DNA model early DNA damage ?

PHYSICAL STAGE
step-by-step modelling of **physical interactions** of incoming & secondary ionising radiation with biological medium (liquid water)

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

PHYSICO-CHEMICAL/CHEMICAL STAGE
- **Radical** species production
- Diffusion
- Mutual chemical interactions

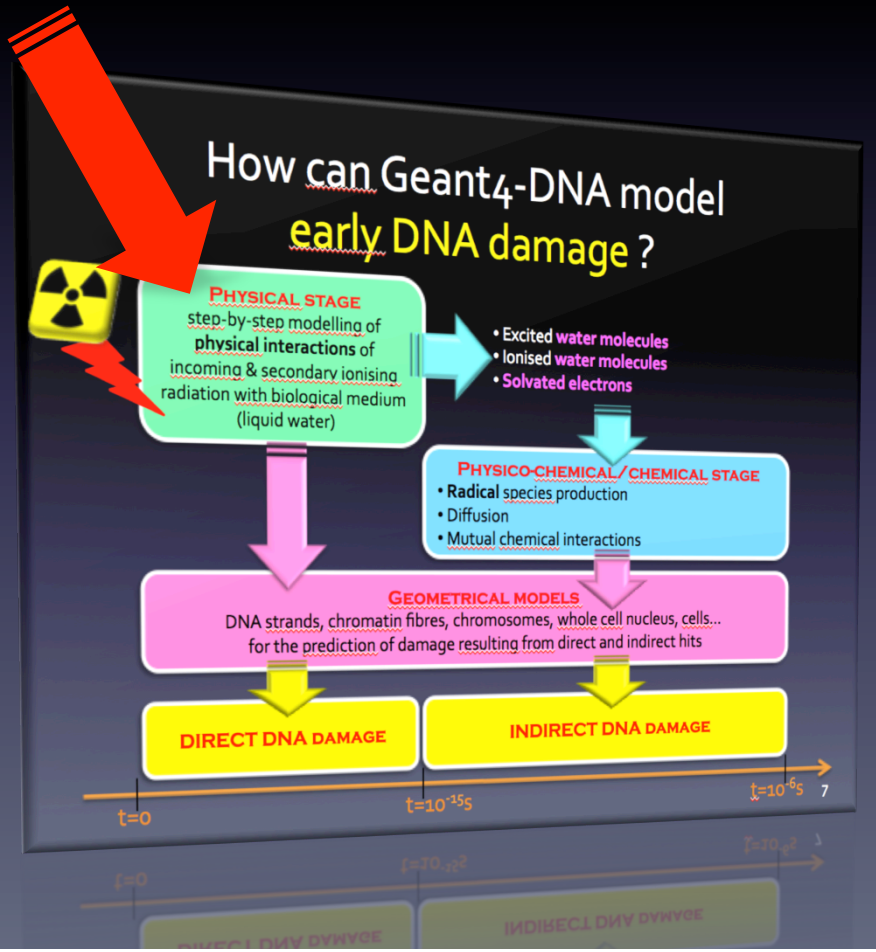
GEOMETRICAL MODELS
DNA strands, chromatin fibres, chromosomes, whole cell nucleus, cells…
for the prediction of damage resulting from direct and indirect hits

DIRECT DNA DAMAGE

INDIRECT DNA DAMAGE

t=0 $t=10^{-15}s$ $t=10^{-6}s$

2) PHYSICAL STAGE



Physics models available in Geant4 10.2BETA

- Geant4-DNA physics models are applicable to liquid water
  - Main component of biological matter
- They can reach the very low energy domain down to electron thermalization
  - Compatible with molecular description of interactions (5 excitation & ionisation levels of the water molecule)
  - Sub-excitation electrons (below ~9 eV) can undergo vibrational excitation, attachment and elastic scattering
- Purely discrete
  - Simulate all elementary interactions on an event-by-event basis (nanometer scale geometries)
  - No condensed history approximation
- Models can be purely analytical and/or use interpolated data tables
  - For eg. computation of integral cross sections
- Can be run in MultiThreading mode from Geant4 10 since December 2013
- They use the same software design as all electromagnetic models available in Geant4 (« standard » and « low energy » EM models and processes)
  - Allows the combination & addition of models and processes
  - Allows combination of discrete/condensed models

Overview of physics models for liquid water

Overview

10.2 BETA
26 June 2015

- **Electrons**
  - **Elastic scattering**
    - Screened Rutherford and Brenner-Zaider below 200 eV
    - Updated alternative version by Uehara from 10.2B
    - Partial wave framework model by C. Champion et al., 3 contributions to the interaction potential
  - **Ionisation**
    - 5 levels for H_2O
    - Dielectric formalism & FBA using H. Heller optical data up to 1 MeV, and low energy corrections, derived from the work of D. Emfietzoglou et al.
    - Improved alternative version by D. Emfietzoglou and I. Kyriakou from 10.2B
  - **Excitation (*)**
    - 5 levels for H_2O
    - Dielectric formalism & FBA using H. Heller optical data and semi-empirical low energy corrections, , derived from the work of D. Emfietzoglou et al.
    - Improved alternative version by D. Emfietzoglou and I. Kyriakou from 10.2B
  - **Vibrational excitation (*)**
    - M. Michaud *et al.* xs measurements in amorphous ice
    - Factor 2 to account for phase effect
  - **Dissociative attachment (*)**
    - C. Melton xs measurements

(*) only available in Geant4-DNA

See Med. Phys. 37 (2010) 4692-4708 (link)
Appl. Radiat. Isot. 69 (2011) 220-226 (link)
Med. Phys. 42 (2015) 3870 (link)

- **Protons & H**
  - **Excitation (*)**
    - Miller & Green speed scaling of e^- excitation at low energies and Born and Bethe theories above 500 keV, from M. Dingfelder *et al.*
  - **Ionisation**
    - Rudd semi-empirical approach by M. Dingfelder *et al.* and Born and Bethe theories & dielectric formalism above 500 keV (relativistic + Fermi density)
  - **Charge change (*)**
    - Analytical parametrizations by M. Dingfelder *et al.*
  - **Nuclear scattering**
    - Classical approach by Everhart *et al.*
- **He^0, He^+, He^{2+}**
  - **Excitation (*) and ionisation**
    - Speed and effective charge scaling from protons by M. Dingfelder *et al.*
  - **Charge change (*)**
    - Semi-empirical models from M. 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)

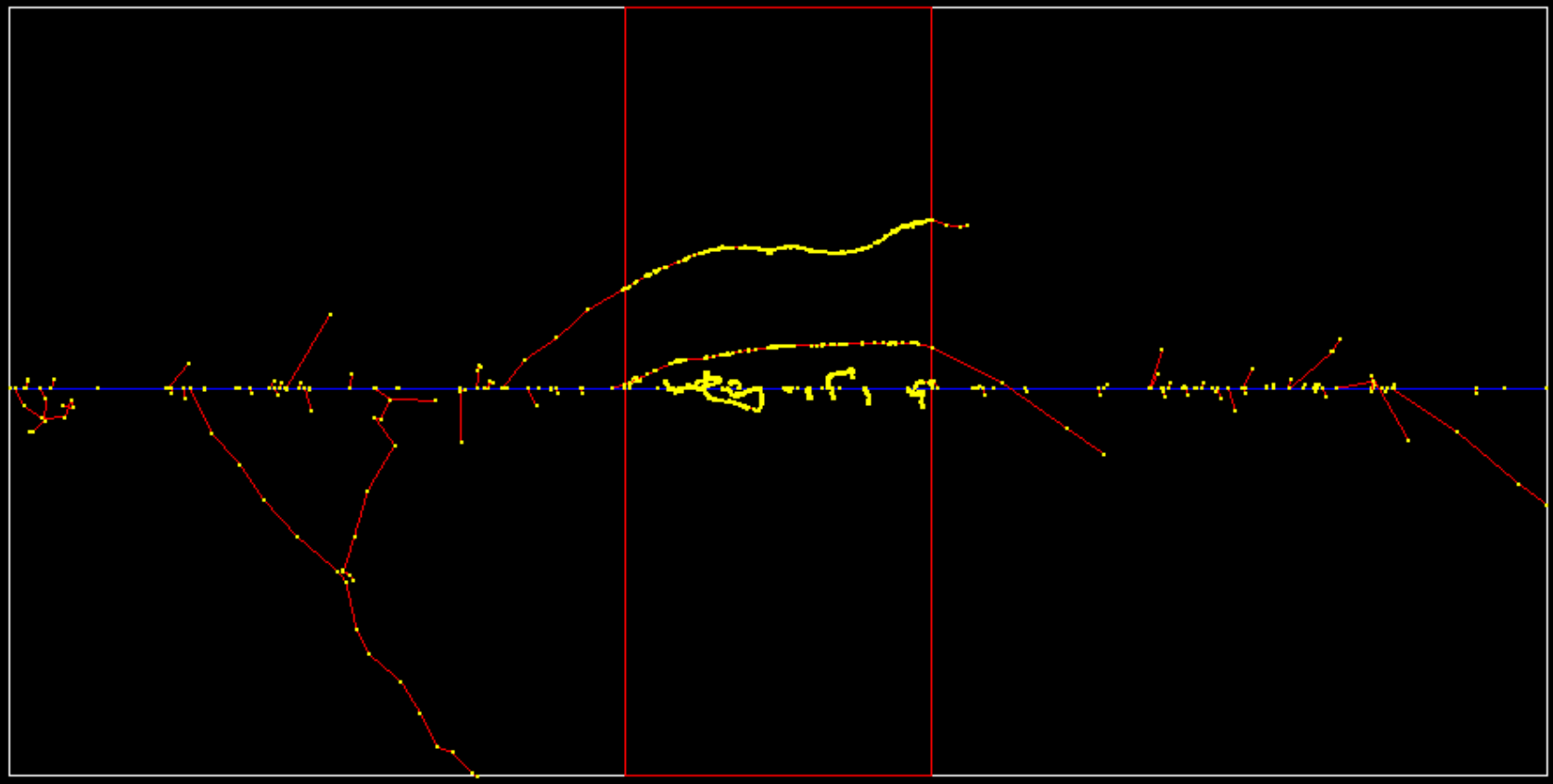
Multiscale combination of EM processes

Thanks to a unified software design, users can **easily combine Geant4-DNA processes and models** with existing Geant4 physics such as:

- Geant4 **photon** processes and models
  - Photoelectric effect, Compton sc., Rayleigh sc., pair production
  - Livermore (EPDL97) included by default
- Geant4 alternative **electromagnetic processes and models for charged particles**
  - Ionisation, bremsstrahlung, elastic scattering, etc…
  - Electrons, positrons, ions, etc…
- Geant4 **atomic deexcitation** (fluorescence + Auger emission)
  - EADL97
- …and also Geant4 **hadronic physics**

Mixed physics lists in geometrical regions: the « microdosimetry » extended example

Overview



/gps/particle ion
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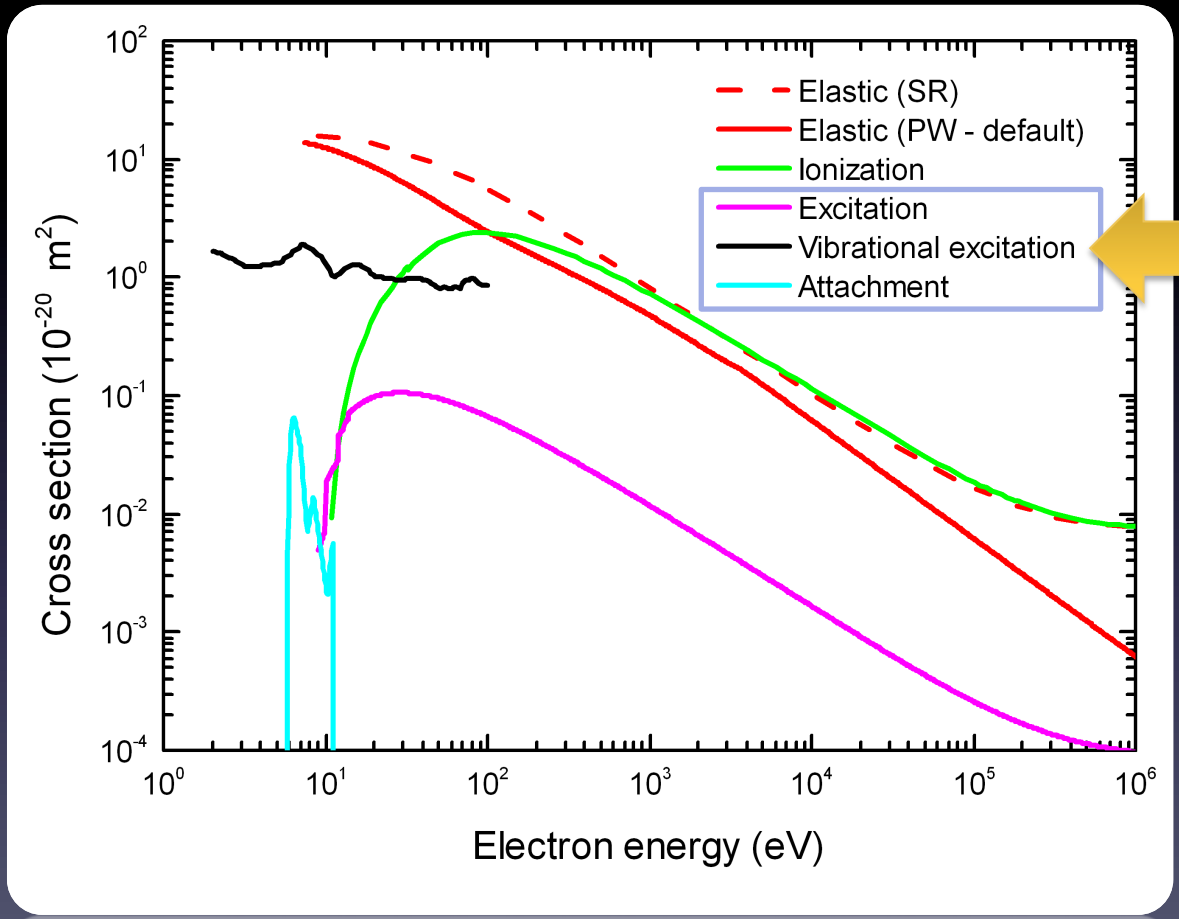
/gps/energy 240 MeV

Courtesy of V. Stepan (CENBG)

See Nucl. Instrum. and Meth. B 273 (2012) 95-97 (link)
Prog. Nucl. Sci. Tec. 2 (2011) 898-903 (link)

Verification

Eg. : electron cross sections



Verification

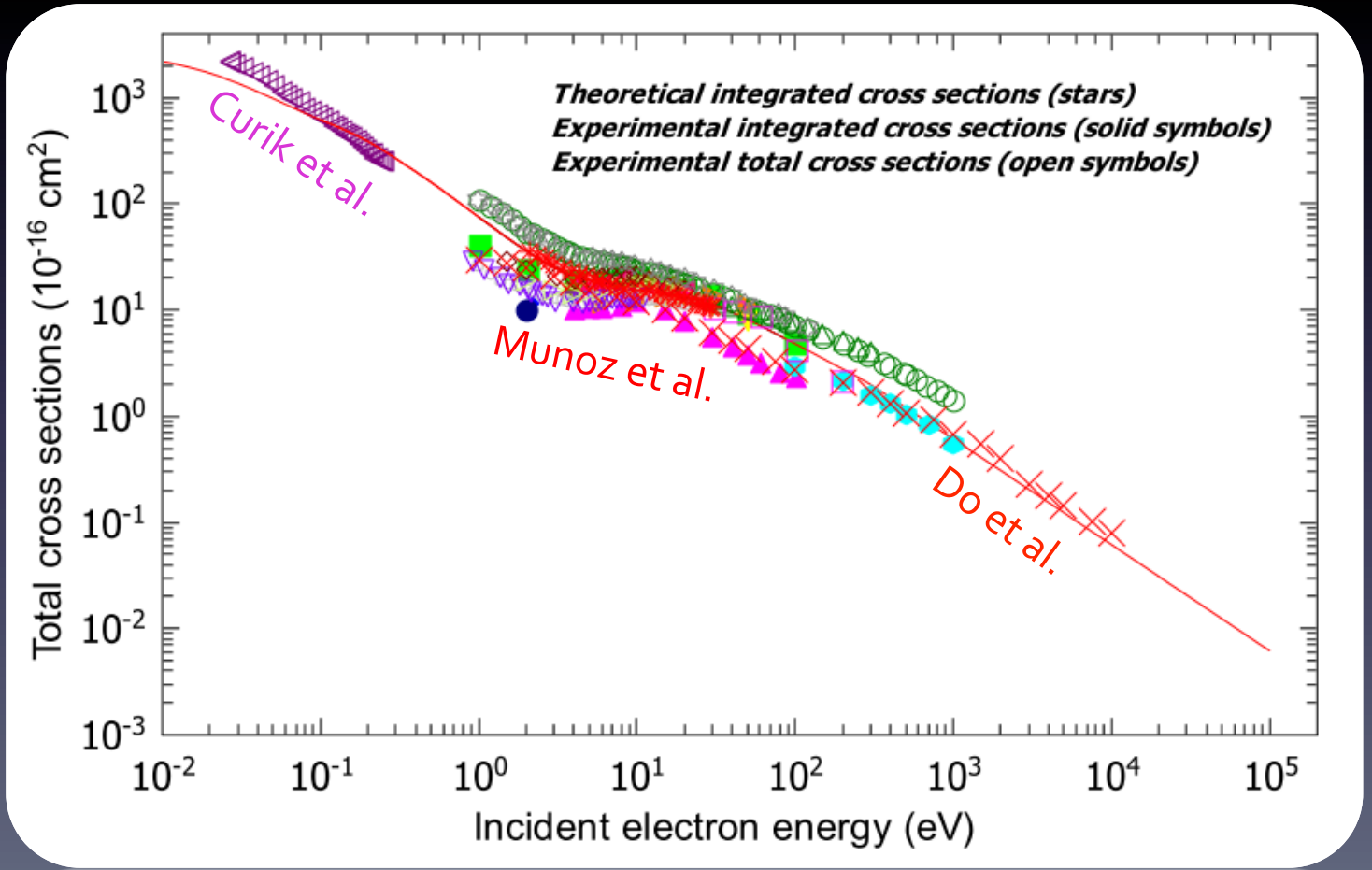
ranges, stopping powers

See Med. Phys. 37 (2010) 4692-4708 (link) and NIMB 269 (2011) 2307-2311 (link)

Verification

Electron elastic scattering cross section

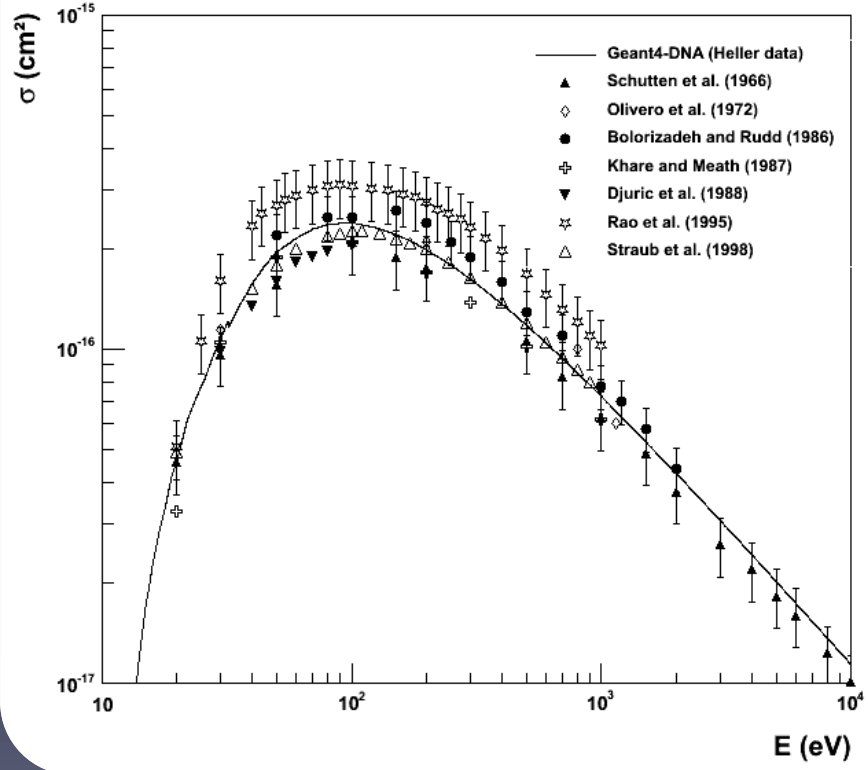
Based on the theoretical work of C. Champion *et al.* in the partial wave framework and with a spherical potential includes three distinct terms: a **static** contribution and two fine correction terms corresponding to the **correlation-polarization** and the **exchange** interactions



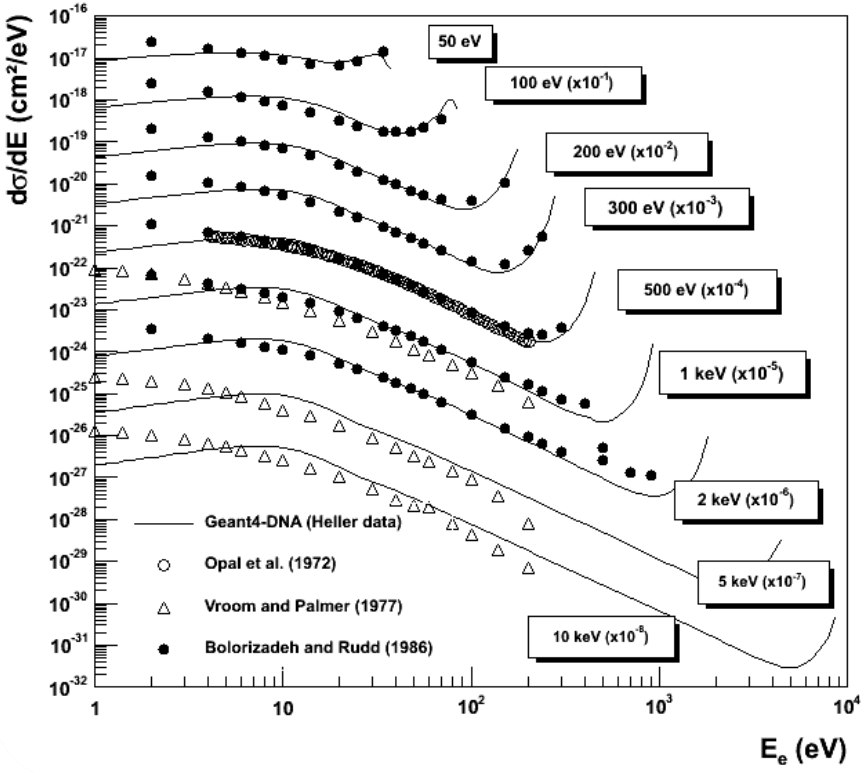
Verification

Electron ionisation

Total XS

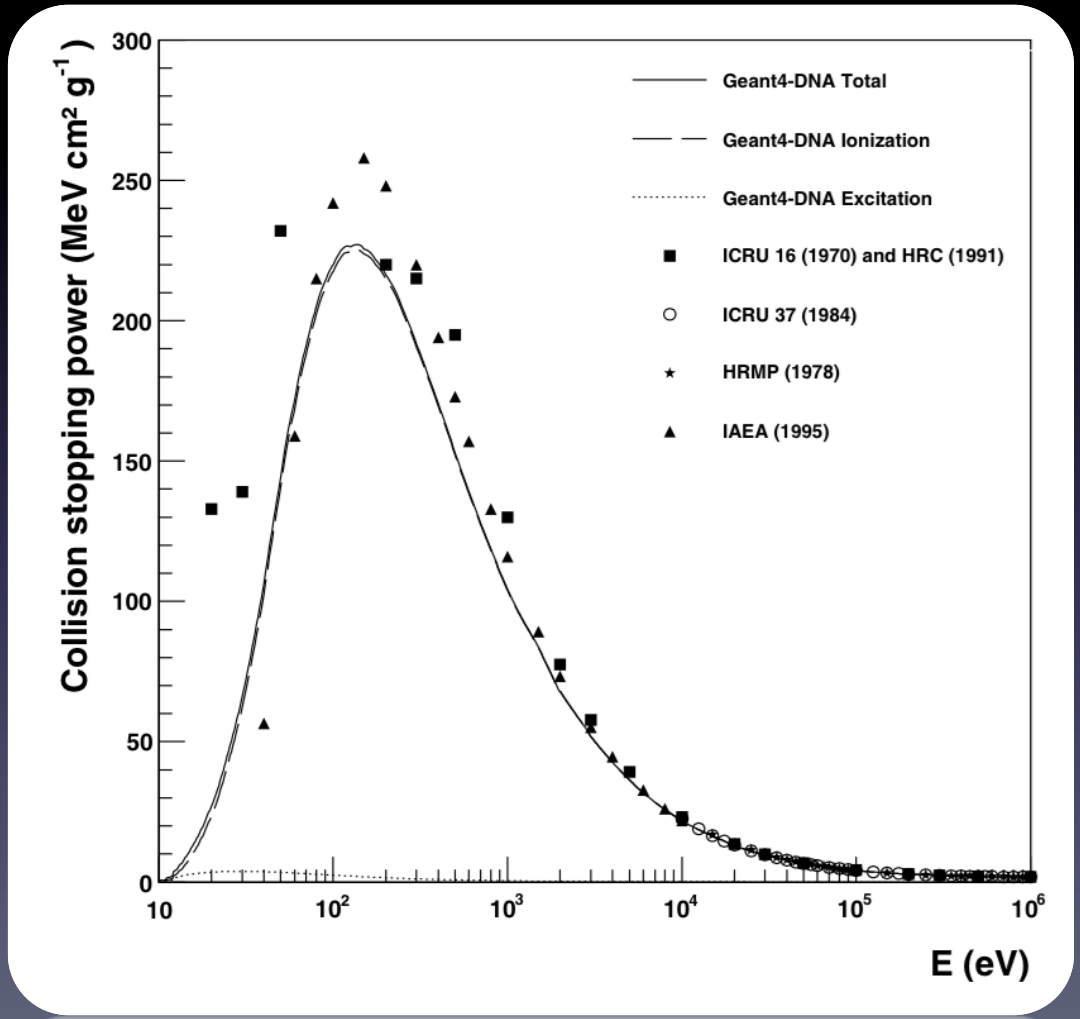


Differential XS



Verification

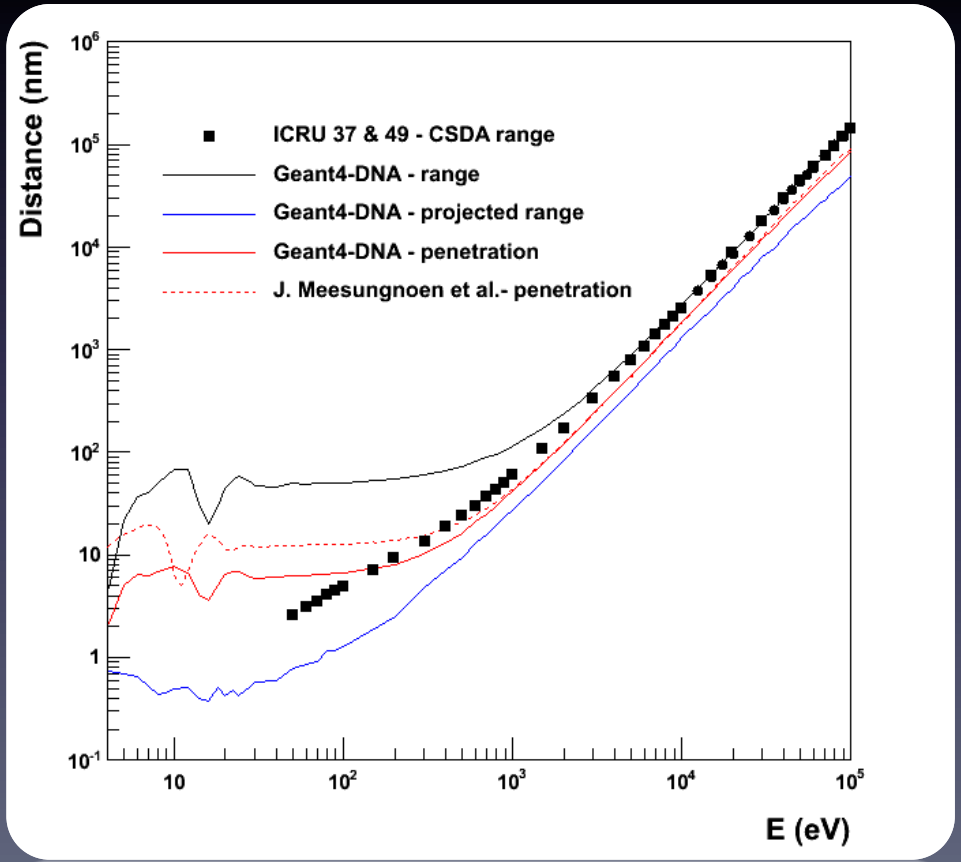
Electron stopping power



Electron range, projected range and penetration

- Obtained with the partial wave elastic scattering model
- Compared to ICRU recommendations and to penetration MC calculations

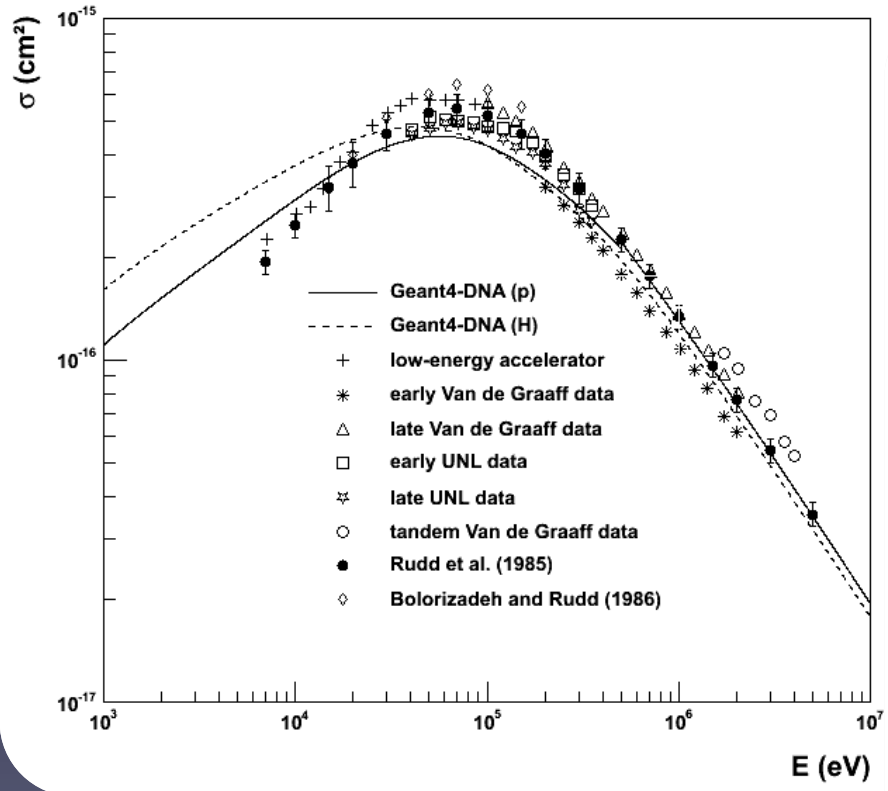
by Meesungnoen *et al*. (including a 2 factor on elastic and vib. excitation cross sections measured in ice)



Verification

Proton & Hydrogen ionisation

Total XS



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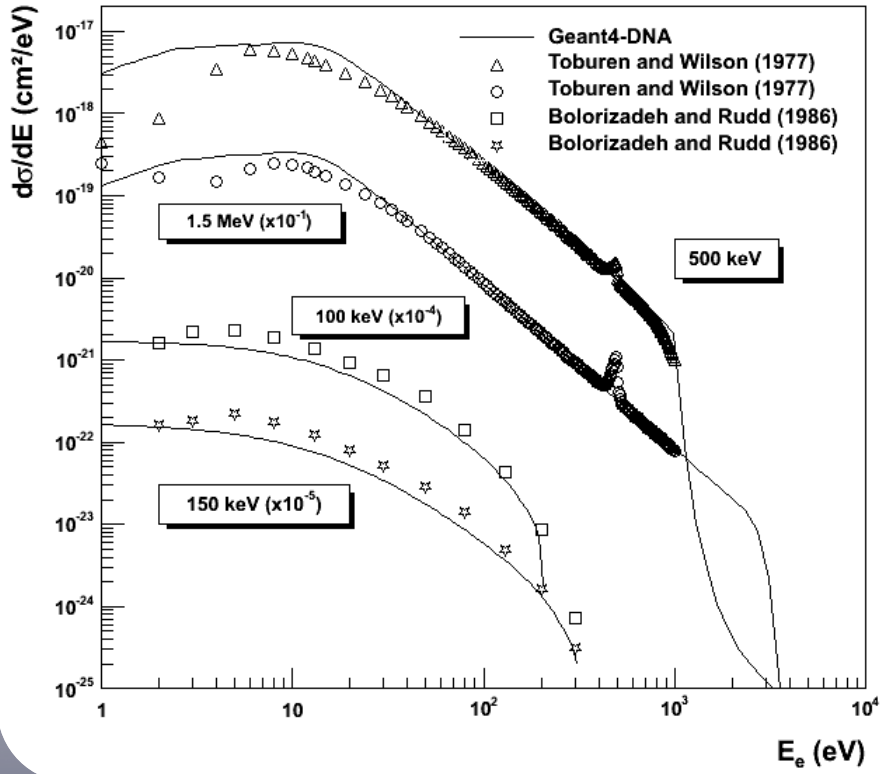
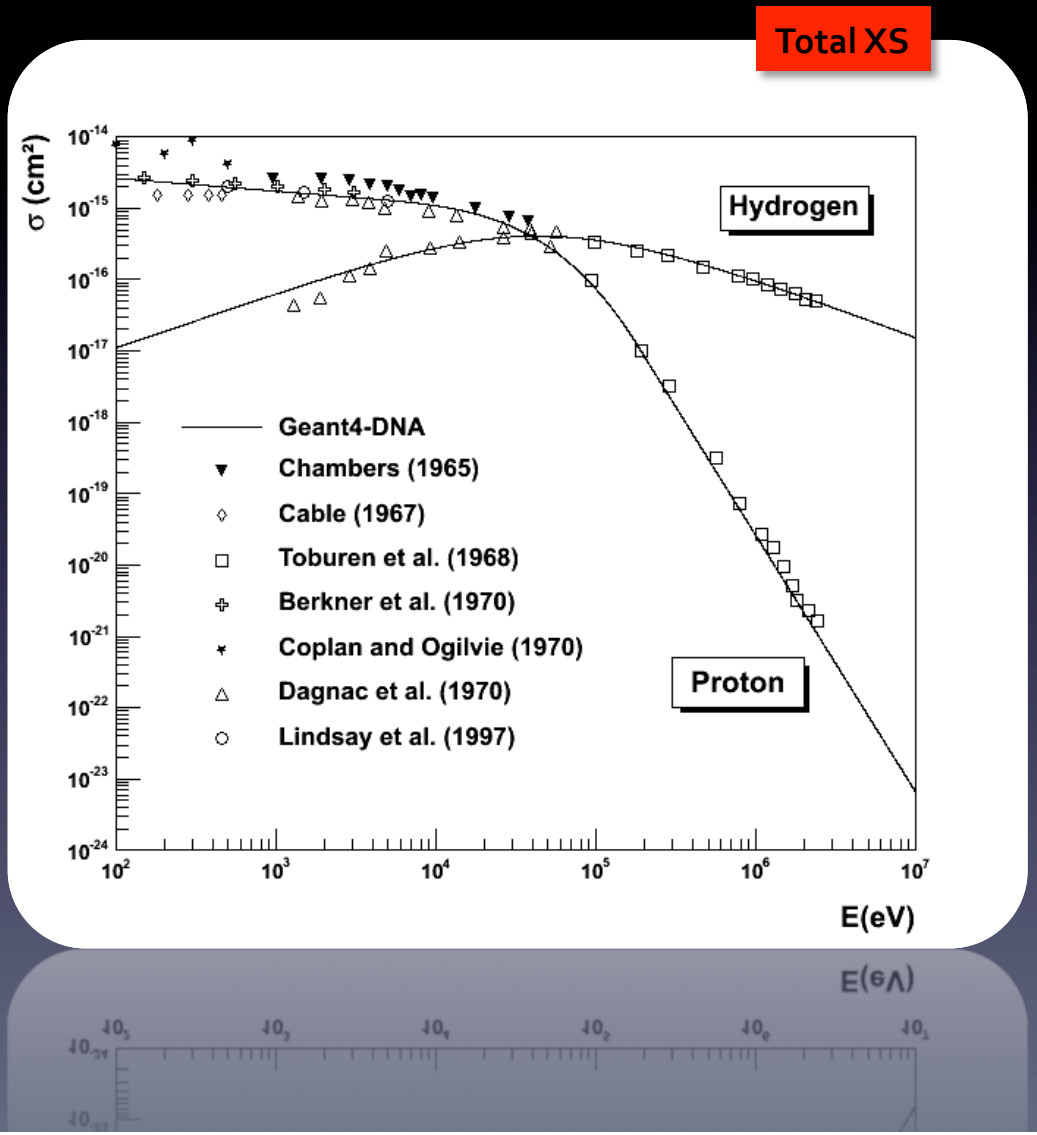


Verification

Proton and Hydrogen charge exchange

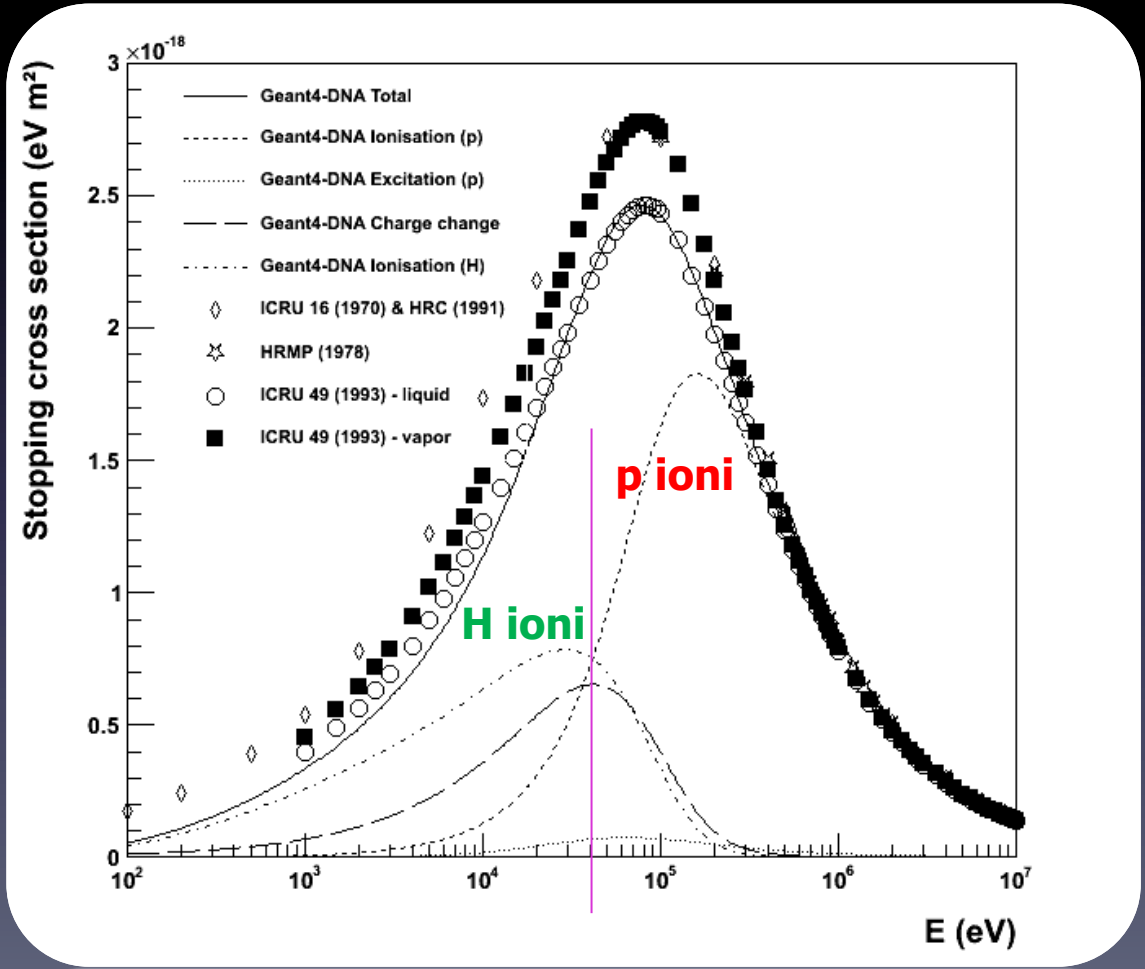
Total XS



Verification

Proton stopping cross section in liquid water

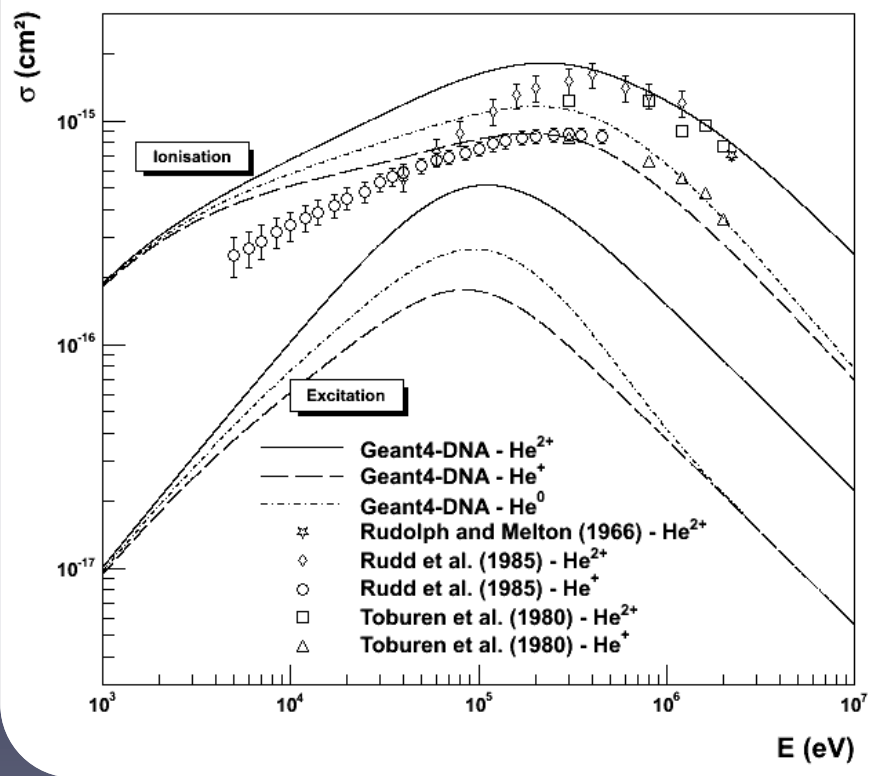
- Contributions of **ionisation** (p, H), **excitation** (p) and **charge change**
- Comparison to recommendations (ICRU, HRMP) for **liquid** and **vapour** water



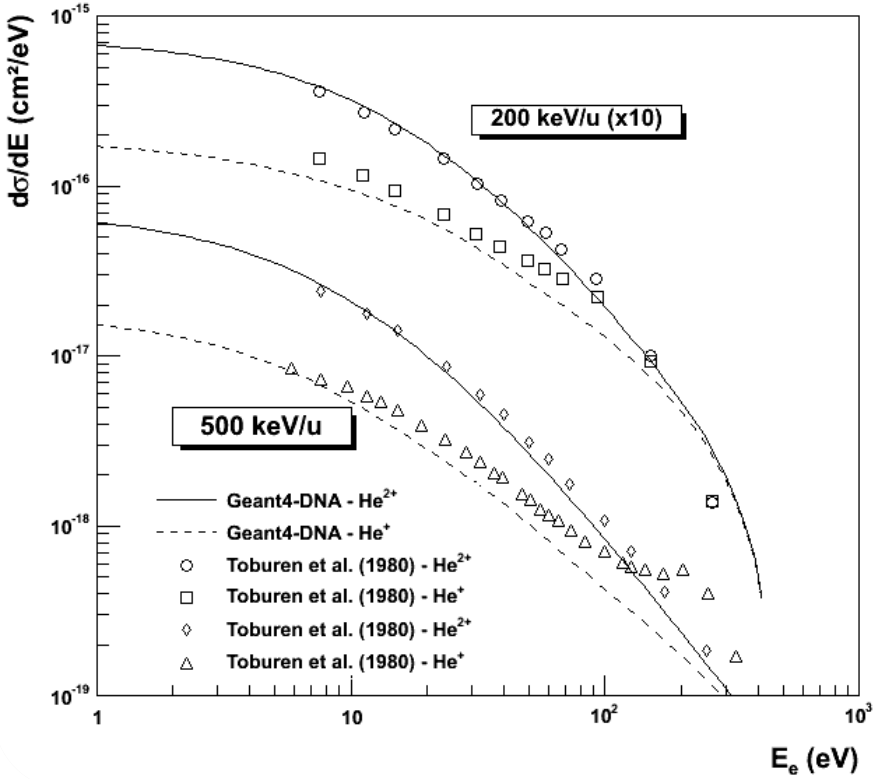
Verification

Helium ionisation

Total XS



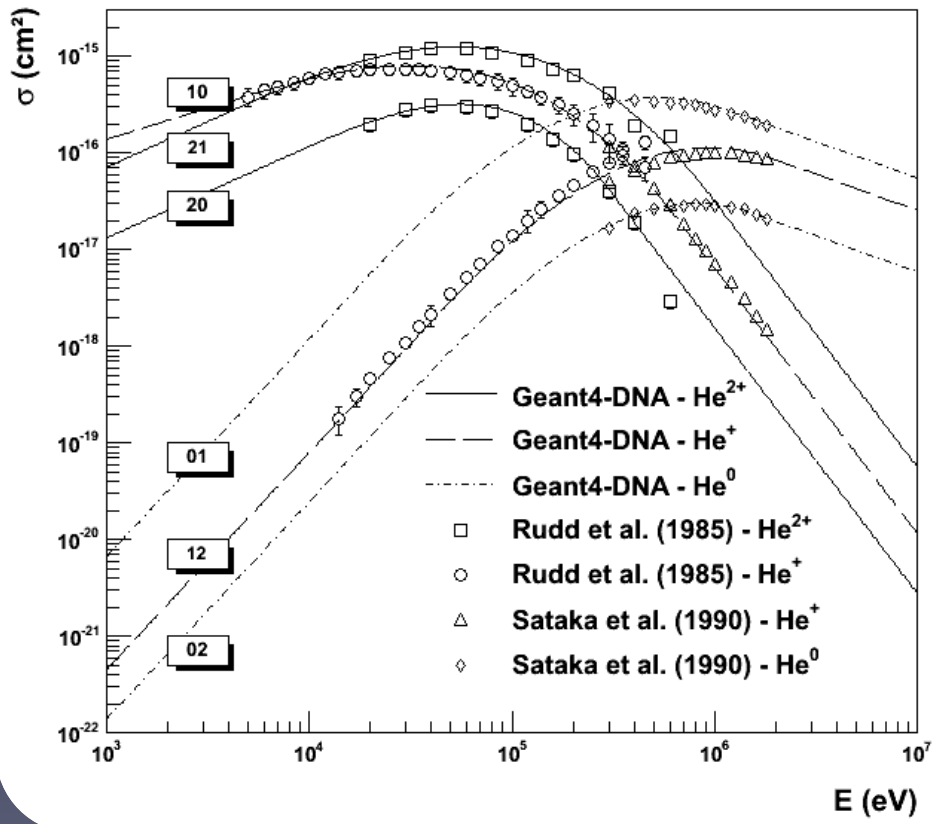
Differential XS



Verification

Helium charge exchange

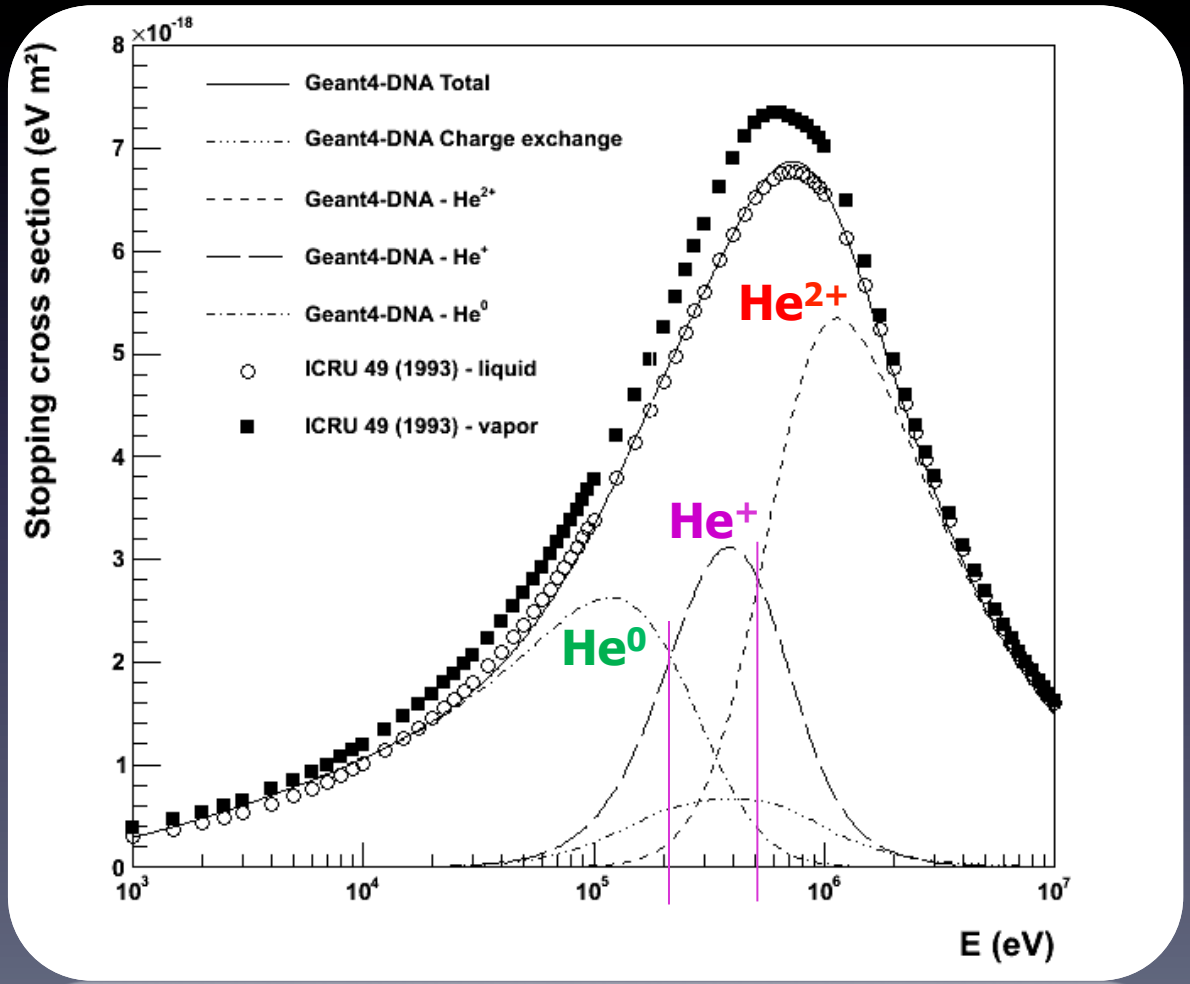
Total XS



Verification

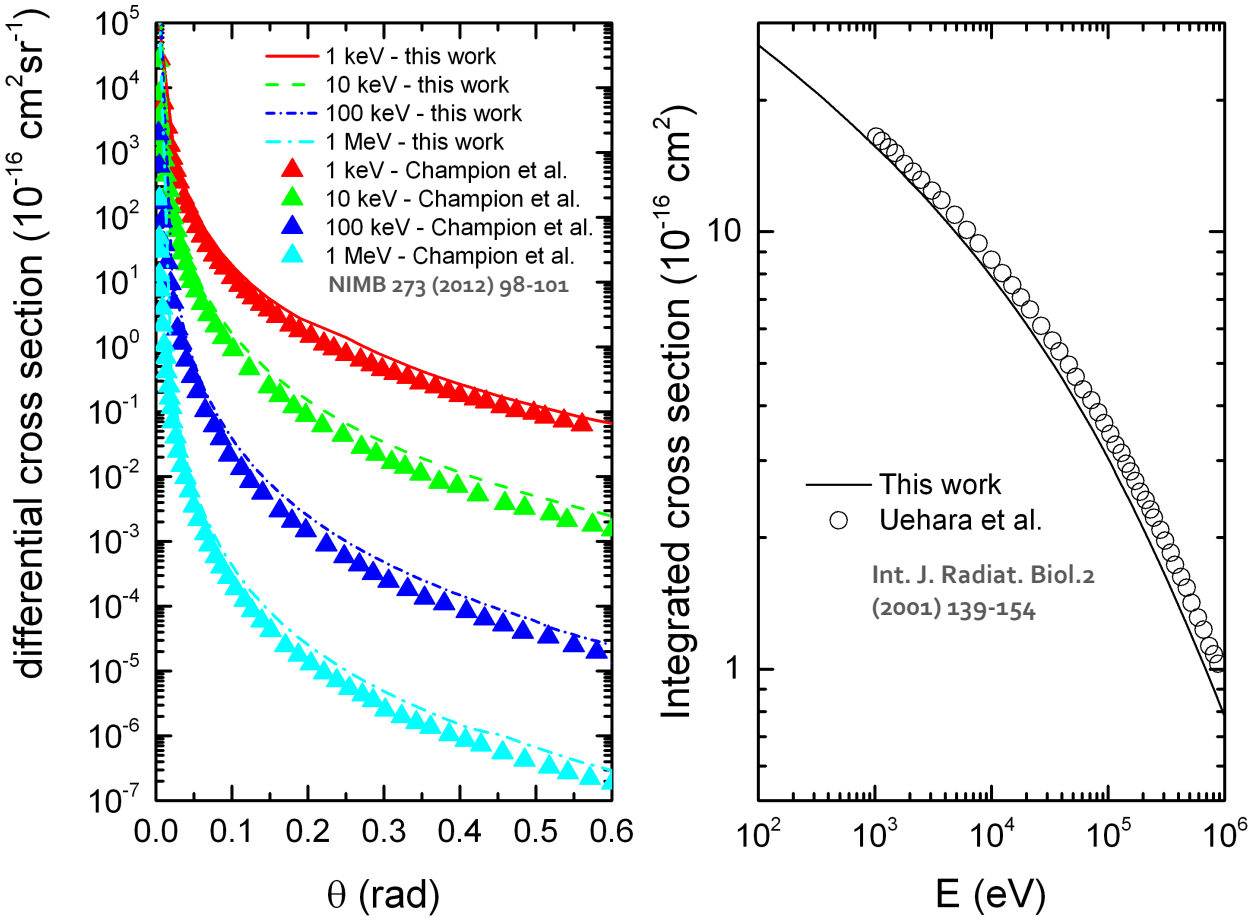
Helium stopping cross section

- Contributions of **3 charged states** of Helium
- Comparison to recommendations (ICRU) for **liquid** and **vapour** water



Verification

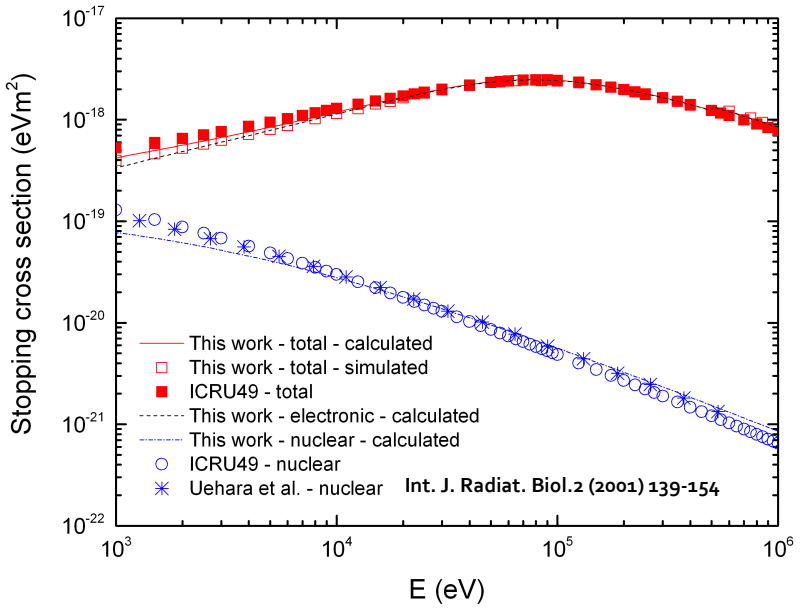
Differential cross section and Integral cross section for protons



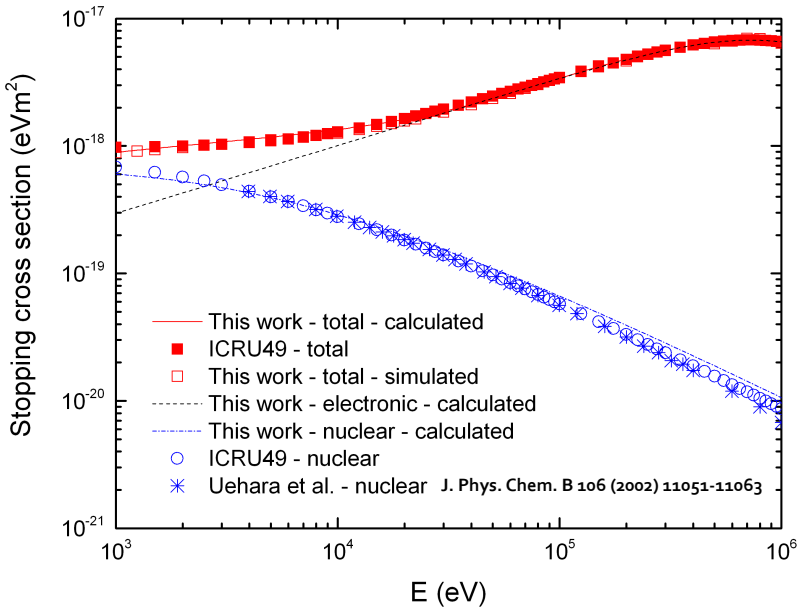
Verification

Stopping cross section

Protons



Alphas



Total, electronic and nuclear stopping cross sections

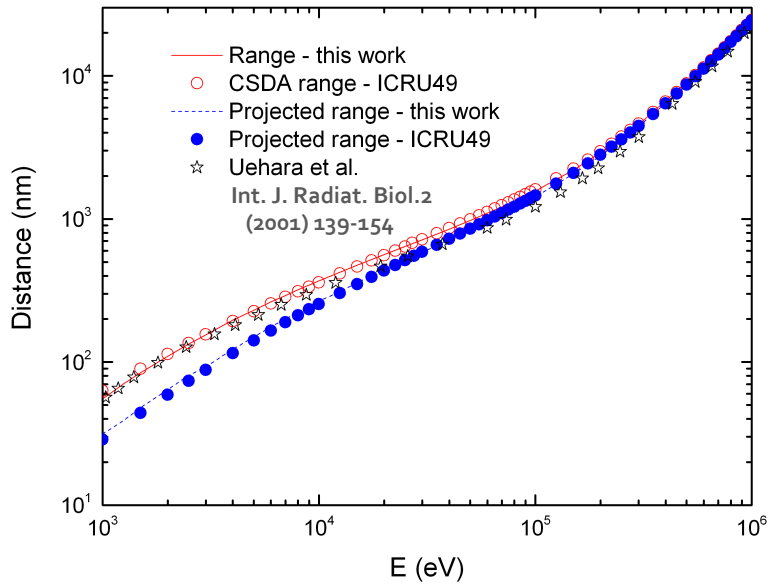
- calculated from Geant4-DNA cross sections
- simulated with Geant4-DNA

compared to ICRU49 and Uehara et al. Monte Carlo simulations

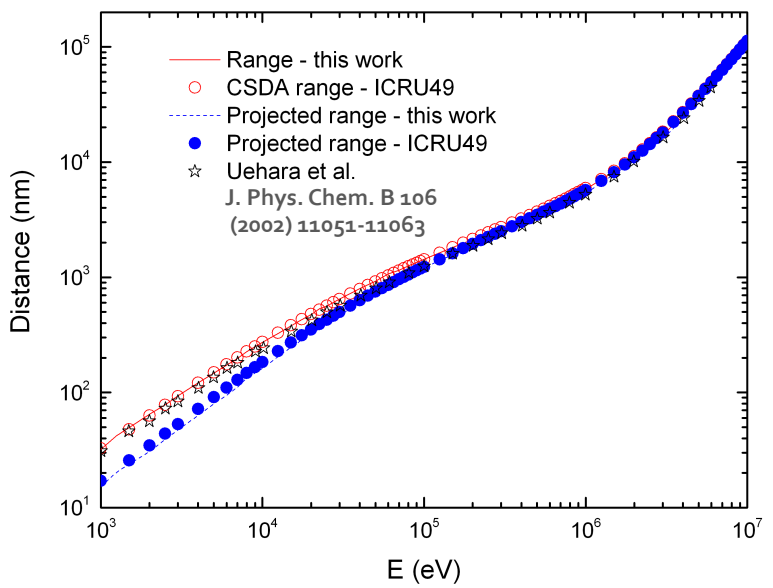
Verification

Range and projected range

Protons



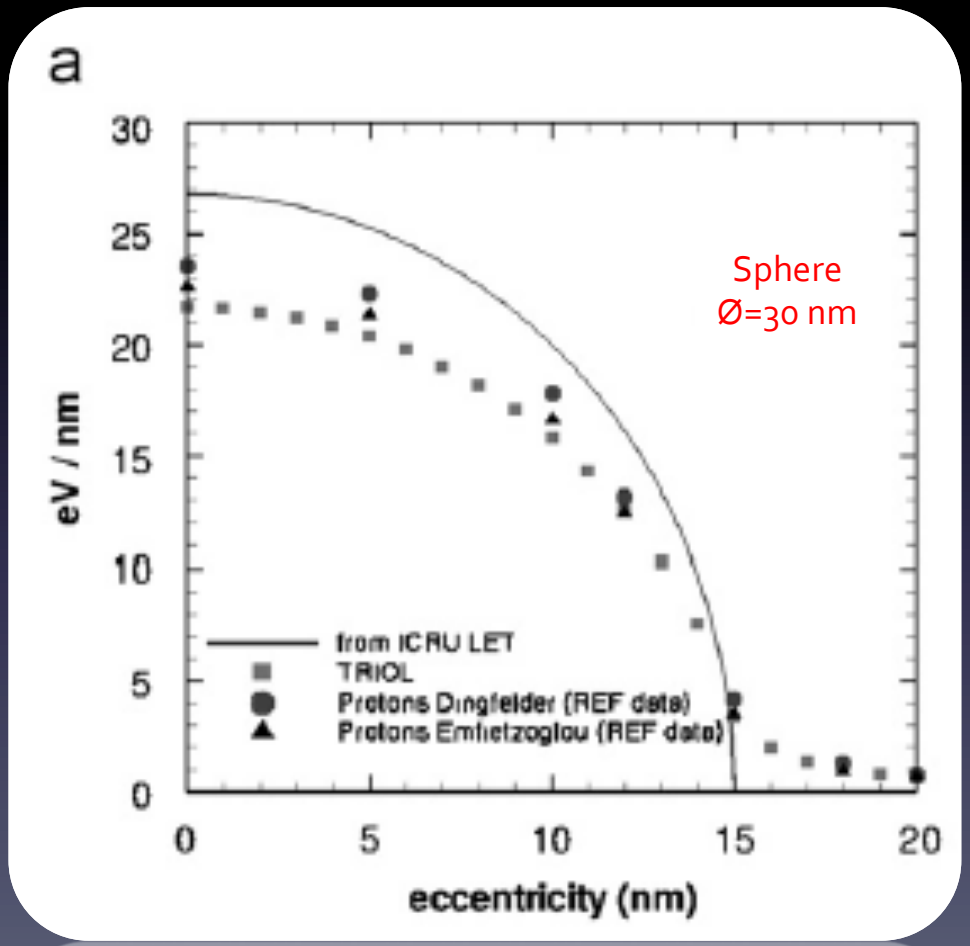
Alphas



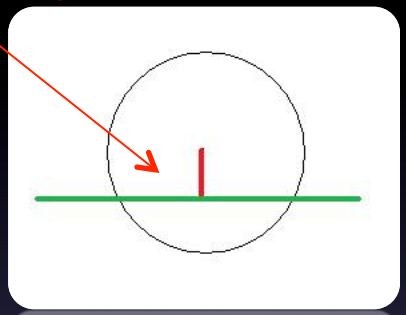
All Geant4-DNA processes are taken into account: excitation, ionization, charge-exchange and elastic scattering down to the tracking cut-off energy values

Verification

Mean energy deposition of protons



eccentricity



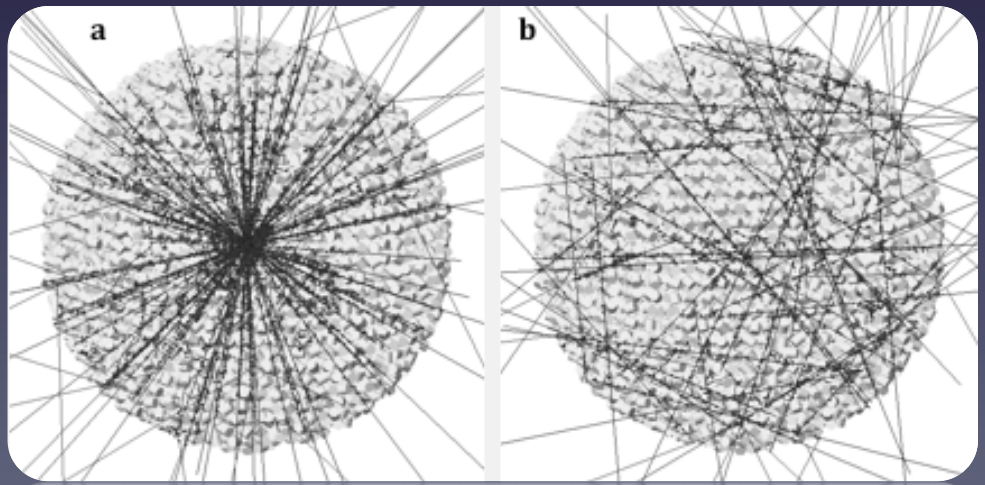
Mean energy deposit per event for 1 MeV proton tracks going through spherical volume of water with 30 nm of diameter. The source was placed at 100 nm from the target. The full line represents the energy deposit calculated using the LET values published in the ICRU report 49

Appl. Radiat. Isot. 69 (2011) 220-226

Verification

Energy deposition in nanometer size targets

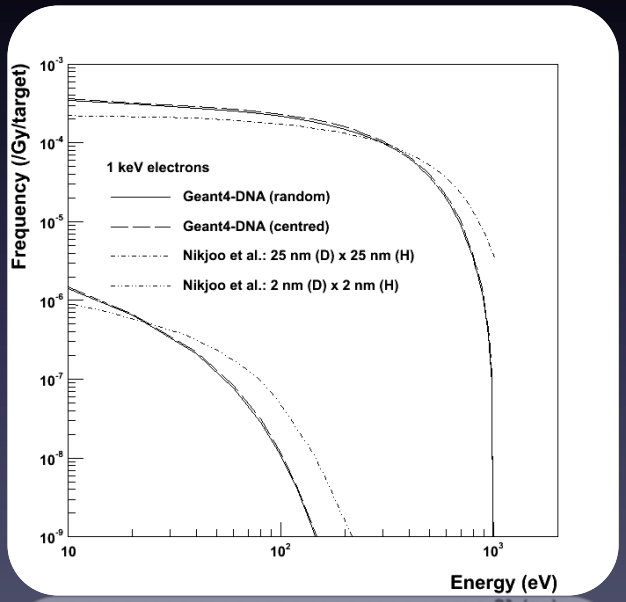
- We have recently evaluated performances of Geant4-DNA physics models in very small size targets
- Simulate frequencies of energy deposition in cylindrical targets of biological interest : 2 nm x 5 nm (DNA bases), 10 nm x 5 nm (nucleosome), 25 nm x 25 nm (chromatine fiber)
- Comparison with literature simulations (MOCAX series of MC codes)
- Geometry implemented from a voxellized phantom containing randomly oriented cylindrical targets
- Two shooting methods : centred or random



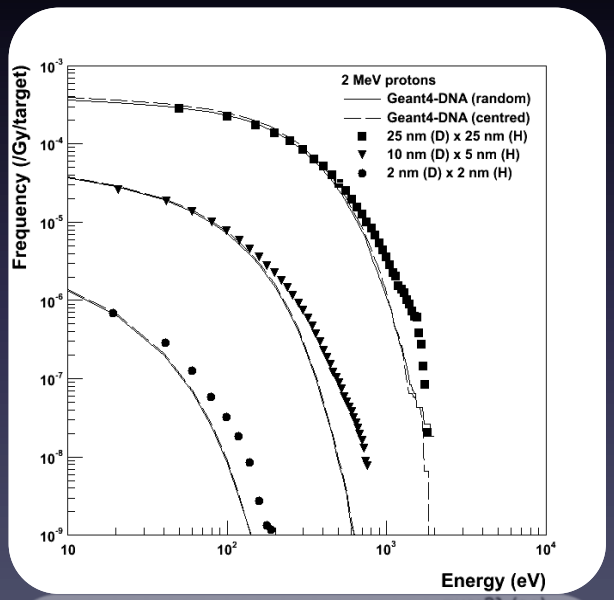
Verification

Frequency of energy deposition: comparison with MOCAX series

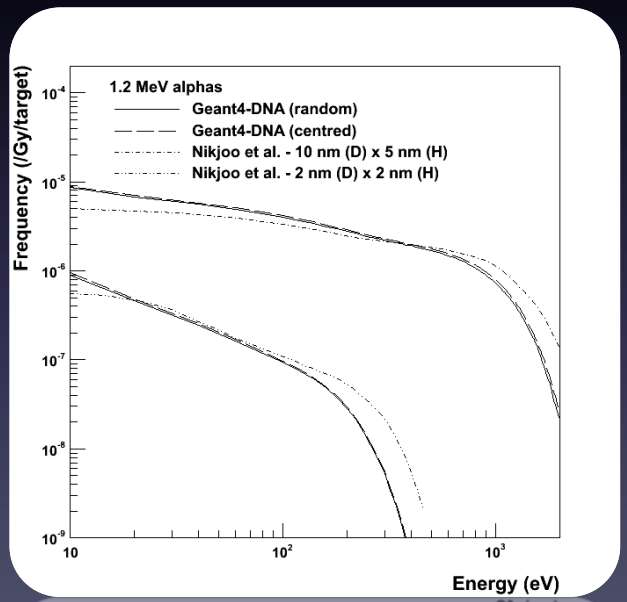
1 keV electrons



2 MeV protons



1.2 MeV alphas

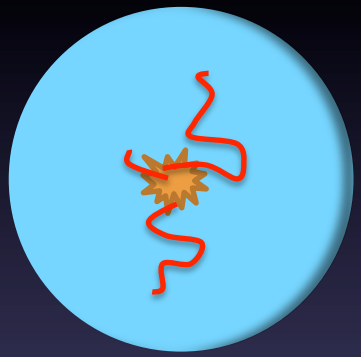


See NIMB 306 (2013) 158-164

Verification

Dose Point Kernel simulations

- Accurate test of electron transport in small scale geometries
- We compared Geant4-DNA electron Dose Point Kernels (DPK) in liquid water with several MC codes
  - CPA100
  - EGSnrc
  - FLUKA 2011.2.15
  - MCNPX 2.7.0
  - PENELOPE 2006



- 4 electron energies : 10 keV, 30 keV, 50 keV and 100 keV and 120 bins (r/r_{CSDA})
- Geant4-DNA partial wave elastic scattering model
- Kolmogorov-Smirnov test used to compare Geant4-DNA with the other Monte Carlo codes

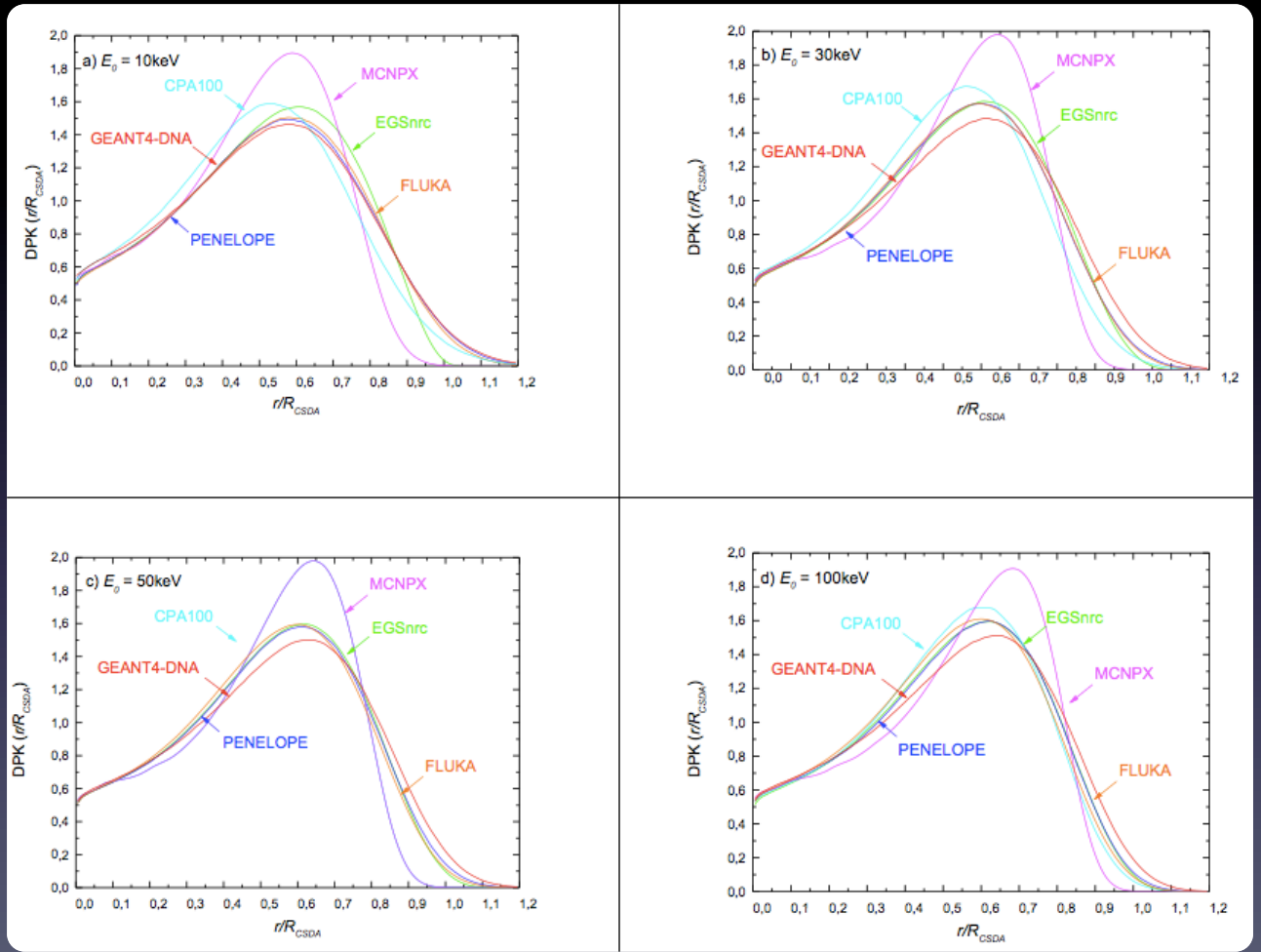
See Appl. Radiat. Isot. 83 (2014) 137-141 (link)

Verification

DPK simulations in liquid water

- Geant4-DNA is compatible with EGSnrc, PENELOPE and FLUKA
- But not compatible with CPA100 (30 keV and 50 keV) and with MCNPX* (all energies)

*
- v2.7.0
- F8 tally
- EFAC=0.917
- transport cutoff of 1 keV
- ITS option
- ESTEP = 10 or 100



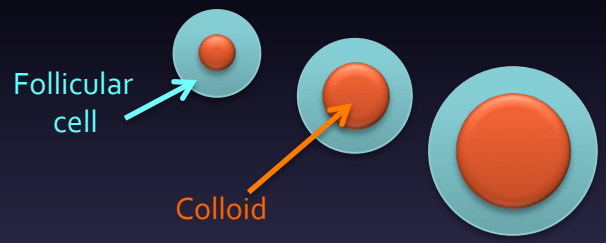
The geometrical granularity used in this study might be too large to get accurate DPK profiles using MCNPX

See Appl. Radiat. Isot. 83 (2014) 137-141 (link)

Verification

S-values simulations in liquid water

- Alternative accurate test of electron transport in small scale geometries
- We compared Geant4-DNA electron S-values in liquid water with several MC codes
  - CPA100
  - EGSnrc
  - EPOTRAN/CELLDOSE
  - MC4V
  - MCNP
  - PENELOPE



$$\overline{D}(r_T \leftarrow r_S) = \tilde{A}_{r_S} S(r_T \leftarrow r_S),$$

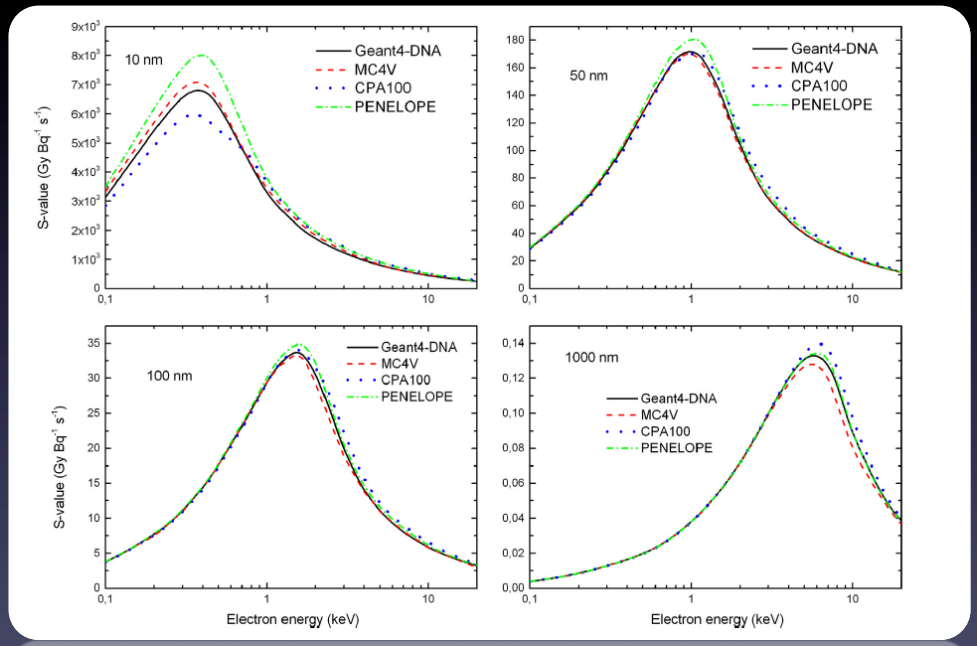
See NIMB 319 (2014) 87-94 (link)

- Electron energies
  - monoenergetic case in a sphere of liquid water
  - 5 iodine isotopes: 131, 132, 133, 134, 135 in context of thyroid targeted immunotherapy
    - Two concentric spheres of liquid water separated by 10 microns :
      inner sphere with varying radius (colloid) and outer sphere with 10 micron thickness (follicular cell)

Verification

S-values simulations in liquid water

Monoenergetic electrons

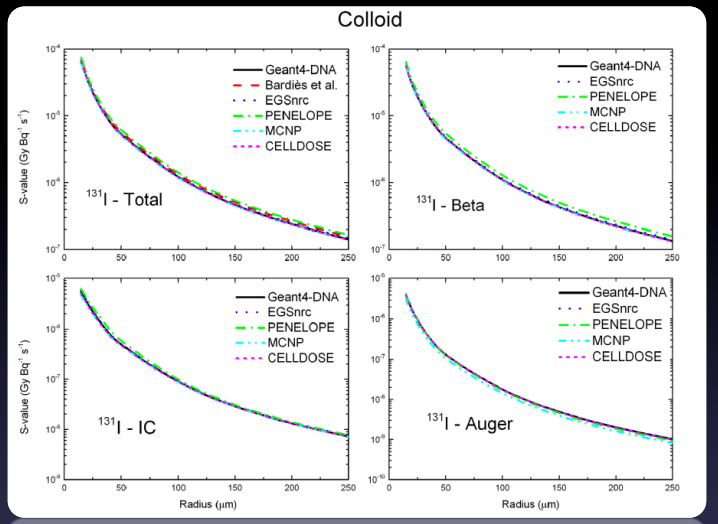


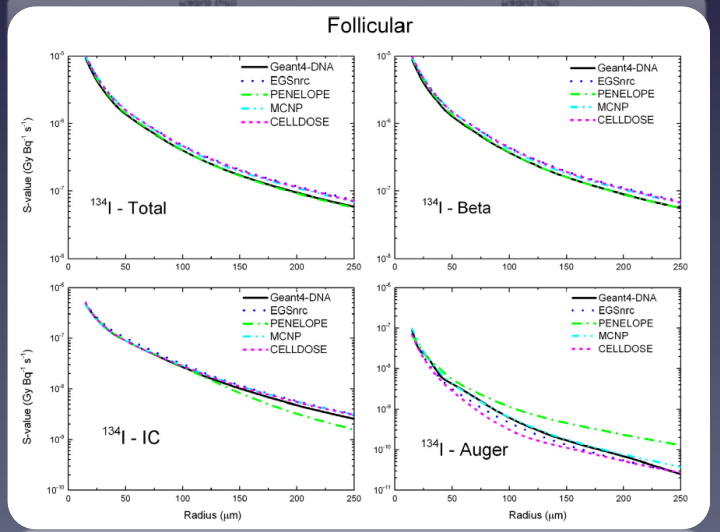
Best agreement with MC4V

See NIMB 319 (2014) 87-94 (link)

Iodine : colloid and follicular

Best agreement with CELLDOSE

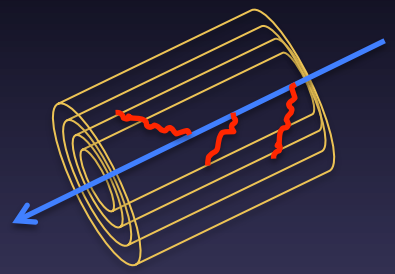




Verification

Radial doses

- Investigation of Geant4-DNA performance for radial dose distribution around ion tracks
  - Protons, alphas, C, O, Fe
  - MeV–GeV range
- Comparison to published data
  - Analytical calculations
  - Monte Carlo simulations
  - Experimental data in tissue equivalent gas



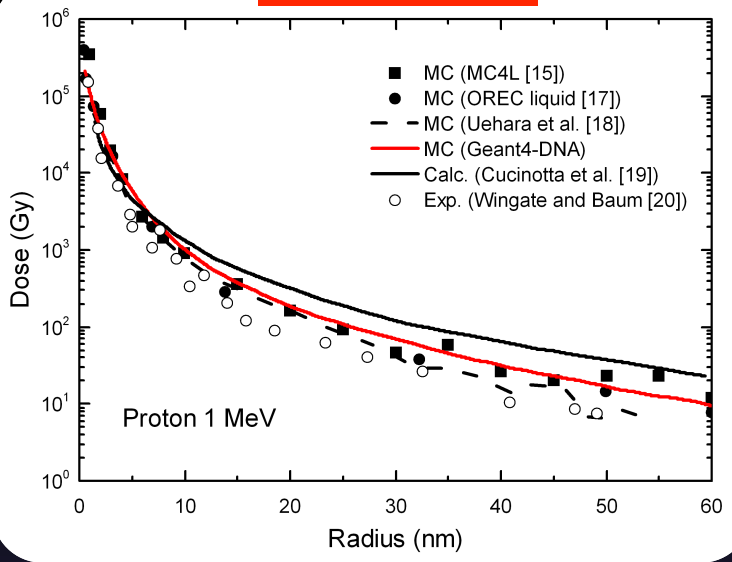
See NIMB 333 (2014) 92-98 (link)

Verification

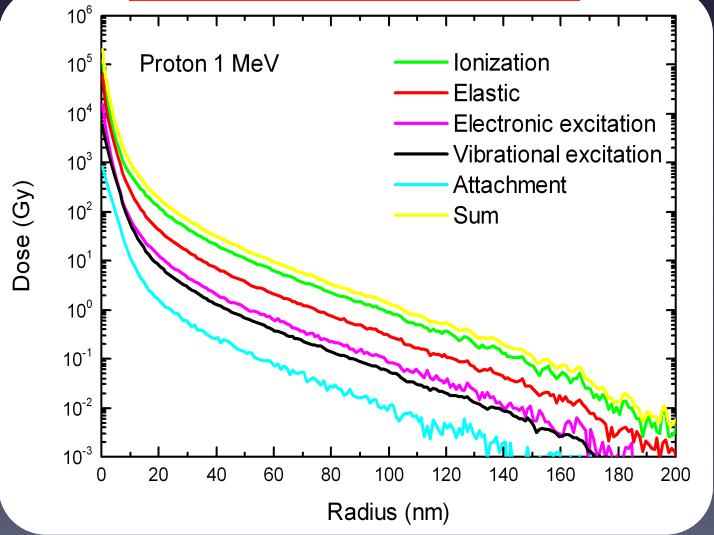
Radial doses

- General good agreement of dose profiles with a variety of literature data
- Selection of results for 1 MeV protons
  - Dose profile
  - Geometrically restricted LET
  - Individual process contribution to absorbed dose

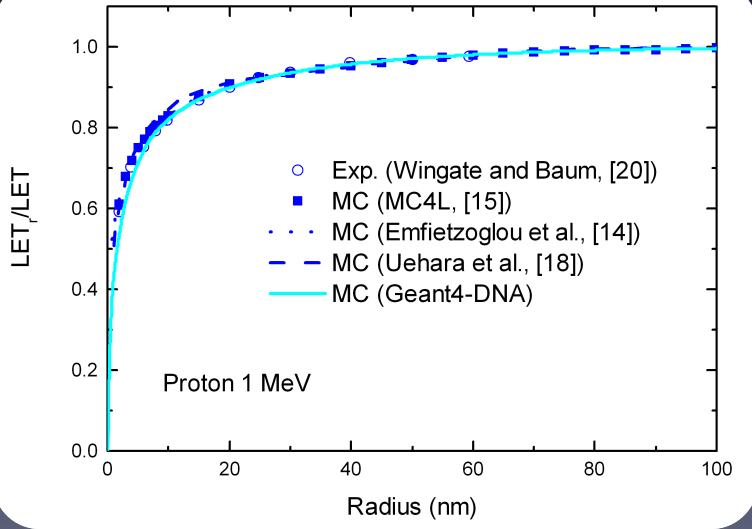
Dose profile



Process contribution

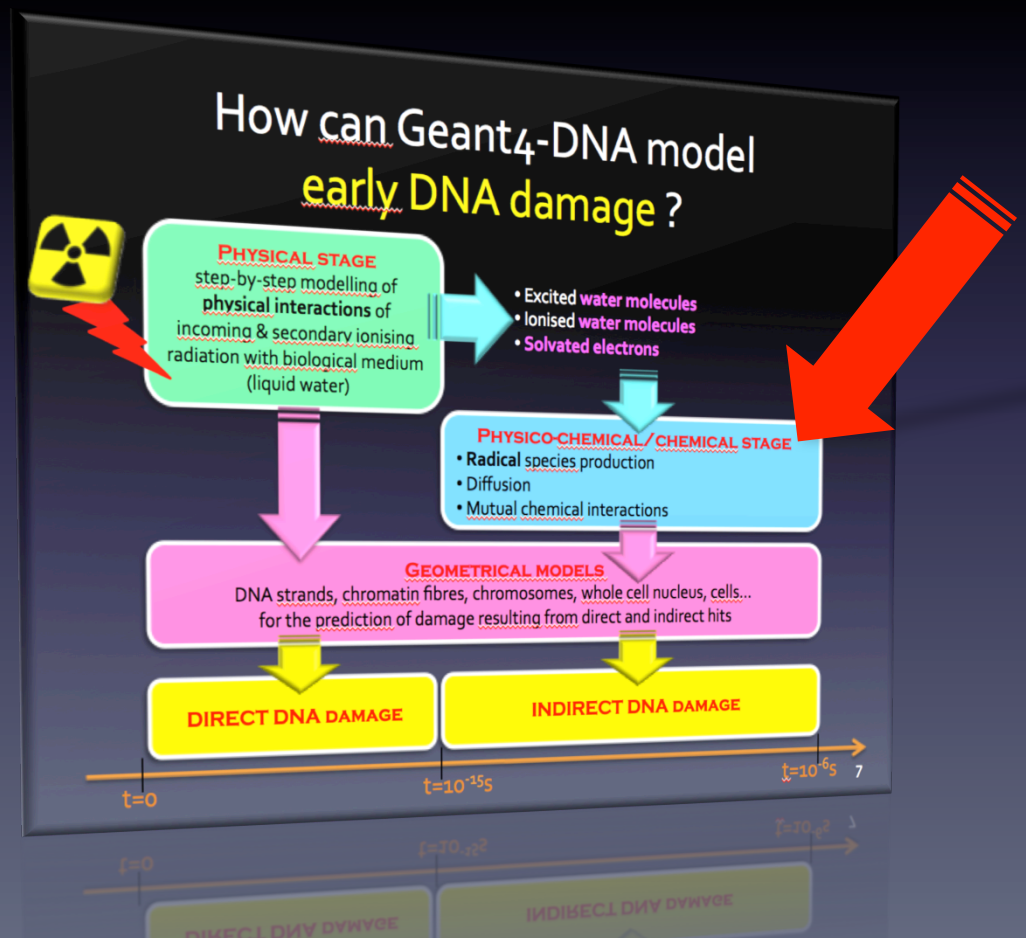


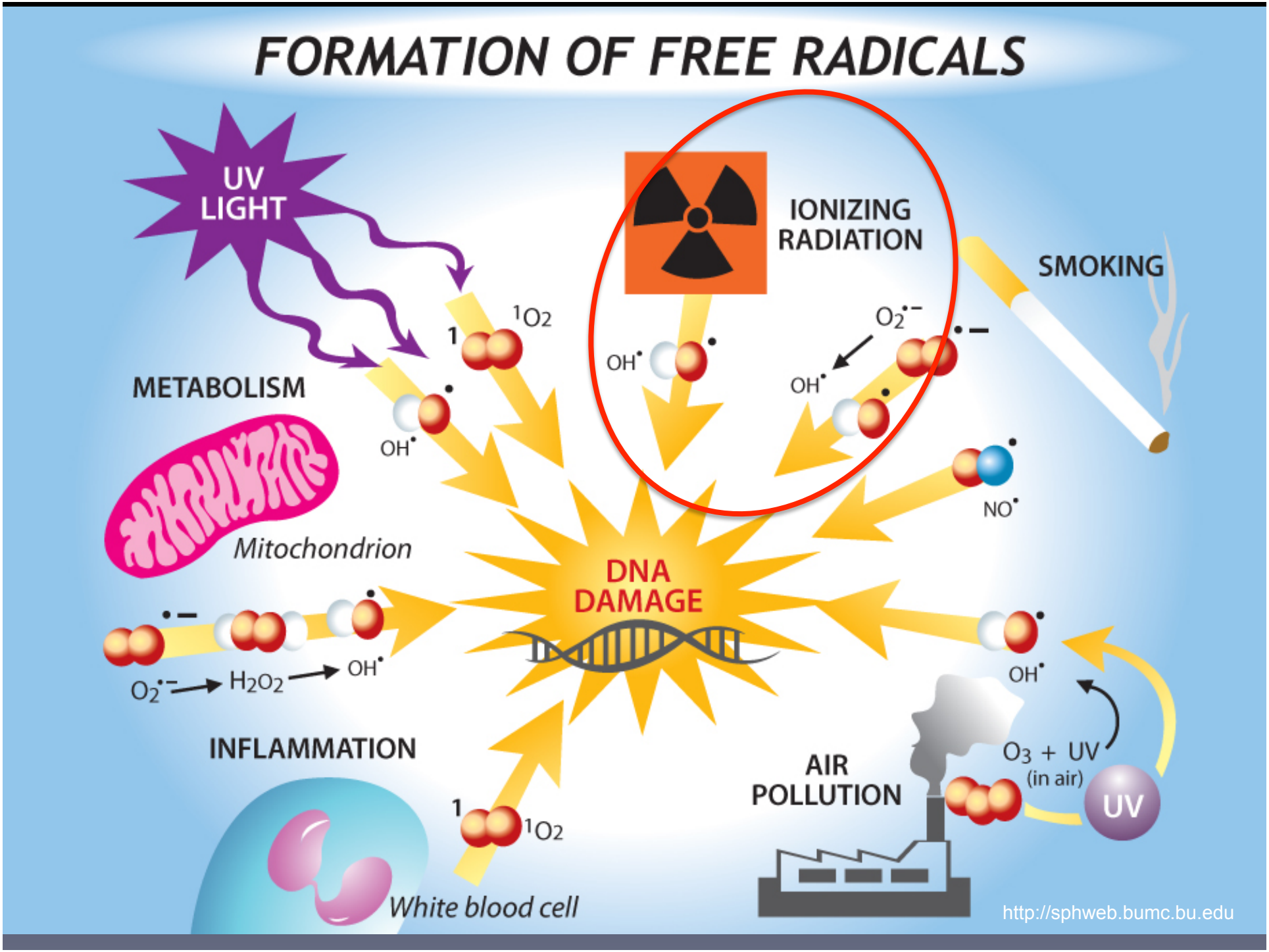
Restricted LET



See NIMB 333 (2014) 92-98 (link)

3) PHYSICO-CHEMICAL & CHEMICAL STAGE




FORMATION OF FREE RADICALS
UV LIGHT
IONIZING RADIATION
SMOKING
METABOLISM
Mitochondrion
DNA DAMAGE
INFLAMMATION
White blood cell
AIR POLLUTION
O3 + UV (in air)
UV
NO•
OH•
O2•−
H2O2
1O2
http://sphweb.bumc.bu.edu

Hirayama *et al*, 2009

Contribution of indirect effects

Survival vs Dose with different DMSO concentrations

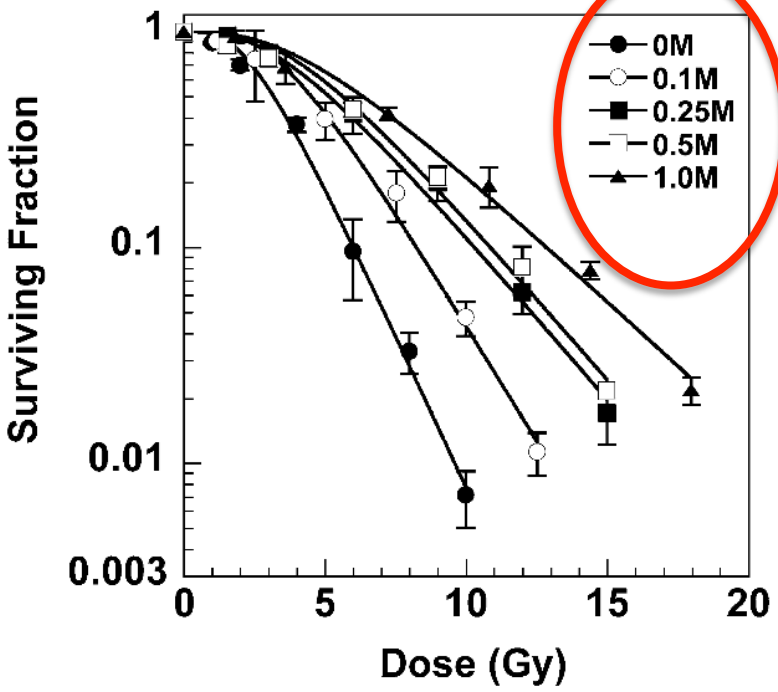


FIG. 1. X-ray survival of V79 cells in the presence of DMSO. Error bars represent the standard deviations (n = 2–3). These curves were fitted by the single-hit multitarget equation as described in the Materials and Methods.

Contribution of indirect effects VS LET

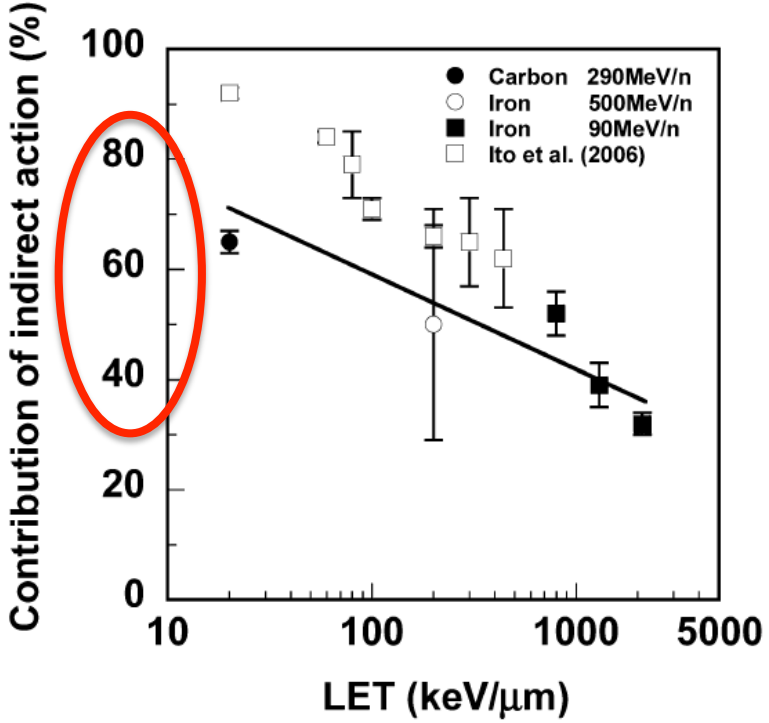


FIG. 4. LET dependence of the contribution of indirect action in cell killing. The error bars are standard errors for a protectable fraction calculated from a regression line. Data from Ito *et al.* for HL-60 cells (*6*) are plotted in the figure.

Challenge

extend Geant4 for the modeling of radiation chemistry

Geant4

- Simulations with Geant4 are HEP oriented
  - Sequential handling of tracks
  - Simulation based on geometrical space, where interaction length is the main quantity of interest
    - No time synchronization
- No individual molecules
- No Brownian motion

Key requirements for Geant4-DNA RC

1. A generic system for handling interactions between tracks
2. Molecular species as tracks and targets
3. Brownian motion
4. Chemical reactions

Modelling water radiolysis

- **Water radiolysis** = dissociation of water molecules by ionising radiation
  - Creation of oxydative species
  - They can interact chemically with one another or with the « biological medium » (« non-direct effects ») and interfere with the normal functioning of cells

- **Stage 1 : Physico-chemistry stage**

  we start from altered water molecules which underwent changes in their electronic configuration from physical processes occuring during the « Physical stage »
  - Electronic excitation, ionisation
  - The electronic rearrangement may lead to their dissociation
    - We use branching ratios and positioning of dissociation products, which can be modified by the user

Modelling water radiolysis

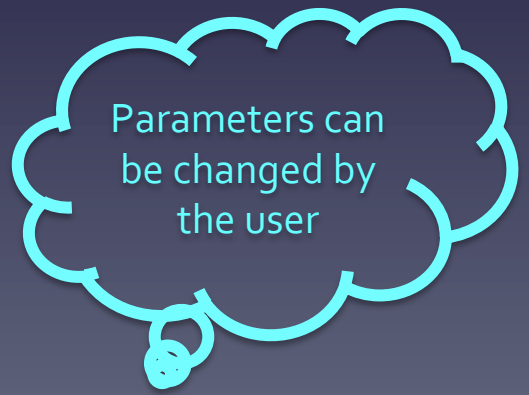
- **Stage 2 : Chemistry stage**

  the dissociative products can recombine to form new chemical species

  - A new stepping algorithm was developed to handle this recombination and more generally manage collisions between tracks
    - Requires the synchronization of tracks during simulation
      - G4VITProcess encapsulates and allows deportation of information related to a track
    - All tracks are transported simultaneously during dynamic or fixed « time steps »
  - A table of chemical reactions and their reaction rates must be provided

- All parameters are provided through a « Chemistry list » as Geant4 users would do with a « Physics list »
  - G4EmDNAChemistry

- Note that the chemistry can be started as a standalone application
  - Input user defined « physics » phase space



$t=10^{-15}s$ $t=10^{-12}s$

Physico-chemical stage

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

Electronic state	Dissociation channels	Fraction (%)
All single ionization states	$H_3O^+ + \bullet OH$	100
Excitation state A1B1: (1b1) → (4a1/3s)	$\bullet OH + H\bullet$ $H_2O + DE$	65 35
Excitation state B1A1: (3a1) → (4a1/3s)	$H_3O^+ + \bullet OH + e^-_{aq}$ (Al) $\bullet OH + \bullet OH + H_2$ $H_2O + DE$	55 15 30
Excitation state: Rydberg, diffusion bands	$H_3O^+ + \bullet OH + e^-_{aq}$ (Al) $H_2O + DE$	50 50
Dissociative attachment	$\bullet OH + OH^- + H_2$	100

- Products thermalize down to their energy of diffusion at equilibrium

$t=10^{-15}s$ $t=10^{-12}s$ $t=10^{-6}s$

Chemical stage

Species	Diffusion coefficient D (10^{-9} m^2 s^{-1})
H_3O^+	9.0
$H^\bullet$	7.0
OH^-	5.0
e^-_{aq}	4.9
H_2	4.8
$^\bullet OH$	2.8
H_2O_2	2.3

InConstructMolecules()

We followed 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^{10} M^{-1} s^{-1})
$H_3O^+ + OH^- \rightarrow 2\,H_2O$	14.3
$^\bullet OH + e^-_{aq} \rightarrow OH^-$	2.95
$H^\bullet + e^-_{aq} + H_2O \rightarrow OH^- + H_2$	2.65
$H_3O^+ + e^-_{aq} \rightarrow H^\bullet + H_2O$	2.11
$H^\bullet + {}^\bullet OH \rightarrow H_2O$	1.44
$H_2O_2 + e^-_{aq} \rightarrow OH^- + {}^\bullet OH$	1.41
$H^\bullet + H^\bullet \rightarrow H_2$	1.20
$e^-_{aq} + e^-_{aq} + 2\,H_2O \rightarrow 2\,OH^- + H_2$	0.50
$^\bullet OH + {}^\bullet OH \rightarrow H_2O_2$	0.44

InConstructReactionTable()

Kreipl *et al*, 2009

How to use Geant4-DNA for radiation chemistry ?

- Three examples have been released publicly in Geant4 10.1 (December 2014) in the « extended examples/medical/dna » category of Geant4 examples
  - CHEM1: activating chemistry
  - CHEM2: altering chemistry run
  - CHEM3: user interactivity and visualization
- Note
  - Examples can be run in MultiThreading mode
  - Chemistry works in with G4_WATER material

CHEM1: chemistry activated in a few lines…

- **CHEM1** : most basic example to start from : electron of 100 keV in liquid water
  - Physics initialization output is displayed
  - The table of chemical reactions is printed
  - G4ITStepManager processes the chemical stage, time step after time step
  - Illustration of usage of « chemistry » macro commands « /IT/… »:
    - Verbosity
    - Stop of simulation after a certain time duration
    - Or after a maximum number of steps in time

Geant4 10.1

CHEM1: a C++ bit of coding
chemistry is activated using 3 instructions…

PhysicsList

- Register the G4EmDNAChemistry « physics-chemistry list »

  RegisterConstructor("G4EmDNAChemistry");

Action Initialization

- In Build() method, creation of a StackingAction

StackingAction

- Start handling of chemistry tracks at new stage

  G4DNAChemistryManager::Instance()->Run();

The chemistry module is triggered when all physical tracks have been processed

CHEM1

Initialization of chemistry: List of chemical reactions & reaction rates

Reaction	Reaction Rate [dm3/(mol*s)]
H3O^1 + e_aq^1 -> H^0	2.11e+10
H3O^1 + OH^-1 -> No product	1.43e+11
OH^0 + e_aq^1 -> OH^-1	2.95e+10
OH^0 + OH^0 -> H2O2^0	4.4e+09
OH^0 + H^0 -> No product	1.44e+10
e_aq^1 + e_aq^1 -> OH^-1 + OH^-1 + H_2^0	5e+09
e_aq^1 + H^0 -> OH^-1 + H_2^0	2.65e+10
e_aq^1 + H2O2^0 -> OH^-1 + OH^0	1.41e+10
H^0 + H^0 -> H_2^0	1.2e+10

Verbose(1) Occuring reactions

```
*** G4ITStepManager starts processing
At time :       1 ps  Reaction : e_aq^1 (-17) + OH^0 (-31) -> OH^-1 (-44)
At time :       1 ps  Reaction : OH^-1 (-44) + H3O^1 (-30) -> No product
At time : 6.45607 ps  Reaction : e_aq^1 (-5) + H3O^1 (-36) -> H^0 (-45)
At time : 60.8395 ps  Reaction : e_aq^1 (-18) + OH^0 (-29) -> OH^-1 (-46)
At time : 66.8395 ps  Reaction : e_aq^1 (-6) + OH^0 (-39) -> OH^-1 (-47)
At time : 85.5181 ps  Reaction : H3O^1 (-34) + OH^-1 (-46) -> No product
At time : 273.448 ps  Reaction : e_aq^1 (-15) + H3O^1 (-22) -> H^0 (-48)
At time : 2.95012 ns  Reaction : OH^-1 (-47) + H3O^1 (-40) -> No product
At time : 4.32185 ns  Reaction : H^0 (-48) + OH^0 (-43) -> No product
At time : 102.369 ns  Reaction : OH^0 (-25) + OH^0 (-35) -> H2O2^0 (-49)
*** G4ITStepManager ends at time : 1 mus
```

Verbose(2) Detail of time steps: reaction & duration

```
*** G4ITStepManager starts processing
Step N°1          T= 1 ps          dt= 0 ps
At time :       1 ps  Reaction : e_aq^1 (-17) + OH^0 (-31) -> OH^-1 (-44)
Step N°2          T= 1 ps          dt= 0 ps
At time :       1 ps  Reaction : OH^-1 (-44) + H3O^1 (-30) -> No product
Step N°3          T= 1 ps          dt= 0 ps
Step N°4          T= 2.47796 ps    dt= 1.47796 ps
Step N°5          T= 4.45607 ps    dt= 1.97811 ps
Step N°6          T= 5.45607 ps    dt= 1 ps
At time : 6.45607 ps  Reaction : e_aq^1 (-5) + H3O^1 (-36) -> H^0 (-45)
Step N°7          T= 6.45607 ps    dt= 1 ps
Step N°8          T= 7.45607 ps    dt= 1 ps
```

Verbose(3) Detail of time step duration calculation

```
*** Start Of Step N°1 ***
Current Global time : 1 ps
*** Time stepper returned : 5.75774 ps  ***
*** The minimum time returned by the processes is : 0 ps  ***
*** End Of Step N°1 ***
Previous global time : 1 ps      Chosen time step :0 ps
It has also reached the user time limit
Next global time : 1 ps

*** Start Of Step N°2 ***
Current Global time : 1 ps
*** Time stepper returned : 0 ps  ***
*** The minimum time returned by the processes is : 1.37133 mus ***
At time :       1 ps  Reaction : e_aq^1 (-17) + OH^0 (-31) -> OH^-1 (-44)
*** End Of Step N°2 ***
Previous global time : 1 ps      Chosen time step :0 ps
It has also reached the user time limit
Next global time : 1 ps

*** Start Of Step N°3 ***
Current Global time : 1 ps
```

(verbose level is selected using UI commands)

Chem1

Verbose(4)

Maximum detail:

- trackID (<0)

- Pre & post-step positions

- Volumes

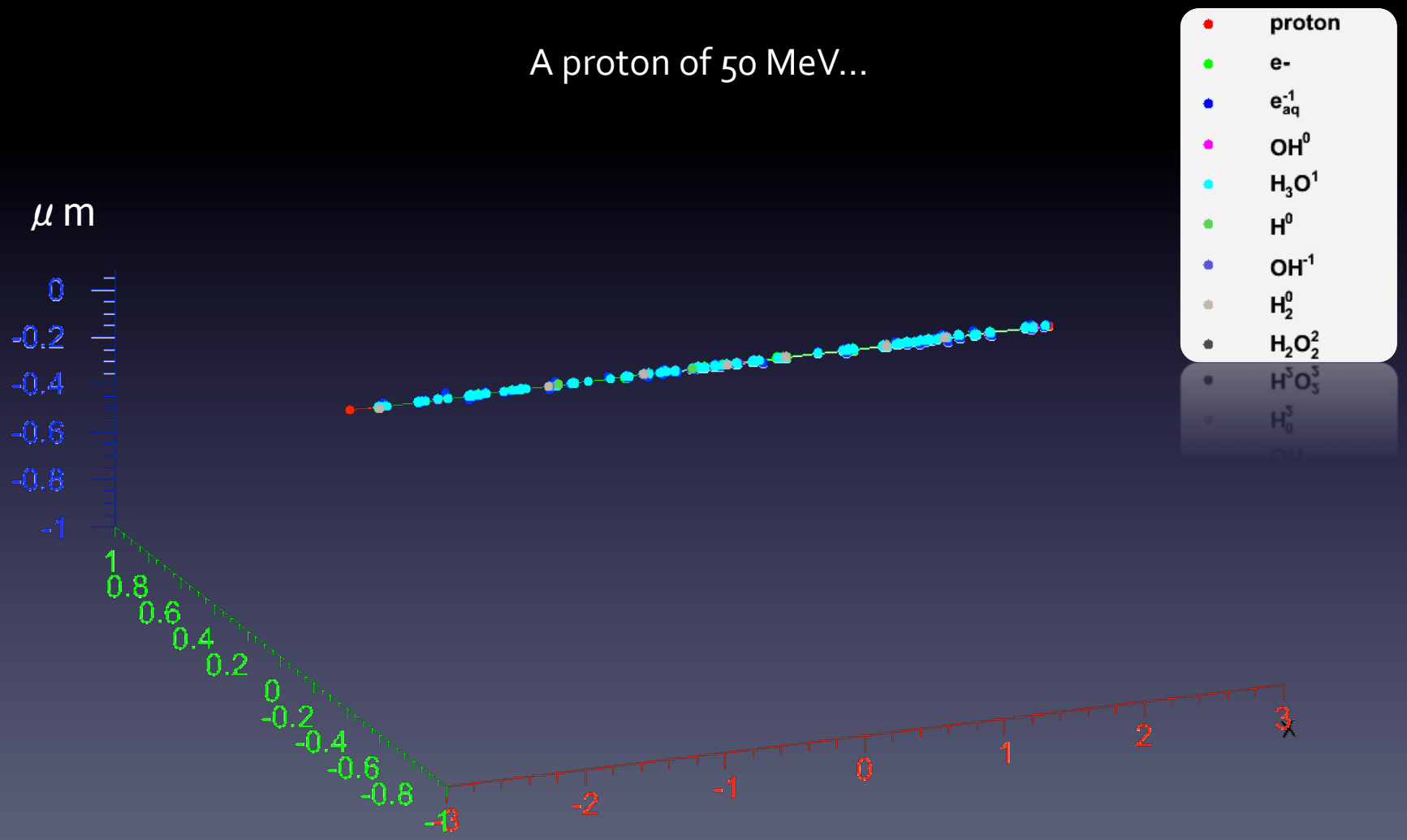
- Chemical processes

```
*** Start Of Step N°690 ***
Current Global time : 983 ns
*** Time stepper returned : 19.1 ns  ***
*** The minimum time returned by the processes is : 423 ns  ***
*** G4ITStepManager::DoIt ***
#Name             trackID        Position                    Pre step volume          Post step volume         Process
H2O2^0            -49            -1.72151 34.0136 547.013 nm World                    ---
H2O2^0            -49            -8.90779 34.3314 551.789 nm ---                      World                    ---
H^0               -45            21.9088 116.817 782.284 nm  World                    ---
H^0               -45            31.1115 111.402 793.733 nm  ---                      World                    ---
H3O^1             -42            85.5884 46.4426 637.807 nm  World                    ---
H3O^1             -42            72.0196 28.3613 665.425 nm  ---                      World                    ---
OH^0              -41            83.6411 34.7605 516.665 nm  World                    ---
OH^0              -41            91.1481 30.1629 519.493 nm  ---                      World                    ---
H3O^1             -38            324.262 -271.008 426.759 nm World                    ---
H3O^1             -38            312.068 -247.209 427.064 nm ---                      World                    ---
OH^0              -37            -71.0606 95.1782 601.204 nm World                    ---
OH^0              -37            -84.1067 89.3457 605.028 nm ---                      World                    ---
OH^0              -33            -35.1879 26.5308 490.142 nm World                    ---
OH^0              -33            -51.6536 21.4202 485.287 nm ---                      World                    ---
H3O^1             -32            -209.089 -86.6681 538.456 nm World                   ---
H3O^1             -32            -226.995 -71.0708 558.886 nm ---                     World                    ---
H3O^1             -28            211.802 33.1836 689.88 nm   World                    ---
H3O^1             -28            209.842 41.4445 686.271 nm  ---                      World                    ---
OH^0              -27            37.9608 -22.8459 599.226 nm World                    ---
OH^0              -27            43.2044 -32.3502 612.772 nm ---                      World                    ---
H3O^1             -26            -90.0303 149.063 533.231 nm World                    ---
H3O^1             -26            -85.82 143.123 537.115 nm   ---                      World                    ---
H3O^1             -24            147.105 -93.1899 562.529 nm World                    ---
H3O^1             -24            148.283 -88.0984 579.717 nm ---                      World                    ---
OH^0              -23            70.8409 -72.7203 608.782 nm World                    ---
OH^0              -23            67.1325 -80.1111 616.982 nm ---                      World                    ---
OH^0              -21            -101.317 37.9856 567.374 nm World                    ---
OH^0              -21            -107.4 38.0837 582.761 nm   ---                      World                    ---
H3O^1             -20            121.284 -29.92 558.34 nm    World                    ---
H3O^1             -20            133.84 -47.7341 557.5 nm    ---                      World                    ---
e_aq^1            -19            -102.995 95.2003 637.85 nm  World                    ---
e_aq^1            -19            -89.0731 92.5995 617.164 nm ---                      World                    ---
*** End Of Step N°690 ***
Previous global time : 983 ns    Chosen time step :17.1 ns
Next global time : 1 mus

*** G4ITStepManager has finished processing a track list at time : 1 mus
*** G4ITStepManager ends at time : 1 mus
```

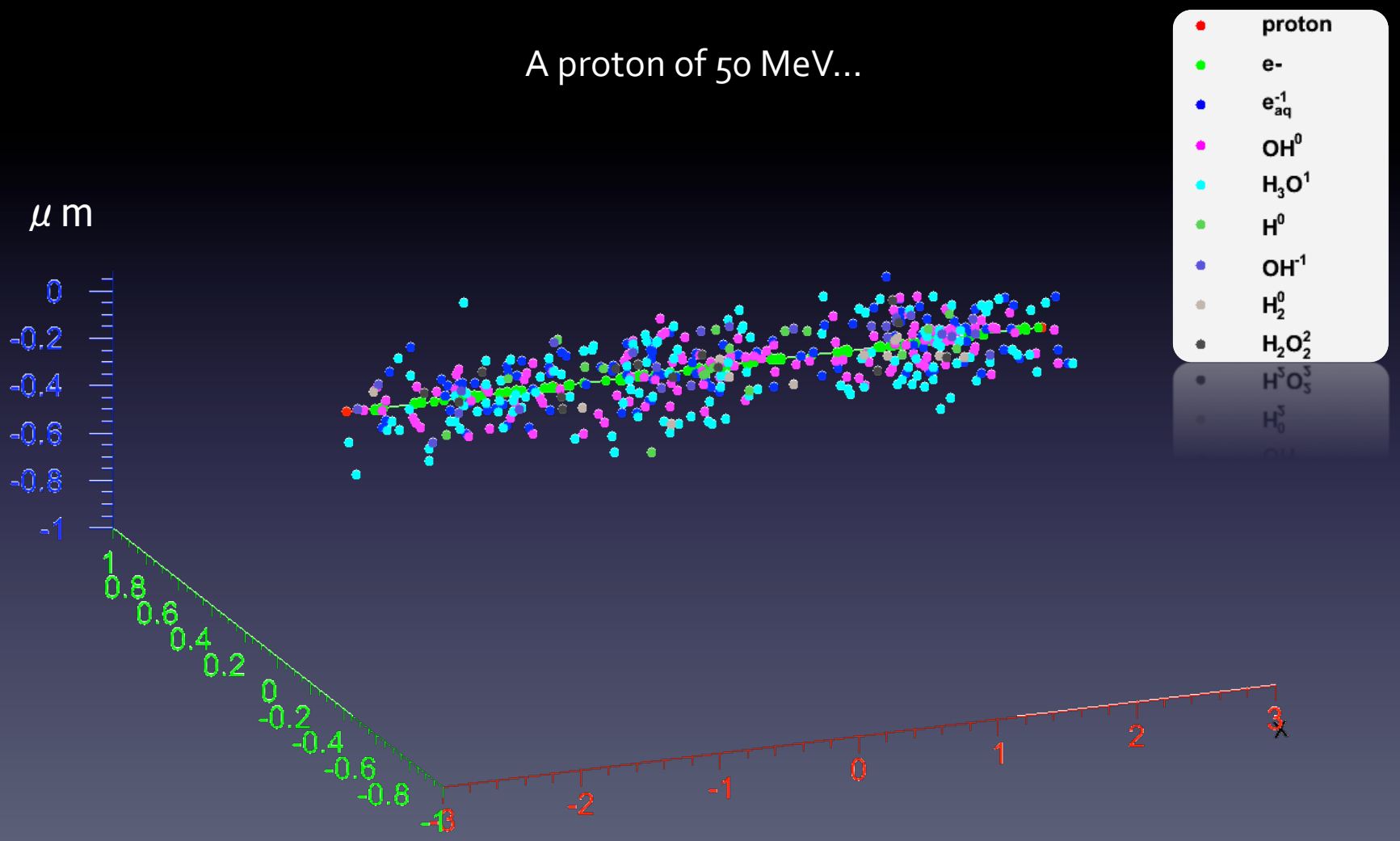
Situation at 1 picosecond

A proton of 50 MeV...



Situation at 1 microsecond

A proton of 50 MeV...



Two other chemistry examples

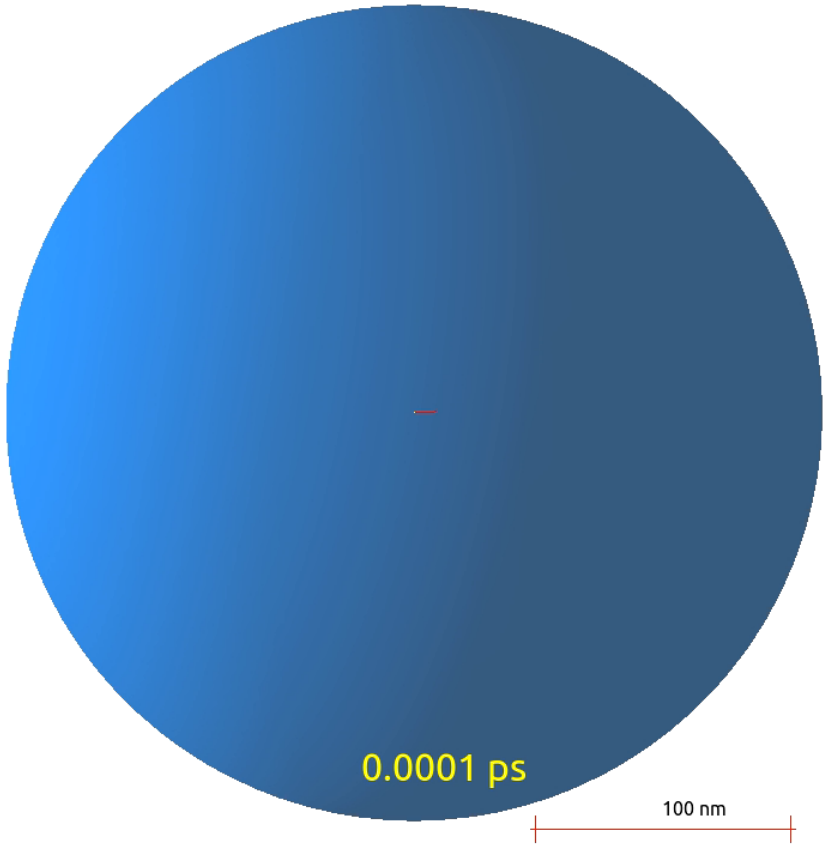
- **CHEM2**
  - How to access information at the time step level
  - How to set user minimum time step limits using a G4UserTimeStepAction user action class (TimeStepAction)
    - Informs G4ITStepManager of the selected minimum time steps
  - How to retrieve information from a given time step
    - Molecule names, reaction products…
- **CHEM3**
  - How to handle user interactivity
    - SteppingAction, TrackingAction, visualization
  - Enables drawing of cumulative trajectory of species

CHEM3

Geant4-DNA generated track of **1 keV electron**, followed up to **100 ns** during chemical stage. Using pre-release Geant4 10.1 code.

First, the **physical stage** is modeled, using Geant4-DNA physics: the 1 keV electron track is fully slowed down and thermalized in a **150 nm sphere** of liquid water. **Yellow points** correspond to interaction events in liquid water.

Next, the **physico-chemical / chemical stage** is simulated for the first 100 ns. **Individual radical species** diffusing in space and reacting with each other are shown as colour trails, the color coding chemical species type.



http://dx.doi.org/10.6084/m9.figshare.978887

Definition of radiochemical yield *G*

Number of molecules of a given species

for 100 eV of deposited energy

Time-dependent radiochemical yield

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

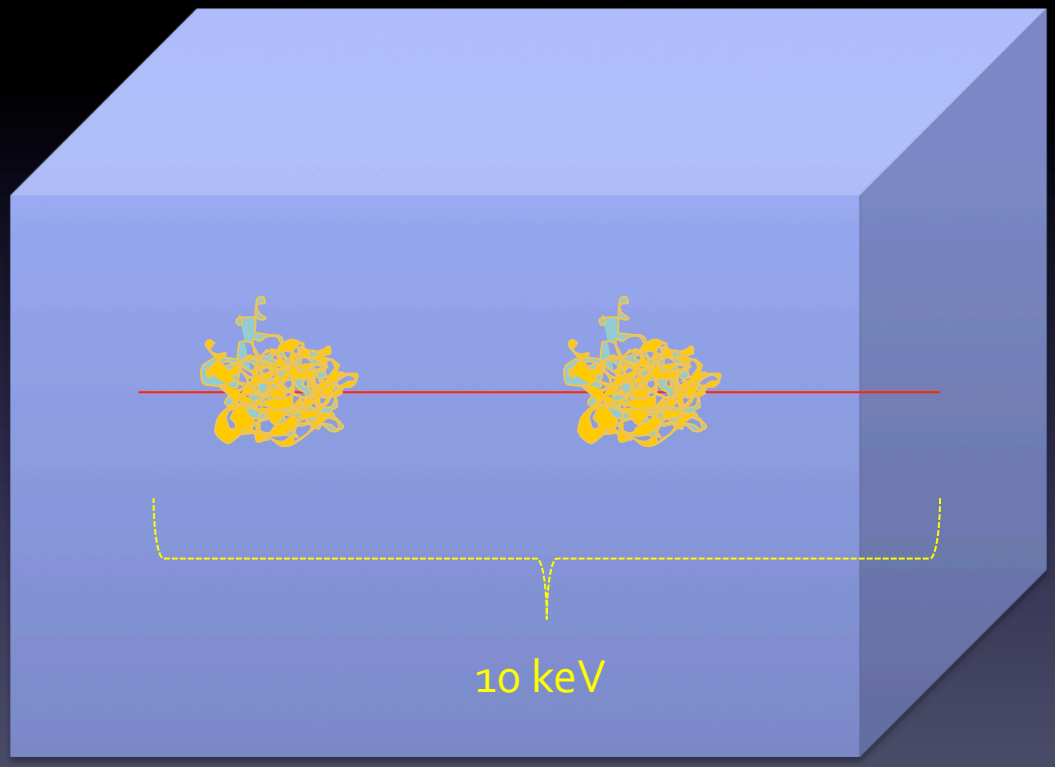
Number of molecules at time *t*

Deposited energy scaling to 100 eV

An observable quantity commonly used to evaluate chemistry modeling accuracy…

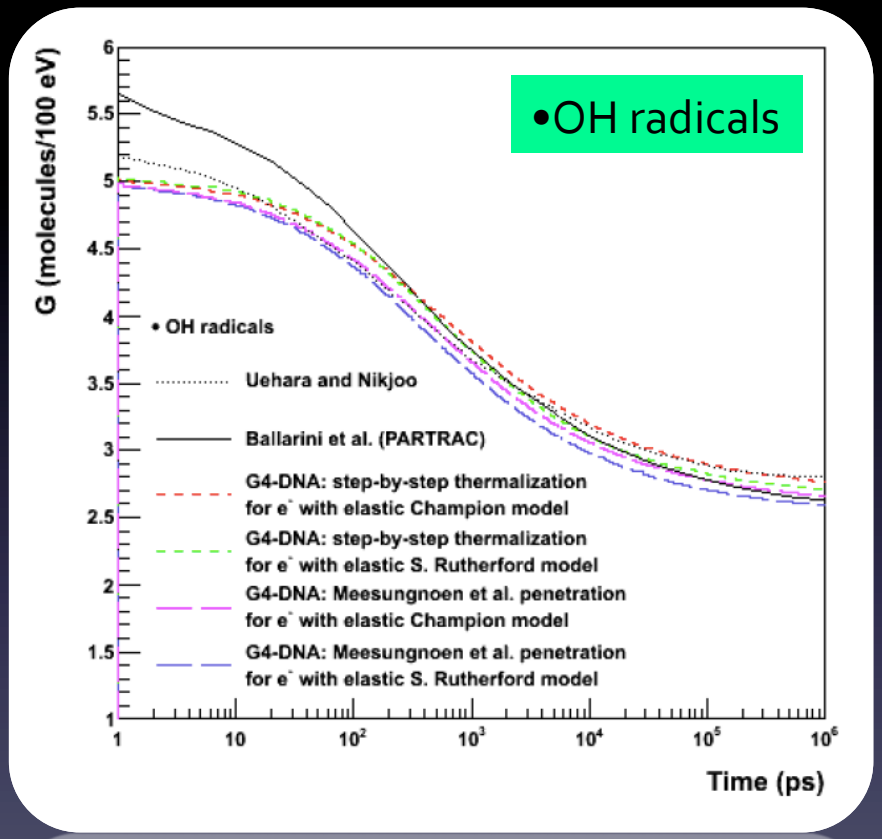
SIMULATION SETUP #1

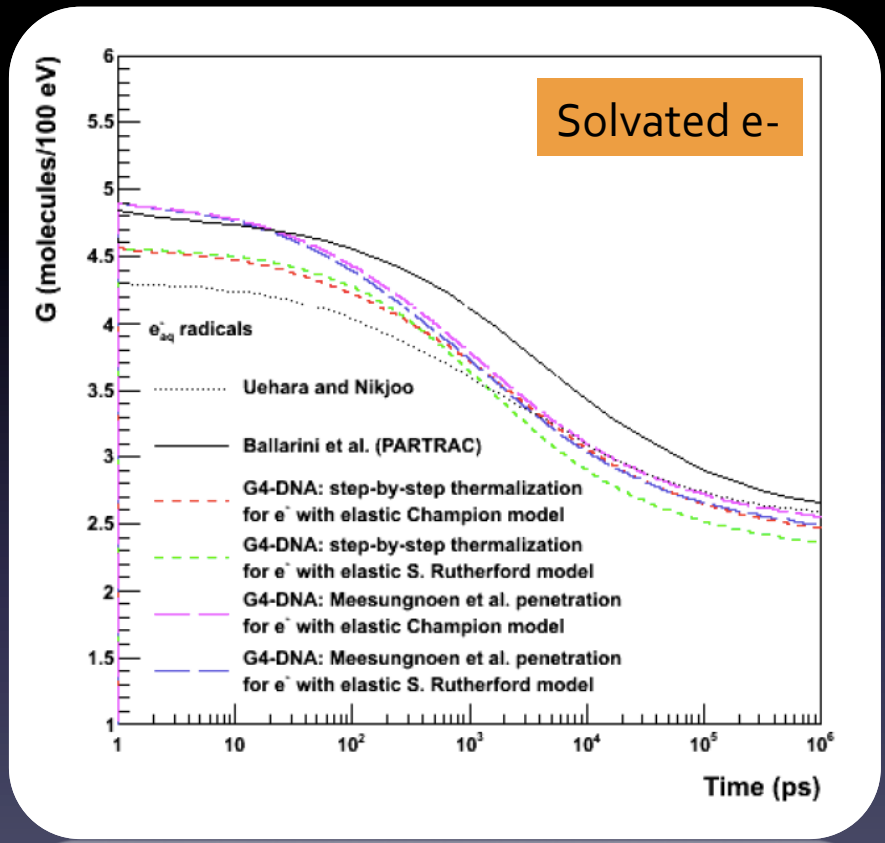
- 1 MeV electrons in infinite liquid water volume
- Only the first 10 keV deposit energy are taken into account for the chemistry



PARTRAC: Ballarini et al., REB (2000),39:179-188
Uehara and Nikjoo, J. Radiat. Res. (2006),47:69-81

Radiochemical yields VS time



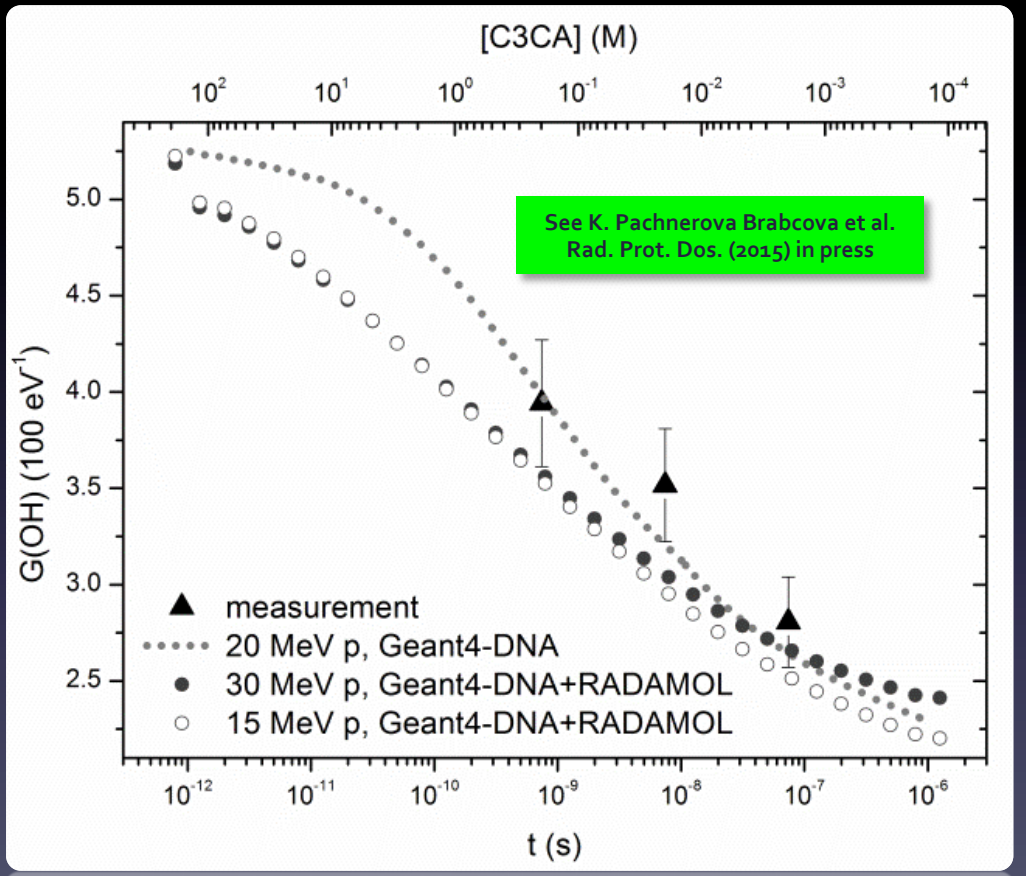


- Effect of the two **alternative** electron elastic scattering models of Geant4-DNA
- Results are obtained in **30 minutes** on a cluster of 80 CPUs (Physics + Chemistry)

See Prog. Nucl. Sci. Tec. 2 (2011) 503-508 (link)

Radiochemical yields VS time

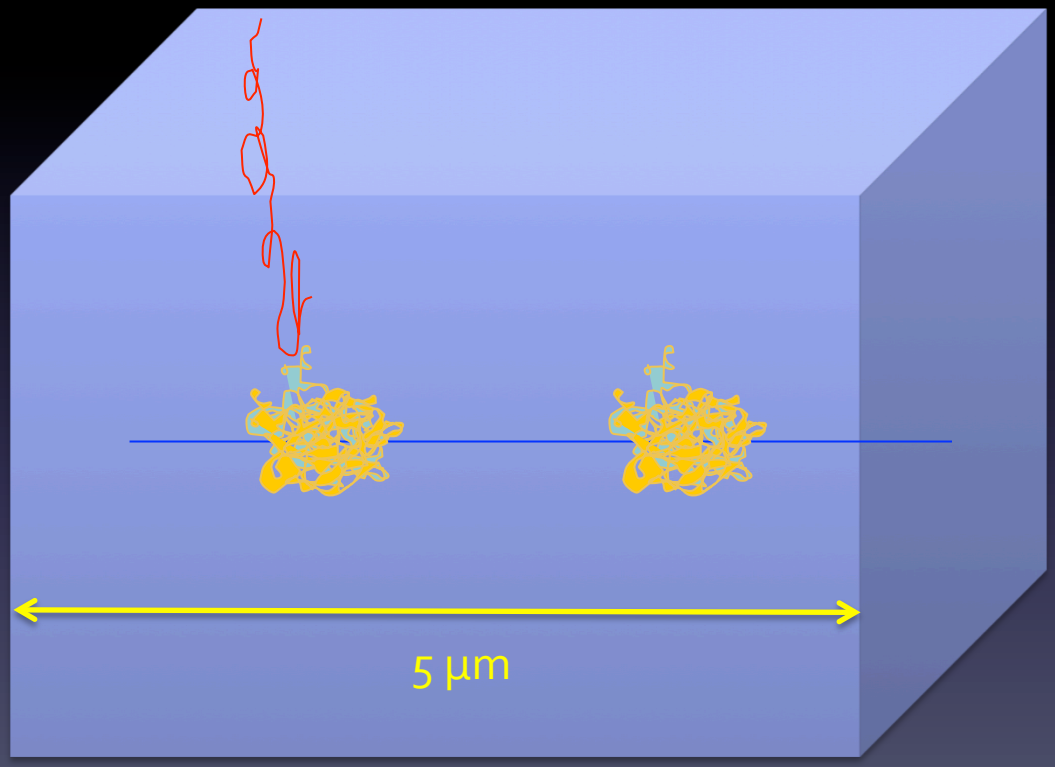
- We compared measured G values of OH radicals in liquid water to Monte Carlo simulations
- Experiment
  - 30 MeV proton beam at NPI in Prague
  - Target is coumarin-3-carboxylic acid scavenger (C3CA), 3 concentrations (2, 20, 200 mM). C3CA forms fluorescent product with OH, 7-hydroxycoumarin-3-carboxylic acid (7-OH-C3CA) The inverse of the reaction rate k [C3CA] corresponds to the time scale of the reaction.
- Simulations
  - Geant4-DNA physics + RADAMOL for radiolysis (15 & 30 MeV) developed at NPI (M. Davidkova et al.)
  - Geant4-DNA physics + radiolysis (20 MeV)
  - Same geometry as in previous setup : we selected three energies in order to to cover the energy decrease of protons in the sample



Calculated OH radical yields in time are in acceptable agreement with the experimental data, notably when utilising Geant4-DNA chemistry simulation capabilities

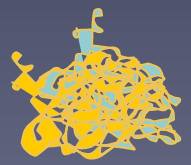
SIMULATED SETUP #2

- Protons in 5 µm finite cube of liquid water
- When a particle leaves the cube, it is taken out from the simulation



Proton

Electron

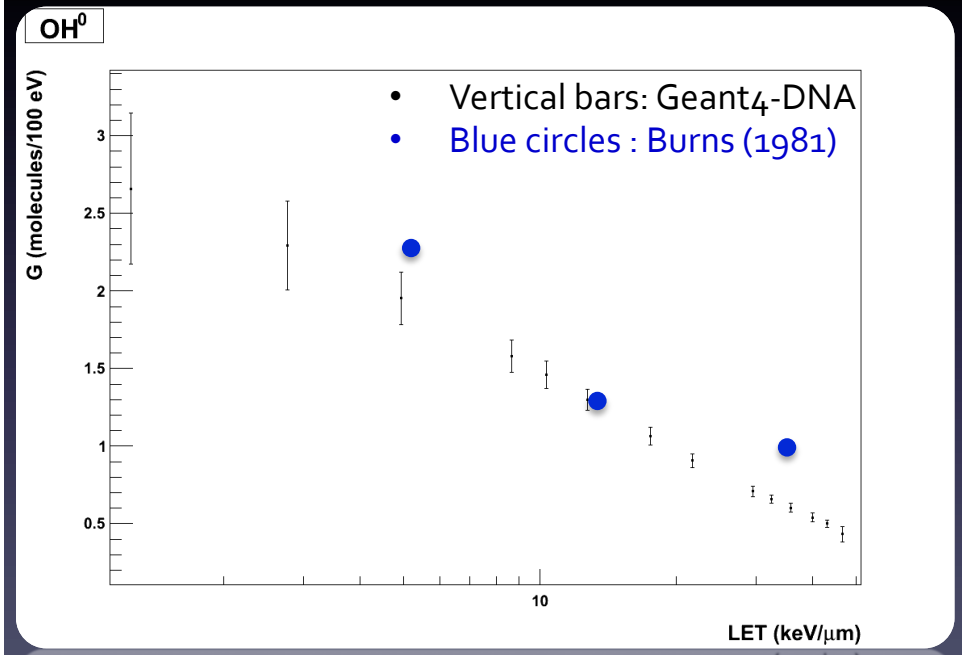


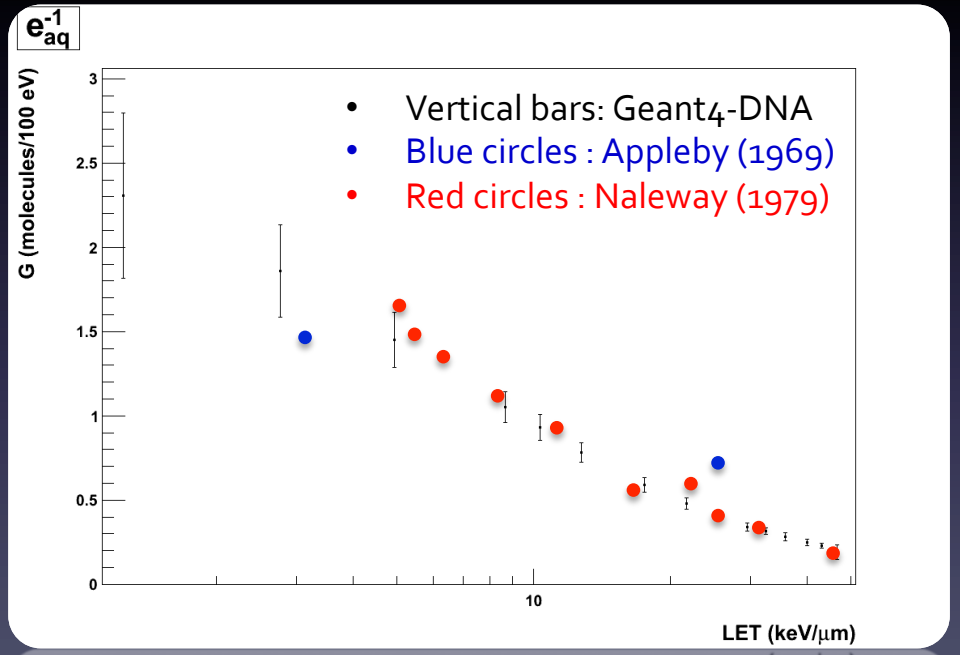
Secondaries

Radiochemical yields VS LET

•OH radicals

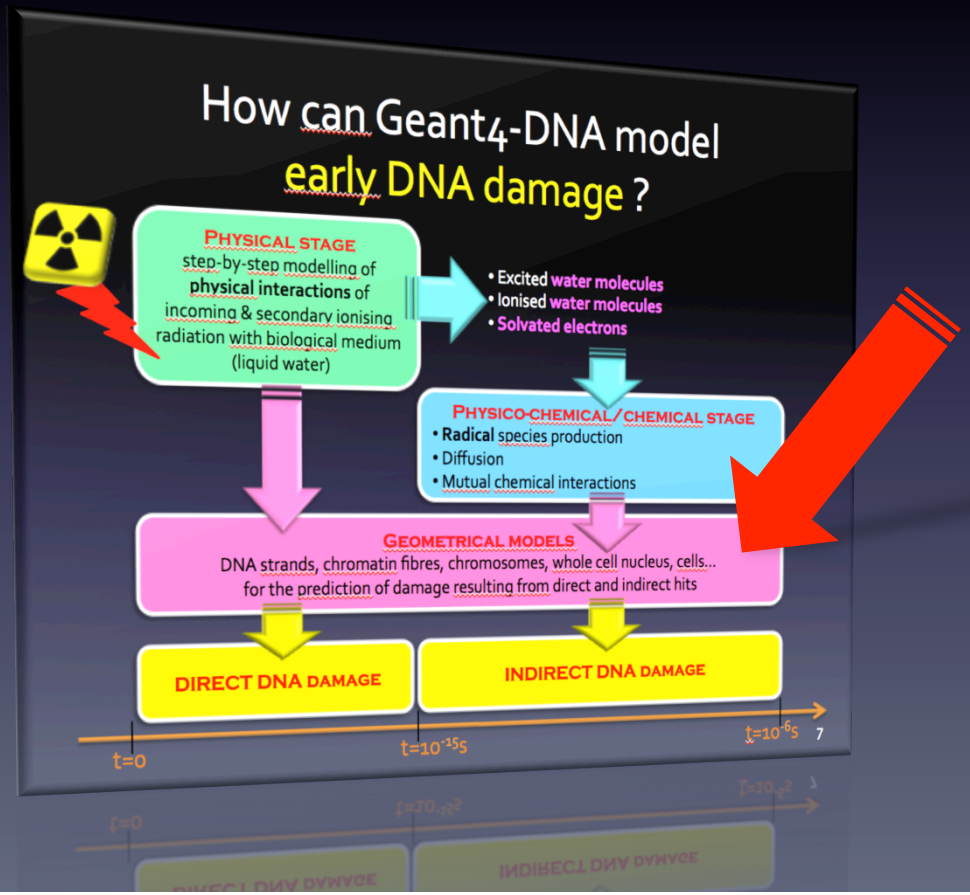
Solvated e-



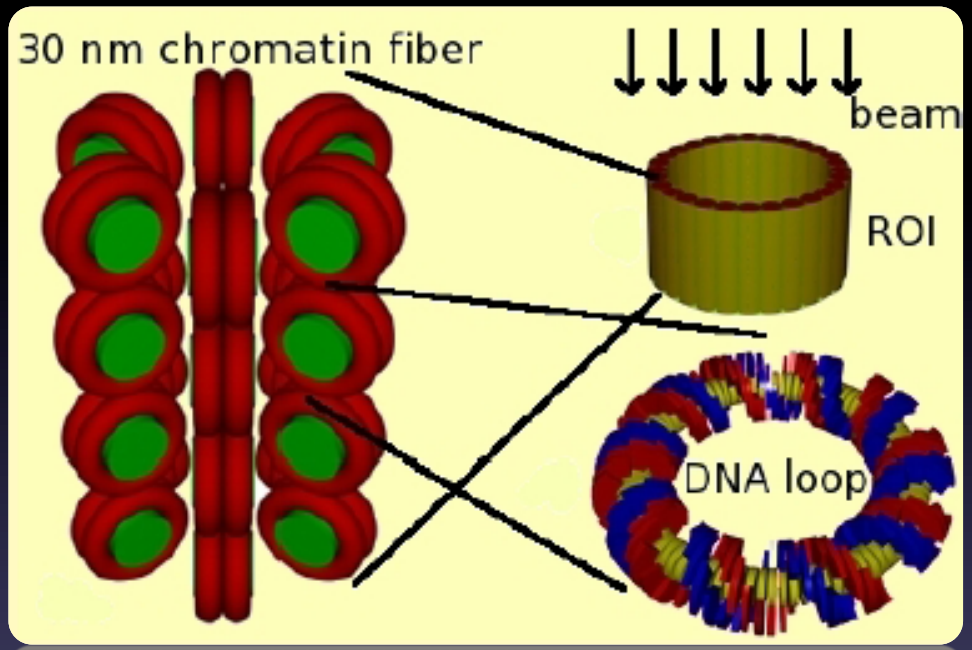


See J. Comput. Phys. 274 (2014) 841-882 (link)

4) GEOMETRICAL MODELS



Investigation of TSB invariance



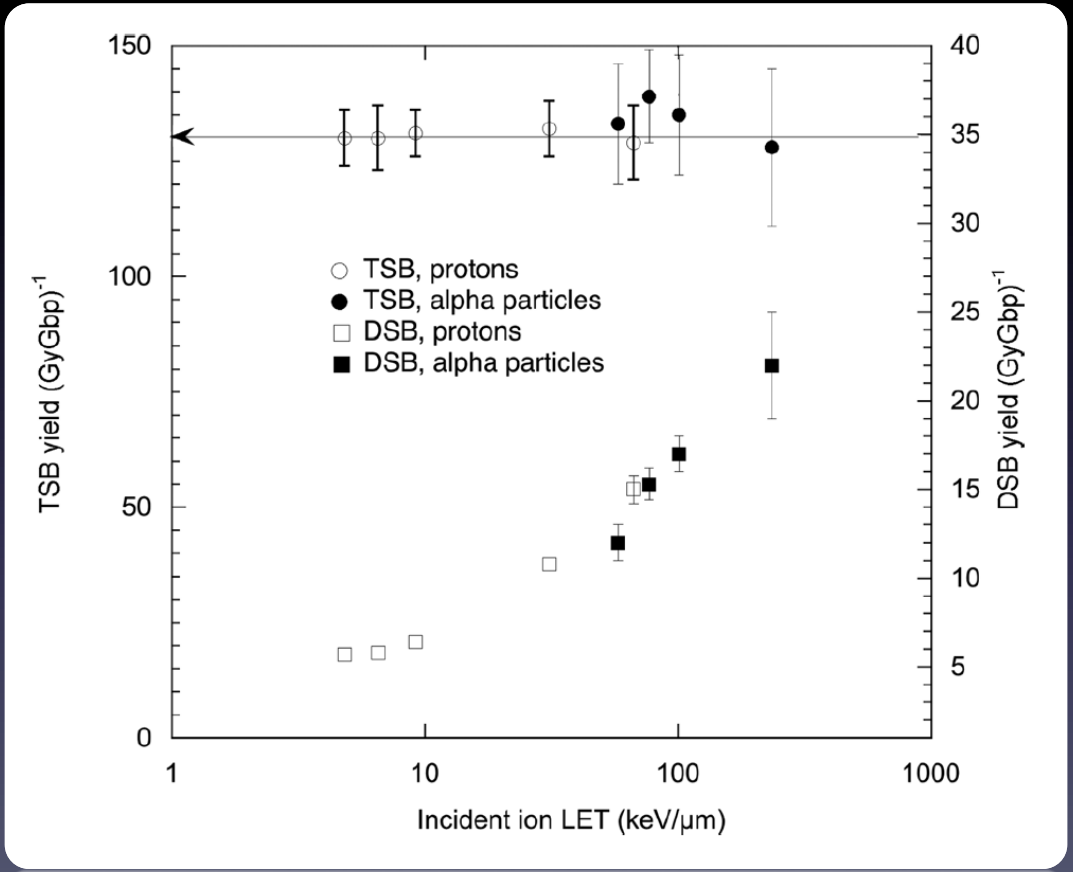
900 fragments of 30-nm chromatin fiber were put into a cylindrical shell (ROI) with a central diameter and height of 10 µm and 5.25 µm, respectively.

- The direct **total strand break (TSB) yield** is the number of DNA strand breaks directly produced by the ionizing particles per unit dose and base pair [(GyGbp)-1].
- The TSB has been reported to be independent of the LET and type of radiation
- Can we explain why using Geant4-DNA ?

Med. Phys. 38, 4147-4153 (2011)

Direct TSBs & DSBs vs LET

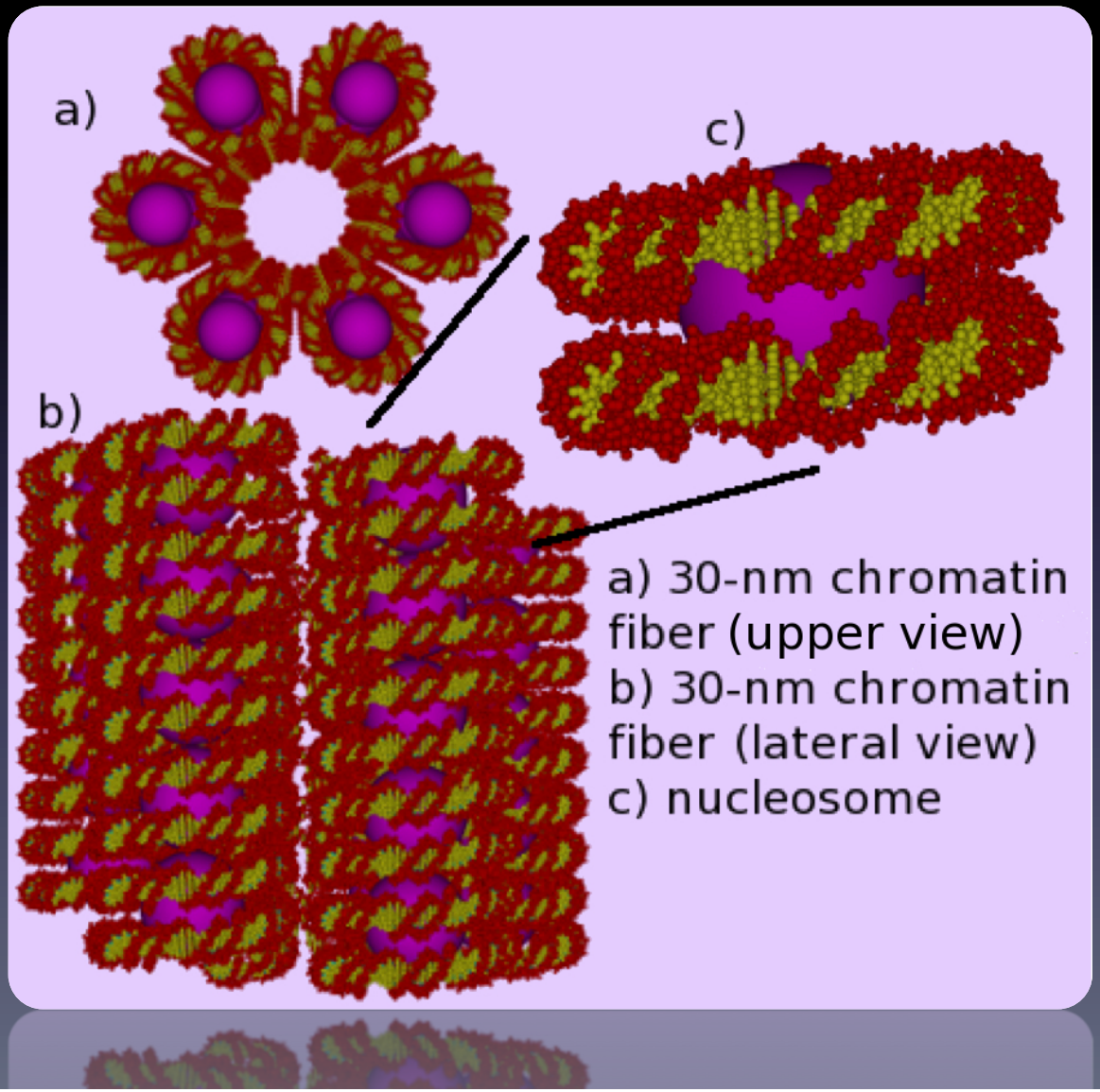
- Absorbed dose in the ROI : 100 Gy
- « Unlike the results obtained for the total TSB yield, the DSB probability increases with the incident radiation LET as previously reported »



Med. Phys. 38, 4147-4153 (2011)

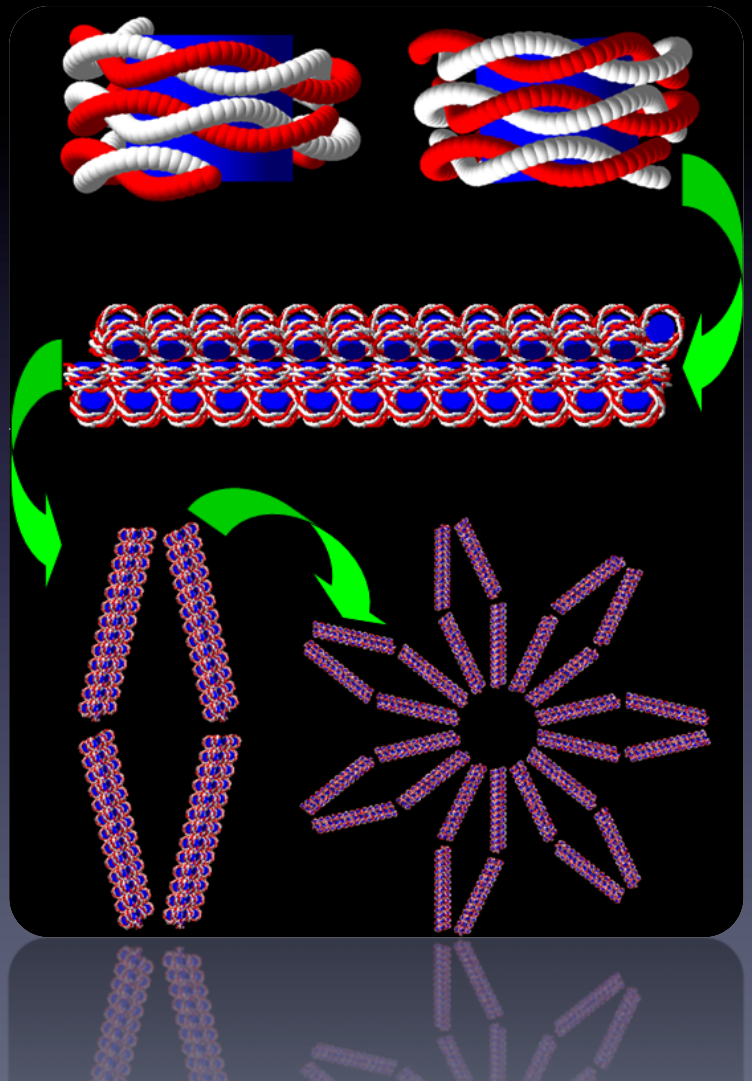
See Comp. Phys. Comm. 184 (2013) 12 (link)

B-DNA atomistic geometrical model



- By M. Bernal et al. (Campinas U., Brazil)
- All DNA atoms are accounted for explicitly.
- Five organization levels of the genetic material, from the nucleotide pair up to the 30-nm chromatin fiber.
- The DNA chain is continue along the whole chromatin fiber.
- Complies with the packing ratio of each structure.
- Subroutine available to determine which is the closest atom with respect to an arbitrary point in space.
- Target = volume defined as the union of all atoms conforming the sugar-phosphate group
- Can be downloaded from the Journal web site

« wholeNuclearDNA »
extended example



Nucleosome

- 200 bp / nucleosome
- DNA diameter = 2.16 nm
- Histone = cylinder of 6.5 nm in diameter and 5.7 nm in height

Chromatin fiber

- 90 nucleosomes / fiber
- 7 nucleosomes / turn
- D = 31 nm
- L = 161 nm

Chromatin fiber loop

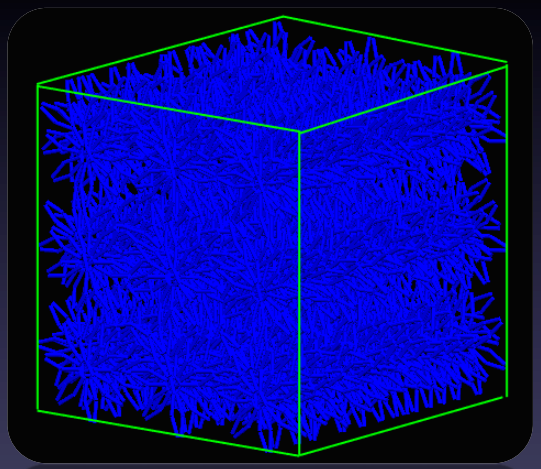
- 4 fibers / loop assembled in a diamond shape
- 7 loops to form a "flower"*

* W. Friedland et al, Rad. Res 59 (2003), 401-410

« wholeNuclearDNA » extended example

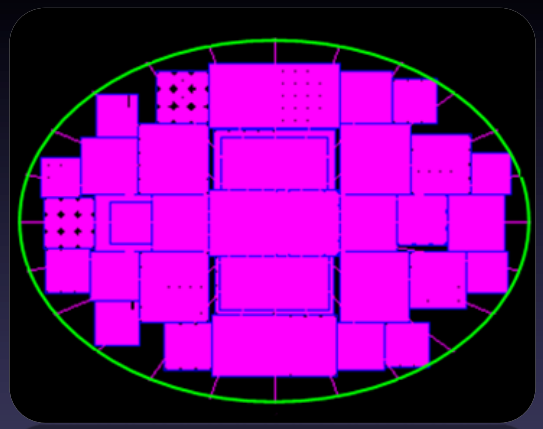
« DetectorConstruction » class: implementation of an elliptical cell nucleus with similar dimensions of fibroblast grown on a microscopic plate at confluence

Chromosome domain example



Per nucleus
- **23 pairs of chromosomes**
- **11875 flowers or 83125 loops**
- **332 500 chromatin fibers**
- **29 925 000 nucleosomes**
- **~ 6 Gbp**

« Fibroblast » cell nucleus



- Nucleus-shape: ellipsoid
- Dimensions: 19.7 * 14.2 * 5 μm^3
- V = 732 μm^3
- 0.42 % of DNA / nucleus

Output: a ROOT file containing an n-tuple with the following values only for energy transfer points located in the backbone region:
-**Particle type** at the origin of the energy deposition
-**Process type (ionization, excitation)**
-Information on the **DNA strand** (flag 1 / 2)
-**Coordinates of the energy deposition** (x,y,z)
-**Energy deposition** amount

See NIMB 298 (2013) 47-54 (link)

http://pdb4dna.in2p3.fr
http://geant4-dna.org

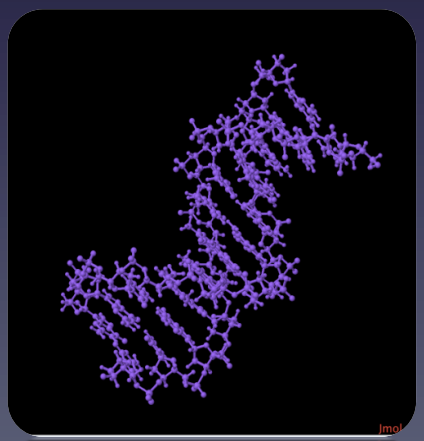
A new interface to describe geometries in Geant4-DNA

- PDB : Protein Data Bank

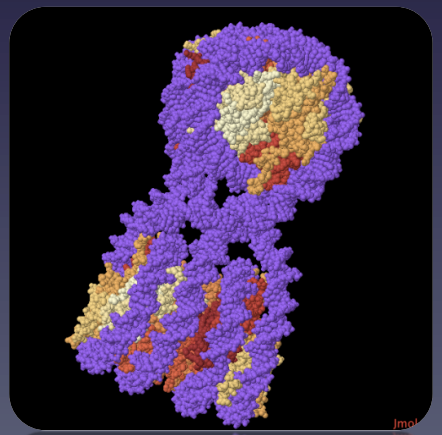
  http://www.rcsb.org/pdb/

  - 3D structure of molecules
  - Proteins
  - Nucleic acids
- Description of DNA molecules
  - 1FZX.pdb
    - Dodecamer
    - 12 DNA base pairs
    - (2,8 x 2,3 x 4,01 nm³)
  - 1ZBB.pdb
    - Tetranucleosome
    - 2 nucloosomes : 347 pairs of bases
    - (9,5 x 15,0 x 25,1 nm³)

```
HEADER    STRUCTURAL PROTEIN/DNA                08-APR-05   1ZBB
TITLE     STRUCTURE OF THE 4_601_167 TETRANUCLEOSOME
...
ATOM      1  O5'  DA I   1      70.094  16.969 123.433  0.50238.00      O
ATOM      2  C5'  DA I   1      70.682  18.216 123.054  0.50238.00      C
ATOM      3  C4'  DA I   1      69.655  19.289 122.776  0.50238.00      C
...
TER   14223      DT J 347
...
HELIX    1   1 GLY A   44  SER A   57  1                                14
HELIX    2   2 ARG A   63  ASP A   77  1                                15
...
SHEET    1   A 2 ARG A  83  PHE A  84  0
SHEET    2   A 2 THR B  80  VAL B  81  1  O  VAL B  81   N  ARG A  83
```



1FZX.pdb



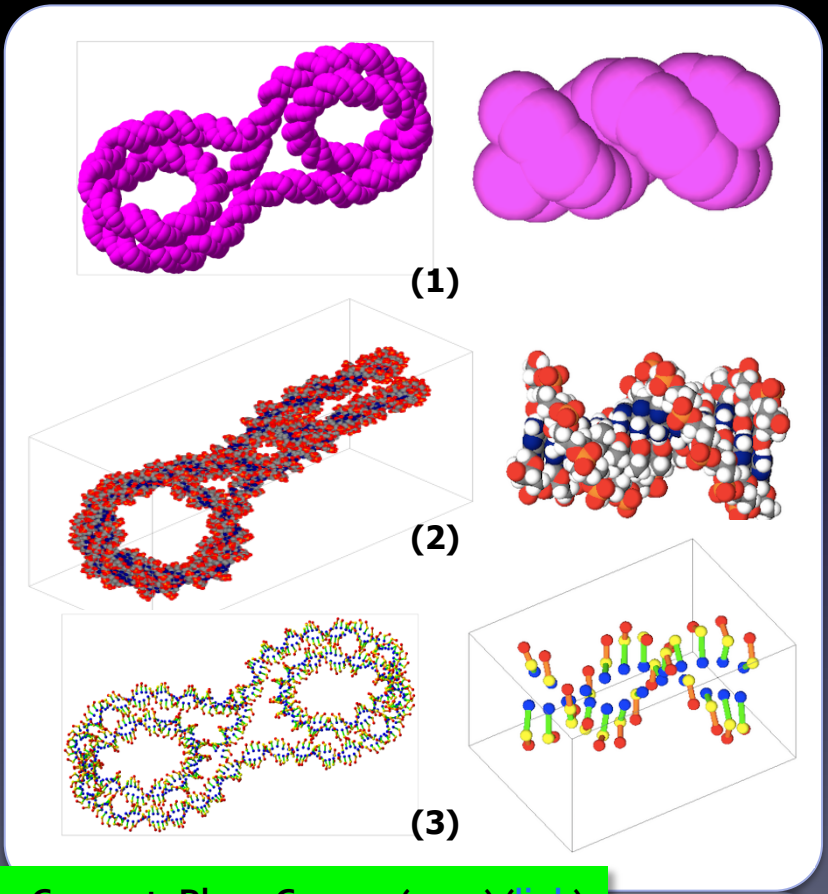
1ZBB.pdb

http://pdb4dna.in2p3.fr
http://geant4-dna.org

« PDB4DNA » suite

Click

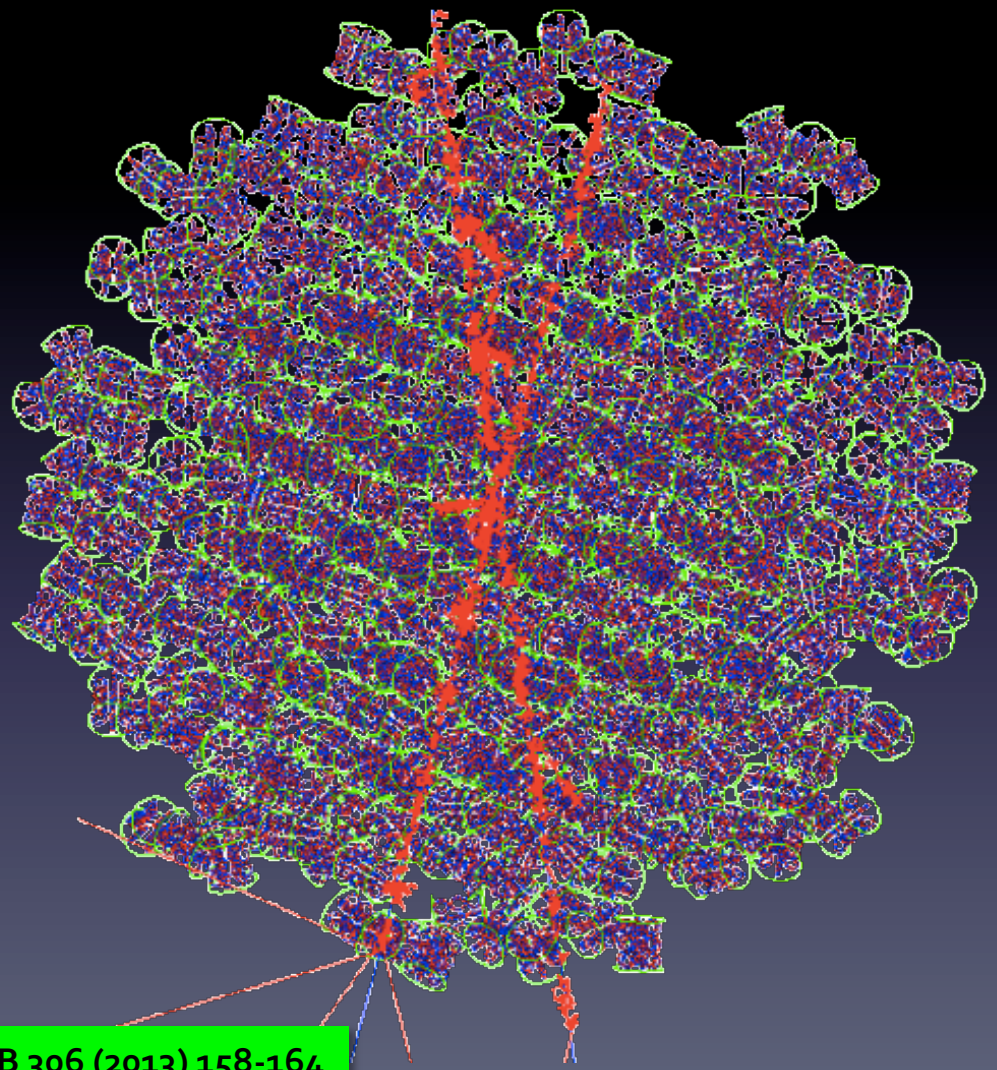
- 1) A C++ library
  - Reading of PDB files
  - Build bounding boxes from atom coordinates
  - Search for closest atom from a given point
  - Geometry and visualization : 3 granularities
    - (1) Barycenter of nucleotides
    - (2) Atomistic
    - (3) Barycenter of nucleotide components
- 2) A Geant4-DNA example
  - Water box surrounding the molecule
  - The output results consists in a ROOT file, containing for each event:
    - energy deposit in bounding boxes
    - number of single strand breaks (SSB)
    - number of double strand breaks (DSB)
- Available on-line under Geant4 license



See Comput. Phys. Comm. (2015) (link)

Towards DNA and cell geometries

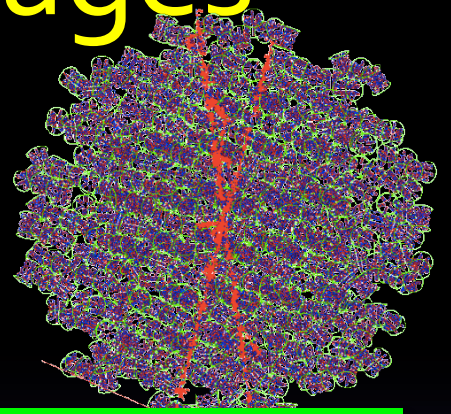
- DPK simulations and previous nanobeam simulations (see nanobeam advanced example) have shown that the Geant4/ Geant4-DNA transport is accurate at nanometer scale
- Being included in Geant4, Geant4-DNA can use Geant4 geometry modelling capabilities
- We have built a cell nucleus (15 µm diameter) containing 6×10^9 base pairs of DNA in the B-DNA conformation
  - Containing randomly oriented and non-overlapping fragments of chromatine fibers
  - Based on voxellized nucleus phantom (see microbeam advanced example)



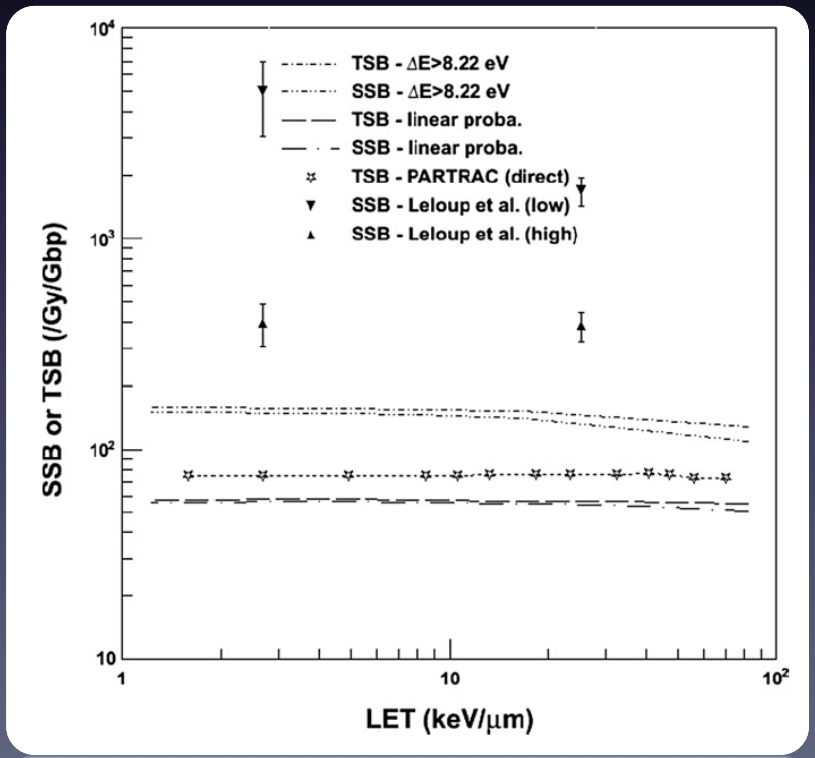
See NIMB 306 (2013) 158-164

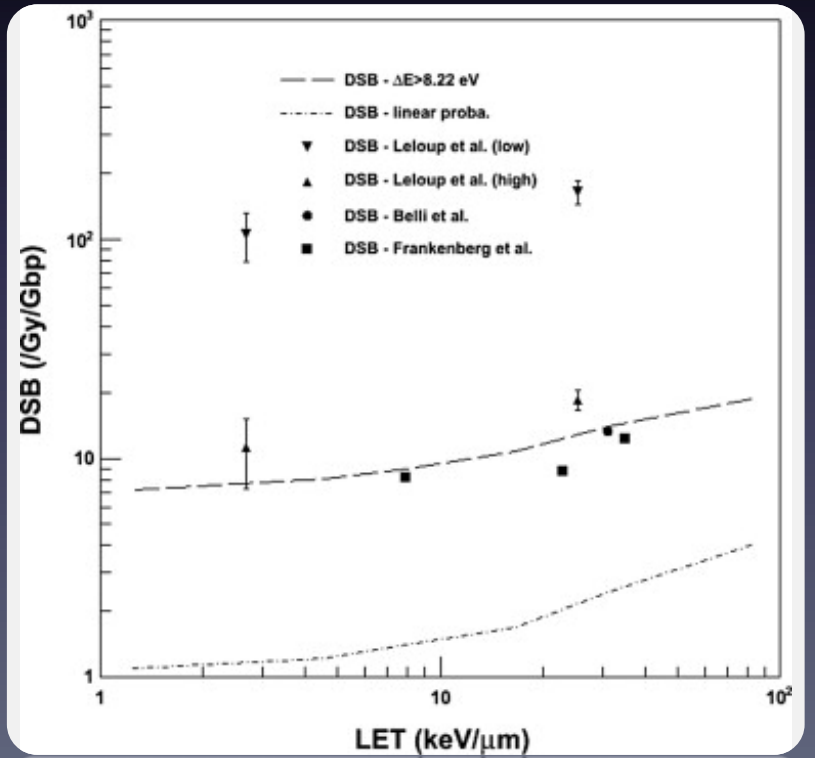
Estimating DNA damages

- Possibility to investigate direct single and double strand breaks
- Results depend mainly on
  - Energy threshold value for induction of a single strand break
    - Fixed threshold (8.22 eV)
    - Linear probability (à la PARTRAC)
  - Geometrical volumes of sugar-phosphate groups (backbone)
- Reasonnable agreement with experimental data
  - Difficult to clearly distinguish direct from non-direct effects

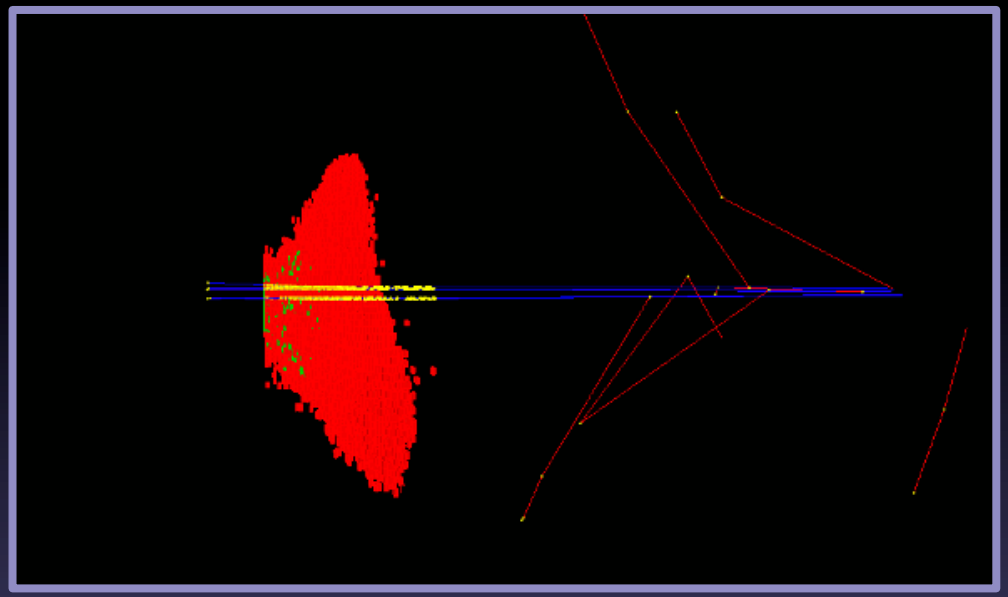


See NIMB 306 (2013) 158-164





« microbeam » advanced example



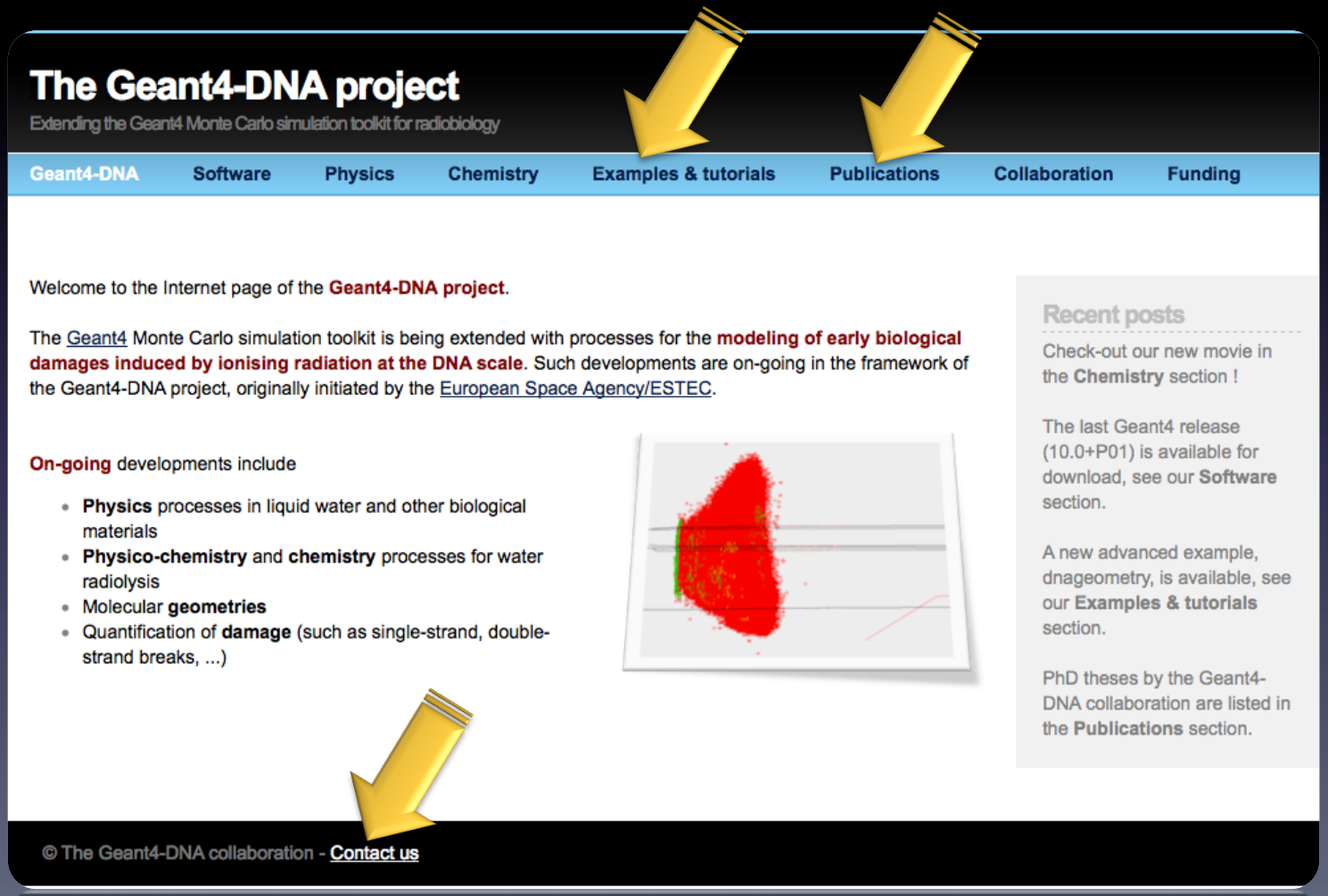
- Simulation of single HaCat cell targeted irradiation using a focused alpha particle microbeam @ CENBG, Bordeaux, France
- Implements a realistic 3D cellular phantom constructed from confocal imaging and ion beam elemental chemical analysis
  - Nucleus, nucleoli, cytoplasm
  - About 5×10^4 voxels, each of size $360 \times 360 \times 160$ nm^3
- By default, uses Geant4 « low energy » Livermore-based electromagnetic physics
- Can extract energy deposition per voxel

See Rad. Prot. Dos. 133 (2009) 2-11 (link)

5) Where to find more information ?

Geant4-DNA website

A unique web site for Geant4-DNA: **http://geant4-dna.org**



Geant4 Virtual Machine

http://geant4.in2p3.fr

A virtual Linux PC with Geant4 and tools fully installed

Windows™
Mac™
Linux™

Full open access

Thank you for your attention
…and a special thank you to

Theory & MC experts

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

Our youngest developers

Julien Bordes (INSERM, Toulouse, France) – PhD on-going
Morgane Dos Santos (CNRS, IMNC, France)
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Ioanna Kyriakou (Ioannina University, Greece)
Sylvain Meylan (IRSN, France) – PhD on-going
Shogo Okada (KEK, Japan)
Yann Perrot (LPC Clermont, France)
Trung Q. Pham (Hanoï, Vietnam)
Jae Ik Shin (NCC, Korea)
Vaclav Stepan (NPI, Prague, Czech Rep.)
Hoang N. Tran (Ton Duc Thang U., Vietnam)