The physical basis for the biological action of heavy ions

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New Journal of Physics 10 (2008) 075004 (15pp)
Received 29 January 2008
Published 28 July 2008
Online at http://www.njp.org/
doi:10.1088/1367-2630/10/7/075004

Abstract. The physical properties of heavy ions determine to some extent their biological action. The spatial pattern of energy deposition is different from that by sparsely ionizing radiations like x- or γ-rays. The interaction with atomic electrons may lead to large local energy depositions in sensitive targets. Dose is essentially determined by particle fluence and the linear energy transfer (LET) of the projectile. The biological action depends on the number of targets hit by the particle and the probability to cause an effect by a single traversal which is called the ‘action cross section’. Action cross-section increases with LET approaching the geometrical cross section of sensitive targets. A detailed analysis shows that ion tracks have a certain structure produced by the action of more energetic far-reaching electrons liberated by the initial interactions of the incoming ion. Track structure is analysed using a simple model based on classical collision dynamics describing at least the essential features. It is shown that very high energies are deposited in the track centre which may lead to large local concentrations of initial lesions. The radial extension of tracks can lead to damage in sensitive targets even if they are not directly traversed. Track structure analysis can account for this in a qualitative way but the quantitative agreement is still poor. The models are not able to explain the higher relative biological effectiveness (RBE) of heavy ions compared to x- or γ-rays. Biological factors such as lesion clustering and repair processes have additionally been taken into account. This can be done by ‘phenomenological models’ incorporating track structure analysis and assumptions on the dependence of biological effectiveness on local energy density.
1. Introduction

The effectiveness of ionizing radiations to induce biological alterations depends on the way how the energy is deposited in the system. Densely ionizing radiations are more effective than photons or fast electrons, the quantitative extent is given by the ‘relative biological effectiveness (RBE)’ which is defined as the ratio of the doses to create the same effect by the reference radiation (commonly $^{60}\text{Co-}\gamma$-radiation) and by the radiation in question. A common descriptor of radiation quality is ‘linear energy transfer’ (LET), the energy locally imparted by a charged particle per unit distance traversed (ICRU 1970, 1993a, b). LET is conceptually different from ‘stopping power’ which stands for the energy lost by the incoming particle. LET does not take into account the microscopic structure of energy deposition and has, therefore, some limitations. RBE depends on LET but not in unambiguous manner as the same LET can be achieved by different ions depending on their charge and speed. The increased effectiveness of heavy ions compared to x- or $\gamma$-rays plays an important role both in radiotherapy and in radiation protection.

The energy deposition by heavy charged particles is quite different from that of sparsely ionizing radiations. Ionizations are formed along distinct paths that are reflected in the distribution of primary lesions in cell nuclei crossed by an ion which can be made visible with the aid of immunochemical techniques (Jakob et al 2003).

This paper discusses the relevance of energy deposition by heavy charged particles in relation to their biological action in a general way. It is not the aim to give a comprehensive review of all model approaches to be found in the present literature but to describe some of the underlying principles and their limitations.

2. Dose, fluence, LET and action cross sections

Dose $D$ is the common exposure parameter in radiobiology, it is measured in $\text{Jkg}^{-1}$ with the special unit ‘Gray’ (Gy). Dose $D$ is related to the particle fluence $\Phi$ (number of particles per unit area) by the expression

$$D = L \Phi / \rho,$$

where $L$ stands for LET and $\rho$ for the density of the exposed medium. Dose is a macroscopic continuous quantity while fluence is of discrete nature. This difference is especially important with low doses. Biological objects are structured and it is generally assumed that they contain sensitive targets whose radiation-induced alterations are responsible for the measured effects. Energy can only be deposited if such a target is hit by a particle, the amount is a function of target size and particle type. ‘Low doses’ correspond to low fluences according to equation (1).
Figure 1. The fraction of targets (geometrical cross section 100 µm²) receiving at least one hit by ⁶⁰Co-γ-rays (LET = 0.22 keV µm⁻¹) or by a heavy ion (LET = 100 keV µm⁻¹) (solid lines). Fractions with more than 1 hit are given by dashed lines.

Similar considerations apply to the quantity ‘dose rate’. It is an important parameter for sparsely ionizing radiations. Dose rate effects can only be expected if the critical target is hit more than once.

In the case of high-LET projectiles, only a few targets are actually hit, receiving a minimum energy deposition which depends on the LET of the ion while the majority are untouched. Strictly speaking this is true for all types of ionizing radiations. With photons, energy transfer occurs essentially by electrons, i.e. also by discrete processes. Because of their low LET, however, this plays a role only with very low doses. Figure 1 shows the fraction of hit targets (assumed geometrical cross section of 100 µm², representing approximately the nucleus of a mammalian cell) for ⁶⁰Co-γ-rays with a LET of 0.22 keV µm⁻¹ (ICRU 1970) and an ion with an assumed LET of 100 keV µm⁻¹ as a function of dose.

One sees that for doses of < 1 mGy virtually all targets receive a hit with the sparsely ionizing radiation while with the ion, even at a dose of 0.1 Gy, a substantial fraction remains unhit. It has to be pointed out, however, that these estimates are based on the assumption that the ion path has a very small radial extension. With heavier ions and higher particle velocity the situation is quite different as discussed below.

The fractions of targets with more than one hit are also given in the figure. They are important for the consideration of dose rate effects as pointed out above. If one assumes that at least 10% of the critical targets must receive more than one hit for dose rate effects to be observable one can conclude that with γ-rays they may be relevant for doses above about 1 mGy while the corresponding value for α-particles is about 0.1 Gy and even larger for heavier ions. The relevance of dose rate effects with regard to space radiation, where heavy ions are an important component has been discussed by Schimmerling and Cucinotta (2006).
While a necessary condition for a target to be inactivated is that it is hit by a particle, this is by no means sufficient. Whether a biological reaction is caused depends on many, normally not very well-known parameters. Formally, the probability per unit fluence for a reaction to occur is described by the ‘action cross section’. If every target hit is inactivated by the passage of a particle the action cross-section approaches the geometrical cross section of the sensitive structure.

Figure 2 displays experimental cross sections for the inactivation of V79 Chinese hamster cells (nuclear area 100 \( \mu m^2 \)) derived from the final exponential slope of the survival curves. They increase with LET approaching the geometrical nuclear cross section with high LET values. There appears to be, however, a certain structure, particularly with very high LET values. This will be discussed below.

A first simple theoretical approach is based on the LET-concept and is exemplified here using cell inactivation. Let us assume that the survival curve can be described by a simple exponential dose–effect relationship. The surviving fraction \( y \) is then given by

\[
y = e^{-D/D_0}
\]

and with equation (1)

\[
y = \exp\left(-\frac{L}{\rho D_0} \cdot \Phi\right) = \exp -\sigma_i \Phi,
\]

\(\sigma_i\) is the inactivation cross section.

**Figure 2.** Experimental cross sections for the inactivation of V79 Chinese hamster cells (data from Stoll et al 1995 and unpublished experiments by S Koch and P Schmidt). Error bars represent standard errors. The broken curve represents a crude theoretical approach based on the LET-concept (see below).
Targets are hit according to a Poissonian distribution. The dose deposited by a single passage \(z_1\) in a spherical target of volume \(V\), radius \(r\) and cross section \(\sigma_g\) is given by

\[
z_1 = \frac{L \bar{l}}{\rho V} = \frac{L}{\rho \sigma_g},
\]

where \(\bar{l} = 4/3r\) is the mean path length in a sphere.

The surviving fraction can then be given as

\[
y = \sum_{\nu} \frac{e^{-\sigma_g \Phi}}{\nu!} e^{-\nu L/\rho \sigma_g D_0} = e^{-\sigma_g \Phi \cdot e^{\sigma_g \Phi (L/\rho \sigma_g D_0)}} = e^{-\sigma_g \Phi (1 - e^{-L/\rho \sigma_g D_0})}. \tag{3}
\]

The inactivation cross-section is then

\[
\sigma_i = \sigma_g (1 - e^{-L/\rho \sigma_g D_0}). \tag{4}
\]

This relationship is inserted in figure 2 as a dashed line. One sees that the general behaviour is well described but there are systematic deviations, particularly in the medium- and high-LET range. The systematic underestimation between about 20 and 1000 keV \(\mu m^{-1}\) reflects the increase in RBE which is obviously not covered by the simple theoretical analysis. The data can be better fitted by 'phenomenological models' (see below) but a comprehensive theoretical treatment is still missing.

The structure in the dependence of inactivation cross sections with very high LET becomes even more obvious if one considers smaller objects as demonstrated in figure 3 where inactivation cross sections for haploid yeast are displayed. Their x-ray survival curve follows

**Figure 3.** Inactivation cross sections with different heavy ions for haploid yeast (data from Kiefer et al 1983). Error bars represent standard errors. The dotted line shows the relationship computed according to equation (4) with \(D_0 = 60\) Gy and a nuclear cross section of 1.4 \(\mu m^2\). The geometrical cross section is indicated by the dashed line.
a straight exponential with a $D_0$-value of 60 Gy, the nuclear cross section is estimated to be 1.4 $\mu$m$^2$ (Kiefer et al. 1983). Astonishingly one finds inactivation cross sections which are considerably larger than the nuclear area and also a decrease of $\sigma_i$ with very large LET-values. This pattern has already been predicted by Katz in 1967 (Butts and Katz 1967) and attributed to the microscopic pattern of energy deposition. It became quite clear from this treatment that track structure plays an eminent role in the interaction of heavy ions not only with biological, but also with technical systems if they contain essential microstructures.

The analysis so far considered heavy ion paths as straight lines with negligible radial dimensions. This is far from reality and does not take into account the primary physical interactions. Dose, being a macroscopic continuous quantity, loses its meaning at micro- or nanometre dimensions and has to be replaced by the stochastic quantity ‘specific energy’ $z$. It has no unique value but follows a statistical distribution and constitutes the stochastic microscopic counterpart of dose which may then be defined as the expectation value of specific energy. These questions are treated within the framework of ‘microdosimetry’ (for a comprehensive introduction into this branch of science, see Rossi and Zaider 1996).

To account for the fact that energetic electrons can deposit energy far off the track centre the quantity ‘restricted LET’, $\text{LET}_\Delta$, has been introduced where $\Delta$ indicates the maximum electron energy. $\text{LET}_\infty$ is numerically equal to stopping power. Stopping powers for heavy ions have recently been tabulated (ICRU 2005).

3. Track structure

Heavy charged particles interact mainly with the electrons of atoms and molecules. The liberated electrons may possess sufficient energies to travel considerable distances from their point of origin in the path’s centre. The track is hence by no means a straight line and looks rather like a ‘test tube brush’ (R Katz).

Track structure has been analysed by a number of authors using analytical approaches (Butts and Katz 1967, Chatterjee and Schaefer 1976, Kiefer and Straaten 1986), more recently Monte-Carlo-computer codes have been preferred (see e.g. Dingfelder 2006). It is beyond the scope of this paper to give a detailed review of this field but rather to concentrate on general aspects.

Butts and Katz (1967) were the first who developed a track structure model and used it to analyse the inactivation of viruses and bacteria by heavy charged particles. Chatterjee and Schaefer (1976) subdivided the track into a ‘core’ (high-energy density) and ‘penumbra’ (low-energy density) region which is operationally helpful but should not be taken to suggest that the interaction mechanisms are different. The ions collide with atomic electrons which are liberated with different starting energies and ejection angles depending on the ion’s speed.

The behaviour is illustrated here by using the model of Kiefer and Straaten (1986). It is based on classical collision dynamics and thus a simplified approach but measurements in simulated microscopic detectors showed that there are no large differences between the theory and the experiment (Schmollack et al. 2000). Figure 4 illustrates the track structure in a very schematic way.

Quantitative treatment (Kiefer and Straaten 1986) leads to the following relations. The penumbra radius $x_p$ measured in micrometres, depends only on ion speed (or specific energy $E$ m$^{-1}$, given in MeV u$^{-1}$) and not on atomic number or charge:

$$x_p = 6.16 \times 10^{-2} \ (E \ \text{m}^{-1})^{1.7}.$$ (5)
Figure 4. A schematic track structure model. The ion path is shown as a heavy dotted line. Electrons (light lines) are ejected at different energies and directions. The maximum radial extension, the penumbra radius $x_p$, is governed by the relationship between electron energy (and range) and ejection angle.

Table 1. Properties of different ions which all have a LET of 90 keV $\mu$m$^{-1}$.

| Ion   | Specific energy (MeV u$^{-1}$) | $Z^*/\beta^2$ | Penumbra-radius ($\mu$m) |
|-------|-------------------------------|---------------|---------------------------|
| $^2$He | 1.05                          | 1629          | 0.07                      |
| $^6$C  | 20.7                          | 837           | 10.6                      |
| $^{10}$Ne | 74.4                        | 700           | 94.7                      |

The energy deposited in the track varies with radial distance from the track centre and reaches zero at the penumbra radius. The energy density $\rho_c$, i.e. the deposited energy per unit mass in water is given by

$$\rho_c = 1.25 \times 10^{-4} \frac{Z^2}{\beta^2} x^{-2},$$

where $Z^*$ is the ion’s effective charge, $\beta$ ion velocity relative to that of light in vacuo and $x$ radial distance from the track centre measured in micrometres. Equation (6) states that energy density falls with the inverse square of radial distance. This feature is found in most track models.

The common quantity to describe the influence of ionization density is LET. It is, however, not unequivocal as different ions with different energies may have the same value as seen from the examples in table 1.

It is obvious that the same LET may be reached either by light ions with low specific energy or with heavier particles with higher speed. This means also that the heavier projectile has a larger penumbra radius and that energy deposition at microscopic scales is quite different. This is illustrated in figure 5 where energy density is plotted versus radial track extension. The local energy deposition is very large near the track centre reaching values around 1000 Gy but it falls rather rapidly. The ions differ in penumbra extension, the more energetic ones deliver less in the centre because the same energy is spread over a larger radial distance. This is shown more clearly in figure 5(b).

Energy density may fall to very small values at large distances from the track centre. In this case, only very few electrons are involved and energy deposition also follows a stochastic
Figure 5. (a) Energy density versus radial track extension for three different ions with an identical LET of 90 keV µm$^{-1}$. (b) As in (a) but with initial part enlarged.

distribution. This feature is not yet incorporated in current track structure models. It may be particularly important as ‘track end electrons’ show a higher biological effectiveness (Goodhead and Nikjoo 1990).

This feature can also be expressed in a different way: for a given ion, LET increases with decreasing velocity and hence also decreasing penumbra radius, i.e. the track becomes ‘thinner’. For very heavy ions penumbra electrons may contribute significantly to the action cross section which is then governed to a large extent by the penumbra radius. Larger LET means then smaller tracks and hence smaller action cross sections which leads to the unexpected finding that the cross-section decreases with increasing LET. This uncommon feature has been termed ‘thin out’ by R Katz. It plays a role only with very heavy ions and is clearly seen in figure 3 with haploid yeast whose nuclear cross section is comparable with penumbra extensions. With the larger mammalian cells (figure 2) the effect described is less obvious but still observable.

The analysis of biological heavy ion effects has to take into account the stochastic nature of energy deposition in sensitive sites. There are two aspects to be considered, first the distribution of hits that is governed by particle fluence and target geometrical cross section, and the variation according to equation (6) describing the fluctuation of dose per single hit, which depends on the radial distance between the target and the track centre, which is commonly called the ‘impact parameter’. According to the width of the track a target may experience an energy deposition

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Figure 6. (a) Doses delivered by single particle traversals in targets of 1 µm radius. Note that both ions have the same LET. (b) As in (a) but with a target radius of 5.6 mm (corresponding to a geometrical cross section of 100 µm²).

Even if the track centre lies outside the target. The actual amount depends both on the penumbra radius and the energy density within the track. The latter is a function of $Z^*/\beta^2$, i.e. of projectile charge, mass and specific energy. If one calls the ‘local dose’ delivered by a single ion traversal $z_1$, the variation may be described by a distribution function $f(z_1)$ which can be evaluated with the aid of equation (6). Figure 6 displays the energy deposition by single traversals as a function of impact parameter. It is seen that substantial target doses may be reached even if the ion does not directly hit the sensitive site. This depends both on the target size and on the ion specific energy. The examples given correspond roughly to a yeast (figure 6(a)) or a mammalian cell nucleus (figure 6(b)).

Track structure also plays an influential role for the estimation of particle traversals through a given object. Depending on ion-type and especially its specific energy the fraction of hit entities can be substantially larger than calculated using the LET approximation as clearly shown in figures 6(a) and (b). Cucinotta et al (1998) introduced an ‘effective cross-sectional area’ which is composed of the object’s and the track’s cross section. As penumbra radii may be very large but with very small energy densities the authors use a ‘cut-off dose’ by which an effective track radius is defined. If a value of 1 mGy and an object cross section of 100 µm² are chosen, effective cross-sectional areas may be up to a factor of 200 larger than the object cross section (Cucinotta et al 1998).
In the case of \( \nu \) multiple traversals the tracks overlap and the distribution function is then the \( \nu \)-fold convolution of \( f(z_1) \) (Kellerer and Rossi 1972, Kiefer 1982)

\[
f_\nu(z) = f^{*\nu}(z_1),
\]

where the superscript \( \nu^* \) indicates the \( \nu \)-fold convolution.

This formalism can be applied to analyse exponential survival curves where the x-ray survival is given by

\[
y = e^{-D/D_0}.
\]

The surviving fraction after ion exposure with a fluence \( \Phi_1 \) and a target cross section \( \sigma_g \) is then

\[
y = \sum_\nu \frac{e^{-\sigma \Phi} (\sigma \Phi)_\nu}{\nu!} \int f^{*\nu}(z_1) e^{-z/D_0} \, dz.
\]

The first two terms describe the Poissonian distribution of hits. The integral is a Laplace transform of \( f^{*\nu}(z_1) \). It is well known that the Laplace transform of a convolution equals the product of the unconvoluted expression

\[
\int f^{*\nu}(z_1) e^{-z/D_0} \, dz = \left( \int f(z_1) e^{-z/D_0} \, dz \right)^\nu,
\]

so that

\[
y = \sum_\nu \frac{e^{-\sigma \Phi} (\sigma \Phi)_\nu}{\nu!} \left( \int f(z_1) e^{-z/D_0} \, dz \right)^\nu.
\]

The summation yields

\[
y = \exp \left[ -\sigma_g \Phi \left( 1 - \int f(z_1) e^{-z/D_0} \, dz \right) \right].
\]

If the distribution of \( z_1 \) is neglected one has a single value of \( z_1 = L/\rho \sigma_g \) and equation (9) reduces to equation (3). The approach described can be extended to ‘shouldered survival curves of the single-hit-multi-target’-type as detailed elsewhere (Kiefer 1982).

The influence of track structure can be most clearly seen with small targets. Figure 3 demonstrates that yeast inactivation cross sections exceed considerably the dimensions of the cell nucleus, which cannot be understood within the framework of the LET-concept. The experimental data were reanalysed on the basis of equation (3) using the track model of Kiefer and Straaten (1986), the quantitative comparison is displayed in figure 7 for Kr, Xe, Pb and U ions.

It is seen that the qualitative behaviour is adequately described but there are still large quantitative differences. It is unlikely that different track models would give substantially different results as they all share common features.

The reasons for the discrepancies between theoretical and experimental values become clearer if one considers RBE. Haploid yeast does not show RBE-values greater than 1 with the ions available but it is well known that also with this object a higher effectiveness can be demonstrated (Korogodin et al 1996, Lyman and Haynes 1967, Shvedenko and Petin 2000) but with other ion types as used here. Our more recent experiments with Chinese hamster cells show that ions in the LET-range between about 10 and 1000 keV \( \mu \text{m}^{-1} \) are more effective than x-rays as also published by others (Wulf et al 1985). Experimental RBE-values are plotted in figure 8 compared to theoretical estimations. It is obvious that the increased effectiveness is
**Figure 7.** Experimental cross sections for the inactivation of haploid yeast as in figure 3 (symbols) compared to theoretical values calculated according to equation (9) using the track model of Kiefer and Straaten (1986) (broken lines). The horizontal broken line indicates the nuclear geometrical cross section. Error bars indicate standard errors.

**Figure 8.** Measured RBE-values for V79 Chinese hamster cells (diamonds) (data from Stoll et al 1995 and unpublished experiments by S Koch and P Schmidt). Theoretical estimates were calculated using the LET-concept (broken lines) or applying the track structure model according to equation (9) (open circles). Error bars indicate standard errors.
not explained by the theoretical analysis, neither by the LET nor the track structure approach. There are only small differences between the two models because of the comparatively large size of the mammalian cell nucleus. It is clear from this comparison that increased RBE cannot be explained by track structure although it has to be taken into account when calculating action cross-sections.

RBE decreases even below unity for very high LET-values. This can be understood if one considers the action cross sections. They reach or even exceed the geometrical cross-section which means that in that region the target is inactivated by the traversal of every particle irrespective of the transferred energy. In this saturation region, more energy is deposited than actually required for the inactivation, i.e. some of the energy is actually lost and the effectiveness consequently reduced.

4. Discussion

Track structure plays an important role for the understanding of biological heavy ions effects. Because of the influence of far-reaching penumbra electrons, the effective action cross-sections can be considerably larger than estimated from the size of the sensitive target. Particularly, with particles of large specific energy (and hence large penumbra radii) a substantial fraction of the dose may be sparsely ionizing as the energy density is low at greater distances from the track centre. That this is the case has been shown by the ‘reappearance of the oxygen effect’ in yeast with very heavy ions with large specific energies (Schöpfer et al 1984).

Energy density which is used as a parameter for track structure description is an average value (comparable to dose at macroscopic dimensions) and depends on the number of interacting electrons. If the electron fluence is low there will be only few energy deposition events and the quantity energy density loses its unequivocal meaning. In this situation ‘track-end’ electrons may play an important role and contribute significantly to the biological effectiveness of heavy ions. They are also produced by ultrasoft x-rays whose increased effectiveness is well documented (see e.g. Goodhead and Nikjoo 1990). The time factor has so far not been mentioned, and dose rate influences were not discussed.

Although track structure is obviously important it cannot explain the increased effectiveness of densely ionizing radiations in a straightforward manner, as shown above. To address this question, it is necessary to consider targets much smaller than cell nuclei and study energy deposition at the chromosomal and DNA level. There have been a number of attempts, mainly applying Monte-Carlo computations (see e.g. Friedland et al 2003, Kundrat and Stewart 2006, Ponomarev et al 2001), showing that random breakage models are not applicable at molecular dimensions with densely ionizing radiations and that DNA double strand breaks (DSB) are formed in clusters (Fakir et al 2006). They are not resolved by standard techniques which would lead to an underestimating of DSBs. Their formation in mammalian cells shows only a slightly higher RBE with heavy ions (Prise et al 1998), which may be due to the fact that small DNA fragments are not detected. Larger RBE-values have been reported for yeast (Kiefer et al 2002) and in plasmid DNA (Brons et al 2003). These authors applied a modified track structure model and were able to show a good fit to their experimental data. But even in those instances where a higher effectiveness of DSB induction with heavy ions could be shown, the actual values are too small to explain RBE-values found for chromosome aberration, mutations or cell killing.

DNA DSB can be repaired in cells and it is quite clear that repair proficiency has a distinct influence on the RBE for cellular endpoints (Zyuzikov et al 2001) as already suggested by

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Alper (1984). Any model for cellular radiation effects had to, therefore, include repair of initial DNA lesions. This cannot be achieved only by an analysis of physical parameters. One has hence to recur to so-called ‘phenomenological models’. They start from x-ray dose effect curves and use track structure models to derive the behaviour after heavy ion exposure. This approach was first introduced by Katz to explain cell inactivation (Katz et al. 1971, Roth et al. 1976) and was later extended to mutagenesis (Cucinotta et al. 1996) and neoplastic transformation (Waligorski et al. 1987). The basic idea is to divide the interaction of a heavy charged particle into a ‘γ-like’ and a typical ‘ion’ component. The first is represented by the outer parts of the track (the penumbra) while the latter is found in and close to the track centre. ‘Gamma-like’ action follows a multi-hit kinetic mechanism as with x-rays while ‘ion-like’ action is essentially described by a single hit mechanism. The division between the two is deduced from experimental data, and it is claimed that dose effect curves can be predicted over a wide range of LET. The formalism has been applied to estimate space radiation risk (Cucinotta et al. 2003) and to the planning of tumour radiation therapy (Katz and Cucinotta 1999).

A different approach has been introduced by Scholz and Kraft, termed the ‘local effect model’ (Scholz and Kraft 1994, 1996). The idea here is that the biological effect is determined by the distribution of local energy density in the cell’s sensitive structure which is taken to be the nucleus. Starting from the x-ray survival curve, effect levels are correlated with dose. The nucleus is subdivided into infinitesimal sections and the energy density in them computed using a track structure approach. The ‘local dose’ is then transformed into an effect level so that a distribution in infinitesimal effects is obtained. The total effect is then obtained by integration over the whole nucleus. The model seems to work well to predict cell survival for a whole range of ions. It is used mainly for the planning of radiotherapy with carbon ions (Kraft et al. 1999, Krämer and Scholz 2006, Krämer et al. 2003, Scholz et al. 2006). Recently, the model has been extended to include clustering of DNA DSB (Elsässer and Scholz 2006).

In summary, one has to conclude that the local distribution of energy deposition in sensitivity structures plays an important role in the understanding of biological heavy ion action and has to be taken properly into account. It is able to explain the decrease in RBE for very high LET-values but it does not suffice to explain fully the increased effectiveness in a quantitative way. The interplay between the distribution of initial DNA lesions and repair processes adds another important biological feature which cannot be understood solely by the physics of heavy ion interactions (Goodhead 2006). The formation of initial lesions and their interaction can not yet be fully explained by available models.

The quantitative description of biological heavy ion effects is further complicated by the ‘bystander effect’. It has been shown for several endpoints that cells can be damaged even if they were not traversed by a particle (Hall 2003). This may suggest that the concept of action cross section is meaningless. It certainly plays a role at very low fluences but it is not yet clear to what extent it influences the quantitative outcome of experiments with higher fluences and many cells.

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