Photo-activation therapy with high-Z nanoparticles: modelling at a micrometer level and experimental comparison

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• Context and objectives
• Simulation results (PENELOPE)
• Experimental comparison
• Code comparison with GEANT4
• Conclusions and Prospects
• **Photo-activation therapy**: combines low energy X-ray beams with high-Z elements (iodine, gold, gadolinium, platinum...).
• Discovery of the radiosensitive effect due to the iodinated contrast products (ICP) in interventional radiology *(Norman et al, Radiology (1978)).*

• Studies continued by the team INSERM / ESRF: treatment of high grade gliomas *(clinical trial of phase I)*
  
  ICP : Enhancement factor ~ 2 (for 10 mg/ml). Do not integrate cells.

  
  Survival response up to a factor of 4, treating cancerous mice with gold-nanoparticles (AuNP) of 1.9nm (RX tube at 250kVp).

• Such radiobiological enhancement not explained by macroscopic physical model. Modelling at the lower scale.

• Zhang et al. (*Biomed Microdevices (2009)*): Comparison of macroscopic dose calculations for a homogeneous gold-water model and nano-structured. Homogeneous case: overestimation of the dose up to 16%.

• Modelling the nanoparticles.
Objectives, Monte Carlo simulations:

- **Challenge**: find an appropriate physical observable to correlate with biological data.

- **Gold and gadolinium nanoparticles (AuNP & GdNP)**: dose and electron spectra emitted from NP under irradiation (*PENELOPE*).

- **Unicellular geometry with gadolinium**: comparison with experiments made at ESRF (European Synchrotron Radiation Facility) (*PENELOPE*).

- **Unicellular geometry with nanoparticles of gadolinium** (*GEANT4*).
Electron range in water (Penelope tables)

- Approximately 2.5 µm → nucleus scale
- Approximately 40 µm → cellular scale
- Approximately 140 µm → tissue scale
- Approximately 50 nm → macromolecules
• **PENELOPE**: Monte Carlo code adapted for low energy electron and photon transport (lower limit of electron transport: 50 eV). Variance reductions ++.

• First study: Dose deposition and spectra of secondary particles emitted from a single AuNP and GdNP.
Simulation results

Spectra from GdNP

- X-ray beam energy: 52 keV. Diameter of GdNP: 10 nm.
- Gd K-edge: 50.2 keV.
- Au K-edge: 80.7 keV.

- Relaxation cascade and X-ray interaction with shell and sub-shell well described in Penelope.
Electron spectra emitted from a 10 nm diameter AuNP and GdNP as a function of beam energy.

- **Quantity**

  - More electrons produced in Gold except after the sharp Gadolinium K-edge.

- **Mean energy**

  - Mean energy lower after the Gd K-edge, provides a more “local” dose deposition.
• Dose deposition at 500nm around a AuNP of 100nm with a 85 keV X-ray beam.
  - In water
  - With a centred AuNP

- AuNP : Increase of the dose up to a factor 100 with quasi-isotropic diffusion.

  § Beam energies: 31, 49.5, 51, 65, 80 (synchrotron) and 1253 keV (Co60).

  § 5 experimental conditions:

<table>
<thead>
<tr>
<th>Control</th>
<th>Internal GdNP</th>
<th>External GdNP</th>
<th>Magnevist</th>
<th>Internal &amp; external GdNP</th>
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</thead>
</table>

  § Concentrations:

  » Internal Gd: 0.6 mg/mL

  » External Gd: 2.1 mg/mL (1.8 mg/mL for the incubated case)

(cf. F. Taupin presentation on Monday (GRC))
• Simulation: Unicellular geometry.

Nanoparticles substituted with homogeneous water-gadolinium mixture localized into or outside the cell (experimental concentrations).
Experimental comparison

Dose Enhancement Factor

DEF = \frac{\text{Dose (Gd)}}{\text{Dose (water)}}

- Maximum DEF obtained of \sim 1.15 for internal and external Gd.

Experimental SER

\text{SER}_{4\text{Gy}} = \frac{\text{Survival at 4Gy (control)}}{\text{Survival at 4Gy (Gd)}}

- Experimental SER_{4\text{Gy}} much higher (up to 2.25 for 65 keV).
Size of the extra-cellular medium: 15 to 110 µm. Same size for the X-Ray beam.
Comparison of electron spectra incoming on the nucleus for all energies and conditions. (ex: int\&ext Gd / water)

Experimental comparison normalized at 65 keV:
Good correlation.

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• **GEANT4** : General purpose Monte Carlo code allowing to transport particles in matter for a wide range of applications (high energy physics, nuclear, space, medical…).

• Electromagnetic physical models for low energy electron and photon transport :
  - Livermore
  - Penelope
  - DNA

• Advantages compared to PENELOPE code :
  - Flexible
  - Complex geometries
  - Access to more detailed track information

• Drawbacks :
  - Lack of variance reductions for small structures.
• Macroscopical DEF: Cube of 1 cm.

• Microscopical DEF: Cell.

• Coherent results between PENEOLOPE and GEANT4: problem of statistics for the small volumes (variance reduction).
• Cell geometry: consideration of nanoparticles of different sizes (R = 15 – 50 nm)

• Coherent results between homogeneous / NP. Auto-absorption of low-energy electrons into the NP.
- **Photon interactions**: photoelectric, Compton, Rayleigh
- **Electron interactions**: Ionization, multiple scattering
Conclusions:

- Nanoparticle model (*PENELOPE*): Study of secondary particles emitted under irradiation for different beam energies and comparison Gd/Au.
- Unicellular model (*PENELOPE*): calculation of DEF and electron spectra incoming on the nucleus for different conditions.
- Comparison with experimental data (*PENELOPE*): encouraging results.
- Limitation of *PENELOPE* modeling large number of nanoparticles: GEANT4.
- Validation GEANT4 / *PENELOPE*. Very long simulation time with NP for acceptable statistic.

Prospects:

- Improve GEANT4 physical model for nanostructures applications.
- Investigation of track information.
• **LM2S:**
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• **Supervisors:**
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  - Mélanie Flaenders (*INSERM / ESRF*)
  - Jean-Luc Ravanat (*LAN, CEA Grenoble*)
  - Sébastien Incerti (*CENBG, Bordeaux*)

Thank You for your attention
• Comparison of electron spectra between PENELOPE and GEANT4. (52 keV, NPGd 10 nm diameter). **Good correlation.** Lack of statistic for GEANT4.
• Gd properties:
  K-edge: 50.2 keV, Z: 64, density: 7.9 g/cm³
• Au properties:
  K-edge: 80.7 keV, Z: 79, density: 19.3 g/cm³

• 1µm dose deposition of particles emitted from a AuNP as a function of energy and diameter:
• Normalization at 65 keV to compare the tendency between the Nucleus DEF and $\text{SER}_{4\text{Gy}}$.

• Model and observable not well adapted for comparison with SER.

• Remarks:
  - Limited size of external volume.
  - Biological effects not limited to physical dose.