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
Outline

- **Context** of the Geant4-DNA project

- **On-going developments**
  - The **physics** content of Geant4-DNA
  - Modelling **water radiation chemistry**
  - Geometries down to the DNA scale

- Geant4-DNA **user examples and applications**

- Where to find **more information**

[Suggested references]
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 & physico-chemistry processes, detailed geometrical descriptions of biological targets down to the DNA size, 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 limitations

- Strong limitations prevent the usage of Geant4 for the modelling of biological effects of ionising radiation at the sub-cellular scale
  - Condensed-history approach
    - no step-by-step transport on small distances
  - Low-energy limit applicability of models is limited
    - 250 eV for Livermore Low Energy EM models
    - 100 eV for Penelope Low Energy EM models
  - No description of target molecular properties
    - liquid water, nucleotides
  - Simulation of particle-matter interactions
    - no mutual interactions
  - Only physical interactions
The Geant4-DNA project

- Initiated in 2001 by Dr Petteri Nieminen at the European Space Agency/ESTEC

- Main objective: to 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 damages (for eg. up to 1 microsecond after irradiation, for now) in the context of manned space exploration missions

- Providing an open source access to the scientific community that can be easily upgraded & improved

- 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-category of the electromagnetic category of Geant4
  - $G4INSTALL/source/processes/electromagnetic/dna

How can Geant4-DNA model radiation biology?

Physics stage
step-by-step modelling of physical interactions of incoming & secondary ionising radiation with biological medium (liquid water)

Physicochemistry/chemistry stage
- Radical species production
- Diffusion
- Mutual interactions

Geometry stage
DNA strands, chromatin fibres, chromosomes, whole cell nucleus, cells… for the prediction of damages resulting from direct and indirect hits

Biology stage
DIRECT DNA damages

Biology stage
INDIRECT DNA damages (dominant @ low LET)

Mathieu’s talk
Physics models available in Geant4 9.5

- 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 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
Overview of 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 H₂O
    - Dielectric formalism & FBA using Heller optical data up to 1 MeV, and low energy corrections
  - Excitation
    - 5 levels for H₂O
    - 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

- **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.

- **He⁰, He⁺, He²⁺**
  - 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**
  - Ionisation
    - Speed scaling and global effective charge by Booth and Grant

### Overview of Geant4-DNA physics processes and models available in Geant4 9.6 Beta for liquid water

<table>
<thead>
<tr>
<th>Particles</th>
<th>e⁻</th>
<th>p</th>
<th>H</th>
<th>He⁺⁺⁺, He⁺⁺, He⁺, He⁰</th>
<th>C, N, O, Fe,...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elastic scattering</td>
<td>&gt; 9 eV – 1 MeV</td>
<td>-</td>
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<tr>
<td></td>
<td>Screened Rutherford</td>
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<td></td>
<td>&gt; 7.4 eV – 1 MeV</td>
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<td></td>
<td>Rutherford Champion</td>
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<tr>
<td>Excitation</td>
<td>9 eV – 1 MeV</td>
<td>10 eV – 500 keV</td>
<td>10 eV – 500 keV</td>
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<tr>
<td></td>
<td>Born</td>
<td>Miller Green</td>
<td>Miller Green</td>
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<td>500 keV – 100 MeV</td>
<td>500 keV – 100 MeV</td>
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<tr>
<td>Charge Change</td>
<td>-</td>
<td>100 eV – 10 MeV</td>
<td>100 eV – 10 MeV</td>
<td>-</td>
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<td></td>
<td>Dingfelder</td>
<td>Dingfelder</td>
<td>Dingfelder</td>
<td></td>
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<tr>
<td>Ionisation</td>
<td>11 eV – 1 MeV</td>
<td>100 eV – 500 keV</td>
<td>100 eV – 100 MeV</td>
<td>1 keV – 400 MeV</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Born</td>
<td>Rudd</td>
<td>Rudd</td>
<td>Effective charge scaling from same models as for proton</td>
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<tr>
<td></td>
<td></td>
<td>500 keV – 100 MeV</td>
<td>500 keV – 100 MeV</td>
<td>1 keV – 400 MeV</td>
<td></td>
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<tr>
<td>Vibrational excitation</td>
<td>2 – 100 eV</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
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<tr>
<td></td>
<td>Michaud et al.</td>
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</tr>
<tr>
<td>Attachment</td>
<td>4 – 13 eV</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Melton</td>
<td></td>
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</tbody>
</table>
Electron process cross sections cover energy range up to 1 MeV down to either
- 7.4 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.
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

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

Electron ionisation
- 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)
Proton & Hydrogen ionisation

Total XS

Differential XS

Geant4-DNA
Toburen and Wilson (1977)
Bolorizadeh and Rudd (1986)

15 MeV (x10^4)
100 keV (x10^4)
50 keV (x10^4)
Proton and Hydrogen charge exchange
- Contributions of ionisation (p, H), excitation (p) and charge change
- Comparison to recommendations (ICRU, HRMP) for liquid and vapour water
Helium ionisation

**Total XS**

- Production cross section ($\sigma$) vs. energy ($E$) for different He ions.

**Differential XS**

- Differential cross section ($d\sigma/dE$) vs. energy loss ($E_a$) for He ions.

- Graphs show comparisons between different models and experimental data.

- Key data points and models include:
  - Geant4-DNA - $\text{He}^{2+}$
  - Geant4-DNA - $\text{He}^+$
  - Rudolph and Melton (1965) - $\text{He}^{2+}$
  - Rudd et al. (1985) - $\text{He}^{2+}$
  - Rudd et al. (1985) - $\text{He}^+$
  - Toburen et al. (1980) - $\text{He}^{2+}$
  - Toburen et al. (1980) - $\text{He}^+$
Helium charge exchange

Total XS
Contributions of 3 charged states of Helium

Comparison to recommendations (ICRU) for liquid and vapour water
Addition of new models

- One can easily extend Geant4-DNA physics models using a process/model approach
  - Common design for all Geant4 EM software
  - Easier test & maintenance

- Each physical interaction is described by a process class
  - Eg. G4DNA\text{Ionisation}

- Each process classes uses one or several alternative or complementary model classes, which computes
  - Eg. G4DNA\text{RuddIonisationModel}
  - The physical interaction total cross section from the selected model (theoretical, semi-empirical, empirical,...)
  - The physical interaction final state
    - Creation of secondary particles
    - Changes applied to incident particle
  - Classes already exist for handling of data tables (eg. total & diff xs) and interpolation
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 \(\sim 7.4\) 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 \(\sim 10\) 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

See Prog. Nucl. Sci. Tec. 2 (2011) 898-903
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

Incident 5 MeV proton
Contribution of indirect effects

Survival / Dose with different DMSO concentrations

Contribution of indirect effects VS LET

**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.

**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.

*Contributions of Direct and Indirect Actions in Cell Killing by High-LET Radiations, Hirayama et al, 2009*
Extending Geant4 for radiochemistry modelling

<table>
<thead>
<tr>
<th>What is missing in Geant4 for modelling radiation chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>- In Monte-Carlo simulations:</td>
</tr>
<tr>
<td>- Tracks are processed one after another without influencing each other.</td>
</tr>
<tr>
<td>- The simulation is not time-based but space-based where the relevant value is the interaction length</td>
</tr>
<tr>
<td>- The dynamical objects are not synchronised in time</td>
</tr>
<tr>
<td>- Geant4 does not handle molecules neither brownian motion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proposed developments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Develop a general purpose interacting tracks system</td>
</tr>
<tr>
<td>2. Implement classes for handling molecules in Geant4</td>
</tr>
<tr>
<td>3. Introduce Brownian motion and chemical reactions in Geant4</td>
</tr>
</tbody>
</table>
Molecular species & reactions

### Molecular species & diffusion

<table>
<thead>
<tr>
<th>Electronic state</th>
<th>Decay Channel</th>
<th>Fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ionization states</td>
<td>H₂O⁺ + •OH</td>
<td>100</td>
</tr>
<tr>
<td>Excitation state A₁B₁: (1b₁) → (4a₁/3s)</td>
<td>•OH + H⁺</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>H₂O + DE</td>
<td>35</td>
</tr>
<tr>
<td>Excitation state B₁A₁: (3a₁) → (4a₁/3s)</td>
<td>H₂O⁺ + •OH + e⁻aq</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>•OH + •OH + H₂</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>H₂O + DE</td>
<td>30</td>
</tr>
<tr>
<td>Excitation state: Rydberg, diffusion bands</td>
<td>H₂O⁺ + •OH + e⁻aq</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>H₂O + DE</td>
<td>50</td>
</tr>
</tbody>
</table>

### Chemical reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Reaction rate (10¹⁰ M⁻¹ s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H⁺ + e⁻aq + H₂O → OH⁻ + H₂</td>
<td>2.65</td>
</tr>
<tr>
<td>H⁺ + •OH → H₂O</td>
<td>1.44</td>
</tr>
<tr>
<td>H⁺ + H⁺ → H₂</td>
<td>1.20</td>
</tr>
<tr>
<td>H₂ + •OH → H⁺ + H₂O</td>
<td>4.17x10⁻³</td>
</tr>
<tr>
<td>H₂O₂ + e⁻aq → OH⁻ + •OH</td>
<td>1.41</td>
</tr>
<tr>
<td>H₂O⁺ + e⁻aq → H⁺ + H₂O</td>
<td>2.11</td>
</tr>
<tr>
<td>H₂O⁺ + OH⁻ → 2 H₂O</td>
<td>14.3</td>
</tr>
<tr>
<td>•OH + e⁻aq → OH⁻</td>
<td>2.95</td>
</tr>
<tr>
<td>•OH + •OH → H₂O₂</td>
<td>0.44</td>
</tr>
<tr>
<td>e⁻aq + e⁻aq + 2 H₂O → 2 OH⁻ + H₂</td>
<td>0.50</td>
</tr>
</tbody>
</table>

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

However these parameters can be modified by the user.

Kreipl et al, Radiat Environ Biophys, 2009
Situation at 1 picosecond
Situation at 1 microsecond
Radiochemical yields: prototype results

- Comparison done with incident 1 MeV electrons in infinite water volume simulated by PARTRAC and Uehara and Nikjoo. Only the first 10 keV deposit energy are taken into account for the chemistry.
- Effect of the two alternative electron elastic scattering models.
- Results are obtained in 30 minutes on a cluster of 80 CPUs (Physics + Chemistry).
- No dissociative attachment.
Radiochemistry perspectives

- Recent developments
  - Prototype of radiochemistry modelling
  - General purpose prototype for interacting tracks

- Perspectives
  - Combination of the chemical stages with Geant4’s geometry modelling capabilities
  - Simulation of early direct and indirect effects of radiation on DNA

- Along with on-going experimental validation
  - Radiochemistry: radiochemistry experiments on-going at LRad/CEA in Saclay in collaboration with Dr G. Baldacchino
  - Radiobiology: microbeam cellular irradiation facility in CENBG in Bordeaux
MODELLING SMALL-SIZE GEOMETRIES
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 (e.g. cylinders)
  - Usage of voxellized geometries (« cellular phantoms ») built from confocal microscopy of cells

- 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

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.

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

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?

900 fragments of 30-nm chromatin fiber were put into a cylindrical shell (ROI) with a central diameter and height of 10 \( \mu \)m and 5.25 \( \mu \)m, 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?

The site-hit probability per unit dose is statistically independent of the type and energy of the incident particle and energy, within $0.028 \pm 0.02$

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
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

<table>
<thead>
<tr>
<th>Example code name</th>
<th>Purpose</th>
<th>Location</th>
<th>Availability</th>
</tr>
</thead>
</table>
| 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 |
Geant4-DNA perspectives

- **By 2012-2013**
  - Inclusion of cross section models
    - Alternative more accurate models for liquid water
    - New models for A, T, G, C, sugar-phosphate
    - CTCM & quantum approaches in collaboration with C. Champion & R. Rivarola et al.
  - Delivery of first public example of water radiochemistry

- **Mid-term**
  - Prediction of direct and non-direct DNA damages in plasmids & 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?
The Geant4-DNA project

Extending the Geant4 Monte Carlo simulation toolkit for radiobiology

Welcome to the Internet page of the Geant4-DNA project.

The Geant4 Monte Carlo simulation toolkit is being extended with processes for the modeling of early biological damages induced by ionising radiation at the DNA scale. Such developments are on-going in the framework of the Geant4-DNA project, initiated in 2000 by the European Space Agency/ESTEC.

On-going developments include

- **Physics** processes in liquid water and other biological materials
- **Chemistry** and physico-chemistry processes
- Molecular geometries
- Quantification of damages (single-strand, double-strand breaks, ...)

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**Recent posts**
The last Geant4 release (9.5) is available for download, see our Software section.
The Geant4-DNA project
Extending the Geant4 Monte Carlo simulation toolkit for radiobiology

The Geant4-DNA developments are described in the following publications.

Any report or published results obtained using the Geant4-DNA software shall cite the following publication:


General scope papers


Physics processes and models
Virtual machine from the Internet

- Download a fully working virtual SL5.7 Linux machine with up-to-date Geant4 & Geant4-DNA releases
  - Includes many other tools
- Works on Windows and Mac
- Requires VmWare or VirtualBox
- Web site
- Updates from Twitter

@Geant4VM on Twitter
In summary

- Geant4-DNA is based on Geant4
  - You can benefit from Geant4 existing capabilities in Geometry, Navigation, Ray-tracing, etc...
  - Many classes already exist
    - Eg. Data management of cross section tables, etc...

- Geant4-DNA is open source
  - We deliver a default set of physics and physico-chemistry / chemistry processes & models
    - They can/will be improved over time
    - Any one who is interested can join Geant4-DNA and propose his/her own models, keeping full ownership of his/her own developments

You’re very welcome to join this effort if interested
The Geant4-DNA collaboration thanks all theoreticians who are helping us for the development of this extension in the Geant4 toolkit, in particular:

- Dr M. Bernal (Campinas U., Brazil)
- Dr C. Champion (Metz U. & CENBG/IN2P3/CNRS from Sept. 1st, France)
- Dr M. Dingfelder (East Carolina U., NC, US)
- Dr D. Emfietzoglou (Ioannina U., Greece)
- Dr B. Grosswendt (PTB, Germany)

We also thank Dr W. Friedland (Helmholz Zentrum, Munich, Germany), developer of PARTRAC, for his guidance and constant support, since the early days of Geant4-DNA.
Thank you for your attention