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Title	Monte Carlo simulation of free radical production under keV photon irradiation of gold nanoparticle aqueous solution. Part II: local primary chemical boost.

Abstract

For the past two decades, gold nanoparticles (GNPs) have been investigated as a radiosensitizing agent for radiation therapy. Many theoretical studies have shown that GNPs increase the dose deposition for keV photon irradiation, both at macro and nano-scales, due to a high photon-gold interaction probability. We studied by Monte Carlo simulations the production of radiolysis chemical products (OH and H₂O₂) following an ionization event induced by a 20-90 keV photon in a nanoparticle (NP). We focused here on the primary chemical processes occurring around nanoparticles. In the micrometer range, we obtained an excess of chemical species following GNP ionization, as compared to a reference water nanoparticle (WNP) ionization. This difference came from the dominant processes of photon interaction, i.e., Compton for water and photoelectric for gold, which are characterized by different emitted-electron energy spectra. The overproduction of chemical species could be up to 5 times higher for GNP, depending on the photon energy. The mean concentration of chemical species in a 100 nm sphere is higher for GNPs compared to WNPs due to Auger electrons when the nanoparticle radius was equal to 5 nm. On the contrary, it was quite comparable when the nanoparticle radius was equal to 50 nm. This reveals that gold Auger-electrons do not necessarily induce a significant boost of chemical species in the vicinity of GNP, as compared to WNP. For large GNPs, the local effect (i.e., within a few hundreds of nm from the NP surface) is not to induce a large yield near the ionized GNP, but rather to increase the chance of this event to occur, due to higher photon-gold interaction probability than that of water.

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- We calculate free radical production around a gold nanoparticle (GNP) or a water nanoparticle (WNP) in water, for single keV photon absorption.
- In the micrometer range from NP surface, radicals are overproduced of radicals by GNP (photoelectric effect) compared to WNP (Compton scattering).
- In the nanometer range, radicals are overproduced by small GNP compared to WNP due to Auger electrons, and comparable for large NP.

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Monte Carlo simulation of free radical production under keV photon irradiation of gold nanoparticle aqueous solution. Part II: local primary chemical boost.

13 Floriane Poignant^a, Hela Charfi^a, Chen-Hui Chan^b, Elise Dumont^{b,d}, David
14 Loffreda^b, Benoit Gervais^c, Michaël Beuve^a

^a*Univ. Lyon, Univ. Claude Bernard Lyon 1, CNRS/IN2P3, IP2I Lyon, F-69622,
16 Villeurbanne, France.*

^b*Univ Lyon, Ens de Lyon, CNRS UMR 5182, Université Claude Bernard Lyon 1,
17 Laboratoire de Chimie, F-69342 Lyon, France*

^c*CIMAP, unité mixte CEA-CNRS-ENSICAEN-UCBN 6252 BP 5133, F-14070 Caen,
20 Cedex 05, France*

^d*Institut Universitaire de France, 5 rue Descartes, 75005 Paris*

Abstract

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For the past two decades, gold nanoparticles (GNPs) have been investigated as a radiosensitizing agent for radiation therapy. Many theoretical studies have shown that GNPs increase the dose deposition for keV photon irradiation, both at macro and nano-scales, due to a high photon-gold interaction probability. We studied by Monte Carlo simulations the production of radiolysis chemical products ($\bullet\text{OH}$ and H_2O_2) following an ionization event induced by a 20-90 keV photon in a nanoparticle (NP). We focused here on the primary chemical processes occurring around nanoparticles. In the micrometer range, we obtained an excess of chemical species following GNP ionization, as compared to a reference water nanoparticle (WNP) ionization. This difference came from the dominant processes of photon interaction, i.e., Compton for water and photoelectric for gold, which are characterized by different emitted-electron energy spectra. The overproduction of chemical species could be up to 5 times higher for GNP, de-

48 *Email address: michael.beuve@univ-lyon1.fr (Michaël Beuve)*

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Keywords: gold nanoparticles, photon irradiation, water radiolysis, free radical production, Monte Carlo simulation

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1. Introduction

Over the past two decades, the use of high-atomic-number (Z) nanoparticles (NPs) has been of high interest due to their radiosensitizing properties. Several pre-clinical studies have shown the efficiency of gold NPs (GNPs) to enhance the effect of radiation therapy, in particular when using low energy (keV) X-rays [1, 2]. The origin of NP enhanced radiotherapy may originate from complex physical, chemical and biological mechanisms. The relative contribution of each stage remains under investigation [3]. Theoretical approaches, such as Monte Carlo (MC) simulations, may help to better understand how early physical and chemical stages could impact a biological system and lead, for instance, to cell death increase.

MC studies have shown that, for keV X-rays, a significant increase of dose deposition may be reached for sufficiently large gold concentration [4, 5]. At such energies, the photo-electric effect dominates for high- Z materials and the photon interaction probability with GNP is much larger than the interaction probability with biological tissues. Other MC studies have suggested that the heterogeneity of dose deposition in the vicinity of NPs may further contribute to the enhancement, due to an hypothetical release of low-energy electrons.

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Following a photo-ionization of a high-Z NP, **desexcitation** processes result in the emission of a cascade of secondary electrons called Auger cascade. It might be responsible for a high energy deposition in the vicinity of the GNP, and has often been associated with GNP efficiency, by presumably inducing an increased biological effectiveness similar to that observed in hadrontherapy [4, 5, 6, 7, 8].

While there have been many MC studies of the physical stage and dose deposition, simulation studies of the chemical stage are scarce [9, 10, 11]. In particular, GNP impact on water radiolysis has hardly been investigated, although it was suggested to be a crucial step that may connect the physical effect to the biological consequences [3]. In a previous work [12], we studied, on a macroscopic scale, the impact of GNPs on free radical yields for 20-90 keV photon irradiation. We showed that for a GNP concentration of $1 \text{ mg} \cdot \text{mL}^{-1}$, the increase of yields is well correlated to the macroscopic dose enhancement. Yields were found to mostly depend on the photon energy and, to a lesser extent, on the NP radius for a given mass concentration of GNPs. As previous MC studies at nanometric scale pointed out the importance of dose heterogeneity and, in particular, the high energy deposition in the vicinity of the GNP [13, 8, 14, 15, 16, 17, 18], we wished to focus, in this study, on the production of chemical species at the nanoscale. In particular we searched for a possible boost of radical production near the GNP, which might lead to local enhancement of radical recombination.

The goal of this work was thus to investigate, in a systematic way, the production of free radicals for keV photon irradiation in water around one GNP, following the absorption of a photon by this nanoparticle. It was compared to the production of chemical species following a photon absorption in a ~~nanoparticle made of water~~ (WNP), to highlight the specificity of gold material. We focused in particular on the production of **oxydative** species (hydroxyl radicals $\bullet\text{OH}$ and hydrogen peroxide H_2O_2). To calculate these chemical species production, we implemented a MC simulation which models the physical, physico-chemical and chemical steps.

This paper is organized as follows. In section 2, the MC tool and simulation

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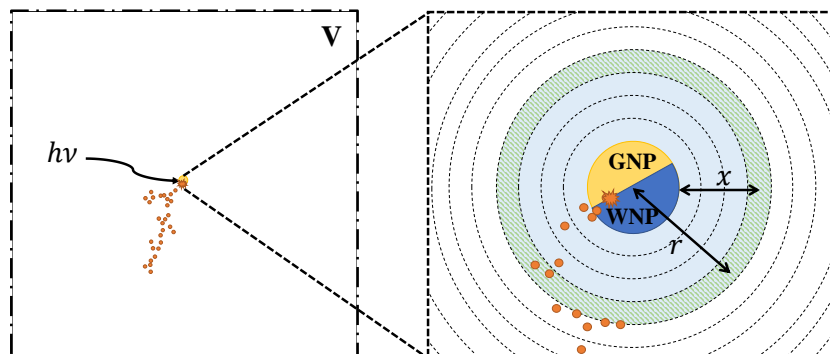


Figure 1: **Schematic view of the geometry.** Orange dots represent excited or ionized water molecules or chemical species produced following the NP ionization. On the right, the dashed green and blue area represents the scoring volume used to calculate radical species concentration in spherical concentric shells, $c_X(x)$ and $C_X(x)$.

geometry are presented. Section 3 presents the radial distribution of chemical
50 species around a NP. Section 4 discusses and concludes on the results.

2. Material and methods

2.1. Geometry

The geometry considered for the calculation is described in Fig. 1. We defined a
GNP placed at the center of a volume V filled with liquid water. The half length
205 of V was chosen to be larger than the maximum range of the most energetic
photo-electron in water. The GNP was ionized by a photon whose energy varied
206 from 20 to 90 keV. The half length of the volume was hence larger than 160 μm .
207 The systematic study of the NP-size impact on chemical species yields were
208 performed with four NP radii (5 nm, 12.5 nm, 25 nm and 50 nm). To analyze
209 the specificity of gold material, the calculation was also performed for a spherical
60 the specificity of gold material, the calculation was also performed for a spherical
NP made of water with the same radius.

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232 *2.2. Monte Carlo simulation for water radiolysis*

233 Our calculation was based on the Monte Carlo simulation MDM, and the full
234 description of the model is available elsewhere [12, 19, 20]. In short, 3 con-
235 secutive stages were performed to calculate the yield of chemical species. The
65 physical stage consisted of an event-by-event tracking of electrons in the differ-
237 ent media (water or gold) down to thermalization energy at 300 K (37 meV).
238 Photons were not explicitly tracked, and we only considered the photoelectric
239 effect and the Compton scattering as they dominate at the investigated photon
240 energies. The photon ionization impact was randomly distributed within the
241 NP. At the end of the physical stage, the surrounding water molecule may be
242 found either excited (H_2O^*) or ionized (H_2O^+ , H_2O^{2+} and H_2O^-), and the
243 medium contained thermalized electrons. The electrons in GNP for which the
244 energy was too low to escape the GNP surface were no longer tracked, as they
245 did not lead to additional water molecule excitation or ionization.
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251 This stage was followed by a physico-chemical stage during which the medium
252 relaxes, leading to the production of primary chemical species. The different
253 branching ratios of each molecular rearrangement are given elsewhere [20]. At
254 the end of this stage, the outcome consisted of spatial distribution of chemical
255 species in water, with a majority of e_{aq}^- , H_3O^+ and $\bullet\text{OH}$.
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257 Finally, during the chemical stage, the primary chemical species diffused and
258 interacted with each other. More than 50 chemical reactions were considered.
259 In our simulation, this phase was simulated up to 10^{-6} s. The method used to
260 calculate the yields and to optimize the computing time, as well as the list of
261 standard chemical reactions of water radiolysis, are available elsewhere and will
262 not be discussed in this paper [20, 21, 22, 12]. In this study, we did not consider
263 any possible specific reactions at the surface of the GNP.
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269 *2.3. Calculated quantities*

270 We calculated 4 different quantities to characterize the production and distri-
271 bution of chemical species around one NP. We calculated (1) the mean number
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287 of chemical species X following one single ionization event in the NP R_X^1 ; (2)
288 the radial number of chemical species, which is the differential of this number
289 in the radial distance $\frac{\partial R_X^1}{\partial r}$; (3) the radial concentration of the chemical species
290 X , $c_X(r)$, as the concentration of X averaged over the spherical shell of radius
291 r and of thickness δr and centered around the GNP, as represented in dashed
292 green and blue in Fig. 1. This quantity is related to the previous one through
293 the relation,
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$$298 \quad c_X(r) = \frac{1}{4/3\pi((r^3 + \delta r) - r^3)} \int_r^{r+\delta r} \frac{\partial R_X^1}{\partial r'} dr'. \quad (1)$$

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300 Finally, we calculated (4) the spherical concentration defined as concentration
301 per ionized NP, averaged over sphere centered on the nanoparticle and limited
302 by the nanoparticle surface on one side, and the radial distance r on the other
303 side, as represented in blue in Fig. 1,
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$$308 \quad C_X(r) = \frac{1}{\frac{4}{3}\pi(r^3 - R_{\text{NP}}^3)} \int_{R_{\text{NP}}}^r \frac{\partial R_X^1}{\partial r'} dr'. \quad (2)$$

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310 To have a common origin for all NP radii, the results are presented as a function
311 of the distance from NP surface, $x = r - R_{\text{NP}}$. We shall refer to $c_X(r)$ and $C_X(r)$
312 as $c_X(x)$ and $C_X(x)$.
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316 3. Results

317 3.1. Average number of chemical species per nanoparticle ionization

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319 Tab. 1 gives the average number of chemical species ($R_{\bullet\text{OH}}^1$ and $R_{\text{H}_2\text{O}_2}^1$) for
320 various E_{photon} , two NP radii ($R_{\text{NP}} = 5$ and 50 nm), calculated both at 10^{-12}
321 and 10^{-6} s following the photon absorption.
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325 For the smallest GNPs, the number of $\bullet\text{OH}$ produced at 10^{-12} s varied from 721
326 ($E_{\text{photon}} = 20$ keV), up to 2912 ($E_{\text{photon}} = 70$ keV), due to the increase of the
327 photo-electron energy. It then dropped at $E_{\text{photon}} = 90$ keV, as there is a high
328 fluorescence emission in this case. The mean free path of the emitted photons is
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343 very large compared to the volume of the simulated system and the probability
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115 of interaction is low. This latter was neglected in our simulations. If the GNP
346 was embedded in a volume of water larger than the photon mean free path, the
347 photon would deposit its energy in the volume, but most of the time far away
348 (several mm at least) from the ionized GNP. The same variation of $R_{\bullet\text{OH}}^1$ and
349 $R_{\text{H}_2\text{O}_2}^1$ was obtained with regard to E_{photon} , regardless of other parameters (e.g.,
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120 radius, time ...). The number of chemical species decreased with increasing GNP
353 radius due to the energy loss in the GNP. This was particularly visible at 20
354 keV: at 10^{-12} s, the number of $\bullet\text{OH}$ decreased from 721 to 571 when the radius
355 of the GNP increased from 5 nm to 50 nm. The same trends were observed with
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357 H_2O_2 .

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125 For WNP, the number of chemical species was hardly impacted by the NP size.
360 The number of chemical species, at fixed time, first decreased from 20 keV to
361 50 keV, before increasing again. The first drop was due to the fact that, at
362 20 keV, the photo-electric effect remained non-negligible, in which case all the
363 photon energy was deposited. As the Compton effect became dominant, only
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130 part of the photon energy was deposited. This was compensated by the fact
366 that the average Compton electron energy increased with the photon energy, so
367 that the number of species per photo-ionization increased above 50 keV.
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370 The number of chemical species generated per photo-ionization was systemati-
371 cally higher for GNPs than WNPs, with two exceptions. For $E_{\text{photon}} = 20$ keV
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135 and $R_{\text{NP}} = 50$ nm, the number of chemical species for GNPs was below that of
374 WNP, due to a particularly high energy absorption within the GNP. At 10^{-6} s,
375 $E_{\text{photon}} = 20\text{keV}$, $R_{\text{NP}} = 5$ nm, and regardless of the time, the number of $\bullet\text{OH}$
376 for GNP was also below that of WNP, while it was not the case of H_2O_2 . This
377 denotes the fact that in this specific case, the recombination of $\bullet\text{OH}$ was par-
378 ticularly important, leading to a high number of H_2O_2 . Finally, as expected,
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140 the largest difference between GNPs and WNPs was obtained at 70 keV. In this
381 case, the photo-electron emitted from the GNP had the largest kinetic energy,
382 while the Compton electron in water still had a limited kinetic energy.
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Energy	10^{-12} s				10^{-6} s			
	•OH		H ₂ O ₂		•OH		H ₂ O ₂	
	GNP	WNP	GNP	WNP	GNP	WNP	GNP	WNP
	$R_{\text{NP}} = 5$ nm							
20 keV	721	673	33	28	256	288	135	118
50 keV	2070	460	81	20	934	198	350	81
70 keV	2912	501	112	21	1385	211	482	88
90 keV	1560	618	63	25	671	264	270	108
	$R_{\text{NP}} = 50$ nm							
20 keV	571	674	25	28	212	288	107	118
50 keV	1960	455	76	19	906	196	329	80
70 keV	2820	500	107	21	1365	211	462	88
90 keV	1401	617	56	26	625	263	239	108

Table 1: Average number of chemical species produced per GNP/WNP ionization for different times, photon energies and GNP radii. The statistical uncertainty was below 1 %.

3.2. Spatial distribution

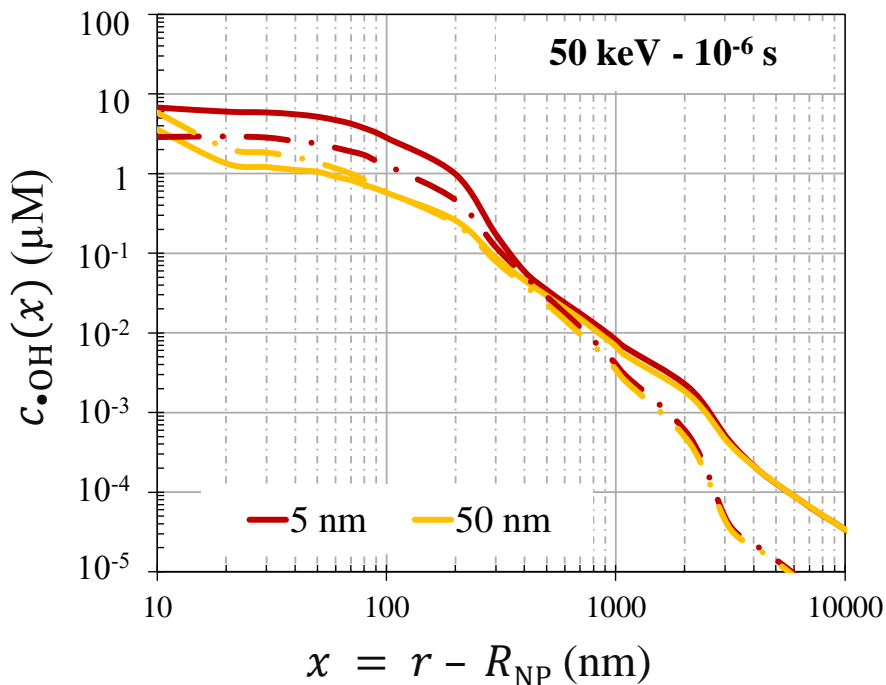


Figure 2: Radial concentration $c_{\bullet\text{OH}}(x)$ as a function of x ($E_{\text{photon}} = 50$ keV and $t = 10^{-6}$), for two R_{NP} . Solid line shows results for a GNP and dashed line for a WNP.

Fig. 2 shows the radial concentration $c_{\bullet\text{OH}}(x)$ of $\bullet\text{OH}$ following an ionization event in the NP, as a function of the distance to the NP surface $x = r - R_{\text{NP}}$.

The radial concentration was maximum near the NP surface and dropped severely for higher values of r . This decrease was proportional to $1/r^2$. It is due to the dependency in r^2 of spherical shell volume when r increases, and to a lesser extent to the differential number of chemical species. Such tendency was similar regardless of the photon energy, both at 10^{-12} s (not shown here) and 10^{-6} s. The global shape of the radial distribution was not specific to the material, as WNP showed the same tendency.

Due to $\bullet\text{OH}$ recombination and diffusion, the radial concentration decreased

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512 with increasing t over the whole r range for $\bullet\text{OH}$. For H_2O_2 (not shown here),
513 $c_{\text{H}_2\text{O}_2}(x)$ dropped for $x < 200$ nm over the time period 10^{-12} to 10^{-6} . This
514 drop was due to outward diffusion, which is of the order of 100 nm for 1 μs . On
515 the contrary, H_2O_2 increased for larger radii.
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518 Increasing the NP radius R_{NP} decreased $c_{\bullet\text{OH}}(x)$ below 200 nm, regardless of
519 photon energy, time t , chemical species or material. There are two reasons for
520 this. First, by definition of the radial concentration, the number of species is
521 normalized to the volume of the shell. For a given value of x , this volume
522 increases with increasing R_{NP} . Second, the part of the absorbed energy inside
523 the NP, which increases with increasing R_{NP} , corresponds to the stopping of
524 low-energy electrons. When increasing the NP radius, less low-energy electrons
525 escape the NP and less species are produced close to the surface.
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529 The spatial distribution of chemical species also depended on photon energy.
530 To better analyze this dependency, we calculated the radial number of chemical
531 species, instead of the radial concentration as the latter was strongly impacted
532 by the r^2 normalization. Fig. 3 displays the radial number of chemical species
533 $\bullet\text{OH}$, $\frac{\partial R_{\bullet\text{OH}}^1}{\partial r}$, as a function of the distance to the NP surface x .
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536 For GNP, some structures are visible around $x = 100$ nm and 1000 nm, regard-
537 less of the photon energy. The first structure came from LLS ($S > N$) Auger
538 electrons emitted with an energy lower than 2 keV, which had ranges lower than
539 ~ 160 nm in water. The second structure came from LMS ($S > M$) Auger elec-
540 trons emitted with an energy between 8-12 keV, which corresponded to a range
541 in water around 1000-2000 nm. Another structure is visible for large x , which
542 corresponded to the end of photo-electron path. As shown in Tab. 2, these
543 photo-electrons have different energies depending on the photon energy and the
544 shell from which they are ejected. This phenomenon was particularly visible for
545 $E_{\text{photon}} = 90$ keV. As the probability to ionize the K-shell was overwhelming
546 in this case, many photo-electrons were ejected with an energy around 9 keV.
547 These electrons therefore contributed to the boost of the number of chemical
548 species observed around 1000 nm.
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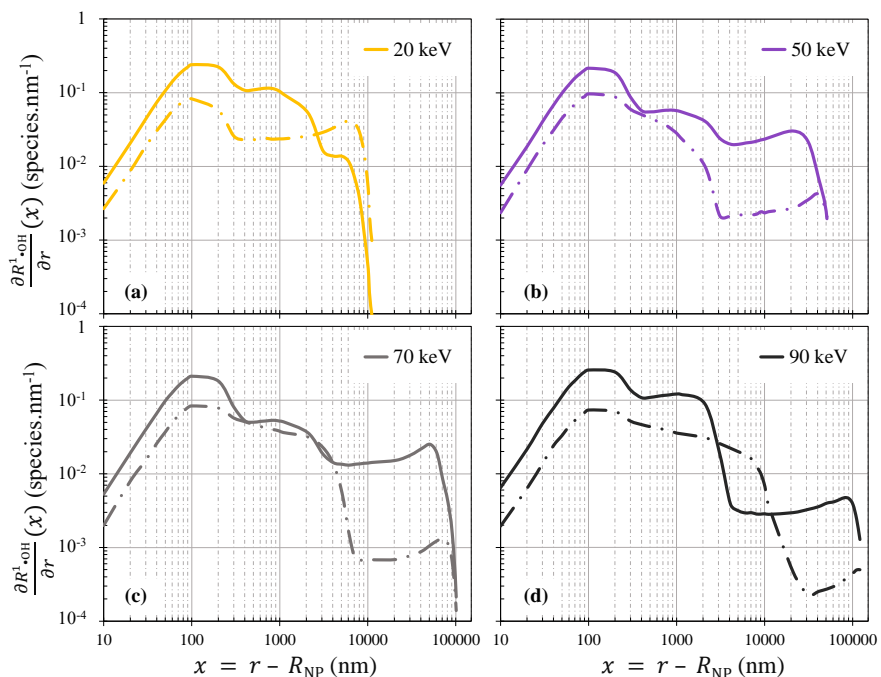


Figure 3: Radial number of chemical species $\frac{\partial R_{\bullet}^{\text{OH}}}{\partial r}$ as a function of x . In each panel, results are given for GNP (solid line) and WNP (dashed line). Results are displayed for $E_{\text{photon}} = 20, 50, 70$ and 90 keV. $R_{\text{NP}} = 5$ nm, and $t = 10^{-6}$ s.

185 For WNP, the progressive decrease of $\frac{\partial R_{\bullet}^{\text{OH}}}{\partial r}$ with x was related to the energy
594 distribution of Compton electrons. An exception was noticeable for 20 keV: as
595 the photo-electric effect remained non-negligible, the radial number of chemi-
596 cal species was a combination of the radial number following a photo-electric
597 event producing a ~ 19.5 keV photo-electron, and the radial number following
598 a Compton event producing a broad energy distribution below 1400 eV.
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602 When comparing GNP and WNP, the first striking fact was that $\frac{\partial R_{\bullet}^{\text{OH}}}{\partial r}$ re-
603 mained higher at longer distances ($x > \sim 10\,000$ nm) for GNP. This is explained
604 by the fact that, on average, the Compton electron had an energy lower than
605 a photo-electron energy. At very small distance ($x < 100$ nm), the number of
606 chemical species was higher for GNP compared to WNP when $R_{\text{NP}} = 5$ nm.
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607 On the contrary, it was lower for GNP compared to WNP when $R_{\text{NP}} = 50$ nm.

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Atomic shell	K			L			$\geq M$		
	P.	E.	R.	P.	E.	R.	P.	E.	R.
E_{photon}									
20 keV	0	-	-	77	6-8	0.9-1.5	23	> 17	5.3-7.4
50 keV	0	-	-	77	17-18	5.3-6	23	> 47	35-42
70 keV	0	-	-	77	56-58	49-53	23	> 67	68-74
90 keV	77	9	1.8	16	76-78	88-92	7	> 87	> 111

Table 2: **Probability** (P. in %) of ionizing the shell K,L or above, photo-electron energy (E. in keV) and range of the photo-electron in water (R. in μm) following an ionization event in gold with a photon of energy E_{photon} .

To better quantify the relative difference between GNP and WNP, we calculated the difference of spherical concentration of GNP and WNP, to that of WNP,

$$\frac{C_{X,\text{GNP}}(x) - C_{X,\text{WNP}}(x)}{C_{X,\text{WNP}}(x)}, \quad (3)$$

for the two extrema sizes of NPs investigated here. Results are shown in Tab. 3
 200 for $\bullet\text{OH}$. The results confirmed that, for $R_{\text{NP}} = 50$ nm, the spherical concentration of WNP for small volumes (10 and 100 nm thick) were higher than that of GNP, except when the photon energy was equal to 90 keV. This was due to non negligible energy loss in the GNP. When the considered volume increased ($x = 1000$ nm), the concentration for GNPs was higher than that of WNP. For
 205 even larger volumes ($x = 10$ μm), the concentrations were higher for GNPs, with one exception ($E_{\text{photon}} = 20$ keV). This translated the fact that, on average, GNPs generated more chemical species than WNP following one photon ionization event, but far away from the GNP (i.e., beyond 100 nm).

4. Discussion and conclusion

210 In this work, we investigated the production and spatial distribution of radical species following keV-photon ionization of a GNP or a WNP embedded in a volume of water. We focus on the local production of radicals, meaning that

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x	10 nm	100 nm	1 000 nm	10 000 nm	100 000 nm
$t = 10^{-6}$ s - $R_{\text{NP}} = 5$ nm					
20 keV	122	164	327	-11	-11
50 keV	137	123	68	289	354
70 keV	165	154	53	77	561
90 keV	233	248	196	30	159
$t = 10^{-6}$ s - $R_{\text{NP}} = 50$ nm					
20 keV	-9	39	238	-26	-26
50 keV	-39	-22	25	264	365
70 keV	-33	-15	9	57	547
90 keV	18	55	152	8	134

Table 3: Relative difference (in %) of spherical $\bullet\text{OH}$ concentration in a x nm thick shell around a nanoparticle.

Compton and fluorescence photons, which release their energy at least millimeters away from the NP, were not taken into account. Radial concentrations showed a high maximum near the nanoparticle surface which rapidly decreased when the distance to the nanoparticle increased. This is a purely geometric effect due to the r^2 increase of the concentric shells used as scoring volume. As a consequence, both GNPs and WNPs showed very similar radial concentration profiles.

Different specificities were obtained for gold compared to water:

(1) We observed that, on average, a GNP ionization can produce up to ~ 5.5 more chemical species than an ionization event in a WNP, as a photo-electron carries more energy than a Compton electron, the later dominating photon-water interactions at the investigated energy. Besides, as photo-electrons are more energetic than Compton electrons, GNP radial concentrations are higher than WNP radial concentrations at distances larger than few micrometers.

(2) Chemical species produced by the interaction of Auger-electrons with water

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735 molecules following an ionization event in GNPs induced a minor boost in the
736 radial number. This boost appeared around 100 nm and 1000 nm.

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230 (3) Both $\bullet\text{OH}$ and H_2O_2 had very similar distributions. In particular, H_2O_2
740 production was not particularly higher due to Auger electrons. The Auger
741 electrons are indeed significant for GNP ionization, but their effect is rather
742 comparable to that of Compton electrons produced by WNP ionization.
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745 (4) The concentration of chemical species was not necessarily higher for GNP
746 compared to WNP near the ionized NP (within a few hundreds of nm), despite
235 the Auger electron cascade when the GNP was large. The absorption of low-
747 energy electrons within the GNP produced a drop of the number of chemical
748 species near the surface with respect to the case of smaller GNPs.
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752 Attempting an extension of these results to biological systems, one may expect
753 that, on average, a cellular target containing or located near a large ionized
240 GNP ($x < 200$ nm) does not suffer a higher concentration of chemical species,
754 compared to the ionization of a water molecule. However, it may experience a
755 higher occurrence of this event, as the cross section for gold-photon interaction
756 is higher than that of water-photon interaction at these energies. In other words,
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758 the major effect of gold is not to induce a high concentration boost of chemical
245 species compared to water, but rather to increase the chances of having an
760 ionization, due to a high probability of photon-gold interaction compared to
761 photon-water interaction.
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767 In interpreting our results from a biological perspective, it is important to keep
250 in mind that biological media contain many scavenging elements. Besides,
768 cells might catalyse complex reactions inducing an additional boost of chem-
769 ical species production. Our calculation may therefore only characterize the
770 primary chemical events at very short time generated by one photo-ionization
771 event. *In vitro* data showed that GNPs often appear clustered together in vesi-
772 cles [23, 24, 25, 26, 27], which might roughly be represented by large GNPs.
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776 Our calculated spherical concentrations may be used to estimate the primary
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791 chemical boost experienced by cellular components when they internalize GNPs.
792 Typically, a size of 10 nm may represent the dimension of a membrane; a size of
793 100 nm may represent the dimensions of an organelle (mitochondria, lysosome);
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260 a size of 1000 nm may represent the dimensions of a large organelle (large lyso-
796 some); a size of 10 000 nm may represent a nucleus. As our calculation showed,
797 the number of chemical species following an ionization event decreases for large
798 GNPs, especially in its vicinity. At first sight, it thus appears less advantageous
799 to have aggregates rather than isolated GNPs. However, if GNPs accumulate
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265 in a specific zone of the cell, an accumulation of damages may occur near the
803 GNPs, due to a high probability of photon-gold interaction. Such accumulation
804 might be deleterious for the cell.
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818 **References**

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