Geant4 simulations for microdosimetry at the cellular level and nanobeam design

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on behalf of the Physics Biology group

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Geant4 2005
November 3\textsuperscript{rd}-10\textsuperscript{th}, 2005
Consequences of environmental stress at the biological tissue and cell scales

Two facilities @ CENBG on a state-of-the-art low energy Singletron electrostatic accelerator (p, d, α up to 3.5 MeV)

- a microbeam line (resolution in vacuum < 1 µm) for
  - bio-sample analysis through Scanning Transmission Ion Microscopy, Particle Induced X-ray Emission & Rutherford Back Scattering
  - targeted cellular irradiation in single ion mode

- an upcoming nanobeam line (~2006) mainly for analysis with a resolution in vacuum of about 50 nm

3D microtomography

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Ministère des Affaires Etrangères (France)

Low dose irradiation & cellular response

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Simulations (microdosimetry & ray tracing)

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Why Monte Carlo simulation?

Looking for a simulation tool able to perform...

- **True ray-tracing**
  - ion transport in focusing quadrupoles to characterize the microbeam line performances and predict / adjust the nanobeam line focusing capabilities
  - understand and reduce scattering along the line: collimator edges, diaphragms, pipe residual air...
  - understand and reduce scattering inside the cellular irradiation chamber: ion detector, extraction window, culture foil where cells attach...

- **Microdosimetry and cell damage**
  - estimate the absorbed dose in single ion irradiation mode
  - model DNA damage and survival at the cell level
  - compare with other irradiation techniques (alpha emitters, macro beam)

Geant4
Ray-tracing at the sub-micron scale
Field models for the nanobeam line quadrupole magnets

Oxford Microbeams Ltd, U.K.

- Map recently computed with VF Opera 3D
- Mesh:
  - 14 x 14 x 240 mm³
  - 27225 nodes

Simple quadrupole field model like in class
G4QuadrupoleMagField
\[ B_x = y \, G \] and \[ B_y = x \, G \]

3D quadrupole field map from Opera 3D
&
3D linear interpolation from advanced Purging Magnet code

<table>
<thead>
<tr>
<th>Gradients for 3.5 MeV protons</th>
<th>( G_1 ) (T/m)</th>
<th>( G_2 ) (T/m)</th>
<th>( G_3 ) (T/m)</th>
<th>( G_4 ) (T/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple field model</td>
<td>-11.97863</td>
<td>16.50520</td>
<td>9.866786</td>
<td>-6.244526</td>
</tr>
<tr>
<td>3D map field</td>
<td>-12.1492</td>
<td>16.7577</td>
<td>9.8990726</td>
<td>-6.2398758</td>
</tr>
</tbody>
</table>

Gradient computation fully automated with Geant4
Nanobeam line ray-tracing

Beam maximum external envelope

Object collimator

Switching magnet

Diaphragm

Image plan

5 µm diameter object collimator

Intermediate image size 200 nm x 900 nm

Electrostatic plates

60 nm x 80 nm

DOUBLET

TRIPLET

1727 V & 2916 V

Without electrostatic deflection

With electrostatic deflection

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Comparison in high (PIXE) and low flux (STIM) modes

Geant4 versus TRAX (reference)

- Nice agreement between TRAX and Geant4 (square field model, no map)
- Sharp STIM image, distorted PIXE image (chromatic and spherical aberrations)
- Compatible with probe size requirements
- Pure vacuum, no collimators
Beam optics

\[ x_i = f(x_0, y_0, \theta_0, \Phi_0, \delta, \text{Parasitic}) \]
\[ y_i = g(x_0, y_0, \theta_0, \Phi_0, \delta, \text{Parasitic}) \]

\[ x_i = A_0 + A_1 x_0 + A_2 y_0 + A_3 \theta_0 + \ldots + A_n \nu_1^j \nu_2^k \nu_3^l + \ldots \]

\( A_n : \text{aberration coefficient of order} \ j + k + l \) written

\[ A_n = \langle x | \nu_1^j \nu_2^k \nu_3^l \rangle \]

Example : \( <x | \theta \Phi^2> \)

\( \delta = \Delta P / P = \Delta E / 2E \)
### List of quadrupole dominant aberration coefficients

<table>
<thead>
<tr>
<th>Order and Type</th>
<th>Coefficients</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st INTRINSIC</td>
<td>$&lt; x</td>
<td>x &gt; = 1/D_x$</td>
</tr>
<tr>
<td></td>
<td>$&lt; y</td>
<td>y &gt; = 1/D_y$</td>
</tr>
<tr>
<td></td>
<td>$&lt; x</td>
<td>\theta &gt;$</td>
</tr>
<tr>
<td></td>
<td>$&lt; y</td>
<td>\Phi &gt;$</td>
</tr>
<tr>
<td>1st PARASITIC</td>
<td>$&lt; x</td>
<td>U_n &gt;$</td>
</tr>
<tr>
<td></td>
<td>$&lt; y</td>
<td>V_n &gt;$</td>
</tr>
<tr>
<td></td>
<td>$&lt; x</td>
<td>\alpha_n &gt;$</td>
</tr>
<tr>
<td></td>
<td>$&lt; y</td>
<td>\beta_n &gt;$</td>
</tr>
<tr>
<td>2nd INTRINSIC</td>
<td>$&lt; x</td>
<td>\theta\delta &gt;$</td>
</tr>
<tr>
<td></td>
<td>$&lt; y</td>
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<td>$&lt; y</td>
<td>y\delta &gt;$</td>
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<tr>
<td>2nd PARASITIC</td>
<td>$&lt; x</td>
<td>\Phi\rho_n &gt;$</td>
</tr>
<tr>
<td></td>
<td>$&lt; y</td>
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<td>\theta\varepsilon_n &gt;$</td>
</tr>
<tr>
<td></td>
<td>$&lt; y</td>
<td>\Phi\varepsilon_n &gt;$</td>
</tr>
<tr>
<td>3rd INTRINSIC</td>
<td>$&lt; x</td>
<td>\theta^3 &gt;$</td>
</tr>
<tr>
<td></td>
<td>$&lt; y</td>
<td>\Phi^3 &gt;$</td>
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<td></td>
<td>$&lt; x</td>
<td>\theta\Phi^2 &gt;$</td>
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<tr>
<td></td>
<td>$&lt; y</td>
<td>\Phi\theta^2 &gt;$</td>
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<td>5th INTRINSIC</td>
<td>$&lt; x</td>
<td>\theta^5 &gt;$</td>
</tr>
<tr>
<td></td>
<td>$&lt; y</td>
<td>\Phi^5 &gt;$</td>
</tr>
</tbody>
</table>

Geant4 ray tracing capabilities

- Calculation up to any order for TRAX (ray-tracing reference code in the microbeam community) and Geant4, up to order three with Zgoubi (second reference code)
- \( N = 32 \) rays generated from a point source to reach order 3 in \( \theta, \Phi \) and order 1 in \( \delta \)
- 32 coefficients \( A_n \) extracted from matrix inversion of the 32 ray positions on target

\[
N = (3 + 1)(3 + 1)(1 + 1)
\]
Quantitative predictions: intrinsic aberration coefficients

<table>
<thead>
<tr>
<th></th>
<th>TRAX</th>
<th>Geant4 3D MAP</th>
<th>Geant4 square (1)</th>
<th>Geant4 square (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_x = \langle x</td>
<td>x \rangle$</td>
<td>6.3557E+01</td>
<td>6.36174+01</td>
<td>6.356E+01</td>
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<tr>
<td>$\langle x</td>
<td>\theta \rangle$</td>
<td>-3.4937E-01</td>
<td>-1.04303E+02</td>
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<td>$\langle x</td>
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<td>-2.0354E+03</td>
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<td>-2.0331E+03</td>
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<td>$\langle x</td>
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<td>3.5625E+02</td>
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<td>$D_y = \langle y</td>
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<tr>
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<td>1.2357E-01</td>
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<tr>
<td>$\langle y</td>
<td>\phi \phi \rangle$</td>
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<td>-3.6385E+02</td>
<td>-3.7019E+02</td>
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<tr>
<td>$\langle y</td>
<td>\theta^2 \phi \rangle$</td>
<td>2.2920E+02</td>
<td>1.39732E+04</td>
<td>2.2980E+02</td>
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<tr>
<td>$\langle y</td>
<td>\phi^3 \rangle$</td>
<td>1.4896E+02</td>
<td>-8.81738E+02</td>
<td>1.4939E+02</td>
</tr>
</tbody>
</table>

3D map: spherical terms dominant

(1) using TRAX’s gradients
(2) using GEANT4’s gradients
units are µm, mrad and %

Next tasks

- increase **field map granularity** around paraxial region and investigate spherical terms dominance & parasitic
- compare with **Enge’s fringing field model**
- use nanobeam line simulation for **fine alignment** (grid-shadow techniques)
- investigate effect of **multiple scattering in very low pressure residual air** (Geant4 VS experiment)
Microdosimetry at the cellular scale
Cellular irradiation setups

CENBG Focused Microbeam

- Alpha beam
- Object collimator $\Phi=5 \mu m$ (platinum)
- Beam pipe (aluminium)
- Diaphragm $\Phi=10 \mu m$ (platinum)
- Beam pipe (aluminium)
- Magnetic volume: 4 quadrupoles with fringing field
- Beam pipe (aluminium)
- Collimator $\Phi=10 \mu m$ (platinum)
- Gas detector (silicon)
- Exit window (Si$_3$N$_4$)
- Ambient air
- Culture foil (polypropylene)
- Cells in KGM (water)
- Microscope slide (glass)

CEA/SP2A Macrobeam

- Alpha beam
- Gold foil
- Beam pipe (vacuum)
- Extraction window (Mylar)
- Culture layer (Mylar)
- Cells in growing medium (water)
- Ambient air
- Culture foil (plastics)
- Cells in KGM (water)

CEA/SP2A Electrodeposited sources

238/239 Pu

- Alpha beam
- Gold foil
- Beam pipe (vacuum)
- Extraction window (Mylar)
- Culture layer (Mylar)
- Cells in growing medium (water)
- Ambient air
- Culture foil (plastics)
- Cells in KGM (water)

- 100,000 cells / 1.54 cm$^2$
- Nuclei distant of at least 20 µm from each other
- No overlap

Two « reasonable » cell geometries
Hits and absorbed dose distributions

Percentage of hit nuclei within the parallelepiped cell population irradiated with the CEA/DPTA 9.3 MeV alpha macrobeam. The plain circles represent Geant4 predictions and the dashed curve shows the corresponding Poisson fit, with a mean equal to one. The plain triangles and the dotted curve correspond to a Poisson distribution of mean 2. For illustration, the other plain curves show Poisson fits for means ranging respectively from 3 to 10.

Absorbed dose distribution within an elliptic nucleus for 3 MeV incident alphas. The dose reaches 0.4 ± 0.1 Gy/alpha. About 0.5% of incident alphas crossing the culture foil hit neighbor cells.

Percentage of hit nuclei within the ellipsoid cell population irradiated with the Pu alpha emitter through a mylar thickness of 0.9 µm for an irradiation time of 5 min 12 s (plain circles), 10 min 24 s (plain triangles) and 15 min 36 s (plain squares). The corresponding Poisson fits are shown. The mean for an irradiation time of 5 min 12 s (dashed line) reaches 0.5 alpha per nucleus and is proportional to the irradiation duration (dot line for 10 min 24 s and mean of 1.0 alpha per nucleus; dot-dashed line for 15 min 36 s and mean of 1.5 alpha per nucleus).
HaCat nucleus confocal imaging after irradiation

After irradiation with 5 alphas (3MeV)  
After irradiation with 50 alphas (3 MeV)

Dedicated keratinocyte cell line expressing the histone **H2B-GFP protein** and immunofluorescence using an antibobody against **phosphoryled H2AX histones (γ-H2AX)**
Realistic cellular geometries

- Estimation of the **absorbed dose**: need for a realistic geometry
- Conversion of **confocal microscopy images** into Geant4 **parameterised volumes** (G4PVPParameterisation) for the cell cytoplasm and the cell nucleus

**Next tasks**

- **Resolution** increase (256x256 and above) expected for cytoplasm and nucleus
- Average **nucleus chemical composition** will be measured from STIM, PIXE, RBS @ AIFIRA

Stack of 2D confocal images of nucleus marked with H2B-GFP (size 64x64)

Geant4 nucleus model 4015 voxels (0.396 x 0.396 x 0.611 µm³ each)

VC++ conversion application
  - Pixel extraction
  - RGB noise subtraction
  - Centering
  - Voxel local coordinates and intensity

Ellipsoid cytoplasm (KamLAND) (not marked yet)

3D reconstruction of confocal images

\[ \bar{D} = 0.29 \text{ Gy} \]

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Going beyond “à la PARTRAC”

Most advanced simulation tool of radiation damage at DNA level

Modular structure written by W. Friedland et al. at GSF, Munich (20 years) :

• simulation of cellular nucleus DNA content
  Geometry module

• simulation of proton or alpha interactions through the chosen cell geometry
  Track structure module

• simulation of secondary electron interactions
  Track structure module

• simulation of damages to DNA (direct hits and OH. radicals)
  Effect module

• simulation of chemical effects of species (pre-chemical & chemical)
  Chemistry module

• extraction of biological damages (ssbs, dsbs, fragments,...)
  Damage module

PARTRAC simulates processes from the initial irradiation \( t = 0 \) up to \( t = 10^{-6} \) s.
Repair processes are not simulated yet.
The nucleus geometry in PARTRAC

- human fibroblast cell nucleus
- 46 chromosomes
- 6 Gbp of chromatin
- irregular crossed linker structure
- atom by atom approach (center coordinates and Van der Waals radius)

R. Friedland et al., RPC 72 (2005) 279-286

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Geant4-DNA
Simulation of Interactions of Radiation with Biological Systems
at the Cellular and DNA Level

Based on
Geant 4

Partly funded by

R. Capra, S. Chauvie, R. Cherubini, Z. Francis, S. Gerardi, S. Guatelli, G. Guerrieri, S. Incerti,
B. Mascialino, G. Montarou, Ph. Moretto, P. Nieminen, M.G. Pia, M. Piergentili, C. Zacharatou

+ biology experts (E. Abbondandolo, G. Frosina, E. Giulotto et al.)

Centre d'Etudes Nucléaires de Bordeaux - Gradignan
Geant4-DNA : programme

• Geant4-based “sister” activity to the Geant4 Low-Energy Electromagnetic Working Group

• Simulation of nano-scale effects of radiation at the cell and DNA level

• Three levels
  – Macroscopic : calculation of dose, develop useful associated tools
  – Cell : cell modelling, processes for cell survival, damage etc
  – DNA : DNA modelling, physics processes at the eV scale, processes for DNA strand breaking, repair...

• On-going activities : anthropomorphic phantoms, cell survival models, low energy physics extensions down to the eV scale, etc...

• Key elements
  – Rigorous software process
  – Collaboration with domain experts (biologists, physicians)
  – Team including groups with cellular irradiation facilities
Geant4 DNA Physics processes will be presented in a few days at the
14th Symposium on microdosimetry Venezia, Italy, 13-18 November 2005
by the Geant4-DNA collaboration
and in a few minutes
see Ziad FRANCIS’ talk
Simulation of Interactions of Radiation with Biological Systems at the Cellular and DNA Level

Estimating the cancer risk for human exposure to space radiation is a challenge that involves a wide range of knowledge in physics, chemistry, biology, and medicine.

Traditionally, the biological effects of radiation are analyzed in top-down order, i.e., evaluation of the absorbed macroscopic radiation dose at a given location in the biological tissue is translated to the degree of danger it presents, and dose limits are consequently set that are considered to be acceptable.

A novel approach, based on the new-generation object-oriented Geant4 Monte Carlo Toolkit, proceeds in a reverse order, from bottom to top, by analyzing the nano-scale effects of energetic particles at the cellular and DNA molecule level.

This project is sponsored by the European Space Agency (ESA) and is pursued by a multidisciplinary European team of biologists, physicians, physicists, space scientists, and software engineers.
The objective of the Aurora Programme is first to formulate and then to implement a European long-term plan for the robotic and human exploration of solar system bodies holding promise for traces of life.
Geant4 simulation space environment + spacecraft, shielding etc. + anthropomorphic phantom

Dose in organs at risk

Phase space input to nano-simulation

Oncological risk to astronauts
Risk of nervous system damage

Geant4 simulation with biological processes at cellular level (cell survival, cell damage…)

Geant4 simulation with physics at eV scale + DNA processes

Scenario for AURORA

INFN Genova
Validations of Geant4 for focused micro & nanobeams

Simulation of ion propagation in the microbeam line of CENBG using GEANT4
S. Incerti, Ph. Barbette, B. Courtou, C. Michel-Habib, Ph. Moretta
Centre d’Etudes Nucléaires de Bordeaux - Gradignan, OLYCOM, Université Bordeaux 1, IN2P3, UMR 5008, 33110 Gradignan cedex, France

1. Introduction
The Monte Carlo code GEANT4 was first developed in FORTRAN at CERN to simulate particle-matter interactions [1]. The new GEANT4 project began in December 1996. GEANT4 is a highly available object-oriented code, written in C+++, allowing complete flexibility, extendibility and interworking with external software libraries. String and event analysis, computer-generated data,...3. All physics processes, models and visualization modules are entirely assembled in the user-defined code, which is documented using manuals, examples.

Simulation of Cellular Irradiation With the CENBG Microbeam Line Using GEANT4
S. Incerti, Ph. Barbette, B. Courtou, C. Michel-Habib, Ph. Moretta
Centre d’Etudes Nucléaires de Bordeaux - Gradignan, OLYCOM, Université Bordeaux 1, IN2P3, UMR 5008, 33110 Gradignan cedex, France

1. Introduction
The Centre d’Etudes Nucléaires de Bordeaux-Gradignan (CENBG) will be equipped during summer 2005 with the first microbeam facility in Europe. The CENBG facility will have the unique feature of delivering a single microbeam of highly charged ions (with high density) for the production of cellular irradiation. The project is based on the use of the CENBG 1D Six-Foil Gradient Facility. This facility is able to produce microbeams of several ions, allowing multiple targets. In this paper, we present results from the use of this facility in order to irradiate cells with different beam profiles and with different fluences, allowing the study of the effects of the different profiles and fluences on the irradiation of cells.
Making Geant4 easily available: VMware

VMware is a software allowing to run on a unique machine (desktop, laptop) two operating systems simultaneously. For example, it allows you to run a virtual Linux machine under a classical Windows PC. The Centre d’Etudes Nucléaires de Bordeaux-Gradignan, a CERN/IN2P3/INRAE laboratory, is happy to provide free of charge to Geant4 users a set of four files for VMware Workstation version 4.5 or later for Windows, containing the latest version of Geant4 with Sc. Linux 3.03 as well as several utilities (ROOT, ROOT-Minger IDE...). Once fully decompressed, these files can be read directly by your VMware Workstation software: launch VMware on your PC, open the decompressed files and you will receive a real Sc. Linux 3.03 machine with the latest version of Geant4 already installed.

System minimum requirements:
- desktop or laptop PC running Windows with the VMware Workstation software version 4.5 or later installed
- at least a 1 GHz processor driven Pentium III
- at least 256 Mo of RAM for the virtual machine (it means at least 512 Mo for the PC)
- 10 Go of free disk space available
- a screen resolution of 1024 x 768 (may be changed with root privileges)

More precisely, the distribution contains:
- Operating system: Sc. Linux 3.03
- Current Geant4 version: 7.1 with full set of data files
- ROOT
- Source-Navigator IDE
- CERNLIB 2003
- OpenOffice
- Editors: Lyx, Zimbra, OpenOffice...

Decompression:
- for the four files corresponding to your VMware version (4.5 or 5.0) (be careful, several compression levels when decompressing).
- The total decompressed files size is about 2.5 Go and reach 10 Go when fully decompressed.

Please, read the instructions in the corresponding README (4.5 or 5.0) file before installing.

If you do not own a version of VMware Workstation version 4.5 or later, you may still download the full evaluation version (license will expire within a few weeks).

Thank you for your attention!