Biophysical Modelisation for innovative therapy : radiotherapy and nanoparticles

Inter-WP1/WP3 LabEx day – 2017-02-20

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Supervisor : **Michael BEUVE**, Co-supervisor : **Etienne TESTA**

Financial Support : LabEx PRIMES

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1) Context

- Radiosensitizing effect with NP experimentally observed but yet not fully understood

[1]

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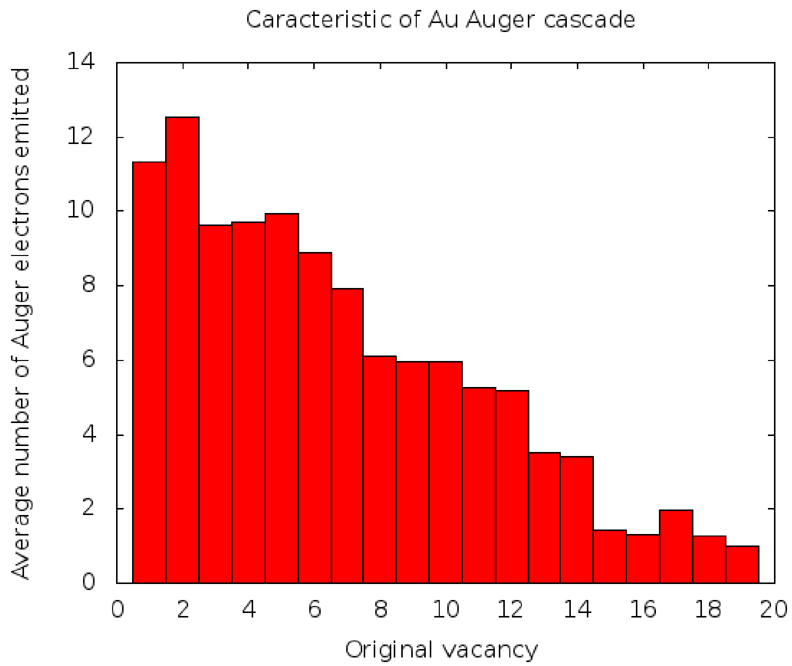

*Results from PJ Lartaud

- Origins :

Interaction gold/photon :
- Photoelectric effect and Auger cascade

→ Local boost of secondary electron production

[1]

1) Context

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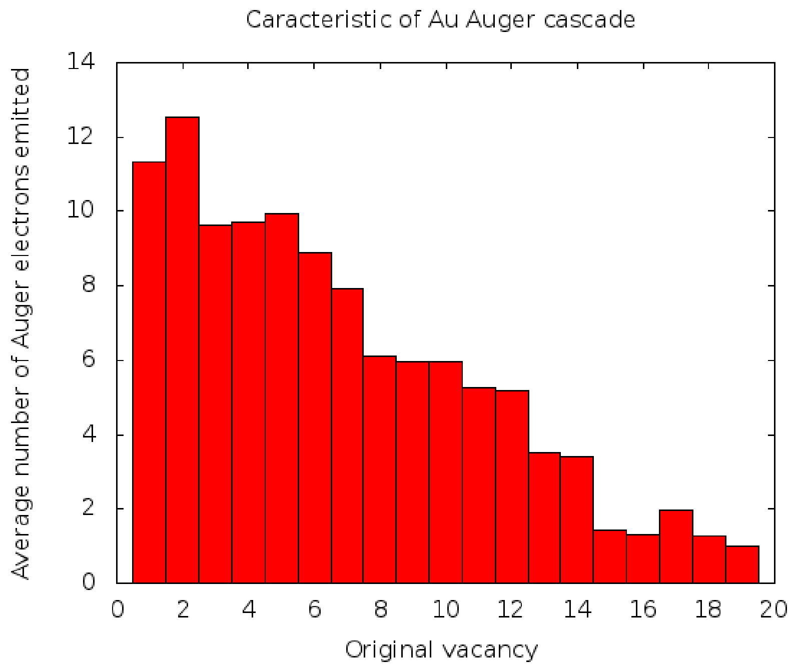

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⇒

local increase of the dose
+
local boost of free radicals production

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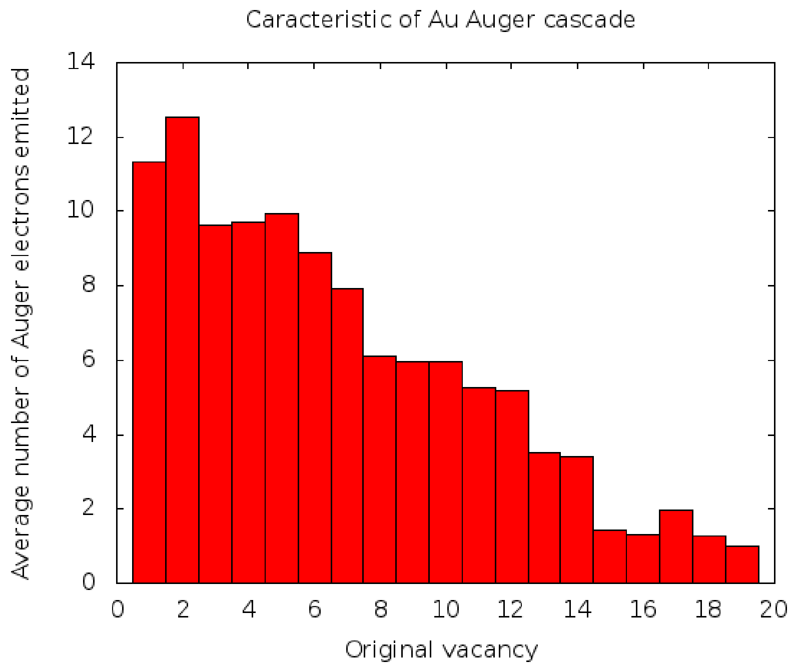

*Results from PJ Lartaud

- Origins :

Interaction gold/photon :
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→ Local boost of secondary electron production

local increase of the dose
+
local boost of free radicals production

increase

cell death

[1]

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2) Need for simulations

- Challenges

  - Time scale : 10^{-15} to 10^{-12} second
  - Spatial scale : **nano**-dosimetry

→ Effect which can’t be observed directly

→ Monte Carlo simulation

[2]

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3) Simulation aim (1) Physical-chemical quantification

MDM : Monte Carlo simulation

[3]

3) Simulation aim (1) Physical-chemical quantification

MDM : Monte Carlo simulation

Distribution of energy deposition on nanoscale

[3]

3) Simulation aim (1) Physical-chemical quantification

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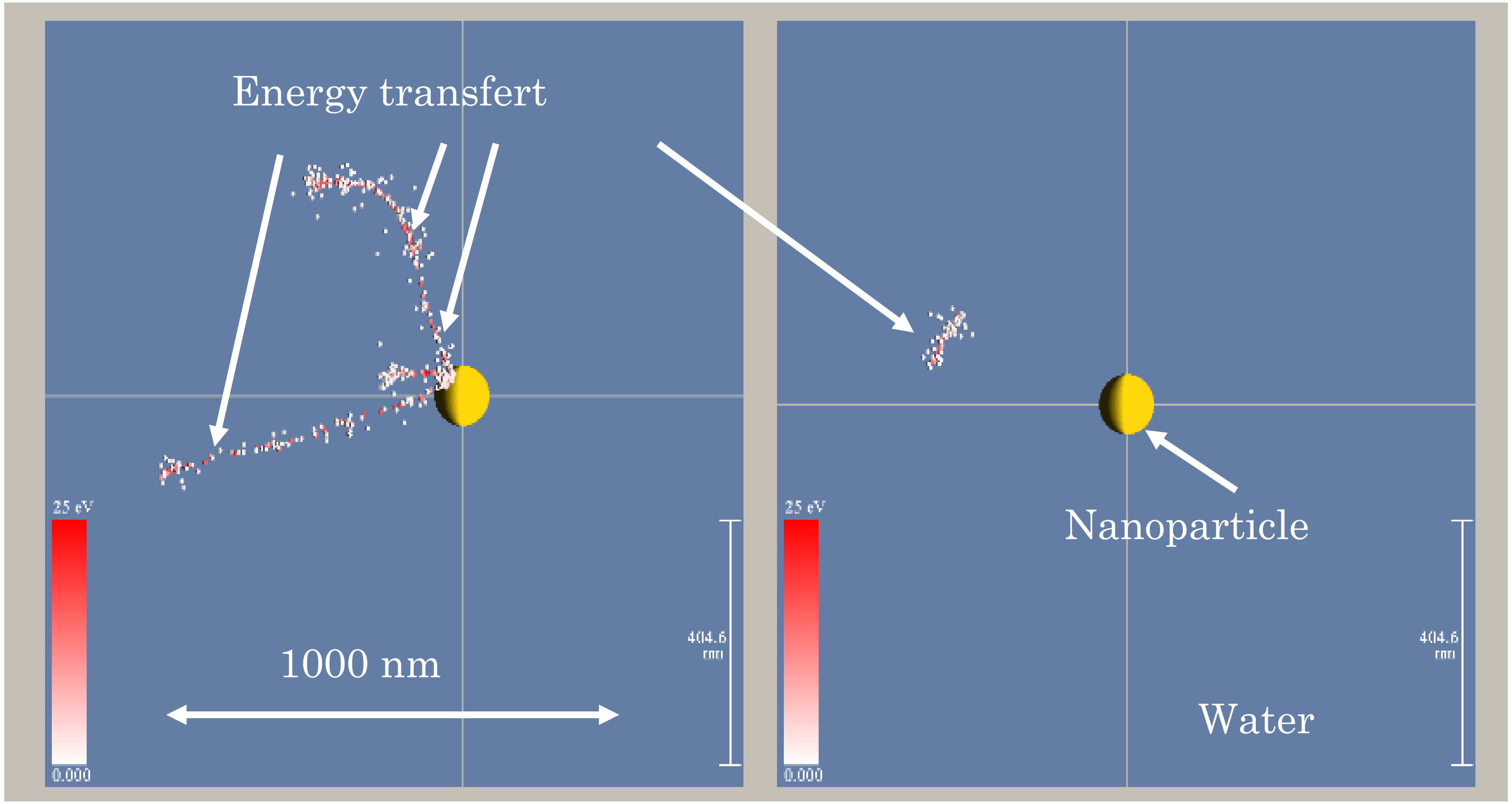
- Distribution of energy deposition on nanoscale
- Production of free-radicals

[3]

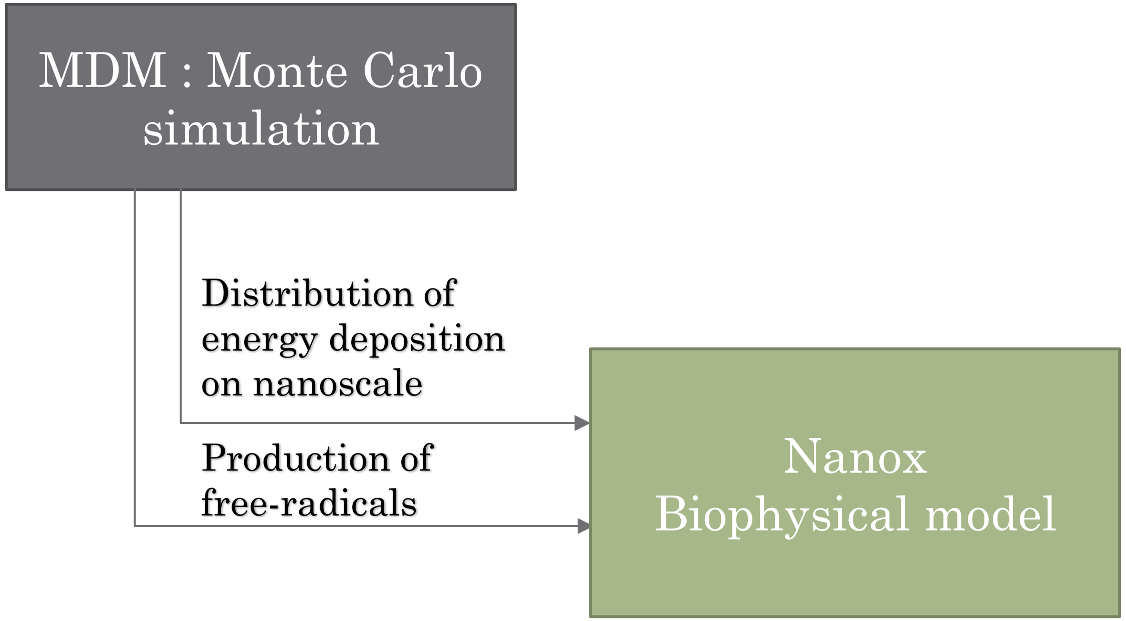
3) Simulation aim (1) Physical-chemical quantification



Track of a 20 keV photon interacting in gold VS in water (by Compton effect)

[4]

3) Simulation aim (2)
Predict the radiosensitizing effect



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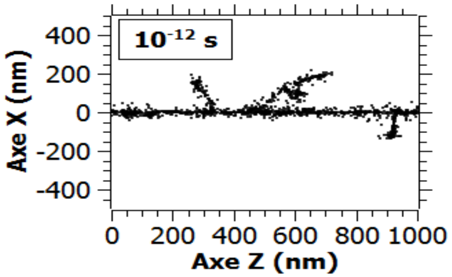
Distribution of energy deposition on nanoscale

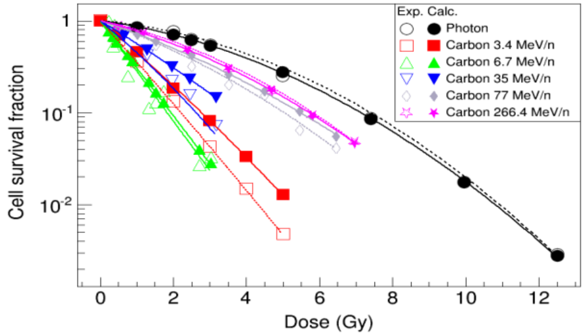
Production of free-radicals (2)



Trace irradiation ion carbone 65 MeV (1)

Nanox Biophysical model

Cell survival curves



Nanox VS Exp. : Survie cellulaire pour irradiation de photons/carbons de cellules type V79 (3)

Cell death
Radiosensitizing effect

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

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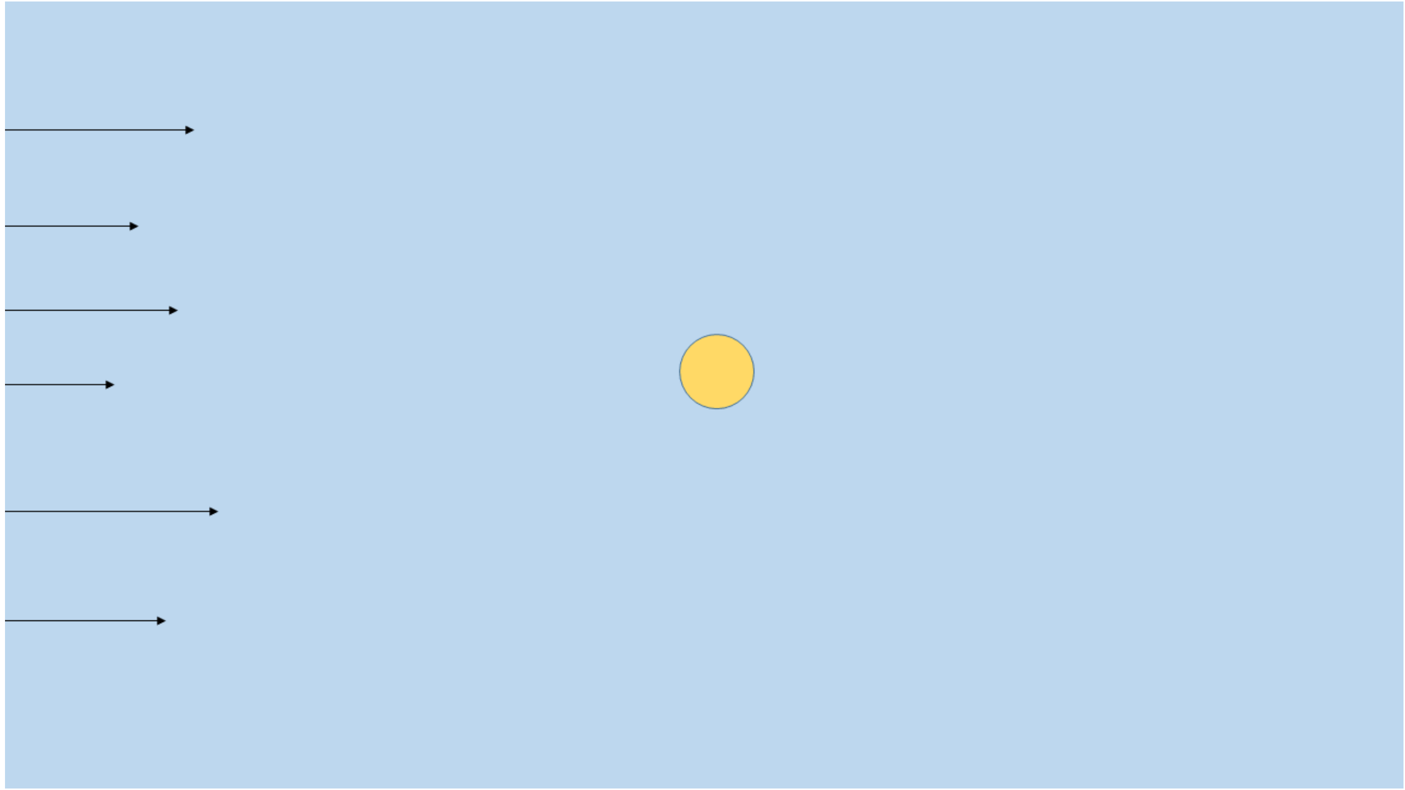
4.1) Physics models (1)



[6]

4.1) Physics models (2)

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

Table : Summary of the interactions simulated in MDM

[7]

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Table : Summary of the interactions simulated in MDM

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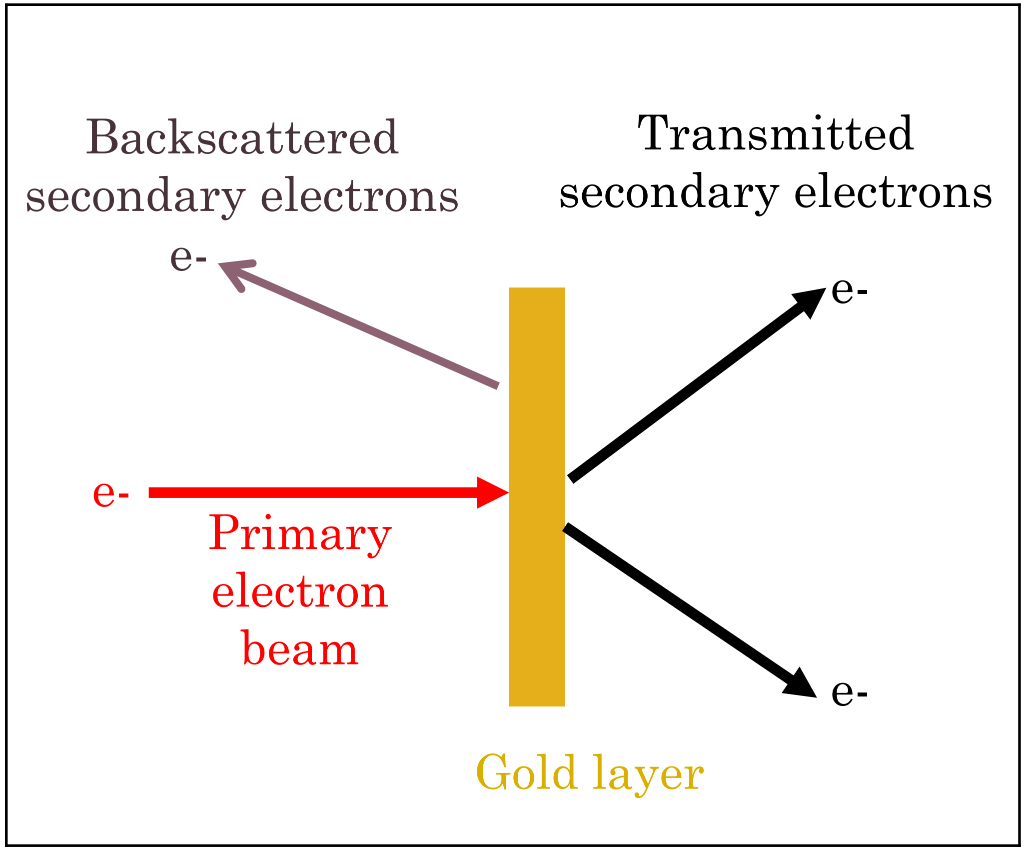
4.2) Benchmarking (1) Simulation set up

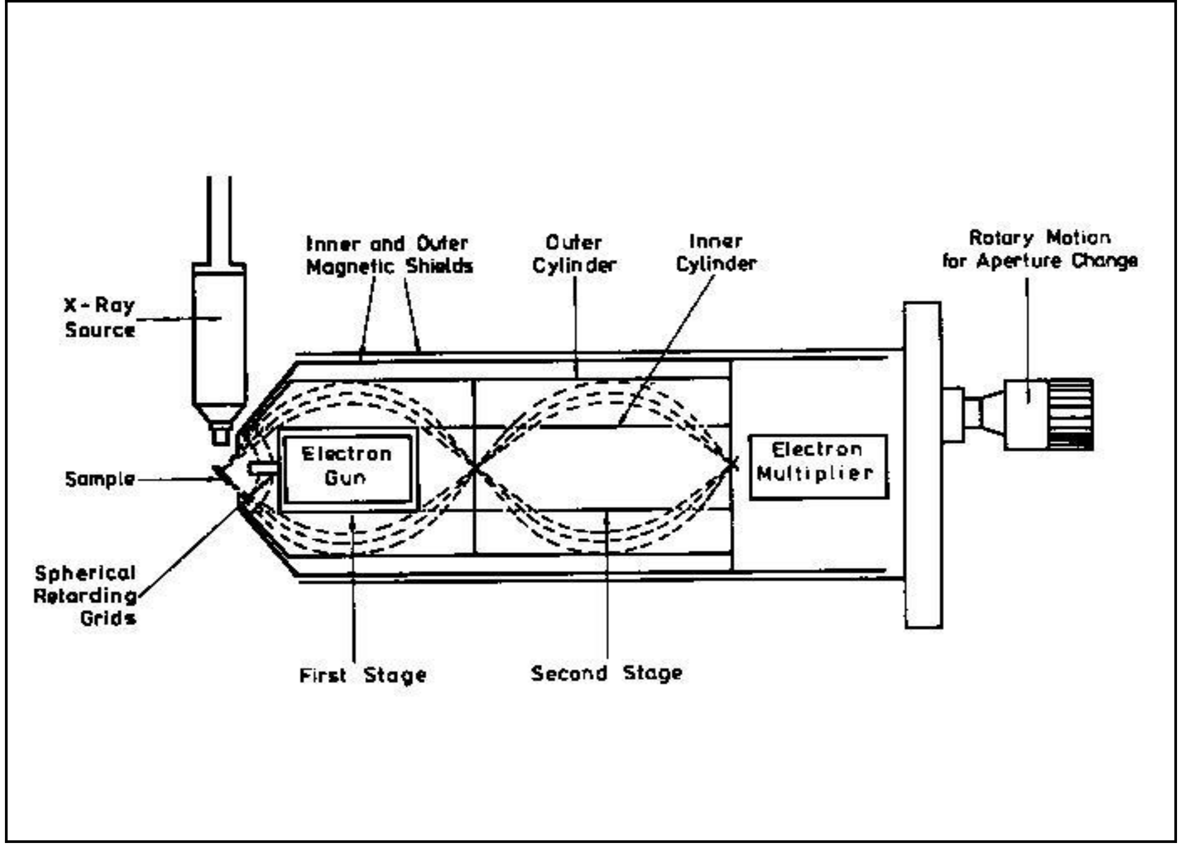
1) Yield of transmitted electrons
2) Yield of backscattered electrons
3) Energy of backscattered electrons

Simulation



4.2) Benchmarking (1) Simulation set up

Experimental work



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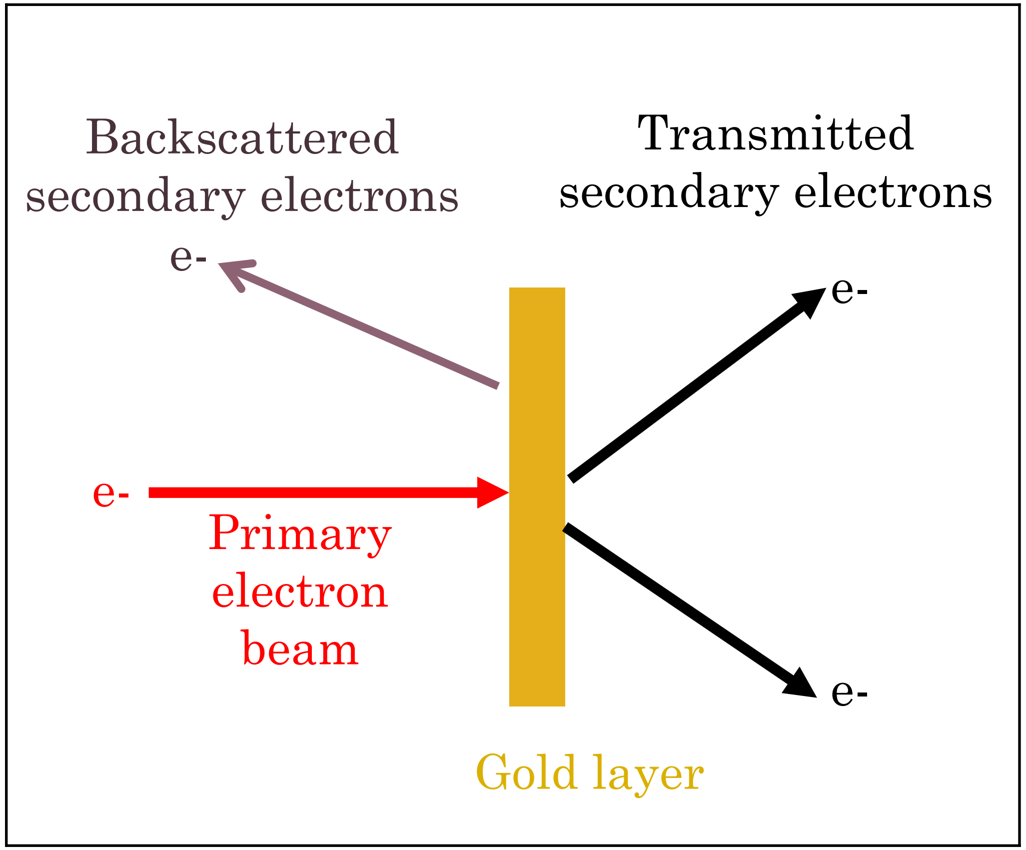

[8]

4.2) Benchmarking (2)
Yield of transmitted electrons (1)

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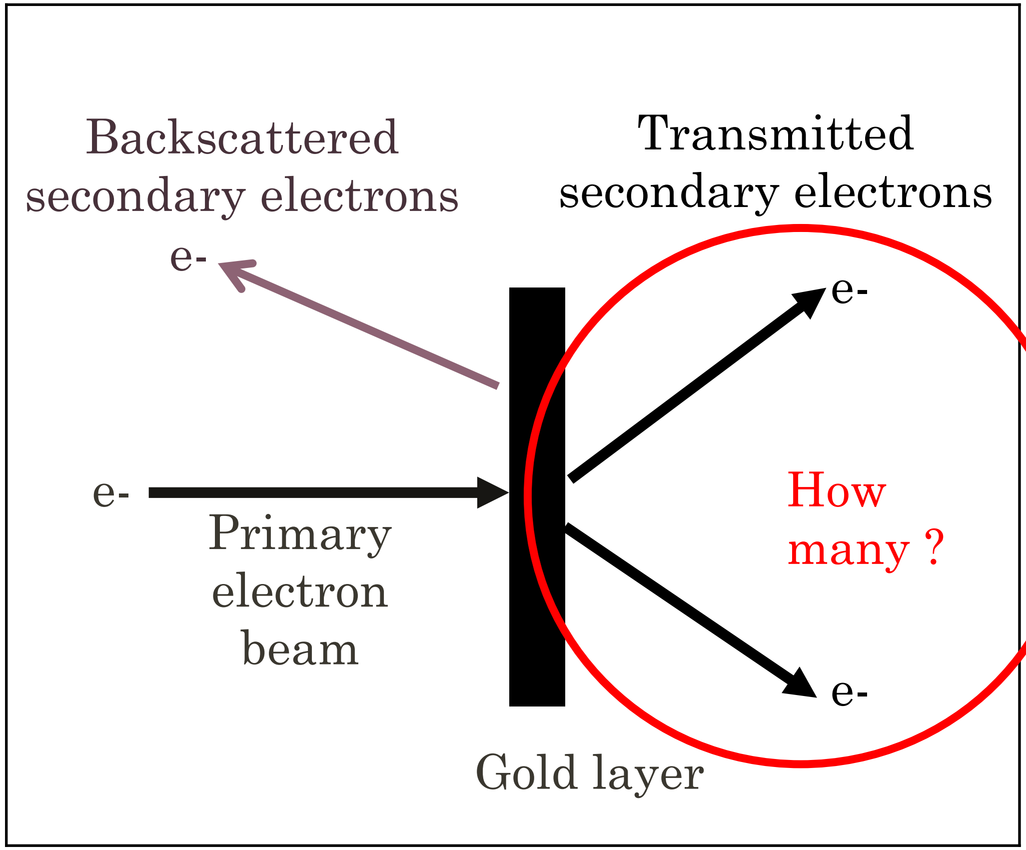
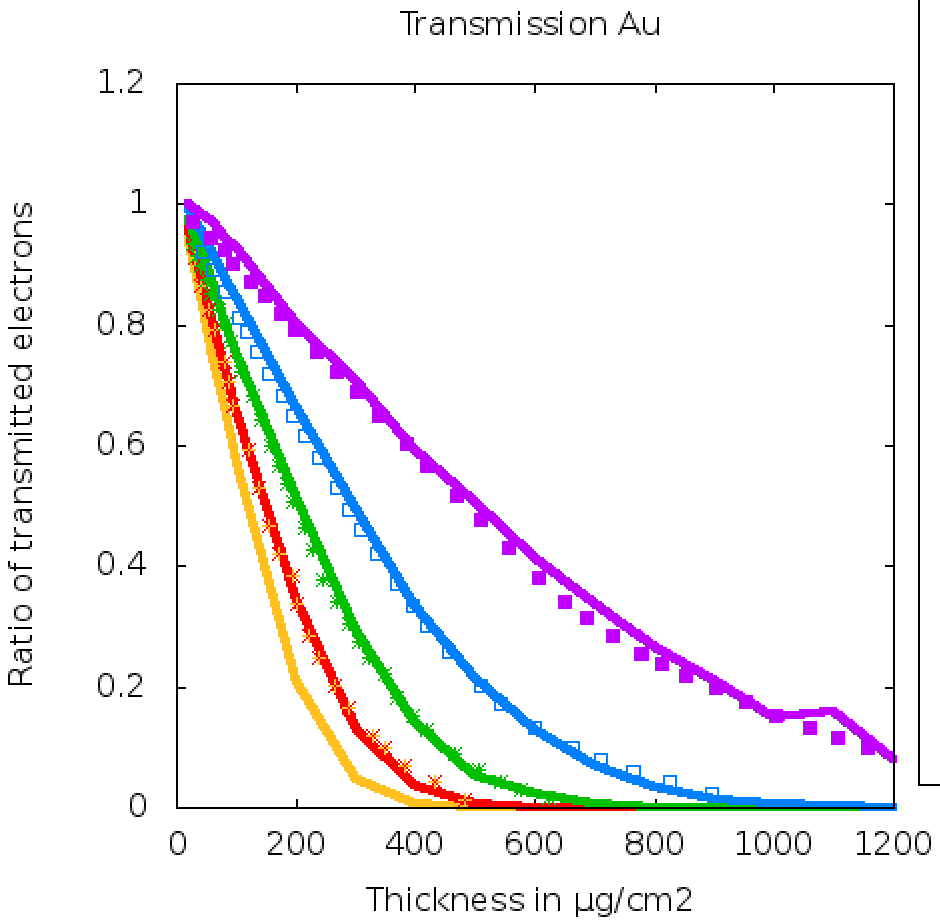
Simulation



4.2) Benchmarking (2) Yield of transmitted electrons (2)

Energy > 50 eV



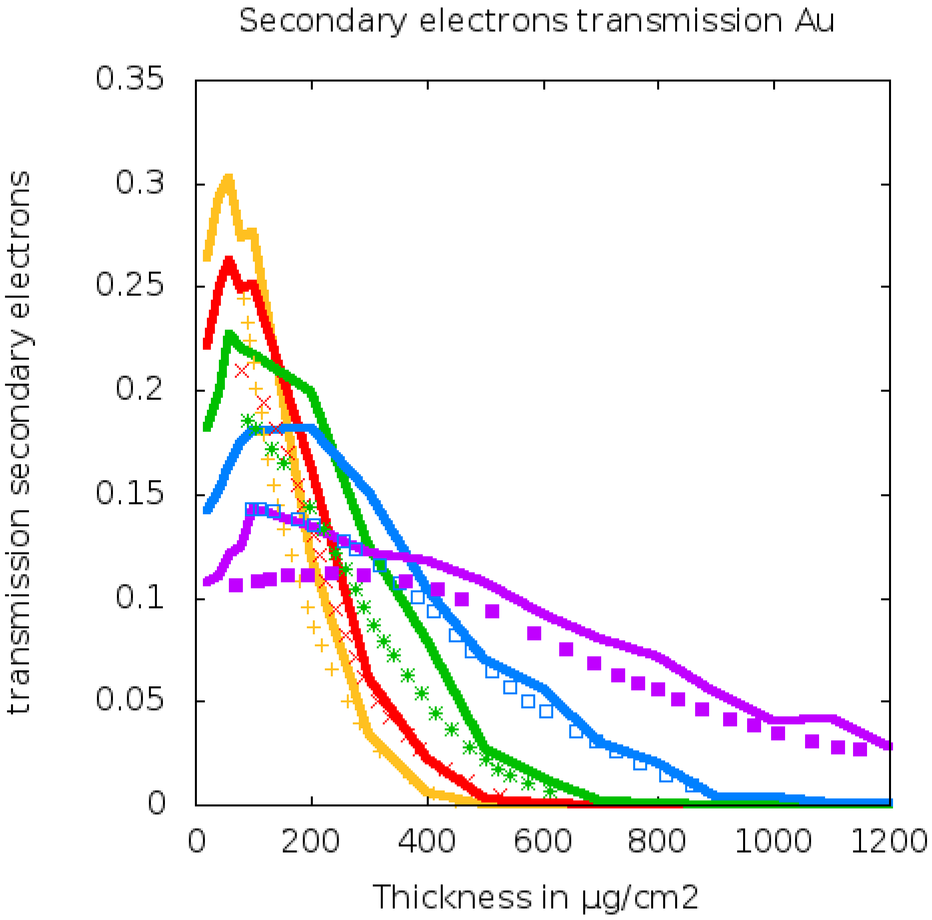
Primary beam energy :

9.3 keV
11 keV
13.4 keV
17.3 keV
25.2 keV

- Solid lines : Simulation
- Dots : Experimental (2)

100 μg/cm2 = 51,76 nm

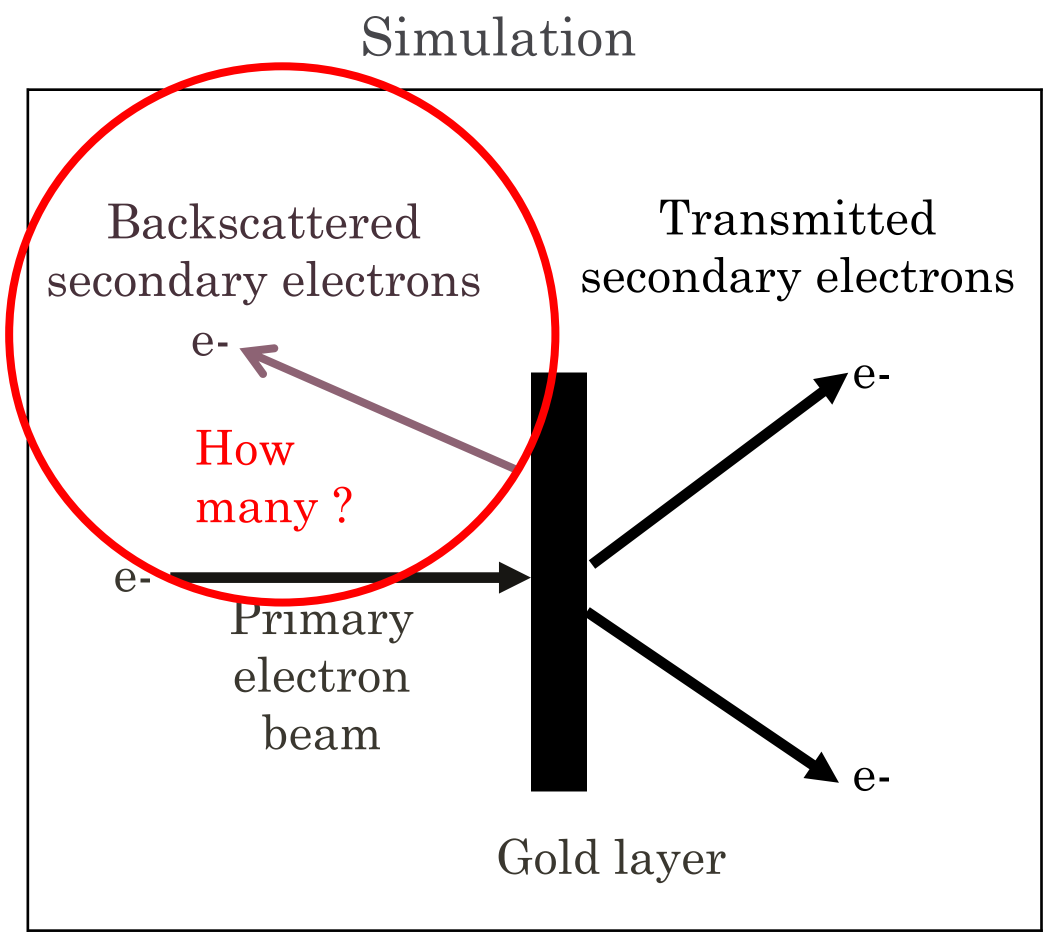
Energy < 50 eV



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

4.2) Benchmarking (3)
Yield of backscattered electrons (1)

1) Yield of transmitted electrons
2) Yield of backscattered electrons
3) Energy of backscattered electrons



4.2) Benchmarking (3) Yield of backscattered electrons (1)

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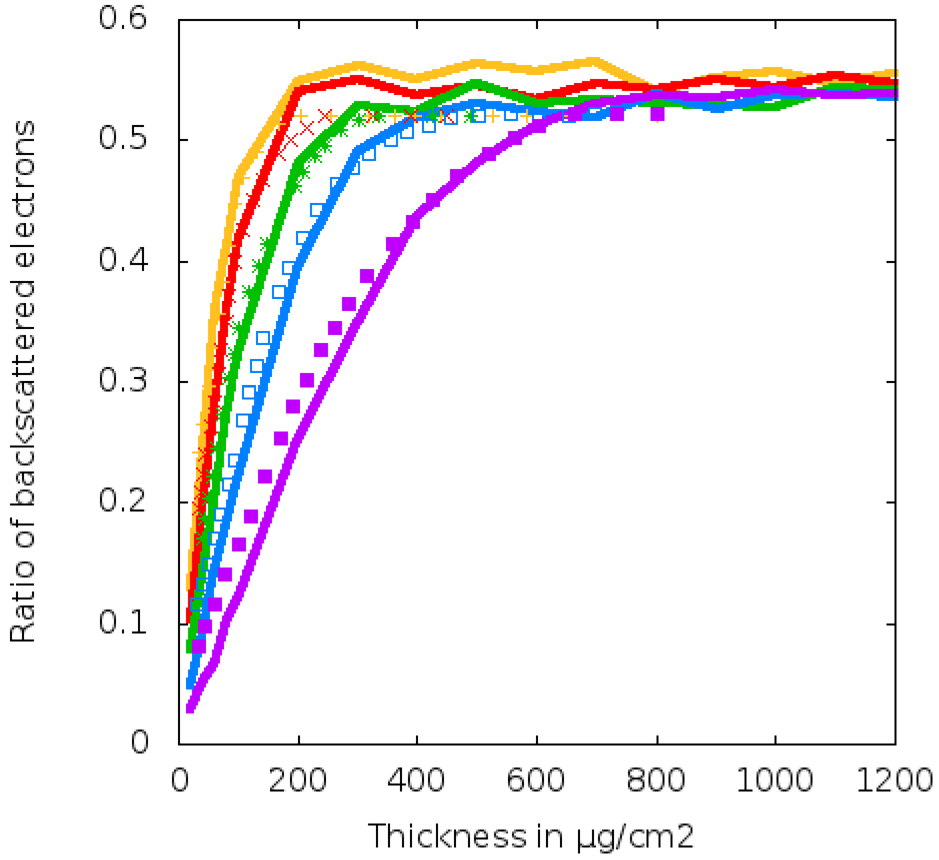

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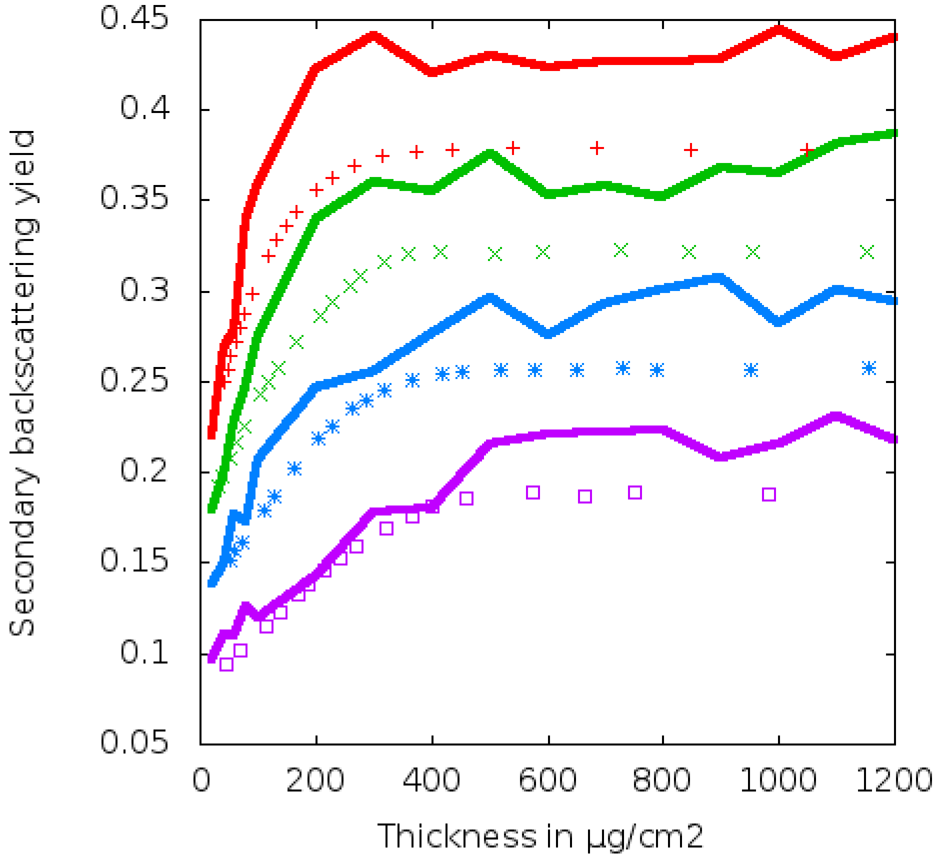
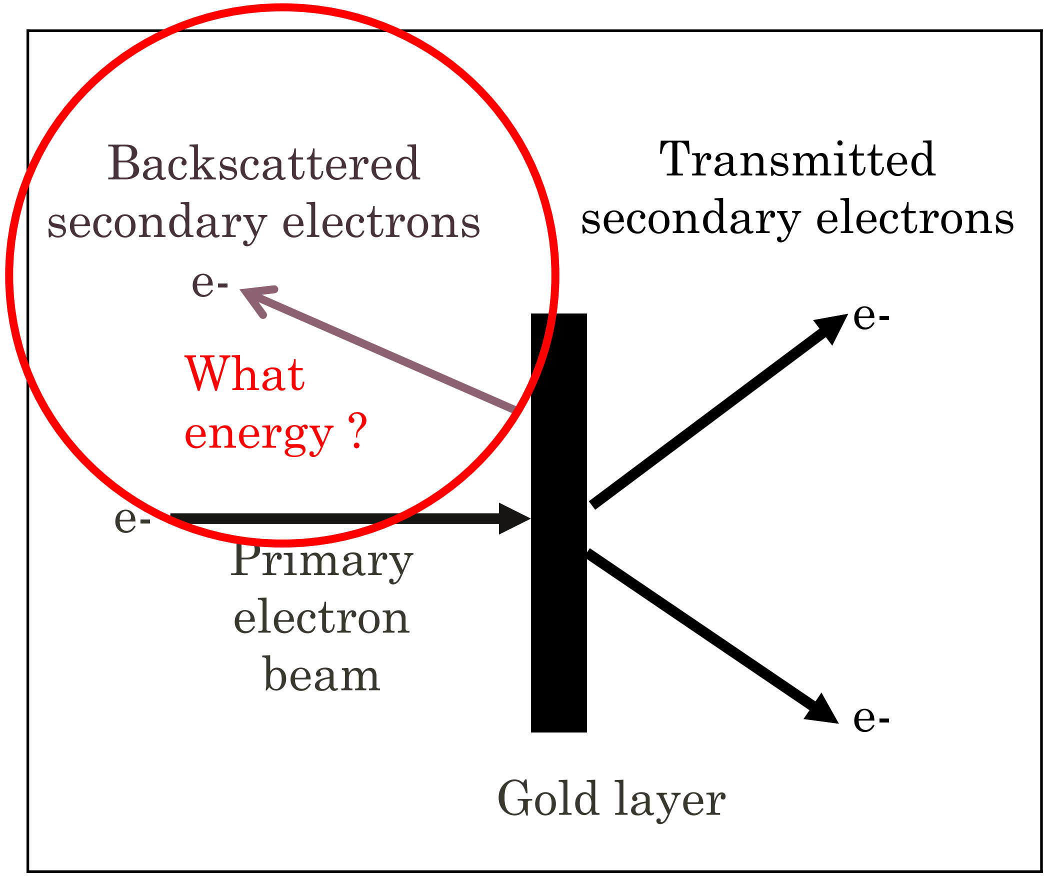


(2) Reimer, L. and Drescher, H. (1977). Secondary electron emission of 10-100 kev electrons from transparent films of al and au. *Journal of Physics D: Applied Physics*, 10(5):805

4.2) Benchmarking (4)
Energy of backscattered electrons (1)

1) Yield of transmitted electrons
2) Yield of backscattered electrons
3) Energy of backscattered electrons

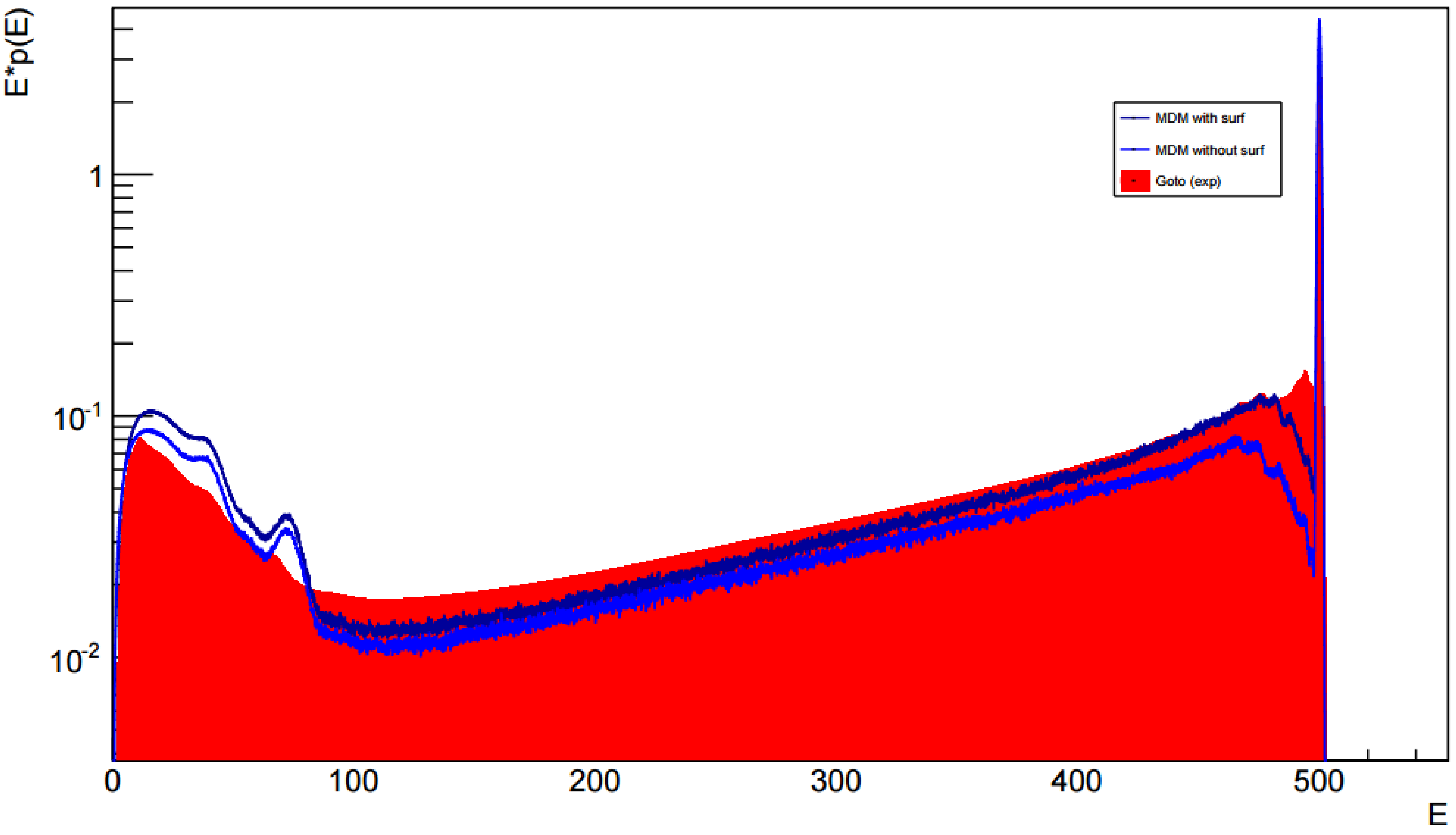
Simulation



4.2) Benchmarking (4)
Energy of backscattered electrons (2)

Energy distribution of backscattered electrons on a thick gold foil for primary electron beam at 500 eV, normalized to the bin size, the solid angle and the number of primary particles

Conclusion : globally accurate results but can be raffined



(5) Exp. Work from : 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)

4.2) Benchmarking (5) Conclusion

- Overall good results
  - Transmission/backscattering yields good for primary and secondary electrons for primary particle energy range [10:80] keV

  ⟶ Good production of particles expected out of NPs
  - Energy spectrum comparable to experience

  ⟶ Still requires to develop/adjust some models (surface plasmons under construction!)
- Limited to tests on a macroscopic solid but results convincing enough to go to NP stage

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5) Coming next !

- Nanodosimetry profiles [ongoing work]
  - If an effect is observed, coupling with Nanox
  - If no effect : free radicals production data
- Short term questions :
  - Is there really a dosimetric effect coming from the Auger cascade ?
  - How accurate the simulation has to be : atomic model enough, solid physics model with plasmon (bulk, surface) ? (6)
- Long term goal :
  - Quantify the effect (6)
  - Find the key parameters to get an optimum in radiotherapy treatment (6)

(6) K. Haume et al., Gold nanoparticles for cancer radiotherapy: a review, *Cancer Nanotechnology,* Basic Translational and Clinical Research, 2016, **7**:8

Thanks for listening !

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

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6) Biblio

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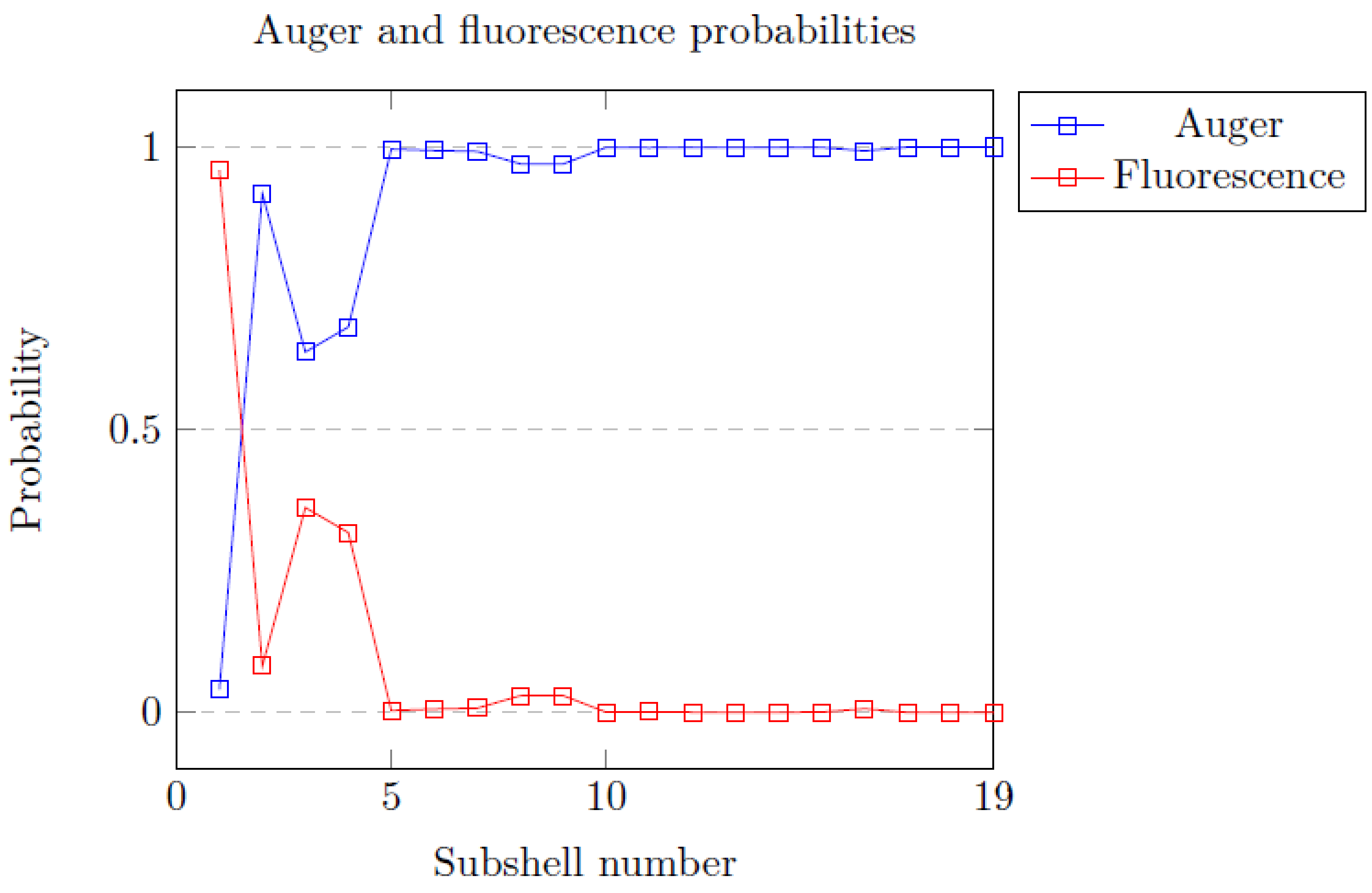
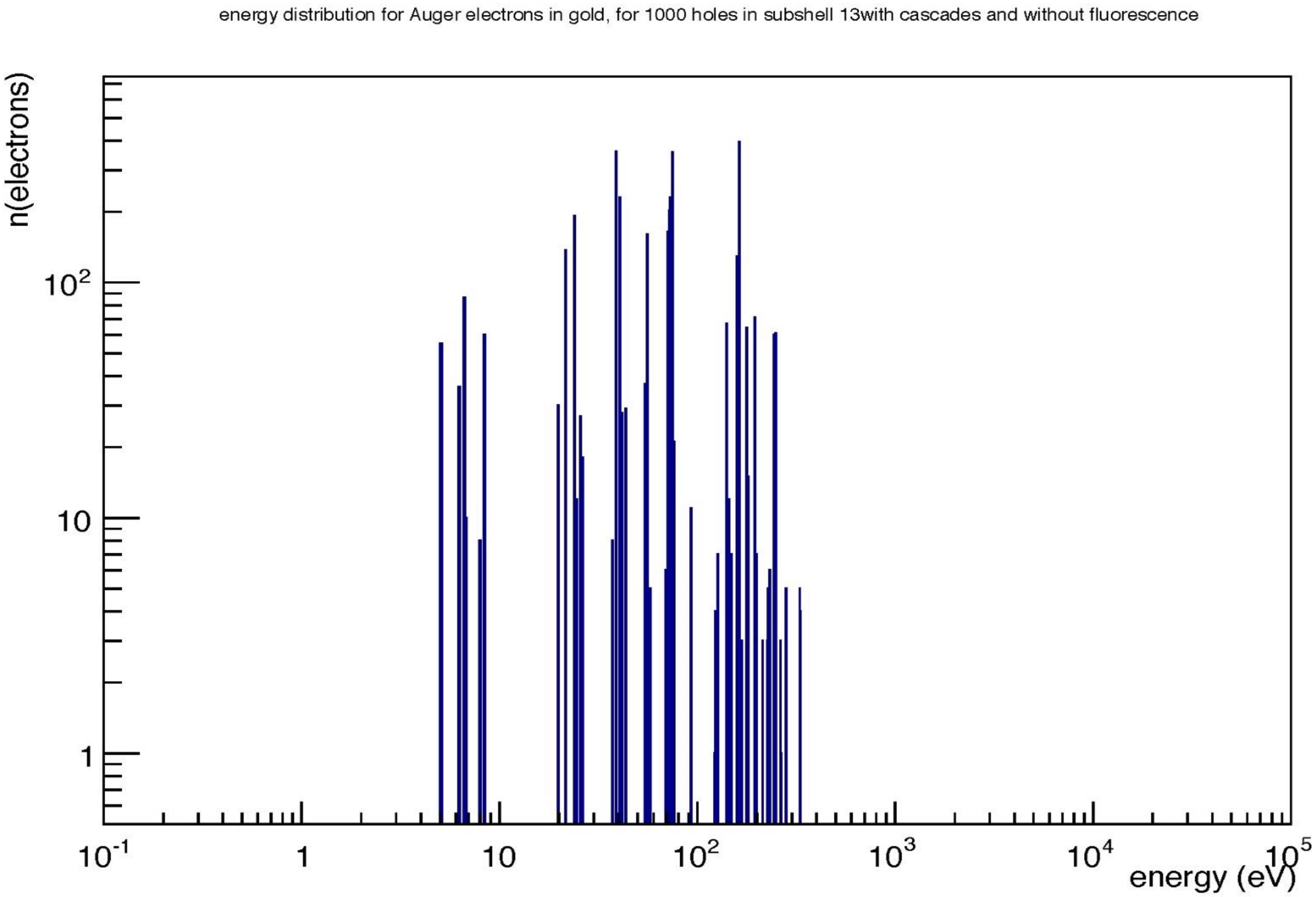
ANNEXE (1)

couche	nb e^-	sous-couche	label	spin	Energy (ev)	n° MDM
K	2	$1s^2$	K	$1s_{1/2}$	80725	1
L	8	$2s^2$	L1	$2s_{1/2}$	14353	2
		$2p^6$	L2L3	$2p_{1/2}$	12534	3
				$2p_{3/2}$	11919	4
M	18	$3s^2$	M1	$3s_{1/2}$	3425	5
		$3p^6$	M2M3	$3p_{1/2}$	3148	6
				$3p_{3/2}$	2743	7
		$3d^{10}$	M4M5	$3d_{3/2}$	2291	8
				$3d_{5/2}$	2206	9
N	32	$4s^2$	N1	$4s_{1/2}$	762.1	10
		$4p^6$	N2N3	$4p_{1/2}$	642.7	11
				$4p_{3/2}$	546.3	12
		$4d^{10}$	N4N5	$4d_{3/2}$	353.2	13
				$4d_{5/2}$	335.1	14
		$4f^{14}$	N6N7	$4f_{5/2}$	87.6	15
				$4f_{7/2}$	84.0	16
O	18	$5s^2$	O1	$5s_{1/2}$	107.2	17
		$5p^6$	O2O3	$5p_{1/2}$	74.2	18
				$5p_{3/2}$	57.2	19
		$5d^{10}$	O4O5	$5d_{3/2}$	11.66	20
P	1	$6s^1$	P1	$6s_{1/2}$	9.2257	21
TOTAL	79					

ANNEXE (2)

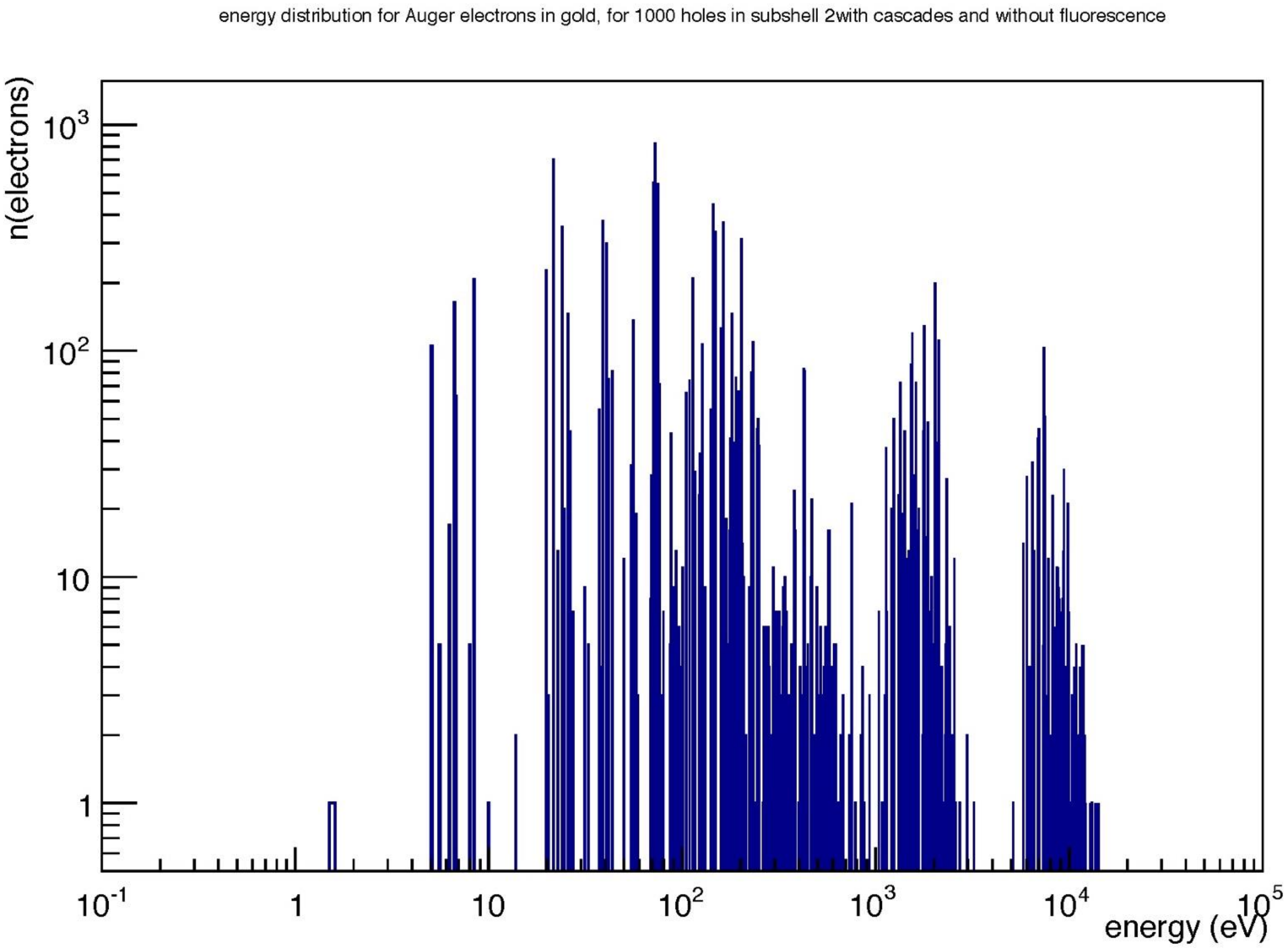

Auger and fluorescence probabilities
Probability
1
0.5
0
0
5
10
19
Subshell number
Auger
Fluorescence

ANNEXE (3)



- Original vacancy : 13
- 1000 holes
- Energy distribution of emitted Auger electrons

ANNEXE (4)



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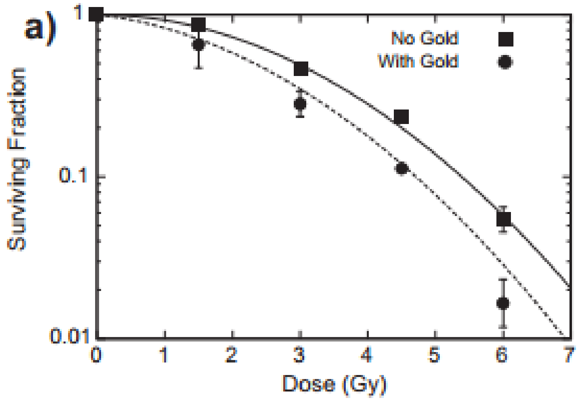
- 1000 holes
- Energy distribution of emitted Auger electrons

ANNEXE (5)

- Piste explorée, résultats prometteurs

Modèle	Limites	Nouveau modèle
Physico-chimique : Ex : Geant4-DNA	En cours de développement Précision nanométrique limitée à l'eau	MDM
Biophysique : Ex : LEM	Effets stochastiques partiellement simulés	Nanox



- Cellules MDA-MB-231 avec photons à 6 MV

S. J. McMahon et al., Radiotherapy and Oncology 100 (2011) 412-416