RESEARCH ARTICLE

Energy deposition and dose enhancement using Monte Carlo derivative sampling: applications in brachytherapy

H Khan¹, ZU Koreshi², U Aziz^{3*}, SR Sheikh³ and SA Ahmad⁴

¹ Department of Sciences & Humanities, National University of Computer and Emerging Sciences, Islamabad, Pakistan.

² Faculty of Graduate Studies, Air University, Islamabad, Pakistan.

³ Department of Mechatronics Engineering, Air University, Islamabad, Pakistan.

⁴ Department of Strategic Studies, National Defence University, Islamabad, Pakistan.

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Abstract: Energy deposition and radiation dose distribution by the use of gold, a high-Z biocompatible element in water solution, is estimated as a function of source energy typical of brachytherapy sources (15 keV, 20 keV, 30 keV, 40 keV, 80 keV, 90 keV, 150 keV, 300 keV, 1 MeV), solution concentration (5–25 mg Au/g H₂O), and solution placement (1–2 cm concentric shells). Monte Carlo (MC) simulations are carried out with the MCNP5 code, compared with other widely used MC codes such as PENELOPE and GEANT, to validate the dose estimates, which may vary considerably due to artifacts and data libraries, and extended to a sensitivity analysis using perturbation estimates. The energy deposition and radiation dose are estimated as a function of monoenergetic source radiation energy, and concentration of gold in solution. MC simulation is carried out in the coupled photon-electron radiation mode for x-rays emanating from a radiation source implanted in a water cell, for which results are valid for a cancer cell modelled by a spherical water phantom. For carrying out sensitivity studies, the Monte Carlo perturbation feature with material perturbations was used to sample derivatives in a single run which were used in a Taylor series to estimate both dose and Dose Enhancement Factor (DEF) from single MC runs. Close agreement was found between dose estimates from MCNP5, PENELOPE and GEANT, in spite of artifacts such as cut-offs in electron transport. It was also found that dose increases with energy of a source, and that dose enhancement, for a given concentration, decreases with source energy. The perturbation estimates result in enhanced computational efficiency.

Keywords: Brachytherapy, dose enhancement, energy deposition, gold nanoparticles, Monte Carlo simulation.

INTRODUCTION

Energy deposition from radiation is of use for several engineering and medical applications, such as the design of radiation shields and in the treatment of cancer. This research carried out simulations to estimate the dose in a water cell similar to a cancer cell in composition. In nuclear medicine, radiation nuclide therapy (RNT) is used for the treatment of organs such as the thyroid, bones, heart, liver and for the treatment of cancer in organs such as the lungs, breast, colon and rectum, prostate, stomach, and liver. Nuclear radiation, in the form of X-rays, gamma rays and charged particles, can damage the DNA (deoxyribonucleic acid) molecules of cancer cells that carry the genetic information and pass it from one generation to the next, to stop their further division. RNT is used both externally as ‘tele-therapy’ and internally as brachytherapy, or ‘short-distance therapy’. The number of cancer cases globally is expected to grow from 14.1 million in 2012 to 24 million by 2035 (Common Cancer Types - National Cancer Institute; Worldwide cancer data - World Cancer Research Fund). Improvements in cancer therapy, such as the dose enhancement by radiation and better computational methods for its estimation, the focus areas of research reported in this paper are thus of paramount importance to the science and technology of medicine. Of the 200 or more radioisotopes used in nuclear medicine (Radioisotopes in Medicine), common

* Corresponding author (umair.aziz@mail.au.edu.pk; <https://orcid.org/0000-0002-9554-0725>)

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radioisotopes include technetium ^{99m}Tc , iodine ^{125}I , palladium ^{103}Pd , iridium ^{192}Ir , cesium ^{137}Cs , and cobalt ^{60}Co .

Important radionuclides for brachytherapy include the conventional encapsulated (Perez-Calatayud *et al.*, 2012) low dose rate (LDR) sources (< 200 cGy per hour) Ir-192, and high dose rate (HDR) sources (> 1200 cGy per hour) (Pisansky *et al.*, 2008; Mose *et al.*, 2013; Mobit *et al.*, 2016). Permanent brachytherapy sources (Lechtman *et al.*, 2011) such as ^{125}I and ^{103}Pd with energy < 50 keV are commonly used LDR sources, with typical implants of 50-80 metallic seeds encasing isotopes, used for the treatment of prostate cancer, uveal melanomas and brain tumours.

For calculations for dose distribution MC methods (Kalos & Whitlock, 2008) and general-purpose codes, such as EGSnrc, GEANT (Allison *et al.*, 2006), PENELOPE (Salvat *et al.*, 2006) and MCNP (Team, 2008) have been extensively used (Jabbari, 2011; Seco, 2016) for simulating the transport of radiation from radiation seeds in the medium consisting of tissue, and material in the vicinity of the cancer. These codes have produced fast and accurate results which have been experimentally validated and benchmarked.

A further development in brachytherapy has been the possibility of injecting high-Z biocompatible elements such as gold and gadolinium in solution form through fenestrations of cancer cells to improve the effectiveness of therapy. The method thus requires elements of dimensions small enough to be delivered into tumour cells so that the effects of radiation are localized and restricted to the 'bad' cells while sparing the healthy 'good' cells. The determination of radiation dose, in addition to the previously mentioned factors, now extends to a determination of the choice of element, its size and shape, and injection procedure in solution form. The requirements of particle size necessitate the range down to nanoscale ($\sim 10^{-9}$ m) which compares with the diameter of an atom ($\sim 10^{-10}$ m), thus introducing nanotechnology to the field of brachytherapy (Jain *et al.*, 2012; Chatterjee *et al.*, 2013).

In brachytherapy, the use of gold nanoparticles (GNPs) is an active area of research to determine possible dose enhancement (Bahreyni Toossi *et al.*, 2012; Brivio *et al.*, 2017; Safigholi & Song, 2018; Gray *et al.*, 2019; Jangjoo *et al.*, 2019) to make the therapy more effective. Nanoscale, at which the wavelength of incident electromagnetic radiation can become of the order of atomic dimensions casts doubts on the reliability

of simulation results from Monte Carlo codes due to several artifacts.

The effects of such artifacts for electron transport have been investigated (Almansa *et al.*, 2006; Koivunoro *et al.*, 2012; Archambault & Mainegra-Hing, 2015) with EGSnrc, GEANT and PENELOPE codes and in some cases 'large discrepancies' (> 3%) have been found between MCNP5 dose distributions and the 'reference codes' concluding that MCNP5 electron transport calculations are not accurate at all energies and in every medium by general clinical standards. Similarly, comparisons have been made (Yu *et al.*, 2017) between EGSnrc, GEANT4, MCNP5 and PENELOPE for mono-energetic electron beams in a water-filled sphere of radius varying from 0.25–4.5 cm for beam energies of 0.5 MeV, 1.0 MeV, and 5.0 MeV and found to have differences below 10% by tuning parameters associated with multiple scattering algorithms at the expense of increased computation time. It can thus be anticipated that MCNP5 may differ due to its inadequate low-energy treatment of electron transport. Šidlová and Trojek (2010) have carried out electron transport comparisons of MCNPX, Penelope and EGSnrc, for electrons of 20–450 keV in water, lead and tungsten. These comparisons were focused on bremsstrahlung, energy deposition in matter, electron ranges and production of secondary electrons by gamma radiation. Thus, preliminary runs are carried out to compare dose estimates from MCNP5 with Penelope and Geant4 (Almansa *et al.*, 2006).

Thus, benchmarking and validating MC results have become particularly relevant not only for radiation dose but also for the resulting biological absorbed dose, which is the ultimate quantity of interest varying from organ to organ. With the objective of determining radiation dose distribution and the dose enhancement factor (DEF) by the use of gold, a high-Z biocompatible element, this work carries out MC simulation, using MCNP5, for simulating coupled photon-electron radiation transport from x-rays emanating from a radiation source implanted in tumour, modelled by a spherical water phantom, to estimate the energy deposited and the subsequent biological dose. Good comparisons are presented for point mono-energetic source in water (Luxton & Jozsef, 1999; Almansa *et al.*, 2006). While water phantoms are used for representing configurations similar to soft tissue, full anthropomorphic phantoms are also used to carry out detailed simulation for the dose (Neves *et al.*, 2014).

For MC simulations in brachytherapy (Lechtman *et al.*, 2013; Mesbahi *et al.*, 2013; Asadi *et al.*, 2015) it has been shown that photon source energy and

concentration are important factors that determine DEF while the size of GNPs is not so important (above the K-edge energy). Thus, in this work, a homogenous model with considerable savings on the computational effort, as well as a sensitivity capability is used to extract crucial information on the DEF from independent parameters.

The MCNPX code has been used (Mesbahi *et al.*, 2013) for simulating mono-energetic photon beams (50–120 keV), ^{60}Co beam, and 6 & 18 MV photon beams, while GEANT4 simulations have been carried out (Banoqitah & Djouider, 2016) for estimating the DEF from high energy photons from ^{192}Ir (0.380 MeV), ^{137}Cs (0.662 MeV) and ^{60}Co (1.2 MeV) for gadolinium ($Z = 64$) nanoparticles in a heterogeneous model with concentrations ranging from 10–70 mg/g brain tumour.

In this work, the source energy of interest is 15 keV – 1 MeV typical of brachytherapy sources (15 keV, 20 keV, 30 keV, 40 keV, 80 keV, 90 keV, 150 keV, 300 keV, 1 MeV), while the gold particles in solution form with water were assumed to comprise a homogenous mixture with concentrations in the range 5–25 mg Au/g H_2O . While MCNP has the capability of modelling very detailed heterogeneous configurations, this paper considers a homogenous model solely to demonstrate (i) results from benchmarked problems and (ii) for obtaining MC sensitivity estimates for a ‘bulk’ material to demonstrate validity of MC perturbation and quantifying increased computational efficiency.

For comparison, dose estimates from MCNP5 were compared with published results from PENELOPE and GEANT. The second objective of this work was to estimate the effect of small changes in solution concentration on the resulting radiation dose from a single MC simulation rather than estimating changes from MC re-runs where the effect is vulnerable to be masked in the uncertainty of the estimate itself. Such MC perturbation analysis has applications in brachytherapy for estimating dose perturbations when implants are present in the vicinity of an organ receiving radiation from an implanted source (Yu *et al.*, 2017). However, it is yet to be used in simulation for brachytherapy studies and can provide great computational efficiency leading to optimal designs based on ‘best’ experimental parameters such as radiation energy, concentration of gold in solution and material placement for maximizing an objective function of interest.

There is still no consensus on the optimal size, shape and distribution of GNPs. Experimental and pre-clinical evidence for mouse tumours showing a 1-year survival rate of 86% following a dose of 26 Gy, with 1.9 nm

intravenously administered GNPs vs 20% for tumours not laden with GNPs (Jain *et al.*, 2012), indicates that nanotechnology offers promising improvements in brachytherapy. This work is aimed to further improve the understanding of determining possible improvements in delivered dose by applying Monte Carlo simulation, and the MC perturbation capability (Rief, 1984; Koreshi & Lewins, 1990), to lead to optimal experimental configurations.

METHODOLOGY

Monte Carlo simulation

The Monte Carlo code MCNP5 is used to carry out a coupled photon-electron simulation of radiation transport to estimate the dose distribution, from a point isotropic photon source typical of brachytherapy sources (30 keV for ^{125}I - 1.25 MeV for ^{60}Co) located at the origin of a sphere, in concentric shells of water of thickness 0.5 mm up to a radius of 15 cm. A solution of gold and water is then considered in the shells located 1–2 cm from the center and the F6 (energy deposition) and *F8 (pulse height) tallies are used for phantom dosimetry. Photon and electron data for air, water and gold are based on ENDF/B-VI (Release 8). In the MCNP ‘detailed physics’ simulation, coherent (Thomson) scattering is included, and fluorescent photons produced from photoelectric absorption are included and electrons produced from photon collisions are transported in a ‘condensed history’ method that accumulates the effects of many individual collisions into single steps sampled probabilistically. The F6 tally given as equation (1)

$$D = \frac{\rho_a}{m} \int dE \int dt \int dV \int d\Omega \sigma_t(E) H(E) \phi(\vec{r}, \hat{\Omega}, E, t) \text{ MeV g}^{-1} \dots(1)$$

where D is dose, m is mass, ρ_a is atomic density, t is time, E is energy, V is volume, Ω is solid angle, ϕ is scalar flux scored over volume (track length/volume) cm^{-2} , σ_t is microscopic total cross-section and H is heating number (MeV/collision),

from MCNP is converted from MeV/g to yield the dose in $\text{nGy cm}^2 \text{Bq}^{-1} \text{hr}^{-1}$ to compare with Almansa *et al.* (2006). The results plotted are for $\dot{D} = \kappa r^2 D \text{ nGy cm}^2 \text{Bq}^{-1} \text{hr}^{-1}$ where $\kappa = 576 \text{ nGy cm}^2 \text{Bq}^{-1} \text{hr}^{-1} / (\frac{\text{MeV}}{\text{g}})$.

Monte Carlo perturbation sampling

Perturbation algorithms in MC simulation (Rief, 1984) extended the capability of MC methods to sensitivity studies and optimization (Koreshi & Lewins, 1990). The

change in a response function such as dose D , due to a variation in an independent parameter, such as material density ρ , expressed as a Taylor series in equation (2)

$$D(\rho) = D(\rho_o) + D'(\rho_o)\delta\rho + \frac{1}{2!}D''(\delta\rho)^2 + \dots \quad \dots(2)$$

can be used with first- and second-order derivatives D' and D'' from a single run. Thus, when the change in a parameter is small enough to be of the order of the statistical uncertainty of a MC estimate, then the difference from two independent runs may mask the actual difference. In order to circumvent such inaccuracy, the derivatives are sampled in a single simulation. The energy deposition for a 'perturbed' design (D^{new}) can thus be estimated from a Taylor series in terms of a 'reference' design (D^{ref}).

Material composition

The material used in this work is water with gold solution which has density $\rho = 1.04 \text{ g cm}^{-3}$, very close to that of soft tissue $\rho = 1.04 \text{ g cm}^{-3}$ [with a four-component simplified composition hydrogen (H), carbon (C), nitrogen (N) and oxygen (O) with weight percentages: 10.454, 22.663, 2.49, 63.525%, respectively] and the photon cross-sections for both (water and soft tissue) are almost indistinguishable so that conclusions drawn for energy deposition would hold for both materials to a reasonably acceptable order.

RESULTS AND DISCUSSION

Benchmarking of radiation dose and dose distribution

To compare MCNP5 results for energy deposition from a mono-energetic point isotropic source at the centre of a sphere of radius 15 cm, the F6 tally in 0.5 mm thick concentric shells were used with 1 million histories for each source energy level. From the results shown in Figure 1, it is seen that there is good agreement with the results given in the literature (Almansa *et al.*, 2006). When normalized to a reference dose from a 1 MeV source, it is seen that the lowest energy, 15 keV, has an energy deposition of about 65% of the reference which falls off rapidly to less than 10% in 1.5 cm of water. With a further increase in energy, the relative intensities drop but the deposition sustains to greater depths, which is less important in brachytherapy than to give a localized deposition from a low-energy source.

MCNP simulations were carried out on an Intel(R) Core (TM) i7-2620M CPU @ 2.70GHz with an installed memory of 8.00 GB (3.24 GB usable) and 32-bit Operating system with Windows 7 Professional.

The DEF shown in Figure 2 gives the extent and magnitude as a function of source energy and concentration confirming the trend of direct variation with concentration and inverse variation with source

Figure 1: Energy deposition for mono-energetic photons of energy E : 15 keV⁻¹ MeV

Figure 2: Dose enhancement factor (DEF) vs. distance for $E = 40$ keV, 50 keV, 90 keV, 1 MeV for varying concentrations $5, 10, 25$ mg Au/g H_2O

energy. The rate of ‘fall’ or ‘rise’ of DEF in the solution region is indicative of the slightly longer spatial effect of the high-energy photons as compared to low-energy photons.

For ophthalmic brachytherapy with ^{125}I (mean energy 35.49 keV), a full three-dimensional heterogeneous model (Asadi *et al.*, 2015) simulating 10^7 – 10^9 histories, for 50 nm GNPs, estimate the DEF for $7, 10, 18$ and 30 mg/g as $1.9, 2.2, 3.2$ and 4.6 for the tumour phantom compared with $1.9, 2.3, 3.3$ and 4.8 in the water phantom, respectively.

As given in Table 1, this work, for a water phantom with 10^6 simulations with a maximum time ~ 35 minutes in a homogenous mixture model for the solution gives, for 40 keV and concentrations of $5, 10, 25$ mg/g maximum DEFs (Figure 3) of $1.8, 2.5, 4.6$. DEF has been found to lie in the range 1.4 – 3.7 with the highest DEF for 90 keV (Mesbahi *et al.*, 2013); the effect of GNP size was not considerable (Lechtman *et al.*, 2011; Mesbahi *et al.*, 2013) while concentration and energy were important. These simulations (Lechtman *et al.*, 2011; Mesbahi *et al.*, 2013) carried out for 7 and 18 mg Au/g H_2O for $30, 50, 100$ nm GNPs and energies between 50 – 18 MeV, report highest DEF of 3.5 at 90 keV followed by 3.0 at 50 keV both for 30 nm GNPs and 18 mg/g concentration.

Table 1: Max DEF for 1M simulations vs E and concentration; CPU time (mins) shown in brackets

No.	E (keV)	$\alpha = 5$	$\alpha = 10$	$\alpha = 25$
1	40	1.7854 (33.17)	2.5398 (35.48)	4.6537 (17.86)
2	50	1.7394 (40.53)	2.4521 (42.47)	4.4529 (21.56)
3	90	1.5204 (59.56)	2.0398 (58.19)	3.5861 (31.02)
4	1000	1.0046 (98.71)	1.0091 (101.78)	1.0221 (71.46)

For high energy sources, with 10^8 source particles simulated, it is reported (Banoqitah & Djouider, 2016) that a maximum DEF is 1.45 within the tumour when implanted with 70 mg/g Gd for the lowest energy (^{192}Ir), and that the DEF varies directly with concentration and inversely with source energy e.g. for a concentration of 30 mg/g it decreases from 1.24 to 1.09 when photon energy increases from 0.380 MeV (^{192}Ir) to 1.20 MeV (^{60}Co). The results for this work show similar trends at high energy (1 MeV), i.e., a maximum DEF increasing very slowly from 1.0046 to 1.0221 as concentration increases from 5 mg/g to 25 mg/g.

Figure 3: Maximum dose enhancement factor vs. energy for varying concentrations 5, 10, 25 mg Au/g H₂O

MC perturbation estimates

The simulations carried out for the results presented in previous sections were computationally intensive, which usually requires in excess of one hour for high energy (1 MeV). Thus, MC would be inefficient for carrying out sensitivity studies where the effect of perturbations, such as the solution concentration of gold in water, on

the DEF would be required. If a change is small then the statistical uncertainty in the results from two independent simulations, from which the change in the outcome is being estimated, could mask the effect of the change and hence produce unreliable results. Thus, perturbation MC was examined to obtain first- and second-order derivative changes, shown in Figure 4, in concentration of the gold solution in the range 5–25 mg Au/g H₂O. For this, a single run at a reference design of 5 mg Au/g H₂O was carried out and derivatives were obtained for the energy deposition to predict results for 15 mg Au/g H₂O in 35.24 minutes compared with 33.17 minutes as given in Table 1.

The 1st and 2nd order perturbation results, 15 mg (1PT) and 15 mg (2PT) respectively, for estimating the energy deposition at 15 mg/g are almost identical due to the small magnitude of the perturbation rendering the 2nd derivative an almost insignificant contribution. A better idea of the differences from re-run estimates $(\Delta D)_r$ compared with perturbation theory estimates $(\Delta D)_p$ is depicted in Figure 5, where the ratio γ , given by equation (3), remains ~ 1 in the gold solution region (1–2 cm) but at the boundary where there is a sharp jump, the perturbation estimates are also unreliable, since the magnitude of the perturbation exceeds the validity of 2nd order Taylor series.

Figure 4: Energy deposition (MeV/g) vs. distance for photon energy 40 keV: (a) two independent MC simulations; (b) 5 mg simulation compared with 2nd order perturbation theory estimate for 15 mg perturbed case; (c) 5 mg simulation compared with 1st order perturbation theory estimate for 15 mg perturbed case; (d) all four cases

Figure 5: Energy deposition (MeV/g) vs. distance for photon energy 40 keV: (a) differences from independent re-runs $(\Delta D)_r$ and differences based on perturbation estimate $(\Delta D)_p$; (b) ratio of differences γ

Figure 6: Differences in energy deposition (MeV/g) vs. distance for photon energy 40 keV: (a) differences based on 2nd order perturbation estimate $(\Delta D)_p$; (b) standard errors in estimates of $(\Delta D)_p$

$$\gamma \equiv \frac{D^{new} - D^{ref}}{D_p^{new} - D^{ref}} \dots(3)$$

A further test of the reliability of the results is given in Figure 6 which shows the magnitude of the second-order perturbation estimate and the errors R for which the 68% confidence limit of a result is where is the estimate of the change in estimated dose from 2nd order MC perturbation sampling, increasing from 10^{-4} to $\sim 5 \times 10^{-3}$ at the outer edge of the sphere.

CONCLUSIONS

In this work, the dose enhancement by injecting gold in solutions was estimated as a function of source energy and solution concentration. The important photon interaction for materials with high atomic number (Z) is the photoelectric effect for which the cross-section varies as $\mu_{PE} \sim \frac{\rho Z^3}{E^3}$ (where μ_{PE} is photoelectric attenuation coefficient) so that low energy and high- Z are desirable for dose enhancement which is localized to the tumour due to the short range of photoelectrons and Auger electrons in the surrounding medium which for electrons of energy 0.1 MeV is ~ 100 microns in water and ~ 15 microns in gold so that the effect of gold will require thin layers (of the order of ~ 10 nm) to utilize the energy of photoelectrons in water. At this energy, the photoabsorptions were estimated to be $\sim 13.5\%$ of all interactions.

Computational efficiency in MC simulation for estimating small changes in parameters has been demonstrated using a perturbation feature of MC simulation, thereby greatly reducing the computational effort to perform simulations in brachytherapy, extending its applicability to full-scale heterogeneity sensitivity studies pertinent to the modelling of nanoparticles in implanted solutions.

Important conclusions from this research were: (i) MCNP dose estimates were found to be in acceptable agreement with PENELOPE and GEANT in spite of artifacts such as cut-offs in electron transport (Archambault & Mainegra-Hing, 2015), (ii) dose increases with energy of a source, (iii) dose enhancement, for a given concentration, decreases with source energy, and (iv) MC perturbation theory is valid and useful, due to enhanced computational efficiency, for the practically important range of material density in solutions of gold and water, assumed homogeneously mixed.

Conflict of interest

Authors declare that they have no conflict of interest.

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