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DOI:

[10.1088/2057-1976/aa69cc](https://doi.org/10.1088/2057-1976/aa69cc)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Sotiropoulos, M., Taylor, M., Henthorn, N., Warmenhoven, J., Mackay, R. I., Kirkby, KJ., & Merchant, M. (2017). Geant4 interaction model comparison for dose deposition from gold nanoparticles under proton irradiation. *Biomedical Physics & Engineering Express*, 3, [025025]. <https://doi.org/10.1088/2057-1976/aa69cc>

Published in:

Biomedical Physics & Engineering Express

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Geant4 interaction model comparison for dose deposition from gold nanoparticles under proton irradiation

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Abstract

Gold nanoparticles (GNPs) have shown a potential as a radiosensitizer in radiotherapy. The radiosensitization effect is thought to be linked to the increased dose deposition around the GNP. Monte Carlo simulations have been implemented for the calculation of the dose distributions around the GNPs and have been used for the calculation of the dose enhancement. They have also been imported to radiobiological models to predict biological endpoints. This work assessed the implications of different physical interaction models on the dose distribution and dose enhancement of GNPs surrounded by water under proton irradiation. The Penelope and Livermore physical interaction model implementation of the Geant4 simulation toolkit were compared considering the following parameters: i) GNP size, ii) proton energy, and iii) alternative physics model parameters in the gold or water medium. We found that neither the dose distribution nor the dose enhancement is sensitive to the model selection after the first 100 nm from the GNP surface. Within the first 100 nm the Livermore models calculated a higher dose, attributed to a higher production of low energy secondary electrons inside the GNP.

Keywords: Gold Nanoparticles, radio-sensitizer, Geant4-DNA, Proton Beam

1. Introduction

The ultimate goal of radiation therapy is to deliver high radiation dose to the tumour, while sparing the normal tissues and organs at risk. Usually the dose in the tumour is constrained by the prescribed limits to dose in the normal tissues including organs at risk, since high dose to normal tissues is linked to increased treatment side effects. Therefore, new methods are under investigation in order to boost the dose at the tumour site, while sparing the adjacent tissues. Gold nanoparticles (GNPs) have demonstrated radiosensitization potential *in vivo* and *in vitro*, under irradiation with x-rays, electrons, and protons (Hainfeld *et al* 2004, Liu *et al* 2010, Polf *et al* 2011, Kim *et al* 2012).

While the radiosensitization effect may also be attributed to biological or chemical mechanisms, the physical interaction of the radiation with the GNPs is the main contributing factor to the effect through the production of secondary radiation. This is due to the production of low energy secondary radiation which deposits energy close to the GNP, enhancing the local dose. Monte Carlo (MC) simulations for the quantification of the local dose enhancement have been implemented by many groups (McMahon *et al* 2011b, Leung *et al* 2011, Wälzlein *et al* 2014, Lin *et al* 2014, Xie *et al* 2015).

As each MC code utilizes different interaction models, a wide range on the dose values has been reported. For instance, in the case of x-ray irradiation Li *et al.* (2014) reported a dose enhancement value difference of a factor of 2 between the Penelope-2011 (Salvat *et al* 2011) and Geant4 code (Agostinelli *et al* 2003, Allison *et al* 2006). Moreover, dose distributions around the GNPs have been used in combination with radiobiological models (Lechtman *et al* 2013, Lin *et al* 2015, McQuaid *et al* 2016) in order to calculate biological endpoints such as cell survival.

This interest in the nanoscale simulations raises a fundamental question; whether the physical interaction model selection can affect the predicted dose distribution around the GNP. Although different models for the interaction of protons with gold are provided in various MC codes for the simulation of protons with gold, we have selected to limit our study to one code that provides two different interaction models. Doing so will allow us to examine the differences due to the physical interaction models which otherwise may be masked by differences between codes. Therefore, we are investigating the effect of the interaction model selection on GNPs under proton irradiation for one of the most widely used Monte Carlo codes for nanoscale simulations, the Geant4 simulation toolkit.

2. Materials and Methods

2.1. Monte Carlo simulations

Figure 1. A.) The irradiation Geometry: The GNP is irradiated by a parallel proton beam (blue) starting and ending at the GNP inner surface. B.) The proton irradiation results in the production of secondary electrons (red). The scoring spherical shells are shown as dashed lines, with the vertical line separating the shells to hemispheres.

The Geant4 v10.2 simulation toolkit was adopted for the calculation of the dose deposition around the GNP. In Geant4 a physical interaction is described by a “process” which can combine multiple physics “models”, depending on the region of the defined geometry and energy range. A collection of processes and corresponding models is referred as the “Physics List”. Two “Physics Lists”, namely “Livermore” and “Penelope” (Geant4 Collaboration 2015), are appropriate for the interactions of protons with the GNP. These “Physics Lists” allow the tracking of photons, electrons, positrons and protons. Both “Physics Lists” implement the same proton interaction models, while the photon, electron, and positron models are “Physics List” specific. The recommended applicability limit for electrons in “Livermore Physics List” is 250 eV, but can be used down to 10 eV with reduced accuracy. For the “Penelope Physics List” the applicability limit is 100 eV. In the framework of the

Geant4-DNA project (Incerti *et al* 2010, Bernal *et al* 2015), an alternative “Physics List” is available for liquid water simulating the dominant physical interactions of electrons down to thermalization energy (~ 25 meV).

For this study we combine either the “Livermore” or “Penelope” “Physics List” for the GNP with the Geant4-DNA “Physics List” for the surrounding water. In the reference scenario electrons, positrons, and protons are simulated, with the production threshold for electrons set to 10 eV for the “Livermore/Geant4-DNA” or 250 eV for the “Penelope/Geant4-DNA” combination. The influence of other production threshold values is also investigated.

The “Livermore” and “Penelope” “Physics Lists” incorporate the so called condensed history (CH) algorithms for the calculating of the energy loss of the charged particles. In this formalism the interactions of the charged particle are not calculated in an event-by-event fashion, but the cumulative effect of a number of interactions is considered. The simulation of a single particle track is broken down into a series of smaller segments called steps. For the Multiple Coulomb Scattering the default “Urban” model is being used in both cases.

The improved de-excitation models introduced in the 10.2 version of Geant4 (Incerti *et al* 2016) are activated in order to simulate fluorescence, Auger electron production, and particle induced x-ray emission (PIXE).

The “Physics Lists” and models used are summarized in Table 1. In the text we keep the term “Physics List” to refer to the default model combination provided by Geant4 and we will use the term “Mixed Physics List” to emphasize the “Physics List” combining “Livermore” or “Penelope” models with Geant4-DNA models. For instance, “Livermore Physics List” is referred to the Geant4 default “Physics List”. On the other hand the term “Livermore Mixed Physics List” means the combination of the “Livermore Physics List” for the nanoparticle and the Geant4-DNA “Physics List” for the surrounding water material.

Table 1. “Physics List” combinations (i.e. “Mixed Physics Lists”) used in the comparison for the proton interactions with the gold (GNP) or water nanoparticle (WNP), and surrounding water.

	GNP	WNP	Water	denoted as
“Physics List”	Livermore		Geant4-DNA default	<i>Livermore</i>
	Livermore, Auger Off		Geant4-DNA default	<i>AugerOff</i>
	Livermore		Geant4-DNA/Emfietzoglou*	<i>Emfietzoglou</i>
	Penelope		Geant4-DNA default	<i>Penelope</i>
	N/A	Geant4-DNA default	Geant4-DNA default	<i>DNA default</i>

**Emfietzoglou models for ionization and excitation up to 10 keV, otherwise identical to Geant4-DNA default*

2.2. Irradiation geometry

A single GNP with the radii of 1.0, 7.5, or 25.0 nm immersed in a water sphere representing the surrounding water environment with the radius of 1 μm was simulated. The GNP was irradiated with 3, 25, or 100 MeV protons instantiated from the inner half-surface of the sphere defining the GNP as depicted in Figure 1. The dose deposition was scored between the GNP surface and the water outer boundary in spherical shells with logarithmic thickness, forming the Radial Dose Distribution (RDD). Also, the dose deposited to two hemispherical shells formed by cutting the spherical shells perpendicular to the beam direction was scored.

Similarly to the GNP irradiations a control case of an equivalent water nanoparticle (WNP) was irradiated in order to calculate the Dose Enhancement Ratio (DER) in each case. The DER is defined as the ratio of the dose deposited from a GNP to that of a hypothetical WNP, and it is an index of the

local dose enhancement. In all cases enough particles were simulated to ensure mean statistical uncertainty less than 2%.

The protons only cross the water or gold nanoparticles volume and are “killed” outside of this NP volume. The energy deposited in the water volume surrounding the nanoparticles is therefore solely from the electrons produced inside the nanoparticles volume.

3. Results

The case of a single gold or water nanoparticle surrounded by water is simulated. The influence of the secondary production threshold, GNP size, proton energy, model selection on the calculated RDD and DER, and directionality of the RDD and DER are under investigation.

3.1. Dependence of the dose distribution and dose enhancement on the secondary production threshold

Figure 2. (A.) RDD and (B.) the DER for a GNP with a radius of 25.0 nm, irradiated with 25 MeV protons. Either the “Livermore” with the cut-off of 10, 100, 250 eV or “Penelope Mixed Physics List” with the cut-off of 100, and 250 eV is being used, denoted as Liv and Pen respectively. The dose percentage difference from the “Livermore Mixed Physics List” with 10 eV cut-off is presented.

Figure 2 shows the impact of the cut-off threshold to the RDD (A.) and the DER (B.) for a 25.0 nm GNP irradiated with 25 MeV protons incorporating the “Livermore” or “Penelope” “Mixed Physics List”. In the range 100 nm – 30 μ m an agreement of less than 3% is observed for the RDD, with respect to the “Livermore Mixed Physics List” - 10 eV cut-off. In Figure 3 the spectra of the electrons escaping the GNP and WNP of the previous scenarios, as well as the spectrum generated from the Geant4-DNA “Physics List” are also presented. For the following sections we focus on the “Livermore” - 10 eV cut-off and “Penelope” - 250 eV cut-off “Mixed Physics List”.

Figure 3. Spectra of the escaping electrons from the (A.) GNP and (B.) WNP. Either the “Livermore” with the cut-off of 10, 100, 250 eV or “Penelope” “Mixed Physics List” with the cut-off of 100, and 250 eV is being used. In the case of the WNP results from the Geant4-DNA “Physics List” are also presented.

3.2. Dependence of the dose distribution and dose enhancement on the GNP size

Figure 4 shows the RDD (A.) and the DER (B.) for a GNP irradiated with 25 MeV protons incorporating either the “Livermore” or “Penelope” “Mixed Physics List”. Three GNP radii were considered; i.e. 1, 7.5, and 25 nm. RDDs are normalized per initial proton crossing the GNP. The RDDs for all the GNP sizes are very similar and no difference from the model choice is observed after the first 100 nm. DERs are not affected by the “(Mixed) Physics List”; after the first 100 nm the DERs are similar and equal to about 14, until the maximum range of the secondary electrons. The maximum energy transferred to a free electron by a 25 MeV proton is calculated to be ~ 50 keV, corresponding to a maximum range of ~ 40 μm . After that distance there is not any contribution to the dose from the electrons produced inside the GNP and the RDD decreases sharply.

Figure 4. (A.) RDD and (B.) the DER for a GNP with a radius of 1.0, 7.5, or 25.0 nm, irradiated with 25 MeV protons. Either the “Livermore” or “Penelope Mixed Physics List” is being used denoted as Liv and Pen respectively.

3.3. Dependence of the dose distribution and dose enhancement on the proton energy

Figure 5 demonstrates the energy dependence in the “(Mixed) Physics List”, by comparing the (A.) RDD and (B.) the DER for a 25 nm radius GNP, irradiated with 3, 25, and 100 MeV protons. Neither the RDD nor the DER is affected by the “(Mixed) Physics List”. The RDD and DER are independent of the energy for distances ranging from around 20 nm to the maximum secondary electron range and reaches the value of 14 after the first 200 nm.

Figure 5. (A.) RDD and (B.) the DER for a GNP with a radius of 25 nm, irradiated with 3, 25 or 100 MeV protons. Either the “Livermore” or “Penelope” “Mixed Physics List” is being used denoted as Liv and Pen respectively.

3.4. Dependence of the dose distribution and dose enhancement from a GNP on selected model

Figure 6 shows the (A.) RDD and (B.) DER for the selection of models described in Table 1 for a 25 nm radius GNP irradiated with 25 MeV protons. Again the “(Mixed) Physics List” only affects the

first 20 nm, and the DER reaches the value of 14 independently of the “(Mixed) Physics List”. No influence by the Auger production is observed with the “AugerOff” “(Mixed) Physics List”.

Figure 6. (A.) RDD and (B.) the DER for a GNP with a radius of 25 nm, irradiated with 25 MeV protons. The “Livermore”, “Penelope”, “Emfietzoglou”, or “AugerOff” “Mixed Physics Lists” is used as described in Table 1.

3.5. Dependence of the dose distribution from a WNP on selected model

Figure 7 shows the (A.) RDD and (B.) DER for the selection of models described in Table 1 for a 25 nm radius WNP irradiated with 25 MeV protons. The “DNA-Default” case, which is the Geant4-DNA default models in both the WNP and the surrounding water, delivers the highest dose in the close vicinity of the GNP. After 20 nm all the models result in similar dose deposition (agreement within 5%), except the DNA-default where differences of about 20% are observed with respect to the “Livermore Physics List”. The inclusion of the Auger electron production does not affect the RDD (agreement within 5%) or the DER.

Figure 7. RDD of a WNP with a radius of 25 nm, irradiated with 25 MeV protons. The “Livermore”, “Penelope”, “Emfietzoglou”, “AugerOff” or “DNA-Default” “Mixed Physics List” is used as described in Table 1. The dose percentage difference from the “Livermore Physics List” is also presented.

3.6. Directionality of the dose distribution and dose enhancement

Figure 8 presents the impact of the directionality of the proton beam to the (A.) RDD and (B.) DER, for a GNP with the radius of 25 nm irradiated by 25 MeV protons. The “Livermore Mixed Physics List” is used with the cut-off of 10, 100, and 250 eV. The minus sign (-) denotes the direction of the beam, while the plus (+) denotes the opposite direction.

Figure 8. (A.) RDD and (B.) the DER for a GNP with a radius of 25 nm, irradiated with 25 MeV protons. The “Livermore Mixed Physics List” with the cut-off of 10, 100, 250 eV is being used, with minus/plus (-/+) sign denoting the beam forward/opposite direction. The dose percentage difference from the “Livermore Mixed Physics List” with the cut-off of 10 eV for each direction is also presented.

4. Discussion

The results presented in this work do not demonstrate any practical difference in the radial dose distributions or the dose enhancement ratio by the model combinations (i.e. “Mixed Physics Lists”), except if an accurate dose is needed within the first 100 nm from the GNP surface.

The “Penelope Physics List” has been used in many recent publications, for either calculating the RDD, DER, or in order to create dose distributions to import to a radiobiological model (Leung *et al* 2011, Lin *et al* 2015). This selection is based on the original paper presenting the suitability of the “Penelope” models for nanodosimetric (i.e. DNA damage) studies (Bernal and Liendo 2009). On the other hand, simulations based on the “Livermore Physics List” have demonstrated good agreement in reproducing energy spectra of gold nanoparticles or thin foils under photon or proton irradiation (Casta *et al* 2014, Incerti *et al* 2015). This work suggests that the choice of the “Physics List” is not important as long as accurate dose estimation close to the GNP is not necessary. It is important to note that the comparison between the “Penelope” and “Livermore” “Physics Lists” is only for the GNP volume. For the water material surrounding the GNP the same Geant4-DNA models are used in all cases.

The difference between the “Livermore” and “Penelope” “Mixed Physics List” in the first 20 nm may be attributed to the production threshold value. Electrons with energy less than 250 eV will deposit the energy locally. This energy corresponds to approximately 10 nm range in water, so within this range a reduced dose is expected within the first 10 nm when compared to the 10 eV cut-off. This effect is reduced with the GNP size, which validates that this reduction is due to the threshold cut-off value and the range of the low energy electrons. Moreover, a limitation in the electron production

arises from the ionization model. Current Geant4 proton ionization models cannot simulate the production of δ -rays below the mean ionization energy of the material. However, the same model is used in both cases, and similar influence is expected. The spectrum of the electrons escaping the GNP is presented in Figure 3. A strong dependence to the secondary production cut-off value is observed. Nonetheless, regarding the electron production by the gold material and the implications on the dose deposition, it only influences the production of the low energy electrons that deposit its energy close to the GNP vicinity.

In terms of computational efficiency, the use of the Livermore models with the cut-off value of 10 eV increases the computational time by a factor of about 2. More specifically, the “Livermore”, “AugerOff”, “Emfietzoglou”, and “Penelope” “Mixed Physics List” achieved 3.0, 2.1, 2.5, and 1.4 M particles/hr respectively for the reference case of a 25 nm GNP irradiated with 25 MeV protons. For the benchmarking an Intel Core i5@2.6 GHz with 8 GB DDR3 RAM running MacOSX 10.11 was used. With the lower cut-off value, a much higher number of low energy electrons is produced inside the GNP and subsequently has to be followed by the much more computationally intensive Geant4-DNA models utilized in the surrounding water medium.

The Geant4-DNA models are used for the dose deposition calculations in the water surrounding the GNP. Within the Geant4-DNA framework a selection of different models are available for the dominant processes, especially of ionization and excitation of electrons. Both the default models and the “Emfietzoglou” models for ionization and excitation were investigated with no noticeable difference found. While both are based on the same formalism, the latter are considered more accurate in the low energy regime (Kyriakou *et al* 2015, 2016). However, the Emfietzoglou models are only applicable for electron energies up to 10 keV with the default models used otherwise, resulting in identical dose distribution.

The “Mixed Physics List” selection for simulating the WNP (shown in Figure 7) has an influence on the calculated RDD, and consequently on the DER. Calculating the dose around the WNP when using the Geant4-DNA default “Physics List” for the interactions inside the WNP results in a higher RDD. When using the “Penelope Physics list”, a noticeably lower dose is observed for the same reasons described earlier. While this difference can affect the calculated DER, it is only significant within the first 20 nm.

Electrons produced from proton interactions generated preferentially towards the forward direction. Accordingly to our results in Figure 8 this is true for the high energy electrons (energy greater than 10 keV). As a result an increase to the RDD of the hemisphere towards the direction of the beam is observed. In contrast, the DER is higher for the backwards direction. We assume that the backscattering is higher inside the GNP, resulting to a higher DER for the opposite direction.

Another potentially limiting factor of the validity of the current gold models available in Geant4 for nanoscale simulations is the fact that they are based on condensed history algorithms. Although a good agreement of Geant4 simulations with experimental data has been demonstrated for spectrum reproduction of thin gold foils or GNPs (Casta *et al* 2014, Incerti *et al* 2015), the development of more accurate gold models should improve the secondary electron production. Recently, a discrete electron transport model for Geant4 was developed (Sakata *et al* 2016) but has not become available in the public release. This improvement is expected to influence the low energy spectrum and consequently the dose deposition in the close vicinity of the GNP.

The experimental setup of this work has been chosen primarily for the evaluation of the Geant4 models available for nanoscale simulation and therefore it has been as simple as possible. McKinnon *et al* (2016) implemented a more realistic geometry comprising the simulation of the full proton track structure through and outside the NP. The different geometry implemented resulted to different dose enhancement values. On the other hand the spectra of the electrons escaping the GNP generated are very similar. It has to be noted that a simulated spectrum strongly depends on the model selection and

cut-off values. The inclusion of the atomic de-excitation has only minor effect on the dose enhancement, as also reported by our study.

GNPs are not uniformly distributed into the cell. Clusters of vesicles (a vesicle is a spherical structure resulting from the acquisition process of the GNP from the cell and with typical diameters of 300 nm) containing the GNP are formed, localizing the GNPs predominately into the cytoplasm, without entering the cell nucleus (Sadauskas *et al* 2009, Peckys and De Jonge 2011, Peckys and Jonge 2014, Stefančíková *et al* 2014). Therefore, the GNPs are away from the nucleus where the DNA is located. In order to achieve a radiosensitization enhancement effect from the GNPs, the increase in the dose has to be significant at a spatial distance of a few μm , comparable to the cell nucleus. As the difference between the two models is located within the first 20 nm, no significant implications are expected for the DNA damage and subsequently no impact in the radiosensitization effect.

Although the dose deposition has been extensively used to compare the radiation effects around the GNP, its macroscopic character hides the underlying details of the secondary electron track structure. As long as DNA damage is the main target of the physical component of the GNP radiosensitization, further attention has to be paid to the track structure of the secondary radiation. Recently the nanodosimetry paradigm has been used in order to assess the DNA damage (Grosswendt 2005, Garty *et al* 2010). Within the nanodosimetry framework the dose deposition profile is not directly considered. Instead the ionisation cluster size distribution is scored in a volume representing a DNA segment of a few base pairs, and then is used to correlate radiation quality to DNA damage. This kind of calculation is more sensitive to the model selection (Lazarakis *et al* 2012) and further work is planned in order to elucidate the effect of the model selection in the presence of GNPs.

RDDs calculated by Geant4 Monte Carlo simulations have been utilized in radiobiological models that predict cell survival. More specifically the Local Effect Model (LEM) has been implemented for the calculation of the GNP radiosensitization, demonstrating a good agreement with experimental values (McMahon *et al* 2011a, McQuaid *et al* 2016). Current GNP formulations have been shown not to enter the cell nucleus. Under such circumstances the “Mixed Physics List” selected should not have any influence on the final results, as DNA is would be located at too great a distance away from the GNP.

Another case where the “Mixed Physics List” selection might be important is when the free radical production is under consideration. Overall, the free radical production should be more sensitive to the physical interaction model and production threshold used. The initial free radical production is directly proportional to the dose deposition, or equivalently to the secondary electron production (Tran *et al* 2016). As Tran *et al* demonstrated, the time evolution of the distribution suggests that the free radicals on average stay in their initial positions. In the case of high free radical density produced in close proximity to the GNP, these free radicals recombine to water reducing the local concentration. As a result, the effect of the “Mixed Physics List” on the RDD is expected to propagate to the free radical production, therefore increasing instantaneous free radical production within the first 20 nm. The new discrete models for the electron transport for gold (Sakata *et al* 2016) are expected to have the strongest impact on the free radical enhancement.

Considering a more realistic distribution of GNPs within a cell, as described for example in (Peckys and De Jonge 2011, Peckys and Jonge 2014), where vesicles containing the GNP are formed, the “Mixed Physics List” selection should not have any effect because of the multiple contributions of the adjacent GNPs for each point neutralizing the dose enhancement effect.

5. Conclusion

The Geant4 models for the interactions of gold and water with protons were compared in order to investigate whether the “Mixed Physics List” selection may influence the dose or dose enhancement

around a GNP. It was found that for radial distances larger than 100 nm from the surface of the GNP no substantial difference should be made by the model combinations of the “Physics Lists” studied. For distances less 100 nm, differences are observed but the relevance depends strongly on the application. Unless more accurate models implementing event-by-event algorithms for the gold interactions with charged particles become available, the dose uncertainty within the first 100 nm is expected to be high.

The simulated simple irradiation conditions in this paper were selected in the view of establishing a benchmarking geometry that can be later used to compare data from other Monte Carlo codes. An inter-comparison with other codes for nanoscale simulations is envisaged in order to improve the uncertainty estimation in dose deposition calculations of Monte Carlo codes.

Acknowledgements

This work has been supported by Marie Curie Actions - Initial Training Networks (ITN) as an Integrating Activity Supporting Postgraduate Research with Internships in Industry and Training Excellence (SPRITE) under EC contract no. 317169.

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