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Effect of a static magnetic field on nanodosimetric quantities in a DNA volume

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EFFECT OF A STATIC MAGNETIC FIELD ON NANODOSIMETRIC QUANTITIES IN A DNA VOLUME

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Short title: Effect of a magnetic field on track structure
Index Terms: Radiotherapy, nanodosimetry, magnetic field, secondary electrons, Geant4, Monte Carlo, cluster size
Abstract

Purpose: With the advent of MRI (magnetic resonance imaging) guided radiation therapy it is becoming increasingly important to consider the potential influence of a magnetic field on ionising radiation. This paper aims to study the effect of a magnetic field on the track structure of radiation to determine if the biological effectiveness may be altered.

Methods: Using the Geant4-DNA (GEometry ANd Tracking 4) Monte Carlo simulation toolkit, nanodosimetric track structure parameters were calculated for electrons, protons and alpha particles moving in transverse magnetic fields up to 10 Tesla. Applying the model proposed by Garty et al. the track structure parameters were used to derive the probability of producing a double strand break (DSB).

Results: For simulated primary particles of electrons (200 eV – 10 keV), protons (300 keV – 30 MeV) and alpha particles (1 MeV – 9 MeV) the application of a magnetic field was shown to have no significant effect (within statistical uncertainty limits) on the parameters characterising radiation track structure or the probability of producing a DSB.

Conclusions: The null result found here implies that if the presence of a magnetic field were to induce a change in the biological effectiveness of radiation, the effect would likely not be due to a change in the track structure of the radiation.
Introduction

With the advent of magnetic resonance image (MRI) guided radiation therapy and the interest in MRI guided proton therapy (Lagendijk et al. 2008; Raaymakers et al. 2008), it is becoming increasingly important to consider the potential influence of a magnetic field on ionising radiation. While the change in macroscopic dose distribution by a magnetic field has been studied (Raaymakers et al. 2008, Nettelbeck et al. 2008), there is also a need to investigate any effects on the DNA scale that may alter the biological effectiveness of the radiation.

When a charged particle moves through a magnetic field, it is affected by the Lorentz force. This can lead to an altered path of the particle where the force from the magnetic field acting on the particle depends on the particle’s charge and kinetic energy, the magnetic field strength and its direction relative to the particle’s direction of travel. Protons or light ions moving through matter produce delta electrons with a spectrum of energies; this will lead to the magnetic field affecting some particles with a greater force than others. This will result in changes to the path of charged particles which may modify the track structure of the radiation. As the biological effectiveness of radiation depends largely on its track structure on a DNA scale (Goodhead 2006), nanodosimetric methods are ideally suited to evaluate any changes that may lead to altered biological effectiveness (Bug et al. 2010).
In this paper Monte Carlo (MC) methods were used to investigate the possibility of an applied magnetic field altering the biological effectiveness of radiation. This was done by simulating electron, proton and alpha particle tracks and calculating nanodosimetric parameters related to the particle track structure (Grosswendt et al. 2007). Furthermore, the model proposed by Garty et al (Garty et al. 2010) was used to estimate the probability of producing a double strand break. Changes to the calculated values of these parameters induced by the application of a magnetic field may indicate a change to the biological effectiveness of the radiation.

Note it is assumed here that the applied magnetic field has no significant effect on the cross sections of physical interactions. A detailed investigation of this is beyond the scope of this paper. As, for instance, the magnitude of the Zeeman splitting of molecular levels can be estimated from the value of the Bohr magneton to be of order $10^{-4}$ eV per Tesla, magnetic field effects should indeed be negligible for the magnetic field strengths (of up to 10 T) considered in this study.

**Methods**

In this study the Geant4 Very Low Energy Extension (GEometry ANd Tracking 4) (Chauvie et al. 2007; Incerti et al. 2010a) for water (otherwise known as Geant4-DNA) was used for all MC simulations as it has the capability of tracking charged particles down to very low energies (a few eV) in the presence of a magnetic field. Geant4 version
9.3 with the Electromagnetic Low Energy package 6.9 (EMLOW6.9) was used for all simulations. Geant4-DNA tracks particles down to a minimum energy, below which the particles are 'killed' and deposit their energy locally. For electrons this low energy tracking limit is 4 eV, for protons 100 eV and for alpha particles 1 keV.

As the DNA molecule is the most radiation sensitive target in a cell (Goodhead 2006) that may have different conformations, two different sensitive target volumes were considered as can be seen in figure 1. The smaller target volume represents a DNA segment, modelled with a liquid water filled cylinder 3.4 nm in height and 2.3 nm in diameter, which is approximately the size of 10 base pairs of DNA. This length of DNA represents the length within which two strand breaks (SB) on opposite sides of the DNA backbone can combine to create a double strand break (DSB), which is typically taken as the type of damage that may be likely to result in significant biological effects, possibly including genomic instability, carcinogenesis or even cell death (Goodhead 2006; Khanna and Jackson 2001).
The second scoring volume was a larger liquid water filled cylinder of 10 nm height and 6 nm diameter intended to represent a nucleosome, i.e. a longer segment of the DNA molecule wrapped around a histone which has also been suggested to be a relevant target volume (Nikjoo 2003). This second target may also be interpreted as a segment of DNA surrounded by a volume of water that corresponds to the range limit from which free radicals produced outside the DNA volume can migrate into it via diffusion, potentially causing indirect damage (Bug et al. 2010). In this way, results obtained for this second sensitive volume could, in principle, be used for a crude approximation of the indirect damage done to the DNA molecule. Note that free radical production and diffusion would have to be modelled for this purpose.
The two sensitive volumes were placed in the centre of the ‘world volume’ which was a water filled cube of edge length 150 nm. The dimensions were chosen such that secondary particles (deriving from the interactions of delta electrons generated by the incident primary particles) produced within this volume would have the sensitive volumes within their $R_{95}$ range (range for deposition of 95 % of energy). If such secondary particles were to be produced at distances greater than this from the centre of the world volume they would not be able to contribute significantly to ionisations in the sensitive volumes.

A monoenergetic pencil beam of primary particles was applied at the surface of either target volume with an initial direction pointing to the target volume centre. This was done so that the initial conditions would be identical in all cases. As this work aims for a relative comparison of parameters with and without an applied magnetic field the choice of impact parameter should have little effect on the results. As such, the described set up was used to keep consistent with previous work (Bug et al. 2010).

The magnetic field can be seen in figure 1 to be applied normal to the initial direction of the beam. When applying a magnetic field in Geant4 there are several parameters that can be set in order to ensure an adequate level of accuracy in the modelled trajectory of charged particles. Probably the most important of these is the maximum step length, which is the maximum distance the particle will move in a straight line before its direction of travel is recalculated; this will take the action of the Lorentz force into account. In order for the simulated steps to mimic the curvature of a charged particle’s
path, the step length should be small compared with the theoretical radius of curvature the particle trajectory would have in the absence of interactions. This radius of curvature, which would apply to the particle travelling in a vacuum, depends on the magnetic field strength and on the charge and velocity of the particle. To estimate an upper bound for the maximum step length, the smallest radius of curvature in a vacuum of the primary particles used was therefore determined for the investigated radiation fields and energy ranges. This was found to be about 2.4 µm for electrons with an initial kinetic energy of 50 eV in a 10 T magnetic field.

The value for the maximum step length was determined by running the simulation as described above but with no physical models of interaction used, other than the step limiter. Thus, the particle was effectively travelling through a vacuum and not interacting with the environment at all. In this way the effect of the magnetic field on the path of the particle could be clearly seen. The simulated particle trajectory was a regular polygon from which an estimate of the radius of curvature was obtained and compared to the theoretical value. This estimated curvature from the simulations matched the theoretical values within 0.005 % for all particles and energies when a step length of 0.01 nm was used.

The ‘chord distance’ (distance from theoretical circle of curvature to particles approximate linear trajectory over each step) can also be set, with smaller values producing more accurate paths. This parameter was chosen to be a factor of 10 smaller than the step length. This was done so that the deviation of the simulated track from the
circle of curvature would be relatively small compared to the size of each individual step. As there are only two sensitive volumes used here and their geometries are fairly simple, this value was sufficient.

Primary particle energies between 200 eV and 10 keV for electrons, between 300 keV and 30 MeV for protons and between 1 MeV and 9 MeV for alpha particles were used as these represent a wide range of unrestricted LET (linear energy transfer) values so that both densely and sparsely ionising radiation may be tested. The LET values of primary particles used here vary between a few keV/µm and about 220 keV/µm, where this data was obtained from the STAR (stopping power and range) databases of (Berger et al. 2005). Magnetic field strengths up to 10 T were investigated.

For each combination of magnetic field strength, particle type and initial energy, primary particle tracks were simulated (i.e. $10^5$ particle tracks for alphas and protons and $10^6$ for electrons). The ionisations occurring were scored for the two target volumes to obtain the ionisation cluster size distribution, i.e. the probability distribution of the number of ionisations produced in a sensitive volume (Grosswendt et al. 2007).

From the ionisation cluster size distributions two nanodosimetric parameters related to the particle track structure were calculated: $M_1$ (mean number of ionisations in a sensitive volume per incident particle) and $F_2$ (cumulative probability for an incident particle to produce at least two ionisations in a sensitive volume). This parameter $F_2$ has been suggested to be related to the probability for producing a complex lesion within a short
segment of DNA (Grosswendt 2005). Furthermore, using the model proposed by Garty et al (Garty et al. 2010), the probability $P_{DSB}$ of producing a double strand break was calculated. Briefly, this is done by assuming that each ionisation has a fixed probability ($p_{SB} = 11.7 \%$) of producing a strand break and then using a straightforward combinatorial approach to determine the frequency distribution of DNA strand breaks from the probability distribution of the number of ionisations within the DNA segment volume, as calculated using MC methods. The probability for a DSB is then obtained by assuming that the individual lesions are randomly distributed over the two strands of the DNA and that a DSB will result whenever both strands have been damaged. It should be noted that the parameter $P_{DSB}$ is dimensionless as it represents the probability for a single primary particle to generate a DSB.

An inherent property of the model is that the conditional probability for an ionisation cluster to lead to a DSB increases with increasing ionisation cluster size. Thus, $P_{DSB}$ will be best suited to reveal a potential magnetic field effect on the high cluster-size tail of the ionisation cluster size distributions. The cumulative probability of 2 or more ionisations, $F_2$, on the other hand, will show magnetic field effects on the low cluster-size tail as it depends only on the first few points of the distribution (which is normalised to unity). Both parameters link the physical properties of the radiation field to its biological effects and are therefore best suited to study any magnetic field dependence of the latter.

The statistical significance of the variation with magnetic field of the different nanodosimetric parameters, such as $M_1$ or the probability of producing a DSB, was
assessed using a Chi square test and finding the $p$-value for the observed value of $\chi^2$ to occur (Ross 2005). A change induced by the applied magnetic field in a calculated parameter was only deemed significant if the associated $p$-value was less than 0.05. The test hypothesis was that there was no influence of the magnetic field. If this hypothesis is true, the dispersion of the values obtained for all magnetic field strengths would be just the effect of random sampling. Therefore, the Chi square value was calculated using the following formula:

$$
\chi^2 = \sum_i \left( \frac{x_i - x_0}{u_i} \right)^2
$$

(1)

Where $x_0$ is the relevant value obtained for no applied magnetic field, $x_i$ is the value for the $i$-th value of magnetic field and $u_i$ is the statistical uncertainty associated with $x_i$. The statistical uncertainty of calculated parameters was estimated using the same methods as described by Bug et al. (Bug et al. 2010).
Results

Protons and alpha particles:

The investigated nanodosimetric parameters derived from the ionisation cluster size distributions of both primary proton and alpha particle beams showed, within statistical uncertainty, no significant change for different magnetic field strengths within the two sensitive volumes. Figure 2 shows the ratios of the calculated values of $M_1$ for different proton energies and magnetic field strengths to the respective value obtained without magnetic field for the two sensitive volumes. Different symbols correspond to different values of the magnetic field. This way of presentation of the results offers the advantage that data points corresponding to the same energy have similar uncertainty. Hence, for clarity of the figure, error bars can be omitted at the symbols and rather be indicated by error band about unity as shown in the figure. The dash-dotted lines are smooth interpolation curves to a deviation from unity by the respective statistical uncertainty at the energy values of the data points. These uncertainties were obtained by the procedure described in (Bug et al. 2010).

It should be noted that a lack of observable change in the $M_1$ ratios does not necessarily imply that there is no change to the track structure at all. An exhaustive analysis of the physical aspects of the radiation track structure would require considering the higher moments of the ionisation cluster size distributions. This is not the aim of this paper.
whose scope is the influence of a magnetic field on the biological radiation effects, which will be shown later using the results obtained for the quantity $P_{DSB}$.

A systematic effect such as a monotonic magnetic field dependence would show in figure 2 by the same vertical arrangement of the symbols which can be seen to not be the case. Furthermore, it is obvious that most of the individual data points are found within the uncertainty band. In few exceptional cases, such as for 10 MeV and 10 T in the DNA segment or for 5 T at 0.5 MeV in the nucleosome, departures from unity are encountered that are up to almost a factor two outside the error band.
For all magnetic field strengths and particle energies tested, however, no statistically significant change was caused by the magnetic field. This is demonstrated by table 1 that lists the $\chi^2$ and associated $p$ values. The smallest $p$-value was 0.14 and applies to the variation of $M_1$ for 0.7 MeV protons in the nucleosome. Hence all $p$-values exceed the 0.05 threshold and have to be counted as statistically insignificant.
Table 1. $M_1$ and $P_{DSB}$ data for proton and alpha particle’s

It should be noted that the $\chi^2$ tests performed on the other quantities determined from the simulations, such as the nanodosimetric track structure parameter $F_2$, also showed no statistically significant effect for an applied magnetic field.

A similar outcome was obtained for the influence of a magnetic field on the probability of producing a DSB in the DNA segment for all energies of either proton or alpha particles. This is demonstrated in figure 3 where the ratio of $P_{DSB}$ for a given magnetic field strength compared to the case of no magnetic field is shown. Again, any apparent change induced by the magnetic field is well within statistical uncertainty limits, even though the parameter $P_{DSB}$ typically showed greater variation than other calculated parameters such as $M_1$ or $F_2$. The relative changes of $P_{DSB}$ with magnetic field strength were less than 1 % for alpha particles at all investigated energies. For protons, the largest relative difference is about 5 %, at 1 T and 30 MeV. For all combinations of particle type and kinetic energy, the variation with magnetic field was, however, not statistically significant under the chosen criteria. As demonstrated by the last columns of table 1, the corresponding $p$-values are never lower than 0.77.
Electrons:

The effect of a magnetic field on the nanodosimetric parameters of track structure of a monoenergetic electron beam has previously been studied (Bug et al. 2010). As such here only the additional information on calculated probabilities of producing a DSB, $P_{DSB}$. 

![Figure 3](Image)
Figure 4 shows the ratio of $P_{\text{DSB}}$ values with an applied magnetic field compared to the case of no magnetic field as a function of the initial electron energy. It is evident that within statistical uncertainties there is no change induced by the applied magnetic field, regardless of field strength. This is in agreement with (Bug et al. 2010) where no significant change to $M_1$ or $F_2$ was found. Here, for $P_{\text{DSB}}$ values, the largest relative difference seen was about 5%. Occurring for the case of 10 T magnetic field strength at 10 keV electron energy, this deviation is equal in size to the statistical uncertainty. The largest $\chi^2$-value calculated according to equation 1 was found for energy 500 eV and corresponds to a $p$-value of about 0.86 which is not statistically significant under the chosen criteria.
Discussion

As can be seen from figures 2 through 4, the uncertainties used in the chi square tests for statistical significance of the observed variations in the calculated nanodosimetric parameters with magnetic field show a large variation with particle energy. This is not due to a change in the number of primary particle histories simulated, as the same value of primary particles was used for each data point shown in the figures. The reason is rather the variation of the investigated parameters with primary particle energy. For protons in the investigated energy range, the total value of $M_1$ strongly decreases with energy from about 3.2 and 11 at 300 keV to about 0.08 and 0.25 at 30 MeV for the DNA segment and the nucleosome, respectively. Similarly, the absolute value of $P_{DSB}$ for protons varied in the considered energy range from about 3.2 % at 300 keV to about 0.02 % at 30 MeV. And $P_{DSB}$ for electrons decreases from about 1.4 % at 200 eV to about 0.02 % at 10 keV. For the data of alpha particles shown in figure 2b, the variation of uncertainties is much smaller, but consistent with the uncertainties for protons of the same velocity or reduced energy: between 0.25 MeV and 2.5 MeV kinetic energy for protons the uncertainty also has only minor variations and is slightly below 1 %.

In principle, the uncertainties could be reduced by increasing the number of primary particles in the Monte Carlo simulations. If the observed variation with magnetic field strength were only due to the statistics of the Monte Carlo method, the accuracy achieved in the present work should be sufficient. A systematic effect from the application of a magnetic field should be expected to have a monotonic, in first order, linear dependence
on field strength. This should have shown as a systematic pattern in the arrangement of the data points in figures 2 through 4 corresponding to different magnetic field for the same particle energy, which was not observed.

In conclusion, the results indicate that the application of a magnetic field normal to an incident beam of directly ionising radiation will have no significant impact on the track structure of the radiation at a DNA level, as determined by the nanodosimetric parameters derived from the ionisation cluster size distributions. This was tested for a wide range of particle LET values. In addition, the probability for a single primary particle to produce a DSB in a short segment of DNA was not affected by the application of a magnetic field. This implies that if the presence of a magnetic field were to induce a change in the biological effectiveness of radiation, the effect would likely not be due to a change in the track structure of the radiation. This work is being complemented with an experimental study to continue the investigation of the effect, if any, of a magnetic field on the biological effectiveness of radiation.

**Declaration of interest**

The authors report no declarations of interest.
References


### Table 1: \( \chi^2 \) values, as calculated according to equation 1, and associated \( p \) values for the variation of some nanodosimetric parameters with magnetic field strength for protons and alpha particles of the given energies. For each particle type, 5 values of magnetic field different from zero were investigated such that the degrees of freedom were 5.
Figures

Figure 1. Geometry used in MC simulations with primary particles of electrons as example beam. The pencil beam was directed along the x-axis, starting at the surface of the DNA volume, with the magnetic field in the direction of the y-axis as indicated. The magnetic field was uniform across all volumes, including the world volume.

Figure 2. Values of the mean ionisation cluster size $M_1$ produced by protons in a DNA segment (a) and a nucleosome (b) for different magnetic field strength $B$, normalised to the respective value at $B = 0$ T. The dash-dotted lines indicate the statistical uncertainties due to the Monte Carlo calculation that were calculated as in (Bug et al. 2010).

Figure 3. Probability of producing a DSB as a function of primary particle kinetic energy for different magnetic field strength normalised to $P_{DSB}$ at 0 T, for primary particles of protons (a) and alpha particles (b). The dash-dotted lines indicate the statistical uncertainties due to the Monte Carlo calculation.

Figure 4. Probability of a primary electron producing a DSB in a short DNA segment as a function of initial kinetic energy for different magnetic field strengths normalised to $P_{DSB}$.
at 0 T. The dash-dotted lines indicate the statistical uncertainties due to the Monte Carlo calculation which were calculated as in (Bug et al. 2010).