

Biophysical Modelisation for innovative therapy : radiotherapy and nanoparticles

Inter-WP1/WP3 LabEx day – 2017-02-20

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Financial Support : LabEx PRIMES



Table of content

- **1) Context**
- **2) Need for simulations**
- **3) Simulation aims**
 - Physical-chemical quantification
 - Radiosensitizing effect prediction
- **4) Monte Carlo simulation MDM**
 - Physical models
 - Benchmarking
- **5) Coming next**
- **6) Biblio**

1) Context

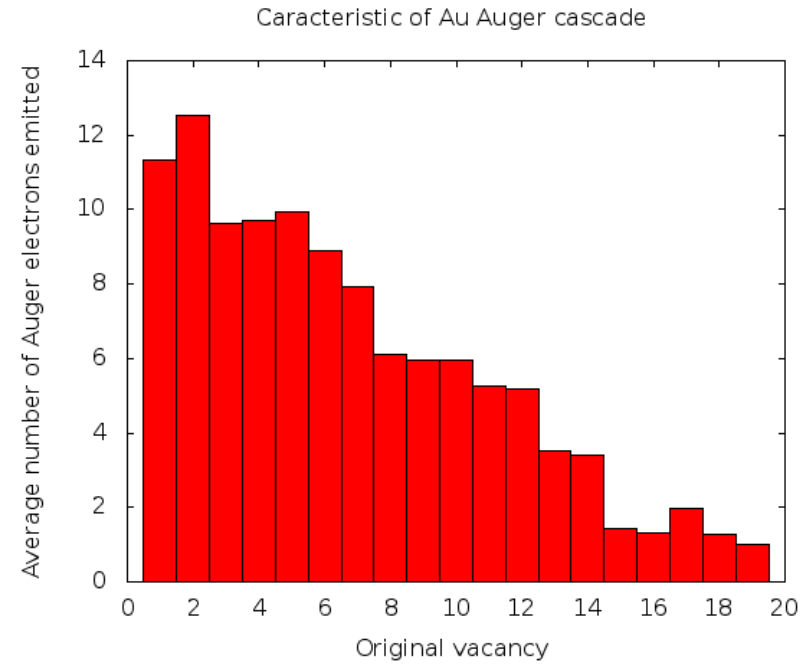
- Radiosensitizing effect with NP experimentally observed but yet not fully understood

1) Context

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

- Origins :

Interaction gold/photon :
- Photoelectric effect and Auger cascade
→ Local boost of secondary electron production

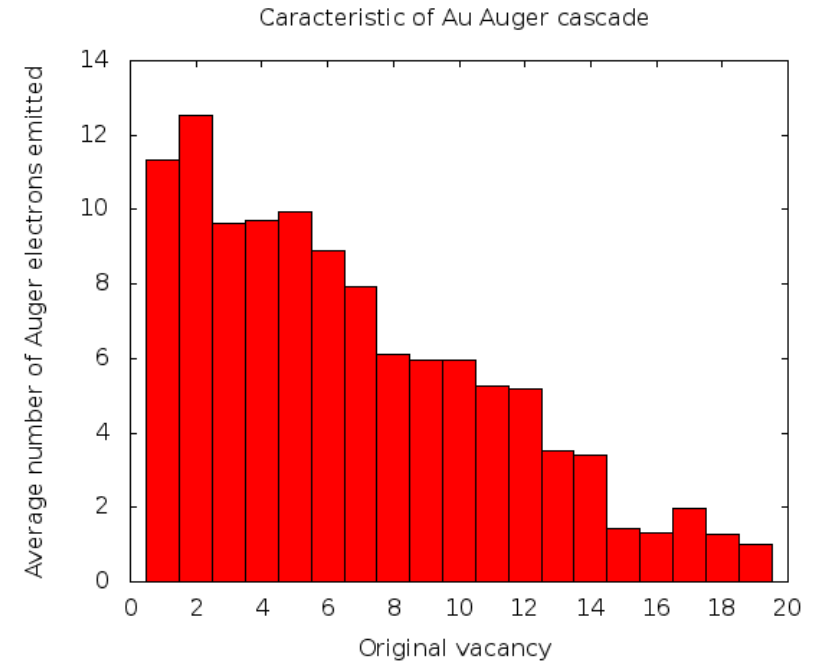


*Results from PJ Lartaud

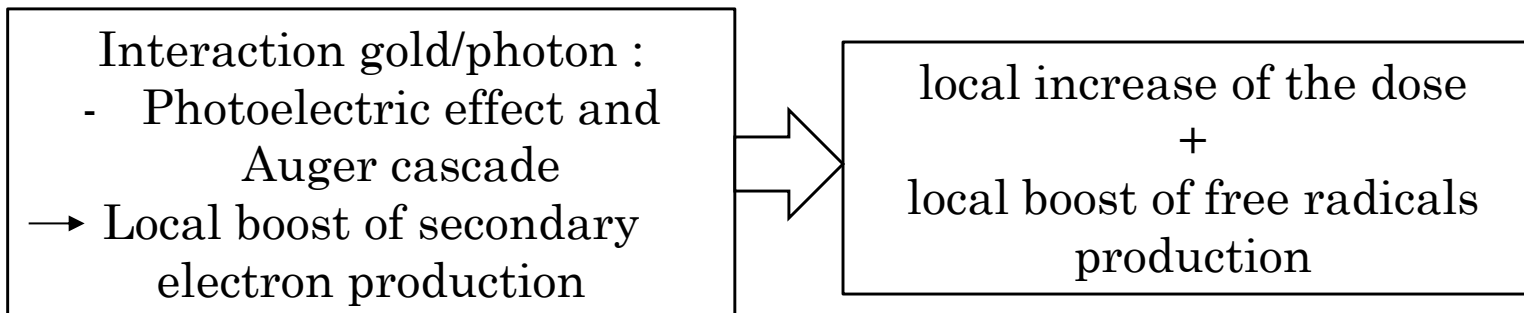
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- Radiosensitizing effect with NP experimentally observed but yet not fully understood

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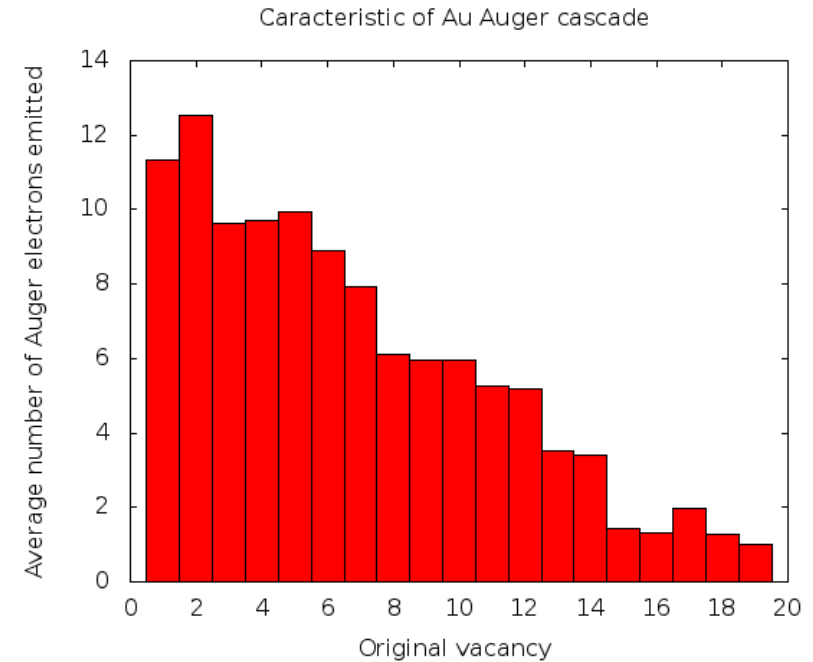
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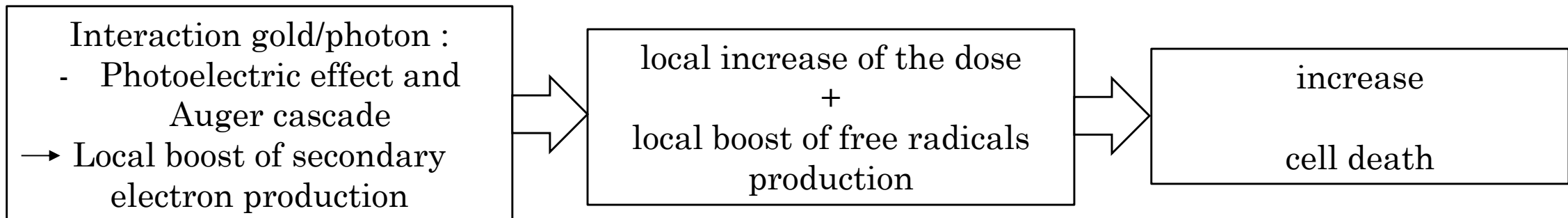


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2) Need for simulations

- Challenges

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

➔ Effect which can't be observed directly

➔ Monte Carlo simulation

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3) Simulation aim (1)

Physical-chemical quantification

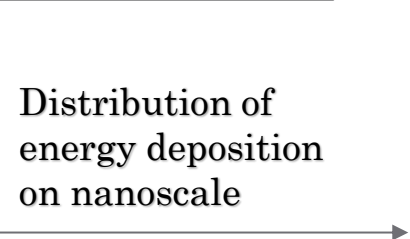
MDM : Monte Carlo
simulation

3) Simulation aim (1)

Physical-chemical quantification

MDM : Monte Carlo
simulation

Distribution of
energy deposition
on nanoscale



3) Simulation aim (1)

Physical-chemical quantification

MDM : Monte Carlo
simulation



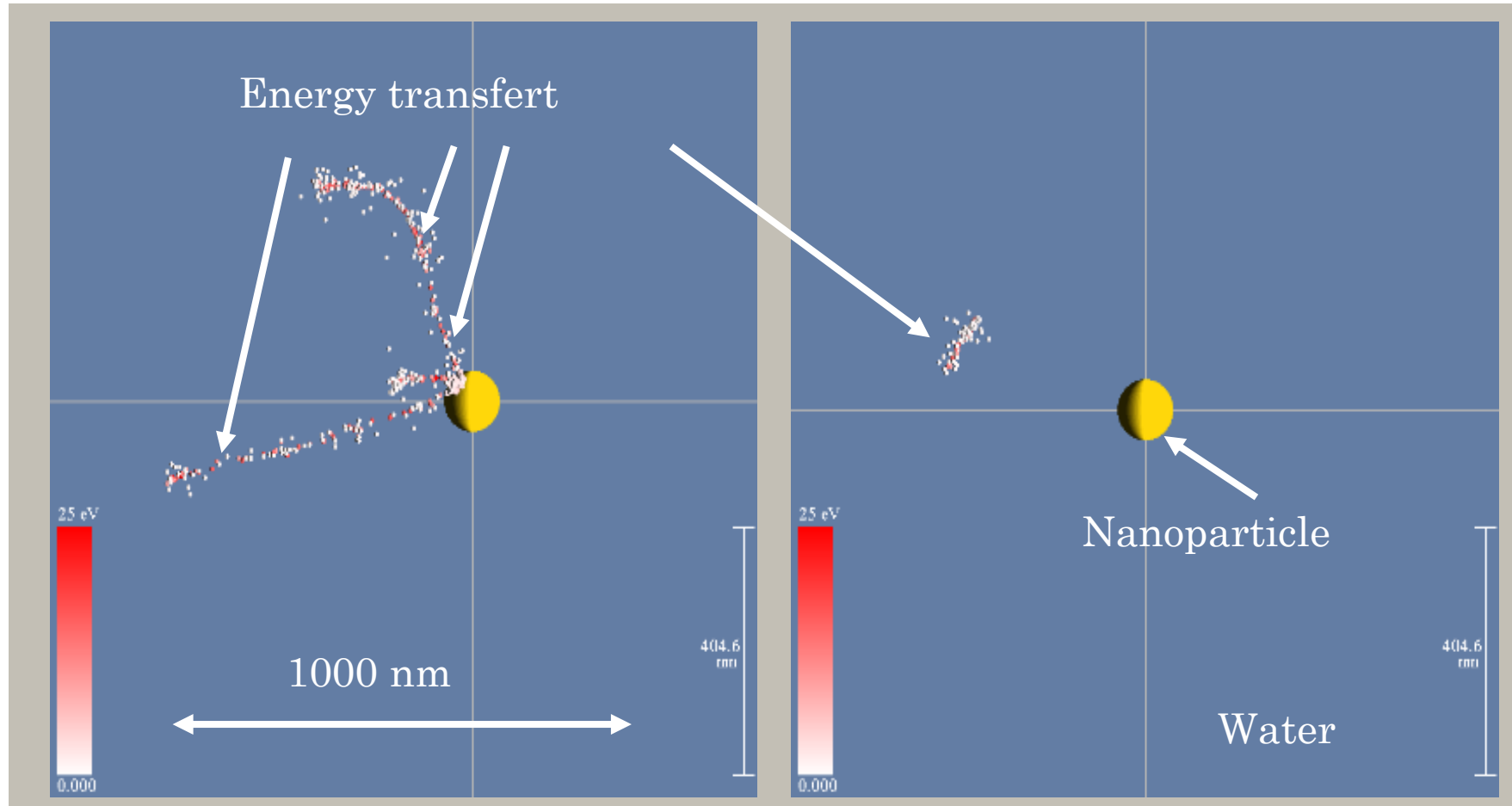
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graph TD; A[MDM : Monte Carlo simulation] --> B[Distribution of energy deposition on nanoscale]; A --> C[Production of free-radicals];
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Distribution of
energy deposition
on nanoscale

Production of
free-radicals

3) Simulation aim (1)

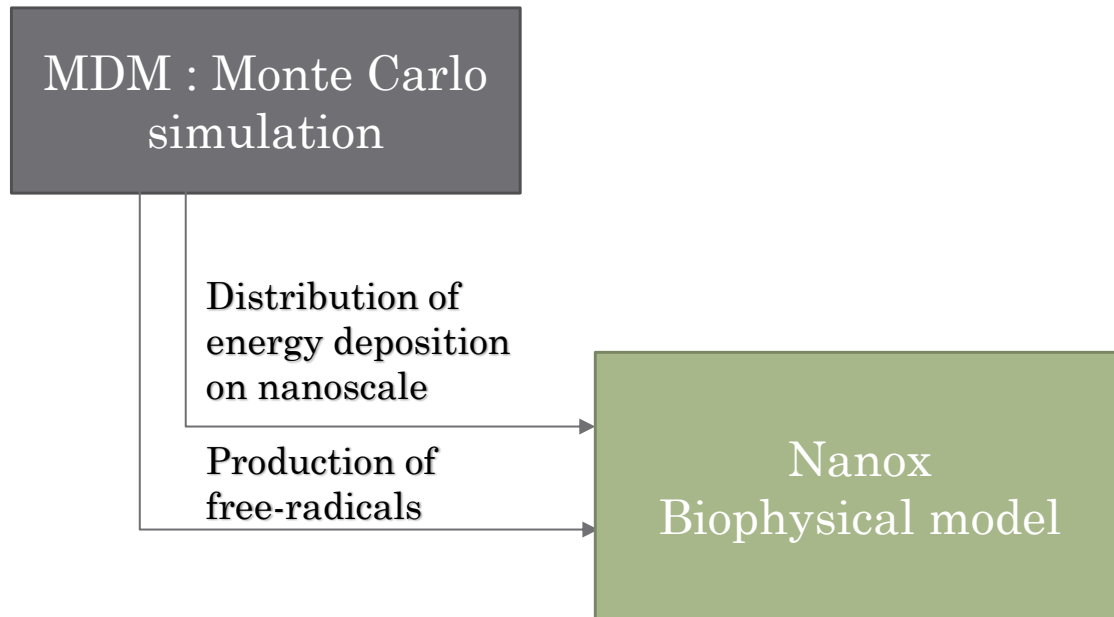
Physical-chemical quantification



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

3) Simulation aim (2)

Predict the radiosensitizing effect



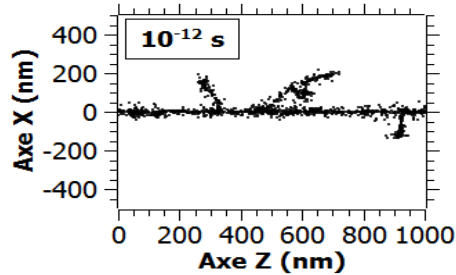
3) Simulation aim (2)

Predict the radiosensitizing effect

MDM : Monte Carlo simulation

Distribution of energy deposition on nanoscale

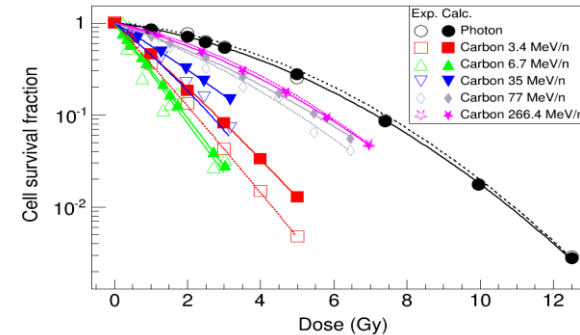
Production of free-radicals (2)



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)

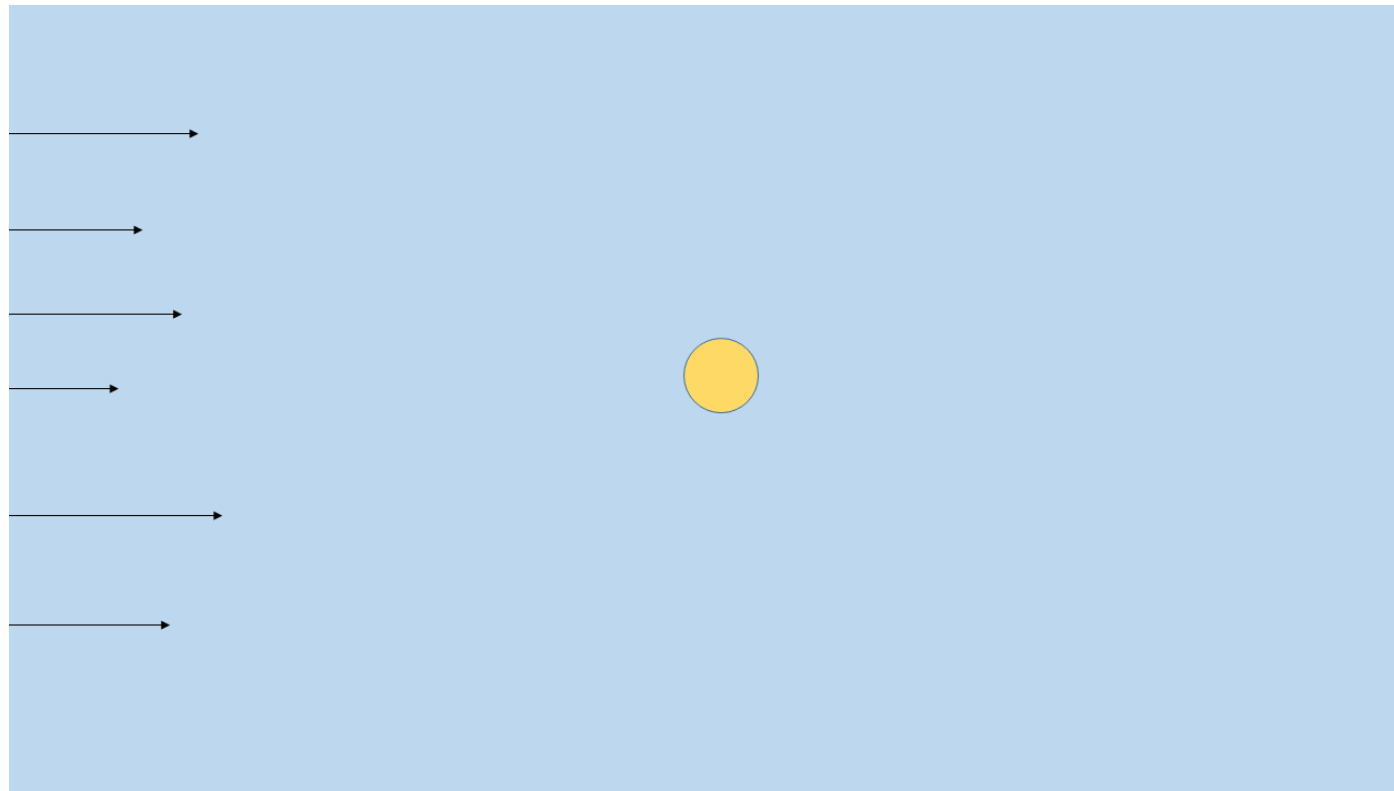
Cell death
Radiosensitizing effect

(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)



4.1) Physics models (2)

Particle	Process	MDM		"Standard Simulation"	
		Metal (gold)	Water	Metal (gold)	Water
Electrons	Phonons	++		++	
	Plasmons (surface, volume) (solid physics model)	++			
	Core Ionization (atomic model)	++	++	++	++
	Elastic scattering	++	++	++	++
	Decay (Auger and fluorescence)	++	++	++	++
	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

4.1) Physics models (2)

Particle	Process	MDM		"Standard Simulation"	
		Metal (gold)	Water	Metal (gold)	Water
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	Electrons attachment		++		++
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	Surface barrier : affinity function	++	++		
Photons	Compton scattering	++	++	++	++
	Photoelectric effect	++	++	++	++

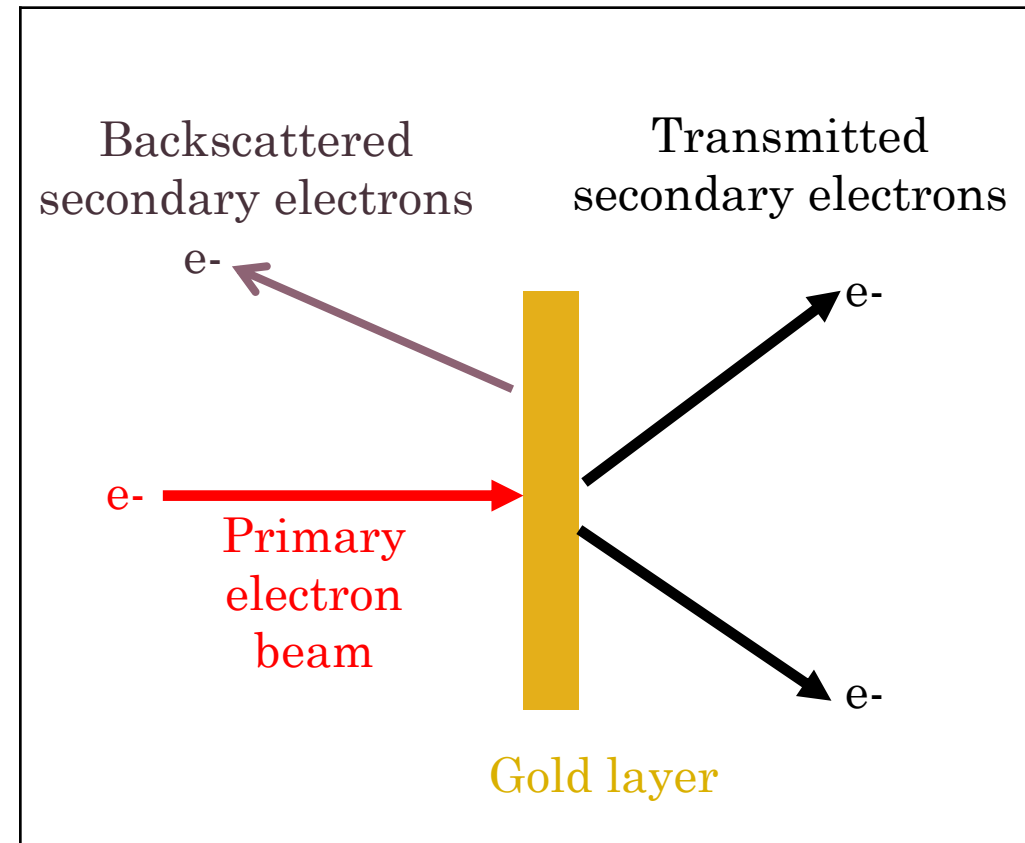
Table : Summary of the interactions simulated in MDM

4.2) Benchmarking (1)

Simulation set up

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

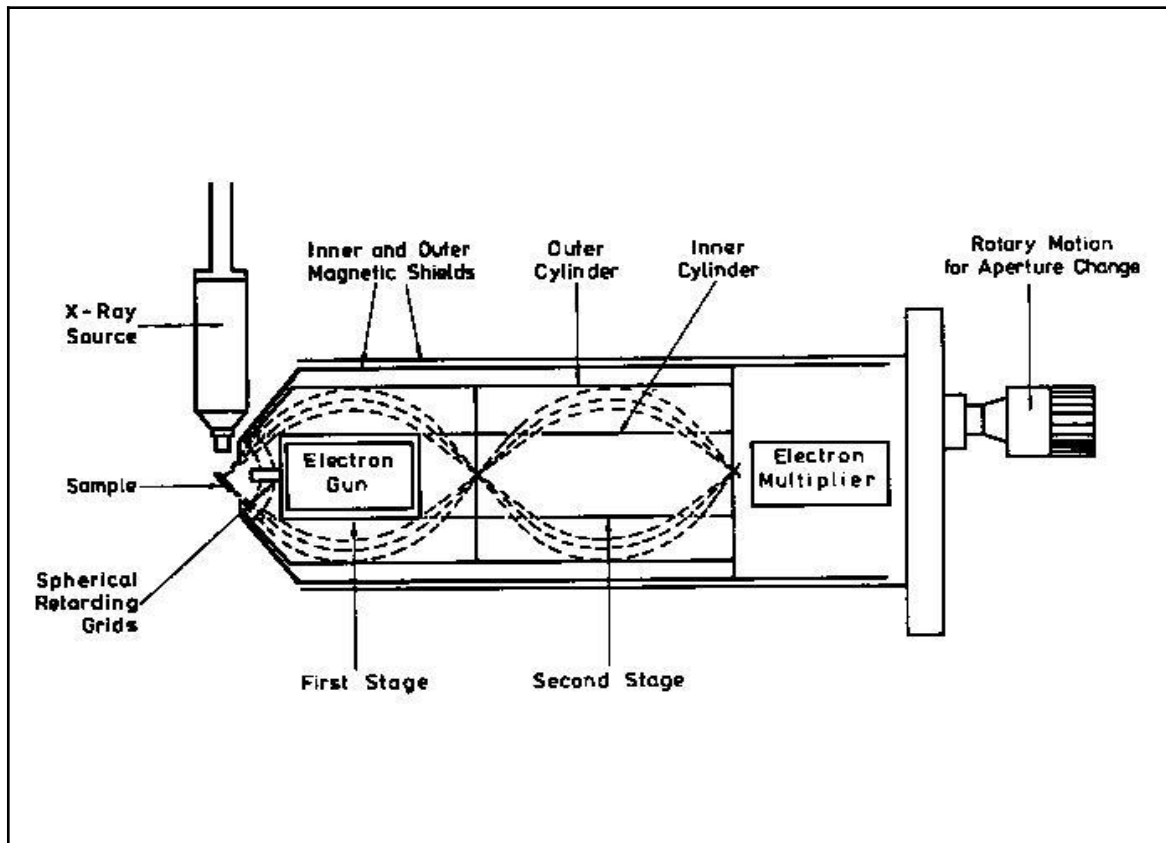
Simulation



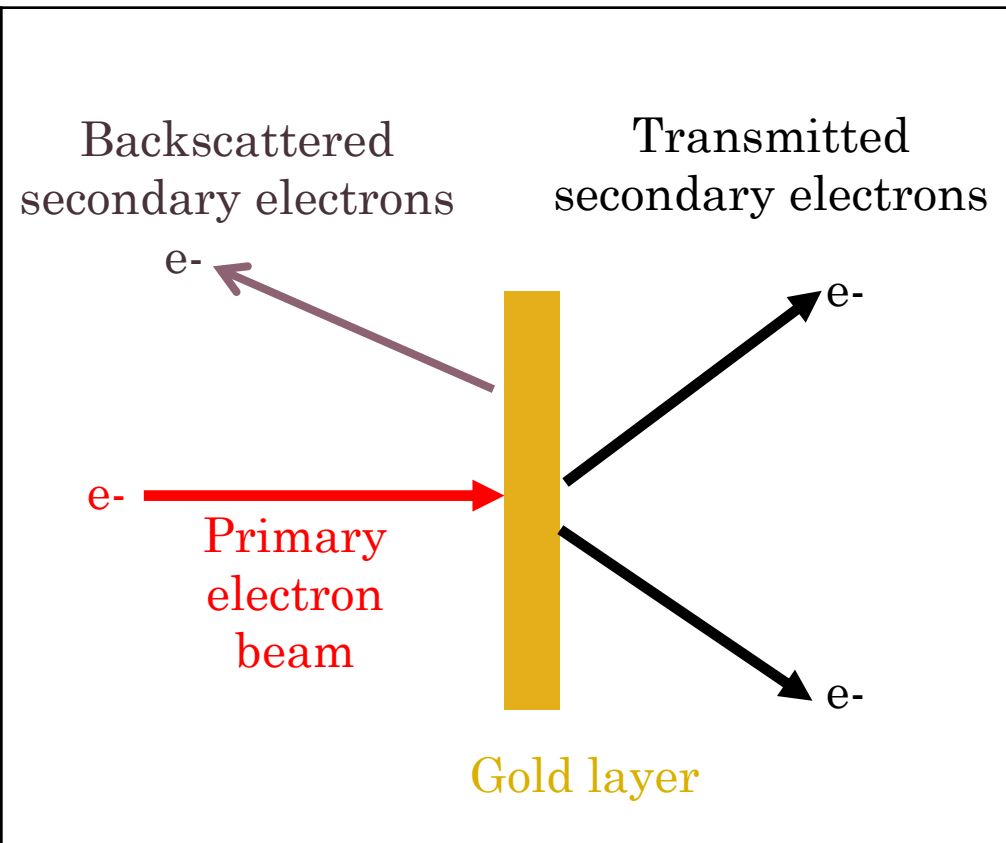
4.2) Benchmarking (1)

Simulation set up

Experimental work



Simulation

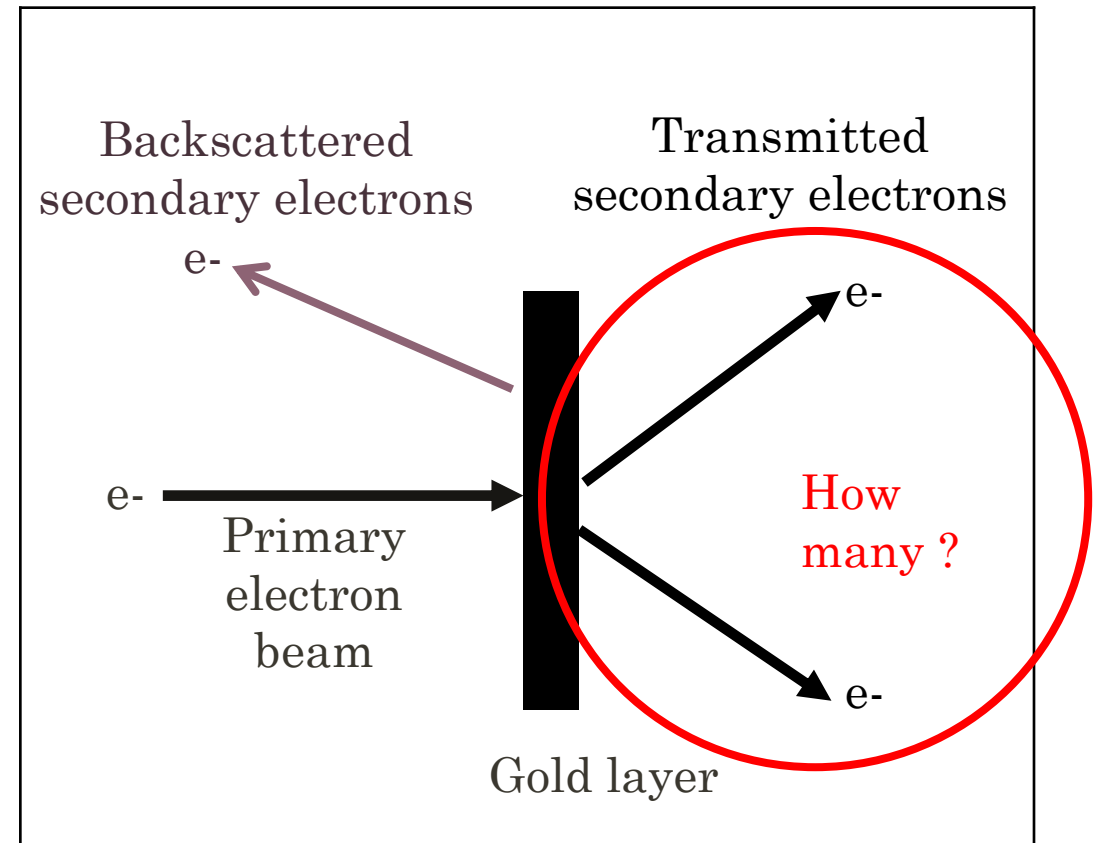


4.2) Benchmarking (2)

Yield of transmitted electrons (1)

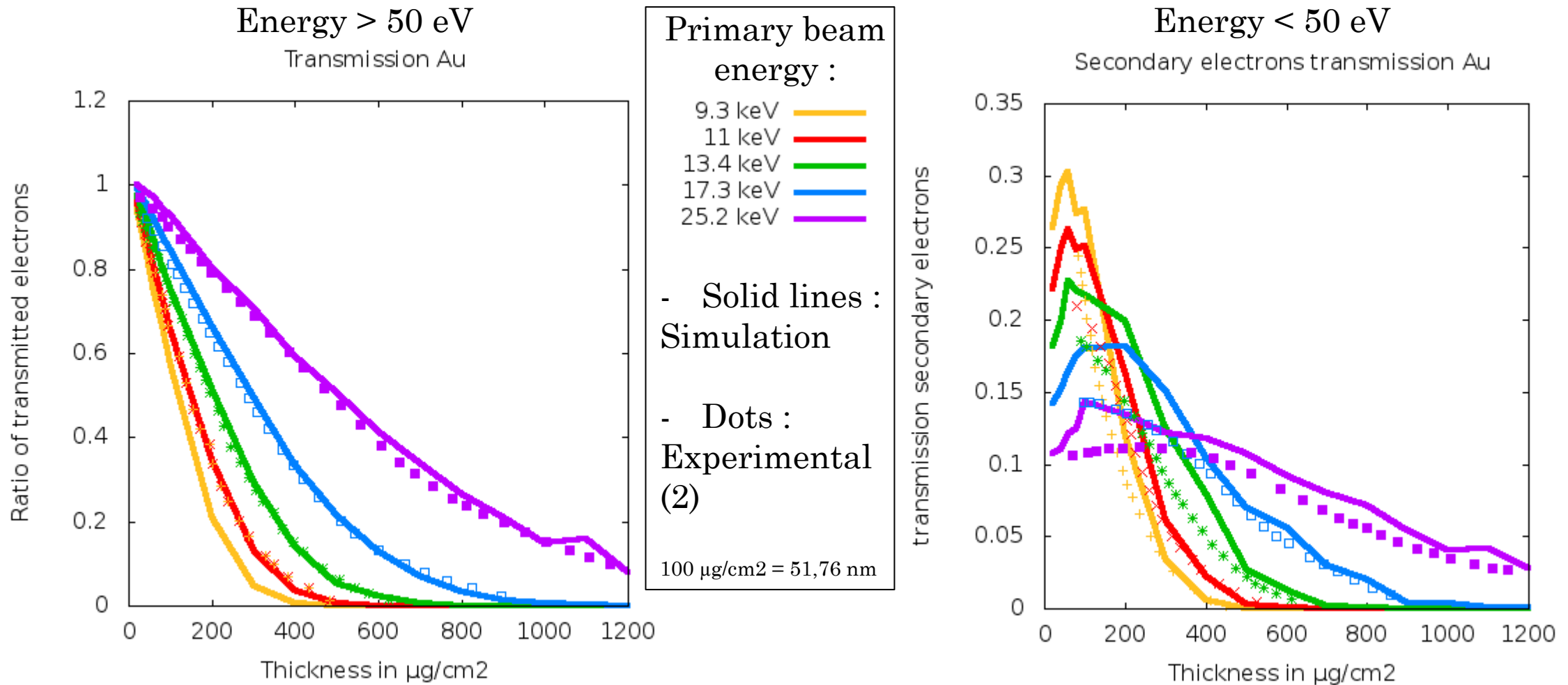
Simulation

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



4.2) Benchmarking (2)

Yield of transmitted electrons (2)

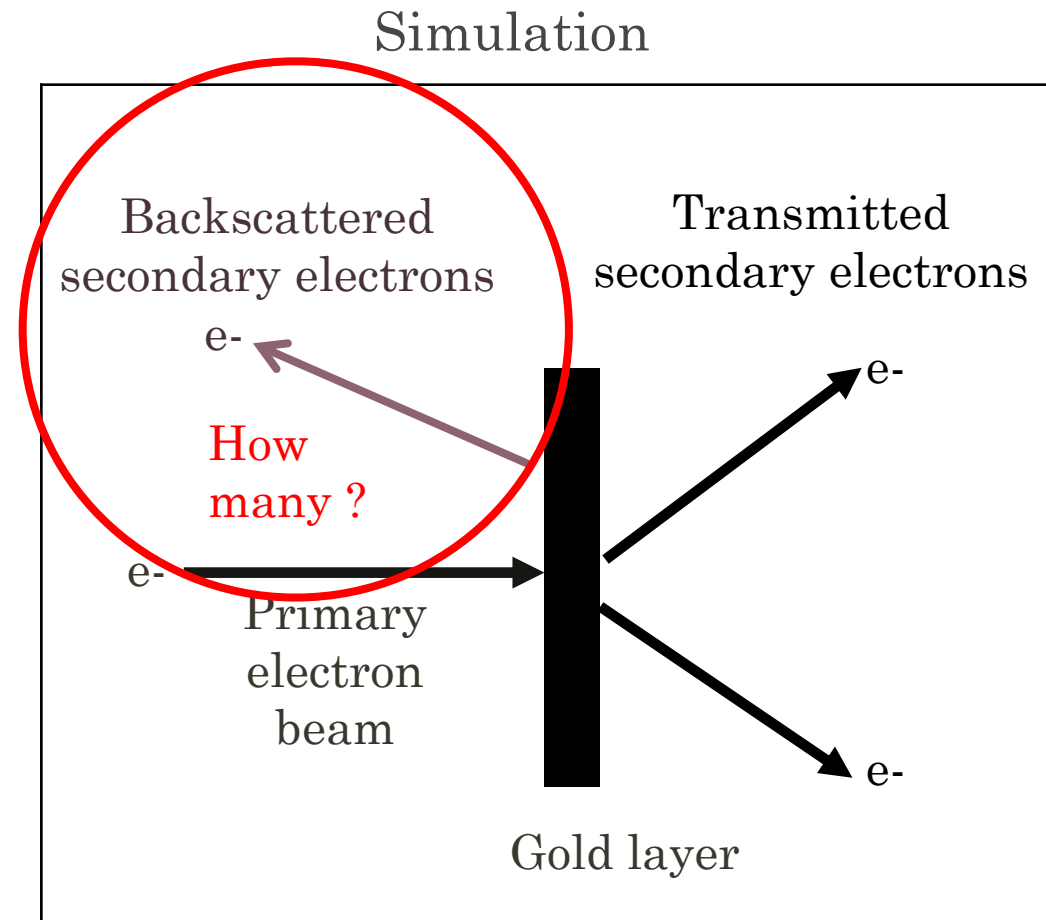


(2) Reimer, L. and Drescher, H. (1977). Secondary electron emission of 10-100 keV electrons from transparent films of Al and Au. *Journal of Physics D: Applied Physics*, 10(5):805

4.2) Benchmarking (3)

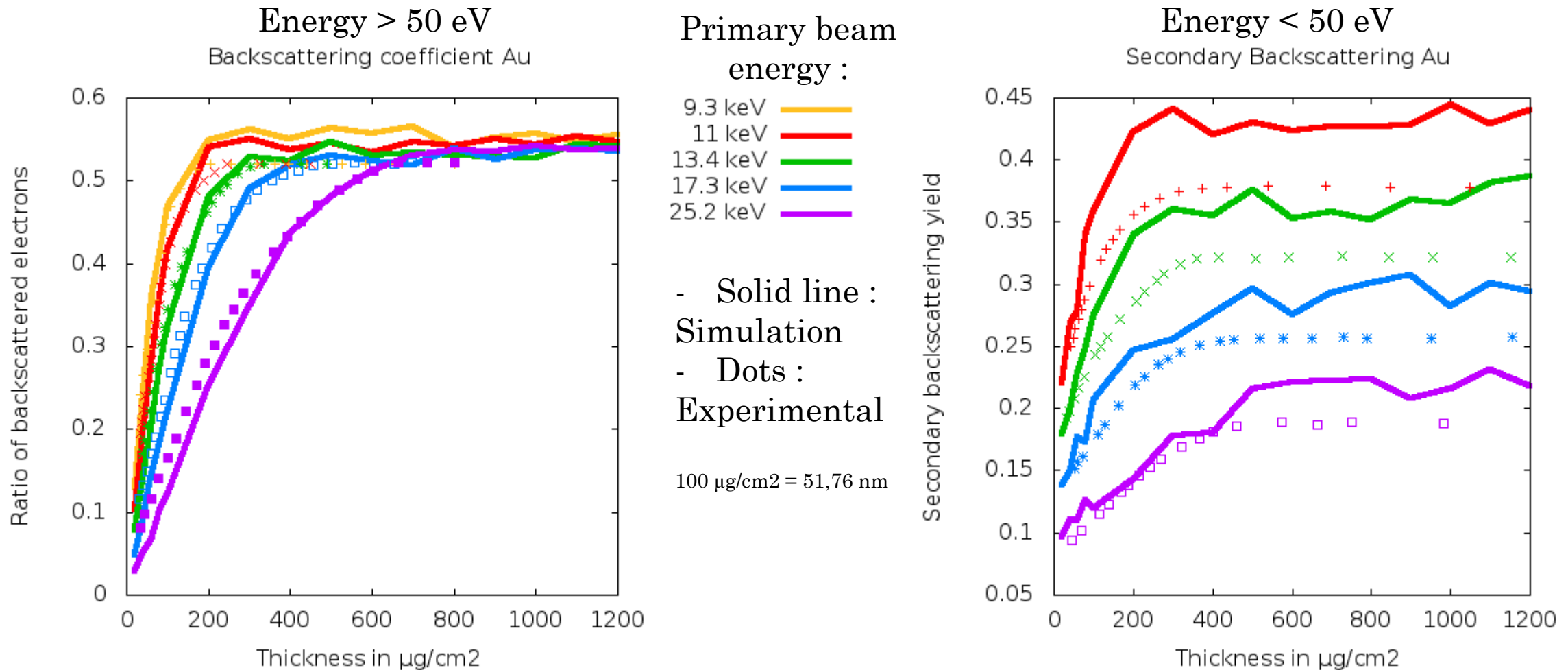
Yield of backscattered electrons (1)

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



4.2) Benchmarking (3)

Yield of backscattered electrons (1)

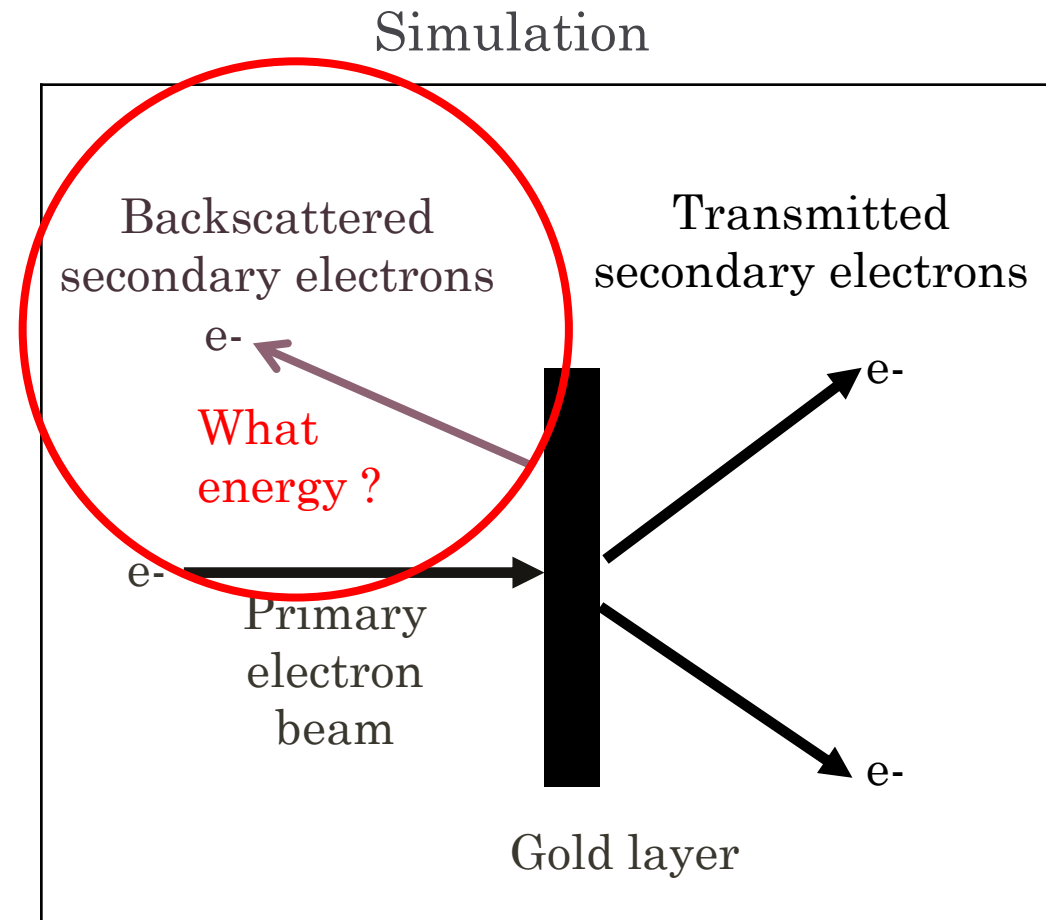


(2) Reimer, L. and Drescher, H. (1977). Secondary electron emission of 10-100 keV electrons from transparent films of Al and Au. *Journal of Physics D: Applied Physics*, 10(5):805

4.2) Benchmarking (4)

Energy of backscattered electrons (1)

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

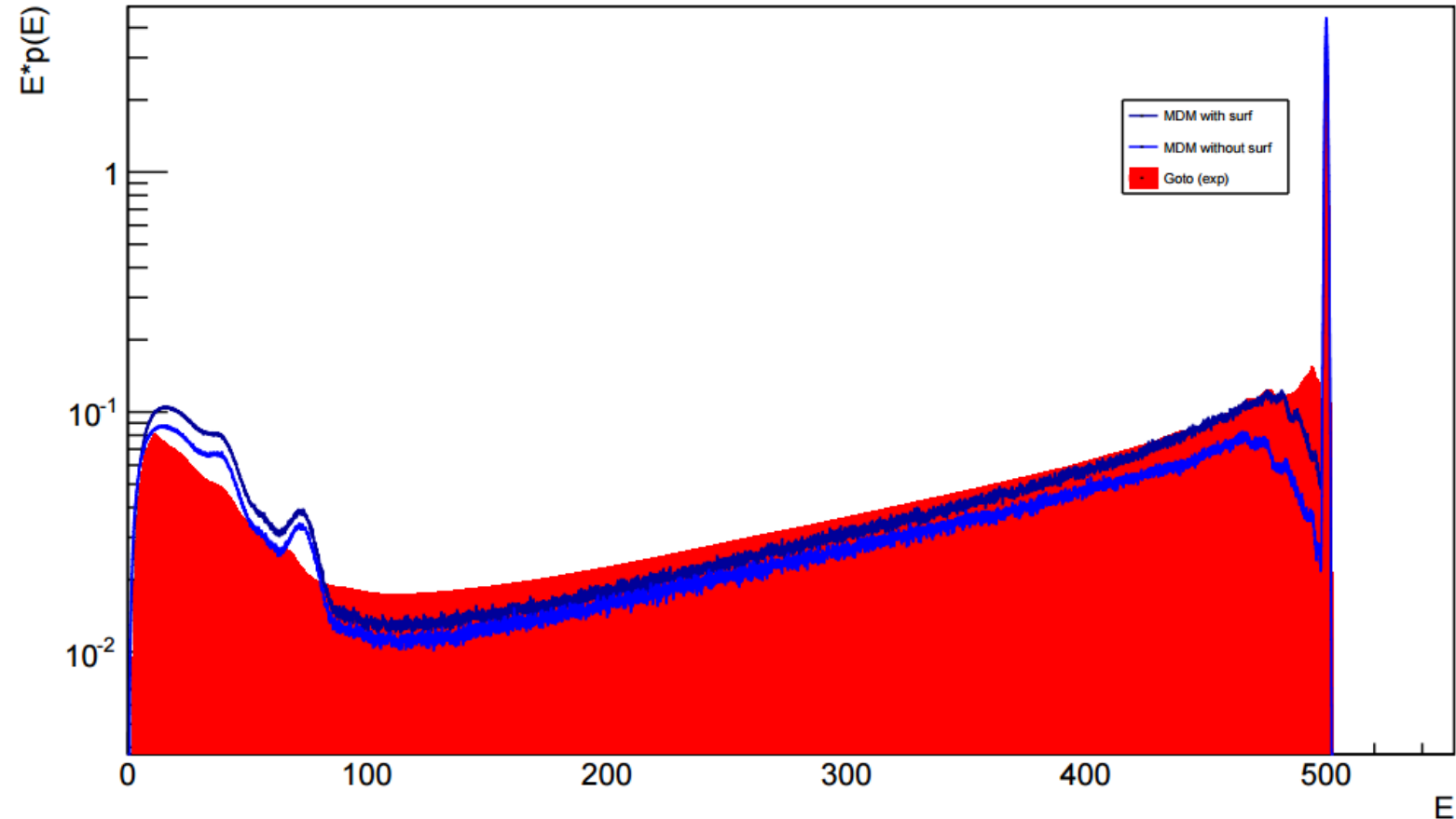


4.2) Benchmarking (4)

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



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)



Thanks for listening !

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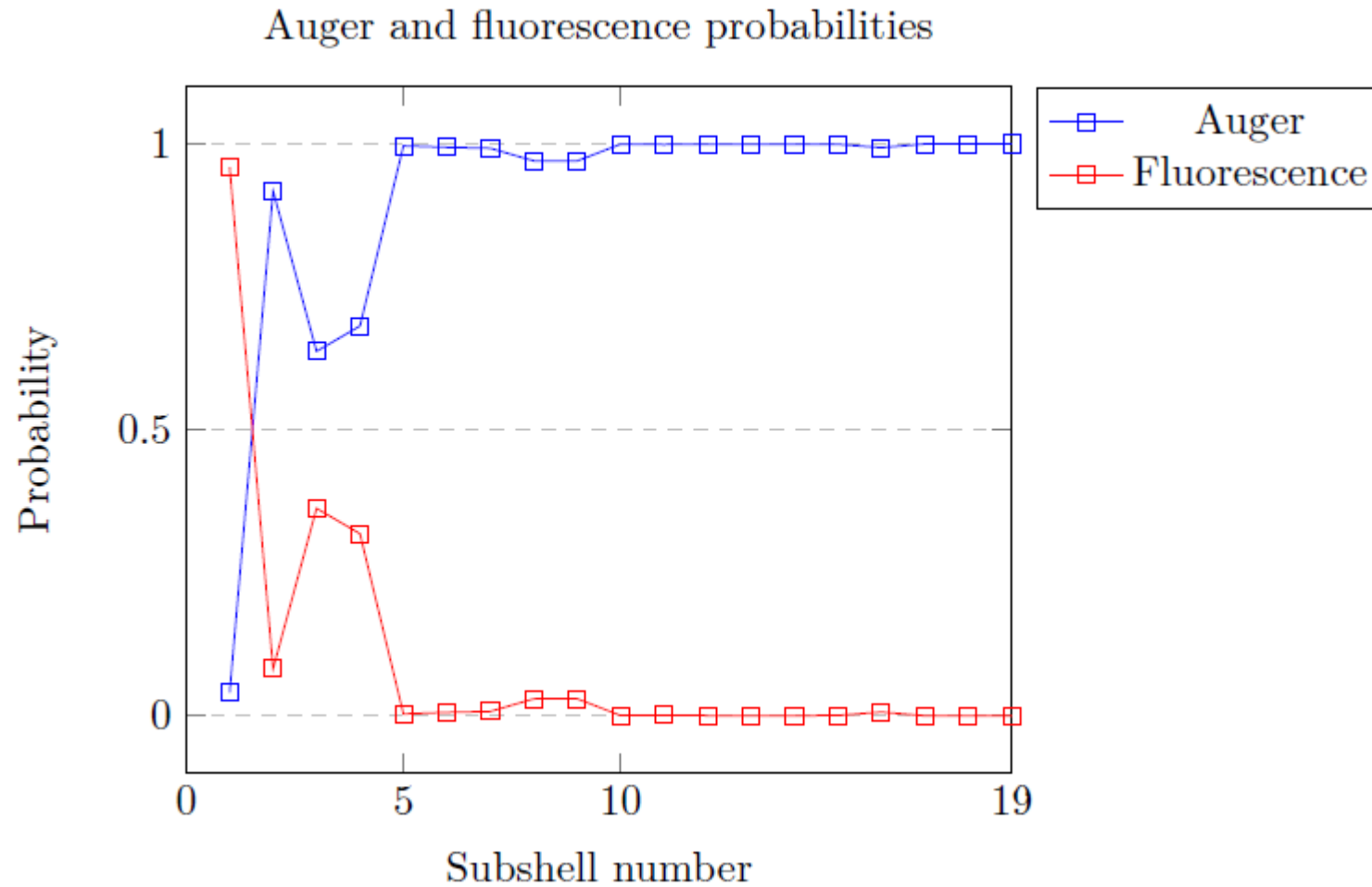
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- (4) Reimer, L. and Drescher, H. (1977). Secondary electron emission of 10-100 keV electrons from transparent films of Al and Au. *Journal of Physics D: Applied Physics*, 10(5):805
- (5) Y. Takeichi, K. Goto, True Auger Electron Spectra Measured with a Novel Cylindrical Mirror Analyser (Au, Ag, Cu), *Surface and interface analysis*, vol. 25, 17-24 (1997)
- (6) K. Haume *et al.*, Gold nanoparticles for cancer radiotherapy: a review, *Cancer Nanotechnology* Basic, Translational and Clinical Research, 2016, 7:8

ANNEXE (1)

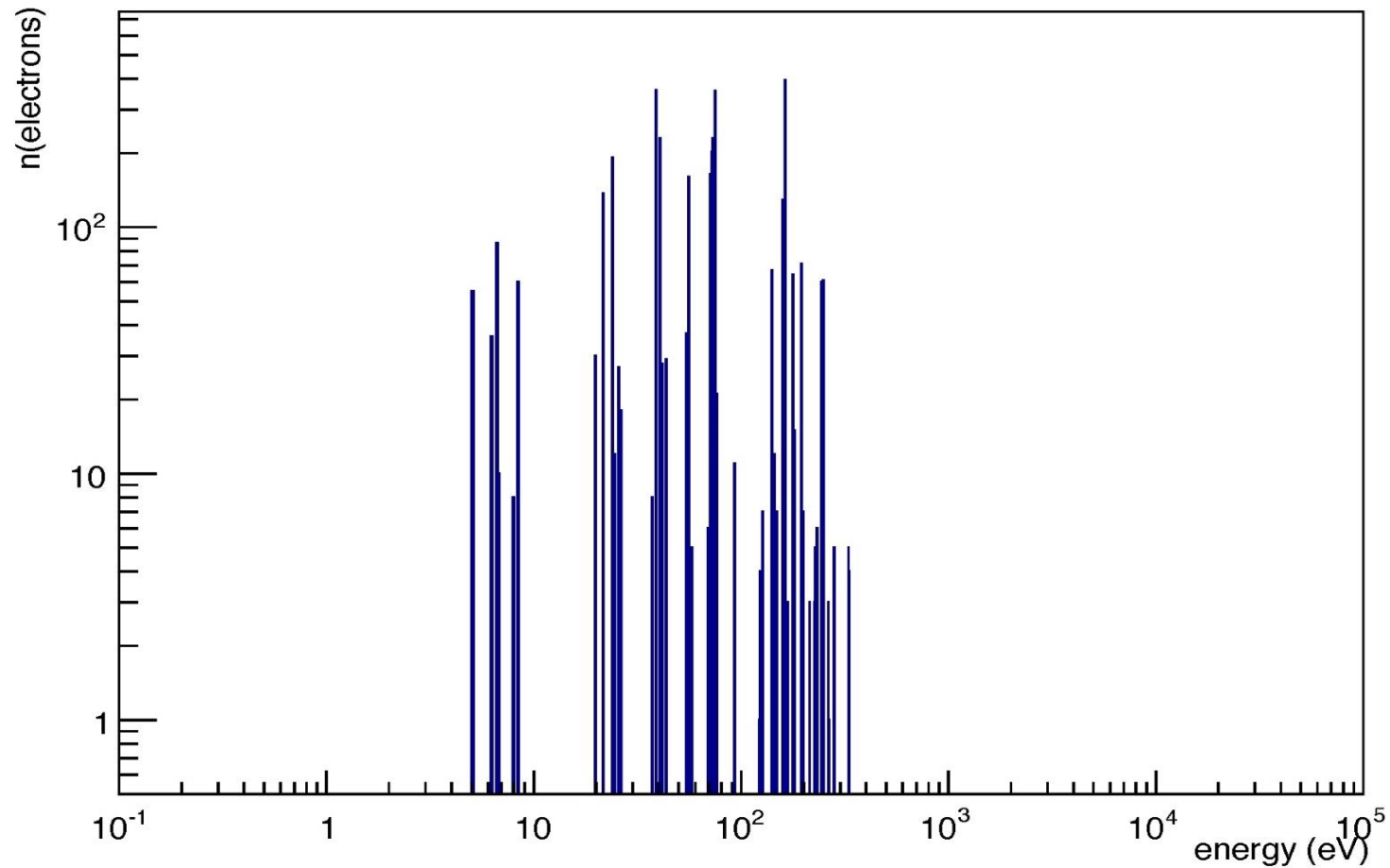
couche	nb e^-	sous-couche	label	spin	Energy (ev)	n° MDM
K	2	$1s^2$	K	$1s_{1/2}$	80725	1
L	8	$2s^2$	L1	$2s_{1/2}$	14353	2
		$2p^6$	L2L3	$2p_{1/2}$	12534	3
				$2p_{3/2}$	11919	4
M	18	$3s^2$	M1	$3s_{1/2}$	3425	5
		$3p^6$	M2M3	$3p_{1/2}$	3148	6
				$3p_{3/2}$	2743	7
		$3d^{10}$	M4M5	$3d_{3/2}$	2291	8
				$3d_{5/2}$	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)



ANNEXE (3)

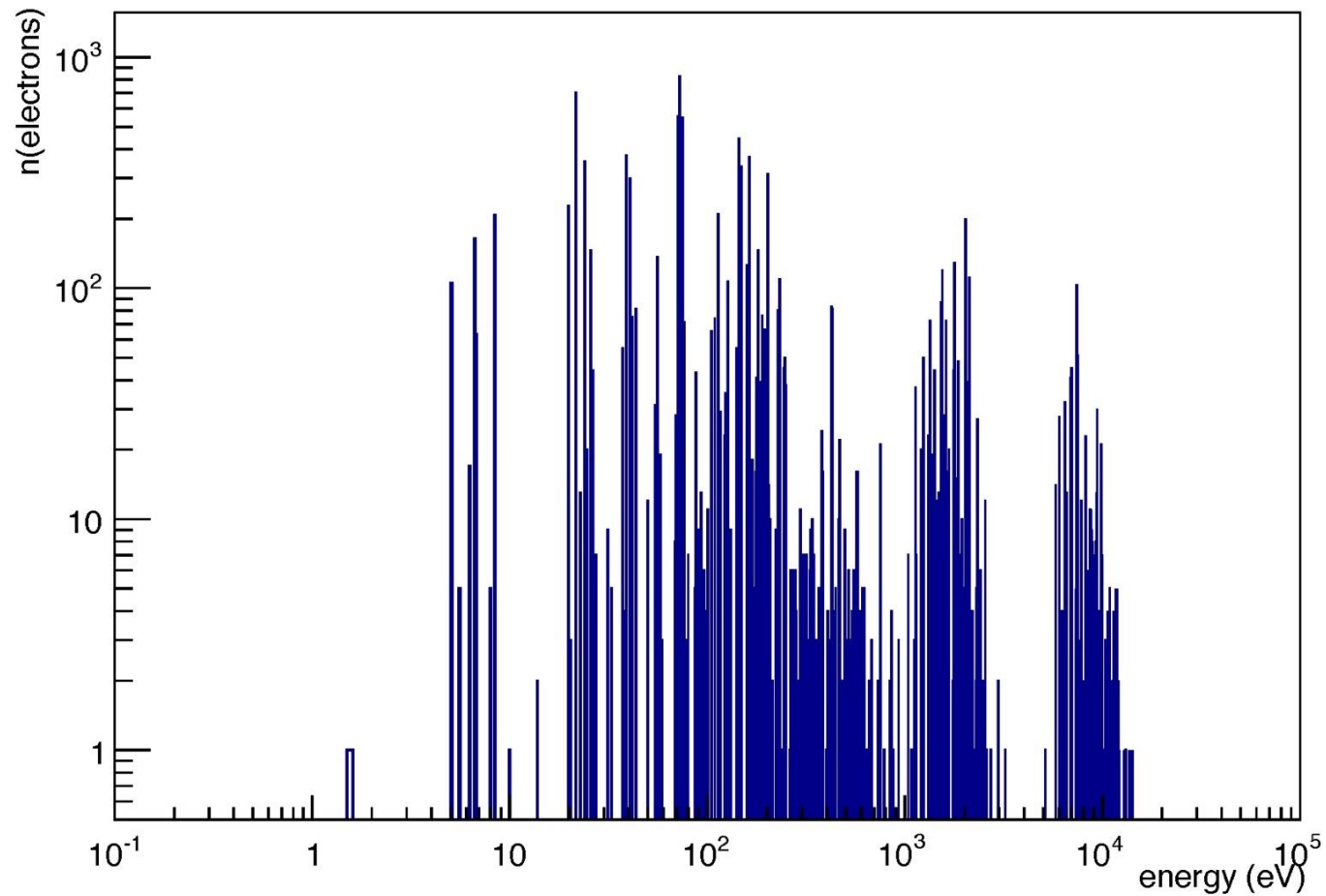
energy distribution for Auger electrons in gold, for 1000 holes in subshell 13 with cascades and without fluorescence



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

ANNEXE (4)

energy distribution for Auger electrons in gold, for 1000 holes in subshell 2 with cascades and without fluorescence

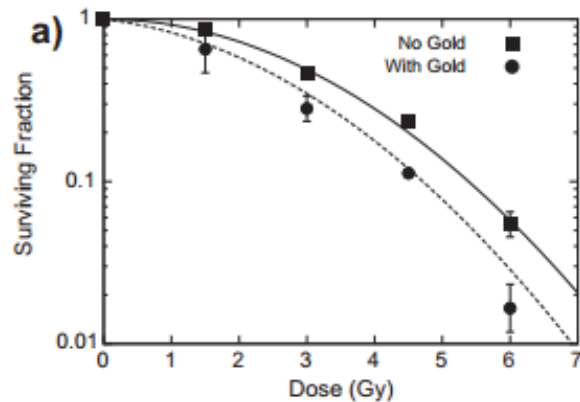


- Original vacancy : 13
- 1000 holes
- Energy distribution of emitted Auger electrons

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*