Biophysical modeling of the radiosensitizing effect of gold nanoparticles (GNP)

Conference MCMA2017 – 17/10/2017

Floriane POIGNANT, PhD student at the IPNL
Supervisor : **Michael BEUVE**, Co-supervisor : **Etienne TESTA**
Financial Support : LabEx PRIMES

Nanoparticles and radiotherapy

- **Radiosensitizer** : used to increase the effect of dose within the tumor, by confining the product inside the cancer cells

- **Nanoparticles** :
  - Radiosensitizing effect observed both in vivo/vitro
  - Origin still under investigation

[1]

Physical and chemical origin of radiosensitization?

Interaction photon + NP:
- Auger cascade

⇒ Boost of local secondary electrons

→

++ local dose
&
++ free radicals

→

++
Cell death

[1]

Context · Goal · State of the art · Material & method · Results

Challenges

- Time scale: from 10^{-18} second
- Spatial scale: **nano**-dosimetry

⇨ **Study with Monte Carlo simulations**

[2]

1. **Quantify**, at nanometric scale, the **impact of nanoparticles** on physical and chemical radio-induced processes

2. Implement the results in a **biophysical model** to reproduce experimental radiosensitizing effects

[3]

Simulation Monte Carlo [1-2]

Dose deposition distribution on nanometric scale

Free radical production

Biophysical model [3]

Cell survival curves

Predict cell death
Radiosensitizing effect ?

(1) Gervais B *et al*, **Numerical simulation of multiple ionization and high LET effects in liquid water radiolysis,** *Radiat. Phys. Chem.* **75** 493–513, 2006
(2) B. Gervais *et al.*, **Production of HO2 and O2 by multiple ionization in water radiolysis by swift carbon ions**, *Chemical Physics Letters, 410 330-334*, 2005
(3) M Cunha *et al*, **NanOx, a new model to predict cell survival in the context of particle therapy**, *Phys. Med. Biol.* **62** 1248, 2017

[4]

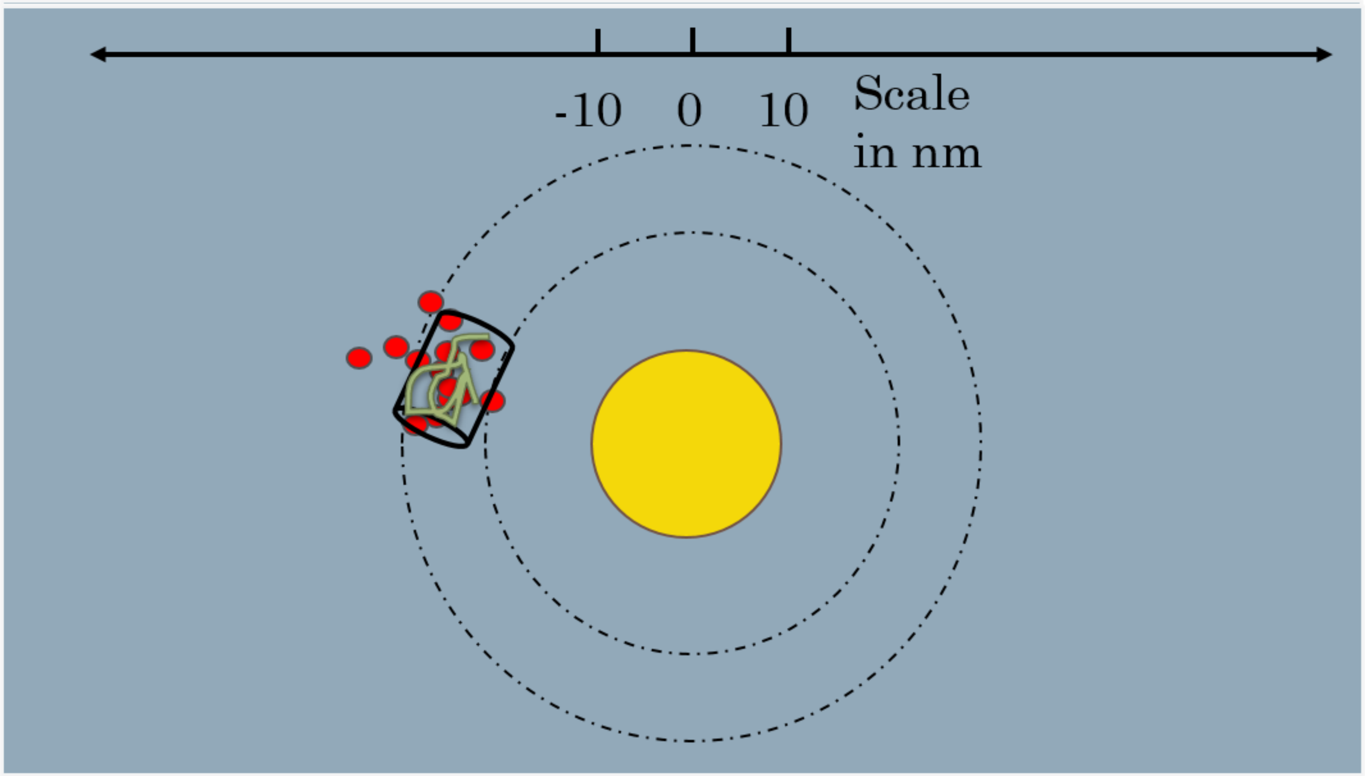
State of the art

- **Most elaborated micro/nano-dosimetric study [4]** :

	Model [4]	Limits
MC Simulation	Geant4 + Geant4-DNA	- Atomic physical model for gold - Energy cut in gold 250 eV
Biophysics	LEM	- Average radial dose - Chemistry not applied

(4) *S. McMahon*, **Biological consequences of nanoscale energy deposition near irradiated heavy atom nanoparticles**, *Scientific Reports* **1**, Article number: 18, 2011

Context | Goal | State of the art | Material & method | Results



[6]

Nanodosimetry study

- **System**
  - GNP of a given radius R_{GNP} of 5 to 50 nm in water
  - Photons (20 keV – 90 keV) decomposed in sub-contributions
  - Target $(10\ nm)^3$ at

  $R_{GNP} < d_{target} < R_{GNP} + 200\ nm$
- **Irradiation of a few Gy**
- **Dose in the target at d_{target} ? = Specific energy**
- **Computing time challenging**

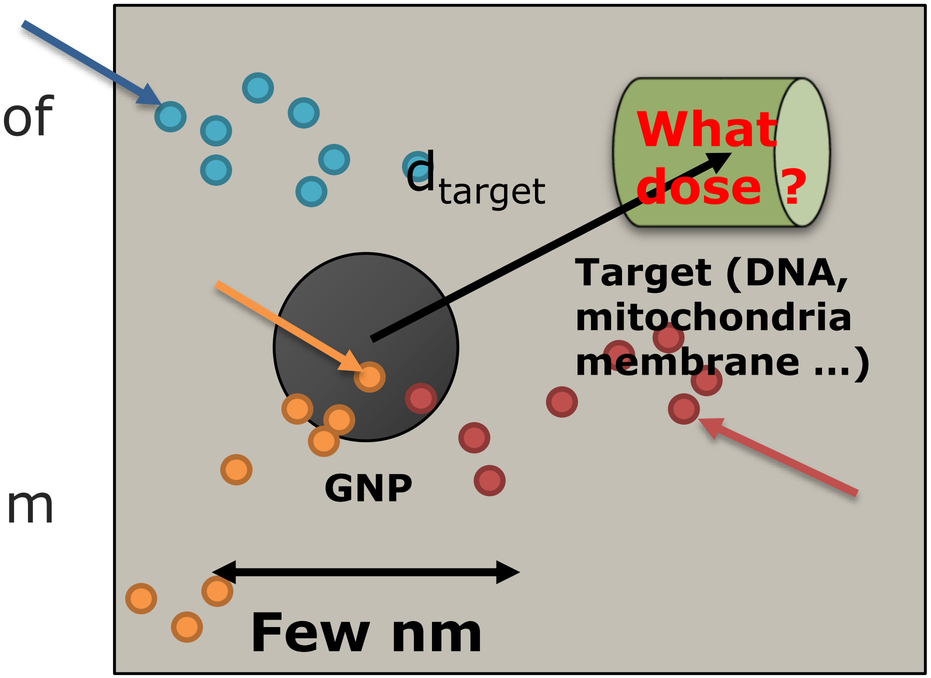


Illustration of nanodosimetric study in sensitive cell targets

[7]

Context | Goal | State of the art | Material & method | Results

Positioning wrt state of the art

	Model [4]	**Limits**	**Our model**	**Improvement**
MC Simulation	Geant4 + Geant4-DNA	- Atomic physical model for gold - Energy cut in gold 250 eV	MDM + CHEM	- Solid state model for gold - Down to thermalization
Biophysics	LEM	- Average radial dose - Chemistry not applied	NanOx	- Closer to biological reality - Radical species

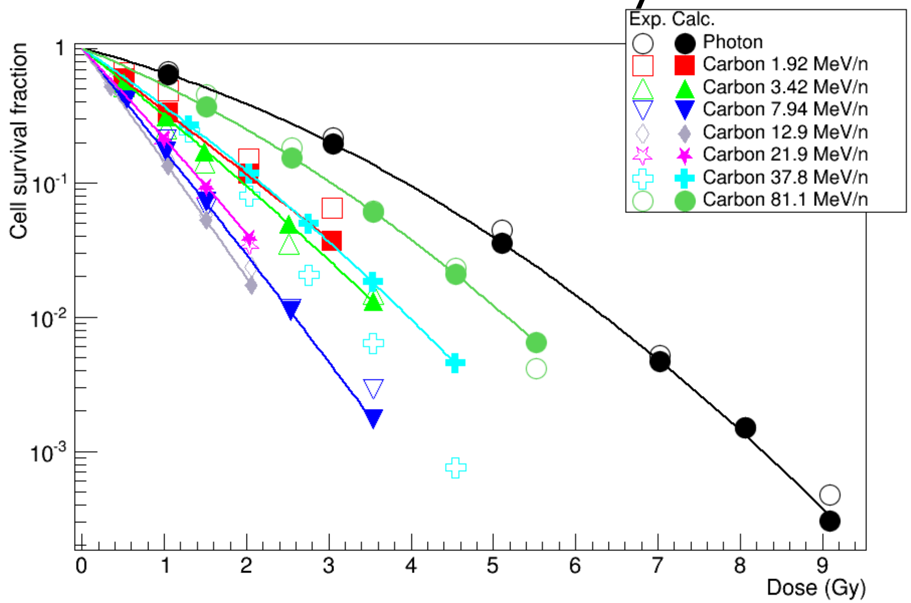
(4) *S. McMahon,* **Biological consequences of nanoscale energy deposition near irradiated heavy atom nanoparticles**, *Scientific Reports* **1**, Article number: 18, 2011

Context | Goal | State of the art | ...sults

Contact : monini@ipnl.in2p3.fr

NanOx [3]

- **Nan**odosimetry and **Ox**idatve stress: biophysical model predicting cell survival upon irradiation
- **Goal**: calculation of the mean number of cells killed by a given dose
- **Postulate**: cell survival expressed in terms of components related to:
  - Local lethal events inducing direct cell killing
  - Non-local events (e.g. free radical stress)
- Originally for **hadrontherapy**



Cell survival prediction for HSG line

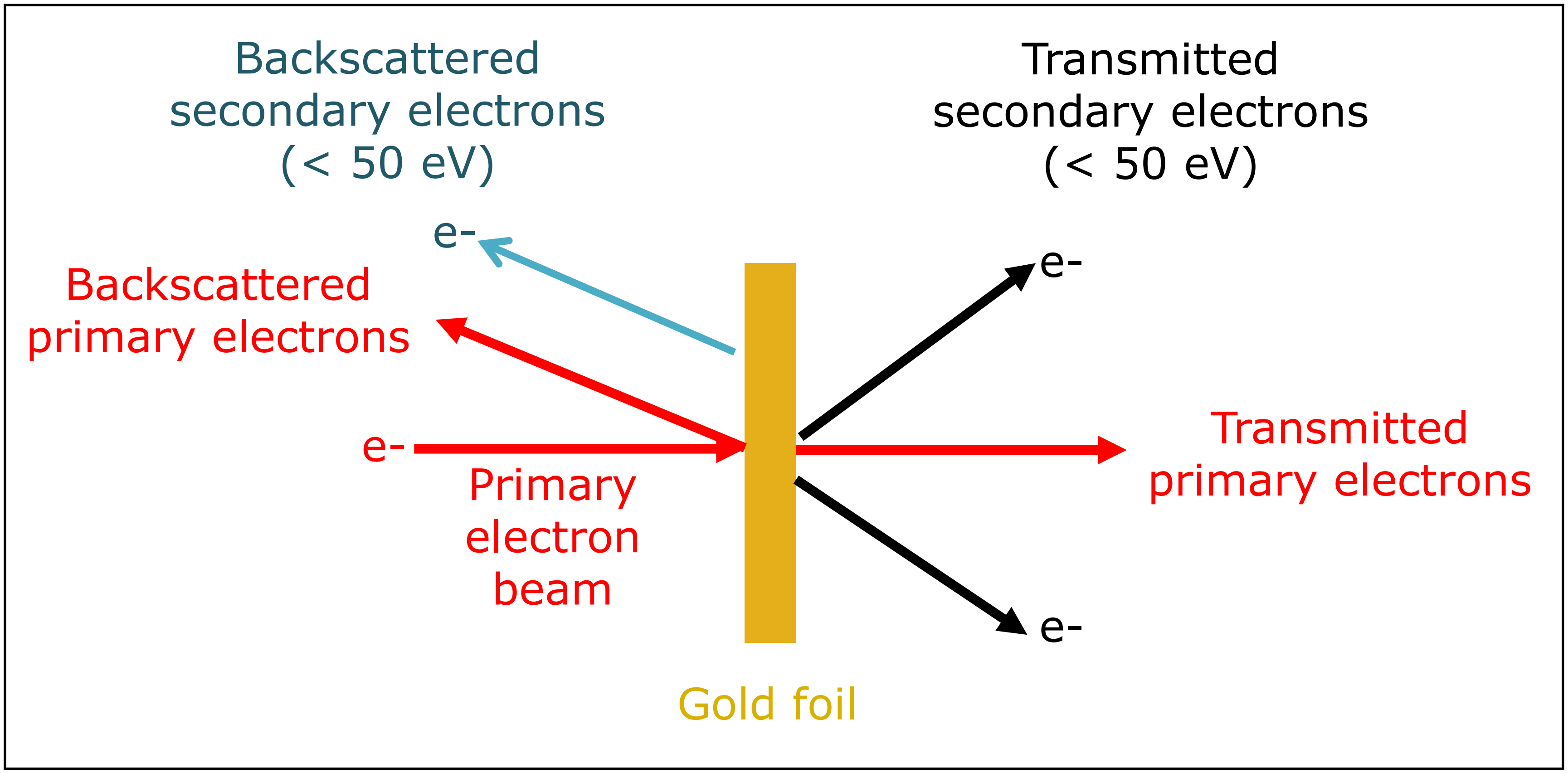
(3) M Cunha *et al*, **NanOx, a new model to predict cell survival in the context of particle therapy**, *Phys. Med. Biol.* **62** 1248, 2017

Physical models for gold/particles

		MDM		"Standard Simulation"	
Particle	Process	Metal (gold)	Water	Metal (gold)	Water
Electrons	Phonons	++		+	
	Plasmons (surface, volume) (solid physics model)	++			
	Core Ionization (atomic model)	++	++	++	++
	Elastic scattering	++	++	++	++
	Auger and fluorescence	++	++	++	++
	Double ionization		++		
	Electrons attachment		++		++
	Molecule vibration		++		++
	Electronic excitation		++		++
	Surface barrier affinity function	++	++		
Photons	Compton scattering	++	++	++	++
	Photoelectric effect	++	++	++	++

[10]

Benchmarking : system



[11]

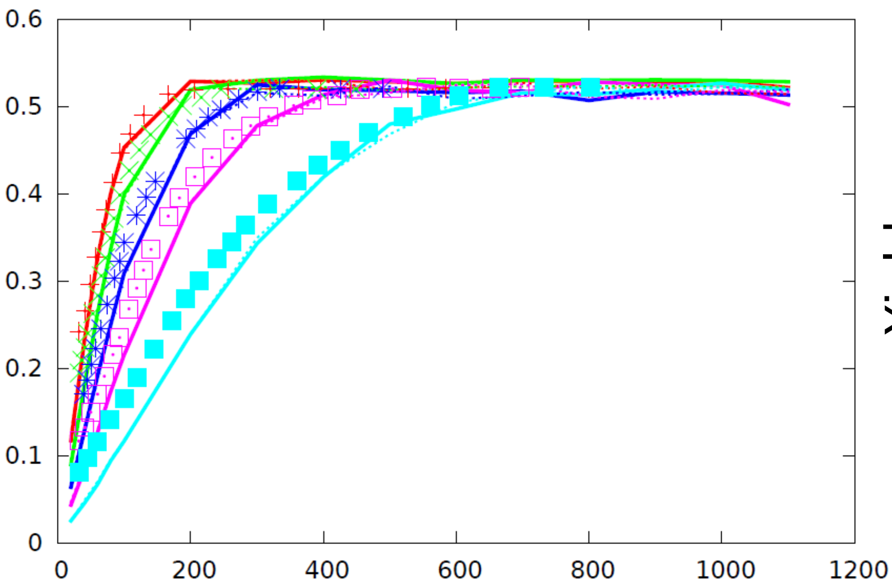
Benchmarking : system

- Yield $= \dfrac{Number\ of\ electrons\ backscattered/transmitted}{Number\ of\ electrons\ sent}$
- Energy distribution
- Experimental work from literature
- MDM results with/without surface plasmons

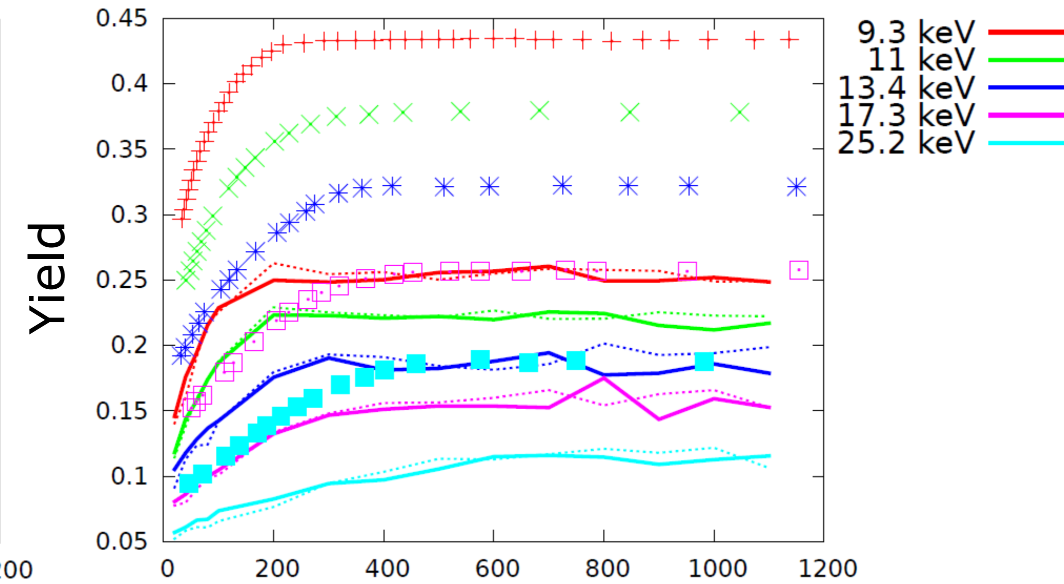
[12]

Backscattered electron yields

Primary electrons (> 50 eV)



Secondary electrons (< 50 eV)



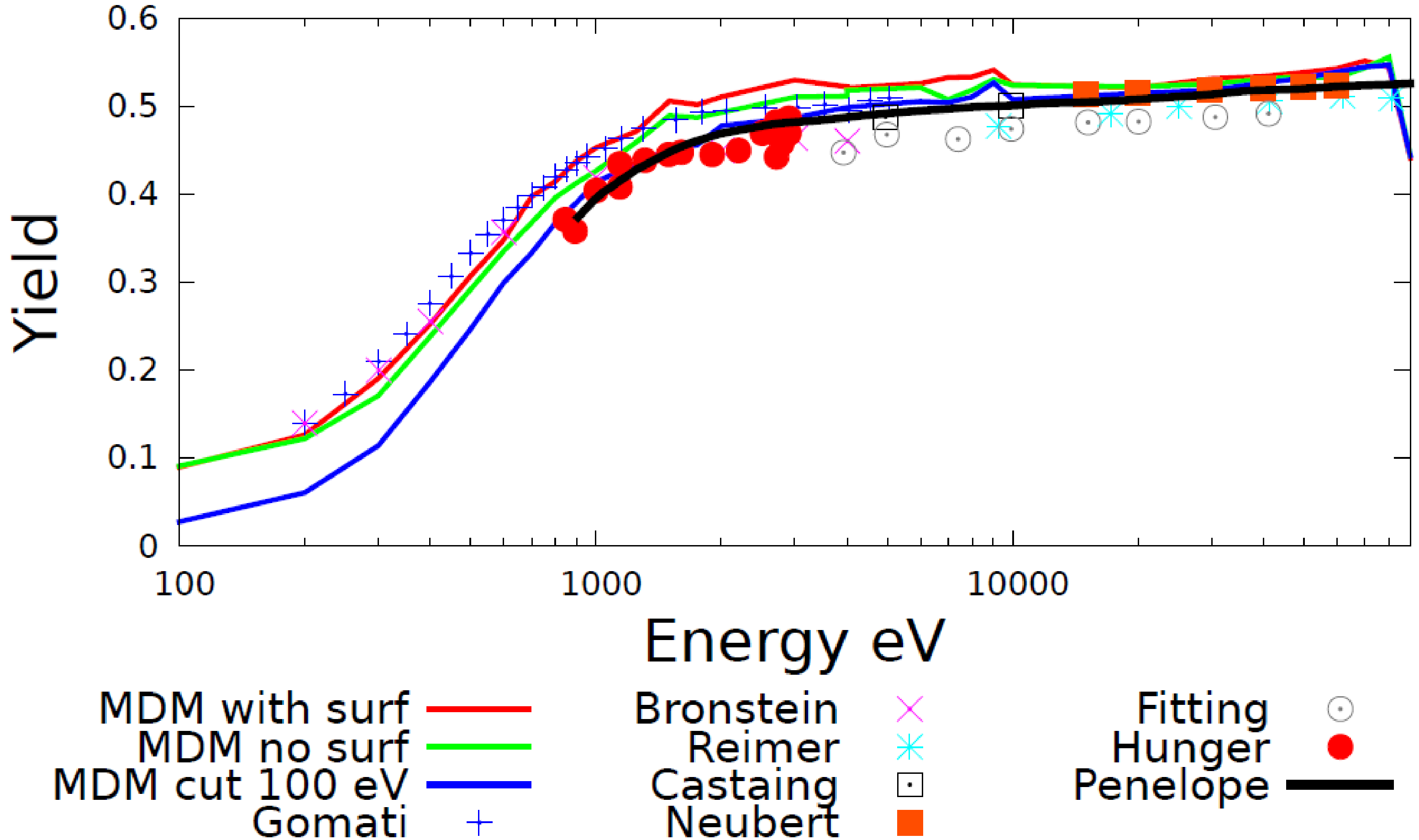
Thickness in µg/cm²

(100 µg/cm2 = 51,76 nm)

(5) Reimer, L. and Drescher, **H. Secondary electron emission of 10-100 kev electrons from transparent films of al and au,** *Journal of Physics D: Applied Physics*, 10(5):805, 1977

Context | Goal | State of the art | Material & method | Results 1/3

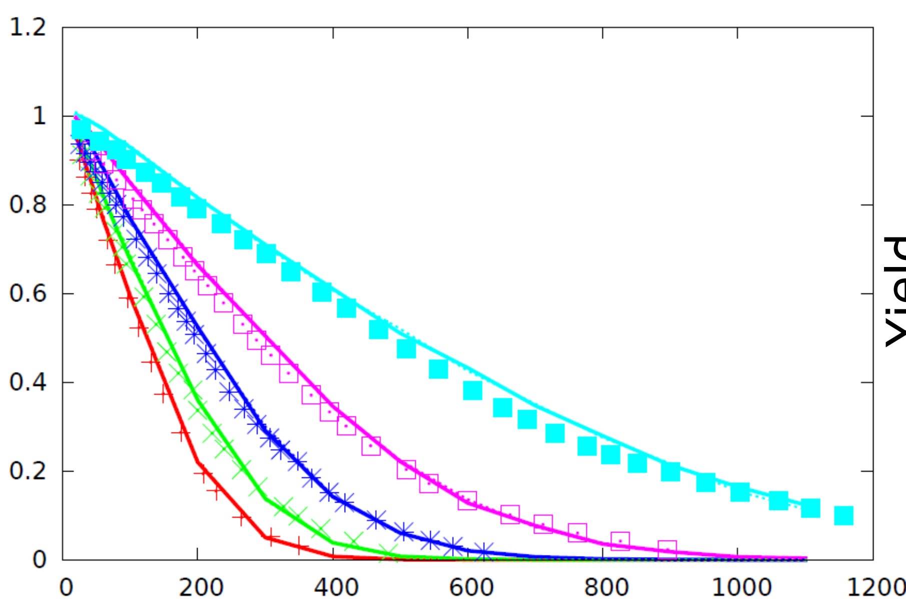
Backscattered electron yields



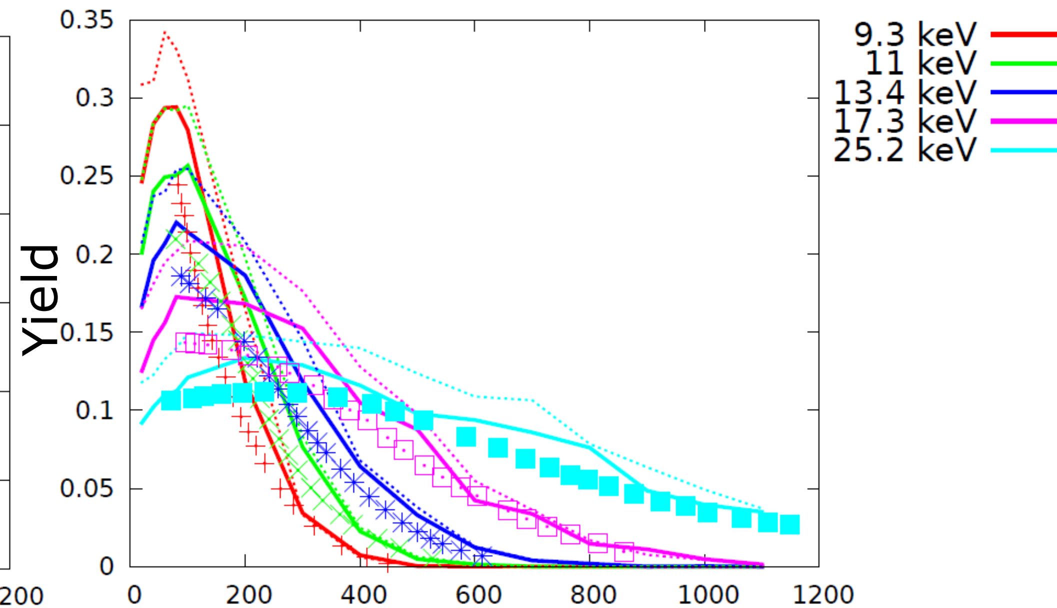
[14]

Transmitted electron yields

Primary electrons (> 50 eV)



Secondary electrons (< 50 eV)



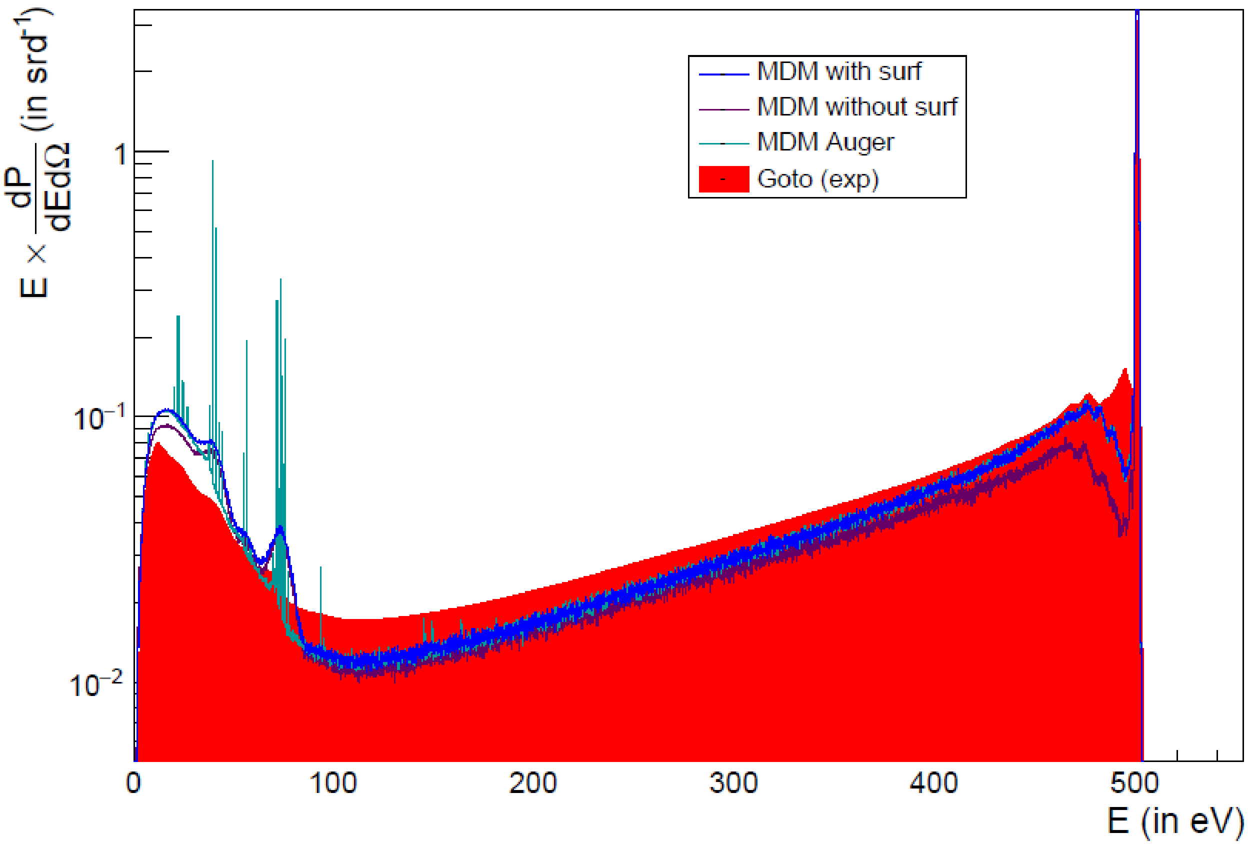
Thickness in µg/cm²

(100 µg/cm2 = 51,76 nm)

(5) Reimer, L. and Drescher, **H. Secondary electron emission of 10-100 kev electrons from transparent films of al and au,** *Journal of Physics D: Applied Physics*, 10(5):805, 1977

Context | Goal | State of the art | Material & method | Results 1/3

Energy distribution of backscattered electrons, multiplied by the energy, for a primary beam at 500 eV, normalized per incoming electrons and to the solid angle



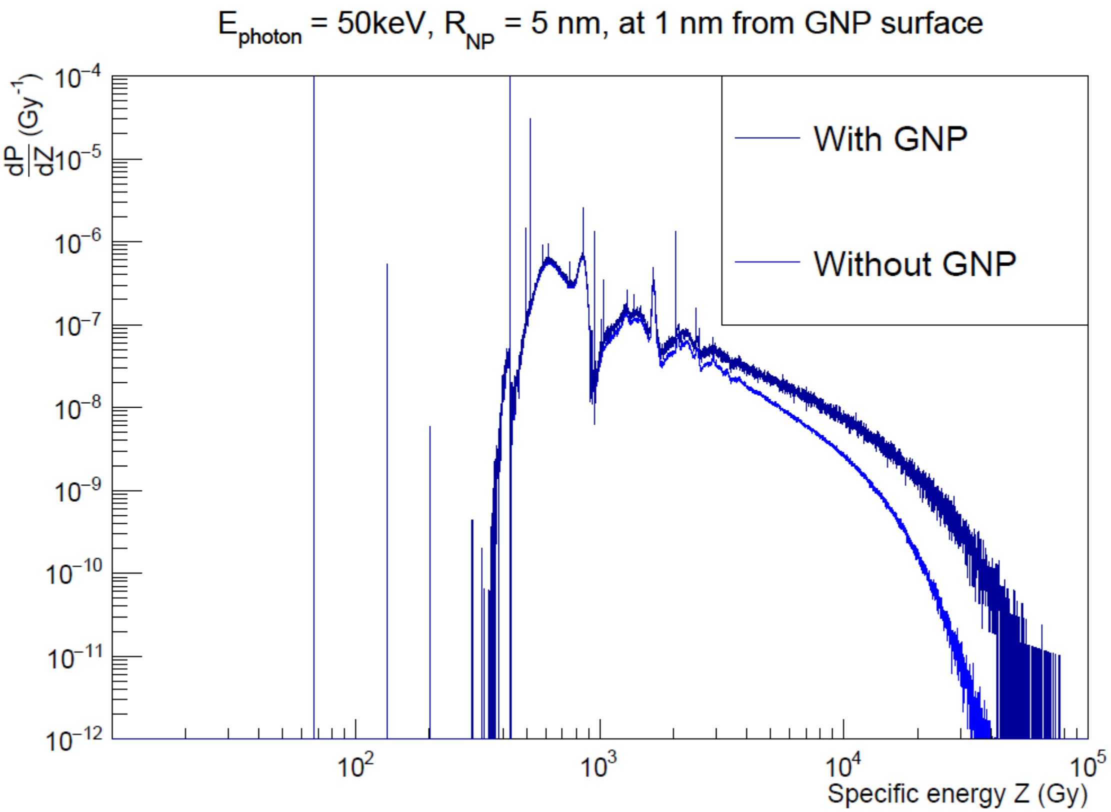
(6) Y. Takeichi, K. Goto, **True Auger Electron Spectra Measured with a Novel Cylindrical Mirror Analyser (Au, Ag, Cu)**, *Surface and interface analysis*, vol. 25, 17-24, 1997

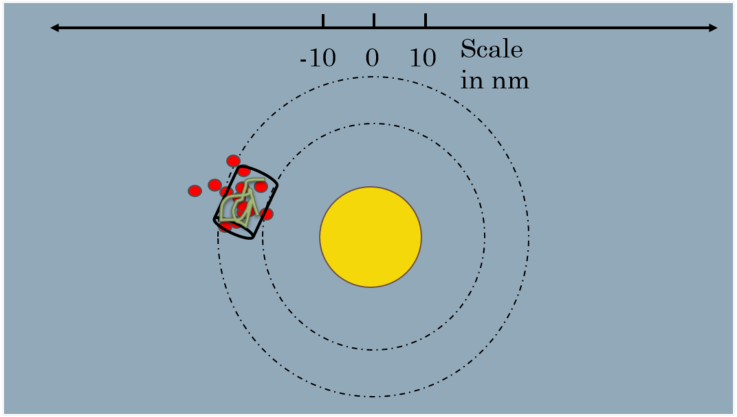
Conclusion on MC validation

- Results in close agreement with experience for **[0-90] keV** for electron/gold interaction
  - For electron **yields**
  - For energy **spectra**
- Test limited to macroscopic or 1D-nanoscopic scale, but convincing enough to go to nanometric scale
- Surface plasmons do not impact much yields, but have consequences on energy distribution
- Ongoing publication

Context | Goal | State of the art | Material & method | Results 2/3

Nanodosimetry: comparison with/without GNP

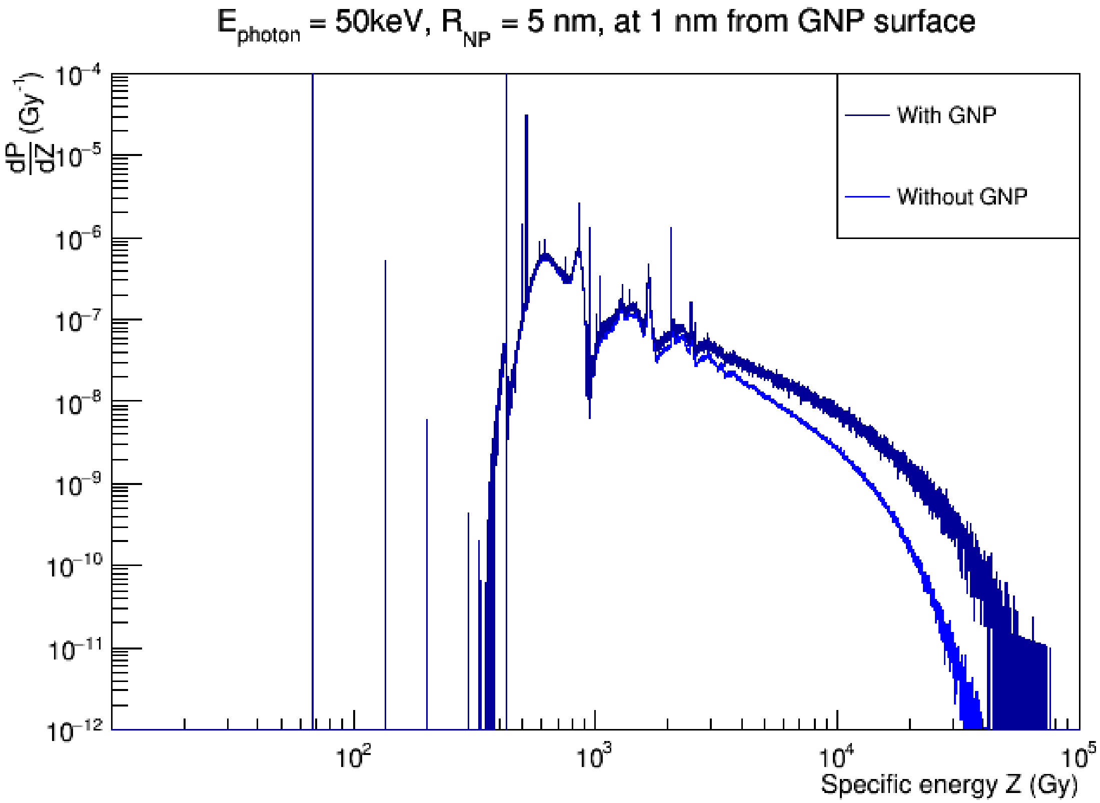


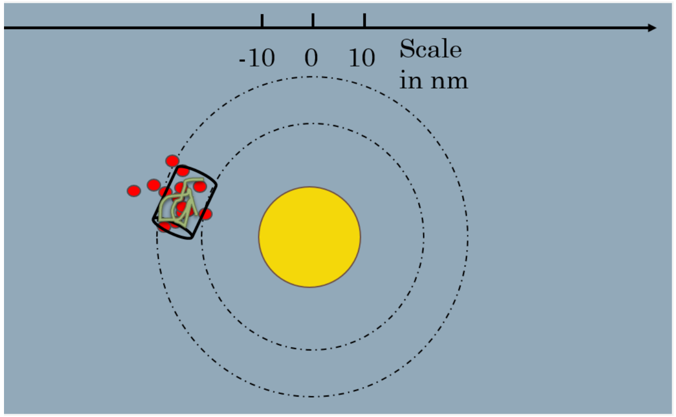


[18]

Context | Goal | State of the art | Material & method | Results 2/3

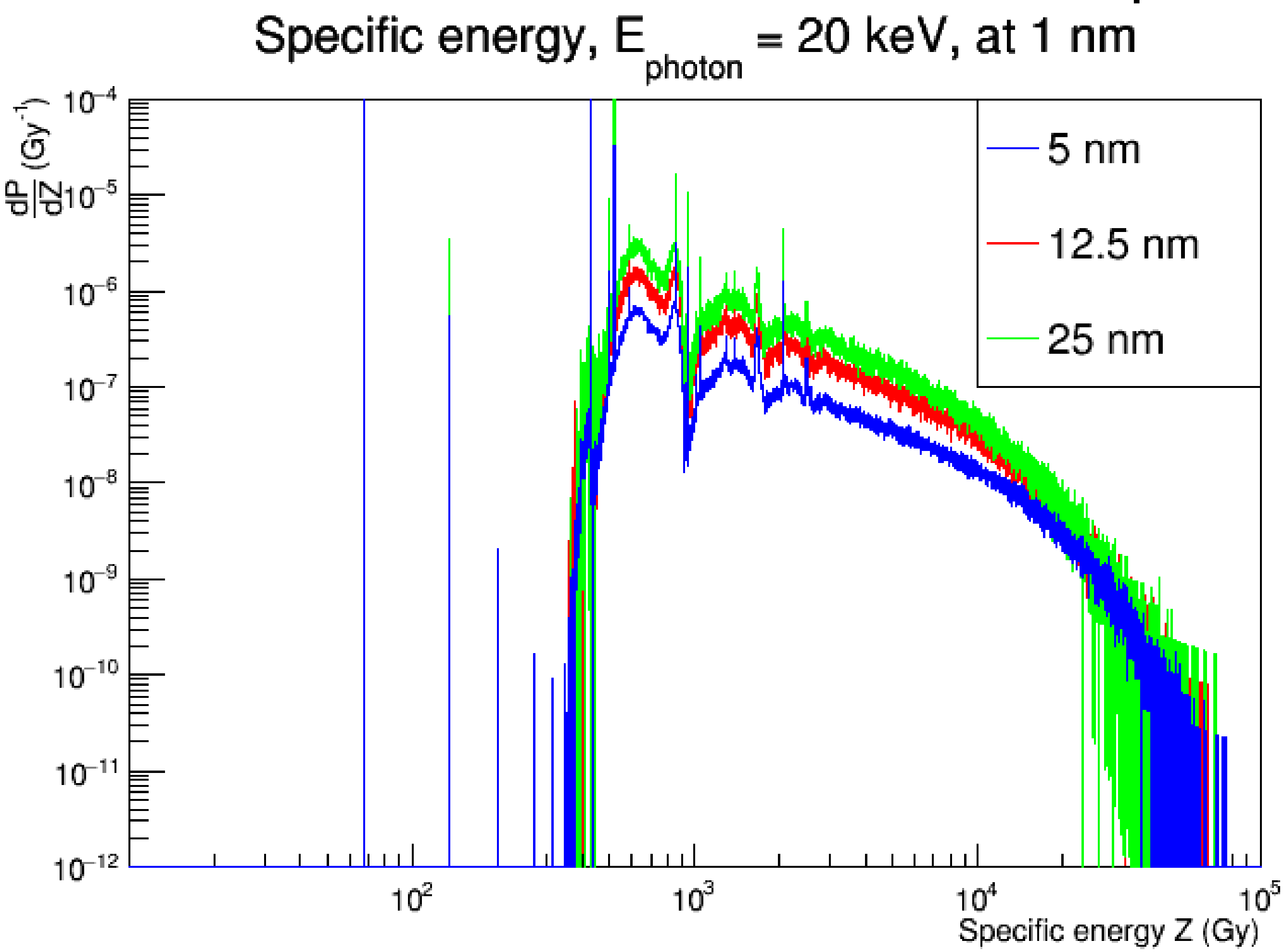
Nanodosimetry: comparison with/without GNP





[18]

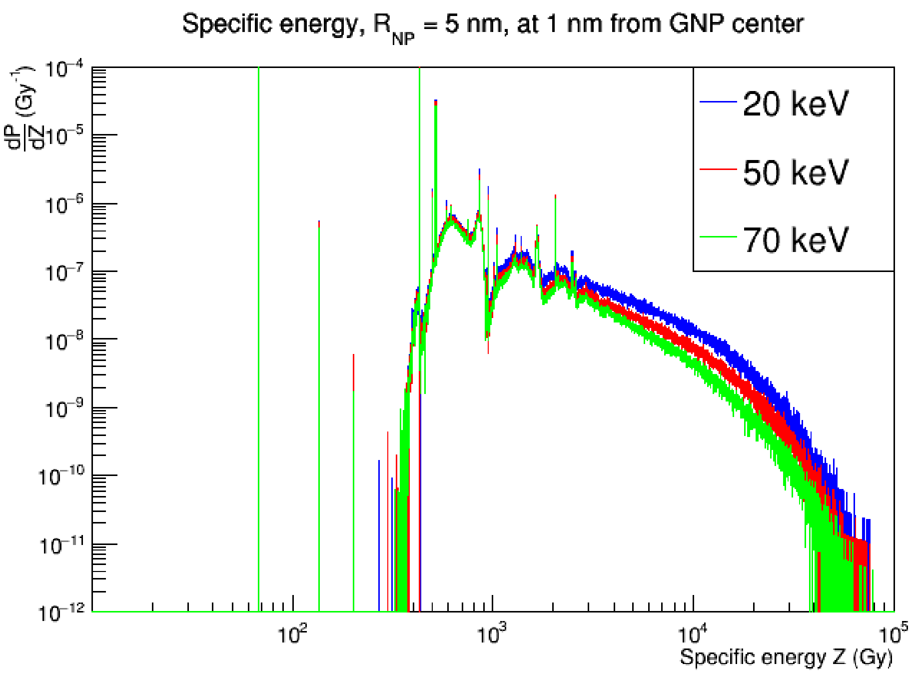
Comparison at fixed E_{photon}



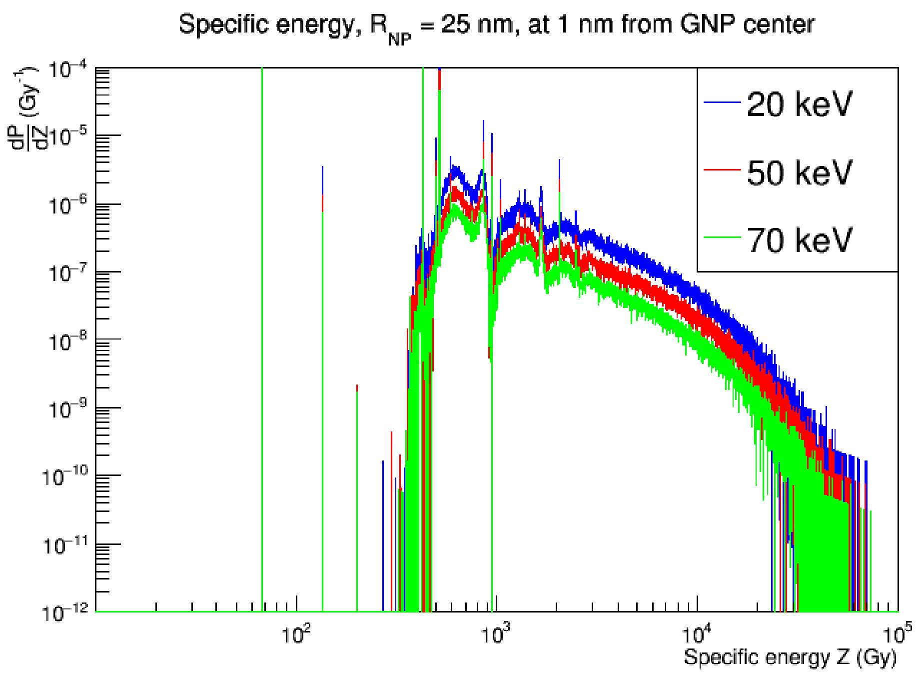
[19]

Comparison at fixed R_{GNP}

R_{GNP} = 5 nm



R_{GNP} = 25 nm



[20]

Conclusion regarding nanodosimetry

- **Local** boost of dose deposition in nano-targets similar to hadrontherapy
- The boost depends :
  - On the size of the GNP mostly
  - Energy if large GNP
- **Range of action**
  - 20 nm for R_{GNP}=5 nm
  - 200 nm for R_{GNP}=50 nm
- Biological consequences: the GNP must be **close to a target** if R_{GNP} small

[21]

Free radical production (preliminary results) – Work by H. Charfi (M2)

- Free radical species production
  - H_2O_2
  - $OH^{\cdot}$
  - e_{aq}

- For different GNP concentration, times

- (for now) the radical species produced do not interact with the GNP

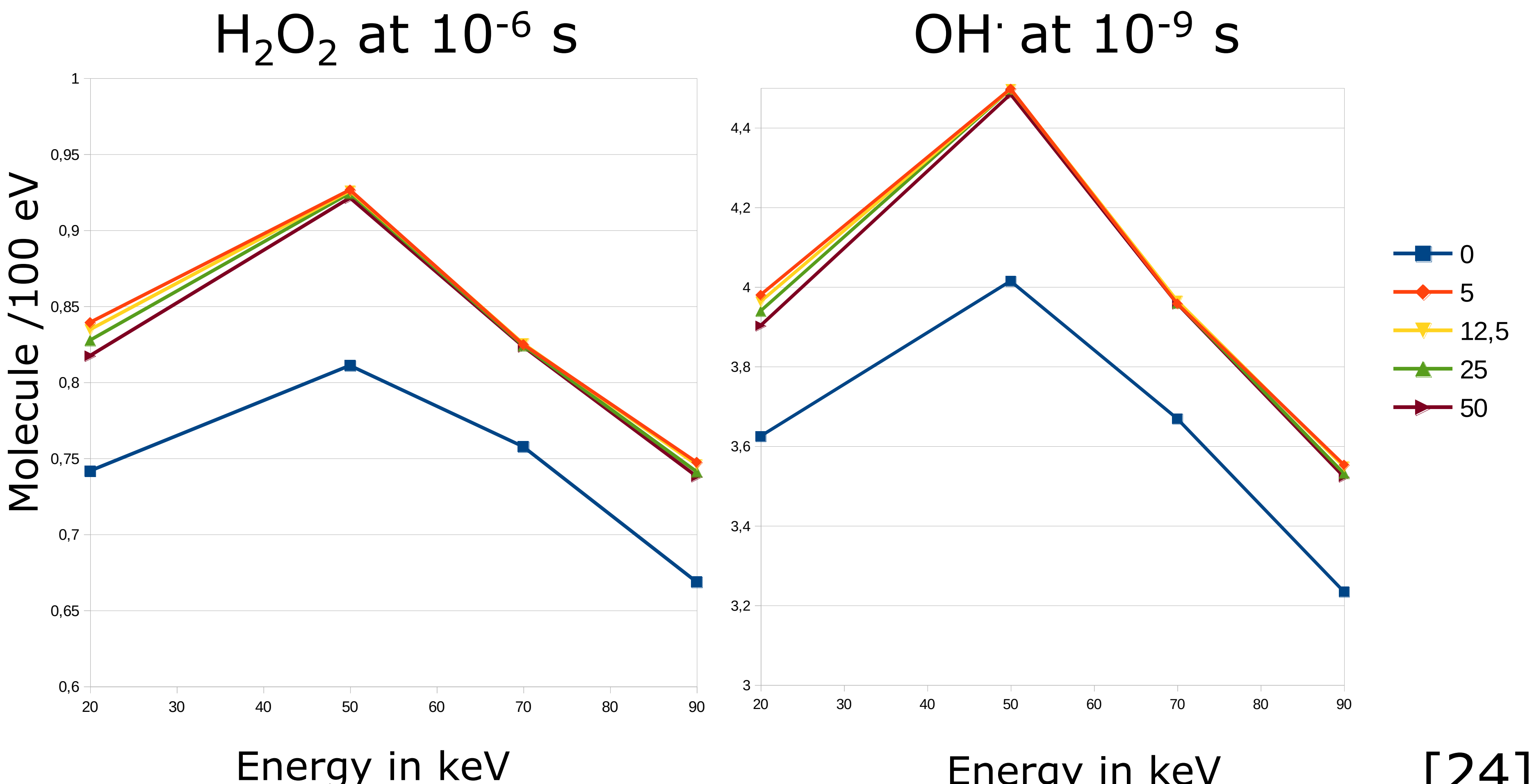
[22]

Free radical production at 1 mg/mL

Radius GNP	5 nm	12,5 nm	25 nm	50 nm
mg/mL	1	1	1	1
nM of GNP	164	10	1,3	0,16
N GNP in $(10\ \mu m)^3$ cell	~ 100 000	~ 6 000	~ 800	~ 100

[23]

Free radical production at 1 mg/mL



[24]

Contexte | Objectif | State of the art | Matériel & méthode | Résultats

Comparison to experience

OH$^{\cdot}$ at 10^{-6} s at 20 keV for R_{GNP} = 16,25 nm

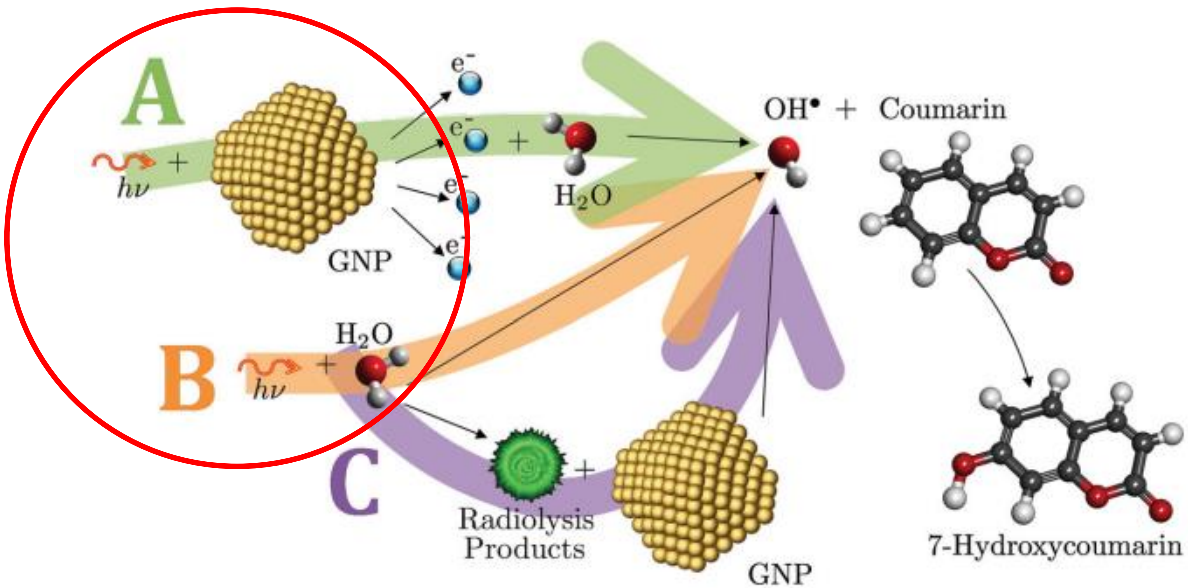


Figure from [6]

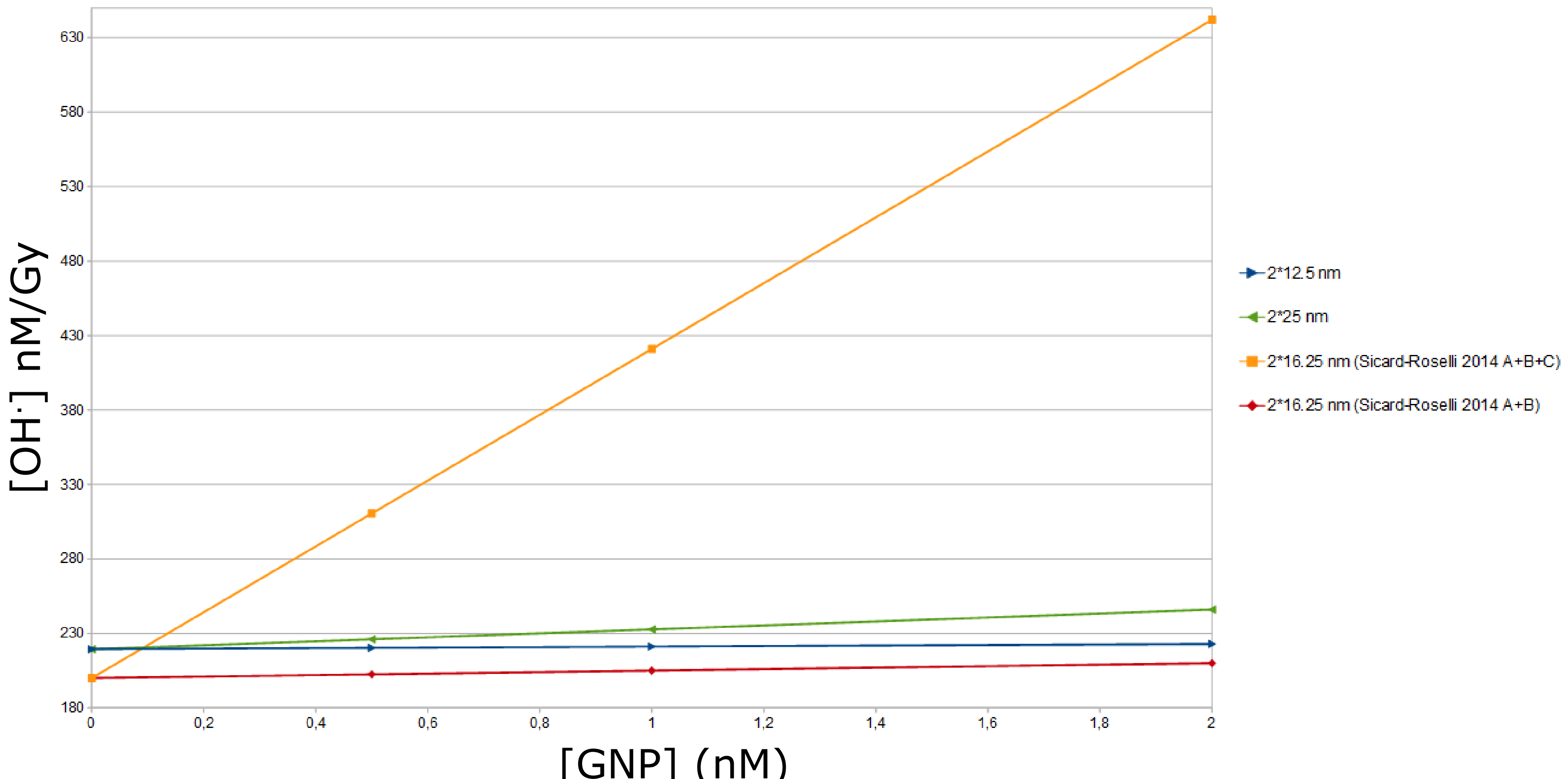
(6) C. Sicard-Roselli, *et al*, **A New Mechanism for Hydroxyl Radical Production in Irradiated Nanoparticle Solutions**, *Small*, 10, No. 16, 2014, Pages 3338-3346

UNIVERSITÉ DE LYON

PRIMES UNIVERSITE DE LYON

Contexte | Objectif | State of the art | Matériel & méthode | Résultats

OH· at 10^{-6} s at 20 keV



(6) C. Sicard-Roselli, *et al*, **A New Mechanism for Hydroxyl Radical Production in Irradiated Nanoparticle Solutions**, *Small*, 10, No. 16, 2014, Pages 3338-3346

Conclusion on free radical production

– Increase of free radical production (H_2O_2, $OH^\cdot$)
  - More efficient for small GNP at fixed massic concentration

- Underestimation of $OH^\cdot$

Scenario 1: interaction of radical species with GNP
- Test with arbitrary constants
- Ongoing collaboration with ENS, DFT calculation for gold/water interface
- Measurement of reaction constants ?

Scenario 2: impact of the measurement technic
- Need for extra experiments with different technics

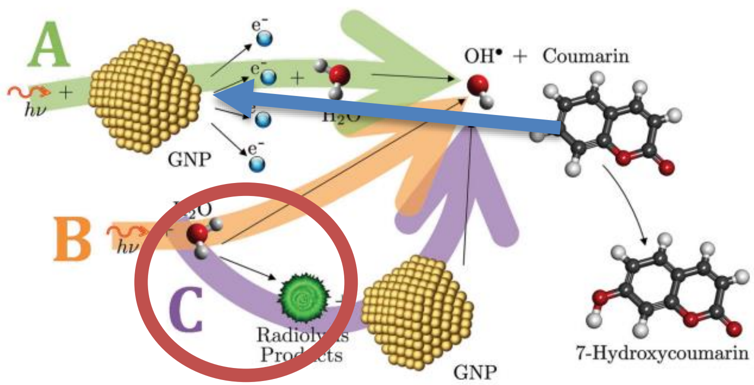


Figure from [9]

(9) C. Sicard-Roselli, *et al*, **A New Mechanism for Hydroxyl Radical Production in Irradiated Nanoparticle Solutions**, *Small*, 10, No. 16, 2014, Pages 3338-3346

Perspectives

- Implement in NanOx
- Obtain cell survival
- Answer questions:
  - Physical effect: which biological target for which effect?
  - Chemical effect: quantify the consequences

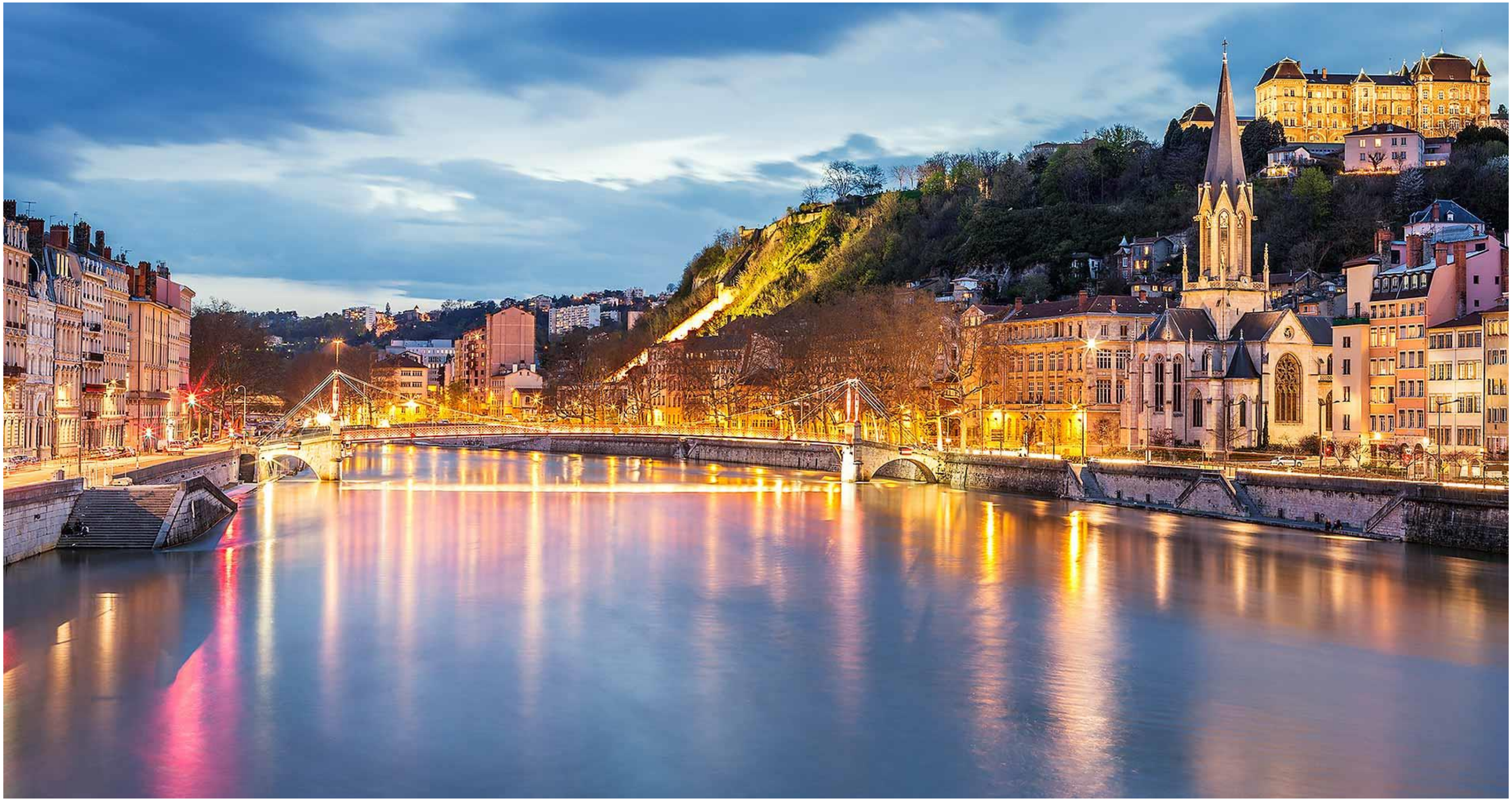
Thanks for listening!

Aknowledgement : PJ Lartaud, H. Charfi, B. Gervais, A. Ipatov, M. Cunha, C. Monini, T. Bacle, E. Testa, M. Beuve.

In collaboration with the Labex PRIMES groups : LRCM (C. Rodriguez), LPC (G. Montarou), GIN (F. Esteve), LAN (J. L. Ravanat), ILM (O. Tillement)

This work was supported by the LABEX PRIMES (ANR-11-LABX-0063) of Université de Lyon, within the program "Investissements d'Avenir" (ANR-11-IDEX-0007) operated by the French National Research Agency (ANR).

Thanks for listening!



ANNEXE (1)

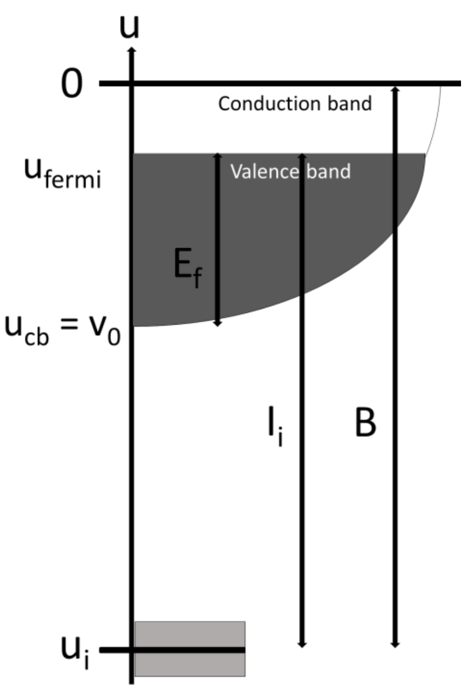


Fig. a : *Metallic model (gold)*

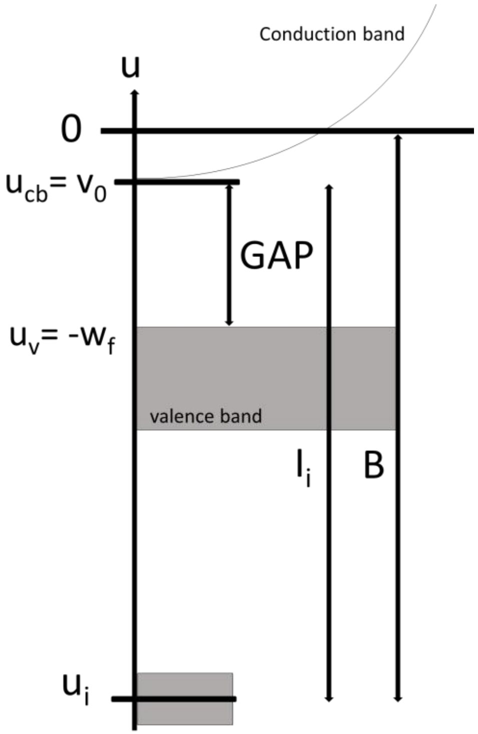
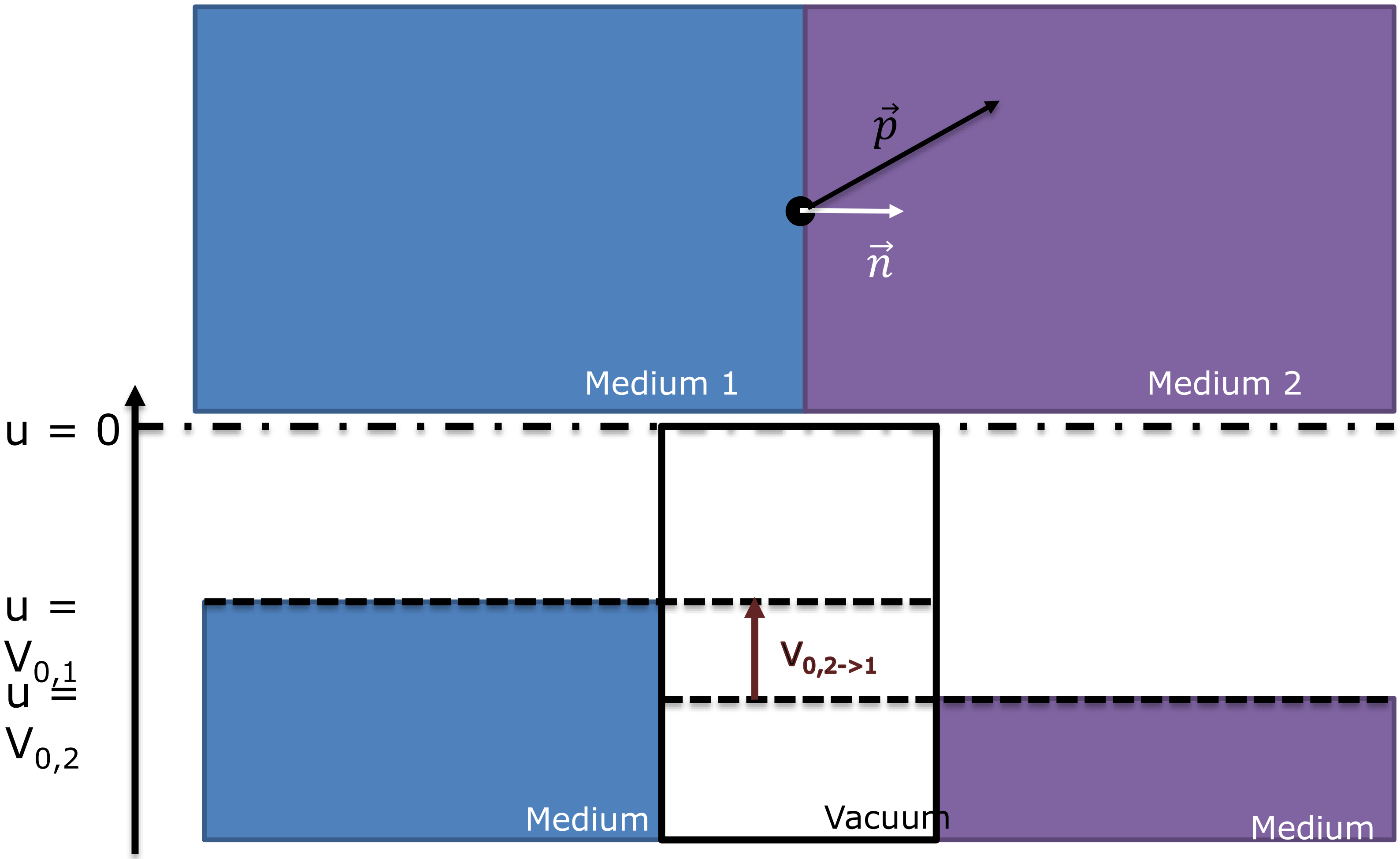
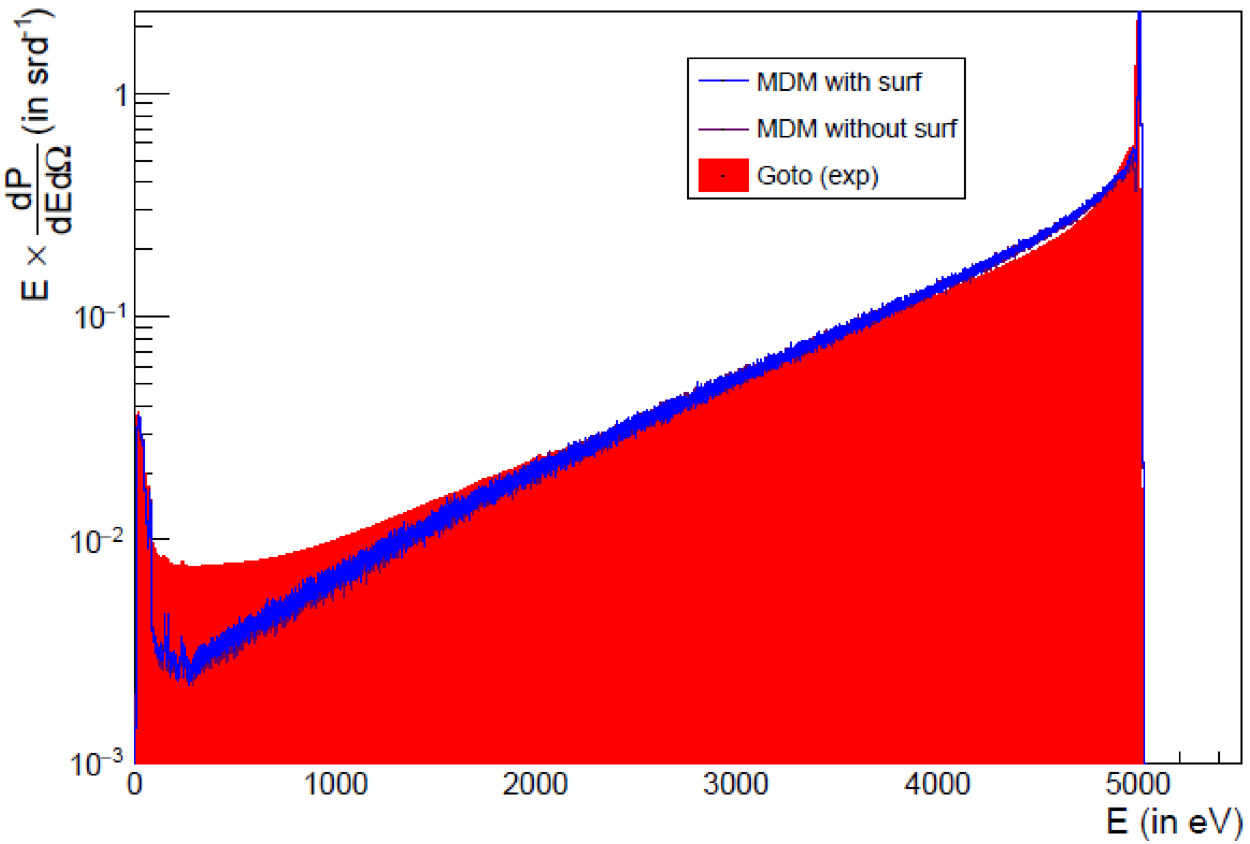


Fig. b : *Water model*

ANNEXE (2)

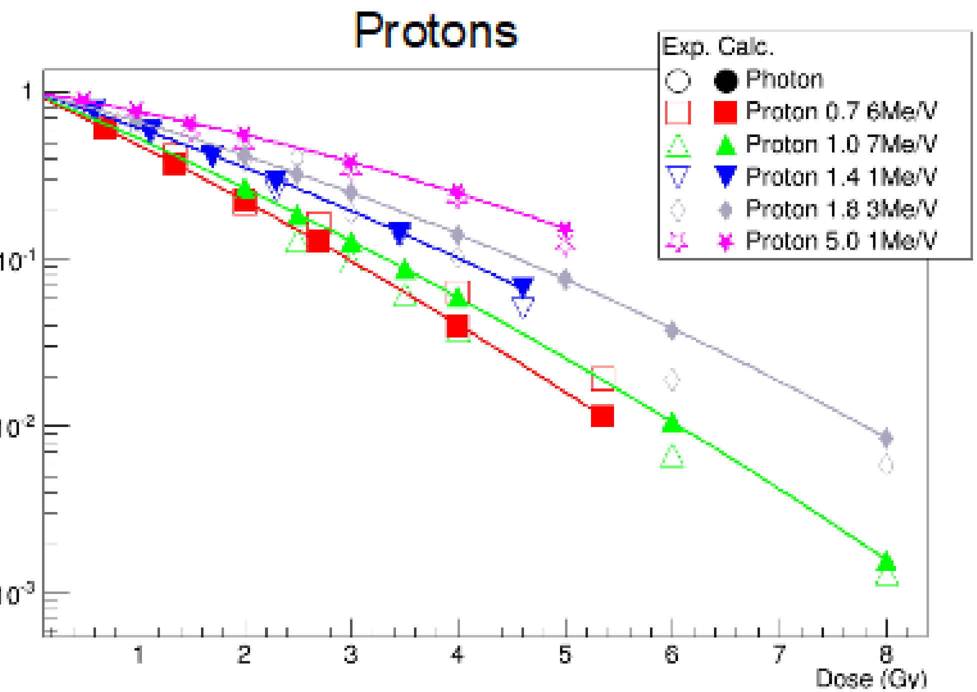

$\vec{p}$
$\vec{n}$
Medium 1
Medium 2
u = 0
u =
$V_{0,1}$
u =
$V_{0,2}$
$V_{0,2\text{->}1}$
Medium
Vacuum
Medium

ANNEXE (3)

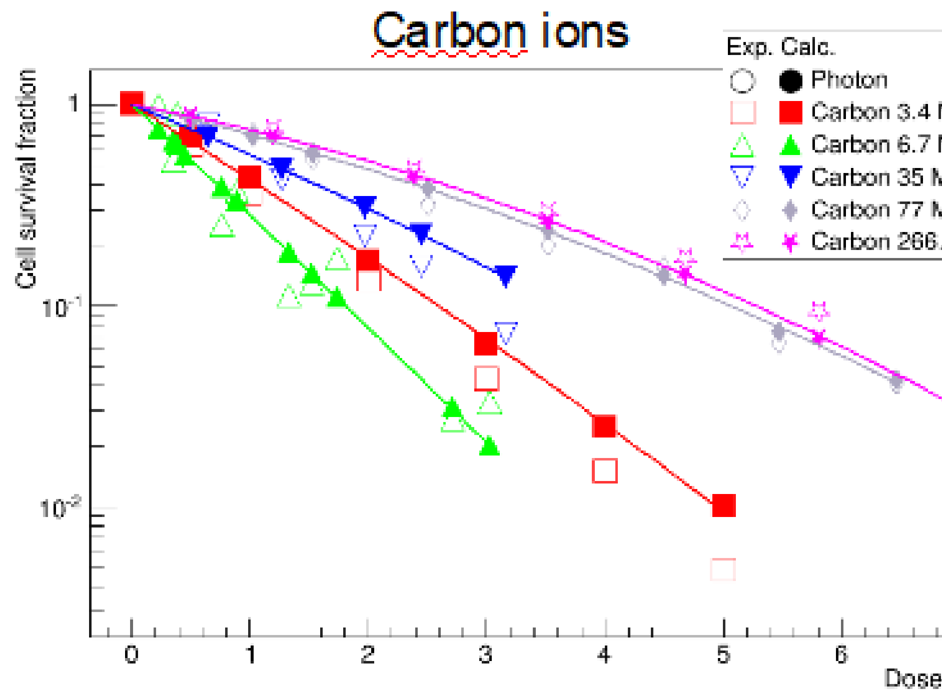


(6) Y. Takeichi, K. Goto, **True Auger Electron Spectra Measured with a Novel Cylindrical Mirror Analyser (Au, Ag, Cu)**, *Surface and interface analysis*, vol. 25, 17-24, 1997

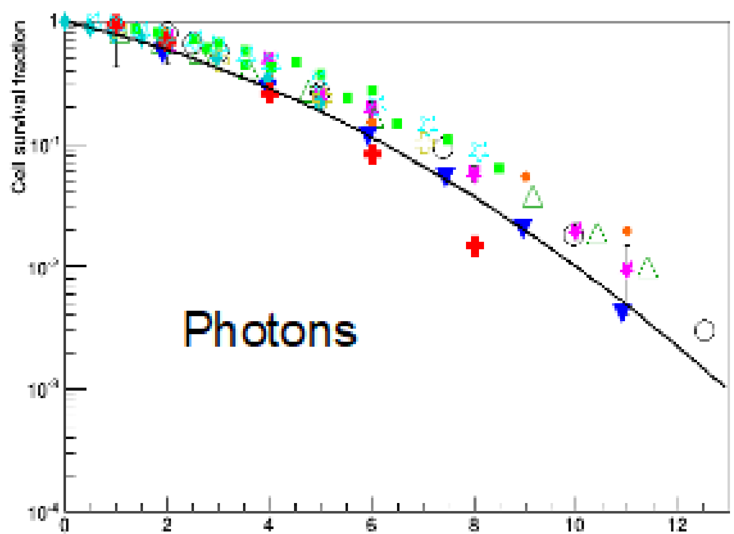
V79 cells



Protons
Exp. Calc.
Photon
Proton 0.7 6MeV
Proton 1.0 7MeV
Proton 1.4 1MeV
Proton 1.8 3MeV
Proton 5.0 1MeV
Dose (Gy)



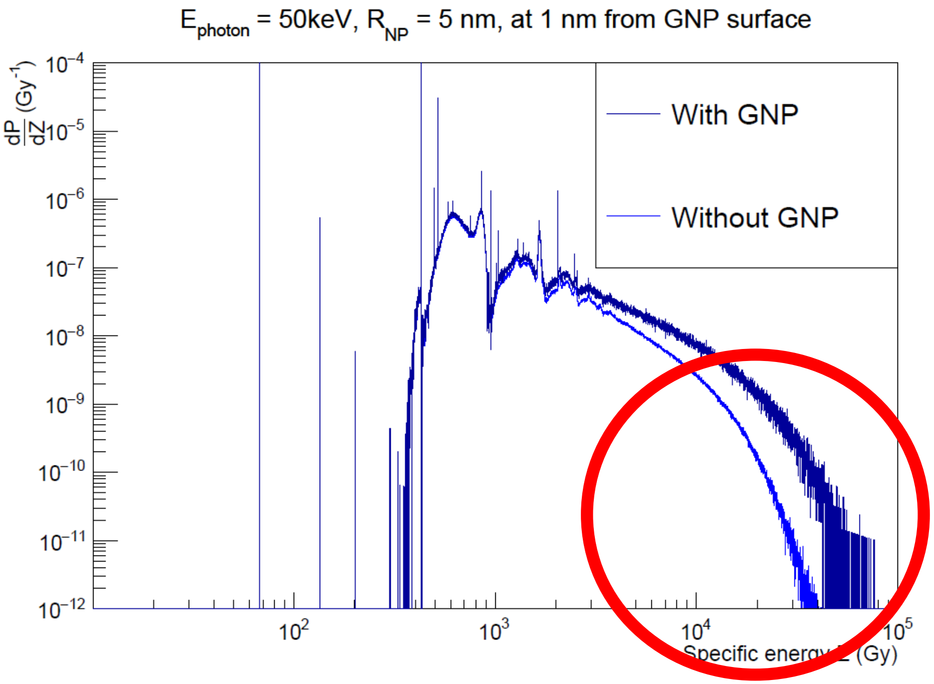
Carbon ions
Exp. Calc.
Photon
Cell survival fraction
Dose



Cell survival fraction
Photons

Context | Goal | State of the art | Material & method | Results 2/3

Nanodosimetry: similarities with hadrontherapy



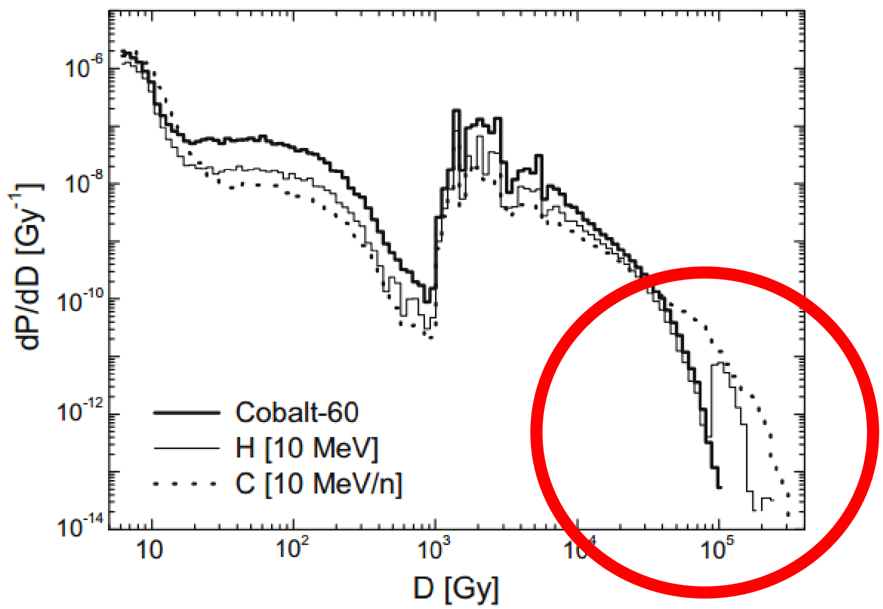
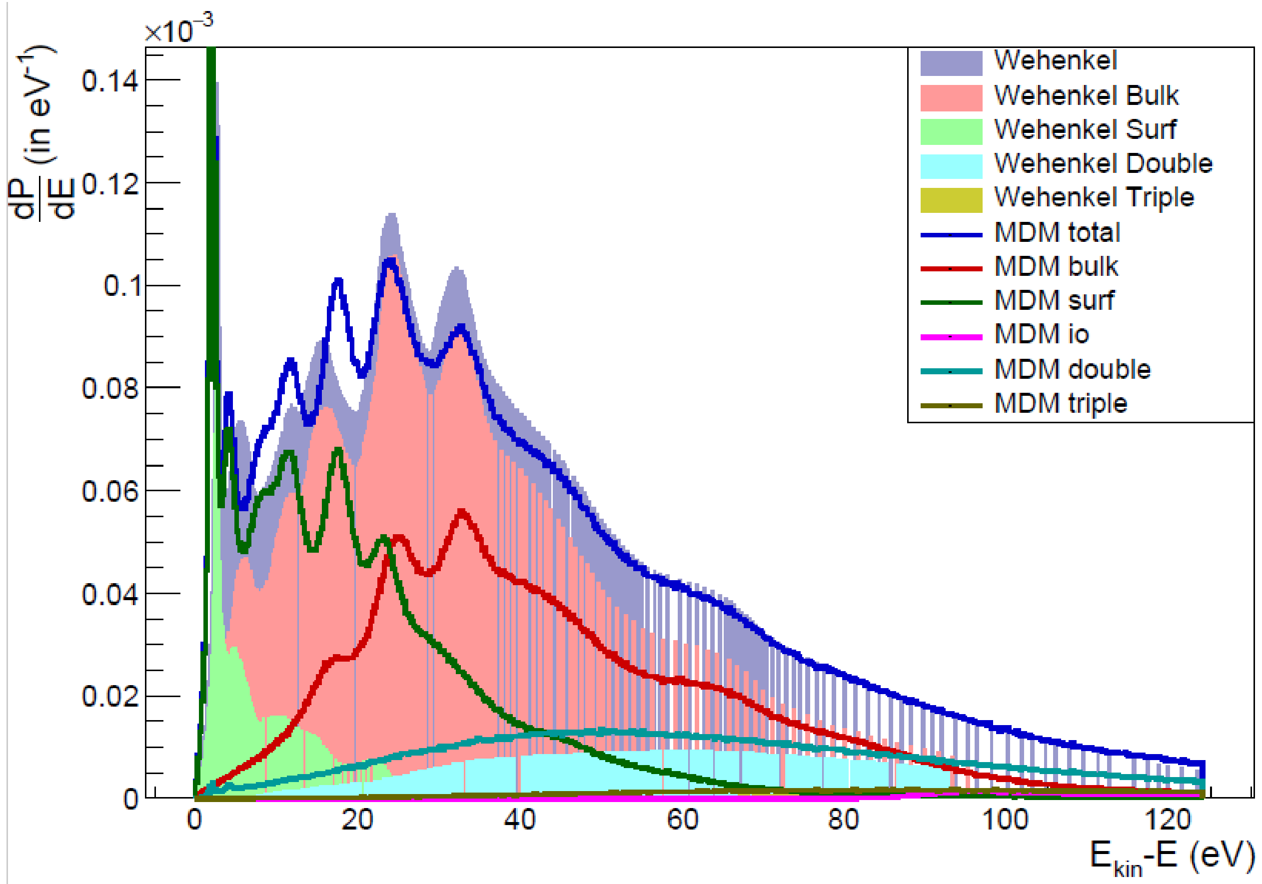


Fig. 2. Histogram of local dose calculated for a water sample of $50 \times 50 \times 10\ \mu m^3$ irradiated at a dose of 1 Gray with a beam of ^{60}Co *γ-rays*, H[10 MeV] and C[10 MeV/n]. The mesh resolution is 10 nm.

(8) M. Beuve, A. Colliaux, D. Dabli, D. Dauvergne, B. Gervais, G. Montarou, E. Testa, **Statistical effects of dose deposition in track-structure modelling of radiobiology efficiency**, *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms*, Volume 267, Issue 6, March 2009, Pages 983-988

Transmitted electron energy at 35 keV and 20 nm



(7) C. Wehenkel, **Mise au point d'une nouvelle méthode d'analyse quantitative des spectres de pertes d'énergie d'électrons rapides diffuses dans la direction du faisceau incident,** *Journal de physique*, vol. 36(2), 199-213, 1975