http://geant4.org

The Geant4-DNA project

Overview & status

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on behalf of the « Geant4-DNA » collaboration
and the
« Electromagnetic Physics » working groups of the Geant4 collaboration

KIT Tutorial, October 25-26, 2011, Karlsruhe

Outline

- Context of the Geant4-DNA project
- On-going developments
  - The physics content of Geant4-DNA
  - A multi-scale approach in Geant4
  - Modelling water radiation chemistry
  - Geometries down to the DNA scale
- Geant4-DNA user examples and applications
- Where to find more information

Suggested references

Context

- Many Monte Carlo codes are already available today for the simulation of track structures at the molecular scale
  - E.g. PARTRAC, TRIOL, PITS, KURBUC, NOREC…
  - include physics & physicochemistry processes, detailed geometrical descriptions of biological targets down to the DNA size, even repair mechanisms (PARTRAC)…
- Usually designed for very specific applications
- Not so 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)

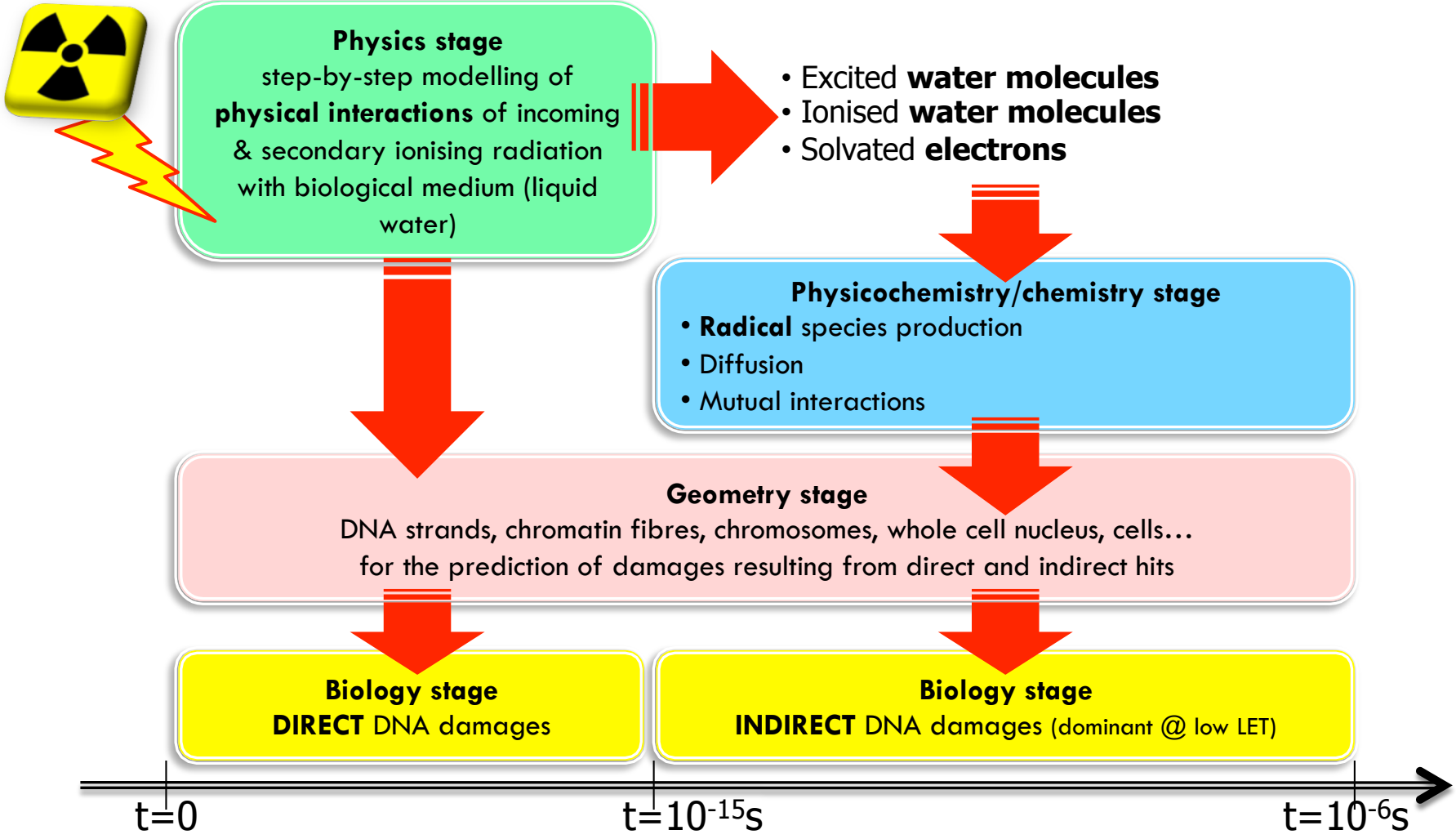
See Int. J. Model. Simul. Sci. Comput. 1 (2010) 157–178

The Geant4-DNA project

- Initiated in 2001 by Dr Petteri Nieminen at the European Space Agency/ESTEC
- Main objective: to adapt 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 damages (up to 1 microsecond after irradiation, for now)
  - providing an open source access to the scientific community
- Phase 1 started in 2001
  - Delivered work package reports and a user requirement document
- Phase 2 ongoing since 2004
  - First prototypes of physics models were added to Geant4 in 2007
  - Currently an on-going interdisciplinary activity of the Geant4 collaboration « low energy electromagnetic physics » working group
  - Coordinated by CNRS/IN2P3 since 2008
- A full independent sub-package of the electromagnetic package of Geant4 from Geant4 9.5 beta
  - $G4INSTALL/source/processes/electromagnetic/dna

Geant4 9.5 BETA

How can Geant4-DNA model radiation biology ?



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On-going developments: Geant4-DNA physics

Physics models available in Geant4 9.4

- Geant4-DNA physics models are applicable to liquid water, the main component of biological matter
  - Extension to DNA materials is currently in progress (A, T, G, C, sugar-phosphate)
- They can reach the very low energy domain (sub-eV limit) 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
  - No condensed history approximation
- Models can be purely analytical and/or use interpolated data tables
  - For eg. computation of integral cross sections
- Since December 2009, they use the same software design as all electromagnetic models available in Geant4 (« standard » and « low energy » EM models)
  - Allows the combination of processes (see later)

Overview of current physics models

- **Electrons**
  - Elastic scattering
    - Screened Rutherford and Brenner-Zaider below 200 eV
    - Champion's approach (partial wave framework, 3 contributions to the interaction potential)
  - Ionisation
    - 5 levels for H_2O
    - Dielectric formalism & FBA using Heller optical data up to 1 MeV, and low energy corrections
  - Excitation
    - 5 levels for H_2O
    - Dielectric formalism & FBA using Heller optical data and semi-empirical low energy corrections
  - Vib. Excitation
    - Michaud *et al.* xs measurements in amorphous ice
    - Factor 2 to account for phase effect
  - Dissociative attachment
    - Melton *et al.* xs measurements

See full details in Med. Phys. 37 (2010) 4692-4708 and Appl. Radiat. Isot. 69 (2011) 220-226

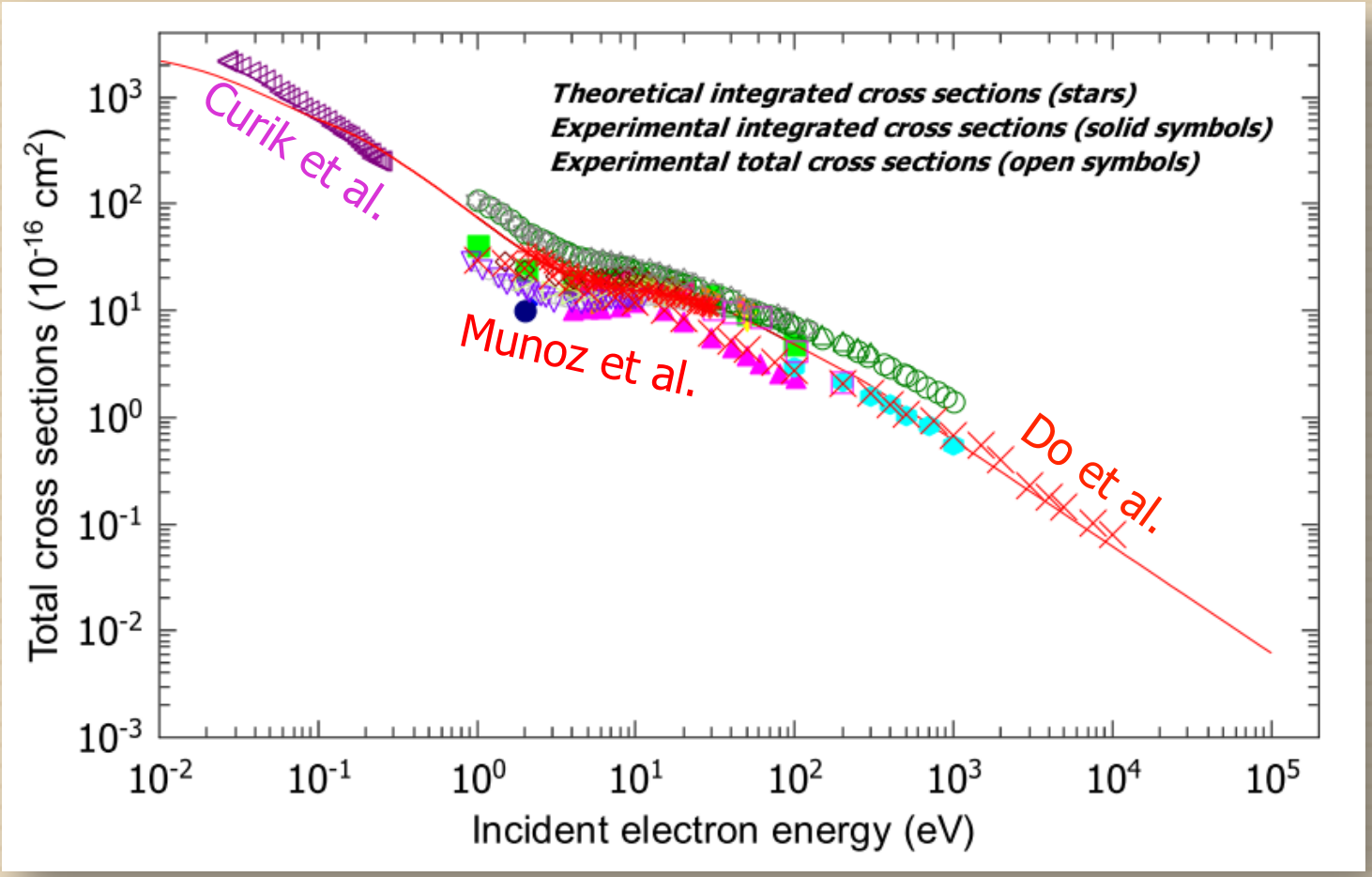
- **Protons & H**
  - Excitation
    - Miller & Green speed scaling of e^- excitation at low energies and Born and Bethe theories above 500 keV
  - Ionisation
    - Rudd semi-empirical approach by Dingfelder *et al.* and Born and Bethe theories & dielectric formalism above 500 keV (relativistic + Fermi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

Overview of Geant4-DNA physics models available in Geant4 9.4 for liquid water

Prelim.

Analytical, interpolated and new models

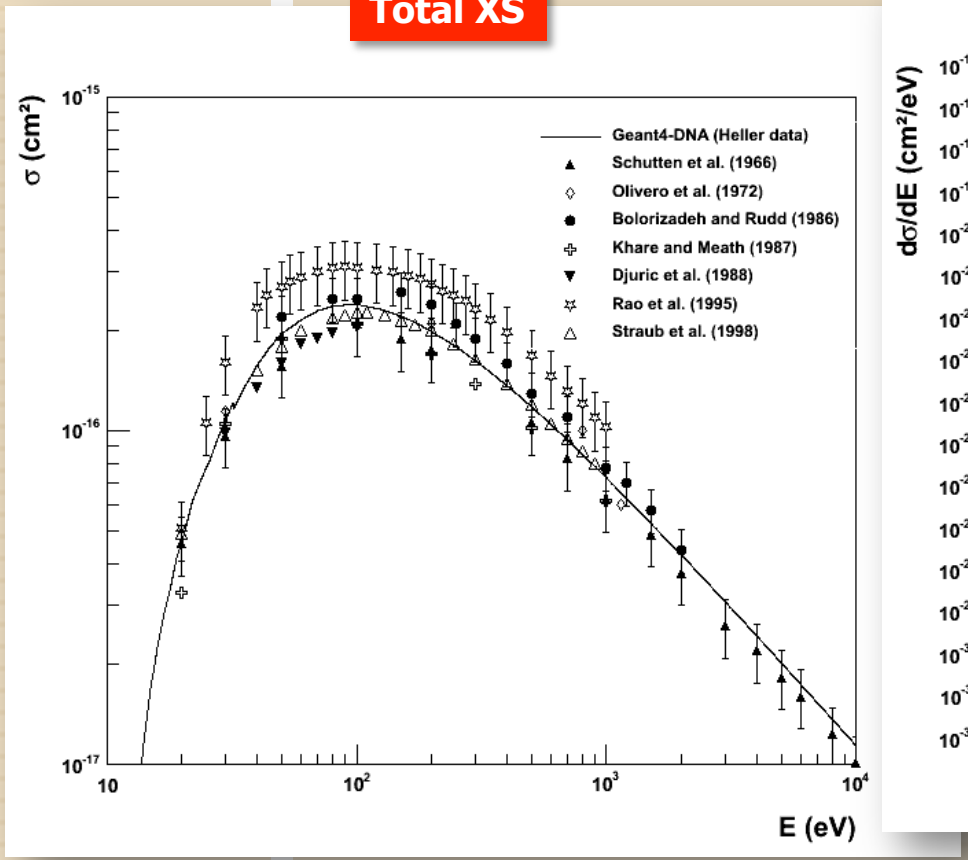
Particles	e-	p	H	a, He+, He^0	C, N, O, Fe,…
Elastic scattering	> 9 eV – 1 MeV Screened Rutherford >4 eV – 1 MeV Champion	-	-	-	-
Excitation A_1B_1, B_1A_1, Ryd A+B, Ryd C+D, diffuse bands	9 eV – 1 MeV Born	10 eV – 500 keV Miller Green 500 keV – 100 MeV Born	10 eV – 500 keV Miller Green	Effective charge scaling from same models as for proton 1 keV – 400 MeV	-
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		Effective charge scaling 0.5 MeV/u – 10^6 MeV/u
Vibrational excitation	2 – 100 eV Michaud et al.	-			
Attachment	4 – 13 eV Melton				



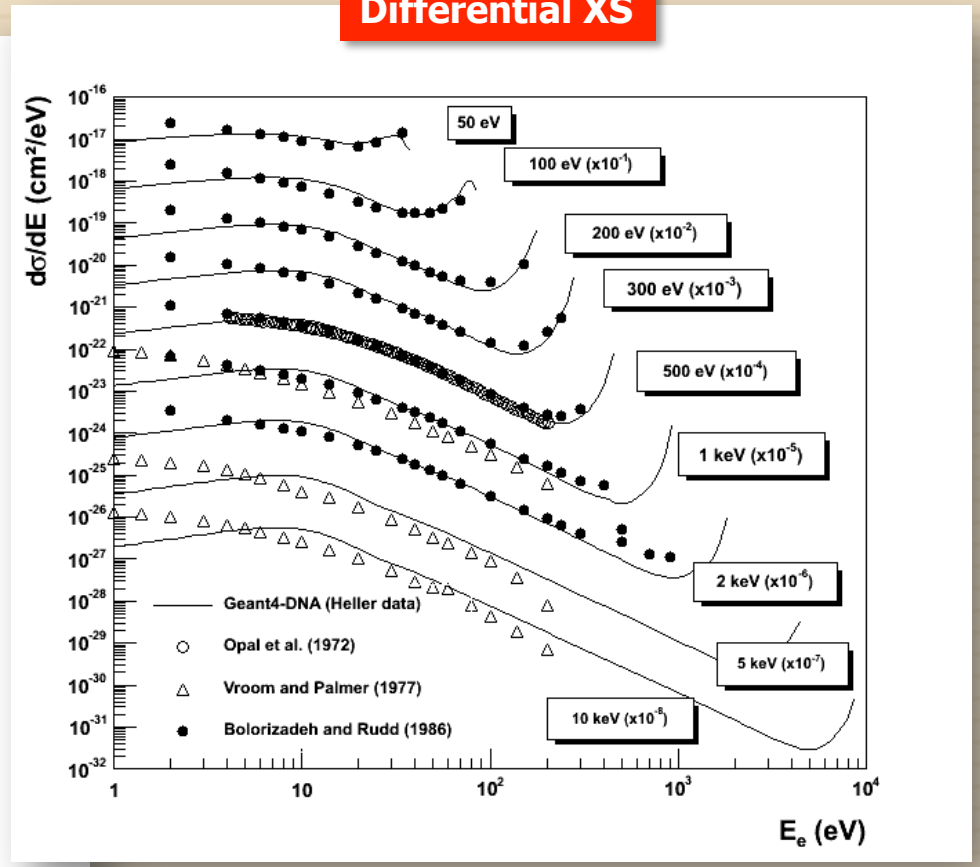
10 Electron elastic scattering cross section

- Theoretical cross section model reaches **10 meV**
- 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

Total XS

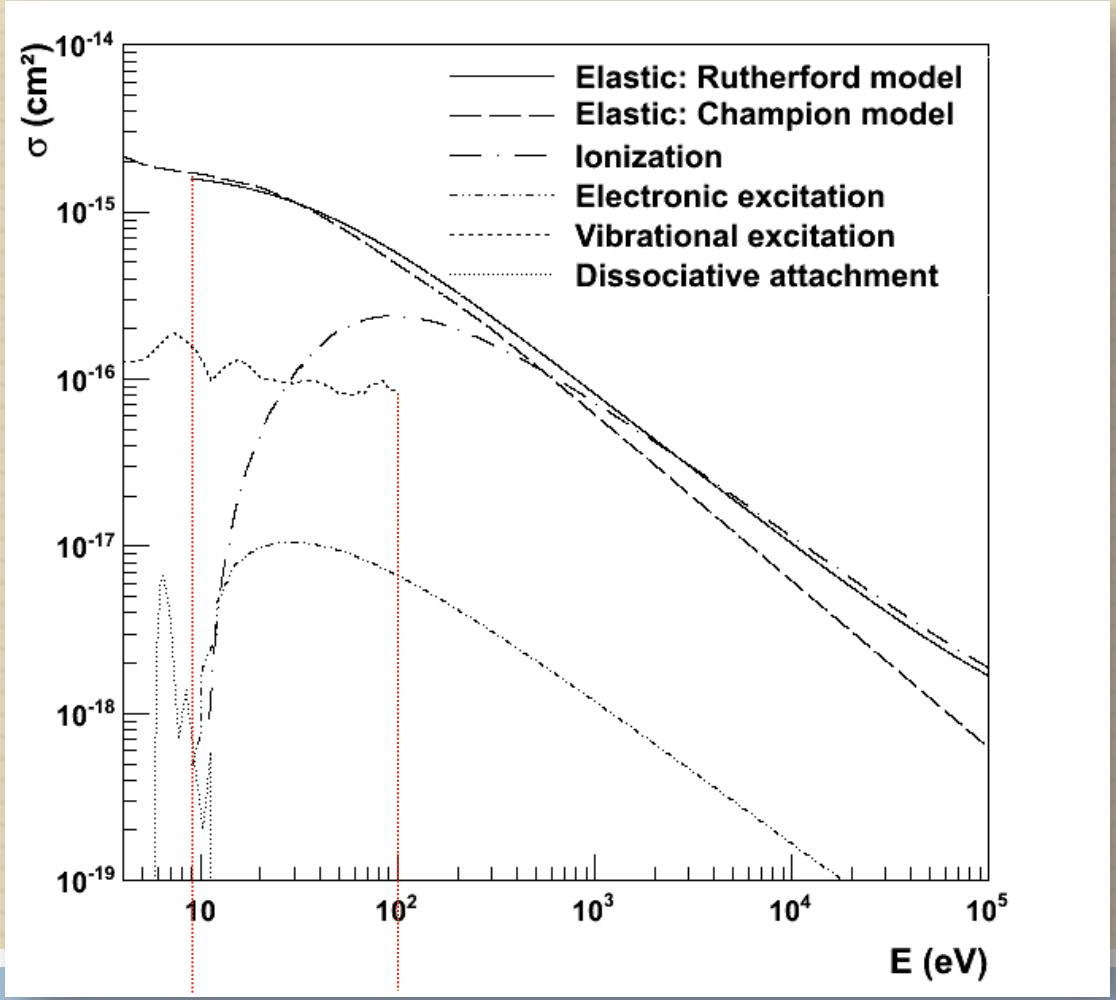


Differential XS



11 Electron ionisation

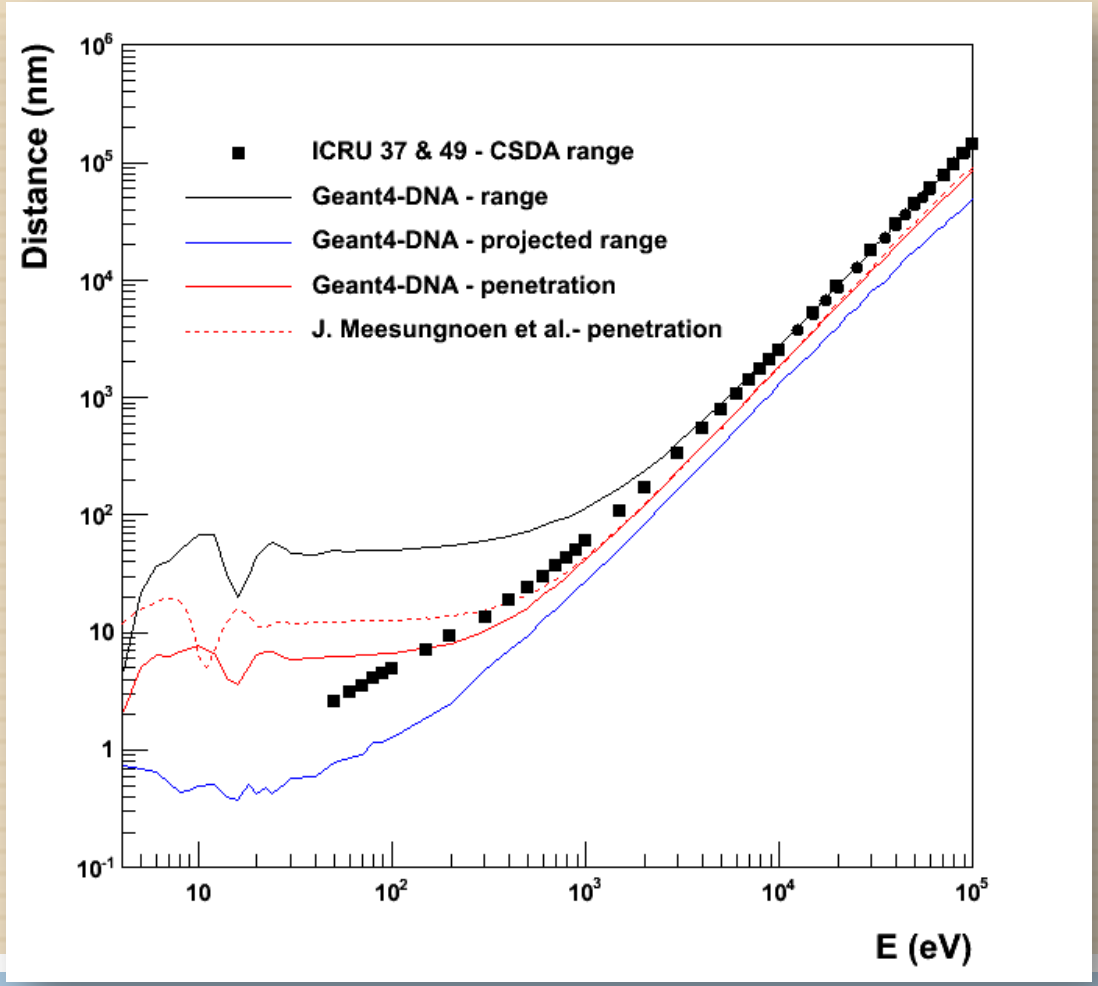
Electron process cross sections in liquid water



Electron process cross sections cover energy range up to **1 MeV** down to either

- **4 eV** for the **Champion** elastic scattering model
- or **9 eV** for the **Screened Rutherford** elastic scattering model (default model)

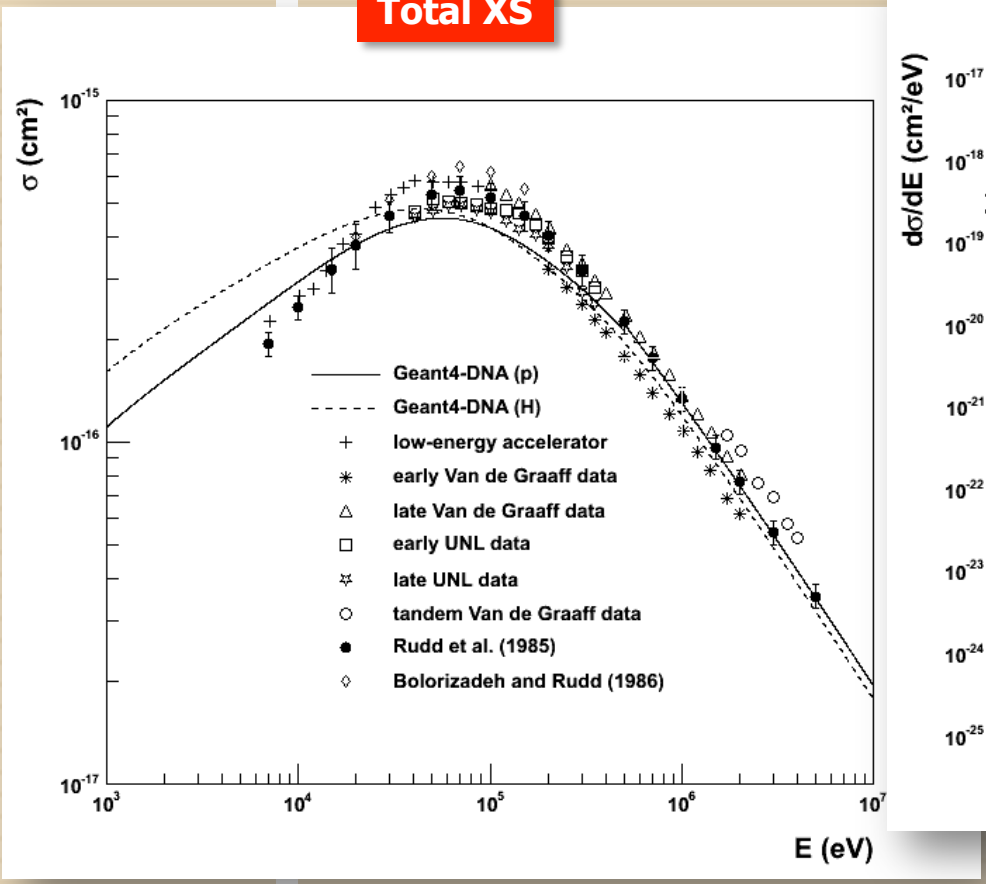
These low energy limit can be extended down to lower energies by the user in his /her **Physics List**



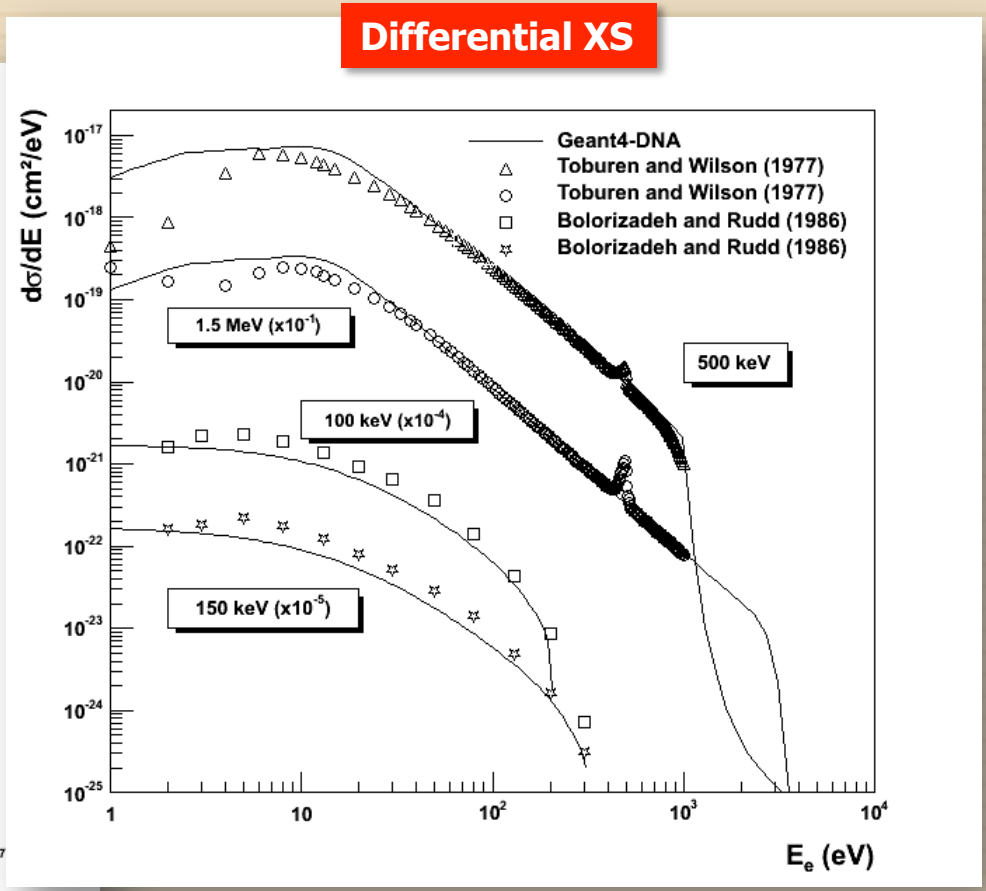
Electron range, projected range and penetration

- Obtained with the **C. Champion** elastic scattering model (down to **4 eV**)
- 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)

Total XS



Differential XS



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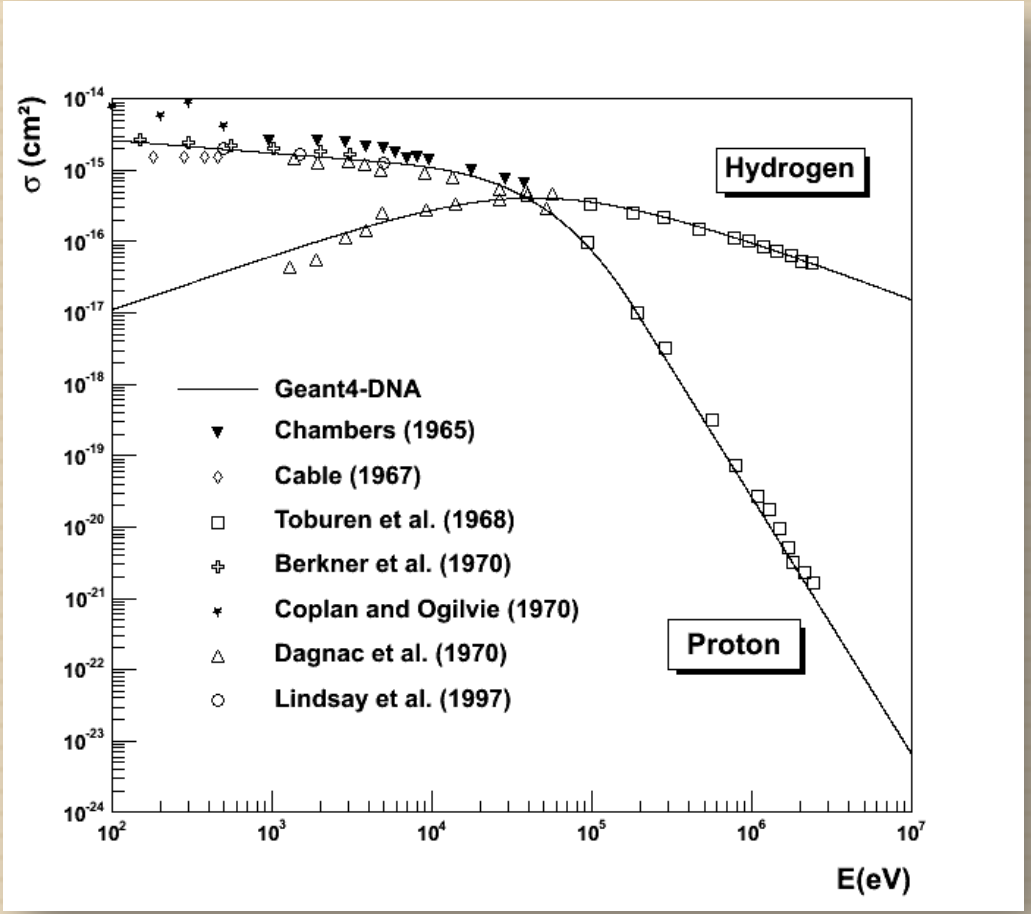
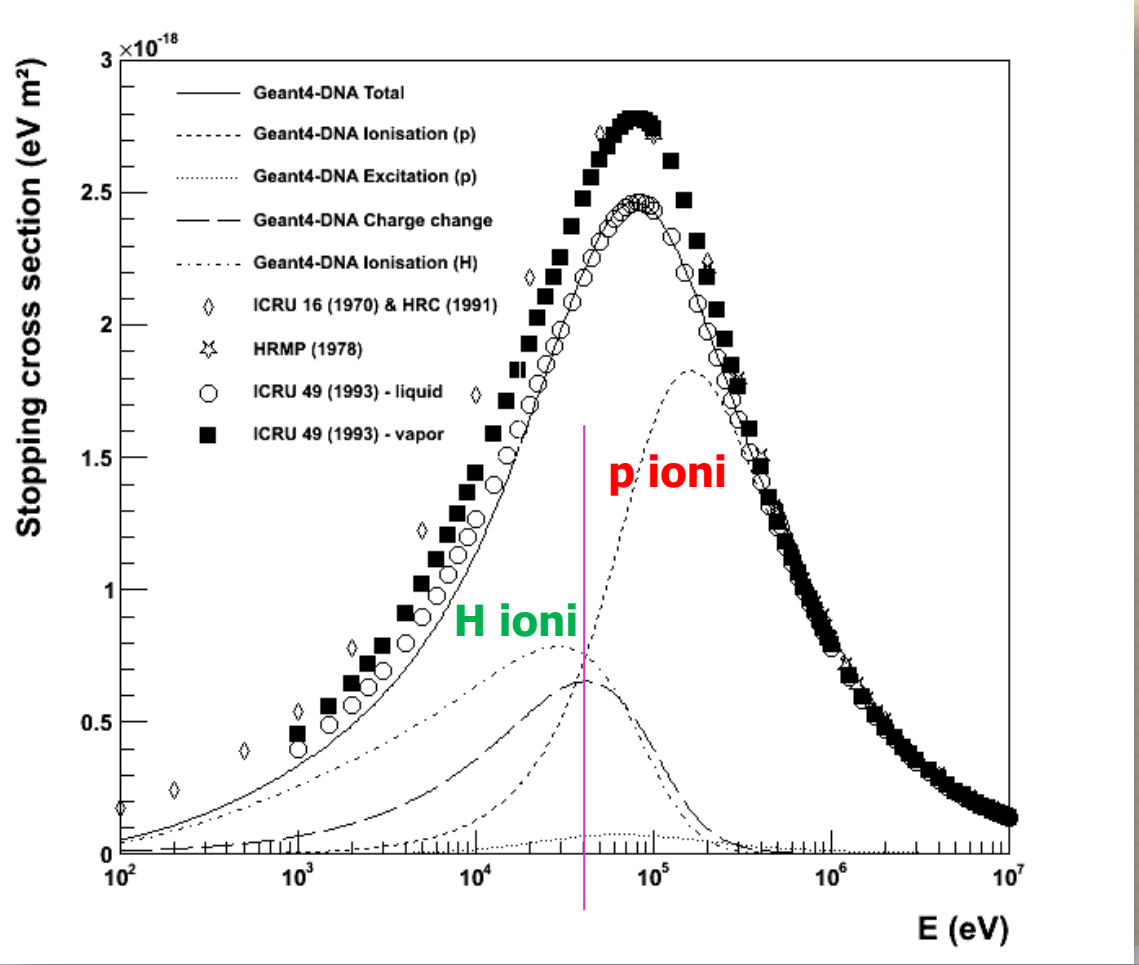
Proton & Hydrogen ionisation

Total XS



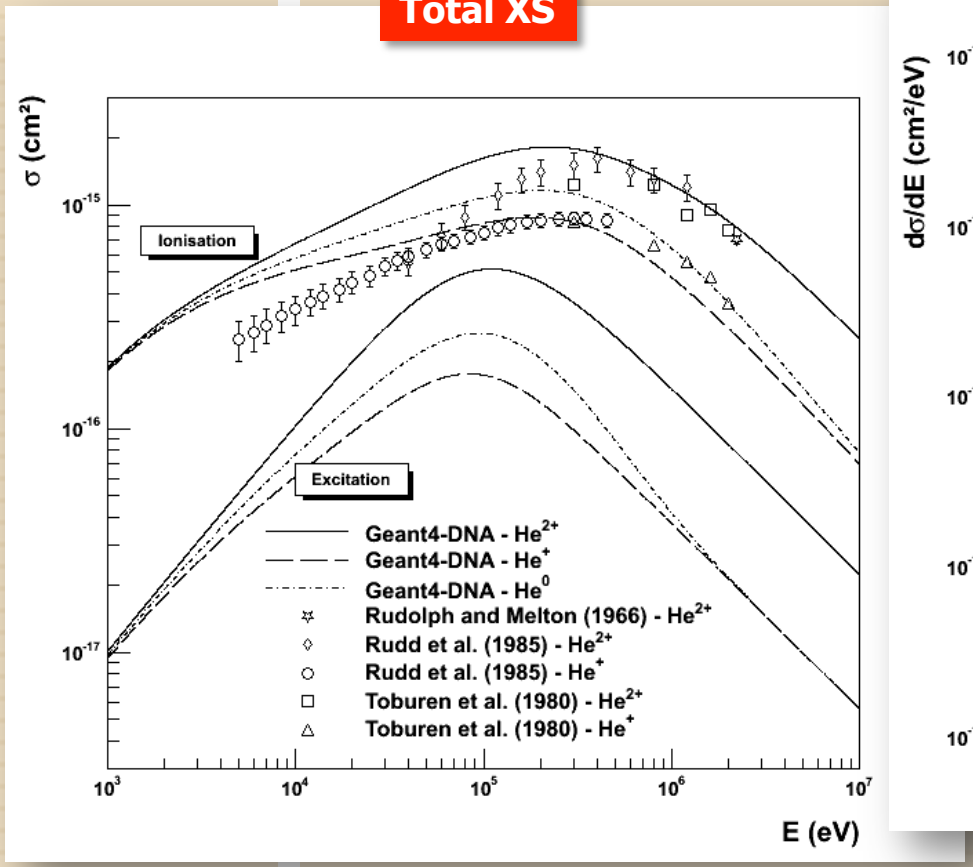
Proton and Hydrogen charge exchange

Proton stopping cross section in liquid water

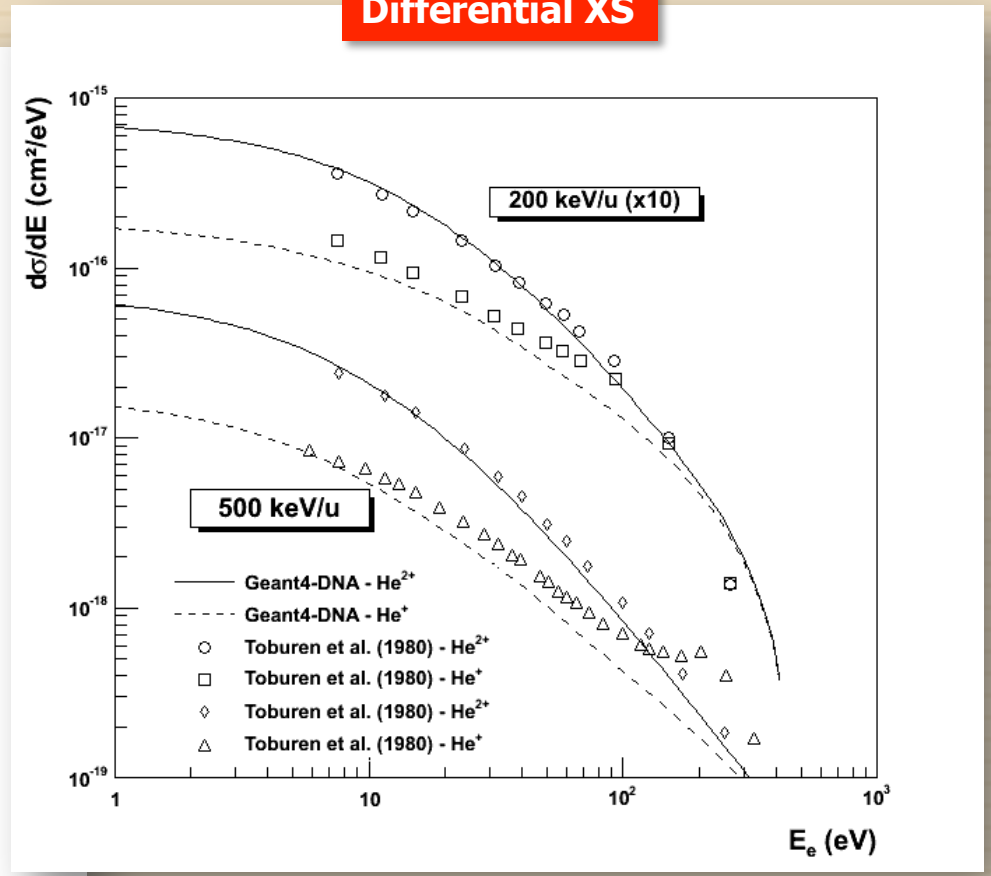


- Contributions of **ionisation** (p, H), **excitation** (p) and **charge change**
- Comparison to recommendations (ICRU, HRMP) for **liquid** and **vapour** water

Total XS



Differential XS



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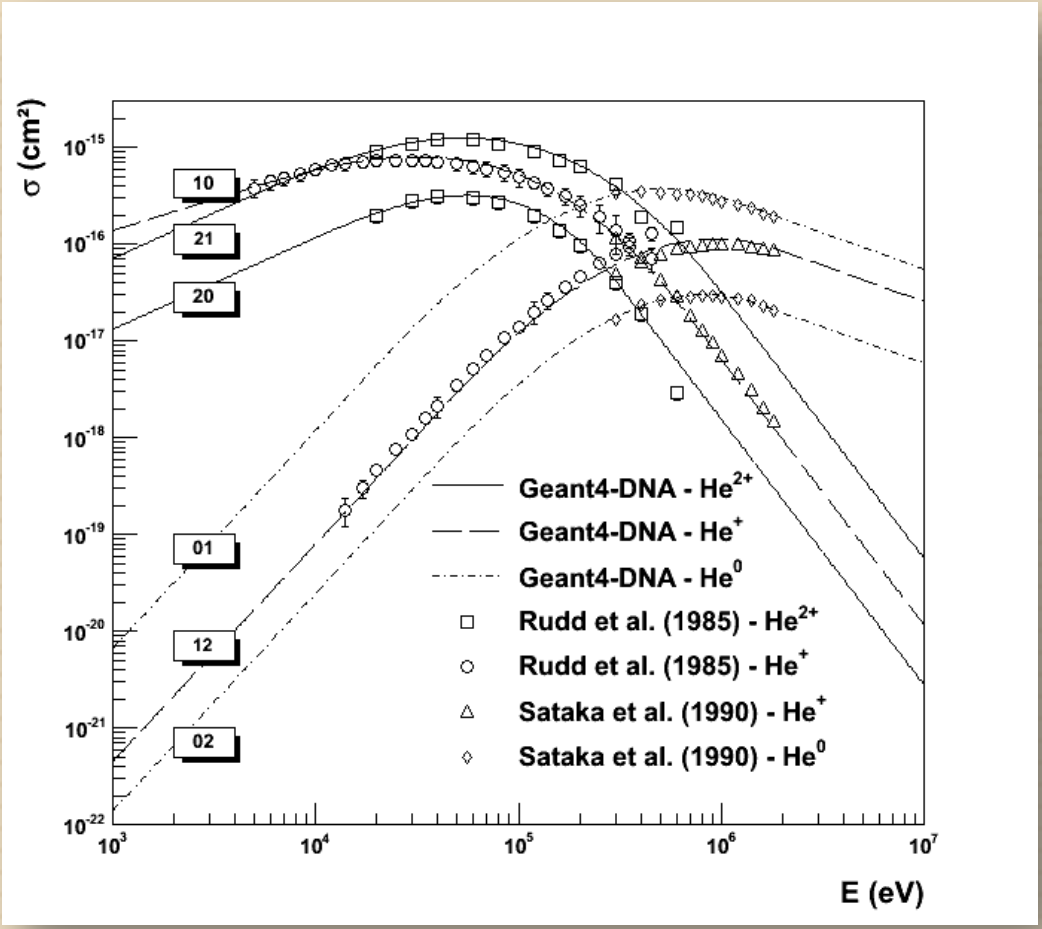
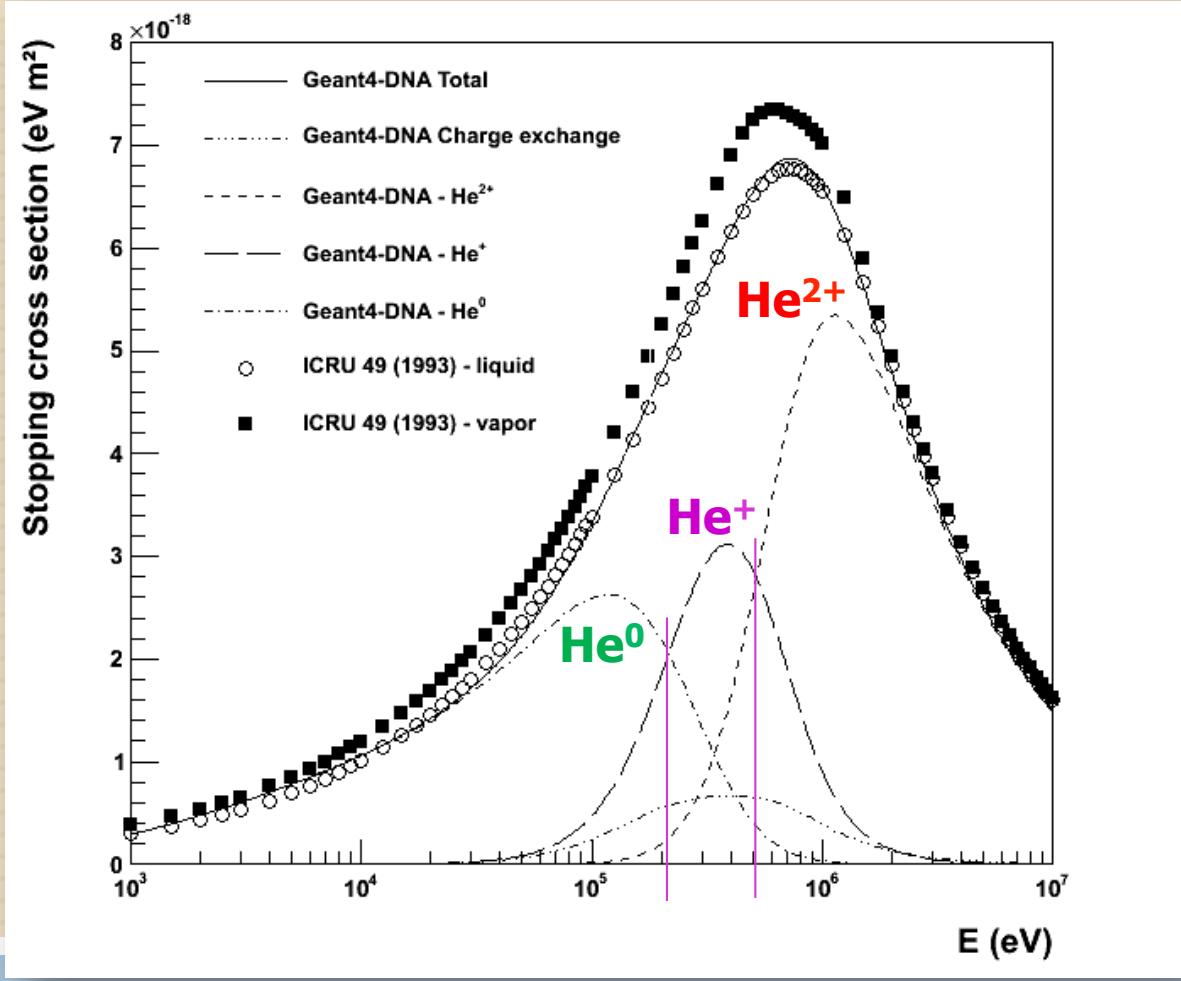
Helium ionisation

Total XS



Helium charge exchange

Helium stopping cross section



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

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On-going developments: multi-scale simulations

Multi-scale approach

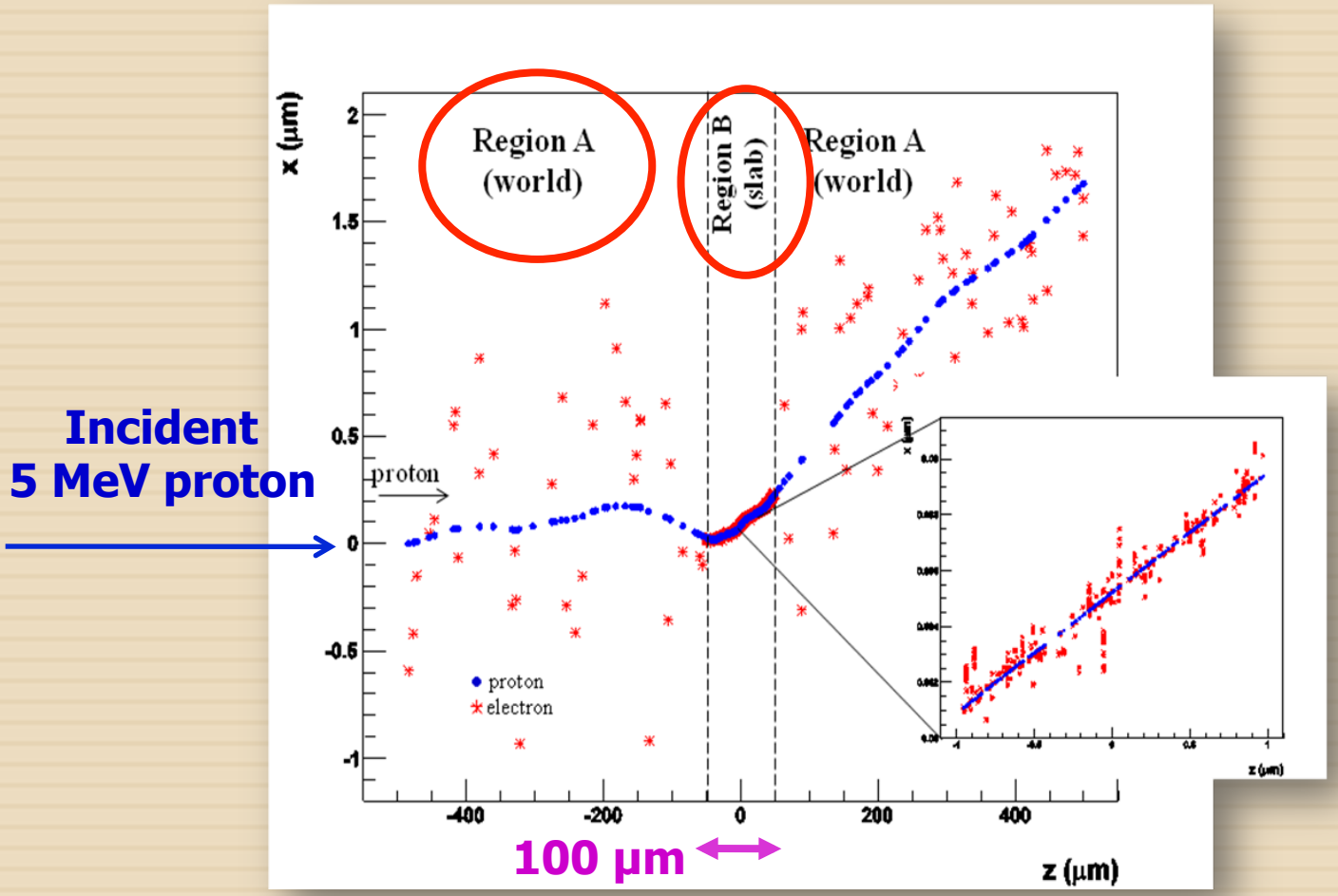
- Geant4-DNA physics processes simulate explicitly all interactions as purely discrete processes and do not use condensed history approximations
  - main drawback: computing performance penalty (by default, e^- are tracked down to ~9 eV)
  - usage should be limited to small size volumes

- Geant4 electromagnetic physics processes do not simulate explicitly all interactions with such accuracy (condensed-random-walk approach)
  - are much less demanding in computing performance.
  - cover a larger energy range up to ~10 PeV

- Since Geant4 9.4, the unified software design adopted in Geant4 EM physics allows naturally the combination of Geant4-DNA processes with Geant4 electromagnetic processes
  - condensed-random-walk processes could be used to simulate the radiation environment surrounding astronauts on board the ISS in space, taking into account high energy incoming cosmic particles and modeling their interactions within spacecraft material, until they finally reach the target cells of interest, where Geant4-DNA discrete processes would take over

Use case

« microdosimetry » advanced example



- Located in $G4INSTALL/examples/advanced
- **Region A** : activation of **Geant4 Standard EM** processes
- **Region B** : activation of **Geant4-DNA** processes
- the user can select the energy threshold separating Standard and DNA processes

Combination of processes

- The user must describe which physics processes and models are active/inactive per detector region

Geant4 9.5 BETA

- One can combine in a single Physics list
  - Geant4 EM Standard Physics processes for electrons, protons, He, C, N, O, Fe and gammas
  - Geant4 EM Low Energy Physics processes for electrons and photons
  - Geant4-DNA processes for e^-, p, H, He^{q+}, C, N, O, Fe
  - Eg. : shoot gamma with Geant4 Standard EM Physics (10 eV-10 TeV) and track secondary electrons using Geant4-DNA

On-going developments:
water radiation chemistry in Geant4

Water radiolysis in Geant4 ?

- The « physics stage » generates ionized and excited water molecules as well as thermalized electrons
  - Water molecules decay into molecular radical species
  - Electrons convert into solvated electrons

- Geant4 simulates particle interactions with matter
  - Molecules are not defined
  - Particles can not interact mutually
  - Brownian diffusion does not exist

- Geant4 must be significantly extended in order to model water radiolysis

Handling molecules, diffusion and chemical reactions in Geant4

- Definition of classes for the description of static and dynamic properties of molecules, in a similar way to what exists for particles
  - G4MoleculeDefinition for static properties
    - name, number of atoms, decay table of decay channels…
  - G4Molecule for dynamic properties
    - electronic configuration, diffusion coefficient…
- Time is sliced in small steps to simulate Brownian diffusion
- Two approaches for mutual interactions
  - Step-by-step: fixed time steps (or dynamical time steps)
  - (Independent Reaction Times)
- A new general design for Interacting Tracks
  - process inheritating from G4VProcess, including a model manager
- Associated to a stack manager for interacting tracks

Molecular species & reactions

Molecular species & diffusion

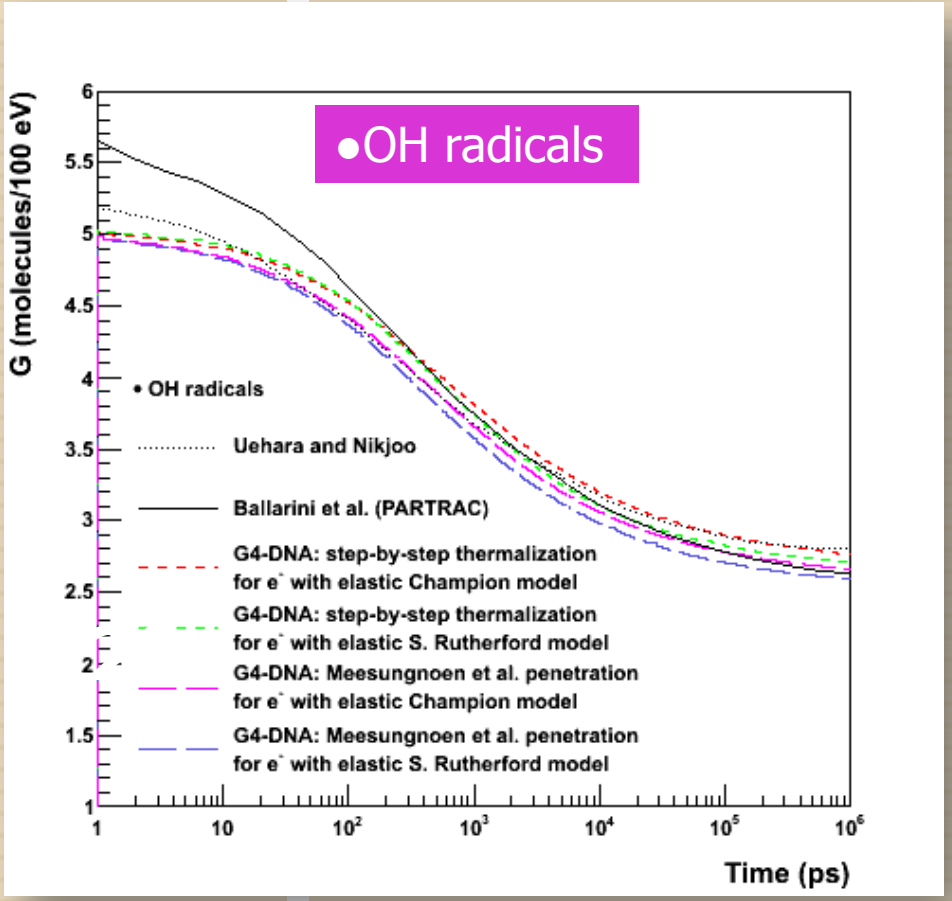
Electronic state	Decay Channel	Fraction (%)
All ionization states	$H_3O^+ + \bullet OH$	100
Excitation state A1B1: (1b1) → (4a1/3s)	$\bullet OH + H\bullet$ H_2O + DE	65 35
Excitation state B1A1: (3a1) → (4a1/3s)	$H_3O^+ + \bullet OH + e^-_{aq}$ $\bullet OH + \bullet OH + H_2$ H_2O + DE	55 15 30
Excitation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

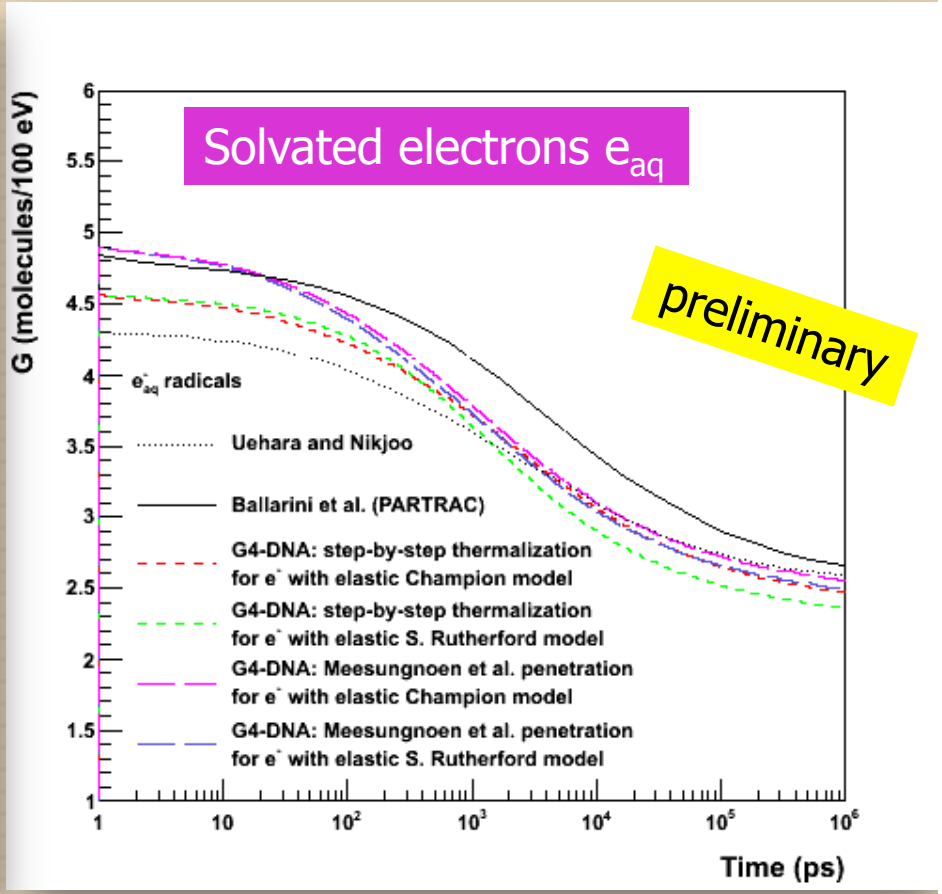
Species	Diffusion coefficient D (10^{-9} m^2 s^{-1})
e^-_{aq}	4.9
$\bullet OH$	2.8
$H\bullet$	7.0
H_3O^+	9.0
H_2	4.8
OH^-	5.0
H_2O_2	2.3

Chemical reactions

Reaction	Reaction rate (10^{10} M^{-1} s^{-1})
$H\bullet + e^-_{aq} + H_2O \rightarrow OH^- + H_2$	2.65
$H\bullet + \bullet OH \rightarrow H_2O$	1.44
$H\bullet + H\bullet \rightarrow H_2$	1.20
$H_2 + \bullet OH \rightarrow H\bullet + H_2O$	4.17×10^{-3}
$H_2O_2 + e^-_{aq} \rightarrow OH^- + \bullet OH$	1.41
$H_3O^+ + e^-_{aq} \rightarrow H\bullet + H_2O$	2.11
$H_3O^+ + OH^- \rightarrow 2\ H_2O$	14.3
$\bullet OH + e^-_{aq} \rightarrow OH^-$	2.95
$\bullet OH + \bullet OH \rightarrow H_2O_2$	0.44
$e^-_{aq} + e^-_{aq} + 2\ H_2O \rightarrow 2\ OH^- + H_2$	0.50

For this prototype software, we followed the set of parameters published by the authors of the PARTRAC software.





Radiochemical yields: prototype results

- tracking of sub-thermalization electrons down to 25 meV: step-by-step tracking of sub-excitation electrons or single step using Meesungnoen fit to thermalization distance and random direction
- Effect of the two alternative electron elastic scattering models
- Comparison to results for incident 1 MeV electrons in 1 mm^3 water volume simulated by PARTRAC and Uehara and Nikjoo.

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On-going developments: modelling geometries at the DNA scale

Objective

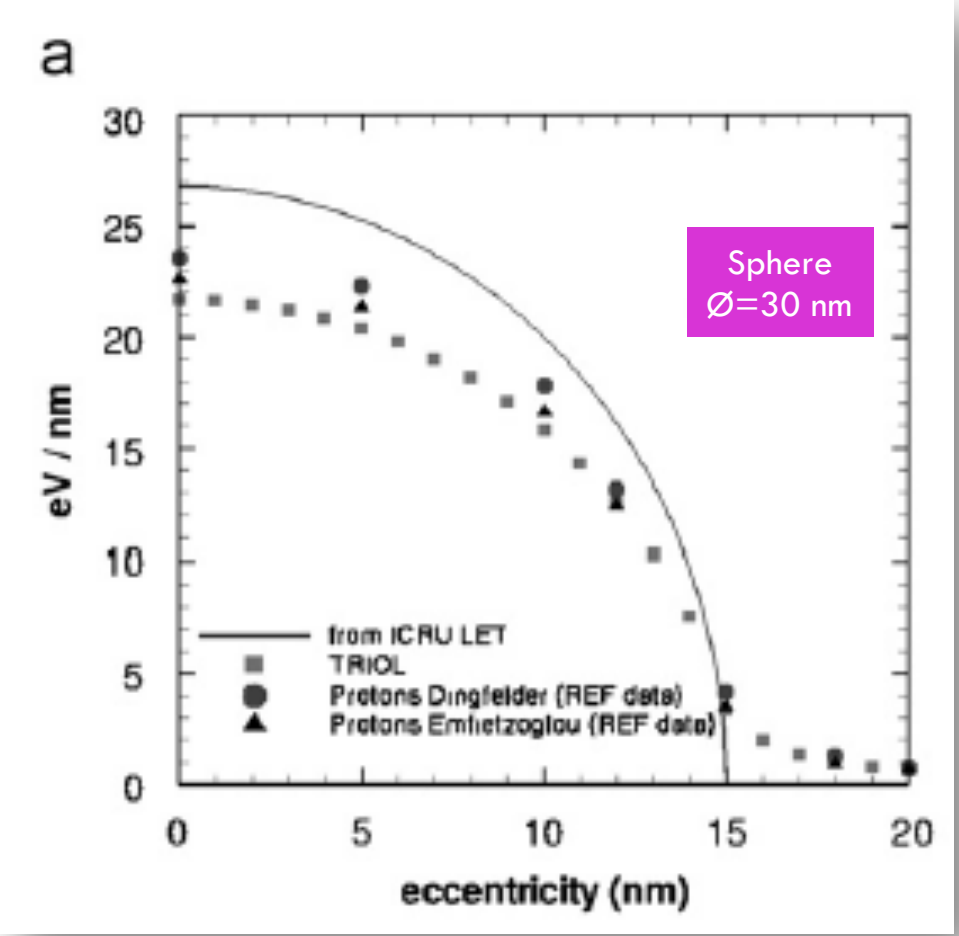
- Try to model the geometrical features of a realistic biological cell, down to the « DNA scale », using Geant4 geometry modeling capabilities
  - Combination of simple shapes (eg. cylinders)
  - Usage of voxellized geometries (« cellular phantoms ») built from confocal microscopy of cells

See Rad. Prot. Dos. 133, 1 (2009) 2-11

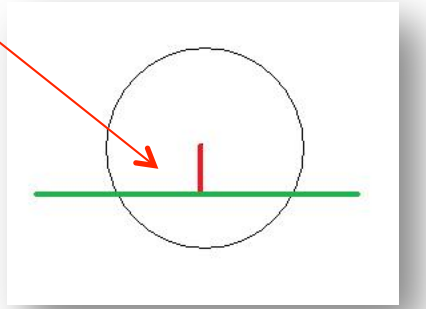
- Doing this, one could simulate
  - Elementary energy deposits from ionising radiation in selected geometrical targets (such as DNA strand) for the modeling of direct effects of radiation
  - Water radiolysis around chromatin fibres for the modeling of non-direct effects by oxydative radicals

- Some of these geometrical models will be included in the Geant4-DNA extension

Mean energy deposit of protons

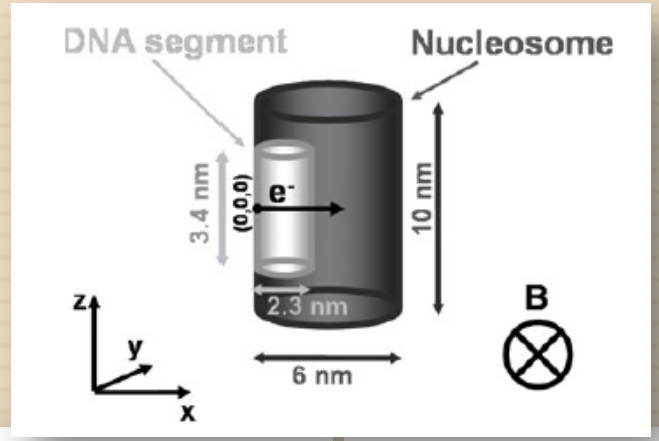


eccentricity

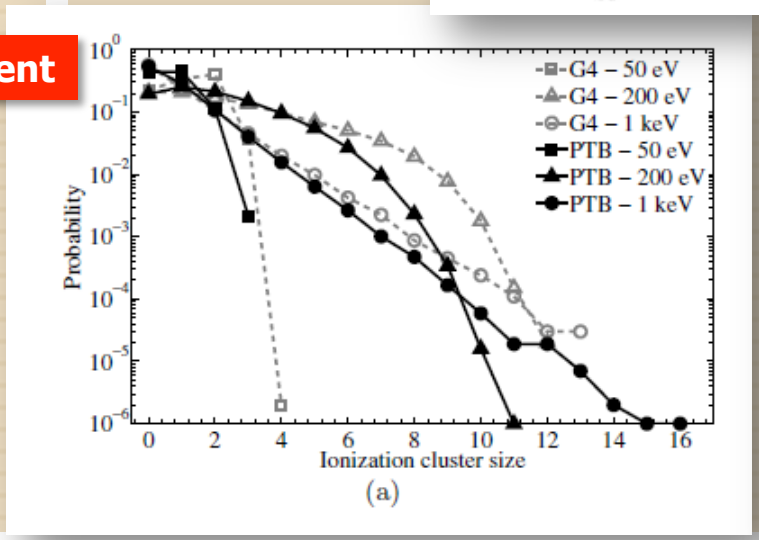


Mean energy deposit per event for 1 MeV proton tracks going through spherical volume of water with 30 nm of diameter. The source was placed at 100 nm from the target. The full line represents the energy deposit calculated using the LET values published in the ICRU report 49

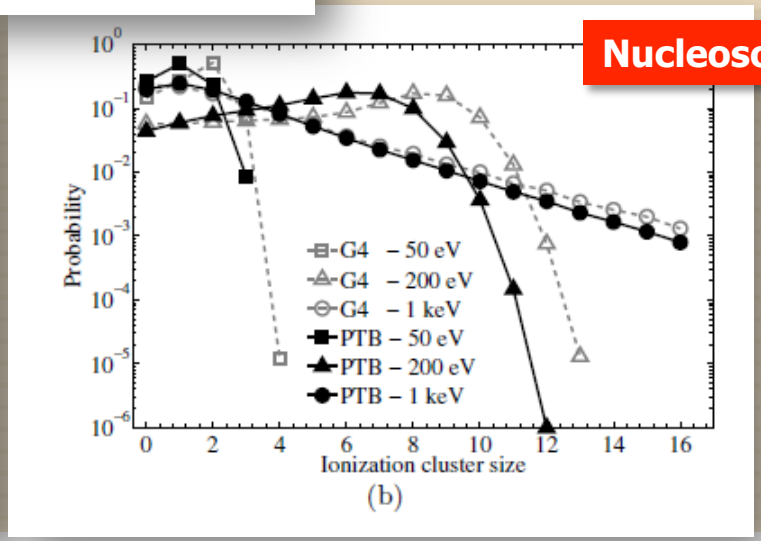
Appl. Radiat. Isot. 69 (2011) 220-226



DNA segment



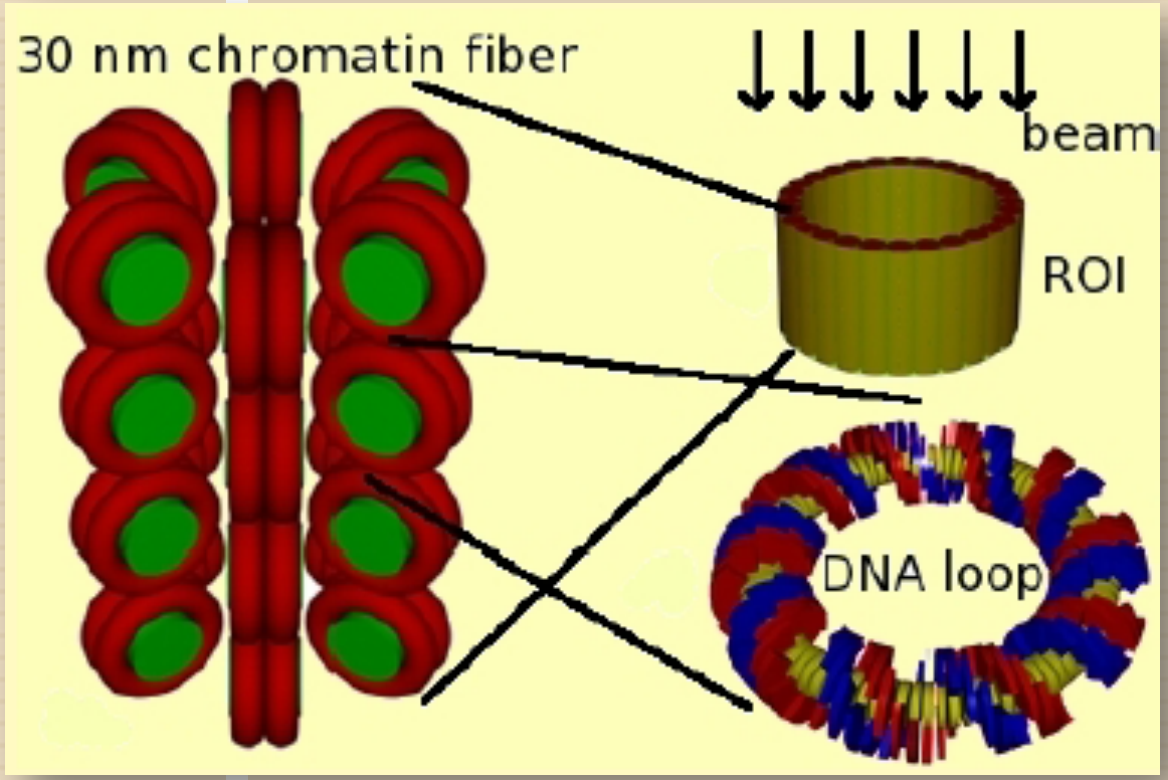
Nucleosome



A user example: ionisation clusters in nanometric volumes

- Comparison **Geant4-DNA** VS **PTB microdosimetry** code by M. Bug, B. Grosswendt et al.
- In two nanometer-size volumes: **DNA segment** or **nucleosome**

Eur. Phys. J. D (2010) 1-8

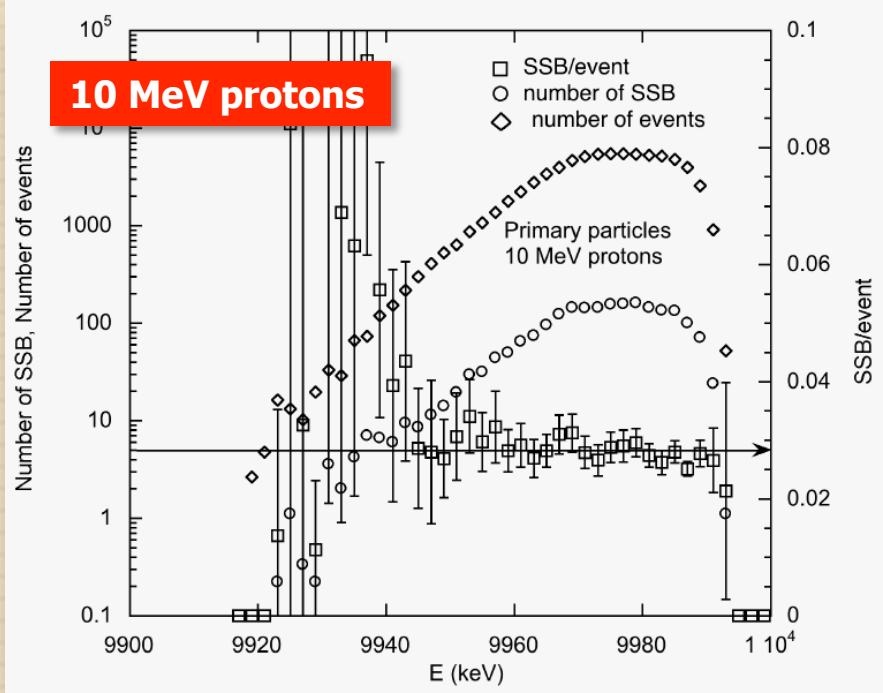


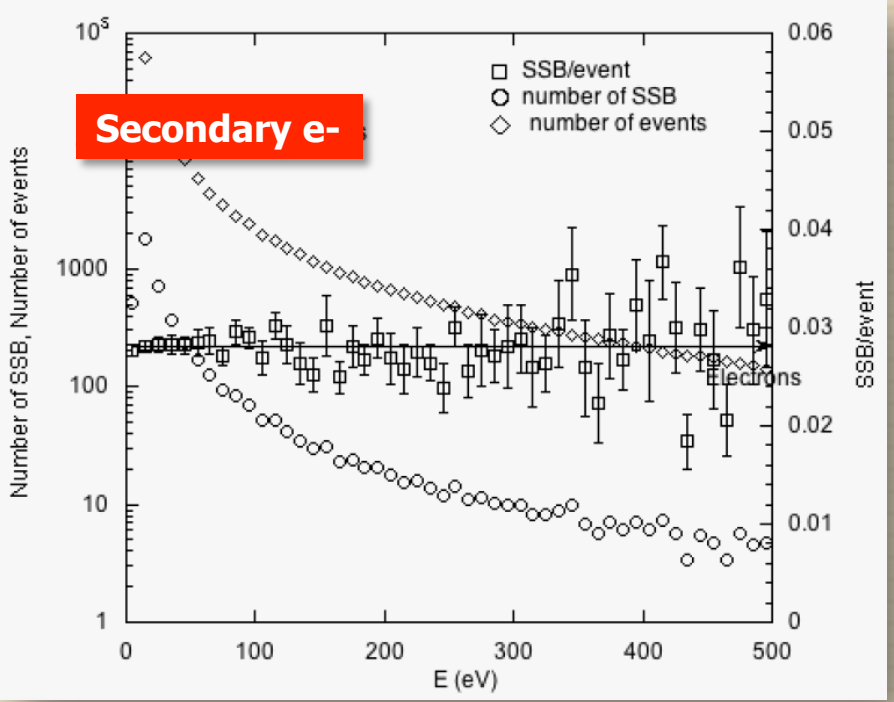
900 fragments of 30-nm chromatin fiber were put into a cylindrical shell (ROI) with a central diameter and height of 10 µm and
5.25 µm, respectively.

Investigation of TSB invariance

- 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)





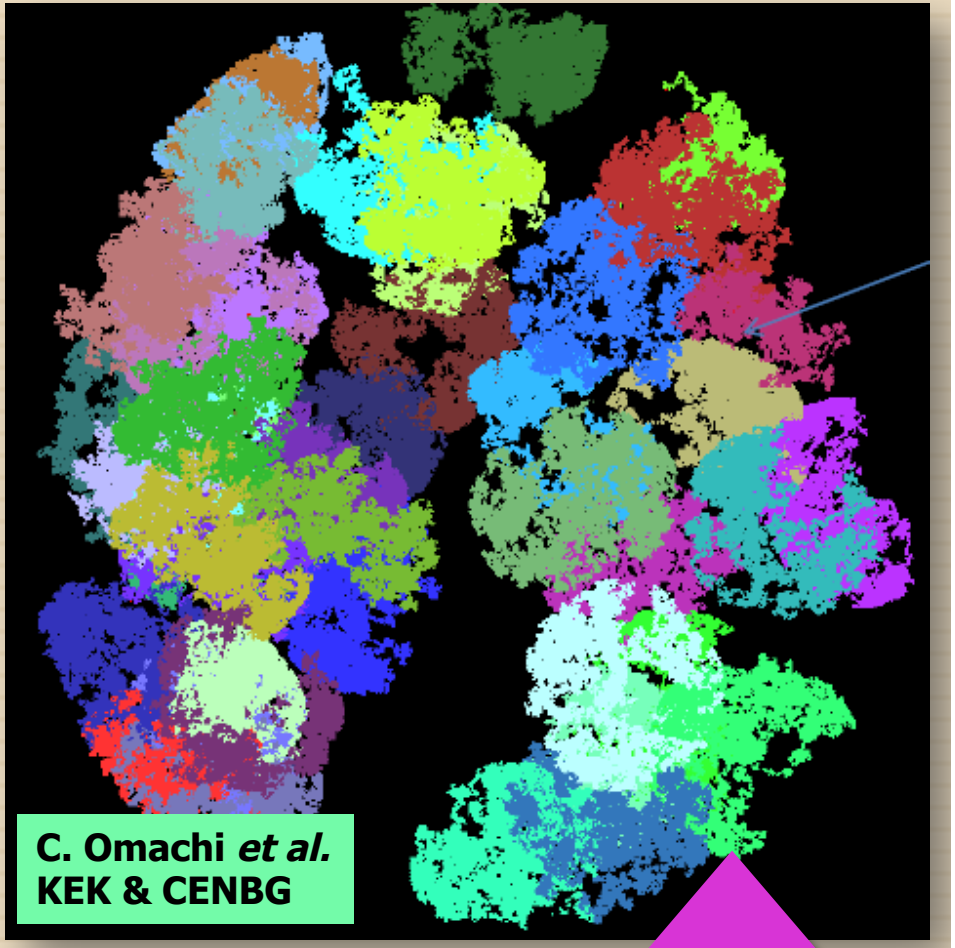
Particles	E (MeV) (MeV)	LET (keV/μm)	SSB/event (Ion)	SSB/event (Sec. e^-)	SSB/event (Total)
Protons	0.5	66.9	0.025 ± 0.006	0.026 ± 0.001	0.026 ± 0.002
	1	31.0	0.027 ± 0.004	0.027 ± 0.001	0.027 ± 0.001
	5	9.2	0.028 ± 0.003	0.028 ± 0.001	0.028 ± 0.001
	7	6.5	0.027 ± 0.003	0.028 ± 0.001	0.028 ± 0.002
	10	4.8	0.029 ± 0.003	0.029 ± 0.001	0.028 ± 0.001
Alpha particles	2	235.0	0.03 ± 0.01	0.030 ± 0.004	0.031 ± 0.007
	5	101.2	0.029 ± 0.007	0.028 ± 0.001	0.028 ± 0.003
	7	76.9	0.030 ± 0.006	0.029 ± 0.001	0.029 ± 0.003
	10	58.0	0.028 ± 0.005	0.028 ± 0.001	0.028 ± 0.004

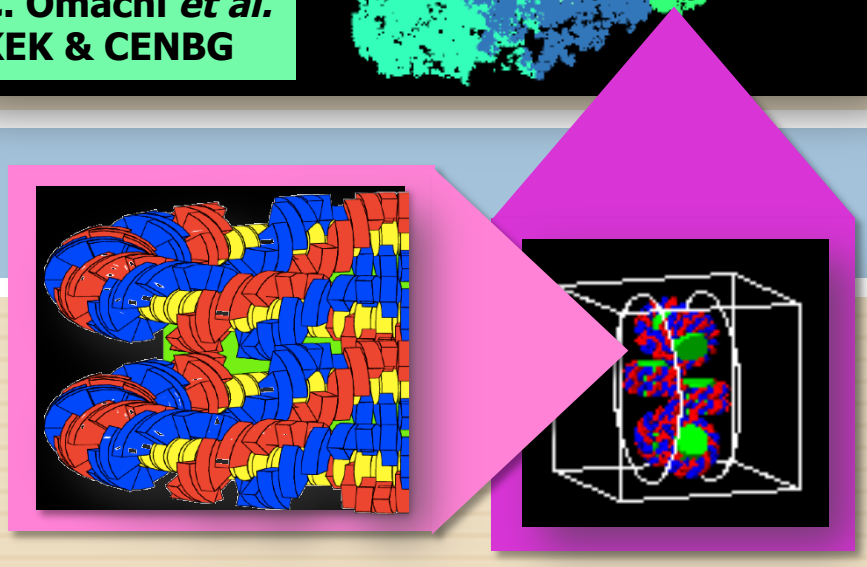
TSB invariance

- The site-hit probability per unit dose is statistically independent of the type and energy of the incident particle and energy, within 0.028 ± 0.02
- The ratio between the total volume occupied by the targets and that defined by the ROI is 0.029 and explains the site-hit probability value

A cell nucleus ?

- Investigating the possibility to describe a full human cell nucleus including **46 chromosomes**
- Global shape of the nucleus is obtained from **confocal microscopy of (HaCaT/(H2B-GFP)Tg) cells,** sliced into elementary voxels
- Smallest geometrical elements are **phosphodiester groups** of the DNA
- Each chromosome is made of a **random-walk pattern** of « chromatin slices »
- Each « chromatin slice » has **6 histones,** each having two DNA loops of 100 bp each, in a B-DNA conformation
- Total number of base pair reaches **$3x10^9$** with at A-T:G-C ratio of **60%**
- All geometrical elements contain **liquid water**





Geant4-DNA examples

Examples included in Geant4

- We provide you with several ready-to-use examples directly included in Geant4 allowing you to start to use Geant4-DNA Physics processes
  - « Extended » electromagnetic examples
  - « Advanced » examples
- They are a good starting point for users interested in Geant4-DNA
- Do not hesitate to contact us
  - In case you encounter technical difficulties
  - In case you need advice in order to customize these Geant4-DNA examples to your specific needs

Examples included in Geant4

Example code name	Purpose	Location	Availability
dnaphysics	• Usage of Geant4-DNA Physics processes • *variable density*	$G4INSTALL/examples/advanced	**from Geant4 9.5 BETA**
microdosimetry	Combination of Standard EM or Low Energy EM processes with Geant4-DNA Physics processes	$G4INSTALL/examples/advanced	**from Geant4 9.5 BETA**
TestEm12	Dosimetry in spherical shells	$G4INSTALL/examples/extended	**from Geant4 9.5 BETA**
TestEm2	Usage of Physics list builders	$G4INSTALL/examples/extended	from Geant4 9.4
TestEm14	Extraction of cross sections	$G4INSTALL/examples/extended	from Geant4 9.4

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Perspectives

Geant4-DNA perspectives

- By 2012
  - Inclusion of quantum models
    - Alternative more accurate models for liquid water
    - New models for A, T, G, C, sugar-phosphate
  - Inclusion of nuclear stopping for p & He
  - Delivery of first prototype of water radiochemistry classes

- Mid-term
  - Prediction of direct and non-direct DNA damages in cell nuclei
  - Verification (with other codes) and validation (with experimental data)

- Please check the Geant4 upcoming releases

Where to find more information about Geant4-DNA ?

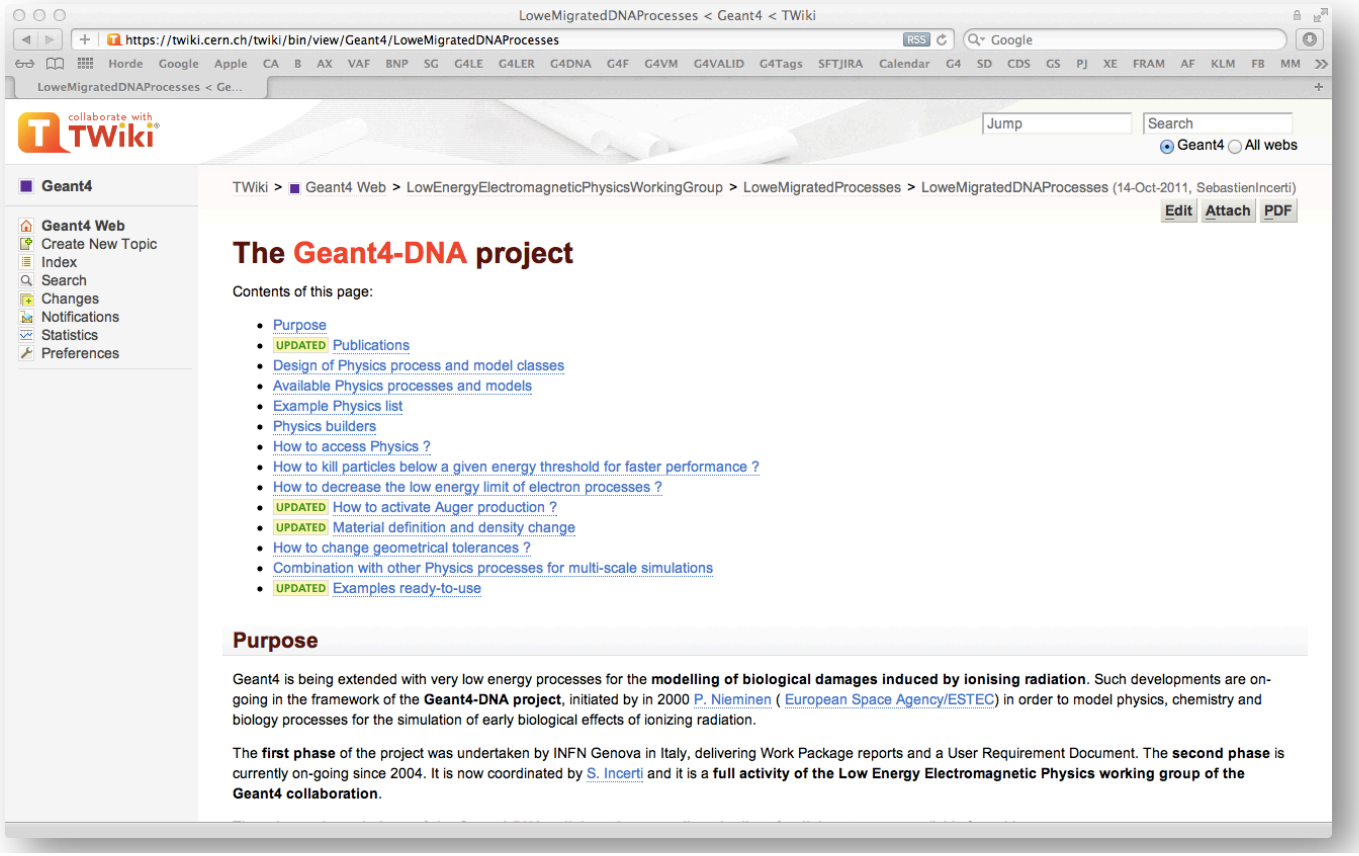
Geant4-DNA from the Internet

- Geant4 web site: http://geant4.org

  → Low Energy Electromagnetic Physics working group page

  - https://twiki.cern.ch/twiki/bin/view/Geant4/LoweMigratedDNAProcesses

Geant4-DNA TWiki



Geant4-DNA from the Internet

- Geant4 @ IN2P3 web site
  - http://geant4.in2p3.fr
  - Download a free Geant4 Virtual Machine
    - based on VMWare™ & VirtualBox™
  - Linked to Geant4-DNA Twiki page
  - Geant4-DNA publications

@Geant4VM
on Twitter

- ESA / AO6041 project web site
  - http://geant4.in2p3.fr/spip.php?rubrique14

A selection of recent publications

- Physics
  - Geant4 hadronic physics for space radiation environment,
    A. V. Ivanchenko *et al.*, **International Journal of Radiation Biology (2011)**, in press
  - Electron and proton elastic scattering in water vapour,
    C. Champion *et al.*, **Nucl. Instrum. and Meth. B (2011)**, in press
  - Combination of electromagnetic Physics processes for microdosimetry in liquid water with the Geant4 Monte Carlo simulation toolkit,
    V. N. Ivanchenko *et al.*, **Nucl. Instrum. and Meth. B (2011)**, in press
  - Recent Improvements in Geant4 Electromagnetic Physics Models and Interfaces
    V.Ivantchenko *et al.*, **Prog. Nucl. Sci. Tech. (2011)**, in press
  - Stopping power and ranges of electrons, protons and alpha particles in liquid water using the Geant4-DNA package,
    Z. Francis, **S. Incerti, M. Karamitros, H.N. Tran**, C. Villagrasa, **Nucl. Instrum. and Meth. B (2011) in press**
  - Molecular scale track structure simulations in liquid water using the Geant4-DNA Monte Carlo processes,
    Z. Francis *et al.*, **Appl. Radiat. Isot. 69 (2011) 220-226**
  - Comparison of Geant4 very low energy cross section models with experimental data in water,
    S. Incerti *et al.*, **Med. Phys. 37 (2010) 4692-4708**
  - 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**
- Physico-chemistry / chemistry
  - Modeling radiation chemistry in the Geant4 Toolkit
    M. Karamitros *et al.*, **Prog. Nucl. Sci. Tech. (2011)**, in press
- Overview of Geant4-DNA
  - The Geant4-DNA project,
    S. Incerti *et al.*, **Int. J. Model. Simul. Sci. Comput. 1 (2010) 157–178**
- Some applications in cellular biology
  - The invariance of the total direct DNA strand break yield,
    M. A. Bernal *et al.*, **Med. Phys. 38 (2011) 4147-4153**
  - Effect of a magnetic field on the track structure of low-energy electrons: a Monte Carlo study,
    M. U. Bug *et al.*, **Eur. Phys. J. D (2010) 1-8**
  - Monte Carlo dosimetry for targeted irradiation of individual cells using a microbeam facility,
    S. Incerti *et al.*, **Rad. Prot. Dos. 133, 1 (2009) 2-11**
  - A comparison of cellular irradiation techniques with alpha particles using the Geant4 Monte Carlo simulation toolkit,
    S. Incerti *et al.*, **Rad. Prot. Dos. 122, 1-4 (2006) 327-329**
  - Simulation of cellular irradiation with the CENBG microbeam line using Geant4,
    S. Incerti *et al.*, **IEEE Trans. Nucl. Sci. 51 (4) (2004) 1395-1401**

Links to journals on
http://geant4.in2p3.fr

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- Finally we invite you to contact us if your are interested in joining this « open source » effort based on Geant4 for further development, extension and validation

Geant4-DNA needs you
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Thank you for your attention