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Investigation of track structure and condensed history physics models for applications in radiation dosimetry on a micro and nano scale in Geant4

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Keywords

investigation, models, applications, geant4, physics, track, radiation, dosimetry, history, micro, condensed, nano, scale, structure

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Investigation of Track Structure and Condensed History physics models for applications in radiation dosimetry on a micro and nano scale in Geant4

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Abstract

Monte Carlo methods apply various physical models, either condensed history (CH) or track structure (TS), to simulate the passage of radiation through matter. Both CH and TS models continue to be applied to radiation dosimetry investigations on a micro and nano scale. However, as there has been no systematic comparison of the use of these models for such applications there can be no quantification of the uncertainty that is being introduced by the choice of physics model. A comparison of CH and TS models available in Geant4, along with a quantification of the differences in calculated quantities on a micro and nano scale, has been undertaken in this study. A sphere of liquid water was simulated, with an incident beam of monoenergetic electrons with kinetic energy between 50 eV and 10 keV. The energy deposition (typical of microdosimetry) and number of ionisations (typical of nanodosimetry), per incident particle, were recorded in a water sphere with diameter varying between 1 nm and 1 m. The simulations were repeated using the following physics packages: Livermore (CH), Penelope (CH) and Geant4-DNA (TS).

Results indicated that substantial differences were present between calculated physical quantities, depending on the physics model, target diameter and ratio of the target diameter and mean track length of the incident electron. In the case of the smallest targets, the calculated energy deposition was higher when using the CH models, while the number of ionisations was typically underestimated. In larger targets the energy deposition was in good agreement for all physics models, however the number of ionisations was significantly underestimated by the CH approach, in some cases by almost two orders of magnitude. Regarding CH models, the parameter that had the greatest impact on the results was found to be the threshold of production of secondary particles; when this was minimized the CH and TS results showed the best agreement.

Introduction

The field of radiation dosimetry has many sub-fields, one of the most prominent being microdosimetry (Rossi and Zaider 1996); the investigation and analysis of radiation interactions with matter on a microscopic

scale. Microdosimetry has been developed over the past few decades in response to a need to link the physical effects of radiation interactions with biological consequences, particularly for applications in radiation protection and radiobiology. When considering the biological effects of radiation, one of the key questions has been determining the most relevant biological target for investigation (Goodhead 2006); for example, is the most radiation sensitive site an entire organ, a single cell, or some sub-cellular component such as DNA or other sub-cellular structures? In recent years the biological targets of interest have moved to smaller and smaller sizes (Goodhead 2006), ultimately leading to the development of nanodosimetry (Grosswendt 2006, Rabus and Nettelbeck 2011).

This continued development of radiation dosimetry for smaller and smaller target sizes required the development of stochastic, rather than deterministic, quantities to characterise a given radiation field. Typically, when considering radiation interactions on a *large* scale, deterministic quantities like radiation dose and Linear Energy Transfer (LET) can be used to characterise the quantity and quality of the radiation absorbed by a target. However, when considering *small* targets, the inherently stochastic nature of radiation interactions requires the use of stochastic quantities to characterise the radiation field and its impact on a target. This raises the question of how small a target needs to be before necessitating the move from the deterministic to the stochastic regime.

When considering quantities that characterise a radiation field on a stochastic regime two of the most common are the energy deposition in a volume (per incident particle) and the ionisation cluster size distribution (ICSD, that is, the number of ionisations in a target volume, per incident particle). These quantities are dependent upon the radiation field and can also be dependent upon the characteristics of the target, such as orientation relative to radiation field and the target size, atomic composition and density. However, while these quantities can provide valuable data to characterise a radiation field, it can be difficult, or even impossible with current technological limitations, to directly measure them. This limitation has led to Monte Carlo (MC) simulations becoming a common tool for radiation dosimetry investigations.

Monte Carlo radiation simulations apply various physical models (either analytical or parameterised models) to simulate the passage of radiation through matter. These models can be broadly split into two categories; track structure and condensed history.

The track structure (TS) approach involves the approximation of radiation interactions as discrete events, with the explicit simulation of every single interaction of a particle as it passes through a medium (Nikjoo et al 2006, Nikjoo et al 2016). TS models require total and differential interaction cross sections of the particles with matter, for all processes considered. In this case the mean free path of the particle (calculated from the total interaction cross section) determines the position of the next interaction, with relative cross sections of all considered processes determining the type of interaction. Following this, the energy loss and change in direction of the particle after an interaction takes place are calculated using the differential cross sections for the relevant process. Though this method is well suited to the calculation of stochastic quantities it can suffer from the limitation of being prohibitively time consuming. An additional current limitation of these models is the scarcity of available cross section data, leading to a very limited selection of materials that can be simulated.

The condensed history (CH) approach condenses several physical interactions into a single simulated ‘step’ (Nahum 1999, Nikjoo et al 2006), thus speeding up the simulation at the cost of accuracy and is often applied to calculate deterministic quantities such as radiation dose. This is possible because the energy lost by the particle can be distributed over each simulated step giving a reasonable approximation of the gradual energy loss of radiation in matter. CH models typically rely upon the stopping power of the particle to determine the energy loss and a multiple scattering theory of elastic collisions for change in direction after each simulated step. A major strength of these models is their applicability to a large variety of materials thanks to an abundance of available stopping power data.

While there are several MC codes available for public use (for a review of some of the available codes the reader is referred to (Dingfelder et al 2008, Nikjoo et al 2006), including many different physical models which can be applied to a given radiation type and medium, there are often few guidelines on the appropriate application of these models.

A common application of MC in radiation biology, and particularly nanodosimetry, is to calculate the ionisation cluster size distribution (ICSD) within a target of interest. This has been done for a variety of biological targets and radiation fields and using a variety of physical models, including both TS (Rabus and Nettelbeck 2011, Lazarakis et al 2012a, Burigo et al 2016) and CH approaches (Byrne et al 2015, McNamara et al 2016) and sometimes a combination of both types of models (Kuncic et al 2012, Douglass et al 2013). However, given the different approaches used by the different physics models it stands to reason that the ICSD will be somewhat dependent upon the chosen models. Additionally, even when the ICSD is not the main parameter of interest, the accurate production and tracking of secondary particles can still play a critical role in the calculation of other parameters such as energy deposition when considering very small targets. This relationship between ionising events and energy deposition has been briefly discussed by McMahon (McMahon et al 2011) when simulating the radiation-induced energy deposition enhancement in the close vicinity of nanoparticles. McMahon deduced that it was the number of ionising events in the nanoparticle which determined the energy deposition enhancement, independent of any other factors.

As discussed previously, CH models combine several interactions into a single simulated step. This means that fewer physical interactions are simulated (e.g. fewer ionising events) and hence fewer secondary particles will be produced, leading to faster simulations. A limitation of this is the assumption that all of the energy of those secondary particles that are not simulated will be deposited locally. If this is not the case, then the energy deposition in the target may not be accurately described by the simulation. This can be particularly problematic when simulating sub-micron volumes, when the secondary particles may have a longer range than the diameter of the target volume. This implies that CH models may not always be appropriate for application to very small volumes. This is a situation that is of particular interest to the field of radiobiology, with a growing number of studies investigating energy deposition in sub-micrometer target volumes (Kyriakou et al 2017, Cunha et al 2016, Spirou et al 2015, Liamsuwan et al 2012, McMahon et al 2011, Hultqvist et al 2010, Nikjoo et al 2008, Stewart et al 2002, Cucinotta et al 2000).

Yet, as there has been no systematic comparison between CH and TS models (and experimental results are typically not available for direct validation) there can be no quantification of the uncertainty that is being introduced by the choice of physics model. Furthermore, given the current limitations of TS models, it may not always be possible or practical to apply them to every simulation. This necessitates the occasional use of CH models in the calculation of stochastic quantities with, currently, unknown uncertainties. In general, the result of a measurement is only an estimate of the true value of the quantity measured and thus is complete only when accompanied by a statement of the uncertainty of that estimate (JCGM 2008). This means that a systematic investigation of the appropriateness of different physics models for the calculation of stochastic quantities is essential to having a complete understanding of the current strengths and limitations of MC methods in radiation dosimetry.

In this work a systematic study of the impact of the choice of different physics models and the variation of some of their associated parameters on the calculation of energy deposition and ICSD, as relevant to radiation dosimetry, will be presented.

Materials and Methods

Geant4 is a Monte Carlo toolkit that can simulate the passage of radiation through matter using a variety of different physics models, including both CH and TS models. Geant4 version 10.02.p02 (Agostinelli et al 2003, Allison et al 2006, Allison et al 2016, Bernal et al 2015, Incerti et al 2010) was used to simulate the passage of electrons through liquid water. Electrons were chosen as they are produced as secondary particles to all types of biologically relevant radiation and thus the accurate simulation of electrons is a critical factor in any radiation protection or radiobiology investigation. Liquid water was used as a simulated medium as it is the most common material used to stand in for biological matter (Goodhead 2006).

Mono-energetic beams of electrons were simulated, emitted at the centre of the target, a sphere of liquid water. The ICSD and energy deposition per incident particle were recorded in spheres of diameter; 1 nm, 10 nm, 100 nm, 1 µm, 10 µm, 1 m.

Electron beams with energies between 50 eV and 10 keV were simulated. Such energy range has been selected based on the papers (Goodhead 2009) and (Nikjoo and Goodhead 1991). X-rays, gamma-rays and electrons with kinetic energy below 100 keV produce a high number of electrons with energy below few keV throughout the irradiation target. The contribution to the dose deriving from such low energy electrons can be up to 50% when irradiated with photons or electrons (Nikjoo and Goodhead 1991). In proton and heavy ion therapy, secondary electrons do have a kinetic energy below few hundreds keV in the Spread Out Bragg Peak in the target tumor, therefore, also in this case, the major part of energy is deposited via electrons with energy below 10 keV. From this observation it follows that the results of this work can be applied to clinical KV, MV beams, ^{60}Co sources, low energy beta emitters, proton and heavy ion therapy.

The w-value, which has been calculated in this simulation study, is defined here as w = E/J, where E is the mean energy deposition and J is the mean number of ionisations, within the target volume, per incident electron. Note that in large targets, where the entire radiation track is confined, this is equivalent to the W-value as defined by the ICRU report 31 (ICRU-31 1979). As the w-value for electrons in liquid water is only weakly dependent upon the electron kinetic energy, it is a good candidate for evaluating how the relationship between E and J varies depending on the choice of physics model, for a range of electron energies.

The following physics models were selected in the physics lists of the Geant4 application developed and used in this work:

- TS model: Geant4-DNA option 4 (for a detailed description of these models the reader may refer to (Kyriakou et al 2016, Incerti et al 2010). This model was chosen as it has proven to provide good agreement with experimental and theoretical values in the literature when calculating the w-value in water (Kyriakou et al 2015).
- CH models: Livermore, Penelope (for a detailed description of these models refer to (Perkins et al 1991a, Perkins et al 1991b, Apostolakis et al 1999, Salvat et al 2001)). Specifically the G4EmLivermorePhysics and G4EmPenelopePhysics constructors were adopted (Ivantchenko et al 2011).

For simulations using CH models the following parameters were also fixed:

- Production cut (units: mm and/or eV). This is the threshold of production of secondary particles. When an ionisation occurs a secondary electron should be produced. However, if the range (or the kinetic energy) of the secondary electron is below the production cut the electron will not be produced and all of its associated energy will be deposited locally in the medium. Note: by default, the minimum cut value is set to 990 eV. This minimum value can be changed in the simulation. In

this case, the chosen energy is converted to a particle range which is then applied as the production cut.

Production cuts of either 250 eV (a low energy limit for Livermore models has not been clearly established but 250 eV is typically applied (Guatelli et al 2007)), 100 eV (low energy limit of Penelope models recommended in (Sempau et al 2003) and adopted in Geant4) or 10 eV were applied (lowest possible limit of Livermore models). Note 10 eV was only applied to the Livermore models, as Penelope is only available down to 100 eV as stated above.

- Lowest electron energy (units: eV): if the kinetic energy of an electron falls below the "lowest electron energy" (LEE), then the electron is assumed to deposit all of its energy locally. In this work the LEE was fixed equal to the default value of 100 eV, and, alternatively, equal to 1 eV. The LEE is changed only for the CH approach, while for the TS models, the LEE is equal to 9 eV.

Each of the above combinations of physics models and parameters were applied in the simulation of energy deposition and ICSD, with the results discussed below. Statistical uncertainties are not shown on the plots illustrating the results; sufficient numbers of primary particles were simulated to ensure statistical uncertainties of 3% or less in all cases.

Results and Discussion

Number of Ionisations (ICSD)

The ICSD's were calculated for monoenergetic electrons with energy between 50 eV and 10 keV. Figure 1 shows, as example, the number of ionisations produced by 10 keV electrons for CH models relative to Geant4-DNA models, with respect to the parameter R defined as the ratio of target diameter and average track length of the incident electrons, as calculated by Francis et al (Francis et al 2011). A value of R equal to one is obtained when the target diameter is equal to the mean particle track length, a value of less than one when the target diameter is smaller than the mean particle track (i.e. it is possible that only a segment of the particle track is recorded inside the target, depending on the detour factor (Berger et al 2005)). R is greater than one when the target diameter is larger than the mean particle track (i.e. on average, the entire particle track is recorded inside the target).

When considering ICSD's the physics model and choice of parameters had a significant impact on the results for all investigated R values. The only close agreement between the CH models and the TS models was observed when using the Livermore approach with a 10 eV production cut and a 1 eV LEE. With this combination of physics models and parameters the observed differences were between approximately 4% and 22%, for all of the simulated target sizes. Conversely, when using a higher production cut the agreement with TS results was significantly worse, with differences of almost two orders of magnitude when a 250 eV cut was applied, regardless of the CH model used or the target size.

When considering the ICSD's at simulated energies lower than 10 keV the same trend occurred, with the best agreement between TS and CH models consistently found when using the Livermore approach with a 10 eV production cut and a 1 eV LEE. Similarly to the 10 keV case described above, for all other simulated electron kinetic energies (down to 50 eV) the worst agreement with TS values was consistently found when using a higher production cut, with differences between about 50% (at 50 eV) and almost two orders of magnitude (at 5 keV).

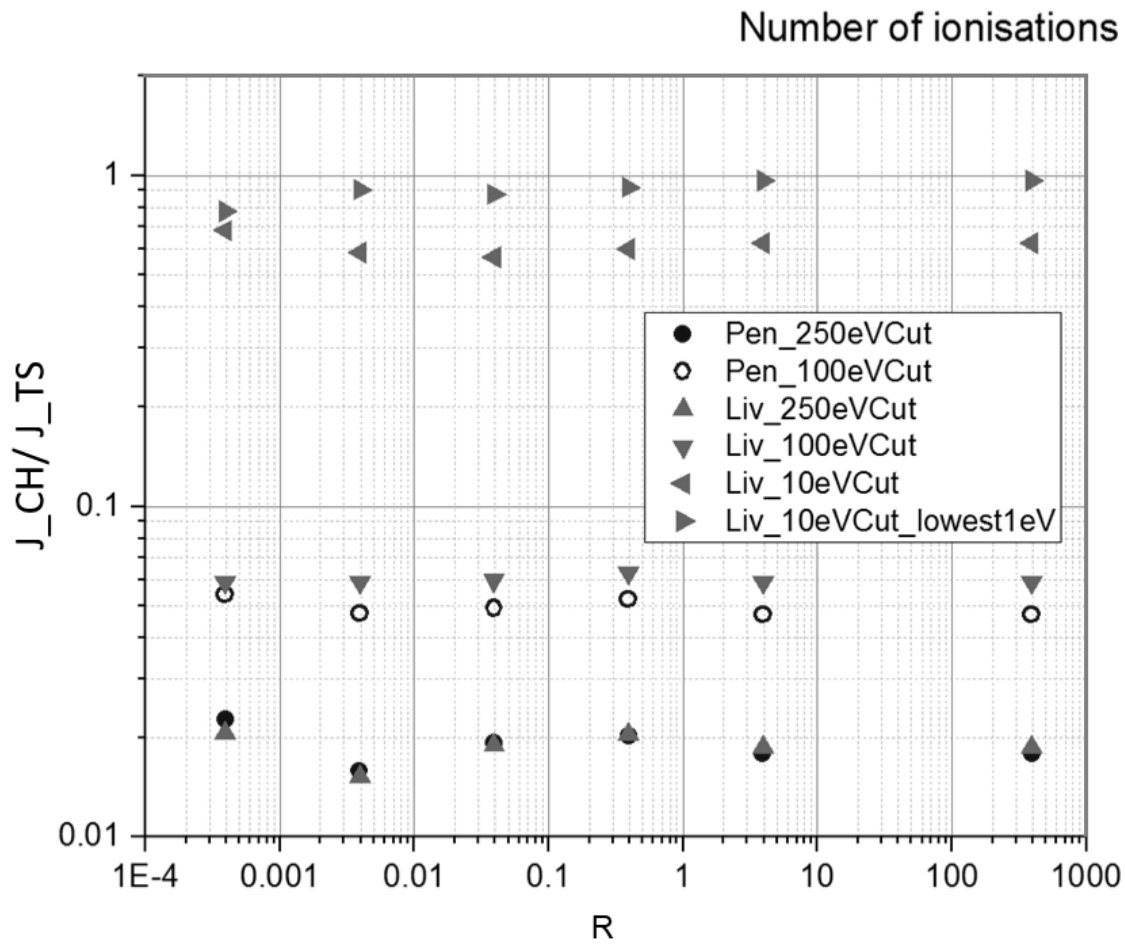

Figure 1. The ratio of mean number of ionisations (J) to Geant4-DNA, for 10 keV electrons, calculated using Livermore and Penelope models and different combinations of production cut and LEE, with respect to R defined as the target diameter divided by the mean track length of incident electrons. In all cases the default value of LEE (100 eV) was used, unless otherwise indicated by lowest1eV showing a value of 1 eV was applied.

Energy deposition

The energy deposition distributions were calculated for monoenergetic electrons with energy between 50 eV and 10 keV. Figure 2 shows, as example, the energy deposition for CH models relative to Geant4-DNA models, as a function of R for incident electrons with energy equal to 10 keV. It is possible to observe that the largest differences between energy depositions calculated using CH and TS models are found when considering the smallest target diameter, in this case 10 nm and 1 nm. This is to be expected as one of the basic assumptions of the CH method of modelling physical interactions is that several interactions will take place within the target volume. For example, the Geant4 Physics Reference Manual describes the modelling of the fluctuating energy loss of particles in a thin target using CH models to be reliable only when the mean energy loss in the target is greater than a few times the mean excitation energy of the material (Geant4 Collaboration 2016), which would typically require several interactions to take place.

As a general trend, in small target volumes with R smaller than one, CH models calculate average recorded energy deposition per incident particle significantly different from the results obtained with the TS models. The largest differences, of about one order of magnitude, were observed when considering low energy

electrons (100 eV or lower) in a 1 nm diameter target volume, with differences of about 30% or higher present for all energies in the target with 1 nm diameter. When considering larger target volumes (still with R < 1) the differences were smaller, with differences of between ~10% and 60% observed. For energies above 500 eV differences of 40% or greater were only observed when less than 10% of the particle track was recorded inside the target volume.

When R > 1 all the alternative physics models calculate the same energy deposition, as expected.

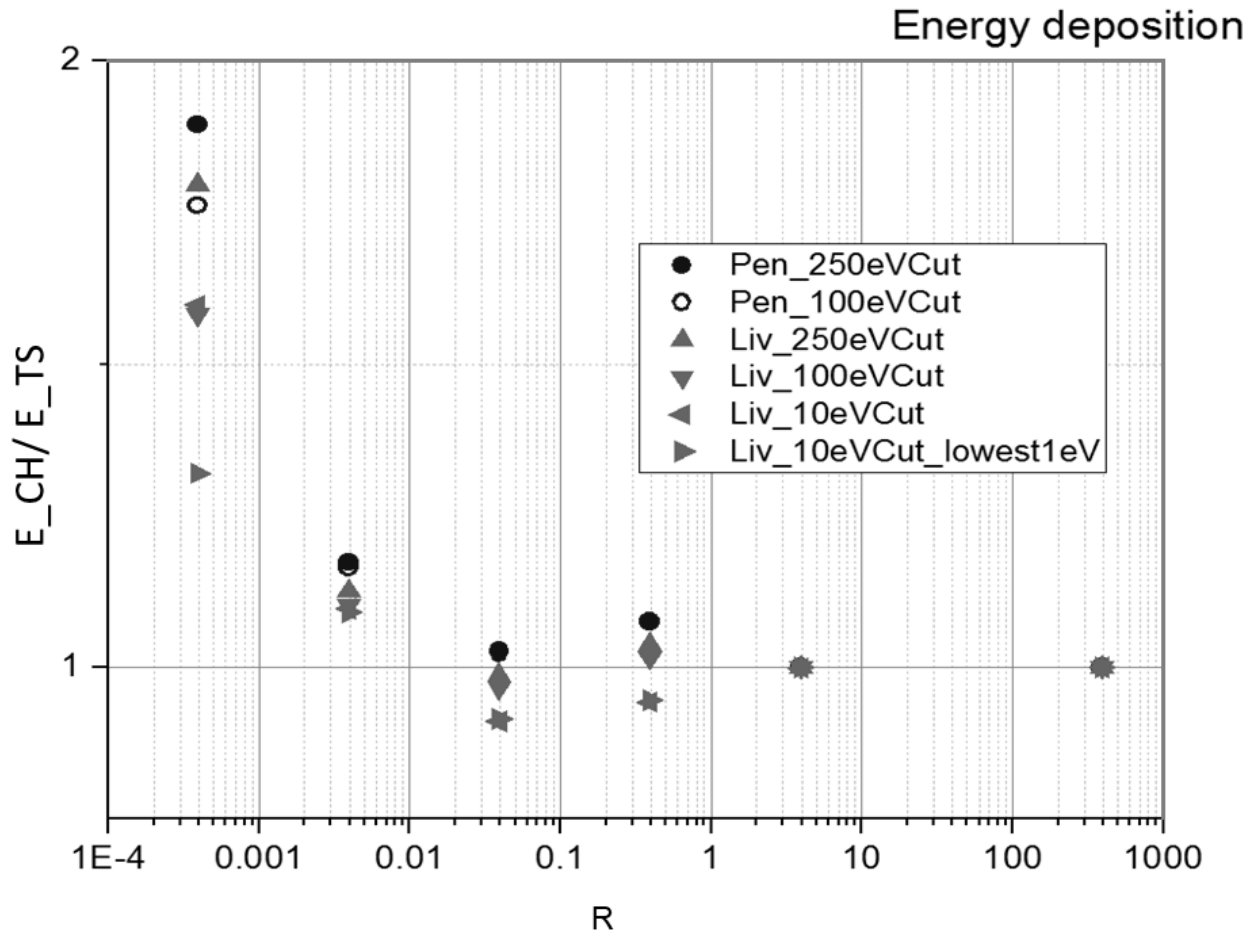

Figure 2. The ratio of mean energy deposition to Geant4-DNA, for 10 keV electrons, calculated using Livermore and Penelope models and different combinations of production cut and LEE, as a function of R. R is the ratio of the target diameter and the mean track length of the incident electrons. In all cases the default value of LEE (100 eV) was used, unless otherwise indicated by lowest1eV showing a value of 1 eV was applied.

When considering the total number of interactions taking place within the target, one must bear in mind that at low energies electrons undergo a large amount of elastic scattering events which may have a significant impact on the spatial distribution of interactions. A significant difference between the TS and CH physics models is the simulation of elastic scattering interactions. In Geant4 the TS models simulate every elastic scattering interaction as a discrete event, while the CH models condense several interactions into a single simulated event. For electrons in liquid water, as the kinetic energy decreases the elastic scattering cross section increases, with the elastic mean free path (mfp) correspondingly becoming smaller and smaller for lower electron energies (Champion 2003). This means that for very low electron energies there is a

significant amount of backscattering occurring, with low energy electrons almost as likely to be scattered in the backwards direction as the forwards direction (Incerti et al 2010). However, as there may be several scatter interactions combined into a single simulated event when using the CH models, the impact of these individual backscatters on the track structure of the electrons on the scale of the mfp of the particle can be reduced. Thus the accurate modelling of elastic interactions can be expected to be a particularly vital component of the simulation when the mfp of the particle is of the same order of magnitude as the target size.

For electron kinetic energies above about 100 eV, the mfp of inelastic interactions for electrons in liquid water increases with increasing kinetic energy; for a 100 eV electron the inelastic mfp is about 1 nm, while for a 10 keV electron it's about 30 nm (Emfietzoglou et al 2017a). This means that in the smallest targets investigated here, of 1 nm and 10 nm diameters, for a 10 keV electron there is a high probability of no inelastic interactions taking place. Even for 100 eV electrons, with a mfp of about 1 nm, there is a high probability of only zero or one inelastic interaction taking place in the smallest volume. This high probability of only a few, or no, inelastic interactions taking place means that there is a correspondingly high probability of, on average, only a very small energy deposition within the volume. This means that the assumptions that drive the use of condensed history physics models may not be valid. In this case it has been shown that the inadequacy of these assumptions can lead to differences of about 90% or more in the recorded energy deposition when the mfp of the incident particle is larger than the volume (i.e. see figure 2) .

As there are multiple electrons in a water molecule, occupying several different atomic orbitals, the required energy to ionise a water molecule varies depending on which orbital is being ionised. This means that the deposited energy may also vary, as can the secondary electron energy. Most often, impact ionisations will result from interactions with the most loosely bound electrons (Emfietzoglou et al 2017b), however interactions with tightly bound electrons can also take place with a lower frequency of occurrence. An example of this can be seen in Figure 3, which shows the frequency of the energy deposition produced by 10 keV electrons in a 10 nm diameter target, calculated by means of the CH and TS models and varying the production cut. The Figure shows that there is a small but non-negligible probability of ionisations occurring with electrons in the most tightly bound orbital with a binding energy of about 530 eV. It is also possible to observe that there are two distinct peaks in the energy deposition histogram when using the Livermore and Penelope physics models, and one distinct peak when using the Geant4-DNA models. In all cases the peak at about 530 eV results from the ionisation of the most tightly bound electrons in the water molecule. In the case of Livermore and Penelope models the secondary peak, at either 100 eV or 250 eV corresponds to the production cut applied in the simulation.

w-value

Figure 4 shows the calculated w-value with respect to the initial electron kinetic energy for a target volume of 1 m diameter, calculated using different physics models and parameters. The expected result in a large volume (in this case, 1 m) is that w should be fairly constant at about 23 eV (Kyriakou et al 2015). It can be seen that the best agreement with expected values are obtained using either the Geant4-DNA models (TS model), or the Livermore models with a 10 eV production cut and 1 eV LEE. Generally, the higher the production cut the worse the agreement with expected values. This has to be expected as the production cut dictates how many secondary electrons are produced, which directly impacts the number of ionisation interactions that may take place. As the production cut is increased the number of secondary electrons produced is reduced translating in a reduction of number of ionisations, and therefore an increase in the w-value. This happens because w is inversely proportional to the mean number of ionisations J.

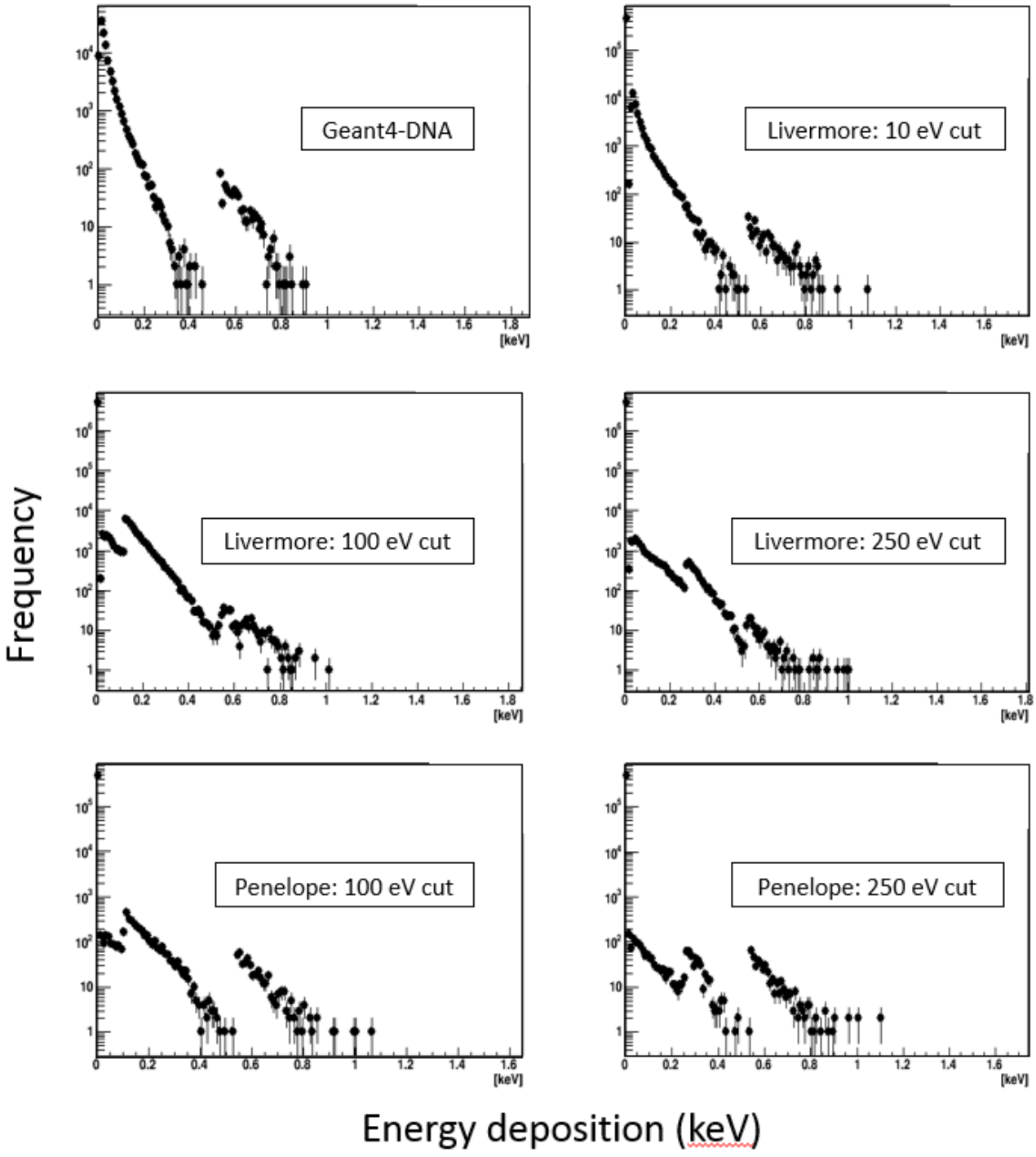

Figure 3. Frequency of the energy deposition, per incident particle, given by 10 keV electrons in a 10 nm diameter target, calculated using different physics models. The peak at about 530 eV is due to the ionisation of tightly bound electrons. The secondary peak observed when using Livermore and Penelope models results from the application of a production cut.

For CH models, when the LEE is fixed to 100 eV, there can be secondary electrons that only undergo a single interaction (i.e. if the kinetic energy is 100 eV or less, all the electron energy is deposited locally in a single interaction). This is why, at an initial kinetic energy of 50 eV or 100 eV, w is equal to the initial kinetic energy

of the electron in all cases where the LEE is not altered, for both Livermore and Penelope models. This means that both the production cut and the LEE have a significant impact on the results and need to be carefully considered when the track length is bigger than the dimensions of the target.

When the particle track length is bigger than the dimensions of the target, w remains fairly constant in targets with diameter down to 10 nm, as calculated by means of the Geant4-DNA physics. For smaller diameter targets, w is slightly reduced with an average value of about 17 eV. This means that as smaller sections of the track are contained in the target, both E and J reduce at a similar rate, indicating a strong linear correlation with a positive gradient between the number of ionisation interactions and the energy deposition of the particle, i.e. the fewer the ionisations that are recorded the lower the energy deposition of the particle.

When using the Livermore and Penelope models the energy deposition and the number of ionisations in the target both decrease as the target gets smaller; this can be expected as only a smaller and smaller section of the track is recorded. However, when only a section of the track is contained in the target, the number of ionisations and the energy deposition of the particle do not decrease at the same rate, with the energy deposition decreasing faster than the number of ionisations, indicating a non-linear relationship between the number of ionisations and the energy deposited in the volume.

When simulating the lowest electron kinetic energies the value of w is typically underestimated when using the Livermore models with a LEE of 1 eV. This indicates either; an over estimation of the production of secondaries or an underestimation of the energy deposition, in the target.

The same general relationship between w and initial electron kinetic energy shown in Fig. 4 was also observed in smaller target volumes, with w generally being overestimated for higher kinetic energies when CH models were used. This overestimation of w is due to a combination of an underestimation of J and an overestimation of E that was present for all simulated target sizes.

The results show the fundamental differences in the simulation of individual radiation tracks by the two classes of physics models considered, CH and TS, with the CH approach demonstrating a stronger dependence upon the parameters of the models rather than the diameter of the target. This means that even for very small targets the CH models, particularly the Livermore models, were capable of producing results similar to those of the TS models.

The calculated w has only a weak dependence on R, however it has a strong dependence on simulation model parameters as well as the initial electron kinetic energy. The weak dependence on R is because the target size (represented by R) is the sample size of the radiation tracks that is used to calculate E and J. Changing the sample size will impact the variance of E and J significantly, but may not alter the mean values significantly over a large number of simulations where statistical uncertainty is minimised as it does not directly affect the method of calculation of the radiation track. Whereas the impact of changing simulation model parameters or the initial kinetic energy of electrons may impact both the mean values and the variance of E and J as this will directly impact the method of calculation of the radiation tracks.

Figure 5 shows the Pearson coefficient with respect to the target diameter. Each point of the plot is derived considering the E and J calculated for all the kinetic energies of the incident electrons, for a single target size and combination of parameters (LEE and production cut). The Pearson coefficient is calculated using the following formula:

$$Pearson\ coefficient = \frac{cov(E,J)}{\sigma_E \sigma_J}$$

Where $cov(E,J)$ is the covariance of E and J, σ_E is the standard deviation of E, and σ_J is the standard

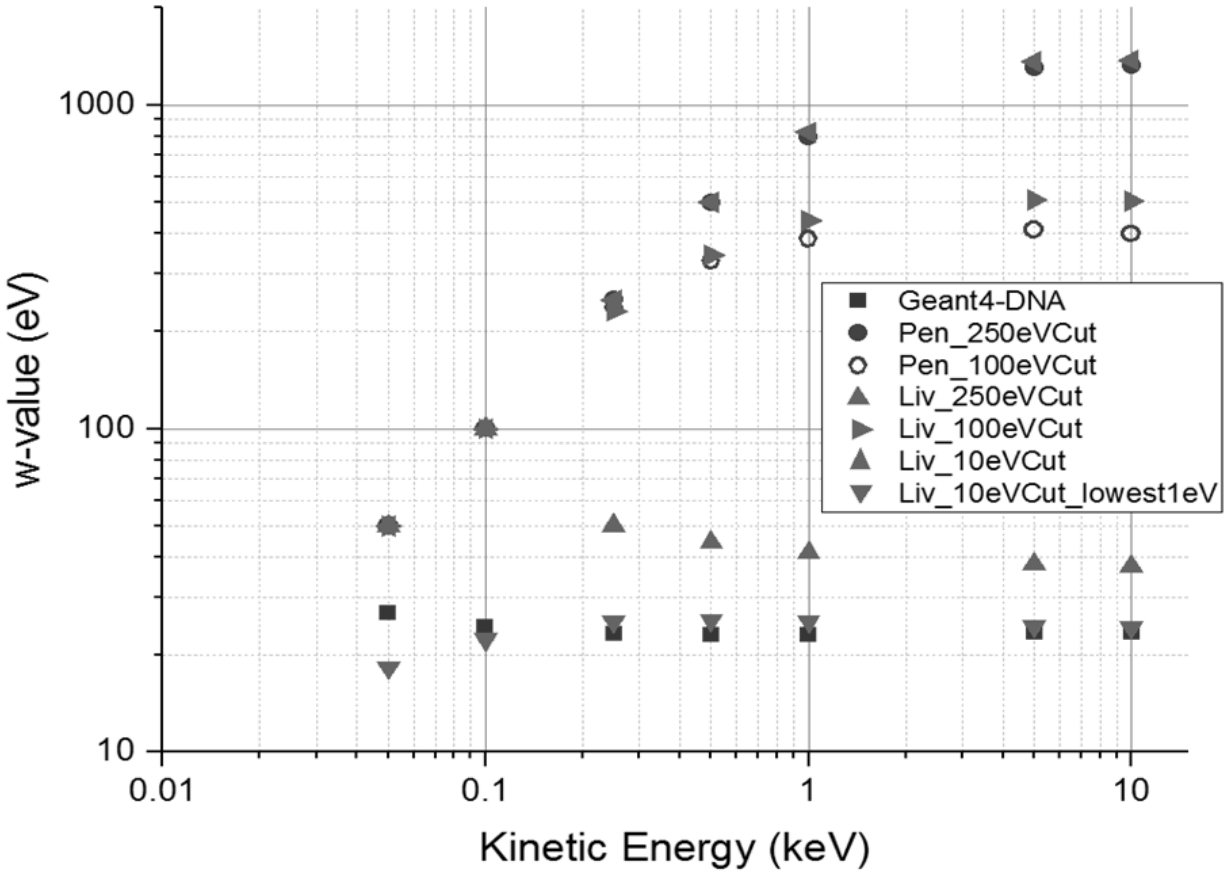

Figure 4. The value of w calculated as a function of the electron initial kinetic energy using different physics models and combinations of production cuts and LEE, in a 1 m diameter sphere. The production cut applied is indicated in the legend. In all cases the default value of LEE (100 eV) was used, unless otherwise indicated by lowest1eV showing a value of 1 eV was applied.

deviation of J. The Pearson coefficient is a measure of the linear correlation between two variables, in this case E and J, calculated for all the kinetic energies of the incident electrons. Thus here the Pearson coefficient indicates the strength of the linear correlation between the number of ionisations (J) and the energy deposition (E) for electrons with kinetic energies between 100 eV and 10 keV, as a function of target size. A positive linear correlation means that as the particle undergoes more ionisation interactions it deposits more energy. When the Pearson coefficient is equal to 1 there is a strong linear correlation with a positive gradient, when it is equal to zero there is no indication of a linear correlation, when the Pearson coefficient is equal to -1 there is a strong linear correlation with a negative gradient. In this case, for a statistically significant linear correlation with a positive gradient at the p-value smaller than 0.05, the correlation coefficient must be equal to or greater than 0.811, as determined using the hypothesis test described by Bewick et al (Bewick et al 2003) and Miles and Banyard (Miles and Banyard 2007).

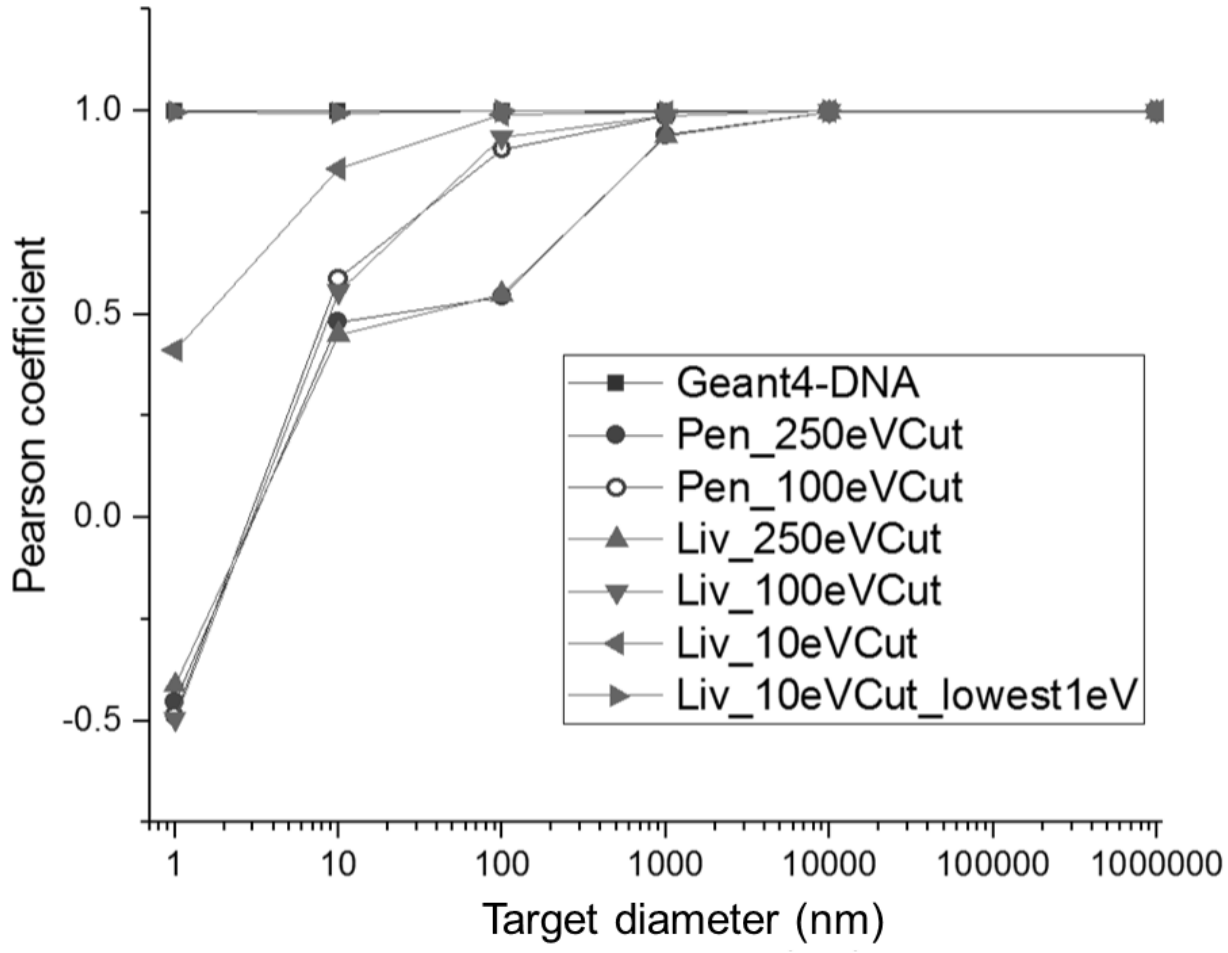

Figure 5. The Pearson coefficient describing the strength of the linear correlation between E and J for electrons in liquid water with energies between 100 eV and 10 keV, with respect to the target diameter. A value of greater than 0.811 indicates a strong linear correlation. For clarity of the plot only results up to 1 mm are shown; 1 m target results are all constant at unity, the same as the 1 mm target. In all cases the default value of LEE (100 eV) was used, unless otherwise indicated by lowest1eV showing a value of 1 eV was applied.

For large volumes (targets with dimensions bigger than the incident particle track length) all physics models show a strong linear correlation with a positive gradient, with little difference in the strength of correlation between physics models. When smaller volumes (targets with dimensions smaller than the incident particle track length) are simulated, the choice of physics model has a larger impact on the correlation between J and E. For electrons of 10 keV or lower kinetic energy in liquid water, when simulating a target with diameter of less than about 1 µm, the strength of the linear correlation between E and J reduces for most of these physics models at different target sizes.

The Geant4-DNA results, as shown in Figure 5, exhibit a strong linear correlation between J and E for all target sizes. The CH models (both Livermore and Penelope) generally show a loss of linear correlation at the smallest target sizes, as discussed below.

When a production cut of either 250 eV or 100 eV is applied a loss of linear correlation begins to occur for volumes smaller than about 1 µm. For the smallest volume, 1 nm, a negative correlation coefficient is observed for all CH models except for the Livermore model with a 10 eV production cut. When the

Livermore model with a 10 eV cut and 1 eV LEE is used a strong linear correlation with a positive gradient is observed; this is because of the significant increase in the number of secondary electrons produced. As discussed earlier, when one does not reduce both the production cut and LEE, for energies of 100 eV and lower the maximum possible number of ionisations is 1 regardless of the initial kinetic energy. Only when the LEE is reduced, an increase in the number of ionisations is observed that becomes closer to that calculated by means of Geant4-DNA. This has a significant impact on the number of ionisations produced, as low energy electrons have a peak in the inelastic cross section at about 100 eV in liquid water.

This means that the choice of physics model can have a significant impact on the results of the simulation, with the magnitude of the impact changing depending on the size of the target volume with respect to the particle track length and the physical quantities calculated.

Summarising, when the target is large enough to encompass the entire radiation track

- the calculated energy deposition does not exhibit a dependence upon the choice of physics model, and is in agreement for all physics models and combinations of parameters, and
- the calculated ICSD exhibits a strong dependence on the choice of physics models and parameters.

When the target diameter is smaller than the radiation track, but still larger than the mfp of the incident particle

- the calculated energy deposition exhibits a strong dependence upon the *class* of physics model (TS or CH), and exhibits a weak dependence upon the specific CH physics model and parameters chosen, and
- the calculated ICSD exhibits a strong dependence upon the choice of physics model and parameters.

When the target is smaller than the mfp of the incident radiation

- the calculated energy deposition exhibits a strong dependence upon the *class* of physics model (TS or CH), and also depends strongly upon the specific CH physics model and parameters chosen, and
- the calculated ICSD exhibits a strong dependence upon the choice of physics model.

Typically Penelope models produced slightly larger differences than Livermore models in the physical quantities under study. The CH models almost always underestimated the mean number of ionisations.

In all cases the best agreement between CH and TS models was found using the Livermore models with a 10 eV production cut and 1 eV LEE.

Conclusions

In liquid water, for electrons with 10 keV or lower kinetic energy in targets with diameter smaller than 1 µm, the choice of physics model and associated parameters have a significant impact on the recorded energy deposition and ionisation cluster size distribution.

Generally, it was found that a key quantity was the size of the target volume compared to the track length of the radiation. Target volumes with a diameter smaller than the radiation track length require a different physical approach with respect to targets encompassing the entire radiation track.

It was observed that the ICSD was particularly sensitive to the choice of physics model and parameters for all target sizes, though with careful choice of parameters the CH models produced similar results to the track structure models, with differences as low as 15%.

The results indicate that energy deposition produced by the incident electrons became more sensitive to the choice of physics model, that is the choice between TS and CH, as the target diameter was reduced below

the track length of the incident electrons. Furthermore, while varying the parameters of the CH models had a significant impact on the recorded energy deposition of the electrons, there was no combination of models and parameters that produced results similar to the TS simulations in very small volumes. In general, these results indicate that when the diameter of the volume of interest is smaller than the track length of the particle the choice of TS or CH physics model is likely to have a significant impact on the recorded energy deposition.

The best agreement between TS and CH models was consistently found when using the Livermore model with a 10 eV production cut and 1 eV lowest electron energy (LEE). This is likely because of the increased accuracy afforded the simulation by the extended tracking of low energy electrons. Though the only material simulated was liquid water it is hypothesized here that the relationships discussed above may extend to other materials, as the physics models are implemented in an identical fashion in the Geant4 toolkit, independent of material.

The results of this research have significant impact on studies which intend to investigate the physics mechanism at the basis of the radiobiological effects of radiation at cellular and sub-cellular level in radiotherapeutic applications (Incerti et al 2016), such as the investigation of dose enhancement produced by high-Z nanoparticles (e.g. (Sakata et al 2016, Douglass et al 2013, Engels et al 2016, McKinnon et al 2016a, McKinnon et al 2016b)), the characterisation of radio-emitters for Targeted Particle Therapy (e.g. (Huang et al 2012)), the study of the effect of radiation in cellular targets other than the nucleus (e.g. (Byrne et al 2013, Byrne et al 2016)) or in the presence of a magnetic field (Bug et al 2010, Lazarakis et al 2012b). This work has also impact in microdosimetry which is a powerful approach in radiation protection in nuclear labs, aviation and space missions (e.g. (Guatelli et al 2008, Davis et al 2014)).

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