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Nanodosimetry: Bridging the gap to radiation biophysics

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ABSTRACT

Nanodosimetry strives to link phenomenological dosimetric concepts like radiation quality and relative biological effectiveness to measurable physical quantities related to the track structure of ionising radiation. The ultimate goal of nanodosimetry is therefore to determine novel dosimetric quantities that include the initial biological or biophysical action of ionising radiation. As a step towards this, experimental and numerical techniques have been developed to characterise particle track structure based on the formation of ionisation clusters within a target volume comparable in mass per unit area to a DNA segment. Several attempts have been made to connect the nanodosimetric parameters derived from these ionisation cluster size distributions to biological radiation effects.

This work gives an overview of the basic aspects of nanodosimetry, including a discussion of two nanodosimetry-based approaches used to derive estimators of biological effectiveness of ionising radiation. It also includes preliminary results from an ongoing Monte Carlo study into the limitations of using the physical properties of liquid water to approximate those of DNA in nanodosimetric modelling. The findings suggest an overestimation of radiobiological effectiveness may occur when the cross section data for liquid water are used as a substitute for those of DNA.

1. Introduction

It is well-known that the track structure of ionising radiation plays a key role in radiation-induced damage to biological cells, where the nucleus of a cell is particularly susceptible as it contains the genetic information in the form of DNA. The sub-cellular distribution of interactions characterising track structure is therefore an important factor in the biological effectiveness of ionising radiation.

Since established conventional dosimetric quantities like absorbed dose (ratio of the energy absorbed in a piece of matter to its mass) rely on macroscopic averages, an elaborate system of auxiliary quantities such as radiation quality and biological effectiveness is needed to account for the influence of particle track structure. When applied to microscopic volumes, such as those considered for micro- or nanodosimetry, these macroscopic dosimetric quantities become meaningless for lack of their implicit assumption that energy deposition is continuous.

The field of microdosimetry was conceived about half a century ago in response to the challenge of relating the aforementioned auxiliary concepts to measurable properties of particle track structure on the microscopic scale. This led to the founding of concepts like linear energy transfer (LET), which characterises the radiation quality of an ionising particle by the energy deposited per unit length of its track.

In the development of microdosimetry, evidence was accumulating that the appropriate target size for linking track structure properties with biological effectiveness of radiation should be in the nanometre regime rather than of micrometer dimensions typical of a cell nucleus. For instance, Goodhead (1994) found a pronounced maximum in the radiobiological effectiveness to occur (for most biological endpoints) at an LET of 100 keV/μm, which corresponds to a mean free path for ionisations (in water) of about 2 nm. Several other investigations corroborate the idea that the initiation of radiation-induced damage to biological cells is dominated by inelastic interactions occurring at the site of the DNA or within its vicinity (Goodhead and Thacker, 1977; Cox et al., 1977; Goodhead, 1977; Brenner and Ward, 1992; Nikjoo et al., 1999). It is now well accepted that the DNA molecule is the critical target for radiation-induced damage to biological cells (Goodhead, 2006).

The challenge to develop an extension of microdosimetry to equivalent target sizes in the nanometre regime has faced a series of virtually insurmountable obstacles (Amols et al., 1990). These arise from the fact that the target sizes are too small to reach a secondary particle equilibrium and to apply the concept of the *W*-value, which is the mean energy (independent of target size)

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required to produce an ion pair (Grosswendt, 2002). Consequently, the conversion of direct measurements of ionisation to quantities of dosimetric interest, such as energy deposition, is almost impossible for sub-micrometric target sizes of condensed matter (Amols et al., 1990). A potential solution to this dilemma arose from the finding of Brenner and Ward (1992), who showed clusters of multiple ionisations produced by ionising radiation (of different quality) within sites 2 nm–3 nm in size to correlate well with the yield of double strand breaks (DSBs). This led to the development of nanodosimetry.

This paper gives a brief overview of nanodosimetry, focusing on the attempts to correlate nanodosimetry-based characteristics of particle track structure with the biological effectiveness of ionising radiation. It also discusses the results from a recent investigation into the limitations of using the water-for-DNA approximation in nanodosimetric Monte Carlo modelling.

2. The concept of nanodosimetry

Motivated by the findings of Brenner and Ward (1992), nanodosimetry aims to establish a concept of radiation quality building on measurable properties of the particle track structure's ionisation component. The key rationale is that the stochastics of radiation interactions are governed by the magnitude of the cross sections for different interaction processes, such that the ionisation component is considered to be representative of the entire track. Hence, characterisation of particle track structure in nanodosimetry is based on the formation of ionisation clusters within a specified volume of matter, which is generally chosen to be comparable in mass per unit area to a short segment of DNA. Such a volume is generally modelled as cylindrical in shape to mimic the basic geometry of a DNA segment.

When a particle track passes by or penetrates a target volume, such as that described above, the number of ionisations produced within the volume is referred to as the ionisation cluster size ν. The radiation quality Q associated with this particle is characterised by the statistical distribution of probabilities $P(\nu|Q)$ that ν ionisations occur within the target volume (Grosswendt, 2004). This probability distribution depends on the radiation quality of the particle as well as the geometrical characteristics of the target volume (i.e. cylinder's diameter) and its relative orientation with respect to the particle track. Usually these parameters would be included in the notation for the probability distribution in question (Grosswendt, 2004, 2005, 2006), however as this paper only considers ionisation cluster size distributions of particles traversing the centre of the cylinder in a plane at half its height, the notation for the distribution is simply $P(\nu|Q)$.

The influence of radiation quality on the ionisation cluster size distribution is illustrated in Fig. 1 for 5 MeV protons ($^1H^+$), 20 MeV alpha particles ($^4He^{2+}$), 60 MeV carbon ions ($^{12}C^{6+}$) and 100 MeV neon ($^{20}Ne^{10+}$) ions. These distributions were obtained from Monte Carlo simulations of the track structure in propane of density 1.0 g/cm^3 for the particles traversing the centre of a cylindrical volume (2 nm in height and diameter). The kinetic energies of these particles were chosen in such a way to give the same velocity, and hence stopping power proportional to Z^2 according to Bethe's theory (Bethe, 1930), where Z is the charge of the ion.

While the particles may have the same stopping power, their ionisation cluster size distributions are noticeably different as evident in Fig. 1. For loosely ionising 5 MeV protons, the ionisation cluster size distribution is characterised by a probability of almost 80% for a cluster size of zero, which drops to 18% for a cluster size of one and then rapidly decreases with further increase in cluster size. For 20 MeV alpha particles, the probability of obtaining a cluster size of zero is about 40%, while for

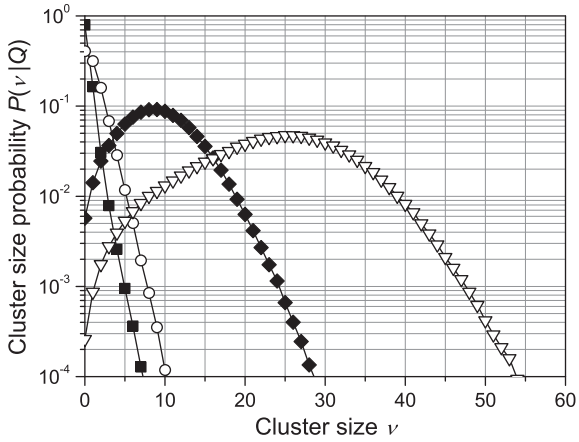

Fig. 1. Ionisation cluster size distributions obtained by Monte Carlo simulation for the radiation qualities: 5 MeV protons (squares), 20 MeV alpha particles (circles), 60 MeV carbon ions ($^{12}C^{6+}$, diamonds) and 100 MeV neon ions ($^{20}Ne^{10+}$, triangles). The distributions were derived from simulated track structures of particles passing through the centre of a propane cylindrical target (2 nm in height and diameter) of density 1.0 g/cm^3.

cluster sizes of one or two it is 32% and 18%, respectively. Beyond a cluster size of two, the probability decreases with increasing cluster size at a slower rate than that exhibited by the 5 MeV protons. The ionisation cluster size distributions for 60 MeV carbon ions and 100 MeV neon ions, on the other hand, are characterised by an initial increase in probability to a maximum cluster size of 9 and 26, respectively. In both cases, the probability for a cluster size of zero is well below 1%. Beyond the maximum, both distributions exhibit a steady decrease in probability with increasing cluster size, where probabilities greater than 1% are observed for cluster sizes up to 19 and 41 for the carbon and neon ions, respectively.

While the ionisation cluster size distributions shown in Fig. 1 were obtained from Monte Carlo simulations of particle track structure, they can also be determined experimentally using so-called nanodosimeters which measure ionisation clusters formed in macroscopic volumes of dilute gas. The underlying experimental concept (Chmelewski et al., 1973; Pszona, 1976) was realised in the construction of three different types of nanodosimeter: the track-nanodosimetric counter (De Nardo et al., 2002); the jet counter (Pszona et al., 2000); and the ion-counting nanodosimeter (Garty et al., 2002a,b). The track nanodosimeter detects electrons, while the latter two devices detect positive ions. All of these measuring instruments determine ionisation cluster size distributions equivalent to those expected for nanometric targets in condensed matter, such as a nucleosome or segment of DNA. The equivalence of these frequency distributions is based on a theoretical relation between the first statistical moment M_1 (i.e. mean) of the ionisation cluster size distribution and the physical properties of the target (Grosswendt, 2004).

For the case when the particle track traverses the centre of a target filled with a substance of molecular mass m_{mol}, the cluster size distribution is dominated by direct ionisations, and the mean cluster size is given by:

$$M_1(Q) = D\rho\frac{\sigma_{ion}(Q)}{m_{mol}} \quad (1)$$

where D and ρ are the diameter and mass density, respectively, of the target volume. The radiation quality Q is defined by the type and energy of the particle, such that $\sigma_{ion}(Q)$ is the ionisation cross section for a target molecule. According to this equation, the ionisation cluster size distributions of two different materials and/or

densities have the same mean if the following relation holds for the product of the target diameter and density $D\rho$:

$$(D\rho)_B = (D\rho)_A \left(\frac{\sigma_{\text{ion}}}{m_{\text{mol}}}\right)_B \Big/ \left(\frac{\sigma_{\text{ion}}}{m_{\text{mol}}}\right)_A \quad (2)$$

where A and B refer to the two different targets. It has been shown that two cluster size distributions of the same mean have also approximately the same second moment and are overall similar in shape (Grosswendt, 2004).

Equation (2) can be used to determine the required gas pressure in the nanodosimeter to produce cluster size distributions equivalent to those expected in a nanometric target of condensed matter. Another use of this equation is to define the pressure ratio for two different gases where measurements in macroscopic volumes are expected to yield the same mean ionisation cluster size. This prediction has been experimentally validated by Hilgers (2010), who measured ionisation cluster size distributions of protons and alpha particles in propane and nitrogen of different pressures.

3. Nanodosimetry and radiation biophysics

The origin of nanodosimetry was the urge to develop concepts of dosimetry that take into account the track structure and provide measurable physical quantities related to the initial biophysical action of the radiation on the most radiation sensitive unit in biological cells, which is the DNA. Since the advent of nanodosimetry, different approaches have been proposed that relate the nanodosimetric ionisation cluster size distributions to initial damage to the DNA molecule (Grosswendt, 2005; Garty et al., 2006, 2010). In this work, the term "biological effectiveness" is used synonymously for this initial damage, namely the formation of lesions resulting from ionisations occurring in the DNA or its vicinity. Strictly speaking, this effectiveness relates to biophysics rather than biology. It is not linked to a particular biological endpoint, but rather only to the physical or physio-chemical properties of the biomolecule DNA. We adopt this relaxed use of the term biological effectiveness to comply with the terminology used to date in nanodosimetry literature.

3.1. Grosswendt's track structure approach

The first approach developed by Grosswendt (2005), and therefore referred to as Grosswendt's approach, was motivated by the hope of finding a quantity derived from the statistical distribution of ionisation cluster sizes to correlate with biological effectiveness. If such a nanodosimetric quantity was found, then biological effectiveness could be directly derived from measurements of ionisation cluster size distributions. Furthermore, as this quantity would also be characteristic of track structure, it should itself constitute a link between biological effectiveness and a new concept of radiation quality based on track structure properties.

Grosswendt's rationale was the following: a single strand break (SSB), which is a lesion in one of the two strands of the DNA double helix, may be induced by a radiation interaction within a segment of DNA or chemical reactions of hydroxyl radicals. Having a life time corresponding to a diffusion length of several nanometres, these radicals are formed by water radiolysis and are responsible for the indirect damage of radiation to the DNA. In order to have either a direct or indirect damage in a segment of DNA, at least one "relevant" radiation interaction must occur in the DNA segment or surrounding water molecules. Although, *a priori*, it is unknown what exactly specifies such a relevant interaction, it may be presumed that the probability for such an interaction is proportional to the probability P_1 of a single ionisation occurring within this volume. Consequently, the probability to produce a single strand break in a short segment of DNA is expected to be proportional to the probability of obtaining an ionisation cluster size of one. In this paper, the postulate will be referred to as Grosswendt's first hypothesis.

In a similar way, Grosswendt (2005) argued that in order to produce a double strand break in a short segment of DNA, at least two relevant interactions must occur within a segment of the DNA molecule or its vicinity. As each relevant interaction is expected to occur with a probability proportional to that for an ionisation, the overall probability for at least two relevant interactions should also be proportional to the cumulative probability F_2 for having ionisation cluster sizes of two or more. This is Grosswendt's second hypothesis, where the cumulative probability F_k for inducing at least k ionisations is given by:

$$F_k(Q) = \sum_{\nu=k}^{\infty} P_{\text{ion}}(\nu|Q) \quad (3)$$

While the first of Grosswendt's hypotheses seems more evident, the second one is not straightforward given the fact that probability distributions of several interaction events generally require the convolution of single event probability distributions. Support for this second hypothesis has been obtained from a systematic comparison of the relative energy dependence for cumulative probabilities F_k with that of the theoretical biological effectiveness of Simmons and Watt (1999), where the best agreement was observed for $k = 2$ (Grosswendt, 2004).

Both hypotheses have been tested with several sets of radiobiological data available in the literature (Grosswendt, 2004, 2005, 2007). One of the few systematic experimental investigations was carried out by Taucher-Scholz and Kraft (1999), who studied the influence of radiation quality on the yield of DNA strand breaks in SV40 viral DNA. Their data for the cross section of DSB induction as a function of LET for different light ions are indicated by the solid symbols in Fig. 2. The open symbols represent data for the cumulative probability F_2 obtained from Monte Carlo simulations of ionisations cluster formation in a liquid water cylinder equivalent in size to a small segment of two convolutions of the DNA (2.3 nm in diameter and 3.4 nm in height). It should be noted that for all ions investigated, the measured biological cross sections and the F_2 values obtained from simulation exhibit the same LET dependence when scaled using one single factor. This agreement is somewhat

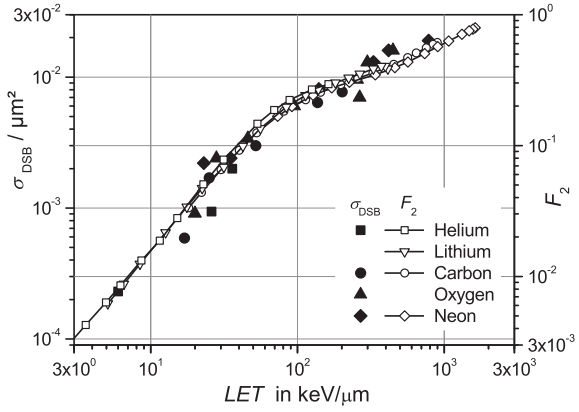

Fig. 2. Comparison of the dependence of cross section σ_{DSB} for double strand break formation in SV40 viral DNA (Taucher-Scholz and Kraft, 1999) on the LET (left-hand y-axis) and the nanodosimetric track structure parameter F_2 (right-hand y-axis) for helium, lithium, carbon, oxygen and neon ions. The F_2 values were derived from Monte Carlo simulations of the ionisation cluster formation in a cylindrical water target of dimensions equivalent to DNA segment of 10 base pairs.

astonishing given the rough approximation inherent to the Monte Carlo calculations, namely that interaction cross sections of liquid water are substituted for those of the DNA molecule.

In the case of SSBs, however, the LET dependence of the cross sections derived by Taucher-Scholz and Kraft (1999) and the probability for an ionisation cluster size of one did not agree equally as well as those for DSBs. The discrepancy may stem from the use of gel electrophoresis to measure the yield of SSBs, where recent investigations by Smiałek et al. (2009) have shown that this technique is unsuitable for accurate detection of single strand breaks.

3.2. The Combinatorial approach

A second independent approach to establish a link between nanodosimetric ionisation cluster size distributions and radiobiological effectiveness is that proposed by Schulte (Garty et al., 2006, 2010). While the starting point is also the formation of ionisation clusters in a target volume the size of a DNA segment, a simple model is used to convert ionisation cluster size distributions into probability distributions of DNA lesions. In brief, the model is characterized by two basic assumptions. The first assumption is similar to Grosswendt's, namely that any ionisation occurring in the target volume has the same probability of leading to a DNA strand break. This probability p_{SB} is assumed to be independent of both where the ionisation occurred and the number of ionisations induced within the target. It is a free parameter in the model, which was determined by data fitting of the predicted yield of double strand breaks obtained from radiobiological assays on plasmid DNA (Leloup et al., 2005; Garty et al., 2006, 2010). The model's prediction for DSB induction is based on its second assumption that the induced lesions are randomly distributed over the two DNA strands and lead to a DSB whenever both strands within the considered segment are damaged.

Both assumptions of the model imply that straightforward application of combinatorics can be used to determine the conditional probabilities for converting an ionisation cluster of size ν to a cluster of lesions of size n_{SB} or to a DSB (Garty et al., 2006, 2010). In the first case, the conditional probabilities $P(n_{SB}|\nu; p_{SB})$ are obtained from the binomial distribution with a success probability equal to p_{SB}. In the second case, more intricate mathematics is needed to derive an analytical expression for the conditional probability $P(\mathrm{DSB}|\nu; p_{SB})$ that ν ionisations in the sensitive volume result in a DSB (Garty et al., 2006).

Fig. 3 shows the simulated results for 300 keV protons traversing a cylindrical water target of the same size as two convolutions of DNA. At this kinetic energy, which is at the high-energy shoulder of the Bragg peak for the energy dependent stopping power, the most likely ionisation cluster size is two. Significant probabilities are also observed for ionisation cluster sizes up to eight. Using the value $p_{SB} = 0.117$ obtained by Garty et al. (2010), the corresponding distribution of strand break cluster size peaks at zero, and probabilities in excess of 1% are seen for cluster sizes up to four. When converting distributions of ionisation clusters to those of lesions, the redistribution of probabilities toward smaller cluster sizes is an inherent consequence of the first model assumption.

The probability for a double strand break in a DNA segment sized target volume as obtained by the Combinatorial model can be considered a nanodosimetric estimate for biological effectiveness. The potential of this model to produce such an estimate has been exploited to define nanodosimetry-based quality factors for radiation protection, particularly in the space environment where ion radiation is a concern (Schulte et al., 2008). The proposition was to define these quality factors as the ratio of the DSB formation probabilities (according to the Combinatorial model) for ion

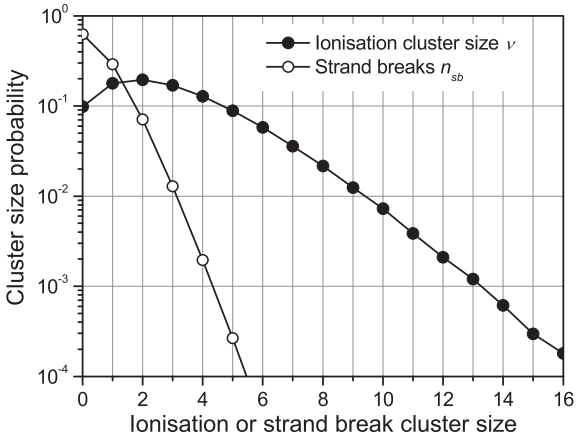

Fig. 3. Probability distribution of ionisation cluster size (filled circles) and strand break cluster size (open circles) for 300 keV protons traversing the centre of a cylindrical water target (2.3 nm in diameter and 3.4 nm in height) in the plane perpendical to the cylinder's axis. The ionisation cluster size probabilities were obtained by Monte Carlo simulation using the Geant4-DNA toolkit, and the strand break cluster size probabilities were derived using the Combinatorial model (Garty et al., 2010).

radiation qualities and those of low-LET electrons, which are used as the reference radiation. Nanodosimetric quality factors attained in this way (Schulte et al., 2008) were in reasonably good agreement with the conventional quality factors set by the ICRP (2003). Recent progress in this area, which considers target volumes corresponding to longer segments of DNA, has shown a tendency for the derived nanodosimetric quality factors to be in closer agreement with the ICRP values (Schulte, 2010).

3.3. Comparison of both approaches

Although both the Grosswendt and Combinatorial approaches start from practically the same ionisation cluster size distributions (obtained either by Monte Carlo simulation or nanodosimetric measurement), no attempt has yet been made to directly compare their outcomes. Such a comparison can be seen in Fig. 4, with a plot of the probability for double strand break formation and the cumulative probability F_2 for an ionisation cluster size of two or more. These

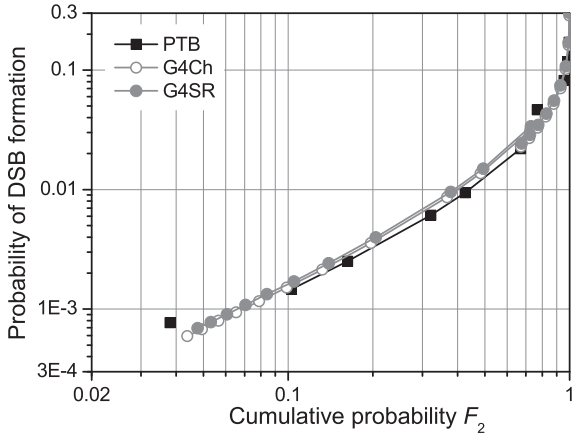

Fig. 4. Correlation between the Monte Carlo derived probability for double strand break (DSB) induction, as predicted by the Combinatorial model, and cumulative probability F_2 for an ionisation cluster size of two or more by particles with an LET between 5 keV/μm and 220 keV/μm. These values were derived from the ionisation cluster size distributions simulated with the PTB code (PTB) and Geant4-DNA code, where G4Ch and G4SR correspond to the respective Screened Rutherford and Champion models used for electron elastic scattering.

values were derived from Monte Carlo simulations of the ionisation cluster size distributions for proton and alpha particles centrally passing a cylindrical liquid water target (2.3 nm in diameter and 3.4 nm in height) in a plane at half its height. The energy of the protons ranged from 300 keV to 10 MeV (i.e. LET values of about 5 keV/μm to 55 keV/μm), while the energy of the alpha particles were between 1 MeV and 10 MeV (i.e. LET values of about 55 keV/μm to 220 keV/μm). The simulations were performed using the PTB code (Grosswendt, 2002) and the Geant4-DNA extension Monte Carlo code, which features so-called very low-energy electromagnetic processes (Chauvie et al., 2007; Incerti et al., 2010). The results labelled *G4SR* and *G4Ch* refer respectively to the Geant4-DNA simulations obtained with the two different possible models for the treatment of electron elastic scattering: cross sections based on the Screened Rutherford model and those derived from the Champion model (Champion, 2003). Note that in the figure, no distinction is made between protons and alpha particles.

Despite exhibiting a similar trend, minor discrepancies can be seen between the simulation results obtained with the PTB code and the two variations of Geant4-DNA, which are almost identical. For F_2 values below about 0.3, a linear relation between F_2 and the probability of DSB formation can be seen in the double-logarithmic presentation, which supports Grosswendt's second hypothesis of proportionality between F_2 and p_{DSB}. In this range, F_2 values correspond to loosely ionising particles with LET values below about 20 keV/μm. On the other hand, F_2 values between about 0.5 and the maximum possible value of 1.0 exhibit a DSB probability that tends to an almost divergent behaviour as function of F_2. These findings suggest that Grosswendt's second hypothesis is no longer valid when the ionisation cluster size distributions have insignificant probabilities for no ionisation or single ionisation within the target volume. The explanation for this lies in an inherent feature of the Combinatorial approach which leads to a higher conditional probability for larger ionisation clusters to be converted into a DSB as opposed to that for smaller ionisation clusters. Using the ionisation-to-lesion conversion probability $p_{SB} = 0.117$ (Garty et al., 2010), this conditional probability is only 0.7% for an ionisation cluster size of two, while for ionisation cluster sizes of 8 and 25, this probability is 13% and 60%, respectively. Referring back to Fig. 1, the latter two values of cluster size corresponds to the peaks for carbon and neon ions for the respective particle energy. For these ionisation cluster size distributions, it is therefore expected that if such a correlation should exist between the DSB formation probability and the cumulative probability for a minimum cluster size, this minimum size should be greater than two.

The question of what is the most probable minimum cluster size for which the cumulative probability is representative of DSB generation may be answered within the framework of the Combinatorial model (described above) by Bayesian methods. As a detailed discussion is beyond the scope of this paper, only the outcome of this analysis will be stated. The output of the Bayesian analysis is in this case the likelihood that a DSB was formed by an ionisation cluster of at least a minimum size. Using the ionisation-to-lesion conversion probability p_{SB} (as above), one can obtain the likelihood distribution as a function of minimum cluster size for each ionisation cluster size distribution. For the proton and alpha particle data shown in Fig. 1 (which correspond to respective LET values of about 7.9 keV/μm and 31.5 keV/μm), this likelihood distribution has a pronounced maximum at a minimum cluster size of two, such that F_2 is a good estimate for p_{DSB}. For 60 MeV carbon ions (LET of about 292 keV/μm) and 100 MeV neon ions (LET of about 743 keV/μm), however, the maximum value in the distribution occurs at a minimum cluster size of 6 and 11, respectively. For the carbon ions, the maximum likelihood is about three times larger than that of obtaining a minimum cluster size of two. In the case of neon ions, a minimum cluster size of 11 is five times more likely than a minimum cluster size of two. Consequently, the parameter F_2 for these two radiation qualities is not expected to represent p_{DSB}.

4. Recent progress towards DNA-equivalent nanodosimetry

So far, the search for a connection between the ionisation cluster size distributions, nanodosimetric characteristics of particle track structure and estimators for biological effectiveness (i.e. those derived from the Grosswendt and Combinatoric models) has not addressed the issue of using appropriate physical data for the interaction medium.

Experimentally determined ionisation cluster size distributions for a particular radiation quality are generally based on measurements in simple gases like propane and nitrogen. The Monte Carlo simulations carried out for comparison with these nanodosimetric experiments are also based on the cross section data of these gases. For the purpose of establishing a link between micro- or nanodosimetry and the biophysical or biological effects of radiation, Monte Carlo track structure simulations are commonly based on the cross section data of liquid water. For example, the recent development of the nanodosimetric track structure simulation capabilities of the Geant4 Monte Carlo toolkit (Geant4-DNA project) was only for the cross section data base of liquid water for energies down to the ionisation threshold (Chauvie et al., 2007; Incerti et al., 2010). The reason for this is that water is the most ubiquitous molecule encountered in biological cells, including the cell nucleus. While this rationale may be sound for the study of track structure details on a micrometer scale, the use of liquid water cross sections to represent those of biological matter, namely the DNA, may bias nanodosimetric quantities at the DNA level.

This prompted a systematic study at the PTB to determine experimentally the cross sections for the interaction of electrons and ions with DNA constituents, with particular focus on the primary particle energies where the underlying high-energy approximations of theoretically derived cross sections cannot be assumed valid. The vision of the project is to implement the measured cross sections into the PTB Monte Carlo track structure code to facilitate more realistic investigations of the radiation interaction and track structure properties at the DNA level. So far, measurements have been performed for the electron scattering cross sections in tetrahydrofuran, which is a biomolecule substitute for the deoxyribose group in the DNA backbone. An outline of the aspects of these measurements is given here. For a detailed account of the methods and procedures the reader is referred to the work of Bug et al. (submitted for publication). In brief, the measured cross sections for primary particles between 20 eV and 1 keV include: total cross sections; differential elastic cross sections with respect to the scattering angle; and double differential ionisation cross sections with respect to the scattering angle and secondary electron energy. Both the total and differential cross sections were measured absolutely using two independent setups, where scattering angles between 3° and 135° were used to obtain the differential cross sections. The cross section data outside this angular range and for electron energies higher than 1 keV were obtained by extrapolations based on theoretical models (Bug et al., submitted for publication). The cross section data sets were integrated into the PTB track structure code, which was modified to allow for the use of a sensitive volume of different material composition to that of its surrounding.

The modified PTB track structure code was used to investigate ionisation cluster formation in a target volume immersed in water and filled with either liquid water or THF of mass density 1.00 g/cm^3 and 0.85 g/cm^3, respectively. The mass density for THF was

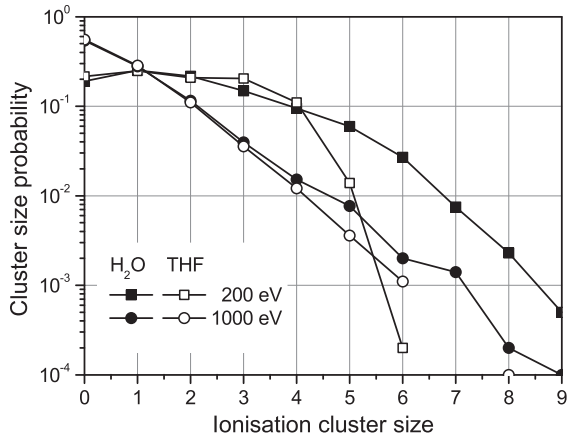

Fig. 5. Comparison of simulated ionisation cluster size distributions produced by electrons of 200 eV (squares) and 1 keV (circles) penetrating a cylindrical target (2.3 nm in diameter and 3.4 nm in height) surrounded by water. The solid and open symbols correspond to the target volume filled with liquid water and gaseous tetrahydrofuran (THF), respectively, where the mass density of THF was 0.85 g/cm^3.

chosen to correspond to that expected for a short DNA segment of 10 base pairs containing all four types of nucleic bases, where five of each are present. The target volume was a cylinder (2.3 nm in diameter and 3.4 nm in height), where primary electrons with kinetic energies up to 1000 eV penetrated the target in the plane perpendicular to the cylinder's axis at half its height. The simulations were performed using the relevant cross sections of the materials.

Fig. 5 shows the ionisation cluster size distributions obtained for 200 eV and 1000 eV electrons for the different cases when the target was filled with liquid water or THF. For the 200 eV electrons, the probability of obtaining an ionisation cluster size of three or four is greater in THF than in water, while the probability of a cluster size of five or more is substantially less. The distribution of ionisation cluster sizes for 1000 eV electrons, on the other hand, exhibits higher probabilities for cluster sizes of two or more in water than in THF. The smaller deviation between cluster size probabilities observed for the 1000 eV electrons than for the 200 eV electrons is presumably due to the relativistic projectile energy.

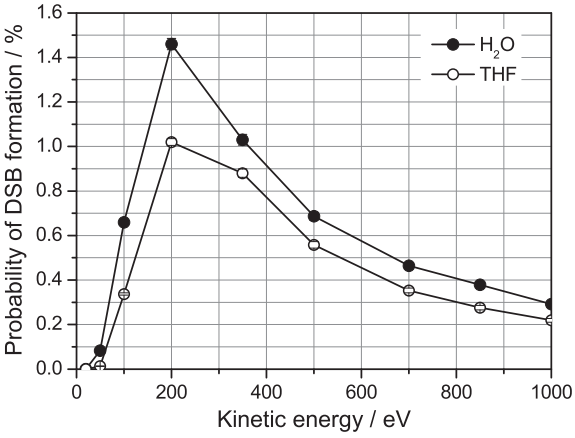

Fig. 6. Energy dependence of the probability for electrons to induce a double strand break (DSB) in a cylindrical target filled with liquid water (filled symbols) or gaseous THF (open symbols) of mass density 1.00 g/cm^3 and 0.85 g/cm^3, respectively. The electrons were normally incident on the surface of the cylinder (2.3 nm in diameter and 3.4 nm in height) at half its height. In both cases, the volume surrounding the target was filled with water. The DSB probability was derived from simulated ionisation cluster size distributions using the Combinatorial model.

The Combinatorial model (Garty et al., 2010) was then used to convert the simulated ionisation cluster size distribution for different energy electrons (interacting in a target volume of liquid water or THF) to the probability of producing a DSB. The results of these calculations are shown in Fig. 6 as a function of initial electron energy up to 1000 eV. In both liquid water and THF targets, a maximum in the probability of DSB formation can be seen at an electron energy of 200 eV. Given the coarse spacing of data points with respect to electron energy, the true maximum probably occurs at an energy between 250 eV and 300 eV. (The maximum value in the two different targets is assumed to be at approximately the same energy given their similar relative energy dependence). The higher probabilities of DSB formation in the water target, which is as much as 45% for 200 eV electrons, suggest that nanodosimetric simulations using the cross section data for water to substitute those for biological matter may lead to an overestimation of the biophysical effectiveness. In view of the similar relative energy dependence exhibited by the different target materials, if such a shortcoming does exist then perhaps it can be corrected by the introduction of a scaling factor. In order to confirm this presumption, further refinement of the track structure code using experimentally determined cross sections for electrons and ions in other DNA constituents is planned.

5. Conclusion

Nanodosimetry characterises particle track structure by the probability distribution of ionisation clusters formed in target volumes that are equivalent in mass per unit area to nanometric volumes of condensed matter, such as a short segment of DNA. In this work, two different approaches have been discussed that relate parameters derived from these probability distributions to the biological effectiveness of a particular radiation quality.

The first of these approaches is that of Grosswendt (2005), which assumes among other things that the cumulative probability F_2 for obtaining an ionisation cluster size of two or more in a DNA segment of 10 base pairs is proportional to the probability for inducing a double strand break. The other approach, referred to as the Combinatorial approach (Garty et al., 2006, 2010), uses combinatorics to obtain the conditional probabilities for a certain ionisation cluster of size ν to lead to a strand break cluster size of n_{SB} within the same DNA segment. In this approach, the probability for an ionisation to be converted into a strand break is used as a free parameter, which was determined experimentally in a plasmid DNA assay (Leloup et al., 2005).

Support for Grosswendt's presumption was demonstrated in Fig. 2 with the similar relative dependence on LET of F_2 values derived from simulated particle tracks (in water) and radiobiological data of DSB formation for a particular biological endpoint. However, direct comparison of the DSB probability p_{DSB} obtained by the Combinatorial approach and Grosswendt's F_2 values (Fig. 4) suggests that these two quantities may be proportional only for low-LET radiation qualities. Further investigations are therefore needed to establish the relationship between radiobiological effectiveness and nanodosimetric quantities, where the radiation quality for the radiobiological assays should ideally be characterised by nanodosimetric measurements of ionisation cluster size distributions. These studies should also address the question of which target size is the most relevant for the correlation of nanodosimetric quantities and biological effects. For the simulations, one needs to consider the importance of modelling the geometrical structure of the DNA within the target (Zhang and Tan, 2010) and using the cross sections of DNA as opposed to those of liquid water. While most of these cross sections still await measurement, simulations based on measured cross section data of THF

(substitute for deoxyribose in the DNA backbone) suggest that the water-for-DNA approximation may lead to an overestimation in the radiobiological effectiveness.

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