Monte Carlo simulation on low-energy electrons from gold nanoparticle in radiotherapy

James C L Chow1,3, Michael K K Leung2, Sean Fahey3, Devika B Chithrani3 and David A Jaffray1,2

1 Department of Radiation Oncology, University of Toronto and Radiation Medicine Program, Princess Margaret Hospital, University Health Network, Toronto, Ontario M5G 2M9, Canada; 2 Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada; 3 Department of Physics, Ryerson University, Toronto, Ontario, Canada.

james.chow@rmp.uhn.on.ca

Abstract. This study investigated the low-energy electrons (LEEs) produced when a gold nanoparticle (GNP) is irradiated by photon beams. The secondary electrons emitted from a GNP (diameter = 100 nm), interacting with photon beams with energies equal to 35, 73.3 and 600 keV, were simulated using the Geant4 Monte Carlo code. The phase spaces of the secondary electrons were then used to simulate the LEEs in water using the NOREC Monte Carlo code. All secondary electrons emitted by the GNP, and all LEEs produced by each secondary electron were tracked in Monte Carlo simulations. It is found that the energy distributions of the LEEs from the GNP do not vary significantly between different photon beam energies. Moreover, the 660 keV photon beam produced more LEEs travelling to a longer range than photon beams of lower energies (35 and 73.3 keV). This higher energy deposition and longer range LEEs produced by the 660 keV photon beam can enhance the cell kill. Based on our Monte Carlo results, it is concluded that the unexpected close of the radiosensitization enhancement factors of the 35 (1.66) and 660 keV (1.18) photon beams from our previous measurements is because of the cell kill enhancement with the increased LEE yield and range in the 660 keV photon beam.

1. Introduction

It is generally believed that cancerous cell can be killed by ionizing photon beams that are energetic enough to detach electrons from atoms in the strand of the deoxyribonucleic acid (DNA). This may induce a damage of DNA strand called double-strand break (DSB), which separates the DNA into two pieces.1,2 Since DNA is essential for the cell reproduction process, damaging the DNA means stopping the growth of cancerous cell or cell kill. On the other hand, electromagnetic radiations are ionizing when the photon energy is larger than 124 eV. Therefore, for the electron to be ionizing, it must have sufficient energy (i.e. > 124 eV), and must interact with atoms of the target (i.e. DNA strand).

There are studies suggesting that most energy deposited by the ionizing photon beams is transferred to a large number of low-energy electrons (LEEs) in the cell medium. These LEEs are in the energy range of 3 – 20 eV and produced by a cascade effect of photon beams in the medium.3-5 These LEEs, which may have energy lower than the ionization thresholds, are found to yield substantial DNA damages such as single-strand break (SSB) and DSB.3,4 This finding prompts us to think about the cancerous cell killing algorithm caused by the ionizing photon beams, and challenges the general...
understanding that cell kill only happens when the DNA interacts with secondary electrons with energy higher than the onset of ionization.

Gold nanoparticle-enhanced radiation therapy employs gold nanoparticle (GNP) uptake by a tumour under a photon beam irradiation to enhance the biological effective dose or treatment outcome. 

Hainfeld et al. used the 1.9 nm GNPs with concentration of gold up to 7 mg Au/g in tumours of mice for radiation therapies using the 250 kVp photon beam. They found that the one-year survival rate was 86% versus 20% with and without using GNP in the treatment. This great improvement of treatment outcome is because of the achievement of the high metal content in tumours necessary for the significant high atomic number \( (Z) \) radioenhancement. As more photoelectrons interact with DNA strands in the cancerous cell to produce DNA damage, the yield of cell kill is increased and hence a better treatment outcome can be achieved. The addition of GNP to the tumour increases the biological effective dose, which is the required dose reaching the cells where adverse effect occurs.

When the photon beam energy is in the range of 100 keV – 1 MeV, Compton interaction is dominant to produce secondary electrons. Since the cross-section of Compton scattering does not depend on the \( Z \) as in the case of the photoelectric effect, adding GNP to the tumour should not benefit the biological effective dose for photon beams in the Compton energy range compared to photoelectric (energy < 50 keV). This can be seen from our previous works of Monte Carlo simulations, where we found that for the 35 keV photon beam, adding GNP to water or tumour can increase the number of photoelectric interaction over 2900 times. While for the higher energy of 660 keV photon beam in which Compton interaction is dominant, adding GNP to water or tumour can only increase the number of Compton interaction by 6 times. Therefore, a combination of GNP addition and photon beam with low energy such as 35 keV should produce more secondary electrons compared to that of the higher photon beam energy of 660 keV. However, according to our measurements, the radiation sensitization enhancement factor (REF), defined as the ratio of dose (without GNPs)/dose (with GNPs) at 10% survival for HeLa cells, for the 35 keV photon beam is 1.66, while that for the 660 keV photon beam is 1.18. The increase of the REF from decreasing the photon beam energy from 660 to 35 keV is just about 1.4 instead of 483 times higher based on the increased number of interactions in Monte Carlo simulations. The disagreement between the Monte Carlo results and measurements shows that more work should be done in order to understand the relationship between the dosimetry/energy deposition of the GNP and cell kill due to the DNA damage.

One potential explanation of the above disagreement of REF is that the cell kill is heavily dependent on the LEE mentioned above. As the photon beam with higher energy (i.e. 660 keV) should be able to produce much larger number of LEE than the low energy, it results in the REF value of the 660 keV photon beam within the same order of magnitude compared to the 35 keV beam. In order to justify this point of view, Monte Carlo simulations were used to study the interactions of LEE produced by an irradiated GNP using photon beams with different energies. The aim of this study is to predict the yield and energy distribution of the LEE from the irradiated GNP to understand the relationship between the cell kill in terms of the REF and photon beam energy.

2. Methods

The LEEs generated by the secondary electrons from the GNP were simulated through two phases. Phase 1 involved the Monte Carlo simulation on the secondary electrons emitted by the irradiated GNP using photon beams with energies equal to 35, 73.3 and 660 keV. The Geant4 Monte Carlo code was used to determine the phase spaces of the secondary electrons. Phase 2 was the Monte Carlo simulation on the LEEs based on the phase spaces of the secondary electrons from Phase 1. The NOREC Monte Carlo code was used to track all electrons produced by every secondary electron with energy down to the LEE range. Simulations of the Geant4 and NOREC were performed on the General Purpose Cluster (GPC) supercomputer at the SciNet from the University of Toronto. A single core of the GPC was assigned to a simulation of specific photon beam energy. Therefore, three simulations (35, 73.3 and 660 keV) were run.
in parallel. A low statistic error can be achieved by using a large number of histories. In this work, two hundred and fifty million of histories were run using the Geant4 code followed by the NOREC.

2.1 Simulation geometry and setup

The simulation geometry is shown in Fig. 1. A spherical GNP with a diameter of 100 nm was centered inside a cubic tracking volume consisting of water. The NP was irradiated by photon beams with energies of 35, 73.3, and 660 keV. The cross-sectional diameter of the photon beam was taken to be 100 nm, and the axis of the beam was aligned with the center of the NP. With increasing beam energy, the linear dimension of the cubic tracking volume was increased from 0.3 to 1.5 mm to compensate for the longer electron path. Two hundred and fifty million photon histories were used at each beam energy. In Geant4, production thresholds are defined in terms of distance, which is then internally converted into an energy threshold below which no secondary particles are generated. A universal threshold of 100 nm is used for all particle types. For each electron emitted from the irradiated GNP, the total energy deposited, and the range were tracked in water. The simulation time ranged from 10 to 50 hours depending on the energy of the photon beam.

![Figure 1. Schematic diagrams (not to scale) showing the simulation geometry of the GNP in a water cube irradiated by a photon beam.](image)

2.2 Monte Carlo simulation using Geant4

Geant4 (GEometry ANd Tracking 4) is a Monte Carlo toolkit for the simulation of the transports and interactions of photons and electrons through matter. The algorithm of particle transport in Geant4 contains four levels: “Run”, “Event”, “Track” and “Step”. The level “Run” defines the initialization and termination of a particle and the number of history. “Event” is the simulation of interaction in one history. “Track” is an intermediate level between “Event” and “Track”, while “Step” defines the particle advancing one step in the medium.

The support for low-energy interactions is necessary for small target volumes (of the order of nanometers in this study), to ensure that the particle trajectories are accurately modelled. In our simulation we used the Penelope-based Geant4 low-energy library,\textsuperscript{17,18} which has been verified to be in excellent agreement with the original PENELOE code and is more suitable for microdosimetry applications.\textsuperscript{19,20} Geant4 includes routines that allow for the precise definition of complex particle transport volumes and tools to visualize and analyze the simulation results. Release 9.0 was used to simulate the energy distributions of the secondary electrons emitted from a GNP irradiated by the photon beams.

2.3 Monte Carlo simulation using NOREC

Since Geant4 can only track electron down to energy of 250 eV, another specific Monte Carlo code, should be used to track energy spectral results of secondary electrons, generated by the Geant4 with energy down to about 10 eV. NOREC is a package containing a single-scattering Monte Carlo electron
track-structure code for water.\textsuperscript{16} NOREC can simulate electron histories in an energy range from 7.4 eV to 1 MeV and is based on the earlier Oak Ridge Electron Code (OREC).\textsuperscript{21} The algorithm of NOREC employs the ELAST database, developed at the National Institute of Standards and Technology, for the differential cross sections of elastic scattering of electrons by atoms. Phase shifts are calculated by the Dirac equation using the WKB approximation. For tracking the LEEs with energy between 10 eV and 7.4 eV, a subroutine is called in the code to terminate the event-by-event transport and select a single additional step to bring the electron below the subexcitation energy threshold. The remaining energy is then recorded at the location of the last inelastic collision.

Although this code only works in a homogeneous medium of water, it does not affect calculations of the energy spectrum and yield of the LEEs because only the inhomogeneity of GNP has been considered in the Geant4. The idea is to obtain the secondary electron phase spaces using the Geant4 when the incident photon beam interacts with the GNP, and input the energy spectral result to NOREC to obtain the energy spectrum and yield of the LEEs. Modifications of the NOREC were done to allow the code to run more than one history. With both the Geant4 and NOREC, secondary electrons generated by the photon beams can be tracked with energy down to the level of the LEE.

3. Results and discussion

Figures 2(a), 2(b) and 2(c) show the energy spectra of the secondary electrons emitted from the GNP when irradiated by photon beams with energies equal to 35, 73.3 and 660 keV, respectively. The intensities of the energy distributions in Figs. 2 are normalized to the maximum intensities in the figures. Fig. 2(a) shows that the energies of the secondary electrons emitted from a GNP irradiated by a 35 keV photon beam are mainly in the range from 21 to 33 keV. The energy spread increases with increasing photon beam energy as shown in Figs. 2(b) and 2(c). In Fig. 2(c), the continuous energy distribution between 0 to 500 keV represents the Compton spectrum with the full energy peak at 580 keV. This shows that Compton interaction is dominant in the 660 keV photon beams, while photoelectric interaction is dominant in the 35 and 73.3 keV photon beams.

Figure 2. Energy spectra of the secondary electrons emitted by the GNP when irradiated by the (a) 35 keV, (b) 73.3 keV and (c) 660 keV photon beams. All intensities in the spectra are normalized to the maximum values in the figures.

Figures 3(a), 3(b) and 3(c) show the energy distributions of the LEEs produced by the secondary electrons with energy distributions in Figs. 2(a), 2(b) and 2(c), respectively. Figures 3(a), 3(b) and 3(c) represent the total energy distributions of the LEEs in water and all intensities of the energy distributions are normalized to their maximum values in the figures. It can be seen in Figs. 3(a), 3(b) and 3(c) that the energy distributions of the LEEs for the total interactions are very similar between different energies. This is further supported by the distributions of interaction type of the LEEs with different energies as shown in Fig. 4 that the distribution of the LEE interaction does not change significantly as the photon beam energy is changed. This shows that the dependence of the secondary electron spectrum from the GNP on the energy distribution of the LEEs is not significant.
Table 1 shows the summary of simulation data using the NOREC. Since the incident electrons deposit all energy within the simulation tracking volume, the total energy deposited is equal to the total energy of the incident electrons. The total number of interaction or event is highly dependent on the incident energies per number of history, and higher energy electrons will go through many more events to deposit all of their energy. With the same number of history, it can be seen that the 660 keV photon beam can deposit about 15 times more energy than the 35 keV beam from the generated LEEs. Table 2 shows the volume in which the interactions occur for each spectrum, and the maximum range of electrons in each spectrum. The volume is assumed to be rectangular, and is obtained by multiplying the difference of the maximum and minimum x, y and z values. At higher energies the electrons are much more penetrating and the interactions occur in a much larger volume. The energy deposited in all three photon beams in Table 1 is very close, hence suggesting that there is a greater dose enhancement when using lower energy photon beams, which agrees with previous studies. However, since it is found in Table 2 that the LEEs produced by the 660 keV photon beams can spread more than 100 times further than the 35 keV, the increased energy deposition (Table 1) and spread from the LEEs should result in a larger cell kill. This may explain why the REF value of the 35 keV photon beam is not about 483 times larger than that of the 660 keV, by considering only the increased number of photoelectron due to the photoelectric enhancement.
Table 1. Number of histories, events and total energy deposited for the LEEs from the GNP irradiated by the 35, 73.3 and 660 keV photon beams. It can be seen that the number of event and total deposited energy are nearly equal for 3000 absorbed or scatted 35 keV photons and for 200 absorbed or scatted 660 keV photons.

| Energy  | Number of history | Number of Event | Total energy deposited |
|---------|------------------|-----------------|------------------------|
| 35 keV  | 3000             | 925689          | $7.334 \times 10^7$ eV |
| 73.3 keV| 1200             | 9217073         | $7.307 \times 10^7$ eV |
| 660 keV | 200              | 9271881         | $7.356 \times 10^7$ eV |

Table 2. Sampling volumes and maximum ranges of the LEEs studied in Table 1.

| Energy  | Volume ($\mu m^3$) | Maximum range ($\mu m$) |
|---------|--------------------|-------------------------|
| 35 keV  | 44303              | 22.064                  |
| 73.3 keV| $1.648 \times 10^6$ | 82.273                  |
| 660 keV | $1.823 \times 10^6$ | 2501.9                  |

4. Conclusions
Monte Carlo simulations on the secondary electrons generated by the interaction between the GNP and photon beams, and LEEs produced by the secondary electrons from the GNP were carried out using the Geant4 and NOREC code. It is found that the energy distributions of the LEEs with different photon beam energies do not depend significantly on the energy spectra of the secondary electrons from the GNP. Moreover, increased deposition and spread of energy due to the LEEs were found for the 660 keV photon beam, when compared to the lower photon beam energies of 35 and 73.3 keV. It is concluded that higher photon beam energies of 660 keV can produce more LEEs with longer interaction range, and result in an enhancement of cell kill.

Acknowledgement
The authors would like to acknowledge the contribution from Professor Martin Lee, University of Toronto, who passed away on 21st April 2009. His enthusiastic support of this study is very much missed. The authors would also like to acknowledge the SciNet HPC Consortium in the University of Toronto for providing computing support (SciNet RAC Allocations for 2010).

References
[1] Obe G, Johannes C, and Schulte-Frohlinde D 1992 DNA double-strand breaks induced by sparsely ionizing radiation and endonucleases as critical lesions for cell death, chromosomal aberrations, mutations and oncogenic transformation. *Mutagenesis* 7 3
[2] Sokolov M V, Smilenov L B, Hall E J, Panyutin I G, Bonner W M, Sedelnikova O A 2005 Ionizing radiation induces DNA double-strand breaks in bystander primary human fibroblasts *Oncogene* 24 7257
[3] Bodia B, Cloutier P, Hunting D, Huels M A, and Sanche L 2000 Resonant formation of DNA strand breaks by low-energy (3 to 20 eV) *Sci.* 287 1658
[4] Sanche L 2005 Low energy electron-driven damage in biomolecules *Eur. Phys. J. D* 35 367
[5] Lu Q B, Kalantari S, and Wang C R 2007 Electron transfer reaction mechanism of cisplatin with DNA at the molecular level *Molecular Pharmaceutics* 4 624
[6] Hainfeld J F, Slatkin D N, Smilowitz H M 2004 The uses of gold nanoparticles to enhance radiotherapy in mice *Phys. Med. Biol.* 49 N309
[7] Hainfeld J F, Dilmanian F A, Slatkin D N, and Smilowitz H M 2008 Radiotherapy enhancement with gold nanoparticles *J Pharm Pharmacol.* 60 977
[8] Cho S H 2005 Estimation of tumour dose enhancement due to gold nanoparticles during typical radiation treatments: a preliminary Monte Carlo study *Phys. Med. Biol.* 50 N163
[9] Roa W, Zhang X, Guo L, Shaw A, Hu X, Xiong Y, Gulavita S, Patel S, Sun X, Chen J, Moore R, and Xing J Z 2009 Gold nanoparticle sensitize radiotherapy of prostate cancer cells by regulation of the cell cycle Nanotechnology 20 375101

[10] Rahman W N, Bishara N, Ackerly T, He C F, Jackson P, Wong C, Davidson R, Geso M 2009 Enhancement of radiation effects by gold nanoparticles of superficial radiation therapy Nanomedicine 5 136

[11] Chithrani D B, Jelveh S, Jalali F, van Prooijen M, Allen C, Bristow R G, Hill R P and Jaffray D A 2010 Gold nanoparticles as radiation sensitizers in cancer therapy Rad. Res. 173 719

[12] Chow J C L, Leung M, Chithrani D, Lee M, Oms B, and Jaffray D 2009 Dosimetry on gold nanoparticle: a microscopic and macroscopic study using Monte Carlo simulations Med. Phys. 36 2512

[13] Leung M, Chow J C L, Chithrani D, Lee M, Oms B and Jaffray D 2009 Characterization of the spatial and energy distribution of electrons emitted from a gold nanoparticle irradiated by x-rays using Monte Carlo simulations Med. Phys. 36 2819

[14] Agostinelli S et al 2003 GEANT4 – A simulation toolkit Phys. Res. A 506 250

[15] Semenenko V A, and Steward R D  2004 A fast Monte Carlo algorithm to simulate the spectrum of DNA damages formed by ionizing radiation Rad. Res. 161 451

[16] Semenenko V A, Turner J E, and Borak T B 2003 NOREC, a Monte Carlo code for simulating electrons tracks in liquid water Radiat. Environ. BioPhys. 42 213

[17] Spiga J, Siegbahn E A, Brauer-Krisch E, Randaccio P, and Bravin A 2007 The GEANT4 toolkit for microdosimetry calculations: Application to microbeam radiation therapy (MRT) Med. Phys. 34 4322

[18] Stewart R D, Wilson W E, McDonald J C, and Strom D J 2002 Microdosimetric properties of ionizing electrons in water: A test of the PENELOPE code system Phys. Med. Biol. 47 79

[19] Jones B L, Krishnan S, Cho S H 2010 Estimation of microscopic dose enhancement factor around gold nanoparticles by Monte Carlo calculations Med. Phys. 37 3809

[20] Mainardi E, Donahue R J, Wilson W E, and Blakely E A 2004 Comparison of microdosimetric simulations using PENELOPE and PITS for a 25 keV electron microbeam in water Rad. Res. 162 326

[21] Turner J E, Hamm R N, Souleyrette M L, Martz D E, Rhea T A, and Schmidt D W 1988 Calculations for beta dosimetry using Monte Carlo code (OREC) for electron transport in water Health Phys. 55 741