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# A method for converting dose-to-medium to dose-to-tissue in Monte Carlo studies of gold nanoparticle-enhanced radiotherapy

**B Koger**[1] **and C Kirkby**[1,2,3]

[1] Department of Physics and Astronomy, University of Calgary, Calgary, Alberta, T2N 1N4, Canada
[2] Department of Oncology, University of Calgary, Calgary, Alberta, T2N 1N4, Canada
[3] Department of Medical Physics, Jack Ady Cancer Centre, Lethbridge, Alberta, T1J 1W5, Canada

E-mail: bmkoger@ucalgary.ca

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**Abstract**

Gold nanoparticles (GNPs) have shown potential in recent years as a means of therapeutic dose enhancement in radiation therapy. However, a major challenge in moving towards clinical implementation is the exact characterisation of the dose enhancement they provide. Monte Carlo studies attempt to explore this property, but they often face computational limitations when examining macroscopic scenarios. In this study, a method of converting dose from macroscopic simulations, where the medium is defined as a mixture containing both gold and tissue components, to a mean dose-to-tissue on a microscopic scale was established. Monte Carlo simulations were run for both explicitly-modeled GNPs in tissue and a homogeneous mixture of tissue and gold. A dose ratio was obtained for the conversion of dose scored in a mixture medium to dose-to-tissue in each case. Dose ratios varied from 0.69 to 1.04 for photon sources and 0.97 to 1.03 for electron sources. The dose ratio is highly dependent on the source energy as well as GNP diameter and concentration, though this effect is less pronounced for electron sources. By appropriately weighting the monoenergetic dose ratios obtained, the dose ratio for any arbitrary spectrum can be determined. This allows complex scenarios to be modeled accurately without explicitly simulating each individual GNP.

  

Keywords: gold nanoparticles, Monte Carlo, radiation therapy

S Online supplementary data available from stacks.iop.org/PMB/61/2014/mmedia

(Some figures may appear in colour only in the online journal)

## 1. Introduction

Recently, the use of gold nanoparticles (GNPs) in radiation therapy has shown promise as a means of therapeutic enhancement. When exposed to radiation, GNPs enhance local dose due to a greater number of photoelectric x-ray interactions with gold than with soft tissue, an effect that increases as x-ray energy decreases. GNPs can also be designed to preferentially collect in solid tumours; uptake ratios of 19:1 (gold in tumour to gold in normal tissue) have been reported in mice (Hainfeld *et al* 2013). Additionally, gold is generally inert within the body (Lewinski *et al* 2008). New therapies can be explored that combine the benefits of GNPs with current advances in radiation therapy.

A relatively new concept, GNP-enhanced radiation therapy (GERT) was first explored *in vivo* in mice in 2004 and showed enhanced survival in mice treated with GNPs and radiation versus radiation alone (Hainfeld *et al* 2004). A follow-up study in 2005 quantified the dose enhancement due to GNPs through the use of Monte Carlo simulations (Cho 2005). Further *in vitro* and *in vivo* experiments have confirmed and expanded upon these findings (Hainfeld *et al* 2010, 2013, Berbeco *et al* 2012, Kumar *et al* 2013, Lechtman *et al* 2013). Monte Carlo studies have expanded upon this work, exploring GERT dose enhancement in macroscopic (McMahon *et al* 2008, Cho *et al* 2009) and microscopic (Verhaegen *et al* 2005, Jones *et al* 2010, Lechtman *et al* 2011, Leung *et al* 2011, Zygmanski *et al* 2013b) contexts.

Accurate dosimetry in the presence of GNPs is necessary for GERT to become a clinical reality, but there are several challenges to this. Planning a course of radiation therapy requires accurate calculations of radiation transport through patient tissue or tumor volumes that are directly irradiated, as well as peripheral tissues that are exposed to scattered radiation. In cases of external beam treatments, radiation is typically transported through the patient across distances of centimeters to tens of centimeters, and doses are calculated to voxels with dimensions on the order of a few millimeters. Within each voxel, the tissue properties of density and chemical composition are effectively averaged. In this work we refer to properties on this scale (millimeters or greater) as *macroscopic*. In Monte Carlo studies investigating tissue infused with GNPs, a macroscopic approach to dose calculation models a voxel as containing a homogeneous mixture of soft tissue and gold with a single effective atomic number and density (Cho 2005, Cho *et al* 2009, Garnica-Garza 2009).

However, some of the energy deposited within a material modelled as a homogeneous mixture of gold and tissue will specifically be deposited within the GNPs and therefore be of no direct consequence to the soft tissue in which GNPs are situated (McMahon *et al* 2011b). Work in this area indicates that biological effects depend on the detailed picture of electron tracks at the sub-cellular scale (McMahon *et al* 2011a). Isolating the mean dose-to-tissue (excluding gold) from macroscopic calculations to a mixture is important, both as a starting point from which to build detailed track structure simulations and for accurate dosimetry. Zhang *et al* found that a bulk mixture approximation overestimated the dose enhancement by up to 29% for the specific scenario they modeled (Zhang *et al* 2009). This work seeks to expand on those findings and establish a systematic means of converting doses generated in mixed media to more relevant doses absorbed by the tumor or soft tissue.

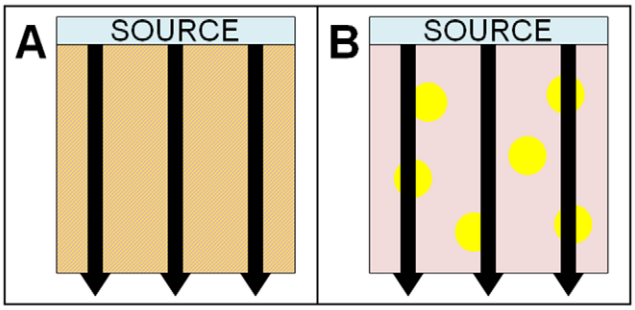


**Figure 1.** Schematic showing the two geometries used in this study. (A) shows the homogeneous mixture of tissue and gold, whereas (B) shows tissue containing spherical gold nanoparticles.

In this study, Monte Carlo simulations were used to calculate doses to a medium containing GNPs at the microscopic level for a variety of source energies, GNP bulk densities, and GNP sizes. The results were compared to the results of a second set of simulations, where the medium in question was modeled as a gold-tissue mixture. This led to a simple methodology for converting doses obtained from the mixture approximation to meaningful tissue doses, enabling the accurate simulation of complex GNP-infused geometries with limited computational power.

## 2. Materials and methods

Using the PENELOPE Monte Carlo code system (Salvat *et al* 2011) with the penEasy package (Sempau *et al* 2011), we simulated the irradiation of two microscopic cavities, shown in figure 1. The first cavity (figure 1(A)) contained a homogeneous mixture of gold and ICRU four-component tissue (ICRU 1989), generated using the *material.exe* program contained within PENELOPE. The second cavity (figure 1(B)) contained spherical GNPs randomly distributed in a medium of ICRU four-component tissue. In all cases, the cavity was cubic, with side lengths ranging from 220 nm to 18.5 $\mu$m.

In order to facilitate the development of a conversion factor that can be applied to a variety of scenarios, several assumptions were made. First, it was assumed that the simulated cavities were located within a larger volume that also contained GNPs of the same size, bulk density, and distribution. Due to this, it was also assumed that electronic equilibrium existed within the cavities for simulations involving photon sources. This assumption was necessary for the method used to calculate total energy deposition in the cavity.

Because dose enhancement due to GNPs varies with source energy, the determination of a conversion factor depends on the exact composition of the source spectrum. Rather than limit the results to a few spectra, the cavity was instead irradiated with a wide array of monoenergetic photon and electron beams. From these results, the conversion factor for any given spectrum can be constructed by using a weighted average of conversion factors by each energy in the spectrum.

The beam energy for photon and electron simulations ranged from 150 eV to 2 MeV. Several common spectra were also used to provide a practical benchmark. Spectra for orthovoltage beams of peak energies 100, 200, and 300 keV were obtained using the software SpekCalc (Poludniowski *et al* 2009). The spectrum from a 6 MV Varian Clinac beam was also

**Table 1.** Summary of the variable simulation parameters: GNP diameter, GNP concentration, source energy, and material type. For each possible combination of the four variables, a simulation was performed.

| | | |
|---|---|---|
| GNP diameter (nm) | | 2, 10, 20, 50, 100 nm |
| GNP concentration (mg Au/g tissue) | | 5, 10, 15, 20, 30 mg Au/g tissue |
| Source energy | Electron | 150 eV–6 MeV (68 total energies) |
| | Photon | 150 eV–2 MeV (99 total energies) |
| Material type | | Bulk mixture *or* explicit GNP |

used (Sheikh-Bagheri and Rogers 2002). In all cases, the source was modeled as a square field covering the cavity, with side lengths equal to the side lengths of the cavity. The beam was impingent perpendicularly on the surface of the cavity. To investigate the effects of different GNP diameters, simulations were performed for each of 2, 10, 20, 50, and 100 nm GNPs. Similarly, the concentration of GNPs was set at 5, 10, 15, 20, or 30 mg Au/g tissue. For each combination of parameters, two simulations were performed—one for each cavity described in figure 1. Table 1 summarizes each of these variable parameters.

The cavity was cubic with side lengths ranging from 220 nm to 18.5 $\mu$m. The cavity volume was chosen individually for each simulation based on the GNP diameter and concentration to ensure a specific integer number of GNPs. The cavities had, at minimum, 500 randomly distributed GNPs, to ensure negligible variation in dose based on GNP placement within the cavity. At maximum, the cavities had 4000 GNPs due to computational limitations. It was found that, for the GNP diameters and concentrations investigated in this study, changing the cavity size and number of GNPs had no appreciable effect on the dose ratio. Specifically, for simulations with GNPs of diameter 2 nm, 4000 GNPs were simulated for all concentrations. For simulations with GNPs of diameter 10 nm, the number of GNPs for gold concentrations of 5, 10, 15, 20, and 30 mg Au/g tissue was set to 500, 989, 1483, 1977, and 2964, respectively. For simulations with GNPs of diameters of 20, 50, or 100 nm, 500 GNPs were simulated for all concentrations.

Enough histories were performed such that the uncertainty in the dose was less than 1%, typically about $10^7$ histories. All PENELOPE simulation parameters were set conservatively to allow for explicit particle transport. Photon and electron cutoffs were set at 100 eV, the parameters C1 and C2 were set at 0, and WCC and WCR were set at 100 eV. The variance reduction technique *interaction forcing* was utilized for photon beams of energy greater than 4 keV to reduce computation time. All photon interactions were forced, with the forcing parameter set to 1000 for photon sources between 4 and 30 keV and 5000 for photon sources above 30 keV.

Doses were determined as follows. First, energy deposition was scored within the tissue region using the *tallyEnergyDeposition* tally in penEasy. For the simulations using bulk mixture, this scored the energy deposited to the bulk mixture material; for explicit GNP simulations, this scored the energy deposited to only the tissue. Using MATLAB, the data from the tally files were read and converted to dose by dividing the energy deposited by the material mass. This provided the dose due to primary radiation and interactions within the cavity itself.

However, due to the small size of the cavity, a large amount of energy is carried out of the cavity in the form of photons and electrons. Since the cavity is assumed to be in electronic equilibrium for photon sources, this same fluence of particles enters the cavity from interactions in the surrounding medium and deposits dose. To account for this, a series of simulations were run in which the electrons leaving the cavity, measured with the *tallyParticleCurrentSpectrum* tally in penEasy, were transported back through the cavity until all of their energy was deposited. Preliminary work indicated that, for photon source cases, greater than 99.5%

of the energy of the electrons leaving the cavity was deposited in the tissue, rather than the GNPs, when these electrons were re-introduced back into the cavity (under the assumption of electronic equilibrium). Thus, by assuming that all of this residual electron energy was deposited in the tissue, the same result was achieved without the need for subsequent simulations. The level of error due to this assumption was less than 0.5%. Note that this same assumption was not necessary for electron source cases because the results are normalized per electron incident on the cavity.

Equations (1)–(3) demonstrate the approach used to obtain a dose conversion ratio. First, the total energy deposited in the tissue was determined by adding the energy of the electrons leaving the cavity and the primary energy deposited in the tissue. As mentioned above, this step was not performed for electron sources. The dose to the tissue was determined by dividing the total energy deposited to the tissue by the mass of the tissue medium (mixture or pure tissue) in which it was deposited. A dose ratio, DR, was then calculated as the ratio of dose-to-tissue (in the explicit GNP simulations) to dose-to-mixture (in the gold/tissue mixture simulations) with identical parameters. This ratio can then be used to convert doses to the gold-tissue mixture to a pure-tissue dose.

$$E_{\text{dep, tis}} = E_{\text{dep, primary}} + E_{\text{e}^-\text{, remaining}} \tag{1}$$

$$D_{\text{tis}} = \frac{E_{\text{dep, tis}}}{m_{\text{tis}}} \tag{2}$$

$$\text{DR} = \frac{D_{\text{tis}}}{D_{\text{mix}}} \tag{3}$$

## 3. Results

The dose ratio, as defined in equation (3), is plotted versus the monoenergetic photon energy in figure 2. Each of the three subplots represents a different gold concentration—5, 10, and 20 mg Au/g tissue. The three data sets in each subplot represent different GNP diameters—2, 10, and 50 nm. Uncertainty in the dose ratio, not shown in the plot, is less than 1.0% for 90% of the data and never greater than 1.5%. Some data was excluded from this plot for the sake of readability, including 20 and 100 nm GNP and 15 and 30 mg Au/g tissue. A complete data set is included in supplemental material (stacks.iop.org/PMB/61/2014/mmedia).

In general, the dose ratio is closest to unity for small GNP diameters and low gold concentrations, conditions that most closely represent a homogeneous mixture. Likewise, the dose ratio tends to decrease with increasing GNP diameter and concentration. Below 2 keV, the dose ratio remains roughly constant, with minor variations due to N-shell effects at or below approximately 500 eV, regardless of source energy and GNP properties. The dose ratio is also roughly constant above 200 keV.

However, between 2 and 100 keV, the dose ratio is highly dependent on energy, as well as GNP diameter and concentration. Most of the variances in the dose ratio in this region correspond to the K, L, and M shell edges of gold. The M-edges fall between 2 and 4 keV, corresponding to the first major shift in the dose ratio. Similarly, the L- and K-edges, at 11–15 and 81 keV, respectively, correspond to the two other major changes in dose ratio. As photon energy exceeds the binding energy of a given sub-shell in gold, the number of photon interactions in gold increases. This causes an influx of electrons into the medium, including both photoelectric and Auger emissions. While the homogeneous mixture scores all of this

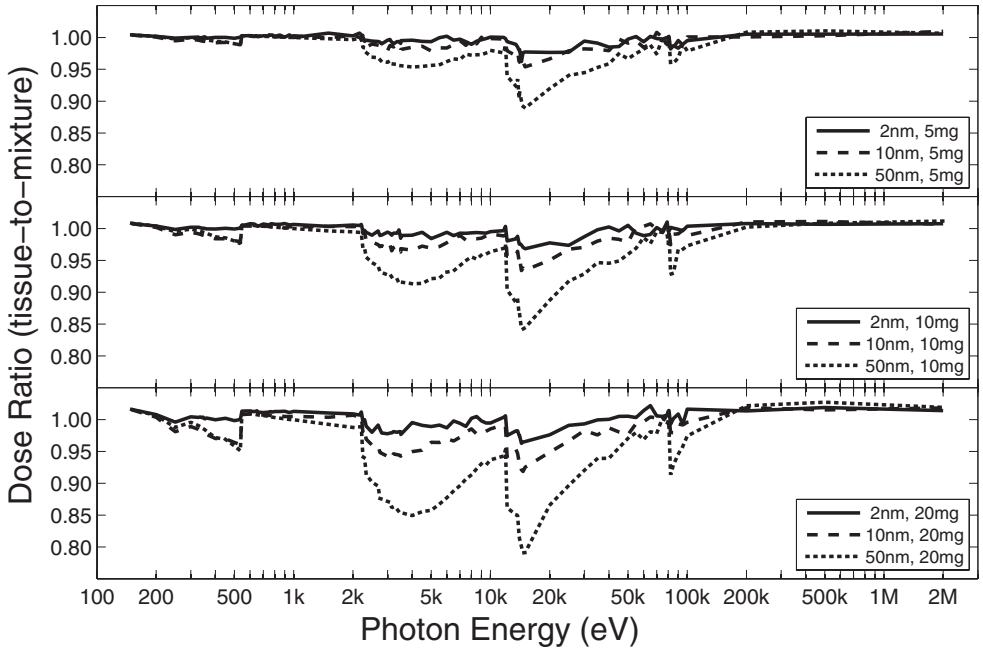


**Figure 2.** Dose ratio (real-GNP simulations to mixture simulations) versus monoenergetic photon energy for a subset of the simulated scenarios. For each data set, the legend gives the GNP diameter, in nm, and the gold concentration, in mg Au/g tissue.

increased energy, when the GNPs are explicitly modeled, these electrons deposit some or all of their energy within the GNP. In a relative sense, the mean dose to the surrounding tissue is less than that in the corresponding homogeneous gold-tissue mixture scenario, leading to the observed decrease in the calculated ratio. This effect is enhanced with larger GNPs.

The dose ratio versus monoenergetic electron energy is shown in figure 3. Similar to figure 2, it includes the same subset of GNP diameters and concentrations. Uncertainty in the dose ratio, not shown in the plot, is less than 1.0% in all cases. A complete data set is included in the supplemental material.

In all cases shown in the figure, the dose ratio is within about 2% of unity, between 0.98 and 1.02. The value of this dose ratio is mostly dependent on the range of the source electrons and how it compares to the distance between GNPs. For very low-energy electron sources, below 2 keV, the dose ratio is above unity. This is because nearly all of the energy of these low-energy electrons is deposited within a short range, where the electrons are much more likely to deposit energy in tissue than in GNPs. The value of the dose ratio at this point is mainly dependent on the difference in mass density between pure tissue and the tissue-gold mixture. While the energy deposited is the same for both materials, the mixture will have a larger mass than an equal volume of pure tissue, leading to a lower dose deposited in the mixture than in the pure tissue.

For energies between approximately 2 keV and 20 keV, the dose ratio is dependent on both the diameter and concentration of GNPs. At these energies, the range of the electrons becomes comparable to the distances between GNPs. For simulations involving 50 nm GNPs, which have a comparatively larger separation than smaller GNPs, electrons are more likely to deposit energy in the tissue than in the gold, leading to a dose ratio greater than unity. Contrastingly,

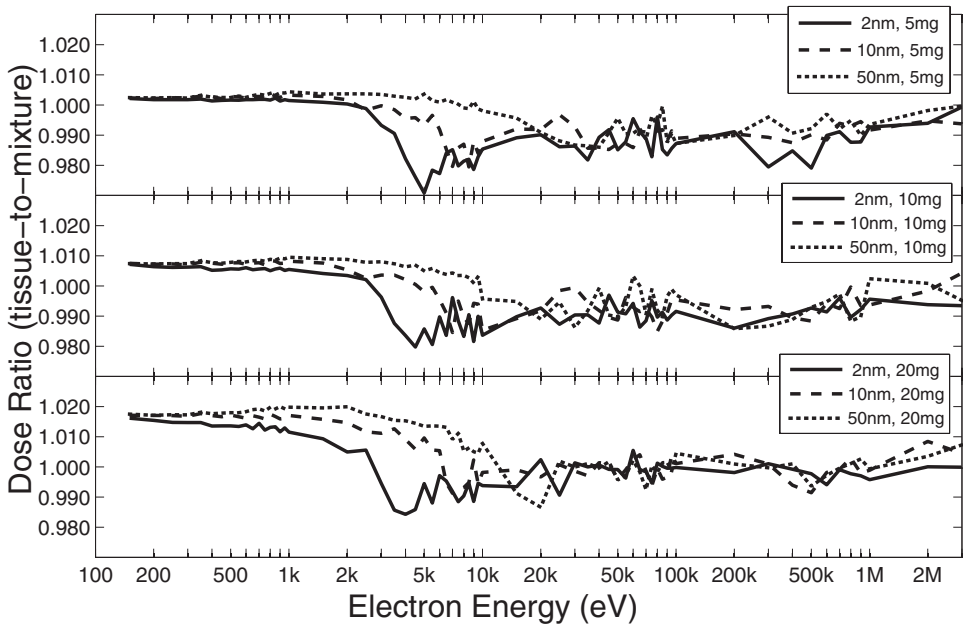


**Figure 3.** Dose ratio (real-GNP simulations to mixture simulations) versus monoenergetic electron energy for a subset of the simulated scenarios. For each data set, the legend gives the GNP diameter, in nm, and the gold concentration, in mg Au/g tissue.

**Table 2.** Results of several simulations using photon spectra as the source energy. Dose ratios were obtained from the spectral simulations (FPSS) and from calculations with the monoenergetic data (calculated). Uncertainties are given to two standard deviations.

| Spectrum energy | GNP diam (nm) | GNP conc (mg Au/g tis) | Dose ratio (FPSS) | Dose ratio (calculated) |
|---|---|---|---|---|
| 100 kVp XStrahl | 10 | 20 | $0.981 \pm 0.008$ | $0.984 \pm 0.003$ |
| 200 kVp XStrahl | 2 | 20 | $1.010 \pm 0.011$ | $1.010 \pm 0.004$ |
| 200 kVp XStrahl | 50 | 20 | $0.972 \pm 0.011$ | $0.975 \pm 0.005$ |
| 300 kVp XStrahl | 10 | 5 | $0.999 \pm 0.009$ | $0.999 \pm 0.006$ |
| 6 MV Varian Clinac | 10 | 10 | $1.010 \pm 0.018$ | $1.008 \pm 0.004$ |

the smaller, 2 nm GNPs have a shorter distance of separation, and thus a greater likelihood of energy deposition within the GNPs. This leads to a lower dose ratio than for larger GNPs. For electron source energies above 20 keV, the dose ratio tends towards unity, within simulation uncertainty. Here, the range of the electrons no longer plays a role, as the electrons pass completely through the cavity.

Several simulations were performed using spectral photon sources as described in the methods. Note that these spectra were not calculated at depth but rather were assumed to be directly incident on the cavity. Table 2 shows a summary of these results. Dose ratios due to explicit full photon spectrum simulations (FPSS) were obtained directly from the simulations. The 'calculated' dose ratios were determined by weighting the dose ratios from the monoenergetic simulations with the fluence of the spectrum used. The dose ratio was assumed to remain unity for all energies above 2 MeV. In both cases, the uncertainty is given to two

standard deviations. Both FPSS and calculated dose ratios agreed to well within the calculated uncertainties.

## 4. Discussion

The purpose of this study was to determine a method through which macroscopic GNP simulations may be used to give a more relevant, microscopic dose. This was done through the determination of a dose conversion ratio—the ratio of dose given to tissue when GNPs are explicitly simulated to the dose given to a homogeneous mixture of tissue and gold that approximates GNPs in tissue. Overall, these dose ratios were found to be dependent on both the source energy used and the diameter and concentration of the GNPs being simulated.

Translating from the endpoint of this work, mean dose-to-tissue on a microscopic scale, into a direct enhancement due to biological effects is a complex process. Recent studies that have shown that nanoscale heterogeneities due to GNPs, as well as effects due to interactions of the GNPs themselves within the nucleus or other organelles, play a role in GNP radiosensitisation (McMahon *et al* 2011a, Garnica-Garza 2013, Cai *et al* 2013). The method presented herein does not account for any nanoscale heterogeneity in energy deposition, as it effectively averages energy deposition events through a tissue medium, nor do we attempt to translate the result into a biological endpoint. However, the dose ratio presented here is a useful quantity. Planning the delivery of ionizing radiation involves the calculation of radiation transport over tens of centimeters through heterogeneous media. In scenarios that would take advantage of the enhanced radiosensitization associated with GNPs, it may be feasible and perhaps necessary to optimize parameters such as beam spectrum to achieve an optimal effect at a desired depth for a given GNP distribution and density. Modern treatment planning systems could conceivable do this, but would do so through the calculation of dose on a macroscopic (mm or greater) scale. With the macroscopic aspects of these problems addressed, biological models from the literature could be incorporated to predict the ultimate biological effect (Lechtman *et al* 2013, Zygmanski *et al* 2013a). The methods presented here are also applicable to dosimetry measurements in which non-tissue materials, such as radiochromic film (Rakowski *et al* 2015) and alanine dosimeters (Guidelli and Baffa 2014), are utilized to verify GNP dose enhancement.

With monoenergetic photons sources, the dose ratio varied by as much as 31% between the scenarios that explicitly simulated GNPs and scenarios that relied on a tissue-gold mixture. Within this ratio, there is a strong dependence on source energy, GNP size, and gold concentration. The relationship between this dose ratio and energy is quite complex, as illustrated in figure 2. The increases and decreases in the dose ratio correspond to the photoelectric edges of gold, as described in the Results.

The relationship between the dose ratio and GNP diameter and concentration, on the other hand, is simple. When the GNPs are the smallest, 2 nm diameter in this case, the GNPs in the tissue appear quite homogeneous, largely resembling a mixture of tissue and gold. In fact, the dose ratio of the simulations that were performed for 2 nm GNPs never deviated more than 5% from unity. As the GNPs become larger, electrons generated within the GNPs lose more energy in the gold, on average, before emission into the surrounding tissue medium. Similarly, as the gold becomes more concentrated, the GNPs are more likely to absorb energy from any particles traversing the cavity. This leads to a larger deviation from unity for the dose ratio. Deviations as large as 31% from unity were found when simulating GNPs of large diameter (50, 100 nm).

For electron sources, the dose ratio is relatively constant, within 2% of unity for the scenarios modeled. The energy of the source electrons is the main factor in determining the dose

ratio, with the dose ratio for low-energy electrons showing that the mixture actually underestimates the dose delivered to the tissue, while high-energy electrons have a dose ratio near unity. For electron energies that fall between 2 keV and 20 keV, the GNP diameter also affects the ratio. As the GNP diameter increases, the average distance between GNPs also increases for the same gold concentration, leading to increased energy deposition in tissue relative to gold when the range of the electrons is on the order of this separation distance.

The dose ratios determined from monoenergetic sources can be utilized to provide dose ratios for arbitrary spectral sources. In order to apply the provided monoenergetic dose ratios to a spectral source, the dose ratios should be weighted by the fluence of both the photon and electron fluence at the site of interest. In this work, dose ratios determined through this method were equivalent, within the calculated uncertainties, to those dose ratios obtained from explicitly simulating each spectrum. Note that the dose ratios presented in this work are not calculated at depth, but rather assume that the source is directly adjacent to the cavity. Thus, when hoping to apply dose ratios to a simulation done at depth, the spectrum of interest is the spectrum of photons and electrons measured at the depth at which the dose ratio is to be applied. In practice, this means that if the volume in question is large enough to alter the spectrum by an appreciable amount, several dose ratios may need to be applied at various points in the volume.

Because the dose ratios are highly dependent on the geometry of the GNPs, investigators hoping to use these ratios for dose conversion should be acutely aware of the conditions that they wish to emulate, including both the diameter and concentration of GNPs. Note that this study only evaluates solid, spherical GNPs; it is unknown how the dose ratio would change under other GNP shapes, such as gold nanorods or nanoshells.

When calculating the energy deposited in the photon simulations, it was assumed that electronic equilibrium existed within the cavity due to identical, surrounding cavities that were also subject to the same monoenergetic photon source. This assumption would weaken due to any heterogeneity in GNP distribution, near field edges or buildup regions, or in the vicinity of other heterogeneities. The results suggest that the calculated ratio approaches unity for energies greater than roughly 200 keV. Given that this corresponds to electron ranges of less than a few hundred $\mu$m, any ratio derived by integrating the calculated monoenergetic results over a spectrum would only be sensitive to disequilibrium conditions on similar distance scales.

There is also some concern with the Monte Carlo transport of particles with energies below 1 keV, due to both quantum mechanical effects (Thomson and Kawrakow 2011) and the inaccuracy of interaction cross sections below this threshold (Salvat *et al* 2011). In most practical cases, the dose ratios of such low-energy sources are not expected to impact the results in any meaningful way due to the small proportion of photons below 1 keV in a given spectrum. In this study, photons with energies below 1 keV were found to make up less than 0.001% of the photons escaping the simulation cavity. Still, the data included in this study for source energies below 1 keV should be used with caution.

## 5. Conclusions

A method of converting macroscopic doses to tissue doses has been developed for use in gold nanoparticle Monte Carlo simulations. This was done through the development of a dose ratio, defined as the ratio of the dose absorbed by tissue in simulations that explicitly model GNPs to the dose absorbed by a homogeneous mixture of tissue and gold. It was found that the dose ratio was highly dependent on both the source energy and the diameter and concentration of the GNPs being modeled. This effect was more pronounced for photon sources than electron

sources. Dose ratios ranged from 0.69 to 1.04 for photon sources and from 0.97 to 1.03 for electron sources. Because the dose ratio was determined for a variety of monoenergetic photon and electron sources, dose ratios can be determined for any arbitrary spectrum. Through this method, complex macroscopic scenarios can be simulated accurately without the need to explicitly model each individual gold nanoparticle, reducing the dependency on computational power.

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