In-silico calculations of DNA damage induced by α-particles in the $^{224}$Ra DaRT decay chain for a better understanding of the radiobiological effectiveness of this treatment

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A B S T R A C T

Diffusing alpha-emitters radiation Therapy (DaRT) is an interstitial brachytherapy technique using $^{224}$Ra seeds. For accurate treatment planning a good understanding of the early DNA damage due to α-particles is required. Geant4-DNA was used to calculate the initial DNA damage and radiobiological effectiveness due to α-particles with linear energy transfer (LET) values in the range 57.5–225.9 keV/μm from the $^{224}$Ra decay chain. The impact of DNA base pair density on DNA damage has been modelled, as this parameter varies between human cell lines. Results show that the quantity and complexity of DNA damage changes with LET as expected. Indirect damage, due to water radical reactions with the DNA, decreases and becomes less significant at higher LET values as shown in previous studies. As expected, the yield of complex double strand breaks (DSBs), which are harder for a cell to repair, increases approximately linearly with LET. The level of complexity of DSBs and radiobiological effectiveness have been found to increase with LET as expected. The quantity of DNA damage has been shown to increase for increased DNA density in the expected base pair density range of human cells. The change in damage yield as a function of base pair density is largest for higher LET α-particles, an increase of over 50% for individual strand breaks between 62.7 and 127.4 keV/μm. This change in yield shows that the DNA base pair density is an important parameter for modelling DNA damage particularly at higher LET where the DNA damage is greatest and most complex.

1. Introduction

Diffusing alpha-emitters radiation therapy (DaRT) is a brachytherapy technique involving the interstitial placement of $^{224}$Ra seeds. A preliminary clinical trial using DaRT for the treatment of locally advanced recurrent squamous cell carcinomas of the skin and head and neck has shown the treatment to be safe and effective and further larger scale clinical trials are ongoing [1]. In this trial between 3 and 169 seeds were implanted, with a mean activity on the day of insertion of 55 μCi. Fig. 1 shows the decay chain of $^{224}$Ra, showing the four α-particles produced per decay of $^{224}$Ra with different initial kinetic energy values up to 8.79 MeV.

The high linear energy transfer (LET) and short range of α-particles makes them ideal candidates for targeted radiotherapy. For conventional brachytherapy the short range in tissue is a practical limitation for the use of most α-particle sources as the typical range is only of the order of a few cells. In DaRT, however, diffusion of the daughter products, in particular $^{220}$Rn, away from the implanted seed increases the range over which dose is deposited up to several millimetres [2]. DaRT is a promising candidate for brachytherapy due to several factors. The high LET of α-particles causes more complex DNA damage which is harder for the cell to repair [3]. The half-lives of the $^{224}$Ra decay chain are suitable for clinical use, enabling dose to be delivered in a short timeframe but long enough for practical use. Finally, DaRT allows for targeting of treatment regions whilst minimising dose to surrounding normal tissues. Due to the multiple decay steps and diffusion of daughter products the distribution of...
types and complexity of strand breaks has previously been proposed [8] more likely to lead to cell death [7]. A methodology for describing the cell to repair, with more complex DSBs being even harder to repair and considered to be the most critical damages as these are harder for the cell to repair. In particular, double strand breaks (DSBs) are the deoxyribose-phosphate backbone is with the OH $\cdot$ DNA-radical reactions are possible, but the predominant reaction for age is caused by the reaction of water radicals and the DNA. Several death due to ionising radiation [5]. DNA damage occurs due to two 1.1. DNA damage

Damage to the DNA is considered to be the primary cause of cell death due to ionising radiation [5]. DNA damage occurs due to two mechanisms — direct and indirect. Direct damage is caused by the interaction of radiation directly with the DNA molecules. Indirect damage is caused by the reaction of water radicals and the DNA. Several DNA-radical reactions are possible, but the predominant reaction for the deoxyribose-phosphate backbone is with the $\text{OH}^\cdot$ radical [6].

DNA damage can lead to cell death when damage cannot be repaired by the cell. In particular, double strand breaks (DSBs) are considered to be the most critical damages as these are harder for the cell to repair, with more complex DSBs being even harder to repair and more likely to lead to cell death [7]. A methodology for describing the types and complexity of strand breaks has previously been proposed [8] and is used in this work. Fig. 2 describes the definitions of DSBs used in this work. Briefly, a DSB is defined as having at least one strand break on each strand of the DNA backbone within 10 base pairs. DSBs are further classified into simple DSBs and complex DSBs: a simple DSB having only two individual strand breaks one on either side of the double-helix, and a complex DSB containing these two breaks plus additional strand breaks on either strand. DSBs are classified further due to the damage source; direct DSBs consisting of strand breaks only due to the direct effect, indirect DSBs consisting of DSBs only from the indirect effect, hybrid DSBs having breaks from both effects where if either effect was removed the cluster would no longer be a DSB, and mixed DSBs consisting of all other DSBs containing direct and indirect damages.

Higher LET radiation produces more dense track structures and as a consequence strand breaks are more likely to be closer together leading to more clustered complex damages which have a higher probability of causing cell death. This increase in DNA damage complexity is one of the benefits of high LET treatments such as DaRT. Due to this variation in DNA damage different radiation qualities result in different biological outcomes for a given dose. Radiobiological effectiveness (RBE) aims to quantify this difference for a given radiation quality compared to photon irradiation and is defined as [9]:

$$RBE = \frac{Dose_{endpoint \text{ (photon)}}}{Dose_{endpoint \text{ (quality)}}}$$

where the endpoint is defined as some quantity of interest, for example the surviving fraction of cells or the number of DSBs.

In this study the initial DNA damage is calculated and classified by complexity and damage source, and RBE is calculated using total DSB and complex DSB yield as the endpoints for $\alpha$-particles in DaRT.

1.2. Monte Carlo simulation of DNA damage

Monte Carlo codes can be used to investigate in-silico the distribution and complexity of radiation induced DNA damage. Here, Geant4 [10–12] is adopted with the Geant4-DNA low energy track structure extension for liquid water [13–16] which is extensively used to simulate the interaction of particles down to the nano-scale. Geant4-DNA has been used in previous studies to simulate the DNA damage caused by $\alpha$-particles [17–20]. However, no previous studies have used large geometries of the order of the size of the cell nucleus. At energies around the Bragg peak there is a significant change in LET across such a volume. Due to this rapidly changing LET a small DNA geometry has been chosen for this study to minimise the variation in LET across the volume. The benefit of this choice compared to previous studies is that the damage for a given LET can be determined. In this study the initial DNA damage is calculated using Geant4-DNA due to both the direct and indirect effects for mono-energetic $\alpha$-particles in the range 0.1–9 MeV, to cover all stages of the $^{224}\text{Ra}$ decay chain and the $\alpha$-particle range. In addition, the RBE for DSB induction has
been calculated as a function of LET, which has not previously been calculated for α-particles.

Typically, simulations of DNA damage model the cell in a fixed geometry configuration however, base pair density and chromatin compaction change throughout the cell cycle and differ between cell lines. The typical variation in base pair density between human cell lines is 0.007–0.057 bp/nm, assuming 6.4 Gbp per cell and a spherical nucleus of radius 3 - 6 μm [4]. The effect of base pair density has been studied previously for proton irradiation [21] and chromatin compaction was studied for proton and α-particle irradiation [22].

2. Methods

2.1. Geant4 simulation geometry

Geant4 (version 11.0) was used in this study. All volumes are constructed of liquid water due to the availability of track structure physics models in Geant4-DNA, see [23]. To reduce simulation time whilst maintaining calculation accuracy a combined physics list was constructed which uses G4EmDNAPhysics_option2 within the nucleus plus a 9 nm margin and G4EmStandardPhysics_option4 for all other volumes. A detailed description of the models used in the G4EmDNAPhysics_option2 constructor is provided in [13]. The G4EmStandardPhysics_option4 constructor uses a range of models and was chosen as it has been recommended for medical applications [24]. The cut-off value for secondary particle production was 5 eV and the region using the G4EmDNAPhysics_option2 physics list was increased beyond the nucleus by a margin of 9 nm, to minimise the difference in secondary particle distribution incident on the DNA geometry. All irradiation simulations, as described in Section 2.2, are carried out in a parallel world of the same size, without any of the DNA geometry using an adaption of the G4EmDNAChemistry_option3 constructor [25].

The DNA geometry was simulated as a small section of a simplified cell nucleus containing a uniformly spaced grid of short sections of chromatin fibre, see Fig. 3. Spheres were used to represent the deoxyribose-phosphate molecules of the DNA backbone, arranged in a simplified B-DNA structure consisting of a right-handed double helix, with a radius of 1 nm, 10.5 base pairs per turn and a pitch of 3.4 nm [26]. Nucleotide base pairs are randomly placed within the DNA back bone structure following the same helical structure with equal probability of a cytosine–thymine or guanine–adenine pair. Nucleosome units comprising of a strand of DNA containing 147 base pairs forming a left-handed helix around a histone represented by a cylinder of 5.5 nm radius and 5.5 nm height [27] were repeated to represent a segment of chromatin fibre. The chromatin fibre segments are placed within a cuboid target volume which represents the simplified cell nucleus. This simplified cell nucleus is placed within a much larger world volume.

For initial simulations of the DNA damage 14 chromatin fibre strands, containing 296,352 base pairs of DNA were placed in a cube nucleus of side length 300 nm, which has a base pair density of 0.011 bp/nm², chosen to be representative of a typical human cell [28]. The cubic geometry and short segments of chromatin fibre were chosen for simplicity and to limit the size of the volume, all volumes are simulated as liquid water. These results are discussed in Section 3.1. Subsequent simulations vary the base pair density to investigate the impact on DNA damage, see Section 3.2.

Mono-energetic α-particles are incident on the DNA geometry with kinetic energies in the range 0.1–9 MeV, covering all stages of the 224Ra decay chain and the α-particle range. LET is calculated for each incident kinetic energy as the unrestricted LET using the ICRU-90 electronic stopping power data [29] in Geant4 for the mean α-particle kinetic energy within the nucleus. The same geometry was irradiated with photons from a 60Co source, which decays producing photons with energies of 1.17 and 1.33 MeV, to calculate RBE, see Eq. (1).

The α-particles are generated on a spherical surface 1 μm from the centre of the nucleus to ensure the DNA geometry is irradiated from all angles. The initial kinetic energy was varied to simulate the DNA damage along the full range of the α-particles, including in the Bragg peak. The angular distribution of emission from the surface was limited so that only α-particles crossing the nucleus were simulated. For the 60Co source, photons are generated on a spherical surface 5 mm from the centre of the DNA geometry to ensure charged particle equilibrium is established [30]. The aim of this irradiation geometry is to reproduce the variation in incidence angle at which DNA fibres would be irradiated in a realistic cell geometry with chromatin folding.

2.2. DNA damage scoring

DNA damage occurs due to two effects, direct and indirect, as described in Section 1.1. Whilst damage to the nucleotide bases also occurs, strand break damage is considered to be the most critical therefore only strand breaks are considered in this study. Each source of damage is calculated separately, and the location of the strand break used to determine the complexity of the strand break.

Direct damage is simulated by scoring energy deposits within each deoxyribose-phosphate sphere and up to a radius of 0.35 nm. This additional volume surrounding the deoxyribose-phosphate sphere is to take into account the transfer of charge from the hydration shell to the deoxyribose-phosphate molecule, which is considered to be part of the direct damage [31–34]. The linear damage method [35] is applied to each deoxyribose-phosphate volume whereby energy deposits greater than a maximum threshold, 37.5 eV, always result in a strand break; deposits less than a minimum threshold, 5 eV, do not cause a strand break; and a linear probability of damage occurring is applied for energy of deposits between the two thresholds.
The Geant4-DNA constructor \textit{G4EmDNAChemistry\_option3} simulates the radiolysis of water using the Independent Reaction Time (IRT) method \cite{36}. The IRT method calculates the time to reaction for all pairs of reactants based on the diffusion rates and reactions are determined starting with the shortest reaction times. Reaction products are inserted based on the positions of the reactants, and reactions of the remaining reactants with this product are added to the possible reactions. In this way reactions are tracked without explicitly simulating diffusion until either all possible reactions occur, or the time limit is reached. \textit{G4EmDNAChemistry\_option3} has been adapted to include the reactions and reaction rates of the deoxyribose-phosphate backbone and nucleotide bases with the water radicals \cite{6}. The IRT model has been adapted to include reactions with stationary molecules.

Indirect damage is simulated to be due to the reaction between the deoxyribose-phosphate backbone and OH\(^-\). Not all reactions between a radical and the deoxyribose-phosphate result in a strand break, previous studies have shown that there is a probability of 40.5\% that a strand break is induced \cite{19,33,34}. Radicals are tracked up until 5 ns and are removed from the simulation if they are more than a distance, \(d_{kill} = 9\) nm, from the DNA \cite{19,33,34}. This distance is determined based on the distance travelled by the radicals in 5 ns and it is assumed that all radicals generated further away than this distance would be scavenged by the medium. Histones are assumed to be perfect scavengers of all radiolysis products as modelled previously \cite{32–34}.

Clustering of damage was carried out following the Geant4 simulation using an adapted version of the clustering algorithm in the clustering example in Geant4 \cite{14}, which is based on the DBSCAN algorithm \cite{37}. The algorithm has been adapted to the geometry used in this work to classify clusters by the base pair ID of the DNA molecule rather than the position and to further classify DSBs due to damage source, as defined in \cite{8}, as direct, indirect, hybrid and mixed.

3. Results

Fig. 4a shows the change in kinetic energy along the path of the \(\alpha\)-particles in the DaRT decay chain in liquid water. The LET of an \(\alpha\)-particle also changes significantly along the path as shown in Fig. 4c, reaching a maximum at the Bragg peak and decreasing in the distal region. These simulations show that, as expected, the range of \(\alpha\)-particles from DaRT is less than 100 \(\mu\)m and the LET changes rapidly around the Bragg peak. Due to this rapid change in LET, a small DNA geometry has been used for the simulation of DNA damage. Fig. 4b shows LET as a function of kinetic energy, showing that, as the \(\alpha\)-particle loses kinetic energy, the LET increases up to a maximum at the Bragg peak, and decreases again at lower kinetic energies. The track structure of \(\alpha\)-particles depends on the LET. Due to this change in track structure, the distribution of water radicals created also varies as a function of LET. Fig. 4d shows the mean distance between the initial positions of OH\(^-\) radicals. The initial positions of the OH\(^-\) radicals are closer together at higher LET due to the increased energy deposition per unit length. At higher LET OH\(^-\) radicals are created closer together, this increases the likelihood of radical recombination, resulting in fewer radicals available to cause indirect damage through reactions with the DNA.
Fig. 5. Strand break yield per Gy and per Gbp. Points with LET values on the proximal section of the particle track before the Bragg peak are shown as closed points. LET values on the distal section are plotted as open points. As a function of (A) LET and (B) kinetic energy. Double strand break (DSB) yield per Gy per Gbp as a function of LET (C) and kinetic energy (D). DSB yield classified by source type as a function of LET (E) and kinetic energy (F). Radiobiological effectiveness (RBE) as a function of LET (G) and kinetic energy (H). Horizontal error bars indicate the difference in the mean value of the α-particle when entering and exiting the nucleus. Vertical error bars are the standard error on the mean, for repetitions of the same simulation with different seeds.
3.1. DNA damage yield and RBE

Whilst the DNA geometry was chosen to minimise the change in LET across the volume, there is still some variation particularly for the lowest energy \(\alpha\)-particles. Error bars in LET (and kinetic energy) indicate the difference in the mean value of the \(\alpha\)-particle when entering and exiting the nucleus.

Figs. 5a and 5b show the number of individual strand breaks for direct and indirect damage. The relative proportion of direct and indirect damage varies with LET, with the proportion of indirect damage decreasing from 82.4% at the lowest LET to 70.1% at the highest. There is a slight decrease in the yield of direct strand breaks with LET, whilst the indirect damage decreases with LET more significantly than direct damage. When plotted as a function of kinetic energy, see Fig. 5b, it can be seen that the indirect damage yield is lowest around 0.5 MeV around the Bragg peak. The change in the amount of indirect damage is due to the track structure of the radicals created around the primary \(\alpha\)-particle track. As shown in Fig. 4d the radicals are produced closer together around 0.5 MeV than at higher or lower kinetic energies, thus the probability of radical recombination increases, resulting in fewer radical species to react with the DNA — reducing the overall yield of indirect damage. Between the 0.5 MeV and the maximum kinetic energy there is a reduction in indirect damage by a factor of approximately 2.3 and the mean distance between OH\(^+\) is reduced by a factor of approximately 1.9, see Fig. 4d.

Figs. 5c and 5d show the DSB yield as a function of LET and kinetic energy respectively. The total yield of DSBs shows a small initial increase for low LET after which it is approximately constant. In this work the total yield of DSBs was calculated to be 15.0 ± 0.2 Gy\(^{-1}\) Gbp\(^{-1}\) at 104 keV/\(\mu\)m. Experimental measurements show lower yields of DSBs, of the order of 7–9 Gy\(^{-1}\) Gbp\(^{-1}\) in a similar LET range [38,39].

The complexity of DSBs increases significantly with LET as shown by the increase in complex DSBs and corresponding decrease in simple DSBs. Complex DSBs are considered to be much more difficult for the cell to repair. The increase in complex DSBs, as seen in Fig. 5c and 5d is expected at higher LET where more energy is deposited in a small distance leading to more damages closer together.

As the number of strand breaks in a DSB increases, the damage becomes more complex and more difficult for a cell to repair. The number of strand breaks in a DSB and hence the complexity of the damage, also varies as a function of LET. Fig. 6 shows the size distribution of DSBs categorised into damage type, a subset of the LET values have been plotted for clarity. Considering all DSB types, it can be seen that the total number of DSBs and the complexity of the DSBs increase with LET. For direct, indirect and hybrid DSBs the distribution of DSB size is similar for all LET values. Mixed DSBs, however, show a marked increase in both the number of DSB and the complexity with LET. This suggests that the combined effects of the direct and indirect mechanisms cause the most significant damage for high LET \(\alpha\)-particles.

The proportion of DSBs due to each source of damage also varies with LET as shown in Fig. 5e and 5f, with mixed DSBs consisting of both individual breaks from both indirect and direct mechanisms becoming the dominant damage type for high LET. DSBs due to only the direct effect are approximately constant with LET, whereas there is a significant decrease in indirect DSBs.

The DSB yield for \(^{60}\text{Co}\) was calculated to be 6.9 ± 0.5 Gy\(^{-1}\) Gbp\(^{-1}\) and the complex DSB yield 1.2 ± 0.2 Gy\(^{-1}\) Gbp\(^{-1}\). Figs. 5g and 5h show the RBE calculated with two different endpoints, DSB induction (RBE\(_{\text{DSB}}\)) and complex DSB induction (RBE\(_{\text{DSB,complex}}\)) relative to \(^{60}\text{Co}\). There is an increase in RBE\(_{\text{DSB}}\) and RBE\(_{\text{DSB,complex}}\) with LET, showing that the damage done by an \(\alpha\)-particle changes along the path length and is greatest around the Bragg peak. RBE\(_{\text{DSB}}\) increases more significantly with LET. As complex DSB are considered to be more difficult for the cell to repair and therefore more likely to lead to cell death, this increase in RBE\(_{\text{DSB}}\) is important for understanding the DNA damage due to DaRT.

3.2. DNA base pair density

DNA base pair density varies between cell lines and locally throughout the cell cycle. The spacing of the chromatin fibre segments was varied to study the impact of base pair density on the DNA damage. In these simulations 60 chromatin fibre segments, containing approximately 1.3 million base pairs, were placed in cuboid target volumes, the width and chromatin fibre spacing of which was varied to change the base pair density in the range 0.007–0.057 bp/nm\(^2\) to be representative of the base pair density range of human cell lines. The nucleus volume size, and therefore also the path length through the geometry varies between geometries. For larger geometries the \(\alpha\)-particle travels a greater distance in the nucleus leading to a greater total energy deposition and hence greater DNA damage. Therefore, to compare the DNA damage due to different densities, the yields are normalised to the total path length of the primary \(\alpha\)-particle in the nucleus. The largest DNA geometry is larger than for the simulation results in Section 3.1, therefore the same initial \(\alpha\)-particle kinetic energies could not be used whilst maintaining a low variation in LET across the volume. For these results initial \(\alpha\)-particle kinetic energies in the range 3–8 MeV were simulated.

For all incident LET values there is an approximately linear increase in total, indirect and direct individual strand breaks, simple, complex and total DSBs with increasing base pair density in the expected range of human cells. This is shown in Fig. 7a–d for the minimum and maximum LET values simulated. This trend is in agreement with previous studies of base pair density for proton irradiation [40]. This shows that base pair density is an important simulation parameter for the accurate quantification of DNA damage. In addition, the rate of increase in strand breaks with base pair density is greater for higher LET \(\alpha\)-particles, as shown in Fig. 7e, with an increase of over 50% between 62.7 and 127.4 keV/\(\mu\)m. Therefore correctly modelling the density is particularly important at the end of the \(\alpha\)-particle track where the most significant and complex damage occurs.

Whilst there is an increase in the number of DSB, the distribution of DSB size and hence complexity is approximately constant for all damage sources as shown in Fig. 8 for 127.4 keV/\(\mu\)m \(\alpha\)-particles. This suggests that in this density range the proximity of neighbouring chromatin fibre segments does not affect the complexity or source of strand damage, which is expected as complex strand breaks are located on the same chromatin segment therefore the spacing should not influence the complexity.

4. Discussion

This study aims to better understand the DNA damage due to \(\alpha\)-particles in the \(^{224}\text{Ra}\) decay chain of DaRT treatments. It has been shown that the DNA damage changes along the path of the \(\alpha\)-particle which is important for understanding the DNA damage in DaRT where the spatial and temporal distribution of \(\alpha\)-particles is complex.

These simulations show that the overall yield of indirect damage is reduced and the proportion of DSB caused by the indirect effect is reduced for higher LET. The proportion of indirect damage is particularly important when modelling hypoxic tumours where reduced oxygen levels reduce the effectiveness of the indirect effect. Hypoxia is a significant cause of tumour resistance to radiotherapy and therefore the effect of LET on the proportion of damages is an important factor for treatment planning. In treatments such as DaRT where the LET is higher, DNA damage is less dependent on the indirect effect and therefore treatment is less sensitive to hypoxia. Thus, the relative decrease in importance of the indirect effect for higher LET radiation is an additional benefit of \(\alpha\)-particle therapies such as DaRT. The complexity of mixed DSB has been shown to increase with LET. These DSB are not dependent on both mechanisms and so are less sensitive to hypoxia.

Whilst there are previous studies simulating the DNA damage caused by \(\alpha\)-particles, there is significant variation in the simulation...
Fig. 6. Double strand break (DSB) yield per Gy per Gbp as a function of DSB size, classified by source type for a range of LET values. (A) Total DSB, (B) direct DSB, (C) indirect DSB, (D) mixed DSB and (E) hybrid DSB. Scales are the same for all plots to facilitate direct comparison, lines are plotted to guide the eye. Vertical error bars are the standard error on the mean, for repetitions of the same simulation with different seeds.

Fig. 7. Yield of individual strand breaks (A, C) and double strand breaks (DSB) (B, D) per unit path length as a function of base pair density. Gradients of the linear fit for individual strand break yields in as a function of LET (E). Scales are the same for individual strand breaks and DSB respectively to facilitate direct comparison, lines are plotted to guide the eye. Vertical error bars are the standard error on the mean, for repetitions of the same simulation with different seeds.
parameters. The DNA model geometry has a significant impact on the damage calculated, one example of which is the effect of base pair density as shown in Section 3.2. Therefore results are specific to the geometry used here. In addition, damage models differ significantly for both direct and indirect damage. Therefore, it is difficult to compare the simulated DNA damage with other studies which use very different geometries and simulation parameters. A foreseeable next step is to perform a parameter sweep for a given geometry.

All volumes in the simulations are assumed to be liquid water, including the DNA molecules, because of the availability of cross section models in Geant4-DNA. Only electronic interactions of the primary $\alpha$-particle and secondary electrons are considered, hadronic interactions are not included in the simulation. It is expected that the effect of hadronic interactions on the DNA damage from the $\alpha$-particles will be small.

The initial DNA damage has been simulated for mono-energetic $\alpha$-particles. In DaRT the kinetic energy of $\alpha$-particles incident on a cell will depend on the position relative to the DaRT seed. The diffusion of the daughter products of $^{224}$Ra increases the range of treatment to several millimetres [2], therefore diffusion needs to be modelled to simulate the distribution of $\alpha$-particles incident on a cell surrounding a DaRT source. In addition to the $\alpha$-particles simulated in this work, DNA damage will occur due to $\beta$-particles in the decay chain and the recoil of the heavy ions. The impact of the dose distribution due to diffusion and all particles in the DaRT decay chain on the initial DNA damage has not been simulated in this work but will be included in a future development.

5. Conclusions

In this study the initial DNA damage has been calculated using Geant4-DNA due to $\alpha$-particles in the DaRT decay chain. The LET of an $\alpha$-particle changes significantly over its path. Therefore, a small geometry has been chosen to minimise the variation in LET across the volume to study the impact of LET on DNA damage.

Results show that the DNA damage changes significantly with LET and therefore along the path of the $\alpha$-particle. This is important for a good understanding of the DNA damage in DaRT where four different $\alpha$-particles are emitted with different initial kinetic energies. In particular, it has been shown that the proportion of damage due to the indirect effect is reduced at higher LET. As expected, RBE has been shown to increase with LET and is greatest around the Bragg peak. The quantity of DNA damage is significantly affected by the base pair density in the range expected in human cells and is therefore an important parameter in the simulation of DNA damage. The impact of base pair density is greatest for higher LET $\alpha$-particles which cause the greatest and most complex damage.

Initial results are promising towards characterising the DNA damage due to DaRT and assessing the radiobiological effectiveness of this treatment.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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